Kazan (Volga region) Federal University
Institute of Fundamental Medicine and Biology
Department of Morphology and General Pathology

Inflammation

Lecture 4

Lecturer
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Definition

Inflammation is a protective response involving host cells, blood vessels, and proteins and other mediators that is intended to eliminate the initial cause of cell injury, as well as the necrotic cells and tissues resulting from the original insult, and to initiate the process of repair.

Inflammation is

- A protective response involving host cells, blood vessels and proteins
  - Goals are:
    - eliminate the initial cause of cell injury
    - Remove necrotic cells and tissue
    - Initiate the process of repair
- Also a potentially harmful process
  - Components of inflammation that are capable of destroying microbes can also injury bystander normal tissue

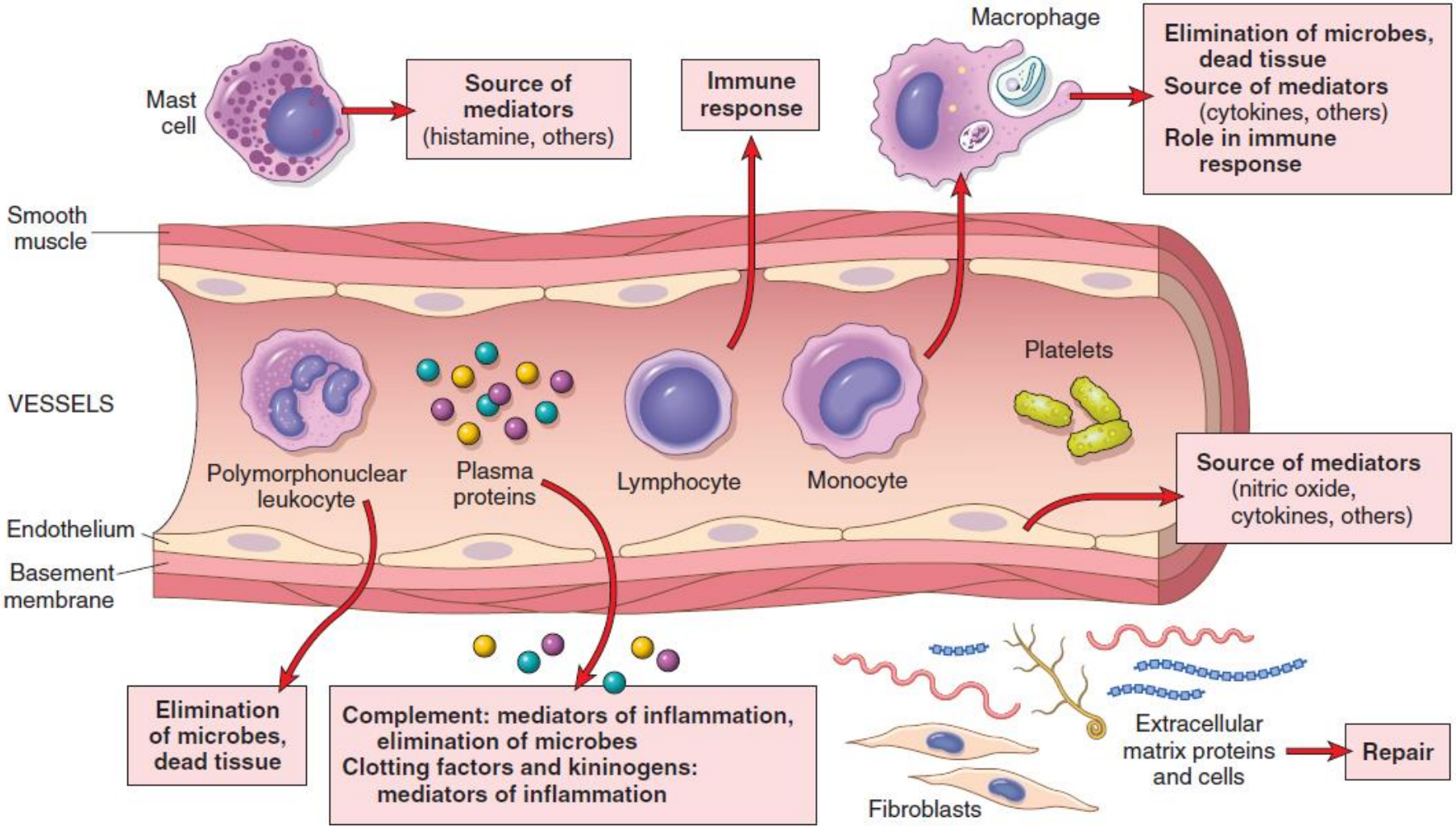
Cells

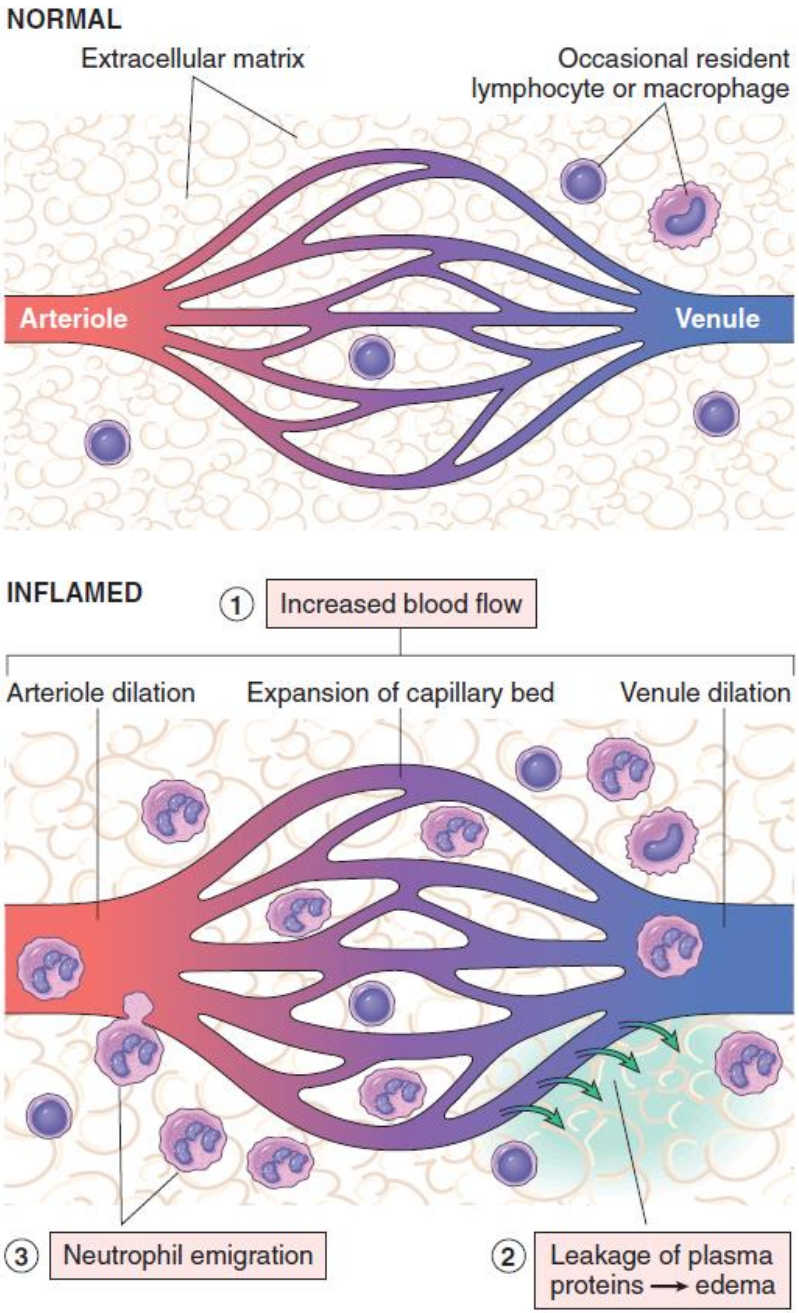
Platelets
Granulocytes (PMNs, Mast, etc)
Monocyte/Macrophages
Lymphocytes
Fibroblasts

Proteins

Complement, Pentraxins, MBL, Ficolins
Coagulation
Kininogens
Proteoglycans

Components of inflammation





Main components:

– **Vascular changes**

- Vasodilation
- Vascular permeability
- Increased adhesion of white blood cells

– **Cellular events**

- Cellular recruitment and activation of neutrophils (polymorphonuclear leukocytes)

VASCULAR CHANGES

In acute inflammation

- **1. Vasodilation:**

- The reactions of blood vessels

- Alterations in vascular caliber (diameter)

- Causes decrease in blood pressure

- **2. Vascular leakage and edema**:

- The accumulation of fluid and proteins of plasma in the extravascular tissues (interstitium)

- **3. Leukocyte emigration** to extravascular tissues

A. Margination and rolling

B. Activation and adhesion

C. Transmigration

1. Vasodilation

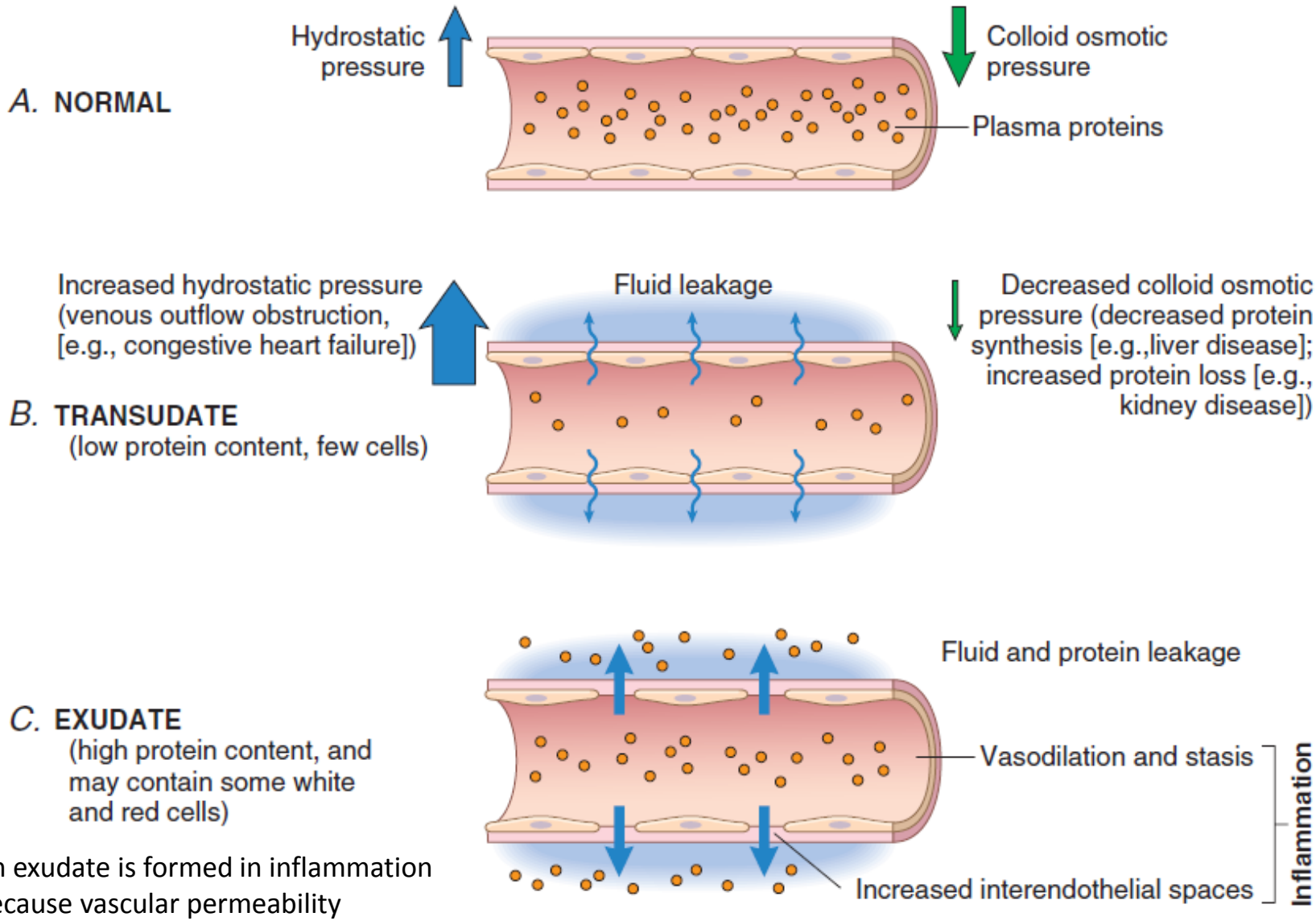
- Change in vessel **flow**
  - NO, histamine➔vascular smooth muscle➔ vasodilation➔increased blood flow (heat & redness)
  - Stasis: slowed blood flow, hyperviscosity
  - Margination of circulating leukocytes & endothelial activation

- Followed by increased permeability of the vasculature
  - Formation of an early **transudate** (protein-poor filtrate of plasma) gives way to **exudate** (protein-rich filtrate) into extracellular tissues

2. Vascular leakage and edema

- Change in vessel permeability
  - Histamines, bradykinins, leukotrienes cause endothelial cell contraction that widens intercellular gaps of venules
  - Outpouring of protein-rich fluid (exudate) into the extracellular tissues leads to:
    - Reduction of intravascular osmotic pressure
    - Increase in extravascular/interstitial osmotic pressure
  - Increase of interstitial osmotic pressure leads to edema (water and ions)

Formation of transudates and exudates



An exudate is formed in inflammation because vascular permeability increases as a result of the increase in interendothelial spaces.

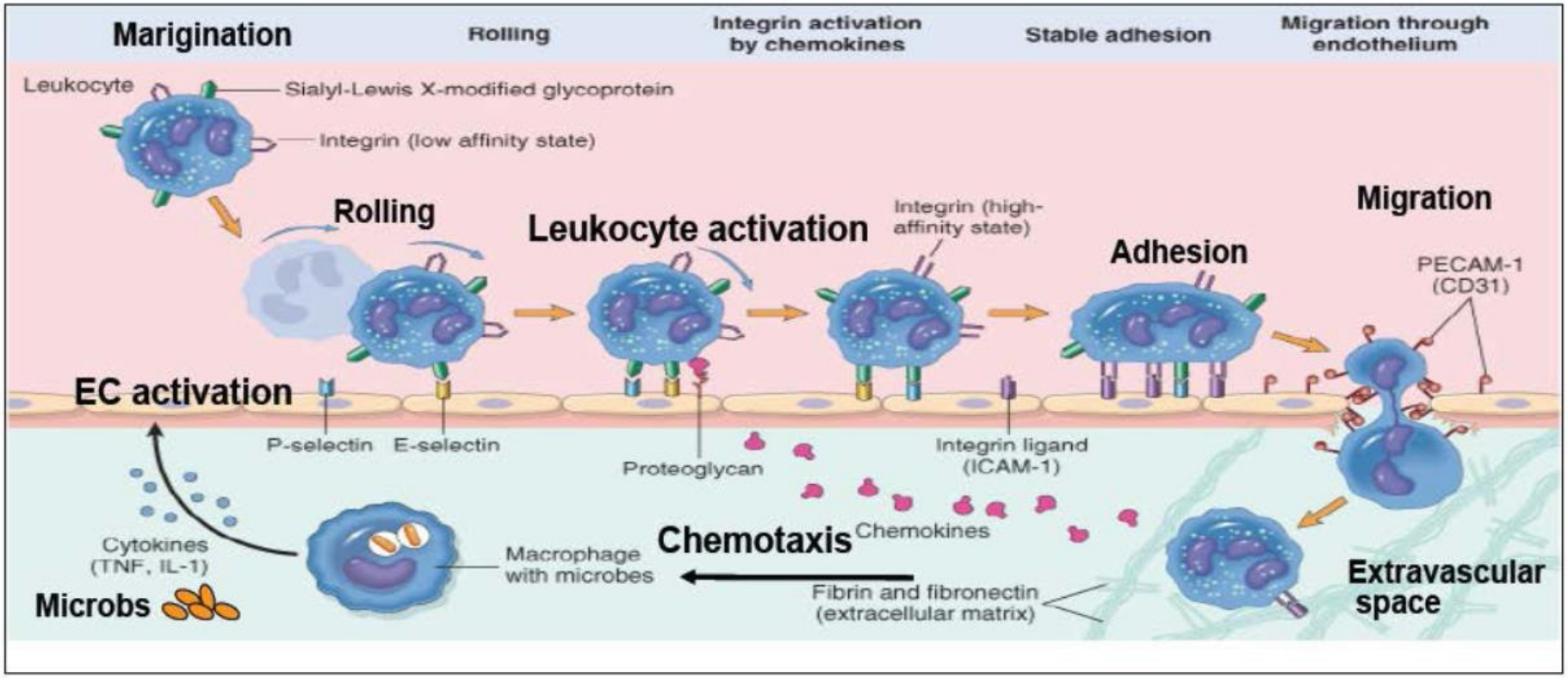
3. Leukocyte emigration to extravascular tissues

Leukocytes leave the vasculature through the following sequence of events:

A. margination and rolling

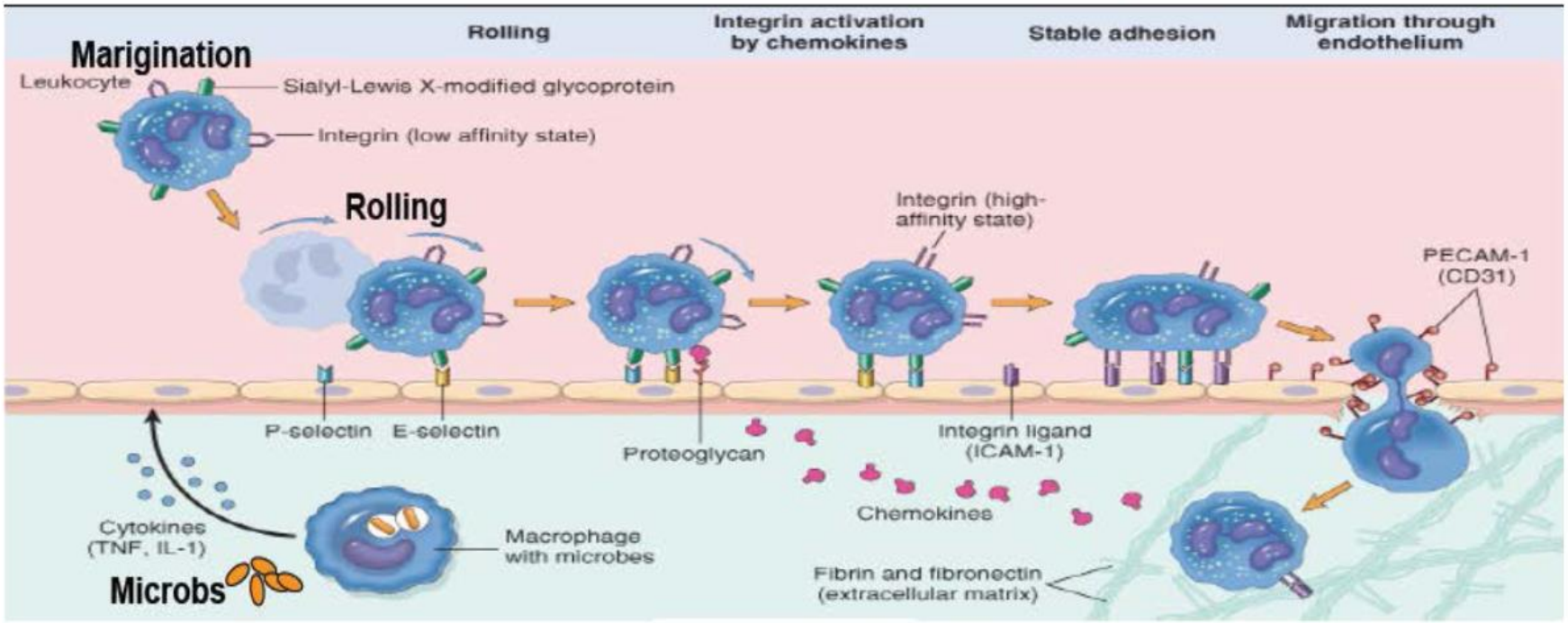
B. activation and adhesion

C. transmigration



A. Margination and Rolling

- Fluid (**exudate**) leaves the vessel, leukocytes **"marginate"** along the endothelial surface
- In the process of **"rolling"** individual and then rows of leukocytes tumble slowly along the endothelium, adhere through surface **adhesion molecules on endothelial** cells and their complementary **ligands on leukocytes**

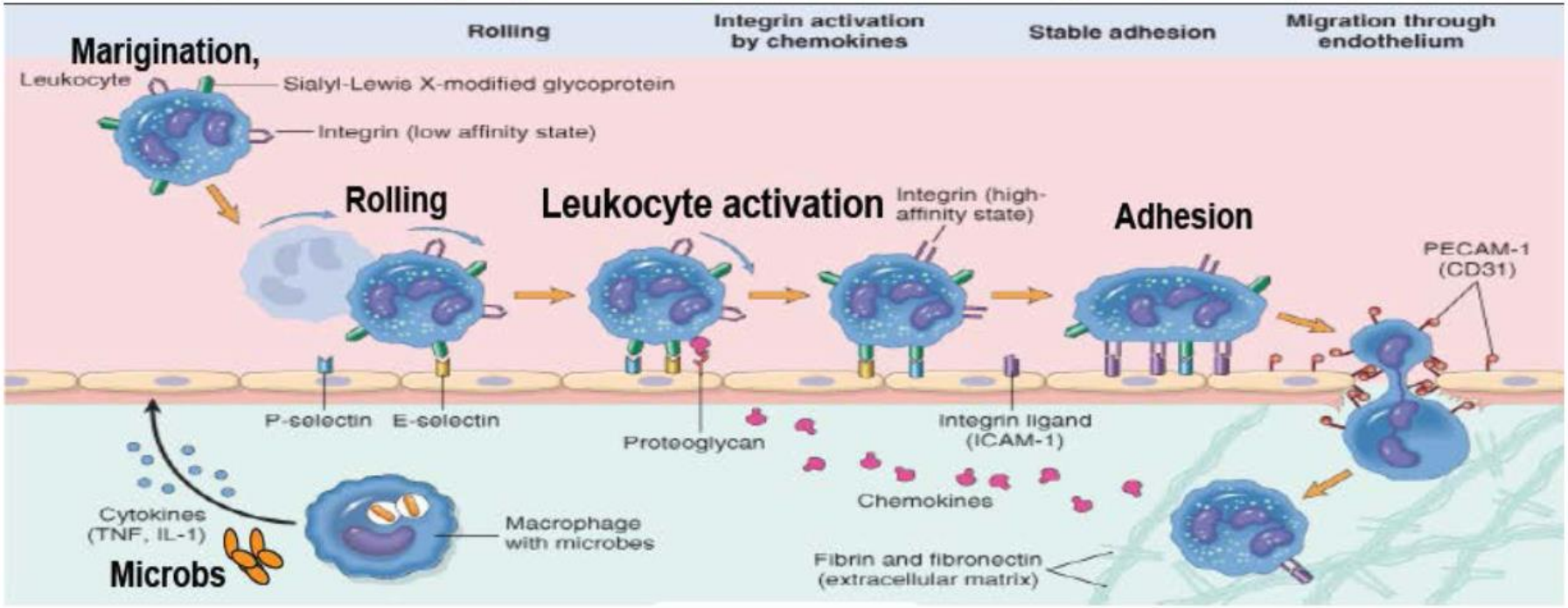


B. Activation and Adhesion

Adhesion is mediated by selectin family (adhesion molecules)

- **E-selectin** (endothelium)
- **P-selectin** (platelets, endothelium)
- **L-selectin** (leukocytes)

Selectins that are upregulated on endothelium by cytokines (TNF-α, IL-1) at injury sites bind leukocyte surface molecules (*i.e.*, **Sialyl-Lewis X modified GP, P-selectin glycoprotein ligand(PSGL-1), integrins, CD34**)



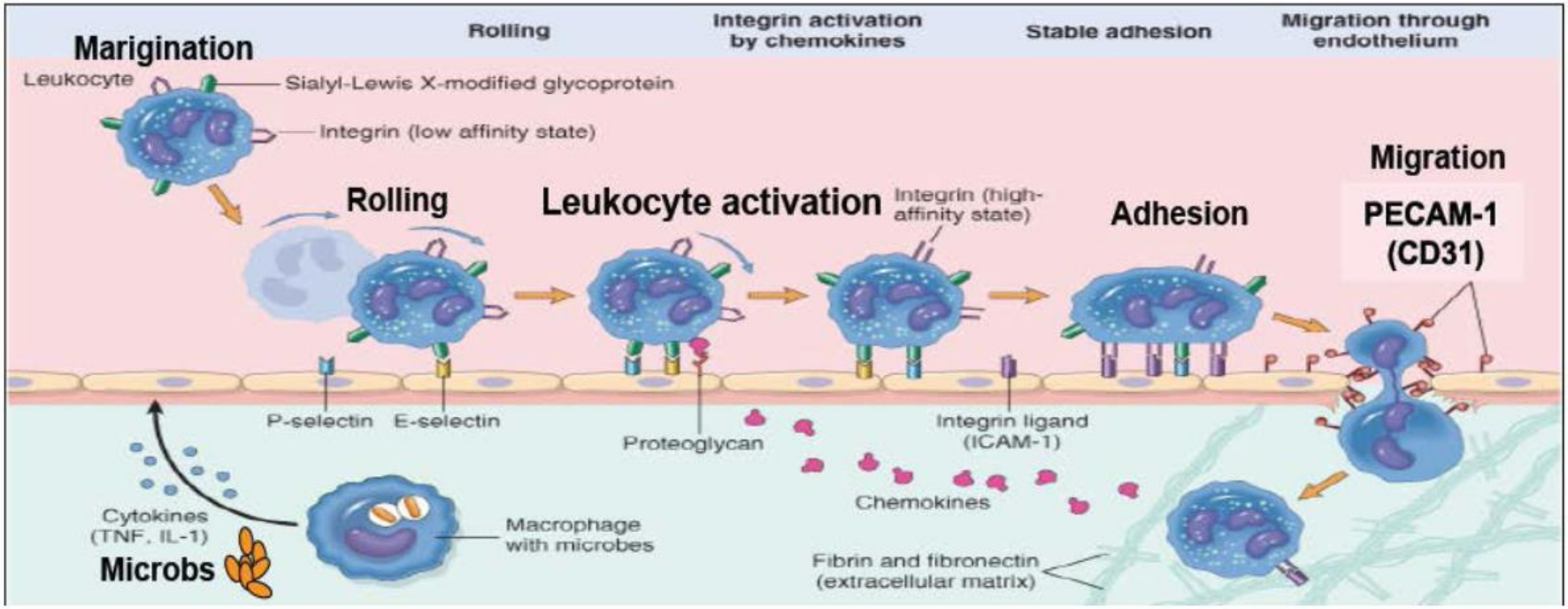
Endothelial and Leukocyte Adhesion Molecules

Endothelial Molecule	Leukocyte Molecule	Major Role(s)
Selectins and Selectin Ligands		
P-selectin	Sialyl–Lewis X–modified proteins	Rolling
E-selectin	Sialyl–Lewis X–modified proteins	Rolling and adhesion
GlyCam-1, CD34	L-selectin*	Rolling (neutrophils, monocytes)
Integrins and Integrin Ligands		
ICAM-1 (immunoglobulin family)	CD11/CD18 integrins (LFA-1, Mac-1)	Firm adhesion, arrest, transmigration
VCAM-1 (immunoglobulin family)	VLA-4 integrin	Adhesion
Others		
CD31	CD31 (homotypic interaction)	Transmigration of leukocytes through endothelium

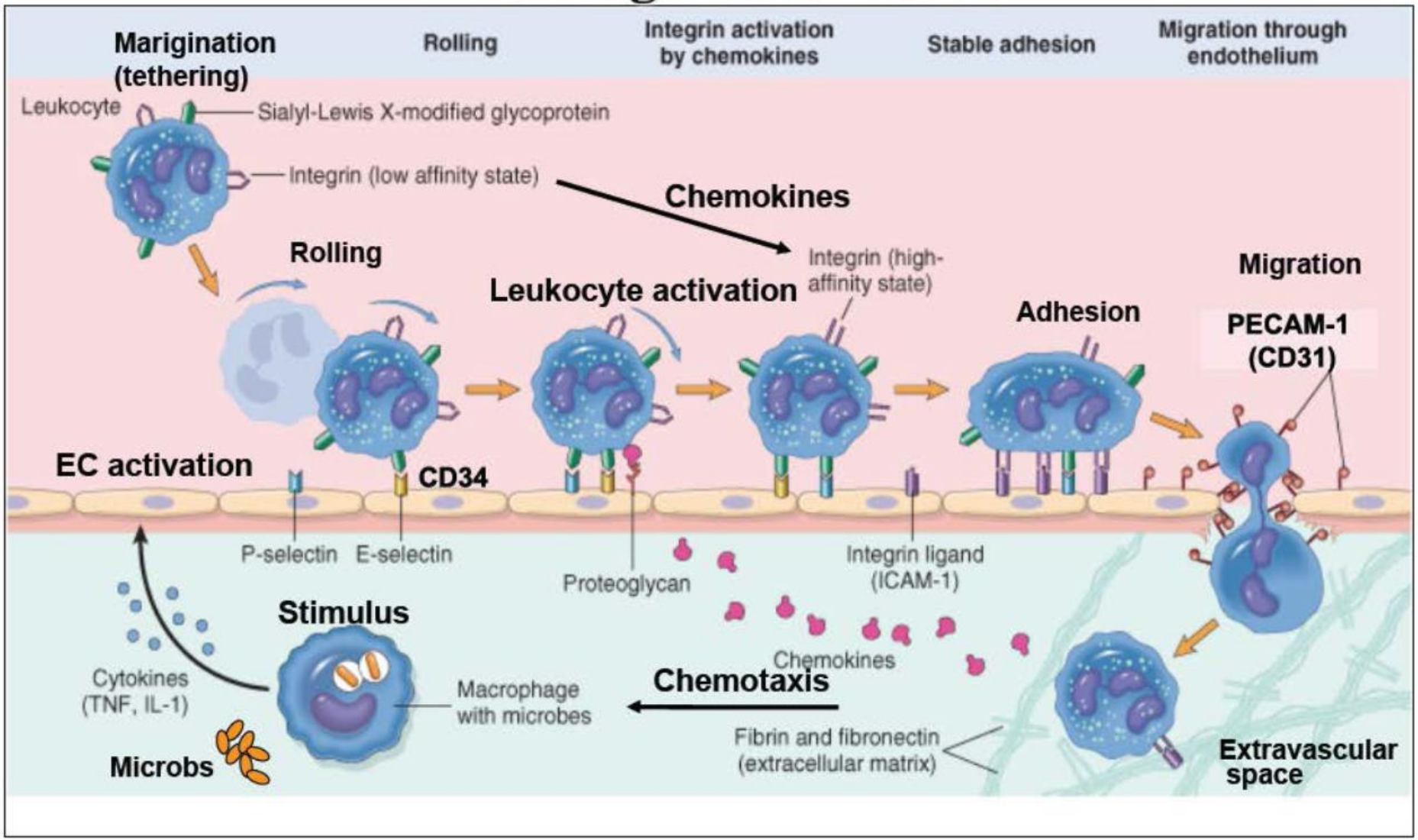
*L-selectin is also involved in the binding of circulating lymphocytes to the high endothelial venules in lymph nodes and mucosal lymphoid tissues, and subsequent homing of lymphocytes to these tissues.
ICAM-1, intercellular adhesion molecule-1; LFA-1, leukocyte function–associated antigen-1; Mac-1, macrophage-1 antigen; VCAM-1, vascular cell adhesion molecule-1; VLA-4, very late antigen-4.

C. Transmigration (diapedesis)

- Occurs after firm adhesion within the system of venules and capillaries via **PECAM –1 (CD31)** (platelet-endothelial cell adhesion molecule) on endothelial cells, neutrophils, monocytes/macrophages, lymphocytes
- Upregulation of endothelial cell ligands (integrins) for adhesion molecules results in activation/adhesion of different populations of leukocytes (monocytes, lymphocytes, *etc*)



The multistep process of leukocyte migration through blood vessels



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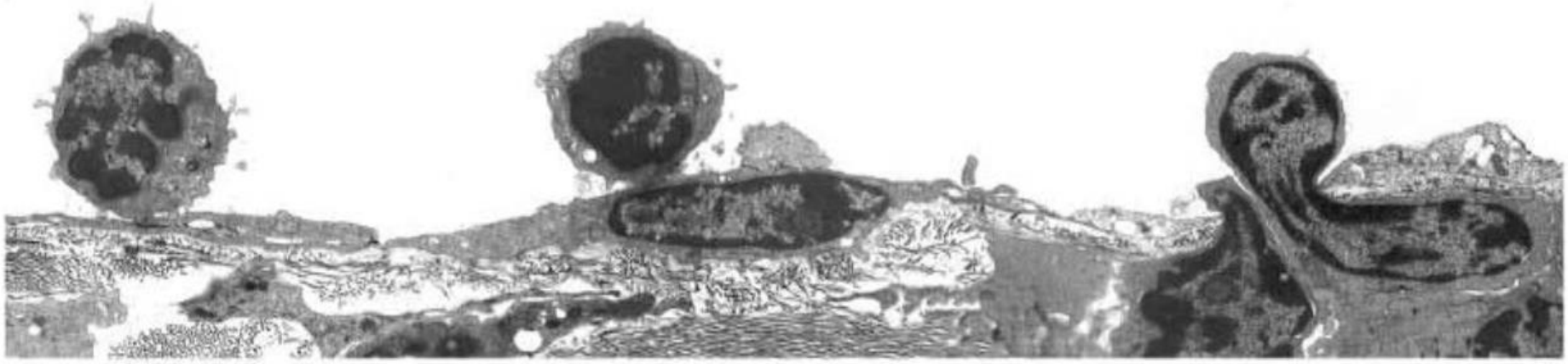
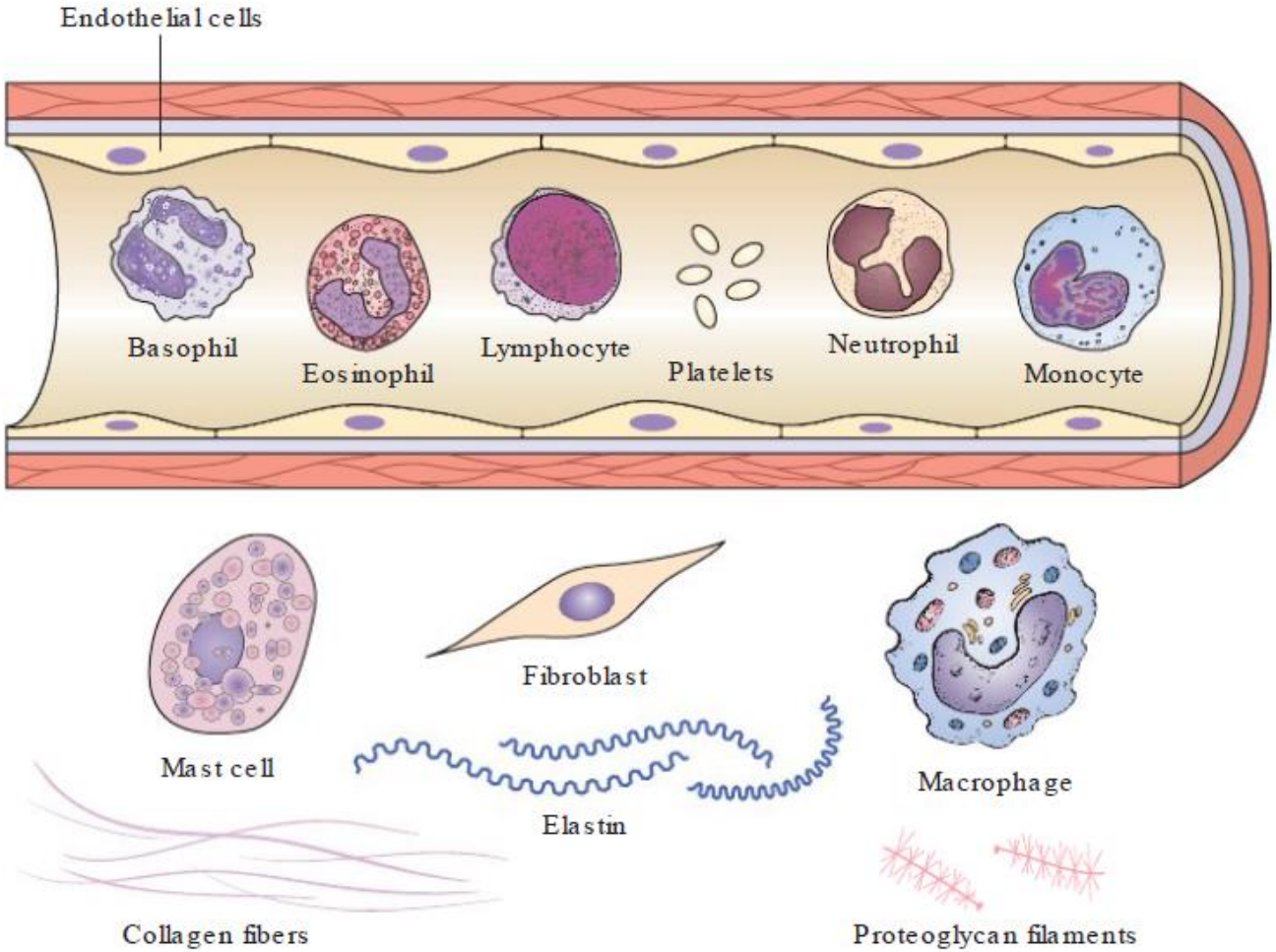


CELLULAR EVENTS

Leukocyte activation and mechanisms of microbial killing

Cells of inflammation



Endothelial cells

- Provide selective permeability barrier
- Regulate leukocyte extravasation
- Regulate and modulate immune response through synthesis and release of inflammatory mediators
- Regulate immune cell proliferation through secretion of hematopoietic colony-stimulation factors (CSFs)
- Participate in repair process through the production of growth factors that stimulate angiogenesis and extracellular matrix synthesis

Platelets

- Release number of inflammatory mediators (over 300 proteins) which:
- Increase vascular permeability
- Alter chemotactic, adhesive, proteolytic properties of the endothelial cells

Neutrophils

- Are highly mobile, arriving in the site of injury within 90 min. of injury
- Engulf bacteria and cellular debris through phagocytosis
- Granules contain enzymes and antibacterial substances
- Have oxygen-dependent metabolic pathways that generate toxic reactive oxygen and nitrogen
- Have a short life span. They die by apoptosis and disappear within 24 to 48 hours after entering the site of injuty

Eosinophils

- Appear in the site of I. 2-3 hours
- Granules contain highly toxic protein that cannot be phagocyted

- Present in chronic inflammation

Basophils and mast cells

- Basophils mostly prominent in allergic reactions mediated by IgE. Binding of IgE triggers release of histamine and vasoactive agents from the basophil granules
- Mast cells particularly prevalent along mucosal surfaces of the lung, GIT, dermis of the skin. Activations results in release of the preformed contents of their granules: histamine, proteases, VEGF, arachidonic acid metabolites, cytokines: TNF-α, IL-16

Receptors involved in leukocyte activation

1. Toll-like receptors (TLRs)
2. Different seven-transmembrane G-protein-coupled receptors
3. Receptors for cytokines (e.g., IFN-γR)
4. Opsonins and their receptors
   - Antibodies (specific opsonins recognized by FcγRs)
   - Complement (mainly CR1 that recognizes breakdown products of C3 by either the classical or the alternative pathway)
   - Plasma "early activation proteins": C-reactive protein (CRP), Serum amyloid protein (SAP), fibronectin, fibrinogen; lectins: mannose binding lectin (MBL)

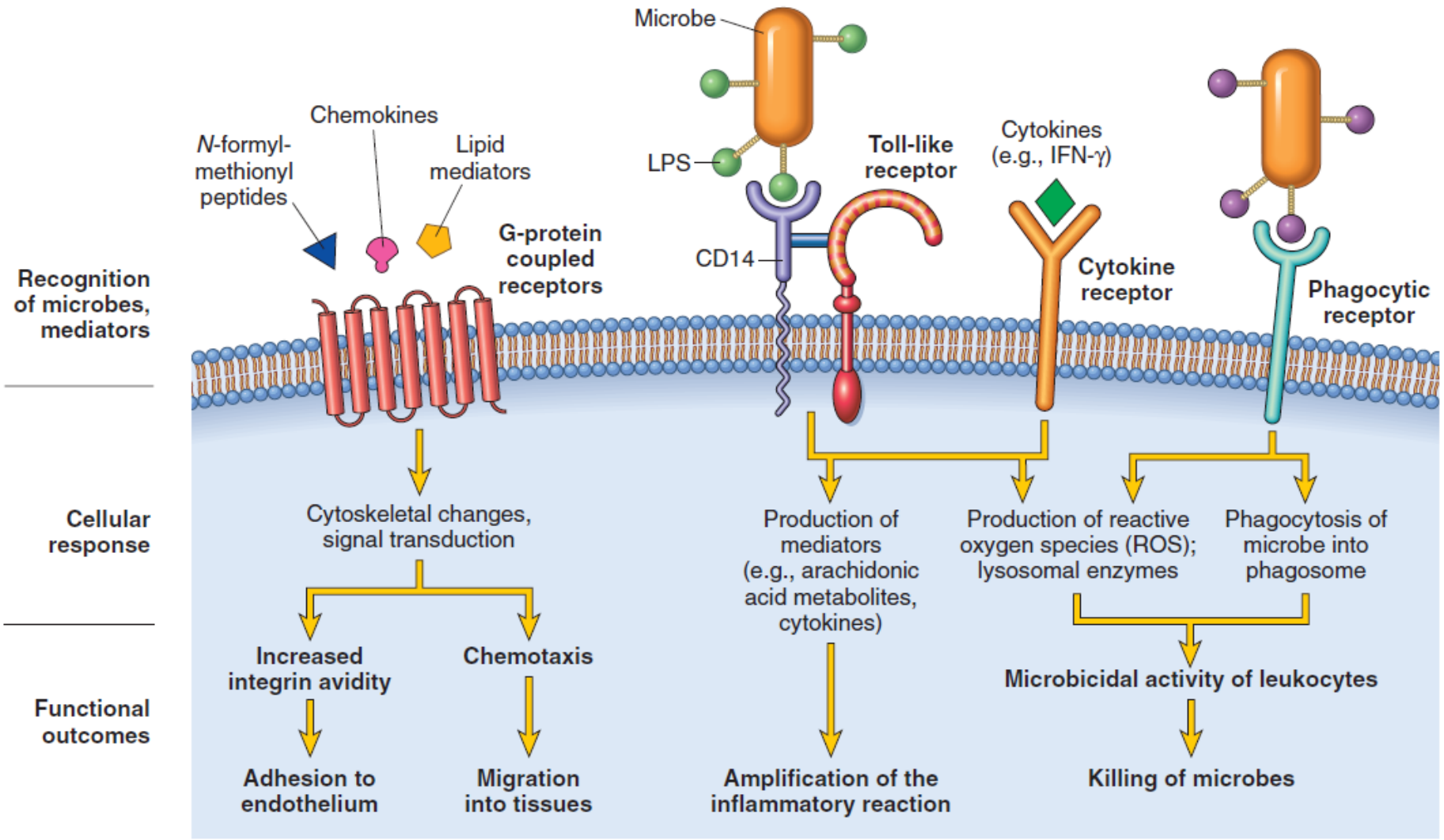
Cytokines & Chemokines

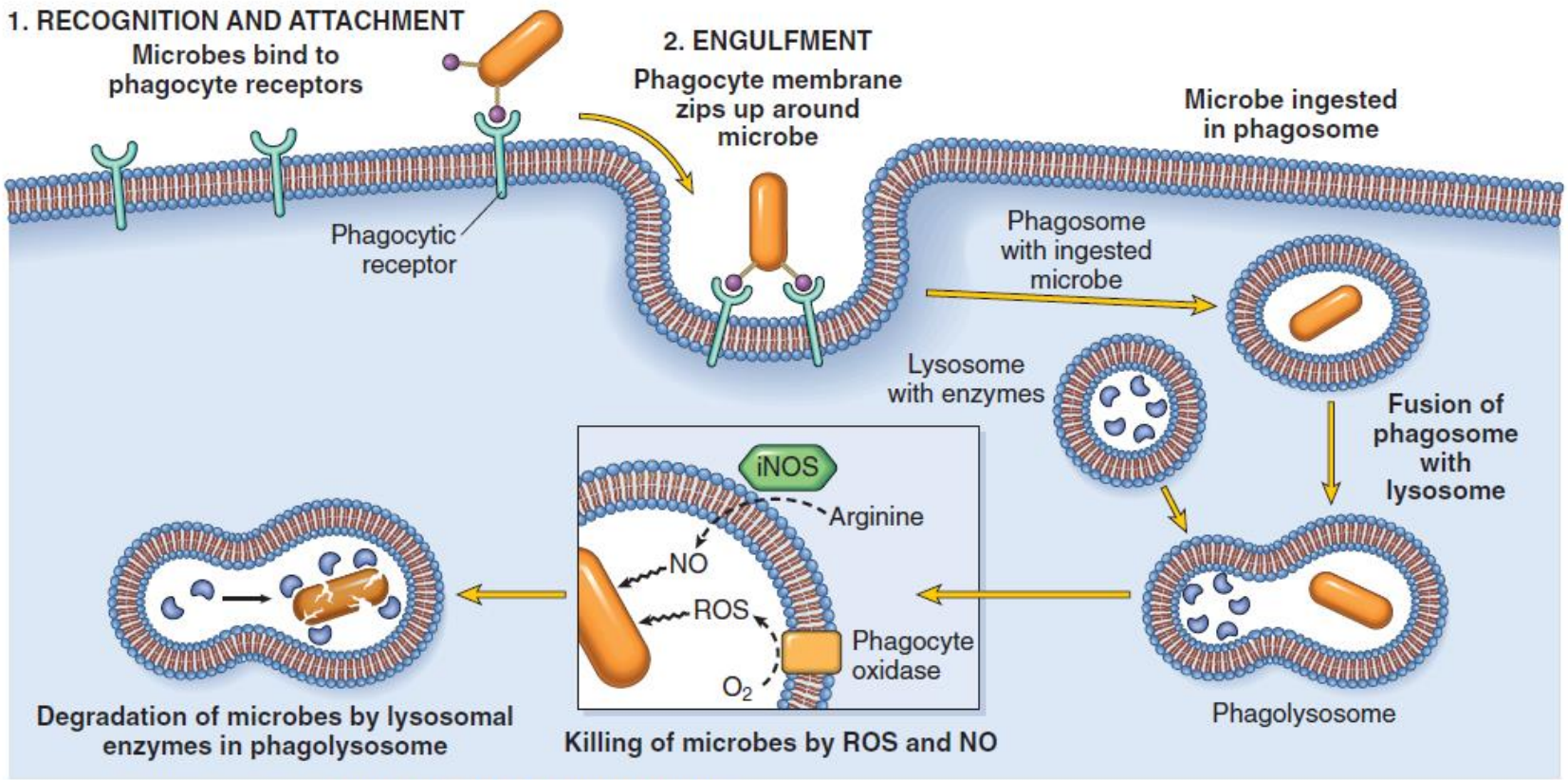
Cytokines

- small proteins that modify the interactions between cells (15-30 kD)
- produced by activated lymphocytes and macrophages, also by endothelium, epithelium, connective tissue

Chemokines

- small proteins (8-10 kD) that act primarily as chemoattractants for specific types of leukocytes (chemotaxis)

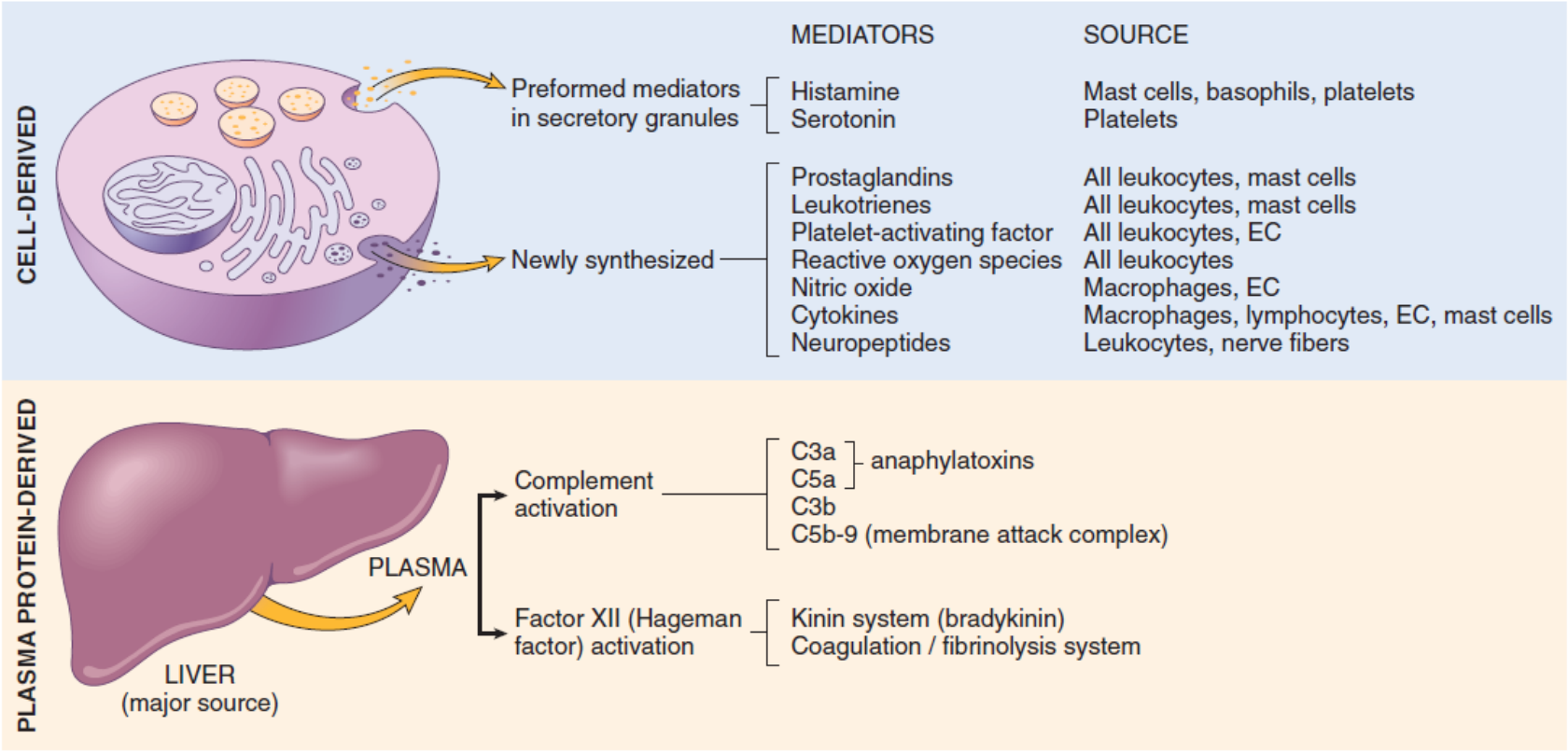

Recognition of microbes, mediators
Cellular response
Functional outcomes
N-formyl-methionyl peptides
Chemokines
Lipid mediators
G-protein coupled receptors
Microbe
LPS
CD14
Toll-like receptor
Cytokines (e.g., IFN-γ)
Cytokine receptor
Phagocytic receptor
Cytoskeletal changes, signal transduction
Production of mediators (e.g., arachidonic acid metabolites, cytokines)
Production of reactive oxygen species (ROS); lysosomal enzymes
Phagocytosis of microbe into phagosome
Increased integrin avidity
Chemotaxis
Microbicidal activity of leukocytes
Adhesion to endothelium
Migration into tissues
Amplification of the inflammatory reaction
Killing of microbes


1. RECOGNITION AND ATTACHMENT
Microbes bind to phagocyte receptors
Phagocytic receptor
2. ENGULFMENT
Phagocyte membrane zips up around microbe
Microbe ingested in phagosome
Phagosome with ingested microbe
Lysosome with enzymes
Fusion of phagosome with lysosome
iNOS
Arginine
NO
ROS
Phagocyte oxidase
O_2
Phagolysosome
Degradation of microbes by lysosomal enzymes in phagolysosome
Killing of microbes by ROS and NO
3. KILLING AND DEGRADATION

CHEMICAL MEDIATORS OF INFLAMMATION

Chemical mediators

- **Source** of chemical mediators:
  - May be produced locally by cells at the site of inflammation
  - may be derived from circulating inactive precursors (typically synthesized by the liver) that are activated at the site of inflammation
- **Cell-derived mediators:**
  - normally sequestered in intracellular granules
  - rapidly secreted upon cellular activation or are synthesized de novo in response to a stimulus
- **Plasma protein–derived mediators:**
  - complement proteins, kinins
  - circulate in an inactive form
  - typically undergo proteolytic cleavage to acquire their biologic activities.


CELL-DERIVED
MEDIATORS
SOURCE
Preformed mediators in secretory granules
Histamine
Mast cells, basophils, platelets
Serotonin
Platelets
Newly synthesized
Prostaglandins
All leukocytes, mast cells
Leukotrienes
All leukocytes, mast cells
Platelet-activating factor
All leukocytes, EC
Reactive oxygen species
All leukocytes
Nitric oxide
Macrophages, EC
Cytokines
Macrophages, lymphocytes, EC, mast cells
Neuropeptides
Leukocytes, nerve fibers
PLASMA PROTEIN-DERIVED
PLASMA
LIVER
(major source)
Complement activation
C3a
C5a
anaphylatoxins
C3b
C5b-9 (membrane attack complex)
Factor XII (Hageman factor) activation
Kinin system (bradykinin)
Coagulation / fibrinolysis system

Mediator	Source(s)	Actions
Cell-Derived		
Histamine	Mast cells, basophils, platelets	Vasodilation, increased vascular permeability, endothelial activation
Serotonin	Platelets	Vasoconstriction
Prostaglandins	Mast cells, leukocytes	Vasodilation, pain, fever
Leukotrienes	Mast cells, leukocytes	Increased vascular permeability, chemotaxis, leukocyte adhesion and activation
Platelet-activating factor	Leukocytes, mast cells	Vasodilation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst
Reactive oxygen species	Leukocytes	Killing of microbes, tissue damage
Nitric oxide	Endothelium, macrophages	Vascular smooth muscle relaxation; killing of microbes
Cytokines (TNF, IL-1, IL-6)	Macrophages, endothelial cells, mast cells	*Local*: endothelial activation (expression of adhesion molecules). *Systemic*: fever, metabolic abnormalities, hypotension (shock)
Chemokines	Leukocytes, activated macrophages	Chemotaxis, leukocyte activation
Plasma Protein–Derived		
Complement	Plasma (produced in liver)	Leukocyte chemotaxis and activation, direct target killing (MAC), vasodilation (mast cell stimulation)
Kinins	Plasma (produced in liver)	Increased vascular permeability, smooth muscle contraction, vasodilation, pain
Proteases activated during coagulation	Plasma (produced in liver)	Endothelial activation, leukocyte recruitment

IL-1, IL-6, interleukin-1 and -6; MAC, membrane attack complex; TNF, tumor necrosis factor.

Notice

The steps of the inflammatory response can be remembered as the **five Rs**:

(1) recognition of the injurious agent,

(2) recruitment of leukocytes,

(3) removal of the agent,

(4) regulation (control) of the response

(5) resolution(repair)