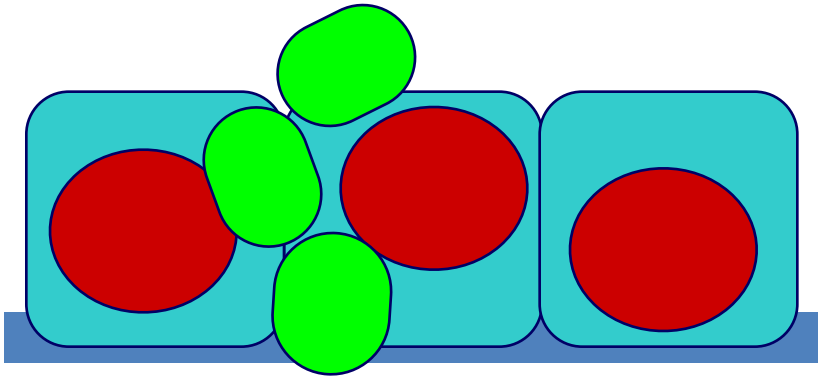
Type I hypersensitivity

Gell & Coombs Classification

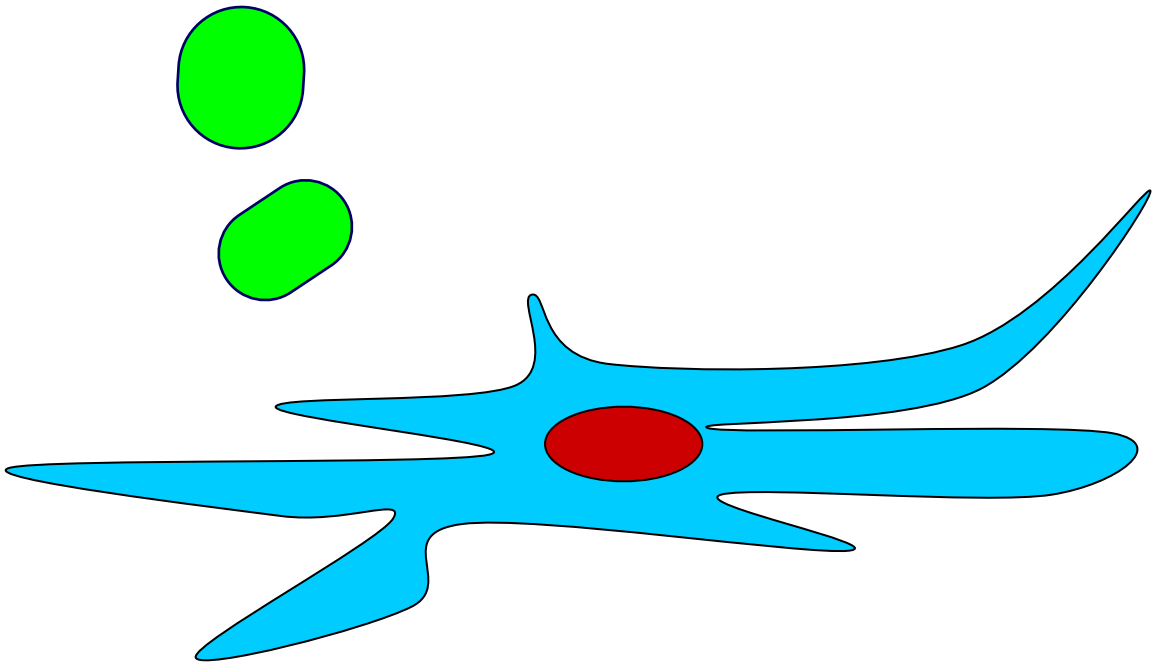
- **Type I Hypersensitivity: IgE mediated**
- **Type II Hypersensitivity: Ab-mediated cytotoxic**
- **Type III Hypersensitivity: ImmuneComplex-mediated cytotoxic**
- **Type IV Hypersensitivity: DTH mediated (cellular cytotoxicity)**

IgE-mediated immune responses are much like any other immune response and involves the same regulators

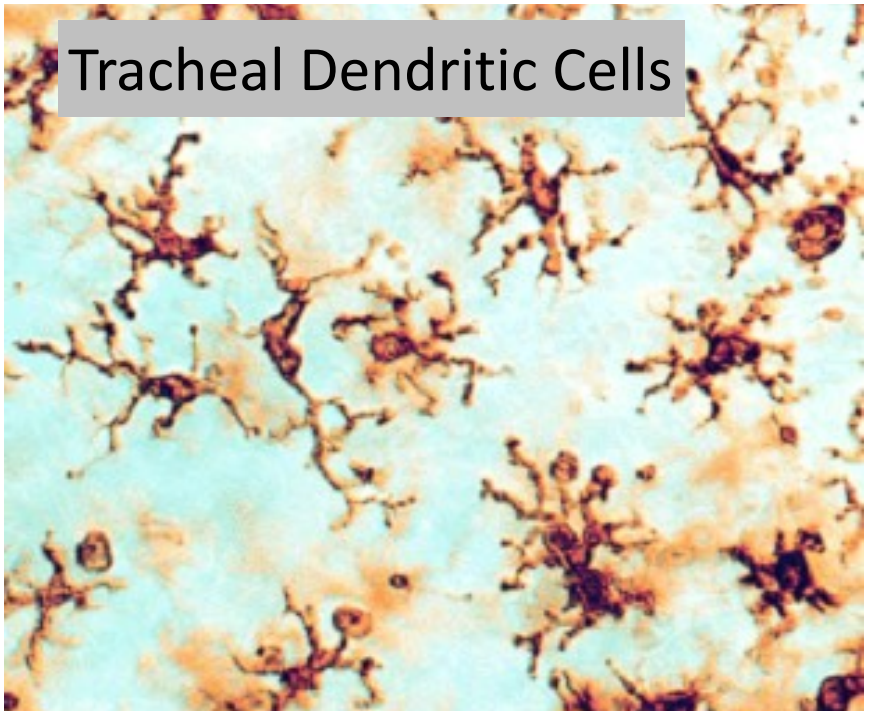
Non self protein from allergen or pathogen

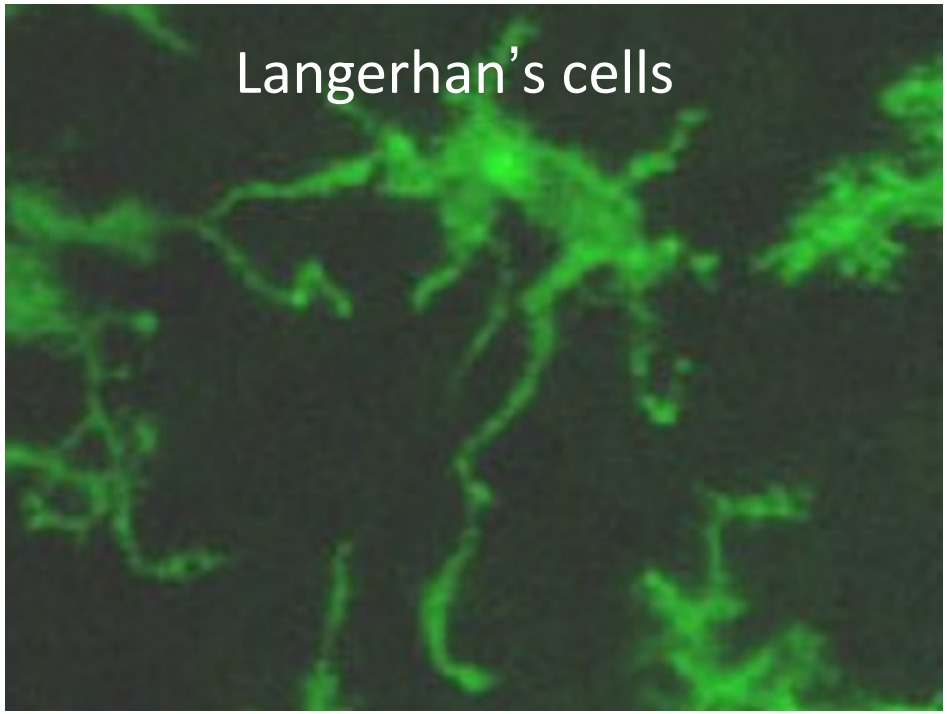


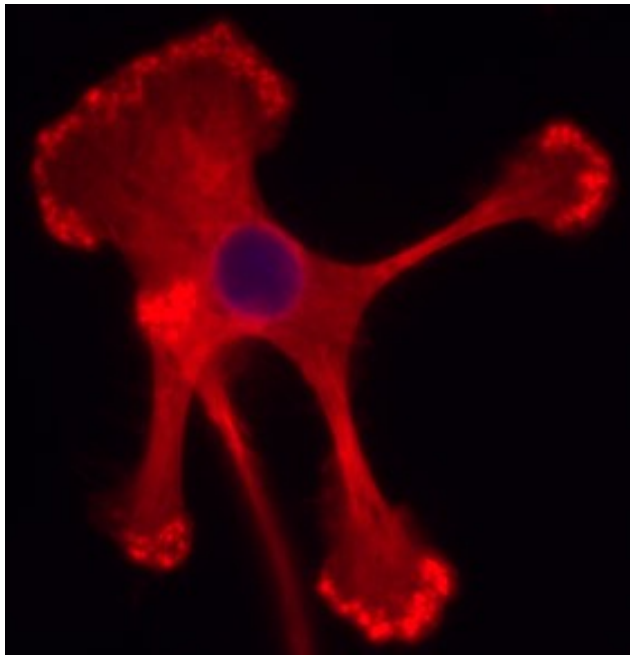
Barrier: Skin, gut, lung, eye, nose etc



Dendritic cells to site of inflammation

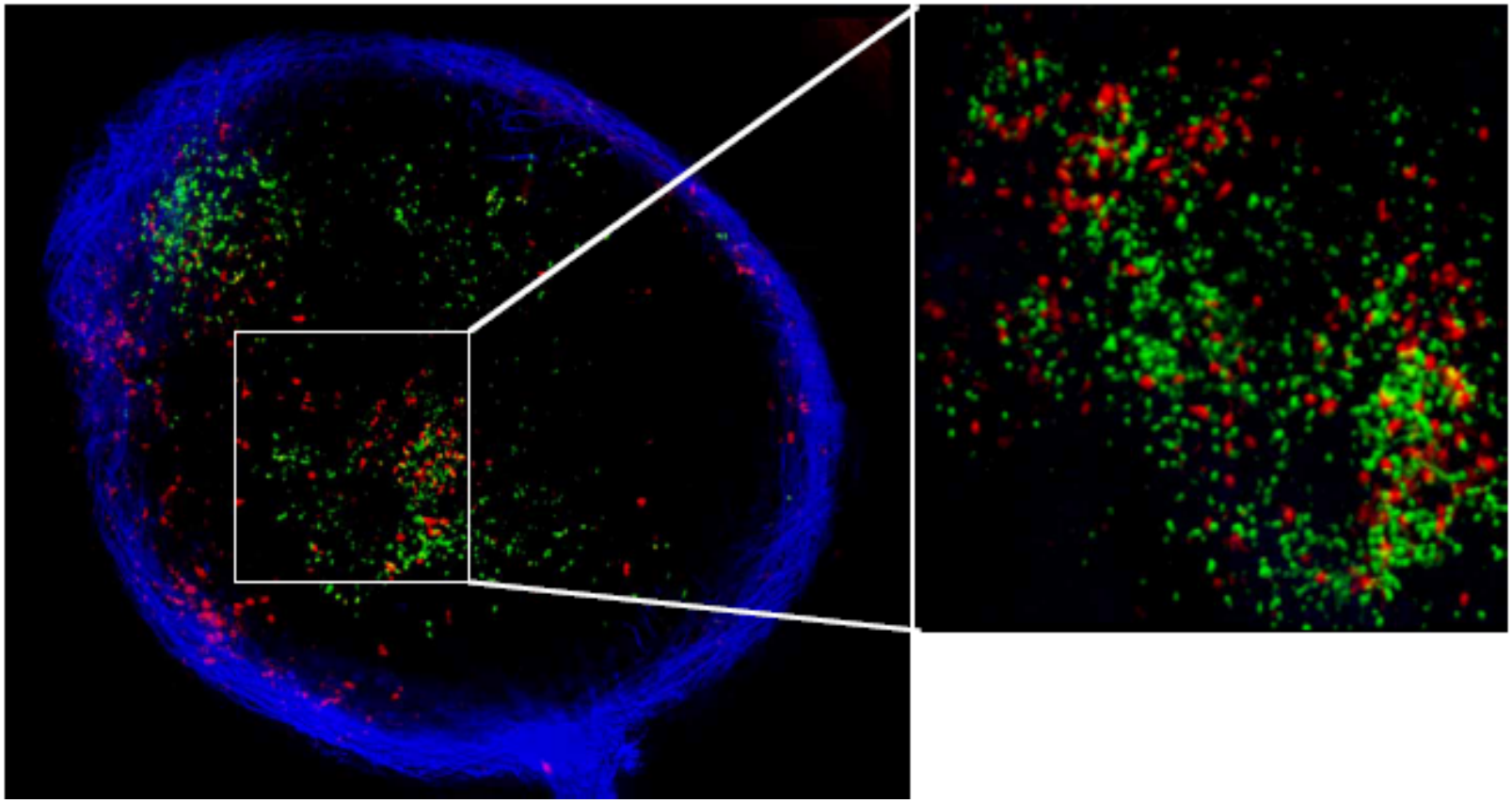

Tracheal Dendritic Cells


Langerhan’s cells



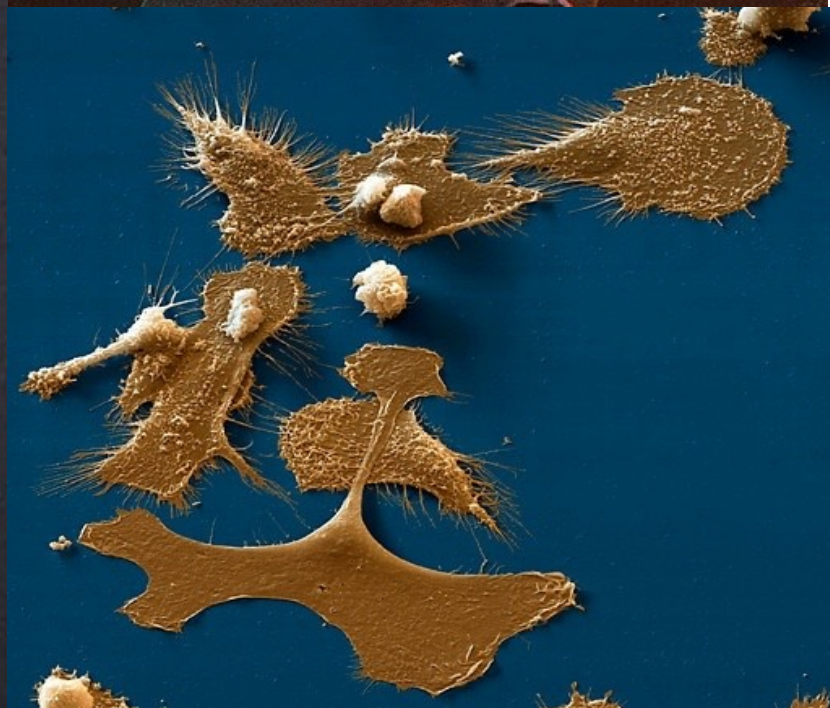
Early entry of DC to the lymph node

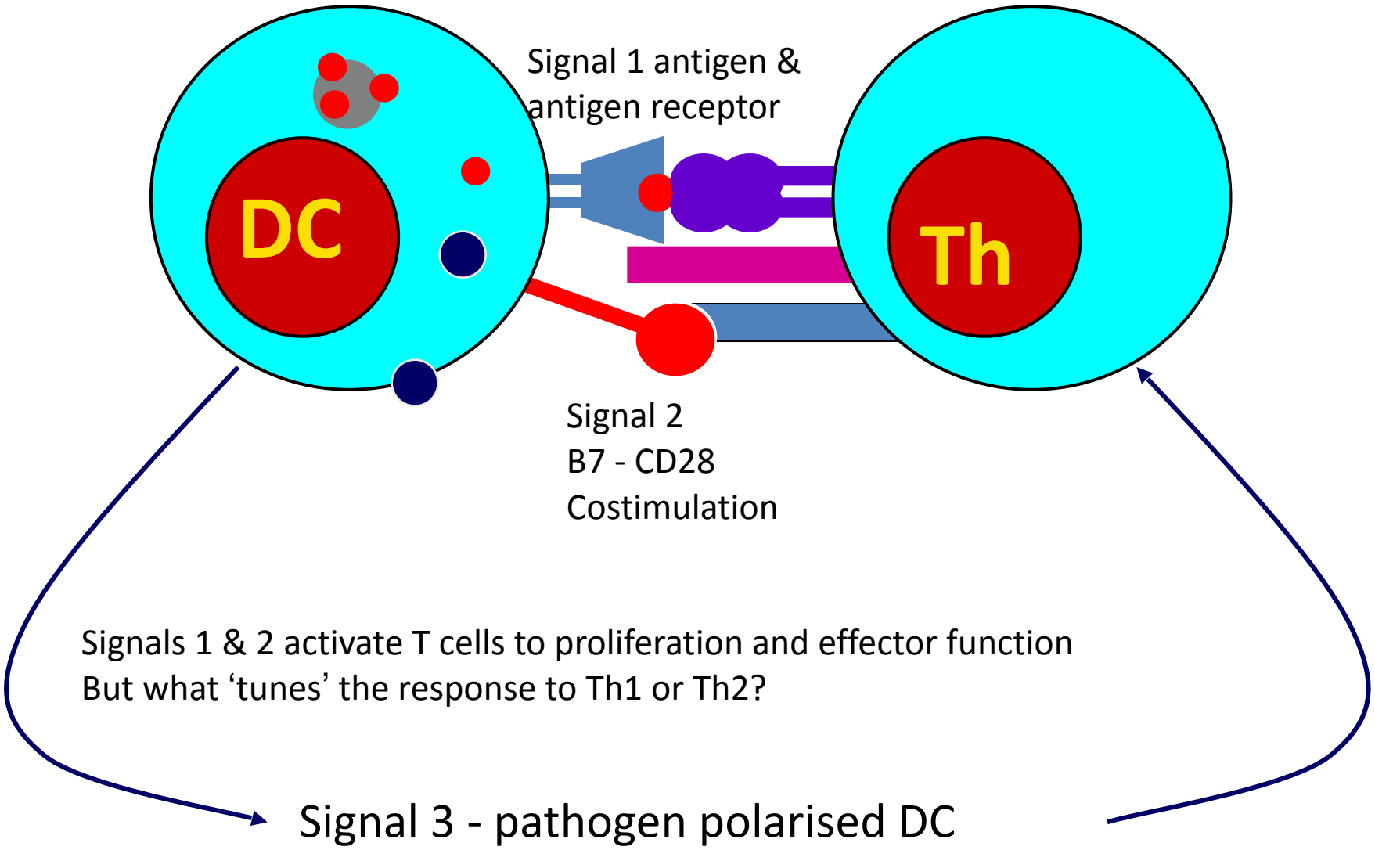
Mempel, T.R et al *Nature* **427**: 154-159, 2004.



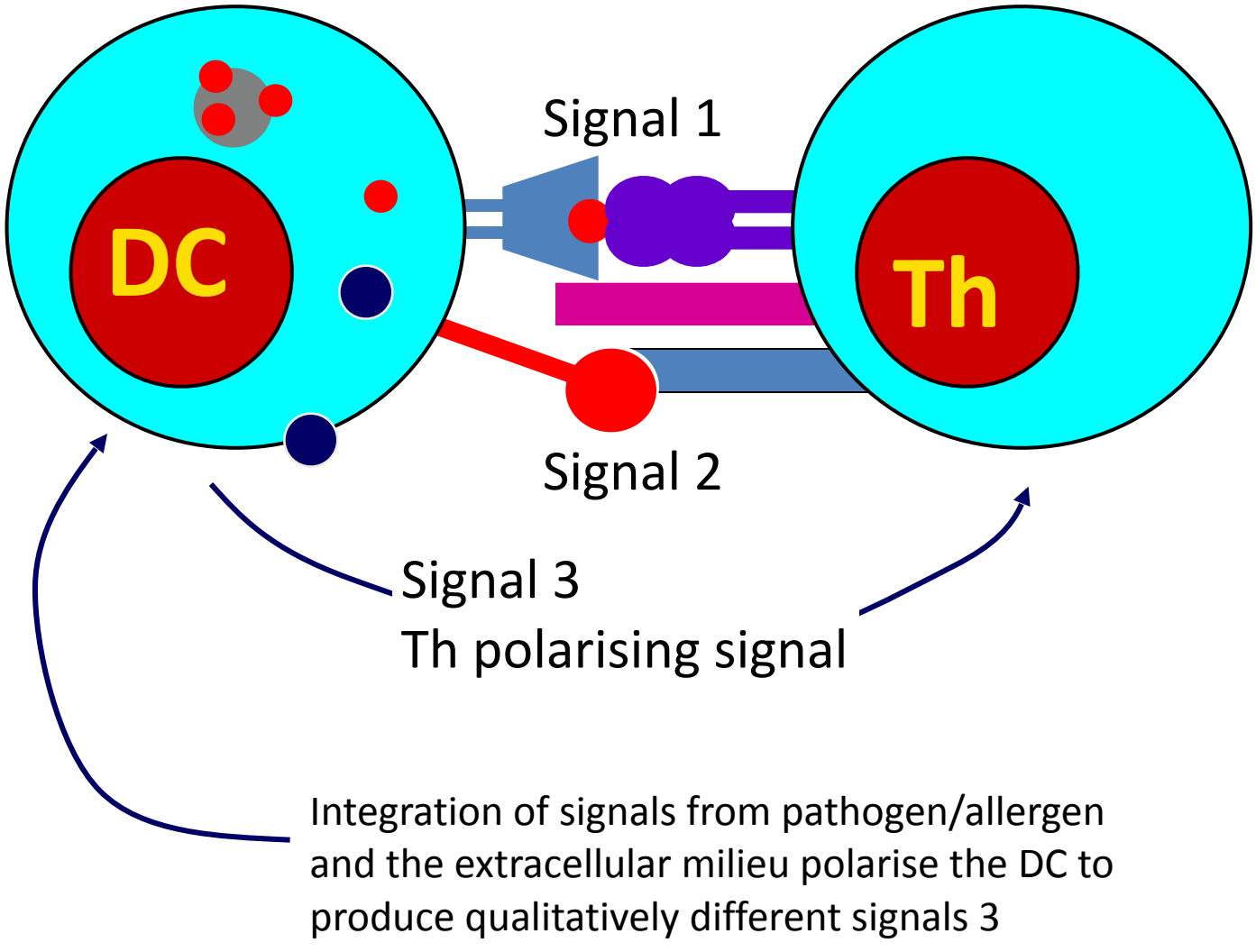
More information than is provided by the antigen is exchanged between the DC and T cell

DC have a profound influence on the properties of the T cell that develops




Signal 1 antigen &
antigen receptor
DC
Th
Signal 2
B7 - CD28
Costimulation
Signals 1 & 2 activate T cells to proliferation and effector function
But what 'tunes' the response to Th1 or Th2?
Signal 3 - pathogen polarised DC

Polarised DC subsets



The properties of the Ag influences the DC to drive the development of appropriate Th cells

Microbial Patterns

Janeway & Medzhitov 2002 Ann Rev Immunol 20 197-216

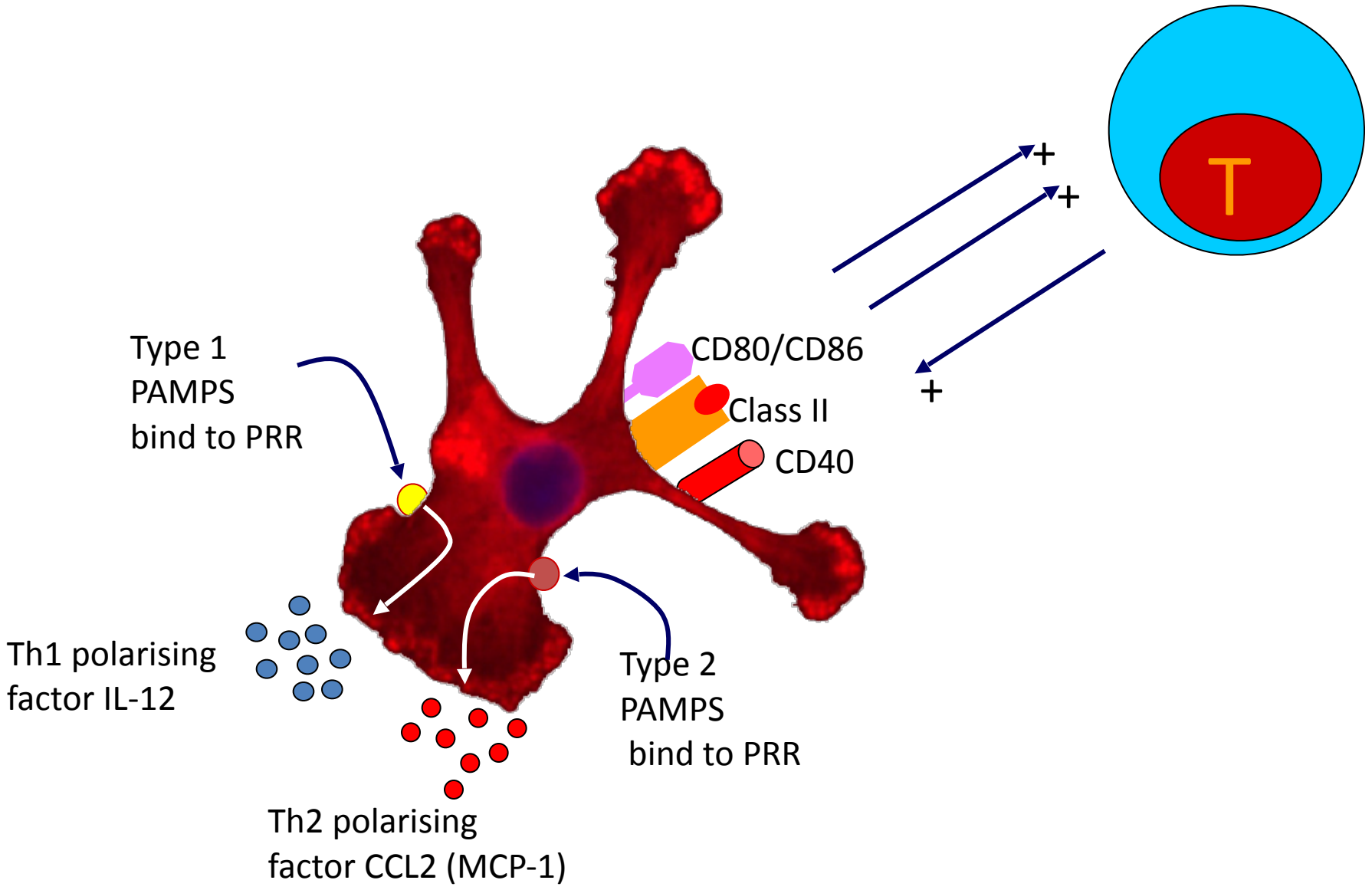
Pathogen-associated molecular patterns (PAMPs)

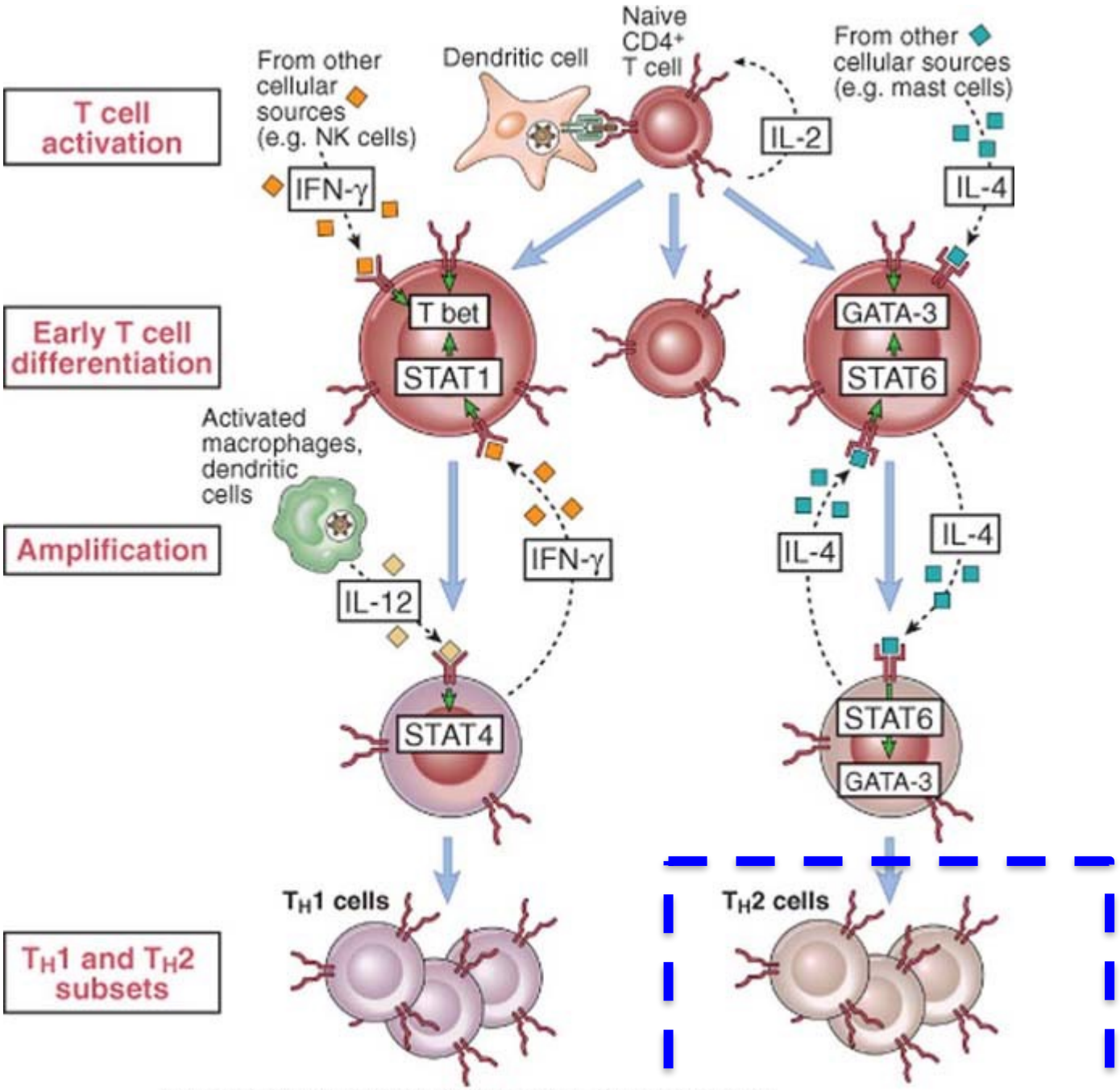
- Conserved microbial molecules shared by many pathogens
- Include:
  - Bacterial lipopolysaccharides
  - Peptidoglycan
  - Zymosan
  - Flagellin
  - Unmethylated CpG DNA

Pattern Recognition Receptors (PRR)

- Include:
  - Toll like receptors
  - Receptors for apoptotic cells
  - Receptors for opsonins
  - Receptors for coagulation and complement proteins

Type 1 and 2 DC Polarising PAMPS





Switch recombination to IgE

A three signal process:

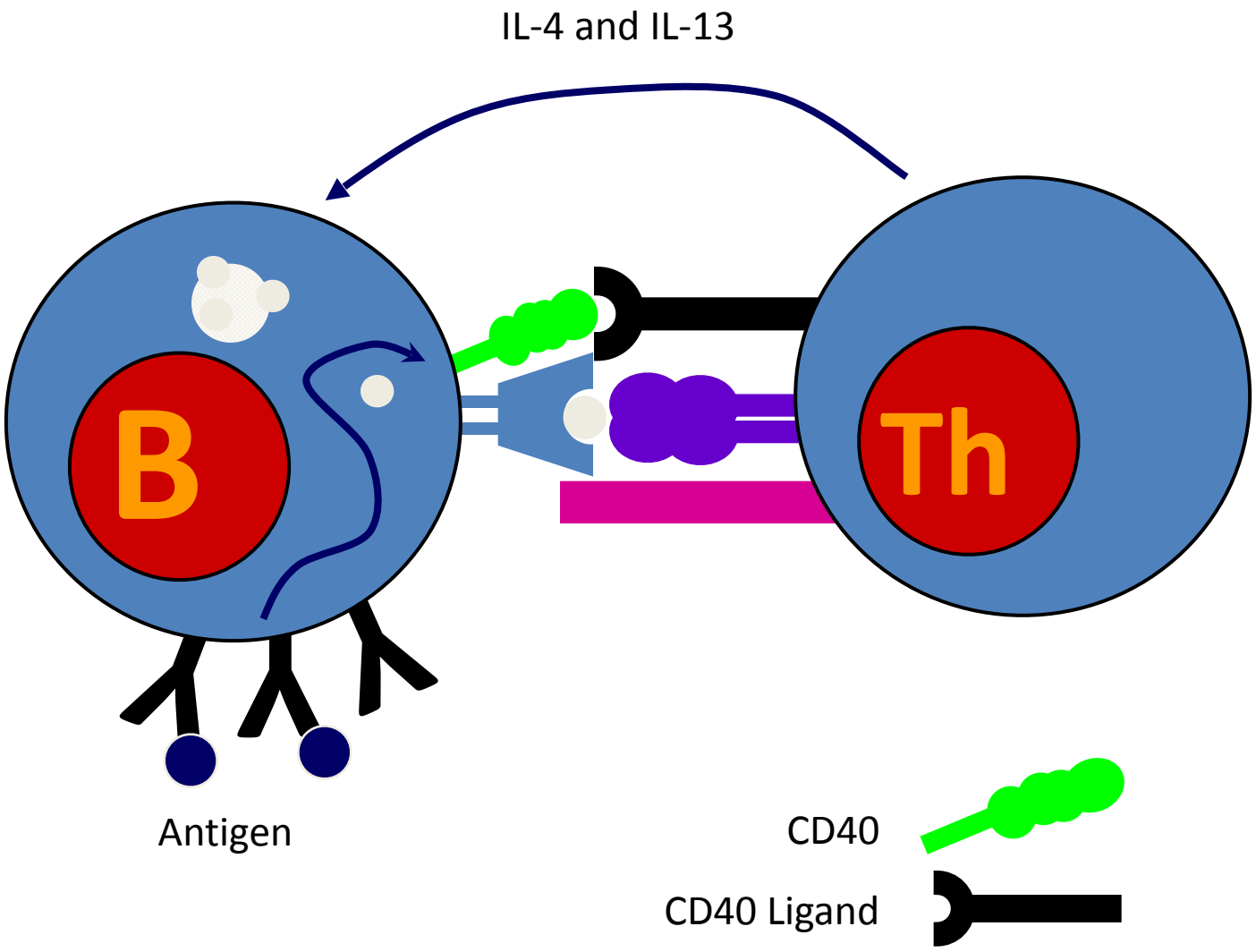
1. Antigen – controls entire process
2. Soluble help via IL-4 or IL-13 from T helper cells
3. Cognate help via CD40 L from T helper cells

Switch recombination to IgE

A three signal process:

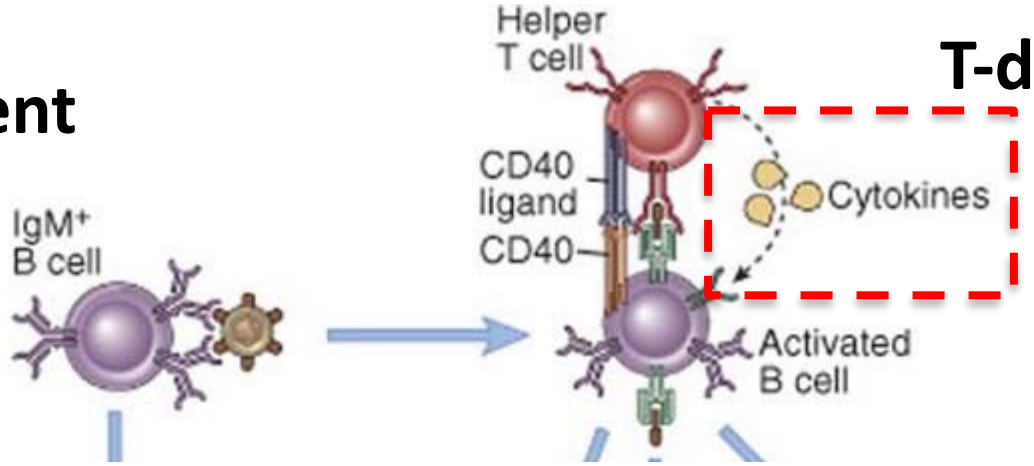
1. Antigen
2. Soluble help via IL-4 or IL-13 from T helper cells
3. Cognate help via CD40 L from T helper cells

T cell help to B cells



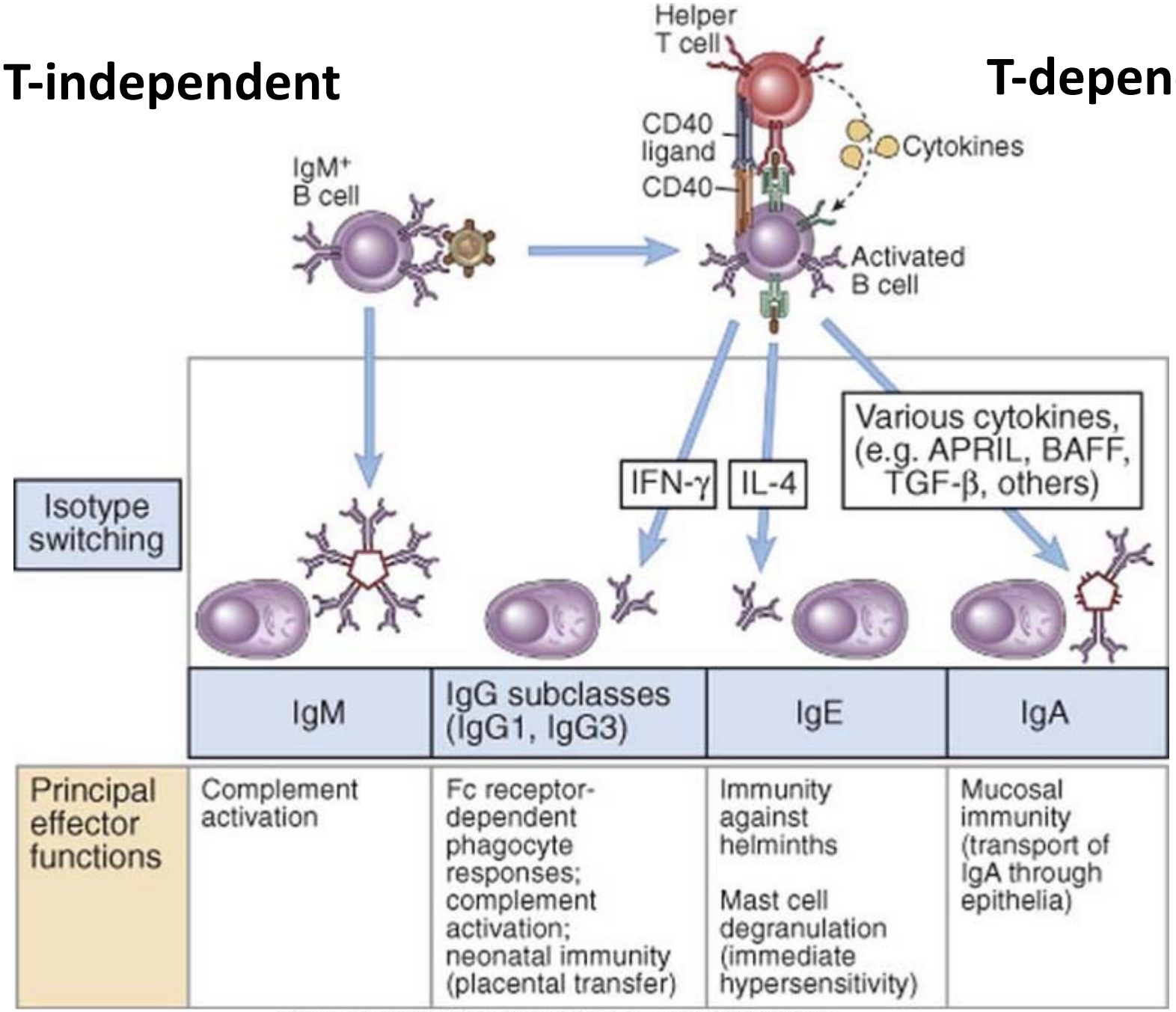
T-independent

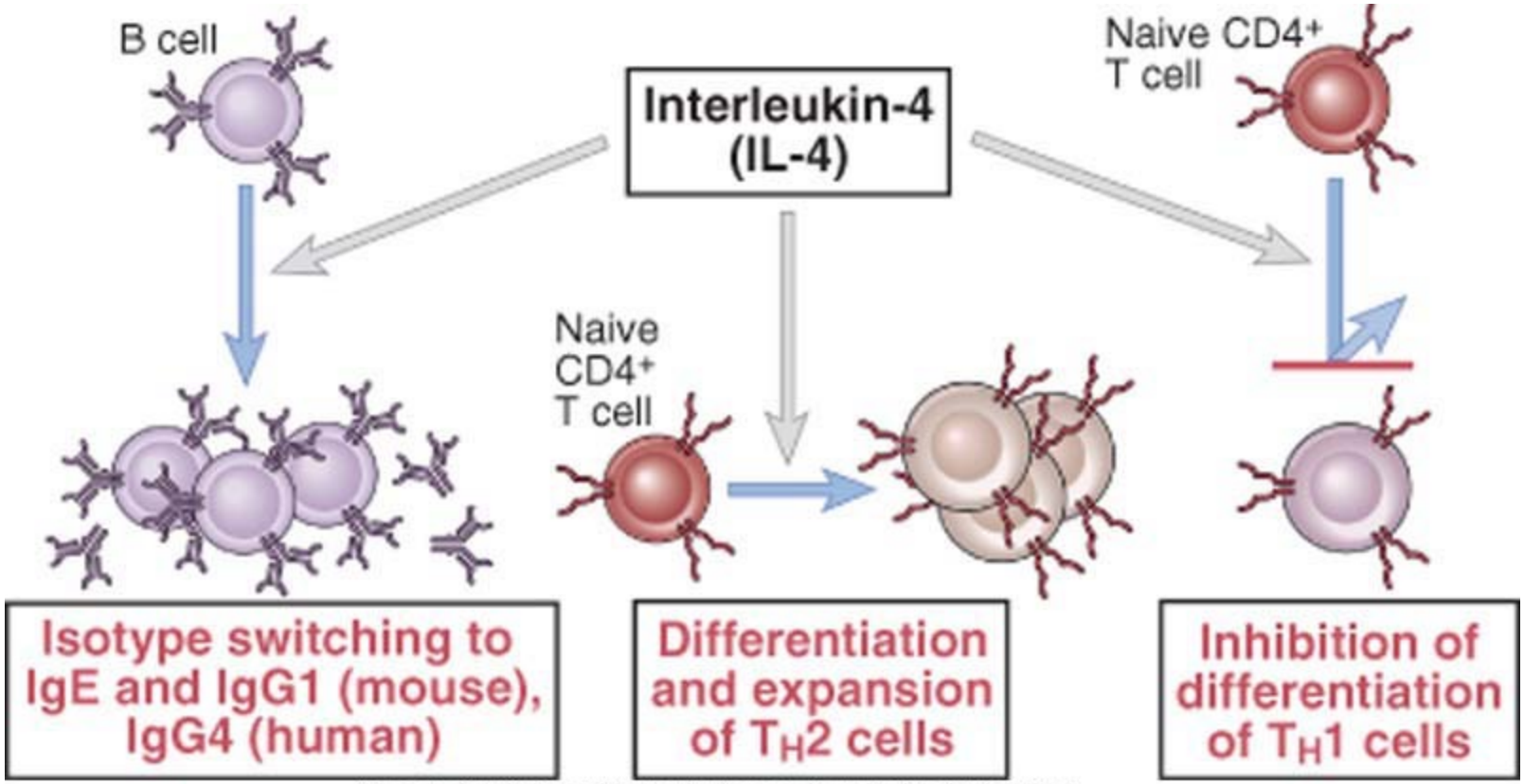
T-dependent



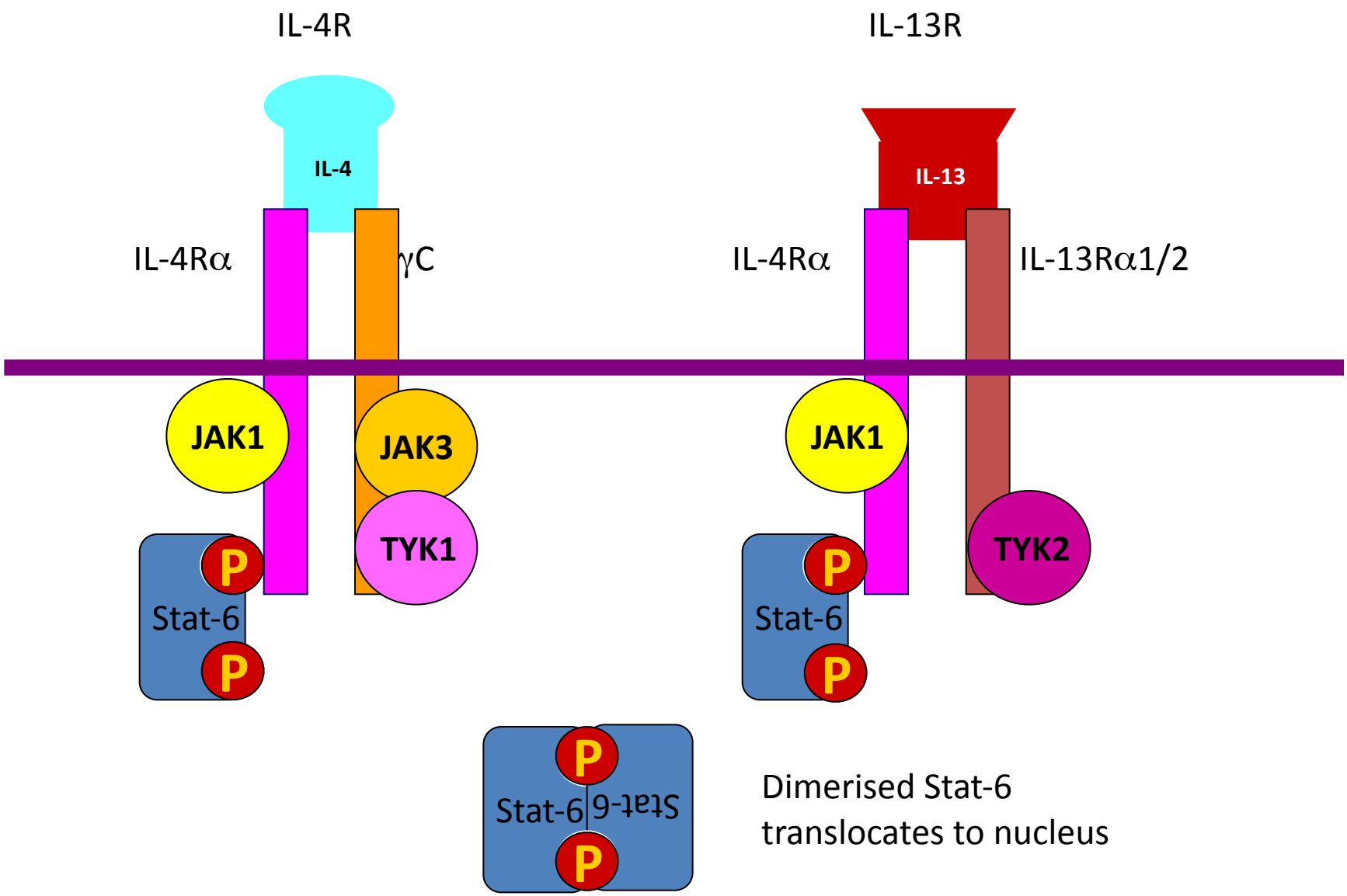
T-independent

T-dependent





Soluble help via IL-4 or IL-13 from T helper cells

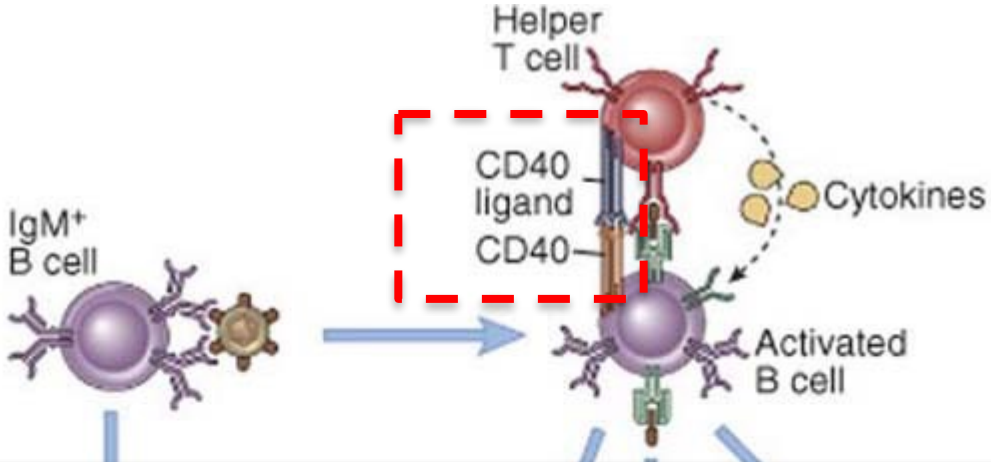


Dimerised Stat-6
translocates to nucleus

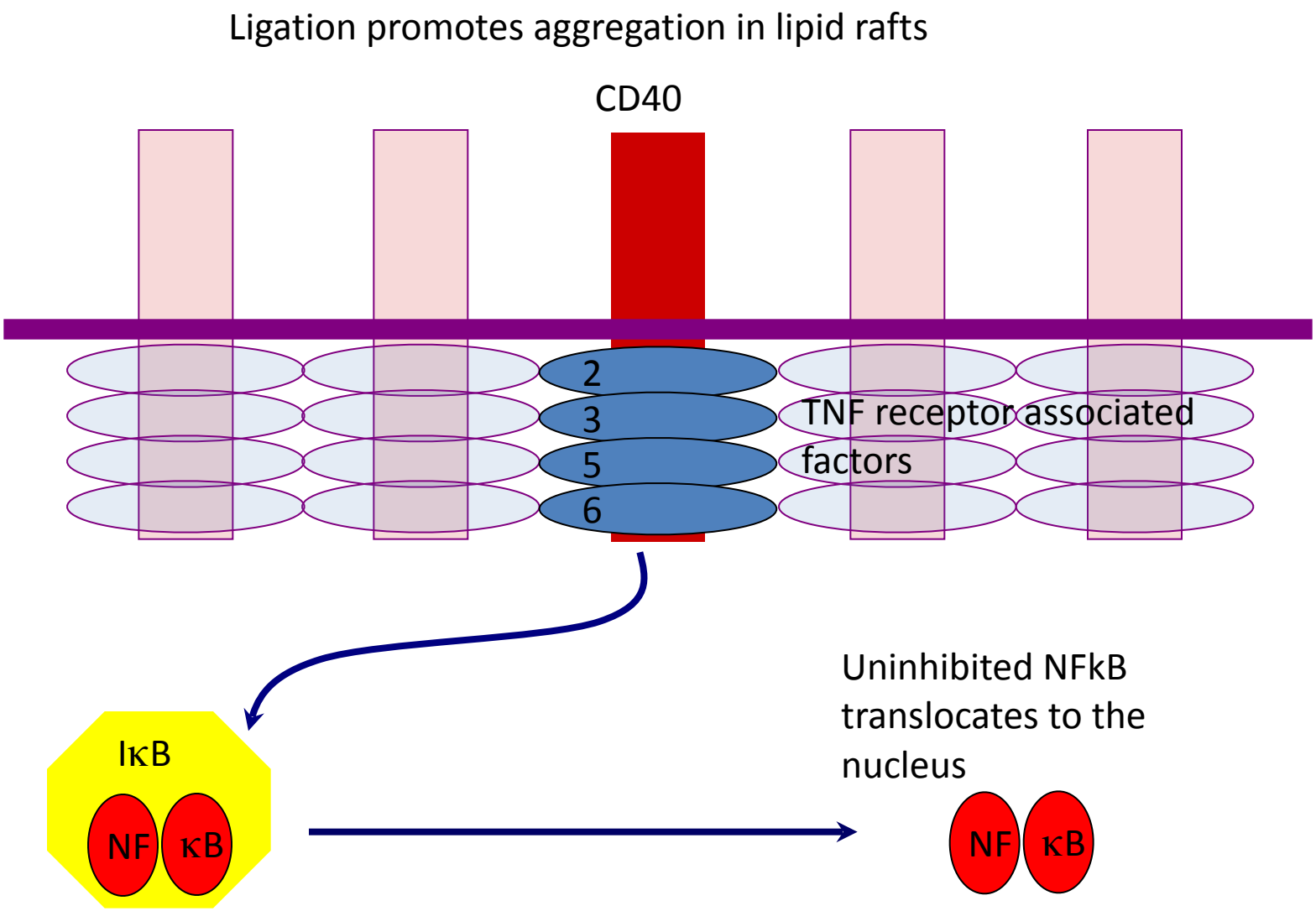
Switch recombination to IgE

A three signal process:

1. Antigen
2. Soluble help via IL-4 or IL-13 from T helper cells
3. Cognate help via CD40 L from T helper cells


Helper
T cell
CD40
ligand
CD40
Cytokines
IgM+
B cell
Activated
B cell

Cognate help via CD40 L from T helper cells

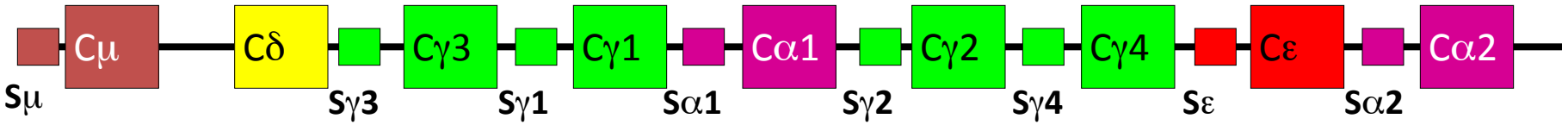


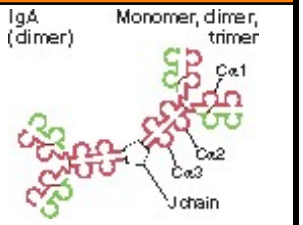
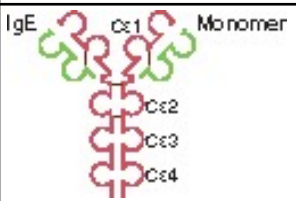
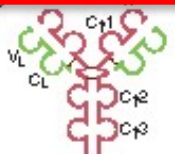
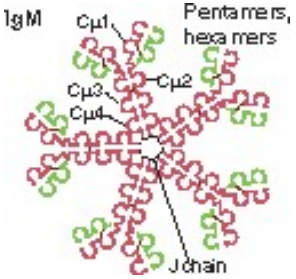
NF-kB responsive elements

GGGCTGGG TGAGCTGRGCTGAGCTGRGCTGAGCTRARNT
CCCGACCCGACTCGACYCGACTCGACYCGA TCGAYTYNA

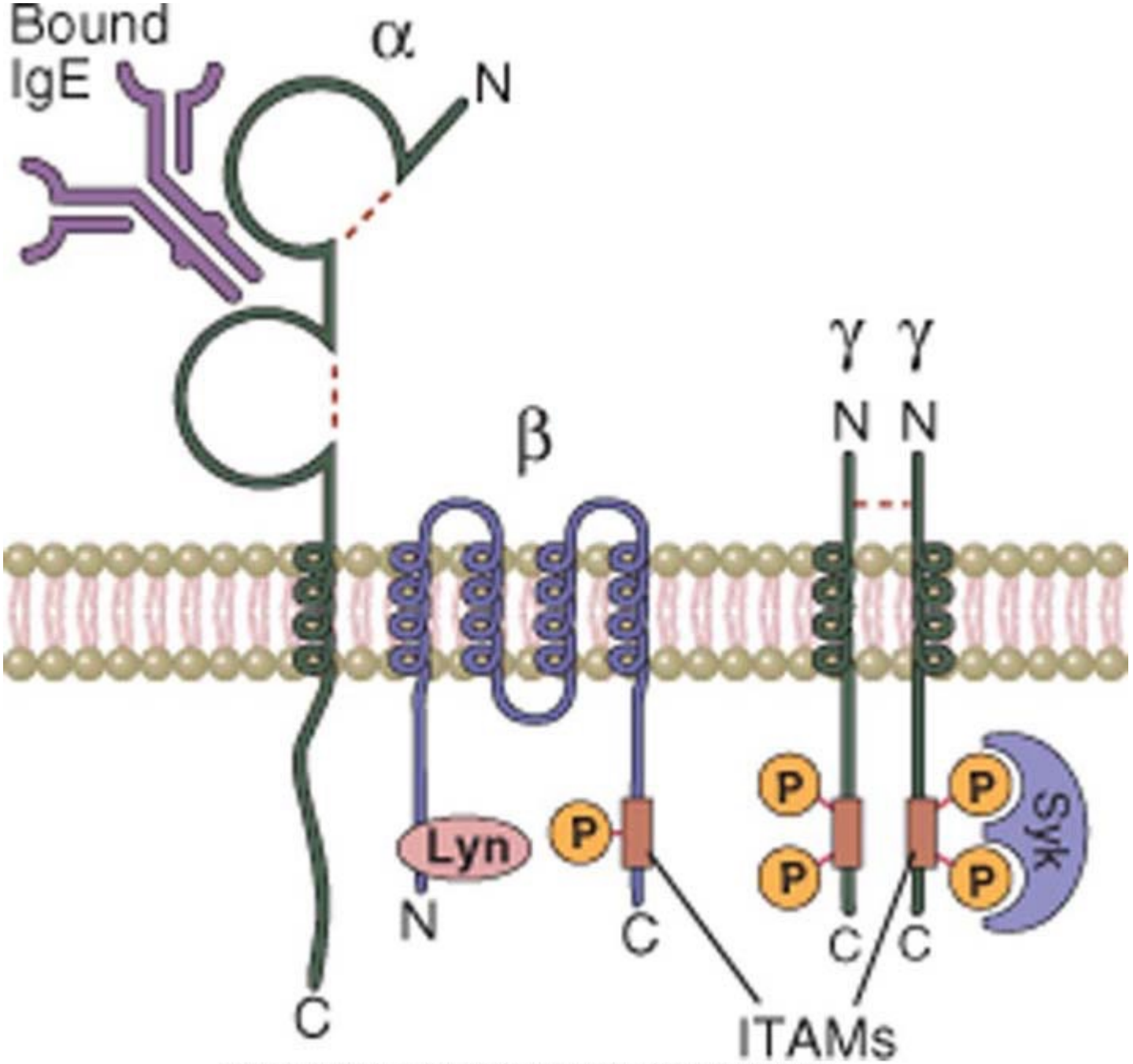
GGGCTGGG
CCCGACCC(Exonuclease activity

End fill-in reactions TGAGCTGRGCTGAGCTGRGCTGAGCTRARNT
ACTCGACYCGACTCGACYCGAC TCGAYTYNA



isotiopo	Sottotipo	Concentrazione nel siero (mg/ml)	Emivita nel siero (giorni)	Forma secreta
IgA	1,2	3,5	6	
IgD	-	-	3	-
IgE	-	0,05	2	
IgG	1-4	13,5	23	
IgM	-	1,5	5	

FcR	Affinity for immunoglobulin	Cell Distribution	Function
Fc γ RI (CD64)	High (Kd ~ 10^{-9} M) binds IgG1 and IgG3	Macrophages, neutrophils; also eosinophils	Phagocytosis, activation of phagocytes
Fc γ RIIA (CD32)	Low (Kd > 10^{-7} M)	Macrophages, neutrophils; eosinophils, platelets	Phagocytosis; cell activation (inefficient)
Fc γ RIIB (CD32)	Low (Kd > 10^{-7} M)	B lymphocytes, dendritic cells, macrophages	Feedback inhibition of B cells, macrophages, dendritic cells
Fc γ RIIIA (CD16)	Low (Kd > 10^{-6} M)	NK cells	Antibody-dependent cell-mediated cytotoxicity
Fc γ RIIIB (CD16)	Low (Kd > 10^{-6} M) GPI-linked protein	Neutrophils, other cells	Phagocytosis (inefficient)
Fc ε RI	High (Kd > 10^{-10} M) binds monomeric IgE	Mast cells, basophils, eosinophils	Cell activation (degranulation)
Fc ε RII (CD23)	Low (Kd > 10^{-7} M)	B lymphocytes, eosinophils, Langerhans cells	Unknown
Fc α R (CD89)	Low (Kd > 10^{-6}M)	Neutrophils, eosinophils, monocytes	Cell activation?



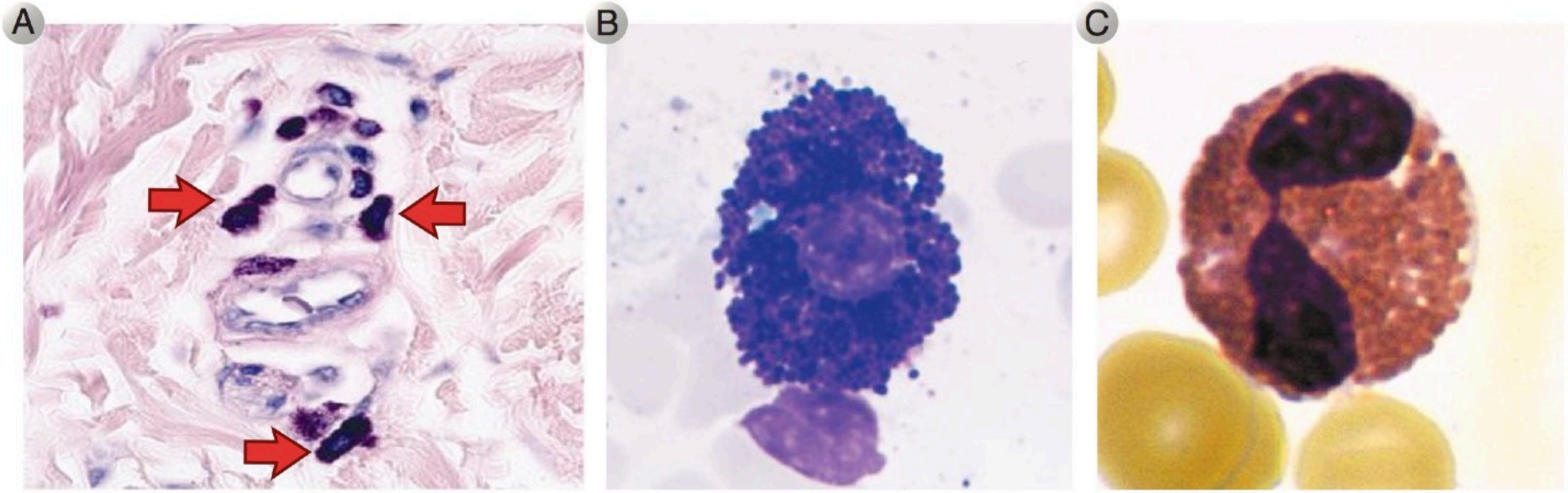


FIGURE 20.2 Morphology of mast cells, basophils, and eosinophils. Photomicrographs of Wright-Giemsa–stained perivascular dermal mast cells (**A,** *arrows*), peripheral blood basophil **(B)**, and peripheral blood eosinophil **(C)** are presented. Note the characteristic blue-staining cytoplasmic granules of the basophil and red staining of the cytoplasmic granules in the eosinophil. *(**A,** Courtesy of Dr. George Murphy. **B** and **C,** Courtesy of Dr. Jonathan Hecht, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts.)*

Mast cell (resting condition)

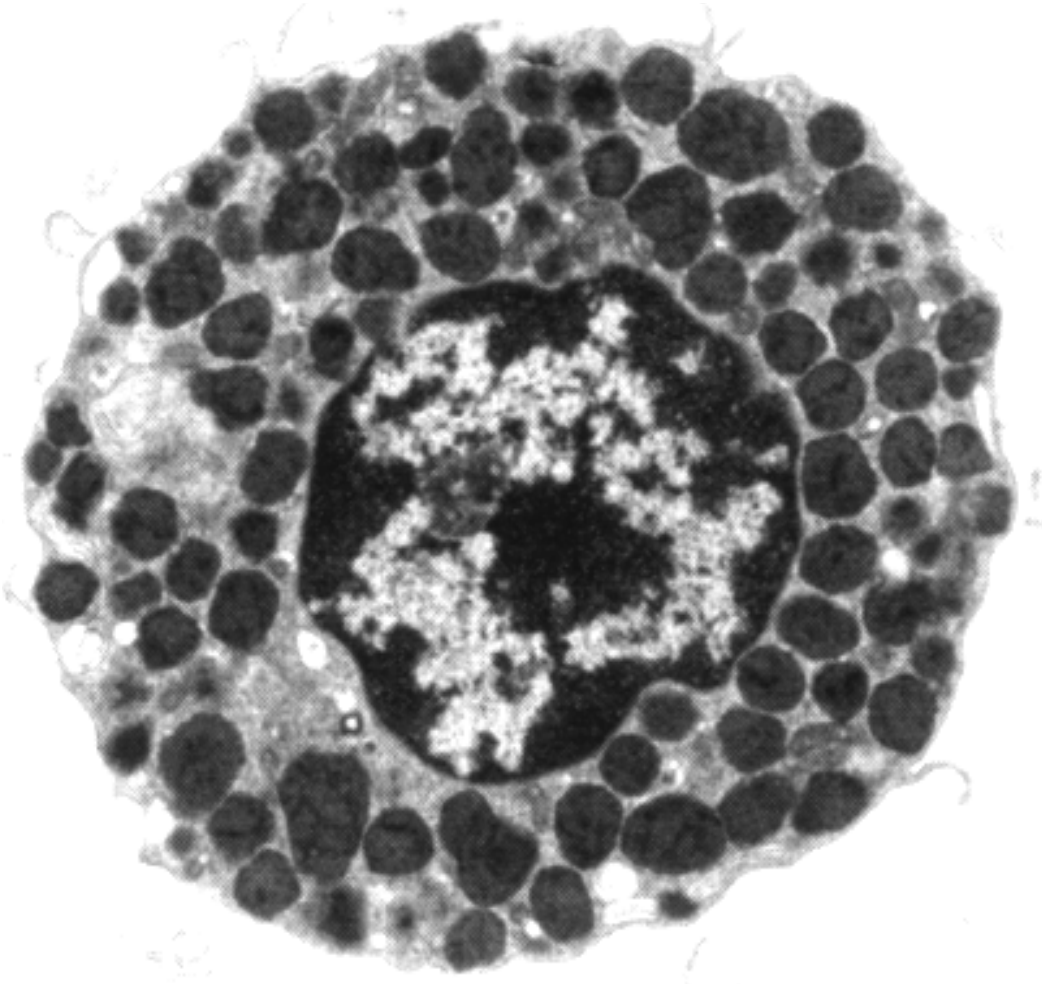


TABLE 20.1 Properties of Mast Cells, Basophils, and Eosinophils

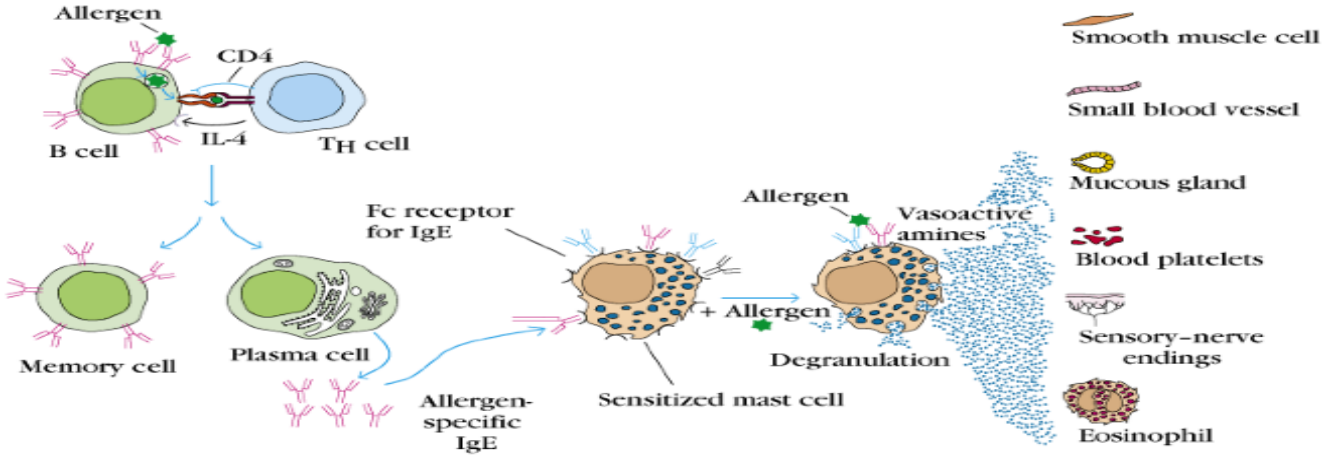
Characteristic	Mast Cells	Basophils	Eosinophils
Major site of maturation	Bone marrow precursors mature in connective tissue and mucosal tissues	Bone marrow	Bone marrow
Location of cells	Connective tissue and mucosal tissues	Blood (~0.5% of blood leukocytes); recruited into tissues	Blood (~2% of blood leukocytes); recruited into tissues
Life span	Weeks to months	Days	Days to weeks
Major growth and differentiation factor (cytokines)	Stem cell factor, IL-3	IL-3	IL-5
Expression of FcεRI	High	High	Low
Major granule contents	Histamine, heparin and/or chondroitin sulfate, proteases	Histamine, chondroitin sulfate, protease	Major basic protein, eosinophil cationic protein, peroxidases, hydrolases, lysophospholipase

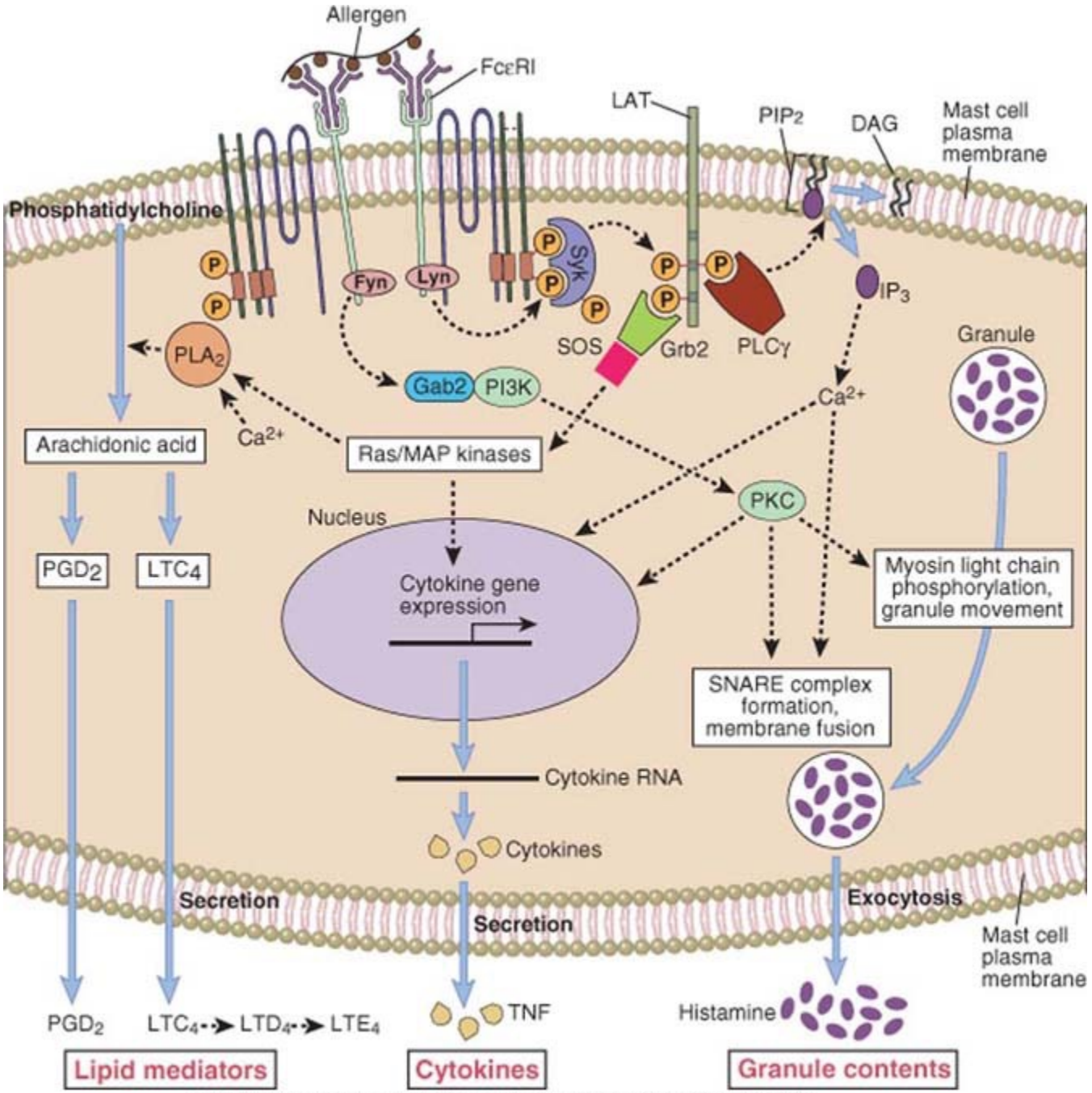
FcεRI, Fcε receptor type I; *IL*, interleukin.

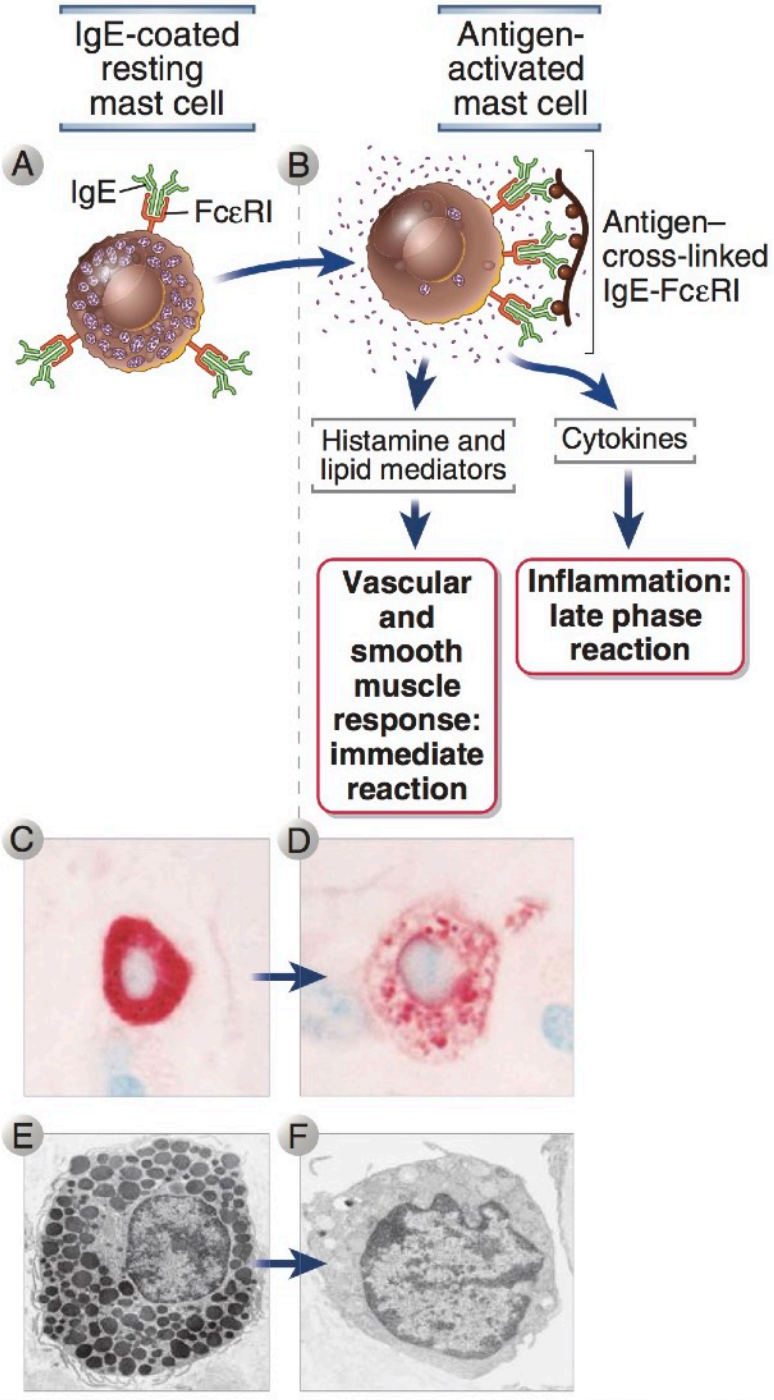
Antibody Isotope	Isotype-specific effector functions
IgG	- Opsonization of antigens for phagocytosis by macrophages and neutrophils - Activation of the classical pathway of complement - Antibody-dependent cell-mediated cytotoxicity mediated by natural killer cells - Neonatal immunity: transfer of maternal antibody across the placenta and gut - Feedback inhibition of B cell activation
IgM	- Activation of the classical pathway of complement - Antigen receptor of naive B lymphocytes
IgA	- Mucosal immunity: secretion of IgA into the lumens of the gastrointestinal and respiratory tracts - Activation of complement by the lectin pathway or by the alternative pathway
IgE	Mast cell degranulation (immediate hypersensitivity reactions)
IgD	Antigen receptor of naive B lymphocytes

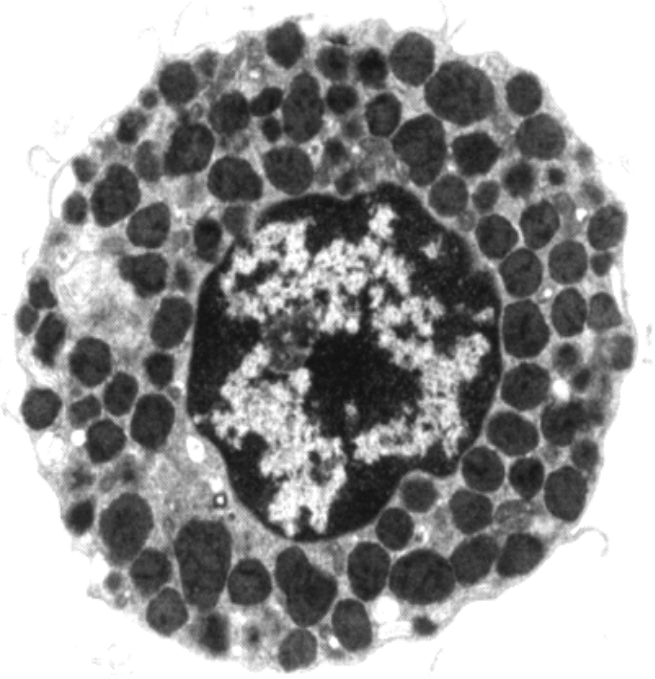
What is the sequence of events in an IgE-mediated hypersensitive response?

1. The plasma cells secrete IgE.
2. These IgE bind to Fc receptors on sensitized mast cells and blood basophils.
3. When the allergen appears again it cross-links the mIgEs and causes degranulation, releasing granules.
4. Mediators within these granules act on the surrounding tissues such as smooth muscle, small blood vessels, and mucous glands.

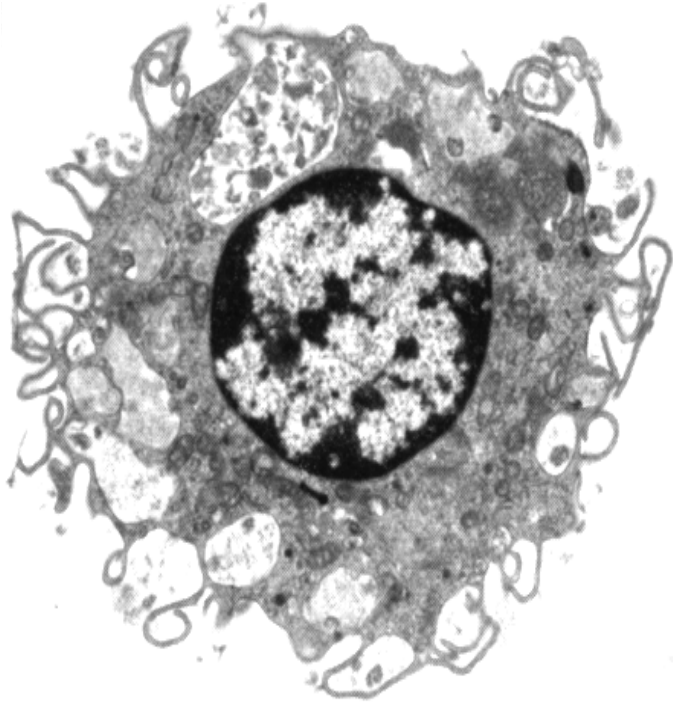





IgE-coated resting mast cell
Antigen-activated mast cell
A
IgE
FcεRI
B
Antigen–cross-linked IgE-FcεRI
Histamine and lipid mediators
Cytokines
Vascular and smooth muscle response: immediate reaction
Inflammation: late phase reaction
C
D
E
F



Resting Mast cell

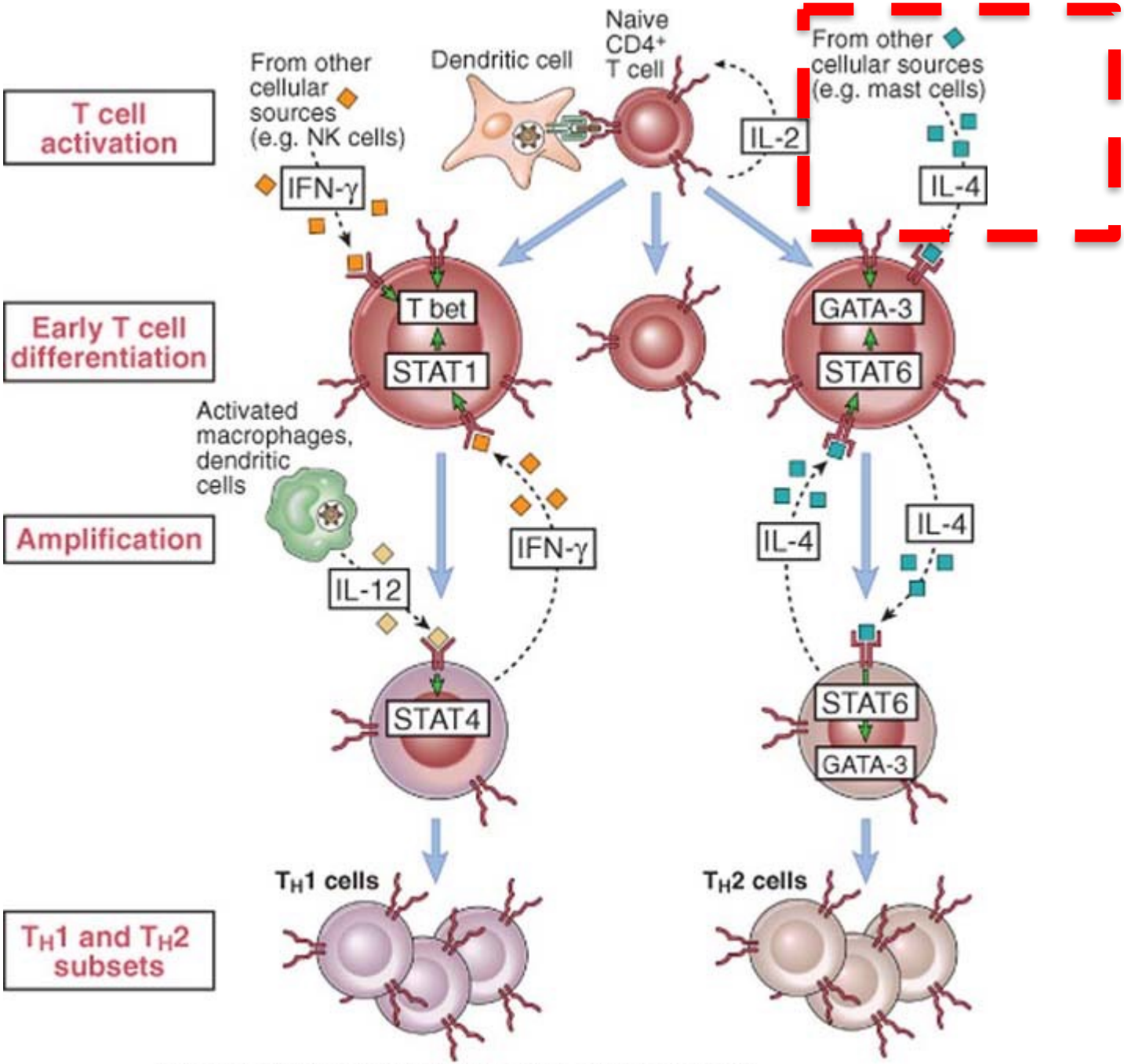


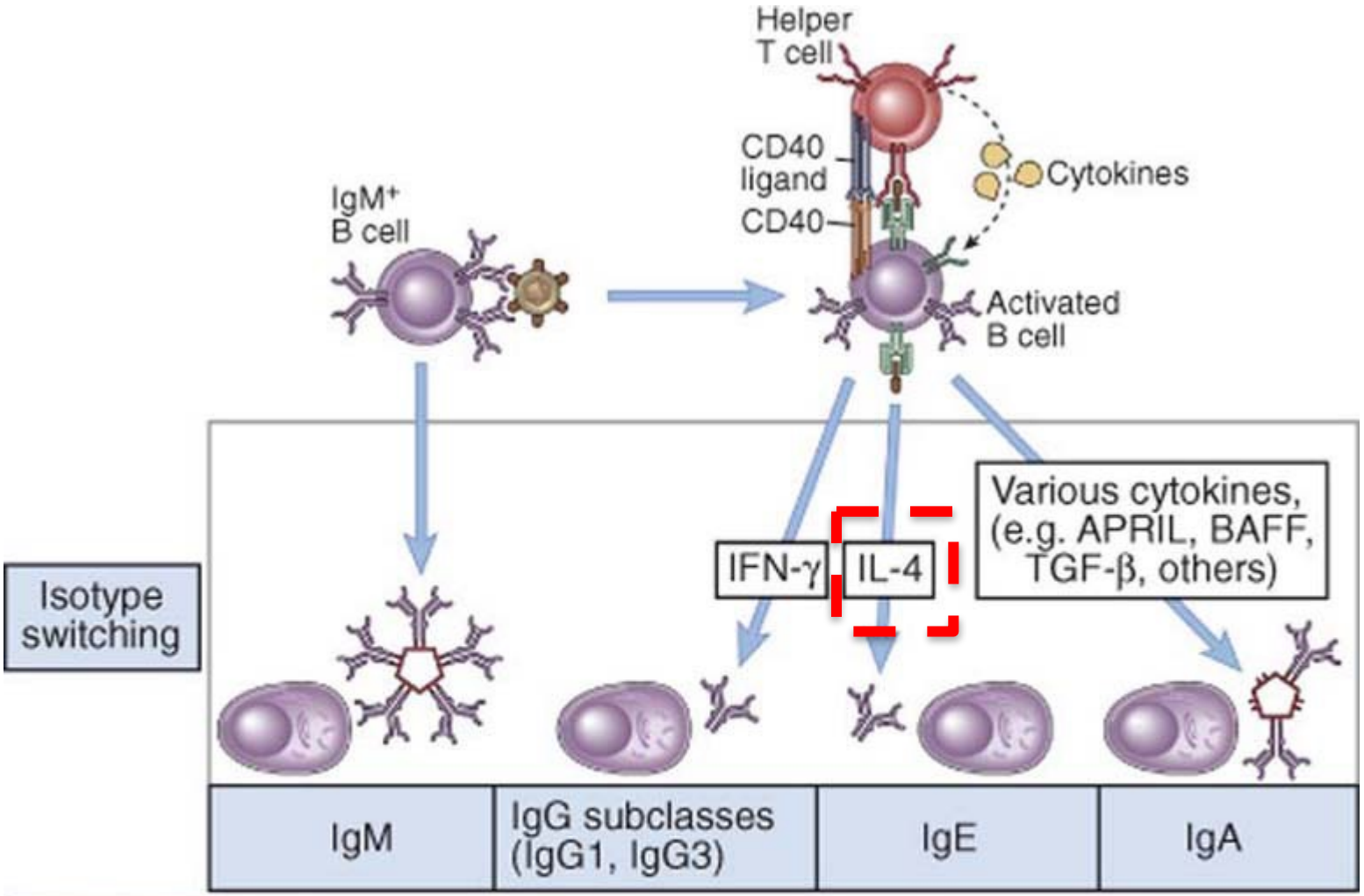
Degranulated mast cell

TABLE 20.2 Mediators Produced by Mast Cells, Basophils, and Eosinophils

Cell Type	Mediator Category	Mediator	Function/Pathologic Effects
Mast Cells and Basophils			
	Stored preformed in cytoplasmic granules	Histamine	Increase vascular permeability; stimulate smooth muscle cell contraction
		Enzymes: neutral proteases (tryptase and/or chymase), acid hydrolases, cathepsin G, carboxypeptidase	Degradation of microbial structures; tissue damage/remodeling
	Major lipid mediators produced on activation	PGD_2	Vasodilation; bronchoconstriction; leukocyte chemotaxis
		Leukotrienes C_4, D_4, E_4	Prolonged bronchoconstriction; mucus secretion; increased vascular permeability
		PAF	Vasodilation; increased vascular permeability; leukocyte adhesion, chemotaxis, degranulation, oxidative burst
	Cytokines produced on activation	IL-3, TNF, MIP-1α	Mast cell proliferation; inflammation (late-phase reaction)
		IL-4, IL-13	IgE production; mucus secretion
		IL-5	Eosinophil production and activation
Eosinophils			
	Stored preformed in cytoplasmic granules	Major basic protein, eosinophil cationic protein	Toxic to helminths, bacteria, host cells
		Eosinophil peroxidase, lysosomal hydrolases, lysophospholipase	Degradation of helminthic and protozoan cell walls; tissue damage/remodeling
	Major lipid mediators produced on activation	Leukotrienes C_4, D_4, E_4	Prolonged bronchoconstriction; mucus secretion; increased vascular permeability
	Cytokines produced on activation	IL-3, IL-5, GM-CSF	Eosinophil production and activation
		IL-8, IL-10, RANTES, MIP-1α, eotaxin	Chemotaxis of leukocytes

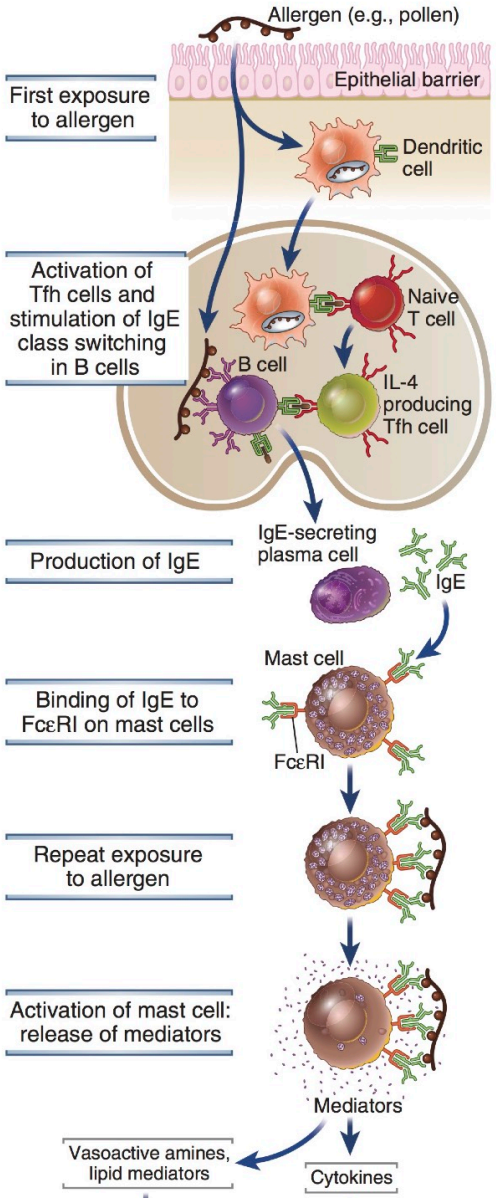
FcεRI, Fcε receptor type I; *GM-CSF,* granulocyte-monocyte colony-stimulating factor; *MIP-1α,* monocyte inflammatory protein 1α; *PAF,* platelet-activating factor; *PGD_2,* prostaglandin D2; *RANTES,* regulated by activation, normal T cell expressed and secreted; *TNF,* tumor necrosis factor.





	IgM	IgG subclasses (IgG1, IgG3)	IgE	IgA
Principal effector functions	Complement activation	Fc receptor-dependent phagocyte responses; complement activation; neonatal immunity (placental transfer)	Immunity against helminths Mast cell degranulation (immediate hypersensitivity)	Mucosal immunity (transport of IgA through epithelia)

FIGURE 20.1 Sequence of events in immediate hypersensitivity reactions. Immediate hypersensitivity diseases are initiated by the introduction of an allergen, which stimulates IL-4–producing helper T cell responses and IgE production. IgE sensitizes mast cells by binding to FcεRI, and subsequent exposure to the allergen activates the mast cells to secrete the mediators that are responsible for the pathologic reactions of immediate hypersensitivity.



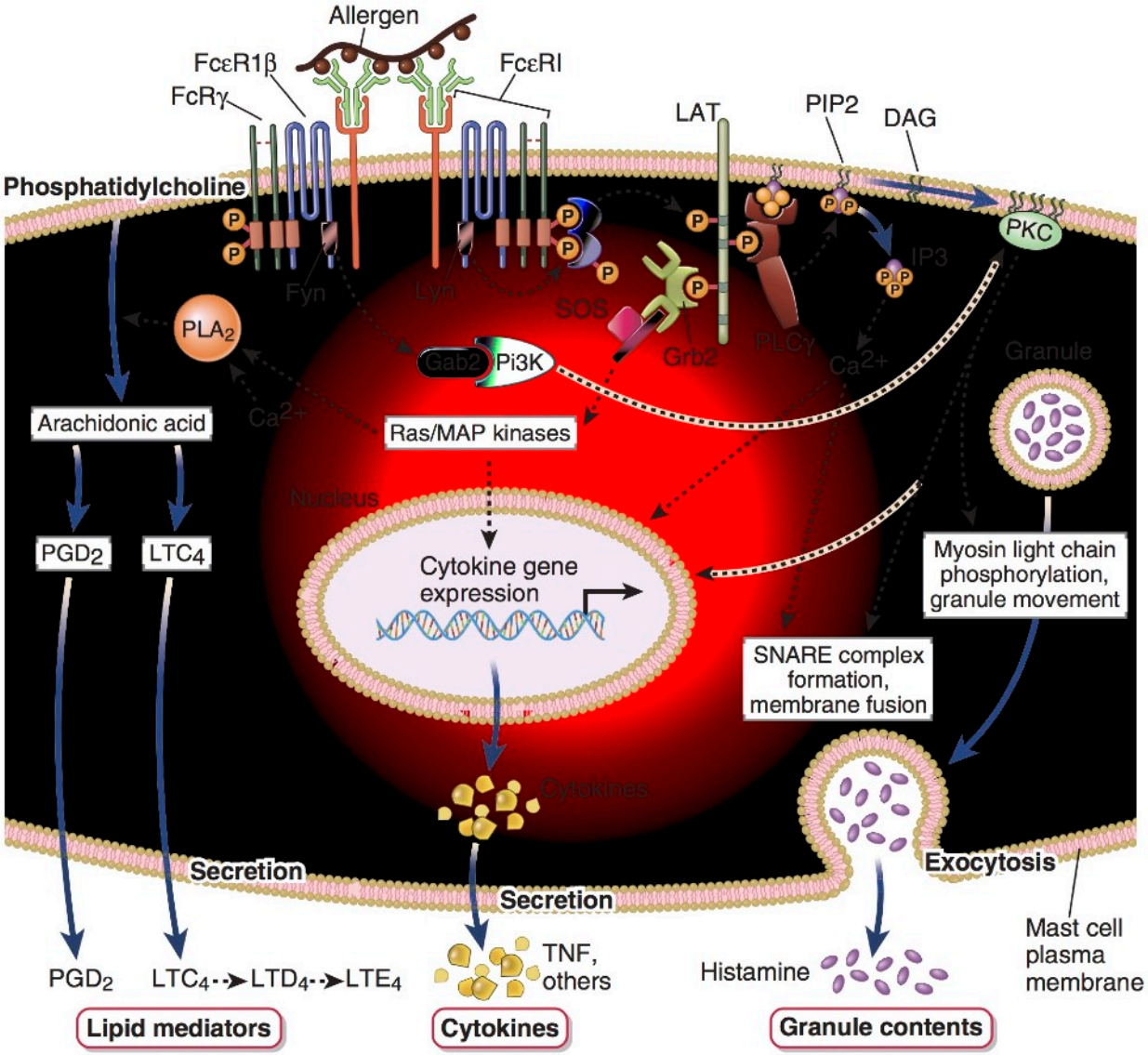
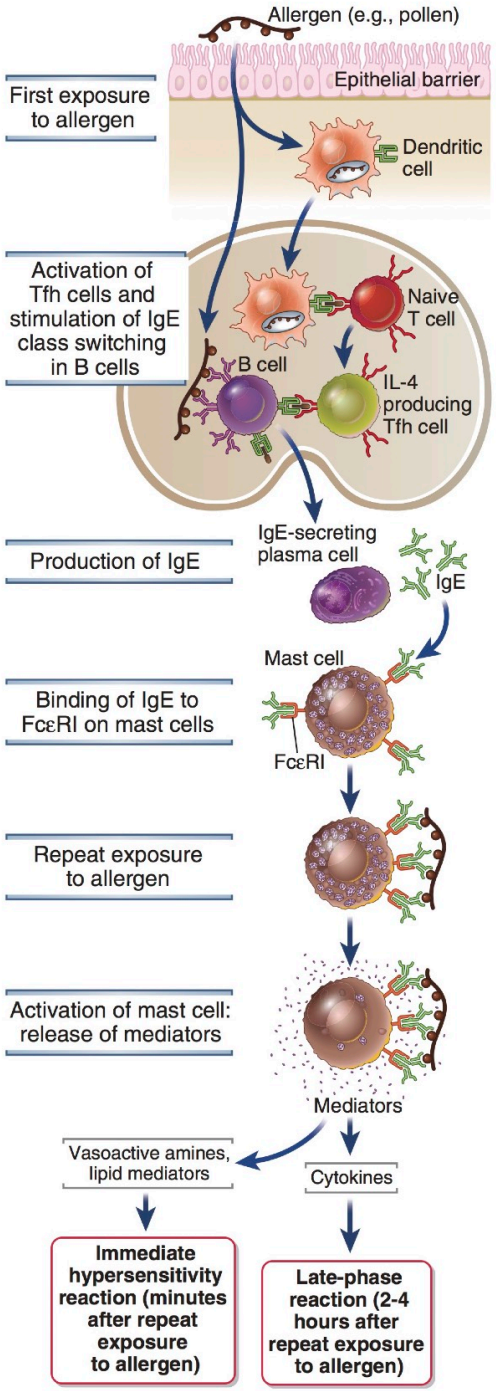
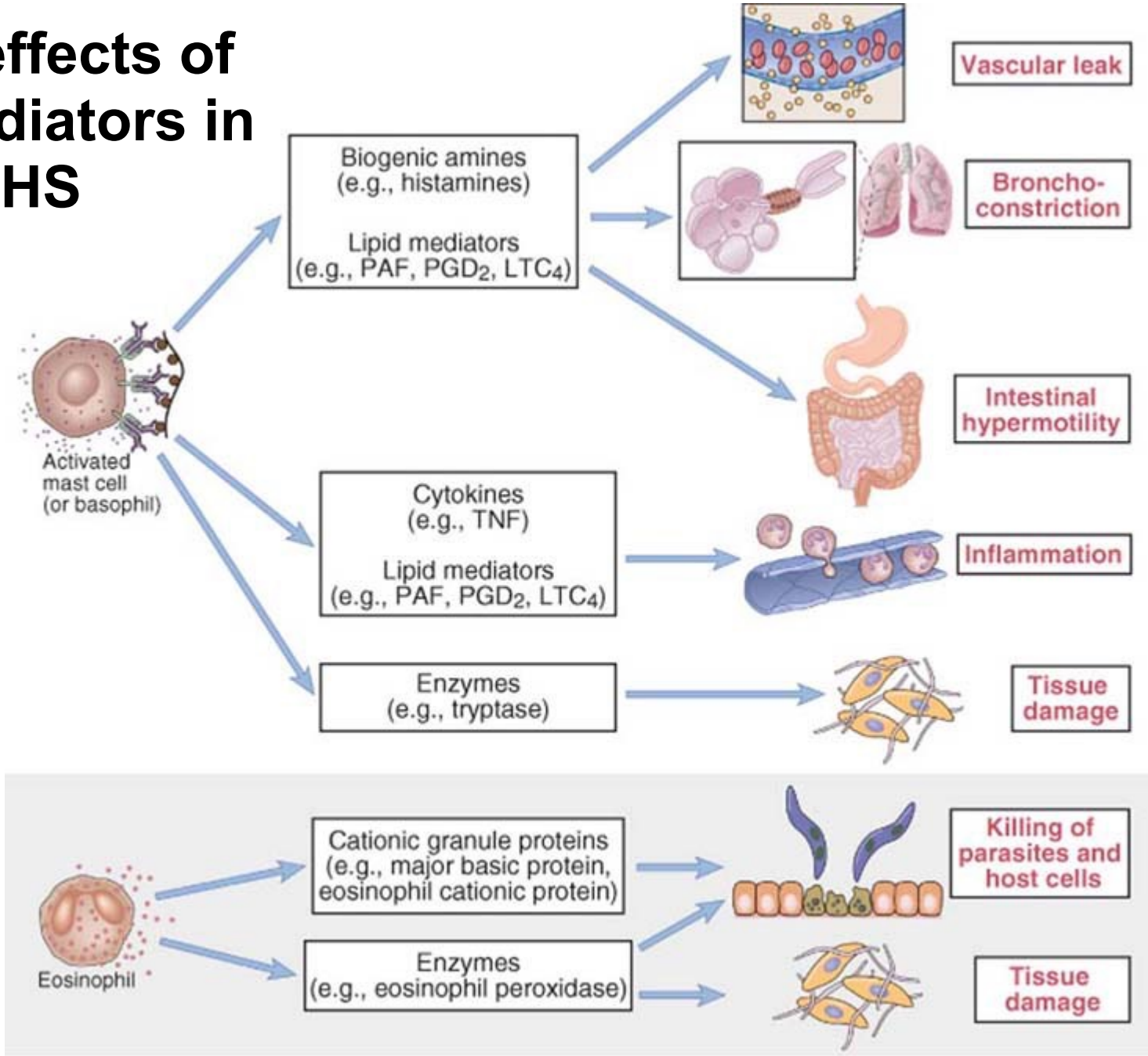


FIGURE 20.5 Biochemical events of mast cell activation. Cross-linking of bound IgE by antigen activates protein tyrosine kinases (Syk and Lyn), which in turn cause activation of a MAP kinase cascade and phospholipase Cγ (PLCγ). PLCγ catalyzes the release of IP3 and DAG from membrane PIP2. IP3 causes release of intracellular calcium from the endoplasmic reticulum. Calcium and DAG activate PKC. Calcium, MAP kinases, and PKC promote cytokine gene transcription, leading to secretion of cytokines. PKC and calcium also enhance granule exocytosis, releasing histamine and other preformed mediators. Calcium and MAP kinases combine to activate the enzyme cytosolic PLA_2, which initiates the synthesis of lipid mediators, including prostaglandin D_2 (PGD_2) and leukotriene C_4 (LTC_4).

FIGURE 20.1 Sequence of events in immediate hypersensitivity reactions. Immediate hypersensitivity diseases are initiated by the introduction of an allergen, which stimulates IL-4–producing helper T cell responses and IgE production. IgE sensitizes mast cells by binding to FcεRI, and subsequent exposure to the allergen activates the mast cells to secrete the mediators that are responsible for the pathologic reactions of immediate hypersensitivity.



Biological effects of different mediators in type I HS



Mast cell activation affects many tissues

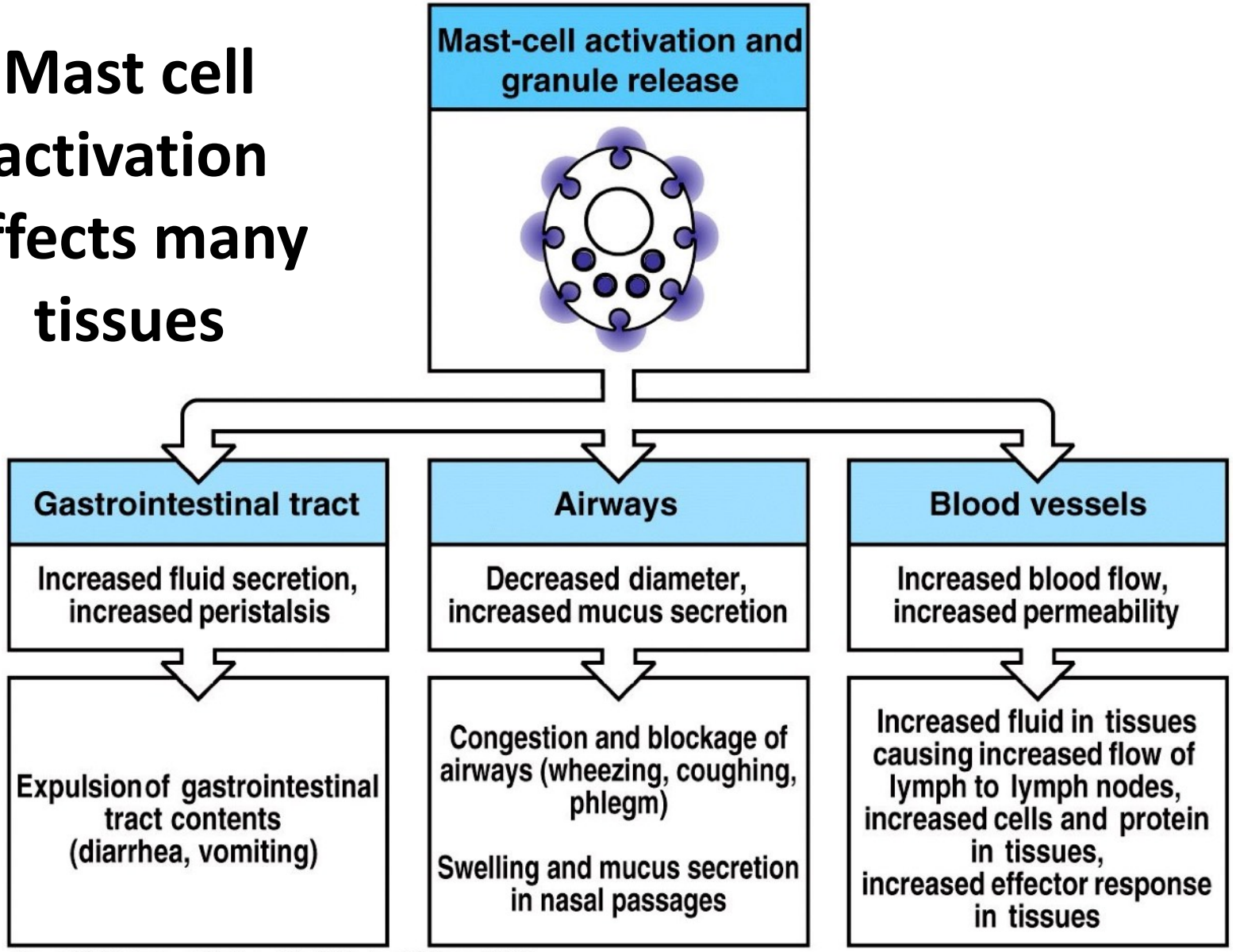


Figure 12-11 Immunobiology, 6/e. (© Garland Science 2005)

Take-home messages on mast cells:

- Located in nearly all vascularized peripheral tissues
- Contain many packets of membrane-bound granule, ready for release upon activation by an allergen
- Can also release cytokines (thus they wear multiple immunological hats)

…and their Fc receptors…

- High affinity receptor FcRI binds to IgE at extremely low serum concentrations (1×10^{-7} M). This receptor has ITAM as its cytosolic domain, thus it can initiate the process of degranulation via tyrosine phosphorylation.

Of course, these effects can be good…

- Vasodilation and increased vascular permeability usher in plasma and inflammatory cells (such as esinophils, neutrophils) to attack the pathogen

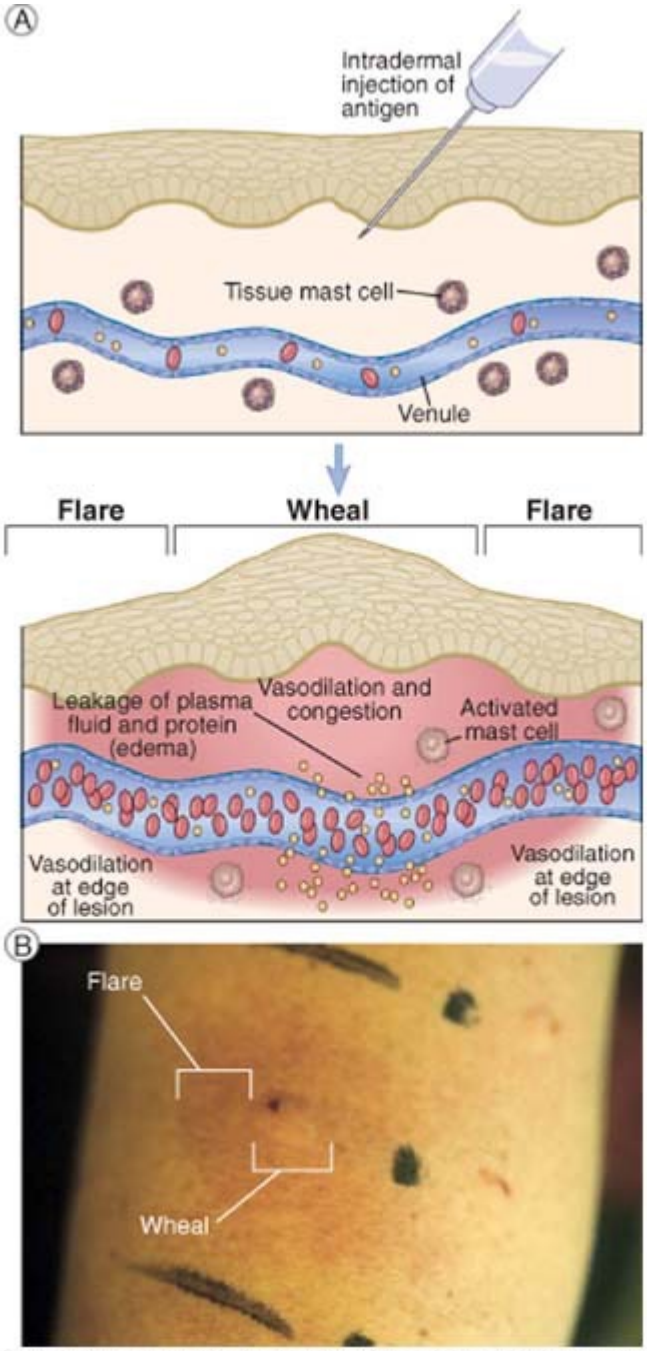
However, when these effects go overboard, the result is problematic:

- Anaphylactic shock – extreme smooth muscle contraction compromises control of the bladder and GI tract and causes bronchiole constriction
- Allergic rhinitis – excess mucous is released. More commonly known as hay fever, this ailment affects 10% of the US population
- Food allergies – a variety of symptoms
- Asthma – bronchoconstriction and excess mucous

TABLE 19.1 Classification of Hypersensitivity Diseases

Type of Hypersensitivity	Pathologic Immune Mechanisms	Mechanisms of Tissue Injury and Disease
Immediate: Type I	IgE antibody, Th2 cells	Mast cells, eosinophils, and their mediators (vasoactive amines, lipid mediators, cytokines)
Antibody-mediated: Type II	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, for example, hormone receptor signaling, neurotransmitter receptor blockade
Immune complex–mediated: Type III	Immune complexes of circulating antigens and IgM or IgG antibodies	Complement- and Fc receptor–mediated recruitment and activation of leukocytes
T cell–mediated: Type IV	1. $CD4^+$ T cells (Th1 and Th17 cells) 2. $CD8^+$ CTLs	1. Cytokine-mediated inflammation and macrophage activation 2. Direct target cell killing, cytokine-mediated inflammation

CTLs, Cytotoxic T lymphocytes; *Ig,* immunoglobulin.



And just look at all these popular allergens!

TABLE 16-1 COMMON ALLERGENS ASSOCIATED WITH TYPE I HYPERSENSITIVITY

Proteins
- Foreign serum
- Vaccines

Plant pollens
- Rye grass
- Ragweed
- Timothy grass
- Birch trees

Drugs
- Penicillin
- Sulfonamides
- Local anesthetics
- Salicylates

Foods
- Nuts
- Seafood
- Eggs
- Peas, beans
- Milk

Insect products
- Bee venom
- Wasp venom
- Ant venom
- Cockroach calyx
- Dust mites

Mold spores

Animal hair and dander

What's available in the Western medicine arsenal of drugs?

- Anti-histamines – block the binding of histamine on target cells
- Immunotherapy – treat the patient with increasing doses of the allergen (hyposensitization) to reduce severity of the response.

Treatment approaches for IgE-mediated Allergy

Target step	Mechanism of treatment	Specific approach
T_H2 activation	Reverse T_H2/T_H1 balance	Injection of specific antigen or peptides Administration of cytokines, eg, IFN-γ, IL-10, IL-12, TGF-β Use of adjuvants such as CpG oligodeoxynucleotides to stimulate T_H1 response
Activationof B cell to produce IgE	Block co-stimulation Inhibit T_H2 cytokines	Inhibit CD40L Inhibit IL-4 or IL-13
Mast-cell activation	Inhibit effects of IgE binding to mast cell	Blockade of IgE receptor
Mediator action	Inhibit effects of mediators on specific receptors Inhibit synthesis of specific mediators	Antihistamine drugs Lipoxygenase inhibitors
Eosinophil-dependent inflammation	Block cytokine and chemokine receptors that mediate eosinophil recruitment and activation	Inhibit IL-5 Block CCR3

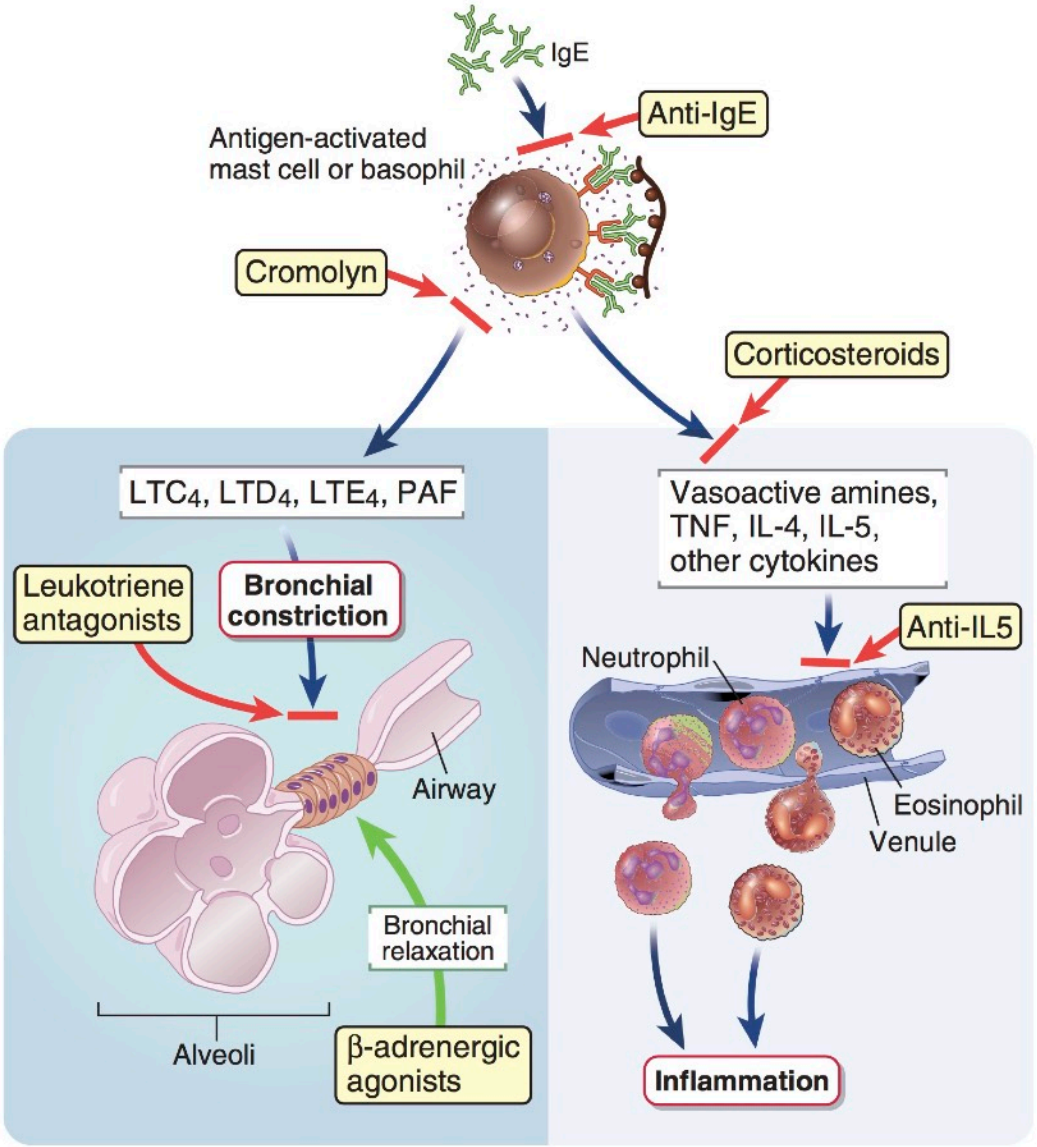
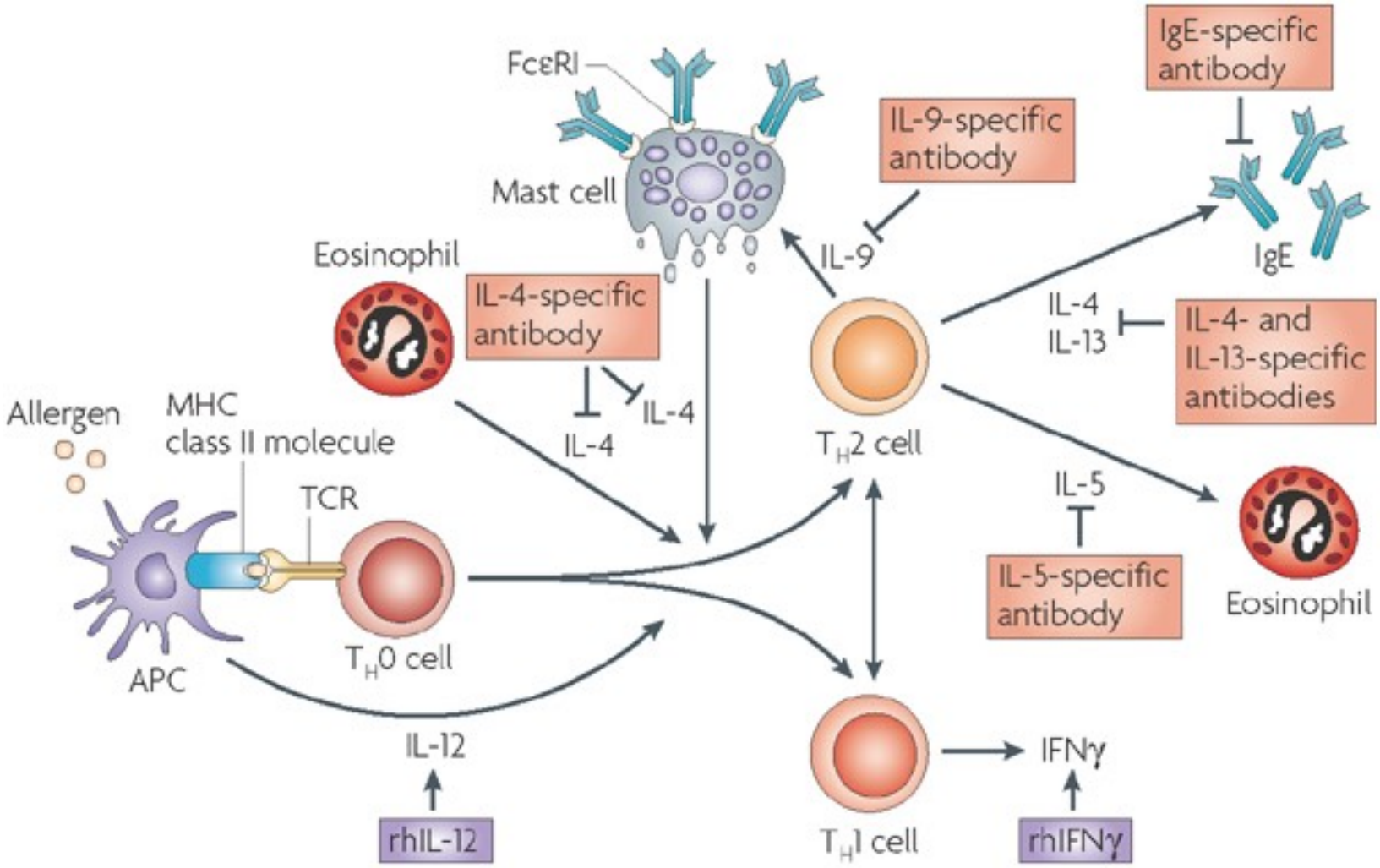


FIGURE 20.10 Mediators and treatment of asthma. Mast cell–derived leukotrienes and PAF are thought to be the major mediators of acute bronchoconstriction. Therapy is targeted both at reducing mast cell activation with anti-IgE, mast cell degranulation with inhibitors such as cromolyn and at countering mediator actions on bronchial smooth muscle by leukotriene antagonists and bronchodilators such as inhaled β-adrenergic receptor agonists. Mast cell–derived cytokines are thought to be the major mediators of sustained airway inflammation, which is an example of a late-phase reaction; corticosteroid therapy is used to inhibit cytokine synthesis, and antibodies are used block the actions of the cytokines. Cytokines are also produced by helper T cells *(not shown)*.



Nature Reviews | Immunology

What's available in the Western medicine arsenal of drugs?

- Anti-histamines – block the binding of histamine on target cells
- Immunotherapy – treat the patient with increasing doses of the allergen (hyposensitization) to reduce severity of the response.

- **Or, PREVENTION, find another home for Fido, and don't eat those strawberries!**

The chemically active effectors within the granules released via degranulation are called mediators. This group includes:

- Histamines
- Leukotrienes
- Prostaglandins
- Cytokines

TABLE 16-3 PRINCIPAL MEDIATORS INVOLVED IN TYPE I HYPERSENSITIVITY

Mediator	Effects
Primary	
Histamine	Increased vascular permeability; smooth-muscle contraction
Serotonin	Increased vascular permeability; smooth-muscle contraction
Eosinophil chemotactic factor (ECF-A)	Eosinophil chemotaxis
Neutrophil chemotactic factor (NCF-A)	Neutrophil chemotaxis
Proteases	Bronchial mucus secretion; degradation of blood-vessel basement membrane; generation of complement split products
Secondary	
Platelet-activating factor	Platelet aggregation and degranulation; contraction of pulmonary smooth muscles
Leukotrienes (slow reactive substance of anaphylaxis, SRS-A)	Increased vascular permeability; contraction of pulmonary smooth muscles
Prostaglandins	Vasodilation; contraction of pulmonary smooth muscles; platelet aggregation
Bradykinin	Increased vascular permeability; smooth-muscle contraction
Cytokines	
IL-1 and TNF-α	Systemic anaphylaxis; increased expression of CAMs on venular endothelial cells
IL-2, IL-3, IL-4, IL-5, IL-6, TGF-β, and GM-CSF	Various effects (see Table 12-1)