IMMUNITY TO BACTERIAL INFECTIONS

- Chapter 18

Bacterial Diseases

- Many Infectious agents and many diseases
- Bacteria can Infect any part of the body
- Cause disease due to
  - Growth of the microbe in a tissue
  - Produce Bacterial factors that are harmful to host
  - Elicit an inflammatory response that causes damage
    - but also leads to acquired immunity

Gram Positive Bacteria

- Clostridium species
- Staph aureus

Fig 18.1

Gram Negative Bacteria

- E. coli
- Moraxella species

Fig 18.1
Steps of Bacterial Infection

1. Attachment of bacterium to host tissue
   - Persistence and growth called colonization

2. Invasion into deeper host tissues and production of toxins
   - Results in host cell and tissue injury

3. Inflammation at site of invasion
   - Initiated by antibody binding to bacterium
   - Initiated by complement activation at bacterial surface
   - Initiated by wound healing mechanisms
     - All can activate complement pathways that alters vascular permeability and activates local macrophage (Mφ) and neutrophils (PMNs)
Inflammation at site of invasion

Factors that promote colonization, entry, and progression to disease

- Bacterial Alginate
  - Promotes adherence to host tissue

- Bacterial LPS and pilus
  - Promote persistence by resisting complement and phagocytosis

- Bacterial Type III secretion system
  - Deliver enzymes and toxins that
    - injure host tissues or
    - diminish host immune responses
    - Includes signaling proteins, proteases, and superantigens

Innate Immune Effectors and Bacterial Infection

- Major mediators of resistance to bacterial infections

- High numbers of bacteria on skin and mucous membranes

- Usually do not cause disease

- Commensal organisms

- Physical and physiologic barriers prevent entry or destroy quickly after entry
### Immune System Function and Resistance to Bacterial Infection

- Major mediators of resistance to extracellular bacterial infections is **ANTIBODIES**
  - Provide protective immunity by Killing live organisms through
    - Opsonophagocytosis = promotion of complement mediated phagocytosis
    - Neutralizing bacterial toxins to prevent damage and intense damaging inflammatory responses

### Innate Immune Effectors and Bacterial Infection

**Table 18.1 Innate immune effectors mediating resistance to bacterial infection**

<table>
<thead>
<tr>
<th>Type of mechanism and examples</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical and physiologic barriers</td>
<td>Skin, sebum, mucosal epithelial cells, mucus, and mucous flow</td>
</tr>
<tr>
<td>Enzymatic and protein effectors</td>
<td>Lysozyme, proteases, antimicrobial peptides, iron-sequestering proteins, complement</td>
</tr>
<tr>
<td>Recognition of PAMP</td>
<td>TLRs, TLR2 and peptidoglycan and glycopeptides, TLR4 and LPS, TLR5 and bacterial flagella, TLR9 and CpG DNA</td>
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<tr>
<td>Endocytic pattern recognition molecules</td>
<td>Mannose receptor/scavenger protein</td>
</tr>
<tr>
<td>Soluble collectins</td>
<td>CR3</td>
</tr>
<tr>
<td>Complementarity</td>
<td>Mannose-binding lectin</td>
</tr>
<tr>
<td>Surfactant proteins A and D</td>
<td></td>
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</tbody>
</table>

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**Immunity to extracellular bacteria by antibodies:**

- Antibodies and complement result in opsonization via FcReceptors (FcR) or Complement Receptors (CR) on Mφ and PMN

- Antibody can activate classical complement pathway resulting membrane attack complex (MAC) and opsonization via CR

- Antibodies can also trigger antibody-dependent cell-mediated cytotoxicity (ADCC) by PMN with FcR and CR release proteases, nucleases, lipases, and ROIs

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**Immunity to extracellular bacteria by antibodies:**

- Antibodies and complement result in opsonization via FcReceptors (FcR) or Complement Receptors (CR) on Mφ and PMN

- Antibody cannot activate classical complement pathway resulting membrane attack complex (MAC) because of the thick cell wall, but can do opsonization via CR

- Antibodies can also trigger antibody-dependent cell-mediated cytotoxicity (ADCC) by PMN with FcR and CR release proteases, nucleases, lipases, and ROIs
Immunity to extracellular bacteria by antibodies

Immunity to intracellular bacteria by cell mediated immunity (CMI)

- Bacterial antigens present in the cytoplasm of infected host cell
  - Processed via endogenous pathway and presented to CD8+ T cells (cytotoxic T lymphocytes or CTLs) on MHC class I

- Bacterial antigens present in the endosomes of infected host cell
  - Processed via the exogenous pathway and presented to CD4+ helper T cells (TH) on MHC class II

- Some TH cells (TH1) can initiate a DTH response
  - Activates Mφ and kill bacteria and host cell via proteases and ROI

- Bacterial antigens present on the surface of the infected host cell can be bound by antibodies and targeted for killing by NK cells using ADCC

Bacterial Virulence Factors: How they Thwart Host Immunity

- Virulence factors are anything that bacteria use to cause disease
  - Examples:
    - Proteins, glycolipids, carbohydrates, teichoic acids, peptidoglycan, metabolites, enzymes, toxins

- Impede the function of lymphocytes and granulocytes
  - Proteins, enzymes, and toxins

- Overstimulate inflammation so normal defenses do not work
  - Glycolipids like LPS, cell wall structures like teichoic acids ad peptidoglycan, also enterotoxins and bacterial superantigens

- Prevent phagocytosis
  - Carbohydrates like LPS side chains and capsular polysaccharides

- Evade Complement mediated killing
  - Lots of ways...
Bacteria Evade Complement mediated killing

- Prevent activated complement components from attaching to the bacterial cell wall or outer membrane
  - Presence of capsule or calyx outside bacterial cell
- Prevent CR on phagocytes from binding activated complement on bacterial surface
  - Long or bulky surface components
- Divert activation of MAC from bacterial membrane
  - Expression of certain surface proteins
- Cleave, Inactivate, or disassemble activated complement components
  - Expression of enzymes
- Prevent membrane insertion of complement complex
  - Outer membrane Resistance to insertion
  - Secretion of inhibitors

Bacterial Virulence Factors continued…

- Biofilms
- Quorum Sensing
- Bacterial Pathogenesis through these mechanisms

Bacterial Virulence Factors continued…

- Biofilms
  - An organized growth of many microbial cells in a microcolony
  - Establishment of cell-to-cell communication network using soluble factors
- Communication occurs by Quorum Sensing
  - The time when the bacteria has reached a critical mass where the cells in the biofilm can detect and respond to each other
- Concentration of signaling molecules is high enough to bind to receptors and initiate gene transcription of virulence factors
  - = Bacterial Pathogenesis
- Example:
  - Dental plaque and the pathology of cavities
Biofilm Maturation Pathway

Examples of Quorum sensing molecules

Mechanism of quorum sensing
R = transcription regulator
I = biosynthetic enzyme
HSL = quorum sensing molecule
ABCDEF = virulence factors

Microbial Virulence Factors continued

- Yersina pestis
- Causative agent of “the bubonic plague” or Black Death
- 13th and 14th centuries devastated European populations
- Estimated 33% death of population

- Yop proteins block
  - inflammatory response
  - and promote apoptosis of Mφ

Type III Secretion System and molecular factors involved in pathogenesis of Yersina

- Binding to collagen fibrillar matrix
- Complement activation
- Immune suppression
- Pneumonia
- Type III secretion apparatus
- Disruption of cytoskeletal elements
Bioterrorism

Guest Lecturer

Dr. Mary-Pat Stein