Natural Defense Mechanisms (Innate Immunity)

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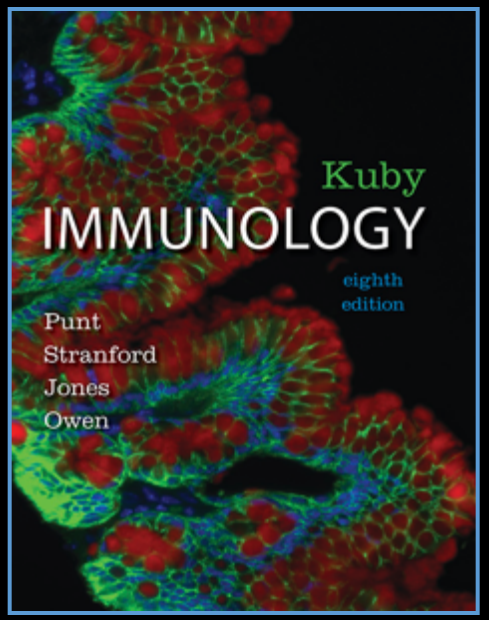


•Kuby Immunology

• Eighth Edition

CHAPTER 4 & 5

Objectives

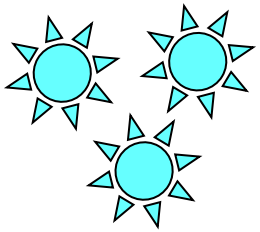
- + To know First (non-specific immunity) and second (adaptive immunity) lines of defense
- + To understand the Complement system, its activation and how it involves in pathogen killing.
- + To recognize the importance of accumulation of inflammatory cells for clearance of infection
- + To know the role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

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

Viruses e.g.

Influenza

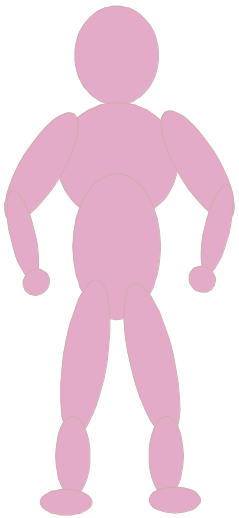
Polio

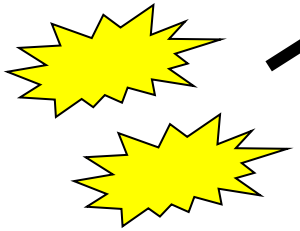


Parasites e.g.

Tapeworms

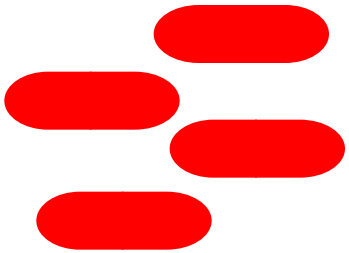
Malaria





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
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

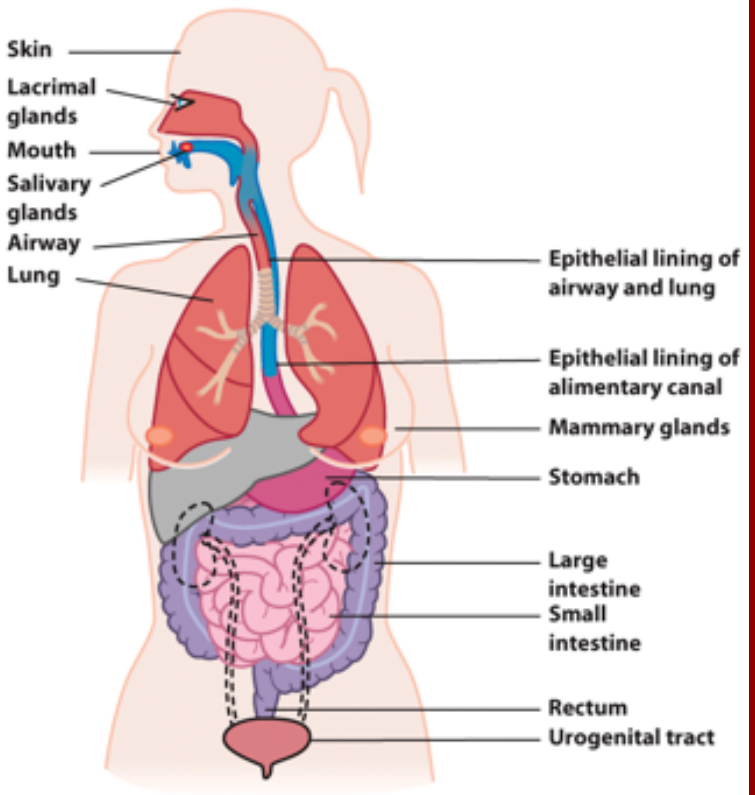


Figure 4-2
Kuby Immunology, Eighth Edition

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 protien 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)**

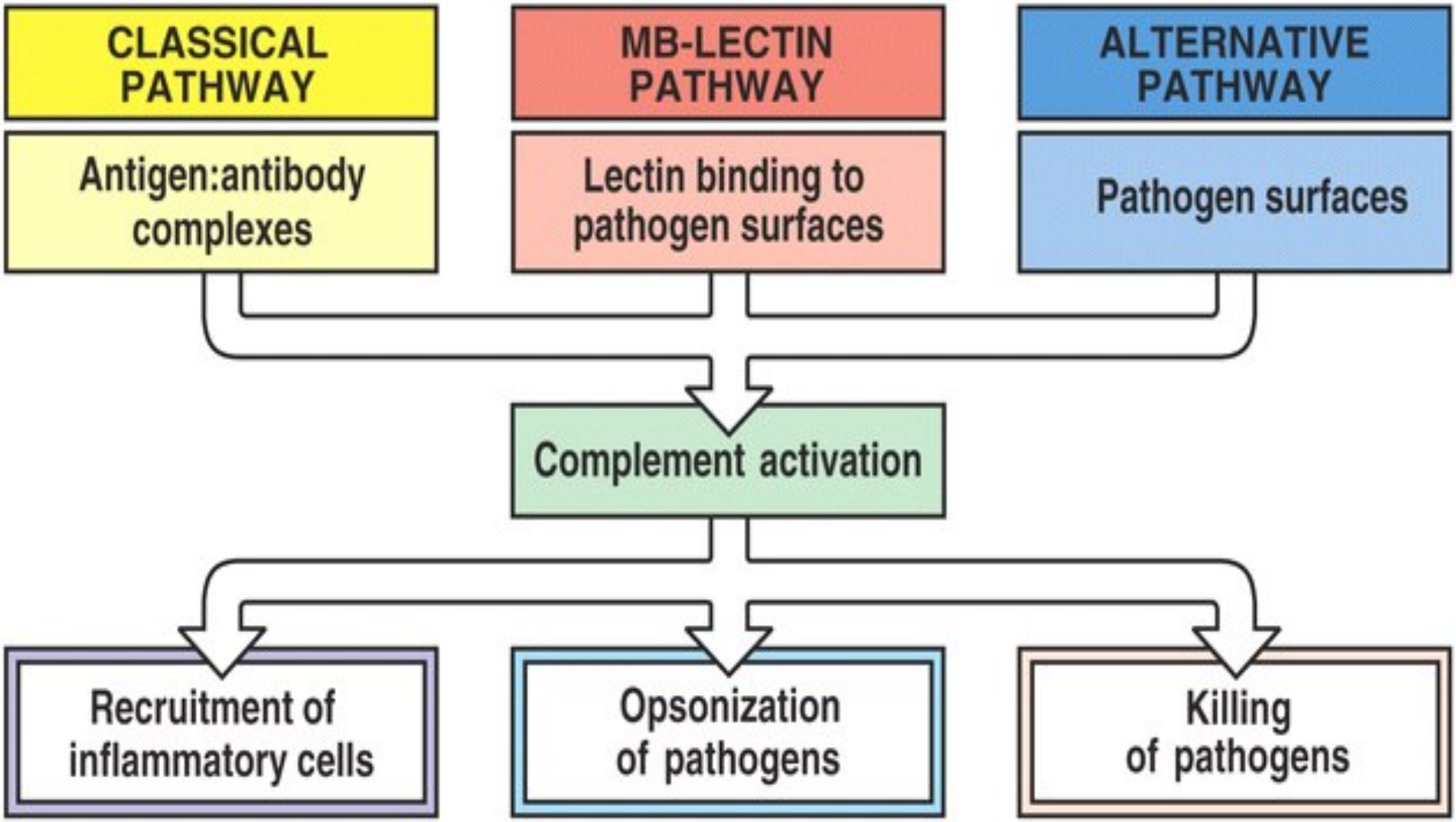
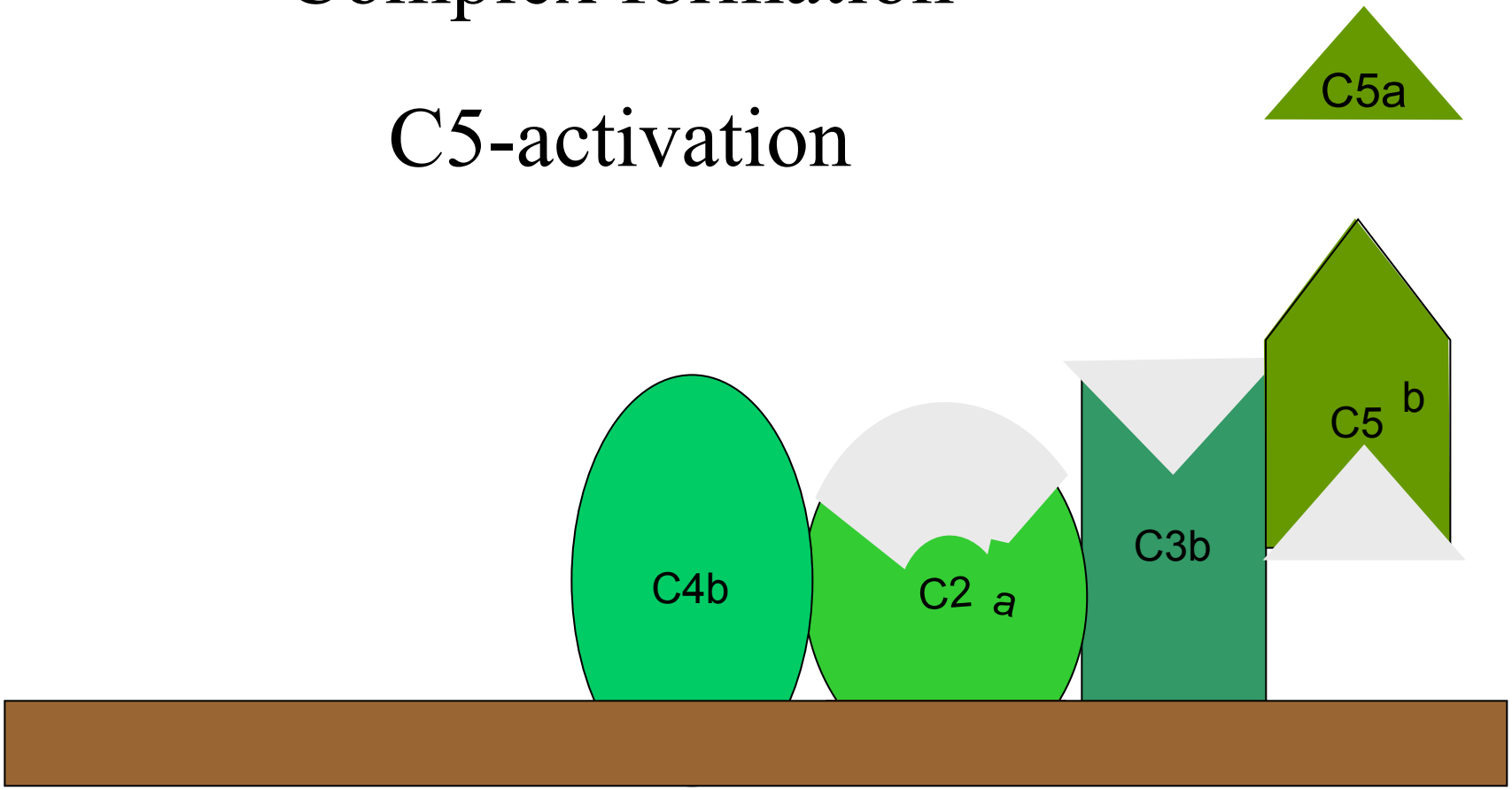


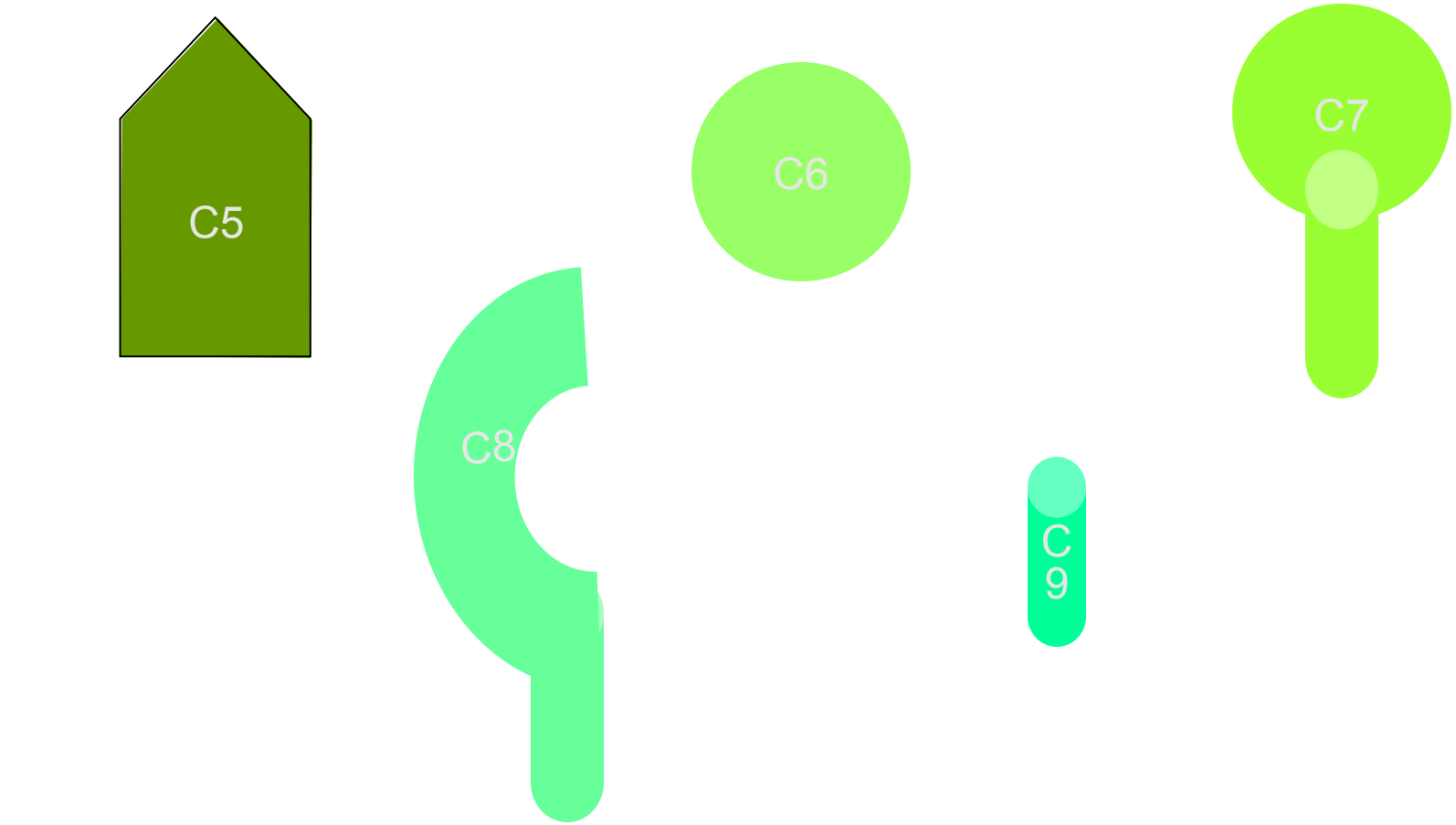
Figure 2-18 Immunobiology, 6/e. (© Garland Science 2005)

Membrane Attack Complex formation

C5-activation

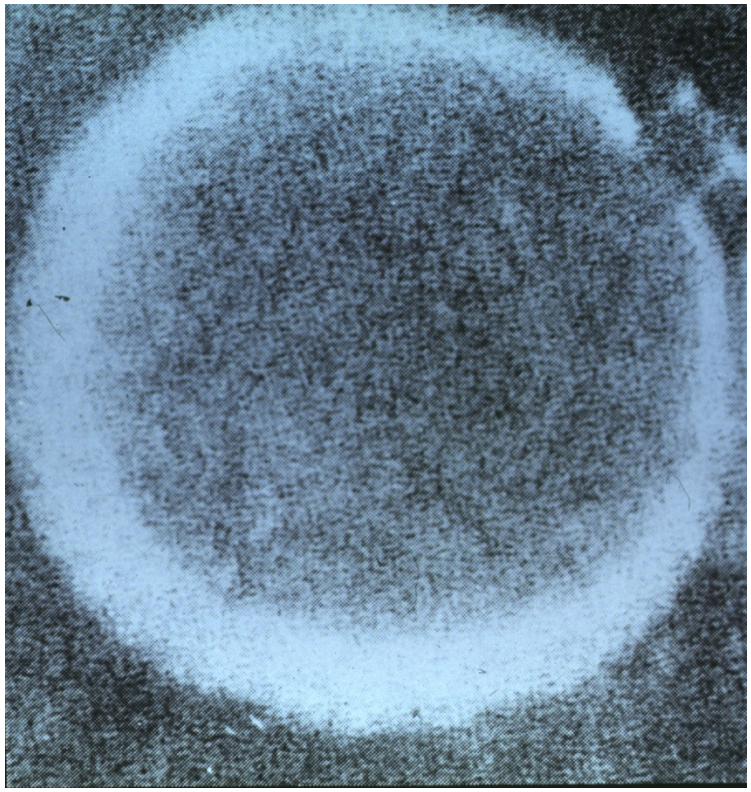


Components of the Membrane Attack Complex



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.

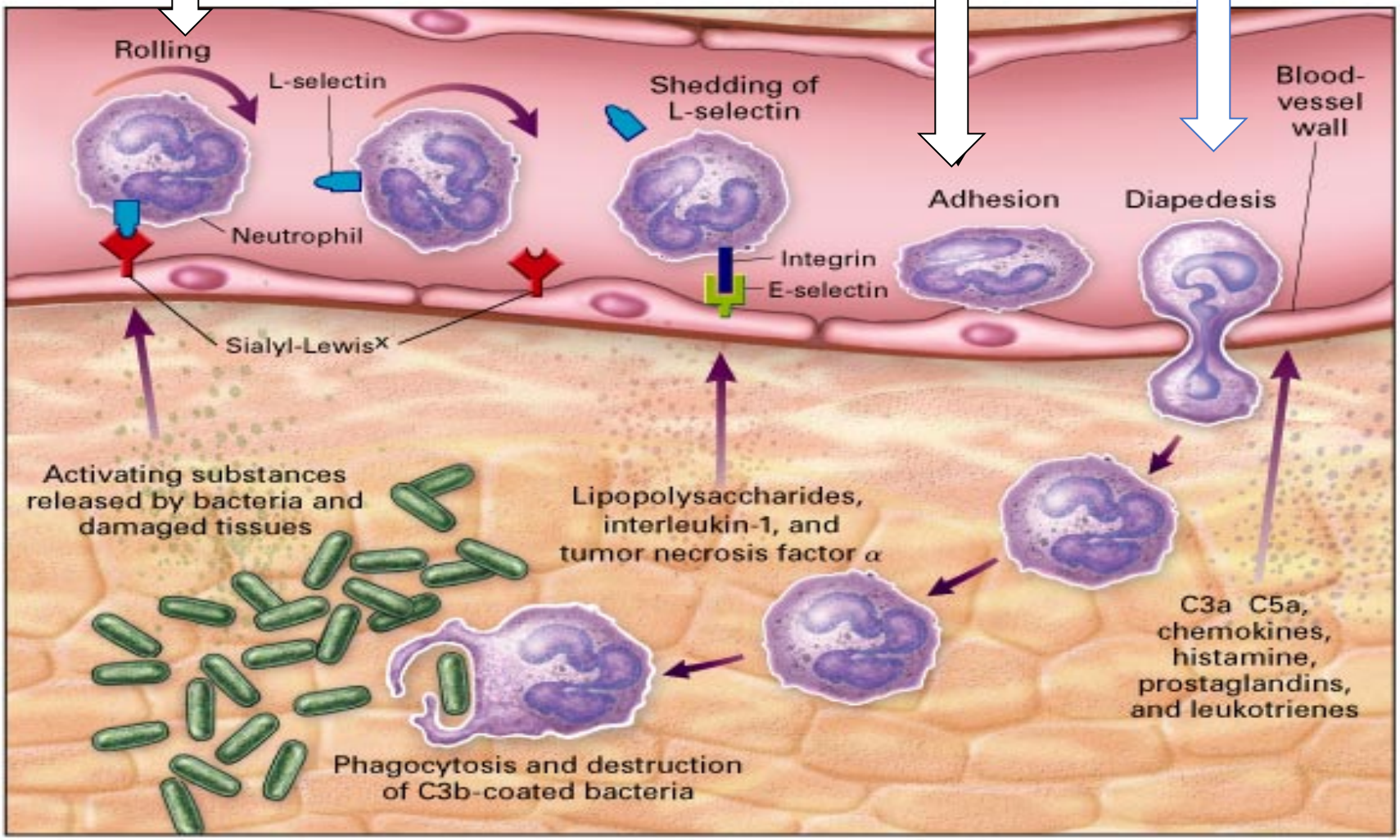
- Coating of bacteria enhances phagocytosis

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 :

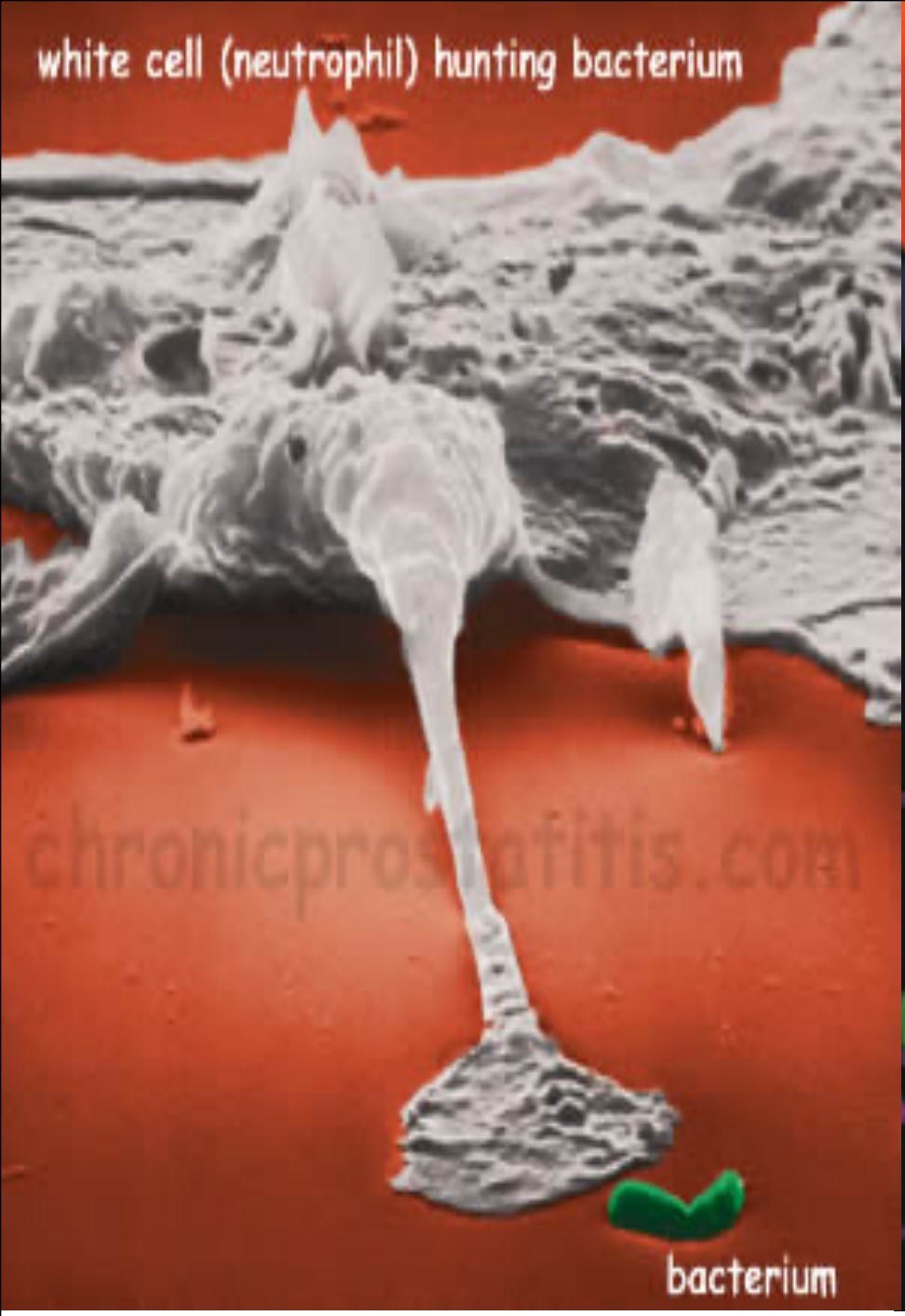
- Become Macrophages when they leave the blood and enter the tissues.

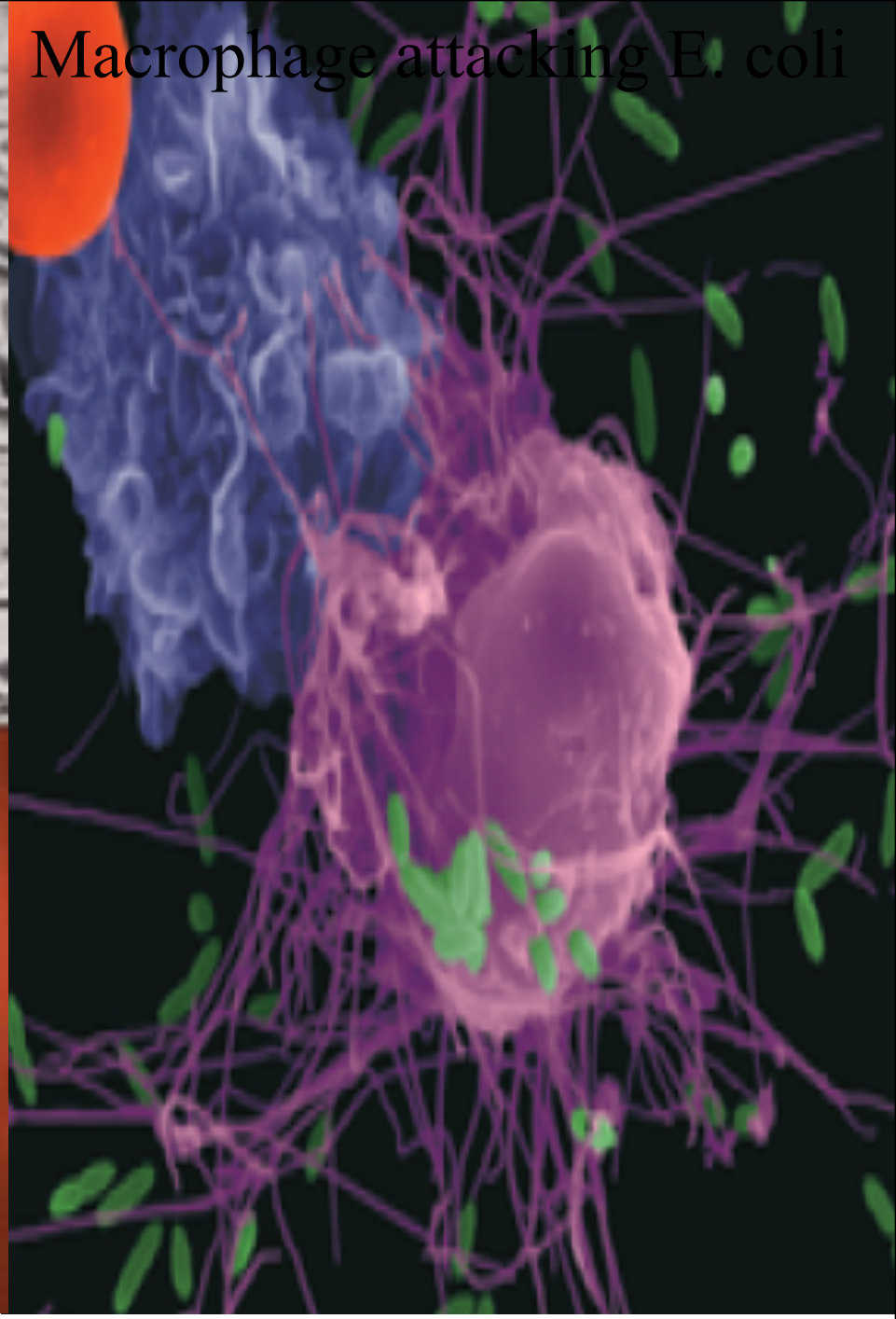
Neutrophils: (Phagocytic cells)

Eosinophils: (Allergy and Parasitic infections)

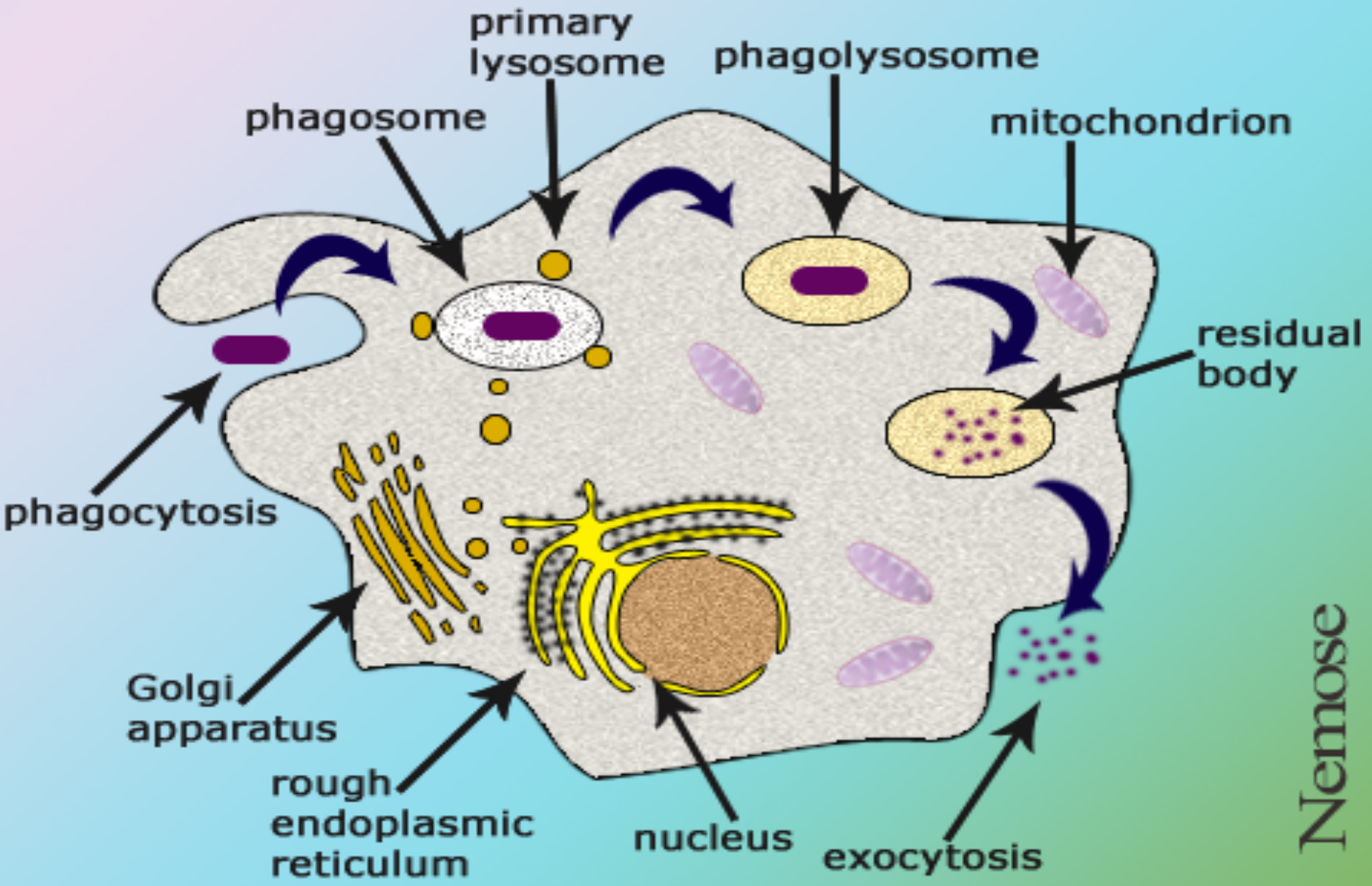
Natural Killer (NK) cells: (Kill tumor cells and virus infected cells)

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
Interleukin-1 family	IL-1α, IL-1β, IL-1Ra, IL-18, IL-33	IL-1 was the first noninterferon 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.
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.

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