CHAPTER 6

Cell Differentiation

☛ **Q.1. Give various theories of carcinogenesis.**

Ans. **Theories of Carcinogenesis**

Several theories have been put forward to explain why a cell becomes neoplastic producing cancer. Some of them are being discussed.

1. Virus Theory of Carcinogenesis : Murphey and Rous (1911) discovered the possibility of viruses being carcinogenic agents. Both DNA and RNA viruses are **oncogenic** *i.e.* cause cancer in man and other animals. e.g. viruses cause malignant tumours in fish, frogs, mice, rats, squirrels, dogs, deer and horses. The **Polyoma virus** causes tumour in mice and **Simian virus** 40 (SV 40) in monkeys. **Avian Sarcoma virus** (ASV) causes sarcoma in birds while **Avian Leukosis virus** causes leukemia in birds. In man **Epstein Barr viruse (EB virus)** is related with **Burkitt's lymphoma,** and **nasepharyngeal carcinoma; Herpes simplex type 2** with cervical cancer. Viruses associated with tumour are known as **oncoviruses.**

Mechanism of carcinogenesis : On entering the host cell, the viral DNA gets inserted into the DNA of host chromosomes at specific region and becomes an integral part of host DNA. The incorporation of viral DNA gives two main changes in the host cell : (i) lack of control of cell division and cell motility and (ii) changes in cell contact. With these changes a normal cell is transformed into a cancerous cell losing its balance over the rate of multiplication and other functions.

The incorporated viral DNA can act in two following ways :

(i) the viral DNA might contain a gene/genes whose products might transform the normal cells to malignant cells. or (ii) Viral DNA might influence host cell DNA directly, causing mutations.

The viruses that cause cancer are called **oncogenic viruses** and the genes of an oncogenic virus which are responsible for these transformation are known oncogenes. In the absence of oncogenes a virus is unstable to transform the normal cell into cancer cell. In case of sarcoma viruses, transformation of cells is effected by a single oncogene. Its continued expression is necessary for the transformation and also the maintenance of transformed state of the host cells.

A virus usually multiplies in specific cells of a specific host. Such cells are called **permissive cells** and the cells in which such virus fails to grow and multiply, are called **nonpermissive cells.**

2. Faulty DNA Repair Mechanism : DNA repair mechanism is very important for the body cells because it corrects mutations introduced by

replication error and these mutations are found to be carcinogenic. e.g. persons suffering from **xeroderma pigmentosum** (XP) develop malignant changes in the skin on exposure to ultraviolet light from sun. This disease is caused because of disorder of DNA repair mechanism. Similarly, other genetic disorders in man like Fanconi's anemia and Bloom's syndrome which are caused by the deficient repair systems are found to be carcinogenic.

3. Mutation Theory of Carcinogenesis : Jacobson (1958) has suggested that mutations may cause genetic disorders in a normal somatic cell that may destroy its machinery that controls synthesis of hormones and enzymes necessary for repressing cell division in the normal cells. The mutations may involve either (i) by mutations in the genes that gives repressor proteins and thus unblock inactive genes making them functional. or (ii) mutations in the repressed genes themselves.

A number of chemical mutagens have been observed to cause cancer. Some of the **carcinogenic substances** are polycyclic hydrocarbons occurring in tars, certain dyestuffs and azo dyes, mustard gas, b-napthylamine, aminophenol and plastic films of various materials. Even radiations from various radioactive substances also produce chromosomal breaks and reunion and lead to cancerous growth in normal cells.

4. Metabolic Theory of Carcinogenesis : According to **Warburg** (1956), the normal cells become cancerous when their cellular respiratory mechanism is injured through carcinogenic agents. Once the aerobic respiratory mechanism is damaged, the cells depend on anaerobic metabolism i.e. glycolysis. The energy liberated during glycolysis is far less than in the aerobic respiration and is not capable of maintaining structural integrity and organization of the cells and cells become cancerous. **Oppenheimer** has demonstrated that cancerous growth developed in the skin. If the oxygen supply to skin cells was cut off by embedding plastic films in the skin.

Again experiments in this direction, however, suggest that actually the cancer growth disturbs the respiratory mechanism. Because the tumour cells synthesize protoplasm so actively that they exhaust the energy reserves soon.

5. Irritation Theory : According to some scientists, the cancer may also be produced in cells which are irritated continuously. e.g, chewing betel and betelnuts cause irritation and cancer of tongue and throat. The chemical irritation by tobacco is said to cause lip cancer.

Though a number of theories have been put forward to explain possible mechanism of **carcinogenesis.** e.g., none of them can be considered as the exclusive factor and the problem of cancer is still an unsolved riddle for cell physiologists.

6. Hormonal Distrubance : In aged persons, the hormonal balance is disturbed and this causes cancer. **Mammary cancers** are very common in some strains of mice, cancer of mammary glands and uterus are common. In mice, removal of ovaries reduced incidence of mammary cancers, It means that improper amount of ovarian hormone produces mammary cancer.

7. Defective Immunity Hypothesis : Each body has its immunity or defence mechanism by which it combats the foreign materials and foreign agents. Possibly in a normal individual the defective or cancerous cells are destroyed in some way by immunological action. While the defence mechanism fails under special conditions the cells become cancerous. It may be because of insufficient number of lymphocytes.

☛ **Q.2. Write down the characteristics of cancer cells.**

Ans. Characteristics of Cancer Cells

A. Structural Characteristics

Study of cancer cells under electron microscope reveals many fine structural variations or abnormalities of cellular organelles, but some can be specifically linked with malignancy. The structural variations can be as under:

1. Ergastroplasm and ribosomes : The ergastoplasm and ribosomes are more abundant in cancer cells. Formation of polysomes by the union of various ribosomes is more frequent. This is associated with the rapid growth of cancer cells.

2. Nucleus : The molecules of cancer cells are usually enlarged and irregularly distributed chromatin. The **interchromatin** and **perichromatin granules,** that are formed of RNA and proteins are more abundant in the nucleus of cancer cells. Sometimes, their nucleus contains some **nuclear bodies** of 0.2-2m diameter that contains concentric fibrillar, granular or lamellar structures. The nuclear membrane is pushed into deep infoldings or blebs containing cytoplasmic material. The nucleus of cancer cells may contain proteins, glycogen, lipids or viruses.

3. Pathological cytoplasmic inclusions : The cytoplasm of cancer cells from different regions is found to contain different types of inclusions. e.g. colloidal substance is found in the cytoplasm of thyroid cancer cells, mucus in cancer, milk in mammary tumor, melanin pigment in melanomas, and secretion granules in intestinal carcinoids.

4. Golgi complex : Golgi complex of common cells is poorly developed but in cancer cells of exocrine glands (pancreas etc.) it is developed considerably.

5. Plasma membrane : The plasma membrane of cancer cells usually remains unchanged, except the intercellular connections that may become more numerous in keratinizing epitheliomas whereas tight junctions become less numerous.

6. Mitochondria : Mitochondria of cancer cells are often swollen and lack various structural details. Their cristae may be few, parallel, irregular or concentric.

7. Disorganized cytoskeleton : The normal cells have a cytoskeletion of **microtubules** and **microfilaments** arranged in some regular fashion and help in coordinated cell movement.

B. Functional Characteristics

1. Reduced cellular adhesion : Normal cells show **stickiness** or **adhesiveness** and there is specificity in adhesion because cells of one type stick to the cells of same type. e.g. liver cells stick to liver cells and kidney cells to other kidney cells. When isolated cells of pancreas and liver are incubated together, the liver cells aggregate to form small piece of liver tissue and pancreatic cells form pancreatic tissue.

2. Loss of contact inhibition : It two or more normal cells in a culture come in contact with their plasma membrane, they stop moving and also stop growing and dividing. This ceassation of movement, growth, DNA synthesis and cell division after cell contact is known as **contact inhibition.** The normal cells in a culture arrange themselves in a monolayer on the wall of glass vessel and stop dividing after that.

On the contrary, a malignant cell, when it is confronted by either a malignant cell or a normal cell, does not get obstructed and even does not stop dividing. Since a result, cultures of malignant cells form clumps rather than monolayers and are capable of proliferating to many times the cell density. Loss of contact enables cancer cells to dissociated from neighbauring cells and infiltrate other organs.

3. Immoratalization : Normal cells in culture do not multiply indefinitely e.g. human cells in culture die after about 50 generations. But the transformed or neoplastic cells can multiply indefinitely. Cell cultures infected with *mouse sarcoma virus* can be kept as long as the nutrients are available and there is no overcrowding.

4. Lower serum requirements : In a tissue culture medium, the cancer cells require much less concentration of serum for their growth than the normal cells. For example, normal fibroblasts of mouse in tissue culture medium require 10% foetal calf serum while the same cells transformed by SV 40 can grow in 1-10% serum concentration.

5. Loss of anchorage : Normal cells grow and divide in medium when attached to some rigid substratum, but the cancer cells can grow and multiply even in suspended condition. Such character helps in isolating cancer cells from normal cells.

6. Invasiveness : Because of loss of contact and decreased adhesiveness, cancer cells are able to dissociate themselves from neighbouring cells and can invade other tissues and organs. The invasion is brought about by changes in the plasma membrane.

7. Increased sugar transport : Cancer cells consume more glucose then normal cells because these grow and multiply faster than the normal cells. Therefore, there is an increased sugar transport across the cell surface.

8. Molecular changes in cell membrane components : The structural details of plasma membrane remain same in normal and neoplastic cell but :

(i) the surface glycoproteins like MW 46,000 etc. disappear from the surface of neoplastic cell membranes.

(ii) in cancer cells glycolipid-gangliosides, on the surface of cell membrane, are less concentrated and are only of one type GM3, whereas in normal cells the gangliosides are of different types-GM1, GM2, GM3 and GM4.

9. Increased rate of glycolysis : In cancer cells, the rate of aerobic respiration is low, consequently the anaerobic respiration or glycolysis is more rapid. It is evidenced by an increased concentration of lactic acid in tumour cells and a corresponding increase in glucose uptake.

10. Increased secretion of proteolytic enzyme : Cancer cells secrete large amounts of proteolytic enzymes except those of blood forming tissues. The inactive enzyme **protease** or **cell-factors,** secreted through the cancer cells act on inert serum protein, **plasminogen,** and forms a **plasmin.** Plasmin removes many extrinsic proteins from cell surface and signals the cell to divide.

11. Defective electric communication : Normal cells have specific electric connections. In cancer cells these connections are observed to be defective.

12. Increased negative charge on cell membrane : In neoplastic cells there is an increase in the negative surface charge. It is demonstrated by an increased anodic mobility of cells.

13. Increased rate of glycolysis—Warburg (1920) suggested that aerobic respiration (Kreb's cycle) is depressed in tumour cells and glycolysis is considerably increased. Which causes increased deposition of lactic acid and increase in the uptake of glucose. This may be because of injury to the aerobic respiratory system.

14. Selective agglutination by lectins : Lectins are proteins that can bind to the receptors which are branched chain sugar molecules on the surface of cell membranes. By binding, lectins cause clumping of cells known **agglutination.**

In normal cells the lectin binding sites are few, diffused and immobile. So the intercellular bridges formed through lectins are few and agglutination fails to occur. In cancerous cells these sites are mobile within the membrane causing concentration of binding sites in one region. It results in agglutination.

☛ **Q.3. Write a short note on radiations.**

Ans.

Radiations

Radiations of various types. *i.e.,* X-rays, α, β and γ-rays and UV lights all induce tumours in man and animals. While passing through the tissues, these release energy which alters various macrcomolecules of the cell including nucleic acids. It causes increased rate of mutations in the irradiated cells.

The degree of effect on a tissue depends on total radiation dose, physical characteristics of radiation and on features of affected tissues. The short exposure to high concentration of radiation or repeated doses of low radiations are carcinogenic.

Q.4. What to you mean by chemical carcinogens ?

Ans. **Percivall Pott** (1775) and **Volkmann** (1874) reported occupationally related chemical carcinogens. As then thousands of chemicals are found to be carcinogenic. **Polycyclic hydrocarbons,** like 1 : 2, 5 : 6, dibenzenthracene, 3 : 4 benzypyrene gives cancer at the site of local application.

Aromatic amines like 2-naphthylamine and benzidine cause cancer of urinary bladder. **A20-days** cause liver cancer and **amino fluorenes** cause cancer of liver and urinary bladder. **Alkylating** agents like **mustard gas, methylnitrosourea** and **nitrosamine** and different inorganic compounds like **asbetos fibres, beryllium, nickel, arsenic,** and **chromates** are all carcinogenic.

The mechanism of chemical carcinogenesis has not been understood. All carcinogens appear to induce irreversible changes in the target cells. Most of the organic carcinogens either react with DNA or are metabolized within the cells which cause mutations.

Hence carcinogens induce cancer :

(i) by depression of **forbidden gene transcriptions** for enzymes that stimulate cell division.

(ii) by repression for normal gene activities, and

(iii) by the accumulation of mutation defects brought about by carcinogens.

Q.5. Give the characteristics of malignant tumours.

Ans. **1. Invasiveness and Spread :** Cancers or malignant tumours are uncapsulated and invasive. These enhibit excessive growth and infiltration into adjacent tissues. Though, the slowly expanding malignant tumours may be enclosed in a fibrous membrane, they extend into the adjacent normal tissue along a broad front.

2. Rate of Growth : The rate of cell production in cancerous tissue exceeds the rate of cell death. It leads to tumour formation. These outgrow their blood supply and the rapidly increasing number of cells compress the small blood vessels. This is known as **ischaemic necrosis.**

3. Differentiation : The malignant tumours are usually poorly differentiated. Their cells may exhibit different degree of resemblance to the tissue cells from which these have originated. The partial loss of differentiation is known as **dysplasia** and complete loss, so that the tumour no longer resembles the tissue of its origin is called **anaplasia.** The less differentiated the tumour is, the more difficult it is to identify its tissue of origin.

4. Metastasis : Invasiveness of cancers permits their cells to penetrate into blood vessels, lymphatics and body cavities, providing them opportunity for spread to locations remote from the site of origin and gives **secondary tumours** of **metastases.** With few exceptions all cancers can metastasize.

☛ **Q.6. What are causes of carcinogenesis ?**

Ans. Causes of Carcinogenesis

The process of conversion of a normal cell to malignancy is called carcinogenesis and the agents which cause this are known as **carcinogens.**

Carcinogenesis is a complete process involving interaction of many factors, some of which favour tumour development and others which appear to provide some protection against it. **Carcinogenic factors** can be classified into two categories :

1. Exogenous influences are exerted by the complex environment in which we live, such as radiations, pollutants etc. and,

2. Genetically determined factors which in total determine an individual's susceptibility to develop a particular cancer on exposure to carcinogens.

There is great variation in the intensity and length of exposure to individual carcinogens necessary to cause tumour development. A **subthreshold** dose of a carcinogen will not produce a tumour but subthreshold doses of two separate carcinogens given together may initiate tumour. This is known as **syncarcinogenesis.** Combination of certain substances which by themselves are not carcinogenic in combination with a subthreshold dose of a carcinogen do cause tumour development. This phenomenon is known as **cocarcinogenesis** and such a substance as **cocarcinogen** or **promoter.** For example, the application of **croton oil** which itself is not carcinogenic, along with subthreshold dose of **methyl-cholanthrene** on the skin of mouse induces tumour development.

☛ **Q.7. Give the classification of tumours.**

Ans. The tumours are classified as **benign** and **malignant** discussed as follows :

1. Malignant tumours : The malignant tumours are cancerous. Their cells are poorly differentiated as high rate of mitosis, nuclear polymorphism and abnormal mitosis. They penetrate into blood vessels, lymphatics and body cavities and may be carried to remote areas of the body. The cells might have pseudopodia-like processes which help them to penetrate new areas of the body and induce **secondary tumours** also known as **metastasis.**

2. Benign tumours : Tumours that remain localized in a specific area at the site of origin, forming a single mass enclosed in a capsule, are known as **benign tumours.** Usually, these are not fatal. But sometimes they press the vital centres and prove to be fatal. The benign tumours are normally slow growing, differentiated and their cells exhibit infrequent mitosis, little cytological changes and no chromosomal abnormalities.

☛ **Q.8. What different types of cancer ?**

Ans. **Types of Cancer**

About two hundred different types of cancers have been studied. These are broadly classified into following groups :

1. Sarcoma : Sarcoma are tumours of connective tissue, cartilage, bone and muscles which are of mesodermal origin. These constitute about 2 percent of human cancers. Sarcomas are named according to the tissue in which these are formed :

(i) rhabdomyosarcoma : Sarcoma of striped muscles.

(ii) leiomyosarcoma : Sarcoma of smooth muscles.

(iii) osteosarcoma : Cancer of bone.

(iv) chondrosarcoma : Cancer of cartilage cells.

(v) liposarcoma : Cancer of adipose tissue

(vi) fibrosarcomas : Sarcomas of fibrous connective tissue.

2. Leukaemias : These include the neoplastic proliferation of leukocyte precursors in the bone marrow and are described as **myeloproliferative disorders.** These lead to increase in the number of leukocytes that infiltrate into different other tissues and organs, producing general enlargement of organs or formation of tumours. Leukaemias constitutes about four percent of human cancers and can be :

(i) Myeloblastic leukaemia,
(ii) Lymphoblastic leukaemia,
(iii) Promyelocytic leukaemia,
(iv) Erythraemic myelosis,
(v) Megakaryocytic leukaemia,
(vi) Monocytic leukaemia

3. Carcinoma : Carcinoma includes tumours of brain, breast, skin and cervical region. These are derived from epithelial tissue, originating either from ectoderm or endoderm which occur as solid tumours, located in the nervous tissue on body surfaces or in the associated glands.

Carcinoma are the commonest cancer. About 85 percent of cancers are carcinomas. Carcinomas may be :

(i) adeno carcinoma : The tumours of glands, and

(ii) squamous carcinoma : The cancers of epithelial tissue.

4. Lymphomas : In lymphomas, the lymph nodes, bone-marrow, liver and spleen produce excessive lymphocytes. These constitute about 5 percent of human cancers. **Hodgkins' disease** and **mycosis fungoides** are examples of lymphoma.

5. Glomangioma : These lesions arise from the glomus bodies, the arterio-venous anastomoses.

6. Gliomas : Tumours of glial cells in the central nervous system.

7. Melanomas : These are tumours of pigment cells. ●

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