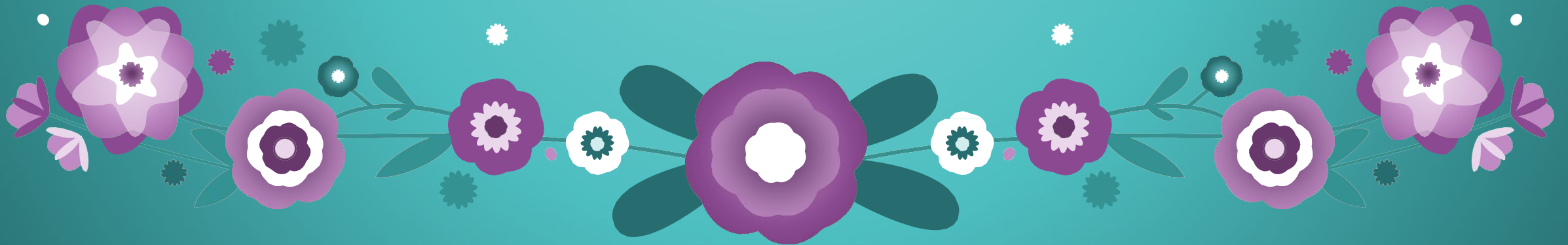


NEOPLASIA

Molecular Basis of Cancer

LEC.5

Dr. Raghad Hanoon



Fundamental principles of carcinogenesis:

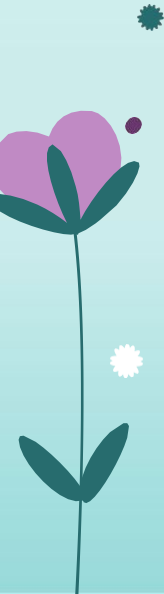
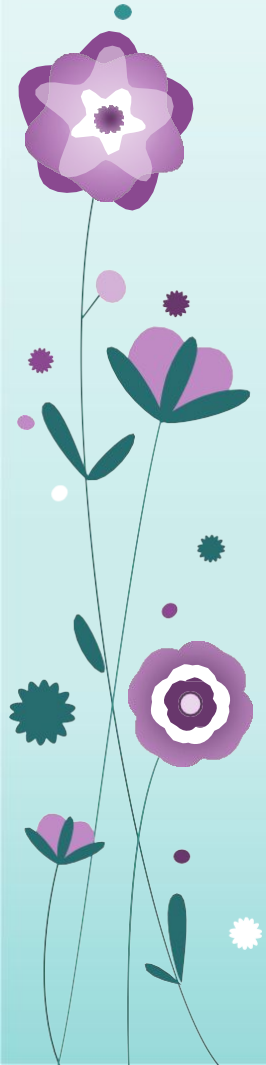
- **Nonlethal genetic damage** lies at the heart of carcinogenesis
- Such genetic damage (or mutation) may be **acquired** by the action of environmental agents, such as chemicals, radiation, or viruses, or it may be **inherited** in the germ line.
- Tumors are monoclonal: A tumor is formed by the clonal expansion of a single precursor cell that has acquired genetic damage (founding cell).

***Four classes of genes are the principal targets of genetic damage:**

- I. Growth promoting **protooncogenes** (dominant genes, can transform cells into malignant cells with single allele is damaged).*
 - II. Growth inhibiting **cancer suppressor genes** (recessive genes, can transform cells into malignant cells only if both alleles of gene are damaged).*
 - III. **Genes that regulate the apoptosis.***
 - IV. **DNA repair gene**, disability of DNA repair genes can predispose to widespread mutation & neoplastic transformation.*
- 

Eight fundamental changes in cell physiology are considered the hallmarks of cancer.

1. Self-sufficiency in growth signals
2. Insensitivity to growth-inhibitory signals
3. Evasion of apoptosis
4. Defects in DNA repair
5. Limitless replicative potential (immortality)
6. Sustained angiogenesis
7. Invasion and metastasis
8. Evasion of immune surveillance

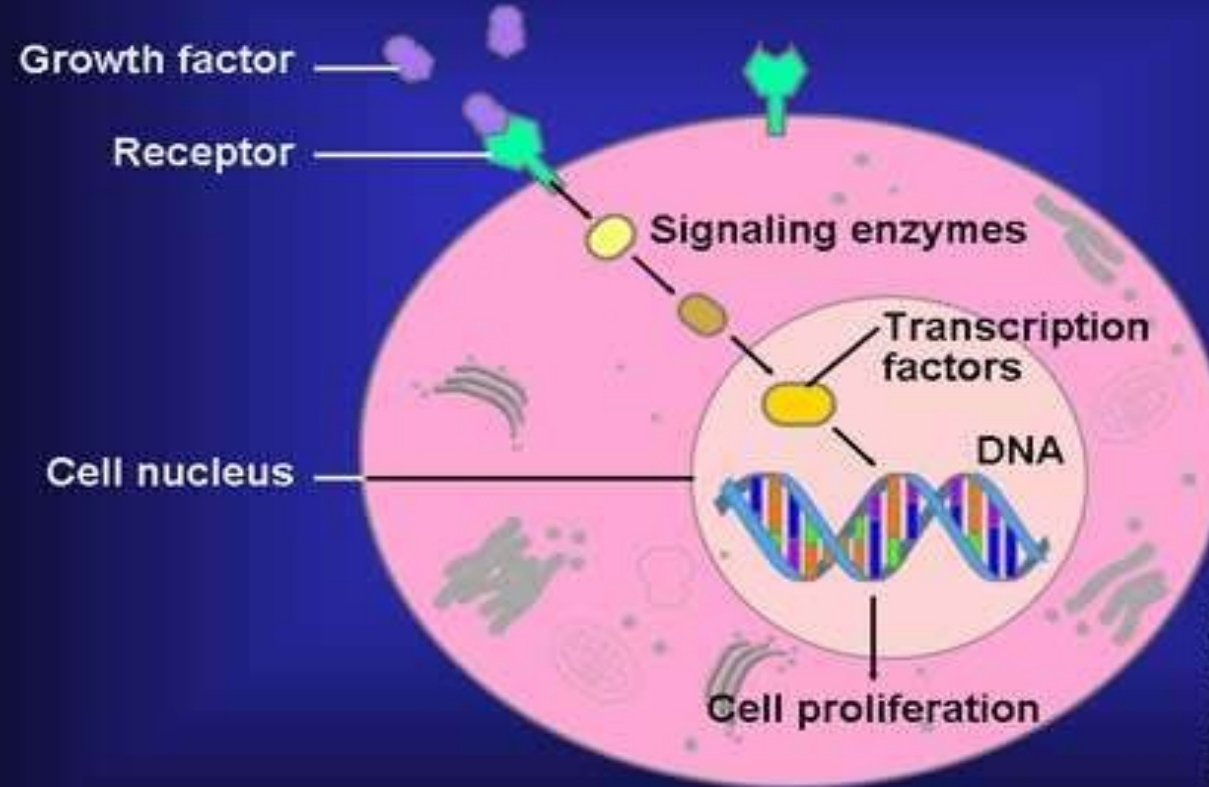


1. Self-sufficiency in growth signals

- In a normal cell, Proto-oncogenes have multiple roles, participating in cellular functions related to growth and proliferation.
- Self sufficiency for growth to a cancerous cell is provided by *oncogenes*, which are the mutant proto-oncogenes.
- Oncogenes encode proteins called *oncoproteins* that promote cell growth, even in the absence of normal growth-promoting signals.

Proto-Oncogenes and Normal Cell Growth

Normal Growth-Control Pathway



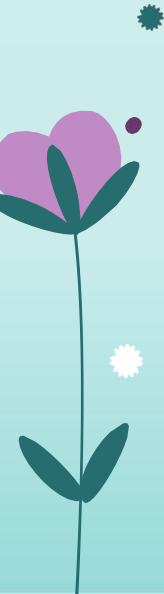
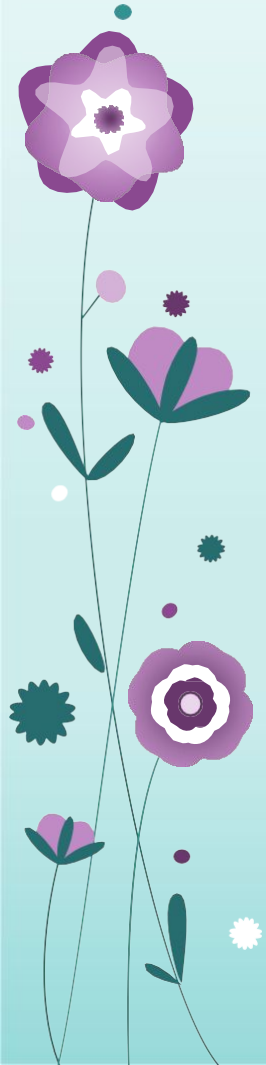
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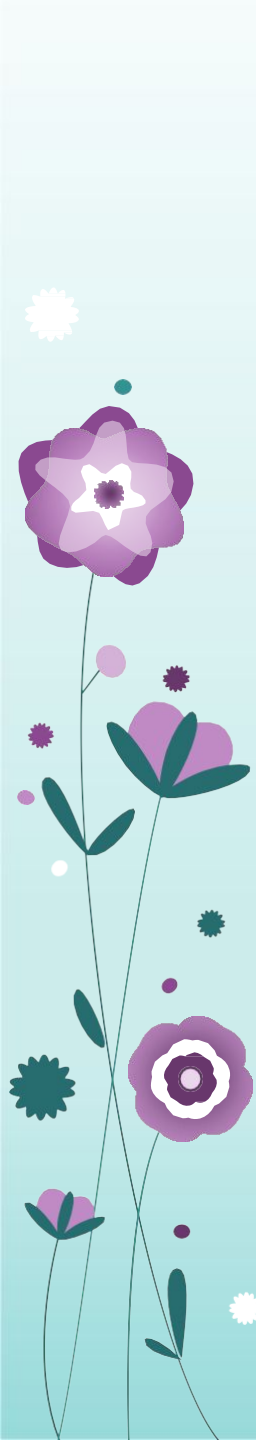
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Mechanisms of action of Oncoproteins:

A. Growth Factors

- **Normally** cell require stimulation by GFs to undergo proliferation.
- **Cancer cells** acquire the ability to synthesize their own GFs.
- Examples: - Glioblastomas secrete PDGF
- Sarcomas secrete TGF- α



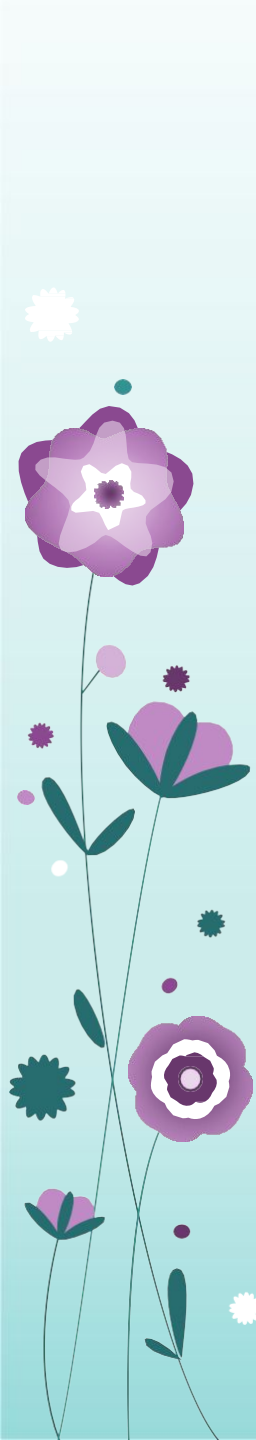


B. Growth Factor Receptors

- Mutant genes lead to one of two consequences:
 1. **Formation of mutant receptor proteins** that deliver continuous mitogenic signals to cells, even in the absence of the relevant growth factor in the environment.
 2. **Overexpression of growth factor receptors**, which can render cancer cells hyper-responsive to normal levels of the growth factor that would not normally trigger proliferation. For example:
 - *EGFR*; is overexpressed squamous cell carcinomas of the lung, glioblastomas, and epithelial tumors of the head and neck.
 - *HER2/NEU*; is amplified in approximately 20% of breast cancers.
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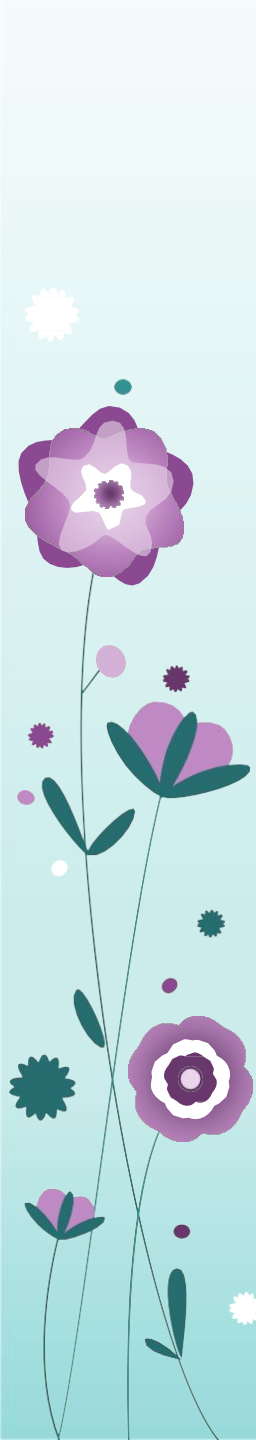
C. Signal transduction proteins

- Cancer cells acquire autonomous growth by *mutation in the genes that control the signaling pathway* (transfer of signal from inner side of cell membrane to nucleus).
- Two important genes that control this pathway (**Ras**.... increase cells proliferation & **ABL**.....inhibit cell proliferation).
- **Mutant Ras:** present in **30%** of human cancers (e.g. colon and pancreatic adenocarcinoma).
- In **CML(chronic myeloid leukemia)**, the **ABL gene** is translocated from its normal habitat on chromosome 9 to chromosome 22. The resultant chimeric gene encodes a constitutively active, oncogenic **BCR-ABL** tyrosine kinase.



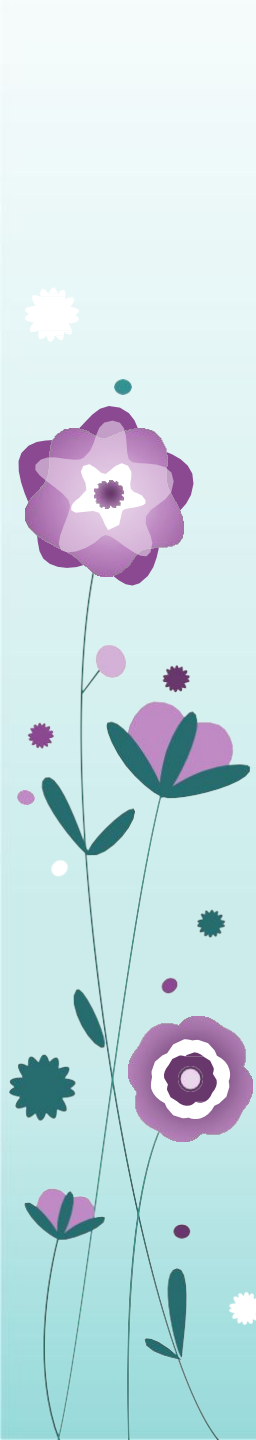
D. Nuclear Transcription Factors:

- Mutations affect the genes that regulate transcription of DNA may result in autonomous growth of cancers.
 - e.g. *Myc gene*
 - *Dysregulation of MYC* expression is seen in Burkitt's lymphoma
 - *MYC is amplified* in some cases of breast, colon, lung, and many other carcinomas.
- 



E. Cell cycle control proteins (Cyclins and Cyclin-Dependent Kinases)

- Normal cell cycle is consisting of five phases (G_0 , G_1 , S, G_2 , M).
 - All these phases are under control of proteins (Cyclins & Cyclins dependent Kinase).
 - Mutations that dysregulate the activity of cyclins and CDKs would favor cell proliferation.
 - *E.g. Cyclin D overexpression* is seen in many cancers (breast, esophagus & liver).
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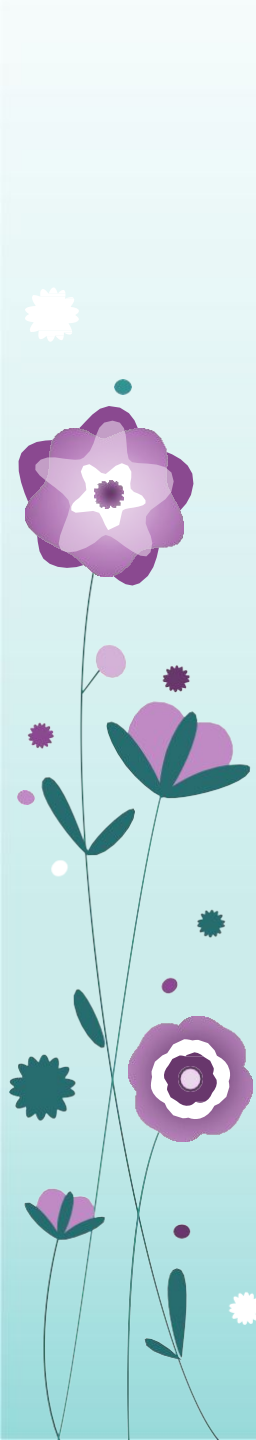


2. Insensitivity to Growth-Inhibitory Signals (Tumor Suppressor Gene)

- **Disruptions** of **tumor suppressor genes** make the cells resistant to inhibition of growth & increase their proliferation.

Examples:

1. **RB gene:** discovered initially in **Retinoblastoma**, but recently proved it lost in many tumors (breast cancer, bladder & lung cancer, **osteosarcoma**).
 2. **Adenomatous Polyposis coli (APC) gene:** Individuals born with Loss or mutant of one of alleles of APC gene, they **develop hundreds to thousands of adenomatous polyps in the colon** which on second decade of life one or more of these polyps will undergo malignant transformation (**colorectal carcinoma**).
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3. P53:

- * With homozygous loss of *p53*, **DNA damage goes unrepaired, mutations become fixed in dividing cells**, and the cell turns onto a one-way street leading to malignant transformation.
 - * More than 70% of malignant human tumor show defect in functions of P53.
 - * Most of mutations in P53 are acquired & less commonly they are inherited mutations like *Li-fraumeni syndrome* (patient have many cancers like sarcomas, breast cancer, leukemia, brain tumors, adrenal tumors).
- 

3. Genomic Instability due to defects in DNA repair

- Although humans swim in environmental agents that are mutagenic (e.g., chemicals, radiation, sunlight), cancers are relatively rare outcomes **because the cell is able to repair DNA damage and the death of cells with unrepairable damage.**
- Defects in **three types of DNA-repair systems** contribute to different types of cancers;

1. Defect in DNA mismatch repair gene:

Ex. HNPCC (Hereditary nonpolyposis colon carcinoma (Lynch syndrome))

- Characterized by familial carcinomas of the colon affecting predominantly the cecum and proximal colon.

2. Defect in nucleotide excision repair gene:

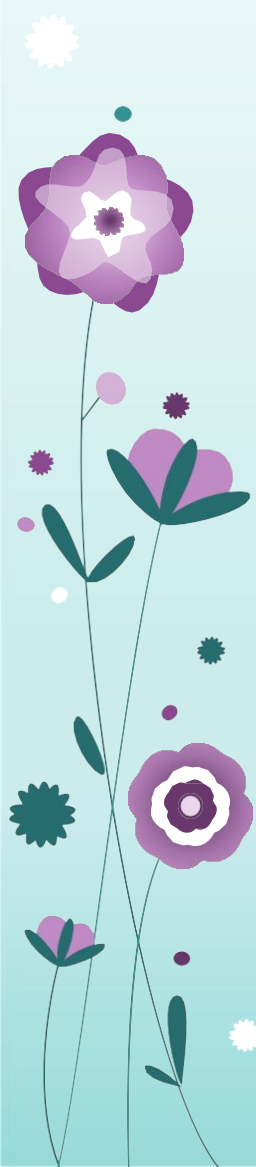
Ex. Xeroderma Pigmentosum; is an autosomal recessive disorder caused by a defect in DNA repair that is associated with a greatly **increased risk for cancers arising in sun exposed skin.**

3. Defects in DNA Repair by Homologous Recombination:

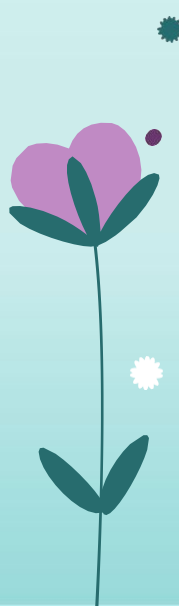
- Germ line mutations in two genes, **BRCA1 and BRCA2**, account for **50% of cases of familial breast cancer.**
- In addition to breast cancer, women with **BRCA1** mutations have a higher risk for developing epithelial **ovarian** cancers, and men have a slightly higher risk for developing **prostate** cancer. Likewise, germ line mutations in the **BRCA2** gene increase the risk for developing breast cancer in both men and women, as well as cancers originating from the **ovary, prostate, pancreas, etc.**

4. Evasion of apoptosis.

- **Normally**, there are two pathways that lead to apoptosis: **the extrinsic pathway**, which is mediated by *TNF- Fas receptor* & inhibited by FLICE protein (FLIP). and **the intrinsic pathway** (also known as the mitochondrial pathway), *is mediated by* BAX, BAK genes & inhibited by bcl2 gene.
- *Changes in mechanism of apoptosis in malignant tumors are:*
 - Decrease level of Fas protein (CD95).
 - Increase level of FLICE protein (FLIP); which inhibits apoptosis by inhibit activation of caspases.
 - Reduced levels of pro-apoptotic BAX resulting from loss of p53.
 - Increase level of Bcl2 gene which inhibits apoptosis (as in 85% of B-cell lymphoma).

A decorative illustration on the left side of the slide featuring a tall, thin green stem with several purple flowers of different sizes and shapes, some with white centers, and small green leaves. There are also small white star-like flowers scattered around.

5. Limitless replicative potential (immortality)

- Most of **normal** human cells have capacity of **50 to 70 doublings**, after this, the cells lose the capacity to divide (due to **loss of Telomerase enzymes** which is important in DNA replication).
 - In malignant tumors, there is **increased level of Telomerase**.
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- A decorative illustration on the right side of the slide featuring a tall, thin green stem with several purple flowers of different sizes and shapes, some with white centers, and small green leaves. There are also small white star-like flowers scattered around.

6. Sustained Angiogenesis:

- Most of cancers cannot grow more than 1 to 2 mm in diameter or thickness unless they are vascularized.
- *Angiogenesis has many effects on tumor growth:*
 1. Supplies nutrients & oxygen.
 2. Newly formed endothelial cells during angiogenesis, will stimulate the growth of adjacent tumor cells by secretion of polypeptides (like platelets growth factor).
 3. Angiogenesis is also important for development of metastasis.
 - Cells of malignant tumor are the main inducer of angiogenesis by their production of growth factors (**Angiogenetic factors**); the most two important ones are:
 - 1 Vascular endothelial growth factor.
 - 2 Fibroblast growth factor.

7. Invasion and metastasis

- The Metastatic pathway of cancer can be divided into **two phases**:

1. Invasion of Extracellular matrix: Include the following steps

- I. Detachment of tumor cells from each other (by losing of E- cadherin & B-catenin molecules).
- II. Degradation of Extracellular Matrix (by Metalloproteinase).
- III. Attachment of tumor cells to new Extracellular Matrix components.
- IV. Migration of tumor cells to the vessels (mediated by Cytokines).

2. Vascular dissemination & Homing of tumor cells:

-**In circulation**, Tumor cells are liable to destruction by host immune cells.

- To avoid such destruction, tumor cells are **arranged themselves into small emboli** (by adhesion to circulating leukocytes & platelets).

-**Then** tumor cells **leave circulation** by adhesion to the endothelial cells & destruction of basement membrane of vessels, to **enter the extracellular matrix of metastatic site**.

-**Distribution of metastasis** can be predicted by the location of primary tumor & its vascular & lymphatic drainage e.g. *cancer of breast is expected to involve the lung & bones of thorax*.

-Some cancers have *unexpected metastatic pathway* e.g. *caner of lung metastasize to the adrenal glands*.

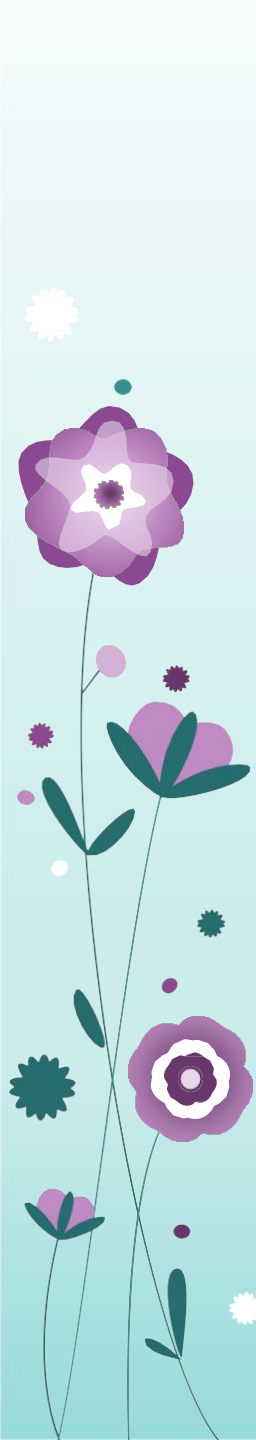
8. Evasion of immune surveillance

- **Immune surveillance:** refer to recognition & destruction of tumor cells by the immune system.
- Cancer cells **express a variety of antigens (Tumor antigens) that stimulate the host immune system**, which appears to have an important role in preventing the development of cancers.

- **Cell mediated immunity** is the dominant antitumor mechanism.

1. Cytotoxic T lymphocyte;

- CTLs are **the major** immune defense mechanism against tumors, **recognize peptides** that are displayed bound to **class I(MHC)** molecules.
- CTLs play a **protective role against virus-associated neoplasms (e.g., EBV- and HPV-induced tumors).**

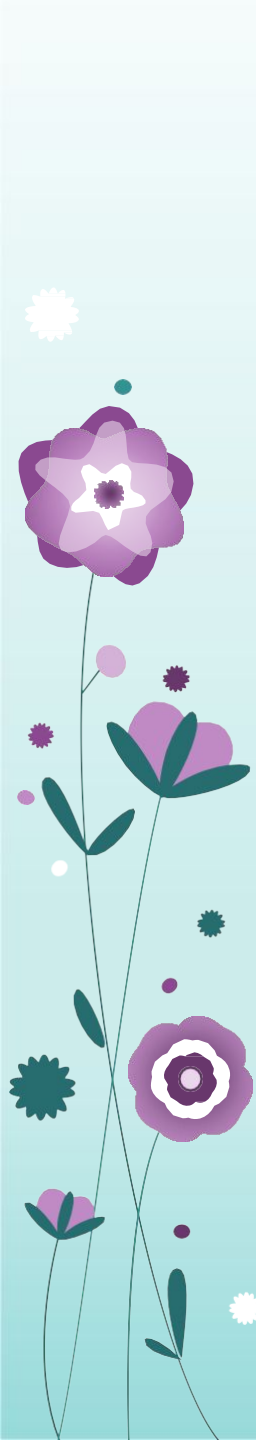


2. *Natural killer cells:*

- **First line** of defense against tumors.
- Are capable of **destroying tumor cells** without prior sensitization.
- After activation with IL-2, NK cells can **lyse a wide range of human tumors**.
They recognize stress-induced antigens that are expressed on tumor cells and cells that have incurred DNA damage and are at risk for neoplastic transformation.

3. *Macrophage:*

- Activated macrophages exhibit cytotoxicity against tumor cells.
 - They may kill tumors by mechanisms similar to those used to kill microbes (**e.g., production of reactive oxygen metabolites or by secretion of TNF**).
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- Despite antigenicity, tumor cells develop mechanisms to escape or evade the immune system. Several mechanisms may be operative:

1. Selective outgrowth of antigen-negative variants:

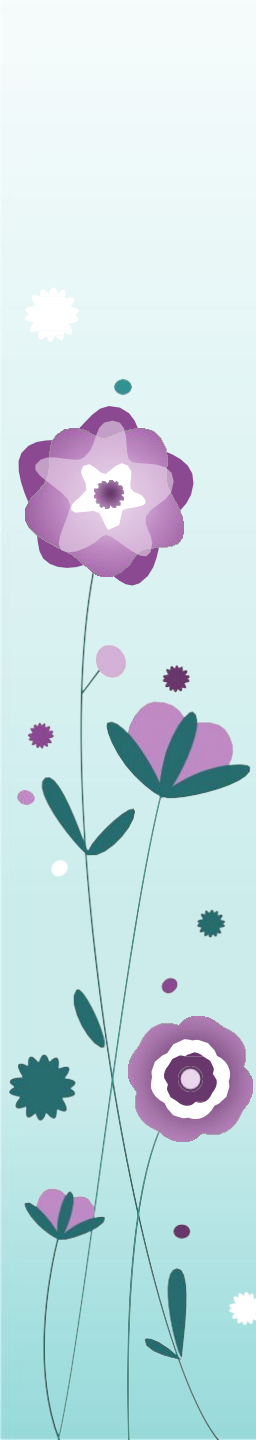
- During tumor progression, strongly immunogenic subclones may be eliminated.

2. Loss or reduced expression of MHC molecules:

- Tumor cells may fail to express normal levels of HLA (human leukocytes antigens) class I molecules, thus escaping attack by cytotoxic T cells.

3. Lack of costimulation:

- Sensitization of T cells requires two signals, one by a foreign peptide presented by MHCI molecules and the other by costimulatory molecules.
 - Although tumor cells may express peptide antigens with class I molecules, they often do not express costimulatory molecules.
- 



4. *Immunosuppression:*

- Many oncogenic agents (e.g., chemicals and ionizing radiation) suppress host immune responses.
- Tumors or tumor products also may be immunosuppressive, for example, TGF- β , secreted in large quantities by many tumors, is a potent immunosuppressant.

5. *Antigen masking:*

- The cell surface antigens of tumor cells may be hidden or masked from the immune system by glycocalyx molecules, such as sialic acid- containing mucopolysaccharides.

6. *Apoptosis of cytotoxic T cells:*

- Some melanomas and hepatocellular carcinomas express FasL. It has been postulated that these tumors kill Fas-expressing T lymphocytes that come in contact with them, thus eliminating tumor-specific T cells.
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THANKYOU

