The Immune System Deals with a Huge Range of Pathogens
### 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>

### Other causes of death

- Cardiovascular conditions: 16.7 million
- Infectious diseases: 14.9 million

- Asthma and chronic obstructive pulmonary diseases: 3.0 million
- Neoplastic diseases: 7.1 million
- Injuries: 5.2 million
- All other causes of death
Not Only Organisms Vary, but also Disease

- **Acute disease**: clinically apparent infection
- **Latent illness**: disease may recur by being released from latency
- **Recurrent illness**: Reinfection or latent organism
- **Subclinical**: acute or chronic illness without symptoms
Host Immune Response

- **Apparently absent**: lack of response to prions, superficial fungi
- **Innate immunity**: first-line and bridging defense (already covered in course)
- **Adaptive immune response**: T and B mediated; lifelong immunity
- **Immunopathology**: overly vigorous immune response leads to tissue injury
- Or some combination of the above
Host Response Depends on:

- Type of organism
- Dose of organism
- Site of infection
- Natural history of the infection
- Host factors
  - Age
  - Immunocompetance
  - Sex
  - Genetics
  - Nutrition
The Great Escape....

• Hiding within cells without antigenic expression - many organisms
• Lurking on the periphery - superficial fungi
• Pool of non-immune individuals - measles, recent outbreaks of whooping cough
• Changing surface structure
  – Population level - influenza virus
  – Sequentially as part of life cycle - trypanosomes
Th1 vs Th2 Responses

• Most organisms will induce a combination of Th1 and Th2 cytokines
  – **Th1**: IFN-γ, IL-2 favor cell-mediated immunity and class switch to opsonizing antibody (macrophages, CTL, DTH, NK)
  – **Th2**: IL-4, IL-5, IL-13 - favor IgE response and some Ig subclasses, parasitic infections
  – **Th17**: Produce IL-17, pro-inflammatory
  – **Treg**: Produce regulatory cytokines; tolerance

• Dominance of one response may influence outcome
  – Leishmania
  – Trypanosomes
  – Tuberculosis
Viruses and some bacteria induce IL-12 secretion by dendritic cells that can activate NK cells to produce IFN-\(\gamma\).

Other pathogens (e.g., worms) do not induce IL-12 expression by dendritic cells but may cause NK1.1\(^+\) T cells to synthesize and secrete IL-4.

Naive CD4 T cells, activated in the presence of IL-12 and IFN-\(\gamma\), are committed to differentiate into TH1 cells.

Naive CD4 T cells activated in the presence of IL-4 are committed to differentiate into TH2 cells.
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-α, slgA, NK
- Viremia - neutralizing Ab
- Replication in target organ
  - Complement, CTL, NK, Ab, IFN
Innate vs. Adaptive Immunity to Viruses

Innate immunity

- Virus
- Type I IFN
- 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

Fig. 15-6

Copyright © 2003, Elsevier Science (USA). All Rights Reserved.
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 IPC, the plasmacytoid dendritic cells
- Viral RNA or DNA recognized by a variety of receptors:
  - Endosome:
    - TLR 3 (ds RNA) (mostly in PDC)
    - TLR 7 (ss RNA) (mostly in PDC)
    - TLR9 (DNA)
  - Cytoplasm:
    - PKR (ds RNA)
    - RIG-I and MDA-5 (ds RNA)
    - Unidentified cytoplasmic DNA detector
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 Class I to escape from CTL but become sensitive to NK.

Fig 12-7
IL-12 in Viral and Bacterial Infections

Fig. 11-7
Adaptive Responses to Viruses

Fig. 15-6
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
Cytotoxic T Cells in Viral Infection

Figure 6-29 The Immune System, 2/e (© Garland Science 2005)
Virus-induced immunopathology

- **Immune complexes** - glomerulonephritis and vasculitis
- **Direct damage** - lysis of infected and bystander cells
- **Autoimmunity** - diabetes? MS?
- **Release of activating mediators** - chronic inflammation
- **Damage by CD4 cells**, for example in herpes stromal keratitis
# Immune Evasion by Viruses

<table>
<thead>
<tr>
<th>Mechanism of immune evasion</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigenic variation</td>
<td>Influenza, rhinovirus, HIV</td>
</tr>
<tr>
<td>Inhibition of antigen processing</td>
<td>Herpes simplex</td>
</tr>
<tr>
<td>Blockade of TAP transporter</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Removal of class I MHC molecules from the ER</td>
<td></td>
</tr>
<tr>
<td>Production of cytokine receptor homologues</td>
<td>Vaccinia, poxviruses (IL-1, IFN-γ)</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus (chemokine)</td>
</tr>
<tr>
<td>Production of immunosuppressive cytokine</td>
<td>Epstein-Barr virus (IL-10)</td>
</tr>
<tr>
<td>Infection of immunocompetent cells</td>
<td>HIV</td>
</tr>
</tbody>
</table>

**Abbreviations:** ER, endoplasmic reticulum; HIV, human immunodeficiency virus; TAP, transporter associated with antigen processing.

Representative examples of different mechanisms used by viruses to resist host immunity are listed.

Copyright © 2003, Elsevier Science (USA). All Rights Reserved.
VIRAL INHIBITION OF MHC CLASS I PRESENTATION

The pathway of class I MHC-associated antigen presentation is shown, with examples of viruses that block different steps in this pathway. CMV, cytomegalovirus; CTL, cytolytic T lymphocyte; EBV, Epstein-Barr virus; ER, endoplasmic reticulum; HSV, herpes simplex virus; TAP, transporter associated with antigen processing.
Figure 18-4
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W.H. Freeman and Company
### Table 18-2

**Some influenza A strains and their hemagglutinin (H) and neuraminidase (N) subtype**

<table>
<thead>
<tr>
<th>Species</th>
<th>Virus strain designation</th>
<th>Antigenic subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>A/Puerto Rico/8/34</td>
<td>H0N1</td>
</tr>
<tr>
<td></td>
<td>A/Fort Monmouth/1/47</td>
<td>H1N1</td>
</tr>
<tr>
<td></td>
<td>A/Singapore/1/57</td>
<td>H2N2</td>
</tr>
<tr>
<td></td>
<td>A/Hong Kong/1/68</td>
<td>H3N2</td>
</tr>
<tr>
<td></td>
<td>A/USSR/80/77</td>
<td>H1N1</td>
</tr>
<tr>
<td></td>
<td>A/Brazil/11/78</td>
<td>H1N1</td>
</tr>
<tr>
<td></td>
<td>A/Bangkok/1/79</td>
<td>H3N2</td>
</tr>
<tr>
<td></td>
<td>A/Taiwan/1/86</td>
<td>H1N1</td>
</tr>
<tr>
<td></td>
<td>A/Shanghai/16/89</td>
<td>H3N2</td>
</tr>
<tr>
<td></td>
<td>A/Johannesburg/33/95</td>
<td>H3N2</td>
</tr>
<tr>
<td></td>
<td>A/Wuhan/359/95</td>
<td>H3N2</td>
</tr>
<tr>
<td></td>
<td>A/Texas/36/95</td>
<td>H1N1</td>
</tr>
<tr>
<td></td>
<td>A/Hong Kong/156/97</td>
<td>H5N1</td>
</tr>
<tr>
<td>Swine</td>
<td>A/Sw/Iowa/15/30</td>
<td>H1N1</td>
</tr>
<tr>
<td></td>
<td>A/Sw/Taiwan/70</td>
<td>H3N2</td>
</tr>
<tr>
<td>Horse (equine)</td>
<td>A/Eq/Prague/1/56</td>
<td>H7N7</td>
</tr>
<tr>
<td></td>
<td>A/Eq/Miami/1/63</td>
<td>H3N8*</td>
</tr>
<tr>
<td>Bird</td>
<td>A/Fowl/Dutch/27</td>
<td>H7N7</td>
</tr>
<tr>
<td></td>
<td>A/Tern/South America/61</td>
<td>H5N3</td>
</tr>
<tr>
<td></td>
<td>A/Turkey/Ontario/68</td>
<td>H8N4</td>
</tr>
<tr>
<td></td>
<td>A/Chicken/Hong Kong/258/97</td>
<td>H5N1†</td>
</tr>
</tbody>
</table>

*H3N8 has recently been shown to cause flu-like illness in dogs; the species shift occurred with no reassortment of genes.

†As of 2006, a dangerous new H5N1 avian strain has infected approximately 175 humans with 50% mortality.
Latency: herpesviruses
HSV-1
EBV (B cells)
HHV6 (T cells)
VZV (recurrence is shingles)
### Table 15-3. Mechanisms of Immune Evasion by Viruses

<table>
<thead>
<tr>
<th>Mechanism of immune evasion</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigenic variation</td>
<td>Influenza, rhinovirus, HIV</td>
</tr>
<tr>
<td>Inhibition of antigen processing</td>
<td></td>
</tr>
<tr>
<td>Blockade of TAP transporter</td>
<td>Herpes simplex</td>
</tr>
<tr>
<td>Removal of class I MHC molecules from the ER</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Production of cytokine receptor homologues</td>
<td>Vaccinia, poxviruses (IL-1, IFN-γ)</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus (chemokine)</td>
</tr>
<tr>
<td>Production of immunosuppressive cytokine</td>
<td>Epstein-Barr virus (IL-10)</td>
</tr>
<tr>
<td>Infection of immunocompetent cells</td>
<td>HIV</td>
</tr>
</tbody>
</table>

*Abbreviations: ER, endoplasmic reticulum; HIV, human immunodeficiency virus; TAP, transporter associated with antigen processing.*

Representative examples of different mechanisms used by viruses to resist host immunity are listed.

Copyright © 2003, Elsevier Science (USA). All Rights Reserved.
Immunity to Bacteria

- Cell wall type (G+/G-)
  - Invasiveness
    - Toxin
  - Intracellular
  - Extracellular
Innate Immunity to Bacteria

- Phagocytes (macrophages and neutrophils)
- Complement
- IFN-γ production by NK cells
- Acute phase proteins and early cytokines
Immunity to Extracellular Bacteria

Antibody is very effective against extracellular bacteria.

Cytokines: activate antibody response, activate macrophages, induce inflammation.
IgA in Resistance to Microorganisms

Polymeric IgA is transported into the gut lumen through epithelial cells at the base of the crypts.

Polymeric IgA binds to the mucus layer overlying the gut epithelium.

IgA in the gut neutralizes pathogens and their toxins.

Fig 10.20 © 2001 Garland Science
<table>
<thead>
<tr>
<th>Infection process</th>
<th>Host defense</th>
<th>Bacterial evasion mechanisms</th>
</tr>
</thead>
</table>
| Attachment to host cells  | Blockage of attachment by secretory IgA antibodies | Secretion of proteases that cleave secretory IgA dimers (Neisseria meningitidis, N. gonorrhoeae, Haemophilus influenzae)
Antigenic variation in attachment structures (pili of N. gonorrhoeae) |
| Proliferation              | Phagocytosis (Ab- and C3b-mediated opsonization)  | Production of surface structures (polysaccharide capsule, M protein, fibrin coat) that inhibit phagocytic cells
Mechanisms for surviving within phagocytic cells
Induction of apoptosis in macrophages (Shigella flexneri) |
|                            | Complement-mediated lysis and localized inflammatory response | Generalized resistance of gram-positive bacteria to complement-mediated lysis
Insertion of membrane-attack complex prevented by long side chain in cell-wall LPS (some gram-negative bacteria) |
| Invasion of host tissues   | Ab-mediated agglutination                         | Secretion of elastase that inactivates C3a and C5a (Pseudomonas) |
| Toxin-induced damage to host cells | Neutralization of toxin by antibody               | Secretion of hyaluronidase, which enhances bacterial invasiveness |
There are many types of *S. pneumoniae*, which differ in their capsular polysaccharides.

**Figure 11.1**

- **Individual infected with one type of *S. pneumoniae***
- **Response clears infection***
- **Subsequent infection with a different type of *S. pneumoniae* is unaffected by response to first type***
- **New response clears infection***

© 2001 Garland Science
Immunity to Intracellular Bacteria

Fig. 15-2
Cell-Mediated Immunity Destroys Intracellular Bacteria

Fig. 15-4
Immune evasion: intracellular bacteria

- Inhibition of phagolysosome formation
  - *Mycobacterium tuberculosis*
  - *Legionella pneumophila*
- Scavenging of reactive oxygen intermediates
  - *Mycobacterium leprae*
- Inhibition of phagolysosome formation, escape into cytoplasm
  - *Listeria monocytogenes* (hemolysin protein)
Bacterial Cell Walls Have Adjuvant Effects

- Trigger inflammatory mechanisms
- Activation of complement
- Activation of macrophages - upregulation of costimulatory molecules
- Polyclonal B cell activation
- IL-1 dependent polyclonal T cell activation
Bacterial Superantigens

<table>
<thead>
<tr>
<th>Enterotoxin</th>
<th>Mice</th>
<th>Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEB</td>
<td>$V_\beta 7, 8.1-8.3, 17$</td>
<td>$V_\beta 3, 12, 14, 15, 17, 20$</td>
</tr>
<tr>
<td>SEC 2</td>
<td>$V_\beta 8.2, 10$</td>
<td>$V_\beta 12, 13, 14, 15, 17, 20$</td>
</tr>
<tr>
<td>SEE</td>
<td>$V_\beta 11, 15, 17$</td>
<td>$V_\beta 5.1, 6.1-6.3, 8, 18$</td>
</tr>
<tr>
<td>TSST-1</td>
<td>$V_\beta 15, 16$</td>
<td>$V_\beta 2$</td>
</tr>
</tbody>
</table>

*Abbreviations: SE, staphylococcal enterotoxin; TSST, toxic shock syndrome toxin*. 

Copyright © 2003, Elsevier Science (USA). All Rights Reserved.
Th1 vs Th2 in Immunity to Bacteria

<table>
<thead>
<tr>
<th>Infection</th>
<th>Response</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leishmania major</td>
<td>Most mouse strains: T\textsubscript{H}1</td>
<td>Recovery</td>
</tr>
<tr>
<td></td>
<td>BALB/c mice: T\textsubscript{H}2</td>
<td>Disseminated infection</td>
</tr>
<tr>
<td>Mycobacterium leprae</td>
<td>Some patients: T\textsubscript{H}1</td>
<td>Tuberculoid leprosy</td>
</tr>
<tr>
<td></td>
<td>Some patients: Defective T\textsubscript{H}1 or dominant T\textsubscript{H}2</td>
<td>Lepromatous leprosy (high bacterial count)</td>
</tr>
</tbody>
</table>
Bacterial Immunopathology

Low quantities (plasma conc. <10^{-9} M)
- Local inflammation
  - Leukocyte
    - Activation
  - Adhesion molecule
    - Endothelial cell
  - IL-1, chemokines

Moderate quantities
- Systemic effects
  - Brain
    - Fever
  - Liver
    - Acute-phase proteins
  - Bone marrow
    - Leukocytes

High quantities (plasma conc. ≥10^{-7} M)
- Septic shock
  - Heart
    - Low output
  - Blood vessel
    - Thrombus
    - Low resistance
  - Liver
    - Hypoglycemia
Granuloma - incomplete elimination of bacteria; leads to immunopathology
Bacteria and Autoimmunity

Fig. 18-8

Self-reactive T cells and/or Ab:

e.g. Rheumatic fever

Copyright © 2003, Elsevier Science (USA). All Rights Reserved.
Immunity Depends on:

• Type of parasite
  – *Unicellular and lives inside cells*, then phagocytosis, ADCC, cytotoxic T cells, other cell-mediated responses that lead to killing of infected cells or the parasite within cells may be involved
  – *If it’s large*, then phagocytosis is ineffective
    • *Granuloma, ADCC (schistosomes)*, perhaps antibodies and C
Immunity depends upon (cont)

• Life cycle
  – Parasites that go through different forms (malaria) will probably induce different immune responses

• Host Immune status:
  – Immunocompetence
  – Age
Th1 vs Th2 in Parasite Immunity

• Depending on the parasite, balance of Th1 vs. Th2 may be critical
  – Leishmania - Th1 responses required for protection
  – Schistosomes (helminths) - Th2 responses involved
Schistosomes

- Parasitic worms
- Induce **IL-4** (class switch to IgE), **IL-5** (recruits eosinophils)
- Favors **Th2** response, IgE expression
- **IgE** binds to Fc receptors on eosinophils
- ADCC against the worm; release of major basic protein
- Other mechanisms important: CTL, macrophages
IgE Mediated Killing of Helminths
Mast-cell activation and granule release

**Gastrointestinal tract**
- Increased fluid secretion, increased peristalsis
  - Expulsion of gastrointestinal tract contents (diarrhea, vomiting)

**Airways**
- Decreased diameter, increased mucus secretion
  - Expulsion of airway contents (phlegm, coughing)

**Blood vessels**
- Increased blood flow, increased permeability
  - Edema
  - Inflammation
  - Increased lymph flow and carriage of antigen to lymph nodes

Figure 10-18  The Immune System, 2/e © Garland Science 2005
Th1 Responses in Leishmania

[Diagram showing Th1 and Th2 responses with arrows for IL-2, IL-10, TNF, IFN-γ, IL-4, and macrophage activation.]
**Table 15-5. Mechanisms of Immune Evasion by Parasites**

<table>
<thead>
<tr>
<th>Mechanism of immune evasion</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigenic variation</td>
<td>Trypanosomes, <em>Plasmodium</em></td>
</tr>
<tr>
<td>Acquired resistance to complement, CTLs</td>
<td>Schistosomes</td>
</tr>
<tr>
<td>Inhibition of host immune responses</td>
<td>Filaria (secondary to lymphatic obstruction), trypanosomes</td>
</tr>
<tr>
<td>Antigen shedding</td>
<td>Entamoeba</td>
</tr>
</tbody>
</table>

*Abbreviation: CTL, cytolytic T lymphocyte.*
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.

Fig 11.3 © 2001 Garland Science