

Mediators of Immediate Hypersensitivity

Mast-cell products, effector mechanisms, and tissue injury

From IgE receptor cross-linking to immediate and late-phase reactions

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Learning outcomes

Identify

Preformed granule contents

Newly generated lipid products

Secreted cytokines

Explain

Vascular leakage and edema

Bronchospasm and mucus

Leukocyte influx and injury

Integrate

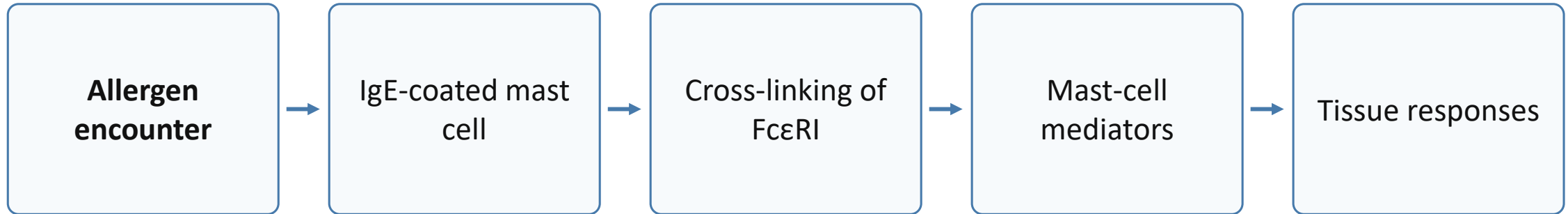
Immediate reaction versus late phase

Eosinophil tissue damage

Allergic clinical phenotypes

Central question: How can one activated mast cell generate different clinical patterns?

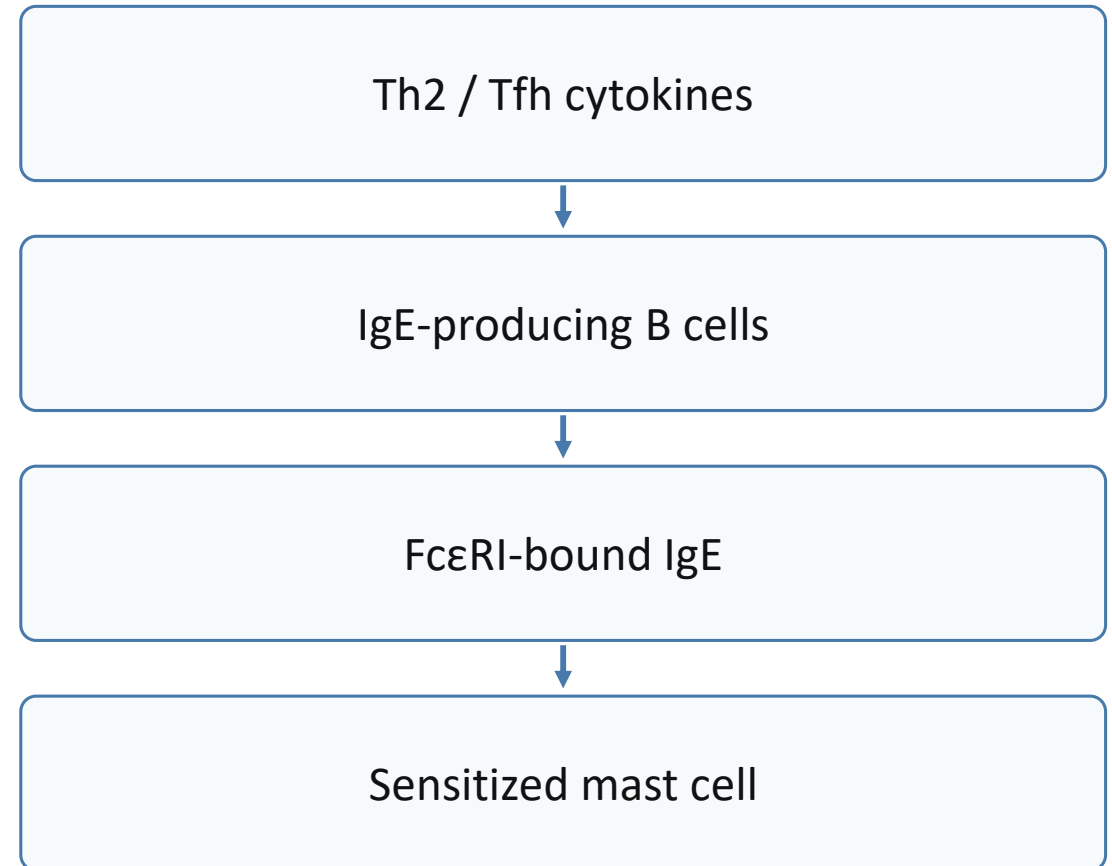
Type I hypersensitivity: The effector sequence



Mediator identity determines the pattern and timing of injury.

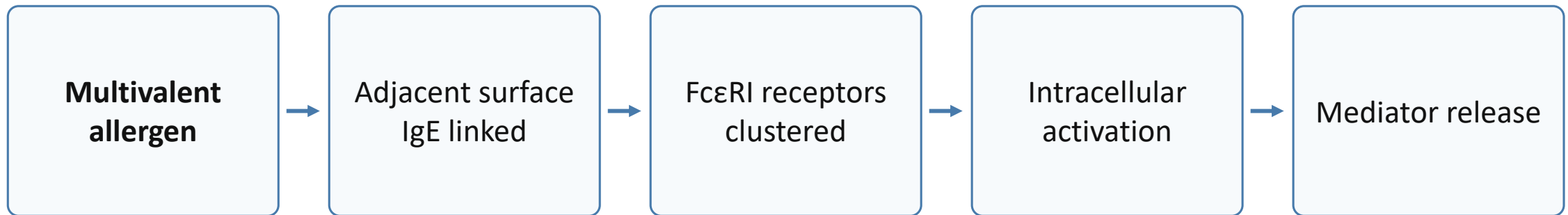
Sensitization precedes mast-cell mediator release

- Environmental allergen stimulates a type 2 immune response.
- IL-4 and IL-13 promote B-cell switching to IgE.
- IgE binds high-affinity FcεRI on mast cells.



IgE coating prepares the mast cell for rapid reaction upon re-exposure.

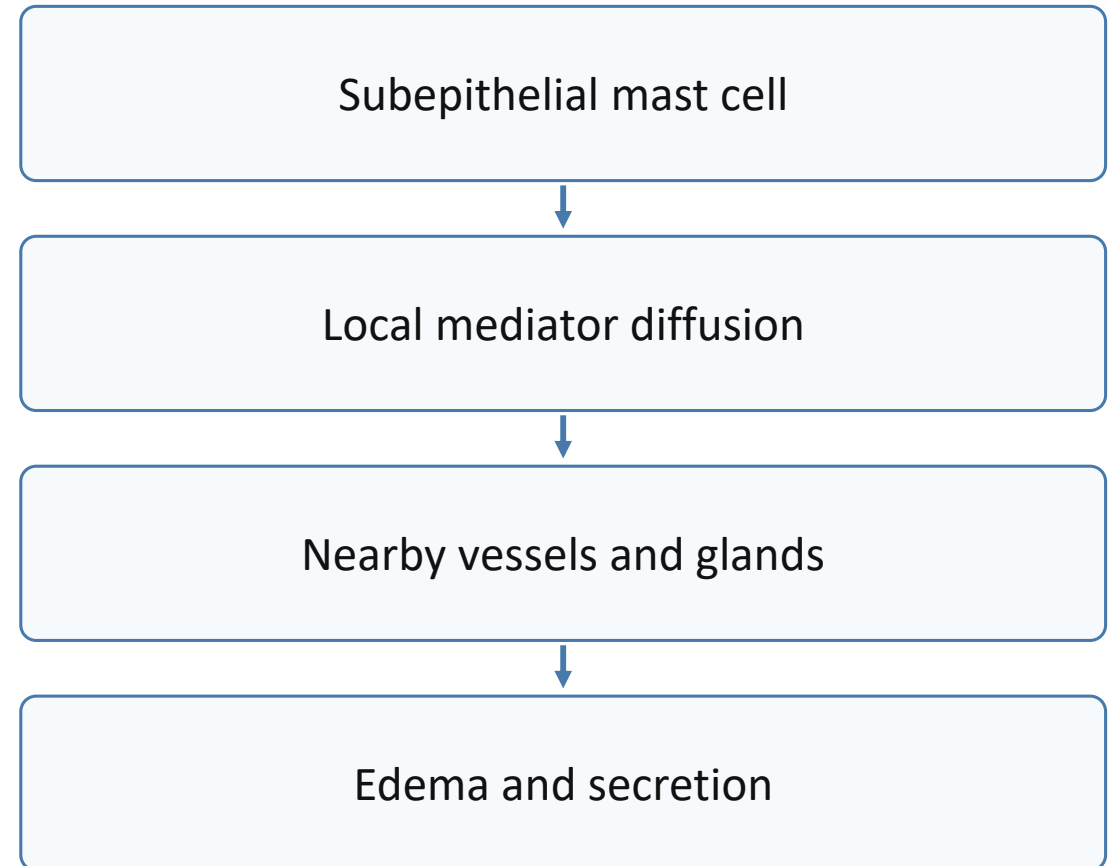
Antigen cross-linking initiates release



Cross-linking converts allergen recognition into effector activity.

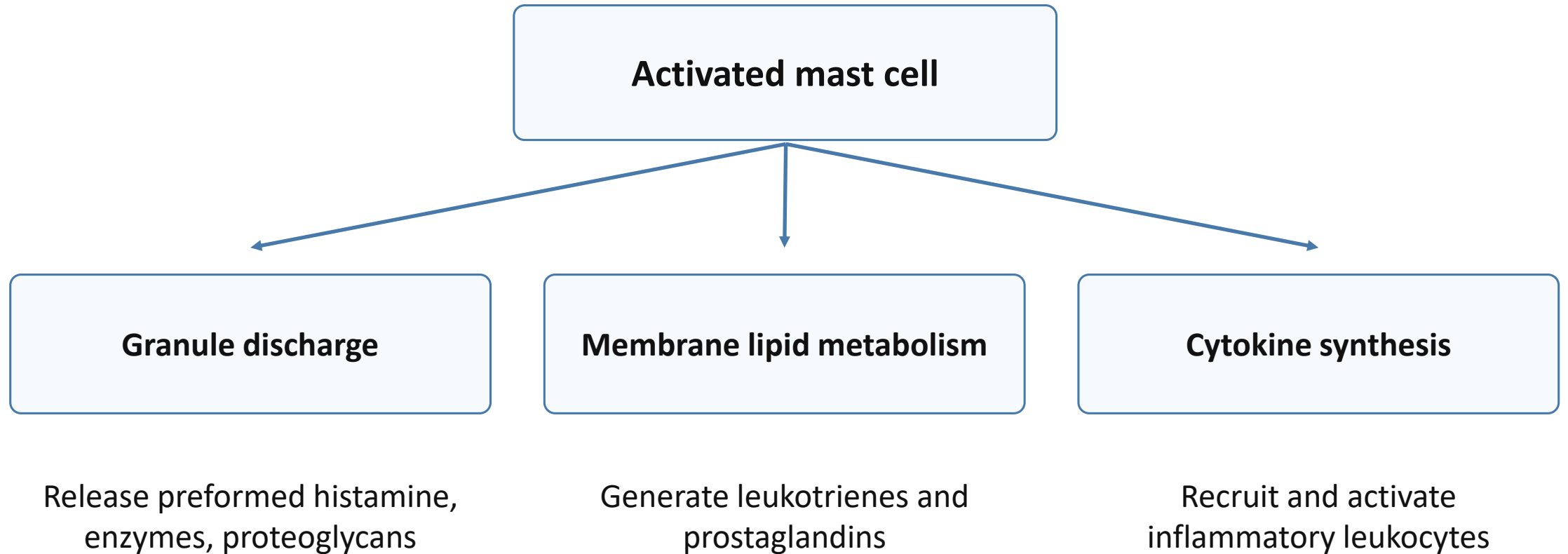
Why mast-cell location matters

- Mast cells are concentrated near small blood vessels, nerves, and subepithelial tissues.
- Released mediators act directly on vascular endothelium, glands, and smooth muscle.
- Anatomical placement helps explain the rapid onset of local symptoms.



Local concentration and tissue proximity shape the visible reaction.

Three concurrent activation programs



One trigger launches rapid and sustained effector programs.

Immediate and late-phase responses

After re-exposure to allergen

Within minutes

2–24 hours

Vasodilation, edema, mucus secretion
and smooth-muscle spasm

Leukocyte infiltration, epithelial injury
and sustained inflammation

A later inflammatory phase can persist without renewed antigen exposure.

Mast-cell mediator families

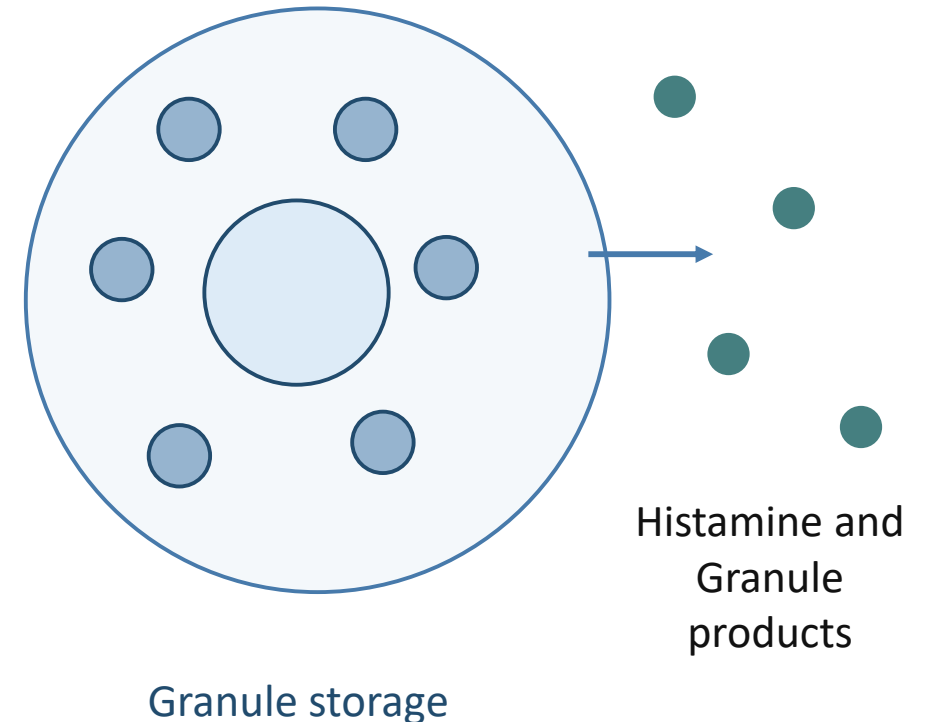
Mediator family	Principal components	Dominant effect
Preformed granule	Histamine; Proteases; Proteoglycans	Rapid tissue responses; Storage / injury
Lipid products	Leukotrienes; Prostaglandin D ₂	Bronchospasm, leakage, chemotaxis
Cytokines	TNF; IL-1; IL-4; Chemokines	Recruitment and Th2 amplification

Timing differs because some products are stored whereas others are synthesized.

Preformed granules provide an immediate supply

- Mast-cell granules contain biologically active products before re-exposure.
- Receptor-induced degranulation expels these products into nearby tissue.
- This rapid discharge precedes newly synthesized cytokine effects.

Mast-cell degranulation (schematic)



Stored mediators explain why tissue changes can begin within minutes.

Three categories of granule contents

Vasoactive amines

Histamine

Vascular permeability

Smooth-muscle and gland
effects

Enzymes

Tryptase; Chymase

Acid hydrolases

Tissue injury / mediator
generation

Proteoglycans

Heparin

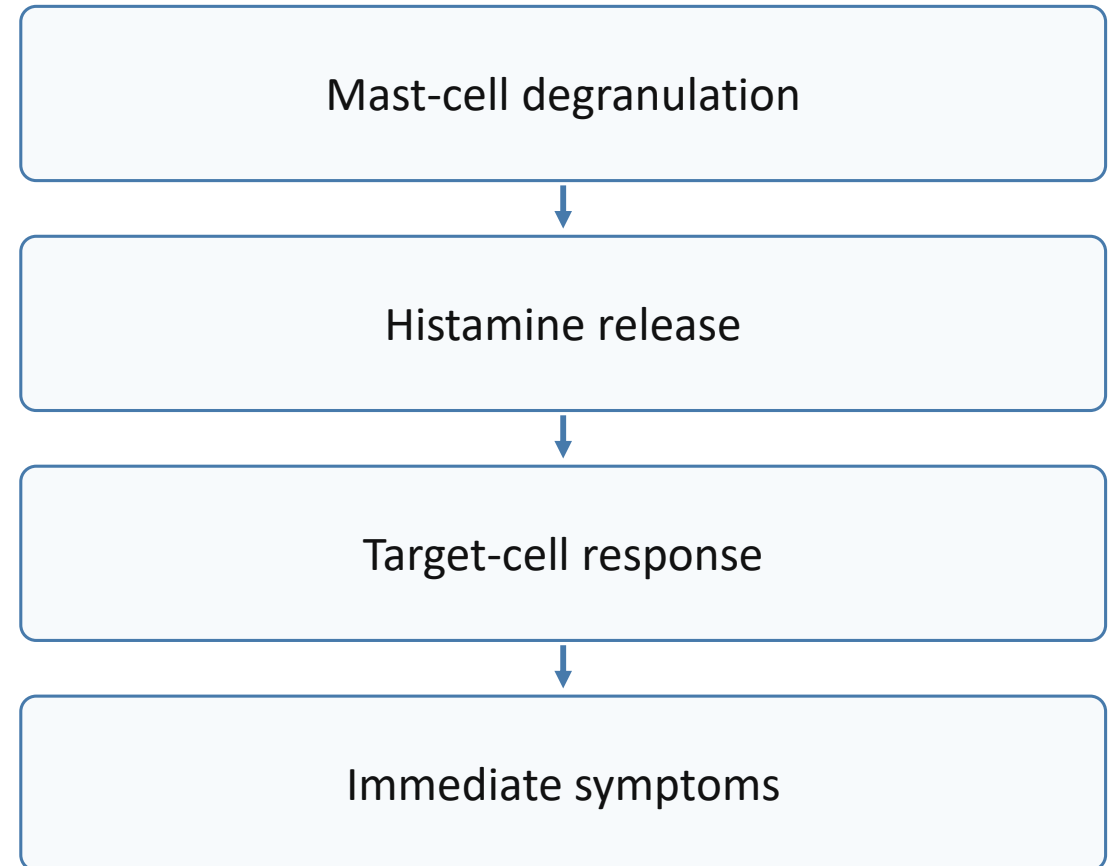
Chondroitin sulfate

Packaging and storage of
amines

All are preformed, but their functions are not interchangeable.

Histamine is the dominant granule amine

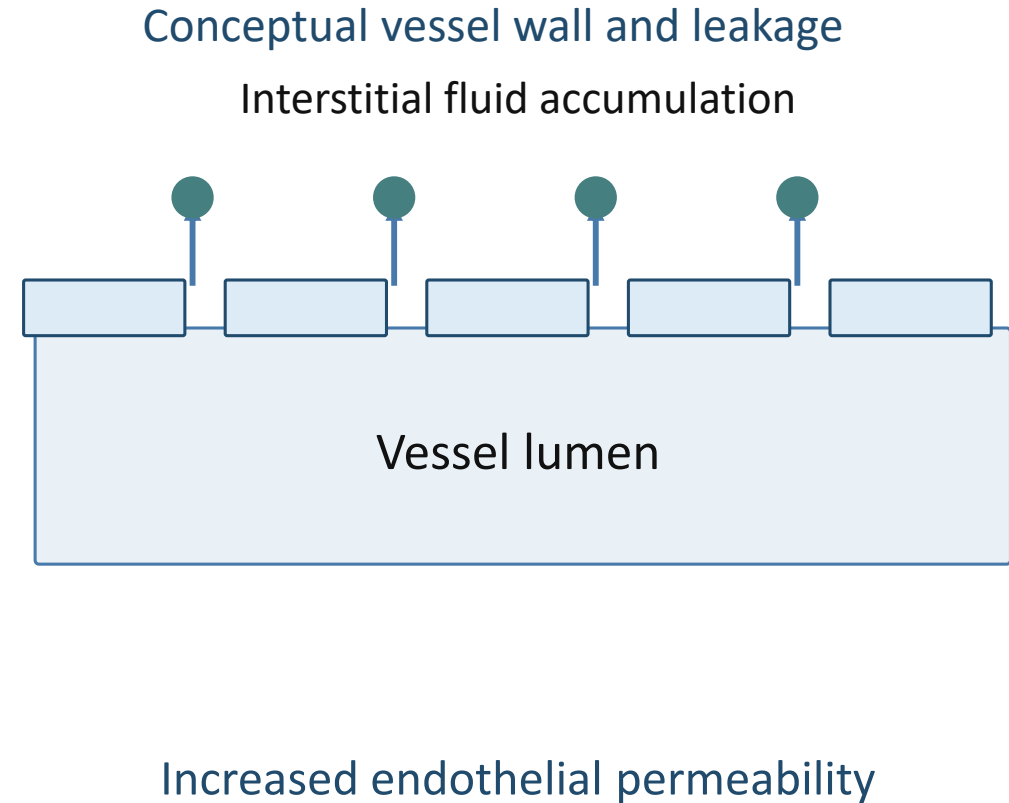
- Histamine is the most important mast cell–derived vasoactive amine.
- It acts rapidly on local vascular, smooth-muscle, and glandular targets.
- Its combined effects account for characteristic early allergic manifestations.



Histamine links a molecular product to a rapid multisystem phenotype.

Histamine increases vascular permeability

- Histamine enhances vascular leakage from the microcirculation.
- Extravasation of fluid produces local tissue edema.
- Leakage contributes to swelling in immediate hypersensitivity.

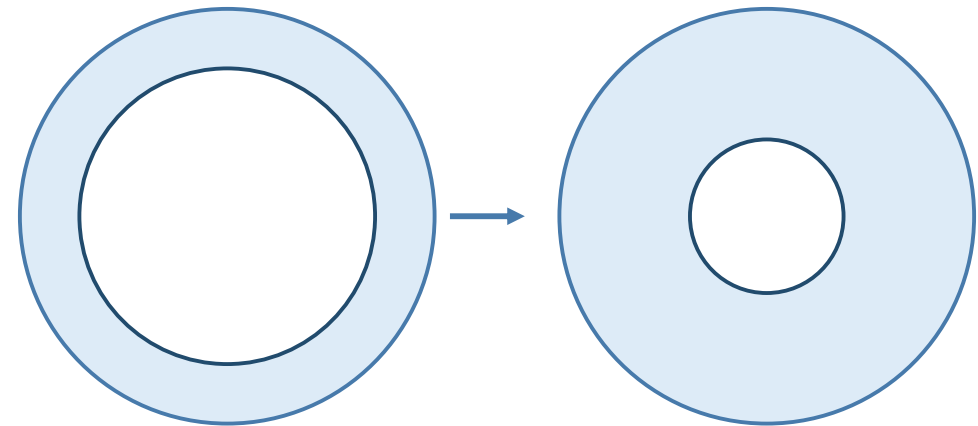


Edema is a functional consequence of mediator-driven vascular leakage.

Histamine contracts smooth muscle

- Histamine can induce intense smooth-muscle contraction.
- Bronchial constriction contributes to narrowed airways.
- Contraction provides a mechanistic basis for immediate respiratory symptoms.

Bronchial lumen (conceptual cross-sections)



Before contraction

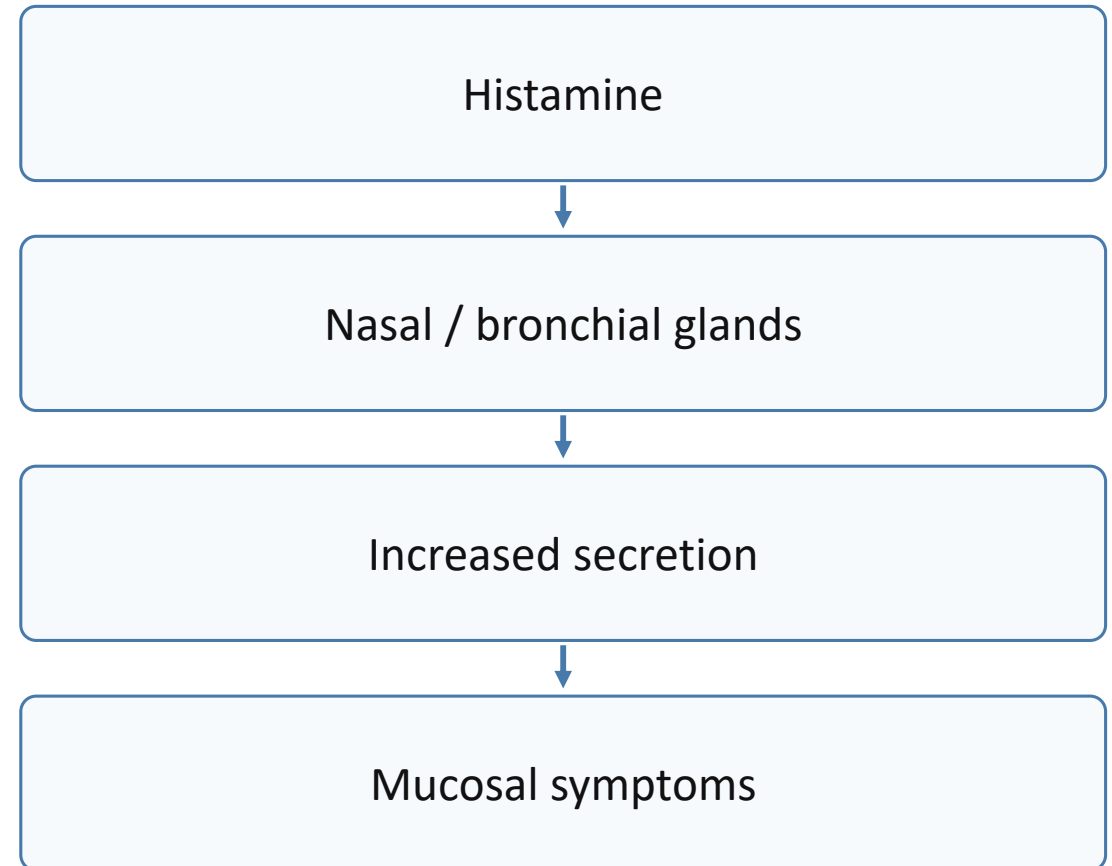
After contraction

Schematic; Illustrates functional narrowing

Bronchospasm is not solely an inflammatory-cell infiltration effect.

Histamine stimulates mucus secretion

- Histamine stimulates glands in nasal, bronchial, and gastric mucosa.
- Enhanced secretion accompanies other early tissue effects.
- In the upper airway, mucus production helps explain rhinorrhea.



A single mediator can act on both the vascular and secretory compartments.

Histamine acts on several tissue compartments

Blood vessels

- Greater vascular permeability
- Fluid movement into interstitium
- Rapid edema

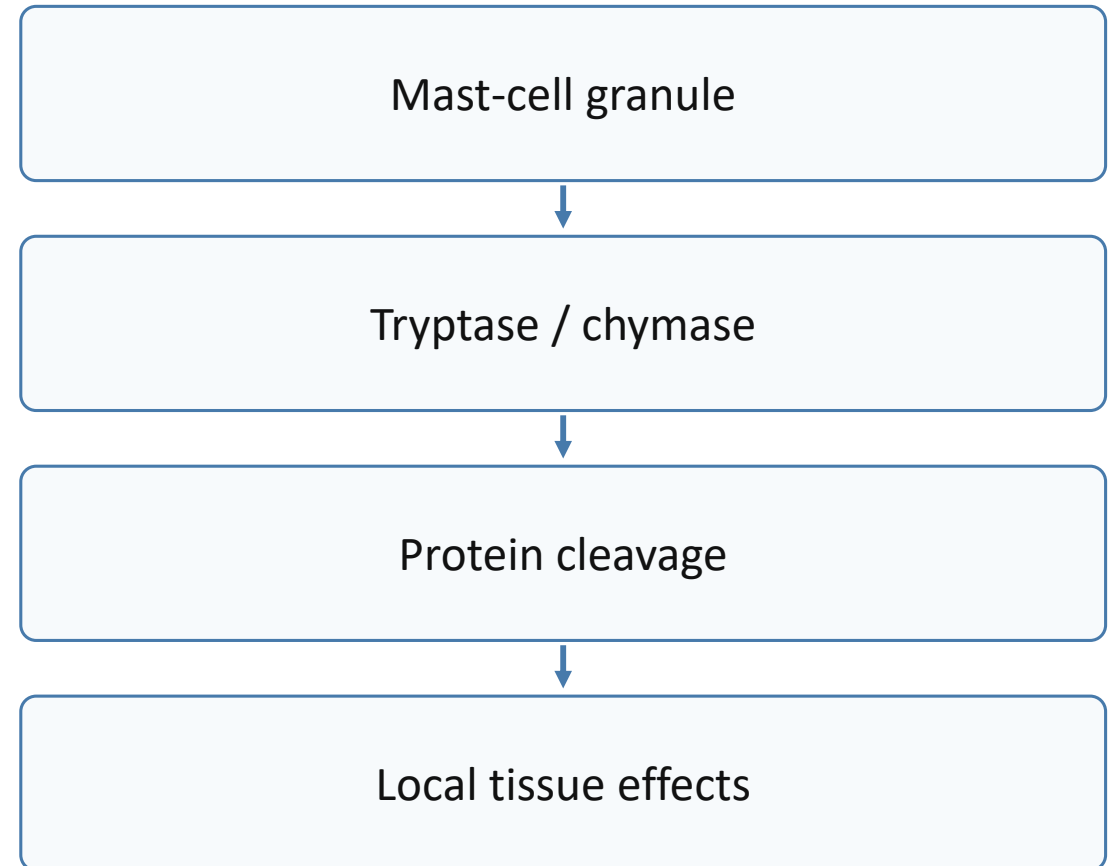
Smooth muscle and glands

- Contraction contributes to airway narrowing
- Glandular activation increases mucus
- Symptoms vary with involved organ

The target tissue—not only the mediator—determines the phenotype.

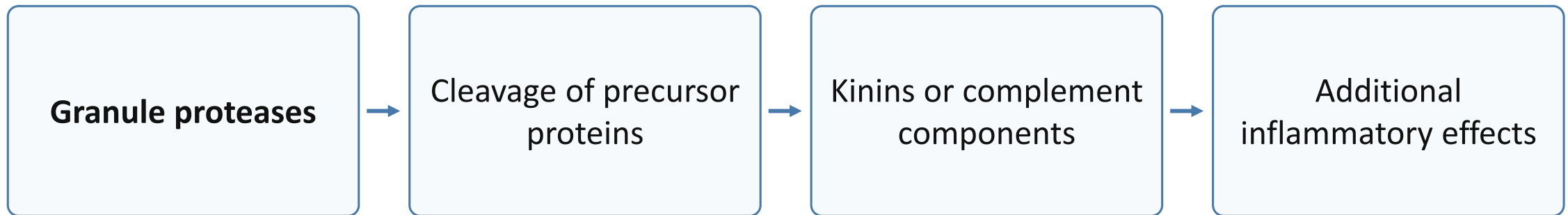
Mast-cell neutral proteases: Tryptase and chymase

- Granule matrix contains neutral proteases, including tryptase and chymase.
- Acid hydrolases are additional granule enzymes.
- Proteolysis can produce damage beyond transient vascular leakage.



Proteases represent a tissue-injury arm of mast-cell degranulation.

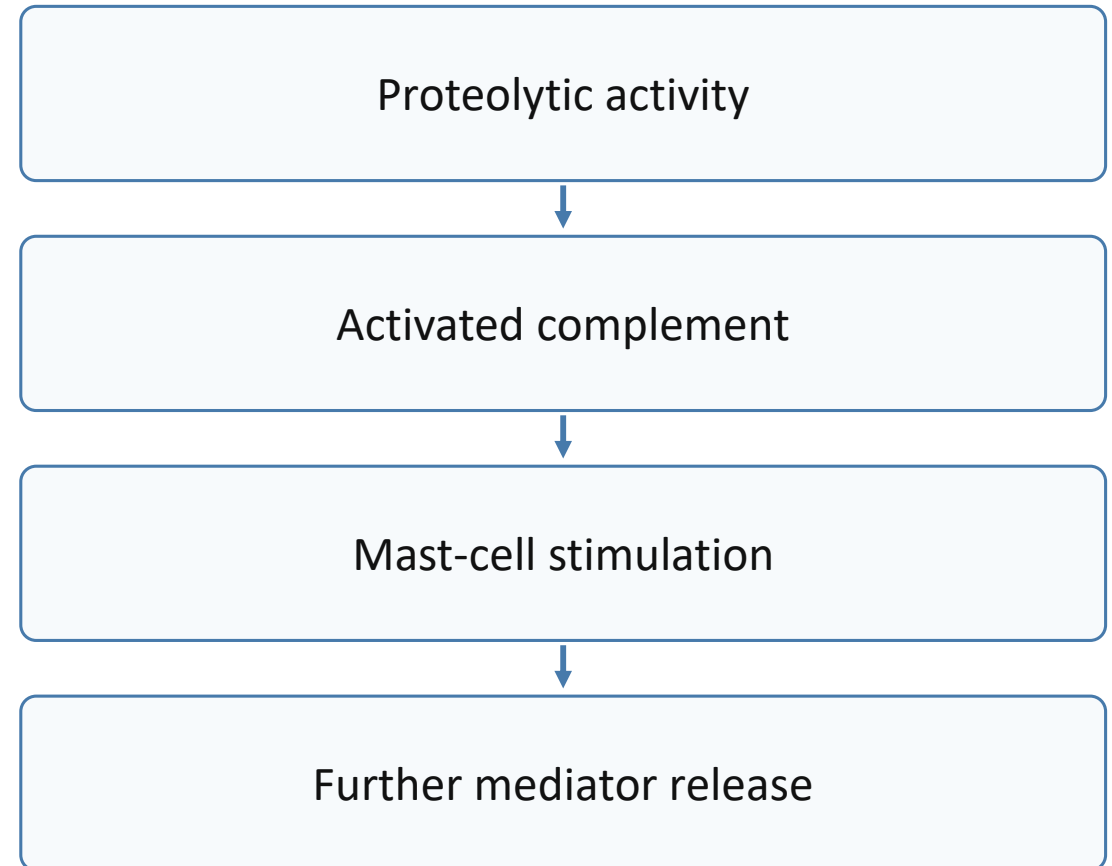
Proteases can amplify soluble mediator generation



Kinin and complement generation as protease-associated effects.

Complement fragments can reinforce mast-cell activation

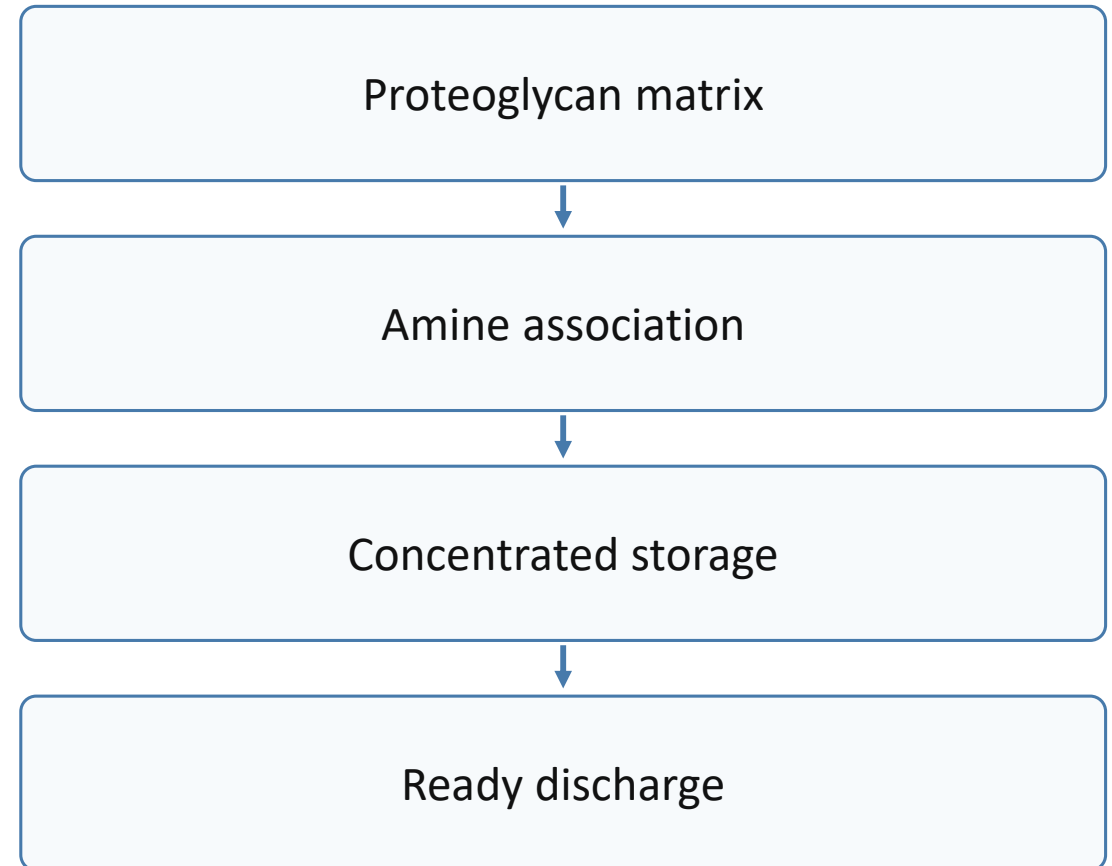
- Activated complement components may be generated by granule enzymes.
- C3a and C5a can themselves act as mast-cell activators.
- This gives complement and mast-cell pathways potential for reciprocal reinforcement.



Complement activation is an additional trigger, not proof of IgE dependence.

Proteoglycans organize the granule contents

- Heparin and chondroitin sulfate are granule proteoglycans.
- They help package and store bioactive amines.
- Their major teaching role in this section is intragranular organization.



Storage chemistry is part of the mechanism of rapid mediator release.

Heparin and chondroitin sulfate

Heparin

- A familiar anticoagulant molecule
- Stored in mast-cell granules
- Also contributes to granule packaging

Chondroitin sulfate

- Granule-associated proteoglycan
- Supports packaging and amine storage
- Distinct from a vasoactive amine

Do not confuse granule storage constituents with the chief symptom-producing amine.

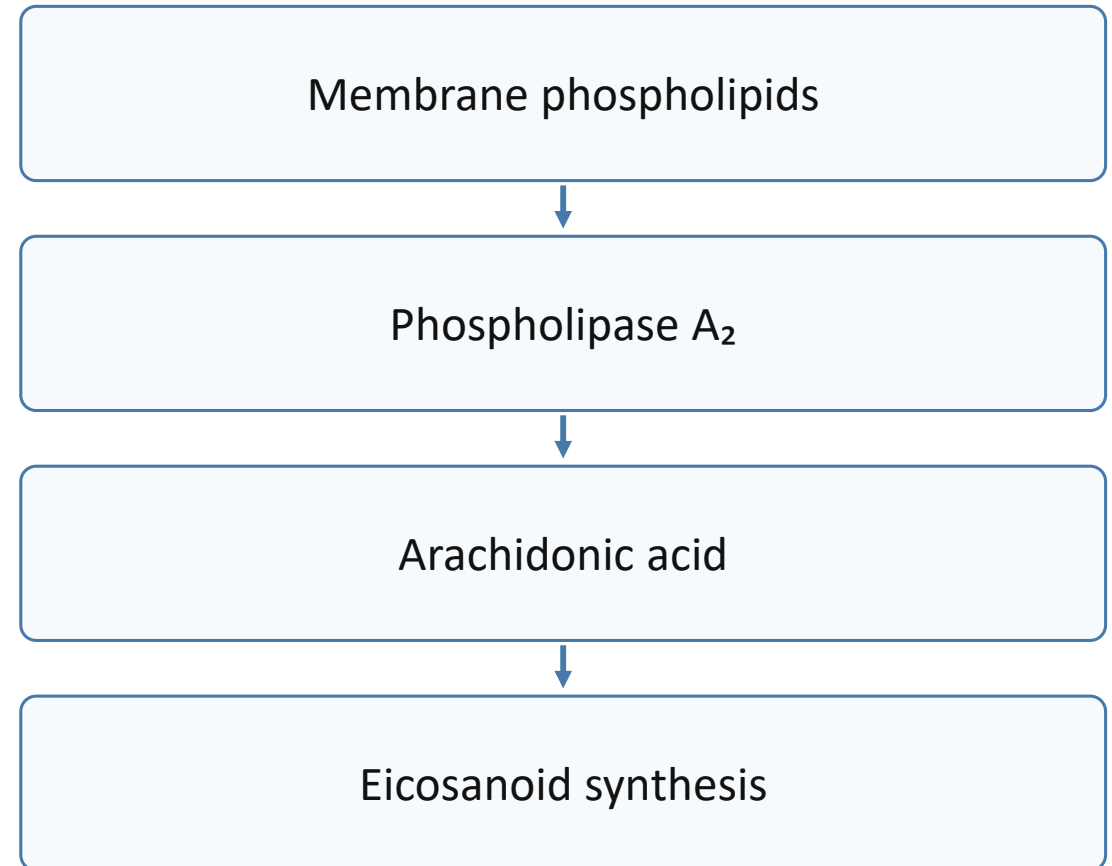
Preformed mediator mechanisms compared

Component	Immediate function	Pathobiologic interpretation
Histamine	Permeability, contraction, mucus	Dominant early functional changes
Proteases	Protein cleavage and tissue damage	Can generate kinins / complement fragments
Proteoglycans	Amine packaging and storage	Permit high local granule concentration

Only histamine should be presented as the principal vasoactive amine.

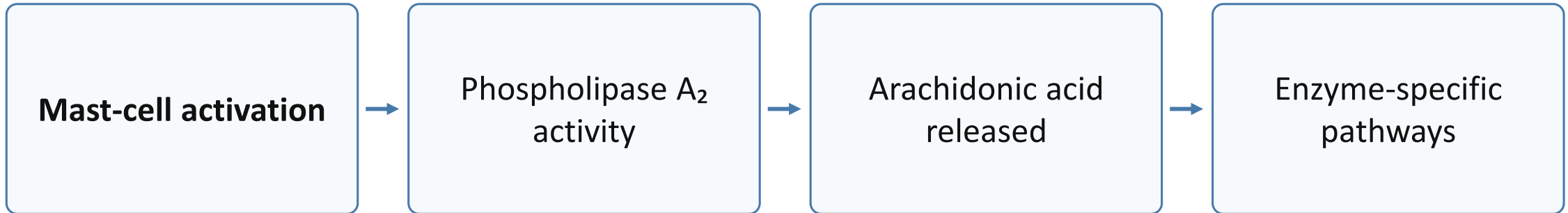
Lipid mediators are synthesized following activation

- Unlike stored histamine, major lipid mediators derive from membrane phospholipids.
- Mast-cell activation stimulates phospholipase A₂.
- Arachidonic acid is the precursor for the major downstream products.



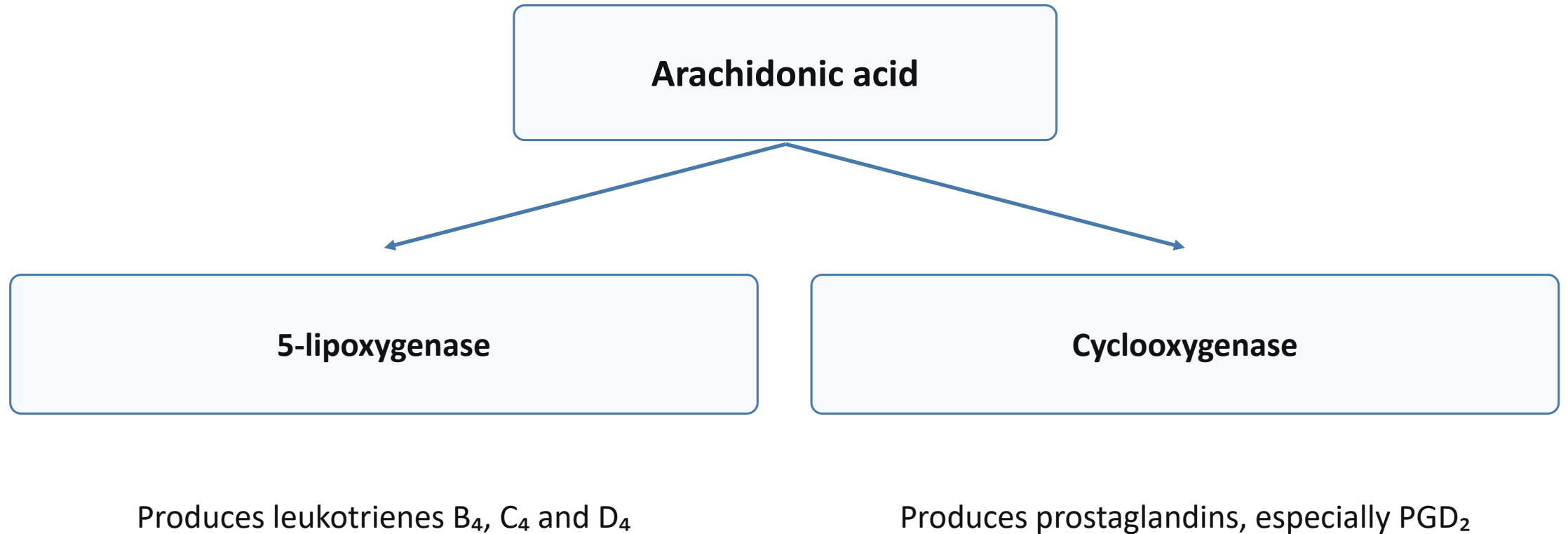
Release of a precursor enables multiple distinct lipid mediator outputs.

Phospholipase A₂ initiates eicosanoid synthesis



Membrane lipid metabolism is an independent response to FcεRI signaling.

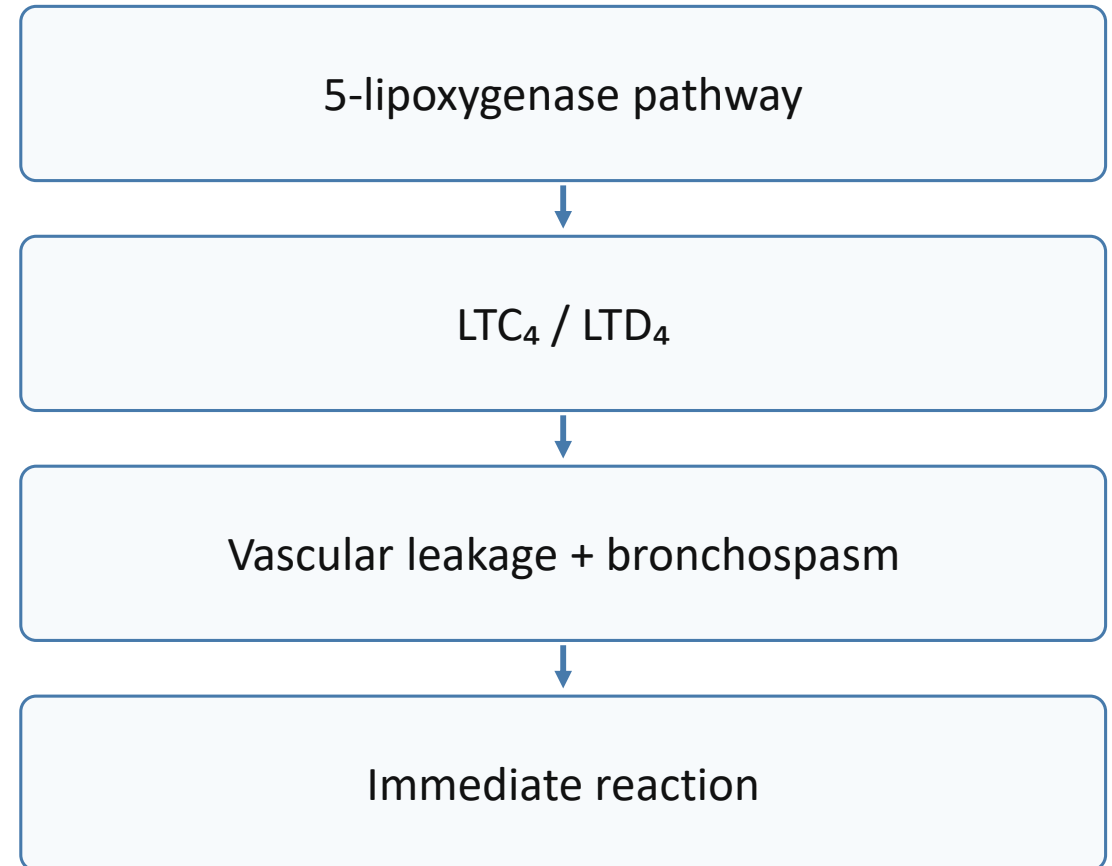
Arachidonic acid enters two principal pathways



Different enzymes yield products with different dominant target effects.

Cysteinyl leukotrienes produce strong tissue responses

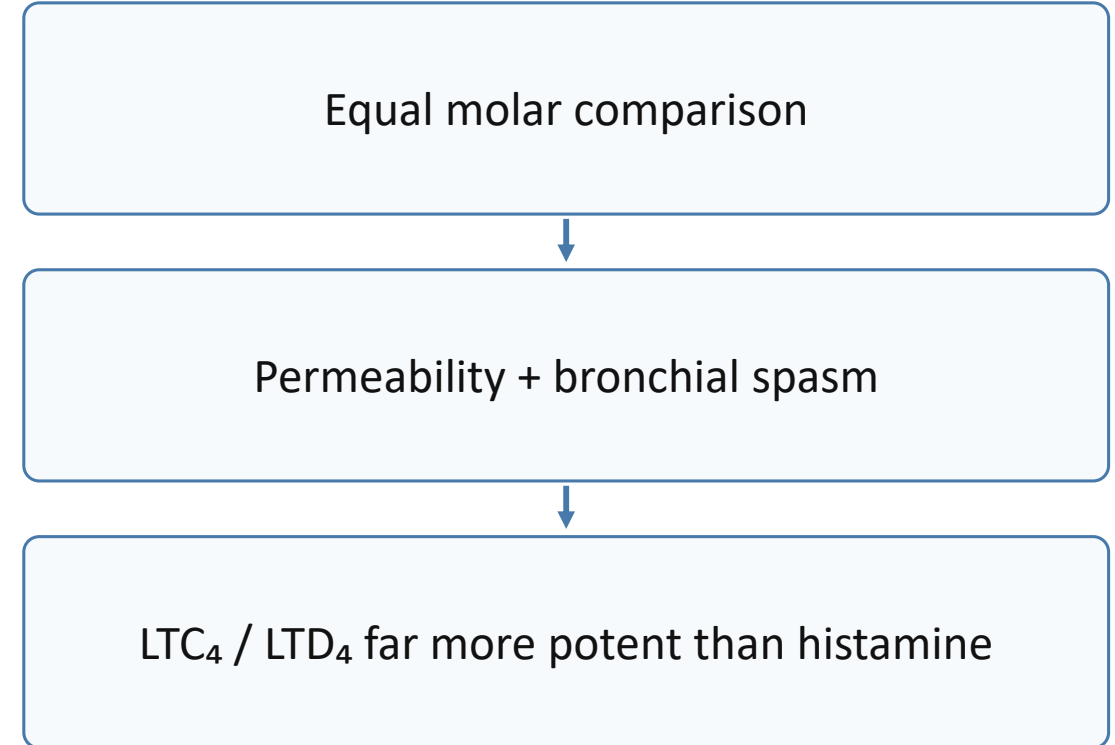
- Leukotrienes C₄ and D₄ are powerful vasoactive and spasmogenic agents.
- They markedly increase vascular permeability.
- They also produce pronounced bronchial smooth-muscle contraction.



Cysteinyl leukotrienes contribute to edema and airway narrowing.

Leukotriene potency is an important distinction

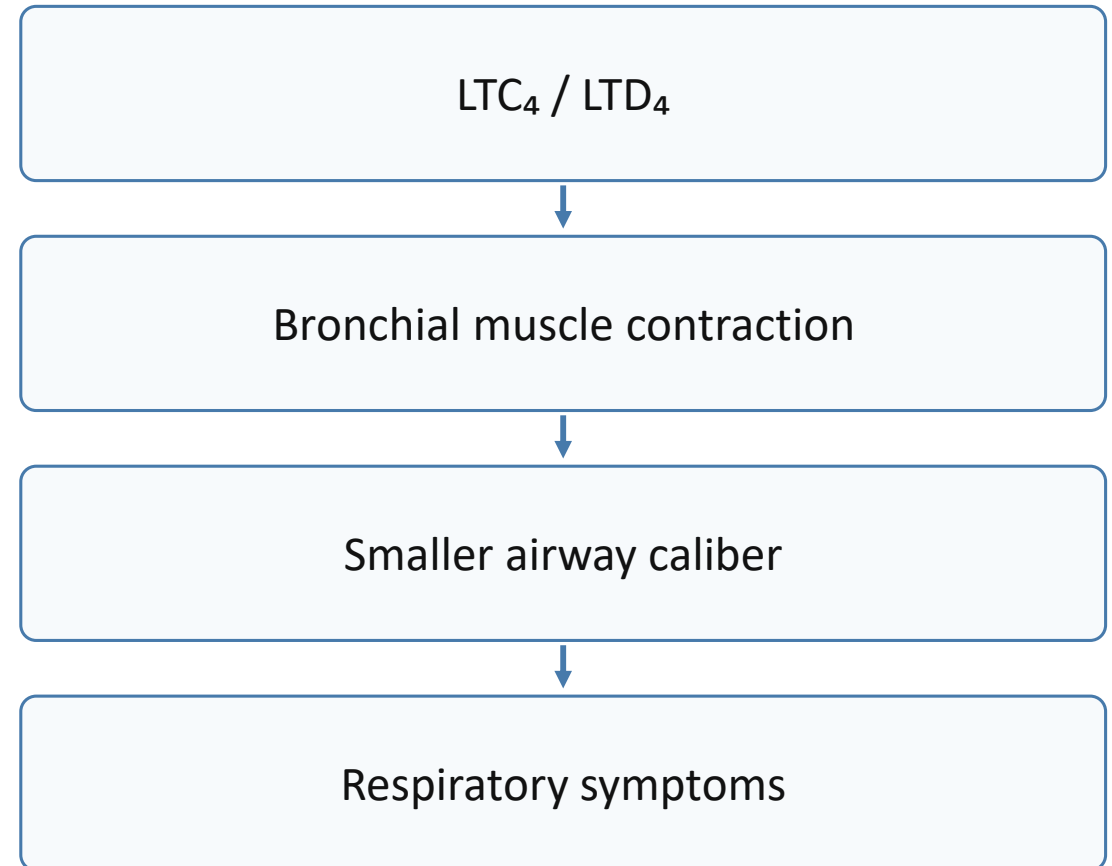
- On a molar basis, LTC₄ and LTD₄ are several thousand times more active than histamine.
- The comparison refers to vascular permeability and bronchial smooth-muscle contraction.
- Potency is not equivalent to a claimed concentration or clinical effect size.



A strong molecular effect cannot be substituted for unreported patient-level measurements.

Cysteinyl leukotrienes and bronchospasm

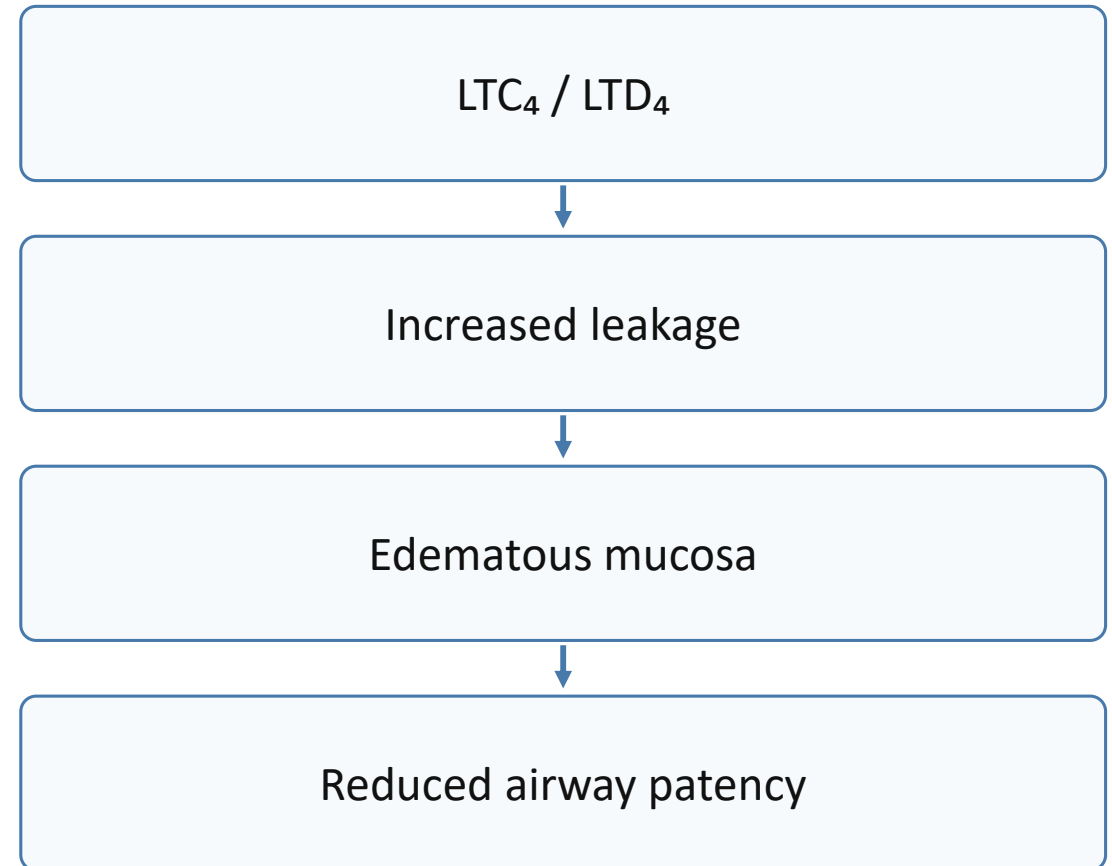
- LTC₄ and LTD₄ directly support bronchial smooth-muscle contraction.
- Narrowing of the airway lumen produces functional airflow obstruction.
- This effect complements bronchospasm induced by histamine and PGD₂.



Several mediator families converge on the bronchial smooth-muscle target.

Cysteinyl leukotrienes and edema

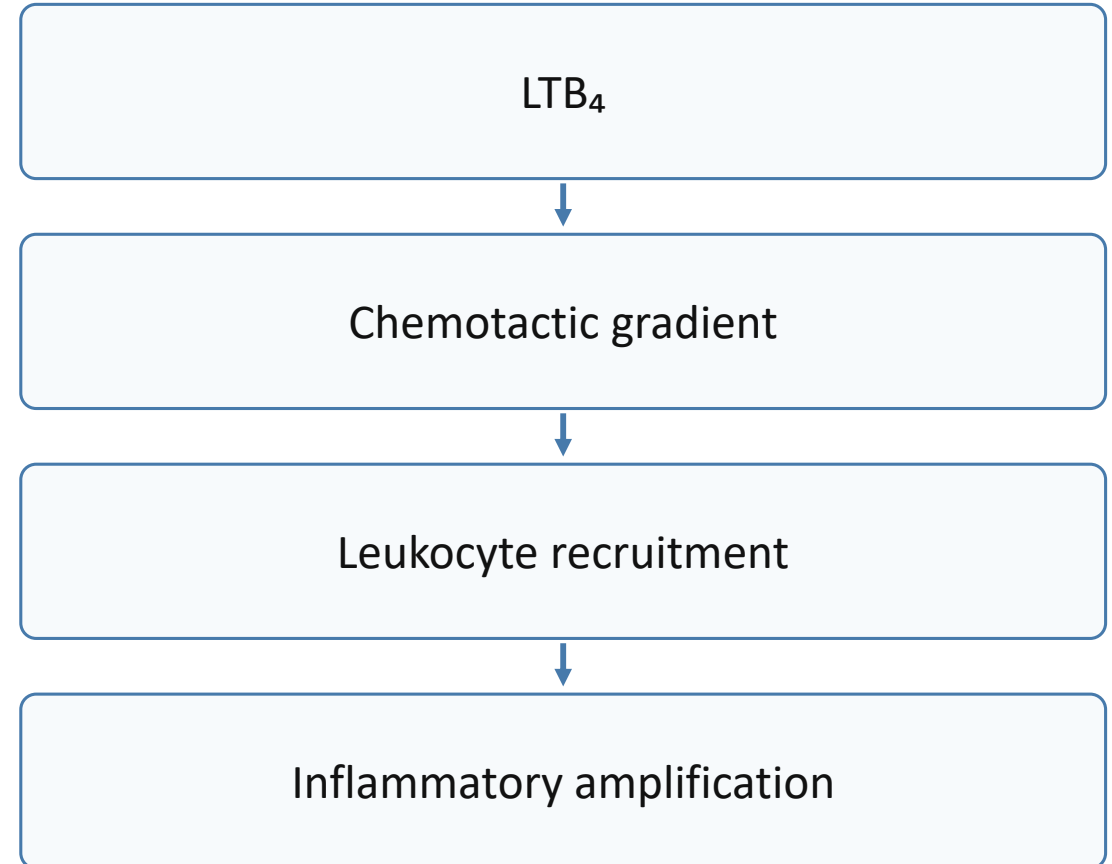
- LTC₄ and LTD₄ increase microvascular permeability.
- Leakage of plasma-rich fluid creates local swelling.
- The same lipid products can affect both vessels and airway smooth muscle.



Vascular leakage and bronchoconstriction can reinforce functional obstruction.

Leukotriene B₄ is predominantly chemotactic

- LTB₄ is highly chemotactic for neutrophils, eosinophils, and monocytes.
- Its major emphasis is leukocyte recruitment rather than direct bronchospasm.
- This links newly formed lipids to the cellular component of inflammation.



Do not assign the same dominant function to every leukotriene.

Leukotrienes: Functional division

LTB₄

Chemotaxis

Neutrophils

Eosinophils / monocytes

LTC₄

Vasoactive

Vascular leakage

Bronchial contraction

LTD₄

Spasmogenic

Airway smooth muscle

Increased permeability

Chemical family membership does not imply identical biological activity.

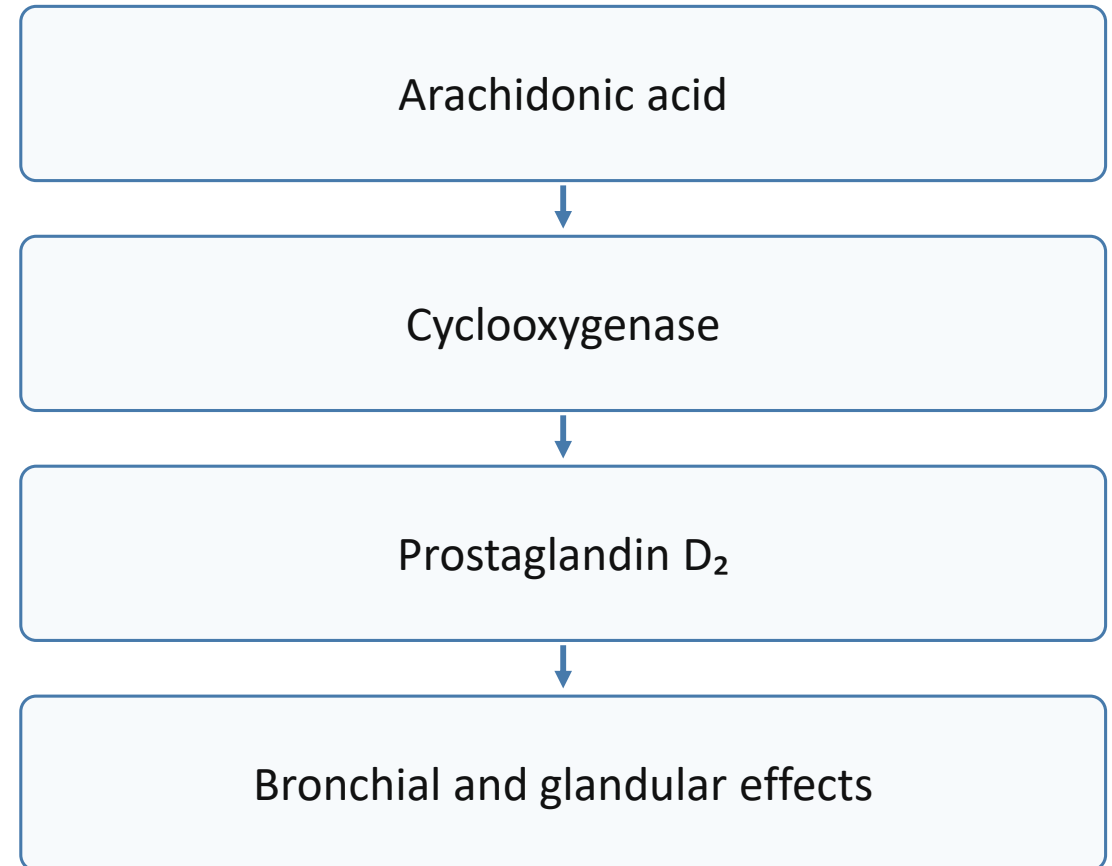
Leukotriene mechanisms at a glance

Mediator	Primary targets	Key consequence
LTB ₄	Circulating leukocytes	Chemotaxis and cell recruitment
LTC ₄	Vasculature; Bronchial smooth muscle	Leakage and bronchospasm
LTD ₄	Vasculature; Bronchial smooth muscle	Leakage and bronchospasm

LTB₄ and the cysteinyl leukotrienes occupy complementary roles.

Prostaglandin D₂ arises from cyclooxygenase

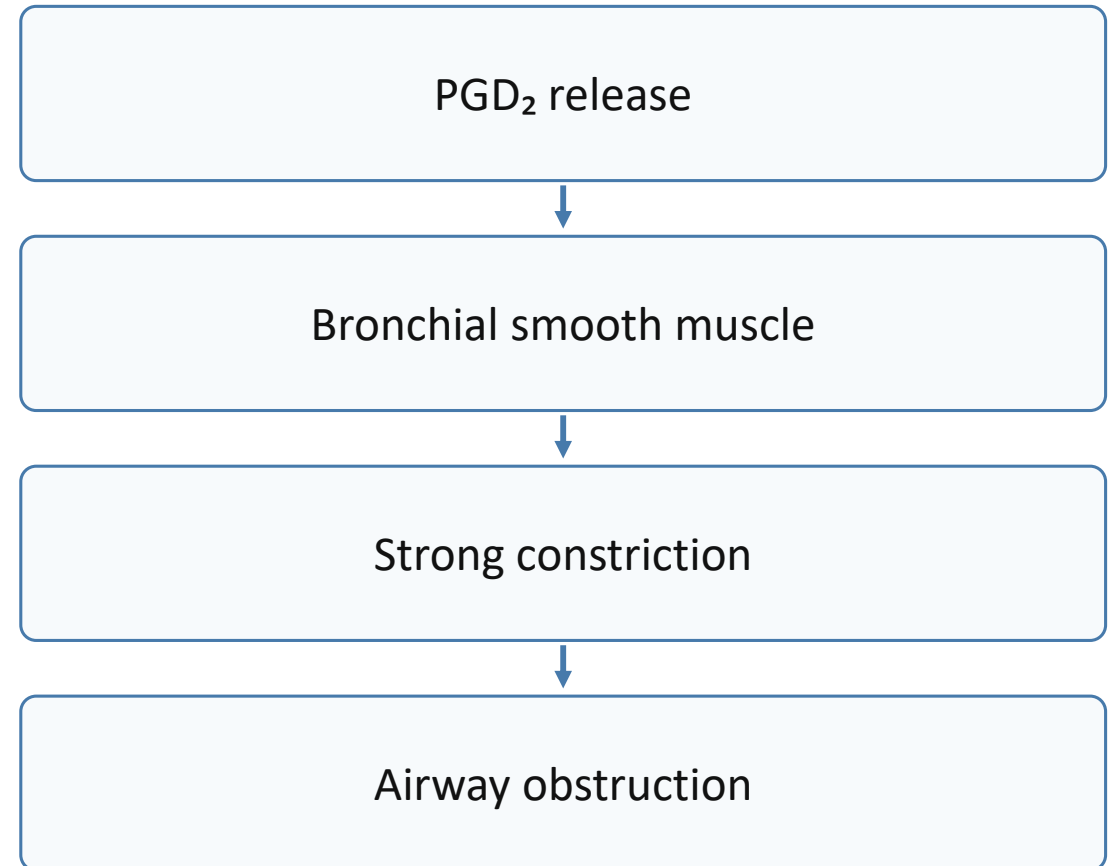
- PGD₂ is the most abundant prostaglandin produced by mast cells in this pathway.
- Its production follows arachidonic acid metabolism by cyclooxygenase.
- Its biological effects overlap with, but do not duplicate, leukotrienes.



PGD₂ is the central prostaglandin in this textbook discussion.

PGD₂ is a potent bronchospastic mediator

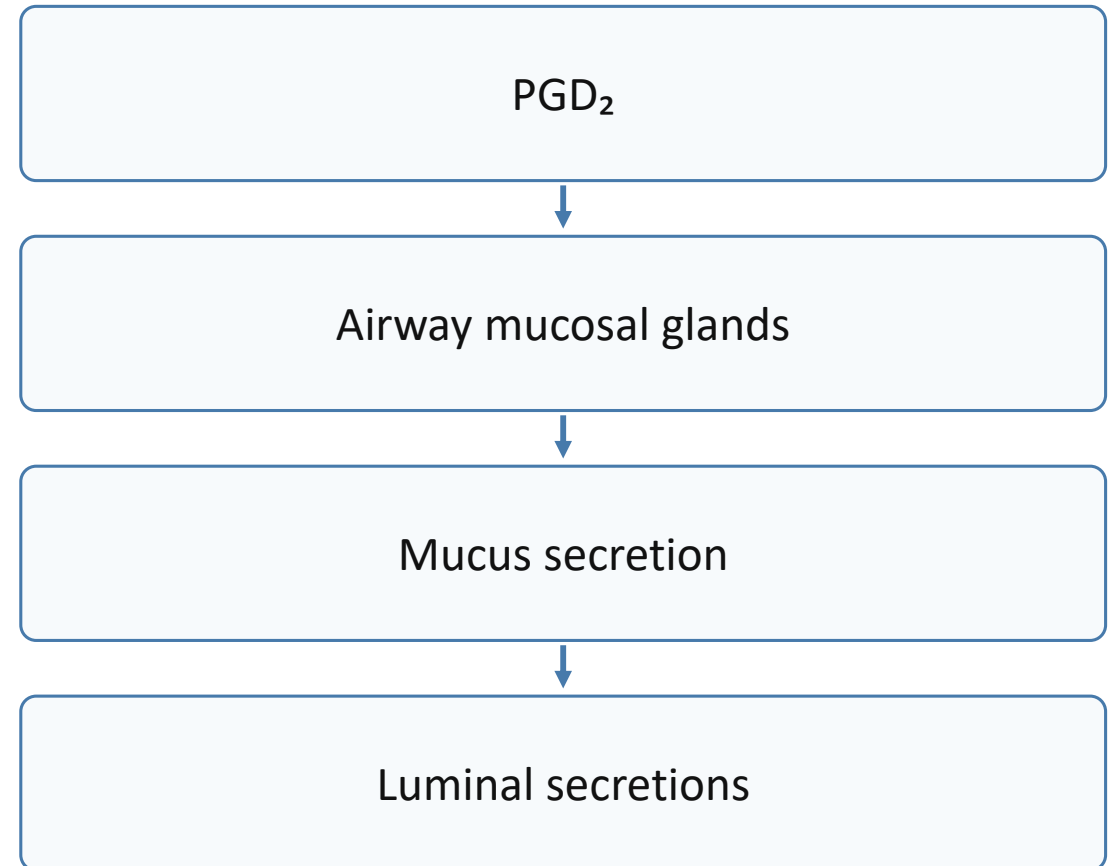
- PGD₂ causes intense bronchospasm.
- It acts alongside histamine and LTC₄ / LTD₄ at the airway level.
- Multiple chemical pathways converge on a single clinical effect.



No one mediator explains every episode of bronchospasm.

PGD₂ also increases mucus secretion

- PGD₂ promotes increased mucus production.
- The secretory effect accompanies bronchoconstriction.
- Together, narrowing and secretion can intensify airway symptoms.



Airflow compromise may reflect both contraction and secretion.

5-lipoxygenase versus cyclooxygenase

5-lipoxygenase products

- LTB₄: Leukocyte chemotaxis
- LTC₄ and LTD₄: Leakage and spasm
- Multiple functional leukotrienes

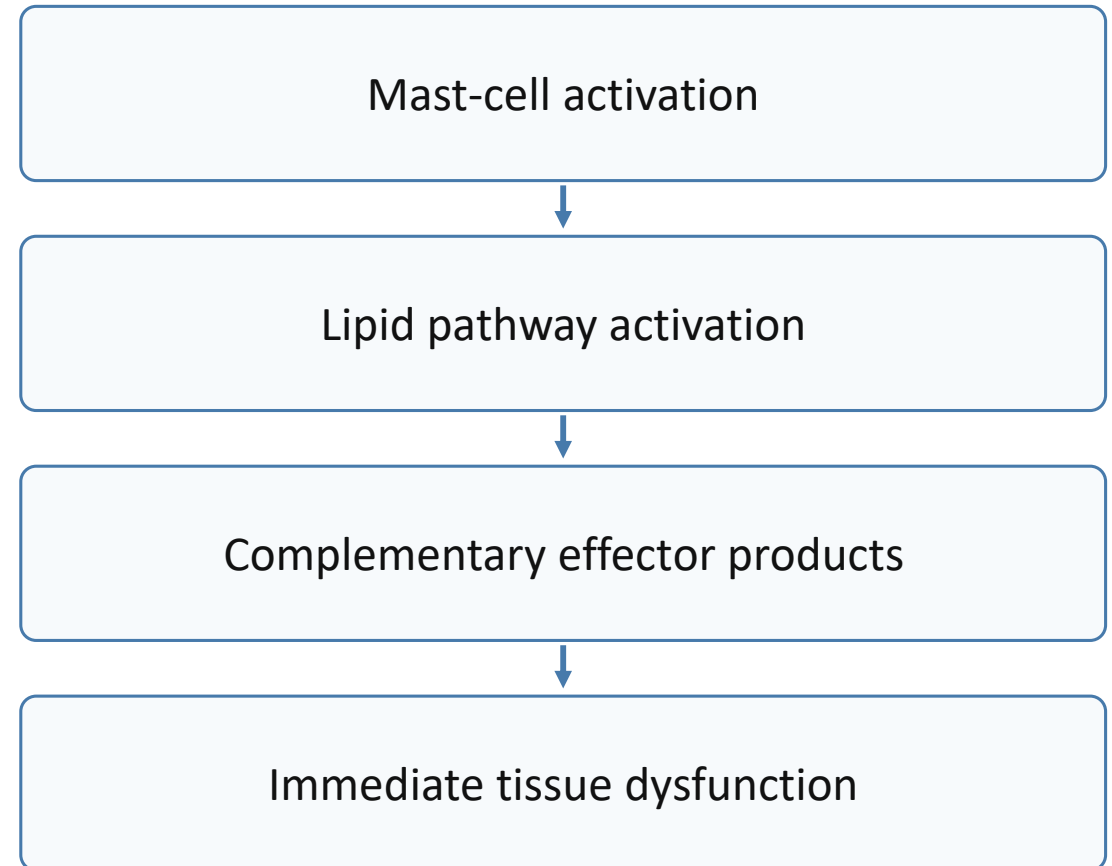
Cyclooxygenase product

- PGD₂ is prominent in mast cells
- Marked bronchospasm
- Increased mucus secretion

Trace the enzyme before assigning a lipid mediator and its effect.

Multiple lipids coordinate the immediate reaction

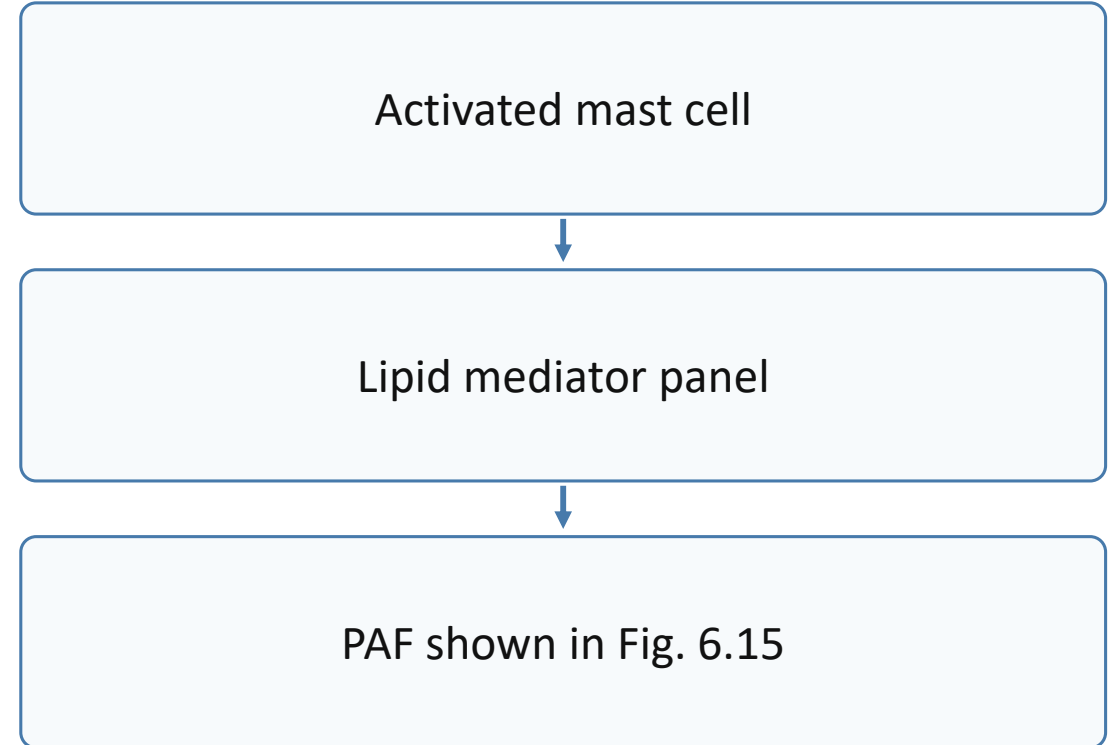
- Leukotrienes and prostaglandins are synthesized following mast-cell activation.
- Cysteinyl leukotrienes accentuate spasm and permeability.
- PGD_2 adds bronchospasm and increased mucus secretion.



The mediator combination is functionally broader than any one product.

Platelet-activating factor appears in the source scheme

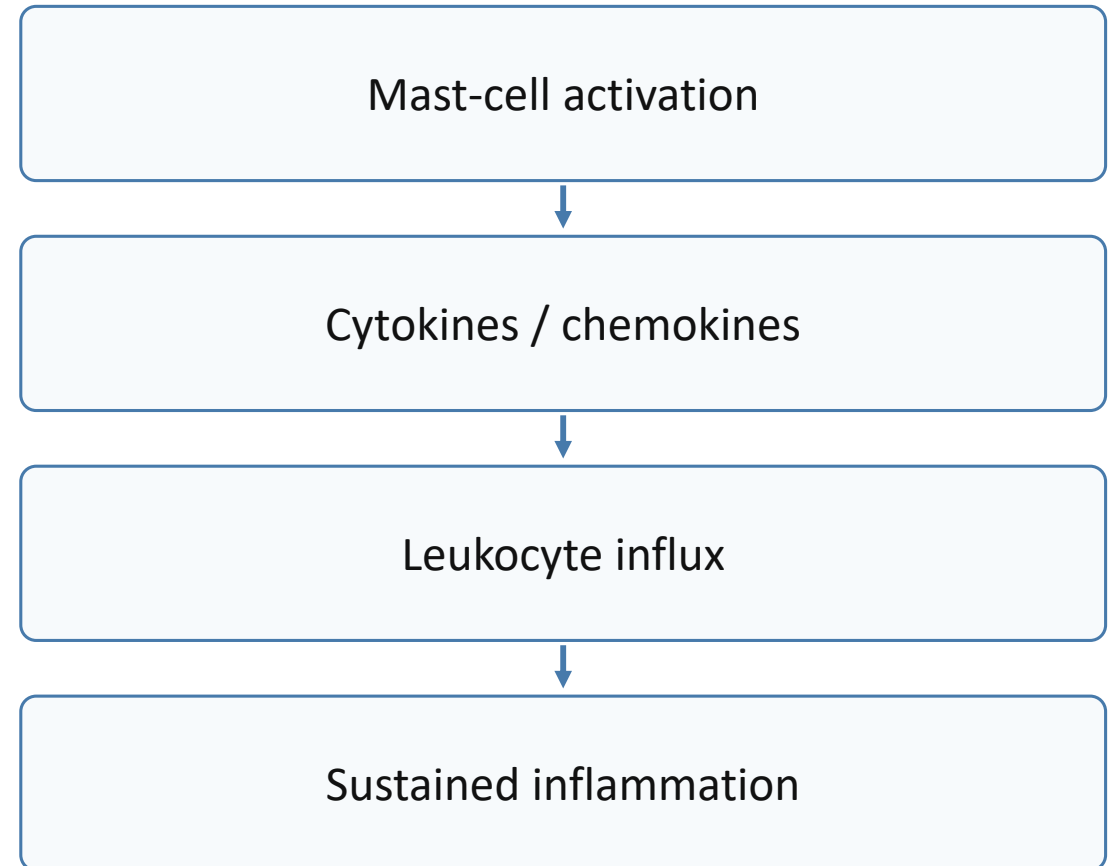
- The Robbins mast-cell mediator diagram also identifies platelet-activating factor (PAF).
- The adjacent text develops the arachidonic acid–derived mediators in greater detail.
- PAF is retained in the overall mediator inventory without assigning additional unverified effects.



The figure establishes inclusion; It does not provide detailed PAF mechanisms here.

Cytokines extend the reaction beyond degranulation

- Activated mast cells synthesize and secrete cytokines and chemokines.
- These products recruit other leukocytes to the affected tissue.
- Their actions are central to the late-phase inflammatory response.



Cytokine signaling bridges the immediate and cellular phases.

Mast-cell cytokine outputs

TNF and IL-1

Promote leukocyte recruitment

Support inflammatory
infiltration

Contribute to the late phase

Chemokines

Guide leukocyte migration

Increase local infiltrates

Recruit additional effectors

IL-4

Amplifies type 2 immunity

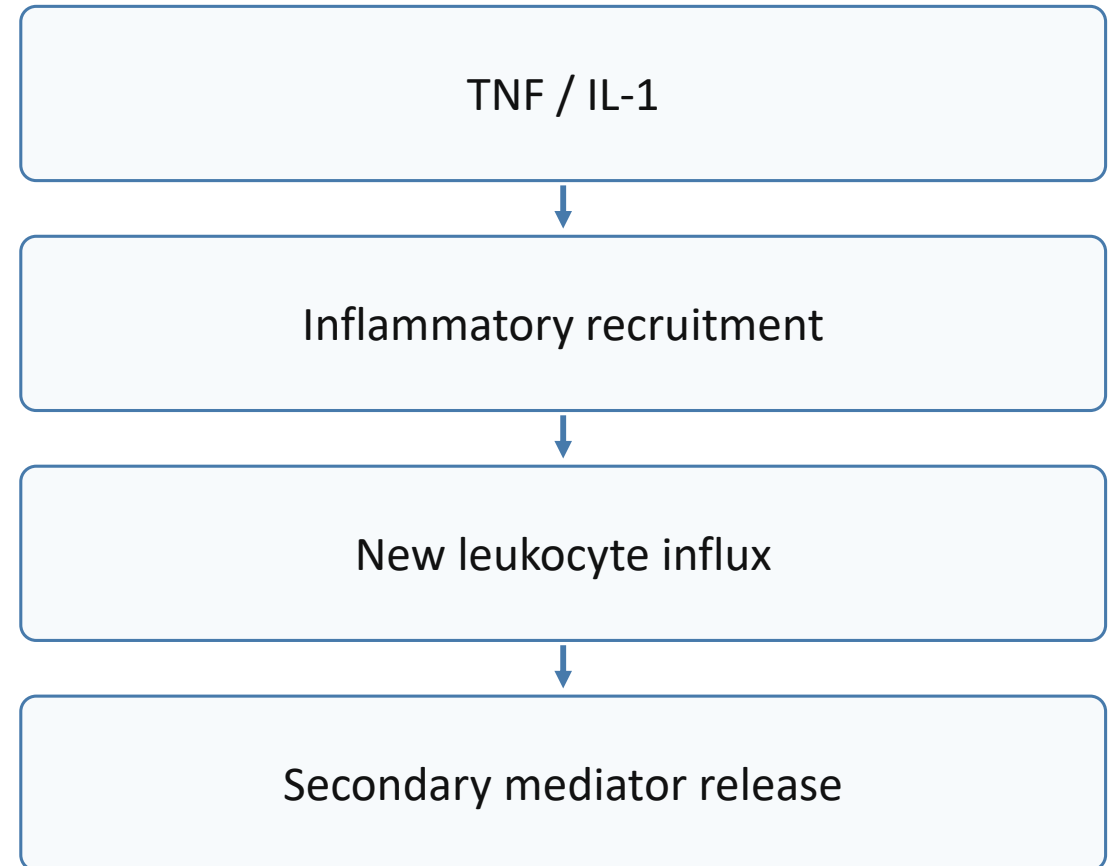
Reinforces Th2 response

Sustains allergic bias

Different cytokines act on cell trafficking and immune-program amplification.

TNF and IL-1 promote leukocyte recruitment

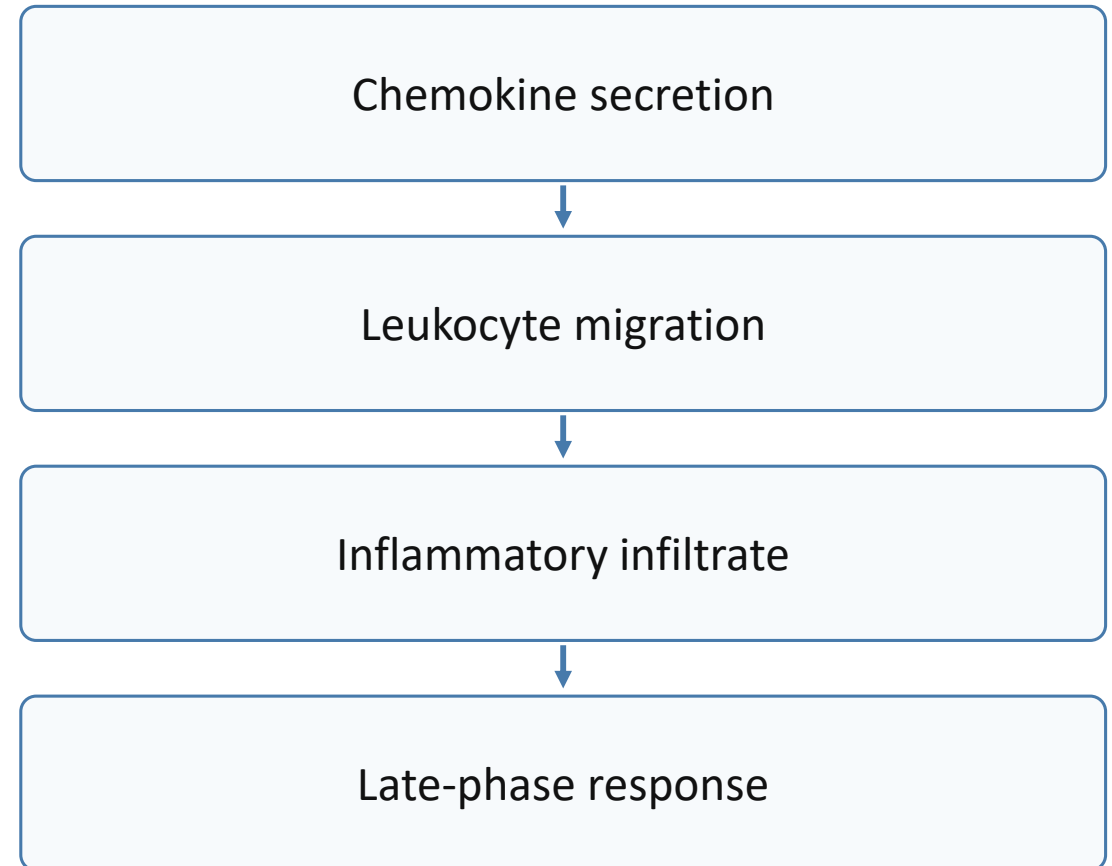
- Mast cells can release TNF and IL-1 following activation.
- These mediators are associated with leukocyte recruitment.
- Recruited cells can provide an additional source of inflammatory cytokines.



A cytokine cascade can outlast the initial granule discharge.

Chemokines give cellular recruitment direction

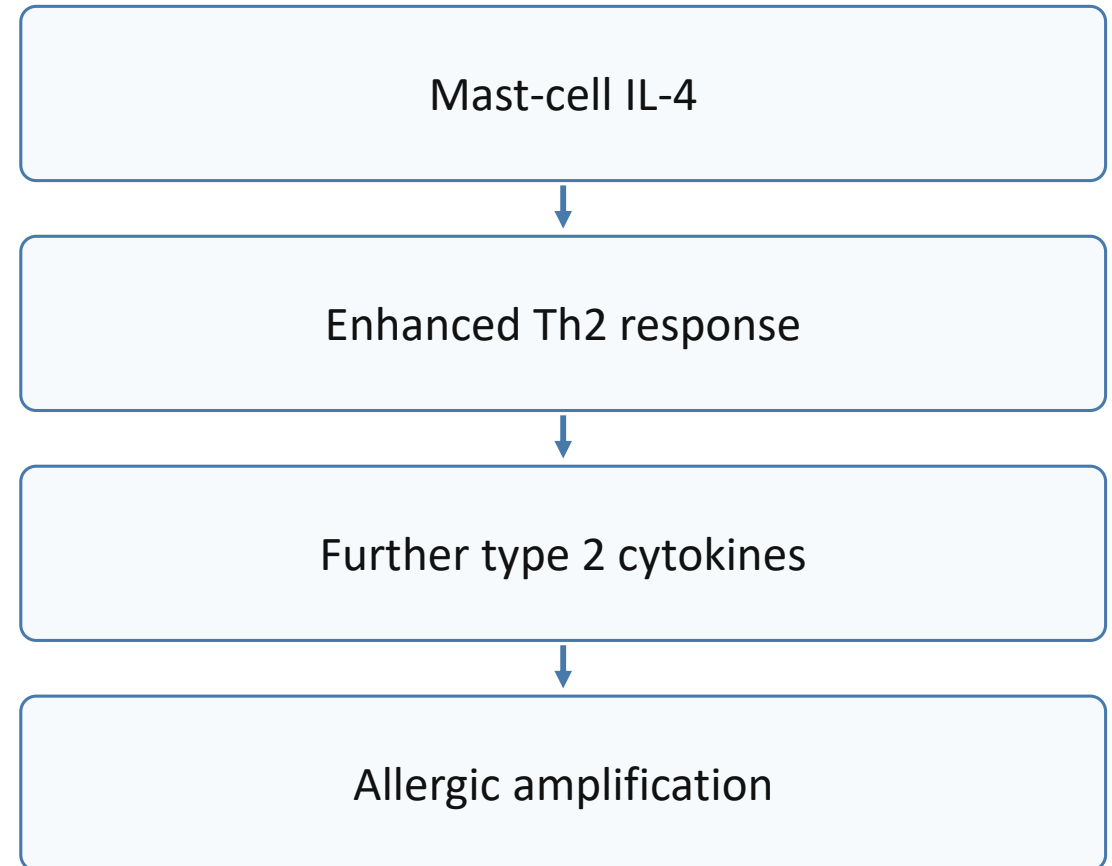
- Chemokines attract specific leukocyte populations into affected tissue.
- Their sources include mast cells and, later, other inflammatory cells.
- Epithelial cells also add chemokines to the local environment.



Recruitment is an organized molecular process, not random cell accumulation.

IL-4 amplifies the type 2 immune response

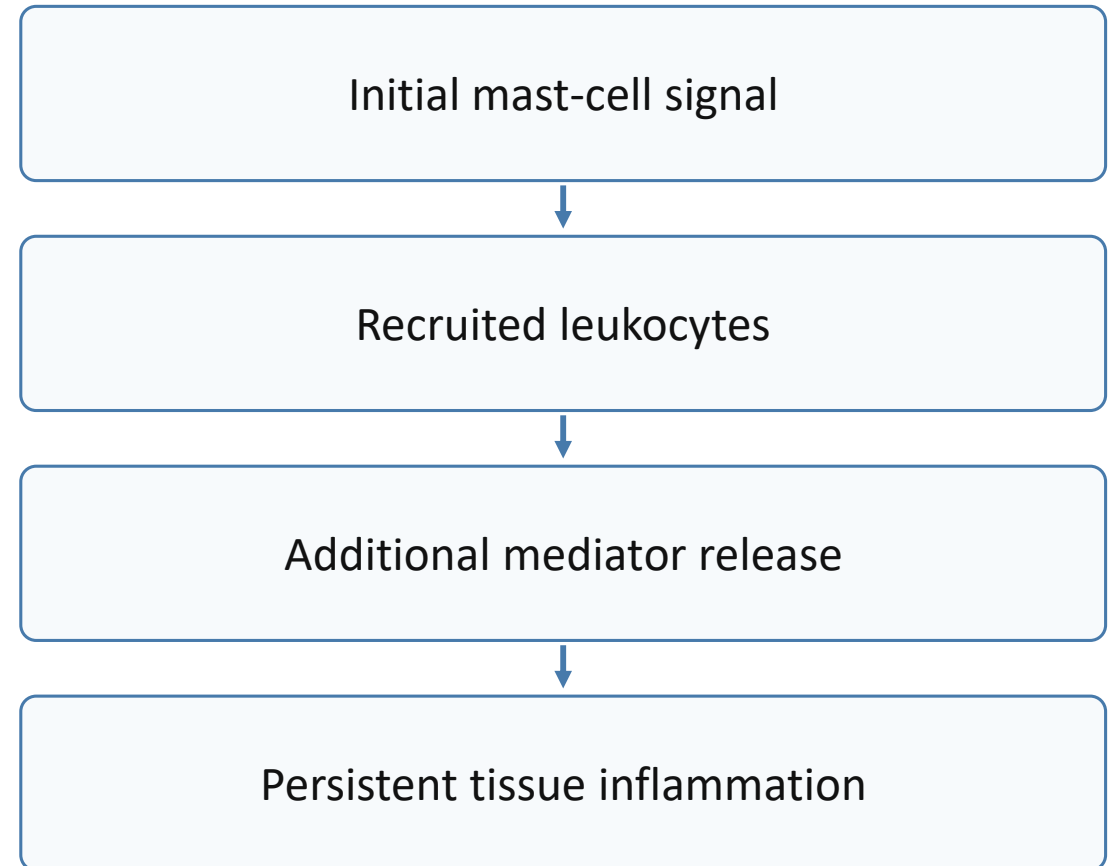
- Mast-cell–derived IL-4 can amplify ongoing Th2 responses.
- Type 2 polarization sustains IgE-associated allergic inflammation.
- The amplification mechanism is distinct from direct smooth-muscle contraction.



IL-4 chiefly shapes immune programming rather than immediate edema.

Recruited leukocytes become new mediator sources

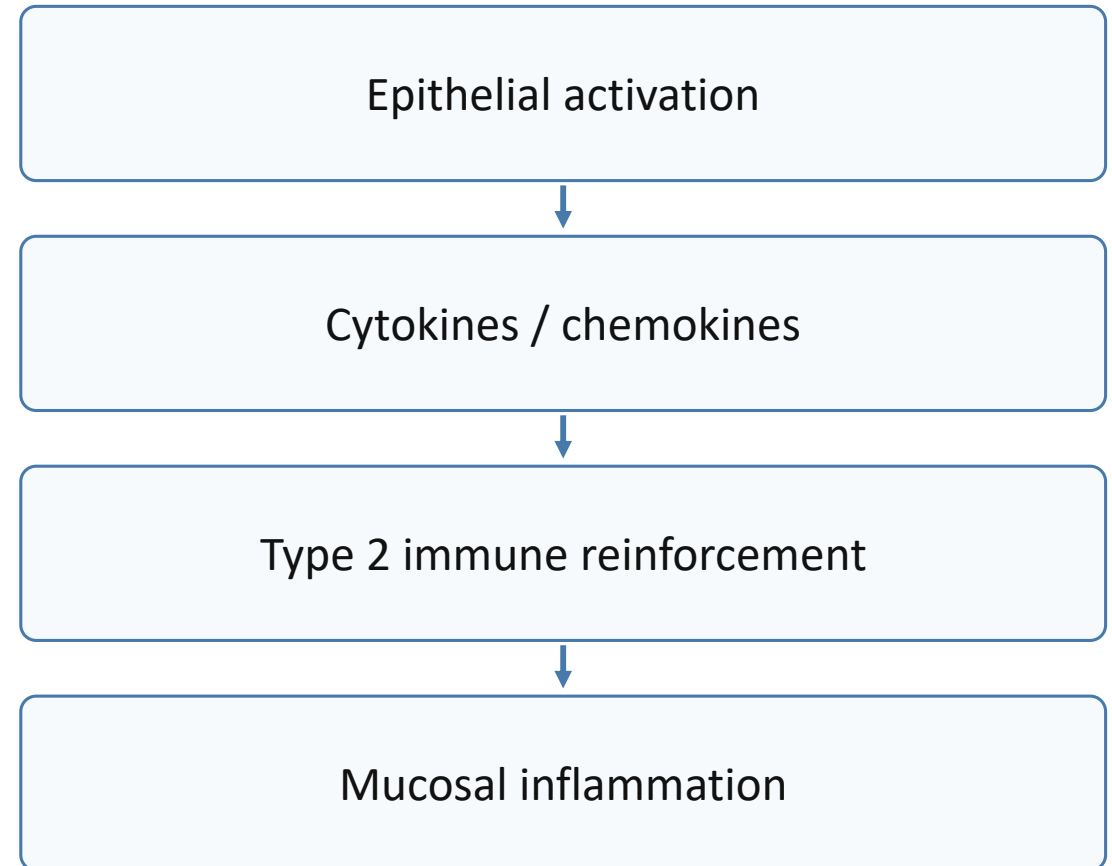
- Leukocytes drawn into tissue release additional cytokines and other inflammatory products.
- The reaction can become self-sustaining after the initiating antigen exposure.
- Late-phase injury therefore cannot be inferred from mast-cell contents alone.



Later cellular contributors broaden the mediator repertoire.

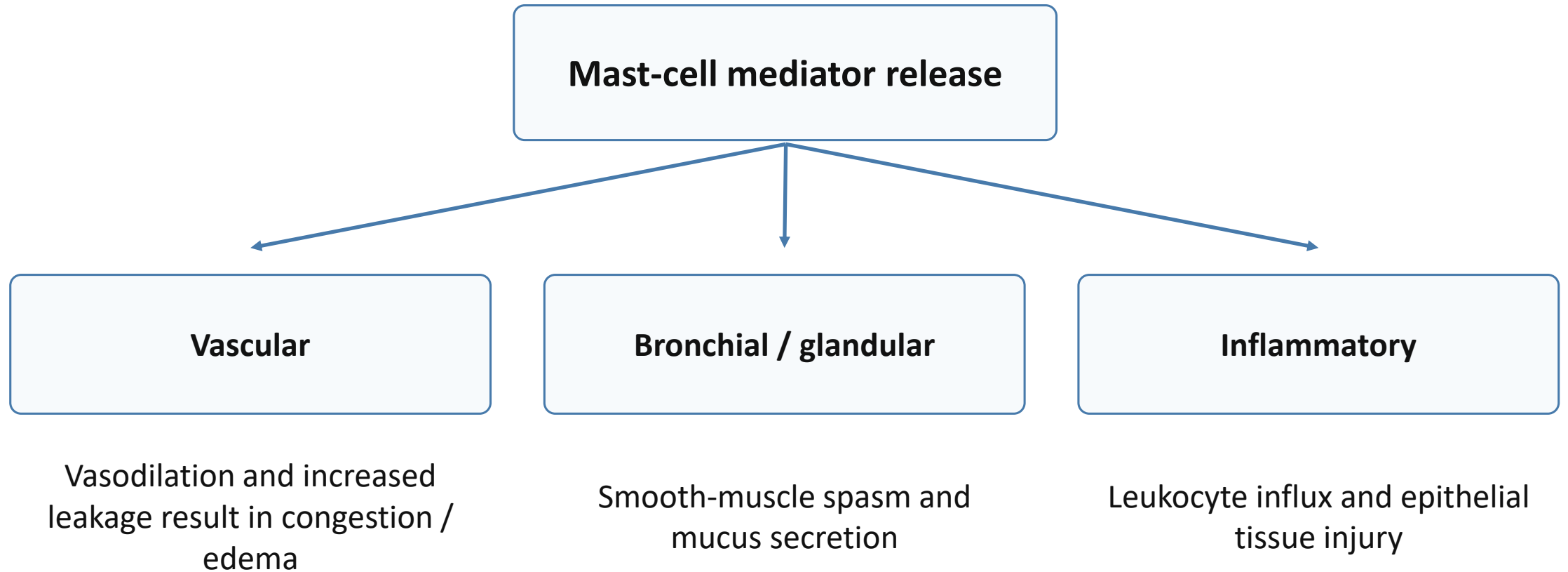
The epithelium actively shapes allergic inflammation

- Epithelial cells are not passive bystanders during allergy.
- They produce cytokines and chemokines that support recruitment.
- Epithelial signals may promote Th2 differentiation.



The target organ becomes part of the inflammatory circuit.

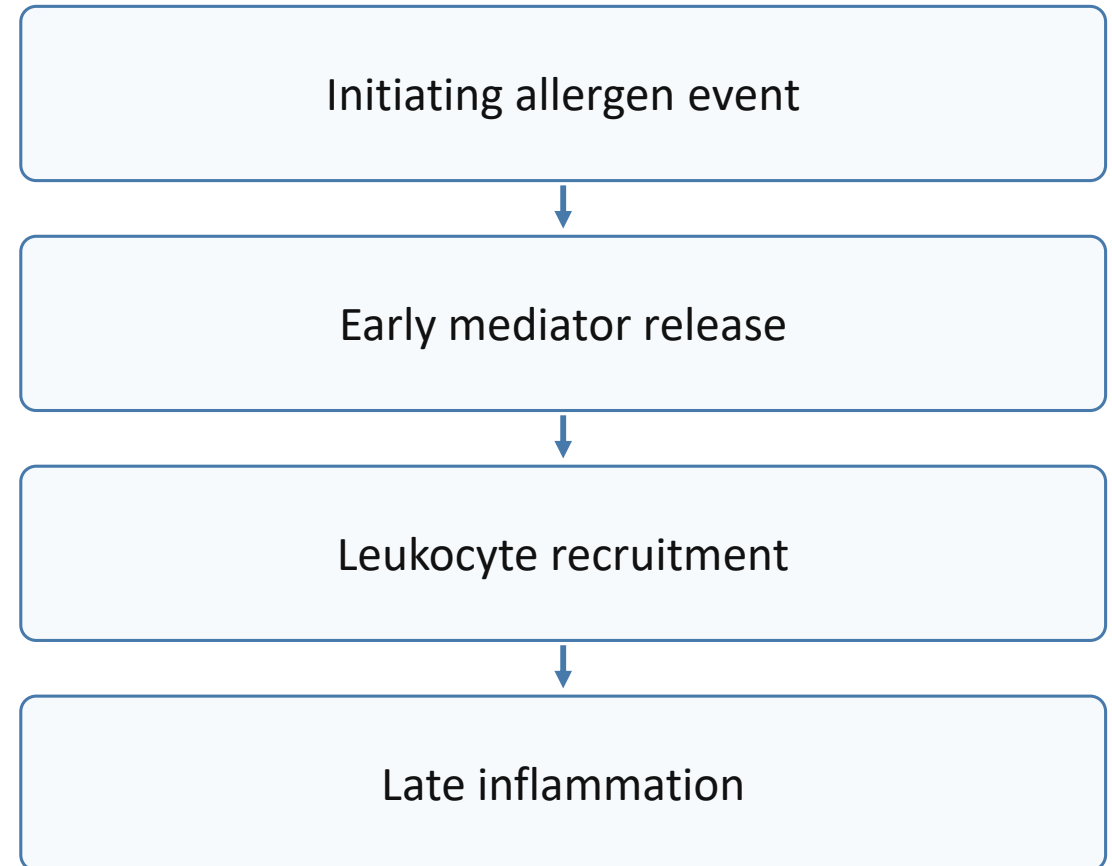
Three major tissue response modules



The clinical picture depends on which module predominates.

The late phase can proceed without renewed exposure

- The late reaction amplifies inflammation after the immediate event.
- Further exposure to the original allergen is not required.
- Activated and recruited leukocytes maintain the local response.



A persistent symptom need not represent a new allergen challenge.

The two phases differ in timing and morphology

After re-exposure to allergen

Within minutes

2–24 hours



Rapid vasodilation, vascular congestion
and edema

Eosinophils, neutrophils and T cells
infiltrate the tissue

The late-phase response approximately 2–24 h after challenge.

Immediate phase versus late-phase pathology

Immediate phase

- Vascular and smooth-muscle abnormalities
- Congestion, edema and secretion
- Mast-cell amines / lipids dominate

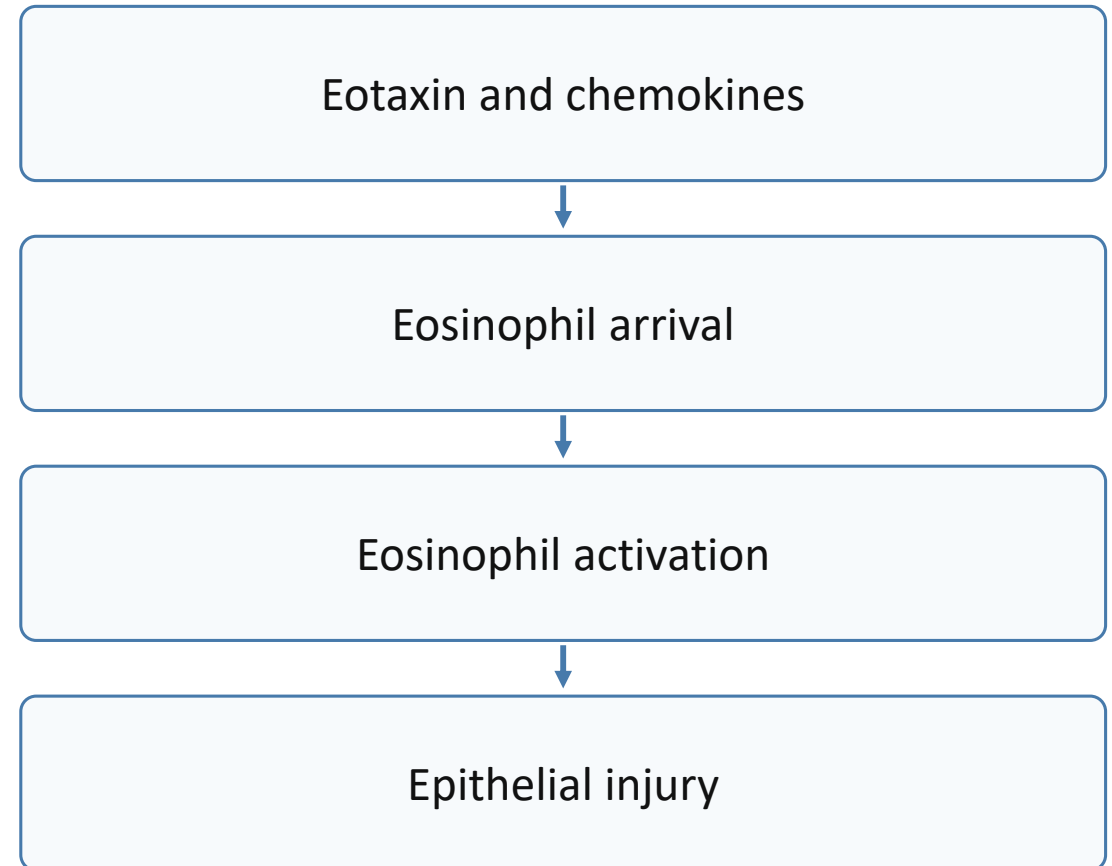
Late phase

- Inflammatory cell recruitment
- Eosinophils, neutrophils and T cells
- Cytokines / chemokines are prominent

Do not equate symptom onset and inflammatory tissue damage.

Eosinophils are frequent late-phase effectors

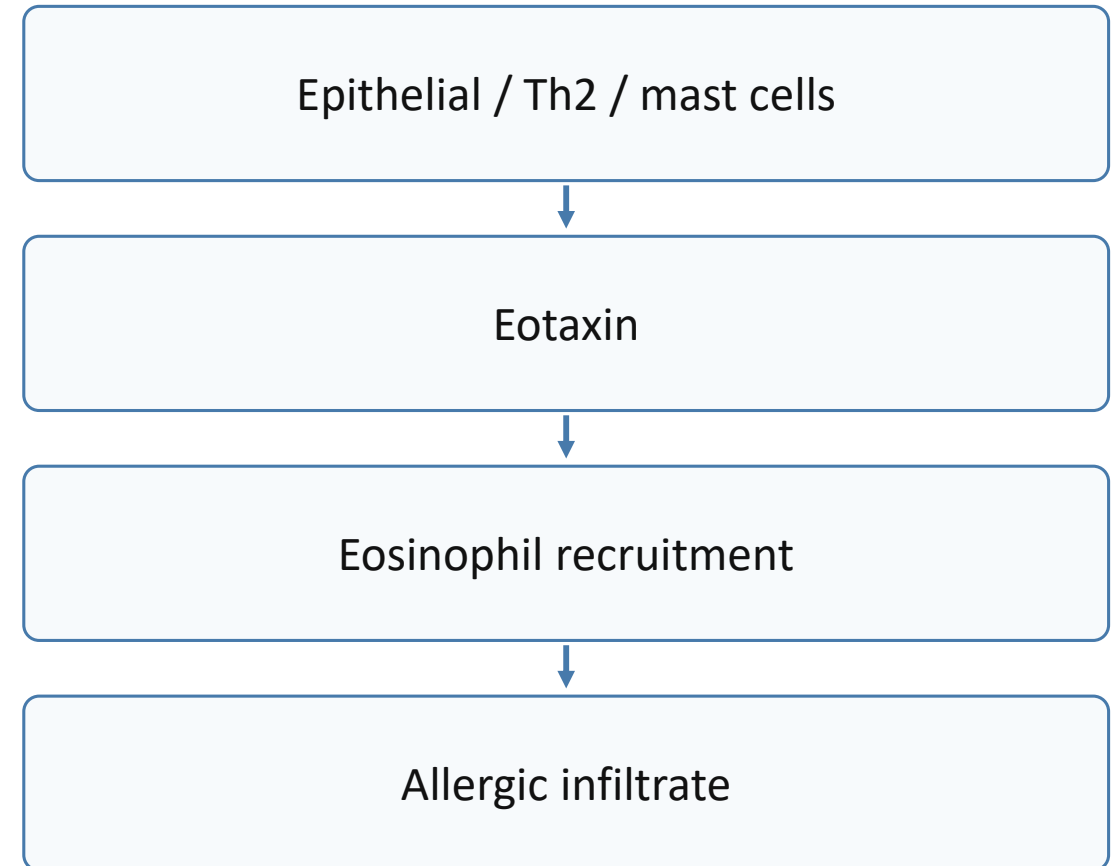
- Eosinophils are often abundant in late allergic lesions.
- Recruitment depends on chemokines, including eotaxin.
- These cells can directly injure epithelium when activated.



Eosinophils convert cellular infiltration into tissue damage.

Eotaxin recruits eosinophils to allergic tissue

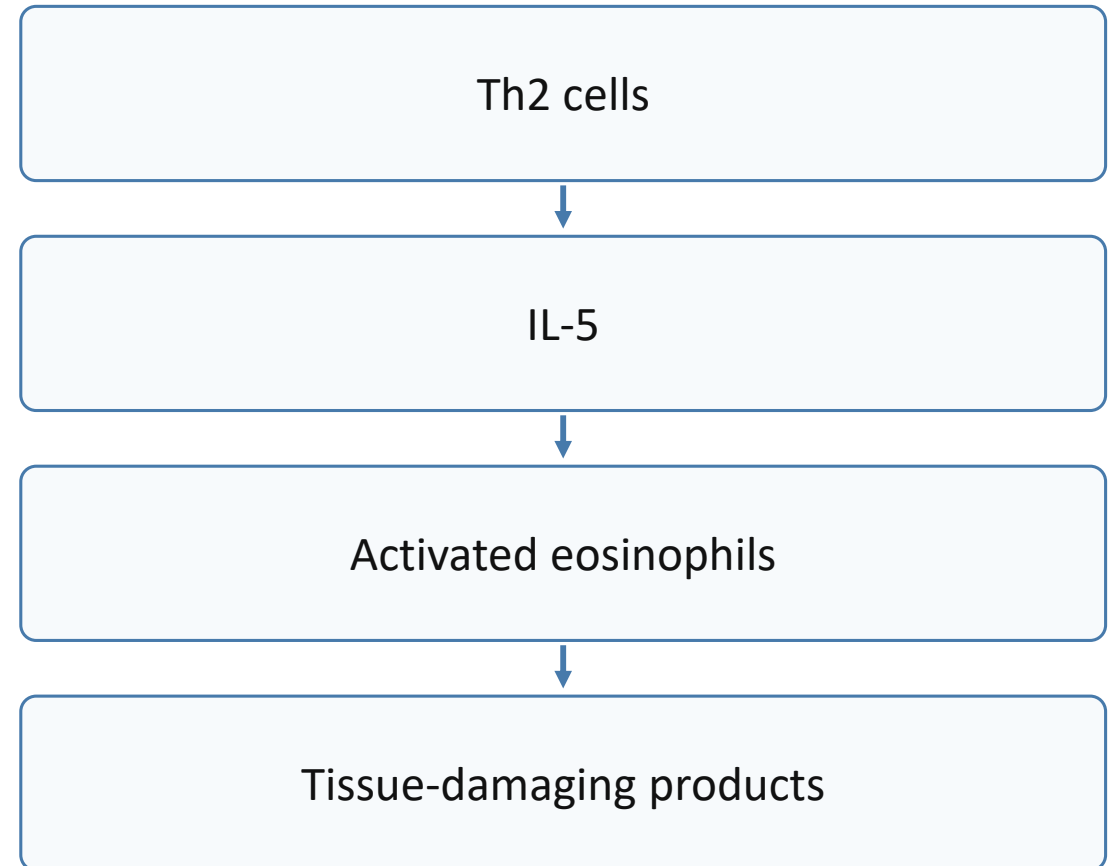
- Eotaxin is one of the chemokines attracting eosinophils.
- Epithelial cells, Th2 cells, and mast cells can produce relevant chemokines.
- Multiple source cells cooperate to concentrate eosinophils in tissue.



A chemotactic signal can be multicellular in origin.

IL-5 activates eosinophils

- IL-5 is a signature Th2 cytokine and a powerful eosinophil activator.
- Activated eosinophils release products that injure surrounding tissue.
- This provides a causal bridge from Th2 responses to epithelial damage.

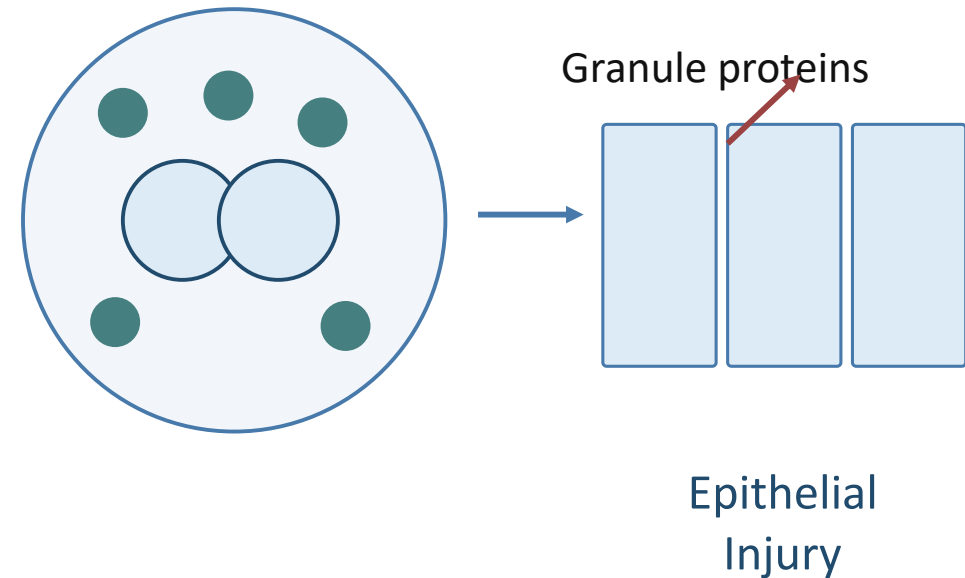


Recruitment and activation are distinct requirements for eosinophil injury.

Eosinophil granule proteins damage epithelium

- Activated eosinophils release major basic protein and eosinophil cationic protein.
- Proteolytic enzymes contribute additional injury.
- The combined products can injure epithelial surfaces in allergic disease.

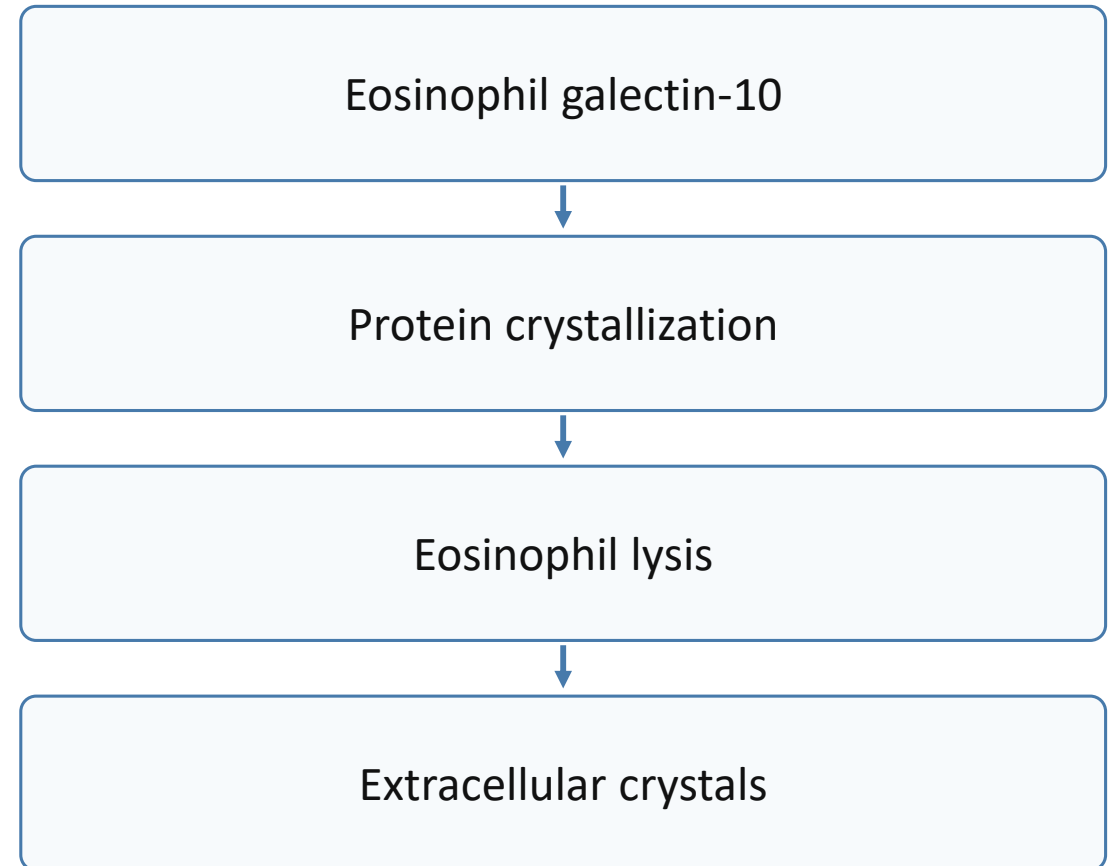
Eosinophil-mediated epithelial injury



Late-phase injury is mediated by infiltrating cells as well as soluble signals.

Galectin-10 can form Charcot–Leyden crystals

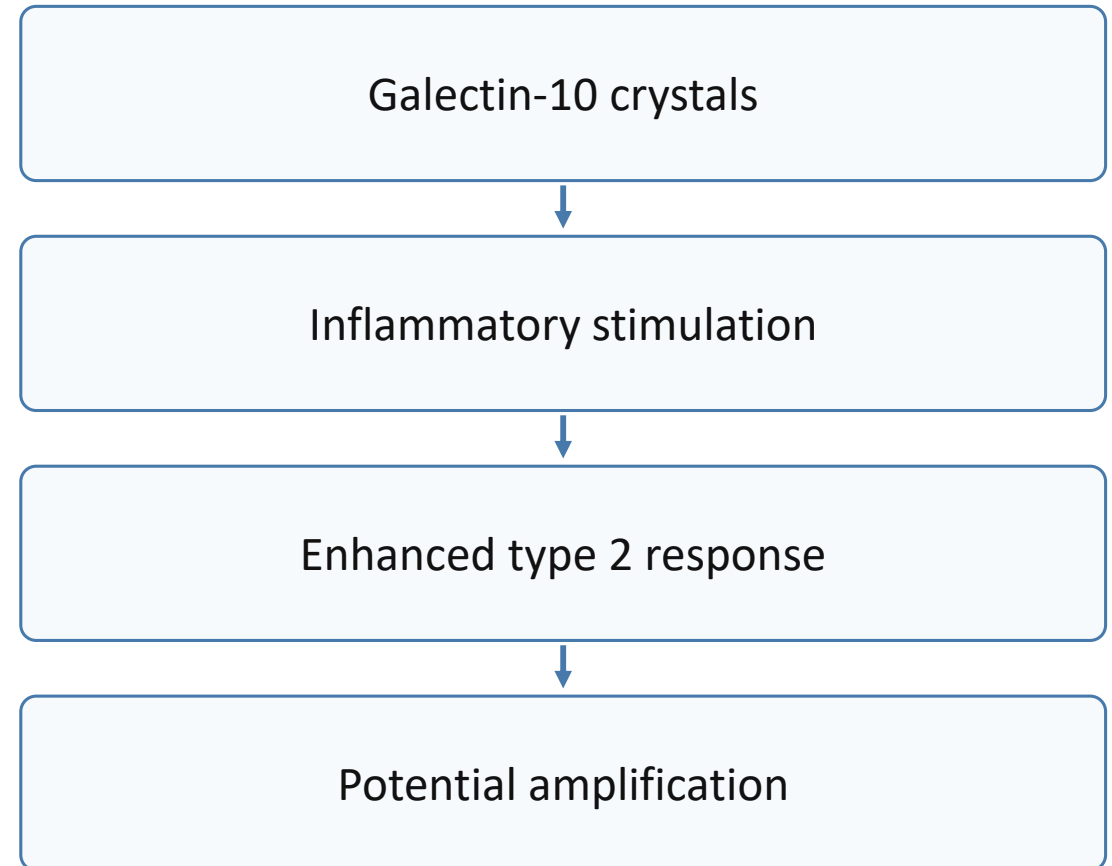
- Eosinophils contain abundant galectin-10.
- After activation, this protein can crystallize into Charcot–Leyden crystals.
- Following eosinophil lysis, extracellular crystals may be found in asthma sputum.



Charcot–Leyden crystals are a consequence of eosinophil-associated inflammation.

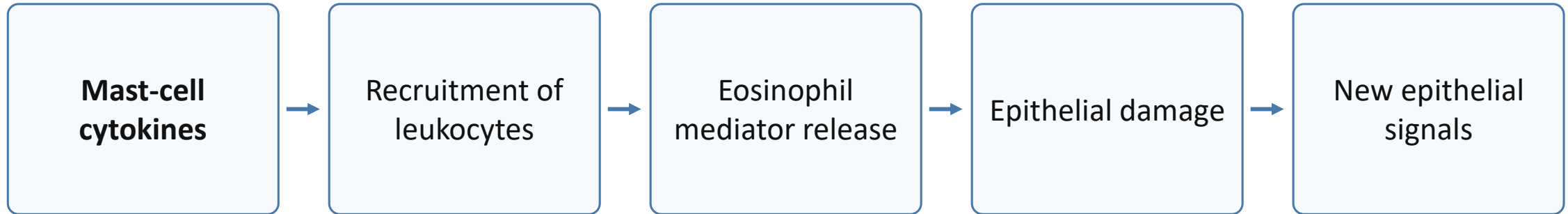
Charcot–Leyden crystals may amplify inflammation

- The crystals can promote inflammatory activity.
- They can enhance Th2-type responses.
- Them as potential contributors to allergic reactions.



The source uses qualified language; A contributory role is not sole causation.

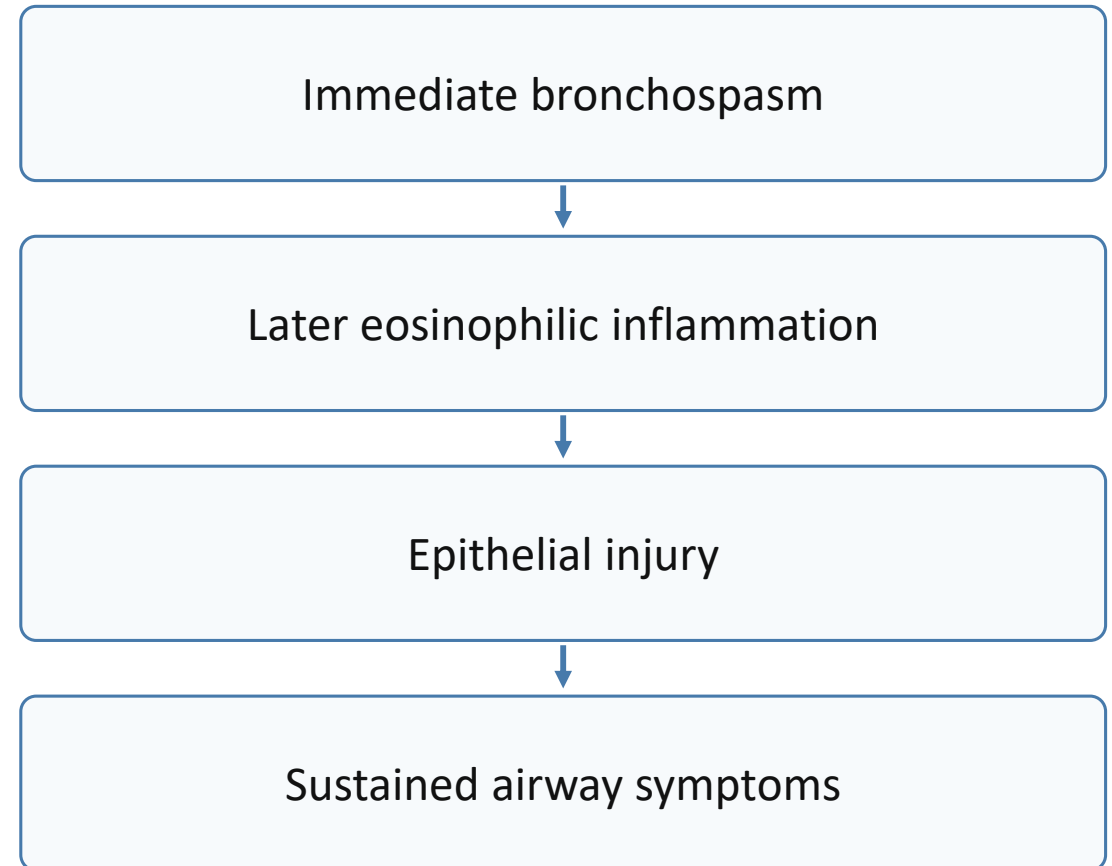
Late-phase tissue injury becomes a feedback process



The recruited cells and epithelium can sustain the response.

Allergic asthma prominently involves the late phase

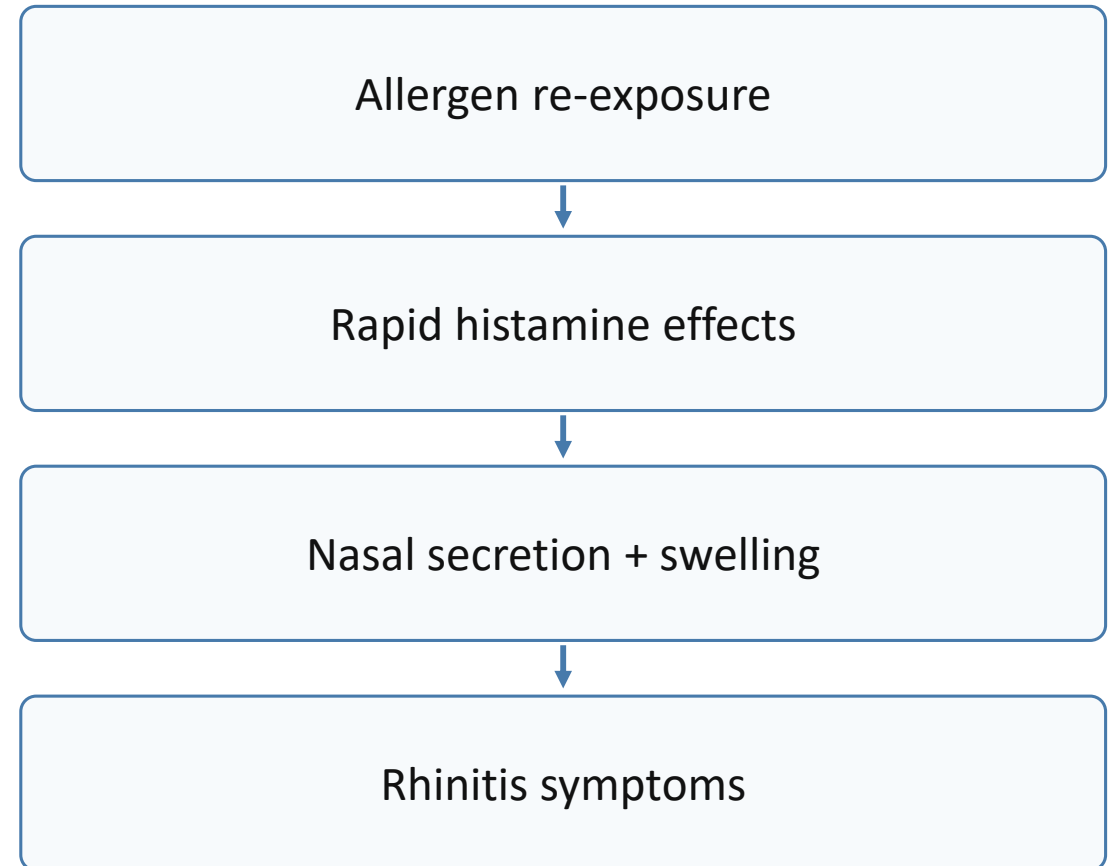
- The late-phase reaction is a major contributor to symptoms in some type I hypersensitivity disorders.
- Allergic asthma is an important example.
- Airway obstruction can reflect bronchospasm plus inflammatory tissue injury.



An asthma phenotype cannot be understood from histamine alone.

Allergic rhinitis is a useful immediate-phase example

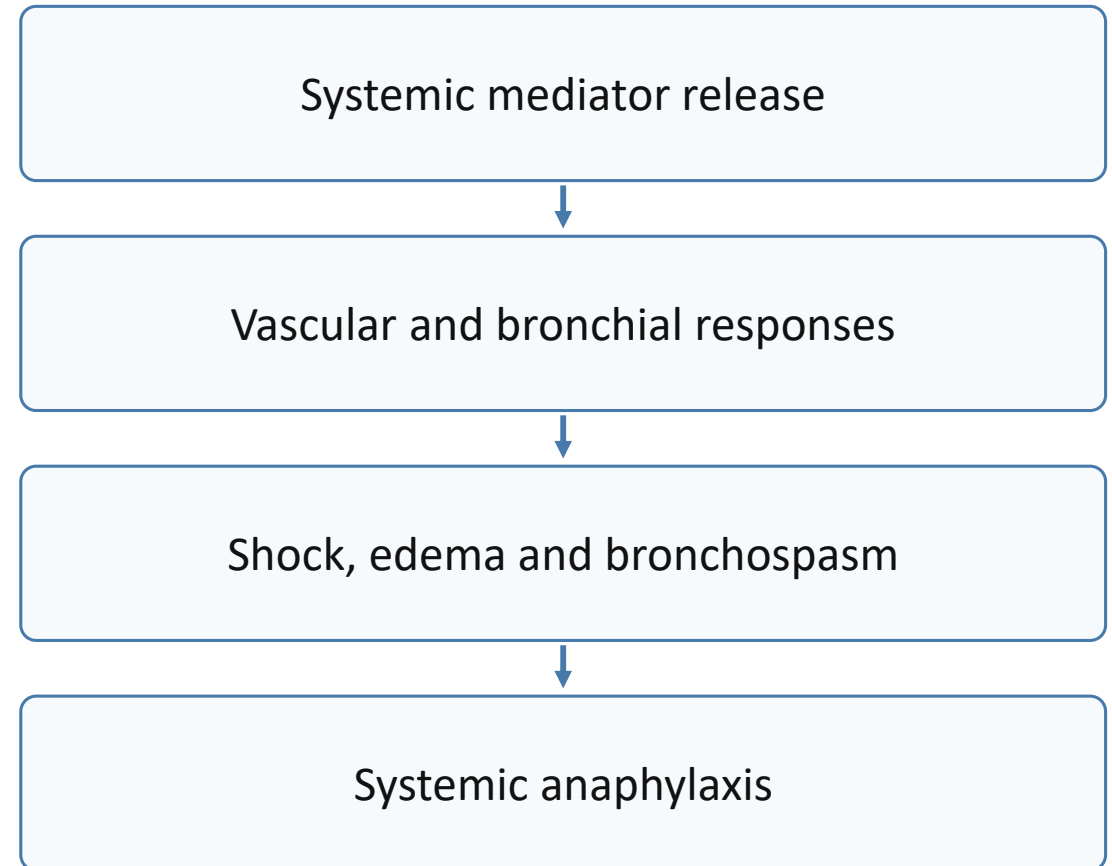
- Histamine stimulates nasal mucus secretion and promotes vascular leakage.
- These effects explain rapid nasal symptoms after exposure.
- The textbook contrasts antihistamine benefit in rhinitis with broader anti-inflammatory needs in asthma.



The dominant effector phase influences the therapeutic mechanism.

Systemic anaphylaxis reflects widespread effects

- Robbins characterizes systemic anaphylaxis by vascular shock, widespread edema, and bronchospasm.
- Diffuse vascular effects and airway constriction create a life-threatening syndrome.
- This is a clinical extension of the same mediator mechanisms seen locally.



Systemic distribution makes common mediator actions far more dangerous.

Local versus systemic clinical manifestations

Local allergic reactions

- Allergic rhinitis: Mucus and inflammation
- Asthma: Muscle spasm and late injury
- Urticaria: Localized skin reaction

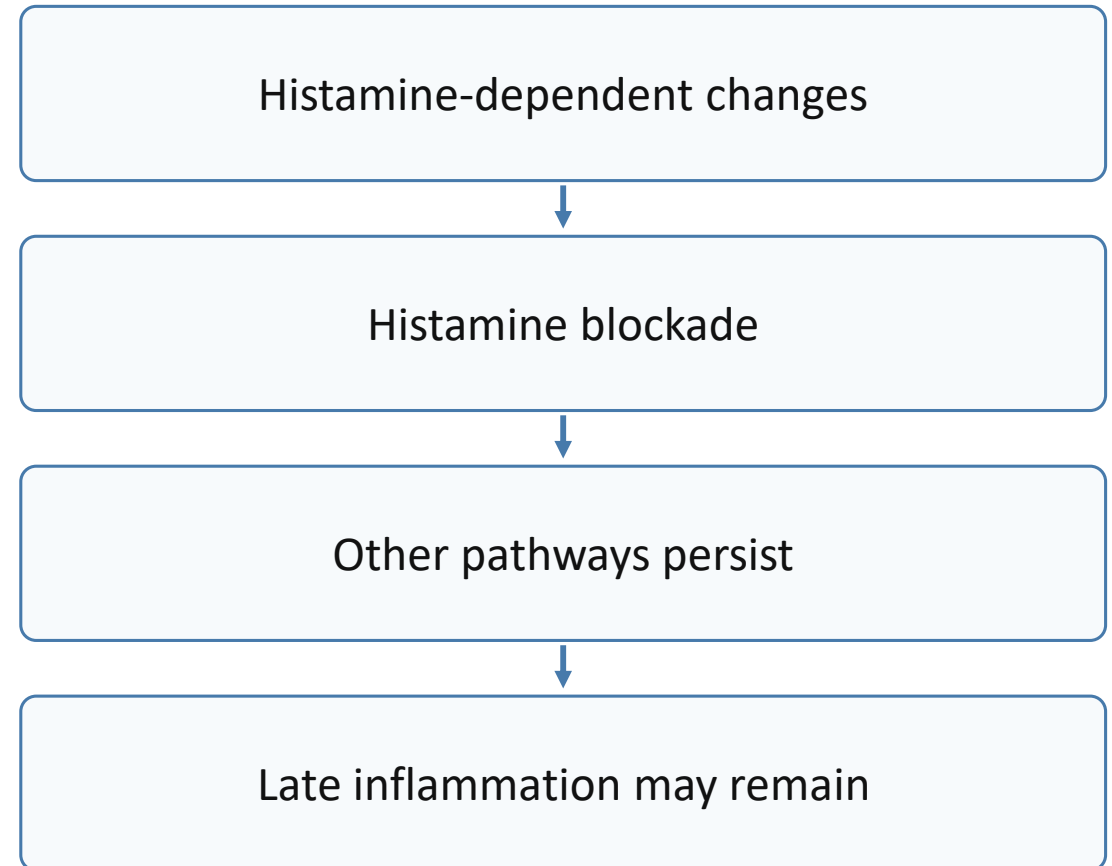
Systemic anaphylaxis

- Generalized vascular dysfunction
- Widespread edema and airway effects
- Potential circulatory collapse

Anatomical distribution is crucial in determining clinical severity.

Why antihistamines do not address every phase

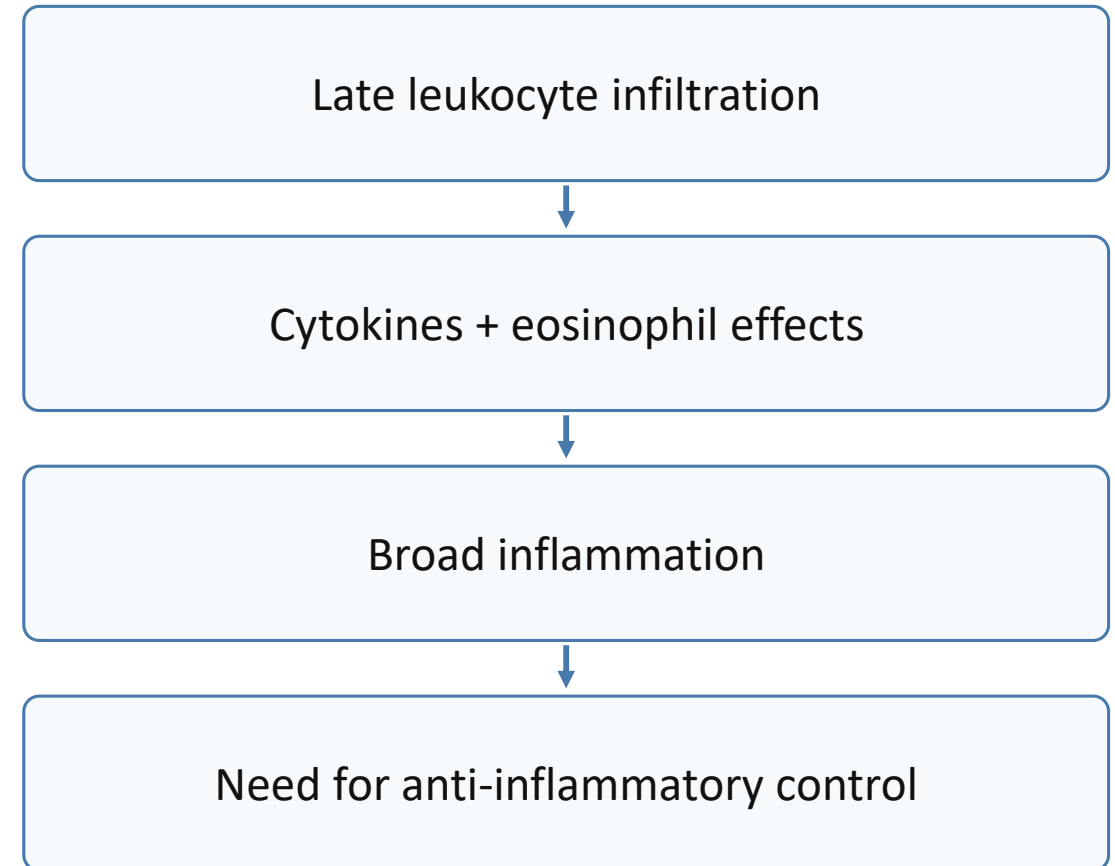
- Antihistamines counter the actions of histamine.
- Late-phase pathology involves cytokines, eosinophils, and epithelial injury.
- Blocking one early amine does not eliminate these later mechanisms.



Treatment targets must match the dominant pathological mechanism.

Why anti-inflammatory treatment matters in asthma

- Late-phase inflammatory injury in allergic asthma.
- The text contrasts broad anti-inflammatory steroids with histamine-targeted treatment.
- Mechanistically, suppressing inflammation addresses more than immediate amine effects.



This is mechanistic teaching, not a patient-specific treatment protocol.

Mediator–manifestation map

Clinical manifestation	Principal implicated mediators	Pathological explanation
Edema	Histamine; LTC ₄ / LTD ₄	Increased vascular permeability
Bronchospasm	Histamine; LTC ₄ / LTD ₄ ; PGD ₂	Smooth-muscle contraction
Mucus secretion	Histamine; PGD ₂	Glandular stimulation
Late tissue damage	TNF; IL-1; Chemokines; Eosinophil products	Cell recruitment and epithelial injury

A manifestation often has multiple convergent mediator pathways.

Clinicopathologic application: Acute nasal symptoms

Shortly after allergen exposure, a sensitized person develops nasal secretion and mucosal swelling.

Interpretation

- Which preformed mediator best explains rapid onset?
- Which two tissue effects account for these symptoms?

Histamine → vascular leakage and increased mucus secretion.

Clinicopathologic application: Persistent airway symptoms

An allergic airway reaction is followed hours later by continued symptoms with eosinophil-rich mucosal inflammation.

Interpretation

- What phase of hypersensitivity is represented?
- Which signals recruit and activate eosinophils?

Late phase → chemokines / eotaxin and IL-5.

Clinicopathologic application: Mediator distinction

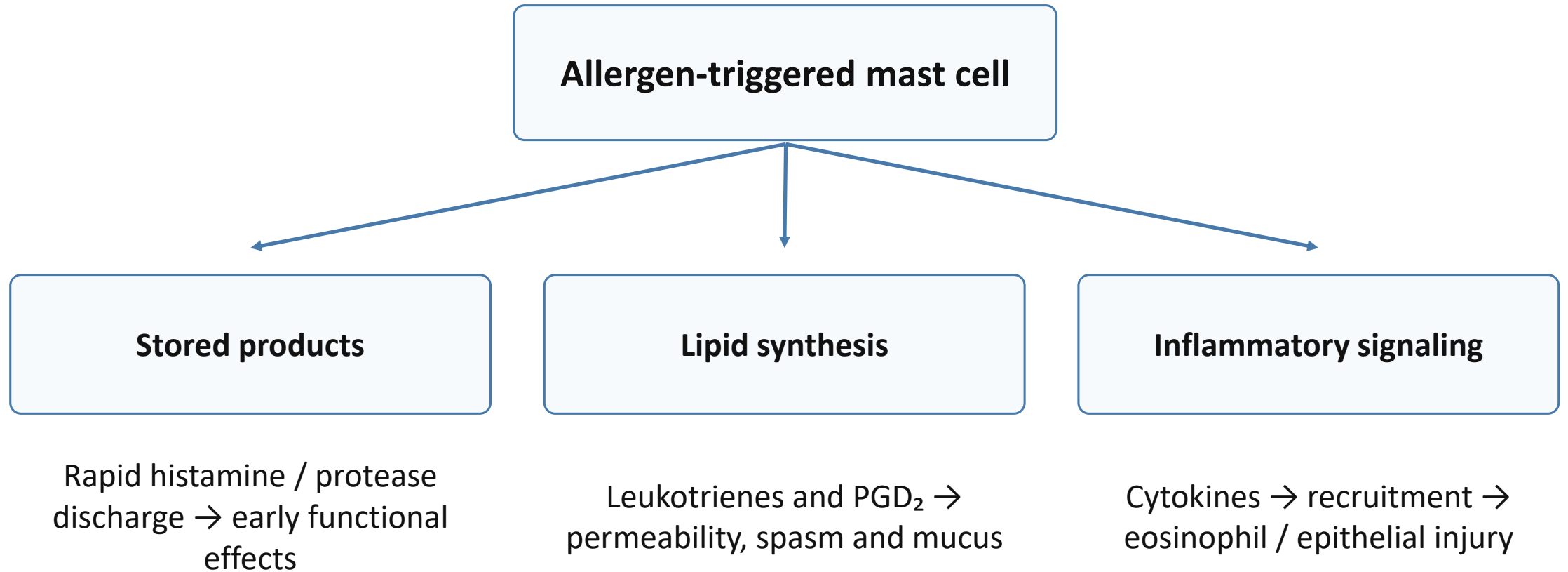
A newly synthesized leukotriene attracts neutrophils, eosinophils, and monocytes to the reaction site.

Interpretation

- Identify the leukotriene.
- Contrast its dominant effect with LTC₄ and LTD₄.

LTB₄ drives chemotaxis; LTC₄ / LTD₄ drive leakage and spasm.

Integrated mechanism: From mediators to injury



The immediate and late responses arise from interconnected, distinct programs.

High-yield distinctions for examination

Preformed versus newly synthesized

- Histamine, enzymes, proteoglycans: Stored
- Leukotrienes / PGD₂: Lipid-derived
- Cytokines: Recruitment and amplification

Distinct lipid functions

- LTB₄: Chemotaxis
- LTC₄ / LTD₄: Permeability and spasm
- PGD₂: Bronchospasm and mucus

Classify by origin, principal target, and timing—not by name alone.

Three mechanistic take-home messages

Early phase

Histamine and lipids

Vascular changes

Airway and gland effects

Late phase

Cytokines and chemokines

Leukocyte influx

Eosinophil tissue damage

Clinical translation

Different target organs

Different mediator mixtures

Phase-specific therapeutic logic

A molecular inventory becomes useful only when linked to tissue consequences.

Primary source and limits

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026), Chapter 6: Diseases of the Immune System

Core section: Mediators of Immediate Hypersensitivity (p. 184)

Supporting context: mast-cell sensitization, late-phase reaction, and clinical examples (pp. 183–186)