Tumor Immunology
(Cancer)

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Tumors arise from accumulated genetic mutations

Mutations
Usually have >6 mutations in both activation/growth factors and tumor suppressor genes.

Types of genes that control cancer
Oncogenes

Oncogenes can be receptors or activation/signaling proteins.

Mutations lead to changes in tissue growth and further progression can result in tumors.

*APC- adenomatous polyposis coli gene. Tumor suppressor.
Types of genes that control cancer

◆ Tumor suppressor genes
  – cancer arises when the tumor suppressor genes stop working, lack of growth inhibitory signals.
  – These genes are part of normal control of cell cycle, usually inhibiting growth-promoting factors and cell division.

◆ Cell Death Proteins
  – The cell death proteins are either activating or inhibiting cell death, apoptosis.

Inherited predisposition to cancer

◆ Most inherited cancer genes are mutated tumor suppressor genes.

◆ These inherited genes can result in early onset of cancer (higher predisposition).

Immunological Surveillance
(Burnet, Thomas)

Hypothesis: Tumors are constantly arising. A major role of the immune system is to eliminate this constant threat. Tumors get through when immune system fails.

Evidence:
◆ Pro: Incidence of cancer is higher in conditions of immunosuppression, ie. Transplant recipients, AIDS.

◆ Con: Those tumors seem to be largely of viral origin, so findings are no different than for any infectious agent.

New Theory
Adaptive immune response can kill tumors BUT tumor cells evade host immune response

Mechanisms of Tumor Escape
◆ Antigen loss
◆ Loss of MHC or TAP
◆ Production of inhibitory cytokines (TGFb)
◆ Expression of FasL

Tumor Seen as Self
◆ Do not initiate inflammation
◆ Induction of tolerance
Immune Response to Tumors

◆ Cell Mediated
  – Cytokines from activated CD4+ T cells.
    TNF-α and LT-α (TNF-β) directly toxic to some tumor cells.
  – CD8+ CTL, NK cells, and macrophages activated by IFN-γ from CD4+ T cells.

◆ Antibody Response
  – ADCC and Complement lysis possible.

What is the Anti-Tumor Immune Response?

◆ Tumor infiltrating lymphocytes including CTLS and NK cells were isolated from tumors.

◆ These CTLS were specific for tumor antigens.
  What are these tumor antigens?

I. Identification of Tumor Antigens

![Diagram of tumor antigens identification process]

Biochemical identification:
- Purify MHC from tumor cells, elute peptides.
- Isolate peptides by HPLC and determine sequence

Use T cell clones to screen tumor cell cDNA library.
Confirm with synthetic peptide of predicted sequence

Sources of Antigens that Stimulate Anti-tumor Immune Responses

◆ Fundamentally related to the neoplastic process
  – Mutated oncogenes, suppressor genes (ras, p53)
  – New antigens generated by translocation (bcr/abl fusion protein)
  – Antigens derived from oncogenic virus (EBV, HPV)

◆ Coincidental antigens
  – Overexpressed normal differentiation antigen
  – Re-expressed oncofetal antigen
II. Types of Tumor Antigens

- Rexpressed embryonic antigens. Self antigens. (oncofetal proteins).
- Differentiation antigens. Overexpressed normal proteins such as melanocyte regulation proteins expressed in melanomas can become antigens.
- Viral antigens. Oncogenic viruses.
- Mutated self proteins. Point mutations of normal cellular genes (unique tumor antigens).

Origins of Shared Human Tumor Antigens

- Cancer/Testes Antigens - MAGE, BAGE, GAGE
- Differentiation Antigens - Tyrosinase, Melan-A, TRP-1, TRP-2
- Overexpressed proteins - HER-2/neu, p53
- Viral proteins - HPV-E7

Shared Tumor Antigens

Differentiation antigens

- Overexpressed proteins found in tumors from unique cell type.
- Immune system was probably not tolerized in thymus to these antigens.
  - Examples: Melanoma tumor antigens which are proteins used in melanin production.
  - MART-1, tyrosinase.
**Cancer Therapies**

**I. Prevention**
Most preventive agents can be effective at different stages along the progression towards cancer.

**TABLE 1. Mechanisms of Action of Chemo Preventive Agents.**

<table>
<thead>
<tr>
<th>AGENT</th>
<th>MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>Inhibition of cyclooxygenase-2</td>
</tr>
<tr>
<td>Folate</td>
<td>Increased intracellular folate pools</td>
</tr>
<tr>
<td>Calcium</td>
<td>Binding of bile and fatty acids</td>
</tr>
<tr>
<td>Estrogens</td>
<td>Decreased synthesis of secondary bile acids</td>
</tr>
<tr>
<td>Estrogens</td>
<td>Decreased production of insulin-like growth factor 1</td>
</tr>
<tr>
<td>Estrogens</td>
<td>Direct effects on colorectal epithelium</td>
</tr>
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**II. Older Cancer Treatments**
SLASH/BURN/POISON

- **Slash** ➔ Surgery
- **Burn** ➔ Radiation
- **Poison** ➔ Chemotherapy

**III. New Targeted Cancer Treatments**
Enhance immune response to tumors

- **CK therapy**
  IL-2, IFN-g, TNF-a given in IV doses.
- **Adoptive transfer of anti-tumor immune cells**
  lymphokine-activated killer (LAK) cells, tumor infiltrating lymphocytes (TILs)
- **Cancer vaccines**
  - Irradiate tumor cells inject back into patient.
  - Shared tumor antigens as vaccines.
- **Manipulate costimulation**
  - Add B7. Block CTLA4
Two Signals Required for T cell Activation

Epithelial Cells
Tumor Cells

APC

TCR

CD28

Peptide/MHC

B7

No Proliferation
(Anergy?)

Proliferation

IL-2

T Cell

T Cell

Dendritic Cells
Macrophages
Act. B cells

B7 Transfected tumor cells are rejected

B7+ K1735 Melanoma cells are rejected

Combinatorial Tumor Vaccines

- B7 plus IL-2
- B7 plus IL-12
- GM-CSF plus CTLA-4 blockade
- Surgical reduction plus CTLA-4 blockade
- Chemotherapy plus CTLA-4 blockade
Skin and hair depigmentation as a result of treatment of B16 tumors with anti-CTLA-4 and GM-CSF producing vaccines

Strategies Based on Knowledge of Antigenic Peptides

- **Active Immunization:**
  - Peptide: With adjuvant, linked to helper peptide, pulsed on APC
  - Peptide followed by immunostimulatory cytokines
  - Recombinant virus: Epitope together with genes encoding cytokines, costimulatory molecules, or other immunomodulatory agents

- **Passive Immunotherapy:**
  - Adoptive transfer of anti-tumor lymphocytes expanded in culture by stimulation with antigenic peptides
Antibody-based therapy

- Tumor-specific therapies: Not very successful due to lack of true tumor specific antigens, some problems with delivery
- Anti-CD20 (Rituximab), anti-Her2/Neu (Herceptin)
- Immunotoxins: Antibody specific to tumor used to deliver toxic molecule to lyse tumor cells.

Oncolytic Viruses

- Viruses naturally selected or lab engineered to grow in and specifically kill tumor cells.
  - Example: Engineer measles virus to interact with specific receptor that is overexpressed on tumor cells.
  - Example: Vesicular stomatitis virus (VSV) can replicate in tumor cells deficient in IFN pathway. Tumor cells with mutations in their interferon response can be rapidly killed by VSV.
- Advantages of oncolytic viruses
  - Can elicit host immune response against tumor
  - Limited resistance developed