Neoplasia 5

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HALLMARKS OF CANCER

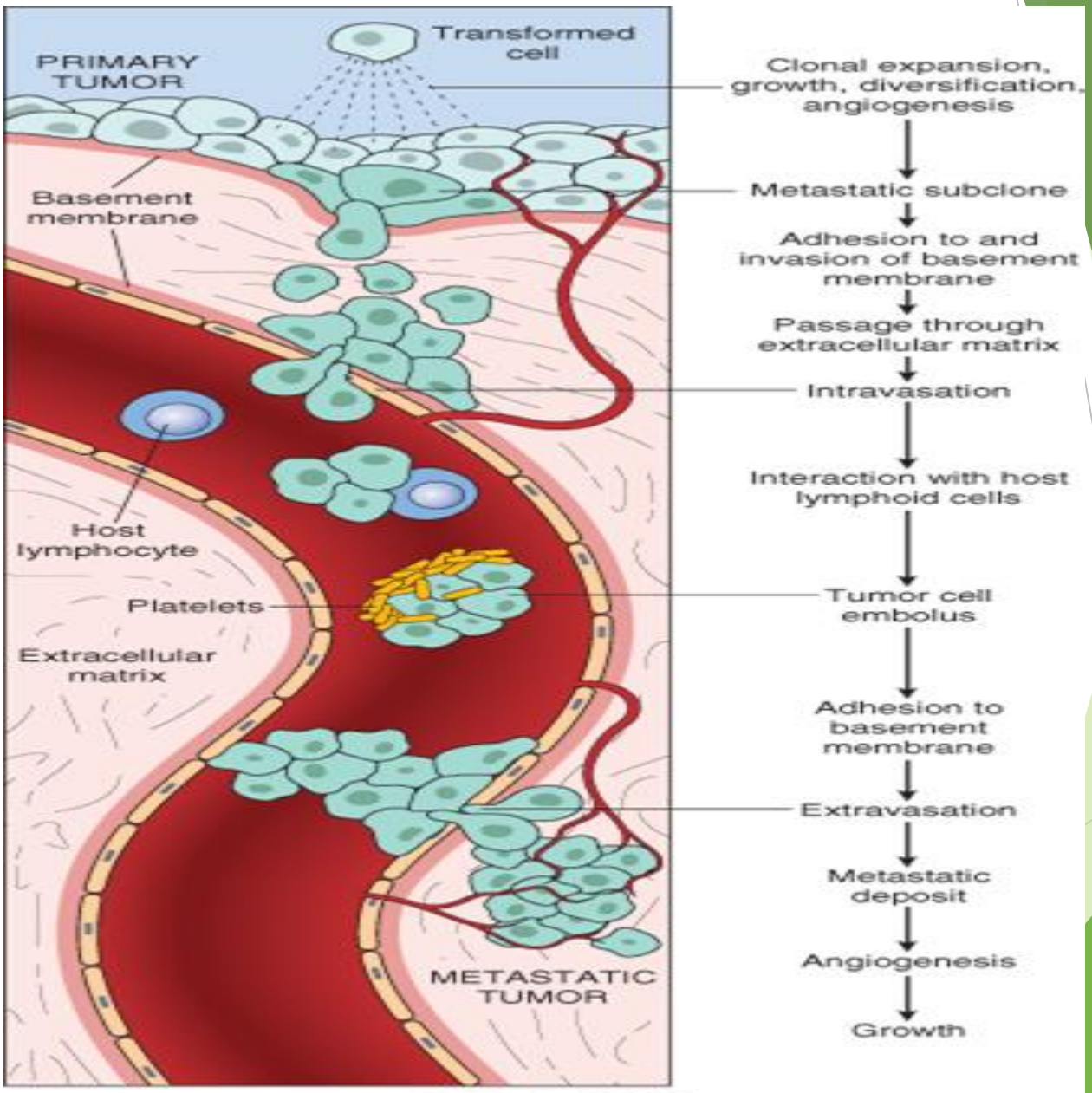
- All cancers display eight fundamental changes in cell physiology, which are considered the hallmarks of cancer.

- • 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

VII. Invasion and Metastasis

- Invasion, and metastasis, the major causes of cancer related morbidity and mortality, result from complex interactions involving cancer cells, stromal cells, and the extracellular matrix (ECM).
- The metastatic cascade can be subdivided into two phases:
- (1) Invasion of ECM
- (2) Vascular dissemination and homing of tumor cells.

METASTATIC PATHWAY:



1- MECHANISM OF INVASION OF ECM:

- 1- Detachment of tumor cells →Inactivation of E-Cadherin OR activation of ß catenin→ detachment of cells
- - Loss of function of E-Cadherin in many CAs –

2- Degradation of ECM by proteases e.g.

Matrix Metalloproteinase (MMPs)

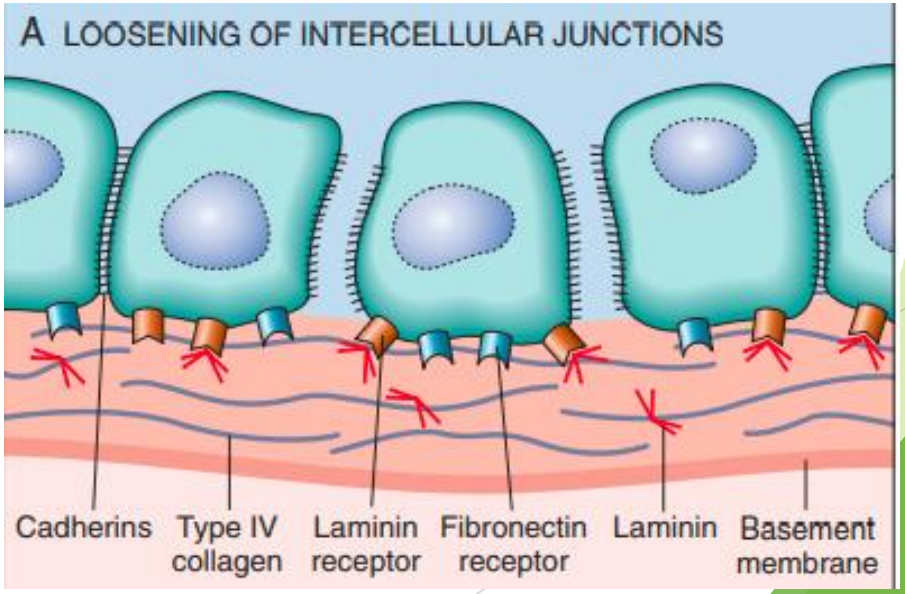
Cathepsin D, Type IV collagenase

- Result of digestion of ECM → Cleavage products have hemotactic activity for more tumor cells

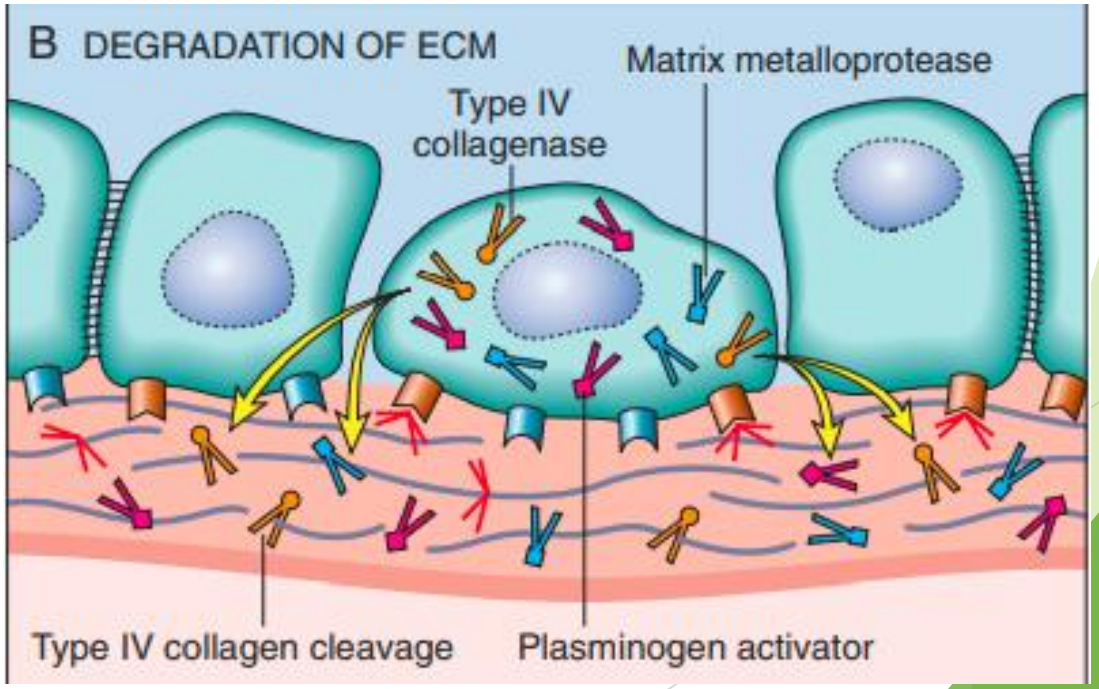
I. Invasion of Extracellular Matrix

- Invasion of the ECM initiates the metastatic cascade and is an active process that can be resolved into several sequential steps:

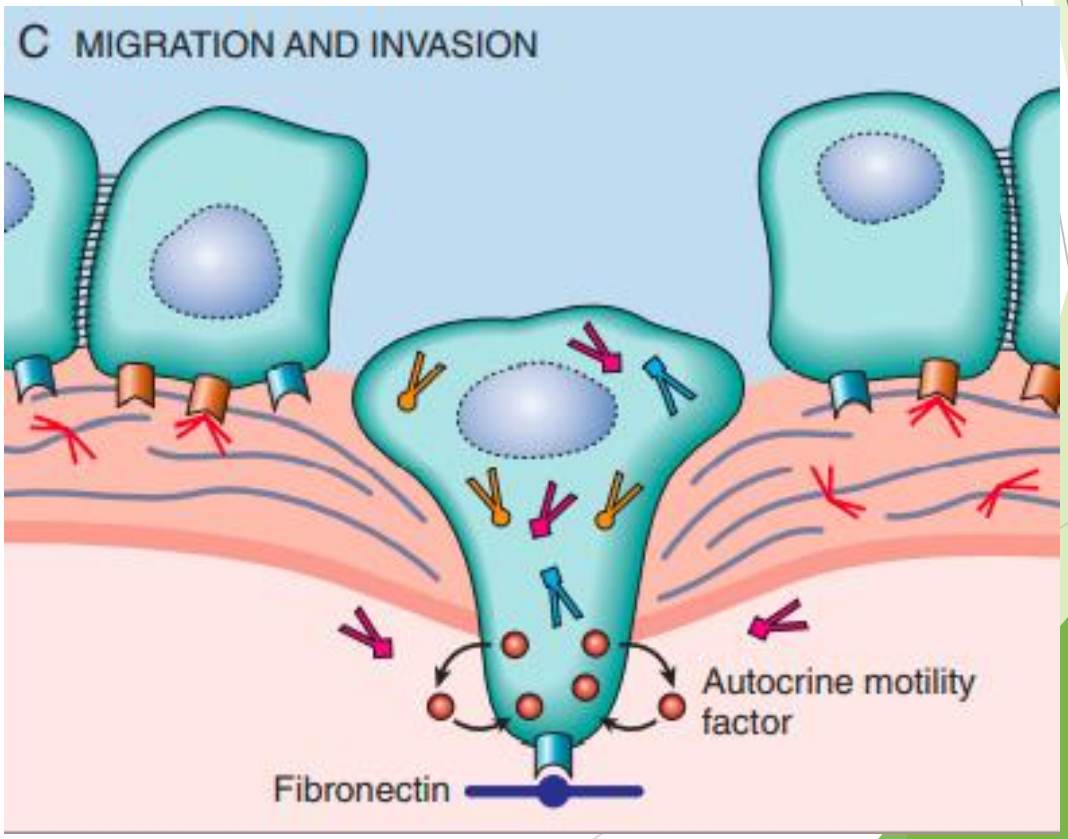
- A. Loosening of intercellular connections between tumor cells

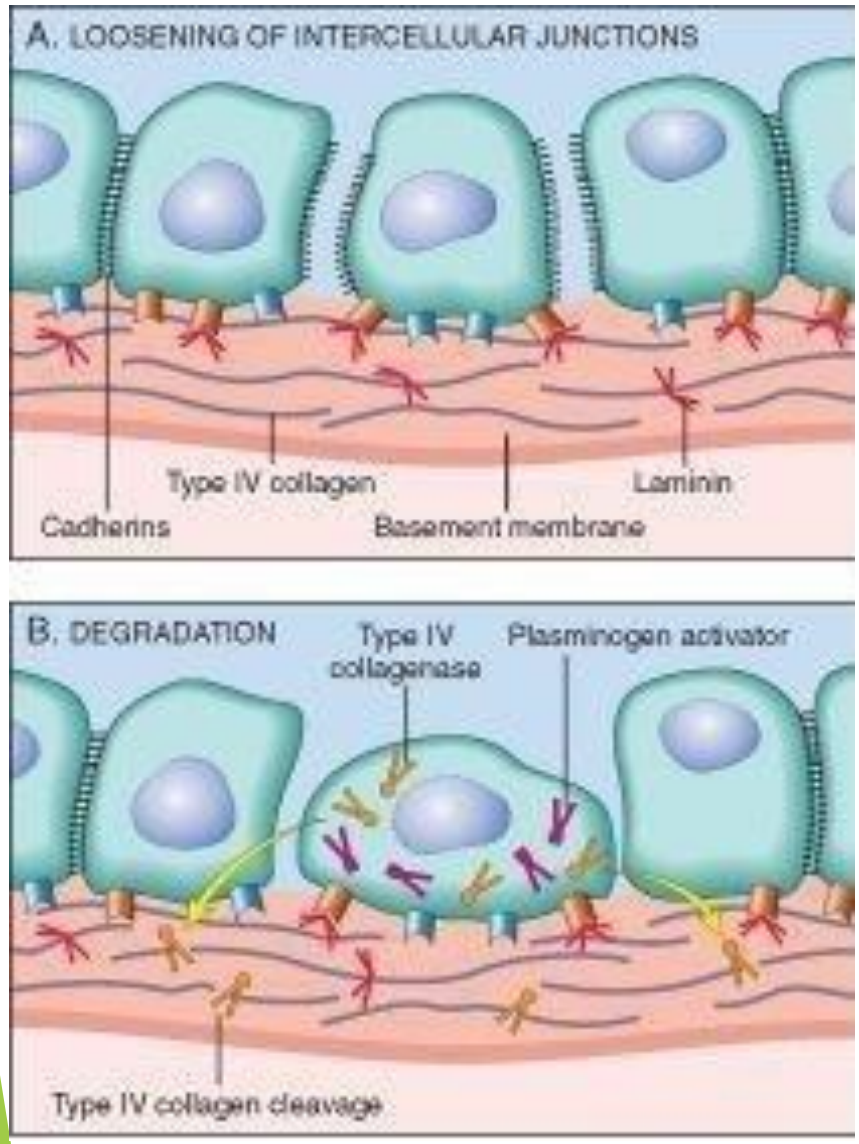


- B. Local degradation of the basement membrane and interstitial connective tissue



- C. Changes in attachment of tumor cells to ECM proteins.
- D. Locomotion




A. LOOSENING OF INTERCELLULAR JUNCTIONS
Cadherins
Type IV collagen
Basement membrane
Laminin
B. DEGRADATION
Type IV collagenase
Plasminogen activator
Type IV collagen cleavage
C. ATTACHMENT
Type IV collagen
Laminin receptor
Fibronectin receptor
Laminin
D. MIGRATION
Autocrine motility factor
Fibronectin

II. Vascular Dissemination and Homing of Tumor Cells

- Because of their invasive properties, tumor cells frequently escape their sites of origin and enter the circulation.

- if neglected, virtually all malignant tumors will eventually produce macroscopic metastases.

2- Vascular dissemination:

1- Invasion of the circulation:

Adhesion to endothelium→ retraction of endothelium → vessel

2- Attack by NK cells, some escape by formation of a thrombus/embolus

3- Escape from circulation:

Adhesion to endothelium→ retraction of endothelium → escape to tissue

The site at which metastases appear is related to two factors:

- The anatomic location and vascular drainage of the primary tumor:
- metastases occur in the first capillary bed available
- The tropism of particular tumors for specific tissues, due to adhesion molecules,

WHAT INFLUENCES SITE OF METASTASES ?

- Anatomical Location
- Complimentary adhesion molecule between tumor cells & target organs
- Chemoatractants liberated by target organs
- Protease inhibitors present in certain tissues

EXAMPLES OF TROPISM (HOMING)

- Lung Carcinoma → Adrenals & Brain
- Neuroblastoma → Liver & Bone

Less common sites of metastases include muscle, skin, thyroid, breast, heart …etc.

❖Spleen & Cartilage are almost never involved by metastatic tumors.

IIIV. Evasion of Immune Surveillance

- Normal function of the immune system is to constantly “scan” the body for emerging malignant cells and destroy them.

- Cancer cells express a variety of antigens that stimulate the host immune system, which appears to have an important role in preventing the emergence of cancers

- Despite the antigenicity of cancer cells, the immune response to established tumors is ineffective, due to acquired changes that allow cancer cells to evade anti-tumor responses and foster pro-tumor responses.

- Defining mechanisms of immune evasion and “immunomanipulation” by cancer cells has led to effective new immunotherapies that work by reactivating latent host immune responses.

Tumor Antigens.

- All of cancer -induced mutations may generate new protein sequences (neoantigens) that the immune system has not seen and therefore is not tolerant to it.

- Viral proteins that are expressed in cancer cells transformed by oncogenic viruses, e.g human papilloma virus (HPV) and Epstein-Barr virus (EBV).

- Since the immune system is capable of recognizing and eliminating cancers, it follows that tumors that reach clinically significant sizes must be composed of cells that are either :

- Invisible to the host immune system
- Express factors that actively suppress host immunity.

Genomic Instability as an Enabler of Malignancy

- The preceding section identified the eight defining features of malignancy, all of which appear to be produced by genetic alterations involving cancer genes.

- How do these mutations arise? Although humans are awash in environmental agents that are mutagenic (e.g., chemicals, radiation, sunlight), cancers are relatively rare outcomes of these encounters.

- This state of affairs results from the ability of normal cells to sense and repair DNA damage.

Genomic Instability as an Enabler of Malignancy

- The importance of DNA repair in maintaining the integrity of the genome is highlighted by several inherited disorders in which genes that encode proteins involved in DNA repair are defective.

- Individuals born with inherited defects in DNA repair genes are at greatly increased risk for the development of cancer

Genomic Instability as an Enabler of Malignancy

- Individuals may have defects in three types of DNA repair systems:
- **Mismatch repair.**
- **Nucleotide excision repair.**
- **Recombination repair**

1. Hereditary Nonpolyposis Colon Cancer Syndrome(**Lynch syndrome**)

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

- **It results from defects in genes involved in DNA mismatch repair.**

2. Xeroderma Pigmentosum

- 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.

- Caused by inherited loss of nucleotide excision repair.

3. Diseases With Defects in DNA Repair by Homologous Recombination

- A group of autosomal recessive disorders comprising:
- Bloom syndrome.
- Ataxia-telangiectasia.
- Fanconi anemia.

3. Diseases With Defects in DNA Repair by Homologous Recombination

- Characterized by hypersensitivity to **DNA-damaging agents, such as ionizing radiation** (in Bloom syndrome and ataxia-telangiectasia), or to **DNA cross-linking agents**, such as nitrogen mustard (in Fanconi anemia).

Familial breast cancer

- Evidence for the role of **DNA repair genes** in the origin of cancer also comes from the study of hereditary breast cancer.
- 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 substantially higher risk for developing **epithelial ovarian cancers**, and men have a slightly higher risk for developing **prostate cancer**
- Both genes seem to function, at least in part, in the homologous recombination DNA repair pathway.

Tumor-Promoting Inflammation as an Enabler of Malignancy

- **Infiltrating cancers provoke a chronic inflammatory reaction which can be so extensive as to cause systemic signs and symptoms, such as:**

- **Anemia (the so-called "anemia of chronic disease").**
- **Fatigue.**
- **Cachexia.**

- Infiltrating cancers provoke a chronic inflammatory reaction.

- In patients with advanced cancers, this inflammatory reaction can be so extensive as to cause systemic signs and symptoms, such as **anemia (**the so-called "anemia of chronic disease"), **fatigue**, and **cachexia**.

- However, studies carried out on cancers in animal models suggest that inflammatory cells also modify the tumor microenvironment to enable many of **the hallmarks of cancer**.

- These effects may stem from direct interactions between inflammatory cells and tumor cells, or through indirect effects of inflammatory cells on other **resident stromal cells**, particularly cancer-associated fibroblasts and endothelial cells.

Proposed cancer-enabling effects of inflammatory cells and resident stromal cells include the following:

1. Release of factors that promote proliferation, e.g EGF.
2. Removal of growth suppressors.
3. Enhanced resistance to cell death.
4. Angiogenesis. Inflammatory cells release numerous factors, including VEGF, that stimulate angiogenesis
5. Invasion and metastasis. Proteases released from macrophages foster tissue invasion.
6. Evasion of immune destruction, A variety of soluble factors released by macrophages contribute to an immunosuppressive tumor microenvironment.

The end

Questions