



Color code:
Important in red
Extra in blue



Immunology
MED438

Natural Defense Mechanisms



Objectives

- To know First (non-specific immunity) and second (adaptive immunity) lines of defense
- To understand the Complement system, its activation and how it involves in pathogen killing.
- To recognize the importance of accumulation of inflammatory cells for clearance of infection
- To know the role of cytokines as mediators which regulate inflammation

The main function of the immune system is to protect from infections:

Viruses e.g.
Influenza , Polio



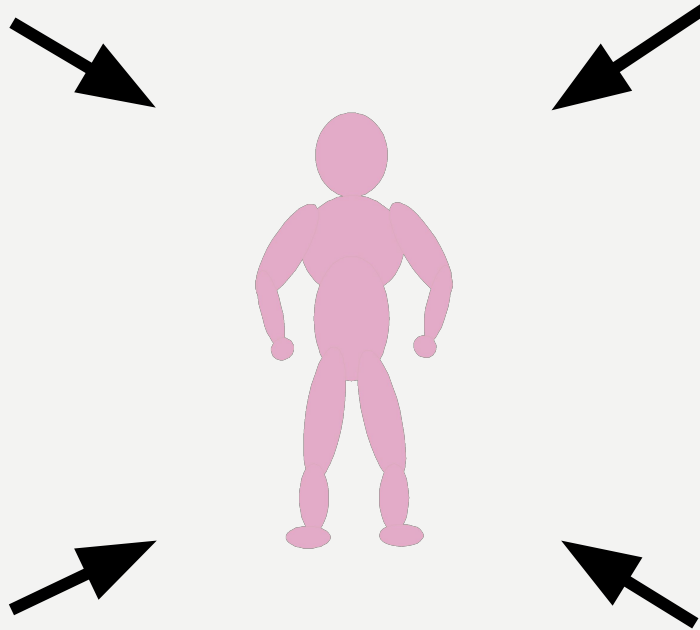
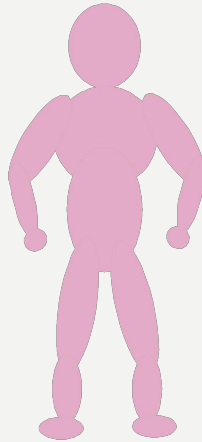
Fungi e.g.
Candida , albicans



Parasites e.g.
Tapeworms , Malaria



Bacteria e.g.
Tubercule bacillus
Staphylococci



First and Second Lines of Defense

Nonspecific Defense Mechanisms		Specific Defense Mechanisms (Immune System)
<u>First</u> Line of Defense		<u>Second</u> Line of Defense
<ul style="list-style-type: none">● Skin.● Mucous Membranes.● Secretions of both.	<ul style="list-style-type: none">● Phagocytic WBCs.● Antimicrobial proteins.● The Inflammatory Response.	<p>Lymphocytes (T Cells and B cells)</p> <p>Antibodies (Secreted from B Lymphocytes)</p>

*There are 3 lines of defense but these two are more common.

*Monocytes circulate in blood and when they become macrophages in infectious tissues, they cannot revert back.

Non-specific Defense Mechanisms

First Line Defense

- **Natural (Innate) immunity**
- **Physical** (skin/mucous membranes)
- **Mechanical** (coughing, sneezing, vomiting, action of cilia in trachea “will remove all fluids retained by coughing”).
- **Biochemical** barriers “Most important. they’ll attack microbes and disintegrate their cell wall” (antimicrobial peptides, lung secretions, mucus, saliva, tears).

Biochemical Barriers

- **Body secretions** contain anti-bacterial substances e.g. saliva, tears and sweat.
- **Antimicrobial peptides** (e.g., defensins, hepcidins)
- **Normal bacterial flora.** (**Compete** with pathogenic bacteria for nutrients)

Physical and mechanical barriers

- Skin, **impermeable** to microbes.
- **Mucous** membranes lining the gastrointestinal, genitourinary and respiratory tracts.
- Other protective mechanisms:
 1. Shedding of outer skin layers.
 2. Coughing and sneezing.
 3. Flushing of urine.
 4. Vomiting.
 5. Mucus and cilia in respiratory tract.

Inflammation

- ➔ **Definition:** Inflammation is the first response of the immune system to infection or irritation.
- ➔ It consists of a series of **vascular** & **cellular** changes that occur in **response** to various stimuli.
E.g. infections, injury, radiation etc.

Goals of inflammation:

1. Prevent and limit infection and further damage
2. Interact with adaptive immune system
For example, Monocytes / Macrophages
serve as a link between the adaptive and innate
Immunity by antigen presentation
3. Prepare the area of injury for healing

Microbial infections initiate inflammations

As bacteria possess an array of pro-inflammatory molecules:
E.g. Lipopolysaccharides (LPS)
Superantigen in gram-negative
bacteria (endotoxin).

The Complement system



- Consists of a group of serum proteins initially present in **inactive** form (pro-enzymes) and produced in liver.
- **Activation** occurs in **cascade** (one component or more activating another) after enzymatic cleavage. Once components become activated they produce important biological effects that **initiate inflammation**.
- This system plays an important role in **linking** Innate & Adaptive immunity

3 Pathways of activation:

All the three pathways are responsible for the cleavage (activation) of C3 convertase.

<p>A) Classical. (Requires antigen-antibody binding)</p>	<p>B) Lectin. (Activated by mannan binding protein binding mannose groups (not found in humans) of bacterial carbohydrates)</p>	<p>C) Alternative (Activated by bacterial products)</p>
<p>(C1, C4, C2, C3, C5, C6, C7, C8, C9)</p>	<p>(C4, C2, C3, C5, C6, C7, C8, C9)</p>	<p>(C3, C5, C6, C7, C8, C9)</p>

Activation of the proteins will decrease their levels. For example, activation of C5 will cause it to break into smaller parts (C5a and C5b). **C5a** will diffuse into cell tissues and **C5b** will adhere to the bacterial cell wall.

For lab analysis: we check **C4** and **C3**.
 In the case of **low C4** and **low C3** --> Classical Activation (low because they were activated).
 In the case of **low C3** only --> Alternative activation.
component breakage (a and b) happens until C5.
 Afterwards, C5b will bind with C6-9

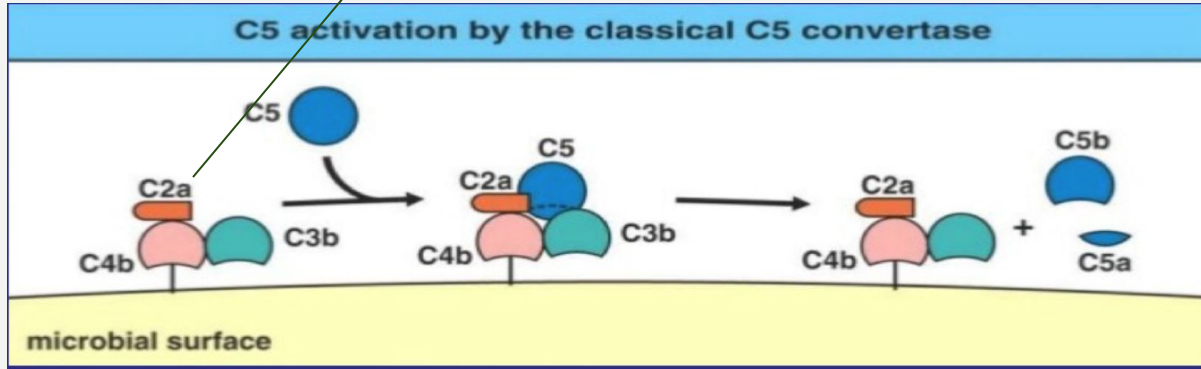
The Complement System

Process of activation (Biological effects of complement activation):

<h2>Recruitment of Inflammatory Cells</h2> <p>(Anaphylatoxin functions)</p> <p>a components attract WBCs & trigger an inflammation. (mainly by C3a & C5a)</p>	<h2>Opsonization of Pathogens</h2> <p>(Coating of bacteria enhances phagocytosis)</p>	<h2>Killing of Pathogens</h2> <p>(Cell lysis)</p>
<ol style="list-style-type: none">1- Trigger degranulation (granular leukocytes release their substances)2- Attract additional inflammatory cells3- Induce smooth muscle contraction and increase vascular permeability	<p>b component attaches to bacterial cell walls, inviting phagocytes to do their job efficiently. (mainly by C3b but to a lesser extent C4b)</p>	<p>Membrane Attack Complex (C5b-9)</p> <p>(Illustrated in next slide)</p>

The complement system

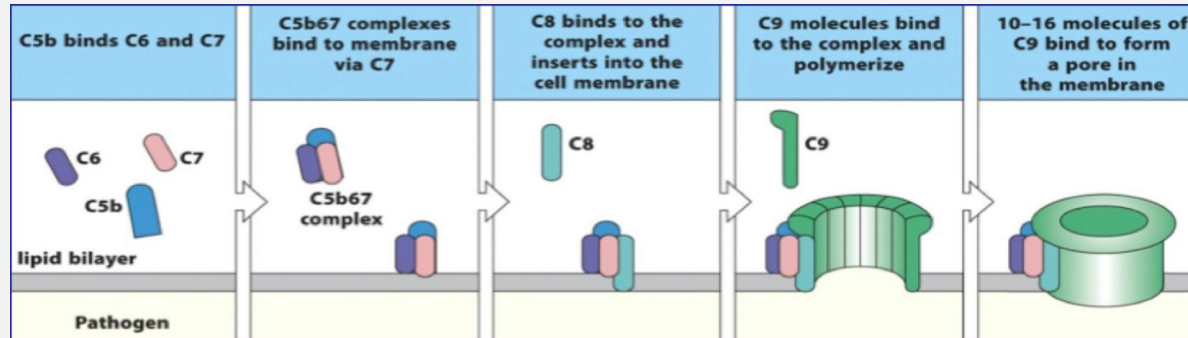
C5 activation: C5 Convertase



C5 activation:
The (C4b,C2a,C3b) complex works as a C5 convertase which breaks C5 into C5a and C5b.

Membrane Attack Complex Formation:

Insertion of lytic complex into cell membrane, cylindrical in shape.



Membrane attack complex formation (MAC formation):

- 1-C5b assembles with C6 and C7 and binds into the membrane.
- 2-C8 binds to the complex.
- 3-C9 binds and forms the hole in the membrane of the pathogen.

Process of chemotaxis: is the directional movement of an organism (WBCs) in response to a chemical stimulus (substances released by leukocytes).

Rolling on vessel wall

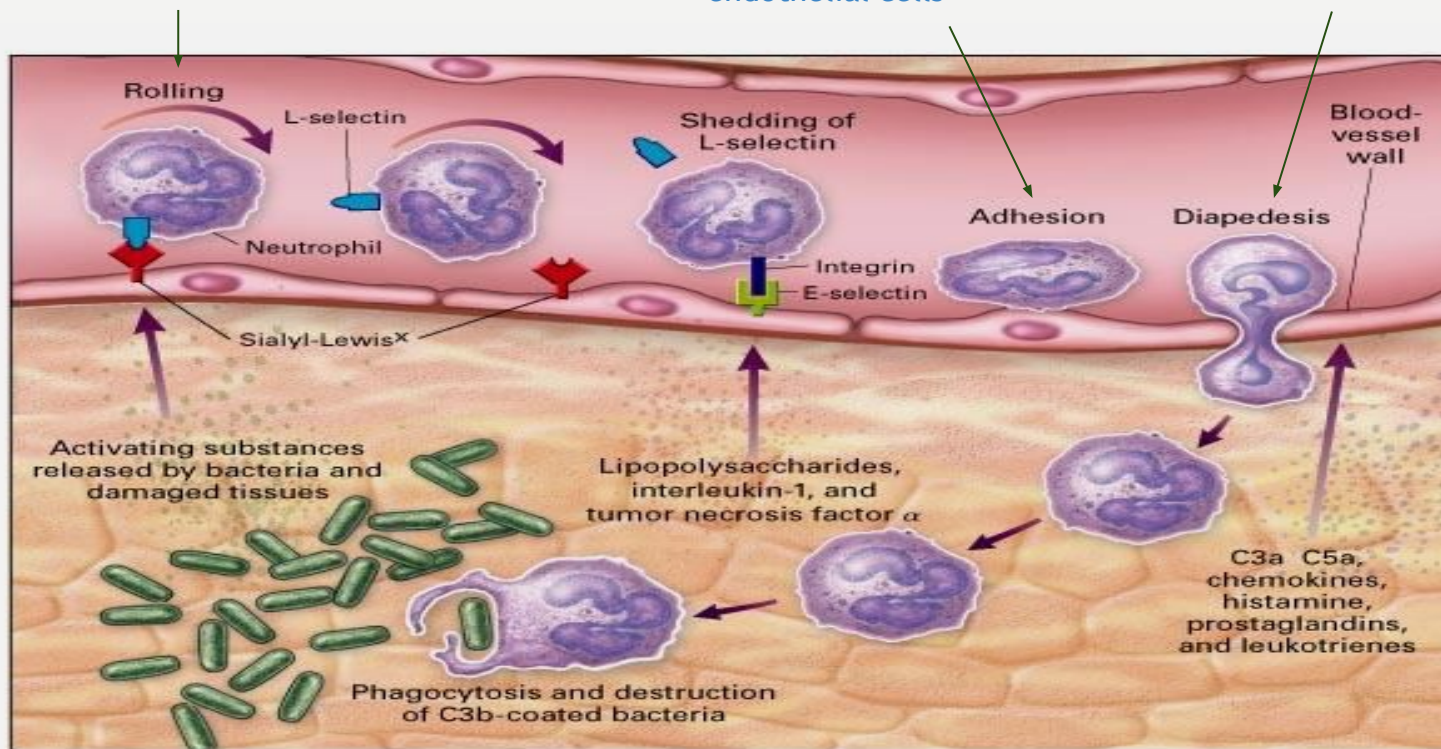
It slows down the neutrophils in the blood vessels

Adhesion (attach)

Stick the neutrophils to the endothelial cells

Diapedesis (Pass through)

The neutrophil leaves the blood vessel

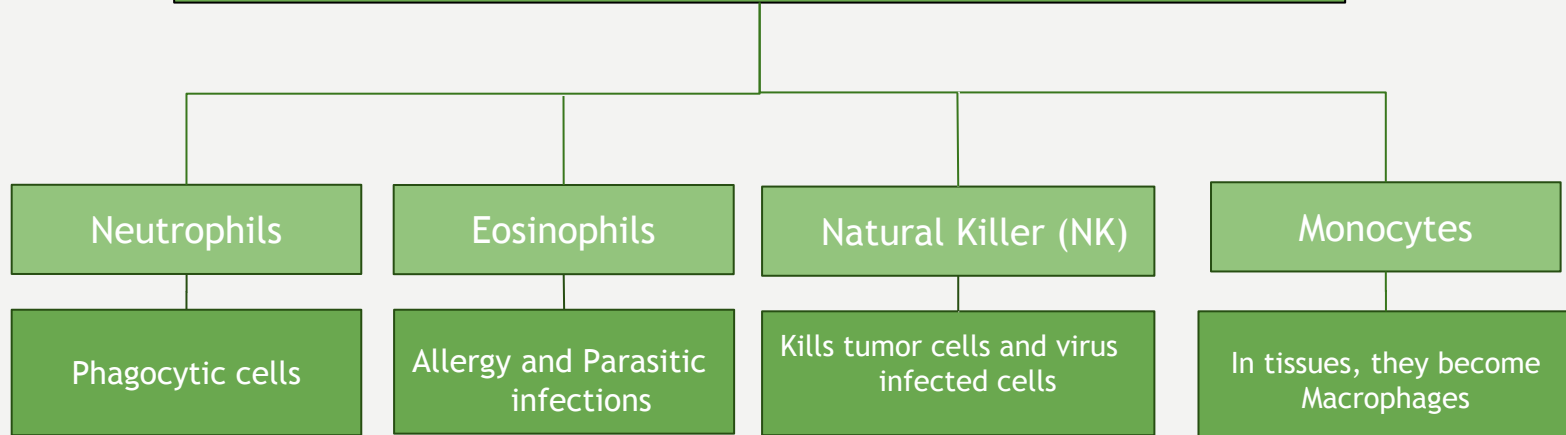


C3a and C5a Mediate Vasodilation as well as Chemotaxis (Anaphylatoxin functions).

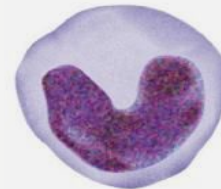
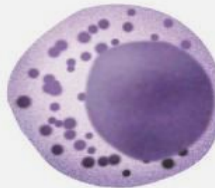
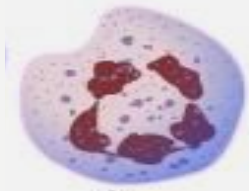
They will recruit more inflammatory cells to the site of injury through chemotaxis

Cells Attracted to Inflammation Site

Types of Cells attracted to the site of infection that mediate inflammation:



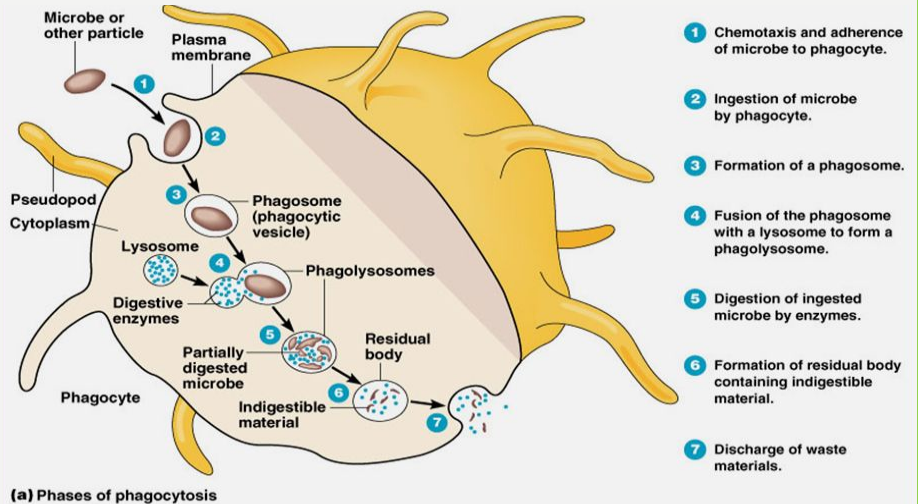
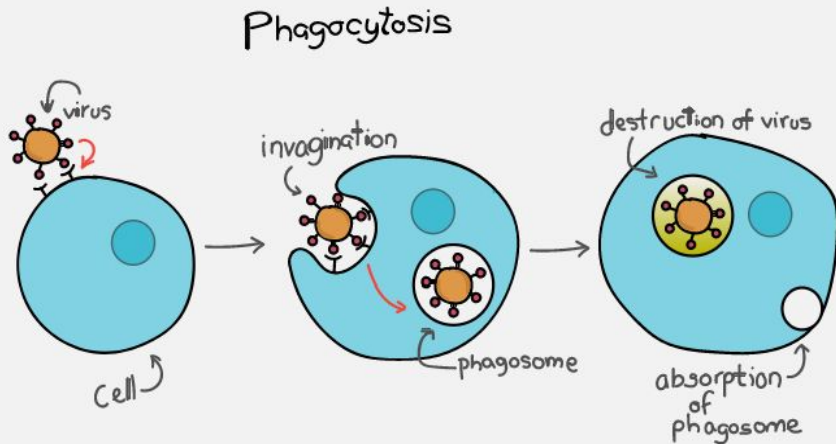
Are weak phagocytes



Phagocytosis

After they reach the inflammation site, phagocytic cells (neutrophils & macrophages) start the process of **phagocytosis**: The process by which a cell **engulfs** a solid particle such as bacteria to form **internal vesicle** known as **phagosome**.

Note: First, the invader gets **phagocytosed**, then **engulfed in phagosomes**. After that, lysosomes **fuse** into the phagosome to **process** the invader. What's left of it is **residual bodies** that leave the phagocytic cell through **exocytosis**.



Cytokines

They are Soluble molecules, produced by **different cells**, that control cell functions e.g. **differentiation, proliferation activation or inhibition.**

01

Interleukins

- Produced primarily **by macrophages** and **lymphocytes** in response to a pathogen.
- Many types, e.g. IL-1, IL-2, IL-3 etc

02

Interferons

- **Protects** against viral infections
- Produced and released **by virally infected cells** in response to viral infections.

03

Tumor necrosis factor (TNF)

- Secreted mainly **by macrophages**
- **Induces fever** by acting as an **endogenous pyrogen** (substance released from inside the body that produces fever)
- Increases synthesis of inflammatory serum proteins
- Increase expression of adhesion molecules on endothelial cells and vascular permeability

Take home message

- Non-specific (innate immunity) acts as a first line of defense against invading pathogens.
- Innate immunity is an important initial step for generation of adaptive immune response.
- Inflammation is vital for controlling infection and limiting tissue damage.

Quiz:

1. What is the main function of interferons?

- a) Induce fever
- b) Protects against viral infections
- c) Increase expression of adhesion molecules
- d) Increase synthesis of inflammatory serum protein

2. C3a and C5a are responsible for:

- a) Anaphylatoxin functions
- b) cell lysis
- c) coating of bacteria
- d) None of the above

3. Which type of cytokines acts as endogenous pyrogen?

- a) Interferons
- b) Interleukins
- c) TNF
- d) All of the above

4. Which component is mainly involved in phagocytosis?

- a) C3b
- b) C4b
- c) C5b
- d) C4a

5. Which one of the following requires antigen-antibody binding?

- a) Classical pathway
- b) Lectin pathway
- c) Alternative pathway
- d) None of the above

6. Which of the following is considered the second line of defense

- a) Lymphocytes
- b) Phagocytic WBCs
- c) Antibodies
- d) A and C

Team Leaders:

Sedra Elsirawani

Ibrahim Aldakhil

Team Members:

- | | |
|-----------------------|------------------------|
| 1. Noura Alturki | 1. Alwaleed Alsaleh |
| 2. Lama Alzamil | 2. Muhannad Makkawi |
| 3. Shahad Althaqeb | 3. Abdullah Basamh |
| 4. Leena Alnassar | 4. Hashem Halabi |
| 5. Joud Aljebreen | 5. Amjad Albaroudi |
| 6. Renad Alkanaan | 6. Abdulrahman Alhawas |
| 7. Shahad Bin Selayem | 7. Mohammed Alhuqbani |
| 8. Sara Alflajj | |



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