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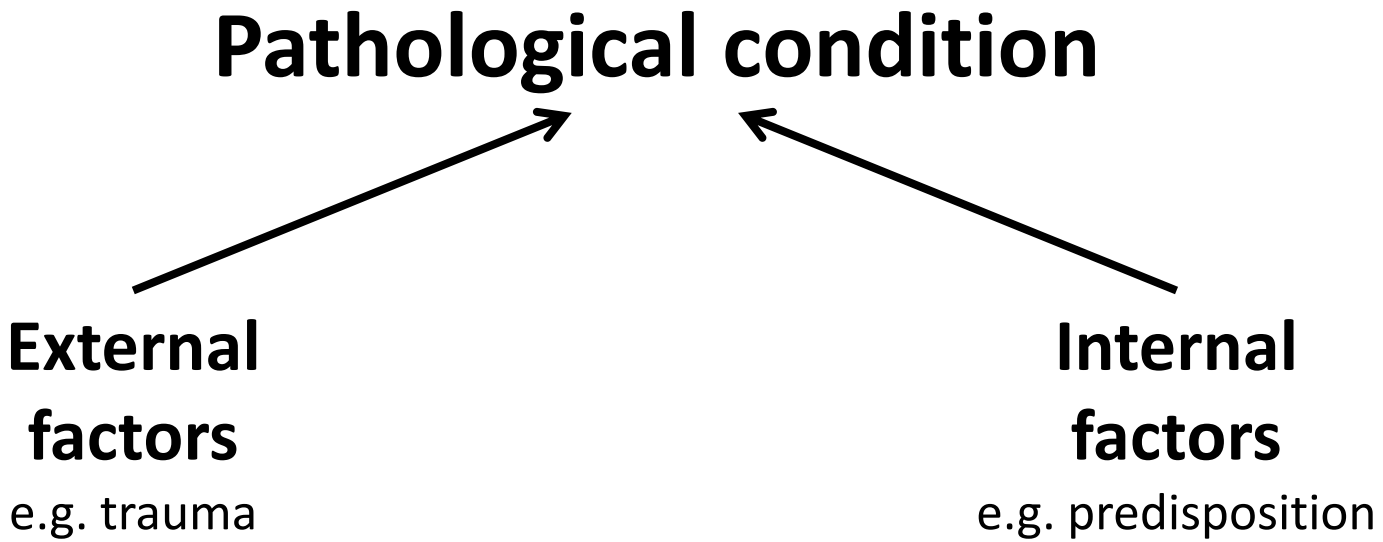
Anaphylactic reaction

Canonical concept of pathophysiology



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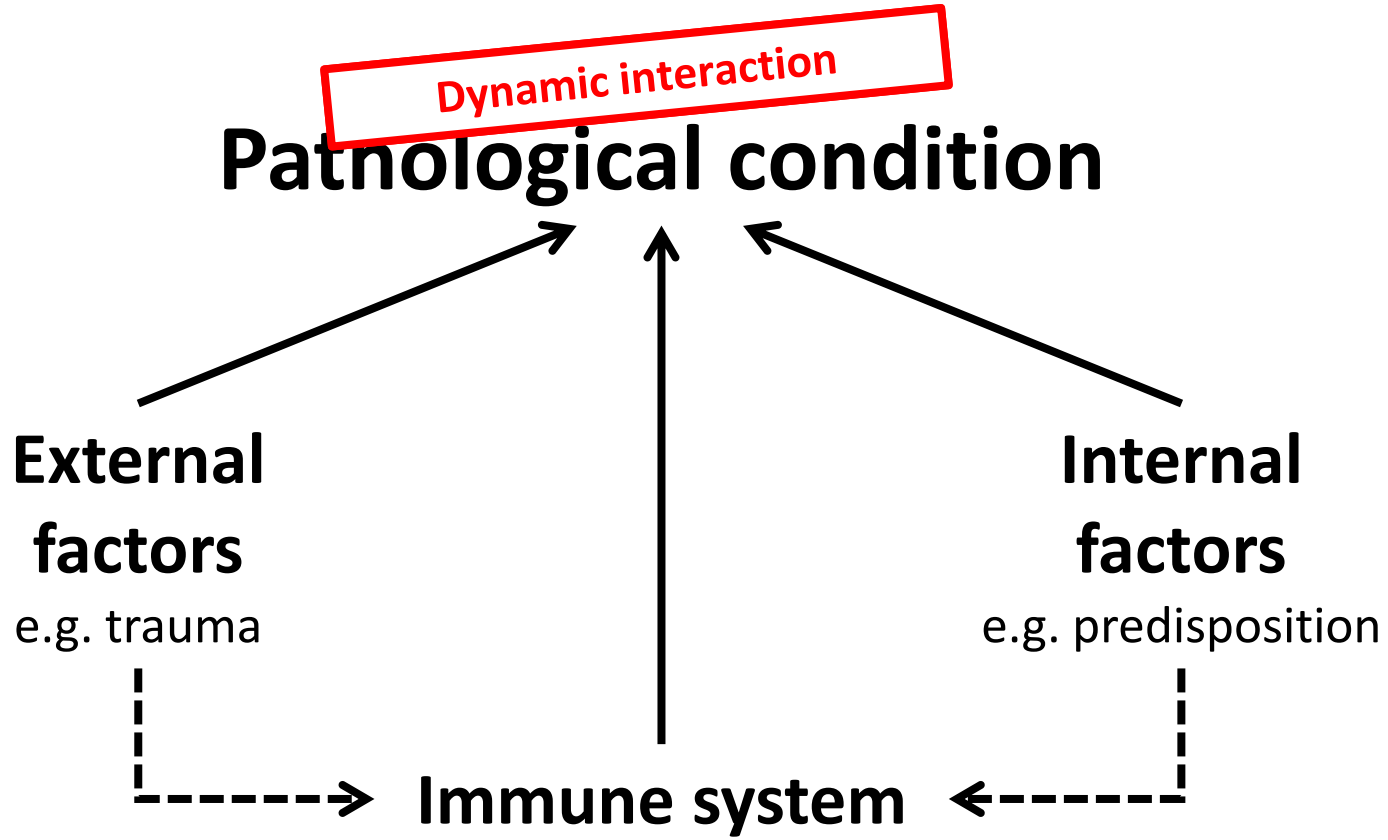
“Updated”concept of pathophysiology



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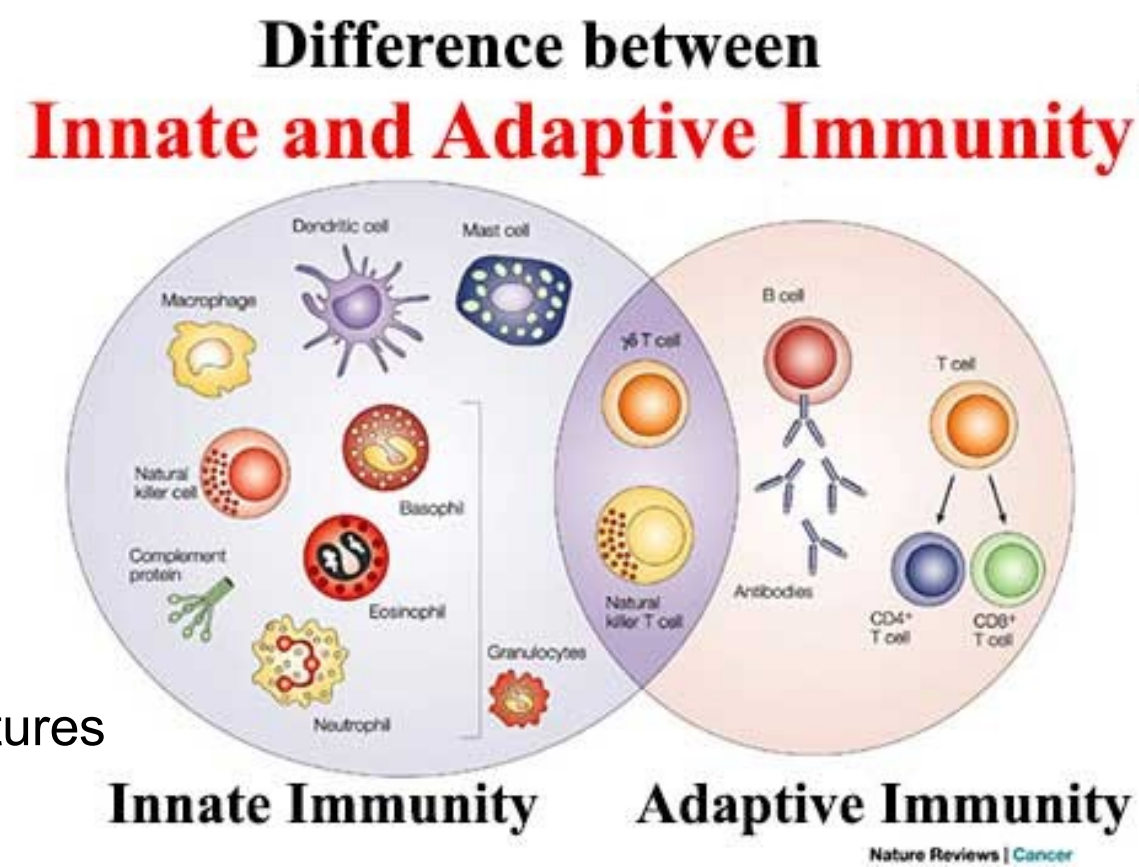
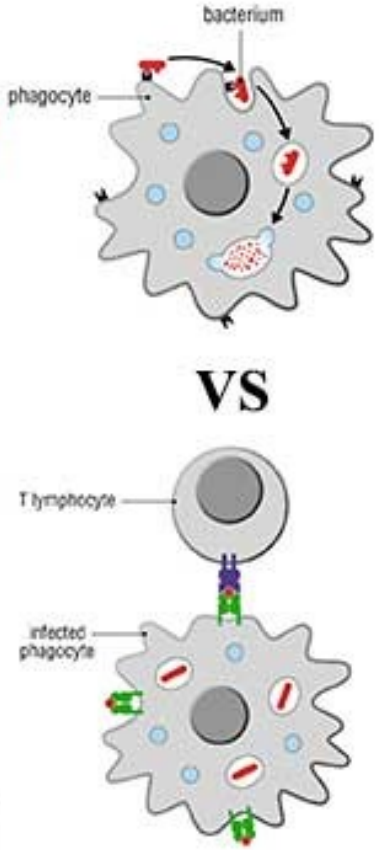
Immunity

- Innate
  - Non-specific
  - The first line of defense
  - Universal tool
    (pathogen, tissue damage)
- Adaptive, acquired
  - Specific
  - The second line of defense
  - Defense against non-self structures
    (pathogen, tumor cells)
  - Only in vertebrates





https://microbiologyinfo.com/difference-between-innate-and-adaptive-immunity/

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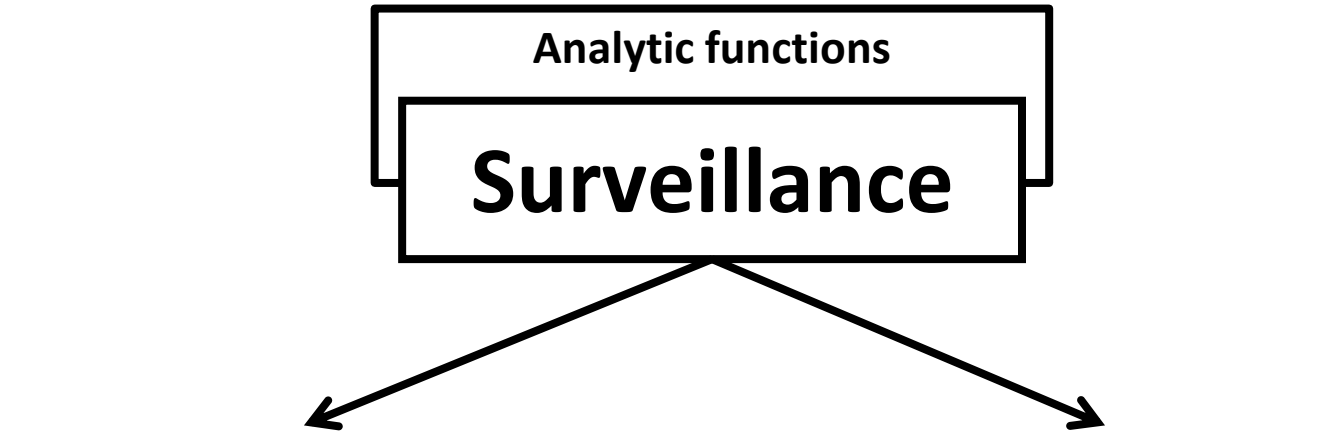
Innate immunity



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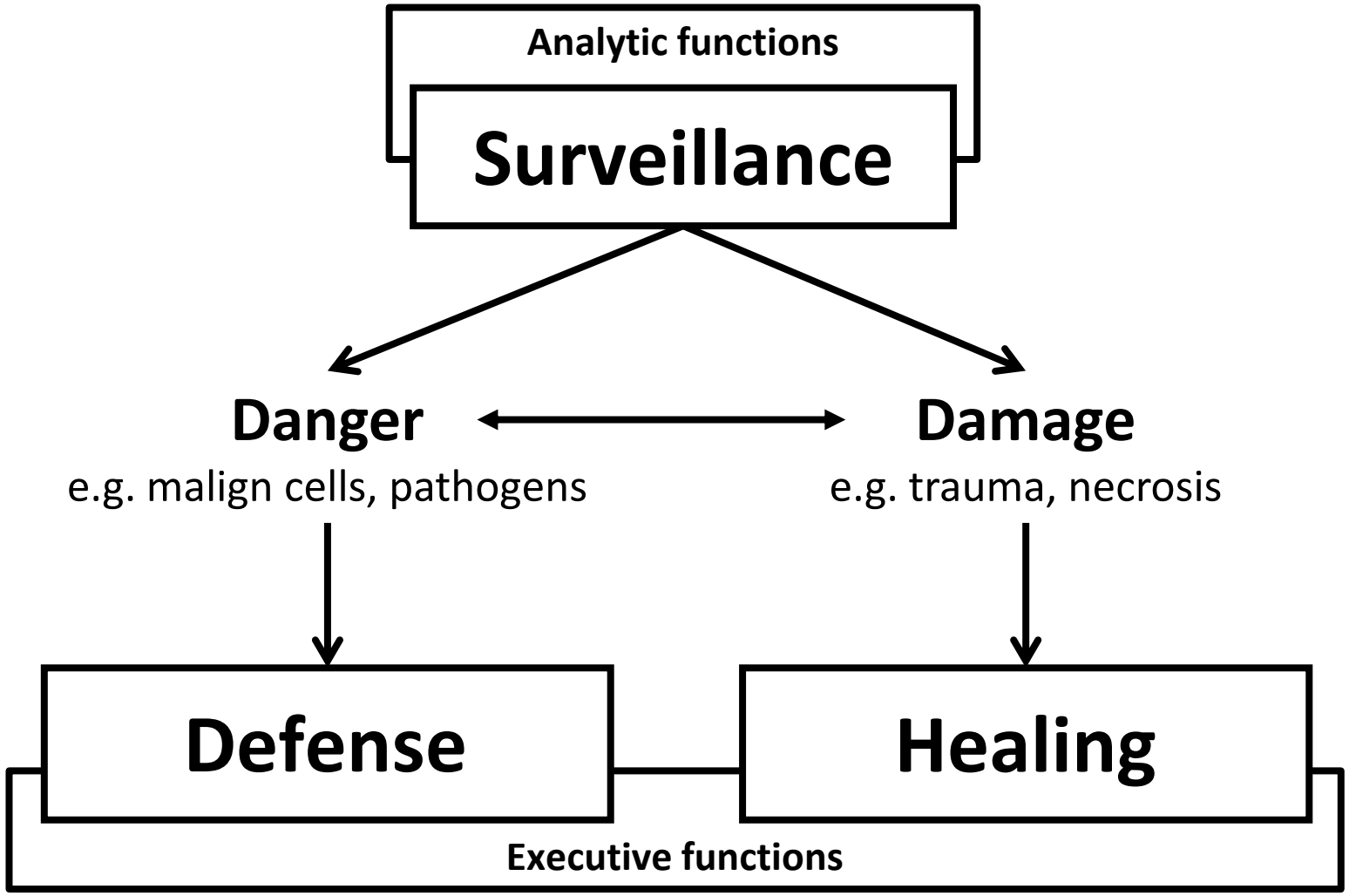
Innate immunity



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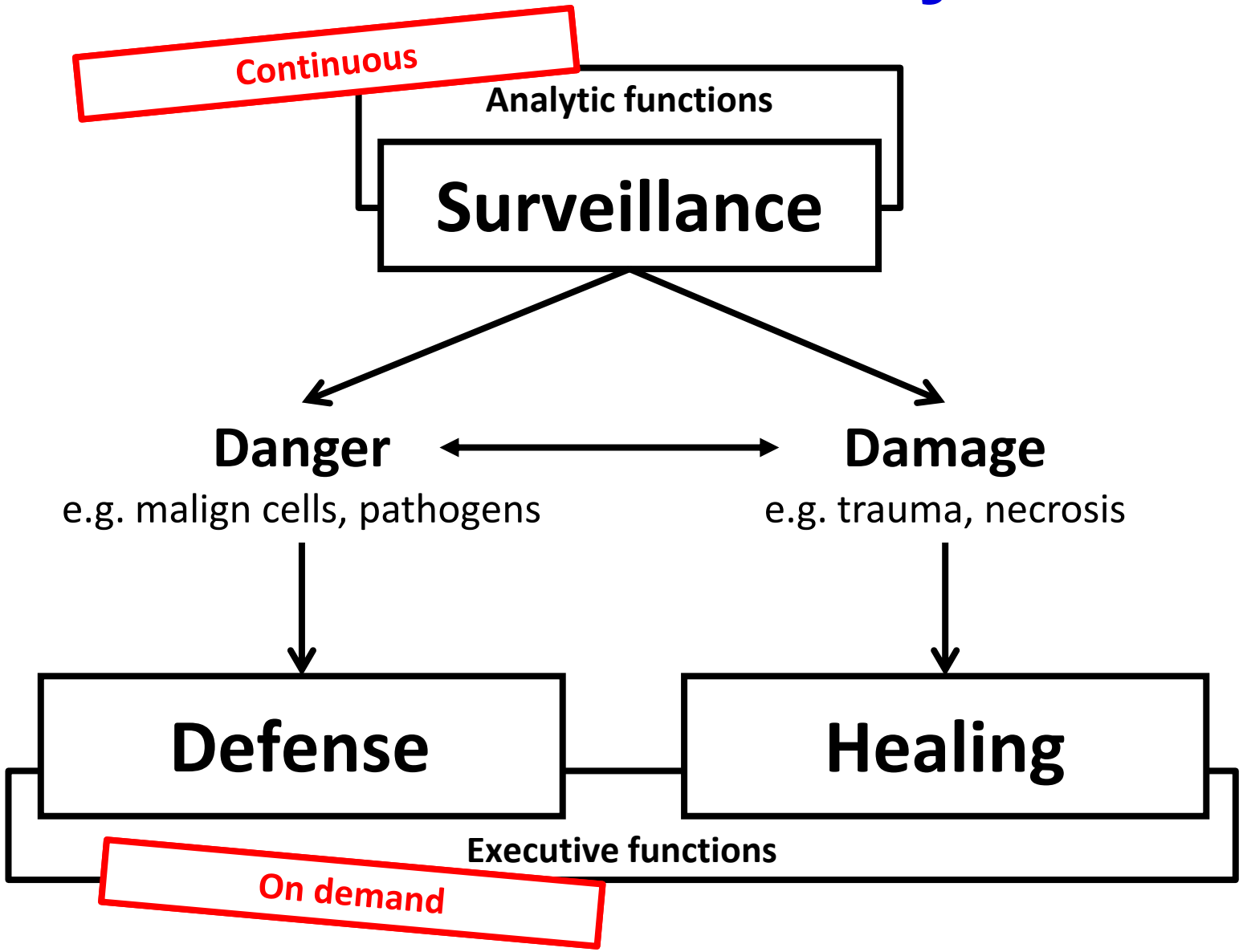
Innate immunity



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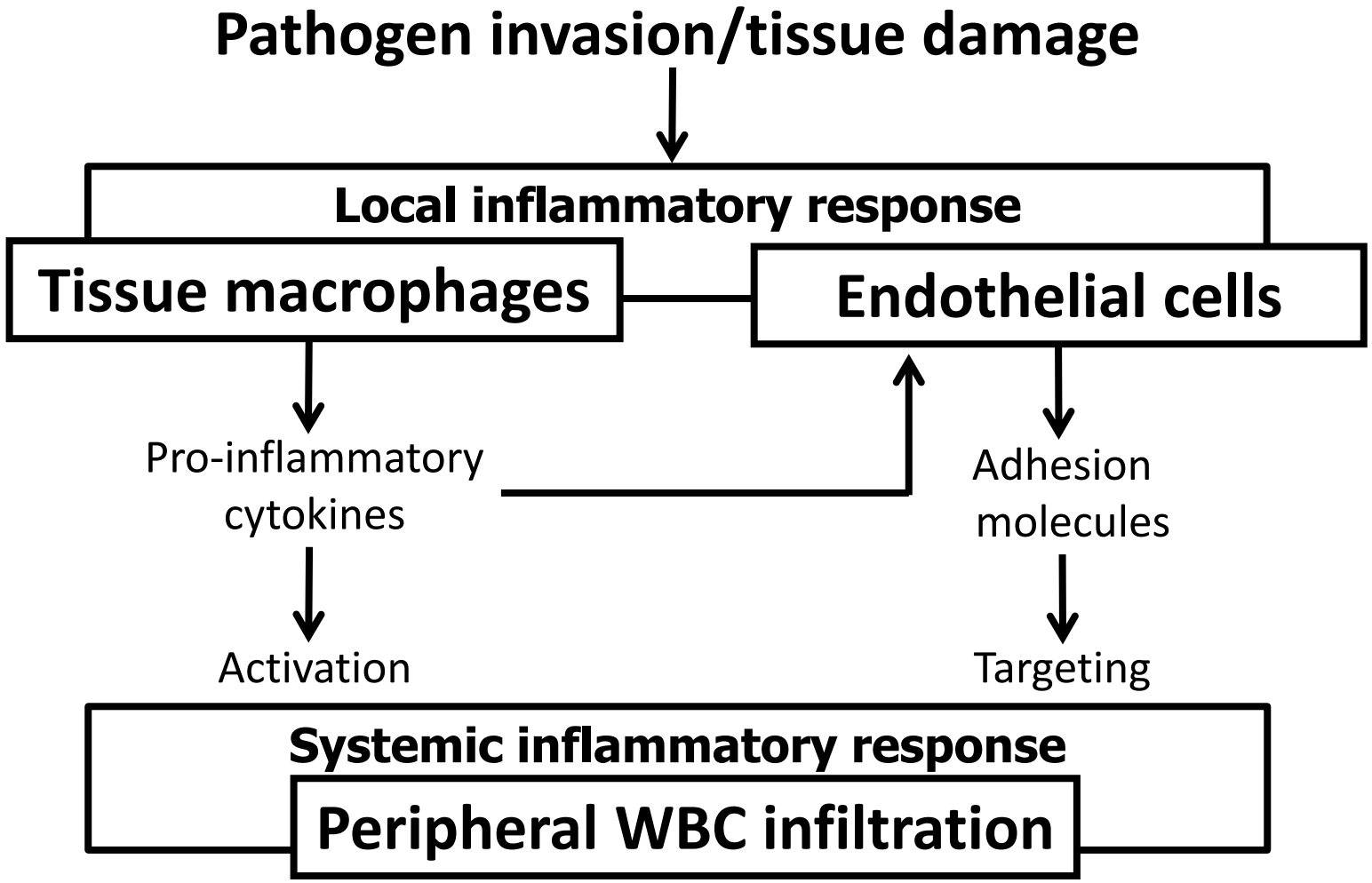
Pathogen invasion/tissue damage
Local inflammatory response
Tissue macrophages
Endothelial cells
Pro-inflammatory cytokines
Adhesion molecules
Activation
Targeting
Systemic inflammatory response
Peripheral WBC infiltration

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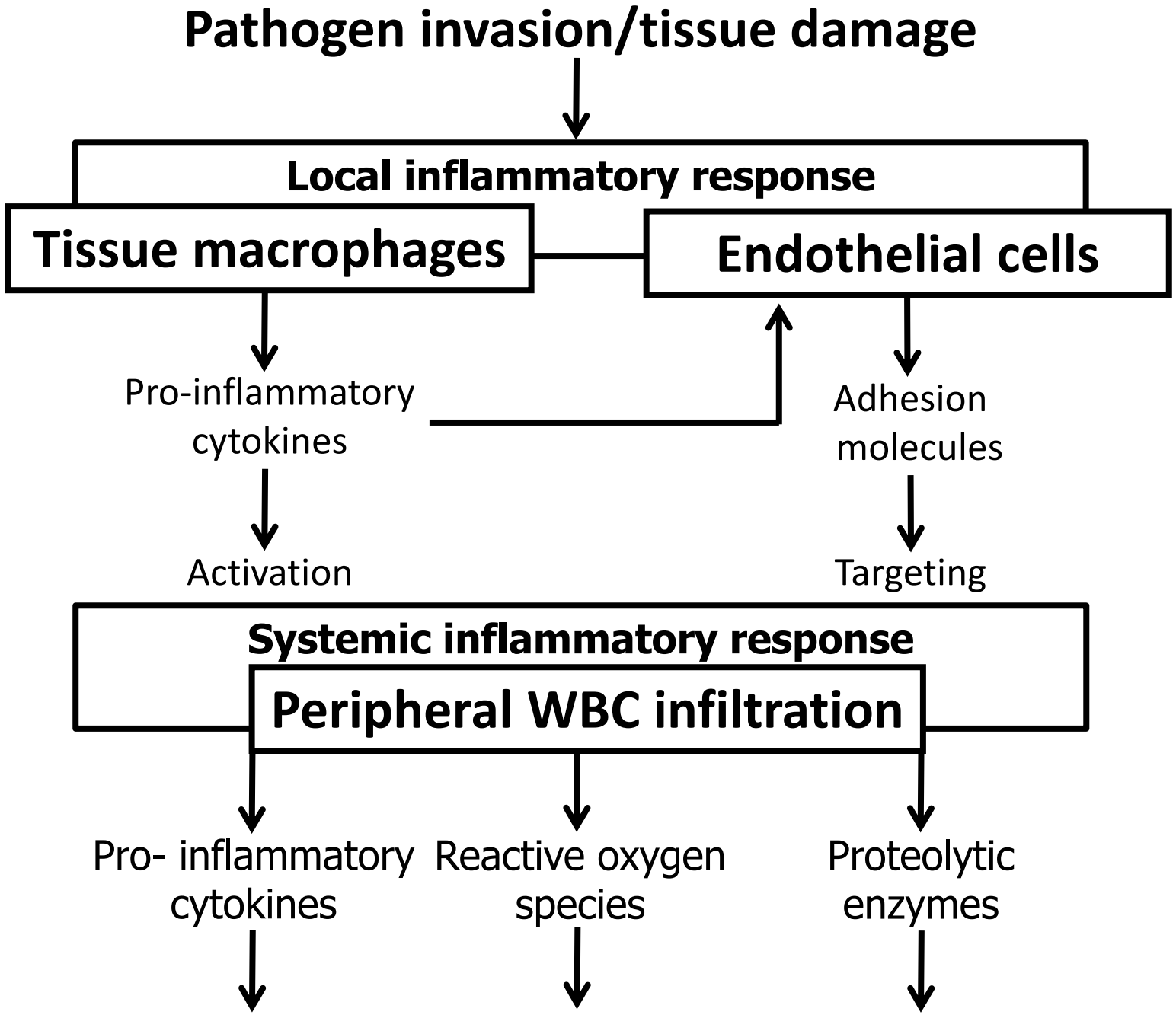

Inflammation associated tissue damage may be worse than initial pathology

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Adaptive immunity

	B cell response	CD4+ T cell response	CD8+ T cell response
Type of immunity	Humoral	Cellular	Cellular
Precursor cell	B lymphocyte	CD4+ precursor	CD8+ precursor
Effector cell	Plasma cell	CD4+ helper	CD8+ Cytotoxic T lymphocyte
Receptors recognize antigenic epitopes presented as	Linear and conformational epitopes on foreign antigens	Antigenic peptides on class II molecules	Antigenic peptides on class I molecules
Mediator molecules	Immunoglobulins (Igs)	Cytokines	Perforins, Granzymes, Cytokines
Persistence of effectors	Yes	No	No
Anamnestic (memory) response	Yes	Yes	Yes

Adapted from https://www.sciencedirect.com/topics/immunology-and-microbiology/adaptive-immune-system

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Classes of immunoglobulins

Class of Antibody	Serum levels	Structure	Biological functions
IgM	5%	Monomer Pentamer	Membrane-bound immunoglobulin on the surface of immature and mature B cells First antibody produced in a primary response to an antigen First antibody produced by the fetus Efficient in binding antigens with many repeating epitopes, such as viruses Classical complement activation
IgD	0.3%	Monomer	Membrane-bound immunoglobulin on the surface of mature B cells No biological effector function known
IgA	7-15%	Monomer Dimer	Predominant antibody class in secretions (saliva, tears, breast milk) and mucosa First line of defence against infection by microorganisms
IgG	85%	Monomer	Most abundant class with four isotypes - IgG1, IgG2, IgG3, IgG4 Crosses the placenta Opsonization
IgE	0.02%	Monomer	Defence against parasite infections Associated with hypersensitivity reactions (allergies) Found mainly in tissues

Moura, Rita & Agua-Doce, Ana & Weinmann, Pamela & Graça, Luis & Fonseca, João. (2008). B cells: From the bench to the clinical practice. Acta reumatológica portuguesa. 33. 137-54.

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Immunopatological conditions

- Hypersensitivty
  - Reaction against harmless antigen
  - Antibody-mediated or cell-mediated
- Autoimmune diseases
  - Reaction against autoantigen
- Immunodeficiency
  - Deffect of immune system
  - Genetically determined or acquired

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Hypersensitivity

- Immune response that is more damaging than helpful
- Gell and Coombs clasification
  - Type I - immediate hypersensitivity
  - Type II - is caused by specific antibody binding to cells or tissue antigens
  - Type III - is mediated by immune complexes
  - Type IV - is the only class of hypersensitive reactions triggered by antigen-specific T cells

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Type of hypersensitivity	Immunopathologic mechanisms	Mechanisms of tissue injury and disease	Examples
Type I reaction: Immediate hypersensitivity	IgE antibody	Mast cells and their mediators (vasoactive amines, lipid mediators, cytokines)	Anaphylactic reaction Allergies
Type II reaction: Antibody mediated	IgM, IgG antibodies against cell surface or extracellular matrix antigens	Opsonization and phagocytosis of cells Complement-and Fc receptor-mediated recruitment and activation of leukocytes (neutrophils, macrophages) Abnormalities in cellular functions, e.g., hormone receptor signaling	Haemolitic anemias Transfusion reaction Erythroblastosis fetalis Graves`disease Myasthenia gravis
Type III reaction: **Immune complex mediated**	Immune complexes of circulating antigens and IgM or IgG antibodies	Complement-and Fc receptor-mediated recruitment and activation of leukocytes	Vasculitis Revmatoid arthritis Post-streptococ glomerulonephritis
Type IV reaction: **T cell mediated**	1. $CD4^+$ T cells (delayed-type hypersensitivity) 2. $CD8^+$ CTLs (T cell-mediated cytolysis)	1. Macrophage activation, cytokine-mediated inflammation 2. Direct target cell killing, cytokine-mediated inflammation	Tuberculosis Syphilis Contact dermatitis

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Atopy vs. allergy vs. anaphylaxis

- **At**

In **1906** C.Pirquet and B.Schick observed unwanted reactivity in chlildren after repeated application of diphteric serum – they called the reaction serum illness – term **„allergy“**

- **Al** **clinical manifestation** of inappropriate IgE immune response to allergens.

  Alle is rapid and predictable.

– **Anap**

In **1911** Ch.Richet and P.Portier studied influence of extract of sea animals (jelly-fish) in dogs. Rapid shock reaction which followed they termed as **anaphylactic** – unwanted (in contrast with prophylaxis)

  reaction in humans and

  (against) and φύλαξις *phylaxis* (protection).

1920 A. F. Coca **atopy** vs. genetically predisposition

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Atopy vs. allergy vs. anaphylaxis

- **Atopy** (Greek *ατοπία - placelessness*) is an inborn **predisposition** for exaggerated IgE mediated immune reaction to harmless environmental antigens (allergens).

- **Allergy** is a **clinical manifestation** of inappropriate IgE immune response to allergens. Allergy occurs after sensitisation, allergy is rapid and predictable.

- **Anaphylaxis** is an acute systemic (multi-system) and severe Type I Hypersensitivity allergic reaction in humans and other mammals. The term comes from the Greek words ανα *ana* (against) and φύλαξις *phylaxis* (protection).

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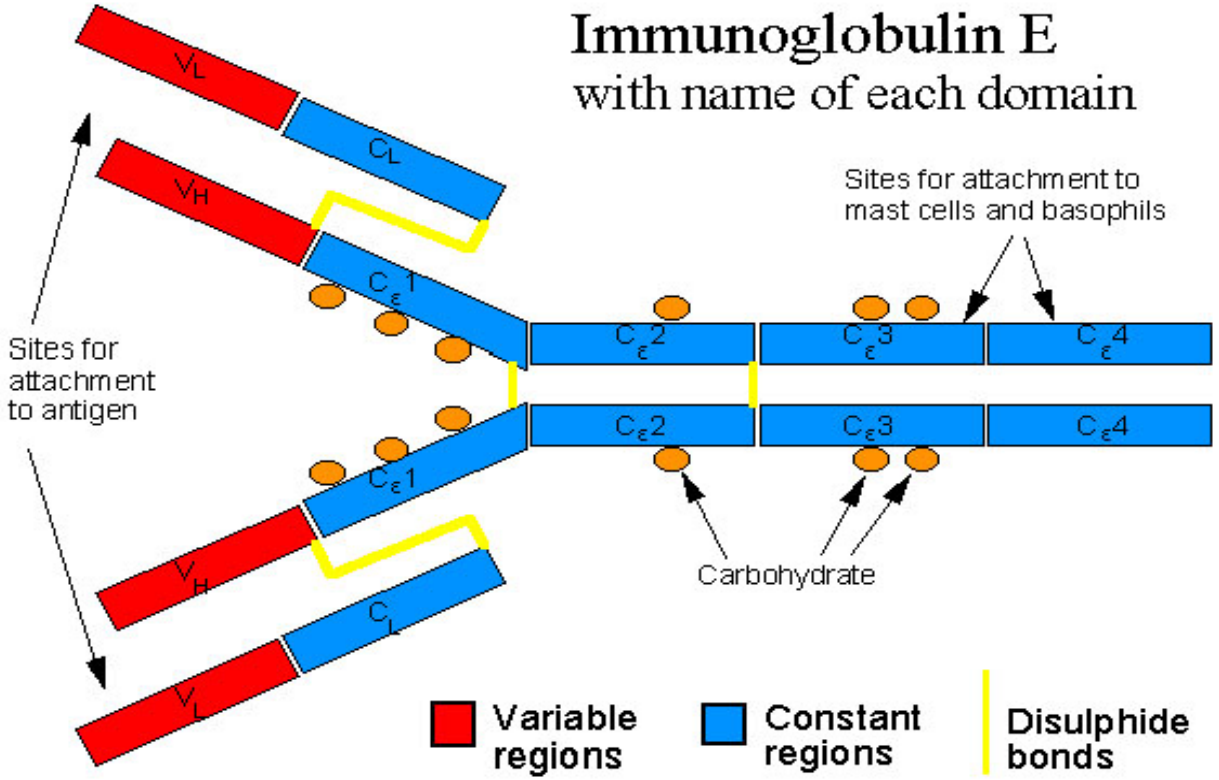
Immediate hypersensitivity: Type I reaction

- exposure to an antigen
- activation of TH2 cells specific for the antigen
- production of IgE antibody
- binding of the antibody to Fce receptors of mast cells
- triggering of the mast cells by re-exposure to the antigen, resulting in the release of mediators from the mast cells and the subsequent pathologic reaction



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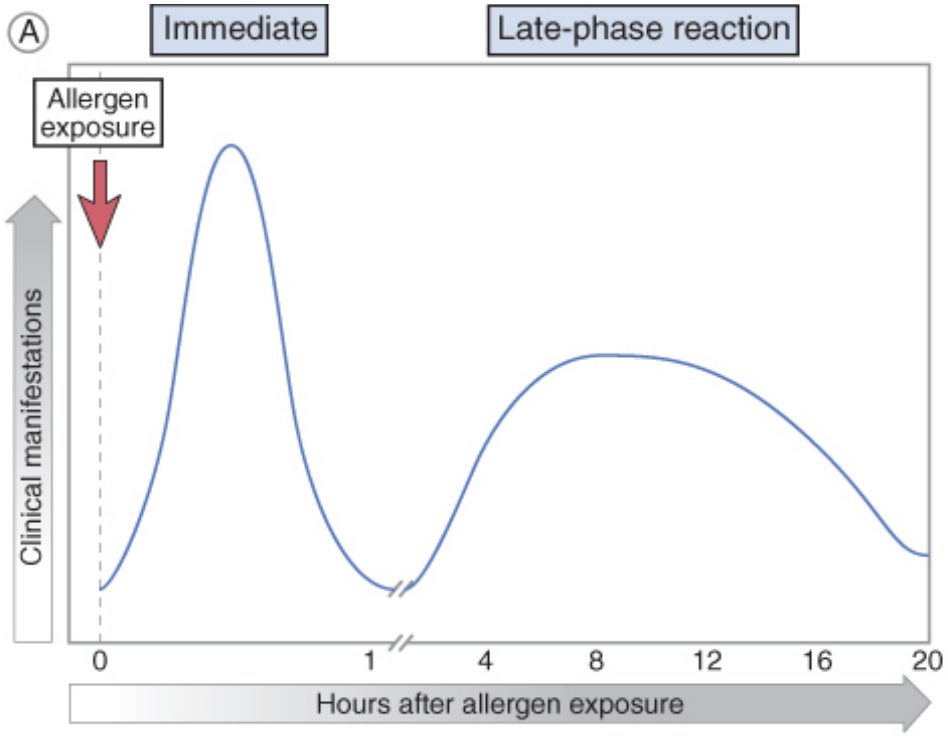
Immediate hypersensitivity: Type I reaction

The clinical and pathologic manifestations

- Immediate reaction
  - Degranulation of mast cells and eventually basophils
- Late-phase reaction
  - Inflammation mediated leukocytes infiltrating from periphery (neutrophils, macrophages, lymphocytes, eosinophils, basophils)



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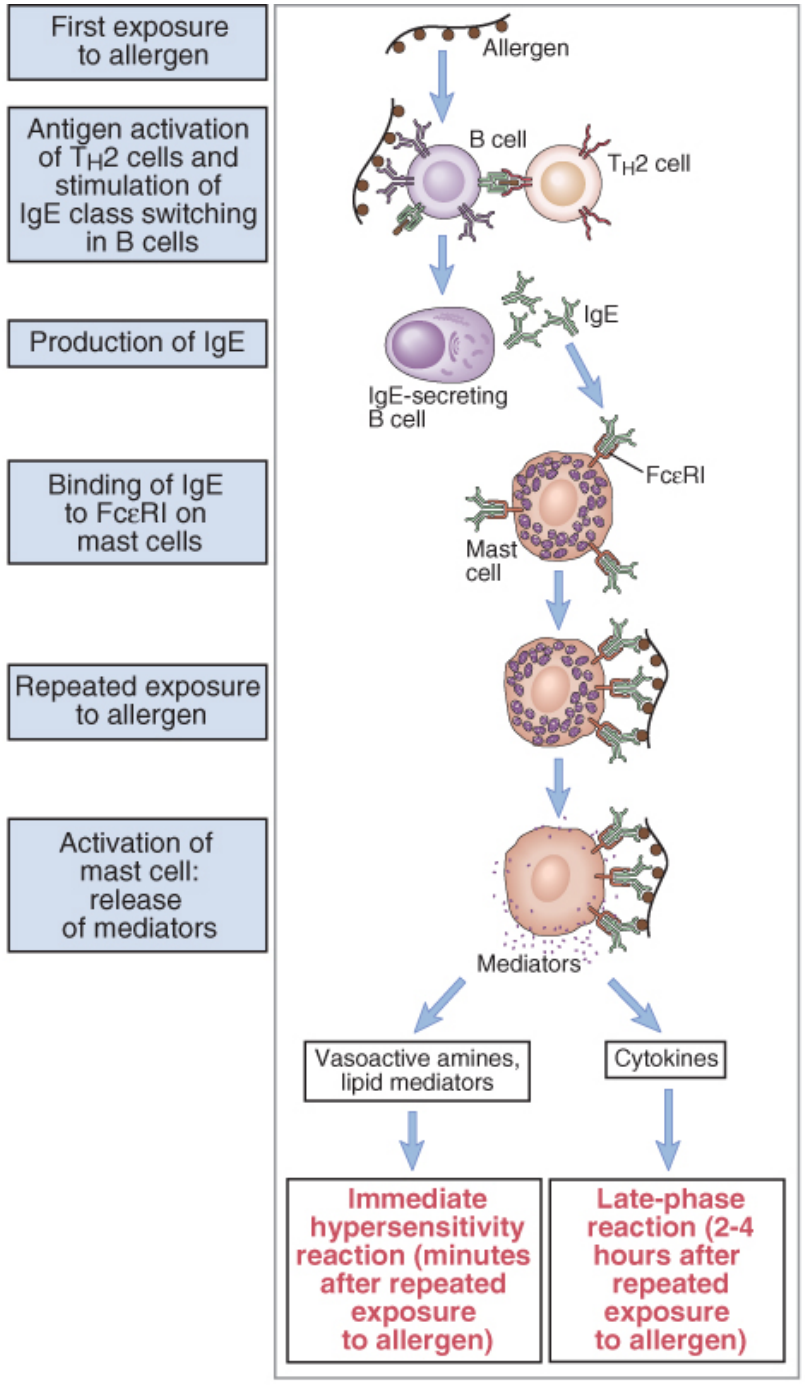

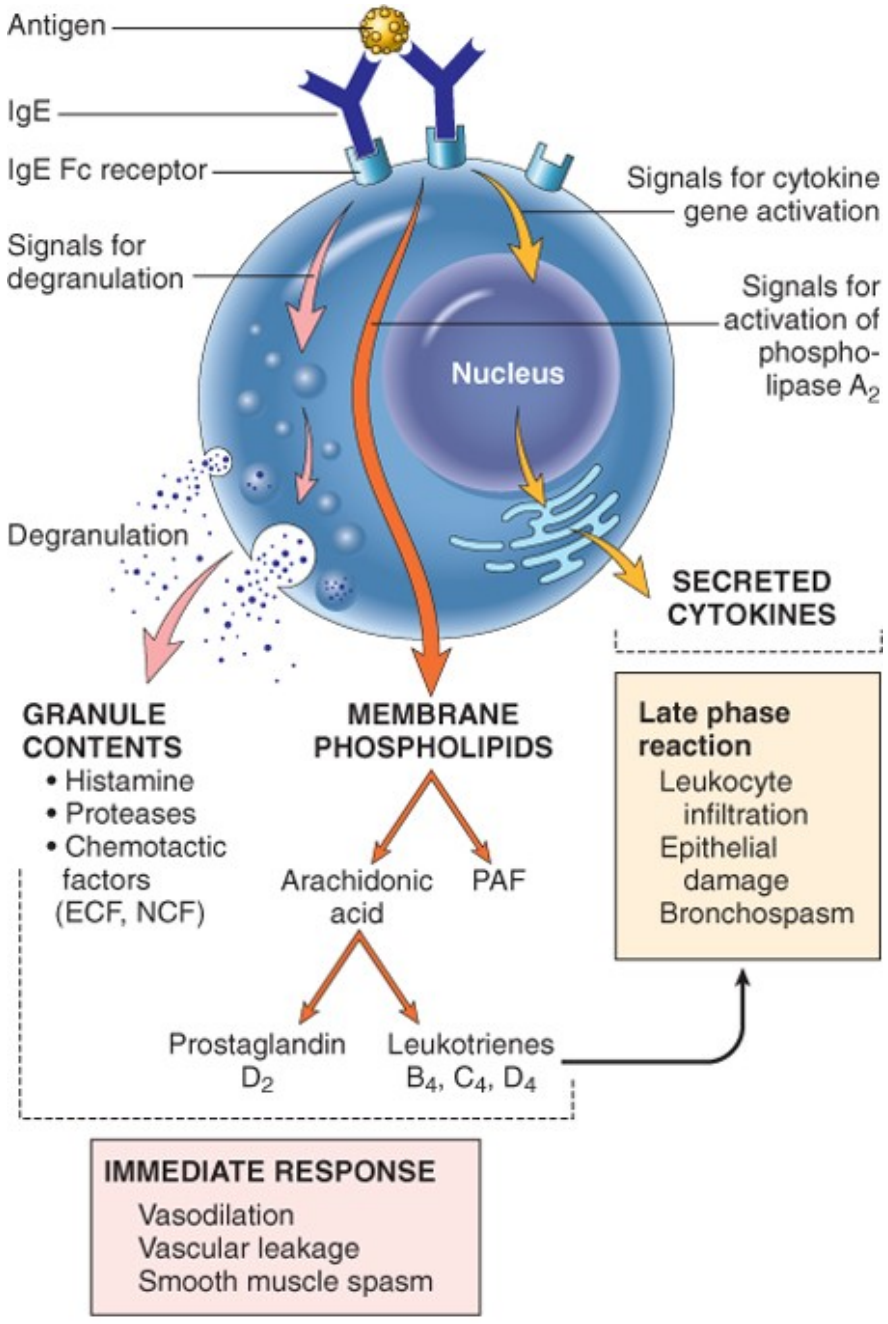

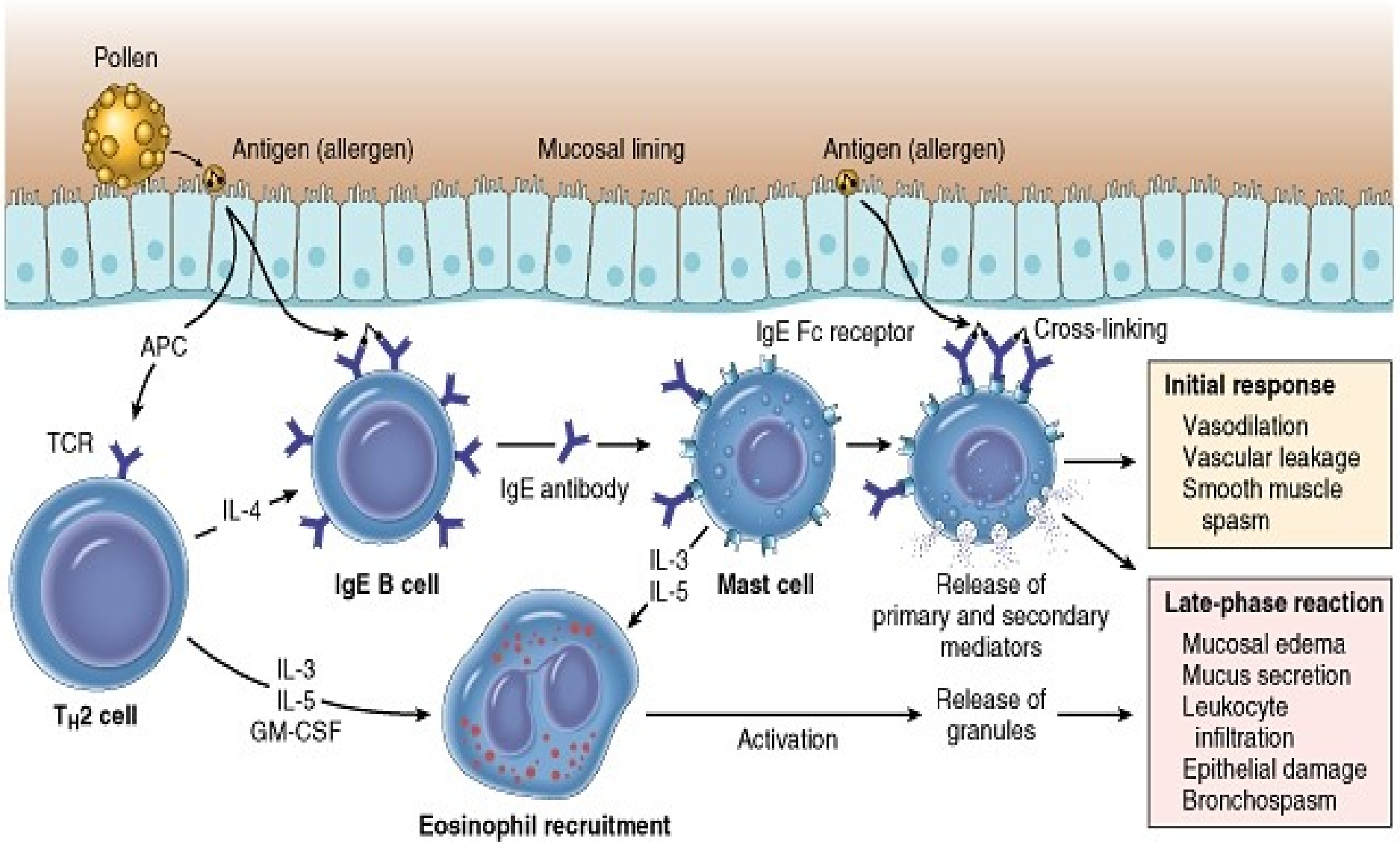

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Mast cell

- ✓ Mast cells and basophils are functionally similar
- ✓ Basophils circulate in blood
- ✓ Mast cells are localized in perivascular space

- In perivascular space of all subcutaneous/submucosal tissues,
- Including conjunctiva, upper/lower respiratory tracts, and gut

➢ Activation of mast cells by binding of multivalent antigens to the IgE – FcεRI complex

➢ Response of mast cells to activation

- Degranulation - secretion of the preformed mediators by a regulated process of exocytosis,
- Production and secretion of arachidonic acid derivates (leukotuirens and prostaglandins,etc.),
- Production and secretion of cytokines and chemokines

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Mediators derived from Mast Cells

- Biogenic amines
  - histamine
- Granule proteins and proteoglycans (Enzymes)
  - Serine proteases
- Lipid mediators
  - Prostaglandins, leukotrienes
- Cytokines
  - IL-1, IL-3, IL-4, IL-5, IL-6, GM-CSF, TGF-β, TNF-α

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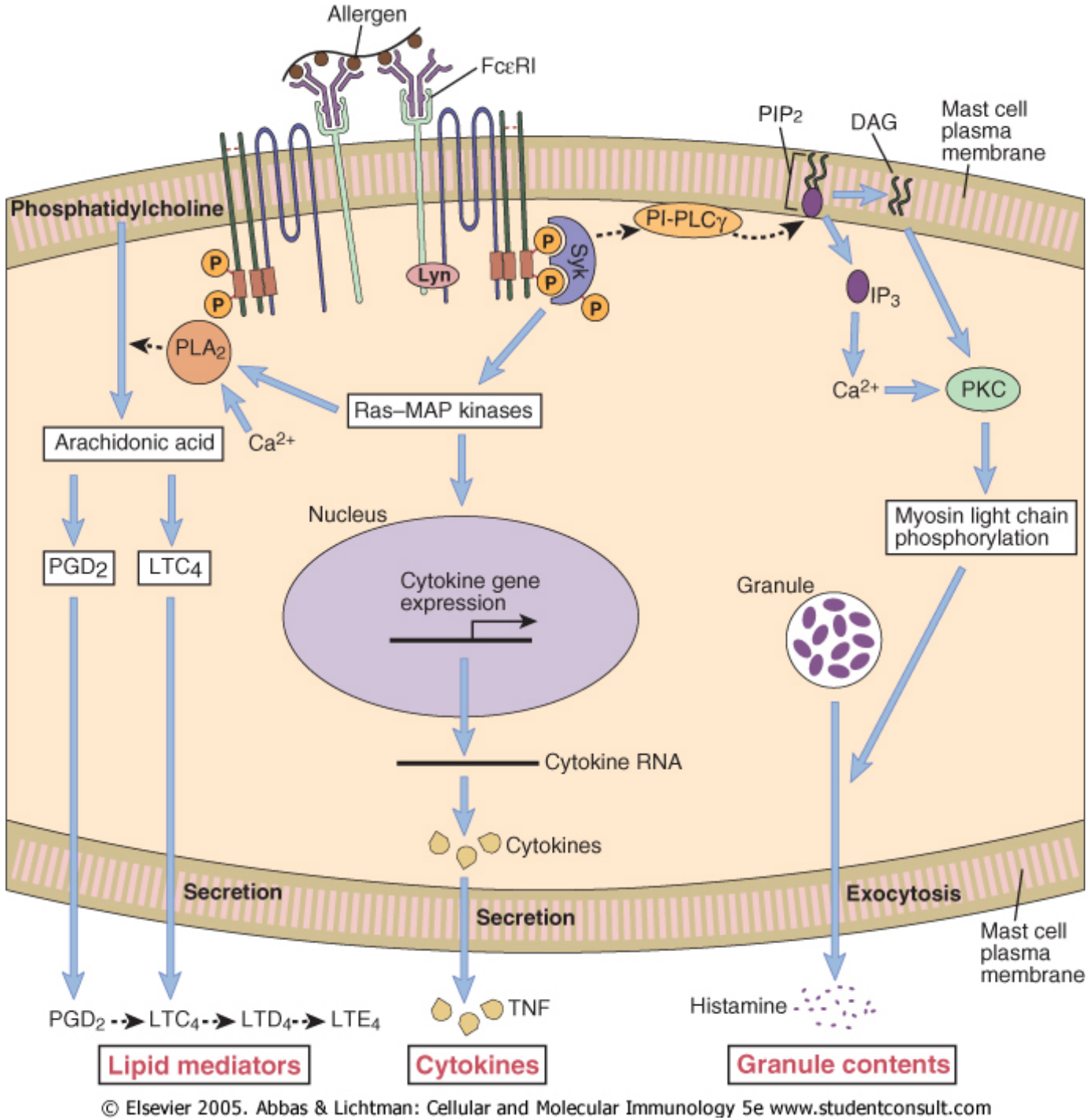
Mast cell activation



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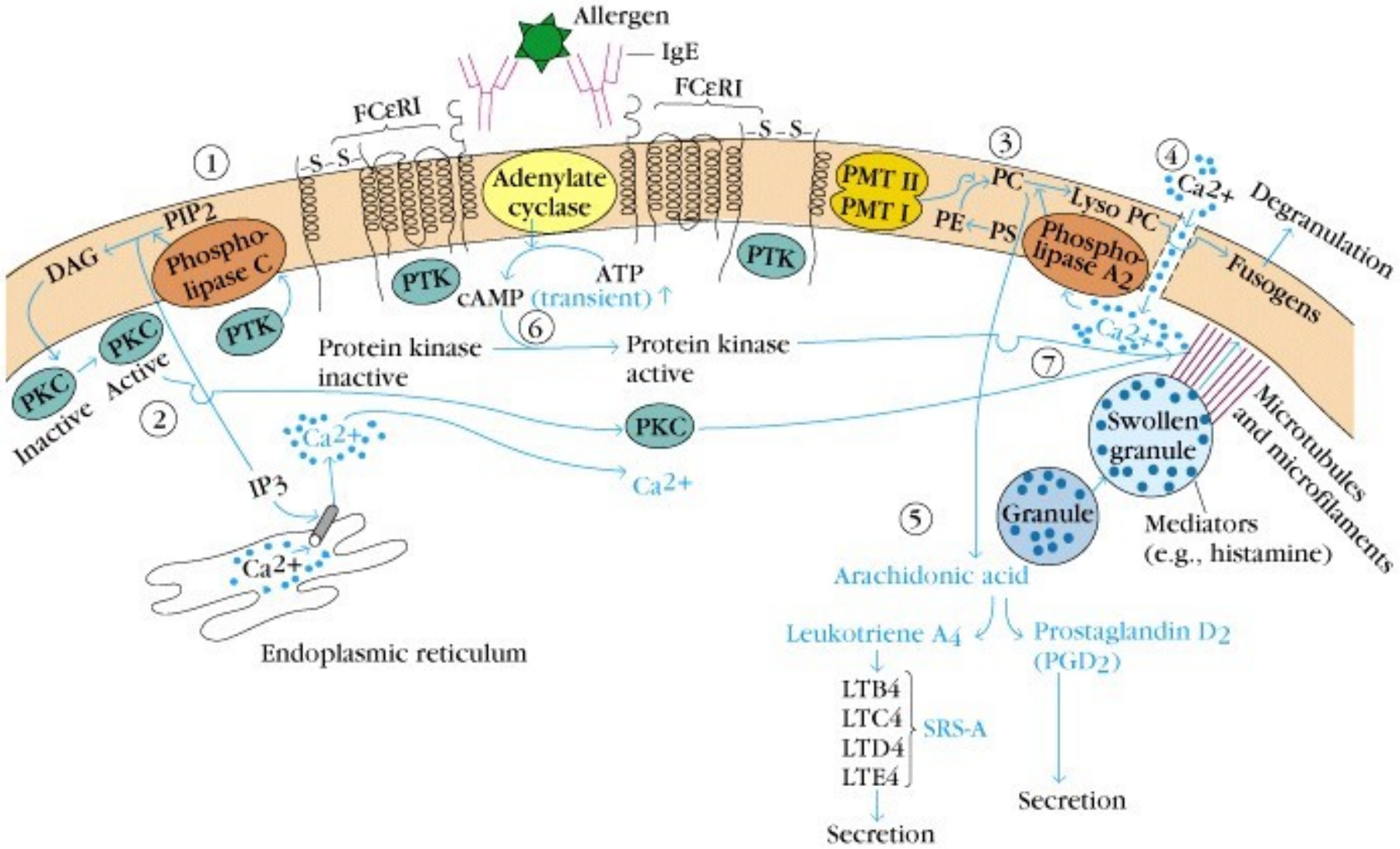
Mast cell degranulation



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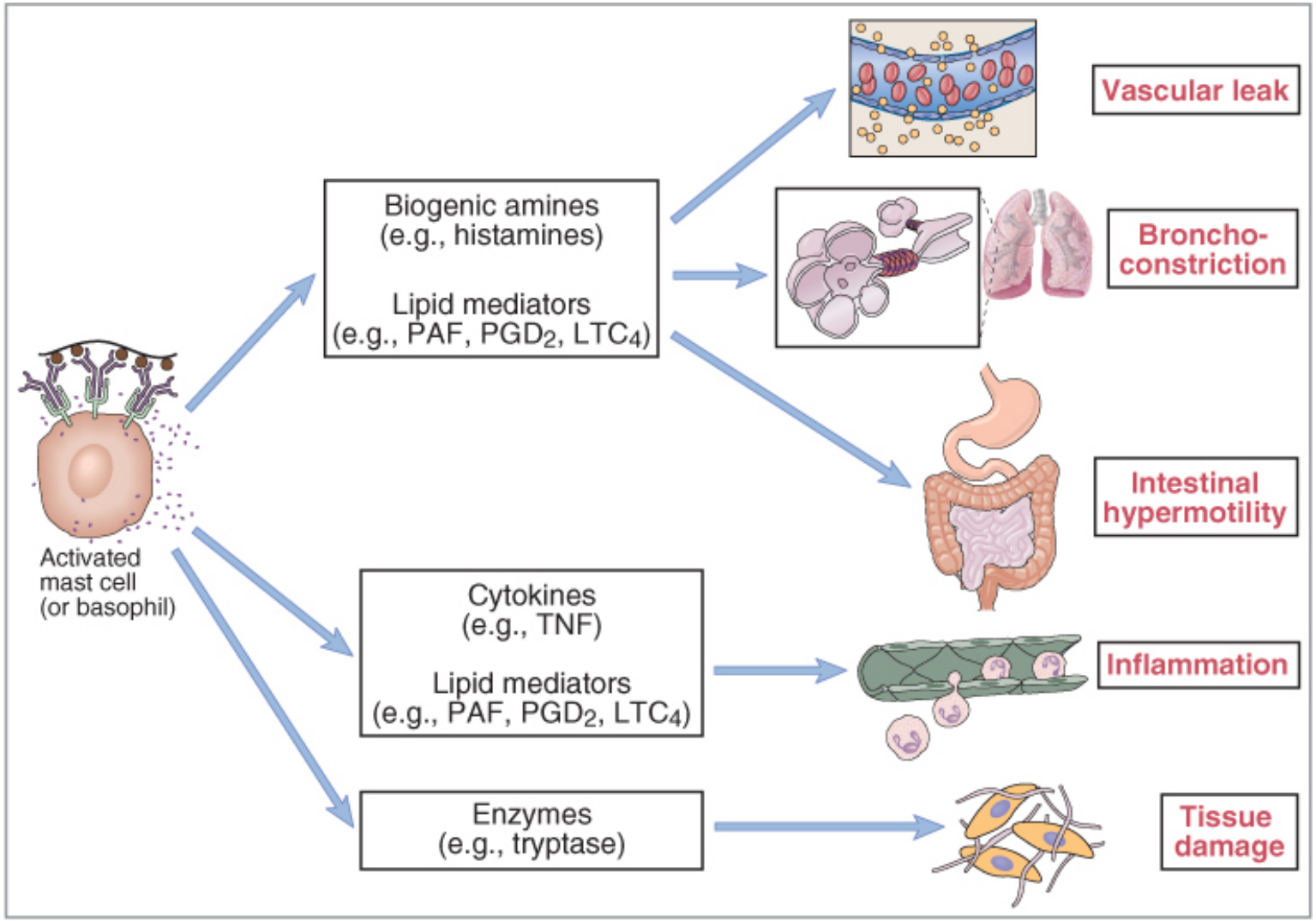
Biological effect of mediators



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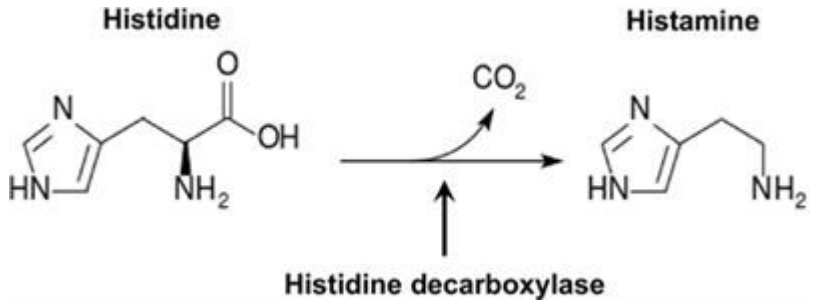
Biological effect of histamine

- **H_1- receptors**
  - Constriction of smooth muscle
  - Increased vascular permeability
  - Irritation of sensitive nerves
  - Vasodilation
  - Prostaglandin genration
- **H_2-receptors**
  - Stimulation of HCl secretion
  - Positive chronotropic and ionotropic effect
  - Release of histamine from mast cells and basophils
- **H_3-receptors** (nerve cells).
  - Regulatory function – after activation – decrease of histamine and other mediators production in CNS
- **H_4-receptory** (eosinophils, bone marrow, lung)
  - Regulation of immune system



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Tissue Effects of Histamine

- Cardiovascular
  - Decreased blood pressure
  - Increased heart rate
  - Edema (separation of endothelial cells & increased permeability)
- Respiratory
  - Bronchoconstriction
- Gastrointestinal
  - Smooth muscle contraction and diarrhea
- Skin
  - Urticaria

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Smooth Muscle Spasm

✓Bronchospasm
- Respiratory distress
- "Tight Chest"
- Wheezing

✓GI Tract Spasm
- Nausea, vomiting
- Cramping, diarrhea

✓Bladder Spasm
- Urinary urgency
- Urinary incontinence

Vasodilation and Increased Capillary Permeability

✓Tissue edema, urticaria (hives), itching

✓Laryngeal edema
- Airway obstruction
- Respiratory distress
- Stridor

✓Distributive shock
- Vasodilation
- Fluid likeage

Effects of other mediators

Leukotriens

LTC4, LTD4, LTE4, LTB4

- Potent bronchoconstrictors
- Increased vascular permeability
- Slower onset than histamine
- Effects last longer than histamine

Prostaglandins

PG D_2

- Vasodilation
- Bronchospasm
- Increased capillary permeability

Kinins

- Vasodilation
- Increased capillary permeability
- Bronchoconstriction
- Stimulates vascular endothelium to release vasoactive factors (Prostacyclin, NO)

Platelet-Activating Factor

- Causes platelets to aggregate and release inflammatory products
- PAF causes profound wheal-and-flare response, smooth muscle contraction & increase capillary permeability

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Immediate hypersensitivity: Type I reaction

Clinical manifestation

- **Localized reaction**
  - ✓Asthma bronchiale
  - ✓Nasal allergy
  - ✓Atopic dermatitis
  - ✓Food allergy
- **Systemic (anaphylactic reaction)**
  - ✓Generalized, life-threatening, shock

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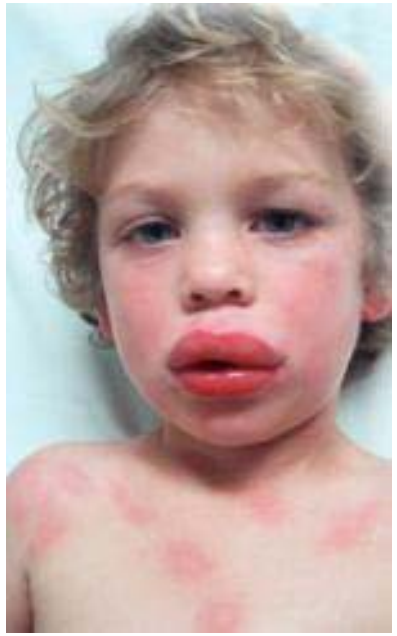
Clinical picture and manifestation

- Symptoms depend on:
  - Sensibilization level of patient
  - Place of allergen entry
  - Allergen type
- Mucous membrane, derm
  - ✓Erythema, exanthema, pruritus, edema
- Respiratory system
  - ✓ Acute rhinitis, nasal obstruction, sneezing, irritation to cough, breething problems
- GIT
  - ✓vomitus, colic, diarrhoea



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Clinical picture and manifestation

- Cardiovascular system:
  - ✓Palpitation, tachycardia, hypotension, arrhytmia
- Urogenital system:
  - ✓Picture of renal colic
- General symptoms:
  - ✓Cognition disorders, spasms

Causes of Deaths

- Laryngeal edema and acute bronchospasm with respiratory failure >70%
- Circulatory collapse - 25%
- Other <5% - ?Cerebral? ?MI?

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Anaphylaxis vs. anaphylactoid reaction

- Anaphylaxis
  - Systemic reaction of multiple organ systems to antigen-induced IgE-mediated immunulogic mediator release in previously sensitized individual
- Anaphylactiod reaction
  - Non-IgE mediated -
  - Anaphylatoxins-mediated
  - No sensitization needed, may occur after first contact with anaphylatoxin
  - Clinical manifestation and treatment similar to anaphylactic reaction

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Anaphylatoxins (Histamine liberators)

- Nonimmunologic histamine release or complement activation
- Bee sting venom
- Iodinated contrast
- Some drugs
  - Antibiotics (Vancomycin)
  - Muscle relaxants (atracurium, mivacurium)
  - Opioids (morphine, meperidine, codeine)
  - Thiobarbiturates

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Complement

- **“**activation follows both **immunologic** (Ab-mediated, i.e., classic pathway) **and nonimmunologic** (alternative) **pathways** to include a series of multimolecular, self-assembling proteins that liberate biologically active complement fragments of C3 & C5”
- C3a & C5a “anaphylatoxins”
- Release histamine, contract smooth muscle, increase capillary permeability and stimulate interleukin synthesis
- C5a interacts with specific high-affinity receptors on white blood cells & platelets initiating leukocyte chemotaxis, aggregation & activation
- Aggregated leukocytes embolize to various organs, producing microvascular occlusion & liberation of inflammatory mediators such as arachadonic acid metabolites, O_2 free radicals & lysosomal enzymes

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Treatment of Type I reaction

- **Adrenaline i.v.**

  Stimulation of cAMP production due to binding to b-receptors in mast cells (cAMP inhibits histamine release from mast cells)

- **Corticosteroids i.v.**

  Inhibition of leucotrien synthesis

  Inhibition of inflammatory cells infilration in place of allergy reaction

  Inhibition in cytokine production

- **Antihistaminics**

  Inhibition of H1 and H2 receptors in terminal cells

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Summary

- 4 types of hypersensitivities
- 3 involve antibodies
- Anaphylaxis mediated by IgE
- Anaphylactoid is Ab independent

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Summary

- Anaphylaxis
  - Bronchospasm
  - Vasodilation, increased capillary permeability
  - Associated with profound CV collapse
  - Urticaria

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Summary

- Mediators
  - Histamine
  - Leukotrienes & Prostaglandins
  - Kinins
  - Platelet-activating Factor
  - Complement

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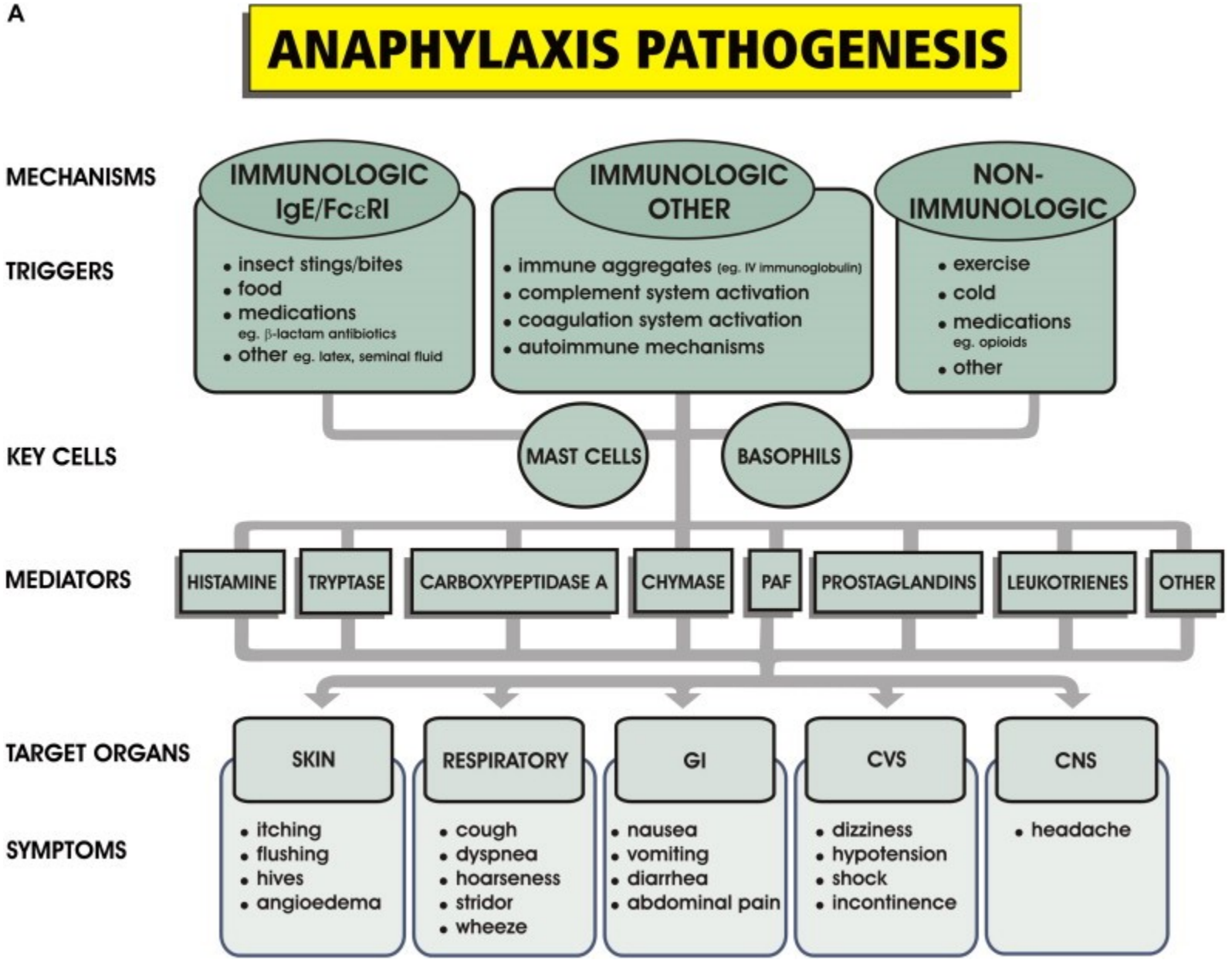

Simons FER. 9. Anaphylaxis. *Journal of Allergy and Clinical Immunology*. 2008;121:S402–S407.

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