Tumor Immunology

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The scope of lecture

1) Immune responses that develop to cancer cells

2) Escape of cancer cells

3) Therapies: clinical and experimental

Immunologic perspective

Cancer cells can be viewed as altered self cells that have escaped normal growth-regulating mechanisms.

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 Immunity

- General Principles
  - Tumors not entirely self
    - Express non-self proteins
  - Immune-mediated recognition of tumor cells may be “positive mechanism of eliminating transformed cells
    - Immune surveillance

Tumor Antigens

- Tumor Specific Antigens
  - Present only on Tumor cells
  - Recognized by cytotoxic T cells
    - Bound by class I MHC
  - Several antigens in humans found that are not unique for tumor, however are generally not expressed by normal tissue
    - Melanoma-associated antigen-1 (MAGE-1):
      - Embryonal protein normally expressed in testis
        - Melanomas, breast ca, lung ca

Tumor Antigens

- Tumor Associated Antigens
  - Not unique to tumors, shared by normal cells
    - Differentiation- specific antigens
      - CALLA (CD10) in early B cells
      - Prostate specific antigen PSA

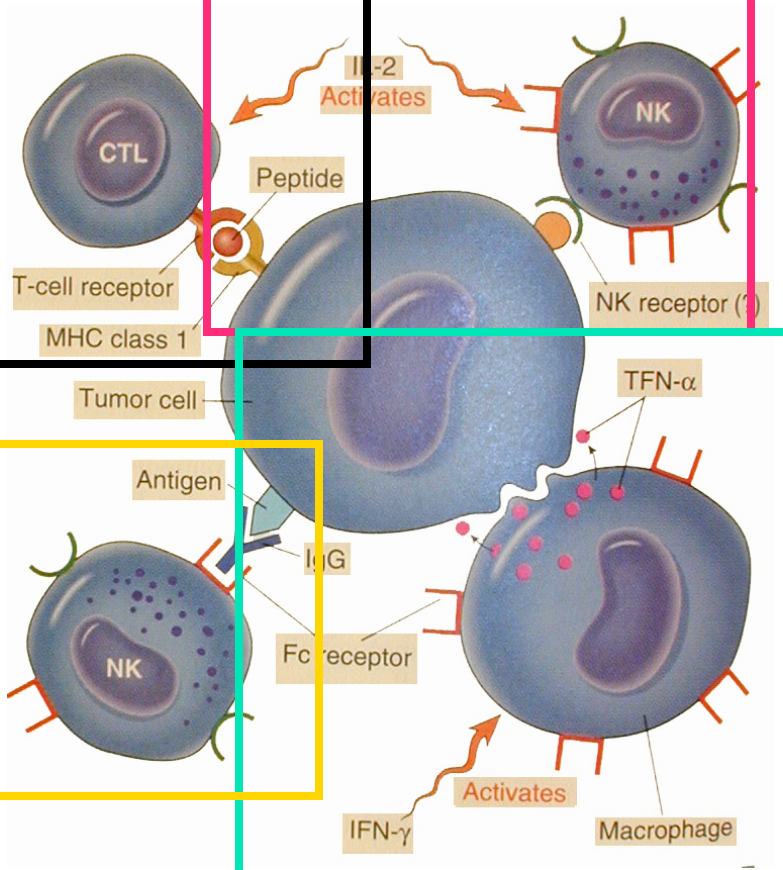
Antitumor Effector Mechanisms

- Cytotoxic T-cells
  - MHC restricted CD-8 cells (viruses)
- NK cells
  - Destroying tumor cells without prior sensitization
- Macrophages
  - Ifn-gamma
- Humoral Mechanisms
  - Via complement and NK cells

Antitumor Effector Mechanisms

Cytotoxic T-cell

NK cell

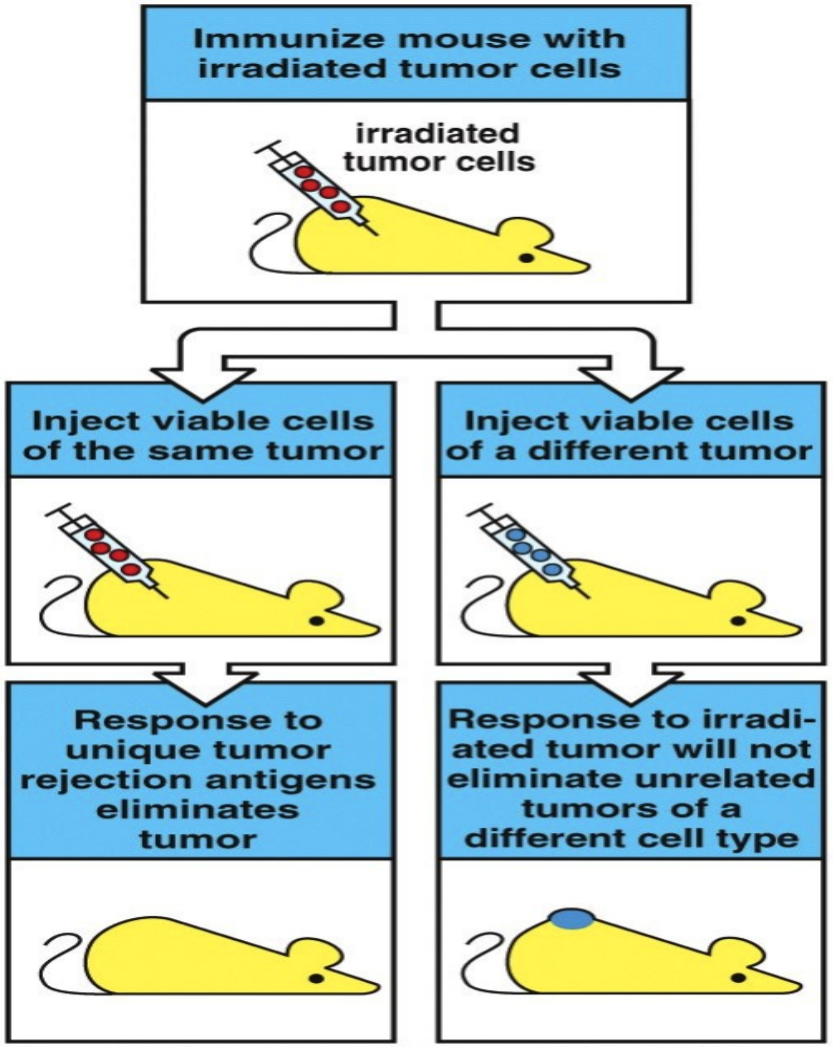


Humoral Mechanisms

Macrophage

Kumar et al. Basic Pathology 6th ed. Figure 6-32

Tumor-specific Immune Response



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)

IMMUNOSURVAILLANCE

- Argument for:
  - Increased cancer in immunodeficient hosts
    - 200x increase in immunodeficiencies (lymphoma)
      - X-linked lymphoproliferative disorder (XLP
        - EBV related
- Escape Mechanism Theories
  - Selective outgrowth of antigen-negative variants
  - Loss or reduction of HLA (escape T-cells)
  - Immunosuppression (Tumors secrete factors TGF-b)

Tumor killing

Non-specific: NK cells, γδ T cells (NKG2D), macrophages, NK T cells

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

Immune Recognition of Tumor

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

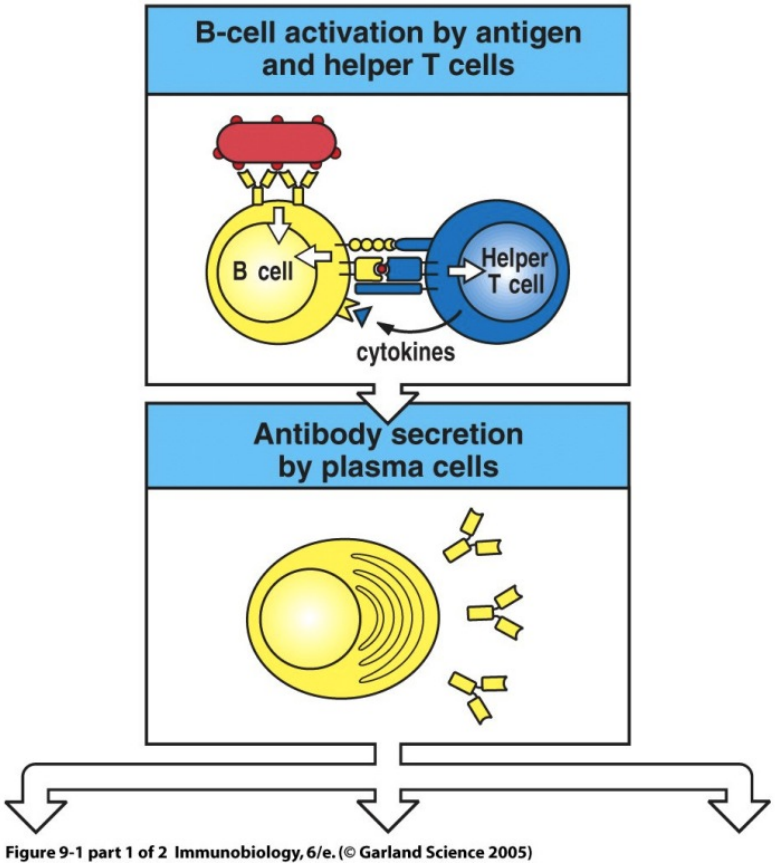
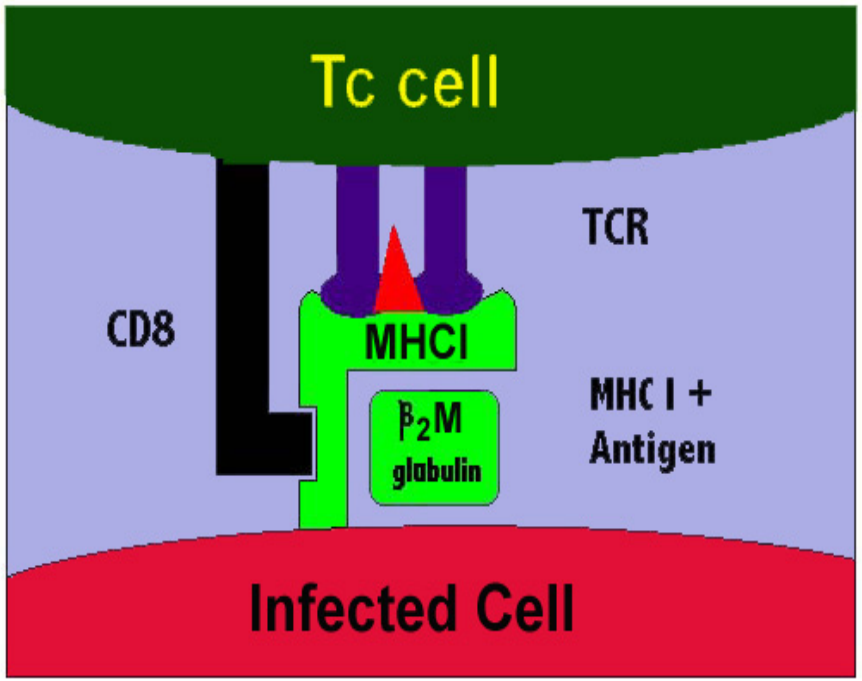


Figure 9-1 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)



Tumor Antigens

Tumor „Specific“ Ag

1) MHCI plus abnormal cell proteins (Brc-Alb, Philadelphia chromosome, CML)
2) MHCI plus viral proteins(EBV, SV40, polyoma virus)
3) Abnormal glycosylation
4) Idiotypes of myelomas and lymphomas

Tumor Associated Antigens

1) Oncofetal Ag (alphafetoprotein – hepatoma, carcinoembryonic Ag – colon ca.)
2) Melanoma Ag (MAGE-1, Melan-A)
3) Her/neu Ag (GFR)
4) EPCAM (epithelial cell adhesion molecule, carcinomas)
5) Differentiaion Ag (CALLA: common acute lymphoblastoid leukemia antigen CD10 pre-B cells)

Anti-tumor immunity

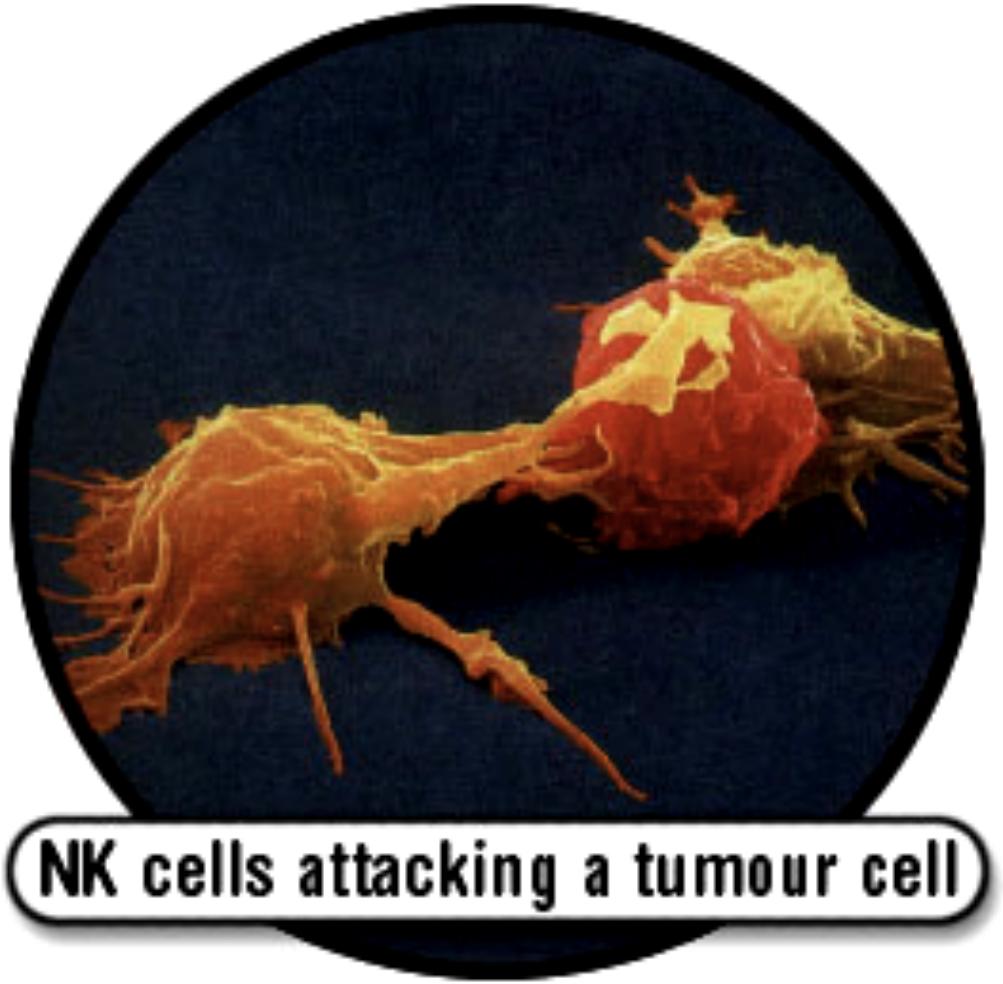
Anti-tumor immunity involve the same mechanisms as in anti-infection immunity, transplantation immunity or allergy.

- Complement
- Lysozyme
- Cytokines

- Phagocytosis
- NK cells

- Antibodies
- Tcells

Tumor Immunology



NK cells attacking a tumour cell

IMMUNOTHERAPY

- Replace suppressed components of immune system or stimulate endogenous responses
  - Adoptive Cellular Therapy
    - Incubation of lymphocytes with IL-2 to generate lymphokine activated killer (LAK) cells with potent antitumor activity
      - Enriched tumor specific cytotoxic T cells
        - Tumor infiltrating lymphocytes (TIL)

Cytokine Therapy

- Activate specific and nonspecific (inflammatory) host defenses.
  - Interferon-a, TNF-a, Il-2, IFN-g
    - IFN-a activates NK cells, increase MHC expression on tumor cells
      - Used for hairy cell leukemia

Antibody-Based Therapy

- Antibodies as targeting agents for delivery of cell toxins “magic bullet”
- Direct use of antibodies to activate host immune system
  - Her-2/neu in advance breast cancer

Cancer Immunotherapy

1) Immune adjuvans

-BCG (Bacillus Calmette Guérin) *Mycobacterium bovis*

-mph >IL-1>Th, breast tumors, malignant melanoma

-*Corynebacterium parvum*

- *DNCB (dinitrochlorobenzene) >>> DTH reaction*

Cancer Immunotherapy

2) Cytokine therapy

-IFN, IL-1, IL-2, IL-3, IL-4, IL-5, GM-CSF, TNF

Interferons

IFN alfa and beta - antiviral state, IFN gamma – activation

IFN-alfa >> hematologic malignances, melanoma, renal cancer, breast cancer (low degree of malignity)

-increase of tumor cell MHCI and mph MHCII >> CTL activity

-IFN gamma >> increase the activity of Tc, NK, mph,

Tumor necrosis factors

- TNF alfa and beta > -decrease the proliferation of tumor cells and killing
  -decrease the angiogenesis
  - adverse reactions

Systemic administration of high level of a given cytokine has been shown to lead to serious and even life threatening consequences.

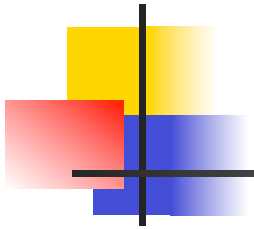
Cancer Immunotherapy

TIL and LAK cells

-in vitro Tc activation (X-irradiated tumor cells and IL-2)
-activation with IL-2 without tumor cells >> LAK cells
(activated NK, NC cells)
-systemic IL-2 >> vascular leak syndrom, shock

Tumor cell Vaccines

- autologous tumor cells +BCG
- engineered tumor cells which produce cytokines (IL-2, GM-CSF,..)



Thank You