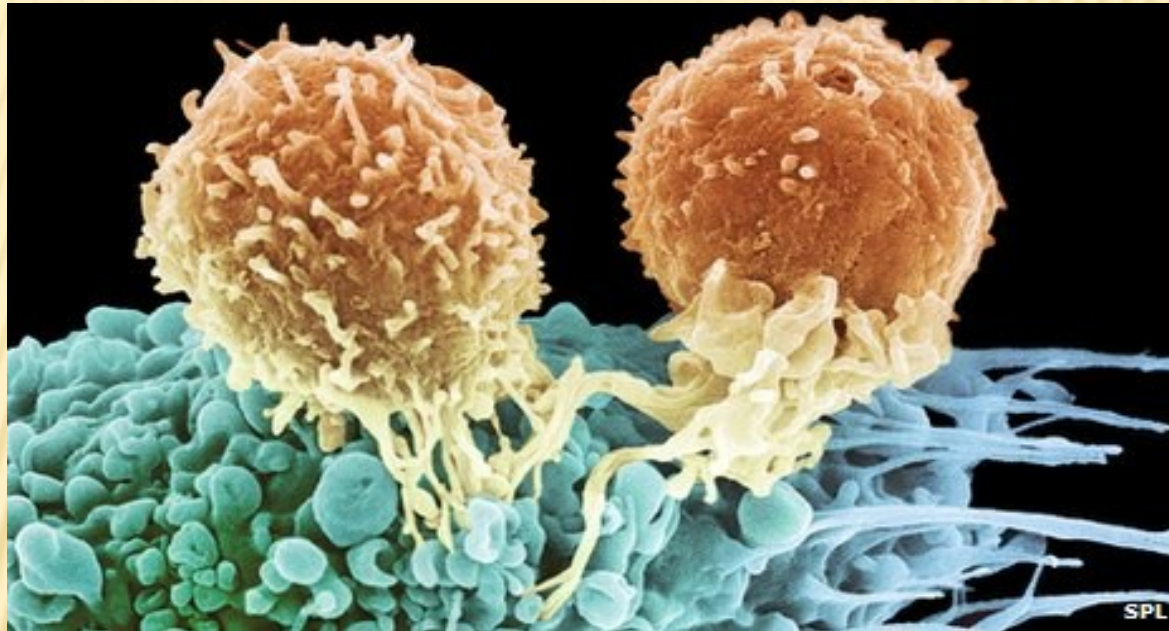


CANCER IMMUNOPATHOLOGY



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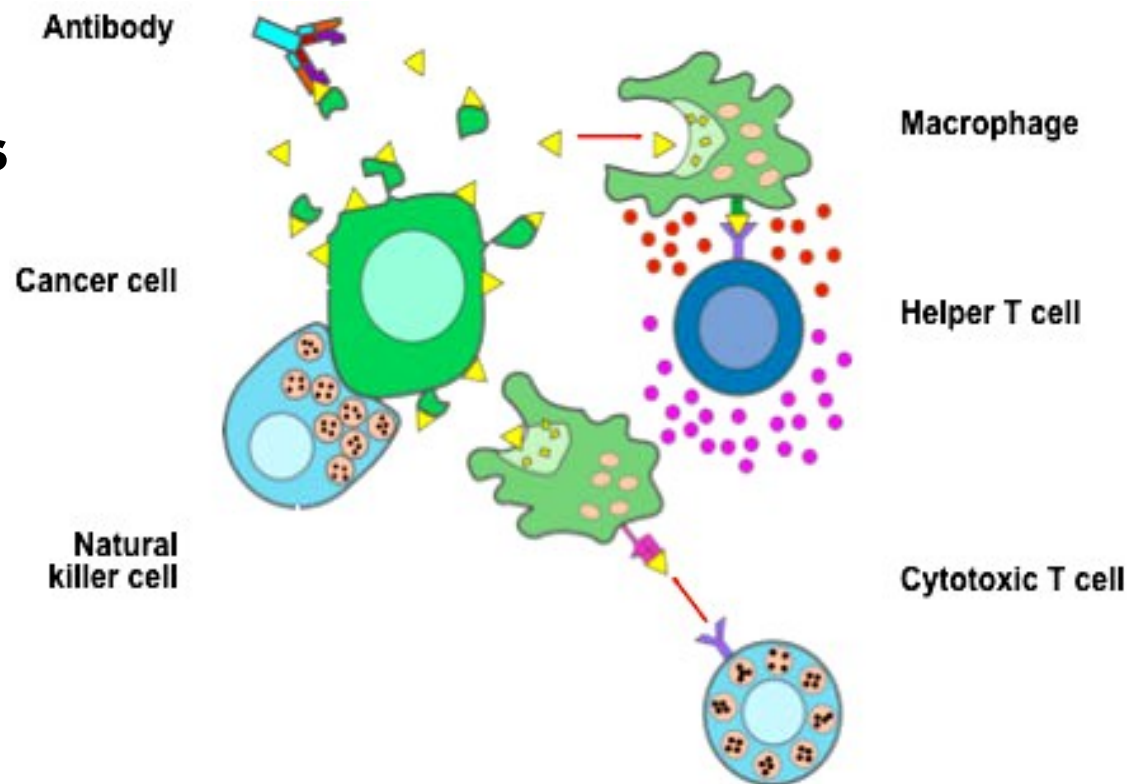
INTRODUCTION

Tumor: cells that continue to replicate, fail to differentiate into specialized cells, and become immortal.

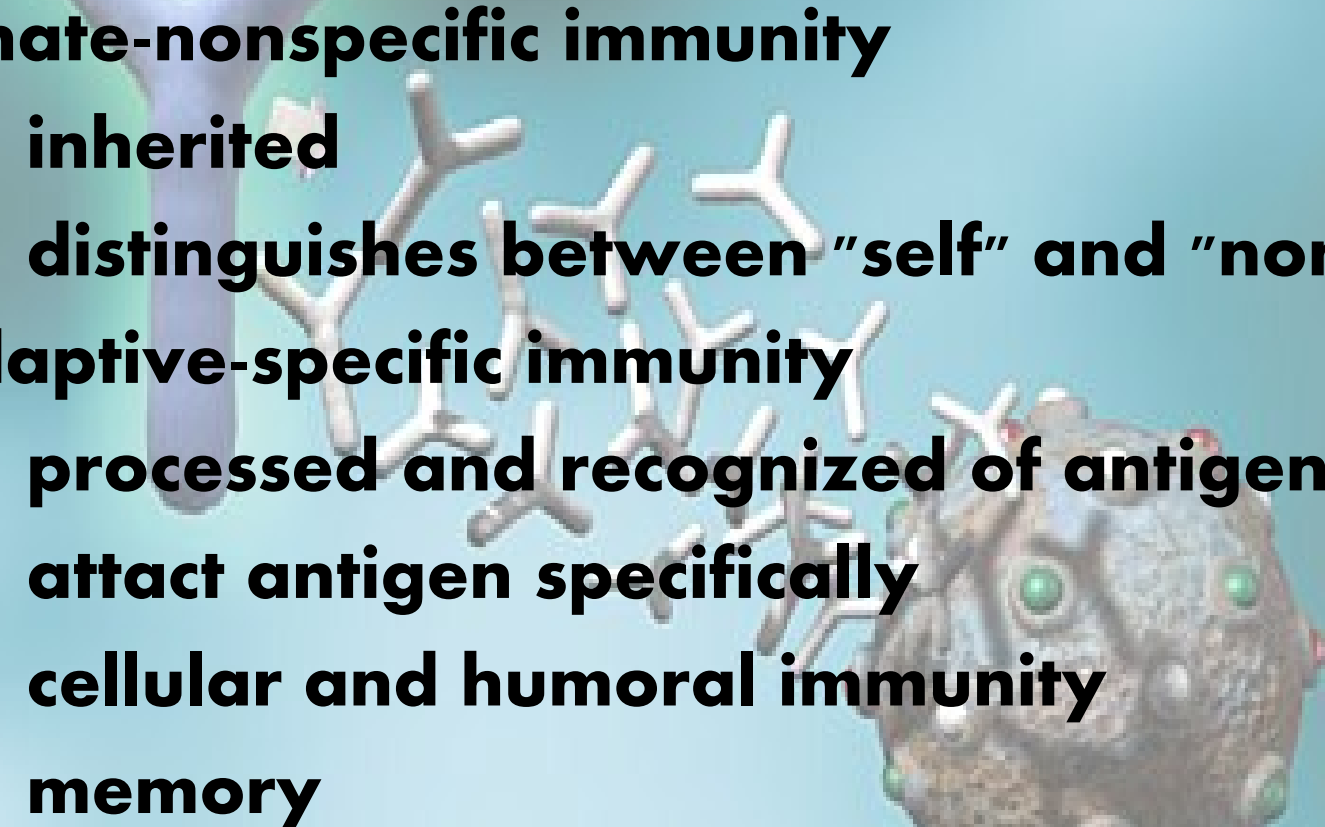
- **Malignant: A tumor that grows indefinitely and spreads → cancer**
- **Benign: A tumor that is not capable of metastasis**

Body's defenses against cancer


- When normal cells turn into cancer cells, surface antigens changes.
- Patrolling cells of the immune system provide continuing bodywide surveillance, spying out and eliminating the cells by:
 - cytotoxic T cells
 - natural killer cells
 - macrophages.

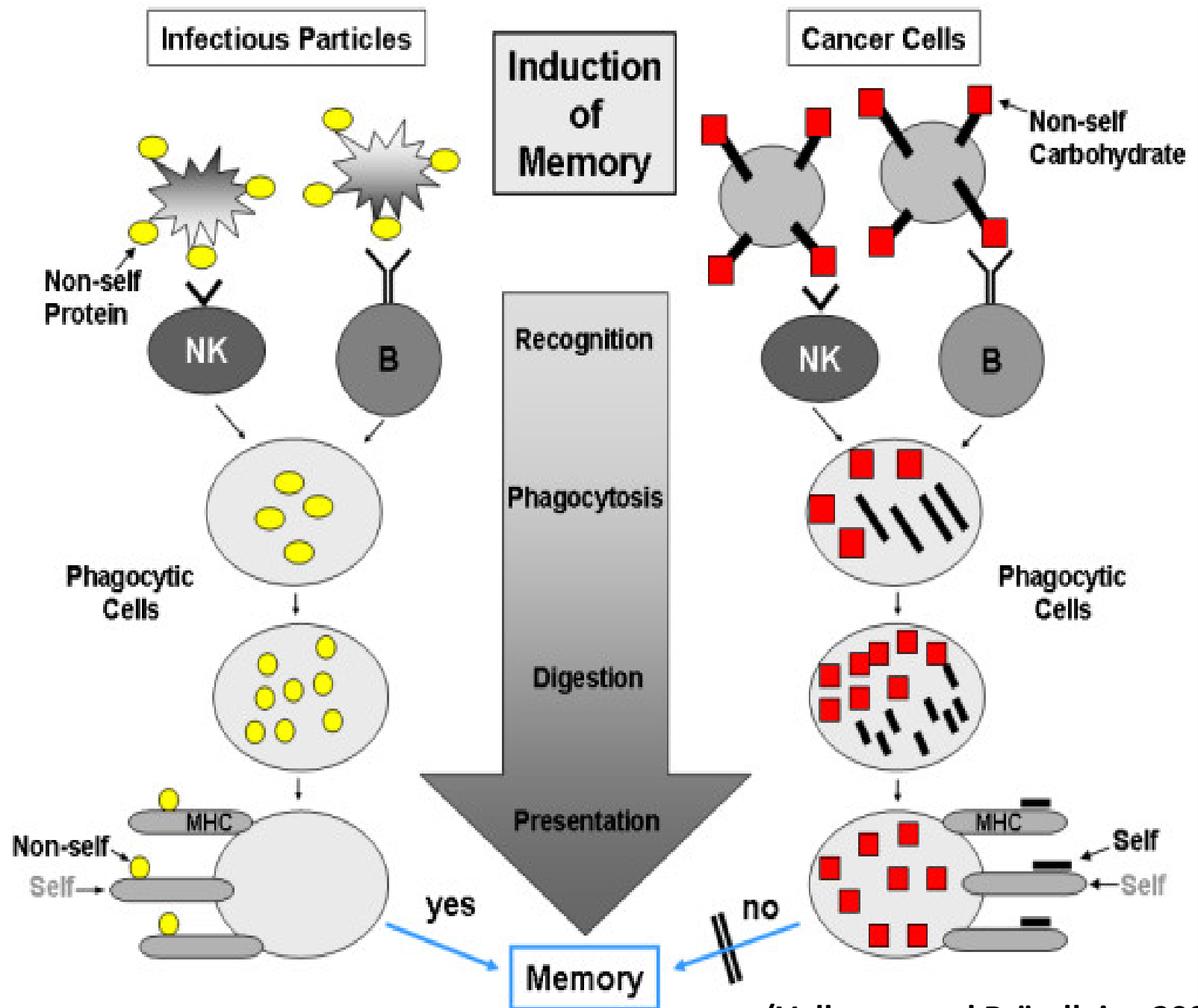


IMMUNE SYSTEM

- 
- **Innate-nonspecific immunity**
 - inherited
 - distinguishes between "self" and "non-self"
 - **Adaptive-specific immunity**
 - processed and recognized of antigen
 - attact antigen specifically
 - cellular and humoral immunity
 - memory

IMMUNE RESPONSE TO TUMOR CELLS

- The natural immunity → immune surveillance
 - NK cells recognizes and destroys all invasive/ change particles
 - Phagocytic cells clean and transport the garbage
 - Memory ?
- 
- Infectious particles (protein-epitope) → Th are stimulated → CTL and B cells are generated → memory
 - Cancer cells (carbo-epitope) → recognition fails
 - phagocytic cells cannot present carbohydrat structures
 - Peptides associated with carbohydrate structures are "self" structures → memory does not occur.



(Vollmers and Brändlein , 2007)

TUMOR CELLS KILLING

➤ Non-specific:

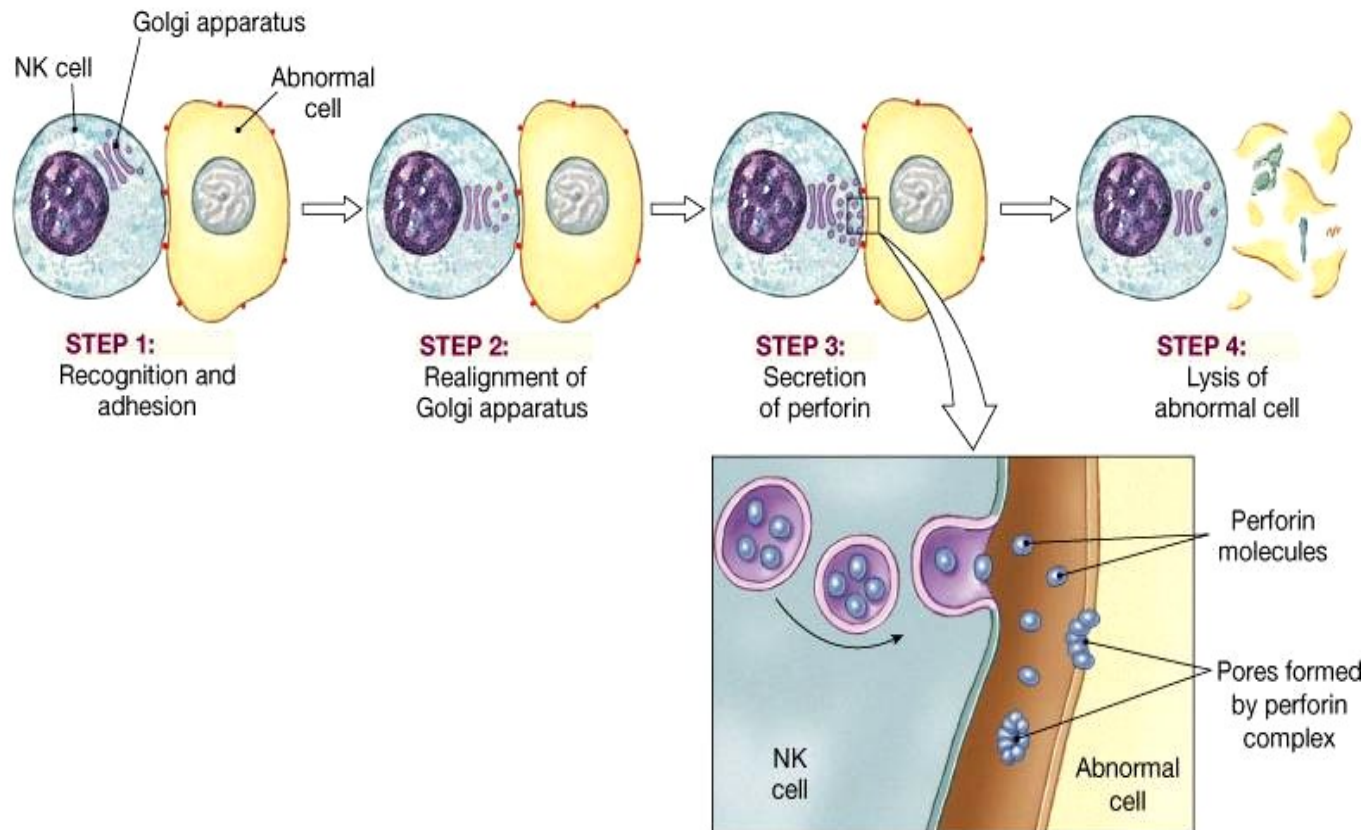
- NK cells
- $\gamma\delta$ T cells (NKG2D)
- Macrophages
- NK T cells

➤ Antigen-specific:

- Antibody (ADCC, opsinization)
- T cells (cytokines, Fas-L, perforin/granzyme)

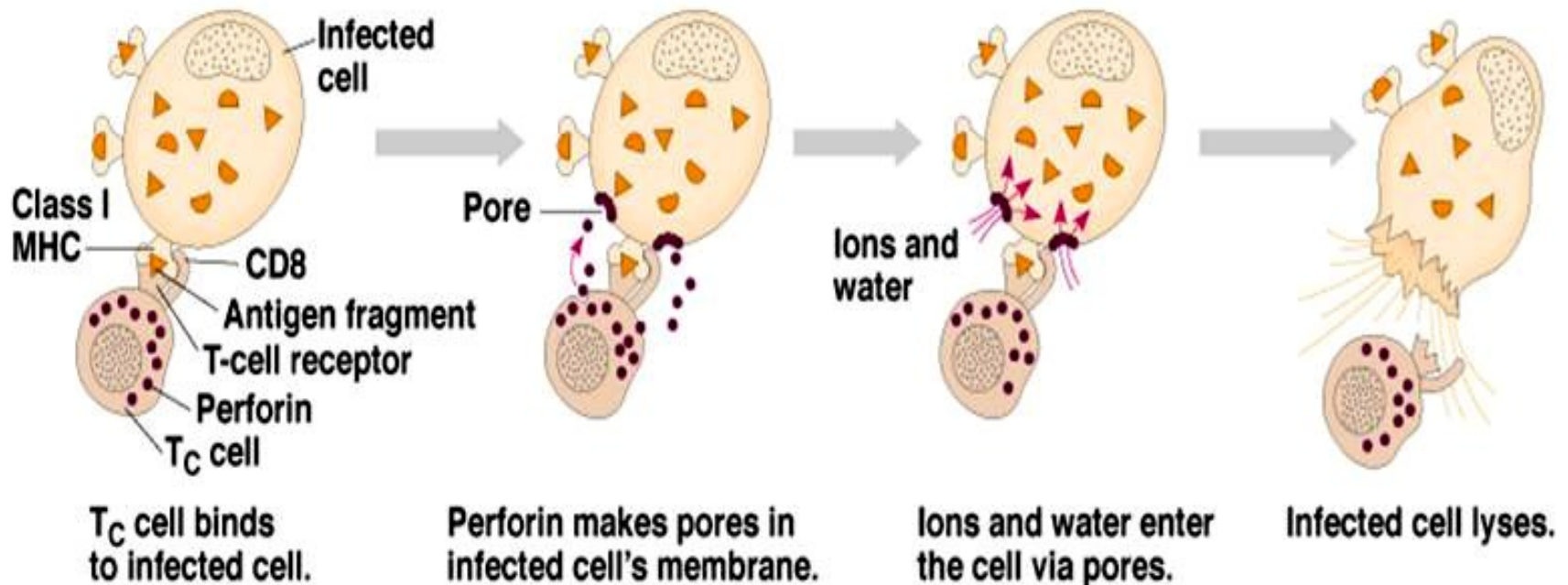
Natural Killer Cells

- Patrol the body and attack virus-infected / cancer cells
- Recognize cell surface markers on foreign cells
- Destroy cells with foreign antigens
- Rotation of the Golgi toward the target cell and production of perforins
- Release of perforins by exocytosis
- Interaction of perforins causing cell lysis+



Cytotoxic T (Tc) Cells

- Killer Ts or CD8
- Destroy target cells
- Recognize and kill all infected/cancer cells
- Release perforin → lysis of infected/cancer cells.
- Produce cytokines → phagocytosis and inflammation



CANCER IMMUNOSURVEILANCE

➤ **Past:**

- a host-protective function
- carried out by the adaptive immune system only at the earliest stages of cellular transformation

➤ **Now:**

- the broader term “cancer immunoediting”
- recognize the innate and adaptive immune system
- not only to protect the host from tumor development but also to sculpt, or edit, the immunogenicity of tumors that may eventually form.

CANCER IMMUNOEDITING (three “E”s)

1. Elimination phase

eradicates the developing tumor

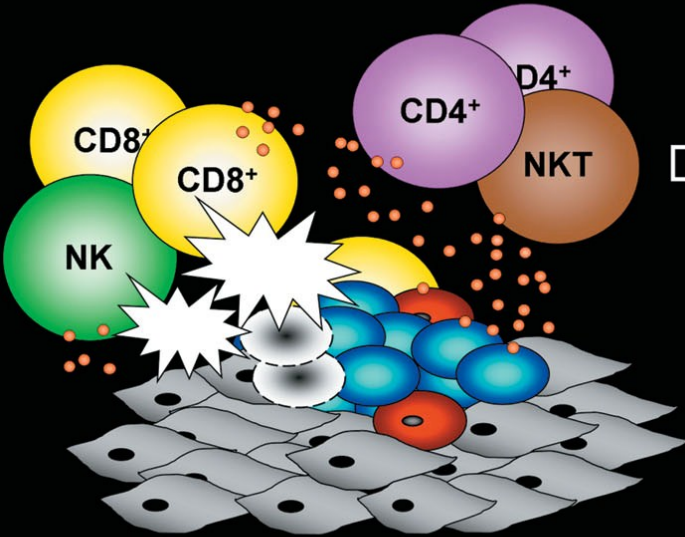
2. Equilibrium phase

- tumor bed containing many genetically unstable and mutating tumor cells
- many of the original tumor cell escape variants are destroyed
- new variants arise → resistance to immune attack.
- new population of tumor clones with reduced immunogenicity
- the longest of the three phases and may occur over a period of many years in humans

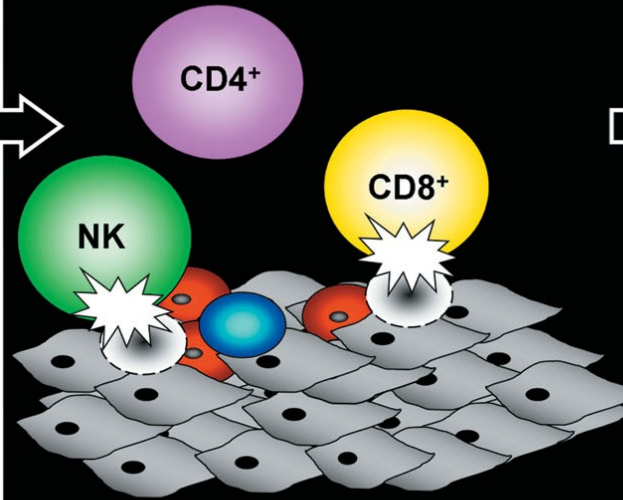
3. Escape phase

- tumor cell variants selected in the equilibrium phase now can grow in an immunologically intact environment
- tumor expand in an uncontrolled manner

Elimination

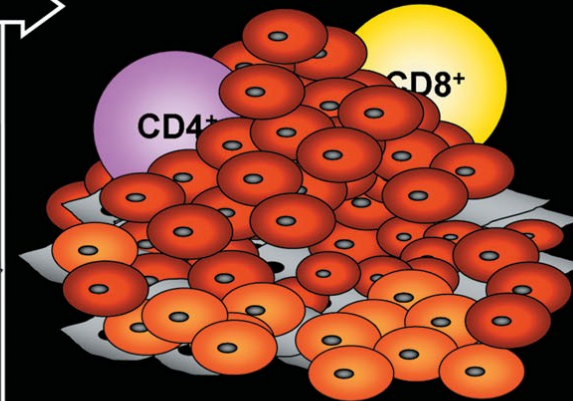


Equilibrium



Genetic instability/tumor heterogeneity

Escape

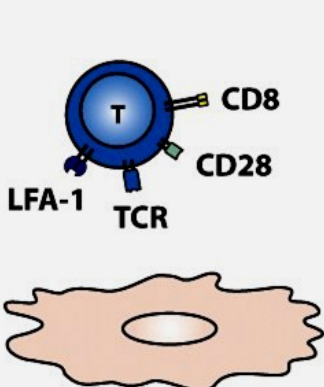
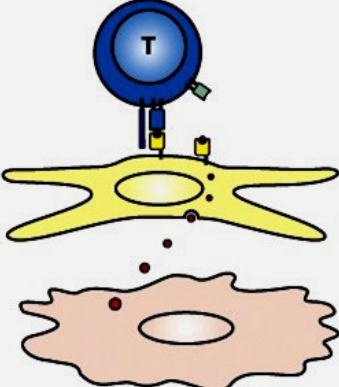
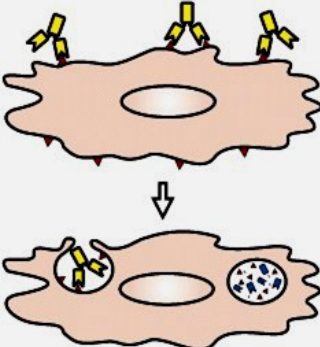
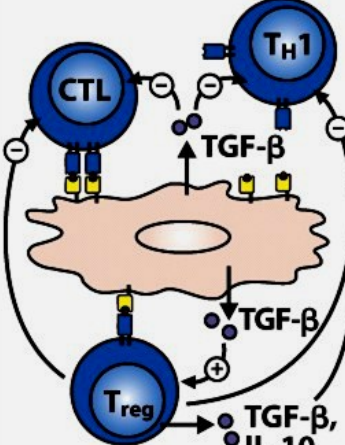
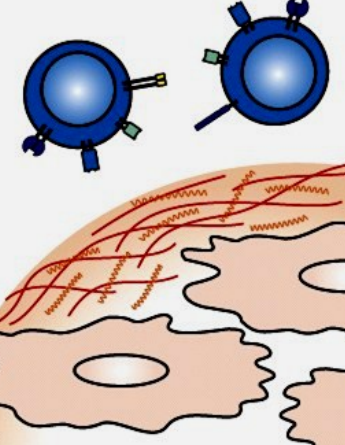


Immune selection

- developing tumor cells
- tumor cells variants
- additional tumor variants
- Underlying stroma and nontransformed cells

CANCER CELLS ESCAPE FROM IMMUNOSURVEILLANCE

- **Low immunogenicity**
- **Tumor cells as self antigen**
- **Antigenic modulation**
- **Tumor-induced immunosuppression**
- **Tumor-induced privileged site**

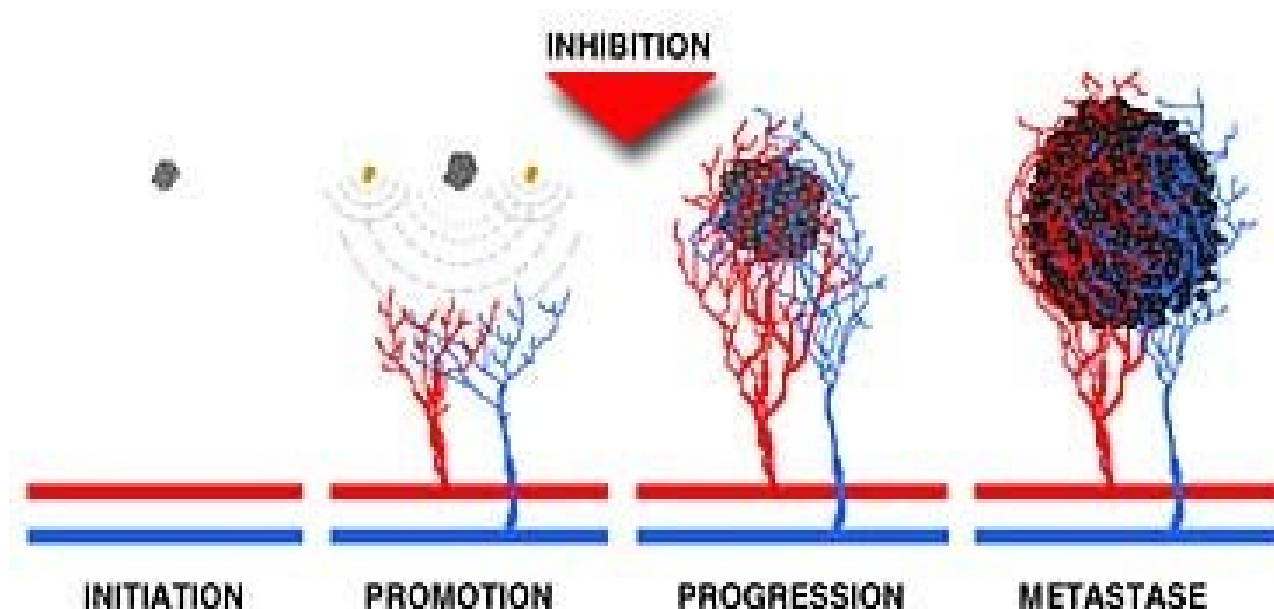
Low immunogenicity	Tumor treated as self antigen	Antigenic modulation	Tumor-induced immune suppression	Tumor-induced privileged site
<p>No peptide:MHC ligand No adhesion molecules No co-stimulatory molecules</p>	<p>Tumor antigens taken up and presented by APCs in absence of co-stimulation tolerize T cells</p>	<p>Antibody against tumor cell- surface antigens can induce endocytosis and degradation of the antigen. Immune selection of antigen-loss variants</p>	<p>Factors (e.g., TGF-β) secreted by tumor cells inhibit T cells directly. Induction of regulatory T cells by tumors</p>	<p>Factors secreted by tumor cells create a physical barrier to the immune system</p>
				

TUMOR ANTIGENS

- **Tumor-specific transplantation antigens (TSTA)**
 - unique to tumor cells, not expressed on normal cells
 - responsible for rejection of the tumor
- **Tumor associated transplantation antigens (TATA)**
 - expressed by tumor cells and normal cells
 - Tumour-associated developmental Ag (TADA)
 - Tumour-associated viral Ag (TAVA)
- **Tumor-associated developmental antigens or onco-fetal antigens**
 - alpha-fetoprotein (AFP)
 - carcino-embryonic antigen (CEA)
- Prostate-specific antigen (PSA)

Cancer angiogenesis

- New blood vessel development is an important process in cancerous growths
- Play a role in the dissemination of cancer leading to metastasis formation
- supplying nutrients and oxygen and removing waste products
- growth factors and cytokines can promote angiogenesis,
- most important is vascular endothelial growth factor (VEGF)



CANCER AND INFLAMMATION

➤ Inflammation can cause cancer

- Chronic infection (HPV/Hepatitis B and C virus) leads to cervical and hepatocellular carcinoma
- Intrinsic mechanisms of cells prevent unregulated proliferation or the accumulation of DNA mutations.
- Tumor suppressor pathways that mediate DNA repair, cell cycle arrest, and apoptosis

➤ Cancer can cause inflammation

- Pre-malignant tumors are “wound-like”
- First phase → body treats early tumors as wounds
- mast cells are responsible for providing MMP → biological active form of VEGF → stimulate the pro-tumorigenic angiogenic switch
- Early tumor → COX-2 is expressed by stromal cells
- In larger tumors → COX-2 is expressed by the dysplastic epithelium
- Later tumor growth → pro-inflammatory factors (MMPs) come under direct control by the tumors

EFFECT OF AGING AND STRESS TO CANCER

- **Cancer risk increases with age**
 - aging lymphocytes accumulate genetic errors
→ decrease effectiveness
 - thymus function declining with age → decrease in cell-mediated immune competence.

- **Stressful experience decrease immunological function → cancer**
 - The end result of chronically stressed → stimulatory signals to adrenal glands → stress hormones (cortisol and epinephrine)

STRESS HORMON

- Increase the production of free radicals → DNA damage and impaired immune function
- Increase inflammation through the production of pro-inflammatory cytokines → impair immune function and promote cancer growth
- Reduce the ability of abnormal cells to undergo apoptosis and DNA repair, important self-regulating anticancer mechanisms
- Stimulate the production of IGF-1, VEGF and other growth factors that can promote tumor cell growth

IMMUNOTHERAPY

- **Active Immunotherapy**

Stimulation of active host immune response to tumor

- **Passive Immunotherapy**

transfer of immune effectors

- **Antiangiogenesis**

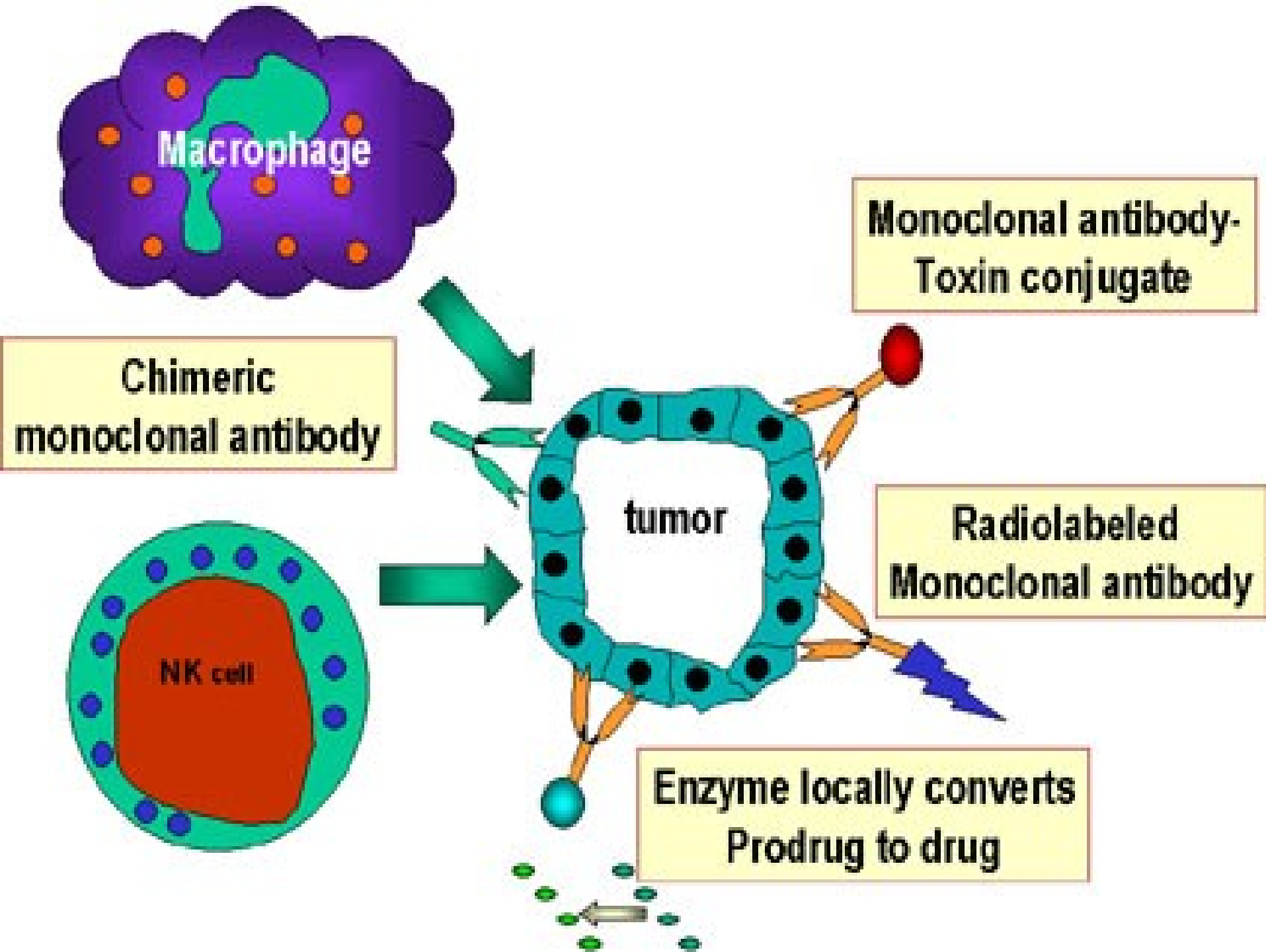
inhibiting angiogenesis can slow down or prevent the growth and spread of cancer cells in humans

1. **ACTIVE IMMUNOTHERAPY**

- Vaccination with tumor cells and tumor antigens (type 16 HPV, adenovirus, melanoma, plasmids dendritic cells and cytokine vaccines)
- Augmentation of host immunity to tumors with costimulators and cytokines (IL-2, IL-4, IFN- γ , GM-CSF)
- Blocking inhibitory pathways to promote tumor immunity (CTLA)
- Nonspecific stimulation of the immune system (BCG)

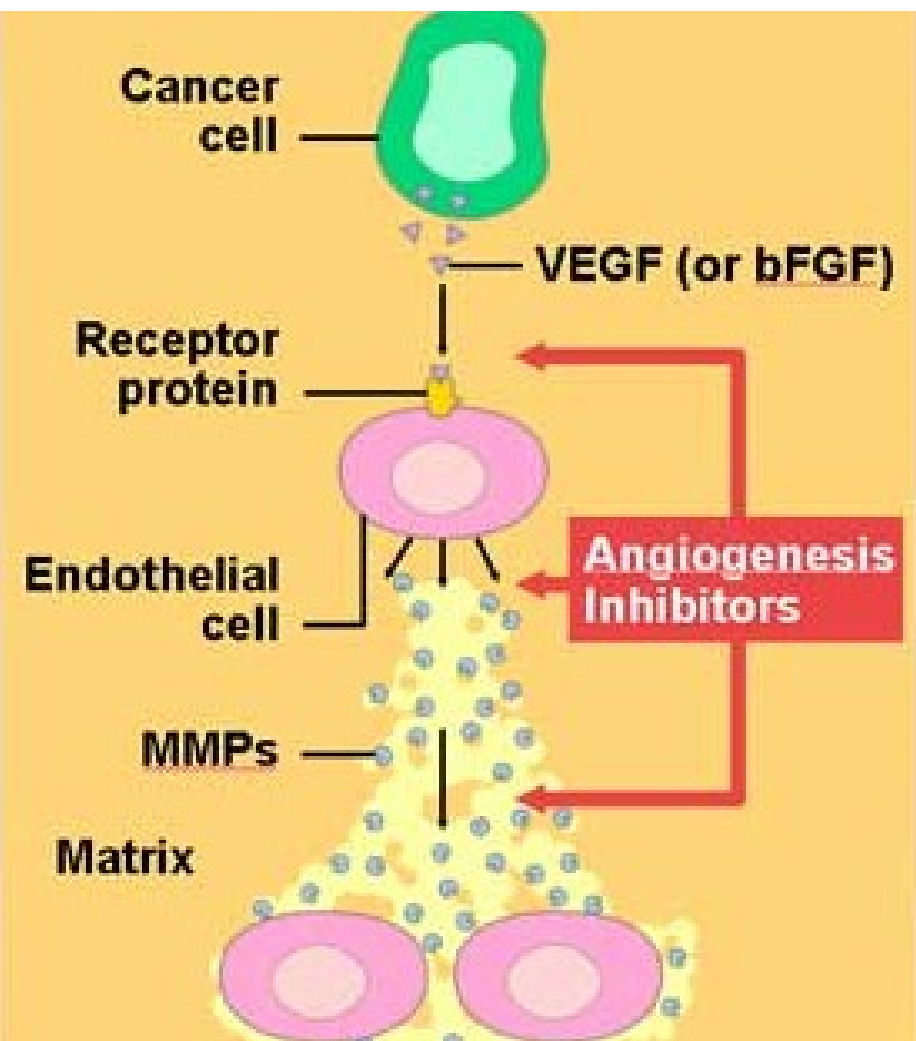
2. PASSIVE IMMUNOTHERAPY FOR TUMOR

- Antibodies against tumor cells
 - Monoclonal antibodies against specific tumor antigen (CD20/Her2/CD 33/VEGF)
 - Monoclonal antibodies attached with toxin or radioactive isotope
- Adoptive cellular therapy
 - Transfer of lymphocytes : lymphokine- activated killer (LAK) → IL-2 activated T and NK cells,
 - Tumor-infiltrating lymphocytes (TIL)
 - NK cells and dendritic cells

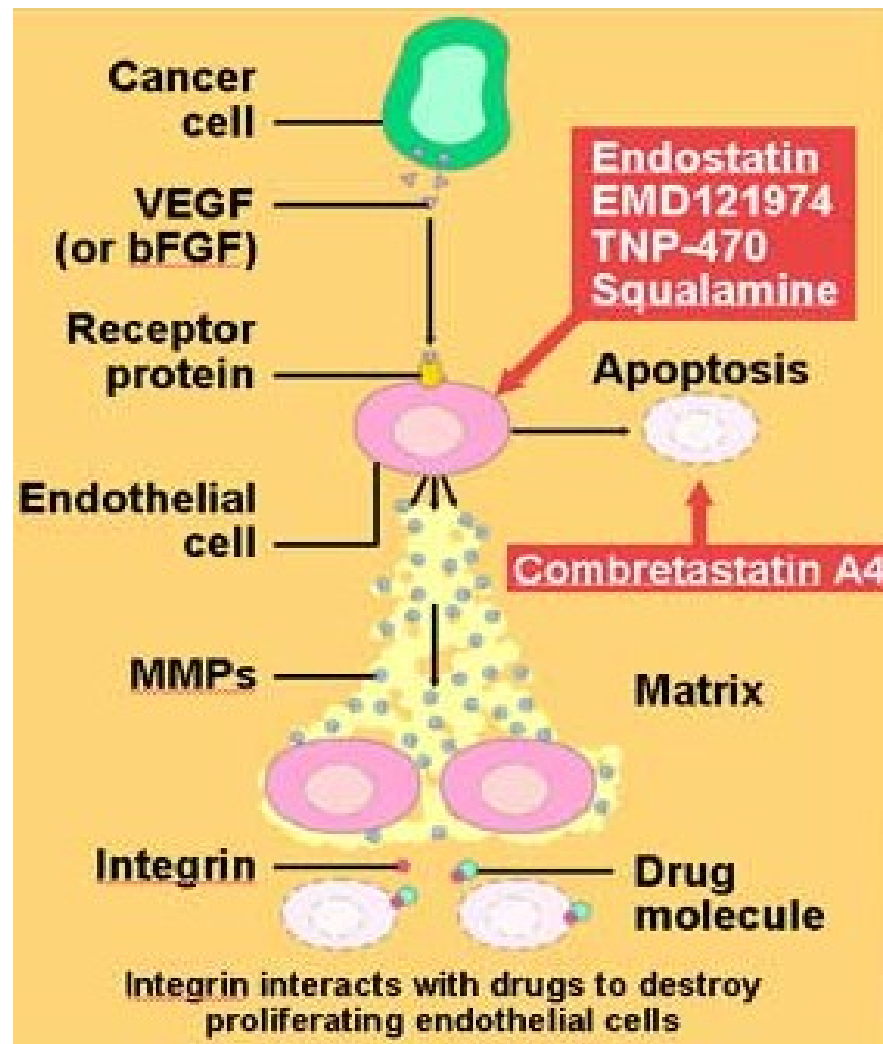


3. ANTIANGIOGENESIS

- Inhibiting endogenous angiogenic factors: bFGF (basic Fibroblast Growth Factor) and VEGF
- Inhibiting degradative enzymes (MMPs)
→ degradation of the basement membrane of blood vessels
- Inhibiting endothelial cell proliferation
- Inhibiting endothelial cell migration
- Inhibiting the activation and differentiation of endothelial cells



Angiogenesis inhibitors



Inhibit angiogenesis directly



Thank You