Immunity to Viruses

Patricia Fitzgerald-Bocarsly
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The Battle Inside Your Body

New discoveries show how the IMMUNE SYSTEM fights off disease
The Immune System Deals with a Huge Range of Pathogens

Roitt, 2003
Cardiovascular conditions, 16.7 million
Infectious diseases, 14.9 million
Neoplastic diseases, 7.1 million
Asthma and chronic obstructive pulmonary diseases, 3.0 million
Injuries, 5.2 million
All other causes of death

## Infectious diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Annual deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory infections</td>
<td>3.96</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>2.77</td>
</tr>
<tr>
<td>Diarrheal diseases</td>
<td>1.80</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1.56</td>
</tr>
<tr>
<td>Vaccine-preventable childhood diseases</td>
<td>1.12</td>
</tr>
<tr>
<td>Malaria</td>
<td>1.27</td>
</tr>
<tr>
<td>STDs (other than HIV)</td>
<td>0.18</td>
</tr>
<tr>
<td>Meningitis</td>
<td>0.17</td>
</tr>
<tr>
<td>Hepatitis B and C</td>
<td>0.16</td>
</tr>
<tr>
<td>Tropical parasitic diseases</td>
<td>0.13</td>
</tr>
<tr>
<td>Dengue</td>
<td>0.02</td>
</tr>
<tr>
<td>Other infectious diseases</td>
<td>1.76</td>
</tr>
</tbody>
</table>

Figure 18-1
Kuby IMMUNOLOGY, Sixth Edition
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Immune Responses to Viruses

- Viruses are dependent on the host cell genetic material to replicate
- Heterogeneous
- Mechanisms of resistance are diverse
  - Innate
  - Adaptive
Viral Life Cycle: Different Immune Mechanisms Operate at throughout Cycle

Roitt, 2003
Mechanisms Differ with Site

- **Initial infection** - replication in epithelium and draining LN
  - IFN-alpha, sIgA, NK
- **Viremia** - neutralizing Ab
- **Replication in target organ**
  - Complement, CTL, NK, Ab, IFN
Innate vs. Adaptive Immunity to Viruses

Innate immunity
- Virus
- Antiviral state
- NK cell
- Infected cell
- Killing of infected cell

Adaptive immunity
- B cell
- Antibody
- Neutralization
- CD8+ CTL
- Infected cell
- Killing of infected cell

Protection against infection
Eradication of established infection

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Sequential Activation in Viral Infection

- IL-12, IFN-α
Interferon $\alpha/\beta$ in viral infection

- Produced by many cell types as well as the “professional IFN-alpha producing cells”, the plasmacytoid dendritic cells (pDC)
- Viral RNA or DNA recognized by a variety of signaling receptors that lead to IFN production:
  - **Endosomal sensors of viral nucleic acids:**
    - TLR 7 (ss RNA) (mostly in pDC)
    - TLR9 (DNA) (mostly in pDC)
    - TLR3 (dsRNA) (mostly in mDC)
  - **Cytoplasmic sensors of viral nucleic acid:**
    - PKR (ds RNA)
    - RIG-I and MDA-5 (ds RNA)
    - Cytoplasmic DNA detector
Interferon $\alpha/\beta$ in viral infection

- Antiviral effects
- Augment and recruit NK cells
- Upregulates IL-12 receptors
- Upregulation of Class I and Class II MHC
- Regulation/induction of adaptive immune responses
- Induction of Th1
- Establishment of T memory
NK Cells

- Primary role in viral infections
- Viruses down-regulate Class I to escape CTL, but this makes infected cells more susceptible to lysis by NK cells
- With virus-specific antibody, can mediate ADCC - important in neonatal varicella
- Produce cytokines (e.g. IFN-gamma) involved in macrophage activation and adaptive responses
• Non-phagocytic cells
• Lymphoid lineage but don’t rearrange receptors
• Kill by release of granule contents in the area of an immunological synapse
• Perforin pokes holes in the membranes, proteases digest cell
• Target cell dies by apoptosis

Fig 1.6 © 2001 Garland Science
Natural Killer Cells

**Fig 12-6**

NK cell 

Virus-infected cell → Killing of infected cells

**A**

Macrophage with phagocytosed microbes

IFN-γ

IL-12

Killing of phagocytosed microbes

**B**
Recognition of Virus-infected Targets by NK Cells

“Missing self”: whereas CTL must see antigen with MHC Class I, NK cells are inhibited by the expression of MHC Class I - healthy cells are not killed. Many viruses downregulate MHC Class I to escape from CTL but become sensitive to NK.
IL-12 in Viral Infections

- Produced by antigen presenting cells (some DC, macrophages) in response to viruses
- Triggered through TLR or other pattern-recognition receptors
- Activates NK cells, Th1 cells, CD8 cells
- Leads to upregulation of cell-mediated immunity against virus-infected cells
Adaptive Responses to Viruses

**Innate immunity**
- Viral infection
- Antiviral state
- NK cell, infected cell → Killing of infected cell

**Adaptive immunity**
- Type I IFN
- B cell → Antibody
- Neutralization
- CD8+ CTL, infected cell → Killing of infected cell

**Protection against infection**

**Eradication of established infection**

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THE GOAL OF IMMUNIZATION: MEMORY

- Initial immune response
- Protective immunity
- Immunological memory

Antibody and effector T cells

Time (days): 7, 14, 21, 28, 35, 42

- First infection
- Inapparent reinfection
- Mild or inapparent reinfection

Fig 10.16 © 2001 Garland Science
<table>
<thead>
<tr>
<th>Source of B cells</th>
<th>Unimmunized donor</th>
<th>Immunized donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of specific B cells</td>
<td>$1:10^4 - 1:10^5$</td>
<td>$1:10^3$</td>
</tr>
<tr>
<td>Isotype of antibody produced</td>
<td>IgM &gt; IgG</td>
<td>IgG, IgA</td>
</tr>
<tr>
<td>Affinity of antibody</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Somatic hypermutation</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>
Antibodies in Viral Infection

- Bind and neutralize extracellular virus - IgG, IgM, IgA
- Bind infected cells - ADCC, complement lysis - IgG
- Block virus/cell interactions - IgG, IgM, IgA
- Agglutinate virus particles - IgM
- Opsonize virus particles for clearance - IgM, IgG
- **Presence of antibody does not equal immunity! (e.g. HIV)**
IgG in ADCC against Virally-Infected Cells

Diagram:
- Surface antigen
- IgG
- Antibody-coated cell
- Low-affinity FcγRIII
- NK cell
- Killing of antibody-coated cell
Cytotoxic T Cells in Viral Infection: Activation in the Lymph Node

Licensing of antigen-presenting dendritic cell

Co-stimulatory signal

Uncertainty remains about whether simultaneous binding of $T_H^1$ cell to APC is required for activation of CTL-P

Licensing may also occur when Toll-like receptors (TLRs) on APC bind microbial products

Figure 14-1
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Cytotoxic T Cells Effector Fxn. In the Periphery

Figure 14-6
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Cytotoxic T Cells in Viral Infection

-CTL recognizes virus-infected cell
-CTL programs target cell to die
-CTL moves to another target cell
-First target cell dies

Figure 6-29 The Immune System, 2/e (© Garland Science 2005)
QuickTime™ and a Cinepak decompressor are needed to see this picture.
Virus-induced immunopathology (when too much of a good thing isn’t so good!)

- glomerulonephritis and vasculitis
- lysis of infected and bystander cells
- diabetes? MS?
- chronic inflammation, for example in herpes stromal keratitis
REVENGE OF THE Killer Microbes
Are we losing the war against infectious diseases?
Viruses and Immune Evasion

• Viruses spend a great deal of their genetic machinery on immune evasion
• Diverse mechanisms of immune evasion
Viral Immune Evasion Strategies

- Latency
- Antigenic variation - individual and population level
- Cytokine inhibition (inhibitors, decoy receptors, immunosuppressive cytokines, etc.)
- Transcription factor decoys
- Interruption of antigen processing/presentation
- Infection of immunocompetent cells
Assignment:

Create a resume to apply for the job of immunoevasive virus. The resume should have:

• **Introduce yourself** (name, education: i.e. type of virus, host)

• **Goal:** focus on ability to replicate and evade the immune response

• **Specific Experience (job history):**
  – Whom do you infect?
    • What cells are infected?
  – **Attributes:** briefly describe the disease you cause
  – **Specific skills:** how do you evade the immune system? **concentrate your effort here**

• **Provide 2 references!!!!**
  • Journal articles that can attest to your qualification for the job and your ability to get along with others (not kill all the hosts)!!!!!!
Choose:

- HIV
- Measles
- Herpes Simplex
- Epstein Barr Virus
- Pox virus (e.g. vaccinia, smallpox, etc.)
- Cytomegalovirus
- Rhinovirus