Classification, pathogenesis and diagnostics of allergic diseases

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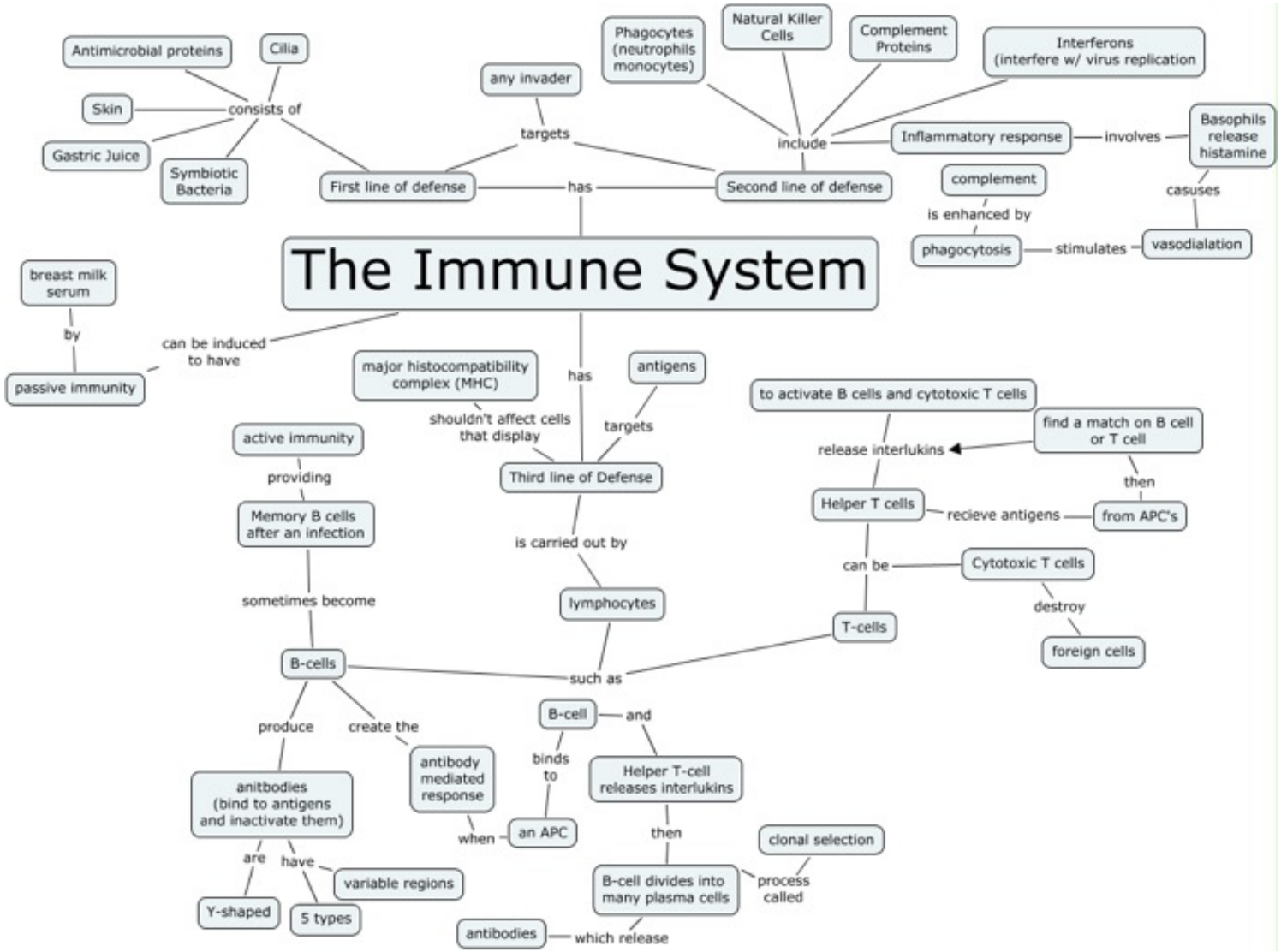
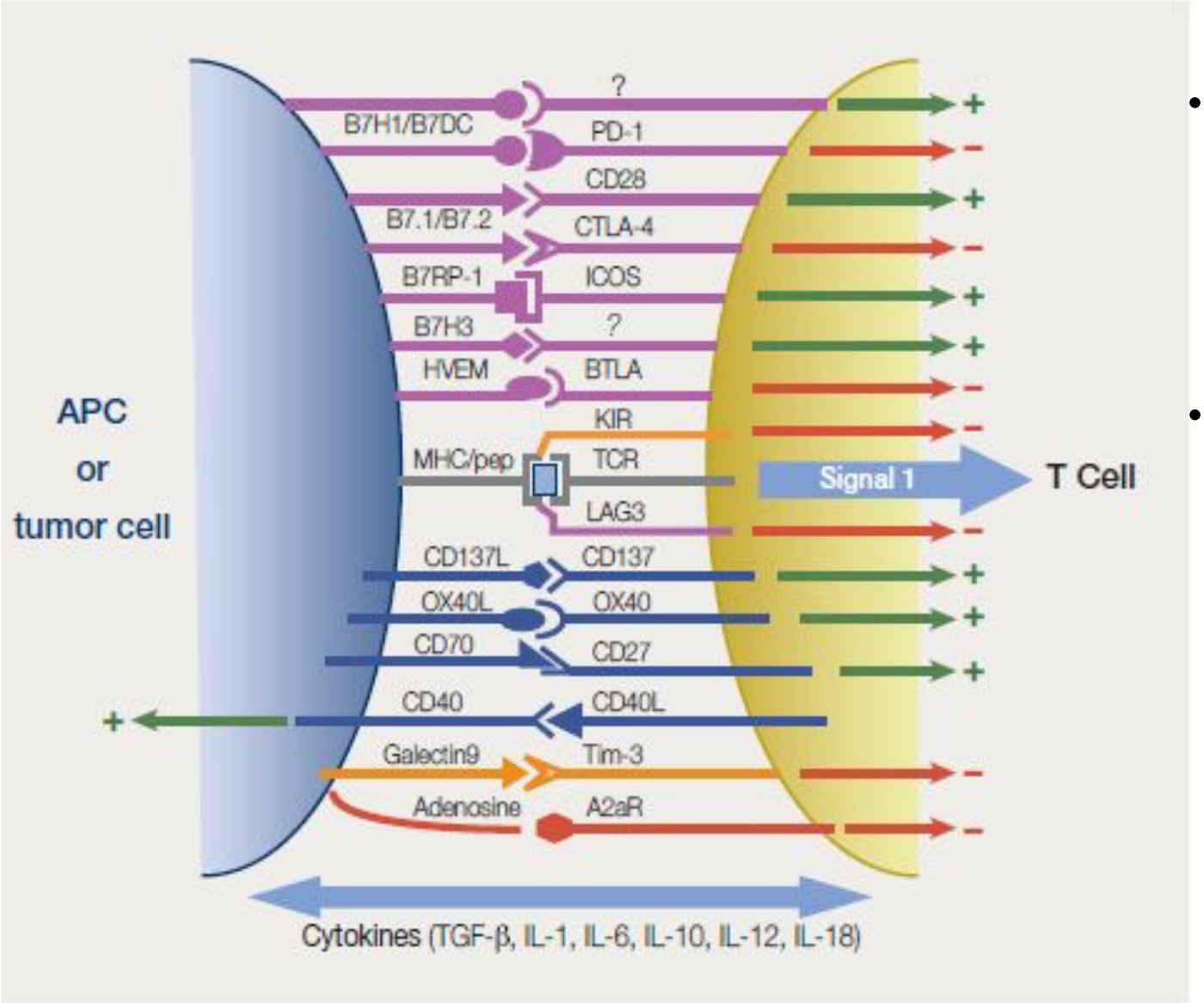
Of all the body's organs, the immune system may be the most challenging to coordinate. The system is collection of individual immune cells, immune cell aggregates, immune tissues, and immune organs.





- Billions of immune cells communicate with each other.
- Functional integration of the immune system is accomplished mainly by cell-to- cell communication
- Every immune system cell is equipped with different surffface molecules and is able to synthesize and release a variety of small molecules that travel to other cells and stimulate those cells to become either more active or less active

Many common biologic mechanisms prevent immune responsiveness to harmless environmental factors and to self-antigens.

Tolerance

Immune tolerance normally ensure that immune effector cells are not activated against host tissues or innocuous agents.


New England Journal Of Medicine 365;2, July 14, 2011

Allergy: immune reaction to a non replicating (harmles) substance (protein, chemical, drug, metal), which leads to clinical symptoms like.

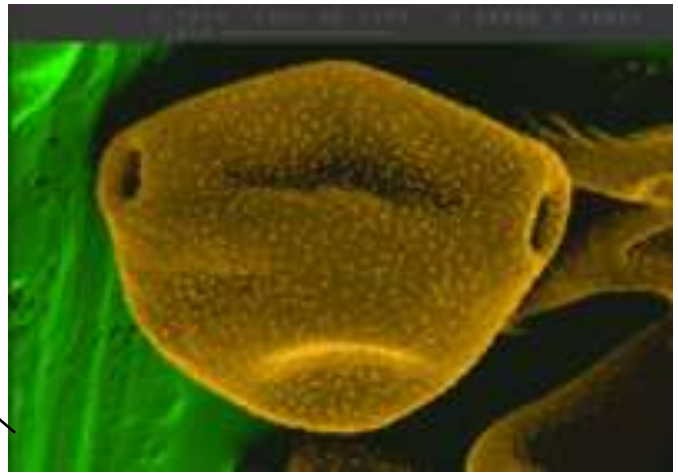
In contrast to infections: symptoms are caused almost exclusively by the immune reaction, not by the „bug“ (virus, bacteria, etc.)

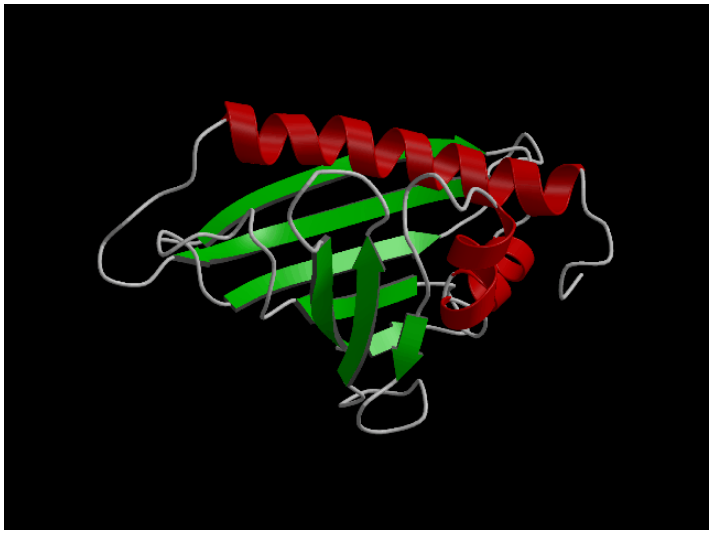
Allergens

- Non-reproducing foreign substances
- Mostly Proteines/Glykoproteines
  - Of animal or vegetable origin
  - Drugs/Chemicals

The allergy is **not** directed to pollen,
but to proteins within pollen !

Pollen = carrier (grain) + allergen (surface) + lipids





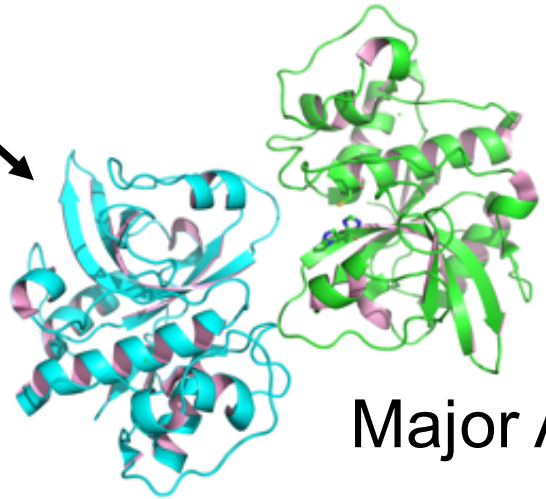
Betula verrucosa 1
Bet v 1

Major Allergen

House dust mites allergens are a common cause of asthma and allergic symptoms worldwide

- *D. pteronyssinus* (european)
- *D. farinae* (american)
- feed on organic detritus, such as flakes of shed human skin

The mite's gut contains potent digestive enzymes (proteases) that persist in their feces



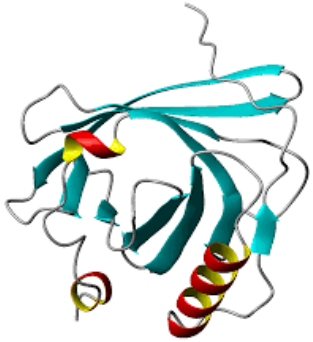
Der p 1

Major Allergen

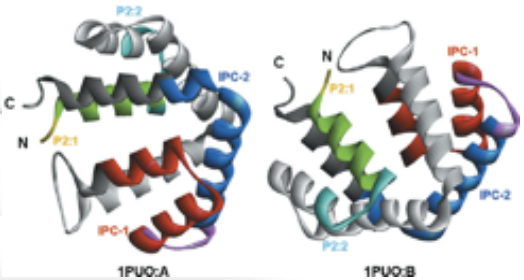
Allergic to your Pet?

Hilger C, Zahradnik E. Allergologie 2015;38:83-90

Can f 1
saliva



Fel d 1
saliva and skin



spezies	Allergen	Proteinfamilie	UniProtKB accession No	Apparentes MG in kDa	Allergenquelle	Sensibili-sierungsra-te in %[1]	In-vitro-Diagnostik verfügbar
Katze	Fel d 1	Sekretoglobin	P30438; P30440	18	Speicheldrüse, Haut	60 – 100	ja
	Fel d 2	Serumalbumin	P49064	69	Leber	14 – 23	ja
	Fel d 3	Cystatin	Q8WNR9	11	Haut	10	nein
	Fel d 4	Lipokalin	Q5VFH6	22	Speicheldrüse	63	ja
	Fel d 5	IgA	–	400	Speichel, Serum	38	nein
	Fel d 6	IgM	–	800 – 1000	Serum	–	nein
	Fel d 7	Lipokalin	E5D2Z5	17,5	Zunge	38	nein
	Fel d 8	Latherin	F6K0R4	24	Speicheldrüse	19	nein
Hund	Can f 1	Lipokalin	O18873	23 – 25	Zunge	50 – 75	ja
	Can f 2	Lipokalin	O18874	19	Zunge, Speichel-drüse	22 – 30	ja
	Can f 3	Serumalbumin	P49822	69	Leber	25 – 35	ja
	Can f 4	Lipokalin	D7PBH4	18	Zunge	35	nein
	Can f 5	Kallikrein	P09582	28	Urin	70	ja
	Can f 6	Lipokalin	H2B3G5	27 – 29	Speicheldrüse	61	nein

Bee / Wasp Allergy

Api m 1	Phospholipase A_2		
Api m 3	Saure Phosphatase		
Api m 4	Mellitin	Phospholipase A_1	Ves v 1
Api m 10	Icarapin	Antigen 5	Ves v 5
Api m 2	Hyaluronidasen		Ves v 2
Api m 5	Dipeptidylpeptidasen		Ves v 3
Api m 12	Vitellogenine		Ves v 6

Types of allergic reactions

Immediate type Reaction

< 1h

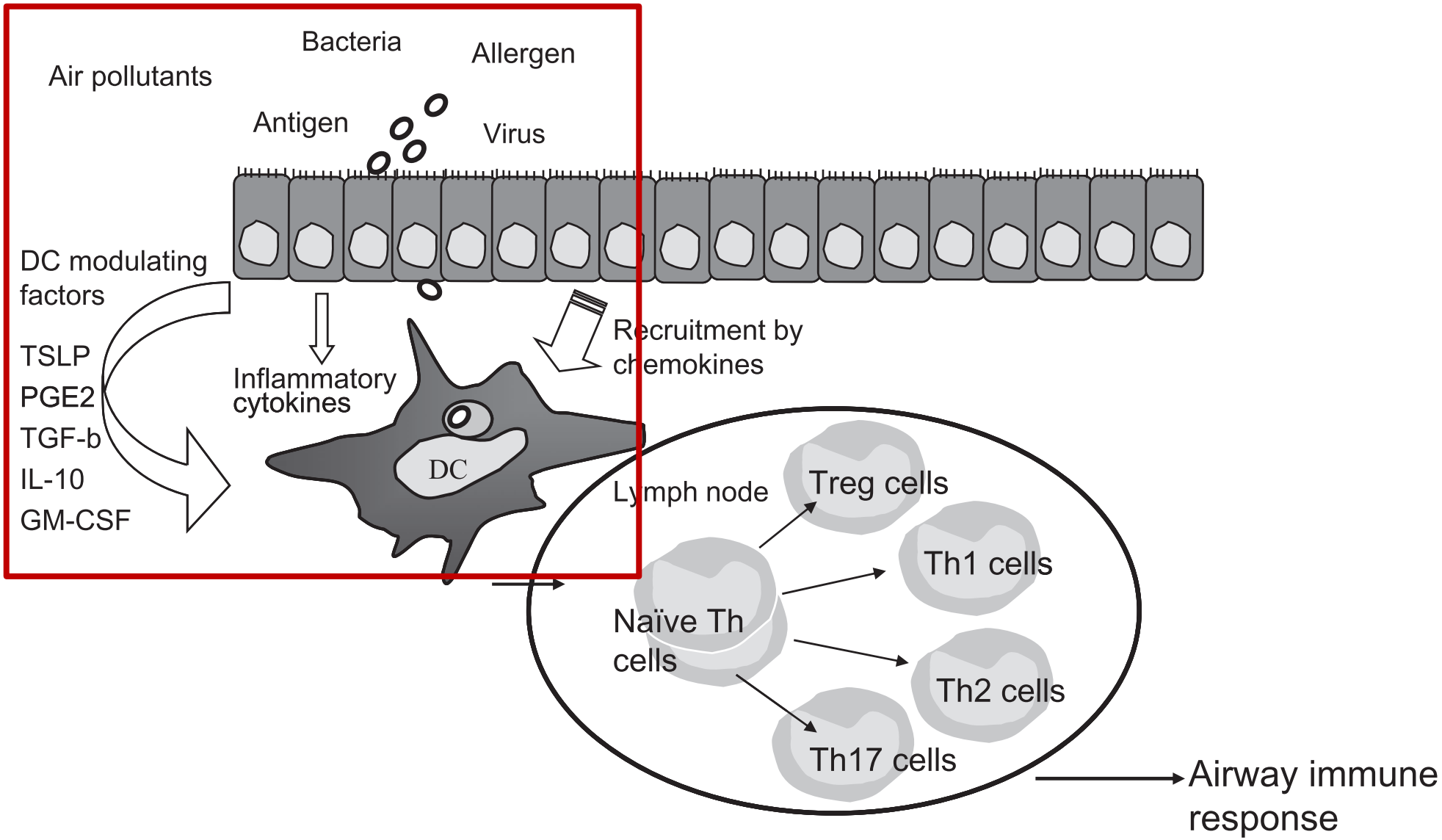
Type of Reaction	Time Before Clinical Signs	Characteristics	Examples
Type I (Anaphylactic)	<30 min	IgE binds to mast cells or basophils; causes degranulation of mast cell or basophil and release of reactive substances such as histamine	Anaphylactic shock from drug injections and insect venom; common allergic conditions, such as hay fever, asthma
Type II (Cytotoxic)	5–12 hours	Antigen causes formation of IgM and IgG antibodies that bind to target cell; when combined with action of complement, destroys target cell	Transfusion reactions, Rh incompatibility hemolytic anmenia, thrombocytopenia, granulocytopenia
Type III (Immune Complex)	3–8 hours	Antibodies and antigens form complexes that cause damaging inflammation	Arthus reactions, serum sickness
Type IV (Delayed Cell-Mediated, or Delayed Hypersensitivity)	24–48 hours	Antigens activate T_C that kill target cell	Rejection of transplanted tissues; contact dermatitis, such as poison ivy; certain chronic diseases, such as tuberculosis

delayed type Reaction

> 24h

Sensitisation

Airway immune response



J. van Tongeren et al. Allergy 2008: 63: 1124–1135

The immune system is highly specific and needs danger signals to become activated

How can a harmless/innocuous substance like a pollen potentially induce an IgE mediated immune reaction ?

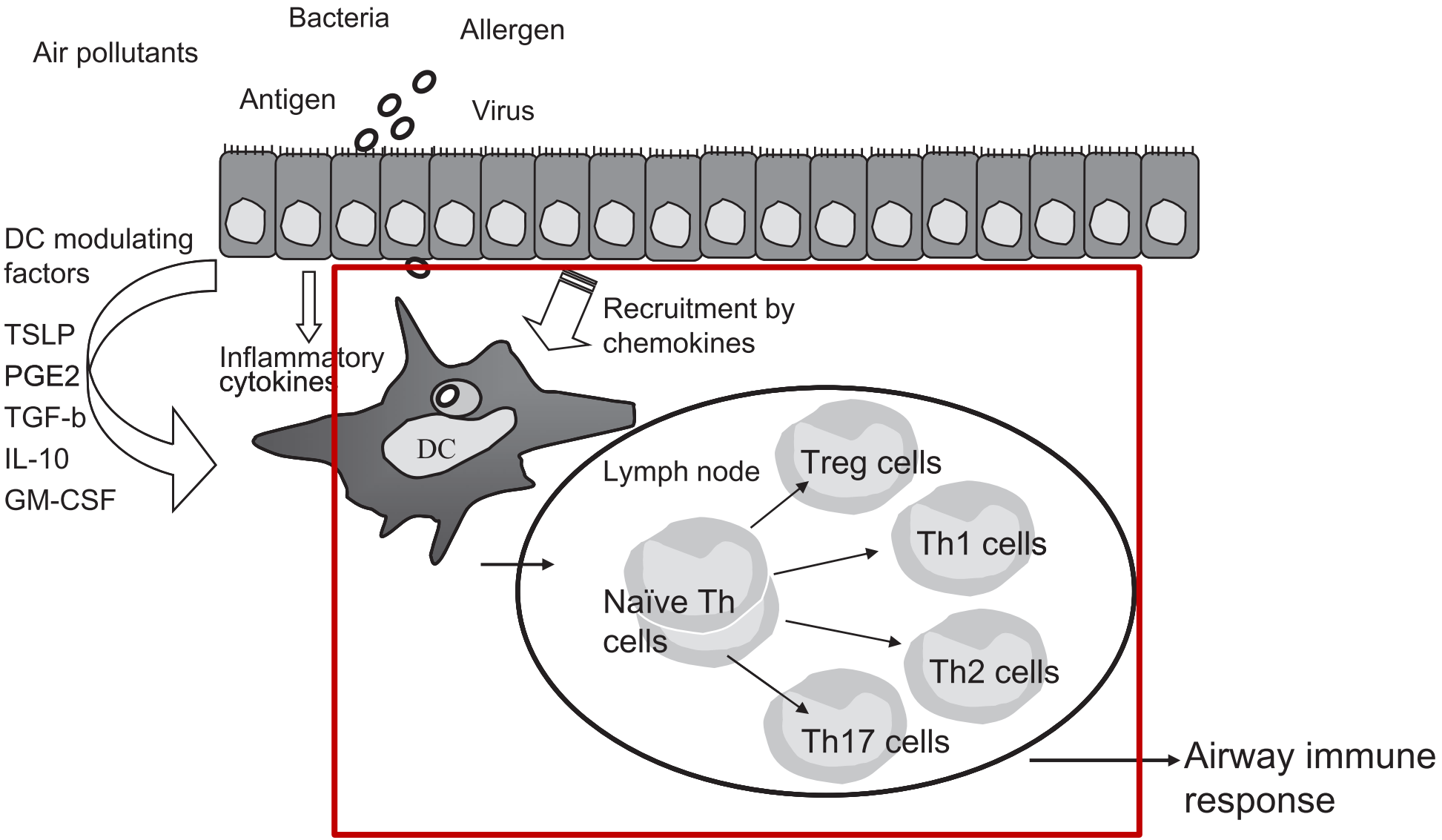
Ability of „innocuous“ proteins to activate immune system

1. House dust mite allergen Der p1: cysteine protease cleaves tight junction protein occludin → Increased epithelial permeability and facilitating its entry into the tissue

2. House dust mite allergen Der p2: structural and functional homology with MD-2, LPS-binding component of TLR 4 signaling complex → facilitates signaling through direct interactions with the TLR4 complex

3. Pollen-associated lipid mediators (PALMs): When pollen grains are hydrated on the respiratory epithelia, they release allergens and eicosanoid lipids → so-called pollen-associated lipid mediators (PALMs) → act as stimulators of DC

Airway immune response



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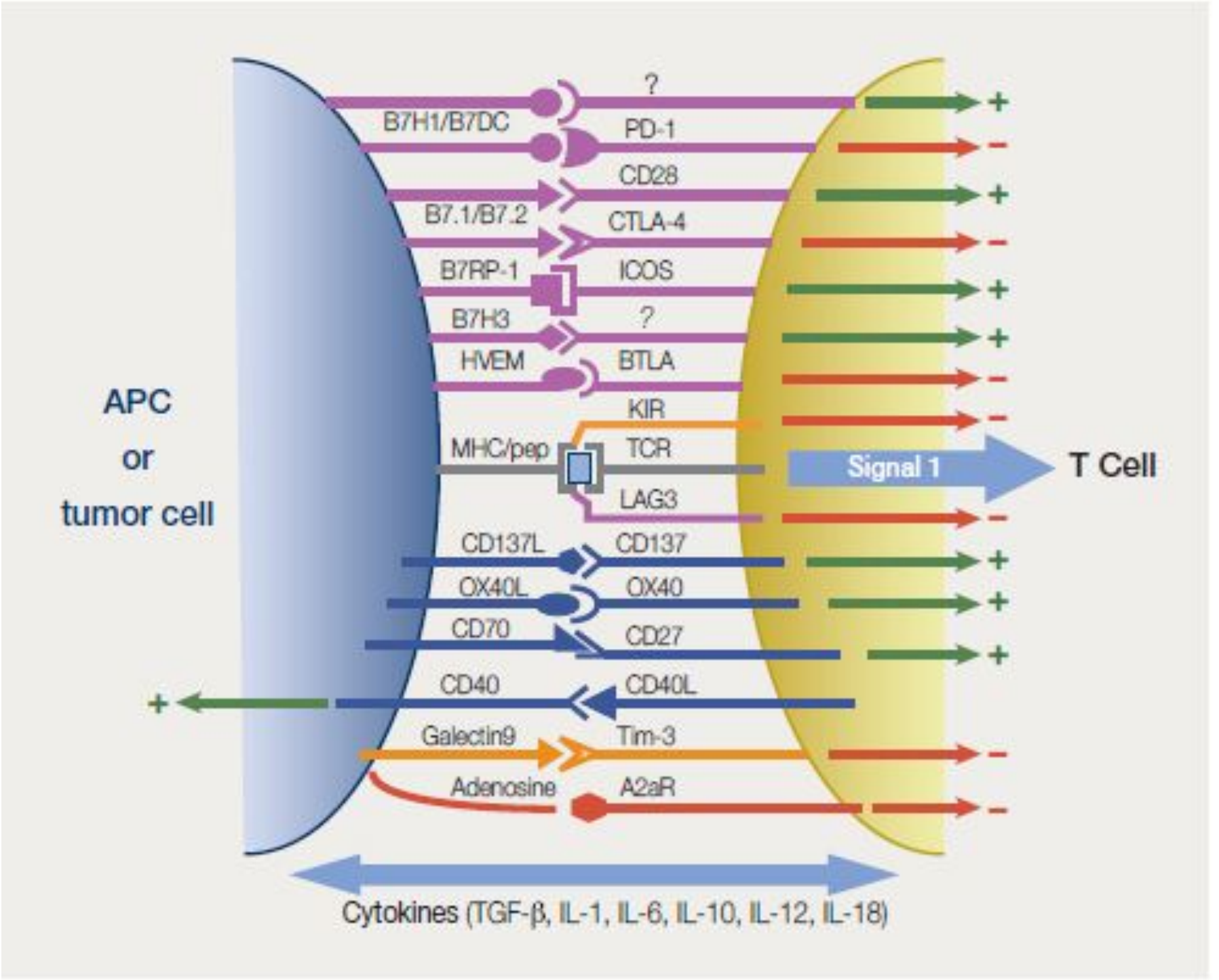
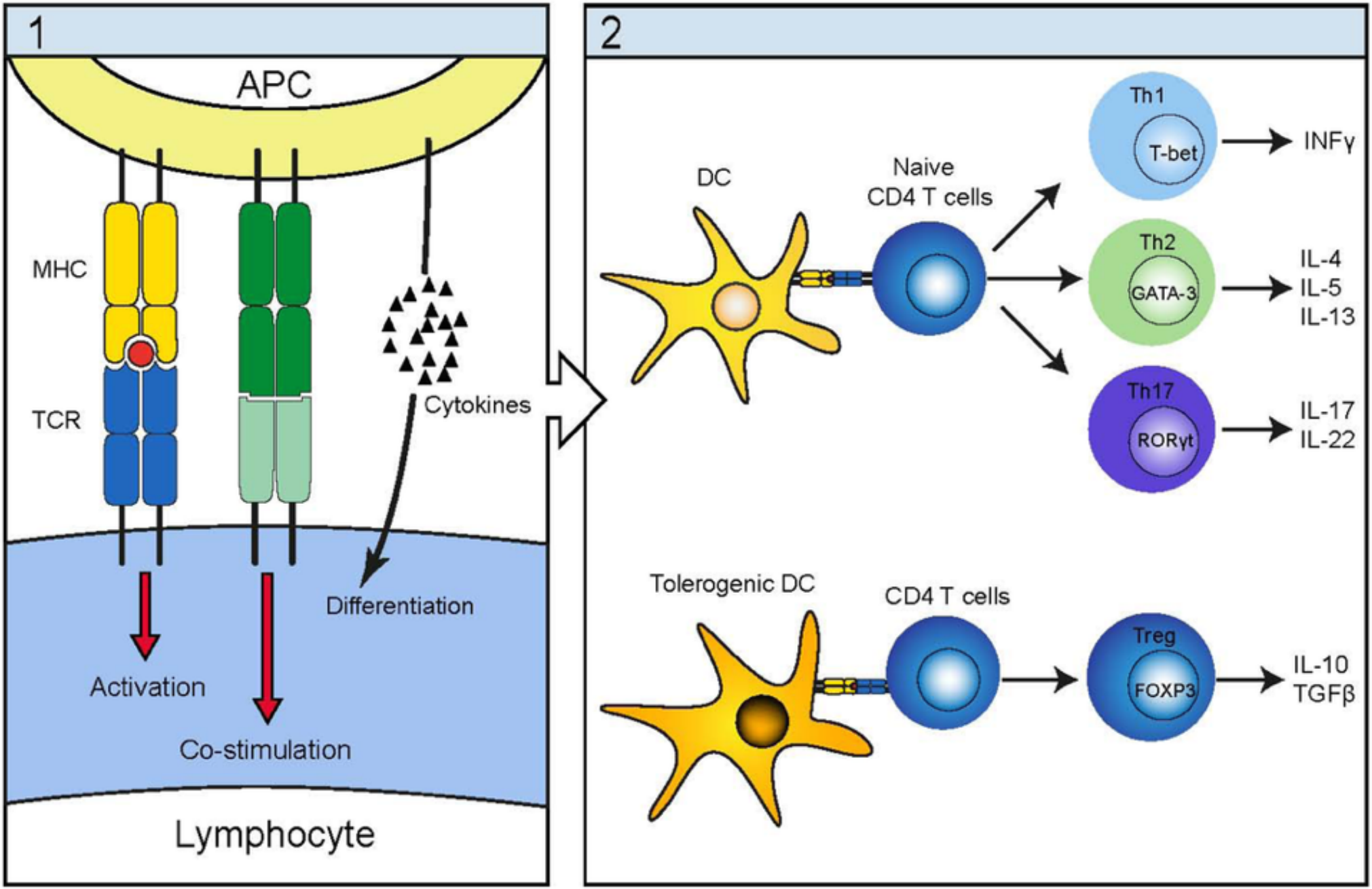
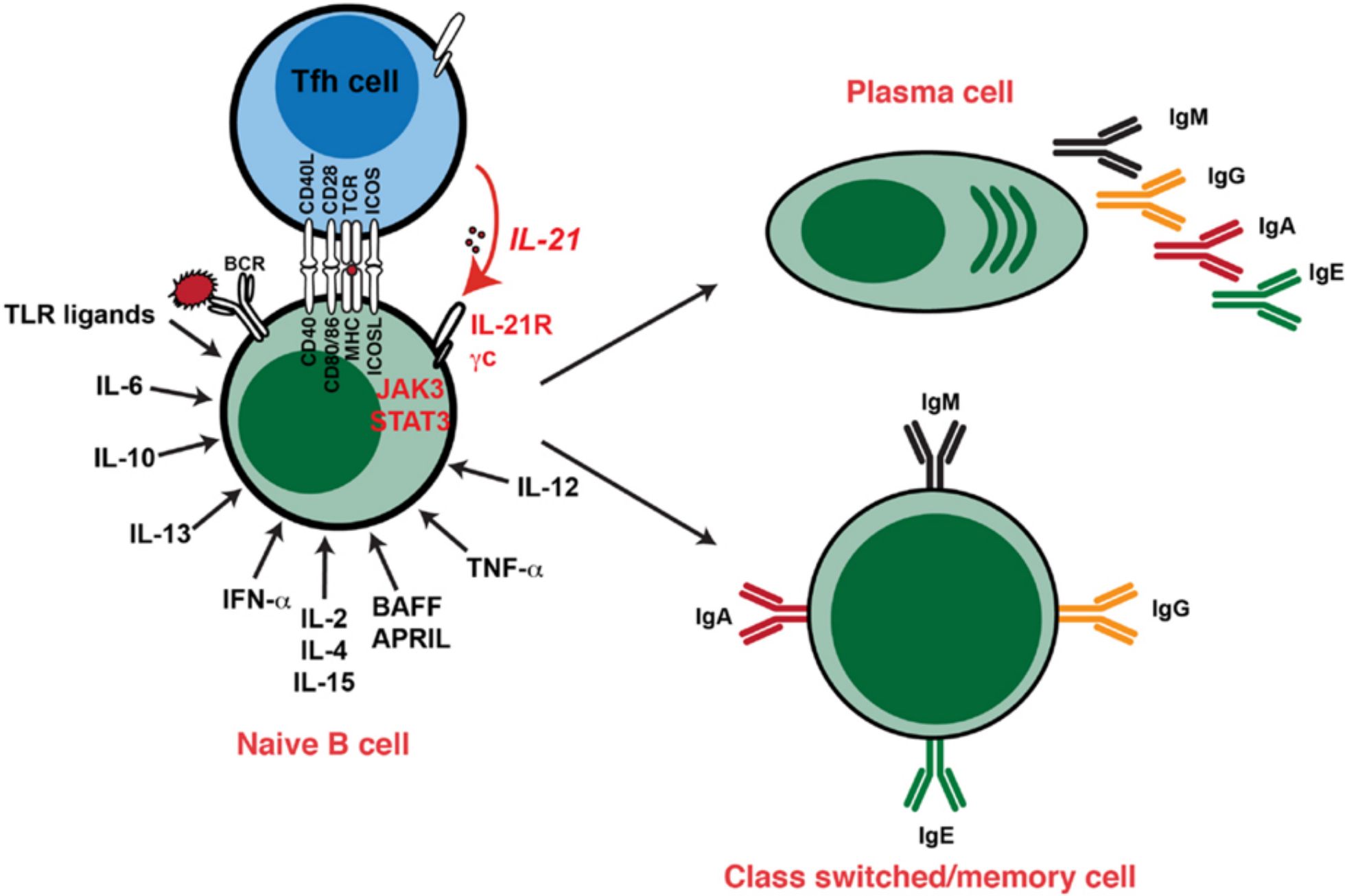
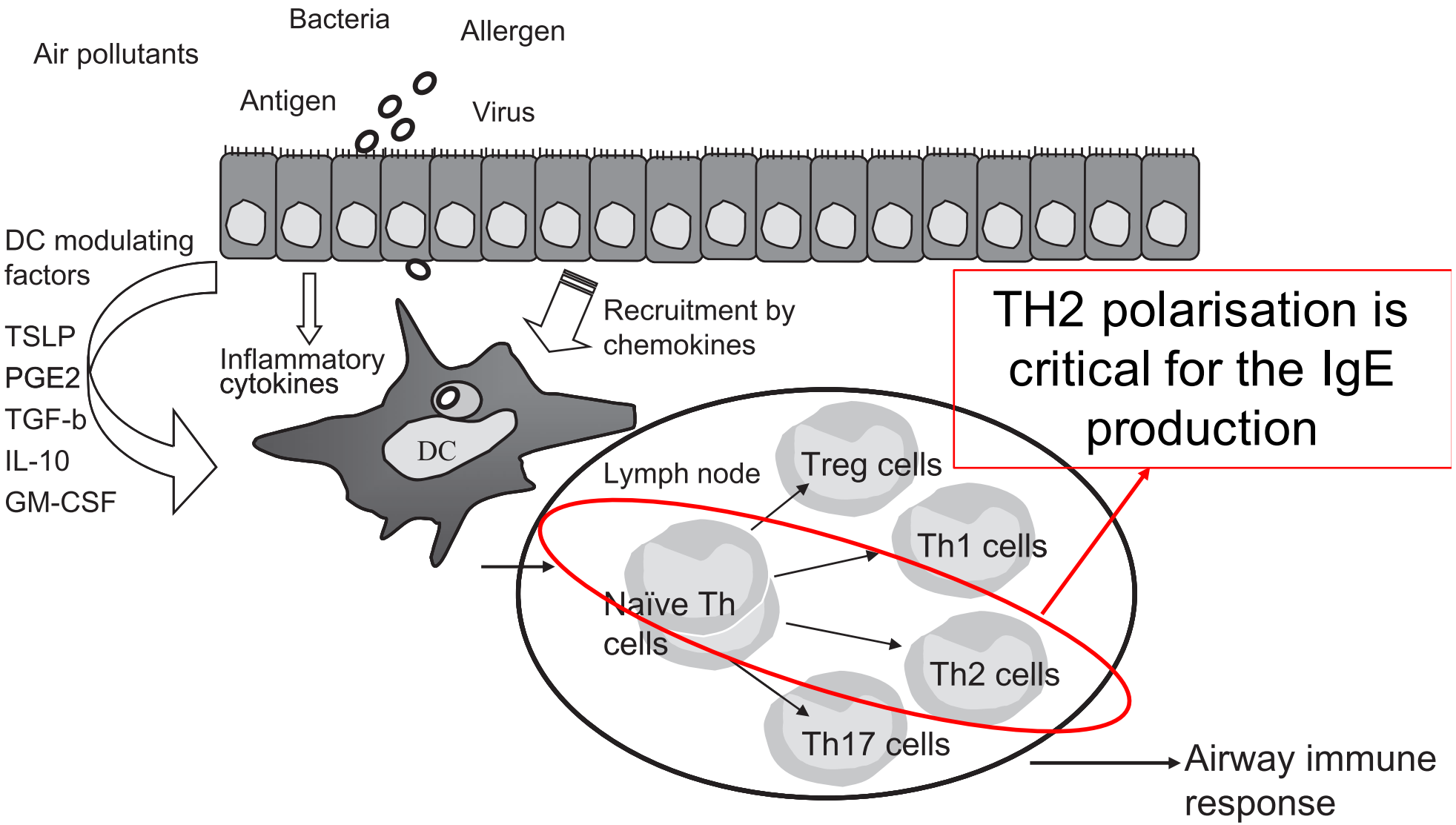

APC
or
tumor cell
?
B7H1/B7DC
PD-1
CD28
B7.1/B7.2
CTLA-4
B7RP-1
ICOS
B7H3
?
HVEM
BTLA
KIR
MHC/pep
TCR
LAG3
Signal 1
T Cell
CD137L
CD137
OX40L
OX40
CD70
CD27
CD40
CD40L
Galectin9
Tim-3
Adenosine
A2aR
Cytokines (TGF-β, IL-1, IL-6, IL-10, IL-12, IL-18)


1
APC
MHC
TCR
Cytokines
Differentiation
Activation
Co-stimulation
Lymphocyte
2
DC
Naive
CD4 T cells
Th1
T-bet
INFγ
Th2
GATA-3
IL-4
IL-5
IL-13
Th17
RORγt
IL-17
IL-22
Tolerogenic DC
CD4 T cells
Treg
FOXP3
IL-10
TGFβ


Tfh cell
CD40L
CD28
TCR
ICOS
IL-21
BCR
TLR ligands
IL-21R
γc
CD40
CD80/86
MHC
ICOSL
JAK3
STAT3
IL-6
IL-10
IL-12
IL-13
TNF-α
IFN-α
IL-2
IL-4
IL-15
BAFF
APRIL
Naive B cell
Plasma cell
IgM
IgG
IgA
IgE
IgM
IgA
IgG
IgE
Class switched/memory cell

Airway immune response



J. van Tongeren et al. Allergy 2008: 63: 1124–1135

What drives Th2 polarisation ?

- antigen dose,
- nature of the antigen,
- direct cell-to-cell interaction with APCs
- the cytokine receptors available on the naive cell
- Genetic predisposition
- enviromental factors
- gastrointerstinal Flora

Hygien-Hypothesis

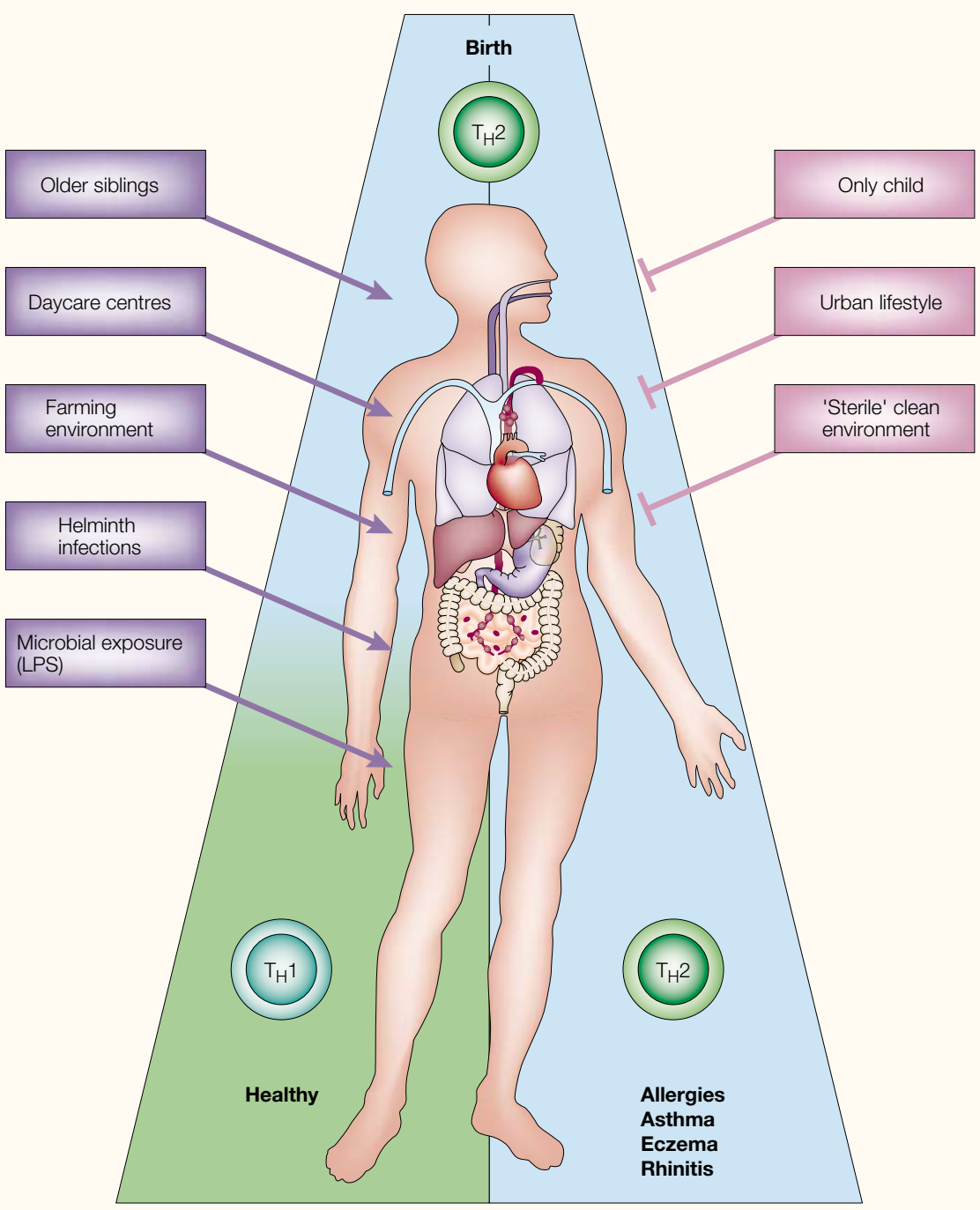
«Western» Lifestyle

Traditional Lifestyle

Th2
IL-4, IL-5

Allergy-Epidemic

Allergy-Prevention



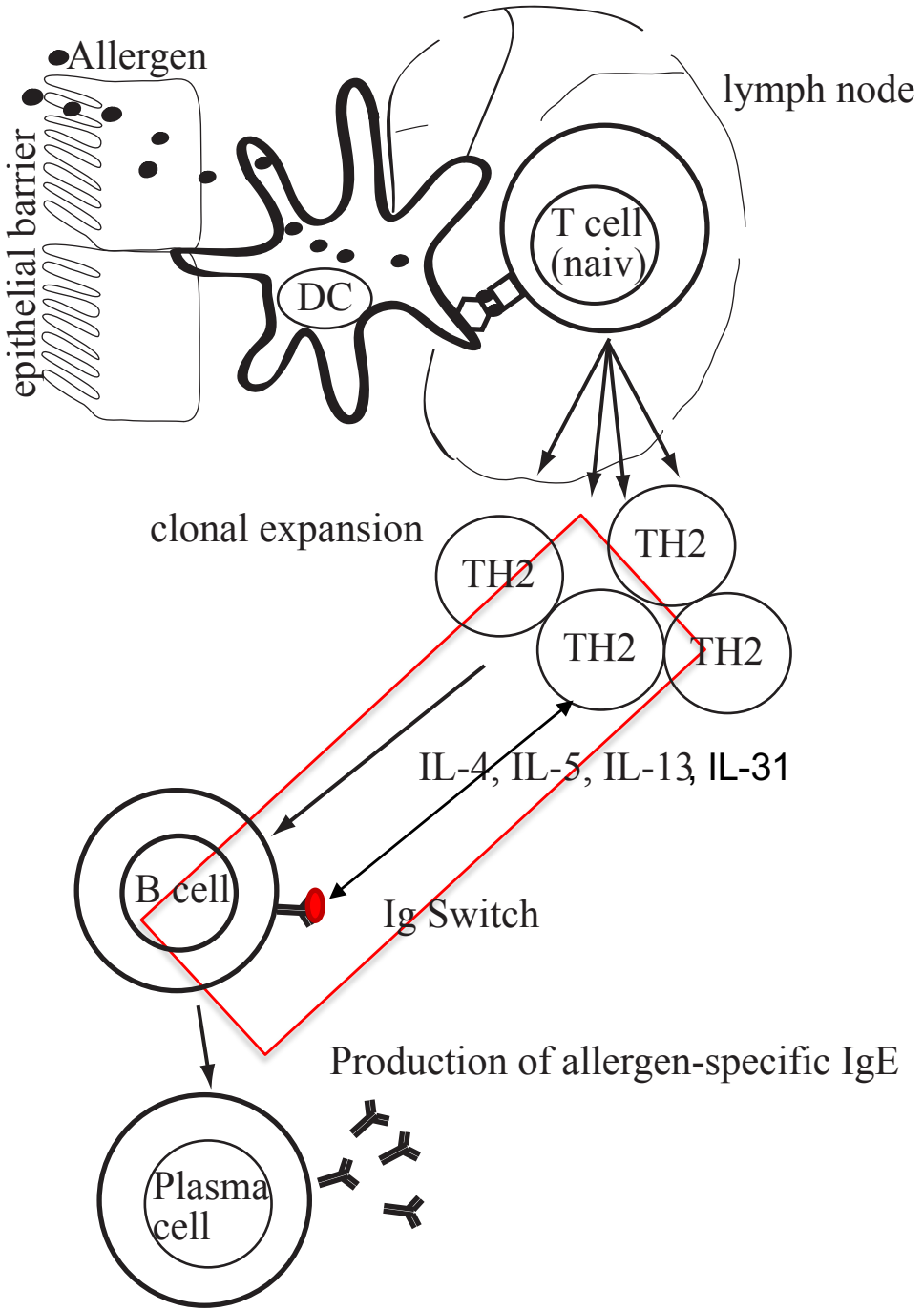
Gern et al. Nature Reviews 2002

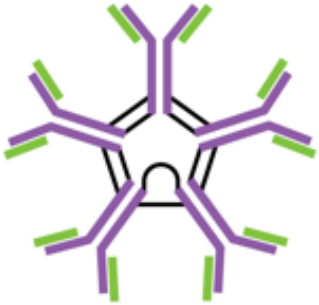
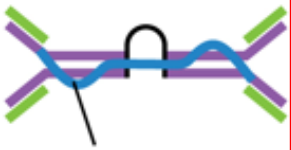
Microbial exposure boosts Th1 response

Protective effect of the farm environment

Protective effect by parasite infection

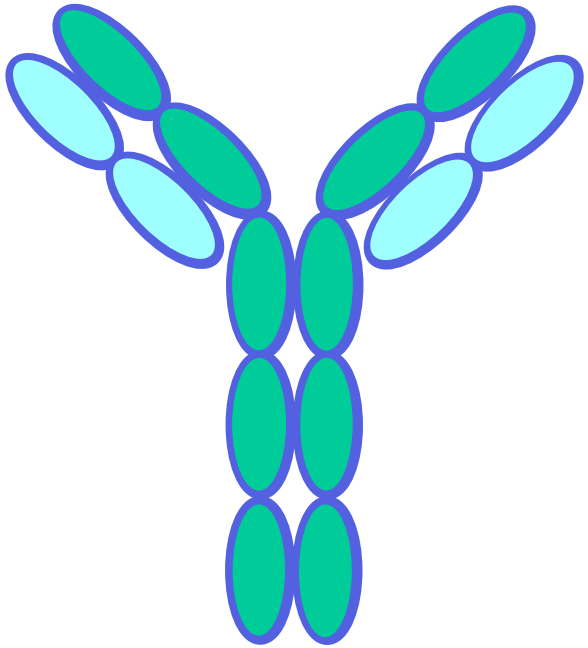
Sensitization Phase



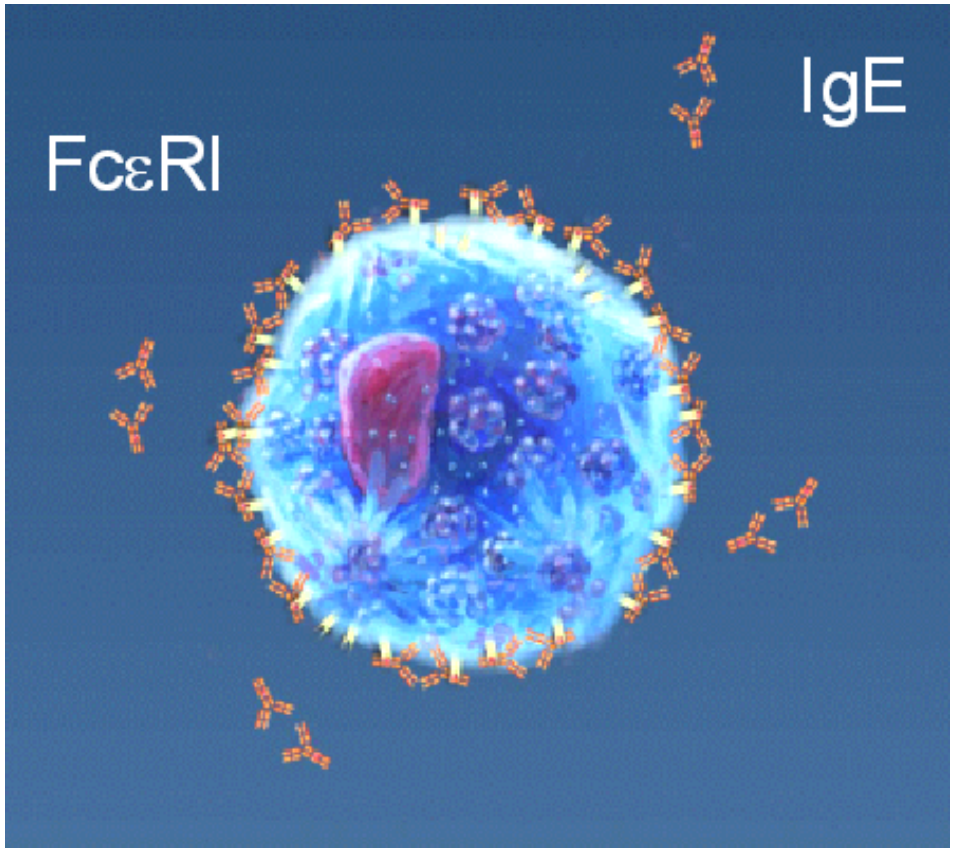
The Five Immunoglobulin (Ig) Classes					
	IgM pentamer	IgG monomer	Secretory IgA dimer	IgE monomer	IgD monomer
					
Heavy chains	μ	γ	α	ε	δ
Number of antigen binding sites	10	2	4	2	2
Molecular weight (Daltons)	900,000	150,000	385,000	200,000	180,000
Percentage of total antibody in serum	6%	80%	13%	0.002%	1%
Crosses placenta	no	yes	no	no	no
Fixes complement	yes	yes	no	no	no
Fc binds to		phagocytes		mast cells and basophils	
Function	Main antibody of primary responses, best at fixing complement; the monomer form of IgM serves as the B cell receptor	Main blood antibody of secondary responses, neutralizes toxins, opsonization	Secreted into mucus, tears, saliva, colostrum	Antibody of allergy and antiparasitic activity	B cell receptor

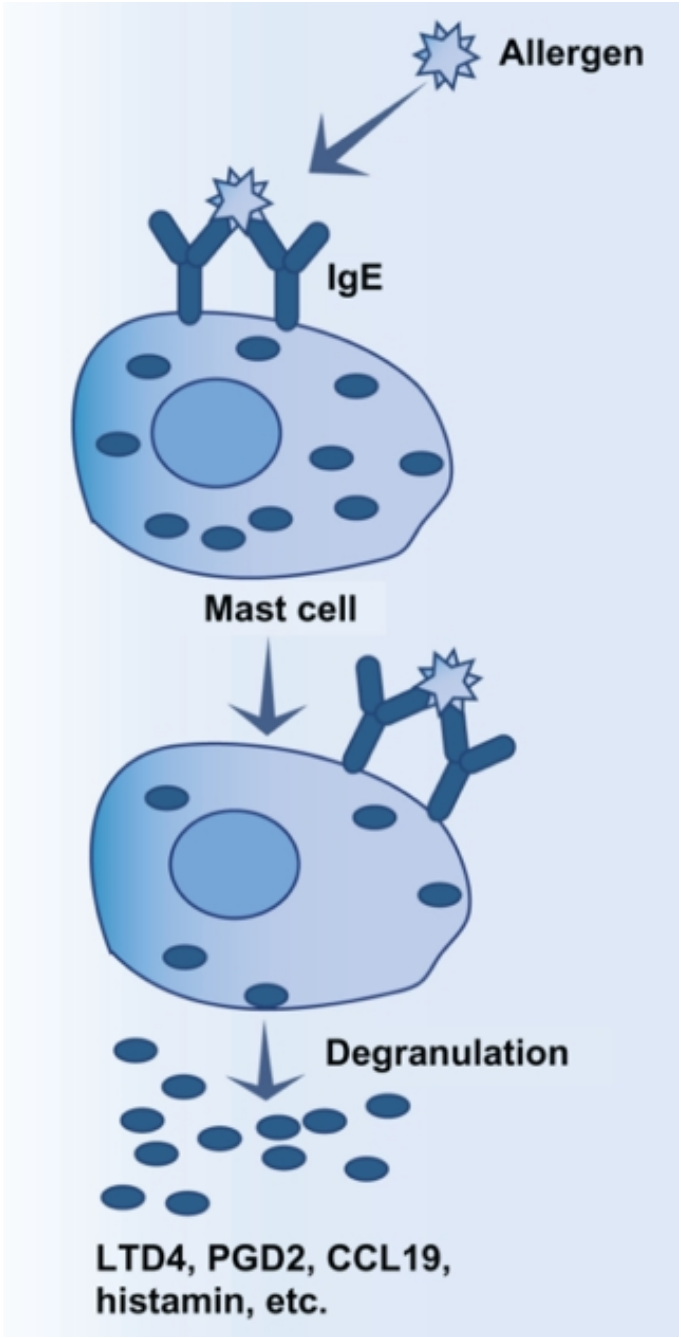
Type-I (immediate hypersensitivity)

Antigen-**Specific**
IgE Antibody



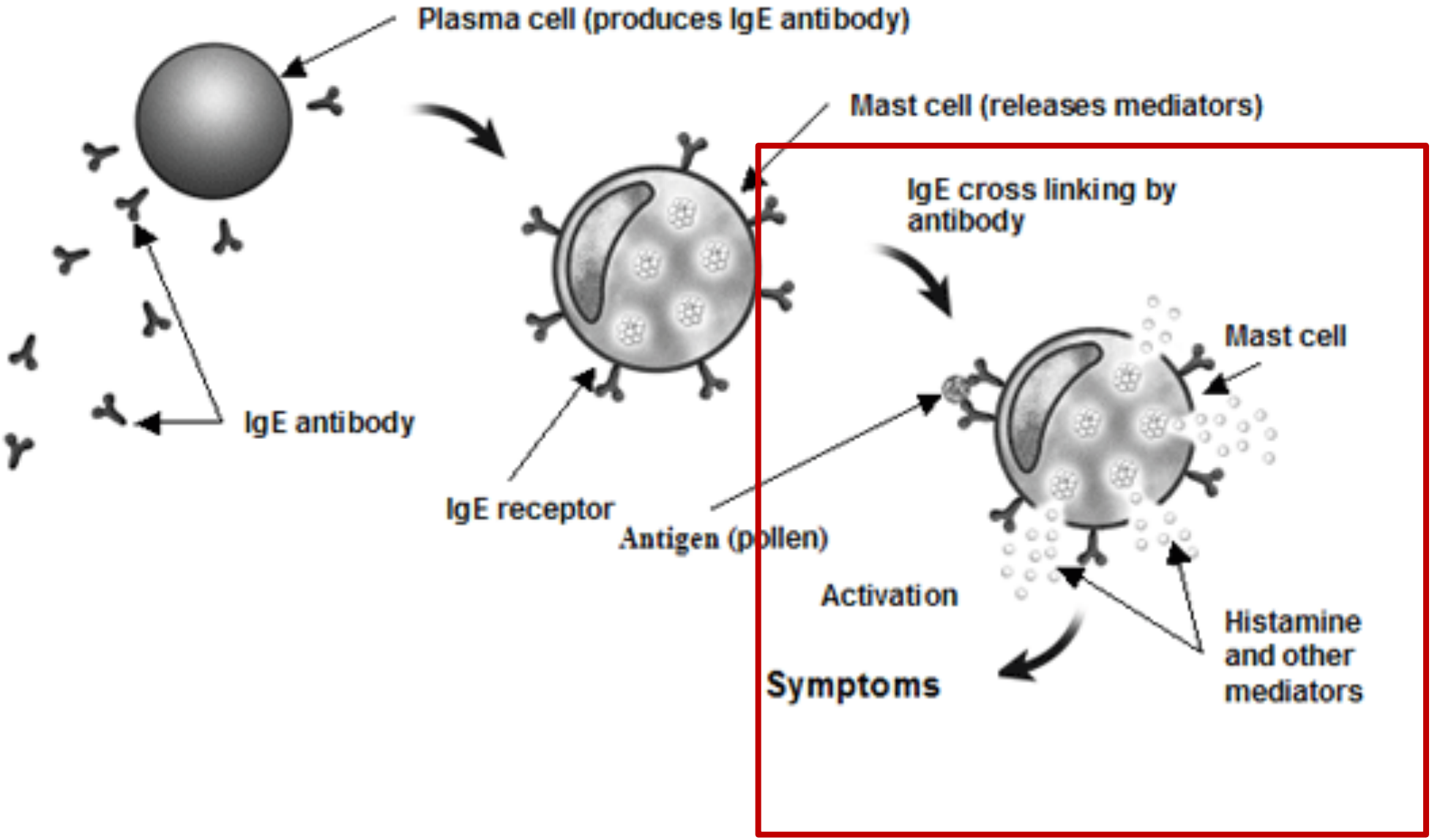
Mastcells



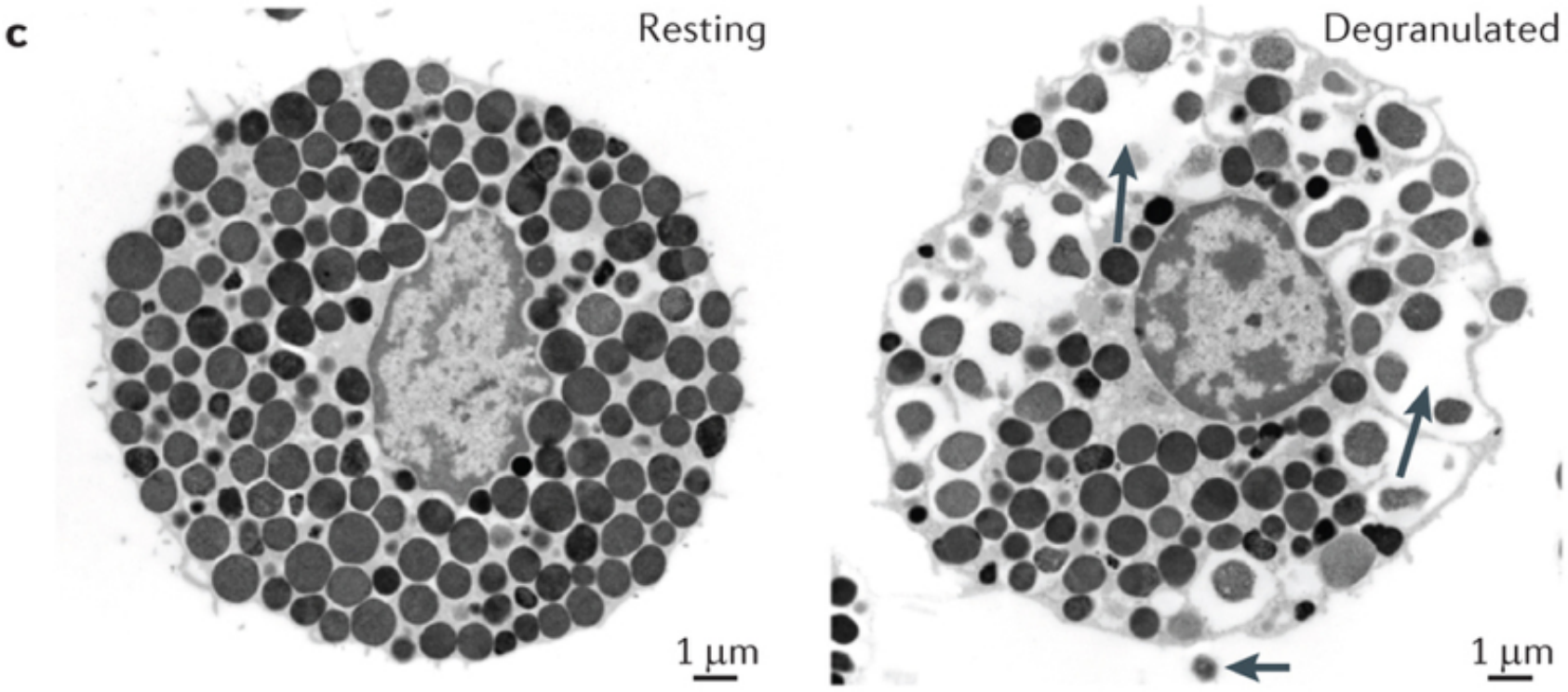


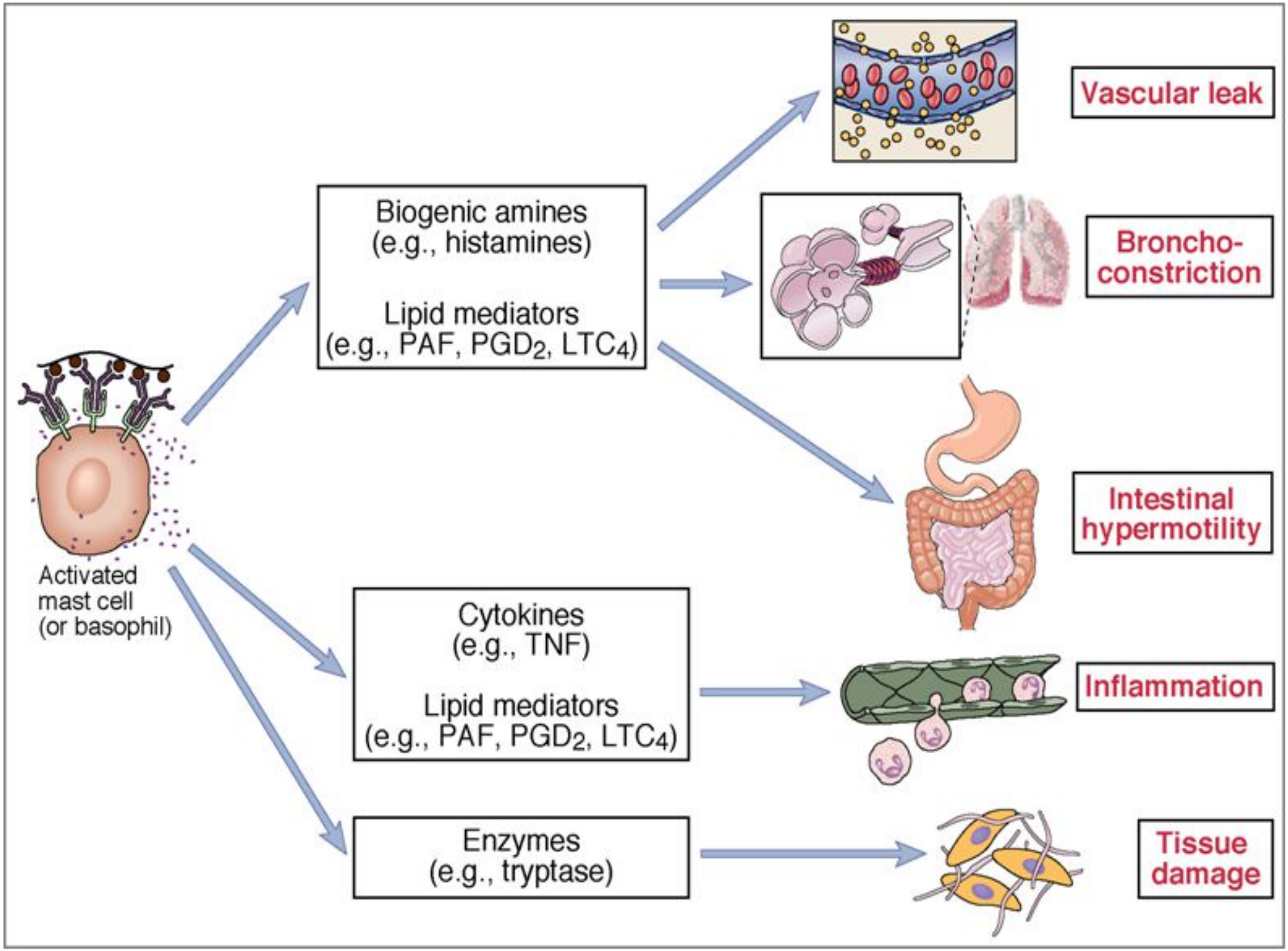
Cross linking of 2 Fc-IgE-RI
Is required for mast cell activation

Mediator release


Plasma cell (produces IgE antibody)
Mast cell (releases mediators)
IgE cross linking by antibody
Mast cell
IgE antibody
IgE receptor
Antigen (pollen)
Activation
Histamine and other mediators
Symptoms

Mast cell



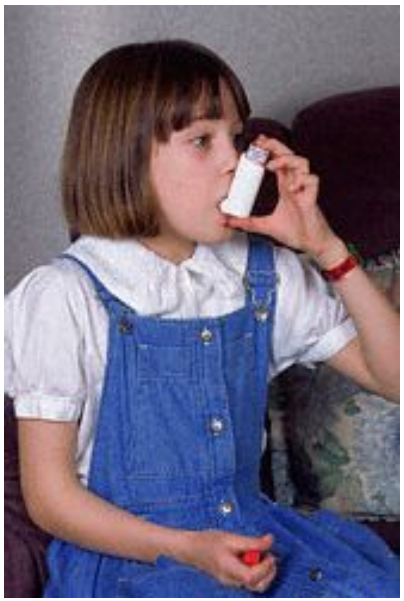

Biogenic amines
(e.g., histamines)
Lipid mediators
(e.g., PAF, PGD2, LTC4)
Cytokines
(e.g., TNF)
Lipid mediators
(e.g., PAF, PGD2, LTC4)
Enzymes
(e.g., tryptase)
Activated
mast cell
(or basophil)
Vascular leak
Broncho-
constriction
Intestinal
hypermotility
Inflammation
Tissue
damage

Symptoms of IgE mediated (immediatet) reaction

Eyes:
Conjunctivitis

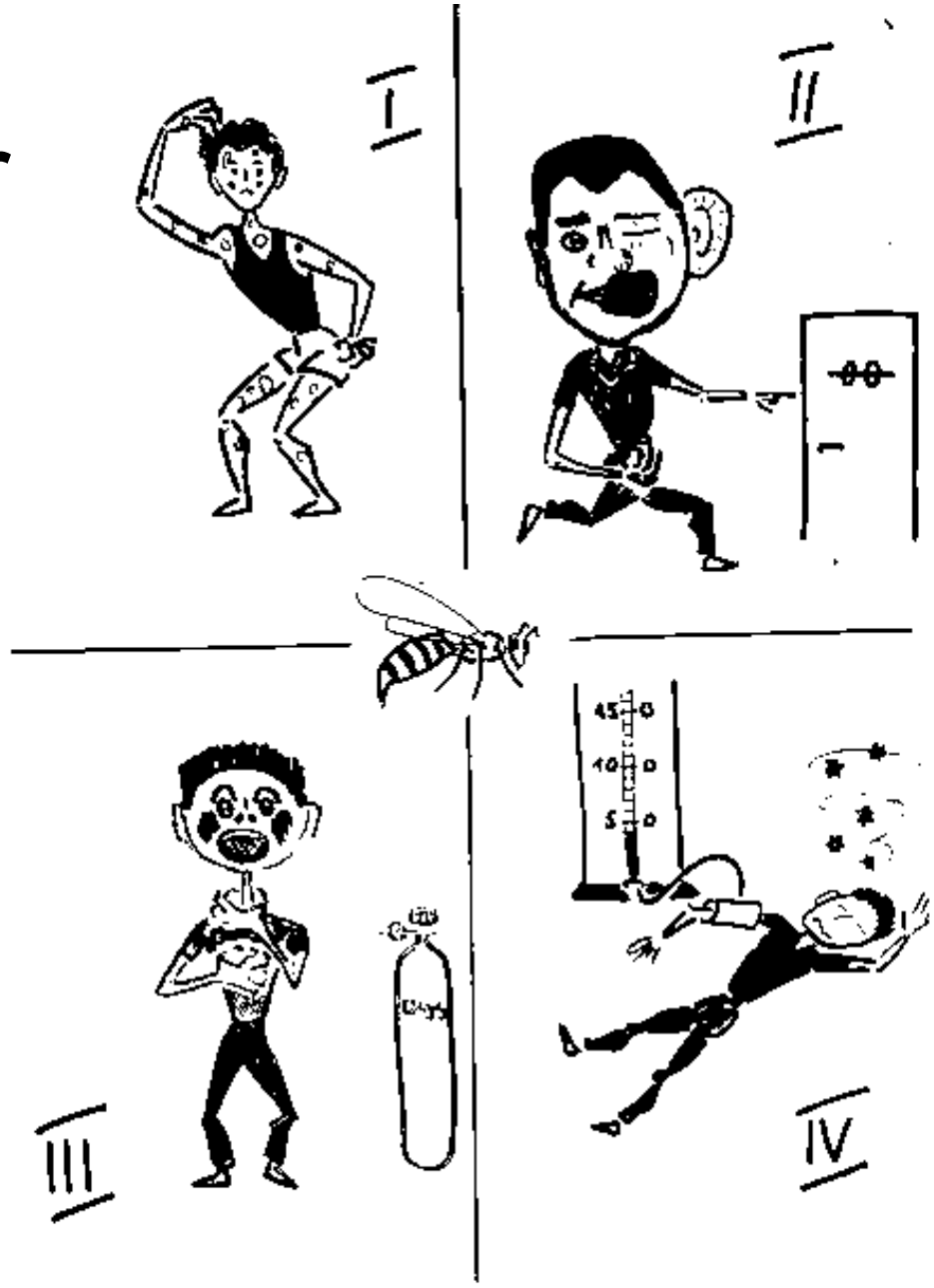
Nose:
Rhinitis

Lungs:
Asthma



Skin:
Urticaria
Angioedema

Classification of allergic reactions according to Mueller



Anaphylaxis

= potentially life threatening situation; rapid onset

Massive mediator release

different organs are involved (skin, respiratory, cardiovascular system)

most frequent cause in Switzerland: hymenoptera venom allergy, drug allergy, food allergy

Is anaphylaxis always IgE mediated???

No, Anaphylaxis may involve other mechanisms than IgE, e.g.:

- Complement activation
- IgG and IgM immune complexes
- Non-immunologic mechanisms
- Pseudo allergies (radio contrast media)
- Toxic effects of insect venom
- Non-steroidal anti-inflammatory drugs

Food Allergy

Adverse reaction Food

1. Toxic

2. Nontoxic
   A) Immune mediated
      - IgE mediated
      - Non-IgE mediated

   B) Non immune mediated (food intolerance)
      - enzymatic (e.g. lactase deficiency)
      - pharmacological (abnormal reactivity to substances e.g. amines)
      - undefined (e.g. food additive intolerance)

2 Groups of food allergy

Food sensitization develops
as a consequence of crossreaktivity
with airborne allergens

Food sensitization occurs
by gastrointestinal tract
(often stable proteins)

Mostly adults, cross reactivity

Mostly in children
“real food allergy”

Oral allergy syndrome

Sensitization to heat/pepsine labile plant-derived proteins in patients with pollen allergy

Cross reactivity between homologous plant derived proteins and pollen proteins

Bet v1 → nuts, apple, kiwi

heated normally well tolerated

Allergen cross reactivity seems to be due to IgE antibodies that recognize structurally similar epitopes on different proteins that are phylogenetically closely related or present evolutionarily conserved structures

Food allergy - crossreaktivity

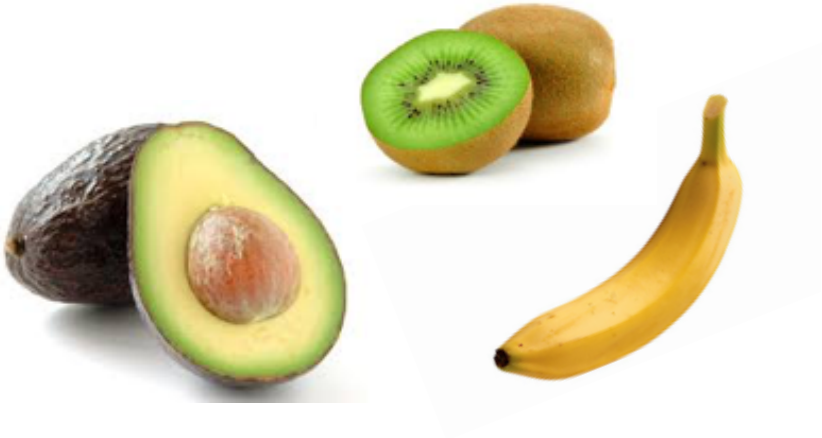
celery-birch-mugwort-**spices** syndrome




shellfish and dust mite allergy


Food allergy - crossreaktivity

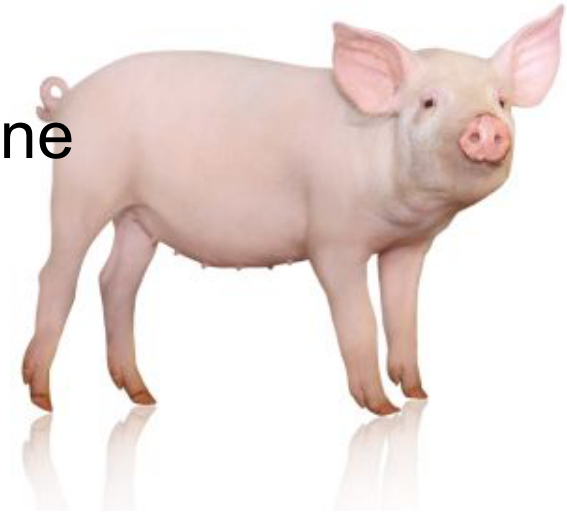
Latex-fruit syndrome



Cat-pork syndrome

Fel d 2

Pig serum albumine



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Food sensitization develops
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“real food allergy”

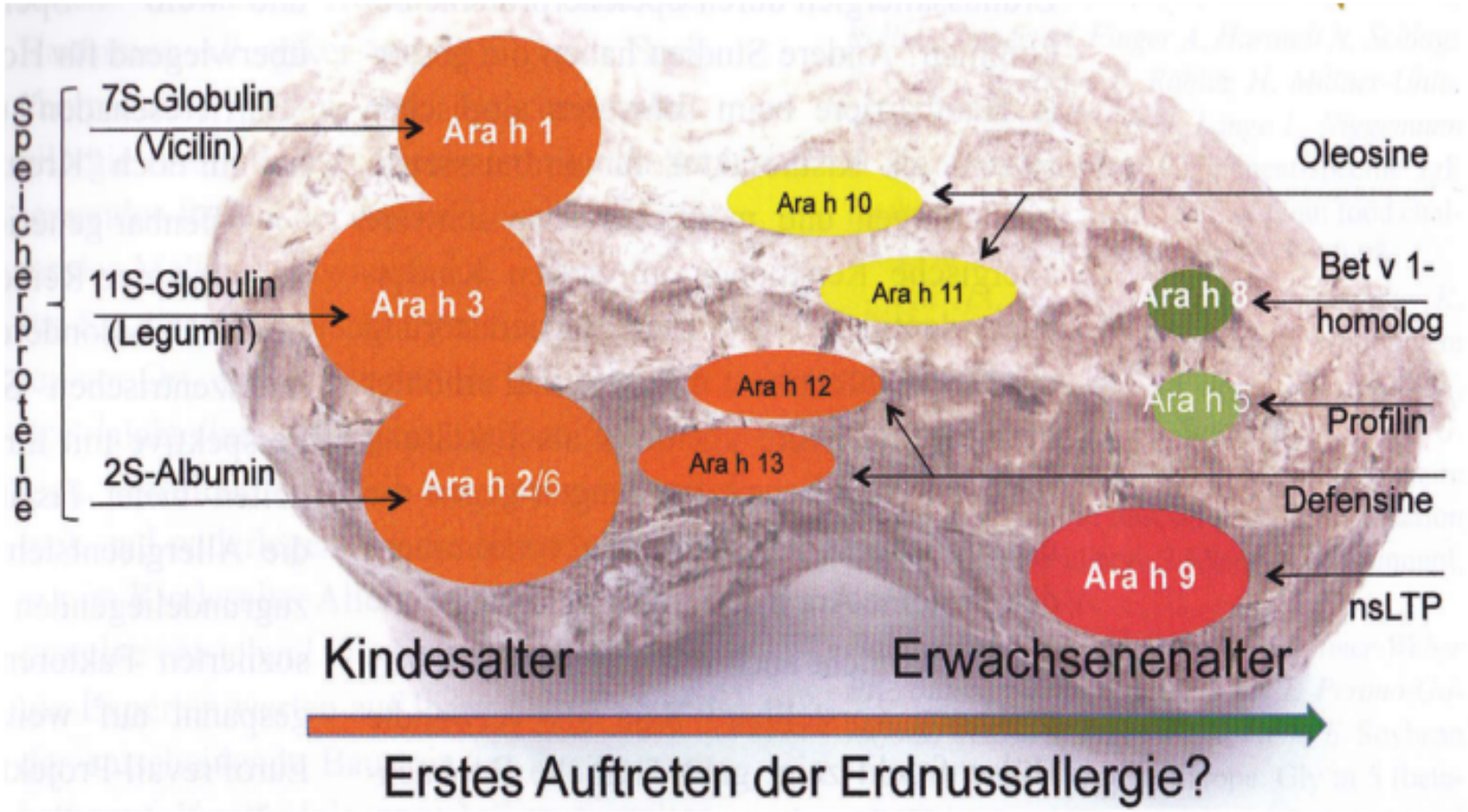
Lipid transfer proteins

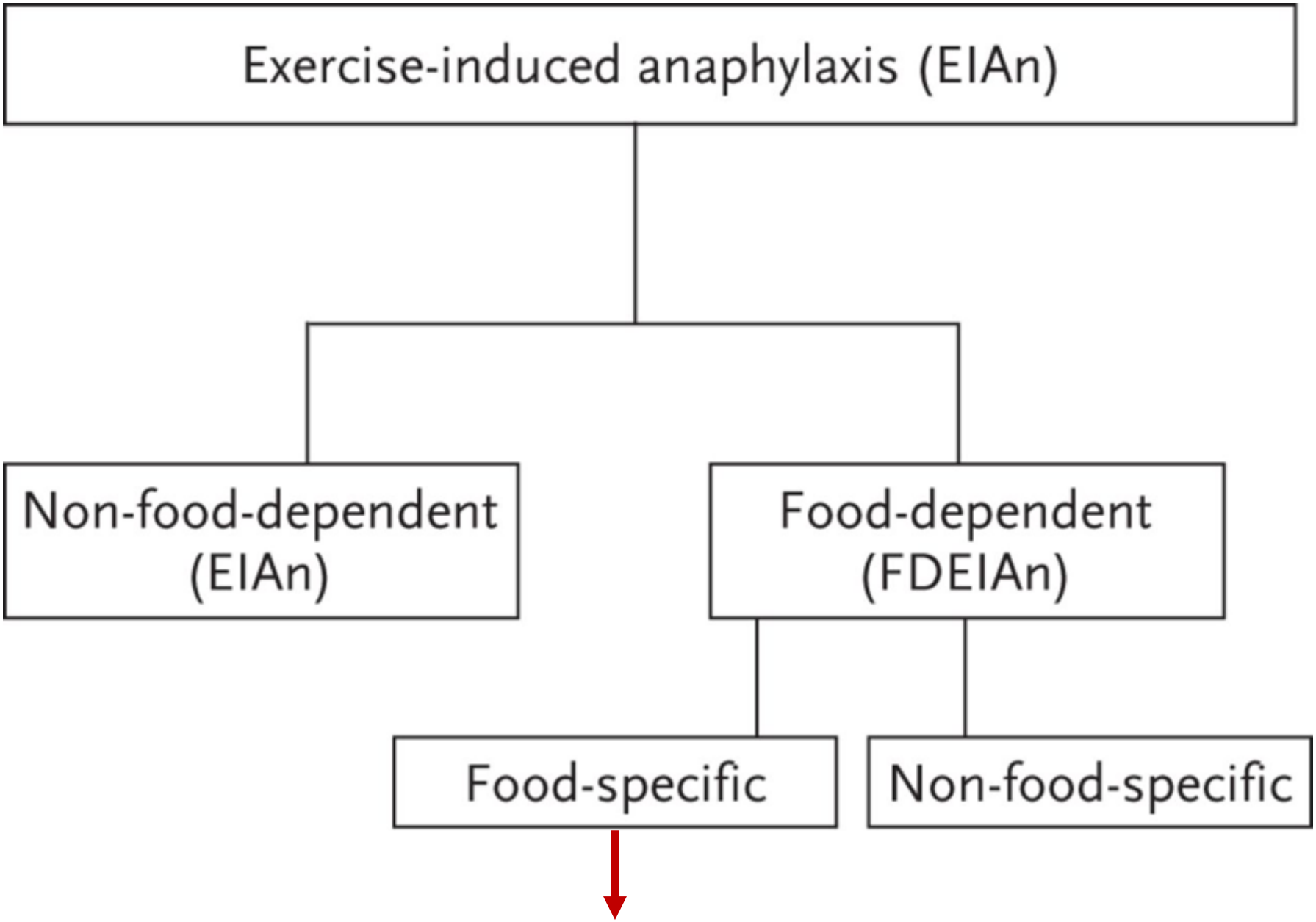
Role in defence against fungi and bacteria

Heat stable, begin to unfold above 95°, protein refold on cooling

More severe allergic reactions

Peanut allergy




Exercise-induced anaphylaxis (EIAn)
Non-food-dependent (EIAn)
Food-dependent (FDEIAn)
Food-specific
Non-food-specific
Tri a 19

Bee / Wasp Allergy

Api m 1	Phospholipase A_2		
Api m 3	Saure Phosphatase		
Api m 4	Mellitin	Phospholipase A_1	Ves v 1
Api m 10	Icarapin	Antigen 5	Ves v 5
Api m 2	Hyaluronidasen		Ves v 2
Api m 5	Dipeptidylpeptidasen		Ves v 3
Api m 12	Vitellogenine		Ves v 6

Hymenoptera venom allergy

- the prevalence of an allergy systemic reaction after a Hymenoptera sting is estimated between 1 and 7 % in Europe
- Mortality: 200 cases pro year in Europe
- One of the most frequent cause of Anaphylaxis in adult population
- bee sting 50 µg (30-140 mg) of venom proteins , after a wasp sting 3–5 µg of venom proteins are introduced to the body of the victim
- Toxic reaction > 50-100 stings (in adults); > 10 stings (in children)

Local reactions after hymenoptera stings

Large local reaction=
Swelling exceeding 10 cm

Not an Allergy !

Drug allergy

IgE mediated drug allergies (immediate reactions)

Anaphylactic IgE-mediated reactions Flushing, pruritus, urticaria, angioedema, laryngeal edema, rhinorrhea, conjunctivitis, shortness of breath, wheezing, bronchospasm, nausea, vomiting, diarrhea, hypotension	**Antibiotics** Beta-lactams Penicillins, cephalosporins, amino-penicillins Fluroquinolones Ciprofloxacin, levofloxacin	Sepsis Meningitis Pneumonia Pyelonephritis
	Chemotherapy drugs Platins Carboplatin, cisplatin, oxaliplatin	Primary and recurrent metastatic cancers (breast, ovarian, colon)
	Monoclonal antibodies Rituximab, trastuzumab	Chronic inflammatory diseases, cancers (leukemias, breast, ovarian)

Desensitization often possible!!!

Non-IgE mediated drug allergies (immediate reactions)

Anaphylactoid **Direct mast cell/basophil, complement, and leukotriene metabolism reactions** Flushing, pruritus, urticaria, angioedema, throat tightness, shortness of breath, nausea, vomiting, diarrhea, hypotension, hypertension, back and/or abdominal pain	**Aspirin/NSAIDs**	Cardiac protection, asthma w/ nasal polyposis, chronic inflammatory diseases (RA, Crohn's)
	Vancomycin	MRSA
	Chemotherapy drugs Taxenes Paclitaxel, docetaxel	Primary and recurrent metastatic cancers (breast, ovarian, colon)

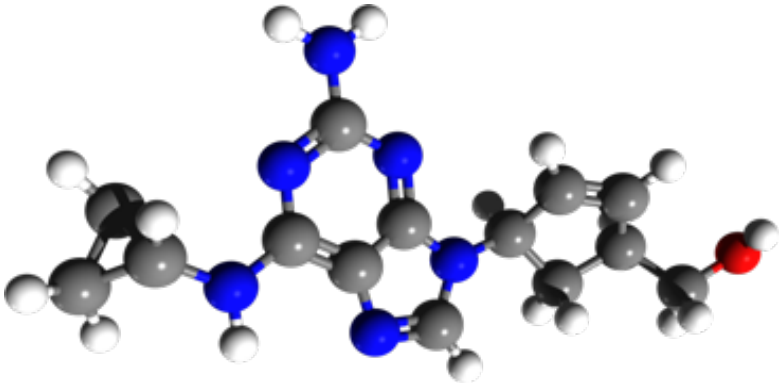
Pseudo-allergic reactions radio contrast media: direct membrane effects related to the osmolarity of contrast media solution

Symptoms of T cell mediated drug allergy

- Makulo-papular Exanthem
- bullous Exanthem
- Acute generalized exanthematous Pustulosis (AGEP)
- Stevens-Johnson Syndrome (SJS) toxic-epidermal Necrolysis (TEN)
- DRESS, Hepatitis, interstitial Nephritis, Pneumonitis

Chemical structure of drug molecule

No protein drugs, small molecules
1-2 kDa, haptens

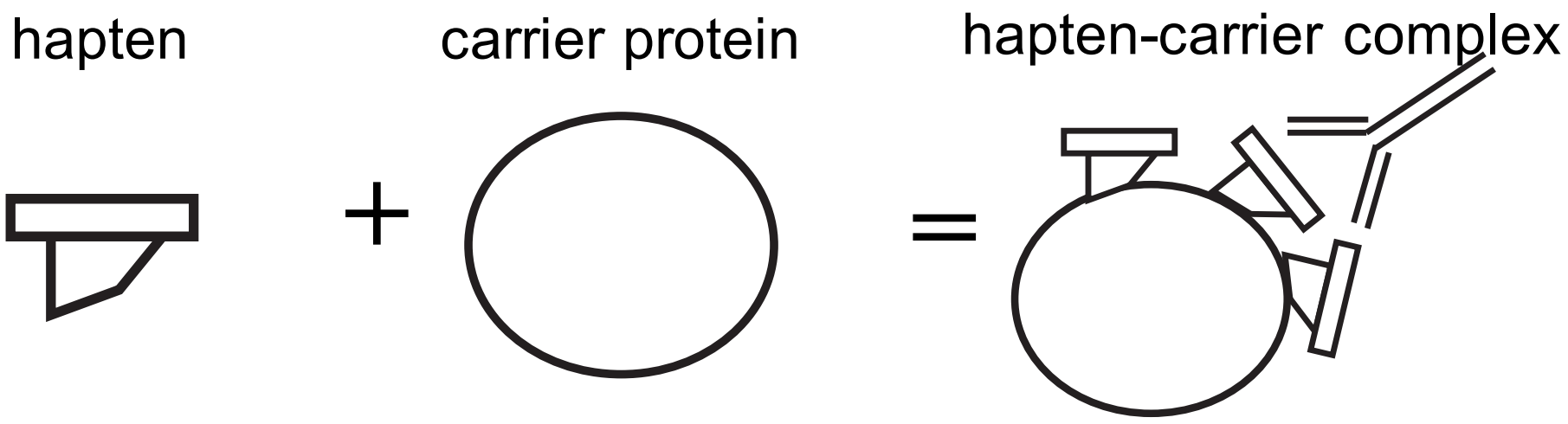


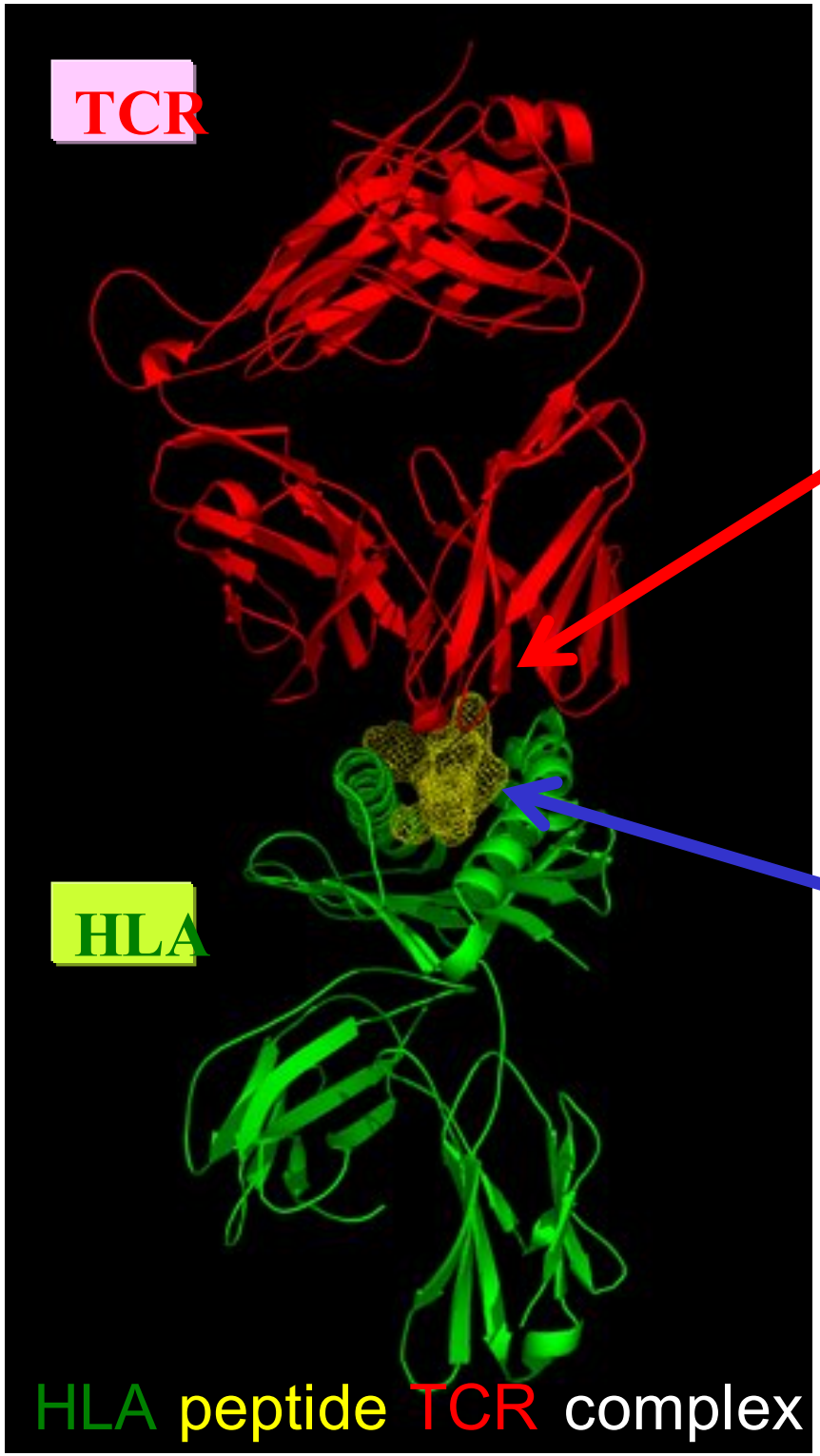
Protein drugs
Large molecules >20 kDa

Haptens

Small molecules alone are not immunogenic!

Haptens = reactive chemical substances binding to a larger protein → hapten-carrier complex forms neo-antigenic determinants able to induce both a T-cell and B-cell immune response.





p-i concept:

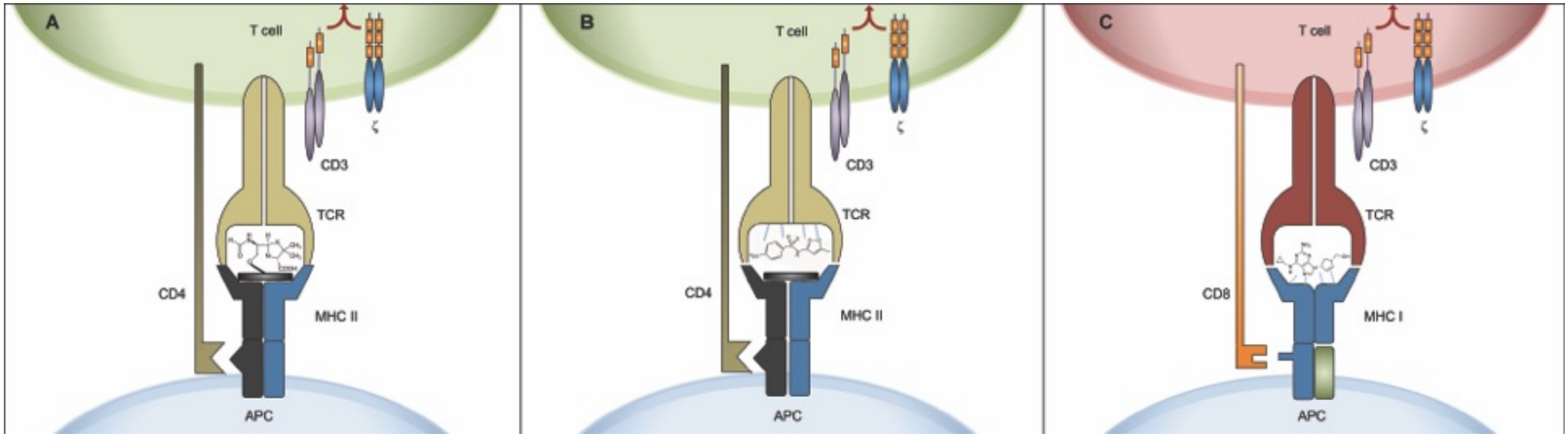
a) **the drug binds first to the TCR** (by non covalent bonds; not restricted to a HLA-allele)

or

b) **the drug binds first to the HLA molecule**, and the HLA-peptide-drug complex is then recognized by the TCR

(HLA-class I restricted, CD8)

Hapten **p-i (TCR)** **p-i (HLA)**



Immune reaction **Pharmacological interaction**

Contact Dermatitis

Contact Dermatitis

non-infectious reaction of the skin to external substances

<u>Allergic contact dermatitis</u>

T- Zell mediated immune response to contactallergens like:

- Nickel, lanolin, Peru balsam or potassium dichromate
- jewellery, medication cosmetics, dyes impregnating agents

<u>Irritative contact dermatitis</u>

Non immune mediated response to physical, chemical irritants and physical influences

- rubbing, pressure, heat and cold or UV rays
- water, soap, disinfectants,

Allergic Contact Dermatitis

- The reaction usually occurs 24–48 hours after contact with the allergenic substance.
- The skin is inflamed and reddened, it may swell up and blisters or papules may appear.
- These symptoms are often combined with severe itching.
- The skin reaction appears at the site of the body where the skin came into contact with the irritant, but may also spread to nearby or remote regions of the skin.

Allergic Contact Dermatitis

Allergic Contact Dermatitis from a Henna Tattoo
N Engl J Med 2008; 359:627 August 7, 2008

Diagnostics of allergic diseases

Diagnostics of allergic diseases

- Medical history
- Symptoms
- Tests

Diagnostics of allergic diseases

Typ I Hypersensitivity

Skin pricktest

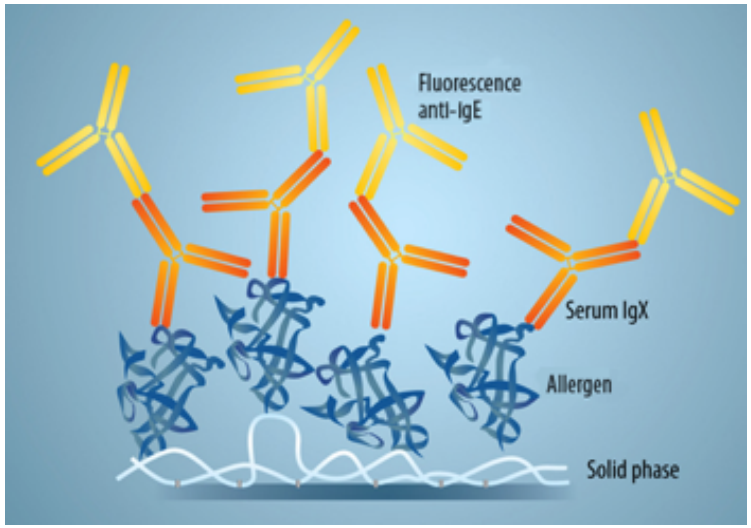
Prick-to-prick Test

Diagnostics of allergic diseases

In-Vito Test and molecular allergy diagnostics

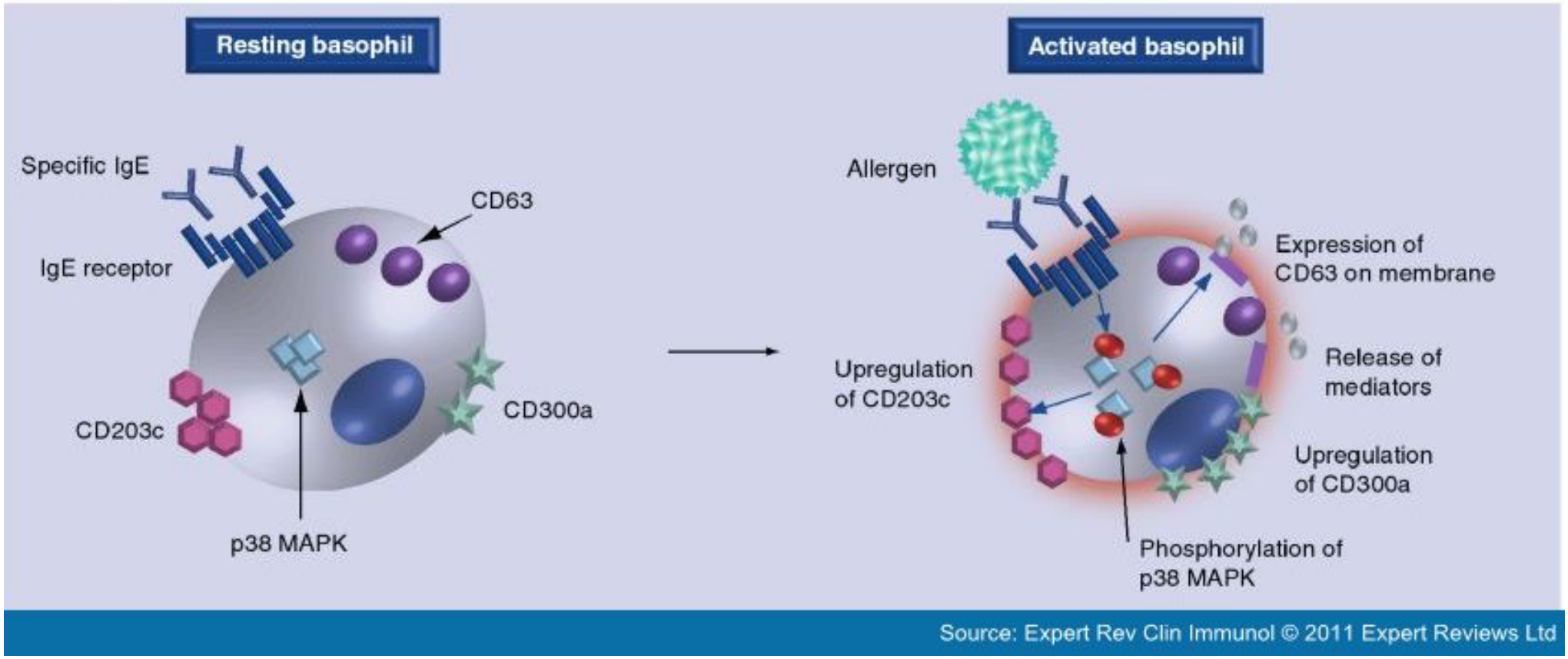
Type I Hypersensitivity

Serum IgE



Diagnostics of allergic diseases

Basophil activation Test



Conjunctival provocation tests (CPT, allergen solution)

No standardization of CPT; no grading of ocular reactions

Digital image analysis possesses the potential of being an objective evaluation method compared to the wide-spread subjective

Dogan et al. Int Arch Allergy Immunol 2014;163:59–68

Oral provocation tests

Food challenge Tests

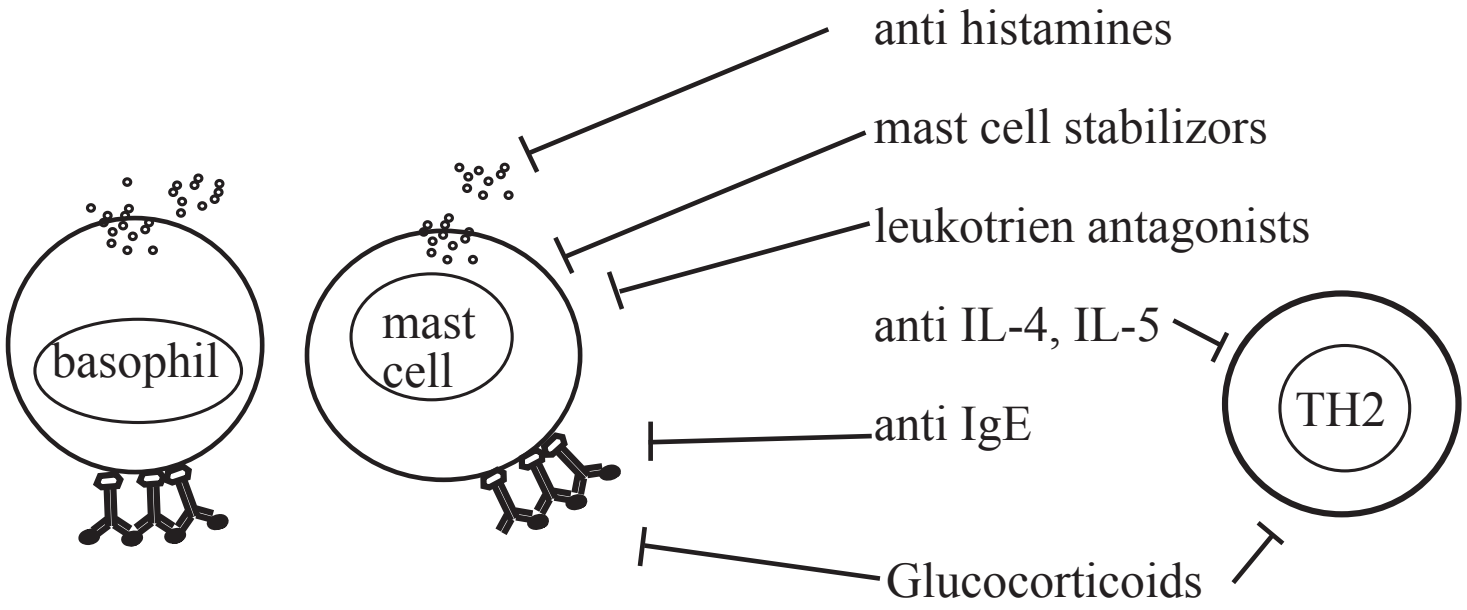
Patch Tests
Type IV Hypersenstivity

Therapy principles

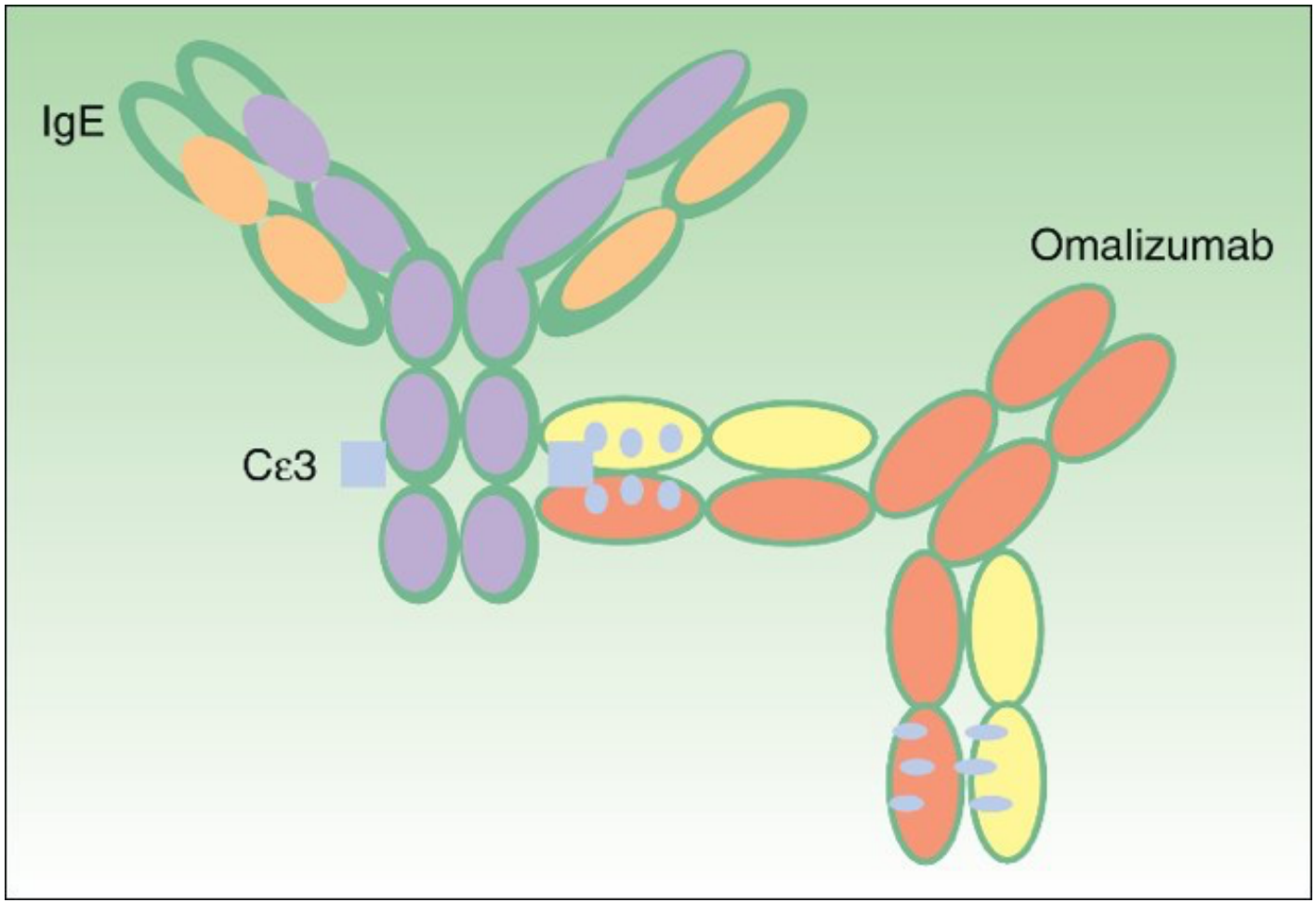
Therapy principles

1. Symptomatic therapy
- antihistamines
- corticosteroids
- leukotrien antagonists
- antiasthmatics (inhalativ medication)
- biologics (Omalizumab, anti-IgE), (Mepolizumab anti-IL5)

Inhibition of inflammatory mediatores released during effector phase:



Anti IgE therapy (omalizumab)



Binding of omalizumab to the ce3 domain of IgE.

Adapted from Francés et al. 2014 Actas Dermosifiliogr. 2014;105:45-52. - Vol. 105 Num.01

Therapy principles

Allergen-specific Immunotherapy alters course of disease

Bee keepers

http://www.spiegel.de/fotostrecke/imkern-extrem-27-kilogramm-bienen-am-koerper-fotostrecke-70505.html

Systemic reactions in 45% of beekeepers with <15 bee sting / year

No/less systemic reactions in Beekeepers with
> 200 bee sting / year

Why???

Allergen-specific Immunotherapy

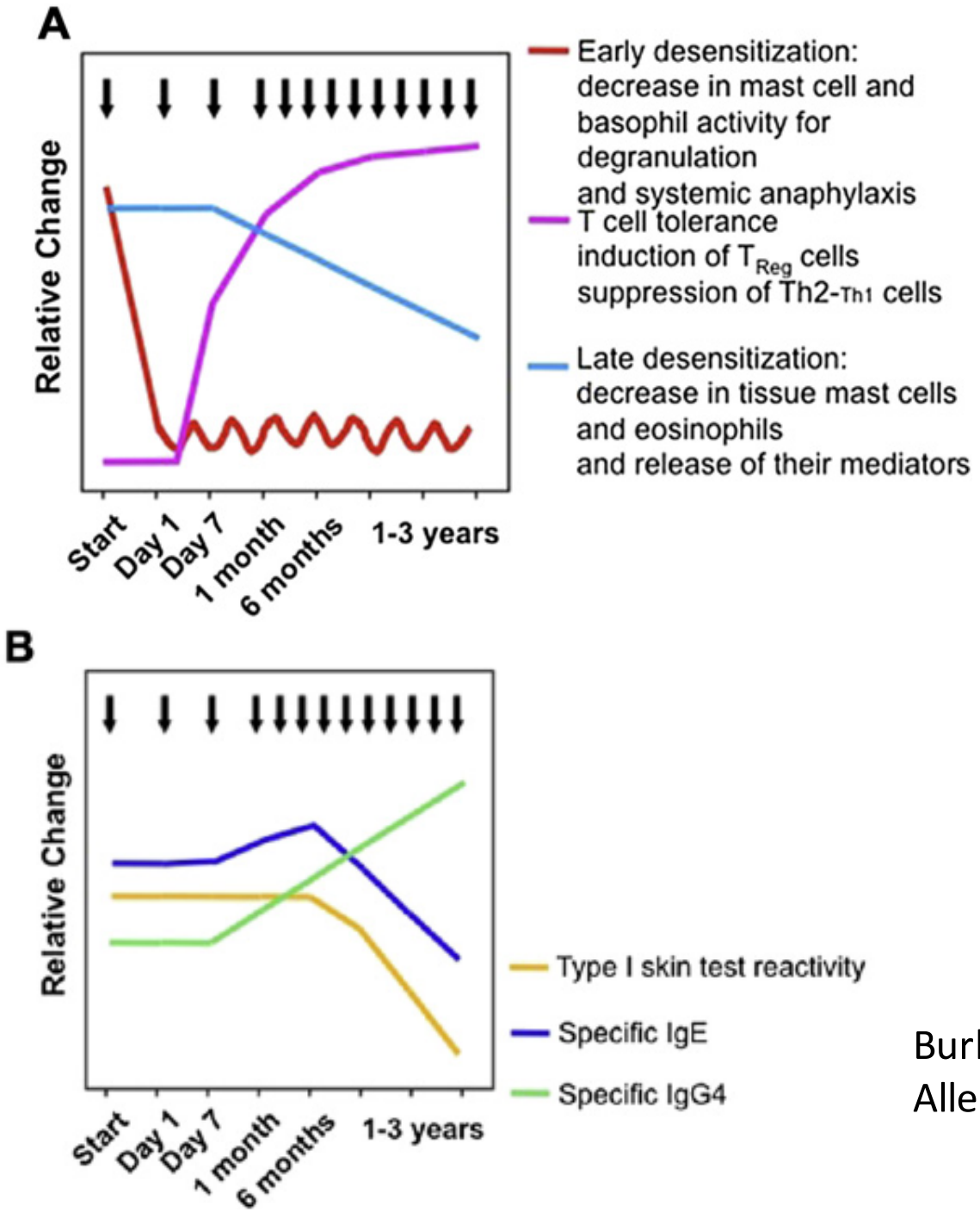
Reduktion allergischer Symptome

Calderon et al. JACI 2011;127:30-8
Radulovic et al. Allergy 2011;66:740-52

Asthma prevention

Douglas et al. Pediatrics 1968; 42: 793
Jacobsen et al. Allergy 2007;62:943-8
Möller et al. JACI 2002; 109: 251-256
Schmitt J et al. JACI 2015;136:1511-6

Mechanisms of SIT



Burks et al. J
Allergy Clin Immunol 2013;131:1288-96.

Definitions

Allergy: immune reaction to a non replicating (harmles) substance (protein, chemical, drug, metal), which leads to clinical symptoms like.

Atopy: genetic determined readiness to react by IgE formation to substances taken up via aerogen or gastro-intestinal routes

Sensitization: immune reaction to a foreign substance (proven in skin tests, serology, cellular tests...)

Summary

Immune **tolerance** normally ensure that immune effector cells are not activated against host tissues or innocuous agents

Allergic inflammation is characterized by **IgE-dependent** activation of **mucosal mast cells** and an infiltration of eosinophils

Production of IgE antibody is regulated mainly by **Th2 cells**. Activated **Th2 cells trigger IgE** production in B cells through a combination of signals, including secreted cytokine **(IL-4, IL-13, IL-5)**

The fundamental strategy of **immunotherapy** for allergic diseases is to correct dysregulated immune responses by inducing peripheral allergen tolerance