

Neoplasm

THE MOLECULAR BASIS OF CANCER

Lecture 4

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The learning objectives

At the end of this lecture the students must understanding the following topics

- 1- The molecular basis of cancer.
- 2- The carcinogenesis .
- 3- Viral oncogenesis .
- 4- Mechanisms of local invasion and distal metastasis.

1. Non-lethal genetic damage lies at the heart of carcinogenesis. **This damage (mutation) may be**

A. Acquired by environmental factors such as

- Radiation,
- Chemical substances
- Viruses

B. Inherited in the germ line.

The tumor mass is the result of **clonal expansion of a single progenitor cell** that incurred the genetic damage.

Progenitor cell is that from which another cell or a family of cells is descended, (an ancestor; a parent).

2. Involvement of normal regulator genes. Three classes of normal regulator genes are involved in carcinogenesis;

- a. The growth promoting proto-oncogenes.
- b. The growth inhibiting cancer suppressor genes.
- c. Genes that control programmed cell death. The programmed cell death is termed apoptosis.

These three types of genes are the principal targets of genetic damage. Mutant alleles of the first group are considered dominant.

Both normal alleles of the second group must be damaged or absent (most of cases). For this reason they are called recessive oncogenes.

The third group may act in both ways.

Oncogenes are derived from proto-oncogenes; these are cellular genes that promote normal growth & differentiation.

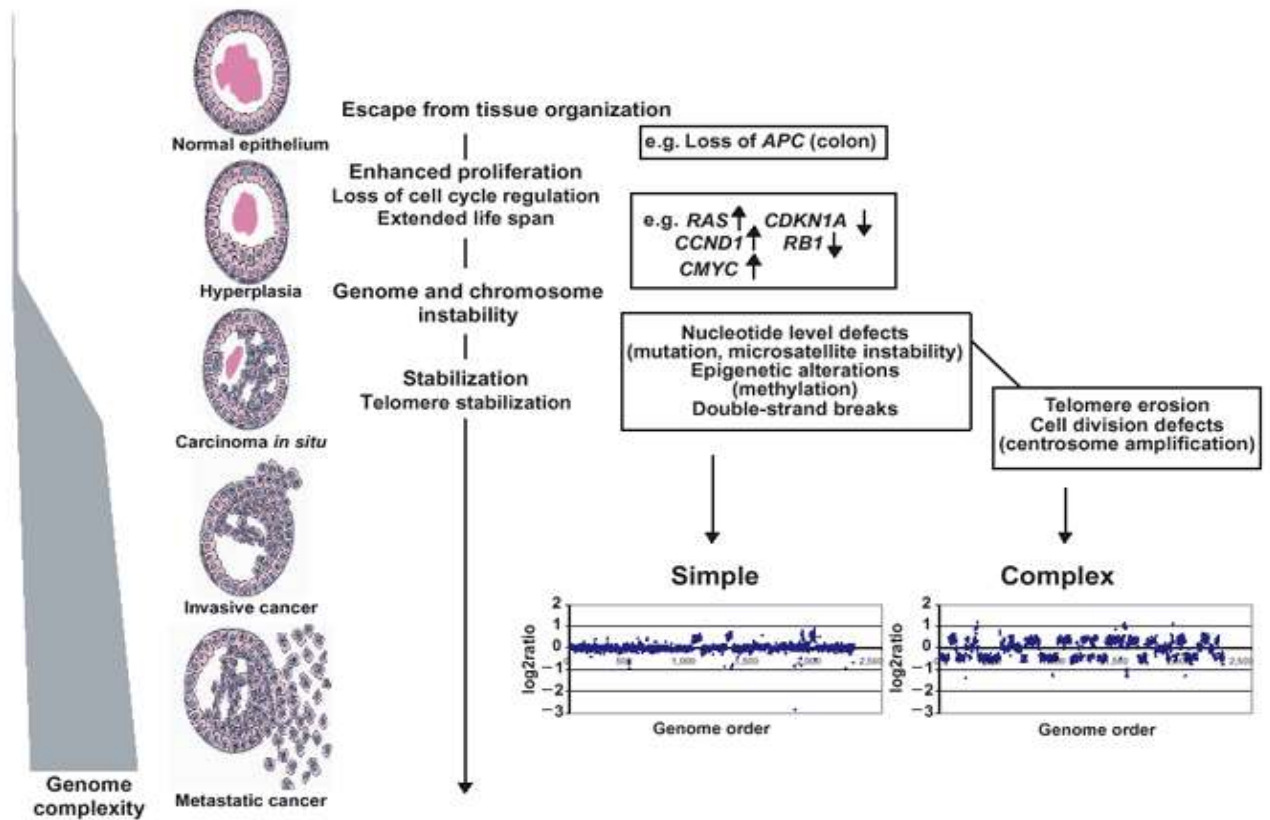
3. **Genes regulating repair of DNA damage.** A fourth category of genes are those that regulate repair of damaged DNA. These affect cell proliferation or survival indirectly by influencing the ability of the organism to repair non-lethal damage in other genes. Both alleles must be inactivated to induce genomic instability. In this respect, they can be considered as tumor suppressor genes.
4. **Carcinogenesis** is a multi-step process at both the phenotypic and the molecular (genetic) levels.

At the phenotypic level, excessive growth, local invasiveness & distant metastasis are acquired in a stepwise fashion a phenomenon called **tumor progression**.

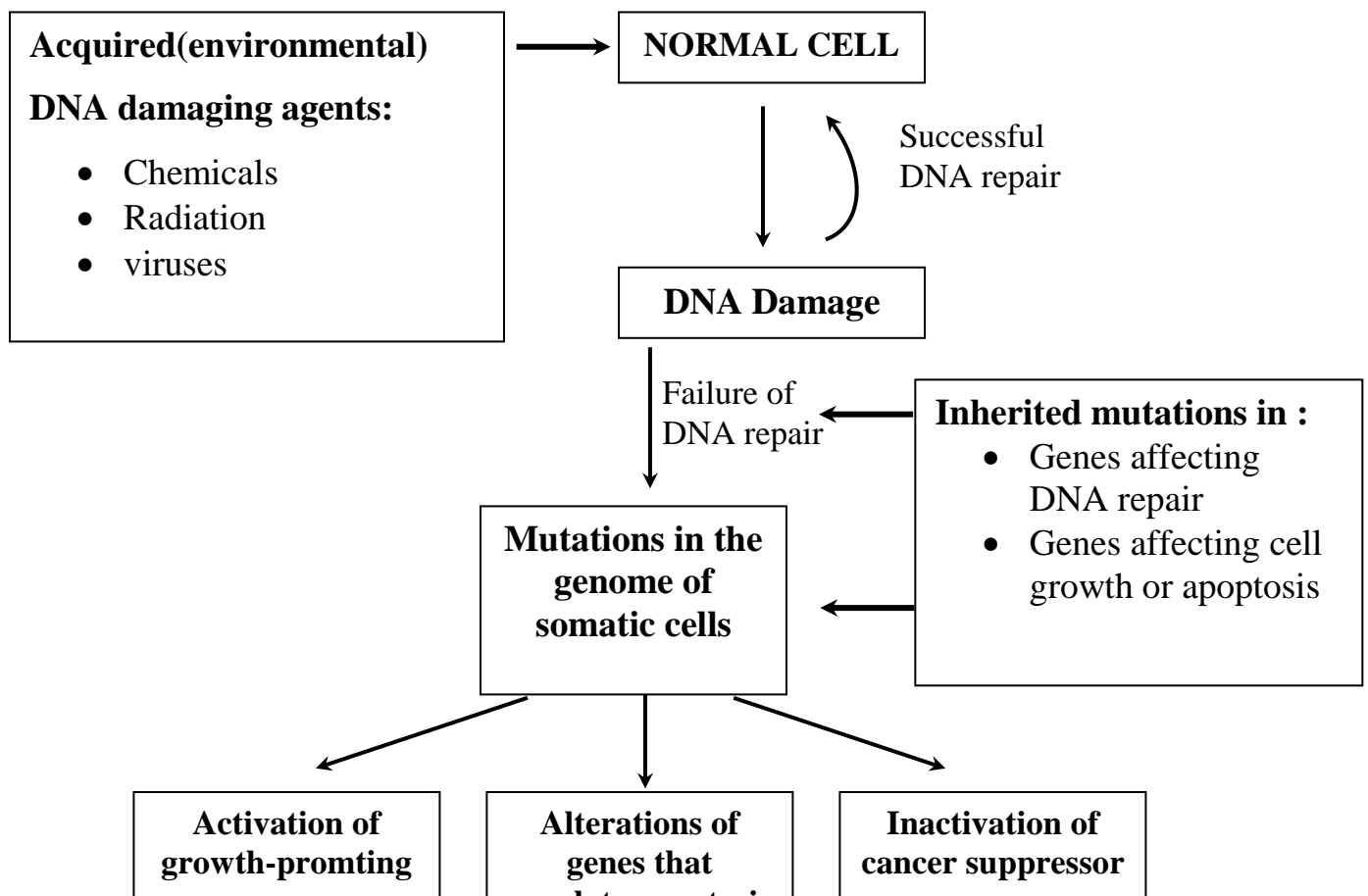
(Phenotypic: pertaining to the observable features of organisms)

At the genetic (molecular) level, these features are due to accumulation of genetic lesions that are favored or facilitated by defects in the DNA repair.

Fortunately, in most if not all instances, no single mutation is sufficient to transform a normal cell into a cancer cell. Carcinogenesis is thus a multistep process resulting from the accumulation of multiple genetic alterations that collectively give rise to the transformed phenotype and all of its associated hallmarks, Every cancer reveals multiple genetic alterations involving activation of several oncogenes & loss of tumor suppressor genes.



A simplified scheme of the molecular basis of cancer



VIRAL CARCINOGENESIS

DNA oncogenic viruses: some of these viruses contain oncogenic sequences like **human papilloma virus**. Others like **hepatitis B virus** & **Epstein Bar virus (EBV)** do not contain oncogenic sequences so they act indirectly. The DNA virus must be integrated in the DNA of the host cell. Early genes containing the promoters & core protein genes must be integrated. Late genes (coat protein genes) are excluded. When these genes are integrated they code for the production of transforming proteins, which bind to cellular proteins that regulate growth.

RNA oncogenic viruses: all RNA viruses involved in carcinogenesis are **retroviruses** i.e. they contain the enzyme reverse transcriptase. The latter helps in DNA synthesis by these viruses.

CANCER SUPPRESSOR GENES

The most important of these are the Rb (retinoblastoma) & P53 genes. Loss or malfunction of key regulatory proteins that these genes encode can cause malignancy

The retinoblastoma gene (Rb)

The of Rb protein (pRb) active form serves as a brake to DNA replication in cell cycle.

Mutation renders the protein inactive & thus the cell divides non-stop.

The mutations of the Rb lead to neoplastic proliferation of the retinal cells.

In the **familial form of retinoblastoma**, all somatic cells inherit one mutant Rb gene from a carrier parent. The second mutation affects the Rb locus in one of the retinal cells after birth.

In the **sporadic form of retinoblastoma**, on the other hand, both mutations at the Rb locus are acquired by the retinal cells after birth.

p53

Another very important gene; it is the guardian of the genome or the molecular policeman.

p53 prevents replication of damaged or faulty DNA. It either stops the cell in the G1 phase or promotes apoptosis.

Faulty p53 molecules allow cell with damaged DNA to survive & replicate. The existing mutation will pass to the progeny cells, which will have the chance to accumulate additional mutations to pass to neoplasia.

P53 gene is the single most common target of genetic alteration in human tumors. 50% or more of human tumors have either loss of p53 gene in both alleles or have what is called “a negative dominant mutation”.

P53 is called into action in emergency breaks after exposure to irradiation, UV light or mutagenic chemicals. The accumulated wild type p53 binds to

DNA & stimulates transcription of several genes that mediate the two major effects of p53:

- a. Cell cycle arrest &
- b. Apoptosis.

GENES THAT REGULATE APOPTOSIS

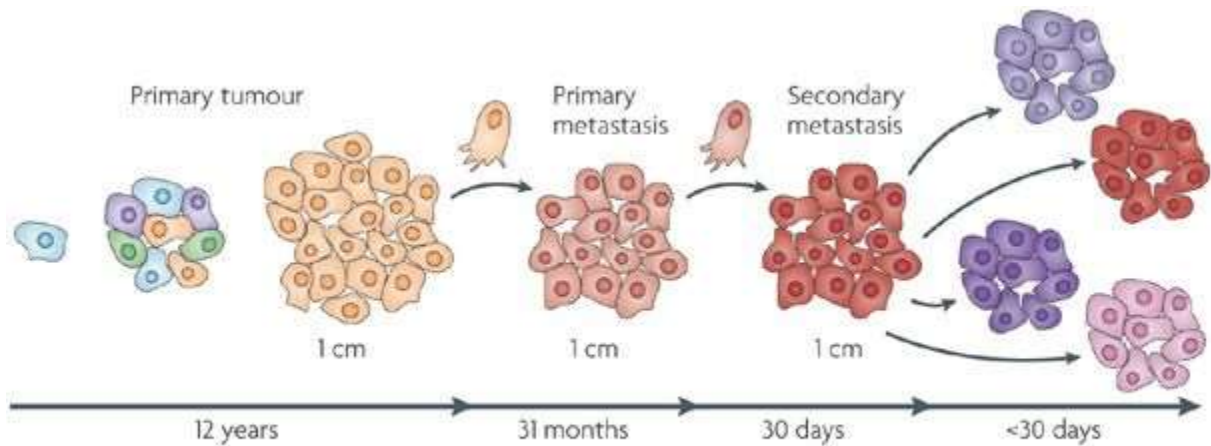
These genes either prevent programmed cell death (apoptosis) e.g. bcl-2, or induce programmed cell death e.g. bax & bad genes. Juxtaposition of immunoglobulin heavy chain gene located on chromosome 14q with bcl-2 located on chromosome 18q causes over-expression of bcl-2. By a not well-understood mechanism this over expression protects lymphocytes from apoptosis; they survive causing lymphadenopathy

The tumor suppressor gene P53 mediates up-regulation of the bax gene promoting apoptosis.

GENES THAT REGULATE DNA REPAIR

There are several inherited disorders in which genes that encode proteins involved in DNA repair are defective. Those are at great risk of developing cancer.

DNA repair genes are not oncogenic but allow mutations in other genes in normal cell cycle.

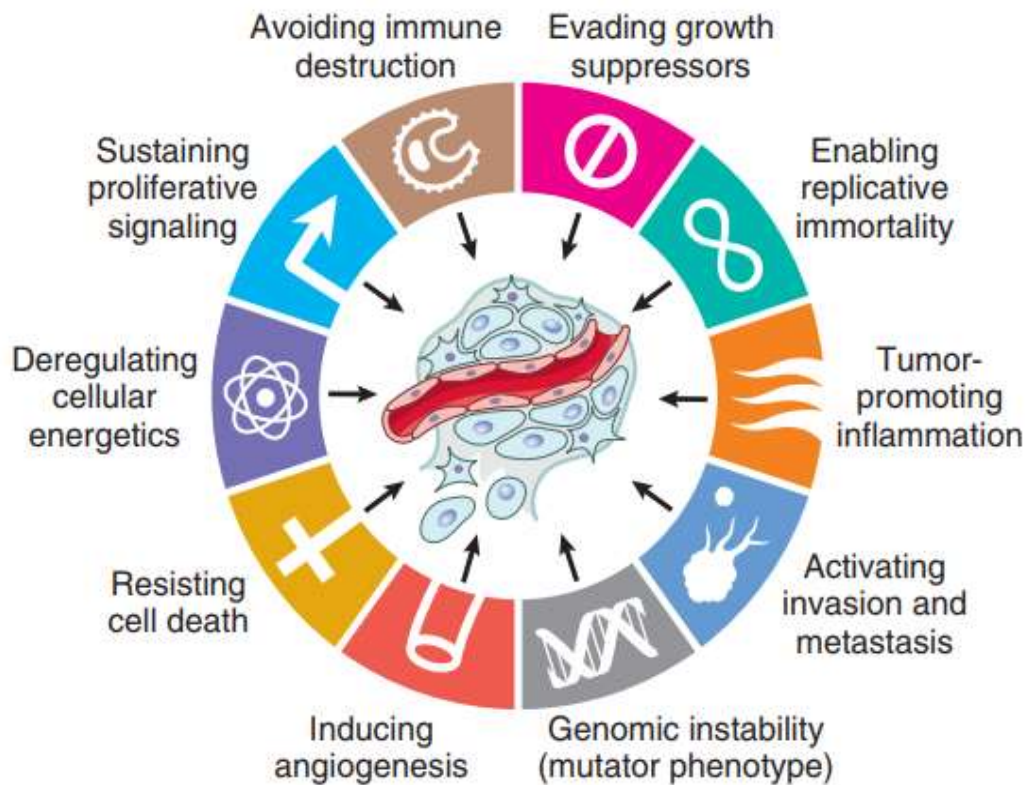


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biological properties of cancer cells.

It appears that all cancers display eight fundamental changes in cell physiology, which are considered the hallmarks of cancer. These changes are consist of the following:

- Self-sufficiency in growth signals
- Insensitivity to growth-inhibitory signals
- Altered cellular metabolism
- Evasion of apoptosis
- Limitless replicative potential (immortality)
- Sustained angiogenesis
- Invasion and metastasis
- Evasion of immune surveillance



Eight cancer hallmarks and two enabling factors (genomic instability and tumor-promoting inflammation). Most cancer cells acquire these properties during their development, typically due to mutations in critical genes.

Mechanism of local and distant spread:-

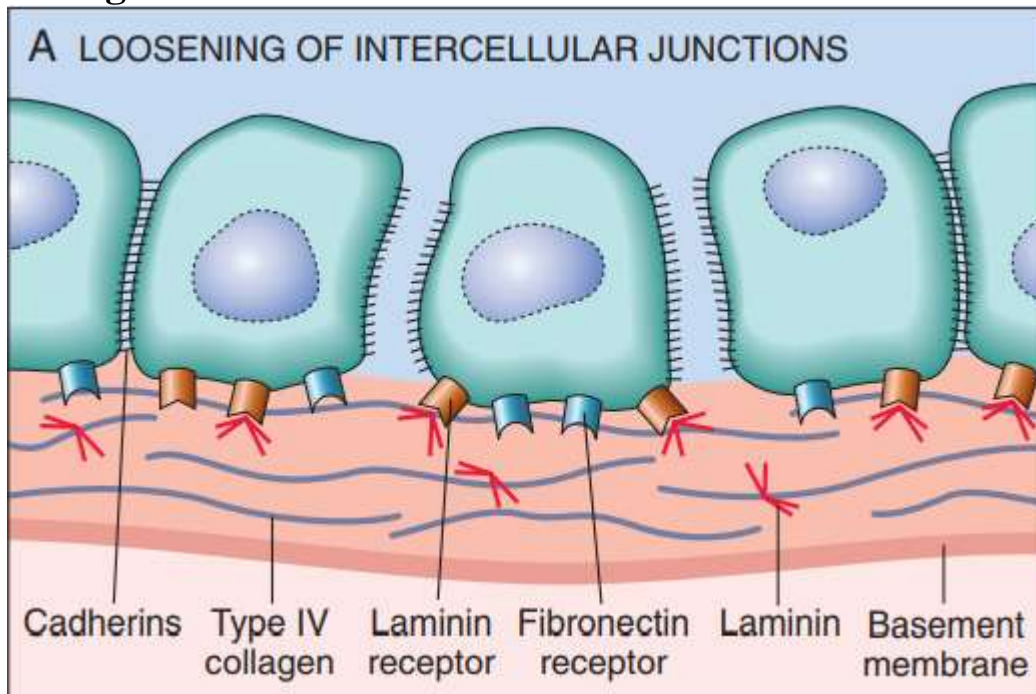
Invasion and metastasis are biologic hallmarks of malignancy.

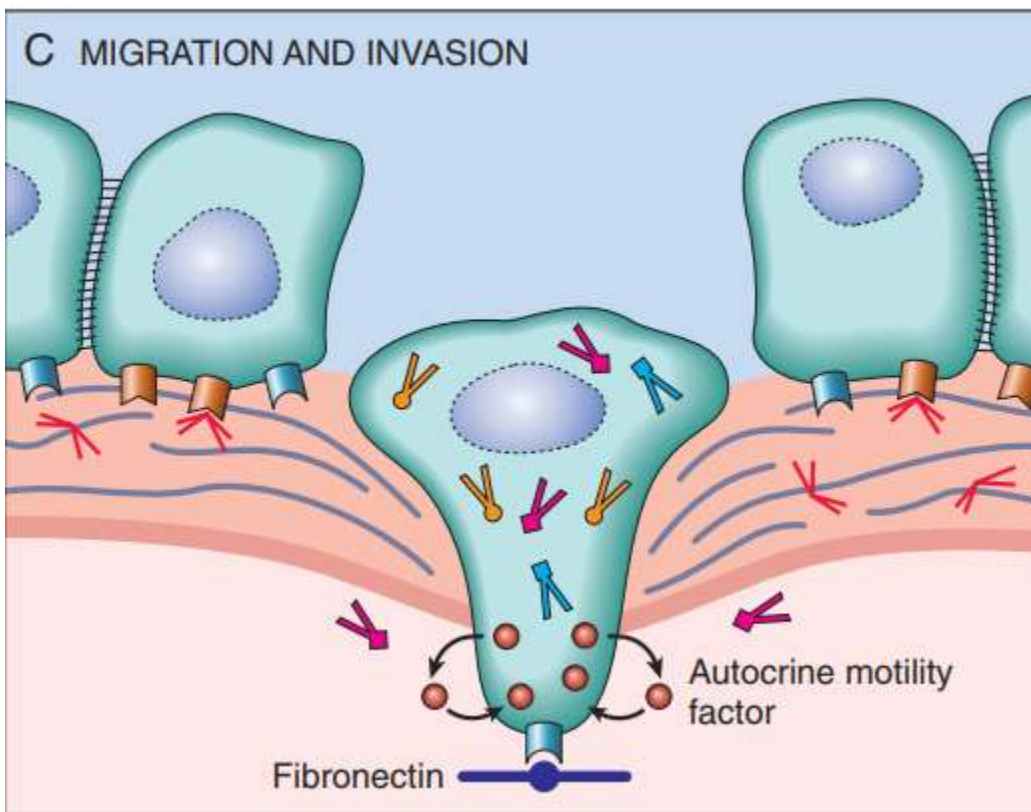
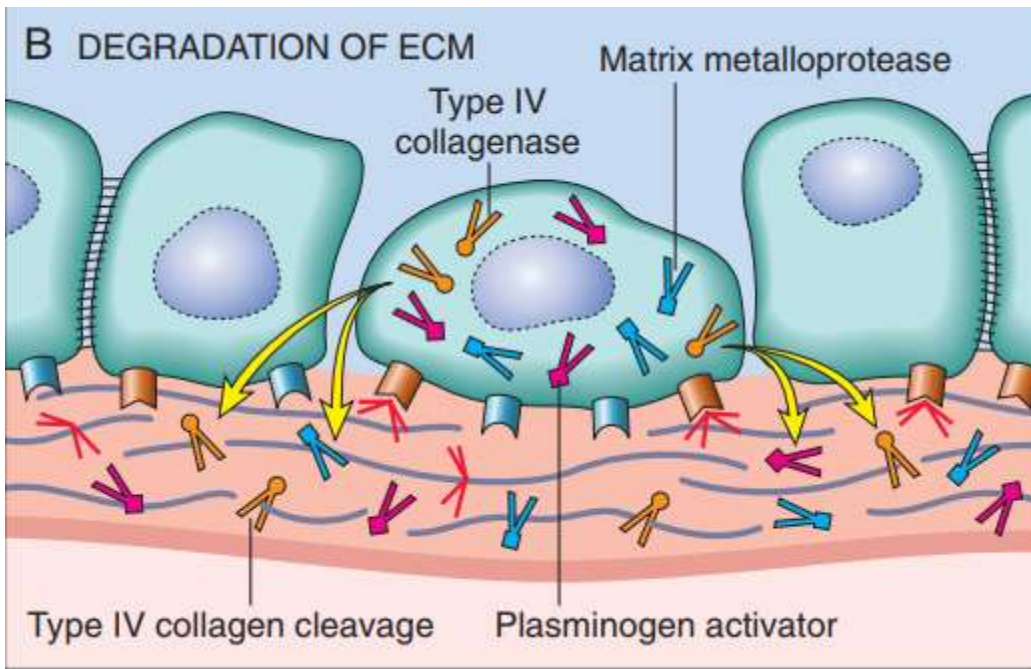
The spread of tumors is a complex process involving a set of steps.

1- Invasion of extracellular matrix:

Human tissues are organized into a series of compartment separated from each other by two steps of extracellular matrix, basement membrane and interstitial CT, the tumor cells must interact with ECM at several stages, a carcinoma must first breach the underlying basement membrane, then traverse the interstitial CT and gain access to the circulation by penetrating the vascular BM, this cycle is repeated when tumor cell emboli extravasate at a distant site, invasion of ECM is an active process that can be resolved into four steps:

- 1- Detachment of tumor cells from each other.**
- 2- Attachment of tumor cells to matrix components.**
- 3- Degradation of ECM.**
- 4- Migration of tumor cells.**





Vascular dissemination and homing of tumor cells once in the circulation tumor cells are vulnerable to destruction by the host immune cells, in the blood stream, some tumor cells form

emboli by aggregating and adhering to circulating leukocytes, particularly platelets, aggregated tumor cells are afforded some protection from the antitumor host effector cells, extravasation of free tumor cells or tumor emboli involves adhesion to the vascular endothelium followed by egress through the BM by mechanism similar to these involved in invasion.

The site of extravasation and the organ distribution of metastasis can generally be predicted by the location of primary tumor and its vascular or lymphatic drainage, however in many cases the natural pathways of drainage do not readily explain the distribution of metastasis e.g. some tumor as lung cancers tend to involve the adrenals but almost never spread to skeletal muscles such organ tropism may be related to expression of adhesion molecules by tumor cells whose ligands are expressed on the endothelium of target organs another novel mechanism of site-specific homing involves chemokines and their receptors chemokines are involved in directed movement (chemotaxis) of leukocytes. So that the site at which metastases appear is related to two factors:

- 1- the anatomic location and vascular drainage of the primary tumor,
- 2- and the tropism of particular tumors for specific tissues.

e.g. human breast cancer cells express high levels of the chemokine receptor genes, the ligands for these receptors are highly expressed only in those organs where breast cancer metastasizes, so the application of blocked chemokine receptors may limit metastasis.

