

Mediators of Inflammation

Vascular response • leukocyte recruitment • regulatory circuits

From initiating stimuli to amplified—and ultimately resolved—inflammation

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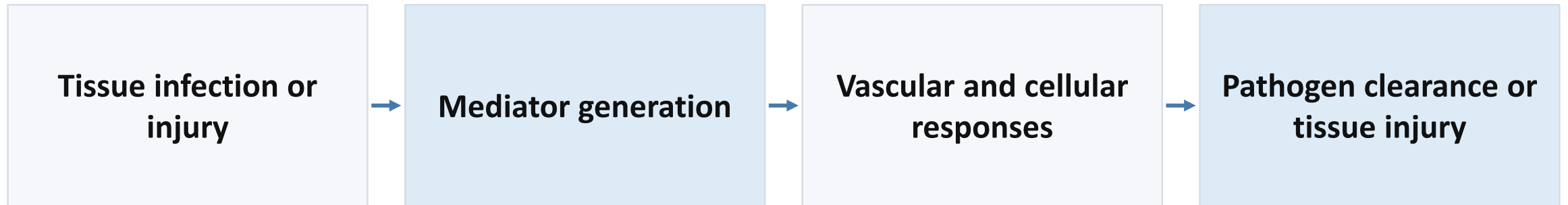
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Learning objectives

- Classify inflammatory mediators by origin and activation mechanism.
- Link individual mediators to vascular changes, leukocyte recruitment, pain, and fever.
- Explain mediator amplification, redundancy, and termination.
- Connect mediator biology with representative therapeutic and disease implications.

Inflammatory mediators: The central concept



Four major families organize acute inflammation

Mediator class	Representative examples	Dominant functions
Vasoactive amines	Histamine	Early vascular change
Eicosanoids	Prostaglandins, leukotrienes	Vessels, pain, fever, recruitment
Cytokines / chemokines	TNF, IL-1, CXCL8	Endothelial and leukocyte activation
Complement fragments	C3a, C5a, C3b	Inflammation, opsonization

Cell-derived versus plasma-derived mediators

Cell-derived

- Stored granules: Rapid release of histamine
- Newly synthesized: Eicosanoids and cytokines
- Produced at an inflammatory focus

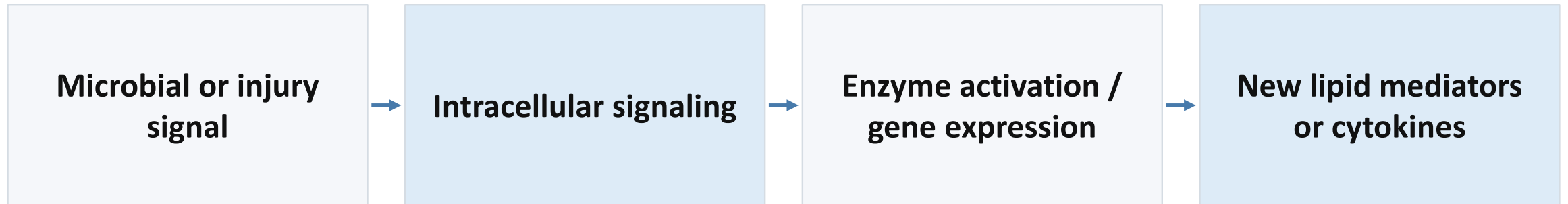
Plasma-derived

- Synthesized largely in liver
- Circulate as inactive precursors
- Activated through proteolytic cascades

Preformed granules provide immediate signals



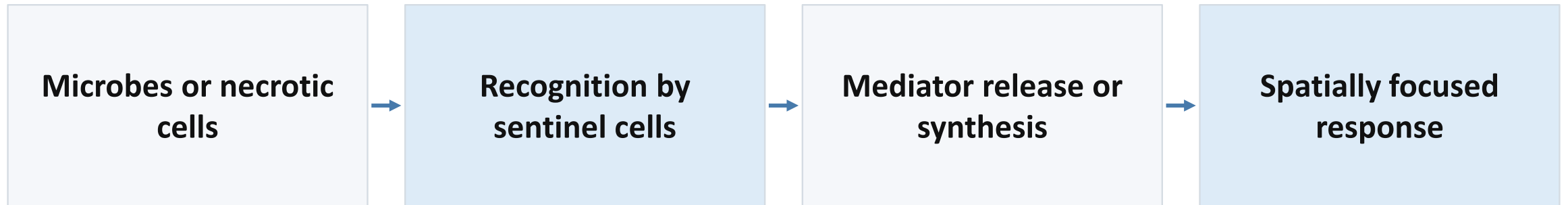
De novo mediator synthesis provides flexible responses



Sentinel cells initiate local mediator production

Source cell	Illustrative mediator output	Role
Mast cell	Histamine, lipid mediators	Rapid vascular response
Macrophage / dendritic cell	TNF, IL-1, chemokines	Recruitment and amplification
Endothelial cell	Eicosanoids, chemokines	Local vascular regulation
Neutrophil / platelet	Lipid mediators, PAF	Recruitment and cross-talk

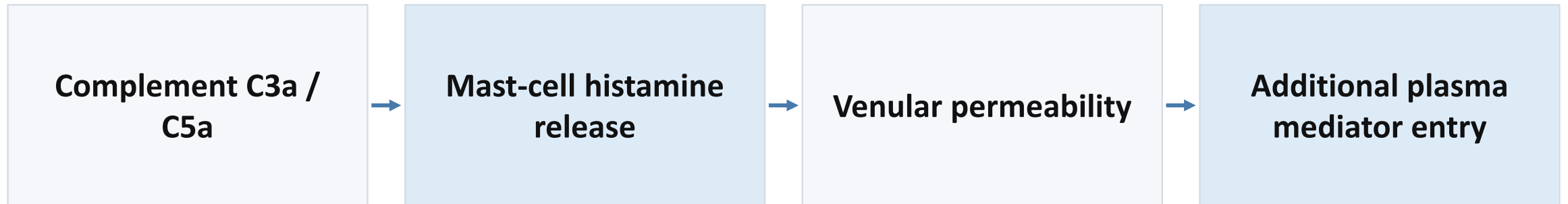
Mediator generation is stimulus dependent



Short half-lives limit collateral injury

- Most inflammatory mediators act briefly and undergo rapid degradation or inactivation.
- Release generally ceases when the initiating stimulus disappears.
- Local generation and short-lived activity help restrict inflammation to the site of injury.
- Active anti-inflammatory signals further promote termination.

Amplification: Mediators activate other mediators



Redundancy makes inflammatory defense robust

Convergent effects

- Histamine and leukotrienes: Permeability
- TNF and IL-1: Endothelial activation
- C5a and LTB₄: Leukocyte recruitment

Why it matters

- Blocking one mediator may leave parallel pathways active
- Overlapping pathways preserve host defense
- Effects depend on cell type, location, and timing

Map mediators to the response they produce

Tissue-level response	Illustrative important mediators
Vasodilation	Histamine; prostaglandins
Increased venular permeability	Histamine; LTC ₄ /LTD ₄ /LTE ₄ ; bradykinin
Leukocyte recruitment	TNF, IL-1; chemokines; LTB ₄ ; C5a
Pain and fever	PGE ₂ ; bradykinin; IL-1 and TNF

Histamine: A stored vasoactive mediator

- Mast cells near small vessels are the richest tissue source.
- Basophils and platelets also contain histamine.
- Histamine is stored in preformed granules and can be released rapidly.
- Its vascular effects dominate the immediate transient reaction.

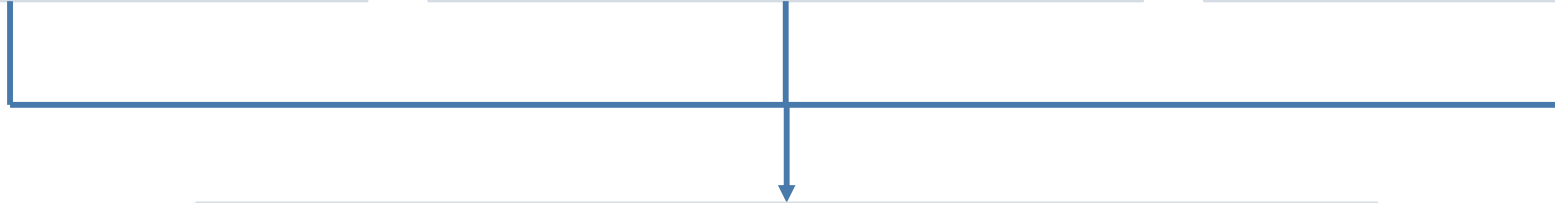
Three major routes to mast-cell degranulation

Physical injury, heat, cold

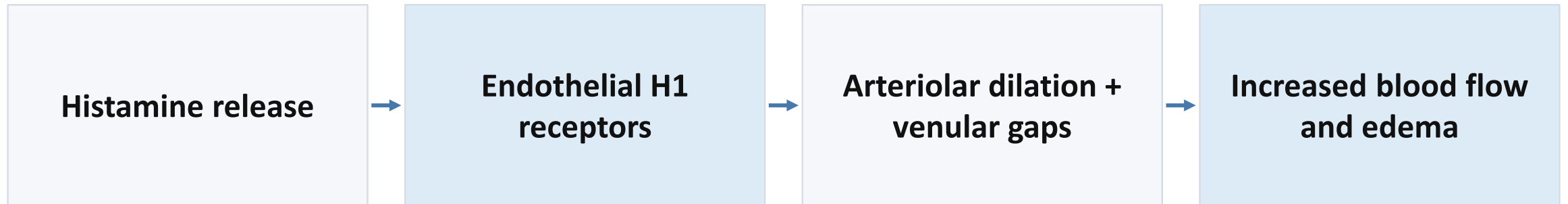
IgE-dependent activation

C3a / C5a signaling

Mast-cell histamine release



Histamine H1 signaling changes microvessels



Why the immediate permeability phase is transient

- Histamine opens interendothelial gaps principally in postcapillary venules.
- Plasma proteins and fluid leave the intravascular compartment.
- Histamine is rapidly inactivated; This early permeability response is short lived.
- Other mediator families can sustain or add to subsequent vascular changes.

Histamine receptors have distinct physiological roles

Receptor	Principal association
H1	Allergic response and microvascular effects
H2	Gastric acid regulation
H3	Modulation of neurotransmitter release
H4	Immune-cell functions

Serotonin is not interchangeable with histamine

Histamine

- Prominent mast-cell granule mediator
- Arteriolar dilation and venular permeability
- Well-established early inflammatory action

Serotonin

- Found in platelets and neuroendocrine cells
- Acts as a vasoconstrictor
- Importance of this effect in inflammation is uncertain

Clinical correlation: Rapid edema after allergen exposure

A patient develops raised, itchy wheals shortly after allergen exposure.

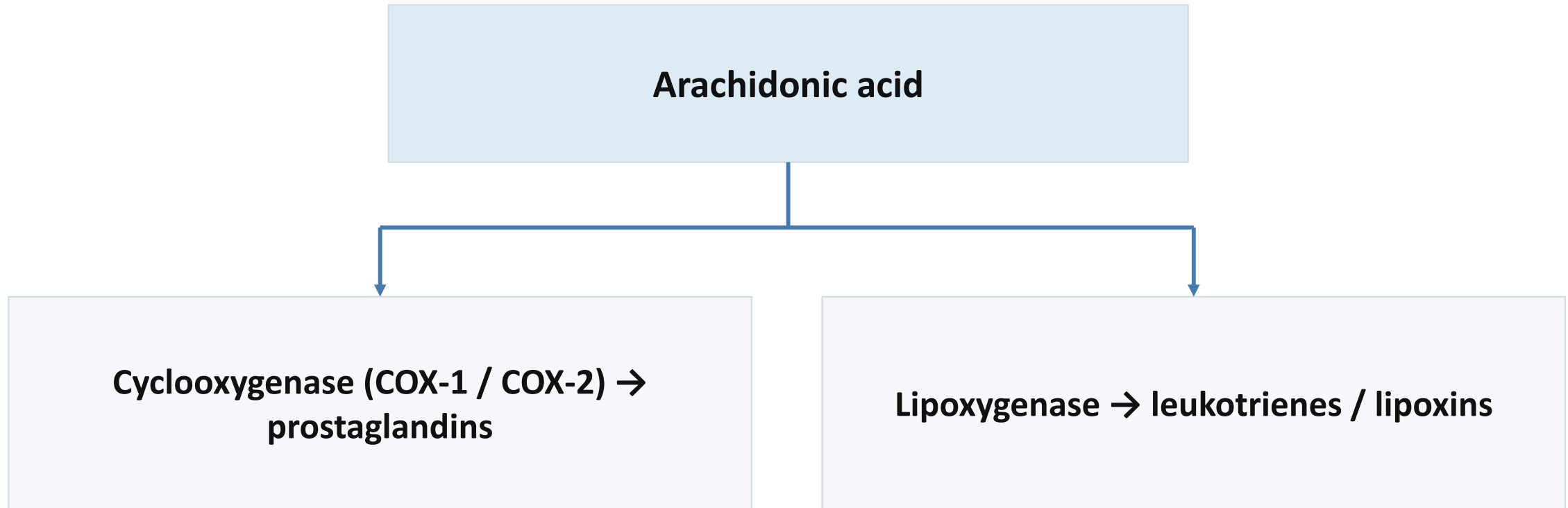
- Which preformed mediator can explain the immediate vascular change?
- What receptor on the microvascular endothelium mediates its dominant effect?

Discuss the mechanism before revealing the explanation in speaker notes.

Arachidonic acid is a membrane-derived substrate



Two enzyme branches generate different eicosanoids



Prostaglandins regulate vascular and systemic responses

- Produced by mast cells, macrophages, endothelium, and other cells.
- COX-1 and COX-2 participate in prostaglandin synthesis.
- Important effects include vasodilation, edema amplification, pain, and fever.
- Different prostaglandins have different vascular and platelet effects.

Major prostaglandins are functionally distinct

Mediator	Emphasized inflammatory effect
PGD ₂ / PGE ₂	Vasodilation; increase permeability effects
PGE ₂	Pain sensitization and fever
PGI ₂ (prostacyclin)	Vasodilation; inhibits platelet aggregation
TXA ₂ (thromboxane)	Vasoconstriction; promotes platelet aggregation

Prostacyclin and thromboxane form an opposing pair

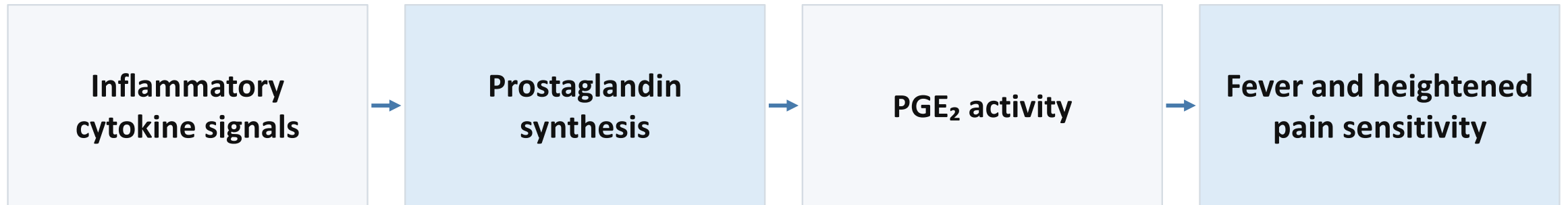
PGI₂: Endothelium

- Vasodilation
- Inhibits platelet aggregation
- Antithrombotic vascular tendency

TXA₂: Platelets

- Vasoconstriction
- Promotes platelet aggregation
- Prothrombotic vascular tendency

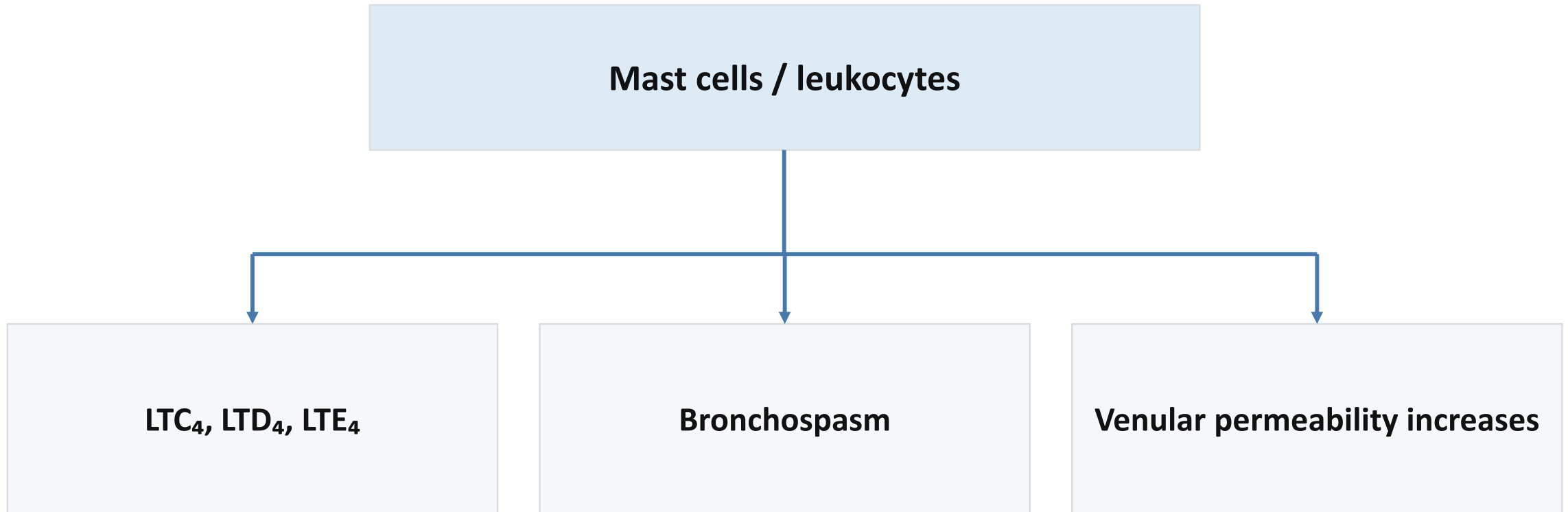
PGE₂ connects inflammation to pain and fever



Leukotriene B4 is a potent neutrophil signal



Cysteinyl leukotrienes affect airways and vessels



Lipoxins counter leukocyte recruitment

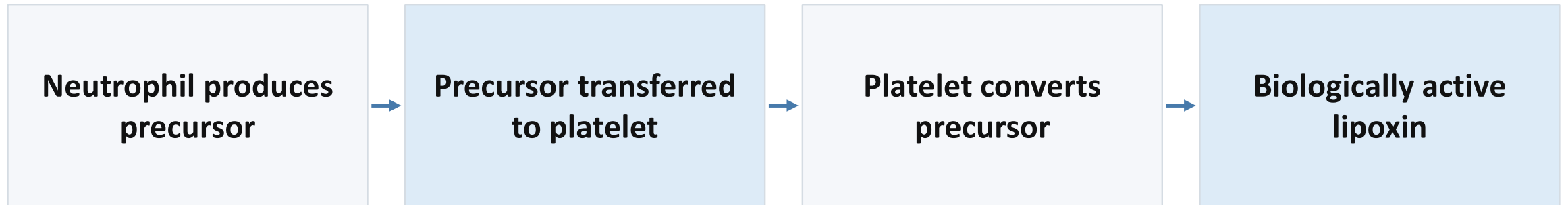
LTB₄

- Promotes neutrophil chemotaxis
- Enhances adhesion and activation
- Propagates an acute response

Lipoxins

- Inhibit neutrophil chemotaxis
- Reduce adhesion to endothelium
- Contribute to active restraint of inflammation

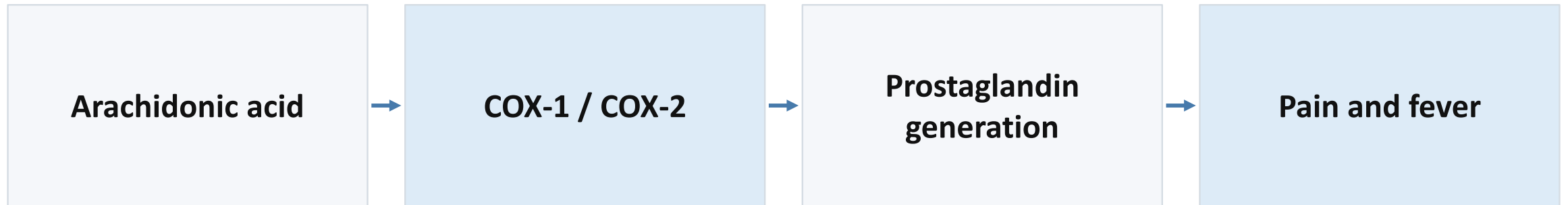
Lipoxin production illustrates cell cooperation



Resolution is not just loss of stimulus

- Inflammatory mediator profiles can switch during the response.
- Lipoxins antagonize leukotriene-driven neutrophil recruitment.
- IL-10 and TGF- β also participate in anti-inflammatory signaling.
- The source also describes proposed pro-resolving lipid families whose roles remain under study.

NSAIDs act on the prostaglandin pathway



COX inhibition requires a benefit–risk perspective

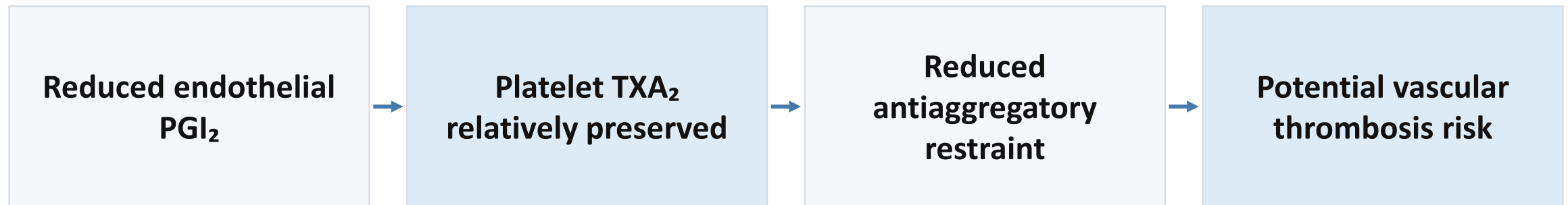
Expected benefit

- Reduced prostaglandin synthesis
- Anti-inflammatory activity
- Pain and fever relief

Biological trade-off

- COX-1 also contributes to gastric protection
- COX-2 is not exclusively pathological
- Selective COX-2 blockade may shift platelet–vascular balance

Selective COX-2 inhibition can alter thrombosis balance



Glucocorticoids act at several inflammatory nodes

Affected biological target	Consequence
Phospholipase A2 / COX-2 pathways	Reduced eicosanoid synthesis
Pro-inflammatory cytokine gene expression	Reduced TNF and IL-1 signaling
Inducible nitric oxide synthase	Less inflammatory NO production
Multiple inflammatory proteins	Broad rather than single-pathway suppression

Leukotriene-pathway therapies illustrate specificity

5-lipoxygenase inhibition

- Reduces leukotriene biosynthesis
- Acts outside the COX pathway
- Useful strategy in asthma

Leukotriene receptor blockade

- Reduces responses to leukotrienes
- Acts at the target receptor
- Useful strategy in asthma

Clinical correlation: Asthma and leukotrienes

A patient with asthma develops reversible bronchospasm during an inflammatory episode.

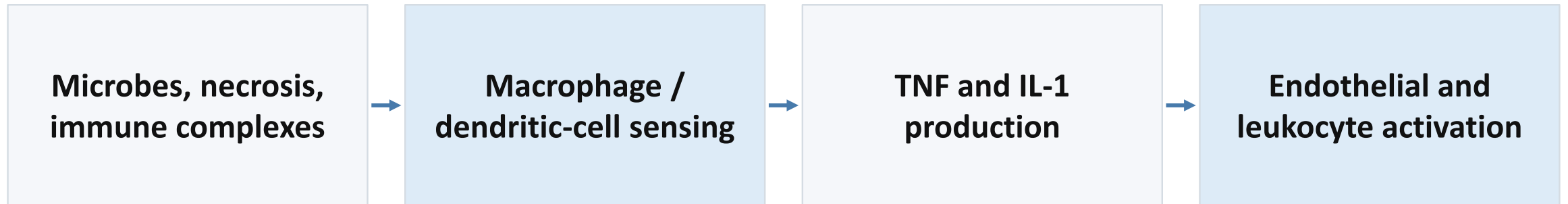
- Which arachidonic acid metabolites directly promote bronchospasm?
- Why would a COX inhibitor not directly block their synthesis?

Discuss the mechanism before revealing the explanation in speaker notes.

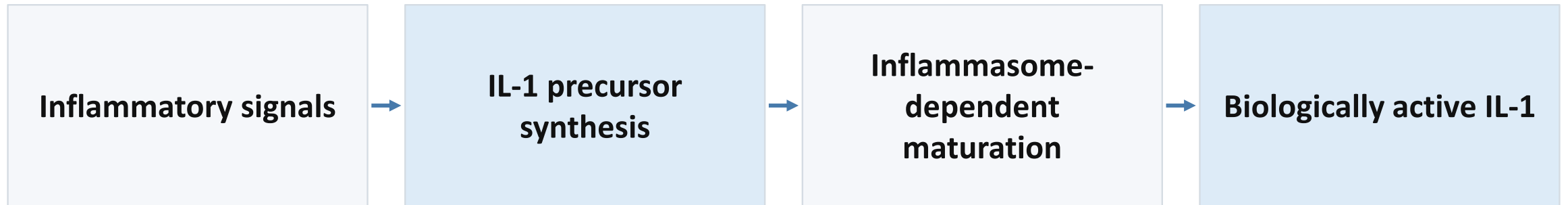
Cytokines provide a cell-to-cell signaling network

- Proteins produced by immune cells and many stromal or epithelial cells.
- Often function locally, but some also cause systemic responses.
- Biological actions overlap; The outcome depends on the target cell.
- Major acute-inflammatory mediators include TNF, IL-1, IL-6, and chemokines.

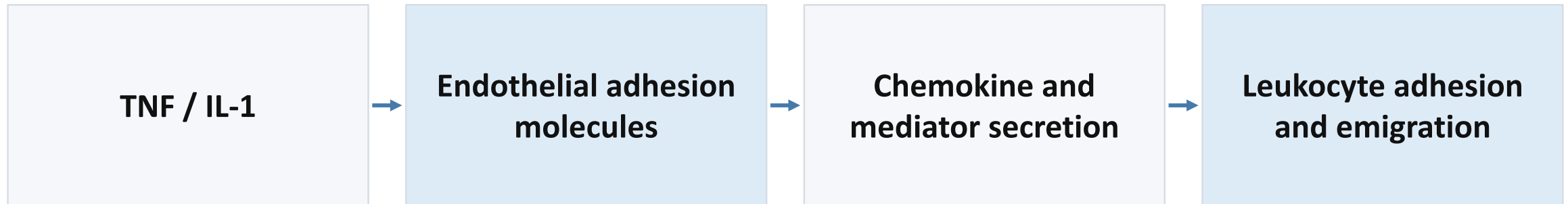
TNF and IL-1 are triggered by danger signals



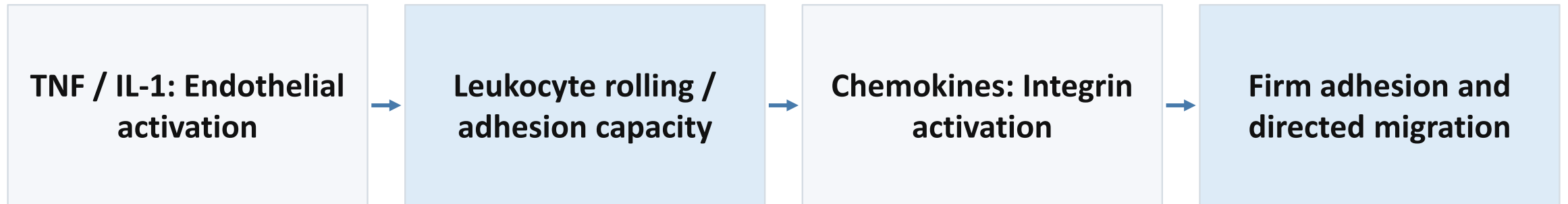
Mature IL-1 depends on inflammasome processing



TNF and IL-1 convert endothelium into an active interface



Cytokines connect endothelial adhesion with chemotaxis



TNF and IL-1 amplify local cellular responses

Target	Response
Neutrophils	Enhanced responsiveness to inflammatory stimuli
Macrophages	Increased microbicidal activity; NO signaling
Fibroblasts / stromal cells	IL-1 promotes collagen synthesis and proliferation
Endothelium	Adhesion molecules and procoagulant activity

Systemic cytokine effects are context dependent

Protective acute-phase response

- Fever
- Leukocytosis
- Acute-phase protein synthesis

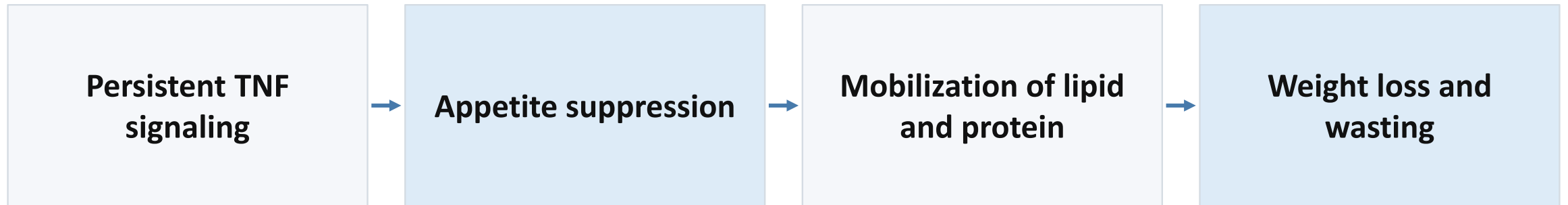
Excessive or sustained signaling

- Metabolic disturbance
- Hypotension / shock
- Catabolic effects including cachexia

IL-6 drives the systemic acute-phase response



Sustained TNF contributes to cachexia



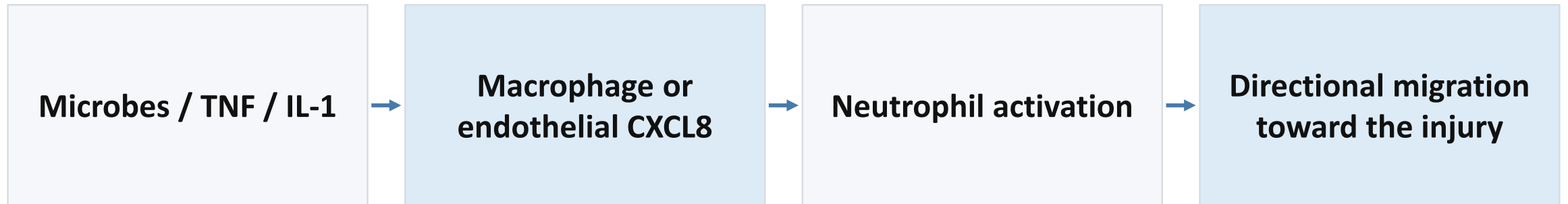
IL-17 recruits phagocytes indirectly



Chemokines are guidance cues for leukocytes

- Small chemoattractant proteins with specialized receptor interactions.
- Act on seven-transmembrane G protein–coupled receptors.
- Displayed on endothelium and extracellular matrix proteoglycans.
- Regulate leukocyte recruitment and normal tissue positioning.

CXCL8 exemplifies neutrophil-directed chemotaxis



CC chemokines target different leukocyte subsets

Illustrative chemokine	Emphasized attraction
CCL2 (MCP-1)	Monocytes
CCL11 (eotaxin)	Eosinophils
CCL3 (MIP-1 α)	Monocytes and other leukocytes
CXCL8 (for contrast)	Mainly neutrophils

Cysteine patterns define four chemokine families

Family	Representative	Characteristic
CXC	CXCL8	Cysteines separated by one residue
CC	CCL2 / CCL11	First two conserved cysteines adjacent
C	XCL1	Lacks two of four conserved cysteines
CX3C	CX3CL1	Three residues separate first cysteines

Immobilized chemokines create a directional signal



Homeostatic chemokines also organize normal tissues

Inflammatory chemokines

- Induced by microbial / tissue injury signals
- Recruitment to an injured site
- Often temporary

Homeostatic chemokines

- Constitutively produced
- Position cells in lymphoid tissues
- Support tissue architecture

Targeting cytokines also changes host defense

A patient receiving a TNF antagonist develops a mycobacterial infection.

- How does TNF inhibition help chronic inflammatory disease?
- Why can the same intervention impair defense against intracellular microbes?

Discuss the mechanism before revealing the explanation in speaker notes.

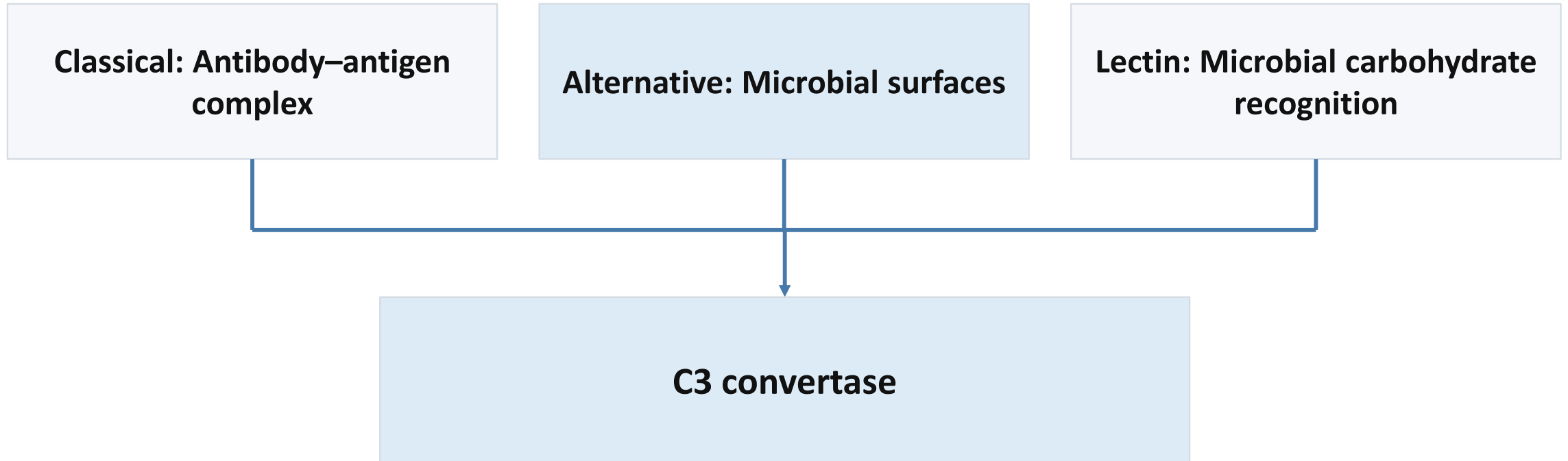
TNF, IL-1, and IL-6 have overlapping but distinct emphasis

Cytokine	High-yield role
TNF	Endothelial activation; chronic catabolic effects
IL-1	Endothelial activation; important fever contribution
IL-6	Systemic acute-phase response
Chemokines	Chemotaxis and leukocyte integrin activation

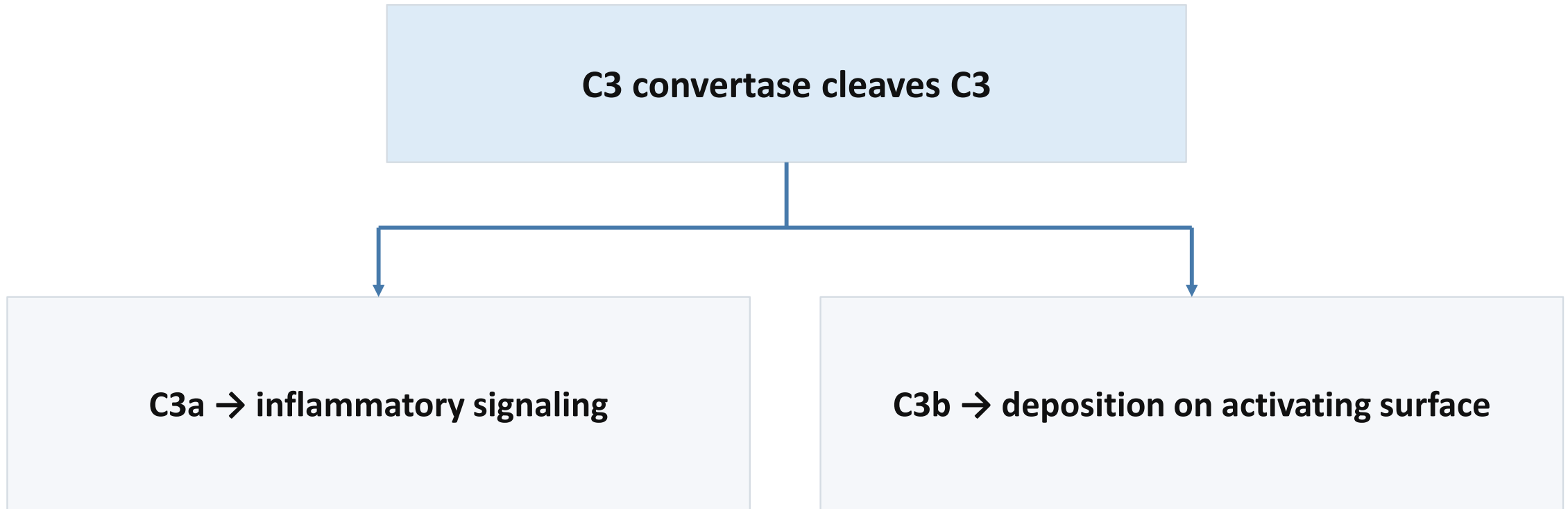
Complement is an amplified plasma-protein cascade

- Many complement proteins circulate in inactive forms.
- Proteolytic activation creates enzymatic amplification.
- C3 cleavage is the central convergence step.
- Cleavage fragments mediate inflammation, opsonization, and cell lysis.

Three initiation pathways converge on C3



C3 cleavage separates soluble and surface-bound effects



C5 cleavage diversifies complement effector outputs

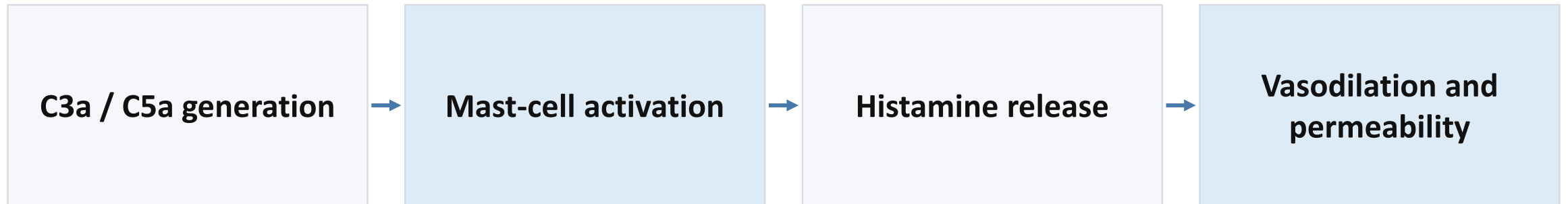
C5 convertase cleaves C5

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graph TD; A[C5 convertase cleaves C5] --> B[C5a → inflammatory activation]; A --> C[C5b → C6–C9 membrane attack complex];
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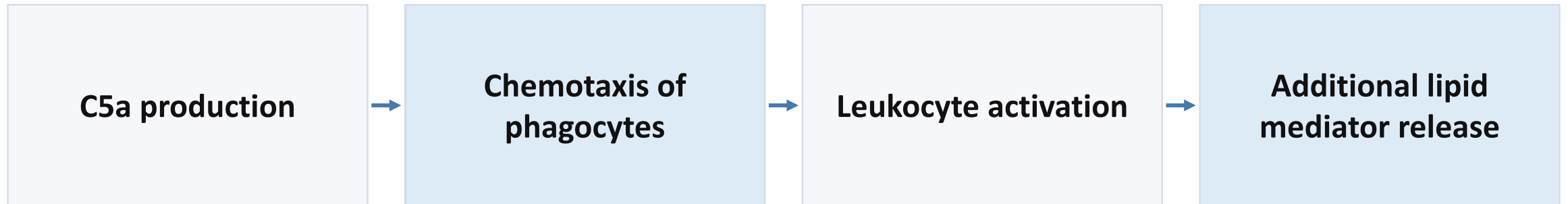
C5a → inflammatory activation

C5b → C6–C9 membrane attack complex

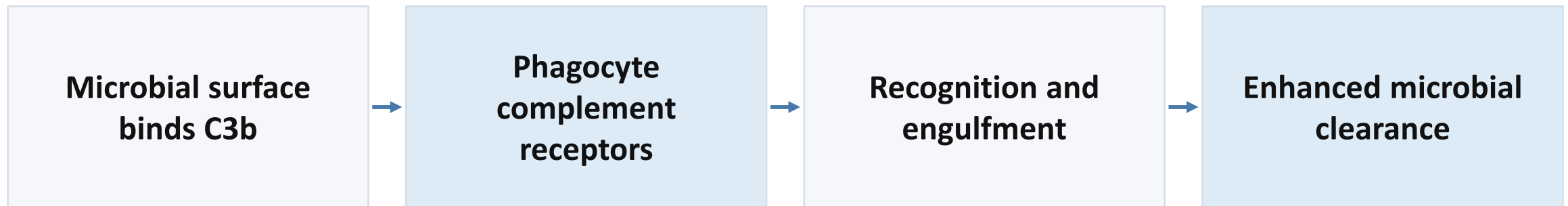
Anaphylatoxins promote vascular inflammation



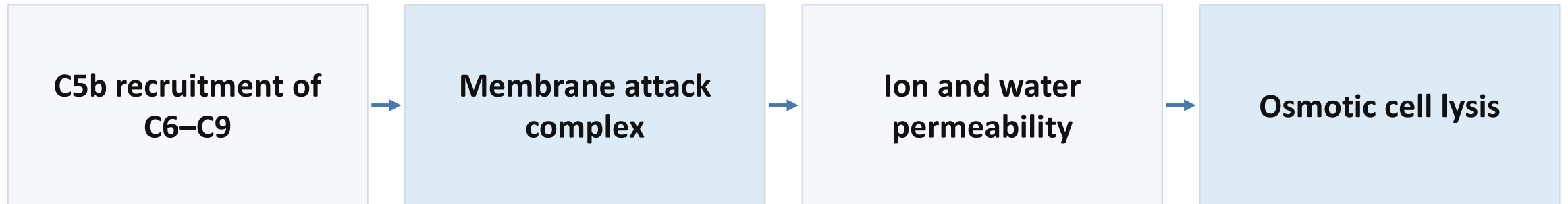
C5a recruits and activates leukocytes



C3b functions as a surface-bound opsonin



The membrane attack complex directly damages membranes



Complement regulators protect healthy host cells

Regulator	Mechanism / disease association
C1 inhibitor	Restrains C1 activation; deficiency → hereditary angioedema
CD55 (DAF)	Restrains C3 convertase formation
CD59	Inhibits membrane attack complex assembly
Factor H	Regulates alternative pathway C3b activity

Dysregulated complement illustrates disease mechanisms

Defect / context	Associated consequence
C1 inhibitor deficiency	Hereditary angioedema
Loss of GPI-anchored CD55 / CD59	Paroxysmal nocturnal hemoglobinuria
Factor H pathway dysregulation	Atypical hemolytic uremic syndrome
Terminal complement deficiency	Susceptibility to Neisseria infection

Clinical correlation: Complement-mediated hemolysis

Blood cells undergo complement-mediated lysis after loss of GPI-anchored membrane proteins.

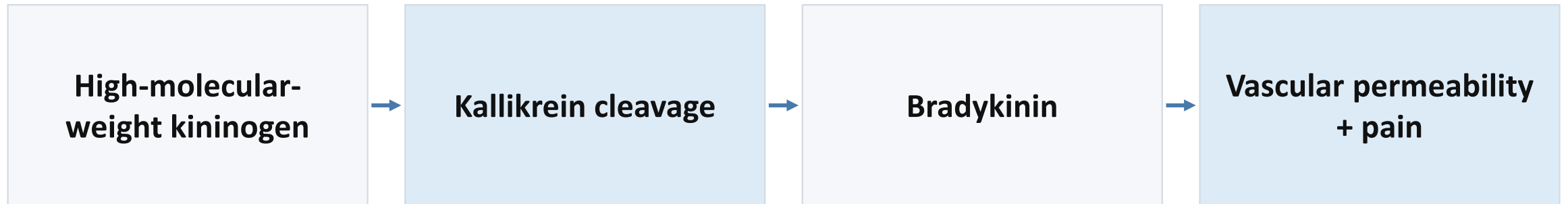
- Which two regulators are reduced on affected cells?
- What disease results from loss of this complement protection?

Discuss the mechanism before revealing the explanation in speaker notes.

Platelet-activating factor links several cell types

- PAF is a phospholipid-derived mediator produced by platelets and multiple inflammatory cells.
- It can induce platelet aggregation and leukocyte activation.
- Concentration-dependent effects include vascular and bronchial responses.
- PAF antagonists have not established therapeutic benefit in studied inflammatory diseases.

Bradykinin comes from a plasma proteolytic pathway



Histamine and bradykinin overlap, but differ in origin

Histamine

- Stored mainly in mast-cell granules
- Very rapid release on degranulation
- Vascular H1-receptor effects

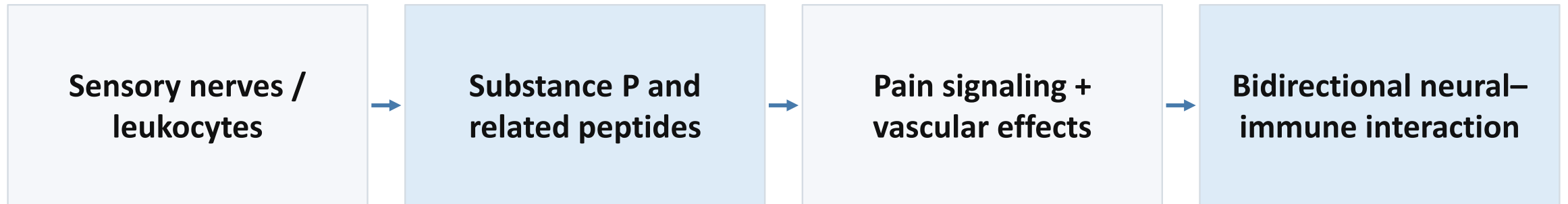
Bradykinin

- Cleaved from circulating kininogen
- Generated by kallikrein
- Pain, permeability, vasodilation

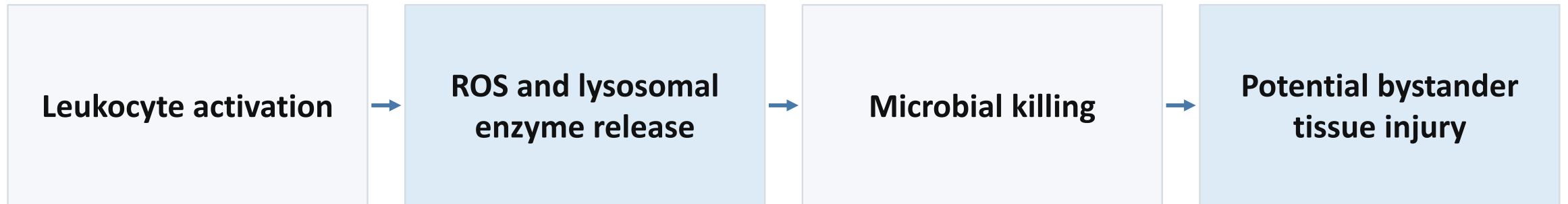
Coagulation and inflammation share signaling interfaces

- Thrombin can activate protease-activated receptors on several cell types.
- Coagulation and inflammation often occur in the same injured tissue.
- Fibrin cleavage products may have inflammatory effects.
- A direct causal role of clotting products in every inflammatory setting is not established.

Neuropeptides provide neuroimmune communication



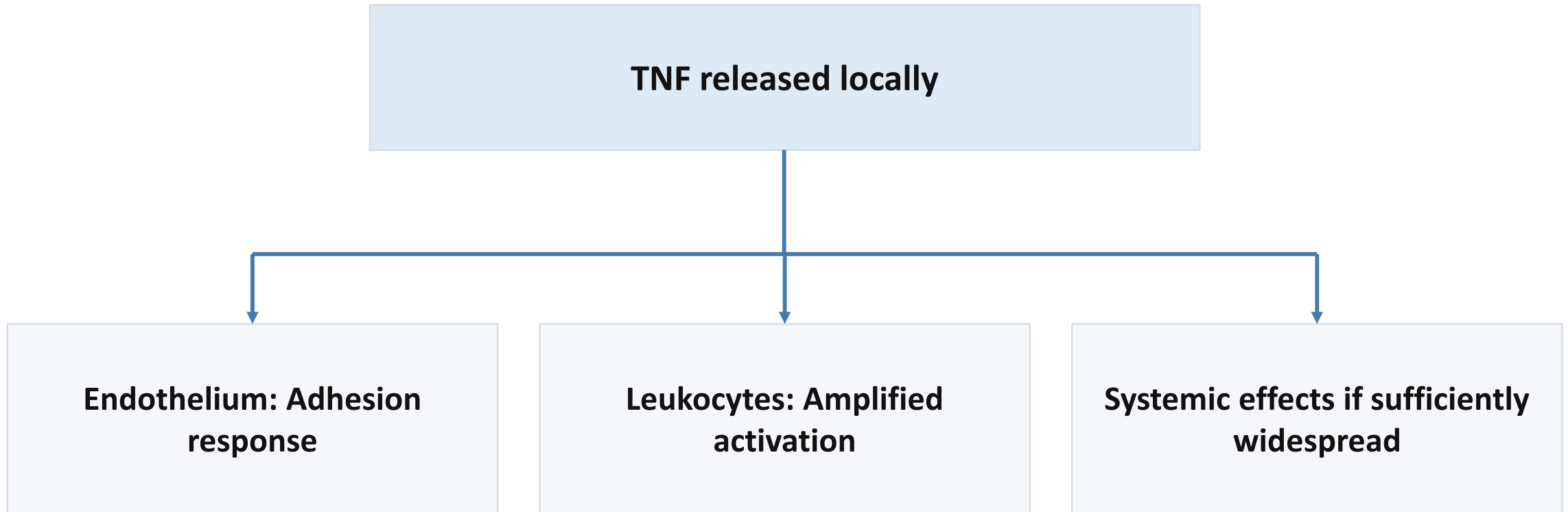
Tissue damage may arise from leukocyte effector products



Use the response to identify likely mediators

Observed phenomenon	Prioritize these signals
Immediate arteriolar dilation	Histamine; vasodilator prostaglandins
Early edema	Histamine, bradykinin; cysteinyl leukotrienes
Neutrophil chemotaxis	CXCL8, LTB ₄ , C5a
Systemic fever / acute-phase reaction	IL-1, TNF, IL-6; PGE ₂

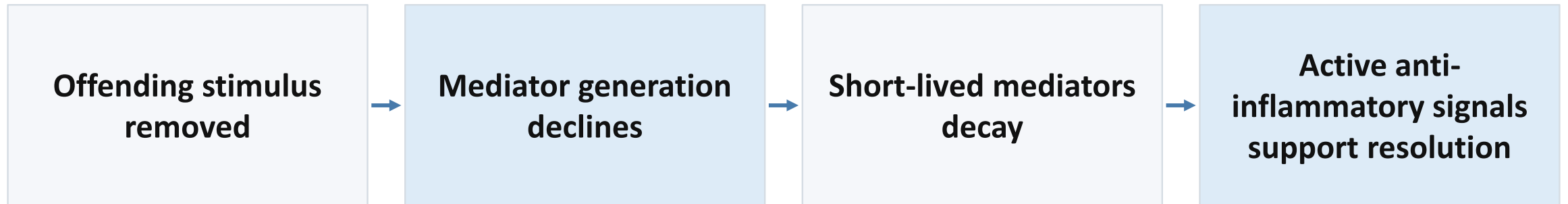
One mediator can affect several compartments



Three forms of mediator interaction

Relationship	Example	Consequences
Amplification	C5a → mast-cell histamine	Accelerated vascular response
Convergence	TNF + IL-1 → endothelium	Overlapping recruitment programs
Antagonism	Lipoxins opposing leukotriene actions	Restriction of neutrophil traffic

Removing the insult does not instantly reset tissue



Clinical synthesis: Inflammatory pain and swelling

After a minor tissue injury, warmth, swelling, and tenderness appear.

- Identify a mediator explaining local vasodilation.
- Identify one pathway explaining edema and one mediator implicated in pain.

Discuss the mechanism before revealing the explanation in speaker notes.

Interpret mediator-directed treatment by its target

Intervention class	Direct target	Major limitation / trade-off
H1 blockade	Histamine H1 signaling	Does not block all edema pathways
NSAIDs	Cyclooxygenase activity	Physiological prostanoid functions also affected
TNF antagonism	TNF signaling	Can compromise antimycobacterial host defense
Complement inhibitors	Selected C3 / C5 activation	Host-defense implications depend on target

Retrieval practice: Interpret five mediator effects

- Which mediator is preformed in mast-cell granules?
- Which arachidonic-acid product activates neutrophils?
- Which cytokine drives a major acute-phase protein response?
- Which complement fragment is a major opsonin?
- Which plasma-derived peptide causes pain and increased permeability?

Core distinctions to retain

Question	Answer
Rapid preformed vascular mediator?	Histamine
Lipid mediator favoring resolution?	Lipoxins
Endothelial-activation cytokines?	TNF and IL-1
Opsonin from complement?	C3b
Leukocyte-guidance protein family?	Chemokines

Reference and scope

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026).

Chapter 3: Inflammation and Repair — Mediators of Inflammation and related sections.

Teaching diagrams are original editable schematics; no textbook figures reproduced.