Non-Specific Immunity

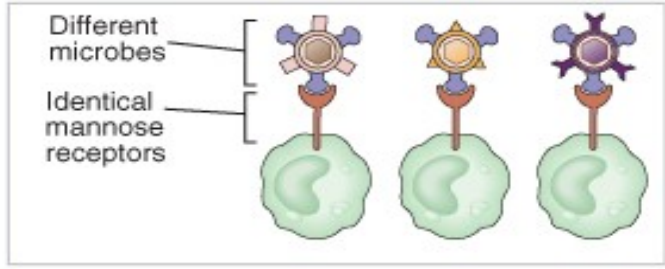
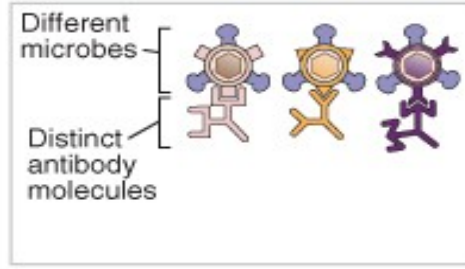
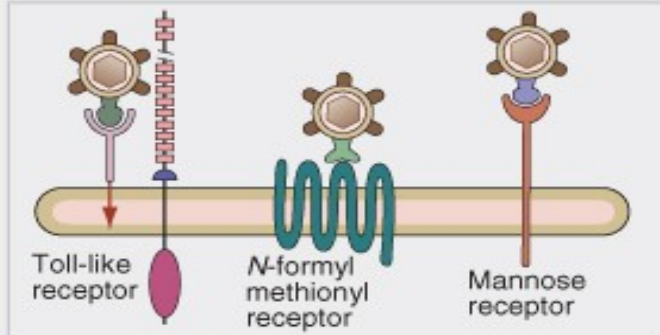
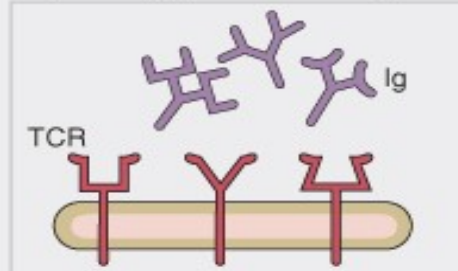
Innate (natural, native, non-specific) immunity

- Always present, ready to recognise and eliminate microbes. Does nor react with non-microbial substances.
- Frequently eliminates microbes before the specific immunity becomes active.
- Receptors are encoded in the germline, are not a product of recombination of genes.

Differences between the Innate and Acquired Immunity

- Innate Immunity
  - Universal
  - Rapid
  - Lacks memory
- Acquired Immunity
  - Not universal
  - ‘Slow’ to develop
  - Memory
  - Specific but in some situations reacts to autoantigens
  - ‘Plays to the tune of the innate immune system’

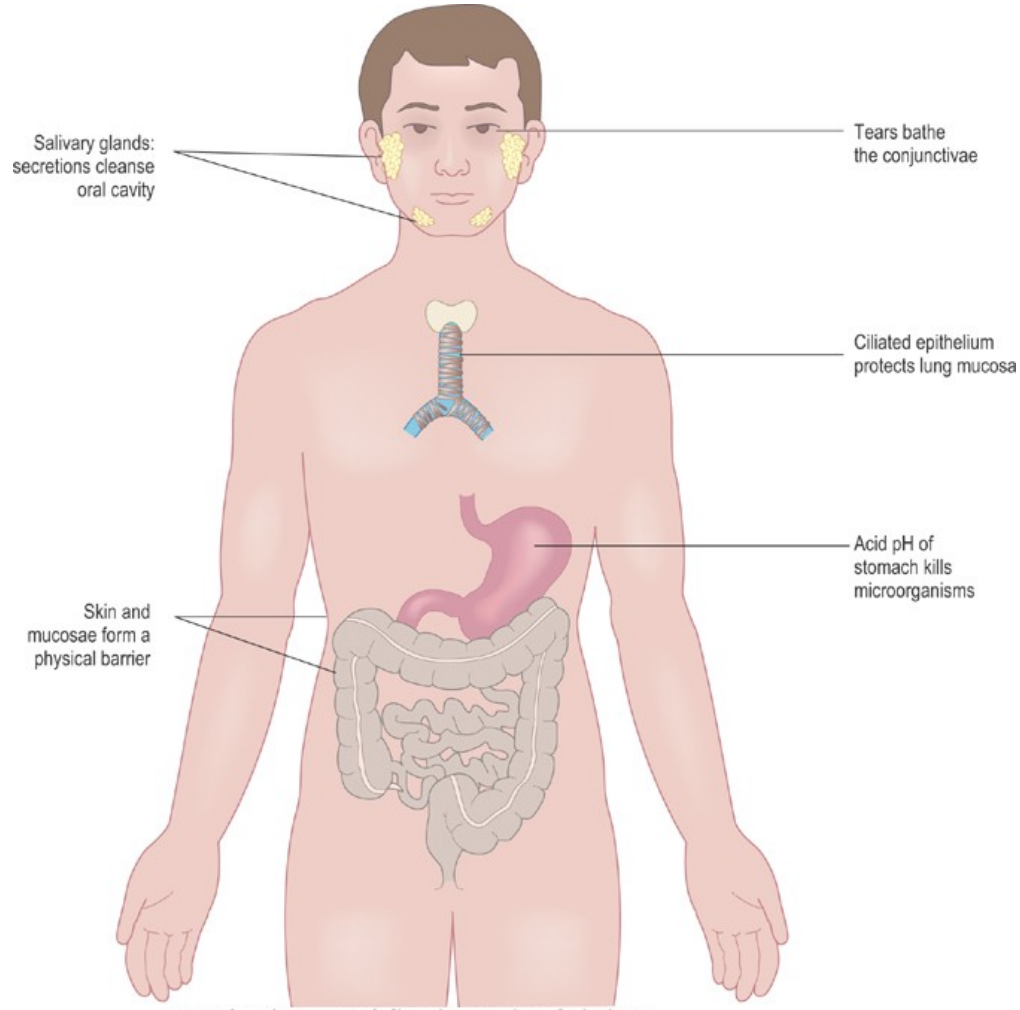
Differences between innate and specific immunity

	Innate immunity	Adaptive immunity
Specificity	For structures shared by classes of microbes ("molecular patterns") 	For structural detail of microbial molecules (antigens); may recognize nonmicrobial antigens 
Receptors	Encoded in germline; limited diversity 	Encoded by genes produced by somatic recombination of gene segments; greater diversity 
Distribution of receptors	Nonclonal: identical receptors on all cells of the same lineage	Clonal: clones of lymphocytes with distinct specificities express
Discrimination of self and nonself	Yes; host cells are not recognized or they may express molecules that prevent innate immune reactions	Yes; based on selection against self-reactive lymphocytes; may be imperfect (giving rise to autoimmunity)

Basic components of non-specific defence

- Non Specific barriers
  - Anatomical/Physiological
- Acute phase reactants and Inflammation
  - Complement/Interferons/CRP
- Innate cells
  - PMN/Macrophages/NK cells

Non-specific barriers of human body

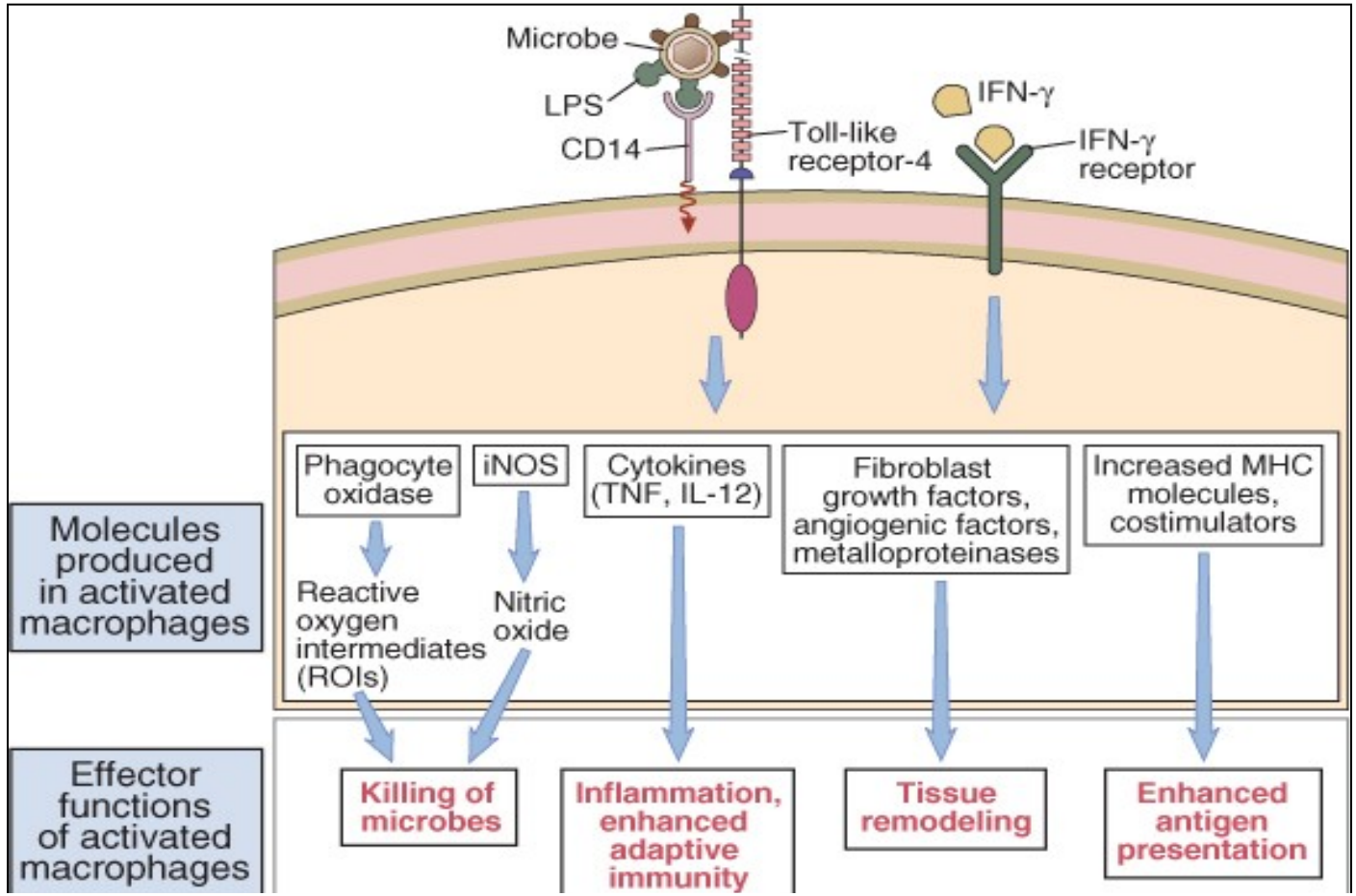


PAMPS – patogen-associated molecular patterns (Endotoxin, mannose, double-stranded RNA, unmelylated CpG nucleotides)

PRR- Pattern recognition receptors - recognize PAMPS.

TOLL-like receptors –surface or intracellular receptors recognizing various PAMPS. Expressed on dendritic cells, macrophages, granulocytes, epitelial cells…. They induce activation of these cells.

Activation by Toll-like Receptors and by Cytokine Receptors



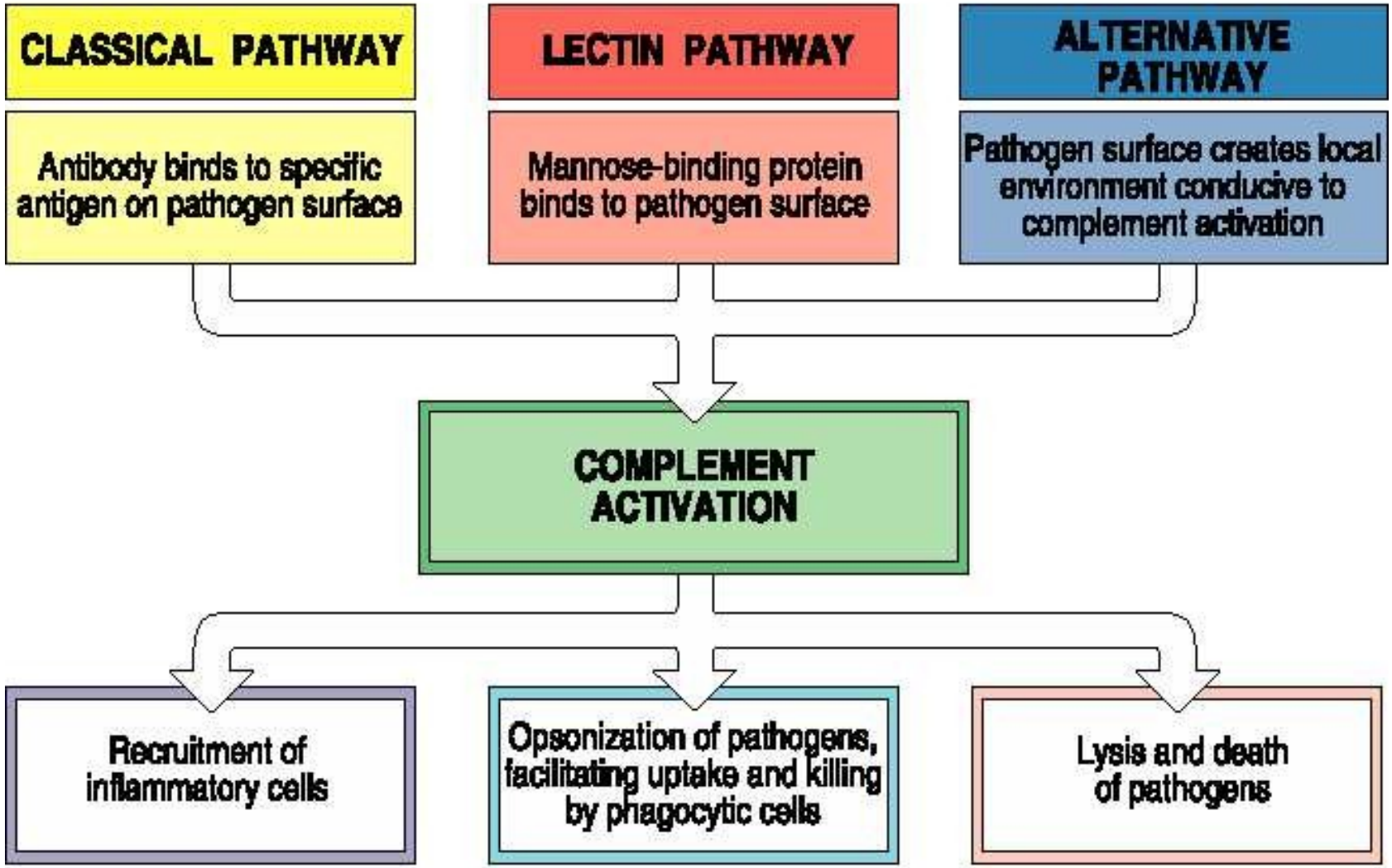
The Complement System

General features of the Complement System Activation

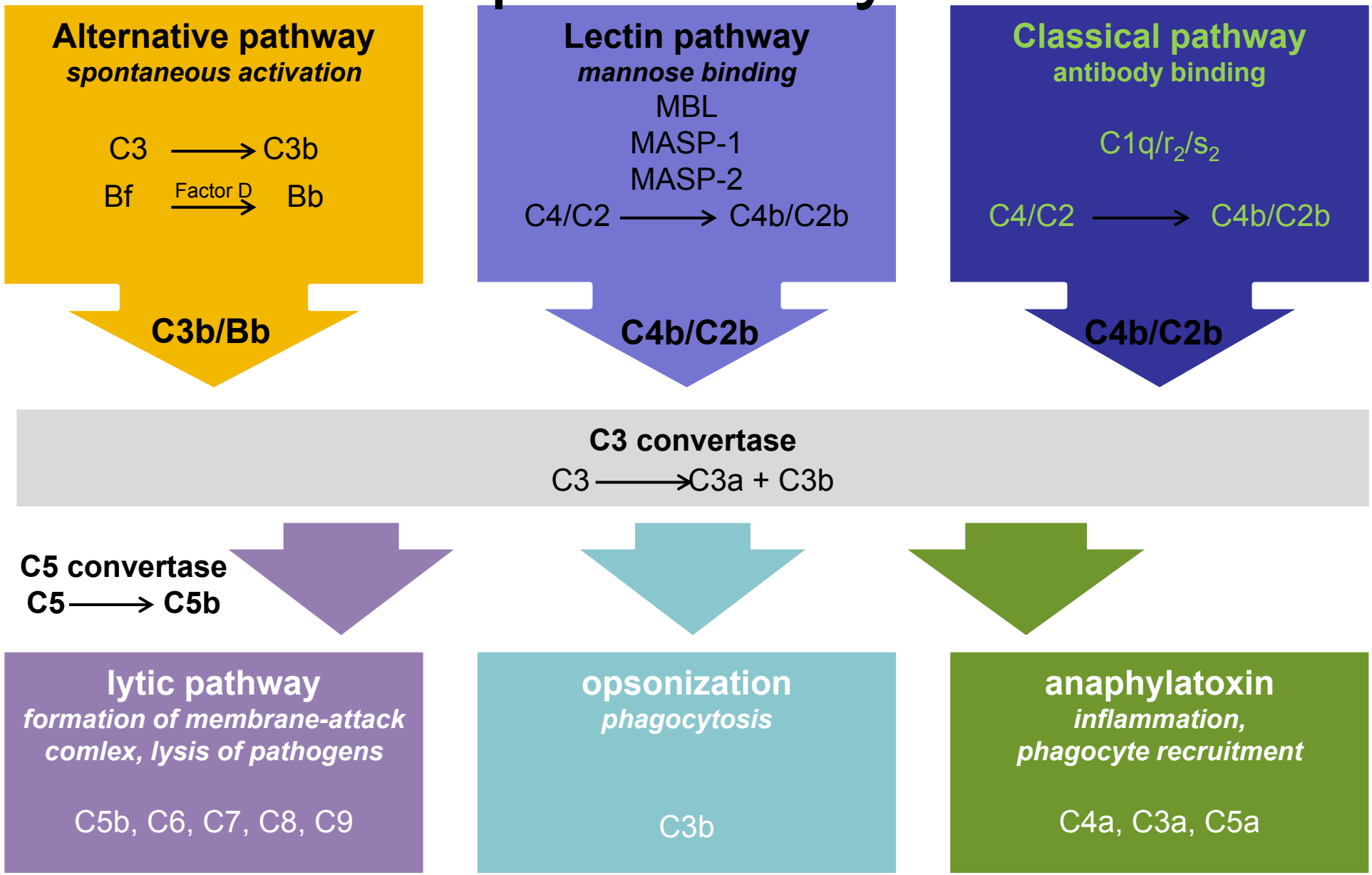
- Inactive, preformed protein is activated by the proteolytic cleavage.
- It is cleft into the smaller part (called a) and a bigger part (called b).
- Usually the bigger part has also proteolytic activity, while the smaller part has various other biological activities (chemotactic, anaphylatoxic).
- Component C6-C9 are activated without cleavage, they just „attach“ to the complex of the other complement components.

Activation of the complement sytsem

Figure 7.27



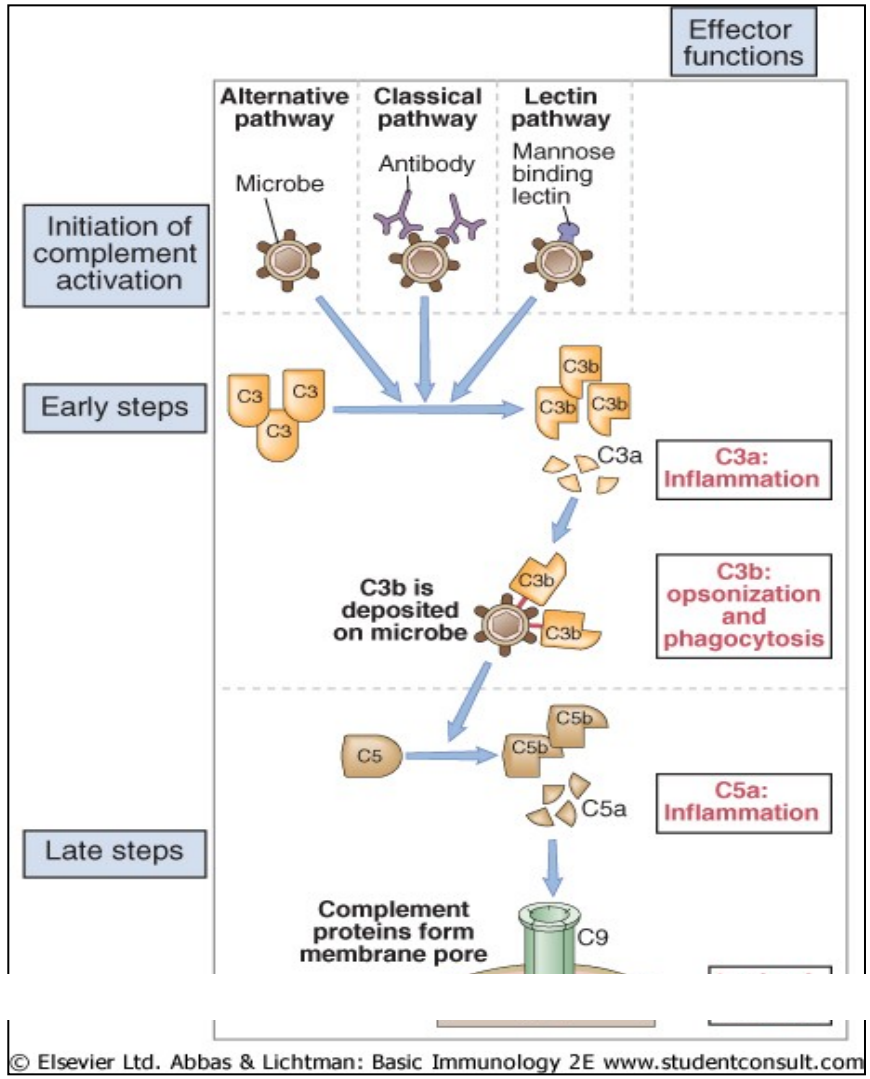
Complement system



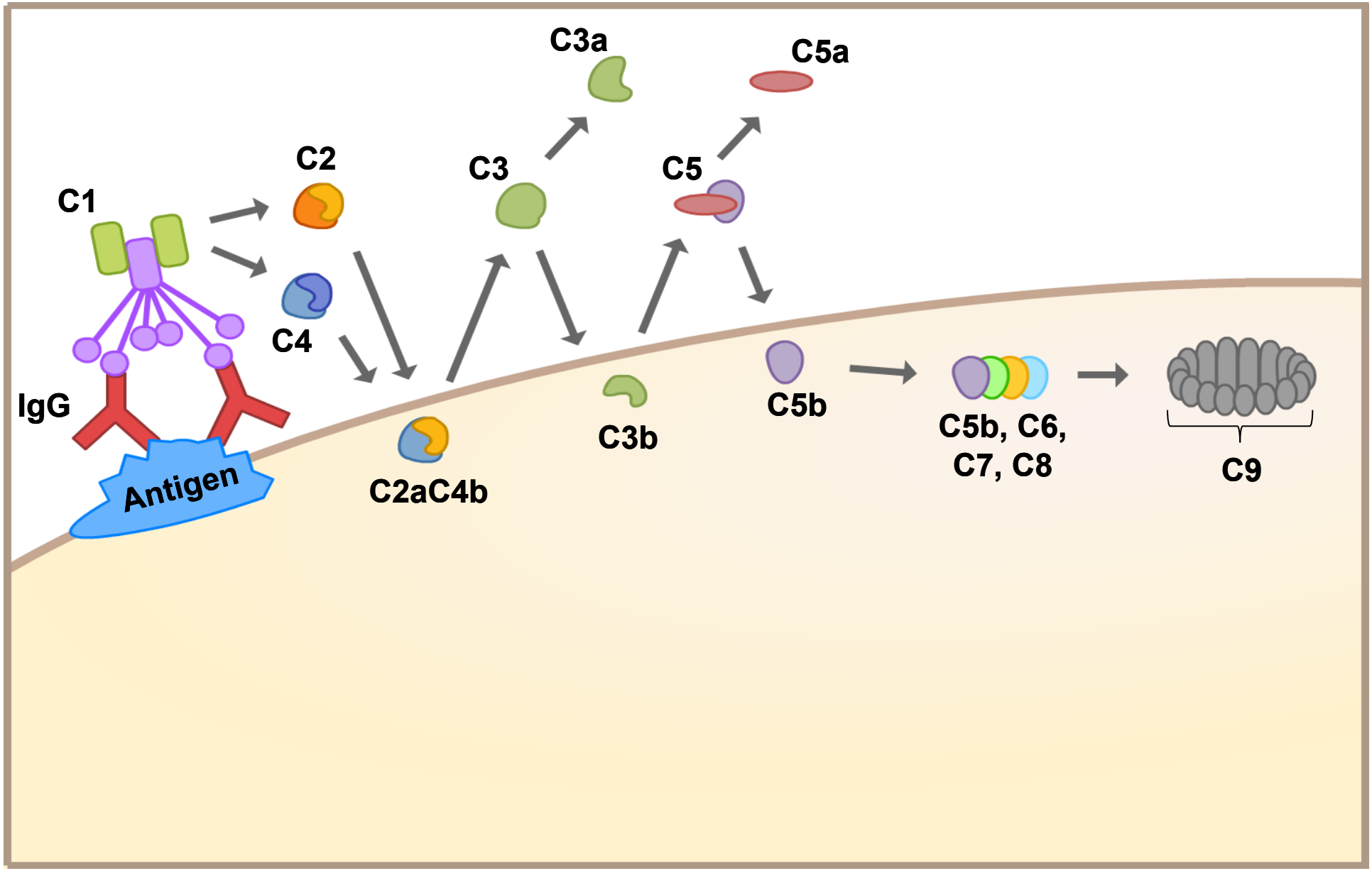
Complement system activation

- Classical pathway:
  - Complexes IgG-antigen, IgM-antigen,
  - C-reactive protein
- Alternative pathwas
  - Lipopolysaccharide of G- bacteria
  - Cell wall of some bacteria
  - Cell wall of the yeasts (zymozan)
  - Aggregated IgA
- Lectin pathway:
  - Mannose and other sacharides

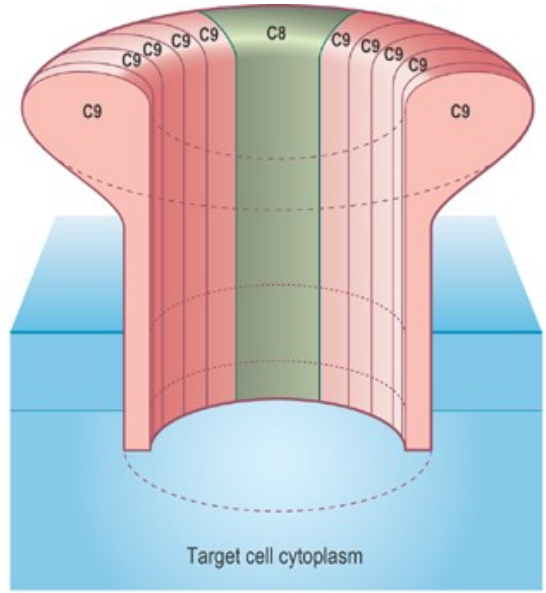
The Complement System



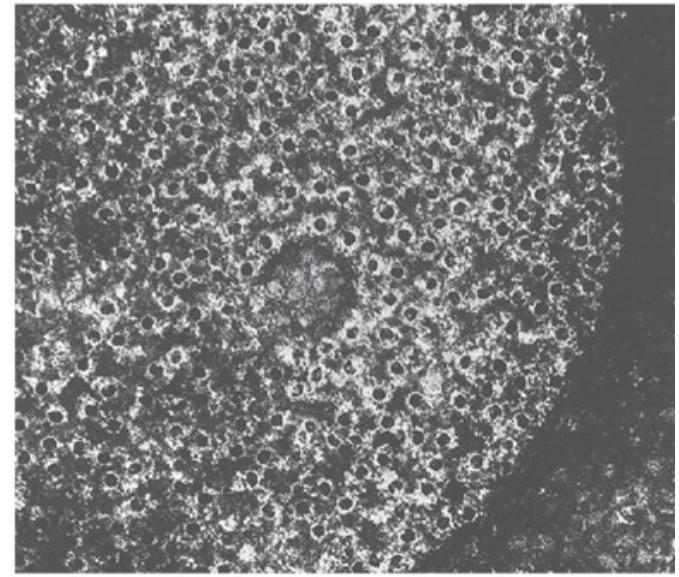
Classical pathway complement activation



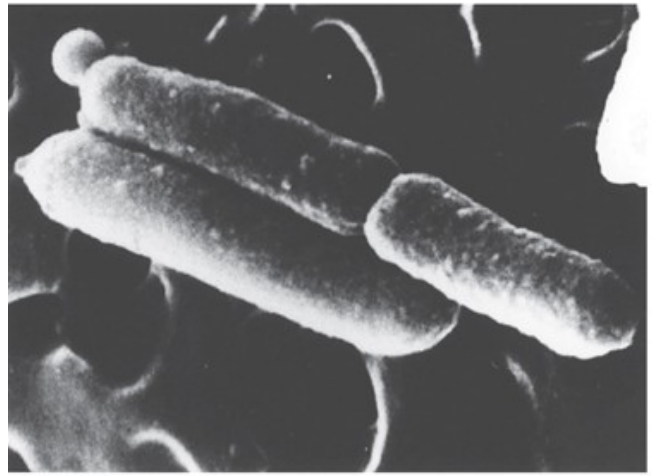
Effect of C9



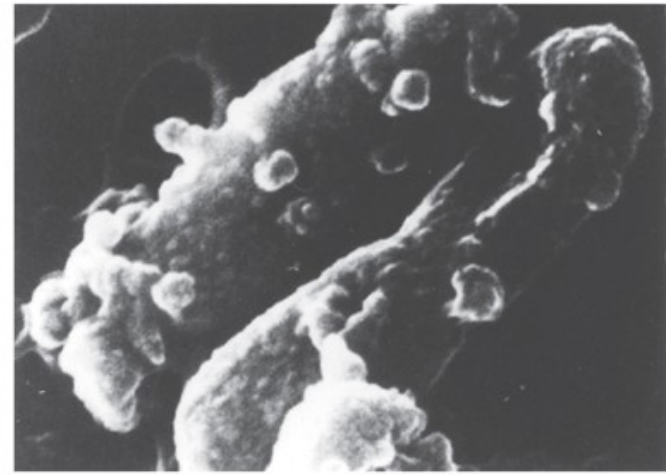
(a)



(b)

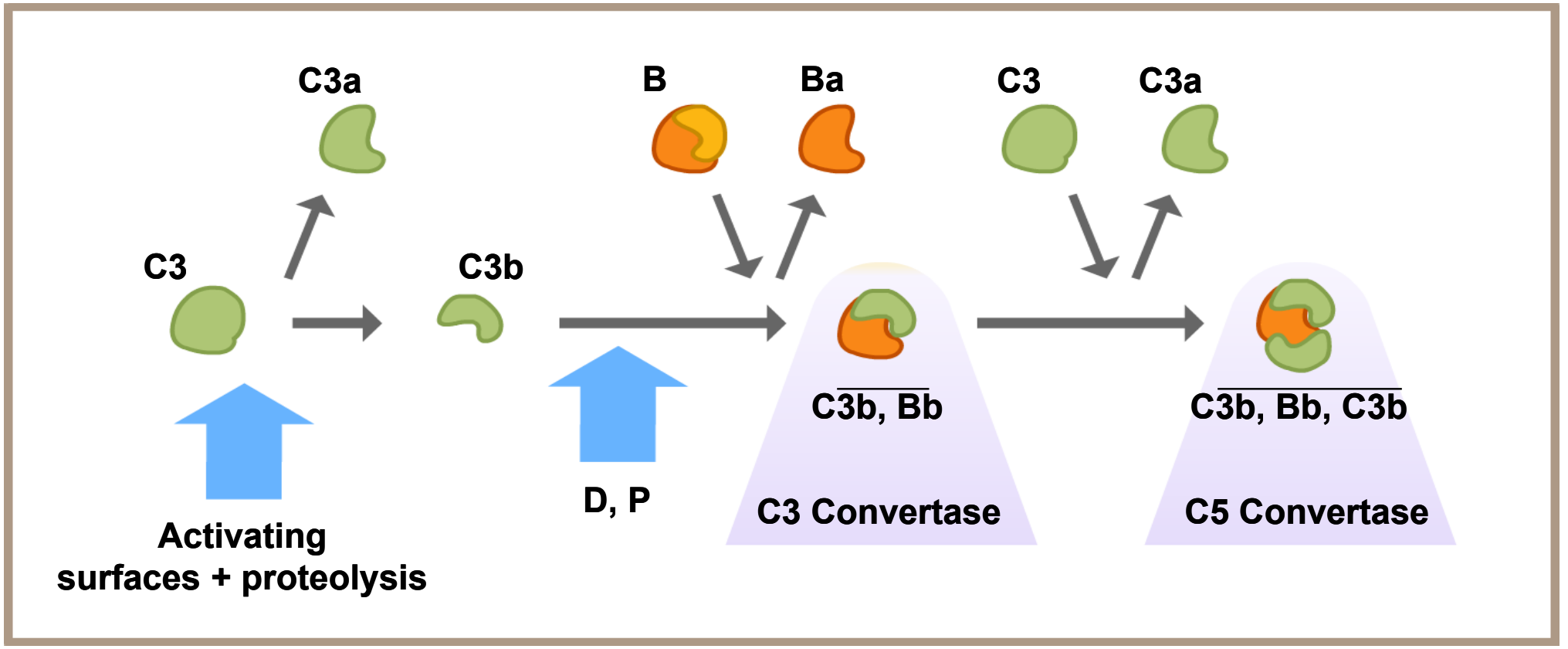


(c)



(d)

Actiation of Alternative Pathway of the Complement system



Biological effects of activated complement system

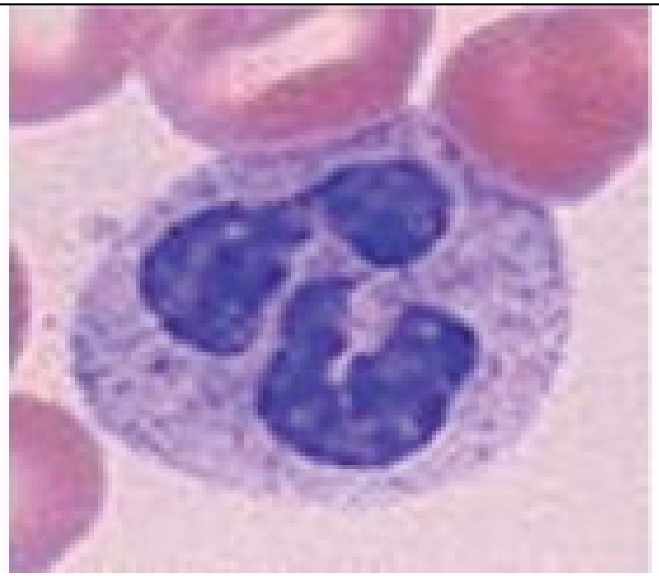
- C9 - cytolytic effect
- C3b - opsonisation
- C3a, C5a – anaphylatoxins, liberation of histamine
- C5a - chemotaxin

Phagocytosis

Phagocytic cells

- Polymorphonuclear granulocytes
- Monocytes + macrophages
- Dendritic cells mainly non-activated cells. After activation they loose most of their phagocytic activity.

Polymorphonuclear granulocyte



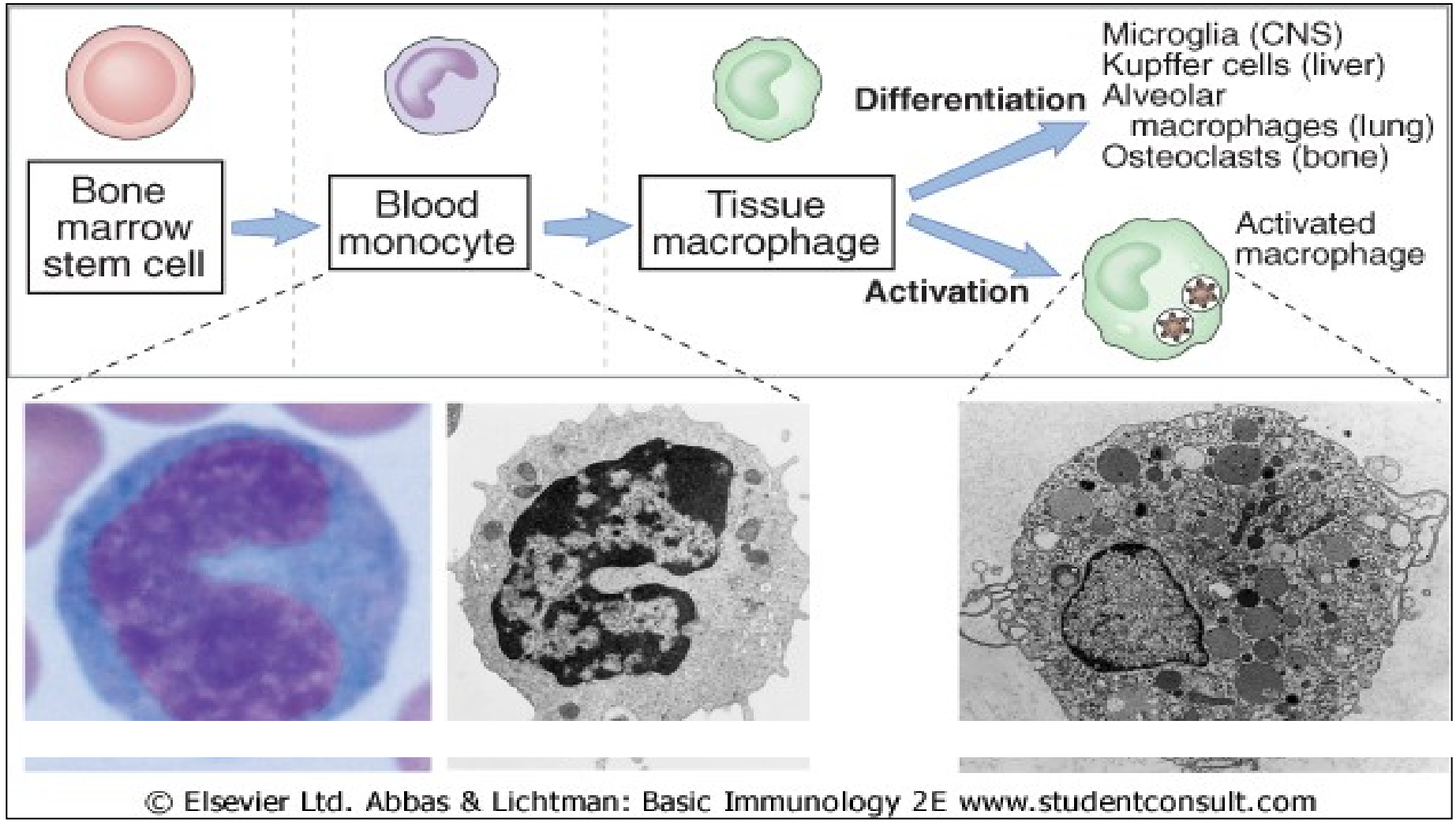
Normal blood count (in adults)

- Erythrocytes: 4-5 x 10^{12}/l
- Thrombocytes: 150-300 x 10^{9}/l
- Leukocytes: 4-9 x 10^{9}/l
  - **Granulocytes: 55-70%**
  - **Eosinophils: 1-4%**
  - **Basophils: 0-1%**
  - **Lymphocytes: 24-40%**
  - **Monocytes: 3-8%**

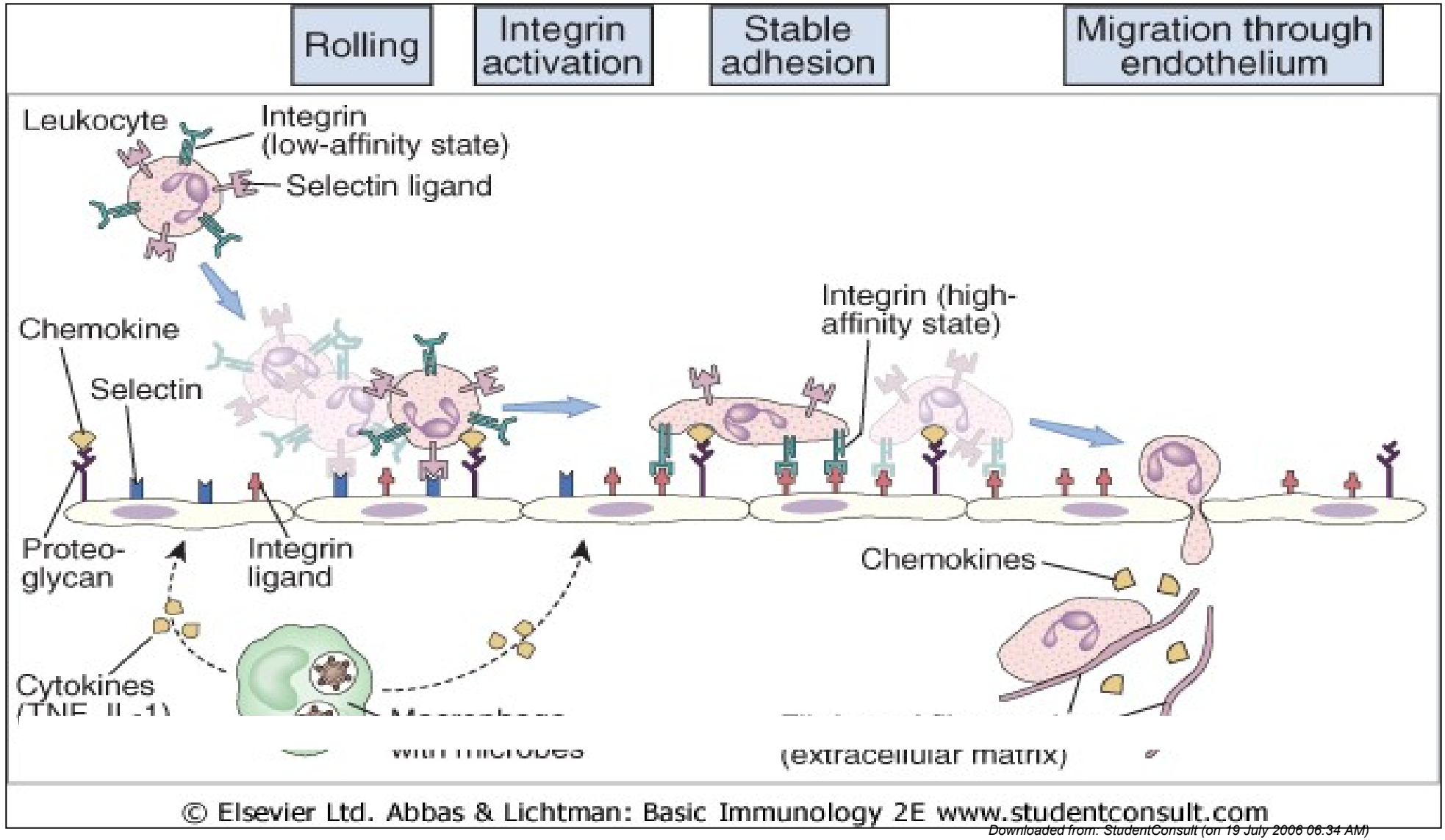
Macrophages

- Derived from blood monocytes.
- Connective tissue macrophages
  - Kupffer cells (liver)
  - Alveolar macrophages (lungs)
  - Microglia (CNS)
  - Osteoclasts (bone)
  - Peritoneal macrophages

Development of macrophages



Extravasation of leukocytes



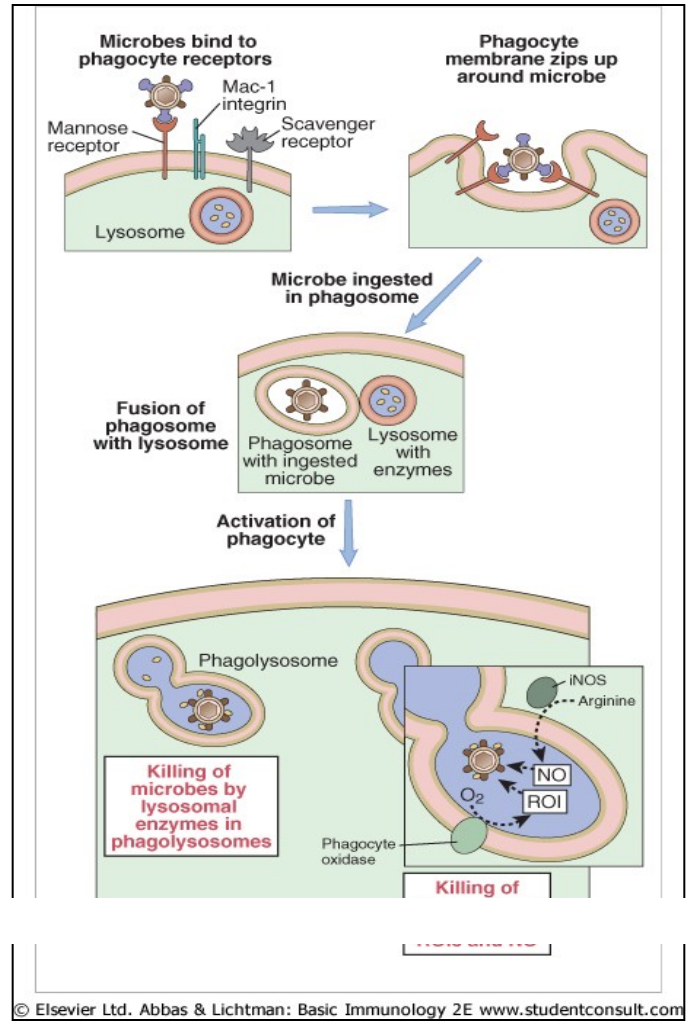
Chemotaxins

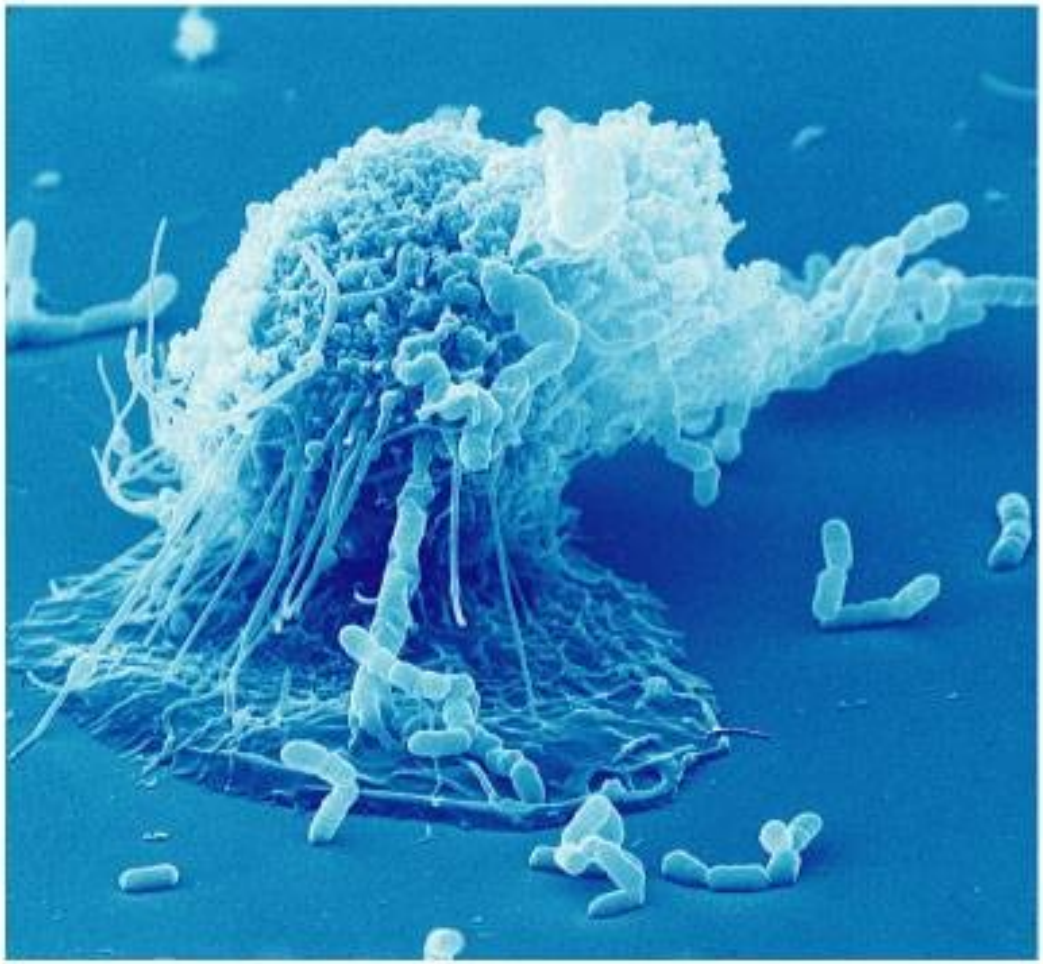
- Attract phagocytic cells
- Products of destroyed cells
- C5a
- IL-7, IL-1
- Leukotriens

Opsonins

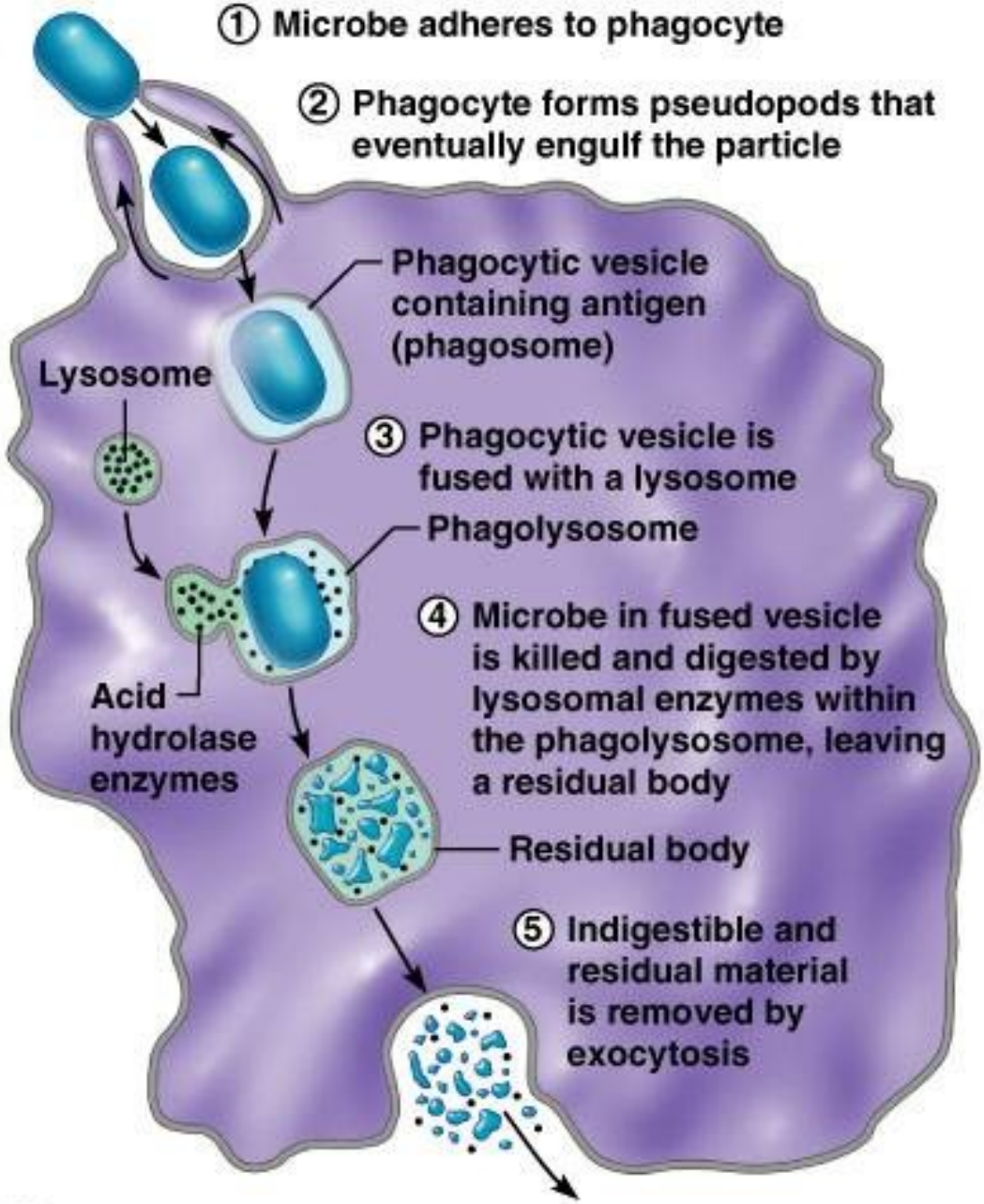
- Substances enhancing phagocytic process by improving attachment of the particle to the phagocytic cell.
- Specific: IgG, (IgM only indirectly by activation of the complement system)
- Non- specific: C3b, fibronectin….

Steps of phagocytosis





(a)



(b)

Killing mechanisms of phagocytic cells

- Reactive metabolites of oxygen (H_2O_2, hydroxyl radical (.OH), superoxide aniont (O_2^-), singletted oxygen ($.O_2$)
- Reactive nitrogem intermediates (NO, NO_2)
- Hydrolases: protease, lipases, DNAses
- Low pH
- Lysozyme
- Lactoferin
- Defensins – antimicrobial polypeptides

Class of mechanism	Specific products
Acidification	pH=~3.5–4.0, bacteriostatic or bacteriocidal
Toxic oxygen-derived products	Superoxide O_2^-, hydrogen peroxide H_2O_2, singlet oxygen $^1O_2$, hydroxyl radical $OH^{\cdot}$, hypohalite OCl^-
Toxic nitrogen oxides	Nitric oxide NO
Antimicrobial peptides	Defensins, cationic proteins
Enzymes	Lysozyme — dissolves cell walls of some Gram-positive bacteria. Acid hydrolases — further digest bacteria
Competitors	Lactoferrin — binds Fe, vitamin B_{12} binding protein

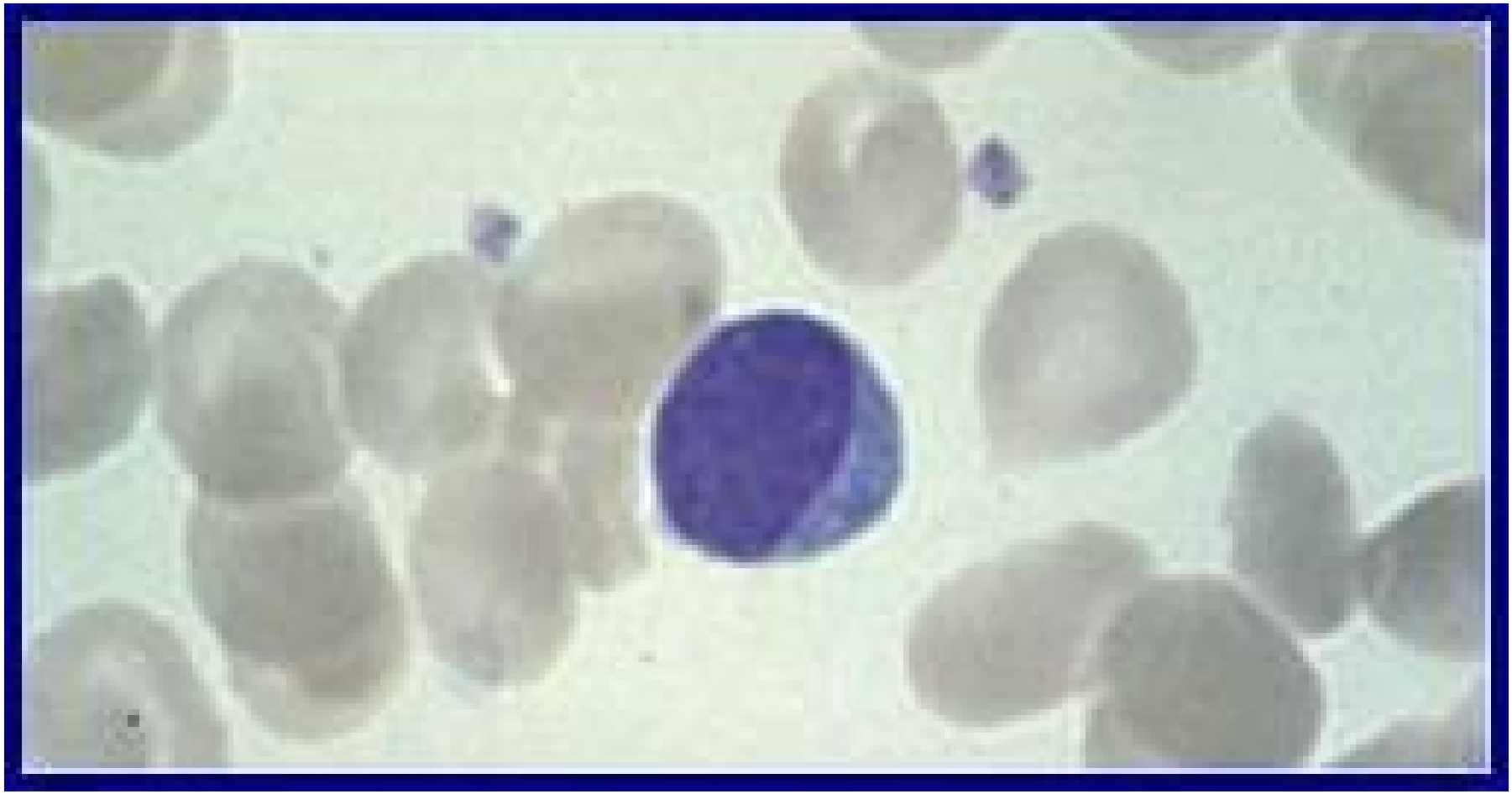
Lysozyme

- Cleaves cell walls of G+ bacteria
- Present in granules of neutrophil granulocytes, in plasma, secretions.

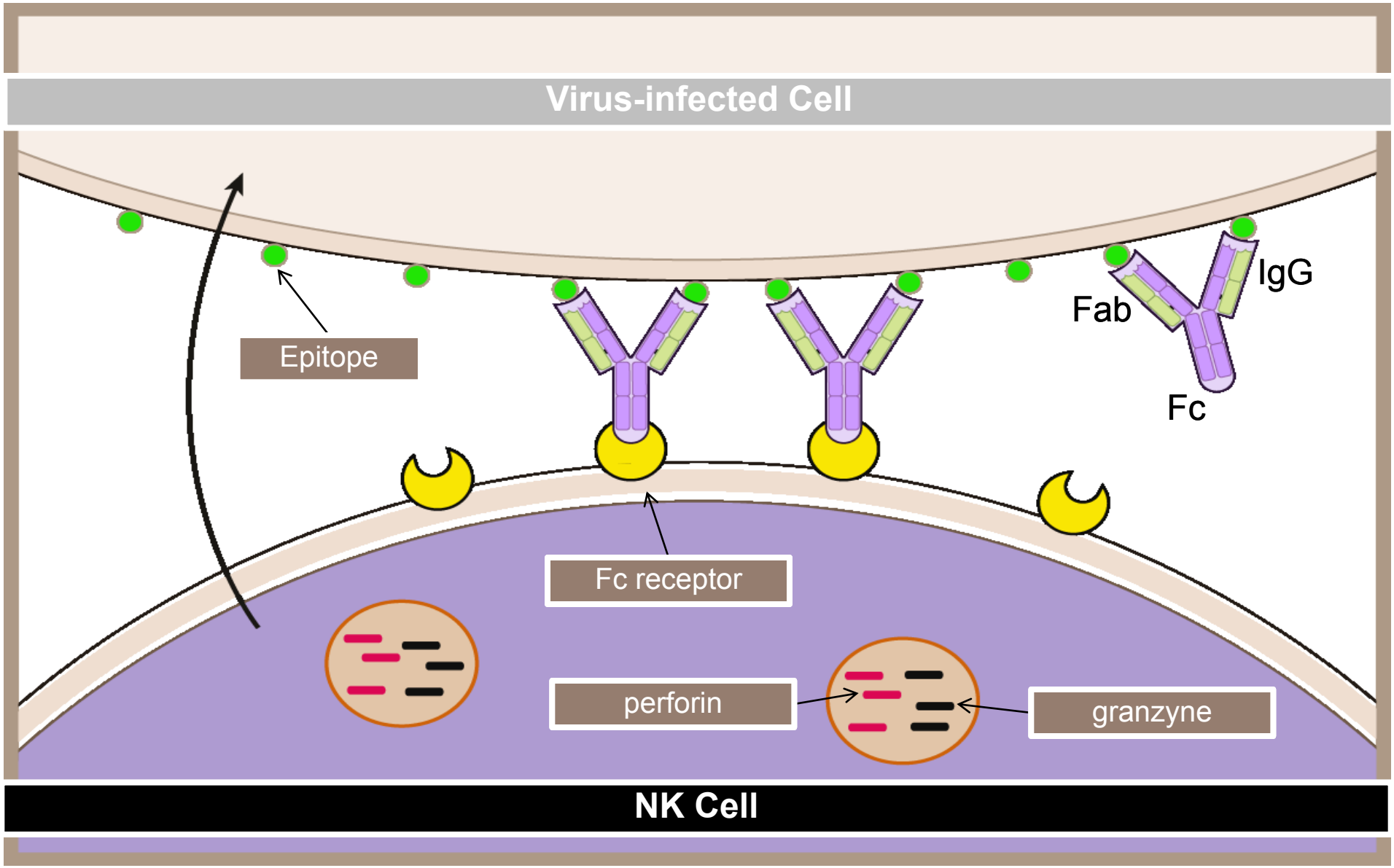
Natural killers (NK cells)

- Originate in non-T non-B lymphocyte lineage.
- Morphologically: large granulated lymphocytes (LGL).
- Recognition of target cells in antigen non-specific.
- Virus infected and tumor cells are killed.
- Target cells are recognised mainly by decreased HLA-I expression.
- Cytotoxic mechanisms are similar to Tc cells: perforin and induction of apoptosis.

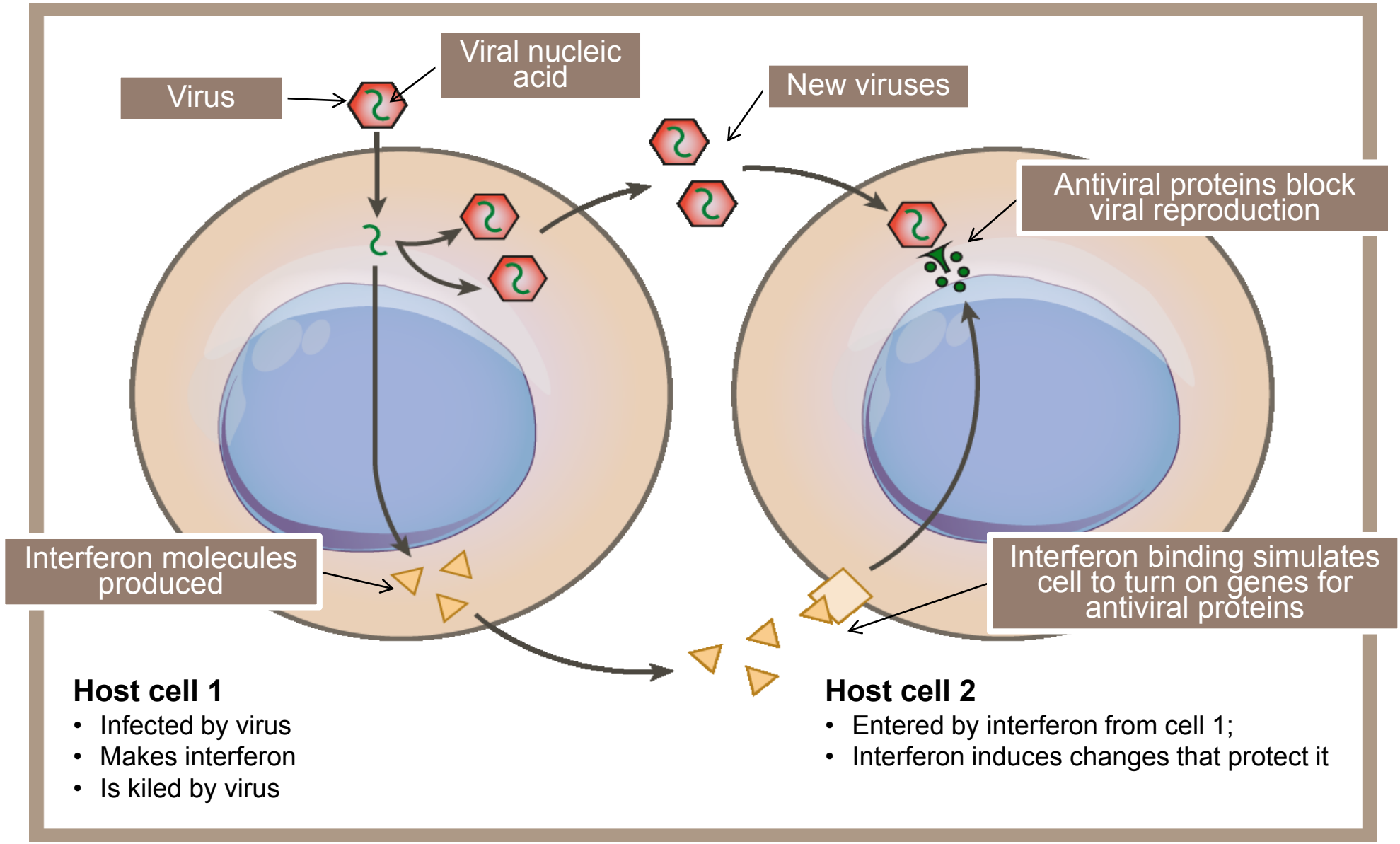
Large granulated lymphocyte



Antibody dependent cellular cytotoxicity (ADCC)



The action of interferon (IFN)



Inflammation

- A rapid response to wounding and infection
- An important consequence of innate immunity
- Cardinal features
  - *rubor* (redness), *calor* (heat), *tumor* (swelling), *dolor* (pain)
- Local consequences of inflammation
  - Increased blood flow to affected area
  - Recruitment of phagocytes to affected area, particularly neutrophils and macrophages
  - Alteration of vascular permeability leading to entry of soluble molecules from the plasma

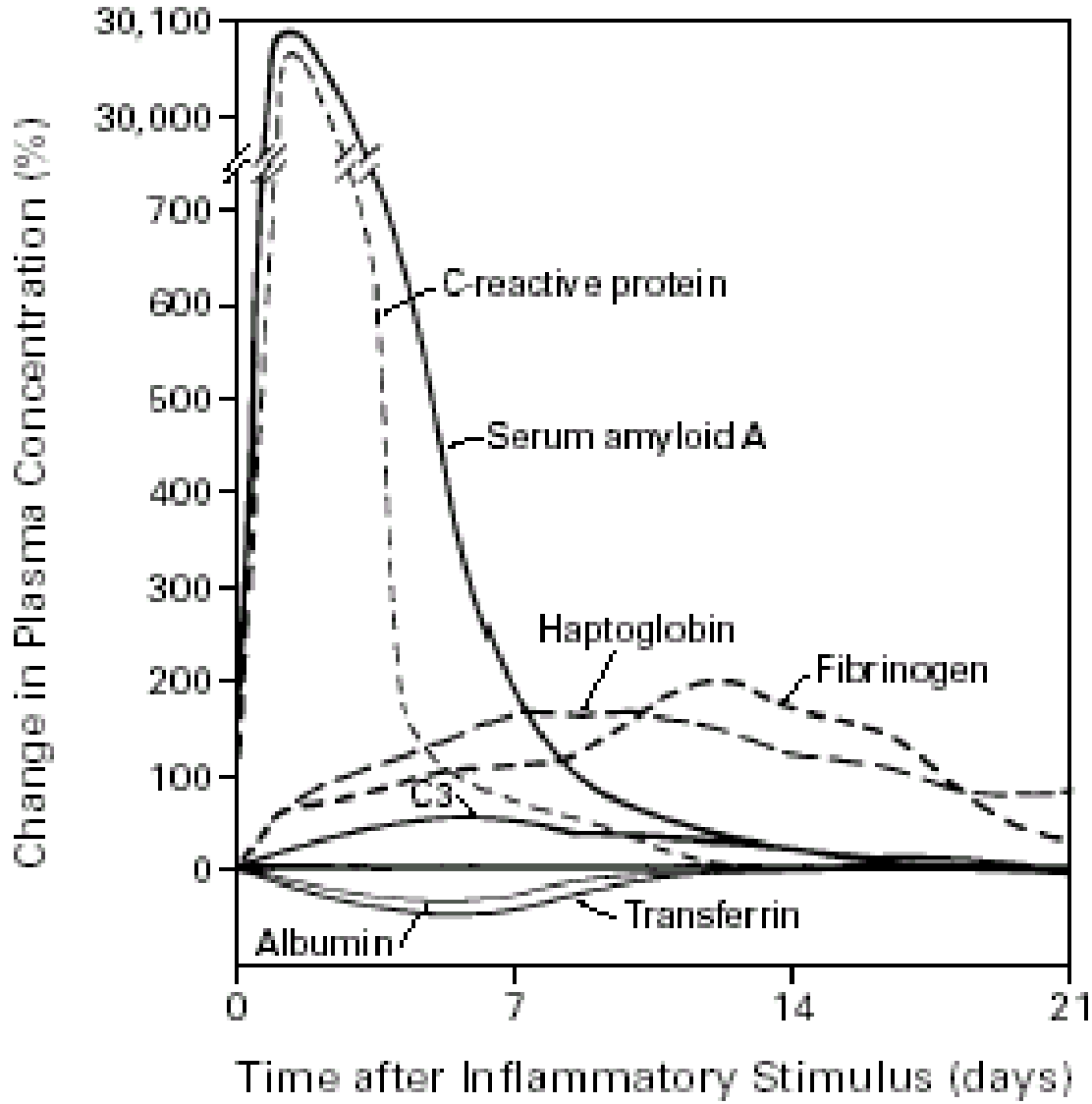
General symptoms and signs of inflammation

- Orchestrated mainly by IL-1, IL-6, TNF-α
- Fever
- Fatigue, somnolence
- Loss of appetite
- Laboratory signs: leukocytosis, increased ESR, increase in accute phase proteins, decreased levels of iron and zinc in serum.

Accute-phase proteins

- Serum levels are increased during inflammation
- Produced by the liver after stimulation by IL-1, IL-6, TNF-α
- Best known: C-reactive protein
- Others: Complement components, A1-AT, fibronectin..

Accute phase response

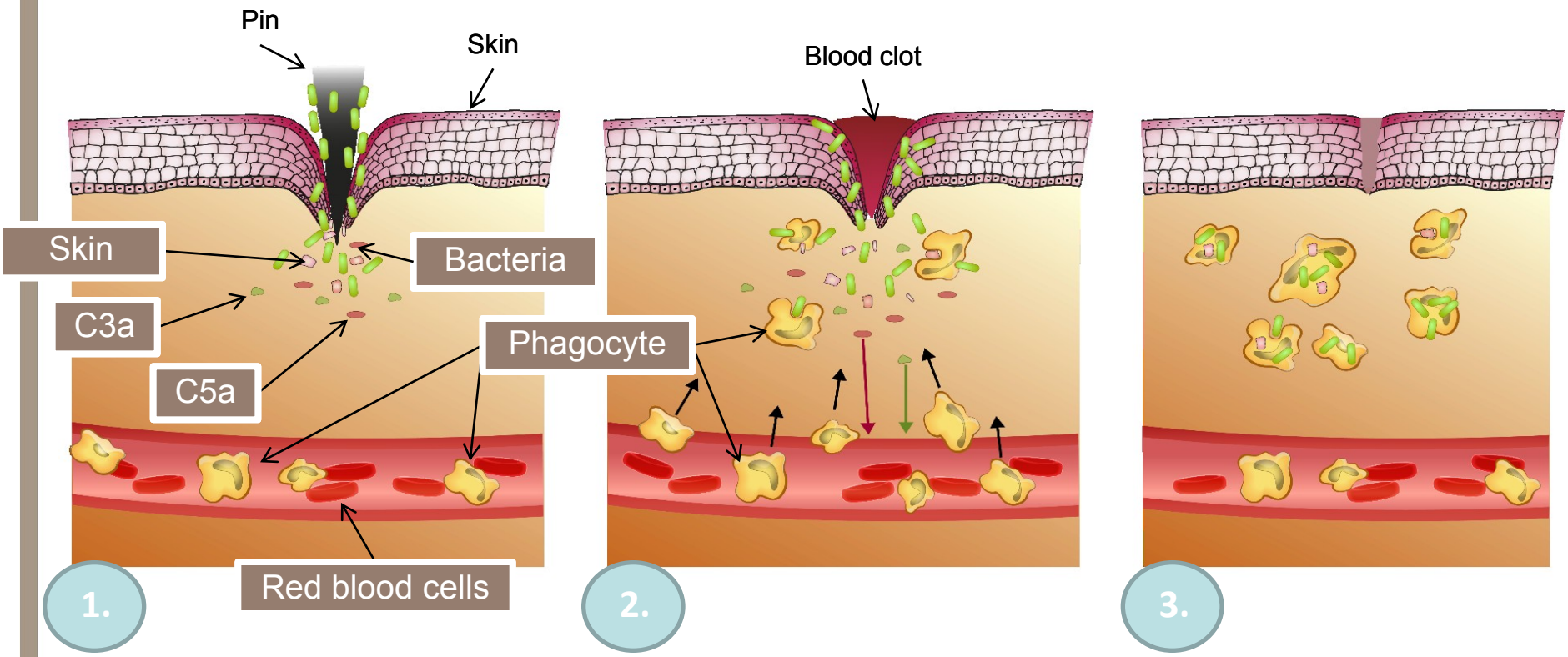


Initiation of inflammatory response

Step 1
Damaged tissues increasing blood flow to the area

Step 2
Histamines cause capillaries to leak, releasing phagocytes and clotting factors into the wound

Step 3
Phagocytes engulf bacteria, dead cells, and cellular debris



Drugs modulating inflammatory process

- Glucocorticoids
- Non-steroidal anti-rheumatic (anti-phlogistic) drugs (acidosalicylic acid, paracetamole,…)
- Antimalarics
- Gold
- Monoclonal antibodies against inflammatory cytokines and adhesion molecules