A Light Introduction to ImmunoPathology

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Responses to Infection

Non-specific ➔ Early Induced ➔ Specific ➔ Protective Memory

- Innate immunity (0–4 hours): Recognition by pre-formed, non-specific effectors ➔ Removal of infectious agent
- Early induced response (4–96 hours): Recruitment of effector cells ➔ Recognition, activation of effector cells ➔ Removal of infectious agent
- Late adaptive response (>96 hours): Transport of antigen to lymphoid organs ➔ Recognition by naive B and T cells ➔ Clonal expansion and differentiation to effector cells ➔ Removal of infectious agent
- Protective immunity: Recognition by pre-formed antibody and effector T cells ➔ Removal of infectious agent
- Immunological memory: Recognition by memory B cells and T cells ➔ Rapid expansion and differentiation to effector cells ➔ Removal of infectious agent
Course of A Typical Acute Infection (Adaptive Response)
<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Major Immune Defense Mechanism(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>Antibody (Immune complex and cytotoxicity)</td>
</tr>
<tr>
<td>Mycobacterial</td>
<td>DTH and granulomatous reactions</td>
</tr>
<tr>
<td>Viral</td>
<td>Antibody (Neutralization), TCTL and DTH</td>
</tr>
<tr>
<td>Protozoal</td>
<td>DTH and antibody</td>
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<td>Worms</td>
<td>Antibody (Atopic, ADCC) and granulomatous reactions</td>
</tr>
<tr>
<td>Fungal</td>
<td>DTH and granulomatous reactions</td>
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# Pathogens, Compartments, and Host Defense

## Site of infection

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>Intracellular</th>
<th>Extracellular</th>
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<tbody>
<tr>
<td></td>
<td>Cytoplasmic</td>
<td>Interstitial spaces, blood, lymph</td>
</tr>
<tr>
<td></td>
<td>Vesicular</td>
<td>Epithelial surfaces</td>
</tr>
</tbody>
</table>

## Organisms

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<tr>
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<tbody>
<tr>
<td>Viruses</td>
<td>Mycobacteria</td>
<td>Viruses</td>
</tr>
<tr>
<td>Chlamydia spp.</td>
<td>Salmonella</td>
<td>Bacteria</td>
</tr>
<tr>
<td>Rickettsia spp.</td>
<td>typhimurium</td>
<td>Protozoa</td>
</tr>
<tr>
<td>Listeria</td>
<td>Leishmania</td>
<td>Fungi</td>
</tr>
<tr>
<td>monocytogenes</td>
<td>spp.</td>
<td>Worms</td>
</tr>
<tr>
<td>Protozoa</td>
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</tbody>
</table>

## Protective immunity

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<th>Extracellular</th>
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<tbody>
<tr>
<td>Cytotoxic T cells</td>
<td>T-cell and NK-cell dependent macrophage activation</td>
<td>Antibodies, especially IgA</td>
</tr>
<tr>
<td>NK cells</td>
<td></td>
<td>Inflammatory cells</td>
</tr>
<tr>
<td>T-cell dependent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>macrophage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>activation</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Antibodies, complement</td>
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<tr>
<td></td>
<td></td>
<td>Phagocytosis neutralization</td>
</tr>
</tbody>
</table>

## Additional Organisms

- Neisseria gonorrhoeae
- Worms
- Mycoplasma
- Streptococcus pneumoniae
- Vibrio cholerae
- Escherichia coli
- Candida albicans
- Helicobacter pylori
### Direct Mechanisms of Tissue Damage by Pathogens

<table>
<thead>
<tr>
<th>Pathogenic mechanism</th>
<th>Exotoxin production</th>
<th>Endotoxin</th>
<th>Direct cytopathic effect</th>
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</thead>
<tbody>
<tr>
<td></td>
<td><img src="image1" alt="Exotoxin" /></td>
<td><img src="image2" alt="Endotoxin" /></td>
<td><img src="image3" alt="Direct cytopathic effect" /></td>
</tr>
</tbody>
</table>
#### Indirect Mechanisms of Tissue Damage by Pathogens

<table>
<thead>
<tr>
<th>Indirect mechanisms of tissue damage by pathogens</th>
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<tbody>
<tr>
<td>Immune complexes</td>
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</tbody>
</table>

- **Immune complexes**
- **Anti-host antibody**
- **Cell-mediated immunity**
Table in Syllabus Gives Examples of Agents and Disease

<table>
<thead>
<tr>
<th>Infectious agent</th>
<th>Direct mechanisms of tissue damage by pathogens</th>
<th>Indirect mechanisms of tissue damage by pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exotoxin production</td>
<td>Immune complexes</td>
</tr>
<tr>
<td></td>
<td>Endotoxin</td>
<td>Anti-host antibody</td>
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<tr>
<td></td>
<td>Direct cytopathic effect</td>
<td>Cell-mediated immunity</td>
</tr>
<tr>
<td>Pathogenic mechanism</td>
<td></td>
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<tr>
<td>Tonsilitis, scarlet fever</td>
<td>Gram-negative sepsis, Meningitis, pneumonia, Typhoid, Bacillary dysentery, Wound infection, Plague</td>
<td>Kidney disease, Vascular deposits, Glomerulonephritis, Kidney damage in secondary syphilis, Transient renal deposits, Rheumatic fever, Hemolytic anemia, Tuberculosis, Tuberculoid leprosy, Aseptic meningitis, AIDS, Lyme arthritis, Schistosomiasis, Herpes stromal keratitis</td>
</tr>
<tr>
<td>Boils, toxic shock syndrome</td>
<td>Smallpox, Chickenpox, shingles, Hepatitis, Poliomyelitis, Measles, subacute sclerosing panencephalitis, Influenza</td>
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<tr>
<td>Food poisoning</td>
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<tr>
<td>Diphtheria</td>
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<tr>
<td>Tetanus</td>
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<tr>
<td>Cholera</td>
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</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>Escherichia coli, Haemophilus influenzae, Salmonella typhi, Shigella, Pseudomonas aeruginosa, Yersinia pestis</td>
<td>Variola, Varicella-zoster, Hepatitis B virus, Polio virus, Mumps virus, Influenza virus, Herpes simplex virus, Most acute infections</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td></td>
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<tr>
<td>Corynebacterium diphtheriae</td>
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<tr>
<td>Clostridium tetani</td>
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<tr>
<td>Vibrio cholerae</td>
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<tr>
<td>Mycobacterium tuberculosis</td>
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<tr>
<td>Mycobacterium leprae</td>
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<td></td>
</tr>
<tr>
<td>Lymphocytic choriomeningitis virus</td>
<td></td>
<td></td>
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<tr>
<td>Human immunodeficiency virus</td>
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<tr>
<td>Borrelia burgdorferi</td>
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<tr>
<td>Schistosoma mansoni</td>
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<td></td>
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<tr>
<td>Herpes simplex virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
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</tr>
</tbody>
</table>
Bacteria
IMMUNE MECHANISMS IN BACTERIAL SKIN INFECTION

1. NEUTRALIZATION OF TOXIN
2. OPSONIZATION PHAGOCYTOSIS
3. COMPLEMENT MEDIATED LYSIS
4. VASODILATION VASOPERMEABILITY
5. T-CELL ACTIVATION
6. MACROPHAGE CLEARING OF TISSUE

BACTERIA

EPIDERMIS MECHANICAL BARRIER
Bacteria: First Line of Defense

- **Antibody** and complement
  - neutralization of toxin
  - opsonization
  - cytolysis

- Production of anaphylatoxins C3a and C5a

- Influx of phagocytes: Neutrophils (C5a) and monocytes
Gram+ staphylococci (drained abscess, pus)

PMNs, Neutrophils are first line of defense
Gram-, *Neisseria meningitidis* (child, CSF)
Reminder:
Biological Activities of Complement

- Enhancement of immune response
- Lysis of foreign cells and bacteria
- Opsonization and bacterial phagocytosis
- Solubilization and clearance of immunocomplexes
- Chemotactic anaphylatoxin
- Vasodilation
- Smooth muscle contraction
- Degranulation

- To lymph node

- C3b
  - CR1

- C3d
  - CR2

- MAC

- C3a, C3b

- C3a, C4a, C5a

- Ab
  - Antigen

- Neutrophils
  - Basophils
  - Eosinophils
  - Mast cells

- Degranulation
Reminder: Neutrophil Chemotaxis, Migration, Activation
Reminder: Macrophage Response to Bacterial Components

- **Complement receptors**
- **LPS receptor**
- **CD14**
- **TLR4 (LPS)**
- **Mannose receptors**
- **Scavenger receptors**
- **TLR2 (bacterial cell wall)**
- **Glucan**

**Interaction with bacteria**
- **Phagocytosis**
- **Lysosomes**
- **Phagosome-lysosome fusion**
- **Destruction of intracellular pathogen**
- **Phagosome**
- **Phagolysosome**
- **Activated macrophage**

**Systemic**
- **TNF-α, IL-1, IL-6**
  - Liver: acute-phase protein production
  - Bone marrow: neutrophil mobilization
  - Hypothalamus: fever

**Local**
- **IL-12**
  - T-cell differentiation
- **IL-8**
  - Chemotactic recruitment of PMNs
- **IL-6**
  - Activation of lymphocytes
  - Activation of vascular endothelium
  - Activation of monocytes and lymphocytes

**Release of proinflammatory mediators**
Mycobacterium

DTH and granulomatous reactions
Normal Lung Pathology

1. Lung
2. Horizontal fissure of right lung
3. Heart
4. Acute margin
5. Obtuse margin
6. Brachiocephalic trunk
7. Trachea
8. Left common carotid artery
9. Left subclavian artery

http://www.med.umich.edu/
Active/Reactive Tuberculosis: Pathology

Miliary TB: Small granulomas with areas of caseous necrosis, occurring primarily in the upper lobes, is most characteristic of secondary (reactivation) tuberculosis.

http://www.granuloma.homestead.com
Airway Erosion and Caseation
Cavitation required to spread disease

Upper lobe with caseation, grey bands of fibrosis (scar tissue) and cavity formation

Cavities near the apex of the lung: allow coughing up of liquefied necrotic material

Relatively normal lower lobe of the lung

Cheesy white spherical foci of necrosis

http://www.granuloma.homestead.com/
Mycobacterium tuberculosis (lung section)
Hallmark of Disease: Granuloma Formation

- Necrotic lesion evident during tuberculosis pneumonia.

- Giant cell w/peripherally arranged nuclei, eosinophilic cytoplasm.

Protective immunopathology to *M. tuberculosis* requires a granulomatous response which contains organisms, and memory T\textsubscript{Helper} cell generation.
Development of Granulomas....
good pathology vs. bad pathology
Granuloma Formulation: Molecular Mechanism

“It should be possible to explain the laws of physics to a barmaid.” -- Albert Einstein

- Containment of infection
- Activation to limit pathogen growth

Tissue

Vascular

T Helper Cells

IFN-γ

IL-12

Cellular Activation

CTLS

Granuloma
ROLE OF T-CTL AND TDTH IN MYCOBACTERIAL IMMUNITY

- INFECTION OF MONOCYTES
- LYSIS OF INFECTED CELLS
- PHAGOCYTOSIS
- ACTIVATED MACROPHAGES
- DESTRUCTION OF INTRACELLULAR ORGANISMS
- CURED NO LESIONS

Resting Mac: P-L fusion inhibition
Activated Mac: P-L fusion

T-CTL
TDTH
LYMPHOKINES
During active disease, the granuloma loses its protective capabilities to control infection, resulting in development of necrotic lesions.

Effective vaccination limits disease progression, preventing development of caseating granulomas (necrotic lesions).

Protective immunopathology to *M. tuberculosis* requires generation of memory T “Helper” cells to assist in producing a granulomatous response.

The T Helper cell response allows the granuloma to function to (1) contain organisms (2) without progression to necrotic lesion formation.
Viral Agents

Antibody (Neutralization), TCTL and DTH
**Antibody to virus**
Binds to viral receptors and blocks attachment to cell.

**Class I**
CD8⁺ T<sub>CTL</sub> reacts with viral antigens on surface of infected cell, perforin release causes lysis of infected cells.

**Class II**
CD4⁺ T<sub>DTH</sub> reacts with viral antigens on surface of infected cell, lymphokines attract and activate phagocytosis by macrophages.
Time Course of Viral Infection and Host Response

**Non-specific ➔ Specific**

- Production of IFN-α, IFN-β, TNF-α, and IL-12
- NK-cell mediated killing of infected cells
- T-cell mediated killing of infected cells

IFN-γ

Virus titer

Time after viral infection (days)
Mechanisms Available to Combat Viral Infection

1. Infection replication in epithelium and draining nodes
2. Viraemia
3. Replication in target organ
4. Killing of virally infected cells (immunopathology)
Parasitic Worms

Antibody (Atopic, ADCC) and granulomatous reactions
Helminth Infections
Schistosomal Life Cycle
(Bilharzia)
Schistosomiasis
Schistosomal Egg Granulomas and Fibrosis

- Schistosomal eggs imbed in the liver; the immune system counteracts.
- Scar tissue forms to encapsulates the egg (granuloma).

Causative agents: Cercariae invade skin of host (bottom). Male and female *S. mansoni* or *S. heamatobium* worms mating (right). Female lays 300-1000 eggs per day (center).
Granulomas during Schistosome Infection (establishment of a $T_H^2$ skewed response)

Source: http://www.homepage.montana.edu/~awmsg/granulo.html
Parasitic Worms: Role of Lymphatics

- Terminal Lymphatics are blind-ended, endothelium-lined tubes present in most tissues in similar numbers to capillaries. Lymphatics drain into collecting Lymph Nodes.

- In acute inflammation, the lymphatic channels become dilated and drain away fluid (inflammatory exudate); this limits the extent of tissue oedema.

- Antigens are carried to the regional lymph nodes for processing by APCs and further recognition by lymphocytes.

- If the lymphatic system becomes blocked either as a result of acute inflammation severe tissue edema may occur. An extreme case is filariasis (infection by parasitic larvae), resulting in elephantiasis.
• Microfilariae (thousands) circulate in blood. Worm larvae migrate through lymphatic channels, becoming trapped in lymph nodes and tissues.

• Immune response to microfilariae contributes to pathology.

Causative agents:
Wuchereria bancrofti and Brugia malayi;
Onchocerca volvulus
(onchocerciasis: (river blindness).
Fungal Agents

DTH and granulomatous reactions
Figure 15.3. Immune response to fungal agents. Gross pathology of lung tissue demonstrates fungal induced granulomatous pneumonitis (A) and associated PAS stained *Histoplasma* located within giant cells on histological examination (B). Similar cellular response is evident upon infection with *Aspergillus* (C) shown with silver stain, caused by antigens released from the etiological agent isolated from sinus maxillary tissue (D).
Fungal Infections: T cell Immunity
(Chromomycosis*)

*A localized chronic mycosis of skin, characterized by rough, irregular inflammatory lesions (dermatitis) caused by several dark-colored fungal agents.
Aspergillus fumigatus (invasive, lung tissue)
Evasion of Host Responses
Bacterial Evasion of Immune Response

- Secrete Toxins.
- Inhibit Chemotaxis.
- Block Complement Mediated Pathways.
- Outer Capsules to Block Attachment, Phagocytosis.
- Outer Coat Resistant to Degrative Enzymes.
- Inhibit Lysosomonal Fusion.
- Escape from Phagosome.
- Turn off Cytokine Activation.
- Inappropriate Cytokine Activation.
## Some Mechanisms for Evading Immune Defenses

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localization in protective niches</td>
<td>Latent syphilis, Tapeworm (Echinococcus)</td>
</tr>
<tr>
<td>Intracellular location</td>
<td>Histoplasmosis, Herpesvirus Varicella HIV</td>
</tr>
<tr>
<td>Antigenic modulation</td>
<td>Malaria, Trypanosomiasis Relapsing fever</td>
</tr>
<tr>
<td>Preservation of receptor sites after reaction with antibody</td>
<td>Influenza virus,</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Malaria, measles, HIV Tuberculosis (Anergy)</td>
</tr>
<tr>
<td>Inappropriate Immune Response (Immune Deviation)</td>
<td>Lepromatous Leprosy, Chronic Mucocutaneous Candidiasis</td>
</tr>
</tbody>
</table>
M. Leprae Polar Responses and Pathogenesis

FORMS OF LEPROSY

TUBERCULOID

BORDERLINE

LEPROMATOUS

DELAYED HYPERSENSITIVITY

ANTIBODY PRODUCTION
**M. Leprae Polar Forms**

*Case 48, Geha and Notarangelo*

**Tuberculoid leprosy**
- Low number organisms, low infectivity
- Granulomas and local inflammation
- $T_{H1}$ cytokines

**Lepromatous leprosy**
- Florid growth, high infectivity
- Disseminated infection
- $T_{H2}$ cytokines
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Macrophage Response to Bacterial Components

Phagocyte ingests and degrades Gram-negative bacteria and is activated by LPS to secrete cytokines

LPS -> TLR4

Local
- IL-1
  - Activates vascular endothelium;
  - Activates lymphocytes;
  - Local tissue destruction;
  - Increases access of effector cells
- IL-8
  - Chemotactic factor for leukocytes;
  - Increases access of effector cells;
  - Activates integrin binding;
  - Activates PMNs
- TNF-α
  - Activates vascular endothelium;
  - Increases vascular permeability leading to entry of IgG, complement, cells, fluids
- IL-6
  - Lymphocyte activation;
  - Increased antibody production
- IL-12
  - Activates NK cells;
  - Induces differentiation of CD4 T cells into Th1 phenotype

Systemic
- Fever
  - Production of IL-6
- Fever
  - Mobilization of metabolites
  - Shock
- Fever
  - Induces acute-phase protein production
• Resting Mac: P-L fusion inhibition
• Activated Mac: P-L fusion