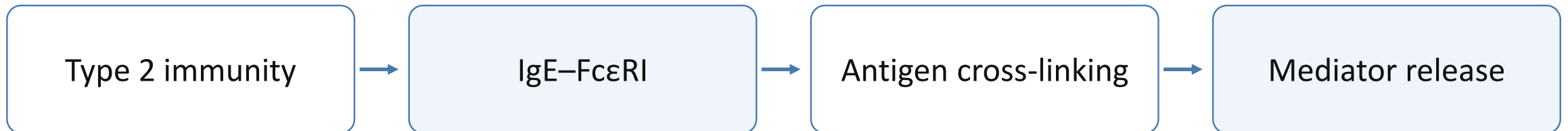


Sensitization and Activation of Mast Cells

Type I hypersensitivity: from IgE sensitization to tissue responses



Dr Abu Suraih Sakhri

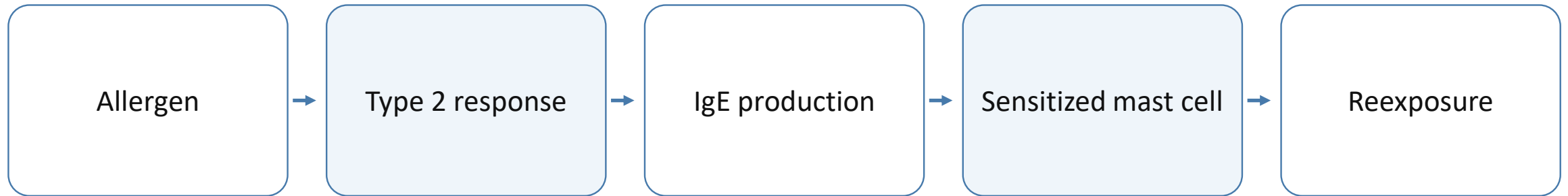
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Learning objectives

- Explain how type 2 immunity generates IgE and sensitizes tissue mast cells.
- Describe FcεRI binding, multivalent-antigen cross-linking and activation.
- Distinguish degranulation, lipid synthesis and cytokine production.
- Connect mast-cell activation to immediate, late-phase and non-IgE responses.

Immediate hypersensitivity depends on a sensitized host



- Allergen exposure may initiate type 2 immune responses and IgE synthesis.
- IgE attaches to tissue mast cells before the eliciting encounter.
- Reexposure activates these cells and produces rapid tissue effects.

Sensitization and activation are different events

Sensitization

IgE binding produces a mast cell prepared to recognize its specific antigen.

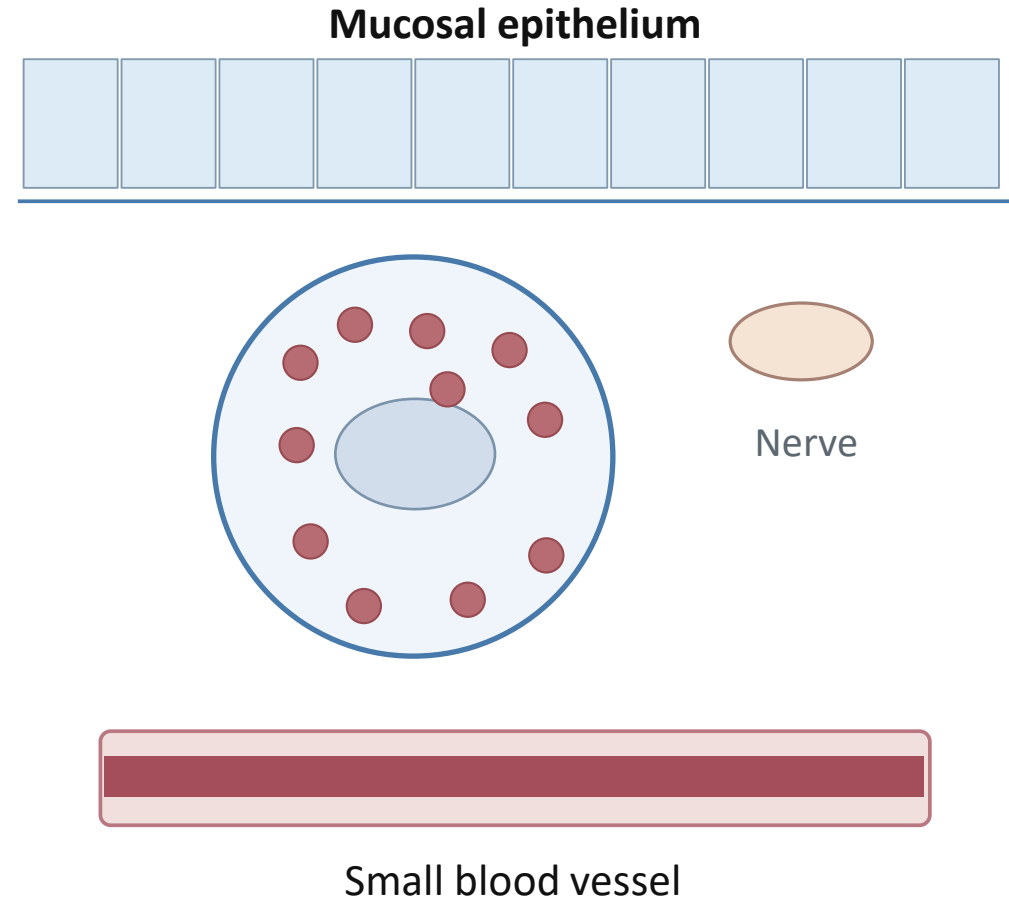
Activation

Antigen-mediated receptor cross-linking initiates cellular responses.

- Sensitization: FcεRI on mast cells becomes occupied by IgE.
- Activation: The relevant allergen cross-links cell-bound IgE–FcεRI complexes.
- Only activation initiates the mediator-release program described here.

Mast cells are strategically distributed sentinels

- Mast cells derive from the bone marrow and reside widely in tissues.
- They are abundant near small vessels, nerves and subepithelial surfaces.
- This positioning helps explain rapid local vascular and mucosal reactions.



Schematic: Subepithelial tissue

Perivascular mast cells can rapidly affect vascular function

Mediator release beside vessels

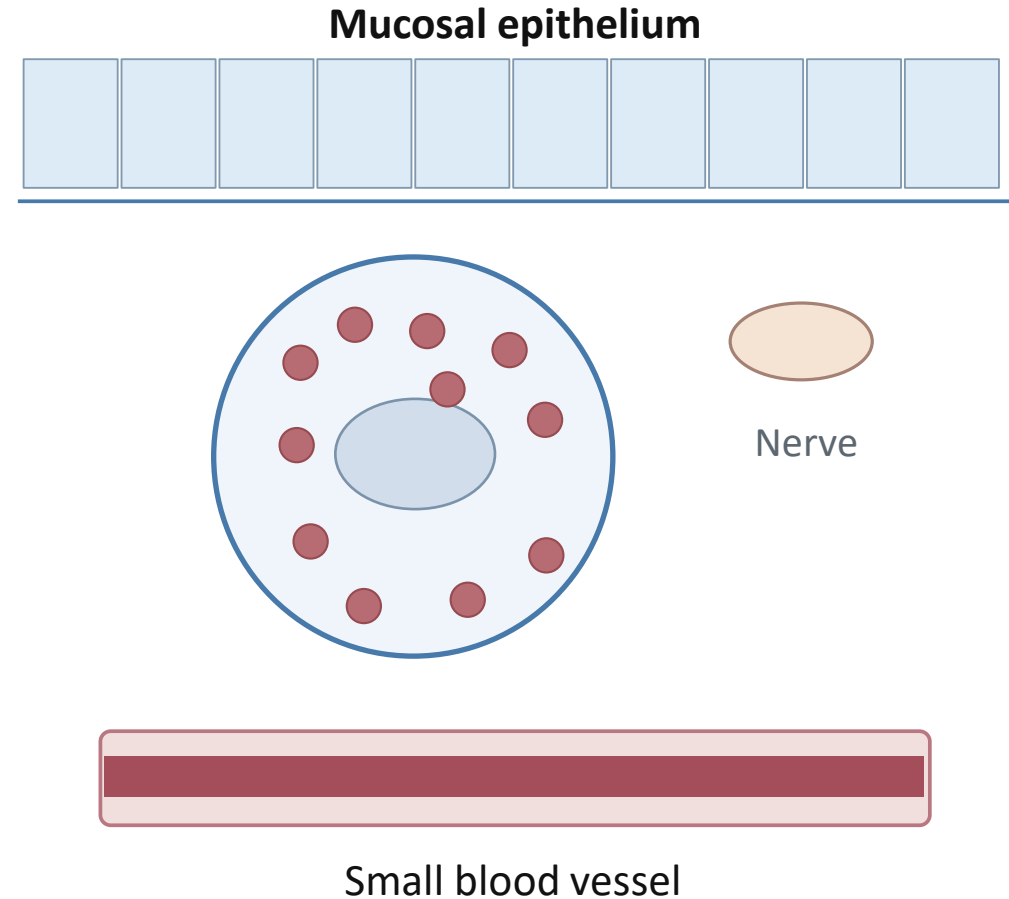
Leads to

Vasodilation and vascular leakage

- Mast cells lie near small blood vessels, placing released mediators close to vascular targets.
- Increased vascular permeability produces local tissue edema.
- Vasodilation contributes to congestion in immediate reactions.

Subepithelial location supports mucosal reactions

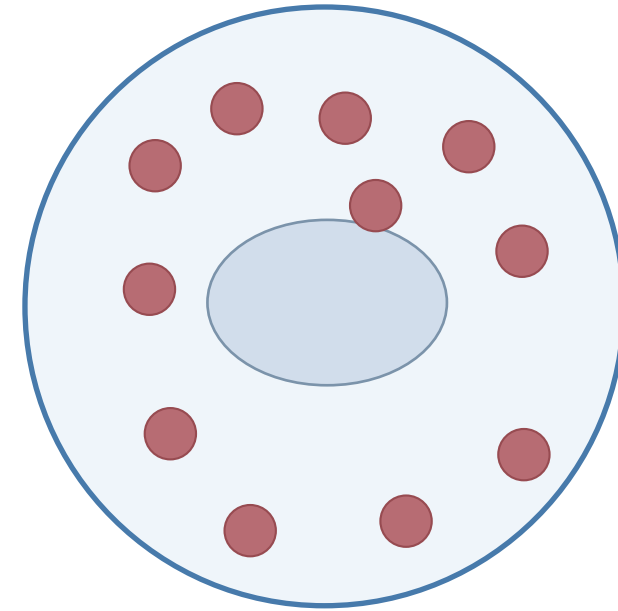
- Subepithelial mast cells are positioned close to environmental entry surfaces.
- Activated mast cells can alter secretory and smooth-muscle responses.
- Tissue location influences the clinical pattern of local allergy.



Schematic: Subepithelial tissue

The mast cell granule is a preformed mediator store

- Membrane-bound cytoplasmic granules contain biologically active mediators.
- Preformed contents can be released quickly once activation occurs.
- Degranulation differs from subsequent synthesis of lipid mediators and cytokines.



Mast cell

Original schematic—not histology

Acidic granule proteoglycans explain toluidine blue staining

Acidic granule proteoglycans

Leads to

Binding of basic dyes such as
toluidine blue

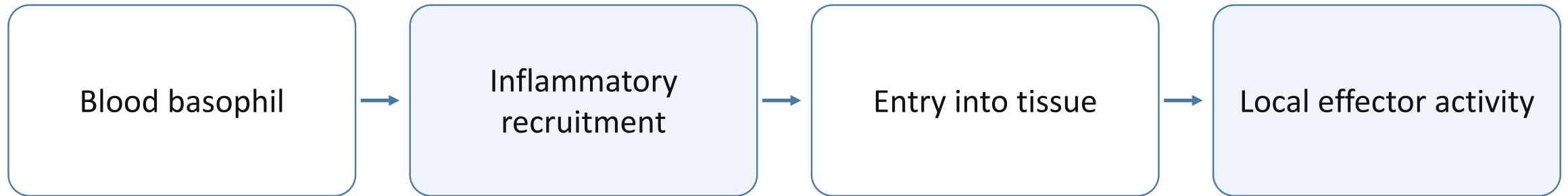
- Granules contain acidic proteoglycans with affinity for basic dyes.
- Toluidine blue can demonstrate the granule-rich cytoplasm.
- This is a cellular staining property—not evidence of antigen specificity.

Mast cells and basophils share functional features

Feature	Mast cell	Basophil
Usual location	Resident in tissues	Circulates in blood
IgE receptors	FcεRI present	FcεRI present
Granules	Present	Present
Inflammatory sites	Already resident	Can be recruited

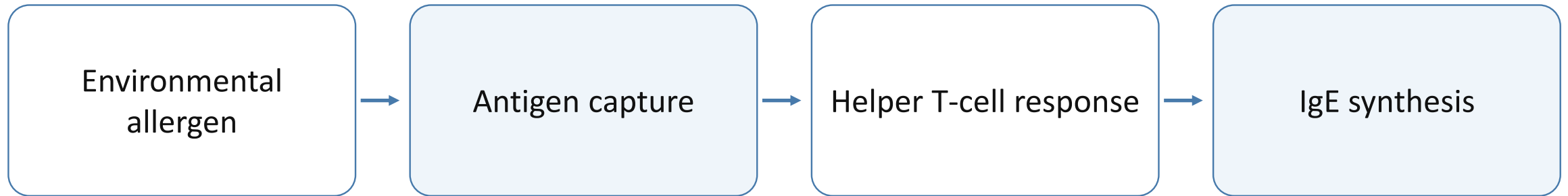
Their principal normal anatomic compartments differ.

Basophils are recruited from the circulation



- Basophils are present in small numbers in circulating blood.
- Unlike mast cells, they are not normally resident tissue cells.
- They may be recruited to an inflammatory site like other granulocytes.

Sensitization begins with recognition of an allergen



- Only some environmental antigens elicit a sufficiently strong type 2 response to act as allergens.
- Antigen captured at a barrier can initiate helper T-cell responses.
- The allergen-specific response precedes mast-cell sensitization.

Epithelial injury provides type 2–promoting signals

Barrier response

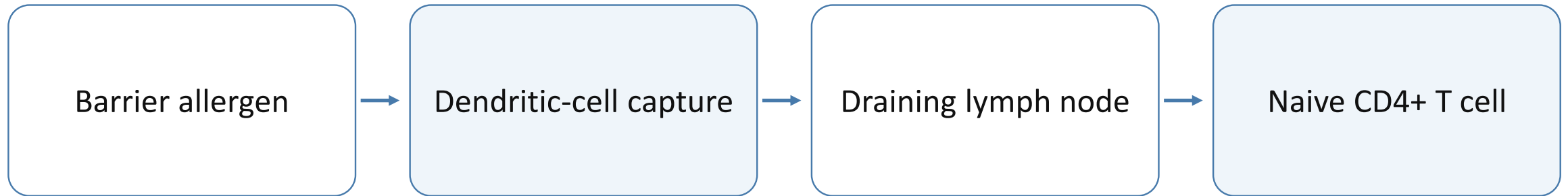
Damaged epithelium releases IL-25, IL-33 and TSLP.

Immune consequence

Signals contribute to the generation of type 2 immune responses.

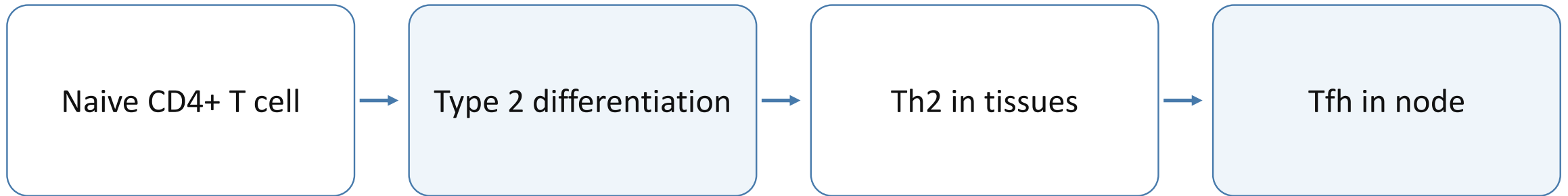
- Injured epithelial cells can produce IL-25, IL-33 and TSLP.
- These cytokines favor type 2 responses following exposure to some environmental antigens.
- The epithelial barrier therefore contributes actively to immune sensitization.

Dendritic cells link the barrier to lymphoid tissue



- Dendritic cells capture antigens from their site of entry.
- They transport captured antigens to draining lymph nodes.
- Antigen presentation to naive CD4+ T cells begins adaptive sensitization.

Naive CD4⁺ T cells enter type 2 differentiation



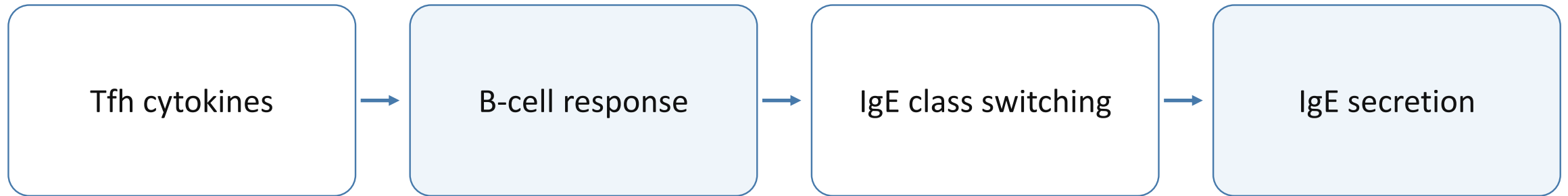
- Antigen presentation and epithelial cytokine signals promote Th2-type responses.
- Th2 cells migrate into peripheral tissues to participate in local inflammation.
- Related Tfh cells remain within lymphoid tissue and support B cells.

Tfh and Th2 cells act in different compartments

Cell population	Predominant context	Relevant action
Tfh	Lymphoid organs	IL-4 / IL-13 support IgE switching
Th2	Peripheral tissues	IL-5 supports eosinophils
Th2	Mucosal tissue	IL-13 supports mucus secretion

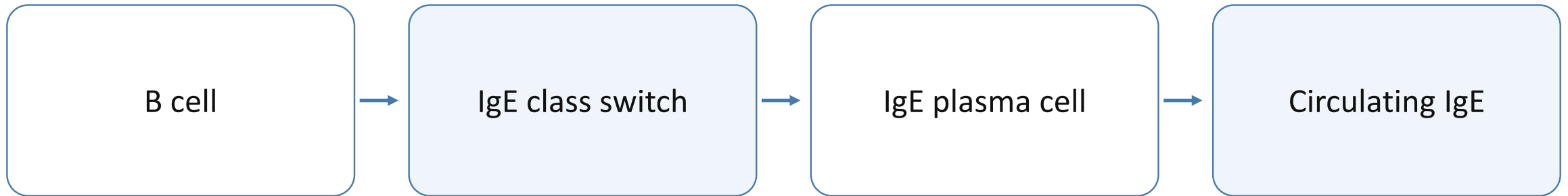
- Tfh cells in lymph nodes help B cells switch to IgE production.
- Th2 cells at tissue sites promote eosinophil activation and mucosal responses.
- Both are contributors to the coordinated type 2 allergic response.

IL-4 and IL-13 support IgE class switching



- Tfh-derived IL-4 and IL-13 act on B cells in lymphoid organs.
- These signals promote isotype switching to IgE.
- The resulting IgE provides antigen recognition capacity to mast cells.

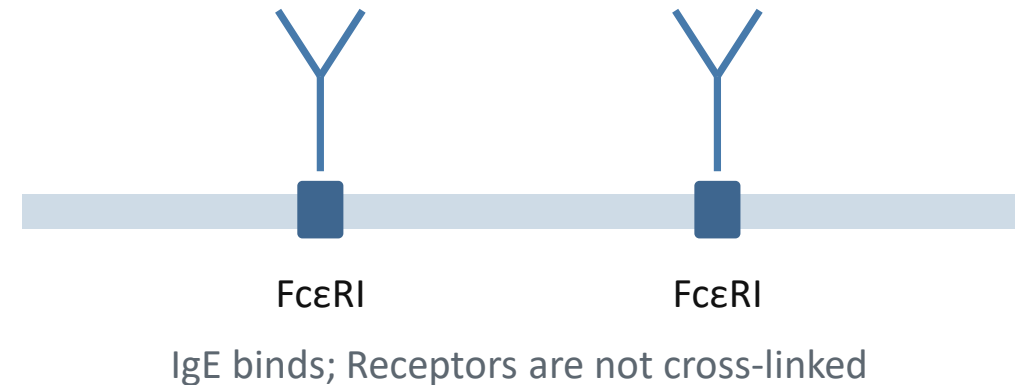
IgE-producing plasma cells supply sensitizing antibody



- B-cell differentiation yields plasma cells that secrete IgE.
- The antigen specificity of the IgE comes from the adaptive B-cell response.
- IgE can subsequently attach to FcεRI on mast cells.

FcεRI is the high-affinity receptor for IgE

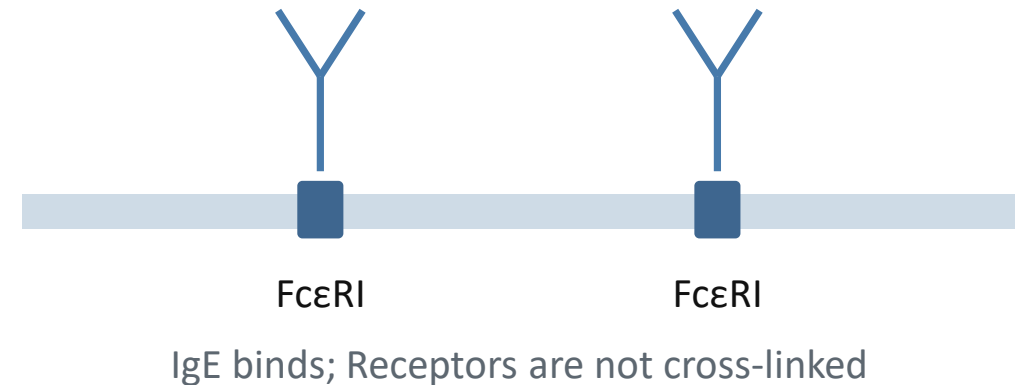
- FcεRI recognizes the Fc portion of IgE.
- Mast cells and basophils express this receptor at their surfaces.
- High-affinity binding lets IgE arm cells for subsequent antigen encounters.



Schematic

IgE binds by Fc while Fab remains antigen-facing

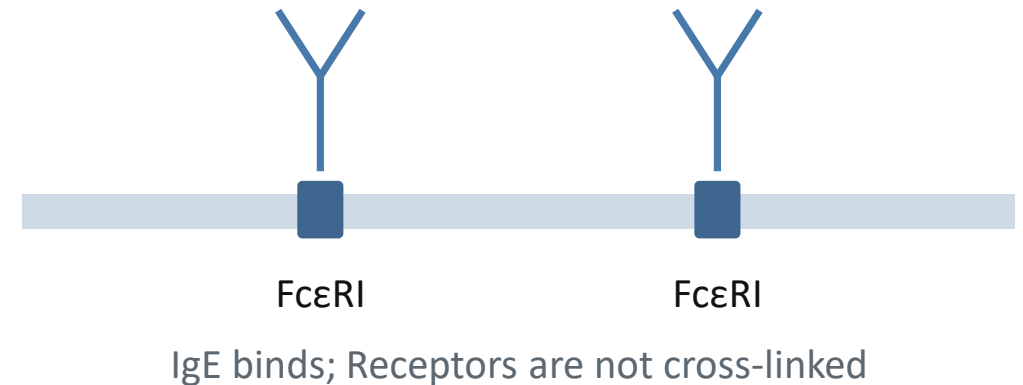
- The IgE Fc portion binds the high-affinity receptor on the cell surface.
- The antigen-binding ends remain positioned to encounter allergen.
- This arrangement couples antibody specificity to mast-cell activation.



Schematic

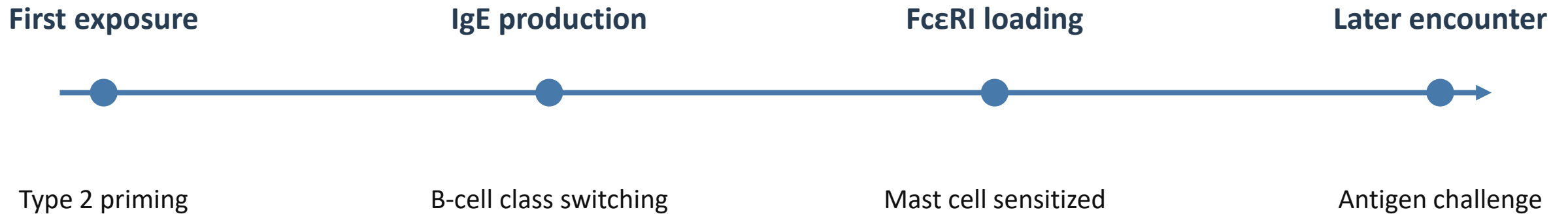
An IgE-coated mast cell is sensitized—not necessarily activated

- Surface occupancy of FcεRI by IgE is termed sensitization.
- The sensitized cell is poised to react if the corresponding antigen returns.
- Antigen-mediated receptor cross-linking is the initiating event for activation.



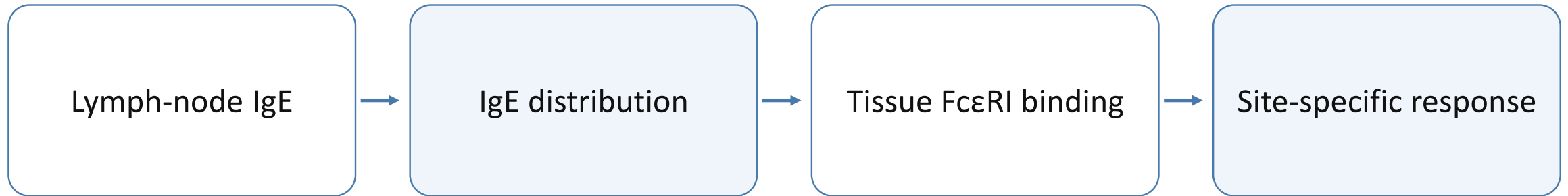
Schematic

First exposure establishes immune recognition and preparedness



- The initial allergen encounter induces helper T-cell and B-cell responses.
- IgE synthesis and receptor binding occur during sensitization.
- The full immediate response is triggered when antigen subsequently activates sensitized cells.

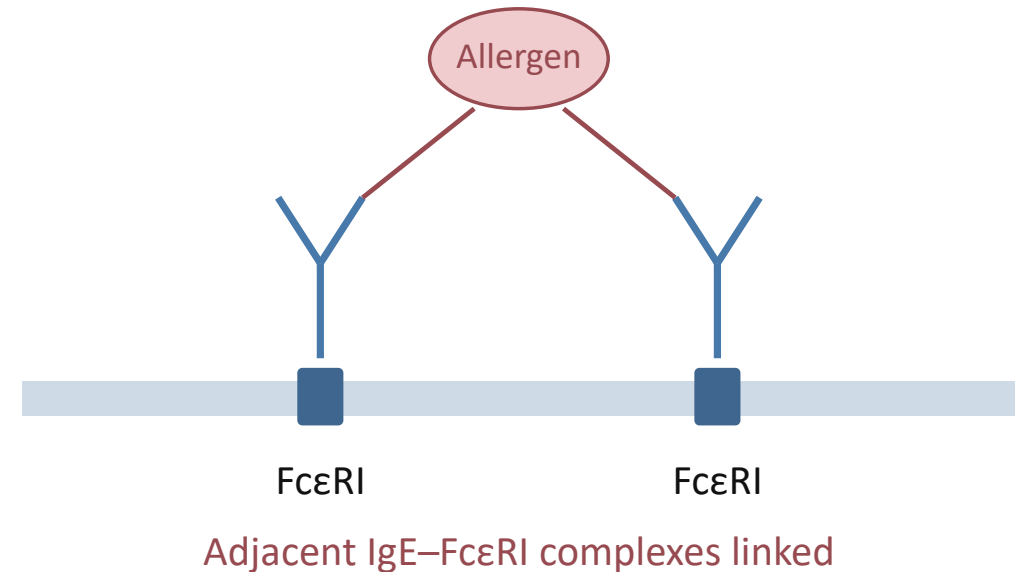
Sensitization links systemic immunity to local effector sites



- IgE is generated through lymphoid immune responses.
- Receptor-bound IgE arms mast cells embedded within diverse tissues.
- The same type of antigen challenge can yield different symptoms across organs.

Reexposure initiates recognition on the mast-cell membrane

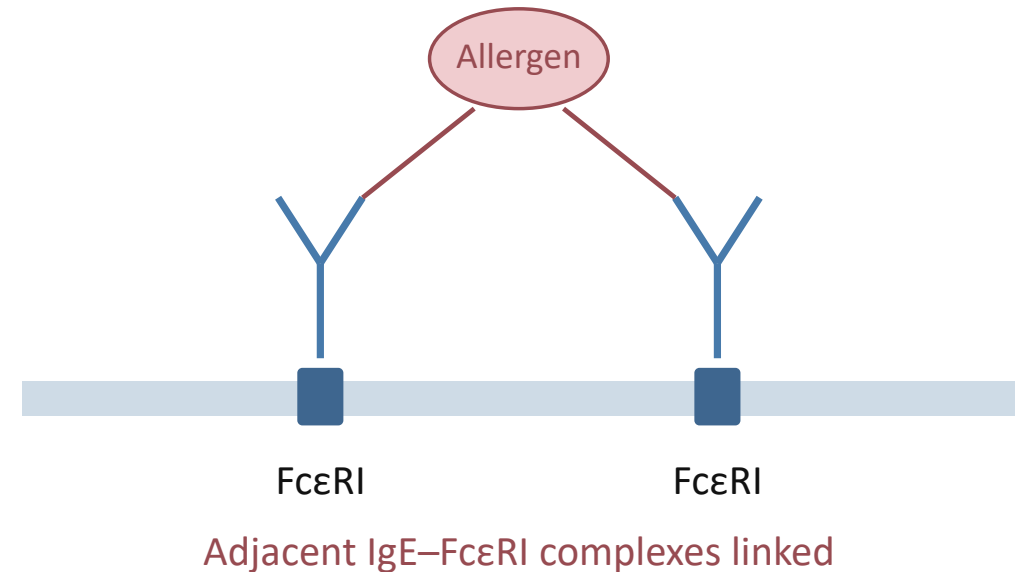
- The triggering antigen binds IgE that is already attached to FcεRI.
- The allergen must bring adjacent IgE molecules together for the described activation process.
- Recognition is translated into receptor clustering and signal initiation.



Schematic

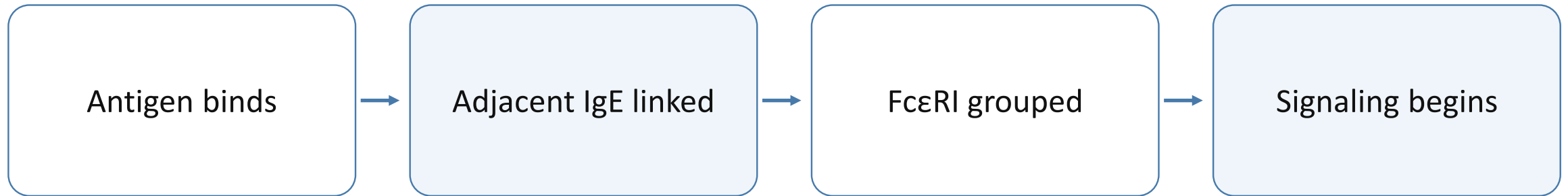
A multivalent allergen cross-links adjacent IgE molecules

- A multivalent antigen can engage more than one surface-bound IgE molecule.
- This links their underlying FcεRI receptors.
- Receptor proximity initiates activation signals inside the mast cell.



Schematic

Cross-linking is the key transition to activation



- Antigen bridges neighboring IgE–receptor complexes.
- The associated Fc receptors are brought together at the membrane.
- Signal transduction follows from the receptor cytoplasmic regions.

Receptor signaling coordinates more than one effector pathway

Immediate discharge

Preformed granule mediators

New lipid products

Membrane-derived
inflammatory mediators

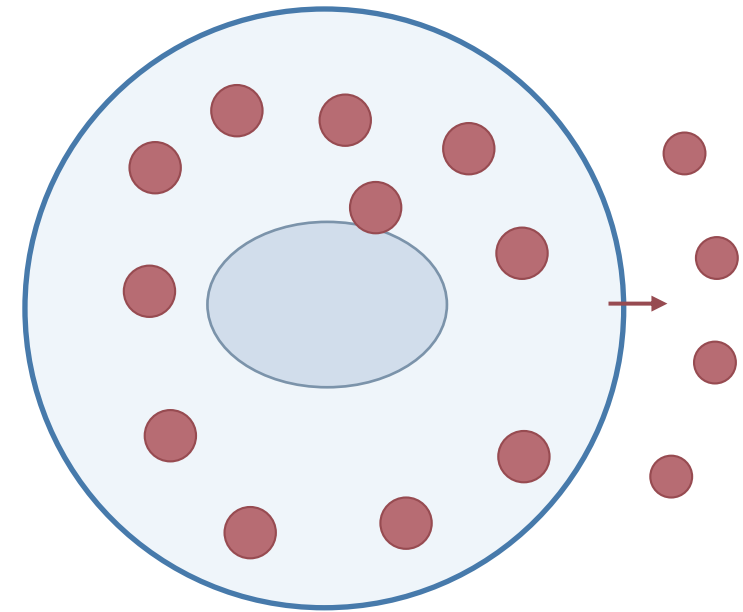
Cytokine program

Recruitment and sustained
inflammation

- Signals initiated at FcεRI induce release of stored granule contents.
- Additional signaling promotes synthesis of new lipid mediators.
- Activation also promotes cytokine production and the late-phase response.

Granule discharge releases preformed mediators

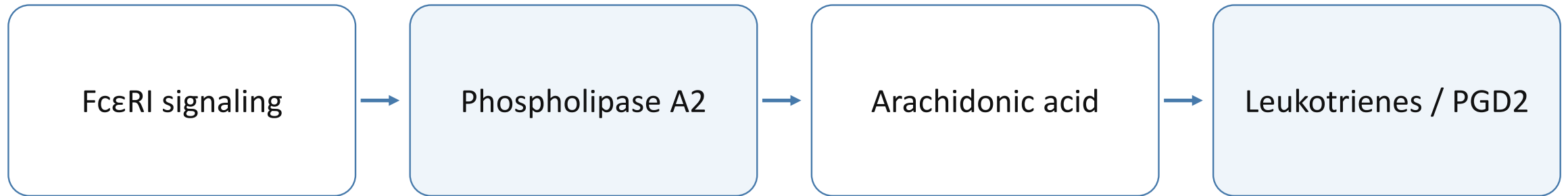
- Degranulation rapidly transfers stored mediators to extracellular tissue.
- Histamine and proteases are among the important granule products.
- This branch helps initiate the earliest vascular and smooth-muscle responses.



Activated mast cell

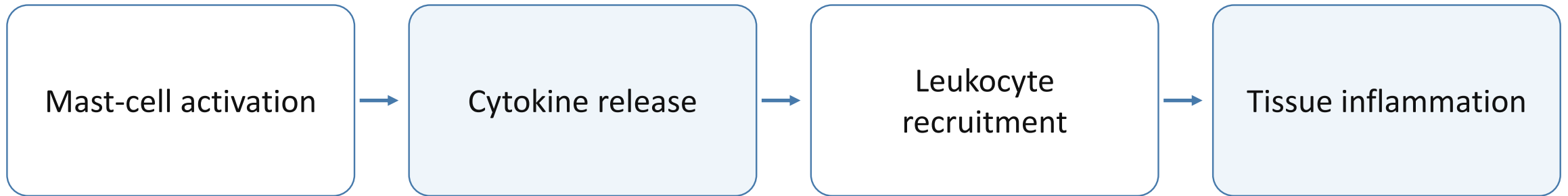
Original schematic—not histology

Mediator synthesis begins after cellular activation



- Mast-cell activation initiates generation of newly synthesized lipid mediators.
- Phospholipase A2 converts membrane phospholipids to arachidonic acid.
- Downstream leukotrienes and prostaglandins contribute to tissue effects.

Cytokine production sustains the inflammatory cascade



- Activated mast cells synthesize cytokines and chemokines.
- Mediators including TNF, IL-1 and chemokines promote recruitment of leukocytes.
- The inflammatory-cell influx contributes to the late-phase reaction.

Mast-cell activation has three major outputs

Preformed

Histamine, proteases and
proteoglycans

Lipid-derived

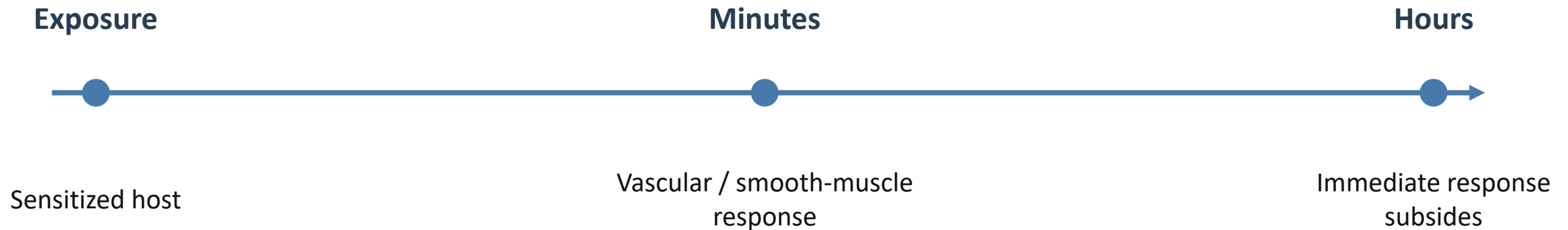
Leukotrienes and
prostaglandin D2

Transcriptional

Cytokines and chemokines

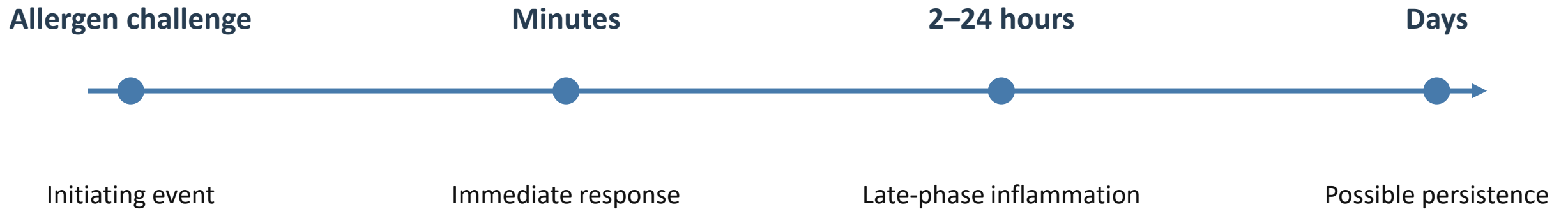
- Stored granule contents act rapidly.
- Newly formed lipid mediators amplify vasoactive and bronchial responses.
- Cytokines and chemokines connect the trigger to later inflammation.

Immediate reactions typically emerge within minutes



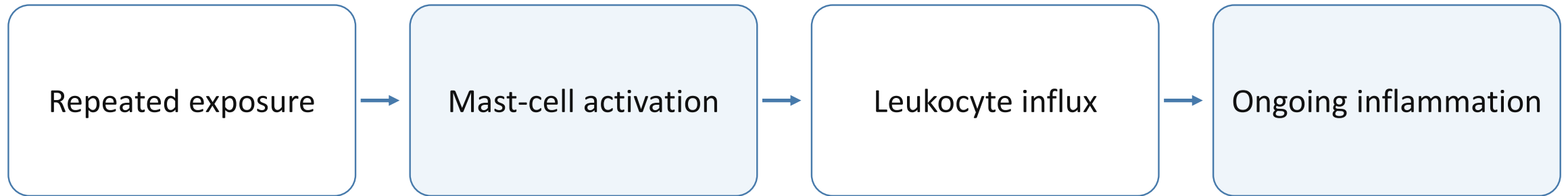
- The immediate phase is rapid after allergen challenge in a sensitized individual.
- It features vasodilation, vascular leakage and tissue-dependent smooth-muscle or secretory effects.
- These responses often diminish over the following hours.

Late-phase reactions can follow without another exposure



- A second inflammatory response may begin 2–24 hours after challenge.
- Additional allergen exposure is not required for this subsequent phase.
- Leukocyte influx and epithelial damage can maintain symptoms for days.

Local hypersensitivity can become chronic inflammation



- Recurrent exposures generate repeated immediate and delayed episodes.
- Recruited inflammatory cells produce additional cytokines and other mediators.
- The resulting disease may be chronic despite a rapidly triggered initiating mechanism.

IgE is not the only route to mast-cell activation

IgE dependent

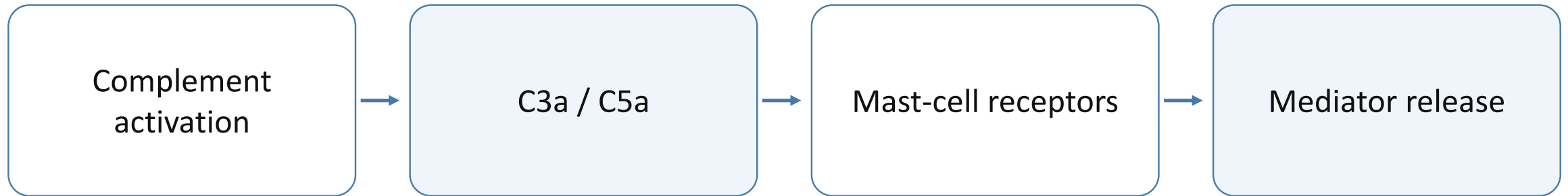
Allergen cross-links FcεRI-bound IgE.

IgE independent

Other stimuli directly or indirectly activate mast cells.

- Some mast-cell triggers do not require allergen–IgE cross-linking.
- Complement products, certain drugs, signaling molecules and physical conditions are described activators.
- These pathways can produce reactions resembling immediate hypersensitivity.

Complement anaphylatoxins can activate mast cells



- C3a and C5a are designated anaphylatoxins.
- They can act through receptors on mast-cell membranes.
- Their effects may mimic some manifestations of anaphylaxis without the IgE cross-linking sequence.

Certain drugs can act as alternative mast-cell stimuli

Drug exposure (examples:
Codeine, morphine)

Leads to

Possible mast-cell activation
without IgE cross-linking

- Codeine and morphine among agents that can activate mast cells.
- This mechanism is distinct from the classic allergen-mediated IgE cross-linking sequence.
- A drug-associated immediate reaction does not by itself prove antigen-specific IgE.

Adenosine, chemokines and venom components are additional triggers

Adenosine

Non-antigenic chemical
stimulus

IL-8

Chemokine named as an
activator

Melittin

Bee-venom component

- The text lists adenosine and IL-8 among mast-cell activators.
- Melittin, a component of bee venom, is also included.
- These examples illustrate the diversity of mast-cell activation signals.

Physical stimuli may activate mast cells

Heat

Physical stimulus

Cold

Physical stimulus

Sunlight

Physical stimulus

- Heat and cold are listed physical triggers.
- Sunlight is another reported physical stimulus.
- Recognizing this group helps separate antigen-specific sensitization from stimulus-triggered activation.

IgE and non-IgE triggers must not be conflated

Feature	IgE-dependent route	Other mast-cell triggers
Preparation	Prior IgE sensitization	No required IgE priming
Initiator	Relevant multivalent allergen	Complement, drugs, physical factors
Key step	IgE–FcεRI cross-linking	Other membrane/stimulus pathways
Common endpoint	Mediator release	Mediator release

Both converge on mast-cell mediator release and overlapping manifestations.

Mediators account for the outward manifestations of activation

Vessels

Dilation and increased permeability

Smooth muscle

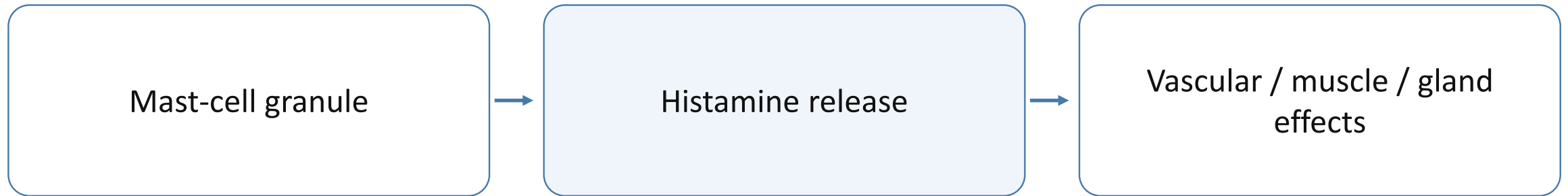
Contraction and spasm

Glands / mucosa

Increased secretions

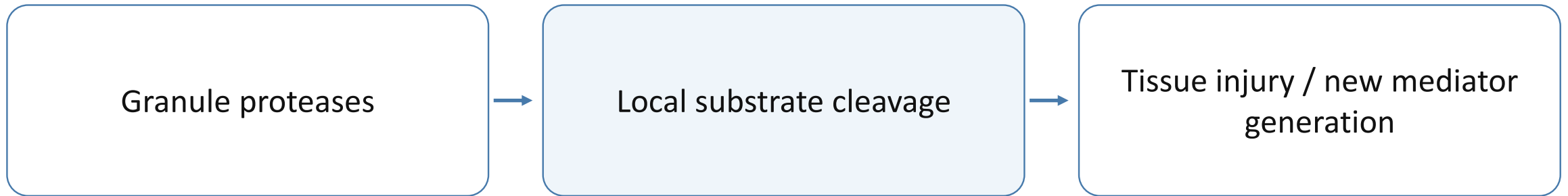
- Mast-cell mediators influence vessels, smooth muscle and glands.
- Some initiate rapid symptoms; Others recruit inflammatory cells.
- The local tissue response depends on where mast cells are activated.

Histamine is a major rapid granule mediator



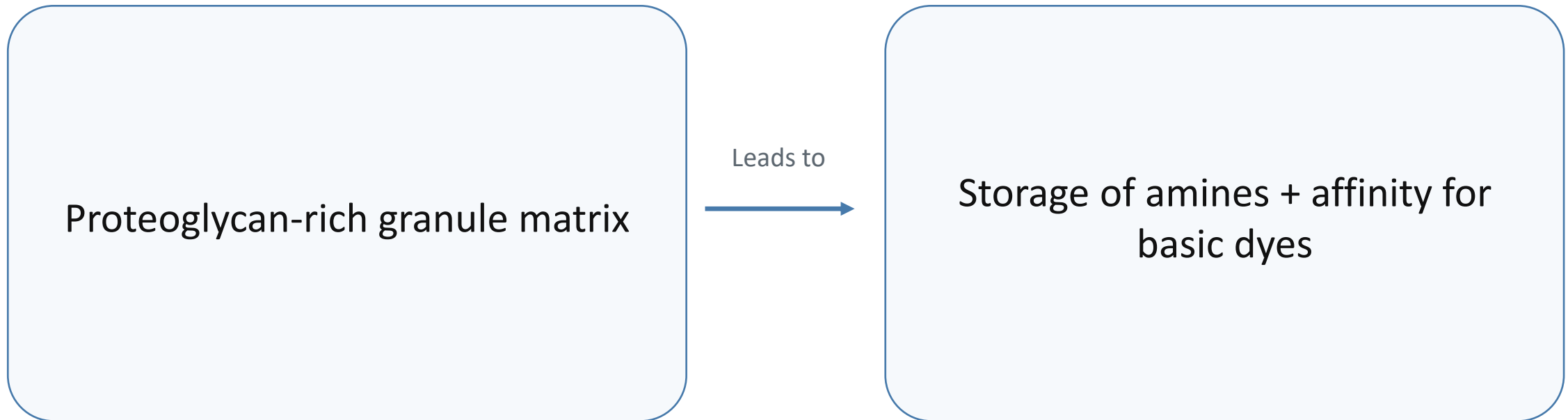
- Histamine is stored as a vasoactive amine within mast-cell granules.
- It increases vascular permeability and contracts smooth muscle.
- It also stimulates secretion from nasal, bronchial and gastric glands.

Mast-cell proteases can promote tissue injury



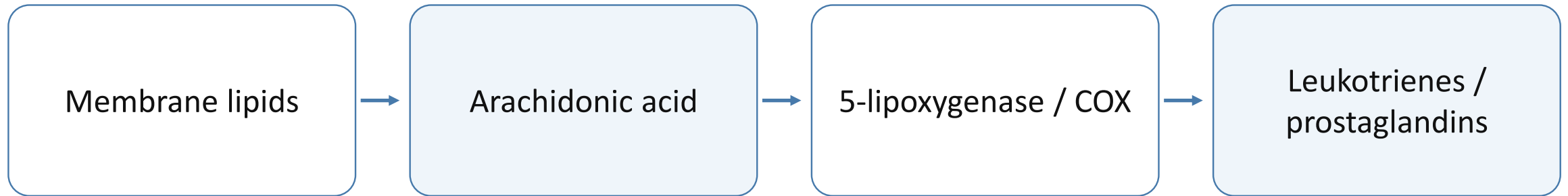
- Granule enzymes include tryptase, chymase and acid hydrolases.
- These enzymes can damage tissue and act on precursor proteins.
- Some downstream products include kinins and complement components.

Granule proteoglycans help package stored mediators



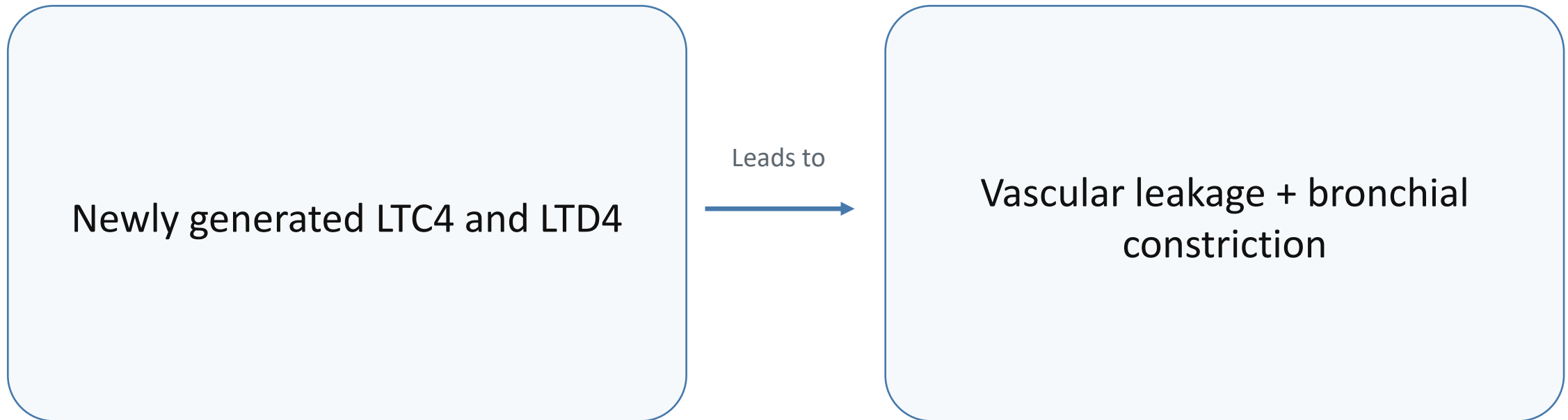
- Heparin and chondroitin sulfate are cited proteoglycans.
- They aid storage and packaging of the granule amines.
- Their acidic chemistry also explains affinity for basic stains.

Arachidonic-acid metabolism yields new lipid mediators



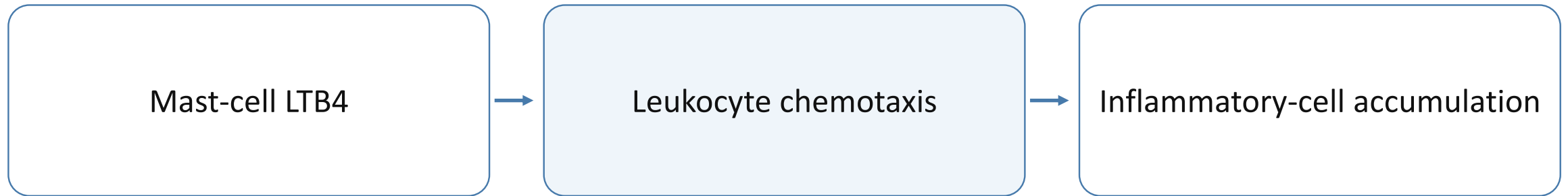
- Mast-cell activation stimulates phospholipase A2 activity.
- Membrane phospholipids yield arachidonic acid.
- Lipoxygenase and cyclooxygenase pathways generate distinct mediator families.

LTC4 and LTD4 intensify vasoactive and spasmogenic effects



- Leukotrienes C4 and D4 are potent vasoactive and spasmogenic agents.
- They increase vascular permeability and contract bronchial smooth muscle.
- These actions reinforce acute airway and vascular reactions.

LTB4 has a different principal inflammatory role



- Leukotriene B4 is chemotactic for inflammatory leukocytes.
- Neutrophils, eosinophils and monocytes as responsive cells.
- Its role links lipid mediator production to cellular recruitment.

Prostaglandin D2 contributes to bronchial responses

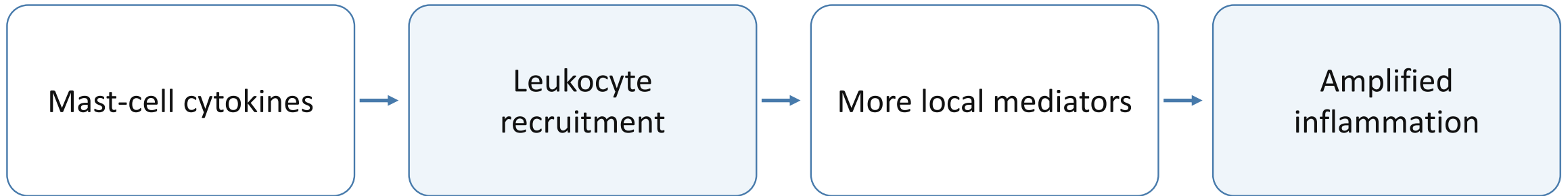
COX pathway → prostaglandin D2

Leads to

Bronchospasm + mucus secretion

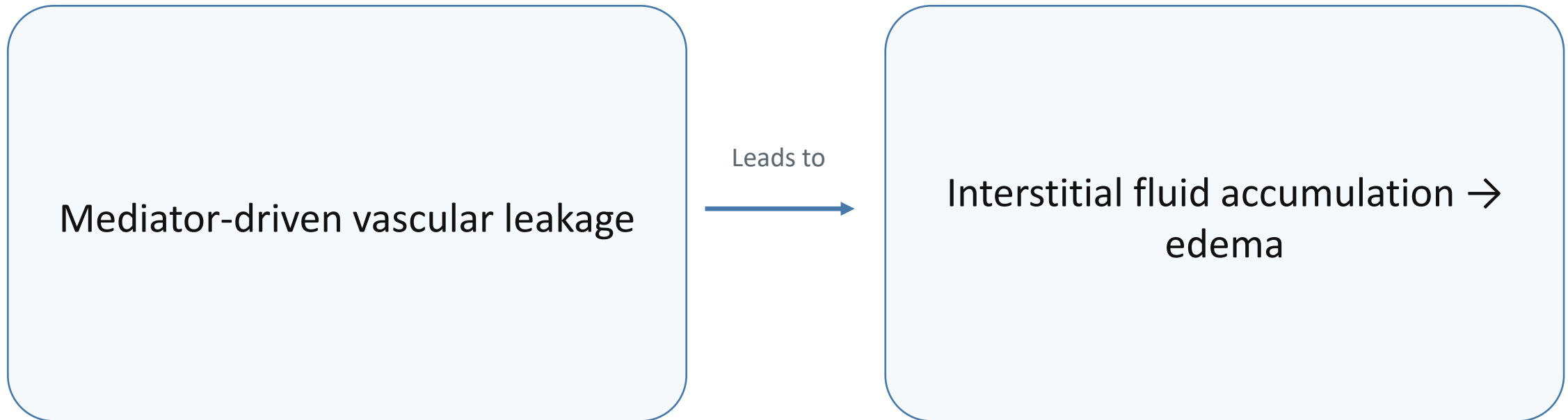
- Prostaglandin D2 is the prominent mast-cell cyclooxygenase product described.
- It causes intense bronchospasm.
- It also increases mucus secretion.

Mast-cell cytokines recruit and amplify inflammatory cells



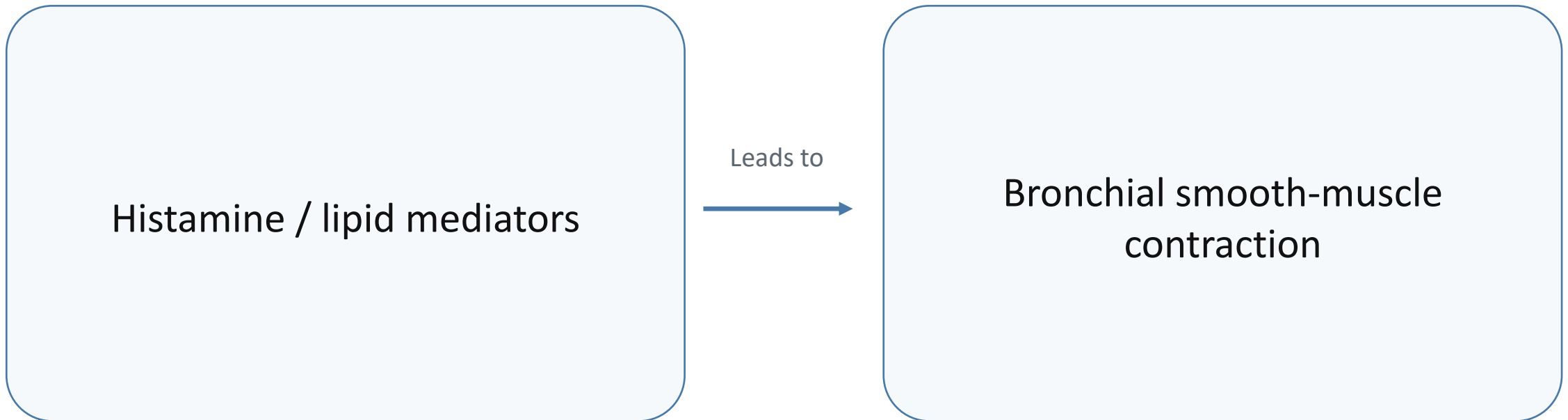
- TNF, IL-1 and chemokines contribute to leukocyte recruitment.
- IL-4 can amplify the type 2 helper-T-cell response.
- Recruited leukocytes provide further sources of cytokines.

Vascular edema arises from altered vessel permeability



- Released mediators act on nearby microvasculature.
- Vascular leakage causes movement of fluid into surrounding tissue.
- This process helps explain swelling in immediate reactions.

Smooth-muscle spasm underlies important airway effects



- Mast-cell mediators can cause intense bronchial smooth-muscle contraction.
- Bronchial narrowing contributes to airflow obstruction.
- The mechanism is particularly relevant to immediate allergic airway reactions.

Mucus secretion is another direct tissue response

Rapid effect

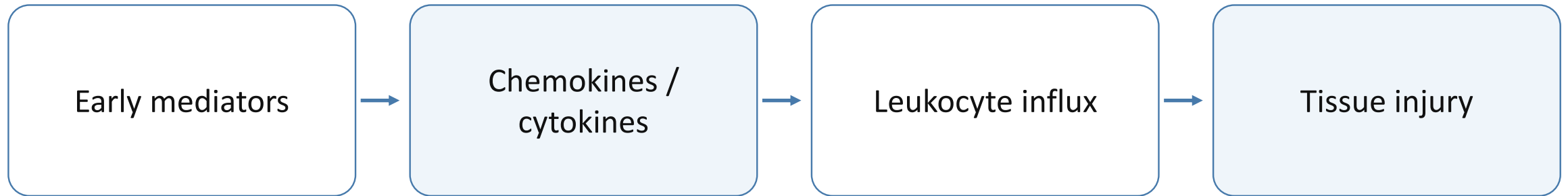
Histamine acts on secretory tissues.

Type 2 support

IL-13 enhances epithelial mucus output.

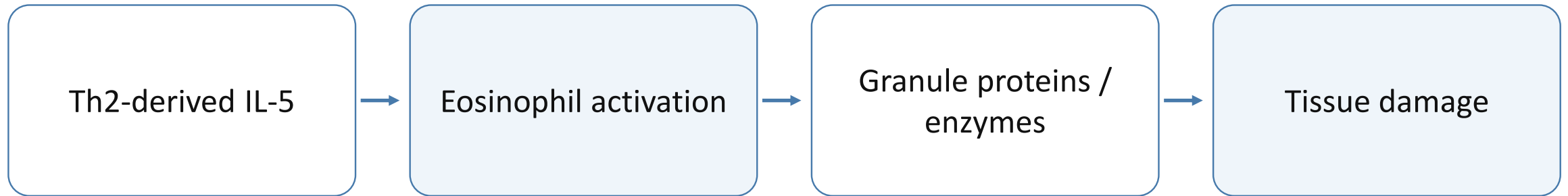
- Histamine can increase glandular secretion.
- IL-13 from type 2 responses also stimulates epithelial mucus production.
- Mucosal hypersecretion contributes to symptoms in allergic airways.

The late phase is a recruited-cell inflammatory response



- Eosinophils, neutrophils and T cells can enter affected tissue.
- Mast-cell cytokines and other local signals promote recruitment.
- Inflammatory cells contribute further mediators and epithelial injury.

IL-5 and eosinophils strengthen allergic tissue injury



- IL-5 is a major eosinophil-activating type 2 cytokine.
- Eosinophils contribute proteolytic enzymes and toxic granule proteins.
- This effector axis helps sustain the late inflammatory phase.

The tissue pattern differs between immediate and late phases

Feature	Immediate phase	Late phase
Typical onset	Minutes after challenge	2–24 hours later
Prominent response	Vascular / smooth-muscle / secretory	Leukocyte-rich inflammation
Tissue features	Congestion and edema	Eosinophils, other leukocytes; Epithelial injury

- Immediate lesions emphasize congestion, edema and smooth-muscle effects.
- Late lesions emphasize inflammatory cellular infiltration and epithelial damage.
- These phases can overlap clinically.

Allergic rhinitis illustrates a mucosal immediate response

Activation at nasal mucosa

Leads to

Secretions, swelling and
inflammation

- Local allergen challenge can cause nasal discharge and secretions.
- Histamine contributes to rapid glandular and vascular effects.
- Subsequent inflammation may sustain symptoms after the initial reaction.

Asthma illustrates immediate and late-phase mechanisms

Immediate

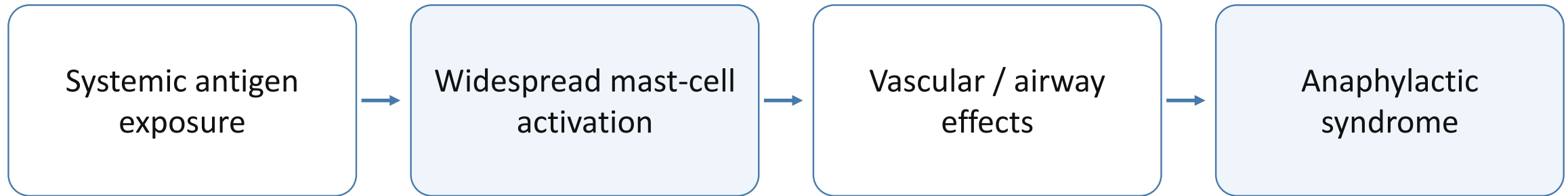
Bronchial smooth-muscle constriction

Late

Inflammatory infiltration and epithelial injury

- Early bronchial smooth-muscle contraction produces airflow obstruction.
- Late inflammatory-cell recruitment contributes tissue injury and sustained symptoms.
- These overlapping components explain why not all symptoms are purely histamine-mediated.

Systemic anaphylaxis shows the consequence of widespread activation



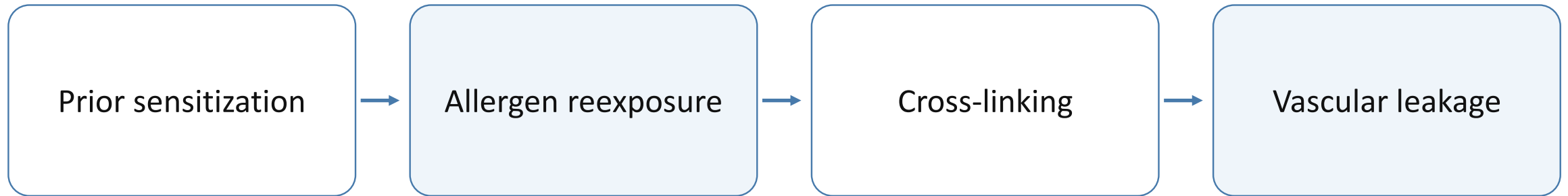
- Systemic immediate hypersensitivity can produce widespread edema.
- Vascular dilation may lead to shock; Airway compromise may accompany laryngeal edema or bronchospasm.
- The triggering event can be sudden in a sensitized individual.

The site of allergen entry shapes the clinical syndrome

Site	Typical tissue effect
Skin	Localized rash, hives or edema
Upper airway	Rhinitis with increased secretions
Bronchi	Airway smooth-muscle constriction
Intestine	Smooth-muscle contraction / increased peristalsis

The same basic cellular mechanism therefore produces heterogeneous clinical presentations.

Case application: Why can repeat exposure cause hives?



- A previously sensitized individual encounters the relevant allergen again.
- The antigen bridges adjacent IgE–FcεRI complexes on tissue mast cells.
- Rapid mediator release increases local vessel permeability and generates edema.

Case application: A rapid reaction without demonstrated IgE

Observation	Supported interpretation
Rapid onset	Compatible with mast-cell mediator effects
Drug / physical trigger	Non-IgE activation is possible
IgE sensitization	Cannot be assumed without evidence

- A patient develops flushing-like or immediate symptoms after a listed non-IgE trigger.
- Mast-cell mediator release can occur independently of classic antigen-specific cross-linking.
- The reaction mechanism cannot be inferred solely from its rapid onset.

Diagnostic reasoning must separate mechanism from phenotype

Phenotype

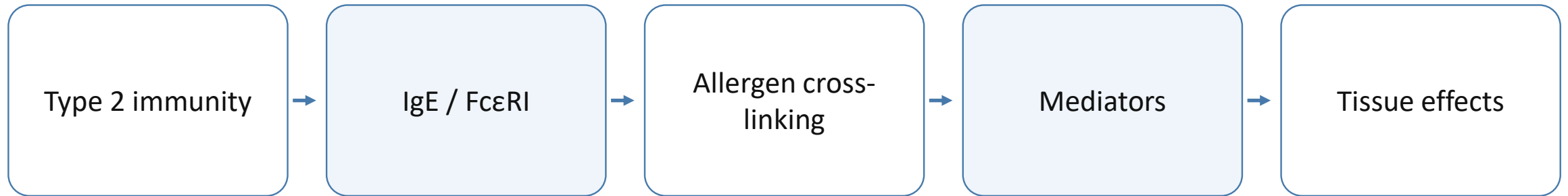
Vascular, bronchial or secretory response

Mechanism

IgE cross-linking versus alternative activation

- Edema, wheeze or secretions indicate effector physiology, not a unique initiating pathway.
- IgE-mediated allergy requires antigen-specific sensitization and triggering.
- Other mast-cell activators can produce overlapping immediate manifestations.

A unified model links immunity to immediate tissue effects



- Tfh / Th2 responses produce an IgE-driven sensitizing environment.
- IgE binding to FcεRI establishes mast-cell readiness.
- Cross-linking elicits mediators that produce immediate effects and recruit cells.

Three discriminations organize this topic

Stage

Sensitization ≠ activation

Product

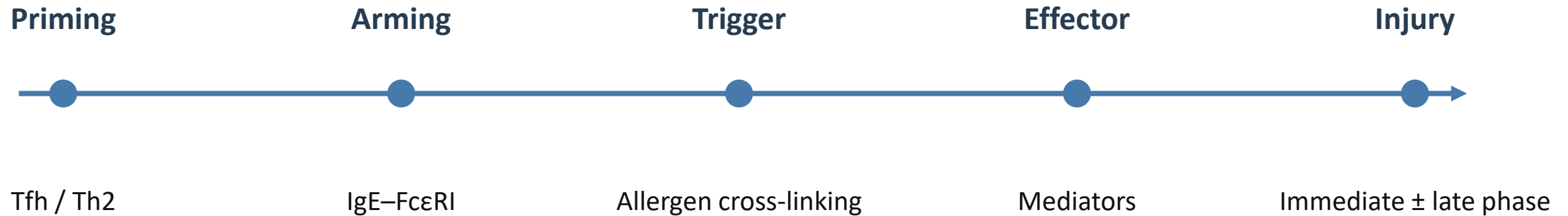
Stored ≠ newly made

Time

Minutes ≠ 2–24 h

- First exposure and IgE coating are distinct from receptor cross-linking.
- Stored granule contents differ from newly synthesized lipids and cytokines.
- An immediate effector response is distinct from later leukocyte-rich inflammation.

Applied synthesis: Follow the cell from priming to disease



- An allergen elicits IgE through a type 2 helper-T-cell response.
- IgE persists on mast-cell FcεRI, enabling recognition at a future encounter.
- Cross-linking triggers early and delayed pathways whose organ-specific effects cause clinical allergy.

Primary source and terminology

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition.

- FcεRI: high-affinity IgE Fc receptor on mast cells and basophils.
- Tfh: T follicular helper cell; Th2: type 2 helper T cell.
- TSLP: thymic stromal lymphopoietin; PGD2: prostaglandin D2.