Immediate hypersensitivity

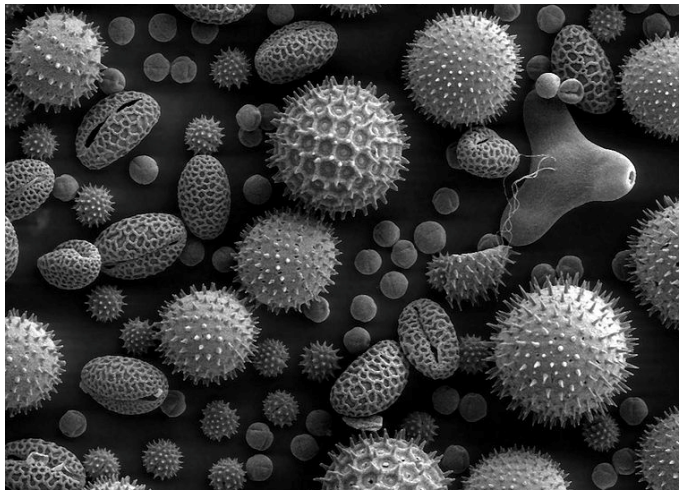
Allergy / Atopy

Immediate hypersensitivity

Mechanisms

Allergens

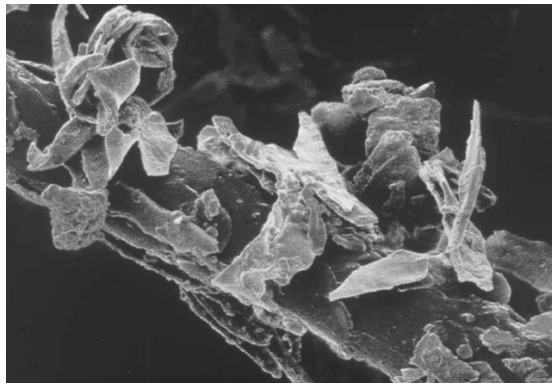
dust mites (feces)



pollens

food

drugs



animal dander

Sensitization

1 - Dendritic cells (DC) capture antigens (allergens)

2 - DC partially process allergens and bring them to lymphnodes

3 - Naïve CD4 T cells are activated to differentiate into Th2

4 - Th2 secrete IL-4, IL-5 and IL-13

5 - Unprocessed allergen activate allergen-specific B cells

6 - IL-4 and IL-13 co-activate allergen-specific B cells

7 - Allergen-specific B cells promote IgE switching
and differentiate into IgE-secreting plasmacells → high IgE

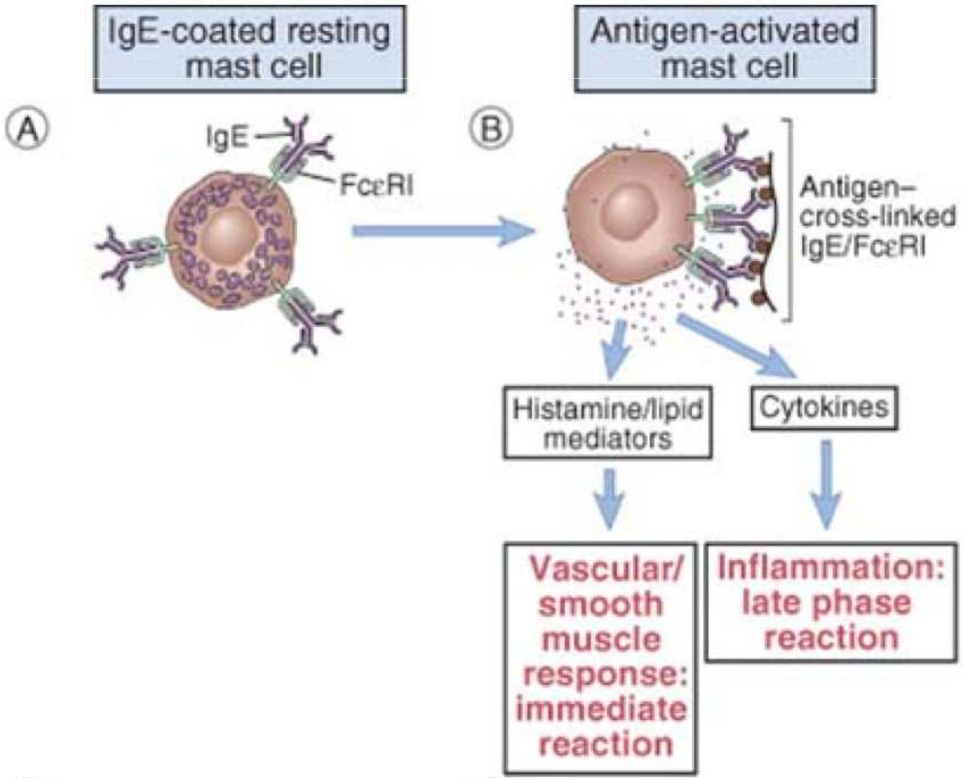
8 - IL-5 activates eosinophils

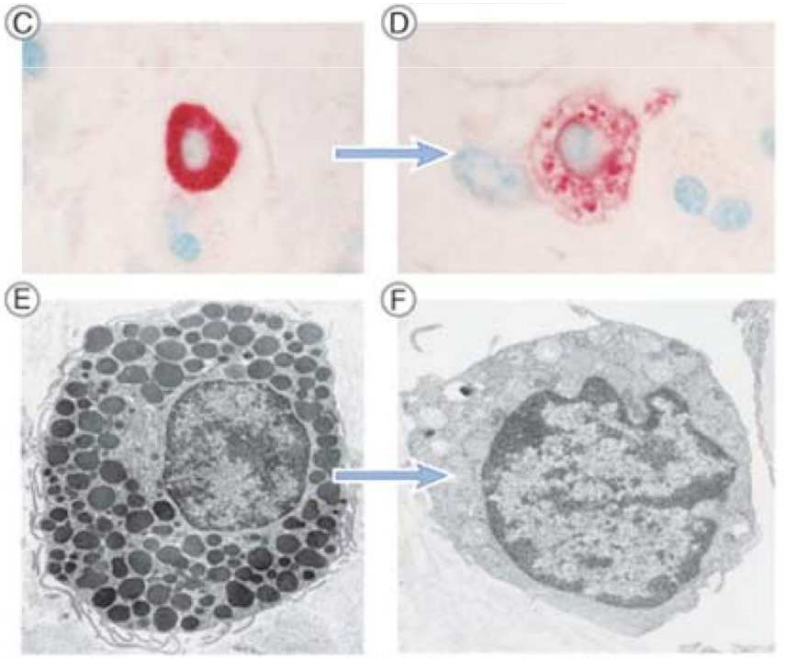
Triggering

1 - Antigen-specific IgE enter the circulation and bind to the FcεR1 on basophils and mastocytes

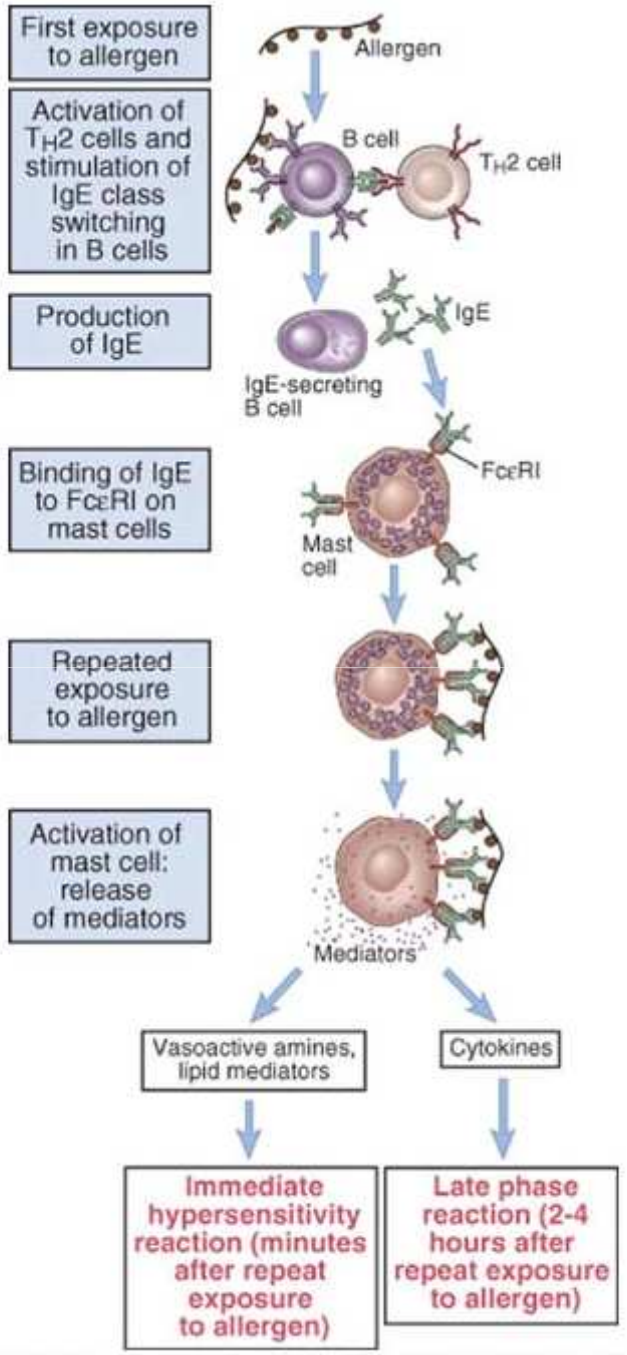
2 - Expression of FcεR1on basophils and mastocytes is enhanced

3 - Allergen binds to IgE bound to FcεR1. Upon crosslinking of FcεR1 by multivalent allergens, degranulation of basophils and mastocytes is triggered

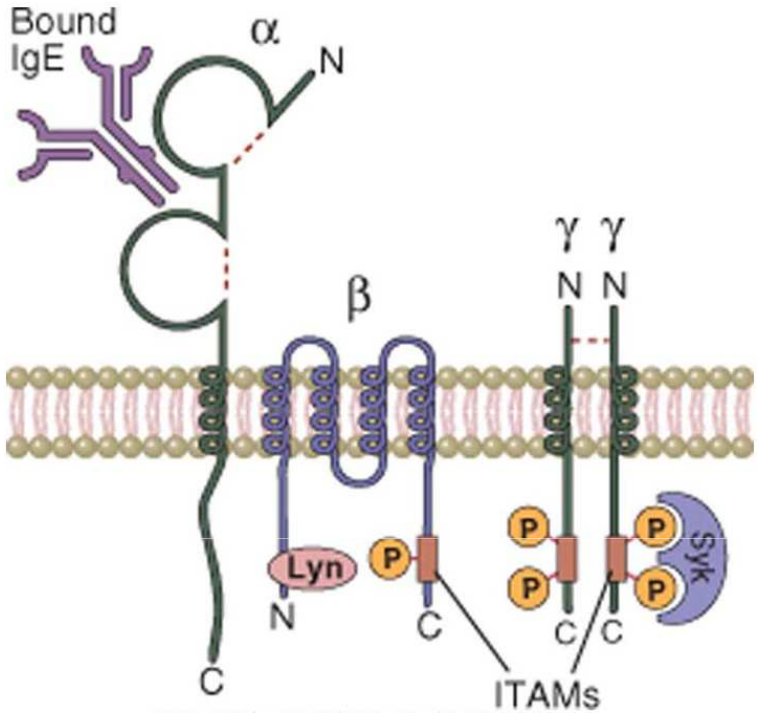




Sequence of events



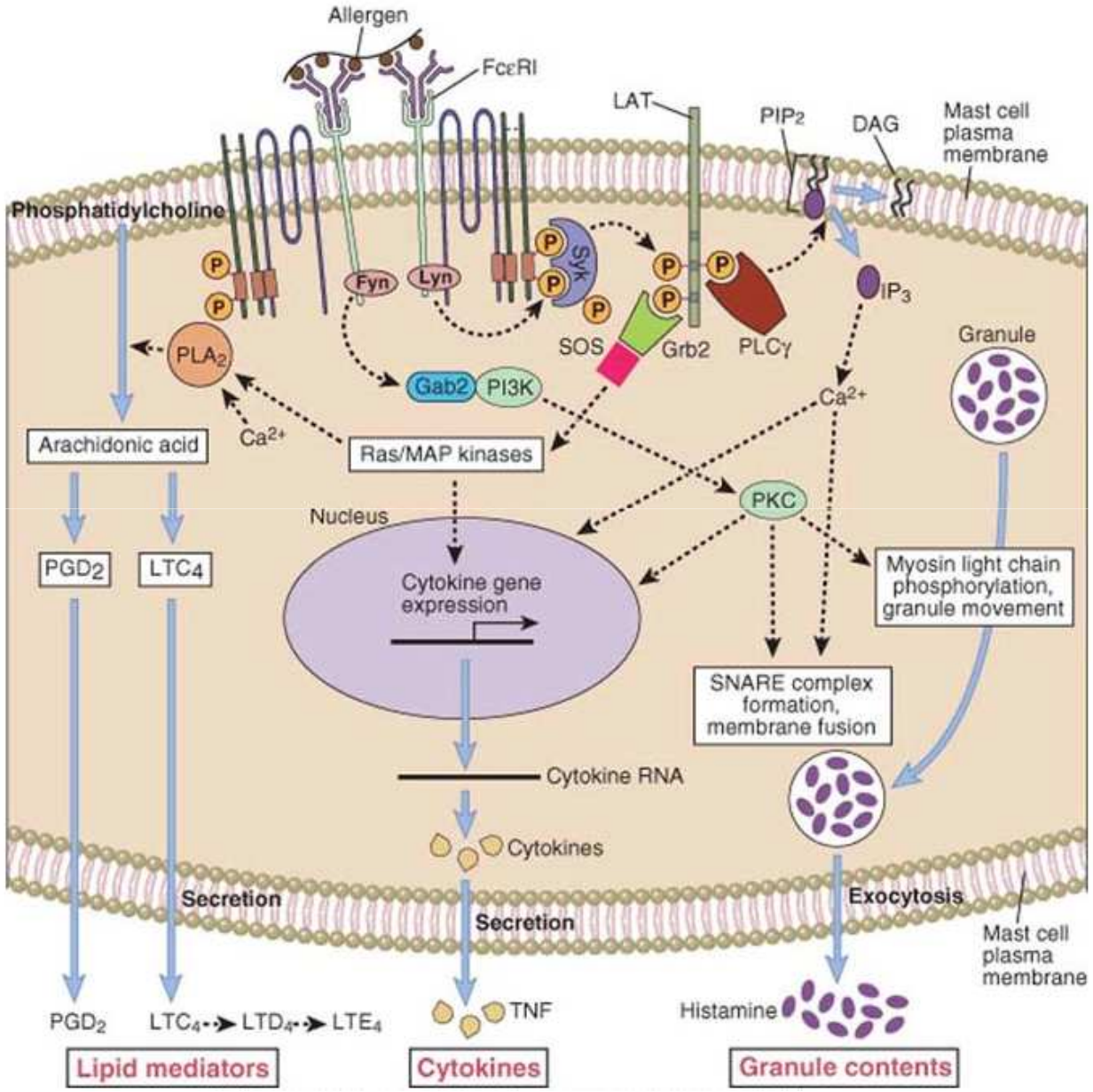
Structure of the high-affinity IgE Fc receptor (FcεR1)



In non-atopic individuals, FcεR1 on the surface of circulating basophils and tissue mastocytes are normally occupied by polyclonal IgE

In atopic individuals, large amounts (~1,000 times normal) of antigen-specific oligoclonal IgE are produced upon first encounter with allergen
Therefore, FcεR1 on the surface of circulating basophils and tissue mastocytes are mostly occupied by antigen-specific oligoclonal IgE

Mastocyte activation



alternative activation:

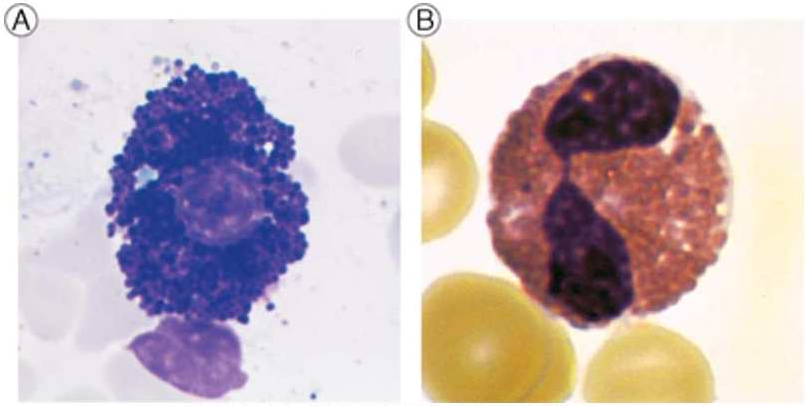
- Chemokines
- C5b

- Neuropeptides

Immediate hypersensitivity

Cellular and soluble mediators

Cellular mediators



Characteristic	Mast cells	Basophils	Eosinophils
Major site of maturation	Connective tissue	Bone marrow	Bone marrow
Major cells in circulation	No	Yes (0.5% of blood leukocytes)	Yes (~2% of blood leukocytes)
Mature cells recruited into tissues from circulation	No	Yes	Yes
Mature cells residing in connective tissue	Yes	No	Yes
Proliferative ability of mature cells	Yes	No	No
Life span	Weeks to months	Days	Days to weeks
Major development factor (cytokine)	Stem cell factor, IL-3	IL-3	IL-5
Expression of FcεRI	High levels	High levels	Low levels (function unclear)
Major granule contents	Histamine, heparin and/or chondroitin sulfate, proteases	Histamine, chondroitin sulfate, protease	Major basic protein, eosinophil cationic protein, peroxidases, hydrolases, lysophospholipase

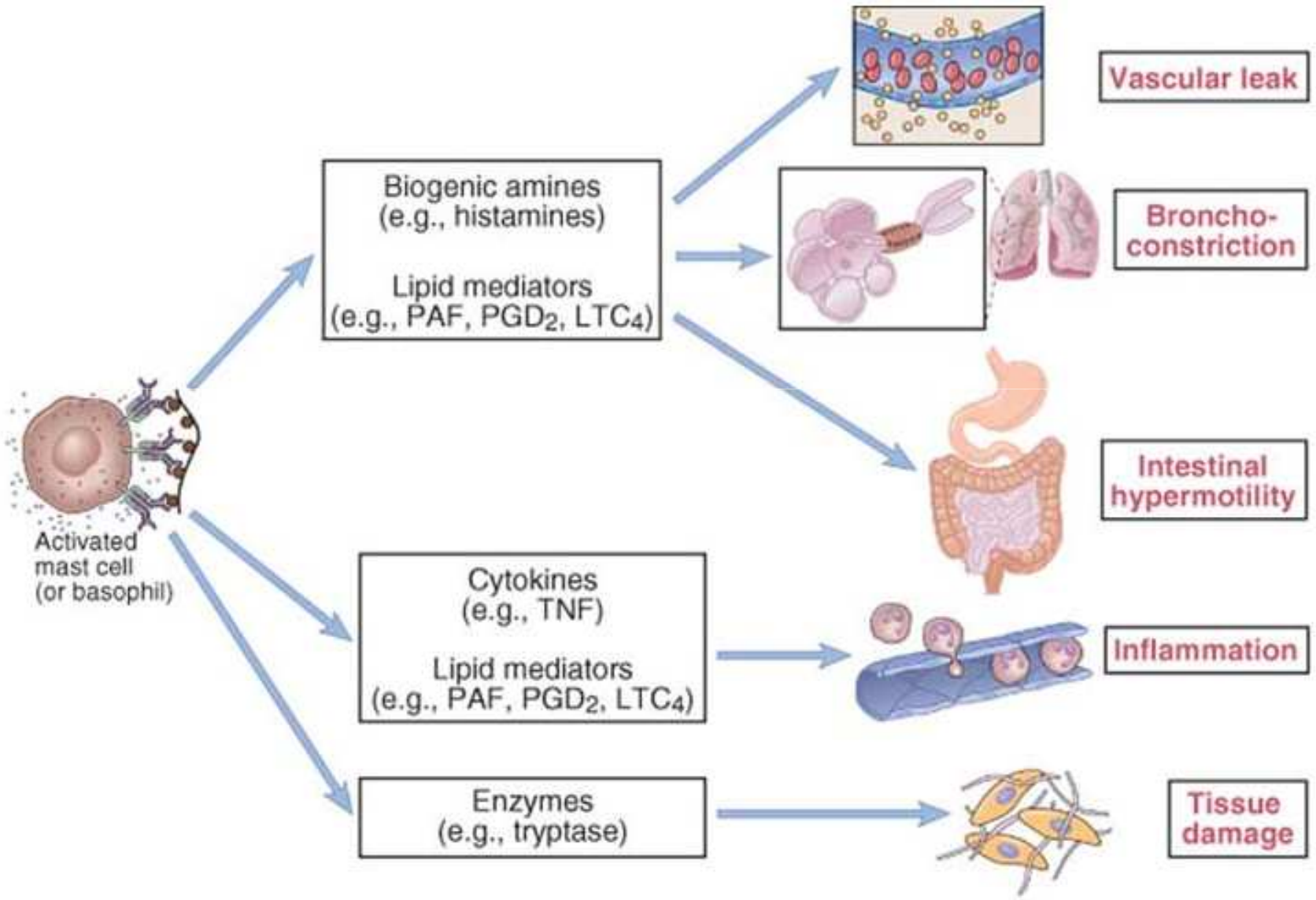
Soluble mediators: activated basophils/mastcells

Class of product	Examples	Biological effects
Enzyme	Tryptase, chymase, cathepsin G, carboxypeptidase	Remodel connective tissue matrix
Toxic mediator	Histamine, heparin	Toxic to parasites Increase vascular permeability Cause smooth muscle contraction
Cytokine	IL-4, IL-13	Stimulate and amplify T_H2-cell response
	IL-3, IL-5, GM-CSF	Promote eosinophil production and activation
	TNF-α (some stored preformed in granules)	Promotes inflammation, stimulates cytokine production by many cell types, activates endothelium
Chemokine	CCL3	Attracts monocytes, macrophages, and neutrophils
Lipid mediator	Prostaglandins D_2, E_2 Leukotrienes B4, C4	Cause smooth muscle contraction Increase vascular permeability Stimulate mucus secretion
	Platelet-activating factor	Attracts leukocytes Amplifies production of lipid mediators Activates neutrophils, eosinophils, and platelets

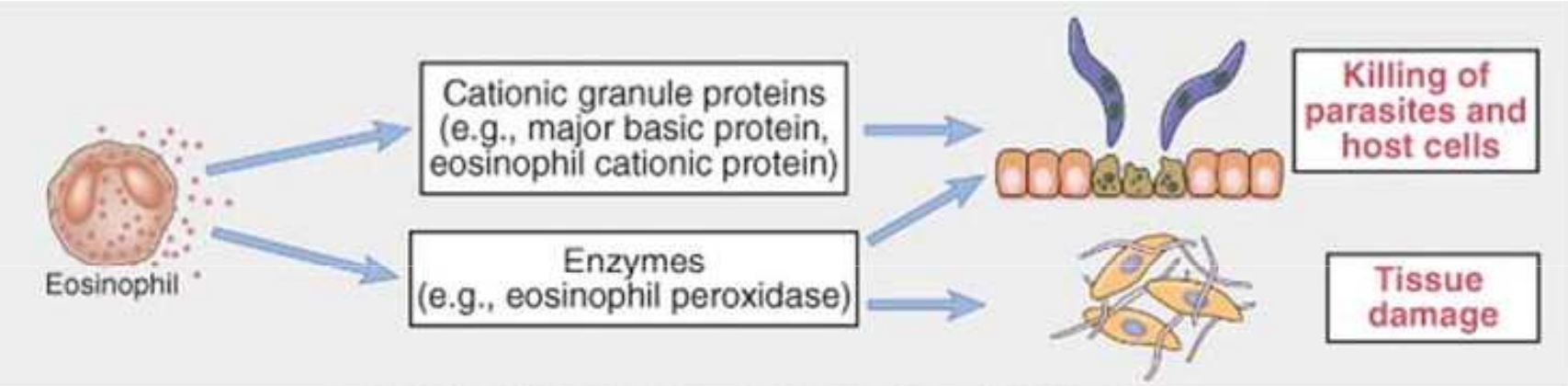
Soluble mediators: activated eosinophils

Class of product	Examples	Biological effects
Enzyme	Eosinophil peroxidase	Toxic to targets by catalyzing halogenation Triggers histamine release from mast cells
	Eosinophil collagenase	Remodels connective tissue matrix
	Matrix metalloproteinase-9	Matrix protein degradation
Toxic protein	Major basic protein	Toxic to parasites and mammalian cells Triggers histamine release from mast cells
	Eosinophil cationic protein	Toxic to parasites Neurotoxin
	Eosinophil-derived neurotoxin	Neurotoxin
Cytokine	IL-3, IL-5, GM-CSF	Amplify eosinophil production by bone marrow Cause eosinophil activation
	TGF-α, TGF-β	Epithelial proliferation, myofibroblast formation
Chemokine	CXCL8 (IL-8)	Promotes influx of leukocytes
Lipid mediator	Leukotrienes C4, D4, E4	Cause smooth muscle contraction Increase vascular permeability Increase mucus secretion
	Platelet-activating factor	Attracts leukocytes Amplifies production of lipid mediators Activates neutrophils, eosinophils, and platelets

Biologic effects: activated basophils/mast cells

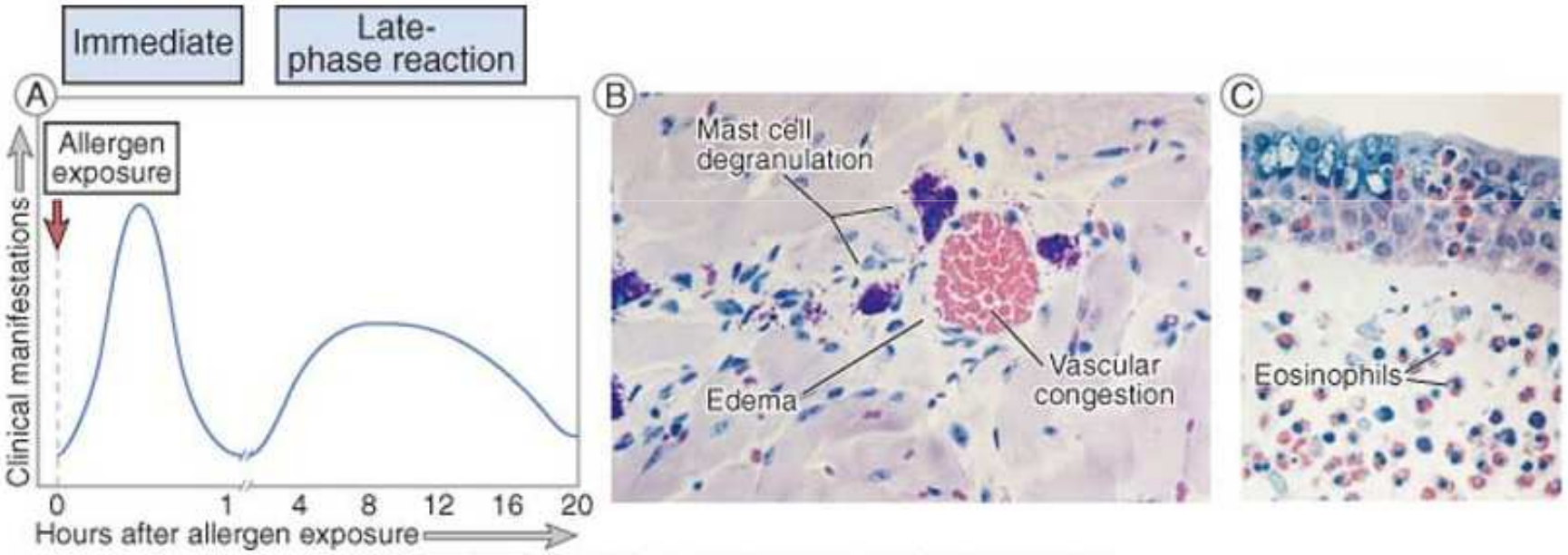


Biologic effects: activated eosinophils



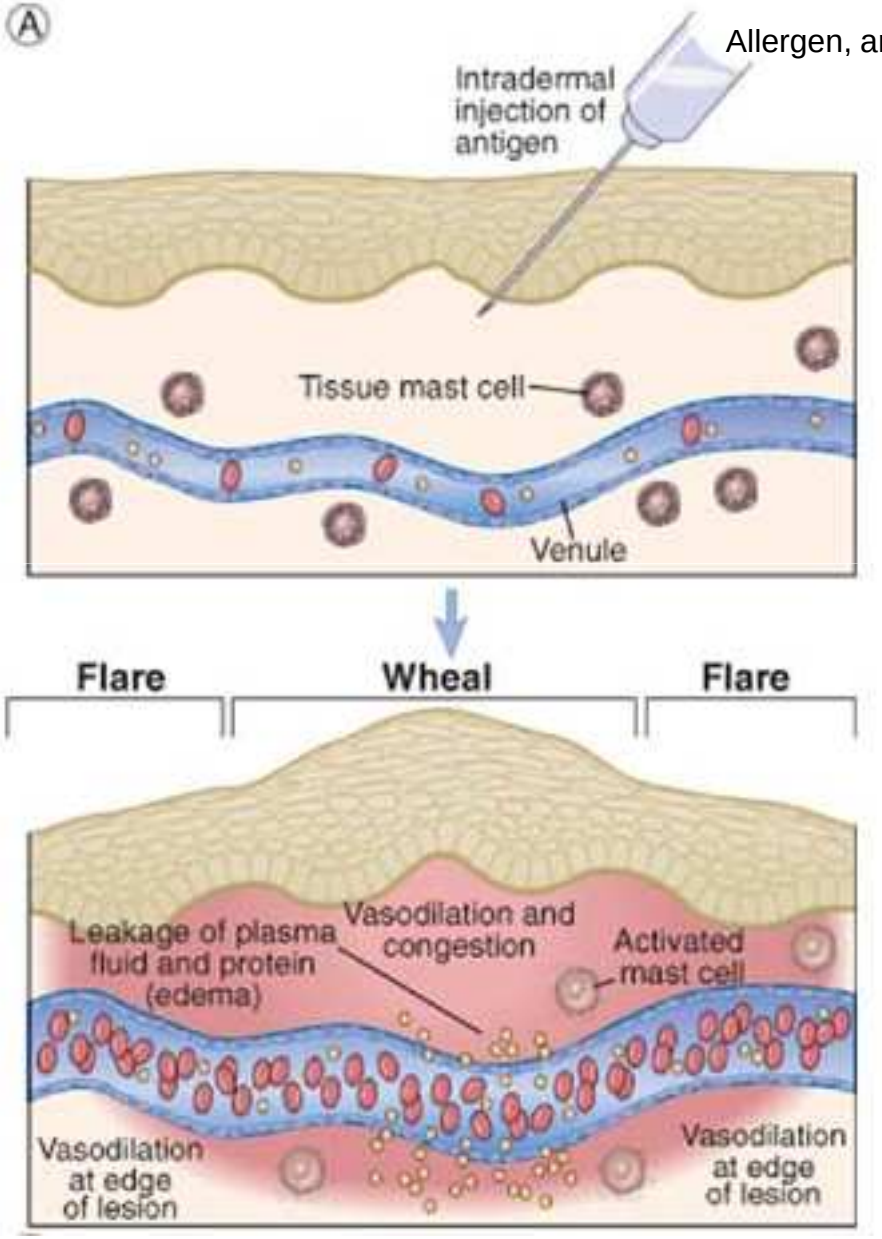
IgE-mediated allergic reactions			
Syndrome	**Common allergens**	**Route of entry**	**Response**
Systemic anaphylaxis	Drugs Serum Venoms Food, e.g. peanuts	Intravenous (either directly or following oral absorption into the blood)	Edema Increased vascular permeability Laryngeal edema Circulatory collapse Death
Acute urticaria (wheal-and-flare)	Animal hair Insect bites Allergy testing	Through skin Systemic	Local increase in blood flow and vascular permeability
Seasonal rhinoconjunctivitis (hay fever)	Pollens (ragweed, trees, grasses) Dust-mite feces	Inhalation	Edema of nasal mucosa Sneezing
Asthma	Danders (cat) Pollens Dust-mite feces	Inhalation	Bronchial constriction Increased mucus production Airway inflammation
Food allergy	Tree nuts Shellfish Peanuts Milk Eggs Fish Soy Wheat	Oral	Vomiting Diarrhea Pruritis (itching) Urticaria (hives) Anaphylaxis (rarely)

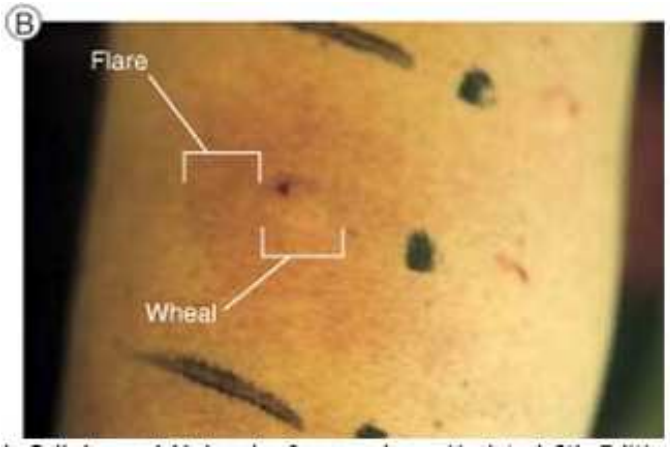
Phases of the allergic response



Cutaneous wheal and flare reaction

Allergen, anti-IgE mAbs, anaphylotoxins (C5a, C4a, C3a)



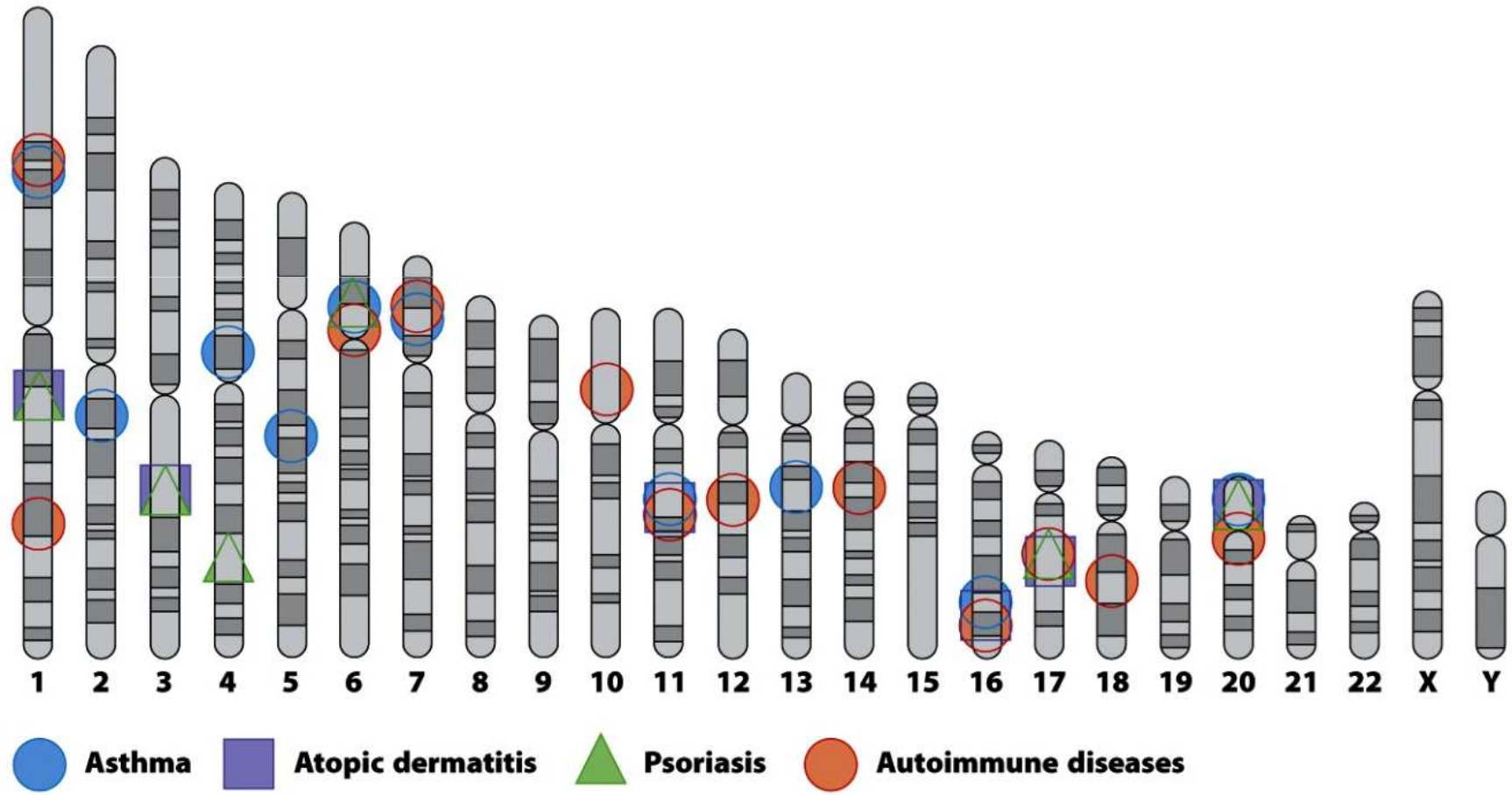


Phases of the allergic response

Immediate hypersensitivity

Genetic bases

Susceptibility loci



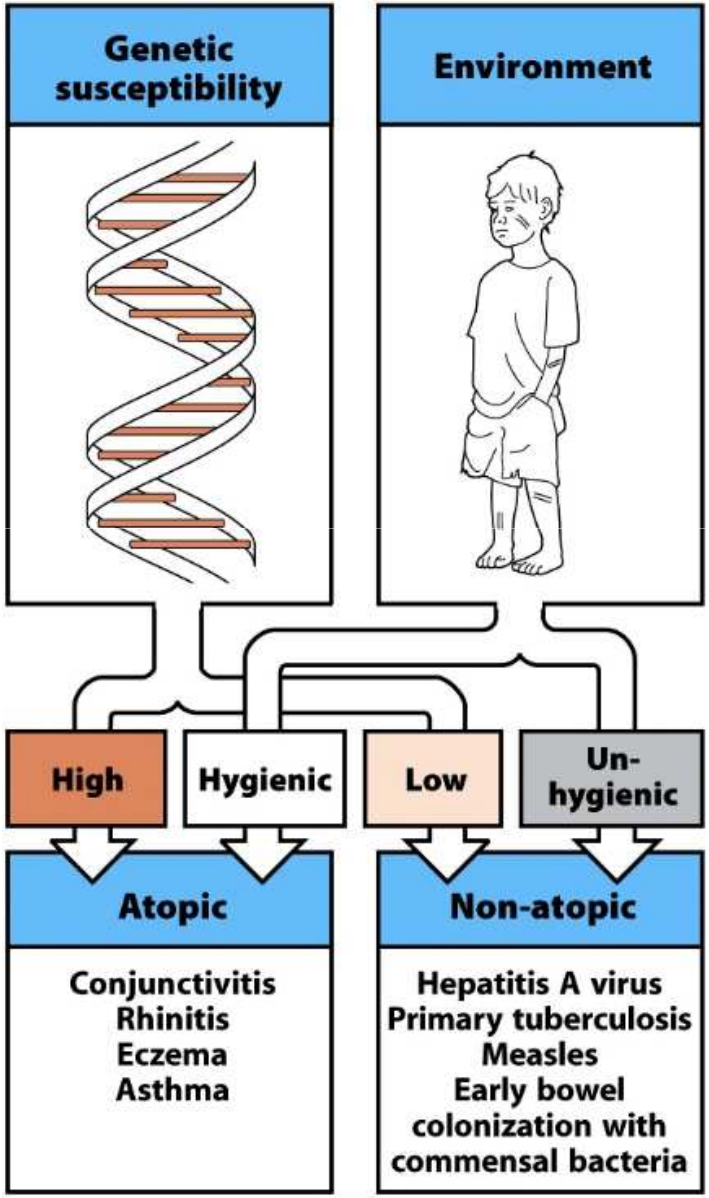
Candidate susceptibility genes

Gene	Nature of polymorphism	Possible mechanism of association
IL-4	Promoter variant	Variation in expression of IL-4
IL-4 receptor α chain	Structural variant	Increased signaling in response to IL-4
High-affinity IgE receptor β chain	Structural variant	Variation in consequences of IgE ligation by antigen
MHC class II genes	Structural variants	Enhanced presentation of particular allergen-derived peptides
T-cell receptor α locus	Microsatellite markers	Enhanced T-cell recognition of certain allergen-derived peptides
ADAM33	Structural variants	Variation in airway remodeling
β_2-Adrenergic receptor	Structural variants	Increased bronchial hyperreactivity*
5-Lipoxygenase	Promoter variant	Variation in leukotriene production†
TIM gene family	Promoter and structural variants	Regulation of the T_H1/T_H2 balance

Candidate susceptibility genes and location

Chromosomal location	Candidate genes	Putative role of gene products in disease
5q	Cytokine gene cluster (IL-4, IL-5, IL-13), CD14, β_2-adrenergic receptor	IL-4 and IL-13 promote IgE switching, IL-5 promotes eosinophil growth and activation; CD14 is a component of the LPS receptor which, via interaction with TLR4, may influence the balance between T_H1 vs. T_H2 responses to antigens; β2-adrenergic receptor regulates bronchial smooth muscle contraction
6p	Class II MHC	Some alleles may regulate T cell responses to allergens
11q	FcεRI β chain	Mediates mast cell activation
12q	Stem cell factor, interferon-γ, STAT6	Stem cell factor regulates mast cell growth and differentiation; interferon-γ opposes actions of IL-4; STAT6 mediates IL-4 signal transduction
16	IL-4 receptor α chain	Subunit of both IL-4 and IL-13 receptors
20p	*ADAM33*	Metalloproteinase involved in airway remodeling
2q	*DPP10*	Peptidase that may regulate chemokine and cytokine activity
13q	*PHF11*	Transcriptional regulator involved in B cell clonal expansion and Ig expression

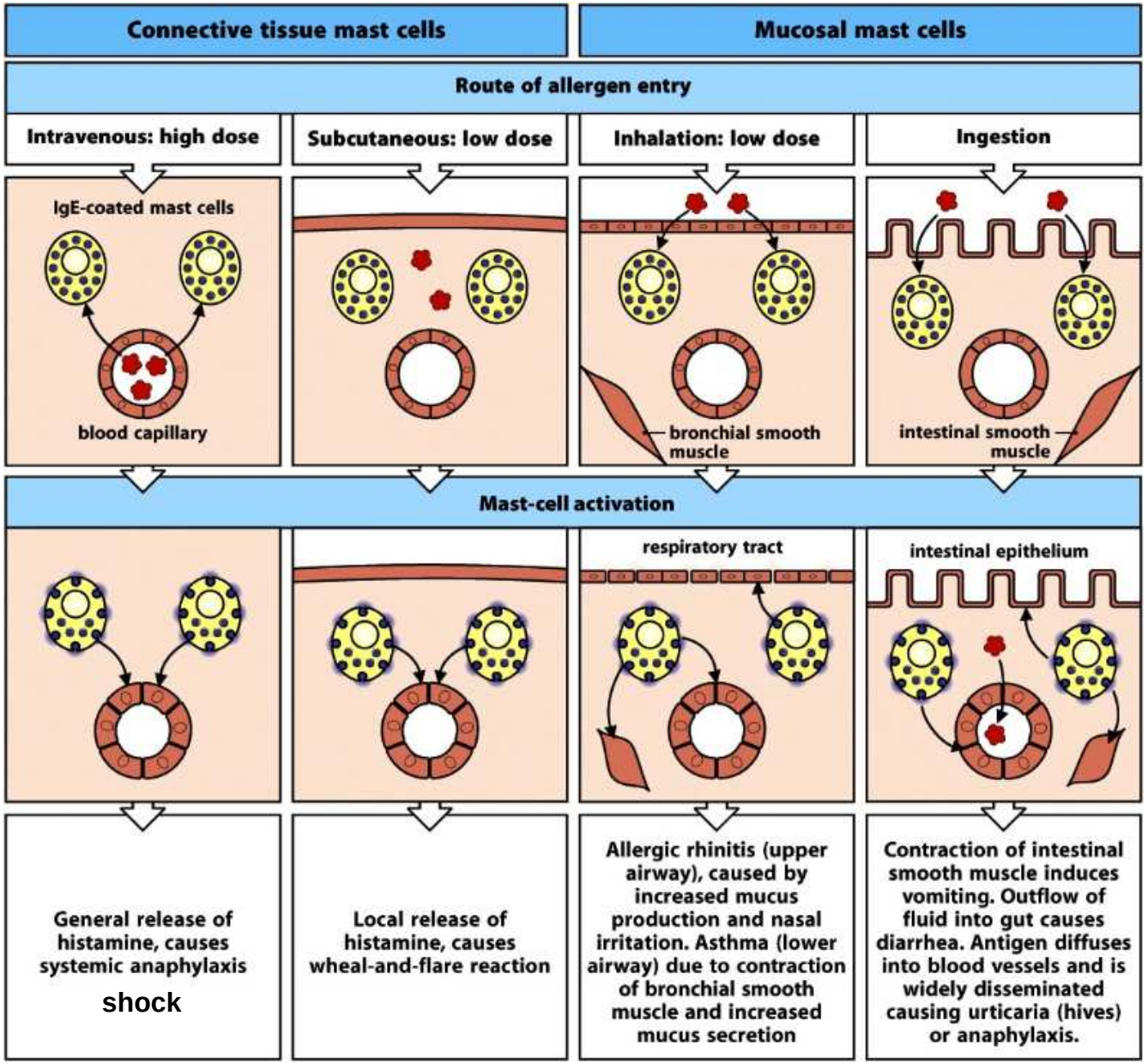
Role of environment



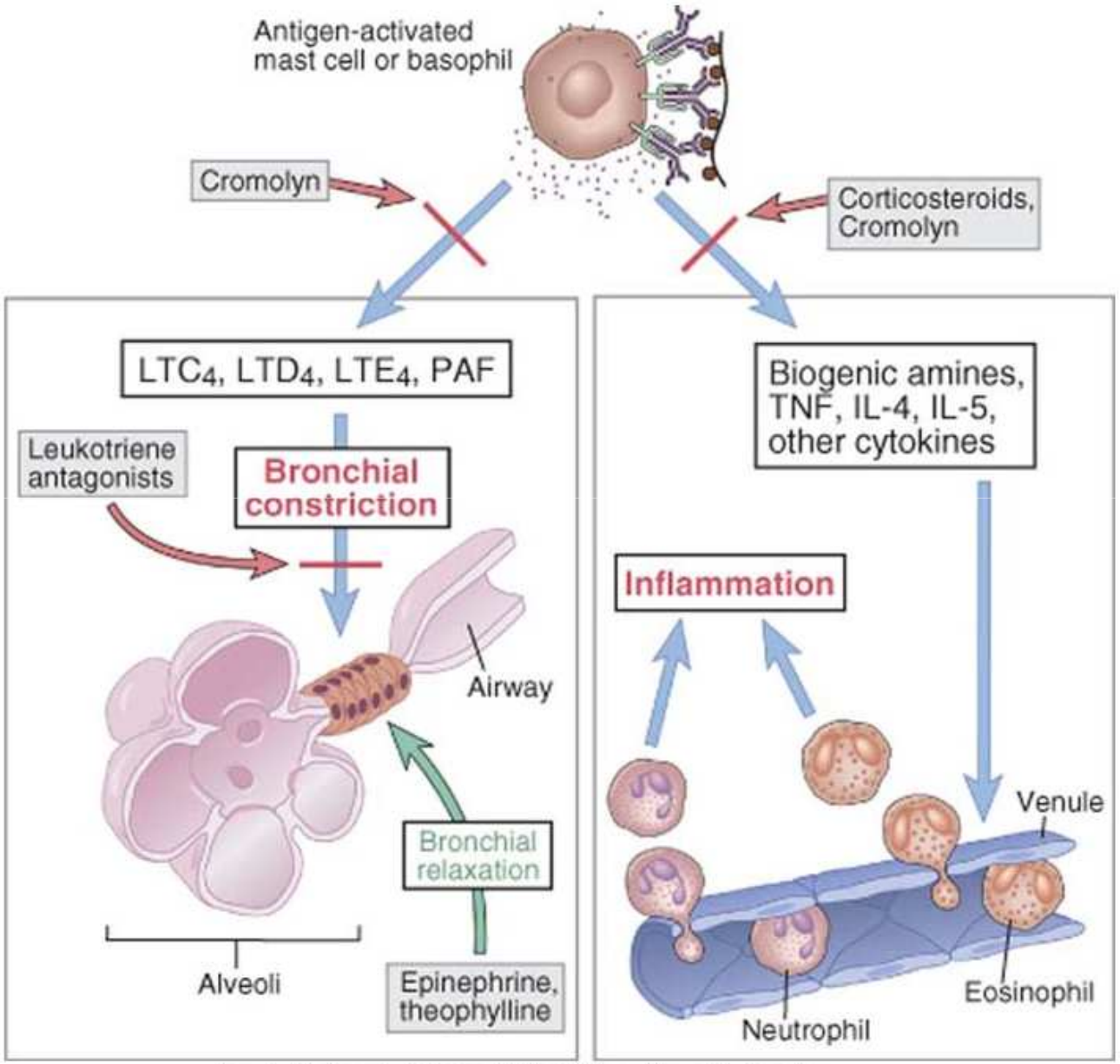
Immediate hypersensitivity

Clinical manifestations

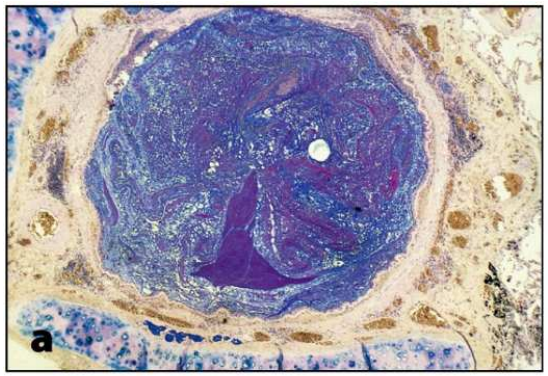
Symptoms depend on dose and route of allergen entry



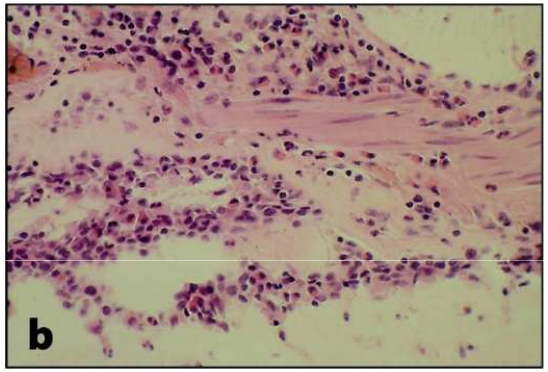
Athsma


Antigen-activated mast cell or basophil
Cromolyn
Corticosteroids, Cromolyn
LTC4, LTD4, LTE4, PAF
Leukotriene antagonists
Bronchial constriction
Airway
Bronchial relaxation
Alveoli
Epinephrine, theophylline
Biogenic amines, TNF, IL-4, IL-5, other cytokines
Inflammation
Venule
Eosinophil
Neutrophil

Pathological features of athsma



obstructed bronchus



infiltrated submucosa