Lecture 14: Evasion of the Immune System by Pathogens
(based on lecture by Dr. Arturo Casadeval, Einstein)
Questions to Consider

- How do pathogens evade or subvert the immune system to prevent their elimination?
- How can the immune responses contribute to pathogenesis?
Pathogenic Microbes

In general

- Replicate in the host (exception – tapeworm)
- Spread to new hosts (exception – *B. Anthracis*)
- Avoid stimulating strong responses
- Usually do not kill host quickly

*Many pathogenic microbes persist because they do not elicit an effective immune response and/or evade the response once it occurs*
Strategies For Evasion Or Subversion Of Host Defenses

- Antigenic variation (12-1)
- Latency (12-2)
- Avoidance of killing (12-3)
- Immunosuppression (12-4)
Theme 1: Antigenic Variation

- Pathogens alter surface antigens to avoid the immune system
- Important strategy for pathogenic microbes cleared by antibody
- Mechanism can be fixed (pneumococcus), random (influenza) or gene encoded (trypanosomes)
- Bottom line strategy: “change clothes”
Pneumococcus
*Streptococcus Pneumoniae*

- Encapsulated bacterium
- Antibody response essential for clearance of infection
- 84 types (or serotypes) known
- Structural differences in the capsular polysaccharide translate into antigenic differences ("types")
- Immunity is type specific: immune system deals with each type as if new pathogen
Pneumococcal Pneumonia
Streptococcus Pneumoniae: A Pathogen Exhibiting Fixed Antigenic Variation

There are many types of *S. pneumoniae*, which differ in their capsular polysaccharides.
Influenza Virus

- Antigenic variation caused by antigenic “drift” and “shift”
- Segmented RNA genome contributes to ability to undergo antigenic changes
- **Antigenic drift** results from point mutations to surface hemagglutinin and neuraminidase
- **Antigenic shift** results from a reassortment of RNA genome to generate new antigenic type

1918 FLU – AN EXAMPLE OF ‘SHIFT’
2008 FLU – AN EXAMPLE OF ‘DRIFT’
2009 ‘SWINE FLU’ – AN EXAMPLE OF ‘SHIFT’
Influenza Virus Exhibits Antigenic Drift And Antigenic Shift

**HEMAGlutinin and Neurominidase ‘spikes’**

**Antigenic drift**
- Neutralizing antibodies against hemagglutinin block binding to cells
- Mutations alter hemagglutinin epitopes so that neutralizing antibody no longer binds

**Antigenic shift**
- Antigenic shift occurs when RNA segments are exchanged between viral strains in a secondary host
- No cross-protective immunity to virus expressing a novel hemagglutinin

*Immunobiology, 6/e. (© Garland Science 2005)*
## The Great Pandemics

<table>
<thead>
<tr>
<th>PANDEMIC</th>
<th>YEAR</th>
<th>DEATHS</th>
<th>TYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Russian flu</td>
<td>1889-90</td>
<td>1 million</td>
<td>H2N2?</td>
</tr>
<tr>
<td>Spanish flu</td>
<td>1918-20</td>
<td>40-100 million</td>
<td>HINI</td>
</tr>
<tr>
<td>Asian flu</td>
<td>1957-58</td>
<td>1 million</td>
<td>H2N2</td>
</tr>
<tr>
<td>Hong Kong flu</td>
<td>1968-69</td>
<td>1 million</td>
<td>H3N2</td>
</tr>
<tr>
<td>Swine flu</td>
<td>2009</td>
<td>3,606 (as of 9/12/09)</td>
<td>H1N1*</td>
</tr>
<tr>
<td>Bird flu</td>
<td>???</td>
<td>???</td>
<td>H5N1</td>
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*NOVEL H1N1 CAUSED BY REASSORTMENT OF 4 STRAINS OF PREVIOUSLY CIRCULATING INFLUENZA A VIRUS
Trypanosomes

- Cause sleeping sickness
- Main surface antigen is the variant specific glycoprotein (VSG)
- Antigenic variation is result of genetic programming of VSG. Genome contains more than 1000 VSG genes
- Immune system is unable to clear infection because surface antigen is constantly changing
Trypanosomes

*T. congolense*  
*T. brucei brucei*
Trypanosome Undergo Antigenic Changes By Genetic Programming

There are many inactive trypanosome VSG genes but only one site for expression

Inactive genes are copied into the expression site by gene conversion

Many rounds of gene conversion can occur, allowing the trypanosome to vary the VSG gene expressed

The clinical course of trypanosome infection

Number of parasites

Levels of antibodies

Infection

Time (weeks)
Theme 2: Latency

- Some viruses persist by ceasing replication until immunity wanes
- Examples: herpes simplex virus (HSV) and Epstein-Barr virus (EBV)
- Without replication no viral peptides are produced and immune system is not stimulated
- Bottom line strategy: “lay low”
Herpes Simplex Virus (HSV)

- Cause of cold sores, herpes encephalitis
- Virus persists in sensory neurons. These cells have low levels of MHC expression
- Certain stimuli like stress, bacterial infections, hormonal changes cause virus to activate
- Immune system controls local manifestations of viral infection (i.e. Cold sore) but does not eradicate latent virus in neurons
- Herpes zoster: causes chickenpox, becomes latent and then can reactivate as shingles
Herpes Virus - Coldsores

ENVELOPE SURROUNDS ICOSAHEDRAL CAPSID

Primary infection

Latent phase

Recurrence of infection

Fig 11.4 © 2001 Garland Science
Epstein Barr Virus (EBV)

- Cause of infectious mononucleosis
- Also a herpes virus
- Infects B cells and causes them to proliferate. Controlled by cd8 t cells which kill the B cells
- A fraction of B cells survive with latent infection of EBV
- Mechanism of latency involves production of a viral protein that interferes with degradation of viral peptides
- Latent infection may be responsible for certain lymphomas (Burkitt’s, Hodgkin’s)
Theme 3: Escape Killing

- Certain pathogens induce strong immune responses but have evolved strategies to escape killing.
- Persistence of infection results from ability to survive
- Bottom line strategy: “avoid line of fire”
Mycobacterium Tuberculosis: Inhibition Of Lysosomal Fusion

Bacteria survives By avoiding the Contents of the Lysosome

M. TUBERCULOSIS

PHAGOCYTIC VESICLE

LYSOSOMES

NUCLEUS

MYCOBACTERIA IN MACROPHAGES
Listeria Monocytogenes: Escape From The Lysosome

Bacteria survives by avoiding the contents of the lysosome through escape into the cell cytoplasm.
Toxoplasma Gondii: Generates Own Vacuole

Parasite survives by creating own vacuole which isolates it from the rest of the cell.

Toxo in human brain
Treponemes Coat Themselves With Host Proteins

- *Treponema pallidum* – spirochete that causes syphilis
  - Avoids recognition by antibodies by coating itself with host proteins

- *Borrelia burgdorferi* – spirochete that causes lyme disease
  - Avoids killing by complement by coating itself with host proteins
Viral Subversion of the Immune System

- Pathogenic viruses have evolved mechanisms to avoid immune clearance by "subverting" the immune system
  - Inhibition of humoral immunity
  - Inhibition of inflammatory response
  - Blocking of antigen processing
  - Immunosuppression of host
Strategies By Which Viruses Can Affect Immune Response

<table>
<thead>
<tr>
<th>Viral strategy</th>
<th>Specific mechanism</th>
<th>Result</th>
<th>Virus examples</th>
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<tr>
<td>Inhibition of humoral immunity</td>
<td>Virally encoded Fc receptor</td>
<td>Blocks effector functions of antibodies bound to infected cells</td>
<td>Herpes simplex Cytomegalovirus</td>
</tr>
<tr>
<td></td>
<td>Virally encoded complement receptor</td>
<td>Blocks complement-mediated effector pathways</td>
<td>Herpes simplex</td>
</tr>
<tr>
<td></td>
<td>Virally encoded complement control protein</td>
<td>Inhibits complement activation of infected cell</td>
<td>Vaccinia</td>
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### Strategies By Which Viruses Can Affect Immune Response

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<th>Result</th>
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<td>Inhibition of inflammatory response</td>
<td>Virally encoded cytokine homologue, e.g., β-chemokine receptor</td>
<td>Sensitizes infected cells to effects of β-chemokine; advantage to virus unknown</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td></td>
<td>Virally encoded soluble cytokine receptor homologue, e.g., IL-1 receptor homologue, TNF receptor homologue, interferon-γ receptor homologue</td>
<td>Blocks effects of cytokines by inhibiting their interaction with host receptors</td>
<td>Vaccinia Rabbit myxoma virus</td>
</tr>
<tr>
<td></td>
<td>Viral inhibition of adhesion molecule expression, e.g., LFA-3 ICAM-1</td>
<td>Blocks adhesion of lymphocytes to infected cells</td>
<td>Epstein–Barr virus</td>
</tr>
<tr>
<td></td>
<td>Protection from NFκB activation by short sequences that mimic TLRs</td>
<td>Blocks inflammatory responses elicited by IL-1 or bacterial pathogens</td>
<td>Vaccinia</td>
</tr>
</tbody>
</table>
Immunosuppression and Inappropriate Immune Responses

- Pathogens can suppress immune responses
  - Toxins can act as superantigens
  - HIV-mediated depletion of CD4 T cells
  - Leprosy: humoral or cellular suppression
Toxins As Superantigens

- **Superantigens** are proteins that bind antigen receptor of large numbers of T cells resulting in:
  - Cytokine dysregulation
  - T cell proliferation and apoptosis
  - Depletion of T cells
  - *Staphylococcus* and *Streptococcus* produce toxins that function as super-ags
Toxic Shock Syndrome 1980

- Epidemic of TSS in menstruating women – 940 cases, 40 deaths
- Toxin produced by *Staph aureus* bound to T cell receptor
- Rely tampons designed to absorb 20x more fluid but resin filtered toxin
- We continue to see TSS sporadically
Mycobacterium Leprae

Two forms:
1. Lepromatous: strong Ab weak CMI
2. Tuberculoid: strong CMI weak Ab
Two Forms Of Leprosy Reflect Differences In Tissue Reaction

Infection with *Mycobacterium leprae* can result in different clinical forms of leprosy

There are two polar forms, tuberculoid and lepromatous leprosy, but several intermediate forms also exist

<table>
<thead>
<tr>
<th>Tuberculoid leprosy</th>
<th>Lepromatous leprosy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organisms present at low to undetectable levels</td>
<td>Organisms show florid growth in macrophages</td>
</tr>
<tr>
<td>Low infectivity</td>
<td>High infectivity</td>
</tr>
<tr>
<td>Granulomas and local inflammation.</td>
<td>Disseminated infection. Bone, cartilage, and diffuse nerve damage</td>
</tr>
<tr>
<td>Peripheral nerve damage</td>
<td></td>
</tr>
<tr>
<td>Normal serum immunoglobulin levels</td>
<td>Hypergammaglobulinemia</td>
</tr>
<tr>
<td>Normal T-cell responsiveness. Specific response to <em>M. leprae</em> antigens</td>
<td>Low or absent T-cell responsiveness. No response to <em>M. leprae</em> antigens</td>
</tr>
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Two Forms Of Leprosy Reflect Differences In Inflammation Arising From Difference In Cytokine Responses

Infection with *Mycobacterium leprae* can result in different clinical forms of leprosy

<table>
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<th>Cytokine patterns in leprosy lesions</th>
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<tr>
<td><strong>T(_H)1 cytokines</strong></td>
</tr>
<tr>
<td>Tuberculoid</td>
</tr>
<tr>
<td>IL-2</td>
</tr>
<tr>
<td>IFN-(\gamma)</td>
</tr>
<tr>
<td>TNF-(\beta)</td>
</tr>
<tr>
<td><strong>T(_H)2 cytokines</strong></td>
</tr>
<tr>
<td>Tuberculoid</td>
</tr>
<tr>
<td>IL-4</td>
</tr>
<tr>
<td>IL-5</td>
</tr>
<tr>
<td>IL-10</td>
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</table>
For many infections the disease is caused by the immune response. Other pathogens require immune system components to survive.

Two examples:
- Respiratory syncytial virus
- Mouse mammary tumor virus
Respiratory Syncytial Virus (RSV)

- Major pulmonary pathogen in children
- Responsible for 90,000 admissions and 4,500 deaths in U.S.A. each year
- Causes bronchiolitis
- Early vaccine resulted in enhanced infection: no neutralizing antibodies with polarization of response to $T_h2$
- $T_h2$ cells release IL-3, IL-4, IL-5 which induce bronchospasm, eosinophilia
Summary

- Persistence requires avoiding host defenses or subverting them to support replication
- Pathogens have evolved many strategies to avoid host defenses
- In some infections the immune response is part of the problem: it can cause tissue damage or, in some cases promote pathogen replication
- Each example teaches us about the nature of the immune response and some of its potential weaknesses
Questions to Consider

- How do pathogens evade subvert the immune system to prevent their elimination?
- How can the immune responses contribute to pathogenesis?
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