4F9

►Metastasis Suppressor KAI1/CD82

F-box and Leucine-rich Repeat Protein 1 – Fbxl1

►Ubiquitin Ligase SCF-Skp2

FAB Classification

Definition

French-American-British Classification; Standardized classification system for acute leukemias based on morphology.

►Chromosomal Translocation t(8;21)

Fab Fragment

Definition

A proteolytic fragment of the immunoglobulin molecule resulting from digestion with the enzyme papain.

►Anti-HER2/Neu Peptide Mimetic

FAC

Definition

*F*ocal *a*dhesion *c*omplex is a multiprotein complex that is transiently formed inside the cell in response to ligand binding to integrins. FAC is attached to actin filaments that allow the cell to exert the mechanical tension required for cell movement. FAC can also activate other downstream signaling pathways that can alter cell ►migration.

►Osteopontin
►Integrin Signalling

FACS

Definition

Individual cells can be characterized and separated in a machine called a fluorescence-activated cell sorter (FACS) that measures cell size, granularity, and fluorescence due to bound fluorescent antibodies as single cells pass in a stream past photodetectors. The analysis of single cells in this way is called flow cytometry and the instruments that carry out the measurements and/or sort cells are called flow cytometers or cell sorters.

Factor Ia

Definition

►Fibrin

Factor V

Definition

Proaccelerin, Labile Factor; Cofactor of the blood coagulation cascade without enzymatic activity.

►Proteinase-activated Receptors

Factor VII

Definition

Proconvertin; Serine proteinase that is involved in blood coagulation. It binds to tissue factor, where it is activated by thrombin, factor Xa or another activated factor VIIa molecule, bound to tissue factor. It can stimulate proteinase-activated receptor 2.

►Proteinase-activated Receptors

Factor VIII

Definition

Procofactor of the blood coagulation cascade. It is produced by vascular endothelial cells. It is mainly bound to ►von Willebrand factor (vWF) in the circulation. Upon conversion by thrombin or factor Xa, the active cofactor (factor VIIIa) is released from vWF and forms a complex with factor IXa which in turn activates factor X.

►Proteinase-activated Receptors

Factor IX

Definition

Christmas Factor; Serine proteinase of the coagulation pathway. It activates factor XI and prekallikrein

►Proteinase-activated Receptors

Factor X

Definition

Stuart-Prower Factor; Serine proteinase of the coagulation pathway. It is produced by the liver and circulates in the blood stream. It is activated to form factor Xa by factor IXa and factor VIIa. Together with factor Va, it activates prothrombin. It can also stimulate proteinase-activated receptors 1 and 2.

►Proteinase-activated Receptors

Factor XI

Definition

Plasma Thromboplastin Antecedent; Serine proteinase of the blood coagulation cascade. It is produced by the liver and is converted by factor XIIa and thrombin to enzymatically active factor XIa.

►Proteinase-activated Receptors

Factor XII

Definition

Hageman Factor; Serine proteinase of the coagulation pathway. It activates factor XI and prekallikrein.

►Proteinase-activated Receptors

D-factor

►Leukemia Inhibitory Factor

FAD

Definition

Abbreviation for Final Appraisal Document.

►National Institute for Health and Clinical Excellence (NICE)

FADD

Definition

Fas-associated protein with death domain (FADD) is a protein that bridges Fas that belongs the ►tumor necrosis factor (TNF) family and other death receptors

to ►caspase-8 to form death inducing signaling complex (►DISC) during cell death.

►Methoxyestradiol
►FLICE Inhibitory Protein
►Apoptosis

FADD-like Antiapoptotic Molecule 1

►FLICE Inhibitory Protein

FADD-like ICE

►Caspase-8

FAE

Definition

Fumaric acid ester.

►Dimethylfumarate

FAK

►Focal Adhesion Kinase

Familial Adenomatous Polyposis

Definition

FAP; Is an autosomal dominant disease characterized by the presence of at least one hyndred polyps in the large bowel and by several extracolonic manifestations, which include polyps in other organs, desmoid tumors, dental abnormalities, osteomas, and congenital hypertrophy of the retinal pigmented epithelium. An inherited disease of the large intestine marked by the formation of numerous glandular polyps that typically become malignant if they are left untreated. In most cases it is caused by inactivation of the APC gene (►APC gene in Familial Adenomatous Polyposis).

►Colorectal Premalignant Lesions
►APC Gene in Familial Adenomatous Polyposis

Familial Breast Cancer

Definition

Familial clustering of breast cancer due to inherited germ line mutations in breast-cancer risk genes, BRCA1, BRCA2, and probably in additional genes that so far have no been identified.

►BRCA1/BRCA2 Germline Mutations and Breast Cancer Risk.

Familial Cancer

Definition

If a cancer is familiar, it is more common in relatives of an affected individual than in the general population. The level of aggregation is usually measured as a relative risk in affected families as compared to all families. A relative risk of 2.0 implies a two-times higher risk for the offspring of an affected parent.

Breast cancer, for example, is two-times more common in daughters whose mothers had breast cancer. The risks can be measured between parents and offspring, between siblings or between any first-degree relatives.

Familial aggregation is found in all types of cancer. The highest familial risks are observed for thyroid and testicular cancers, with familial risks between 5 and 10. Higher than 3.0 are the risks for ►melanoma, ►prostate cancer, ►endometrial cancer and squamous cell ►skin cancer. The breast and colon cancer the risk is about 2.0.

The reasons for familial cancer are inherited susceptibility. A shared environment and common patterns of behavior also play a role. Familial aggregation of ►lung cancer and ►cervical cancer (relative risk about 2.0) can be partially explained by environmental factors. Inherited cancers are a subgroup of familial cancers where the genetic component is obvious. In

many cases the underlying genes have been identified and gene tests are available for some cancer-related genes. Inherited cancers are often monogenic and confer a high risk in those family members who have inherited the defective gene. The frequency of disease is described by penetrance, which is 100% if all carriers of the defective gene contract cancer. Inherited cancers include cancers at many sites and syndromes at multiple sites.

►Colon Cancer
►Breast Cancer Genes BRCA1 and BRCA2
►Familial Adenomatous Polyposis

Familial Cancer Syndrome

Definition
Occurrence of specific heritable cancer types in a familial manner.

►Familial Cancer

Familial (constitutional) Panmyelocytopathy (type) Fanconi

►Fanconi Anemia

Familial Hypoplastic Anemia Fanconi

►Fanconi Anemia

Familial Polyposis Coli

Definition
FAP.

►Familial Adenomatous Polyposis
►APC Gene in Familial Adenomatous Polyposis

FAMP

►Fludarabine

FANC Genes

Definition
Designation of genes, whose ►homozygous or ►hemizygous mutations cause ►Fanconi anemia.

FANCJ

►BACH1 Helicase

Fanconi Anemia

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Synonyms
Familial (constitutional) panmyelocytopathy (type) Fanconi; Familial hypoplastic anemia Fanconi

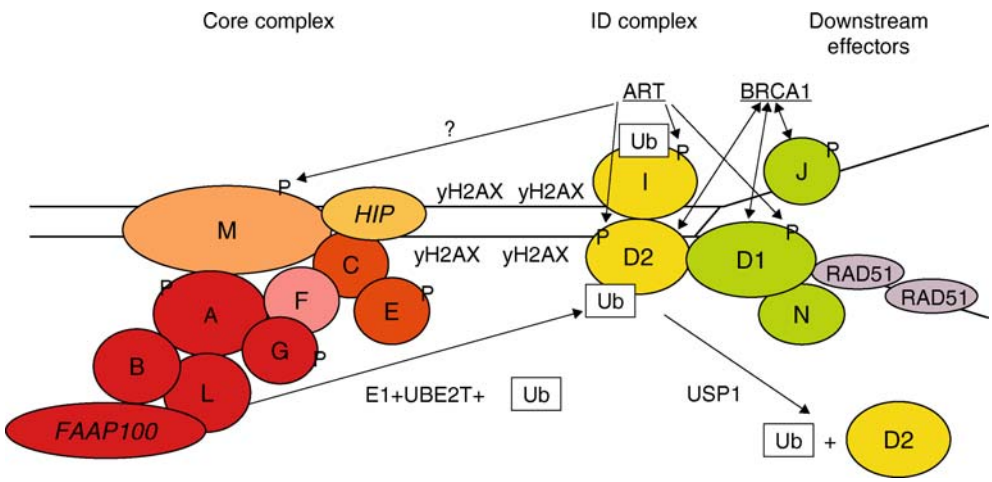
Definition
Fanconi anemia (FA) is a human inherited disorder clinically characterized by variable congenital anomalies, bone marrow failure and cancer susceptibility. Cellular features include genomic and chromosomal instability and hypersensitivity to DNA-crosslinking agents. FA is a rare recessive disease with an overall prevalence of about 1 in 300,000, but much higher prevalence in selected populations.

Characteristics
Approximately 70% of FA patients display variable presence of (intrauterine) growth retardation, hyper- and hypopigmentations of the skin, radial ray and external ear defects, microcephaly, microphthalmia, and malformations of the inner organs including most

frequently kidney, gastrointestinal tract, heart and brain. FA is genetically heterogeneous comprising at least 13 ►complementation groups (A to N). Underlying these subtypes are biallelic (in case of the X-chromosomal group FA-B hemizygous) mutations in 13 different genes (*FANCA*, *-B*, *-C*, *-D1*, *-D2*, *-E*, *-F*, *-G*, *-I*, *-J*, *-L*, *-M* or *-N*). The products of the FA genes interact with themselves and with a number of other proteins in a common pathway. The FA pathway for genomic maintenance, also called FA/BRCA pathway (Fig. 1), is a DNA damage-activated signaling pathway, important for the recognition of ►DNA-interstrand crosslinks and the initiation of repair of these lesions by nucleotide excision repair, ►translesion synthesis and ►homologous recombination. FA patients have defects in the FA pathway and share a high risk for the occurrence of characteristic malignancies at relatively young age. Approximately 23% of FA patients develop one kind of neoplasm or more during lifetime. In most cases, there are sharply increased risks for ►acute myeloid leukemia (AML) during childhood and ►squamous cell carcinomas (SCC) becoming effective during young adulthood. These risks are associated with defects of any of the FA genes except *FANCD1* and *-N*. Associated with defects of the latter is a different risk combination with earlier onset. *FANCD1* is also known as ►*BRCA2* and *FANCN* as ►*PALB2*. ►Biallelic mutations in either of them consistently result in a type of FA with strong risks for developmental types of cancer during infancy including ►medulloblastoma and ►nephroblastoma (►Wilms tumor), and AML. In particular defects of *FANCD1* and *-N* include a number of cases with multiple tumors. FA-D1 and -N patients invariably succumb to their malignancies at early age. Given the high degree of genomic instability and elevated mutation rates seen in FA cells, there is little doubt about a causal relationship between the FA-specific defect of genomic maintenance and the emergence of cancer in FA patients.

Myelodysplastic Syndromes (MDS)

In ►myelodysplastic syndromes, bone marrow precursor cells fail to differentiate properly such that not enough mature erythrocytes, leukocytes and thrombocytes arrive at the periphery. MDS is a frequent hematological disorder in FA. It occurs in ~7% of all patients. MDS is generally considered a premalignant condition, but less so in the context of FA. FA-related MDS progresses to ►leukemia more slowly compared to MDS in non-FA patients; it obviously follows a different natural course. Thus, FA patients may suffer from MDS for many years without developing overt leukemia. Nevertheless, the presence of MDS affects the prognosis of FA: The estimated 5-year-survival rate of FA patients with MDS amounts to only 0.09 as opposed to 0.92 in patients without MDS. Wherever



Fanconi Anemia. Figure 1 Model of the FA/BRCA signaling network. A DNA interstrand-crosslink stalls a replication fork. ATR is activated and phosphorylates FANCM, FANCD2, FANCI and FANCD1/BRCA2. The FA core complex (FANCA, -B, -C, -E, -F, G, -L and -M, *orange* to *red*) is assembled and loaded onto double-stranded DNA through FANCM and the Hef-interacting protein, HIP (FAAP24). The active FA core complex translocates along DNA and, as a E3 ligase, monoubiquitates FANCD2 and FANCI by means of UBE2T as the E2 ligase and FANCL as the E3 catalytic subunit. The ID complex (FANCI and -D2, *yellow*) is directed to chromatin at the stalled replication fork via γH2AX. The active ID complex, supported by BRCA1, recruits downstream effector proteins (*green*). While FANCJ/BRIP1 is thought to stabilize the replication fork and enable translesion synthesis, FANCD1/BRCA2 in combination with FANCN/PALB2 uploads RAD51 (*violet*) and is attributed a role in restart of the replication fork after homologous recombination. All of the latter proteins colocalize in repair foci. Adapted from Wang (2007).

possible, MDS is treated by ►hematopoietic stem cell transplantation (HSCT) to diminish the risk of transition to AML.

Leukemia

The most common malignancy arising in FA patients is leukemia. Its overall cumulative incidence is 37% (33% by age 40). The median age of onset is 14 years, thereafter the incidence rate of leukemia levels out at <1% per year. With 94% of all leukemias, AML predominates in FA with the relative risk being about 500- to 800-fold increased. ►Acute lymphoblastic leukemia (ALL) amounts to only 6%, in contrast to 84% of leukemias in the general population being ALL. Chronic myelomonocytic leukemia (CMML) or ►Burkitt lymphoma have been reported in single cases.

All FAB subclasses are represented in FA-associated AML, albeit with different proportions compared to the general population. There are more FA patients in the M4 and M6 and fewer in the M1 and M2 subclasses than in non-FA AML patients. Monosomy of chromosome 7 and partial tri- or tetrasomies of chromosome 3q, occurring as clonal aberrations in bone marrow and detectable also in peripheral blood leukocytes, are proven risk factors for the development of MDS and AML. AML may be the first and only manifestation of FA in otherwise unsuspicious patients.

Solid Tumors

The overall risk of FA patients for the emergence of solid tumors exceeds that of the general population by nearly 50-fold, with higher risks for selected tumors. The rate of solid tumors rises more than linearly and reaches 10% per year by age 45. If the competing death risks of anemia and leukemia could be removed, the estimated cumulative probability of solid tumors in FA patients would amount to 76% by that age.

The median age of onset of cancer in FA, including solid tumors and leukemia, is 16 years, whereas it is 68 years in the general population. In up to 25% of FA cases with all types of malignancies, the diagnosis of neoplasm precedes the diagnosis of FA, an extreme example being a 49-year-old patient with bilateral carcinoma of the breast, who developed MDS and AML following chemotherapy.

The incidence of solid tumors in FA patients increases beyond disease-associated rates after ►HSCT with the rate of tumor development in the HSCT group being 2.8-fold the rate in the untransplanted FA group. Conditioning, especially following regimens including total body irradiation, but also immunosuppression or posttransplant complications such as chronic graft versus host disease or infections, sharply enhance the risk for malignancies with poor survival. Most of these tumors are head and neck cancers, often involving the tongue.

Squamous Cell Carcinoma of the Head and Neck (HNSCC)

The most typical solid tumors in FA are ►HNSCC and ►SCC of the genital region in females. HNSCC in FA includes tumors of the tongue, gingiva, oropharynx and larynx. The cumulative lifetime incidence of HNSCC is about 700-fold increased with a median patient age of 31 years. In addition, there is an ~2,300-fold increased risk compared to the general population to develop carcinoma of the esophagus. FA patients with HNSCC are usually young, non-smokers and non-drinkers. Females are more often affected than males, particularly among those patients, in whom the diagnosis of FA was made after the diagnosis of cancer. This may reflect the overall survival advantage of female FA patients. FA-associated HNSCC is not fundamentally different from sporadic HNSCC, except a potential sensitivity to crosslinking agents. HNSCC initially presents as chronic ►inflammation or just red or white mucosal spots or minor lesions such that the diagnosis is often delayed. This delay leads to poor therapeutic success and no better than 50% 2-year-survival rates with this aggressive tumor type. A sensitive brush method for obtaining cells from the tongue and oral cavity of FA patients may facilitate monitoring of early cell changes and thereby contribute to the prevention of this devastating type of malignancy.

SCC of the Vulva and Cervix

The cumulative probability to develop carcinoma of the vulva is 4,300-fold, that to develop carcinoma of the cervix is 200-fold increased in FA patients. The occurrence of SCC of the vulva, cervix and anus may not only be promoted by FA, but additionally be triggered by human papilloma virus infections. It has been reported that 54% of all FA patients with these tumors had HPV-associated ►condylomas before the occurrence of cancer.

Liver Tumors

Liver tumors are frequent in FA and in the great majority follow androgen therapy for aplastic anemia. They are often multiple and mostly include adenomas (benign focal nodular hyperplasia or peliosis), seldom ►hepatocellular carcinomas (HCC). In rare cases, both adenomas and HCC can be found in the same patient. Adenomas without liver cell dysplasia are not considered premalignant changes and usually regress upon discontinuation of androgen therapy. The median age of onset of these tumors is 13 years and the cumulative incidence is 46% by age 50. The development of liver tumors due to androgen therapy is not specific for FA patients. The risk for HCC may depend on the length of term of therapy and on the specific

type of androgen used. Oxymetholone and methyltestosterone appear to be associated more frequently with the occurrence of HCC, whereas patients treated with danazol develop adenomas, but may be less affected by HCC.

Other Tumors

Solid neoplasms occasionally found in FA patients include ►brain tumors and ►renal carcinomas, ►breast cancer, ►basal cell carcinoma, ►neuroblastoma, ►desmoid tumors, gonadoblastoma, ►melanoma, neurilemmoma and ►osteosarcoma. A major factor thought to promote tumor development in FA is oxidative stress. *In vitro* experiments suggest that FA cells are more sensitive than non-FA cells towards the effects of reactive oxygen species.

FA Gene Involvement in Neoplastic Disease of Non-FA Individuals

Among the known ►breast cancer risk genes, three are authentic FA ►genes. These include the downstream effector genes of the FA/BRCA pathway, *FANCD1* = *BRCA2*, *FANCN* = *PALB2* and *FANCJ* = ►*BRIP1*. *BRCA2* is considered a high-penetrance breast cancer susceptibility gene with heterozygous mutations increasing the risk more than tenfold. Heterozygous *BRCA2* mutations are associated with female and male breast cancer, ovarian cancer and pancreatic carcinoma in familial forms. All of these cancers show allelic loss at the *BRCA2* locus consistent with the tumor suppressor function of the gene.

FANCN = *PALB2* has been identified as a low-penetrance susceptibility gene for female and male breast cancer with ►monoallelic truncating germline mutations causing a 2.3 times higher risk for female breast cancer at all ages and a relative risk of 3.0 for women under 50 years of age. This low-penetrance susceptibility is surprising since PALB2 is functionally associated with ►BRCA2 and biallelic mutations in both genes cause a similar, severe type of FA.

FANCJ = *BRIP1* interacts with the ►BRCT domain of ►BRCA1. Heterozygous inactivating mutations in ►*BRCA1* predispose to breast cancer and inactivation of ►BRIP1 abrogates certain BRCA1 functions. Consistently, heterozygous truncating germline mutations in the *FANCJ* gene *BRIP1* have been shown to represent low-penetrance breast cancer susceptibility alleles and confer an approximately twofold increased risk at all ages and a relative risk of 3.5 for carriers aged less than 50 years.

Studies of *FANCA*, *-C*, *-D2*, *-E*, *-F* and *-G* in familial breast cancer cases did not identify any truncating mutations. However, there are not enough data to date, which would exclude that certain mutations in some of these FA genes might enhance, for instance, breast cancer risk, as has been proposed for three different common mutations in *FANCC* by study of FA families.

Inactivation of the FA/BRCA pathway through hypermethylation of the *FANCF* gene has been reported for a variety of spontaneous malignancies including cervical, ovarian, bladder and ►non-small-cell lung cancer, AML, and HNSCC. The proportion of cases affected by *FANCF* silencing in each of these tumor types is relatively low, a maximum being reported 21% *FANCF*-methylated ovarian carcinomas in one study. Of note, the *FANCF* gene is located adjacent to a hot-spot region for hypermethylation on chromosome 11p15. Functional suppression of imprinted genes in this region has been found in many tumor types. Thus, *FANCF* ►hypermethylation may well occur incidentally due to spreading of the ►epigenetic modification.

The occasional involvement of germline or rare somatic FA gene mutations and ►LOH has also been reported in some sporadic cancers. As with *FANCF* hypermethylation, only a minority of tumors in non-FA individuals reveals mutations in FA genes, with *BRCA2* predominating. In pancreatic carcinoma cell lines, the proximal FA pathway was inactivated in 9.5%, and *BRCA2* in 7% of cases. One explanation is that sporadic disruption of the FA pathway causing genomic instability might be an early event during malignant transformation in a subset of tumors, preferentially among FA-typical cancers that occur in non-FA patients. Alternatively, it could be a later phenomenon during tumor advancement studies of microsatellite instability were incompatible with selective pressure for functional loss of BRCA2 in tumor evolution, but fitted closely with the absence of selection. This suggests that *BRCA2* inactivation occurs at a time when positive or negative selection for or against such event has been lost, implying that disruption of the FA/BRCA pathway in sporadic cancer is rather a stochastic phenomenon with neutral genetic drift during tumor progression. This resembles silencing of *FANCF*. Where it occurs, it is often found in only some proportion of tumor cells. Cancer rates in obligate FA heterozygotes comparable to those in the general population (apart from carriers of mutations in the FA genes mentioned above) also argue against disruption of the FA/BRCA2 pathway as an event initiating tumorigenesis.

The functional consequences of disruption of the FA pathway in sporadic cancer have not fully been explored. Nevertheless, drug-induced inhibition of the FA/BRCA pathway has been suggested as a potential route to sensitization of tumors to DNA-crosslinking agents. It has been proposed as a means of targeted chemotherapy. However, once the cell death pathway is compromised, e.g. by silencing of ►TP53, and disconnected from the FA pathway in tumor cells, no benefit of such therapy is to be expected.

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FAP

Definition

►Familial Adenomatous Polyposis

Farnesyl Lipid

Definition

C15 isoprenoid lipid, an intermediate in the ►HMG-CoA reductase mevalonate biosynthetic pathway, used in the biosynthesis of ►farnesylated proteins.

Farnesylated

Definition

A molecule that has a posttranslational modification that adds a fifteen carbon fatty acid residue.

Farnesyltransferase

Definition

Enzyme that adds farnesyl residues to protein molecules as a posttranslational modification.

FAS

Definition I

Synonym APO-1, CD95 Fas, also known as APT1, tumor necrosis factor receptor superfamily member 6 (TNFRSF6), CD95, APO-1 and FAS1 is a type I membrane protein of about 40 kD. It was originally identified by mouse monoclonal antibody called anti-Fas or anti-APO-1. In the 6th Workshop and conference on Human Leukocyte Differentiation Antigens (Kobe, 1996), Fas was designated as CD95. The gene maps to 10q24 and is mutated in Autoimmune Lymphoproliferative Syndrome. The protein mediates apoptosis through sequential activation of ICE-like caspases (Casp 4, Casp 5, Casp 3) and may also be involved in autoimmune diabetes.

►Apoptosis
►Chemokine

Definition II

►Fatty Acid Synthase

Fas-associated Death Domain

►FLICE Inhibitory Protein

Fas Associated with a Death Domain

Definition

FADD; Is a 208 amino acid protein that is encoded by two exons located on chromosome 11q13.3. It consists of an N-terminal death-effector-domain (DED) and a C-terminal death domain (DD). FADD functions as cytosolic adaptor molecule critical for apoptotic signaling by death receptors of the TNF receptor I (TNFR1) superfamily.

►FADD
►Caspase-8

FAS I

Definition
Type I fatty acid synthase found in mammals and fungi; a multifunctional polypeptide.

►Fatty Acid Synthase

FAS II

Definition
Type II fatty acid synthase found in prokaryotes, plants, and mitochondria. It consists of an acyl carrier protein and seven structurally independent monofunctional enzymes.

►Fatty Acid Synthase

Fas Ligand

Definition
FasL is a cell-surface member of the TNF family of proteins. Binding of Fas ligand to Fas triggers apoptosis in the Fas-bearing cell.

►FAS
►Apoptosis
►Apoptosis-Induction for Cancer Therapy

Fasciclin I

Definition
FASI; contains sequences that allows binding integrins and glycosaminoglycans in vivo.

►Periostin

Faslodex

Definition
Trade name for ►fulvestrant, an estrogen receptor antagonist used in the treatment of advanced ►breast cancer, and marketed by AstraZeneca.

FASN

►Fatty Acid Synthase

FAT

Definition
The focal adhesion targeting domain of focal adhesion kinase mediates paxillin and talin binding.

►Focal Adhesion Kinase

Fatty Acid Synthase

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Synonyms
FAS; FASN

Definition
Fatty acid synthase is a key enzyme which regulates the de novo biosynthesis of long-chain fatty acids.

Characteristics
Structure and Function
Fatty acid synthase (FAS) is a key enzyme that regulates the de novo biosynthesis of long-chain fatty acids from acetyl-CoA and malonyl-CoA in the presence of

NADPH. There are two types of FAS. ►FAS II, found in prokaryotes, plants, and mitochondria, consists of an acyl carrier protein (ACP) and seven structurally independent monofunctional enzymes. Each of these enzymes is encoded by a separate gene that produces a unique protein which catalyzes a single step in fatty acid synthesis. Mammalian FAS, named ►FAS I, consists of two identical multifunctional polypeptides. Each monomer of FAS I contains seven distinct catalytic domains starting from the N-terminal. These catalytic domains including β-ketoacyl synthase (KS), malonyl/acetyltransferase (MAT), dehydrase (DH), enoyl reductase (ER), β-ketoacyl reductase (KR), acyl carrier protein (ACP), and thioesterase (TE).

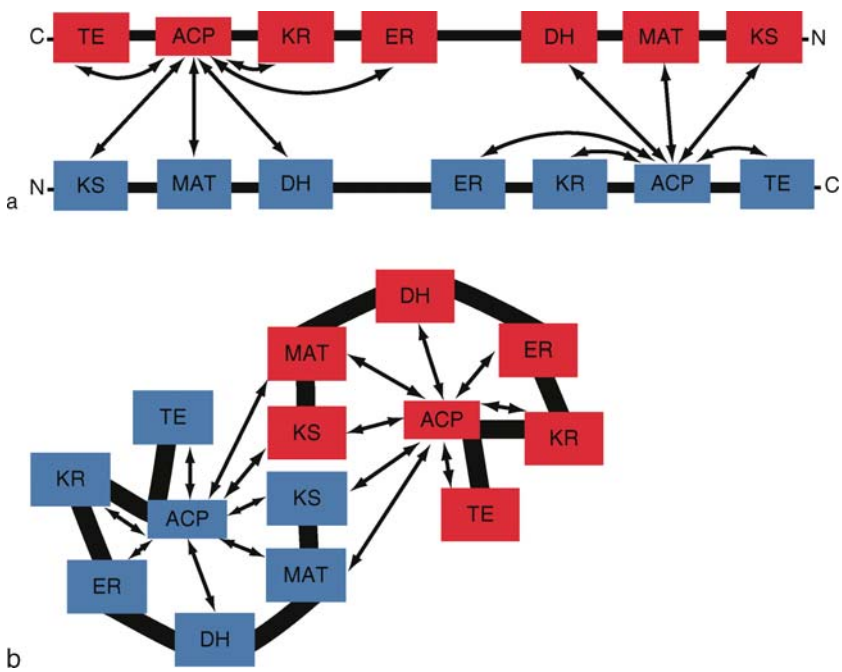
Two models have been proposed for the structure of FAS. The conventional model is based on crosslinking studies with the bifunctional reagent, 1, 3-dibromopropanone (DBP). In this model, two identical monomers are arranged in a head to tail orientation that allows functional interactions across the monomer interface (Fig. 1a). The second model is based on functional mutant complementation and improved DBP crosslinking studies. These studies suggest that the FAS monomers form a coiled conformation that allows for a variety of intra- and intermonomer functional domain interactions (Fig. 1b). In this model, both of KS and MAT domains are located in the center of the FAS dimer and can interact with the ACP groups on either of the monomers.

FAS in Normal Tissues

FAS I plays an essential role during embryonic development and a key role in energy homeostasis in adult mammals. Most normal tissues preferentially use circulating dietary fatty acids for the synthesis of new structural lipids. Thus, FAS expression is generally low to undetectable in most human normal tissues and is high only in the lipogenic tissues, such as liver and adipose tissues. In liver and adipose tissues, fatty acid synthesis occurs when it is necessary to store excess calories from carbohydrates as ►triglycerides. FAS expression is tightly controlled by nutrients through transcriptional induction and regulated by insulin, glucagon, glucocorticoids, and thyroid hormone. During starvation, fatty acid oxidation is activated to produce free fatty acids for survival, and FAS activity is rapidly downregulated. The effect of nutrients and ►hormones on the expression of lipogenic genes is mostly mediated by the sterol regulatory element-binding protein-1 (►SREBP-1). In adipose tissue, the ►transcription factor, ►peroxisome proliferator-activated receptor γ PPARγ, is critical for regulating both adipogenesis and lipogenesis. Activation of PPARγ stimulates fatty acid synthesis and storage.

FAS and Cancer

Elevated expression of FAS has been observed in many human tumors, including carcinoma of the breast,



Fatty Acid Synthase. Figure 1 Two models for the organization of FAS [1].

prostate, colon, ovary, endometrium, mesothelium, lung, thyroid, and stomach. Moreover, overexpression of FAS in breast, prostate, and thyroid ►cancers has been associated with more aggressive malignancies. The differential expression of FAS in normal and tumor tissues has led to FAS being considered as a target for anticancer therapy. Abnormally active endogenous fatty acid metabolism appears to be important for cancer cell proliferation and survival. The data from clinical studies and animal models indicate that tumor cells constitutively express high levels of FAS and undergo significant endogenous fatty acid biosynthesis. In contrast to liver and adipose tissues, the function of elevated endogenous synthesis of long-chain fatty acid in most human cancers is not for energy storage; the new synthesized fatty acids are converted into ►phospholipids, not triglycerides. In cancer cells, overexpression of FAS seems to be independent of the regulatory signals found in normal tissues. Recent studies indicate that ►mitogen-activated protein kinases (MAPKs) and ►PI3 kinases pathways ►(PI3K signaling) are likely involved in FAS regulation via SREBP-1c. Inhibition of MAP and PI3 kinases downregulates SREBP-1 levels, thereby reducing FAS expression and fatty acid synthesis in transformed human cancer cells. Deletion of the major SREBP-binding site from the FAS promoter abrogates the transcription activity of FAS. The constitutive activation of the MAPK and PI3 kinase AKT signaling pathways in cancer cells leads to elevated levels of FAS and sustained fatty acid synthesis.

FAS Inhibitors as Potential Cancer Chemotherapeutic Agents

Several FAS inhibitors have been developed to study the loss of FAS function in tumor cells. These inhibitors include ►cerulenin, the cerulenin derivative, ►C75, the β-lactone, ►orlistat, and the ►green tea polyphenol, epigallocatechin-3-gallate (EGCG). Cerulenin, C75 and orlistat are selective inhibitors of tumor cell growth.

Cerulenin, (2R, 3S)-2, 3-epoxy-4-oxo-7, 10-trans, *trans*-dodecadienamide, was the first identified "specific" inactivator of FAS. It is a natural antibiotic product of the fungus *Cephalosporium ceruleans*. Cerulenin irreversibly inhibits FAS by binding covalently to the active site cysteine thiol in the β-ketoacyl-synthase domain. Cerulenin is selectively cytotoxic to a number of established human cancer cell lines including leukemias, breast, colon, brain, ovary, and prostate. The inhibition of fatty acid synthesis by cerulenin has been shown to be dose-dependent. The cytotoxic effect generally parallels the level of endogenous fatty acid synthesis in human breast tumor cells. FAS inhibition by cerulenin leads to apoptotic cell death in ►breast cancer, ►prostate cancer, ►brain cancer, and ►colon cancer cells. However, cerulenin's chemical instability renders it ineffective as a systemic anticancer agent.

C75, a potent derivative of cerulenin, is a more stable FAS inhibitor. Structurally, it is a cell-permeable α-methylene-γ-butyrolactone, designed to be less reactive and potentially safer than cerulenin. In vivo and in vitro studies have confirmed the selective toxicity of C75 against tumor cells. C75-mediated inhibition of FAS increases malonyl-CoA levels and inhibits carnitine palmitoyltransferase 1 (CPT-1) activity, preventing the oxidation of newly synthesized fatty acids. High levels of malonyl-CoA and low levels of CPT-1 may represent mechanisms whereby FAS inhibition leads to tumor cell death. C75 treatment of mesothelioma and prostate tumor (►Prostate cancer, clinical oncology) ►xenografts in ►nude mice leads to significant inhibition of tumor growth. Subcutaneous xenografts of MCF-7 ►breast cancer cells in nude mice treated with C75 showed fatty acid synthesis inhibition, ►apoptosis, and reduced tumor growth with no normal tissue toxicity. C75 has also been used as an antiobesity treatment in animal models. Treating obese mice with C75 produces a profound reduction in body weight and food intake.

►Orlistat (also known as Xenical or tetrahydrolipstatin), a US Food and Drug Administration (FDA)-approved drug used for treating ►obesity, is a saturated derivative of lipstatin and works by inhibiting pancreatic and gastric lipases in the lumen of the gastrointestinal tract to decrease systemic absorption of dietary fat. Orlistat is also a rather potent and selective inhibitor of FAS. It inhibits the thioesterase domain of FAS which is responsible for releasing palmitate from the ACP of the enzyme. Orlistat has been reported to have antitumor activity in many tumor cell models because of its ability to block the activity of FAS. Cell cycle arrest induced apoptotic cell death and downregulation of the ►Her2/neu (erbB-2) ►oncogene have been observed in orlistat treated breast cancer cells. Orlistat is also able to effectively inhibit the growth of prostate tumor ►(prostate cancer, clinical oncology) ►xenografts implanted in nude mice.

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Fatty Acid Transport

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Definition

Is the process through which free fatty acids pass through the membranes of cells. The term may include: uptake of fatty acids from the blood or the extracellular space; release of fatty acids from the cell interior to the extracellular space or blood; and transport of fatty acids within the cell across intracellular membranes during biosynthesis and metabolism. While all three types of transport may occur in tumor cells this essay concentrates on the characteristics and mechanisms for free fatty acid entry into tumor cells.

Characteristics

Fatty acids serve multiple functions in cells and their transport from arterial blood plasma to the cell interior is necessary for cell growth and survival. Fatty acid oxidation is a major source of energy for heat production and generation of ATP for biosynthesis and growth. During metabolism fatty acids are incorporated into several complex lipids required for cell structure and function. Fatty acids also play important roles in cell signaling; they are anchors for attachment of specific signaling proteins to membranes and they are converted to several types of ►lipid mediators involved in intra- and extracellular cell signaling mechanisms. The essential long chain polyunsaturated fatty acids, linoleic (C18:2n6), linolenic (C18:3n3), eicosapentaenoic (C20:5n3) and docosahexaenoic (C22:6n3) acids, which are obtained from dietary sources, play particularly important roles in cell signaling, membrane structure, growth and control of fatty acid transport. If dietary fat consumption exceeds the need, fatty acids are stored in white adipose tissue as triacylglycerols for subsequent release during postprandial and longer periods of food deprivation.

Fatty acids greater than 8 carbons in chain length are not very water soluble and are transported in the blood bound to plasma albumin. The plasma albumin-fatty acid pool is maintained by release of free fatty acids from plasma lipoproteins (catalyzed by endothelial lipoprotein lipase) and by release of free fatty acids from lipid stores. Fatty acids bound to plasma albumin dissociate from the albumin binding sites to maintain a plasma free fatty acid concentration of 7–10 nM. This plasma free fatty acid pool is a major source of free fatty acids for cell consumption. Accumulation of high free fatty acid concentrations inside cells, however, is toxic for cell structure and function and specific intracellular fatty acid binding proteins (FABPs) are present in cells to maintain low free fatty acid concentrations. Specific isoforms of these FABPs are expressed in different organs and tissues.

Characteristics - Tumor

Transplantable solid rodent tumors and human cancer xenografts grown in nude rats have ready access to the free fatty acid pool in arterial blood plasma. Cancers that arise spontaneously undoubtedly also have access to plasma fatty acids. Arteriovenous difference measurements in arterial and tumor venous blood plasma samples collected across solid tumors in vivo or during perfusion in situ indicate that substantial rates of fatty acid uptake occur. Thirty-five to 45% of the total fatty acids in arterial blood plasma is removed during one pass of the arterial blood through a fast-growing rat hepatoma. Similar uptakes (35 to 45%) occur for each of the seven major plasma fatty acids in rat arterial blood: myristic, palmitic, palmitoleic, stearic, oleic, linoleic and arachidonic acids. Consequently, larger amounts of the more abundant plasma fatty acids, oleic, linoleic and arachidonic acids are removed. Since tumor fatty acid uptake is proportional to the arterial plasma fatty content of each fatty acid, there is no preferential uptake of any single fatty acid. Each of five different human cancer xenografts, ER^+ and ER^- MCF-7 breast, PC3 prostate, CFDT1 renal transitional and FaDu pharyngeal carcinomas, grown in nude rats removes fatty acids from the arterial blood plasma. Fatty acid uptake by human tumors also occurs in proportion to the concentration of the individual fatty acid in arterial blood plasma. However, the rates and efficiencies of fatty acid uptake in human cancer xenografts are different and are directly proportional to the tumor growth rate.

Growth and incorporation of [^{3}H]thymidine into DNA in rodent tumors and human cancer xenografts in vivo or during perfusion in situ are directly dependent on the availability and uptake of plasma ►linoleic acid. Plasma linoleic acid concentrations, tumor linoleic acid uptakes and growth rates are increased in tumor-bearing rats fed diets enriched in linoleic acid. Similar stimulations of tumor growth occur when tumor-bearing rats are subjected to an acute fast, except that the elevation in plasma linoleic acid content in the acutely fasted rats is derived from lipolysis of host fat stores. In contrast, the absence of linoleic acid in arterial blood plasma, as occurs in tumor-bearing rats fed a linoleic acid-deficient diet, inhibits growth and the rate of [^{3}H]thymidine incorporation into tumor DNA. Linoleic acid-dependent growth in rodent tumors and human cancer xenografts results from the conversion in the tumor of linoleic acid to

13-hydroxyoctadecadienoic acid (13-HODE). 13-HODE, a mitogen in these tumors, is a product of lipoxygenase activity and is released into the tumor venous blood plasma. Depending on the tumor type 1 to 10% of the linoleic acid removed from the arterial blood is converted to 13-HODE. Thus, tumor growth rates are directly proportional to both linoleic acid uptake and 13-HODE release.

Arterial blood plasma long chain polyunsaturated fatty acids affect tumor growth differently; whereas the n6 fatty acid, linoleic acid, increases tumor growth, the presence of ►n3 fatty acids in arterial blood plasma inhibits tumor growth. In tumor-bearing rats fed a diet containing both linoleic acid and n3 fatty acids, the rates of linoleic acid uptake, 13-HODE production,[^{3}H]thymidine incorporation into DNA and growth are suppressed. Each of the n3 fatty acids, α-linolenic, stearidonic, eicosapentaenoic and docosahexaenoic acids, inhibits fatty acid transport; a 50% inhibition occurs at a plasma n3 fatty acid concentration of about 0.15 mM. Most interesting, uptake of all plasma saturated, monounsaturated and n6 polyunsaturated fatty acids is depressed by n3 fatty acids. However, tumor uptake of n3 fatty acids is not inhibited. Other dietary agents also inhibit tumor fatty acid transport and growth. These include, ►melatonin and some conjugated linoleic acid isomers and *trans* fatty acids. As with n3 fatty acids, the inhibition of tumor fatty acid transport is directly proportional to the arterial blood plasma content of the inhibitor. Melatonin, which is present in the diet and is the natural hormone of the pineal gland, is the most potent inhibitor of tumor fatty acid transport yet discovered. A plasma concentration of 0.1 nM melatonin causes a 50% inhibition of fatty acid transport. In addition to inhibitions of both fatty acid transport and 13-HODE release, these agents cause significant reductions in the intratumor cAMP content, [^{3}H] thymidine incorporation and phosphorylated-MEK and -ERK1/2 (►MAP Kinase). Significantly, these inhibitions caused by n3 fatty acids, melatonin, CLA isomers and *trans* fatty acids are reversed by the addition of either 8-bromo-cAMP or pertussis toxin to the arterial blood containing these agents. [Pertussis toxin catalyzes the ADP-ribosylation of the α subunit of inhibitory heteromeric guanine nucleotide G proteins and reactivates the inhibited adenylyl cyclase activity. 8-bromo-cAMP is a cell-permeable analog of cAMP that is resistant to hydrolysis by phosphodiesterases.] Addition of 13-HODE to the arterial blood restores phosphorylated-MEK and -ERK1/2 and [^{3}H]thymidine incorporation but not fatty acid transport. The results strongly suggest that fatty acid transport and growth in rodent tumors and human cancers are dependent on an elevated intratumor cAMP content and that the inhibition of fatty acid transport is mediated by an inhibitory ►G protein-coupled receptor(s).

Mechanisms

The mechanism for fatty acid transport in eukaryotic cells is not yet clearly resolved. Two hypotheses, transport by passive diffusion and transport by protein–mediated carriers, have been presented and studied extensively in model membrane vesicles and cultured cells. Lipophilic non-ionized free fatty acids rapidly penetrate membrane vesicles and red cells, a process that has been termed flip-flop to describe movement of the fatty acid across the membrane leaflet barrier. The barrier to flip-flop is increased by ionization of the fatty acid and may be further increased by changes in the lipid phases in cell membranes of different cells. These findings strengthen the hypothesis for fatty acid transport via protein-mediated carriers. Three groups of membrane protein carriers that contribute to fatty acid transport have been identified in mammalian cells. Fatty Acid Transport Proteins (FATP1–6) are a family of proteins that have distinct tissue distributions. Several but not all of the FATP isoforms transport fatty acids across cell membranes; several also have long chain fatty acid Co-A synthetase (LCACS) activity, which may be important for retention of the fatty acid inside the cell. Evidence also indicates that the plasma membrane protein Fatty Acid Translocase (FAT/CD36) is involved in fatty acid uptake in heart, skeletal muscle and adipose tissue. Control of fatty acid transport by FATP isoforms and FAT/CD36 may involve movement of the carriers between intracellular membranes and the plasma membrane. A Fatty Acid Binding Protein in plasma membranes (FABPpm) that is present in heart, intestine, liver and adipocytes may also play an important role in fatty acid transport. Since all of these proteins may be present in cells, cooperative activities (as yet undefined) may occur among the different protein carriers.

The requirement for high intratumor cAMP is a unique property that appears to control fatty acid transport in solid tumors. The mechanisms that maintain the high intratumor cAMP content are not known but may be catalyzed by stimulatory G_sPCR(s) (►G proteins). This cAMP requirement is not easily reconcilable with the current understanding of fatty acid transport mediated by either passive diffusion or by protein carriers. Depletion of intratumor cAMP and inhibition of fatty acid transport caused by n3 fatty acids, melatonin or CLA isomers is dose-dependent and complete at high inhibitor concentrations. Despite the fact that arterial blood plasma fatty acid concentrations remain available to the tumor, fatty acid transport into the tumor is inhibited. However, addition of either 8-bromo-cAMP or pertussis toxin to the

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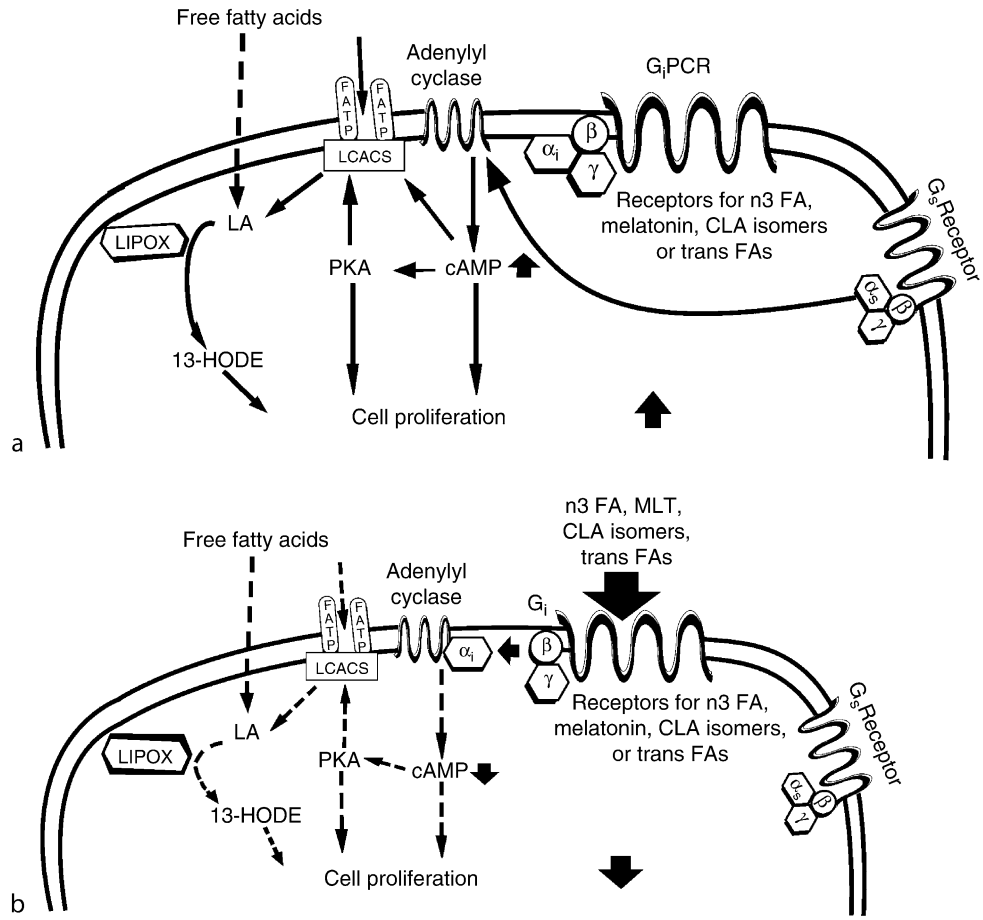

Fatty Acid Transport. Figure 1 Schematic representations for fatty acid transport (a) and control of transport (b) by dietary inhibitors. (a) The sequence of events associated with elevated intratumor cAMP, uptake of linoleic acid, 13-HODE production and cell proliferation are designated by solid arrows. (b) Attenuation of intratumor cAMP and fatty acid transport caused by binding of n3 fatty acids, melatonin, CLA isomers or *trans* fatty acids to inhibitory G protein-coupled receptors is designated by dashed arrows. Abbreviations are: G_iPCR, inhibitory G protein-coupled receptors; G_sPCR, stimulatory G protein-coupled receptor; 13-HODE, 13-hydroxyoctadecadienoic acid; LCACS, long chain fatty acid acyl-Co A synthetase; LIPOX, lipoxygenase, LA, linoleic acid; PKA, protein kinase A.

inhibitor-containing arterial blood restores intratumor cAMP and fatty acid transport. Reversal of the inhibition by these agents indicates that inhibitory G_iPCR(s) (►G proteins) for n3 fatty acid, melatonin and CLA isomers mediate the reduction of intratumor cAMP and inhibition of fatty acid transport. Rat hepatoma 7288CTC and the human cancer xenografts contain one or both of the inhibitory G protein-coupled melatonin receptors, MT_1 and MT_2. Compound S20928, a specific antagonist for melatonin receptors MT_1 and MT_2, increases intratumor cAMP and mitigates the melatonin inhibition. There is as yet no direct evidence that inhibitory G protein-coupled receptors for n3 fatty acids, CLA isomers or *trans* fatty acids exist in solid tumors. mRNA for FATP1 is over-expressed in a rat hepatoma suggesting that FATP1 may mediate fatty acid transport in hepatomas and other tumors. If that is the case, the activity of FATP1 as a fatty acid transport carrier in these tumors may require cAMP (Fig. 1).

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n3 Fatty Acids

Definition

n3 long chain polyunsaturated fatty acids (n3 PUFAs), also known as ω3 PUFAs, are a group of dietary fatty acids that have important roles in several physiological functions. They are characterized by the position of the terminal *cis*-olefinic bond, which is located 3 carbon atoms from the methyl end of the carbon chain. The n3 PUFA, α-linolenic acid (C18:3n3), is present in several plant oils and is a precursor in animal tissues of stearidonic (C18:4n3), eicosapentaenoic (C20:5n3) and docosahexaenoic (C22:6n3) acids. Marine fish and oils derived from them are important dietary sources for the C18 through C22 n3 PUFAs. The position of the terminal cis-olefinic bond in n3 PUFAs distinguishes them from the n6 or ω6 PUFAs in which the location of the terminal *cis*-olefinic bond is 6 carbons from the methyl end of the carbon chain. Dietary n3 PUFAs (►Fatty acid uptake) have a negative effect on growth of established solid tumors, whereas the dietary n6 PUFA, linoleic acid (C18:2n6) [►linoleic acid] has a positive tumor growth effect. The mechanisms for interaction among n3 and n6 PUFAs are a conundrum in cancer biology.

►Fatty Acid Transport

Fbl1

►Ubiquitin Ligase SCF-Skp2

FcR

Definition

Fc Receptor; Cell surface receptor which binds the Fc moiety of some immunoglogulin classes. Fc stands for crystallizable, nonantigen binding fragment of an immunoglobulin molecule obtained by papain digestion.

►Autoantibodies

FDA

Definition

The Food and Drug Administration is an agency of the United States Department of Health and Human Services and is responsible for regulating food, dietary supplements, drugs, cosmetics, medical devices and radiation emitting devices, biologics, and blood products in the United States.

FDG

Definition

^{18}F-Fluorodeoxyglucose; Glucose analog labeled with the positron emitter ^{18}F enabling detection of tumor manifestation sites due to altered glucose metabolism. FDG represents the most important biomarker for positron emission tomography.

►Positron Emission Tomography
►Salivary Gland Malignancies

Fecal Immunochemical Test

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Synonyms

Immunochemical fecal occult blood test; Immunological fecal occult blood test; iFOBT; Fecal occult blood test; FIT

Definition

A fecal immunochemical test for hemoglobin is a test designed to detect hemoglobin in feces using an antibody raised against human hemoglobin. It is one of a class of technologies referred to as ►fecal occult blood test (FOBT).

Characteristics

Fecal immunochemical tests (FIT) incorporate an antibody specific for human hemoglobin; such react with the globin protein moiety of hemoglobin.

Fate of Hemoglobin in the Gastro-Intestinal Tract

The globin moiety of hemoglobin is a protein and as such is rapidly digested in stomach or small intestine such that it is no longer detectable by immunochemical methods. Ingestion of blood volumes of up to 100 mL has not resulted in detectable immunoreactive hemoglobin in feces, based on reports using some of the earlier types of FIT. In other words, FIT are selective for colorectal bleeding, especially where the bleeding is occult (i.e. not visible to the naked eye). This is different from the chemical, specifically guaiac-based, FOBT which can return a positive result for blood derived from the proximal as well as distal ►GI tract.

FIT technology differs from chemical-based FOBT that react to the peroxidase activity of heme (Fig. 1). In feces, hemoglobin is subject to degradation by endogenous digestive enzymes (albeit at a much slower rate than in small intestine and stomach) and by bacterial enzymes. As shown in Fig. 1, this releases heme from globin. FIT technology detects globin and not heme and so is not subject to the factors that interfere with methods that depend on detection of heme. Heme itself is degraded by bacterial enzymes. Globin itself is progressively degraded at widely varying rates in feces.

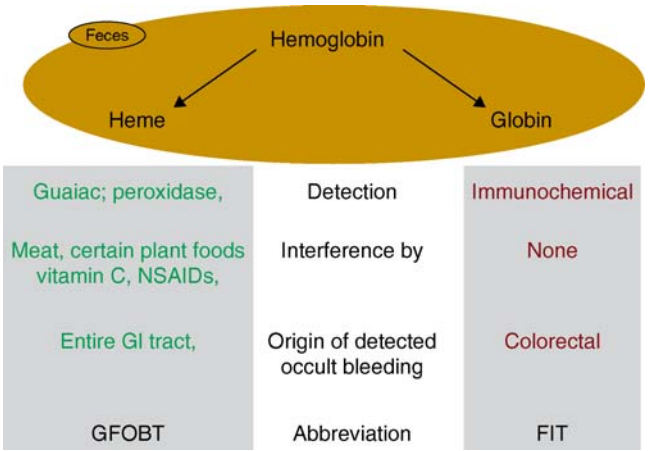
Because fecal immunochemical test technology is so different from that of the chemical methods, because it reacts to a different analyte (i.e. globin not heme) and because it provides the option of quantification of fecal hemoglobin rather than being limited to qualitative assessment as is the case for GFOBT, it is recommended that the terminology "fecal immunochemical test" be applied and abbreviated as FIT, to emphasize that it is a quite different technology and analyte from chemical FOBT.

Uses for FIT

The primary use of FIT is in screening for colorectal cancer. Chemical FOBT have been proven to reduce mortality and incidence in four randomized controlled trials. Comparative studies have shown FIT to be more sensitive for cancer and more sensitive for colorectal adenomas than guaiac-based FOBT. An hemagglutination-FIT has been shown to be superior to a high-sensitivity guaiac-FOBT in that it achieved the same higher sensitivity for cancer but required less than half as many colonoscopies to achieve this. In other words, FIT improve sensitivity for colorectal cancer and adenomas but not at the cost of unacceptable deterioration in specificity.

FITs are not subject to interference by diet or drugs and maintenance of an adequate specificity is not dependent on proscription of certain foods or drugs as is the case for guaiac-FOBT. This, together with the improved stool-sampling methods characteristic of FIT, makes it easier for screenees and improves participation rates in screening.

It is not advisable to use FIT as an all-purpose test for fecal blood as it is selective for colorectal bleeding. If used in this setting, such as in the context of iron-deficiency, it should be combined with a chemical test. However, it is important to note that the negative predictive value of either guaiac-FOBT or FIT is not 100% and many consider their use should be confined to screening for colorectal cancer where they act as an aid to early detection; as such they serve to identify those most likely to have colorectal neoplasia and so in need of a diagnostic procedure such as ►colonoscopy.



Fecal Immunochemical Test. Figure 1 Fate of hemoglobin in feces and detection of products by the various fecal occult blood test (FOBT) technologies.

Quantifiable FIT

Several of the latest FIT allow quantification of fecal hemoglobin. Results show that fecal hemoglobin concentration corresponds to the "stage" of neoplasia. People with cancer have the highest levels on average, those with a normal colon the lowest levels while those with adenomas have intermediate levels. Studies such as these show that patients with advanced adenomas (size greater than 1 cm, villous change or high grade dysplasia) do have occult bleeding. In other words, the higher the level of fecal hemoglobin the more likely that neoplasia is present.

The advantage of fecal hemoglobin measurement is that it returns full control of sensitivity and specificity to the doctor managing screening. It enables the doctor to set the level of fecal hemoglobin that would trigger follow-up diagnostic colonoscopy. At the population level, such an approach allows flexible choice of a test specificity:sensitivity ratio, so controlling the colonoscopy rate to that which is feasible for a health care system.

Types of FIT Currently Available

A variety of test technologies are employed in the currently available tests. This includes latex agglutination, membrane diffusion devices for detecting immunogold- or latex-labeled antibodies, hemagglutination, and magnetic particle agglutination. The end point for some tests are read by eye while others may also be read by a machine designed specifically for the particular technology and its endpoint. Some devices are designed for simplicity and development in an office-setting while others are designed for large scale development in a laboratory – automated processing, development and reading may be available.

Internationally, there are no set criteria that a test manufacturer should follow when setting the specifications for a test. As such, different tests may behave differently with differences in the quantity of hemoglobin to which they react as well as the nature of the hemoglobin antigen that they detect.

A test result may be quantitative, providing a measure of the concentration of hemoglobin in feces, or qualitative, providing an indication as to whether the fecal hemoglobin is considered to have reached a level likely to reflect the presence of neoplastic pathology in the colon or rectum.

Stool-Sampling Procedures

The nature of the fecal sample is an important component of a test. Each test comes with its own characteristic stool-sampling device. These include devices that keep the sample dry and so more likely to keep the antigen stable and others that use devices that include liquid and in which hemoglobin degradation might proceed during specimen transit unless samples are kept cold.

Most devices require the stool to be kept clear of toilet bowl water when sampling while a few require sampling to be undertaken from a stool kept clear of water. The range of sampling devices include wooden spatulas that smear feces onto a card, probes that absorb or wick materials from feces when poked into the stool, probes that trap feces into grooves when poked into the stool, and brushes that sample toilet bowl water from the surface of the immersed stool. Some provide precise control of stool sample quantity while others do not provide such control.

Most manufacturers provide packaging that enables samples to be sent by mail to a processing laboratory.

As hemoglobin can be rapidly degraded in feces especially at room temperature or above, whole stools should never be sent to a laboratory for sampling by the laboratory. Rather, the appropriate stool-sampling device provided for a test must be used. It is likely that different tests vary in their capacity to detect partially degraded hemoglobin. This will be dependent on the antibody used but there is little published material to guide users.

Performing an in-office GFOBT as part of a digital rectal examination has been common practice especially in the USA. However, usually only one rather than the recommended two or three stool samples is obtained. Recently this approach has been evaluated in a large group of asymptomatic subjects where it was found to be unsatisfactory. Screening based on digital sampling of stool as part of a rectal examination cannot be recommended and manufacturer's recommendations for obtaining stool samples should be followed.

Biology of Bleeding from Colorectal Neoplasia

The fact that microscopic bleeding may arise from cancers or adenomas, provides the basis for the use of FOBT to aid early detection of colorectal neoplasia. Blood loss is variable from day-to-day and may fall within the normal range. Furthermore, blood of colorectal origin is not uniformly distributed within a stool and often is found on the surface. Consequently, it is usually recommended that when screening for colorectal cancer, samples from at least two separate stools be collected. It is also recommended that the stool surface be sampled rather than the stool interior or an homogenate.

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Fecal Occult Blood Test

Definition

FOBT; A fecal occult blood test finds blood in the stool by placing a small sample of stool on a chemically treated card, pad, or wipe. Then a special chemical solution is put on top of the sample. If the card, pad, or cloth turns blue, there is blood in the stool sample. A fecal occult blood test may be used to check for ►colon cancer, but it is never used to diagnose this condition. Other tests for ►colon cancer include a digital rectal examination, sigmoidoscopy, colonoscopy, or CT scan.

►Fecal Immunochemical Test

Felty Syndrome

Definition

Is a rare disorder that involves rheumatoid arthritis, a swollen spleen, decreased white blood cell count, and repeated infections. The cause of Felty syndrome is unknown. It is more common in people who have had rheumatoid arthritis for a long time. People with this syndrome are at risk of infection because they have a low white blood cell count.

Female Sex Hormones

Definition

Estrogens and progestagens.

►Estrogenic Hormones

Feminization

Definition

Rarely occurs in ►adrenocortical carcinoma and is the result of an increased production of estrogen by the tumor cells. Males usually develop breasts (gynecomastia), and girls present with precocious telarche (isolated unilateral or bilateral breast development).

►Childhood Adrenocortical Carcinoma

Fenestration

Definition

The architecture of the endothelial cells comprising the lymph capillaries carries large windows allowing entrance of lymph fluid, particles, and cells into the lymphatic system.

►Sentinel Node

FERM

Definition

There is a homology to Protein 4.1, ezrin, radixin, and moesin, which are members of the 4.1 superfamily of actin binding proteins. It is the N-terminal domain of FAK, which interacts with growth factor receptors and other transmembrane proteins.

►Focal Adhesion Kinase
►ERM Proteins

FERM Domain

Definition

Is name of the protein 4.1 family domain and stands for F (four point one) E (ezrin) R (radixin) M (moesin). It is a unique module involved in the linkage of cytoplasmic proteins to the membrane.

►Neurofibromatosis 2

Fermentation Products

Definition

Dietary fiber including resistant starches, complex carbohydrates and cellulose, have been put forward as cancer protective food components. The theory is that dietary fiber may protect against ►colon cancer through absorption of risk factors and especially through secondary events resulting from the fermentation of carbohydrates by the microflora. These will lead to fecal bulking, increased speed of colon transit, increase of nitrogen metabolism, increased bacterial load in the colon, acidification and finally to the production of short chain fatty acids (SCFA). Butyrate, one of the major SCFA, is considered to be beneficial due to its trophic effects as an essential nutrient to the colon epithelium. Suggested mechanisms of cancer prevention at a cellular level have been reported to be the promotion of differentiation, induction of apoptosis and inhibition of proliferation in colon tumor cell lines. These mechanisms are classified as suppressing activities of cancer preventing agents

►Biomarkers

Ferredoxin Reductase

Definition

A 54 kDa flavoprotein, synonym adrenodoxin reductase, a mitochondrial enzyme responsible for transferring electrons from NADPH to ►cytochrome P450, via ferredoxin, to substrates, during steroidogenesis.

►Fragile Histidine Triad

Ferritin

Definition

Is a crystalline lattice protein, 450 kDa, that can sequester up to 450 atoms of iron. As the metal accumulates within ►macrophages, increasing amounts of ferritin are synthesized to safely contain the toxic metal. Ferritin is a main intracellular iron storage protein and consists of 24 light and heavy subunits. Each ferritin complex can store about 4,500 iron (Fe^{3+}) ions.

►Asbestos
►Phase 2 Enzymes

Ferruginous Bodies

Definition

Are ►asbestos fibers that, in respiratory tract tissues, have become coated with iron-rich material derived from ferritin/hemosiderin. The bodies typically are associated with ►macrophage clusters. Over time, catalytic iron is released from the ferritin coat, possibly by action of macrophage hydrogen peroxide.

F

FET

Definition

^{18}F-Fluoroethyltyrosine; Amino acid (tyrosine) labeled with the positron emitter ^{18}F enabling detection of tumor manifestation sites (especially brain tumors) due to increased transport of amino acids and increased protein biosynthesis.

►Positron Emission Tomography

Fetal Hamartoma of the Kidney

►Mesoblastic Nephroma
►Hamartoma

α_1-fetoglobulin

►Alpha-Fetoprotein – Modern

α-Fetoprotein

Definition

AFP; 70 kD glycoprotein synthesized in early embryonal development by cells of the yolk sac, liver and

gastrointestinal tract. A tumor marker for hepatocellular carcinoma.

►Hepatoblastoma

α-feto-protein

►Alpha-Fetoprotein – Modern

Feto-specific Proteins

►Alpha-Fetoprotein – Historical

Fetuin

►Alpha-Fetoprotein – Modern

Fetuin-A

►Alpha-Fetoprotein – Modern

FEV1

Definition

Forced expiratory volume in one second. Following a maximal inspiration, the volume of air exhaled in the first second during a maximally forced expiration.

►Chronic Obstructive Pulmonary Disease and Lung Cancer

Fever

Definition

Is defined as an elevation of the body temperature that exceeds the normal daily variation.

►Fever of Unknown Origin

Fever of Obscure Origin

►Fever of Unknown Origin

Fever of Unexplained Origin

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Fever of Unknown Origin

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Synonyms

Fever of unknown origin; Fever of unexplained origin; Pyrexia of unknown origin; Fever of obscure origin

Definition

Fever of unknown origin is a clinical syndrome of ►fever that does not resolve spontaneously within 3 weeks and the cause remains unknown after extensive workup. Fever is defined as an elevation of the body temperature that exceeds the normal daily variation. The hypothalamus controls the body temperature and a normal body temperature is ordinarily maintained because the hypothalamic thermal regulatory centre balances the excess heat production derived from metabolic activities in the muscles and the liver with heat dissipation from the skin and lungs. Normally, healthy adult individuals have a mean oral temperature of 36.8°C ± 0.4°C. The temperature is a little bit higher in the

evening. Fever of unknown origin is an important clinical challenge. In 1961 Petersdorf and Beeson [1] defined it in their first report as an illness characterized by fever of more than 3 weeks' duration, with temperatures of more than 38.3°C and failure to identify the origin of the fever despite 1 week of hospitalization. Because of the development of diagnostic procedures, increasing costs of hospital care and the increasingly outpatient work-up, the definition was modified in 2003 and a hospital setting was no longer needed for assessment of the illness.

Characteristics

Over the last decades, several case-series have examined the underlying diseases for fever of unknown origin. More than 200 causes have been reported to cause fever of unknown origin.

After work-up, fever of unknown origin has generally been considered to be caused by infections, neoplasms, inflammatory or a heterogeneous group of other diseases. The most common infections reported in the literature are tuberculosis and intra-abdominal abscesses. Other important causes are temporal arthritis and other collagen vascular diseases and venous thromboembolism. One is unable to establish the causal diagnosis in 9–25% of the cases.

In the early case-series, the proportion of cancers varied between 7 and 24%. Although most causes of fever of unknown origin resolve spontaneously, the risk of occult cancer remains a concern. It is important to emphasize that most studies on the origin of fever of unknown origin did not include any control groups or a reference standard and criteria and the final diagnosis was defined in many different ways.

Cancer and Fever of Unknown Origin

Although several studies have been conducted on the association between fever of unknown origin and a subsequent diagnosis of cancer, the studies have been small, based on 40–300 patients, several studies have been based on referral centers and almost all studies lack control groups.

Nearly all common cancers in the literature had a link to fever of unknown origin. In the referral centre, case-series of a proportion of cancer diagnosed in patients with fever of unknown origin has decreased from about 30% of cases in the 1970s to 9–20% in the 1990s. It has been suggested that improved diagnostic imaging with e.g. CT and MRI has improved the detection of otherwise occult solid tumors.

In 2005 a large, Danish population-based study based on health care databases assessed the risk of cancer in 43,205 patients hospitalized from 1977 to 1997 with fever of unknown origin. Data on patients with a discharge diagnosis of fever of unknown origin were linked to the Danish Cancer Registry. The incidence rate of cancer was compared with the expected cancer incidence rate in the general population. The median follow-up was 6.3 years: 9,932 of the patients were more than 60 years old, 399 cancer cases were diagnosed during the first year of follow-up among the 43,205 patients with a relative risk (standardized incidence rate ratio) of 2.3 (95% CI: 2.1–2.5). The relative risk was raised for various types of cancer. Especially for ►Hodgkin disease (relative risk 27.8 95% CI: 15.9–45.1), non-Hodgkin ►lymphoma (relative risk 9.9 95% CI: 7.1–13.3), ►leukemia (relative risk 5.6 95% CI: 3.9–7.8) and ►multiple myeloma (relative risk 4.4 95% CI: 2.1–8.0), as well as sarcoma (relative risk 6.6 95% CI: 3.6–11.1) and solid tumors in the liver (relative risk 6.1 95% CI: 3.2–10.7), gall bladder (relative risk 2.7 95% CI: 0.9–6.3), brain (relative risk 4.1 95% CI: 3.5 – 6.2), kidney (relative risk 2.6 95% CI: 2.6; 95% CI: 1.4 – 4.5), colon (relative risk 2.7 95% CI: 2.0–3.5), and pancreas (relative risk 3.7 95% CI: 2–3–5.6).

During 1–19 years for hospitalization for fever of unknown origin 1,097 cancer cases were observed compared with 977.8 cancer cases expected. During the follow-up period, there was still an increased relative risk of hematological cancer as Hodgkin disease (relative risk 2.1 95% CI: 1.1–3.8), non-Hodgkin lymphoma (relative risk 1.4 95% CI: 1.0–1.9), leukemia (relative risk 1.7 95% CI: 1.3–2.2) and multiple myeloma (relative risk 1.6 95% CI: 1.0–2.4), liver (relative risk 1.9 95% CI: 1.1–2.9), brain (relative risk 1.4 95% CI: 1.0–1.9) and kidney cancer (relative risk 1.5 95% CI: 1.1–2.1). Until publication of the Danish study, the former studies on cancer risk had included a total of 1,200 fever of unknown origin patients. The absolute risks of cancer during the first year of follow-up were low, much lower than those reported in former studies.

Diagnosis

There are no randomized clinical trials in the literature about the clinical utility of different diagnostic strategies. Mourad et al. [2] has suggested the following minimal to qualify as fever of unknown origin: comprehensive history, physical examination, complete and differential blood cell count,, blood film reviewed by hematopathologist, routine blood chemistry, urinanalysis and microscopy, blood and urine cultures, antinuclear antibodies, rheumatoid factor, human immunodeficiency virus antibody, cytomegalovirus IgM antibodies, heterophil antibody test, Q-fever serology, chest radiography, hepatitis serology. To obtain a cancer diagnosis abdominal CT scan is the most central diagnostic test, but further diagnostic work up depends of symptoms and findings.

Prognosis of Cancer Associated with Fever of Unknown Origin

The underlying disease is the main predictor for the outcome of fever of unknown origin. Four studies have shown that 52–100% of patients with fever of unknown

origin and cancer will die within 5 years after the diagnosis. In the Danish database study of the 399 cases of cancer, the extent of cancer was compared for cases associated with fever of unknown origin and similar cancer 3,958 cases that did not have fever of unknown origin. Cancer diagnosed in patients with fever of unknown origin during the first year of follow-up was associated with higher prevalence of metastases and an increased mortality ratio of 1.4. After 1 year of follow-up, the cumulative survival among cancer cases was about 50% and after 2 year about 35%.

A diagnosis of cancer subsequent to hospitalization because of fever of unknown origin does not necessary imply an extremely poor prognosis.

Conclusion

The existing literature has consistently shown that fever of unknown origin is a marker of occult cancer. The last Danish study showed that this association in a population-based setting is weaker than reported in former studies, but the relative risk remains increased many years subsequent to the hospitalization for fever of unknown origin for hematological cancer, liver, brain and kidney cancer. Fever of unknown origin is associated with more advanced cancer disease and a poor prognosis compared with similar cancer patients without fever of unknown origin, but the prognosis is not extremely poor.

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FEV1/FVC Ratio

Definition

The ratio of the forced expiratory volume in one second to the forced vital capacity.

►Chronic Obstructive Pulmonary Disease and Lung Cancer

FGD1

Definition

Faciogenital dysplasia 1 was the first identified gene product responsible for this disease. It functions as an activator for the small GTPase Cdc42, which in turn serves to activate N-WASp and other actin-related events.

►Cortactin

FGF

Definition

Fibroblast growth factor.

►Fibroblast Growth Factors

FGFR3

Definition

Fibroblast Growth Factor Receptor 3; A receptor for fibroblast growth factors, oncogenically activated by point mutations in ►urothelial carcinoma, ►cervical cancer, and certain benign skin tumors.

FH

►Fumarate Hydratase

FHIT

Definition

►Fragile Histidine Triad Gene; The *FHIT* gene is a member of the histidine triad gene family and is considered to be a tumor suppressor gene. The common fragile site FRA3B is located within this gene.

►Fragile Sites

Fibrin Degradation Products

Definition

FDP; Fibrin or ►fibrinogen is proteolytically degraded into fibrin degradation products (fibrinolysis). ►Plasmin, a major extracellular serine protease, plays a role in this process. Fragments D and E are major fibrin degradation products. Fragment D contains C-terminal globular domains (γC of the γ chain and βC of the β chain). Fragment E contains the central portion of fibrinogen.

Fibrin

Definition

Factor Ia; A protein that is involved in blood clotting. It is produced by the liver as a soluble precursor, fibrinogen, which circulates in the blood stream.

►Proteinase-Activated Receptors

Fibrinogen

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Definition

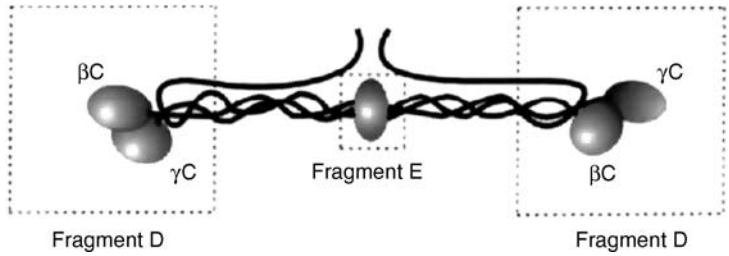
Is a major plasma glycoprotein (350 kDa) that plays an important role in blood clotting, cellular and matrix interactions, ►inflammation, wound healing, and neoplasia.

Characteristics

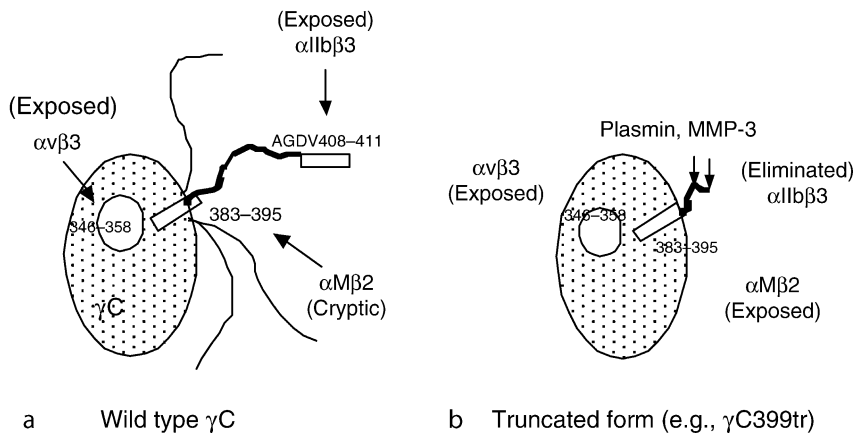
Fibrinogen is a 340 kDa glycoprotein that consists of two identical disulfide-linked subunits. Each subunit is composed of three nonidentical polypeptide chains: alpha, beta, and gamma. The beta and gamma chains have conserved C-terminal domains of about 250 amino acid residues (designated βC and γC, respectively). The crystal structure of the isolated γC domain, as well as that of the γC and βC domains in the fibrinogen D fragment, revealed that both domains are similarly folded. A minor 420 kDa form of fibrinogen (fibrinogen-420) has an alternative extended form of the alpha chain (αE), which has a C-terminal domain (designated αEC) whose sequence and fold are highly homologous to those of the βC and γC domains. Fibrinogen binds to CD54 (ICAM-1) through the frist IgG domain (8KVILPRGGSVLVTC21 of CD54). CD54 binds to Fibrinogen γ-chain (117NQKIVNLKEKVAQLEA133).

Fibrinogen is polymerized into fibrin network, and this process is triggered by thrombin. Polymerized fibrin is further cross-linked by factor XIII. Fibrin or fibrinogen is proteolytically degraded into ►fibrin degradation products (FDP) (fibrinolysis). Plasmin, a major extracellular serine protease, plays a role in this process. Fragments D and E are major fibrin degradation products. Fragment D contains C-terminal globular domains (γC of the γ chain and βC of the β chain). Fragment E contains the central portion of fibrinogen (Fig. 1). The γC domain has been shown to interact with several ►integrin cell adhesion receptors (αvβ3, α5β1, αIIbβ3, αXβ2 (p150,95), and αMβ2 (Mac-1)) and the αEC domain binds to avβ3 and aMβ2 (Fig. 2).

Integrins are a family of cell ►adhesion receptors that recognize extracellular matrix ligands including fibrin (ogen) and cell surface ligands. Integrins are transmembrane α–βheterodimers, and at least 18α and 8β subunits are known. It has been well established that integrins transduce signals inside the cells upon ligand binding, and integrin functions are regulated by the signals from inside the cells. According to the crystal structure of the human γC domain, γC has a C-terminal fibrin-polymerization domain, a single calcium-binding site, and a deep binding pocket. Several integrins recognize γC. Integrin αIIbβ3 in platelets, αvβ3 in endothelial cells, and αMβ2 in leukocytes recognize γC and play an important role in thrombus formation, angiogenesis, and inflammation; respectively. This domain does not have an RGD motif, a prototype integrin recognition sequence. αIIbβ3 recognizes the C-terminal sequence ($HHLGGAKQAGDV^{400–411}$) of γC. Deletion of the QAGDV sequence at the C-terminal region of the γC domain in mice induces a defect in platelet aggregation. Integrins αMβ2 and αXβ2 (p150,95) in leukocytes recognize residues 190–201 and 383–395 of γC. The αM I-domain directly interacts with this sequence. αvβ3 is a fibrinogen receptor in endothelial cells and αvβ3-fibrinogen interaction may play a key role in angiogenesis associated with wound healing and tumorigenicity. αvβ3 also recognizes γC. Although αIIbβ3 requires $HHLGGAKQAGDV^{400–411}$ of γC for binding, this sequence is not important for recognition by αvβ3. The residues 190–201 and 346–358 in γC sequences are involved in αvβ3 binding. Although they are spatially distinct sequences, they are adjacent in the three-dimensional structure. Residues 346–358 do not support



Fibrinogen. Figure 1 Domain structure of fibrinogen, and its proteolytic fragments D and E.



Fibrinogen. Figure 2 Integrin binding to the γC domain of fibrinogen.

the binding of αIIbβ3 or αMβ2 to fibrinogen. Thus αvβ3 binds to γC in a manner distinct from αMβ2 and αIIbβ3.

Fibrin(ogen) is found deposited in the majority of human and experimental animal tumors. The deposition of fibrin(ogen), along with other adhesive glycoproteins, into the extracellular matrix (ECM) serves as a scaffold to support the binding of growth factors and to promote the cellular responses of adhesion, proliferation, and migration during ►angiogenesis and tumor growth. Fibrin(ogen) degradation products (FDPs) generated during fibrinolysis have been implicated in tissue inflammation associated with the adult respiratory distress syndrome, disseminated intravascular coagulation, and septic shock. Plasma concentrations of FDP fragment D are markedly elevated in these disorders. Activation of fibrinolysis and the resulting generation of FDPs, including fragment D, contribute to lung vascular injury. Fragment D detaches endothelial monolayers from the substratum, and that fragment D increased endothelial monolayer permeability. FDP fragment D increases secretion of endothelial plasminogen activators and that fragment D may be a critical mediator linking activation of fibrinolysis to vascular endothelial injury in inflammatory disorders.

The isolated γC or its truncation mutant γC399tr, which lacks the αIIbβ3-binding site, induces ►apoptosis of endothelial cells, while native fibrinogen or fragment D does not have such effects. γC or γC399tr blocks tube formation by endothelial cells on matrigel through inducing apoptosis. Colon carcinoma cells that were engineered to secrete γC grow much slower than non-secreting cells in vivo while they grow at comparable rate in vitro, suggesting that γC secretion affects tumor growth through blocking angiogenesis in vivo. γC399tr effectively blocks tumor growth, and suppresses intratumoral microcirculation. Soluble native fibrinogen and fragment D do not bind to fully activated αvβ3, but soluble γC and γC399tr truncation mutant does. Thus the αvβ3-binding site is cryptic in native fibrinogen and fragment D, but is exposed in γC and γC399tr. These findings shed a new light on fibrinogen functions, and γC and γC399tr are potential therapeutics.

At least three integrins bind to the γC domain. The C-terminal AGDV sequence (408–411) is required for αIIbβ3, residues 383–395 are recognized by αMβ2, and residues 346–358 are uniquely involved in binding to αvβ3. In the C-terminal, approximately 20 residues are missing in the crystal structure of the γC domain,

probably because these residues take various conformations due to their flexibility. Truncation of the C-terminal 12 residues (400–411) of the isolated γC domain (γC399tr) eliminates the AGDV motif required for αIIbβ3 binding and exposes the αMβ2-binding site. Our preliminary results suggest that the αvβ3-binding site is not accessible in native fibrinogen and in fragment D, but is exposed in the isolated recombinant γC domain and γC399tr. It is unclear whether the αvβ3-binding site becomes further accessible by the truncation.

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Fibroadenoma

Definition

Benign tumor characterized by the proliferation of fibrous (stromal) and glandular tissue.

►Cowden Syndrome

Fibroblast

Definition

A cell of the mesenchymal lineage, which is a connective tissue cell.

Fibroblast Growth Factor 2

Definition

Synonym FGF2 basic FGF; is a broad spectrum and pleiotropic mitogen for growth and differentiation, affecting epithelial and endothelial cells, smooth muscle cells, and osteoblasts. FGF2 incites tumor angiogenesis, is expressed by various tumor cell lines, and seems to be biologically important in tumor progression and metastasis.

►Fibroblast Growth Factors

Fibroblast Growth Factors

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Synonyms

HBGF; Heparin-binding growth factors

Definition

Fibroblast growth factors (FGFs) constitute a large family of growth and differentiation factors. The family comprises two prototypic members, acidic FGF (aFGF, FGF1) and the basic FGF (bFGF, FGF2), as well as 21 additionally related polypeptide growth factors that have been identified to date. The designation "FGF" is historical and refers to the fact that the first members of the family stimulated fibroblast proliferation. In fact, FGFs can act on a wide range of cells, especially of mesodermal and neuroectodermal origin.

Characteristics

Common characteristics of members of the FGF protein superfamily are a high affinity for heparin and heparin-like glycosaminoglycans as well as a high sequence homology within a central core domain of 120 amino acids. During embryonic development, FGFs are curcially involved in embroyonic development, and in many processes such as wound healing, hematopoiesis, and particularly angiogenesis. FGFs are also implicated in the maintenance of an undifferentiated state in embryonic stem cells. Most FGFs interact with a family of high-affinity cell surface receptor tyrosine kinases (RTK). Although more than 20 FGFs with different effects on various target cells have been identified, only four different FGF receptor isotypes (FGFR1–4) exist. By expression of different splice variants of FGFR1–3, four *FGFR* genes encode a broad variety of different isoforms which differ in their FGF ligand-binding profiles. For instance, one particular splice variant, FGFR2IIIb, is mainly expressed on epithelial cells and represents the receptor for FGF7 (also named

keratinocyte growth factor, KGF). Within the classical FGF family, FGF11–14, also known as FGF homologous factors (FHF1–4), represent a subclass of FGFs. This subclass is characterized by the fact that, although FHFs can bind heparin like the classical FGFs, they are unable to activate FGFRs and interact with intracellular target proteins.

Regulation

Due to their affinity for heparin-like glycosaminoglycans, the majority of secreted FGFs are bound to ►extracellular matrix (ECM) components. Locally stored FGFs can be released from this extracellular reservoir by at least two mechanisms. One mechanism involves enzymatic degradation of ECM, e.g., during wound repair or tumor cell invasion. Alternatively, the carrier protein FGF-BP (FGF-binding protein) binds FGFs in a noncovalent manner and shuttles them from their ECM storage site to their cell surface receptors.

Clinical Relevance

Besides their ability to regulate proliferation and differentiation, some FGFs are important angiogenic inducers. Increased FGF activity in malignant tumors results from stromal as well as cancer cells and in turn acts on cancer cells as well as the surrounding stroma, and especially the vasculature. In selected cancer types, activating mutations in specific FGFRs or altered expression of isoforms have been described. Due to their multiple effects on tumor growth, FGFs, their receptors, and FGF-BP have been analyzed in various tumor cell types as potential tumor and/or progression markers. Moreover, in the future, selective inhibition of FGF/FGFR-signaling, e.g., by thalidomide, could exploit the crucial function of FGF-signaling in cancer for therapy.

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Fibroblasts

Definition

Are a mesenchymal cells that secrete growth factors and ►extracellular matrix. Tissue-specific fibroblasts are uniquely suited to maintain connective tissues of a given organ.

►Desmoplasia
►Chemical Carcinogenesis
►CXC Chemokines
►Metastasis

Fibrofolliculomas with Trichodiscomas and Acrochordons

►Birt–Hogg–Dubé Syndrome

Fibrogenesis

Definition

Refers to the scarring that takes place in the liver (or any organ) where connective tissue replaces the normal cells within the injured organ (the cells are commonly hepatocytes in the liver).

Fibroid

Definition

Refers to benign (non-cancerous) tumors that grow in, on or outside of the wall of the uterus. They usually range in size from as small as a pea to as large as a grapefruit. About 20–25% of all women have fibroids, and they are very common in women over 30. Women over the age of 35 have between a 20 and 40% chance of having fibroids. Synonym fibromyoma, ►uterine leiomyoma or myoma, uterine fibroids only exceptionally undergo a malignant change towards uterine cancer, but almost never develop into cancer.

Fibromas

►Uterine Leiomyoma

Fibromyoma

►Uterine Leiomyoma, Clinical Oncology

Fibronectin

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Definition

Is a large adhesive glycoprotein and a normal constituent of extracellular fluids, extracellular matrices, most basement membranes and certain cell types. It is implicated in a variety of different biological phenomena such as cell ►adhesion, establishment and maintenance of normal cell morphology, cell ►migration, differentiation, transformation, hemostasis, thrombosis, wound healing, ►transformation and ontogeny.

Characteristics

The molecule consists of two similar but non-identical polypeptide subunits, which are disulphide-linked at the carboxyl terminus. The longer α-chain and shorter β-chain each contain two free SH-groups and 60 cysteine residues, many of which appear to be involved in intrachain disulphide loops. Fibronectin is glycosylated at about 4–6 sites within the protein via arginine (N-linked), which account for 4–5% of the molecular weight of the molecule. Major sugar residues in glycosylation units are mannose, galactose, glucosamine and sialic acid.

Both α and β chains consist of similarly ordered globular domains:

1. Amino-terminus
2. Gelatin-binding domain
3. Cell adhesive/attachment domain
4. Heparin-binding domain
5. Carboxy-terminus (Fig. 1)

Forms of Fibronectin

Cellular fibronectins are secreted by various cell types, such as fibroblasts, epithelial and endothelial cells, chondrocytes, ►macrophages and platelets, which organize them into extracellular matrices. Cellular fibronectins appear to be more interesting, in the context of neoplastic disease, than plasma fibronectin because their expression is affected by oncogenic transformation.

Functions

Fibronectin is implicated in a variety of different biological phenomena such as cell adhesion via its receptors (Fig. 2) and the establishment and maintenance of normal cell morphology as a component of the ►extracellular matrix (ECM).

Fibronectin is also implicated in hemostasis and thrombosis. Fibronectin contains binding domains for cells, gelatin (collagen), heparin and some other proteoglycans, DNA, hyaluronic acid and fibrin.

Structure

Each polypeptide chain consists of internal repeats of three types of homologies termed type I, II, and III repeat. There are 12 type I repeats, 2 type II repeats and 15–18 type III repeats (Fig. 1). Each exon of the single gene encodes one type I or type II repeat. Most type III repeats are encoded generally by two exons, but this pattern is altered at three positions that exist as a single exon, and where alternative splicing occurs. Type I repeats are ~40 amino acids long, type II are ~60 and type III are ~90, as originally shown in bovine plasma fibronectin.

Fibronectin Polymorphism

The diversity observed among fibronectins is due to both alternative splicing of the single primary transcript and due to post-translational modifications.

Post-Translational Modifications

Fibronectin undergoes glycosylation that appears to stabilize fibronectin molecules against proteolysis. In addition, the degree of glycosylation may influence the interaction of the protein with cells; for instance, higher amounts of glycosylation decrease the avidity for collagen. Other post-transcriptional modifications of fibronectin include phosphorylation and sulfation. Fibronectin is phosphorylated on a serine residue near the carboxy terminus. Certain fibronectin variants are found to be tyrosine-linked sulfated.

Alternative Splicing

►Alternative splicing is a widespread gene regulation mechanism able to generate diversity in a reversible way and without requiring the expression of new genes. Some eukaryotic genes, such as the gene encoding for

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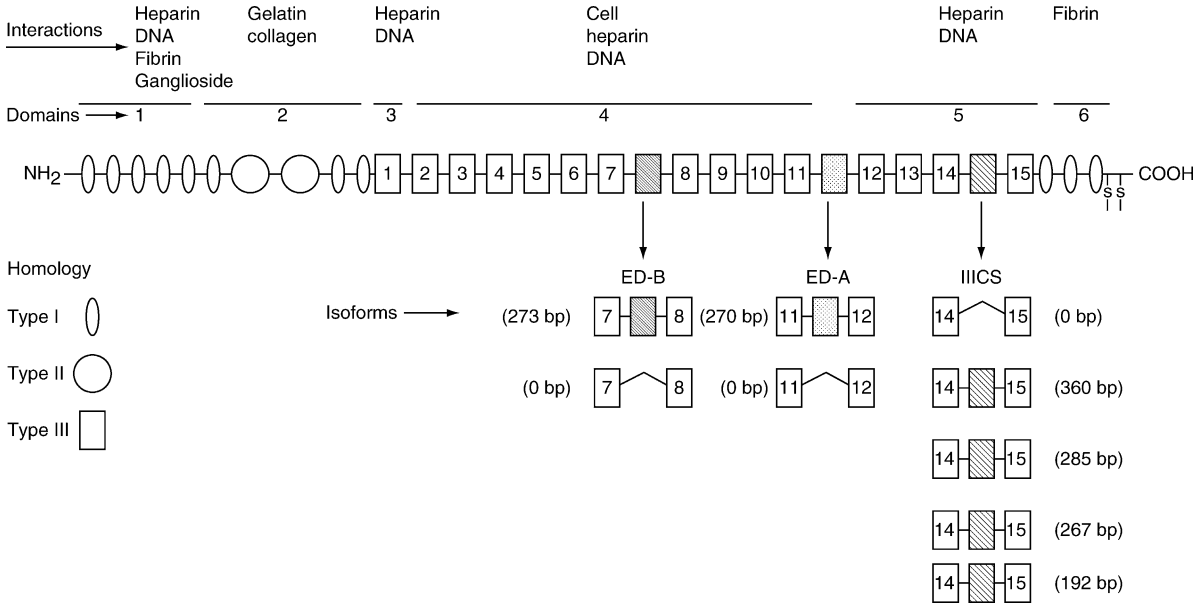
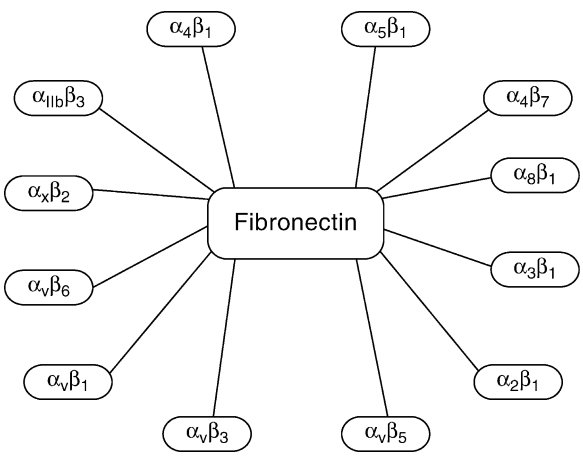


Fibronectin. Figure 1 Fibronectin molecule. Diagrammatic representation of the domain structure of fibronectin. Shown are homology repeats and different sites of alternative splicing (ED-B, ED-A and IIICS), giving rise to different isoforms of fibronectin.



Fibronectin. Figure 2 Fibronectin interactions with integrins. Different integrins that interact with fibronectin.

tenascin, produce multiple isoforms by alternative mRNA splicing. In general the exon changes caused by alternative mRNA splicing do not produce radically different proteins. Rather, they produce a set of similar proteins called protein isoforms.

Alternative splicing in fibronectin occurs in three regions of the primary transcript and generates 20 different isoforms that differ in the number of internal repeats. The regions of variation are: type III constant region (IIICS), extra domain A (ED-A) and extra domain B (ED-B). The same regions in rats are known as V, EIIIA and EIIIB, respectively.

Alternative splicing of fibronectin mRNA is regulated in a cell-, tissue- and developmentally-specific manner. Furthermore, it has been demonstrated that the splicing pattern of fibronectin mRNA is deregulated in transformed cells and in malignancies. The fibronectin isoforms containing the IIICS, ED-A and ED-B sequences are expressed more in transformed cells and in tumor tissues than in their normal counterparts. Because of the preferential expression of ED-B and de novo glycosylated fibronectin variants in fetal and tumor tissues, these fibronectin isoforms are known as oncofetal or embryonic fibronectins.

- IIICS region is situated between the last two type III homology repeats. This region of fibronectin undergoes complex patterns of alternative splicing; it may be totally included, partially included or excluded and may yield up to five different isoforms. IIICS domain is also subject to glycosylation. This fibronectin variant results from the addition of an α-N-acetyl-galactosamine to a threonine residue in a hexapeptide segment (Val-Thr-His-Pro-Gly-Tyr) located in the IIICS domain. De novo glycosylation of fibronectin is associated with cellular immaturity, cancer formation and the malignancy of breast, gastric and oral carcinomas.
- ED-A is situated between 11th and 12th type III homology repeats and it is the second region of alternative splicing. It is a single exon that is either included or omitted from the mature mRNA. This variation is tissue specific, and ED-A is not found in the mRNA of liver where plasma fibronectin is

synthesized. In human adult tissues, ED-A fibronectin has a restricted expression in certain tissues such as renal and colonic mucosa. ED-A is also present in normal adult myocardium where it is deposited as spots in the interstitium.

- The third region of variation is ED-B that is localized in the middle of the cell binding domain 4, between seventh and eighth type III homology repeats. ED-B is itself a complete type III homology repeat composed of 91 amino acids and coded by a single exon, which is either included or omitted from the mature mRNA. ED-B is the most conserved fibronectin region with 100% and 96% homology with rat and chicken fibronectin, respectively. ED-B containing fibronectin, with very few exceptions (superficial synovial cells, intima of some vessels and areas of interstitium of ovary, functional layer of endometrium during the proliferative phase and isolated areas of basement membrane of celomic epithelium), is reported to be absent in normal tissues. It has a greater expression in the intima of vessels of fetal brain cortex, stomach, jejunum, thymus and lungs of 8- to 12-week-old fetuses and tumor tissues as established by immunohistochemistry using the monoclonal antibody BC-1 (specific for ED-B containing fibronectin). In tissues from older fetuses (20–22 week old) only basal portions of gastric and duodenal glands were found positive for ED-B fibronectin. This suggests that ED-B fibronectin undergoes a programmed expression during ontogenesis.

Biological Significance of ED-B

The biological significance of ED-B is unknown. Its proximity to the cell-binding region suggests a role in cell adhesion and migration. This is also supported by the expression of ED-B in fetal tissues and during angiogenesis. In both the cases, cell migration and interactions are required. So far, no binding peptide is located to the ED-B repeat. But the ED-B domain seems to enhance cell adhesion and spreading. This adhesion effect of the ED-B may be mediated via conformational changes. It has been reported that insertion of the ED-B in fibronectin causes conformational changes in the molecule. The conformational changes induced by the ED-B in the downstream segment of the fibronectin may improve the access to the integrin binding sites in the ninth and tenth type III repeats. It has been shown that ED-B domain with its neighboring type III repeats is important in promoting cell adhesion.

Fibronectin Isoforms in Disease

Expression of fibronectin isoforms differs in disease. Although the expression of ED-A, ED-B and de novo glycosylated fibronectin is not disease specific, it is correlated with tissue modulation processes and particularly with connective tissue formation (fibroplasia).

Dilated cardiomyopathy (DCM) is a heart muscle disease in which alterations to cardiomyocytes result in changes in the composition of the ECM, including increase in the deposition of fibronectin, laminin and collagens in the intercellular spaces and in the vicinity of blood vessels. In patients with DCM, ED-A is detected as spots in the interstitium like in normal hearts. In contrast, ED-B and de novo glycosylated fibronectin, which are not seen in normal adult myocardium, are expressed in DCM. Re-expression of the ED-B and de novo glycosylated fibronectin in the adult heart was also found in myocardial hypertrophy in the rat. ED-A is synthesized by the synovial lining fibroblast-like (type B) cells. The expression of ED-A seems to be correlated with activated or transformed states of synovium. De novo glycosylated fibronectin was present in the synovial fluid of patients with rheumatoid arthritis. Patients with osteoarthritis also produce the same variant of fibronectin although at lower levels. De novo glycsylated fibronectin was also proposed as a predictor of preterm birth. High levels of this fibronectin variant were detected in the cervicovaginal secretion of women during the second and third trimesters of pregnancy.

Fibronectin Isoforms and Cancer

Fibronectin isoforms are detectable at higher levels in tumors, whereas they are least or not at all expressed in normal adult tissues. In pituitary adenomas the presence of ED-A and ED-B has been reported. They were localized in the adenoma neovasculature, especially in the endothelium and smooth-muscle layers of the vessel walls. Expression of ED-A and ED-B fibronectins was also shown in human colorectal carcinomas and in tumors derived from rat colon carcinoma. ED-A labeling was detected in all the samples of human carcinomas in the stroma separating the tumor glands but also in normal colon stroma. Apart from ED-A and ED-B, the glycosylated isoform of fibronectin is also expressed in colorectal cancer but is absent from the normal tissue. Increased expression of ED-B fibronectin mRNA was observed in different types of ►lung cancer including adenocarcinoma, ►squamous cell carcinoma, small cell carcinoma and large cell carcinoma. These results suggest that in lung cancer alternative splicing of fibronectin mRNA in ED-B domain occurs irrespective of type of cancer or degree of differentiation. In liver cancer both ED-A and ED-B mRNAs are increased in malignant tumors whereas ED-B mRNA was also detected in benign neoplasms.

►Tissue Inhibitors of Metalloproteinases (Timps)

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Fibrous Dysplasia

Definition

A tumor-like space-occupying process characterized by the production of immature bone and sometimes of hyaline cartilage by fibrous tissue elements.

►Bone Tumors

Fibulins

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Synonyms

BM90, FBLN-1; FBLN-2; S(1-5), T16, EFEMP1, FBLN-3; MBP1, UPH1, H411, EFEMP2, FBLN-4; DANCE, EVEC, UP50, FBLN-5; Hemicentin, him4, FIBL6, HMCN1, FBLN-6

Definition

Are a family of secreted glycoproteins that are deposited in various extracellular structures such as basement membranes, elastic fibers, proteoglycan aggregates and fibronectin microfibrils. Fibulins have been shown to play an important role in organogenesis and vasculogenesis. Current evidence suggests that fibulins may acts as tumor suppressors or tumor promoters.

Characteristics

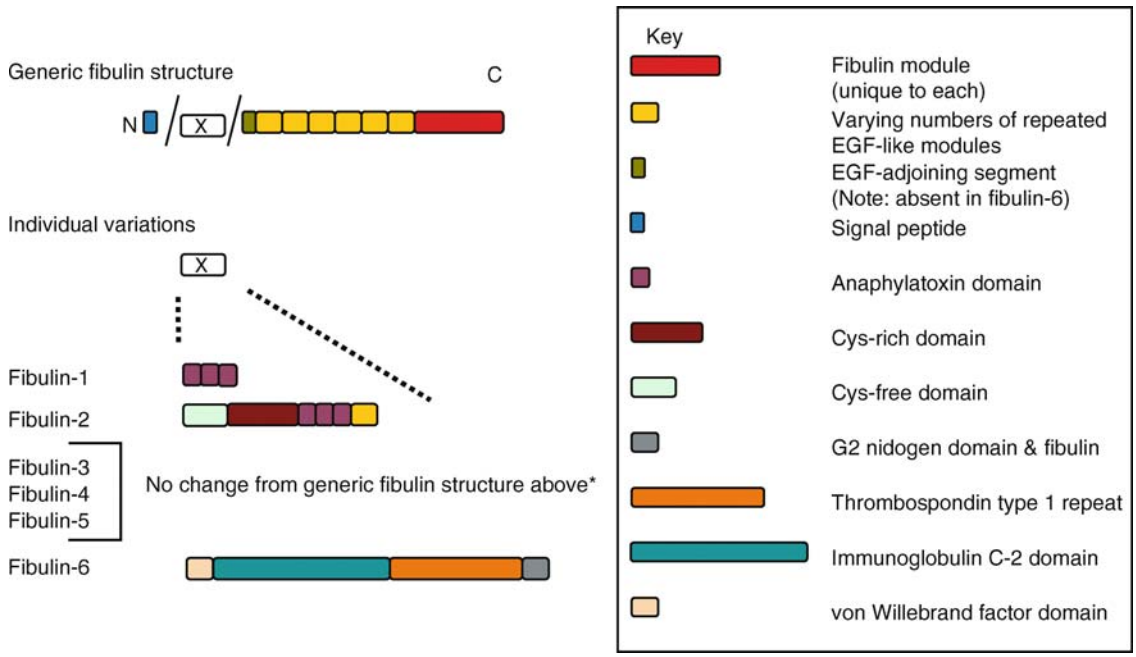
Fibulins arise as products from six distinct genes, termed fibulin 1-6, each residing on separate chromosomes. The fibulin isoforms vary in size from 50 to 200 kDa and are comprised of a collection of repeated calcium-binding epidermal growth factor (cbEGF)-like domains, which consist of rod-like elements with globular domains at the ends, and a unique C-terminal fibulin-type module (Fig. 1). Fibulins are prominently expressed in the blood and blood vessels but have also been found to reside in the lung, heart, liver, brain and other bodily tissues. Of the six fibulins identified to date, cancer-associated linkages have been documented for fibulin-1, -3, -4 and -5.

Fibulin-1

Fibulin-1 was the first member of the fibulin family identified. It consists of an N-terminal signal sequence, three anaphylatoxin (AT) repeats, nine EGF-like domains, eight of them processing the consensus sequence for calcium ligation, and an alternatively spliced fibulin-type C-terminal domain (FIB), giving rise to four possible variants, fibulin-1A to -1D. Variants-1C and -1D have been found to reside in most tissues and cell lines, whilst variants-1A and -1B have been detected at low levels in the human placenta. Current evidence suggests that fibulin-1 may act as a tumor suppressor or ►oncogene, depending on cellular context and/or which splice variant is expressed. Overexpression of fibulin-1D in human fibrosarcoma-derived cell lines suppresses anchorage-independent growth, motility and matrigel invasion *in vitro* and delays tumor formation *in vivo*. Similarly, elevated expression of fibulin-1D or addition of purified protein inhibits cells ►adhesion, spreading and motility *in vitro*. In addition, ectopic overexpression of fibulin-1D inhibits transformation by the papillomavirus E6 gene, possibly through a protein-protein interaction mechanism. Fibulin-1 can interact with positive (fibronectin and laminin) and negative (aggrecan and veriscan) regulators of cell motility, thus influencing cell movement and tumor progression. Elevated expression of fibulin-1 in ovarian and breast carcinomas has been reported (►Ovarian cancer, ►breast cancer), with there being an increased level of fibulin-1C:-1D seen in the former tumor tissue type. Serological screening of cDNAs identified fibulin-1 protein as an immunogen in patients with breast cancer. Similarly, dendritic cells obtained from fibulin-1 seropositive patients demonstrated a T cell response to the presence of fibulin-1. DNA microarray studies of lung adenocarcinomas demonstrated a close association of fibulin-1 and -2 with matrix metalloproteinase-2 expression, a promoter of ►metastasis and tumor invasion. The mechanism by which fibulin-1 promotes or inhibits tumorigenesis is unclear at present. However, available data suggest that there are specific binding functions for fibulin-1D that are not shared by fibulin-1C.

Fibulin-2

Fibulin-2 consists of an additional 400 amino acid long N-terminal domain, which is composed of



Fibulins. Figure 1 Schematic representation of the fibulin family structure. The structure of a generic fibulin is shown, with individual variations between family members represented underneath. The six secreted glycoproteins comprising the family are characterized by a unique fibulin-type module at the C-terminus and repeated epidermal growth factor (EGF)-like domains. Splice variants (known to exist for fibulins-1 to -4) are not illustrated. *Fibulins -3 and -4 have five EGF-like modules followed by a sixth with an insertion. There is no insertion in the sixth EGF-like domain of fibulin-5. Fibulins -3, -4 and -5 share ~50% amino acid homology.

cysteine-rich and cysteine-freesubdomains and nine EGF-like domains, which are a similar type to the EGF domains of fibulin-1. The role of fibulin-2 in cancer is unknown at present; however, recent studies have identified fibulin-2 as an overexpressed metastasis-associated gene in solid tumors of diverse types.

Fibulin-3

Fibulin-3 consists of five ►cbEGF-like modules and a carboxy-terminal domain III. Various alternatively spliced fibulin-3 transcripts have been identified which show a partial or complete deletion of the amino-terminal domain I. Fibulin-3 has been shown to positively and negatively regulate cell proliferation *in vitro*. Expression of fibulin-3 mRNA has been reported during the processes of cell growth arrest and senescence and is also upregulated in transformed cell lines. Microinjection of *in vitro* translated fibulin-3 mRNA into normal human fibroblasts stimulated DNA synthesis of injected cells, as well as some surrounding cells. Endogenous levels of fibulin-3 have been shown to inhibit proliferation, invasion, and angiogenic sprouting of endothelial cells in the presence of vascular endothelial growth factor. The ability of fibulin-3 to inhibit these tumorigenic variables suggests a possible role in reducing tumor angiogenesis and consequently tumor growth both *in vivo* and *in vitro*. Lastly, the rat homologue of fibulin-3 has been shown to associate with DA41, as determined by yeast two-hybrid assay. The DA41 protein interacts with the tumor-suppressor protein DAN, indicating that fibulin-3 might have an indirect role in the regulation of cell growth through a network of molecular interactions. Further work is required to determine the role of fibulin-3 in cancer.

Fibulin-4

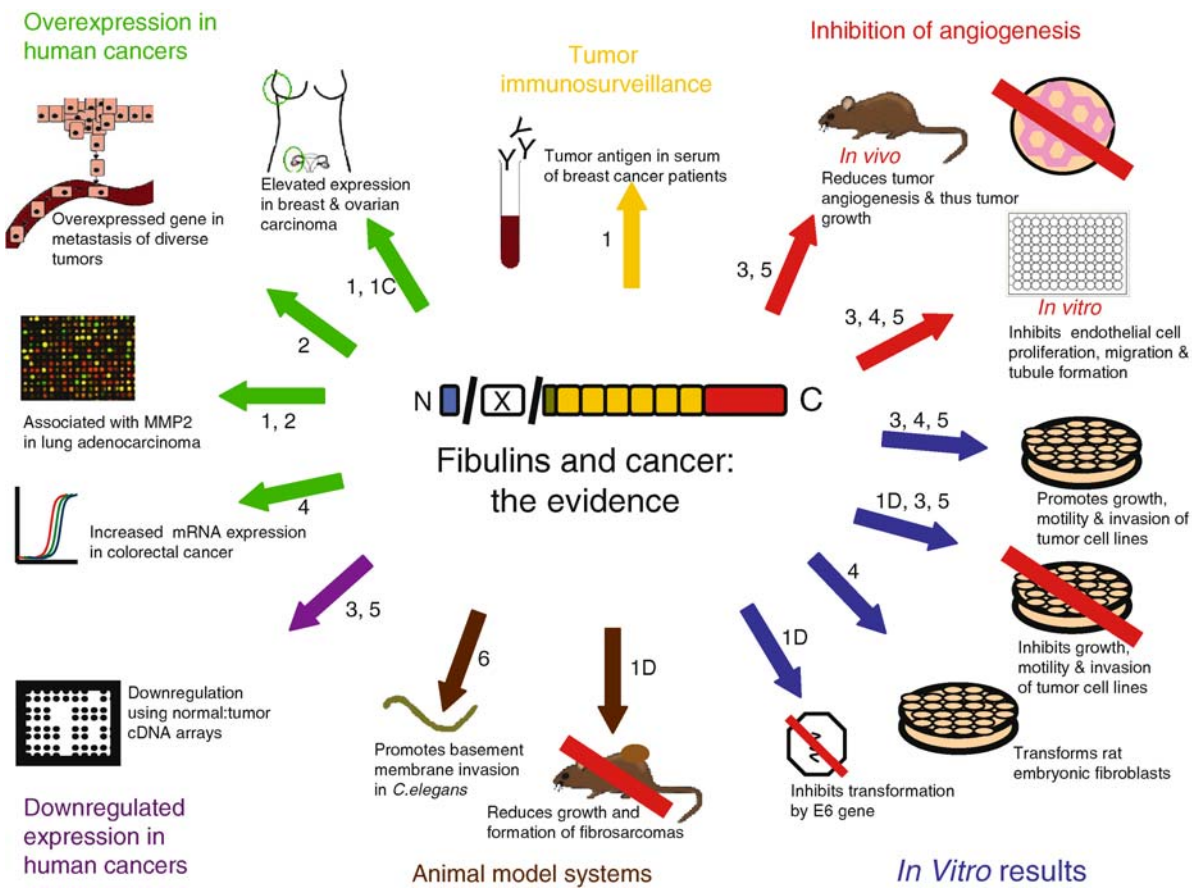
Fibulin-4 also consists of five cbEGF-like modules and a carboxy-terminal domain III. The human fibulin-4 gene is localized to 11q13, a region commonly amplified in a variety of human cancers. Mouse fibulin-4, originally identified as a specific protein partner for mutant p53, displays both mutant p53-dependent and -independent oncogenic properties. Fibulin-4 has been shown to induce cell proliferation and increase rates of neoplastic transformation by synergizing with mutant p53 protein. Elevated expression of fibulin 4 mRNA has been reported in a panel of paired normal/tumor human colon tissue biopsies (►Colon cancer). The exact mechanism responsible for the increased fibulin-4 levels in colorectal tumors is unknown at present. Further work is necessary to determine whether altered fibulin-4 expression is prevalent in other tumor types.

Fibulin-5

Similar in structure to fibulin-3 and -4, fibulin-5 is composed of six cbEGF-like domains followed by a globular C-terminal module which differs from other fibulins by the presence of integrin-binding RGD motif. Recent studies suggest that fibulin-5 may suppress or promote tumorigenesis. In human tissues derived from 68 patients, fibulin-5 mRNA expression was altered in 65% of the tumors, of which 95% showed down-regulation and 5% demonstrated up-regulation. The reduction of fibulin-5 expression was most prominent in cancers of the kidney, breast, ovary and colon. Importantly, fibulin-5 was expressed aberrantly in 68% of metastatic human malignancies (17 of 25 cases), of which 100% showed down-regulated expression of fibulin-5. Paradoxically, fibulin-5 expressing HT1080 cells exhibite enhanced DNA synthesis and increased cell ►migration to fibronectin as compared with control cells. In the presence of synthetic basement membranes, fibulin-5 expressing HT1080 cells invaded significantly better than control HT1080 cells. In addition, vascular smooth muscle cells derived from fibulin-5 knockout mice exhibited increased proliferation and migratory responses to mitogenic stimulus, with these effects being inhibited by the overexpression of fibulin-5. In short, the ability of fibulin-5 to enhance the malignancy of human fibrosarcoma cells and to down-regulate mRNA expression in human tumor tissue suggests that aberrant fibulin-5 may affect cancer cell growth in a context and/or tumor-specific manner.

Fibulin-6

Fibulin-6 was first identified in *Caenorhabditis elegans* (*C. elegans*), with orthologues in human and mice. It consists of a series of predicted cbEGF-like domains, followed by a single unusual EGF-like domain at the carboxy terminal. The ability of cells to invade through basement membranes and enter new tissues is crucial to the spread of cancer. To date, there is no direct evidence linking fibulin-6 to cancer. However, the ability of fibulin-6 to promote invasiveness *in vivo* has been reported using *C. elegans* as a model system. Further studies are necessary to elucidate fibulin-6 participation in invasiveness and possibly in ►carcinogenesis.



Fibulins. Figure 2 Fibulin family and cancer: the evidence. A summary of the available evidence linking members of the fibulin family with cancer. The individual fibulins linked to each process are shown in bold beside an arrow leading to a graphic representation of the findings.

Conclusion and Perspective

Fibulins are emerging as key contributors to carcinogenesis as indicated by their proposed involvement in tumorigenic mechanisms such as proliferation, adhesion, motility and invasion (Fig. 2). Their relevance to diagnosis and therapeutic implications in cancer is not fully clear at present. Fibulin-1, which is highly expressed in the blood and has been identified as an immunogen in patients with breast cancer, could aid in the detection of specific variants or processed forms of this protein via the development of a highly sensitive serum-based assays. Analysis of fibulin levels in more accessible biological materials, such as serum and urine, is warranted. Therapeutically, recombinant forms of fibulin-1, -4 and -5 might have potential as tumor suppressive or anti-angiogenic agents. Fibulin-1 protein can inhibit the adhesion and motility of a broad range of tumor cell types with minimal effects against primary cells. Using a retroviral-based gene-therapy approach, overexpression of fibulin-5 *in vivo* promotes wound closure. Lastly, the ability of recombinant fibulin-4 protein to inhibit angiogenesis *in vitro* suggests a possible therapeutic role in the treatment of cancer. In summary, further work is needed to fully resolve the complex role of fibulins in tumor development and progression.

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Field Cancerization

Definition

A concept to explain how multiple primary tumors and recurrences occur in a given tissue. First described for head and neck ►squamous cell carcinoma, but also recognized to occur in many other organs systems including skin, lung, breast, anogenital, colon, bladder. Stem cells exposed to carcinogens may become genetically altered, giving rise to clones of altered daughter cells. These undergo subsequent rounds of cell division, with each individual cell becoming a potential target for further genetic events and, consequently, malignant progression.

Field Defect

Definition

A phenomenon where grossly normal-appearing tissue which has pre-cancerous genetic changes. This tissue can be considered at risk for becoming a pre-malignant lesion and is hypothesized to occur in cancers which are commonly multifocal or locally recur after surgical removal of previously found growths.

►Carcinoid Tumors

Field Effect

Definition

Explanation for induction of multiple abnormalities within a single tissue. Where a "field" of cells is exposed to a given carcinogen, multiple unrelated lesions may arise.

►Malignancy-associated Changes

FIGO

Definition

International Federation of Gynecology and Obstetrics (FIGO); www. figo.org.

►Ovarian Cancer

Filipodia

Definition

Long thin protrusions at the periphery of cells and neuronal growth cones. They are composed of F-actin bundles and play a role in cell polarization and motility.

Finger-like membrane protrusions which are used by cells for ►migration. Thin, spike-like cytoplasmic protrusions containing actin filament bundles and generated on the leading edge of a crawling cell.

►Calpain
►Plexins

Final Appraisal Document

Definition

Final on guidance on a new health technology produced for by the UK's National Institute for Health and Clinical Excellence for the NHS.

►National Institute for Health and Clinical Excellence

Finasteride

Definition

Is an antiandrogen that acts by inhibiting type II 5-alpha reductase, the enzyme that converts testosterone to dihydrotestosterone (DHT). It is used as a treatment in benign prostatic hyperplasia (BPH) in low doses, and ►prostate cancer in higher doses.; is marketed as Proscar, Propecia, Fincar, Finpecia, Finax, Finast, Finara, Finalo, Prosteride, Gefina, Finasterid IVAX).

Fine Needle Aspiration Biopsy

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Synonyms

Fine needle aspiration (FNA); Fine needle aspiration cytology (FNAC); Needle biopsy; Needle aspiration biopsy (NAB); Skinny needle; Thin needle; Aspiration cytology

Definition

Is defined as the removal of cells using a fine gauge needle from a lump or mass for diagnostic purposes.

Characteristics

Background

The diagnosis of cancer requires analysis of tissue or cell samples under the microscope. Although physical exam, radiological imaging, and laboratory tests are useful in determining which lumps might be malignant, these tests are not specific and all lesions must be sampled and examined under a microscope to determine the precise nature. The removal of a sample for examination under a microscope is called a *biopsy.* One of the biopsy methods used for cancer diagnosis is called a *needle biopsy.* There are 2 types of needle biopsies: core needle biopsy and fine needle aspiration biopsy (FNAB). *Core needle biopsy* removes a small cylinder of tissue and involves microscopic examination of intact tissue as a slice, called ►histology. FNAB withdraws cells and microscopic pieces of tissue which are evaluated under the microscope as individual cells and clusters of cells. FNAB is easier to obtain, causes less discomfort, is less invasive, and is more cost effective than core needle biopsy. The disadvantage of FNAB is that it cannot always provide the level of information afforded by core biopsy. In many clinical situations, however, both methods are equivalent.

This essay explains the FNAB method.

What is FNAB?

Fine needle aspiration biopsy (FNAB) is a non-surgical diagnostic technique used for the diagnosis of mass lesions. FNAB is not new; it has been successfully practiced in Europe since the 1950s. From Europe, FNAB spread to other parts of the world and is now an established technique used worldwide. The beauty of FNAB is in its simplicity. It requires only needles, syringes, glass slides, stains, a microscope and a skillful operator. Skinny ("fine") hollow needles attached to a syringe are used to extract ("aspirate") cells from a suspicious mass for microscopic examination. Although the procedure is simple, it is not easy, and successful results are obtained only when the procedure is performed and interpreted by a team of experts trained in the art of FNAB. The team optimally consists of a ►cytopathologist, a ►cytotechnologist and for lesions requiring image-guidance, a radiologist. The cytopathologist, a medical doctor with subspecialty training in ►cytology, interprets the results and, in the case of superficial masses, also procures the specimen. The radiologist procures the samples from deep-seated lesions aided by image guidance. The cytotechnologist is responsible for assisting with the FNAB procedure,

the initial microscopic screening, and preliminary diagnosis of slides. He/she may also be responsible for specimen collection, preparation and staining and record keeping. When performed by such a team, FNAB is very sensitive and specific with a diagnostic accuracy approaching that of histology.

FNAB is versatile and can be performed at any body site. Common superficial sites include thyroid, breast, lymph node, salivary gland and subcutaneous tissue. Common deep internal sites include liver, pancreas, kidney, lung, mediastinum, pleura, pelvis, retroperitoneum, bone, brain, retina and deep soft tissue. More recently, a technique called ►endoscopic-ultrasound guided fine needle aspiration (EUS-FNAB) was developed to diagnose tumors in and around the digestive tract.

By using FNAB, a major ►surgical biopsy (►open biopsy) can often be avoided.

What Cellular Characteristics Do Cytologists Study in Order to Make a Microscopic Diagnosis of Cancer?

►Cytologists distinguish normal cells from cancer cells, and recognize the different types of cancer cells by studying the morphologic features of cells. The two components of the cell that cytologists study are the nucleus and the cytoplasm. The nucleus tells the cytologist about the health of the cell and the cytoplasm tells about what kind of cell it is. In cancer, the nucleus looks abnormal. It usually takes up more cell volume and may be darker than a healthy nucleus. It can also have an irregular shape. The abnormal changes in the nucleus are due to the fact that they often contain too much DNA. The cytoplasm gives the cytologist clues about the type of cancer present-whether it is an adenocarcinoma, squamous cell carcinoma, neuroendocrine carcinoma, lymphoma, or sarcoma. The way the cell clusters relate to each other assist the cytologist decide the type of cancer present. Sometimes studying the morphology does not yield enough information to allow the cytologist to decide the type of cancer. In these instances the cytologist uses ancillary ►immunocytochemical stains and other molecular markers on the cellular material obtained from the FNAB procedure to assist in making a definitive diagnosis and distinguish the type of cancer.

Method

Palpation-Guided Aspirates

For superficial palpable lumps, the procedure is optimally performed in a dedicated FNAB outpatient clinic by a cytopathologist with the assistance of a cytotechnologist (Fig. 1). The procedure takes approximately 15 minutes and is performed while the patient is awake. The patient is examined, the mass is localized, and the skin over the mass is cleansed with antiseptic. Local anesthetic may be injected into the skin over the nodule, although many practitioners prefer to perform aspirations without any anesthetic. A fine bore needle (approximately 23–25 gauge) is inserted through the skin and into the mass. A syringe attached to an aspiration device is commonly used to apply suction and the needle is rapidly moved up and down inside the nodule until enough cells and small tissue fragments have been dislodged and drawn up into the needle. The needle is then removed, and a gauze pad is applied with pressure to the biopsy site. After the fine needle aspiration biopsy is completed, a band-aid is applied and the patient is discharged home and can resume usual daily activities.

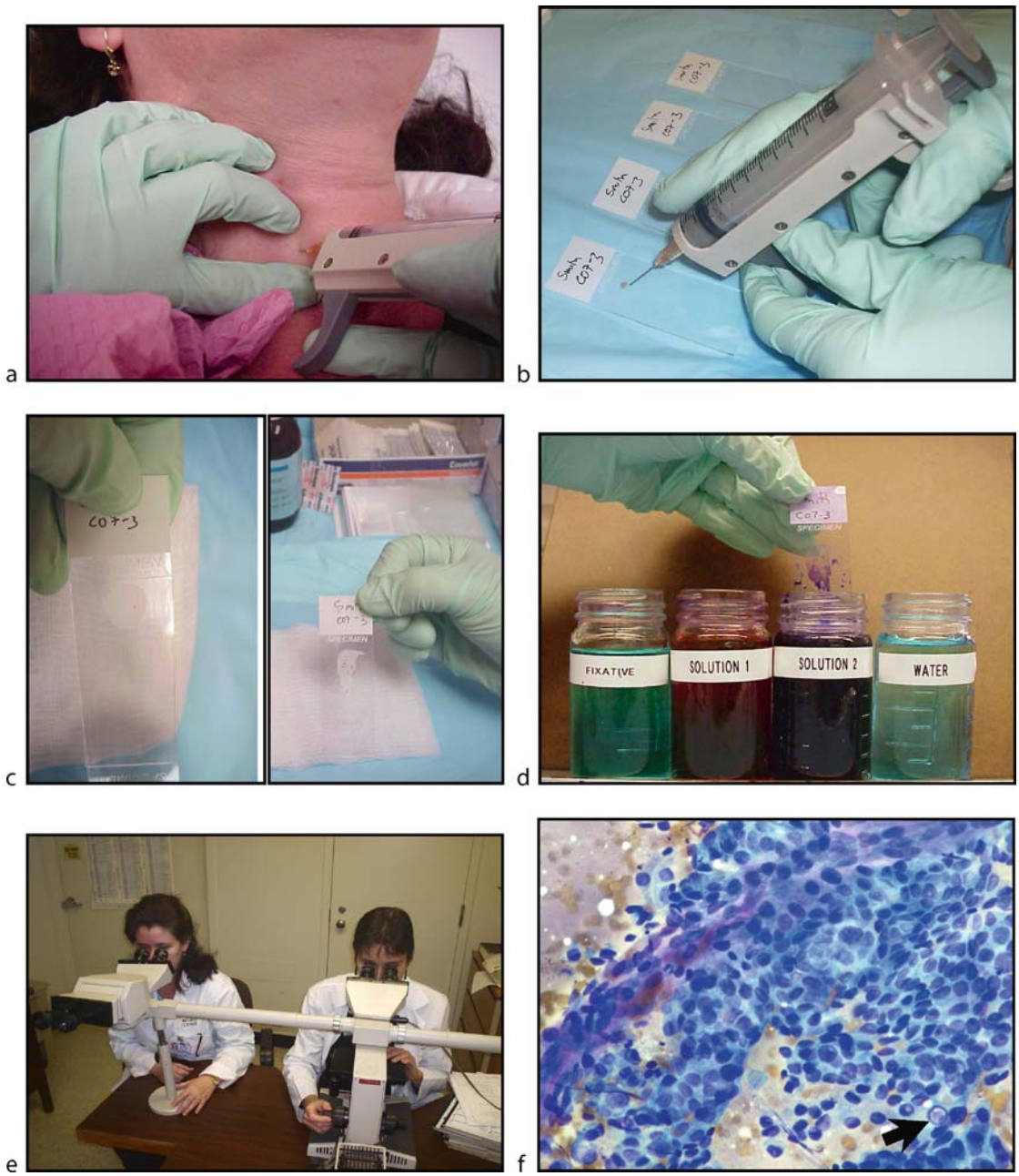
The biopsy material is expelled onto glass slides and smeared into a thin film. A number of samples are usually taken in separate aspirations or "passes" to increase the likelihood that an adequate sample will be obtained. In some facilities, representative smears are selected, stained and microscopically evaluated immediately for adequacy of the sample and for preliminary diagnosis prior to discharging the patient. This is optimal as it assures adequate sampling and appropriate sample triaging. If sufficient diagnostic material is obtained the procedure is terminated, and the patient is discharged. If the immediate microscopic evaluation demonstrates a lesion for which ancillary studies are needed, additional material is obtained immediately to fulfill the specimen requirements. This may include molecular studies (such as flow cytometry, immunocytochemistry, FISH and PCR), microbiology stain and culture, electron microscopy or other studies, as needed. ►Wright-Giemsa and ►Papanicolaou stained smears are routinely prepared in all cases. Cellular material can also be made into a "►cell block" and processed similar to histology.

Deep Seated Aspirations

Deep-seated soft tissue and visceral lesions are amenable to percutaneous FNAB using radiographic image-guidance (CT or ultrasound), which serves to guides the tip of the needle into the mass (Fig. 2). Image guidance can also be useful for difficult to palpate superficial masses or superficial masses located adjacent to vital structures. The technique for deep-seated aspirations is similar to that for superficial masses except that modified longer needles are required and a radiologist, rather than a cytopathologist usually does the FNAB. Optimal diagnostic yield is achieved when a cytologist is present during the procedure. Having the cytologist present allows for microscopic evaluation for adequacy and appropriate triage of the material. As in palpation-guided FNAB, smears are routinely made and if needed, material procured for ancillary studies as determined by the on-site microscopic evaluation.

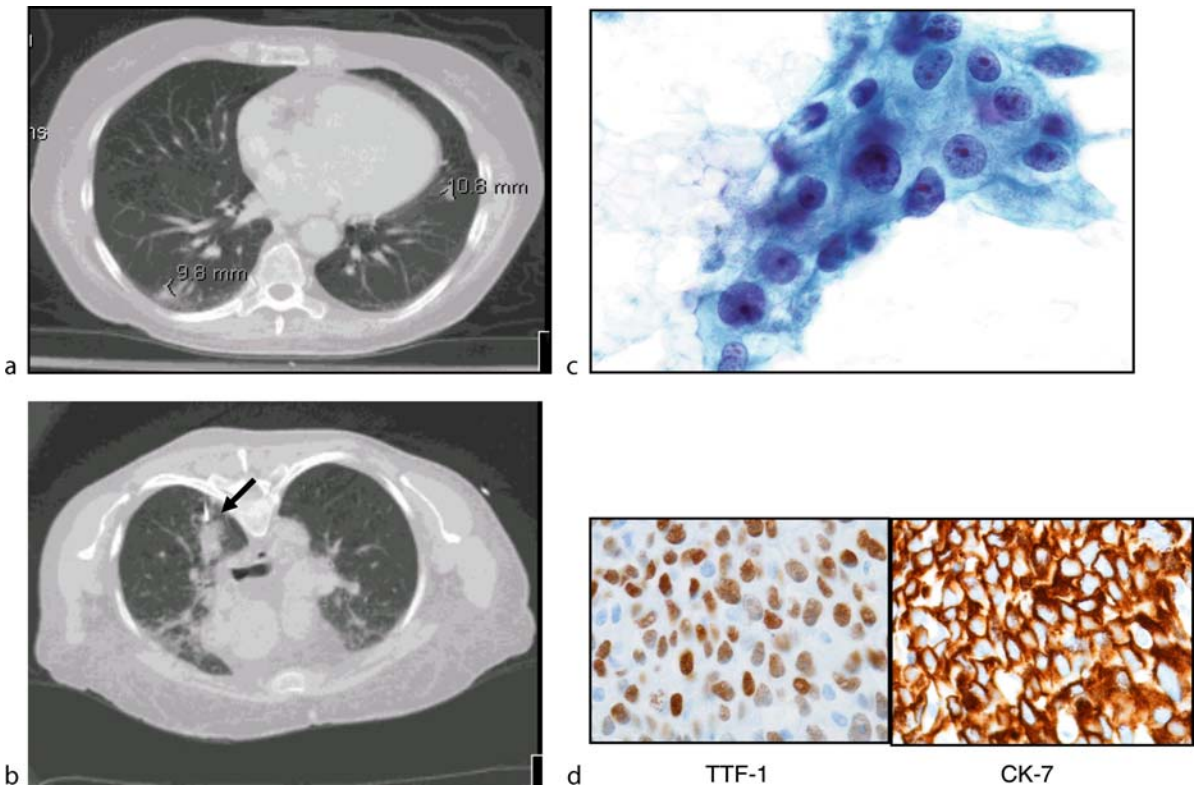
Complications and Contraindications

Complications associated with superficial palpable masses are rare and most commonly consist of minor



Fine Needle Aspiration Biopsy. Figure 1 Example of a palpation-guided FNAB procedure of a 1 cm right thyroid nodule in a 46-year-old female. (a) The needle is shown within the nodule. (b) The needle has been withdrawn from the nodule and the sample is placed in a drop onto a microscopy slide. (c) The specimen is smeared out using a two-slide smearing technique. (d) Representative slides are rapidly stained with a Wright-Giemsa stain. (e) The slides are evaluated microscopically for assessment of adequacy and preliminary diagnosis. Microscopic evaluation in this case demonstrated a papillary thyroid carcinoma. (f) Microscopic view showing the characteristic features of papillary carcinoma. Malignant thyroid cells are arranged in papillary configurations. Note the intranuclear hole (arrow) characteristic of this tumor type. (400× magnification, Wright-Giemsa stain).

bruising at the site. Deep-seated organ aspirations have higher complication rates which include infection, bleeding, peritonitis and pneumothorax. Uncorrected coagulopathy is an absolute contraindication for deep-seated FNAB. Needle tract seeding by tumor cells has also been rarely described in both superficial and deep FNAB; this complication is more commonly seen with core needle biopsy due to the larger needle caliber.



Fine Needle Aspiration Biopsy. Figure 2 Example of a CT-guided FNAB of a lung nodule. This patient was a previously healthy 65-year-old female with multiple pulmonary nodules noted incidentally on a CT scan done for other purposes. (a) CT scan shows bilateral, to numerous to count, pulmonary nodules thought to be suggestive of diffuse involvement of the lung by metastatic carcinoma. (b) CT scan showing the placement of the needle (arrow) within in a right posterior upper lobe nodule. (c) Microscopic view of a smear from the lung nodule demonstrates adenocarcinoma. Note the large malignant appearing cells with abundant cytoplasm and round to irregular nuclei with prominent nucleoli (1000× magnification, Papanicolaou stain). (d) Immunostaining results performed on the cell block shows the tumor to have strong positive nuclear immunostaining for TTF-1 (a marker for lung cells) and cytoplasmic staining for CK7 (also a marker for lung cells). The immunostains confirm that the cancer is actually a primary lung adenocarcinoma and not metastatic.

Generally, there are no absolute contraindications to FNAB of superficial masses.

Diagnostic Accuracy and Yield

When performed and interpreted by a dedicated FNAB team of experts a greater than 95% overall sensitivity and 99% specificity for the detection of cancer can be expected. The failure rate in obtaining a definitive diagnosis is less than 10% in experienced hands. This outcome may occur either when the specimen does not contain enough cells or when the specimen is adequate but overlapping cytologic features between benign and low-grade malignant entities precludes a definitive diagnosis. For such cases, further diagnostic steps such as core or open tissue biopsy are required.

Diagnostic Utility of FNAB

FNAB can provide specific diagnoses for many types of cancers. It is superb for the diagnosis of primary, recurrent and metastatic carcinoma, usually yielding enough information about the carcinoma subtype to start definitive treatment. FNAB is also sensitive for the detection of metastatic melanoma, lymphoma and many sarcomas.

The clinical value of FNAB is not limited to cancers. Most lumps and mass lesions are not cancers and FNAB is very valuable in diagnosing benign tumors, infections, cysts, inflammatory conditions and benign physiological alterations.

Limitations of the FNAB Method of Study

FNAB is a cytological method. In other words, it studies cells rather than intact tissue slices. The study of cells does not allow for evaluation of the relationship of the malignant cells to the supporting tissue as well as histology does. In addition, sometimes the FNAB cannot harvest sufficient cells/tissue for ancillary studies. Due to these limitations,

a histologic diagnosis may sometimes be preferred over a cytologic one.

Examples:

1. Some thyroid tumors require evaluation of the tumor capsule in order to decide if the tumor is benign or malignant; this can only be achieved by histological evaluation.
2. Although ►lymphoma is readily diagnosable by FNAB, sometimes the lymphoma subtype cannot be classified by FNAB to the extent required for optimal oncologic treatment. In this case, a surgical biopsy may be needed.
3. In some centers core needle biopsy is preferred over FNAB for the evaluation of prostatic and non-palpable mammographically detected breast lesions due to the purported higher sensitivity of core biopsy in these instances.

Despite these limitations, FNAB remains the initial diagnostic test of choice in most patients presenting with mass lesions. FNAB has the advantage of decreasing healthcare costs and improving patient care by providing a highly accurate and rapid diagnosis compared to alternative methods.

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Fine-Needle Aspiration Cytology

Definition

FNAC; A simple, inexpensive and well-tolerated method that consists in the aspiration of cells present using a fine needle. Smears, containing cells, are prepared immediately and microscopically examined by a cytopathologist. This method has a high sensitivity and a high specificity.

►Fine Needle Aspiration Biopsy

Firestorm Pattern

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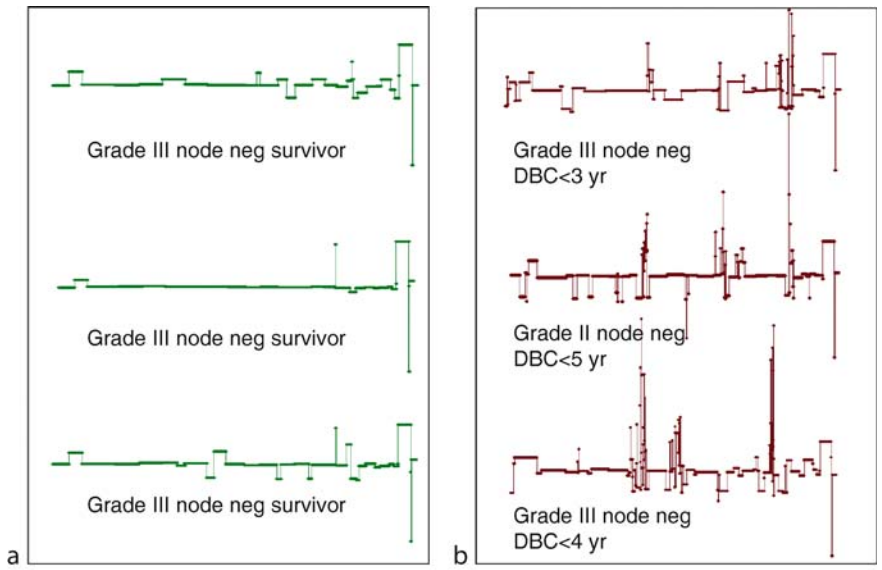
Definition

Firestorm refers to a type of genomic rearrangement, originally identified in breast cancer, characterized by multiple, narrow amplicons on a single chromosome arm usually coupled with deletion of the intervening regions. Firestorm amplicons are usually highly amplified (up to 30x) ►amplification and are maintained contiguously on a single chromosome, but not necessarily associated with their original centromere. There is evidence that firestorms are a marker for poor outcome in breast cancer in patients with otherwise good prognoses.

Characteristics

The term “firestorm” was coined to describe special cases of chromosome rearrangement revealed through high resolution microarray profiling in breast cancer genomes where multiple amplifications and deletions have occurred on a single chromosome arm. Firestorms appear as a series of tightly grouped peaks and valleys in genome profiles of copy number, with the peaks very often containing known or suspected oncogenes. As many as five separate firestorms may be observed in a single tumor genome, yet each one is clearly concentrated on a single arm. This structure is easily contrasted with so-called “simplex” and “saw-tooth” profiles that are characterized by whole chromosome or chromosome arm deletions and duplications distributed among many (“saw-tooth”) or a select few (“simplex”) chromosomes (Fig. 1). Additional information can be found in entries for amplification and amplified in breast cancer in this volume.

Firestorms are characterized by their structure and their potential significance for cancer gene identification as well as for diagnosis and prognosis. Based on the association of amplification and deletion in firestorms, along with their limitation to a single arm, it appears that firestorms are the result of a mechanism based on chromosome mechanics rather than over-replication of a single locus or a genome-wide destabilization of chromosome integrity. Firestorm peaks are frequently associated with known ►oncogenes (e.g. ►MYC, ►CCND1, ►ERBB2) but that the adjacent peaks are non-randomly distributed and may be pointers to novel oncogenes. Finally, based on an analysis of clinical outcomes in Swedish patients from 1985 to the present, there is evidence that a measure of firestorm activity, the



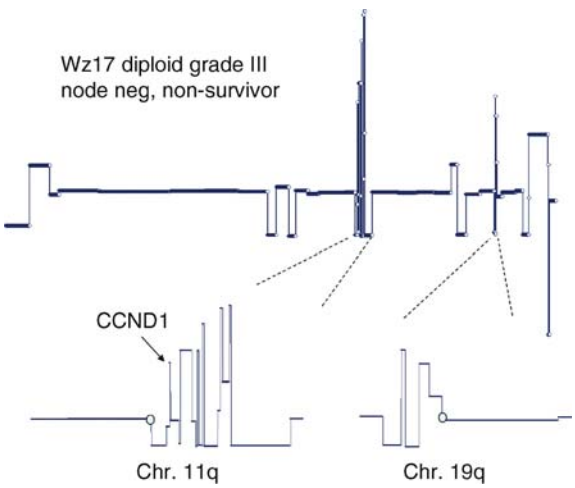
Firestorm Pattern. Figure 1 Comparison of simplex and "firestorm" genomic profiles from patients with similar pathology profiles. DBC: died of breast cancer.

"firestorm index" (F) may be a useful prognostic measure of metastatic disease recurrence.

Contrast with Other Forms of Gene Amplification

Two distinct forms of gene or regional amplification have been known since 1970s. Independently segregating replicons carrying the dihyrofolate reductase gene (DHFR), known as ►"double minutes" (DMs), were described in 1978 by Alt and Schimke and coworkers in murine cells as a result of selection with methotrexate. At about the same time, chromosomal regions carrying tandem copies of a single cytoband (►Homogenously staining region or HSR) were identified in drug resistant lines and later in transformed cell lines and solid tumors In both cases, the interpretation was on amplification of a locus either to overcome drug resistance or, presumably, to advance the replication of a cancer cell.

Firestorms are similar to HSR in that the amplified regions are carried on chromosome arms rather than replicating independently as double minutes. The main distinctions with HSR were revealed through the detailed resolution available with microarray analysis of copy number revealing that firestorms exhibit multiple narrow peaks of amplification and that those amplifications are tightly coupled to deletions of the intervening regions (Fig. 2). Using the ROMA microarray technique on arrays containing 85,000 probes coupled with a breakpoint analysis algorithm it is possible to observe breakpoints in copy number at 50 kbp resolution and to distinguish separate amplifications and deletions spaced less than 100 kbp apart. Thus, HSR refers to a single locus amplified in tandem



Firestorm Pattern. Figure 2 Firestorm amplifications are associated with deletion of the non-amplified regions.

on a chromosome, while firestorm refers to multiple HSR like events on a single chromosome arm.

Figure 1 provides examples of the microarray genome profiles of six pseudo-diploid, node-negative breast tumor samples that contrast the simplex and firestorm types. The genomes are presented in chromosome order, left to right, and represent copy number relative to a standard male primary fibroblast line. The X and Y chromosomes on the right provide scale, the XX/X ratio showing as an increase (duplication) and the Y/0 ratio as a loss. Figure 1a shows typical simplex profiles, most often associated with good prognosis and

long-term survival. Figure 1b provides examples of firestorm profiles in tumors of similar histopathologic status. Irrespective of which chromosome suffers the firestorms there is a similar risk for recurrence, consistent with the common notion that there are multiple pathways toward metastasis.

Figure 2 provides a magnified view of a typical pseudo-diploid genome containing two firestorms along with expanded views of the two firestorms on chromosomes 11 and 19. The expanded views demonstrate the typical pattern in firestorms where multiple, narrow regions are amplified, and, concomitantly, the non-amplified regions are actually deleted. The combination of amplification and deletion has been validated by interphase FISH in all cases tested, revealing one normal chromosome arm and one completely rearranged chromosome arm that is made up of only the amplified regions as has been demonstrated in metaphase chromosomes from cell lines by Gisselsson and co-workers. Thus, firestorms not only result in the gain of up to thirty or more copies of certain loci, but also the loss of the intervening regions, the combination of which may provide both increase in oncogene activity and deletion of tumor suppressors in a single multi-step process.

Mechanism of Firestorm Formation

The genesis of firestorms is very likely through a combination of chromosome breakage and rejoining events of the type first described by Barbara McClintock, based on her cytogenetic observations in maize. She noted that unprotected chromosome ends were likely to fuse after replication creating either a dicentric chromosome or a "ring" chromosome, either of which result in a visible "anaphase bridge" between nuclei at the end of mitosis. These bridged chromosomes would break, either randomly or at preferred sites, resulting in another set of broken ends and a repeat of the process, which she named the breakage-fusion-bridge (BFB) cycle. Elements of this process have been historically been observed in tumor cells as ring chromosomes and other abnormalities and have been implicated in the generation of altered chromosomes visualized cytogenetically.

Breakage-fusion-bridge and related mechanisms such as break induced replication have the power to introduce both amplifications and deletions through repeated rounds of recombination and replication. One of many variations of the way such a mechanism could introduce firestorm patterns is shown in a highly simplified cartoon in Fig. 3. DNA breaks may occur anywhere in the genome, but degradation of telomeres is one way to generate such an unprotected end. Two broken ends may fuse, or a single end may invade its sister (or another chromosome) (Fig. 3a). If linked centromeres separate at nuclear division, the chromosome will eventually break and the daughter nuclei will obtain an unequal complement of loci, along with "invasive" broken ends (Fig. 3b). Subsequent rounds of invasion at random loci, fusion and breakage can lead to repeated amplification of multiple sites (Fig. 3c). Chromosome invasion can also result in pairing and unauthorized DNA replication leading to further amplification of regions near the recombination site (not shown in the figure). Finally, invasion of an unrelated chromosome, perhaps at repeated sequences, may lead to a translocation of the rearranged loci (Fig. 3d).

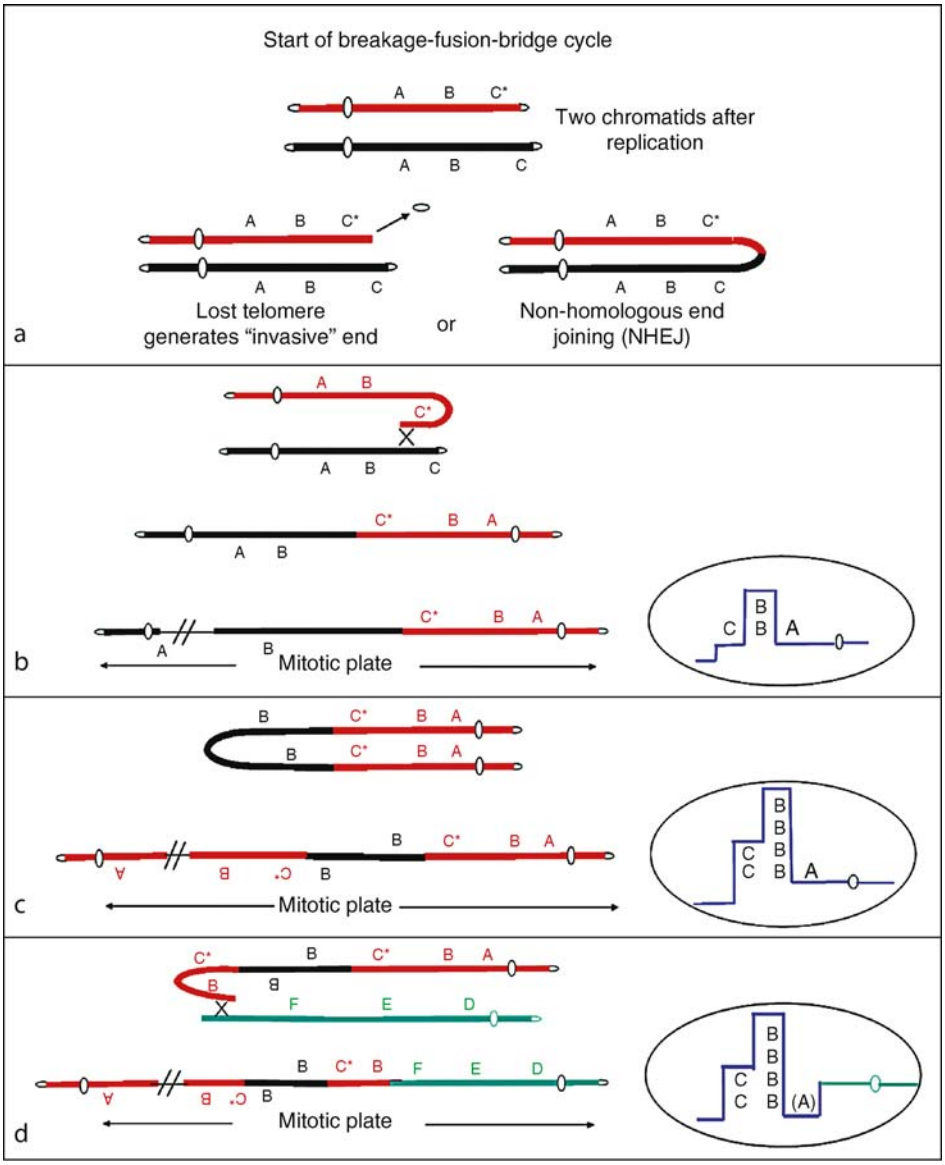
Relation of Patterns to Clinical Outcome

It has long been postulated that complexity of genome rearrangement could serve as a marker for malignant "progression." On first inspection, the highly rearranged "sawtooth" and "firestorm" patterns appeared to correlate with shorter survival in the diploid tumors, presumably due to selection of novel genetic combinations afforded the cancer cells by the opportunity for accelerated recombination. This was documented by developing a mathematical measure of complexity suitable for statistical analysis. Simply using the total number of segments, or events, as a measure does not clearly distinguish a sample with a single firestorm from the simplex pattern with a similar number of events, but the effects of the firestorm appeared by inspection to be much more deleterious to survival. Therefore a measure was chosen that would separate the firestorm patterns from the simplex patterns by scoring the close-packed spacing of the firestorm events, while at the same time incorporating the total number of events. The resulting sum of the reciprocals of the mean of lengths of all adjacent segment pairs ("Firestorm index" or F) accomplished this goal:

$$F = \sum_i \frac{2}{l_i^L + l_i^R} \qquad (1)$$

where i enumerates all the discontinuities with a magnitude above a numerical threshold of 0.1 in the segmented profile, and where $l_i^R (l_i^L)$ denotes the number of probes in the closest neighboring discontinuity on the right (left), or to a chromosome boundary, whichever is closer. The measure works equally well if absolute position in the genome is substituted for probe number. Using this algorithm the firestorm patterns achieve high F values even if only a single arm is affected because of the contribution of event proximity. It has been suggested that adding a factor for amplitude as well as spacing provides an even more effective measure (Anne-Lise Borressen-Dale, personal communication).

Preliminary analyses of a large diploid tumor collection indicated that prognoses in primary breast cancer, measured by the probability of overall survival, was correlated with the morphology of the gene copy



Firestorm Pattern. Figure 3 Example of a mechanism for firestorm formation using the breakage-fusion-bridge (BFB) cycle.

number signature as reflected in F value. Within the balanced group of the samples tested, the magnitude of the signature was independent of such established clinical markers as node status, histologic grade and primary tumor size. It is thus reasonable to expect that the firestorm signature will contribute to the prediction of outcome, perhaps in combination with other known factors.

A clear potential application of such a measure is in the determination of prognosis, with a focus on the identification of patients with such excellent prognoses that systemic therapy is not required or, conversely, such poor prognoses – in spite of clinical measurements that might be misleading in this regard – that systemic treatment is absolutely indicated. For example, a patient with a small, estrogen-receptor positive, node-negative primary breast cancer – all factors that usually indicate a good prognosis – might have an especially poor prognosis as predicted by F.

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First-echelon Node

►Sentinel Lymph Nodes

First-tier Node

►Sentinel Lymph Nodes

FISH

Definition

►Fluorescence in situ hybridization; molecular cytogenetic technique; fluorescently labeled small DNA or RNA probes are hybridized to chromosomes on interphase or metaphase spreads on slides; enables microscopic visualization of genes to define their number and chromosomal localization.

►Amplification
►Aneuploidy

FIT

►Fecal Immunochemical Test
►Fecal Occult Blood Test

Five Elements

Definition

The five elements (wood, fire, earth, metal, and water) concept is a philosophical theory developed in ancient China to explain the composition and phenomena of the physical universe. It is used in Chinese medicine to expound the unity between human and nature, as well as the physiological and pathological relationship and interconnection among the internal organs. The five elements match the five viscera, in which liver, heart, spleen, lung, and kidney correspond to wood, fire, earth, metal, and water respectively. The five elements concept explains the interpromoting and interacting relations, as well as the encroachment and violation in illness condition between the five viscera.

►Chinese versus Western Medicine

FK-506

Definition

Tacrolimus is a macrolide antibiotic. It reduces peptidyl-prolyl isomerase activity by binding to the immunophilin FKBP-12 (FK506 binding protein) creating a new complex. This FKBP12-FK506 complex inhibits both T-lymphocyte signal transduction and IL-2 transcription.

►Rapamycin

FKHL-16

►Forkhead Box M1

FLAME-1

►FLICE Inhibitory Protein

Flavin Monooxygenases

Definition

A family of microsomal ►flavoproteins (FMOs) that catalyze the oxidation of numerous drugs. They possess an NADPH and flavin binding site. The FMO system does not act to oxidize carbon atoms.

►Lead Optimization

Flavonoids

Definition

Are plant secondary metabolites with a diphenylpropane-containing structure. Flavonoids are normal constituents of the diet, as they are present in many fruits, vegetables and beverages. Numerous preclinical studies have shown that flavonoids have anticancer properties, yet some studies have revealed that high doses of some flavonoids can produce carcinogenic effects.

►Resveratrol
►Polyphenols
►Thioredoxin System

Flavopiridol

Definition

Is an experimental drug, derived from a medicinal plant from India, that has been used for centuries in many indigenous medicines. Is a ►cyclin-dependent kinase (cdk) inhibitor, can cause cell cycle arrest, induce apoptosis in cancer cells, and inhibit tumor cell growth in vivo.

Fli1-1

Definition

Friend leukemia virus integration site 1: gene on chromosome 11 encoding for an Ets transcription factor; rearranged with EWS in 85% of ►Ewing sarcoma family tumors.

►Ets Transcription Factors

FLICE

►Caspase-8
►FLICE inhibitory protein

FLICE Inhibitory Protein

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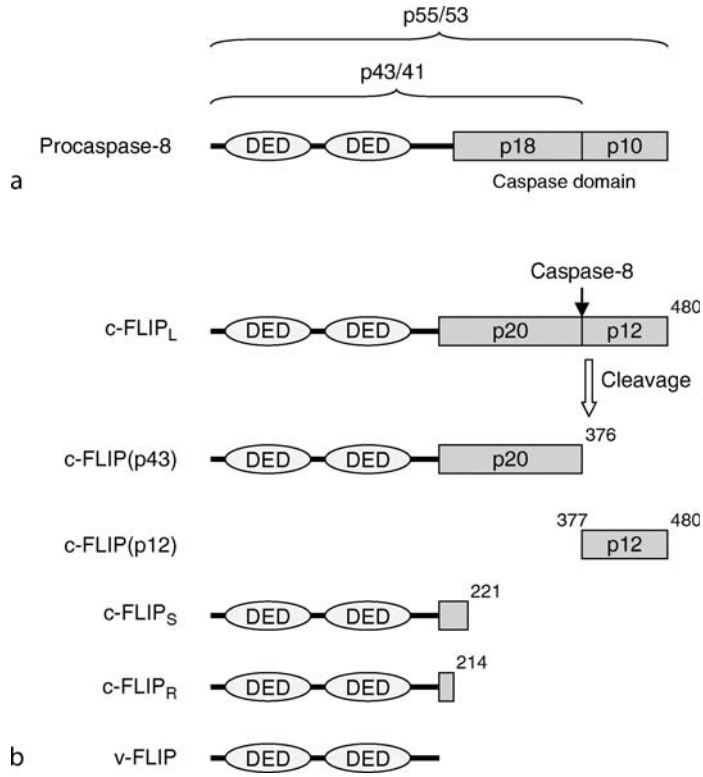
Synonyms

Caspase-eight-related protein; CASPER; Caspase homologue; CASH; Caspase-like apoptosis-regulatory protein; CLARP; Inhibitor of FLICE; I-FLICE; Fas-associated death domain; FADD-like antiapoptotic molecule 1; FLAME-1; MACH-related inducer of toxicity; MRIT

Definition

Human cellular FLICE inhibitory protein (c-FLIP) gene shares sequence homology with ►FADD, procaspase-8 and procaspase-10 and is located on chromosome 2q33–34. c-FLIP has eleven splice variants at the mRNA level. Two of these ►splice variants are considered major splicing variants detectable at the protein level in various types of cells and have been extensively studied thus far. One splice variant is designated the long isoform of c-FLIP (c-FLIP$_L$), which is a 55 kDa protein consisting of 480 amino acids, and the other major splice variant is the short isoform of c-FLIP (c-FLIP$_S$), which is a 26 kDa protein consisting of 221 amino acids. The third form of c-FLIP, designated c-FLIP$_R$, which is a 23 kDa protein consisting of 214 amino acids, is primarily expressed in T and B cells. Both c-FLIP$_S$ and c-FLIP$_R$ contain two ►DEDs, whereas c-FLIP$_L$, has two DEDs and a catalytically inactive caspase-like domain and thus shows overall homology with procaspase-8. c-FLIP$_L$ can be processed at Asp376 by caspase-8, yielding the N-terminal 43 kDa and C-terminal 12 kDa fragments which are termed c-FLIP(p43) and c-FLIP(p12), respectively (Fig. 1).

Some viruses such as herpesvirus saimiri, human herpesvirus 8 and moluscum contagiosum virus also produce DED-containing proteins, which are called viral FLICE-inhibitory protein (v-FLIP). Similar to c-FLIP$_S$, v-FLIP consists of two DEDs (Fig. 1).



FLICE Inhibitory Protein. Figure 1 Structures of procaspase-8 (a) and c-FLIP (b). Two major splice variants of c-FLIP, c-FLIP$_L$ and c-FLIP$_S$, have been extensively studied at the protein level. c-FLIP$_R$ and v-FLIP function in a similar manner to c-FLIP$_S$. c-FLIP$_L$ is processed by caspase-8 at Asp376, generating the N-terminal fragment c-FLIP (p43) and the C-terminal fragment c-FLIP (p12).

Characteristics

Function

c-FLIP primarily functions as a specific inhibitor of ►death receptor-mediated ►apoptosis. c-FLIP proteins can be recruited to the ►DISC by DED interaction. Both short forms of c-FLIP isoforms, c-FLIP$_S$ and c-FLIP$_R$, block death receptor-induced apoptosis by inhibiting procaspase-8 activation at the DISC. The role of c-FLIP$_L$ at the DISC is controversial. Some reports demonstrate that c-FLIP$_L$ functions as an anti-apoptotic protein in a way similar to c-FLIP$_S$, whereas others describe that c-FLIP$_L$ acts as a proapoptotic molecule in certain cellular contexts to facilitate the activation of procaspase-8 at the DISC. Endogenous c-FLIP$_L$ functions primarily as an inhibitor of death receptor-mediated apoptosis because ►siRNA-mediated knockdown of c-FLIP$_L$ augmented DISC recruitment, activation, processing, release of caspase-8, and apoptosis in several ►cancer cell lines. In general, c-FLIP$_S$ completely inhibits cleavage of procaspase-8 by preventing the initial cleavage step of procaspase-8 between the p18 and p10 subunit of the caspase homology domain, whereas c-FLIP$_L$ allows the first cleavage of procaspase-8 into caspase-8 (p43/41) but prevents the final cleavage between the prodomain and the p18 subunit of the p43/41 intermediate to generate active caspase-8 (Fig. 1). v-FLIP can function in a similar way to c-FLIPs to bind to the DISC and inhibit death receptor-induced apoptosis.

Besides inhibition of apoptosis, c-FLIP modulates the activity of ►nuclear factor-κB (NF-κB), ►MAP kinase and ►Wnt signaling pathways, suggesting that c-FLIP may play a critical role in many cellular activities. c-FLIP plays an essential role in heart development since disruption of mouse c-FLIP is prenatally lethal probably due to cardiac failure, resembling the phenotype of caspase $8^{-/-}$ and $FADD^{-/-}$ mice.

Modulation of c-FLIP Level

c-FLIPs are short-lived proteins subjected to ubiquitin (►ubiquitination)/proteasome (►protease)-mediated degradation. Many anticancer agents modulate c-FLIP levels through such a mechanism. However, the underlying mechanism including ►E3 ubiquitin ligases responsible for c-FLIP ubiquitination has not been fully elucidated. A recent study has demonstrated that N-terminal c-Jun kinase (JNK)-dependent phosphorylation and activation of the E3 ubiquitin-protein ligase ►Itch specifically ubiquitinates c-FLIP$_L$ and induces its proteasomal degradation.

In addition to the posttranslational modification, c-FLIP expression can be regulated at the transcriptional level. In this regard, the MAP kinase, PI3 kinase (►PI3K signaling)/Akt, NF-κB, p53 (►p53 protein, biological and clinical aspects) and c-Myc (►Myc oncogene) and JAK/STAT pathways have been suggested to be involved in regulation of c-FLIP expression. c-Myc directly represses c-FLIP transcription while other pathways such as PI3 kinase/Akt, NF-κB and p53 increase c-FLIP transcription. Thus, activation of c-Myc sensitizes cancer cells to death receptor-induced apoptosis.

Role in Carcinogenesis

c-FLIP is expressed abundantly in some tissues, such as heart, skeletal muscle and lymphoid tissues. However, c-FLIP is also expressed in a broad spectrum of normal cells such as endothelial cells, keratinocytes, motoneurons, muscle cells, pancreatic cells, dendritic cells and macrophages, suggesting that c-FLIP is an important regulator of many physiologic processes. Accordingly, dysregulation of c-FLIP might lead to development of many diseases including cancer. c-FLIP is up-regulated in many human tumor cells, including colon, gastric, hepatocellular, ovarian, endometrial carcinoma cells, melanoma, leukemia, and Hodgkin lymphoma cells. Increased c-FLIP/►caspase-8 ratio in ►Epstein-Barr virus-transformed cells results in resistance to death receptor-induced apoptosis. High c-FLIP protein expression is associated with a poor clinical outcome in Burkitt lymphoma. Moreover, transfection of c-FLIP into cancer cells promotes cancer ►metastasis. Thus, elevated c-FLIP levels in tumor tissues may allow tumor cells to escape from the death receptor-mediated apoptotic death. Some studies have shown that c-FLIP is involved in mediating the immune escape of tumors *in vivo*.

The Wnt signaling pathway is involved in ►carcinogenesis as mutations in Wnt signaling are associated with many human cancers. It has been shown that c-FLIP$_L$, together with FADD, boosts the Wnt-signaling pathway through inhibiting β-catenin ubiquitination and proteasomal degradation, thereby contributing to carcinogenesis.

Implications in Cancer Therapy

c-FLIP might be a promising target for cancer therapy. In general, c-FLIP expression correlates with resistance against death receptor-induced apoptosis in a variety of cancer types and c-FLIP-transfected cancer cell lines develop more aggressive tumors *in vivo*. Conversely, downregulation of c-FLIP by antisense oligonucleotides (►antisense DNA therapy), siRNA, or ►small molecule drugs sensitize cells to death receptor-mediated apoptosis. Some small molecule drugs with anticancer activity including DNA-damaging agents, ►histone deacetylase (HDAC) inhibitors, COX-2 (►cyclooxygenase in colorectal cancer) inhibitors, and PPARγ (►peroxisome proliferator-activated receptor and cancer) agonists reduce c-FLIP levels in cancer cells. Given that the death ligand ►TRAIL and agonistic anti-TRAIL receptor DR4 and DR5 antibodies (►TRAIL receptor antibodies) are being tested in clinical trials for treatment of cancer, inhibition of c-FLIP expression in cancer cells is of particular importance for TRAIL- or TRAIL receptor-based cancer therapies. Anticancer agents with c-FLIP-inhibitory activity will greatly sensitize cancer cells to TRAIL- or TRAIL receptor-based cancer therapies.

Recent studies have shown that overexpression of c-FLIP also protects cancer cells from apoptosis induced by certain anticancer drugs including chemotherapeutic agents (►chemotherapy of cancer, progress and perspectives) and the COX-2 inhibitor ►celecoxib. In agreement, siRNA-mediated knockdown of c-FLIP sensitizes cancer cells to apoptosis induced by chemotherapeutic drugs including ►cisplatin, 5-fluorouracil (►fluorouracil) and ►taxol. Thus c-FLIP may also play an important role in mediating cell resistance to chemotherapy.

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Flow Cytometry

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Definition

FCM; Is a method for counting, analyzing and sorting particles e.g. cells in a single cell suspension by their light absorbing or fluorescing properties. Flow

cytometry permits assessment of physical (cell size, shape and internal complexity), chemical (expression of proteins and other molecules) and biological (metabolic pathways e.g. calcium ion flux) attributes of single cells in suspension. (►FACS)

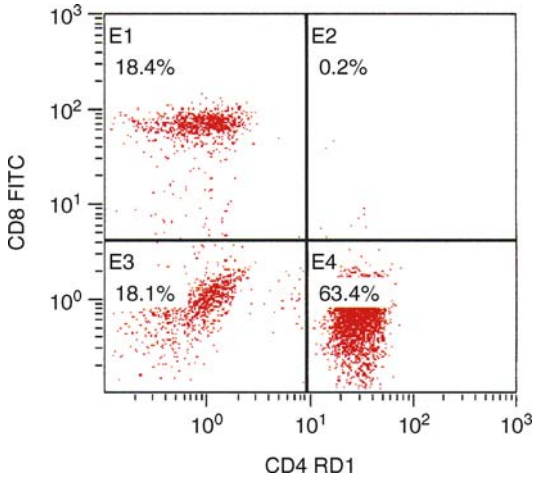
Characteristics

1. The Technology
2. Applications in cancer

The Technology

There are three essential components of a flow cytometer, fluidics, optics and electronics. *Fluidics:* A single cell suspension in a highly controlled fluid stream is forced through a nozzle to induced laminar flow at a high flow rate (meters/sec). A higher-pressure sheath fluid stream surrounds the sample in isotonic fluid and the cells are examined (interrogated) at a point by the excitation light, usually a laser beam. *Optics:* A laser light source generates a monochromatic light beam that passes through the sample stream and gets scattered when it encounters a cell. A simple light scatter plot can identify cells based upon their size, shape and internal complexity. If ►fluorochromes are attached to the cells (either by direct labeling or through conjugated monoclonal antibodies), these absorb the laser light and re-emit a light of longer wavelength (specific to each fluorochrome). Multiple wavelengths can be collected and analyzed at the same time (multicolor analysis). Minimal overlap between generated wavelengths is established prior to collection of the light by a system of filters and dichroic mirrors and later by electronic compensation. ►Epitope density is a major determinant of fluorochromes to be used for conjugating antibodies e.g. low density epitopes can be detected by antibodies bound to phycoerythrin (PE) and high density epitopes would be easily detectable by fluorescein isothiocyanate (FITC). *Electronics:* The light is then collected by photomultiplier tubes and converted into analog electric signals, either in log or linear domains followed by digitization of the signals. Attribution of all the signals associated with a specific cell permits multiparameter analysis. The digital data is collected in a list mode format usually since this allows for complicated analysis and the data can be processed many times. The computer analysis of the data can be performed either by stand-alone software packages or on-line systems with file transfer abilities.

Selection of a subpopulation for further analysis is called gating and can be performed at multiple time-points e.g. live gating- selecting the population at the time of data collection, analysis gating – after the data has been collected in the list mode; other gating strategies include forward and back gating. The data are displayed in graphic formats including histograms, dot plots, contour plots or isometric plots (Fig. 1). Analysis



Flow Cytometry. Figure 1 A dot plot display of two parameters (CD4 and CD8 ►antigens) from a patient with a lymphoproliferative disorder permitting assessment of the expression pattern and the number of positive and negative cells for each ►antigen as well as any co-expression, if present.

of the data requires careful interpretation of the generated histograms and determining an overall pattern of expression of multiple ►antigens. Assessing negative or positive expression of an antigen and viewing co-expression as color-coded histograms requires some basic understanding of binary logic and Boolean gating. Proper instrument setup, calibration, and compensation along with use of appropriate external and internal controls are necessary for misinterpretation of findings.

Flow sorters allow physical separation (sorting) of cells with up to 99% purity for any additional studies such as molecular or functional assays. A comprehensive quality assurance and quality control program has to be established for pre-analytic, analytic and post-analytic stages.

Specimen Issues. Peripheral blood, tumor masses (fine needle aspirates, core biopsies, and incision or excision biopsies) and bone marrow and various body fluids are common specimens analyzed by FCM. Fresh samples are preferred to obtain the cellular population for further analysis, although paraffin embedded tissues have also been analyzed successfully by flow cytometry. An assessment of representative morphology and viability of the single cell suspension allows for a more meaningful interpretation of flow data e.g. by ensuring that the critical tumor cell population has not been lost due to cellular fragility. Dead cells can non-specifically bind antibodies and affect data interpretation.

Applications

Flow cytometry provides an objective measure of multiple attributes of single cells at a great speed

(thousands of cells per second) allowing determination of not only average characteristics of a tumor's cellular population but tumor cell heterogeneity as well. In addition to size, shape and internal complexity determination, Fluorochromes can be used either to directly label molecules inside a cell (e.g. DNA, RNA, thiols) or label monoclonal antibodies directed against specific cell surface or intracellular proteins/molecules. FCM also permits functional assessment e.g. viability, oxidative burst, mitochondrial membrane potential, cell activation using intracellular calcium ion flux, DNA synthesis and cell cycle phase analysis and apoptosis etc. Green fluorescent protein labeling can be used as a gene reporter.

The applications of flow cytometry in cancer include; (i) ►Immunophenotyping of ►hematologic malignancies for diagnosis and prognosis and monitoring ►Residual Disease, (ii) Organ transplantation support, (iii) DNA analysis of S-phase fraction of solid tumors and (iv) determining treatment efficacy.

Immunophenotyping (IP)

Immunophenotypic patterns of cells correspond to different stages of differentiation and function and complement morphologic assessment of tumor cells for correct diagnosis. IP is essential for initial diagnosis and classification, determining certain prognostic variables (e.g. cytokine receptors, multidrug resistance), identifying potential treatment targets and post-treatment follow-up including minimal residual disease assessment.

For lymphoid lesions the FCM provides lineage information (B vs. T-lymphoid) by using antibodies against pan-B antigens (e.g. CD19, ►CD20, CD22) and pan-T antigens (e.g. ►CD3, CD5, CD7). FCM provides information on whether a population is likely to be neoplastic or not. This latter aspect is determined by identifying light chain restriction (clonality) for B-cells and detecting antigen deletion, subset expansion, or aberrant antigen expression for T-cells. Once a population is determined to be neoplastic identifying a relatively unique pattern of antigen expression can be used either to make the diagnosis or complement the diagnostic process by integrating the information with other diagnostic data e.g. morphology and genetics. For lymphoid neoplasms composed of smaller lymphoid cells, immunophenotyping is often considered the gold standard for diagnosis. Expression of certain antigens is related to prognosis e.g. ZAP-70 in ►chronic lymphocytic leukemia and this is optimally measured by FCM.

For ►acute myeloid leukemias, FCM is used in a similar fashion to determine the expression of "immature" (e.g. CD34, TdT, CD117, HLA-DR), "differentiation-related" antigens e.g. CD11b for acute leukemias with monocytic differentiation and "lineage-related" antigens e.g. CD41 and CD61 for megakaryocytic leukemias. The role of FCM in acute leukemia diagnosis includes, a) distinguish acute myeloid from acute lymphoid leukemia, b) correlation with other diagnostic findings such as morphology and genetics, c) recognition of acute biphenotypic subtype and d) prognostic value of antigen expression (e.g. CD7 in AML confers poor prognosis). FCM is also useful in the diagnosis of ►myelodysplastic syndromes e.g. by demonstrating abnormal antigen pattern of myeloid, erythroid and megakaryocytic antigens and accurate blast quantitation.

The presence of antigens on tumor cells is useful in instituting targeted therapy e.g. ►rituximab for CD20+ B-cell lymphomas, alemtuzumab for CD52 expressing chronic lymphocytic leukemia.

The immunophenotype is also useful in follow-up of patients in order to assess residual disease, recurrence and progression/transformation. FCM is extremely useful in differentiating leukemic blasts and hematogones (reactive B-cell precursors), a critical distinction in follow-up marrows of children with B-lineage acute lymphoblastic leukemia. FCM by virtue of its specificity, sensitivity, reliability and established standardization is useful in identifying smaller populations of tumor cells in post treatment specimens, which are below the detection limit of conventional methods (minimal residual disease-MRD); the clinical significance of MRD is established for certain malignancies e.g. childhood acute lymphoblastic leukemia and is being evaluated for others. For follow-up of myeloma patients, abnormal plasma cells (CD19−, CD56+) can be assessed in bone marrow samples, although this technique is somewhat limited by sampling error due to focal distribution of plasma cell clusters.

FCM is not without its limitations. Interpretive errors may be caused by antigens are not always being lineage restricted, non-classic immunophenotypic profile of a tumor, sampling issues (e.g. non-representation of an abnormal plasma cell clusters in the bone marrow aspirate). A better way to interpret the data is not only pay attention to the numbers of cells positive or negative but also the pattern of antigen expression and the composite profile of expression of multiple antigens. The best was is to determine the pattern of antigen expression rather relying on one antigen alone. In expert hands the method is reliable, objective and fast.

Transplant Support

Assessing the numbers and purity of CD34+ stem cells is necessary for stem cell transplant patients since the number of viable CD34+ cells is a crucial factor determining rapid and long-term multilineage engraftment. FCM on ►apheresis products, cord blood or bone marrow ensures adequate numbers of CD34+ cells are present. Harvest products can also be assessed for

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contamination by tumor cells. Other roles of FCM include, assessment of immune reconstitution by determining numbers of B, T and NK cells and their subsets, graft rejection, graft versus host disease and graft versus leukemia effect. FCM is a highly sensitive technique for pre-transplant ►cross matching, HLA ►antibody screening and monitoring post-transplant antibody levels for solid organ transplantation patients.

DNA Ploidy and S Phase Fraction

DNA content of cells can be determined by determining ►fluorescence intensity of DNA binding dyes such as propidium iodide (PI); three populations G0/G1, S and G2/M are easily discernible. FCM is useful when material cannot be obtained for karyotyping, however, it cannot detect balanced translocations and partial chromosome deletions. Since the measurement is that of total DNA content, rather than actual chromosome numbers, the results are in reference to a normal "diploid" population. The DNA histogram plots fluorescence intensity (x-axis) versus the number of cells (y-axis). A majority of the malignancies have an abnormal DNA content (other than diploid) and aneuploid tumors generally have a bad prognosis with a few exceptions. ►S phase fraction: The proportion of cells in S phase – an estimate of the tumor's proliferative activity- can be determined either by PI labeling or by using a dot plot of anti-bromodeoxyuridine and propidium iodide. S phase fraction generally correlates with increasing DNA amount in tumor cells and the grade of tumors e.g. in lymphomas and a higher S phase fraction is generally considered an adverse prognostic variable. Enthusiasm for DNA ►ploidy and S phase fraction determination in routine oncologic practice has been somewhat limited in view of the technological variations and prognostic and predictive information available from other parameters. Improvement and standardization in methodology may lead to enhanced use of DNA ploidy data by FCM in routine clinical practice. Flow karyotyping refers to the use of FCM to analyze or separate chromosomes on the basis of their DNA content.

Determining Treatment Efficacy

The in vitro prediction of cellular sensitivity to treatment can be assessed by FCM by microdrop encapsulation assay and BrDU incorporation proliferative survival assay. Development of treatment protocols may also take into FCM determination of apoptosis.

Newer and Future Applications

Detection of rare circulating tumor cells and circulating endothelial cells may help in assessing tumor progression and response to treatment, however this application with great potential, at present, is not applicable in routine clinical practice, mainly due to technical issues. Cellular RNA content may be useful for the discrimination of acute leukemias and ►multiple myeloma. As the notion of personalized medicine gets further impetus identification antigens against which treatment can be directed will increase in clinical practice. Biological microbeads are useful for flow cytometric immunoassays.

A relatively recent development has been exploitation of a hybrid technology between flow cytometry and image cytometry, the laser scanning cytometry, to quantify fluorescence intensity of individual cells on glass slides. From a dot plot display populations can be selected and the cells that generated the data can be relocated and then visualized with either bright field or epifluorescence microscopy.

The future of flow cytometry appears to be bright. Technological advances will continue to positively impact the use of FCM. Semiconductor quantum dots (Qdots) are likely to be used as fluorophores in view of their exceptional brightness and large Stokes shifts. Multicolor analysis is likely to expand to use additional colors. Photothermal flow cytometry can be used for detection of label-free detection of cells. Rare event detection including identification of single cells is likely to improve with the use of additional approaches to spectral analysis such as Raman spectroscopy and fluorescence resonance energy transfer measurements.

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FLT

Definition

^{18}F-Fluorothymidine; Radionucleoside that accumulates predominantly in proliferating tissues and can therefore be used for non-invasive imaging of proliferation with Positron Emission Tomography (PET).

►Positron Emission Tomography

Fludarabine

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Synonyms

9-β-D-Arabinosyl-2-fluoroadenine (F-ara-A) monophosphate; FAMP; NSC-312887; Fludarabine phosphate

Definition

Is the ►prodrug of 9-β-D-arabinosyl-2-fluoroadenine (F-ara-A), a synthetic halogen-substituted analogue of deoxyadenosine. Fludarabine and the two other related compounds ►cladribine (2-chloro-2′-deoxyadenosine) and ►pentostatin (2′-deoxycoformycin) are collectively referred to as ►purine analogues, although pentostatin is not actually an analogue, but an inhibitor of ►adenosine deaminase. Fludarabine is widely used in the treatment of indolent lymphoproliferative malignancies, ►acute myeloid leukemia, and as a part of the conditioning regimen for ►non-myeloablative allogeneic stem-cell transplantation.

Characteristics

Clinical and Cellular Pharmacology

The development of fludarabine stemmed from the success of the cytosine analogue ►cytarabine (ara-C) in the treatment of acute myeloid leukemia. A similar adenine analogue, Ara-A (vidarabine), was a successful anti-viral agent that had limited anti-cancer activity due to its rapid clearance by adenosine deaminase. Subsequent structural modifications by Montgomery and Hewson resulted in the development of 9-β-D-arabinosyl-2-fluoroadenine (F-ara-A), an adenosine deaminase-resistant derivative of ara-A. Because F-ara-A is poorly soluble, its 5′-monophosphate prodrug – designated fludarabine – was synthesized as the preferred compound for clinical development. *In-vivo*, fludarabine is rapidly and reliably dephosphorylated to F-ara-A, which is then taken up into cells and phosphorylated to its triphosphate (F-ara-ATP), the active compound mediating the anti-neoplastic properties of fludarabine (Fig. 1). The rate limiting step in this conversion process is the phosphorylation of F-ara-A to its monophosphate (F-ara-MP) by ►deoxycytidine kinase.

The current standard dose and administration of fludarabine is 25–30 mg/m^2 via a short infusion (15–30 min); this is substantially lower than the potentially neurotoxic doses used in the initial phase I trials of fludarabine in advanced malignancies, which was up to 260 mg/m^2 over 2–5 min. Pharmacokinetic data of F-ara-A from this phase I study showed a volume of distribution of 44.2 L/m^2, clearance of 4.08 L/h/m^2 and a triphasic elimination phase comprising a rapid distribution phase (5 min) followed by an intermediate elimination phase (1–2 h) and a prolonged terminal elimination phase (10–30 h). Similar kinetics were observed after the typical 30 min infusion. F-ara-A elimination is predominantly renal, with approximately 60% of a bolus recovered in the urine within 24 h. Dose modification for impaired renal function is required.

In circulating leukemic cells, peak F-ara-ATP concentrations are reached at about 4 h after the start of fludarabine infusion. There is considerable inter-individual variation in F-ara-ATP elimination: in patients with ►chronic lymphocytic leukemia (CLL), the intracellular F-ara-ATP half-life ranged from a few hours to several days with a median of 15 h. Based on this data, daily administration schedules are commonly employed in clinical practice.

New oral preparations of fludarabine are available. Their bioavailability range between 55% (tablets) to 75% (liquid).

Mechanisms of Anti-Cancer Activity

The main elements of fludarabine action are illustrated in Fig. 1. Most classical anti-metabolite agents, such as cytarabine, are most active against rapidly dividing cells, where they are readily incorporated into newly synthesized DNA and cause chain termination. The initial expectation was that a similar mechanism of action would apply to fludarabine, and therefore the initial phase I-II trial was conducted in patients with acute myeloid leukemia or ►acute lymphocytic leukemia, diseases with rapidly proliferating cell populations. Although fludarabine showed some anti-leukemic activity, the doses explored (up to 150mg/m^2/day) were associated with prohibitive delayed neurotoxicity including cortical blindness and coma. Later, fludarabine was tested in patients with CLL at substantially lower doses (20–30 mg/m^2/day). CLL was traditionally considered be a disease of slowly proliferating, long-lived leukemic cells, and it was therefore somewhat unexpected when fludarabine, an anti-metabolite agent, was found to be highly effective. This clinical observation led to extensive re-consideration of possible mechanisms accounting for fludarabine activity in non-dividing cells, summarized in Fig. 1. Currently the dominant mechanism of fludarabine in indolent lymphoproliferative disorders is unknown. It is likely that most of the indolent lymphoproliferative disorders, including CLL, are more proliferative than initially thought. There is also evidence to suggest that quiescent lymphocytes are continually breaking and rejoining their DNA, and F-ara-ATP may inhibit DNA repair in this situation.

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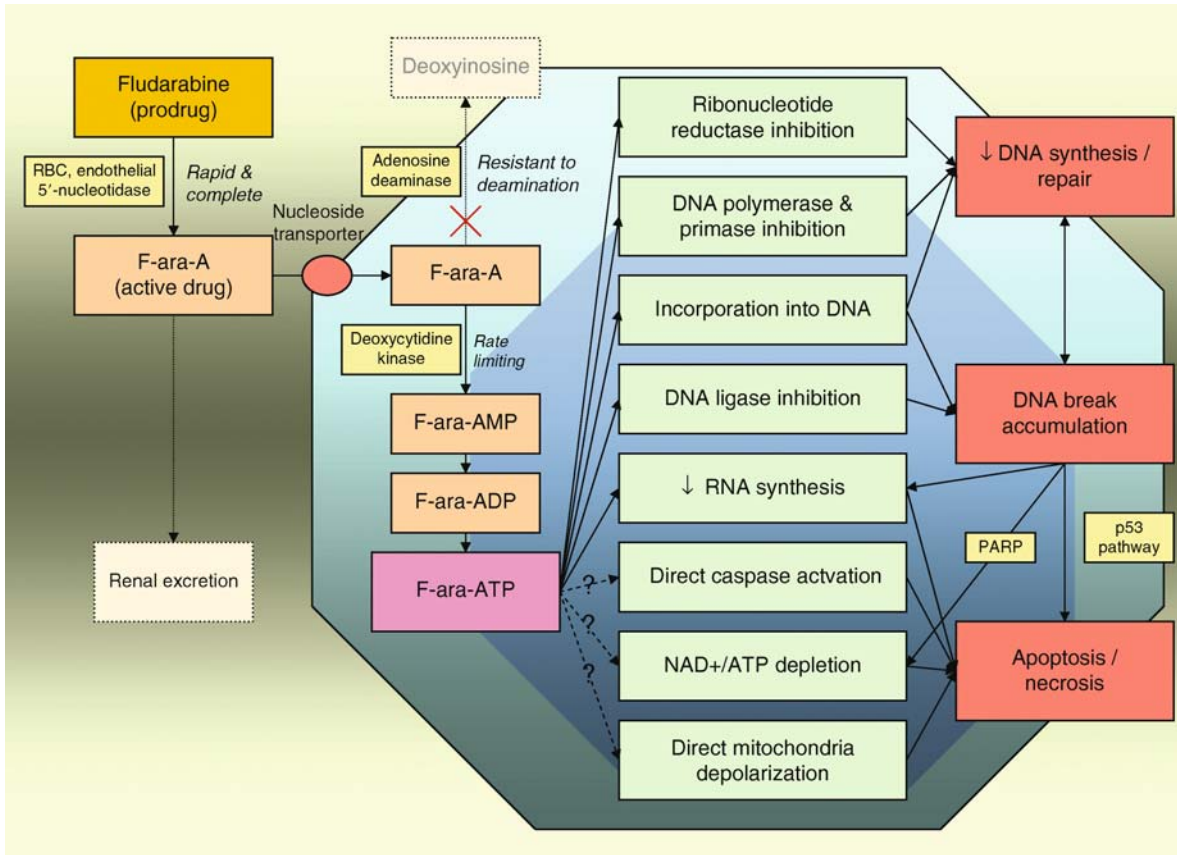

Fludarabine. Figure 1 Major components of Fludarabine metabolism and action. Differential toxicity in leukemia cells may be due to relative abundance of the high-affinity nucleoside transporter, efficient phosphorylation of nucleosides to triphosphate, and increased DNA turnover in tumour cells.

Lastly, it is possible that intracellular accumulation of dATP or its analogues (such as F-ara-ATP) activate ►apoptotic pathways directly without the requirement for DNA damage.

There is mounting clinical evidence that *in-vivo* activity of fludarabine depends strongly on the presence of an intact ►p53 pathway. Patients with mutation and/or deletion of the p53 gene respond less well to fludarabine, and any responses achieved are associated with substantially shorter remissions. ►Microarray experiments have shown that *in-vivo* exposure to fludarabine results in activation of genes associated with the p53 pathway.

Clinical Applications

Fludarabine is primarily used in the treatment of indolent lymphoid malignancies, particularly CLL. In CLL, three large randomized trials have established fludarabine as being the most active single agent, achieving more complete remissions and longer responses than ►chlorambucil or alkylator-based combination regimens. Subsequent *in-vitro* studies showed that the combinination of fludarabine and ►cyclophosphamide was synergistic, primarily due to fludarabine inhibition of the repair of cyclophosphamide-induced DNA damage. Translation of this combination of fludarabine and cyclophosphamide (FC) into the clinic has confirmed this preclinical synergy, with FC established as being more effective than fludarabine in three large randomized trials. More recently, the addition of ►rituximab (a monoclonal antibody directed against the CD20 molecule expressed on the majority of indolent lymphoid malignancies) to FC has resulted in a regimen capable of achieving complete response in 70% of patients treated.

Based on the favorable experience with CLL, fludarabine was also tested in patients with other indolent lymphoproliferative maligancies, particularly ►follicular lymphoma and related ►non-Hodgkin lymphomas. In follicular lymphoma, the combination of fludarabine and ►mitoxantrone achieves superior CR rates and remission durations to ►CHOP, an alkylator-based combination commonly employed in patients with histologically aggressive lymphomas.

Analogous to the experience with CLL, combinations with rituximab are being explored in patients with indolent B-lymphomas with promising activity.

In acute myeloid leukemia, fludarabine has inadequate activity at the maximally tolerated dose to be clinically useful as a single agent. However, Gandhi and Plunkett showed through a series of elegant pre-clinical and translational pharmacologic studies that exposure to fludarabine may increase the effectiveness of cytarabine (ara-C), the most important agent in acute myeloid leukemia therapy. Ara-C is converted to its active metabolite, ara-CTP, in leukemic blasts with the rate-limiting step being conversion to ara-CMP by deoxycytidine kinase. A major cellular target of F-ara-ATP is ►ribonucleotide reductase, a critical enzyme for sustaining intracellular levels of dNTPs, and reduction in intracellular dCTP may reduce the negative feedback on deoxycytidine kinase. Indeed, clinical studies have shown that exposure to fludarabine significantly increases leukemic blast accumulation of ara-CTP following administration of cytarabine. The combination of fludarabine and cytarabine is currently being explored in patients with acute myeloid leukemias associated with the t(8;21) or inversion 16 chromosomal abnormalities, the subtypes where dose-intensity of cytarabine are most crucial.

One of the side effects of fludarabine is lymphocyte depletion and associated predisposition to ►opportunistic infections. Indeed, CD4 and CD8 T-cells may be suppressed for 12 months or more following therapy with fludarabine. This immunosuppressive effect of fludarabine has been successfully exploited in allogeneic stem cell transplantation. Traditionally, large ("myeloablative") doses of chemotherapy ►myeloablative megatherapy and/or radiation were required in stem cell transplantation to suppress host immunity sufficiently to prevent graft rejection; such conditioning regimens are highly toxic, and limit the applicability of stem cell transplantation to younger and fitter patients. New approaches to stem cell transplantation using less intensive regimens ("non-myeloablative" conditioning) incorporate fludarabine with ►cyclophosphamide and/or other agents to achieve similar degrees of transient immunosuppression required for successful engraftment, with substantially less toxicity.

The major side-effect of fludarabine at currently clinically used doses (25 – 30 mg/m^2/day) is ►myelosuppression and pre-disposition to infection. Delayed neurotoxicity due to diffuse widespread demyelination, previously a major problem seen in early trials employing high doses of fludarabine (>100 mg/m^2 bolus, or >40 mg/m^2/day continuous infusion), is not encountered at currently used doses. In addition to infections resulting from neutropenia, the use of fludarabine has been associated with a number of "atypical" infections including *Pneumocystis jiroveci* (PCP) pneumonia, systemic listeriosis and reactivation of herpes family viruses. These are commonly attributed to the CD4 lymphopenia caused by fludarabine, but concurrent ►corticosteroid exposure and the effects of previous chemotherapy are also contributory, as these infections are very rarely seen with single-agent fludarabine.

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Fludarabine Phosphate

►Fludarabine

Fluid Phase Endocytosis

►Endocytosis

Fluorescein Angiography

Definition

Technique involving the systemic injection of sodium fluorescein which allow for the evaluation of the retinal circulation and provides further information on disorders of the choroid, retina, retinal pigment epithelium, and the optic nerve. The fluorescence pattern including staining, leakage, blockage, and pooling provide characteristic patterns that allow for diagnosis and monitoring of multiple disease conditions.

►Uveal Melanoma

Fluorescence

Definition

Fluorescence is secondary photon emission by molecules, which are excited to an energetically higher state

by primary photons. The emission of electromagnetic radiation by a substance, especially of visible light, by the absorption of incident radiation and persisting only as long as the stimulating radiation is continued.

►Photodynamic Therapy
►Flow Cytometry

Fluorescence Cystoscopy

Definition

A type of photodynamic diagnosis that uses endoscopy to investigate the urinary bladder via the urethra.

►Hypericin

Fluorescence Diagnostics

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Synonyms

Tissue spectroscopy; Laser-induced fluorescence diagnosis LIFD; Photodynamic diagnostics

Definition

Fluorescence diagnostics are procedures designed to detect neoplastic tissues based upon spectroscopic recognition of tissue-specific accumulations of natural or artificial fluorescing molecules (fluorophores).

Characteristics

Certain fluorescing dyes selectively accumulate in cancer cells and may, since fluorescing molecules are very rare in the biological environment, serve for sensitive detection of early cancerous lesions in human tissues without interfering with tissue integrity. Some of the dyes used for ►photodynamic therapy present a strong fluorescence, and since they localize to malignant tumors, early attempts were made to use these dyes for tumor diagnosis. Polyporphimer sodium (Photofrin®), for example, is a more effective purified fraction of the classical hematoporphyrinderivate (HpD), which has now obtained clinical approval for various indications in several countries. Polyporphimer sodium has to be applied intravenously and reaches a peak tumor:normal-tissue ratio 48–72 h after injection. The possible wavelengths for stimulation are 405 nm (Soret), 505, 525, 565, and 630 nm (Q-bands). The main advantage of this substance lies in the large clinical experience with its use for Photodynamic Therapy. The disadvantages are a long-lasting ►photosensitivity of the skin, still unsatisfactory tumor selectivity, and the relatively unfavorable longer activation wavelength of 630 nm. New dyes have entered the field, one of which is ►5-aminolevulinic acid (►ALA). This substance is unique in the group of photodiagnostic agents, since it is not fluorescent by itself and has to be transformed by a cellular enzymatic reaction to the natural cellular fluorophore protoporphyrin IX. Since ALA can be absorbed after topical application, it is possible to locally apply by endoscopic spraying. The fast photobleaching kinetics of ALA is a disadvantage, however, this substance has actually gained importance as a photodiagnostic drug.

The autofluorescence features of certain tumors may also allow sensitive detection of early cancers. Background subtracting technology has contributed to sensitivity and specificity of point measuring and imaging systems. However, to date, there are few organ sites where such diagnostic modality is truly established.

Application

Detection of Early Lung Cancer by Fluorescence Bronchoscopy

The bronchoscopic detection of severe dysplasia and early invasive ►lung cancer generally requires the expert analysis. Hematoporphyrin-mediated specific fluorescence was early investigated to improve diagnostic sensitivity during bronchoscopy. A group in Vancouver, trying to implement background subtracting techniques realized that the autofluorescence background differed significantly between tumorous and healthy mucosa. Malignant tumors are characterized by a reduction in elastin- and connective tissue-mediated autofluorescence. Thus, instead of using an exogenous tracer, they developed an imaging system based on autofluorescence characteristics only. This system was commercialized in the mean time under the name ►light-induced fluorescence endoscopy (LIFE) and is gaining rather widespread acceptance. In a recently published multicenter evaluation, the relative sensitivity of white light bronchoscopy enhanced by LIFE versus white light bronchoscopy alone was 6.3 for intraepithelial neoplastic lesions and still 2.7 for invasive cancers. The positive predictive value was 0.33. The authors conclude in that report that autofluorescence bronchoscopy, when used as an adjunct to standard white light bronchoscopy, enhances the ability of the bronchoscopist to localize small neoplastic lesions, especially intraepithelial lesions that

may have significant implication in the management of lung cancer in the future.

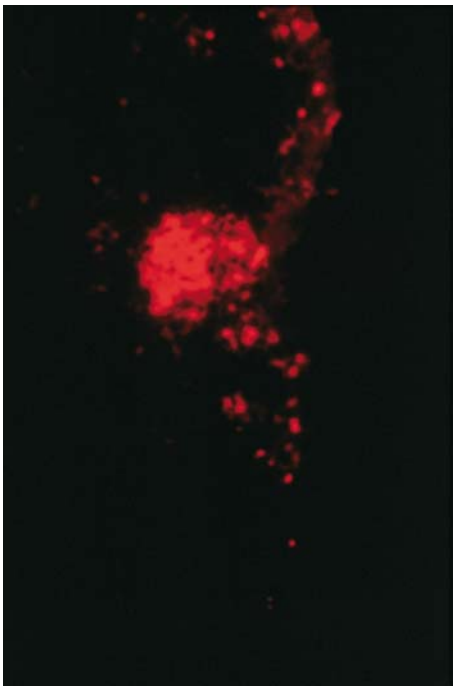
Urinary Bladder

If the success of autofluorescence detection originates from the bronchi, the success of ALA-induced fluorescence detection originates from the urinary bladder. While early attempts had been undertaken with hematoporphyrin fluorescence imaging, the topical use of ALA to induce protoporphyrin IX fluorescence has rapidly set a standard. In their latest assessment, a group from Germany reported in 208 consecutive patients with superficial bladder cancer a best estimate for the sensitivity of ALA-induced fluorescence endoscopy of 93.4% (95% confidence intervals 90–97.3) compared with a value of 46.7% (95% confidence intervals 39.4–54.3) for white light endoscopy. Some autofluorescence based approaches do not find the same acceptance as yet.

Other Organ Sites

Sensitive detection of premalignant conditions or early tumor stages may be considered as the general aim of fluorescence enhanced endoscopic approaches. Based on endoscopic accessibility and upon the presence of a risk group with sufficient incidence of dysplastic or cancerous lesions, research was directed towards patients with ►Barrett esophagus or with ►ulcerative colitis. However, both predisposing conditions are associated with an extended, inhomogeneous chronic inflammatory process that seems to interfere with the homogeneity of the background fluorescence. Neither autofluorescence nor ALA-enhanced fluorescence techniques have been reported to be a worthwhile adjunct to conventional diagnostics. The differentiation of small colonic polyps may be possible by autofluorescence; it is, however, questionable, whether the clinical benefit will justify the effort.

The procedures discussed so far have all dealt with the tissue surface. If microscopic tumor deposits are to be detected at a certain depth in the tissue, more sophisticated techniques are required to isolate the specific fluorescence signal from the abundant autofluorescence originating from the interpositioned normal tissue. Single point measurements may be advantageous over imaging techniques. Using a single point background subtracting measuring device with an excitation wavelength in the red (630 nm), Mang et al [1] were able to detect very small tumor deposits in the skin of breast cancer patients and lymphatic micrometastases (Fig. 1) in a rat model.



Fluorescence Diagnostics. Figure 1 Fluorescence micrograph of a lymph node micrometastases after systemic application of polyhematoporphyrin as photodiagnostic agent. The fluorescence intensity demonstrates the strong accumulation of the photodiagnostic agent within the metastatic deposit [image courtesy to TS Mang, Buffalo, USA].

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Fluorescence in Situ Hybridization

Definition

►FISH; Detection of specific chromosomal structures by hybridization of fluorescence dye-conjugated probes to DNA.

►Leukemia Diagnostics
►Minimal Residual Disease
►Chromosomal Translocations

Fluorescence Resonance Energy Transfer

►Time-Resolved Fluorescence Resonance Energy Transfer Technology in Drug Discovery

Fluorochrome

Definition

Fluorescent compound used to label biomolecules (protein, nucleic acids) with a fluorescent label.

►Flow Cytometry
►FISH

Fluorodeoxyglucose-Positron Emission Tomography

Definition

FDG-PET; is a nuclear medicine imaging method that produces a three-dimensional functional map of the body. To perform this imaging study, patients are injected intravenously with a radioactive tracer that decays by emitting a positron. The most commonly used molecule is fluorodeoxyglucose (FDG). After allowing the tracer to concentrate in organs or tumors (1 h for FDG), patients are placed in the scanner and the images are obtained.

►Childhood Adrenocortical Carcinoma

Fluorouracil

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Synonyms

5-Fluorouracil; 5-FU

Definition

Is a drug primarily used in cancer treatment. It is considered a ►pyrimidine analog belonging to the class of drugs known as ►antimetabolites. This ►chemotherapy agent has been used against cancer for about 40 years and appears to have multiple sites of action. As a pyrimidine analog it is activated inside the cell to a cytotoxic metabolite that is incorporated into RNA and DNA. This action causes ►cell cycle arrest and, in many instances, induces ►apoptosis. Because its main actions involve DNA synthesis, this agent is considered an S-phase specific drug and is active during this phase of the cell cycle in actively dividing cells.

Characteristics

Fluorouracil continues to have wide use in the treatment of cancer. Research over the past several years has increased our understanding of how 5-FU inhibits cell growth and this has led to the development of new strategies that have increased the utility of this anti-cancer drug. However, drug resistance continues to limit the usefulness of this antimetabolite as well as limit the use of some of the newer antimetabolite derivatives of 5-FU.

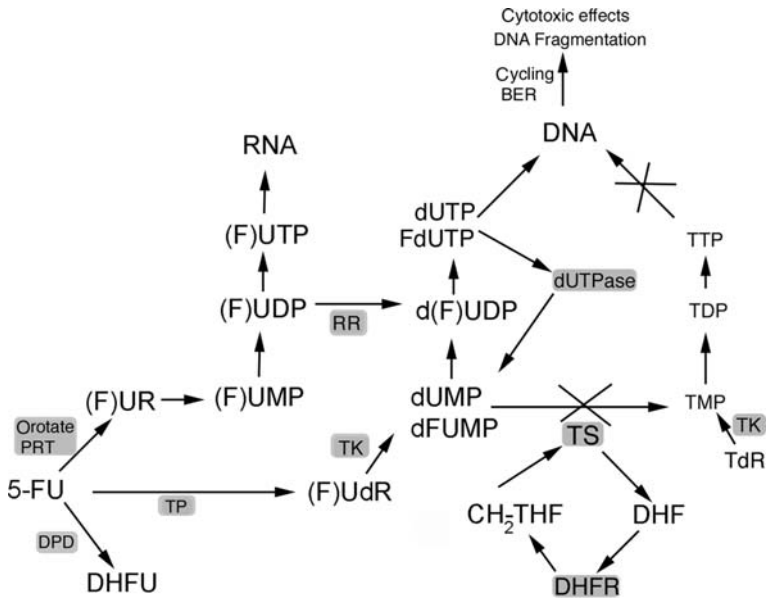
Mechanisms of Action

One of the key actions of 5-FU is the inhibition of thymidylate synthase (TS). Once in the cell 5-FU can be converted to fluorodeoxyuridine by ►thymidine phosphorylase (TP) and then to the monophosphate, FdUMP by thymidine kinase (Fig. 1). FdUMP in the presence of a reduced folate cofactor forms a stable covalent complex with TS, inhibiting activity and blocking de novo thymidylate (TMP) synthesis. Cytotoxic determinants of this mechanism include diminished levels of TMP and TTP. This results in the inhibition of DNA synthesis.

Other pathways that appear to contribute to the cytotoxic action of 5-FU include extensive incorporation of the ribonucleotide metabolite, FUTP into both cytoplasmic and nuclear RNA, disrupting normal RNA homeostasis. The contribution of the RNA pathway to cellular toxicity varies greatly and depends on cell type and the experimental setting. 5-FU can affect ►pre-mRNA processing such as ►polyadenylation as well as mRNA translation, ultimately leading to decreased expression of protein, including key proteins involved in metabolizing 5-FU.

Determinants of Cell Sensitivity to 5-FU

Cancer cells vary widely in their sensitivity to this chemotherapeutic agent, and numerous determinants appear to play a role in whether a cell is sensitive or resistant to 5-FU. Preclinical as well as clinical studies have demonstrated that TS expression is a key



Fluorouracil. Figure 1 Potential pathways for the metabolism of fluorouracil. RR, ribonucleotide reductase; TK, thymidine kinase; DHFR, dihydrofolate reductase; PRT, phosphoribosyltransferase; DPD, dihydropyrimidine dehydrogenase; dUTPase, dUTP nucleotidohydrolase; TS, thymidylate synthase; TP, thymidine phosphorylase.

determinant of 5-FU sensitivity. Quantitation of TS expression in tumors has revealed that low levels of TS correlate with improved response to 5-FU based therapy. Metabolic enzymes also play a role in 5-FU response rates. The catabolic enzyme, dihydropyrimidine dehydrogenase (DPD) initiates the degradation of 5-FU by converting the fluoropyrimidine to dihydrofluorouracil. High levels of DPD in colorectal tumors lead to elevated resistance to 5-FU. Other determinants that play a role include thymidine phosphorylase (TP), which converts 5-FU to an active metabolite known as FUdR (Fig. 1). The ►tumor suppressor ►p53, which regulates gene transcription of a number of key enzymes, is also known to alter cellular sensitivity to 5-FU. Research efforts continue in an attempt to further elucidate the mechanisms of action of 5-FU in the hope of improving its efficacy in the clinic. Results from a number of laboratories have uncovered an additional cytopathic mechanism that is downstream of TS inhibition. This mechanism contributes to 5-FU cytotoxicity through a self-defeating base-excision repair process. Along with the depletion of TTP pools (because of a decrease in de novo TMP synthesis) there is also an increase in dUMP, the normal substrate of TS. Metabolism of dUMP to the triphosphate, dUTP (as well as the conversion of FdUMP to FdUTP) results in elevated pools of these atypical precursors for DNA synthesis. Normally the enzyme, dUTP nucleotidohydrolase (dUTPase) which hydrolyzes dUTP to dUMP, prevents significant dUMP incorporation into DNA. However in the presence of FU metabolites, the efficiency of dUTPase appears to be diminished. It appears that FdUTP effectively ties up the enzyme, allowing dUTP pools to build up. Under these conditions there is a destructive cycle of dUMP (and FdUMP) incorporation into DNA, removal of uracil (and fluorouracil) by the base-excision repair enzyme, uracil-►DNA glycosylase and reincorporation of (F)dUMP, during the synthesis phase of ►DNA repair. The end-point is loss of DNA integrity and cell death. Studies have revealed that levels of dUTPase vary significantly between cell lines. These studies show that elevated dUTPase activity in the cell correlates with lower dUTP pools and diminished DNA fragmentation. Several investigators have also demonstrated that elevated dUTPase correlates with increased resistance to the fluoropyrimidine antimetabolite. Introduction of recombinant vectors, expressing dUTPase, into sensitive cells decreased sensitivity to FUdR (an active metabolite of 5-FU) as well as decreasing dUTP pools and DNA fragmentation. Utilizing ►small interfering RNA (siRNA) strategies, it was shown that suppression of dUTPase, resulted in a significant enhancement of dUTP pools, enhanced DNA fragmentation and a decrease in IC_{50} for FUdR. Clinical evidence points to an association between dUTPase levels, survival and response to 5-FU in colorectal cancer. Higher levels of dUTPase correlate with poorer response to 5-FU therapy. Published studies also provide evidence that dUTPase levels vary widely between individual cancer tumor specimens.

While considerable data has accumulated on the expression characteristics of dUTPase in a number of

cancer cell lines as well as cancer tissues, very little information exists on the expression characteristics of the DNA repair enzyme, uracil-DNA glycosylase (UDG) in cells in relation to 5-FU or its metabolites. It has been estimated that as many as 400 uracil residues could arise in the human genome per day as a result of spontaneous cytosine deamination occurring under physiological conditions. The mutagenic potential of uracil is particularly high because, unlike many other lesions, it can be efficiently used as a template. Like thymine, uracil can base pair with adenine and yield a stable duplex structure. During occurrences of cytosine deamination to uracil, C to T and G to A base substitutions arise. Subsequent rounds of DNA replication lead to transition mutations. Uracil-DNA glycosylases and related enzymes initiate base-excision repair pathways that function to correct misincorporation of dUMP and to correct deaminated cytosine residues in DNA. This process is necessary to prevent the accumulation of mutations, which may lead to genomic instability and pathologic outcomes such as cancer. There are two isoforms of UDG, one located in the nucleus, nUDG (also known as UNG2 or UDG1A) and one that is targeted for ►mitochondrial DNA repair, mUDG (also known as UNG1 or UDG1). Recent evidence indicates that both the nuclear and mitochondrial isoforms of UDG are modulated by 5-FU (and FUdR) treatment in certain cell lines but not in others. Significant modulation occurs at the transcriptional and at least for nUDG at a post-translational level. In normally cycling cells in culture, nUDG protein expression occurs in the G_1 phase of the cell cycle and that during the S to ►G_2 phase transition, nUDG is degraded by a ►ubiquitin-mediated process. Recent evidence also indicates that 5-FU mediates an atypical turnover of nUDG in late G_1/early S phase of the cell cycle. Additional data indicate that for cell lines that do not down regulate nUDG (in response to 5-FU), siRNA-mediated knockdown of nUDG increases resistance to the cytotoxic effects of the FUdR metabolite, increasing the IC_{50} by sixfold. A derived speculation from these findings is that cells can tolerate uracil in DNA (especially base-paired to adenine) much better than they can tolerate DNA strand breaks. So if the cell maintains uracil in DNA until pools of dUTP (and FdUTP) decrease, subsequent DNA repair would be much less deleterious. Therefore it can be inferred that in certain cell lines, damage induced by 5-FU instigates a ►checkpoint mechanism that culminates in the down regulation of UDG. This mechanism protects cells from the destructive, cyclic base-excision repair process created by elevated pools of dUTP. Conversely cells that lack this mechanism, and maintain elevated levels of UDG, are more sensitive to the effects of cyclic base-excision repair and show increased toxicity to fluoropyrimidines. Strategies directed at stabilizing nUDG in cancer cells may provide clinically significant approaches for novel drug development.

Toxic Side-Effects

Toxicity to fluorouracil manifests in several ways. Early symptoms include nausea and anorexia. This is followed by ►stomatitis and diarrhea. Mucosal ulcerations of the gastrointestinal tract may lead to fulminant diarrhea, shock and death. This is most prominent in patients receiving continuous infusion of 5-FU or a combination of 5-FU and ►leucovorin (LV). The major toxicities of IV bolus regimens is ►myelosuppression. Toxicities of infusional 5-FU are a function of dose and duration of exposure. DPD catalyzes the initial step in degrading 5-FU. In a small percentage of the population DPD activity is below average levels for the general population. Administration of 5-FU to these individuals can cause significant life-threatening toxicity. Unfortunately, in most cases this genetic predisposition is not uncovered until administration of 5-FU.

Capecitabine, an Orally Administered ►Prodrug of Fluorouracil

Statistical analyses have indicated that prolonged low-dose infusional 5-FU resulted in higher response rates with some improvement in survival when compared to bolus injection. Because of the labor-intensive nature of prolonged infusional therapy new modes of oral delivery of 5-FU have been formulated. ►Capecitabine is an orally administered fluoropyrimidine carbamate prodrug that is activated to 5-FU by a series of enzymes. Studies suggest that the latter activating enzymes in this series are higher in the tumor relative to normal tissue, rendering a certain degree of selective activation of the prodrug in tumor tissue.

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5-Fluorouracil (5-FU)

Definition

A cytotoxic agent; it blocks the ►methylation reaction of deoxyuridylic acid to thymidylic acid.

►Fluorouracil

Fluoxetine

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Synonyms

Prozac; Selective serotonin reuptake inhibitors SSRIs

Definition

Fluoxetine hydrochloride is a drug used in the clinic for the treatment of depression and for a broad spectrum of psychiatric disorders. Fluoxetine has also been shown to inhibit multidrug resistance extrusion pumps expressed in a variety of cancer cells.

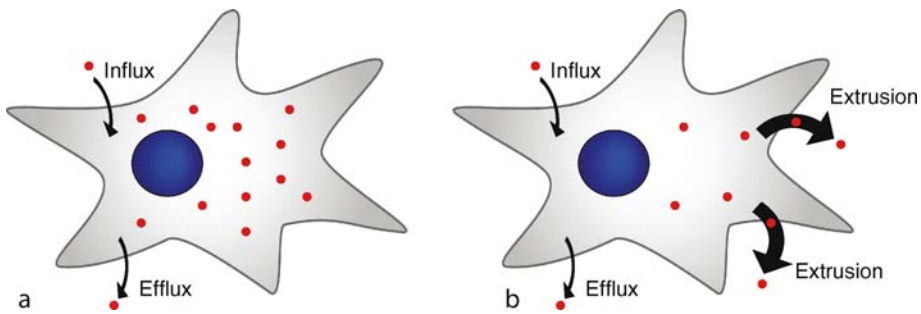
Characteristics

Fluoxetine hydrochloride is a drug used clinically in depression, and in a wide spectrum of psychiatric disorders. Fluoxetine was derived from an antihistamine (diphenhydramine), and found to inhibit reuptake of the neurotransmitter ►serotonin. Fluoxetine is also used (off-label) to treat many other conditions, including Attention-Deficit Hyperactivity Disorder (ADHD). The mechanism by which the drug operates is still unclear. Fluoxetine has been shown to be effective in cancer therapy in two areas; As an anticancer effector inducing apoptosis, as reported *in vitro* for ►Burkitt lymphoma (a type of ►B cell lymphoma), ►glioma and ►neuroblastoma cells, and as a non-selective inhibitor of the ►cancer multidrug resistance (MDR) extrusion pumps.

Multiple Drug Resistance

Multiple drug resistance (MDR) is one of the principal mechanisms by which chemotherapy treatment fails many cancer patients. It affects patients with a variety of blood cancers and solid tumors, including ►breast cancer, ►ovarian cancer, ►lung cancer, lower gastrointestinal tract, liver and ►brain tumors. Tumors usually consist of mixed populations of malignant cells, some of which are drug-sensitive while others are drug-resistant. In a drug-sensitive tumor cell the drug can accumulate to a sufficient level that culminates in cell death (Fig. 1a). The molecular basis of cancer drug resistance is complex and has been correlated to elevated enzymes that can neutralize chemotherapeutic drugs, but more often it is due to the overexpression of extrusion transporters from the ►ABC (ATP-Binding Cassette) Superfamily. These transporters actively pump chemotherapeutic drugs out of the cell, thus reducing the intracellular drug doses below lethal thresholds (Fig. 1b). Chemotherapy kills drug-sensitive cells, leaving behind a higher proportion of drug-resistant cells. As the tumor is recurred, chemotherapy may fail as a consequence of residual drug resistance cells dominating the tumor population.

Among the ►ABC transporters, the most investigated proteins are: ►P-glycoprotein (ABCB1); the multidrug resistance associated proteins (MRPs) of



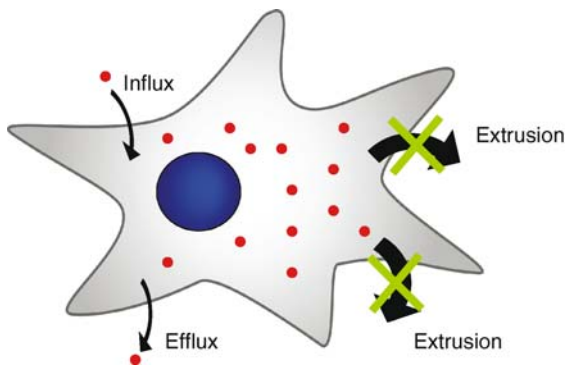
Fluoxetine. Figure 1 Illustration of drug efflux and accumulation in drug-sensitive and in drug-resistant tumor cells. (a) A drug-sensitive tumor cell. Drug molecules (red dots) diffuse across the cell membrane. The influx of the drug is superior to the drug efflux due to the direction of the drug's electrochemical gradient, allowing sufficient drug accumulation inside the cell. The cell nucleus is in blue. (b) A resistant tumor cell combines drug diffusion across the cell membrane with extrusion pumps that expel the drug out of the cell and thus reducing the drug accumulation inside the cell.

which the most studied is the MRP1 (ABCC1); and the breast cancer resistance protein (ABCG2). Those proteins share a similar function – they all expel chemotherapy from the cells, however their structure is different from one another.

Clinical MDR appears in two modes, inherent (intrinsic) and acquired. When the tumor is not responding to the chemotherapeutic treatment, even in the first cycle of administration, it can be defined as an inherent (intrinsic) resistance. The acquired form of drug resistance is defined when the tumor response to chemotherapy treatment is reduced over time (usually after several cycles of administration). Recent findings from cancer ►stem cell research may shed light into our understanding of the biology behind the different modes. High levels of ABC transporters in stem cells (particular ABCG2 in normal stem cells) and the recognition and retention of ABC transporters in cancer stem cells that intrinsically and consistently over-express ABC transporters contribute to the understanding of the phenomena, but still leave the tumor biologist with a vital question: How come some tumors are intrinsically resistance to chemotherapy while others remains sensitive? The role of cancer stem cells in cancer recurrence and in intrinsic vs. acquired MDR needs further studies. It is clear, however, that the impact of cancer stem cells on MDR will become a major factor in designing strategies to overcome drug resistance.

MDR Reversal by Chemosensitization

Drug resistance mediated by extrusion pumps is a problem that holds the key to its solution. In the most direct view, arresting the pump action (Fig. 2) should restore drug accumulation inside the MDR tumor cell to levels comparable to those of a drug sensitive tumor cell (Fig. 1a).



Fluoxetine. Figure 2 A chemosensitized drug-resistant tumor cell. By blocking the extrusion pumps, the drug is allowed to accumulate inside the cell, comparable to the case of a drug-sensitive tumor cell.

Several different names have been given to an agent capable of pump arrest: MDR reversal agent, MDR modulator, chemosensitizer, and pump inhibitor. The ongoing search for chemosensitizers that can apply in the clinic is into its third generation. First-generation chemosensitizers were found among drugs already approved for different indication, such as ►verapamil, cyclosporine A and ►progesterone. Today those drugs are used as *in vitro* benchmarks. They cannot be employed clinically due to dose related adverse effects, toxicity and, in some cases, solubility limitations.

The second and third generations of chemosensitizers were drawn from chemical derivatization of the first-generation molecules and from combinatorial chemistry designed predominantly against ABCB1 (P-glycoprotein). Examples include many compounds that are under development in pharmaceutical companies such as VX-710, XR9051, XR9576, MS-209, GF120918, LY335979, ONT-093, and PSC833 (Valspodar). Some of the compounds reached clinical trials; although they are less toxic and more potent then the first generation compounds, they are still prone to adverse effects, poor solubility, and unfavorable changes in ►pharmacokinetics of the anti-cancer drug. Not all of them fit to blocking different pump proteins. Most of them usually function with one or two pumps and thus are not "multi-pump" blockers. PSC833 (Valspodar) was one of the prominent candidates that reached clinical trials. Valspodar has been extensively investigated both pre-clinically and clinically and found to function as a single-pump blocker (ABCB1). Recently (2006), it has been reported that Valspodar did not improve treatment outcomes and increased the toxicity in a randomize phase III clinical trial in patients with recurring or refractory multiple myeloma. Valspodar treatment was in combination with the chemotherapeutic drugs vincristine, ►doxorubicin and the steroid dexamethasone, compared with treatments that exclude the chemosensitizer.

The diversity among pumps proteins, the heterogeneity of cells in a given tumor as well as variability between patients will probably require treatment with more than one chemosensitizer. Multi-pump blockers, will have distinct self-explanatory advances over single-pump ones. Given the above-discussed need for additional chemosensitizers, it is important to contemplate what it takes to qualify a candidate molecule as an effective chemosensitizer for which pump inhibition is a single or a major mechanism.

We propose that a candidate molecule should meet three *in vitro* criteria prior to investigating its potential *in vivo*. The *in vitro* criteria are based on both functional and mechanistic principles. The most prominent one is cell demise: treatment of a given MDR tumor cell line, with a combination of the candidate molecule

and a chemotherapeutic drug, should significantly enhance cell death, compared with similar treatment with drug alone.

Mechanistic criteria include drug efflux and drug accumulation. Incubating MDR cells with a chemotherapeutic drug, with or without the candidate chemosensitizer, should result in higher intracellular drug accumulation in the latter case. Efflux of a chemotherapeutic drug from MDR cells, preferable under unidirectional conditions, should be significantly faster in the absence of the chemosensitizer candidate, than when it is present. If a candidate chemosensitizer meets all those criteria, there is merit in expanding the evaluation in several directions: testing, in the same cell line, different chemotherapeutic drugs drawn from those known to be substrates of a given MDR pump; testing different additional MDR cell lines; testing MDR cell lines with their parent sensitive lines (upon availability). Comparative studies to known chemosensitizers used as benchmarks, can stringent the evaluation of the candidate molecule.

Fluoxetine as a Multi-pump Chemosensitizer

Fluoxetine belongs among the first-generation of chemosensitizers, namely drugs approved for non-cancer indications and found to act as MDR modulators. Yet, one critical factor sets fluoxetine apart from other first generation members and indicates it may merit a separate category, possibly fourth-generation chemosensitizers. Unlike first-generation chemosensitizers with their drawbacks mentioned above, fluoxetine exerts its ability to chemosensitize MDR cells at low safe doses, well below its human safety range.

In Vitro Studies

Fluoxetine was tested in ABCB1/MDR tumor cells, in ABCC1/MDR tumor cells and in drug-sensitive tumor cells. Test drugs were the chemotherapies: ►Adriamycin (doxorubicin), ►mitomycin C, ►paclitaxel and ►vinblastine. The multi-pump chemosensitizers verapamil and cyclosporine A, shown to affect the ABCB1 and ABCC1 pump proteins, were used as benchmarks. All three criteria were tested.

Cytotoxicity – two measures are useful for evaluation of whether a chemosensitizer candidate meets the *in vitro* cytotoxicity criterion: IC_{50}, the drug concentration that generates 50% inhibition of cell proliferation which, in the case of MDR, is measured in the absence and the presence of a fixed chemosensitizer concentration; RF, the fold change in drug sensitivity, is calculated from the ratio of IC_{50} in the absence to that in the presence of the candidate. Fluoxetine, verapamil, and cyclosporine A were kept at low doses, where they do not affect cell viability. Fluoxetine had no effect on the response of drug-sensitive cells to chemotherapeutic drugs. RF values obtained for human breast cancer, colon cancer, and ►leukemia cell lines as well as mouse leukemia cell line were between 0.9 and 1.1. For doxorubicin, mitomycin C, and paclitaxel, fluoxetine-induced RF values in human ►pancreas cancer cell line and in human brain tumor (both expressing ABCC1 pumps), were in the range of 10–80. The same experiment using the benchmarks yielded RF values of 2–19. In mouse ►melanoma cell lines, and in resistant forms of ►breast carcinoma and ►leukemia (from human source) the RF values with the same drugs span from 20 to 70, where the benchmarks yielded only a minor RF numbers between 2 and 5.

Drug Efflux – The efflux of drugs from drug-sensitive cells was quite slow. Complete depletion of intracellular ►doxorubicin from human breast carcinoma took more than 10 h and was unaffected by fluoxetine or the other benchmarks. Drug efflux from other MDR-expressing pumps (both ABCB1 and ABCC1 proteins) was found to be rather fast. For example, under unidirectional flux conditions it took between 0.5 and 2 h for complete depletion of such cells from intracellular drugs (►doxorubicin, ►vinblastine, ►paclitaxel, and ►mitomycin C). The benchmarks slowed down drug efflux, increasing the time span for complete depletion up to 3–5 h. Fluoxetine showed a remarkable effect by slowing down the efflux, thereby increasing the time for complete depletion, to the range of 8–12 h, close to that of drug-sensitive cells.

Drug Accumulation – Drug accumulation was measured with fluorescent substrate like Rhodamine-123 and actual drugs. The benchmarks were found to increase intracellular drug accumulation compared to cells exposed to drugs alone. This effect was found in inherent and acquired MDR cells, whether the pump-protein was ABCB1 or ABCC1. Fluoxetine increased drug accumulation by three- to sevenfold better than the benchmarks.

In Vivo Studies

Following the *in vitro* findings, fluoxetine was studied in several different mouse tumor models with doxorubicin as the test drug. A number of parameters were unique to these studies: fluoxetine dose was well below human safety limits; it was administrated orally in the drinking water; it was given continuously from tumor inoculation until termination of the experiment. Most of the efforts were on efficacy, but it was initially verified that fluoxetine did not alter the drug's pharmacokinetics, a problem encountered with some previous-generation chemosensitizers. Biodistribution was also tested showing that while fluoxetine generated a 12-fold increase in doxorubicin accumulation in ►lung tumors, it had no effect on drug accumulation in liver, spleen and kidneys of tumor-bearing mice. Several

tumor-bearing mice models have been tested to confirm efficacy. Those included inherent (intrinsically inherent) tumors expressing ABCB1 and separately ABCC1; models of lung metastasis as well as lung tumors (as primary source); human tumors inoculated to immunodeficiency mice and mouse tumors. In all cases fluoxetine attenuated tumor progression and in human tumors it even caused complete regression in 40% of the mice while the other mice from this group showed dramatically decreased tumor size and ►metastatic burden in lung tumors that was mirrored in increased survival rate. The survival rate of animals bearing tumors that was treated with a combination treatment of both chemotherapy and fluoxetine was two- to fourfold more than their controls (including the mice that got only chemotherapeutic drug) in different tumor-bearing mice.

Conclusions

The need to provide cancer patients with an arsenal of clinically approved chemosensitizers that will address the different MDR pump-proteins is still a remaining challenge. Despite the complexity and the multifactorial nature of cancer MDR, encouraging prospects do exist with respect to maturation of the third generation chemosensitizers into established clinical modalities.

Fluoxetine met all three *in vitro* criteria for acting as a chemosensitizer. It is important to emphasize that one criterion may be inconclusive. Fluoxetine also acted as a chemosensitizer *in vivo*. The data indicated that fluoxetine belongs to the category of multi-pump blockers, showing the capacity to reverse MDR generated by two major proteins ABCB1 (p-glycoprotein) and ABCC1 (MRP1), but further studies are required to determine whether MDR reversal is the only or the major mechanism by which fluoxetine works and whether fluoxetine can inhibit other pump proteins such as ABCG2 and other members of the MRP family.

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Fluvastatin

Definition

Member of the ►statins family.

FOBT

Definition

►Fecal Occult Blood Test

Focal Adhesion

Definition

Large complex of proteins that link the cytoskeletal elements of the cell to ►extracellular matrix via the integrin mediated biochemical signaling. Focal adhesions translate the biochemical signals into mechanical signals that are necessary for cell movement. Stable and elongated adhesion plaques (several μm^2 in area) that mediate strong adhesion to the ►extracellular matrix (ECM). Rho-dependent actomyosin contractility is required for maturation of focal adhesions from initial focal complex.

►Endostatin
►Focal Adhesion Kinase
►Exfoliation of Cells
►Tensional Homeostasis

Focal Adhesion Kinase

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Synonyms

FAK

Definition

The nonreceptor ►protein tyrosine kinase focal adhesion kinase (FAK) was originally isolated as a tyrosine-phosphorylated 125-kDa protein in ►v-Src-transformed

chicken embryo fibroblasts. FAK is a signal transducer of integrins and interact with certain soluble growth factors and chemokines. This kinase is involved in cellular processes like cell ►adhesion and spreading, ►migration, proliferation, and cell survival.

Characteristics

FAK consists of a central kinase domain, a large N-terminal ►FERM domain (protein 4.1, ezrin, radixin, and moesin homology), and of a large C-terminal ►FAT domain (focal adhesion targeting domain). Additionally, it comprises three proline-rich regions. The FERM-domain mediates interactions of FAK with growth factor receptors ►EGFR (epidermal growth factor receptor) and ►PDGF (platelet-derived growth factor receptor), which are often overexpressed in tumors and promote cell ►motility and ►invasion. The activation of the non receptor tyrosine kinase Etk (also called Bmx) by extracellular matrix proteins is regulated by binding to the FERM-domain of FAK. The FAT-domain mediates the binding of integrin-associated proteins such as paxillin and talin leading to the formation of focal contacts. An important C-terminal domain of FAK is the FAK-related nonkinase domain (►FRNK) which functions as a negative regulator of kinase activity. Overexpression of the FRNK segment that is separately expressed in certain cell types inhibits cell spreading and cell migration. The kinase domain induces adhesion-induced activation of FAK through phosphorylations of tyrosine residues at tyrosine residues Tyr397, Tyr576, and Tyr577. Additional phosphorylation sites are Tyr861 and Tyr925 in the C-terminal domain. Two proline-rich regions function as binding sites for ►Src-homology domain containing proteins.

FAK Phosphorylation and Regulation

Following attachment of the cell to extracellular matrix, subsequent integrin clustering results in rapid phosphorylation of FAK at Tyr397 and leads to the formation of phosphotyrosine docking sites for several classes of signaling molecules. So the ►phosphorylation of tyrosine residue 397 of FAK creates a high-affinity binding site for the ►SH2 domain of ►Src family tyrosine kinases and leads to the recruitment and activation of ►Src kinase and of p85 subunit of PI3-kinase, phospholipase C, and the adapter protein Grb7. The association of FAK and ►Src follows further phosphorylations of Tyr576, Tyr577, Tyr407, Tyr861, and Tyr925. A number of signaling proteins are phosphorylated and they are involved in adhesion, invasion, and survival signaling of tumor cells. Proline-rich recognition sites for ►SH3 domain-containing proteins provide binding motifs, for example ►Cas, an adaptor protein, or for ►GTPase activating proteins GRAF and ASAP1, which are involved in regulation of small GTP-binding proteins such as ►Rho and Arf proteins that play important roles in cytoskeletal reorganizations (Fig. 1).

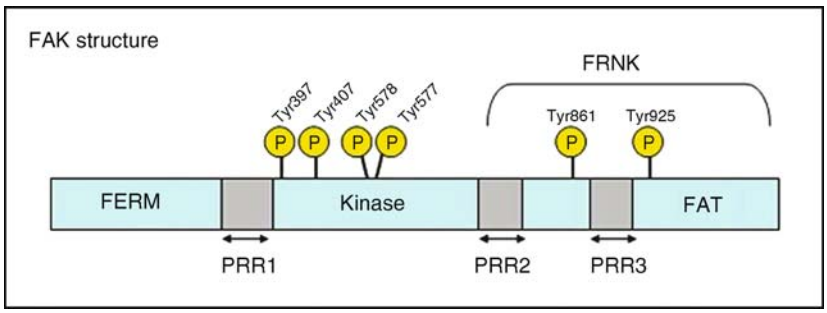
FAK functions in different downstream pathways and some are changed in tumors (Fig. 2).

Focal Contact

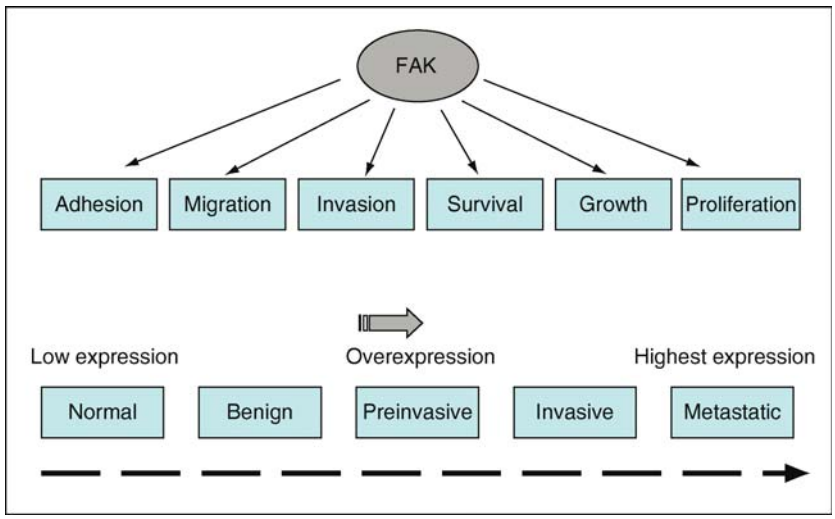
The actin cytoskeleton of cells interacts through integrins with the extracellular matrix. These sites of contact are named focal contacts. Focal contacts are composed of structural and regulatory proteins such as paxillin and talin, which recruit FAK and vinculin to focal contacts. α-Actinin, phosphorylated by FAK, binds to vinculin and crosslinks actomyosin stress fibers, which are further connected to the focal contacts. External signals are transduced into the cell interior that can generate additional cytoskeletal rearrangements.

Regulation of Focal Contacts

The regulation of assembly and disassembly of focal contacts is very important for the motility and migration



Focal Adhesion Kinase. Figure 1 The structure of focal adhesion kinase and tyrosine phosphorylation sites. The schematic illustration demonstrates the important N-terminal (FERM domain), central (kinase domain) and C-terminal domains (FAT and FRNK domains) of FAK with localization of their tyrosine (Tyr) phosphorylation sites and the three proline-rich regions (PRR1–3).



Focal Adhesion Kinase. Figure 2 Overview about the role of FAK signaling in different cellular processes and its overexpression in tumor progression.

of cells. The formation of strong or weak focal contacts is an important determinant whether a cell can migrate or not. It seems to be a cycle between binding of FAK to focal contacts and its release from these structures. The Src-mediated phosphorylation of FAK at Tyr925 leads to a SH2 binding site for ►GRB2 following Ras and ERK2 activation. The ►ERK activation results in the phosphorylation of FAK at Ser910, which subsequently leads to decreased paxillin binding and finally in release of FAK from focal contacts and to its turnover. In contrast, the Erk2-mediated phosphorylation of ►paxillin results in activation and binding of FAK to paxillin at new or growing focal adhesions.

Signaling Pathways in Cancer

Cell Migration

FAK is an important regulator of cell motility and cell migration, which are prominent processes in tumor ►progression and development of ►metastasis. To promote cell movements the FAK/Src complex phosphorylates Cas leading to recruitments of further ►SH2-containing proteins such as the adaptor protein ►Crk. The interaction of Crk with the ►DOCK180/ELMO complex results in ►Rac activation, a small ►Rho family GTPase. ►Rac1 is responsible for plasma membrane protrusions and formation of ►lamellipodia. Paxillin phosphorylation at tyrosines 31 and 118 also leads to Crk binding promoting Rac activation and paxillin is involved in modulation the dynamics of cell adhesion. The activation of RhoA promotes cell contractility and formation of stress fibers, contractile actin-myosin filaments, which are important for focal adhesion assembly. The regulation of RhoA and Rac1 activity is an important step in FAK signaling.

Invasion

To become invasive tumor cells have to degrade the ►basement membrane and migrate into the underlying ►stroma. The invasion of tumor cells through vessel walls and into the surrounding stroma requires the degradation of the ►extracellular matrix. FAK signaling is linked to the production and activity of matrix-degrading metalloproteinases (MMP), which represent important members of degradative proteases that can promote local tissue destruction and tumor-induced neoangiogenesis. For example, the activation of Rac1 and JNK (JUN N-terminal kinase) through the Src–Cas–Crk–DOCK180 complex results in increased MMP2 and MMP9 expression. The focal adhesion turnover is also facilitated by ►calpain-2-mediated cleavage of focal contacts. This protease is activated by ►EGF-induced ►MAPK (mitogen-activated protein kinase) and promotes the migration and invasion of tumor cells. There appears to be a correlation between FAK overexpression in tumors and their invasive and metastatic properties.

Cell Survival

Another role of FAK signaling is to promote the resistance to ►anoikis, a form of ►apoptosis resulting from loss of attachment to the extracellular matrix. The ability to survive in the absence of adhesion is an important characteristic of tumor cells to progress to a malignant phenotype. Several studies showed that inhibition of FAK signaling caused increased apoptosis. In addition, overexpression of FAK increases the adhesion independent growth of several tumor cell types. In contrast, analysis of nontumor cells did not found comparable effects on cell survival. The phosphorylation of tyrosine 397 and the kinase activity

of FAK are required for this process. Binding to the p85 subunit of PI3-kinase and following AKT kinase activation result in prevention of apoptosis. The suppression of anoikis is mediated by binding of FAK to the receptor-interacting protein (RIP), which consequently cannot bind to the dead receptor complex.

Growth and Proliferation

The adhesion-independent growth of tumor cells is an important step in tumor progression. For example, it has been shown that inhibition of FAK reduces the ability of breast cancer cells to grow in an adhesion-independent manner. Furthermore, it was demonstrated that FAK is overexpressed with increased tumor stages. This result was associated with increased rates of cell proliferation. Therefore, FAK may promote tumor growth through inhibition of apoptosis and acceleration of tumor cell proliferation.

Tumor Progression

A ►DMBA/TPA mouse skin carcinogenesis model was used, among others, to investigate the role of FAK in tumor ►progression. The results suggest that FAK expression and FAK-dependent cell signaling are increasingly enhanced with advanced stages of tumor progression and malignant progression. Normal epithelium and benign hyperplastic lesions have low FAK expression, whereas in preinvasive and invasive stages an overexpression of FAK was observed. In metastatic tumors the highest FAK expression was found. This overexpression seems to be a marker for an invasive and metastatic tumor phenotype.

Metastasis

►Metastasis is a process in which circulating tumor cells usually invade into potential host organs by breaking through vessel walls at the primary and secondary tumor site. In the blood flow the cells are exposed to shear forces requiring stabilization of their adhesive interactions under dynamic conditions in fluid flow. Similar to endothelial cells tumor cells can respond to external forces with increased integrin clustering and FAK activation. Exposed to this shear stress, motile cells can show enhanced FAK phosphorylation at the leading edge promoting a number of FAK-mediated tumor cell characteristics, such as migration and survival. This pathway appears to enable metastatic cells to resist shear forces within their target organs, to adhere and successfully colonize target organs.

FAK Overexpression

Many studies reported overexpression of FAK in various tumor types using different detection methods at mRNA, DNA, and protein level. Increased expression was found in patients' specimens of epithelial tumors of colon, liver, breast, ovary, stomach, thyroid, prostate, and oral cavity. Elevated FAK expression was also detected in many tumor-derived cell lines. These expression levels correlate with tumor progression.

Cancer Therapy

Once modified, the involvement of FAK in many cellular processes qualified FAK as a determinating and possibly rate-limiting pathway for tumor progression making this kinase an interesting target for anticancer therapy. In preclinical models, the inhibition of FAK signaling already demonstrated promising therapeutic effects by prevention of tumor cell migration and invasion resulting in higher survival rates. However, further preclinical investigations and clinical studies are necessary to establish FAK as a novel treatment strategy.

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Focal Complex

Definition

Initial and small (<1 μm^2 in area) adhesion plaques formed between integrin receptors of cells and the ►extracellular matrix (ECM). It contains ►integrins and actin binding proteins such as vinculin, talin, and paxillin, as well as actin.

►Tensional Homeostasis

Focal Contact

Definition

A type of anchoring cell junction forming a small region on the surface of a cell that is anchored to the

►extracellular matrix. Attachment is mediated by transmembrane proteins such as integrins, which are linked, through other proteins, to actin filaments.

►Migration

Folate

Definition

The salt of folic acid, a B vitamin containing the amino acid glutamate as part of its chemical structure.

FOLFIRI

Definition

Combination chemotherapy of ►irinotecan, ►leucovorin, and 5-flourouracil (►5-FU). The regimen is commonly used in the treatment of ►colorectal cancer.

►Erlotinib (Tarceva®)

FOLFOX

Definition

Combination chemotherapy of ►oxaliplatin, ►leucovorin, and 5-flourouracil (►5-FU). The regimen is commonly used in the treatment of ►colorectal cancer.

►Erlotinib (Tarceva®)

Folinic Acid

Definition

►Leucovorin

Follicle Stimulating Hormone

Definition

FSH; and luteinizing hormone (LH) are called ►gonadotropins because stimulate the gonads - in males, the testes, and in females, the ovaries. They are not necessary for life, but are essential for reproduction. These two hormones are secreted from cells in the anterior pituitary called gonadotrophs. Most gonadotrophs secrete only LH or FSH, but some appear to secrete both hormones.

Follicular Adenoma, Oncocytic Variant

►Hurthle Cell Adenoma and Carcinoma

Follicular Adenomas

►Follicular Thyroid Tumors

Follicular Carcinoma

►Follicular Thyroid Tumors

Follicular Carcinoma, Oncocytic Variant

►Hurthle Cell Adenoma and Carcinoma

Follicular Lymphoma

Definition

FL; is a common low grade ►B-cell lymphoma, which accounts for ca. 40% of B-cell lymphomas. Typically these lymphomas carry a ►translocation t(14;18), which brings the rearranged ►BCL-2 gene (chromosome 18) under the control of the immunoglobulin enhancer (chromosome 14). Tumors usually express B-cell markers

and surface immunoglobulin. Many patients do not require treatment for a long time. A characteristic feature is a spontaneous "waxing and waning" of the enlarged lymph nodes, which may reflect residual but inefficient attempts of the immune system to eliminate the cancer. FL is not considered curable, except for patients in very early stages of disease. Often this lymphoma transforms into a more aggressive form of lymphoma, diffuse large B-cell lymphoma, which carries a poor prognosis.

►B-cell Tumors

Follicular Thyroid Tumors

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Synonyms

Follicular adenomas; Papillary carcinoma; Follicular carcinoma; Anaplastic carcinomas

Definition

Are tumors derived from the thyrocyte, the cellular unit of ►thyroid follicle. These tumors include benign adenomas, papillary and follicular carcinomas, two entities considered as differentiated carcinomas, and undifferentiated or anaplastic carcinomas.

Characteristics

Clinical thyroid nodules, that are the consequence of abnormal localized growth of the thyroid tissue, are detected in 4–7% of the general population in a iodine sufficient area. The prevalence is higher in countries affected by moderate or severe iodine deficiency. Infraclinical nodules are even more common, depending on the techniques used for screening, and ultrasonography detects nodules in more than 50% of women older than 60 years. About 5% of thyroid nodules are malignant. The annual incidence of thyroid carcinoma, the most common malignancies of endocrine organs, ranges from 1.2 to 3.8 per 100,000, being twice as high in females as in males. The annual mortality rate ranges from 0.2 to 2.8 per 100,000.

Classification

The clinico-pathological classification of thyroid nodules distinguishes: non-neoplastic nodules, found in patients with either hyperplasia or inflammatory and ► autoimmune thyroid diseases, benign follicular thyroid adenomas, including non-functioning or cold nodules (80% of all nodules) and functioning or hot nodules, and thyroid carcinomas. Most thyroid nodules are benign lesions: a follicular adenoma is defined as a benign encapsulated tumor with evidence of follicular cell differentiation.

Less than 10% of cold nodules are malignant follicular thyroid tumors, i.e. thyroid carcinomas. Among these, 75% present evidence of follicular differentiation and thus are designated as differentiated cancers; they include two distinct histotypes, papillary carcinomas (PTC), characterized by distinctive nuclear features, and follicular carcinomas (FTC). Undifferentiated or anaplastic carcinomas are very rare and defined as highly malignant tumors with undifferentiated cells.

Etiology

Several risk factors for thyroid carcinoma have been identified from epidemiological studies. About 3–5% of Papillary thyroid carcinoma (►thyroid carcinogenesis) have a familial component history, and can occur in the context of rare familial syndromes (►familial polyposis coli, ►Cowden disease). Pre-existing benign thyroid diseases increase risk of developing a thyroid carcinoma. In areas with iodine deficiency compared to those with sufficient iodine intake, the prevalence of nodules is higher but the incidence of thyroid carcinoma is identical; follicular and anaplastic carcinomas are more frequent and papillary carcinoma is less frequent. The role of other dietary factors, such as fish consumption, cyanogens and smoking remains unclear.

Radiation exposure during childhood increases the risk of developing ►PTC later in life, probably by inducing chromosomal rearrangement. This can be related to an exposure to external radiation or to radioactive iodine, as a consequence of Chernobyl accident.

Diagnosis

Thyroid nodules are usually asymptomatic. Most of them are found by the patient himself or during a physical examination. The diagnostic evaluation of thyroid nodules essentially relies on serum TSH determination, ultrasonography which is useful for establishing the size of the lesion and its solid or cystic nature and of ► Fine-Needle Aspiration Cytology. In some cases, cytology cannot differentiate adenoma from carcinoma and the use of immunohistochemical markers contributed only marginally to better defining FTC.

Thyroid scan is performed only in patients with a low serum ►TSH level, to ascertain the presence of a hot nodule. Computerized tomography scans and magnetic resonance imaging are performed only in the rare patients with extensive disease. Thyroid carcinomas may release amounts of thyroglobulin in blood but high levels are also found in a variety of benign thyroid diseases and should not be measured.

Treatment

In the vast majority of cases, follicular adenomas are simply followed up with no therapy. Surgery is indicated only when compression or discomfort is present.

Initial treatment of thyroid carcinomas is based on total thyroidectomy with central lymph node dissection in patients with a PTC. Radioiodine is administered post operatively only in patients with either persistent disease or with poor prognostic indicators, such as age $\geq$ 45 years, poorly-differentiated carcinomas and extended disease.

All patients with thyroid cancer are treated post-operatively with levothyroxine.

Follow-up aims to detect persistent or recurrent disease at an early stage and is based on the combined use of thyroglobulin testing following recombinant human TSH stimulation and of neck ultrasonography. The majority of patients are cured, as demonstrated by the work-up performed at 1 year.

Genetics

The putative relationships between adenomas and carcinomas and the mechanisms of ►thyroid carcinogenesis are not clearly understood. Activating point mutations of the *RAS* gene are detected in 30–40% of benign and malignant follicular thyroid tumors. Chromosomal imbalances are also frequent in FTCs, particularly the PAX8-PPARγ1 rearrangement that is found in about 30% FTCs but also in some follicular adenomas. These observations suggest that FTC proceeds from at least two distinct oncogenic events, namely *RAS* mutations and PAX8-PPARγ1 rearrangement. Papillary thyroid carcinomas are characterized in 70% of cases by the presence of either a ►RET/PTC rearrangement, or an activating point mutation of *RAS* or *BRAF* genes. These genetic alterations are independent and nonoverlapping, and induce a constitutive activation of the MAP-kinase pathway. The higher frequency of RET/PTC rearrangements in radiation-associated PTC and also in some adenomas suggest that they may be directly induced by radiation exposure. Overexpression of several growth factors, such as ►MET, ►VEGF, ►FGF1 and 2 and ►IGF1, is believed to be secondary to other oncogenic events. Finally, inactivating mutations of the ►p53 gene are found only in ►anaplastic thyroid carcinomas.

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Folliculin

►Birt–Hogg–Dubé Syndrome

Food-derived Heterocyclic Amines

Definition

Are mutagens formed by the condensation of creatine with amino acids when protein rich foods like meats are cooked at high temperatures. These compounds have been implicated as risk factors for a number of human cancers and cause tumors in animal models.

►Arylamine *N*-Acetyltransferases

Food for Specified Health Use

►Nutraceuticals

FOR

►WWOX

Foreign Substances

►Xenobiotics

Forkhead

Definition

FKHR; ►FOX; ►Forkhead box M1.

Forkhead Box M1

Andrei L. Gartel
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Synonyms

HFH-11B; Trident; WIN; FKHL-16; MPP2

Definition

FoxM1 is a transcription factor of the Forkhead family. The Forkhead family consists of about 50 transcription factors that share a conserved 100 amino acid (Forkhead or winged-helix) DNA binding domain, which is responsible for DNA binding via the consensus TAAACA site. The human FoxM1 gene contains ten exons, and it expressed as three alternatively spliced variants (a, b, c). FoxM1 is generally expressed in dividing cells and it is required for proper cell proliferation. Furthermore, FoxM1 is essential for the execution of ►mitosis, and it is overexpressed in most human cancers. FoxM1 may directly induce tumorigenesis because of its dominant role in cell proliferation. Therefore, FoxM1 is an attractive target for small molecule inhibition in cancer treatment.

Characteristics

FoxM1 expression correlates with the proliferative state of cells. It is expressed in all embryonic tissues and in proliferating cells of epithelial and mesenchymal origin. FoxM1 expression is not detectable in quiescent cells, but it is induced when these cells are stimulated to re-enter cell cycle. Along these lines, FoxM1 is also expressed in the majority of dividing mammalian cells, but its expression is turned off in terminally differentiated, non-dividing cells. Developmental studies suggest that FoxM1 may play a role in the development of nervous system and it is critical during organogenesis. FoxM1 is required for hepatoblast differentiation toward biliary epithelial cell lineages and for embryonic development of pulmonary vasculature. FoxM1 expression is also induced in proliferating cells following lung and liver injury suggesting that FoxM1 is essential for ►tissue regeneration and repair. Similarly, endothelial cell-restricted FoxM1-deficient mice exhibited a marked impairment in endothelial barrier repair and a significant increase in mortality following acute lung injury. Following vascular injury, FoxM1$^{-/-}$ lungs displayed diminished cell proliferation, increased expression of ►CDK inhibitor p27 and decreased expression of ►cyclin B1 and ►Cdc25. Deletion of FoxM1 in endothelial cells led to decreased expression of cell cycle promoting proteins and Cdk activities suggesting that FoxM1 plays a critical role in the restoration of endothelial barrier function following vascular injury.

FoxM1 is induced early during the G1 phase of the cell cycle and its expression continues through S phase and mitosis. Transcriptional activity of FoxM1 is dependent on its phosphorylation because cyclin-CDK1/2-dependent phosphorylation of FoxM1 during the cell cycle is required for the recruitment of the transcriptional co-activator ►p300/CBP. FoxM1 activation is also dependent on Ras-MAPK pathway, which regulates FoxM1 subcellular localization and transcriptional activity. Overall, it is appears that multiple FoxM1 phosphorylation events may regulate its activity during cell cycle progression. FoxM1 is required for the execution of the mitotic program because FoxM1-depleted cells fail to progress beyond the prophase stage of mitosis. FoxM1 transcriptionally activates ►cyclin B, ►survivin, ►Aurora B kinase, ►Cdc25 phosphatase and Plk1, all of which are implicated in mitosis. In addition, FoxM1 induces cell cycle progression through transcriptional induction of Skp2 and Cks1 genes (specificity subunits of Skp1-Cullin1-F-box ubiquitin ligase complex) that leads to the degradation of cell cycle/►cyclin-dependent kinase inhibitors p21^{WAF1} and p27^{KIP1}. FoxM1c also transactivates ►c-myc, c-*fos*, ►*hsp70* and histone *H2B/a* genes all of which are involved in proliferation and tumorigenesis.

FoxM1 is one of the most significantly upregulated genes in human solid tumors. FoxM1 is overexpressed in non-small cell lung carcinomas, anaplastic astrocytomas, glioblastomas, basal cell carcinomas, hepatocellular carcinomas and intrahepatic cholangiocarcinomas. Furthermore, FoxM1 is overexpressed in primary breast tumors, and its depletion by RNA interference (RNAi) in these cancer cells leads to mitotic catastrophe. Since FoxM1 expression is specifically increased in breast carcinomas relative to normal tissue FoxM1 could be involved in promoting cellular transformation of breast epithelial cells. Approximately 60–80% of all breast cancers overexpress estrogen receptor (ER) and ER plays a key role in breast cancer development. It was shown that FoxM1 is a transcriptional regulator of ER expression in breast cancer cells and silencing of FoxM1 expression in breast cancer cells using RNAi resulted in strong inhibition of ER expression. FoxM1 expression is essential for the

development of liver cancer because it was demonstrated that FoxM1$^{-/-}$ mice livers are highly resistant to developing hepatocellular carcinomas in response to a Diethylnitrosamine (DEN)/Phenobarbital (PB) liver tumor induction protocol. Inhibition of FoxM1 transcriptional activity by a cell-penetrating peptide containing amino acids 24-46 of FoxM1►p19^{ARF} also reduced anchorage-independent cell growth and inhibited development of liver cancer in DEN/PB mouse models.

FoxM1 also contributes to cellular transformation by human papillomavirus HPV-16 by interaction with oncogenic HPV-E7 protein. This interaction increases the transforming activity of HPV-E7 and enhances the transcriptional activity of FoxM1. Increased levels of FoxM1 accelerated prostate cancer development and progression in mouse models. Knockdown of FoxM1 by RNAi in several prostate cancer cell lines led to a significant reduction in cell proliferation and anchorage-independent cell growth in soft agar. FoxM1 was significantly overexpressed in basal cell carcinomas (BCCs), but not in ►squamous cell carcinomas. Constitutive expression of the transcription factor ►Gli1, the known target of ►Sonic Hedgehog (Shh) signaling, led to induction of FoxM1 mRNA expression, and coexpression of Gli1 and FoxM1 proteins was observed within the same BCC tumor sample. Since Shh plays a key role in the development of BCC, FoxM1 may be a putative target of Shh pathway. Similarly, in gliomas where Shh is also implicated in tumorigenesis FoxM1 protein has been overexpressed. The levels of FoxM1 expression in human glioma tissues was directly correlated with the glioma grade and inversely correlated with patient survival. Enforced FoxM1 expression in non-tumorigenic glioma cell lines caused them to form xenograft tumors in nude mice, while inhibition of FoxM1 expression by RNAi suppressed their anchorage-independent growth in vitro and tumorigenicity in vivo.

Since FoxM1 is overexpressed in many types of cancer where it may be required for proliferation of cancer cells, it is an attractive target for drug development. To obtain a screening system for the identification of small molecule inhibitors of FoxM1 transcriptional activity in a high-throughput fashion, we developed a cell line that stably expresses doxycycline/tetracycline-inducible FoxM1-GFP, firefly luciferase under the control of multiple FoxM1 response elements, and a control renilla luciferase under the CMV promoter. We used this cell line to screen for FoxM1 transcriptional inhibitors in libraries of small molecules (Challenge Set and Diversity Set) obtained from NCI. We selected only those compounds that specifically inhibit FoxM1 and we identified a well-known thiazole group antibiotic ►siomycin A (NSC-285116) as an inhibitor of the transcriptional activity of exogenous and endogenous FoxM1. In addition, using quantitative real-time RT-PCR, we found that the mRNA levels of the transcriptional targets of FoxM1, such as ►Cdc25, ►survivin and CENPB were sufficiently reduced after ►siomycin A treatment. Furthermore, Siomycin A may antagonize FoxM1 function by at least two distinct mechanisms – one by blocking its phosphorylation, thereby leading to its reduced transactivation ability, and the other by down-regulating its mRNA and protein levels. Using clonogenic assay, siomycin A may act as an effective inhibitor of FoxM1-based cellular transformation. In addition, siomycin A induced potent apoptosis in human breast and liver cancer cell lines, that correlated with inhibition of FoxM1 expression. Now, it is necessary to determine if inhibition of FoxM1 by siomycin A leads specifically to apoptosis of cancer cells, and to test this drug in animal models of human cancer. FoxM1 inhibitors such as siomycin A or other small molecules may have potential as anticancer drugs.

In summary, FoxM1 is often overexpressed in many types of human tumors and it appears that FoxM1 expression is critical in the process of cellular transformation. FoxM1 function is inhibited by several tumor suppressors, such as ►p19 ARF, pRb, p16 and p53 and may be activated by multiple oncogenic signaling pathways suggesting that FoxM1 may be classified as a proto-oncogene. However, it remains to be elucidated if overexpression of FoxM1 in cancer cells is a result of cell transformation that leads to increased proliferation and FoxM1 expression, or whether FoxM1 directly collaborates with other oncogenes to induce cell transformation. In any case, if cancer cells require high levels of FoxM1 expression for their survival, then FoxM1 appears to be an attractive target for anticancer therapy. Identification of the FoxM1 inhibitor siomycin A suggests that targeting of FoxM1 by small molecules is a feasible alternative and in a short time this approach may help to identify novel anticancer compounds for clinical trials.

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Formalin-fixed Paraffin-embedded Tissue

Definition

The usual process needed for a tissue to be studied under the microscope in ►Pathology. Because of this process most high molecular weight DNA is destroyed as well as almost all RNA molecules. Therefore it is a good source of small-sized DNA molecules, and an inconsistent way to get RNA.

Formation of New Blood Vessels

►Angiogenesis

Forward Chemical Genetics

Definition

An approach to studying biology in which a compound that induces a particular biological phenotype is first detected. Subsequently, the affected target and its relationship to the phenotype are identified.

►Small Molecule Screens

FOS

Definition

v-fos FBJ murine osteosarcoma viral oncogene homolog, is a leucine-zipper protein of 380 amino acids and 40 kD. The human FOS gene locus maps at 14q24.3 and the mouse fos gene locus at chromosome 12 (40.00 cM). FOS is a protooncogene and c-Fos is a nuclear phosphoprotein that forms a tight but non-covalently linked complex with c-Jun to the ►AP-1 transcription factor. c-Fos expression increases rapidly upon growth factor stimulation or wounding of cultured cells.

Fossil Tree

►Ginkgo Biloba

F

FOX

Definition

Refers to Forkhead box genes; Encode a family of ►transcription factors that play important roles in regulating the expression of genes involved in cell growth, proliferation, differentiation, and longevity. Many FOX proteins are important to embryonic development and some are implicated in tumorigenesis by their expression level.

►Forkhead box M1

FOXC2

Definition

A forkhead family transcription factor that is expressed in human lymphatic vessels. Studies in mice indicate this transcription factor regulates lymphatic capillary and valve development as deletions of this gene cause aberrant lymphatic vessel development that resembles the human disease ►lymphedema-distichiasis.

►Lymphangiogenesis

FOXO1A

Definition

Is the acronym for forkhead box O1A (►rhabdomyosarcoma), also known as FKHR.

►Beckwith-Wiedemann Syndrome Associated Childhood Tumors

FOXO 3A

Definition
Forkhead box O3A, a member of the forkhead family of transcription factors.

►PUMA

FPC

►Familial polyposis coli
►APC Gene in Familial Adenomatous Polyposis

FRA3B

Definition
The fragile site or region at chromosome region 3p14.2. The constitutive fragile site at 3p14.2 (FRA3B) is the most frequently activated constitutive fragile site, with up to 50% of normal lymphocyte derived metaphases showing the characteristic gaps or decondensation at 3p14.2 after ►aphidicolin treatment. Common or constitutive fragile sites are now known to be fragile regions; i.e. the position of the gaps can occur at many different sites within a fragile region, which may extend up to a megabase in size.

►FHIT
►Fragile Sites

FRA16D

Definition
The fragile site or region at chromosome region 16q23.3.

►WWOX
►Fragile Sites

Fragile Histidine Triad

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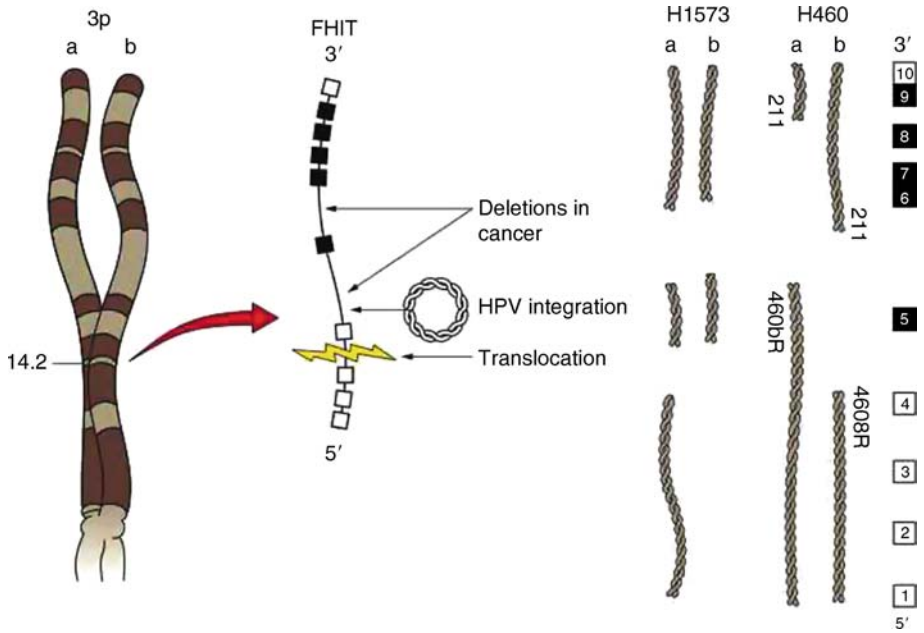
Synonyms
FHIT

Definition
The Fragile Histidine Triad (*FHIT*) gene, at human chromosome region 3p14.2 encompasses a familial ►clear cell renal cancer chromosome translocation breakpoint and the most active chromosomal constitutive ►fragile site, ►*FRA3B*. The gene is inactivated in a large fraction of most types of human cancers, through intragenic ►hemizygous or ►homozygous deletions, ►hypermethylation of regulatory region ►CpG islands, or a combination of these mechanisms, probably as a result of ►DNA damage to the *FRA3B* fragile region.

Characteristics
The Gene
The *FHIT* genomic locus spans >1.6 Mb of DNA, while the *FHIT* cDNA is 1.1 kb. Fig. 1 illustrates the structure of this ►tumor suppressor gene and the positions of fragile region landmarks such as the familial renal cancer translocation and the ►human papillomavirus integration site. The right side of Fig. 1 illustrates the types of biallelic deletions observed in this locus in lung cancer and other cancer-derived cell lines. Sequencing of the gene and isolation of cancer cell deletion endpoints revealed that many deletion endpoints are within recombined LINE-1 repeats, suggesting that ►carcinogen damage to the fragile region is repaired through recombination between LINE-1 (►LINE element) sequences flanking the damaged region, with concomitant loss of portions of the *FHIT* gene. The murine *Fhit* locus is also fragile and the mouse Fhit protein is more than 90% identical to human Fhit. One *Fhit* allele was inactivated in murine ►embryonic stem (ES cells) to create *Fhit* ►knockout mice in which the gene is functionally inactive. Mice heterozygous or homozygous for the mutant *Fhit* locus are fertile, long-lived and exquisitely sensitive to tumor induction by carcinogens.

The Protein
The amino acid coding region begins in exon 5, ends in exon 9 (Fig. 1) and encodes a protein of 147 amino acids.

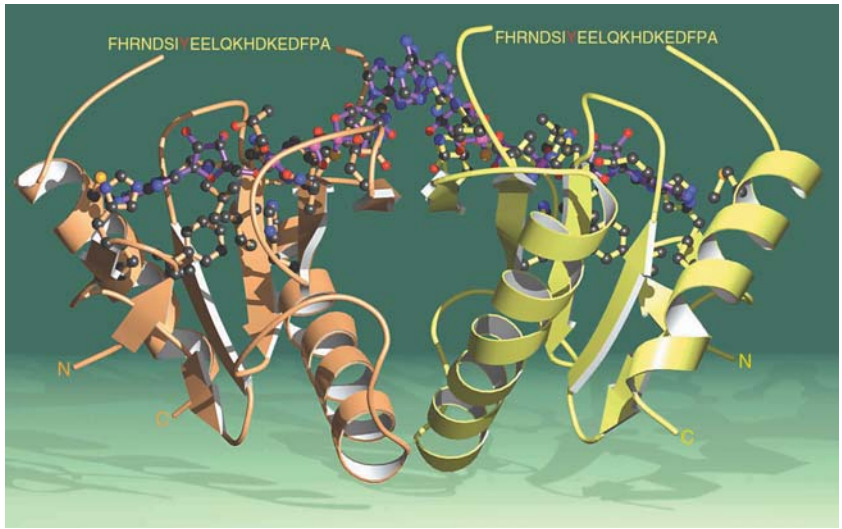


Fragile Histidine Triad. Figure 1 The *FHIT* gene at chromosome region 3p14.2. The gene encompasses *FRA3B* where numerous chromosomal alterations are observed in cancer cells. This locus is highly susceptible in all individuals to carcinogen-induced breakage. As a consequence chromosomal alterations including deletions, insertions and translocations occur. The chromosome alterations frequently lead to loss of parts of the Fhit protein-coding sequence and the consequent loss of Fhit protein expression (on the right are examples of alleles in lung cancer-derived cells). The *FHIT* gene is hemi- or homozygously deleted in the majority of lung, stomach, esophageal and kidney cancers and in a large fraction of many other cancers; point mutations are almost never observed. Fhit protein is absent or reduced in lung, stomach, kidney and other cancers, consistent with a role as a tumor suppressor and fulfilling the prediction that fragile site alterations contribute to the neoplastic process.

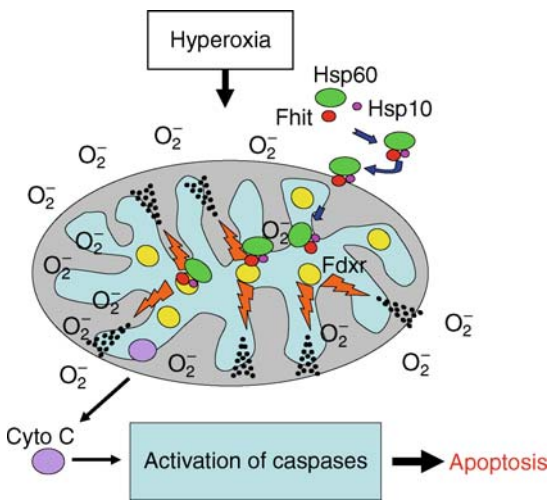
The Fhit protein is a member of a large Histidine Triad (HIT) gene family of nucleotide binding proteins with four conserved histidine residues, three of which occur in a histidine triad, HxHxHxx (where "x" is hydrophobic). There are more than thirty HIT genes in species representing all branches of life. Fhit and its orthologs form a closely related subfamily of HIT proteins, found only in eukaryotes, that bind and hydrolyze dinucleoside oligophosphates, especially diadenosine tri- or tetraphosphates (Ap3A, Ap4A), to produce a nucleoside monophosphate plus a nucleoside di- or tri-phosphate. Site-directed mutagenesis of the conserved Fhit histidine residues to asparagines results in decreased enzymatic activity for each mutation, with the largest change occurring with replacement of the central histidine, H96. Thus, H96 is essential for hydrolysis of the diadenosine tri- or tetra-phosphate but the Fhit H96N mutant still acts as a tumor suppressor, in accord with the proposal that the Fhit-substrate complex sends the tumor suppression signal. Fhit is constitutively dimeric, existing as a highly curved, ten-stranded antiparallel-sheet, which presents nucleotides on the top surface. Amino acids 107-127, following the catalytic site, form an unstructured loop (Fig. 2) within the loop, amino acid Y114 can be phosphorylated by ►Src family kinases and FhitY114 mutant proteins lose apoptotic and tumor suppressor functions. Protein cross-linking and ►proteomics methods were used to characterize a Fhit protein complex involved in triggering Fhit-mediated apoptosis. This complex includes ►Hsp60 and Hsp10 that mediate Fhit import into mitochondria, where it interacts with ►ferredoxin reductase (Fdxr), responsible for transferring electrons from NADPH to cytochrome P450 via ferredoxin (Fig. 3). Fhit restoration significantly increases the production of ►reactive oxygen species (ROS) and the rate of ►apoptosis of lung cancer cells under oxidative stress conditions; conversely, Fhit-negative cells escape apoptosis, carrying serious oxidative DNA damage that may contribute to an increased mutation burden.

Bioactivity

The biological functions of Fhit have been studied in human cancer cell lines stably over-expressing exogenous Fhit. Tumorigenicity was suppressed in gastric, lung, renal and breast cancer lines. Similarly, cancer cell lines infected with adenovirus carrying the *FHIT* gene were killed by apoptosis. Fhit sends signals for apoptosis



Fragile Histidine Triad. Figure 2 Architecture of Fhit–substrate complex. View of the Fhit dimer with bound substrate. Monomers of Fhit are yellow and copper; substrate molecules are purple. Atoms are colored as follows: carbon, black; nitrogen, blue; oxygen, red; phosphorus, magenta; sulfur, orange. The amino acid sequence of the unstructured loop is also shown. (adapted from Pace et al. (1998) Proc Natl Acad Sci USA 95:5484–5489).



Fragile Histidine Triad. Figure 3 Model depicting proposed Fhit signal pathway induced by hyperoxia. Fhit protein binds the Hsp/Hsp10 complex in the cytosol, and is carried to the mitochondria; in the mitochondria Fhit interacts with Fdxr protein and in the presence of H_2O_2, which creates hyperoxic conditions, ROS is generated, leading to release of cytochrome C, followed by apoptosis. Reduced Fhit leads to reduced ROS and reduced apoptosis.

in response to various types of cellular stress: in response to DNA damaging agents such as ►UVC light and ►mitomycin C, Fhit-deficient cells escape apoptosis and accumulate mutations; over-expression of wild-type Fhit leads to reduced expression of activated ►Akt and ►Survivin, reduced expression of cyclophilin A, and reduced expression of phospho ►Chk1; Fhit, when over-expressed, enters mitochondria, interacts with Fdxr protein and causes an increase in Fdxr protein level, associated with generation of ROS and followed by programmed cell death (Fig. 3). Fhit does not affect the *FDXR* transcriptional level but may affect stability of the protein. Fhit localizes in both cytosol (where it interacts with Hsp60 and Hsp10) and mitochondria where it interacts with main mitochondria chain respiratory proteins. Interestingly, Fhit restoration significantly increases the production of ROS in lung and colon cancer-derived cells in response to stressful treatments. Study of Fhit deficient mouse tissue-derived and human cancer-derived cells *in vitro* has led to several important conclusions: Fhit is not a cell cycle regulated gene; repair protein-deficient cancers are more likely to be Fhit-deficient; Fhit-deficient cells show enhanced resistance to UVC, ►mitomycin C and ►ionizing radiation-induced cell killing, possibly due to strong activation of the ►*ATR/CHK1* pathway following DNA damage; Fhit-deficient cells show higher efficiency of homologous recombination repair, a major double-strand break repair pathway. The DNA damage-susceptible *FRA3B/FHIT* chromosome fragile region paradoxically encodes a protein that is necessary for protecting cells from accumulation of DNA damage, through modulation of ►checkpoint proteins and inactivation of Fhit contributes to accumulation of abnormal checkpoint phenotypes in cancer development.

Clinical Relevance

More than 640 reports describe the involvement of Fhit loss in development in nearly every type of cancer. Important findings are that: (i) large fractions of kidney, lung, gastric, colon, pancreatic, breast, cervical and other cancers show absence of expression of Fhit protein, suggesting that its inactivation is critical in the progression of many human cancers, especially cancers of organs directly exposed to environmental carcinogenic agents; (ii) loss of Fhit expression in cancers can result from hemi or homozygous deletion or translocation within the *FHIT* gene or hypermethylation of CpG islands in the promoter region or a combination of these mechanisms; (iii) Fhit loss is a very early step in development of some types of cancers and can be associated with prognostic features or survival; (iv) loss of Fhit protein is associated with loss of other fragile genes in breast cancer; (v) an ►SNP within the *FHIT* locus is associated with development of ►prostate cancer in some families with increased prostate cancer susceptibility; (vi) *FHIT* restoration in a number of malignant cell lines triggers ►apoptosis *in vitro* and in preclinical models; (vii) *Fhit* knockout mouse strains show approximately tenfold enhanced susceptibility to carcinogen-induced tumors and have been useful in development of tumor models for prevention and therapeutic studies; oral Fhit gene therapy can prevent and reverse tumor growth in Fhit-deficient mice; (viii) Fhit enhances ROS-related apoptotic effects of chemotherapeutic agents.

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Fragile Sites

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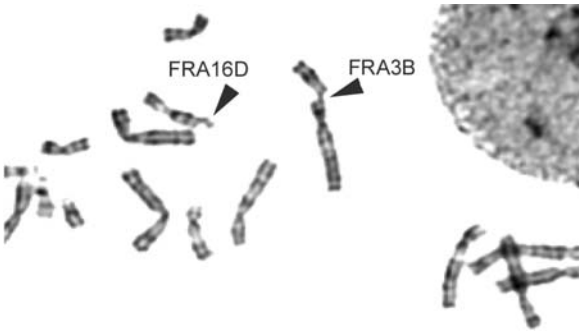
Definition

Fragile sites are specific chromosomal loci that are especially prone to forming gaps and break as seen on ►metaphase chromosomes under conditions of replication stress.



Fragile Sites. Figure 1 Examples of the common fragile sites FRA3B (3p14.2) and FRA16D (16q23) on human chromosomes.

Characteristics

Expressed fragile sites are seen as gaps and breaks on metaphase chromosome preparations of cultured cells. Fragile sites are not usually expressed on chromosomes under normal replication conditions, but rather become detectable under conditions that partially inhibit DNA replication. The formation of gaps and breaks at fragile sites is thought to represent an underlying unusual aspect of chromosome structure or function.

Categories of Fragile Site

Fragile sites are broadly classified into two main categories, rare and common based on their population frequency, pattern of inheritance and method of induction.

Rare Fragile Sites

►Rare fragile sites are seen in a small proportion of individuals and are inherited in a Mendelian manner. Some, such as FRAXA, are associated with human genetic disorders, and their study led to the identification of nucleotide-repeat expansion as a frequent mutational mechanism in humans. There are currently 31 known rare fragile sites. Nine of these have been cloned: FRAXA (Xq27.3), FRAXE (Xq28), FRAXF (Xq28), FRA10A (10q23.3), FRA10B (10q25.2), FRA11B (11q23.3), FRA12A (12q13.1), FRA16A (16q13.11), and FRA16B (16q22.1).

The major group of rare fragile sites is the folate-sensitive group, associated with CGG-repeat expansion. This group includes FRAXA, in the *FMR1* gene, which is responsible for the ►fragile-X syndrome, and FRAXE in the *FMR2* gene, which is associated with nonspecific mental retardation. In addition, an autosomal folate-sensitive fragile site, FRA12A, in the *DIP2B* gene has recently been associated with mental retardation. Other non-folate sensitive rare

fragile sites, characterized by expanded AT-rich minisatellite repeats, are induced by ►bromodeoxyuridine or ►distamycin-A.

Common Fragile Sites

►Common fragile sites (CFSs), comprise the largest class of fragile sites. These sites are found in all individuals and are considered to be a normal component of chromosome structure. Unlike rare fragile sites, CFSs are not caused by expansion of ►trinucleotide repeats. CFSs form gaps and breaks on metaphase chromosomes when DNA synthesis is partially inhibited by folate stress or using compounds such as ►aphidicolin, an inhibitor of DNA polymerases. In addition to forming gaps and breaks on metaphase chromosomes, CFSs exhibit additional features of unstable DNA. They are hot spots for deletions, sister ►chromatid exchanges, ►chromosomal translocations, integration of transfected and viral DNA sequences, and chromosome breaks associated with initiation of gene ►amplification.

There are over 76 different CFSs with one or more seen on most human chromosomes. However, just 20 of these sites account for more than 80% of all gaps and breaks seen in aphidicolin-treated lymphocytes. The most highly expressed of these sites are FRA3B (3p14.2) and FRA16D (16q23). CFS regions span several hundred kilobases to over a megabase of DNA. Despite their size, a number of these sites are fully contained within large genes such as the tumor suppressor genes ►*FHIT* (fragile histidine triad gene) at 3p14 and ►*WWOX* (WW domain containing oxidoreductase) at 16q23.

CFSs appear to be highly conserved during mammalian evolution. ►Orthologs of human CFSs have been found in the ►syntenic regions of a number of other mammalian species, including other primates, cat, dog, pig, horse, cow, Indian mole rat, deer mouse, and laboratory mouse strongly suggesting an underlying function for these sites in the normal functioning of the cell.

Molecular Basis of Fragile Site Expression

Rare Fragile Sites

The expression of all rare fragile sites studied at the molecular level is dependent on an expansion of repeat DNA sequences. Most, such as the folate sensitive fragile site FRAXA (Xq27.3) in the 5′ non-coding region of the *FMR-1* gene, are caused by an expansion of CGG trinucleotide repeats. Normal individuals have anywhere from 1–50 CGG repeats. Whereas, in the disease state the number of repeat units increases dramatically, to 200–2,000 repeats. Trinucleotide repeats are inherited in a Mendelian manner but also follow a phenomenon known as ►anticipation whereby an increase of severity of symptoms and an earlier age of onset of disease is seen in succeeding generations. Other rare fragile sites are associated with an expanded AT-rich minisatellite repeat sequence. The rare fragile sites FRA16B (16q22.1) and FRA10B (10q25.2) are examples in which expansion of the existing AT-rich minisatellite repeats, to 33 and 42 base pairs respectively, is the cause of fragility.

Common Fragile Sites

Less is currently known about the molecular basis of expression of common fragile sites. While similar in appearance to rare fragile sites at the cytogenetic level, common fragile sites are not caused by expansion of trinucleotide or other simple repeat sequences. All common fragile sites are AT-rich and contain numerous repeat elements such as, LINES, SINES, and other long repeat elements. Common fragile sites contain clusters of sequences with a potential for high ►DNA flexibility and formation of unusual DNA structures that could impede DNA replication. Furthermore, these sites are among the last sites in the genome to replicate and late or incomplete DNA replication may contribute to their fragility. Despite these findings there is no clear answer as to why these sites are more sensitive to replication stress than other none fragile loci.

Cellular Regulation of Common Fragile Site Instability

Mechanisms of fragile site expression provide important clues about the consequences of stalled or perturbed replication in mammalian cells. It has been shown that the ►ATR (►ataxia-telangiectasia and rad3-related) protein kinase is crucial for maintaining fragile site stability. ATR is a major cell cycle checkpoint protein that responds to replication stress and stalled replication forks by blocking cell cycle progression. Deficiency of ATR leads to a spontaneous expression of fragile sites that is amplified 8–10 fold when cells are treated with aphidicolin. Consistent with these findings, it has been shown that individuals with the genetic disease ►Seckel syndrome 1 have a hypomorphic mutation in *ATR* and show increased fragile site breakage following exposure of cells to aphidicolin. It has also been shown that the ►*BRCA1*, the ►Fanconi anemia family gene *FANCD2*, *CHK1*, *HUS1* and *SMC1* also play important roles in sensing and ►repair of DNA damage at common fragile sites and that loss of any of these genes leads to an increase in common fragile site expression.

Once broken, CFSs are repaired by a variety of cellular mechanisms. It has been shown that ►*RAD51*, *DNA-PKcs*, and *Ligase IV* are all important for repair of broken sites and that loss of any of these genes causes an increase in detectable gaps and breaks on metaphase chromosomes.

It is hypothesized that increased ►replication stress leads to collapsed or delayed replication forks,

incomplete replication of the associated regions, and large single-strand gaps, some of which can escape ►G2/M checkpoints. CFSs are more prone to forming gaps and breaks under replication stress than are other sites in the genome. When checkpoints are perturbed or absent, as is the case when ATR is lost, instability increases dramatically through out the genome but common fragile sites are more strongly affected. Furthermore, loss of genes that would normally function to repair damaged sites can also lead to an increase in visible gaps and breaks at CFSs on metaphase chromosomes. Thus, breaks at CFSs can serve as "signatures" of increased replication stress and are valuable cytological markers for the study of checkpoint and repair pathways that respond to replication stress.

Clinical Relevance

Rare Fragile Sites

The FRAXA rare fragile site at Xq28 is a cytogenetic manifestation of the expanded CGG repeat mutation in the promoter region of the *FMR1* gene associated with the ►fragile-X syndrome, a leading cause of mental retardation in humans. Large repeat length leads to methylation and transcriptional inactivation of *FMR-1* and thus phenotypic expression of any associated disease. Individuals with a moderate repeat length, 50–100 repeats, are considered to have premutations of the disease. In this moderate repeat expansion state clinical manifestations of the associated disease are possible, including the recently described FXTAS (fragile-X tremor ataxia syndrome) however, symptoms are less severe and less frequent than in the full mutation state. A similar fragile site on the X chromosome, FRAXE (Xq28), is associated with the genes *FMR2* and *FMR3* and can lead to mild mental retardation in some families. FRA11B (11q23.3) on the long arm of chromosome 11 is believed to lead to terminal deletions of chromosome 11 in a small number of cases of Jacobsen syndrome. In addition, an autosomal folate-sensitive fragile site, FRA12A, in the *DIP2B* gene has recently been associated with mental retardation. It is likely that other rare fragile sites will be found to be associated with specific genes and genetic diseases.

Common Fragile Sites

At least two of the thirteen cloned common fragile sites lie within known ►tumor suppressor genes. FRA3B (3p14.2) spans over 500Kb of sequence and is centered on exon 5 of the *FHIT* gene. Deletions within FRA3B (3p14.2) have been found in solid tumors and are associated with loss or alteration of the *FHIT* gene. Specifically, alteration or deletion of the *FHIT* gene has been found to frequently occur in ►Barrett esophagus, gastric, colon, lung and other types of cancer cells. FRA16D (16q23) is centered on exons 6, 7, and 8 of the *WWOX* gene. The *WWOX* gene has been implicated in both ►apoptosis and tumor suppression, and deletions of *WWOX* have been found in a number of gastric adenocarcinomas and multiple myelomas. Consistent with the finding that fragile sites are sensitive to replication stress, there is evidence that deletions at common fragile site regions appear very early during tumorigenesis and precede more global genomic deletions and ►LOH in cells with activated DNA-damage checkpoint response genes such as *ATR* and ►*ATM*. In addition, two groups have reported that the ATR checkpoint pathway is activated very early during tumorigenesis in response to unknown factors that lead to replication stress

These and many similar data suggest that common fragile sites are frequently unstable in cancers and can lead to the deletion or alteration of tumor suppressor genes associated with them. Lower expression or loss of tumor suppressor genes such as *FHIT* or *WWOX* may increase susceptibility for development of certain cancers. Because of this, it is probable that the expression of common fragile sites plays a significant role in the early stages of tumor formation. Additionally, due to the frequency of deletions at common fragile sites early in tumorigenesis, deletions at these sites can be used as signatures of increased replication stress and early tumorigenesis.

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Fragile-X Syndrome

Definition

A genetic disease associated with the rare fragile site FRAX and caused by an expanded CGG trinucleotide repeat in the *FMR1* gene. This is the most common cause of inherited mental retardation.

►Fragile Sites

Fragilomics

Definition

Referring to a systematic large scale study to identify the repertoire of ►fragile sites of the genome, to define the genes disrupted by fragile site activation and to determine the role they might have in human chronic diseases including cancer; the term fragilome was coined in the early 2004s as a linguistic equivalent to the concept of genomics.

Fragment Analysis

Definition

Method for the detection of ►polymerase chain reaction (PCR) fragments. Fluorescence labeled primers enable the detection and exact length calculation of PCR amplificates on sequencing machines.

►Leukemia Diagnostics

Frameshift Mutation

Definition

Is a genetic mutation that inserts in or deletes from a DNA sequence a number of nucleotides not evenly divisible by three. Consequently, the insertion or deletion disrupts the reading frame, or the grouping of the codons, resulting in a completely different translation from the original DNA.

Free Radicals

Definition

Are chemical species that possess at least one unpaired electron and are therefore unstable and highly reactive. The presence of unpaired electrons confers a considerable degree of reactivity upon a free radical. Free radicals can cause cellular damage by reacting with proteins, lipids, carbohydrates and DNA, and they are thought to be involved in the etiology of many human diseases including cancer, cardiovascular disease, and age-related diseases.

►Carotenoids
►Particle-induced Cancer
►Oxidative Stress
►Nonsteroidal Anti-Inflammatory Drugs
►Reactive Oxygen Species

Freeze Surgery

►Cryosurgery in Bone Tumors

FRNK

Definition

FAK-related nonkinase domain, the C-terminal domain of focal adhesion kinase, which functions as a negative regulator of kinase activity. Overexpression of FRNK inhibits cell migration.

►Focal Adhesion Kinase

FTC

Definition

Follicular Thyroid Carcinoma; ►Follicular Thyroid Tumors.

5-FU

►Fluorouracil

Fucosylation

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Definition

Is one of the most popular modifications with ►oligosaccharides on glycoproteins or glycolipid, which is involved in cancer. Fucosylation involves the attachment of a fucose residue to *N*-glycans, *O*-glycans, and glycolipids. *O*-fucosylation, which is a special type of fucosylation, is very important for ►Notch signaling. Increased levels of fucosylation have been reported in a number of pathological conditions, including ►inflammation and cancer. Therefore, certain types of fucosylated glycoproteins or antibodies, which recognize fucosylated oligosaccharides, have been used as tumor markers. The regulatory mechanisms of fucosylation are complicated.

Characteristics

Regulation of Fucosylation

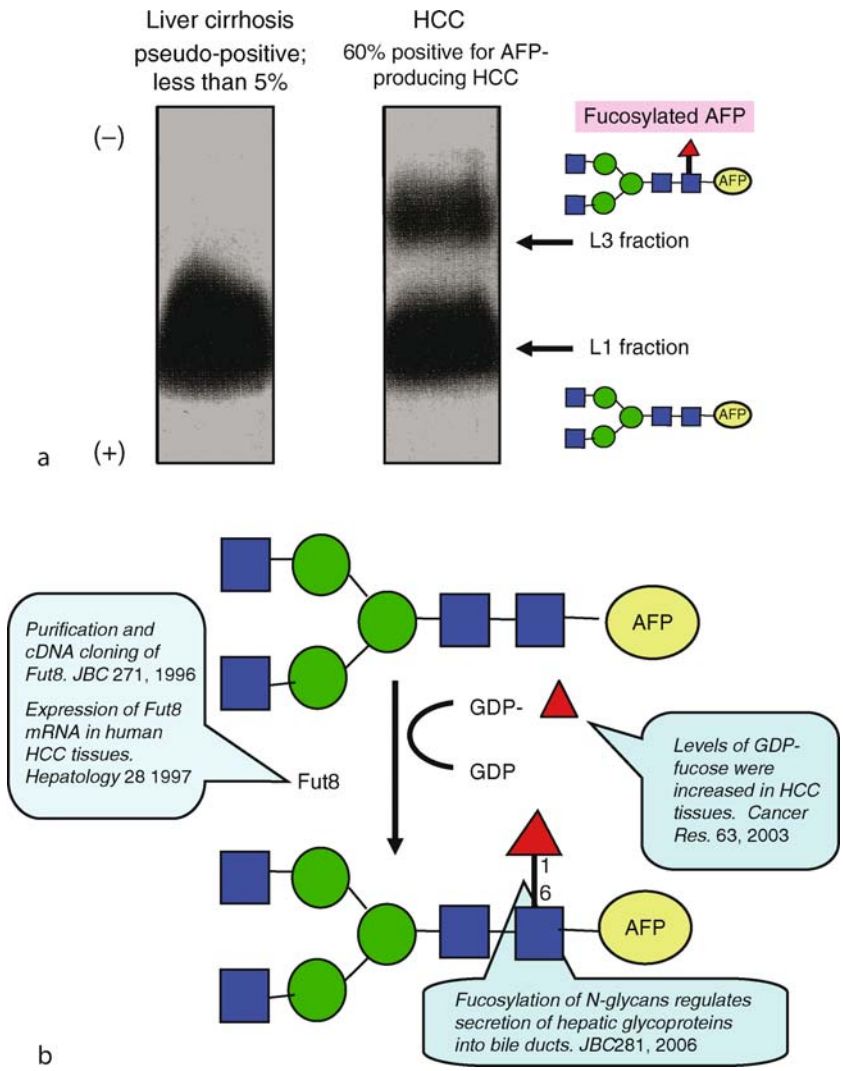
The regulation of fucosylation appears to be complicated, and depends on the type of cells or organs under consideration. Basically, fucosyltransferases, ►GDP-fucose synthetic enzymes, and GDP-fucose transporters are involved in the fucosylation pathway. There are 11 different, known fucosyltransferases (Fut) that have been identified to date, and they are divided into four groups. Fut1 and Fut2 are involved in the synthesis of α1-2 fucose, Fut3, 4, 5, 6, 7, and 9 in the synthesis of α1-3/α1-4 fucose, ►α1-6 fucosyltransferase (Fut8) in the synthesis of α1-6 fucose (►core fucose), and enzymatic activities as fucosyltransferases have not been confirmed in both Fut10 and Fut11. Fut8 has little homology with other fucosyltransferase members and plays an essential role in many biological phenomena because most Fut8 knockout mice die after birth. This drastic change is not observed in other Fut1~9 knockout mice. Core fucose, a product of Fut8 regulates the functions of many growth factor receptors and adhesion molecules. For example, depletion of the core fucose on the EGF receptor inhibits binding to its ligand, leading to the suppression of cell growth and the depletion of core fucose from α3β1 integrin suppresses that attachment of cells to laminin.

►Core Fucosylation and α-Fetoprotein

The expression of Fut8 is quite low in normal liver and increased levels of fucosylated proteins in serum can be used as a tumor marker because numerous serum proteins are produced in the liver. A representative of such a case is fucosylated ►α-fetoprotein (AFP), which can be detected by LCA (lens culinaris) lectin affinoelectrophoresis. AFP is a well-known tumor marker for ►hepatocellular carcinoma (HCC), but it is sometimes also increased in benign liver diseases such as chronic hepatitis and liver cirrhosis. In contrast, fucosylated AFP, referred to ►AFP-L3 (Fig. 1a), is very specific for HCC and was approved as a tumor marker for HCC by the FDA (Food and Drug Administration) in 2005. The molecular mechanisms underlying the production of fucosylated AFP in HCC are complicated. The enhancement of Fut8 is required to produce fucosylated AFP, but this enhancement is insufficient for the production of fucosylated AFP in HCC. GDP-fucose, a donor substrate for many fucosyltransferases is also a key factor in the production of fucosylated proteins. There are two different synthetic pathways for producing GDP-fucose in hepatocytes. One is a de novo pathway and the other is a salvage pathway. The de novo pathway is particularly dominant in hepatocytes and ►FX and GMD plays a pivotal role in the de novo pathway. While the expression of Fut8 is increased in both HCC and liver cirrhosis, the levels of FX are significantly increased in HCC tissues. The levels of GDP-fucose in cells or tissues can be measured using a novel ►HPLC assay and significant increases in GDP-fucose are observed in HCC tissues, compared to the surrounding tissue. In terms of the fucosylation pathway, many factors including fucosyltransferases, GMD, FX, and the GDP-fucose transporter appear to be coregulated. More importantly, fucosylated glycoproteins produced in hepatocytes are secreted into the bile, which is on the apical side of hepatocytes. When the oligosaccharide structures of bile and serum glycoproteins are compared by a lectin blot or 2D mapping, dramatic increases in fucosylation are observed in bile glycoproteins. Fut8 ►knockout mice show a decreased level of hepatic glycoproteins such as α1-acid glycoprotein and α1-antitrypsin in their bile, suggesting that fucosylation regulates the secretion of certain types of hepatic glycoproteins into the bile. The disruption of this system could be one of the mechanisms underlying the increases in fucosylated protein levels, including AFP-L3 in the serum of patients with HCC (Fig. 1b).

Fucosylation and Lewis Antigen

Fut3, 4, 5, 6, 7, and 9 are involved in the synthesis of the Lewis antigen. They function in a cell- or organ-specific manner. Sialyl Lewis X or sialyl Lewis A are used as tumor markers for certain types of cancer. Increases in these Lewis antigens in cancer tissues are correlated with a poor prognosis in colon cancer, due to the high incidence of liver metastasis. The reason for this is that Sialyl Lewis X is a ligand for selection which is expressed in endothelial cells. The first step of tumor metastasis is weak binding through an oligosaccharide and a lectin, followed by strong binding via integrins.



Fucosylation. Figure 1

Although these ►Lewis antigens are fucosylated oligosaccharides, other glycosyltransferases except fucosyltransferases are involved in its synthesis. The donor substrate, GDP-fucose is also important for the synthesis, but the Km values for these Lewis enzymes are different from that of Fut8. This type of fucosylation is also a signal for sorting hepatic glycoproteins into the bile. In the human liver, Fut6 is involved in the synthesis of Lewis types of fucosylation and hepatic glycoproteins with this oligosaccharide structure are present in the bile. In the case of mice, Fut6 is a pseudogene, and therefore the secretion of certain kinds of hepatic glycoproteins into the bile is disrupted in Fut8 knockout mice.

Fucosylated Haptoglobin and Pancreatic Cancer

In terms of glycomics, fucosylated glycoproteins are recognized by several types of ►lectins. These lectins include AAL, UEA, LCA, and AOL. AAL recognizes α1-3/α1-4 and α1-6 fucose, UEA recognizes α1-2 fucose, LCA recognizes the native form of α1-6 fucose with a mannose arm, and AOL recognizes α1-6 fucose more specifically. These lectins could be applicable to a diagnosis of cancer. In western blotting of the AAL lectin using serum from patients with ►pancreatic cancer, approximately 40 kD proteins were found to be highly fucosylated. The N-terminal sequence revealed that this protein was the haptoglobin β chain. The positive rate of fucosylated haptoglobin is 60–80% and the ratio is increased with the progression of the stage pf the disease. Increases in fucosylated haptoglobin levels have been observed in several types of cancer (20–40%) and, it was reported that high levels of fucosylated ►haptoglobin were produced in the advanced stage of ovarian cancer, lung cancer, and breast cancer. Basically, haptoglobin is produced in the

liver and has a low level of fucosylation on its glycans, since the expression of Fut8 is quite low in a normal liver. The ectopic expression of haptoglobin is observed in special conditions such as infections, inflammation, and cancer. The question herein is where fucosylated haptoglobin is produced in patients with pancreatic cancer. A special pancreatic cancer cell, PSN-1 expresses haptoglobin mRNA and produces fucosylated haptoglobin into conditioned medium. However, this case is very rare in comparison with the positive rate for fucosylated haptoglobin (60–80%). If white blood cells infiltrated around pancreatic cancer cells produce haptoglobin, they would be fucosylated, because blood cells express high levels of Fut8. The third hypothesis is that fucosylated haptoglobin produced in the liver is miss-sorted into the blood due to a factor that is secreted from pancreatic cancer cells. To determine which theory is correct, detailed analyses of oligosaccharide structures including the site-directed analysis of haptoglobin oligosaccharides need to be performed. Collectively, fucosylation is highly associated with cancer and additional, detailed information regarding its mechanism would be highly desirable, since it could be a target for novel cancer therapy.

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α1-6 Fucosyltransferase

Definition

Fut8; A glycosyltransferase that transfers fucose onto the innermost *N*-acetylglucosamine in *N*-glycans via an α1–6 linkage. It has no homology with other fucosyltransferases.

►Fucosylation

Fucosyltransferases

Definition

Enzymes that catalyze addition of fucose monosaccharides.

►Lewis Antigens
►Fucosylation

Fucoxanthin

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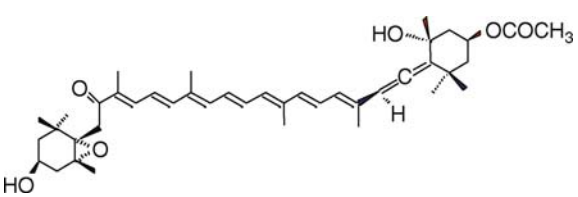
Definition

Is a xanthophyll that contains allenic bond, two hydroxy, keto, and epoxy groups. It is one of the most abundant ►carotenoids accounting for >10% of estimated total natural production of carotenoids. Further, fucoxanthin is the characteristic pigments of brown seaweeds (phaeophyceae) which are the largest occurring group among seaweeds. In South East Asian countries, some brown seaweeds containing fucoxanthin are often used as a food source (Fig. 1).

Characteristics

Effect on Cancer Cell Growth

Cell proliferation is the key in promoting and further progression of carcinogenesis. In a study screening the antiproliferative activity of seaweed extracts on tumor cells, fucoxanthin from the brown seaweed,



Fucoxanthin. Figure 1 Structure of fucoxanthin.

Undaria pinnatifida, is found to be the active principle. When several cancer cells are cultured with fucoxanthin, the cell viability decreases. The antiproliferative activity of fucoxanthin on human cancer cells is generally higher than other carotenoids. Fucoxanthin exhibits the higher activity than β-carotene and astaxanthin on human ►colon cancer cells (Caco-2, HT-29, DLD-1) and human leukemia cell (HL-60). Treatment of Caco-2 cells with fucoxanthin induces morphological changes such as a diminished size and rounded shape. Also, the cell membrane has shrunk with a condensed cytoplasm. The stronger inhibitory effect of fucoxanthin is found in human prostate cancer cells (PC-3, DU 145, LNCap). In this case, the effect of 15 kinds of carotenoids (phytoene, phytofluene, ξ-carotene, lycopene, α-carotene, β-carotene, β-cryptoxanthin, canthaxanthin, astaxanthin, capsanthin, lutein, zeaxanthin, vioaxanthin, neoxanthin, and fucoxanthin) present in foodstuffs is evaluated on the grown of the cancer cell lines. Among the carotenoids, neoxanthin and fucoxanthin cause a remarkable reduction in the growth of prostate cancer cells.

Apoptosis

There is a wealth of information pertaining to apoptosis in anticancer research. ►Macrophages recognize the cells undergoing apoptosis and engulf them without adversely affecting or damaging the neighboring cells. Apoptosis-inducing activities provide a novel means of ►chemoprevention and chemotherapy in the treating cancer. In an investigation on the apoptosis-inducing activity of fucoxanthin, a DNA ladder, which is a characteristic feature of apoptotic cells, is clearly visible in HL-60 cells treated with fucoxanthin. Similar results can be obtained with ►camptothecin, which is known to be a strong apoptosis-inducing agent. The fragmented DNA content designated as the enrichment factor as estimated by sandwich ►ELISA, increases with the concentration of fucoxanthin in the medium. DNA fragmentation, indicating by in situ ►TUNEL (Terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling), reveals that fucoxanthin reduces cancer cell viability by inducing apoptosis. Some apoptosis-inducing agents are known to arrest a specific cell phase. Therefore, it can be presumed that fucoxanthin affects cell cycle.

Mechanism

Fucoxanthin suppresses expression of ►Bcl-2 protein, which is responsible for suppression of programmed cell death as a survival factor. This is indicative of the fact that downregulation of Bcl-2 protein may contribute to fucoxanthin-induced apoptosis in cancer cells. DNA fragmentation induced by fucoxanthin is partially inhibited by a ►caspase inhibitor Z-VAD-fmk. Further, fucoxanthin also regulates the redox signals, and then facilitates the progression of apoptosis through Bcl-2 protein suppression, and caspase-dependent and-independent pathway.

Combination with Troglitazone

►Troglitazone is known to inhibit cell growth and induce apoptosis through the activation of ►PPARγ. Oral administration of troglitazone inhibits the early stage of colon tumorigenesis. On the other hand, preincubation of cancer cells with fucoxanthin remarkably enhances the effect of troglitazone. Therefore, the combined action of PPARγ ligand such as troglitazone and fucoxanthin is more effective on chemoprevention of cancer than troglitazone, and possibly other agents, alone.

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Fulvestrant

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Synonyms

Faslodex

Definition

Was originally known as ICI 182,780 and is now marketed by AstraZeneca under the trade name Faslodex®. The chemical formula of fulvestrant is 7α-[9-(4,4,5,5,5-pentafluoro-pentylsulfinyl)nonyl]estra-1,3,5(10)-triene-3,17β-diol.

Fulvestrant, a steroidal 7α-alkylsulfinyl analog of 17β-►estradiol, is an ►estrogen receptor antagonist with no agonist effects. It is used as an endocrine treatment for postmenopausal women with hormone-sensitive ►advanced breast cancer.

Characteristics

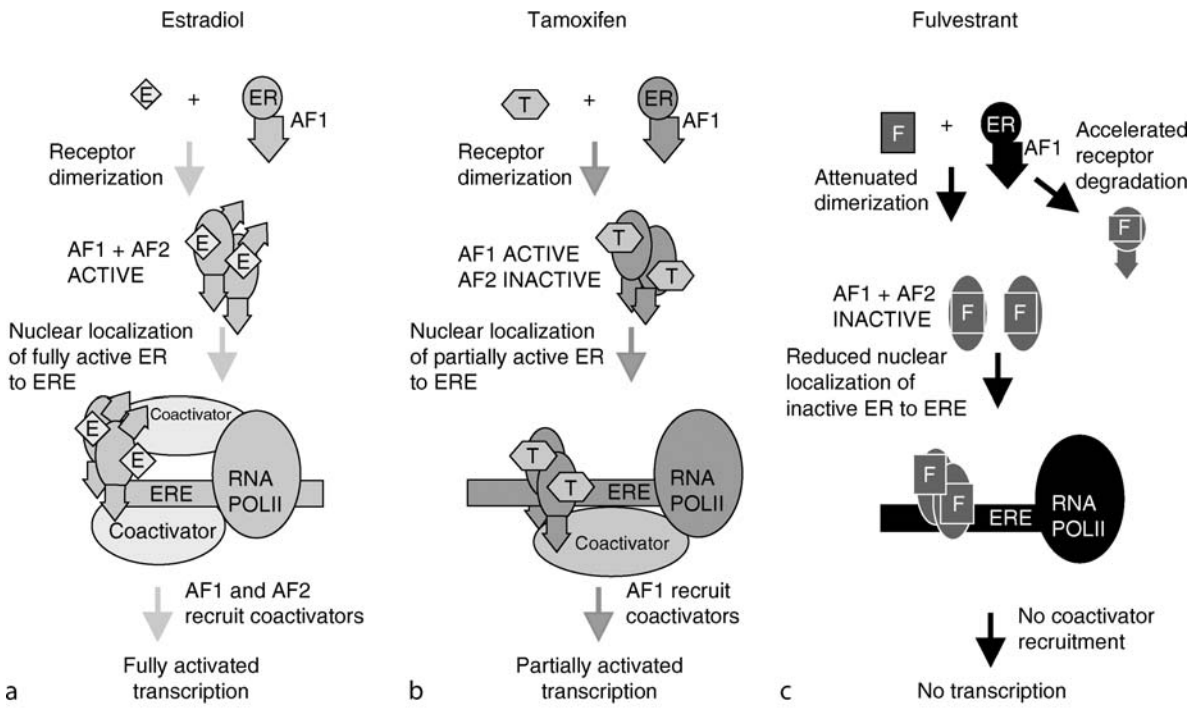
Mode of Action

Currently, more than one million women worldwide are diagnosed with ►breast cancer each year. In postmenopausal women, approximately 75% of breast tumors are hormone sensitive, expressing the estrogen receptor and/or progesterone receptor, and are stimulated to grow in the presence of estrogen. To understand the treatments for hormone-receptor positive breast cancer, we must first understand the role of ►estrogen, a natural circulating hormone that has been shown to drive tumor growth. Once estrogen has bound to the ►estrogen receptor, the receptors dimerize, before translocation to the nucleus, where the complex binds to specific DNA sequences (estrogen response elements) in target genes. Activating functions on the estrogen receptor (AF1 and AF2) recruit protein cofactors, allowing the transcription and expression of the target genes, resulting in increased cell division and tumor progression (Fig. 1).

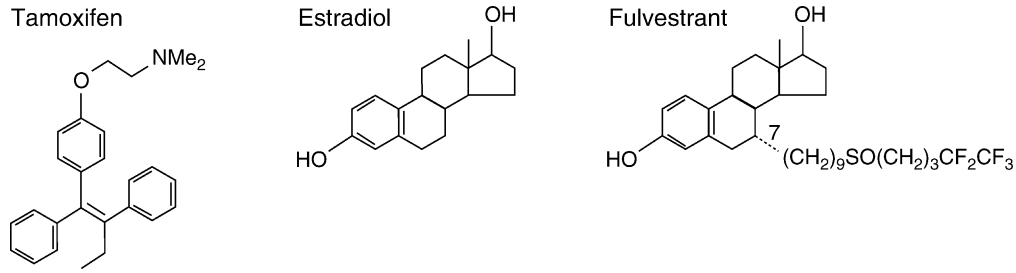
As an estrogen receptor antagonist, fulvestrant exhibits a high estrogen receptor binding affinity and produces a complete receptor blockade. Following binding of fulvestrant, dimerization of the estrogen receptor is impaired and the bound receptor is rapidly degraded, a process unique to fulvestrant amongst the ►antiestrogen receptor agents. Nuclear localization is also disrupted, and both AF1 and AF2 are inactivated, leading to complete abrogation of estrogen signaling through the estrogen receptor (Fig. 1). This also means that fulvestrant has no estrogen agonist activity, which is important, since even partial agonist activity can lead to an increased incidence of endometrial abnormalities and cancer.

As a steroidal analog of estradiol, fulvestrant is structurally distinct from the non-steroidal ►tamoxifen, a selective estrogen receptor modulator, which is also used in the treatment of hormone receptor-positive breast cancer (Fig. 2). Although tamoxifen binds to the estrogen receptor, and permits dimerization and translocation, AF2 is not activated and so the transcription of estrogen-responsive genes is blocked (Fig. 1). However, this block is not complete, since AF1 continues to function, and therefore tamoxifen retains partial agonist activity, with the associated endometrial risks.

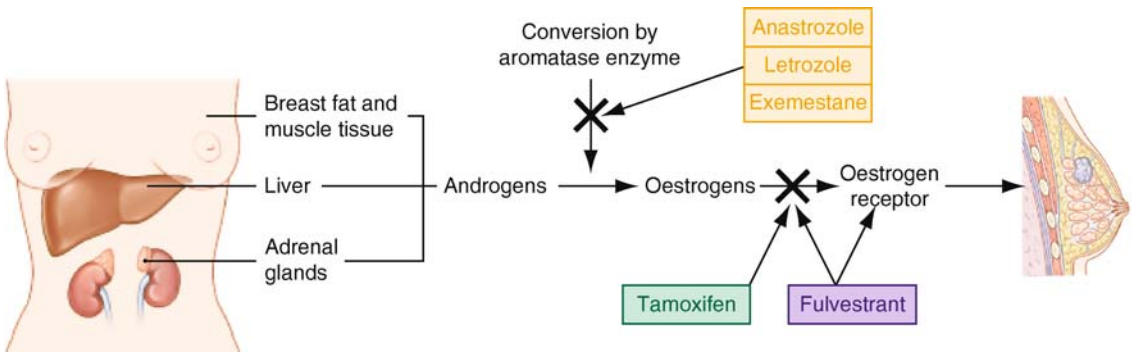
Fulvestrant, with its unique mode of action, is fundamentally different from the third-generation ►aromatase inhibitors such as anastrozole, letrozole or exemestane, which are used to treat breast cancer in an increasing proportion of postmenopausal women.



Fulvestrant. Figure 1 The mode of action of fulvestrant, tamoxifen and estradiol. (Reproduced from Dowsett et al. [2, Fig. 1]. Breast Cancer Res Treat 93:S11–S18 (2005). With kind permission of Springer Science and Business Media.)



Fulvestrant. Figure 2 Chemical structure of fulvestrant.



Fulvestrant. Figure 3 Scheme showing how different endocrine therapies (fulvestrant, tamoxifen, aromatase inhibitors) work in breast cancer.

Following the menopause, most endogenous estrogen is produced via the conversion of adrenal androgens in peripheral tissues. Aromatase inhibitors work by blocking the aromatase enzyme, which catalyzes this conversion, thus reducing the levels of circulating estrogen available to bind to the estrogen receptor (Fig. 3).

Current Utilization of Fulvestrant

While treatment for hormone-sensitive early breast cancer aims to remove the tumor by surgical or radiological techniques followed by adjuvant ►endocrine therapy, treatment for advanced disease is essentially palliative rather than curative, with the emphasis on extending life and preserving quality of life amongst patients. In postmenopausal women with hormone-sensitive advanced breast cancer, it is now standard practice to employ a sequence of endocrine agents, to slow the progression of the disease and delay for as long as possible the requirement for cytotoxic chemotherapy treatment. Consequently, novel endocrine agents that are both effective and lack cross-resistance with existing therapies are required to extend the duration of the sequential treatment regimens.

Fulvestrant is a new therapeutic option that can be added to the hormonal treatment sequence. Results from Phase III clinical trials showed that in postmenopausal women with hormone-responsive advanced breast cancer who had progressed on previous antiestrogen therapy, fulvestrant was at least as effective as anastrozole, in terms of time to progression, objective response rates and survival. This evidence led to its regulatory approval and fulvestrant is currently licensed for use as a second-line endocrine treatment agent for advanced breast cancer after progression or recurrence on an antiestrogen. More recently, Phase III trial data have confirmed fulvestrant activity in the post-aromatase inhibitor setting. Reflecting all these data, fulvestrant is considered in the National Comprehensive Cancer Network guidelines as an option after the failure of first-choice endocrine treatment (tamoxifen or an aromatase inhibitor). Thus, fulvestrant is a valuable addition to the endocrine armory.

Importantly, due to its unique mechanism of action, analyses of patients progressing on fulvestrant have demonstrated continued sensitivity to subsequent endocrine therapies, indicating that fulvestrant lacks cross-reactivity with the ►aromatase inhibitors and tamoxifen.

Administration and Tolerability

Instead of the daily oral dosing used with other endocrine therapies, fulvestrant is given as a monthly

250 mg/5 mL intramuscular injection, which provides slow release of the drug and sustained pharmacologic activity over the dosing interval (28 ± 3 days). The injection is well tolerated locally and may also help to assure treatment compliance. Once in the body, fulvestrant is predominantly bound to plasma proteins and metabolized by the liver, with negligible renal excretion, and it is not implicated in clinically significant drug–drug interactions, making it suitable for use in patients receiving polypharmacy for co-morbid conditions.

Fulvestrant is well tolerated, with most adverse events being mild to moderate in intensity. In clinical trials, the most commonly reported adverse events were nausea, asthenia and pain. Fulvestrant has potential tolerability benefits over some existing treatments, e.g. it is associated with less hot flashes than tamoxifen, and a lower incidence of joint disorders than anastrozole.

Future Uses of Fulvestrant

In recent years, the third-generation aromatase inhibitors, have been shown to be superior to tamoxifen for the treatment of both early and advanced breast cancer. Treatment guidelines currently recommend that an aromatase inhibitor should be used as either the primary endocrine therapy in postmenopausal women, or after 2–3 years of tamoxifen. However, even in this estrogen-deprived environment, some tumors will become resistant to treatment and begin to progress. Therefore, if cytotoxic chemotherapy is to be further delayed, an alternative endocrine therapy must be used. Indeed, as aromatase inhibitors continue to replace tamoxifen in the first-line setting, it is becoming increasingly important to identify agents that are effective after recurrence or progression on these drugs. As previously described, results from both Phase III and Phase II studies suggest that fulvestrant may be active after progression on aromatase inhibitors.

Fulvestrant's unique mode of action and lack of cross-reactivity also invites the possibility of potentially synergistic combinations with other treatment agents. Preclinical data suggest that the combination of fulvestrant with aromatase inhibitors will offer a more effective anti-tumor effect than either agent alone, and Phase III trials are underway to fully evaluate this treatment strategy.

In addition, the epidermal growth factor (EGF) receptor-mediated pathway of gene transcription, which can provide an alternative growth stimulus for breast tumors in the absence of hormone receptors, has also been shown to cross-talk with the estrogen receptor-mediated pathway. This, in turn, has important implications for the development of resistance to endocrine therapy. As fulvestrant increases degradation of estrogen receptors, it may limit the potential for cross-talk with other pathways. Combination treatment with fulvestrant and an agent targeting growth factor receptors (such as gefitinib, lapatinib or trastuzumab) may therefore further limit cross-talk and potentially delay the time of onset of treatment resistance. Currently, several clinical trials are ongoing to investigate the activity of such combination therapy in patients with advanced breast cancer.

Summary

Fulvestrant, a steroidal analog of ►estradiol, is an effective treatment for postmenopausal women with hormone-sensitive advanced breast cancer who have progressed on previous endocrine therapy. With its unique mode of action, fulvestrant provides a valuable addition to the endocrine treatment sequence, with significant benefits for patients. It is administered as a monthly intramuscular injection, and is well tolerated and associated with few adverse events. Fulvestrant may also have a potential use in combination treatment strategies, as the partner of choice with ►EGF receptor inhibitors.

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Fumarase

►Fumarate Hydratase

Fumarate Hydratase

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Synonyms

FH; Fumarase

Definition

Fumarate hydratase is an enzyme that functions in the mitochondrial citric acid cycle, catalyzing the reversible hydration/dehydration reaction in which fumarate is converted to malate.

Characteristics

The human gene encoding fumarate hydratase is located in the chromosome segment 1q42.3-q43. It consists of ten exons that span over 20 kb of genomic DNA. The transcript is approximately 1.8 kb long and is predicted to encode a 510 amino acid polypeptide. The first exon of *FH* encodes a signal peptide that directs the protein to the mitochondrion. There the signal peptide is cleaved, and the remaining mature FH protein forms a functional homotetramer in the mitochondrial matrix. Some processed FH is also present in the cytosol, although the function of this cytosolic FH is unclear. In addition to the mitochondrial signal, the processed FH contains other domains such as alpha-helical and lyase domains. The alpha-helixes form a superhelical core for the tetramer. The functionally active FH enzyme converts fumarate to malate. This hydration reaction is a part of the citric acid cycle (also known as the tricarboxylic acid cycle or the Krebs cycle) which is an essential component of cellular carbohydrate metabolism. In the cytosol, fumarate is produced in the urea cycle and therefore FH is connected to protein metabolism as well. FH is well conserved, human FH sharing a 57% amino acid identity with the *Escherichia Coli* FumC protein, and it belongs to a protein superfamily which includes mostly other enzymes such as aspartase, adenylosuccinate lyase, and argininosuccinate lyase.

The first clues as to the role of FH in human disease came from the identification of two siblings that presented with progressive encephalopathy, dystonia, ►leucopenia, and ►neutropenia. They had elevated levels of lactate in their cerebrospinal fluid and high fumarate excretion in their urine. A ►homozygous mutation was discovered in a conserved region of the *FH* gene in both of these patients. Also, FH deficiency was shown to be present in all tissues studied in the patients, and their healthy parents were shown to carry the mutation in a heterozygous form. Since then, about 20 families with FH deficiency have been reported in the literature. The symptoms are severe and the affected individuals usually die within a few months of birth.

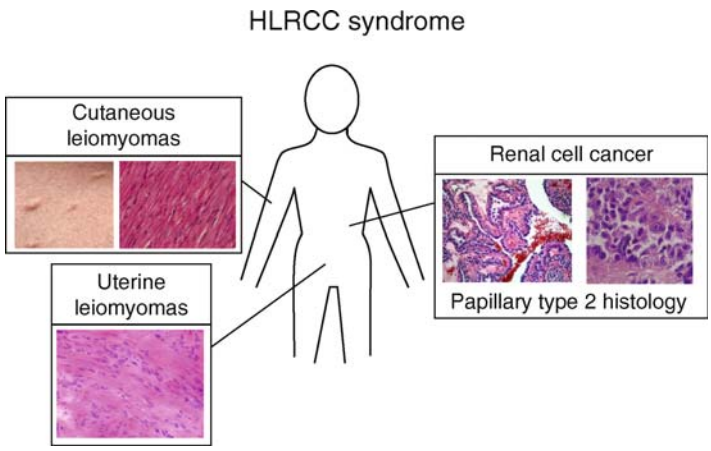
Evidence for yet another role of FH in human disease came from quite a different line of research. The genomic locus harboring the *FH* gene was independently mapped by genetic linkage analysis to segregate with inherited predisposition to ►leiomyoma and ►renal carcinoma; ►Hereditary leiomyomatosis and renal cell cancer (HLRCC), and to ►multiple cutaneous and uterine leiomyomatosis (MCUL). Soon after, these two conditions were shown to be variants of the same syndrome and the underlying gene was identified as *FH*. The tumors showed loss of heterozygosity (►LOH) and retention of the mutated allele, therefore suggesting that the gene acted as a ►tumor suppressor. Also, FH enzyme activity was shown to be reduced in the leukocytes and absent in the tumors of mutation carriers.

Clinical Features of HLRCC/MCUL

Since the first reports indicating the involvement of FH in tumorigenesis, more than 100 families with the HLRCC/MCUL phenotype have been reported in the literature (Fig. 1). Although no population-based studies have been carried out, it seems clear that the prevalence of HLRCC/MCUL is very low. There are reports of HLRCC/MCUL from all around the world, and there seem to be population differences in the phenotype. For example, HLRCC seems to be more common in Finland and North America, whereas in the UK, renal cell cancer is rarely detected in the families segregating heterozygous *FH* mutations. The most common manifestation of HLRCC/MCUL is cutaneous and/or ►uterine leiomyomas. Early-onset renal cell cancer is significantly rarer and is typically of the papillary type II histology.

Cutaneous leiomyomas are small benign tumors of the skin that show as multiple 0.5–2 cm skin-colored nodules, and their tissue of origin is thought to be the arrectores pili muscle of the hair follicle. They can manifest clinically as pain and paresthesias already in childhood, and the age of onset ranges from 10 to 50 in the HLRCC/MCUL families.

Uterine leiomyomas (also known as ►myomas or ►fibroids) are smooth muscle cell tumors that arise within the smooth muscle lining of the uterus, the myometrium. They are some of the most common neoplastic tumors of women, and estimates of affected individuals range from 25% to up to 77% depending on the methods used for the diagnosis. Even though they are benign, they can cause severe morbidity such as aberrant bleeding, abdominal pain and even infertility. In families affected by HLRCC/MCUL, the onset of leiomyomas seems to be earlier than in the general



Fumarate Hydratase. Figure 1 Hereditary leiomyomatosis and renal cell cancer (HLRCC) is an autosomal dominant tumor predisposition syndrome caused by germline mutations in the *fumarate hydratase* gene. The most common features are cutaneous and/or uterine leiomyomas. Predisposition to renal cell carcinoma is present in a subset of families. Typically, HLRCC renal cell carcinomas display papillary type 2 histology.

population. In these families, leiomyomas are also more often symptomatic and therefore they more commonly result in hysterectomy (i.e. the surgical removal of the uterus). In addition to typical leiomyomas, some HLRCC/MCUL patients develop atypical leiomyomas. These are rare variants of leiomyomas which are sometimes hard to discern from uterine leiomyosarcomas. Whether HLRCC/MCUL predisposes to malignant leiomyosarcoma is still a somewhat open question, although some studies suggest that this might indeed be the case.

Familial clustering of ►renal cell cancer was the key finding in the identification of the syndrome HLRCC. In the first family reported, four patients aged 33–48 were identified. Since then, additional cases of renal cell cancer have been detected in some HLRCC/MCUL families, the median age of onset being around 40. The natural history of HLRCC/MCUL renal tumors is malignant with early metastasis often leading to the demise of the patient. In the early reports, all renal cell cancers related to HLRCC/MCUL displayed a distinctive papillary type II histology, although other types of renal tumors, such as collecting duct and clear-cell carcinoma, have been later associated with HLRCC/MCUL as well. HLRCC/MCUL renal tumors are typically unilateral, which is in contrast to other inherited forms of renal cell cancer such as von ►Hippel-Lindau Syndrome (VHL), Hereditary Papillary Renal Carcinoma, and ►Birt-Hogg-Dubé Syndrome (BHD), in which tumors often affect both kidneys.

FH-mutation carriers might be at risk of developing ►Leydig cell tumors and ovarian cystadenomas. Incidental cases of other tumors, such as breast and prostate cancer and some hematological malignancies, have also been reported in HLRCC/MCUL families, although it remains unclear whether any of these are true manifestations of the germline *FH* mutations.

Mutations in the *FH* Gene

The syndrome HLRCC/MCUL is transmitted in an ►autosomal dominant manner, and germline *FH* mutations have been detected in ~85% of all the families displaying the HLRCC/MCUL phenotype. Altogether, ~60 different mutations have been identified. The vast majority (~70%) are single base pair substitutions, of which ►missense mutations comprise about 60%; the rest are non-sense mutations. Small deletions and insertions as well as ►splice site changes have been reported. In addition, whole gene *FH* deletions have been detected in some families. Mutations occur throughout the gene. The mutation R58X has been detected in four families of diverse ethnic and geographical backgrounds in North America. ►Haplotype analysis has suggested that the mutation has occurred independently in these families, indicating that this might represent a mutational hot spot. The same mutation has also been detected in families from the United Kingdom and Australia. Other mutations that have been detected in several families of different geographical backgrounds are, for example, N64T and R190H, and these may represent mutational hot spots as well. The mutations in families with the renal cell cancer phenotype do not differ from those seen in families without these malignant tumors and, in fact, the same mutations have been detected in families with either of the two phenotypes. This has raised the question of whether an additional genomic locus could act as a modifier together with *FH* mutations.

A ►founder effect has been detected at least in populations of the Finnish and Iranian origin. Two

mutations, H153R and a 2-bp deletion in codon 181, have both been identified in three different families in Finland. Similarly, a splice site mutation IVS6-1G>A has been detected in a common haplotype in several families of Iranian origin. Most tumors arising in HLRCC/MCUL families have a second somatic inactivating hit in the *FH* gene. This is often acquired through the loss of the wild-type *FH* by a partial or whole genomic deletion of chromosome arm 1q.

FH mutations are also rarely seen in sporadic tumors. Inactivation of the *FH* gene has been detected in three tumors from the Finnish population, one soft-tissue sarcoma of the lower limb, and two uterine leiomyomas, all showing loss of the wild-type *FH*. However, despite mutation screens comprising hundreds of tumor specimen, no other somatic changes in *FH* have been detected in various tumor types including prostate, breast, colorectal, lung, ovarian, thyroid, head and neck cancers, pheochromocytomas, gliomas, and melanomas. Therefore, it is safe to say that, in general, somatic inactivation of the *FH* gene is a very rare occurrence in human tumors.

As determined by microarray based gene expression analysis, as well as by traditional immunohistochemical methods, ►uterine fibroids carrying *FH* mutations have distinct biological properties which seem to require two hits in the *FH* gene. The molecular mechanisms through which mutations in *FH* lead to tumorigenesis are still far from being well understood. Some evidence suggests that the disruption of FH activity would lead to the stabilization of the ►hypoxia inducible factor-1 (HIF1) under normoxic conditions, thus activating several growth-promoting signaling cascades.

The mutations detected in the recessively inherited developmental disorder FH deficiency are also mostly missense mutations, and they occur throughout the *FH* gene. The mutational spectrum of FH deficiency does not seem to be different from that of HLRCC/MCUL and, indeed, a phenotype compatible with HLRCC/MCUL has been reported in some of the parents of the children affected by FH deficiency.

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Functional Foods

►Nutraceuticals

Functional Vascular Stabilization

►Vascular Stabilization

Fungus

Definition

Member of a class of relatively primitive vegetable organisms. Fungi include mushrooms, yeasts, rusts, molds, and smuts.

Funnel Factors

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Definition

Is a molecule where several oncogenic signals converge and drive the proliferative signal downstream. This transformation-inducing signal inexorably passes and is canalized through the funnel factor. Funnel factors provide a clear reflection of the tumor's transforming potential regardless of the triggering genetic alteration upstream. The level of expression of these factors should correlate with the degree of malignancy of the tumor and the most relevant clinical parameters, such as ►metastasis and survival. Therefore, they may reflect the molecular information and transformation potential for each tumor.

Characteristics

Background of Molecular Human Carcinogenesis

Funnel factors are those final effectors that channel the malignant cellular growth signals, which are transduced through pathways or cascades that induce and mediate changes into the cell physiology. Several of these pathways or cascades are redundant, that is they can trigger a similar cellular effect. There are six acquired capabilities considered to be necessary for the malignant cellular growth: ►self-sufficiency in growth signals, insensitivity to anti-growth signals, limitless replicative potential, resistance to ►apoptosis, sustained ►angiogenesis and, finally, the ability to infiltrate the surrounding tissue and metastasize. Each of these changes in cellular physiology can be brought about through dozens of signaling pathways or cascades, each implicating various genes or proteins. Many different oncogenic alterations may be involved in each biochemical route. This intricate molecular background and its biochemical consequences can help us to understand the great heterogeneity observed in tumors, with over 250 types of malignant human tumors with distinctive clinical and pathological characteristics and thousands of morphological and pathological tumor subtypes.

So far, up to 300 mutated genes implicated in oncogenesis have been identified as human cancer genes. Many oncologists and pathologists ask whether all this information is really important for the management of individual cancer patients. The answer is unknown because only a few molecular targets have been identified in a small number of tumor types. For example, ►amplification of ERBB2 is seen in 25–30% of ►breast carcinomas, ►*EGFR* mutations in less than 10% of ►lung carcinomas, and ►*c-KIT* in the rare ►gastrointestinal stromal tumors; but in most carcinomas, there is no distinctive oncogenic target. In the near future, technological advances will allow us to study the complete genetic background, ►mRNA profiling, and protein expression of individual tumors, and identify a myriad of genetic and biochemical alterations. But even then, attempts to inhibit or counteract single genetic alterations with the use of multiple specific agents would probably be chaotic. Nevertheless, dissection of the biochemical pathways is progressing. We now know which factors are the final growth signaling effectors that can control ►transcription and protein synthesis. Then, it is logical to think that the level of expression of these final effectors, which channel the proliferation signal, can be associated with the real oncogenic role of a pathway in individual tumors.

Cell Signaling in Human Tumors

Among the acquired capabilities of tumor cells, a funnel factor has been described for self-sufficiency in growth signals. This essential oncogenic capability is one of the most extensively studied characteristics of tumor cells, and one that is constitutively activated in nearly all tumors. The process of converting extracellular signals into cellular responses, in this case cell growth and division, is called signal transduction. The growth signal transduction pathway is comprised of ►growth factors, ►growth factor receptors, factors transmitting the growth signal, and the final effector factors, some of which are located in the nucleus to activate ►transcription factors and some in the ►ribosomes to activate protein synthesis. The neoplastic cell, however, may be able to generate signals for survival or proliferation through various mechanisms without depending on exogenous signals. These mechanisms include alterations in the growth factors or receptors, or in the signaling pathways, themselves. Among the latter, the most highly recognized and important are the ►RAS-►RAF-►MAPK (ERK1/2) and ►PI3K-►AKT pathways, which regulate ►mTOR. Specific molecular alterations are detected in these signaling cascades in the majority of tumors. Usually these are single alterations with an oncogenic impact, such as growth factor mutations or RAS mutations; other concomitant genetic alterations are not usually found in these biochemical pathways.

Searching for Funnel Factors: p-4E-BP1

In studies performed in various tumor types, the expression of key cell-signaling factors, including Her1 and Her2 growth factor receptors, as well as the RAS-RAF-MAPK and the PI3K-AKT-mTOR pathways were correlated with the associated clinico-pathological characteristics of these tumors. The downstream factors p70, S6, 4E-BP1, and EIF4E, which play a critical role in the control of protein synthesis, survival, and cell growth, were also analyzed. It was found that ►phosphorylated ►4E-BP1 (eukaryotic ►translation initiation factor 4E binding protein 1) levels in breast, ovary, and prostate tumors were associated with malignant progression and an adverse prognosis, regardless of the upstream oncogenic alterations. Thus, p-4E-BP1 seems to act as a funnel factor for an essential oncogenic capability of tumor cells, self-sufficiency in growth signals, and could be a highly relevant molecular marker of malignant potential. The results showing that 4E-BP1 is associated with the prognosis in breast, ovary and prostate tumors, are supported by other data. In breast cancer, ►phosphorylation of AKT, mTOR and 4E-BP1 has been associated with tumor development and progression; and in prostate cancer, one of the best biomarkers of the mTOR pathway is 4E-BP1, since overexpression of this factor has been highly associated with this type of tumor. Moreover, experimental studies have shown that 4E-BP1 is essential for cell transformation. Transfer of 4E-BP1 phosphorylation site mutants into breast carcinoma cells suppressed their tumorigenicity.

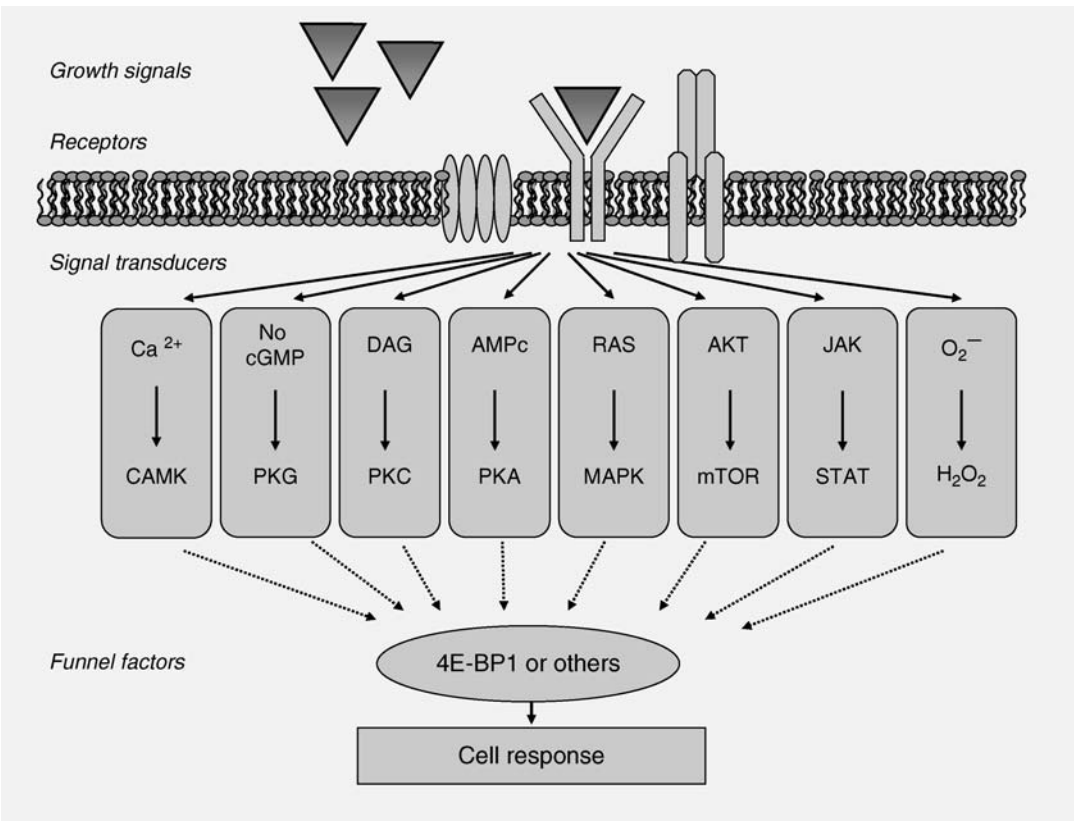
4E-BP1 is a eukaryotic translation initiation factor 4E (EIF4E)-binding protein that plays a critical role in the control of protein synthesis, survival, and cell growth. During ►cap-dependent translation, EIF4E binds to the mRNA ►cap structure and promotes formation of the ►translation initiation complex and ►ribosome binding. When 4E-BP1 is active (non-phosphorylated 4E-BP1) it binds to EIF4E and impedes formation of the initiation complex; translation is then blocked, favoring apoptosis. However, when 4E-BP1 is phosphorylated, the affinity for EIF4E binding is reduced, EIF4E is released, and cap-dependent translation can initiate.

4E-BP1 has seven phosphorylation sites. It is likely that mTOR is the main phosphorylation pathway of 4E-BP1, although other ►kinases may be implicated, such as ►CDK1, ►ATM, ►PI3K-AKT, ►ERK1/2, and perhaps other, still unidentified, kinases. Therefore, 4E-BP1 phosphorylation can be the consequence of many different oncogenic events occurring in several biochemical pathways, including amplification or mutation of growth factor receptors, loss of function or mutations in ►PTEN, ►ATM, ►p53, ►PI3K or ►RAS, or other collateral mechanisms of cellular oncogenic activation (Fig. 1). Because of the elevated number of genetic alterations that regulate 4E-BP1, we propose that the phosphorylated form of this protein can act as a "bottleneck" or funneling factor through which the transforming signals converge, channeling the oncogenic proliferative signal regardless of the upstream specific oncogenic alteration.

The role of other 4E-BP ►isoforms, such as 4E-BP2 and 4E-BP3, in human tumors is still unclear, and it is not known whether they can be activated in 4E-BP1-negative tumors. Study of the EIF protein family will also be determinant when reliable antibodies allow us to analyze their expression in large series of tumors. Recent data have provided novel perspectives into the proliferative and oncogenic properties of EIF4E, since it has been shown to have an impact on nearly every stage of cell cycle progression. Earlier studies have shown that EIF4E levels are substantially elevated in several types of cancers.

Funnel Factors in Other Oncogenic Pathways

Extending the concept of funnel factor, there might be several funnel factors where the final biochemical effect converges for each of the oncogenic capabilities of tumor cells. For example, in the apoptosis pathways,



Funnel Factors. Figure 1 Schematic diagram showing how funneling factors channel the proliferation signal.

where the expression of certain proteins that inhibit apoptosis, such as survivin and livin, might be associated with resistance to apoptosis regardless of the activation of other antiapoptotic or proapoptotic genes that might be present.

Study of the expression profiles of funnel factors from all the cell transformation pathways would allow us to obtain an individual functional-molecular signature for each tumor. This signature, combined with clinical and pathological data would help us to establish the malignant potential of each individual tumor and deduce its potential resistance to conventional chemotherapy and radiotherapy. Obviously, in addition to molecular characterization of tumors for prognostic purposes, it is necessary to study factors that might be potential therapeutic targets, currently one of the most promising areas in the field of cancer treatment. With this functional approach it seems worthwhile to investigate whether these funnel factors can be critical targets for cancer treatment.

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Furin

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Synonyms

Furin; PACE; SPC1; PCSK3; Dibasic processing enzyme; Prohormone convertase; Paired basic amino acid cleaving enzyme

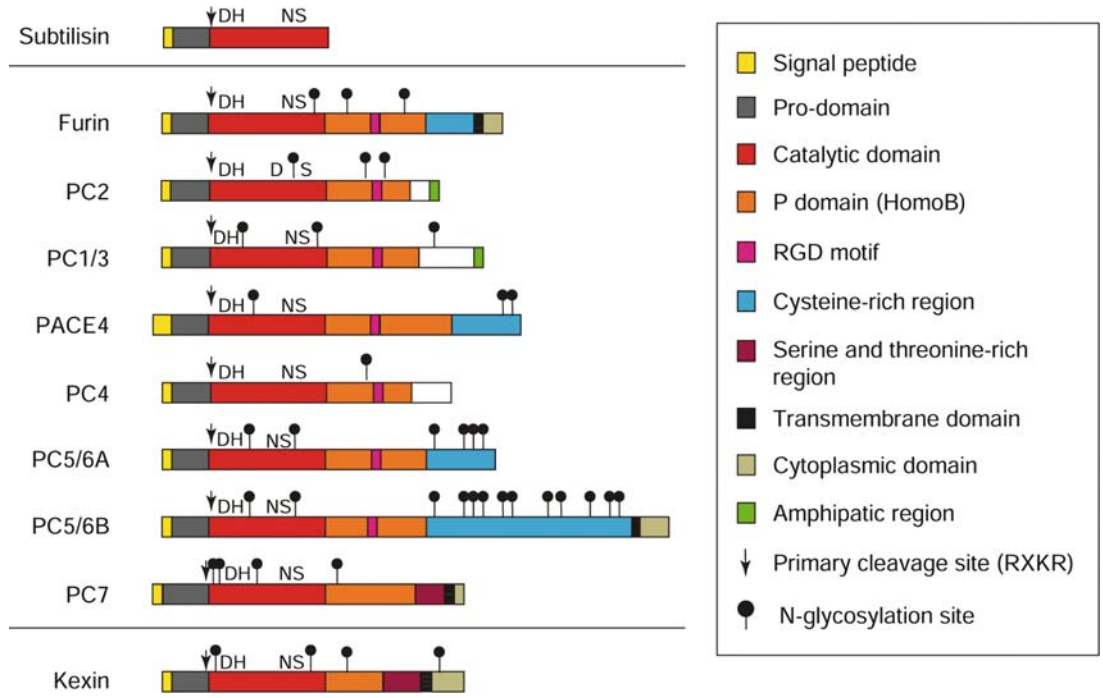
Definition

Furin (E.C. 3.4.21.75) is a highly specialized proteinase that cleaves the unique sequence motifs in a variety of proteins. Normally, following furin cleavage, the target protein is activated and, therefore, it can exhibit its biological activity. Because furin has been discovered first, currently it is the most studied enzyme of the proprotein convertase (PC) family of serine proteinases. Seven distinct proprotein convertases of this family (furin, PC2, PC1/3, PC4, PACE4, PC5/6, and PC7) have been identified in humans, some of which have ►isoforms generated as the result of ►alternative splicing. Structurally and functionally, furin resembles its evolutionary precursor: the prohormone-processing enzyme, kexin (EC 3.4.21.61), which is encoded by the KEX2 gene of yeast *Saccharomyces cerevisiae*. The polypeptide sequence of the furin ►catalytic domain is homologous to that of *Bacillus* subtilisin, an evolutionary precursor of PCs. Furin and related PCs are involved in the limited ►endoproteolysis (►protease activated receptor) of inactive precursor proteins which occurs at the sites marked by paired or multiple basic amino acids.

Characteristics

A wide variety of proteins are initially synthesized as parts of higher molecular weight, but inactive, precursor proteins. Specific endoproteolytic processing of these ►proproteins is required to generate the regulatory proteins in a mature and biologically active form. A large majority of these active proteins, including ►matrix metalloproteinases, growth factors, and ►adhesion molecules are essential in the processes of cellular transformation, acquisition of the tumorigenic phenotype, and metastases formation. The enzyme furin, which is encoded by the *fur* gene, was the first and can be considered the prototype of a mammalian subclass of subtilisin-like proteases. The localization of the gene immediately upstream from the FES ►oncogene (V-FES feline sarcoma viral oncogene homolog) generated the name FUR (for FES upstream region). Furin is similar to other PCs in that it contains a signal peptide, a prodomain, a subtilisin-like catalytic domain, a middle P domain, a cysteine-rich region, a transmembrane anchor, and a cytoplasmic tail (Figs. 1 and 2). Furin and PCs are normally N-glycosylated ►glycoproteins (►glycosylation). Phosphorylation of the cytoplasmic tail is required for the trans-Golgi localization of furin which in vivo exists as di-, mono- and non-phosphorylated forms. Propeptide cleavage is a prerequisite for the exit of furin molecules out of the ►endoplasmic reticulum. The second cleavage in the propeptide occurs in the ►trans-Golgi network, which is followed by the release of the propeptide bound to furin and the activation of furin.

Furin is expressed in all examined tissues and cell lines and is mainly localized in the trans-Golgi

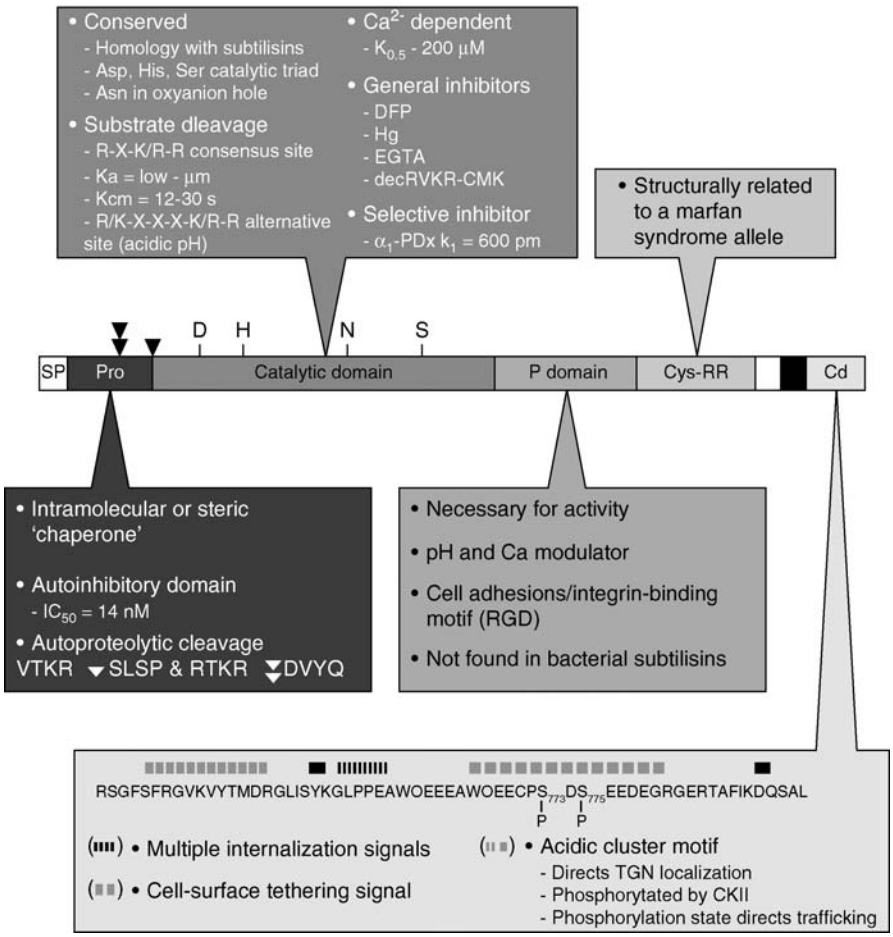


Furin. Figure 1 A modular domain structure of furin and six related PCs. The A and B isoforms of PC5/6 are encoded by the same gene. The structure includes (i) the N-terminal signal peptide, which directs proteins into the secretory pathway, (ii) a pro-domain, which maintains the inactive zymogen state of PCs and which also acts as an intramolecular chaperone for the proper folding, (iii) a catalytic domain with the active site that exhibits an Asp (D)-His(H)-Ser(S) catalytic triad and an additional Asn(N), (iv) a barrel-like structured P domain that regulates enzyme stability, (v) a C-terminal domain that contains membrane attachment sequences, a Cys-rich region and intracellular sorting signals. Adapted from [4].

network. Some proportion of the furin molecules cycles between the trans-Golgi and the cell surface. Furin represents the ubiquitous endoprotease activity within constitutive secretory pathways and normally it is capable of cleaving the Arg-X-(Lys/Arg)-Arg consensus motif, where X is any amino acid type (Table 1). Furin and related PCs are activating proteases and normally they do not inactivate polypeptides. Because of the overlapping substrate preferences and cell/tissue expression, there is a substantive level of redundancy in the PC functionality, albeit certain distinct functions of the individual PCs have also been demonstrated. Furin knockout, however, is lethal in mice. Furin null embryos die because they fail to accomplish ventral closure successfully and to form a looping heart tube. These processes require cellular migration and proliferation, both of which are regulated by furin. Through regulation of cellular migration and proliferation, furin plays an important, albeit incompletely understood role, in cellular transformation, acquisition of the tumorigenic phenotype, cancer progression and metastasis. The expression of furin, however, discriminates sharply between small cell lung cancers, which have no expression, and non-small cell lung cancers, in which furin is overexpressed.

The roles of furin and other PCs in cancer have been characterized as the result of many studies of gene expression and enzyme inhibition. Because of the redundancy, it is not always clear if all PCs present in cancer cell/tissue are directly relevant to tumorigenicity. An enhanced expression of furin and related PCs in cancer is not necessarily an indicator of a poor clinical outcome. There is, however, evidence that high levels of furin-related PCs contribute to tumor growth and metastasis by controlling the activation of key cancer-associated proteins, including matrix metalloproteinases and growth factors such as ►VEGF, ►TGFβ and ►PDGF. The multiple effects of PCs on cell proliferation, motility, adhesion and invasion have led to a concept that in the course of tumor development and progression PCs act as "master switches" of the key tumorigenic protein functionality. If this concept is valid, then PCs could be identified as important therapeutic targets in a number of cancer types. The challenge remains to identify the functionally-relevant, target PC in each cancer type, because it is unlikely that broad-range PC inhibitors would have significant clinically beneficial effects.

No natural protein inhibitors of furin are known. D-Arg-based peptides, α1-anti-trypsin Portland and,



Furin. Figure 2 Furin structure. The 794-residue pre-profurin sequence contains a 24-residue signal peptide, an 83-residue prodomain, a 330-residue subtilisin-like catalytic domain, a 140-residue middle P domain (also termed the "homo B," a 115-residue cysteine-rich region, a 23-residue transmembrane anchor, and a 56-residue cytoplasmic tail. Adapted from [1].

especially the synthetic peptidic inhibitor decanoyl-Arg-Val-Lys-Arg-chloromethylketone, are used to inhibit furin in the cleavage reactions in vitro and in cell-based tests. Inhibition of furin results in a significant reduction in tumor cell invasion. This reduction appears to be associated with a processing blockade of proteins directly involved in the mechanism of invasion including matrix metalloproteinases, growth factors and adhesion signaling receptors such as integrins.

PCs including furin are implicated in many pathogenic states because they process to maturity membrane fusion proteins and pro-toxins of a wide variety of both naturally occurring and weaponized bacteria and viruses, including anthrax and botulinum toxins and H5N1 bird flu, Marburg and Ebola viruses. After processing by furin and the subsequent internalization inthe complex with the respective receptor followed by acidification of the ►endosomal compartment (►endocytosis), the processed, partially denatured, infectious proteins expose their membrane-penetrating peptide region and escape into the cytoplasm. The intact toxins and viral proteins, however, are incapable of accomplishing these processes. Normally, the low pathogenicity viral subtypes have mutations in the cleavage site sequence and thus a reduced sensitivity to furin. Accordingly, proteolytic processing by furin is an important determinant in the overall pathogenicity of viruses and bacterial toxins. Based on these data, PCs, including furin, are promising targets for drug design in a variety of acute and chronic diseases including cancer and infectious diseases.

References

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Furin. Table 1 Furin targets and the sequence of the cleavage sites

Proteinases		P6 P4 P1↓P1′	
FURIN	Furin, two autolytic cleavage sites	RGVTKR↓SLSP	75–76
		KRRTKR↓DVYQ	107–108
MMP-11	Matrix metalloproteinase 11, stromelysin-3	RNRQKR↓FVLS	97–98
MMP-14	Matrix metalloproteinase 14, MT1-MMP	NVRRKR↓YAIQ	111–112
MMP-15	Matrix metalloproteinase 15, MT2-MMP	RRRRKR↓YALT	131–132
MMP-16	Matrix metalloproteinase 16, MT3-MMP	HIRRKR↓YALT	119–120
MMP-17	Matrix metalloproteinase 17, MT4-MMP	QARRRR↓QAPA	125–126
MMP-24	Matrix metalloproteinase 24, MT5-MMP	RRRNKR↓YALT	155–156
MMP-25	Matrix metalloproteinase 25, MT6-MMP	VRRRRR↓YALS	107–108
ADAM-9	A desintegrin and metallopeptidase domain 9	LLRRRR↓AVLP	205–206
ADAM-12	A desintegrin and metallopeptidase domain 12	ARRHKR↓ETLK	207–208
ADAM-19	A desintegrin and metallopeptidase domain 19	PRRMKR↓EDLN	105–206
ADAMTS1	A desintegrin and metalloproteinase with thrombospondin type-1 motif, 1	SIRKKR↓FVSS	252–253
ADAMTS4	A desintegrin and metalloproteinase with thrombospondin type-1 motif (aggrecanase-1), 4	PRRAKR↓FASL	212–213
ADAMTS13	A desintegrin and metalloproteinase with thrombospondin type-1 motif. 13	RQRQRR↓AAGG	74–75
BMP1	Bone morphogenetic protein 1	RSRSRR↓AATS	120–121
BMP4	Bone morphogenetic protein 4	RRRAKR↓SPKH	292–293
Meprin-A	Meprin A alpha	PSRQKR↓SVEN	653–654
BACE1	Beta-site APP-cleaving enzyme 1	GLRLPR↓ETDE	45–46
Serum proteins			
	Albumin	RGVFRR↓DAHK	24–25
VWF	von Willebrand factor	SHRSKR↓SLSC	763–764
F9	Coagulation factor IX	LNRPKR↓YNSG	46–47
PROC	Protein C	RSHLKR↓DTED	199–200
Extracellular matrix			
FBN1	Fibrillin 1	RGRKRR↓STNE	2731–2732
ZPC3	Zona pellucida glycoprotein 3	ASRNRR↓HVTE	301–302
Chaperone			
7B2	Secretogranin V	QRRKRR↓SVNP	181–182
Receptors			
ITGA3	Integrin alpha chain, alpha 3	PQRRRR↓QLDP	875–876
ITGA6	Integrin alpha chain, alpha 6	NSRKKR↓EITE	902–903
LRP1	Low density lipoprotein-related protein 1	SNRHRR↓QIDR	3943–3944
NOTCH1	Notch1	GGRRRR↓ELDP	1665–1666
INSR	Insulin receptor	PSRKRR↓SLGD	762–763
DSG3	Desmoglein 3	KRRQKR↓EWVK	49–50
MET	Hepatocyte growth factor receptor c-met	EKRKKR↓STKK	307–308
CUBN	Cubilin/vitamin B-12 receptor	LQRQKR↓SINL	35–36
SORL1	Sortilin-related receptor	PLRRKR↓SAAL	81–82
HGFR	Hepatocyte growth factor/scatter factor receptor	EKRKKR↓STKK	307–308
Growth factors and hormones			
IGF-1a	Insulin-like growth factor 1a/somatomedin C	PAKSAR↓SVRA	119–120
NTF3	Neurotrophin 3	TSRRKR↓YAEH	138–139
VEGFC	Vascular endothelial growth factor C	HSIIRR↓SLPA	227–228
NPPB	Natriuretic peptide B	TLRAPR↓SPKM	102–103
PTH	Parathyroid hormone	KSVKKR↓SVSE	31–32

Furin. Table 1 Furin targets and the sequence of the cleavage sites (Continued)

Proteinases		P6 P4 P1↓P1′	
TGFB1	Transforming growth factor, beta 1	SSRHRR↓ALDT	278–279
TNFSF12–TNFSF13	Tumor necrosis factor (ligand) member 12-member 13/proliferation-inducing ligand APRIL	RSRKRR↓AVLT	104–105
EDA-A2	Ectodysplasin a isoform	VRRNKR↓SKSN	159–160
NGFB	β-Nerve growth factor	THRSKR↓SSSH	179–180
	Semaphorin 3A	KRRTRR↓QDIR	555–556
Viral envelope glycoproteins			
HO	Hemagglutinin type H5	RRRKKR↓GLFG	344–345
F	Newcastle disease virus F fusion protein	GRRQKR↓LIGA	116–117
F	Parainfluenza HPIV3 F fusion protein	DPRTKR↓FFGG	109–111
P130	Sindbis virus structural polyprotein p130	SGRSKR↓SVID	328–329
prM	Flaviviral prM protein	SRRSRR↓SLTV	215–216, West Nile Virus
		HRREKR↓SVAL	205–206, Dengue virus
UL55	Cytomegalovirus/herpesvirus 5 protein UL55/glycoprotein B	THRTKR↓STDG	460–461
gp160	HIV-1 glycoprotein-160	VQREKR↓AVGL	498–499
Fo	Measles virus fusion protein	SRRHKR↓FAGV	115–116
E2	Infectious bronchitis spike protein	TRRFRR↓SITE	537–538
GP	Marburg virus spike glycoprotein	YFRRKR↓SILW	435–436
env	Ebola envelope glycoprotein	GRRTRR↓EAIV	501–502
BALF4/GP110	Epstein-Barr virus/herpesvirus 4	LRRRRR↓DAGN	432–433
Bacterial endotoxins			
ExoA	Pseudomonas aeruginosa exotoxin A	RHRQPR↓GWEQ	304–305
PA83	Anthrax protective antigen	NSRKKR↓STSA	196–197
α-Toxin	Clostridium alpha-toxin	KRRGKR↓SVDS	398–399
DT	Diphtheria toxin	GNRVRR↓SVGS	218–219
Aerolysin	Aeromonas aerolysin	KVRRAR↓SVDG	455–456
Shiga toxin	Shigella shiga toxin I subunit A	ASRVAR↓MASD	273–274

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Fusin

►Chemokine Receptor CXCR4

Fusion Genes

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Synonyms

Fusion proteins; fusion oncogenes; chimeric genes; chimeric oncogenes; chimeric transcripts; hybrid genes

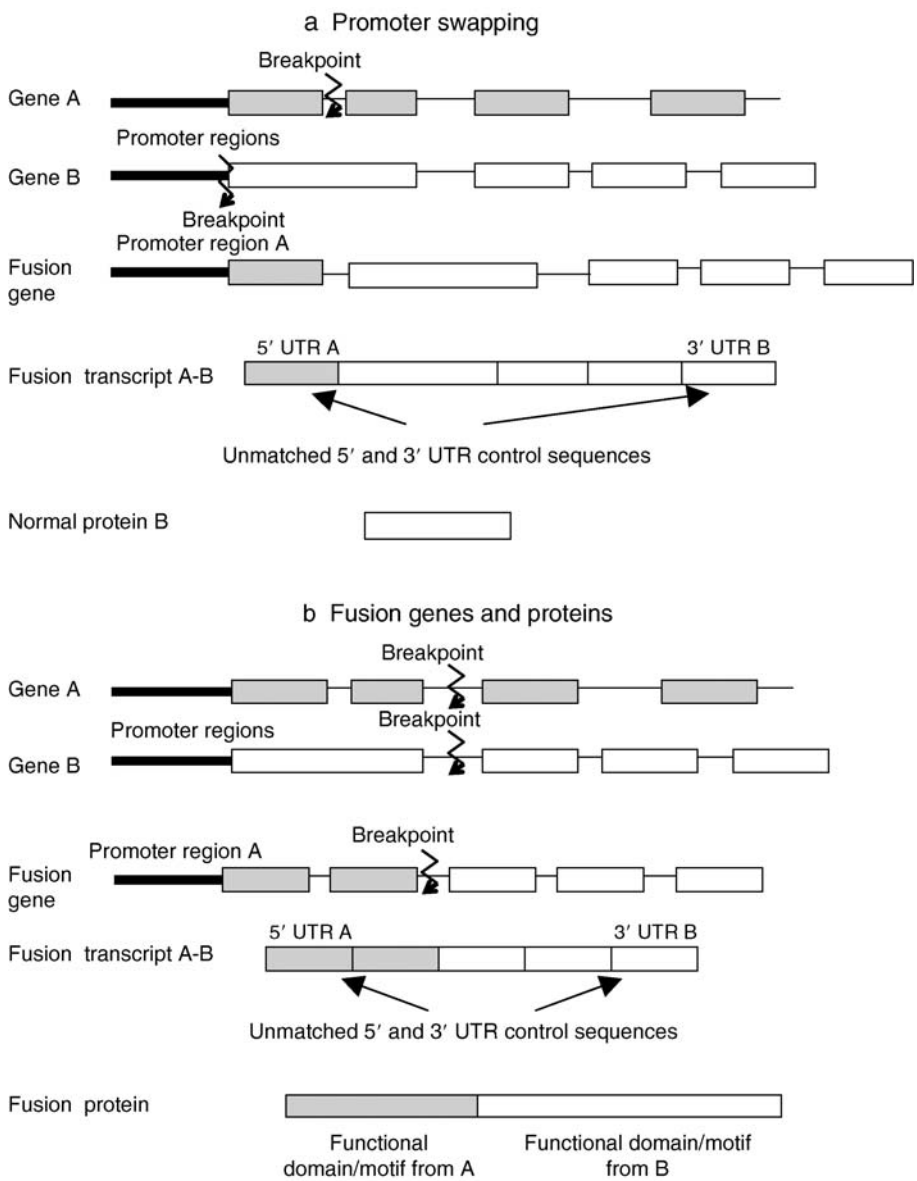
Definition

A hybrid gene created by joining portions of two different genes (to produce a new protein) or by joining a gene to a different promoter (to alter or deregulate a gene transcription).

Characteristics

A wide variety of recurrent molecular alterations has been associated with cancer including ►polymorphisms, changes in gene copy number (amplifications and deletions), point mutations, ►epigenetic modifications and gene fusions due to structural ►chromosomal rearrangements, such as translocations and less frequently inversions. As for these last ones, the genes located at the breakpoints of the rearrangement may be structurally changed with dramatic effects on their products. Molecularly, two events of structural aberrations can be generated: "promoter swapping" (the exchange of promoter control regions) or fusion gene.

In detail (Fig. 1a) "promoter swapping" occurs when the regulatory elements of a gene (promoter and/or enhancer) become aberrantly juxtaposed to a proto-oncogene, thus driving deregulated expression of an oncogene. Molecularly, the breakpoints of the rearrangements occur upstream from the coding region of the partner gene resulting in two chimeric genes which have exchanged their promoter regions, and less frequently noncoding exons. At the genomic level, the



Fusion Genes. Figure 1 A schematic representation of two events of stuctural aberations: (a) Promoter swapping and (b) Fusion genes and Fusion proteins.

3′ partner gene B is placed downstream of the 5′ gene A promoter region. The chimeric transcript contains 5′ ►untranslated regions (UTR) from the A gene and a coding region B that is intact and encodes a normal protein B. This mechanism can be exemplified by the three translocations that characterize Burkitt lymphoma: t(8;14), t(8;22), and t(2;8). All these rearrangements lead to the activation of *MYC*, located on 8q24, by juxtaposing the coding sequences of the gene to one constitutively active immunoglobulin (Ig) genes promoter or regulatory regions (IgH at 14q32, IgK at 2p12, and IgL at 22q11).

Fusion genes (Fig. 1b) arise when the coding regions of the two genes are juxtaposed, resulting in a chimeric transcript that produces a fusion protein with a new altered activity. In detail, in the majority of cases, fusion genes are formed when DNA breaks occur within two different genes mainly within the introns, A and B, and the gene fragments are joined in erroneous combinations. In most cases, the results are two fusion genes: A-B and B-A. On genomic level, the 3′partner gene B is placed under the 5′ gene A promoter control region which dominates the transcription control of the fusion gene. As a result, in the fusion protein the functional domains from the A and B proteins are brought together in a new abnormal combination. In cancer, the genes that are often interrupted by a chromosomal rearrangement are oncogenes , thus harboring fusion oncogenes. An appropriate example of a fusion oncogene is ►BRC/ABL characterizing chronic myelogenous leukemia which is driven by t(9;22)(q34;q11), also known as the ►Philadelphia chromosome, the first translocation to be molecularly characterized. In particular, the translocation fuses the *ABL* gene normally located on 9q34, with the *BCR* gene at 22q11. The BCR/ABL fusion created on the derivative chromosome 22 encodes a chimeric protein with an increased ►tyrosine kinase activity and abnormal localization. Table 1 enlists molecularly characterized recurrent chromosomal rearrangements found in cancers.

Formation Of Fusion Genes

Several factors influence the formation of fusion oncogenes and their role in tumorigenesis. Firstly, the rate at which fusion genes are formed is important. Literature suggests that at least some fusion genes are found in healthy individuals, implying that at least some gene fusions emerge at a notable rate. The mechanisms behind fusions are unknown but the occurrence of several double strand breaks that coincide in time and space are important. The proximity of damaged partner genes at the moments of repair is critical and the localization of chromatin and genomic regions in the interphase nuclei may be critical. Secondly, the presence of a fusion gene in a cell is not enough to cause cancer. Additional genetic or epigenetic changes are also needed and the risk for these additional events to occur affects the outcome. Thirdly, once the fusion is formed, its penetrance, i.e. the proportion of fusion carriers that develop tumors, is determined by selected mechanisms. Interestingly, many fusion oncogenes demonstrate a strict specificity for tumor type. The risk of getting a certain translocation could depend on cell type-specific processes that make the specific genes or DNA regions involved vulnerable to the translocation. It is clear that tumor development in different cell types and tissues locations involves many pathways, distinct genes, and also exogenous factors. A common mechanism for early genetic changes can however be distinguished in a number of different tumor types by specific chromosome rearrangements.

Moreover, the transcriptional orientation of fusion partner genes is essential in order to harbor functional fusion genes. At times, the partner genes are not oriented in the correct direction with regards to their transcriptional orientation, and more complex rearrangements are needed to fuse the partner genes into functional fusion genes. For instance, the EWS-ERG fusion is found in about 10% of Ewing sarcomas and it is the result of a complex rearrangement, a ►translocation and an ►inversion, given that the genes involved are not transcribed in the same centromeric/telomeric direction. This requirement and the necessary presence of critical functional protein parts seem to influence how frequently variant fusion genes are present in tumors. Moreover, to produce a functional fusion gene is necessary that the exons flanking the breakpoints can give rise to splicing events that maintain their reading frames. Overall, the factors that generate double-strand breaks are largely unknown.

Clinical Relevance

Studies over the past decades have revealed that recurring chromosome rearrangements leading to fusion oncogenes are specific features not only of leukemias and lymphomas, but also of certain epithelial tumors. Presently, over 600 recurrent balanced tumor-associated chromosomal rearrangements have been molecularly characterized. However, the data are strongly biased in favor of hematologic malignancies and sarcomas. An important example of a recurrent rearrangement which leads to the development of a targeted therapy is the t(15;17)(q22;q21) in ►acute promyelocytic leukemia which fuses the ►*PML* gene (15q22) with *RARα* gene at 17q21. The PML protein contains a zinc-binding domain called a “ring” finger that may be involved in protein–protein interaction. RARα protein encodes the retinoic acid alpha-receptor protein (►retinoic acid receptors a member of the nuclear steroid/thyroid hormone receptor superfamily. Although retinoic acid binding is retained in the fusion protein, the PML/RARα may confer altered DNA-binding specificity to the RARα ligand

Fusion Genes. Table 1 Molecularly characterized recurrent chromosome rearrangements and fusion genes in cancer

Disease	Affected gene	Rerrangement
Hematopoietic tumor		
Lymphoid		
►Anaplastic Large Cell Lymphoma	NPM-ALK	t(2;5)(q23;q35)
	TPM3-ALK	t(1;2)(q25;p23)
	TFG-ALK	t(2;3)(p23;q21)
	ATIC-ALK	inv(2)(p23q35)
	MSN-ALK	t(X;2)(q11-12;p23)
	CLTCL-ALK	t(2;17)(p23;q23)
►Burkitt Lymphoma, B-cell acute lymphoid leukemia	MYC (relocation of IgH locus)	t(8;14)(q24;q32)
	MYC (relocation of IgK locus)	t(2;8)(p12;q24)
	MYC (relocation of IgL locus)	t(8;22)(q24;q11)
B-cell precursor ALL	E2A-PBX1	t(1;19)(q23;p13)
	E2A-HLF	t(17;19)(q22;p13)
	TEL-AML1	t(12;21)(p12;q22)
	BCR-ABL	t(9;22)(q34;q11.2)
	MLL-AF4	t(4;11)(q21;q23)
	IL£-IgH	t(5;14)(q31;q32)
►Diffuse large B-cell lymphoma	BCL2-IgH	t(14;18)(q32;q21)
	BCL6- variant partners	t(3;v)(q27;v)
	BCL8-IgH	t(14;15)(q32;q11-13)
	FCGR2-Igλ	t(1;22)(q22;q11)
	MUC1-IgH	t(1;14)(q21;q32)
	NFKB2-IgH	t(10;14)(q24;q32)
Extranodal mucosa-associated lymphoid tissue	MALT1-API2	t(11;18)(q21;q21)
	MALT1-IgH	t(14;18)(q32;q21)
	BCL10-IgH	t(1;14)(p22;q32)
	BCL10-Igκ	t(1;2)(p22;p12)
Plasma cells myeloma	FGFR3-IgH and MMSET	t(4;14)(p16;q32)
	MAF-IgH	t(14;16)(q32;q23)
	MAF-Igλ	t(16;22)(q23;q11)
	CCND1-IgH	t(11;14)(q13;q32)
	MUM/IRF4-IgH	t(6;14)(p25;q32)
Pre-T cell lymphoblastic leukemia, lymphoma	MYC (Relocation to TCR α/δ locus)	t(8;14)(q24;q11)
	LYL1 (Relocation to TCRα/σlocus)	t(7;19)(q35;p13)
	TAL2 (Relocation TCRβ locus)	
	SCL (Relocation to TCR α/δ locus)	t(1;14)(p32;q11)
	OLIG2 (Relocation to TCR α/δ)	t(14;21)(q11;q22)
	LMO1(RBTN1) (Relocation to TCR α/δ)	t(11;14)(p15;q11)
	LMO2 (RBTN2) (Relocation to TCR α/δ)	t(11;14)(p13;q11)
	HOX11 (Relocation to TCR α/δ)	t(10;14)(q24;q11)
	HOX1-1L2	t(5;14)(q35;q32)
	CALM-AF10	t(10;11)(p13;q21)
	NUP98-RAP1GDS1	t(4;11)(q21;p15)
Myeloid		
►Acute promyelocytic leukemia	PML-RARα	t(15;17)(q21;q21)
	NPM-RARα	t(5;17)(q35;q21)
	PLZF-RARα	t(11;17)(q23;q21)

Fusion Genes. Table 1 Molecularly characterized recurrent chromosome rearrangements and fusion genes in cancer (Continued)

Disease	Affected gene	Rerrangement
►Acute myeloid leukemia	ETV6- variant partners	t(12;v)(p13;v)
Acute myeloid leukemia	NUP98-variant partners	t(11;v)(p13;v)
	MLL-variant partners	t(11;v)(q23;v)
	AML1-ETO	t(8;21)(q22;q22)
	CBFB-MYH11	inv(16)(p13q22)
	FUS-ERG	t(16;21)(p11;q22)
	CEV14-PDGFRB	t(5;14)(q33;q32)
	P300-MOZ	t(8;22)(q33;q32)
	MOZ-TIF2	inv(8)(p11q13)
	MOZ-CBP	
	DEK-NUP214	t(6;9)(p23;q34)
	RBM15-MKL	t(1;22)(p13;q13)
	MLF1-NPM1	t(3;5)(q25;q34)
	AML1-EVI1	t(3;21)(q26;q22)
Solid tumors		
Sarcomas		
Alveolar rhabdomyosarcoma	PAX3-FKHR	t(2;13)(q3?;q14)
	PAX7-FKHR	t(1;13)(q36;q14)
►Alveolar soft-part sarcoma	TFE3-ASPL	t(X;17)(p11;q25)
Angiomatoid fibrous histiocytoma	FUS-ATF1	t(12;16)(q13;p11)
Dermatofibrosarcoma protubeans	COL1A1-PDGFB	t(17;22)(q13;q13)
Desmoplastic small round cell tumor	EWS-WT1	t(11;22)(p13;q12)
Endometrial stromal sarcoma	JAZF1-JJAZ1	t(7;17)(p15;q21)
►Ewing sarcoma	EWS-FLI	t(11;22)(q24;q12)
	EWS-ERG	t(21;22)(q22;q12)
	EWS-ETV1	t(7;22)(q22;q12)
	EWS-E1AF	t(2;22)(q33;q12)
	EWS-FEV	t(17;22)(q12;q12)
	FUS-ERG	t(16;21)(p11;q22)
Infantile fibrosarcoma	ETV-NTRK3	t(12;15)(p13;q25)
Inflammatory myofibroblastic tumour	TPM3-ALK	t(1;2)(q22;p23)
	TPM4-ALK	t(2;19)(p23;p13)
	CLTC-ALK	t(2;17)(p23;q23)
Low grade fibromyxoid sarcoma	FUS-CREB312	t(7;16)(q33;p11)
Myxoid chondrosarcoma	EWS-CHN	t(9;22)(q22;q12)
	TAF2N-CHN	t(9;17)(q22;q11)
	TCF12-CHN	t(9;15)(q22;q21)
►Myxoid liposarcoma	FUS-CHOP	t(12;16)(q13;p11)
	EWS-CHOP	t(12;22)(q13;q12)
►Synovial sarcoma	SYT-SSX1	t(X;18)(p11;q11)
	SYT-SSX2	
	SYT-SSX4	
Soft-tissue clear cell sarcoma	EWS-ATF1	t(12;22)(q13;q13)

F

Fusion Genes. Table 1 Molecularly characterized recurrent chromosome rearrangements and fusion genes in cancer (Continued)

Disease	Affected gene	Rerrangement
Carcinomas		
►Follicular thyroid carcinoma	PAX8-PPARγ	t(2;3)(q13;p25)
►Papillary thyroid carcinoma	H4-RET (PTC1)	inv(10)(q11.2;q21)
	RIa-RET (PTC2)	t(10;17)(q11.2;q23)
	ELE1-RET (PTC3,4)	inv(10)(q11q22)
	RFG5-RET (PTC5)	
	TPM3-NTRK1 (TRK)	inv(1)(q21q22)
	TPR-NTRK1 (TRK-T1)	inv(1)(q21q25)
	TFG-NTRK1 (TRK-T3)	t(1;3)(q21;q11)
►Prostate cancer	TMPRSS2-ERG	inv(21)(q22.2;q22.3)
	TMPRSS2-ETV1	t(7;21)(p21.2;q22.3)
	TMPRSS2-ETV4	t(17;21)(q21;q22.3)
►Renal-cell carcinoma	PRCC-TFE3	t(X;1)(p11;q21)
	ASPSCR1-TFE3	t(X;17)(p11;q25)
	SFPQ-TFE3	t(X;1)(p11;p34)
	NONO-TFE3	inv(X)(p11;q12)
►Salivary gland tumors (malignant)	CTNNB1- PLAG1	t(3;8)(p21;q12)
	TORC1-MAML2	t(11;19)(q21;p13)
Secretory breast carcinoma	ETV6-NTKR3	t(12;15)(p13;q25)
►Non-small cell lung carcinoma	EMLH-ALK	inv(2)(p21;p23)

complex. Leukemia patients with the *PML/RARα* gene fusion have an excellent response to the all-trans retinoic acid treatment, which stimulates the differentiation of promyelocytic leukemia cells. Similarly, the molecular characterization of the t(9;22)(q34;q11) in chronic myelogenous leukemia, which generates the fusion oncoprotein BCR/ABL, lead to the development of a successful targeted treatment of imatinib.

In contrast to hematological neoplasia, our knowledge regarding fusion genes in solid tumors is very limited, due to the complexity and poor quality of their ►cytogenetic karyotypes, yet they constitute only the 10% of known recurrent balanced chromosome rearrangements. However, fusion oncogenes may be more common in epithelial tumors than previously thought. Usually, translocations in solid tumors result in gene fusions that encode chimeric oncoproteins. The first chromosome abnormalities to be molecularly characterized in solid tumors were an inv(10)(q11.2; q21.2), as the more frequent alteration, and a t(10;17)(q11.2;q23), in ►papillary thyroid carcinoma. These two abnormalities represent the cytogenetic mechanism which activate the proto-oncogene ►*RET* on chromosome 10, by generating the fusion genes forming the oncogene RET/PTC1 and RET/PTC2, respectively. Moreover, other chromosomal rearrangements leading to *RET* activation were recently described and listed in Table 1. A great impact in the study of solid tumors is foreseen by the recent identification of a large subset of ►prostate cancer harboring ►TMPRSS2/ERG, fusions, TMPRSS2/ETV1 and TMPRSS2/ETV4, generated by inv(21)(q22.2;q22.3), t(7;21)(p21.2;q22.3) and t(17;21)(q21;q22.3) respectively. In particular, the gene *fusion* of the 5′ UTR of TMPRSS2 (a prostate-specific gene) to *ERG* or *ETV1* (genes of the ►ETS family), was identified in the majority of prostate cancer. Although the clinical significance of those fusions is unknown, recent investigations indicate that the expression of TMPRSS2/ERG among prostate cancer patients is a strong prognostic factor for disease progression.

Although fusion proteins play an important role in oncogenesis, additional genetic alterations are essential in order to transform cells. Silencing the specific fusion genes that play fundamental roles for the corresponding tumor, blocking targets of fusion proteins and repressing the cooperating events are all promising therapeutic strategies that need to be further investigated. The detection of the intracellular targets of these fusions will harbor new and important insights into molecular pathways that underlie tumor development. Ultimately, a combination of these approaches with

conventional treatments may provide a powerful new approach to treat these fusion-positive tumors.

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Fusion Oncogenes

►Fusion Genes

Fusion Proteins

►Fusion Genes

FVC

Definition

Forced vital capacity. The volume of air that can be forcibly exhaled following maximal inspiration.

►Chronic Obstructive Pulmonary Disease and Lung Cancer

FX

Definition

Human homologue of GDP-4-keto-6deoxymannose-3, 5-epimerase-4-reductase. This enzyme is rate-limiting in the GDP-fucose synthetic pathway.

►Fucosylation

FZD

Definition

Frizzled; seven-pass transmembrane Wnt receptors closely related to G protein-coupled receptors.

►Wnt Signaling