Pathology

Subject :

Lec no : lec-26-

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وَقُل رَّبِّ زِدْنِي عِلْمًا

3. Altered cellular metabolism

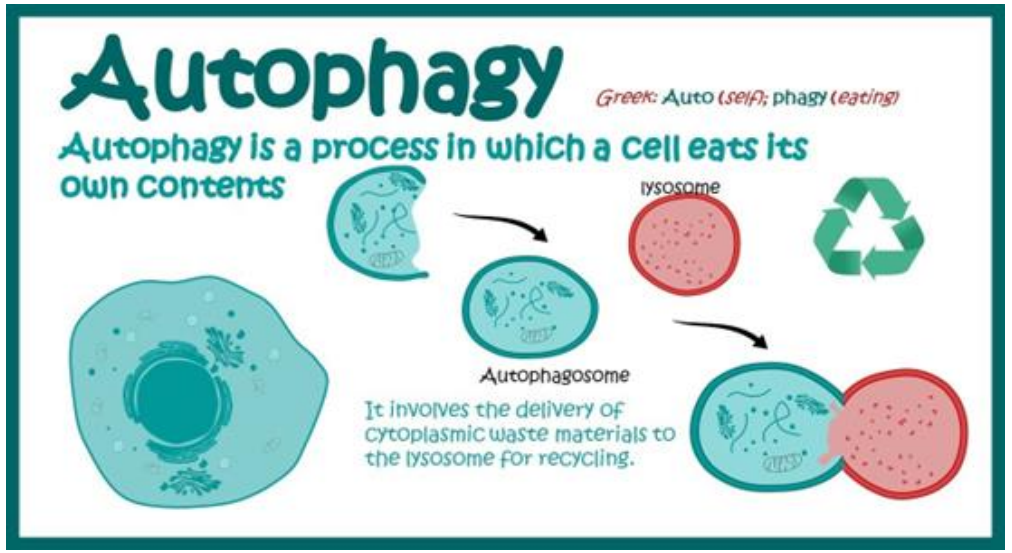
AUTOPHAGY:

- A state of severe nutrient deficiency in which cells arrest their growth and cannibalize their own organelles, proteins, and membranes (into lysosomes) as carbon sources for energy production.

-Cancer cells may accumulate mutations avoiding autophagy OR alter the process making it inefficient.

Result: Prolonged cell life!,

Cancer cells aim to avoid autophagy



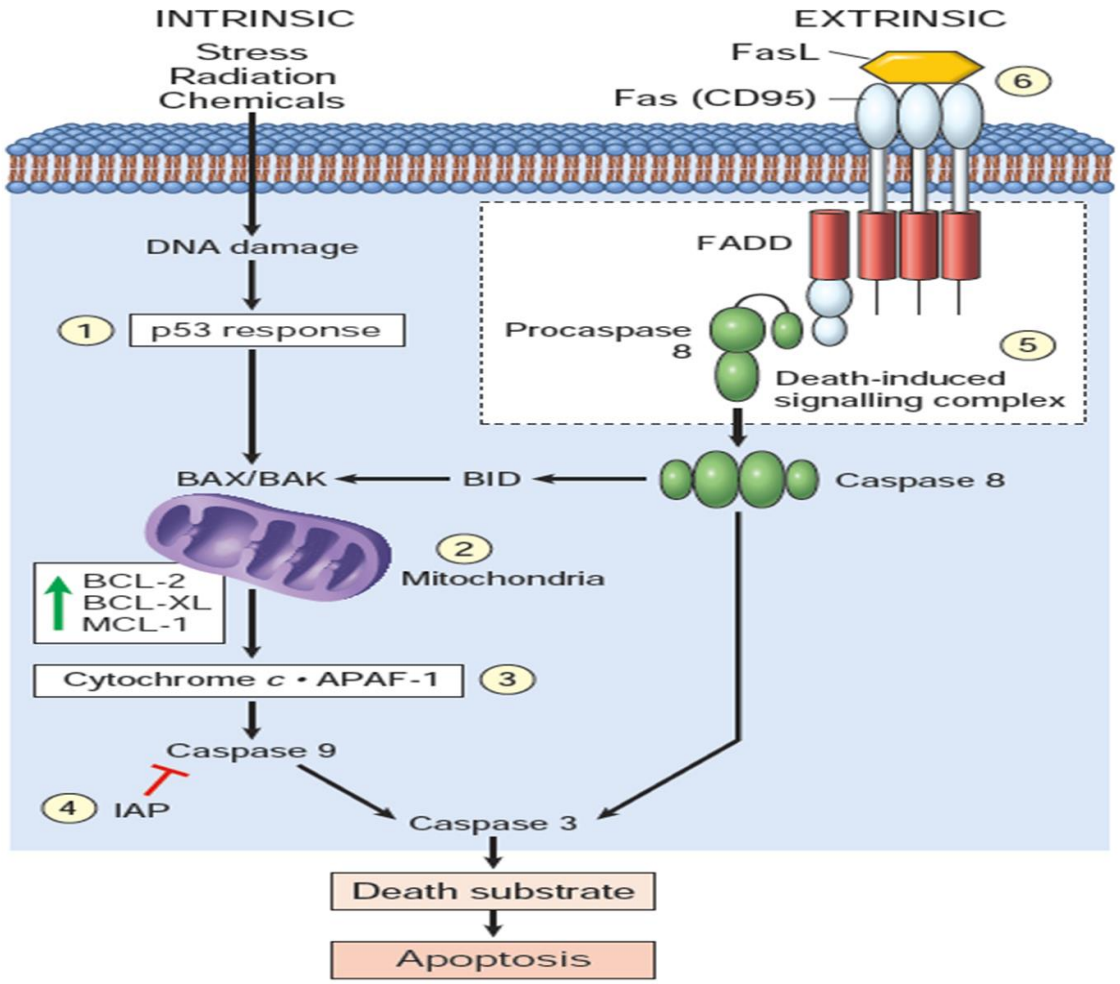
4- Evasion of apoptosis:

BCL-2 Family:

BAX, BAK : Pro-apoptotic

BCL-2 , BCL-XL, MCL1: Anti-apoptotic

BH3-only proteins regulate the balance



- Cancer cells are subject to several intrinsic stresses that can initiate apoptosis, particularly DNA damage.

- Tumor cells frequently contain mutations in genes that regulate apoptosis, making the cells **resistant to cell death.**

Apoptosis:

Extrinsic pathway: - Some tumors have **↓levels of CD95** → ↓ Apoptosis

Intrinsic pathway (*mitochondrial pathway):*

1. **loss of p53 function**, either by way of TP53 mutations (A) or overexpression MDM2. (B)
2. **overexpression of anti-apoptotic members of the BCL2** family, which protect cells from the action of the pro-apoptotic members of the BCL2 family.

* الخلايا السرطانية لا تدخل بمرحلة الشيخوخة وذلك بسبب احتوائها انزيم Telomerase

5.Limitless replicative potential (immortality):

- Most normal cells have a capacity of at most 70 doublings. Thereafter, the cells lose the ability to divide and enter replicative senescence due to the progressive shortening of telomeres at the ends of chromosomes.

بعدها تدخل مرحلة Senescence

Telomeres Are specialized structures at the end of chromosomes that are shortened after each division and may play a role in determining the life of individual cells.

- Shortening is prevented by TELOMERASE (Active in stem cells, not in somatic cells).

تمنع ال Senescence

- **Tumor cells, unlike normal cells, are capable of limitless replication.**
- **In many cancers, telomerase is reactivated.**

6- Sustained Angiogenesis :

- Tumors remain small or in situ (< 1-2 mm,Diameter) without angiogenesis.

Importance of angiogenesis

1- Supplies needed nutrients and oxygen.

2- Newly formed endothelial cells stimulate the growth of adjacent tumor cells by secreting growth factors.

-The resulting tumor vasculature is effective at delivering nutrients and removing wastes, it is not entirely normal; the vessels are leaky and dilated.

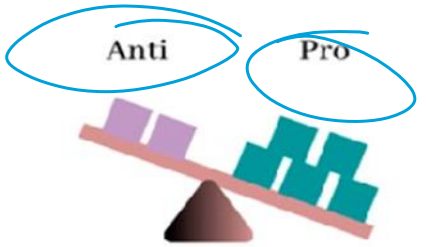
*In Cancer

the Angiogenic factors must be more than Angiogenic inhibitors

-The molecular basis of the angiogenic switch involves increased production of angiogenic factors and/ or loss of angiogenic inhibitors.

Angiogenesis ≈ Antiangiogenesis

Angiogenic Switch



- These factors may be produced by the tumor cells or by inflammatory cells (e.g., macrophages) or resident stromal cells (e.g. fibroblasts).

Angiogenic factors:

* يعرض الـ (HIF-α) عند حدوث الـ Hypoxia في الخلايا ← يفرز (VEGF) vascular endothelial growth factor ← vascular endothelial cell formation

1- Controlled by HYPOXIA which induces angiogenic factors by tumor cells ➡ Hypoxia-Inducible Factor **(HIF-1α)→VEGF** ⟶ stimulates the proliferation of endothelial cells and guides the growth of new vessels toward the tumor.

2- Gain-of-function mutations in *RAS* or *MYC* upregulate the production of VEGF:↑ VEGF

3- Proteases from tumor or stroma can release the basic angiogenic **FGF** stored in the ECM

❖ Anti- angiogenesis:

1. **Thrombospondin1**(TSP-1) induced by P53

- Thus, loss of p53 in tumor cells provides a more permissive environment for angiogenesis

2. **VHL** protein destroys HIF-1 α → No VEGF

- Germline mutation of VHL → von Hippel-Lindau Syndrome → hereditary renal CA, CNS hemangiomas.

3. Angiogenesis inhibitors:

Angiostatin, Endostatin, Vasculostatin from stromal cells in ECM.

↑ vascular density = Poor prognosis

Hall marks of Cancer

7- Ability to invade & metastasize:

the most important factor to differentiate between benign & malignant tumors: invasion & metastasize

-Tumors may generate clones and accumulate mutations, leading increased rate of growth, Invasion, Metastases …

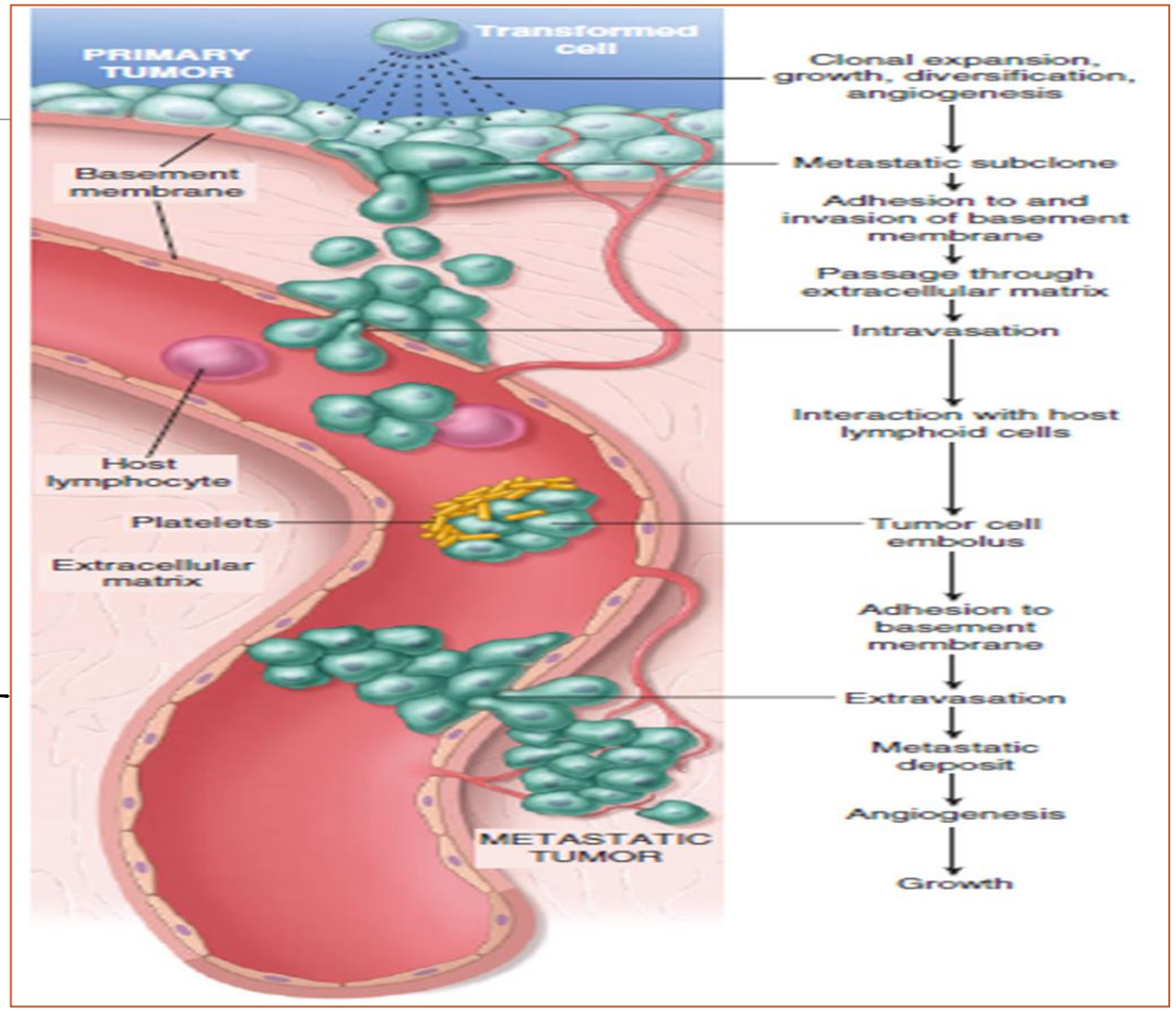
Metastasis occurs in two phases:

1- Invasion of extracellular matrix → like basement membrane

- Composed of collagens, glycoproteins & proteoglycans.

2- Vascular dissemination and homing of tumor cells

تروح لمكان اخر بعيدًا عن primary site of origin



1- Mechanism Of Invasion Of ECM:

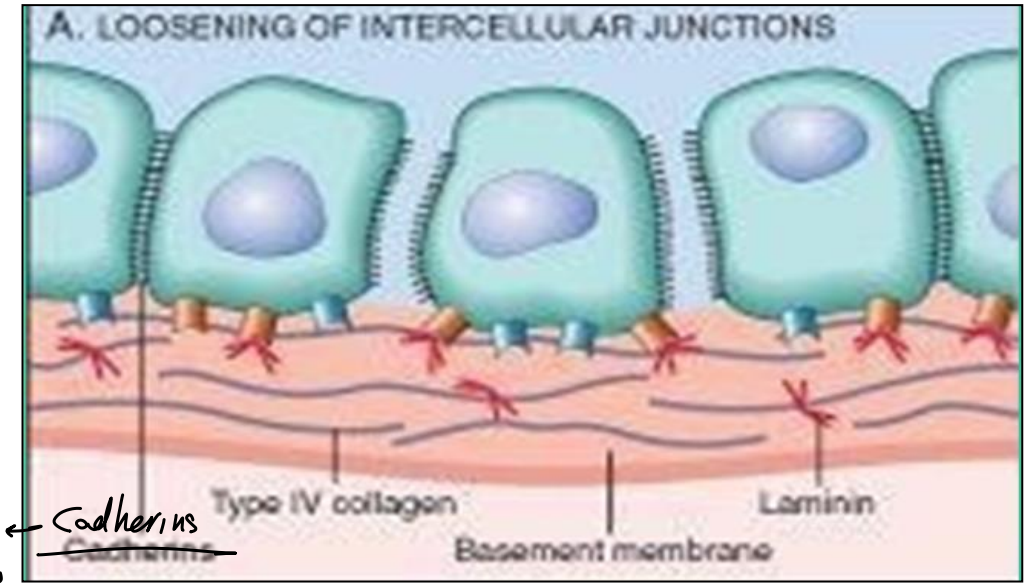
1- Loosening of intercellular connections between tumor cells and Detachment:

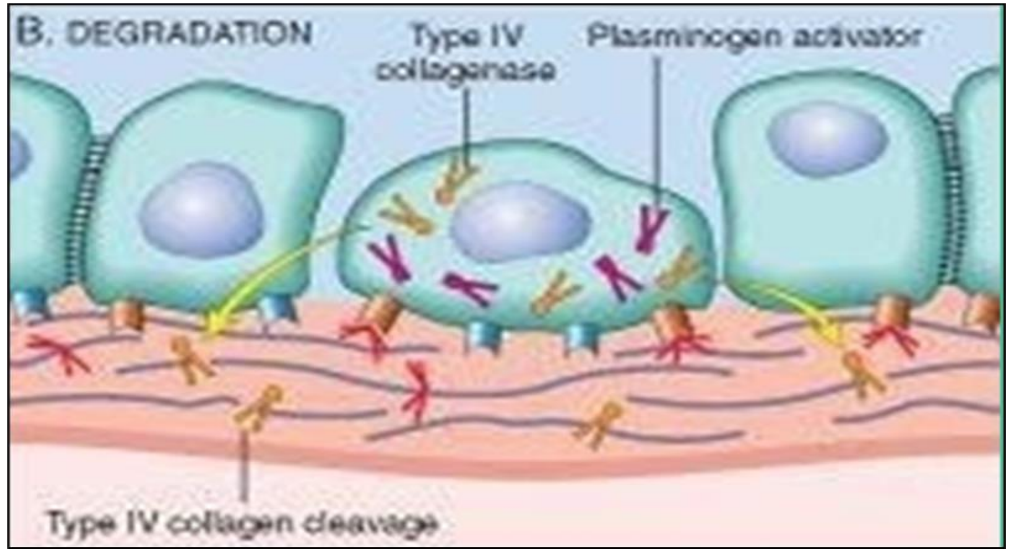
- Inactivation of E-Cadherin OR activation of β catenin→ detachment of cells.

2- Degradation of ECM by proteases:

e.g. Matrix Metalloproteinase (MMPs), Cathepsin D, Type IV collagenase

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



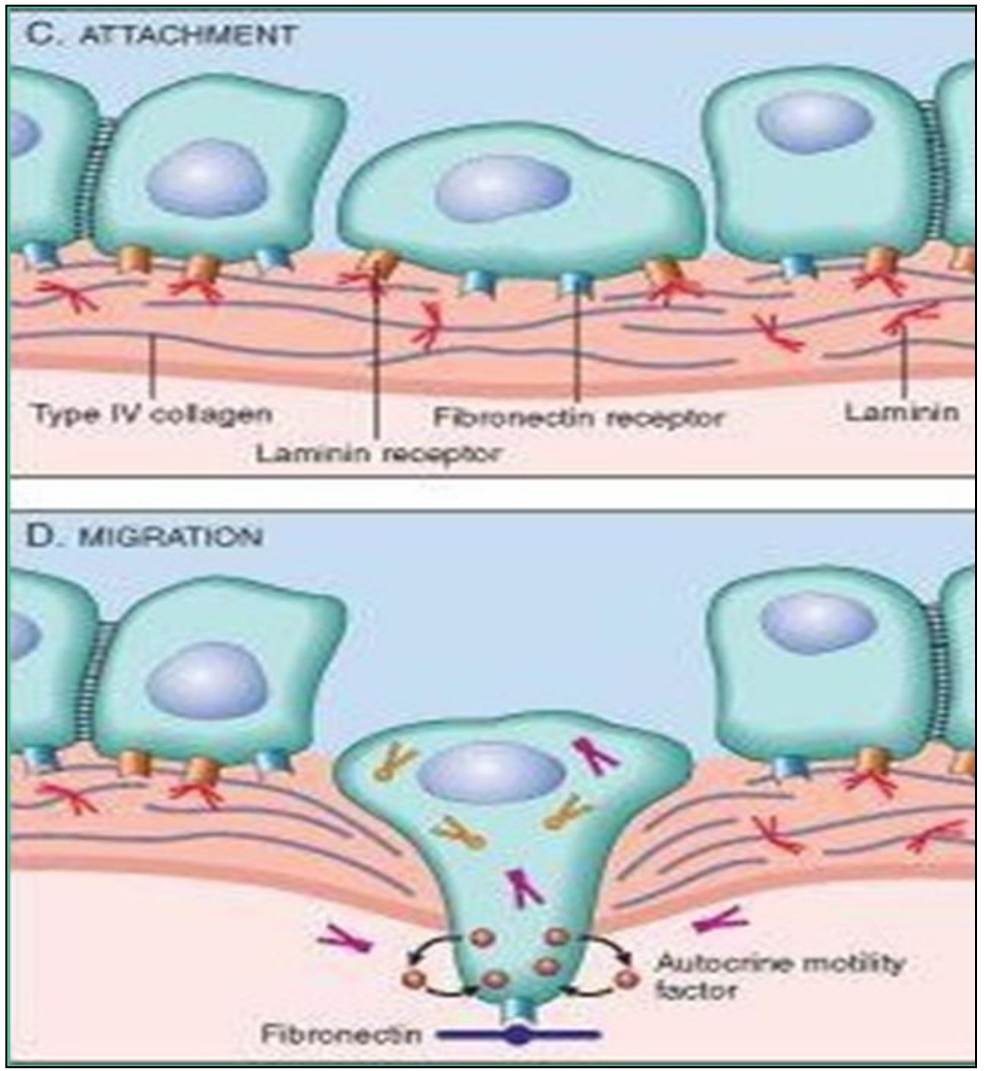


3- Attachment of tumor cells to matrix components

4- Migration of tumor cells (*Locomotion)*:

-Propelling tumor cells through the degraded basement membranes and zones of matrix

- Such movement seems to be directed by
  - Tumor-derived cytokines
  - Motility factor from Stromal cell



Blood vessels الانتشار عن طريق

2- Vascular dissemination:

1- Invasion of the circulation:

Adhesion to endothelium→ retraction of endothelium → vessel

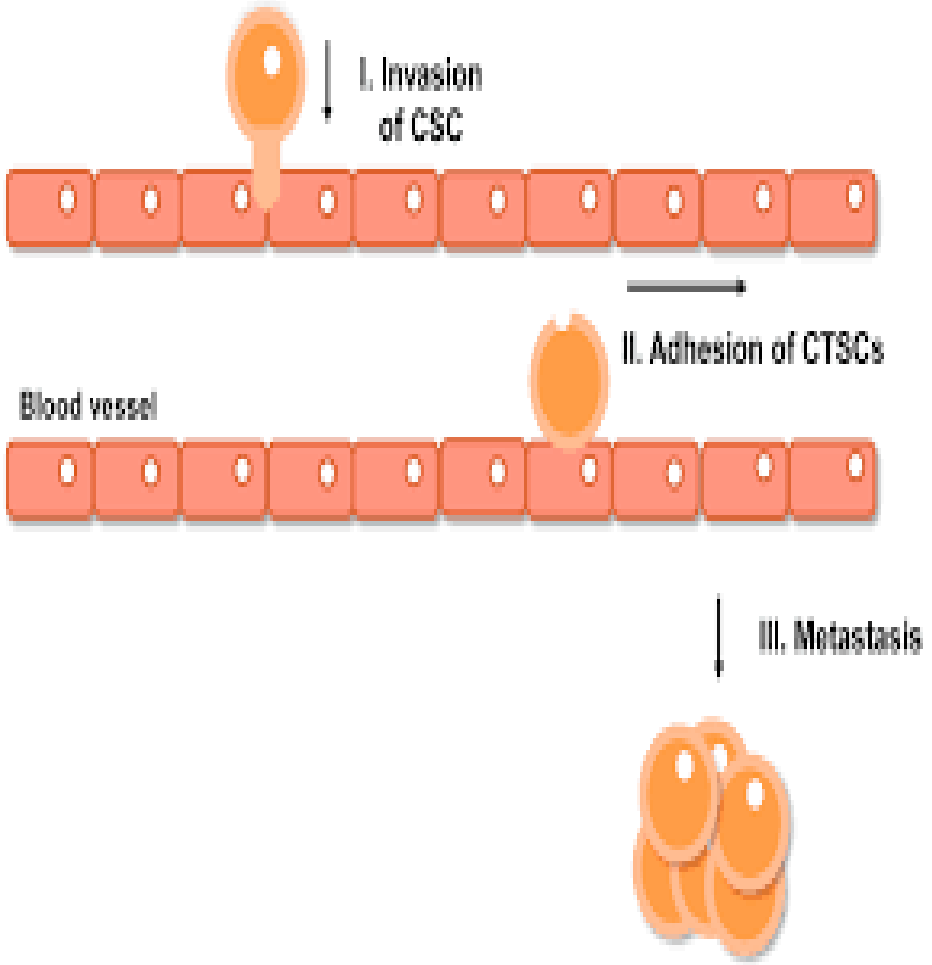
نفتح لدخول الخلية (space)

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

* Some tumors escape the immunity through thrombus & embolus

3- Escape from circulation:

Adhesion to endothelium→ retraction of endothelium → escape to tissue



What influences site of metastases ?

- **Anatomical Location and vascular drainage of the primary tumor**
- Complimentary adhesion molecule between tumor cells & target organs
- Chemoattractants liberated by target organs
- Protease inhibitors present in certain tissues

EXAMPLES OF TROPISM (HOMING)

1. Lung Carcinoma → Adrenals & Brain
2. Neuroblastoma → Liver & Bone

- Less common sites of metastases: muscle, skin, thyroid, heart …etc.

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

8. Evasion of Immune Surveillance

TUMOR IMMUNITY: Host Defense Against Tumors:

-Normal immunity present to protect against the development of tumors
-Tumors have ANTIGENS counteracted by ANTIBODIES in the body

Evidence? عن الأشخاص المصابين بالسرطان { T cells, specific antibodies } وجود الدليل على ذلك ← reactions against antigens on the surface of the tumor cells تفعل (antibodies) عن طريق

- The direct demonstration of tumor-specific T cells and antibodies in patients
- When there is no immunity (immunosuppressed patients) → More Cancers
- Patients with congenital **immune deficiency** have **↑risk of cancer**

حقيقي

Host defenses

*انواع الخلايا أو المواد التي تقوم بعملية استقاء مناعية ضد السرطانات

T lymphocytes

1- CTLs (CD8+ T-Cells)

CD4+ (T-helper)

2- NK cells

3- T helper cells

4- Macrophages

5- Humoral (Antibodies) Lymphocytes type-B تتحول الى

Types of tumor antigens:

1- Products of mutant oncogenes & tumor suppressor genes

2- Mutant proteins in chemical and radiation-induced tumors

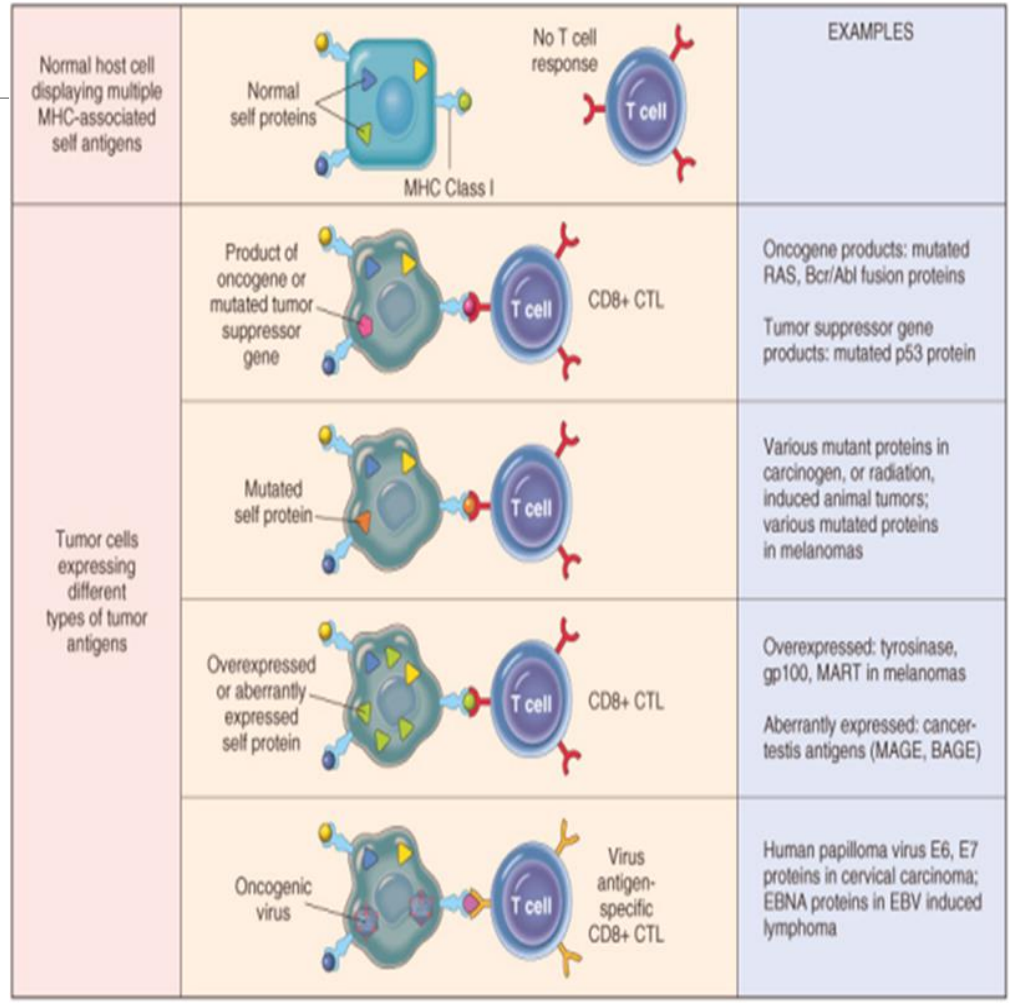
3- Overexpressed or aberrantly expressed cellular proteins.

e.g.: **Tyrosinase in melanoma**

4- Tumor AG produced by oncogenic viruses in HPV (E6,E7)

5- Oncofetal AG: CEA and α fetoprotein

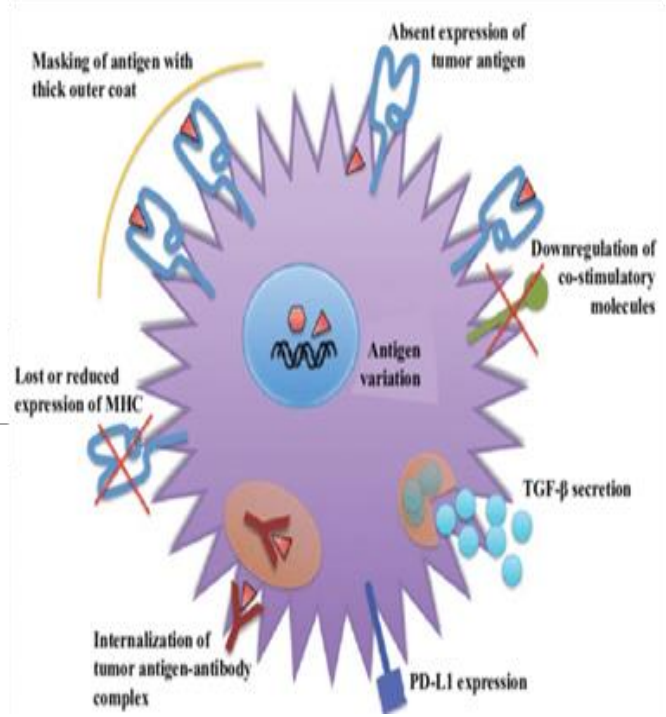
6- Several mucins MUC-1



How do tumor cells escape immune surveillance?

-In immunocompetent patients, tumors may avoid the immune system by :

- Selective outgrowth of antigen-**negative** variants.
- **Loss or reduced expression** of MHC molecules on tumor cell surface
- **Immunosuppression** mediated by expression of certain factors (e.g. Pd-1 ligands) by the tumor cells.
- **Antigen masking**
- **Downregulation of co-stimulatory molecules** (sensitization of T- cells requires costimulatory molecules).



Genomic Instability as an Enabler of Malignancy:

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

- Includes:

- **Mismatch repair**
- **Nucleotide excision repair**
- **Recombination repair**

1- Mismatch repair genes:

- These repair errors in the pairing of nucleotides during cell division (Spell Checkers) e.g. G+T instead of A+T.

- Defective **in (HNPCC – Hereditary Nonpolyposis Colonic Ca. syndrome):**

  - This syndrome accounts for 2-4% of all **colonic ca, AD.**

- Carcinomas of the colon affecting predominantly the cecum and proximal colon (right colon)

- A characteristic finding in the genome of patients with mismatch repair defects is microsatellite instability (MSI).

2- Nucleotide excision repair genes

- **Defective in Xeroderma Pigmentosum:**
  - Autosomal recessive disorder.
  - Increased risk for cancers arising in sun-exposed skin.

-UV rays in sunlight cause cross-linking of pyrimidine residues. The nucleotide excision repair system repairs such DNA damage.

- Several proteins are involved in nucleotide excision repair, and the inherited loss of any one of these can give rise to xeroderma pigmentosum.

3. DNA Repair by Homologous Recombination:

- A group of AR disorders comprising **Bloom syndrome, ataxia-telangiectasia, and Fanconi anemia** is characterized by hypersensitivity to DNA-damaging agents.

Theses have defects in DNA Repair by Homologous Recombination

BRCA-1 & BRCA-2:

- Cells with a defective version of these genes develop chromosomal breaks and severe aneuploidy. Both genes seem to function, at least in part, in the **homologous recombination DNA repair pathway**

- **50% of familial breast cancers & ovarian CA**

- Rarely inactivated in sporadic cases.