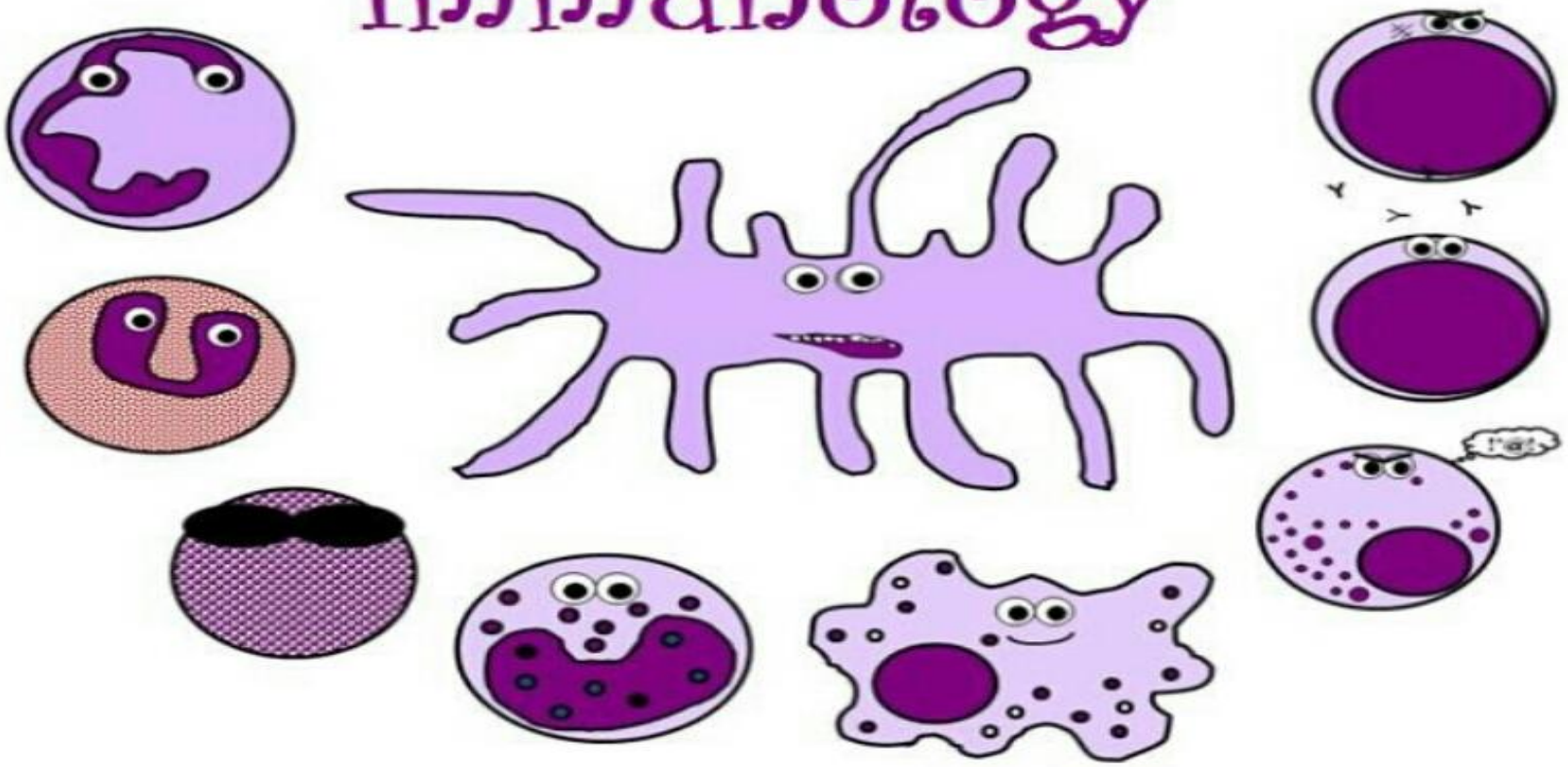
Immunology



Lecture: 2
Subject: Innate Immunity
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Innate Immunity

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Objectives

- Discuss the concept of innate immunity - features, importance.
- Explain how the innate immune system recognizes foreign antigens in general.
- Outline the components of the innate immune system.
- Discuss how these components combat various foreign antigens.

Introduction

- protection against infections that relies on the mechanisms that exist before infection and are capable of rapid response to pathogens
- Innate immunity is the first line of defence against infection
- Characteristics:
  - set up at birth
  - non –specific, but rapidly acting
  - hereditable
  - no immune memory
  - Little individual difference

Innate (Nonspecific) Immunity	
First line of defense	**Second line of defense**
• Intact skin • Mucous membranes and their secretions • Normal microbiota	• Natural killer cells and phagocytic white blood cells • Inflammation • Fever • Antimicrobial substances

Innate Host Defense Mechanisms

- Physical factors
- Biochemical factors
- Microbiological factors
- Fever
- Innate Immune cells
- Cytokines
- Complement system
- Inflammation

1. Physical Factors

1. Skin: microbes sloughed off along with skin cells, Microbes must penetrate several layers
   - Stratified and cornified epithelium provides a **mechanical barrier.**
   - **Indigenous microbial flora** competes with pathogens (*like staph Epidermidis, these bacteria prevent pathogenic bacteria from colonizing our skin*)
   - **Acid pH** inhibits growth of disease producing bacteria. (*Most bacteria like neutral pH*)
   - **Bactericidal long chain fatty acids** in sebaceous gland secretions.
2. Mucous Membranes: are extensions of the skin, which produce mucus to trap microbes, Most lined with cilia.
   - *During respitory tract infections, mucus secretions are over activated in order to trap the pathogen.*

2. Biochemical Factors

1. Low pH in vaginal and urinary tracts, and stomache
   - *It's quite impossible to have 100% sterile food.*
   - *So the acidic media in the stomach kills any microorganism, with the exception of H. Pylori.*
   - *Low pH of the vagina prevents the colonization of most microorganism, with the exception of Candida.*
2. Defensins: short antimicrobial peptides, insert into bacterial membranes and form pores
3. Lysozyme: degrades peptidoglycan
   - Tears contain a high concentration of lysozyme (effective against gram positive microorganisms)
   - *Clinical coorelate: Most of bacterial conjunctivitis is caused by Gram negative bacteria.*
4. Interferon: are cytokines that trigger:
   - *macrophage activation*
   - *production of substances to interfere with RNA **viral** reproduction*

Antimicrobial Peptides/Defensins

- Originally isolated from frog skin based on their ability to kill bacteria
- Small polypeptides (<10kDa) secreted at mucosal surfaces
- Four hundred peptides described to date
- Defensins (four families in eukaryotes, read only)
  - α-defensins (neutrophils and intestinal Paneth cells)
  - β-defensins (epithelial cells)
  - Insect defensins
  - Plant defensins
- Defensins appear to act by binding to outer membrane of bacteria, resulting in increased membrane permeability
- May also play a role in inflammation and wound repair

3. Microbiological Barriers

- Normal Flora: not part of immune system, but are part of first line of defense
- Protection they provide is considerable
  - Competitive exclusion of invading microbes
  - Produce compounds that are toxic to other bacteria. *(note: Most of antibiotics are derived from bacterial Toxins that kill other bacteria).*
  - Stimulates immune system, providing a moderate amount of "exercise" to system, thereby enhancing it's function

4. Fever

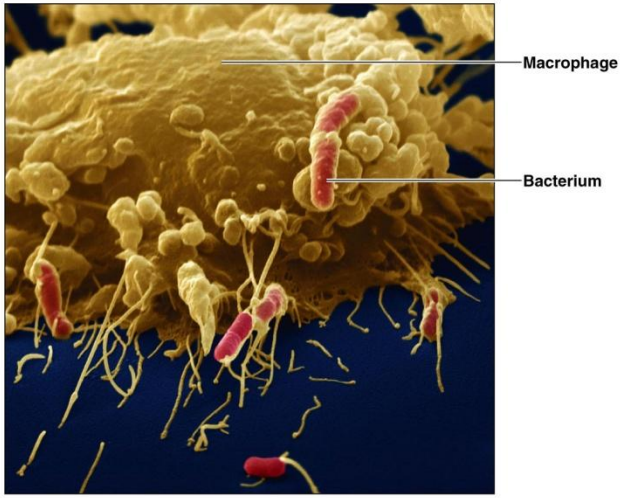
- It's one of the clinical signs of inflammation
- Mechanism of fever:
  1. Higher body temperature occurs as a result of certain cytokines called pyrogens
  2. Cytokines carried in bloodstream to hypothalamus
  3. Hypothalamus responds by raising temperature
- Fever inhibits growth of many pathogens by at least two mechanisms:
  1. Elevates temperature above optimum growth temperature
  2. Activates and speeds up a number of other body defenses

5. Innate Immune Cells

Cell type	Pricipal function(s)
Monocytes/Macrophages	Phagocytosis, inflammation, T-cell activation, tissue repair
Neutrophils	Phagocytosis, inflammation
NK cells	Killing of infected or tumor cells
Dendritic cells	Phagocytosis, activation of naive T-cells
Mast cells	Inflammation
Eosinophils	Defense against parasites

Phagocytes

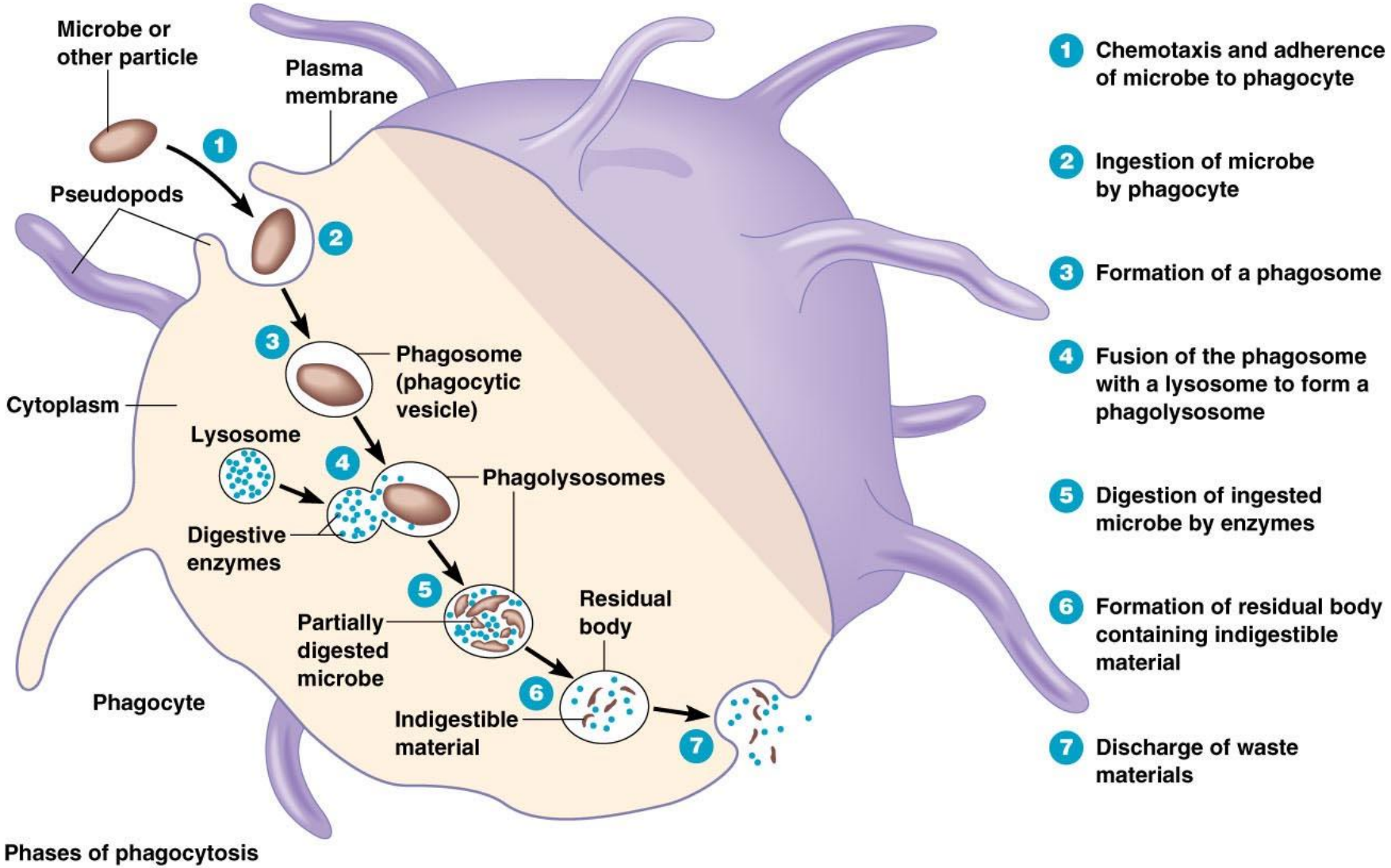
- Performed by Neutrophils and Macrophages
  1. Phagocytosis is the capture and digestion of foreign particles
  2. Chemokines are cytokines that attract macrophages and neutrophils to infected tissues
  3. Opsonins attach to microbes to increase the ability of phagocytes to adhere (opsonization)



Steps of Phagocytosis

- Recognition
- Ingestion- pseudopods engulf microbe through endocytosis
- Vacuole Formation- vacuole contains microbe
- Digestion- vacuole merges with enzymes to destroy microbes
- Exocytosis- microbial debris is released

- Some microorganisms can overcome this mechanism by resisting recognition and ingestion (encapsulated bacteria like S. Pneumonia or H. Influenzae)
- Others can resist digestion, and thus replicate inside phagocytes (like neisseria, chlamydia and rickettsia)



Phases of phagocytosis

Innate Immune Recognition

- All multi-cellular organisms are able to recognize and eliminate pathogens
- Despite their extreme heterogeneity, pathogens share highly conserved molecules, called “pathogen-associated molecular patterns” (PAMPs)
  - *To clarify this idea, think about “the face”, each one of us has his own Facial features, but when you see a human benig, you can tell that this is a human, not an animal. Even without knowing him! This is because you know the “pattern” of human facial features.*
- Host cells do not share PAMPs with pathogens
- PAMPs are recognized by innate immune recognition receptors called pattern-recognition molecules/receptors (PRMs/PRRs)

Typical PAMPs

- Typical PAMPs:
  - Lipopolysaccharides (lipid A in Gram negative bacteria)
  - Peptidoglycans (usually for Gram positive bacteria)
  - Certain nucleotide sequences unique to bacteria. Rare
  - Other bacterial components. Rare
- Binding of Innate immune receptors and PAMPs:
  - Mediate inflammatory cytokines
  - Antigen-presenting cells recognize PAMPs

6. Cytokines

- In response to microbes, macrophage and other cells secrets proteins called cytokines that mediate many cellular reaction in innate immunity. *(Cytokines may be innate or adaptive, depending on the cells that secret it)*
- Cytokines act as
  - Inflammatory mediators
  - Communication between leukocytes and leukocytes and other cells
- 4 kinds:
  - Chemokines: important in chemotaxis of immune cells
  - Interferons: glycoproteins important in the control of viral infections; also help regulate cells involved in immune response
  - Interleukins: important in innate immunity, inflammation, and adaptive immunity (usually for adaptive).
  - Tumor necrosis factors: help kill tumor cells, initiate programmed cell death (apoptosis)

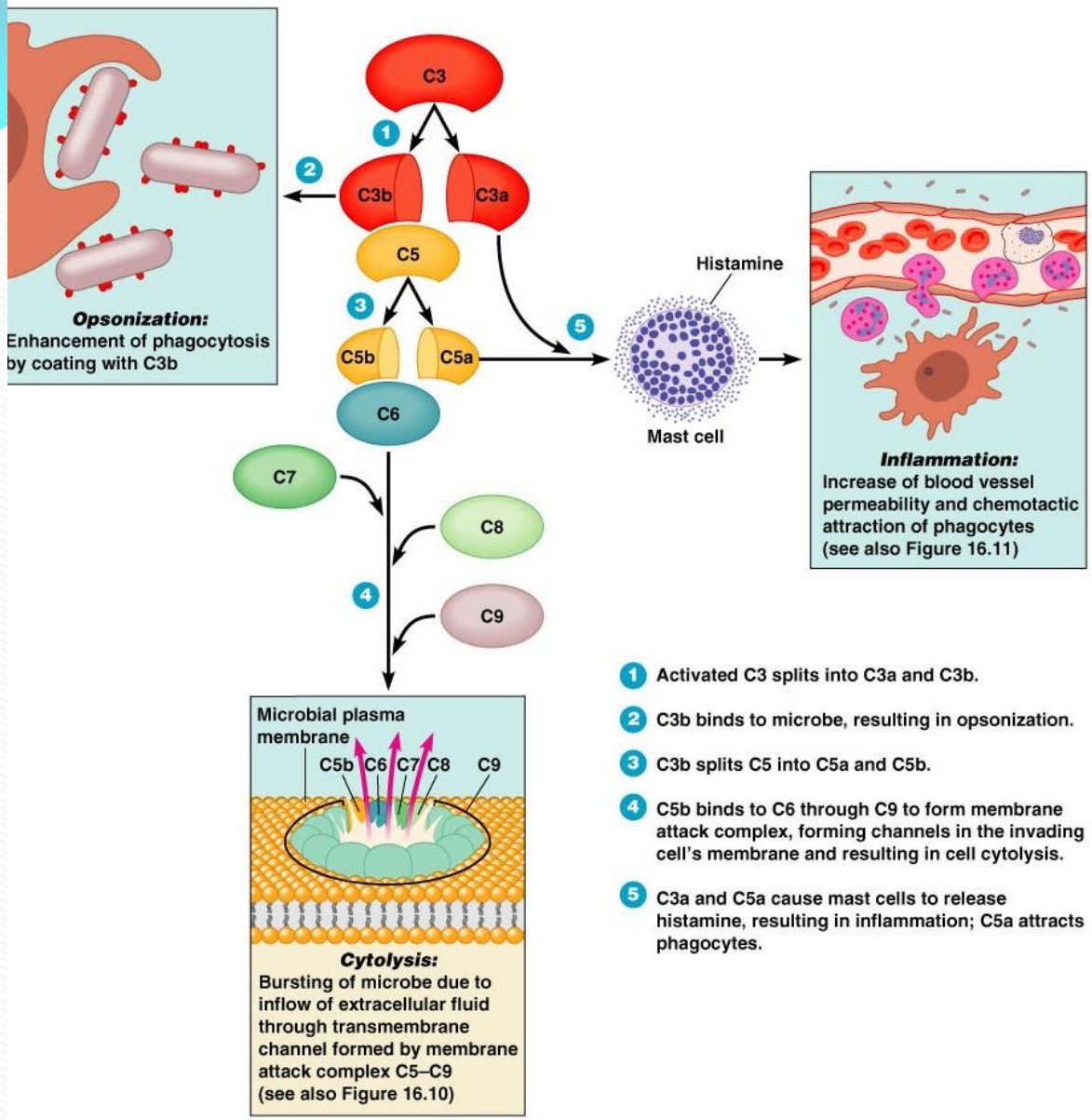
6. Complement System

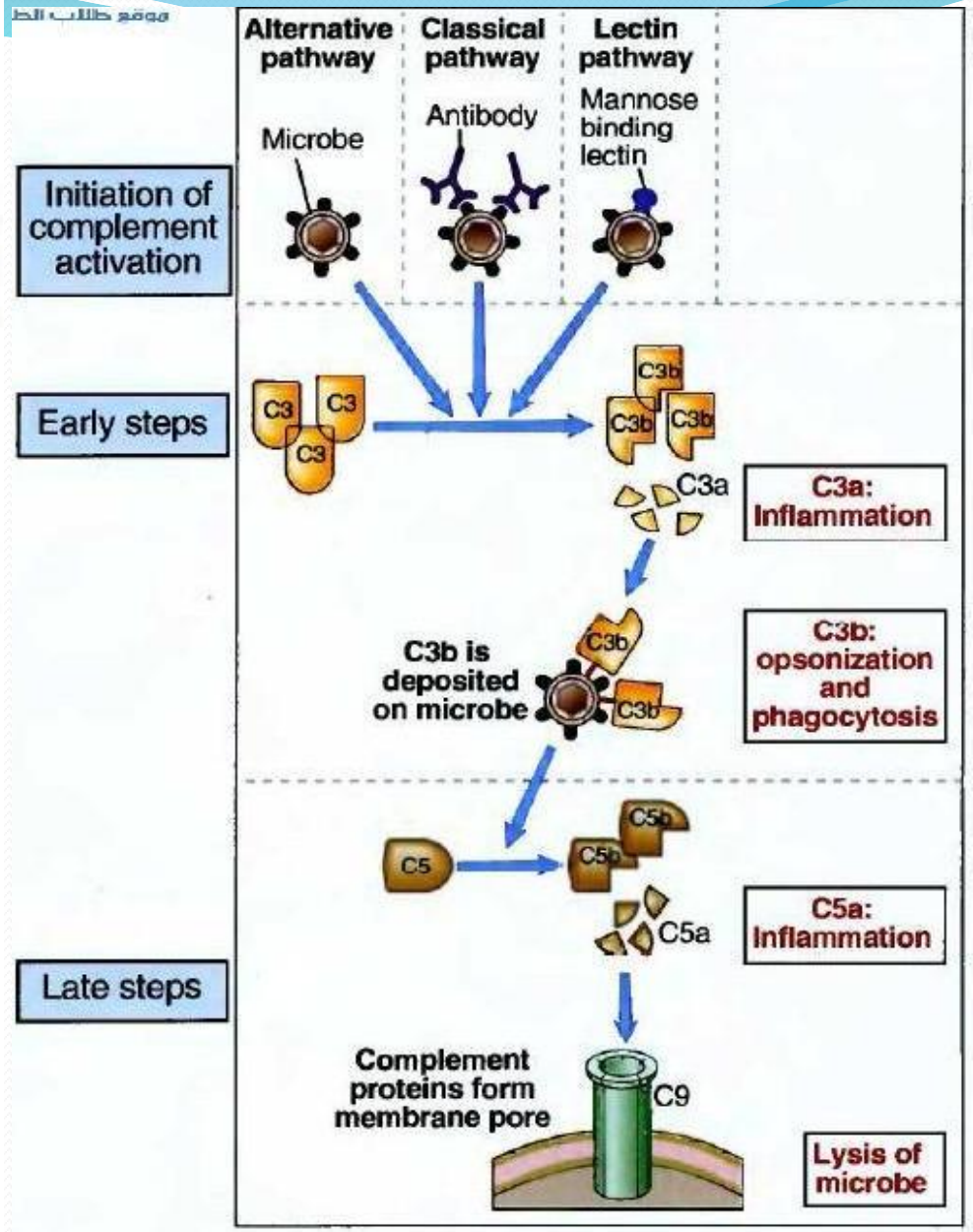
- The complement system is a collection of circulating and membrane associated proteins that are important in defense against microbes.
- Many complement proteins are photolytic enzymes and complement activation involve the sequential activation of these enzymes called the enzymatic cascade.
- Three pathways to activate the complement system
  - Classical: activated by antibody binding to microbes or antigen (adaptive part). *Recognition is specific, but killing is non-specific.*
  - Alternative: directly activated by microbes (innate immunity)
  - Lectin pathway (binding to mannose-containing carbohydrates) (innate immunity- no need for antibodies)

- Host cells have complement regulatory proteins on their surface that protect them from spontaneous activation of C3 molecules while microbes can activate the complement pathway but it have no regulatory proteins
- When pathogen activates the complement system this initiates innate immunity response by three main mechanisms:
  - Inflammation
  - Phagocytosis
  - lysis
  - Opsonization

Opsonization Vs neutralization:

- **Neutralization** means the binding of an antibody to the active (virulent) part of the antigen, therfore inactivating it.
- **Opsenization** means saturation of binding sites of a microbe by an opsonin, labeling it for phagocytosis
- **Note**: some PAMPs cannot be recognised by phagocytes easley, so they require Opsenization.





Summery of the complement system

1. Activation of the complement by one of the previously mentioned pathways.
2. C3 is activated, and cleaved into C3a and C3b
3. Activated C3 will activate C4 and then C5 until C8
4. C5, C6, C7 and C8 activate C9
5. C9 forms MAC (Membrane attack complex), which carry out the final function of microbe lysis

- Some complement may activate phagocytosis and inflammation.
- C3a is a marker for complement activity. Some consider it as a marker for inflamation.

Role of innate immunity in stimulation of adaptive immune response

- Adaptive immune system activation (T or B-cells) need two signals for activation
  - First signal: antigen recognition
  - Second signal: derived by innate immunity

- When innate immunity mechanisms fail to eliminate the pathogen, adaptive immunity is activated, by secreting special cytokines.
- These cytokines are considered as a linkage between adaptive and innate immunity.
- Sometimes these cytokines activate the whole adaptive immunity, but usually it activates specific function (ex: activation of plasma cells to secrete antibodies to facilitate phagocytosis by opsonization)