The Immune System

Innate (non-specific) immunity

Adaptive (specific) immunity

Structure of the immune system

Specific immune mechanisms
Innate immunity
  front line of defense
  not specific
  no immunologic memory (does not get stronger with more exposures)

Epithelial membranes
Stomach acid; tears
Phagocytosis
Neutrophils

Monocytic cells
  monocytes in blood

macrophages in tissue (lungs, liver, etc.)
Mechanisms of nonspecific immunity

Fever

Inflammation
  extravasation
  phagocytosis
  complement

NK cells

Interferons- prevent viral infection
Local Inflammation

Bacteria

Epidermis

Dermis

Antibodies

Antibody-coated bacterium

Lysosomal enzymes

B lymphocyte

Vacuole

Phagocytic cell

PMN leukocyte

Lysosome

Diapedesis

Activation of complement

Dilation, increased permeability of capillary

Release of histamine

Mast cell

Capillary
Mediators of inflammation

Vasodilation, smooth muscle contraction
Increased vascular permeability
Edema, extravasation
  (histamines, protaglandins, kinins)
Extravasation
Chemotaxis
  (cytokines, chemokines, complement)

Systemic response- fever, acute-phase proteins
  C-reactive protein
Non-specific response is rapid

Specific (T or B cell response) takes longer
(if non-specific response fails)
Infiltration of an Inflamed Site by Leukocytes

- Leukocyte infiltration
- Neutrophils
- Monocytes
- T lymphocytes

Intensity vs. Hours
Specific immunity

What is an antigen?

What is memory?

What is immunization?
  active and passive
  naturally and artificially acquired
Clonal selection theory

Individual B and T cells possess the ability to make a specific receptor (each cell makes a different receptor molecule)

Antigen binds to the cell surface receptor and activates the cell

Process takes several days. Effector cells and memory cells are produced. Memory cells can thus be activated faster

Danger model?
Clonal Selection Theory as Applied to B Lymphocytes

First day

Second day

Third day

Fourth day

Fifth day

Development of clone

Memory cells

Plasma cell

Cytoplasm

Nucleus

B lymphocyte

Ribosomes

Endoplasmic reticulum
Clonal selection

It takes awhile
First response isn’t that strong
Memory response is faster AND stronger

Rationale for vaccine development
is it safe?
  live vs killed vs recombinant
does it work?
  see above
B and T cells mediate specific immunity

<table>
<thead>
<tr>
<th></th>
<th>Bone Marrow</th>
<th>Thymus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matures in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of immunity</td>
<td>humoral</td>
<td>cell-mediated</td>
</tr>
<tr>
<td>Secretes</td>
<td>antibodies</td>
<td>cytokines</td>
</tr>
<tr>
<td>Antigen receptor</td>
<td>surface Ig</td>
<td>T cell receptor</td>
</tr>
<tr>
<td>Where found</td>
<td>spleen</td>
<td>blood, lymph</td>
</tr>
<tr>
<td></td>
<td></td>
<td>nodes</td>
</tr>
<tr>
<td>Targets</td>
<td>bacteria,</td>
<td>infected cells</td>
</tr>
<tr>
<td></td>
<td>viruses</td>
<td>tumor cells</td>
</tr>
<tr>
<td>Memory?</td>
<td>Yes</td>
<td>Yes</td>
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</tbody>
</table>
B cells

Formed in bone marrow

Mature when exposed to antigen (T cells regulate with cytokines)

Plasma cells- secrete (release) antibodies

Memory cells- can react more quickly to later exposures to the same antigen

Antibody structure
Antibody (immunoglobulin) isotypes

IgG- most common in serum, secreted in secondary response

IgM- secreted in primary response; also part of antigen receptor on B cells

IgA- most common in secretions

IgE- immediate hypersensitivity (allergy)

IgD- part of cell surface antigen receptor
How do antibodies actually help eliminate antigens?

Opsonization

Complement activation

ADCC

Complement: serum proteins that, when activated, produce a lytic structure that kills target cells.

Products of complement cascade also play a role in inflammation.
Fixation of Complement Proteins

1. Bacterial membrane
   Antibody
   Cell membrane
   Bacterium

2. Complement protein C4
   (Involved in chemotaxis)

3. Soluble complement fixation
   C4a
   C4b
   Complement proteins
T cells regulate the immune response

“Helper” T cells secrete cytokines that regulate the immune response

IL-2 - proliferation of T cells
IL-4, IL-5, IL-6 - activate B cells (and T cells)
γ-interferon - T cell activation

IL-1 is secreted by macrophages; this helps activate T cells also

Macrophages “present” antigen to T cells
Plasma cells secrete antibodies, which can circulate and interact with antigen.

T cell receptor is not secreted - T cell must interact with antigen on target cell surface.

Antigens are “processed” by antigen-presenting cells (lots in lymphoid tissues):
- macrophages
- dendritic cells
- B cells

MHC plays a critical role in antigen presentation.
Effect of an Antigen on B and T Lymphocytes

- Stem cell
  - Antigen
  - B lymphocyte
    - (+) "Helper" cells
    - (-) "Suppressor" cells
    - Clone
      - Memory cell
      - Plasma cell
    - Antibodies
  - T lymphocyte
    - Cytotoxic "killer" T lymphocyte

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Cytokines activate other cells

IL-2 causes TH cells themselves to proliferate (autocrine)

Also causes cytotoxic T cells to proliferate

They (TC) respond to antigen presented in complex with MHC class I

(MHC Class I is on all nucleated cells; MHC Class II has limited distribution)
Interaction of Macrophages, Helper T Cells, and Killer T Cells

- Macrophage with Viral antigen and Class-2 MHC molecule
- Helper T cell
- Interleukin-2
- Infected cell with Class-1 MHC molecule and Viral antigen
- Killer T cell
- Infected cell destroyed

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Immunological tolerance

How can immune system distinguish between self and non-self

“Thymic education”
T cells that might react with self-antigen are eliminated in the thymus (clonal deletion; early mechanism)

Clonal anergy- cells are formed but are not activated against certain antigens (later mechanism)
Cancer immunology

Immune surveillance
   NK cells - early defense mechanism
   MHC Class I inactivates these cells;
   many tumor cells lack MHC Class I

Cytotoxic T cells - antigen specific
   (both types of cells have similar killing mechanisms)
Immunotherapy

Stimulate the immune system
IL-2
Gamma-interferon
TIL (tumor-infiltrating lymphocytes)

Make “specific” therapeutic molecules
Monoclonal antibodies (and antibody fragments)
Cytotoxic T cells
Transplantation immunology

Graft rejection mediated by cytotoxic T cells (important to match tissue; tissue typing)
Immune suppression
  cortisone
  cyclosporin
  newer drugs like rapamycin - less toxic

Xenotransplantation?
Cloning?
## Hypersensitivity reactions

<table>
<thead>
<tr>
<th>Type</th>
<th>Mechanism</th>
<th>Antigen</th>
<th>Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>IgE-Ag triggers Mast cell mediators</td>
<td>Allergen</td>
<td>minutes</td>
</tr>
<tr>
<td>II</td>
<td>IgG or IgM binds to cell surface; ADCC or complement</td>
<td>Cell surface molecule</td>
<td>Few hours</td>
</tr>
<tr>
<td>III</td>
<td>Immune complexes, inflammation</td>
<td>Soluble or particulate</td>
<td>Few hours</td>
</tr>
<tr>
<td>IV</td>
<td>Cytokines (T cells, Macrophages, CTL)</td>
<td>Chemicals, intracellular</td>
<td>1-3 days</td>
</tr>
</tbody>
</table>
Hypersensitivity reactions contribute to disease

Type I- rhinitis; asthma; hives; anaphylaxis

Type II- often directed against blood cells; various types of hemolytic anemia; drug molecules can interact with blood cells and form immunogenic structures

Type III- immune complex disease; usually complexes are cleared, but if not, are deposited in tissue and cause inflammation

Type IV- contact dermatitis (basis for TB skin test)
Autoimmune disease- immune system reacts to self-antigens inappropriately

Cross-reactivity- antibodies or T cells, produced in response to infection, react with tissues (rheumatic fever, rheumatoid arthritis, MS)

Antigens normally hidden from the immune system are exposed (Hashimoto’s thyroiditis)

“Wrong” cells become antigen-presenting cells and trigger immune response

Can be organ-specific or systemic
Treatment

Immune suppression
Plasmapheresis
Removal of thymus

In the future: (?)

Specific T cell inactivation
Vaccination
Oral induction of tolerance
Immune deficiency

Primary (inherited or developmental)

Secondary (viral disease, e.g. AIDS)
Depends on the stage of immune development that is affected

The earlier the defect, the more severe the effect

SCID (severe combined immunodeficiency syndrome) essentially no protection against infection

bone marrow transplants
Summary

Immune response is carried out by white blood cells that circulate between blood and lymphoid organs.

Most infectious organisms activate innate immune mechanisms.

T and B cells recognize specific antigens and generate cell-mediated and humoral immunity, respectively. The response is regulated by T cells.
Defects in the immune system result in increased susceptibility to infection, and may themselves cause disease.

Understanding these mechanisms is important for control of allergies, autoimmune disease, and organ graft rejection.