11.3A: Pathogen-Associated Molecular Patterns (PAMPs) and Danger-Associated Molecular Patterns (DAMPs)

Skills to Develop

1. State how long it takes for early induced innate immunity to become activated and what it involves.
2. State what is meant by pathogen-associated molecular patterns (PAMPs), and the role PAMPs play in inducing innate immunity.
3. Name at least 5 PAMPs associated with bacteria.
4. Name at least 2 PAMPs associated with viruses.
5. Define DAMPs and give two examples.

In order to protect against infection, one of the first things the body must do is detect the presence of microorganisms. The body initially does this by recognizing molecules unique to groups of related microorganisms and are not associated with human cells. These unique microbial molecules are called pathogen-associated molecular patterns or PAMPs. In addition, unique molecules displayed on stressed, injured, infected, or transformed human cells also be recognized as a part of innate immunity. These are often referred to as danger-associated molecular patterns or DAMPs. In all, the innate immune system is thought to recognize approximately $10^3$ molecular patterns.
Figure 1: (left) Structure of a Gram-Negative Cell Wall. The Gram-negative cell wall is composed of a thin, inner layer of peptidoglycan and an outer membrane consisting of molecules of phospholipids, lipopolysaccharides (LPS), lipoproteins and surface proteins. The lipopolysaccharide consists of lipid A and O polysaccharide. (right) The Gram-positive cell wall appears as dense layer typically composed of numerous rows of peptidoglycan, and molecules of lipoteichoic acid, wall teichoic acid and surface proteins.

Examples of microbial-associated PAMPs include:

a. lipopolysaccharide (LPS) from the outer membrane of the Gram-negative cell wall (see Figure 1A);
b. bacterial lipoproteins and lipopeptides (see Figure 1A);
c. porins in the outer membrane of the Gram-negative cell wall (see Figure 1A);
d. peptidoglycan found abundantly in the Gram-positive cell wall and to a lesser degree in the gram-negative cell wall (see Figure 1B);
e. lipoteichoic acids found in the Gram-positive cell wall (Figure 1B);
f. lipoarabinomannan and mycolic acids found in acid-fast cell walls (Figure 2B)
g. mannose-rich glycans (short carbohydrate chains with the sugar mannose or fructose as the terminal sugar). These are common in microbial glycoproteins and glycolipids but rare in those of humans (see Figure 6).

h. flagellin found in bacterial flagella;

d. bacterial and viral nucleic acid. Bacterial and viral genomes contain a high frequency of unmethylated cytosine-guanine dinucleotide or CpG sequences (a cytosine lacking a methyl or CH$_3$ group and located adjacent to a guanine). Mammalian DNA has a low frequency of CpG sequences and most are methylated which may mask recognition by pattern-recognition receptors. Also, human DNA and RNA does not normally enter cellular endosomes where the pattern-recognition receptors for microbial DNA and RNA are located;

j. N-formylmethionine, an amino acid common to bacterial proteins;

k. double-stranded viral RNA unique to many viruses in some stage of their replication;

l. single-stranded viral RNA from many viruses having an RNA genome;

m. lipoteichoic acids, glycolipids, and zymosan from yeast cell walls; and

n. phosphorylcholine and other lipids common to microbial membranes.

**Figure 2: Structure of an Acid-Fast Cell Wall.** In addition to peptidoglycan, the acid-fast cell wall of Mycobacterium contains a large amount of glycolipids, especially mycolic acids. The peptidoglycan layer is linked to arabinogalactan (D-arabinose and D-galactose) which is then linked to high-molecular weight mycolic acids. The arabinogalactan/mycolic acid layer is overlaid with a layer of polypeptides and mycolic acids consisting of free lipids, glycolipids, and peptidoglycolipids. Other glycolipids include lipoarabinomannan and phosphatidylinositol mannosides (PIM). Because of its unique cell wall, when it is stained by the acid-fast procedure, it will resist decolorization with acid-alcohol and stain red, the color of the initial stain, carbol fuchsin. With the exception of a very few other acid-fast bacteria such as Nocardia, all other bacteria will be decolorized and stain blue, the color of the methylene blue counterstain.

Examples of DAMPs associated with stressed, injured, infected, or transformed host cells and not found on normal cells include:

a. heat-shock proteins;

b. altered membrane phospholipids; and

c. molecules normally located inside phagosomes and lysosomes that enter the cytosol only when these membrane-bound compartments are damaged as a result of infection, including antibodies bound to microbes from...
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d. molecules normally found within cells, such as ATP, DNA, and RNA, that spill out of damaged cells.

To recognize PAMPs such as those listed above, various body cells have a variety of corresponding receptors called **pattern-recognition receptors or PRRs** capable of binding specifically to conserved portions of these molecules. Cells that typically have pattern recognition receptors include macrophages, dendritic cells, endothelial cells, mucosal epithelial cells, and lymphocytes.

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

What are DAMPs and why would it be an advantage for them to initiate an inflammatory response similar to PAMPs?

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**Summary**

1. Early induced innate immunity begins 4 - 96 hours after exposure to an infectious agent and involves the recruitment of defense cells as a result of pathogen-associated molecular patterns or PAMPS binding to pattern-recognition receptors or PRRs.

2. Pathogen-associated molecular patterns or PAMPs are molecules shared by groups of related microbes that are essential for the survival of those organisms and are not found associated with mammalian cells. Examples include LPS, porins, peptidoglycan, lipoteichoic acids, mannose-rich glycans, flagellin, bacterial and viral genomes, mycolic acid, and lipoarabinomannan.

3. Danger-associated molecular patterns or DAMPs are unique molecules displayed on stressed, injured, infected, or transformed human cells also be recognized as a part of innate immunity. Examples include heat-shock proteins and altered membrane phospholipids.

4. PAMPs and DAMPs bind to pattern-recognition receptors or PRRs associated with body cells to induce innate immunity.

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