Clinical Immunology
Overview of the Immune System

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The Spectrum of Clinical Immunology

Inflammation
- Immune Response
  - Deficiency
  - Loss of Tolerance
  - Hypersensitivity

Basic Immunology

Clinical Immunology
- Primary
- Secondary

Immunodeficiency
- Autoimmunity
- Systemic
- Organ spec.

Allergy
- Haemolytic Anemia
- Vasculitis
- Tuberculosis
Some definitions...

• **Immunity**
  – our ability to protect ourselves from disease
  – Recognition & removal of foreign material entering body
  – relies on our ability to distinguish between self and non-self
  – can be innate or acquired

• **Immune system**
  – the cells and molecules responsible for immunity and their collective and coordinated response to the introduction of foreign substances (not just infectious)

• **Immunology**
  – study of cells, organs, molecules responsible for immunity & how they respond & interact
  – effects & consequences (desirable/undesirable)
  – can the response be advantageously increased/reduced
The immune system deals with a variety of pathogens

<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><em>Pneumonia</em>&lt;br&gt;<em>Tetanus</em>&lt;br&gt;<em>Sleeping sickness</em>&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><em>Leprosy</em>&lt;br&gt;<em>Leishmaniasis</em>&lt;br&gt;<em>Malaria</em></td>
</tr>
<tr>
<td>Viruses (intracellular)</td>
<td><em>Variola</em>&lt;br&gt;<em>Influenza</em>&lt;br&gt;<em>Varicella</em></td>
<td><em>Smallpox</em>&lt;br&gt;<em>Flu</em>&lt;br&gt;<em>Chickenpox</em></td>
</tr>
<tr>
<td>Parasitic worms (extracellular)</td>
<td><em>Ascaris</em>&lt;br&gt;<em>Schistosoma</em></td>
<td><em>Ascariasis</em>&lt;br&gt;<em>Schistosomiasis</em></td>
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Figure 1.24 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

- The immune system has evolved different methods to deal with the wide variety of pathogens it has to deal with
- 2 key arms of the immune system are innate & adaptive immune responses
Two branches of the immune system

**Innate immunity**
- Microbe
- Innate barriers
- Phagocytes
- Dendritic cells
- Complement
- NK cells

**Adaptive immunity**
- B lymphocytes
- Antibodies
- Effector T cells

**Time after infection**
- Hours: 0, 6, 12
- Days: 1, 4, 7
Time course of an immune response to viral infection

- Type I Interferon (Dendritic Cells)
- Natural Killer Cells
- Cytotoxic T Lymphocytes

Days after viral infection

Virus titer
The Innate Immune System

• Why do we need innate immunity?
  – Microbes multiply at very high rates
  – Overwhelming infection can occur quickly
  – Need a system that detects infection rapidly

• Innate immunity is required to cover the time taken (7-10 days) for adaptive immunity to be generated

• Paramedics at an accident
  – React quickly & efficiently
  – Less specific actions than later “specialists”
Physical components of innate immunity

- Physical barrier between microbes in external environment and host tissue
  - skin & mucosal surfaces

- Multiple levels of physical protection
  - Tight junctions
  - Keratin
  - Mucus assisted by cilia & peristalsis

- Epithelial cells also produce antimicrobial chemicals
  - defensins
  - further impede entry of microbes

- Intraepithelial T cells recognise and respond to a small number of common microbial structures
Cellular components of innate immunity

- Macrophages – large phagocytic tissue cells, responsible for removal of damaged tissue, cells, bacteria etc

- Neutrophils – short-lived scavenger blood cells containing granules of powerful bactericidal enzymes (80% leukocytes)

- Dendritic cells – present antigen to T cells to initiate adaptive immune responses

- Natural Killer (NK) cells – lymphocyte-like cells capable of killing virus infected and tumor cells without the specificity of true lymphocytes

- Mast cells – found in tissues, release inflammatory mediators when damaged and under the influence of IgE antibody
Soluble components of innate immunity

- Several molecules that recognize/respond to microbes and promote innate responses exist in soluble form in blood and ECF.

- Provide early defense against pathogens present outside host cells at some stage of their life cycle.

- Function in two major ways:
  - Bind to microbes & act as opsonins to enhance phagocytosis by macrophages, neutrophil & dendritic cells.
  - Promote inflammatory responses that bring more phagocytes to sites of infections and may also directly kill microbes.

- Complement, cytokines, chemokines, defensins, acute phase proteins.
Various components of innate immunity work at different stages of infection

- Epithelial barriers impair microbial entry into the host

- Resident and recruited phagocytes in subepithelial and other tissues provide protection if the barriers are breached

- Plasma proteins and circulating phagocytes provide protection if microbes reach the blood stream
What does innate immunity recognise?

• Molecular structures that are produced by microbial pathogens – often shared by classes of microbes
  – Pathogen associated molecular patterns (PAMPs)
  – Essential for survival of microbes - ensures the target of the immune response can’t just be discarded by the microbe to evade recognition

• Endogenous molecules that are produced by or released from damaged and dying cells
  – Damage associated molecular patterns (DAMPs)
  – Can be produced as a result of cell damage caused by infection
  – Also produced in response to sterile injury to cells
    • chemical toxins, burns, trauma or low blood supply
  – generally not released by cells dying from apoptosis
### Examples of PAMPs and DAMPs

<table>
<thead>
<tr>
<th>Pathogen-Associated Molecular Patterns</th>
<th>Microbe Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleic acids</td>
<td></td>
</tr>
<tr>
<td>ssRNA</td>
<td>Virus</td>
</tr>
<tr>
<td>dsRNA</td>
<td>Virus</td>
</tr>
<tr>
<td>CpG</td>
<td>Virus, bacteria</td>
</tr>
<tr>
<td>Proteins</td>
<td></td>
</tr>
<tr>
<td>Pilin</td>
<td>Bacteria</td>
</tr>
<tr>
<td>Flagellin</td>
<td>Bacteria</td>
</tr>
<tr>
<td>Cell wall lipids</td>
<td></td>
</tr>
<tr>
<td>LPS</td>
<td>Gram-negative bacteria</td>
</tr>
<tr>
<td>Lipoteichoic acid</td>
<td>Gram-positive bacteria</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td></td>
</tr>
<tr>
<td>Mannan</td>
<td>Fungi, bacteria</td>
</tr>
<tr>
<td>Glucans</td>
<td>Fungi</td>
</tr>
</tbody>
</table>

**Damage-Associated Molecular Patterns**

<table>
<thead>
<tr>
<th>Stress-induced proteins</th>
<th>HSPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystals</td>
<td>Monosodium urate</td>
</tr>
<tr>
<td>Nuclear proteins</td>
<td>HMGB1</td>
</tr>
</tbody>
</table>
How are PAMPs & DAMPs recognized?

- Pattern Recognition Receptors (PRR)

- Most cell types express PRR and are capable of participating in innate immune responses

- Phagocytes & dendritic cells express the widest variety and greatest amount of these receptors in keeping with their fundamental roles

- Expressed on cell surfaces, in phagocytic vesicles and in the cytosol of cells - all of which are locations where microbes may be present

- When these receptors bind PAMPs and DAMPs they activate signal transduction pathways that promote antimicrobial and proinflammatory functions of the cells in which they are expressed
Pattern Recognition Receptors

- Bacterial cell wall lipid (TLR)
- Fungal polysaccharide (Lectin)

**Extracellular**

- Plasma membrane

**Cytosolic**

- NLR
- RLR
- CDS

**Endosomal**

- Microbial DNA
- Microbial RNA
- Bacterial peptidoglycan

- Endosomal membrane
Effector mechanisms of innate immunity

• Inflammation
  – the process by which leukocytes and circulating plasma proteins are brought into sites of infection and activated to destroy and eliminate the offending agents
  – also the major reaction to damaged or dead cells and to accumulations of abnormal substances in cells and tissues

• Anti-viral defense
  – consists of changes in cells that prevent virus replication and increase susceptibility
Phagocytosis and intracellular destruction of microbes

1. Microbes bind to phagocyte receptors
2. Phagocyte membrane zips up around the microbe
3. Microbe ingested in phagosome
4. Fusion of phagosome with lysosome
5. Activation of phagocyte
6. Phagosome with ingested microbe and lysosome with enzymes
7. Killing of microbes by lysosomal enzymes in phagolysosomes
8. Killing of phagocytosed microbes by ROS and NO
Effector functions of macrophages

- Molecules produced in activated macrophages:
  - Phagocyte oxidase
  - iNOS
  - Cytokines (TNF, IL-1, IL-12)
  - Fibroblast growth factors, angiogenic factors, metalloproteinases

- Effector functions of activated macrophages:
  - Killing of microbes
  - Inflammation, enhanced adaptive immunity
  - Tissue remodeling
Anti-viral actions of type I interferons
Effector functions of NK cells

A: NK cell → Injured cell → Killing of injured cells
   Virus-infected cell → Killing of infected cells

B: NK cell → Macrophage with phagocytosed microbes → Killing of phagocytosed microbes
   IL-12 → IFN-γ
Stimulation of adaptive immunity

Signal 1

Signal 2

Lymphocyte receptor

Antigen

Microbial antigen

Innate immune response to microbe

Molecule induced by innate response (e.g., costimulator, complement fragment)

Lymphocyte proliferation and differentiation

Adaptive immune response
**Innate immunity**
- Epithelial barriers
- Phagocytes
- Dendritic cells
- Complement
- NK cells

**Adaptive immunity**
- B lymphocytes → Antibodies
- T lymphocytes → Effector T cells

**Time after infection**
- Hours: 0, 6, 12
- Days: 1, 4, 7
The Adaptive Immune System

- Key cells are T and B lymphocytes
- Lymphocytes express highly diverse membrane receptors
  - Recognise a wide variety of foreign substances
  - Distinguish subtle differences in structure
  - Receptors generated by rearrangement of antigen receptor genes during the development of mature B and T cells from precursor cells
- Provides **diversity** – can respond to a large variety of antigens which is essential to defend against the many potential pathogens in the environment
- Takes about a week to develop but then provides long-term **memory** which ensure a faster, better response when next encountering the same pathogen
Types of adaptive immunity

• **Humoral immunity**
  – Mediated by secreted antibodies
  – Defense against extracellular microbes
  – Antibodies recognise microbial antigens, neutralise their infectivity and target microbes for elimination
  – Antibodies are specialised → activate different effector functions

• **Cell-mediated immunity**
  – Mediated by T cells themselves & their products (cytokines)
  – Defense against intracellular microbes
Phases of adaptive immune responses

- Antigen recognition
- Lymphocyte activation
- Antigen elimination
- Contraction (homeostasis)
- Memory

**Differentiation**
- Antibody-producing cell
- Effector T lymphocyte

**Clonal expansion**
- Naive T lymphocyte
- Naive B lymphocyte

**Antibodies and effector T cells**
- Apoptosis

**Surviving memory cells**

Days after antigen exposure:
- 0
- 7
- 14
- 21
How are T cells activated?

• They need to recognise the foreign pathogen

• T-cells can not directly “see” microbes - only recognise antigens (short peptides) that are presented on the surface of host cells
  – Infected cells
  – Antigen presenting cells

• They need a second costimulatory signal
  – Binding of B7 to CD28
How do T cells recognise antigen?

- APC present peptides to CD4+ T-cells
- MHC class II
- T cell present peptides to CD8+ T-cells
- MHC class I

CD4+ helper T cell

CD8+ cytotoxic T lymphocyte
Antigen Presenting Cells

**Antigen uptake**
- Dendritic cell

**Antigen presentation**
- Costimulator (e.g., B7)
- CD28

**Response**
- Naive T cell activation: clonal expansion and differentiation into effector T cells
- Effector T cell activation: activation of macrophages (cell-mediated immunity)
- Effector T cell activation: B cell activation and antibody production (humoral immunity)

- Effector T cell
- Killed microbe
- Antibody

- Macrophage
- Effector T cell
- Killed microbe
T cell subsets

- Cytotoxic T Cell
  - CD3+ CD8+ IFN-g
  - T FH T Cell
    - CD3+ CD4+ IL-21
  - Th9 T Cell
    - CD3+ CD4+ IL-9

- T Helper Cell
  - CD3+ CD4+
  - Th1 T Cell
    - CD3+ CD4+ IFN-g
  - Th2 T Cell
    - CD3+ CD4+ IL-4
  - Th22 T Cell
    - CD3+ CD4+ IL-22
  - Th17 T Cell
    - CD3+ CD4+ IL-17

- Regulatory T Cell (Treg)
  - CD3+ CD4+ CD25++ IL-10, TGF-b
Effector CD4⁺ T cell Subsets

- Express surface molecules and secrete cytokines
- Activate other cells
- Distinct subsets arise in response to different antigens
Functions of Th1 Cells

Activate macrophages to ingest and destroy internalised microbes

- Extracellular antigens (e.g. bacteria) usually end up in endosomal vesicles
- T cell recognition of peptide-MHC-II complex
- Macrophage activation: destruction of phagocytosed antigen

Class II MHC–associated presentation of extracellular antigen to helper T cells

IFN-γ
Functions of Th2 Cells

Stimulate reactions that serve to eradicate helminthic infections

IL-4 induces IgE antibody responses

IL-5 activates eosinophiles

IL-13 has diverse functions
Functions of Th17 Cells

Secrete cytokines that recruit neutrophils to sites of infection

Neutrophils are a major defense mechanism against extracellular bacteria and fungi
Cytotoxic T-cell responses

Eliminate intracellular microbes mainly by killing infected cells

Endogenously synthesized antigens in nucleated cell (viral or tumor)

Recognise peptide-MHC-I complex

CD8+ cytotoxic T lymphocyte

Granzyme & Perforin

Granule exocytosis

Detachment of CTL

Target cell death
Treg suppress immune responses
How are B cells activated?

- Recognise antigen in its intact, native conformation and do not require antigen to be processed by APC or presented in MHC molecules.
- Antibody molecules expressed on the surface of the B cell act as the B cell receptor (BCR).
- Secondary signals promote increased activation and signalling.
- Once activated, B cells differentiate into plasma cells that secrete antibody molecules.
How are B cells activated?

- Antibodies exist as different isotypes.
- They have different functions at different locations and for different pathogens.
- IgM is the first Ab made, switch to IgG and others later in the response.
Functions of antibodies

- Neutralization of microbes and toxins
- Opsonization and phagocytosis of microbes
- Antibody-dependent cellular cytotoxicity
- Lysis of microbes
- Phagocytosis of microbes opsonized with complement fragments (e.g., C3b)
- Complement activation
- Inflammation
A. Antibodies prevent the binding of microbes to cells and so inhibit infection of host cells.

B. Antibodies inhibit the spread of microbes from an infected cell to adjacent uninfected cells.

C. Antibodies block the binding of toxins to cells and thus inhibit the pathologic effects of the toxins.
Antibodies of certain IgG subclasses bind to microbes and are then recognized by Fc receptors on phagocytes.

Signals from the Fc receptors promote the phagocytosis of the opsonized microbes and activate the phagocytes to destroy these microbes.
Specificity, memory and contraction of adaptive immune responses
Tolerance

Central Tolerance
mechanism by which immature T cells that recognise self antigens are deleted during development in the thymus, sometimes referred to as “thymic education”

Peripheral Tolerance
mechanism by which mature T cells that recognise self antigens in peripheral tissues are rendered incapable of subsequently responding to those antigens