Cancer

Class of diseases of uncontrolled cell growth

Invading normal tissues and organs and eventually spreading throughout the body

Leads to abnormalities in the cell regulatory mechanisms and genetic damage

Carcinogenesis/Oncogenesis/Tumorigenesis:

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Process by which normal cells are transformed into cancer cells

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Changes at the cellular, genetic and epigenetic level

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uncontrolled cell division

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malignant mass.

Types of cancer - More than 100 types of cancers.

Occasionally some cell deviate from normal genetic programme, start to divide abnormally and give rise to tissue masses called tumors or neoplasm (new growth)

Benign tumors - remains confined to its original location, neither invading normal tissues nor spreading to distant body sites. e.g. - common skin wart

Malignant tumors – 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.

Cells from malignant tumor can break off and move through blood or lymphatic system, forming new tumor in other location.

Spreading of malignant tumor throughout body is called metastasis.

Cancer is 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:

1. Exposure to carcinogen: Carcinogen is an agent causing cancer by damaging genome or disrupting cellular metabolic processes. Examples: Radiations (gamma radiations, alpha particles), cigarette smoke, alcohol, arsenic, dioxins. Aflatoxin B1, hepatitis B virus, human papilloma virus.

2. Some virus specially retrovirus

3. Descendants of cancerous cells

4. Certain chromosomal aberrations

5. Sometimes cancer is familial or hereditary.

Four main classes of genes are altered frequently in cancer:

1. Protooncogenes - Protooncogenes required for regulation of normal cell division. Mutant proto-oncogenes called oncogenes – either more active than normal or active at inappropriate time. Causing the gene to be excessively active in growth promotion - either by increased gene expression or production of a hyperactive product.

2. Tumor suppressor genes - Tumor suppressor genes normally restrain growth, so mutaion to them allows inappropriate growth.

3. microRNA (miRNA) gene - Overexpressed miRNA genes act as oncogenes.

4. Mutator gene - Mutator gene makes cell prone to accumulate mutational errors in any gene- leads to cancer.

Cancer results from alterations in critical regulatory genes that control cell proliferation, differentiation, and survival; mutations in proto-oncogenes and tumor-suppressor genes.

Proto-oncogene

Proto-oncogene is any normal gene regulating cell growth and differentiation. They 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
- Nuclear Transcription Factors

Transformation of proto-oncogenes to oncogenes

Transformation results gain-of function. 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.

In first two process, oncogenes encodes “oncoprotein” that differs from normal protein encoded by the corresponding proto-oncogene.

In last two process oncogenes products are identical with normal proteins; but production at higher levels or production in cells where they normally not produced.

Example of oncogene – *v-src* gene of Rous Sarcoma Virus

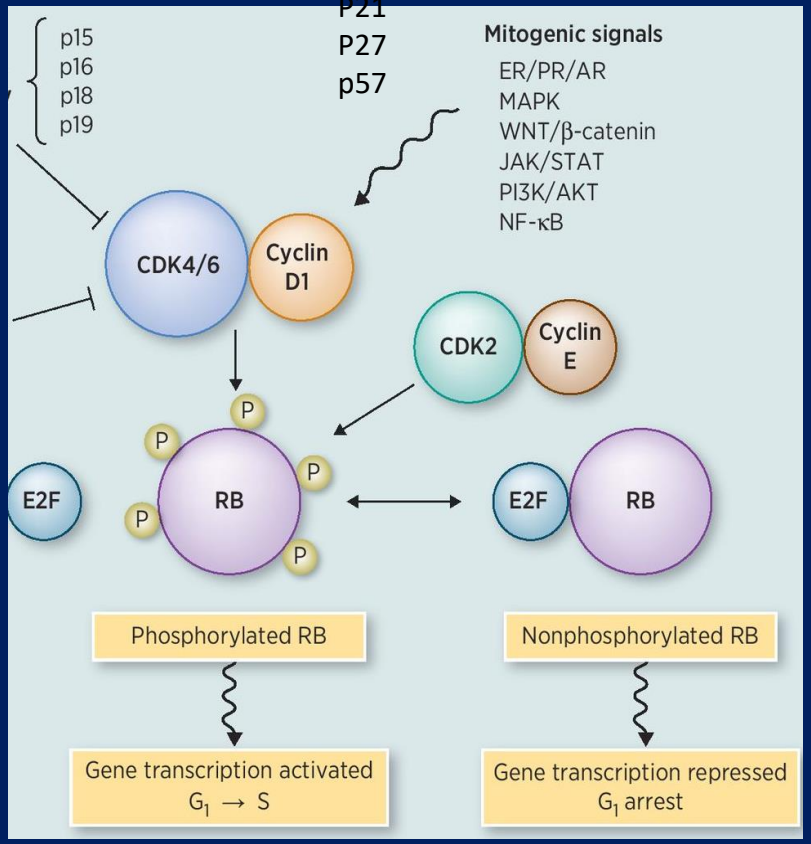
Tumor Suppressor genes

Tumor-suppressor genes generally encode proteins that 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 - Rb (Retinoblastoma), Protein p53

Rb (Retinoblastoma) – as tumor supressor gene



P53 - as tumor supressor gene