Immune response to infectious diseases and malignancy - Tumor Immunology

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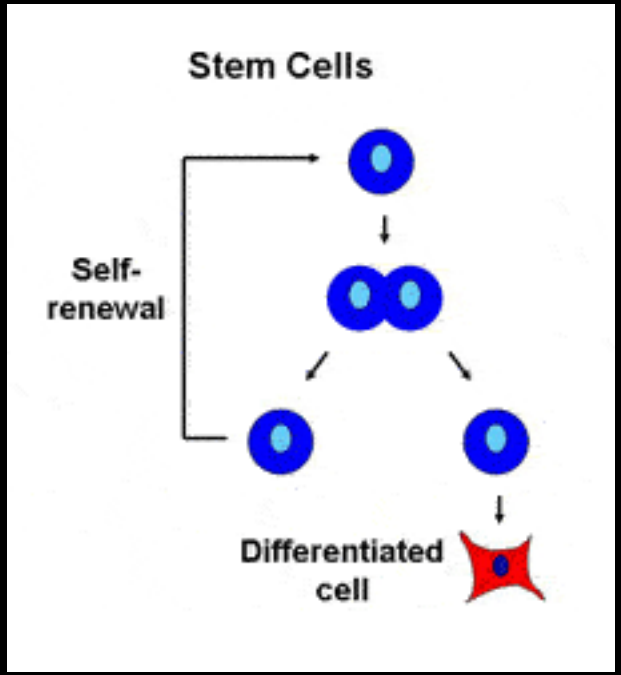
Introduction to tumor

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

1. Malignant: A tumor that grows indefinitely and spreads (metastasis)--also called cancer: kills host
2. Benign: A tumor that is not capable of metastasis: does not kill host



Muscle, Nerve, Bone, Blood

* Pathological cell masses derived by abnormal and uncontrollable clonal expansion of single cell

* Transformation of normal cells to malignant cells by:

a- Spontaneous mutation during daily cell division

b- It may be induced by
- chemical carcinogens
- physical carcinogens
- viruses

* Cells become antigenically different from normal cells

* They are recognized and destroyed by immune system

Etiology Of Tumor

1) Inherited :

Expression of inherited oncogene

e.g. viral gene incorporated into host gene

2) Viral:

- Human papilloma, herpes type 2, HBV, EBV (DNA)
- Human T-cell leuckemia virus (RNA)

3) Chemical:

- Poly cyclic hydrocarbons cause sarcomas
- Aromatic amines cause mammary carcinoma
- Alkyl nitroso amines cause hepatoma

4) Radiological: Ultraviolet & ionizing irradiation

5) Spontaneous: failure in the cellular growth control

Tumor Associated Antigens

1) Viral Antigen :

a- Viral proteins and glycoproteins

b- New antigens produced by virally infected host cells under control of viral nucleic acid

2) Tumor specific antigens :

- Tumor cells develop new antigen specific to their carcinogens

3) Tumor specific transplantation antigens :

- Tumor cells express new MHC antigens due to alteration of normally present MHC antigens

Tumor Associated Antigens

4) Oncofetal antigens:

a- Carcino-embryonic antigens (CEA)

- Normally expressed during fetal life on fetal gut
- Reappearance in adult life:

  GIT, pancreas, biliary system and cancer breast

b- Alpha fetoprotein:

- Normally expressed in fetal life
- Reappearance in adult life; hepatoma

Immune Surveillance System

* During neoplastic transformation, new antigen develop.

* The host recognize them as nonself antigens.

* Cell mediated immune reactions attack these nonself tumor cells.

- Immune response act as surveillance system to detect and eliminate newly arising neoplastic cells.

- This system include :

1) Natural killer (NK) cells

They kill directly tumor cells,helped by interferon, IL-2

Immune Surveillance System

2) Cytotoxic T-cells

They also kill directly tumor cells

3) Cell mediated T-cells (effector T-cells)

They produce and release a variety of lymphokines :

a-Macrophage activation factor that activate macrophag

b-Gamma interferon and interleukin-2 that activate NK

c-Tumor necrosis factor (cachectine)

Immune Surveillance System

4) B-cells :

- Tumor associated antigens stimulate production of specific antibodies by host B-cells

- These specific antibodies bind together on tumor cell surface leading to destruction of tumor through:

a- Antibody mediated-cytotoxicity :

Cytotoxic T-cells —kill→ IgG-coated tumor cells

b- Activation of macrophages

Sensitized T-cells —release→ macrophage activating factor —activate→ macrophages —activate→ IgG-coated tumor cells

c- Activation of classical pathway of complement —leading to→ Lysis of tumor cells

Tumor Escape

Mechanisms by which tumor escape immune defenses:

1) Reduced levels or absence of MHCI molecule on tumor so that they can not be recognized by CTLs

2) Some tumors stop expressing the antigens

These tumors are called “antigen loss variants” (like escape mutants)

3) Production of immunosuppressive factors by tumors e.g. transforming growth factor (TGF-β)

4) Tumor antigens may induce specific immunologic tolerance

Tumor Escape

5) Tumor cells have an inherent defect in antigen processing and presentation

6) Blocking of receptors on T-cells by specific antigen antibodies complex (after shedding of tumor Ag) prevents them from recognizing and attacking tumor cells

7) Antigens on the surface of tumors may be masked by sialic acid-containing mucopolysaccharides

8) Immune suppression of the host as in transplant

patients who show a higher incidence of malignancy

Tumor Antigens

1) Alpha fetoprotein antigen (AFP) in cases of hepatoma

2) Carcinoembryoinic antigen (CEA) in gastrointestinal tumors, tumors of biliary system and cancer breast

3) Cancer antigen 125 (CA 125) in ovarian carcinoma

4) Cancer antigen 15-3 (CA15-3) in breast cancer

5) Cancer antigen 19-9 in colon and pancreatic tumor

6) Prostatic specific antigen (PSA) in prostatic tumors

Tumor antigens

	antigen	function	cancers
CTA (Cancer Testis Antigen)	MAGE1 MAGE3	normal testicular protein	Melanoma Breast & Glioma
TDA (Tumor Differentiation Antigen)	Tyrosinase	melanin synthesis	Melanoma
TAA (Tumor Associated Antigen)	HER-2/neu ERBB3 ERBB4 MUC-1 CEA	receptor tyrosine kinase lubs of epithelia cell adhesion	Breast, ovary, GI, lung, prostate Breast Colorectal cancer
	gp100	melanin polymerization	Melanoma
TSA (Tumor Specific Antigen)	HPV (E7)	viral transforming gene product	Cervical cancer

Tumor Products

a) Hormones :

- Human chorionic gonadotrophins (HCG) are secreted in cases of choriocarcinoma
- Thyroxin (T3 & T4) is secreted in cases of cancer of thyroid gland

b) Enzymes :

- Acid phosphatase enzymes in cases of cancer prostate
- Alkaline phosphatese, lipase and amylase enzymes in cases of pancreas cancer

Cancer

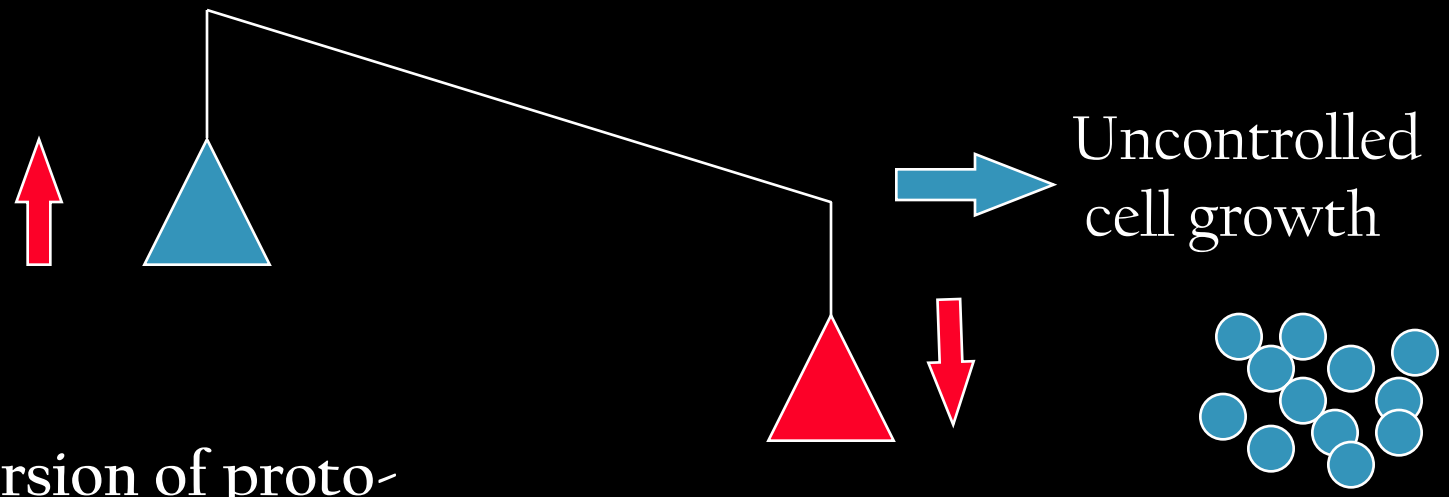
- **Carcinoma:** arising from epithelial tissue, such as glands, breast, skin, and linings of the urogenital, digestive, and respiratory systems (89.3% of all cancers)
- **Sarcoma:** solid tumors of muscles, bone, and cartilage that arise from the embryological mesoderm (1.9% of all cancers)
- **Leukemia:** disease of bone marrow causing excessive production of leukocytes (3.4% of all cancers)
- **Lymphoma, Myeloma:** diseases of the lymph nodes and spleen that cause excessive production of lymphocytes (5.4% of cancers)

Etiology of Cancer

1. Genetic factors: mutations, translocation, amplifications
2. Environmental factors: UV, chemicals, viral infections

- conversion of proto-oncogenes (potential for cell transformation) to oncogenes (cell transformation)
- alteration in tumor suppressor genes

Molecular Basis of Cancer



Conversion of proto-oncogenes to oncogenes:

- amplification of c-erbB2 in breast cancer
- point mutation of c-ras in kidney and bladder cancers
- chromosome translocation of c-myc in Burkitt's lymphoma

Altered tumor-suppressor genes:

- P53 mutation in prostate cancer: failure in cell cycle arrest or apoptosis of prostate tumors
- Rb mutation: fail to prevent mitosis

UV-induced Cancers

- Damage or mutation of DNA:
- Melanoma: metastatic, highly immunogenic, spontaneous rejection
- Non-melanoma cancers:
- Basal cell carcinoma: rarely spreads
- Squamous cell carcinoma: can spread

Chemically-induced Cancers

- Free radicals and other oxidants steal electron from DNA and cause cancer: anti-oxidants (vitamins A, C)

Virally-induced Cancers

DNA viruses: papova (papilloma, SV40), hepatitis, EBV

RNA viruses: retroviruses---> Human T-lymphotropic viruses (HTLV-I and HTLV-II) cause T cell leukemia

Highly immunogenic because of viral antigens

Evidence for Tumor Immunity

- Spontaneous regression: melanoma, lymphoma
- Regression of metastases after removal of primary tumor: pulmonary metastases from renal carcinoma
- Infiltration of tumors by lymphocytes and macrophages: melanoma and breast cancer
- Lymphocyte proliferation in draining lymph nodes
- Higher incidence of cancer after immunosuppression, immunodeficiency (AIDS, neonates), aging, etc.

Tumor-specific Immune Response

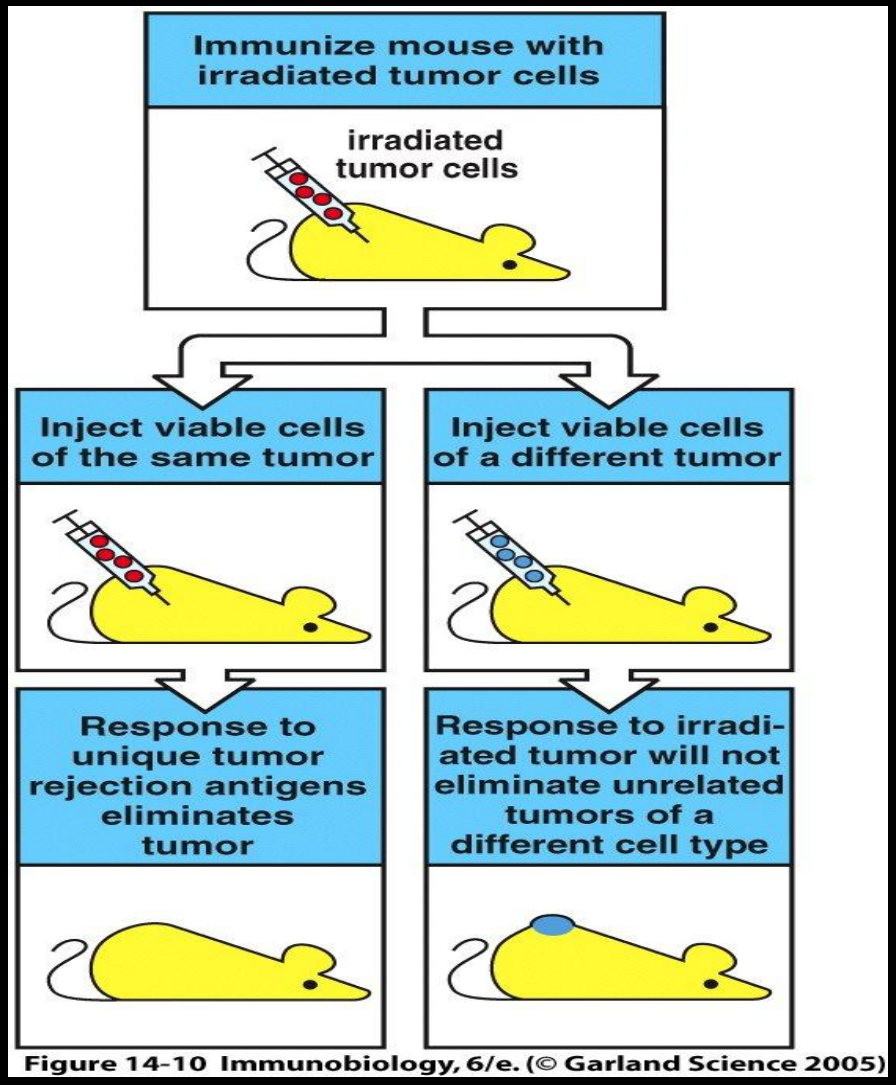


Figure 14-10 Immunobiology, 6/e. (© Garland Science 2005)

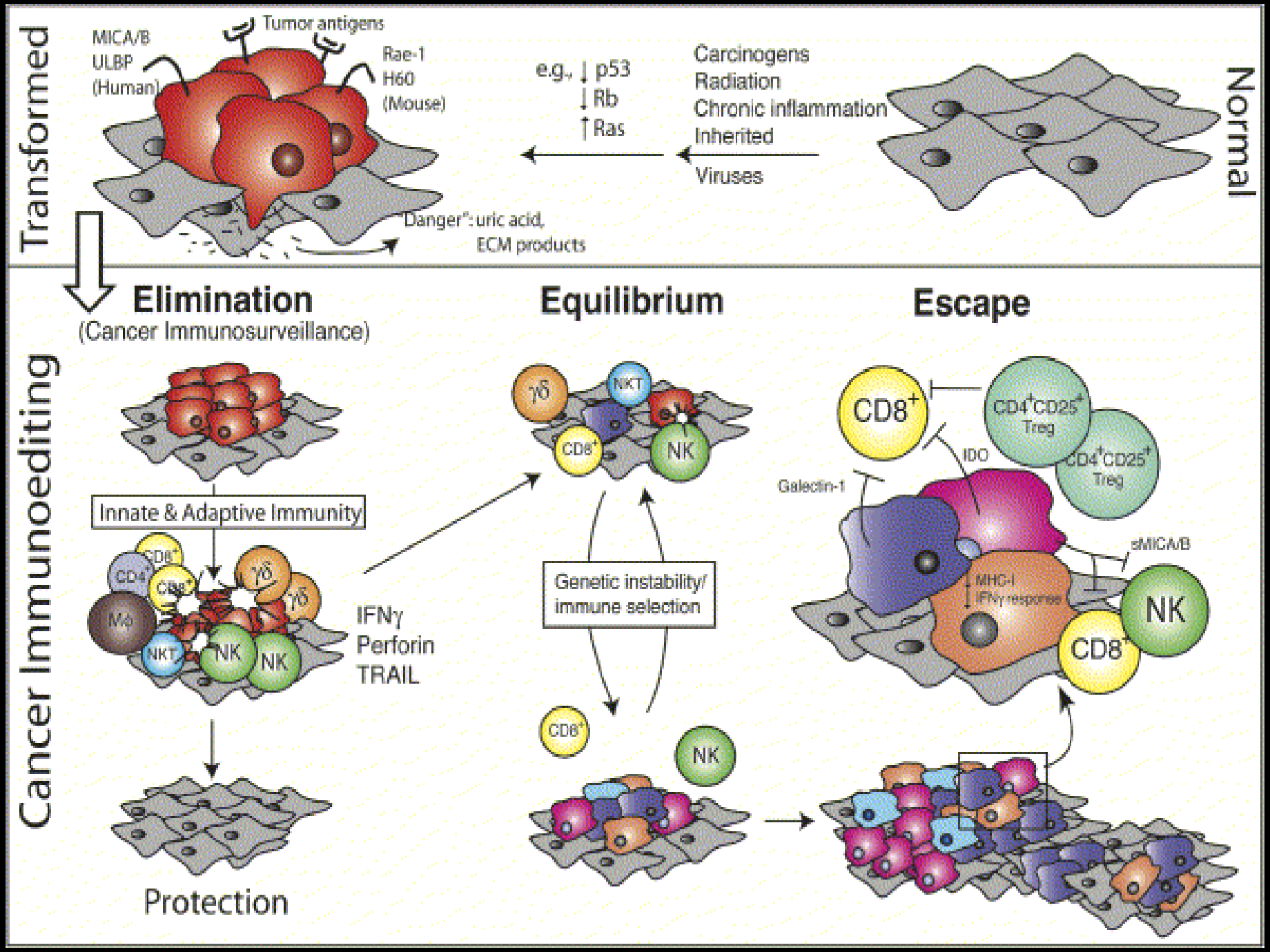
Tumor Immunology

- Cancer immunosurveilance:

  immune system can recognize and destroy nascent transformed cells

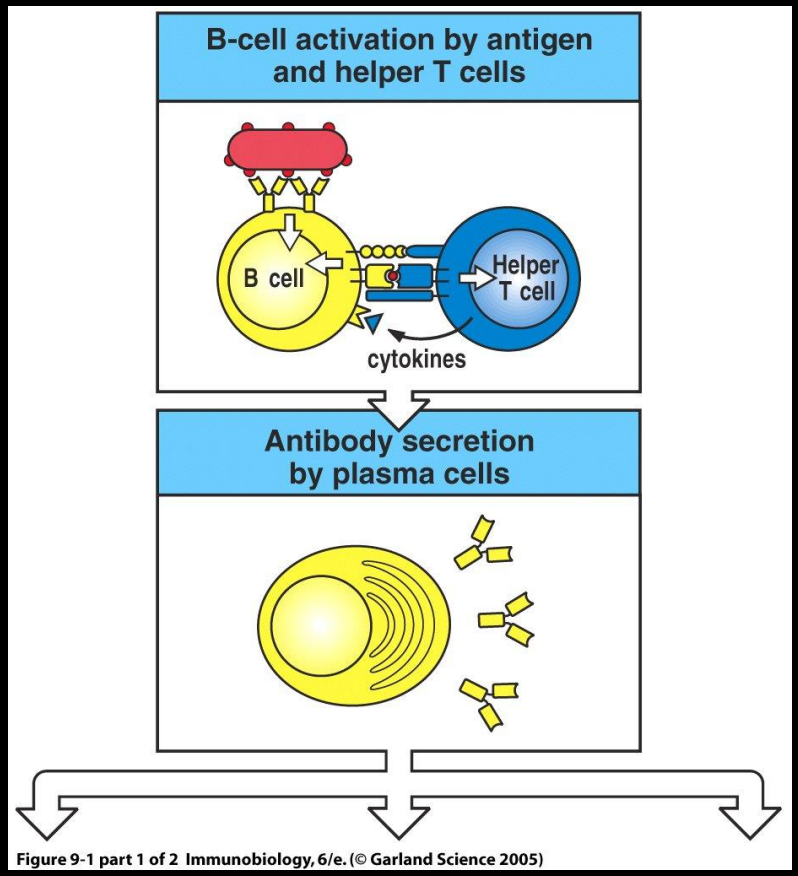
- Cancer immunoediting:

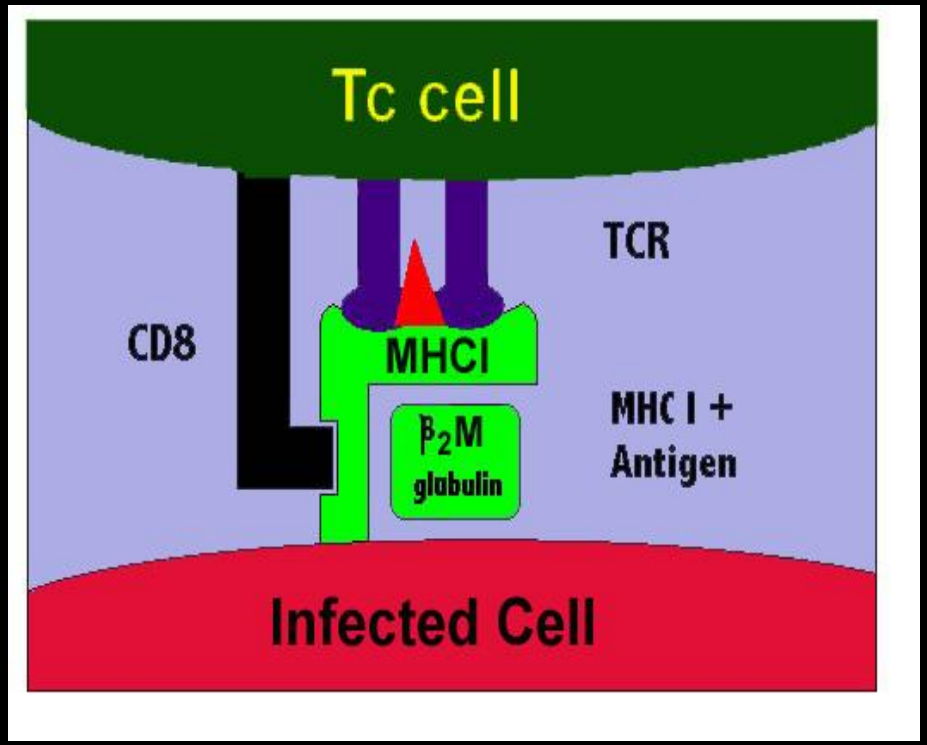
  immune system kill and also induce changes in the tumor resulting in tumor escape and recurrence (epigenetic changes or Darwinian selection)


Transformed
MICA/B
ULBP
(Human)
Tumor antigens
Rae-1
H60
(Mouse)
e.g., ↓ p53
↓ Rb
↑ Ras
Carcinogens
Radiation
Chronic inflammation
Inherited
Viruses
Normal
Danger*: uric acid,
ECM products
Cancer Immunoediting
Elimination
(Cancer Immunosurveillance)
Innate & Adaptive Immunity
IFNγ
Perforin
TRAIL
Protection
Equilibrium
Genetic instability/
immune selection
Escape
CD8+
CD4+CD25+
Treg
IDO
Galectin-1
sMICA/B
MHC-I
IFNγ response
NK

Immune Recognition of Tumor

Antibodies recognize intact antigens while T cells recognize processed antigens associated with MHC



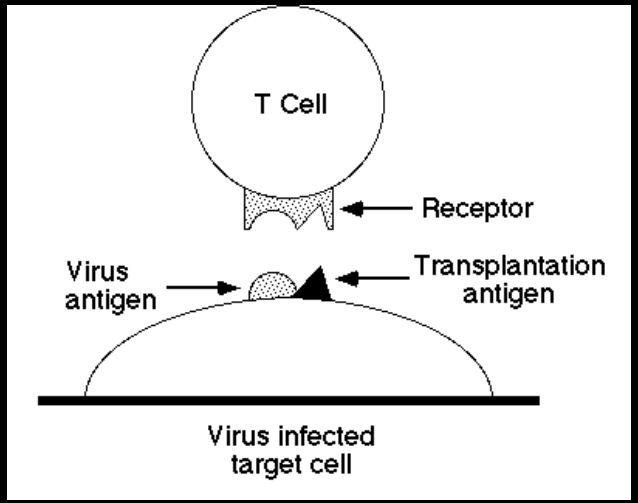


Immune Recognition of Tumor

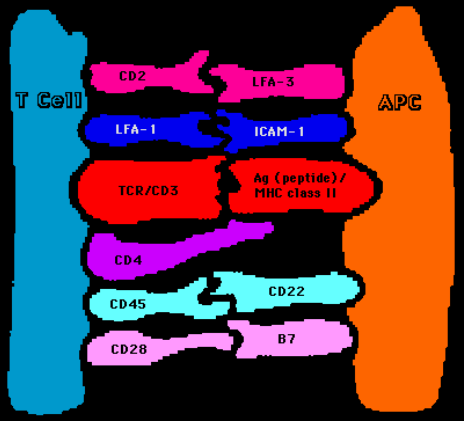
- Repertoire of T cells with low affinity against self proteins exist because of positive and negative selections in the thymus
- Expression of altered self proteins by tumors will increase the affinity of T cells for tumor antigens

Altered Self Proteins and Co-stimulatory Molecules

- Mutated self antigens
- Antigen mimicry: viral antigens
- Expression of cryptic or hidden epitopes

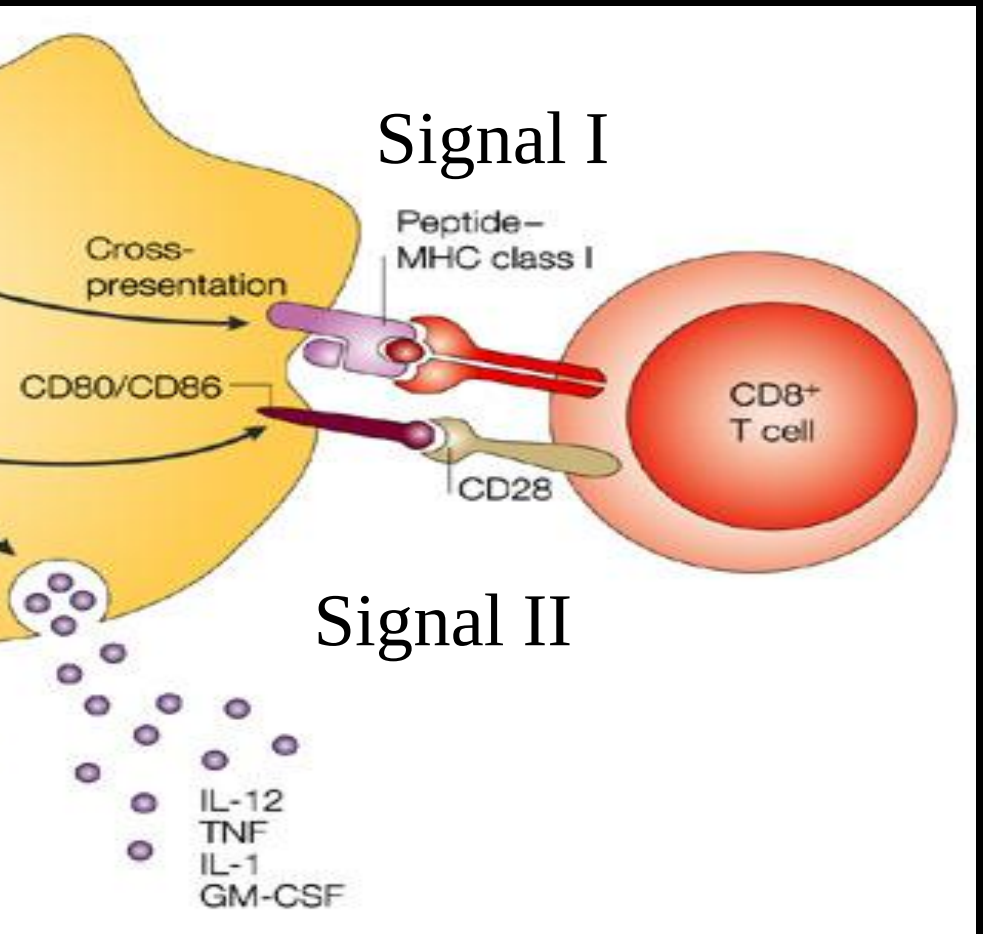


- Expression of co-stimulatory molecules in tumors or cross presentation of tumor antigens by antigen presenting cells (APC)

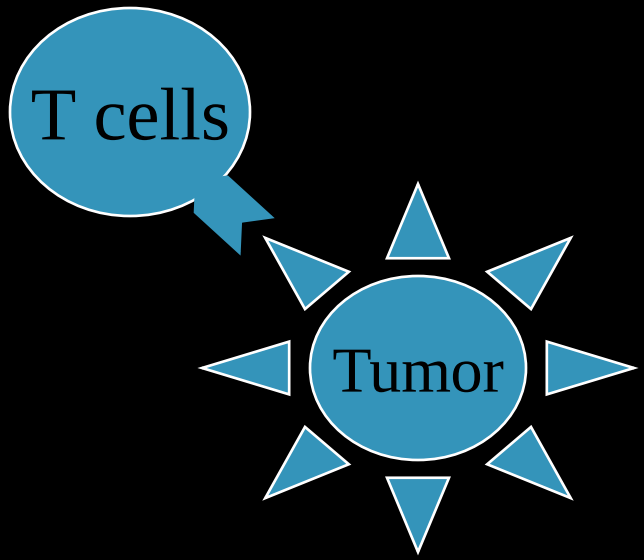


Cross Presentation of Tumor Antigens

Activation of naïve T cells



Effector T cells: killers

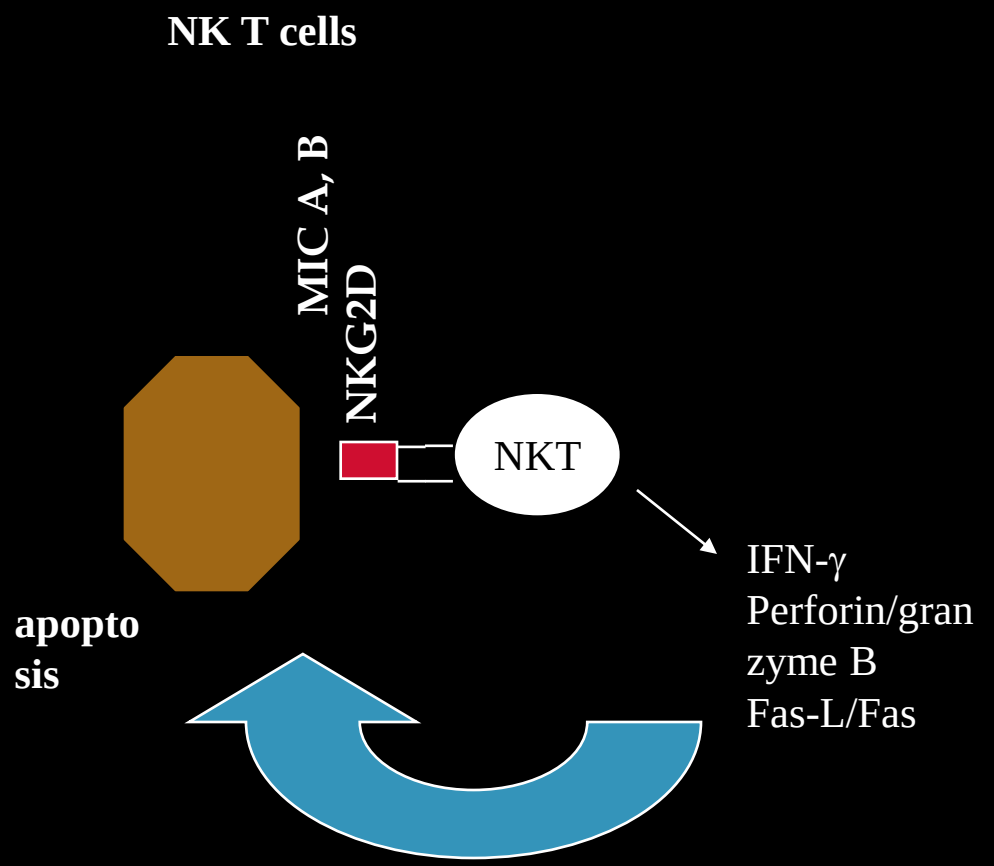


Non-specific Tumor Killing

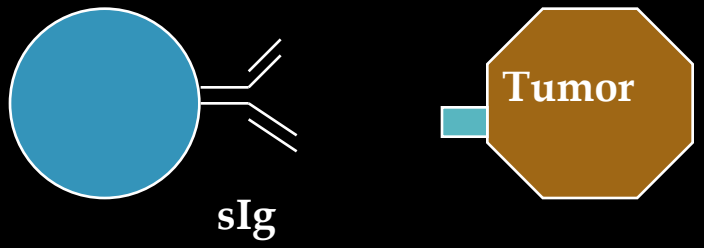
Non-specific: NK cells, γδ T cells, macrophages,

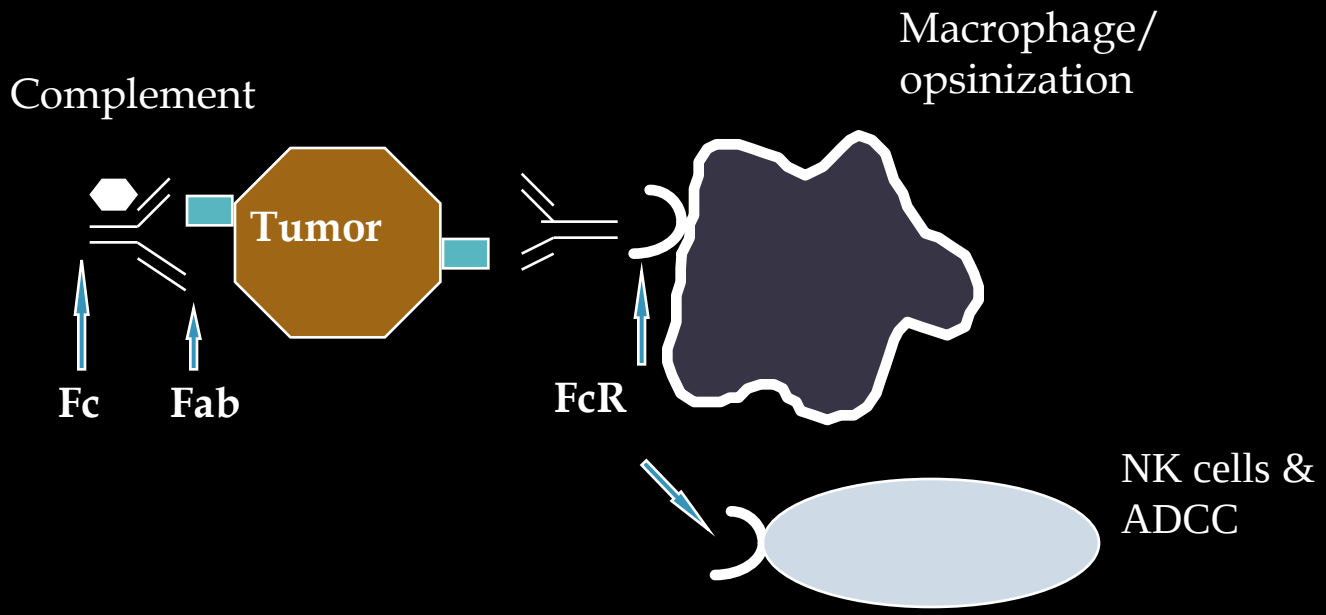
Antigen-specific: Antibody (ADCC, opsinization); T cells (cytokines, Fas-L, perforin/granzyme)

Tumor killing

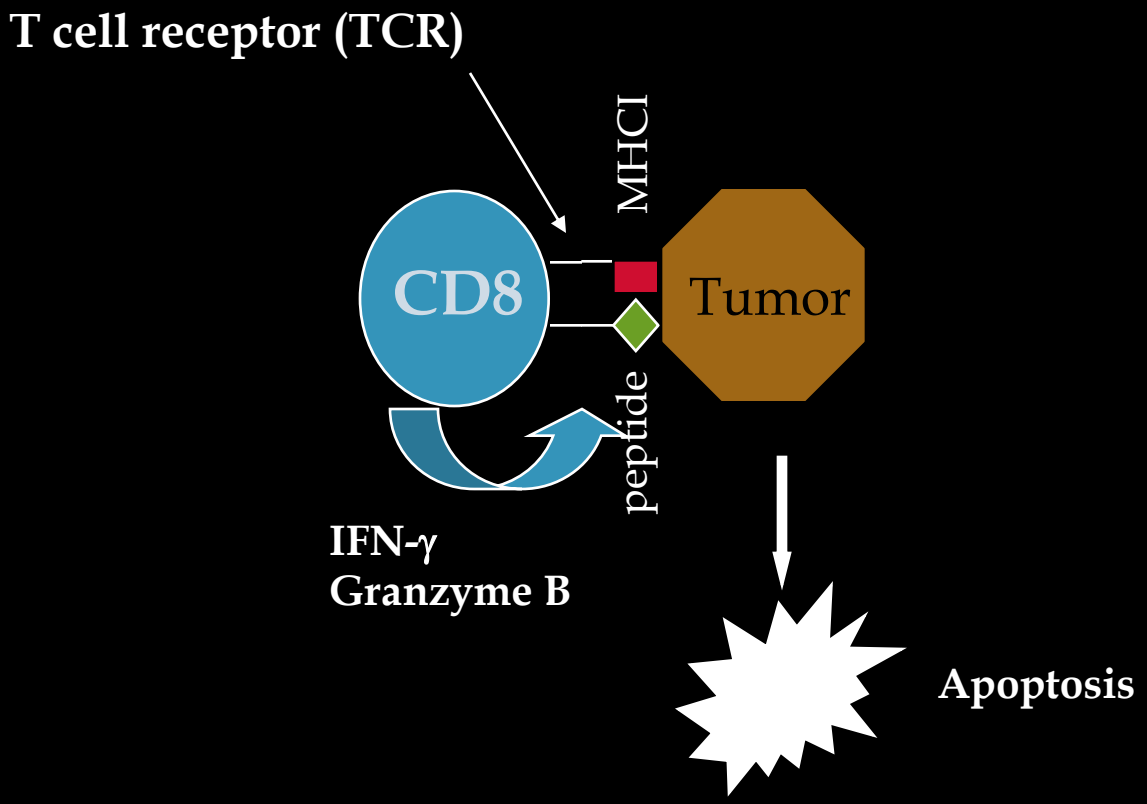


Antigen-specific tumor killing: B cells (opsinization & ADCC)





Antigen-specific Tumor Killing: T Cells



Summary

- Immune system plays a surveillance role in controlling the development of cancer, however, it also induces epigenetic changes in tumors that result in cancer (immune editing)
- Altered expression of antigens by tumors (mutation, viral antigens, cryptic epitopes), expression of co-stimulatory molecules in tumors, or cross-presentation of tumor antigens by APC results in the immune recognition of tumor cells