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Additional study

- Natural killer cells
  - http://www.youtube.com/watch?v=HNP1EAYLhOs
- Complement system
  - http://www.youtube.com/watch?v=dG40kkzbaNk&feature=related
- Cytotoxic T lymphocytes
  - http://www.youtube.com/watch?v=8buaiYBKl7U
  - http://www.youtube.com/watch?v=8buaiYBKl7U

Overview I

Part 1:
- Building blocks of the normal immune system
- Immune deficiency disease

Part 2:
- Immune hypersensitivity and autoimmunity

Part 3:
- Local immune barriers and immune responses
- Role of co-pathogens in disease processes
Overview II: defenses against infection

Components of the immune system

<table>
<thead>
<tr>
<th>Anatomic barriers to infection</th>
<th>Innate defenses-Immediate Responses</th>
<th>Adaptive defenses-Delayed responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermal layer of skin</td>
<td>Non-specific responses</td>
<td>Pathogen specific responses</td>
</tr>
<tr>
<td>Larynx and nasal turbinates</td>
<td>Response is not more effective on second exposure to pathogen</td>
<td>Acquired response - improved response on second exposure to pathogen</td>
</tr>
<tr>
<td>Cilia in trachea and mucus secretions</td>
<td>Complement system* Natural killer cells*</td>
<td>Humoral immunity</td>
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<tr>
<td></td>
<td>Anti-bacterial proteins e.g. lysozyme and lactoferrin in saliva</td>
<td>Cell-mediated immunity</td>
</tr>
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* Functions in innate and adaptive immunity

What stimulates the immune system?

**Antigen:**
- Definition: A (foreign) substance that stimulates antibody production by the immune system
- Antibody Generator – origin of the term
- Examples of antigens
  - bacterial cell wall polysaccharide
  - viral envelope protein
- The immune system needs to be able to distinguish ‘self’ antigens from foreign antigens otherwise destructive autoimmune or hypersensitivity disease will result

Interactions of different parts of the immune response

- Innate immunity → Antibody-independent killing → Antibody-dependent killing
- Humoral immunity → Antibody-dependent cell-mediated cytotoxicity
- Cell-mediated immunity → Cytotoxic lymphocyte mediated killing
Killing of pathogens by the innate immune system

- Complement
- Natural killer cells

Complement-mediated killing. I. Activation of complement

Complement System
- Proteins present in blood
- Enter tissues during acute inflammation
- Protein activation cascade
- Bacterial cell wall directly activates alternative and lectin pathways
- Final common pathway terminates in membrane attack complex – inserts pore into membrane

Complement-mediated killing. II. Mechanism of killing

Activation of complement

Membrane attack complex

Intracellular fluids

Complement proteins

Membrane attack complex

Complement proteins

Intracellular fluids
Natural killer cells

- Important role in innate defense against viruses and cancer cells
- Respond to cytokines released by sick cells [e.g. interferons]
- Kill cells by releasing granules onto cell surface – no phagocytosis [similar mechanism for cytotoxic lymphocytes]
- [Also activated in an antibody-dependent manner]

The adaptive immune response

- Humoral immunity
- Cell mediated immunity

Principle classes of lymphocytes and their function in adaptive immunity

B-lymphocyte = bone marrow derived
T-lymphocyte = thymus derived
Lymphocytes are not static – recirculation between lymphoid tissues in the body (via lymphatics and blood) is required for coordination of local with systemic immune responses.

Humoral immunity = antibody dependent

- Antibody = Immunoglobulin (Abbreviated to Ig)
- Immunity is mediated by secreted antibodies that bind to infectious agents
- Antibodies present in body fluids – mainly blood
- Antibodies are produced by plasma cells
- Plasma cells are derived from B-lymphocytes
- B-lymphocytes are developmentally derived from the bone marrow (in mammals)
- In adults B-lymphocytes circulate in blood and are also present in lymphoid nodes and lymphoid nodules (e.g. tonsils and adenoids)

Antibodies. 1. Structure

You need to know the following:

- Heavy chain
- Light chain
- Variable domain
- Antigen binding site
- Fc region
Antibodies. II. Binding to antigen

- Antigen binds to antigen binding site in hypervariable region. Lock and key analogy – oversimplification but essentially correct.
- High variability of antigen binding site allows antibodies to be generated to (nearly) all infectious agents
- Why two antigen binding sites on each antibody?

Antibodies. III. Classes.

- There are five major classes of antibody
  - Ig A – important for mucosal immunity, dimer
  - Ig M – often first Ab to be produced, pentameric
  - Ig G – most abundant in body
  - Ig E – important for immunity to metazoan parasites, has important role in allergy
  - Ig D -

Antibodies. IV. How do antibodies promote inactivation or killing of infectious agents?

- Antibody-dependent complement-mediated killing
- Antibody-dependent cell-mediated cytotoxicity
Antibody-dependent complement-mediated killing:
Classical activation pathway of complement

- Classical pathway of complement requires antibody – antigen complexes for activation
- Represents an interaction between the innate and humoral immunity systems
- Require prior exposure to be effective

Summary of complement system:
Activators and effector pathways

Antibody-dependent cell-mediated cytotoxicity [ADCC]

- Requires pathogen specific antibody
- Several effector cells e.g. NK cells, macrophages, neutrophils
- Antibody binds to infected cells = opsonization
  - Important role of Fc receptor
- Stimulates binding and destruction by effector cell
Cell-mediated immunity and killing

- Mediated by cytotoxic lymphocytes (CD8+)
- Adaptive response to specific antigens but does not require antibody
- Important for defense against intra-cellular pathogens and cancerous cells

Pathogen specific recognition

Granule-dependent killing mechanism

induces apoptosis in target cell

Immune deficiency disease

- Large diversity of immune deficiency diseases
- Genetic (rare) or acquired
- Manifest as increased susceptibility to infectious agents and sometimes cancers
- Pathogen susceptibility is related to part of immune system that is damaged
  - Humoral immunity = extra-cellular pathogens
    - E.g. bacterial septicemia
  - Cell-mediated immunity = intra-cellular pathogens
    - E.g. mycobacteria, protozoans
- Poorer immunity is also a normal feature of the young and aged

True pathogens and opportunistic pathogens

- Highly pathogenic agents can cause disease in immune competent and immune deficient hosts
- Less pathogenic agents may cause localized disease in healthy, but severe infections in immune deficient

Most pathogenic
- Salmonella
- Pathogenic Escherichia coli

Candida

Cryptosporidium
- Non-pathogenic Escherichia coli

Least pathogenic
Examples of immune deficiency disease

- Failure of passive transfer
- Human immunodeficiency virus

Failure of passive transfer. I.

- Neonates of some species are born with minimal amounts of circulating antibodies e.g. foals, calves, sheep
- Dependent on antibodies present in first milk (colostrum) ingested in first 24 hours of life
- IgG is the most important antibody type
- Failure of passive transfer is an important predisposing factor to infectious disease in neonates
- Causes – insufficient colostrum, poor quality, ingested too late resulting in poor absorption of antibody, mother not exposed to relevant pathogens

Failure of passive transfer. II.

- Septicemia from opportunistic bacteria [e.g. non-pathogenic Escherichia coli] is very common in neonates with failure of passive transfer, frequently fatal
HIV and immune deficiency. I.

Mechanisms of CD4 T lymphocyte loss in HIV infection

Secondary complication of HIV induced immune deficiency

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<td>Pneumocystis</td>
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<tr>
<td>Cryptococcus neoformans</td>
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<tr>
<td>Toxoplasma gondii</td>
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<tr>
<td>Cryptosporidium</td>
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<tr>
<td>Herpes simplex virus</td>
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<tr>
<td>Tuberculosis (M. tuberculosis)</td>
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<tr>
<td>Atypical mycobacteriosis</td>
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<tr>
<td>Neoplasms</td>
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<tr>
<td>- lymphoma</td>
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<tr>
<td>- Kaposi sarcoma</td>
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Example exam questions

- Describe the structure of an antibody
- Name two mechanisms by which antibodies can promote killing of microorganisms
- How does the complement system destroy bacteria?
- Name an important cell type involved in innate immunity