

Neoplasia 5

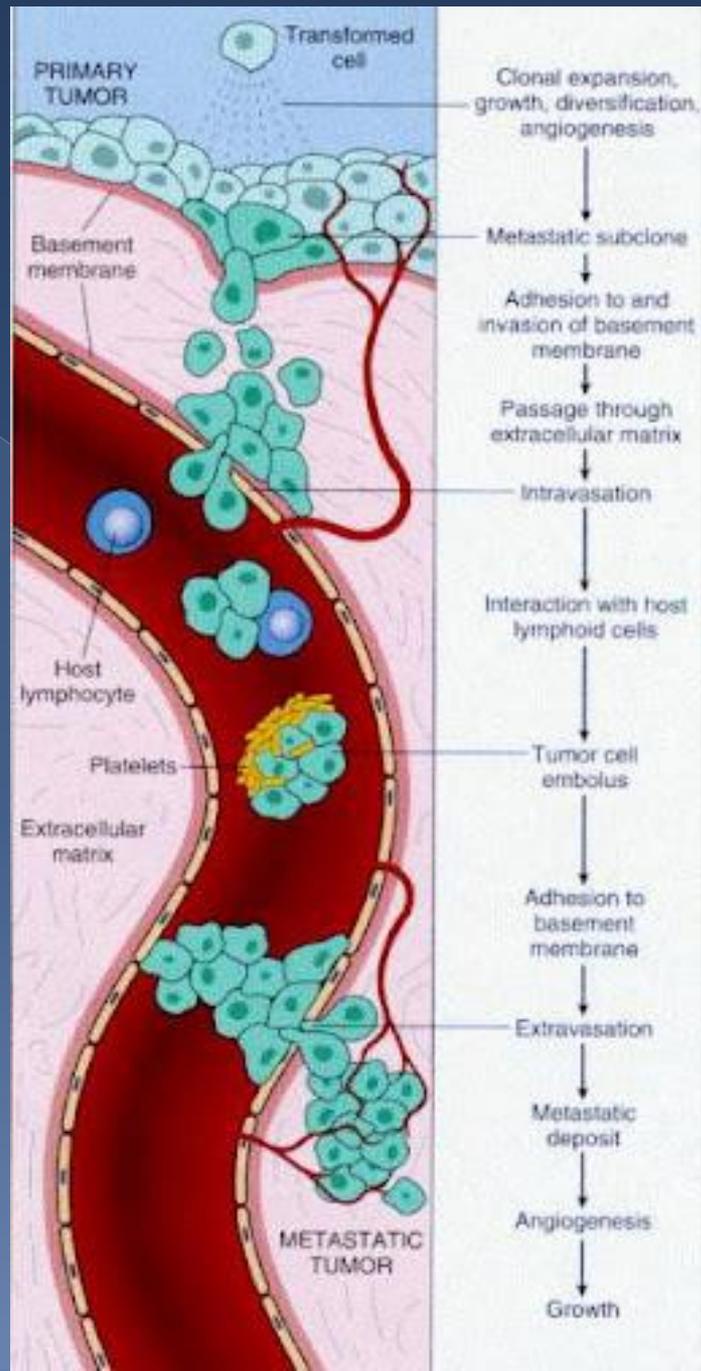
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2-1-2022

VII. Invasion and Metastasis

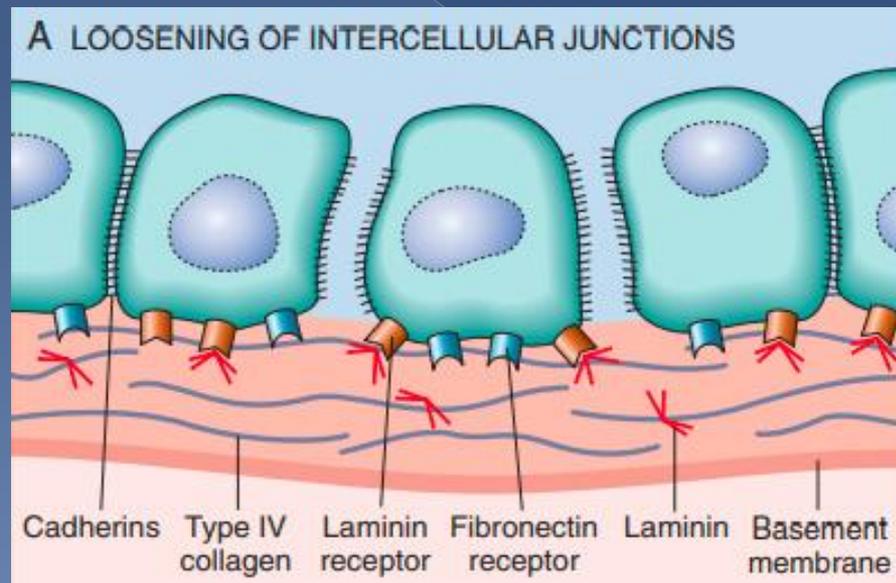
- Invasion, and metastasis, the major causes of cancer related morbidity and mortality, result from complex interactions involving cancer cells, stromal cells, and the extracellular matrix (ECM).

- the metastatic cascade can be subdivided into two phases:
- (1) invasion of ECM
- (2) vascular dissemination and homing of tumor cells.

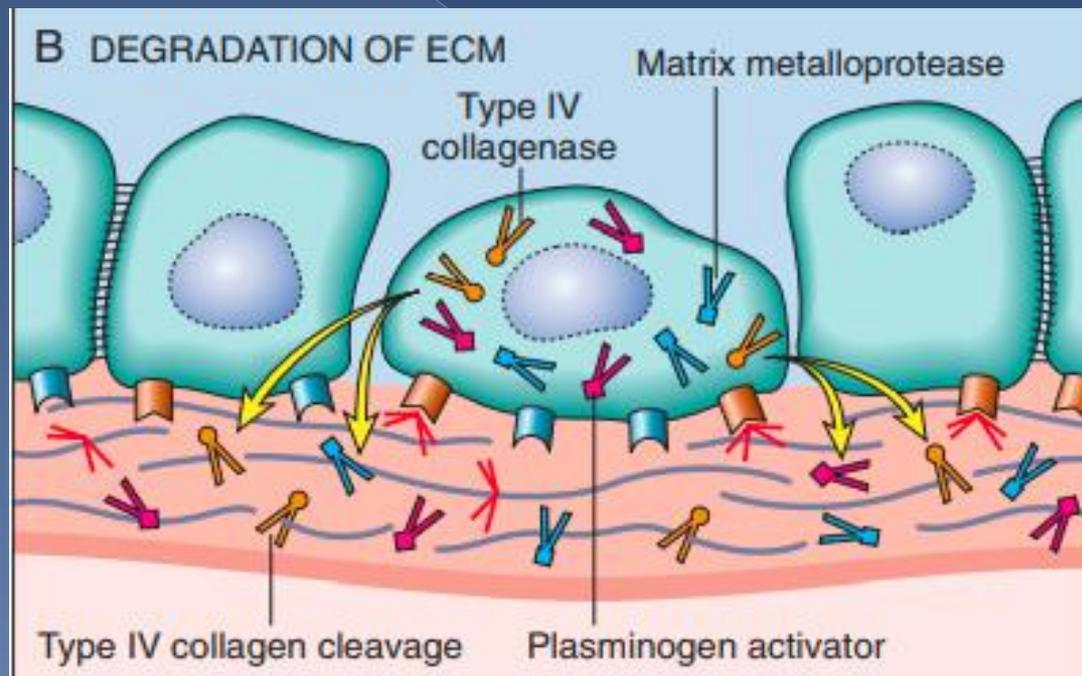


I. Invasion of Extracellular Matrix

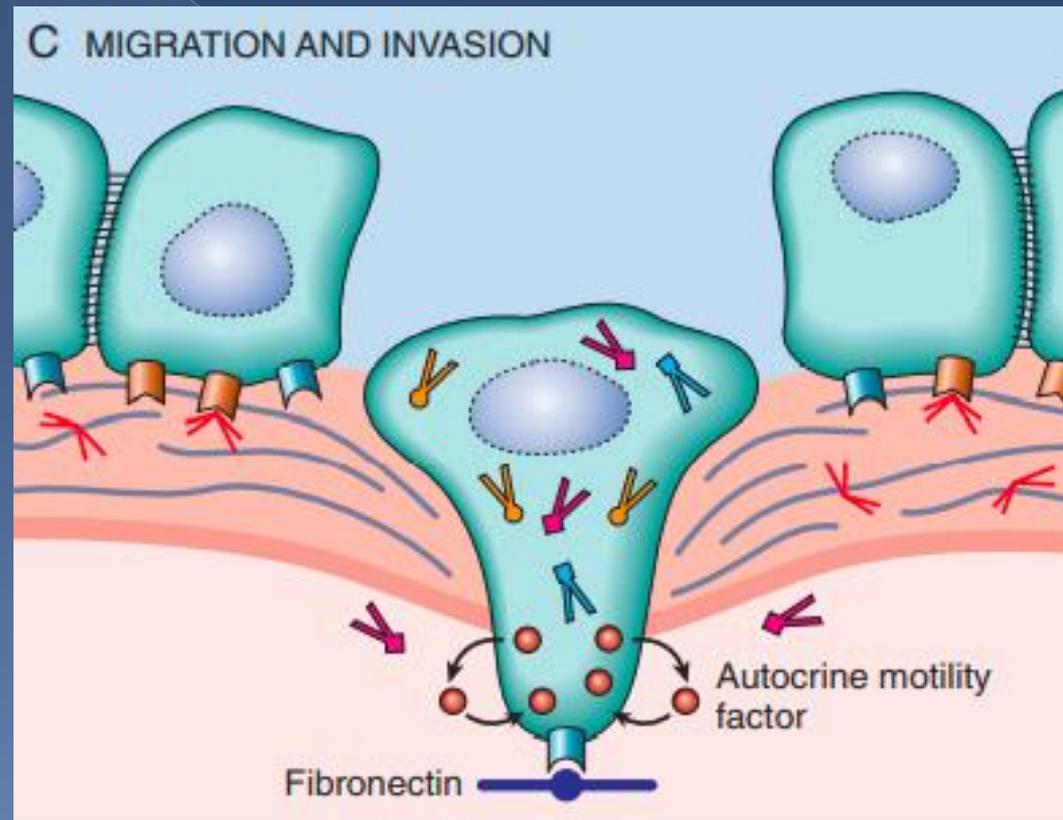
- Invasion of the ECM initiates the metastatic cascade and is an active process that can be resolved into several sequential steps:
- . Loosening of intercellular connections between tumor cells



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



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



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.

- 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,

IIIIV. 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
 - that express factors that actively suppress host immunity.

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

- ⦿ Individuals may have defects in three types of DNA repair systems:
- ⦿ mismatch repair.
- ⦿ nucleotide excision repair.
- ⦿ recombination repair

1. Hereditary Nonpolyposis Colon Cancer 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.
- characterized by hypersensitivity to DNA-damaging agents.

familial breast cancer

- Caused by germ line mutations in two genes, BRCA1 and BRCA2.
- 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.

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.