Infectious diseases

Mar 30, 2005
Robbins and Cotran Chapter 7
pp. 343-411
Tumor immunity

• Immune surveillance
  - Cancer immunoediting
• Tumor-specific antigens
• Tumor-associated antigens
• Anti-tumor effector mechanisms
  - CTL
  - NK cell
  - Macrophages
  - Antibodies
<table>
<thead>
<tr>
<th>Normal host cell displaying multiple MHC-associated self antigens</th>
<th>Tumor cells expressing different types of tumor antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal self proteins</td>
<td>Product of oncogene or mutated tumor suppressor gene</td>
</tr>
<tr>
<td>MHC Class I</td>
<td>Mutated self protein</td>
</tr>
<tr>
<td>No T cell response</td>
<td>Overexpressed or aberrantly expressed self protein</td>
</tr>
<tr>
<td>Oncogenic virus</td>
<td>Virus antigen-specific CD8+ CTL</td>
</tr>
</tbody>
</table>

**Examples**

- Oncogene products: mutated RAS, Bcr/Abl fusion proteins
- Tumor suppressor gene products: mutated p53 protein
- Various mutant proteins in carcinogen, or radiation, induced animal tumors; various mutated proteins in melanomas
- Overexpressed: tyrosinase, gp100, MART in melanomas
- Aberrantly expressed: cancer-testis antigens (MAGE, BAGE)

Human papilloma virus E6, E7 proteins in cervical carcinoma: EBNA proteins in EBV induced lymphoma

Figure by MIT OCW.
<table>
<thead>
<tr>
<th>Anti-tumor immunity</th>
<th>Immune evasion by tumors</th>
</tr>
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<tbody>
<tr>
<td></td>
<td><strong>Failure to produce tumor antigen</strong></td>
</tr>
</tbody>
</table>

- T cell recognition of tumor antigen leading to T cell activation
- Lack of T cell recognition of tumor
- Lack of T cell recognition of tumor
- Inhibition of T cell activation

**Figure by MIT OCW.**
Koch’s postulates

1) The organism is found in lesions of the disease
2) The organism can be isolated as single colonies on solid media
3) Inoculation of the organism causes lesions in experimental animals
4) The organism can be recovered from the experimental animal
Toxin Terminology

• **Exotoxin** = protein toxins of bacteria, in contrast to endotoxin (LPS)
  - Not all exotoxins are secreted; some accumulate inside the bacterium and are released by bacterial lysis

• **Cytotoxin** = target a wide range of cell types, in contrast to neurotoxins, leukotoxins, hepatotoxins, cardiotoxins
More Toxin Terminology

• Toxins can be named for the bacterial species that produce them, such as cholera toxin, Shiga toxin, diphtheria toxin and tetanus toxin
• Toxins can be named for their activities, such as adenylate cyclase, lecithinase
• Toxins can be simply given letter designations, such as exotoxin A
Toxin Classification by Mechanism

- **Type I toxins** bind to the host cell surface, but they are not translocated into the host cell (i.e. superantigens [Sag])
- **Type II toxins** disrupt eukaryotic cell membranes (i.e. phospholipases, and pore-forming toxins)
- **Type III toxins** are A-B toxins, which have a binding (B) component and active (A) component
Superantigens (Type I) Toxins

- Toxic shock syndrome toxin (TSST) (toxic shock syndrome)
- Streptococcal pyrogenic exotoxin (Spe) (toxic shock-like syndrome and scarlet fever)
- Staphylococcal enterotoxin (food poisoning)

Hormone Analog
- STa (heat-stable toxin) (diarrhea)
Superantigens (Type I Toxins)

APC   Helper T cell

Few clones

Peptide

Many clones

SAg
Membrane-Disrupting (Type II) Toxins

- Alpha-toxin (gas gangrene)
- Alpha-toxin (necrosis)
- Listeriolysin O (LLO) (listeriosis)
- Pneumolysin (pneumonia)
- Streptolysin O (SLO) (rheumatic fever)
- Hemolysin A (Hly A) (urinary tract infections and peritonitis)
Membrane-Disrupting (Type II) Toxins

• Two types of membrane-disrupting toxins
  - Pore-forming toxins insert holes in the membrane
  - Enzymes cleave bonds in membrane phospholipids
• Erythrocytes provide a convenient method to assay activity, so these toxins are often called hemolysins
Role of Membrane Disrupting Toxins

- In some cases, the primary role appears to be killing of professional phagocytes, such as neutrophils and macrophages.
- In other cases, they are used by invasive bacteria to escape from a phagosome and enter the host cell cytoplasm.
A-B (Type III) Toxins

- Diphtheria toxin (diphtheria)
- Cholera toxin (cholera)
- LT (heat-labile toxin) (infant diarrhea and traveler’s diarrhea)
- Shiga toxin (dysentery and hemolytic uremic syndrome [HUS])
- Botulinum toxin (botulism)
- Tetanus toxin (tetanus)
- Pertussis toxin (whooping cough)
A-B (Type III) Toxins

• First toxins studied
  - Historically more interest in A-B toxins than Type I or type II

• Simple A-B toxins are synthesized as a single polypeptide
  - Often A and B portions are separated during processing by proteolytic cleavage

• Compound A-B toxins are composed of multiple B monomers
More About A-B Toxins

- Often the surface receptor for the B subunit is the carbohydrate moiety of a glycoconjugate
- Distribution of receptor determines target cell specificity
- In some cases, the A subunit needs to be enzymatically activated within the cytoplasm, by host cell proteins
Mechanisms of Action of A-B Toxins

- Although A-B toxins target many different cell types, many of them catalyze the same reaction
- ADP-ribosylation, the transfer of ADP-ribose from NAD to a target protein, changes the behavior of the target protein
  - Diphtheria toxin inactivates elongation factor-2
  - Cholera toxin constitutively activates a $G_s$ GTP-binding protein that regulates adenylate cyclase
NIAID Category A & B Priority (Bacterial) Pathogens

**Category A**
- Bacillus anthracis
- Clostridium botulinum
- Yersinia pestis
- Francisella tularensis

**Category B**
- Burkholderia pseudomallei
- Coxiella burnetti
- Brucella species
- Burkholderia mallei
- Rickettsia prowazekii
- Ricin toxin
- Epsilon toxin of Clostridium perfringens
- Staphylococcus enterotoxin B
- Food and waterborne bacteria
  - E. coli, Vibrios, Shigella, Salmonella, Listeria, Campylobacter jejuni, & Yersinia enterocolitica
Select Agents (Partial List)

- Rickettsia prowazekii
- Rickettsia rickettsii
- Yersinia pestis
- Ricin toxin
- Shiga-like toxins
- Bacillus anthracis
- Brucella abortus
- Brucella melitensis
- Brucella suis
- Burkholderia mallei
- Burkholderia pseudomallei
- Coxiella burnetii
- Francisella tularensis
- Botulinum neurotoxin
- Clostridium perfringens epsilon toxin
- Shiga toxin
- Staphylococcal enterotoxin
Infection and cancer

- During the past 20 years, 4 new infectious causes of cancer have been discovered:
  - *Helicobacter pylori*, hepatitis C virus (HCV), papillomavirus, and human herpesvirus 8 (HHV-8)
- *H. pylori* causes gastric cancer (2nd most important cause of cancer death worldwide)
- Papillomavirus causes the vast majority of cervical cancer (2nd most important cause of cancer in women)
- Liver cancer caused by hepatitis viruses (ranks 6th in worldwide cancer incidence)
Between 15 and 20% of cancers due to underlying infection

Source:
Mammalian oncoviruses

- Peyton Rous won a Nobel Prize in 1966 for work he published in 1911
- Dulbecco, Temin, and Baltimore 1975
- Bishop and Varmus 1989 for \( v-src \) (Rous sarcoma virus)

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## Viruses linked to human neoplasia

<table>
<thead>
<tr>
<th>Virus</th>
<th>Acute infection</th>
<th>Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human T lymphotropic virus-1</td>
<td>Smoldering leukemia</td>
<td>Adult T cell leukemia</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>Infectious mononucleosis</td>
<td>B cell lymphomas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Burkitt’s lymphoma</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>Hepatitis B</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>Hepatitis C</td>
<td></td>
</tr>
<tr>
<td>Human papilloma virus</td>
<td>Squamous intraepithelial neoplasia</td>
<td>Cancer of the cervix</td>
</tr>
<tr>
<td>Human herpesvirus type 8</td>
<td>?</td>
<td>Kaposi’s sarcoma</td>
</tr>
</tbody>
</table>
Transformation by high-risk HPV

Please see:
HPV tropism for squamous epithelium


Courtesy of L. A. Laimins and F. Fehrmann. Used with permission.
# Infectious group 1 carcinogens

<table>
<thead>
<tr>
<th>Organism</th>
<th>Cancer</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Helicobacter pylori</em></td>
<td>Gastric cancer</td>
<td>Worldwide</td>
</tr>
<tr>
<td><em>Schistosoma haematobium</em></td>
<td>Urinary bladder cancer</td>
<td>Africa and the Middle East</td>
</tr>
<tr>
<td><em>Opisthorchis vivirreni</em></td>
<td>Bile duct cancer</td>
<td>Northeast Thailand</td>
</tr>
</tbody>
</table>

Geographical distribution of schistosomiasis

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Helicobacter pylori

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Please see:
