Immunology

Immunis (latin) → Exempt → Immunity → state of protection from infectious disease

Chinese & Turkish → 15th century → dried crusts from small pox pustules → inhaled into the nostrils OR inserted into small cuts in the skin → Variolation

1718 ► Lady Montagu (British) applied variolation to her own children

1798 ► This technique was improved by Dr. Edward Jenner → Cowpox pustule to eight-year old boy → followed by infection with small pox → did not develop small pox

1881 ► **Louis Pasteur**:

1. Induction of immunity to cholera ►

Aged attenuated strain of *V. cholerae* → Vaccine → (latin 'Vacca' means cow, in honor of Jenner's work with cow pox)

2. Heat attenuated Bacillus anthracis → administered to sheep → prevented anthrax

3. 1885 ► Anti-rabis → He administered 1st vaccine to human → Young boy Joseph Meister

TABLE 1-1 Nobel Prizes for immunologic research

Year	Recipient	Country	Research
1901	Emil von Behring	Germany	Serum antitoxins
1905	Robert Koch	Germany	Cellular immunity to tuberculosis
1908	Elie Metchnikoff Paul Ehrlich	Russia Germany	Role of phagocytosis (Metchnikoff) and antitoxins (Ehrlich) in immunity
1913	Charles Richet	France	Anaphylaxis
1919	Jules Border	Belgium	Complement-mediated bacteriolysis
1930	Karl Landsteiner	United States	Discovery of human blood groups
1951	Max Theiler	South Africa	Development of yellow fever vaccine
1957	Daniel Bovet	Switzerland	Antihistamines
1960	F. Macfarlane Burnet Peter Medawar	Australia Great Britain	Discovery of acquired immunological tolerance
1972	Rodney R. Porter Gerald M. Edelman	Great Britain United States	Chemical structure of antibodies
1977	Rosalyn R. Yalow	United States	Development of radioimmunoassay
1980	George Snell Jean Daussct Baruj Benacerraf	United States France United States	Major histocompatibility complex
1984	Cesar Milstein Georges E. Köhler	Great Britain Germany	Monoclonal antibody
	Niels K. Jerne	Denmark	Immune regulatory theories
1987	Susumu Tonegawa	Japan	Gene rearrangement in antibody production
1991	E. Donnall Thomas Joseph Murray	United States United States	Transplantation immunology
1996	Peter C. Doherty Rolf M. Zinkernagel	Australia Switzerland	Role of major histocompatibility complex in antigen recognition by by T cells

2011	Bruce A. **Beutler (USA)** Jules A. **Hoffmann** (**France**)	Discoveries concerning the activation of innate immunity
	Ralph M. **Steinman (USA)**	Discovered the role of dendritic cell in adaptive immunity

Theories of Immunity: production of antibody ►

1. Selective theory
2. Instructional theory
3. Combined clonal-selection theory

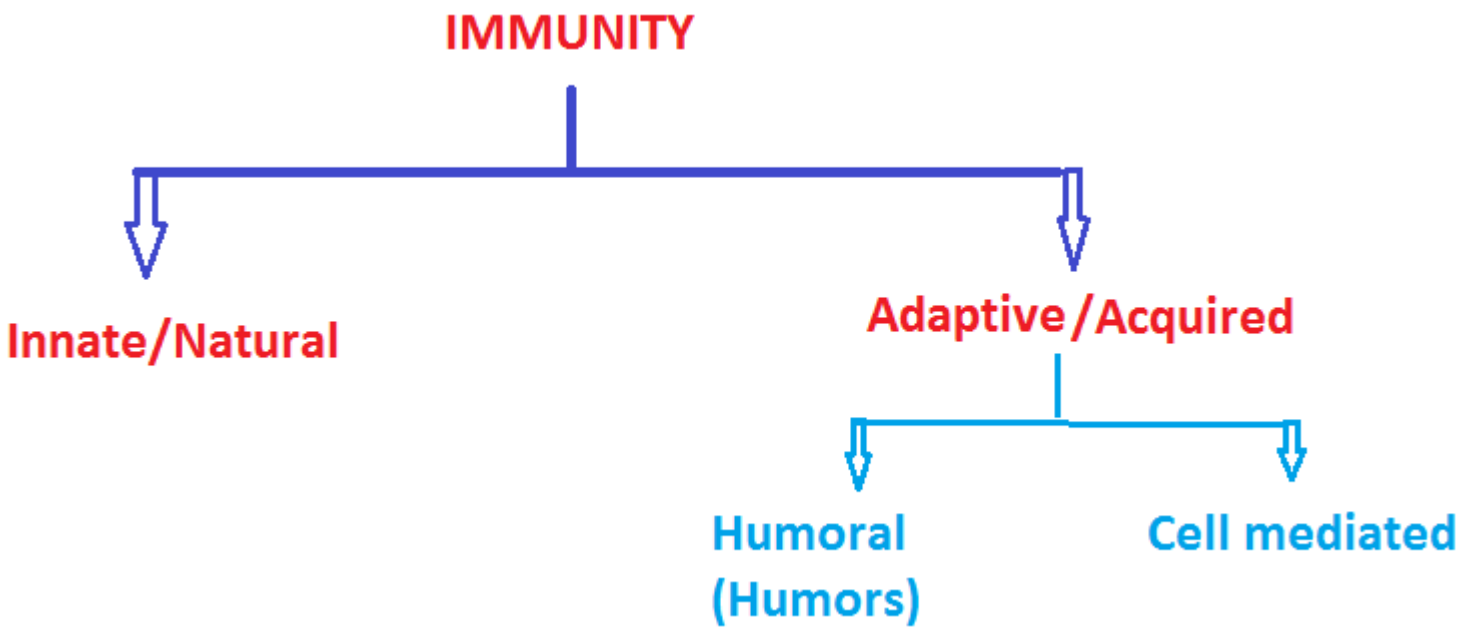


TABLE 1-3 Comparison of adaptive and innate immunity

	Innate	Adaptive
Response time	Hours	Days
Specificity	Limited and fixed	Highly diverse, improves during the course of immune response
Response to repeat infection	Identical to primary response	Much more rapid than primary response
Found in:	All multicellular organisms	Vertebrates only
Substances that trigger:	A limited number of pathogen-associated molecular patterns (PAMPs)	Virtually any component of pathogens
Receptors:	A limited number of Pattern Recognition Receptors (PRRs) expressed on many cells types	Highly variable receptors of 2 types: antibody made by B cells and TCR made by T cells

Innate Immunity

Innate immune effector mechanisms

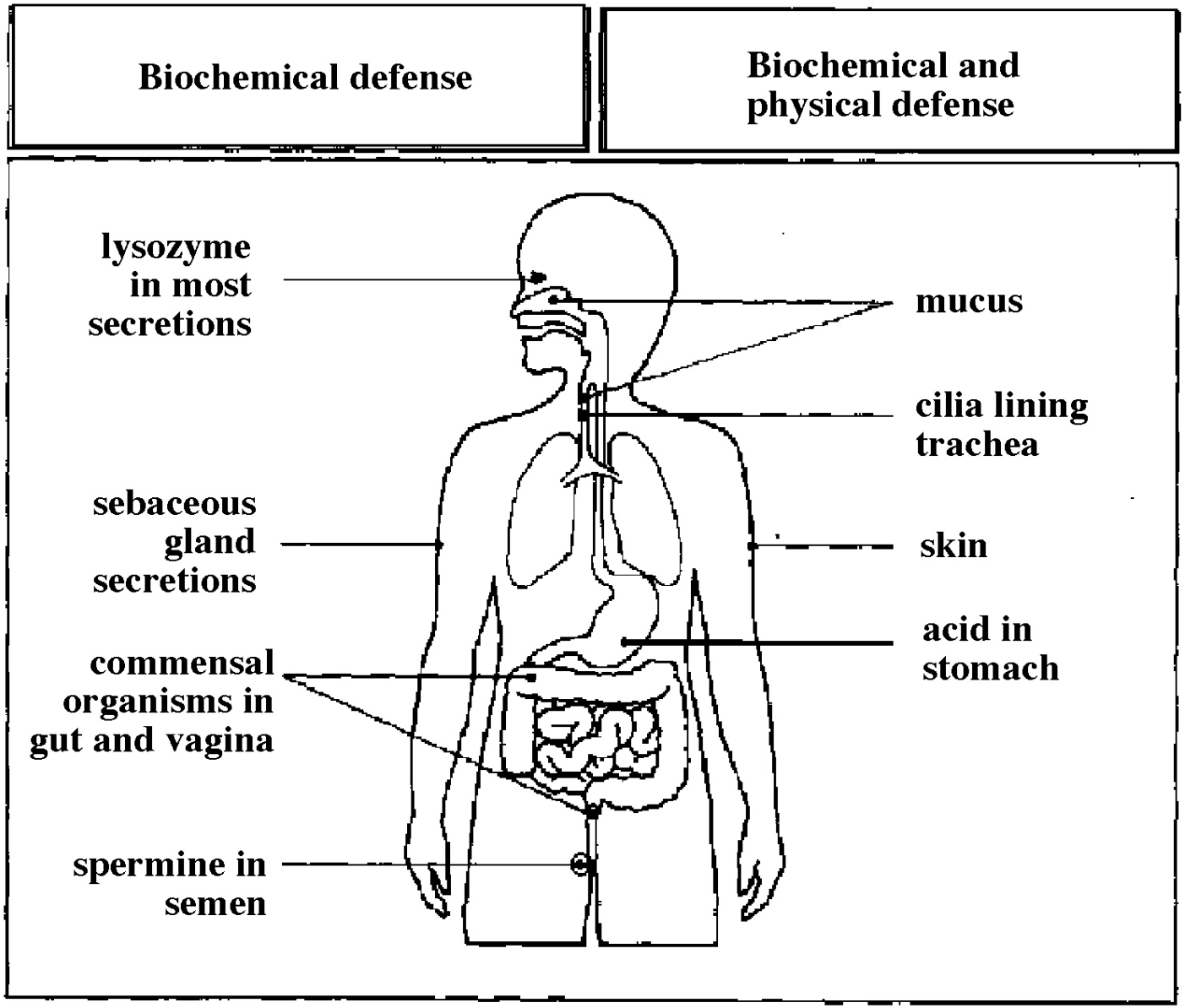
- Physical and biochemical barriers (defensins)
- Phagocytosis and reactive oxygen
- Cell autonomous defenses
  - Apoptosis
  - Interferons and PKR

Innate immune recognition

- Discovery of the Toll-like receptors
- Mammalian TLRs and their ligands
- Non-TLR recognition of PAMPs

Connections between adaptive and innate immunity

Physical & Biochemical barriers



Innate Immunity

Type	Mechanism
Anatomic barriers:	
Skin (epidermis [outer] & dermis [inner])	Mechanical barrier retards entry of microbes. Acidic environment (pH 3-5) retards growth of microbes.
Mucous membrane	Normal flora compete with microbes for attachment sites and nutrients.
Physiological barriers:	
Temperature	Normal body temperature inhibit growth of some pathogens.
Low pH	Acidity of stomach contents kills most ingested organism.
Phagocytic/endocytic: barriers	**Monocytes, neutrophils, tissue macrophages**
Inflammatory barriers:	Tissue damage and infection induced leakage of vascular fluid containing serum protein with antimicrobial activity infux of phagocytes

Immunity in multi-cellular organism

Taxonomic group	Innate immunity	Adaptive immunity	Phagocytosis	Antimicrobial peptides	Graft rejection	T and B cells	Antibodies
Higher plants	+	-	-	+	-	-	-
Invertebrates:							
Porifera (sponges)	+	-	+	?	+	-	-
Annelids (earth worms)	+	-	+	?	+	-	-
Arthropods (insects, etc.)	+	-	+	+	?	-	-
Vertebrates:							
Elasmobranches (sharks, rays)	+	+	+	+	+	+	+ (IgM)
Teleost fish and bony fish (Salmon)	+	+	+	Probable	+	+	+ (IgM)
Amphibians	+	+	+	+	+	+	+ (2 or 3 classes)
Reptiles	+	+	+	+	+	+	+ (3 classes)
Birds	+	+	+	+	+	+	+ (3 classes)
Mammals	+	+	+	+	+	+	+ (7 or 8 classes)

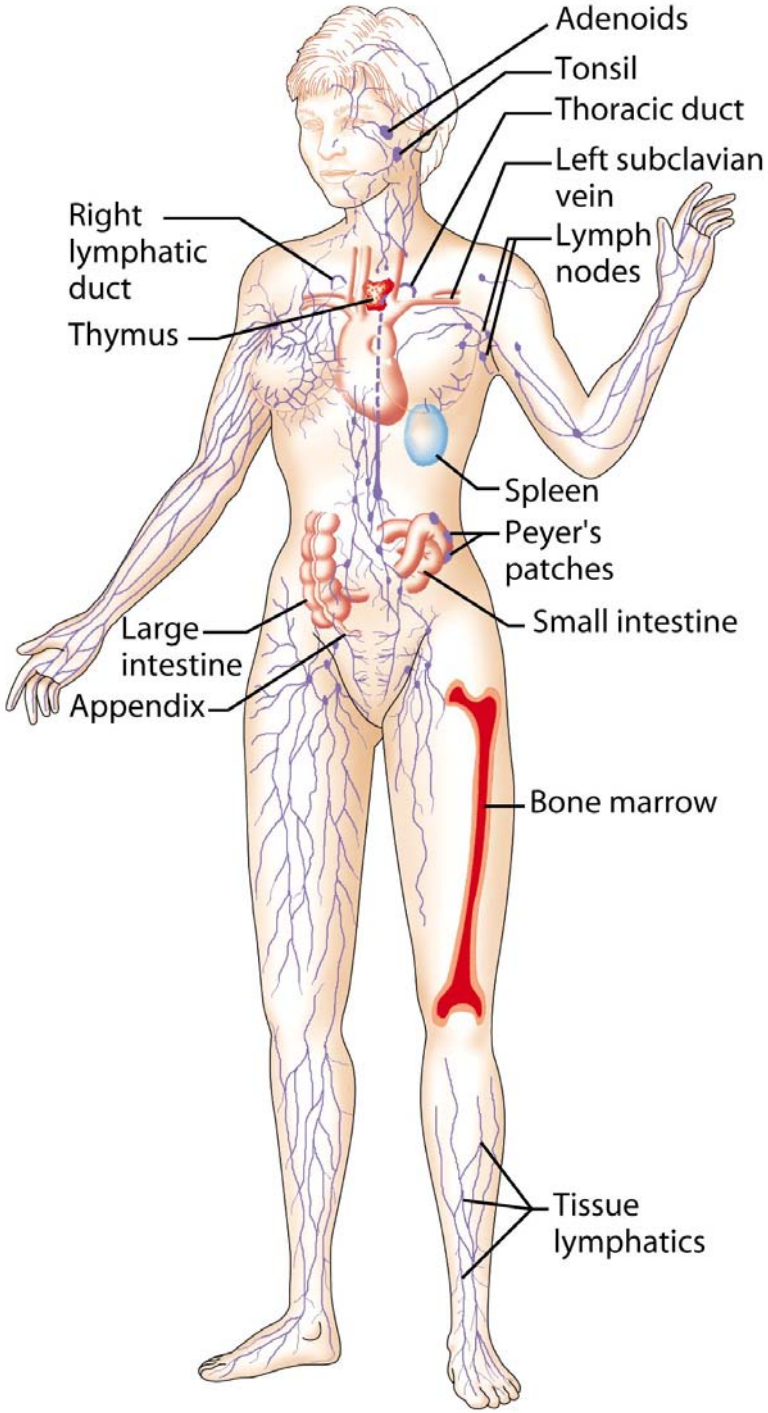
The cells of the immune system spend much of their time in lymphoid organs. They develop (arise) in primary lymphoid organs, and they interact with antigens in secondary lymphoid organs.

Thymus: primary lymphoid organ for T cell development.

Bone marrow: primary lymphoid organ for B cell development.

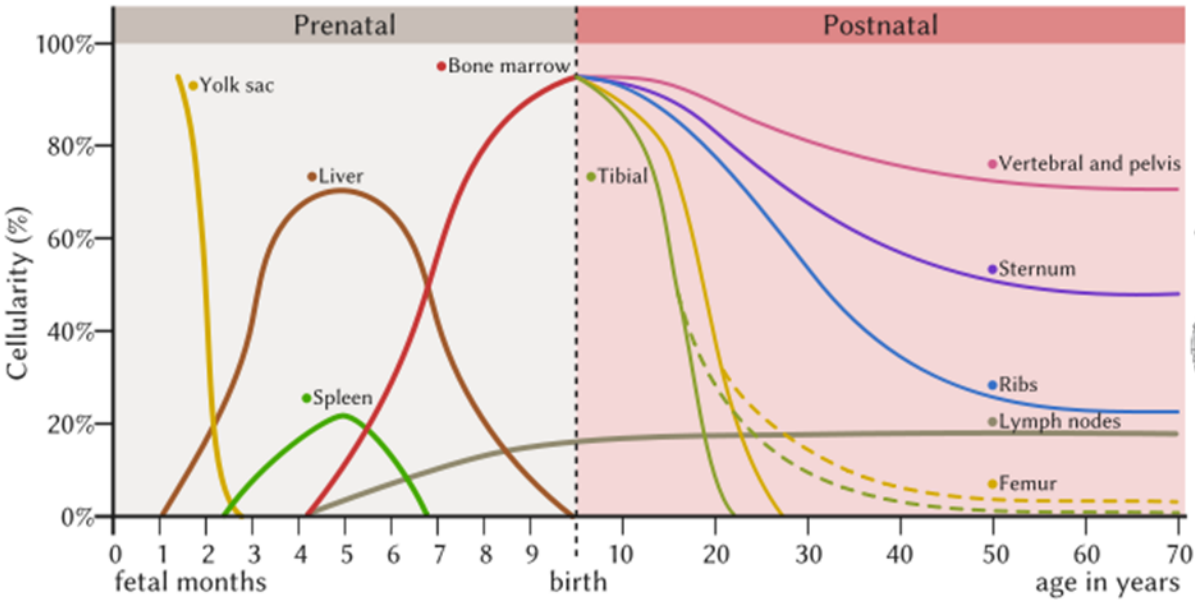
Lymph nodes: collect antigens from tissues

Spleen: collects antigens from blood stream



Hematopoiesis: The formation and development of red and white blood cells.

Pluripotent: able to differentiate in various ways into different cell types.



Normal adult blood cell counts:

RBC: 5×10^6 cells/mm^3

Platelets: 2.5×10^5 cells/mm^3

Leukocytes: 7.3×10^3 cells/mm

Neutrophil: 50-70 %
Lymphocyte : 20-40%
Monocyte: 1-6%
Eosinophil: 1-3%
Basophil: <1%

Hematopoiesis: (1) During 1st week of development begins in embryonic yolk-sac

(2)Yolk sac stem cells ►primitive erythroid cells containing embryonic hemoglobin.

(3) **In the third month of gestation, hematopoietic stem cells migrates from yolk sac to fetal liver → then to spleen.**

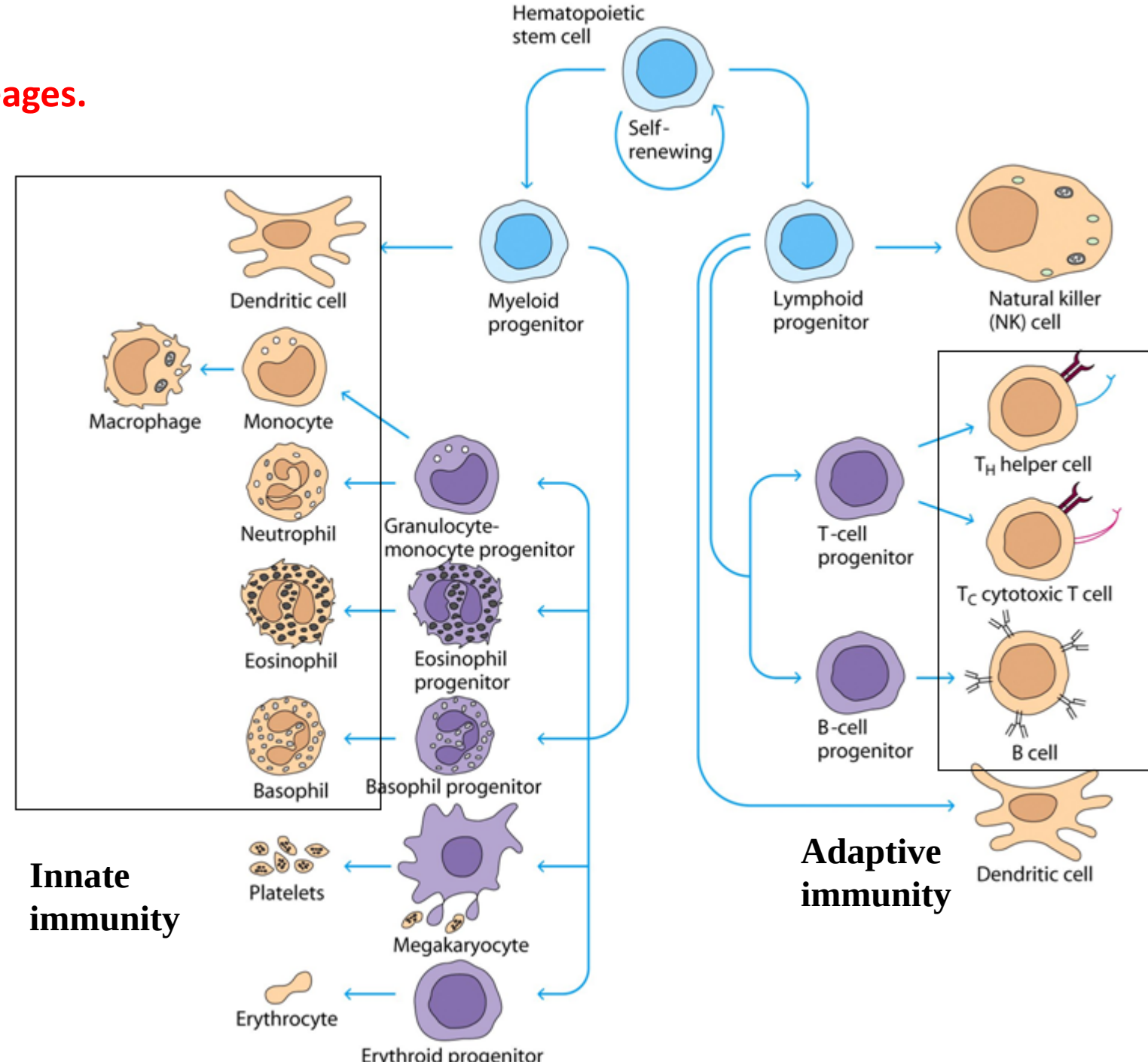
(4) Third to 7th months of gestation, Hematopoiesis occurs in spleen and liver.

(5) After that differentiation of HSCs in bone marrow.

(6) by birth, there is little or no hematopoiesis in liver and spleen.

Blood cells lineages.

Most blood cells act to fight infection



Inflammation

"rubor et tumor cum calore et dolore"

(redness and swelling with heat and pain)

--Cornelius Celsus in De Medicina, 1st century A.D.

later "functio laesa" (disturbance of function) was added

Roman Physician Aulus Cornelius Celsus →

Cardinal signs of inflammation:

→ Dolor (Pain)

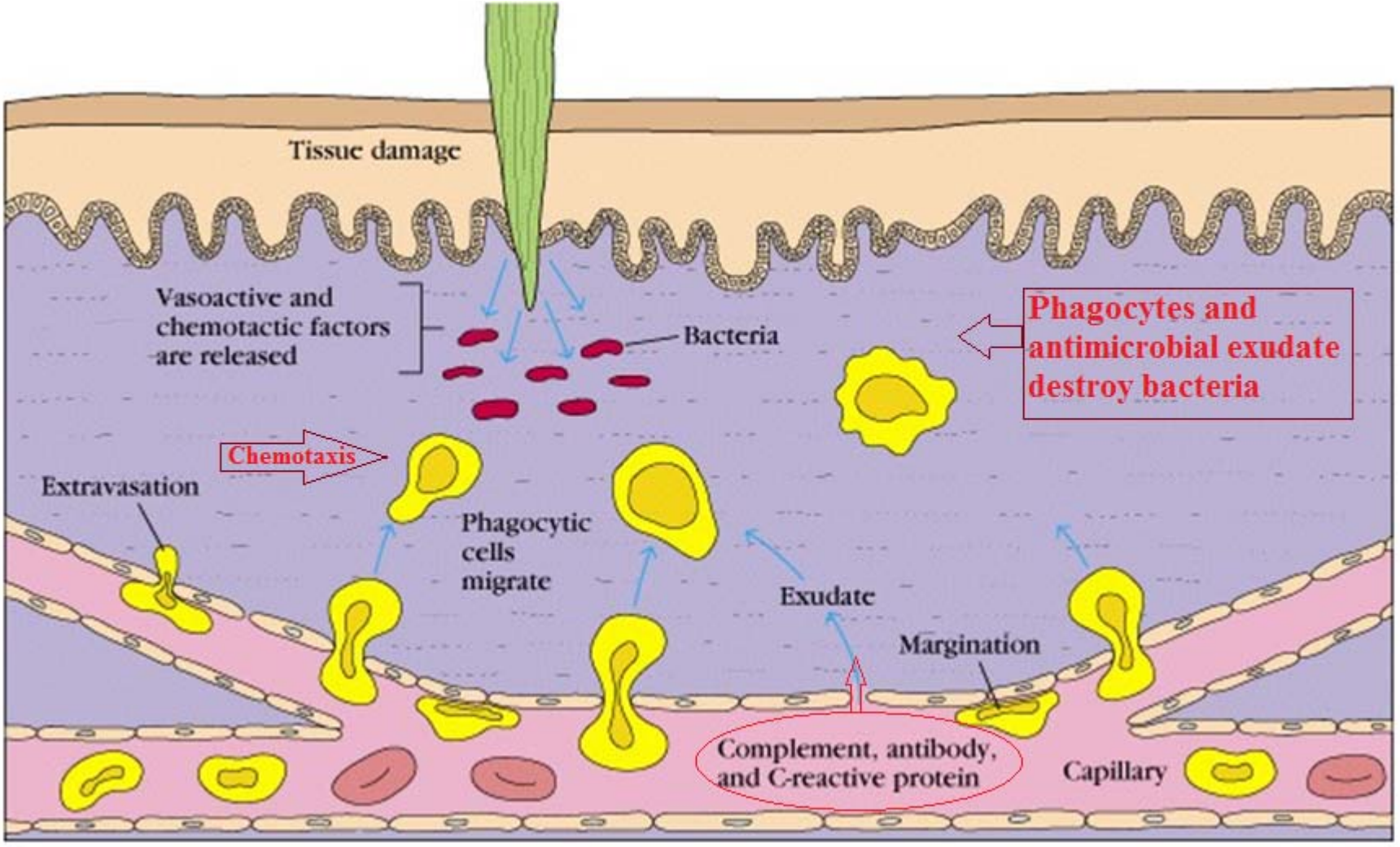
→ Calor (Heat)

→ Rubor (Redness)

→ Tumor (Swelling)

→ Functio laesa (Loss of function)

Inflammation occurs when injured tissues release mediators that promote vasodialation (increased blood flow) and chemotaxis (directed migration) of leukocytes.



Infection can induce inflammation, but even sterile injuries can be sufficient to induce inflammation.

Inflammation causes blood cells to move from blood stream to site of injury.
Blood cells (leukocytes) travel from the blood stream into tissues by a process known as extravasation or diapedesis.
Blood cells can also be attracted to sites of infection by products produced by pathogens, as well as by chemoattractants made by host (chemokines, inflammatory meditators).

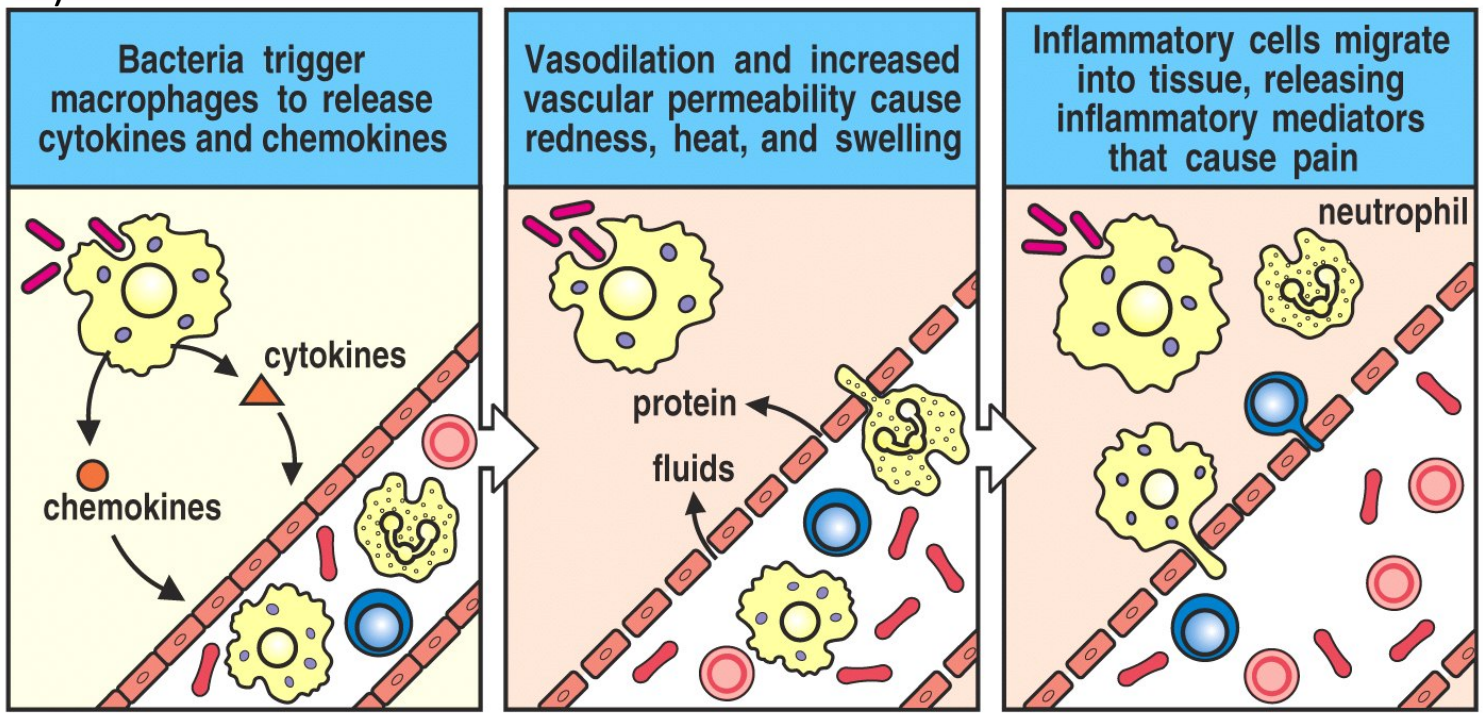
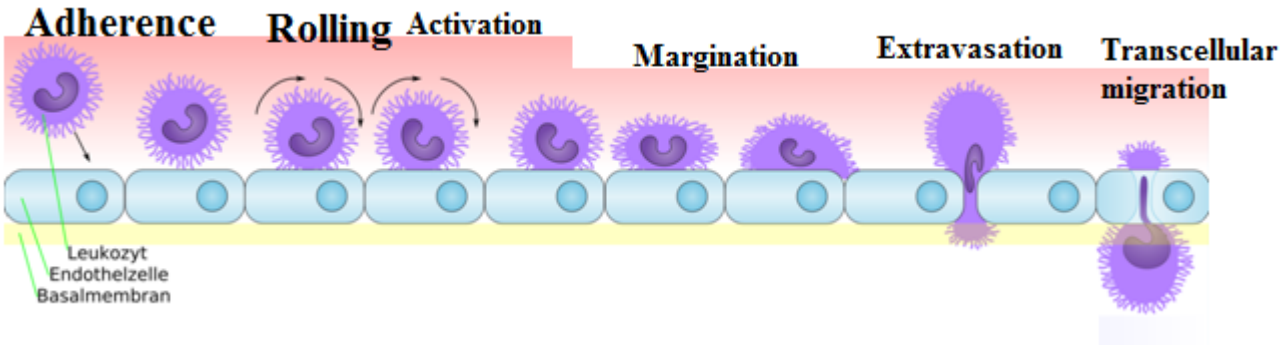


Figure 1-12 Immunobiology, 6/e. (© Garland Science 2005)

Leukocyte extravasation/*diapedesis*, is the movement of leukocytes out of the circulatory system and towards the site of tissue damage or infection.



Edema occurs when an excessive volume of fluid accumulates in the tissues, either within cells (cellular edema) or within the collagen-mucopolysaccharide matrix distributed in the interstitial spaces (interstitial edema)

Inflammation can be induced by immune recognition of infection or tissue damage (usually good)

Inflammation can be induced by immune recognition that is hypersensitive to environmental components or auto-inflammatory or autoimmune (=disease)

Acute inflammation: influx of white blood cells and fluid from blood to fight infection and aid tissue repair

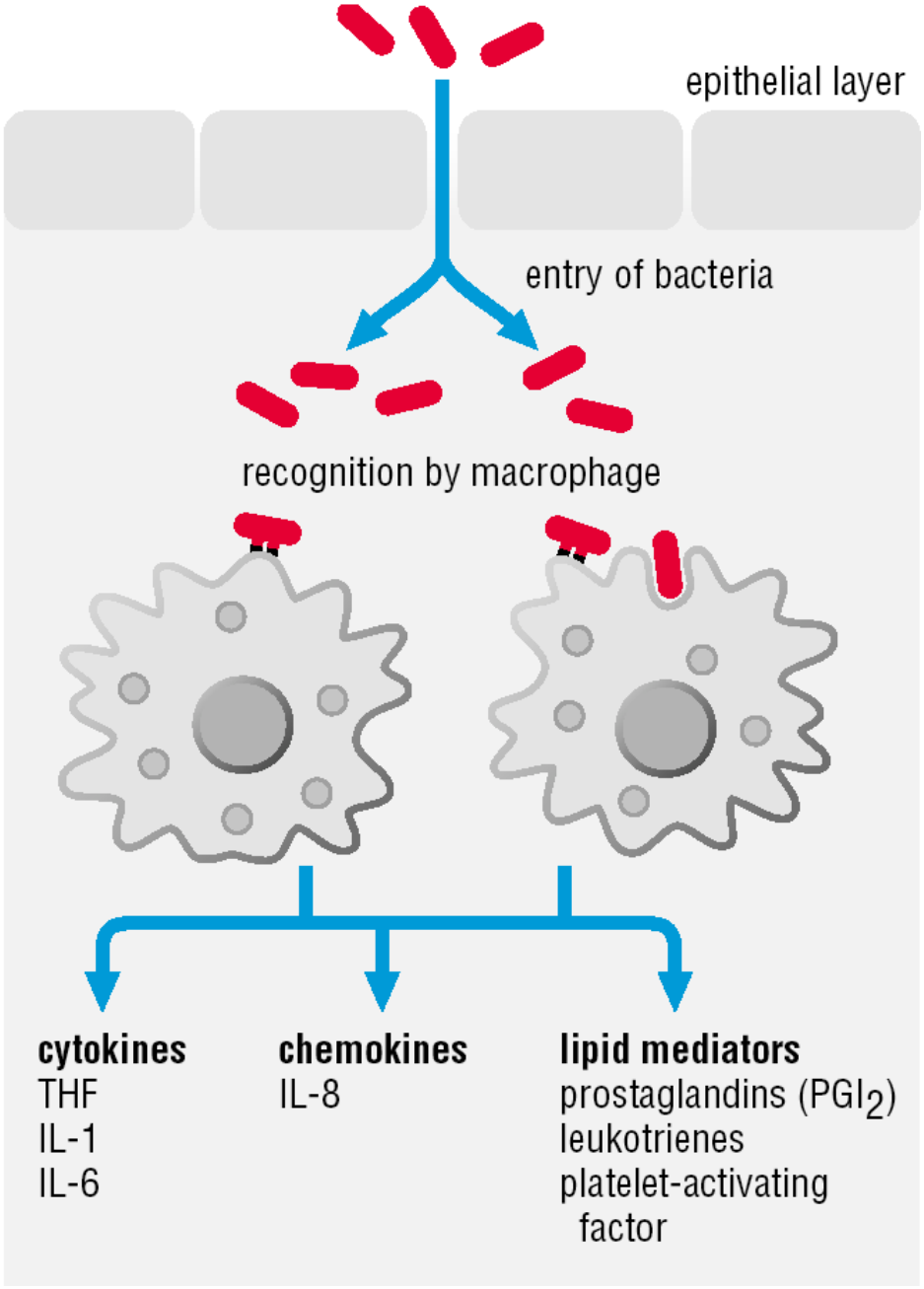
Chronic inflammation: inducer of inflammation is not removed ►

Leads to tissue damage and loss of tissue function (joint destruction, lung fibrosis, etc.)

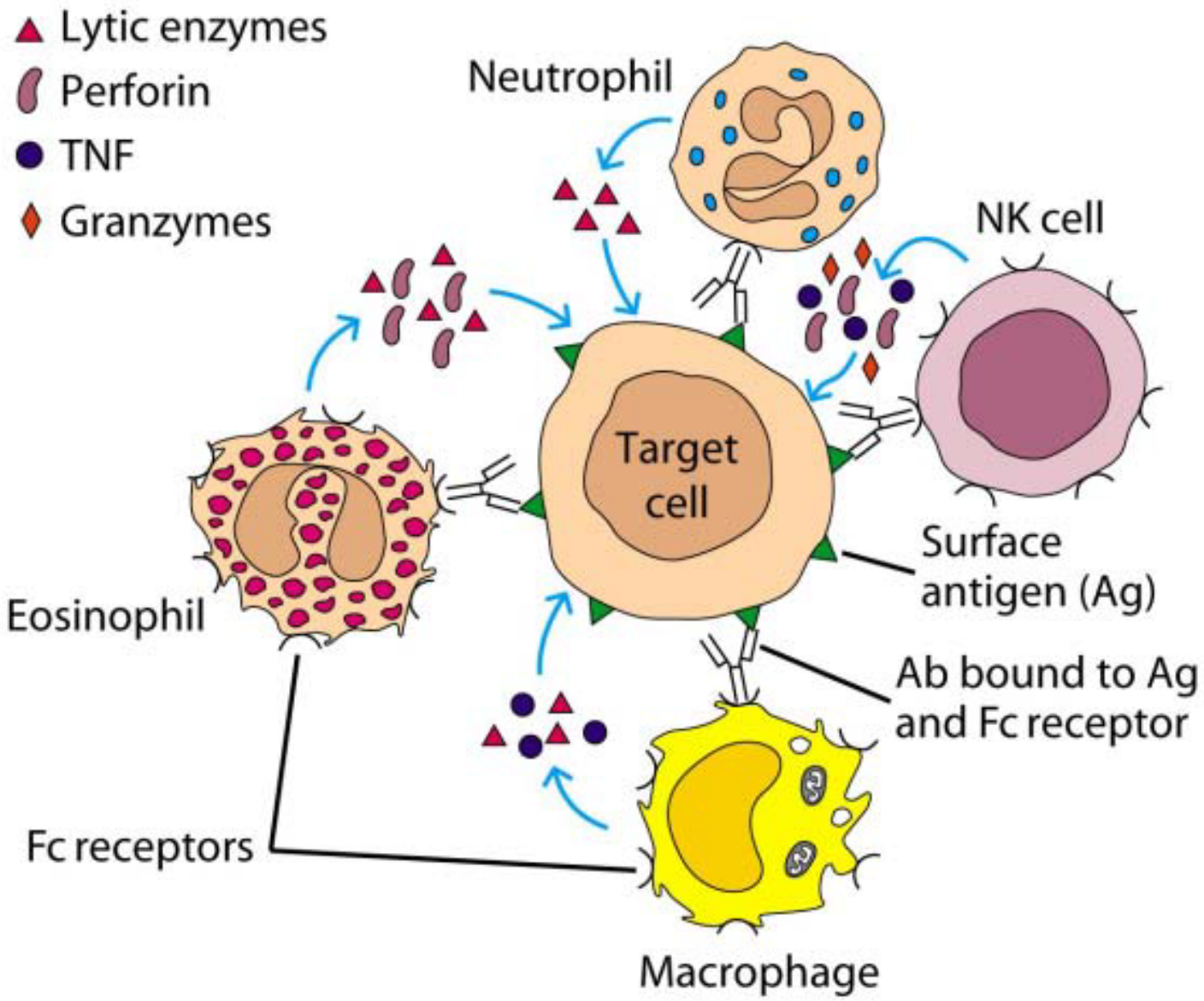
Current view: aggressively fight inflammation in certain chronic diseases to decrease/delay progressive loss of function

Current research suggests that inflammation may play an important role in common chronic diseases including atherosclerosis, type 2 diabetes, neuro degeneration, and cancer

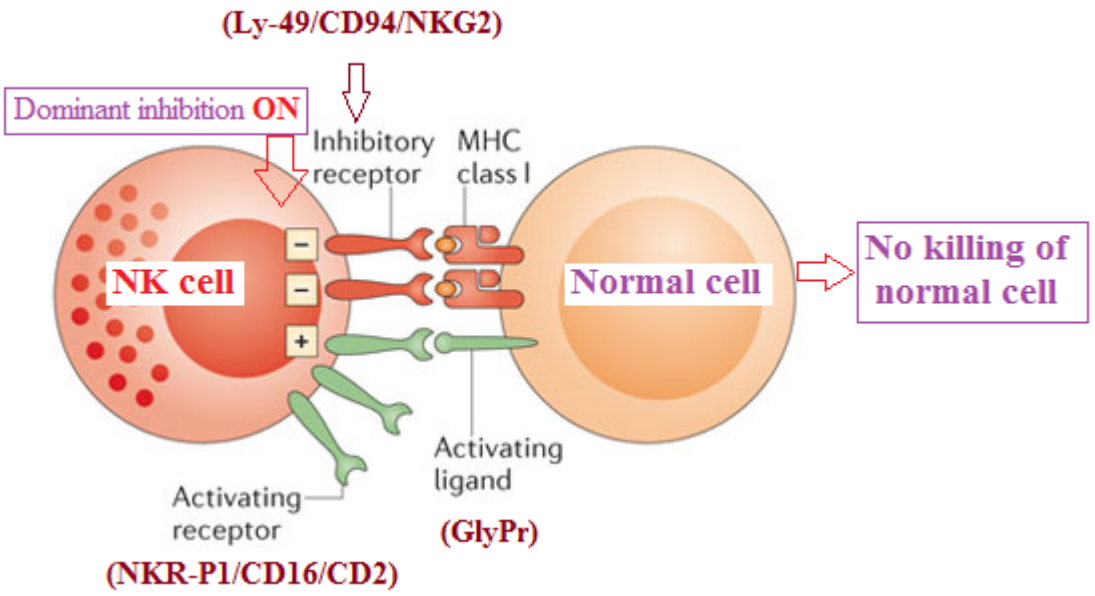
Infection leads to production of inducers of inflammation

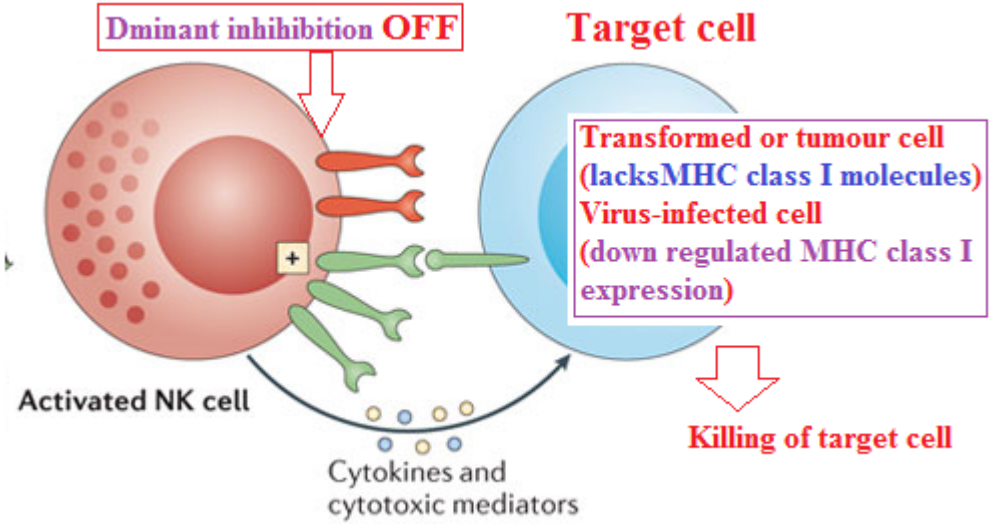


Antibody-dependent Cell-mediated Cytotoxicity (ADCC)

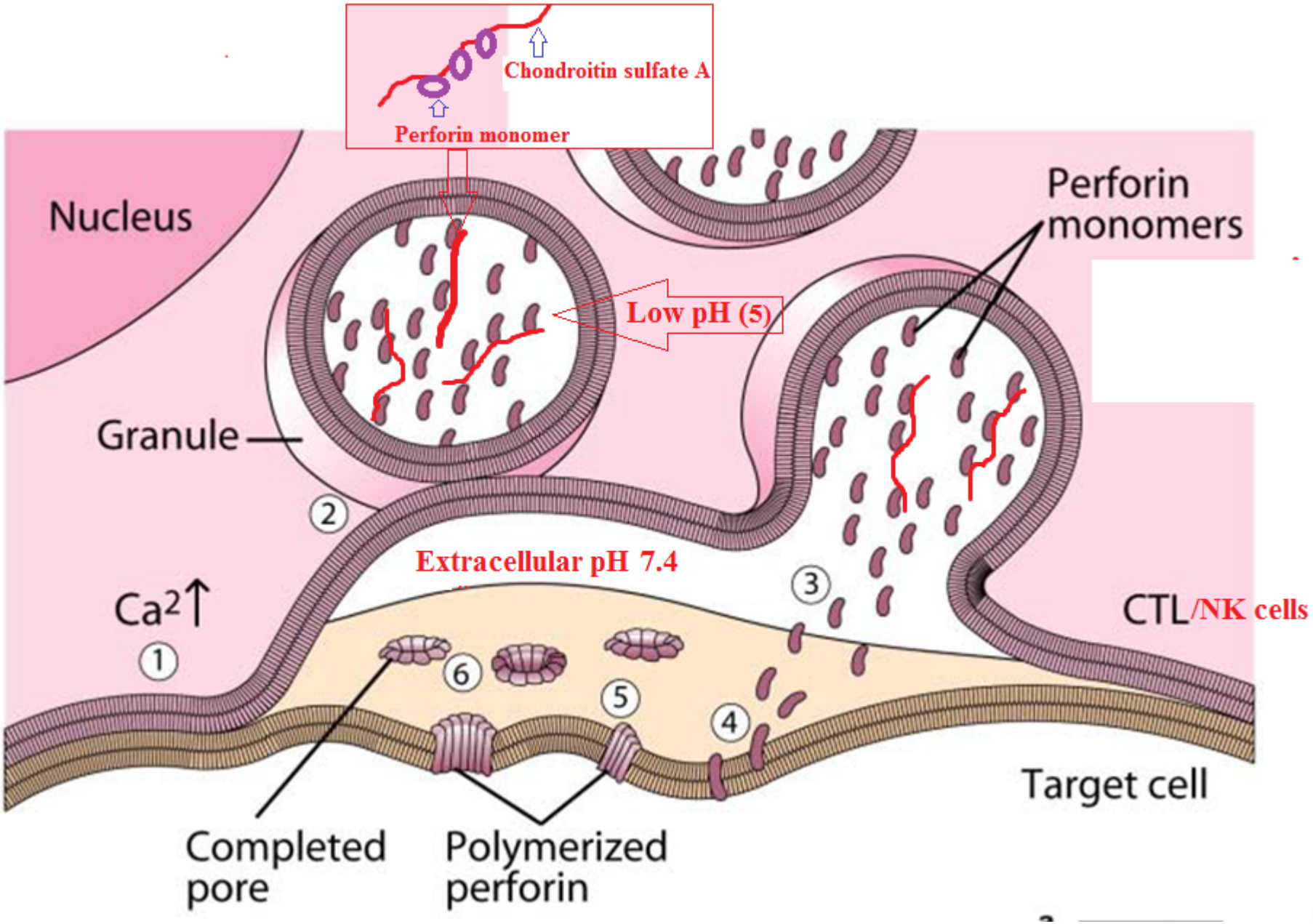


Killing of target cells by NK cells

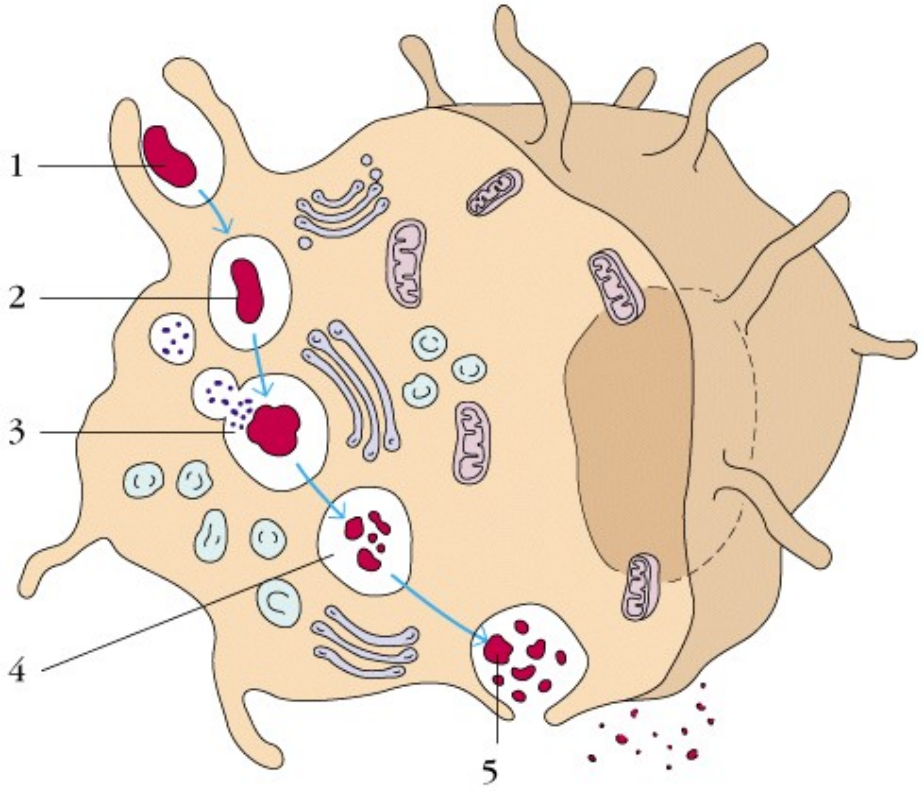




Killing of target cells by NK/CTL cells



Phagocytosis "cellular eating"



1. Bacterium attaches to membrane.
2. Bacterium is ingested, forming phagosome.
3. Phagosome fuses with lysosome.
4. Lysosomal enzymes digest the bacteria.
5. Digested material is released from cell.

Phagocytes ► macrophage, neutrophils, and dendritic cells

The major leukocytes of innate immunity

Cell type	 Neutrophil	 Macrophage	 Dendritic cell	 Natural killer (NK) cell
Function	Phagocytosis ROS & RNS Antimicrobial peptides	Phagocytosis Inflammatory mediators Antigen presntation ROS & RNS Cytokines Complement proteins	Antigen presentation Costimulatory signals ROS IFN Cytokines	Lysis of viral infected cells IFN Macrophage activation

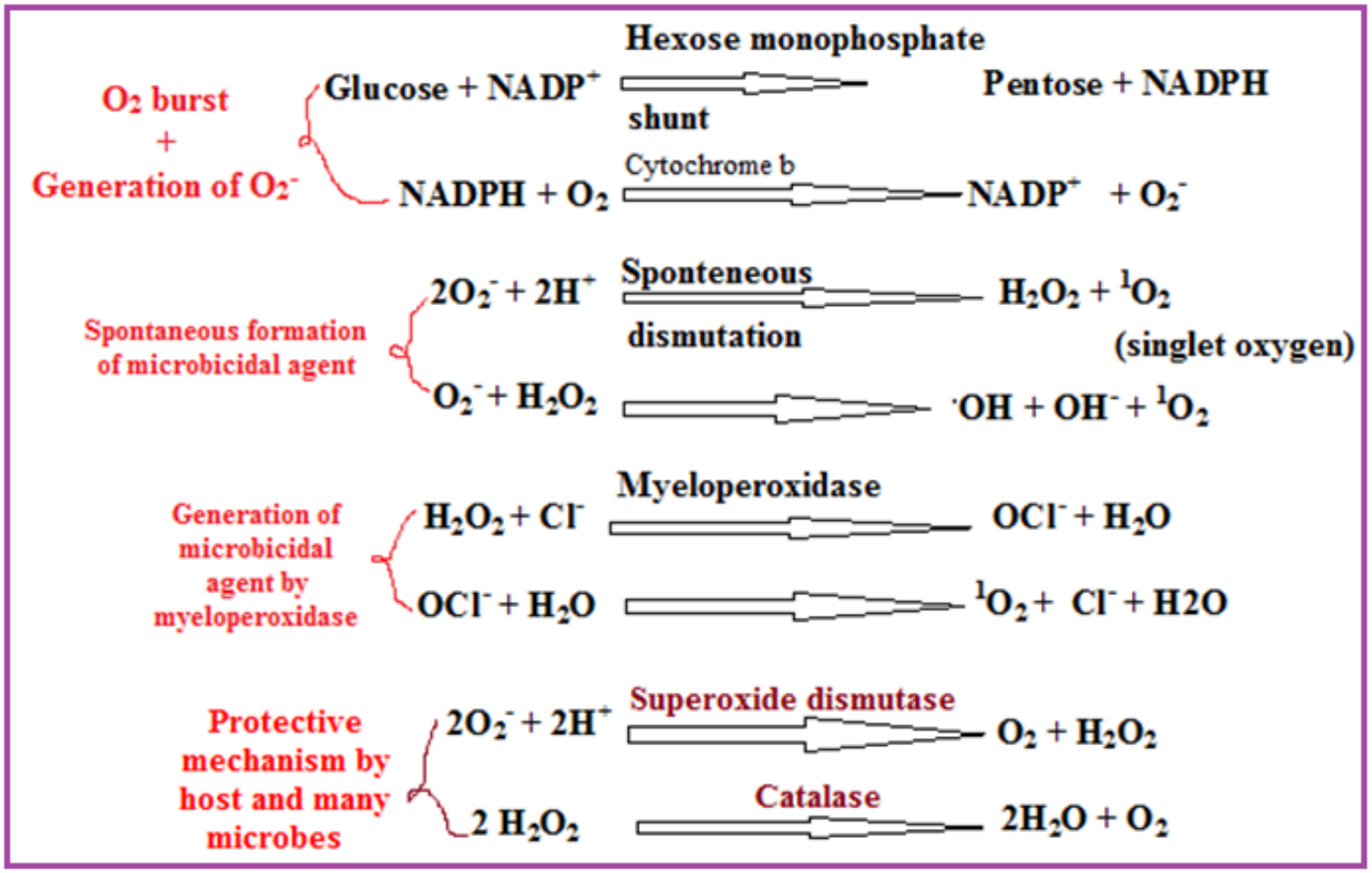
Monocytes have many of the same capabilities as Macrophages.

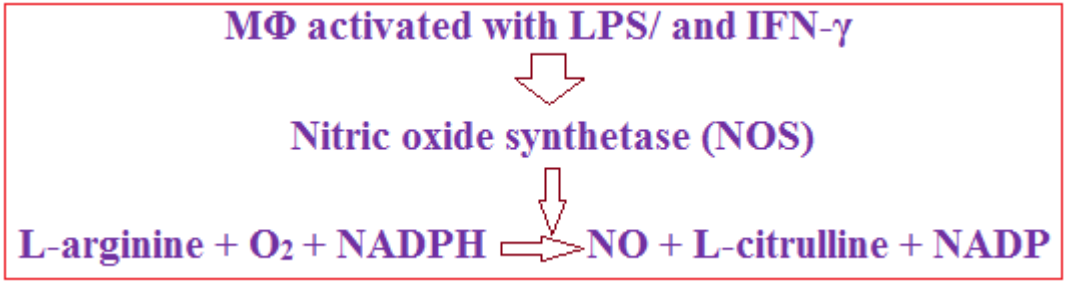
Phagocytes use a variety of methods to destroy ingested microbes.

Mediators of antimicrobial and cytotoxic activity of macrophages and neutrophils

Oxygen-dependent killing	Oxygen-independent killing
Reactive oxygen intermediates	Defensins
$O^{\bullet}_2{}^-$ (superoxide anion)	Tumor necrosis factor α
$OH^{\bullet}$ (hydroxyl radicals)	(macrophage only)
H_2O_2 (hydrogen peroxide)	Lysozyme
ClO^- (hypochlorite anion)	Hydrolytic enzymes
Reactive nitrogen intermediates	**Proteolytic enzymes**
NO (nitric oxide)	**Lactoferin**
NO_2 (nitrogen dioxide)	
HNO_2 (nitrous acid)	
Others	
NH_2CL (monochloramine)	

Oxygen dependent mechanism in phagocytic vacuoles





Some antimicrobial peptides

Peptide	Typical producer species	Typical microbial activity
Defensin family:		
α-defensins	Human (intestinal cells and neutrophil granules)	Antibacterial
β-Defensins	Human (epithelia and other tissue)	Antibacterial
Cathelicidins	Human, bovine	Antibacterial
Magainins	Frog	Antibacterial; antifungal
Cercropins	Silk moth	Antibacterial
Drosomycin	Fruit fly	Antifungal
Spinigerin	Termite	Antibacterial; antifungal

Oxygen independent mechanism in phagocytic vacuoles

Defensins and other cationic peptides:

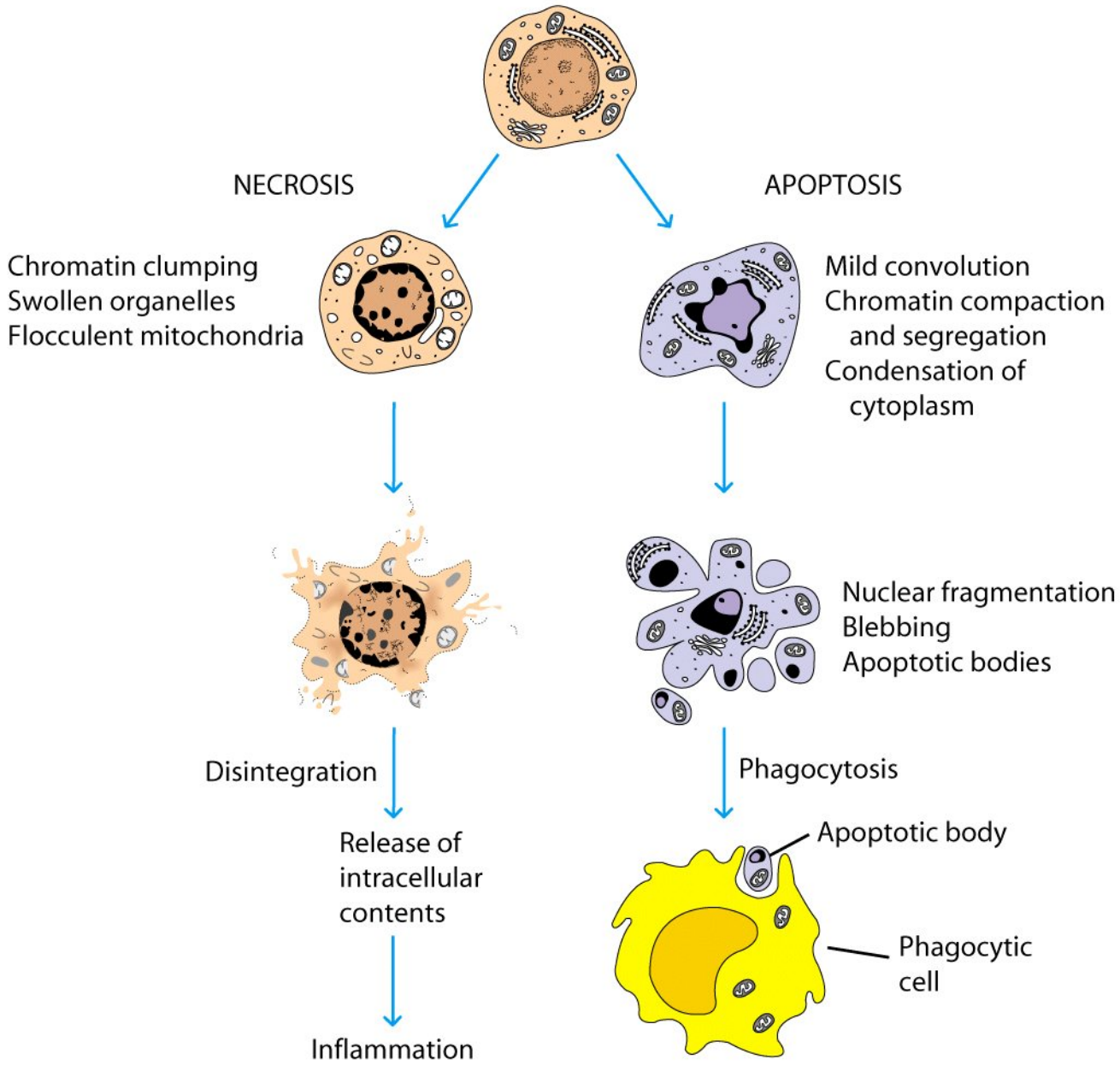
- **Small polypeptides (<10kDa) [6 - 59 a.a. residues] secreted at mucosal surfaces.**
- **Direct bactericidal properties.**
- **Insertion into biological membranes leading to target cell lysis.**
- **Inhibited by cholesterol (specificity).**

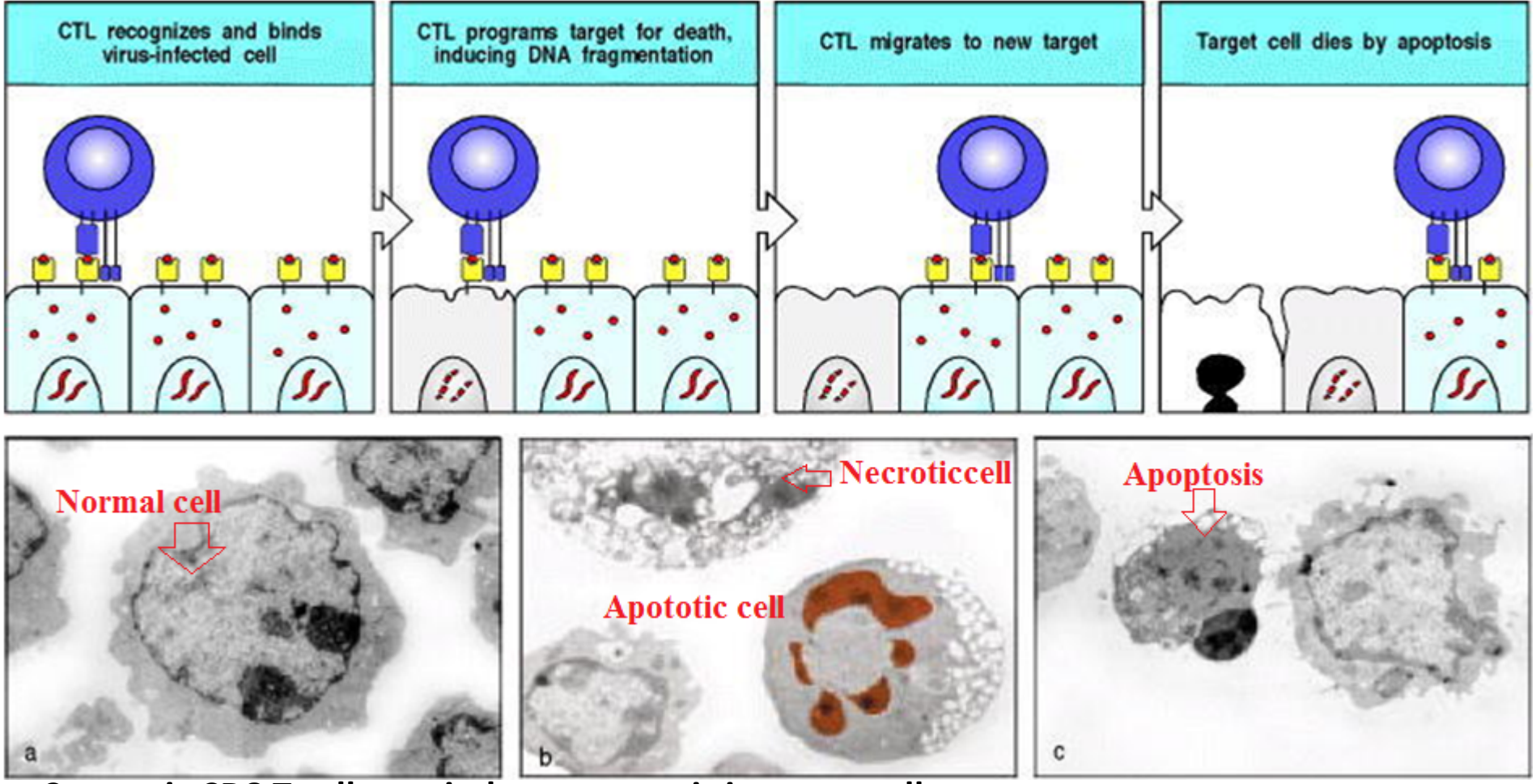
Lysozyme: splits mucopeptide in bacterial cell wall.

Lactoferin: Deprives proliferating bacteria of iron.

Proteolytic/hydrolytic enzymes: digestion of killed bacteria

Cell death by necrosis is more likely to produce inflammation.





Cytotoxic CD8 T cells can induce apoptosis in target cells

Specific recognition of peptide:MHC complexes on a target cell (top panels) by a cytotoxic CD8 T cell (CTL) leads to the death of the target cell by apoptosis. Cytotoxic T cells can recycle to kill multiple targets. Each killing requires the same series of steps, including receptor binding and directed release of cytotoxic proteins stored in lytic granules. The process of apoptosis is shown in the micrographs (bottom panels), where panel a shows a healthy cell with a normal nucleus. Early in apoptosis (panel b) the chromatin becomes condensed (red) and, although the cell sheds membrane vesicles, the integrity of the cell membrane is retained, in contrast to the necrotic cell in the upper part of the same field. In late stages of apoptosis (panel c), the cell nucleus (middle cell) is very condensed, no mitochondria are visible, and the cell has lost much of its cytoplasm and membrane through the shedding of vesicles.

Time Course of Viral Infection