Allergology 2018

Wednesday 16.00-17.30

Timea Berki
Department of Immunology and Biotechnology

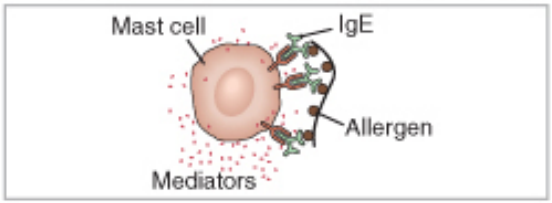
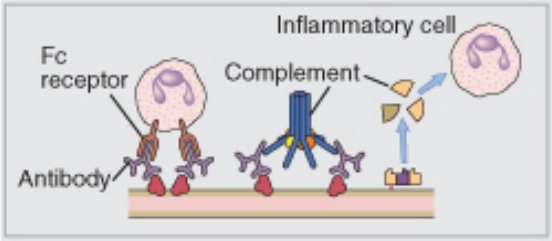
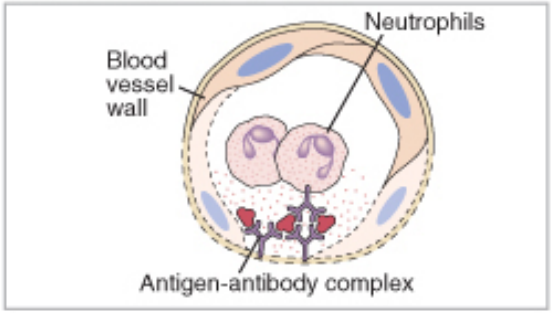
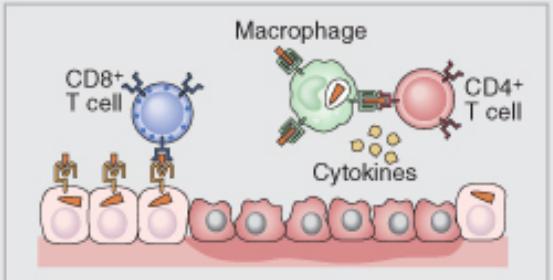
Allergology 2018 Wednesday 16.00-17.30

Timetable

Lecture No.	Date	Thematic	Lecturer
1-2	07. February.	Types and mechanisms of allergies	Berki Tímea
3-4	14. February	Immunology of the Musosa and Skin (MALT, SALT) Diagnostics of allergies	Berki Tímea
5-6	21. February	Upper airway allergies, Rhinitis	Piski Zalán
7-8	28. February	Allergic skin reactions	Gyulai Rolland
9-10	7. March	Lower airway allergies, Asthma	Mosdósi Bernadett
11	14. March	Drug allergies	Kinyó Ágnes
12	14 March	Therapeutic targets in allergies	Pintér Erika
13-14	21 March	Food allergies Test	Sütő Gábor

Hypersensitivity - intolerance

- is a set of undesirable reactions produced by the normal immune system, including allergies and autoimmunity.
- They are usually referred to as an over- reaction of the immune system and these reactions may be damaging, uncomfortable, or occasionally fatal.
- Hypersensitivity reactions require a pre-sensitized (immune) state of the host.
- They are classified in four groups after the proposal of P. G. H. Gell and Robin Coombs in 1963

Type of hypersensitivity	Pathologic immune mechanisms	Mechanisms of tissue injury and disease
Immediate hypersensitivity (Type I)	T_H2 cells, IgE antibody, mast cells, eosinophils 	Mast cell–derived mediators (vasoactive amines, lipid mediators, cytokines) Cytokine-mediated inflammation (eosinophils, neutrophils)
Antibody-mediated diseases (Type II)	IgM, IgG antibodies against cell surface or extracellular matrix antigens 	Complement- and Fc receptor–mediated recruitment and activation of leukocytes (neutrophils, macrophages) Opsonization and phagocytosis of cells Abnormalities in cellular function, e.g., hormone receptor signaling
Immune complex–mediated diseases (Type III)	Immune complexes of circulating antigens and IgM or IgG antibodies deposited in vascular basement membrane 	Complement and Fc receptor-mediated recruitment and activation of leukocytes
T cell–mediated diseases (Type IV)	1. $CD4^+$ T cells (delayed-type hypersensitivity) 2. $CD8^+$ CTLs (T cell–mediated cytolysis) 	1. Macrophage activation, cytokine-mediated inflammation 2. Direct target cell lysis, cytokine-mediated inflammation

IgE:

Atopy

Anaphylaxis

Urticaria

Asthma

IgG:

AIHA

Erythroblastosis

Organ specific autoimmune diaseases

IgG:

Serum sickness

SLE, RA,

Post-Streptococcal glomerulonephritis

T sejt

Contact dermatitis

Multiple sclerosis

Coeliakie

Hypersensitive reactions - Allergies

- **Type I hypersensitivity** is an allergic reaction provoked by re-exposure to a specific type of antigen referred to as an allergen
- IgE mediated -Th2 dependent
- Atopy – hereditary predisposition → Genetic background
- Allergen – abnormal response against common environmental antigens
- Immediate vascular reaction and a late inflammatory response
- Mediated by mucosal and connective tissue mast cells
- If the entire body is involved, then anaphylaxis can take place, which is an acute, systemic reaction that can prove fatal

- **Type IV.hypersensitivity** is a late phase cell mediated immune reaction → delayed type
- The reaction takes two to three days to develop
- An inflammatory response driven by T cell recognition of processed soluble or cell-associated antigens leading to cytokine release and leukocyte activation.
- Contact allergy
- Antigen- bacterial, or small Hapten molecule
- Cell mediated: Th1 cells and macrophages → cytokine
- Mostly skin reaction

Allergic diseases

Type I. Immediate

- Allergic asthma
- Allergic conjunctivitis
- Allergic rhinitis ("hay fever")
- Anaphylaxis
- Angioedema
- Urticaria (hives)
- Eosinophilia
- Penicillin allergy
- Cephalosporin allergy
- Food allergy
- Sweet itch

Type IV reactions

- Allergic contact dermatitis

Overview of mediators released by mast cells in type I hypersensitivity, and their actions:

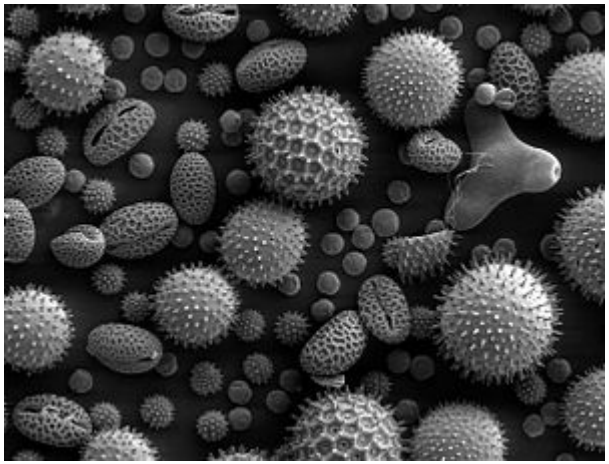
Vasodilation and increased permeability	•Histamine •PAF •Leukotriene C4, D4, and E4 •Prostaglandin D2 •Neutral proteases	
Smooth muscle spasm	•Histamine •PAF •Leukotriene C4, D4, and E4 •Prostaglandin	
Leukocyte extravasation	•Cytokines (e.g. chemokines and TNF) •Leukotriene B4 •Chemotactic factors for neutrophils and eosinophils	
Unless otherwise specified, the reference for this table is:[4]		

Type IV. reactions

allergic contact dermatitis[1]	environmental chemicals (e.g., urushiol from poison ivy oak, nickel)	epidermal necrosis, inflammation, skin rash and blisters
autoimmune myocarditis[1]	myosin heavy chain protein	cardiomyopathy
diabetes mellitus type 1[1]	pancreatic beta cell proteins (possibly insulin, glutamate decarboxylase)	Insulitis, beta cell destruction
granulomas[2]	various, depending on underlying disease	walled off lesion containing macrophages and other cells
some peripheral neuropathies	Schwann cell antigen	neuritis, paralysis
Hashimoto's thyroiditis[1]	thyroglobulin antigen	hypothyroidism, hard goiter, follicular thymitis
inflammatory bowel disease[1]	enteric microbiota and/or self antigens	hyperactivation of T-cells, cytokine release, recruitment of macrophages and other immune cells, inflammation
multiple sclerosis[1]	myelin antigens (e.g., myelin basic protein)	myelin destruction, inflammation
rheumatoid arthritis[1]	possibly collagen and/or citrullinated self proteins	chronic arthritis, inflammation, destruction of articular cartilage and bone
tuberculin reaction (Mantoux test)[3]		

Components of type I allergy

- IgE-dependent
- High-affinity FcεReceptor-dependent
- Mast cells are the primary effector cells
- Allergens



SEM of miscellaneous plant pollens: Pollens are very common allergens.

Differences from the normal immune responses

- The high affinity FcεR is continuously covered by antigen-specific IgE – is sensitized – even in the absence of antigen.
- This is a long-term binding - ~ 2 weeks
- Multivalent allergen will crosslink a few-hundred FceReceptors → immediate signal in Mast cells
- Local reaction: Plasma cells produce IgE in the peripheral tissues
- FcεRs are expressed on Mast cells, basophils, eosinophils and effector cells and APCs

Allergen sources

- **Inhalative allergens**: dust mite excretion, pollen, pet dander or even royal jelly.
- **Food allergens** are not as common as food sensitivity, but some foods such as peanuts (a legume), nuts, seafood and shellfish are the cause of serious allergies in many people.
- Food and Drug Administration (FDA in US) listed eight foods as being common for allergic reactions in a large segment of the sensitive population: peanuts, tree nuts, eggs, milk, shellfish, fish, wheat and their derivatives, and soy and their derivatives, as well as sulfites (chemical based, often found in flavors and colors in foods) at 10ppm and over.
- **Contact allergens**: urushiol, a resin produced by poison ivy and poison oak, which causes the skin rash condition known as urushiol-induced contact dermatitis by changing a skin cell's configuration so that it is no longer recognized by the immune system as part of the body. Various trees and wood products such as paper, cardboard, MDF etc. can also cause mild to severe allergy symptoms through touch or inhalation of sawdust such as asthma and skin rash.[5]

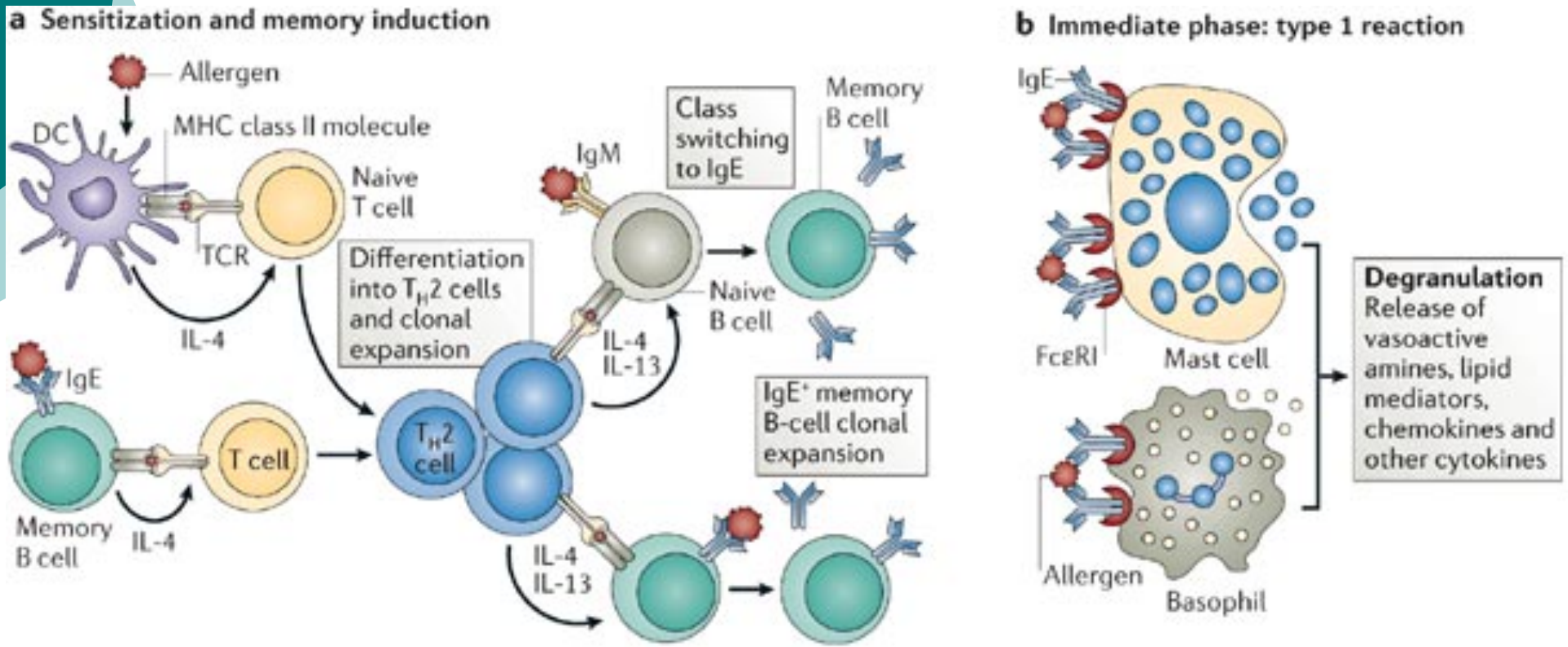
Contact mechanisms with the allergens

- An allergic reaction can be caused by any form of **direct contact** with the allergen:
- **Consuming food** or drink one is sensitive to (ingestion),
- **Breathing in** pollen, perfume or pet dander (inhalation),
- **Direct contact:** brushing a body part against an allergy-causing plant or latex.
- **Systemic exposure**: Other common causes of serious allergy are wasp, fire ant and bee stings, penicillin
- An extremely serious form of an allergic reaction is called anaphylaxis. One form of treatment is the administration of sterile epinephrine to the person experiencing anaphylaxis, which suppresses the body's overreaction to the allergen, and allows for the patient to be transported to a medical facility.

Characteristics of allergens

- Proteins or chemicals (hapten) bound proteins which we meet regularly or chronically
- They are low molecular weight, glycosylated proteins with good solubility in body fuids
- They might have enzyme activity
- Small hapten molecules (e.g. Penicillin) bound to self-proteins (pl. penicillin)
- They induce T-cell dependent immune response
- These antigens do not stimulate the innate immune response, do not cause macrophage activation → there is no inflmmatory reactions → Th2 pathway induction

Stages of IgE mediated allergic reactions



Events in Immediate Hypersensitivity

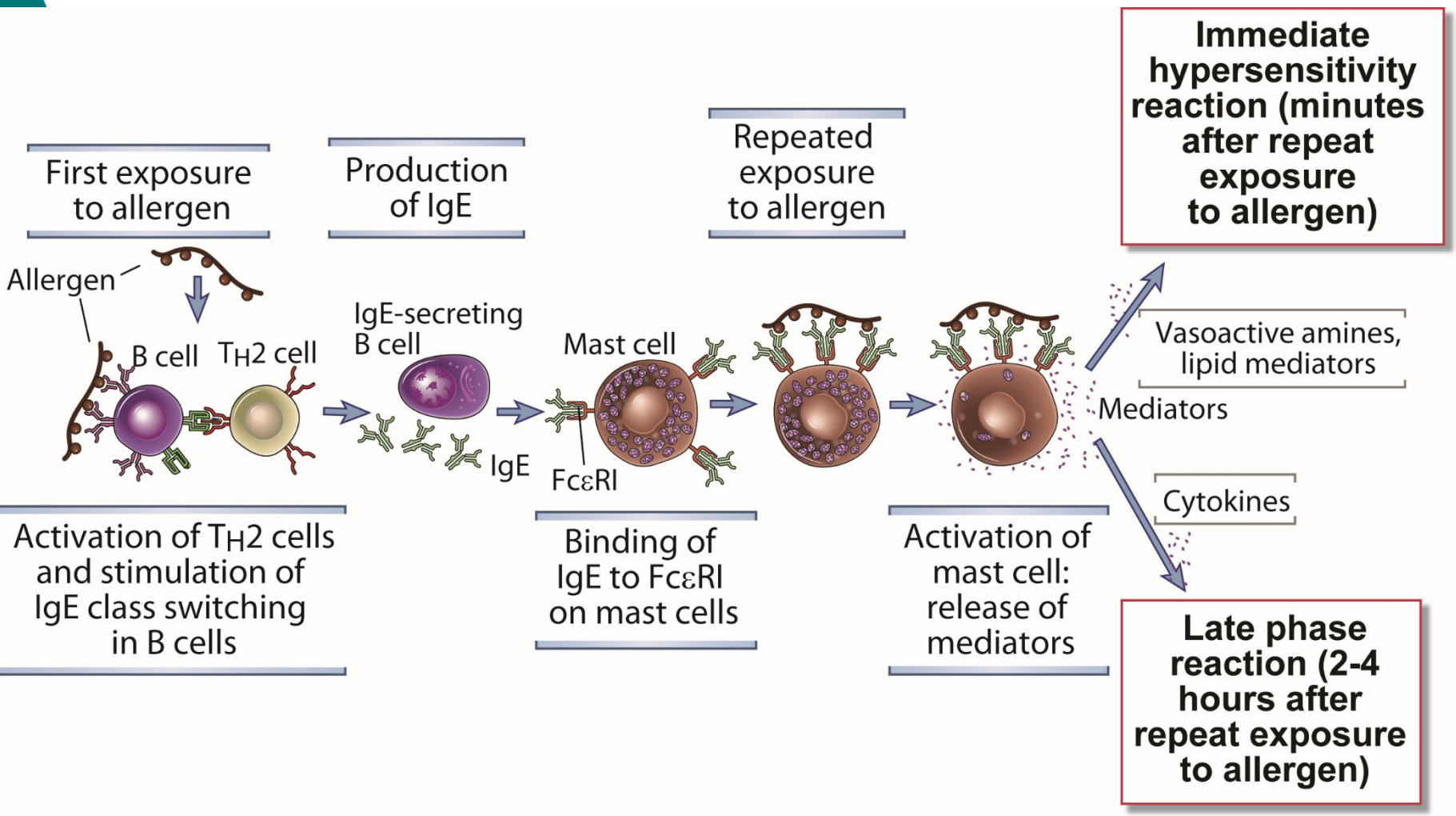
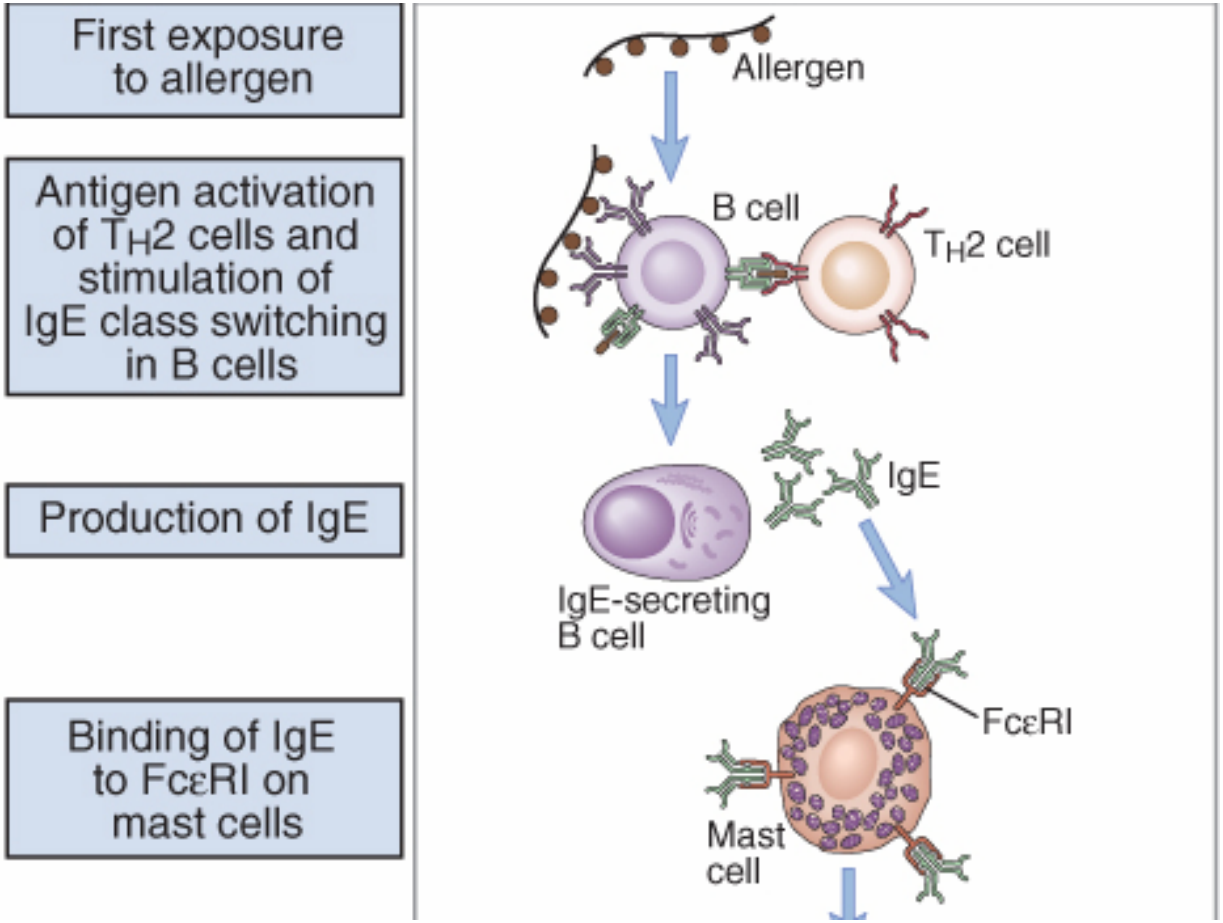
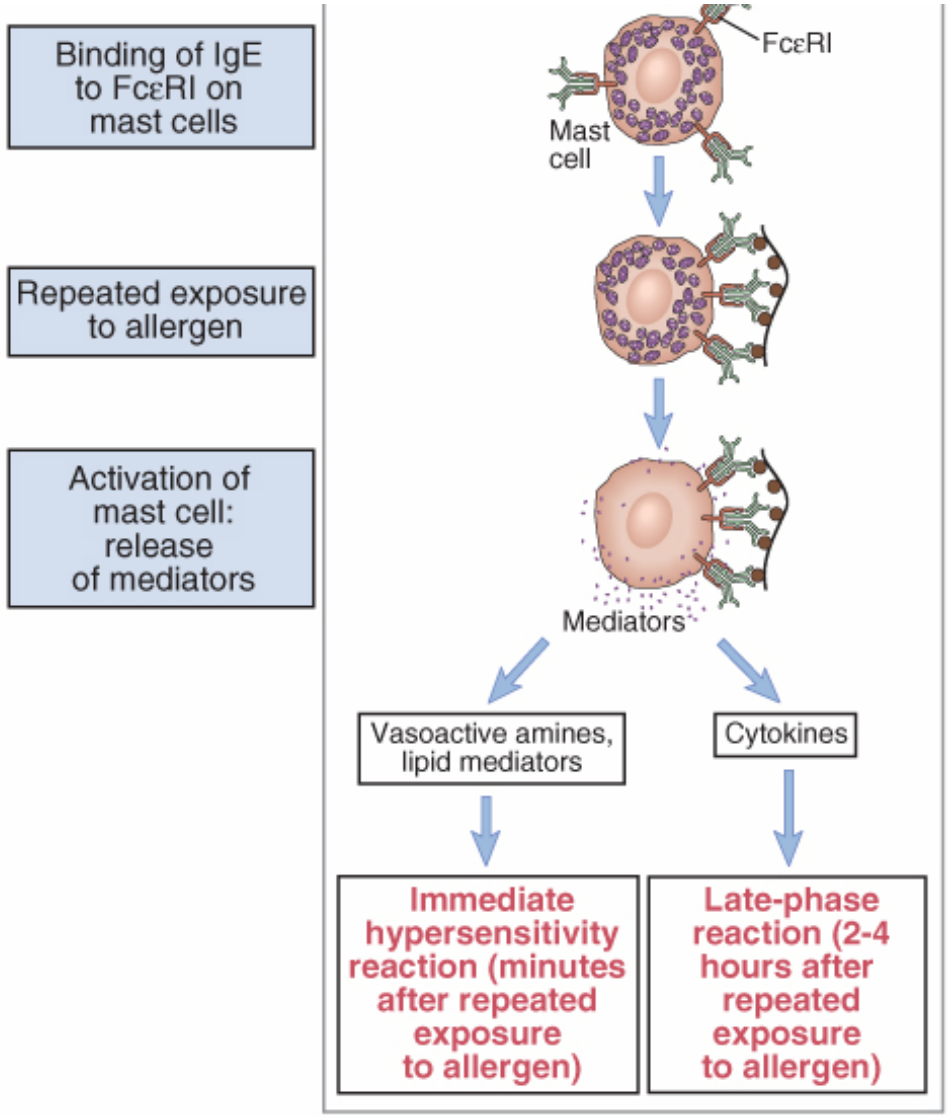


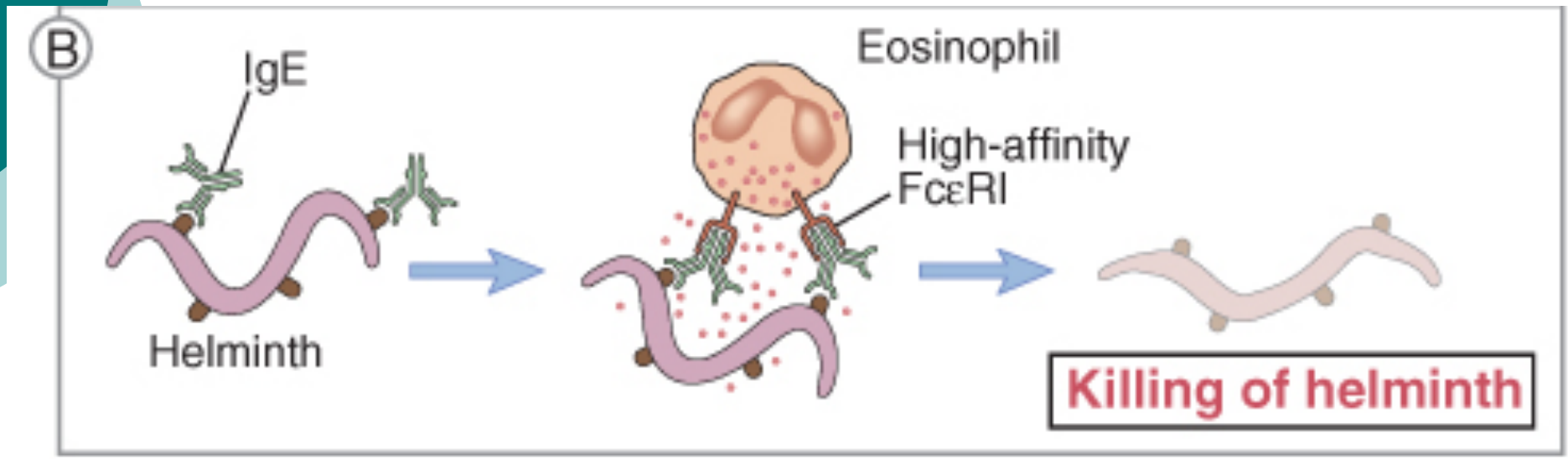
Fig. 19-1

Sensitization = primary immune response



Effector phase




B
IgE
Helminth
Eosinophil
High-affinity
FcεRI
Killing of helminth

IgE isotype switch

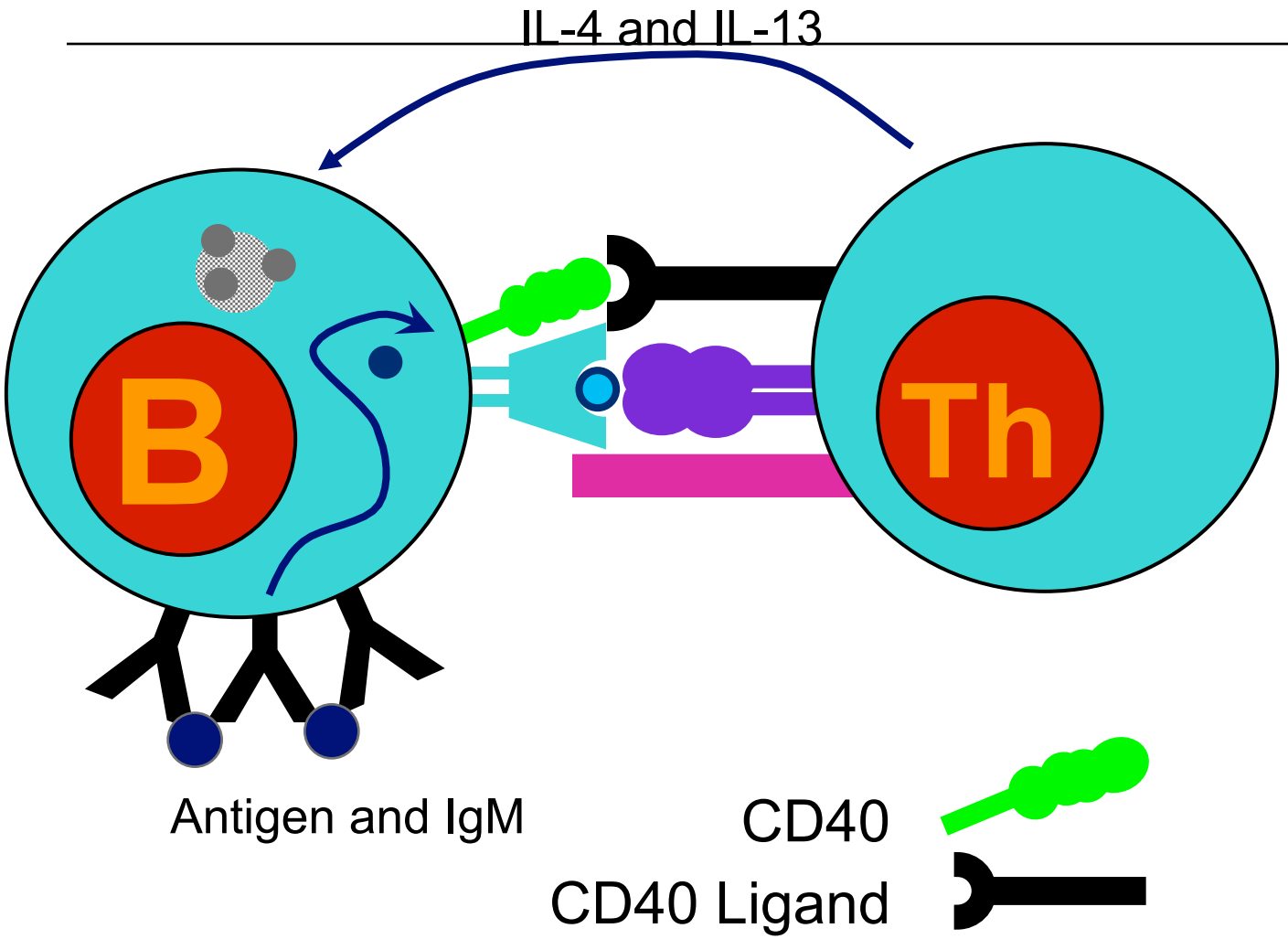
Switch recombination

3 signals:

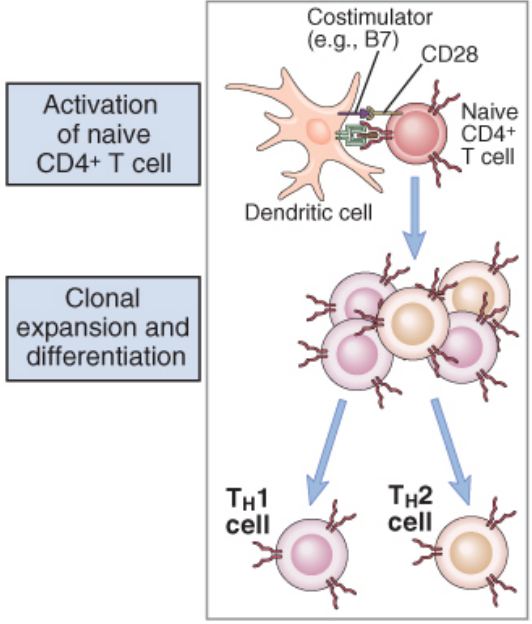
1. Antigen
2. Th2 cytokines: IL-4, IL-13
3. CD40L costimulation by Th2 cells

Convergence by Ig epsilon gene regions (I)

1. Antigen uptake and presentation by B cells

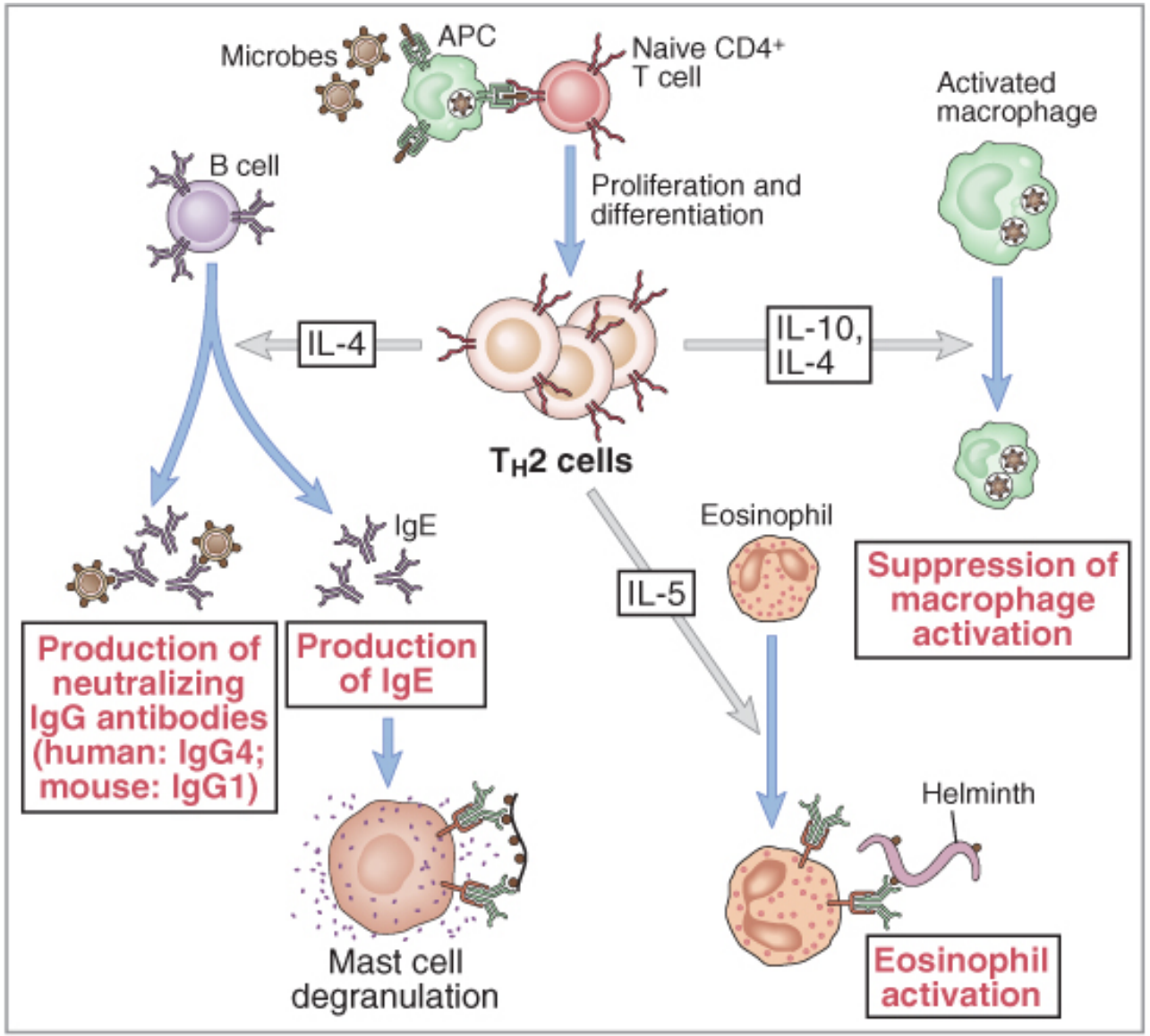


Th1 - Th2 subtypes



Property	T_H1 subset	T_H2 subset
Cytokines produced		
IFN-γ	+++	–
IL-4, IL-5, IL-13	–	+++
IL-10	+/–	++
IL-3, GM-CSF	++	++
Cytokine receptor expression		
IL-12R β chain	++	–
IL-18R	++	–
Chemokine receptor expression		
CCR4	+/–	++
CXCR3, CCR5	++	+/–
Ligands for E- and P-selectin	++	+/–
Antibody isotypes stimulated	IgG2a (mouse)	IgE, IgG1 (mouse)/IgG4 (humans)
Macrophage activation	+++	–

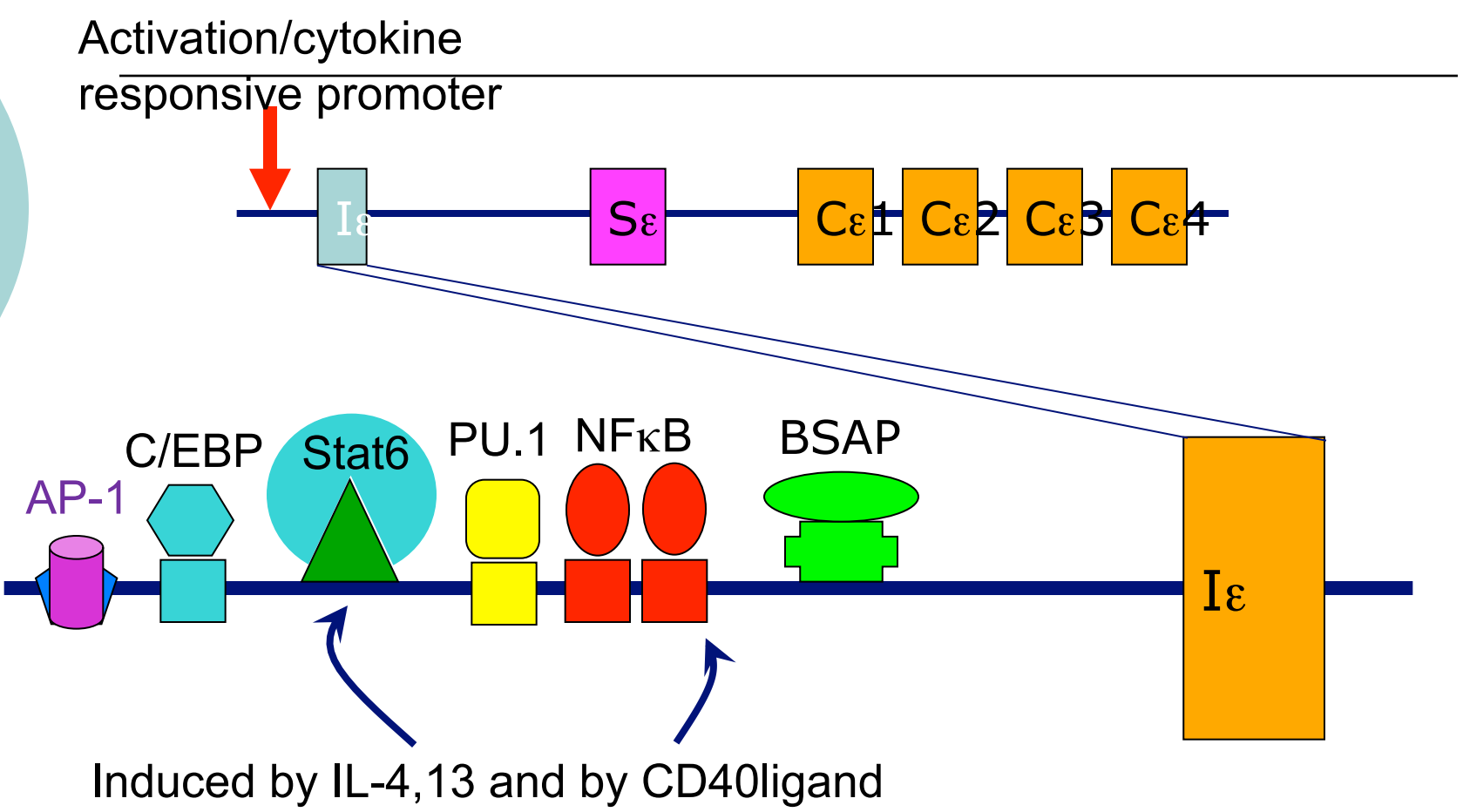
Th2 cytokines stimulate humoral immune response



Role of cytokines in regulating Ig isotype expression

Cytokines	IgM	IgG3	IgG1	IgG2b	IgG2a	IgE	IgA
IL-4	Inhibits	Inhibits	Induces		Inhibits	Induces	
IL-5							Augments production
IFN-γ	Inhibits	Induces	Inhibits		Induces	Inhibits	
TGF-β	Inhibits	Inhibits		Induces			Induces

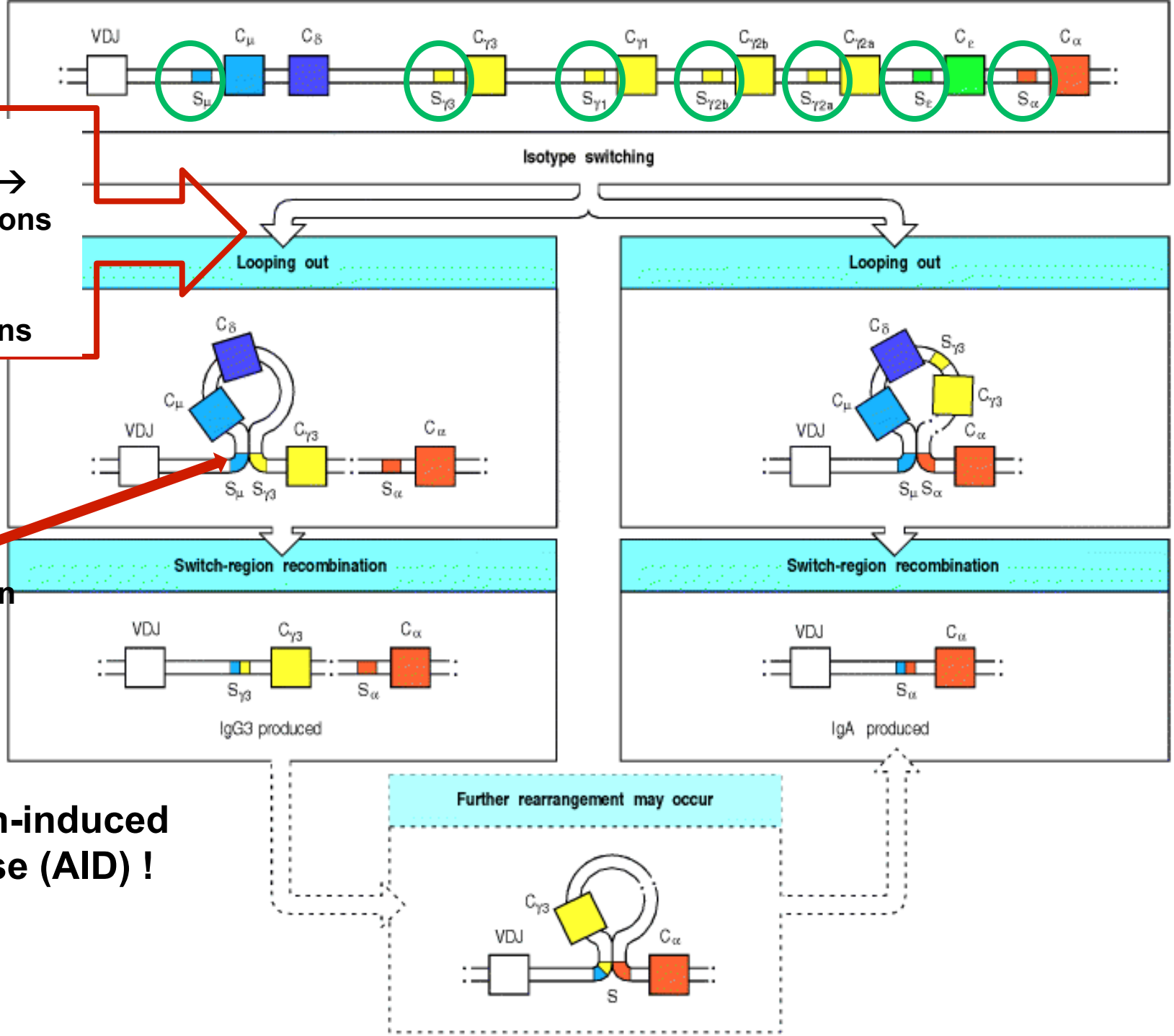
Place of convergence: Iε promoter



BSAP – B cell specific activator protein. C/EBP CCAAT/enhancer binding protein.
PU.1 – Spi1 equivalent in humans, ets transcription factor

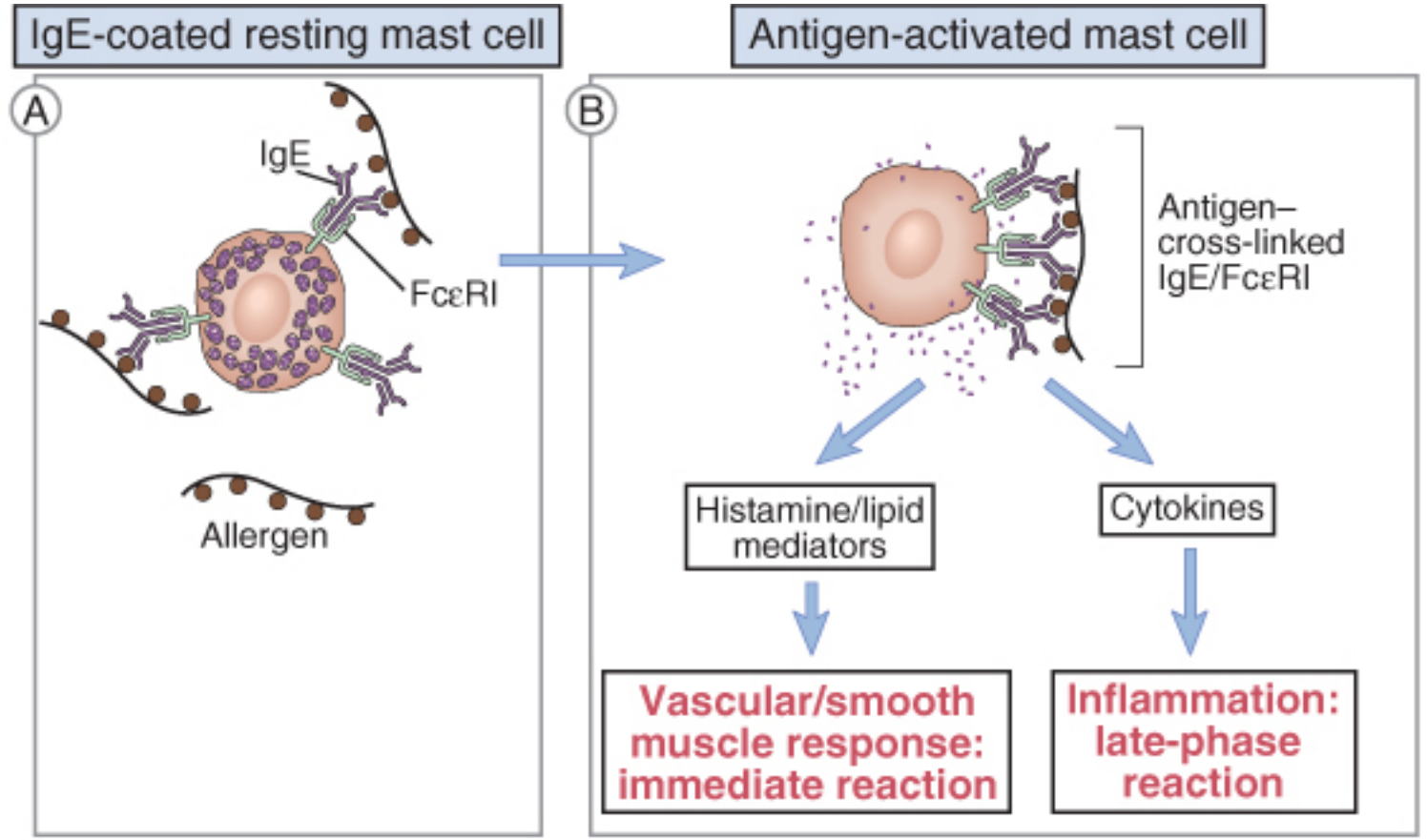
T helper cytokines → transcriptions factors → binding to DNA regions

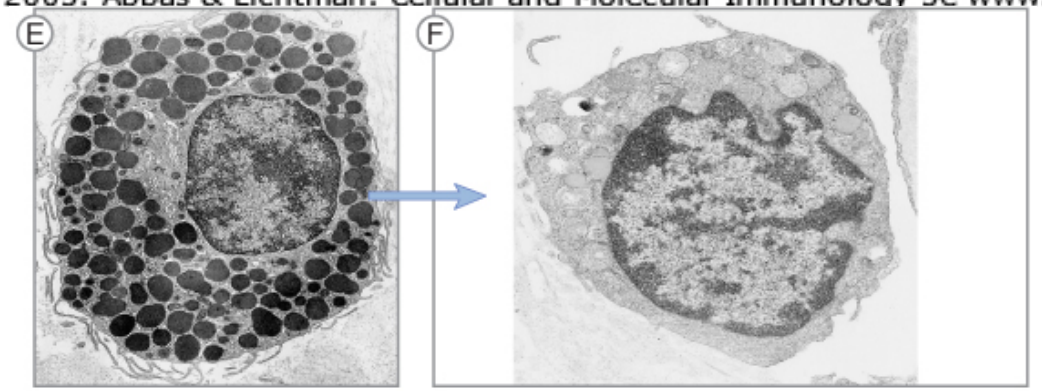
S-region recombination



activation-induced deaminase (AID) !

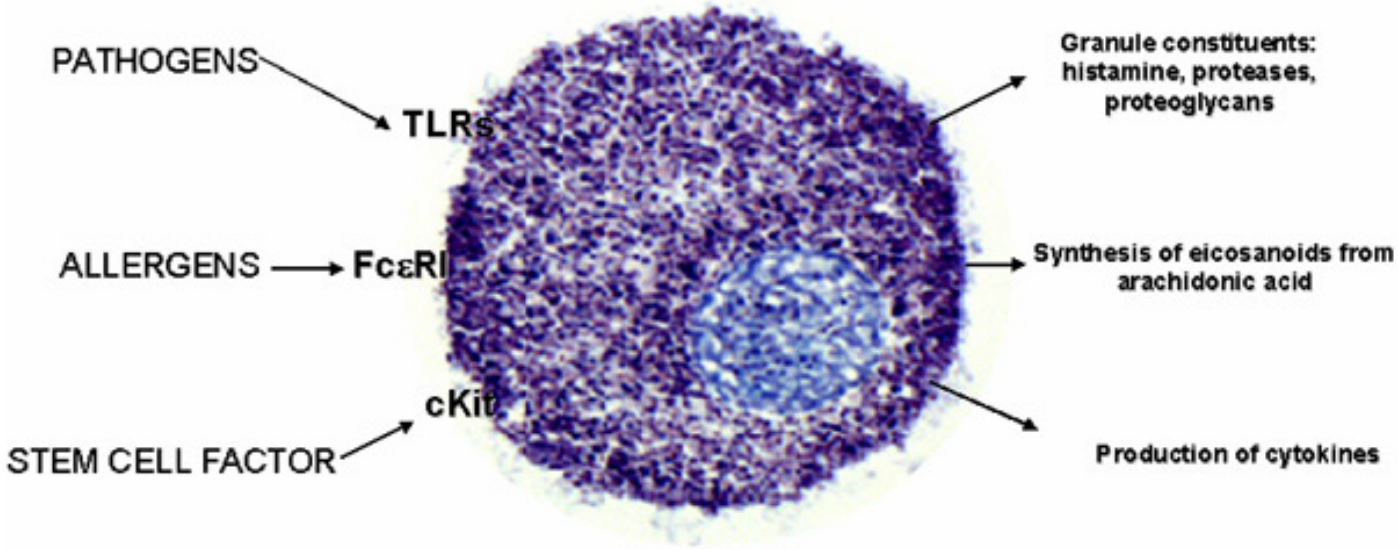
ROLE OF MAST CELLS





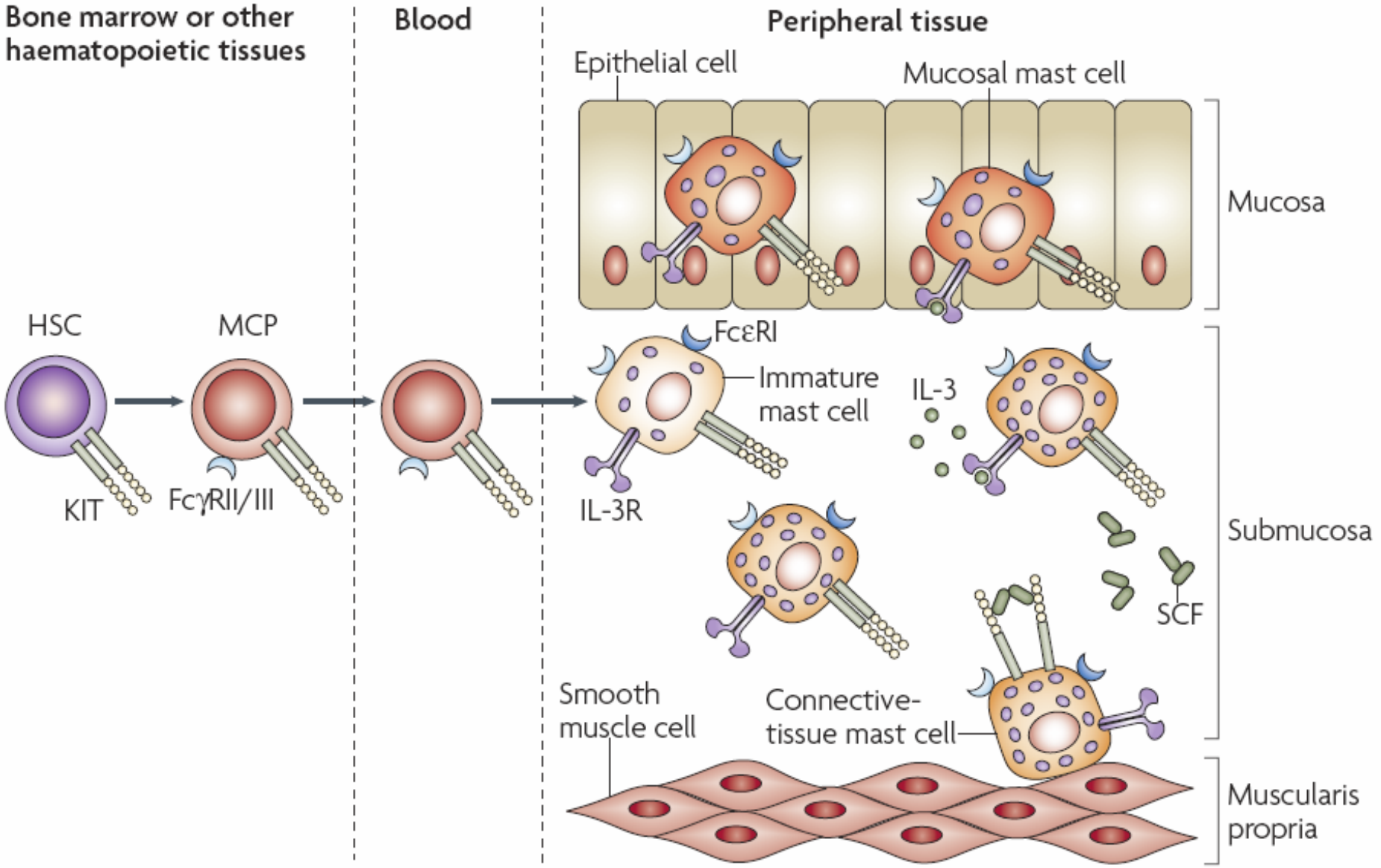
Mast cell activation mechanisms

TLR4 – LPS →IL-1β, TNF-α, IL-6 and IL-13, without mast cell degranulation
TLR2 – peptidoglycan → mast cell degranulation and production of IL-4 and IL-5, IL-6, IL-13
TLR3,7,9 – Poly (I:C), CpG oligonucleotid → release of pro-infalmmatory cyítokines and chemokines



they express several hundred thousand high affinity receptors for IgE (FcεR1) and thus respond to IgE-directed antigens

express the pathogen-recognizing Toll-like receptors (TLRs) which probably account for the ability of mast cells to mount an effective innate immune response


Bone marrow or other haematopoietic tissues
Blood
Peripheral tissue
Epithelial cell
Mucosal mast cell
Mucosa
HSC
MCP
KIT
FcγRII/III
FcεRI
Immature mast cell
IL-3R
IL-3
SCF
Submucosa
Smooth muscle cell
Connective-tissue mast cell
Muscularis propria
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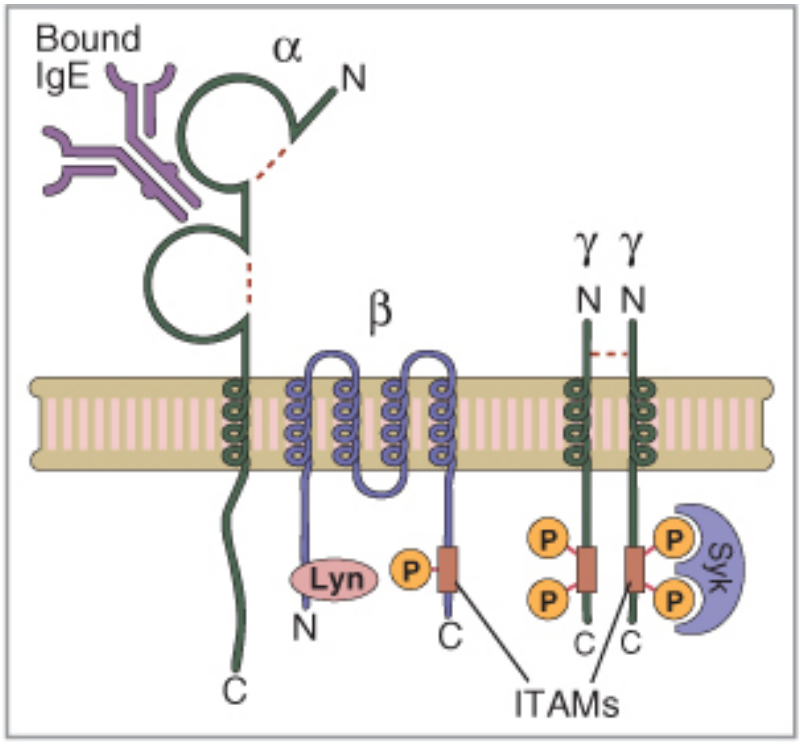
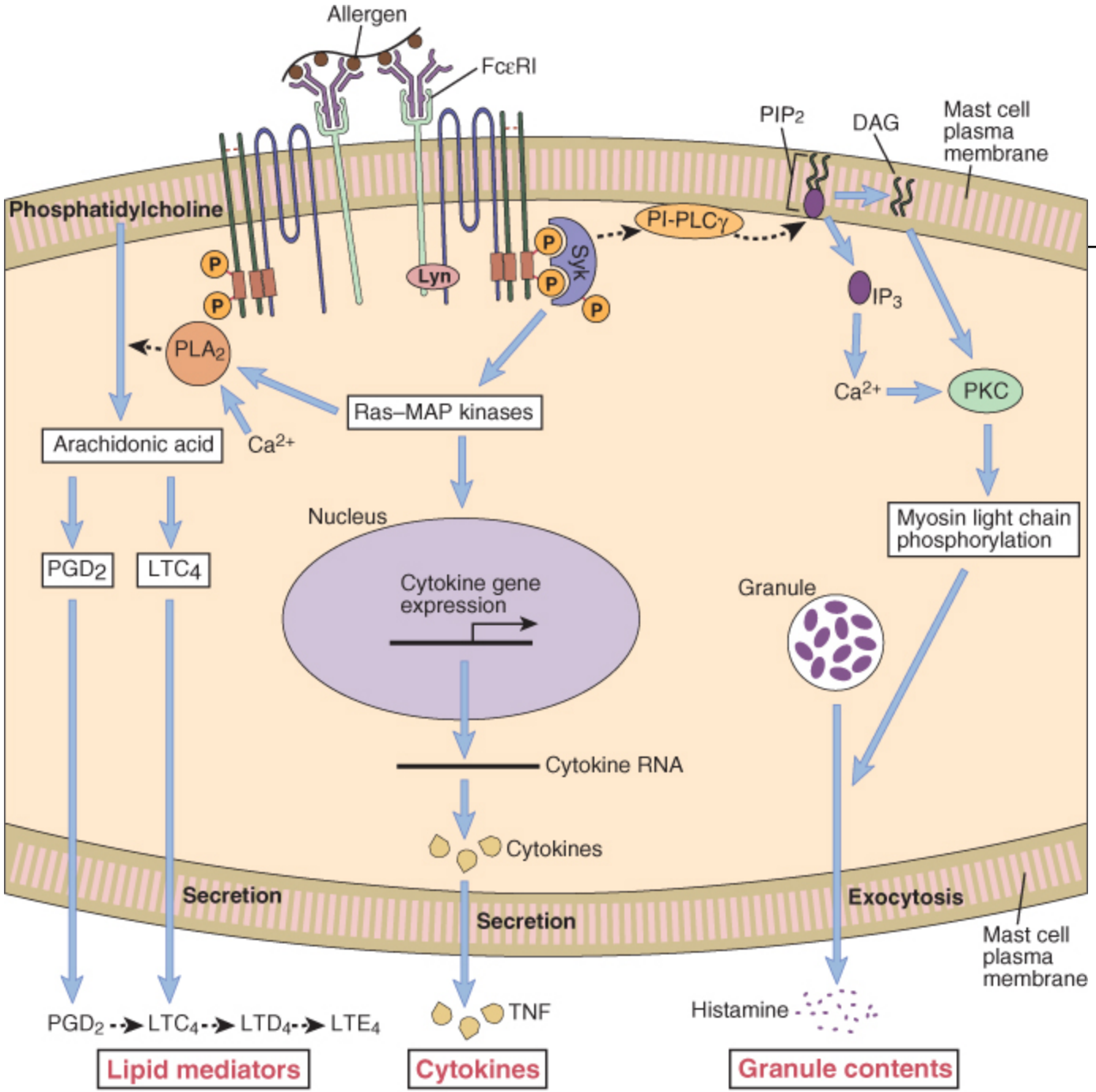
Other mast cell activators

- MIP-1α – macrophage inflammatory chemokine
- C3a, C5a anaphylatoxin –complement
- Neuropeptides – P-substance, somatostatin, VIP
- FcγR - IgG

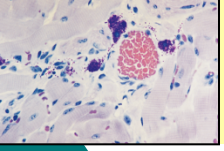
Structure of the high-affinity FcεR (IgE) receptor



Mast cells, basophils, eo., Langerhans cells, macrophages



Biochemical Events of Mast Cell Activation (1)



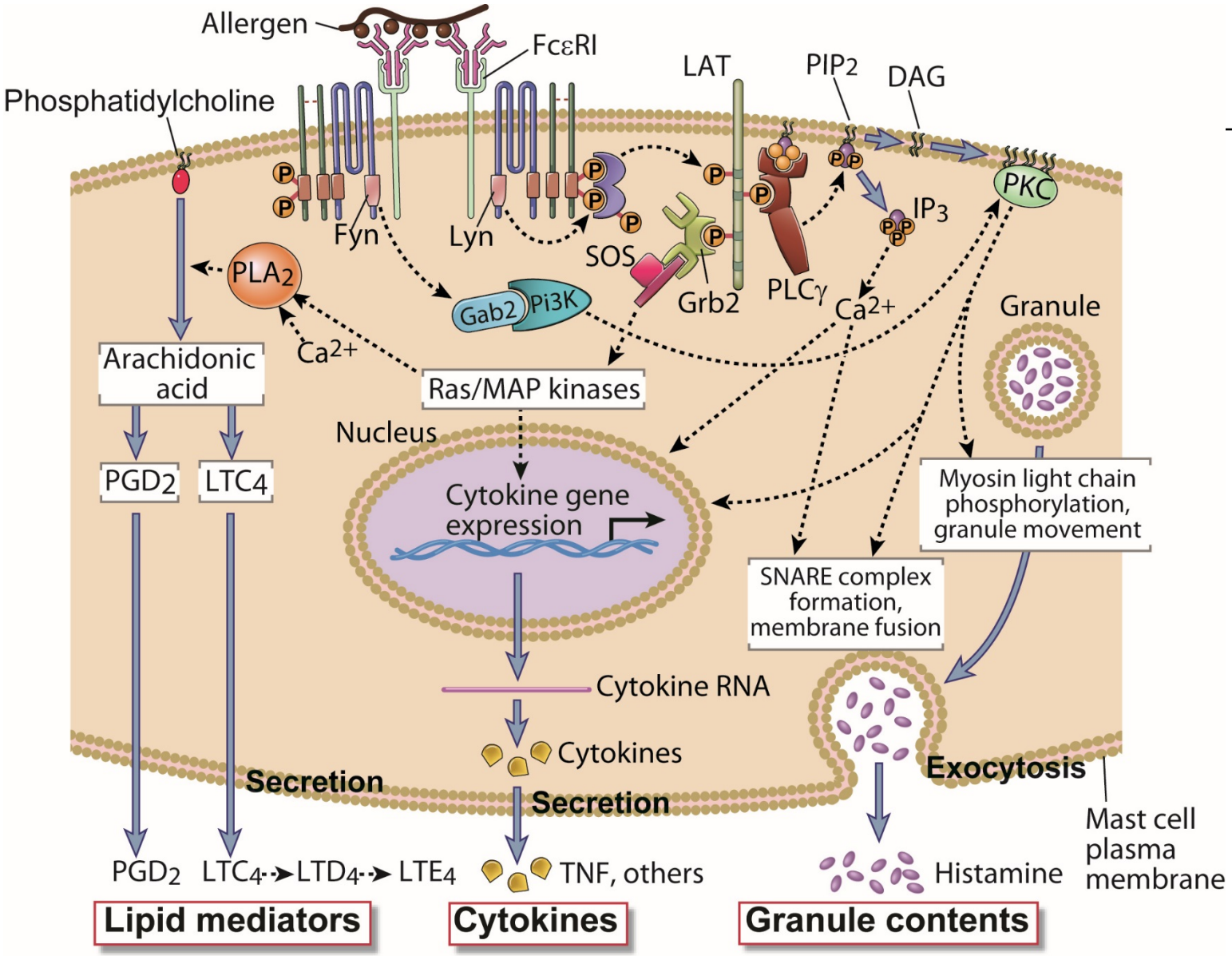


Fig. 1ɔ-ɔ

FcεRI and FcεRII (CD23)

FceRI: - high affinity
- Ig-superfamily

α, β 2γ chains

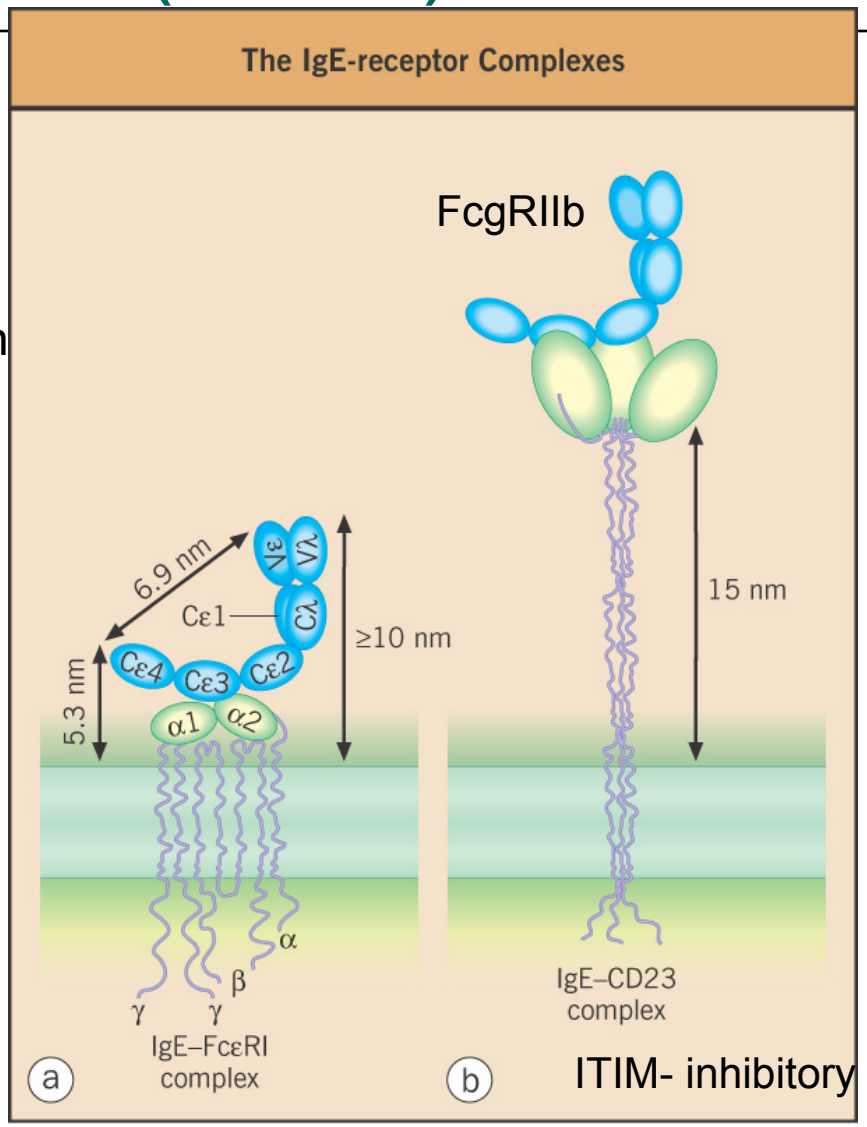
α1 és α2 domain ~80aa.Ig-domain

IgE upregulates its expression

FceRII: - medium affinity
(CD23) - lectin-family
- homotrimer

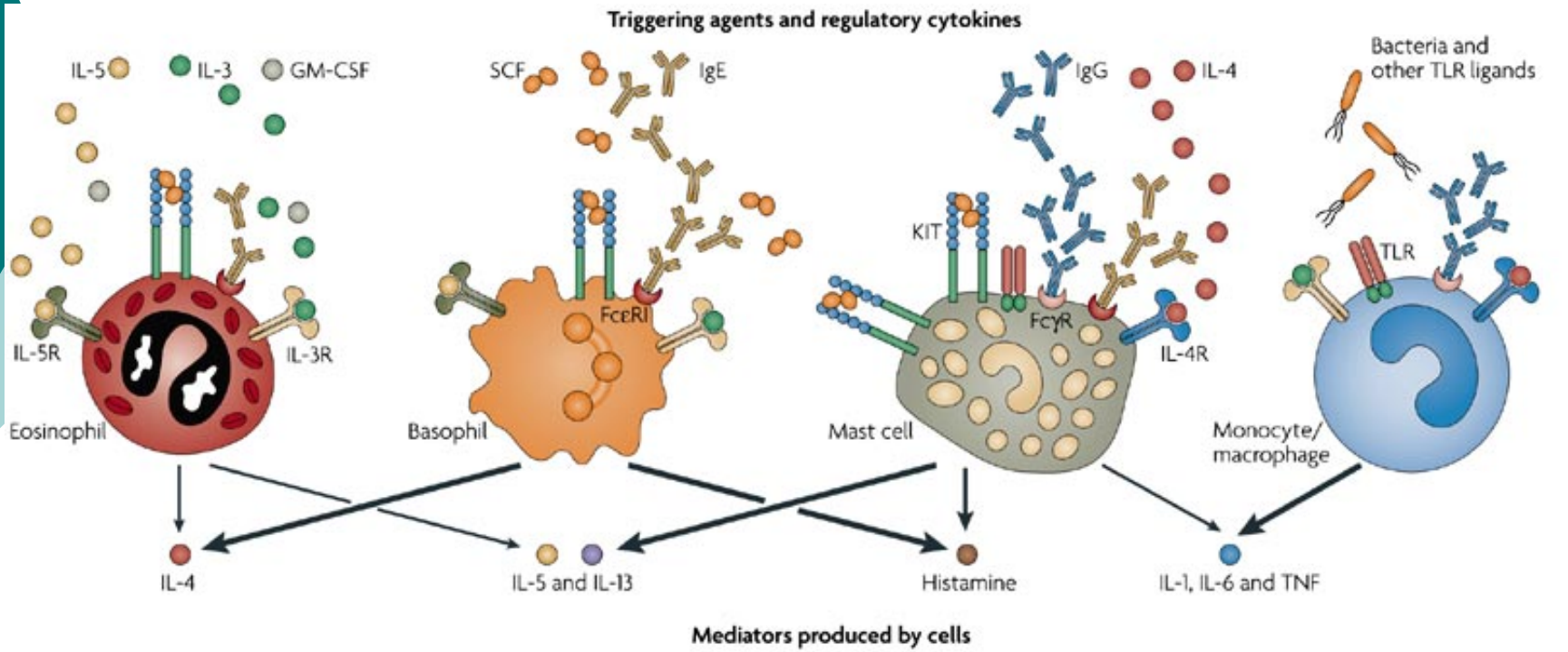
B cells, monocytes, eosinophils
IL-4 induces

Ligand: soluble and mIgE
- complement receptor 2,3,4



ITIM- inhibitory signal

Characteristics	Mas cell	Basophils	Eosinophils
orogin	CD34+ hematopoetic precursor	CD34+ hematopoetic precursor	CD34+ hematopoetic precursor
Mediátorai	Histamin, heparin, chondroitin sulphate, protases	Histamin, chondroitin sulphate, proteases	Major basic protein, eo. Cationic proteins, peroxidase, hydrolase, lysophospholipase
Prolifaretion capacity	Yes	No	No
Life span	Weeks, month	days	Days-weeks
Growth factor	SCF	IL-3	IL-5
FceRI expression	lot	lot	less



Bischoff *Nature Reviews Immunology* **7**, 93–104 (February 2007) | doi:10.1038/nri2018

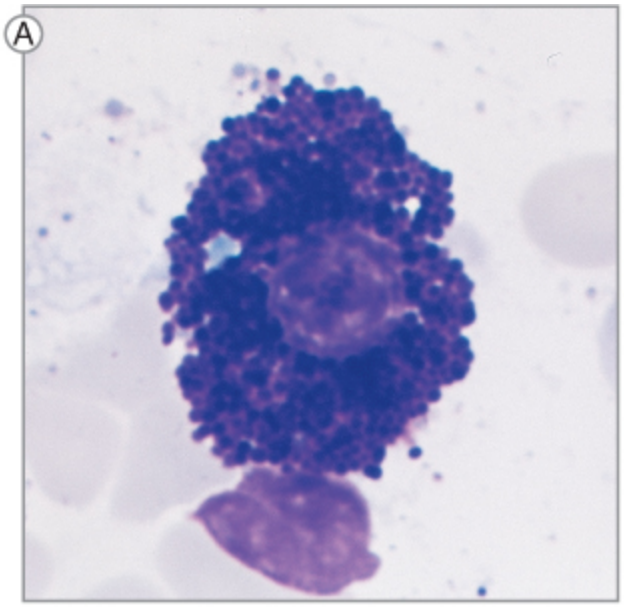
nature REVIEWS IMMUNOLOGY

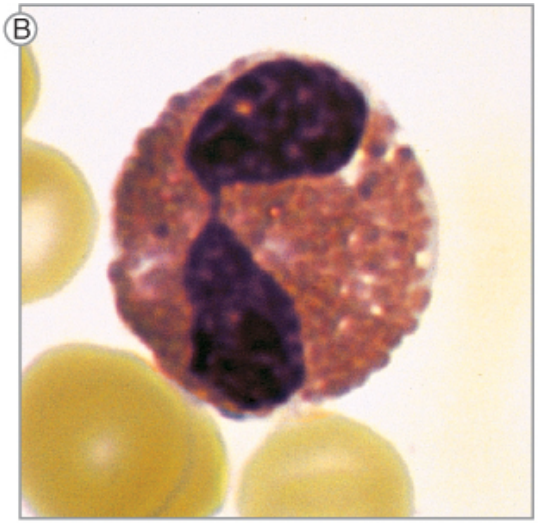
Mast cell mediators

- Biogen amines: histamin, serotonin (H1,2,3,4R) – vasodilation, plasma efflux, SM constriction
- Serin proteases: tryptase, chymase, carboxypeptodaseA, cathepsinG
- Proteoglycans: heparin, chondroitin sulphate – storage matrix
- Lipid mediarors: rapid de novo synthesis

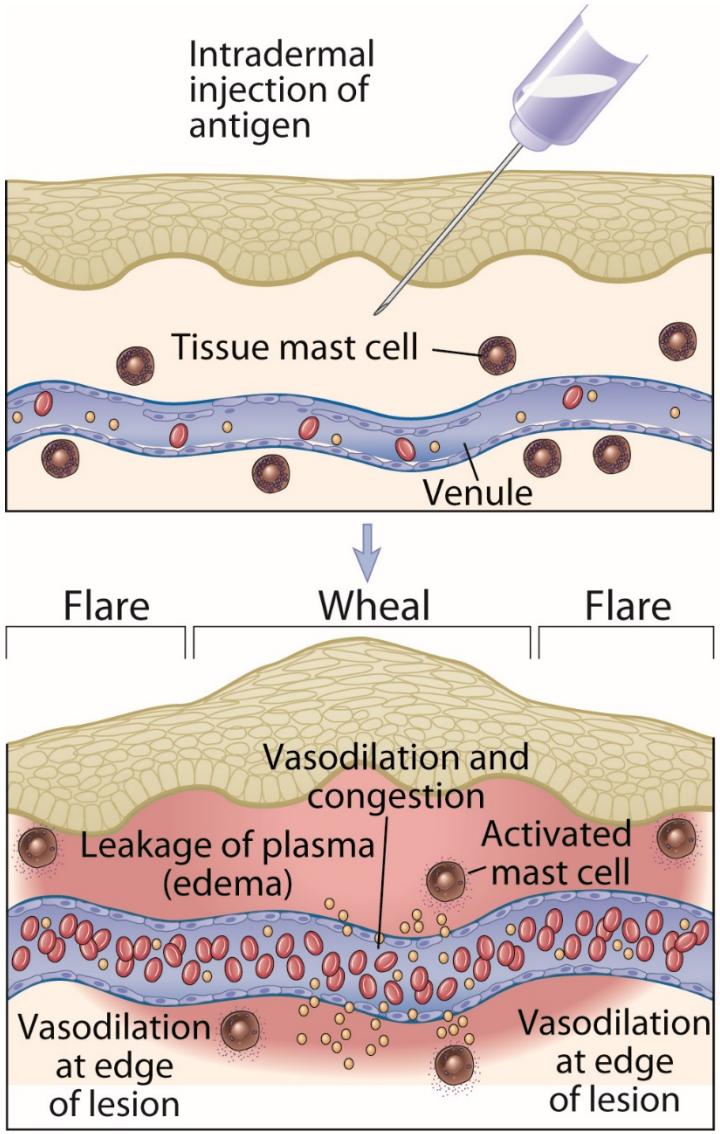
  ProsztaglandinD2, Leuktrien C4,D4,E4, PAF → vasodilation, bronchus contsriction

Cytokines: TNF, IL-1, IL-4, IL-5, IL-6, IL-13, MIP1a, IL-3, GM-CSF





The Wheal and Flare Reaction in the Skin



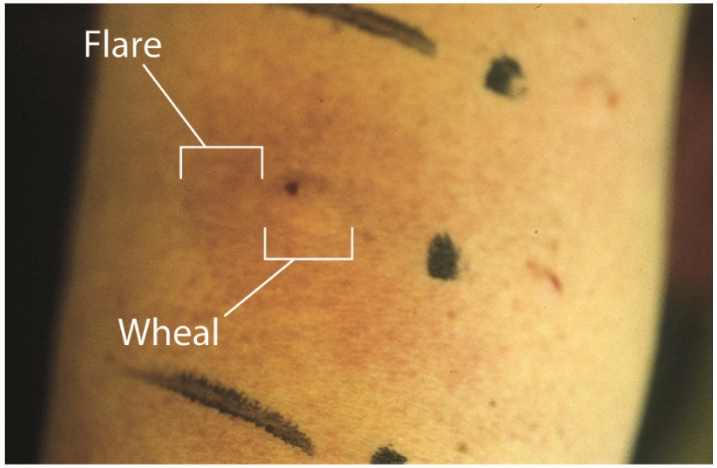
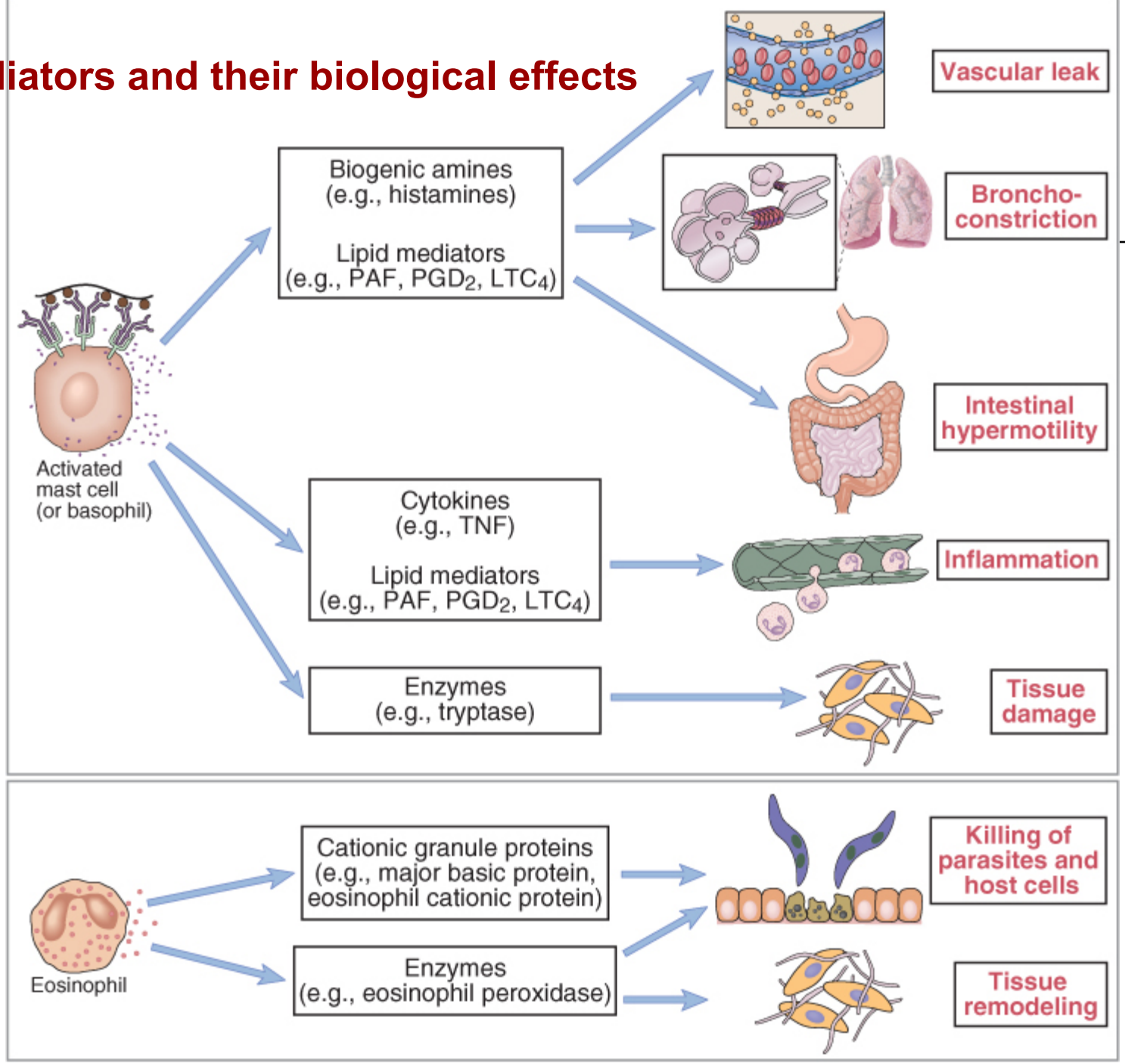
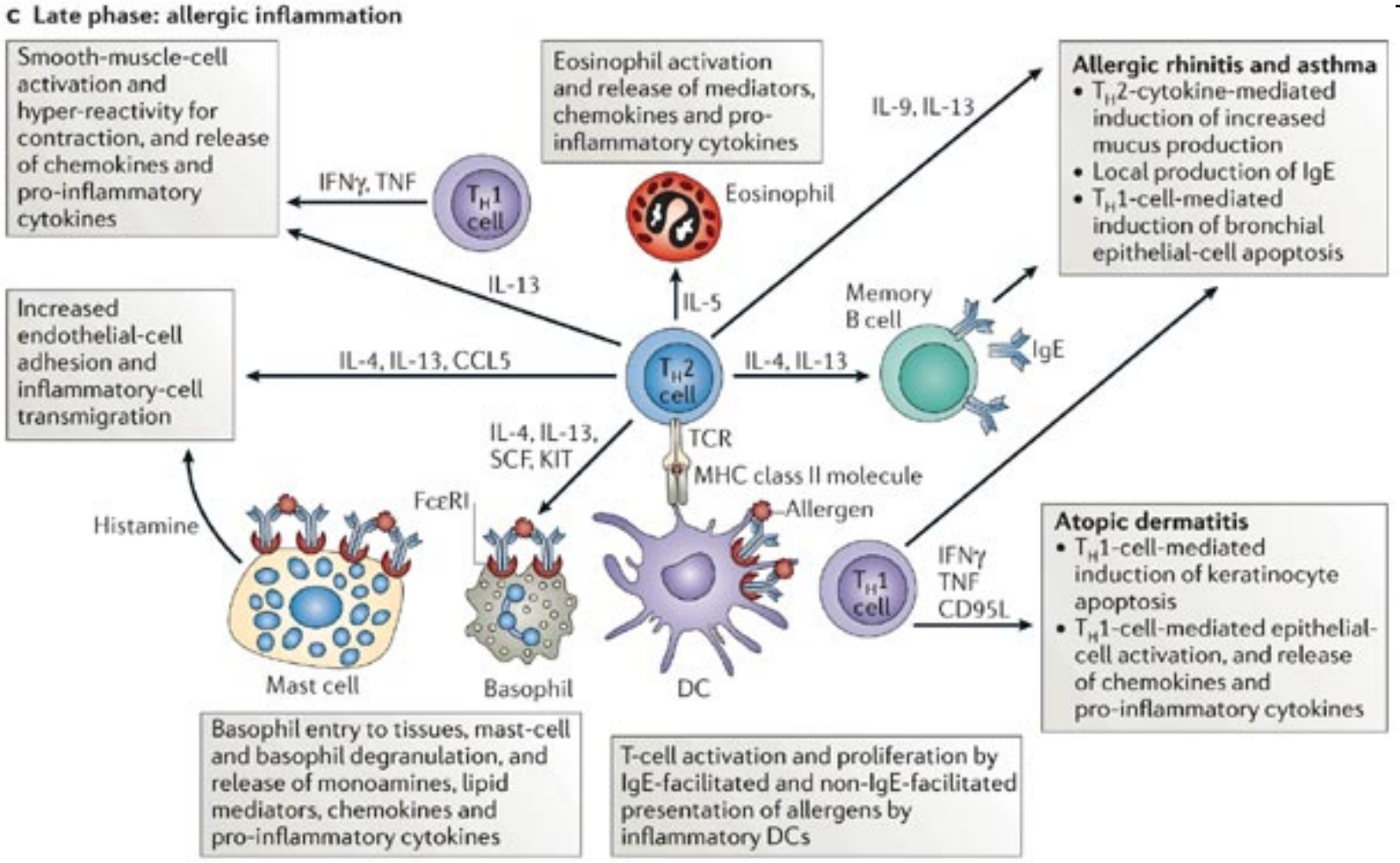


Fig. 19-8

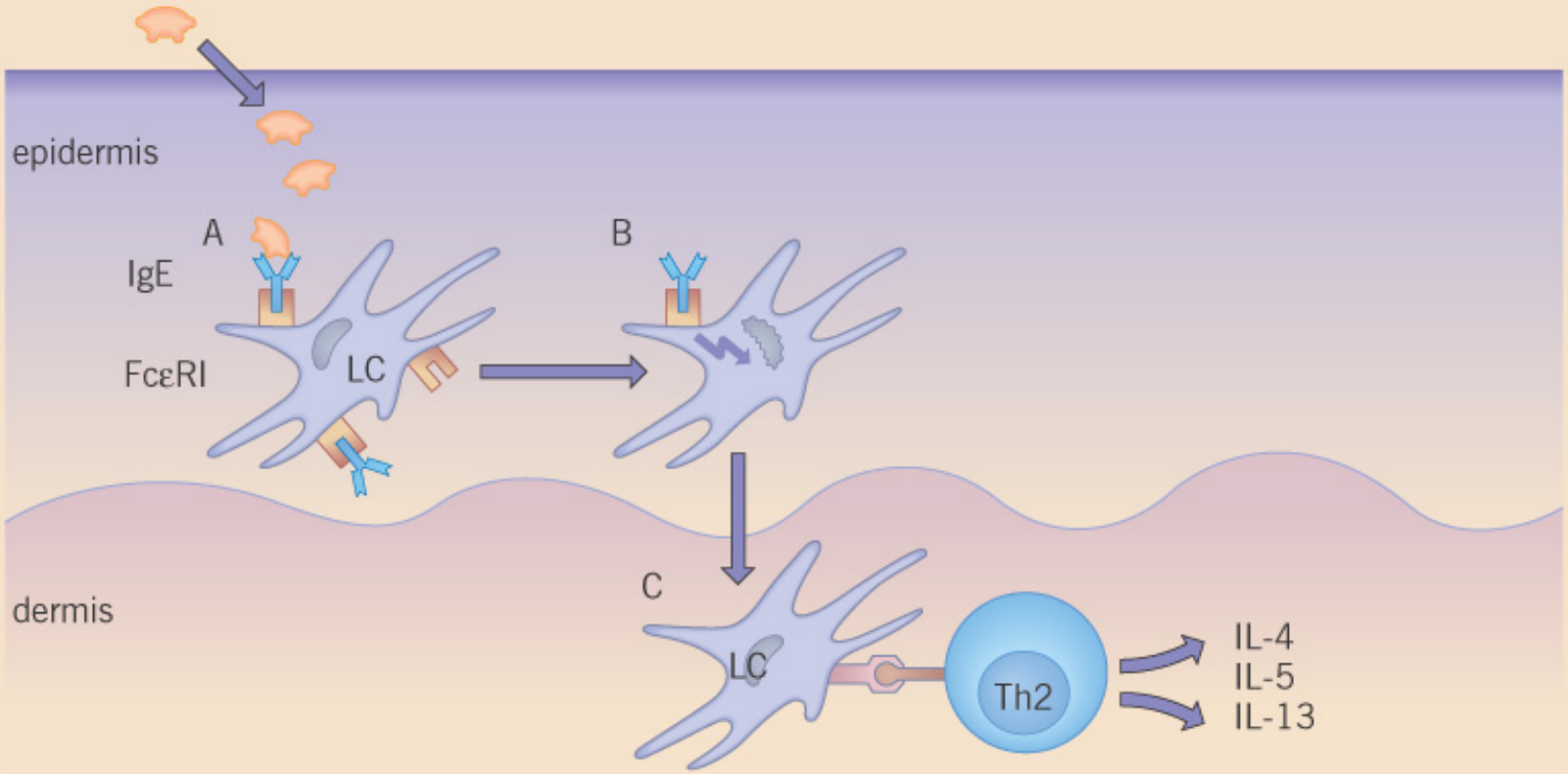
Mediators and their biological effects



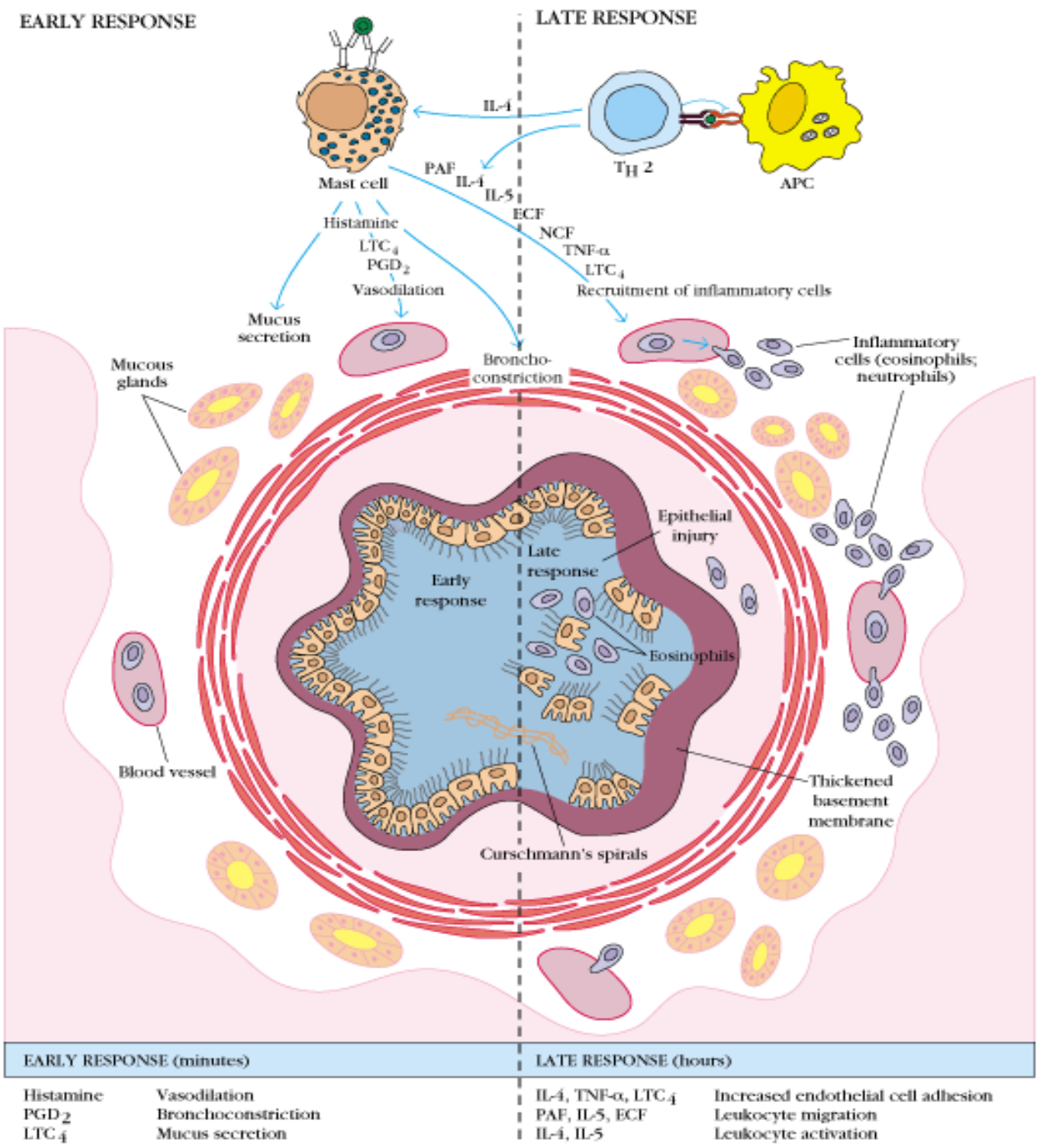
Late phase



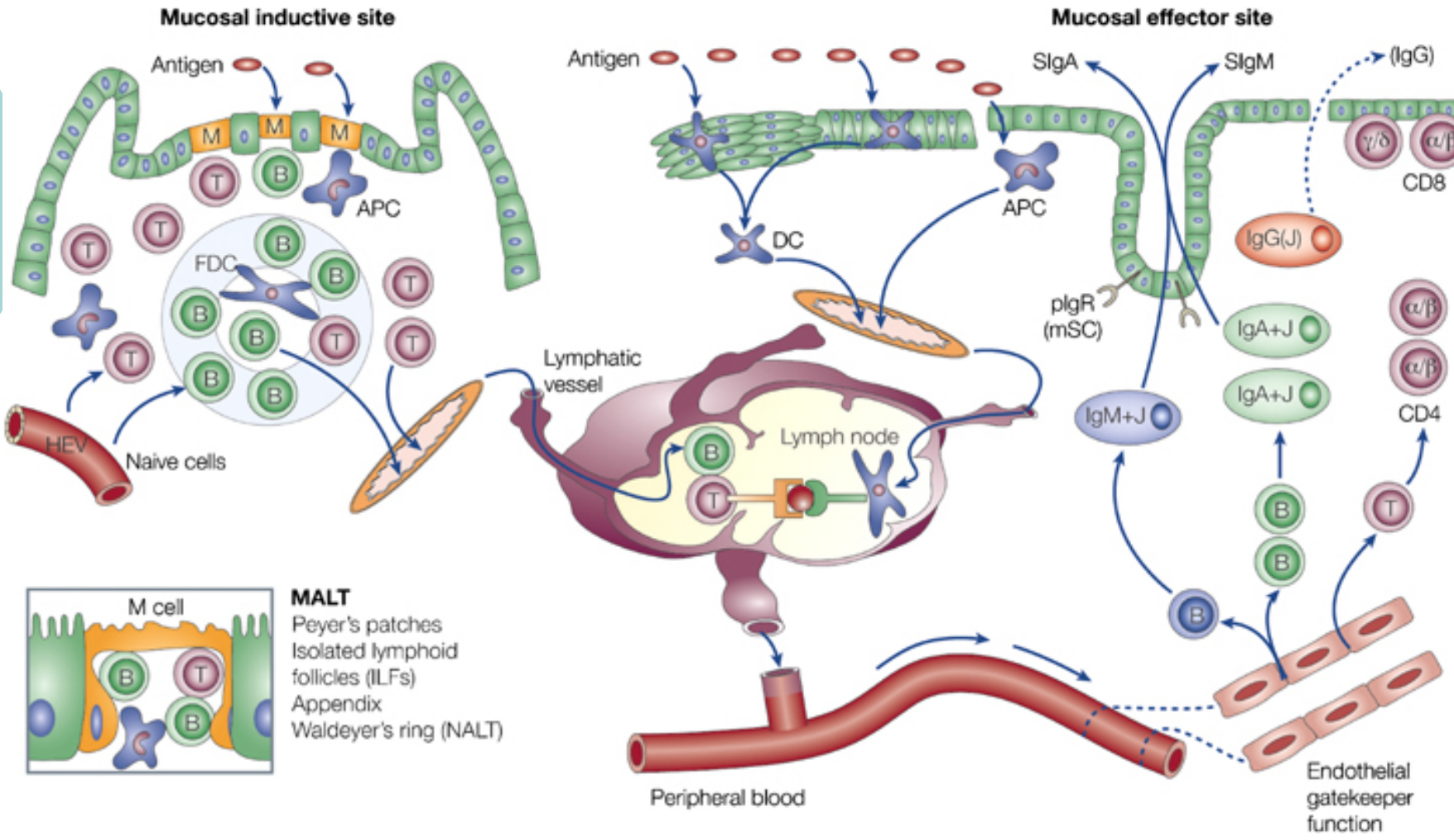
IgE Facilitated Antigen Up-take and Presentation



Holgate, Church and Lichtenstein: Allergy 3rd edition © 2006 Elsevier Ltd


EARLY RESPONSE
LATE RESPONSE
IL-4
Mast cell
T_H 2
APC
PAF
IL-4
IL-5
ECF
NCF
TNF-α
LTC_4
Recruitment of inflammatory cells
Histamine
LTC_4
PGD_2
Vasodilation
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)
LATE RESPONSE (hours)
Histamine
PGD_2
LTC_4
Vasodilation
Bronchoconstriction
Mucus secretion
IL-4, TNF-α, LTC_4
PAF, IL-5, ECF
IL-4, IL-5
Increased endothelial cell adhesion
Leukocyte migration
Leukocyte activation

MALT


Mucosal inductive site
Antigen
M
M
M
T
B
APC
T
T
FDC
B
B
B
B
B
T
T
T
T
HEV
Naive cells
Lymphatic vessel
Lymph node
B
T
Peripheral blood
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
B
B
B
T
Endothelial gatekeeper function
M cell
B
T
B
MALT
Peyer's patches
Isolated lymphoid follicles (ILFs)
Appendix
Waldeyer's ring (NALT)

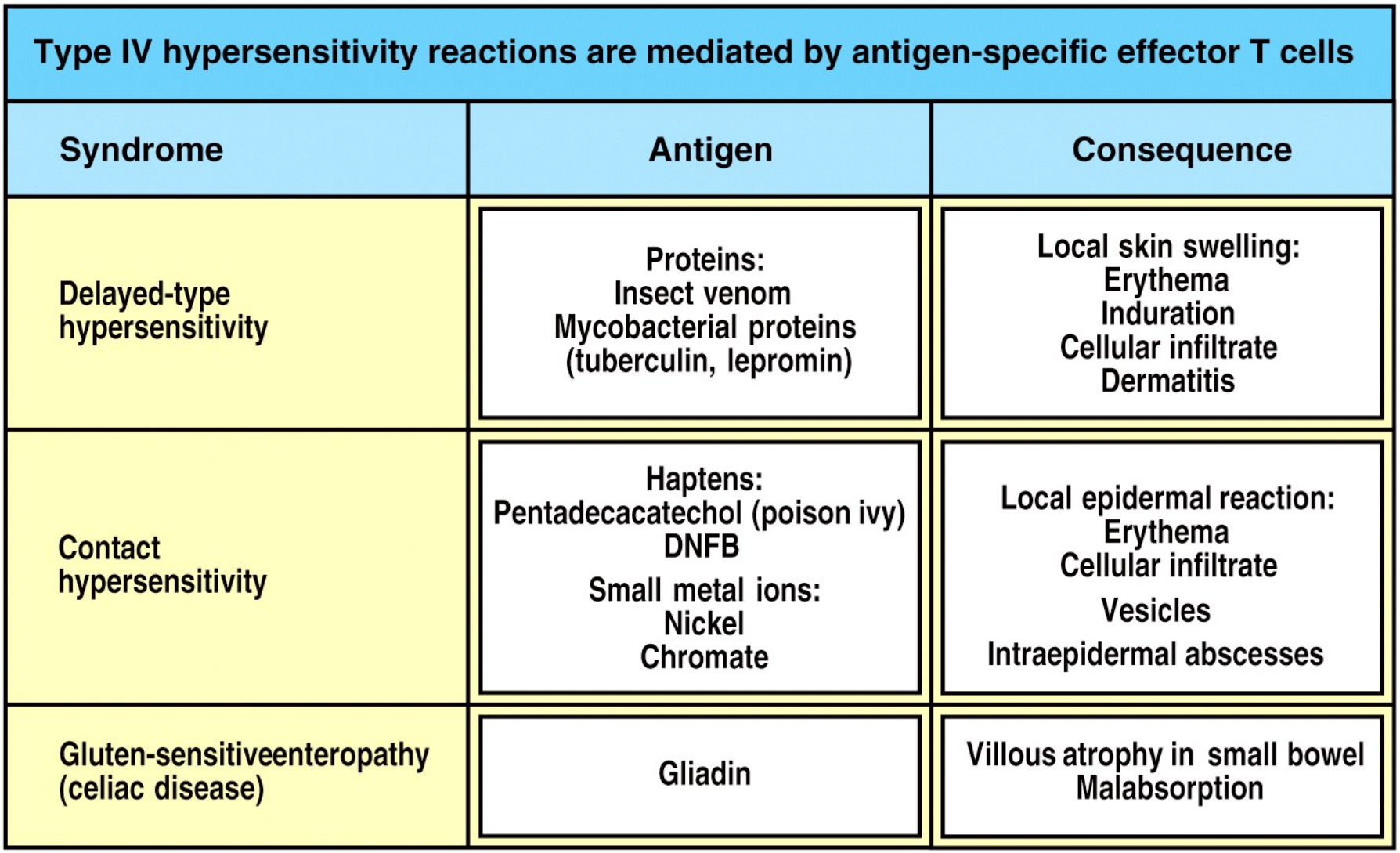


Figure 12-24 Immunobiology, 6/e. (© Garland Science 2005)

TABLE 14-3 INTRACELLULAR PATHOGENS AND CONTACT ANTIGENS THAT INDUCE DELAYED-TYPE HYPERSENSITIVITY

Intracellular bacteria
- *Mycobacterium tuberculosis*
- *Mycobacterium leprae*
- *Listeria monocytogenes*
- *Brucella abortus*

Intracellular fungi
- *Pneumocystis carinii*
- *Candida albicans*
- *Histoplasma capsulatum*
- *Cryptococcus neoformans*

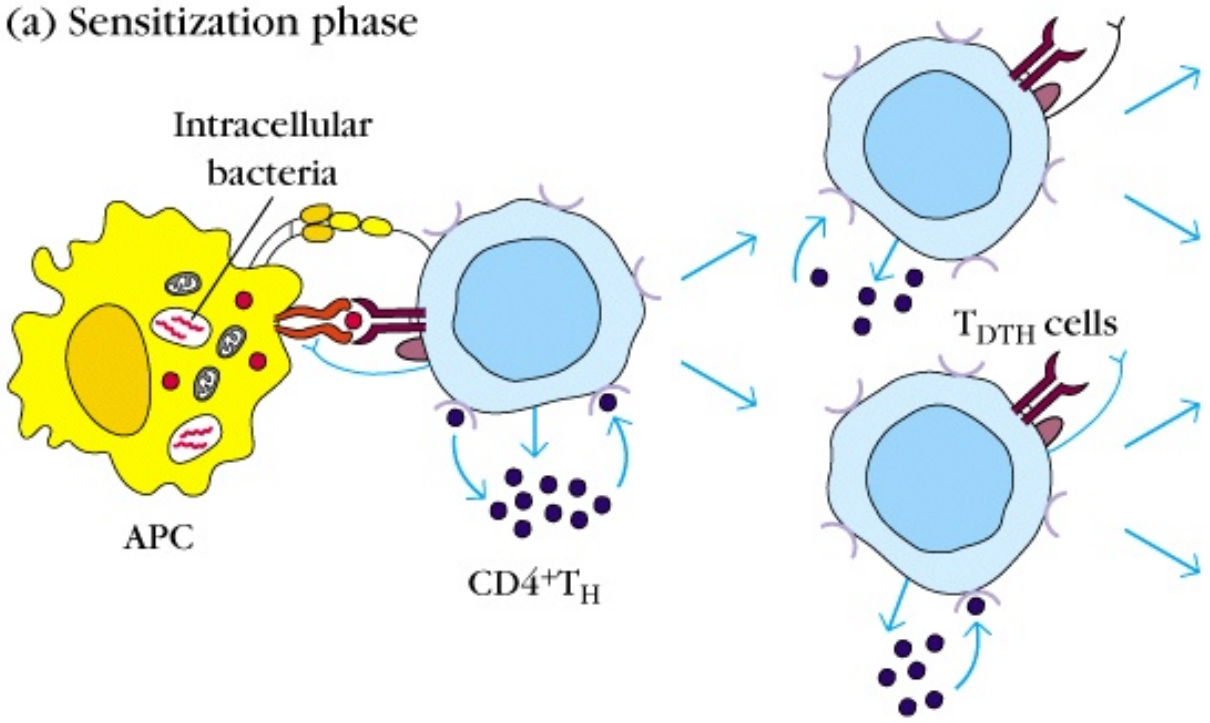
Intracellular parasites
- *Leishmania* sp.

Intracellular viruses
- Herpes simplex virus
- Variola (smallpox)
- Measles virus

Contact antigens
- Picrylchloride
- Hair dyes
- Nickel salts
- Poison ivy
- Poison oak

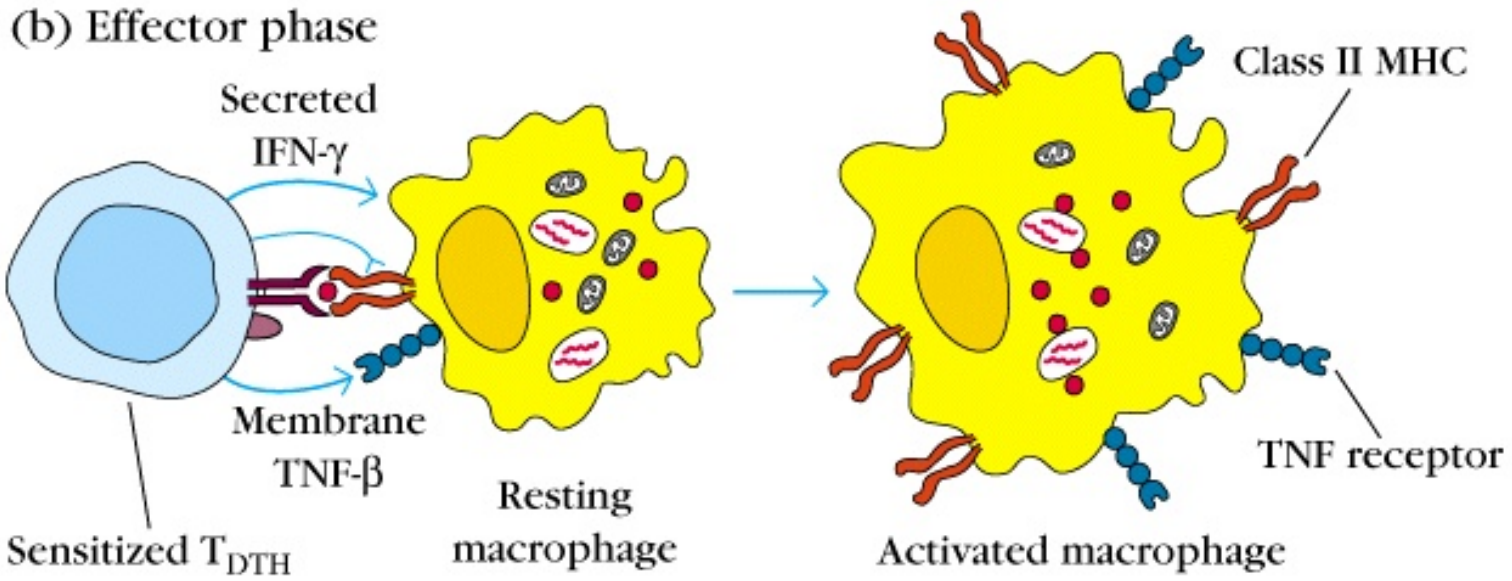
Delayed type IV hypersensitvity (DTH)

I. Sensitization



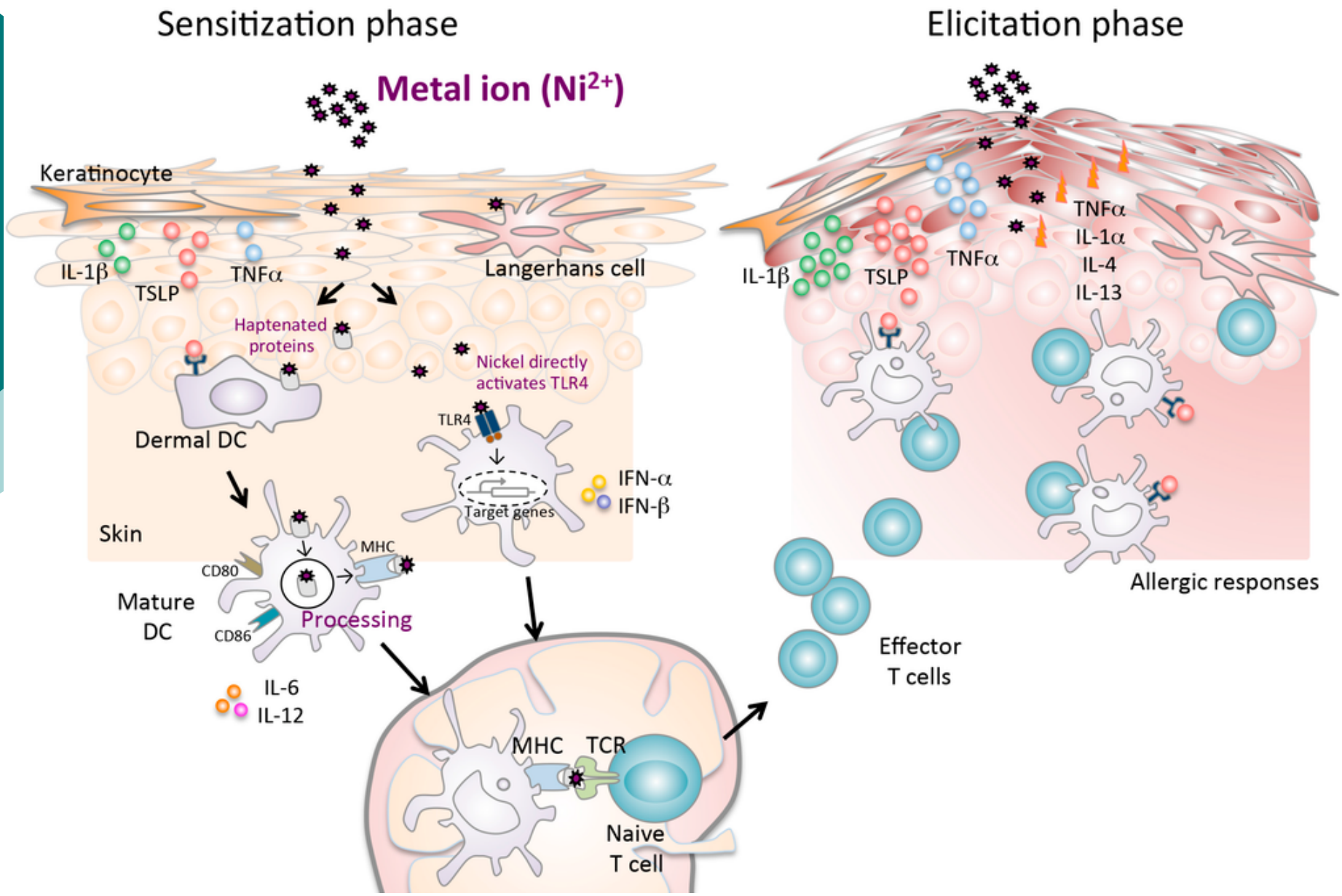
Antigen-presenting cells:	T_{DTH} cells:
Macrophages	T_H1 cells (generally)
Langerhans cells	$CD8^+$ cells (occasionally)

II. Effector phase



T_{DTH} secretions:
- Cytokines: IFN-γ, TNF-β, IL-2, IL-3, GM-CSF
- Chemokines: IL-8, MCAF, MIF

Effects of macrophage activation:
- ↑ Class II MHC molecules
- ↑ TNF receptors
- ↑ Oxygen radicals
- ↑ Nitric oxide


Sensitization phase
Elicitation phase
Metal ion (Ni2+)
Keratinocyte
IL-1β
TSLP
TNFα
Langerhans cell
Haptenated proteins
Nickel directly activates TLR4
Dermal DC
TLR4
Target genes
IFN-α
IFN-β
Skin
MHC
CD80
CD86
Mature DC
Processing
IL-6
IL-12
MHC
TCR
Naive T cell
Effector T cells
TNFα
IL-1α
IL-4
IL-13
Allergic responses

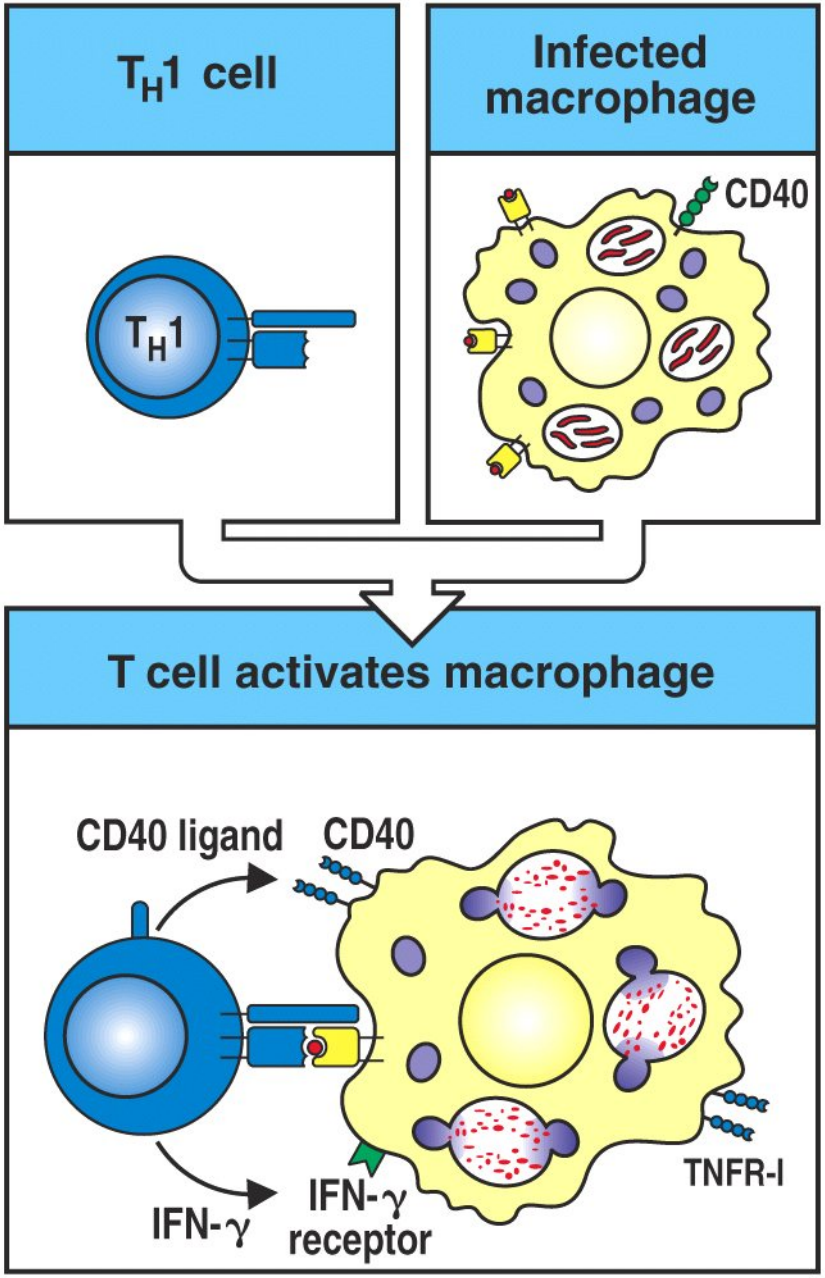


Figure 8-39 Immunobiology, 6/e. (© Garland Science 2005)

Reactive oxigen species

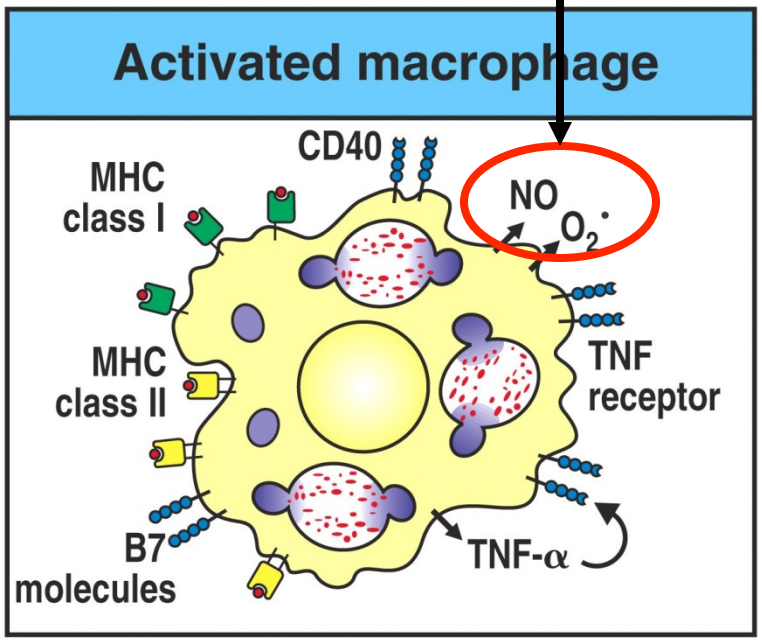
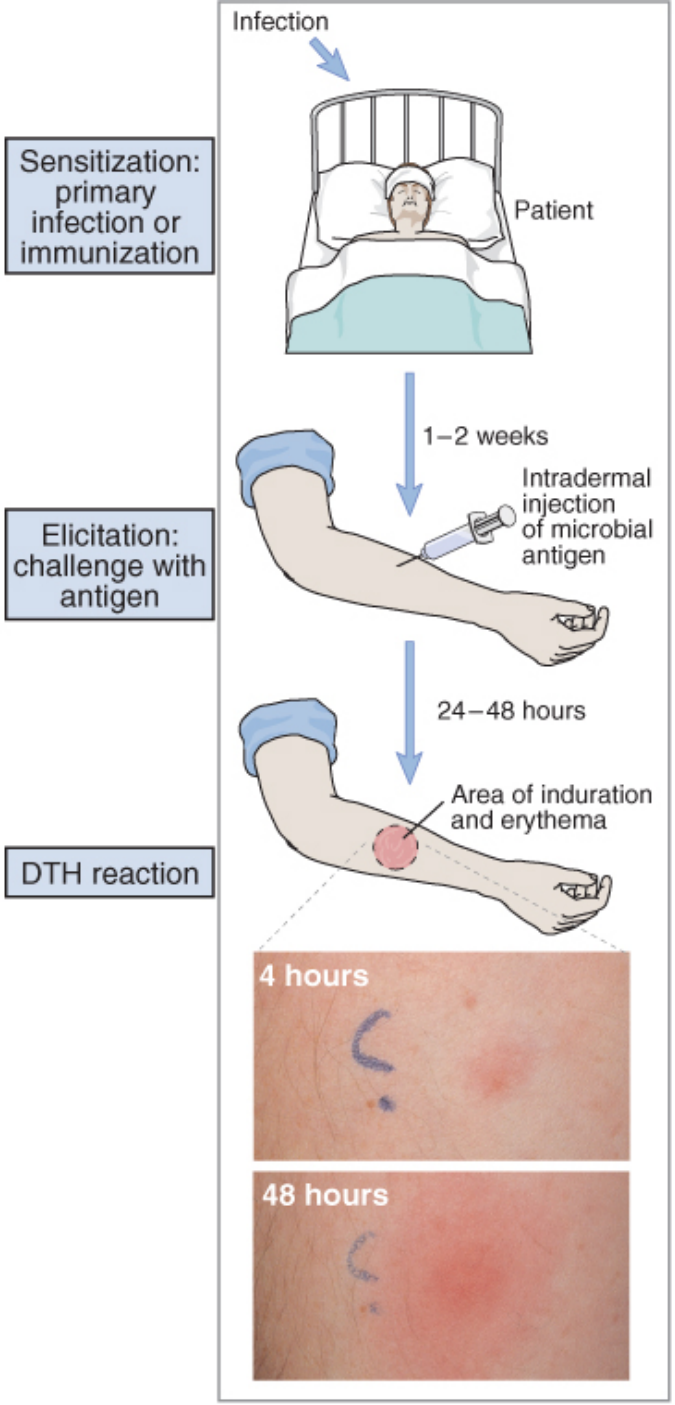


Figure 8-40 Immunobiology, 6/e. (© Garland Science 2005)

DTH in clinic



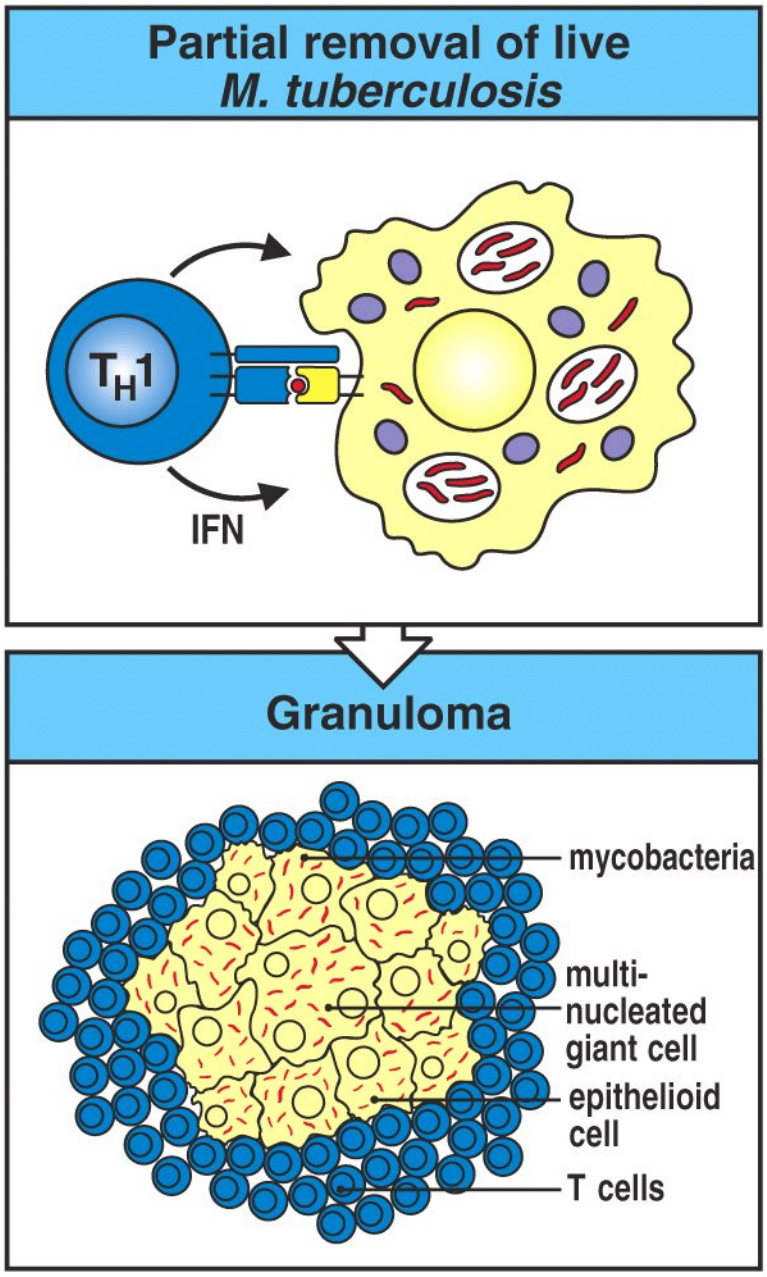


Figure 8-42 Immunobiology, 6/e. (© Garland Science 2005)