Tumor immunology

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Evasion of immune system

- Tumor cells express little antigens cause little immune response, while those caused by virus oncogene cause more effective immune response
- Very rapid tumor spread
- MHC 1 down regulation that can not be recognized by CTL or NK
- The products of tumor cells suppress the anti-tumor immune response as TGF beta, fasL and the involvement of CTLA-4 or PD-1, T reg
- Hidden tumor surface antigens

Immune cells that help tumor cells

- Myeloid derived suppressor cells (MDSCs) are a heterogeneous collection of cell types, including precursors of dendritic cells, monocytes, and neutrophils.Recruited to tumors and suppress anti-tumor innate and T cell responses.
- M2 cells are macrophage confined to tumors promote tumor angiogenesis which favor tumor growth

Tumor antigens

- Old classification
  - TAA, Tumor associated antigen, which are present on some tumor cells with higher levels than on normal cells, can escape from immune system because of self tolerance,
  - TSA, tumor specific antigen, which are present only on tumor cells
- Classification depends on origin
  - Deregulated normal antigen
  - Foreign antigens as viral origin
  - Re-expression of normal fetal antigen
  - Cell Type-Specific Differentiation Antigens

Deregulated normal antigens

1. genetic mutation of normal cellular gene. Examples are tumor suppressor genes. The resulting protein product not found in normal cells, examples; abnormal products of P53, RAS genes. expression of abnormal type as mucin (MUC-1) in breast carcinoma, (TSA)
2. Abnormally located and over-expressed normal cellular proteins (TAA)
   - Abnormal in site, MAGE (melanoma antigen) is normal silent antigen on testis but also in carcinoma of breast, lung and bladder
   - Tyrosinase protein normally expressed in small amount in melanocytes, over expressed in melanoma

foreign antigen

- Oncogenic viruses;
  - antigens expressed by cells infected with some DNA viruses, such as
    - human papilloma viruses (HPV) (E6 and E7 proteins — a risk factor for cervical cancer
    - KSHV (***Kaposi's*** sarcoma-associated herpesvirus ***)*** , the virus that can cause Kaposi's sarcoma
    - Epstein-Barr virus (EBV) — EBNA-1 protein. predisposes to Burkitt's lymphoma
    - hepatitis B — predisposes to liver cancer
  - RNA viruses, retrovirus (HTLV-1) in T cell leukemia.
- Good choice for immunization
- Not unique for each tumor but shared by many tumors caused by that virus

Oncofetal antigens

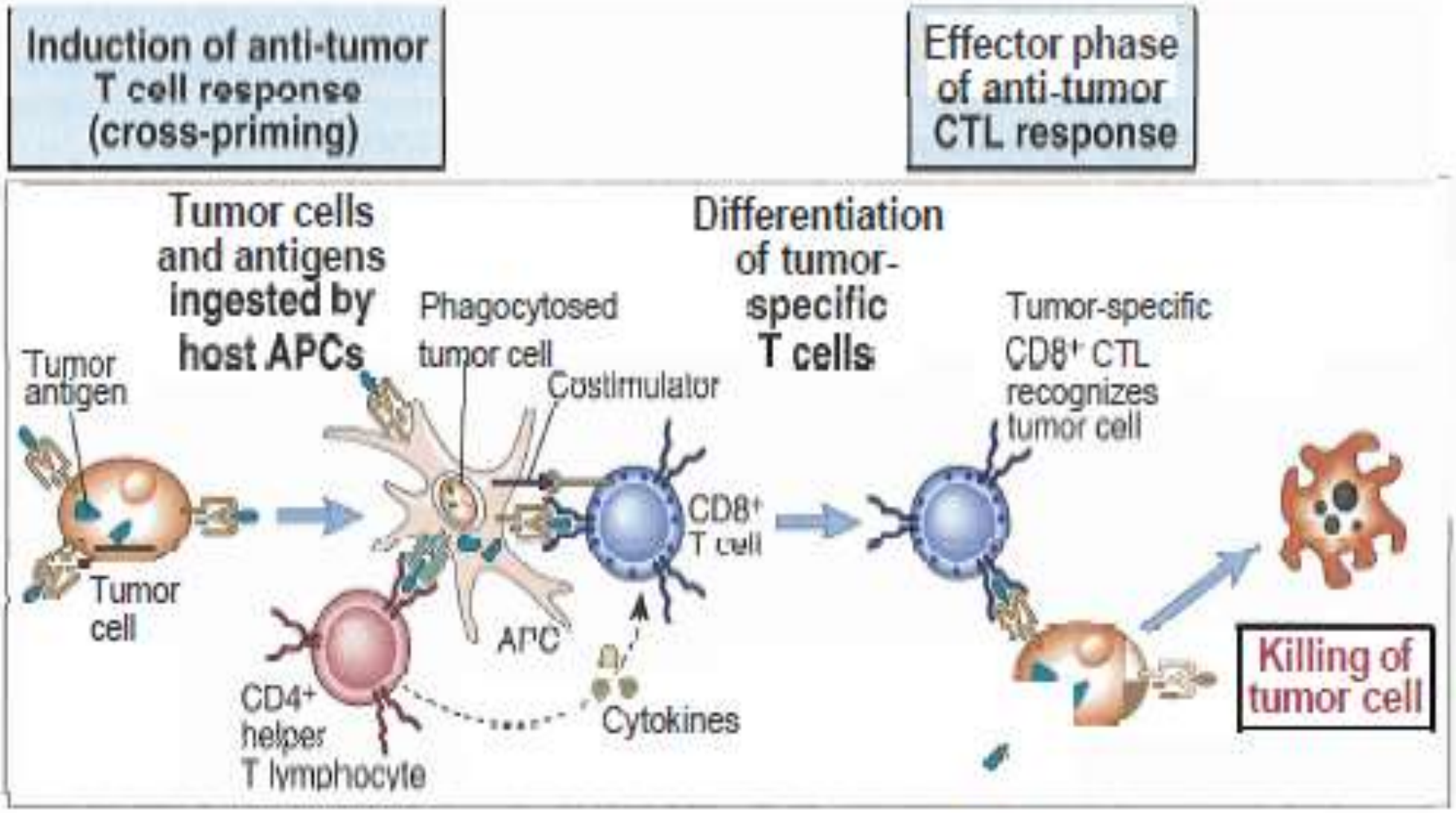
- Oncofetal antigens, present during fetal development but lost during adult life. Reappear with cancer (TSA)
  - Alpha feto proteins in hepatic carcinoma
  - Carcino-embryonic antigen (CEA)in cancer of intestine (colon, pancreas and stomach).
- Cell type specific differentiation antigens, present in different tumors derived from the same cell origin, CD10 and CD20 in B cell derived tumors, TAA

Importance of tumor antigen

- Useful in identifying tumors in general and specific tumors (immunodiagnosis by screening of their presence in blood or antibody produced against them present in the serum), they called tumor markers and can be used for vaccination

Immune response to tumor (immune surveillance)

- Cytotoxic T cells (CTL) are the main immune response.
  - Tumor cells ingested by APC and antigen presented by MHC2 by normal presentation and differentiation of CD4 to TH1. Or on MHC1 (cross presentation). and the stimulation of Tc by this MHC1 is (cross priming).
  - Briefly, tumor cells infected with viral antigens or tumor in APC itself present them to Tc.
  - Activated Tc kill tumor cells and activate macrophages and other cells by IFN gamma and chemokines.
  - Th1 cells role is in activation Tc and macrophages by secreting IFN gamma


Induction of anti-tumor T cell response (cross-priming)
Effector phase of anti-tumor CTL response
Tumor cells and antigens ingested by host APCs
Differentiation of tumor-specific T cells
Tumor antigen
Tumor cell
Phagocytosed tumor cell
Costimulator
CD8+ T cell
APC
CD4+ helper T lymphocyte
Cytokines
Tumor-specific CD8+ CTL recognizes tumor cell
Killing of tumor cell

- Antibodies, but mainly act in tumors caused by viruses or when tumor markers spread in the body fluids ,the tumor cells can be Killed by ADCC by NK. Or by complement activation
- cells escape Tc (low MHC1) is killed by NK cells; secreting EZMs or ADCC
- Lymphocytes from site of tumor, cultured in the presence of IL2(become lymphokine-activated killer cell,LAK) and have the ability to kill tumor cells that escape NK cells
- Macrophages; Stimulated by tumor specific T cells, kill cells directly and secret TNF.

immunotherapy

- Or biologic therapy

1. Augment the host immune response against tumor (active therapy)
2. transfer tumor specific antibodies or T cells (passive therapy)
3. Treatment with cytokines.

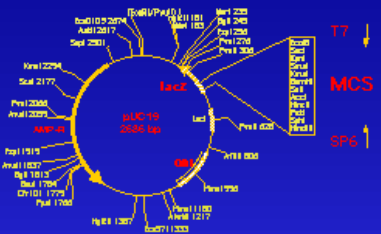
Active therapy,

- Vaccination with killed tumor cells or tumor antigens with adjuvants as cytokine (IFN gamma, IL-12, IL-2) or accessory molecule as B7. and DNA vaccine contains Tumor gene injected in muscles
- Most of them are therapeutic except viral vaccine in tumor caused by virus; it is preventive as Human Papilloma Virus in cervical carcinoma
- Injection of polyclonal lymphocytes activator at site of tumor growth as BCG vaccine or anti-CD3 antibody

anti-idiotype antibodies

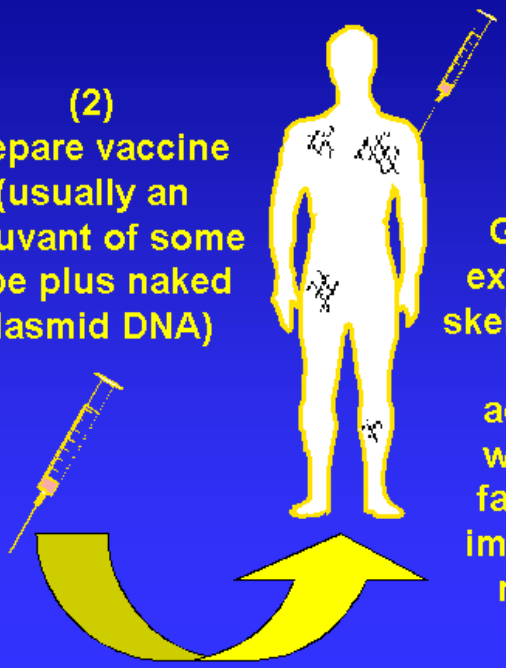
Mouse immunized with antigen, select the antibody produced, re-inject the antibody in other mouse to form anti-idiotype for that antibody; the anti-idiotype resembles antigen in shape. Then use this anti-idiotype as vaccine (it resemble antigen)

DNA Vaccines



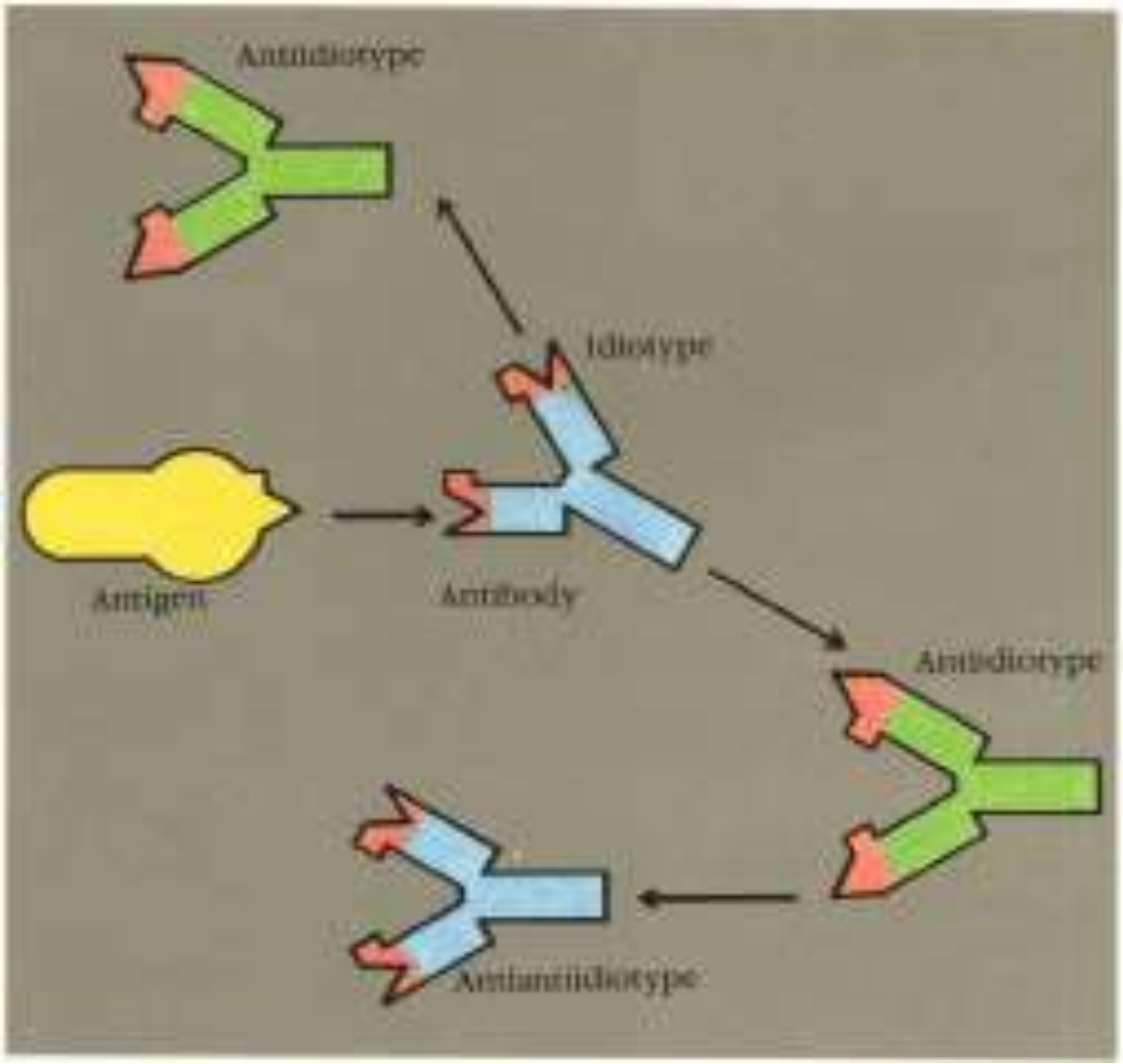
(1)
Insert genes to be expressed (peptide antigen genes, GM-CSF gene, IL2 gene, etc.) into plasmid vector(s)

(2)
Prepare vaccine (usually an adjuvant of some type plus naked plasmid DNA)



(3)
Genes are expressed in skeletal muscle cells or adipocytes where they facilitate an immunologic response

Anti-idiotype



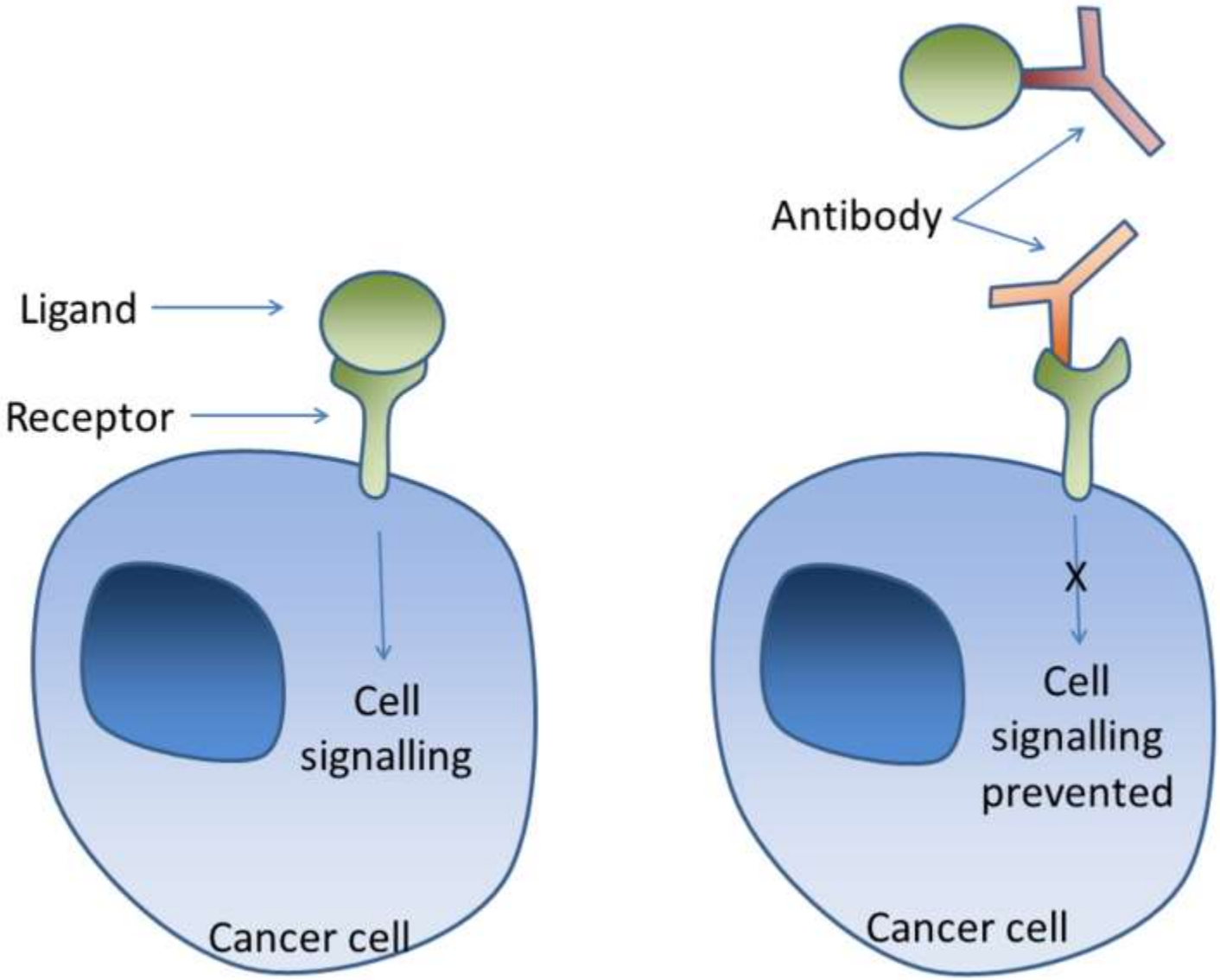
Passive immunotherapy

- Transfer of immune effective T cells or antibodies

1. Adoptive cell transfer.
    1. Tumor infiltrating lymphocytes (TIL) from similar patients , or lymphokine activated killer(LAK) (T cells culture with IL-2 and tumor antigen), is re-transferred to patient. -As in prostate cancer
    2. Inject T cells carry receptor specific for cancer antigen called chimeric antigen receptor. T cells engineered to produce artificial TCR to target a specific antigen (leukemia)

Anti-tumor antibodies

2. Monoclonal antibodies; Injecting mouse with certain tumor antigen then collect B cell and fuse it with plastocytoma to proliferate and produce monoclonal antibodies
   - Example is anti-CD20 in B cell lymphoma (rituximab);activate ADCC or MAC formation; killing of tumor cell
   - Or conjugated Ab with drug (chemotherapy)
   - Antibody block growth receptors as in colon cancer; Inhibit binding of the ligands or protein that important to tumor growth by either binding the ligand itself or to the receptor


Ligand
Receptor
Cell signalling
Cancer cell
Antibody
X
Cell signalling prevented
Cancer cell

Cytokine treatment

- Interleukin-2 and interferon-α are examples of cytokines, proteins that induce immune system against the tumor.
  - Interferon-α in virally caused tumors, it is used in the treatment of hairy-cell leukemia, AIDS-related Kaposi's sarcoma,
  - Interleukin-2 is used in the treatment of malignant melanoma and renal cell carcinoma.

Block inhibitory pathways

- Block CTLA-4 on tumor specific activated T cell to inhibit their death (melanoma)
- Block PD1 tumor specific activated B cell to inhibit their death as in advanced cancers
- Complications; autoimmunity and inflammation

❑Using BCG at site of cancer activate T cells against tumor as in bladder cancer