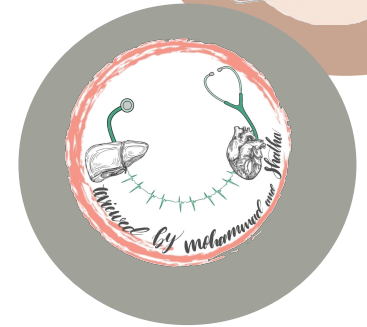


Natural Defense Mechanism (Innate Immunity)

W5
L2

Color index :

- Main text
- Important
- Dr notes
- Females slides
- Male slides
- Extra

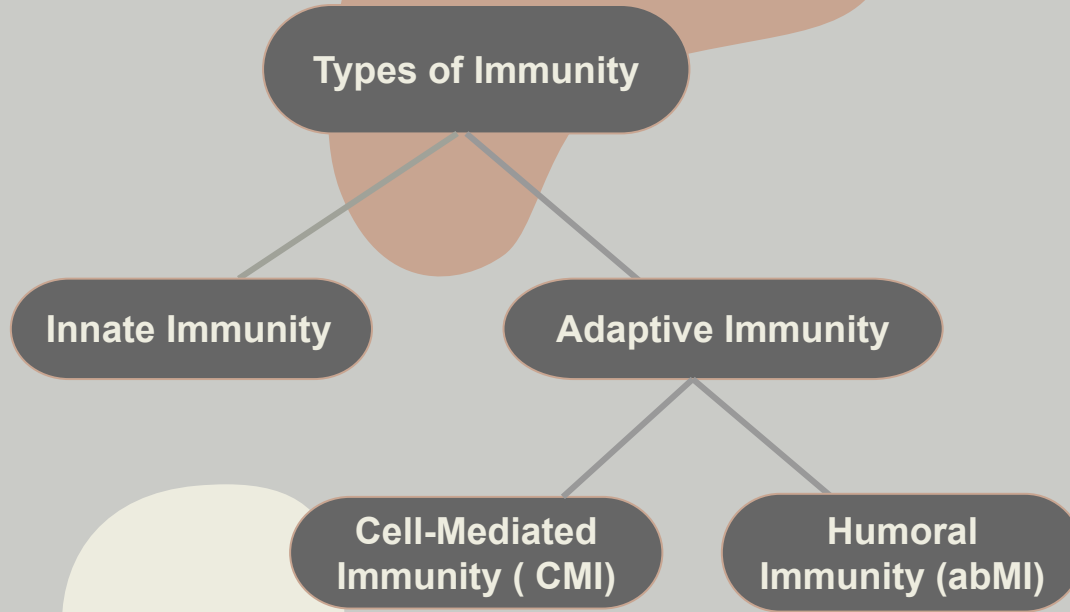


[Editing File](#)

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.

Introduction



[Helpful video](#)

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



Viruses

E.g.
Influenza
polio



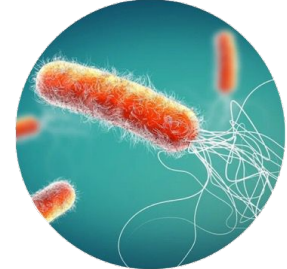
Fungi

E.g.
Candida
albicans



Parasites

E.g.
Tapeworms
Malaria



Bacteria

E.g.
Tubercule bacillus
Staphylococci

First & Second Lines of Defense

Non-Specific Defense Mechanisms

First Line of Defense

Natural (Innate) Immunity

- **Anatomical** (skin, mucous membranes).
- **Mechanical** (Coughing, sneezing, vomiting, action of cilia in trachea)
- **Biochemical** (antimicrobial peptides, lung secretions, mucus, saliva (contain normal bacteria flora), tears)

Anatomical and Mechanical Barriers

- **Physical** : Skin, **impermeable** to microbes (**Protect of infection**).
- **Mucous membranes** lining the gastrointestinal, genitourinary and respiratory tracts.

Other protective mechanisms:

- Shedding of outer skin layers.
- Coughing and sneezing.
- Flushing of urine.
- Vomiting.
- Mucus and cilia in respiratory tract.

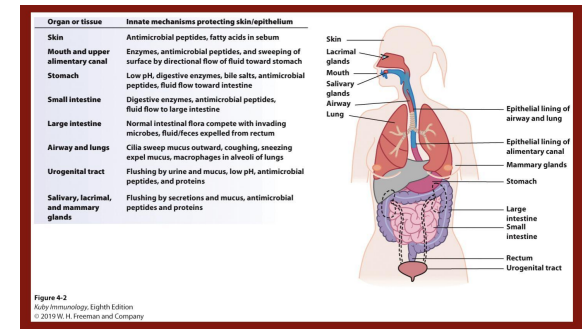
Biochemical Barriers

- **Body Secretions** contain **anti-bacterial** substances e.g. saliva, tears and sweat.
- **Antimicrobial peptides** (e.g., defensins, hepcidins).
- **Normal bacterial flora (in mouth and skin)** (Compete with pathogenic bacteria for nutrients)
- **Phagocytic WBC**
- **The inflammatory response**

Specific Defense Mechanisms

Second Line of Defense

- Lymphocytes.
- Antibodies.



Inflammation

What is inflammation?

- 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.

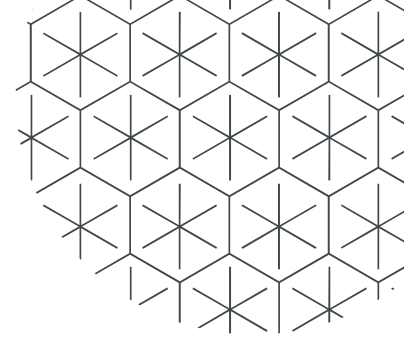
Microbial infections initiate inflammation

As bacteria possess an array of pro-inflammatory molecules: e.g. Lipopolysaccharides (LPS).

Goals:

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

The Complement System



Consist of

a group of **serum protein** initially present in **inactive form**

(There are 20 proteins involved, but only 9 that are major C1,C2,C3,C4,C5,C6,C7,C8,C9)

Activation occurs in

- 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.
- (The 9 proteins are present normally as “pro-enzyme”, inactive form. When complements get activated it's amount will decrease)
- (During activation, protein will be broken into 2 pieces, the smaller gets the letter a, while the largest get b)
- Because pro-enzymes are produced in the liver, people with chronic liver disease will have a problem with their complement system.
- Activation occurs in an enzyme cascade (the activation of one protein leads to the next protein's activation and cleavage break)

Complement system plays an important role in

linking Innate & Adaptive immunity.

(The main role is piercing the cell wall of the antigen which leads to the antigen's death) (cell lysis)

★ Important

The Complement System

3 Pathways of Activation

1. Classical Pathway:

(Requires antigen-antibody binding).

(C1,C4,C2,C3,C5,C6,C7,C8,C9).

2. Lectin Pathway:

(Activated by mannan binding protein binding mannose groups of bacterial carbohydrates).

(MASPs,C4,C2,C3,C5,C6,C7,C8,C9).

3. Alternative Pathway:

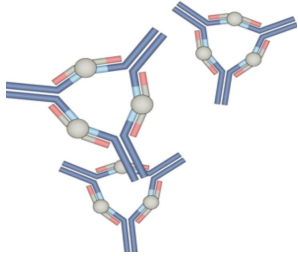
(Activated by bacterial products).

(C3,C5,C6,C7,C8,C9).

Special thanks to
Immunology Team 439

The Complement System

First Pathway Classical pathway



This is called **immune complex** or **antigen-antibody complex**
Which activate C1 complement to cleaving C4 and C2 into two part

Antigens and antibodies are part of adaptive immunity but it participates to activate complement system.
That means, complement system act as bridge between innate and adaptive immunity

Second Pathway Lectin pathway

Microorganism

Mannose group of bacterial carbohydrate

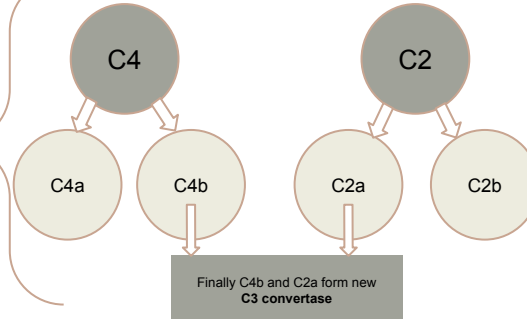
Cell

Mannose binding protein
Or mannose binding lectin (MBL)
have the ability to bind with mannose which found on the surface of many microorganism

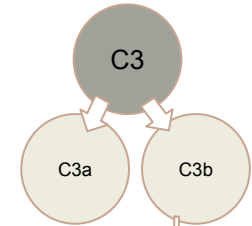
this recognition will activate molecules called MASPs: (MASP1 , MASP2)

MASP-1 and MASP-2 are enzymes responsible for cleaving C4 and C2

This process is repeated again in the Lectin pathway

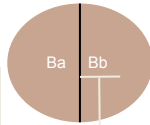


Third Pathway Alternative pathway



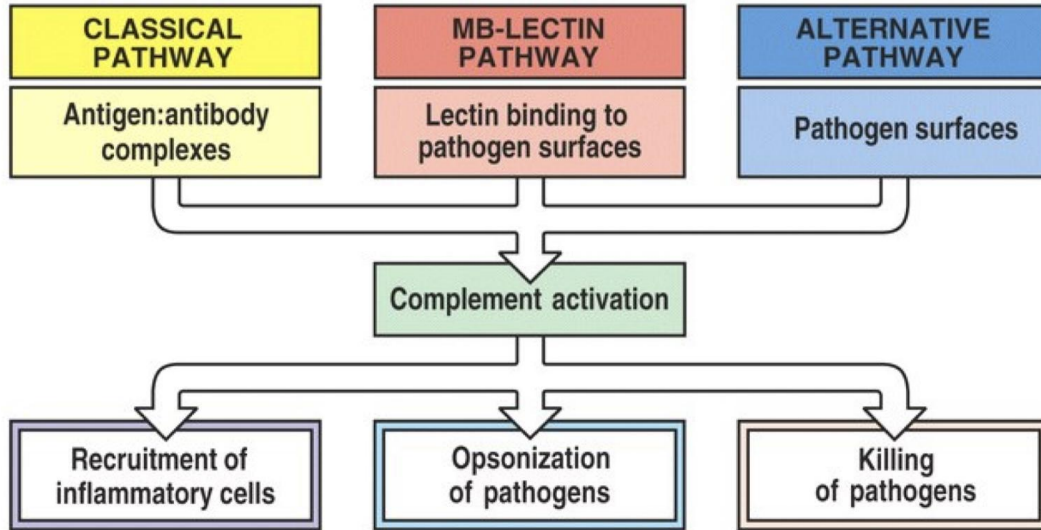
Sticking to microorganism will activate **factor D** to divide **factor B** into two part

Finally c3b and Bb form new **C3 convertase**



The Complement System

(Important)



Membrane Attack Complex Formation (MAC)

Insertion of lytic complex into cell membrane

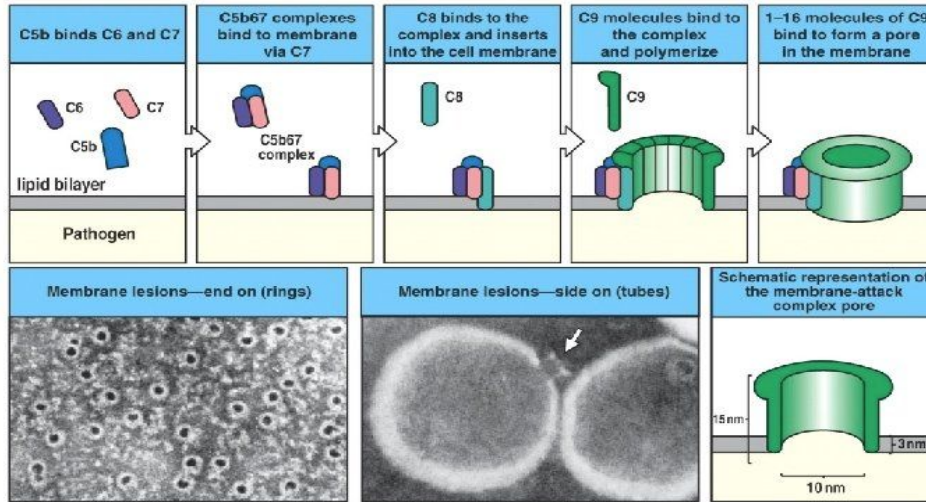


Figure 2-35 Immunobiology, 6/e. (© Garland Science 2005)

1- C5 gets activated

How? The (C2a, C3b, C4b) complex works as a C5 convertase which breaks C5 into C5a and C5b

2- C5b assembles with C6, C7 and binds into the membrane

3- C8 binds to the complex as well

4- C9 binds and forms the hole (pore) in the membrane of the pathogen

C6-C7-C8-C9 Don't break down

Membrane Attack Complex: **C5b, C6, C7, C8, C9**

This structure (hole/pore) that is formed at the pathogen's cell membrane after the activation of the host's complement system, is called the **Membrane Attack Complex Formation**. This disrupts the cell membrane leading to cell lysis and death.

Biological Effects of Complement Activation

C3a

C4a

C5a

Anaphylatoxin Functions

- Trigger **degranulation** (release of substances) of endothelial cells, mast cells or phagocytes.
- Induce **histamine** release from (mast cells) causing smooth muscle contraction and **increase vascular permeability**
- Attract additional **inflammatory cells** to the site of activation. **(meaning they also mediate chemotaxis)**

C3b

C4b

Opsonization

(main opsonin C3b, C4b to a lesser extent)

Coating of bacteria **enhances phagocytosis**.

Note: b part get attached to bacteria cell wall and work as opsonitive to enhance phagocytosis

C5b,C6,
C7, C8,
C9

Direct Cell Lysis

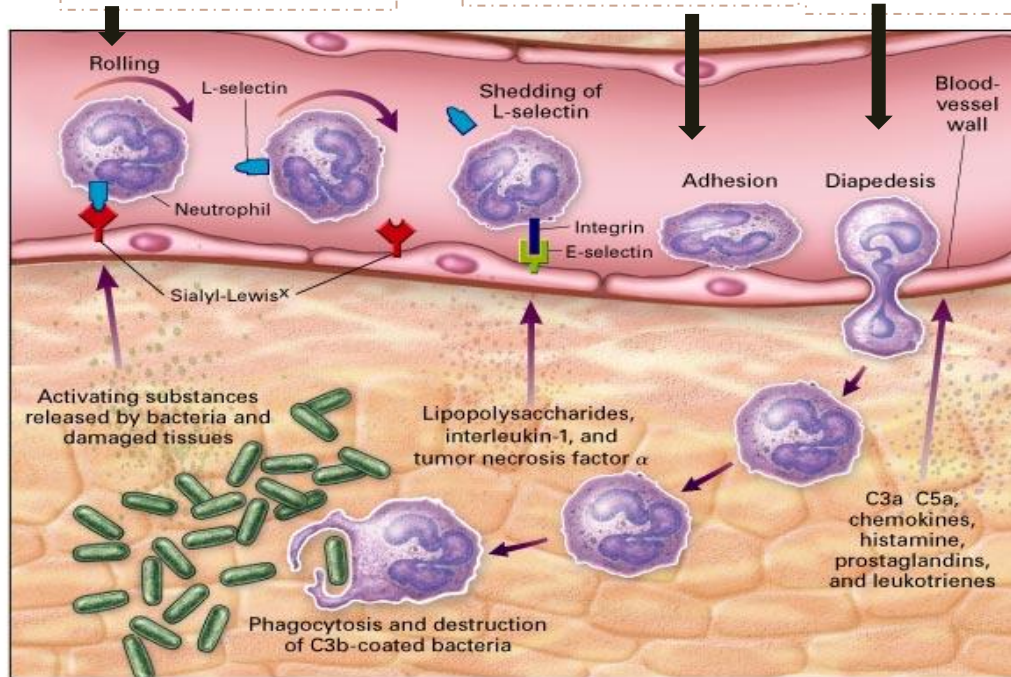
Destruction of bacteria by blasting holes in the bacteria making them leak to death.

Process of chemotaxis: is the movement of the responsible cells to a **specific place of injury** in response to a chemoattractant

- **1)Rolling** on vessel wall and slowing down of Neutrophils in the blood vessel

- **2)Adhesion**
The attachment of the Neutrophil to Endothelial cells

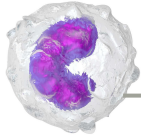
- **3)Diapedesis**(pass through)
Neutrophil squeeze its way out of the blood vessel



Cells Attracted to The Site of Infection that Mediate Inflammation:

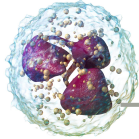
Monocytes

They become macrophages when they leave the blood and enter the tissue



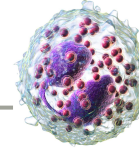
Neutrophils

Phagocytic cell



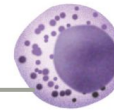
Eosinophils

Allergy and parasitic infections.



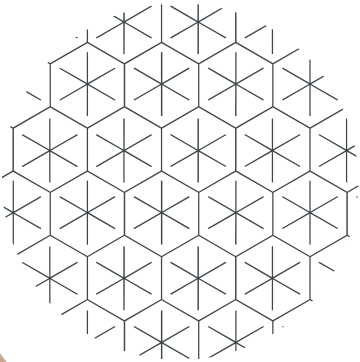
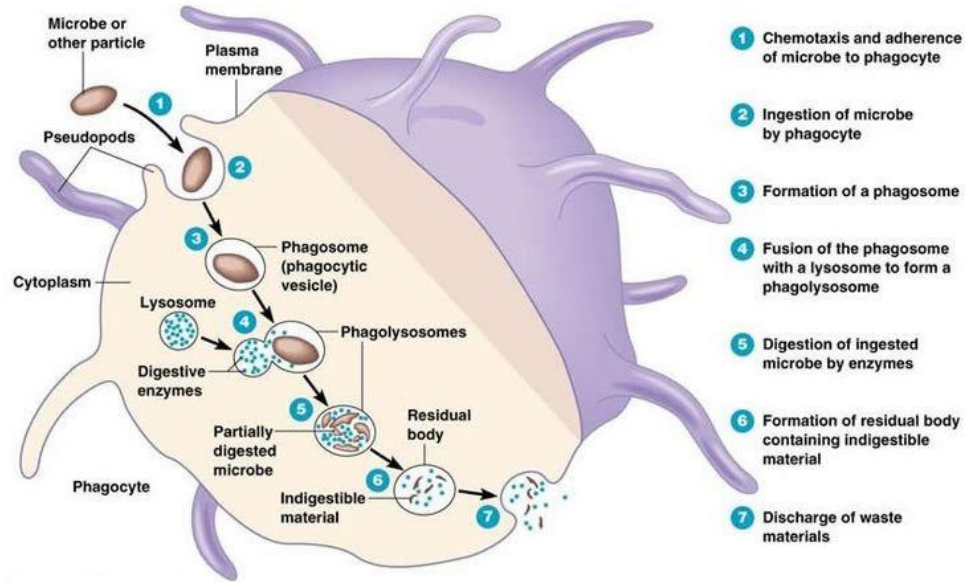
Naturalized killer (NK) cells

Kill tumor cells and virus infected cells



Phagocytosis

Phagocytic cells (**neutrophils & macrophages**) at site of infection start the process of **phagocytosis**, which is the process by which a cell **engulfs** a solid particle such as bacteria to form **internal vesicle** known as **phagosome**.



Cytokines



Soluble molecules (small protein), produced by specific cells of the Immune system that control cell functions e.g. differentiation, proliferation activation or inhibition. Cytokines play an important role in **Innate Immunity and Adaptive Immunity**

Interleukins

Produced primarily by **macrophages** and **lymphocytes** in response to a pathogen.

Interferons

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

Tumor Necrosis Factor (TNF)

Induces fever by acting as an **endogenous pyrogen** (a substance released from inside the body that produces fever).
Increases synthesis of inflammatory serum proteins.

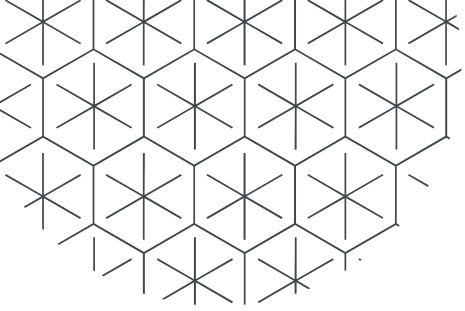


The Six Major Cytokine Families

Family name	Representative members of family	Comments
Interleukin-1 family	IL-1 α , IL-1 β , IL-1Ra, IL-18, IL-33	IL-1 was the first non interferon cytokine to be identified. Members of this family include important inflammatory mediators.
Class 1 (hematopoietin) cytokine family	IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-12, IL-13, IL-15, IL-21, IL-23, GM-CSF, G-CSF, growth hormone, prolactin, erythropoietin/hematopoietin	Members of this large family of small cytokine molecules exhibit striking sequence and functional diversity.
Class 2 (interferon) cytokine family	IFN- α , IFN- β , IFN- γ , IL-10, IL-19, IL-20, IL- 22, IL-24	While the IFNs have important roles in antiviral responses, all are important modulators of immune responses.

The six major cytokine families

Family name	Representative members of family	Comments
Tumor necrosis factor family	TNF- α , TNF- β , CD40L, Fas (CD95), BAFF, APRIL, LT- β	Members of this family may be either soluble or membrane-bound; they are involved in immune system development, effector functions, and homeostasis.
Interleukin-17 family	IL-17 (IL-17A), IL-17B, IL-17C, IL-17D, IL-17F	This is the most recently discovered family; members function to promote neutrophil accumulation and activation, and are proinflammatory.
Chemokines	IL-8, CCL19, CCL21, RANTES, CCL2 (MCP-1), CCL3 (MIP-1 α)	All serve chemoattractant function.



Take Home messages

1

Non-specific (innate immunity) acts as a first line of defense against invading pathogens.

2

Innate immunity is an important initial step for generation of adaptive immune response

3

Inflammation is vital for controlling infection and limiting tissue damage

MCQs

Q1-Non-specific defense mechanism is...?

A) Second line defense	B)antibodies	C) first line defense	D) lymphocytes
------------------------	--------------	-----------------------	----------------

Q2-lectin pathway activated by....?

A)antigen	B) bacteria	C) mannan binding protein	D) antibody
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Q3- activation occurs in?

A)bacterial product	B)cascade	C)pathogen surface	D)host surface
---------------------	-----------	--------------------	----------------

Q4- alternative pathway activated by.....? It composed of.....?

A)bacterial product, c3 c5 c6 c7 c8 c9	B) bacterial product, c2 c5 c6 c7 c8 c9	C)mannan binding protein, c4 c2 c3 c5 c6 c7 c8 c9	D)antigen-antibody binding, c3 c5 c6 c7 c8 c9
---	--	--	--

4:A
3:B
2:C
1:D

MCQs

Q5-in response to a pathogen macrophages and lymphocytes Produce ...?

- | | | | |
|------------------------|----------------|--------|-----------------|
| A) Second line defense | B) Interferons | C) TNF | D) Interleukins |
|------------------------|----------------|--------|-----------------|

Q6-complement activation lead to coating of the bacteria to enhance phagocytosis.

- | | | | |
|----------------------------|-----------------|---------------------------|-----------|
| A) Anaphylatoxin functions | B) Opsonization | C) Mannan binding protein | D) Lectin |
|----------------------------|-----------------|---------------------------|-----------|

Q7- What is the main component involved in Opsonization?

- | | | | |
|--------|--------|--------|--------|
| A) C3a | B) C3b | C) C4a | D) C4b |
|--------|--------|--------|--------|

★ Special thanks to
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