6.1C: Gram-Positive Bacterial PAMPs

Skills to Develop

1. Describe how Gram-positive PAMPS initiate SIRS.
2. Name 2 Gram-positive bacteria that commonly cause healthcare-associated infections (HAIs).

In order to protect against infection, one of the things the body must initially do is detect the presence of microorganisms. The body does this by recognizing molecules unique to microorganisms that are not associated with human cells. These unique molecules are called pathogen-associated molecular patterns (PAMPs). (Because all microbes, not just pathogenic microbes, possess PAMPs, pathogen-associated molecular patterns are sometimes referred to as microbe-associated molecular patterns or MAMPs.)

Molecules unique to bacteria, such as peptidoglycan monomers, teichoic acids, LPS, porins, mycolic acid, mannose-rich glycans, and flagellin are PAMPs that bind to pattern-recognition receptors (PRRs) on a variety of defense cells of the body causing them to synthesize and secrete a variety of proteins called cytokines (def). These cytokines can, in turn promote innate immune defenses such as inflammation, fever, and phagocytosis. This is accomplished primarily by an inflammatory programmed cell death called pyroptosis involving protein cellular complexes called inflammasomes.

Pyroptosis (def), is a programmed inflammatory death of host cells that is mediated by an enzyme called caspase 1 and can be triggered by a variety of stimuli, including pathogen-associated molecular patterns (PAMPs) from microbial infections, as well as danger-associated molecular patterns (DAMPs) produced as a result of tissue injury during cancer, heart attack, and stroke. Pyroptosis results in production of proinflammatory cytokines, rupture of the cell’s plasma membrane, and subsequent release of proinflammatory intracellular contents. It plays an essential role in innate immunity by promoting inflammation to control microbial infections. At highly elevated levels, however, it
can cause considerable harm to the body and even death. The binding of PAMPs to PRRs also leads to activation of the complement pathways (def) and activation of the coagulation pathway (def).

Cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), and interleukin-8 (IL-8) are known as inflammatory cytokines (def) because they promote inflammation. Some cytokines, such as IL-8, are also known as chemokines (def). Chemokines promote an inflammatory response by enabling white blood cells to leave the blood vessels and enter the surrounding tissue, by chemotactically attracting these white blood cells to the infection site, and by triggering neutrophils (def) to release killing agents for extracellular killing.

The mechanism is as follows:

1. The lysis of Gram-positive bacteria causes PAMPs such as peptidoglycan monomers (the building blocks of peptidoglycan (see Figure 1), lipotechoic acids, mannose-rich glycans, and flagellin to be released.

For More Information: The Gram-Positive Cell Wall from Unit 1

2. These PAMPs, in turn, bind to pattern-recognition receptors (PRRs) (def) that are specific for these PAMPs that are found on the surface of body defense cells such as macrophages (def) and dendritic cells (def).

3. Binding of the PAMPs to the PRRs of these defense cells triggers them to release various defense regulatory chemicals called cytokines, including tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), inflammatory chemokines such as IL-8, and platelet-activating factor (PAF) (see Figure 2). The cytokines then bind to cytokine receptors on target cells and initiate an inflammatory response (def). They also activate both the complement pathways (def) and the coagulation pathway (def) (see Figure 2), in a manner similar to endotoxin (LPS) from the Gram-negative cell wall.

YouTube animation illustrating macrophages releasing cytokines. 
Nucleus Medical Art, www. nucleusinc.com

Flash animation illustrating signaling toll-like receptors on defense cells: LTA and TLR-2/TLR-6.

html5 version of animation for iPad illustrating signaling toll-like receptors on defense cells: LTA and TLR-2/TLR-6.

For More Information: Pathogen-Associated Molecular Patterns (PAMPs) from Unit 5

For More Information: Pattern-Recognition Receptors from Unit 5

For More Information: Cytokines from Unit 5

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4. The binding of PAMPs to their PRRs on the surfaces of phagocytic white blood cells called neutrophils (def) causes them to release proteases (def) and toxic oxygen radicals (def) for extracellular killing. Chemokines such as interleukin-8 (IL-8) also stimulate extracellular killing. In addition, cytokines stimulate the synthesis of a vasodilator called nitric oxide.

Flash animation showing the binding of teichoic acid and chemokines to receptors on neutrophils and their subsequent release of killing agents.

html5 version of animation for iPad showing the binding of teichoic acid and chemokines to receptors on neutrophils and their subsequent release of killing agents.

During minor local infections with few bacteria present, low levels of peptidoglycan monomers, lipoteichoic acids, and other Gram-positive bacterial PAMPs are released leading to moderate cytokine production by defense cells such as monocytes (def), macrophages (def) and dendritic cells (def) and, in general, promoting body defense by stimulating inflammation and moderate fever, breaking down energy reserves to supply energy for defense, activating the complement pathway (def) and the coagulation pathway (def), and generally stimulating immune responses (see Figure 2). Also as a result of these cytokines, circulating phagocytic white blood cells such as neutrophils (def) and monocytes (def) stick to the walls of capillaries, squeeze out and enter the tissue, a process termed diapedesis (def). The phagocytic white blood cells such as neutrophils then kill the invading microbes with their proteases (def) and toxic oxygen radicals (def). These defenses will be covered in greater detail in Units 5 and 6.

For More Information: Inflammation from Unit 5

For More Information: the Complement Pathways from Unit 5

However, during severe systemic infections with large numbers of bacteria present, high levels of these Gram-positive PAMPs are released resulting in excessive cytokine production by the defense cells and this can harm the body (see Figure 3). In addition, neutrophils (def) start releasing their proteases and toxic oxygen radicals that kill not only the bacteria, but the surrounding tissue as well.

Harmful effects include high fever, hypotension (def), tissue destruction, wasting, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), and damage to the vascular endothelium. This can result in shock (def), multiple system organ failure (MSOF), and often death.

As seen earlier in this unit, the release of excessive levels of inflammatory cytokines in response to a systemic infection results in:

1. A drop in blood volume or hypovolemia (def). This is caused by the following events:
   a. Extracellular killing by neutrophils damages the capillary walls results in blood and plasma leaving the bloodstream and entering the surrounding tissue.
   b. Depletion of clotting factors during disseminated intravascular coagulation (DIC) can lead to hemorrhaging as the capillaries are damaged.

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c. **Prolonged vasodilation** results in plasma leaving the bloodstream and entering the surrounding tissue.

2. **A drop in blood pressure or hypotension** *(def)*. This is a result of the following events:

   a. **Prolonged vasodilation causes decreased vascular resistance within blood vessels** decreases blood pressure.

   b. **High levels of TNF, inhibit vascular smooth muscle tone and myocardial contractility** decreasing the ability of the heart to pump blood throughout the body.

   c. **Hypovolemia** from capillary damage, plasma leakage, and hemorrhaging.

3. **The inability to deliver nutrients and oxygen to body cells or hypoperfusion** *(def)*. This is a result of the following events:

   a. **Activation of the blood coagulation pathway** can cause clots called microthrombi to form within the blood vessels throughout the body causing **disseminated intravascular coagulation (DIC)** which blocks the flow of blood through the capillaries and, as mentioned above, depletion of clotting factors can lead to hemorrhaging in many parts of the body.

   b. **Increased capillary permeability** as a result of vasodilation in the lungs, as well as **neutrophil-induced injury to capillaries** in the alveoli leads to acute inflammation, pulmonary edema, and **loss of gas exchange in the lungs** *(acute respiratory distress syndrome or ARDS)*. As a result, the blood does not become oxygenated.

   c. **Hypovolemia decreases the volume of circulating blood** and leads to hypotension.

   d. **Hypotension** decreases the pressure needed to deliver blood throughout the body.

6. **Hypoperfusion in the liver can result in a drop in blood glucose level** from liver dysfunction. Glucose is needed for ATP production during glycolysis and aerobic respiration. A **drop in glucose levels can result in decreased ATP production and insufficient energy for cellular metabolism.**

7. The **lack of oxygen** delivery as a result of hypoperfusion causes cells to switch to **fermentation** for energy production. The **acid end products** of fermentation lead to **acidosis** and the **wrong pH for the functioning of the enzymes** involved in cellular metabolism. This can result in irreversible **cell death.**

Collectively, this can result in :

- **End-organ ischemia** *(def)* Ischemia is a restriction in blood supply that results in damage or dysfunction of tissues or organs.

- **Multiple system organ failure (MSOF)** *(def)*. Multiple organs begin to fail as a result of hypoperfusion.

- **Death.**

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For more information: Review of SIRS and Septic Shock from Unit 3

https://bio.libretexts.org/Bookshelves/Microbiology/Book%3A_Microbiology_(Kaiser)/Unit_3%3A_Bacterial_Pathogenesis/6%3A_Introduction_of_Inflammatory_Cytokines_that_Result_in_an_Excessive_Inflammatory_Response/6.1C%3A_Gram-Positive_Bacterial_PAMPs

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Septicemia (def) is a condition where bacteria enter the blood and cause harm. According to the NIH Sepsis Fact Sheet, “Every year, severe sepsis strikes about 750,000 Americans. It’s been estimated that between 28 and 50 percent of these people die - far more than the number of U.S. deaths from prostate cancer, breast cancer and AIDS combined.” Factors contributing to this high rate of sepsis include:

1. An aging US population.
2. Increased longevity of people with chronic diseases.
3. An increase in number of invasive medical procedures performed.
4. Increased use of immunosuppressive and chemotherapeutic agents.
5. The spread of antibiotic-resistant microorganisms.

People that survive severe sepsis may have permanent damage to the lungs or other organs. Approximately 45% of the cases of septicemia are due to Gram-positive bacteria, 45% are a result of Gram-negative bacteria, and 10% are due to fungi (mainly the yeast Candida). Many of these cases of septicemia are health care-associated infections (HAIs) (def).

Pathogenic strains of Staphylococcus aureus producing leukocidin (def) and protein A (def), including MRSA (def), cause an increased inflammatory response. Protein A, a protein that blocks opsonization (def) and functions as an adhesin (def), binds to cytokine receptors for TNF-alpha (def). It mimics the cytokine and induces a strong inflammatory response. As the inflammatory response attracts neutrophils to the infected area, the leukocidin causes lysis of the neutrophils (def). As a result, tissue is damaged and the bacteria are not phagocytosed. Staphylococcus aureus, coagulase-negative staphylococci (def), and Enterococcus species are among the leading Gram-positive bacteria to cause septicemia.

Other examples of damage from Gram-positive PAMPs are Gram-positive bacterial meningitis (def) and pneumonia. The same inflammatory events lead to identical effects in the brain and the decreased delivery of oxygen and glucose to the cells of the brain results in damage and death of brain tissue.

One such example is the pneumococcus, Streptococcus pneumoniae (inf). When S. pneumoniae enters the alveoli (def) of the lungs and is lysed by antibiotics or body defenses, glycopeptide cell wall fragments and teichoic acids bind to receptors on endothelial cells, the alveolar epithelium, and leukocytes causing the release of TNF-alpha, IL-1, and chemokines. This leads to increased vascular permeability that enables serous fluids, red blood cells, and leukocytes to enter the air spaces of the lung where gas exchange occurs. This prevents normal gas exchange.
and the person drowns on his or her own serous fluids (def). From the lungs, \( S.\ pneumoniae \) often invades the blood, crosses the blood-brain barrier, and enters the meninges.

The Centers for Disease Control and Prevention (CDC) Health care-associated infection's website reports that "In American hospitals alone, health care-associated infections account for an estimated 1.7 million infections and 99,000 associated deaths each year. Of these infections:

- 32 percent of all health care-associated infection are urinary tract infections
- 22 percent are surgical site infections
- 15 percent are pneumonia (lung infections)
- 14 percent are bloodstream infections"

| Estimates of Health care-Associated Infections (HCIs) 2011; from CDC |

Gram-positive bacteria such as \( Staphylococcus \) and \( Enterococcus \), along with the normal microbiota Gram-negative bacteria mentioned in the previous section, are among the most common causes of health care-associated infections (HAIs) (def). The three most common gram-positive bacteria causing HAIs are \( Staphylococcus\ aureus \), coagulase-negative staphylococci (def), and \( Enterococcus \) species. Collectively, these three bacteria accounted for 34% of all HAIs in the U.S. between 1990 and 1996. There are over two million HAIs per year in the U.S.

Highlighted Bacterium: \( Staphylococcus aureus \)

Click on this link, read the description of \( Staphylococcus aureus \), and be able to match the bacterium with its description on an exam.

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

- \( Streptococcus pneumoniae \)
- \( Staphylococcus \) species
- \( Enterococcus \) species

Summary

1. PAMPs associated with Gram-positive bacteria include cell wall teichoic and lipotechoic acids, peptidoglycan fragments, mannose-rich sugars, and flagellin.

2. Approximately 45% of the cases of septicemia are due to Gram-positive bacteria.

3. Medically important Gram-positive bacteria include \( Staphylococcus aureus \), coagulase-negative staphylococci, \( Enterococcus \) species, and \( Streptococcus pneumoniae \).
4. The three most common Gram-positive bacteria causing health care-associated infections (HAIs) are *Staphylococcus aureus*, coagulase-negative staphylococci, and *Enterococcus* species. Collectively, these three bacteria accounted for 34% of all HAIs in the U.S. between 1990 and 1996. There are over two million HAIs per year in the U.S.

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. ___________ (ans) and ___________ (ans) are the components of the Gram-positive cell wall that function similarly to the LPS in the gram-negative cell wall in stimulating cytokine production and an inflammatory response.

2. Name 2 Gram-positive bacteria that commonly cause healthcare-associated infections (HAIs).
   A. (ans)
   B. (ans)

3. Why is the inflammatory response needed for the effective removal of *Streptococcus pneumoniae* in the lungs potentially lethal? (ans)

4. Multiple Choice (ans)

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