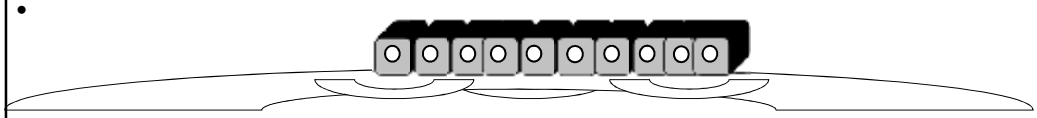
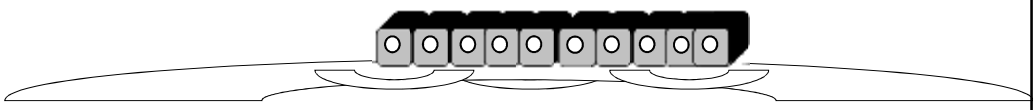
Tumor immunity

Normal cells



Normal cells



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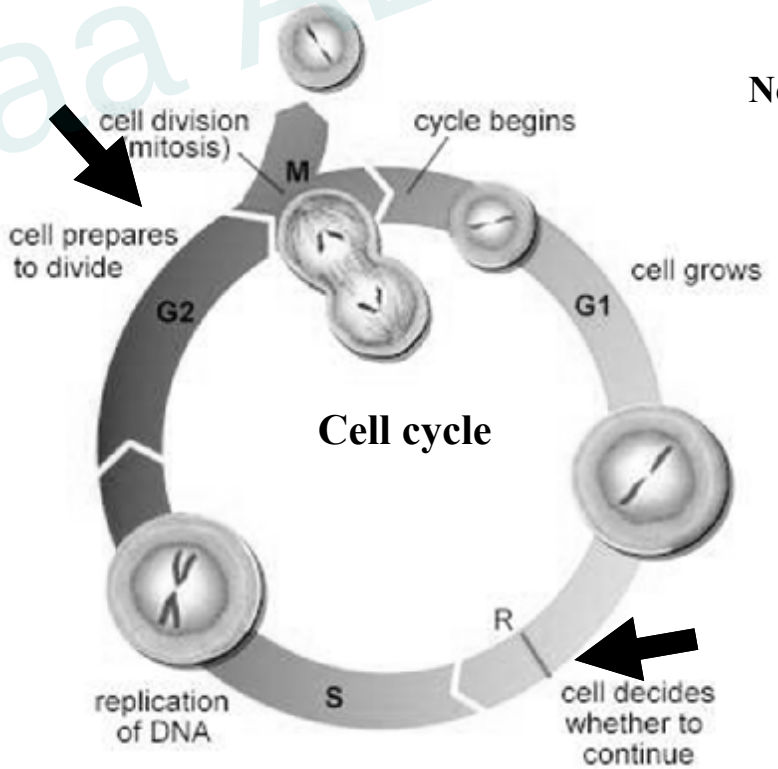
Normal cells



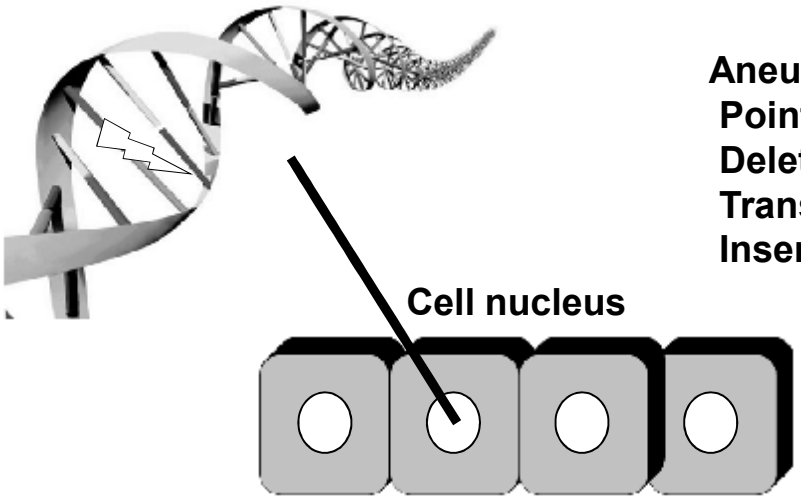
What about cells in tumor?

- Tumor develops when cells in a part of the body begin to **grow out of control.**
-
- Tumor cells are differents from normal cells
- Instead of dying, they continue to grow and
- divide to form new abnormal cells.
-
- Tumor cells develop because of **damage to DNA.**

DNA mutations

Damaging effects of exposure to radiation or a chemical carcinogen

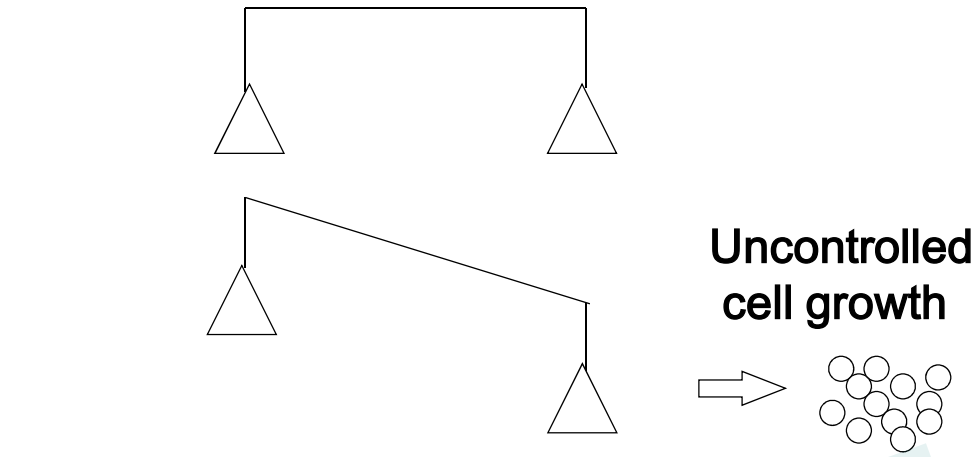
DNA



Mis-copying

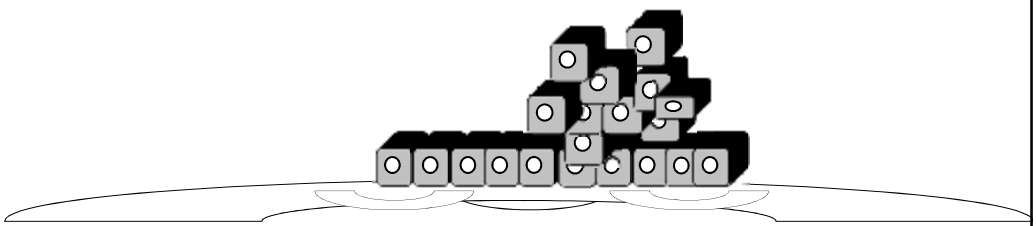
Aneuploid
Point-mutations
Deletions
Translocations
Insertions

Genes contribute to the tumor production

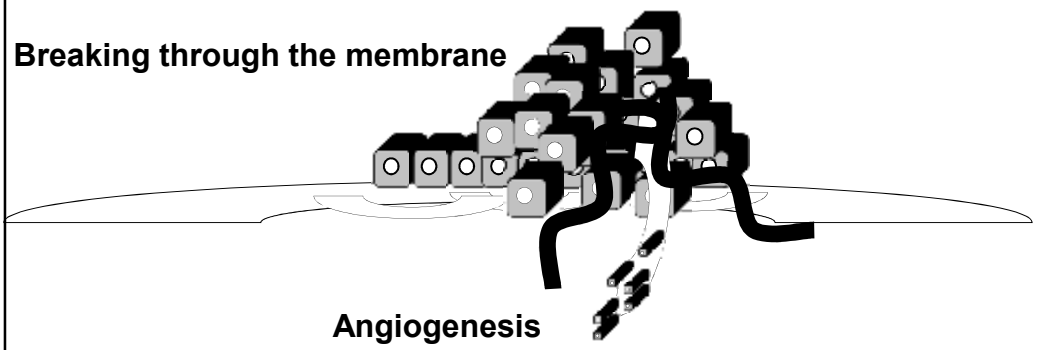


Tumor-suppressor genes Proto-oncogenes

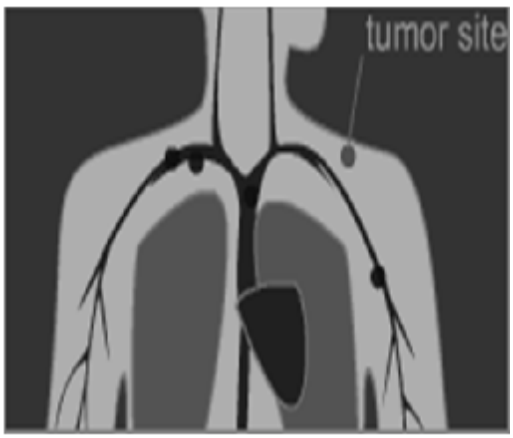
Genetically altered cell



Tumor cells travel metastasis



Tumor cells travel metastasis



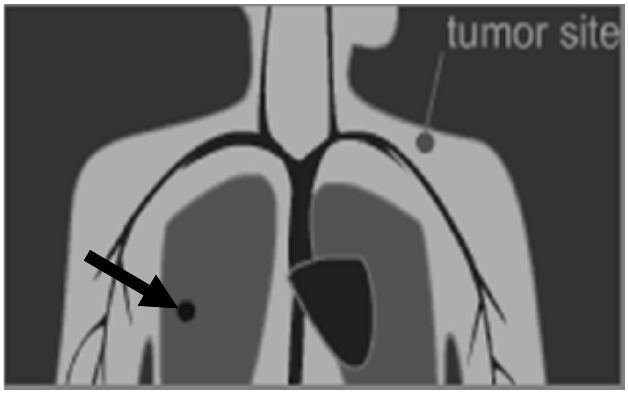
What makes most tumors so lethal is their ability to metastasize ⇨

establish new tumor sites at other locations throughout the body

(Secondary tumors)

•

11. Metastasis
New colony of the tumor



Carcinogens

- * Ionising radiation – X Rays, UV light **melanomas**
- * Chemicals – tar from cigarettes

* Virus infection

- - Papilloma virus (cervical tumor)
- - HCV, HBV (hepatocarcinoma)
- - EBV (Burkitt's lymphoma and nasopharyngeal-
- carcinoma cells)
- - HIV-1 infection and AIDS (lymphoma & sarcoma kaposi)

* Genetic predisposition – Some families are more susceptible to getting certain tumors. Remember *you can't inherit tumor* its just that you may be more susceptible to getting it.

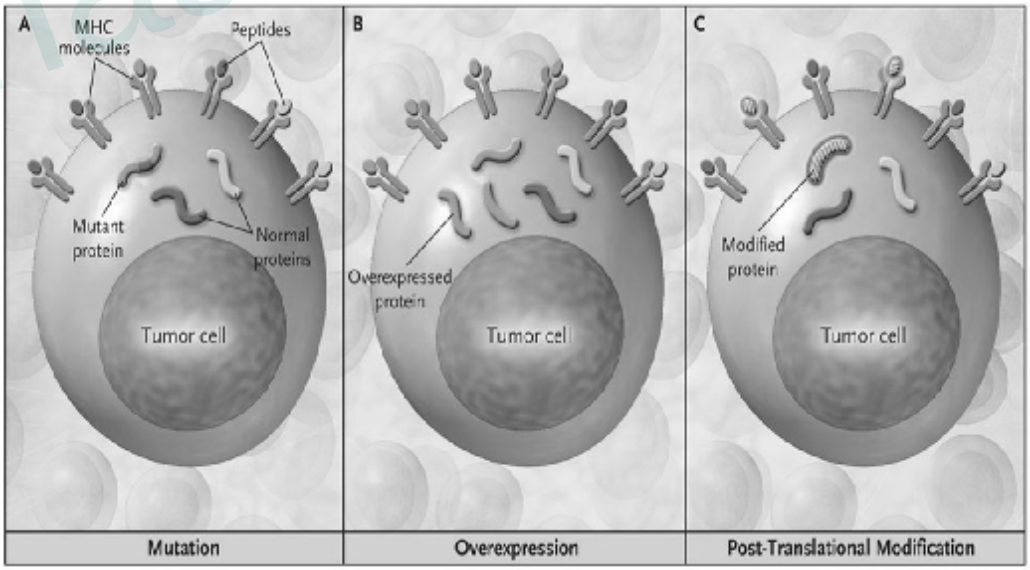
Antigens expressed on tumor cells

Tumor-specific Ag (TSA)

unique to a tumor **TSTA**
Play an important role in tumor rejection
TATA

Tumor-associated Ag (TAA)
shared by normal and tumor cells
do not trigger anti-tumor immunity.
used in diagnosis

Three Ways for Self Ag to Become Tumor Ag



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Antigens expressed on tumor cells

1. Products of Mutated Oncogenes and Tumor Suppressor Genes (p53, P21 ras, bcr-abl)
2. Overexpressed or Aberrantly Expressed Cellular Proteins
   HER2 (breast, ovary) ; MUC1 (intestinal, breast, ovary) tyrosinase in melanoma, PSA (prostate)

TSTA

TATA

3. Tumor Antigens Produced by Oncogenic Viruses

4. Oncofetal Antigens
Alphfetoprotein (AFP) and carcinoembryonic antigen (CEA)

Oncofetal antigens

Glycoprotein, the products of one or more genes expressed during fetal development, repressed after birth.

Proteins reappear in patients with tumor as a result of reactivation of certain genes.

serve in detecting the early oncogenic process

monitoring the efficacy of, and in developing new modalities of tumor treatment.

Alpha fetoprotein (AFP)

- A normal embryonic product during fetal development
- After birth the serum alpha fetoprotein decreases to only trace amounts by 2–5 weeks.
- Normal adult levels (≤ 20 ng/ml) .
- AFP is elevated in primary hepatocellular carcinoma, teratocarcinomas of the ovary or testes.
- Nonhepatic primary tumor generally exhibits an elevation of serum AFP only after spread to the liver.

Carcinoembryonic Antigen (CEA)

Glycoprotein associated with the plasma membrane of tumor cells, it may be released into the blood.
•clinicly.
• CEA indentified in colon, pancreatic, gastric, lung, breast tumor, cirrhosis, ulcerative colitis, pulmonary emphysema.

• CEA elevated in up to 19 % of smokers, 3% of a healthy population.

•The normal range is **<3 µg/L** in an adult non-smoker and **<5 µg/L** in a smoker.

Tumor immunity

1970- The tumor immunosurveillance hypothesis (Burnet):

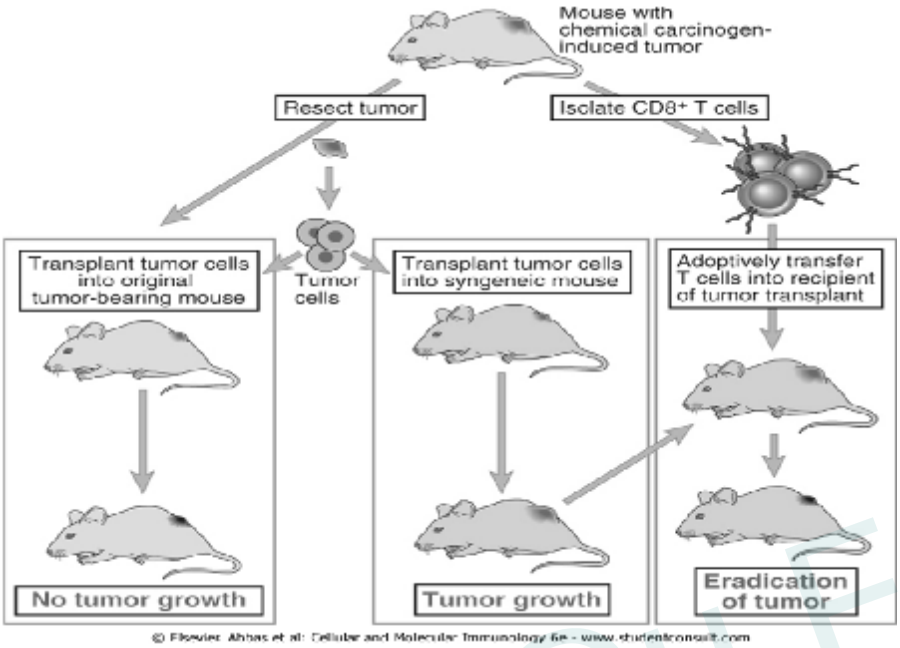
"**sentinel thymus dependent cells of the body constantly surveyed host tissues for nascent transformed cells"**

Burnet FM: The concept of immune surveillance. Prog Exp Tumor Res 13:1-27, 1970

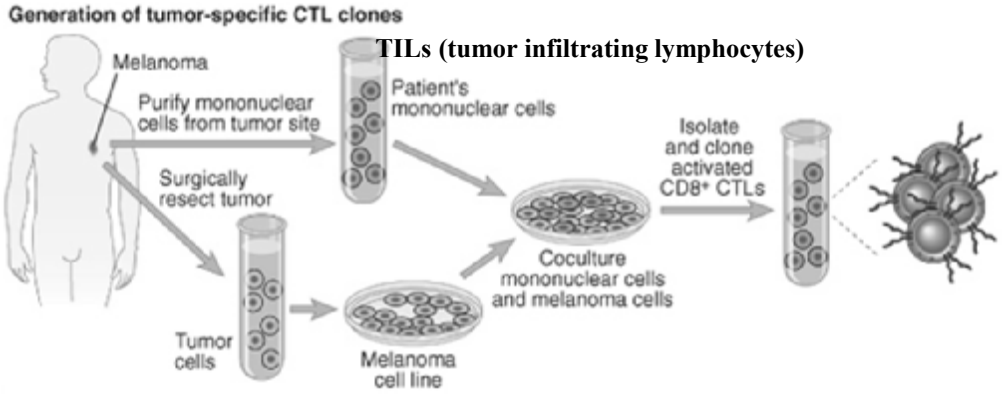
Evidences for tumor immunity

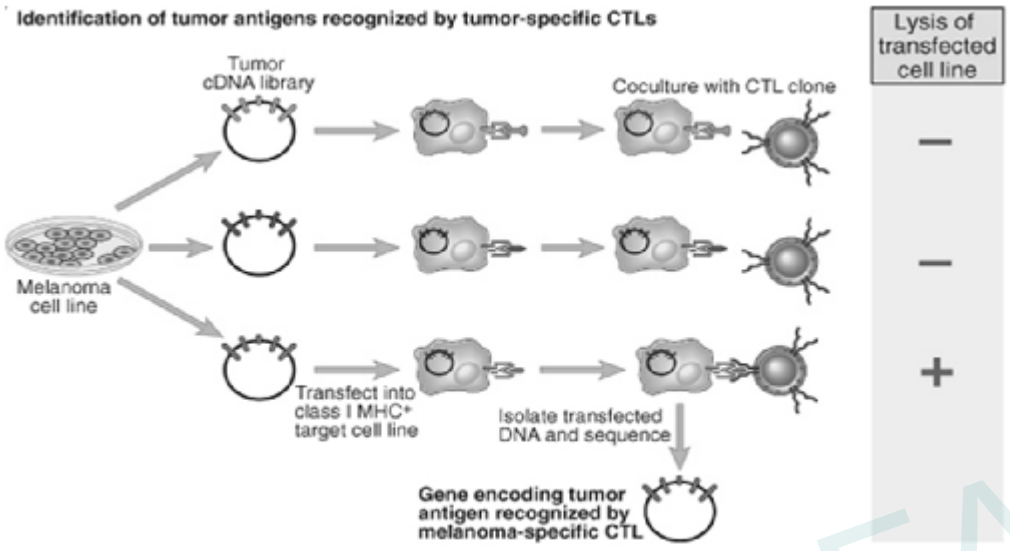
- Lymphocytes infiltration of tumors has been shown to correlate with improved survival for a great variety of solid tumor types.
- Lymphocyte proliferation in draining lymph nodes.
- The high incidence of malignancies in patients receiving chronic immunosuppressive therapy.
- Neonates and aged persons
- Spontaneous regression: melanoma, lymphoma
- Experimental models

Experimental models (1)



Experimental models (2)

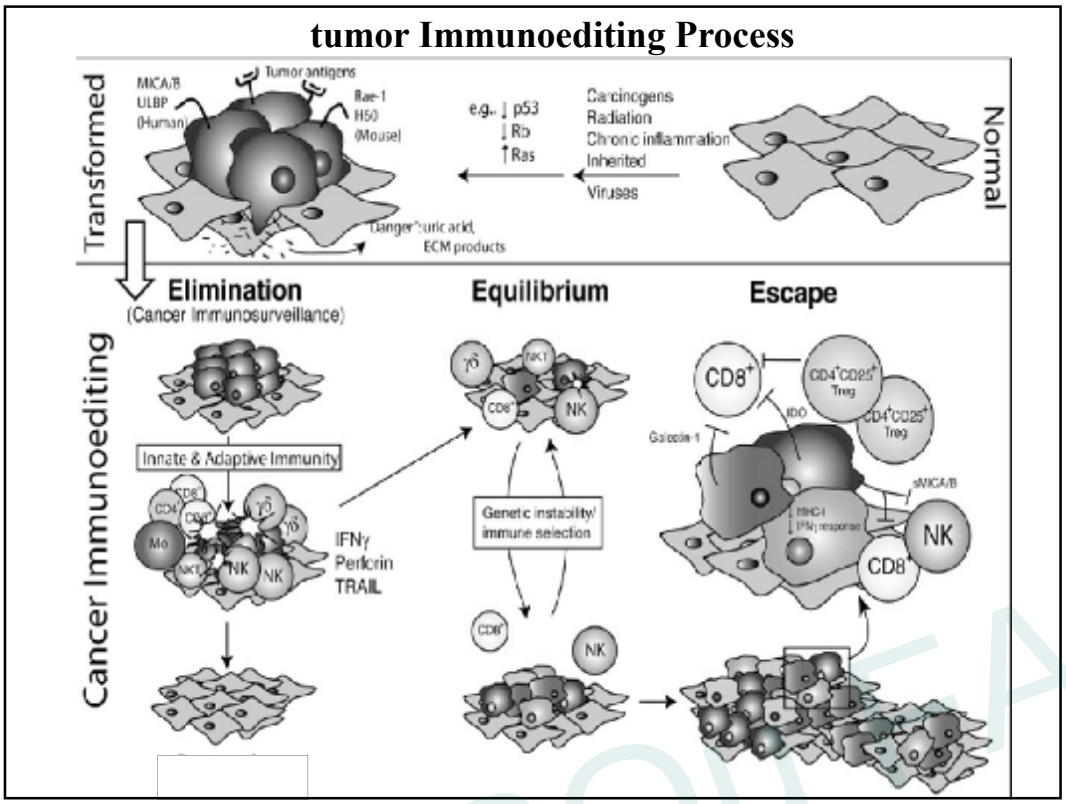




Tumor immunity

The encounter between the immune system and a nascent tumor initiates a process termed **"immunoediting"** that can bring about three outcomes:

- **Elimination** of the tumor.
- **tumor equilibrium**, in which there is immune selection of less immunogenic tumors during an anti-tumor immune response.
- **Tumor escape**, the growth of tumor variants that resist immune destruction.



Immunity and tumor killing

- What cells protect the host from tumor development?
- What are the critical effector functions of the immune system in cancer immunosurveillance?
- How does the immune system Immunosurveillance Network distinguish between a transformed cell and its normal progenitor?

Immunity and tumor killing

What cells protect the host from tumor development?

- **Non-specific or innate immune responses:**

  Dendritic cells, Macrophages, NK cells, γδ T cells, NKT cells.

- **Antigen-specific or adaptive immune responses:**

  B cells (antibodies), T cells (CD4+, CD8+ T cells).

Effector Functions Underlying Immunosurveillance:

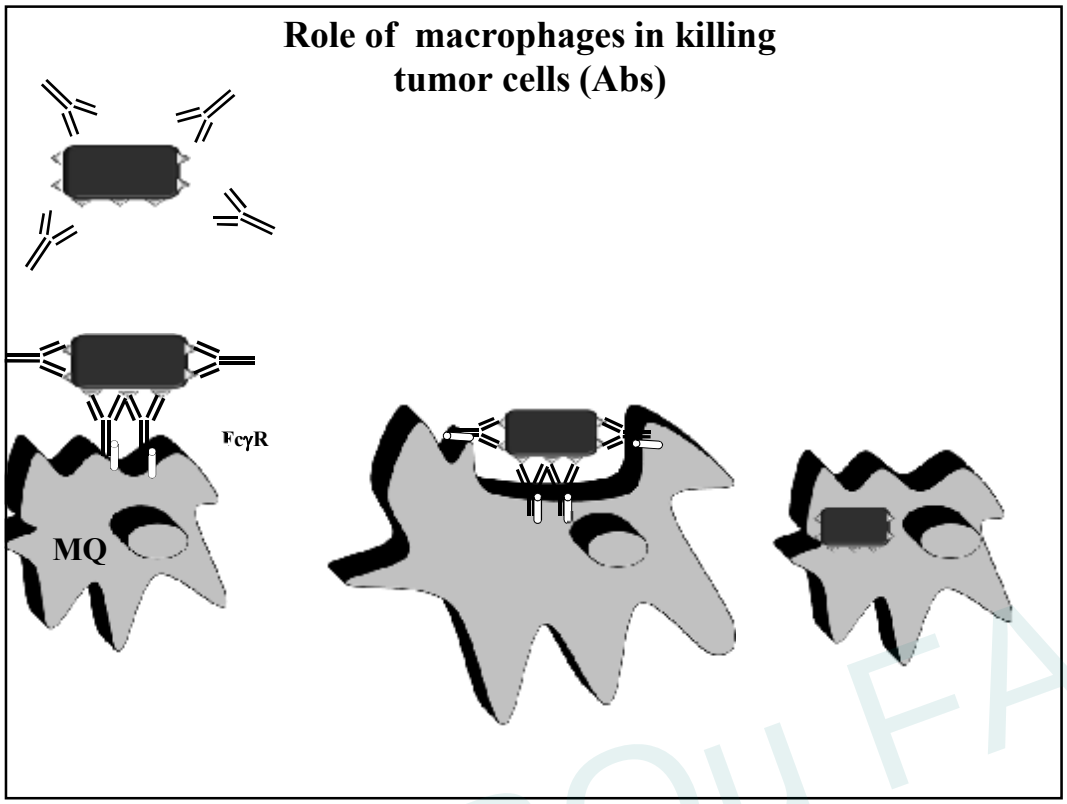
IFN- γ Production

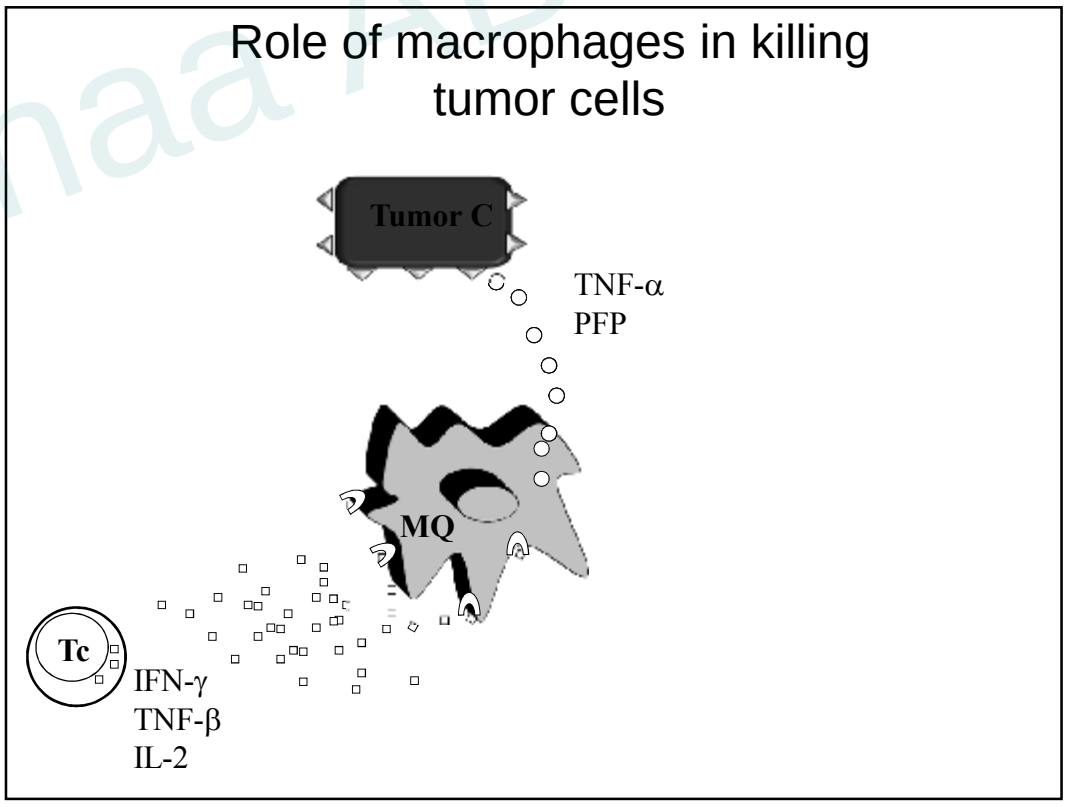
Cytolytic Capacity

Pore forming protein or Perforin (pfp) : Granzyme

Tumor necrosis factors

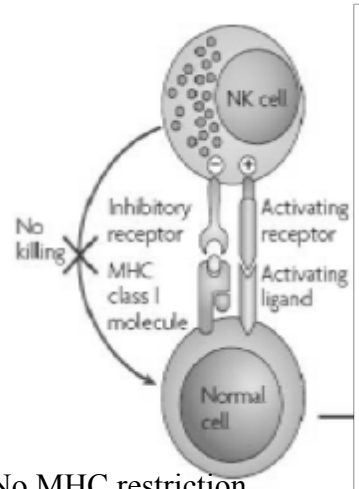
- TNF-related apoptosis-inducing ligand (TRAIL)
- FAS L





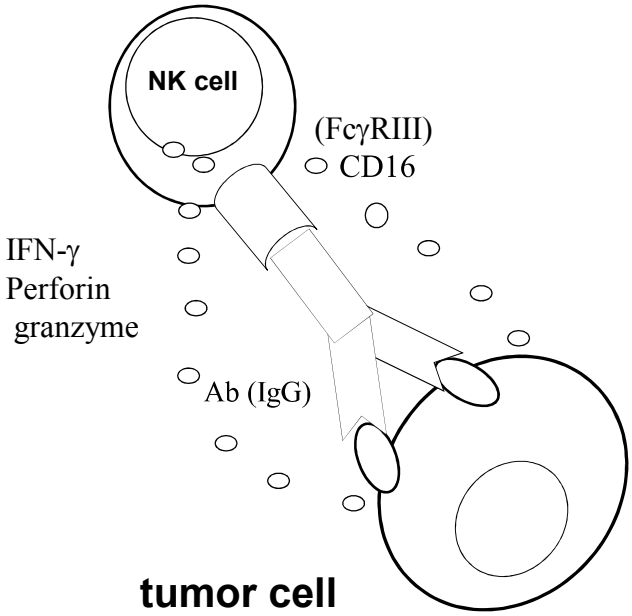
Anti-tumor activity of NK cell

Missing-self recognition of tumor cells

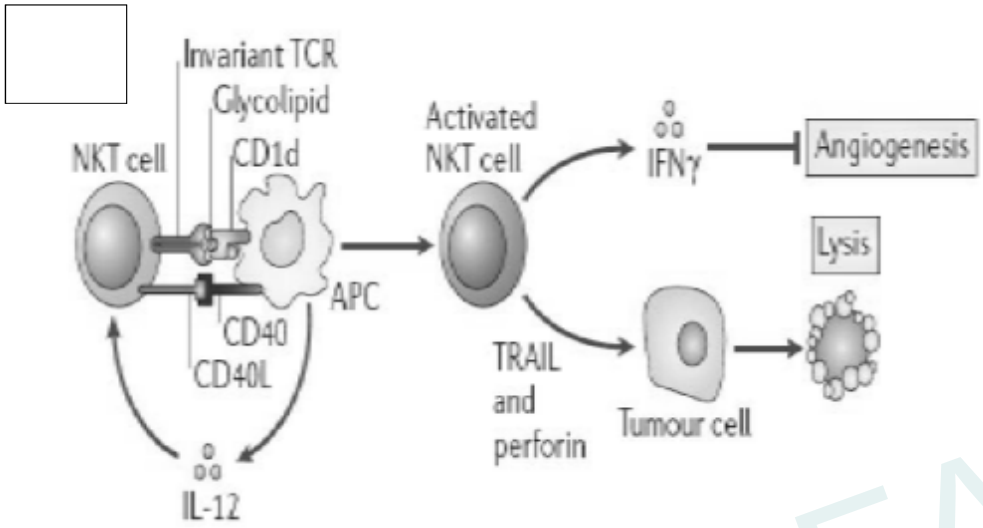


No MHC restriction
Non specific immune response
No immunological memory
(same intensity regardless of repeated exposure)

Antibody-Dependent Cell Cytotoxicity (ADCC)



NKT cells



Antigen: lipid, glycolipid, highly hydrophobic peptides

Immunity and tumor killing

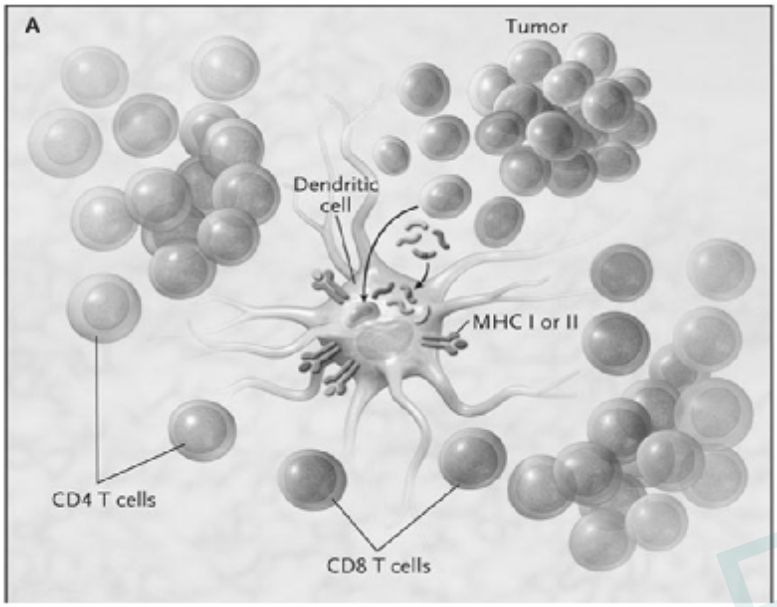
- **Non-specific or innate immune responses:**

  Dendritic cells, Macrophages, NK cells, γδ T cells, NKT cells.

- **Antigen-specific or adaptive immune responses:**

  antibody, T cells (CD4+, CD8+ T cells).

Tumor Ags Eliciting T-Cell Immunity When Presented to Naive T Cells by APC



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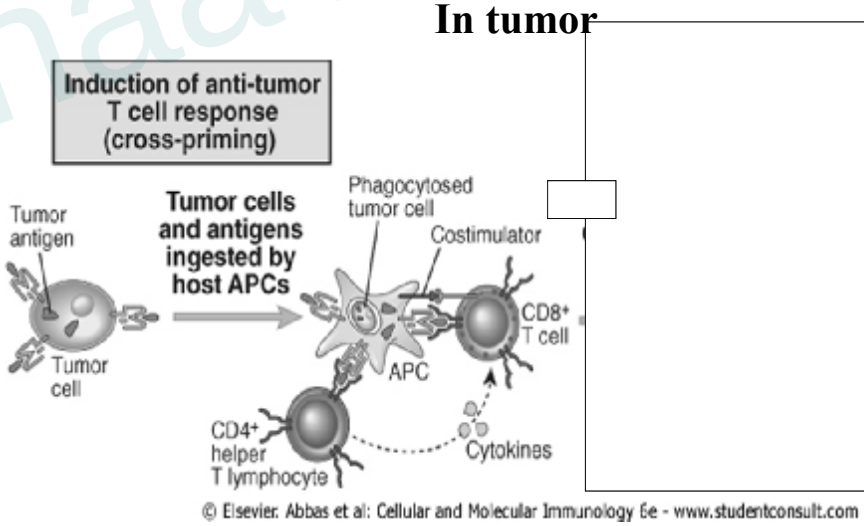
Adaptive immune response In tumor



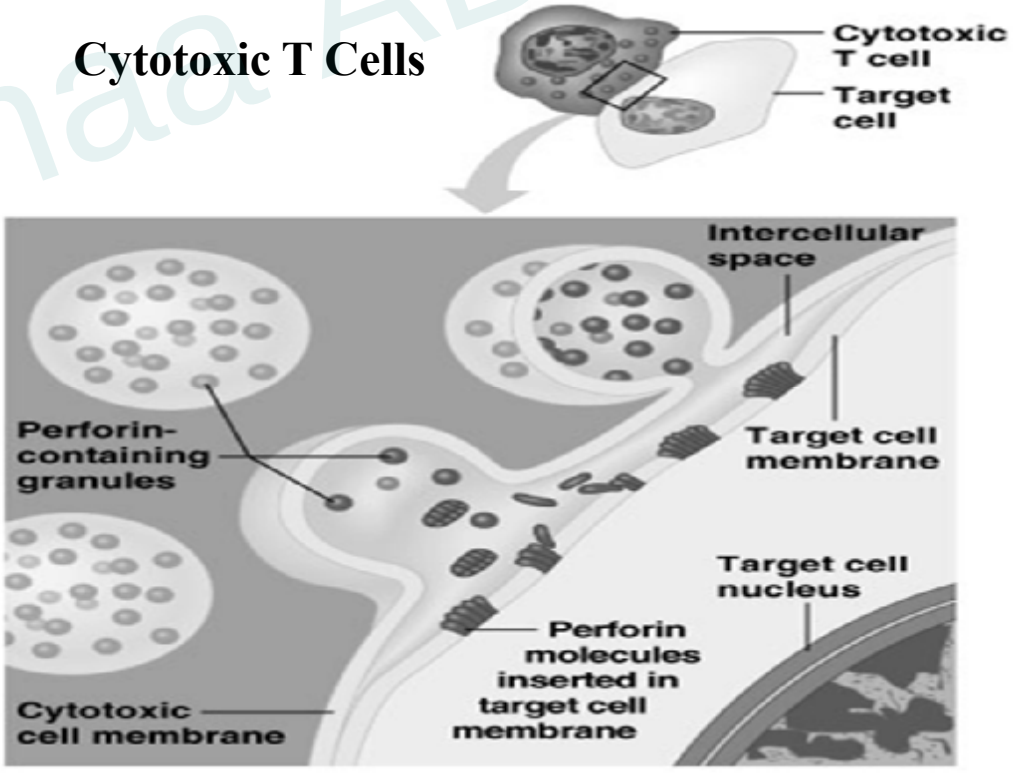
CD8+ T cells (CTL)

✓ Naïve CTLs Can not Kill
✓Signals needed for activation

Ag specific signal (TCR/MHC I + Ag)
Co-stimulatory signal CD28 (CTL)/B7 (APC, MQ)

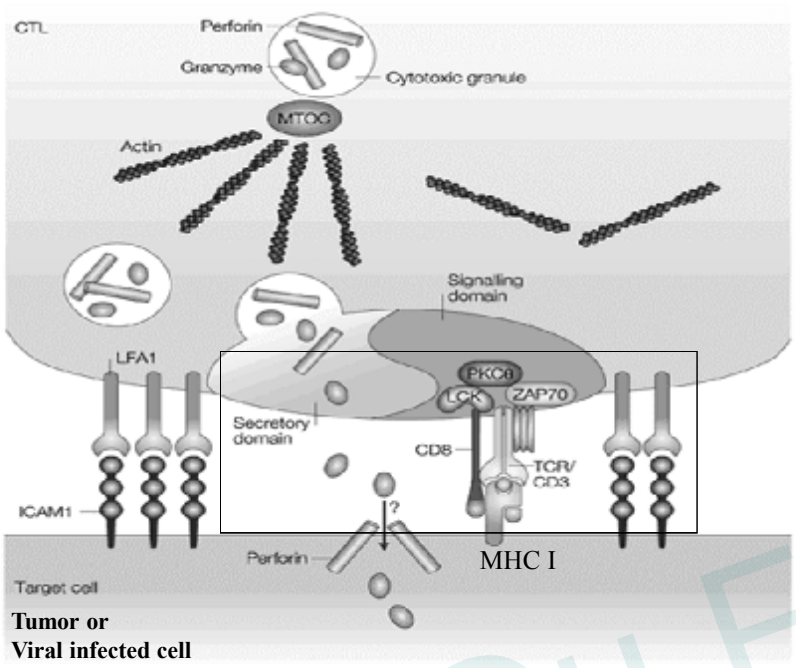
- **Fonctions of CD8+**
- **Secretion of perforin/granzyme B**
- **Expression of FasL to induce apoptosis via binding to Fas.**
- **Secretion of IFN-γ, TNF-β**

Cytotoxic T Cells



Lytic pathway

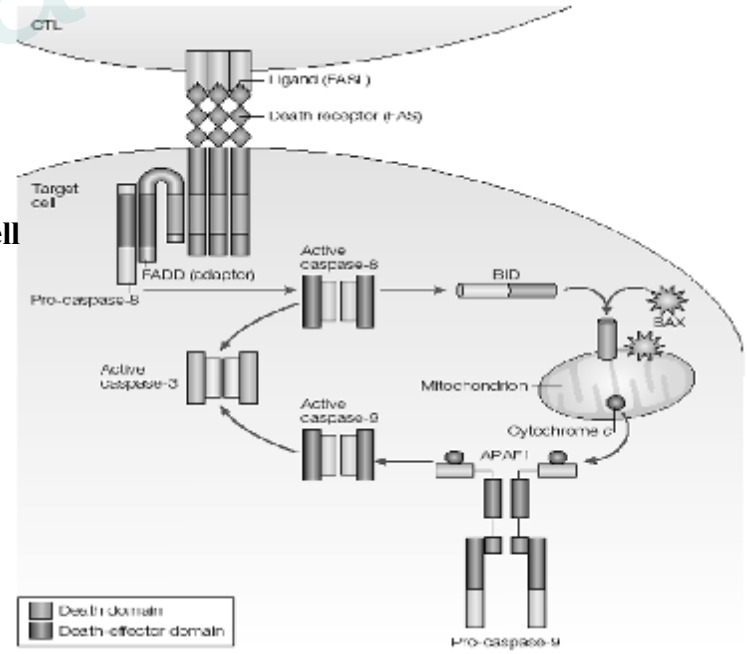
CD8+



Induction of apoptosis by FasL

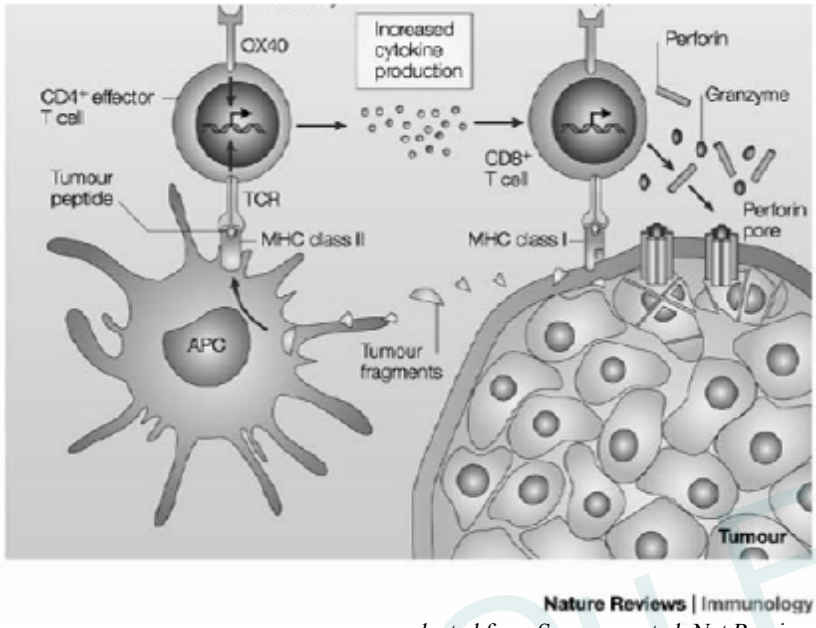
CD8+

Tumor cell



Barry, M. & R. C. Bleackley (2002). Nat Rev Immunol **2**(6): 401-9.

CD8+ and CD4+ T cell cooperation in anti-tumor immunity

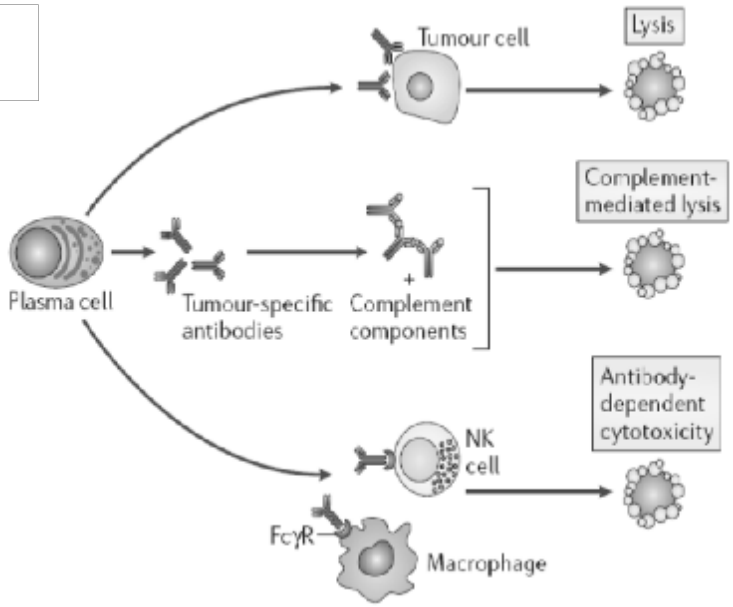


adapted from Sugamura et al, Nat Rev immunol, 2004

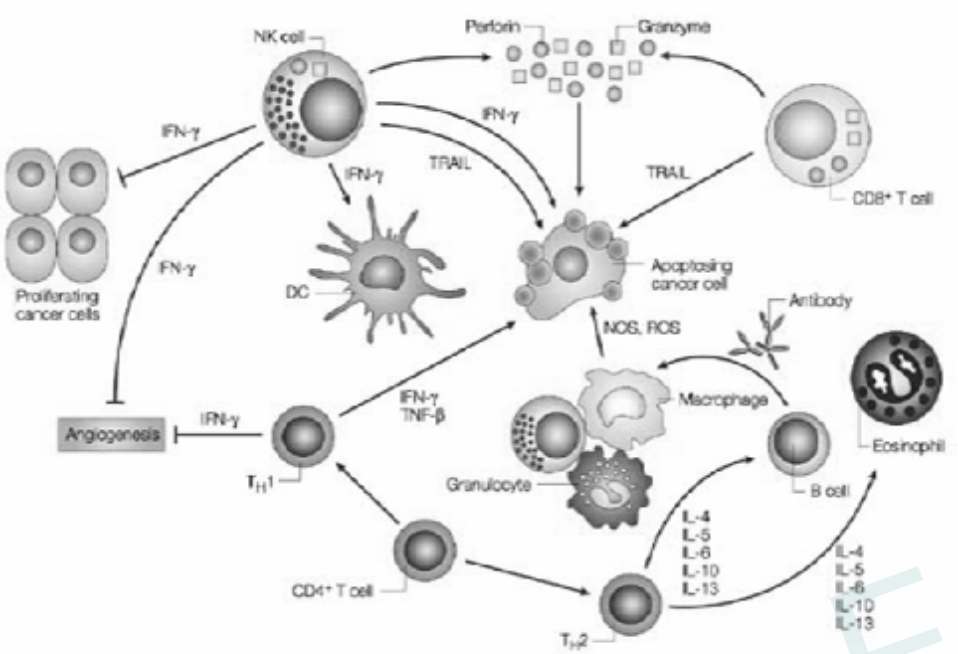
Humoral immune response Anti-tumor

Th2 IL-4
IL-5
IL-6
IL-10
IL-13
IgG1, IgE

Th1 IFN-γ
IgG2a, IgG3



adapted from Zivotgel et al , Nat Rev Immunol 2008

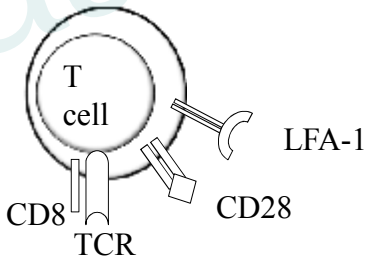


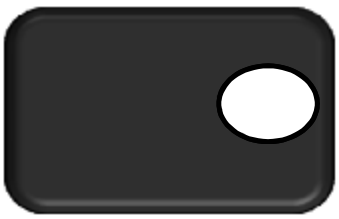
Dranoff, Nat Rev Cancer 2004 **Nature Reviews** | Cancer

The growth and metastatic spread of tumors, to a large extent, depends on their capacity to **evade host immune surveillance and overcome host defenses.**

the strategies of Tumor Immune Evasion

Low immunogenicity

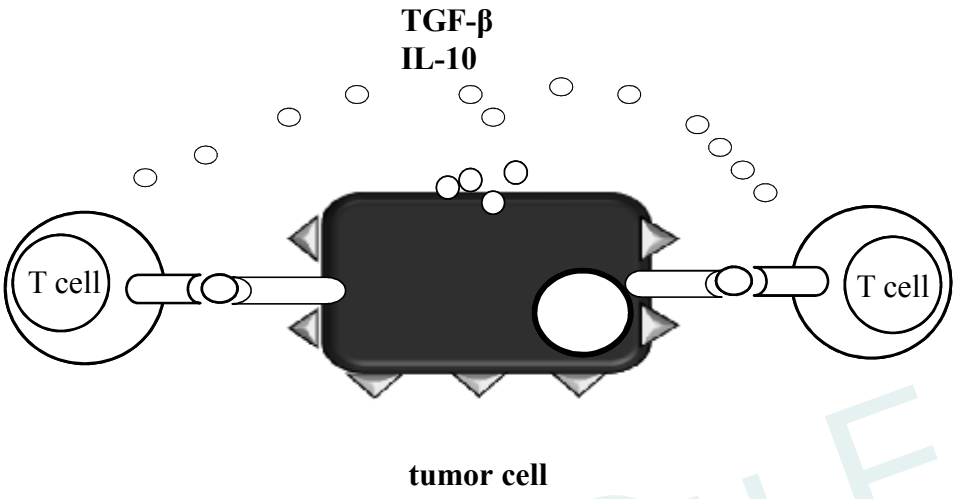




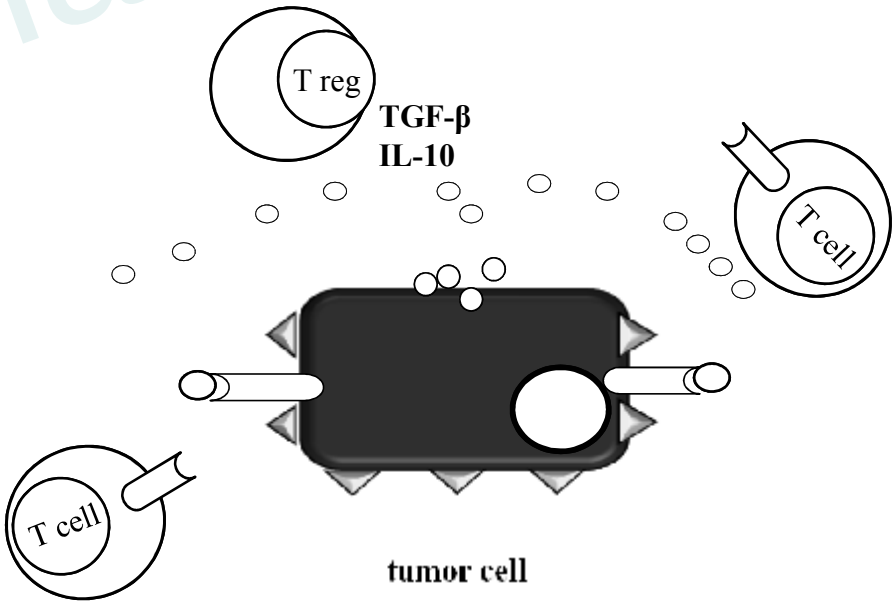
tumor cell

- ❑ No peptide : MHC ligand
- ❑Weak immunogenicity of tumor Ags
- ❑ Antigen masking
- ❑No co-stimulatory molecules
- ❑ No adhesion molecules

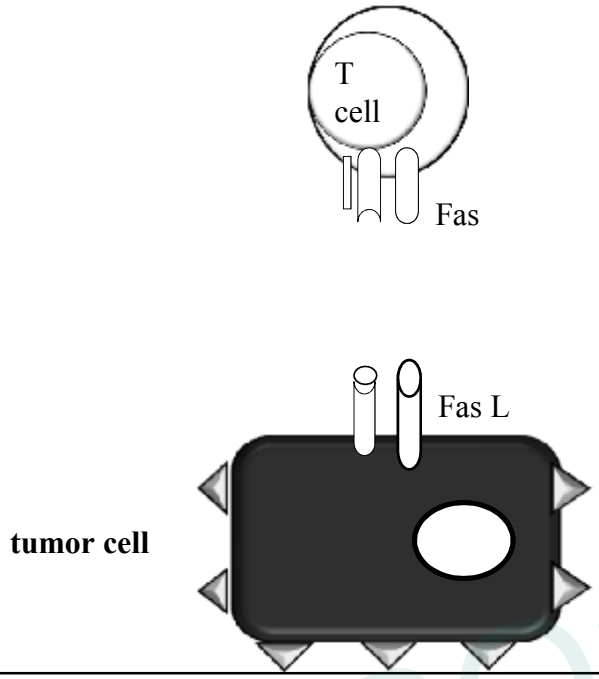
Secretion of immunosuppressive cytokines



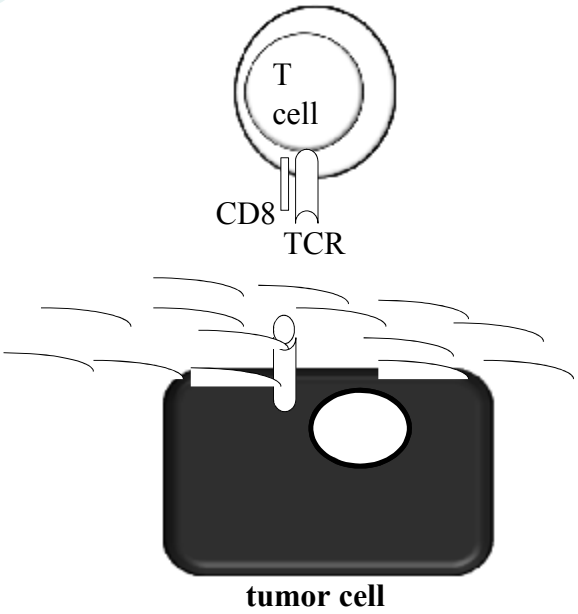
Supression by regulatory T cells



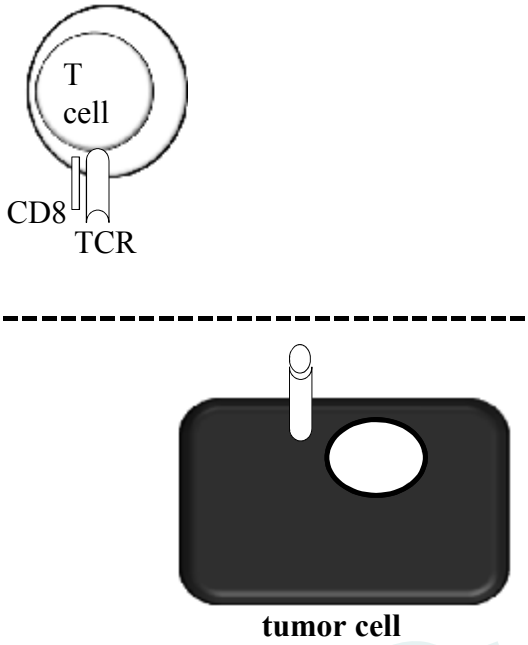
Direct deletion



tumor induced privileged site

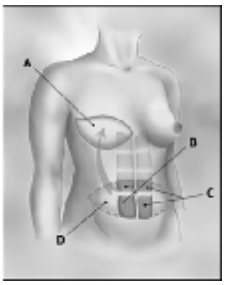


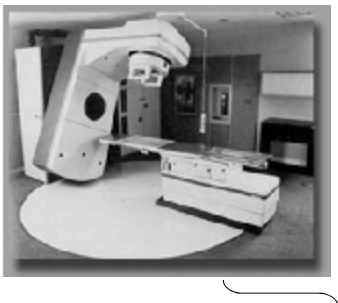
Ignorance



Traditional approaches to treat cancer

Surgery Radiation Chemotherapy





Localized tumors

Metastastic tumors
Affects proliferating cells
(bone marrow, etc.)
Radiation/Drug-resistant tumors

New

Immunotherapy

Immunotherapy in cancer

Active Immunotherapy

- a) **Specific activation: vaccines**
  - Hepatitis B vaccine
  - Human Papilloma virus (HPV) vaccine
- b) **Nonspecific activation**
  - Bacillus Calmette-Guerin (BCG)
  - melanoma, bladder carcinoma

Immunotherapy in cancer

Passive Immunotherapy

– Transfer of preformed Abs, immune cells and other factors into the hosts

- **Abs against tumor Ags** (Abs against Her2/Neu) breast cancer
- **Abs against CD20** expressed on all B cells

non Hodgkin's B cell lymphoma

Abs against IL-2R

Human T lymphotropic virus (HTLV-1)

Immunotherapy in cancer

Passive Immunotherapy

Abs conjugated to toxins, radioisotopes

These enter the cells and inhibit protein synthesis.

Anti-CD20 conjugated to Pseudomonas toxin or ricin toxin (B cell tumors).

Immunotherapy in cancer

Adoptive Transfer of lymphocytes

- Lymphokine-activated killer (LAK) cells which are IL-2 activated T and NK cells melanoma, renal cell carcinoma
- Tumor-infiltrating lymphocytes (TIL) include T cells and NK cells.

Immunotherapy in cancer

Cytokines

- **IL-2:** Activates T cells/NK cells which express IL-2 receptors and leads to their proliferation
- renal cell carcinoma and melanoma,
- **IFNα:** Activates NK cell activity
- Kaposi sarcoma, renal cell carcinoma , melanomas
- **IFN-γ:** Increases class II MHC expression
- ovarian cancers

Thanks