Helminth worm, Schistosomiasis
Trypanosomes, sleeping sickness
Pneumocystis carinii

Ringworm fungus
HIV
Influenza

Candida
Staph aureus
Mycobacterium tuberculosis

Listeria
Salmonella
Streptococcus
Levels of Body Defense

• Skin
  – Barrier to infectious agents

• Nonspecific responses  INNATE
  – Block entry of pathogens
  – Block the spread of infectious agents

• Specific responses  ADAPTIVE
  – Antibody-mediated response
  – Cell-mediated response
Complement System Overview

Fig. 17.2

(a) In some immune responses, complement proteins are activated when they bind to proteins called antibodies (here, the Y-shaped molecules). These antibodies are already bound to a pathogen.

(b) Complement proteins also are activated by binding directly to a bacterial surface.

(c) Cascading reactions produce huge numbers of different complement proteins. These become assembled into many molecules, which form many attack complexes.

(d) The attack complexes become inserted into the plasma membrane or lipid envelope of the pathogen. Each forms a large pore across the membrane.

(e) The pores invite lysis. The pathogen dies because of the severe disruption of its structure.
TWO KEY CELLS IN INNATE IMMUNITY:

Blood monocyte, leaves blood and enters tissues naturally, becomes macrophage

Blood neutrophil, enters tissue in response to infection

BOTH ARE HIGHLY PHAGOCYTIC
This picture did not ‘show up’ in the class lecture
<table>
<thead>
<tr>
<th>Component</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3</td>
<td>susceptible to recurring bacterial infections</td>
</tr>
<tr>
<td>C5-9</td>
<td>susceptible to Neisseria infections (gonorrhea, meningitis)</td>
</tr>
</tbody>
</table>
### The immune system protects against four classes of pathogen

<table>
<thead>
<tr>
<th>Type of pathogen</th>
<th>Examples</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracellular bacteria, parasites, fungi</td>
<td><em>Streptococcus pneumoniae</em>&lt;br&gt;<em>Clostridium tetani</em>&lt;br&gt;<em>Trypanosoma brucei</em>&lt;br&gt;<em>Pneumocystis carinii</em></td>
<td>Pneumonia&lt;br&gt;Tetanus&lt;br&gt;Sleeping sickness&lt;br&gt;<em>Pneumocystis pneumonia</em></td>
</tr>
<tr>
<td>Intracellular bacteria, parasites</td>
<td><em>Mycobacterium leprae</em>&lt;br&gt;<em>Leishmania donovani</em>&lt;br&gt;<em>Plasmodium falciparum</em></td>
<td>Leprosy&lt;br&gt;Leishmaniasis&lt;br&gt;Malaria</td>
</tr>
<tr>
<td>Viruses (intracellular)</td>
<td>Variola&lt;br&gt;Influenza&lt;br&gt;Varicella</td>
<td>Smallpox&lt;br&gt;Flu&lt;br&gt;Chickenpox</td>
</tr>
<tr>
<td>Parasitic worms (extracellular)</td>
<td><em>Ascaris</em>&lt;br&gt;<em>Schistosoma</em></td>
<td>Ascariasis&lt;br&gt;Schistosomiasis</td>
</tr>
</tbody>
</table>

Figure 1-23 Immunobiology, 6/e. (© Garland Science 2005)

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Lymphocytes

• **B lymphocytes** (B cells)
  – Mature in the bone marrow and mediate antibody-directed immunity
  – Produce **antibodies** that respond to **antigens** (molecules produced by microorganisms)

• **T lymphocytes** (T cells)
  – Formed in bone marrow but mature in the thymus
  – Mediate cellular immunity
## Antibody-Mediated and Cell-Mediated Immune Responses

### Table 17.1 Comparison of Antibody-Mediated and Cell-Mediated Immunity

<table>
<thead>
<tr>
<th>Antibody-Mediated</th>
<th>Cell-Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal cellular agent is the B cell. B cell responds to bacteria, bacterial toxins, and some viruses.</td>
<td>Principal cellular agent is the T cell. T cells respond to cancer cells, virally infected cells, single-celled fungi, parasites, and foreign cells in an organ transplant.</td>
</tr>
<tr>
<td>When activated, B cells form memory cells and plasma cells, which produce antibodies to these antigens.</td>
<td>When activated, T cells differentiate into memory cells, cytotoxic cells, suppressor cells, and helper cells; cytotoxic T cells attack the antigen directly.</td>
</tr>
</tbody>
</table>
B LYMPHOCYTE BECOMES AN ANTIBODY-SECRETING PLASMA CELL

Resting B cell

membrane-bound Ig

Encounter with antigen

bacterium

Stimulated B-cell gives rise to antibody-secreting plasma cells

plasma cells

secreted antibody

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This picture did not ‘show up’ in the class lecture
This picture did not ‘show up’ in the class lecture
MACROPHAGES - may need some help to clear intracellular bacteria
CD4+ T HELPER CELLS (Th) ACTIVATE B CELLS AND MACROPHAGES
CD8+ T CELLS BECOME KILLERS (Tc) and ELIMINATE VIRALLY-INFECTED CELLS
B CELLS AND T CELLS ARE ACTIVATED BY SPECIFIC RECOGNITION OF ANTIGEN

THEY PROLIFERATE [MAKE PROGENY]

THEY DIFFERENTIATE TO BECOME ‘EFFECTORS’

THIS PROCESS TAKES DAYS - WHICH IS WHY INNATE IMMUNITY IS THE FIRST LINE OF DEFENSE = NEEDED TO CONTAIN IF NOT CLEAR INFECTION

THE CELLS INVOLVED IN INNATE AND ADAPTIVE IMMUNITY DERIVE FROM PLURIPOTENTIAL HEMATOPOIETIC STEM CELLS (PHSC) IN THE BONE MARROW
WHAT IS ‘ANTIGEN’ = NOT-SELF = FOREIGN PROTEIN

B CELL RECOGNITION:
B cell receptor binds ‘EPITOPE’ on soluble or pathogen associated protein

The B cell receptor is ‘transmembrane’ - within the cell’s membrane.

Antibody is the secreted, soluble form of the B cell receptor
The coat of a poliovirus is made up of multiple copies of three different proteins (indicated in yellow, blue, and pink). Known epitopes on the surface of the virus are shown as white patches. One of the viral coat proteins, VP1 (blue), is shown separately, but folded as it is in the virus particle. This protein contains several different epitopes (white). They are located at the surface of the protein and are exposed on the surface of the virus particle.
Ig: ANTIGEN-BINDING AT ONE END (VARIABLE REGION) AND EFFECTOR FUNCTION AT THE OTHER END (CONSTANT REGION)
B cells and T cells have somewhat similar receptors (Variable and Constant regions) but they use different genes on different chromosomes.
WHAT IS ‘ANTIGEN’ = NOT-SELF = FOREIGN PROTEIN

T CELL RECOGNITION:

T cell receptor binds ‘PEPTIDE-MHC’ complex

Unlike B cells, T cells do not secrete a soluble form of their receptor.
MHC class I: one MHC-encoded protein folds to form peptide binding pocket
MHC class II: two MHC-encoded proteins fold to form peptide binding pocket
Both MHC class I, II are on surface of cells
The APC (antigen presenting cell) makes peptides out of pathogen proteins. The peptides bind to MHC class I or class II, and these peptide-MHC ‘ligands’ go to the cell surface to be recognized by CD8+ or CD4+ T cells, respectively.
Human MHC locus is HLA. Class I genes are HLA-A, B, C. Class II genes are HLA-DP, DQ, DR. The number of known functional alleles in the human population for each gene is shown. The bar heights = # of alleles.
B CELLS AND T CELLS EACH HAVE ONLY ONE RECEPTOR

NEED TO GENERATE LOTS OF DIFFERENT RECEPTORS TO BIND THE ANTIGENIC UNIVERSE

THIS IS DONE BY:

HAVING MANY GENES IN THE LOCUS

DNA RECOMBINATION OF 2-3 GENES TO FORM VARIABLE REGION
(called VDJ recombination)

SLOPPY JOINING OF GENE SEGMENTS
B cells: heavy chain loci, light chain loci on different chromosomes

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Any gene segment can recombine with any other gene segment = combinatorial diversity = many many different variable regions
T cells: two chains of the receptor are encoded by genes on different chromosomes
GENETIC IMMUNODEFICIENCIES IN THE MOLECULAR PATHWAYS FOR VDJ RECOMBINATION CAUSE DISEASE SUSCEPTIBILITY

NO B CELLS, NO T CELLS ARE MADE

This leads to:

SCID = SEVERE COMBINED IMMUNODEFICIENCY DISEASE

= no humoral or cell mediated immunity
### Antibodies Have Multiple Effector Functions

Different antibody ‘classes’ or ‘isotypes’ have different functions.

#### How Are All These Antibody ‘Classes’ Made?
Use Different Constant Region Genes. Variable Region moves by DNA Recombination to Constant Region.
HOW ARE ALL THESE ANTIBODY ‘CLASSES’ MADE?-
Use Different Constant Region Genes.
Start with Variable Region ‘near’ Constant Region Gene for IgM

Variable Region moves by DNA Recombination to another Constant Region Gene
Mutations in AID:

HIGM2 syndrome

No IgG

Susceptibility to recurrent bacterial infections

Isotype Switching: Involvement of Activation Induced Deaminase

DNA RECOMBINATION
CSR= class switch recomb.
same as isotype switching
AID is also essential for **somatic hypermutation** of antibody heavy and light chain genes.
MANY GENES ARE INVOLVED IN T CELL - B CELL AND T CELL - APC INTERACTIONS

DEFICIENCIES IN THESE CAN CAUSE DISEASE:

EXAMPLES:
- MEMBRANE RECEPTORS AND THEIR LIGANDS
- CYTOKINES
Hyper-IgM SYNDROME: no IgG

HIGM2  AID Defect                     Impaired isotype switching

CD40, CD40L IS A SET OF CRITICAL MEMBRANE-LIGAND MOLECULES FOR T-B CELL AND T CELL-MACROPHAGE INTERACTIONS:

HIGM1  CD40L Defect  X-linked  [T cell lacks the molecule]

HIGM3  CD40 Defect                      [B cell, macrophage lack the molecule]

Note that immunodeficiency diseases with similar phenotypes can be caused by different genes
**X-LINKED SCID**

- IL-7R
- IL-4R
- IL-2R
- IL-9R
- IL-15R

These cytokine receptors share the common gamma chain, $\gamma_c$

**Defect in $\gamma_c$**

**Defect in Jak 3**

**B and T cell development**

**B and T cell activation**

**Humans:** B cells develop but don’t respond.
No T cells develop.
<table>
<thead>
<tr>
<th>Deficiency syndrome</th>
<th>Abnormality</th>
<th>Immune defect</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe combined immune deficiency</td>
<td>ADA deficiency</td>
<td>No T or B cells</td>
<td>General</td>
</tr>
<tr>
<td></td>
<td>PNP deficiency</td>
<td>No T or B cells</td>
<td>General</td>
</tr>
<tr>
<td></td>
<td>( \gamma_c ) chain deficiency</td>
<td>No T cells</td>
<td>General</td>
</tr>
<tr>
<td></td>
<td>DNA repair defect</td>
<td>No T or B cells</td>
<td>General</td>
</tr>
<tr>
<td>DiGeorge syndrome</td>
<td>Thymic aplasia</td>
<td>Variable numbers of T and B cells</td>
<td>General</td>
</tr>
<tr>
<td>MHC class I deficiency</td>
<td>Mutant TAP</td>
<td>No CD8 T cells</td>
<td>Viruses</td>
</tr>
<tr>
<td>MHC class II deficiency</td>
<td>Lack of expression of MHC class II</td>
<td>No CD4 T cells</td>
<td>General</td>
</tr>
<tr>
<td>Wiskott–Aldrich syndrome</td>
<td>X-linked; defective WASP gene</td>
<td>Defective polysaccharide antibody responses</td>
<td>Encapsulated extracellular bacteria</td>
</tr>
<tr>
<td>Common variable immunodeficiency</td>
<td>Unknown; MHC-linked</td>
<td>Defective antibody production</td>
<td>Extracellular bacteria</td>
</tr>
<tr>
<td>Deficiency syndrome</td>
<td>Abnormality</td>
<td>Immune defect</td>
<td>Susceptibility</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>----------------------</td>
<td>------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>X-linked agammaglobulinemia</td>
<td>Loss of Btk tyrosine kinase</td>
<td>No B cells</td>
<td>Extracellular bacteria, viruses</td>
</tr>
<tr>
<td>X-linked hyper-IgM syndrome</td>
<td>Defective CD40 ligand</td>
<td>No isotype switching</td>
<td>Extracellular bacteria</td>
</tr>
<tr>
<td>Selective IgA and/or IgG deficiency</td>
<td>Unknown; MHC-linked</td>
<td>No IgA synthesis</td>
<td>Respiratory infections</td>
</tr>
<tr>
<td>Phagocyte deficiencies</td>
<td>Many different</td>
<td>Loss of phagocyte function</td>
<td>Extracellular bacteria and fungi</td>
</tr>
<tr>
<td>Complement deficiencies</td>
<td>Many different</td>
<td>Loss of specific complement components</td>
<td>Extracellular bacteria especially <em>Neisseria</em> spp.</td>
</tr>
<tr>
<td>Natural killer (NK) cell defect</td>
<td>Unknown</td>
<td>Loss of NK function</td>
<td>Herpes viruses</td>
</tr>
<tr>
<td>X-linked lymphoproliferative syndrome</td>
<td>Unknown; X-linked</td>
<td>EBV-triggered immunodeficiency</td>
<td>EBV</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>Gene with PI-3 kinase homology</td>
<td>T-cell numbers reduced</td>
<td>Respiratory infections</td>
</tr>
<tr>
<td>Bloom’s syndrome</td>
<td>Defective DNA helicase</td>
<td>T-cell numbers reduced Reduced antibody levels</td>
<td>Respiratory infections</td>
</tr>
</tbody>
</table>