Module -9

Lecture -2

Genes associated with cancer

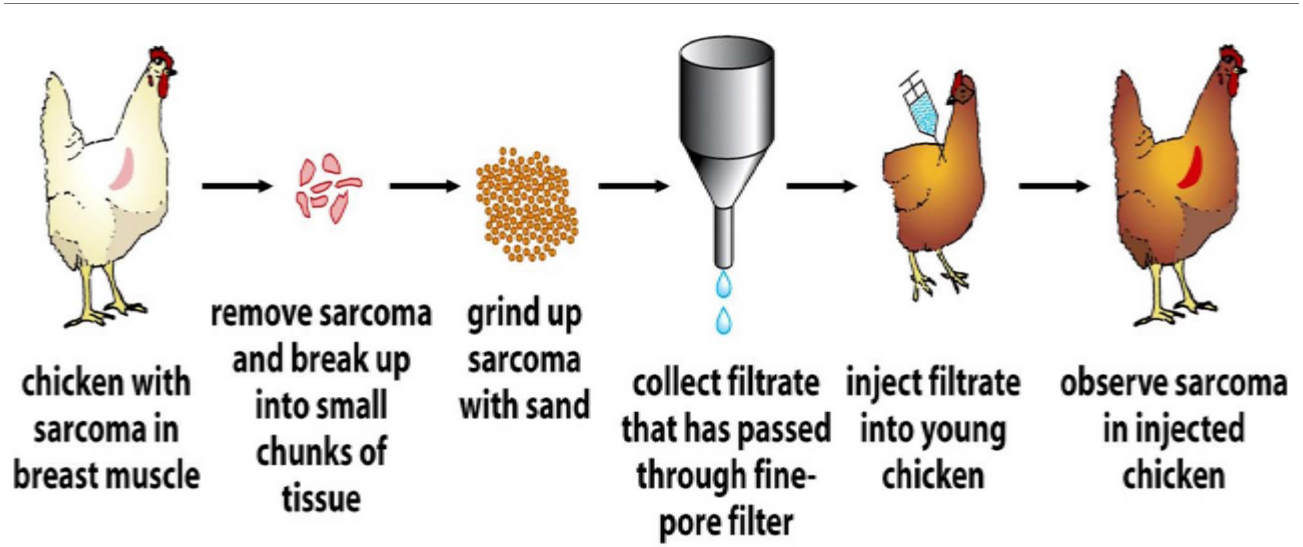
Genes associated with cancer

- As we discussed last time there are about 300 genes associated with cancer
- They can be classified into four types based on their functions
    - **Oncogenes** – growth-promoting
    - **Tumor suppressor genes** – growth-inhibiting/Anti oncogenes
    - **Pro/anti apoptotic genes** – regulate programmed cell death
    - **DNA Repair genes** – involved in DNA repair

Discovery of oncogenes

Let us discuss how oncogenes were discovered.

In 1911, Peyton Rous discovered that a “cell-free” filtrate from the chickens affected by sarcomas could be used to induce tumors in normal chickens.



He observed something interesting. He minced the tissues from the sarcoma tumors of chickens in a buffer and filtered the solution so as to remove the bacteria and tumor cells. Then the cell free filtrate was injected into normal chickens to see if they get cancer. Yes. He did not know what caused the cancer but predicted that it could be a parasite such as a virus.

The active agent was later identified as a retrovirus called “Rous sarcoma virus”

This was the first demonstration of a virus causing cancer

A single gene, *src, was identified to be responsible for these* cancers. The first oncogene was thus identified.

In 1981, Michael Bishop and Harold Varmus found that normal cells contain a gene homologous to the viral *src gene*

v-SRC and c-SRC

The idea was that the virus picked up the normal genes and modified them and upon reinfection could now transform the cells. Thus oncogenes are not alien genes but are actually modified forms of normal genes.

C-SRC was called a proto oncogene - potential to become activated as oncogene. An oncogene is dominant with a gain of function mutation

Discovery of Ras oncogene

If viruses could induce tumors by mutation of a normal cellular gene,
can chemical carcinogens also do it?

Robert Weinberg and his group have indeed shown that DNA extracted from chemically transformed Mouse fibroblasts could transform normal mouse fibroblasts

Identification of that DNA turned out to be the Ras oncogene which was previously known to be associated with sarcoma viruses

In 1982 a human oncogene derived from the bladder tumour cell line EJ was shown to be homologous to the oncogene of Harvey murine sarcoma virus and the cellular proto-oncogene was designated HRAS. The oncogene carried a point mutation—a single nucleotide substitution— (Gly-Val) in comparison to its counterpart protooncogene

Also identified was a homologue of the Kirsten murine sarcoma virus (KRAS2) and a new member of the ras gene family NRAS, that has no viral counterpart.

Further experiments showed that a single oncogene could not transform fully normal rat cells into cancer cells. Two and maybe even more oncogenes were required to effect this conversion. Ras and myc; Ras and adenoviral E1A. Cooperative nature of oncogenes was revealed by these experiments

What do these oncogenes do? Like all the other genes, they also encode for Proteins. What kinds of proteins?

These proteins are the work horses that promote proliferation. We are talking about growth and as can be expected, the oncogene products are
Growth factors
Growth factor receptors
Cell cycle regulators
Cell death regulators
Protein kinases
Transcription factors

Oncogenes encoding growth factors

Oncogene	GF	Cancer
v-sis	PDGF	fibrosarcoma
int-2	FGF-3	breast
k-fgf/hst	FGF-4	gastric cancer, Kaposi sarcoma
trk	NGF	neuroblastoma

Oncogenes encoding growth factor receptors

Oncogene	receptor	cancer
erb-b1	EGFR	sccs of lung and many other tissues
neu	HER-2/Neu	breast, ovary
met	HGFR	osteosarcoma
fms	CSF-1 receptor	sarcoma
ros	Insulin receptor	astrocytoma

Table 1.3 Oncogenes

Oncogenes	Protein Function	Neoplasm(s)
Growth Factors		
sis	Platelet-derived growth factor	fibrosarcoma
int-2	Fibroblast growth factor	breast
trk	Nerve growth factor	neuroblastoma
Growth Factor Receptors		
erb-B1	Epidermal growth factor receptor	squamous cell carcinoma
erb-B2/HER2/neu	Heregulin	breast carcinoma
fms	Hematopoietic colony stimulating factor	sarcoma
ros	Insulin receptor	astrocytoma
Tyrosine kinases		
bcr-abl	Tyrosine kinase	chronic myelogenous leukemia
src	Tyrosine kinase	colon
lck	Tyrosine kinase	colon
Serine-Threonine protein kinases		
raf	Serine-threonine kinase	sarcoma
mos	Serine-threonine kinase	sarcoma
Guanine nucleotide binding proteins		
H-ras	GTPase	melanoma; lung, pancreas
K-ras	GTPase	leukemias; colon, lung, pancreas
N-ras	GTPase	carcinoma of the genitourinary tract and thyroid; melanoma
Cytoplasmic proteins		
bcl-2	Anti-apoptotic protein	non-Hodgkin's B-cell lymphoma
Nuclear proteins		
myc	Transcription factor	Burkitt's lymphoma
jun	Transcription factor (AP-1)	osteosarcoma
fos	Transcription factor (AP-1)	sarcoma

Table 1. Oncogenes related to proto-oncogenes that encode growth factors or growth factor receptors

Oncogene	*Proto-oncogene*	*Original Source*
v-*sis*	PDGF, β chain	Simian retrovirus
v-*erb*-B	EGF receptor	Avian retrovirus
neu	*HER2* receptor	Rat neuroblastoma
v-*fms*	*Csf*-1 receptor	Feline retrovirus
v-*ros*	Insulin receptor, β chain	Avian retrovirus
met	Hepatocyte growth factor receptor	Human osteosarcoma
k-*fgf/hst*	FGF-4	Human stomach cancer, Kaposi's sarcoma
int-2	FGF-3	Murine mammary tumors
trk family	NGF receptor family	Human colon carcinoma
v-*kit*	*Kit* ligand receptor	Feline retrovirus
v-*sea*	Related to insulin receptor	Avian erythroblastosis/ sarcoma virus
v-*erb*-A	Thyroid hormone receptor	Avian retrovirus

PDGF indicates platelet-derived growth factor; EGF, epidermal growth factor; FGF, fibroblast growth factor; NGF, nerve growth factor.
Table adapted from Mendelsohn et al., 2001.

Table 4.1. *Some important retroviral oncogenes*

Oncogene	*Virus*	*Species*	*Tumor type*	*Localization in the cell*	*Main biochemical function*
sis	simian sarcoma virus	monkey	sarcoma	extracellular	growth factor
erbB	avian erythroblastosis virus	chicken	leukemia	cell membrane	tyrosine kinase
fms	feline sarcoma virus (SM strain)	cat	leukemia	cell membrane	tyrosine kinase
kit	feline sarcoma virus (HZ2 strain)	cat	sarcoma	cell membrane	tyrosine kinase
src	Rous sarcoma virus	chicken	sarcoma	inner cell membrane	tyrosine kinase
abl	Abelson murine leukemia virus	mouse	leukemia	cytoplasma	tyrosine kinase
raf	murine sarcoma virus (3611 strain)	mouse	sarcoma	inner cell membrane/ cytoplasm	tyrosine kinase
Ha-ras	Harvey sarcoma virus	rat	sarcoma	inner cell membrane	GTP-binding protein
Ki-ras	Kirsten sarcoma virus	rat	sarcoma	inner cell membrane	GTP-binding protein
akt	AKT8 virus	mouse	thymoma	inner cell membrane/ cytoplasma	serine protein kinase
myc	several avian myelocytomatosis viruses	chicken	leukemia	nucleus	transcription factor
myb	avian myeloblastosis virus	chicken	leukemia	nucleus	transcription factor
rel	avian reticuloendotheliosis virus	turkey	leukemia	nucleus	transcription factor
fos	murine osteosarcoma virus	mouse	osteosarcoma	nucleus	transcription factor
jun	avian sarcoma virus	chicken	sarcoma	nucleus	transcription factor
erbA	avian erythroblastosis virus	chicken	leukemia	nucleus	transcription factor
tax	HTLV1	human	leukemia, lymphoma	nuclear	transcriptional regulator

Table 4.3. *Some important oncogenes in human cancers*

Oncogene	*Tumor type*	*Activation Mechanism*	*Cellular localization*	*Main biochemical function*
TGFA	many carcinomas	overexpression	extracellular	growth factor
FGF1	many solid tumors	overexpression	extracellular	growth factor
WNT1	selected carcinomas	overexpression	extracellular	growth factor
IGF2	many cancers	overexpression	extracellular	growth factor
ERBB1	many carcinomas	overexpression mutation	cell membrane	tyrosine kinase
ERBB2	selected carcinomas	overexpression	cell membrane	tyrosine kinase
KIT	testicular cancers, gastrointestinal stromal tumors	mutation	cell membrane	tyrosine kinase
RET	thyroid and other endocrine gland cancers	mutation inversion	cell membrane	tyrosine kinase
MET	renal and other carcinomas	mutation overexpression	cell membrane	tyrosine kinase
IGFR1	liver and other carcinomas	overexpression mutation (?)	cell membrane	tyrosine kinase
SMO	skin and brain cancers	mutation	cell membrane	G-coupled receptor
HRAS	many cancers	mutation	inner cell membrane	GTP-binding protein
NRAS	many cancers	mutation	inner cell membrane	GTP-binding protein
KRAS	many carcinomas	mutation	inner cell membrane	GTP-binding protein
BRAF	melanoma, colon and other selected cancers	mutation	inner cell membrane, cytoplasm	tyrosine kinase
PI3K	selected cancers	overexpression	inner cell membrane, cytoplasm	phospholipid kinase

Table 4.3. *continued*

Oncogene	*Tumor type*	*Activation Mechanism*	*Cellular localization*	*Main biochemical function*
CTNNB1	colon and liver carcinomas, and others	mutation	inner cell membrane, cytoplasm, nucleus	cytoskeleton transcriptional activation
MYC	many cancers	translocation overexpression mutation	nucleus	transcription factor
MYCN	selected cancers	overexpression	nucleus	transcription factor
MYCL	selected carcinomas	overexpression	nucleus	transcription factor
RELA	leukemias	translocation	nucleus	transcription factor
MDM2/HDM2	sarcomas and other solid tumors	overexpression	nucleus, cytoplasm	transcriptional regulator/ubiquitin ligase
SKP2	selected cancers	overexpression	nucleus, cytoplasm	ubiquitin ligase
CCND1	many cancers	overexpression	nucleus	cell cycle regulation
CCND2	selected cancers	overexpression	nucleus	cell cycle regulation
CDK4	selected cancers	overexpression mutation	nucleus	cell cycle regulation
BCL2	follicular lymphoma and many other cancers	translocation overexpression	mitochondria	apoptotic regulation

TABLE 3.1 SOME EXAMPLES OF ONCOGENES GROUPED TOGETHER BY PROTEIN FORMATIONS

Oncogene Name	Protein Produced	Oncogene Origin	Common Cancer Type*
1. Growth Factors			
v-sis	PDGF	Viral	Sarcomas (monkeys)
COLIA1-PDGFB	PDGF	Translocation	Fibrosarcoma
2. Receptors			
v-erb-b	EGF receptor	Viral	Leukemia (chickens)
TRK	Nerve growth factor receptor	DNA rearrangement	Thyroid
ERBB2	ErbB2 receptor	Amplification	Breast
v-mpl	Thrombopoietin receptor	Viral	Leukemia (mice)
3. Plasma membrane GTP-binding proteins			
KRAS	Ras	Point mutation	Pancreas, colon, lung, others
HRAS	Ras	Point mutation	Bladder
NRAS	Ras	Point mutation	Leukemia
4. Nonreceptor protein kinases			
BRAF	Raf kinase	Point mutation	Melanoma
v-src	Src kinase	Viral	Sarcomas (chickens)

(continues)

TABLE 3.1 SOME EXAMPLES OF ONCOGENES GROUPED TOGETHER BY PROTEIN FORMATIONS (continued)

Oncogene Name	Protein Produced	Oncogene Origin	Common Cancer Type*
SRC	Src kinase	DNA rearrangement	Colon
TEL-JAK2	Jak kinase	Translocation	Leukemias
BCR-ABL	Abl kinase	Translocation	Chronic myelogenous leukemia
5. Transcription factors			
MYC	Myc	Translocation	Burkitt's lymphoma
MYCL	Myc	Amplification	Small cell lung cancer
c-myc	Myc	Insertional mutagenesis	Leukemia (chickens)
v-jun	Jun	Viral	Sarcomas (chickens)
v-fos	Fos	Viral	Bone (mice)
6. Cell-cycle or cell-death regulators			
CYCD1	Cyclin	Amplification, translocation	Breast, lymphoma
CDK4	Cdk	Amplification	Sarcoma, glioblastoma
BCL2	Bcl-2	Translocation	Non-Hodgkins lymphoma

* Cancers are in humans unless otherwise specified. Only the most frequent cancer types are listed.

Source: Becker, Wayne M., Lewis J. Kleinsmith, and Jeff Hardin. *The World of the Cell*, 6th ed. San Francisco: Pearson Education/Benjamin Cummings, 2006, p. 779.

TABLE 3.2 REPRESENTATIVE ONCOGENES OF HUMAN TUMORS		
ONCOGENE	TYPE OF CANCER	ACTIVATION MECHANISM
abl	Chronic myeloid leukemia, acute lymphocytic leukemia	Translocation
akt	Breast, ovarian, and pancreatic carcinomas	Amplification
bcl-2	Follicular B-cell lymphoma	Translocation
*D*1	Parathyroid adenoma, B-cell lymphoma	Translocation
*D*1	Squamous cell, bladder, breast, esophageal, liver, and lung carcinomas	Amplification
*E2A/pbx*1	Acute lymphocytic leukemia	Translocation
*erb*B-2	Breast and ovarian carcinomas	Amplification
Gip	Adrenal cortical and ovarian carcinomas	Point mutation
Gli	Glioblastoma	Amplification
Gsp	Pituitary and thyroid tumors	Point mutation
hox-11	Acute T-cell leukemia	Translocation
lyl	Acute T-cell leukemia	Translocation
c-*myc*	Burkitt's lymphoma	Translocation
c-*myc*	Breast and lung carcinoma	Amplification
L-*myc*	Lung carcinoma	Amplification
N-*myc*	Neuroblastoma, lung carcinoma	Amplification

Oncogene	Type of Cancer	Activation Mechanism
PDGFR	Chronic myelomonocytic leukemia	Translocation
P13K	Ovarian carcinoma	Amplification
PML/RARα	Acute promyelocytic leukemia	Translocation
B-*raf*	Melanoma, colon carcinoma	Point mutation
*ras*H	Thyroid carcinoma	Point mutation
*ras*K	Colon, lung, pancreatic, and thyroid carcinomas	Point mutation
*ras*N	Acute myeloid and lymphocytic leukemias, thyroid carcinoma	Point mutation
ret	Multiple endocrine neoplasia types 2A and 2B	Point mutation
ret	Thyroid carcinoma	DNA rearrangement
SMO	Basal cell carcinoma	Point mutation

Source: Cooper, Geoffrey M. and Robert E. Hausman. *The Cell: A Molecular Approach*, 3rd ed. Washington, DC: ASM Press, 2004, p. 650.

We have learnt that Virus-induced alterations – may introduce their oncogenes into the cells.

All cancers are not caused by viruses.

What are the mechanisms by which a protooncogene is activated to become oncogene?

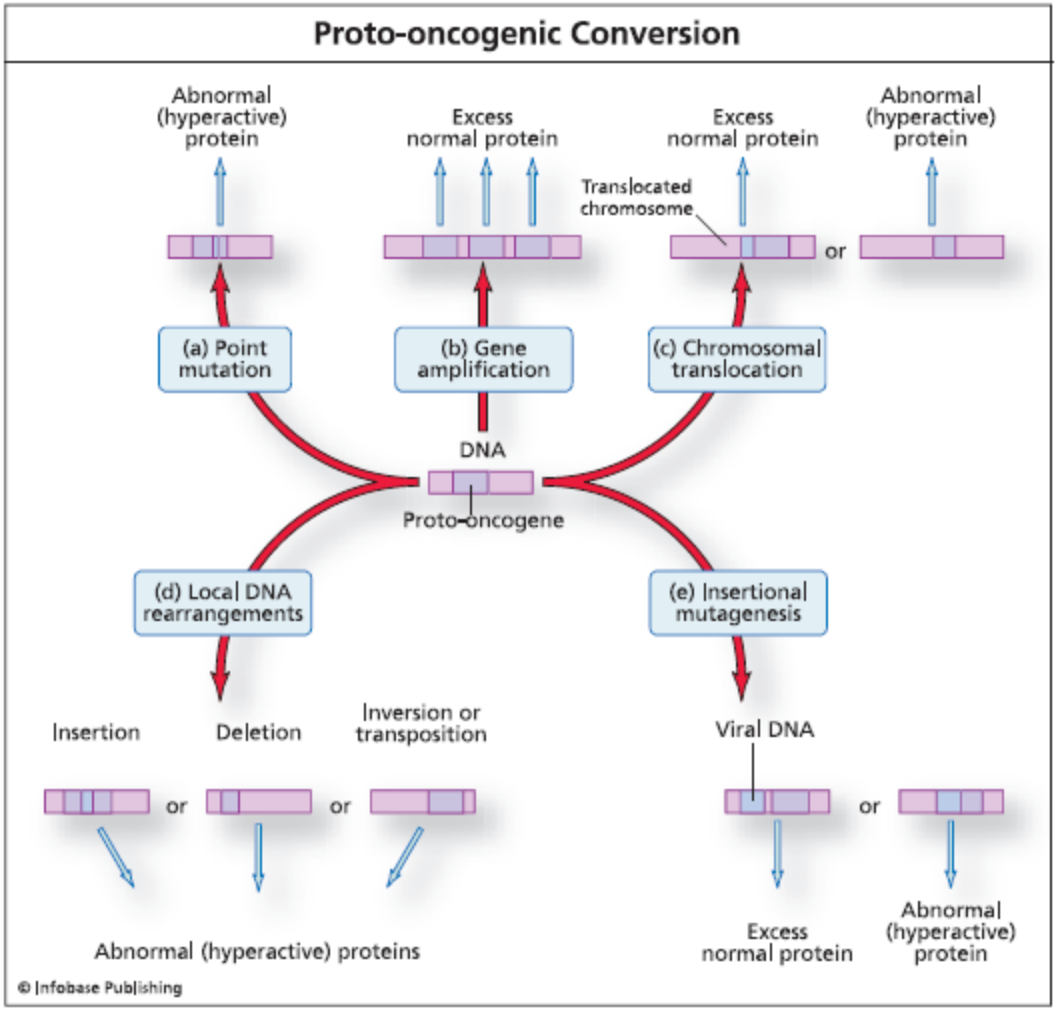


Figure 3.2 There are several methods by which a proto-oncogene is converted into an oncogene.

Molecular Mechanisms of oncogene activation

- Deletion or point mutation – may result in the synthesis of hyperactive protein without change in the normal amount of protein.

A single point mutation in a Ras proto-oncogene can lead to altered gene function.

Ras proteins are small (21 kDa) guanosine triphosphatases (GTPases)
GTP (active) and
GDP-bound (inactive) state

Guanine nucleotide exchange factors (GEFs), increase the amount of GTP-bound Ras

GTPase activating proteins (GAPs) inactivate Ras to GDP-bound form

Ras oncogenes are mutated in 30% of human cancers - colorectal and lung cancers and several forms of leukemia

in some cancers such as pancreatic carcinoma the frequency is as high as 90% K-RAS

The mutations found are confined to codons 12, 13, and 61 and all result in an increase of the GTP-bound form of the protein (constitutive activation)

glycine to valine mutation at *residue 12* or Gly to Asp at residue 13

mutation of Glutamine 61 to Lysine

Ras is an important signaling intermediate in the growth factor signaling via receptor tyrosine kinases and its activation leads to the activation of the MAPK pathway

Gene amplification – multiple copies of a gene - over production of normal protein

two distinct patterns of amplification noticed
high level amplification from a small region of DNA

In contrast, amplification may also cover many megabases of DNA and contain variations in copy number across the amplicon

Double minute chromosomes (DMs) and homogenously staining regions (HSRs) within chromosomes contain high-level amplification of specific genomic regions

Extra copies may be from unusual segregation at mitosis of extrachromosomal fragments

Amplicons are frequently found near the fragile sites in the genome

Amplification of MYC (8q24) was identified in the acute lymphocytic leukaemia
MYCN (2p24), is amplified in many neuroblastomas
MYCL1 (1p34), is amplified in cases of small cell lung carcinoma (SCCL)

Amplification of ERBB2 (also known as HER2) occurs in breast cancer

Table 10.2. *Some characteristic translocations in leukemias and lymphomas*

Translocation	*Genes involved*	*Consequence*	*Cancer type**
t(8;14) (q24;q32) t(2;8) (p12;q24) t(8;22) (q24;q11)	*MYC*, Ig loci	deregulation of MYC	Burkitt lymphoma
t(8;14) (q24;q11)	*MYC, TCRA*	deregulation of MYC	T-ALL
t(14;18) (q32;q21)	*IGH, BCL2*	deregulation of BCL2	follicular lymphoma
t(11;14) (q13;q32)	*IGH, CCND1*	deregulation of Cyclin D1	B-CLL
t(9;22) (q34;q11)	*ABL, BCR*	expression of BCR-ABL fusion protein	CML
t(15;17) (q22;q21)	*PML, RARA*	expression of PML-RARA fusion protein	APL
t(11;17) (q23;q21)	*PLZF, RARA*	expression of PLZF-RARA fusion protein	APL
t(7;9) (q35;34.3)	*TCRB, NOTCH1*	overexpression of truncated NOTCH1 protein	T-ALL
t(3;14) (q27;q32) t(2;3) (p12;q27) t(3;22) (q27;q11)	*BCL6*, Ig loci	deregulation of BCL6	B-cell lymphoma
t(8;16) (p11;p13)	MOZ, CBPA	expression of MOZ-C/EBPα repressor fusion protein	AML

ALL: acute lymphoblastic leukemia, AML: acute myelocytic leukemia APL: acute promyelocytic leukemia, CLL: chronic lymphoblastic leukemia, CML: chronic myeloid leukemia

Chromosome rearrangement s may form a fusion protein that is hyperactive. This mechanism is found predominantly in leukaemias, lymphomas and sarcomas.

Translocation of the oncogene next to the regulatory elements in immunoglobulin B- lymphocyte malignancies or T-cell receptor genes in T-lymphocyte malignancies may lead to inappropriate expression of the oncogene. This could result in the over production of normal protein

Chromosomal translocations are found in both chronic and acute haematopoetic malignancies and in some solid tumours of mesenchymal origin

a gene close to the breakpoint on one derivative chromosome is not altered in its structure but its pattern of expression is altered.

The second is that the structure of a gene (or genes) at the breakpoints is altered. Commonly this involves the fusion of exons from two different genes to give rise to a novel transcript and fusion protein product with altered or novel function.

Several examples of the first type of translocation involve the MYC gene Burkitt's lymphoma, t(8;14)(q24;q32), t(2;8) (p12; q24), and t(8;22)(q24;q11) in which the MYC gene is activated by translocation to the region of an immunoglobulin gene

Immunoglobulin and T-cell receptor genes are involved in many such translocations as they have a natural propensity to re-arrange in the generation of antibody diversity and errors in the process can occasionally lead to interchromosomal translocation.

An example of the second type of translocation is the 9;22 translocation in chronic myelogenous leukaemia that results in the fusion of the Abelson gene (ABL) on 9q34 with the 50 region including the promoter of the BCR gene on chromosome 22. Both genes are broken in introns resulting in the formation of an in-frame fusion mRNA and protein that is unique to these tumour cells. Almost all CML patients show this translocation and express an abnormal 210 kDa protein (normal ABL protein 145 kDa). The derivative chromosome 22 is known as the Philadelphia (Ph) chromosome. A Ph chromosome is also found in some cases of acute lymphoid and myelogenous leukaemia and but here the breakpoint in the BCR gene is different and the fusion protein is 190 kDa. Functional assessment of these two fusions proteins in vivo indicates that the transforming ability of the 190 kDa protein is greater, which may explain its association with acute rather than chronic disease.

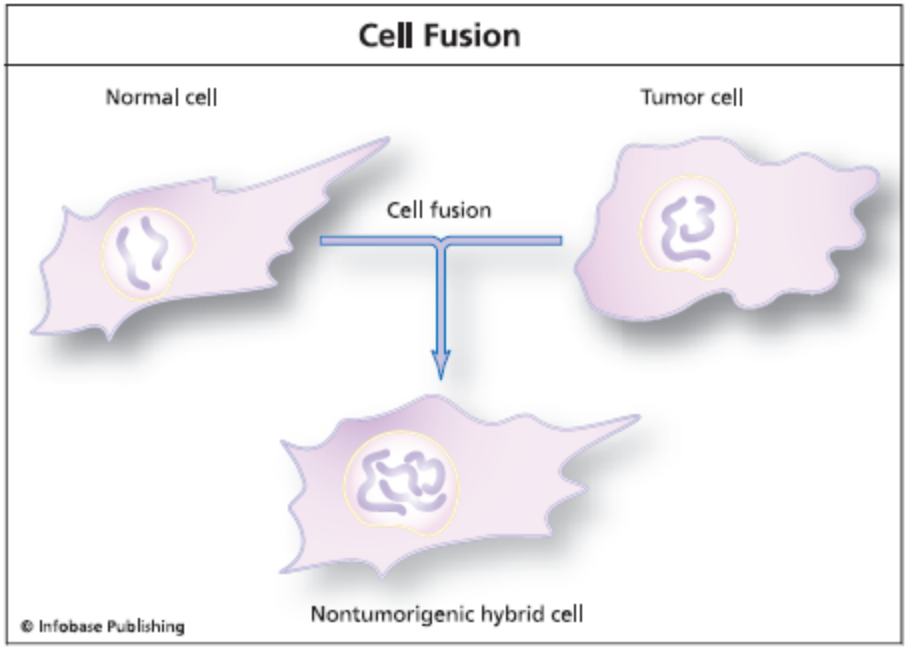


Figure 4.1 Fusion of a normal cell with a cancer cell initially produces a nontumorigenic hybrid cell, which results in suppression of tumorigenicity.

In the case of oncogenes we mentioned that there is a gain of function as a result of a mutation whereas in the case of tumor suppressor genes mutations result in loss of function of the genes.

Mutation is generally in the form of deletion.

Tumor suppressor genes function by inhibting the cell growth or inducing cell death (apoptosis).

Tumor Suppressors

- Usually inactivating mutations lead to an insensitivity to growth-inhibitory signals
- Knudson's **Two-hit hypothesis**

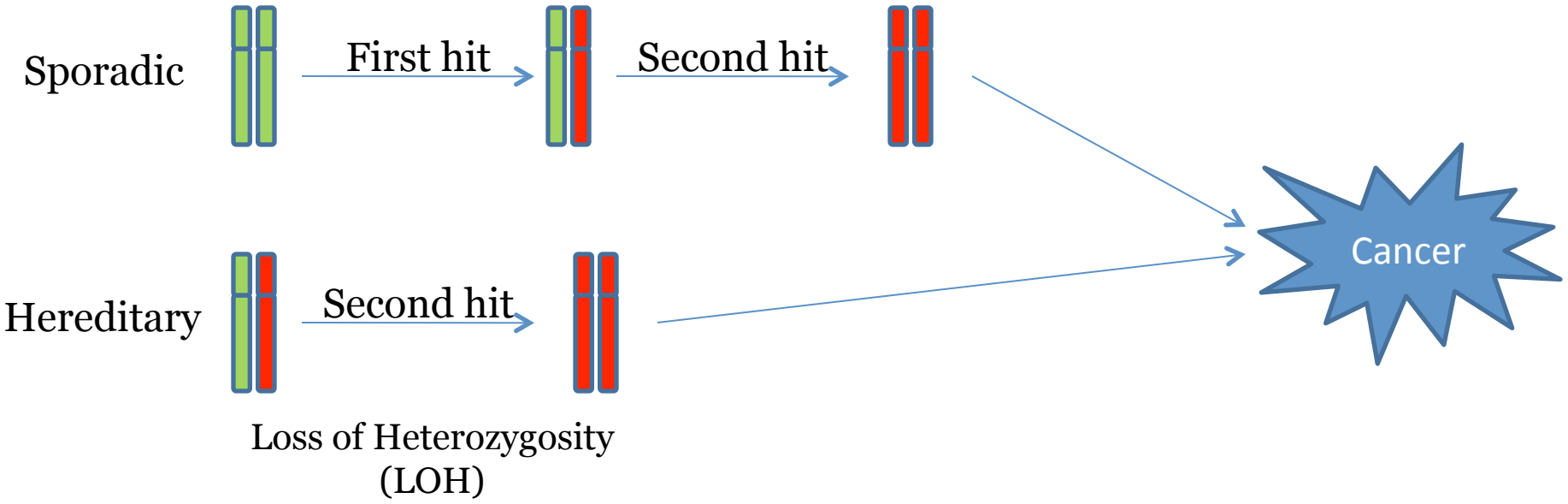


Table 1.4 Tumor Suppressor Genes

TS Gene	Protein Function	Neoplasm(s)
APC	cell adhesion	colon
BRCA 1	transcription factor	breast and ovary
BRCA 2	DNA repair	breast and ovary
CDK4	cyclin D kinase	melanoma
hMLH1	DNA mismatch repair	HNPCC[a]
hMSH2	DNA mismatch repair	HNPCC
hPMS1	DNA mismatch repair	HNPCC
hPMS2	DNA mismatch repair	HNPCC
MEN1[b]	Ret receptor	thyroid
NF1	GTPase	neuroblastoma
p53	transcription factor	colon, lung, breast
Rb	cell cycle checkpoint	retinoblastoma
WT-1	transcription factor	childhood kidney

[a]Hereditary non-polyposis colon cancer.

[b]Multiple endocrine neoplasia.

Table 5.1. *Some dominantly inherited cancer syndromes in man*

Syndrome	*Gene*	*Location*	*Cancer site*	*Function*
Retinoblastoma	*RB1*	13q14	eye, bone	gatekeeper tumor suppressor
Li-Fraumeni	*TP53*	17p13.1	many organs	caretaker tumor suppressor
Hereditary melanoma and pancreatic cancer	*CDKN2A*	9p21	skin, pancreas, others	gatekeeper tumor suppressor
Familial adenomatous polyposis coli	*APC*	5q21	colon, rectum, others	gatekeeper tumor suppressor
Cowden	*PTEN*	10q23.3	many organs	gatekeeper tumor suppressor
Gorlin	*PTCH*	9p22	skin, brain	gatekeeper tumor suppressor
Von Hippel-Lindau	*VHL*	3p25	kidney, adrenal glands, others	gatekeeper tumor suppressor
Hereditary breast and ovarian cancer	*BRCA1* *BRCA2*	17q21 13q12	breast, ovary	caretaker tumor suppressor
HNPCC	*MLH1* *MSH2* others	3p21 2p15-16	colon, endometrium, stomach, others	caretaker tumor suppressor
Multiple endocrine neoplasia type 2	*RET*	10q11.2	thyroid and other endocrine glands	oncogene
Hereditary renal papillary cancer	*MET*	7q31	kidney	oncogene

Typically, these syndromes show high penetrance and the life-time risk of cancer may approach 100%. As a further important characteristic, patients with familial cancers often develop cancers at a significantly lower age than in other 'sporadic' cases. Thus, most sporadic colon or breast cancers present in patients in their sixties or seventies, but familial cases can appear already in the second or third decade of life. In addition, patients with inherited cancers may develop more than one cancer of the same type or cancers of different types. Multifocality or bilaterality is obvious in cancers of paired organs such as breast, kidney or the eyes. Patients with FAP (→13.2) or HPRCC (→15.3) can have literally thousands of individual tumors in their bowel or kidneys, respectively. A theoretical explanation for these properties of

Table 1
Molecular Alterations of Some tumor suppressor Genes in Primary and Invasive Human Tumors

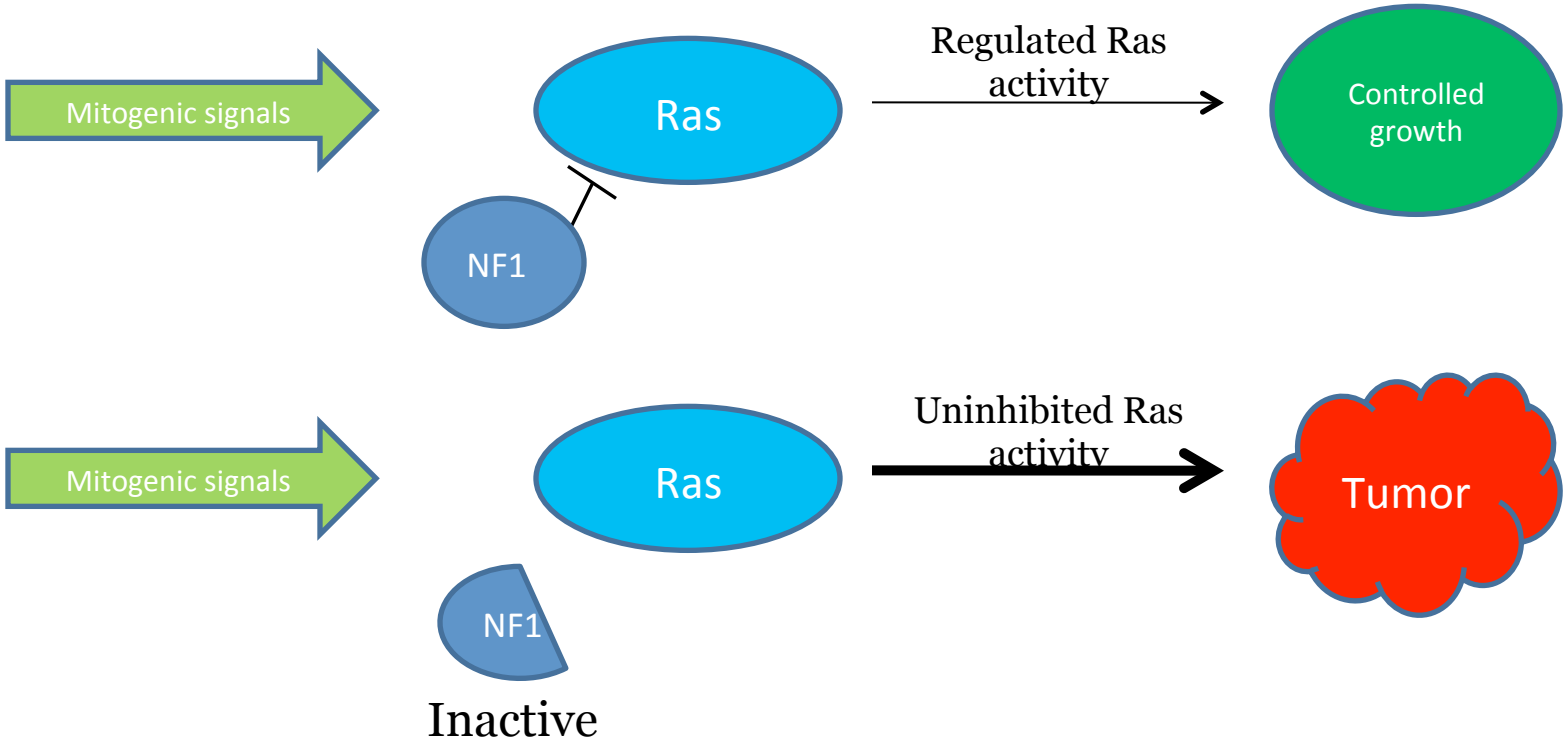
Gene	*Invasive tumors*	*Molecular alterations*	*Refs.*
BRCA1	BC and ovarian cancers and squamous cell carcinomas of the esophagus	LOH, deletion, reduced expression and/or mutation	*(318–324)*
BRCA2	Female hereditary and male sporadic BC	LOH, deletion and/or mutation	*(320,322,325,326)*
Nf1	Neurofibromatosis type 1, neurofibrosarcoma, leukemia, melanoma, shwannoma	Deletion, reduced expression, mutation, splicing alteration	*(196,197,327–345)*
Nf2	Neurofibromatosis type 2, meningiomas, schwannomas, mesotheliomas	Deletion, reduced expression, mutation, splicing alteration	*(198,199,346–358)*
MTS1	Melanomas, sarcomas, esophageal, hepatocellular and lung carcinomas, prostate, cervix, breast, and oral cancer.	LOH, deletion, reduced expression, mutation, methylation	*(98,187,359–368)*
APC	Familial polyposis coli, colorectal tumors, hepatocellular adenoma, oral and ampullary	Deletion, LOH, mutation, reduced expression	*(210–212,369–380)*

TABLE 4.1 EXAMPLES OF HUMAN TUMOR SUPPRESSOR GENES

Gene	Inherited Syndrome	Cancer Type
APC	Familial adenomatous polyposis	Colon
BRCA1	Familial breast cancer	Breast, ovary
BRCA2	Familial breast cancer	Breast
SMAD4	Colorectal cancer	Colon, rectal
NF-1	Neurofibromatosis type 1	Neurofibromas
NF-2	Neurofibromatosis type 2	Schwann cells, meninges
CDKN2A	Familial melanoma	Melanoma, others
p53	Li-Fraumeni	Bone, breast, leukemia, brain, adrenal, others
RB	Hereditary retinoblastoma	Retina, bone, others
HL	Von Hippel-Lindau	Kidney, retina, brain
WT-1	Wilms' tumor	Kidney

Source: Becker, M. Wayne, Lewis J. Kleinsmith, and Jeff Hardin. *The World of the Cell*, 6th ed. Pearson/Benjamin Cummings: San Francisco, 2006, p. 784

- Neurofibromin 1 –inactivates Ras soon after its stimulation by growth factors, i.e., allows for only *transient* activation of Ras



- Cell cycle control by the retinoblastoma (Rb) tumor suppressor protein. Unphosphorylated
- Rb negatively regulates progression into the S phase of the cell cycle by binding to the E2F
- transcription factor. In this complex, E2F is prevented from activating transcription of its target
- genes. During late G1, Rb is phosphorylated by the cyclin D/Cdk4 complex and can no longer sequester
- the E2F transcription factor. E2F then binds to its target S-phase genes, promoting their transcription
- and allowing the cell cycle to progress.

- **p53**

The p53 tumor suppressor is activated

in response to a wide variety of cellular stresses including DNA damage, ribonucleotide depletion, redox modulation, hypoxia, changes in cell adhesion, and the stresses created by activated oncogenes.

The p53 protein can induce growth arrest, promote DNA repair, and stimulate cell death by apoptosis.

Collectively these activities act to maintain genomic stability.

Elimination of p53 function leads to increased rates of mutation and resistance to apoptosis. Thus, p53 is important for several biochemical pathways that are disrupted during tumorigenesis.

Consequently, mutations in p53 are the most frequent genetic change encountered in human cancers.

Table 5.3. *Mechanisms of TP53 inactivation in human cancers*

Mechanism of inactivation
Missense mutations
Nonsense and splice mutations
Deletion of one allele
Overexpression of HDM2 by gene amplification or deregulation
Loss of $p14^{ARF}$ function by gene deletion, mutation or promoter hypermethylation
Loss of function of upstream activators, e.g. ATM or CHK1
Loss of function of downstream effectors, e.g. BAX
Inactivation by altered post-translational modification
Inactivation by viral oncoproteins, e.g. HPV E6

p53 is inactivated by at least three mechanisms.
The most common event is mutation of the p53 gene, which occurs in about 50% of all sporadic human tumors.
As with other tumor suppressors, **mutations** can occur in somatic tissues or can be inherited through the germline. Inherited p53 mutations give rise to the Li-Fraumeni syndrome in which affected individuals develop bone or soft-tissue sarcomas at an early age.

In addition**, non mutational inactivation** of p53 can occur in the presence of viral transforming antigens. For example, the simian virus 40 (SV40) large T antigen binds with p53 and forms an inactive complex, whereas the papilloma virus E6 protein eliminates p53 by causing premature degradation of the protein through the 26S proteosome.

The third mechanism by which p53 activity can be eliminated is by **cytoplasmic sequestration**. p53 that is unable to enter the nucleus cannot induce the expression of downstream effector genes that are necessary for mounting the cellular response to genotoxic stress.

Under normal conditions, levels of p53 are kept minimal by ubiquitination and proteosome-mediated degradation that contributes to the short half-life (3–20 min) of the protein.

A key player in maintenance of low p53 levels is mdm2.

Mdm2 performs this function by interacting with p53 at its *N*-terminus and targets p53 for proteosome- mediated degradation.

Mdm2 and p53 function in a feedback loop where activated p53 stimulates the expression of Mdm2, which in turn reduces the duration of up-regulated p53 activity.

Overexpression of Mdm2 suppresses p53 by preventing its accumulation in response to DNA damage.

Consequently, Mdm2 can function as an oncogene that acts in much the same way as the papilloma virus E6 protein.

In fact, Mdm2 is overexpressed in some tumors such as osteosarcomas.

We have discussed
The discovery of oncogenes particularly about SRC and Ras
Listed the names of a few important oncogenes
Molecular mechanisms by which a protooncogene is activated to oncogene
Tumor suppressor genes
Explained a few important tumor suppressor genes

END