Tikrit University
College of Veterinary Medicine

Lect. 5-Immunology

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IMMUNOLOGY

Lecture 5 **Dr. Muthanna Sultan**

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Junior students **Academic Year 2023-2024**

Innate Immunity - Part1

Definition

Innate immunity consists of many cell types and soluble molecules in tissues and the blood that constantly prevent microbes from invading and establishing infections. If microbes do establish a foothold, innate immune responses provide early defense, before adaptive immune responses can develop.

Function of the innate immunity

Innate immunity stimulates adaptive immune responses and can influence the nature of the adaptive responses to make them optimally effective against different types of microbes.

So based on these information mentioned above , innate immunity

A- serves defensive functions directly and early after infection.

B- provides the danger signals that alert the adaptive immune system to respond.

C- Moreover, different components of the innate immune response often react in distinct ways to different microbes (e.g., bacteria versus viruses) and thereby influence the type of adaptive immune response that develops.

What are the major responses of innate immunity against the microbes?

A- Inflammation

B- Antimicrobial defense

C- Physical and chemical barriers

A-What does mean Inflammation?

Inflammation is the process by which circulating leukocytes and plasma proteins are brought into sites of infection in the tissues and are activated to destroy and eliminate the infective agent.

B-What does mean antimicrobial defense?

Antiviral defense consists of changes in cells that prevent virus replication and increase susceptibility to killing by lymphocytes, thus eliminating reservoirs of viral infection

C-What does mean physical and chemical barriers ?

epithelial barriers such as the skin and lining of the gastrointestinal and respiratory tracts, which function at all times to block microbial entry. In addition, the innate immune system includes several circulating cells, such as neutrophils, and proteins, such as complement, that can help eliminate microbes in the blood.

What are the microbial-antigenic substances and /or products that recognized by innate immune system?

1-Pathogen Associated Molecular Patterns (PAMPs)

PAMPs are molecular structures that are produced by microbial pathogens and the microbial substances that stimulate innate immunity

,PAMPs includes microbial sources of proteins, complex lipids, carbohydrates, an example of PAMPs such as Lipopolysaccharides (LPS).

2- Damage Associated Molecular Patterns (DAMPs)

DAMPs are endogenous materials that are produced by damages and dying cells which caused by infections or by trauma, burns or decreased blood supply .

Note : The cells that dying by apoptosis are **NOT** considered as a part of DAMPs because as we know that apoptosis is a normal physiological mechanism that happening in the body .

How innate immune cells recognize PAMPs and DAMPs?

To recognize PAMPs and DAMPs, The innate immune system uses several types of cellular receptors, which present in different locations in cells, as well as soluble molecules in the blood and mucosal secretions.

There are specific molecules and /or receptors that are expressed in innate immune cells such as macrophages, neutrophils, dendritic cells,

and epithelial cells, these cellular receptors that recognize the pathogens and damage-associated molecules are often called pattern recognition receptors(PRRs)

What happen when PRRs recognize DAMPs and PAMPs?

When these cell-associated pattern recognition receptors (PRRs) bind to PAMPs and DAMPs, they activate signal transduction pathways that promote the antimicrobial and proinflammatory functions of the cells in which they are expressed. In addition, there are many proteins present in the blood and extracellular fluids that recognize PAMPs ,these soluble molecules are responsible for facilitating the clearance of microbes from blood and extracellular fluids by enhancing uptake into phagocytes or by activating extracellular killing mechanisms.

Types of Pathogenic Recognition Receptors (PRRs)

1-Toll Like Receptors (TLRs)

Toll-like receptors (TLRs) are conserved family of pattern recognition receptors expressed on many cell types that recognize products of a wide variety of microbes as well as molecules expressed or released by stressed and dying cells. The ligands that the different TLRs recognize are structurally diverse and include products of all classes of microorganisms

Composition of TLRs

The TLRs are type I integral membrane glycoproteins that contain leucine-rich molecules in their extracellular regions, which are involved in ligand binding, and a Toll/IL-1 receptor (TLR) homology domain in their cytoplasmic tails, which is essential for signaling.

The structural basis of TLR specificities resides in the multiple extracellular leucine-rich modules of these receptors, which bind directly to PAMPs or to adaptor molecules that bind the PAMPs.

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Examples of bacterial products that bind to TLRs

-Lipo Polysaccharides (LPS) and lipoteichoic acid, which are constituents of the cell walls of gram-negative bacteria and gram-positive bacteria, respectively,

-Flagellin, the protein subunit component of the flagella of motile bacteria.

-Nucelic acids that considered as a ligands for TLR ligands which are which make up the genomes of some viruses.

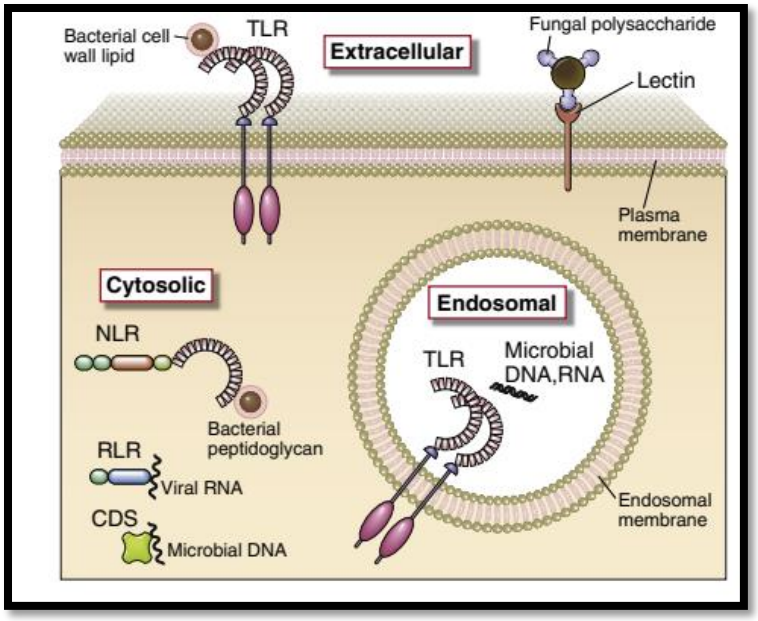

FIGURE: Cellular locations of pattern recognition receptors of the innate immune system.

-The location of TLRs expression

Some pattern recognition molecules, including members of the TLR family and lectin receptors, are expressed on the cell surface, where they may bind extracellular pathogen- associated molecular patterns. Other TLRs are expressed on endosomal membranes and recognize nucleic acids of microbes that have been phagocytosed by cells. Cells also contain cytosolic sensors of microbial infection, including the NOD-like receptor (NLR) family of receptors, RIG-like receptors (RLRs), and

cytosolic DNA sensors (CDS). Only selected examples of microbial PAMPs recognized by these receptors are shown. Cytosolic receptors that recognize products of damaged cells (DAMPs) as well as some microbes.

-What happened when TLR recognized the antigen products(ligands)?

TLR recognition of microbial ligands results in the activation of several signaling pathways and ultimately transcription factors, which induce the expression of genes where products are important for inflammatory and antimicrobial response especially antiviral response.

-What are the transcription factors that are activated by TLR signaling ?

What are The major transcription factors that are activated by TLR signaling pathways?

-Nuclear factor κB (NF-κB)

-Activation protein 1 (AP-1)

-Interferon response factor 3 (IRF3) and IRF7,

-What are the genes and other molecules that induced after recognition of antigens by TLRs?

NF-κB and AP-1 stimulate the expression of genes encoding many of the molecules required for inflammatory responses, including related inflammatory cytokines (such as TNF and IL-1), chemokines (e.g., CCL2 and CXCL8), and endothelial adhesion molecules (e.g: E-selectin) , IRF3 and IRF7 promote production of type I interferons (IFN-α and IFN-β), which are important for antimicrobial response especially anti-viral innate immune responses

2-NOD-Like Receptors

NOD-like receptors (NLRs) are a family of more than 20 different cytosolic proteins, some of which recognize PAMPs and DAMPs and recruit other proteins to form signaling complexes that promote inflammation

3-RIG-Like Receptors

RIG-like receptors (RLRs) are cytosolic sensors of viral RNA that respond to viral nucleic acids by inducing the production of the antiviral type I interferons

4-Cytosolic DNA Sensors and the STING Pathway Cytosolic DNA sensors (CDSs)

These are molecules that detect cytosolic DNA and activate signaling pathways that initiate anti-microbial responses, including type 1 interferon production and autophagy. DNA may be released into the cytosol from various intracellular microbes by different mechanisms

5-Formyl-Peptide Receptors

The formyl peptide receptor-1 (FPR1), expressed on leukocytes, recognizes bacterial peptides containing N-formylmethionyl residues and stimulates directed movement of the cells. Because all bacterial proteins and few mammalian proteins (only those synthesized within

mitochondria) are initiated by N-formylmethionine, FPR1 enables phagocytes to detect and respond preferentially to bacterial proteins.

The bacterial peptide ligands that bind this receptor are some of the most potent chemoattractants for leukocytes.

6-Scavenger Receptors

Scavenger receptors comprise a structurally and functionally diverse collection of cell surface proteins that were originally grouped on the basis of the common characteristic of mediating the uptake of oxidized lipoproteins into cells. Some of these scavenger receptors, including SR-A and CD36, are expressed on macrophages and mediate the phagocytosis of microorganisms. There is a wide range of molecular structures that bind to each scavenger receptor, including LPS, lipoteichoic acid, nucleic acids, β-glucan, and proteins.

7-Receptors for Carbohydrates

Receptors that recognize carbohydrates on the surface of microbes facilitate the phagocytosis of the microbes and the secretion of cytokines that promote subsequent adaptive immune responses.

There are different types of carbohydrates receptors

A- Lectin family receptor

These receptors belong to the C-type lectin family, so called because they bind carbohydrates (hence, lectins) and have been called CLRs (C-type lectin receptors).

B-Mannose receptor

This receptor recognize certain terminal sugar which is mannose which present on the surface of the microorganism and by recognizing this sugar, this receptor will lead to phagocytosis of the microbes.

C- Dectins

Dectin-1 (dendritic cell–associated C-type lectin 1) and dectin-2 are dendritic cell receptors that serve as pattern recognition receptors for two life-cycle stages of fungal organisms. Dectin-1 binds β-glucan, which is a major cell wall component of the yeast form of *Candida albican* while Dectin-2 recognizes high-mannose oligosaccharides on the hyphal form of Candida.