

# Tumor Immunology

# Objectives:

- Introduction to tumors types and aetiology
- Tumors associated antigens and markers
- Evidence for immune reactivity to tumors
- Discuss immune protection against tumors and immune surveillance system
- Discuss immune mediated tumor growth
- Provide an overview of experimental cancer therapies

# Introduction

- Pathological cell masses derived by abnormal and uncontrollable clonal expansion of single cell
- Cells that continue to replicate, fail to differentiate into specialized cells, and become immortal.
- Cells become antigenically different from normal cells
- They are recognized and destroyed by immune system
- Tumors can be:
  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

# Types of 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 Tumor

- **Inherited :**
  - Expression of inherited oncogene
  - e.g. viral gene incorporated into host gene
- **Viral:**
  - Human papillomavirus (HPV)
  - Human T-cell leukemia virus (HTLV-1)
- **Chemical:**
  - Poly cyclic hydrocarbons cause sarcomas
  - Aromatic amines cause mammary carcinoma
  - Alkyl nitroso amines cause hepatoma
- **Radiological:** Ultraviolet & ionizing irradiation
- **Spontaneous:** failure in the cellular growth control

# Tumor Associated Antigens

- **Viral Antigen:** Viral proteins and glycoproteins

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

- **Tumor specific antigens:** Tumor cells develop new antigen specific to their carcinogen

- **Tumor specific transplantation antigens:** Tumor cells express new MHC antigens due to alteration of normally present MHC antigens

- **Oncofetal antigens:**

1. **Carcino-embryonic antigens (CEA)**

Normally expressed during fetal life on fetal gut

Reappearance in adult life:

GIT, pancreas, biliary system and cancer breast

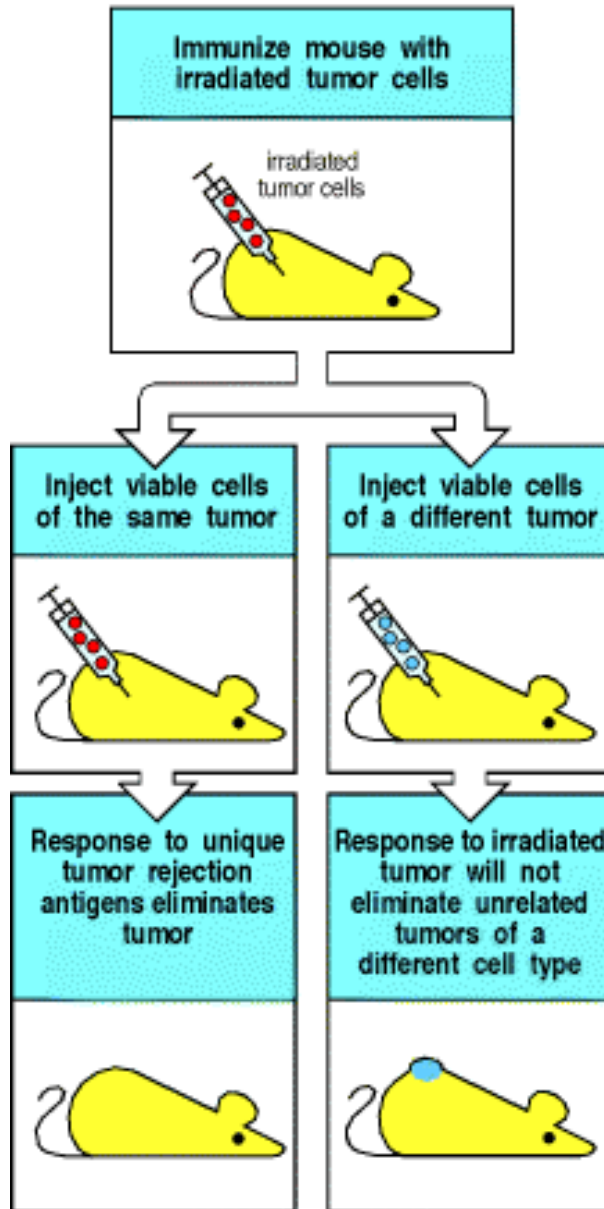
2. **Alpha fetoprotein:**

Normally expressed in fetal life

Reappearance in adult life; hepatoma

# Evidence for Immune Reactivity to Tumors

- Tumors that have severe lympho-reticular infiltration have a better prognosis than those that do not. In other words, the presence of these immune cells (lymphocytes, macrophages, dendritic cells, etc.) within the tumor indicates that the patient's own immune system has recognized the tumor as abnormal and is actively trying to fight it.
- Certain tumors regress spontaneously
- There is an increased incidence of primary and secondary malignancies (particularly lympho-reticular tumors) in immunodeficient patients
- Antibodies and immune T lymphocytes have been detected in patients with tumors.
- The young and the very old have an increased occurrence of tumors.
- Finally, animals can be specifically immunized against various types of tumors



Animal models showed that pre-treatment of mice with killed tumour material could protect against a subsequent challenge.

T cell ablation or T-cell deficient mice removed this protection.

Transfer of T cells from an immunized mouse could protect a naïve mouse from tumour challenge.

# Immune Surveillance System

- During neoplastic transformation, new antigens develop
- The host recognizes them as nonself antigens
- Cell-mediated immune reactions attack these nonself tumor cells
- Immune response acts 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

**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 macrophage

b-Gamma interferon and interleukin-2 that activate NK

c-Tumor necrosis factor alpha (cachectin)

#### 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:
  1. Antibody mediated-cytotoxicity: Cytotoxic T-cells kill IgG-coated tumor cells.
  2. Activation of macrophages: Sensitized T-cells release macrophage activating factor which activate macrophages
  3. 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 MHC I 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”
- 3) Production of immunosuppressive factors by tumor e.g. transforming growth factor (TGF- $\beta$ )
- 4) Tumor antigens may induce specific immunologic tolerance
- 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 Markers

- Tumor markers : They are either
  1. Tumor antigens
  2. Tumor products (enzymes and hormones)
- Tumor products are released in the serum of patients
- They are used to confirm diagnosis and follow up the response to therapy

# 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 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 phosphatase, lipase and amylase enzymes in cases of cancer pancreas

# Applications of Tumor Immunology

- **Diagnosis:**

- Monoclonal antibodies labeled with radioisotope have been used for *in vivo* detection of relatively small tumor foci.
- Antibodies have also been used *in vitro* to identify the cell origin of undifferentiated tumors, particularly of lymphocytic origin.
- Immuno-histological staining is used to confirm suspected metastatic foci, especially in bone marrow

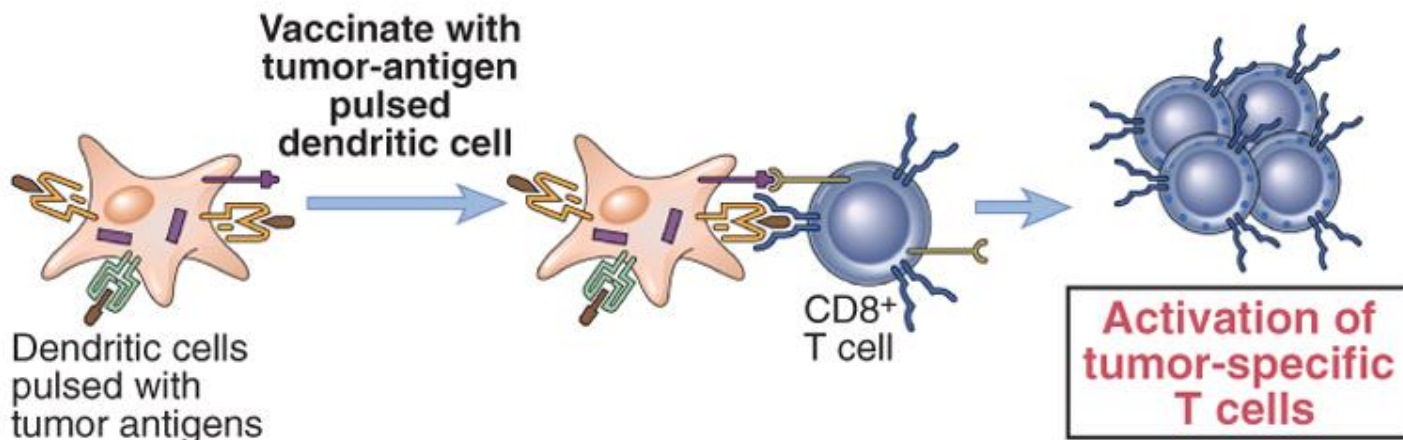
- **Treatment (immune therapy):**

- Vaccination with tumor cells
- Co-stimulators and cytokines
- Block inhibitory pathways
- Non-specific stimulation of the immune system

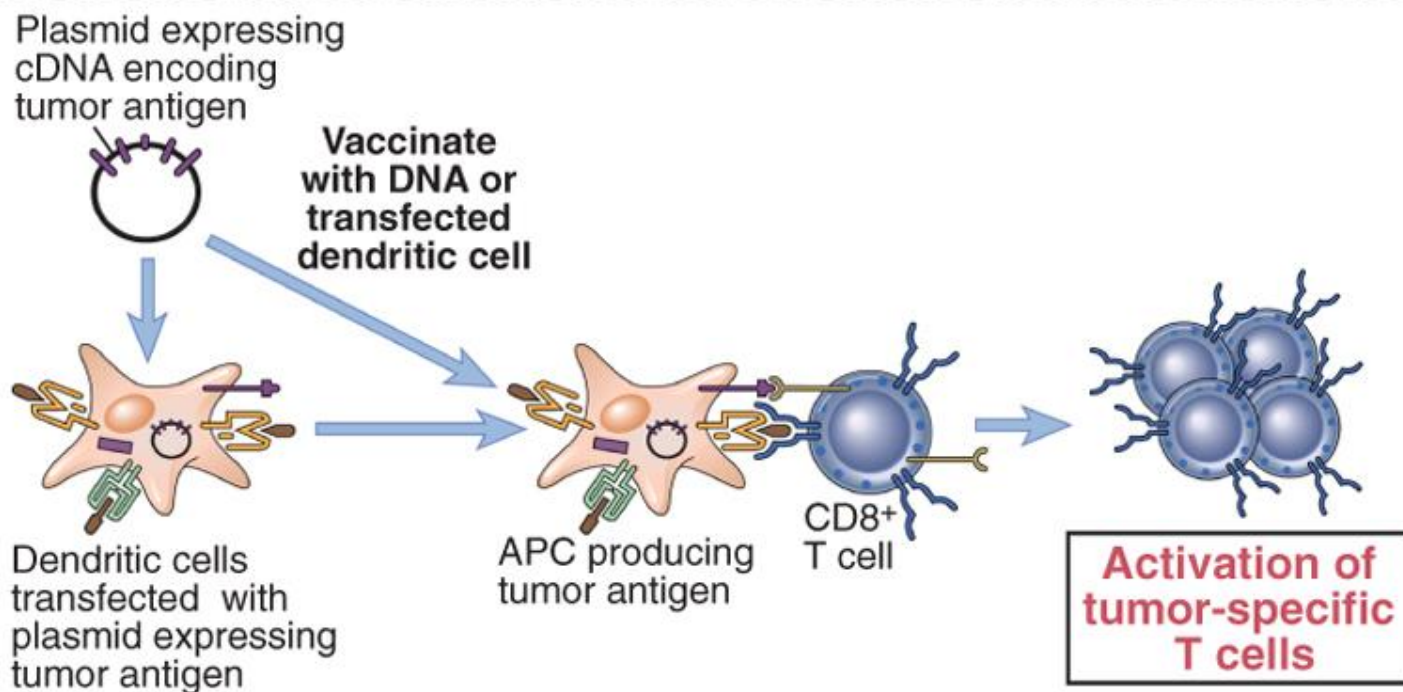
# Tumor vaccines

Type of vaccine	Vaccine preparation	Clinical trials
Killed tumor	killed tumor cells + adjuvants	Melanoma, colon cancer
	tumor cell lysates + adjuvants	Melanoma
Purified tumor antigens	Melanoma antigens	Melanoma
	Heat shock proteins	Melanoma, renal cancer, sarcoma
APC based	DC pulsed with TAA	Various
	DC transfected with TAA	
Cytokine and costimulator-enhanced	Cytokine or B7 gene transfected tumor cells	Various
	APC transfected with cytokines and pulsed with TAA	
DNA	plasmids encoding TAA	Melanoma
Viral vectors	Adenovirus, vaccinia virus encoding TAA +/- cytokines	Melanoma

A



B



# Monoclonal antibodies

---

Name	Product	Type	Target	Condition	Approved
Alemtuzumab	MabCampath	humanized	CD52	CLL, T-cell lymphoma, ALL	2001
Bevacizumab	Avastin	humanized	VEGF	colon, breast, NSC lung cancer	2004
Cetuximab	Erbix	chimeric	EGFR	colon, head and neck	2004
Gemtuzumab ozogamicin	Mylotarg	humanized, toxin-linked	CD33	AML	2000
Ibritumomab tiuxetan	<u>Zevalin</u>	murine	CD20- <sup>90</sup> Y	non-Hodgkin	2002
Rituximab	MabThera	chimeric	CD20	non-Hodgkin	1997
Trastuzumab	Herceptin	humanized	HER-2/neu	breast	1998

CEA-antibody (Arcitumomab) for in vivo diagnostics of colorectal carcinoma

CA125 antibody (Oregovomab) in clinical trial for ovarian cancer

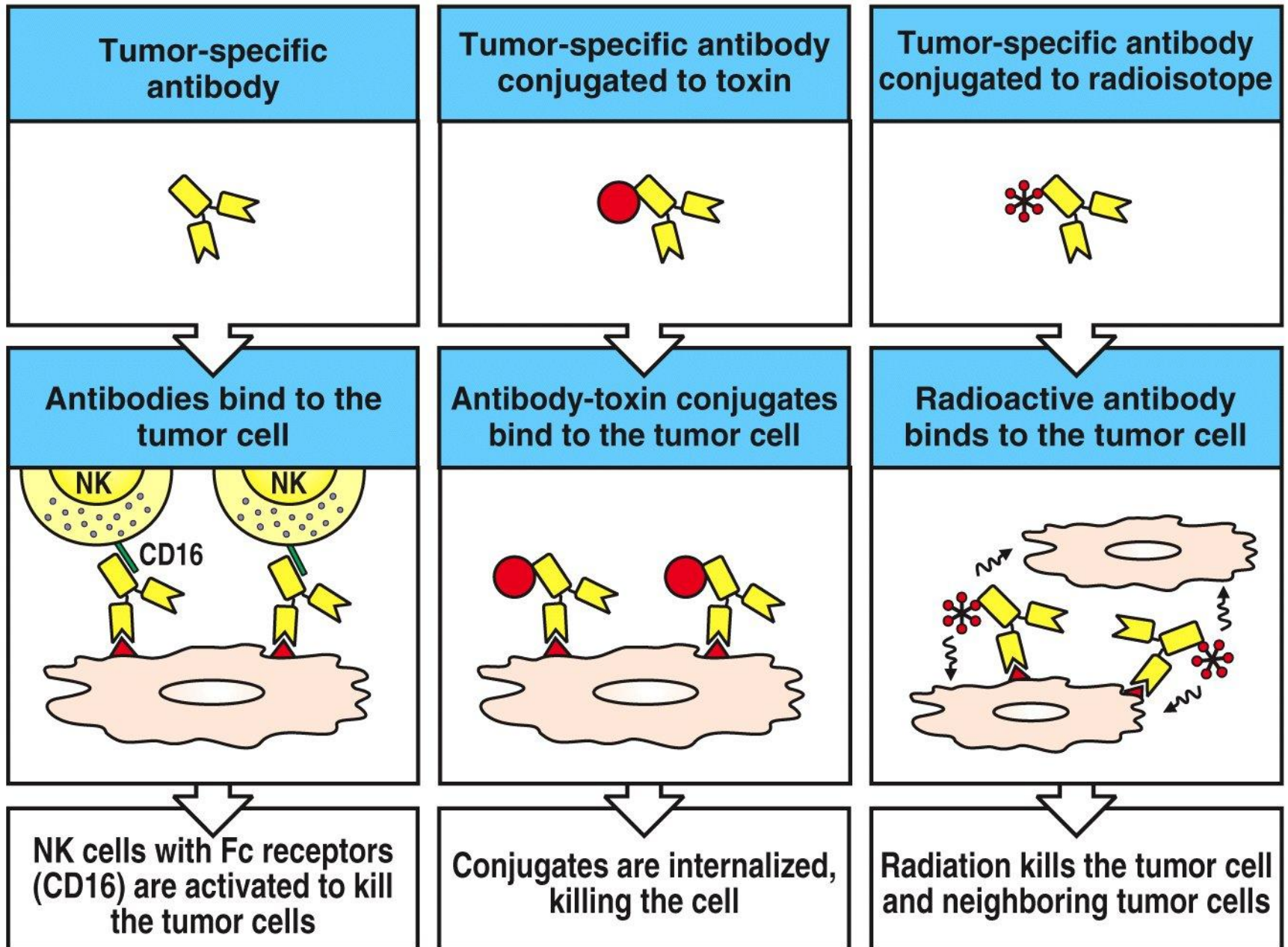


Figure 14-17 Immunobiology, 6/e. (© Garland Science 2005)