

Leukocyte Recruitment to Sites of Inflammation

From endothelial activation to leukocyte emigration

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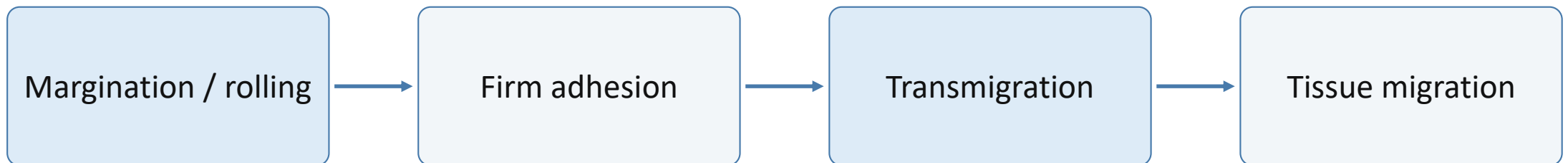
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Learning outcomes

- Explain how vascular stasis favors leukocyte margination.
- Distinguish selectin-dependent rolling from integrin-mediated arrest.
- Describe endothelial transmigration, CD31, and basement-membrane passage.
- Relate cellular recruitment patterns to inflammatory stimuli and clinical consequences.

Leukocyte recruitment is a multistep response

- Circulating phagocytes must leave the vascular lumen to reach microbes and damaged tissue.
- Adhesion molecules and cytokines coordinate sequential, anatomically distinct steps.
- Leukocyte emigration links the vascular phase of acute inflammation to the tissue response.



Why recruited leukocytes matter

- Neutrophils and macrophages ingest and destroy microbes.
- These phagocytes clear necrotic material and foreign substances.
- Macrophages also release growth factors that support tissue repair.
- Activated leukocytes may injure otherwise viable host tissue.

Leukocyte defense carries a cost

Host protection

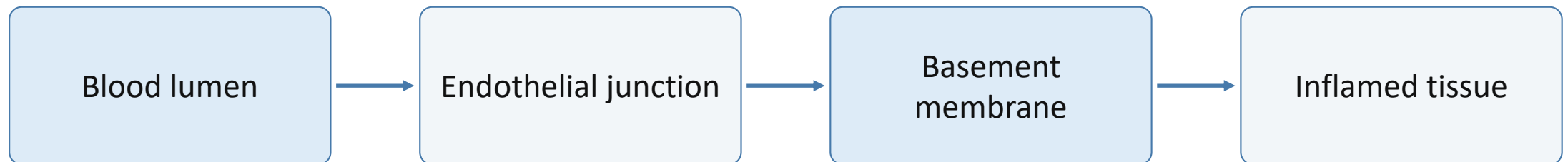
- Phagocytosis of microbes
- Removal of necrotic tissue
- Initiation of repair

Potential host injury

- Toxic microbicidal products
- Damage to normal cells
- Excessive inflammation

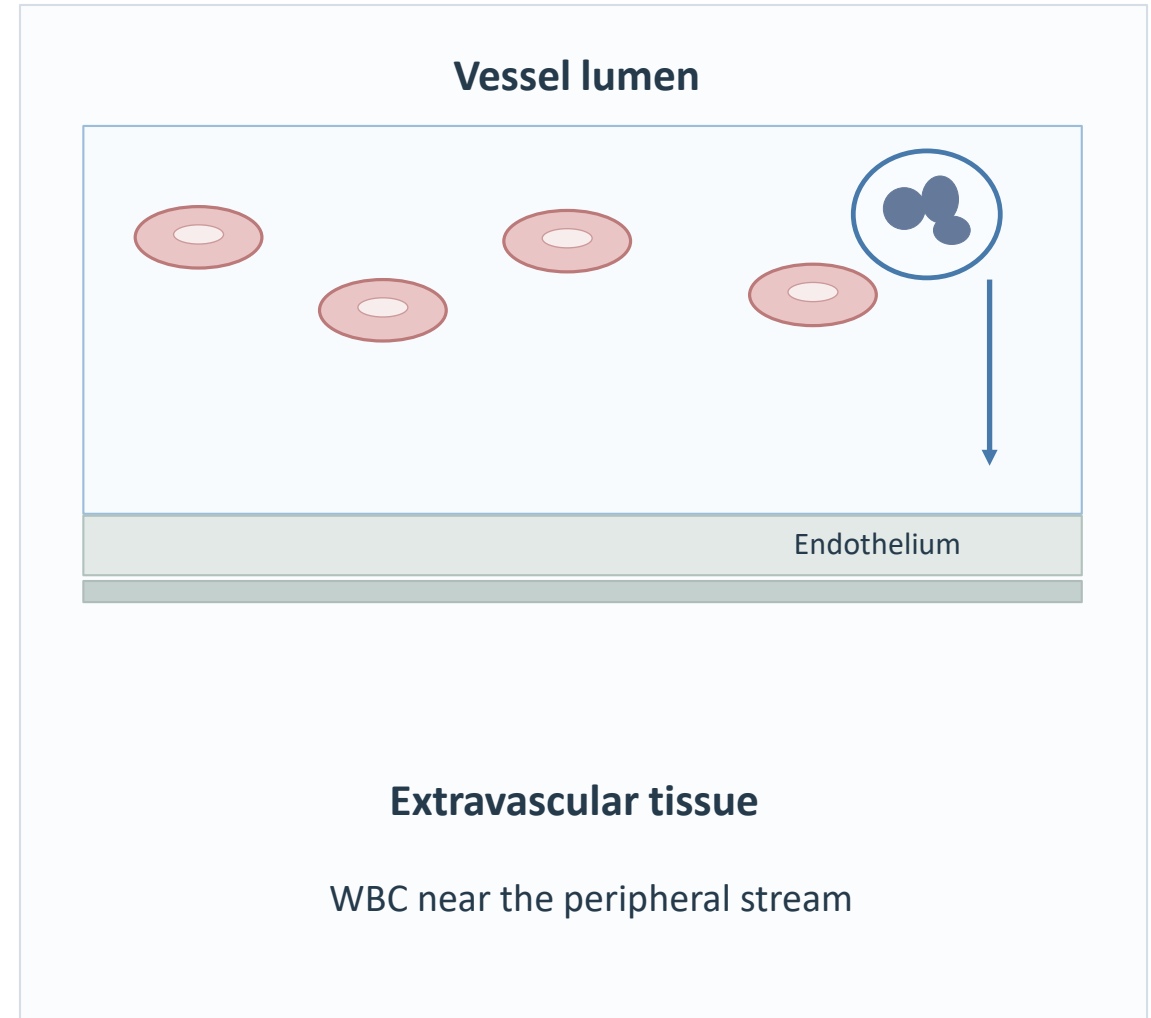
Recruitment crosses distinct compartments

- First: Contact with activated endothelium in the vessel lumen.
- Second: Migration across endothelium and vessel wall.
- Third: Directed interstitial movement toward inflammatory signals.



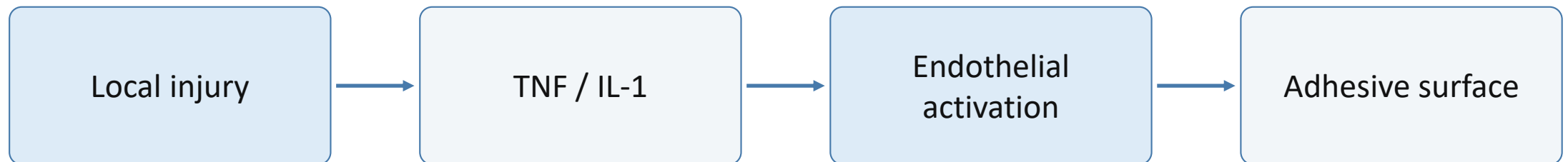
Resting endothelium limits leukocyte traffic

- Normal vascular endothelium generally resists adhesion of circulating leukocytes.
- A leukocyte cannot simply pass through the intact vessel wall without recruitment signals.
- Inflammation induces endothelial changes that permit attachment and emigration.



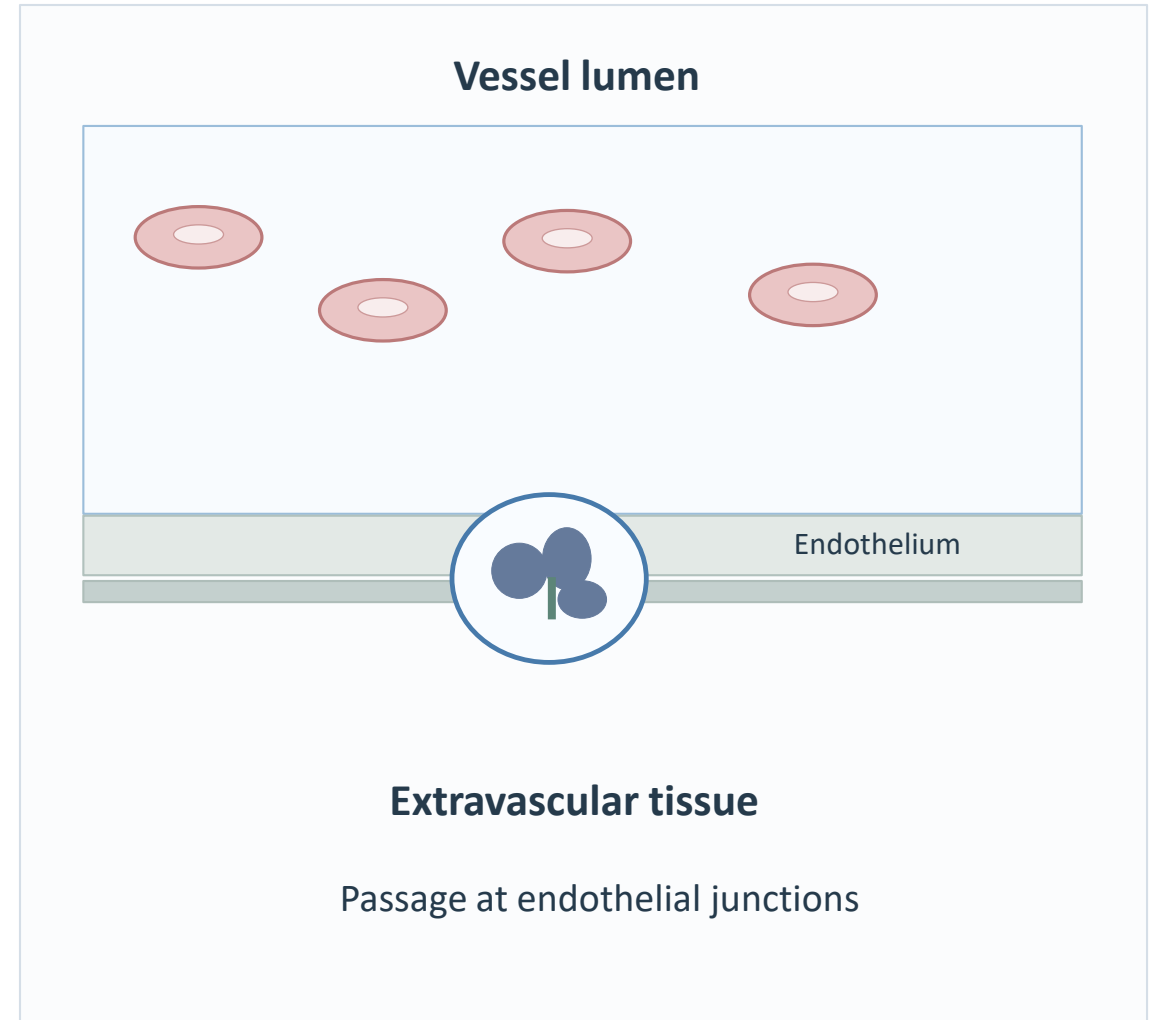
Activated endothelium becomes adhesive

- Microbes and tissue damage activate local sentinel cells.
- Cytokine-driven endothelial activation increases adhesion-molecule expression.
- Chemokines displayed at the endothelial surface activate passing leukocytes.



Postcapillary venules are a principal exit site

- Leukocyte transmigration occurs mainly across postcapillary venules.
- The same microvascular segment is important in increased permeability.
- Leukocyte exit is a regulated junctional process, not simply unrestricted leakage.



The major participating leukocytes

Neutrophils

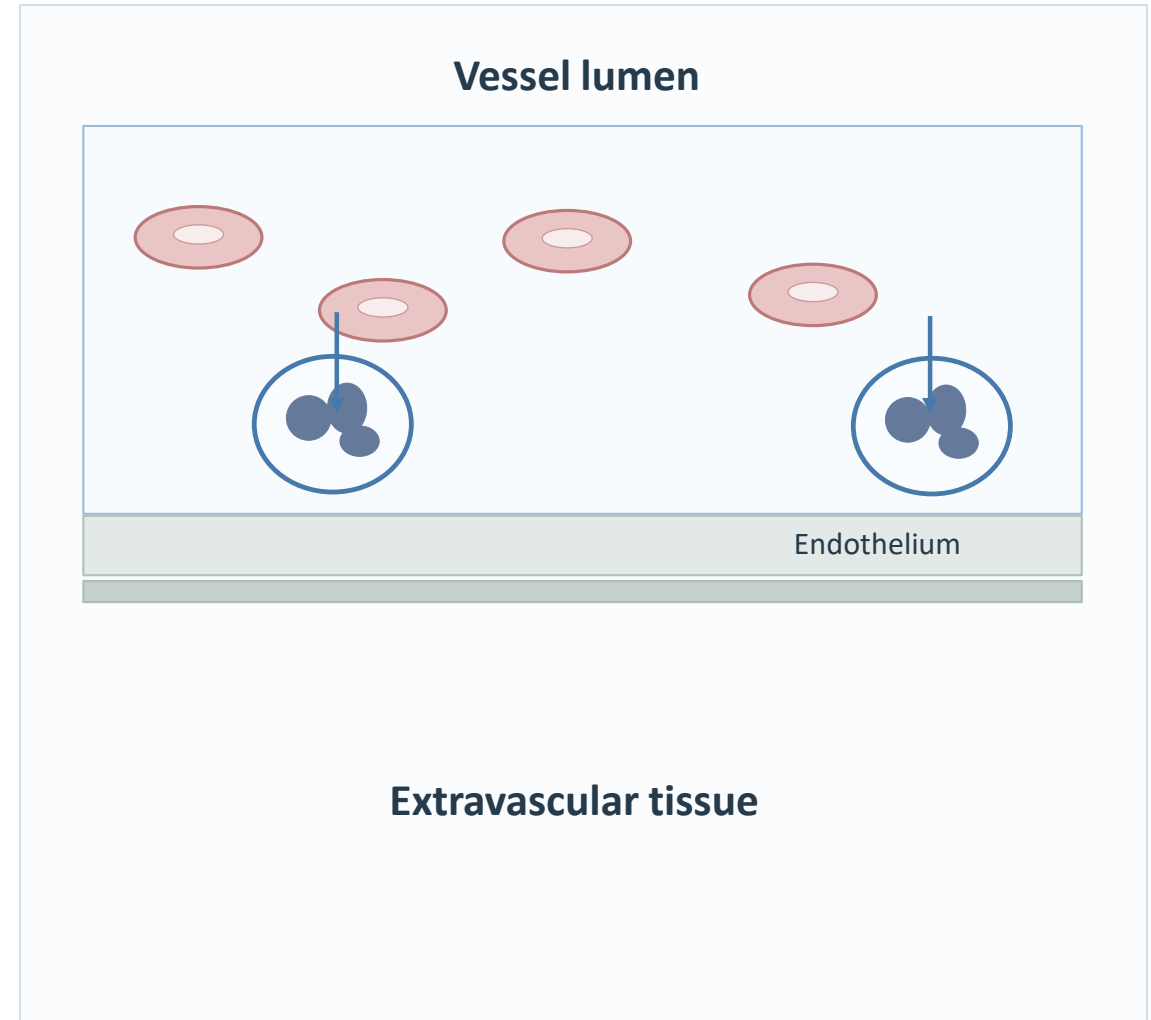
- Numerous circulating phagocytes
- Rapidly recruited in most acute responses
- Short-lived after tissue entry

Monocytes / macrophages

- Become prominent later in typical responses
- Persist longer within tissue
- Participate in clearance and repair

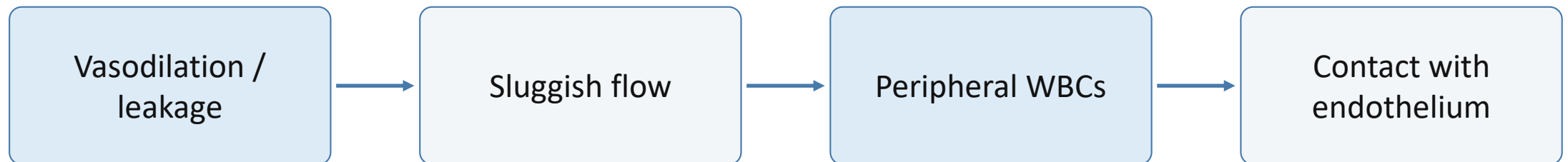
Margination: Movement toward the vessel wall

- Red cells are concentrated in the axial stream in flowing venous blood.
- Leukocytes are displaced toward the vascular periphery.
- Slowed flow increases leukocyte contact with the endothelial surface.



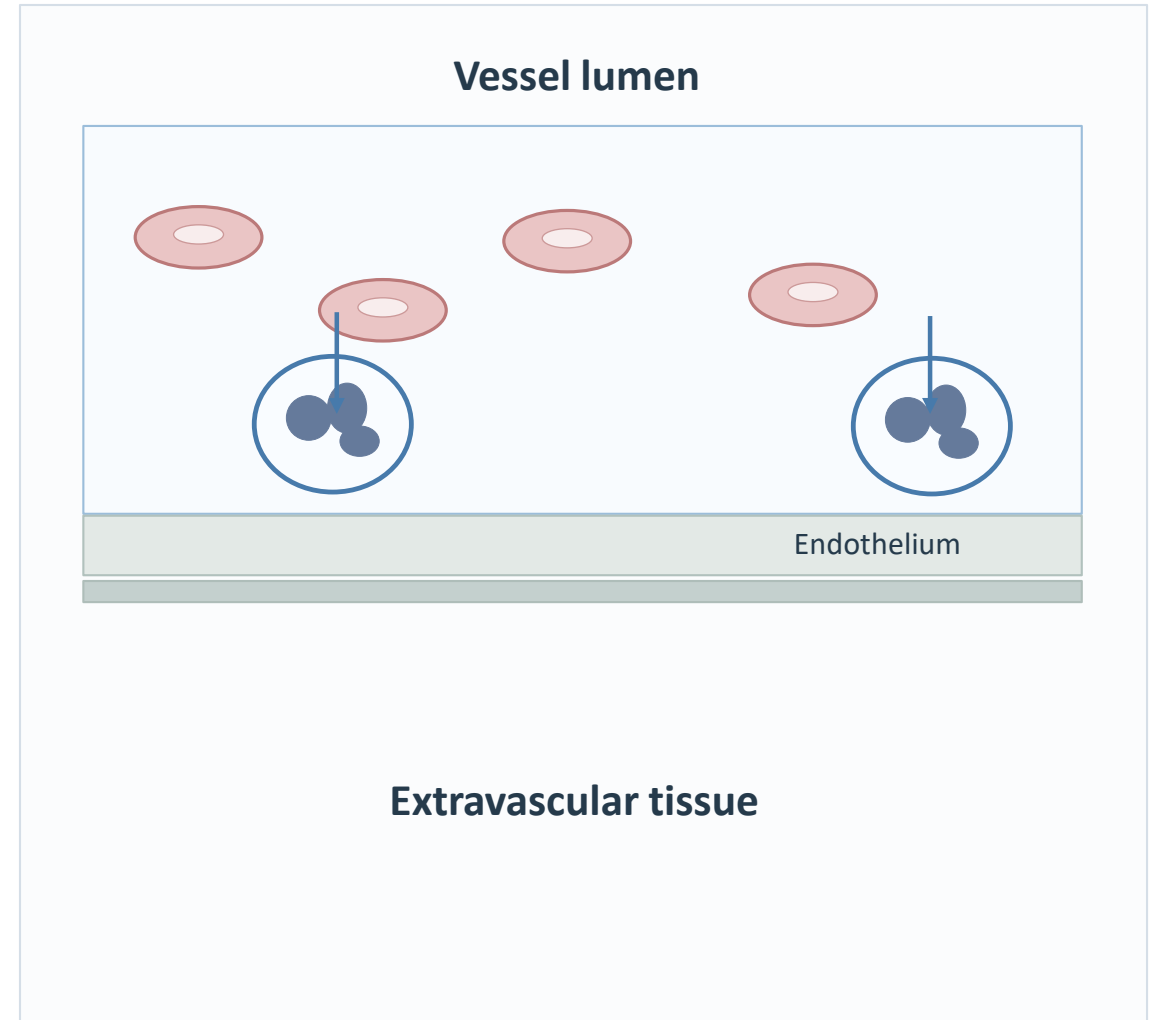
Vascular stasis favors leukocyte margination

- Vasodilation and fluid loss slow microvascular blood flow.
- More leukocytes occupy the peripheral stream as flow becomes sluggish.
- Margination increases opportunities for molecular adhesion.



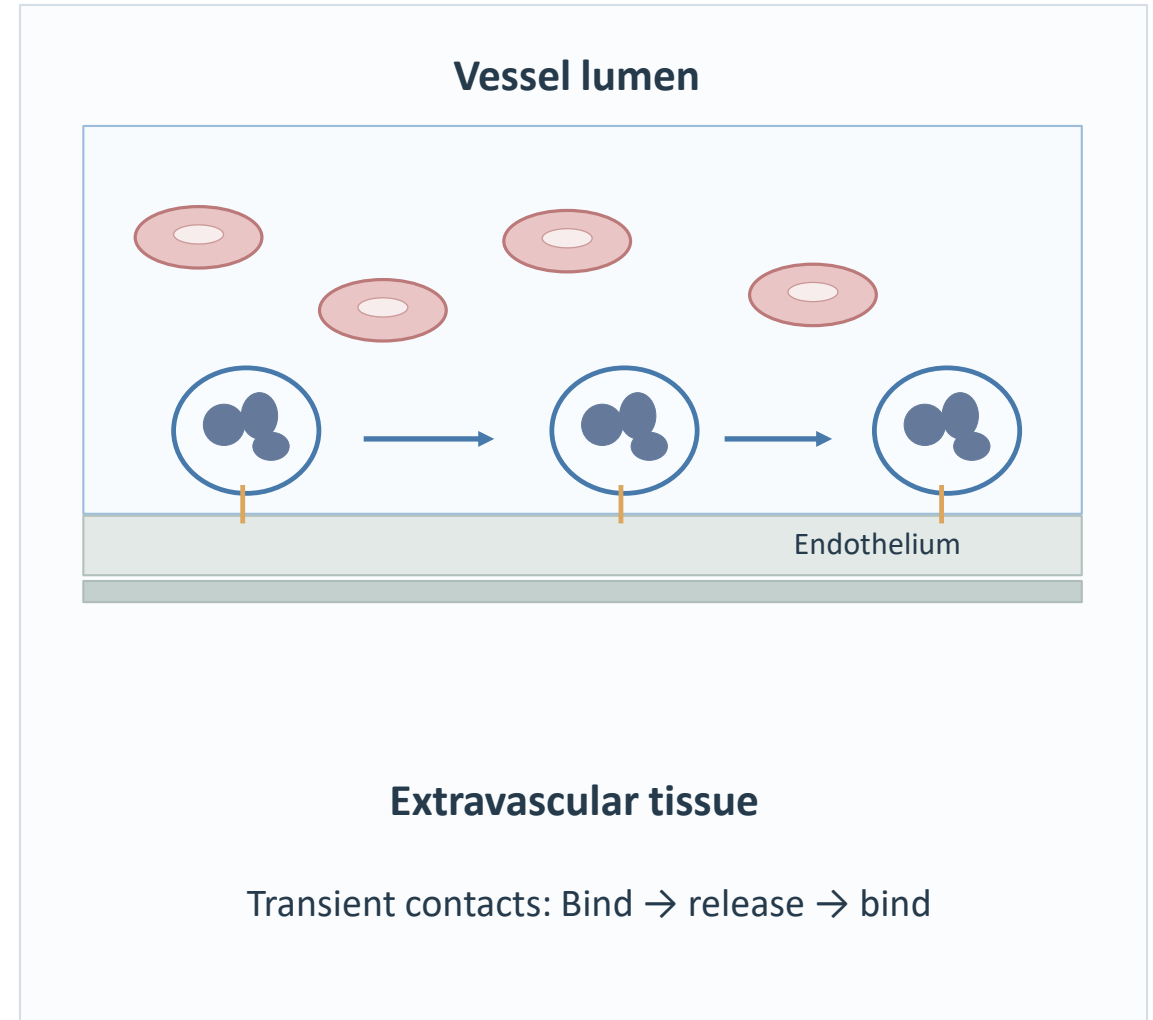
Margination is a positional event

- Margination redistributes circulating leukocytes; It does not itself establish firm attachment.
- Rolling is the next molecular interaction with endothelial adhesion molecules.
- Separating these events prevents conflating altered hemodynamics with receptor–ligand binding.



Rolling consists of repeated weak contacts

- Leukocytes briefly attach to, detach from, and reattach to activated endothelium.
- Rapid bond dissociation allows motion along the endothelial surface.
- The dominant adhesion-molecule family at this stage is the selectins.



Selectins form a three-member family

- L-selectin is found on leukocytes.
- E-selectin is expressed by activated endothelial cells.
- P-selectin is found in platelets and endothelial cells.
- Selectins interact with carbohydrate-bearing ligands.

L-selectin

Leukocyte

E-selectin

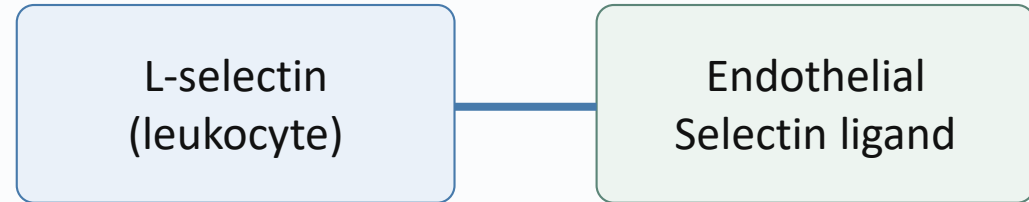
Activated endothelium

P-selectin

Platelets / endothelium

L-selectin is leukocyte-associated

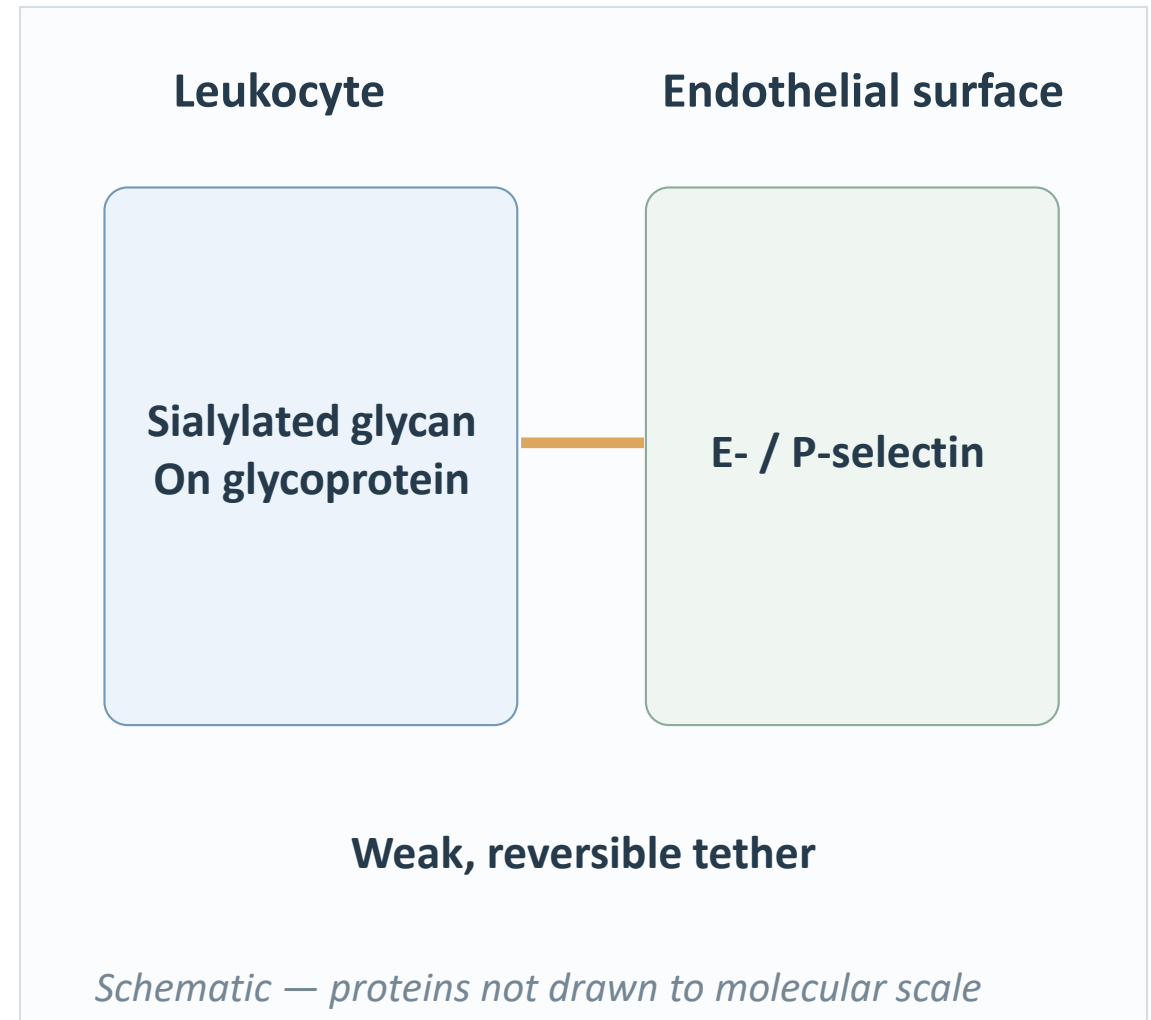
- L-selectin (CD62L) is present on several circulating leukocyte populations.
- Leukocyte microvilli display L-selectin to increase access to endothelial ligands.
- It participates in the rolling family of interactions.



Rolling-associated contact

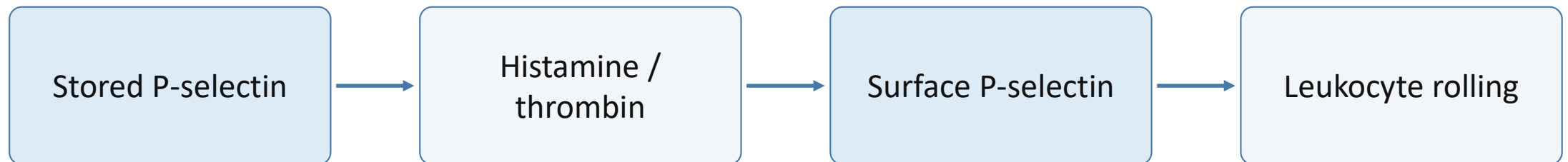
E-selectin is induced by cytokines

- E-selectin (CD62E) is expressed by endothelial cells exposed to TNF and IL-1.
- Its ligands include sialylated glycans on leukocyte glycoproteins.
- Induced E-selectin supports leukocyte rolling at an inflamed focus.



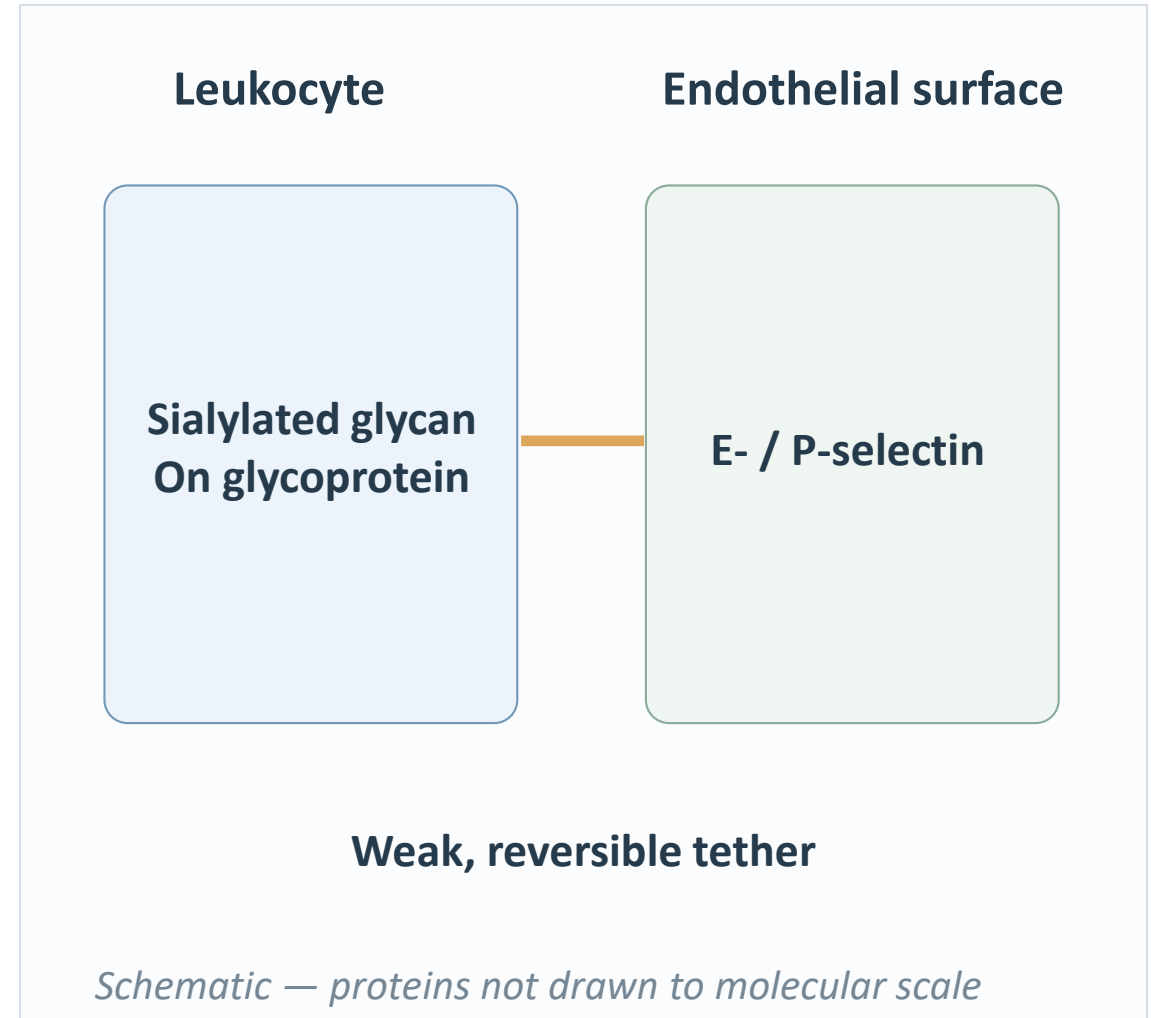
P-selectin can appear rapidly

- P-selectin (CD62P) is stored in endothelial Weibel–Palade bodies.
- Histamine and thrombin stimulate its movement to the cell surface.
- Surface P-selectin binds carbohydrate-bearing leukocyte ligands.



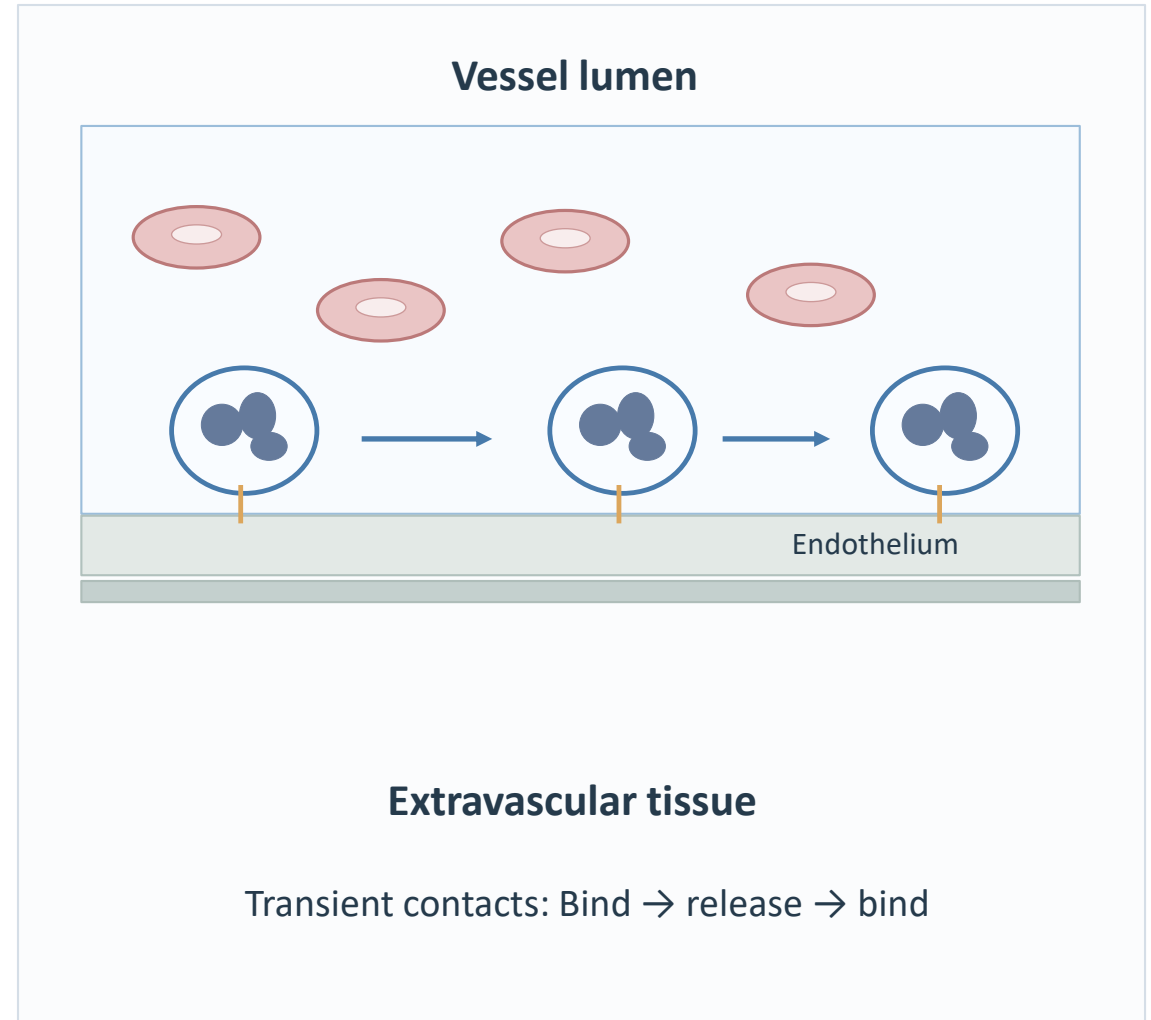
Selectin ligands carry sialylated sugars

- Selectins recognize carbohydrate motifs on mucin-like glycoproteins.
- Sialyl-Lewis X is a representative selectin-binding carbohydrate motif.
- Adhesion depends on matched endothelial and leukocyte ligands.



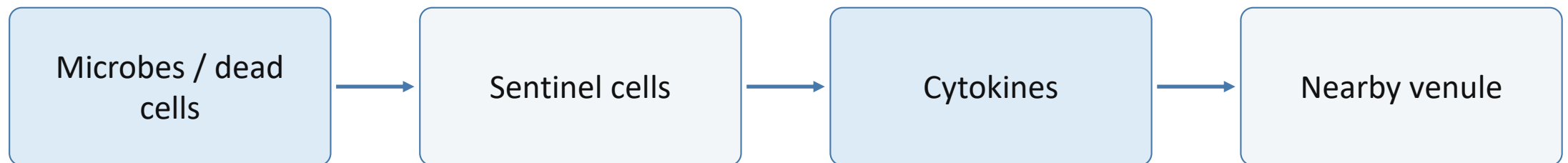
Selectin interactions are easily broken

- Rolling contacts are relatively low-affinity and rapidly reversible.
- Blood-flow forces continually break and reform transient bonds.
- The result is progressive movement, not a fixed stop.



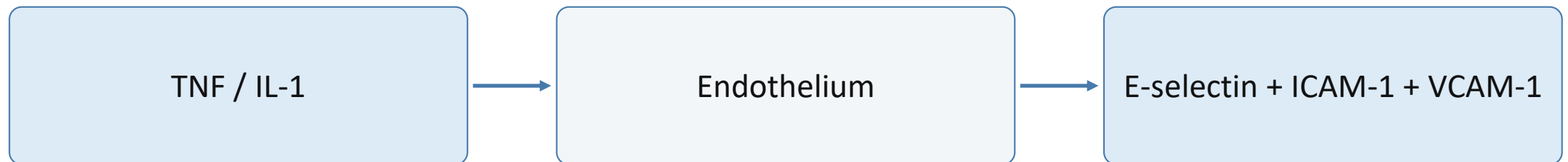
Sentinel cells initiate local recruitment

- Tissue macrophages, mast cells, and endothelium respond to microbes and injury.
- They generate cytokines, including TNF, IL-1, and chemokines.
- Local production helps direct leukocyte recruitment toward the affected tissue.



TNF and IL-1 activate nearby venules

- TNF and IL-1 induce a coordinated endothelial adhesion program.
- The response includes molecules involved in rolling and firm adhesion.
- Endothelial induction localizes inflammatory recruitment to stimulated tissue.



Endothelial responses have different kinetics

Rapid redistribution

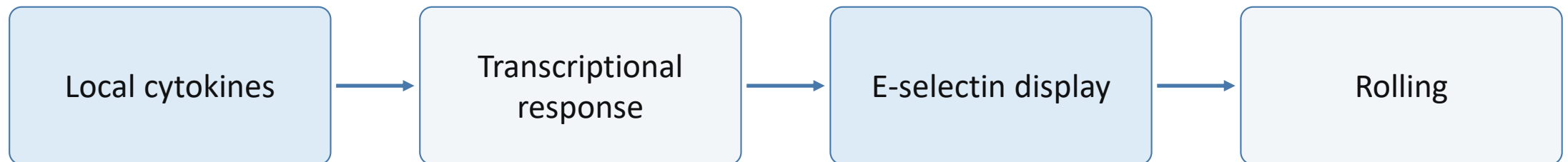
- Histamine or thrombin signal
- Preformed P-selectin reaches the surface
- No de novo synthesis is required for the stored pool

Cytokine-driven induction

- TNF and IL-1 act on endothelial cells
- E-selectin becomes detectable over ~1–2 hours
- Integrin ligands are also upregulated

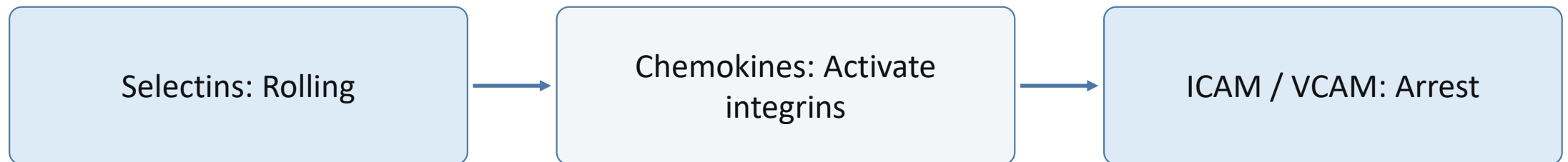
Induced E-selectin appears within 1–2 hours

- TNF and IL-1 produce time-dependent endothelial activation.
- The source describes endothelial E-selectin expression within 1–2 hours.
- This timing is distinct from mobilization of preformed P-selectin.



Endothelial activation coordinates two steps

- Selectin expression favors initial rolling contacts.
- ICAM-1 and VCAM-1 provide ligands for firm integrin-mediated adhesion.
- Chemokine presentation raises integrin affinity on leukocytes.



Rolling and firm adhesion are mechanistically distinct

Rolling

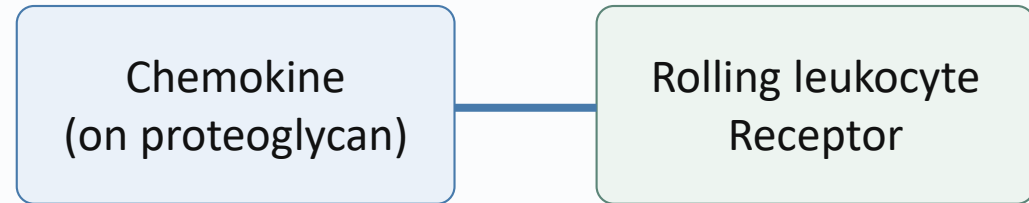
- Selectin-dominated interactions
- Transient, repeatedly disrupted bonds
- Leukocyte continues moving

Firm adhesion

- Activated leukocyte integrins
- Stable binding to ICAM-1 or VCAM-1
- Leukocyte arrests and spreads

Chemokines are displayed on the endothelial surface

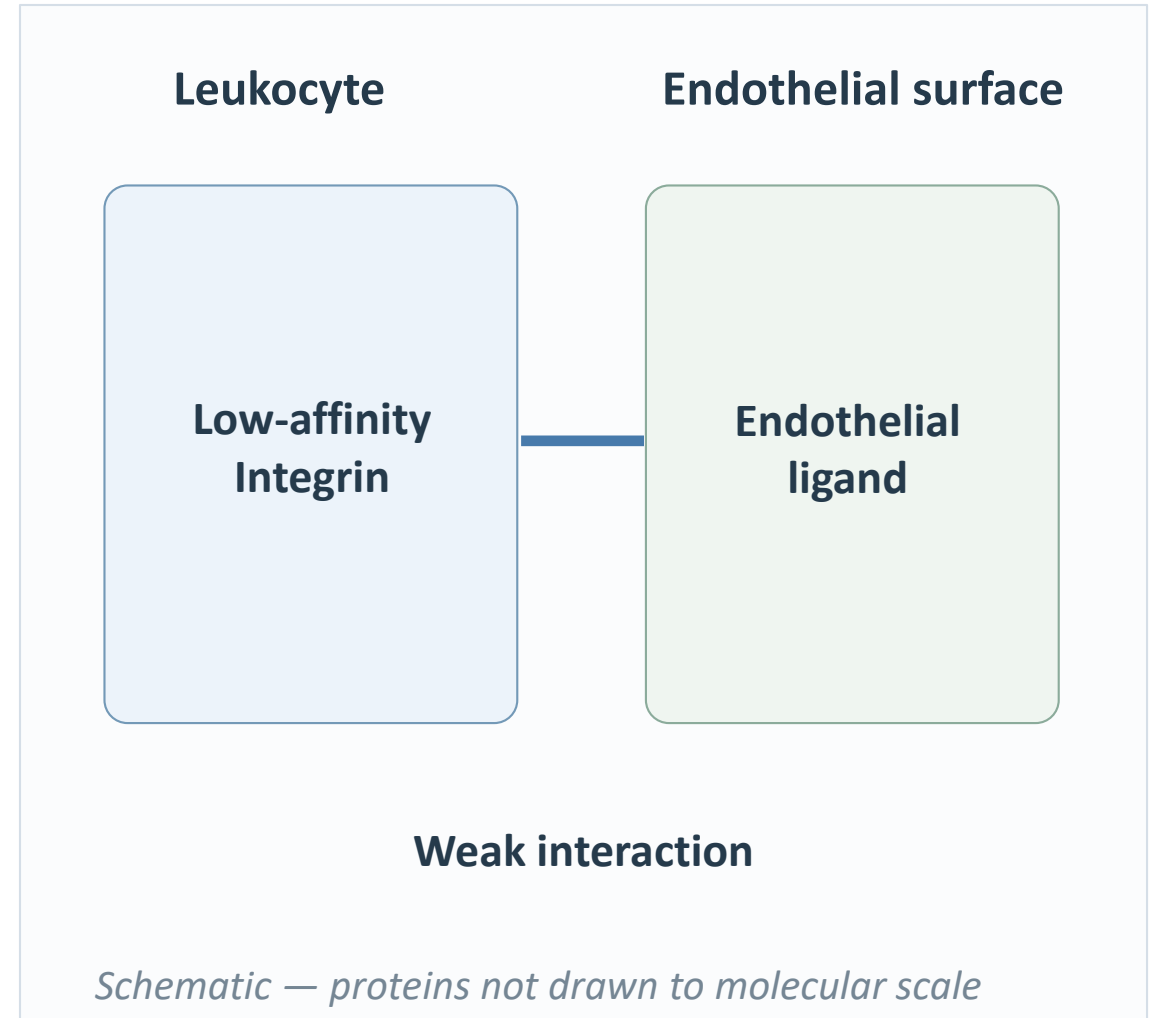
- Locally produced chemokines associate with endothelial proteoglycans.
- Surface presentation exposes rolling leukocytes to concentrated signals.
- Chemokine receptors transmit the activation signals needed for firm adhesion.



Local signaling at the vessel wall

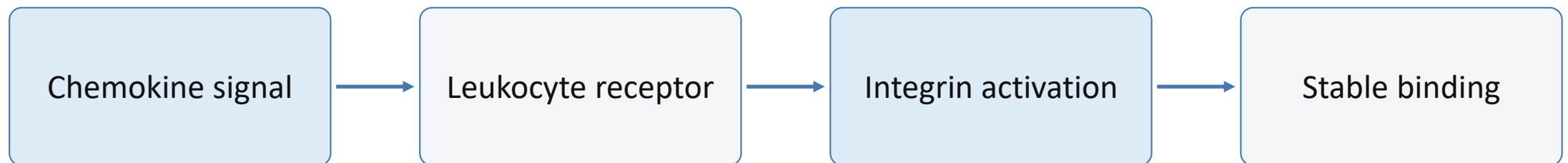
Integrins start in a low-affinity state

- Leukocytes normally carry integrins that do not bind strongly.
- Low integrin affinity permits continued circulation rather than universal adhesion.
- Inflammation must first convert these receptors into a stronger binding state.



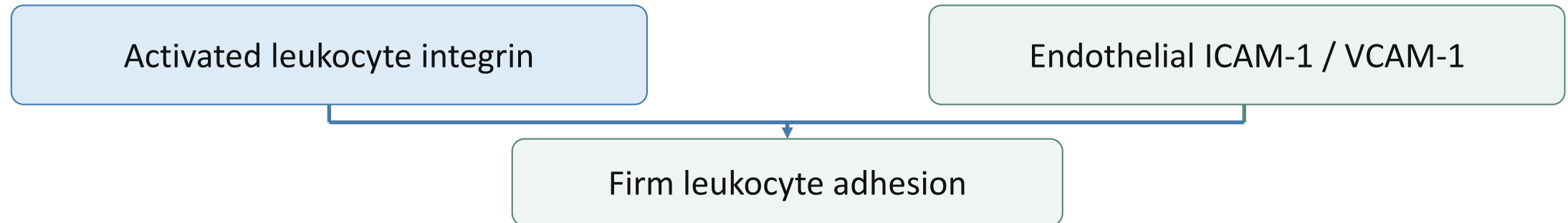
Chemokines increase leukocyte integrin affinity

- Rolling leukocytes encounter chemokines attached to endothelial surfaces.
- Chemokine receptor signaling switches integrins to high-affinity conformations.
- Activated integrins now bind their endothelial ligands firmly.



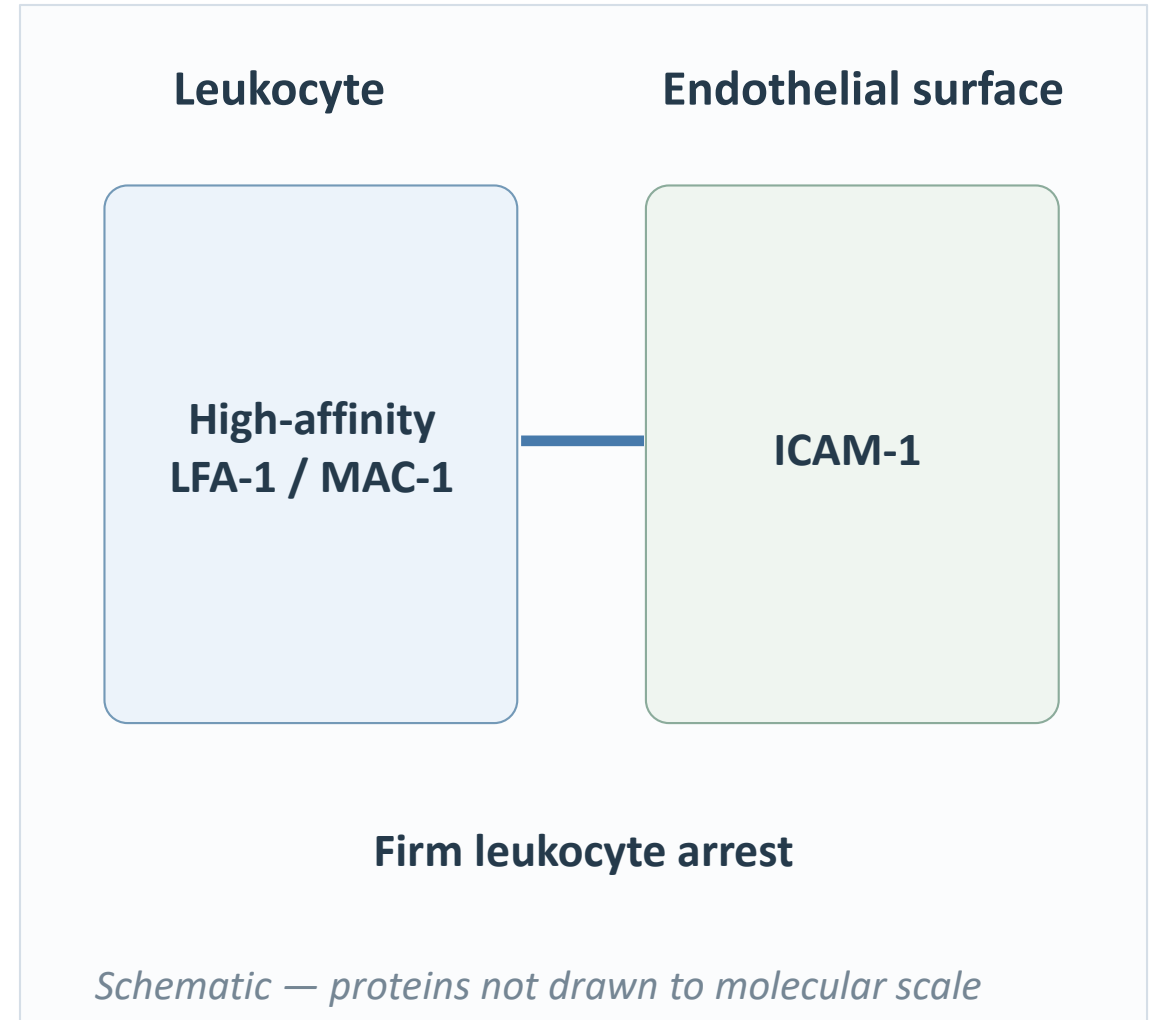
Firm adhesion requires coordinated changes

- The leukocyte increases its integrin-binding capacity.
- The inflamed endothelium increases integrin-ligand expression.
- Together, receptor activation and ligand availability produce firm arrest.



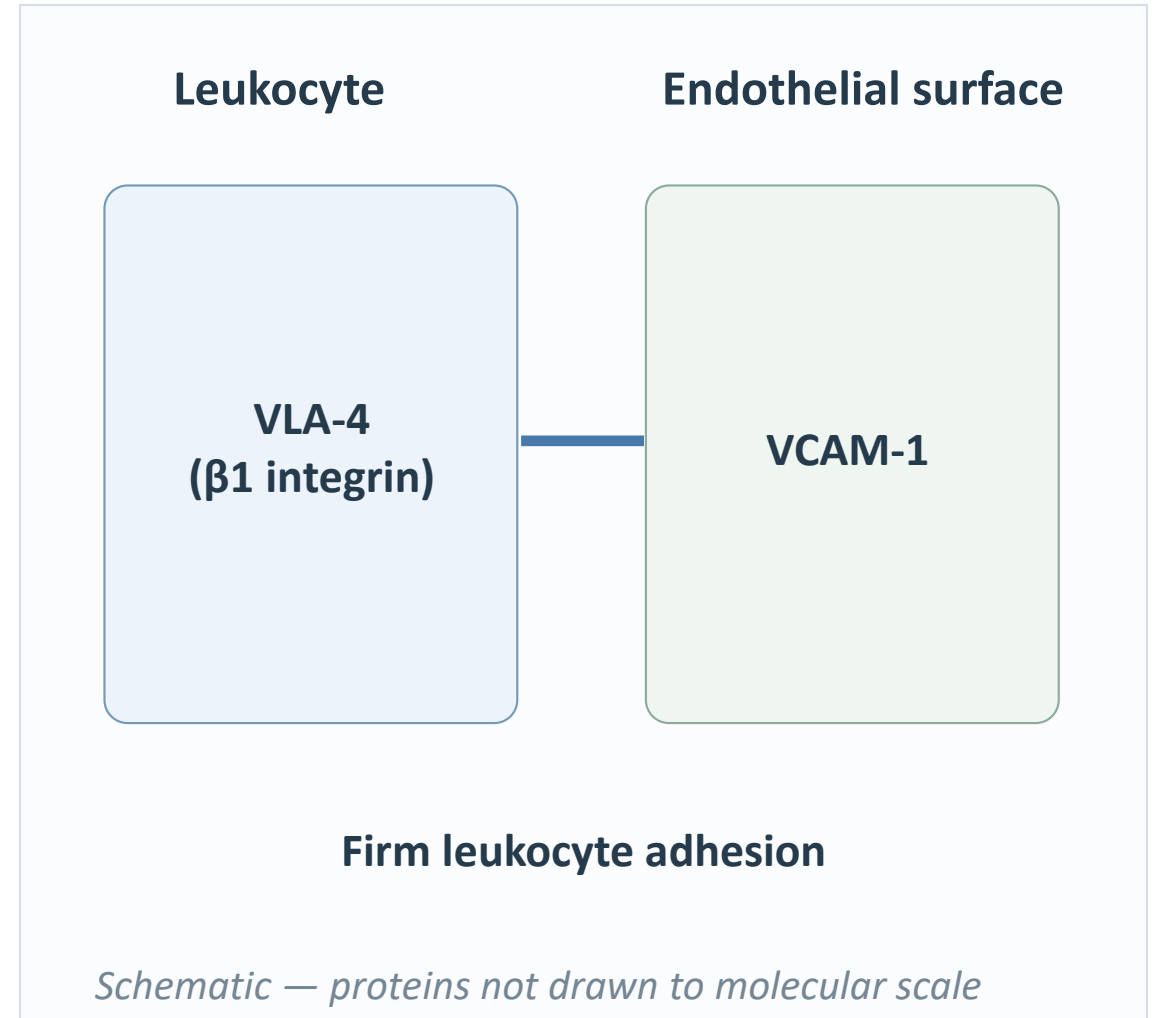
β 2 integrins recognize endothelial ICAMs

- LFA-1 (CD11a/CD18) binds ICAM-1 and ICAM-2.
- MAC-1 (CD11b/CD18) also interacts with ICAM proteins.
- ICAM-1 is increased on activated endothelium.



VLA-4 recognizes VCAM-1

- VLA-4 ($\alpha 4\beta 1$; CD49d/CD29) is a leukocyte $\beta 1$ integrin.
- Activated endothelial cells express VCAM-1.
- VLA-4–VCAM-1 supports firm leukocyte attachment.

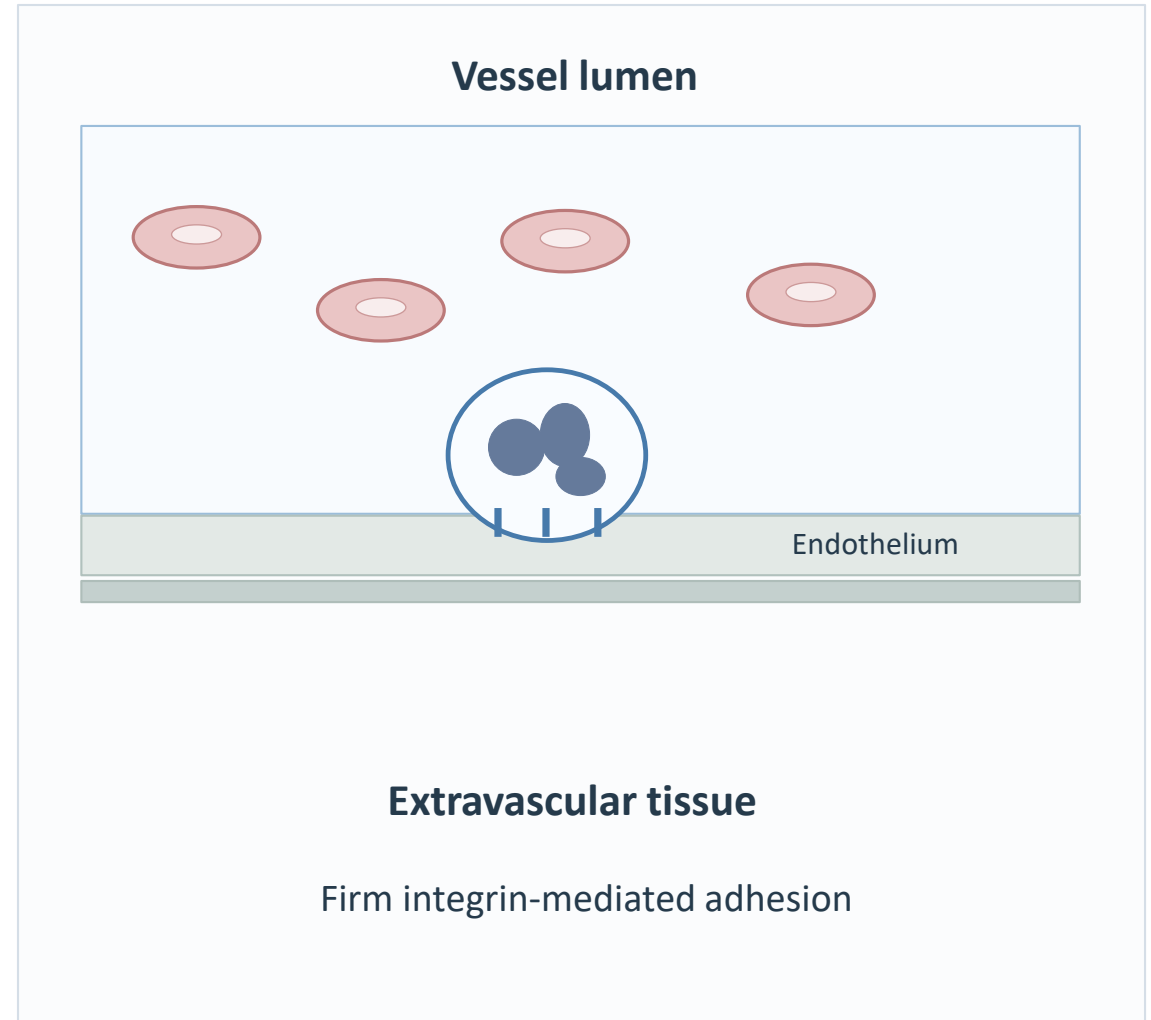


Principal adhesion pairs are specific

Leukocyte molecule	Endothelial partner	Functional stage
Selectin ligands	E-selectin / P-selectin	Rolling
LFA-1 / MAC-1	ICAM-1 / ICAM-2	Firm adhesion
VLA-4	VCAM-1	Firm adhesion
PECAM-1 (CD31)	PECAM-1 (CD31)	Transmigration

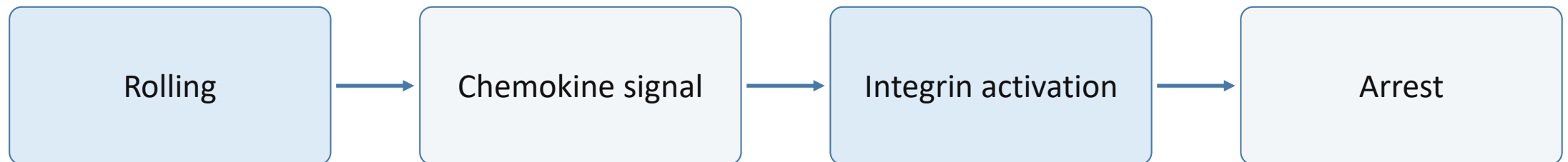
Firmly adherent leukocytes spread out

- Integrin-dependent contacts arrest a rolling leukocyte.
- The cytoskeleton reorganizes as the cell spreads along endothelium.
- This stabilizes the cell before transmigration.



Rolling progresses to stable arrest

- Selectins slow leukocytes with serial reversible contacts.
- Chemokines induce a high-affinity integrin state.
- ICAM-1 / VCAM-1 then bind activated leukocyte integrins.
- The arrested cell is positioned to cross the endothelium.

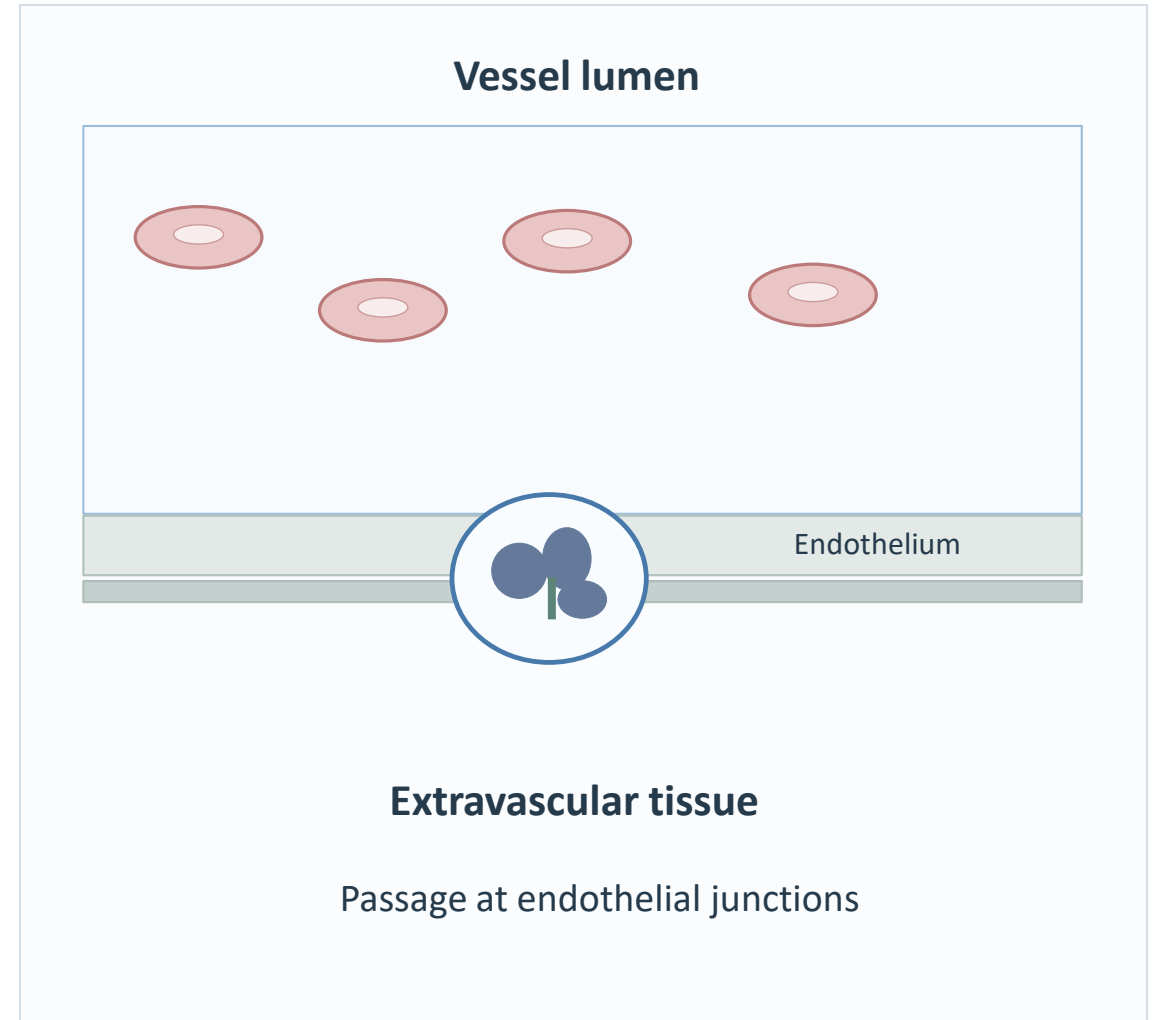


Match each recruitment stage to its molecule

Event	Dominant molecular mediator	Effect
Rolling	Selectins + glycan ligands	Transient tethering
Integrin activation	Chemokines on proteoglycans	Higher integrin affinity
Stable adhesion	Integrins + ICAM / VCAM	Arrest and spreading
Transmigration	PECAM-1 among junction proteins	Cross endothelial barrier

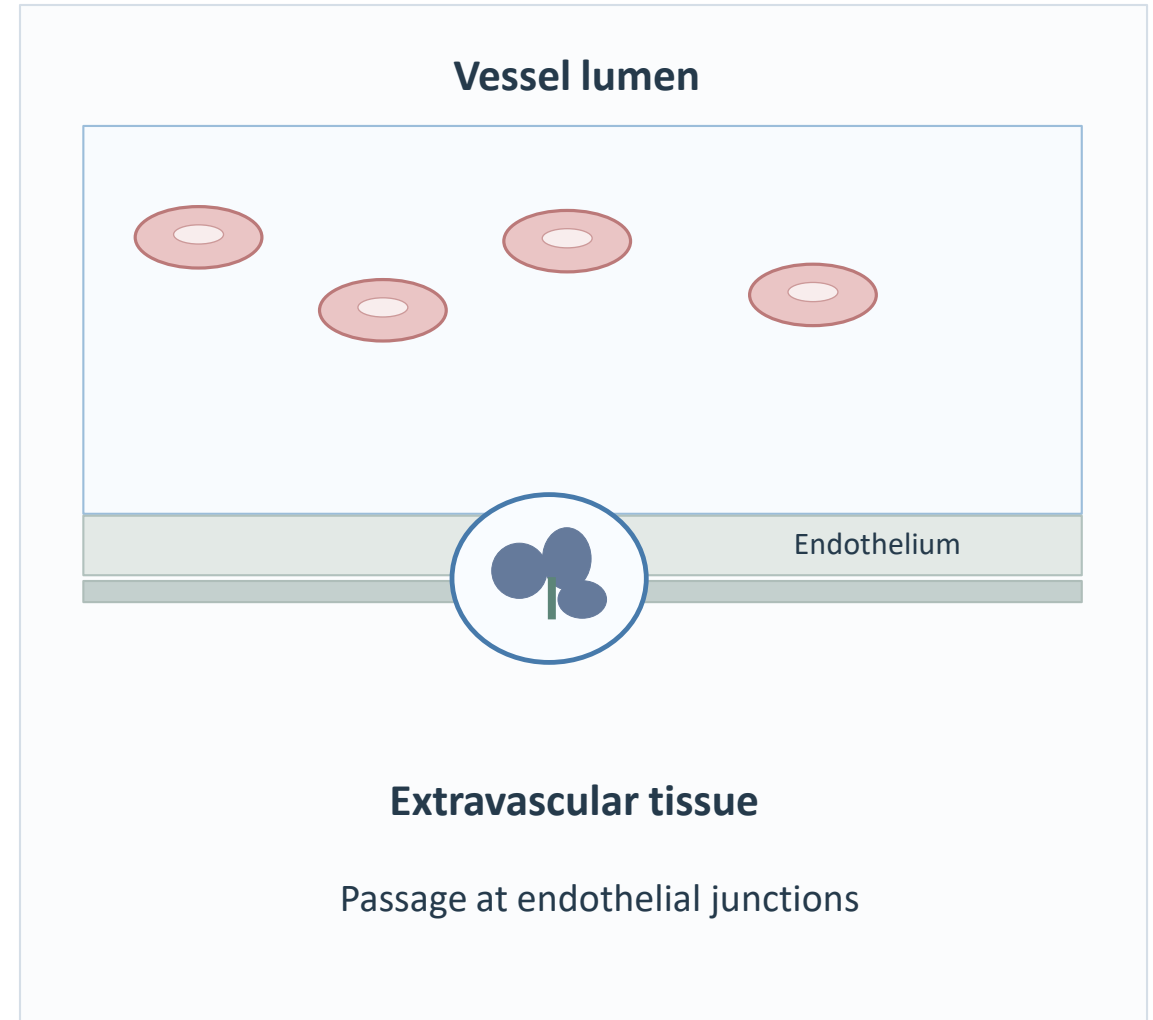
Transmigration is passage through endothelium

- Transmigration (diapedesis) follows stable leukocyte adhesion.
- Leukocytes pass through interendothelial gaps while the endothelium remains intact overall.
- Migration is guided by signals originating from inflamed tissues.



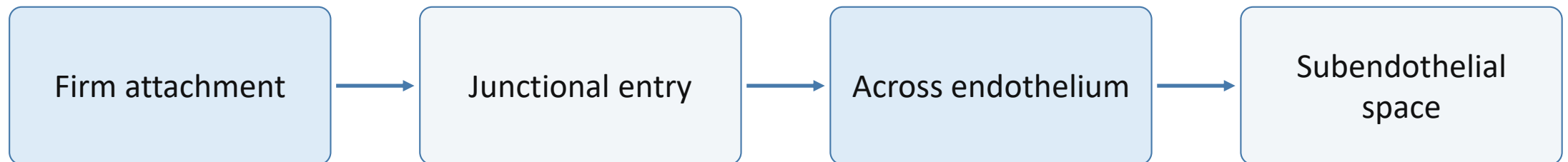
Diapedesis is concentrated in venules

- Postcapillary venules are the main location of leukocyte transmigration.
- Their endothelial junctions are involved in both permeability and cellular exit.
- Adhesion must precede efficient passage across the vessel wall.



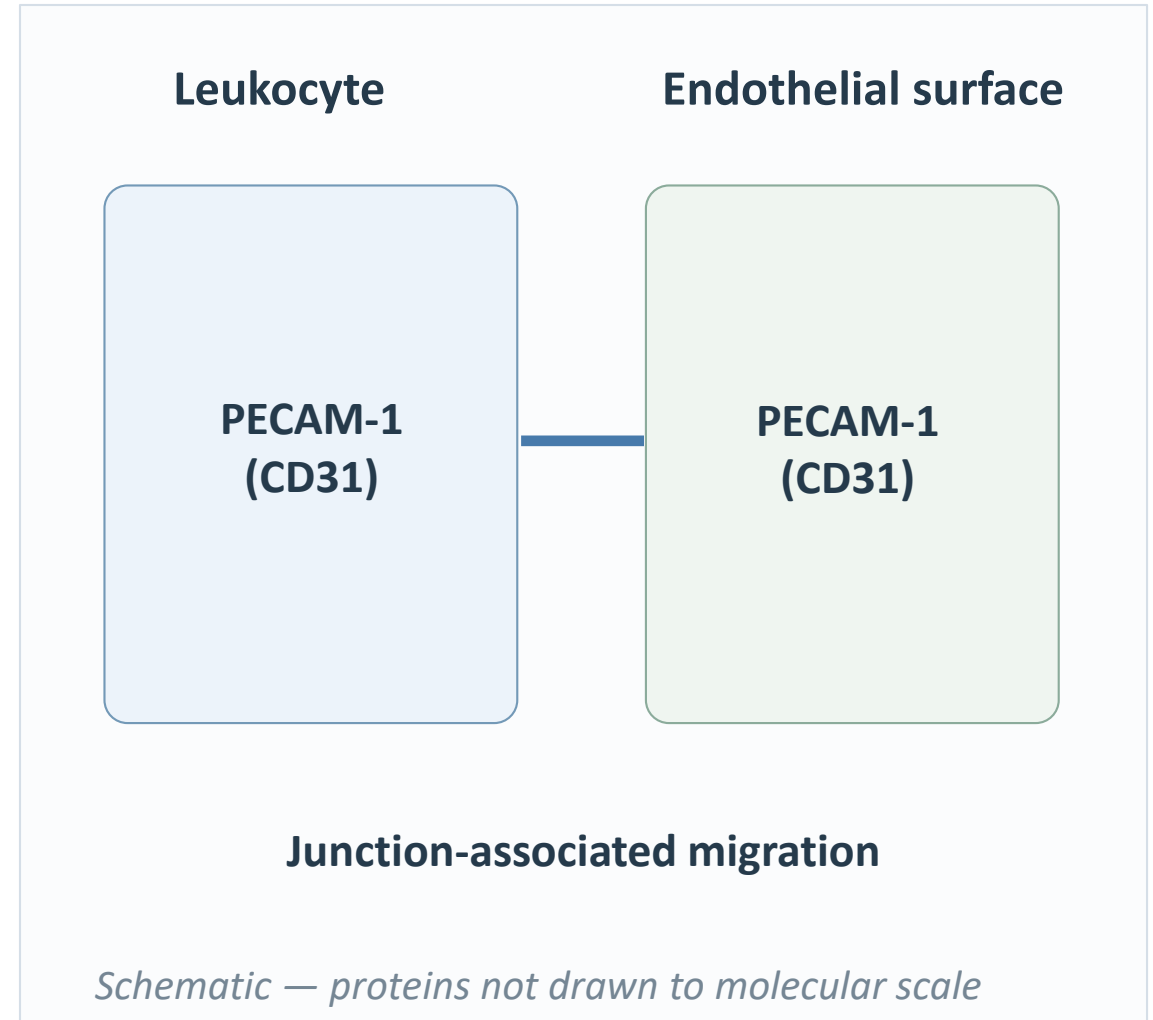
Interendothelial junctions provide a route

- The leukocyte approaches a cell–cell junction after arrest.
- Junction-associated adhesion molecules mediate regulated cellular passage.
- The cell then enters the subendothelial compartment.



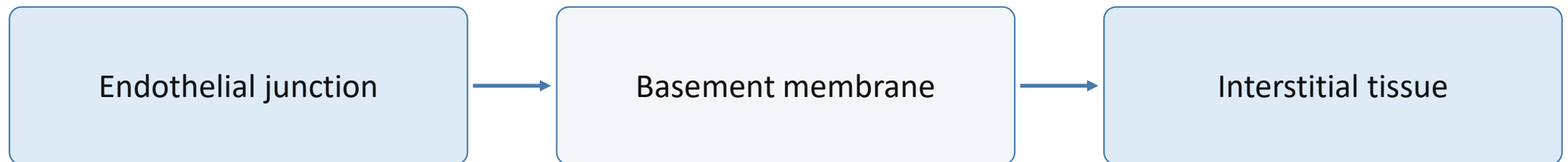
PECAM-1 (CD31) participates in transmigration

- PECAM-1 is an immunoglobulin-superfamily adhesion molecule.
- It is expressed on leukocytes and endothelial cells.
- Homotypic CD31 interactions contribute to the transmigration step.



The basement membrane is crossed after diapedesis

- Following endothelial passage, leukocytes must traverse the basement membrane.
- Collagenases are implicated in permitting matrix penetration.
- The cell then enters the extravascular inflammatory focus.

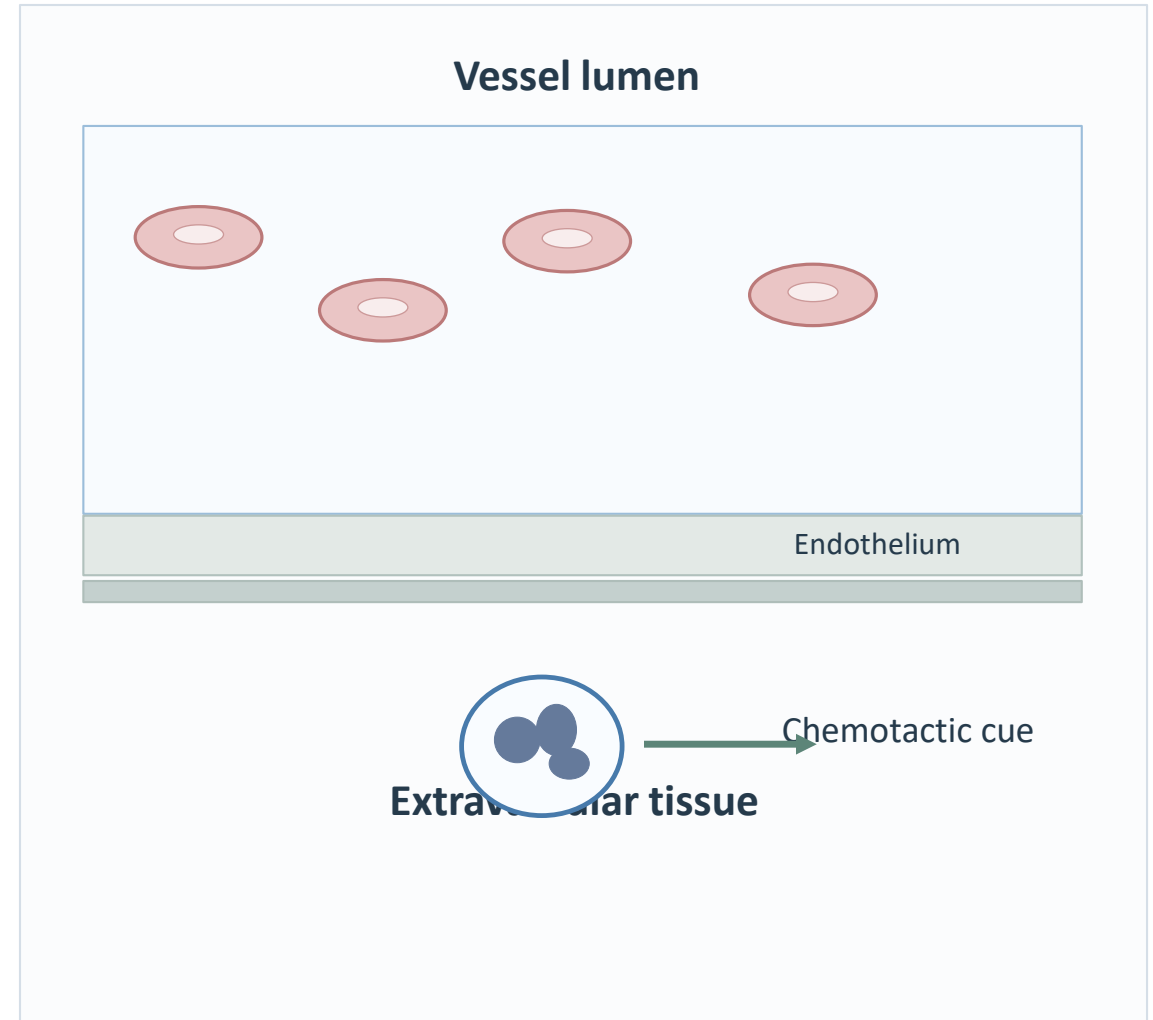


Vascular structure is restored after exit

- Leukocyte passage does not imply permanent destruction of the vessel wall.
- The basement membrane becomes continuous again after emigration.
- Localized remodeling allows defense while preserving vascular integrity.

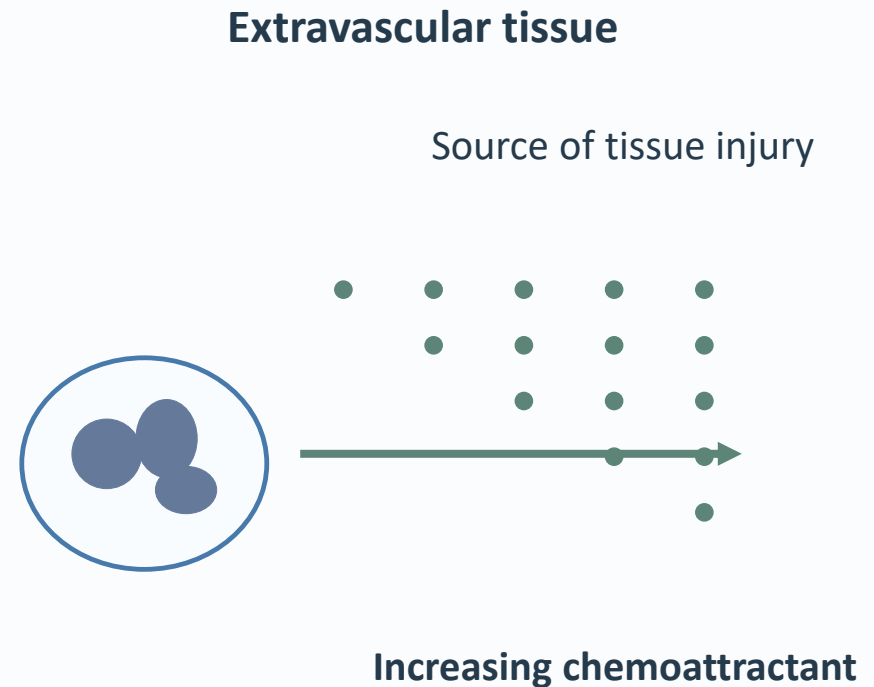
Exit from blood is not the end of recruitment

- Leukocytes accumulate in tissue after they have crossed the vessel wall.
- Directed migration is needed to reach the highest concentration of inflammatory signals.
- The chemotactic stimulus originates from injury or infection.



Chemotaxis follows a chemical gradient

- Chemotaxis is locomotion toward a higher concentration of chemoattractant.
- The stimulus can originate from microbial products or host mediators.
- Cell movement is directional rather than random.



Schematic — concentration trend, not measured data

Chemoattractants may be exogenous or endogenous

Microbe-derived

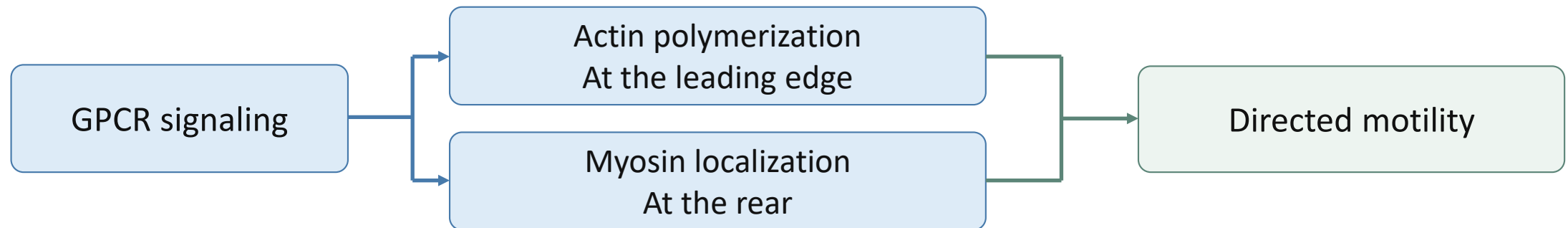
- Bacterial N-formylated peptides
- Other microbial lipids and products
- Signals associated with infection

Host-derived

- Chemokines such as IL-8
- Complement fragment C5a
- Leukotriene B4 (LTB4)

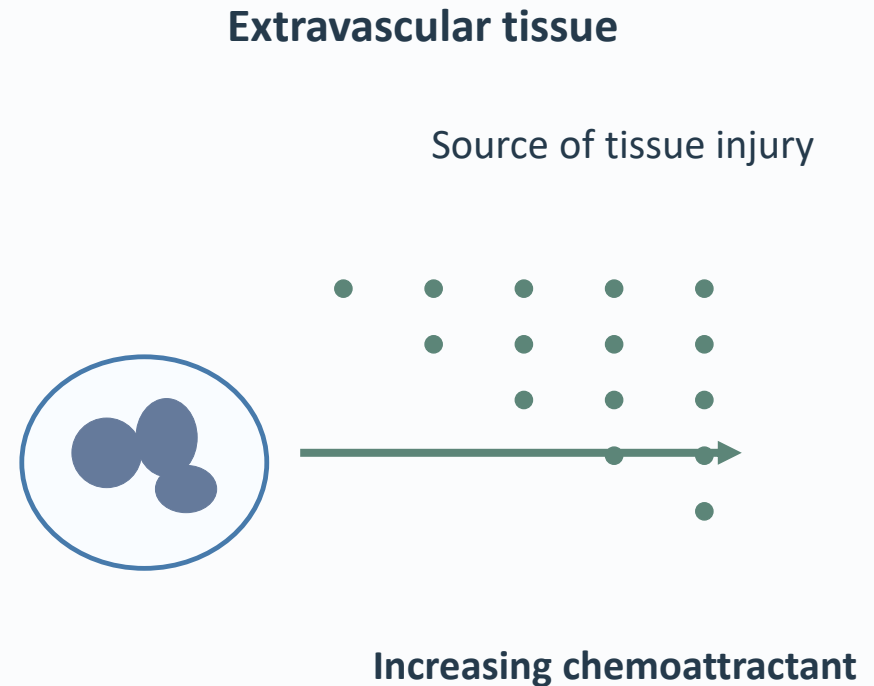
Chemoattractant receptors reorganize the cell

- Chemoattractants activate seven-transmembrane G protein–coupled receptors.
- Second messengers trigger actin polymerization at the leading edge.
- Myosin localization toward the rear supports directed cell movement.



Inflamed tissue determines the direction of travel

- Chemokines and other chemoattractants originate near damaged tissue or microbes.
- Migrating leukocytes follow the spatial gradient toward its source.
- This mechanism concentrates recruited cells where effector function is required.



Schematic — concentration trend, not measured data

Typical early infiltrates are neutrophil-rich

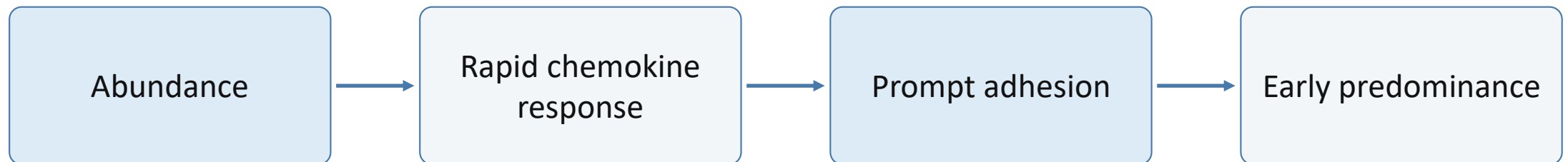
- Neutrophils usually predominate during the first 6–24 hours of acute inflammation.
- They enter quickly in response to chemokines and early endothelial adhesion signals.
- This is a typical pattern, not a universal clock for all inflammatory stimuli.

Monocytes usually follow in the next phase

- In many acute inflammatory reactions, monocytes become prominent after 24–48 hours.
- Recruited monocytes differentiate into tissue macrophages.
- The shift reflects differences in recruitment and survival.

Why neutrophils usually arrive first

- Neutrophils are abundant in circulating blood.
- They respond rapidly to chemokines.
- They interact efficiently with rapidly induced endothelial adhesion molecules.



Most extravasated neutrophils are short-lived

- Tissue neutrophils undergo apoptosis after a relatively brief lifespan.
- Neutrophil disappearance helps make room for later mononuclear infiltrates.
- The cellular profile evolves even when the initial insult is resolving.

Macrophages persist and may proliferate

- Monocyte-derived macrophages survive longer than recruited neutrophils.
- Macrophages may multiply within tissues.
- They become prominent in sustained inflammatory responses and participate in repair.

The inflammatory stimulus changes the infiltrate

- The conventional neutrophil-to-monocyte sequence has important exceptions.
- Different pathogens preferentially evoke distinct leukocyte populations.
- Interpret the cellular composition in relation to cause and timing.

Some bacterial infections remain neutrophil-rich

- In some infections, continued neutrophil recruitment persists for days.
- Pseudomonas infections as an example.
- A neutrophil-rich lesion therefore need not be very early.

Viral infections may recruit lymphocytes early

- Lymphocytes may be among the earliest recruited cells in some viral infections.
- This differs from the conventional early neutrophilic pattern.
- Cell type alone is insufficient to date an inflammatory lesion.

Allergy and helminths favor eosinophils

- Eosinophils may predominate in allergic reactions.
- Helminthic infections are another classic eosinophil-associated stimulus.
- The leukocyte pattern reflects the nature of the immune response.

Some hypersensitivity reactions are mononuclear

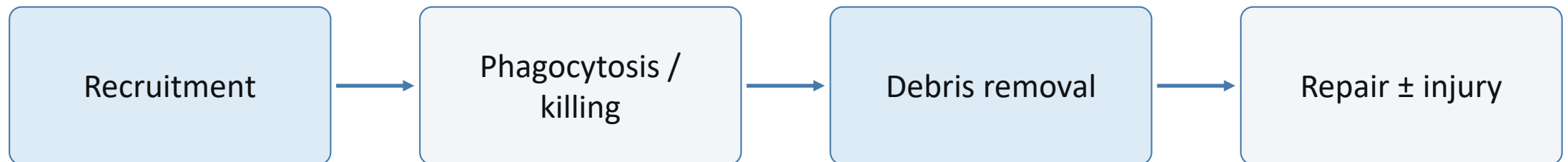
- Activated lymphocytes and macrophages may dominate immune-mediated reactions.
- Plasma cells can also form part of the infiltrate.
- Recruitment is shaped by the underlying adaptive immune response.

Cell composition is a clue, not a diagnosis

Setting	Potential prominent cells	Interpretation
Typical early acute inflammation	Neutrophils	Often 6–24 h
Typical later phase	Monocytes / macrophages	Often 24–48 h
Certain bacterial infections	Persistent neutrophils	Continued recruitment
Some viral infections	Lymphocytes	Stimulus-dependent exception
Allergy / helminths	Eosinophils	Type of inflammatory trigger

Recruitment supports both killing and repair

- Neutrophils and macrophages reach the tissue to remove microbes and debris.
- Macrophages contribute to repair-promoting growth-factor production.
- Microbicidal activity can also cause collateral tissue injury.

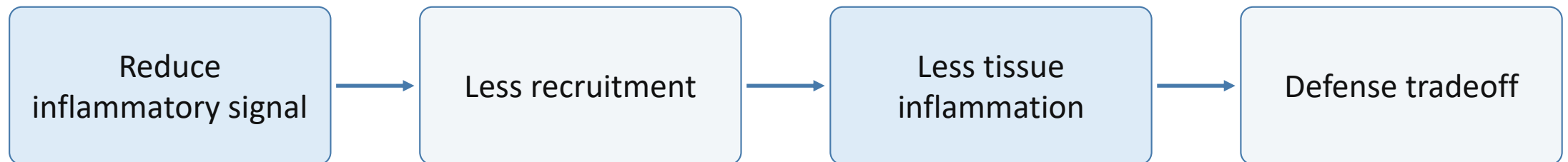


Adhesion defects predispose to infection

- Genetic defects of leukocyte adhesion molecules impair movement from blood into tissues.
- The clinical consequence can be increased susceptibility to bacterial infections.
- This demonstrates that adhesion is essential for protective inflammation.

Therapeutic suppression has an immune cost

- Blocking TNF can attenuate cytokine-dependent inflammatory recruitment.
- Integrin antagonists can diminish leukocyte adhesion.
- Interfering with host defense increases vulnerability to microbial infection.



Clinical application: A fresh skin wound

Clinical vignette (illustrative)

A patient develops focal erythema and swelling around a contaminated cut. Circulating neutrophils must reach the affected tissue.

Which molecular event converts rolling into firm arrest?

- A. Selectin binding alone
- B. Chemokine-induced activation of leukocyte integrins
- C. Permanent endothelial rupture

Case analysis: Firm arrest needs integrin activation

Chemokines → high-affinity integrins → adhesion

- Correct: B — surface chemokines activate leukocyte integrins.
- Activated integrins bind ICAM-1 or VCAM-1 and stop the rolling cell.
- Selectins alone generally mediate transient rolling, not stable arrest.

Clinical application: Recurrent bacterial infections

Clinical vignette (illustrative)

An individual has recurrent bacterial infections and a suspected inherited defect affecting leukocyte attachment to endothelium.

Which phase of the inflammatory response may fail?

- A. Leukocyte adhesion and subsequent tissue entry
- B. Production of circulating erythrocytes
- C. Formation of plasma proteins in the liver

Case analysis: Failure of leukocyte recruitment

Impaired adhesion → impaired tissue defense

- Correct: A — adhesion and emigration can fail despite circulating leukocytes.
- Adhesion molecules are required to establish and maintain contacts with endothelium.
- Increased bacterial infection susceptibility in genetic adhesion defects.

Clinical application: Persistent neutrophils

Clinical vignette (illustrative)

A tissue lesion remains neutrophil-rich several days after infection began. The suspected organism is *Pseudomonas*.

Does neutrophil predominance prove the lesion is less than 24 hours old?

- A. Yes — neutrophils only occur during the first day
- B. No — ongoing recruitment can sustain neutrophil predominance

Case analysis: Interpret kinetics cautiously

The stimulus modifies leukocyte kinetics

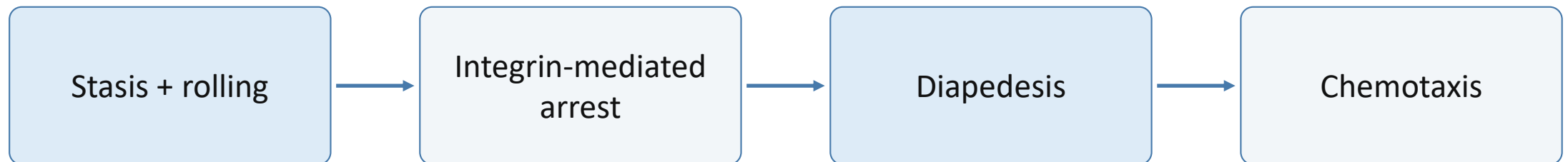
- Correct: B — stimulus can override the typical recruitment sequence.
- Some bacterial infections sustain neutrophil influx for several days.
- Cell type must be interpreted alongside stimulus, clinical course, and tissue findings.

Compare the main molecular checkpoints

Checkpoint	Key molecules	What changes?
Rolling	E-/P-selectin; Selectin ligands	Reversible slowing
Activation	Chemokines; Leukocyte receptors	Integrins gain affinity
Firm adhesion	LFA-1, MAC-1, VLA-4; ICAM / VCAM	Stable cell arrest
Diapedesis	PECAM-1 (CD31) and junction proteins	Exit across endothelium
Chemotaxis	IL-8, C5a, LTB4; GPCR	Migration in tissue

Leukocyte recruitment: Integrated mechanism

- Inflammation produces stasis and activates local endothelium.
- Selectin interactions promote rolling; Chemokines activate integrins.
- Firm adhesion precedes PECAM-associated transmigration.
- Chemotaxis delivers emigrated leukocytes to the site of injury.



Interpretation principles for pathology

- Identify the stage being described before assigning a molecular mediator.
- Distinguish the time course of a typical infiltrate from pathogen-specific exceptions.
- Explain both host-defense benefits and possible tissue injury.
- Remember that an intact endothelium is actively regulated during leukocyte transit.

Primary source and terminology

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Chapter 3, Inflammation and Repair, pages 69–72.
- Sections: Leukocyte Recruitment to Sites of Inflammation; Leukocyte Adhesion to Endothelium; Leukocyte Migration Through Endothelium; Chemotaxis of Leukocytes.
- Source text was provided as Markdown extraction; the original textbook figures were not reproduced.