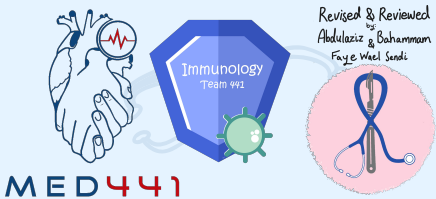


Natural defense mechanisms

Colour index:

Main text

IMPORTANT

Drs notes

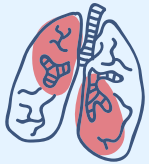
Females slides

Male slides

Extra

Editing file

Objectives:

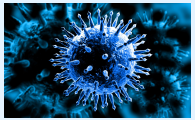


- To know first (non-specific immunity) and second (adaptive immunity) lines of defense.
- To understand the Complement system, it's activation and how it involves in pathogen killing.
- To recognize the importance of accumulation of inflammatory cells for clearance of infection.
- To know the role of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

The main function of the Immune System is to protect from infections such as:

01

Viruses



E.g. Influenza, Polio

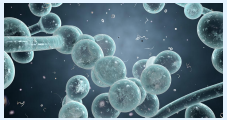
02

Parasites

E.g. Tapeworms, Malaria

03

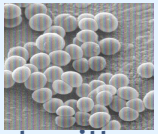
Fungi



E.g. Candida Albicans

04

Bacteria



E.g. Tubercle bacillus, Staphylococcus

First and Second lines of defense

Thanks to Teams 438+439

Non-specific defense mechanisms

First line of defense

Natural (innate) immunity

- Phagocytes (WBC)
- Inflammatory response
- Antimicrobial proteins

Physical and mechanical barriers:

- **Physical** : Skin, impermeable to microbes (Protect of infection)
- Mucous membranes lining the gastrointestinal, genitourinary and respiratory tracts
- **Mechanical**: coughing, sneezing, vomiting, action of cilia in trachea) "will remove all fluids retained by coughing"
- Other protective mechanisms:
  - Shedding of outer skin layers
  - Coughing and sneezing
  - Flushing of urine
  - Vomiting (Help with toxins)
  - Mucus and cilia in respiratory tract

Biochemical barriers:

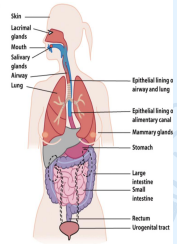
- Body secretions contain antibacterial substances **E.g.** saliva, tears and sweat, mucus, lung secretion
- Antimicrobial peptides **E.g.** defensins, hepcidins
- Normal bacterial flora (Compete with pathogenic bacteria for nutrients)
- "Biochemical is the most important because they'll attack microbes and disintegrate their cell wall"

Specific defense mechanisms

Second line of defense

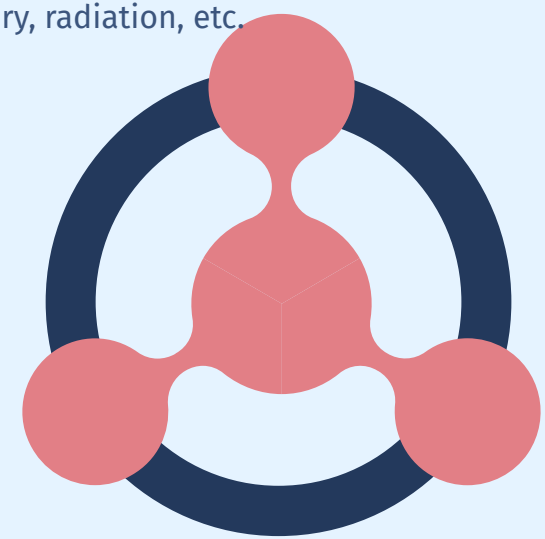
- Lymphocytes
- Antibodies

Organ or tissue	Innate mechanisms protecting skin/epithelium
Skin	Antimicrobial peptides, fatty acids in sebum
Mouth and upper alimentary canal	Enzymes, antimicrobial peptides, and sweeping of surface by directional flow of fluid toward stomach
Stomach	Low pH, digestive enzymes, bile salts, antimicrobial peptides, fluid flow toward intestine
Small intestine	Digestive enzymes, antimicrobial peptides, fluid flow to large intestine
Large intestine	Normal intestinal flora compete with invading microbes, fluid feces expelled from rectum
Airway and lungs	Cilia sweep mucus outward, coughing, sneezing expel mucus, macrophages in alveoli of lungs
Urogenital tract	Flushing by urine and mucus, low pH, antimicrobial peptides, and proteins
Salivary, lacrimal, and mammary glands	Flushing by secretions and mucus, antimicrobial peptides and proteins



What is Inflammation?

- Inflammation is the first response of the immune system to infection or irritation. (It's good because it can tell us that we need help)
- It consist of a series of vascular & cellular changes that occur in response to various stimuli.
- **E.g**. infections, injury, radiation, etc.



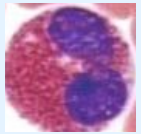
Microbial infections initiate inflammation:

- As bacteria possess an array of pro-inflammatory molecules. **E.g.** Lipopolysaccharides (LPS). (Which serves as an antigen)

Inflammation 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 and repair.

Cells attracted to the site of infection that mediate inflammation:

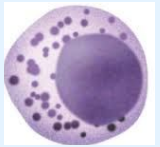


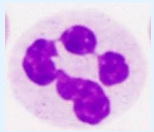
Eosinophils

Allergy and Parasitic infections

Natural killer cells (NK)

Kill tumor cells and virus infected cells



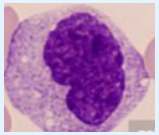


Neutrophils

Phagocytic cells

Monocytes

Become Macrophages when they leave the blood and enter the tissue



The complement system

- The Complement System is a system composed **20** different serum proteins (enzymes). We will discuss the main **9** Proteins of them.
- The complement proteins are non-specific so they are considered part of the innate system.
- Each protein has a number/name (C1,C2,C3 etc..) and are normally in a pro-enzyme form (that means the enzyme is originally in inactive form)
- The Pro-enzyme means that the complement system is in shut state (not doing anything).
- Once the Pro-enzyme is activated (against microbes) Complement System starts, and produce important biological effects that initiate inflammation.
- When the Pro-enzyme is activated against **normal** cells (**originally in the body**), an **autoimmune** disease develops.
- Pro-enzymes are produced in the liver, so people with chronic liver disease will have a problem with their complement system.
- Activation occurs in an enzyme cascade (a cascade is when one protein is activated, this activation leads to the next proteins activation and cleavage -break-)
- Activation of complements occurs by 3 main pathways which are (Classical, Lectin, Alternative) (explained in next slide)
- This system plays an important role in linking Innate & Adaptive immunity.

The complement system

Helpful video 1

Helpful video 2

Helpful video 3

There are 3 main pathways for activation:

Classical pathway	(Requires antigen-antibody binding) **C1,C4,C2,C3,C5,C6,C7,C8,C9**
Lectin pathway	(Activated by mannose binding protein binding mannose groups of bacterial carbohydrate) **MASPs,C4,C2,C3,C5,C6,C7,C8,C9**
Alternative pathway	(Activated by bacterial products) **-C3,C5,C6,C7,C8,C9**

Pathways activate the complement system

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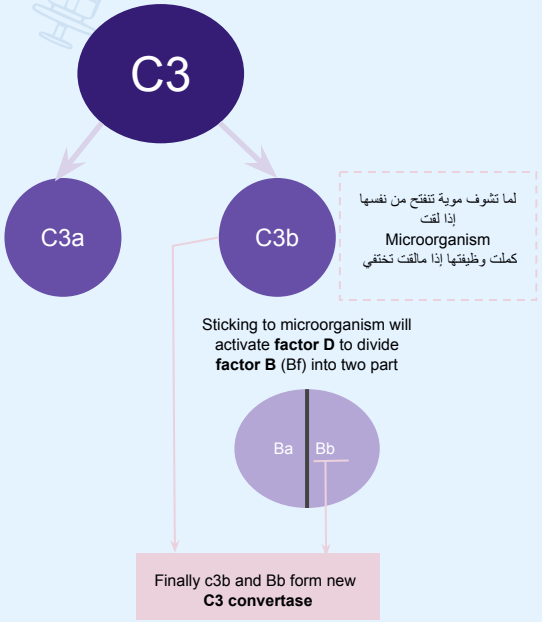
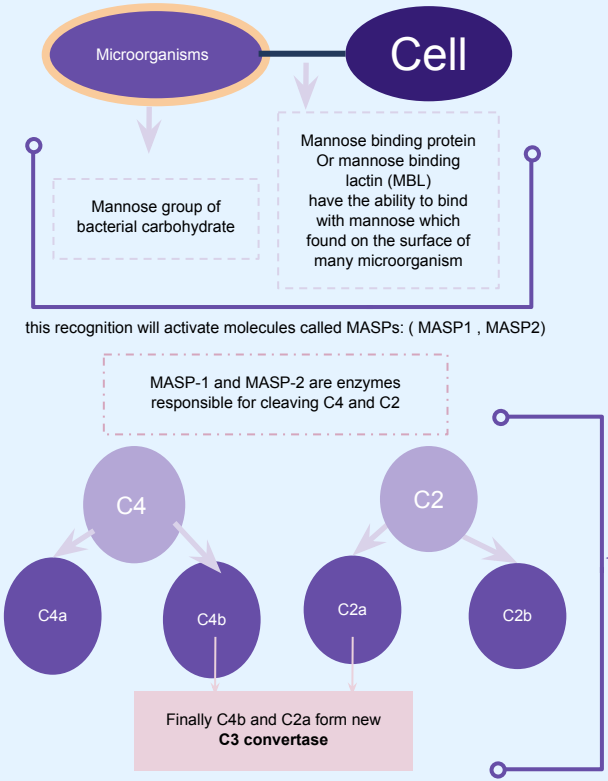
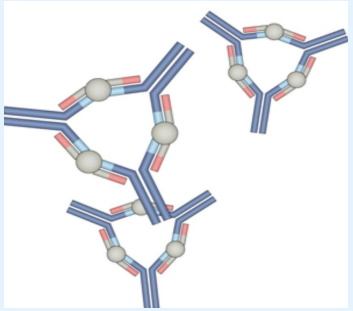
Third pathway
Alternative pathway



Second pathway
Lectin pathway



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

This process is repeated again in the Lectin pathway

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

Biological effects of complement activation

Anaphylatoxin functions
(C3a,C4a,C5a)

Opsonization
(Mainly C3b, C4b to a lesser extent)

Direct cell lysis

- 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.

- Coating of bacteria enhances phagocytosis
- **439 Note**: The (**b**) component attaches to the **b**acterial cell wall and prepares it for phagocytosis

- Destruction of bacteria by blasting holes in the bacteria making them leak to death
- Membrane attack complex: C5b, C6, C7, C8, C9

Membrane attack complex formation (MAC)

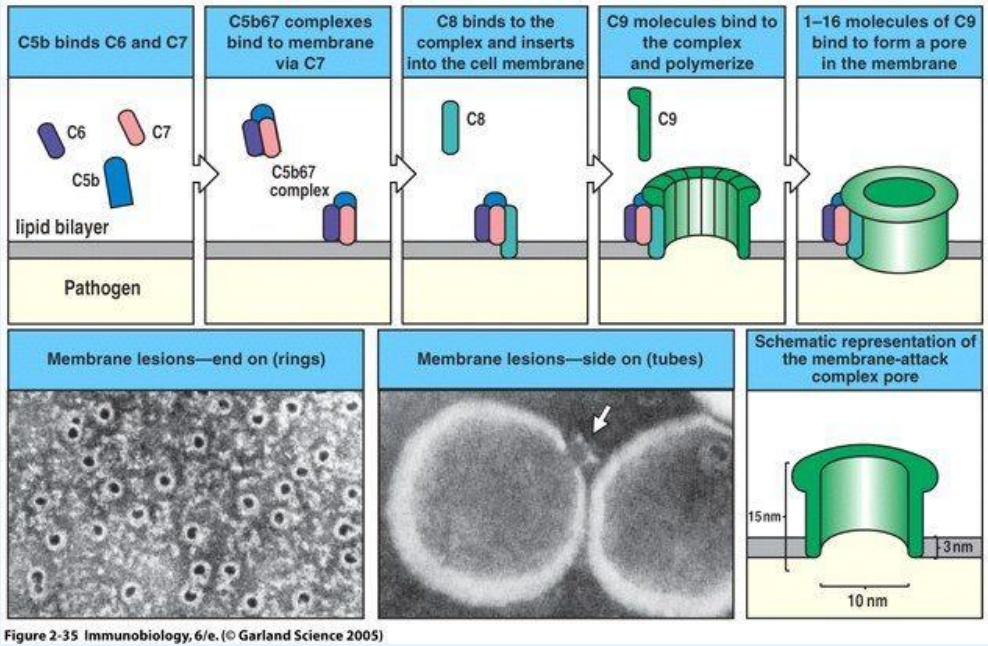


Figure 2-35 Immunobiology, 6/e. (© Garland Science 2005)

1- C5 gets activated

How? The (C4**b**, C2**a**, C3**b**) complex works as a C5 convertase which breaks C5 into C5**a** and C5**b**

2- C5**b** 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

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.

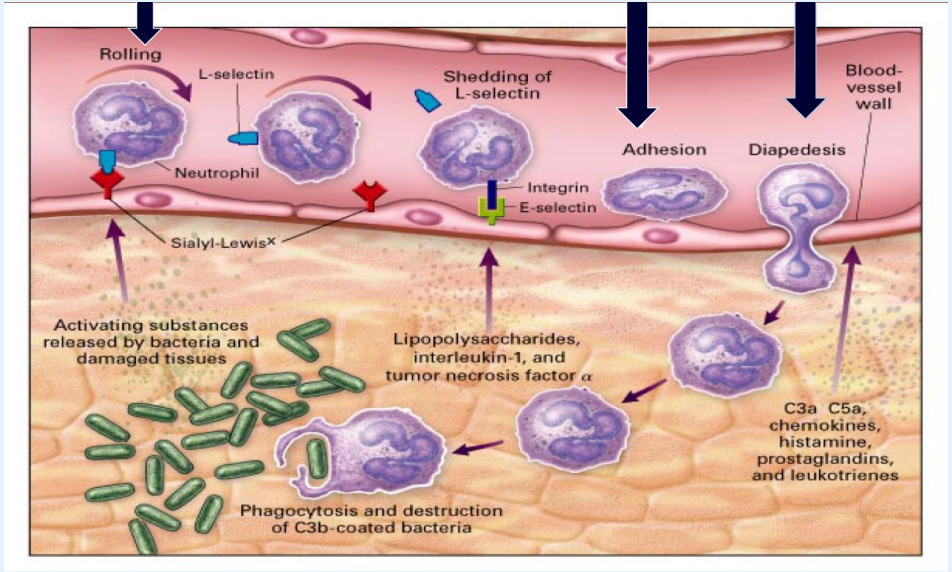
Process of chemotaxis

Helpful video

Rolling on vessel wall and slowing down of Neutrophils in the blood vessel

Adhesion
The attachment of the Neutrophil to Endothelial cells

Diapedesis
Neutrophil squeeze its way out of the blood vessel



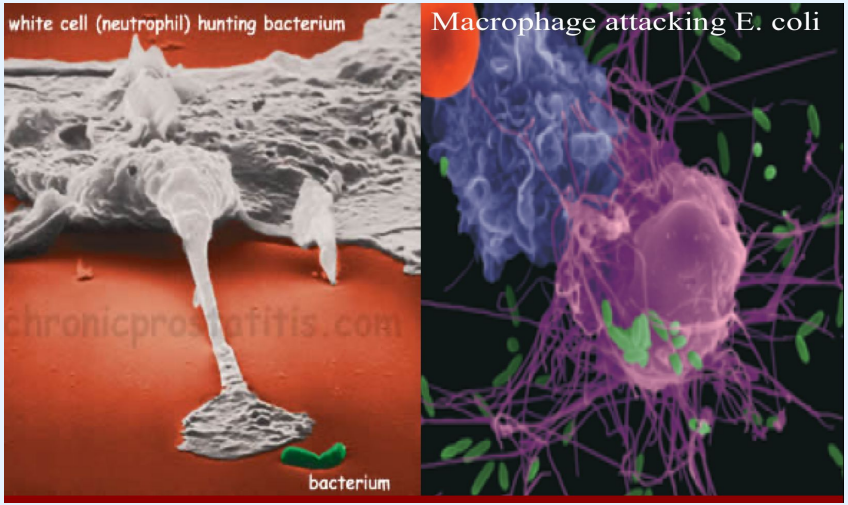
What is Chemotaxis?

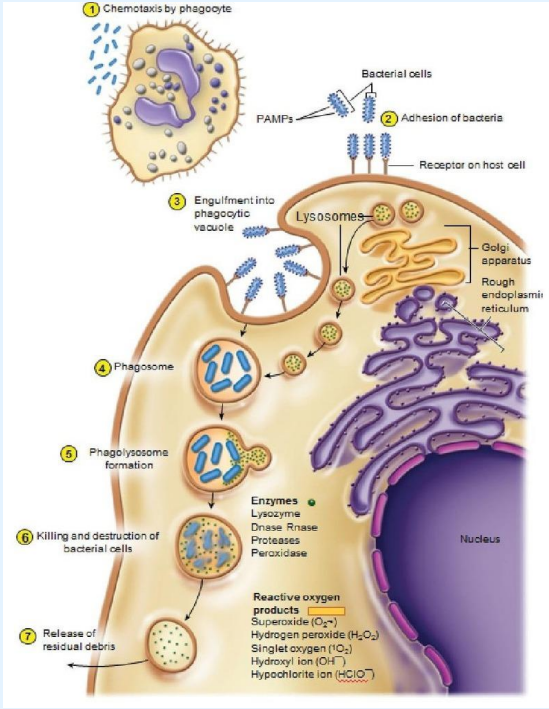
It is a chemically induced signaling process which would allow certain cells (such as macrophages or WBC) to go to the site of infection after they have left the circulation. It uses cytokines, chemokines which are molecules that are responsible for the chemical signaling to guide macrophages & neutrophils to the site of infection (making sure the pathogen is destroyed)

Helpful video

Phagocytosis

Phagocytic cells (**neutrophils & macrophages**) at site of infection start the process of phagocytosis, which is the process by which a cell engulf a solid particle such 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 such as differentiation, proliferation activation or inhibition. Cytokines play an Important role in Innate Immunity and Adaptive Immunity.

1 Interleukins

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

2 Interferons

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

3 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-1α, IL-1β, 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 cont..

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-1α)	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: which of the following plays important role in linking Innate and Adaptive immunity ?			
A- complement system	B-inflammation	C-phagocytosis	D-immune system
Q2: what is the function of Interferons?			
A- increases fever	B- decreases fever	C- protect against viral infections	D- increases synthesis of inflammatory serum
Q3: The classical pathway requires... and it's composed of... ?			
A- antigen , C1-C9	B- mannose , C3,C5-C9	C- antigen-antibody binding , C1-C9	D- antigen-antibody binding , C3,C5-C9
Q4: The C3 convertase is made by the cleaving of?			
A-C4b, C2a	B- C3a, Bb	C-C2b, C4a	D- C4b, C2a, C3b

Q1-A, Q2-C, Q3-C, Q4-A

MCQs

Q5:which one is a major Cytokine family?			
A- interferons	B- interleukins	C- A+B	D-Natural killer
Q6:Produced and released by virally infected cells in response to viral infections are a function of ...?			
A- osponization	B- eosinophils	C- interferons	D- Tumor necrosis Factor
Q7:Allergic and parasitic infection are examples of...?			
A- neteurophils	B- eosinophils	C- parasites	D- Phagasome
Q8:they become macrophages when they leave the blood and enter the tissue are?			
A-Chemokines	B- Naturalized killer cell	C-Interleukins	D- Monocytes

Q5-C, Q6-C, Q7-B, Q8-D

Special thanks and gratitude to
Immunology Team (439)

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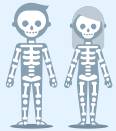

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