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Study Notes on Cancer

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Notes # 1. Subject-Matter of Cancer:

In multicellular organisms, cell division is a normal process. Cells divide for growth, for the development of organs, for healing of wounds and also for the replacement of older and damaged cells. Cell division is a very complex process which is controlled by a regulatory mechanism at both molecular and cellular level.

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Again, in higher multicellular organism, each and every cell belongs to a particular type of tissue like epithelial tissue, connective tissue muscular tissue etc.

Hence, when a cell of a specific tissue divides, it normally produces its own kinds of cell of the tissue to which it belongs. It never produces the cells of other tissues.

Therefore, the process by which cells achieve this specification and specialisation is known as cellular differentiation. Differentiation of cell begins during embryonic gastrulation stage and continues through t formation.

Actually differentiation has a genetic basis and the pro

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results from the interaction of the nucleus and the cytoplasm. After the cells become well-differentiated, they cannot go back normally to the undifferentiated stage unless disturbed internally or externally.

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Therefore, in multicellular organism, the cell division, differentiation and survival of individual cells are carefully regulated to meet the needs of the organism as a whole.

When this regulation is lost due to any reason, the cells behave unusually and defy their control mechanism.

Then the cells grow and divide in an uncontrolled manner, ultimately spreading throughout the body and interf

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with the functions of normal tissues and organs. As a whole, this condition leads to cancer. Cancer develops from defects in fundamental regulatory mechanisms of the cell.

Notes # 2. Meaning of Cancer:

Cancer is a non-infectious disease. It starts at the molecular level of the cell and, ultimately affects the cellular behaviour. Generally, it can be defined as uncontrolled proliferation of cells without any differentiation.

Notes # 3. Types of Cancer:

Cancer is a large class of diverse disease. All types of cancer can result from uncontrolled cell growth and division of any of the different kinds of cells in the body. So there are more than a hundred distinct types of cancer which vary in their behaviour and response to treatment.

The uncontrolled cell growth produces a mass of cells are called tumours or neoplasm tumours may be benign or malignant. A benign tumor remains confined to its original location. They do not invade the surrounding normal

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tissues. They do not spread to distant body sites.

The most common example of tumour is the skin wart. A benign tumour consists of closely resembles normal cells and may function like normal cells. Generally benign tumours are harmless and can usually be removed surgically. However, these tumours may sometimes become quite harmful if they are located in organs like brain and liver.

A malignant tumour does not remain confined to its original location. They are capable of both invading surrounding normal tissue and spreading throughout the body via the circulatory or lymphatic systems. Malignant tumours become life-threatening if, they spread throughout the body.

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Only malignant tumours are properly designated as cancers. The cells of malignant tumour are derived from single cell, thus they are monoclonal in character. Malignant tumour is composed of aberrant cells. They behave like embryonic type, undifferentiated, having irregular, large nucleus, and deficient of cytoplasm. Malignant tumours are generally classified into four main types on the basis of cell type from which they arise.

(i) Carcinomas:

It includes approximately 90% of human cancer. This principally derived from epithelial cells of ectoderm and endoderm. The solid tumours in nerve tissue and in tip of body surfaces or their attached glands are example

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carcinomas. Cervical, breast, skin and brain carcinomas are developed from malignant tumour.

(ii) Sarcomas:

Sarcomas are solid tumours of connective tissues such as muscle, bone, cartilage and fibrous tissue. This type of malignant tumours are rare in human (about 2% of human cancer).

(iii) Lymphomas:

It is a type of malignancy in which there is excessive production of lymphocytes by the lymph nodes and spleen. It accounts for approximately 8% of human cancers. Hodgkin's disease is an example of human lymphoma.

(iv) Leukemia's:

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This type of malignancy arises from the blood forming cell.

Leukemia's are commonly known as blood cancer.

Leukemia's are neoplastic growth (uncontrolled cell growth at the cost of remaining cells) of leucocytes or WBC.

They are characterised by excessive production of WBC of the blood. The name leukemia is derived from Greek leukos (white) + haima (blood) the massive proliferation of leukemia cells can cause a patient's blood to appear milky.

In addition to the types of cancer mentioned above, cancers are further classified according to tissue of origin, for example lung cancer, breast cancer, and the type of cells involved, for example fibro sarcoma arises from fibro-

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erythromoid leukemia's from precursor of erythrocytes. Although there are many kinds of cancer, the four most common cancers are those of prostate, breast, lung and colon/rectum.

Notes # 4. Development of Cancer:

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The development of cancer is a multistep process in which cells gradually become malignant through a progressive series of alterations. This process involves mutation selection for cells with progressively increasing capacity for cell division, survival, invasion and metastasis (spread of cancer cells through the blood or lymphatic system to other

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organ sites).

The first step in the process is when a single cell within a tissue of the organ concerned is genetically modified. The modified cell divides rapidly, although surrounding cells do not—and a mass of tumour cells forms.

These cells constitute a clone where cells are identical in terms of structure, characteristics and function. Rapid cell proliferation leads to the tumorous outgrowth or adenoma or polyp. This tumour is still benign.

Tumour progression continues as additional mutation occur within cells of tumour population. Some of these mutations give a selective advantage to the cell such as rapid growth and the descendants of a cell bearing such a mutation will consequently become dominant within the tumour population.

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This process is known as clonal selection. Clonal selection continues throughout tumour development and, consequently, tumour become more and more rapid, growing and increasingly malignant. The tumour cells

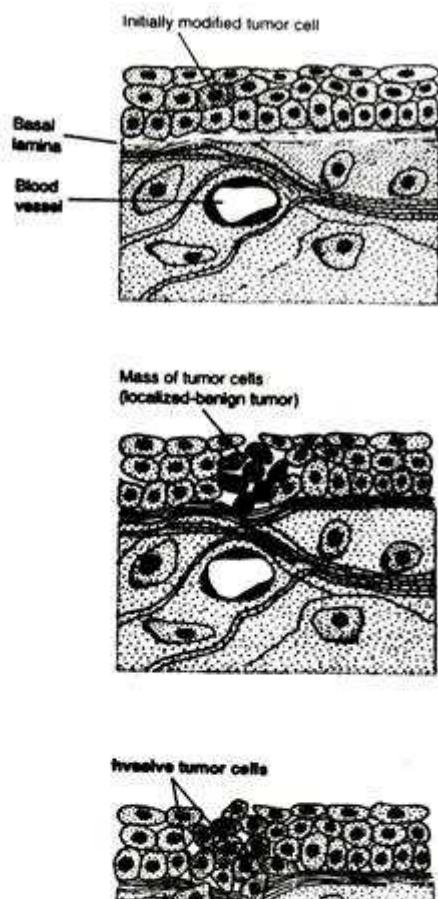
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their rapid proliferation, invades the basal lamina that surrounds the tissue.

Then tumour cells spread into blood vessels that will distribute them to other sites in the body. This is known as metastasis. If the tumour cells can exit from the blood vessels and grow at distant site, they are considered malignant (Fig. 23.1).



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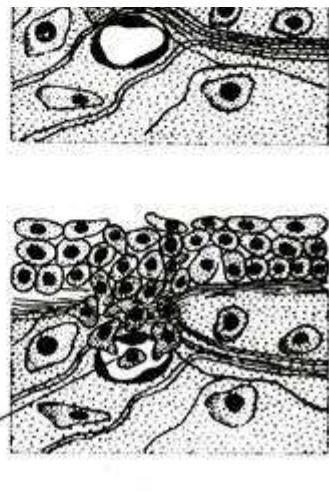


Fig. 23.1: Stages in tumour growth and metastasis.

Notes # 5. Characteristics of Cancer Cells:

The uncontrolled growth of cancer cells results from accumulated abnormalities affecting many of the cell regulatory mechanisms. The process of cell change in which a normal cell loses its ability to control its rate of division and thus becomes a tumour cell is called cell transformation.

Cancer cells shows some typical characteristic properties that are absent in normal cells. Sometimes cancer cell properties are just opposite to the properties of normal cells. Cancer cells in vivo differ from their normal counterparts in the following ways:

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several respects. Some characteristic properties of cancer cells can also be demonstrated by cell culture in vitro.

(i) Immortalization:

Normal cell culture do not survive indefinitely. For example, human cell culture die after about 50 generations. On the other hand, transformed cell cultures can go on indefinitely and remain immortal if the nutrition is provided and overcrowding avoided.

(ii) Loss of Contact Inhibition:

Normal cells growing in tissue culture tend to make cell contacts by adhesion to neighbouring cells. At the points of adhesion some kind of electron-dense plaque is formed in both contacting cells. At the same time there is a slowing down of the amoeboid process which results in contact inhibition of movement. In contrast, cancer cells are unable to form adhesive junctions and do not show this type of contact inhibition.

Experimentally, it has been observed that when normal cells have become completely surrounded by other cells, their mobility stops and they form a monolayer. At the sam

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there is inhibition of growth and the number of cells in the petridish remains practically constant.

On the other hand, cancer cells continue to multiply and pile up forming irregular masses several layers deep. Cancerous cells undergo a change in property of their cell membranes and cell coat such as disappearance of gap junction, loss of coupling changes in glycolipid and glycoprotein and a reduction in gangliosides.

In the cell coat fibronectin, a large glycoprotein found in footprints of moving cultured cells is reduced in cancerous cells. These changes enable the cells to dissociate from neighbouring cells and show loss of contact inhibition.

(iii) Reduced Cellular Adhesion:

Most cancer cells are less adhesive than the normal cells due to reduced expression of cell surface adhesive molecules.

When normal cells are transformed into cancer cells, then a change of stickiness of their cell membrane results. Normal cells show stickiness or adhesiveness.

If normal cells are grown in a liquid nutrient medium a glass vessel, the cells stick to glass wall rather than f

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the medium. But when cancer cells are allowed to grow in nutrient medium, they stick to each other less than do normal cells.

Adhesiveness shows considerable specificity. For example, a liver cell tends to stick with another liver cell and not to other types of cell such as kidney cell. Cancerous cells do not show this property. They are able to mix and stick to any type of normal cell. For example, a malignant liver cell can mix and stick to normal kidney cell. Hence this unusual behaviour of cancer cell explains that cancer cells can invade several normal organs.

(iv) Invasiveness:

One of the most important characteristics of cancer cells is their invasiveness. It is the ability to invade other tissues.

Malignant cells generally secrete proteases that digest extracellular matrix components, allowing the cancer cells to invade adjacent normal tissues. For example, secretion of collagenase by the cancer cells helps to digest and penetrate through basal laminae to invade the underlying connective tissue.

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Cancer cells also secrete growth factors that promote t

formation of new blood vessels. This is known as angiogenesis. Angiogenesis is necessary to support the growth of tumour beyond the size of about a million cells at which point new blood vessels are needed to supply oxygen and nutrients to the multiplying tumour cells.

Actually the growth factor secreted by the tumour cells stimulates the endothelial cells present in the wall of capillaries.

As a result, new outgrowth of the capillaries is formed into the tumour. These outgrowths of capillaries are also helpful for metastasis of malignant cells. Therefore, angiogenic stimulation induces the growth of new blood capillaries which penetrate easily in the tumour tissue and provide the opportunity for the cancer cells to enter the circulatory system. As a result, metastasis process begins.

(v) Failure to Differentiate:

Another general characteristic of most of the cancer cells is that they fail to differentiate. This property is closely related with the abnormal proliferation. Normal cells are fully differentiated. In most fully differentiated cells, cell division ceases. In case of cancer-cells, normal differentiation

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program is blocked at the early stages of differentiation. The relationship between defective differentiation and rapid proliferation is clearly noted in case of leukemia.

All of the different types of blood cells develop from a common pluripotent stem cell in the bone marrow. Some of the descended cells develop erythrocytes but others differentiate to form lymphocytes, granulocytes and macrophages. Cells of each of these types become round as they differentiate but once they become fully differentiated cell division ceases. But leukemia cells fail to undergo terminal differentiation. Instead, they become blocked at early stage of maturation at which they retain their capacity for proliferation and continue to divide.

(vi) Auto stimulation of Cell Division:

Cancer cells produce growth factor that stimulates their own cell division. Such abnormal production of a growth factor by the cancer cell leads to continuous auto stimulation of cell division. This is known as autocrine growth stimulation.

Hence the cancer cells are less dependent on general growth factor produced within the body physiologically from a source for inducing growth of all normal cells. It is also noted that the reduced growth factor dependence of cancer

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cell results from abnormalities in intracellular signalling system.

(vii) Apoptosis:

For every cell, there is a fixed span of life, i.e., time to live and time to die. This cell death is a very orderly process and so it is called Programmed Cell Death or PCD or Apoptosis. Apoptosis is a mechanism of programmed cell death or cell suicide which is essential for the survival of the organism, for the normal development of the organism as the programmed destruction of the organism as the programmed destruction of cells is found during embryogenesis. It also protects the organism by removing damaged cells which may be due to viral infection or due to exposure to radiations. It also inhibits the tumour development and so any defect in the control of apoptosis may lead to cancer.

There are two methods by which cells may die such as:

1. Death by injury that is through mechanical damage to toxic chemicals.

2. By Apoptosis, i.e., through programmed cell death.

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(a) Characteristic changes during apoptosis:

The following distinct morphological changes are found during apoptosis:

1. Shrinkage of cells.
2. Cell forms tight sphere.
3. Cell membrane forms bubble-like blebs on the outer surface.
4. Occurrence of nuclear membrane break.
5. Endonucleolytic clearance of DNA at inter-nucleosomal sites occurs leading to the degradation of chromatin.
6. Breakdown of mitochondria is found with the release of cytochrome C.
7. Breakage of cells into small fragments.
8. Engulfment of cells fragments by phagocytic cells:

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(b) Genetic Control of Apoptosis:

Some apoptosis genes have already been identified which are responsible for switching on or off apoptosis. These genes include ICE (Interleukin-1b-Converting Enzyme) and P53. There are other factors that also regulate the process of apoptosis.

One of them is the signal protein which is released either due to some cell injury or through cytokine mediated pathways. There are some critical proteins or modulating factors which determine whether a cell will be repaired or undergo death.

These genes or factors may initiate some stimuli for cell death or induces cellular susceptibility to apoptosis or initiates some effector mechanisms for apoptosis. Some of the genes or factors responsible for apoptosis are listed in the Table 23.1.

Table 23.1: Gene/Factors

(a) Initiating Stimuli	Function
Tumour Necrosis Factor α receptor family (TNF)	Death signal
Ceramide	gives signal for apoptosis induction.
FAS/Apo-1	Death signal like TNF; For peripheral deletion of T lymphocytes
Nur 77 (Zinc finger containing steroid receptor)	Death signal in thymocytes.
(b) Inducing Cellular susceptibility	
c-myc	produces myc protein which gives cell susceptibility for apoptosis

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Rb-1	Deficiency of Rb-1 gives susceptibility. Rb protein may inhibit P 53 mediated apoptosis
E2F1	induces susceptibility
P 53	apoptosis in response to cell injury is dependent on P 53.
(c) Modulating factors	
DAD 1 gene	gives signal for cell death
BCL-2 gene family	Some members inhibit cell death, such as bcl-2, BCL-X. Members which promote death like bax, bid and bad.
(d) Effector mechanisms	
Caspases, ICE, Ich-1	Genes encoding cysteine proteases which are involved in the effector pathway of apoptosis.

(c) Mechanism of Apoptosis:

There are generally three different mechanisms for apoptosis. These are:

1. Triggered by internal signals, i.e., signals arising within the cell.
2. Triggered by external signals.
3. By Apoptosis-Inducing Factor (AIF).

1. By Internal Signals:

In a normal cell, the protein (BC1-2) produced from a BC1-2 remains on the outer surface of the mitochondria. protein BC1-2 holds the apoptotic protease activating

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1 (Apaf-1). But when the damage occurs in the cell internally due to some reactive oxygen, the Apaf-1 factor is released from BC1- 2-Apaf-1 complex.

This allows the protein Bax to penetrate the mitochondrial membrane causing a leakage of cytochrome C from the mitochondria.

Then the released cytochrome C and Apaf-1 bind to molecules of caspase 9. The complex containing cytochrome C, Apaf- 1, caspase 9 and ATP is called Apoptosome. Caspase 9 is actually one form of protease which cleaves proteins at Aspartic acid residues.

The caspase 9 activates other caspases creating a cascade of proteolytic activity which leads to the lysis of cell through digestion of structural proteins of the cytoplasm and degradation of chromosomal DNA.

2. External Signals:

Some receptor proteins (FAS and TNF) and other mol residing on the surface of the cell are responsible for apoptosis. when cyto- toxic T cells containing complementary factor FASL bind to the target cell, FASL

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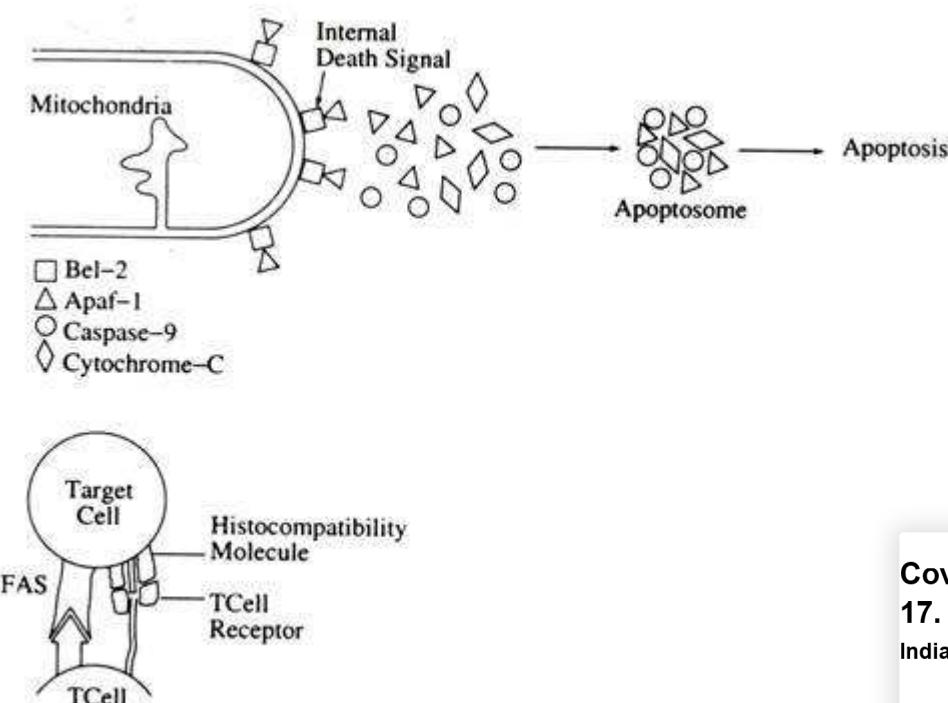
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binds with the FAS of the target cell leading to the death of the cell by apoptosis.

3. Apoptosis-Inducing Factor (AIF):

This AIF is a protein located in the inter-membrane space of mitochondria. When the cell receives the signal for its death, AIF is released from the mitochondria to the cytoplasm. AIF then goes to the nucleus and binds to DNA causing destruction of the DNA and finally the death of the cell.



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In case of cancer, there are some viruses like Human Papilloma Virus (HPV), Epstein-Barr Virus (EBV) produce a special type of protein E6 or BC1-2 which inactivates apoptosis promoter P 53, leading to the proliferation of cancer.

Again those cancer cells without the intervention of viruses also have some techniques to inactivate apoptosis. Some B-cell leukemia's Melanoma (one type of skin cancer), lung cancer cells, colon cancer cells, etc. produce some proteins or factors like BC1-2 "decoy" molecule, Fas L can avoid apoptosis by inhibiting Apaf-1, or binding to Fas leading to proliferation of cancer.

(viii) Density-Dependent Inhibition:

One of the primary distinguishing characteristic features between cancer cell and normal cell is that normal cells show density-dependent inhibition of cell division in culture but cancer cells continue to proliferate independent of cell density.

Proliferation of normal cell continues until they reach finite cell density. Normal cells are very sensitive to cell density. So when they reach a finite density they enter

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state of the cell cycle. But cancer cells continue to divide to high cell density.

(ix) Cellular Characteristics:

Cancer cells can be distinguished from normal cells by microscopic examination. Cancer cells have a high nucleus to cytoplasm ratio, prominent nucleoli, many mitosis, and relatively little specialised structure. Normal cells have a cytoskeleton which consists of microtubules and microfilaments. But the cytoskeleton of cancer cells undergo de-polymerisation and the microtubules disaggregate.

(x) Chromosomal Change:

Normal cell contains normal chromosome number, e.g., normal cells of human beings contain 46 or 23 pairs chromosomes. But in cancer cell the chromosomes can undergo both structural and numerical changes. In human being the parent cell of any cancer has 46 chromosomes. Later, after a series of abnormal divisions the cancer cells contain series of chromosome numbers and karyotype.

The chromosomes swell up and the number of chromosome sets increase owing to the growth of cancer cells. This

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condition is known as aneuploidy. Earlier workers have suggested that in different cancer cell populations there are chromosomal stem lines involving a particular spectrum of chromosome structure and number.

An established cancer cell population will have a modal number in most of the cells over quite long periods and it is relatively stable. Generally speaking, no two karyotypes are identical in cancer cell and no typical chromosome group has been found to be involved. Therefore, the occurrence of any aneuploid cells in a particular tissue may have the possibility to become cancerous cell.

(xi) Interaction With Immune System:

A few normal cells may be transformed in pre-cancer cells every day in each of us in response to radiation, certain viruses or chemical carcinogens in the environment. Because they are abnormal cells, some of their surface proteins are different from those of normal body cells. Such proteins act as antigens and stimulate an immune response that generally destroys these abnormal pre-cancer cells.

If the pre-cancer cells are destroyed by the immune system then how does cancer occur? Further investigation

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demonstrates that there are some transformed cancer cells whose surface proteins are not so changed.

Hence such cancer cells may remain anti-genetically similar to normal cells. As a result, the immune system cells may fail to distinguish the cancer cell from normal cell. Some workers suggest that sometimes cells of the immune system do recognise cancer cells but are not able to destroy them.

In such case, cancer cells can stimulate B cells to produce IgG antibodies that combine with antigens on the surface of the cancer cells.

These blocking antibodies may block the T cells so that they are unable to adhere to the surface of the cancer cells and destroy them. For some unknown reason, the blocking antibodies are not able to activate the complement system that would destroy the cancer cells.

Notes # 6. of Cancer:

Many agents including radiation, chemicals and viruses have been found to induce cancer in both experimental animals and humans. Agents which cause cancers are called car-

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gens. Radiation (Solar ultraviolet ray, X-ray) and chemical carcinogens act by damaging DNA and inducing somatic mutations.

These carcinogens are generally called initiating agent because the induction of mutations in key target genes is supposed to be the initial event leading to cancer development.

Some of the initiating agents that cause human cancers include solar ultraviolet radiation—the major cause of skin cancer. The exposure of the thyroid gland to X-rays greatly increases the incidence of thyroid cancers.

Varieties of chemical carcinogen including tobacco smoke (containing benzo(a)pyrene, dimethyl nitrosamine and nickel compound) and aflatoxin produced by some molds are the major identified cause of human cancer. Other carcinogens induce the cancer development by stimulating cell proliferation rather than inducing mutations. Such compounds are called tumour promoters.

The first suggestion that chemicals can cause cancer dates back to 1761, when a doctor noted that people who use

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suffer from nasal cancer. A few years later a British physician observed a high incidence of cancer of the scrotum among the chimney-sweepers in their youth.

He explained the fact that the chimney soot became dissolved in the natural oil of the scrotum, irritating the skin and, consequently, initiates the development of cancer. On the basis of two separate observations it became evident that certain chemicals (Table 23.1) can cause cancer.

Later, as the industrial revolution moved into twentieth century, more and more incidence of cancer were reported among the workers who were continuously exposed to industrial chemicals.

Table 23.1: Gene/Factors

(a) Initiating Stimuli	Function
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(b) Inducing Cellular susceptibility	
c-myc	produces myc protein which gives cell susceptibility for a
Rb-1	Deficiency of Rb-1 gives susceptibility. Rb protein may inhibit P 53 mediated apoptosis.
E2F1	induces susceptibility
P 53	apoptosis in response to cell injury is dependent on P 53.
(c) Modulating factors	

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DAD 1 gene	gives signal for cell death
BCI-2 gene family	Some members inhibit cell death, such as bcl-2, BCI-X. Members which promote death like bax, bid and bad.
(d) Effector mechanisms	
Caspases, ICE, Ich-1	Genes encoding cysteine proteases which are involved in the effector pathway of apoptosis.

In the early 1940s Peyton Rous observed that repeated application of coal tar to rabbit skin causes tumour to develop, but the tumour disappears when application of the coal tar is stopped. It is also noted that when the skin is treated with turpentine, tumour again reappears.

Normally turpentine does not cause cancer itself. Therefore the coal tar and turpentine are playing two different roles. Some carcinogens induce some normal cells to become irreversibly altered to a pre-neoplastic state.

This is known as initiation and the carcinogens are known as initiation agents. Here coal tar is an initiating agent. On the other hand, some carcinogens stimulate the pre-neoplastic cells to divide and form tumour. This is known as promotion and the carcinogens are termed promoting agents. Here turpentine behaves as promoting agents.

Berenblum observed that painting the skin of a mouse single time with methylcholanthrene rarely causes the

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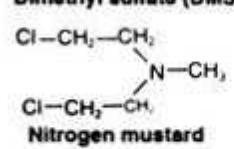
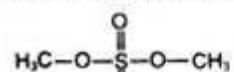
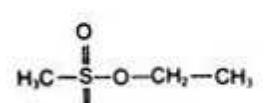
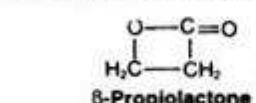
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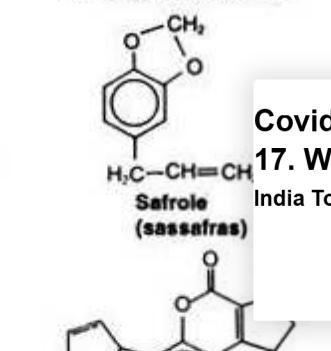
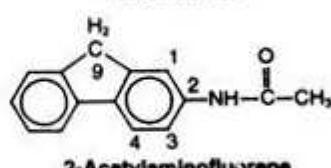
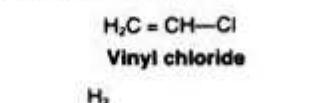
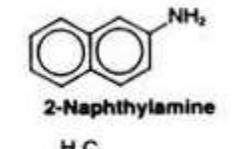
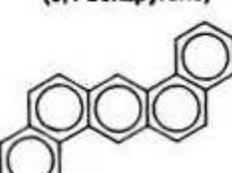
development of tumours. But subsequently application of castor oil (an oil derived from seeds of Croton tiglium) triggers the formation of multiple tumours on the skin which has been exposed previously to methylcholanthren is acting as an initiator whereas castor oil acts as a promoter.

Initiation is a quick, irreversible process that causes a permanent change in a cell's DNA. The carcinogenic chemicals that act as initiating agent are capable to bind with DNA. Hence they interfere with the normal function of DNA and induce somatic mutation and, consequently, bring about stable, inheritable changes in the cell's properties.

DIRECT-ACTING CARCINOGENS



INDIRECT-ACTING CARCINOGENS



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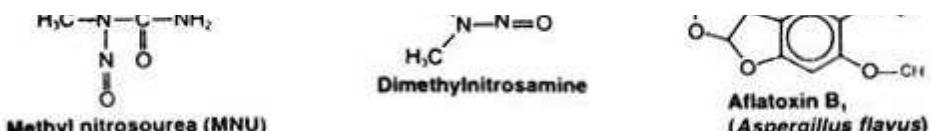
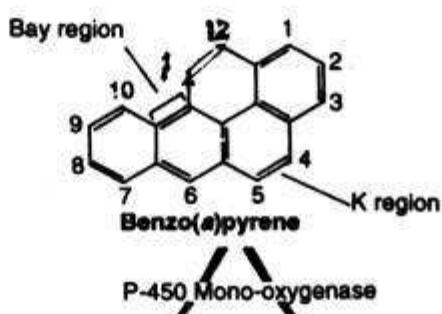


Fig. 23.2: Structure of some direct acting and indirect acting chemical carcinogens.

On the basis of action of chemical carcinogens on DNA, there are two broad categories of carcinogens—direct acting and indirect acting (Fig. 23.2). Direct acting carcinogens are highly electrophilic compounds that react with DNA.

Indirect acting carcinogens are converted to ultimate carcinogens by introduction of electrophilic centres. In other words, indirect acting carcinogens must be metabolised before they can react with DNA.

The steps of metabolic activation of benzo(a)pyrene—a polycyclic aromatic hydrocarbon—are shown in Fig. 23.3.:



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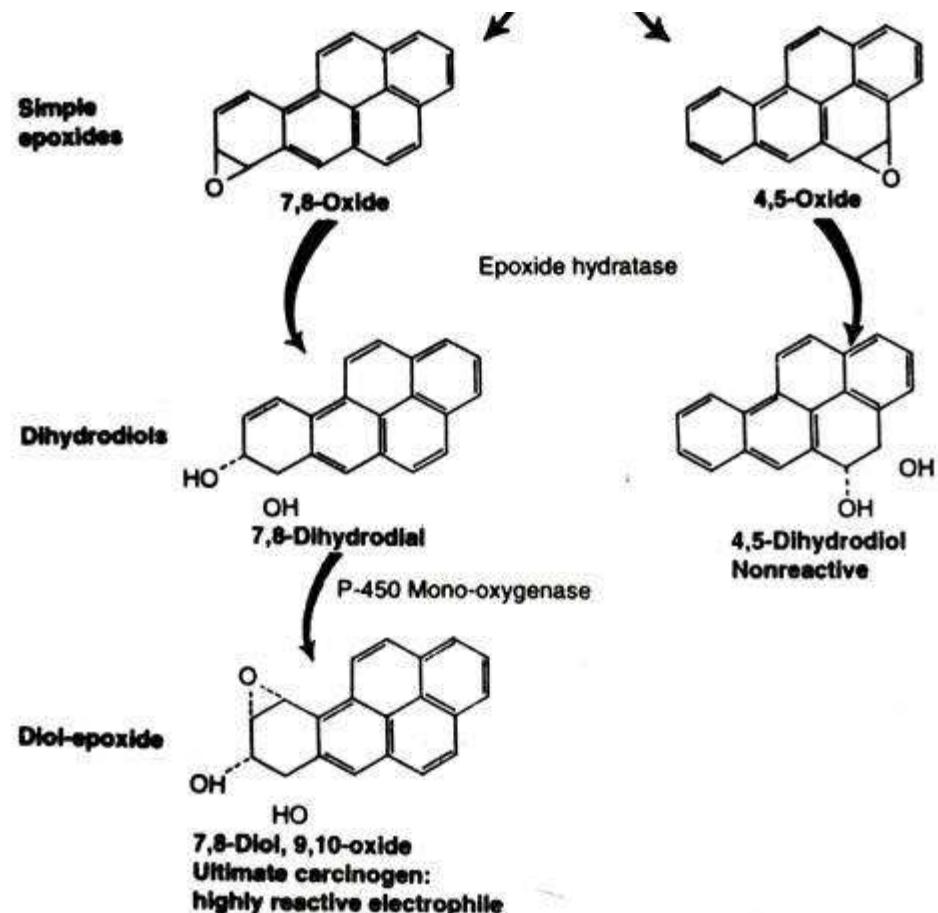


Fig. 23.3: Steps of metabolic activation of benzo(a)pyrene—a powerful carcinogen.

On the other hand, promotion is a gradual, partially reversible process that needs prolonged exposure to promoting agents. If a cell that has already undergone initiation is exposed to a promoting agent, the cell starts to divide and the number of genetically damaged cells go

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As the damaged cells continue to divide, a gradual selection for cells showing higher growth rate and invasive properties occurs—leading to the formation of malignant tumour. The promotion phase continues for longer period. That is why cancer does not develop just after exposure to a carcinogenic agent.

The mechanism of action of promoting agents have come from the studies of phorbol esters which are present in castor oil and act as tumour promoters. Phorbol esters bind to the plasma membrane and activate protein kinase C. Protein kinase C is a component of the phosphoinositide signalling pathway whose activity is normally controlled by the second messenger, diacylglycerol.

The activation of protein kinase C leads to phosphorylation of many target proteins and, consequently, activates the transcription factor AP1 which switches on the transcription of genes involved in stimulating cell proliferation. Therefore, the mode of action of phorbol esters gives an insight into the possible mechanism of action of a promoting agent.

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Energy that travel through space is known as radiation
Natural source of radiation to which humans are gene

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exposed are ultraviolet rays, cosmic rays and emission from radioactive elements. We are also exposed to another high-energy radiation like X-ray. Medical, industrial and military activities generally create the high-energy radiation.

Sunlight has the ability to cause skin cancer in people who spend long hours in the sunlight. Sunlight contains ultraviolet rays which are also absorbed by normal skin pigmentation. Hence, for this reason, dark-stained or black people usually have lower rates of skin cancer than fair-skinned individual.

Because ultraviolet radiation is very weak to pass through the skin, it does not induce any other type of cancer except skin cancer. It is more or less restricted superficially on skin because skin cancer rarely metastasizes.

This type of cancer can be cured by easily removing the affected site surgically. Xeroderma pigmentosum is a type of inherited malignant disease. Individuals with this malignant disease develop extensive skin tumours after exposure to sunlight. Homozygotes for the autosomal recessive mutation responsible for xeroderma pigmentosum are less efficient in the repair of DNA damaged by exposure to ultraviolet

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X-rays are high energy radiation. They are strong enough to penetrate the skin and reach internal organs. X-rays thus make a serious cancer hazard because they are able to induce gene mutation or DNA damage. Many radioactive elements emit radiation. It also acts as carcinogen and causes cancer.

Marie Curie, the co-discoverer of the radioactive elements polonium and radium, died of a form of leukemia that appeared to be caused by her extensive exposure to radioactivity. Another example of radiation-induced cancer occurred in New Jersey in 1920. A group of women was employed by a factory that produced watch which glow in the dark. The luminescent point used to point the watch dial contained radium.

The paint was applied with a fine-tipped brush that the employee frequently wetted with their tongue. During this process, minute quantities of radium were ingested through saliva in the digestive system from where they were readily absorbed and distributed in the different cells and tissues throughout the circulatory system.

Several years later these women suffered from bone ca

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caused by radioactive radium that had gradually become concentrated in their bone.

The most well-known horrifying examples of radiation-induced cancer occurred in Japan and in Nevada of United States. In 1945 atomic bombs were exploded over Hiroshima and Nagasaki. The massive fallout of radioactive elements increased the incidence of leukemia, lymphomas and cancers of the thyroid, breast, uterus and gastrointestinal tract.

Similarly, in Nevada, people suffered from cancer due to the radioactive fallout during nuclear bomb testing. It is suggested that radioactive carcinogen is thought to initiate malignant transformation by causing DNA damage.

Alternatively, it is also explained that subsequent exposure of radiation damaged cells to promoting agents stimulates the cell to divide abnormally and form tumour.

There are many viruses which are capable of causing tumour in animals, humans as well as plants (Table 23.2). These viruses are called tumour viruses or oncovirus. Some viruses have RNA genome and are known as DNA tumor viruses.

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Some tumour viruses have DNA genome and are known as retroviruses. Retrovirus replicates via synthesis of a DNA provirus in the infected cells. In addition, HIV is indirectly responsible for the cancer that develops in AIDS patient as a result of immunodeficiency.

Table 23.2: List of Chemical Carcinogens and Type of Cancer induced by such chemicals

Carcinogen	Type of cancer induced
Acrylonitrile	Colon, lung
4-Aminodiphenyl	Bladder
Aniline derivatives	Bladder
Arsenic compounds	Lung, skin
Asbestos	Lung, mesothelium
Benzene	Leukemia
Cadmium salts	Prostate, lung
Carbon tetrachloride	Liver
Chromium and chromates	Lung, nasal sinuses
Diethylstibestrol (DES)	Uterus, vagina
Lead	Kidney
Mustard gas	Lung, larynx
α -Naphthylamine	Bladder
Nickel	Lung, nose
Organochloride pesticides	Liver
Polychlorinated biphenyls	Liver
Radon	Lung
Soot and tars	Skin, lung, bladder
Vinyl chloride	Liver, lung, brain
Wood and leather dust	Nasal sinuses
Tobacco smoke, which contains the following:	Lung, oral cavity, larynx, esophagus, stomach, pancreas, others
Aminostilbene, arsenic, benz[a]anthracene,	

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benz[a]pyrene, benzene, benzo[b]fluoranthene,
benzo[c]phenanthrene, benzo[j]fluoranthene,
cadmium, chrysene, dibenz[a,c]anthracene,
dibeno[a,e]fluoranthene, dibenz[a,b]acridine,
dibenz[a,j]acridine, dibenzo[c,g]carbazone,
N-dibutylnitrosamine, 2,3-dimethylchrysene,
indeno[1,2,3-c,d]pyrene, S-methylchrysene,
S-methylfluoranthene, α-naphthylamine,
nickel compounds, N-nitrosodimethylamine,
N-nitrosomethylethlamine, polonium-210,
N-nitrosodiethylamine, N-nitrosonornicotine,
N-nitrosoanabasine, N-nitrosopiperidine

The herpes viruses are the most complex animal viruses. The genome length of these viruses is 100-200 Kb. Many herpes viruses cause tumour in many animals such as frogs, chickens, monkeys etc. Epstein-Barr virus, a member of herpes virus, can trigger the development of some human malignancies including Burkett's lymphoma in some region of Africa and nasopharyngeal carcinoma in China.

It also causes B-cell lymphomas in AIDS patient and other immunosuppressed persons. Cell transformation by herpes viruses is not fully understood because of the complexity of their genome. But it is evident that some viral genes are required to induce transformation of lymphocytes.

Of the DNA tumour viruses, the papoviruses are the best studied DNA tumour viruses from the standpoint of

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molecular biology and have received particular attention because they have been critically important as models for understanding the molecular basis of cell transformation.

The genome size of papoviruses is small (approximately 5 Kb). Simian virus 40 (SV₄₀) and polyomavirus are the important and commonly known member of papoviruses. Both these viruses are similar in size and general structure.

A virus usually multiplies in specific cells derived from animals in which the virus normally grows. Such cells are called permissive cells. Cells which do not allow the viruses to grow are called non-permissive cells.

SV₄₀ and polyoma viruses, on entering their respective host cells, undergo one of the two types of behaviour—they enter the permissive cell of the host, undergo the lytic phase, and multiply within host cell, ultimately killing them.

Since a permissive cell is killed as a consequence of virus replication, it cannot become transformed. Sometimes viruses enter non-permissive cells and are not able to multiply, i.e., virus replication is blocked. In this case, viral genome sometimes integrates into cellular DNA.

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expression of specific viral genes results in transformation of the infected cells.

The SV₄₀ and polyoma virus genes that trigger cell transformation have been identified, isolated and sequenced by molecular analysis. The genome of SV₄₀ and polyomavirus are divided into early and late regions. The early region is expressed immediately after infection and is needed for synthesis of viral DNA.

The late region is not expressed until after viral DNA replication has begun. The early region of SV₄₀ codes for two proteins which are known as small (17 Kd) and large (94 Kd) T-antigens. In addition to small and large regions, the genome of polyomavirus contains a third early region which is called as middle T region. It codes for a protein of about 55 Kd.

Experimentally, it has been shown that large T of SV₄₀ is sufficient to induce transformation and the middle T region of polyoma virus is primarily responsible for transformation. During lytic cycle, the early region proteins are needed to initiate viral DNA replication as well as to stimulate host gene expression and DNA synthesis.

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Since the replication viral DNA is dependent on host cell enzymes, therefore stimulation of gene expression of the host cell is a critical event in the viral life cycle. Most of the cells of adult animal cells become non-dividing. So the enzymes required for cell division are not available within the cell.

Therefore they must be stimulated to divide in order to induce the enzymes needed for viral DNA replication. This stimulation of cell division by the early gene products of virus can lead to transformation if the viral DNA becomes stably integrated and expressed in a non permissive cells. The early region proteins of SV₄₀ and polyoma virus induce transformation by interacting with host proteins that regulate cell division.

The papilloma viruses are small DNA viruses. The genome length of such viruses is approximately 8 Kd. Some of these viruses induce only benign tumours such as warts. But some others cause malignant carcinomas— particularly cervical and anogenital cancers. Cell transformation by papilloma viruses occurs from the expression of two early region E₆ and E₇.

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The hepatitis B viruses are another group of DNA virus. They have the smallest genomes which is approximately 3 Kb. These viruses mainly infect the liver cells and cause liver damage. But how they induce cell-transformation is not clearly known.

Possibly tumour results from expression of a viral gene. Alternatively, the chronic cell damage of liver simply induce the continuous cell division which, ultimately, causes the cell transformation.

The retroviruses, one family of RNA viruses, also cause human cancer. For example, human T-cell lymphotropic virus type-I (HTLV- I), a RNA virus, is the causative agent of T-cell leukemia. A related virus (HTLV-II) cause a rare form of leukemia called hairy T- cell leukemia.

HIV (Human immunodeficiency virus) is the causative agent of AIDS. These viruses, i.e., HTLV-I, HTLV-II, HIV, actually does not cause cancer by directly converting a normal cell into a tumour cell. The AIDS patients become susceptible to high incidence of some malignancies like lymphomas and Kaposi's sarcoma due to immunosuppression of the pa-

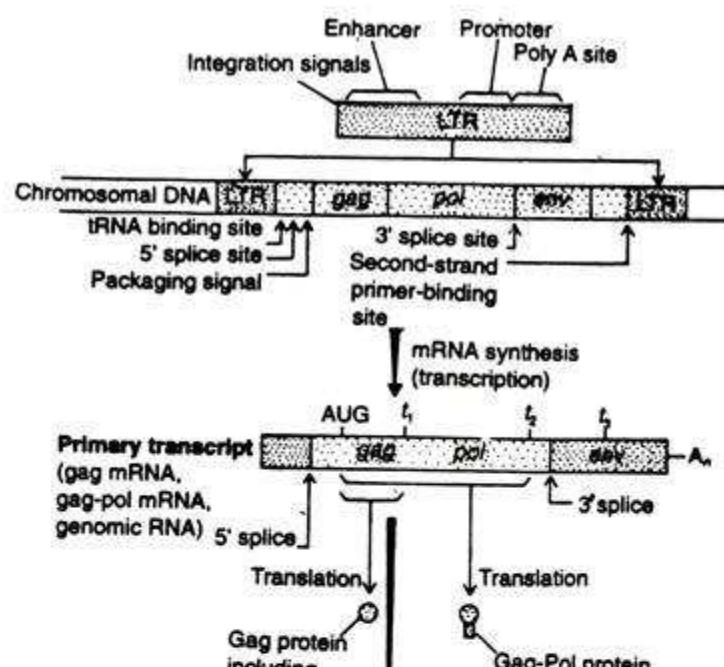
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RNA viruses have an RNA genome which is extended at either end by a long terminal repeat (LTR). The LTR contains many of the signals that allow retrovirus to function (Fig. 23.4). Retroviruses use their genomic RNA as a template to make DNA with the help of reverse transcriptase.

This DNA is then integrated into host's DNA as DNA the provirus. The DNA provirus is transcribed to yield genome length RNA provirus directed transcription involves a promoter—a sequence that directs the RNA polymerase to a specific initiation site and an enhancer—a sequence that facilitates transcription.



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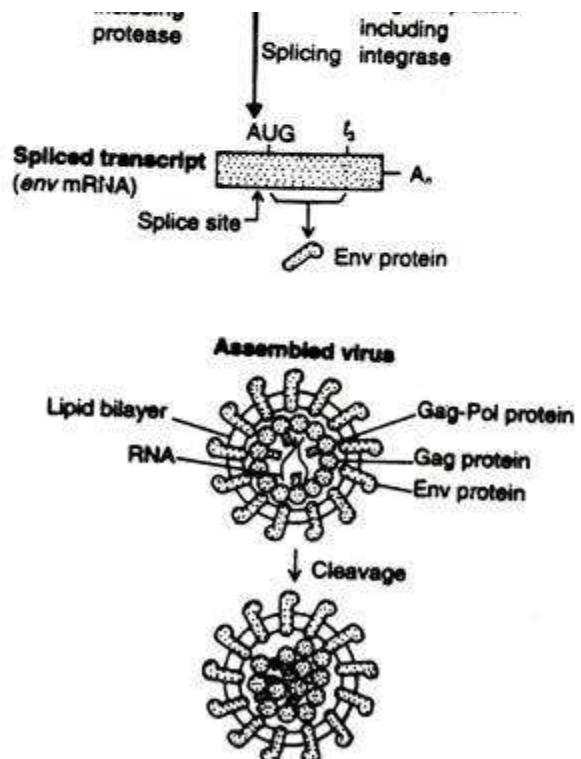


Fig. 23.4: Genetic elements of proviral DNA and the corresponding gene products.

The promoter and enhancer are located in the LTR. The primary transcript serves as the genomic RNA for progeny virus particles and as mRNA for the gag and pol genes. In addition the full length RNA is spliced to yield mRNA for env.

The gag gene encodes the viral protease and structural proteins of the virus particle, pol encodes reverse transcriptase and integrase and env encodes envelope

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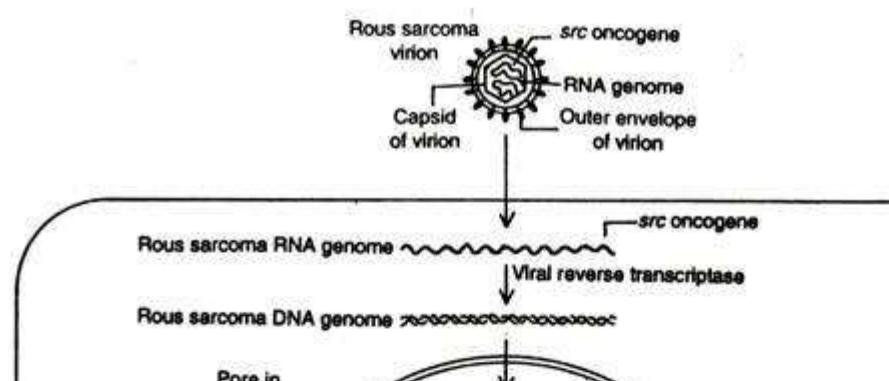
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proteins. These three genes are only required for viral replication but play no role in cell transformation.

This type of retrovirus causes tumour only when any mutation results at the time of integration of pro-viral DNA within or adjacent to host's genome. But there are some other retroviruses which contain specific genes which are responsible for the induction of cell transformation and acts as potent carcinogens.

The first cancer causing gene is found in the retrovirus called Rous Sarcoma virus (Fig. 23.5) that produces sarcomas in chicken. It was later named src gene. Genes like src which are capable of inducing malignant transformation, are referred to as oncogenes. The identification of the first viral oncogene has provided a model for understanding many aspects of cancer development at the molecular level.



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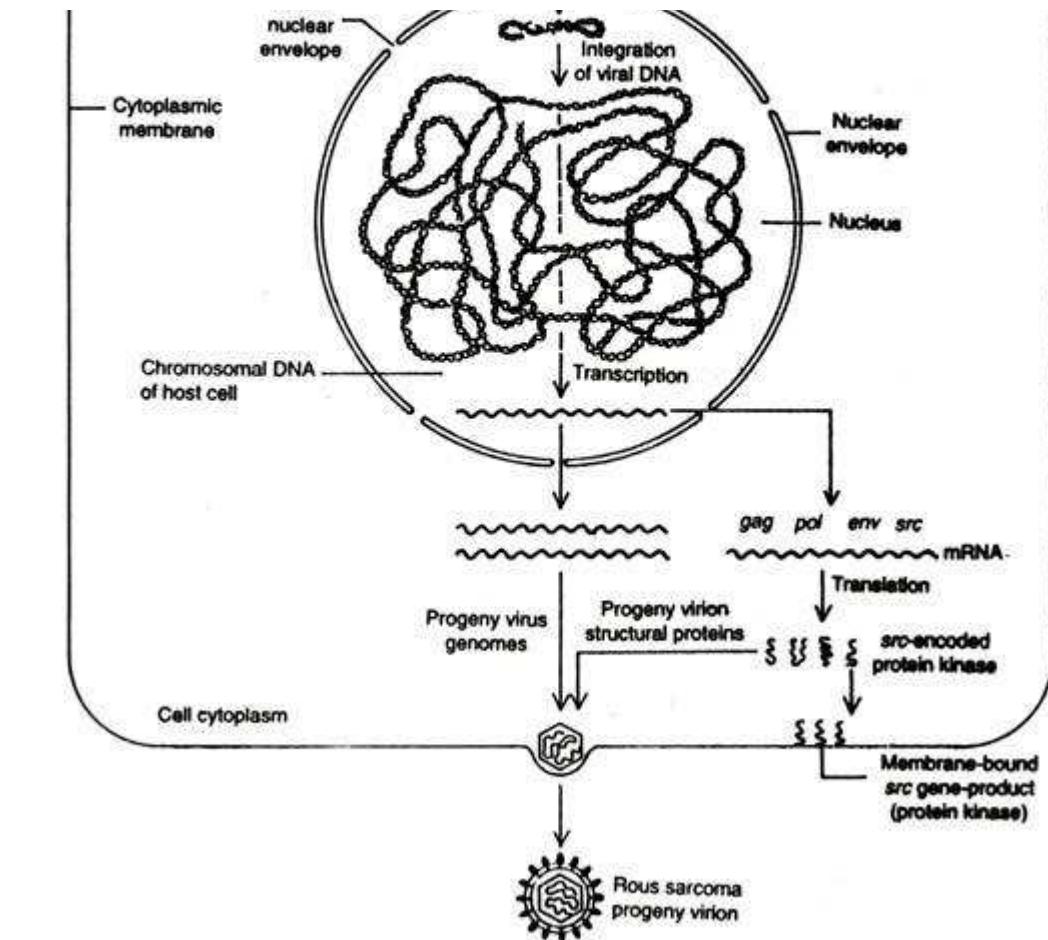


Fig. 23.5: Life cycle of Rous Sarcoma RNA tumour virus.

Notes # 7. Oncogenes:

Oncogene is a type of specific viral gene that is capable of inducing cancer or cell transformation—either in the host or in the tissue in culture. After the discovery of s

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oncogene in RSV, more than 40 different highly oncogenic retroviruses have been isolated (Table 23.3) from a variety of animals like mice, rat, cat, chickens, turkeys, monkeys etc.

All these viruses contain at least one (in some cases two) oncogene like RSV. These oncogene are not needed for viral replication but is responsible for cell transformation. In some cases different viruses contain the same oncogenes. Many of these genes encode protein which, in turn, acts as the key components of signalling pathways that induces cell transformation.

Table 23.3: Examples of Tumour Viruses

Class	Examples	Tumours induced	Organism
DNA viruses:			
Herpesviruses	Lucke virus Epstein-Barr virus (EBV)	Kidney adenocarcinoma Burkitt's lymphoma, nasopharyngeal carcinoma	Frogs Humans
Papovaviruses	Marek's disease virus Shope papilloma virus SV-40 Polyoma	Lymphoma Papillomas Subcutaneous, kidney and lung sarcomas Liver, kidney, lung, bone, blood vessels, nervous tissue, connective tissues	Chickens Rabbits Hamsters Mice
Hepatitis B virus	Human papillomaviruses	Cervical cancer Liver cancer	Humans Duck, Woodchucks, squirrels, bats
Adenoviruses	Human adenoviruses	Subcutaneous, intraperitoneal, intracranial	Hamsters
RNA viruses:			
B-type viruses	Bittner mammary tumor virus	Mammary carcinoma	Mice
C-type viruses	Rous sarcoma virus Murine leukemia viruses (Gross, Moloney, Friend, Rausher and others)	Sarcomas Leukemia	Birds, mice

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TRANSMISSION OF VIRUSES		
Feline leukemia virus	Leukemia	Cats
Murine sarcoma virus	Sarcoma	Mice
Feline sarcoma virus	Sarcoma	Cats
Avian leukemia viruses (avian myeloblastosis and others)	Leukemia	Chickens
Human T-cell leukemia virus	Leukemias/Lymphomas	Humans
Wound tumor virus	Roots and stems	Plants
Plant viruses		

Oncogene in Human Cancer:

Direct evidence for the involvement of cellular oncogenes (the term cellular oncogene is generally used to distinguish this group of cancer-causing genes from viral oncogenes) in human tumour was first derived from gene transfer experiment carried out in the laboratories of Robert Weinberg and Geoffrey Cooper in the early 1980s.

In this process, a DNA segment isolated from tumour cells are artificially introduced into normal cells to see its subsequent changes. DNA isolated from a human bladder carcinoma was found to efficiently induce malignant transformation of recipient mouse cells in culture. This experiment reveals that the human tumour contains a cellular oncogene.

The first human oncogene identified in gene transfer

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experiment was the ras oncogene. The ras oncogenes are not present in normal cells, but they are generated in tumour cells as a consequence of point mutation of the ras proto-oncogene. This results in the change of a single amino acid at critical position of the ras protein molecule encoded by ras gene.

The first such mutation was the substitution of valine for glycine at position 12. A single nucleotide, change which alters codon 12 from GGC (Gly) to GTC(Val) is responsible for the transforming activity. This is detected in bladder carcinoma DNA.

The ras gene encodes membrane-bound guanine-nucleotide binding proteins (G- protein) that plays a central role in the transmission of singles from receptor-bound external growth factor to the cell interior.

During this process, GTP is hydrolysed into GDP. Therefore, Ras protein alternates between active (GTP bound) and inactive (GDP bound) states. But oncogenic ras protein remain in the active GTP bound state and drive unregulated cell proliferation leading to the development of malignancy.

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In human tumour, point mutation is an important mechanism by which proto-oncogenes are converted into oncogenes. Besides this, the gene rearrangement—resulting mainly from chromosome translocation—sometimes lead to the conversion of proto-oncogene to oncogene.

The classical example regarding the conversion of proto-oncogene to oncogene due to translocation of chromosome is the Burkitt's lymphoma. It produces the malignancy of the antibody producing B-lymphocytes.

In this case a piece of chromosome(s) 8 carrying c-myc proto-oncogene is trans-located to the immunoglobulin heavy chain locus on chromosome 14 (Fig. 23.6). Since the antibody genes are extremely active in lymphocytes, the transcriptional regulation of the adjacent myc proto-oncogene is disturbed, resulting in an abnormal pattern of synthesis of the myc protein product.

Such abnormal pattern of expression of the c-myc gene—which encodes transcription factor normally induced response to growth factor stimulation—is sufficient to cell proliferation and contribute to tumour development.

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Normal chromosomes

Translocation

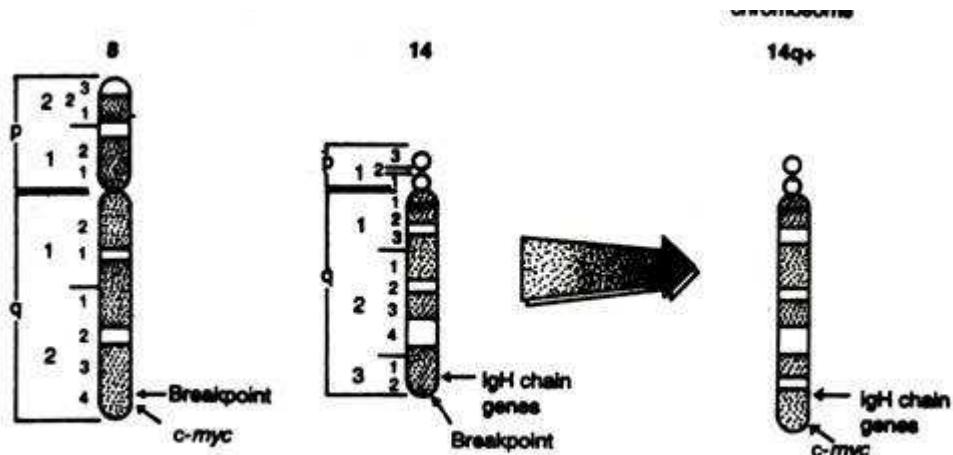


Fig. 23.6: Translocation of a *c-myc* protooncogene from chromosome 8 to 14.

Translocation of some proto-oncogene often causes the rearrangement of coding sequences which lead to the formation of abnormal gene products. In chronic myelogenous leukemia, the *abl* proto-oncogene is translocated from chromosome 9 to chromosome 22 forming Philadelphia chromosome (Fig. 23.7).

The *abl* proto-oncogene which contains two alternative first exon (1A and 1B) is joined to the middle to the *bcr* gene on chromosome 22. Exon 1B is deleted as a result of the translocation. Transcription of the fused gene initiates at the *bcr* promoter and continues through *abl*. Splicing then generates a fused *bcr/abl* mRNA, in which *abl* exon 1A

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sequences are also deleted and bcr sequences are joined to abl Exon 2.

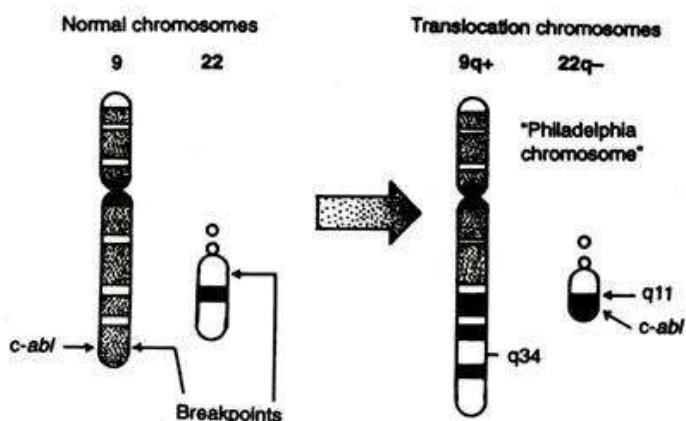


Fig. 23.7: Reciprocal translocation between chromosomes 9 and 22 that produce Philadelphia chromosome.

The bcr/abl mRNA is translated to yield a recombinant bcr/abl fusion protein in which the normal amino terminus of abl proto-oncogene has been replaced by bcr amino acid sequences. The fusion of bcr sequences results in aberrant activity and altered subcellular localisation of the abl protein tyrosine kinase, leading to cell transformation.

Gene amplification occurring in the tumour cell is a common process by which proto- oncogenes are converted to oncogene. Gene amplification takes place due to an increase in the number of copies of a gene resulting from the repeated replication of a region of DNA.

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Therefore, gene amplification leads to the overproduction of a particular protein or enzyme from the amplified gene. A prominent example of oncogene amplification is the involvement of the N-myc gene in neuroblastoma, a tumour of embryonal neuronal cells.

Amplified copies of N-myc gene are frequently present in rapidly growing tumour. Hence it indicates that N-myc amplification is related with the development of neuroblastomas. Amplification of erb B-2 which encodes a receptor protein kinase is similarly associated to the development of breast and ovarian carcinomas.

Table 23.4: Retroviral Oncogenes

Oncogene	Virus	Species
<i>abl</i>	Abelson leukemia	Mouse
<i>akt</i>	AKT8 virus	Mouse
<i>cbl</i>	Cas NS-1	Mouse
<i>crk</i>	CT10 sarcoma	Chicken
<i>erbA</i>	Avian erythroblastosis- ES4	Chicken
<i>erbB</i>	Avian erythroblastosis- ES4	Chicken
<i>ets</i>	Avian erythroblastosis- E26	Chicken
<i>fes</i>	Gardner-Arnstein feline sarcoma	Cat
<i>fgr</i>	Gardner-Rasheed feline sarcoma	Cat
<i>fms</i>	McDonough feline sarcome	Cat
<i>fos</i>	FBJ murine osteogenic	Mouse

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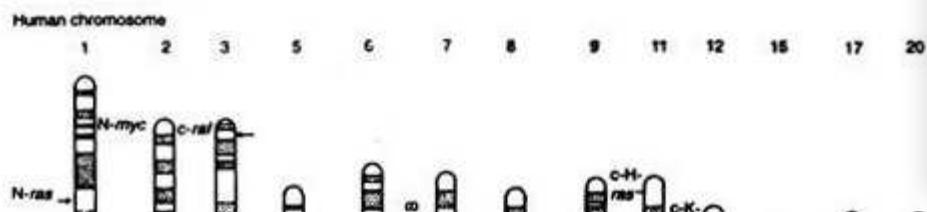
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	sarcome	
<i>fps</i>	Fujinami sarcome	Chicken
<i>jun</i>	Avian sarcoma-17	Chicken
<i>kit</i>	Hardy-Zuckerman feline sarcome	Cat
<i>maf</i>	Avian sarcoma-AS42	Chicken
<i>mos</i>	Moloney sarcoma	Mouse
<i>mpl</i>	Myeloproliferative leukemia	Mouse
<i>myb</i>	Avian myeloblastosis	Chicken
<i>myc</i>	Avian myelocytomatosis	Chicken
<i>qin</i>	Avian sarcoma 31	Chicken
<i>raf</i>	3611 murine sarcoma	Mouse
<i>rash</i>	Harvey sarcoma	Rat
<i>rasK</i>	Kirsten sarcoma	Rat
<i>rel</i>	Reticuloendotheliosis	Turkey
<i>ros</i>	UR2 sarcoma	Chicken
<i>sea</i>	Avian erythroblastosis-S13	Chicken
<i>sis</i>	Simian sarcoma	Monkey
<i>ski</i>	Avian SK	Chicken
<i>src</i>	Rous sarcoma	Chicken
<i>yes</i>	Y73 sarcome	Chicken

Subsequent studies have discovered a number of oncogenes (Table 23.4) which are associated with human tumour.

Among them chromosomal location of some oncogenes are shown in Fig. 23.8.



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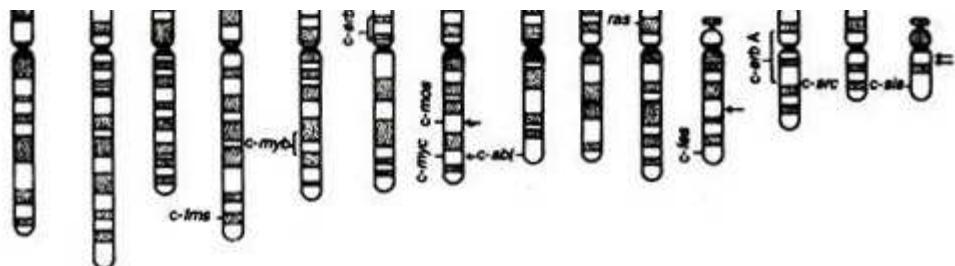


Fig. 23.8: Chromosomal location of some human protooncogenes.

Functions of Oncogene Products:

We have understood that alteration in normal genes, proto-oncogenes, can convert them into oncogenes that code for proteins that are abnormal in structure or are produced in inappropriate amounts. The proteins encoded by the normal genes regulate normal cell proliferation. But the protein encoded by the corresponding oncogene proteins drives the uncontrolled proliferation of the cancer cells.

In addition, some oncogene products involved in other aspects of the behaviour of cancer cells such as defective differentiation and failure to undergo programmed cell death. Besides this, majority of oncogene proteins function as elements of the signalling pathways that regulate cell proliferation in response to growth factor stimulation.

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These oncogene proteins include polypeptide growth factors, growth factor receptors, elements of intracellular signalling pathway and transcriptional factors (Table 23.5).

Table 23.5: Representative Oncogenes of Human Tumours

Oncogene	Type of cancer	Activation mechanism
<i>abl</i>	Chronic myelogenous leukemia, acute lymphocytic leukemia	Translocation
<i>bcl-2</i>	Follicular B-cell lymphoma	Translocation
<i>E2A/pbx1</i>	Acute lymphocytic leukemia	Translocation
<i>erb B-2</i>	Breast and ovarian carcinomas	Amplification
<i>gip</i>	Adrenal cortical and ovarian carcinomas	Point mutation
<i>gli</i>	Glioblastoma	Amplification
<i>gsp</i>	Pituitary and thyroid tumors	Point mutation
<i>hox-11</i>	Acute T-cell leukemia	Translocation
<i>lyl</i>	Acute T-cell leukemia	Translocation
<i>c-myc</i>	Burkitt's lymphoma	Translocation
<i>c-myc</i>	Breast and lung carcinomas	Amplification
<i>L-myc</i>	Lung carcinoma	Amplification
<i>N-myc</i>	Neuroblastoma, lung carcinoma	Amplification
<i>PML/RA/Rα</i>	Acute promyelocytic leukemia	Translocation
<i>PRAD1</i>	Parathyroid adenoma	Translocation
<i>PRAD1</i>	Breast carcinoma	Amplification
<i>rasH</i>	Thyroid carcinoma	Point mutation
<i>rasK</i>	Colon, lung, pancreatic, and thyroid carcinomas	Point mutation
<i>rasN</i>	Acute myelogenous and lymphocytic leukemias, thyroid carcinoma	Point mutation
<i>ret</i>	Thyroid carcinoma	DNA rearrangement

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If the oncogenes induce uncontrolled cell growth that leads to cancer then it is obvious that the products of these genes would act by stimulating all division in some manner.

For example, the product of the v-sis oncogene (the v stands for virus) of simian sarcoma virus is closely related to a polypeptide growth hormone called platelet-derived growth factor (PDGF). This factor produced by platelets promotes wound healing by stimulating growth of cells at wound site.

Simian sarcoma virus with v-sis gene in their genome when injected into the body of woolly monkey, induce sarcoma. They are also able to transform fibroblasts growing in culture to a tumorous state. This type of cellular transformation occurs by a mechanism which is possibly related to the effect of normal PDGF on cells at the wound site.

Other oncogenes encode products that are identical to growth hormone as well as hormone receptors. For example, oncogene erb B and fms encode proteins that are closely related to the receptors for epidermal growth factor (EGF) and colony stimulating factor-1 (CSF-1).

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CSF-1 is a growth factor that stimulates growth and differentiation of macrophages. The receptor of this growth factor is a trans membrane-protein with growth factor domains on the outside of the cell and protein kinase domains on the inside of the cell (Fig. 23.9).

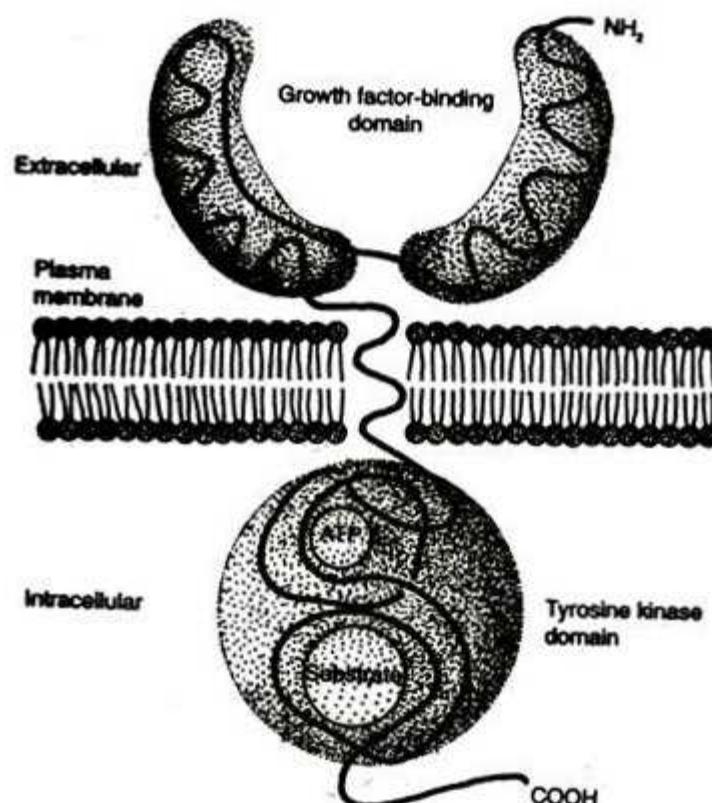


Fig. 23.9: Structure of transmembrane growth factor receptors.

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These receptors are key components in trans-membrane signalling pathways. The erb A gene product is an analog of the nuclear receptor for the thyroid hormone T₃. Therefore, all of the gene products are undoubtedly involved in intercellular communication circuit which control cell division during the growth and development of highly differentiated tissue.

Protein tyrosine kinase is a trans-membrane receptor that is capable of transmitting a perfect signal instructing a cell to divide. Alteration in the structure and function of this enzyme will transmit a wrong signal instructing the cell to divide when it normally should not divide—the result will be tumour formation.

Following the discovery that the src oncogene codes for a protein kinase, more than 20 other oncogenes have also been found to code for protein tyrosine kinases. These oncogene encoded tyrosine kinases can be subdivided into two main classes such as receptor protein tyrosine kinases and non-receptor protein tyrosine kinases.

Receptor protein tyrosine kinases are trans-membran proteins that contain a growth factor receptor domain

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are exposed on the outer surface of the plasma membrane and a tyrosine kinase catalytic domain at the inner surface of the plasma membrane.

In a normal receptor of this type, first appropriate growth such as PDGF, EGF, binds with receptors site and activates protein tyrosine kinase domain. Activation of protein tyrosine kinase stimulates cell proliferation through activation of the membrane associated G protein Ras (Fig. 23.10).

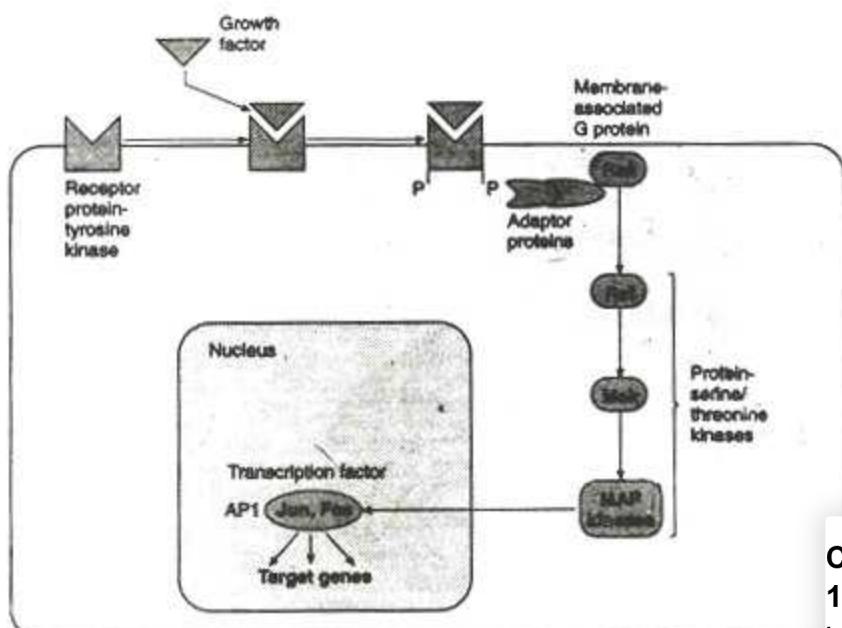


Fig. 23.10: Activation of protein tyrosine kinase that stimulates cell proliferation through activation of membrane associated G protein Ras.

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Activation of Ras triggers the phosphorylation of a series of cytoplasmic protein-serin/threonine kinase, thereby leading to phosphorylation of the nuclear API transcription factor which, in turn, activates genes involved in stimulating cell proliferation.

Oncogenes can code for abnormal receptor protein- tyrosine kinases in which the growth factor binding site is disrupted leading to unregulated activity of the protein tyrosine kinase site.

Non-receptor protein tyrosine kinase are usually bound to the membrane's cytoplasm or free in the cytosol. The non-receptor protein tyrosine kinase is encoded by the src gene. Oncogene-encoded non-receptor kinases often show excessive unregulated protein-tyrosine kinase activity.

Another group of oncogenes code for plasma membrane associated G proteins. In human cancer, ras oncogene shows almost resemblance with cellular ras gene of the host except that ras oncogene is the mutant form in contrast to cellular ras gene.

Hence mutant ras G proteins are produced. They retain

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bound GTP instead of hydrolyzing it to GDP. As a result mutant ras protein in its active form mislead the transmission of signal from external growth factors. Hence the host cells undergo abnormal cell division.

Most of the protein kinase activity showed by mammalian cells catalyses the phosphorylation of the amino acids serine and theonin, not tyrosine. These protein-serine/threonine kinase like protein-tyrosine kinase can be encoded by oncogene.

The most important oncogene belonging to this group is the raf oncogene. It codes for a protein serine/threonine kinase that transmits signals from plasma membrane Ras protein to the cell interior.

Some oncogenes code for proteins that function within the nucleus, particularly in the regulation of gene transcription. The examples of such oncogenes are the jun and fos oncogene which code for proteins that make up the AP₁ transcription factor.

The AP₁ factor regulates the expression of a group of genes that are involved in stimulating cell proliferation. The

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oncogene, associated with several kinds of human cancer, also appears to code for a transcription factor.

Notes # 8. Proto-Oncogene:

It is well-established that oncogenic virus contains a relatively small number of genes which has facilitated the identification of the viral genes that cause cell to become malignant. The first cancer-causing gene to be identified occurs in Rous sarcoma virus, a small retrovirus that produces sarcomas in chickens.

An unexpected feature of retroviral oncogene is their lack of involvement in virus replication while other viral gene involves efficiently in the same process.

Again, the existence of viral oncogene is not an integral part of the virus life cycle. Therefore, the origin and existence of viral oncogene leads to a new line of investigation. Such investigations have led to the surprising discovery that the src gene is not present only in cancer cells.

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Using nucleic acid hybridisation techniques, it has been shown that DNA sequence that is homologous to—

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identical with—the Rous src gene can be detected in the genome of normal cells of a wide variety of organisms including salmon, mice, cows, birds and humans.

The unexpected discovery that cells contain DNA sequences that are closely related to viral oncogenes has been substantiated by studies on a variety of other tumour viruses and, in each case, they resemble genes present in the genome of normal cell.

The term proto- oncogene has been introduced to refer to these normal cellular genes that closely resemble oncogenes. The resemblance of viral oncogenes to proto-oncogene suggests that viral oncogenes may have originally been derived from normal cellular genes.

According to this concept, the first step in the creation of retro-viral oncogenes took place million years ago when the ancient virus infected cells and became integrated in the host chromosomal DNA adjacent to normal cellular proto-oncogenes.

When the integrated pro-viral DNA was later transcribed to regenerate new viral RNA molecules, the adjacent pro-

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oncogene sequences might have been transcribed as well. In this way, a viral RNA molecule containing normal proto-oncogene sequences could have been created.

Since a proto-oncogene would initially serve no useful purpose for a virus, it would be free to mutate during subsequent cycles of viral infection. Such mutation would eventually convert proto-oncogene into an oncogene.

Therefore, the realisation that oncogenic viruses contain genes that cause cell to become malignant raise the question of whether genetic alteration are also involved in non-virus induced cancers. The ability of many carcinogens to act as mutagens provides the reason to believe that genetic changes play a role in non-viral carcinogenesis.

Besides this, recent research suggests that cellular oncogenes are derived from normal proto-oncogenes by at least five mechanisms:

(i) Point Mutation:

The simplest mechanism for converting a proto- oncogene into an oncogene, it involves a single base pair substitution or point mutation.

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(ii) Local DNA Rearrangement:

The second mechanism for creating oncogenes is based on DNA rearrangements that cause either deletions or base sequence exchanges between proto-oncogene and surrounding genes.

(iii) Insertional Mutagenesis:

The evidence of third mechanism comes from the findings that some cancer-causing retrovirus lack oncogenes and these particular viruses cause cancer by integrating a DNA copy of their genetic information into a host chromosome in a region where a proto-oncogene is located and thus disrupt the structure of the host proto-oncogene and thereby convert it into an oncogene.

(iv) Gene Amplification:

The fourth mechanism for creating oncogenes uses gene amplification to increase the number of copies of a particular protogene. This overproduction of copies of a particular proto- oncogene leads to malignant transformation.

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(v) Chromosomal Translocation:

The fifth mechanism for creating an oncogene involves chromosomal translocation. It is a process where a portion of one chromosome is physically broken and joined to another chromosome. As a result, the broken segment containing proto-oncogene is transferred from its normal location to a new location where it is converted as oncogene.

Notes # 9. Tumour Suppressor Genes:

We have now seen how the presence of an oncogene can stimulate uncontrolled cell growth and division, thereby fostering the development of malignancy. Cancer can also be induced by the loss of tumour suppressor genes that normally inhibit cell proliferation.

The term tumour suppressor gene implies that the normal function of gene of this type is to restrain cell growth and division. In other words, tumour suppressor genes act as brakes on the process of cell proliferation and inhibits tumour development.

In many tumours these genes are lost or inactivated, removing negative regulators of cell proliferation and contributing to the abnormal proliferation of tumour cells.

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Normally, the function of tumour suppressor gene is just opposite to oncogene.

The first evidence of the activity of tumour suppressor gene came from somatic cell function experiment done by Henry Harris et al in 1969. The fusion of tumour cells with normal cell yields hybrids that contain chromosomes from both parents.

Such hybrids are usually non-tumorigenic. Suppression of tumorigenicity by cell fusion indicates that genes derived from the normal cell definitely suppress the tumour development.

The first suppressor gene to be identified is involvement in hereditary retinoblastoma, a rare type of eye cancer that develops in children who have a family history of the disease. Such children inherit a chromosomal deletion in a specific region of one copy of chromosome 13.

Although the deletion occurs in all cells, only a few in retina actually become malignant because the initial deletion in chromosome 13 does not cause cancer by itself; for it to develop, a subsequent mutation must also occur in

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same region of the homologous chromosome 13.

It has, therefore, been concluded that chromosome 13 contains a gene on homologous chromosome of a normal diploid cell where such gene normally functions to inhibit retinoblastomas. In inherited retinoblastoma one defected copy of gene is genetically transmitted.

The loss of this single copy of gene is compensated by the identical second copy of the gene present on the same region of the second copy of chromosome 13.

Therefore loss of a single copy of gene is not by itself sufficient to trigger tumour development, but retinoblastoma almost always develops in these individuals as a result of a second somatic mutation leading to further loss of the function of the remaining second copy of normal gene.

The gene lost in hereditary retinoblastoma is called RBI. It is a tumour suppressor gene that codes for the nuclear protein p^{RB} that inhibits expression of a group of genes whose products are needed for uncontrolled cell proliferation in hereditary retinoblastoma a defective or copy of the R

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gene is inherited from the affected person.

Hence a lack of p^{RB} resulting from loss of both copies of RBI (one due to deletion and other due to a second somatic mutation) can lead to uncontrolled proliferation which ultimately causes the development of retinoblastoma. In nonhereditary cases, two normal RBI genes are inherited and retinoblastoma develops only if two somatic mutations in adult inactivate both copies of RBI in the same cell.

Table 23.6: Main classes of oncogenes categorised by nature of their Protein Products

Nature of Protein Product	Examples of Oncogenes	Comments
Growth factors	<i>it sis</i>	Platelet-derived growth factor (PDGF)
Protein-tyrosine kinases	<i>erb B</i>	Membrane receptor of epidermal growth factor (EGF)
	<i>fms</i>	Membrane receptor for colony-stimulating factor-1 (CSF-1)
	<i>src, yes, fgr</i>	Membrane nonreceptor protein tyrosine kinases
Membrane-associated G proteins	<i>ras</i>	Membrane-associated GTP-binding protein
	<i>gsp</i>	$G_i(\alpha$ sub-unit)
	<i>gip</i>	$G_s(\alpha$ sub-unit)
Protein-serine/threonine kinases	<i>raf, mos</i>	Cytoplasmic protein-serine/threonine kinases
Transcription factors	<i>jun, fos</i>	Components of AP1 transcription
	<i>erb A</i>	Thyroid hormone receptor

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Following the discovery of the RBI gene several other

tumour suppressor genes have been identified (Table 23.6).

The second suppressor gene is p⁵³ which is frequently inactivated in a wide variety of human cancer including leukemia's, lymphomas, sarcomas, breast tumour and carcinomas of many tissues including breast, colon and lung.

The p⁵³ protein is a nuclear transcriptional factor that switches on the activity of genes that arrest cells in the G₁ phase of the cell cycle. Normally, the production of the p⁵³ protein is stimulated when DNA is damaged due to exposure to ultraviolet ray or DNA damaging agents.

Hence p⁵³ appears to act like a molecular policeman that checks the cell for DNA damage and prevents the cell from proliferation if damage is detected. The loss of p⁵³ function allows the survival and reproduction of cells in which DNA damage has led to the production of oncogenes and/or the loss of other tumour suppressor genes.

In addition to mediating cell cycle arrest P⁵³ is required to induce apoptosis induced by DNA damage. Unrepaired DNA damage normally induces apoptosis that eliminates cells which might develop into cancer. Cells lacking p⁵³ fail to undergo apoptosis.

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This failure contributes to the resistance of many tumours to chemotherapy. The failure of function of p is thought to account for the high frequency of p⁵³ mutations that lead to inactivation of p⁵³.

Like p⁵³, the INK4 is a tumour suppressor gene that prevents lung cancer. Similarly, two other tumour suppressor genes such as APC and DCC prevent colon cancer. When these genes are deleted or mutated, such cancers develop.

The product of RBI and INK4 tumour suppressor genes regulate cell cycle progression at the same point. These genes inhibit passage through the restriction point in G₁ by suppressing transcription of a number of genes involved in cell cycle progression and DNA synthesis.

A rare hereditary form of colon cancer, familial adenomatous polyposis, is produced due to inherited mutation of the APC gene. In this type of cancer hundreds of polyps or benign colon adenomas are produced within the colon of an individual. Some of these polyps are transformed into malignancy.

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Inactivated or mutated form of some additional tumour suppressor genes is also associated with the development of breast, ovarian and pancreatic carcinomas as well as in some rare inherited cancer syndromes such as Wilm's tumour (a childhood kidney tumour).

The tumour suppressor gene of Wilm's tumour is WT1 which is frequently inactivated in Wilm's tumour. The product of WT1 gene appears to suppress transcription of a number of growth factor inducible genes.

Notes # 10. Prevention and Treatment of Cancer:

There is a general belief among the common people that cancer cannot be cured. Although this is partially true, it depends on several aspects of the patient and the time of detection. In many cases, when it is clinically detected then it is already late and it goes beyond the treatment.

Actually, cancer is a disease that ultimately has to be understood at the molecular and cellular level. In fact cancers can be cured if they are detected at the early stages of its development. In case of hereditary cancer, regular screening may allow early detection.

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Therefore, whether cancer is curable or not is a debatable question. With the help of modern and sophisticated technology, cell biologists are always trying to improve the methods for prevention and treatment of cancer.

The first step in preventing cancer is to identify the agents that cause cancer. For example, it is already known that tobacco smoke causes cancer. So just to prevent the possibility of this type of lung cancer, it is advisable simply to avoid tobacco smoke.

Similarly the discovery of carcinogenic properties of X-ray and sunlight suggests that individuals should avoid unnecessary medical X-ray and use protective lotions during long time exposure to sunlight.

Epidemiological data also allow potential carcinogens to be identified in exposed human population. The epidemiological approach is based on comparison of cancer rates among various groups of people exposed to different environmental conditions.

For example, when Japanese individuals move to the States their susceptibility to developing stomach and li

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cancer changes to reflect the rates for such cancers in the United States.

Therefore, the comparison of the frequency of stomach and lung cancer in Japan, in the United States and in Japanese immigrants to the United States suggests that environmental factors play a prominent role in causing cancer. Epidemiological data have played an important role in identifying some of the environmental factors that may cause cancer.

The Ames test is a rapid screening method for identifying potential carcinogens. This method is based on the rationale that most carcinogens act as mutagens; it measures the ability of potential carcinogens to induce mutations in a strain of bacteria that lack the ability to synthesize the amino acid histidine.

Each bacterial cell that has mutated to a form in which it no longer needs histidine will grow into a colony that can be counted. The number of colonies indicates the mutagenic potency of the substance to be tested.

Chemicals to be tested in the Ames test are first incubated with a liver homogenate because many of the chemicals

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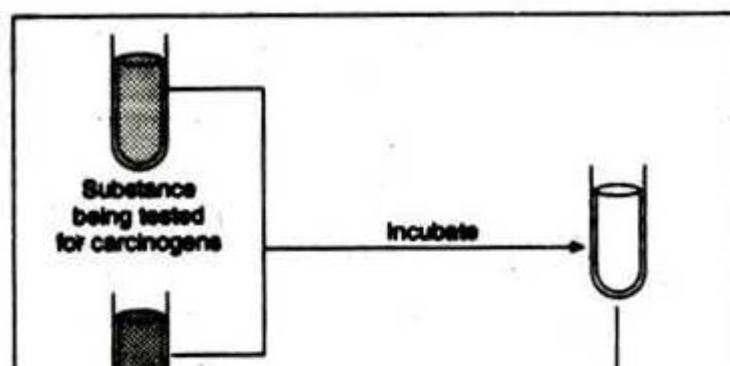
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which humans are exposed only become carcinogenic after they have undergone biochemical modification in the liver (Fig. 23.11) Cancer can be prevented in several other ways A person can modify his life style in order to reduce the risk of developing cancer.

Change of life style sometimes requires minimizing the exposure to carcinogens. Tobacco smoking and extensive meat consumption are the probable causative factors of cancer. If any person method of treatment is most effective when the cancer is detected at the early stage of development and when metastasis has not occurred.

This method is not effective when the cancer has already been disseminated throughout the body by the process of metastasis. Therefore, early detection of cancer is very important for its treatment.



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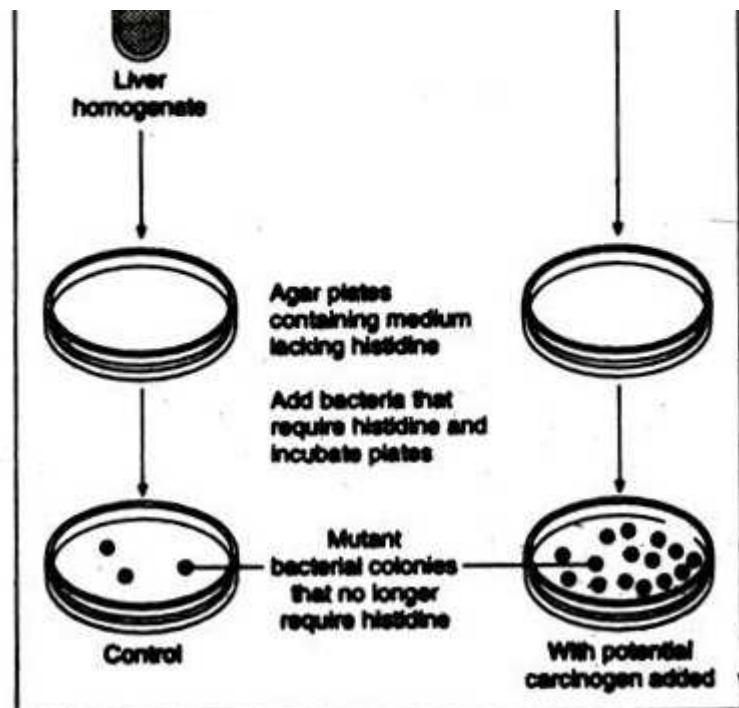


Fig. 23.11: Protocol of Ames Test.

Treatment of cancer-affected part of body with the help of X-radiation is another alternative method of curing cancer. X-ray is very effective for killing the cancer cells that are actively proliferating. The cells that are engaged in DNA synthesis prior to cell division, or are on the way of mitosis, are very sensitive to X-ray.

But the main problem of using X-ray for the treatment of cancer is that normal and healthy dividing cells of the body such as blood-forming cells in the bone marrow are also

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destroyed along with the cancer cells.

Moreover, X-radiation itself is carcinogenic. Hence there is always a chance of developing cancer after X-ray treatment. In spite of such risk posed by X-ray treatment, it is effective for the treatment of certain types of cancers like skin cancer, Hodgkin's disease and specific forms of testicular and bone cancer.

Chemotherapy is another approach for treating cancer. This method is based on the use of certain drugs that are designed to kill the proliferating cells as in radiation treatment. This method is also effective when the cancerous cells have already metastasized.

The drugs are generally injected in the body and the circulatory system helps the drug to spread throughout the body. Some drugs used in cancer chemotherapy are given in the Table 23.7.

Table 23.7: Tumour Suppressor Genes

Gene	Type of cancer
APC	Colon/rectum carcinoma
BRCA1	Breast and ovarian carcinomas
BRCA2	Breast carcinoma
DCC	Colon/rectum carcinoma

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<i>DPC4</i>	Pancreatic carcinoma
<i>INK4</i>	Melanoma, lung carcinoma, brain tumours, leukemias, lymphomas
<i>NF1</i>	Neurofibrosarcoma
<i>NF2</i>	Meningioma
<i>P53</i>	Brain tumours, breast, colon/rectum, esophageal, liver, and lung carcinomas; leukemias and lymphomas
<i>Rb</i>	Retinoblastoma, sarcomas; bladder, breast, and lung carcinomas
<i>VHL</i>	Renal cell carcinoma
<i>WT1</i>	Wilm's tumour

Like radiation, chemotherapeutic drugs also kill the normal and healthy cells along with cancer cells. This type of treatment has also some toxic side-effect-like loss of hair (caused by destruction of hair follicle cells), diarrhea (caused by destruction of cells of the intestinal lining) and susceptibility to infections (caused by destruction of blood cells).

Sometimes two or more combination of drugs are also used for the treatment of cancer.

Besides its side-effects and other disadvantages, it is true that, for certain types of cancer, chemotherapy is very successful for curing cancer like Burkitt's lymphoma, ovarian carcinoma, acute lymphocytic leukemia, Hodgkin's disease,

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lymphomas, mycosis fungoides, Wilm tumour, Ewing's sarcoma, thabdomyosarcoma, retinoblastoma, and embryonal testicular tumours etc.

Table 23.8: Some drugs used in Cancer Chemotherapy

Class	Examples	Mechanism of Action
1. Antimetabolites	Methotrexate 5-Fluorouracil 6-Mercaptopurine	Inhibit enzymatic pathways for biosynthesis of nucleic acids by substituting for normal substrates
2. Antibiotics (substances produced by microorganisms)	Actinomycin D Adriamycin Daunorubicin	Bind to DNA
3. Alkylating agents	Nitrogen mustard Chlorambucil Cyclophosphamide Imidazole carboximides	Crosslink DNA
4. Mitotic inhibitors	Vincristine Vinblastine Taxol	Interfere with mitotic spindle
5. Hormones	Estrogen (for prostate cancer) Cortisone Progesterone Androgens	Inhibit growth of hormone-sensitive cells by interacting with hormone receptors
6. Miscellaneous agents	L-Asparaginase	Hydrolyzes asparagine

Although the use of surgery, radiation and chemotherapy has led to increased survival rates for certain kinds of cancer, many malignancies do not respond well to such treatment. Recent experimentation is attempting to exploit the ability of the immune system to recognize and kill tumour cells. This type of treatment is known as immunotherapy.

The basic principle of immunotherapy is to exploit the ability of the immune system to recognise and kill tu

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cells. Tumour cells tend to show cell surface antigens which make them recognisable by the immune system. Initially, some scientists attempted to utilise a person's own lymphocytes to kill cancer cells.

For this experiment, lymphocytes were isolated from the blood of cancer patients and grown in culture in presence of Interlaken 2 to stimulate the cancers destroying properties of the cell. The result was the isolation of a population of killer T-cells that were specifically targeted against the patient's tumour.

These cells, called tumour-infiltrating lymphocytes (TILs), were injected back into the patients from whom the blood was drawn. TILs are more effective in inducing tumour regression. Recently TILs are made even more effective by using recombinant DNA technique to insert some genes whose product enhances the additional potency of the TILs.

A protein produced by macrophages called tumour necrosis factor (TNF) is effective in promoting the destruction of cancer cells if the TNF gene were inserted into the TILs.

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Obviously, the genetically engineered TILs would be n

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effective than normal TILs and would be more powerful to killing the tumour cells. Currently this technique is being tested in the hope of finding ways to promote immune destruction of cancer cells.

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Give special characters of flowers which are pollinated by wind.  Answers

Name a bat pollinated plant.  Answers

After a vigorous exercise or work we feel pain in muscles. What is the relationship between pain and respiration?  Answers

What is the significance of photosynthesis?  Answers

Which organelle is known as “power house” of the cell?  47 Answer

What is the importance of lichens?  Answers

What makes seeds sprout?  Answers

What is the function of ligase?  Answers

What is fragmentation?  Answers

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