Microbiology 1

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Dr.Saja Ebdah

ARKAN
ACADEMY

Pattern recognition molecules

- Pattern Recognition Receptors (PRRs) are a type of immune receptor that recognizes:

➢ Pathogen-associated molecular patterns (*PAMPs*) **:**

- ✓ Molecules associated with pathogens (like bacteria, viruses, fungi)
- ✓ Examples include bacterial lipopolysaccharides (LPS) and viral RNA.
- ✓ They alert the immune system to microbial invasion.
- ✓ ***Indicate infection*** from an external source

➢ Damage-associated molecular patterns (*DAMPs*)**:**

- ✓ Molecules released by damaged or stressed cells in the body, indicating tissue injury.
- ✓ Examples include ATP, heat shock proteins, and nuclear DNA.
- ✓ They signal cellular damage, often without infection, to prompt a repair or inflammation response
- ✓ Indicate internal cell damage or stress

➢ **There are several main types of bounded- PRRs:**

1. **Toll-like Receptors (TLRs)**
   - *Location:* Found on cell surfaces or in endosomes (membrane-bound).
   - *Function:* Recognize extracellular PAMPs and DAMPs from pathogens or damaged cells, activating immune cells and promoting inflammation.
   - *Mechanism:* TLRs bind to microbial components (like lipopolysaccharide in bacteria) and initiate signaling cascades that activate transcription factors (like NF-κB) to produce pro inflammatory cytokines
   - *Examples:*
     - TLR4: Recognizes lipopolysaccharide (LPS) from gram-negative bacteria.
     - TLR3: Recognizes double-stranded RNA from viruses.
     - TLR2: Detects peptidoglycan from gram-positive bacteria.

2. **NOD-like Receptors (NLRs)**
   - ✓ *Location:* Cytoplasmic receptors.
   - ✓ *Function:* Recognize intracellular bacterial components, forming inflammasomes that lead to inflammatory cytokine activation.
   - ✓ *Mechanism:* NLRs detect bacterial components like peptidoglycan and DAMPs, then recruit proteins to form inflammasomes, which activate pro-inflammatory cytokines, particularly IL-1β.
   - ✓ *Examples:*
     - NOD1 and NOD2: Recognize peptidoglycan from bacterial cell walls.
     - NLRP3: Forms inflammasomes in response to cell stress, leading to IL-1β and IL-18 production.

3. **RIG-I-like Receptors (RLRs)**
   - ✓ *Location:* Cytoplasmic receptors, primarily in cells susceptible to viral infections.
   - ✓ *Function:* Detect viral RNA, triggering interferon production and antiviral responses.
   - ✓ *Mechanism:* RLRs bind to viral RNA, discriminating it from cellular RNA, and initiate signaling to produce type I interferons (such as IFN-α and IFN-β).
   - ✓ *Examples:*
     - RIG-I: Recognizes short double-stranded RNA with a 5’-triphosphate end, typical of some RNA viruses.
     - MDA5: Detects long double-stranded RNA, characteristic of certain viral genomes.

4. **C-type Lectin Receptors (CLRs)**
   - ✓ *Location:* Mostly membrane-bound on cells like macrophages and dendritic cells.
   - ✓ *Function:* Recognize carbohydrate structures on fungal pathogens, facilitating phagocytosis and triggering adaptive immune responses.
   - ✓ *Mechanism:* CLRs bind to carbohydrates (e.g., mannose) on pathogens in a calcium-dependent manner, promoting phagocytosis and antigen presentation.
   - ✓ *Examples:*
     - Dectin-1: Recognizes β-glucan on fungal cell walls.
     - Mannose Receptor: Binds to mannose-rich structures on pathogens, helping to clear fungal infections.

5. **Scavenger Receptors**
   - ✓ *Location:* Mostly found on macrophages and other phagocytic cells.
   - ✓ *Function:* Bind a broad range of ligands, including modified lipoproteins, pathogens, and dead cells, helping in their clearance from the body.
   - ✓ *Mechanism:* Scavenger receptors facilitate phagocytosis and help to maintain tissue homeostasis by removing cellular debris and other waste products.
   - ✓ *Example:*
     - CD36: Engages in the uptake of oxidized low-density lipoproteins (LDLs) and dead cell debris.

6. **N-Formyl Met-Leu-Phe Receptors**:
   - ✓ These receptors are expressed by *neutrophils* and *macrophages* and recognize specific bacterial peptides containing *N-formylmethionyl residues.*
   - ✓ The recognition of these residues acts as a **chemoattractant**, guiding the movement of immune cells toward the site of infection. This process helps *phagocytic cells* (such as neutrophils and macrophages) trace and target bacteria producing these peptides, ultimately leading to an effective immune response

❖ **Summary of Key Functions:**

- ➢ TLRs focus on extracellular and endosomal pathogen components.
- ➢ NLRs detect cytoplasmic bacterial and damage signals, promoting inflammation.
- ➢ RLRs sense viral RNA in the cytoplasm, triggering antiviral defenses.
- ➢ CLRs bind to carbohydrates on fungal pathogens, aiding phagocytosis.
- ➢ ALRs respond to cytoplasmic DNA, particularly during viral infections.
- ➢ Scavenger Receptors remove dead cells and pathogen debris, aiding immune clearance.

- **Characteristics of Antigens Recognized**:
  - ➢ Nucleic Acids: The innate immune system recognizes nucleic acids that are unique to microbes, such as:
    - ✓ Double-stranded RNA (dsRNA) from replicating viruses.
    - ✓ Unmethylated CpG DNA sequences from bacteria.
  - ➢ Proteins: Certain proteins, like N-formylmethionine, which is found in bacterial proteins, are recognized.
  - ➢ Complex Lipids and Carbohydrates: The system detects microbial molecules like:
    - ✓ Lipopolysaccharide (LPS) in gram-negative bacteria.
    - ✓ Lipoteichoic acid and peptidoglycan (PGN) in gram-positive bacteria.
    - ✓ Mannose-rich oligosaccharides that are characteristic of microbes.

- **Proinflammatory Cytokines:**
  - ***General Overview:***
    - ✓ Cytokines are small proteins that play essential roles in *cell signaling* during immune responses. They are involved in processes such as inflammation, immune cell recruitment, and tissue repair.
    - ✓ Proinflammatory cytokines are crucial for initiating and regulating the *acute inflammatory response* to infections and tissue damage. Their secretion is one of the first responses of the innate immune system.

  - ***The Major Proinflammatory Cytokines:***
    - ✓ TNF (Tumor Necrosis Factor), IL-1 (Interleukin-1), and IL-6 (Interleukin-6) are among the most critical proinflammatory cytokines in the innate immune system.
    - ✓ Source: Primarily secreted by *macrophages* and *mast cells*, though other cells, such as **endothelial** and **epithelial cells**, can also produce IL-1 and IL-6.

1. **TNF (Tumor Necrosis Factor):**
   - ✓ Function: TNF is a central mediator of the acute inflammatory response to bacterial infections and other pathogens.
   - ✓ Activation: Produced by macrophages in response to PAMPs (pathogen-associated molecular patterns) and DAMPs (damage-associated molecular patterns), activated through receptors like TLRs (Toll-like receptors), NLRs (NOD-like receptors), and RLRs (RIG-I-like receptors).
   - ✓ Action: TNF can induce inflammation, promote cell proliferation, and trigger cell death in some contexts. It also activates the NF-κB transcription factor, which is involved in inflammatory gene expression.
   - ✓ Role of TNF Superfamily: The TNF superfamily includes a range of cytokines with diverse and essential roles in immune responses, apoptosis, and cell signaling.

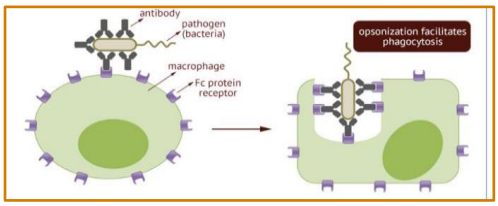
2. **IL-1 (Interleukin-1):**
   - ✓ Function: IL-1 is another critical mediator of the acute inflammatory response, acting similarly to TNF.
   - ✓ Source: Produced by *macrophages*, but also by *neutrophils*, *epithelial cells*, and *endothelial cells*.
   - ✓ Forms: There are two forms of IL-1—IL-1α and IL-1β. The biologically active form is IL-1β.
   - ✓ Activation: IL-1β gene transcription is activated through TLR and NOD signaling, leading to NF-κB activation. The precursor form, pro-IL-1β, is cleaved by the **NLRP3 inflammasome** to produce active IL-1β.
   - ✓ Receptor: IL-1β mediates its effects via the **type I IL-1 receptor**.

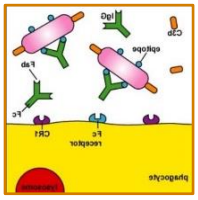
3. **IL-6 (Interleukin-6):**
   - ✓ Function: IL-6 is another important cytokine that plays roles in both *local* and *systemic* inflammatory responses.
   - ✓ Actions:
     - Local Effects: Induces the liver to produce other inflammatory mediators.
     - Systemic Effects: Stimulates the bone marrow to produce neutrophils and supports the differentiation of IL-17-producing helper T cells.

4. **Interferons:**
   - ✓ Type I Interferons:
     - *Function:* The primary cytokines used by the innate immune system to combat **viral infections** are **type I interferons** (IFNs). These cytokines are key for the early response to viral pathogens.
     - *Action:*
       - They initiate an *antiviral state* in cells by activating transcription of genes that confer resistance to viral infection.
       - Promote *sequestration of lymphocytes in* **lymph nodes**, optimizing their chance to encounter viral antigens.
       - Enhance *cytotoxicity* of **NK cells** (natural killer cells) and **CD8+ CTLs** (cytotoxic T lymphocytes), increasing their ability to kill infected cells.
       - Upregulate class I MHC **(major histocompatibility complex)** molecules, improving the recognition of *virally infected cells* by CD8+ CTLs, aiding in viral clearance.

- **Soluble PRR**
  - ➢ Natural antibodies
  - ➢ Complement proteins
- Soluble pattern recognition receptors **(PRRs)** provide early defense against pathogens by performing two key functions:

1. Opsonization**:**
   - ✓ Is the molecular mechanism whereby molecules, microbes, or apoptotic cells are chemically modified to have a stronger attraction to the cell surface receptors on phagocytes and NK cells.
   - ✓ ***Opsonins*** include *antibodies* and *complement* proteins.





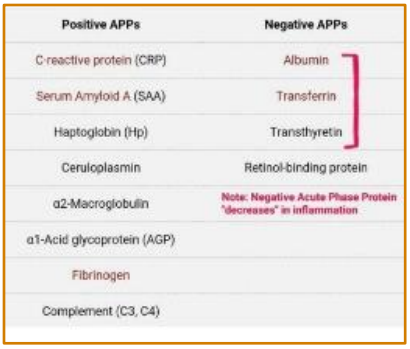
2. Inflammation and Microbial Killing**:** After binding, they promote inflammation to recruit more phagocytes to infection sites and may also directly kill microbes.

- **Natural antibodies**
  - ➢ Natural antibodies are produced by certain subsets of B cells without prior exposure to foreign antigens.
  - ➢ They recognize common molecular patterns found on microbes or stressed and dying cells.
  - ➢ These antibodies are typically specific for carbohydrates or lipids, rather than proteins, and are usually of the **IgM** class.

- **Pentraxins**
  - ➢ The pentraxin family consists of structurally related pentameric proteins, including :
    - ✓ C-reactive protein (CRP), serum amyloid P (SAP), and long pentraxin PTX3.
    - ✓ CRP and SAP bind to both PAMPs and DAMPs and can activate the **classical pathway** of the complement system by binding to C1q.
    - ✓ Proteins like CRP that increase during inflammation are known as acute phase reactants or acute phase proteins

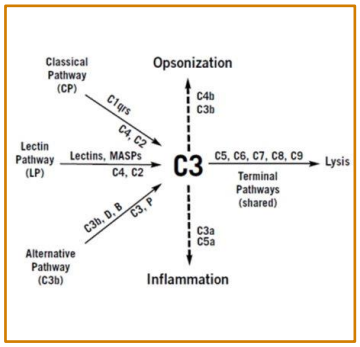
- **Collectins and Ficolins**
  - Collectins are a family of proteins that typically form trimers or hexamers, each containing a collagen-like tail connected to a calcium-dependent **(**C-type**)** lectin head. These proteins are involved in the immune response:
    - ✓ MBL **(**Mannose-binding lectin**)** is a soluble pattern recognition receptor that binds carbohydrates with terminal mannose **and** fucose residues. It activates the lectin pathway of complement activation.
    - ✓ Ficolins are plasma proteins structurally similar to collectins, with a collagen-like domain. However, instead of a C-type lectin domain, ficolins have a fibrinogen-type carbohydrate recognition domain, allowing them to bind different carbohydrate patterns on pathogens.

- **Acute-phase proteins**
  - Acute-phase proteins (APPs) are a class of proteins whose plasma concentrations increase in response to inflammation. This response is called the **acute-phase reaction**.



  - In response to *injury* or *infection*, local inflammatory cells (neutrophil granulocytes and macrophages) secrete a number of **cytokines** into the bloodstream, most notable of which are the interleukins IL1, and IL6, and TNF*α*. The liver responds by producing a large number of **acute-phase reactants*.***
  - Measurement of acute-phase proteins, especially *C*-reactive protein, is a useful marker of inflammation in medical clinical pathology.

- **The complement system**
  - The complement system is a group of proteins that circulate the blood in *inactive form*, until a pattern is sensed with proteins like (*C1q, Lectins*) which leads to a series of reactions of *protein cleavage* and *activation*.
  - Complement has the following functions:
    - ✓ Opsonization of the pathogen (or a dead cell) to ease phagocytosis *(C3b, C4b).*
    - ✓ Generation of anaphylatoxins (*C3a* and *C5a*) to draw in leukocytes and potentiate the immune reponse.
    - ✓ Formation of a *pore in the bacterial cell wall called MAC* (membrane attack complex, *C5b-9*).
  - Complement deficiencies lead to increased *susceptibility* to infections. And is also associated with autoimmune diseases like systemic lupus erythematosus (**SLE**), indicating a role for complement in *maintaining homeostasis*.
  - 3 pathways of complement activation depend on different ***PRR*** but converge at C3 activation.



  - A C3 convertase is formed from activated complement proteins, In the classical and lectin pathways, C3 convertase is made from C2bC4b, while in the alternative pathway, it's made from C3bFb.
  - Each step of complement activation is regulated by soluable and cell surface proteins.

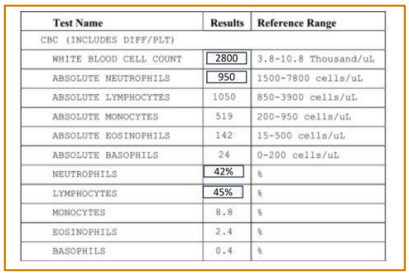
Questions

1. **What is the process by which phagocytes digest engulfed pathogens or particles within the phagosome using enzymes and reactive oxygen species?**
   a) Apoptosis
   b) Exocytosis
   c) Phagolysosome formation
   d) Autophagy

2. **What is the main function of cytotoxic T cells in the immune system?**
   a) Phagocytosis of pathogens
   b) Antibody production
   c) Killing infected host cells
   d) Activating B cells

3. **Which of the following cells is part of innate immunity and is of lymphocytic origin?**
   a) Dendritic cells
   b) Monocytes
   c) Natural killer cells
   d) B cells
   e) Helper T cells.

4. **Which drug can be used in a patient with a slight fever and the following CBC results?**
   a) The results are normal and no treatment is needed.
   b) Intravenous antibodies
   c) IL-12
   d) Granulocyte colony stimulating factor



Test Name	Results	Reference Range
CBC (INCLUDES DIFF/PLT)		
WHITE BLOOD CELL COUNT	2800	3.8-10.8 Thousand/uL
ABSOLUTE NEUTROPHILS	950	1500-7800 cells/uL
ABSOLUTE LYMPHOCYTES	1050	850-3900 cells/uL
ABSOLUTE MONOCYTES	519	200-950 cells/uL
ABSOLUTE EOSINOPHILS	142	15-500 cells/uL
ABSOLUTE BASOPHILS	24	0-200 cells/uL
NEUTROPHILS	42%	%
LYMPHOCYTES	45%	%
MONOCYTES	8.8	%
EOSINOPHILS	2.4	%
BASOPHILS	0.4	%

5. **Toll-like receptors (TLRs) play a crucial role in innate immunity by recognizing:**
   a) Self-antigens
   b) Pattern recognition molecules
   c) T-cell receptors
   d) MHC class II molecules
   e) pathogen-associated molecular patterns (PAMPs).

6. **How many different Toll-like receptors (TLRs) have been identified in humans?**
   a) 2
   b) 5
   c) 10
   d) 20

7. **Which NOD-like receptor (NLR) is associated with inflammasome formation and the release of pro-inflammatory cytokines like IL-1β?**
   a) NOD1
   b) NOD2
   c) NLRP3
   d) NLRP6

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www.arkan-academy.com

+962 790408805