6.2B: Type II Toxins: Toxins that Damage Host Cell Membranes

Skills to Develop

1. Briefly describe the roles of alpha toxin, kappa toxin, and mu toxin, and fermentation by *Clostridium perfringens* in the pathogenesis of gas gangrene.

2. State how the following toxins cause harm and name a bacterium producing each:
   a. leukotoxins such as leukocydin
   b. *Bordetella* tracheal cytotoxin

3. State how Toxin A and Toxin B of *Clostridium difficile* lead to diarrhea and damage to the colon.

Highlighted Bacterium

1. Read the description of *Clostridium difficile* and match the bacterium with the description of the organism and the infection it causes.

Type II toxins are typically phospholipases or pore-forming cytotoxins that disrupt the integrity of eukaryotic cell membranes. Damages host cells release danger-associated molecular patterns (DAMPs) (def) that bind to pattern-recognition receptors (PRRs) causing the release of inflammatory cytokines. This inflammatory response can also further contribute to tissue damage.

1. The **exotoxins** of *Clostridium perfringens* (inf). This bacterium produces at least 20 exotoxins that play a role in the pathogenesis of gas gangrene and producing expanding zones of dead tissue (necrosis) surrounding the bacteria. Toxins include:

   - **alpha toxin** (lecithinase): increases the permeability of capillaries and muscle cells by breaking down lecithin in cytoplasmic membranes. This results in the gross edema (def) of gas gangrene. If the alpha toxin enters the blood it can damage organs. Alpha toxin is also necrotizing (def), hemolytic, and cardiotoxic.
• **kappa toxin** (collagenase): **breaks down supportive connective tissue** *(def)* resulting in the mushy lesions of gas gangrene. It is also necrotizing *(def)*.

• **mu toxin** (hyaluronidase): **breaks down the tissue cement** that holds cells together in tissue.

• **epsilon toxin**: Increases vascular permeability and causes edema and congestion in various organs including lungs and kidneys.

• Additional **necrotizing toxins** *(def)* include beta toxin, iota toxin, and nu toxin.

A major characteristic of gas gangrene is the ability of *C. perfringens* to **very rapidly spread** from the initial wound site leaving behind an expanding zone of dead tissue. This organism spreads as a result of the pressure from fluid accumulation (due to increased capillary permeability from **alpha toxin** and **gas production** *(anaerobic fermentation of glucose)* by the organisms produces hydrogen and carbon dioxide), coupled with the breakdown of surrounding connective tissue (**kappa toxin**) and tissue cement (**mu toxin**).

**2. Leukotoxins.** Leukotoxins, such as leukocidin, are pore-forming toxins that **cause lysis of white blood cells** and other cells involved in immunity by binding to chemokine receptors on these cells and damaging the cell membrane. Leukotoxins is produced by various pyogenic *(def)* bacteria including *Staphylococcus aureus* *(inf)* and *Streptococcus pyogenes* *(inf)*, (group A beta streptococci).

**3. Pseudomonas aeruginosa** produces a variety of toxins that lead to cell lysis and tissue damage in the host. Type II toxins include:

• **Exotoxin U** (Exo U): Degrades the plasma membrane of eukaryotic cells, leading to lysis.

• **Phospholipase C** (PLC): Damages cellular phospholipids causing tissue damage; stimulates inflammation. Delivered by a type 3 secretion system.

• **Alkaline protease**: leads to tissue damage.

• **Cytotoxin**: Damages cell membranes of leukocytes causes microvascular damage.

• **Elastase**: Destroys elastin, a protein that is a component of lung tissue.

• **Pyocyanin**: a green to blue water-soluble pigment that catalyzes the formation of tissue-damaging toxic oxygen radicles *(def)*; impairs ciliary function, stimulates inflammation.

You Tube animation showing Pseudomonas using motility, pili, and exotoxins to cause an infection.

3D Medical Animations Library and Downloads, www.rufusrajadurai. wetpaint.com

**4. Toxin A** and **Toxin B**, produced by *Clostridium difficile* *(inf)*. **Toxin A** damages the membranes of intestinal mucosal cells causing hypersecretion of fluids. In addition, it triggers the production of inflammatory cytokines. Finally, it also attracts and destroys neutrophils, causing them to release their lysosomal enzymes for further tissue damage leading to **hemorrhagic necrosis** *(def)*. **Toxin B** depolymerizes actin damaging mucosal cells cytoskeleton. *Clostridium difficile* causes severe antibiotic-associated colitis and is an opportunistic Gram-positive, endospore-producing bacillus transmitted by the fecal-oral route. *C. difficile* is a common health care-associated infection *(HAIs)* and is the most frequent cause of health-care-associated diarrhea.

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5. *Streptococcus pyogenes* (inf) produces a number of enzymes and toxins that damage cells and tissues and causes inflammation:

- **Streptolysin S**: Causes lysis of red blood cell membranes.
- **Streptolysin O**: Lytic to cells that contain cholesterol in their plasma membrane.
- **Proteases**: Degrade cellular proteins; helps organism spread.
- **DNases**: Degrade cellular DNA; helps organism spread.
- **Streptokinase**: Breaks down fibrin in clots; helps organism spread.
- **Streptococcal pyrogenic exotoxin B** (SPE B): A protease that facilitates bacterial spreading and survival; induces inflammation during *S. pyogenes* infections.

For More Information: Inflammation from Unit 5

6. **Urease and phospholipase**, produced by *Helicobacter pylori* (inf). Urease contributes to acid resistance and epithelial cell damage while phospholipase damages the membrane of gastric or intestinal mucosal cells.

- Flash animation showing induction of stomach and intestinal ulcers by *Helicobacter pylori*.
- HTML5 version of animation for iPad showing induction of stomach and intestinal ulcers by *Helicobacter pylori*.
- YouTube movie of a video endoscopy exam showing duodenal ulcers caused by *Helicobacter pylori*.

7. **Bordetella tracheal cytotoxin**, produced by *Bordetella pertussis* (inf), causes the respiratory cell damage during whooping cough. Cell death, inhibition of ciliary movement by ciliated epithelial cells, and release of the inflammatory cytokine IL-1 triggers the violent coughing episodes, the only way the body can now remove inflammatory debris, bacteria, and mucus.

As mentioned earlier in this unit, many bacteria are able to sense their own population density, communicate with each other by way of secreted chemical factors, and behave as a population rather than as individual bacteria. This is referred to as cell-to-cell signaling or quorum sensing and plays an important role in pathogenicity and survival.
for many bacteria.

**Quorum sensing** involves the production, release, and community-wide sensing of molecules called autoinducers that modulate gene expression in response to the density of a bacterial population. When autoinducers produced by one bacterium cross the membrane of another, they bind to receptors in the cytoplasm. This autoinducer/receptor complex is then able to bind to DNA promoters and activate the transcription of quorum sensing-controlled genes. In this way, individual bacteria within a group are able to benefit from the activity of the entire group.

The outcomes of bacteria-host interaction are often related to bacterial population density. Bacterial virulence, that is its ability to cause disease, is largely based on the bacterium's ability to produce gene products called virulence factors that enable that bacterium to colonize the host, resist body defenses, and harm the body. If a relatively small number of a specific bacteria were to enter the body and immediately start producing their virulence factors, chances are the body's immune systems would have sufficient time to recognize and counter those virulence factors and remove the bacteria before there was sufficient quantity to cause harm. Many bacteria are able to delay production of those virulence factors by not expressing the genes for those factors until there is a sufficiently large enough population of that bacterium (a quorum). As the bacteria geometrically increase in number, so does the amount of their secreted autoinducers.

When a critical level of autoinducer is reached, the entire population of bacteria is able to simultaneously activate the transcription of their quorum-sensing genes and the body's immune systems are much less likely to have enough time to counter those virulence factors before harm is done.

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**Medscape article on infections associated with organisms mentioned in this Learning Object.** Registration to access this website is free.

- *Clostridium perfringens*
- *Streptococcus pyogenes*
- *Staphylococcus aureus*
- *Pseudomonas aeruginosa*
- *Clostridium difficile*
- *Streptococcus pneumoniae*

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**Exercise: Think-Pair-Share Questions**

Explain how the ability of a large population of bacterium, such as *Pseudomonas aeruginosa*, to simultaneously produce toxins and other virulence factors through quorum sensing would be an advantage to that population, as opposed to individual bacteria producing toxins and other virulence factors as soon as they enter the body.

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Summary

1. Type II toxins are typically phospholipases or pore-forming cytotoxins that disrupt the integrity of eukaryotic cell membranes.

2. Damages host cells release danger-associated molecular patterns (DAMPs) that bind to pattern-recognition receptors (PRRs) causing the release of inflammatory cytokines. This inflammatory response can also further contribute to tissue damage.

3. Examples include the exotoxins of Clostridium perfringens that cause gas gangrene, exotoxins of Pseudomonas aeruginosa that causes a variety of opportunistic infections, exotoxins of Streptococcus pyogenes that causes strep throat, the exotoxins of Clostridium difficile that causes antibiotic-associated colitis, and leukotoxins, pore-forming toxins that causes lysis of white blood cells.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following descriptions with the exotoxin:
   - Causes lysis of white blood cells and other immune cells by damaging their cell membrane. It is produced by various pyogenic bacteria including Staphylococcus aureus and Streptococcus pyogenes. (ans)
   - Causes the respiratory damage and violent coughing episodes seen during whooping cough. (ans)
   - Damages the membranes of intestinal mucosal cells causing hypersecretion of fluids; triggers the production of inflammatory cytokines; attracts and destroys neutrophils causing them to release their lysosomal enzymes for further tissue damage leading to hemorrhagic necrosis.
     a. leukotoxins
     b. Toxin A
     c. Toxin B
     d. Bordetella tracheal cytotoxin

2. Usually deep puncture-type wounds are needed for the development of gas gangrene. The resulting infected tissue shows massive edema, is mushy to the touch, and the infection spreads very rapidly through the tissue. In terms of the causative organism and its products, discuss why. (ans)

3. Multiple Choice (ans)

Contributors

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