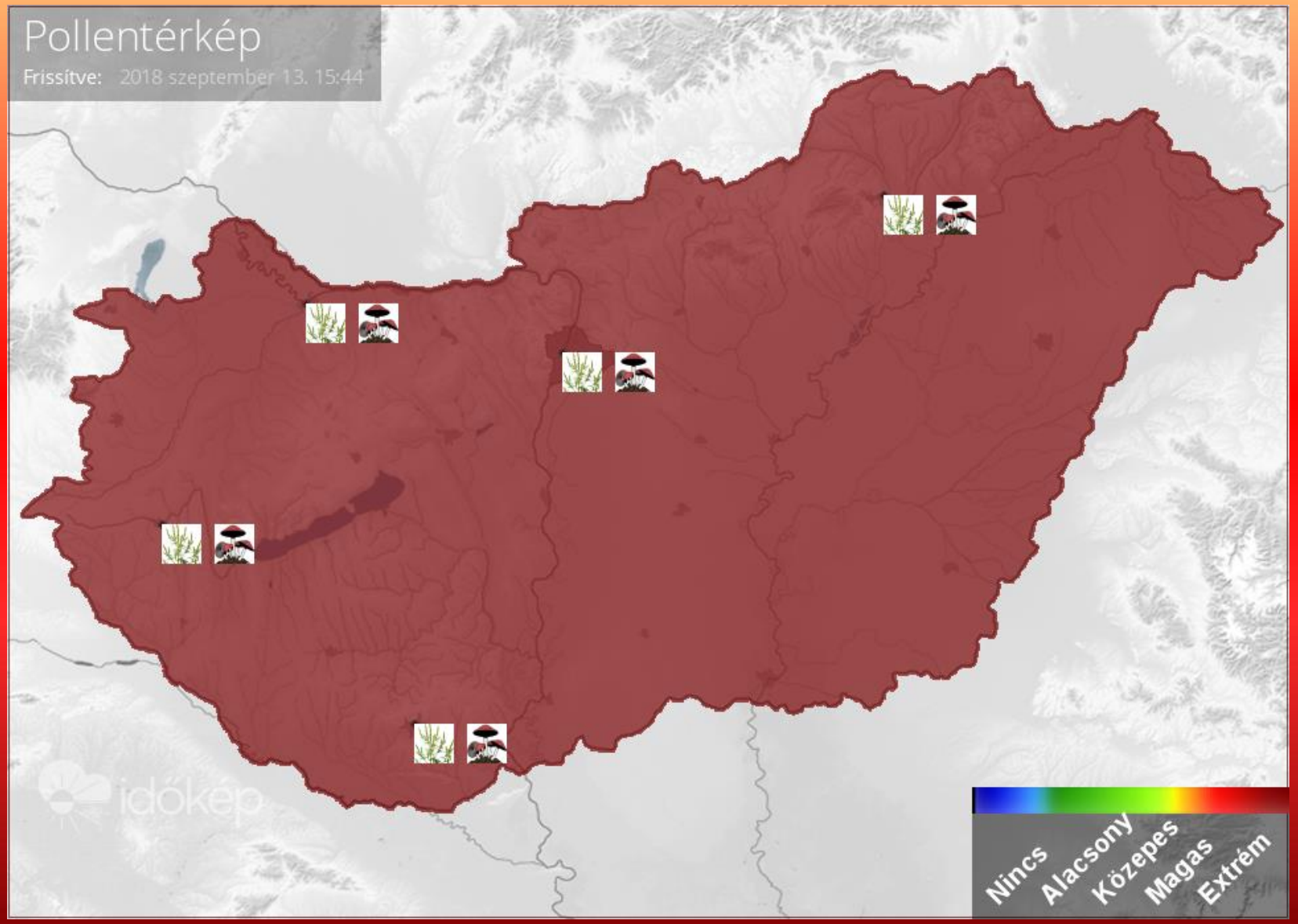
Immunpathology 2018’

Pathomechanism of allergic reactions


Rod Lym@NDSU

Pollen allergy forecast



Comparison of Different Types of hypersensitivity

	type-I (anaphylactic)	type-II (cytotoxic)	type-III (immune complex)	type-IV (delayed type)
antibody	IgE	IgG, IgM	IgG, IgM	None
antigen	Exogenous	cell surface	soluble	tissues & organs
response time	15-30 minutes	minutes-hours	3-8 hours	48-72 hours
appearance	weal & flare	ysis and necrosis	erythema and edema, necrosis	erythema and induration
histology	basophils and eosinophil	antibody and complement	complement and neutrophils	monocytes and lymphocytes
transferred with	antibody	antibody	antibody	T-cells
examples	allergic asthma, hay fever	erythroblastosis fetalis, Goodpasture's nephritis	SLE, farmer's lung disease	tuberculin test, poison ivy, granuloma

Common sources of allergens

Inhaled materials

Plant pollens
Dander of domesticated animals
Mold spores
Feces of very small animals
  eg house dust mites

pollen

house dust mite

Injected materials

Insect venoms
Vaccines
Drugs
Therapeutic proteins

wasp

drugs

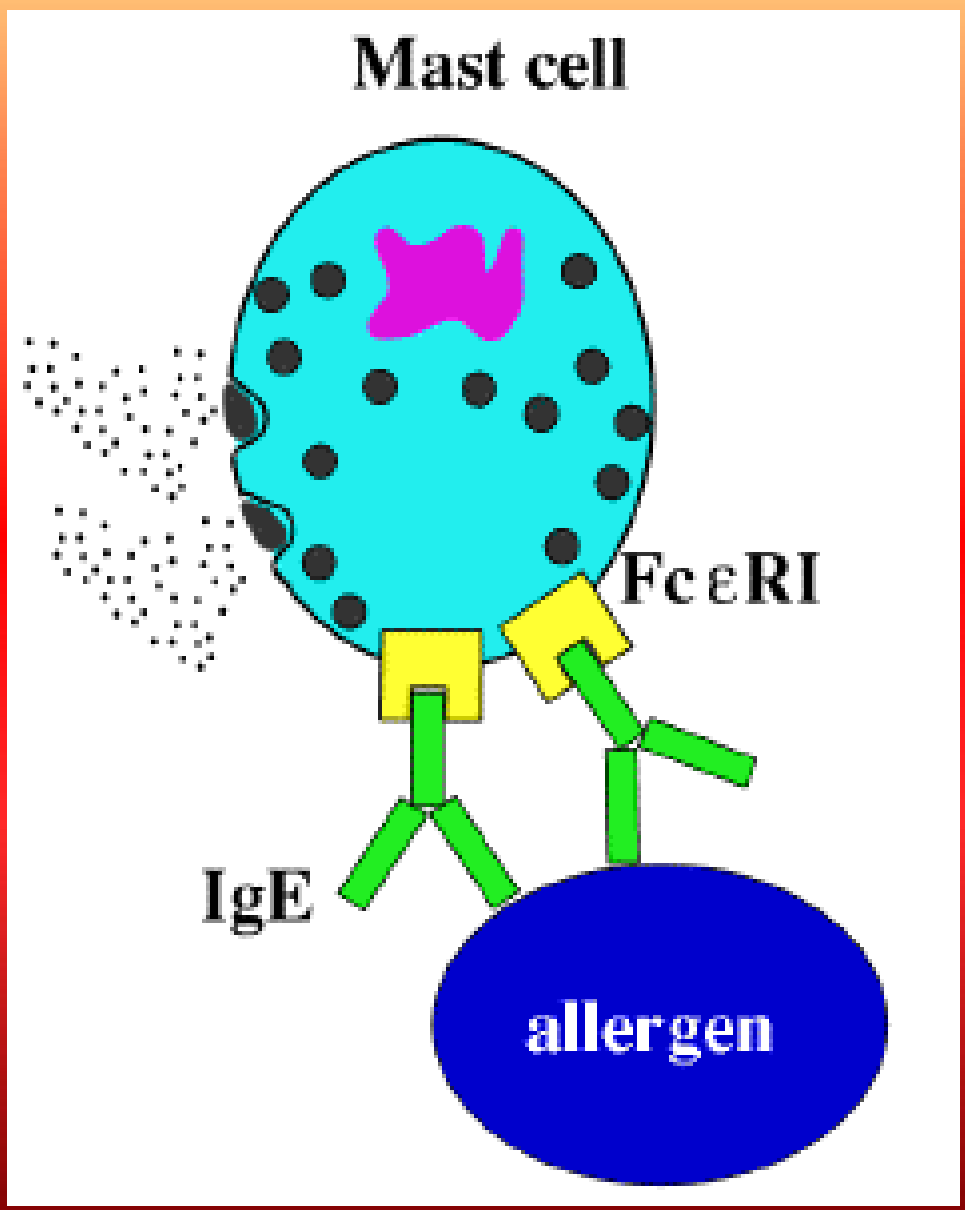
Food and contact allergies

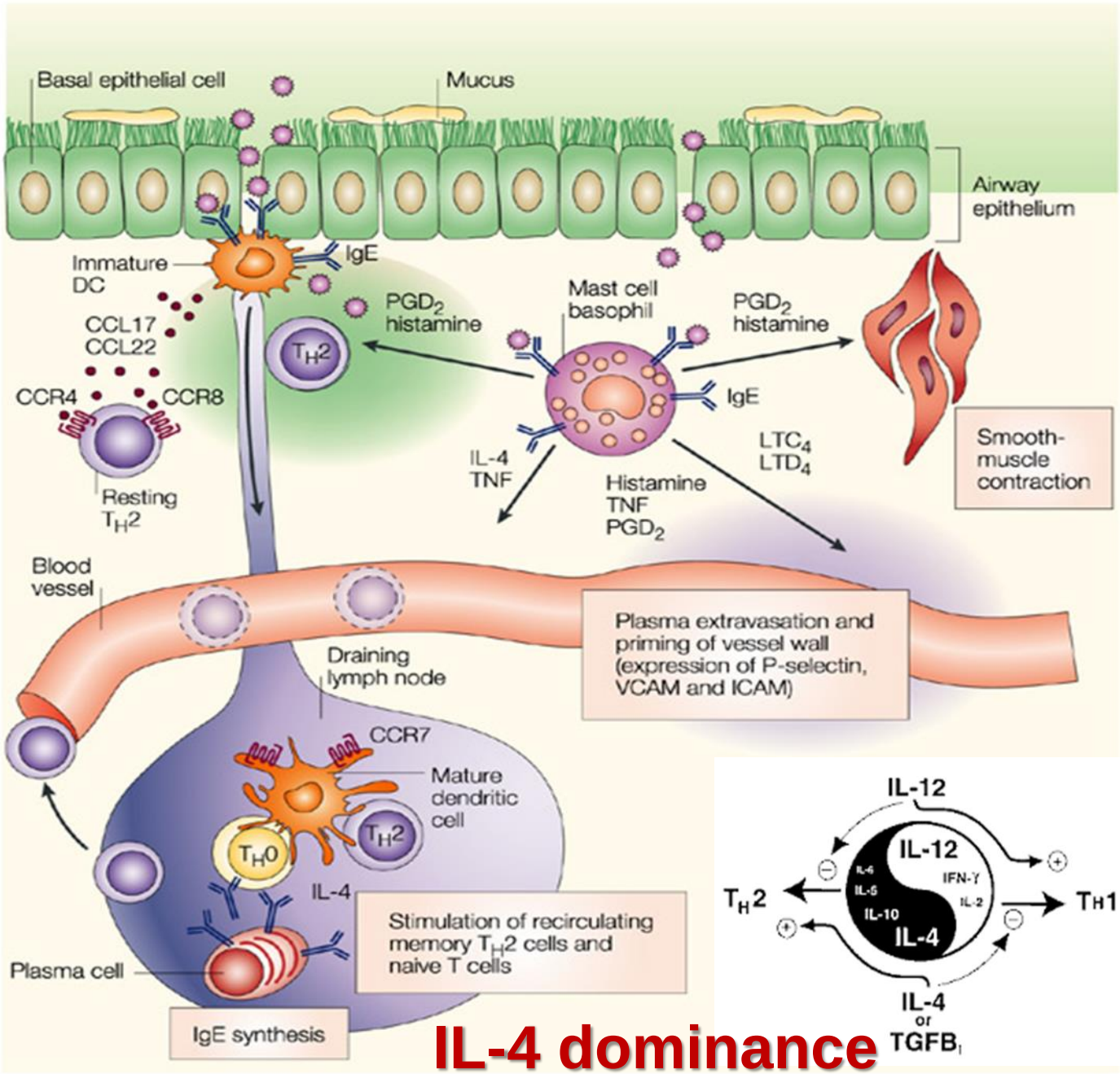
Dust mite

Dust mite allergy caused by the protein found in the fecal matter of the dust mite. The dust mite allergen is heavier than most other types of allergens. Therefore, it must be inhaled close to the source, usually in a stuffed toy, pillow or mattress. Dust mite allergy symptoms affect about ten percent of the population.

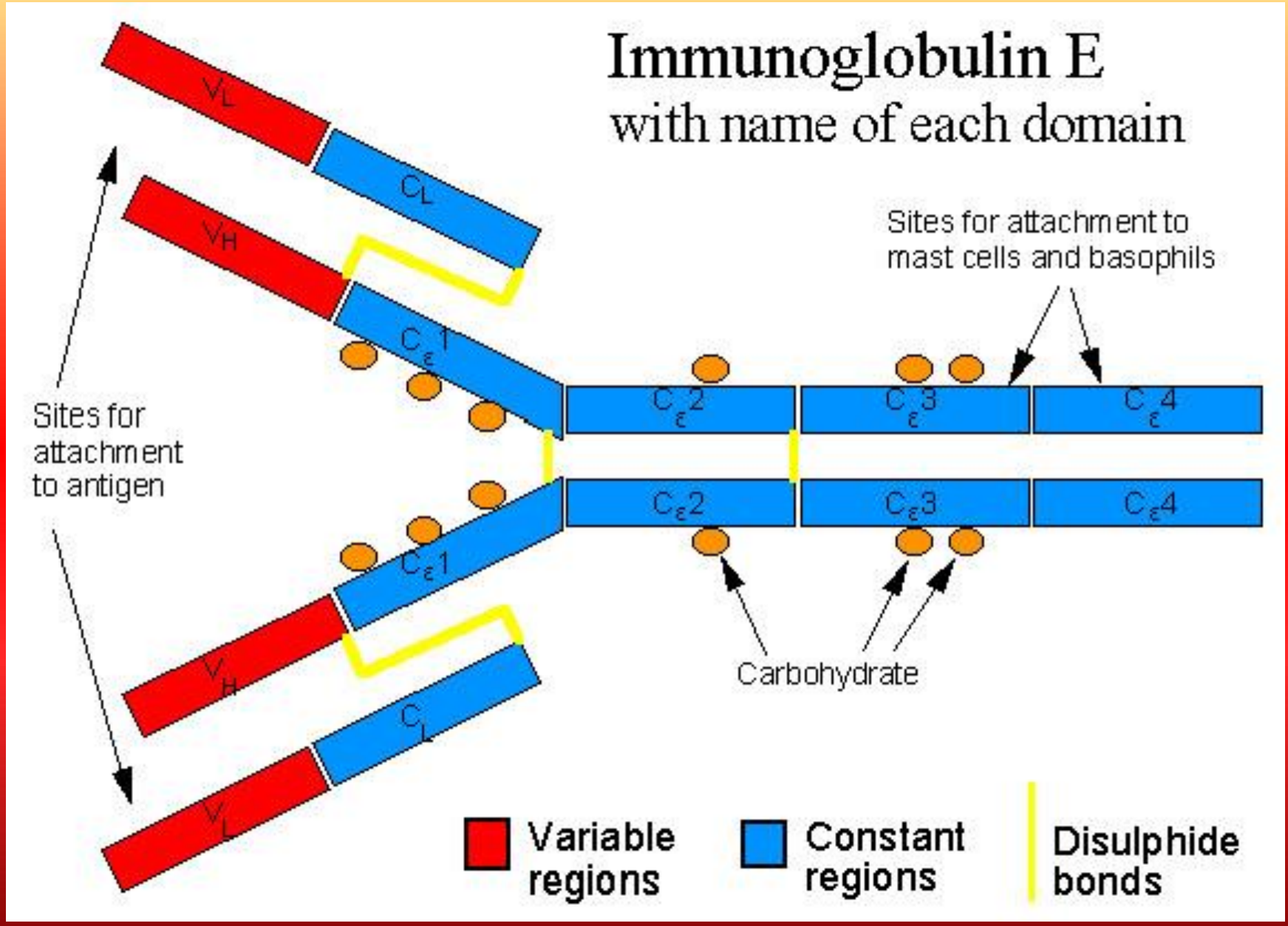
Dust mite allergy symptoms affect some people year-round. Some examples of dust mite allergy symptoms are: runny nose, eczema, persistent stuffy nose or ears, asthma, sitchy or watery eyes, and sneezing.

Type I hypersensitivity

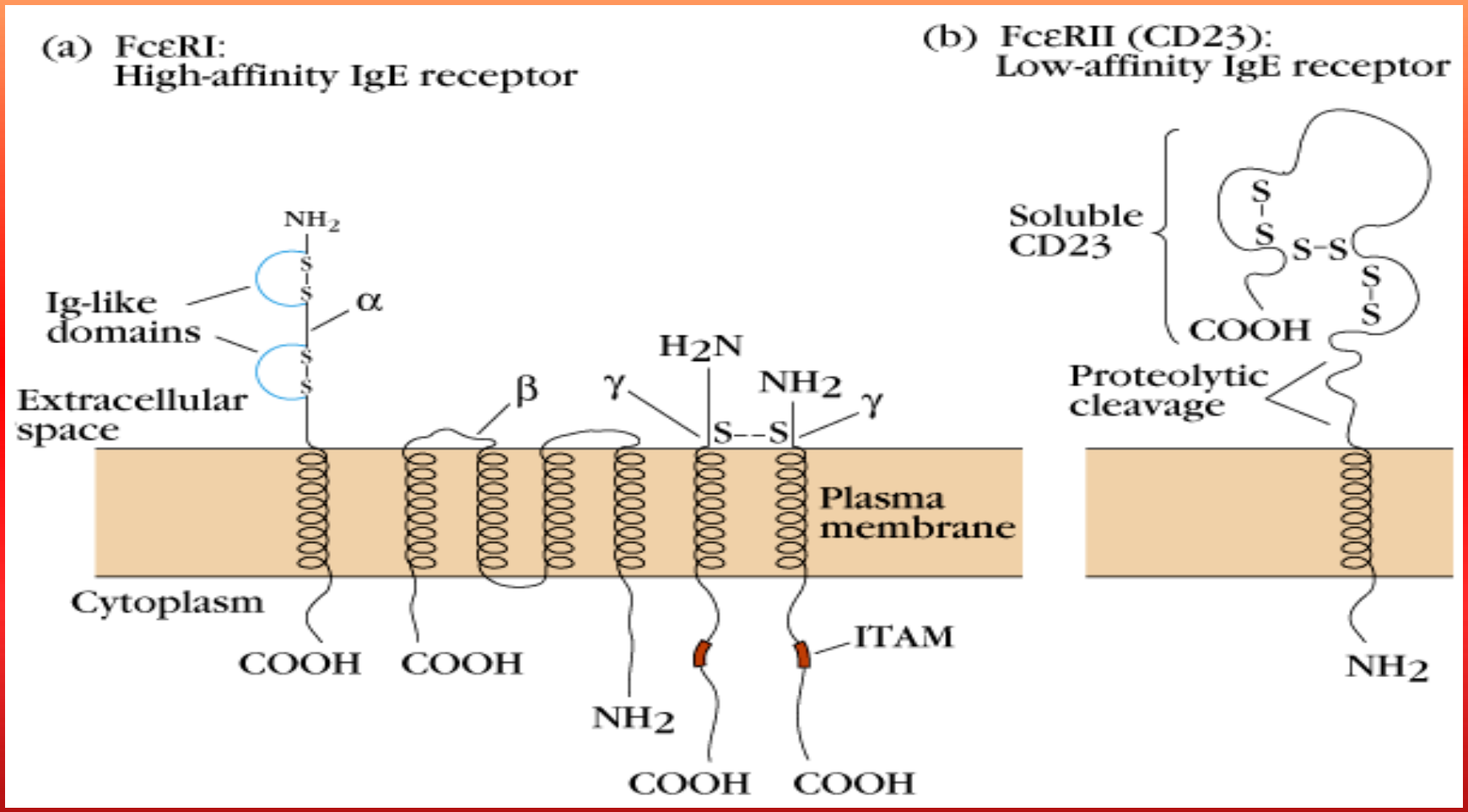




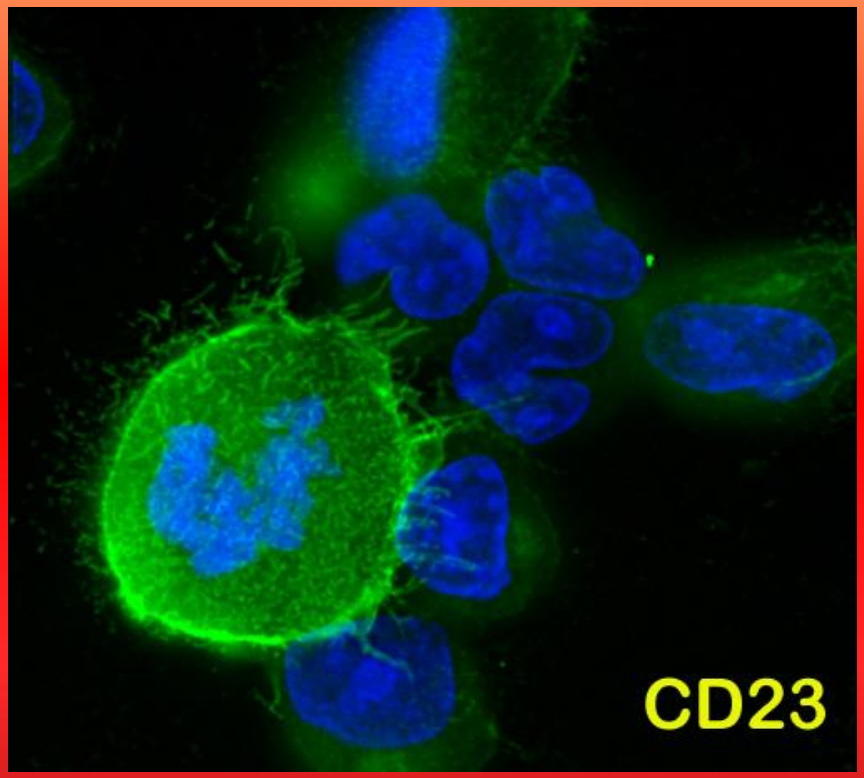
IL-4 dominance

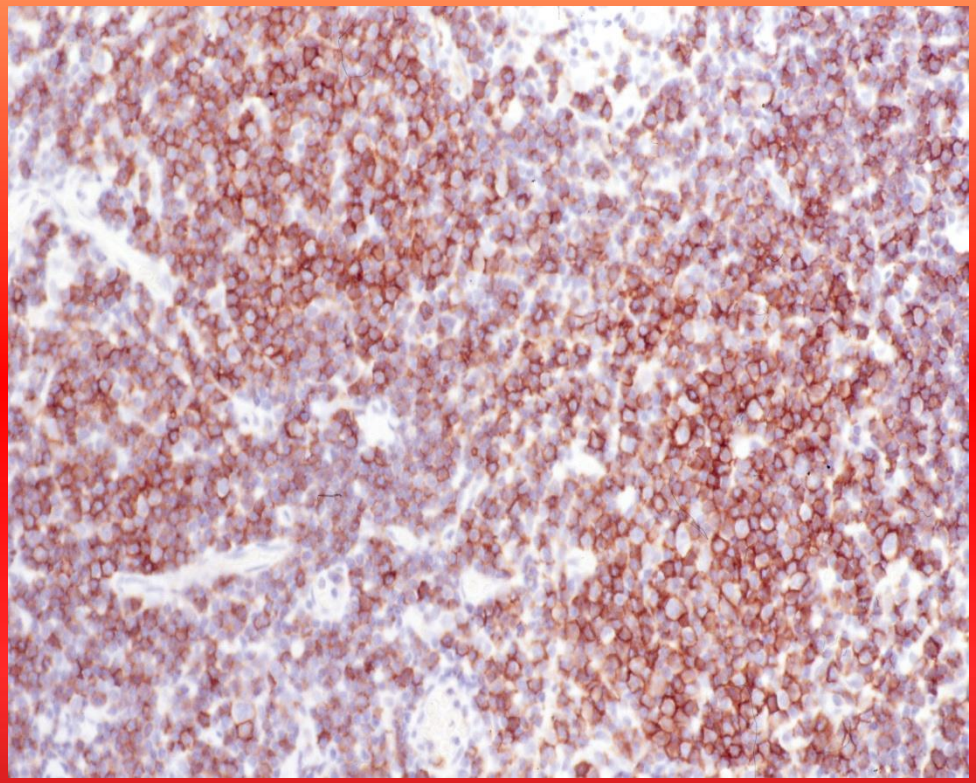

Immunoglobulin E
with name of each domain
V_L
C_L
V_H
$C_\varepsilon 1$
$C_\varepsilon 2$
$C_\varepsilon 3$
$C_\varepsilon 4$
Sites for attachment to mast cells and basophils
Sites for attachment to antigen
Carbohydrate
Variable regions
Constant regions
Disulphide bonds

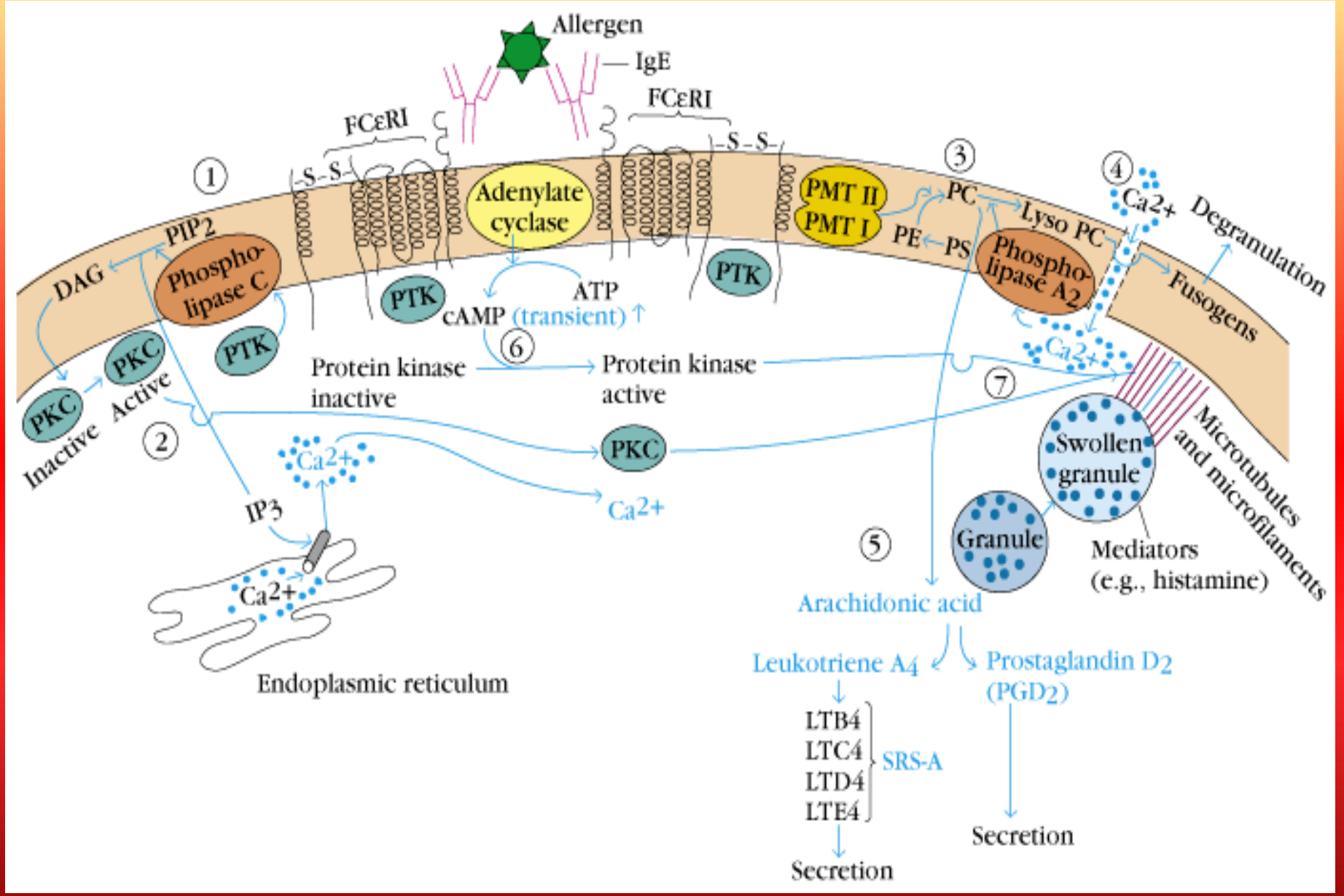
IgE binding receptors

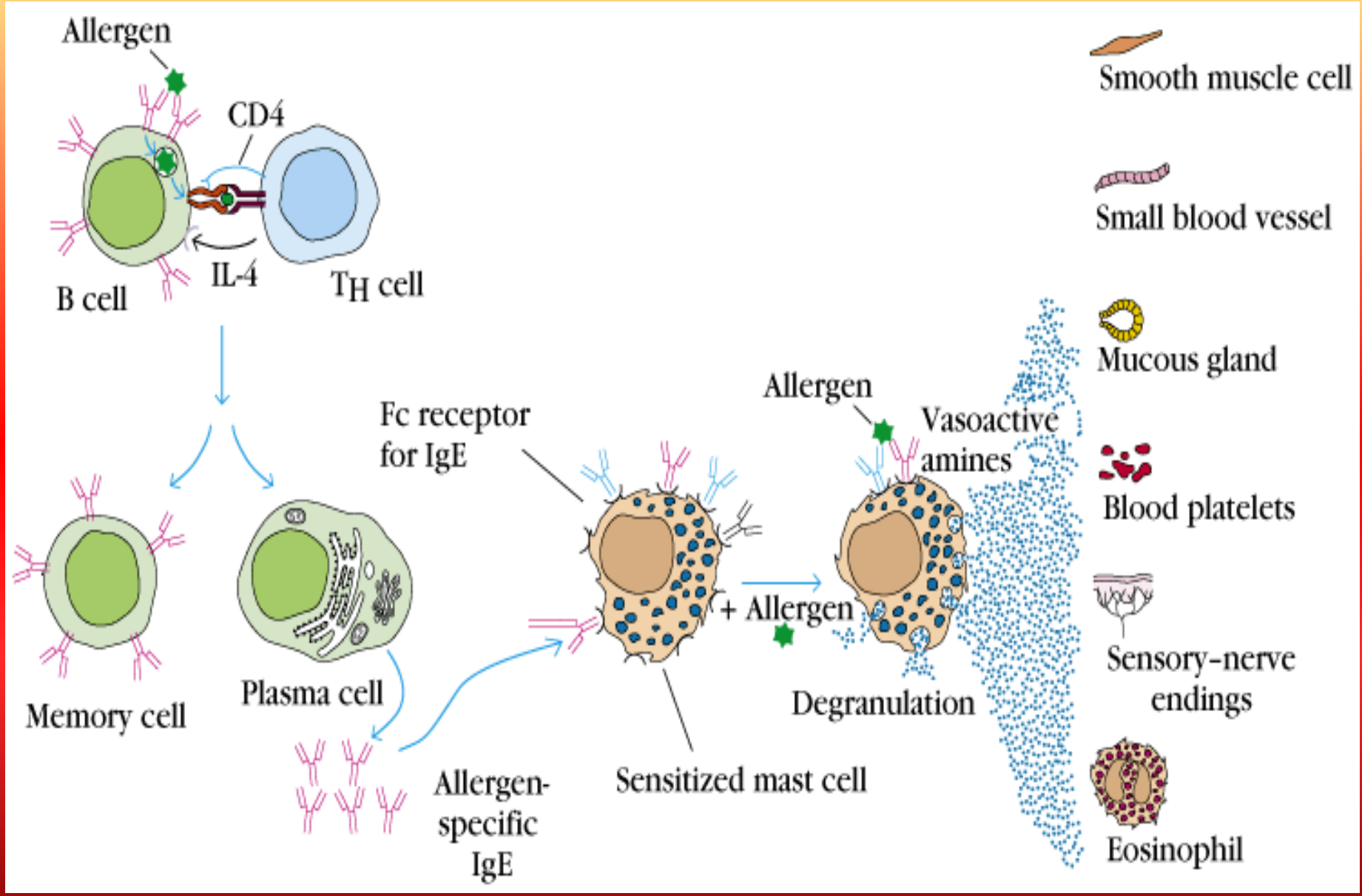


CD23 (low affinity IgE binding receptor) on eosinophyls and B lymphocytes






Allergen
IgE
FCεRI
FCεRI
S–S
S–S
1
Adenylate cyclase
PMT II
PMT I
3
PC
Lyso PC
PE
PS
Phospho-lipase A2
4
Ca2+
Degranulation
Fusogens
PIP2
DAG
Phospho-lipase C
PTK
PTK
PTK
ATP
cAMP (transient)
6
Protein kinase inactive
Protein kinase active
PKC
Active
PKC
Inactive
2
Ca2+
IP3
PKC
Ca2+
Ca2+
7
Swollen granule
Microtubules and microfilaments
Granule
Mediators (e.g., histamine)
5
Arachidonic acid
Leukotriene A4
Prostaglandin D2 (PGD2)
LTB4
LTC4
LTD4
LTE4
SRS-A
Secretion
Secretion
Endoplasmic reticulum


Allergen
CD4
IL-4
B cell
TH cell
Memory cell
Plasma cell
Allergen-specific IgE
Fc receptor for IgE
Sensitized mast cell
Allergen
+ Allergen
Vasoactive amines
Degranulation
Smooth muscle cell
Small blood vessel
Mucous gland
Blood platelets
Sensory-nerve endings
Eosinophil

Pharmacologic Mediators of Immediate Hypersensitivity

Preformed mediators in granules

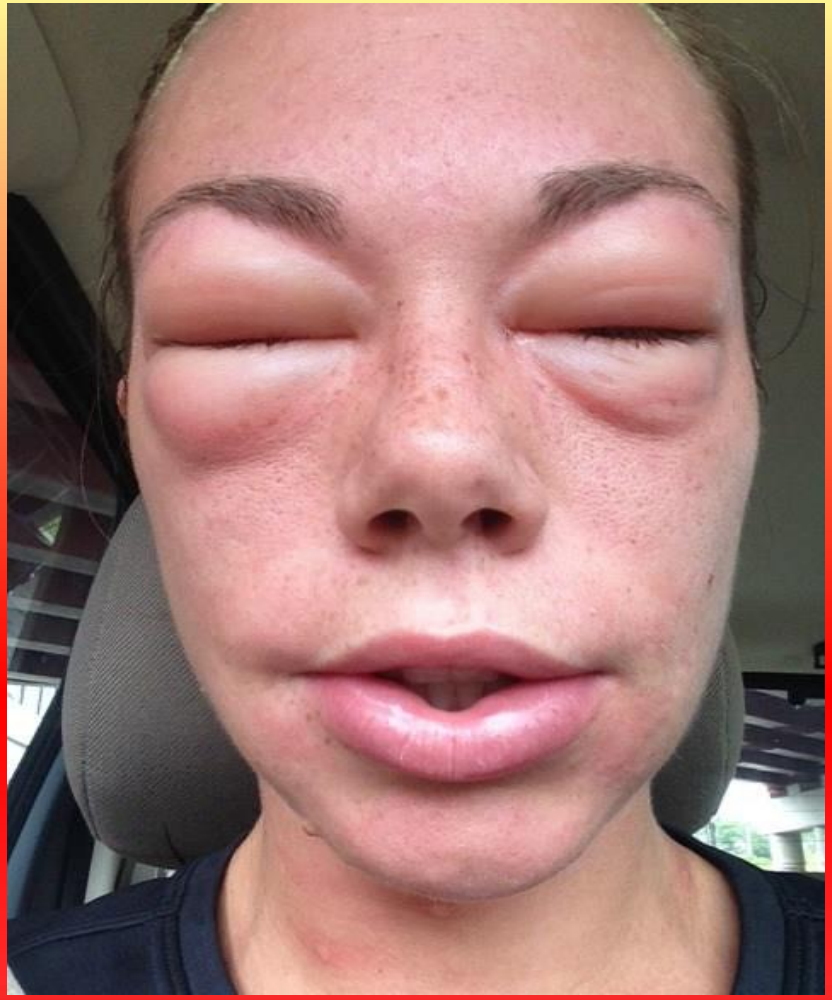
histamine	bronchoconstriction, mucus secretion, vasodilatation, vascular permeability
tryptase	proteolysis
kininogenase	kinins and vasodilatation, vascular permeability, edema
ECF-A (tetrapeptides)	attract eosinophil and neutrophils

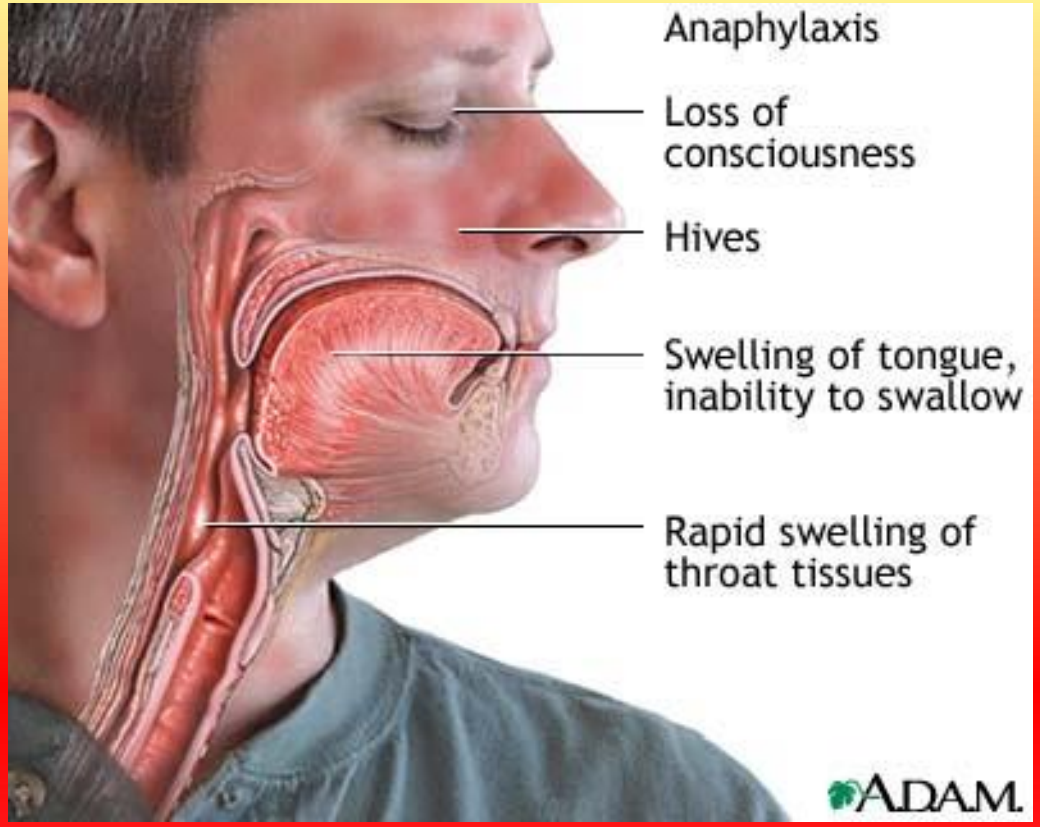
Newly formed mediators

leukotriene B_4	basophil attractant
leukotriene C_4, D_4	same as histamine but 1000x more potent
prostaglandins D_2	edema and pain
PAF	platelet aggregation and heparin release: microthrombi

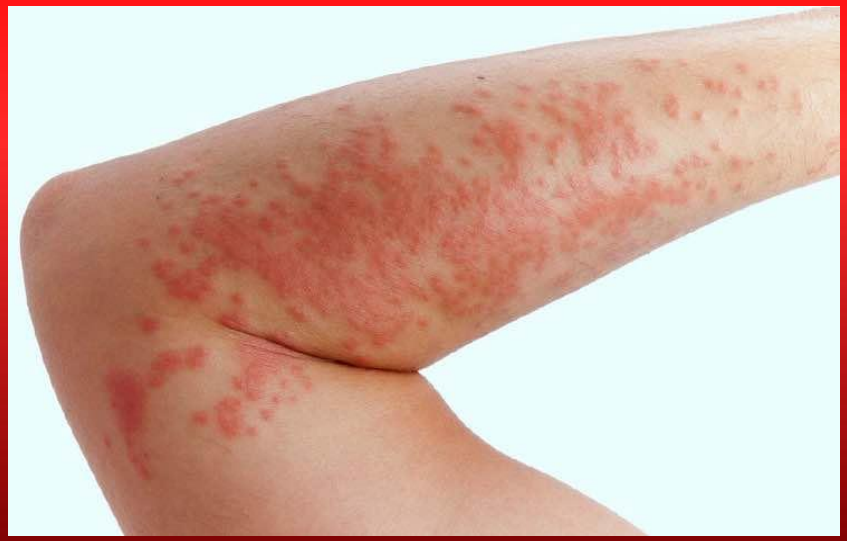
Clinical forms of allergic reactions

- Acute allergy – anaphylaxis
- Subacute and chronic allergies initiated by aeroallergens and food allergens
- Secondary organ failures caused by chronic allergies



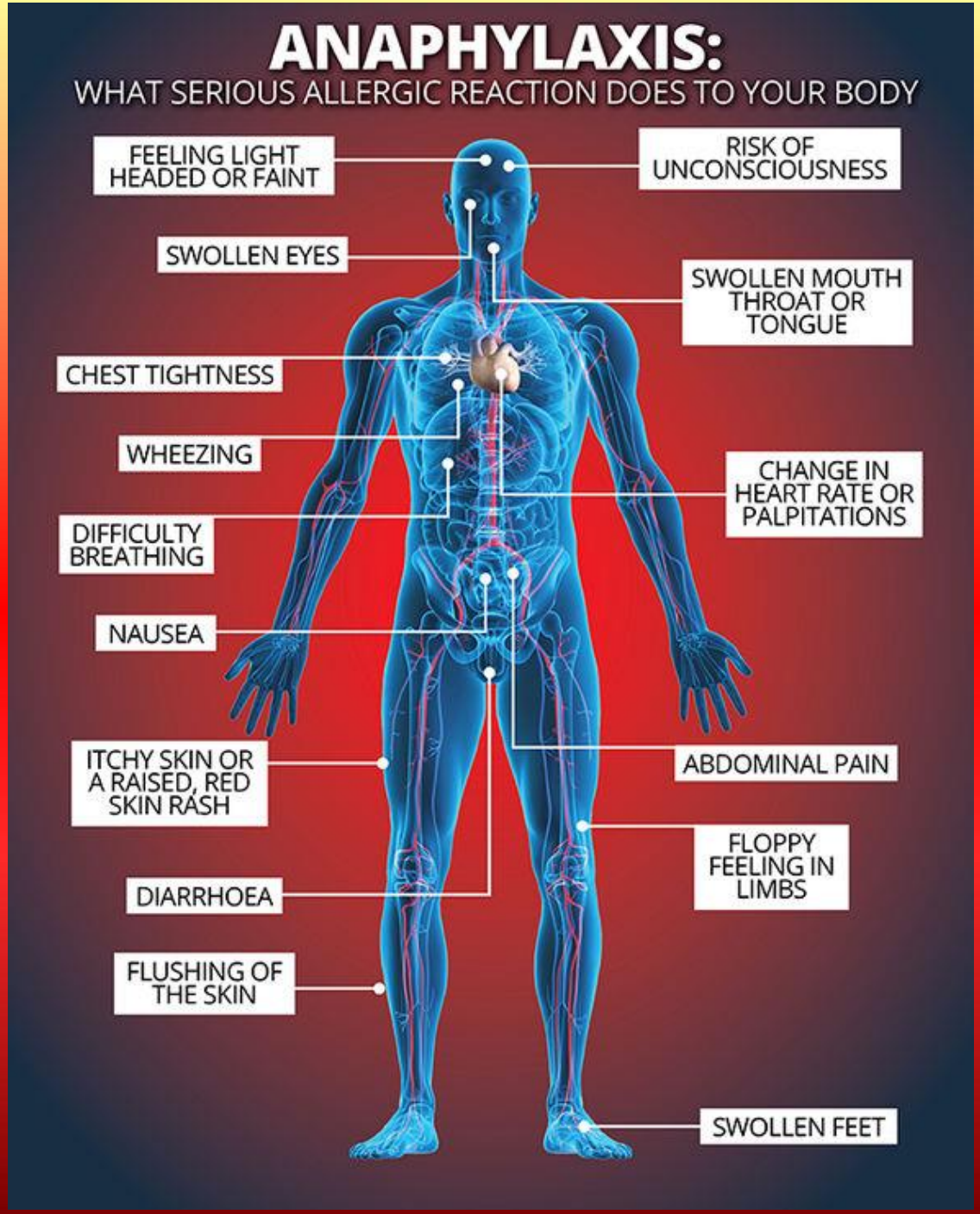


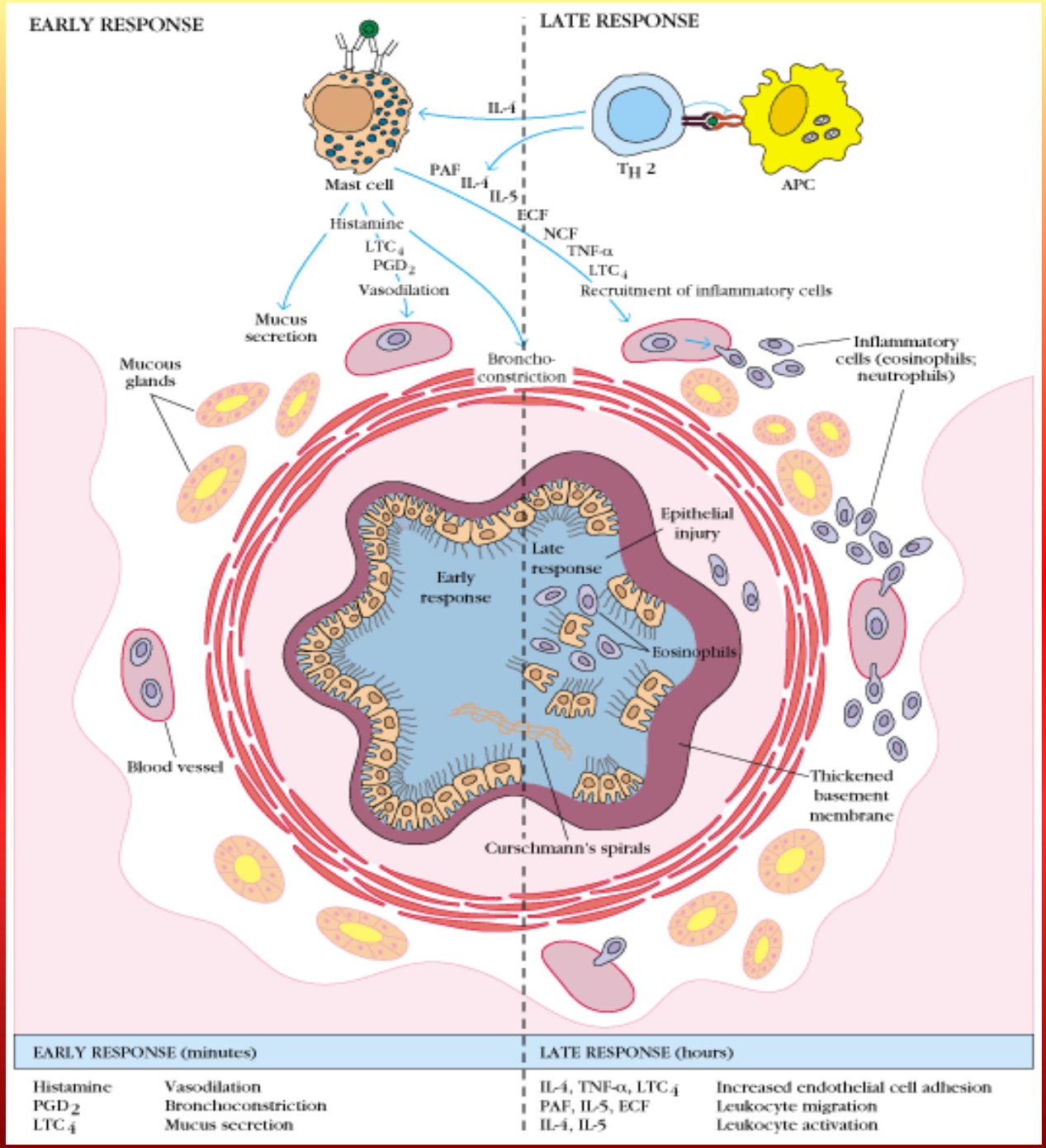
Anaphylaxis is a serious acute allergic reaction that is rapid in onset and may lethal.



ANAPHYLAXIS:

WHAT SERIOUS ALLERGIC REACTION DOES TO YOUR BODY

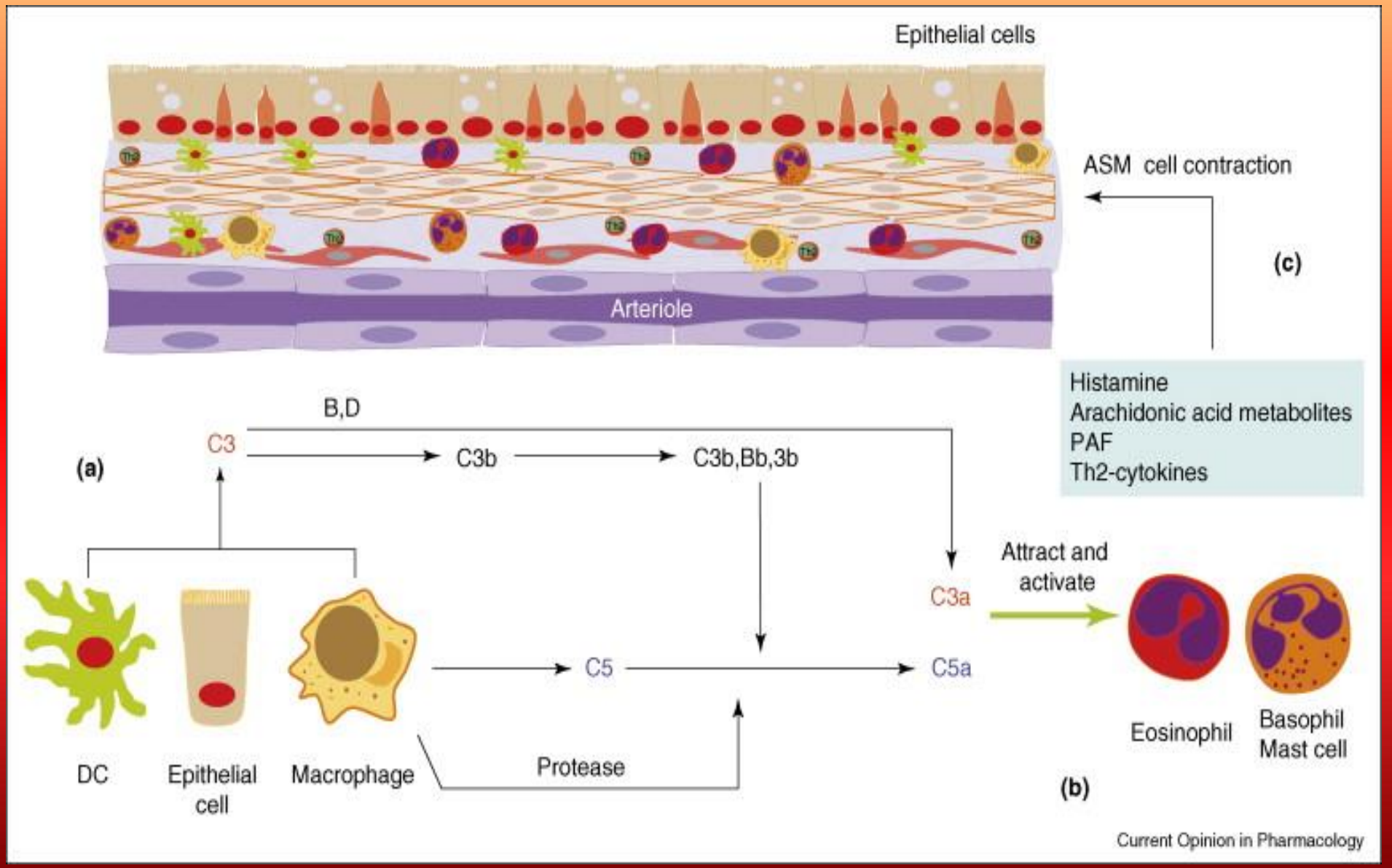



EARLY RESPONSE
LATE RESPONSE
IL-4
PAF
IL-4
IL-5
Mast cell
T_H 2
APC
ECF
NCF
TNF-α
LTC_4
Histamine
LTC_4
PGD_2
Vasodilation
Recruitment of inflammatory cells
Mucus secretion
Broncho-constriction
Mucous glands
Inflammatory cells (eosinophils; neutrophils)
Epithelial injury
Late response
Early response
Eosinophils
Blood vessel
Thickened basement membrane
Curschmann's spirals
EARLY RESPONSE (minutes)
Histamine
PGD_2
LTC_4
Vasodilation
Bronchoconstriction
Mucus secretion
LATE RESPONSE (hours)
IL-4, TNF-α, LTC_4
PAF, IL-5, ECF
IL-4, IL-5
Increased endothelial cell adhesion
Leukocyte migration
Leukocyte activation

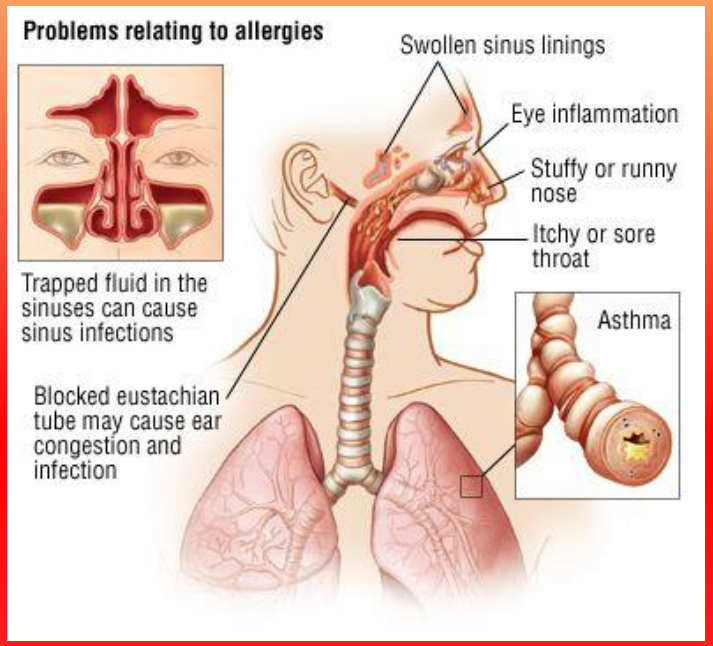
IgG mediated anaphylaxis

- More antigen-specific IgG produced as IgE and FcγRIIIA and FcγRIV on neutrophils can activate anaphylaxis in mouse model.
- Human neutrophils, but also mast cells and basophils, express neither FcγRIIIA nor FcγRIV, but FcγRIIA triggers allergic reactions.
- FcγRIIB have dominant inhibitory effect over positive signals triggered by FcγRIIA.
- Co-engagement of FcεRI with FcγR (both inhibitory and triggering) induces FcγRIIB-dependent inhibition of IgE-induced responses of human basophils.
- IgG antibodies can develop antagonistic roles when engaging low-affinity IgG receptors on granulocytes, but they can trigger allergic reactions by engaging with FcγRIIA expressed by neutrophils, monocytes, macrophages and mast cells, but inhibitory effect if expressed in basophils.

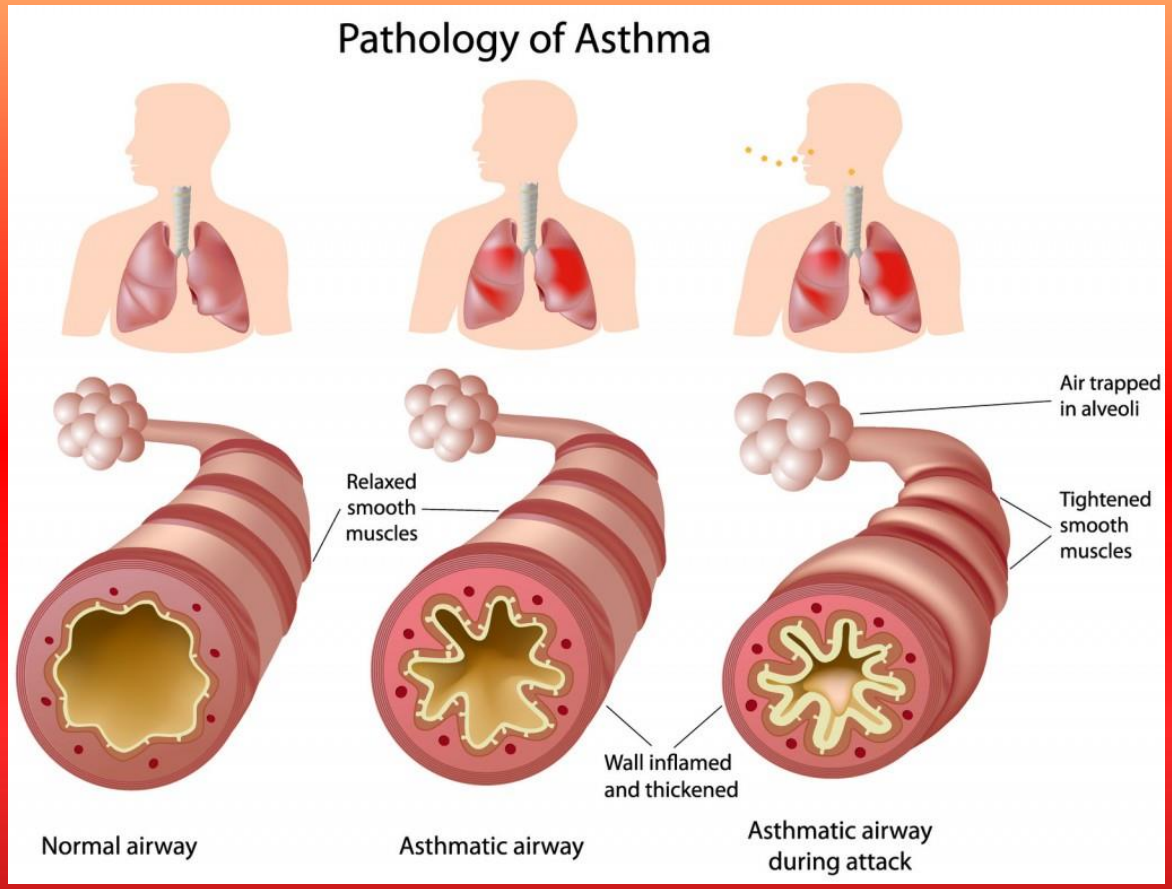
Complement induced allergic asthma



Consequences of respiratory allergy

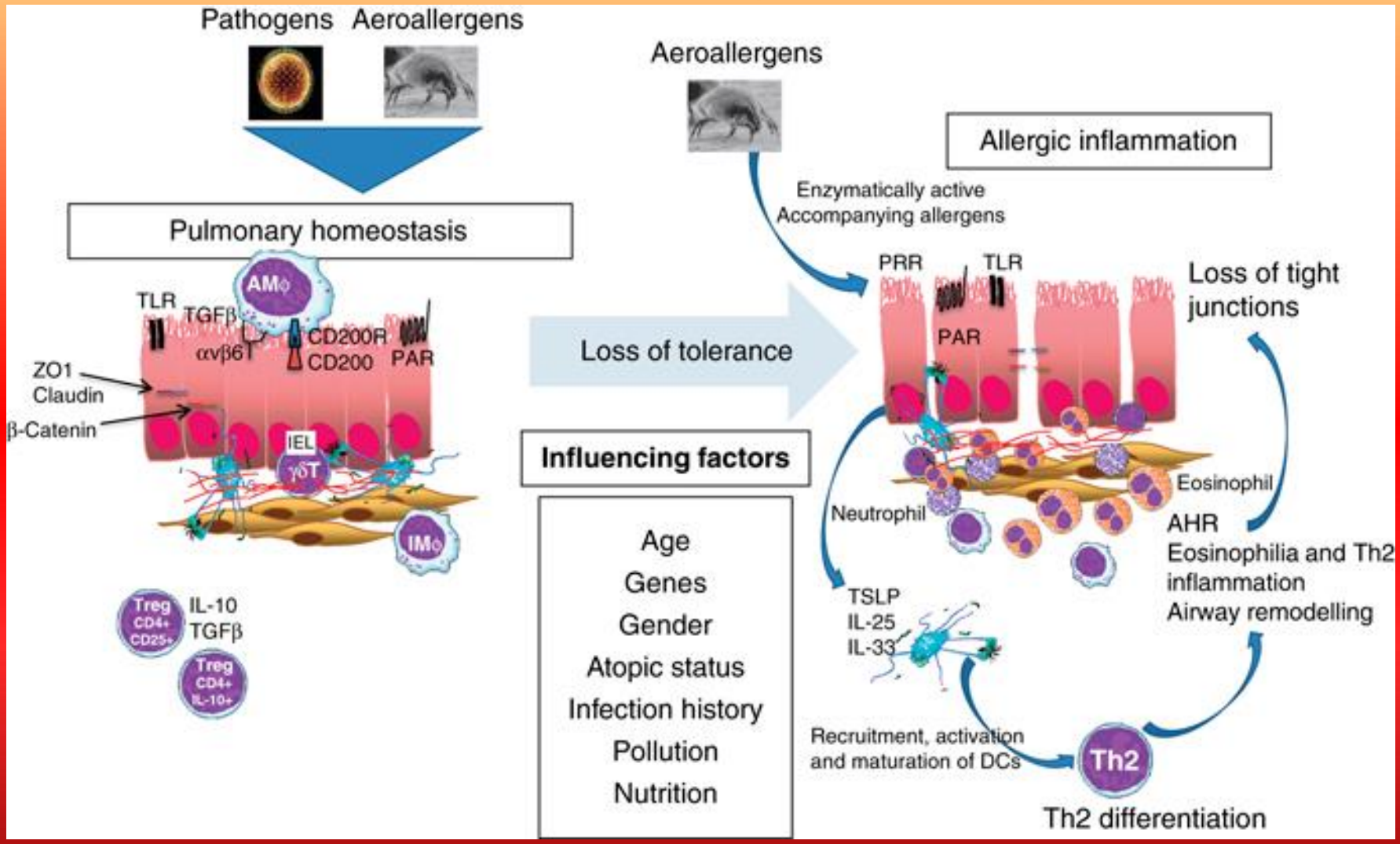


Chronic sinusitis and rhinitis, middle ear, eye and lacrimal gland inflammations

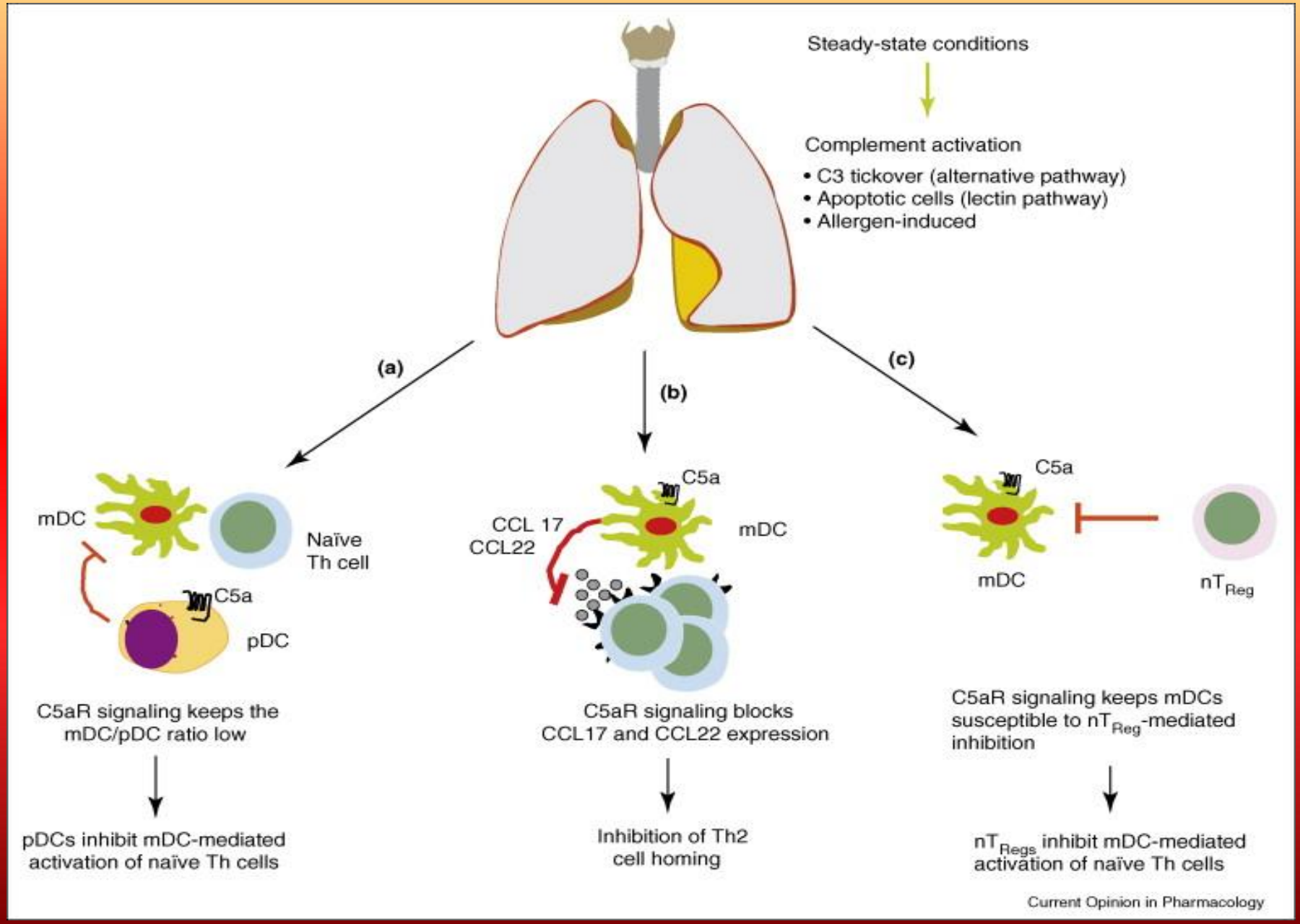


Asthma bronchiale

Pulmonary allergy



Protective role of C5aR signaling in allergic asthma



Cross-reactivity between aeroallergens and food allergens

In respiratory allergy, cross-reactivity between aeroallergens and foods may induce food allergy, symptoms ranging from oral allergy syndrome to severe anaphylaxis. Clinical entities due to IgE sensitization to cross-reactive aeroallergen and food allergen components are described for many sources of plant origin (pollen-food syndromes and associations, such as birch-apple, cypress-peach and celery-mugwort-spice syndromes, and mugwort-peach, mugwort-chamomile, mugwort-mustard, ragweed-melon-banana, goosefoot-melon associations), fungal origin (Alternaria-spinach syndrome), and invertebrate, mammalian or avian origin (mite-shrimp, cat-pork, and bird-egg syndromes). Clinical cases of allergic reactions to ingestion of food products containing pollen grains of specific plants, in patients with respiratory allergy to Asteraceae pollen, especially mugwort and ragweed, are also mentioned, for honey, royal jelly and bee polen dietary supplements, along with allergic reactions to foods contaminated with mites or fungi in patients with respiratory allergy to these aeroallergens.

***Popescu FD*: World J Methodol. 2015**

Artemisia vulgaris

celery-mugwort-spice-syndrome

Apiaceae

Solanaceae

Piperaceae

Anacardiaceae

Liliaceae

mugwort-mustard-syndrome

Cruciferae

*Leguminosae**

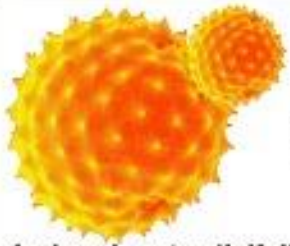
*Rosaceae**

mugwort-peach-association

Rosaceae

mugwort-chamomile-association

Asteraceae



Ambrosia artemiisifolia

ragweed-melon-banana-association

Cucurbitaceae

Musaceae

Birch

Apple Peach Plum Pear Cherry Apricot Almond

Rosaceae

Carrot Celery Parsley Caraway Fennel Coriander Aniseed

Apiaceae

Soybean Peanut

Fabaceae (old Leguminosae)

Hazelnut

Betulaceae

Ragweed

Cantaloupe Honeydew Watermelon Zucchini Cucumber

Cucurbitaceae

Banana

Musaceae

Mugwort

Celery Carrot Parsley Caraway Fennel Coriander Aniseed

Apiaceae

Bell pepper

Solanaceae

Black pepper

Piperaceae

Mustard Cauliflower Cabbage Broccoli

Brassicaceae

Garlic Onion

Liliaceae

Orchard

Cantaloupe Honeydew Watermelon

Cucurbitaceae

Peanut

Fabaceae (old Leguminosae)

White potato Tomato

Solanaceae

Timothy

Swiss chard

Amaranthaceae

Orange

Rutaceae

Food hypersensitivity

Non-allergic food hypersensitivity

Examples:
Lactose –milk – intolerance
Hypersensitivity towards sulphites
Other reactions of unknown mechanisms

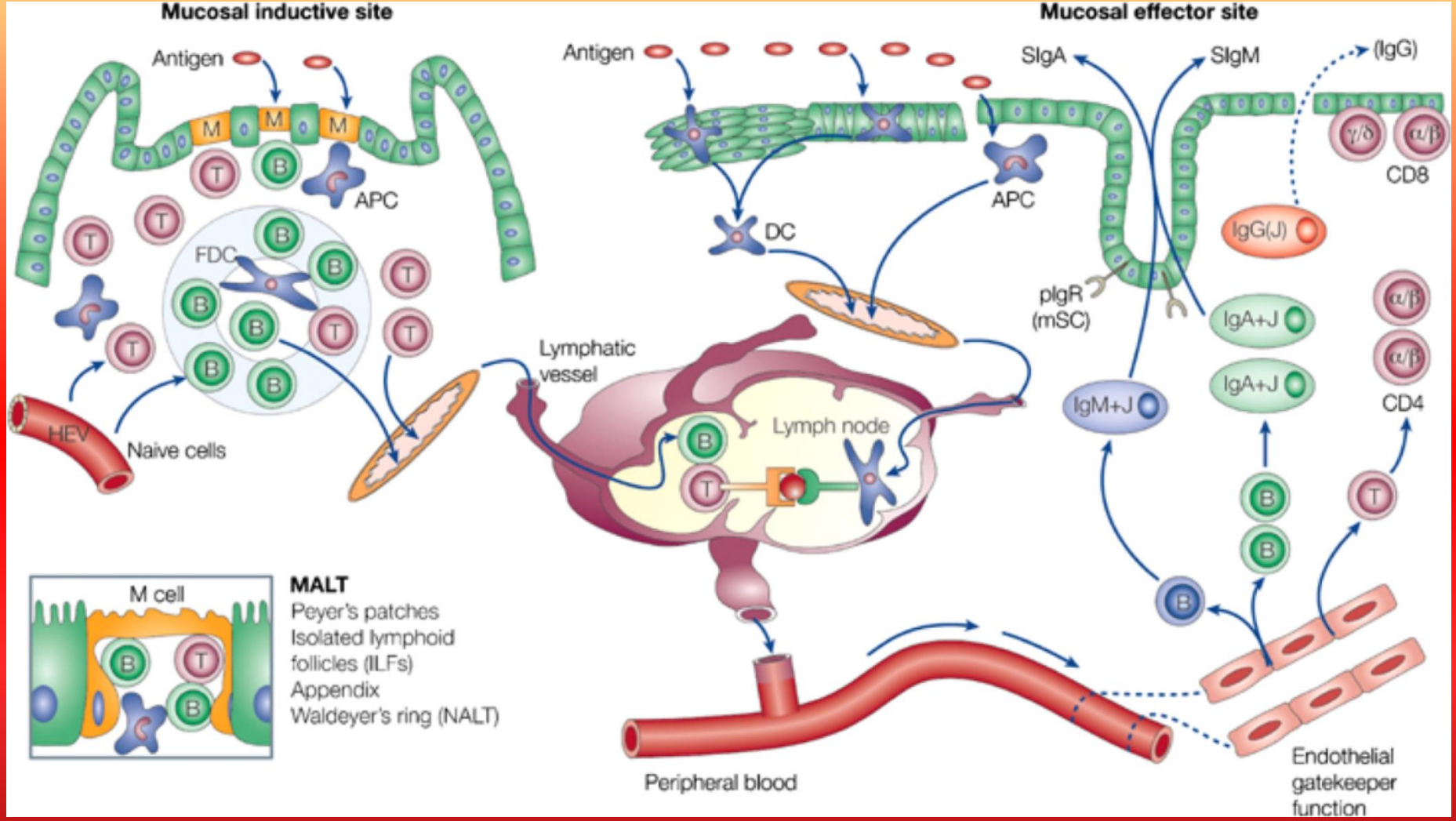
Food allergy

IgE-mediated food allergy

Examples:
Milk, egg, peanut, etc…
Pollen related
Latex related

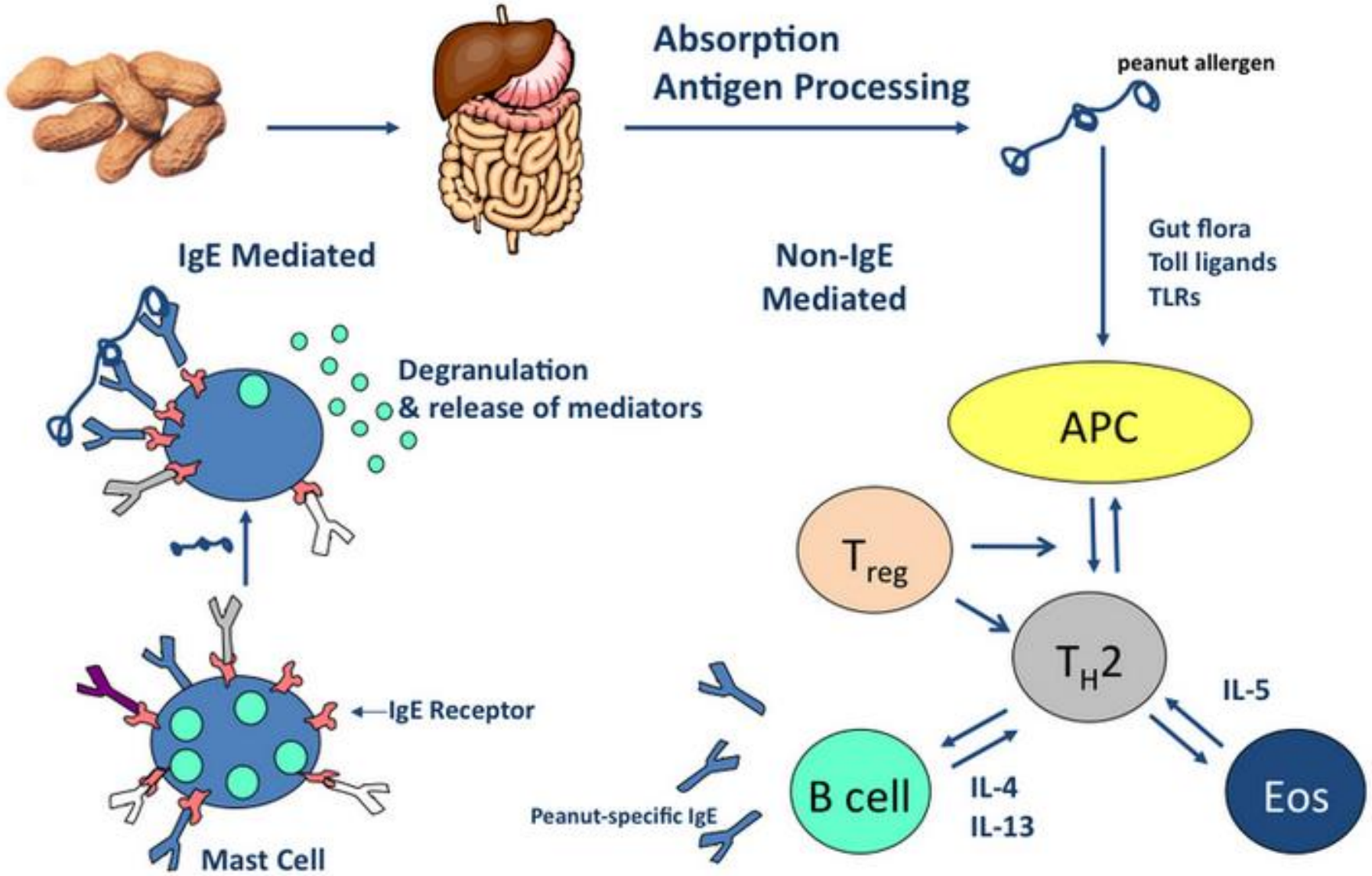
Non-IgE-mediated food allergy

Examples:
Gluten intolerance (Coeliac disease)
Systemic allergic contact dermatitis


Mucosal inductive site
Antigen
M
M
M
T
B
APC
T
T
FDC
B
B
B
B
B
T
T
T
T
B
B
HEV
Naive cells
Lymphatic vessel
Mucosal effector site
Antigen
SIgA
SIgM
(IgG)
γ/δ
α/β
CD8
APC
DC
IgG(J)
pIgR (mSC)
IgA+J
IgA+J
IgM+J
α/β
α/β
CD4
Lymph node
B
T
B
B
B
T
M cell
B
T
B
MALT
Peyer's patches
Isolated lymphoid follicles (ILFs)
Appendix
Waldeyer's ring (NALT)
Peripheral blood
Endothelial gatekeeper function

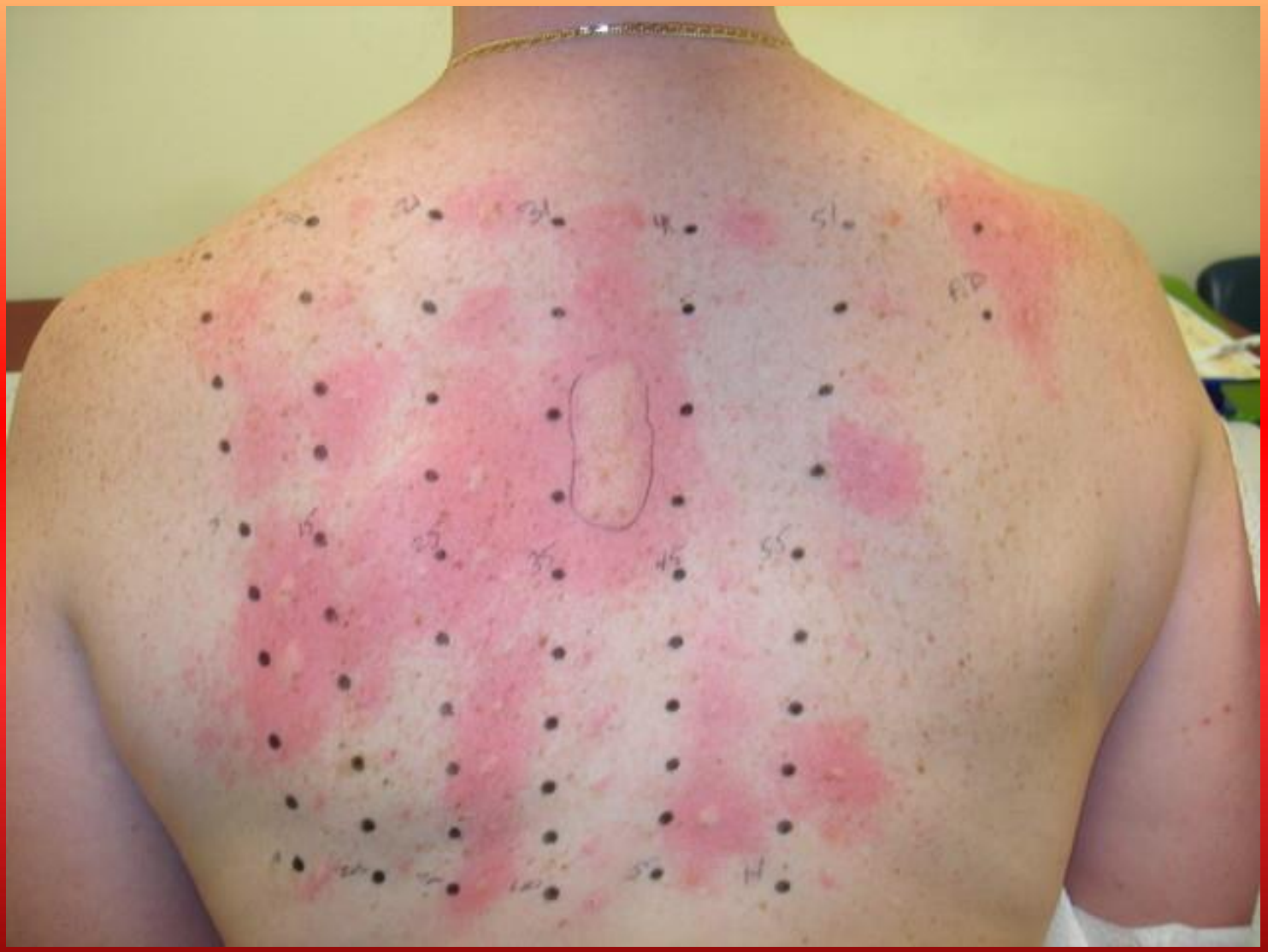
Mechanism of Food Allergen Sensitization

Failure of Oral Tolerance



Food allergy skintest

Skin test

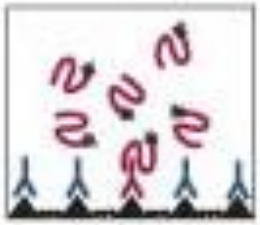


How HESKA® ALLERCEPT® Panels Work

=IgG =IgE =Anti-IgE =FCεRIα

HESKA® ALLERCEPT® Detection System

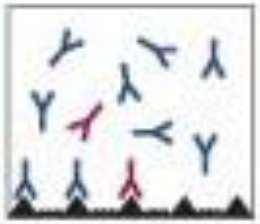
Step 1. Well is coated with allergen and serum is added. Allergen-specific IgE and IgG bind to the allergen.



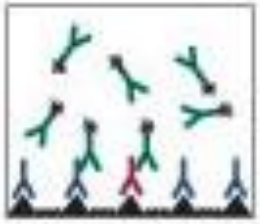
Step 2. FCεRIα is added and binds to IgE only.

Step 3. Enzyme and then substrate is added that produces color, thus labeling IgE.

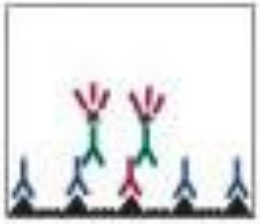
Conventional Anti-IgE Monoclonal and Polyclonal Methods



Step 1. Well is coated with allergen and serum is added. Allergen-specific IgE and IgG bind to the allergen.



Step 2. Polyclonal or monoclonal anti-IgE is added and binds to IgE, but often binds to IgG as well.



Step 3. Enzyme and then substrate is added that produces color, thus labeling IgG, as well as IgE.

Therapeutic relevances

1. **Acute intervention**

(adrenalin, corticosteroid)

2. **Prevention**

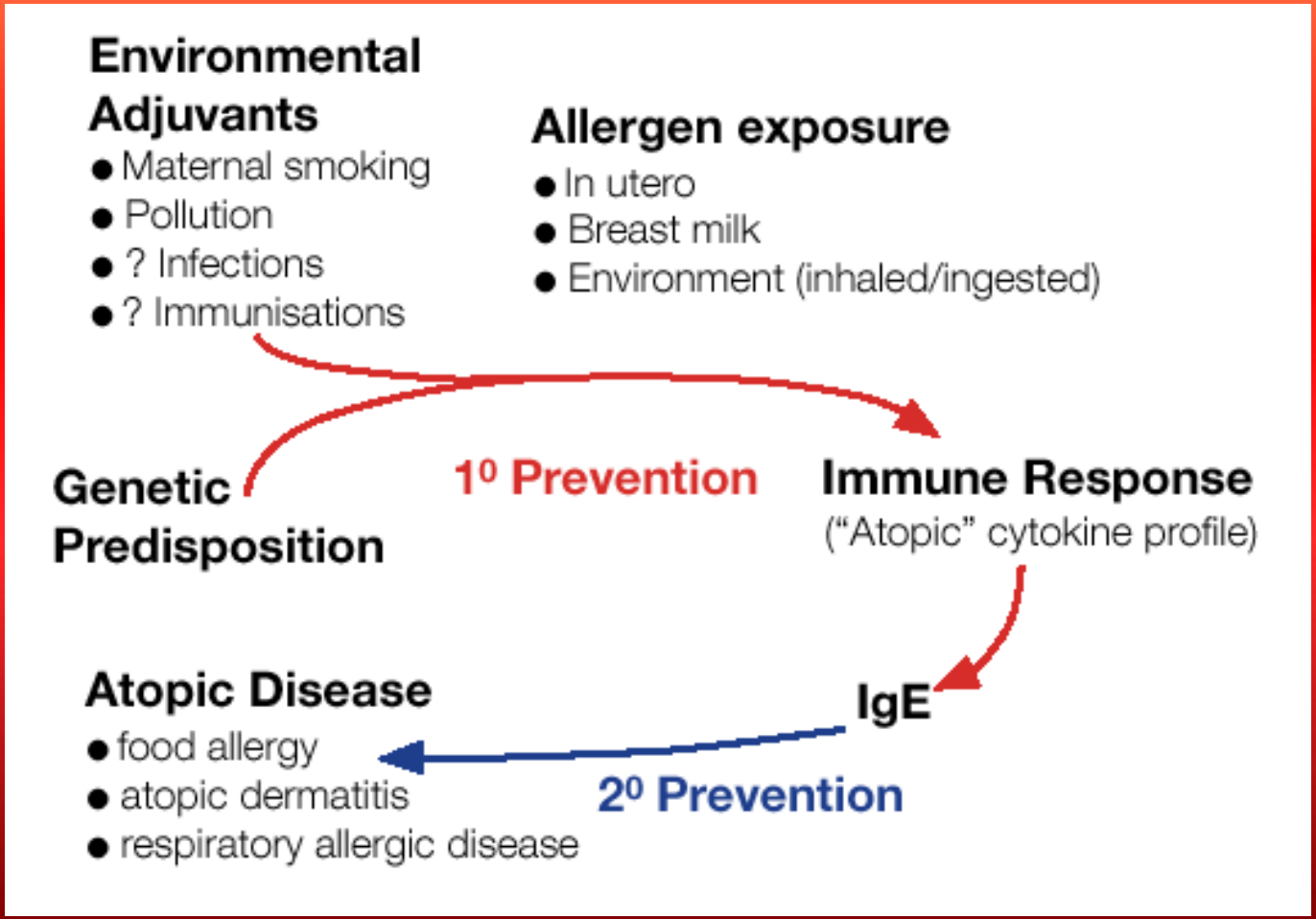
- **Allergen free environment**
- **Desensibilization**

3. **Treatments**

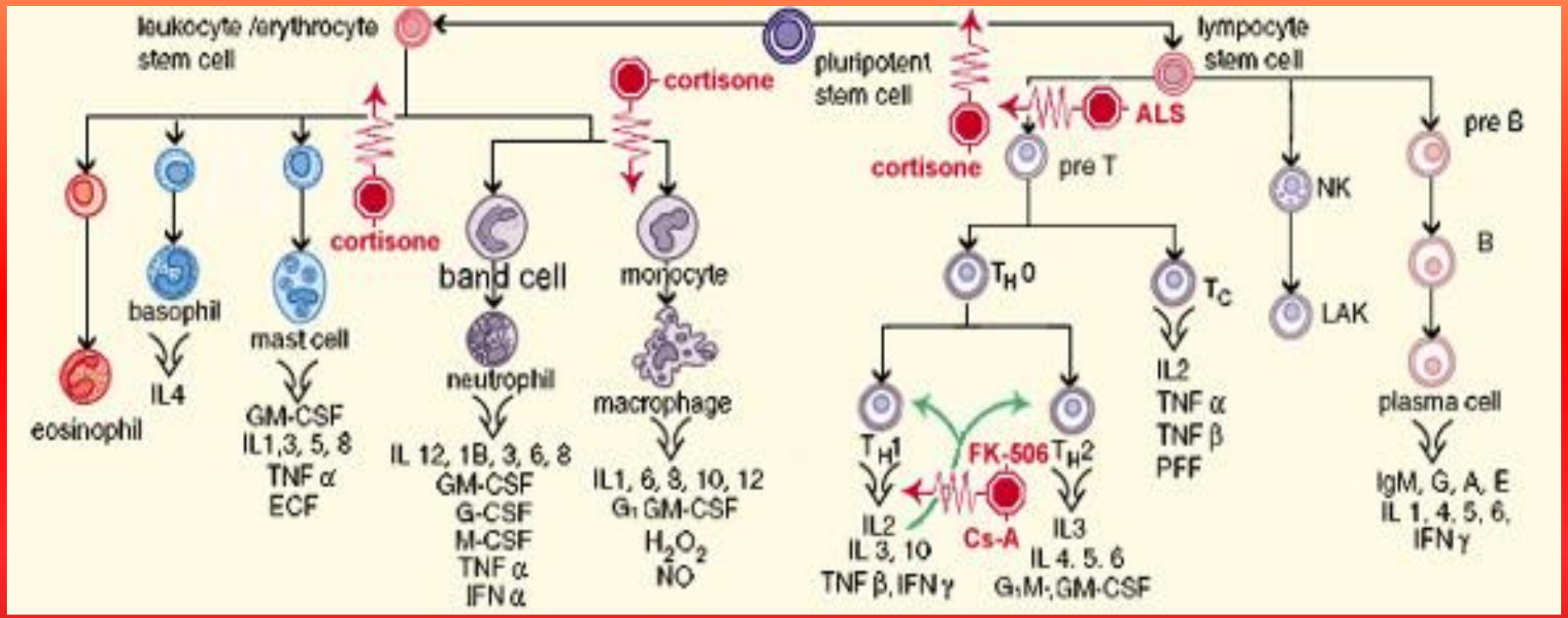
- **Antihistamins**
- **Non-specific immunosuppression**

Prevention

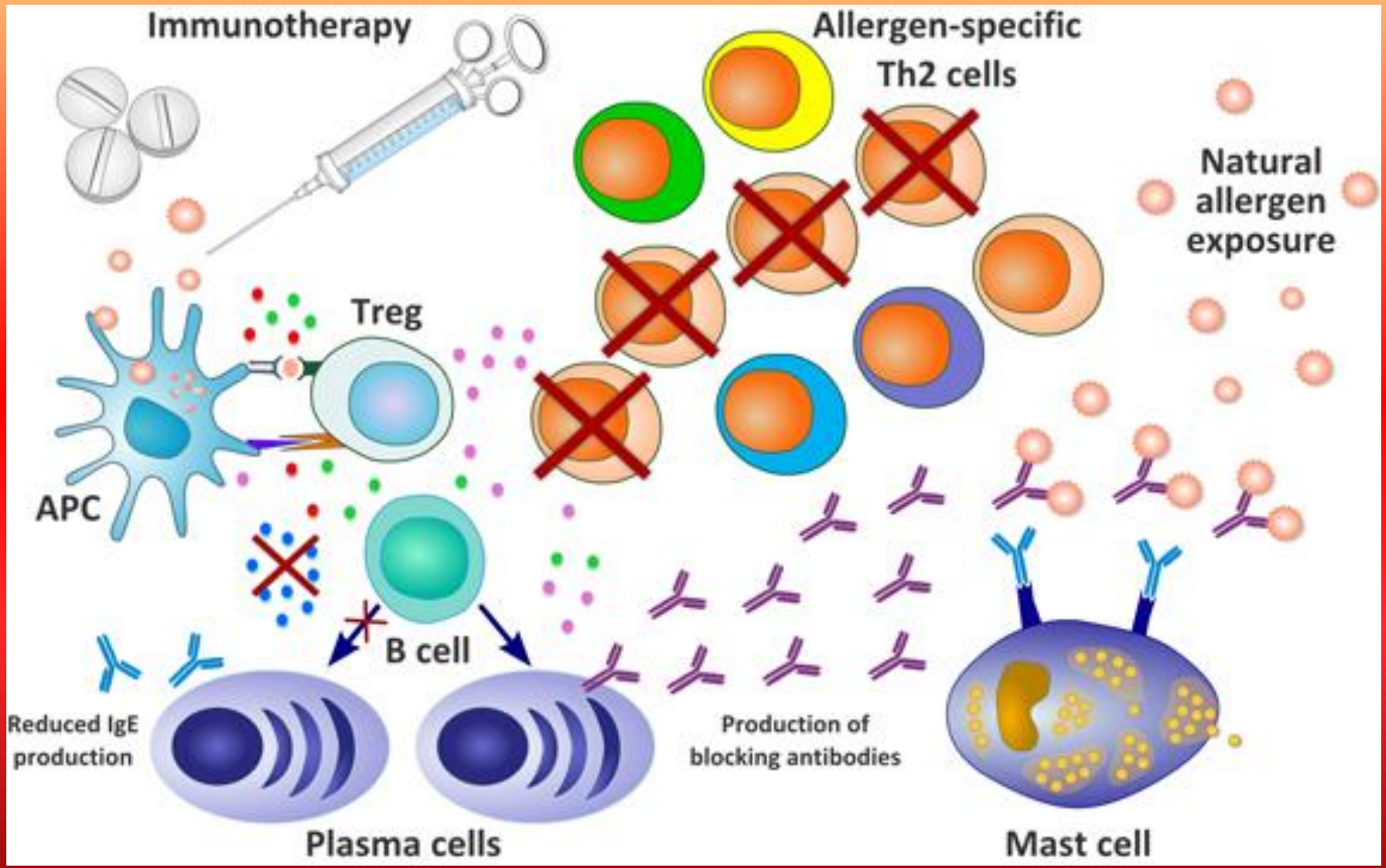
- Allergen free environment
- Primary and secondary prevention



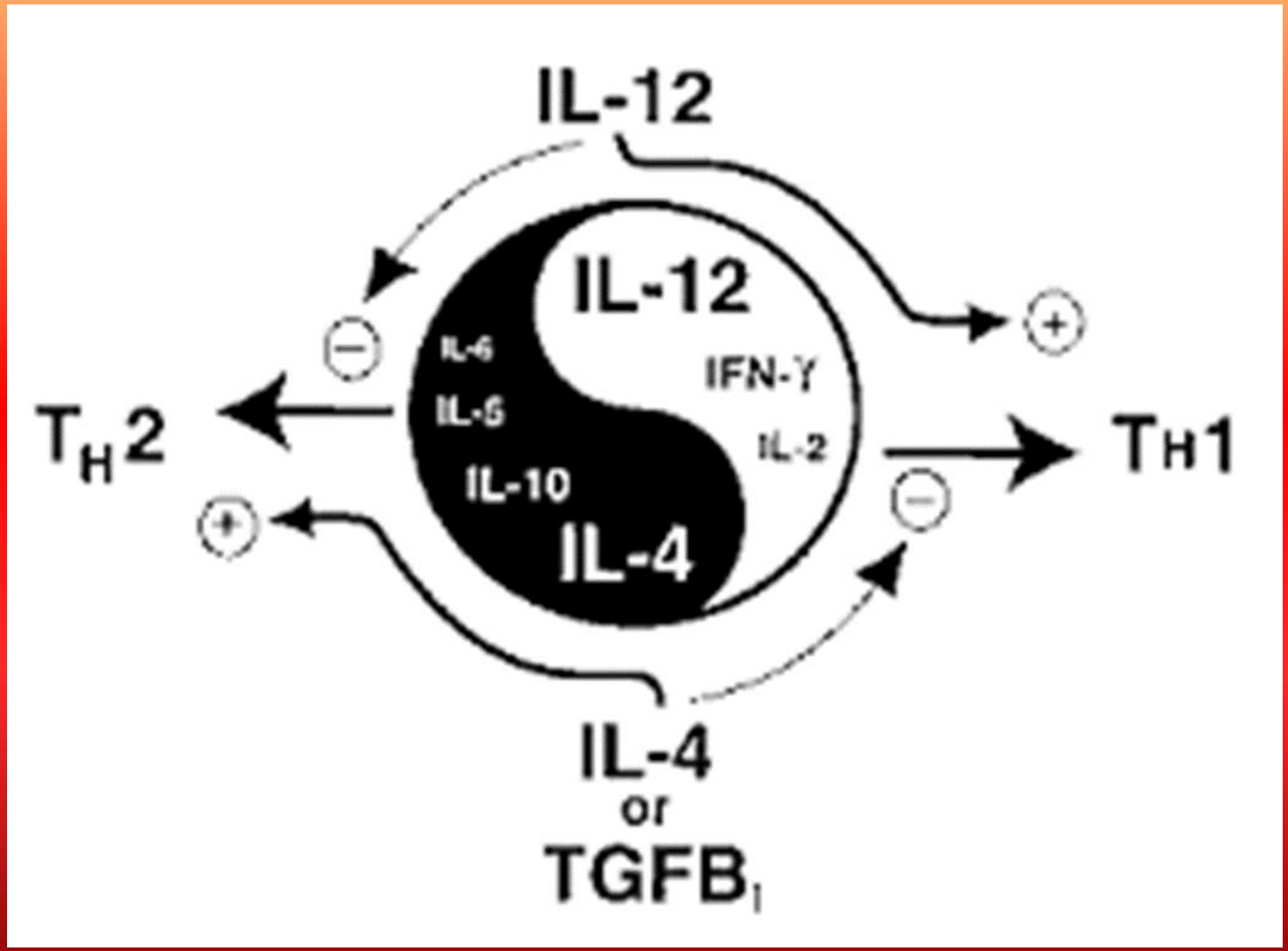
Immunosuppression



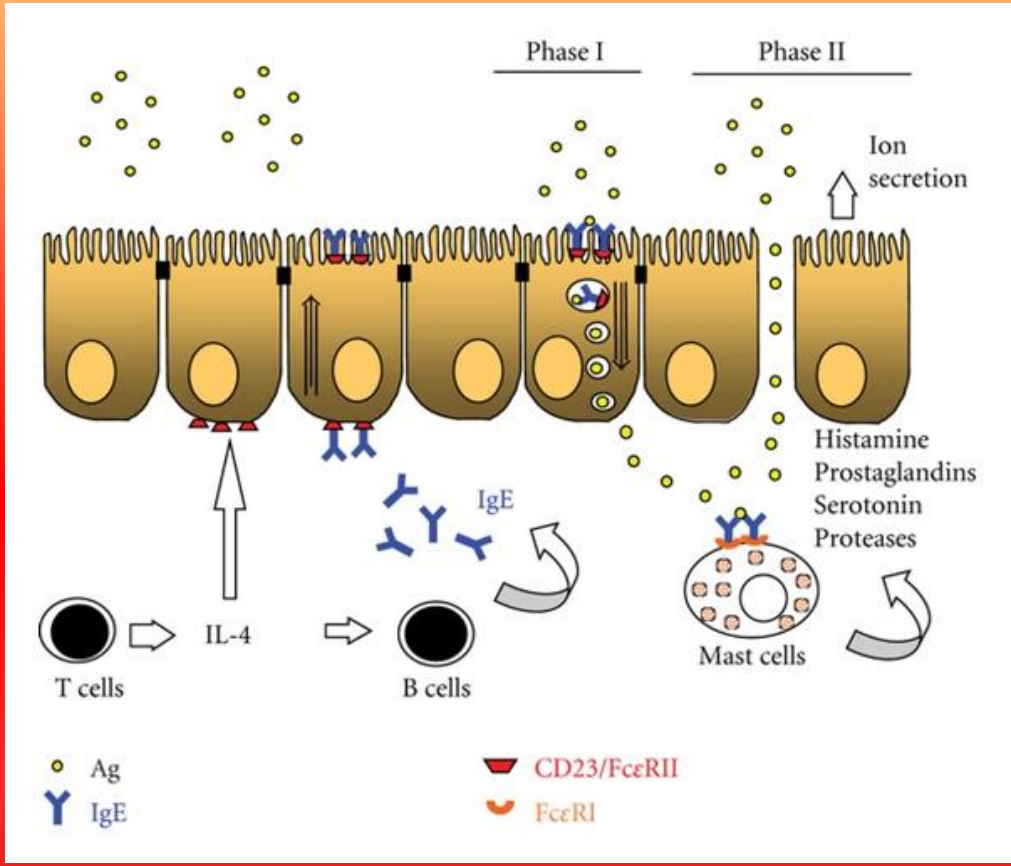
Desensibilisation



Immunological „Yin-Yang”



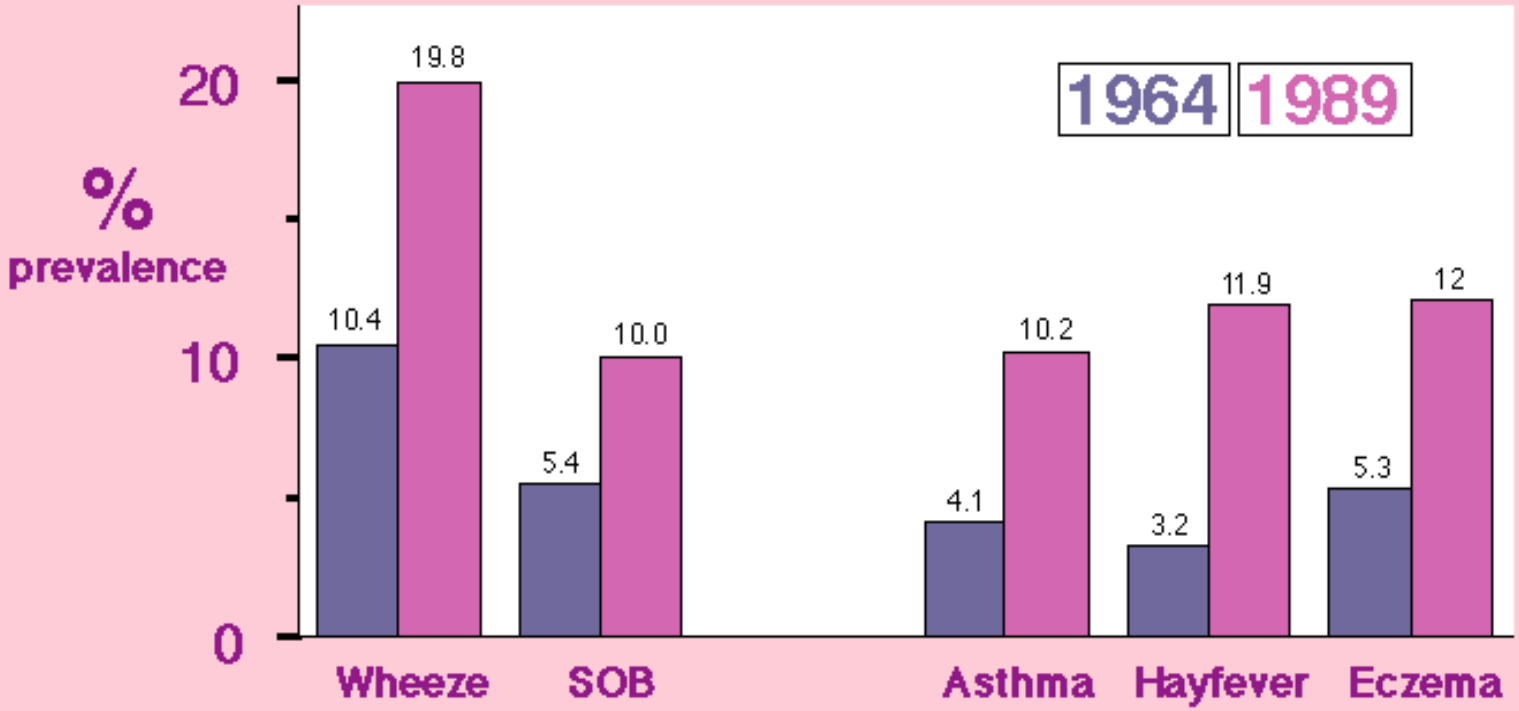
In vivo intranasal anti-CD23 treatment inhibits allergic responses in a murine model of allergic rhinitis.



CD23-dependent transcytosis of IgE and IgE-derived immune complexes across respiratory epithelial cells is likely to play a pivotal role in the initiation and development of airway allergic inflammation and suggest that the targeting of CD23 could be used as a means of therapeutic intervention.

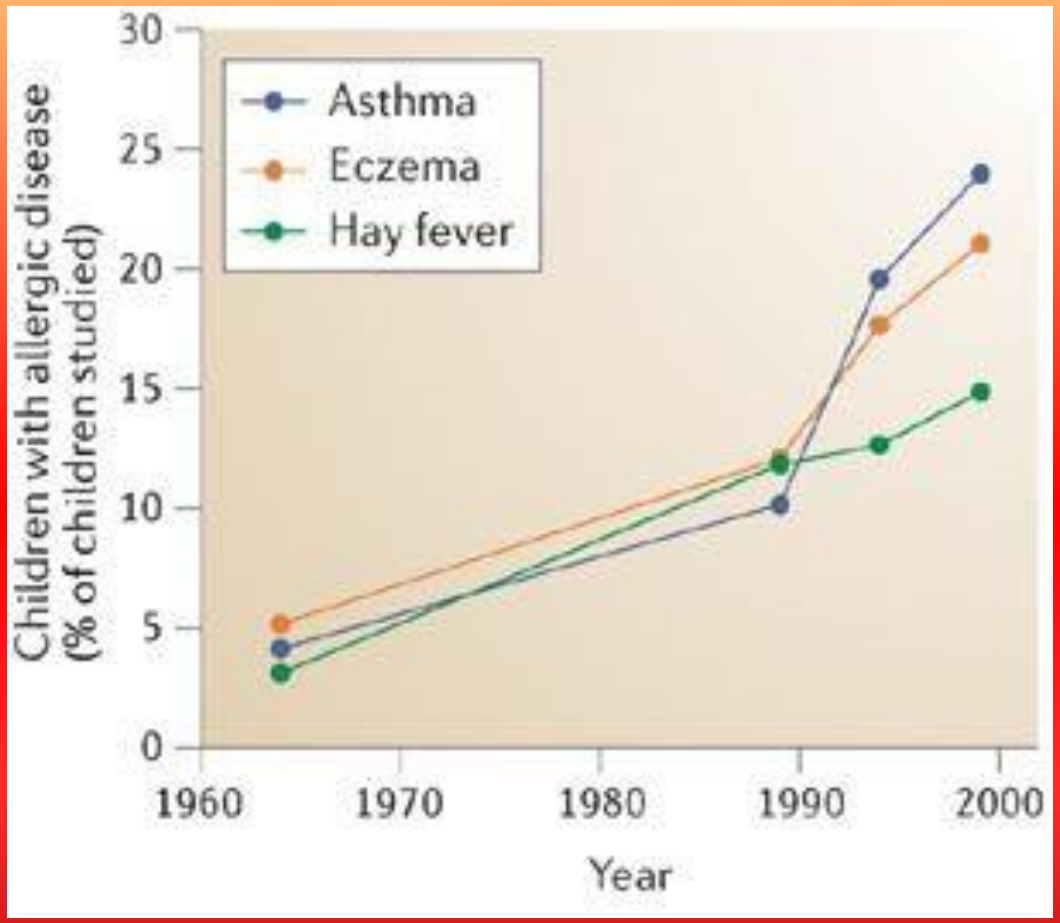
Zhou M1, Du D, Zhao K, Zheng C. : J Mol Histol. 2013

Increasing prevalence of asthma & atopy
Aberdeen 1964 - 1989
schoolchildren aged 8 - 13 yrs inclusive



Ninan TK, Russell G. BMJ 1992;304:873-5

Prevalence of allergic diseases increasing in the industrialized countries continuously



- Diet
- Materrnal diet during pregnancy
- Smoking
- Alterations in microbiota
- Antibiotic treatments
- ?
- ?
- ?

Continuation of the Aberdeen Study

Devereux G.: **Nat Rev Immunol. 2006**