CANCER

Cancer is a class of diseases characterized by out-of-control cell growth. Development of cancer starts by the continual unregulted proliferation of cells, subsequently invading normal tissues and organs and eventually spreading throughout the body. The loss of growth control by cancer cells is a result of accumulation of abnormalities in the cell regulatory mechanisms. In almost all cases of cancer these losses occur due to genetic damage.

Carcinogenesis/Oncogenesis/Tumorigenesis: It is the process by which normal cells are transformed into cancer cells. It is characterized by a progression of changes at the cellular, genetic and epigenetic level that ultimately reprogram a cell to undergo uncontrolled cell division, thus forming a malignant mass.

Types of cancer

Cancer can result from abnormal proliferation of any of the different kinds of cell in the body, so there can be more than 100 types of cancers which can vary in their behavior and response to treatment. The most important issue in cancer pathology is the distinction between benign and malignant tumors. A tumor may be defined as any abnormal proliferation of cells, which may be benign or malignant. A benign tumor, such as a common skin wart remains confined to its original location, neither invading normal tissues nor spreading to distant body sites. A malignant tumor, however, is capable of both invading, surrounding normal tissue and spreading throughout the body via the circulatory or lymphatic system (metastasis). Only malignant tumors are referred to as cancers, and it is their ability to invade and metastasize that makes them so dangerous.

Both benign and malignant tumors are classified according to the type of cells from which they arise:

Type of cancer	**Originating cell type**
Carcinomas	Epithelial cells
Sarcomas	Connective tissue (muscle, bone, cartilage)
Leukaemia and Lymphomas	Blood forming cells and cells of the immune system respectively

Causes of cancer/ Carcinogen

A carcinogen is any substance or agent that is directly involved in causing cancer or increases the risk factor involved in carcinogenesis. This may be due to their ability to damage the genome or to disrupt cellular metabolic processes. Carcinogens increase the risk of cancer by altering cellular metabolism or damaging DNA and induces the uncontrolled, malignant division, ultimately leading to the formation of tumors. The most common carcinogens include radiations (gamma radiations, alpha particles), cigarette smoke, alcohol, arsenic, dioxins. Not only the synthetic compounds / xenobiotics are carcinogens, but the natural agents like Aflatoxin B1 produced by *Aspergillus flavus*, certain viruses such as hepatitis B and human papilloma virus have been found to cause cancer in humans.

Mutation in two broad classes of genes have been implicated in the onset of cancer: proto-oncogenes and tumor suppressor genes. Proto-oncogenes are activated to become oncogenes by mutations that cause the gene to be excessively active in growth promotion. Either increased gene expression or production of a hyperactive product will do it. Tumor suppressor genes normally restrain growth, so damage to them allows inappropriate growth. Many of the genes in both classes encode proteins that help to regulate cell birth (i.e., entry into and progression through the cell cycle) or cell death by apoptosis; others encode proteins that participate in repairing damaged DNA.

Oncogenes

Cancer results from alterations in critical regulatory genes that control cell proliferation, differentiation, and survival. Mutations in two broad classes of genes: proto-oncogenes (e.g., ras) and tumor-suppressor genes (e.g., Anaphase Promoting Complex; APC)—play key roles in cancer induction.

Proto-oncogene

Proto-oncogene is a normal gene regulating cell growth and differentiation. Proto-oncogenes are involved in signal transduction and execution of mitogenic signals, usually through their protein products. Six types of proteins encoded by proto-oncogenes participate in control of cell growth - Growth Factors, Receptors for Growth Factors and Hormones, Intracellular Signal Transducers, Cell-Cycle Control Proteins, Proteins that affect apoptosis and Nuclear Transcription Factors

Transformation of proto-oncogenes to oncogenes

A proto-oncogene converts to an oncogene due to mutation. Conversion, or activation, of a proto-oncogene into an oncogene generally involves a gain-of function by mutation. Thus increases gene expression and enhancing activity of proteins.

Following mechanisms can produce oncogenes from the corresponding proto-oncogenes:

1. Point mutation (i.e., change in a single base pair) in a proto-oncogene that results in a constitutively active protein product.

2. Chromosomal translocation that fuses two genes together to produce a hybrid gene encoding a chimeric protein whose activity, unlike that of the parent proteins, often is constitutive (continuous expression of a gene).

3. Chromosomal translocation that brings a growth regulatory gene under the control of a different promoter that causes inappropriate expression of the gene.

4. Amplification (i.e., abnormal DNA replication) of a DNA segment including a proto-oncogene, so that numerous copies exist, leading to overproduction of the encoded protein.

An oncogene formed by either of the first two mechanisms encodes an "oncoprotein" that differs from the normal protein encoded by the corresponding proto-oncogene. In contrast, the other two mechanisms generate oncogenes whose protein products are identical with the normal proteins; their oncogenic effect is due to production at higher than normal levels or production in cells where they normally are not produced.

Retroviral Oncogenes

Oncogene found in retrovirus Rous sarcoma virus (RSV) causes sarcoma and is therefore called src. The v-src gene of the virus was required for cancer induction. This gene produces a protein kinase that phosphorylates tyrosine residues in other proteins.

Tumor Suppressor genes

Tumor-suppressor genes generally encode proteins that in one way or another inhibit cell proliferation. Five broad classes of proteins are generally recognized as being encoded by tumor-suppressor genes:

1. Intracellular proteins that regulate or inhibit progression through a specific stage of the cell cycle (e.g., p16 and Rb).

2. Receptors or signal transducers for secreted hormones or developmental signals that inhibit cell proliferation (e.g., TGF-β, the hedgehog receptor patched).

3. Checkpoint-control proteins that arrest the cell cycle if DNA is damaged or chromosomes are abnormal (e.g., p53).

4. Proteins that promote apoptosis.

5. Enzymes that participate in DNA repair.

Examples of tumor suppressor genes

i) Rb (Retinoblastoma) - Rb protein binds to the regulatory transcription factor E2F. The factor E2F is required for synthesis of replication enzymes. Upon binding of Rb to E2F, no transcription/ replication can take place. Rb restricts the cell's ability to replicate DNA by preventing its progression from the G1 to S phase. Rb is phosphorylated to pRb by certain Cyclin Dependent Kinases (CDKs). The phosphorylated/ mutated form of Rb (pRb) is unable to complex E2F and therefore, unable to restrict progression from the G1 phase to S phase. When E2F is free it activates factors like cyclins (e.g. Cyclin E and A), which push the cell through the cell cycle by activating cyclin-dependent kinases, this lead to cell division and progression of cancer.

ii) p53 - Protein p53 has many mechanisms of anticancer function. p53 acts as a transcription factor for gene p21. It activates p21 which in turn binds to CDK I (cyclin dependent kinase 1). When p21is complexed with CDK1 the cell cannot continue to the next stage of cell division. A mutant p53 cannot activate p21 protein, thus results in no binding of p21 with CDK1 and as a consequence, no "stop signal" will be available for cell division. This leads to uncontrolled cell proliferation and cancer. More than 50% cases of cancer involve mutation of p53 gene.