Immunology of Cancer
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Objectives

• Provide a perspective of immune responses to tumor cells, and towards tumor cell destruction.

• Describe categories of tumor antigens, and how these categories impact recognition of self.

• Review effector mechanisms in tumor immunity, and detail limitations in responses.

• Present aspects of immunodiagnosis and immunoprophylaxis/immunotherapy to detect and augment response to tumors.
Tumor/Cancer Immunology

The Basics

Cancer immunology studies interactions between the immune system and tumors or malignancies

• Recognition of Cancer Specific Antigens
  1. Immunosurveillance
     • in 1957 Burnet and Thomas proposed that lymphocytes act as sentinels in recognizing and eliminating continuously arising, nascent transformed cells
  2. Immunoediting
     • process by which a person is protected from cancer growth and the development of tumor immunogenicity
       – Elimination
       – Equilibrium
       – Escape
Tumor Antigens

• Normal gene products
  – Turned on at wrong time on incorrect cell
  – Oncogene/oncofetal antigens/embryonic antigens
  – Growth suppression inhibition

• Mutant cellular gene products
  – Somatic mutation or point mutation
  – Genetic rearrangement
  – Can occur naturally or due to carcinogens

• Viral gene products
  – Involved in cellular transformation
  – Retroviral encoded oncogenes
    • Products can lead to chromosomal translocation, point mutations, gene amplification
Tumor antigens/tumor specific transplantation antigens (TATA/TSTA).
<table>
<thead>
<tr>
<th>Category</th>
<th>Type of Antigen</th>
<th>Antigen Name</th>
<th>Types of Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal cellular gene products</td>
<td>• Embryonic</td>
<td>• Oncofetal antigens</td>
<td>• Several</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Melanoma Associated-1; -2</td>
<td>• Lung, pancreas, breast, colon, stomach</td>
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<tr>
<td></td>
<td></td>
<td>• CEA</td>
<td>• Liver, melanoma, carcinoma of bladder, lung, testis</td>
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<td></td>
<td></td>
<td>• AFP</td>
<td></td>
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<tr>
<td></td>
<td>• Differentiation</td>
<td>• Normal intracellular enzymes</td>
<td>• Prostate</td>
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<tr>
<td></td>
<td></td>
<td>• Oncoprotein</td>
<td>• Prostate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Carbohydrate</td>
<td>• Melanoma</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Breast, ovary</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Lymphoma</td>
</tr>
<tr>
<td></td>
<td>• Clonal amplification</td>
<td>• Ig isotype</td>
<td>• Lymphoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• B cell clone Ab</td>
<td></td>
</tr>
<tr>
<td>Mutant cellular gene products</td>
<td>• Point mutations</td>
<td>• Oncogene product</td>
<td>• Several</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Suppressor gene product</td>
<td>• Several</td>
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<tr>
<td></td>
<td></td>
<td>• CDK</td>
<td>• Melanoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Several</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Melanoma</td>
</tr>
<tr>
<td>Viral gene products</td>
<td>• Transforming viral gene</td>
<td>• Nuclear protein</td>
<td>• Cervical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HPV E6 and E7</td>
<td></td>
</tr>
</tbody>
</table>
Activation of cellular proto-oncogenes in human cancer

- A Proto-Oncogene is a normal gene that undergoes mutation to allow increased expression.
  - It may regulate other genes, through functional activation or suppression
  - Typical function in a way to affect cell growth
<table>
<thead>
<tr>
<th>Proto-oncogene</th>
<th>Activation mechanism</th>
<th>Chromosomal change</th>
<th>Associte cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-myc</td>
<td>Genetic rearrangement</td>
<td>Translocation: 8-14. 8-2 or 8-22</td>
<td>Burkitt’s lymphoma</td>
</tr>
<tr>
<td>C-abl</td>
<td>Genetic rearrangement</td>
<td>Translocation 9-22</td>
<td>CML</td>
</tr>
<tr>
<td>C-H-ras</td>
<td>Point mutation</td>
<td></td>
<td>Bladder carcinoma</td>
</tr>
<tr>
<td>C-K-ras</td>
<td>Point mutation</td>
<td></td>
<td>Lung and colon carcinoma</td>
</tr>
</tbody>
</table>
Carcinogen-Induced Tumor Antigens

• Carcinogens can induce mutations in normal genes that were previously silent.

• These mutations can give rise to an array of different gene products.

• There is very little or no cross reactivity in these tumor antigens. Each one appears antigenically unique.
  – Lack of cross reactivity in carcinogen induced tumor antigens is due to the random mutations induced by the chemical or physical carcinogenic substance.
Effector mechanisms in tumor immunity

“Kiss of Death”

Dr. Andrejs Liepins/ Science Photo Library
Effector mechanisms in tumor immunity

• Innate and Adaptive Immunity play important roles

• Dispersed cells easier to target than solid tumors
<table>
<thead>
<tr>
<th>Effector Mechanism</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>B cells and antibodies (ADCC, CDC)</td>
<td>Role in immunity– poorly understood</td>
</tr>
<tr>
<td>T cells (cytolysis, apoptosis)</td>
<td>Critical for rejection of virally- and chemically–induced tumors</td>
</tr>
<tr>
<td>NK cells (cytolysis, apoptosis, ADCC)</td>
<td>Tumor cells not expressing MHC class 1 alleles are effectively rejected by NK cells</td>
</tr>
<tr>
<td>Macrophages and neutrophils (cytolysis and phagocytosis)</td>
<td>Experimentally activated by using bacterial products to destroy or inhibit tumor cell growth</td>
</tr>
<tr>
<td>Cytokines (apoptosis, recruitment of inflammatory cells)</td>
<td>Growth inhibition shown using adoptively transferred tumor cells transfected with cytokines (eg: GM-CSF)</td>
</tr>
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</table>
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ImmunoEditing

• **Elimination**
  – Initiation of the anti-tumor response
  – Innate cells: NK cells for direct apoptosis kiss
    • IFN-\(\gamma\), Chemokines
  – Macrophages
  – Draining to lymphatics
  – Activation of CD4 (Th1) to give help to CD8 cells
    • Cytotoxic T cells home back to tumor to destroy

• **Equilibrium and Escape**
  – Tumor cell variants survive elimination phase
    • Cells continue to expand in uncontrolled manner
**Effector Cells in Tumor Immunity**

**CTLs** – antigen specific and MHC restricted.
- CTLs express CD8.
- CTLs kill their targets by using Perforin, Granzymes, Cytokines (TNF-β, IFN-γ)
- Fas and Fas ligand.

**NK cells** are morphologically large granular lymphocytes (LGLs).
- Non-T and non-B lymphocytes lack surface CD3, CD4, CD8 and CD19. They do not express immunoglobulins or TCRs.
- NK cells express CD16 and CD56.
- NK cells kill by releasing perforin, granzymes and cytokines (IFN-γ and TNF).
- Reaction- nonspecific (they do not use a T cell receptor).

**Lymphokine activated killer cells (LAK cells)** are morphologically LGLs.
- Non-T non-B lymphocytes.
- Reaction– nonspecific.

**NK-ADCC- NK cells** are the major cell type that carries out antibody-dependent cellular cytotoxicity (ADCC).
- NK cells have Fc receptors (CD16) that recognize Fc portion of IgG.
1) CD4+ T cells must recognize antigen presented by MHC class II molecules on an APC (antigen presenting cell; dendritic cell or macrophage).

2) Activated Th1 cell secretes IL-2 and IFN-γ, which activates CTLs.

3) Activation of CTL

4) Activation of NK cells and macrophages (not shown)
## Limitations of effectiveness of immune responses against tumors

<table>
<thead>
<tr>
<th>Tumor Related Mechanisms of Escape</th>
<th>Host Related Mechanisms of Escape</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure of tumor to provide a suitable antigenic target or an effective immune response; - lack of recognizable tumor antigen - lack of MHC class 1 - deficient antigen processing - antigen modulation - antigenic masking of tumor - resistance of tumor to tumoricidal pathways - lack of co-stimulatory signals - production of inhibitory cytokines - shedding of tumor antigens</td>
<td>Failure of host to recognize antigenic tumor cells: - immuno-suppression or immuno-deficiency - deficiency in inducing apoptosis and cell death signaling - infections or old age - deficiency in tumor antigen presentation by host APC - failure of host effector cells to reach the tumor (eg: stromal barrier) - failure of host to kill variant tumor cells - T reg hindrance to tumor immunity</td>
</tr>
</tbody>
</table>
ImmunoDiagnosis

• Immunohistochemistry: Use of antibodies to specific antigens is a powerful tool to detect and identify tumors within tissue.
  – Diagnosis on surgical specimens
  – Identify the original cancer cell phenotype
  – Classify the type of cancer
  – Predict the aggressiveness of the tumor
Tumor ImmunoTherapy

- Stimulate the immune system, reject and destroy tumors.
  - BCG immunotherapy for early stage bladder cancer
  - Imiquimod: topical therapeutic to supplement local production of IFN-γ

- Monoclonal antibodies to target and destroy tumors.
## Examples: Approved ImmunoTherapy (mAb)

<table>
<thead>
<tr>
<th>Name</th>
<th>Trade name</th>
<th>Used to treat</th>
<th>Target</th>
<th>Year approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>Rituxan</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>CD20</td>
<td>1997</td>
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<tr>
<td>Trastuzumab</td>
<td>Herceptin</td>
<td>Breast cancer</td>
<td>Erb b2</td>
<td>1998</td>
</tr>
<tr>
<td>Gemtuzumab ozogamicin</td>
<td>Mylotarg</td>
<td>Acute myelogenous leukemia (AML)</td>
<td>CD33</td>
<td>2000</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Campath</td>
<td>Chronic lymphocytic leukemia (CLL)</td>
<td>CD52</td>
<td>2001</td>
</tr>
<tr>
<td>Ibritumomab tiuxetan</td>
<td>Zevalin</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>CD20</td>
<td>2002</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>Vectibix</td>
<td>Colorectal cancer</td>
<td>EGFR</td>
<td>2006</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Erbitux</td>
<td>Colorectal cancer, Head and neck cancers</td>
<td>EGFR</td>
<td>2004</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Avastin</td>
<td>Colorectal cancer</td>
<td>VEGF</td>
<td>2004</td>
</tr>
</tbody>
</table>
“Current” strategies in experimental immunotherapy

Coico. FIGURE 19.4.
Clinical Vignette
A 63-year-old experienced severe back pain for several weeks before visiting his family physician. He complained of fatigue.

- Blood analysis revealed a red blood cell count of $3.2 \times 10^6 /ul$ (normal $4.2-5.0 \times 10^6 ul$).
- Other indicators:
  - white blood cell count of 2800/ul (normal 5000/µl).
  - a sedimentation rate of 30mm/h (normal <20mm/h).
  - a serum IgG level of 4500 mg/dl (normal 600-1500 mg/dl).
  - IgA and IgM levels were well below normal.

- Skeletal survey showed lytic lesions in vertebrae, ribs and skull. A bone marrow sample revealed 75% infiltration with plasma cells.
- Elevated protein in urine was confirmed.

The patient was diagnosed with multiple myeloma of IgG isotype.
Fig. 38.2 Radiographs of the skull and a long bone in this patient.
The serum IgG was assumed to be monoclonal because of electrophoretic results.

Probing patient serum with antibody to \( \gamma \) chain revealed IgG isotype myeloma protein.

Fig. 38.4 Electrophoresis indicates whether serum immunoglobulins have monoclonal components. (Rosen and Geha, 2004. p244)
The patient was diagnosed with **multiple myeloma** of the IgG isotype. Which of the following would be consistent with this type of malignant tumor plasma cell and its products? [more than one answer correct]

A. Lambda and kappa light chains are found in excessive quantities in urine.
B. Susceptibility to pyogenic infections is affected.
C. Serum IgG consists of IgG1, IgG2, IgG3, and IgG4 in approximately equal proportions.
D. Anemia and neutropenia are present as the result of plasma-cell infiltration in the bone marrow.
E. Serum IgG is primarily monoclonal.
An eight-year old female soccer player developed pain in her lower leg which increased progressively during stretching prior to competition. During a game she collided with another player and broke her leg. X-rays revealed a fractured femur, however spongy appearing lesions were also present throughout her leg long bones. Lab analysis showed highly elevated IgG levels at 4550 mg/dl (normal = 700-1000 mg/dl). She was diagnosed with multiple myeloma. Which of the following statements is characteristic of patients with Multiple Myeloma?

A. M component of high molecular weight is decreased in serum.
B. Relative agammaglobulinemia causes higher susceptibility to pyogenic infection.
C. Treatment includes methl xanthines given to inhibit phosphodiesterase activity.
D. Higher reactivity to polysaccharide antigens is demonstrated.
E. Macrophage malignancy leads to multiple petechial bone lesions.
Summary

• Tumor cells differ from normal counterparts by indefinite proliferation, changes in growth regulation.
• Normal cells can be transformed in vitro by chemical and physical carcinogens, or by transforming viruses. They typically express tumor specific antigens on their cell surface.
• Immune responses to tumors include: CTL mediated cell lysis, NK cell killing, ADCC and macrophage mediated cell killing. There are several cytotoxic factors such as TNF-α and TNF-β.
• Some tumors cells utilize immune response evading mechanisms.
• Cancer immune-therapy includes monoclonal antibodies, antibodies coupled with toxins, chemotherapeutic agents or radioactive elements.
• There are new strategies for cancer immune therapy: identification of specific tumor antigens, effective presentation of tumor antigens, generation of activated CTLs and T helper cells.