Bacterial Mechanisms of Pathogenicity

4th Lecture
4. Toxins

- Poisonous substances produced by microorganisms
- Toxins - primary factor - pathogenicity
- 220 known bacterial toxins
  - 40% cause disease by damaging the Eukaryotic cell membrane
- Toxemia
  - Toxins in the bloodstream
  - Toxigenicity: Capacity of microorganisms to produce toxins.
Two Types of Toxins

1. Exotoxins
   - secreted outside the bacterial cell

2. Endotoxins
   - part of the outer cell wall of Gram (-) bacteria.
Exotoxins versus Endotoxins

(a) Exotoxins are produced inside mostly gram-positive bacteria as part of their growth and metabolism. They are then released into the surrounding medium.

(b) Endotoxins are part of the outer portion of the cell wall (lipid A; see Figure 4.12c) of gram-negative bacteria. They are liberated when the bacteria die and the cell wall breaks apart.
**ENDOTOXINS**

1. Integral part of cell wall
2. Endotoxin is LPS; lipid A is toxic
3. Heat stable
4. Antigenic; questionable immunogenicity
5. Toxoids not be produced
6. Many effects on host
7. Produced only by gram-negative organisms

**EXOTOXINS**

1. Released from the cell before or after lysis
2. Protein
3. Heat labile
4. Antigenic and immunogenic
5. Toxoids can be produced
6. Specific in effect on host
7. Produced by gram-positive & gram-negative organisms
I- Exotoxins

- Mostly seen in **Gram (+) Bacteria**

- Most gene that code for exotoxins are located on **plasmids** or **phages**
Three Types of Exotoxins

1. **Cytotoxins**
   - kill cells e.g. Diphtheria toxin

2. **Neurotoxins**
   - interfere with normal nerve impulses e.g. Botulinum Toxin

3. **Enterotoxins**
   - effect cells lining the G.I. Tract. e.g. Cholera toxin or choleraagen.
Response to Toxins

- If exposed to exotoxins: antibodies against the toxin (antitoxins)
- Exotoxins inactivated (heat, formalin or phenol) no longer cause disease, but stimulate the production of antitoxin
  - altered exotoxins - Toxoids
- Toxoids - modified toxin by heat, chemical, radiation, that have lost their toxicity. Injected to stimulate the production of antitoxins and provide immunity.
**Example: DPT Vaccine**

- **D** - Diphtheria
  - *Corynebacterium diphtheriae*
- **P** - Pertussis
  - *Bordetello pertussis*
- **T** - Tetanus
  - *Clostridium tetani*

DPT - Diphtheria Toxoid
Pertussis Antigen
Tetanus Toxoid
Required Immunizations

1. Diphtheria

2. Pertussis

3. Tetanus

4. Measles

5. Mumps

6. Rubella
   - German Measles

7. Polio

9. Hepatitis B

- Corynebacterium diphtheriae
- Bordetella pertussis
- Clostridium tetani
- Measles virus
- Mumps virus
- Rubella virus
- Polio virus
- Hepatitis B Virus
Most genes that code for exotoxins - plasmids or phages

- Lysogenic convergence
- Diphtheria
- Cytotoxin inhibits protein synthesis - resulting in cell death
- Pseudomembrane
  - fibrin, dead tissue, bacterial cells
Lysogenic Convergence

- Scarlet Fever
- *Streptococcus pyogenes*
  - lysogenic convergence
- cytotoxin - damages blood capillaries and results in a skin rash
  - Strep Throat with a rash
Rash of Scarlet Fever Caused by Erythrogenic Toxins of *Streptococcus pyogenes*
Diseases Caused by Staphylococcal Toxins

Scalded Skin Syndrome  Toxic Shock Syndrome
Diseases caused by Neurotoxins

Botulism

- *Clostridium botulinum*
  - Gram (+), anaerobic, spore-forming rod, found in soil
  - works at the neuromuscular junction
  - prevents impulse from nerve cell to muscle cell
  - results in muscle paralysis
Tetanus  (Lock Jaw)

- *Clostridium tetani*
- Gram (+), spore-forming, anaerobic rod
- Neurotoxin acts on nerves, resulting in the inhibition of muscle relaxation
- Tetanospasmin - “spasms” or “Lock Jaw”
Muscle Spasms of Tetanus are Caused by Neurotoxin of *Clostridium tetani*

Neonatal Tetanus (Wrinkled brow and risus sardonicus)

Source: Color Guide to Infectious Diseases, 1992
Diseases caused by Enterotoxins

- Cholera
  - *Vibrio cholerae*
  - Gram (-) comma shaped rods
Cholera toxin

- Converts ATP into cAMP
- causes cells to excrete Cl\(^-\) ions and inhibits absorption of Na\(^+\) ions
- Electrolyte imbalance
- H\(_2\)O leaves by osmosis
- H\(_2\)O Loss (Diarrhea)

- Two polypeptides: A (active) and B (binding). The A subunit of enterotoxin causes epithelial cells to discharge large amounts of fluids and electrolytes.
Severe cases, 12 - 20 liters of liquid lost in a day

- Untreated cases - Mortality Rate about 50%
- Mortality may be reduced to about 1%
  - administering fluids and electrolytes
Rice-water stool of cholera. The A subunit of enterotoxin causes epithelial cells to discharge large amounts of fluids and electrolytes. Source: Tropical Medicine and Parasitology, 1995
EHEC (Enterohemorrhagic E. coli)

- E. coli (0157:H7)
- Enterotoxin causes a hemolytic inflammation of the intestines
- Results in bloody diarrhea
  - Toxin
    - alters the 60S ribosomal subunit
    - inhibits Protein Synthesis
    - Results in cell death
    - Lining of intestine is “shed”
    - Bloody Diarrhea (Dysentery)
<table>
<thead>
<tr>
<th>Toxin</th>
<th>Bacteria</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endotoxin</td>
<td>Gram-negative lipopolysaccharide</td>
<td>Fever and inflammatory cell stimulation</td>
</tr>
<tr>
<td>Exotoxins</td>
<td></td>
<td></td>
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<tr>
<td>Neurotoxins</td>
<td><em>Clostridium tetani</em></td>
<td>Disordered neuromuscular transmission (tetanus and botulism)</td>
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<tr>
<td></td>
<td><em>Clostridium botulinum</em></td>
<td></td>
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<tr>
<td>Enterotoxins</td>
<td><em>Vibrio cholera, E. coli</em></td>
<td>Diarrhoea</td>
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<tr>
<td>(infectious diarrhea)</td>
<td><em>Bacillus cereus</em></td>
<td></td>
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<tr>
<td>Enterotoxins</td>
<td><em>Staphylococcus aureus</em></td>
<td>Diarrhoea and vomiting</td>
</tr>
<tr>
<td>(food poisoning)</td>
<td><em>Bacillus cereus</em></td>
<td></td>
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<tr>
<td>Tissue-invasive toxins</td>
<td><em>Staphylococcus aureus</em></td>
<td>Tissue destruction by enzymes</td>
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<td></td>
<td><em>Streptococcus pyogenes</em></td>
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<td></td>
<td><em>Clostridium perfringens</em></td>
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<tr>
<td>Pyrogenic toxins</td>
<td><em>Staphylococcus aureus</em></td>
<td>Toxic shock syndrome</td>
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<tr>
<td></td>
<td><em>Streptococcus pyogenes</em></td>
<td>Scarlet fever</td>
</tr>
<tr>
<td>Verotoxins</td>
<td><em>E. coli</em> (O157:H7)</td>
<td>Haemolytic uraemic syndrome</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td><em>Bordetella pertussis</em></td>
<td>Whooping cough</td>
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<td></td>
<td><em>Corynebacterium diphtheria</em></td>
<td>Diphtheria (heart and nerve damage)</td>
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<td></td>
<td><em>Clostridium difficile</em></td>
<td>Pseudomembranous colitis</td>
</tr>
</tbody>
</table>
II- Endotoxins

- Part of outer membrane surrounding gram-negative bacteria.
- Endotoxin is lipid portion of lipopolysaccharides (LPS), called lipid A.
- Effect exerted when gram-negative cells die and cell walls undergo lysis, liberating endotoxin.
- All produce the same signs and symptoms:
  - Chills, fever, weakness, general aches, blood clotting and tissue death, shock, and even death. Can also induce miscarriage.
  - Fever: Pyrogenic response is caused by endotoxins.
### Table 19.3 Comparison of Exotoxins and Endotoxins

<table>
<thead>
<tr>
<th>Property</th>
<th>Exotoxins</th>
<th>Endotoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial source</strong></td>
<td>Gram-positive and Gram-negative species</td>
<td>Gram-negative species only</td>
</tr>
<tr>
<td><strong>Location in the bacterium</strong></td>
<td>Synthesized in the cytoplasm; may or may not be secreted</td>
<td>Component of the outer membrane</td>
</tr>
<tr>
<td><strong>Chemical nature</strong></td>
<td>Protein</td>
<td>Lipopolysaccharide (the lipid A component)</td>
</tr>
<tr>
<td><strong>Ability to form a toxoid</strong></td>
<td>Generally inactivated by heat</td>
<td>No</td>
</tr>
<tr>
<td><strong>Heat stability</strong></td>
<td>Generally inactivated by heat</td>
<td>Heat-stable</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>A distinct toxic mechanism for each</td>
<td>Innate immune response; a systemic response leads to fever, a dramatic drop in blood pressure, and disseminated intravascular coagulation.</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td>Generally very potent; some are among the most potent toxins known.</td>
<td>Not very toxic; small amounts lead to an appropriate response that helps clear an infection.</td>
</tr>
</tbody>
</table>
Endotoxin is LPS
Endotoxins (Continued)

- Endotoxins do not promote the formation of effective antibodies.

- Organisms that produce endotoxins include:
  - *Salmonella typhi*
  - *Proteus spp.*
  - *Pseudomonas spp.*
  - *Neisseria spp.*

- Medical equipment that has been sterilized may still contain endotoxins.
  - *Limulus* amoebocyte assay (LAL) is a test used to detect tiny amounts of endotoxin.
Events leading to fever:

- Gram-negative bacteria are digested by phagocytes.
- **LPS** is released by digestion in vacuoles, causing macrophages to release interleukin-1 (IL-1).
- IL-1 is carried via blood to hypothalamus, which controls body temperature.
- IL-1 induces hypothalamus to release prostaglandins, which reset the body’s thermostat to higher temperature.
Microbial Mechanisms of Pathogenicity: How Microorganisms Cause Disease

- **Number of Invading Microbes**
- **Portals of Entry**
  - Mucous membranes
  - Respiratory tract
  - Gastrointestinal tract
  - Genitourinary tract
  - Conjunctiva
  - Skin
  - Parenteral route
- **Penetration or Evasion of Host Defenses**
  - Capsules
  - Cell wall components
  - Enzymes
- **Damage to Host Cells/ Cytopathic Effects**
  - Direct damage
  - Toxins
  - Exotoxins
  - Endotoxins
  - Hypersensitivity
- **Adherence**
III. B. The Normal Flora of Humans

Types of Symbiosis

- Mutualism
  - A symbiotic relationship in which both species benefit
- Commensalism
  - A symbiotic relationship in which one species benefits, and the other species is neither helped nor harmed
III. B. The Normal Flora of Humans

Types of Symbiosis (cont.)

- Parasitism
  - A symbiotic relationship in which one species benefits, and the other species is harmed
  - Generally, the species that benefits (the parasite) is much smaller than the species that is harmed (the host)
III. B. The Normal Flora of Humans

Normal flora is present in:
- skin
- upper respiratory tract
- oral cavity
- intestine, especially large intestine
- vaginal tract

Very little normal flora in eyes & stomach
III. B. The Normal Flora of Humans

Notably absent in most all internal organs

- Absent in:
  - lower respiratory tract
  - muscle tissue
  - blood & tissue fluid
  - cerebrospinal fluid
  - peritoneum
  - pericardium
  - meninges
III. B. The Normal Flora of Humans

Benefits of the normal flora

- Nutrient production/processing
  eg Vitamin K production by *E. coli*
- Competition with pathogenic microbes
- Normal development of the immune system

Normal flora and opportunistic infections
III. C. Generalized Stages of Infection

1. Entry of Pathogen
   - Portal of Entry

2. Colonization
   - Usually at the site of entry

3. Incubation Period
   - Asymptomatic period
   - Between the initial contact with the microbe and the appearance of the first symptoms
III. C. Generalized Stages of Infection

4. Prodromal Symptoms
   • Initial Symptoms

5. Invasive period
   • Increasing Severity of Symptoms
   • Fever
   • Inflammation and Swelling
   • Tissue Damage
   • Infection May Spread to Other Sites
III. C. Generalized Stages of Infection

6. Decline of Infection

5. Convalescence
Course of Infectious Disease

- Incubation period is the interval between exposure and illness onset.
- Convalescence is a time of recuperation and recovery from illness.
- Depending on various factors an individual may still be infectious during either incubation or convalescence.
Pathogenesis of Infectious Disease

Respiratory or salivary spread

Faecal-oral spread

Venereal spread

Zoonoses
Infections acquired from animals (arthropods, vertebrates).
Human infection controlled by controlling animal infection.

Vector (biting arthropod)

Vertebrate reservoir

Vector-vertebrate reservoir