Cihan University/ Sulaymaniyah

College of Health Science

Medical Laboratory Analysis

4th Stage- 1st Semester

Clinical Immunology

Lecture- 8: Allergy and Allergic Diseases

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Allergy and Allergic Diseases

- **Adaptive Immune Response:** Essential for defense against infections, but can cause allergic reactions to harmless antigens.
- **IgE Function:** Prominent in defense against parasites; causes allergic symptoms in developed nations.
- **Hypersensitivity Reactions:**
  - **Type I:** Immediate, IgE-mediated (e.g., hay fever).
  - **Type II:** IgG-mediated, complement activation.
  - **Type III:** IgG-mediated, FcR-bearing cell activation.
  - **Type IV:** Cellular effectors (e.g., lymphocytes, myeloid cells).
- **Sensitization:** Producing IgE antibodies against allergens (e.g., pollen, food, drugs).
- **Genetics and Atopy:** Genetic predisposition to IgE-mediated allergies; higher risk if both parents are atopic.

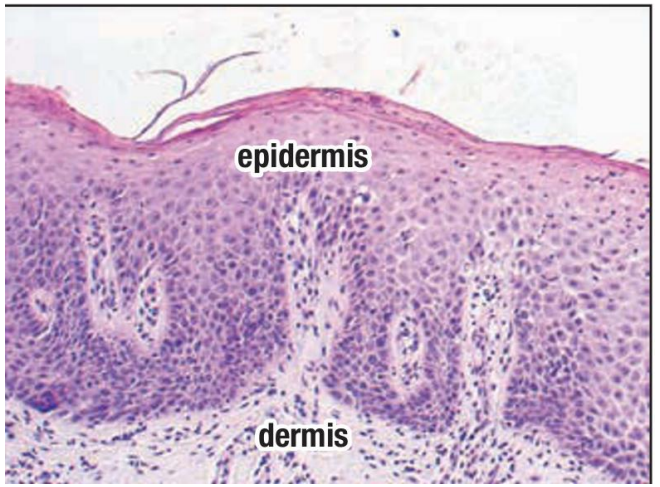
IgE-mediated allergic reactions			
Reaction or disease	**Common stimuli**	**Route of entry**	**Response**
Systemic anaphylaxis	Drugs Venoms Food, e.g., peanuts Serum	Intravenous (either directly or following absorption into the blood after oral intake)	Edema Increased vascular permeability Laryngeal edema Circulatory collapse Death
Acute urticaria (wheal-and-flare)	Post-viral Animal hair Bee stings Allergy testing	Through skin Systemic	Local increase in blood flow and vascular permeability Edema
Seasonal rhinoconjunctivitis (hay fever)	Pollens (ragweed, trees, grasses) Dust-mite feces	Contact with conjunctiva of eye and nasal mucosa	Edema of conjunctiva and nasal mucosa Sneezing
Asthma	Dander (cat) Pollens Dust-mite feces	Inhalation leading to contact with mucosal lining of lower airways	Bronchial constriction Increased mucus production Airway inflammation Bronchial hyperreactivity
Food allergy	Peanuts Tree nuts Shellfish Fish Milk Eggs Soy Wheat	Oral	Vomiting Diarrhea Pruritus (itching) Urticaria (hives) Anaphylaxis (rarely)

IgE and IgE-Mediated Allergic Diseases

- **Immediate Hypersensitivity Reactions:**
  - Caused by activation of mast cells and basophils.
  - Triggered by multivalent antigen bridging IgE on cell surfaces.
- **IgE Characteristics:**
  1. Predominantly localized in tissues.
  2. Tightly bound to mast cells and other cells via high-affinity IgE receptor (FcεRI).
  3. Cross-linking of IgE receptors by antigen leads to release of chemical mediators, causing allergic disease.
- **Understanding IgE Production:**
  - Initial antibody response to environmental antigens can become dominated by IgE in atopic individuals.
  - Factors contributing to this process are still being studied.

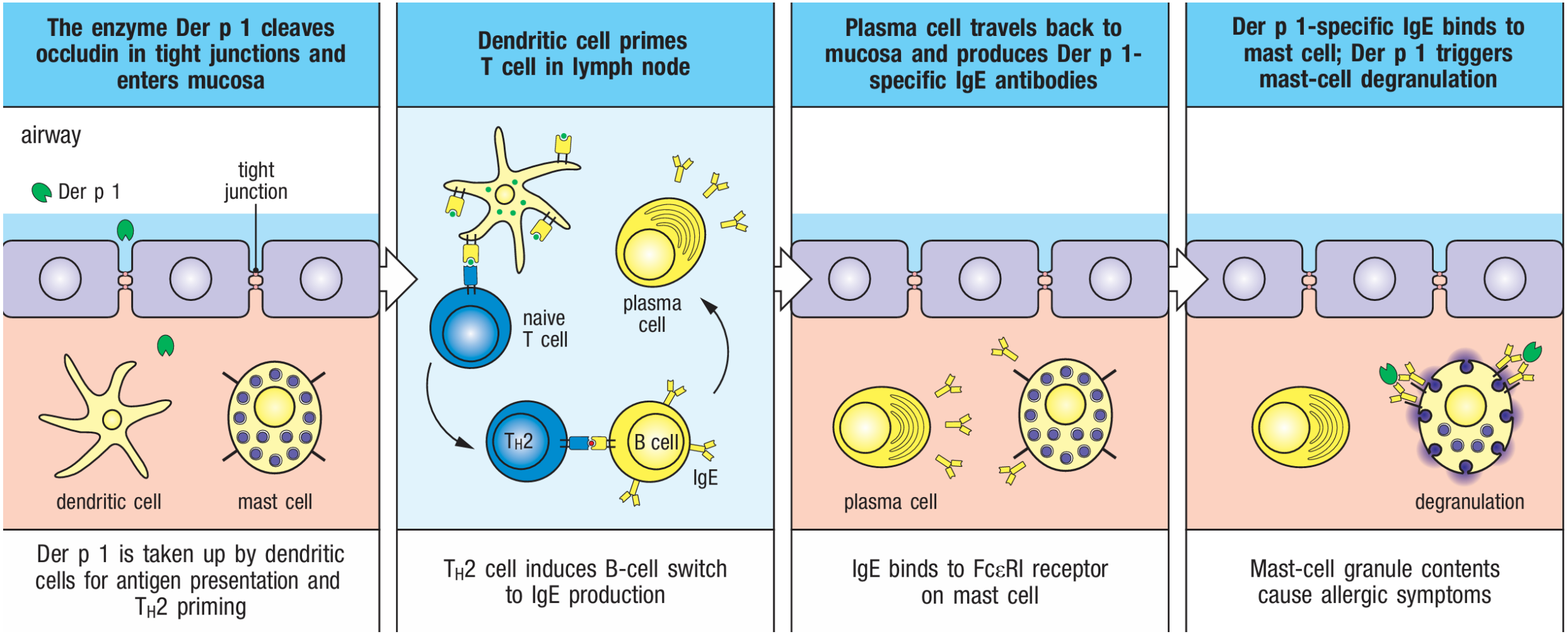
Allergens and Sensitization

- **Common Sensitizing Agents:**
  1. **Proteases:** Frequently cause allergic sensitization.
  2. **Airborne Allergens:** Small, highly soluble proteins (e.g., pollen, mite feces).
  3. **Contact with Mucosa:** Allergen eluted and picked up by dendritic cells.
- **Low-Dose Sensitization:**
  - Promotes strong TH2 response.
  - Minute doses provoke IgE responses in atopic individuals.
- **High-Dose Sensitization:**
  - Examples: Bee venom, food allergens.
  - Larger doses can also lead to sensitization.



Netherton's syndrome

Sensitization to an Inhaled Allergen

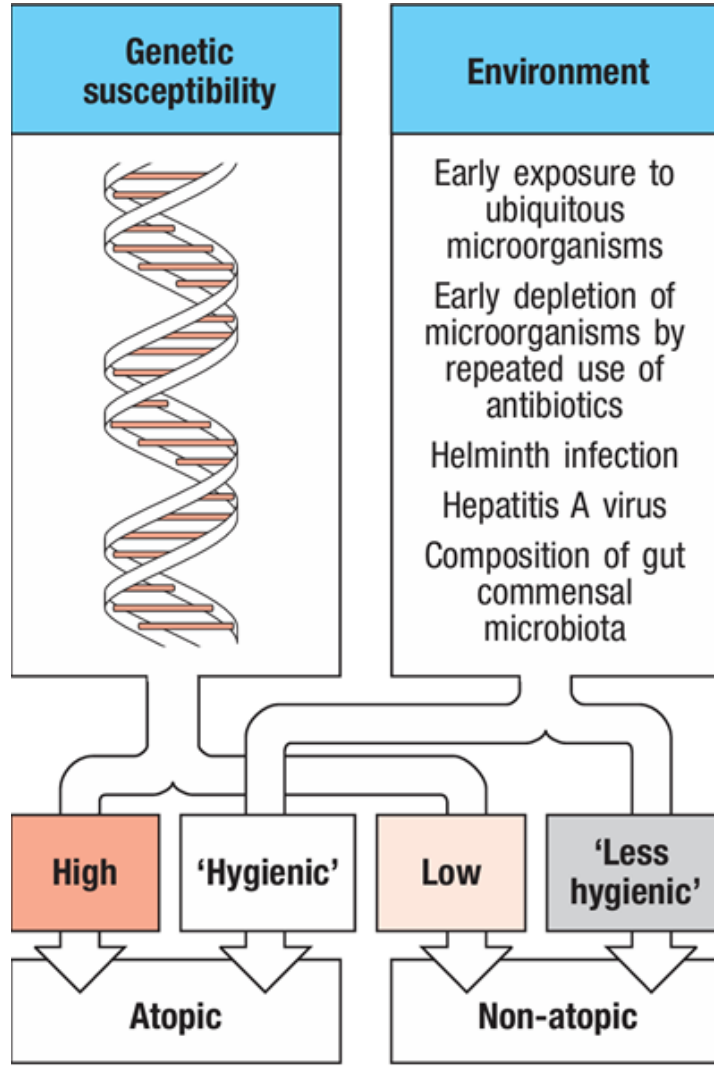


Genetic Factors in Allergic Diseases

- **Susceptibility to Allergic Disease:**
  - Influenced by both genetic and environmental components.
- **Atopy:**
  - Up to 40% of test populations in Western countries show heightened IgE responses.
  - Atopic individuals may develop allergic rhinoconjunctivitis, asthma, eczema (atopic triad).
- **Genome-Wide Association Studies (GWASs):**
  - Over 40 susceptibility genes identified for atopic eczema and allergic asthma.
  - Shared genetic risk alleles for IL-33 receptor and IL-13 loci.
  - Some genes regulate skin-barrier function, linked to atopic eczema.
- **Ethnic Differences:**
  - Variations in susceptibility genes among different ethnic groups.

Environmental and Genetic Factors in Allergic Disease

- **Key Interactions:**
  - Both environmental and genetic factors contribute to the risk of developing atopy (~50% each).
- **Increasing Prevalence:**
  - Higher rates of atopic allergic diseases and asthma in economically advanced regions.
  - Lower incidence in underdeveloped regions, but increased frequency in individuals of African ancestry in the U.S.
- **Hygiene Hypothesis:**
  - Reduced early-life exposure to infections and microorganisms due to urbanization.
  - Potential alteration of intestinal microbiota affecting immune responses.
  - Suggests decreased exposure to common microbes impairs Treg cell production, increasing allergy risk.



Environmental and Genetic Factors in Allergic Disease- cont.

Protective Factors:

- Early exposure to infections (excluding some respiratory infections) appears protective.
- Greater exposure from siblings, daycare, farms, and pets reduces atopy and asthma risk.
- Early gut colonization by commensal bacteria linked to reduced allergy prevalence.

Risk Factors:

- Repeated early-life antibiotic exposure increases asthma risk.
- RSV infections in early childhood linked to higher asthma risk later on.
- Environmental pollutants (e.g., diesel exhaust, ozone) can exacerbate allergic responses, especially in genetically susceptible individuals (e.g., GSTP1, GSTM1 variants).

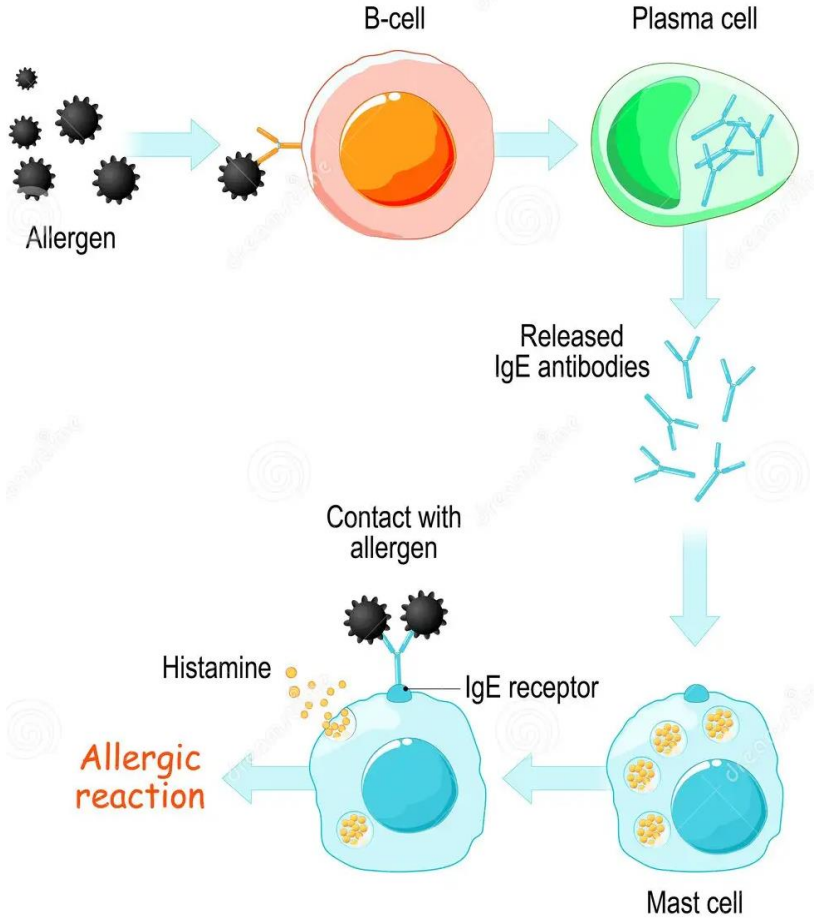
Regulatory T Cells in Controlling Allergic Responses

- **Treg Cell Dysfunction in Atopy:**
  - **Abnormal Type 2 Responses:** Atopic individuals' leukocytes produce substantial TH2 cytokines upon stimulation.
  - **Impaired Suppression:** Treg cells from atopic individuals are less effective at suppressing TH2 cytokine production.
- **Potential Therapeutic Targets:**
  - **Enhancing Treg Function:** Beneficial for asthma and other atopic disorders.
- **Immunoregulatory Molecules:**
  - **IL-35 and IL-27:** Inhibit TH2 responses.
  - **IL-10:** Known suppressor of TH2 and TH17 responses.
  - **Blocking IL-31:** Potentially reduces TH2-driven inflammation.

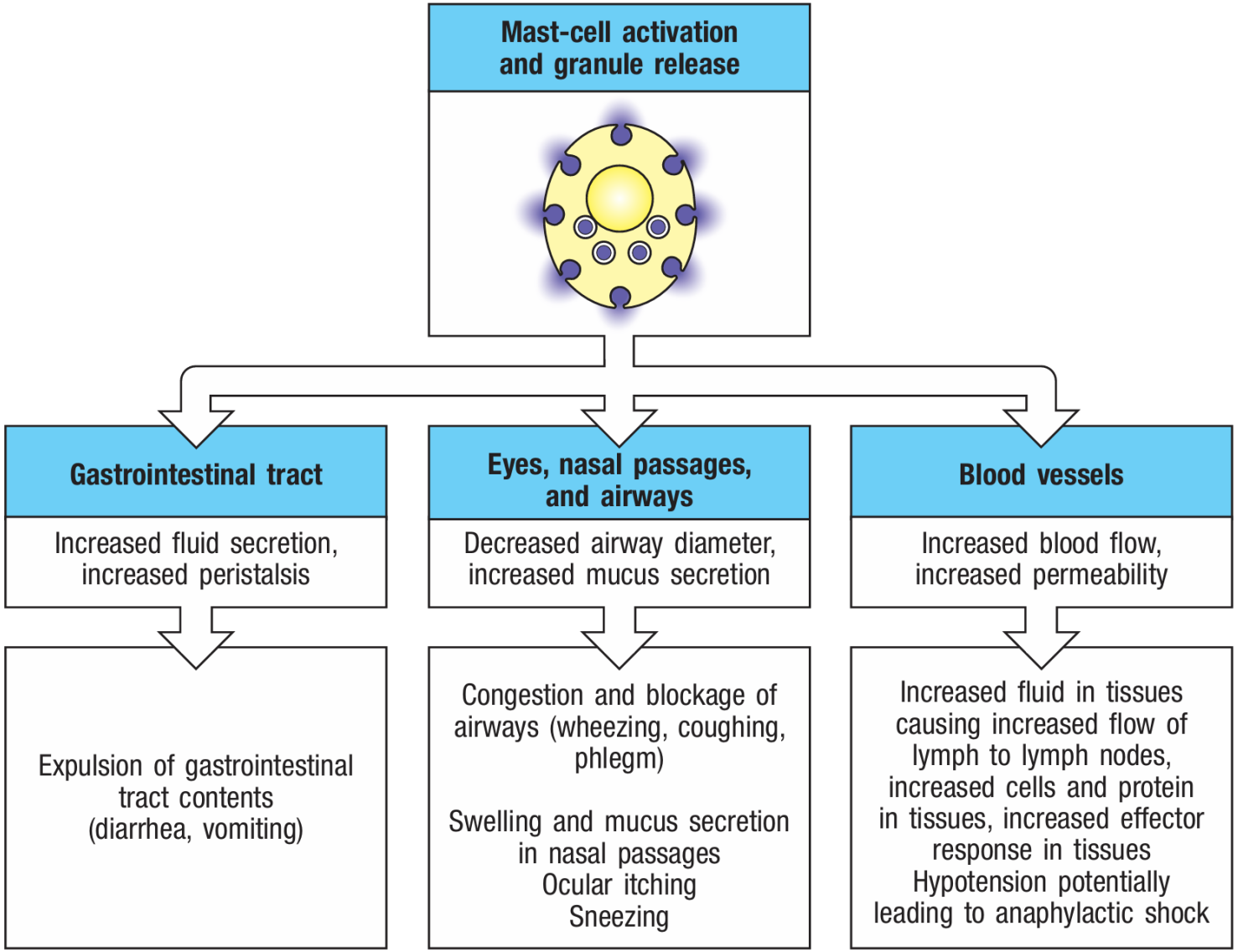
Effector Mechanisms in IgE-Mediated Allergic Reactions

- **Cross-Linking of IgE:** Allergens cross-link preformed IgE on FcεRI receptors of mast cells.
- **Mast Cell Location:** Line external mucosal surfaces to alert immune system to infections.
- **Mediator Release:**
  - **Preformed Granules:** Histamine release.
- **Synthesized Mediators:** Prostaglandins, leukotrienes, platelet-activating factor.
- **Cytokines and Chemokines:** Released upon activation.
- **Dependent on Dose and Route:**
  1. **Swollen Eyes and Rhinitis:** Contact with pollen.
  2. **Anaphylaxis:** Life-threatening circulatory collapse.
- **Sustained Inflammation:**
- **Recruitment of Effector Leukocytes:**
  1. TH2 Lymphocytes
  2. Eosinophils
  3. Basophils

Activation Process



Mast-cell Activation has Different Effects on Different Tissues



Mast Cells: Orchestrators of Allergic Reactions

- **Activation and Degranulation:**
  - Cross-Linking of IgE on FcεRI: Triggers degranulation with low levels of allergen.
- **Release of Mediators:** Preformed (histamine, serine proteases) and newly synthesized (prostaglandins, leukotrienes).
- **Histamine and its Receptors (H1-H4):**
  1. H1: Increases blood flow, vessel permeability, causes itching, sneezing.
  2. H2, H3, H4: Involved in atopic dermatitis, chronic urticaria, and autoimmune disorders.
- **Mediator Functions:**
  1. Prostaglandins: Recruit TH2 cells, eosinophils, basophils; linked to asthma.
  2. Leukotrienes: Sustain inflammatory responses.
  3. TNF-α: Activates endothelial cells, promotes leukocyte influx.

Eosinophils and Basophils in Allergic Reactions

- **Interaction and Regulation:**
- **Cross-Talk:**
  - Eosinophil degranulation triggers mast cell and basophil activation.
  - Regulated by cytokines (IL-3, IL-5, GM-CSF).
- **Role in Allergic Responses:**

A. Eosinophils:

- Accumulate and activate in allergic reactions (e.g., chronic asthma).
- Promote TH2 cell expansion, contribute to tissue damage.

B. Basophils:

- Enhance allergic inflammation through mediator release.

IgE-Mediated Allergic Reactions: Immediate and Chronic Responses

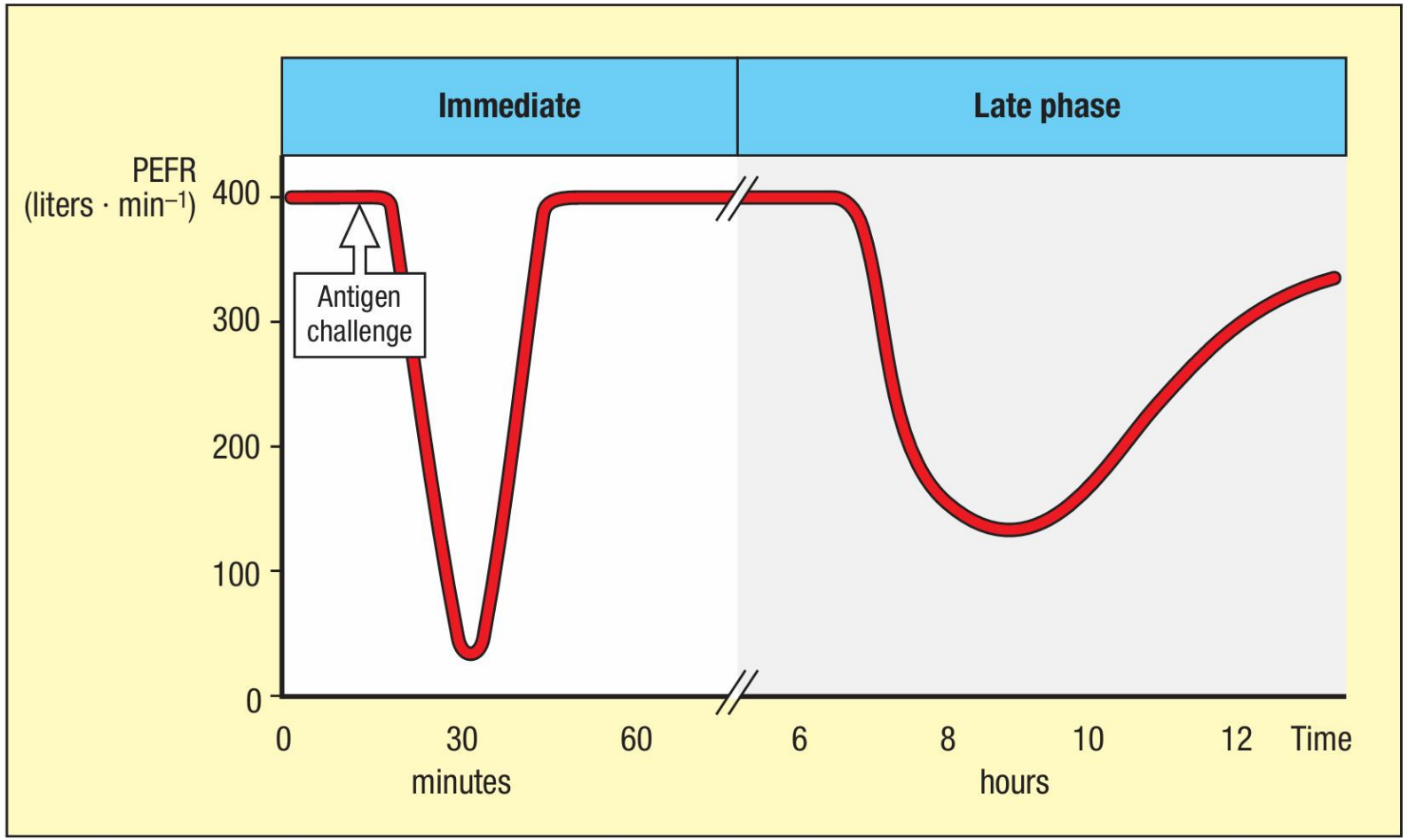
Immediate Reaction:

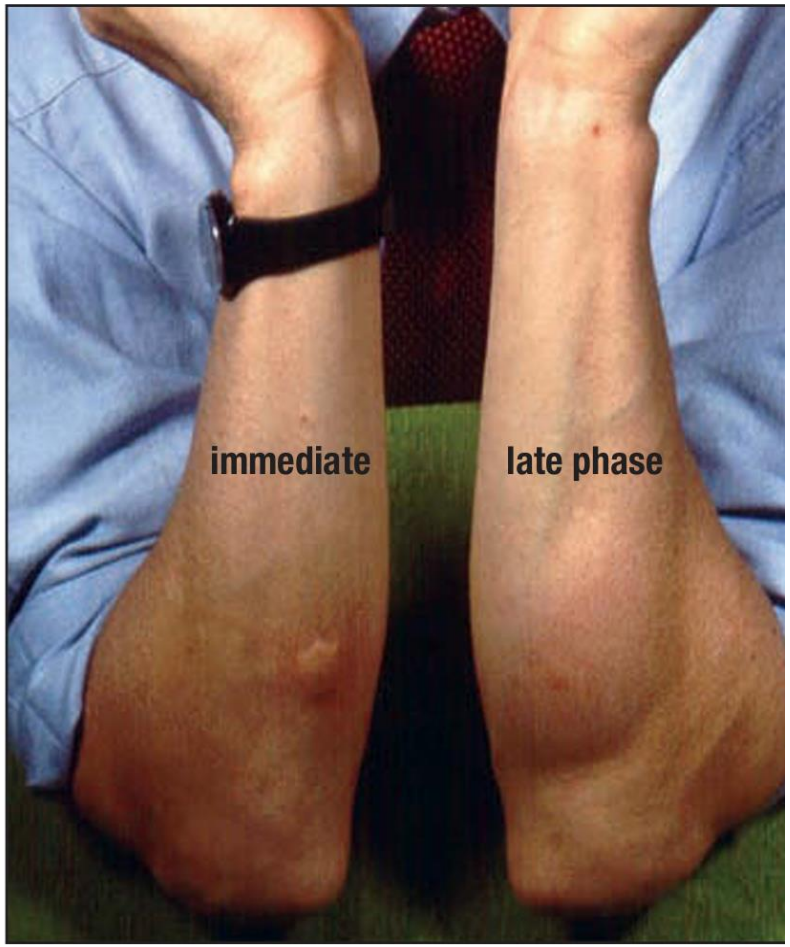
- **Onset:** Within minutes of allergen exposure.
- **Mediators Involved:**
  - Histamine, prostaglandins, other preformed or rapidly synthesized mediators from mast cells. These result in vascular permeability, edema, reddening of the skin, airway narrowing.
- **Symptoms:**
  - Wheal-and-Flare Reaction: Local blood vessel permeability, fluid extravasation, edema.

Late-Phase Reaction:

- **Onset:** Peaks between 3-9 hours after antigen challenge.
- **Mediators Involved:**
  - Continued synthesis and release of inflammatory mediators.
  - Vasodilation, vascular leakage, edema, recruitment of eosinophils, basophils, monocytes, and lymphocytes.
- **Treatment: Glucocorticoids inhibit cell recruitment, blocking late-phase response but not immediate reaction.**

Allergic Reactions in Response to Test Antigens



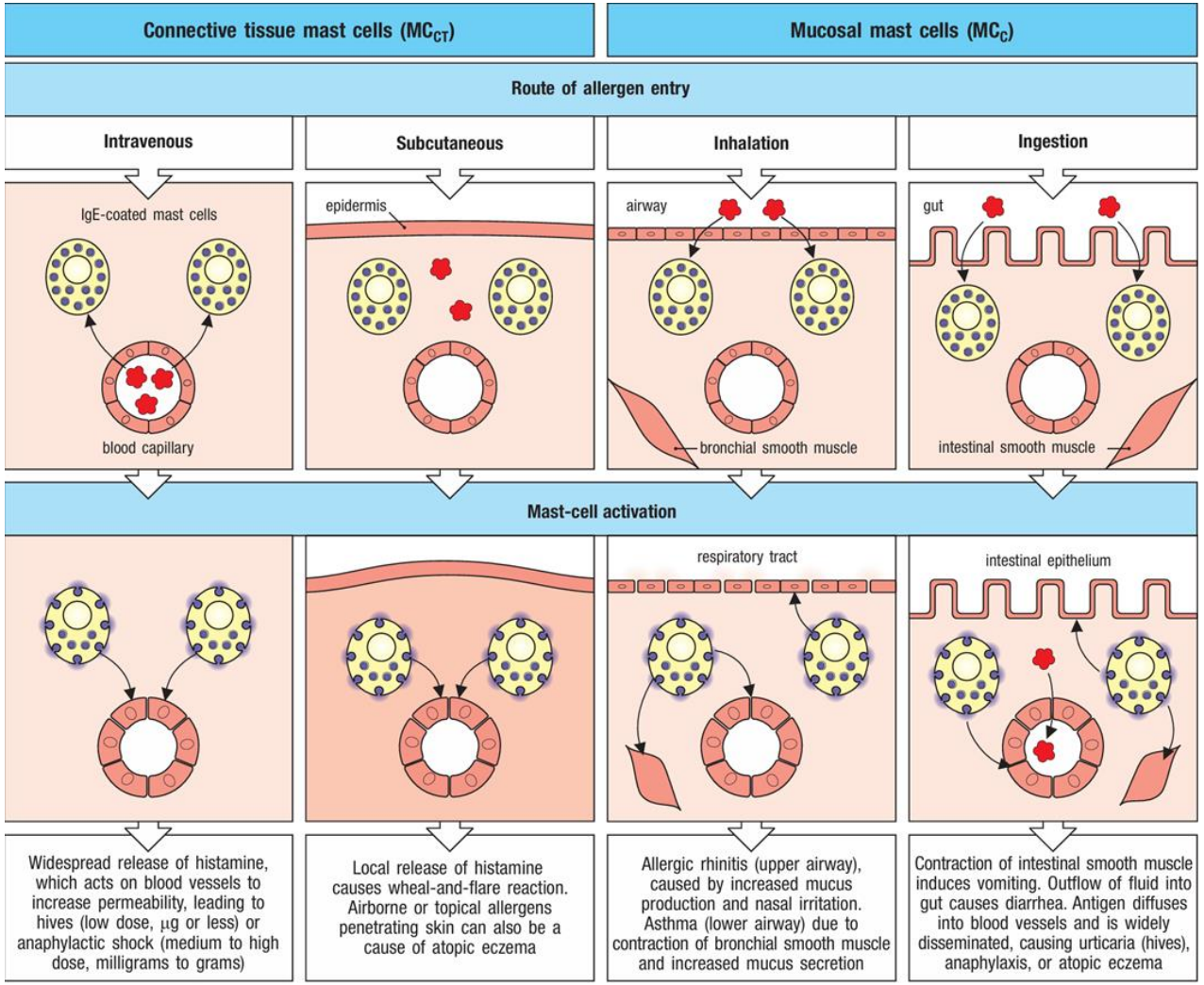


Chronic Allergic Inflammation

- **Long-Term Consequence:**
  - Persistent type 2 immune response driven by TH2 lymphocytes, basophils, eosinophils, and macrophages.
  - Seen in conditions like chronic asthma.
- **Effects:**
  - Persistent edema, airway narrowing.
  - Airway tissue remodeling: Smooth muscle hypertrophy, subepithelial collagen deposition, goblet cell hyperplasia.
- **Allergy Testing:**
  - Skin prick tests to assess sensitization.
  - Measurement of circulating IgE antibodies specific to allergens.
- **Variable Outcomes:**
  - Dependent on IgE levels, route of allergen introduction, dose, and tissue/organ barrier function.

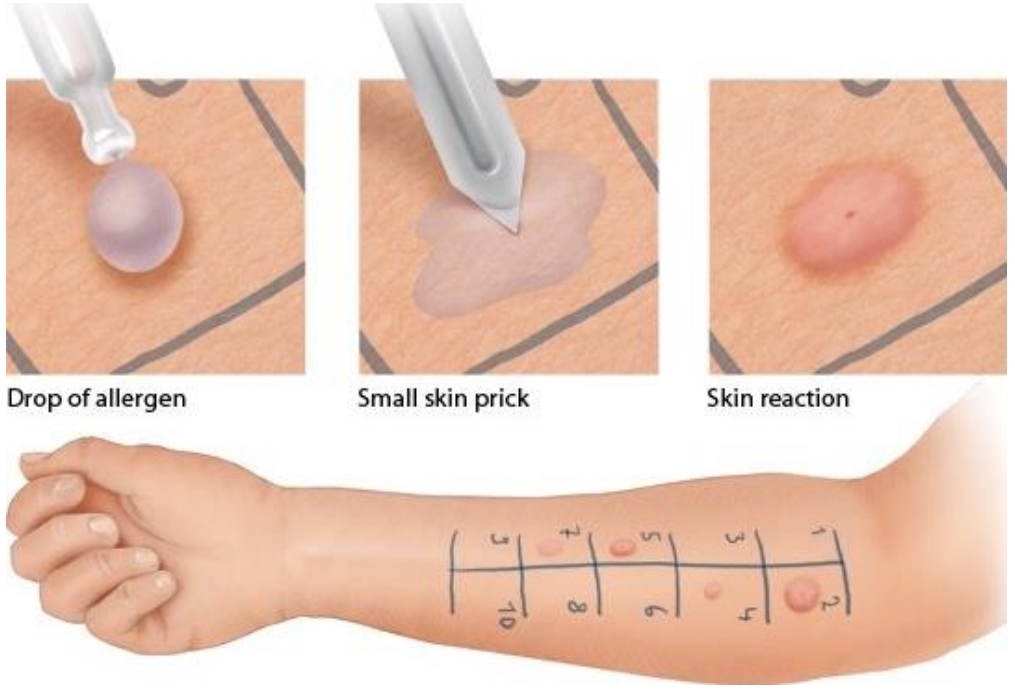
Anaphylaxis: Systemic Allergic Reaction

- **Causes:**
- **Bloodstream Introduction:**
  - Bee or wasp sting, rapidly absorbed allergens.
  - Connective-tissue mast cells activate, releasing histamine and mediators.
- **Common Triggers:**
  - Wasp and bee stings, medications, food allergens (e.g., peanuts).
- **Range:**
  - Mild urticaria (hives) to fatal anaphylactic shock.
- **Acute Urticaria:**
  - Histamine causes itchy, red swellings.
- **Anaphylactic Shock:**
  - Vascular permeability, smooth muscle contraction.
  - Hypotensive shock, respiratory failure.



Mechanism; Anaphylaxis: Systemic Allergic Reaction

- **IgE-Mediated Reaction:**
  - Autoantibodies against FcεRI or IgE can cause chronic urticaria.
  - Omalizumab (anti-IgE antibody) treatment can resolve hives.
- **Massive Mediator Release:**
  - Histamine, leukotrienes lead to severe symptoms.
- **Treatment:**
- **Epinephrine (Adrenaline):**
  - Immediate injection, relaxes airway smooth muscles, reverses cardiovascular effects.
- **Avoidance:**
  - Careful history to avoid known allergens.
  - Skin-prick testing for penicillin or β-lactam antibiotics.
- **Penicillin Allergy:**
  - Acts as a hapten, forming conjugates with self proteins.
- **Intravenous Injection:** Can cross-link IgE, causing anaphylaxis.
- **Testing:**
  - Skin-prick test for risk assessment.



Allergen Inhalation and Respiratory Allergies

- **Respiratory Allergen Entry:**
  - Common route for airborne allergens like pollens.
  - Leads to IgE-mediated allergic reactions.
- **Allergic Rhinitis:**
  - Activation of mucosal mast cells beneath nasal epithelium.
  - **Symptoms:** Intense itching, sneezing, blocked nasal passages, nasal discharge rich in eosinophils.
  - **Common allergens:** Seasonal pollens (grass, tree, ragweed), fungi spores, cat dander, house dust mites, cockroach feces.
- **Allergic Conjunctivitis:**
  - Similar reaction to allergens on the eye's conjunctiva.

Allergic Asthma

- Triggered by allergen-induced activation of submucosal mast cells in lower airways.
- **Symptoms:** Bronchial constriction, increased fluid and mucus secretion, breathing difficulties.
- Can lead to severe, life-threatening attacks.
- Chronic exposure causes airway hyperreactivity and remodeling, leading to permanent narrowing.
- **Chronic Inflammation in Asthma:**
  - Persistent presence of lymphocytes, eosinophils, neutrophils, basophils.
  - Results in thickening of airway walls, hyperplasia, fibrosis, and mucus secretion.
  - Various asthma endotypes: Allergic asthma, exercise-induced, neutrophil-predominant, steroid-resistant.
- **Asthma Exacerbation:**
  - Viral infections (rhinovirus), environmental irritants (cigarette smoke, sulfur dioxide) worsen symptoms.
  - Increased IL-25, IL-33 release, activating ILC2s and chronic inflammation.

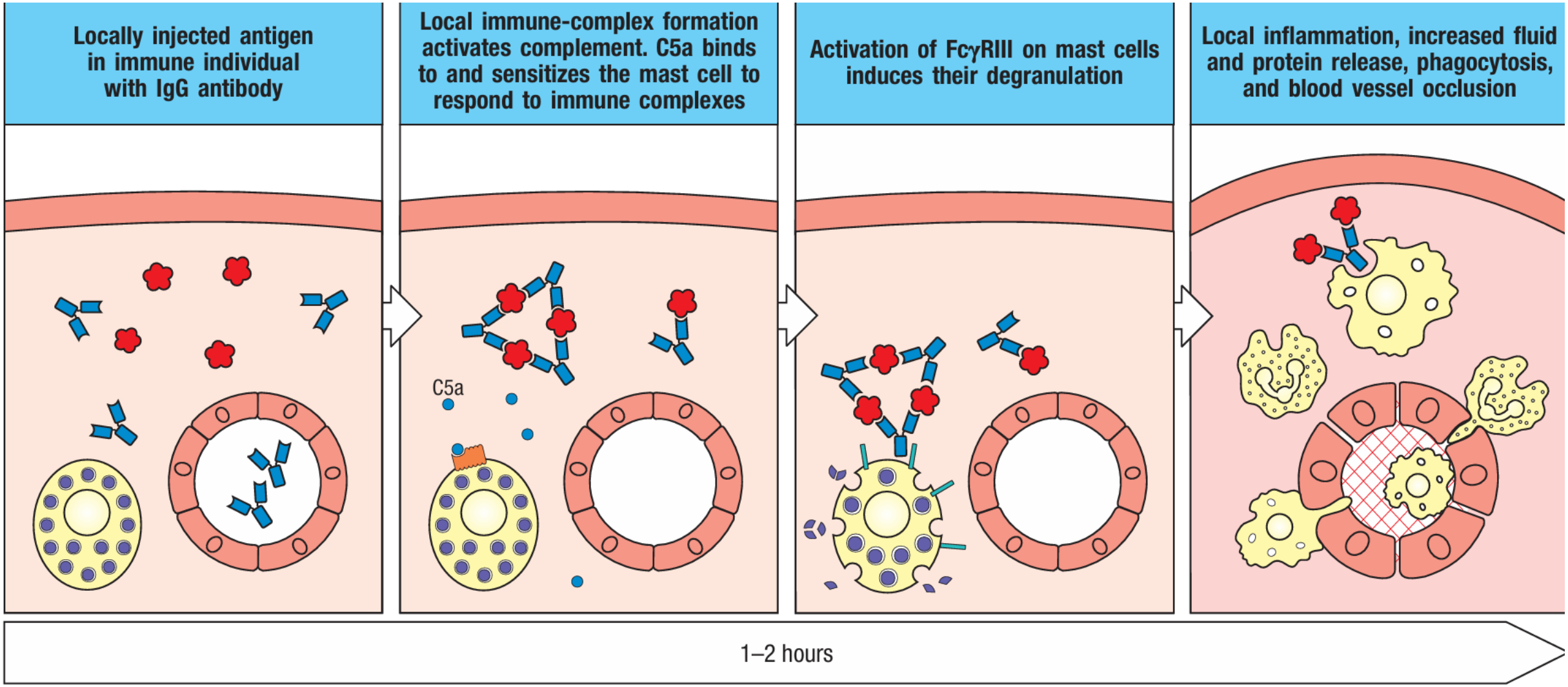
Food Allergies: Symptoms and Systemic Reactions

- **IgE-Mediated Food Allergies:**
  - Swelling of lips and oral tissue, gastrointestinal cramping, diarrhea, vomiting.
  - Systemic reactions: Urticaria, asthma, systemic anaphylaxis.
- **Non-IgE-Mediated Food Allergy:** Example - Celiac disease.
- **Food Intolerances:** Nonimmune, metabolic deficits (e.g., lactose intolerance).
- **Prevalence:**
  - ~5% of children, with peanut allergy being significant.
- **Risk Factors:**
  - Severe eczema in infants increases risk.
  - Introduction of allergen in diet may reduce allergy incidence.
- **Severe Reactions:**
- **Anaphylaxis:** Commonly caused by peanuts, tree nuts, shellfish.
- **Early Introduction:** Feeding peanuts to at-risk infants can reduce allergy risk.
- **Resistance to Digestion:** Food allergens resist pepsin digestion, reach intestines intact.
- **Medication Impact:** Antacids or proton-pump inhibitors may impair digestion, increasing allergy risk.

Non-IgE-Mediated Allergic Diseases

- **Immunological Hypersensitivity:**
  - Involves IgG antibodies, TH1 or TH17 cells, or CD8 T cells.
  - Can produce acute or chronic allergic reactions.
- **Drug-Induced Hypersensitivity:**
- **Mechanism:**
  - Drugs bind to circulating blood cells.
  - Antibody-mediated destruction (e.g., hemolytic anemia, thrombocytopenia) by anti-drug IgG antibodies.
- **Examples:** β-lactam antibiotics like penicillin and cephalosporin.
- **Immune-Complex Formation:**
- **Pathogenesis:**
  - Occurs with large quantities of poorly catabolized antigens.
  - Deposition in tissues causes inflammation and tissue injury.
- **Conditions:**
  - Arthus reaction: Local inflammation in sensitized individuals.
  - Serum sickness: Systemic reaction to injected foreign antigen (e.g., horse serum, monoclonal antibodies).

Non-IgE-Mediated Allergic Diseases



TH1 and CD8 T Cell-Mediated Hypersensitivity Reactions

- **Types:**
  1. Delayed-Type Hypersensitivity (DTH)
  2. Allergic Contact Dermatitis
- **Mechanism:**
- **TH1 Cells:**
  - Recognize peptide:MHC class II complexes.
  - Release cytokines (IFN-γ, TNF-α) to stimulate inflammation.
- **CD8 T Cells:**
  - Recognize intracellular haptenated peptides presented by MHC class I.
  - Cause damage by killing cells or secreting cytokines.
- **Examples:**
  - Mantoux Test: Determines prior exposure to Mycobacterium tuberculosis.
  - Poison Ivy: CD8 T cell response to urushiol oil.
- **Symptoms:**
  - Erythema, swelling, dermal and epidermal infiltrate, vesicles.

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