

Cytokines and Chemokines

Inflammatory signaling, leukocyte recruitment, and systemic responses

Cytokine signals

Leukocyte movement

Systemic responses

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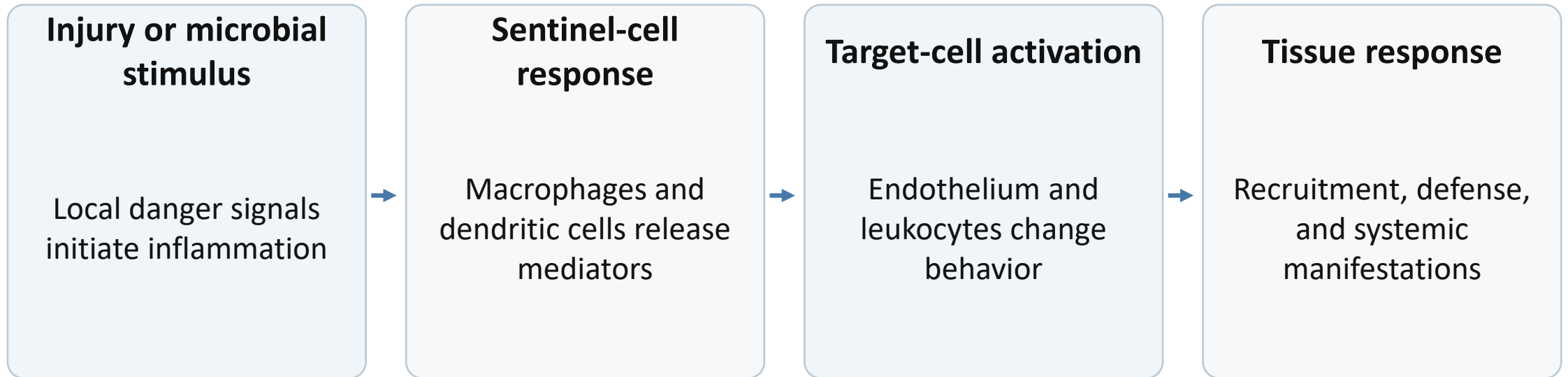
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Learning outcomes

- Identify principal cytokine sources and their major inflammatory actions.
- Explain TNF- and IL-1–driven endothelial and leukocyte activation.
- Relate cytokine effects to fever, acute-phase responses, and cachexia.
- Distinguish chemokine families, receptors, and tissue-specific functions.

Inflammation uses soluble mediators



Cytokines coordinate cells; Chemokines help direct leukocyte movement.

Cytokines: Functional definition

- Protein mediators made by many cell types.
- Regulate and mediate immune and inflammatory reactions.
- Important producers include activated lymphocytes, macrophages, and dendritic cells.
- Epithelial, endothelial, and connective tissue cells can also produce them.

Immune cells and tissue cells both signal

Immune-cell sources

- Activated T lymphocytes
- Macrophages and dendritic cells
- Mast cells; Selected cytokines

Resident-tissue sources

- Endothelial and epithelial cells
- Connective tissue cells
- Site of injury becomes an active signaling compartment

Signaling is not restricted to circulating leukocytes.

Scope: Inflammatory cytokines versus growth factors

- Here, the principal focus is cytokines participating in inflammation.
- Growth factors acting on epithelial and mesenchymal cells are conventionally considered separately.
- Individual mediators can act on multiple cell types and have overlapping effects.
- These slides emphasize tissue responses rather than a full catalogue of immune signaling.

Major cytokines in acute inflammation

Mediator	Main source(s)	Characteristic role
TNF	Macrophages, DCs, mast cells, T cells	Endothelial activation; systemic effects
IL-1	Macrophages, DCs, epithelia	TNF-like actions; prominent fever role
IL-6	Macrophages, other cells	Acute-phase and systemic responses
IL-17	T lymphocytes	Neutrophil and monocyte recruitment

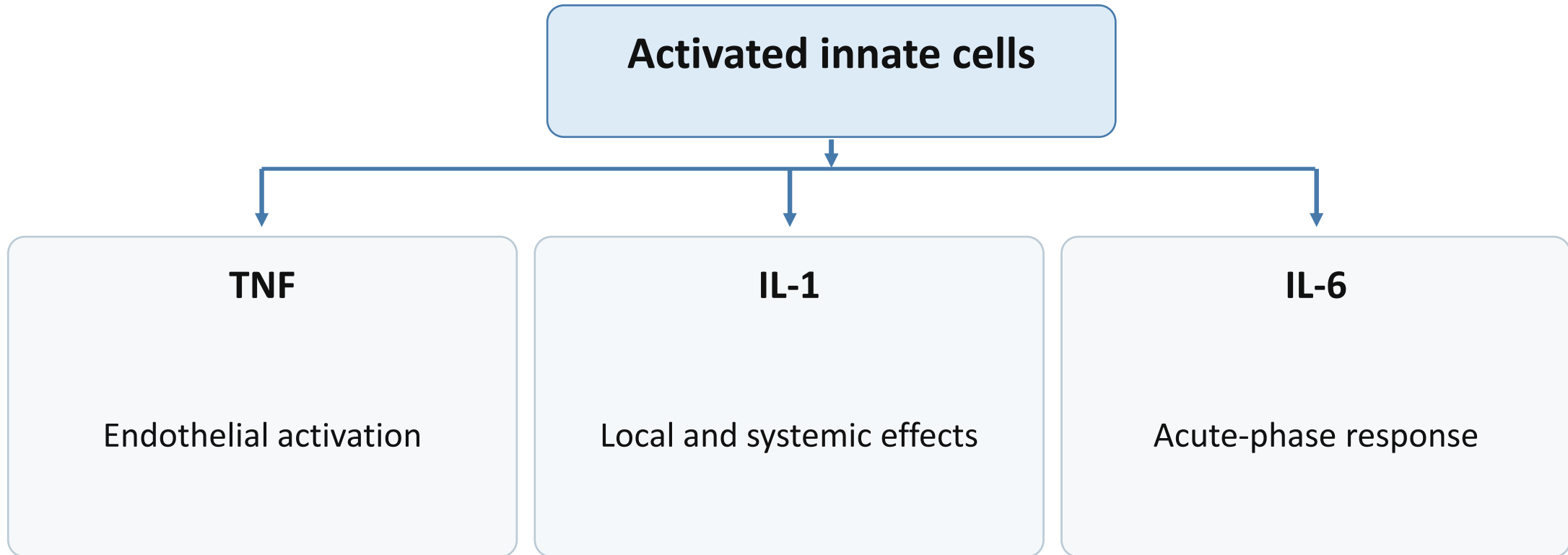
DC = dendritic cell. These mediators have distinct emphases but overlapping actions.

Cytokines highlighted in chronic inflammation

Mediator	Principal source(s)	Key action
IL-12	Dendritic cells, macrophages	Increases interferon- γ production
IFN- γ	T and NK lymphocytes	Activates macrophage microbicidal responses
IL-17	T lymphocytes	Promotes neutrophil / monocyte recruitment

Acute/chronic categories overlap; The classification is functional, not absolute.

Inflammatory signals form an interacting network



These mediators have distinct emphases but substantial functional overlap.

Acute and chronic cytokines overlap

- Cytokines listed under acute inflammation can also act in chronic disease.
- Chronic inflammation includes persistent leukocyte activation and additional lymphocyte-derived signals.
- IL-12, IFN- γ , and IL-17 are prominent mediators in chronic inflammation.
- Avoid treating acute and chronic cytokine lists as mutually exclusive.

TNF is a central inflammatory amplifier

Tumor necrosis factor

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graph TD; TNF[Tumor necrosis factor] --> Endothelium[Endothelium]; TNF --> Leukocytes[Leukocytes]; TNF --> OrganSystems[Organ systems]; Endothelium --> Adhesion[Adhesion molecules and cytokines]; Leukocytes --> Responses[Enhanced responses to stimulation]; OrganSystems --> Fever[Fever and metabolic consequences];
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Endothelium

Adhesion molecules and
cytokines

Leukocytes

Enhanced responses to
stimulation

Organ systems

Fever and metabolic
consequences

The same mediator can have local protective and systemic pathological effects.

Principal cellular sources of TNF

- Activated macrophages and dendritic cells are major sources.
- T lymphocytes and mast cells can also produce TNF.
- The cellular source varies with the initiating stimulus and tissue microenvironment.
- TNF can act on endothelial cells as well as recruited inflammatory cells.

Diverse stimuli trigger TNF and IL-1

Biological stimuli

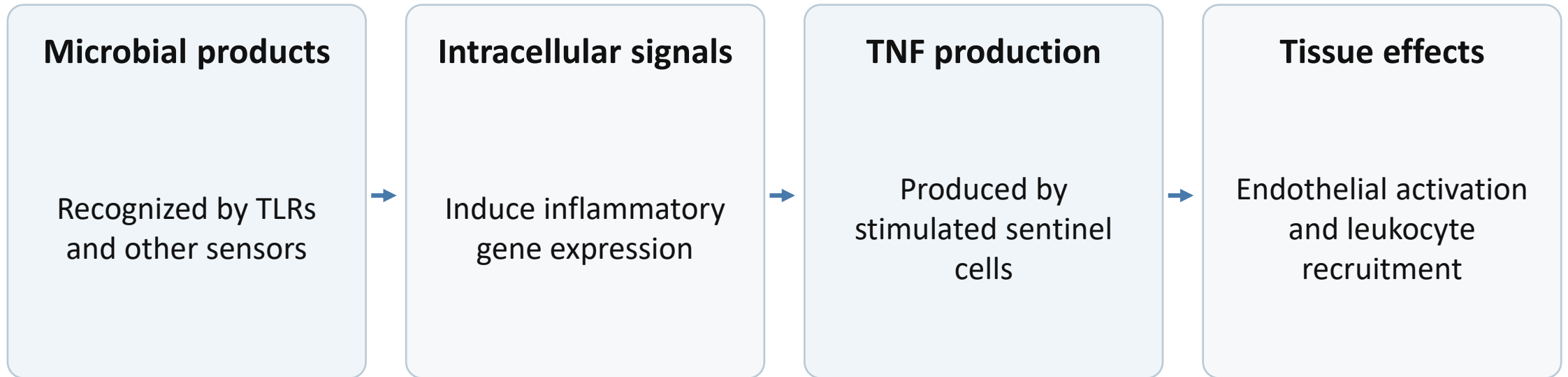
- Microbial products
- Dead or injured cells
- Immune complexes

Other inflammatory stimuli

- Foreign bodies
- Physical injury
- Other local triggers of inflammation

Cytokine release links danger recognition with an organized inflammatory response.

Microbial sensing induces TNF

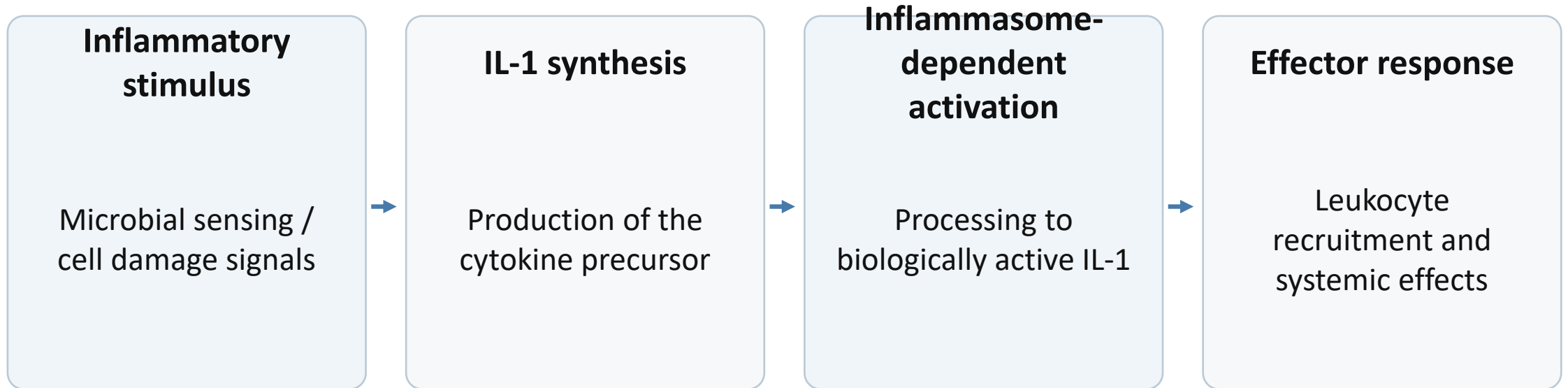


TLR = Toll-like receptor; This is a simplified causal sequence.

IL-1 shares stimuli but has an extra control step

- Macrophages and dendritic cells are major sources of IL-1.
- Some epithelial cells also produce IL-1.
- Signals that induce TNF also stimulate IL-1 synthesis.
- Generation of biologically active IL-1 depends on inflammasome activity.

IL-1 requires synthesis and maturation



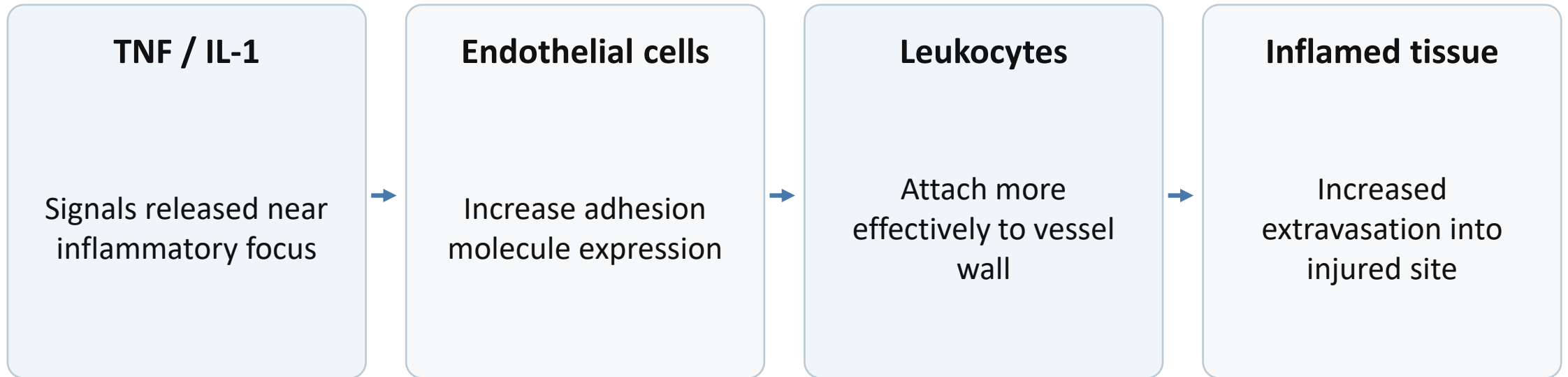
IL-1 protein synthesis and inflammasome-dependent activation are distinct steps.

TNF and IL-1: Overlap and emphasis

Feature	TNF	IL-1
Main source	Macrophages / DCs; T cells and mast cells	Macrophages / DCs; some epithelia
Endothelial effect	Activation, adhesion molecules	Similar endothelial activation
Distinct emphasis	Cachexia / metabolic effects	Stronger role in fever
Upstream control	Microbial sensor signals	Inflammasome-dependent maturation

Overlap is substantial; “distinct emphasis” is not exclusivity.

TNF and IL-1 initiate endothelial activation



Endothelial activation is a prerequisite for efficient leukocyte recruitment.

Endothelial activation changes the vessel wall

- Up-regulates E-selectin and P-selectin.
- Increases endothelial ligands for leukocyte integrins.
- Stimulates additional inflammatory mediators and growth factors.
- Increases the procoagulant activity of the endothelium.

Selectins and integrin ligands are complementary

Selectins

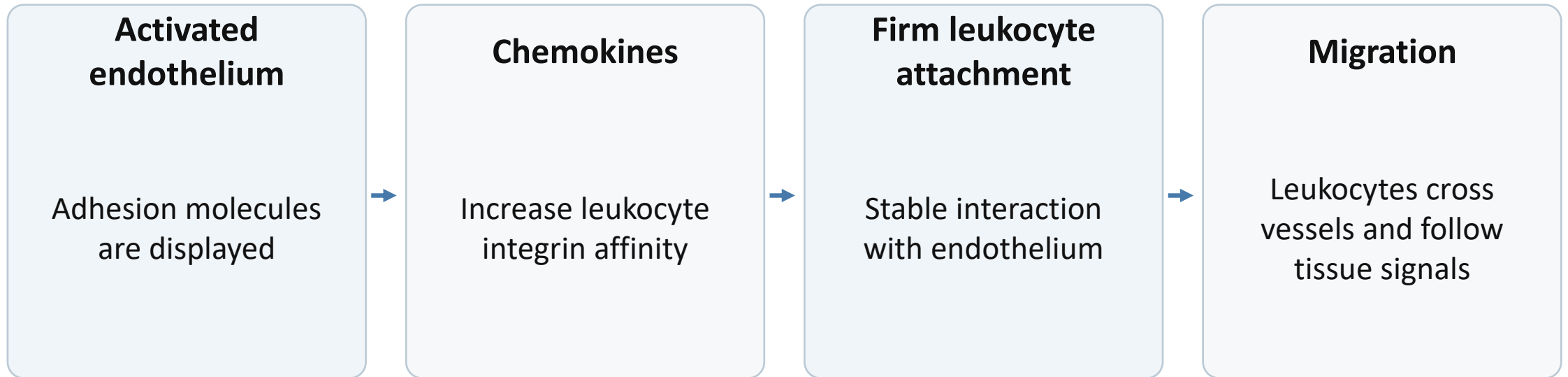
- E-selectin and P-selectin increase after activation.
- Support early interactions between leukocytes and vessel wall.

Integrin ligands

- Endothelial ligands support more stable leukocyte attachment.
- Effective binding is enhanced by chemokine signaling to leukocytes.

Vessel-wall induction and leukocyte integrin activation cooperate.

Leukocyte entry requires sequential signals



The steps represent distinct, coordinated components of recruitment.

Activated endothelium becomes a signaling hub

TNF / IL-1 signal

Chemokines

Recruitment guidance

Cytokines

Amplify inflammatory
communication

Eicosanoids

Additional inflammatory
responses

The activated vascular wall is a source of mediators, not merely a passive barrier.

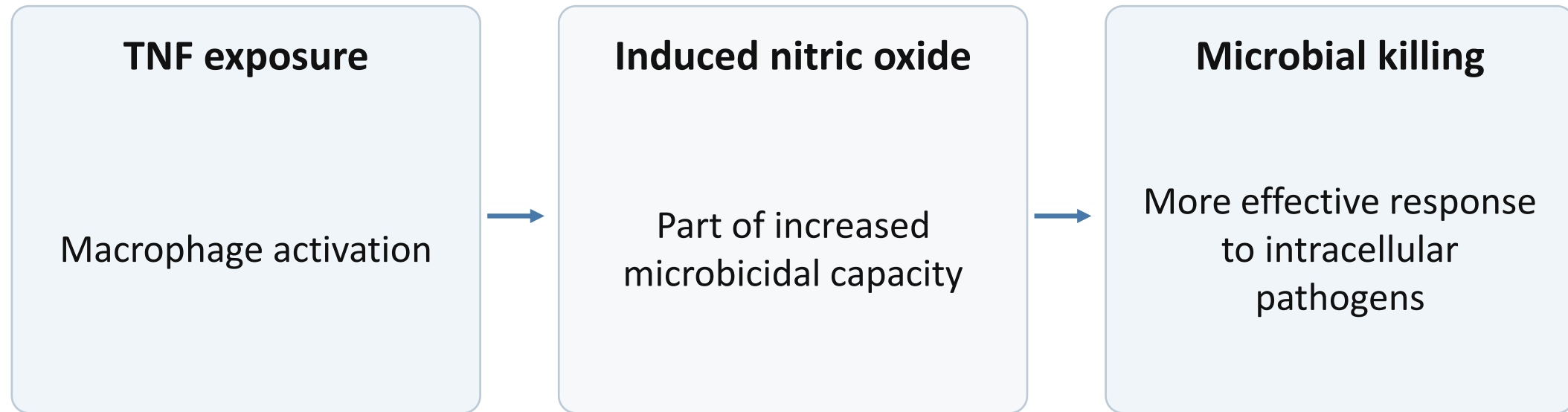
Endothelial procoagulant changes

- TNF and IL-1 can increase endothelial procoagulant activity.
- This links inflammation to shifts in vascular hemostatic behavior.
- When systemic responses become excessive, thrombosis may contribute to pathology.
- Coagulation effects are one component of a wider cytokine response.

TNF augments neutrophil responsiveness

- TNF enhances neutrophil responses to other inflammatory signals.
- Bacterial endotoxin is an example of a cooperating stimulus.
- Augmented activation supports antimicrobial host defense.
- In excessive inflammation, the same responses can contribute to tissue injury.

TNF enhances macrophage microbicidal activity



Induction of nitric oxide (NO) contributes to macrophage microbicidal activity.

IL-1 activates fibroblasts

- IL-1 can stimulate fibroblasts to produce collagen.
- The effect links an inflammatory mediator to mesenchymal cell responses.
- This provides a mechanistic connection between persistent inflammation and matrix deposition.
- The lecture scope is cytokine signaling, not a complete account of scar formation.

IL-1 acts on mesenchymal and immune cells

Mesenchymal responses

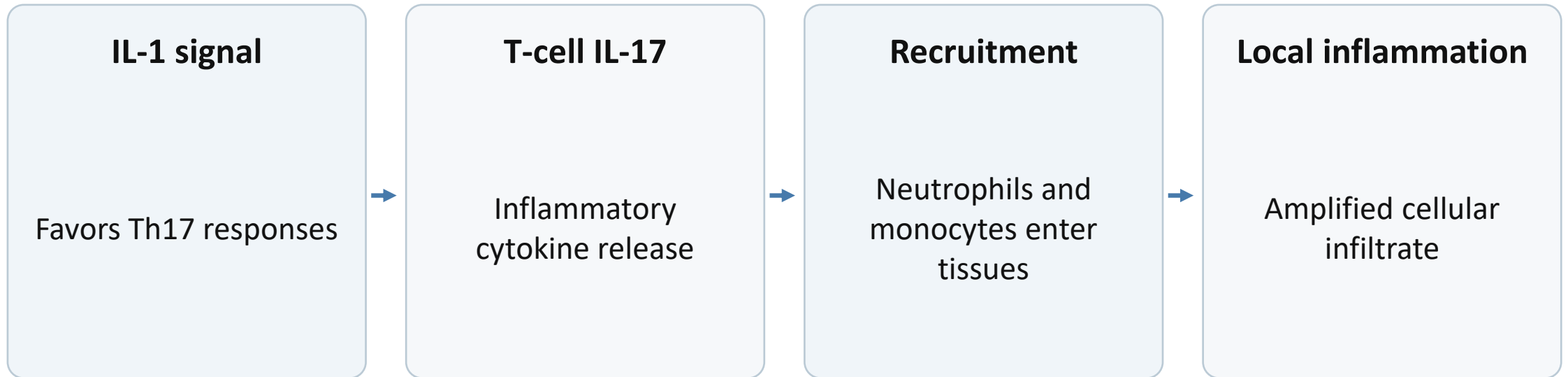
- Fibroblast collagen synthesis
- Proliferation of synovial and other mesenchymal cells

Immune-cell responses

- Stimulation of Th17 responses
- Subsequent enhancement of inflammatory recruitment

One cytokine can influence both tissue remodeling and leukocyte responses.

IL-1 can amplify Th17-associated inflammation



This is an explanatory cytokine sequence, not a complete model of T-cell differentiation.

Local actions of TNF and IL-1

Target	Effect	Inflammatory consequence
Endothelium	Adhesion molecules and ligands	Leukocyte entry
Neutrophils / macrophages	Enhanced activation	Microbicidal defense
Fibroblasts	Collagen synthesis (IL-1)	Matrix production
Synovial cells	Proliferation (IL-1)	Mesenchymal expansion

Different target cells translate the same extracellular signal into distinct outcomes.

Cytokines have local and systemic effects

TNF · IL-1 · IL-6

Local

Adhesion, leukocyte activation

Systemic protective

Fever, leukocytosis, acute-phase proteins

Systemic harmful

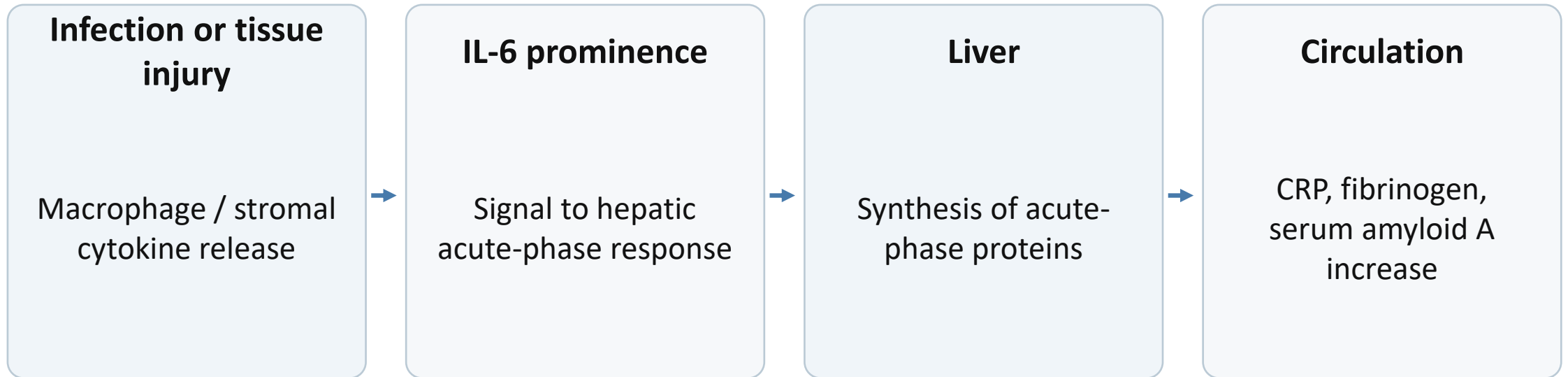
Metabolic and circulatory pathology

Magnitude, duration, and distribution influence whether the response protects or injures.

Fever is a cytokine-driven systemic response

- IL-1 and TNF participate in the febrile response.
- IL-1 has a particularly prominent role in fever.
- Cytokine-associated prostaglandin E₂ contributes to fever.
- Fever is one of several coordinated systemic responses to infection or injury.

Cytokines stimulate the acute-phase response

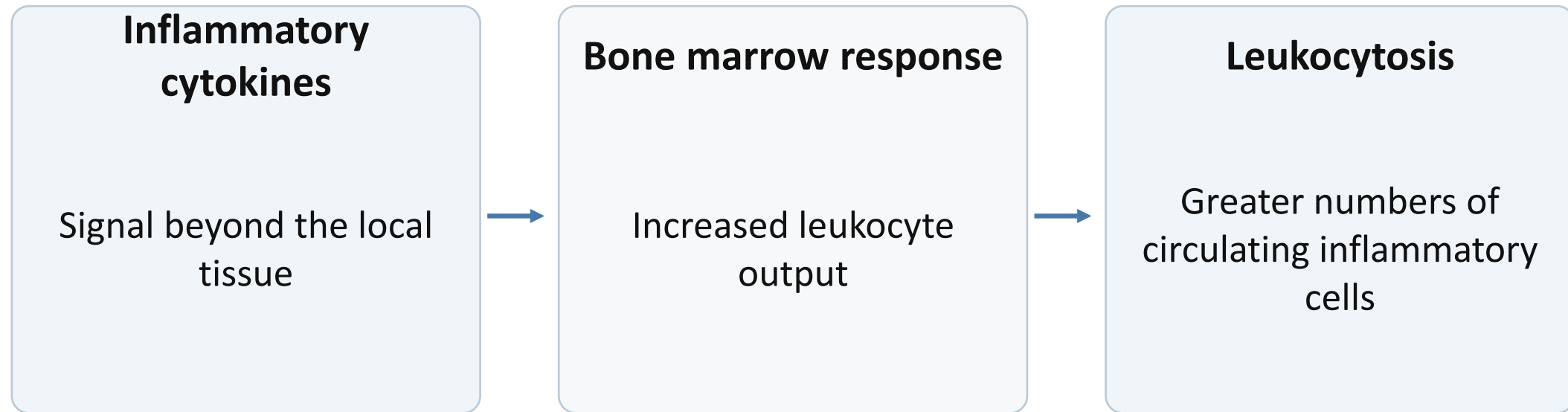


IL-6 is a major driver of hepatic acute-phase protein synthesis.

Acute-phase proteins are downstream readouts

- C-reactive protein (CRP) is an acute-phase protein.
- Fibrinogen and serum amyloid A are additional examples.
- Their synthesis reflects cytokine-driven hepatic responses.
- They are systemic correlates of inflammation, not the initiating cytokines.

Inflammation can increase circulating leukocytes



Leukocytosis increases the circulating pool of host-defense leukocytes.

Systemic responses: Protective and pathological

Protective responses

- Fever
- Leukocytosis
- Increased acute-phase proteins

Potentially pathological responses

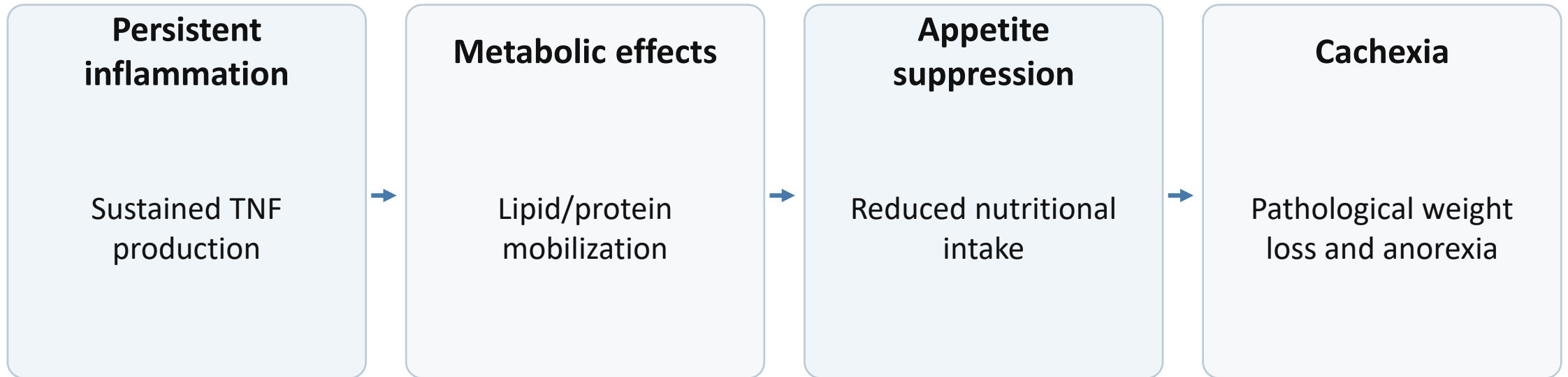
- Circulatory dysfunction
- Abnormal coagulation / thrombosis
- Metabolic derangement and wasting

Physiological defense becomes harmful when responses are excessive or sustained.

TNF participates in systemic metabolic regulation

- TNF promotes mobilization of lipids and proteins.
- TNF suppresses appetite.
- Sustained production promotes negative nutritional and energy balance.
- These actions can contribute to cachexia in chronic disease.

Persistent TNF can contribute to cachexia



Examples include some chronic infections and neoplastic diseases.

Cachexia is not merely a local inflammatory sign

- Cachexia includes anorexia and pathological weight loss.
- It is associated with persistent inflammatory cytokine activity.
- TNF is one important contributor, not a complete single-factor explanation.
- Understanding systemic cytokine action explains why localized disease can cause generalized wasting.

Systemic cytokine effects span multiple organs

Circulating mediators

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graph TD; A[Circulating mediators] --> B[Brain]; A --> C[Liver and marrow]; A --> D[Vessels and tissues]; B --> E[Fever; Appetite modulation]; C --> F[Acute phase; Leukocytosis]; D --> G[Coagulation and metabolic responses];
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Brain

Fever; Appetite modulation

Liver and marrow

Acute phase; Leukocytosis

Vessels and tissues

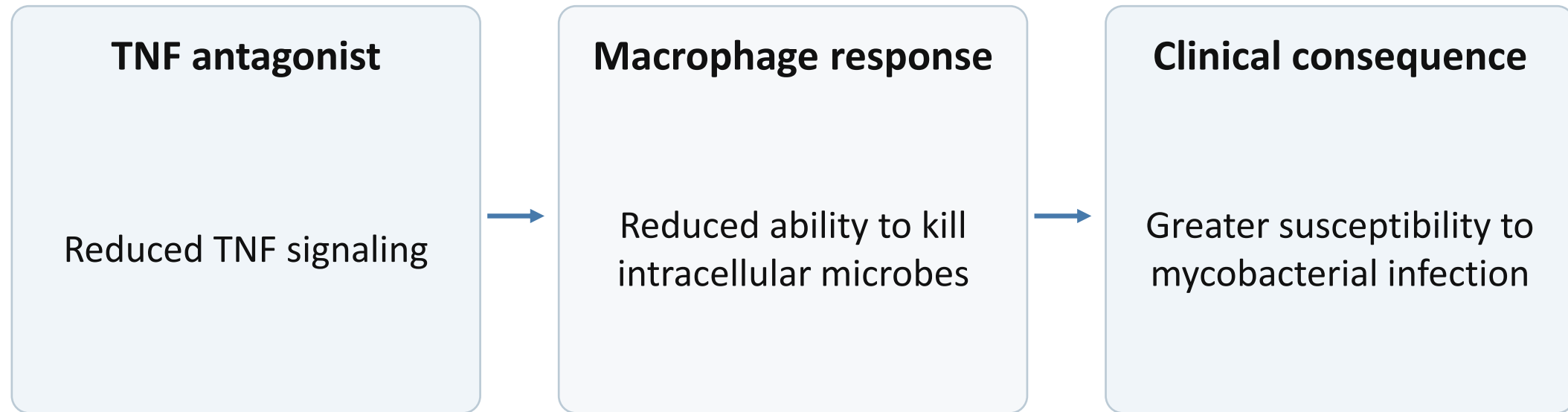
Coagulation and metabolic responses

Circulating inflammatory cytokines affect organs distant from the original lesion.

TNF blockade illustrates clinical relevance

- TNF antagonists are effective treatments for several chronic inflammatory diseases.
- Examples include rheumatoid arthritis and psoriasis.
- Certain forms of inflammatory bowel disease are additional examples.
- Treatment benefit demonstrates the importance of TNF in disease pathogenesis.

TNF blockade can impair intracellular defense



This risk follows directly from the host-defense function of TNF.

TNF and IL-1 inhibition are not interchangeable

TNF blockade

- Notable efficacy in several chronic inflammatory diseases
- Important intracellular infection risk

IL-1 blockade

- Some overlapping biological targets
- Not uniformly as effective for the diseases discussed

Reasons for the difference in effectiveness remain incompletely understood.

Sepsis is not a single-cytokine disease

- Inflammatory systemic responses can involve several cytokines simultaneously.
- Blocking either TNF or IL-1 alone has not improved sepsis outcomes in the studies discussed.
- Redundancy and mediator interactions may limit single-target interventions.
- Therapeutic inference must not be confused with a complete contemporary treatment guideline.

Chemokines specialize in cellular navigation

- Small proteins with a principal role as leukocyte chemoattractants.
- Recruit specific leukocyte populations in inflammation.
- Also organize cell distribution within normal tissues.
- They are typically small proteins of approximately 8–10 kDa.

Chemokines have two biological contexts

Inflammatory chemokines

- Induced by microbes and inflammatory signals
- Promote attachment and migration to sites of injury

Homeostatic chemokines

- Produced constitutively in tissues
- Maintain localization of cells within tissue compartments

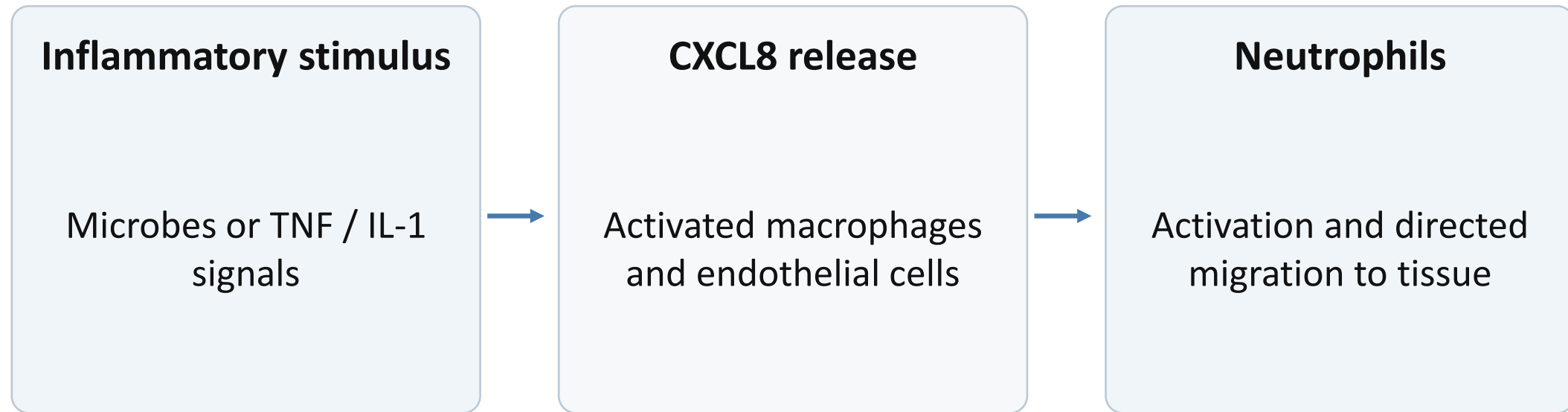
Chemotaxis is essential in both defense and normal tissue organization.

Four chemokine families: Cysteine arrangement

Family	Conserved N-terminal cysteines	Example
CXC	C–X–C: one residue between	CXCL8 (IL-8)
CC	C–C: adjacent pair	CCL2 / CCL11 / CCL3
C	Two of four conserved Cys absent	XCL1 (lymphotactin)
CX3C	C–X ₃ –C: three intervening residues	CX3CL1 (fractalkine)

Classification refers to spacing of conserved cysteine residues.

A subset of CXC chemokines recruits neutrophils

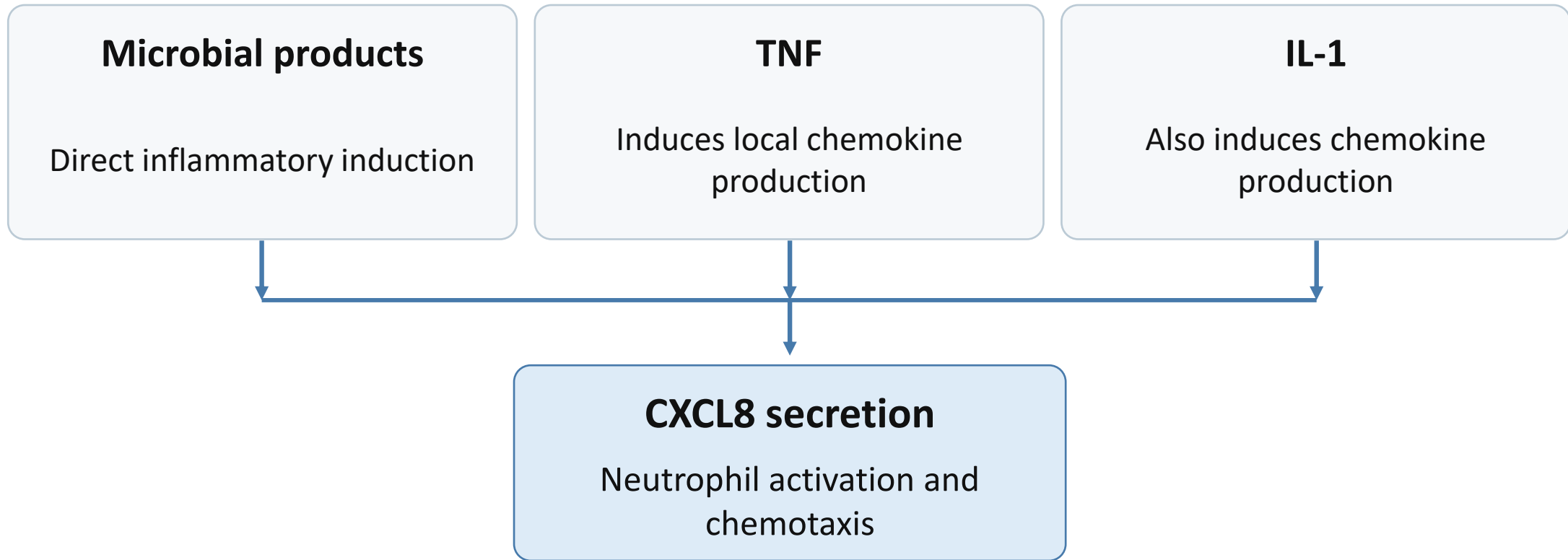


A subset of CXC chemokines is especially active on neutrophils.

CXCL8 is the former interleukin-8

- IL-8 is now designated CXCL8.
- Made by activated macrophages, endothelial cells, and additional cell types.
- Promotes neutrophil activation and chemotaxis.
- Has comparatively limited effects on monocytes and eosinophils.

CXCL8 production is itself cytokine regulated



TNF and IL-1 can indirectly recruit neutrophils by inducing chemokines.

CC chemokines target broader leukocyte sets

- Conserved first two cysteines are adjacent.
- Common targets: Monocytes, eosinophils, basophils, and lymphocytes.
- In general, CC chemokines are less potent than some CXC members for neutrophils.
- Functional overlap exists among the many CC family members.

Illustrative CC chemokines

Chemokine	Alternative name	Source-supported association
CCL2	MCP-1	Monocyte chemoattractant
CCL11	Eotaxin	Relatively selective eosinophil recruitment
CCL3	MIP-1 α	CC-family leukocyte chemoattraction

Examples are not an exhaustive receptor–ligand catalogue.

CCL2 illustrates monocyte recruitment

- CCL2 is also called monocyte chemoattractant protein-1 (MCP-1).
- It belongs to the CC family of chemokines.
- Its name reflects an important monocyte-directed chemoattractant role.
- This differs from neutrophil-dominant CXCL8 signaling.

CCL11 illustrates selective recruitment

- CCL11 is commonly known as eotaxin.
- It shows relatively selective eosinophil recruitment.
- This shows that chemokines can confer leukocyte-subset preference.
- Subset preference helps explain differing cellular compositions of infiltrates.

CCL3 is a further CC-family example

- CCL3 was historically called macrophage inflammatory protein-1 α .
- It is listed alongside CCL2 and CCL11 in the CC group.
- Its inclusion underscores the diversity of leukocyte-active chemokines.
- Family membership alone does not specify an exclusive single target cell.

Rare structural families add specificity

C family

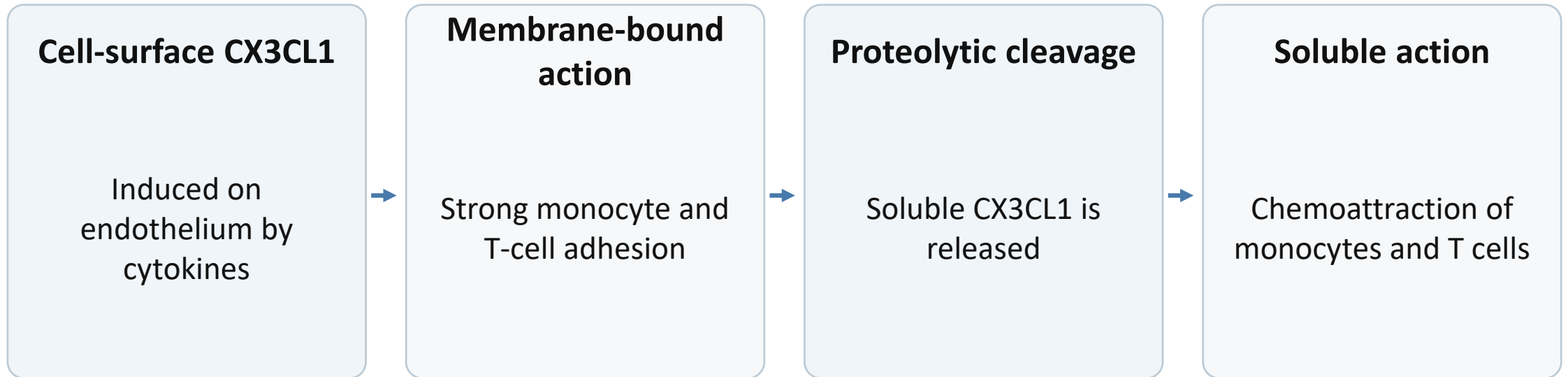
- Example: XCL1 / lymphotactin
- Missing first and third of four conserved cysteines
- Relatively specific for lymphocytes

CX3C family

- Example: CX3CL1 / fractalkine
- Three residues separate first two conserved cysteines
- Can support adhesion or chemoattraction

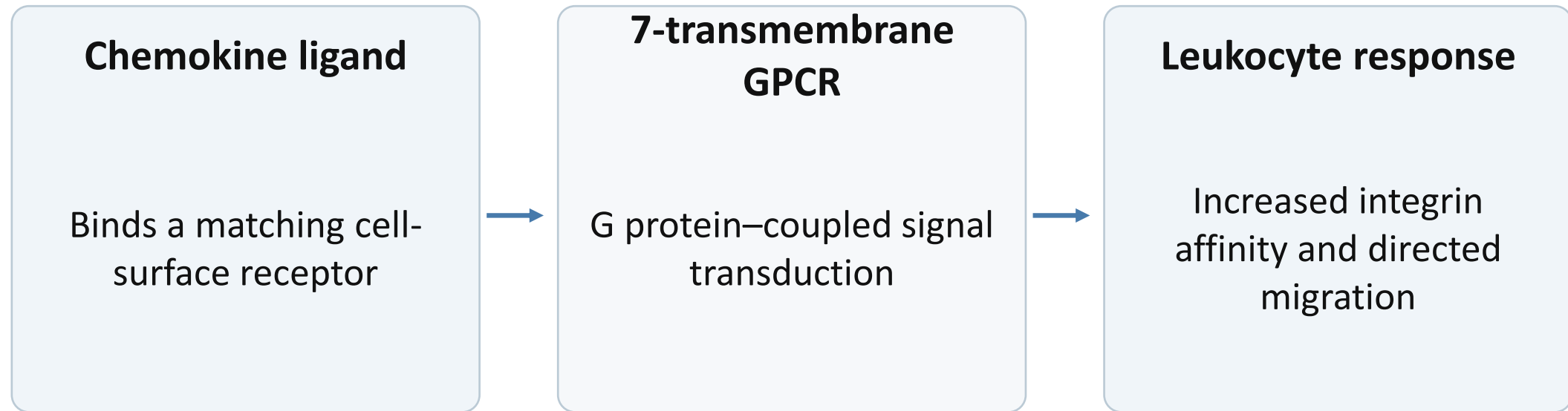
These structural families are not interchangeable with the CXC and CC families.

Fractalkine has two biologically distinct forms



One chemokine therefore supports both attachment and migration.

Chemokine receptors are seven-pass GPCRs

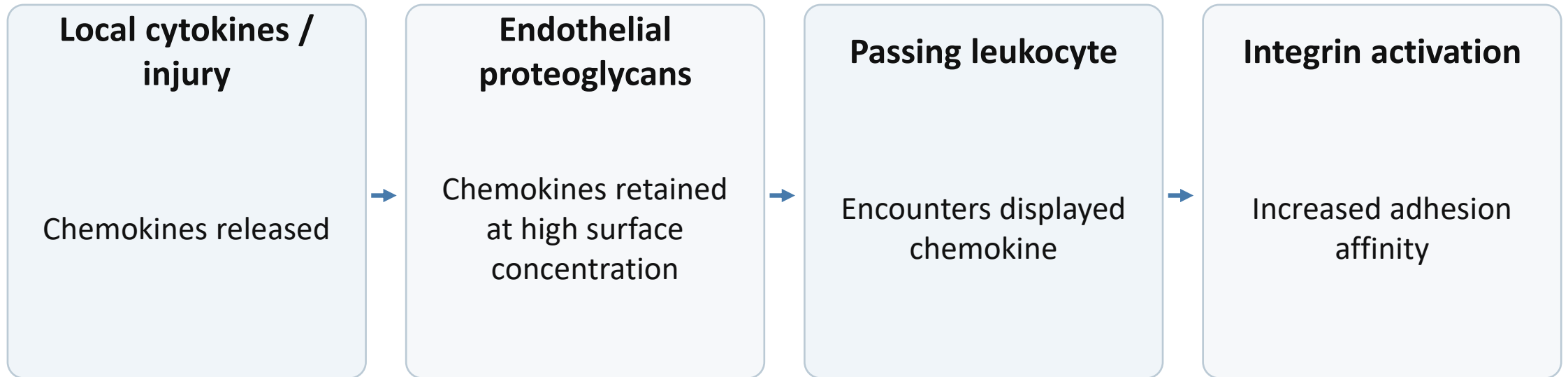


GPCR = G protein-coupled receptor.

Leukocytes express multiple chemokine receptors

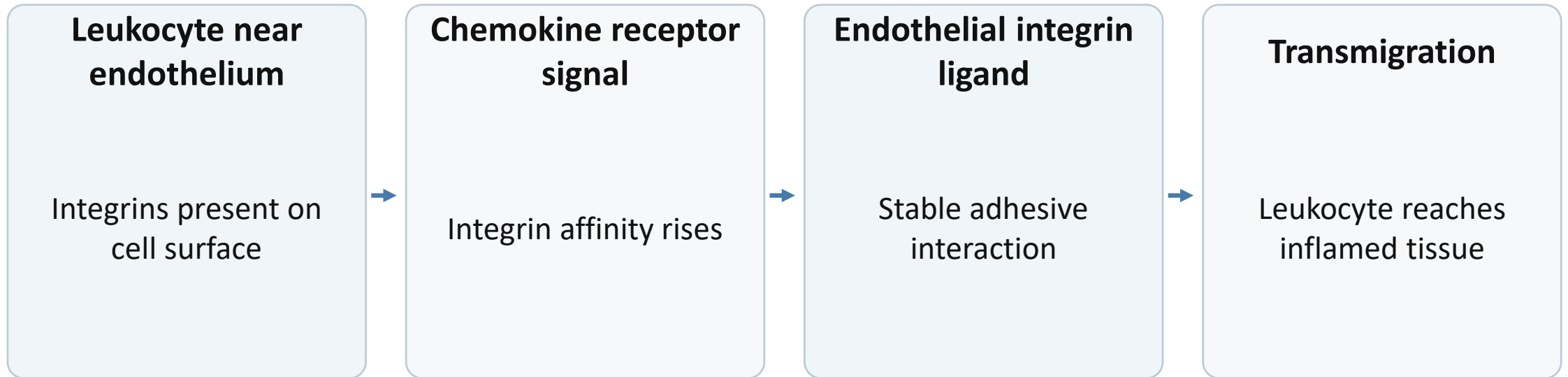
- Most leukocytes display more than one receptor type.
- Consequently, a cell can respond to more than one chemokine signal.
- Multiple ligand–receptor interactions permit overlapping recruitment programs.
- This complexity helps explain difficulty of single-receptor inhibition.

Endothelium presents chemokines to passing cells



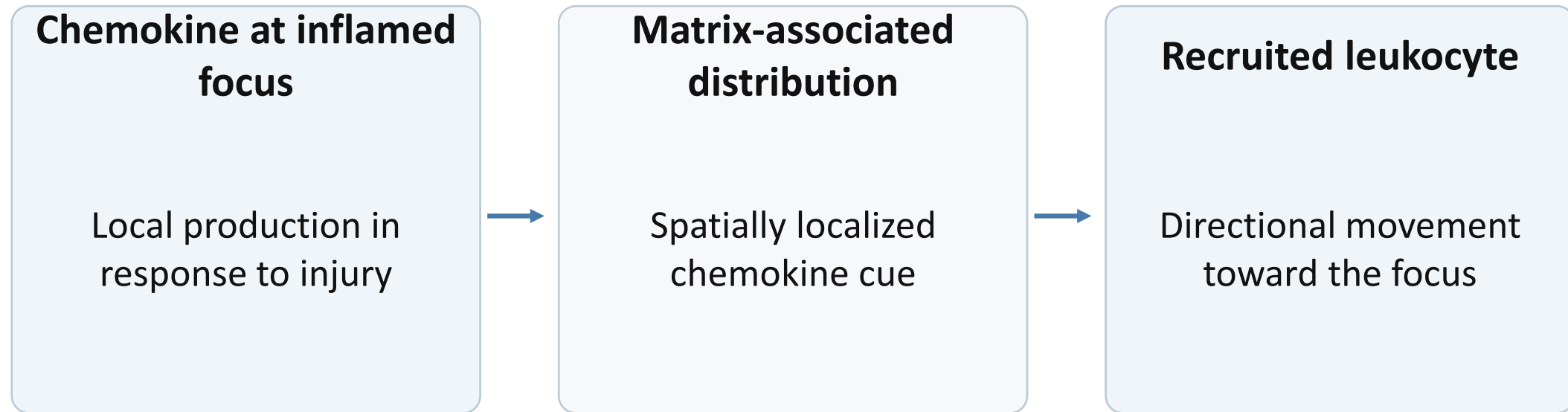
Extracellular matrix proteoglycans can also bind chemokines locally.

Chemokines activate leukocyte integrin binding



Chemokines change leukocyte adhesive behavior rather than merely increasing cell movement.

Tissue gradients direct leukocyte chemotaxis



Directed tissue chemotaxis is a principal inflammatory chemokine function.

Inflammatory versus homeostatic chemokines

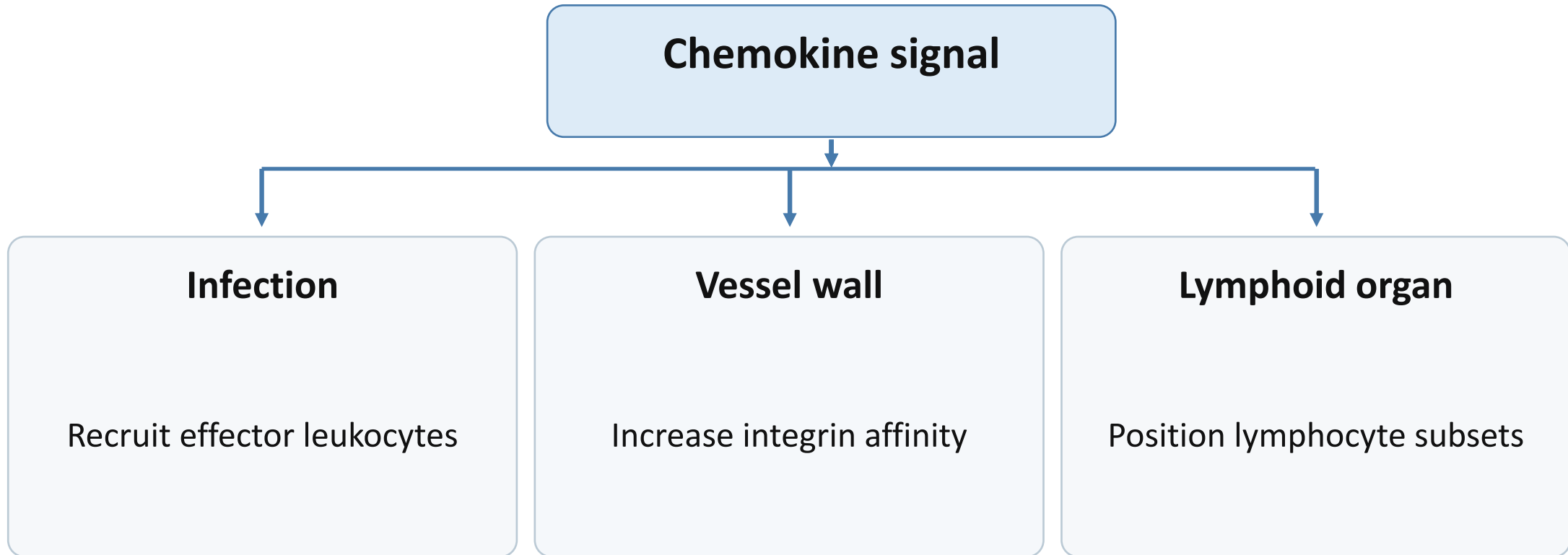
Property	Inflammatory	Homeostatic
Production	Induced by damage / microbes	Constitutive
Principal task	Recruit leukocytes to tissue lesion	Maintain normal tissue organization
Important outcome	Inflammatory infiltrate	Cell positioning in lymphoid tissues

The distinction refers to typical biological roles, not separate protein chemistry.

Homeostatic chemokines organize lymphoid tissue

- Constitutively produced chemokines influence cell localization.
- They help segregate T and B lymphocytes into discrete regions.
- The spleen and lymph nodes show this organized lymphocyte distribution.
- Normal architecture therefore depends in part on chemokine-directed positioning.

Two contexts, one principle: Directed movement



Chemokines convey positional information in both inflammatory and physiological settings.

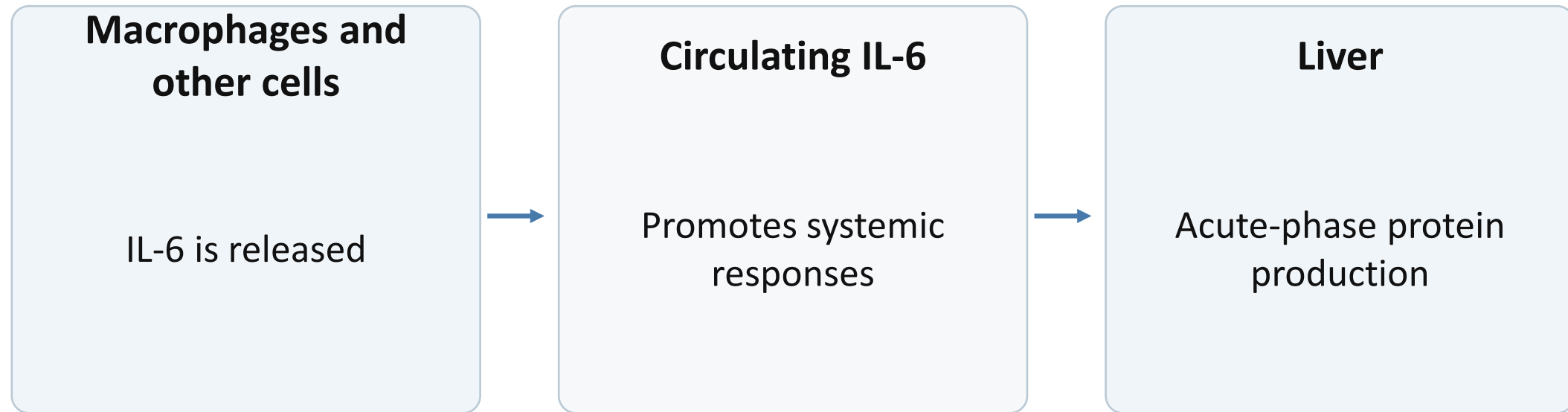
Certain chemokine receptors are HIV coreceptors

- CXCR4 and CCR5 can act as HIV coreceptors.
- They participate in viral binding and entry into susceptible cells.
- Their role in infection is distinct from their usual chemokine-signaling functions.
- This illustrates a noninflammatory consequence of chemokine receptor expression.

Chemokine-targeted therapy is challenging

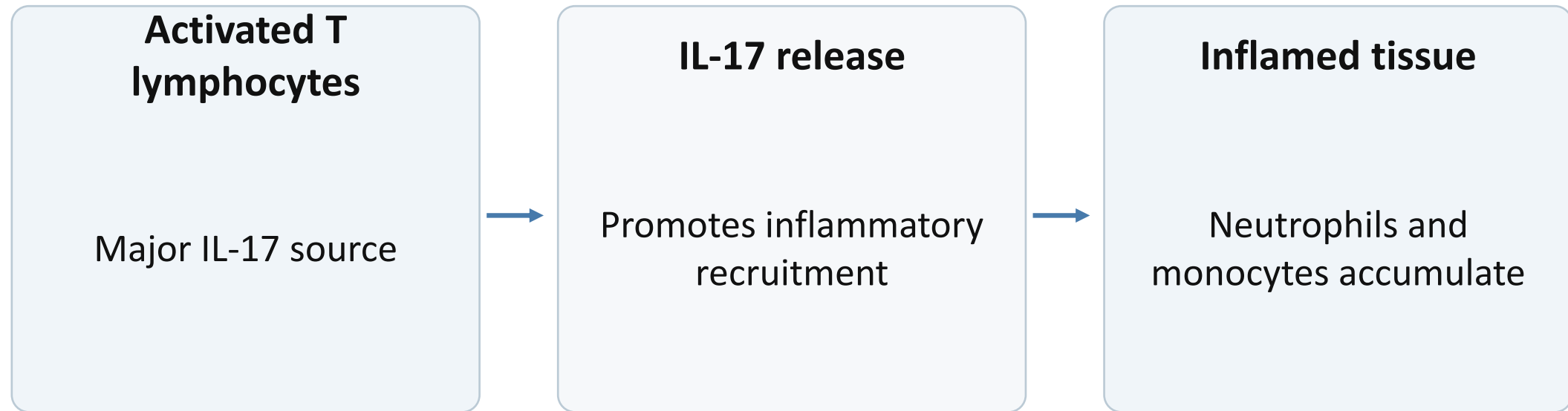
- Chemokine-mediated inflammation is well established experimentally.
- Most leukocytes express multiple receptor types.
- Many chemokine ligands display overlapping leukocyte actions.
- Effective therapeutic chemokine antagonism has proven challenging.

IL-6 is prominent in the acute-phase response



IL-6 participates in local inflammation in addition to systemic reactions.

IL-17 promotes myeloid leukocyte recruitment



IL-17 is relevant to acute as well as chronic inflammatory responses.

Targeting IL-6 and IL-17 has clinical effects

IL-6 receptor inhibition

- Example: Juvenile arthritis
- Interferes with an important inflammatory cytokine pathway

IL-17 inhibition

- Example: Psoriasis
- Reduces signaling associated with myeloid recruitment

Examples illustrate mechanism-based therapy; They are not comprehensive prescribing guidance.

One-page cytokine functional map

Mediator	Primary role emphasized	Cells / systems affected
TNF	Endothelial activation; cachexia	Vessels, leukocytes, metabolism
IL-1	Endothelial activation; fever	Vessels, fibroblasts, systemic
IL-6	Acute-phase response	Liver and systemic sites
IL-17	Recruitment of myeloid cells	Neutrophils and monocytes
Chemokines	Adhesion and chemotaxis	Specific recruited leukocytes

Functional emphasis from Chapter 3; Actions are not mutually exclusive.

Application: Neutrophil-rich inflammation

Clinical reasoning prompt

An infected tissue becomes enriched in neutrophils. Nearby macrophages and endothelial cells are producing inflammatory mediators.

Which named chemokine best illustrates directed neutrophil recruitment?

Mechanistic explanation

CXCL8 (IL-8). It is induced by microbes and TNF / IL-1, and activates and attracts neutrophils.

Application: Cytokine inhibition and infection

Clinical reasoning prompt

A patient receiving a TNF antagonist develops concern for an intracellular infection.

Which normal TNF function explains this susceptibility?

Mechanistic explanation

TNF helps macrophages kill intracellular microbes, in part through NO-associated microbicidal activation.

Application: Endothelial activation

Clinical reasoning prompt

Inflamed endothelium displays more adhesion molecules while passing leukocytes respond to nearby chemokines.

Identify the complementary roles of TNF / IL-1 and chemokines.

Mechanistic explanation

TNF / IL-1 induce endothelial adhesion machinery; Chemokines increase leukocyte integrin affinity and direct tissue migration.

Synthesis: Five mechanistic relationships

- TNF and IL-1 convert danger signals into endothelial activation.
- IL-1 activity requires inflammasome-dependent maturation.
- IL-6 is a major mediator of the hepatic acute-phase response.
- Chemokines connect leukocyte adhesion to directed tissue migration.
- Excess or persistent cytokine activity can produce systemic pathology.

Primary reference

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026).
- Chapter 3: Inflammation and Repair.
- Section: Cytokines and Chemokines; Table 3.7 and Figure 3.10.
- Figure- and table-derived concepts have been redrawn as original editable teaching schematics.