Immunopathology
2025’

Pathomechanism of allergic reactions

II.

Food allergy

A food allergy is a hypersensive reaction that occurs after consuming some foods.

Food hypersensitivity

Non-allergic food hypersensitivity

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

Food allergy

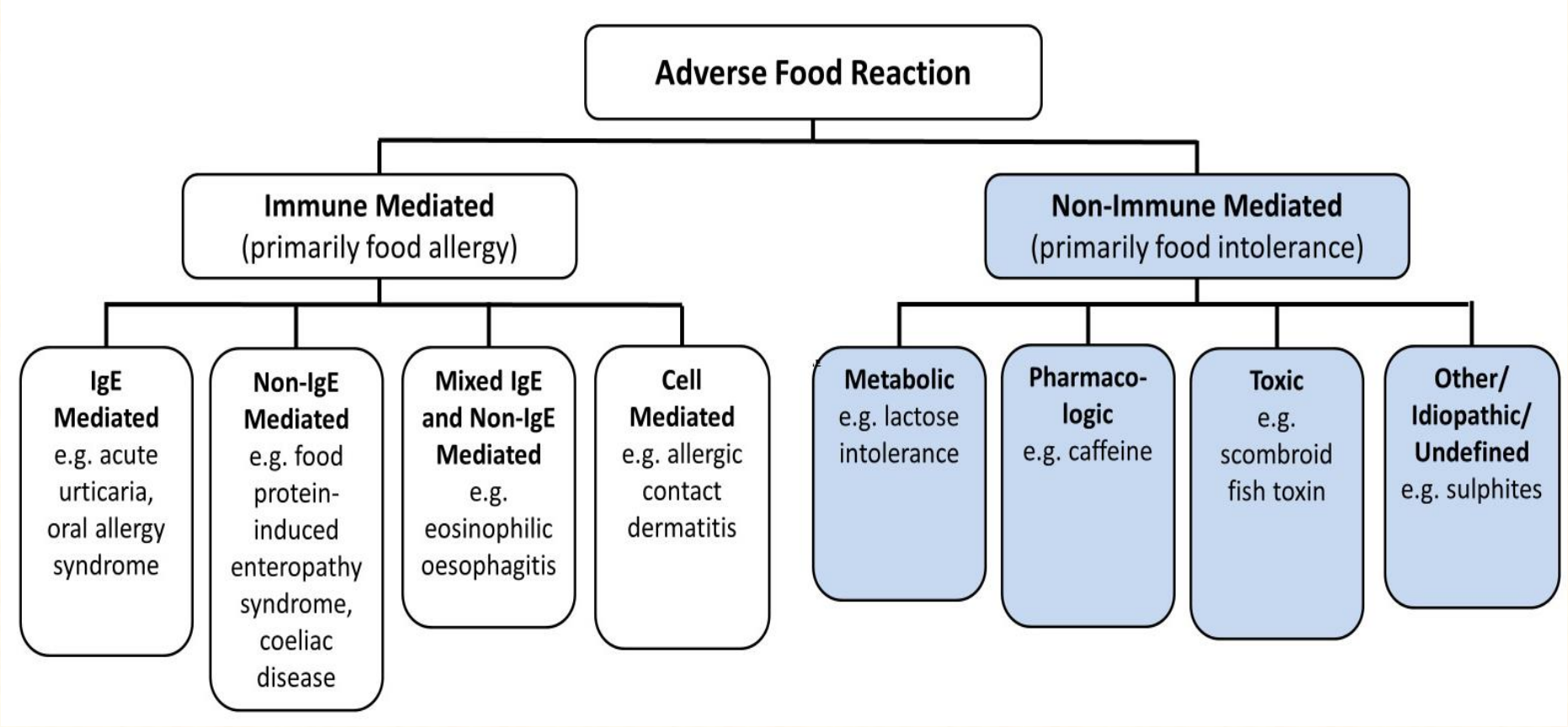
IgE-mediated food allergy

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

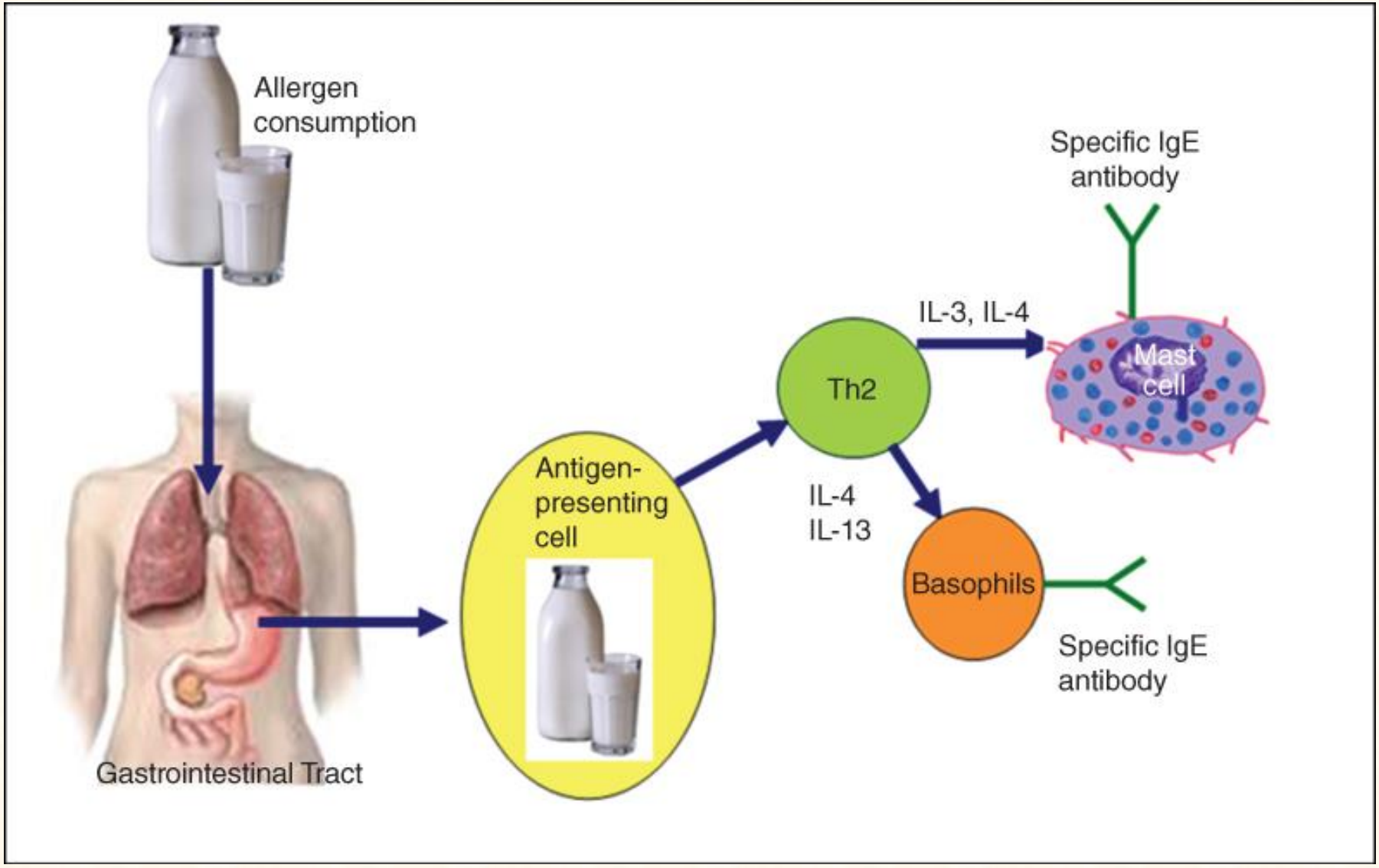
Non-IgE-mediated food allergy

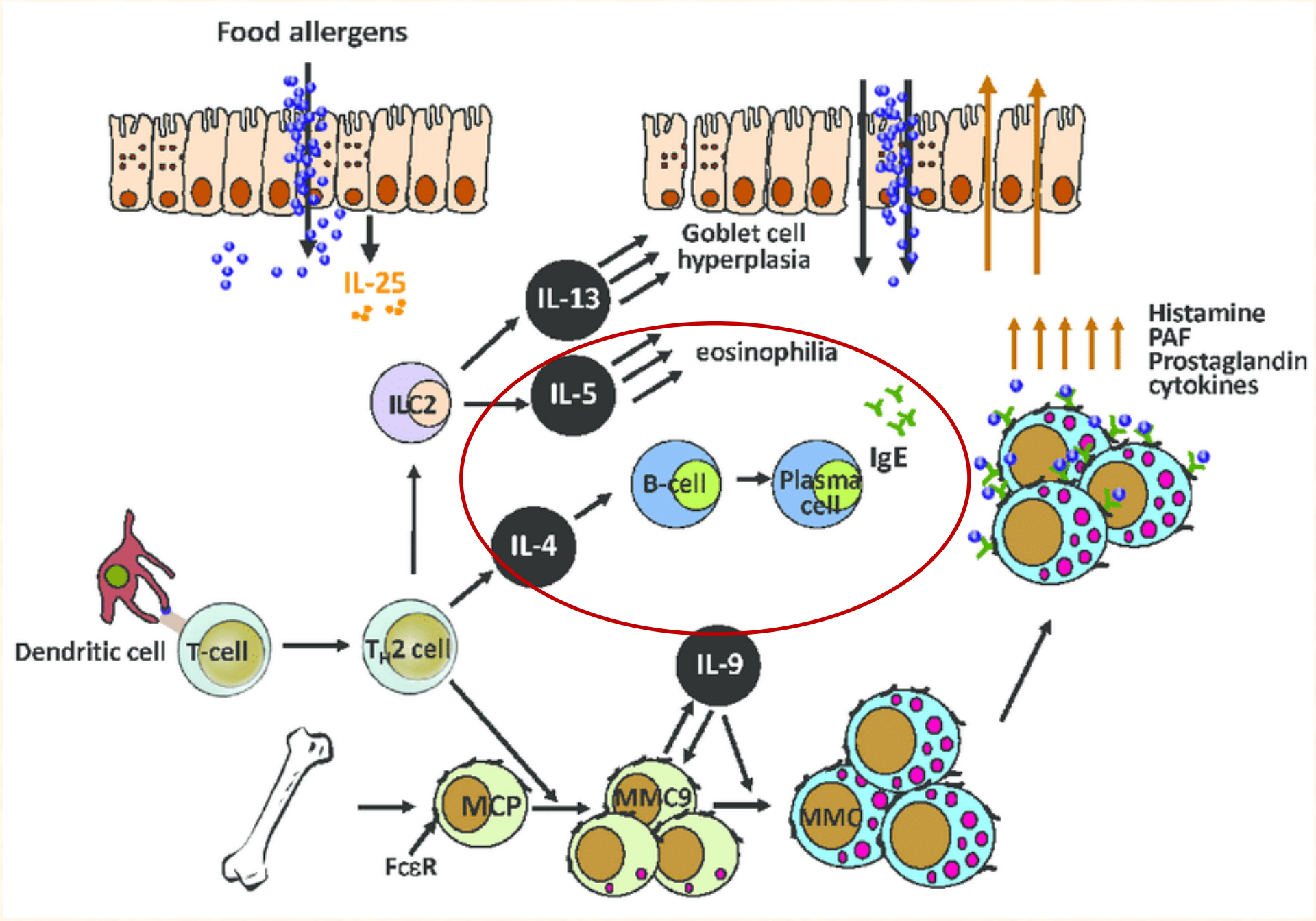
Examples:
Gluten intolerance (Coeliac disease)
Systemic allergic contact dermatitis

Classification of food hypersensitivities



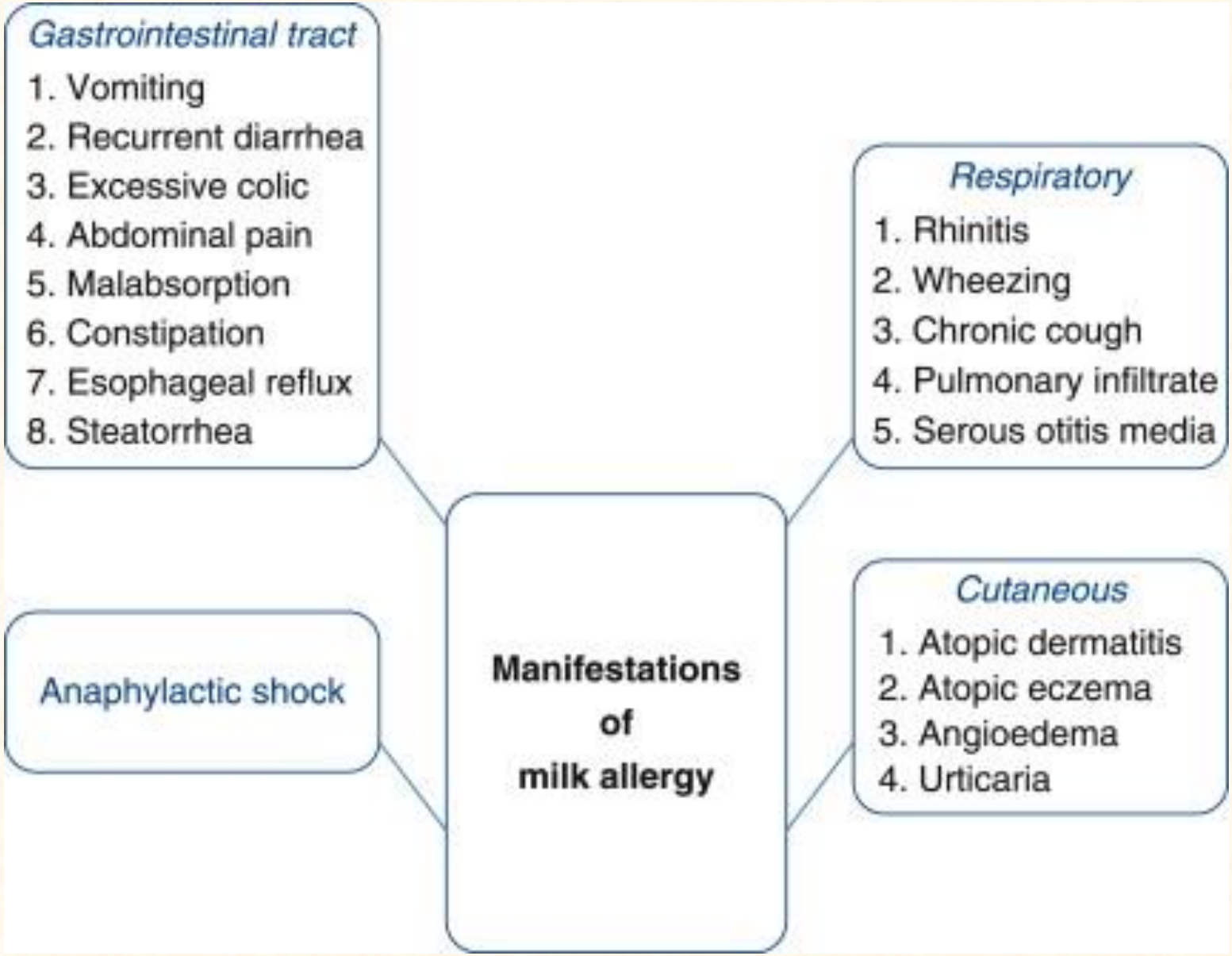
IgE mediated food hypersensitivity



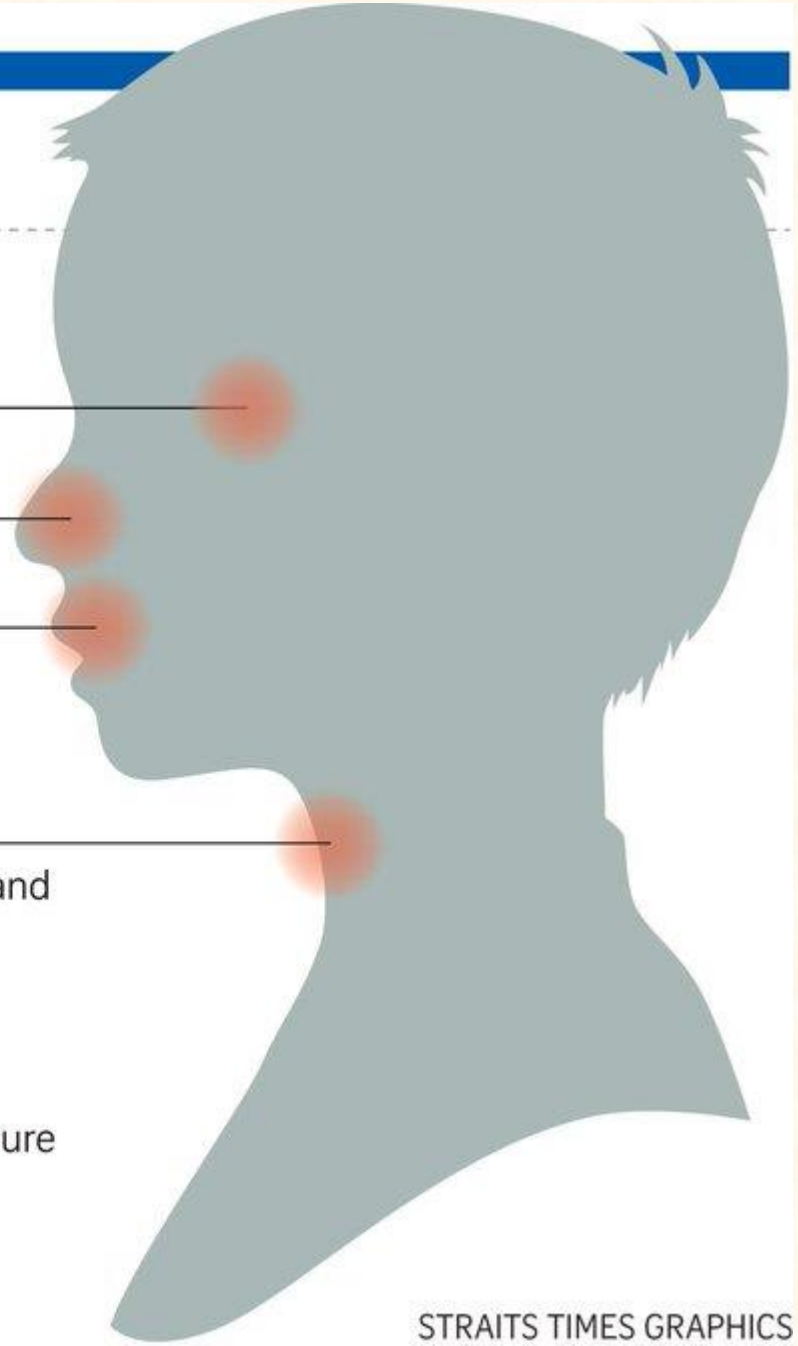

Food allergens
IL-25
Goblet cell hyperplasia
IL-13
eosinophilia
ILC2
IL-5
Histamine
PAF
Prostaglandin
cytokines
IgE
B-cell
Plasma cell
IL-4
Dendritic cell
T-cell
TH2 cell
IL-9
MCP
FcεR
MMC9
MMC

Top 10 Foods You Should Not Eat if You Have Allergic Rhinitis

Milk allergy



Peanut allergy



Symptoms

- Itchy skin or hives, which can appear as small spots or large welts
- A runny or congested nose
- An itching or tingling sensation in or around the mouth or throat
- Nausea
- Anaphylaxis (less common), a potentially life-threatening reaction that impairs breathing and can send the body into shock. Symptoms include:
  - impaired breathing
  - swelling in the throat
  - a sudden drop in blood pressure
  - pale skin or blue lips
  - fainting
  - dizziness

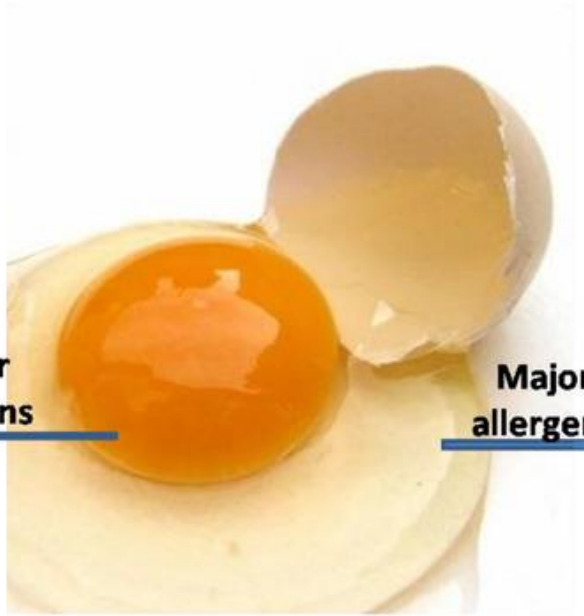
STRAITS TIMES GRAPHICS

Egg allergy

α-livetin (Gal d 5)
- 7% of egg yolk protein
- 70 kDa

YGP42 (Gal d 6)
- 35 kDa

Minor allergens



Major allergens

Ovomucoid (Gal d 1)
- 11% of egg white protein
- 28 kDa
- p*I* about4.1

Ovalbumin (Gal d 2)
- 54% of egg white protein
- 45 kDa
- p*I* about4.5

Ovotransferrin (Gal d 3)
- 12% of egg white protein
- 78 kDa
- p*I* about 6.0

Lysozyme (Gal d 4)
- 3.4% of egg white protein
- 14.3 kDa
- p*I* about11.6


Symptoms of Soy Allergy
Skin Problems
Digestive Disorders
Respiratory Problems
Systemic Problems
© www.medindia.net

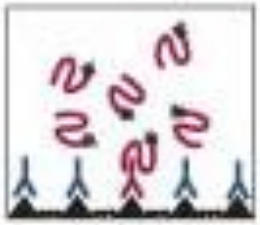
Food allergy skintest

How HESKA® ALLERCEPT® Panels Work

=IgG =IgE =Anti-IgE =FCεRIα

HESKA® ALLERCEPT® Detection System

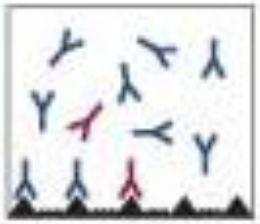
Step 1. Well is coated with allergen and serum is added. Allergen-specific IgE and IgG bind to the allergen.



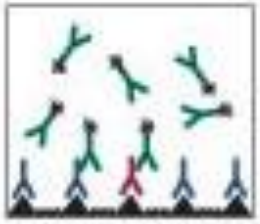
Step 2. FCεRIα is added and binds to IgE only.

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

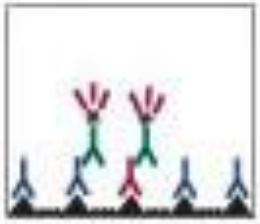
Conventional Anti-IgE Monoclonal and Polyclonal Methods



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.

Non-immunoglobulin E (IgE)-mediated food hypersensitivities

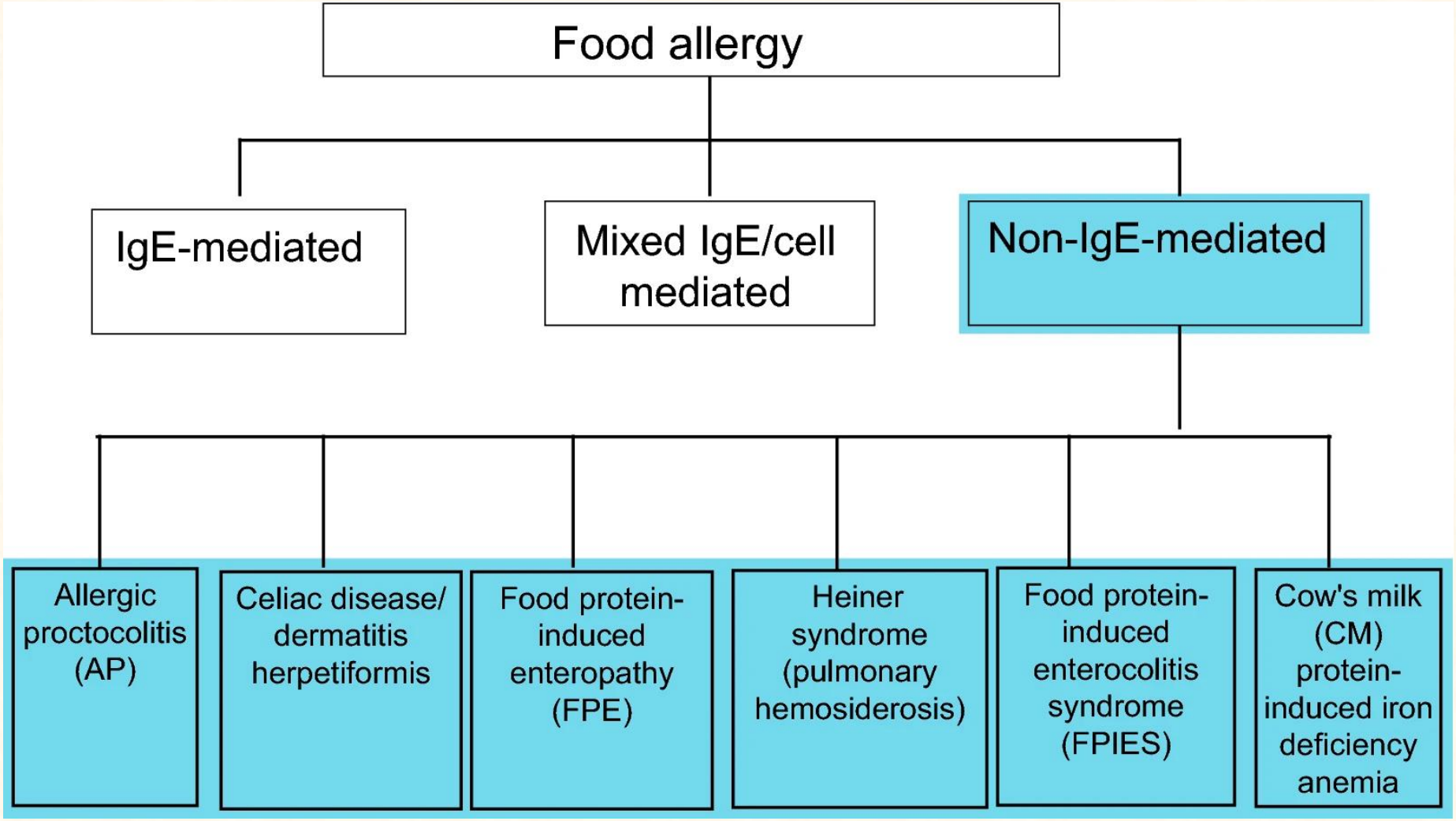
- Non-IgE-mediated food hypersensitivity syndromes predominantly affect the gastrointestinal tract
- Food protein-induced enterocolitis syndrome (FPIES), allergic proctocolitis (AP), food protein-induced enteropathy (FPE) and celiac disease
- FPIES, AP and FPE typically present in infancy and are most commonly triggered by cow's milk protein or soy

Non-allergic food sensitivities

Sensitivity or intolerance to a food for several reasons:

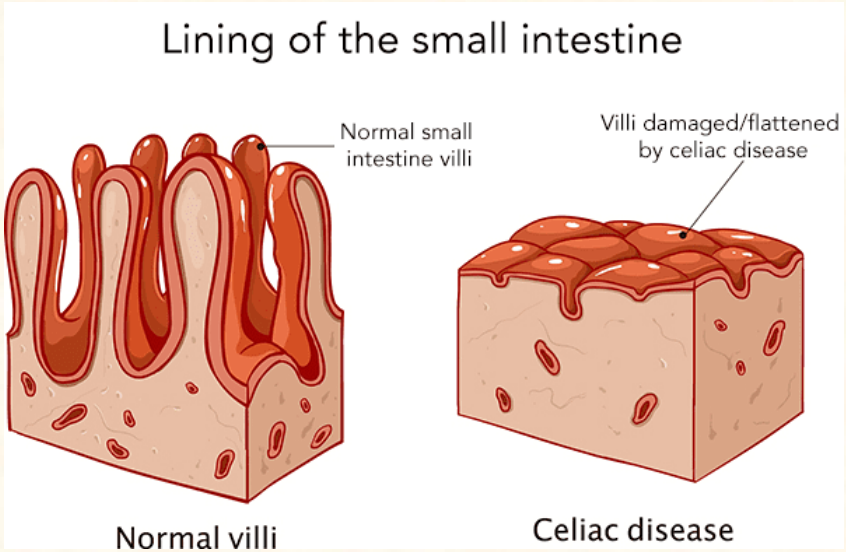
- not having the right enzymes need to digest a certain food (e.g. lactose)
- reactions to food additives or preservatives like sulfites, mononátrium-glutamát (MSG), or artificial colors
- pharmacological factors, like sensitivity to caffeine or other chemicals
- sensitivity to the sugars naturally found in certain foods like onions, broccoli, or Brussels sprouts

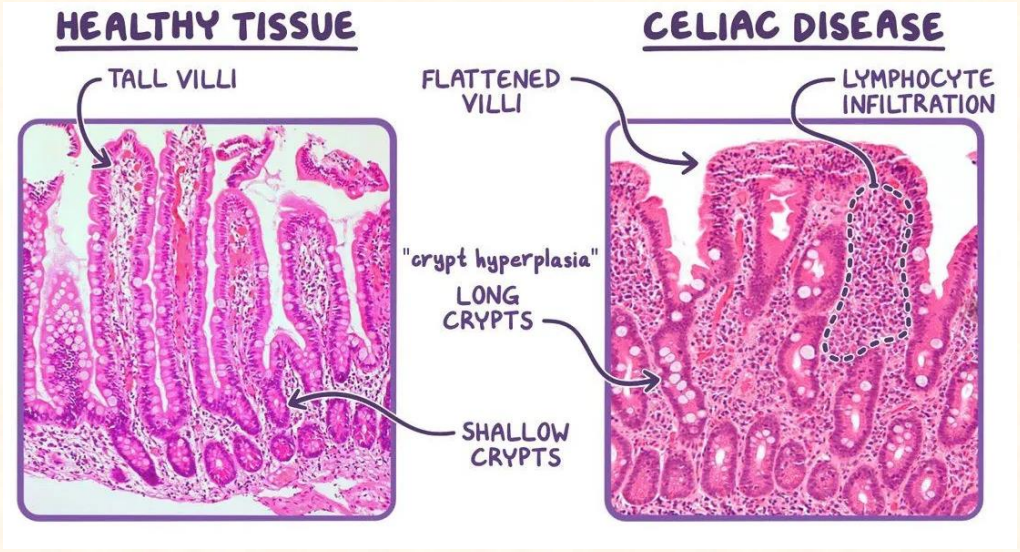
Classification of non-allergic food hypersensitivity



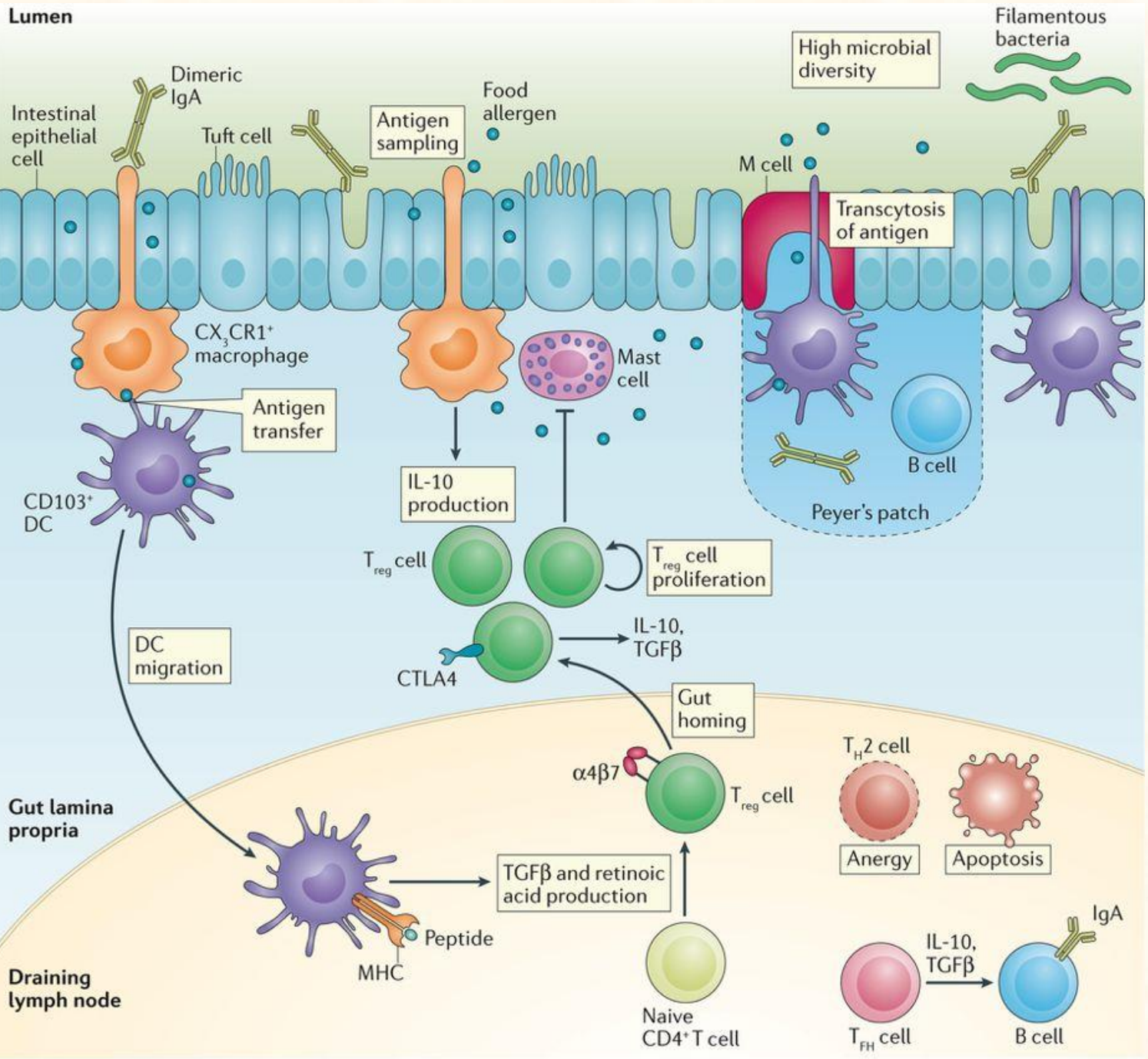
Celiac disease

- Immune-mediated injury caused by the ingestion of gluten (a family of proteins found in grains such as wheat, rye and barley) that leads to villous atrophy in the small intestine in genetically susceptible individuals (strongly associated with HLA-DQ2 and HLA-DQ8).
- Serologic tests and small intestinal biopsy are required to confirm the diagnosis of celiac disease, and management requires life-long adherence to a strict gluten-free diet.





Gluten develops an inappropriate adaptive immune response, gliadin interacts with intestinal cells to disassemble intra-epithelial tight junctions. Gliadin peptides can then pass through the epithelial barrier and activate CD4+ T cells in the lamina propria. Inflammatory cytokines leading to clonal expansion of B cells that produce anti-tissue transglutaminase (anti-TTG) and anti-gliadin antibodies.

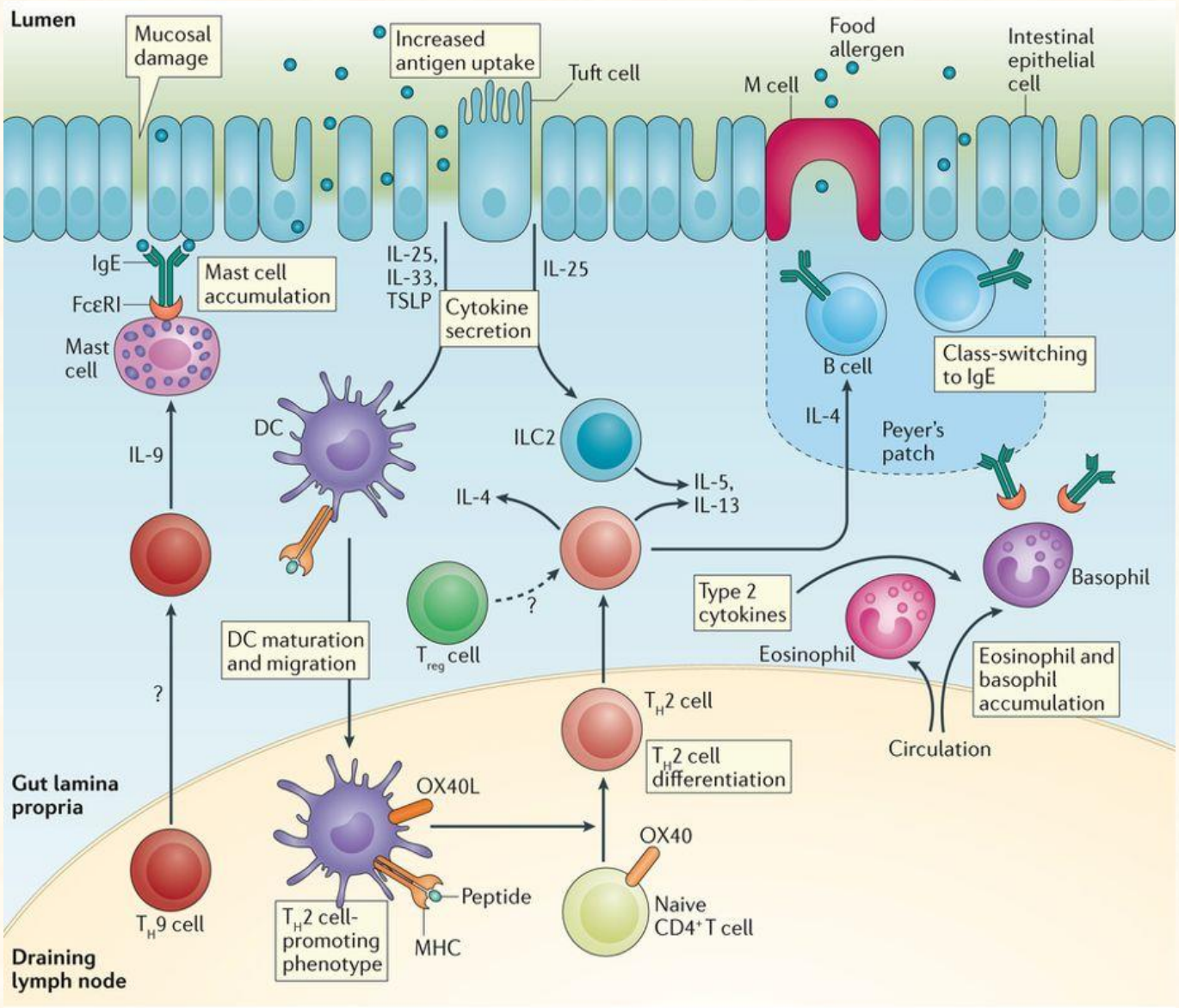


Nature Reviews | Immunology

Immune tolerance to oral antigens in the gut

Macrophages sample antigens in the gut lumen and transfer to CD103⁺ dendritic cells. They express TGFβ inducing naive T cells to differentiate T_{reg} cells.

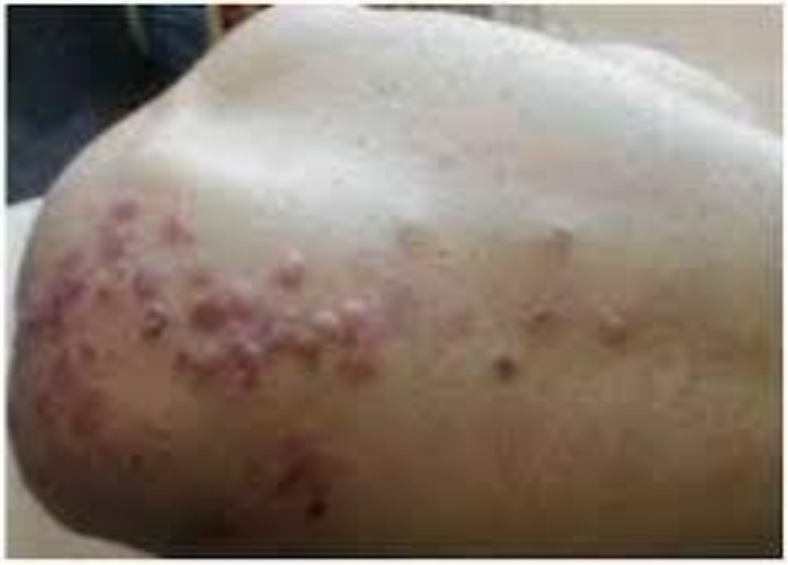
Th2 cell-mediated inflammatory response to oral antigen in the gut

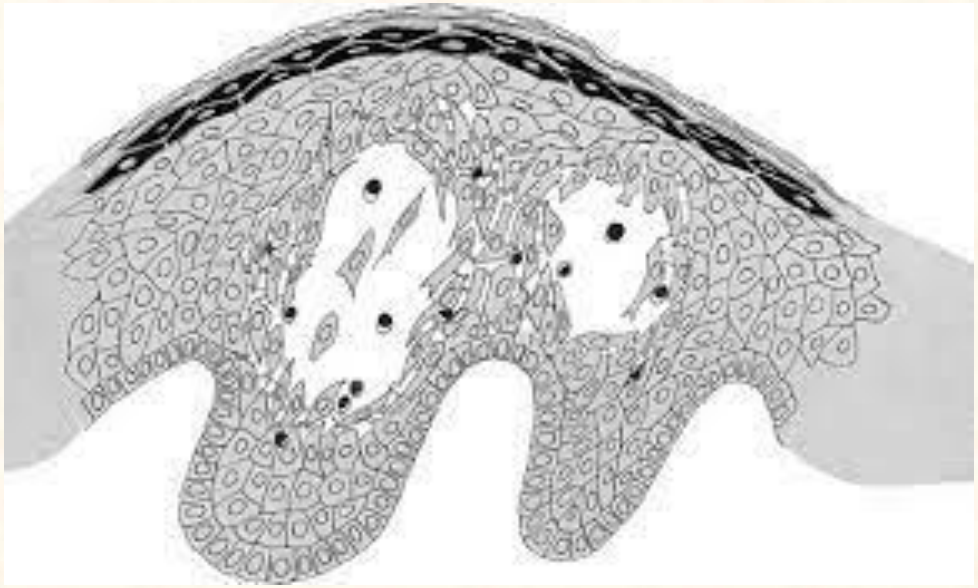


Nature Reviews | Immunology

<u>Epithelial damage</u> or inflammation allows increased antigen entry and promotes the secretion of IL-25, IL-33 and TSLP promote Th2 differentiation and TH2 cell-mediated immune response which includes tissue eosinophil accumulation and IgE class-switching by B cells.

Dermatitis herpetiformis



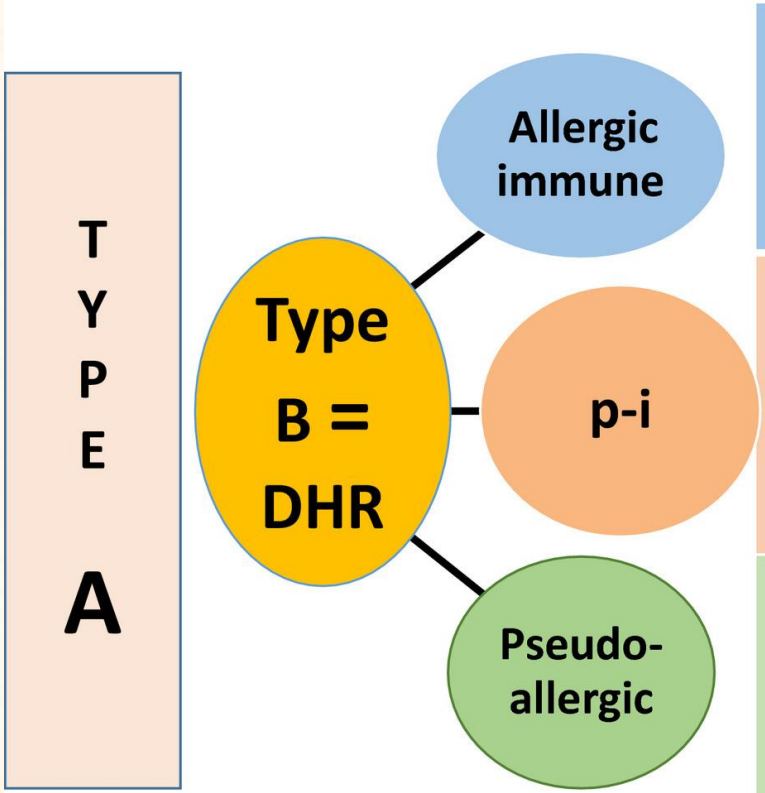


“Celiac disease of the skin" is the chronic skin manifestation associated with celiac disease. It is classically described as clusters of vesicles on the extensor surfaces (“blisters”) that are intensely pruritic.

Drug hypersensitivity reactions (DHR)

They are clinically heterogeneous. (**1**) the allergic-immune mechanism relies on the covalent binding of to proteins, which thereby form new antigens, to which a humoral and/or cellular immune response can develop. In IgE-mediated drug allergies need of a covalent hapten-carrier link for initiation. (**2**) The p-i ("pharmacological interaction with immune receptor") concept represents an off-target activity of drugs with immune receptors (HLA or TCR), which can result in unorthodox, alloimmune-like stimulations of T cells. Some of these p-i stimulations occur only in carriers of certain HLA alleles and can result in clinically severe reactions. (**3**) The "pseudo-allergy" is represented by drug interactions with receptors or enzymes of inflammatory cells, which may lead to their direct activation or enhanced levels of inflammatory products. Specific IgE or T cells are not involved.

Dissection of drug hypersensitivity reactions based on the mode of action of drugs

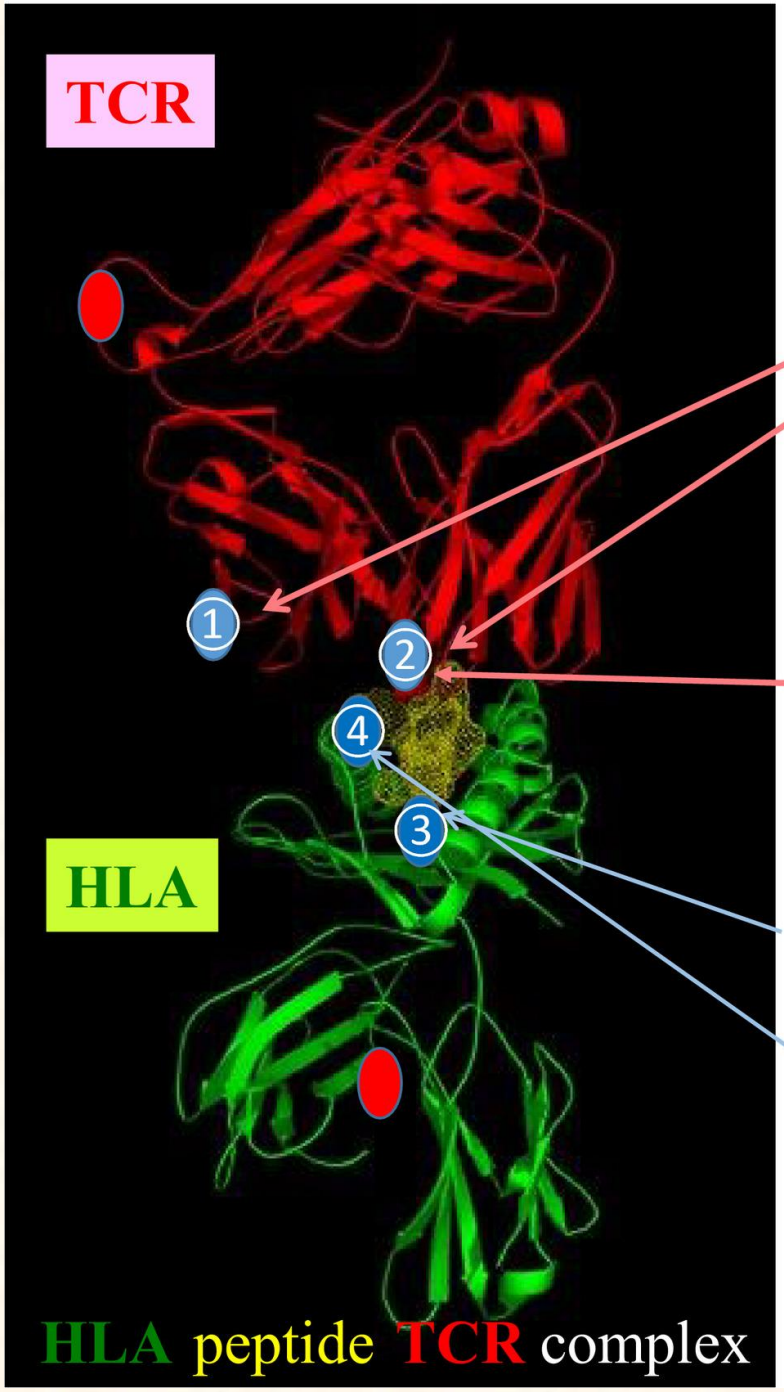


Allergic immune	Formation of a new antigen; Classical allergic form of DHR	**IgE:** *Anaphylaxis, urticaria* **T cells:** MPE (Maculopapular exanthema) **IgG:** haemolytic anaemia, immun-complex disease
p-i	Drugs bind directly to immune receptors (HLA, TCR)	**Only T cells:** MPE, DRESS, SJS/TEN, AGEP, hepatitis
Pseudo-allergic	Drugs bind directly to receptors and enzymes of effector cells, no real allergy	**MRPGPRX2**/ Mast cells *Anaphylaxis/urticaria* **Cyclooxygenase**↓/Leukotriens ↑ *Bronchospasm, asthma, urticaria* ***Bradykinin***↑*: angioedema*

Allergy 2019 Aug;74(8):1457-1471.
doi: 10.1111/all.13765. Epub 2019 Apr 29.

Immune pathomechanism and classification of drug hypersensitivity

Werner J Pichler



pharmacological interaction with immune receptors (p-i concept):

Stimulation depends on:

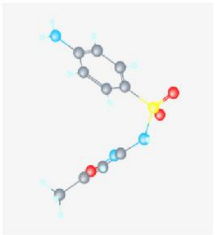
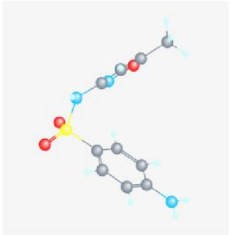
a) affinity of drug binding to HLA or TCR proteins

b) localization of drug binding in **p-i TCR**:

① CDR2; allosteric effect;

② CDR3 of TCR with stimulation or blocking of stimulation as a function of drug binding and

c) orientation ②

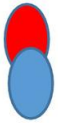
–	+
	
HLA-peptide	HLA-peptide

d) localization of drug binding in **p-i HLA:**

③peptide-binding region of HLA, hidden under peptide or

④peptide-binding region beside peptide (with possible interaction with TCR)

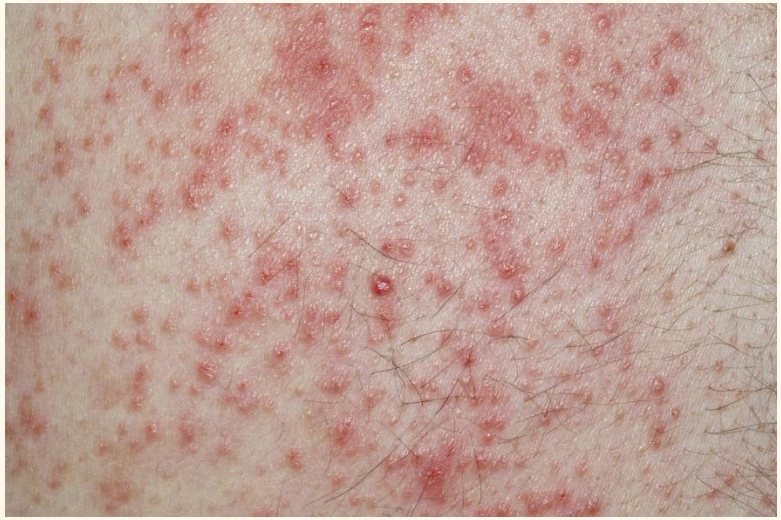
e) Level of T cell activation: activated T cells seem to react easier to drug/p-i than resting T cells (p-i TCR)

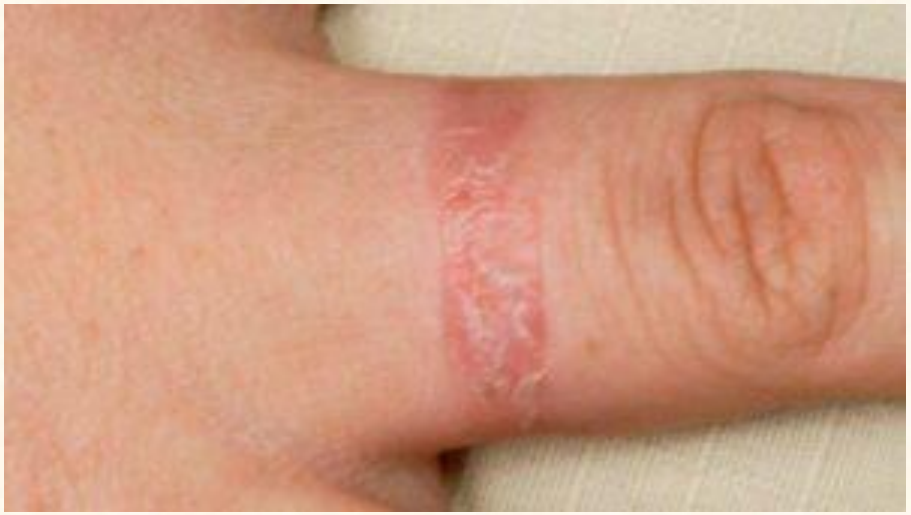


Drug binding without functional consequence

Drug binding with functional consequence

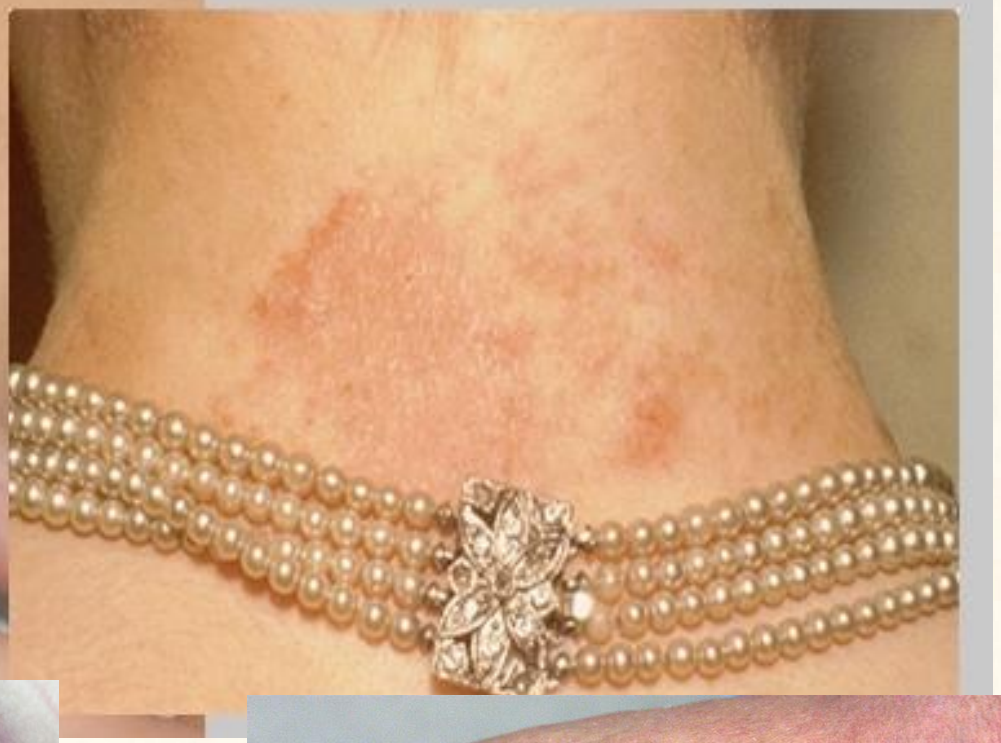
Contact dermatitis

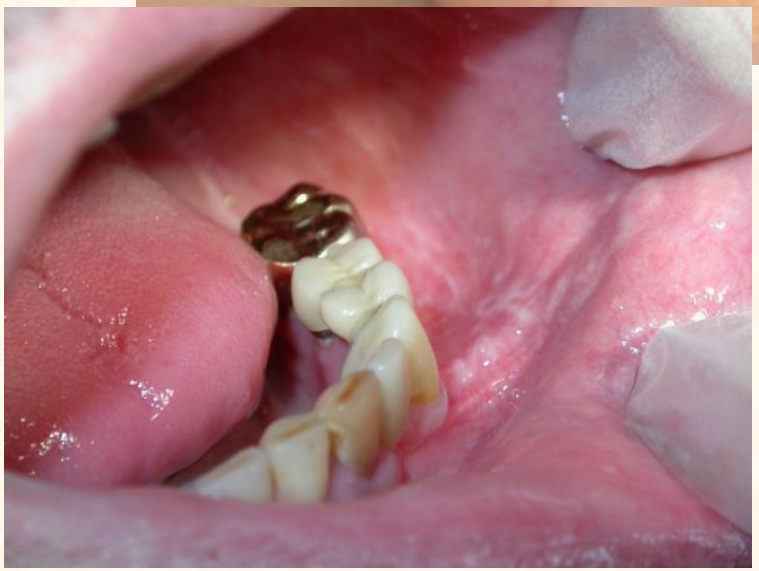


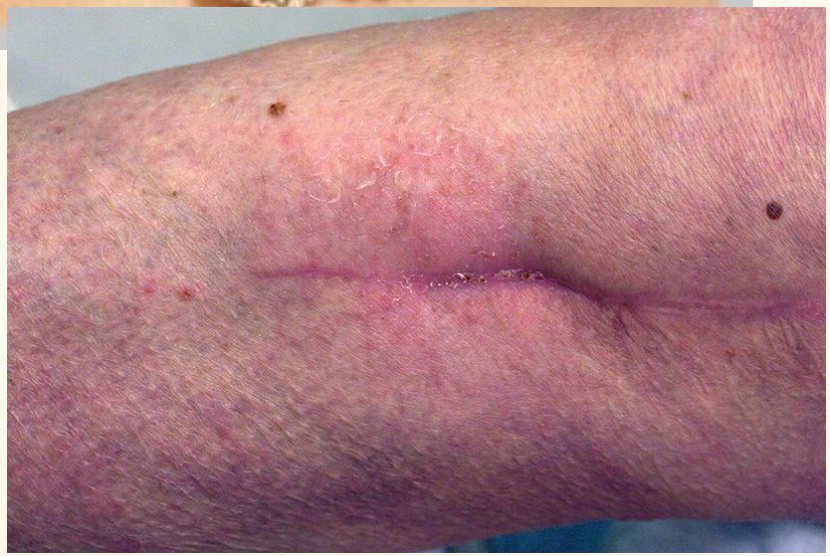


- Contact dermatitis is a type IV hypersensitivity (DTH), and it is an eczema triggered by contact with a particular substance (e.g. metal).
- Eczema is the name for a group of conditions that cause skin to become dry and irritated.

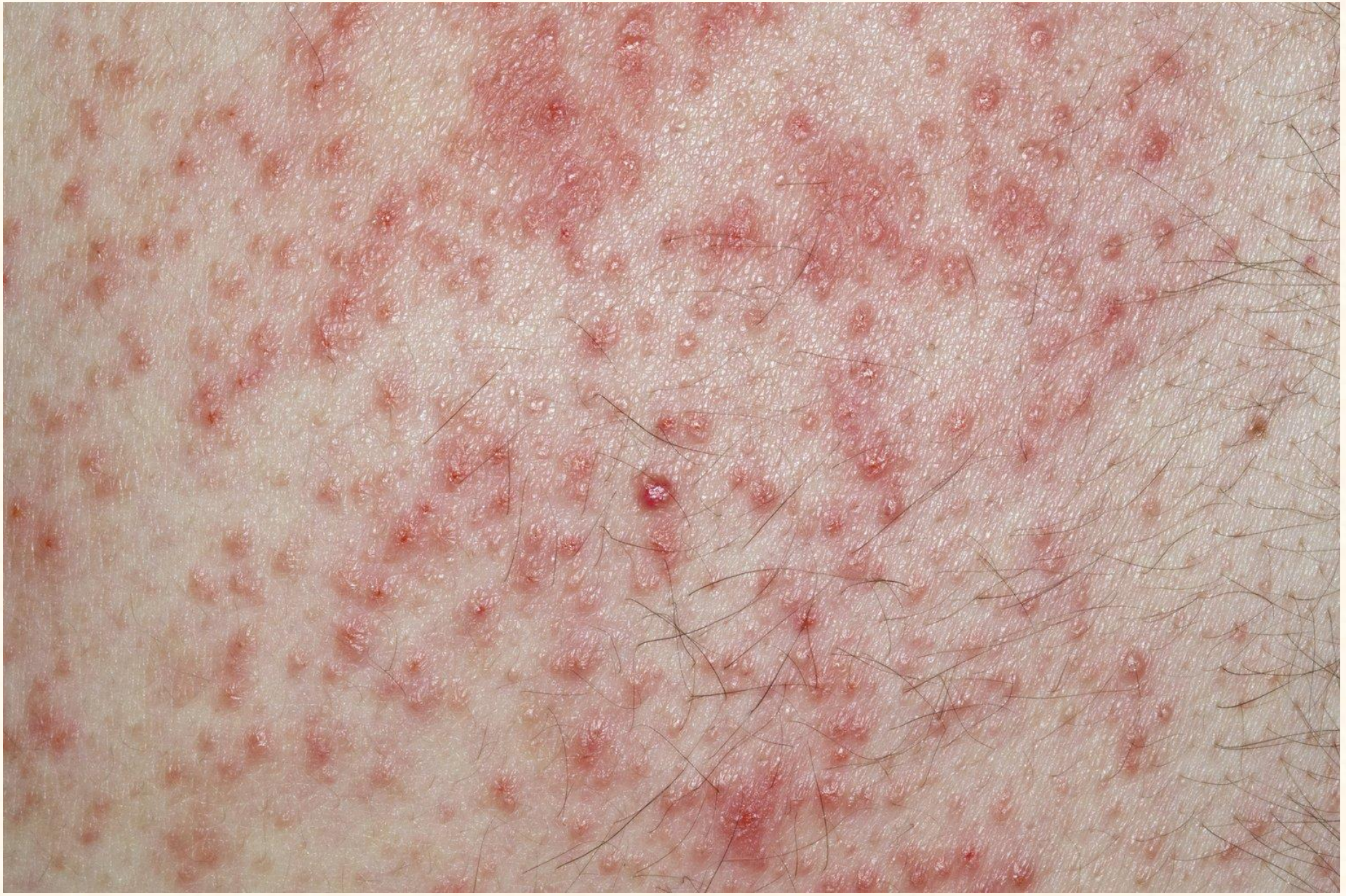
Metal allergy



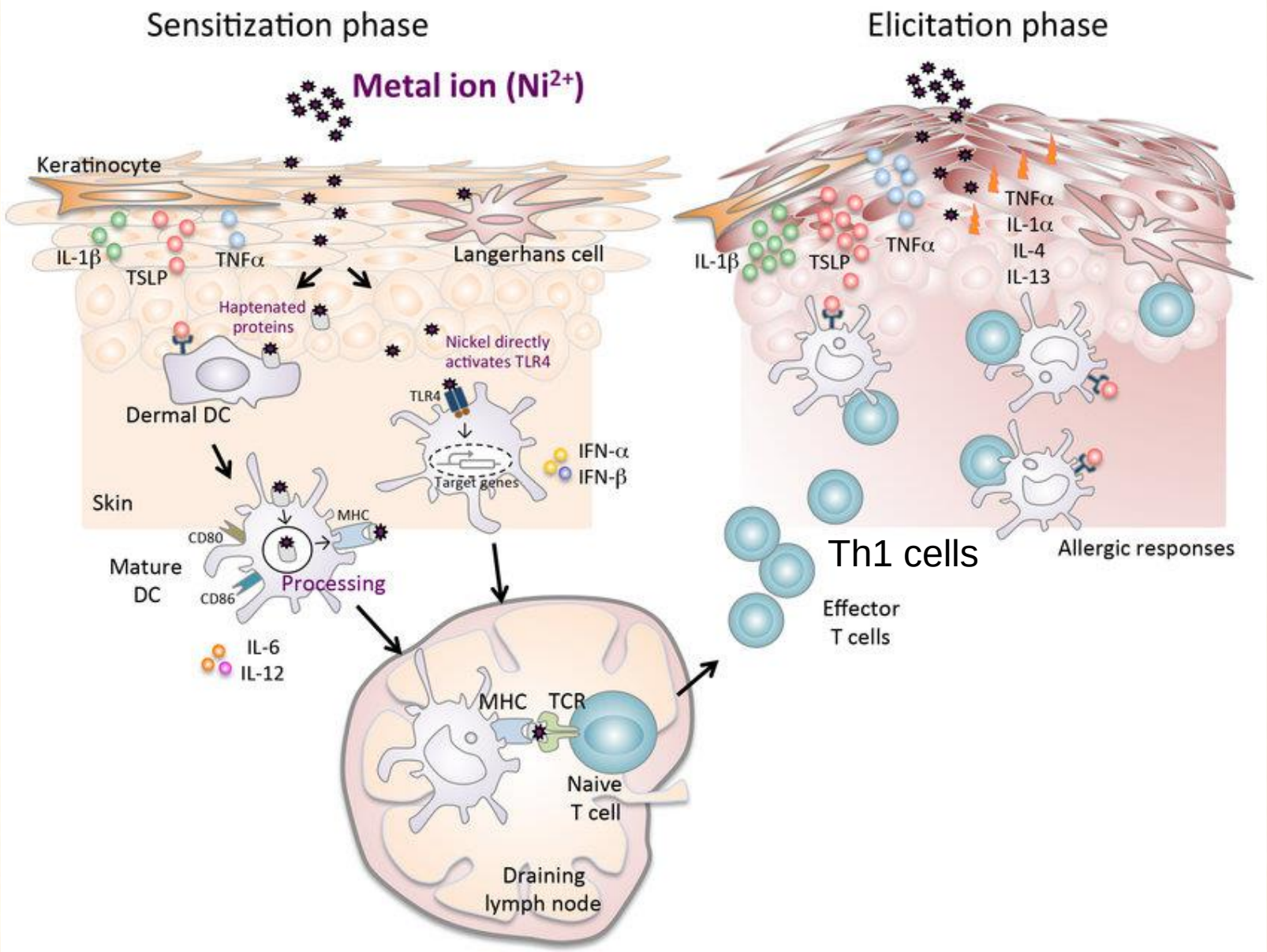




DTH



Pathomechanism of metal allergy



What is the allergy?

- Allergy is a disease in which the immune system makes an inflammatory response to a harmless antigen (allergen). Allergens may be inhaled or ingested, or they may come into contact with the skin.
- Allergy is a misguided reaction to foreign substances by the immune system, the body system of defense against foreign invaders, particularly pathogens. The allergic reaction is misguided in that these foreign substances are usually harmless.