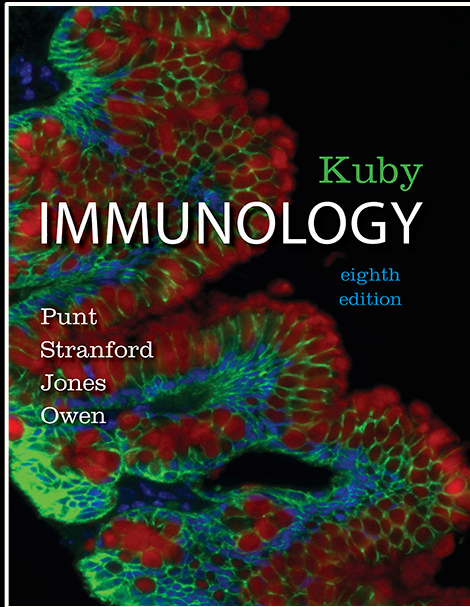


# Natural Defense Mechanisms (Innate Immunity)

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Punt • Stranford • Jones • Owen

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# Kuby Immunology

Eighth Edition

## CHAPTER 4 & 5

# Objectives

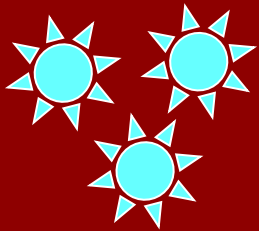
- + To know First (non-specific immunity) and second (adaptive immunity) lines of defense
- + To understand the Complement system, its activation and how it involves in pathogen killing.
- + To recognize the importance of accumulation of inflammatory cells for clearance of infection
- + To know the role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

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

## Viruses e.g.

Influenza

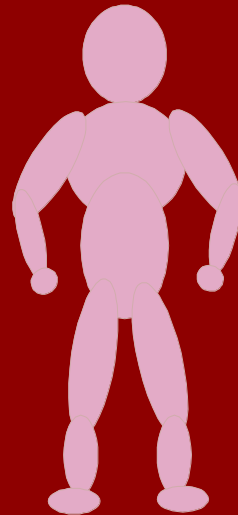
*Polio*



## Parasites e.g.

Tapeworms

Malaria



## Fungi e.g.

*Candida*

*albicans*



## Bacteria e.g.

*Tubercule bacillus*

*Staphylococci*

# First and the second lines of defense:



## NONSPECIFIC DEFENSE MECHANISMS

## SPECIFIC DEFENSE MECHANISMS (IMMUNE SYSTEM)

### First Line of Defense

### Second Line of Defense

- Skin
- Mucous membranes
- Secretions of skin and mucous membranes

- Phagocytic white blood cells
- Antimicrobial proteins
- The inflammatory response

- Lymphocytes
- Antibodies

# 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, tears)

# Anatomical and mechanical barriers

- Skin, impermeable to microbes.
- 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.  
(Compete with pathogenic bacteria for nutrients)



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

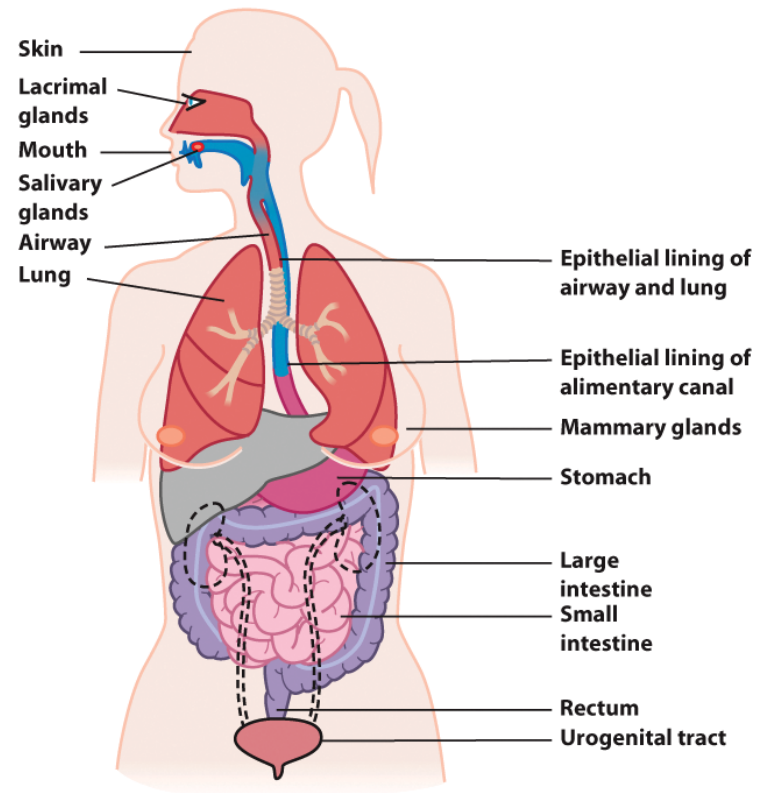


Figure 4-2  
*Kuby Immunology*, Eighth Edition  
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## ■ Inflammation:

■ Inflammation is the first response of the immune system to infection or irritation.

■ 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)

# 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

# The Complement system

- Consists of a group of serum proteins initially present in inactive form
- 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

# The complement system:

3 Pathways of activation :

\* **Classical.** (Requires antigen-antibody binding)

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

\* **Lectin.** (Activated by mannan binding protein binding manose groups of bacterial carbohydrates)

- (-C4,C2,C3,C5,C6,C7,C8,C9)

- **Alternative.**(Activated by bacterial products)

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

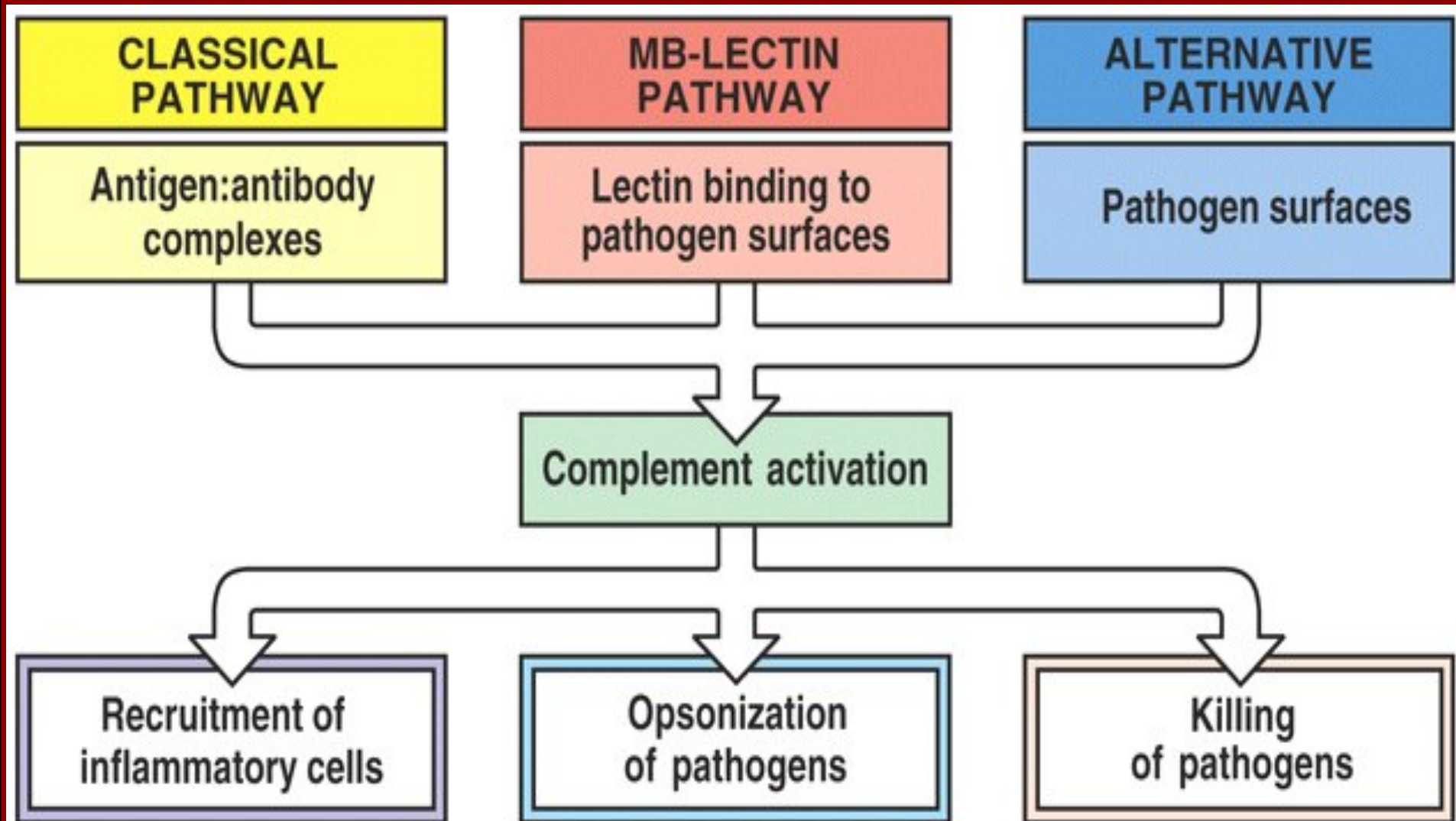
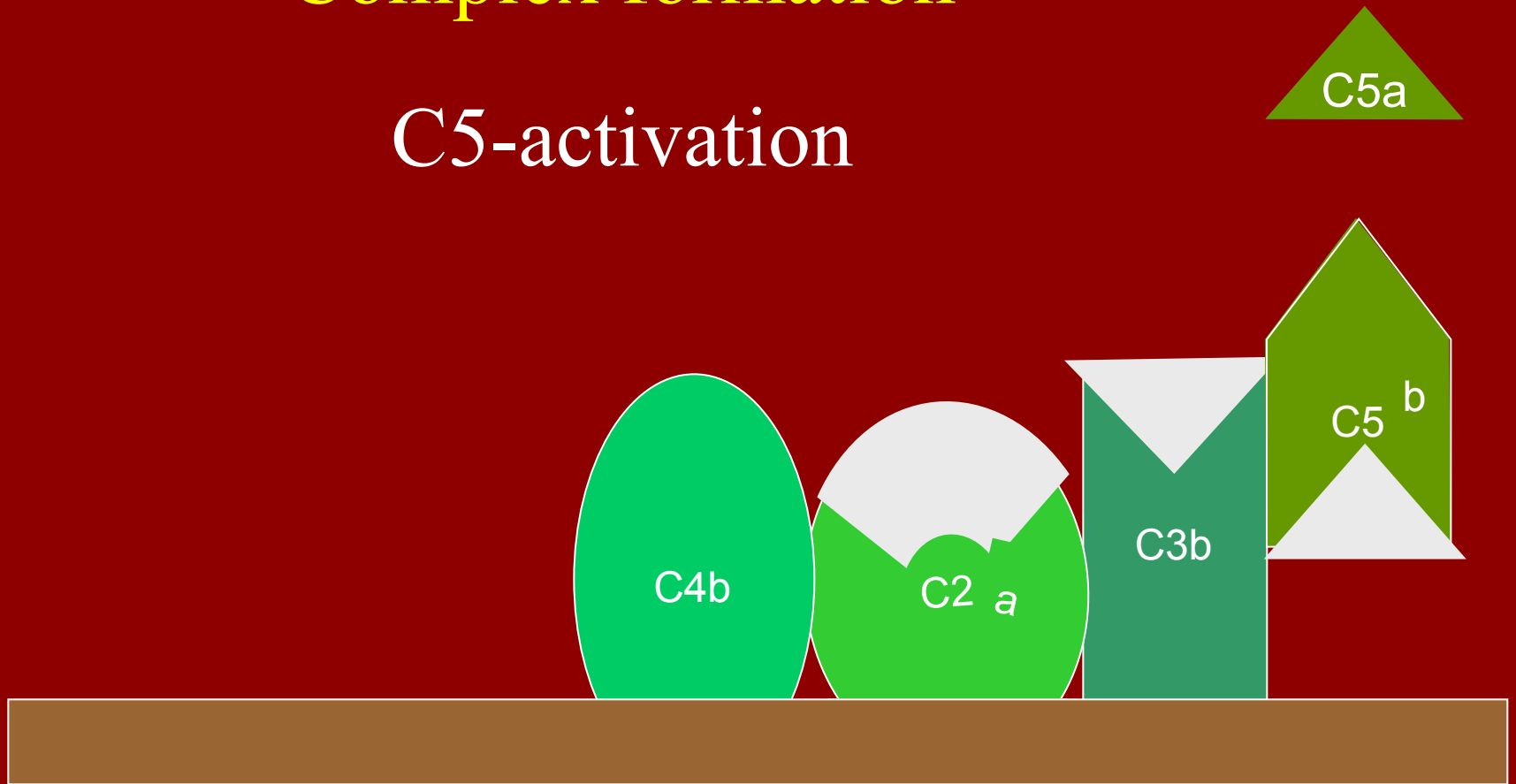


Figure 2-18 Immunobiology, 6/e. (© Garland Science 2005)

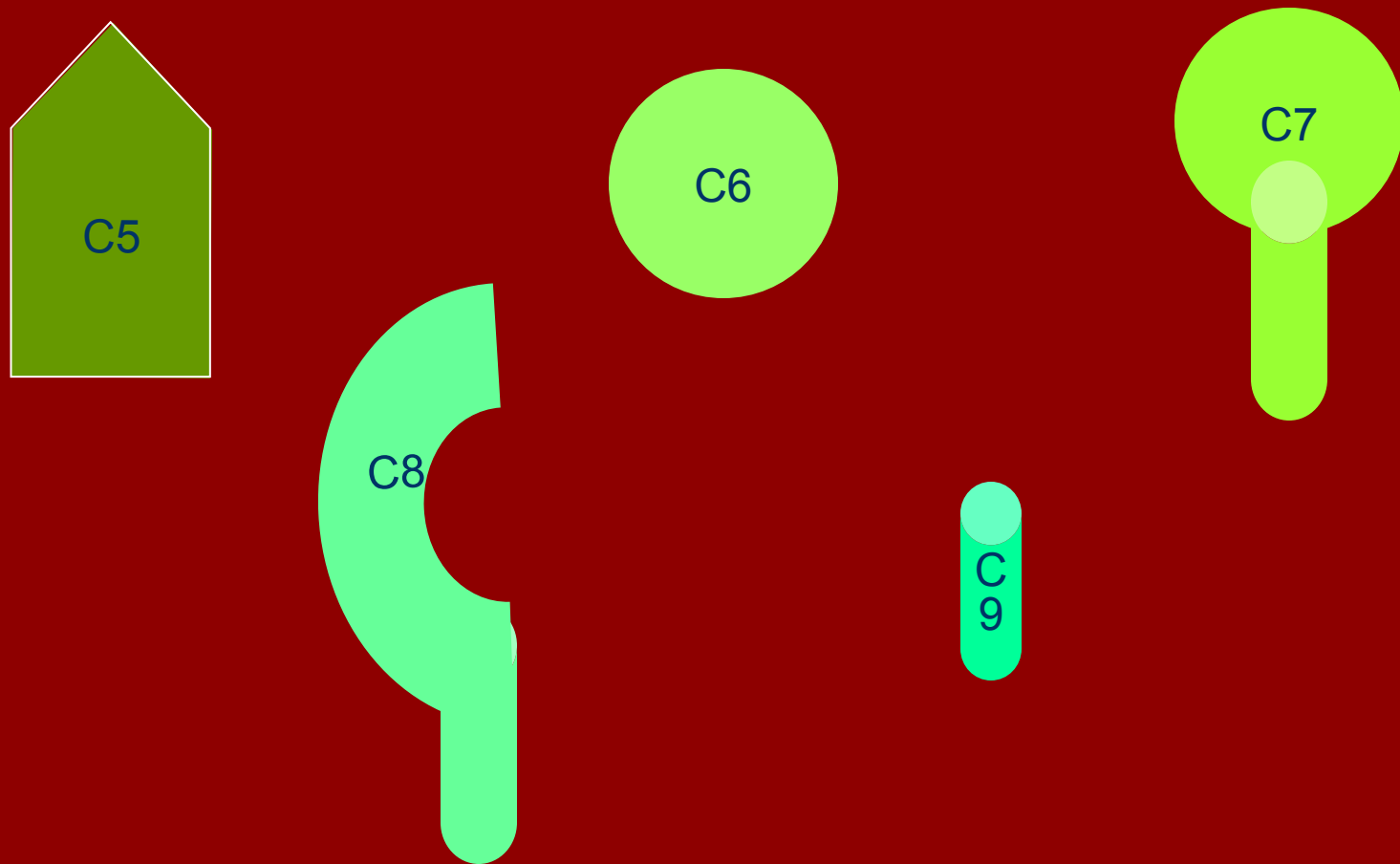
# Membrane Attack Complex formation

C5-activation

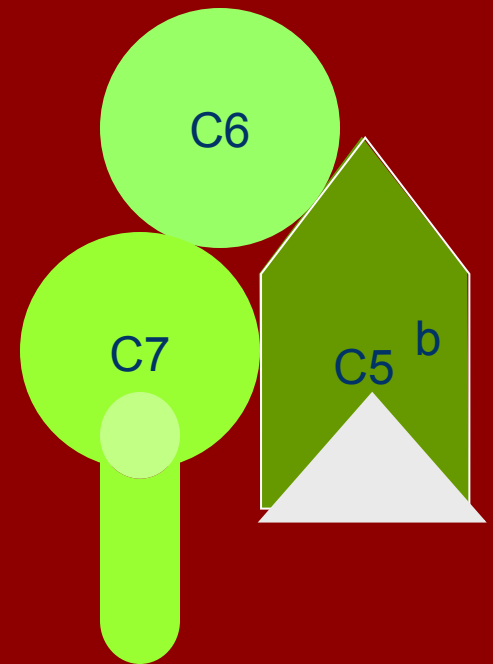




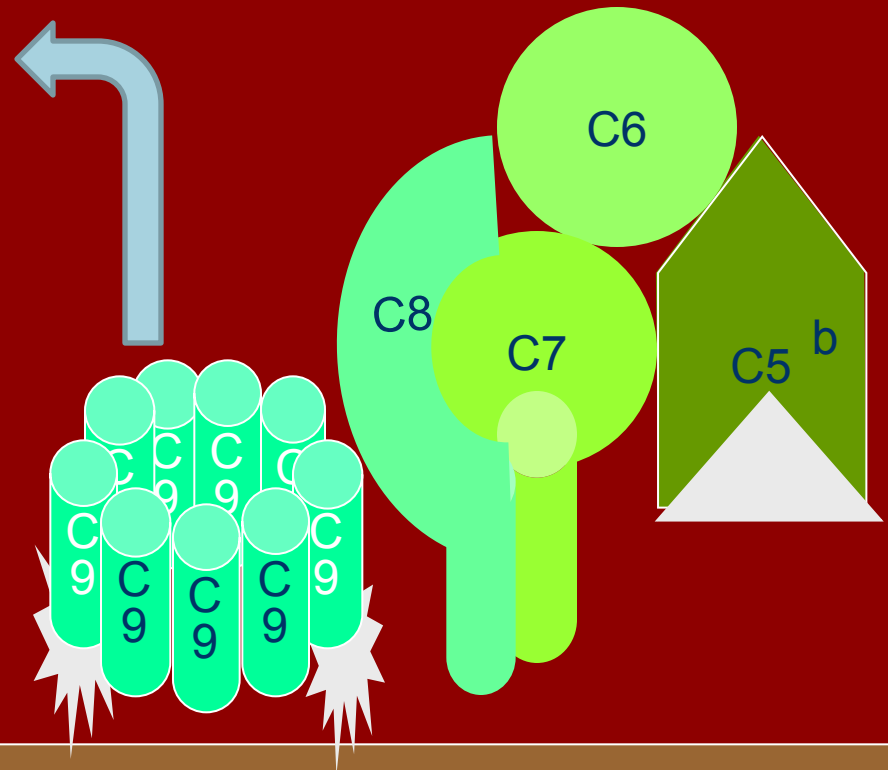
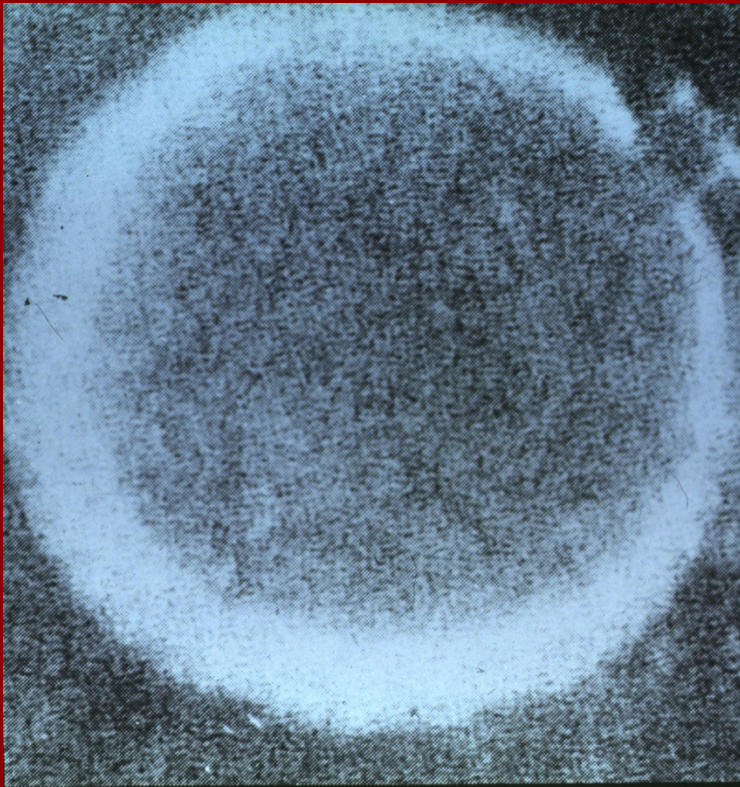
# Components of the Membrane Attack Complex



# Membrane Attack Complex components Assembly



# Membrane Attack Complex formation : insertion of lytic complex into cell membrane



# Biological effects of complement activation

1. Anaphylatoxin functions (e.g. C3a, C5a):

- Trigger degranulation (release of substances) of endothelial cells, mast cells or phagocytes.
- Induce smooth muscle contraction and increased vascular permeability.
- Attract additional inflammatory cells to the site of activation.

2. Opsonization: C3b is the main opsonin and to a lesser extent C4b.

- Coating of bacteria enhances phagocytosis

3. Direct cell lysis:

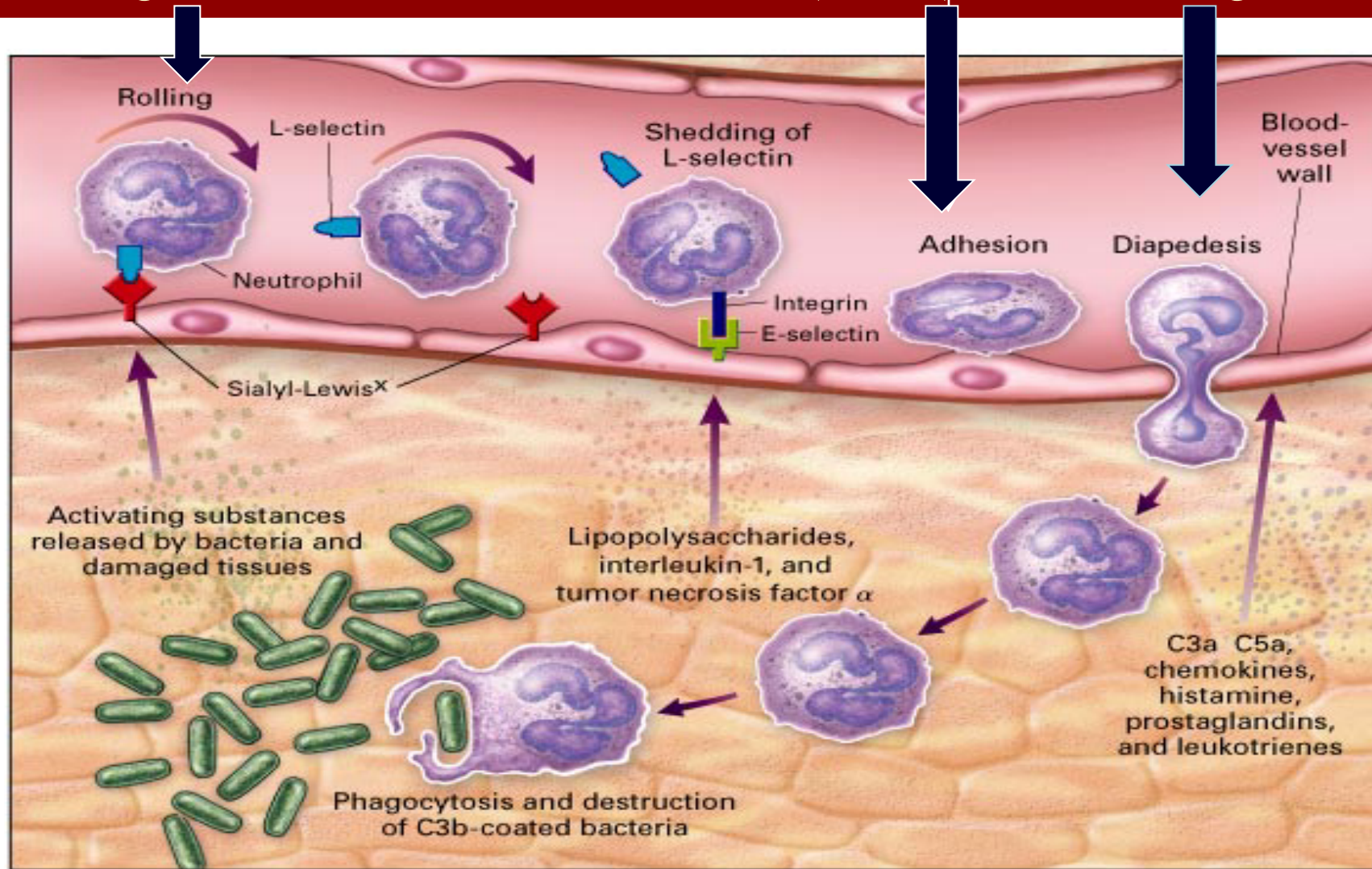
- Destruction of bacteria.

# Process of chemotaxis:

Rolling on vessel wall.

Adhesion (attach)

Pass through.



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

## Monocytes :

- Become Macrophages when they leave the blood and enter the tissues.

**Neutrophils:** (Phagocytic cells)

**Eosinophils:** (Allergy and Parasitic infections)

**Natural Killer (NK) cells:** (Kill tumor cells and virus infected cells)

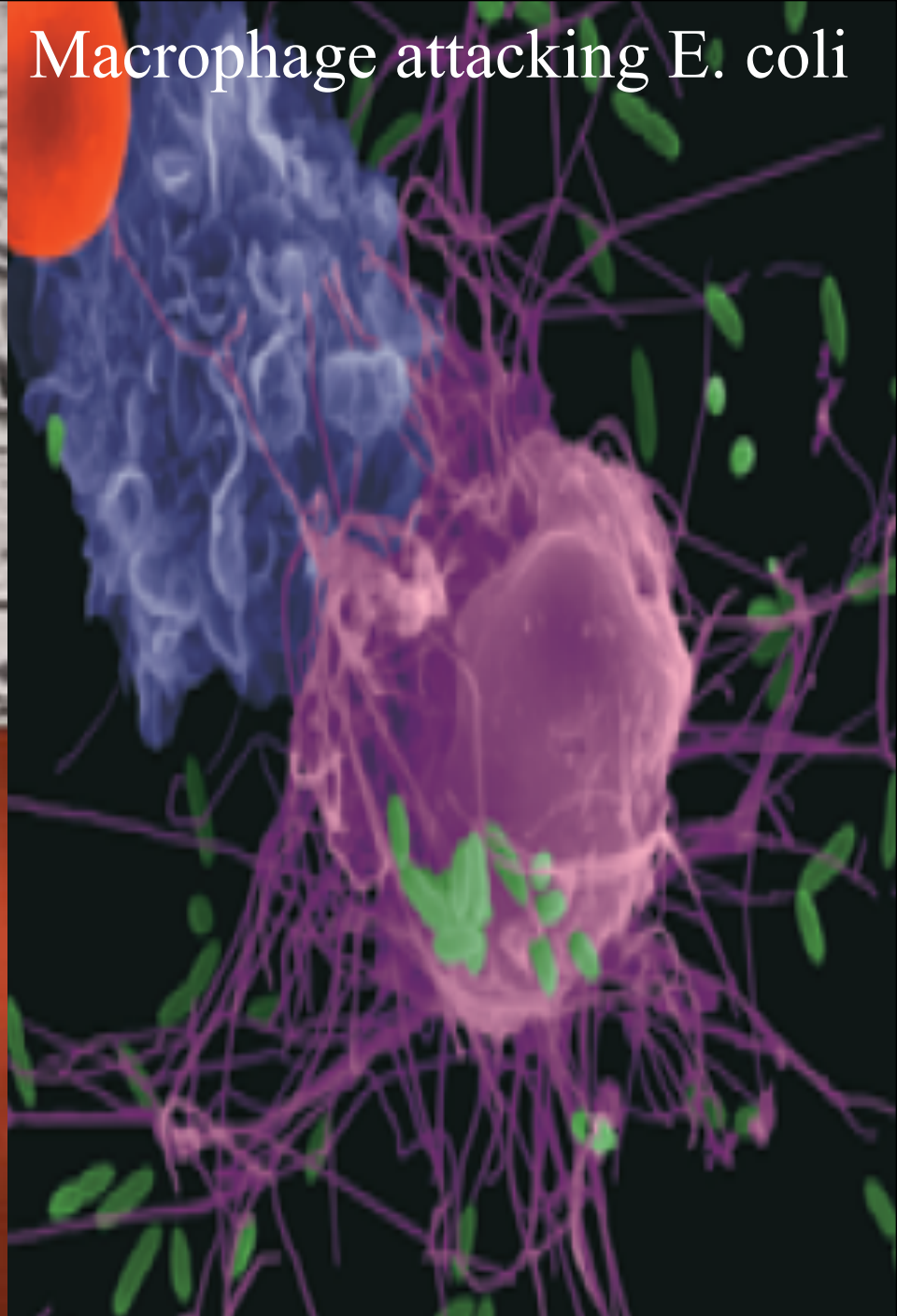
Phagocytic cells (neutrophils & macrophages) at site of infection start the process of **phagocytosis** which is the process by which a cell **engulf** a solid particle such bacteria to form **internal vesicle** known as **phagosome**

white cell (neutrophil) hunting bacterium



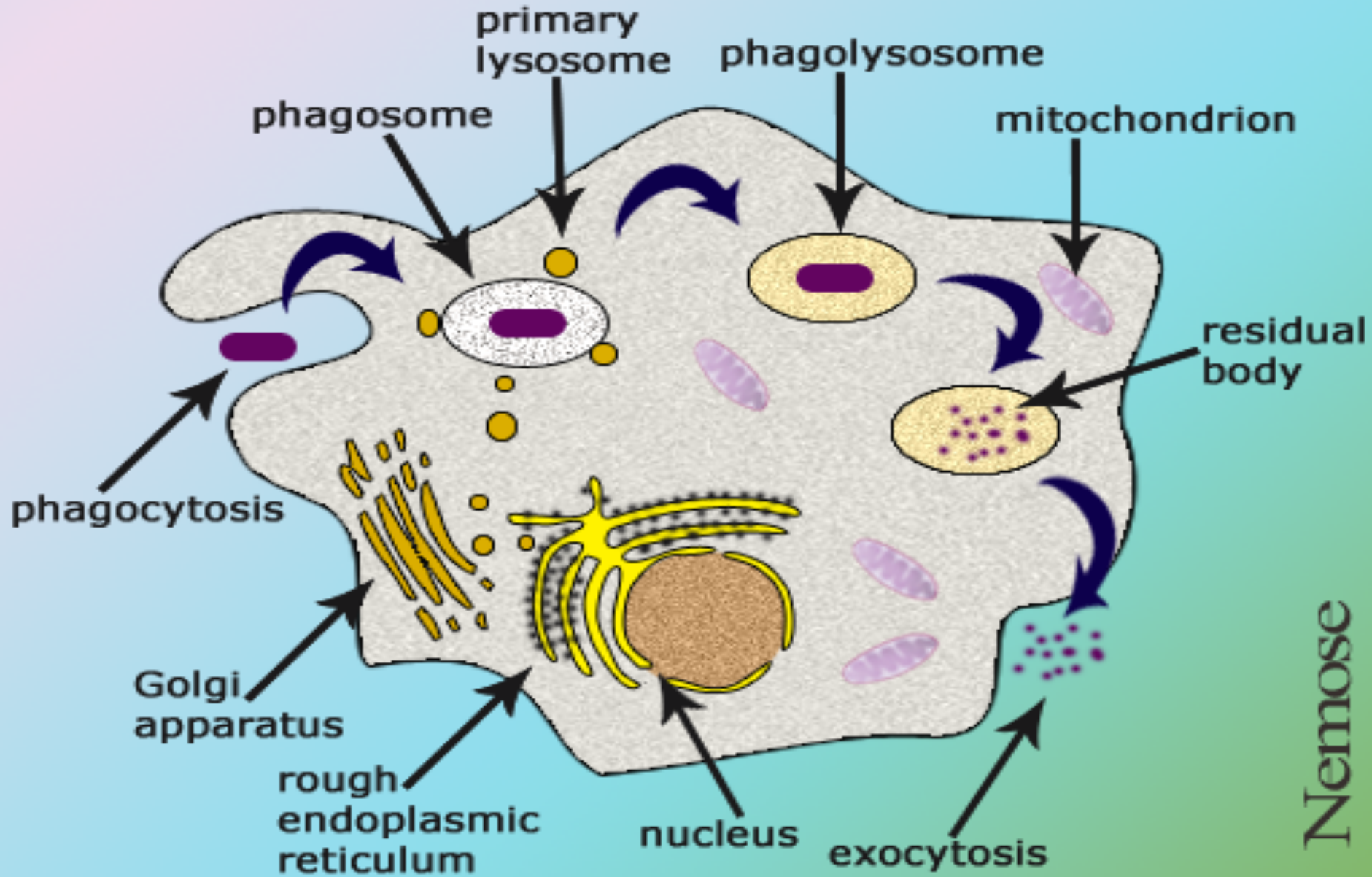
bacterium

Macrophage attacking E. coli





# Phagocytosis



# Cytokines

Soluble molecules, produced by specific cells of the Immune system, that control cell functions e.g. differentiation, proliferation activation or inhibition. Play an Important role in:

**Innate Immunity / Adaptive Immunity**

# The six major cytokine families

Family name	Representative members of family	Comments
<b>Interleukin-1 family</b>	IL-1 $\alpha$ , IL-1 $\beta$ , IL-1Ra, IL-18, IL-33	IL-1 was the first noninterferon cytokine to be identified. Members of this family include important inflammatory mediators.
<b>Class 1 (hematopoietin) cytokine family</b>	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.
<b>Class 2 (interferon) cytokine family</b>	IFN- $\alpha$ , IFN- $\beta$ , IFN- $\gamma$ , 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.
<b>Tumor necrosis factor family</b>	TNF- $\alpha$ , TNF- $\beta$ , CD40L, Fas (CD95), BAFF, APRIL, LT- $\beta$	Members of this family may be either soluble or membrane-bound; they are involved in immune system development, effector functions, and homeostasis.
<b>Interleukin-17 family</b>	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.
<b>Chemokines</b>	IL-8, CCL19, CCL21, RANTES, CCL2 (MCP-1), CCL3 (MIP-1 $\alpha$ )	All serve chemoattractant function.

# Cytokines

## \* **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

# Take home message

- ❑ 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