Immune Responses to Infectious Disease

By: Dr. Suzan Y.
Host-pathogen interaction

- Mechanisms of pathogenicity
- Immune escape mechanisms
- Number of pathogens
- Genes regulating immune responses
- Health condition of the host
<table>
<thead>
<tr>
<th>Pathogenic mechanism</th>
<th>Direct mechanisms of tissue damage by pathogens</th>
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<tbody>
<tr>
<td></td>
<td>Exotoxin production</td>
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<td></td>
<td>Endotoxin</td>
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<td>Direct cytopathic effect</td>
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<tr>
<td><strong>Infectious agent</strong></td>
<td><strong>Streptococcus pyogenes</strong></td>
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<td></td>
<td><strong>Staphylococcus aureus</strong></td>
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<tr>
<td></td>
<td><strong>Corynebacterium diphtheriae</strong></td>
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<td></td>
<td><strong>Clostridium tetani</strong></td>
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<td></td>
<td><strong>Vibrio cholerae</strong></td>
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<td></td>
<td><strong>Escherichia coli</strong></td>
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<td></td>
<td><strong>Haemophilus influenzae</strong></td>
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<td></td>
<td><strong>Salmonella typhi</strong></td>
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<td></td>
<td><strong>Shigella</strong></td>
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<td><strong>Pseudomonas aeruginosa</strong></td>
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<td><strong>Yersinia pestis</strong></td>
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<td></td>
<td><strong>Variola</strong></td>
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<td><strong>Varicella-zoster</strong></td>
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<td><strong>Hepatitis B virus</strong></td>
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<td><strong>Polio virus</strong></td>
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<td><strong>Measles virus</strong></td>
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<td><strong>Influenza virus</strong></td>
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<td><strong>Herpes simplex virus</strong></td>
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<td><strong>Human herpes virus 8 (HHV8)</strong></td>
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Mechanisms of Pathogen-induced tissue Damage (continued)

<table>
<thead>
<tr>
<th>Pathogenic mechanism</th>
<th>Indirect mechanisms of tissue damage by pathogens</th>
<th>Anti-host antibody</th>
<th>Cell-mediated immunity</th>
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</thead>
<tbody>
<tr>
<td><strong>Infectious agent</strong></td>
<td><strong>Immune complexes</strong></td>
<td><strong>Streptococcus pyogenes</strong></td>
<td><strong>Mycobacterium tuberculosis</strong></td>
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<tr>
<td>Hepatitis B virus</td>
<td></td>
<td>Mycoplasma pneumoniae</td>
<td>Mycobacterium lepra</td>
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<tr>
<td>Malaria</td>
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<td>Lymphocytic choriomeningitis virus</td>
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<tr>
<td>Streptococcus pyogenes</td>
<td></td>
<td></td>
<td>Borrelia burgdorferi</td>
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<tr>
<td>Treponema pallidum</td>
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<td></td>
<td>Schistosoma mansoni</td>
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<tr>
<td>Most acute infections</td>
<td></td>
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<td>Herpes simplex virus</td>
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</tbody>
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Bacterial Infections

- 4 steps:
  - Attachment to host cells
  - Proliferation
  - Invasion of host tissue
  - Toxin-induced damage to host cells

- Host defenses act against each of these steps, some bacteria have developed ways to avoid host defences.
Bacterial Infections

- Immunity mainly achieved by antibodies
  - Unless bacteria is capable of intracellular growth
- Depending on # of organisms entering and virulence, different levels of host defense enlisted
  - If inoculum size and virulence is low, phagocytes may be able to eliminate the bacteria
<table>
<thead>
<tr>
<th>Infection process</th>
<th>Host defense</th>
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<tbody>
<tr>
<td>Attachment to host cells</td>
<td>Blockage of attachment by secretory IgA antibodies</td>
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<tr>
<td>Proliferation</td>
<td>Phagocytosis (Ab- and C3b-mediated opsonization)</td>
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<tr>
<td>Invasion of host tissues</td>
<td>Ab-mediated agglutination</td>
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<tr>
<td>Toxin-induced damage to host cells</td>
<td>Neutralization of toxin by antibody</td>
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</tbody>
</table>
Immune responses can contribute to bacterial pathogenesis

- Overproduction of cytokines
  - Septic shock and toxic shock
- Intracellular bacteria
  - Chronic antigenic activation of CD4+ T cells
  - Leads to tissue destruction
  - Characteristics of delayed-type hypersensitivity
  - Leads to development of granuloma and necrosis
SEPTIC SHOCK

Triggering factors:
- systemic infection (bacteraemia)
- microbial cell wall products and/or toxins released from the pathogens

Result:
Systemic activation of neutrophils and macrophages

High level of cytokine (TNF-alpha) production:
  „cytokine storm”

Excessive inflammatory response
Tuberculosis

- Intracellular bacillus
- CD4+ T cell response
  - Responsible for most of the tissue damage
  - This necrosis can be seen when tested for TB
  - Sensitized T cell and activated macrophages is the key factor in immunity.

- Tubercle formed in pulmonary tuberculosis
Defence against **extracellular bacteria**

- **Bacteria producing toxins** (*C. tetani, C. botulinum, C. diphtheriae*)
  - Opsonization - complement, lectin or antibodies
  - Neutralization - antibodies
  - Phagocytosis – neutrophils, macrophages
  - B lymphocytes activation and antibodies secretion (IgM, IgA, IgG1)
  - Antibodies directed against specific polysaccharides of endotoxins can be protective both by enhancing phagocytosis directly and by fixing complement for lysis.
  - Antigenic difference in the polysaccharide component of endotoxins among strains of bacteria cause that the infection with one strain does not generate protective immunity to re infection with different strain of same species.
IgM and IgG antibodies directed against the lipid, IgM is more potent neutralizing antibody than IgG

**Antibody to toxin can neutralize the toxin by several mechanism including:**

- Enhancing clearance by macrophages.
- Blocking binding sites of toxin for its cellular receptor.

**Clostridium tetani**

cause tetanus produce neurotoxin called (tetanospasmin) bind to specific glycolipids in nerve cells in peripheral nervous system

A vaccin prepared from inactivated toxin called toxoid prevent disease by generating antibodies that neutralize the toxin.
**C. botulinum**

Cause food–borne disease occurring when spores or toxin are ingested from contaminated food.
- Botulism is treated with antitoxin.

**Vibrio cholerae**
- Release enterotoxin, antibody to the toxin does not prevent disease,
- Infection with this bacteria induces systemic and mucosal antibody, mucosal IgA prevents attachment of the bacteria in the gut.
- Cholera vaccines induce IgM and IgG, neither IgM nor IgG function well in the intestinal lumen.
**bacteria with Polysaccharide capsule (Streptococci, Neisseria, Staphylococci)**

- Capsular polysaccharide **inhibits phagocytosis** by both macrophages and polymorphnuclear leucocytes
- Opsonization of encapsulated bacteria with antibody and complement is necessary for phagocytes to ingest and kill the pathogens.
- Bacterial vaccines hold great promise for enhancing immunity against encapsulated bacteria
**Streptococcus pyogenes**

- primary pathogenic, human is a carrier
- toxin production → neutralization
- M protein – resistance to phagocytosis → opsonization
- autoimmune-mediated complications:
  - cross-reactivity of antibodies against M protein with host proteins result in rheumatic fever and glumerulonephritis.
Defence against **intracellular bacteria**

- Intracellular bacteria e.g. *Listeria, Mycobacterium, Brucella*
- Antibodies are inefficient
- Phagocytosis – macrophages (IFN-γ production to activate macrophages)
- Th1 response and Th17 response
- (IL-17 production for neutrophils recruitment)
- Cytotoxic T lymphocytes (*Listeria monocytogenes*)
- People with defects of innate and adaptive immunity at risk
- Sensitized T lymphocytes and activated macrophages is the key factor in immunity against intracellular bacteria
Defence against viruses

- Obligatory intracellular parasites
- Interferons $\alpha$ and $\beta$
- Neutralizing antibodies
- Complement activation (virolysis)
- Activity of NK cells attack virus infected cells which express class I MHC.
- Th1 response
- Cytotoxic T lymphocytes (CTL) attack virus infected cell.
- People with T cell immunodeficiency, combined immunodeficiencies and defect in NK cell function (herpesviruses) at risk in Influenza virus and HIV infections.
Influenza – “Flu”

- Cause respiratory illness
- Responsible for some of the worse pandemics in history
- Spherical virion surrounded by lipid bilayer acquired from host
  - 2 glycoproteins – hemagglutinin (HA) and neuraminidase (NA)
  - Antigenic variation in these (mutations leading to new strains) cause problems in developing sustained immunity in the population
<table>
<thead>
<tr>
<th>Response type</th>
<th>Effector molecule or cell</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humoral</td>
<td>Antibody (especially secretory IgA)</td>
<td>Blocks binding of virus to host cells, thus preventing infection or reinfection</td>
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<td></td>
<td>IgG, IgM, and IgA antibody</td>
<td>Blocks fusion of viral envelope with host cell’s plasma membrane</td>
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<tr>
<td></td>
<td>IgG and IgM antibody</td>
<td>Enhances phagocytosis of viral particles (opsonization)</td>
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<tr>
<td></td>
<td>IgM antibody</td>
<td>Agglutinates viral particles</td>
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<td></td>
<td>Complement activated by IgG or IgM antibody</td>
<td>Mediates opsonization by C3b and lysis of enveloped viral particles by membrane-attack complex</td>
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<tr>
<td>Cell mediated</td>
<td>IFN-γ secreted by T&lt;sub&gt;H&lt;/sub&gt; or T&lt;sub&gt;C&lt;/sub&gt; cells</td>
<td>Has direct antiviral activity</td>
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<tr>
<td></td>
<td>Cytotoxic T lymphocytes (CTLs)</td>
<td>Kill virus-infected self cells</td>
</tr>
<tr>
<td></td>
<td>NK cells and macrophages</td>
<td>Kill virus-infected cells by antibody-dependent cell-mediated cytotoxicity (ADCC)</td>
</tr>
</tbody>
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Defence against fungi

• Opportunistic pathogens
• Antibodies are inefficient
• Neutrophils, macrophages, lymphocytes and probably Nk cells play roles against fungi.
• Th1 response (IFN-γ production to activate macrophages)
• Th17 response (IL-17 production for neutrophils recruitment)
• Systemic disease only in immunocompromised individuals
• Most fungal infections of healthy individuals resolve rapidly
• Barriers of innate immunity control most fungi
• Mannose-binding protein recognizes some major fungal pathogens
• Patient with neutropenia or defective neutrophil function appear predisposed to hematogenously disseminated infection with yeast like fungi (Candida spp) or with filamentous fungi (Aspergillus)

patients with defective cell mediated immunity (AIDS patients) are predisposed to mucosal candidiasis or hematogenously disseminated infection with Cryptococcus histoplasmosis.
Defence against protozoan infections

- Chronic non-symptomatic latent infection
- Antigenic variation, different developmental stages (some are intracellular, others are extracellular)
- Intracellular (*Plasmodium, Trypanosoma, Leishmania, Toxoplasma*)
  
  Th1 lymphocytes and activated macrophages

- Extracellular (*Entameba, Giardia, Trichomonas*)

  Antibodies

- Clinical manifestation when immune system is compromised or weakened
Defence against helminths

- chronic persistent infection (e.g. tapeworm, roundworm, pinworms)
- High morbidity, low mortality
- reinfection
- Eosinophils
- Antibody IgE
- later Th1 response (macrophages), CTL.
How do Pathogens evade the immune response?

• Pathogens that infect the human body have evolved a number of different techniques for avoiding the immune response.

• These include:
  – Antigenic variation
  – Antigenic mimicry
  – Evading macrophage digestion
  – Hiding in cells
  – Immune suppression
  – Disarming antibodies
Avoiding the immune response

• **Antigenic variation**
  – Some species of protozoan parasites evade immune response by shedding their antigens upon entering the host.
  – Others (e.g. trypanosomes and malarial parasites) can change the surface antigens that they express so that the specific immune system needs to make a new antibody to respond to the infection. This is known as antigenic variation.

• **Antigenic mimicry**
  – This involves alteration of the pathogen’s surface so that the immune system does not recognise the pathogen as “non-self”.
  – Blood flukes can hijack blood group antigens from host red blood cells and incorporate them onto their outer surface so that the immune system does not respond to the infection.
• **Evading macrophage digestion**
  
  – Macrophages have an important role in the immune system as they phagocytosis and destroy foreign material. Some microbes (e.g. *Leishmania*) are able to avoid enzymatic breakdown by lysosomes and can remain and grow inside the macrophage – this means they are able to avoid the immune system.
  
  – Some bacteria can avoid phagocytosis by releasing an enzyme that destroys the component of complement that attracts phagocytes.
  
  – Other bacteria can kill phagocytes by releasing a membrane-damaging toxin

• **Hiding in cells**
  
  – Bacteria such as *heliobacter* can invade the epithelial lining of the intestine to multiply and divide, then transfer into neighbouring cells without entering the extracellular space where they would be detected.
• **Immune suppression**
  – Most parasites are able to disrupt the immune system of their host to some extent.
  – HIV is an example of this. It selectively destroys T helper cells, therefore disabling the host immune system.

• **Disarming antibodies**
  – Bacteria such as *Staphylococcus aureus* have receptors on their surface that disrupt the normal function of the host’s antibodies.
  – These receptors bind to the constant region (the stem) rather than the normal antigen binding sites. This prevents normal signalling between antibodies and other parts of the immune system such as complement activation or initiating phagocytosis of a bound antigen.
• Virus can evading host defenses by:
  • Block or inhibit production of interferons
  • Inhibition of antigen presentation
  • Evade complement
  • Cause general immunosuppression
Pathogens are not only bad....immunotherapy

Adjuvants

- Derivatives of bacterial cell walls (LPS)
- Bacterial toxins and their non-toxic variants (cholera toxin)

Vectors for antigen delivery

- Attenuated bacterial strains (*Listeria, Salmonella*)
- Bacterial toxins and their non-toxic variants with inserted antigenic epitopes (*B. pertussis ACT*)

Cytotoxic effects

- Immunotoxins containing bacterial toxin bound to an antibody specifically recognizing tumour-associated antigen (*C. diphtheriae* diphtheria toxin, *P. aeruginosa* exotoxin A)
### Localization of infection and type of immune response

<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>Vesicular</td>
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<tr>
<td><strong>Organisms</strong></td>
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<tr>
<td>Viruses</td>
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<tr>
<td>Chlamydia spp.</td>
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<td>Rickettsia spp.</td>
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<tr>
<td>Listeria</td>
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<tr>
<td>monocytogenes</td>
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<td>Protozoa</td>
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<td></td>
<td>Mycobacteria</td>
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<td>Salmonella</td>
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<tr>
<td>typhimurium</td>
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<tr>
<td>Leishmania spp.</td>
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<tr>
<td>Listeria spp.</td>
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<tr>
<td>Trypanosoma spp.</td>
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<td>Legionella</td>
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<td>pneumophila</td>
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<td>Cryptoccucus</td>
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<td>neoformans</td>
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<td>Histoplasma</td>
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<tr>
<td>Yersinia pestis</td>
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<tr>
<td>Protective immunity</td>
<td>Cytotoxic T cells</td>
<td>T-cell dependent macrophage activation</td>
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Infection induced Th1 vs. Th2 responses.

Viruses and some bacteria induce IL-12 secretion by dendritic cells that can activated NK cells to produce IFN-γ

Other pathogens (e.g., worms) do not induce IL-12 expression by dendritic cells but may cause the synthesis and secretion of IL-4

Native CD4 T cells activated in the presence of IL-12 and IFN-γ are committed to differentiate into Th1 cells

Native CD4 T cells activated in the presence of IL-4 are committed to differentiate into Th2 cells