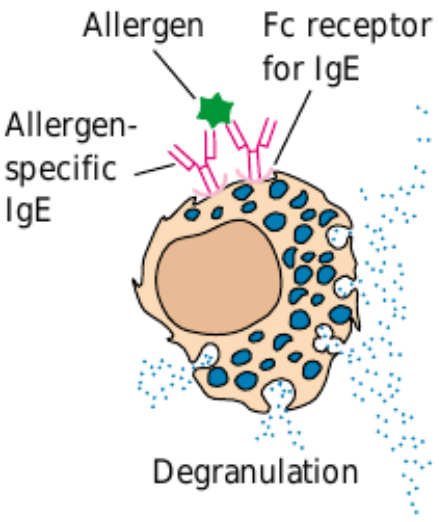
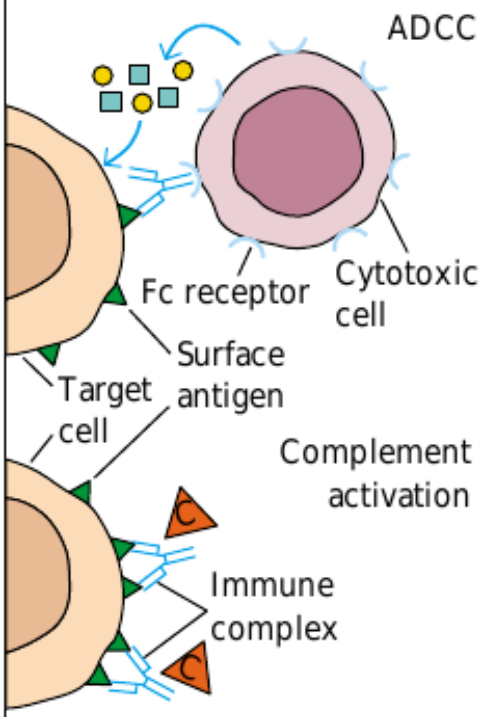
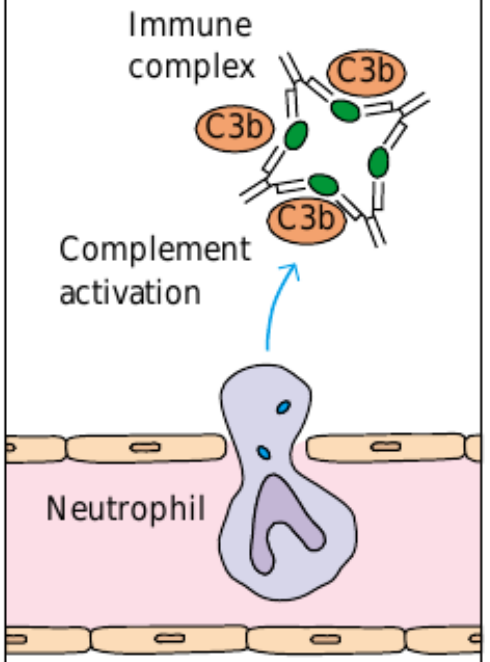
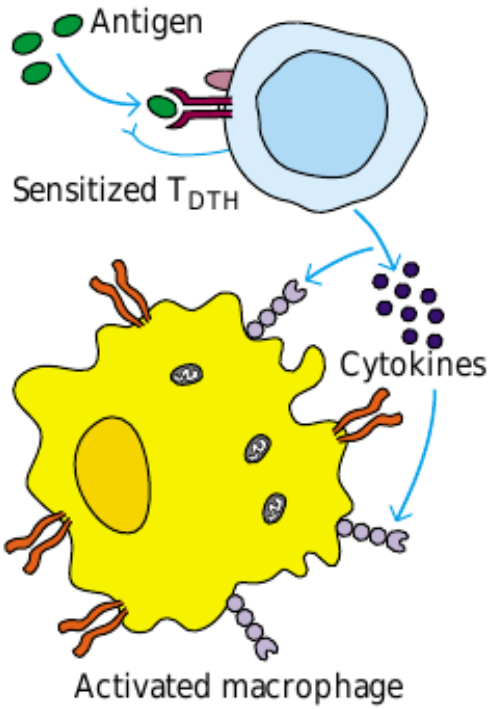
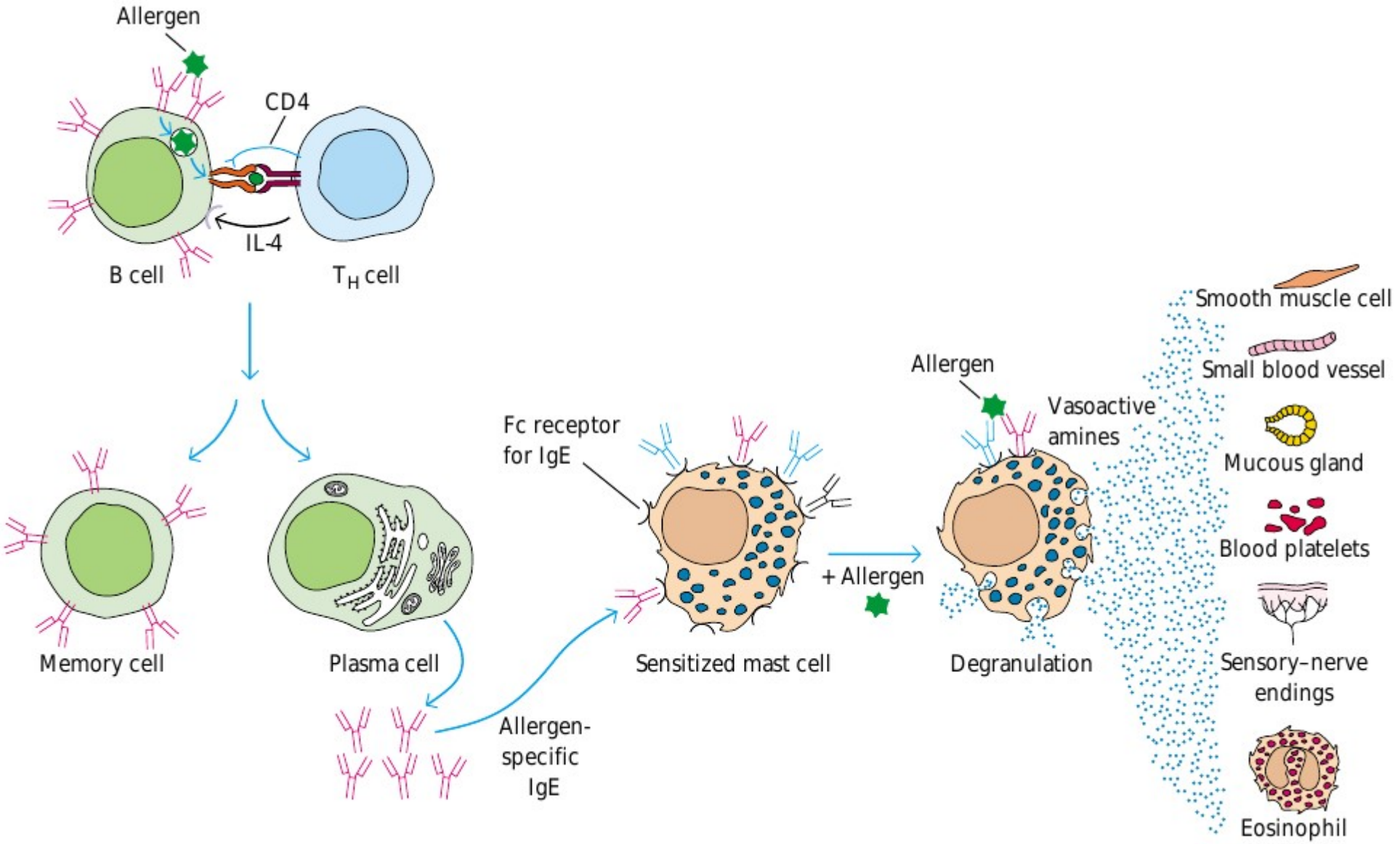
 **Type I**	 **Type II**	 **Type III**	 **Type IV**
IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators	Ab directed against cell surface antigens meditates cell destruction via complement activation or ADCC	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils	Sensitized T_H1 cells release cytokines that activate macrophages or T_C cells which mediate direct cellular damage
Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema	Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia	Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulnephritis, rheumatoid arthritis, and systemic lupus erythematosus	Typical manifestations include contact dermatitis, tubercular lesions and graft rejection

Anaflaktik tip hipersensitivite – Tip I


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

Proteins
- Foreign serum
- Vaccines

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

Drugs
- Penicillin
- Sulfonamides
- Local anesthetics
- Salicylates

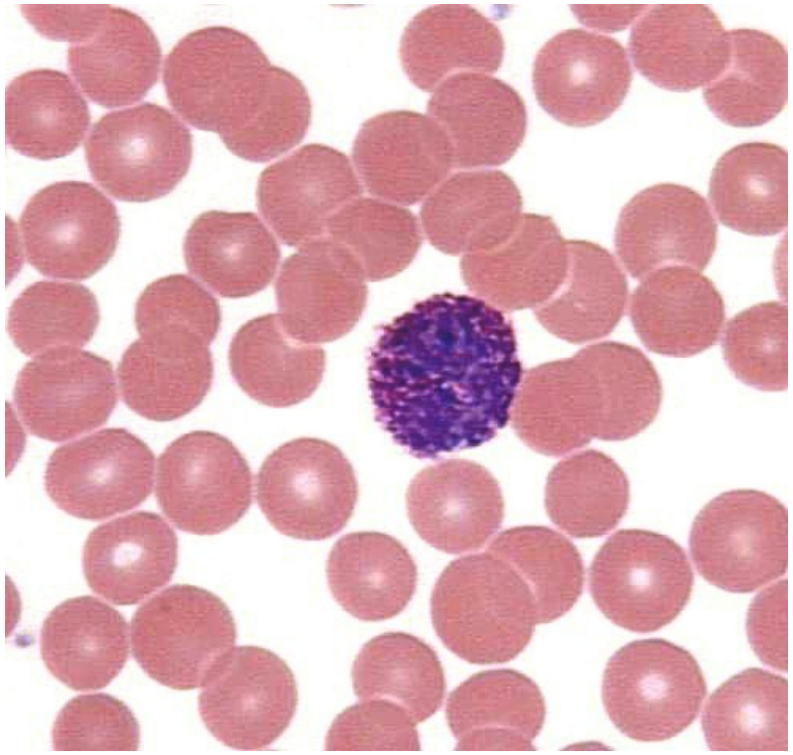
Foods
- Nuts
- Seafood
- Eggs
- Peas, beans
- Milk

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

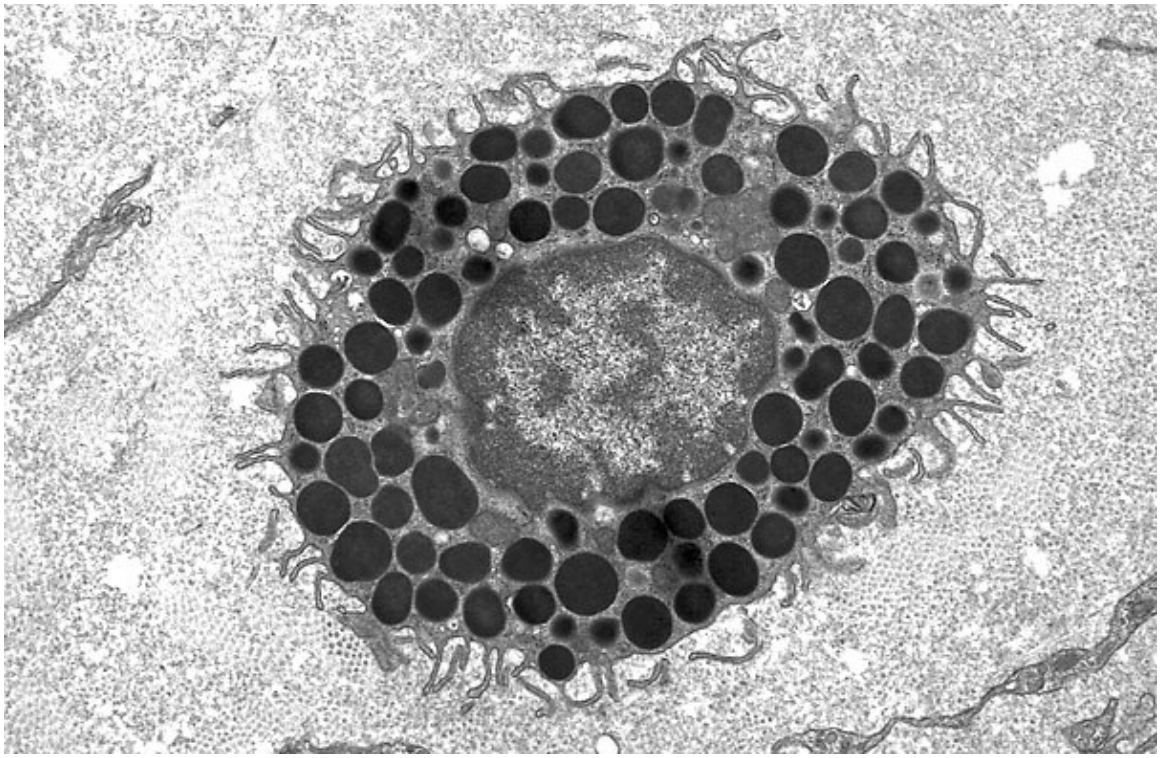
Mold spores

Animal hair and dander

Ortak prekürsör hücre: CD34+



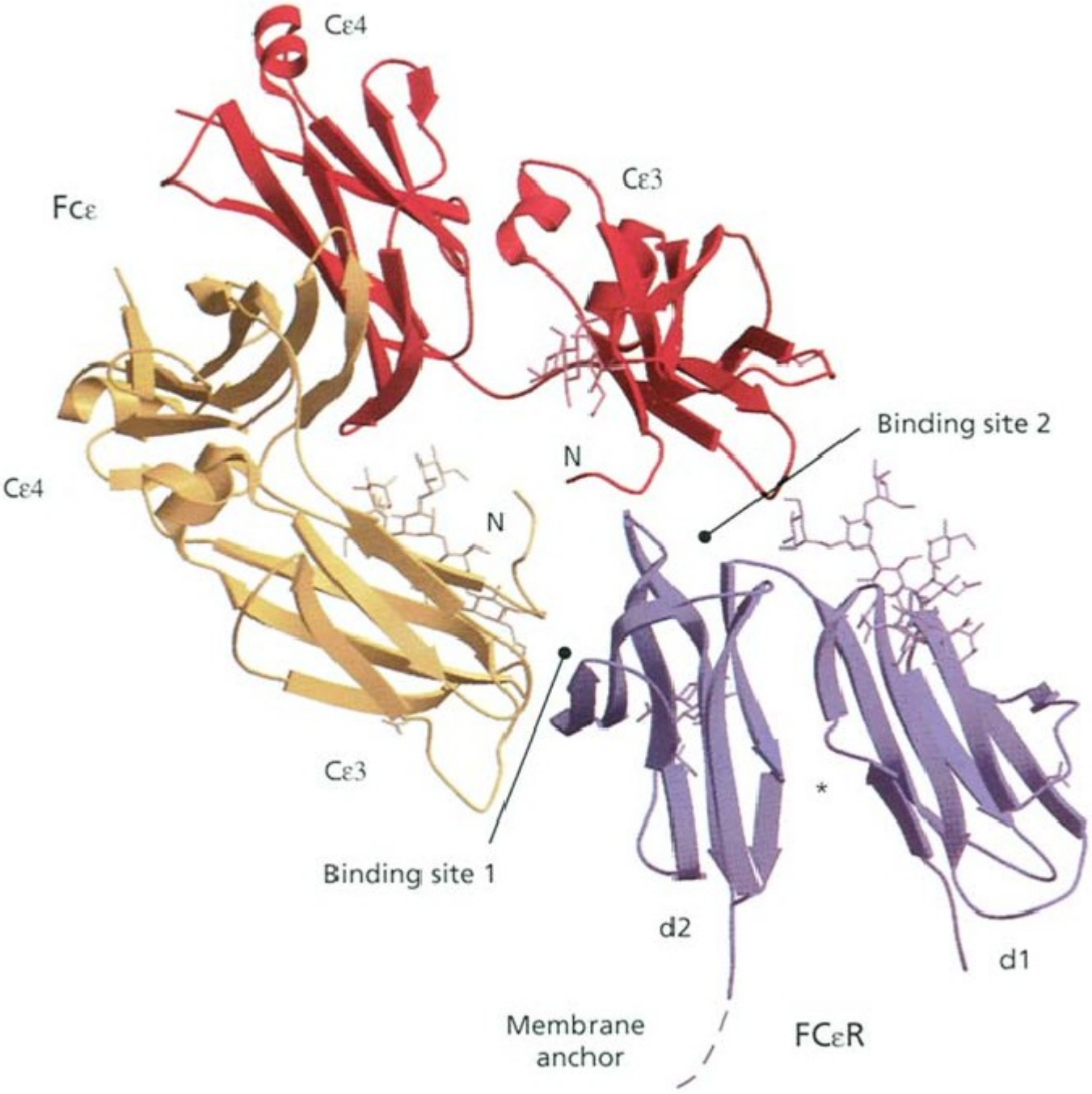
Bazofil

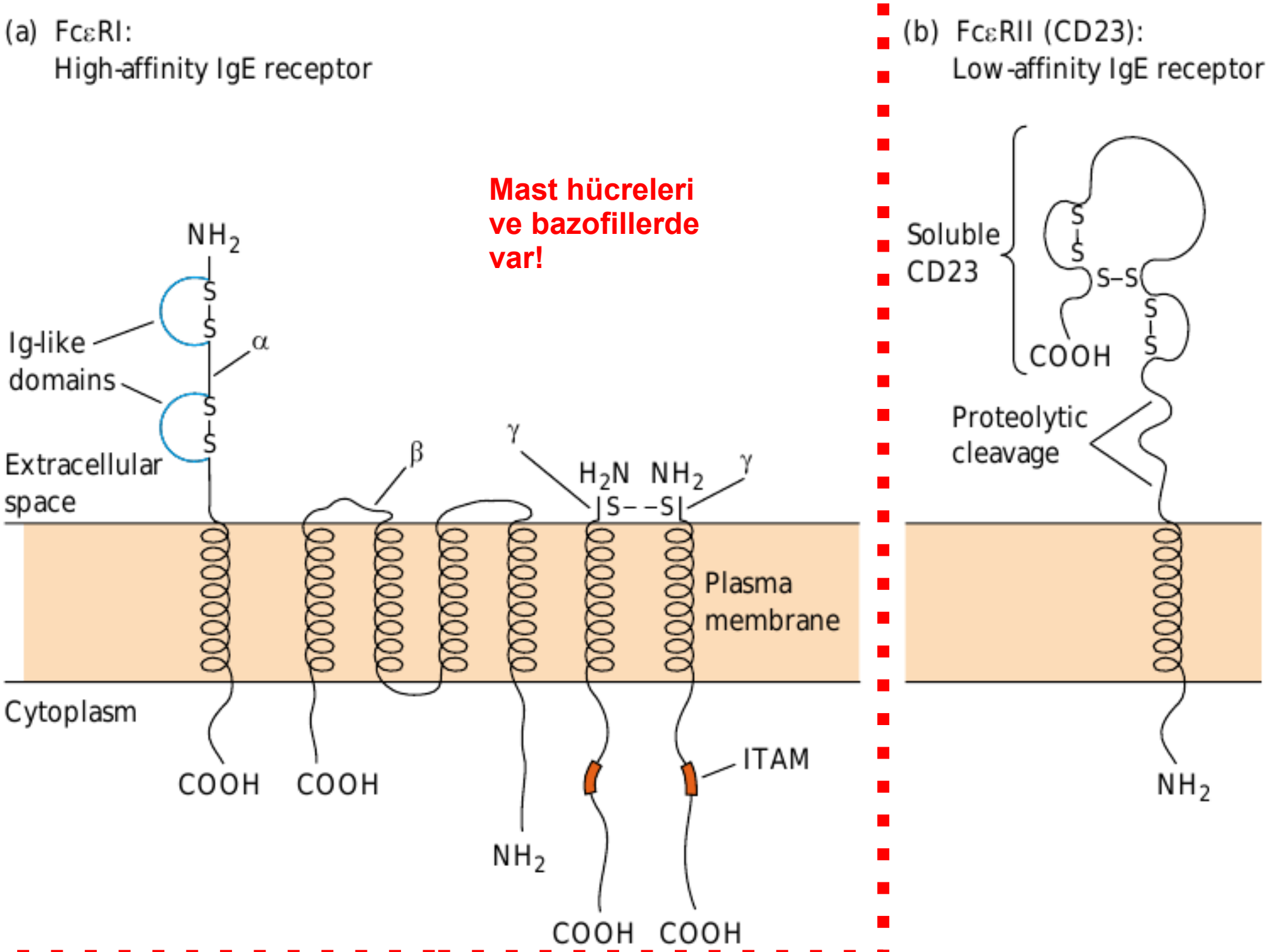


Mast hücresi

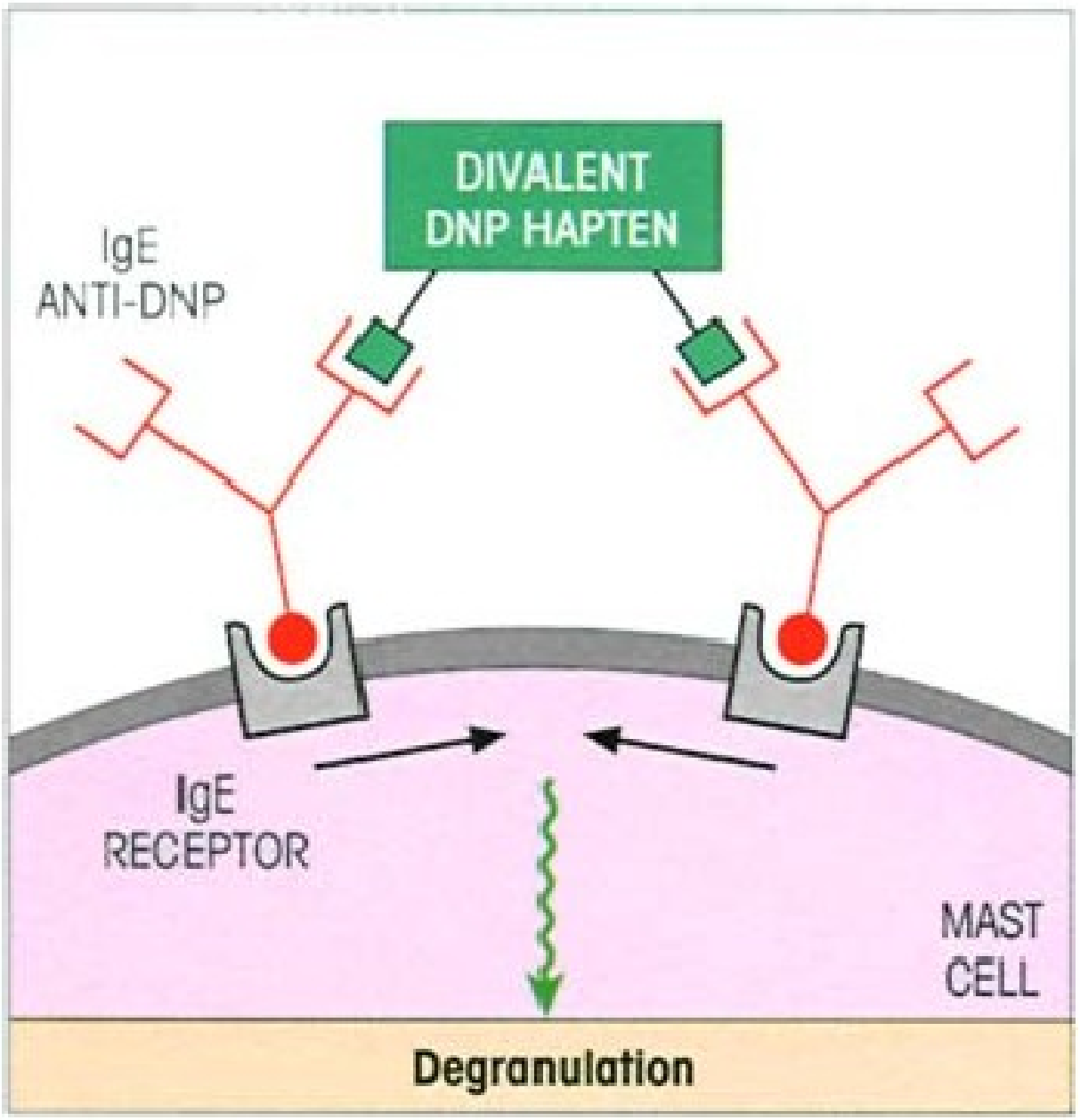
İki tip mast hücresi bulunmakta...

CHARACTERISTICS	MUCOSAL MAST CELL	CONNECTIVE TISSUE MAST CELL
GENERAL		
Abbreviation*	MC_t	MC_{tc}
Distribution	Gut & lung	Most tissues**
Differentiation favored by	IL-3	Fibroblast factor
T-cell dependence	+	–
High affinity Fcε receptor	2×10^5/cell	3×10^4/cell
GRANULES		
Alcian blue and Safranin staining	Blue & brown	Blue
Ultrastructure	Scrolls	Gratings/lattices
Protease	Tryptase	Tryptase & chymase
Proteoglycan	Chondroitin sulfate	Heparin
DEGRANULATION		
Histamine release	+	++
LTC_4: PGD_2 release	25 : 1	1 : 40
Blocked by disodium cromoglycate/theophylline	–	+


Cε4
Cε3
Fcε
Binding site 2
N
Cε4
N
Cε3
Binding site 1
*
d2
d1
Membrane
anchor
FCεR

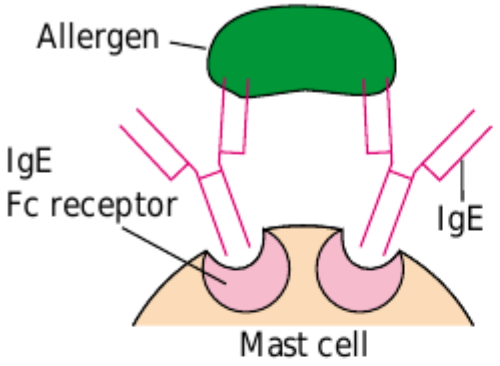

(a) FcεRI:
High-affinity IgE receptor
Mast hücreleri ve bazofillerde var!
NH2
Ig-like domains
α
Extracellular space
β
γ
H2N NH2
γ
S--S
Plasma membrane
Cytoplasm
COOH
COOH
NH2
ITAM
COOH
COOH
(b) FcεRII (CD23):
Low-affinity IgE receptor
Soluble CD23
S–S
COOH
Proteolytic cleavage
NH2

IgE reseptörlerinin kümelenmesi... veee çapraz bağlanması

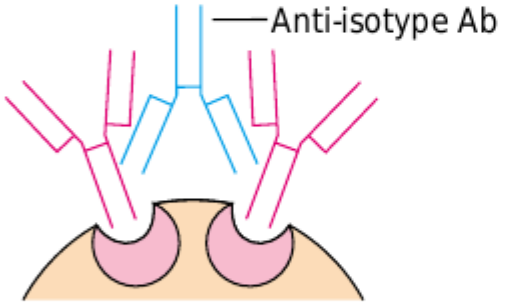


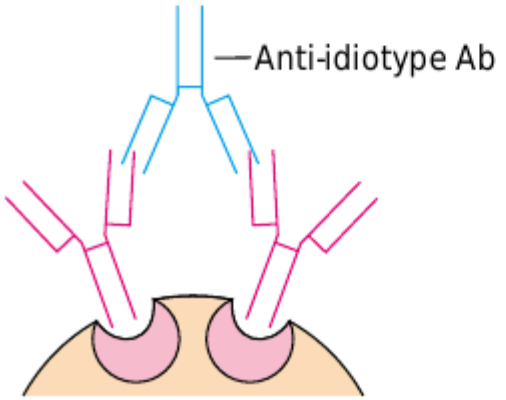
dimer < trimer < tetramer < ...

(a) Allergen crosslinkage of cell-bound IgE

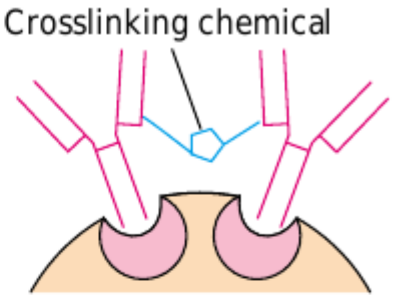


(b) Antibody crosslinkage of IgE

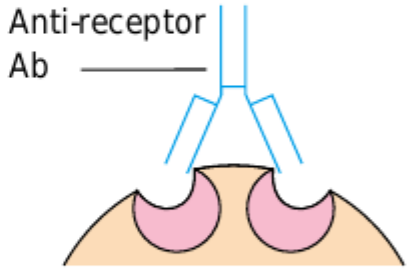




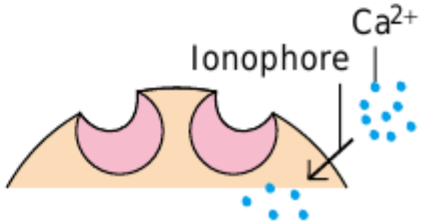
(c) Chemical crosslinkage of IgE

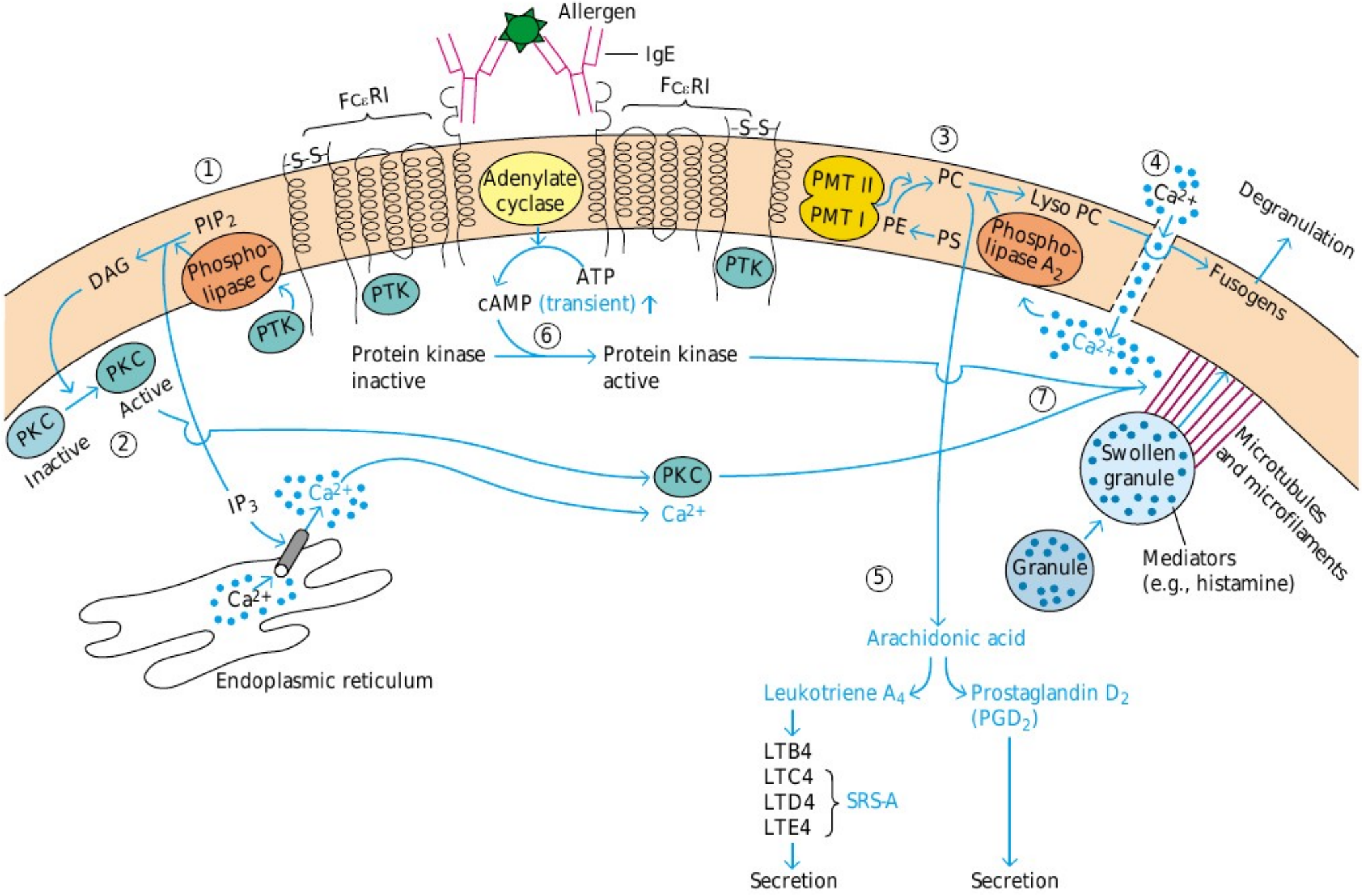


(d) Crosslinkage of IgE receptors by anti-receptor antibody

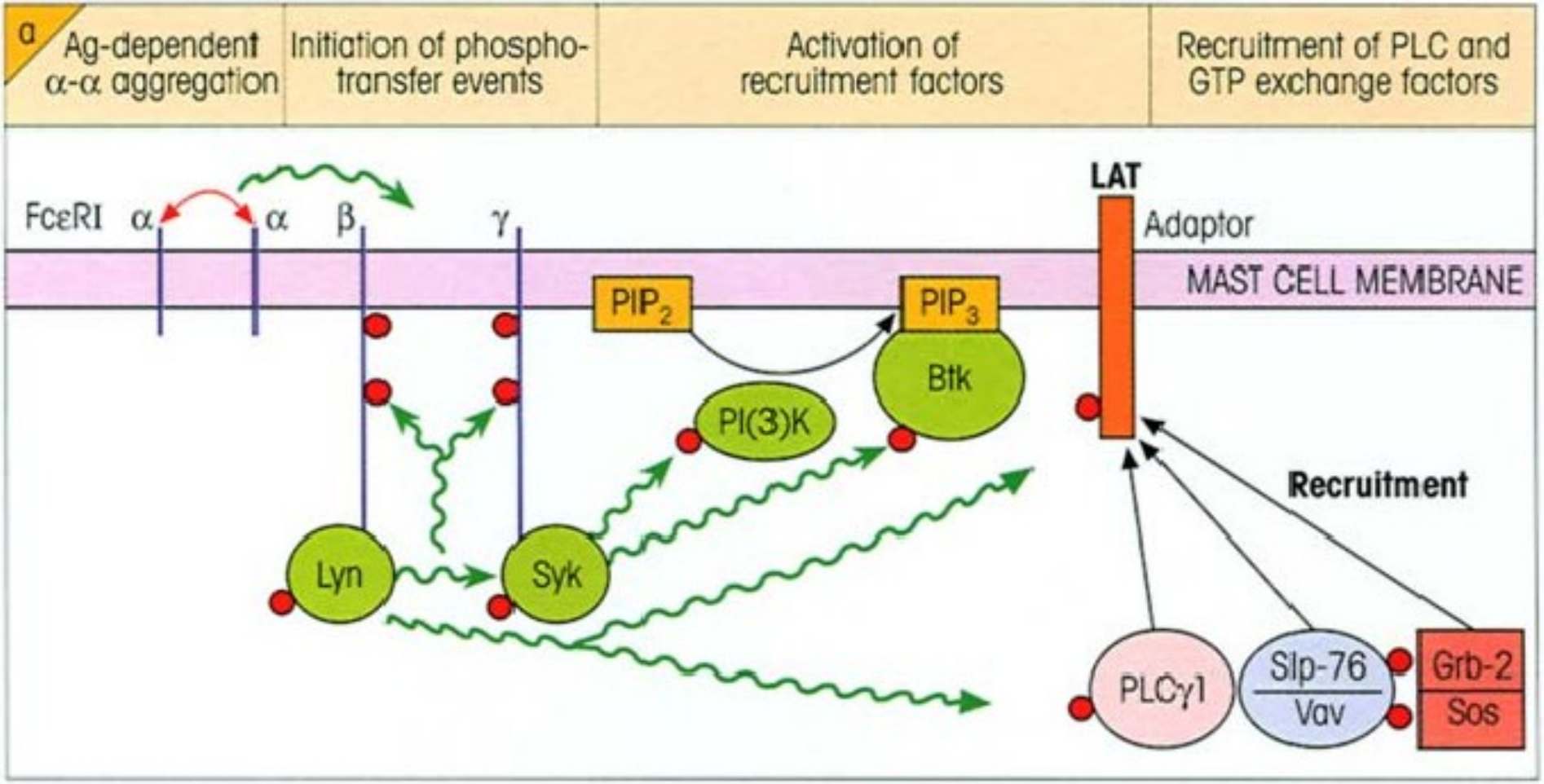


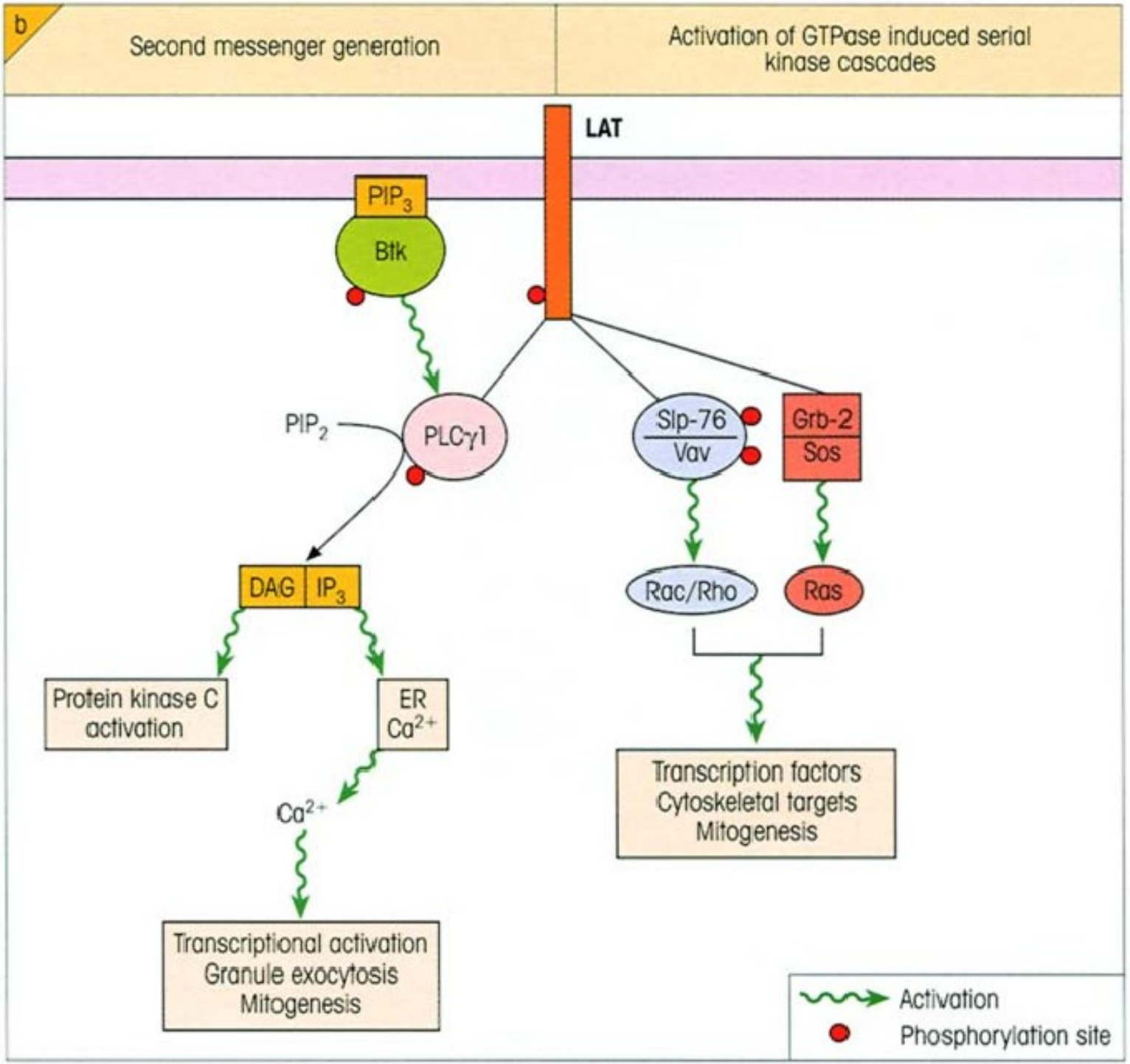
(e) Enhanced Ca^{2+} influx by ionophore that increases membrane permeability to Ca^{2+}

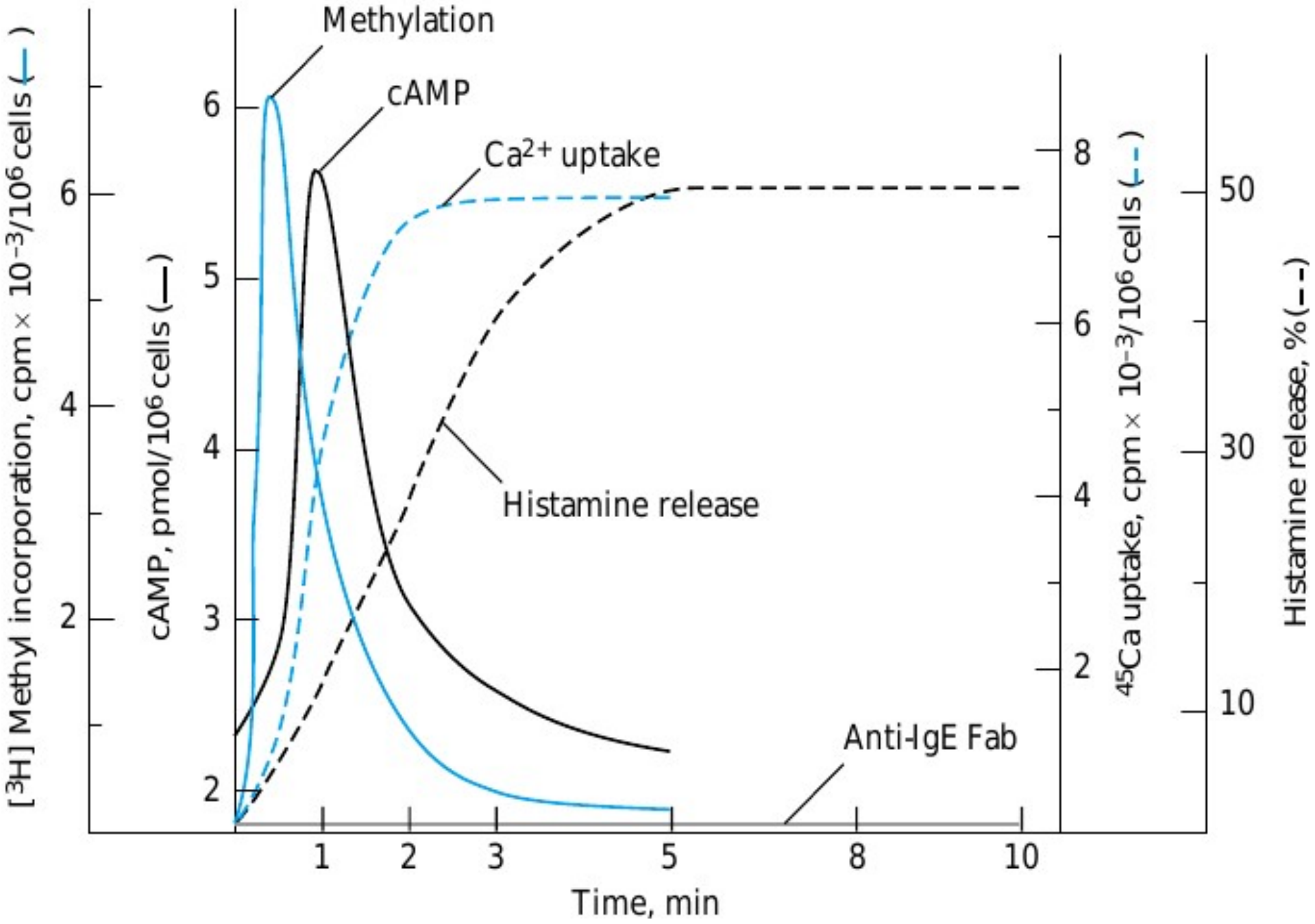



Allergen
IgE
FCεRI
FCεRI
S-S
S-S
①
Adenylate cyclase
ATP
cAMP (transient) ↑
PTK
PTK
PTK
PIP2
DAG
Phospho-lipase C
PKC
Active
PKC
Inactive
②
IP3
Ca2+
Ca2+
Endoplasmic reticulum
Protein kinase inactive
⑥
Protein kinase active
③
PMT II
PMT I
PC
PE
PS
Lyso PC
Phospho-lipase A2
④
Ca2+
Degranulation
Fusogens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

T hücre reseptörlerinin aktivasyonu ile benzerlik...

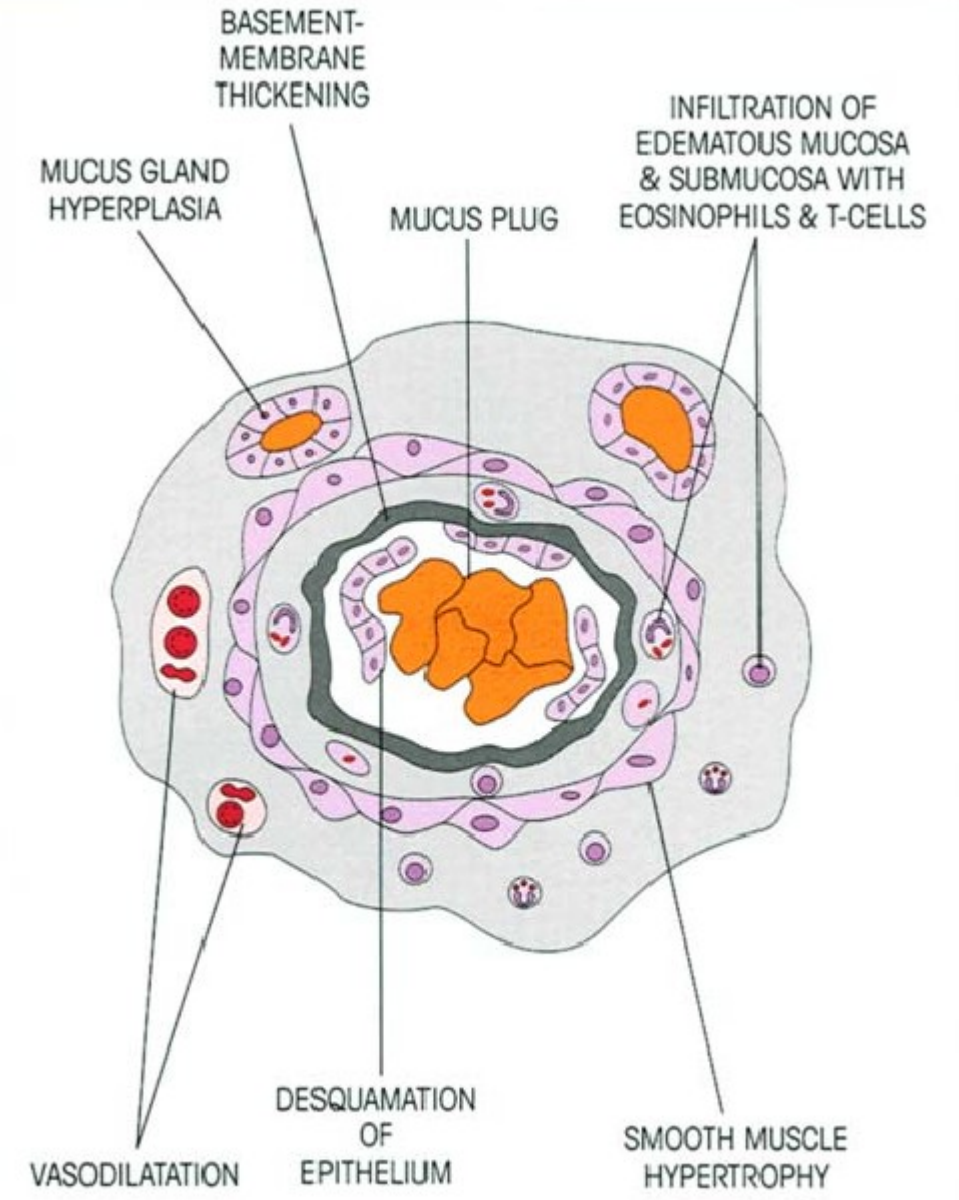



b
Second messenger generation
Activation of GTPase induced serial kinase cascades
LAT
PIP3
Btk
PIP2
PLC-γ1
Slp-76
Vav
Grb-2
Sos
DAG
IP3
Rac/Rho
Ras
Protein kinase C activation
ER Ca2+
Ca2+
Transcription factors
Cytoskeletal targets
Mitogenesis
Transcriptional activation
Granule exocytosis
Mitogenesis
Activation
Phosphorylation site


Methylation
cAMP
Ca2+ uptake
Histamine release
Anti-IgE Fab
[3H] Methyl incorporation, cpm × 10−3/10^6 cells (—)
cAMP, pmol/10^6 cells (—)
45Ca uptake, cpm × 10−3/10^6 cells (– –)
Histamine release, % (– –)
Time, min
1
2
3
5
8
10
2
3
4
5
6
2
4
6
8
10
30
50

Mediator	Effects
	PRIMARY
Histamine, heparin	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)

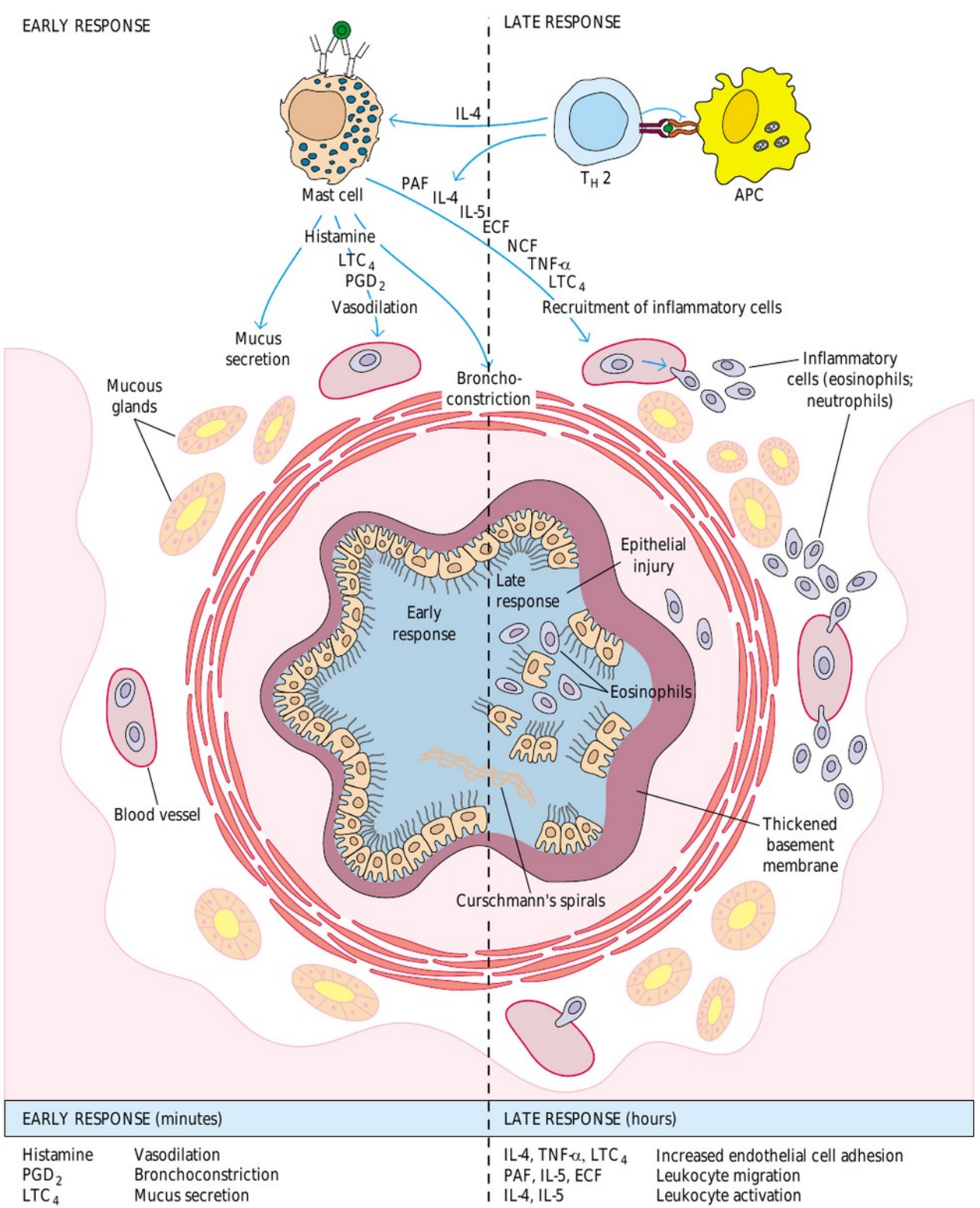
ASTMA



EKZEMA

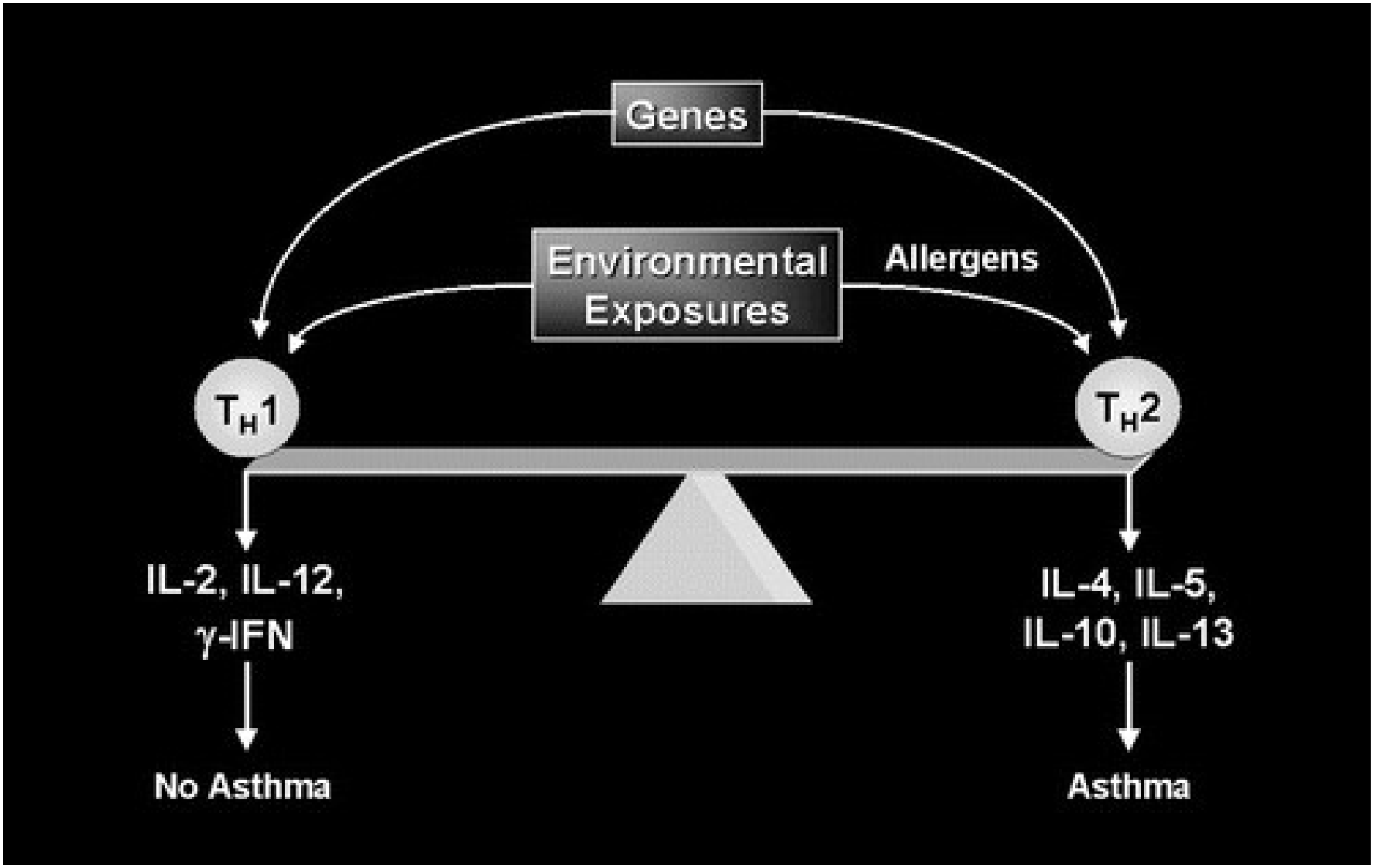
BESİN ALLERJİSİ

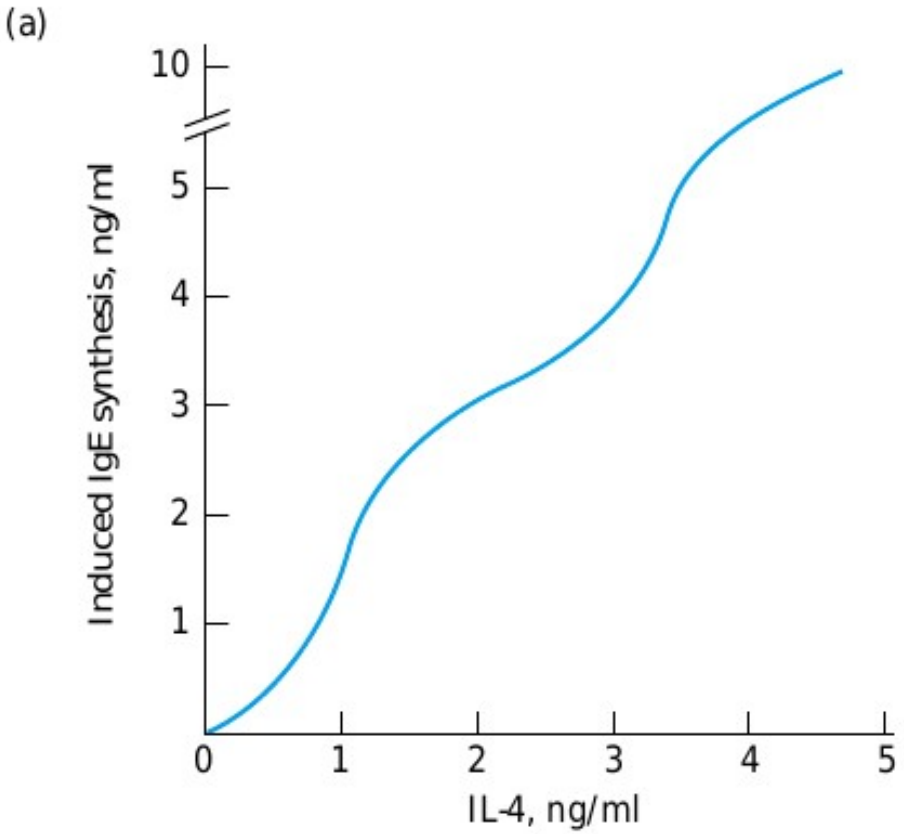
ANAFLAKTİK İLAÇ ALLERJİSİ

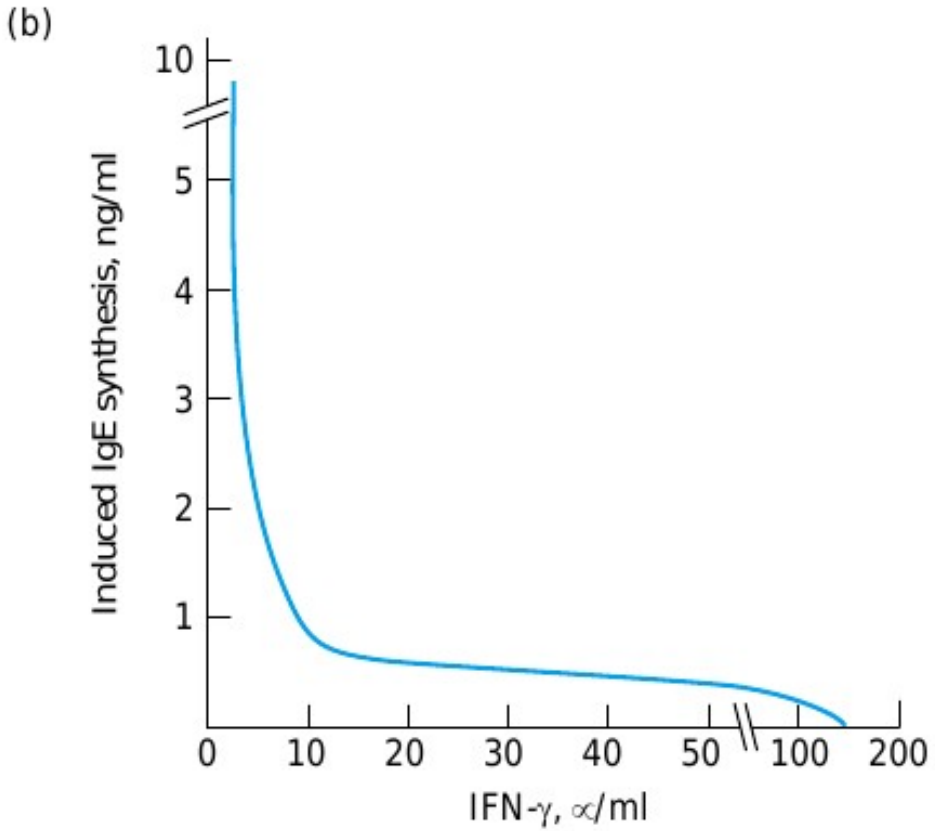


EARLY RESPONSE (minutes)		LATE RESPONSE (hours)	
Histamine	Vasodilation	IL-4, TNF-α, LTC_4	Increased endothelial cell adhesion
PGD_2	Bronchoconstriction	PAF, IL-5, ECF	Leukocyte migration
LTC_4	Mucus secretion	IL-4, IL-5	Leukocyte activation

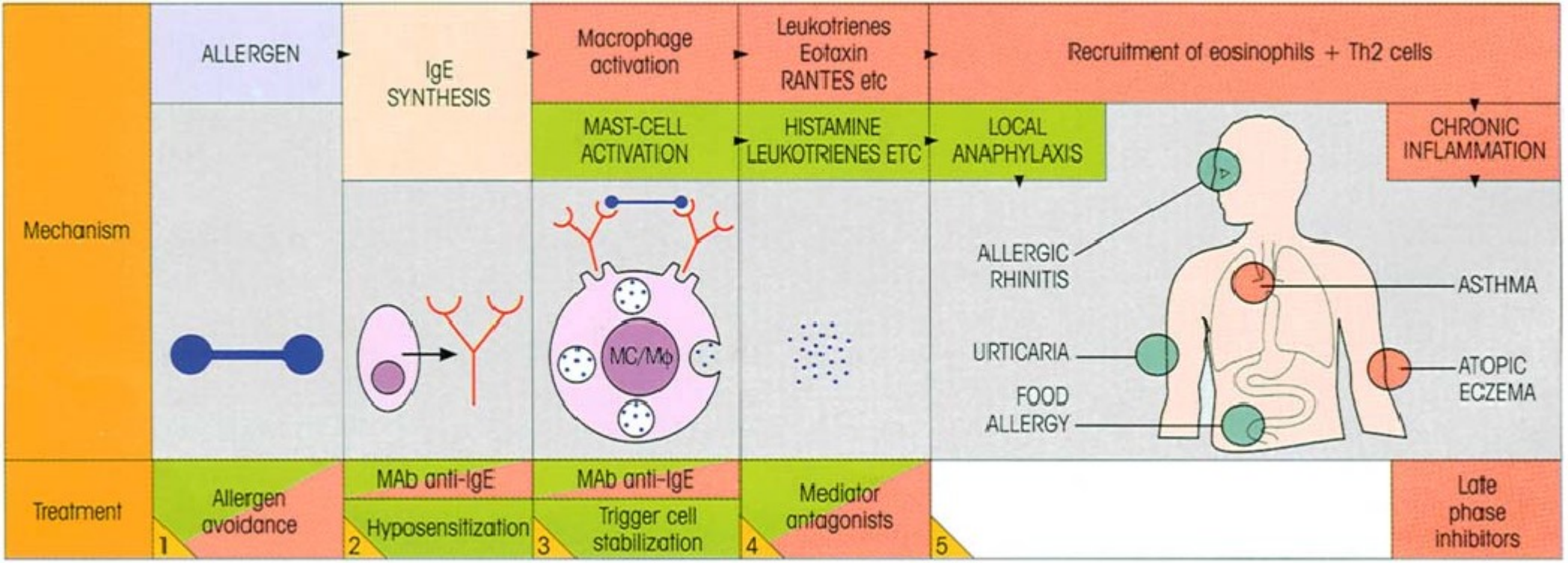
Bronşiyal astmada Th2 hücrelerinin önemi







Plazma hücrelerinden IgE sentezi IL-4 ile indükleniyor!!!

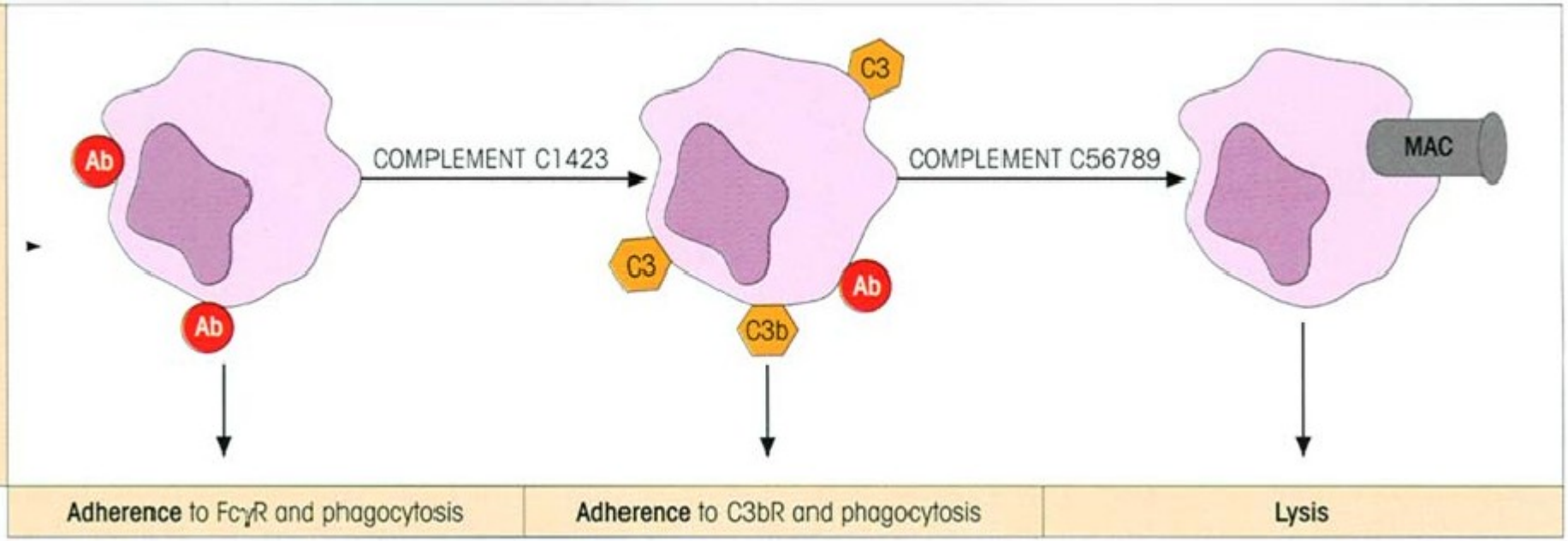

Mechanism
ALLERGEN
IgE SYNTHESIS
Macrophage activation
Leukotrienes Eotaxin RANTES etc
Recruitment of eosinophils + Th2 cells
MAST-CELL ACTIVATION
HISTAMINE LEUKOTRIENES ETC
LOCAL ANAPHYLAXIS
CHRONIC INFLAMMATION
MC/Mφ
ALLERGIC RHINITIS
ASTHMA
URTICARIA
ATOPIC ECZEMA
FOOD ALLERGY
Treatment
Allergen avoidance
1
MAb anti-IgE
Hyposensitization
2
MAb anti-IgE
Trigger cell stabilization
3
Mediator antagonists
4
5
Late phase inhibitors

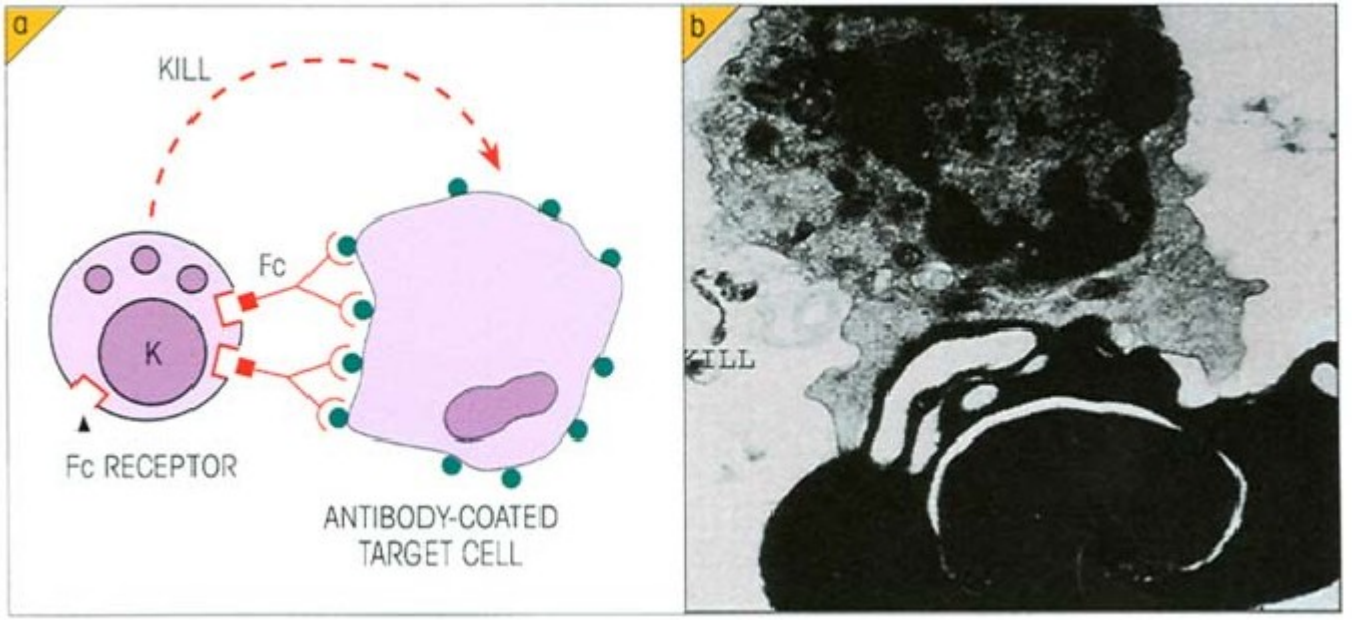

CONT.
H. DUST
MITE
GRASS
SHRUB
TREE

Drug	Action
Antihistamines	Block H_1 and H_2 receptors on target cells
Cromolyn sodium	Blocks Ca^{2+} influx into mast cells
Theophylline	Prolongs high cAMP levels in mast cells by inhibiting phosphodiesterase, which cleaves cAMP to 5′-AMP*
Epinephrine (adrenalin)	Stimulates cAMP production by binding to β-adrenergic receptors on mast cells*
Cortisone	Reduces histamine levels by blocking conversion of histidine to histamine and stimulates mast-cell production of cAMP*

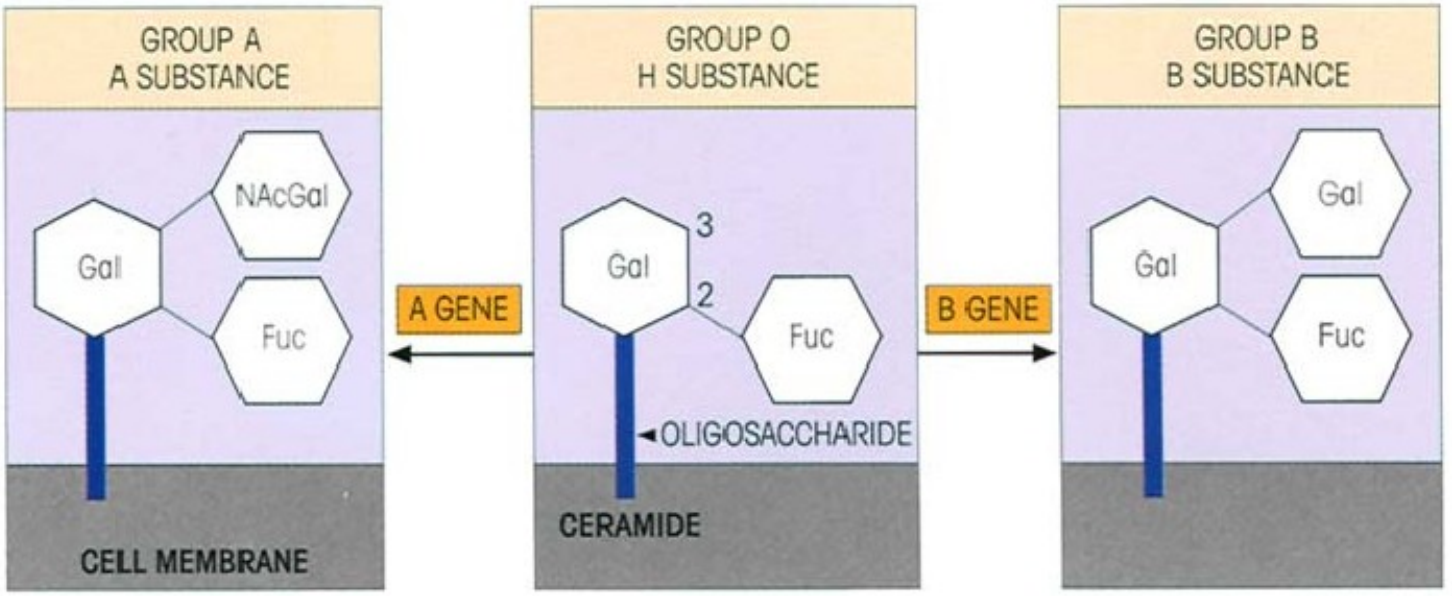
Antikora bağlı sitotoksik hipersensitivite – Tip II

Extracellular cytotoxic attack by K-cells and myeloid cells (ADCC)

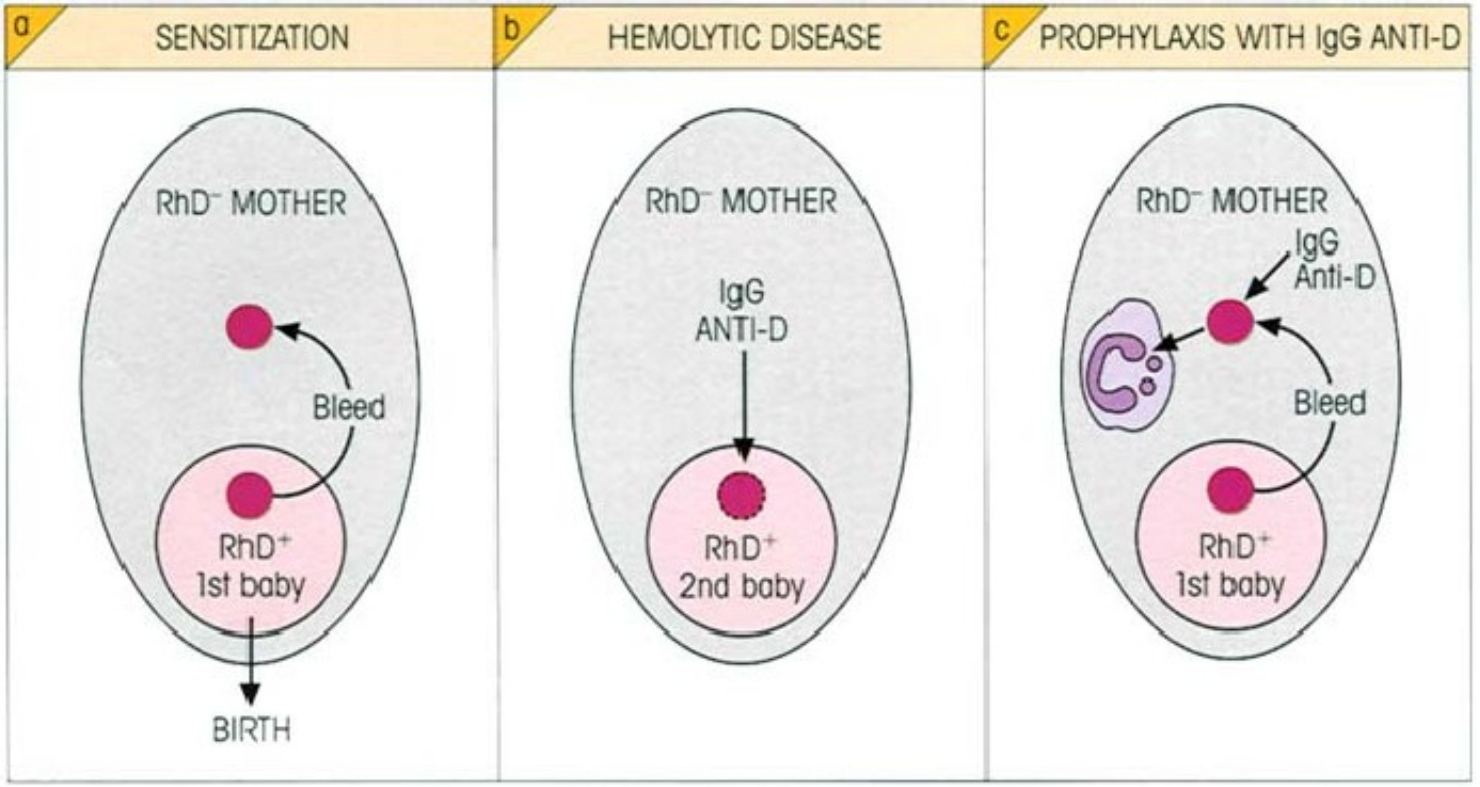




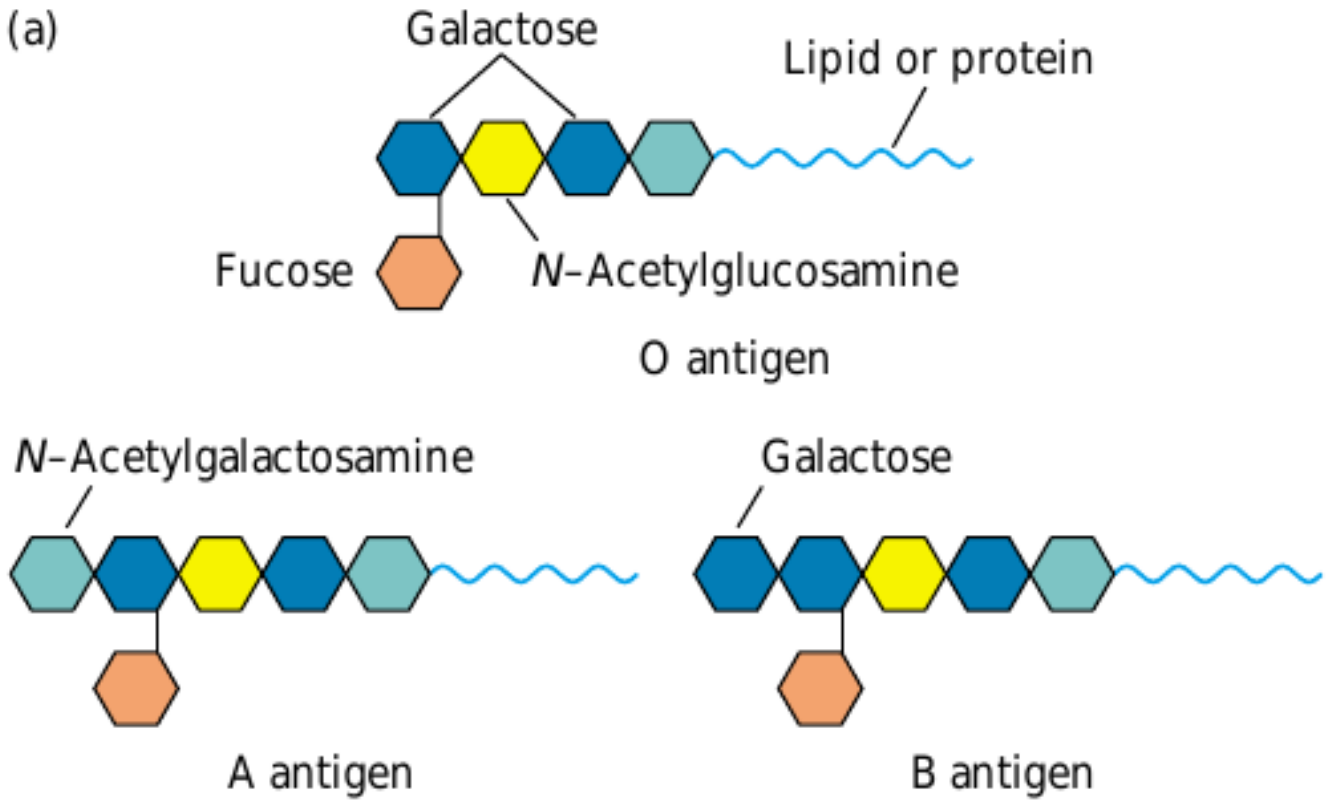
ABO


GROUP A
A SUBSTANCE
NAcGal
Gal
Fuc
CELL MEMBRANE
A GENE
GROUP O
H SUBSTANCE
Gal
3
2
Fuc
OLIGOSACCHARIDE
CERAMIDE
B GENE
GROUP B
B SUBSTANCE
Gal
Gal
Fuc

Rh

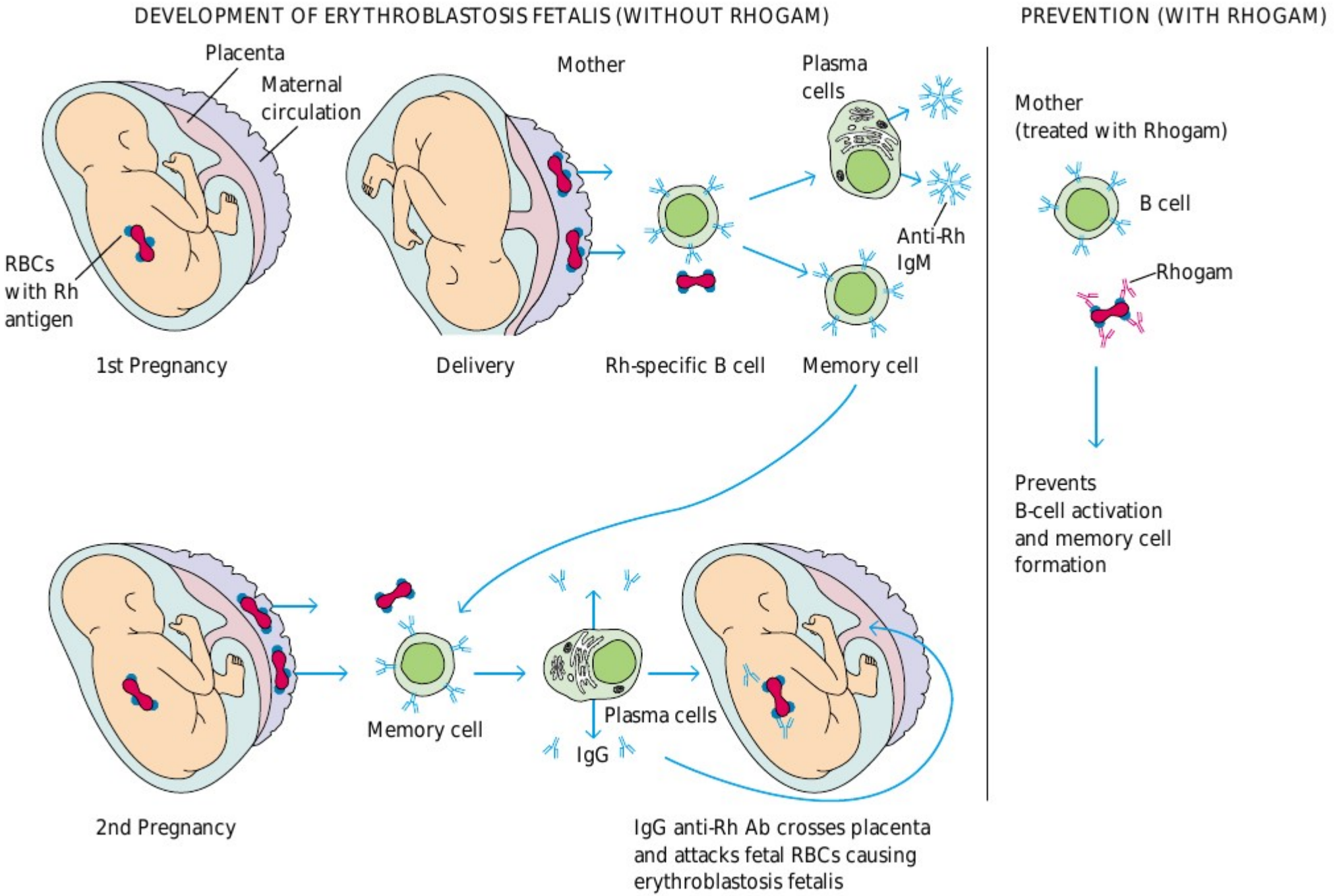

a
SENSITIZATION
RhD⁻ MOTHER
Bleed
RhD⁺
1st baby
BIRTH
b
HEMOLYTIC DISEASE
RhD⁻ MOTHER
IgG
ANTI-D
RhD⁺
2nd baby
c
PROPHYLAXIS WITH IgG ANTI-D
RhD⁻ MOTHER
IgG
Anti-D
Bleed
RhD⁺
1st baby

(a)

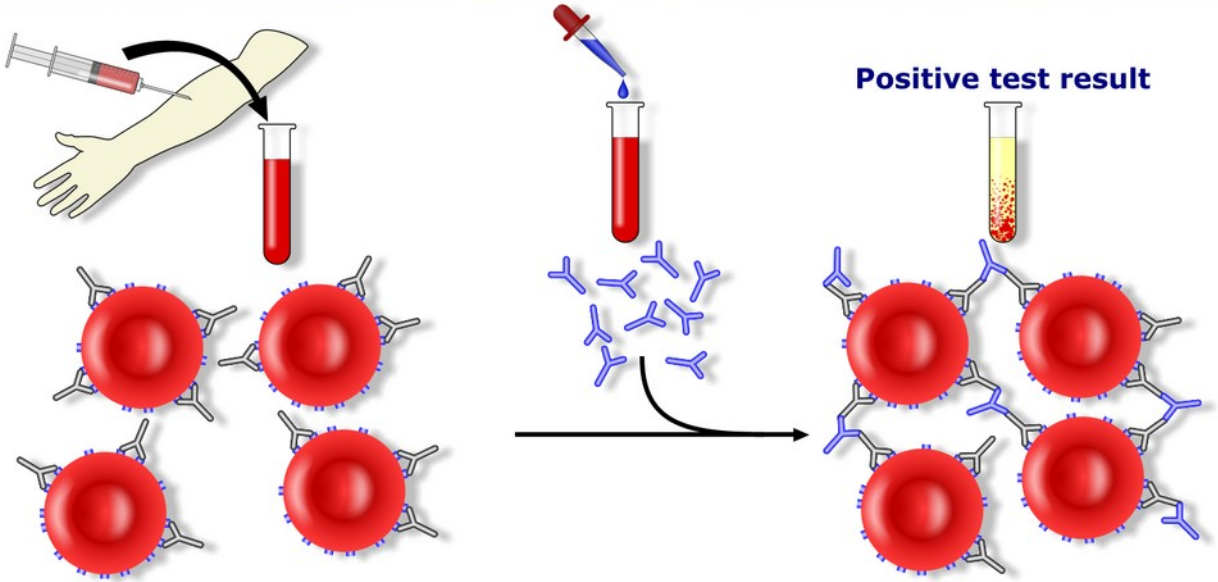


(b)

Genotype	Blood-group phenotype	Antigens on erythrocytes (*agglutinins*)	Serum antibodies (*isohemagglutinins*)
AA or AO	A	A	Anti-B
BB or BO	B	B	Anti-A
AB	AB	A and B	None
OO	O	None	Anti-A and anti-B


DEVELOPMENT OF ERYTHROBLASTOSIS FETALIS (WITHOUT RHOGAM)
PREVENTION (WITH RHOGAM)
Placenta
Maternal circulation
RBCs with Rh antigen
1st Pregnancy
Mother
Delivery
Plasma cells
Anti-Rh IgM
Rh-specific B cell
Memory cell
Mother (treated with Rhogam)
B cell
Rhogam
Prevents B-cell activation and memory cell formation
Memory cell
Plasma cells
IgG
2nd Pregnancy
IgG anti-Rh Ab crosses placenta and attacks fetal RBCs causing erythroblastosis fetalis

Direct Coombs test / Direct antiglobulin test

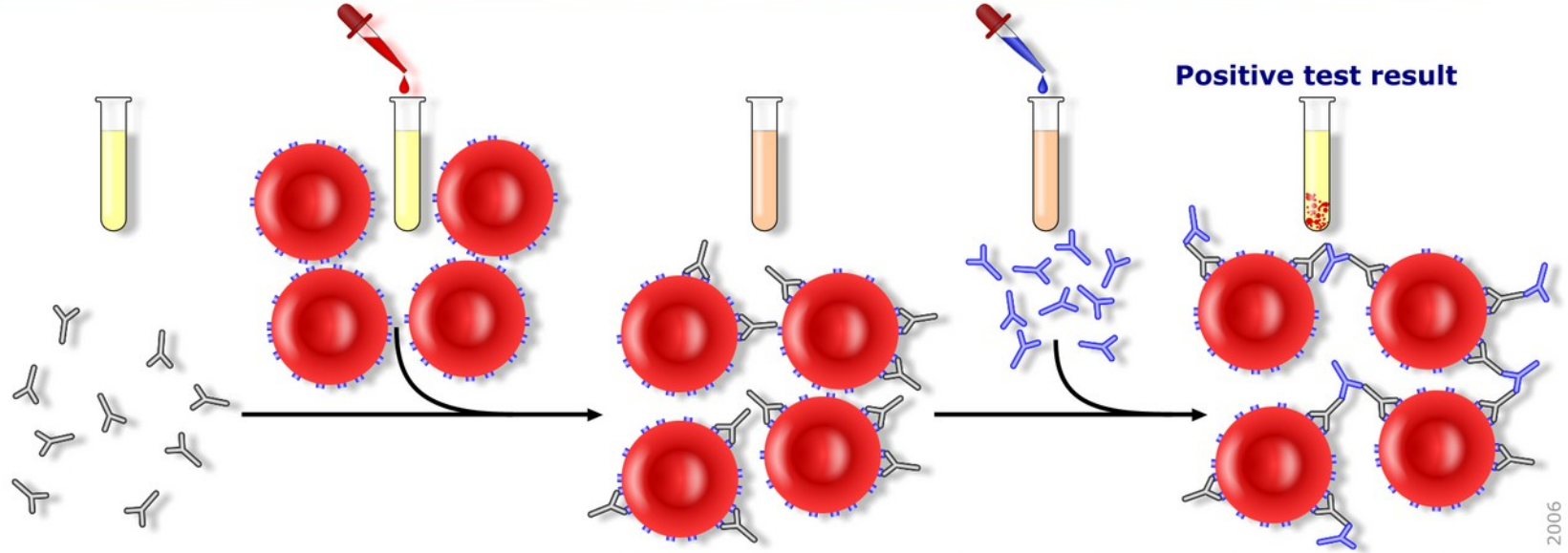


Blood sample from a patient with immune mediated haemolytic anaemia: antibodies are shown attached to antigens on the RBC surface.

The patient's washed RBCs are incubated with antihuman antibodies (*Coombs reagent*).

RBCs agglutinate: antihuman antibodies form links between RBCs by binding to the human antibodies on the RBCs.

Indirect Coombs test / Indirect antiglobulin test



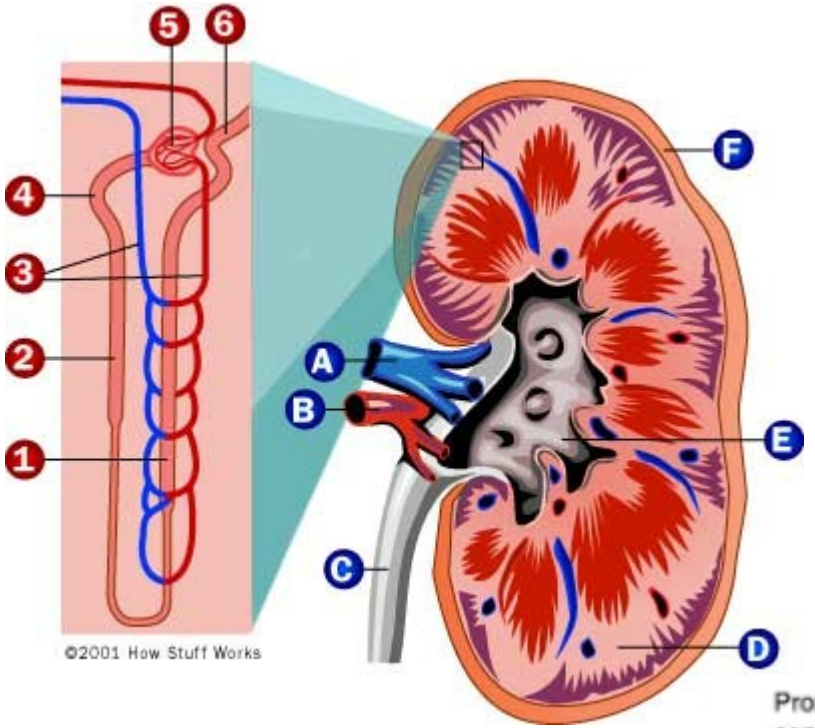
Recipient's serum is obtained, containing antibodies (Ig's).

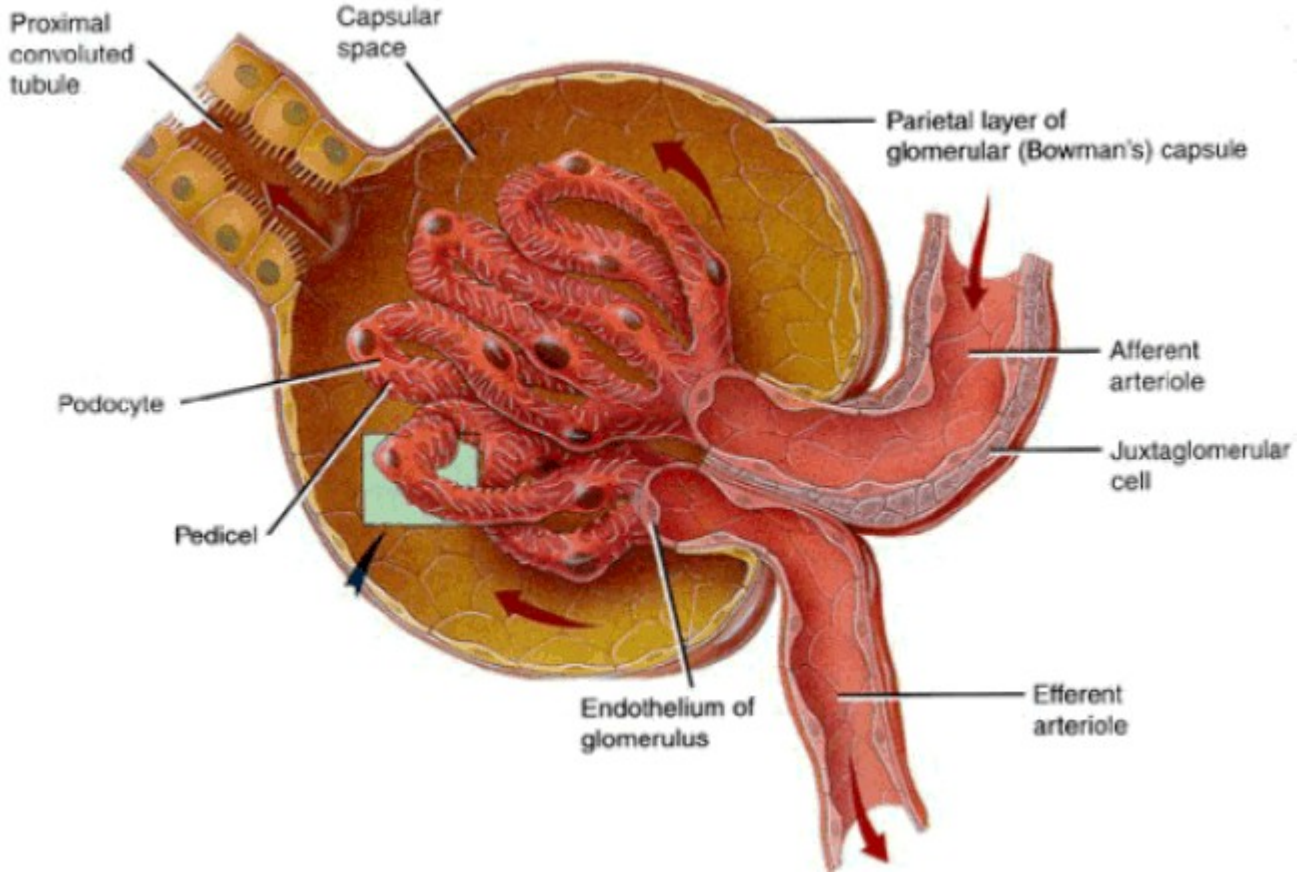
Donor's blood sample is added to the tube with serum.

Recipient's Ig's that target the donor's red blood cells form antibody-antigen complexes.

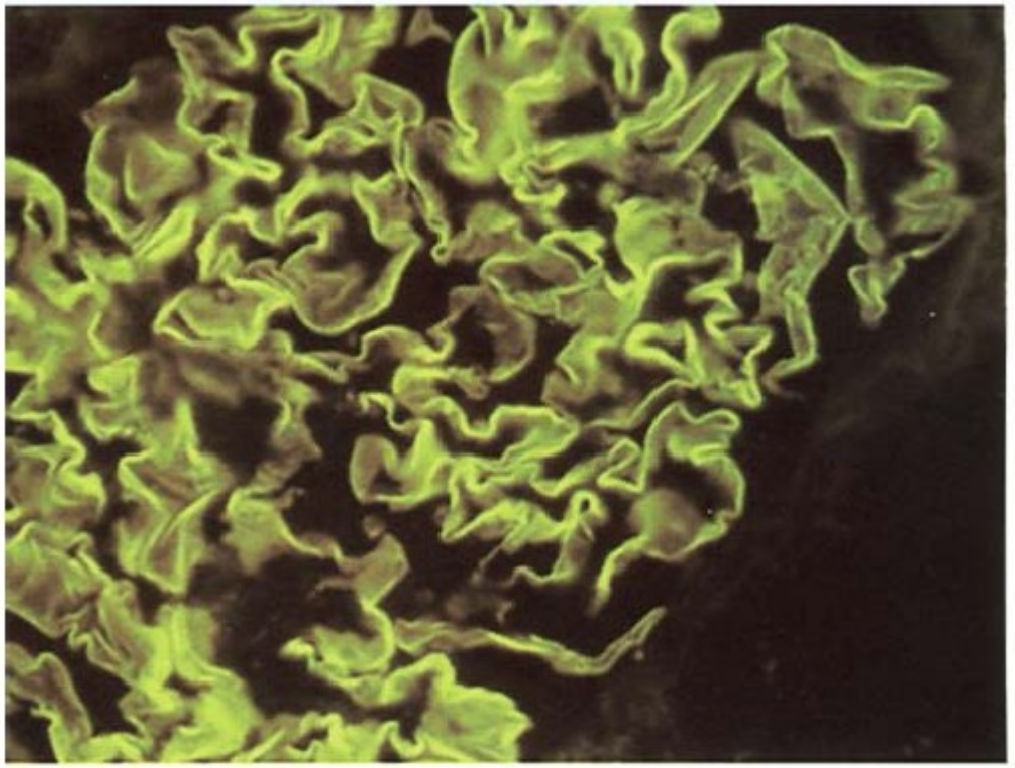
Anti-human Ig's (*Coombs antibodies*) are added to the solution.

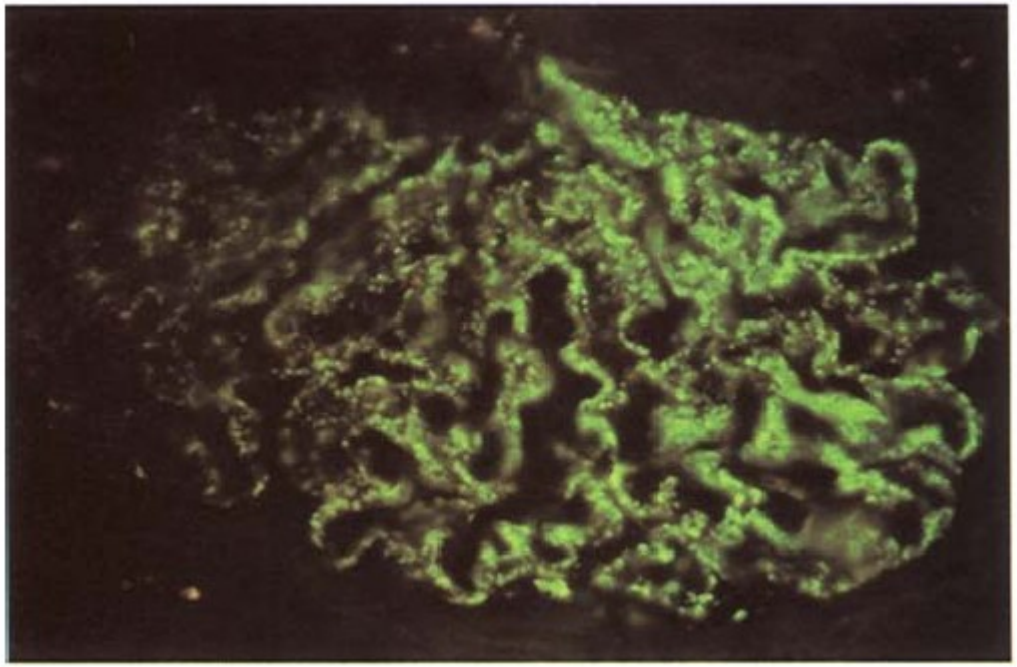
Agglutination of red blood cells occurs, because human Ig's are attached to red blood cells.

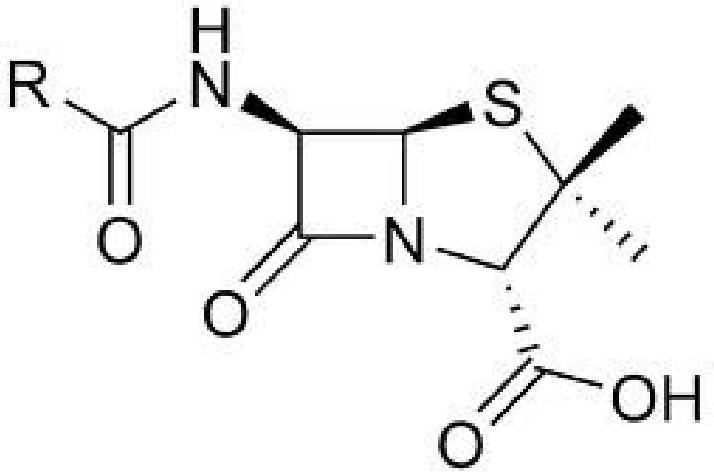

5
6
4
3
2
1
A
B
C
D
E
F
©2001 How Stuff Works


Proximal convoluted tubule
Capsular space
Parietal layer of glomerular (Bowman's) capsule
Afferent arteriole
Podocyte
Juxtaglomerular cell
Pedicel
Endothelium of glomerulus
Efferent arteriole

Glomerulonefrit

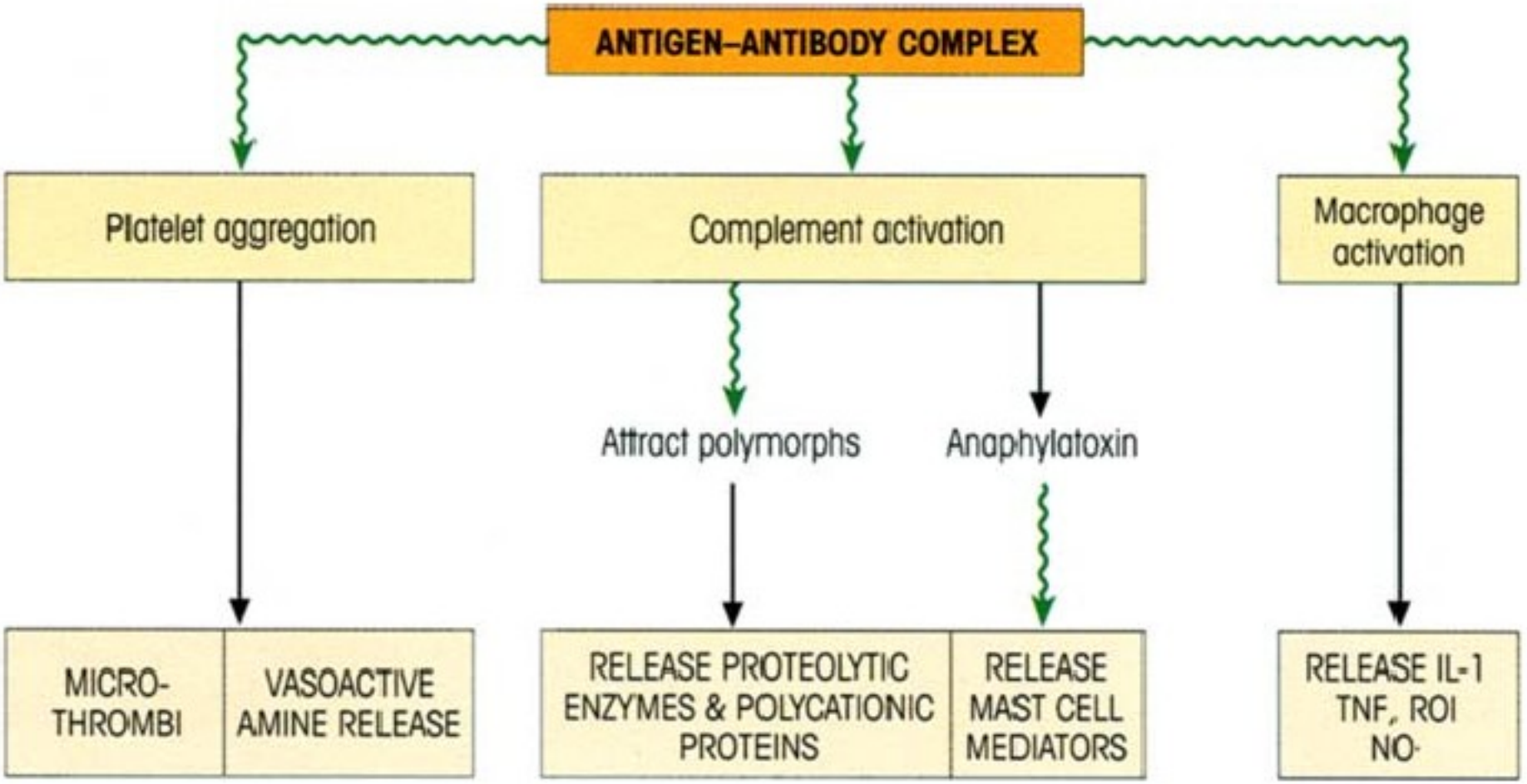




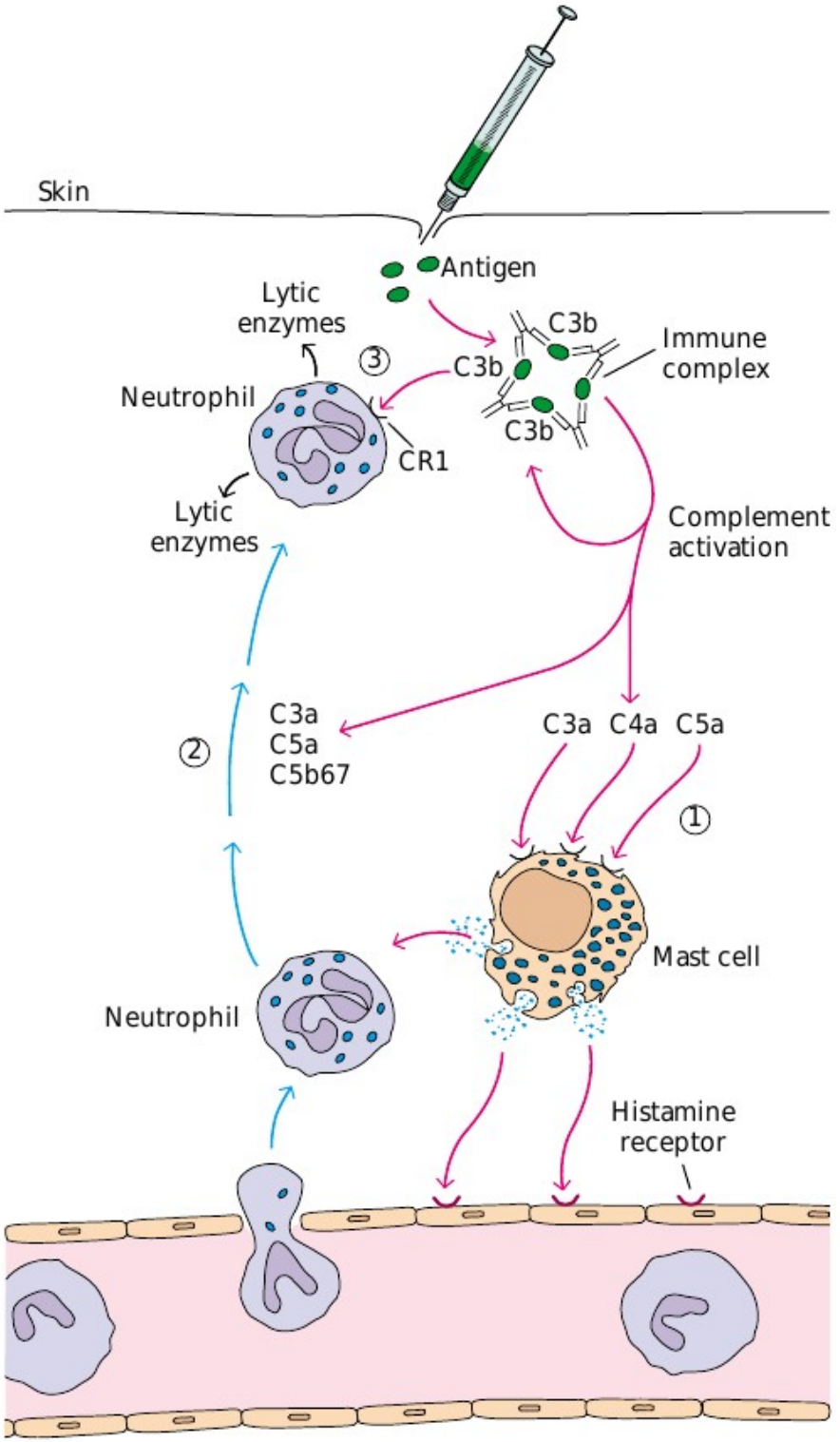


Type of reaction	Antibody or lymphocytes induced	Clinical manifestations
I	IgE	Urticaria, systemic anaphylaxis
II	IgM, IgG	Hemolytic anemia
III	IgG	Serum sickness, glomerulonephritis
IV	T_{DTH} cells	Contact dermatitis

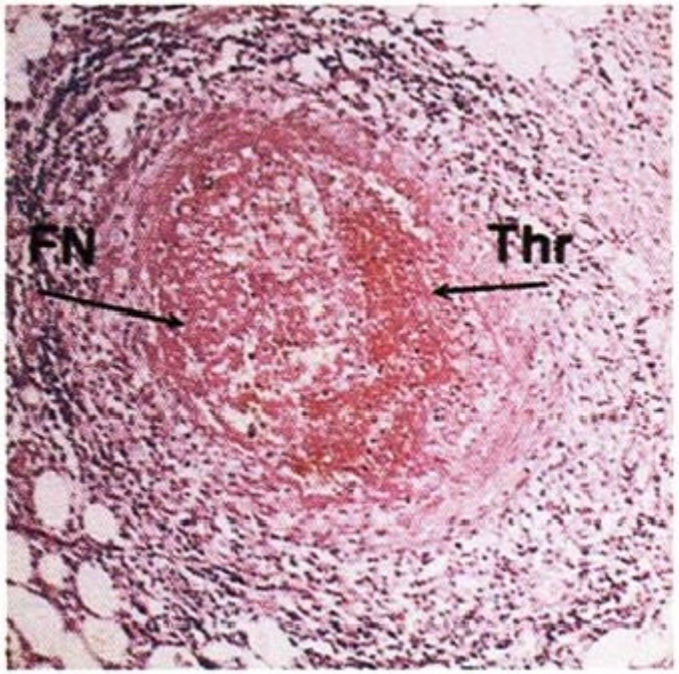
İmmün kompleks ile oluşan hipersensitivite – Tip III

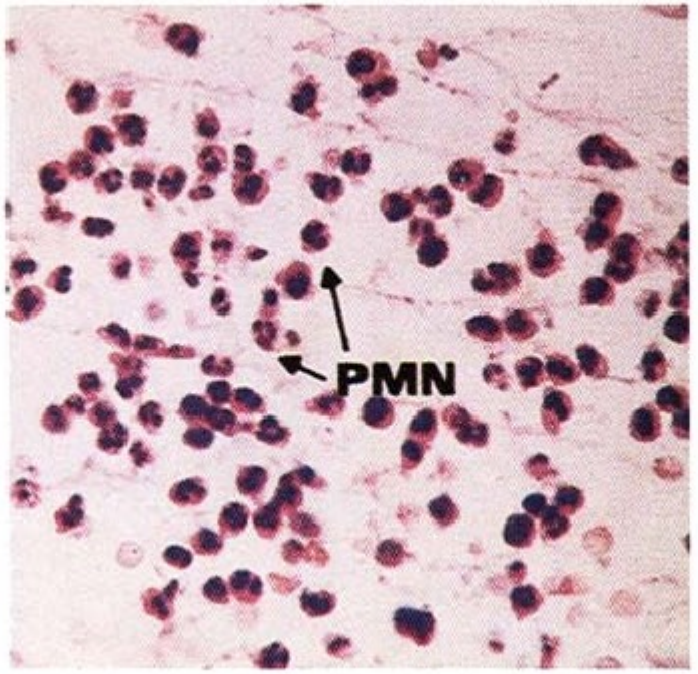

ANTIGEN–ANTIBODY COMPLEX
Platelet aggregation
Complement activation
Macrophage activation
Attract polymorphs
Anaphylatoxin
MICRO-THROMBI
VASOACTIVE AMINE RELEASE
RELEASE PROTEOLYTIC ENZYMES & POLYCATIONIC PROTEINS
RELEASE MAST CELL MEDIATORS
RELEASE IL-1 TNF, ROI NO·

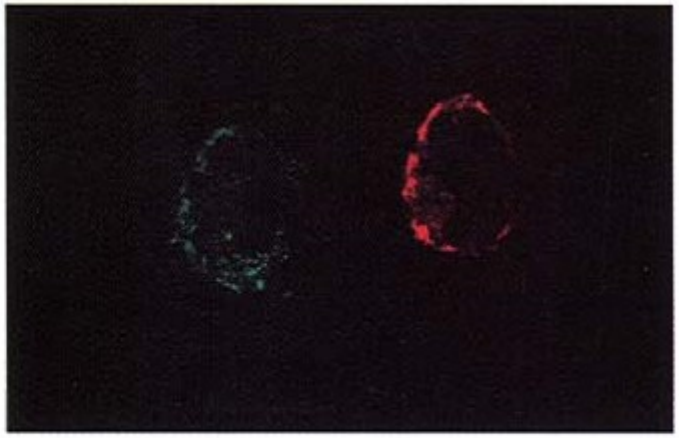
Lokal Arthus reaksiyonu



Arthus reaksiyonu:
Çözünür antijen immünize hayvana intradermal enjekte edildiğinde oluşan immün komplekslerin oluşturduğu lokal reaksiyon...

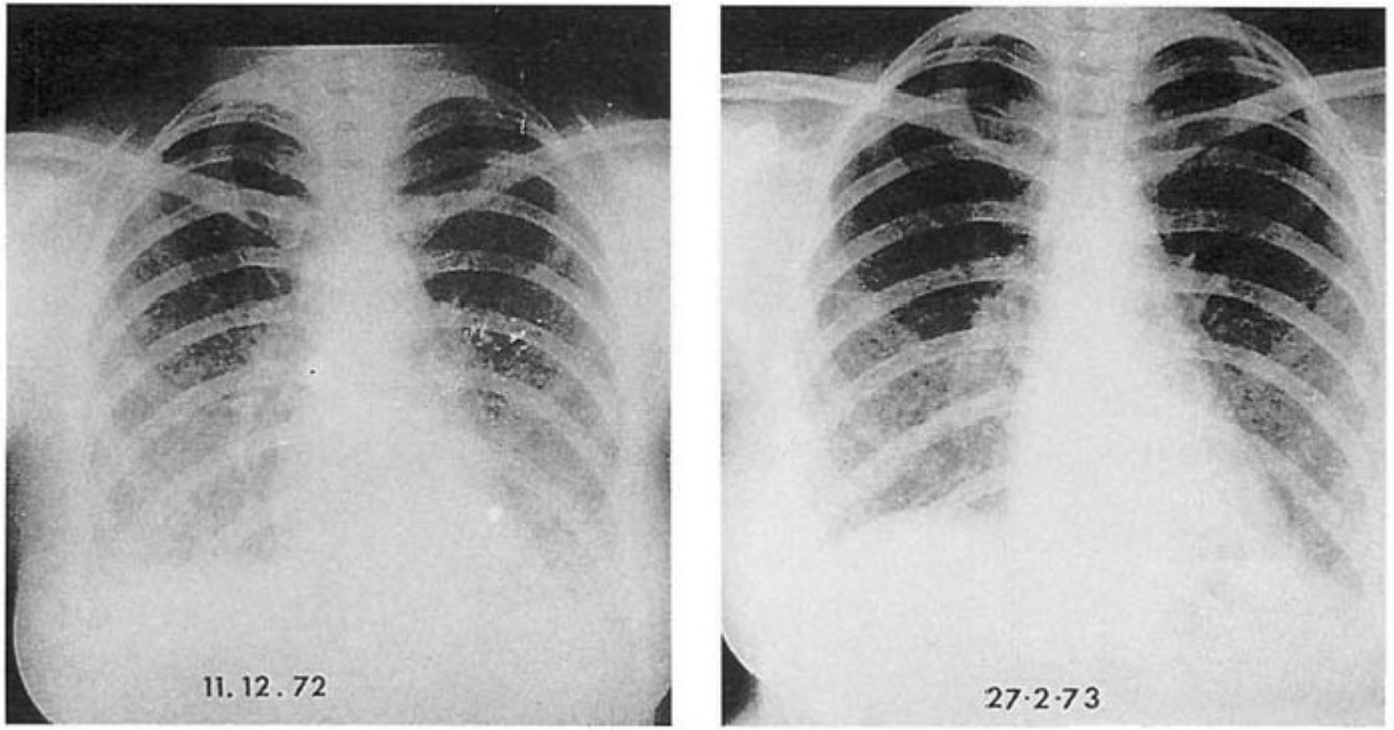






(c)

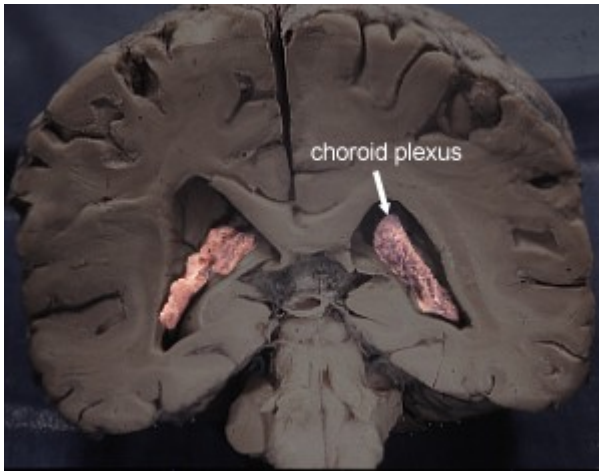
Intrapulmoner Arthus reaksiyonu

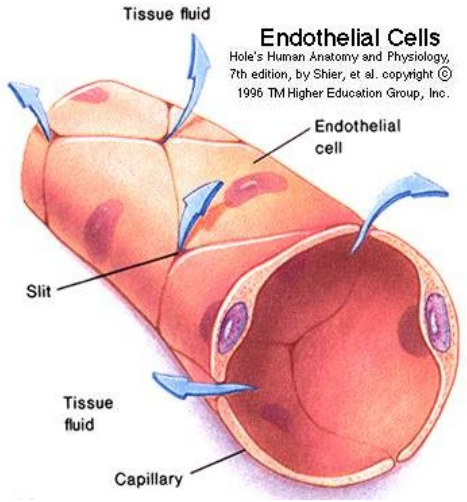


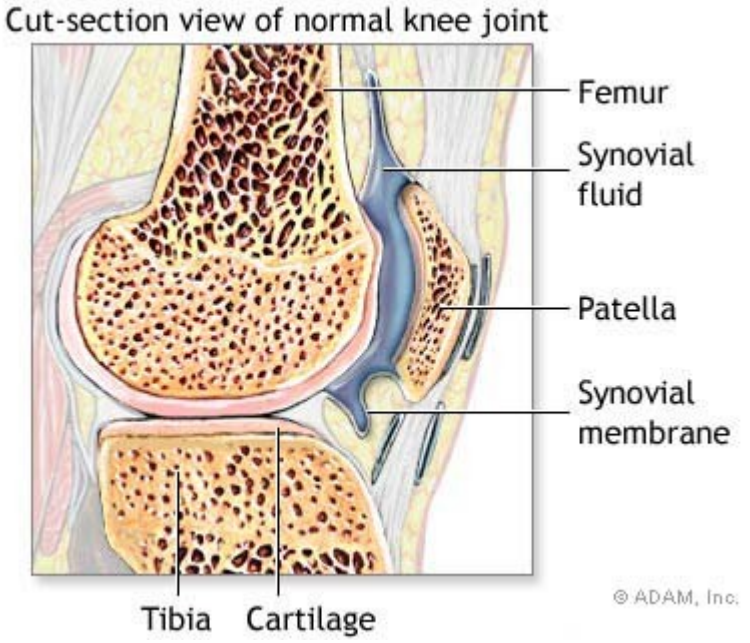
Antijeni cilt altı yerine alveoler mukozadan veriniz!

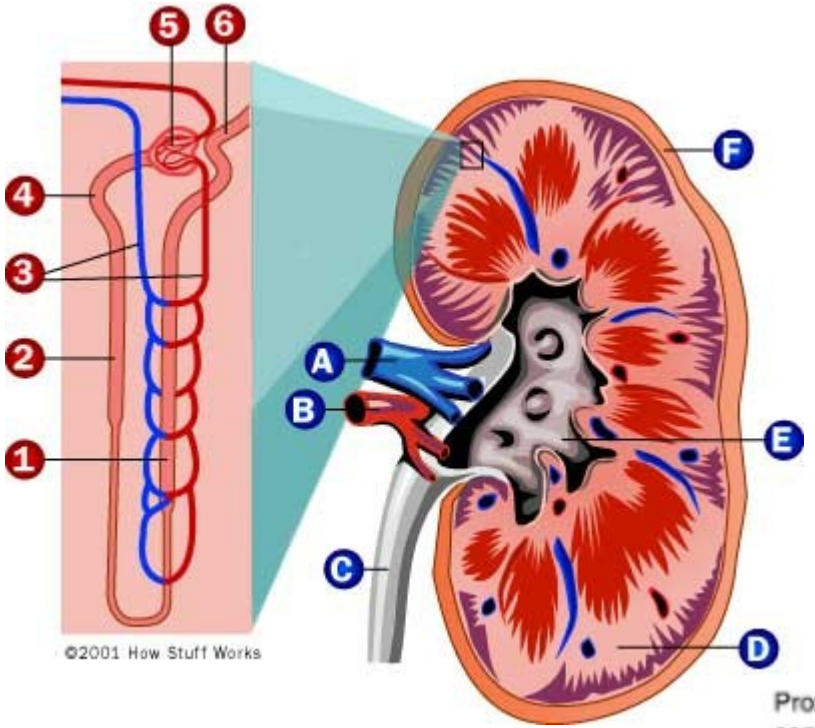
Ya immün kompleksler kanda oluşursa...

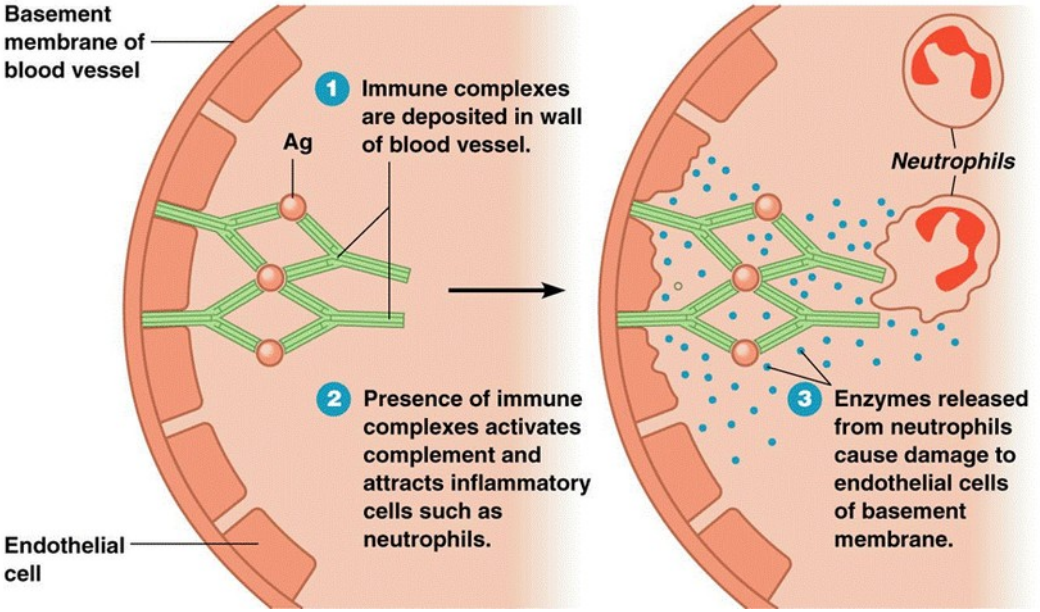
Süzgeçlere takılırlar!

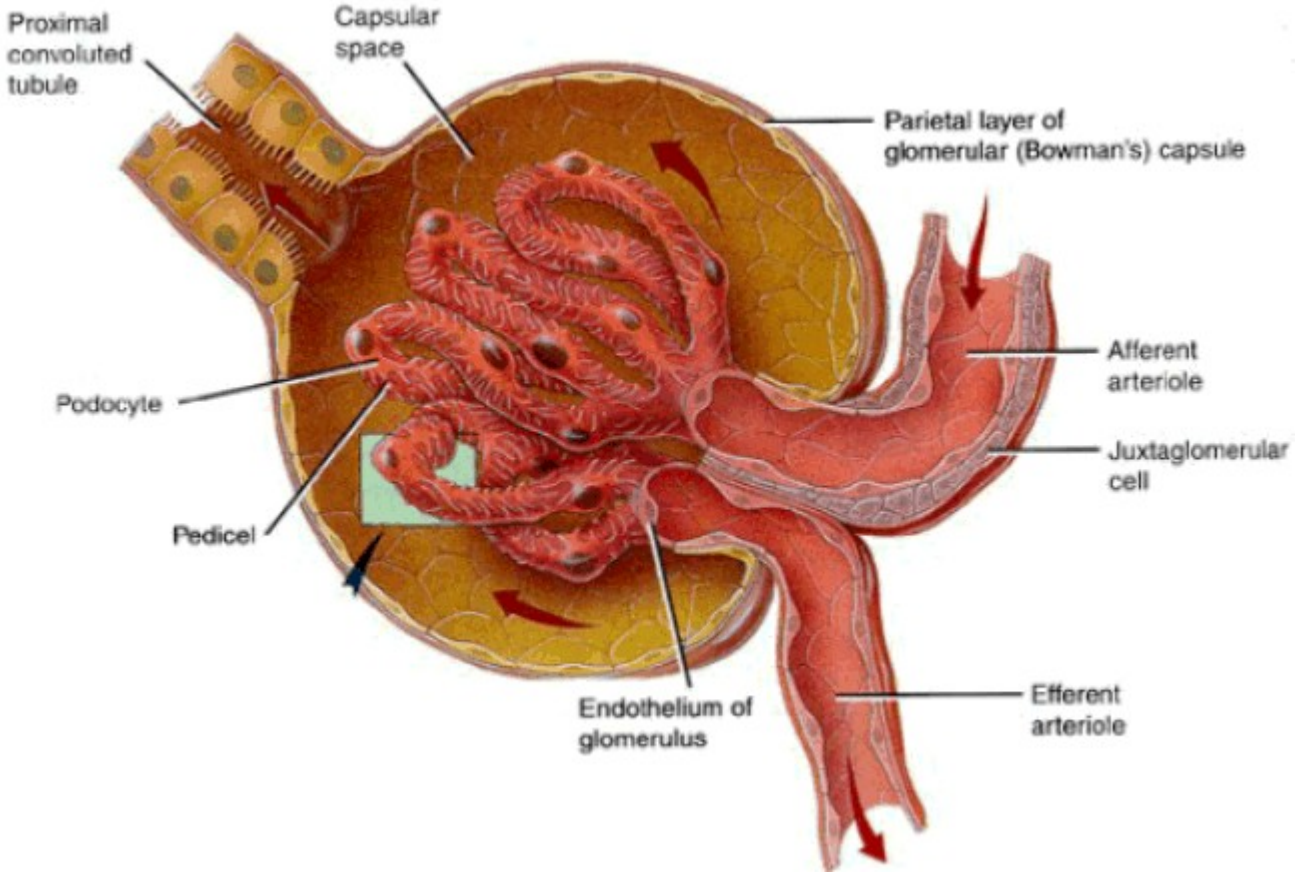




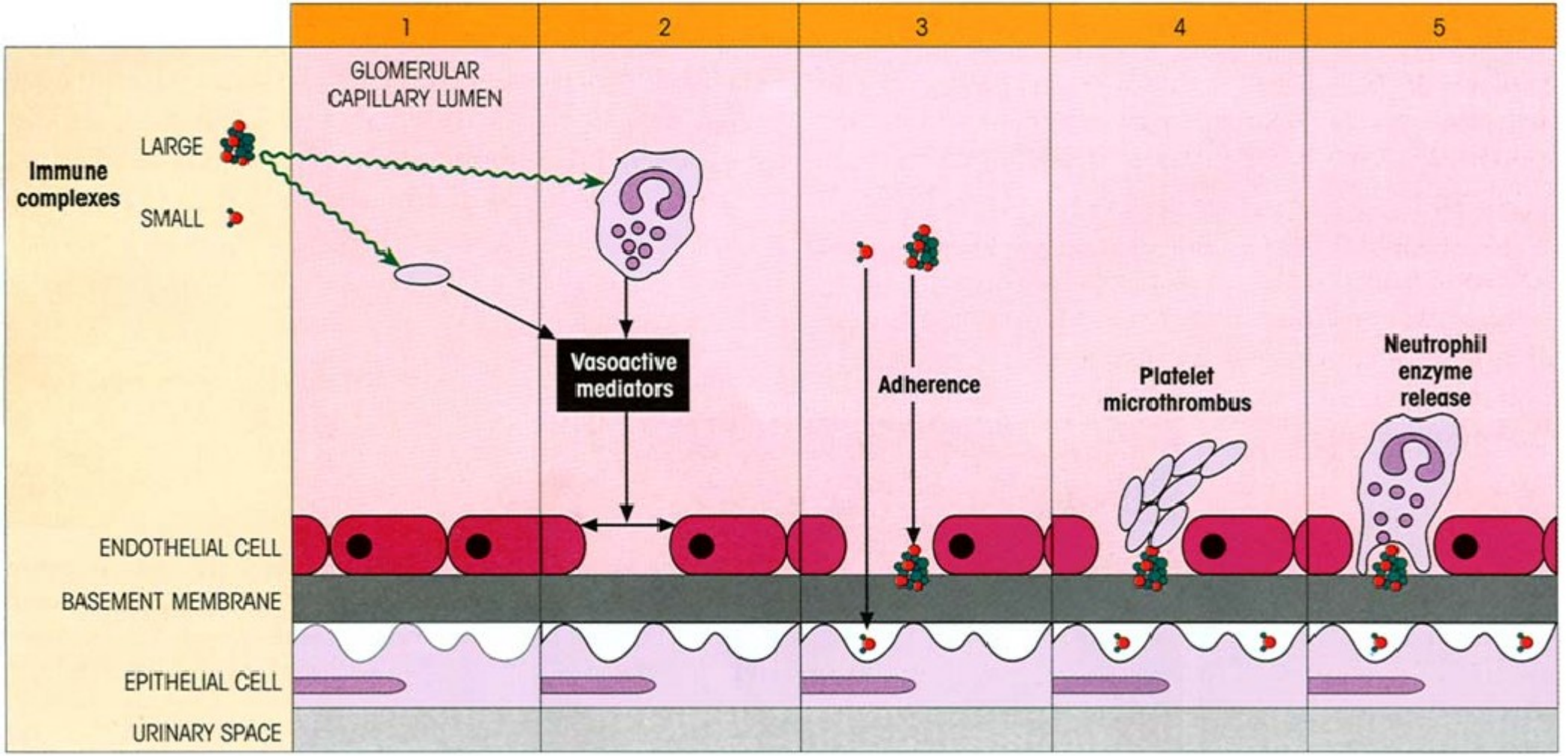


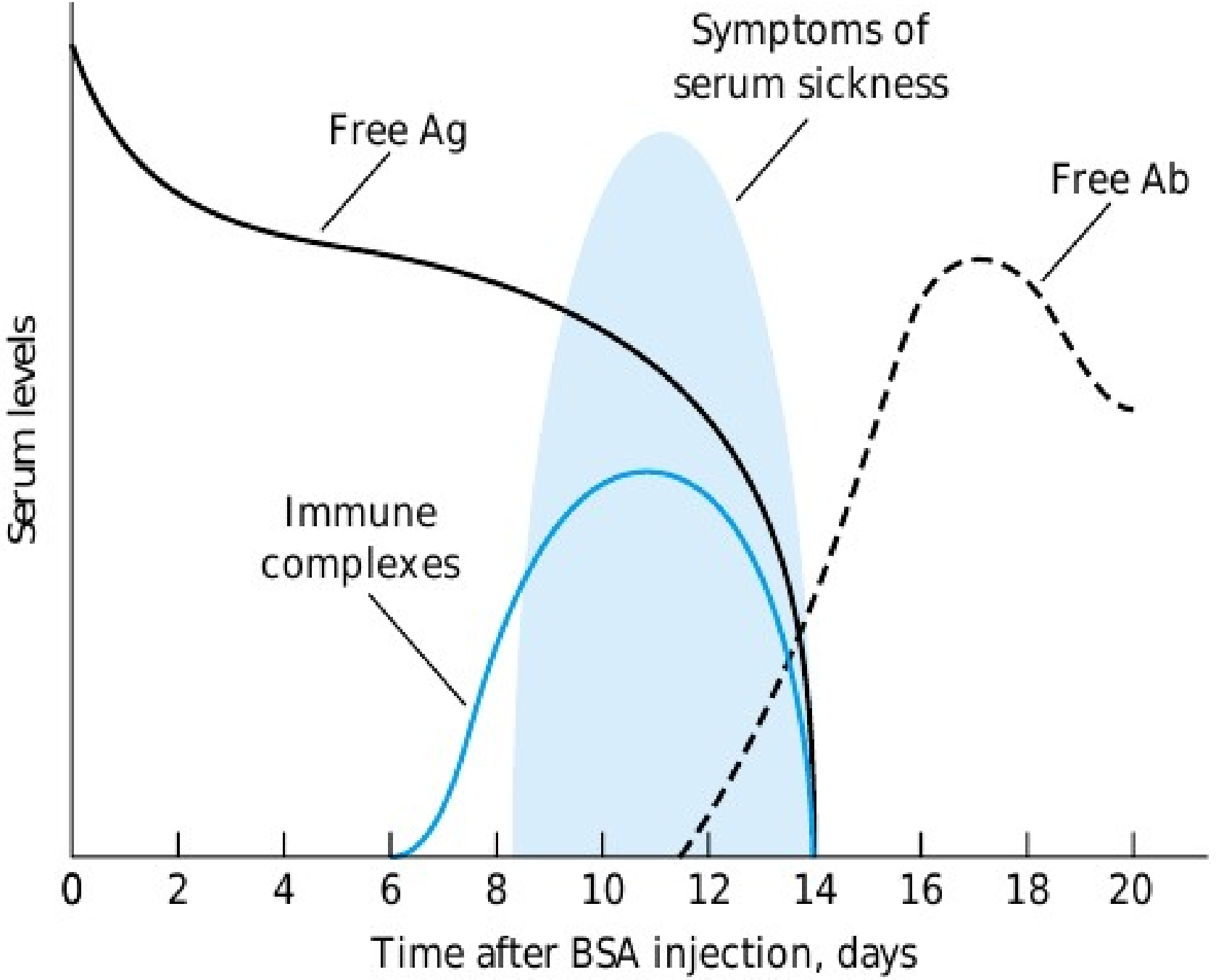

5
6
4
3
2
1
A
B
C
D
E
F
©2001 How Stuff Works


Basement membrane of blood vessel
1 Immune complexes are deposited in wall of blood vessel.
Ag
2 Presence of immune complexes activates complement and attracts inflammatory cells such as neutrophils.
Endothelial cell
Neutrophils
3 Enzymes released from neutrophils cause damage to endothelial cells of basement membrane.


Proximal convoluted tubule
Capsular space
Parietal layer of glomerular (Bowman's) capsule
Podocyte
Afferent arteriole
Juxtaglomerular cell
Pedicel
Endothelium of glomerulus
Efferent arteriole

Generalize... Sistemik Arthus reaksiyonu




Symptoms of
serum sickness
Free Ag
Free Ab
Immune
complexes
Serum levels
0
2
4
6
8
10
12
14
16
18
20
Time after BSA injection, days

Autoimmune Diseases

Systemic lupus erythematosus
Rheumatoid arthritis
Goodpasture's syndrome

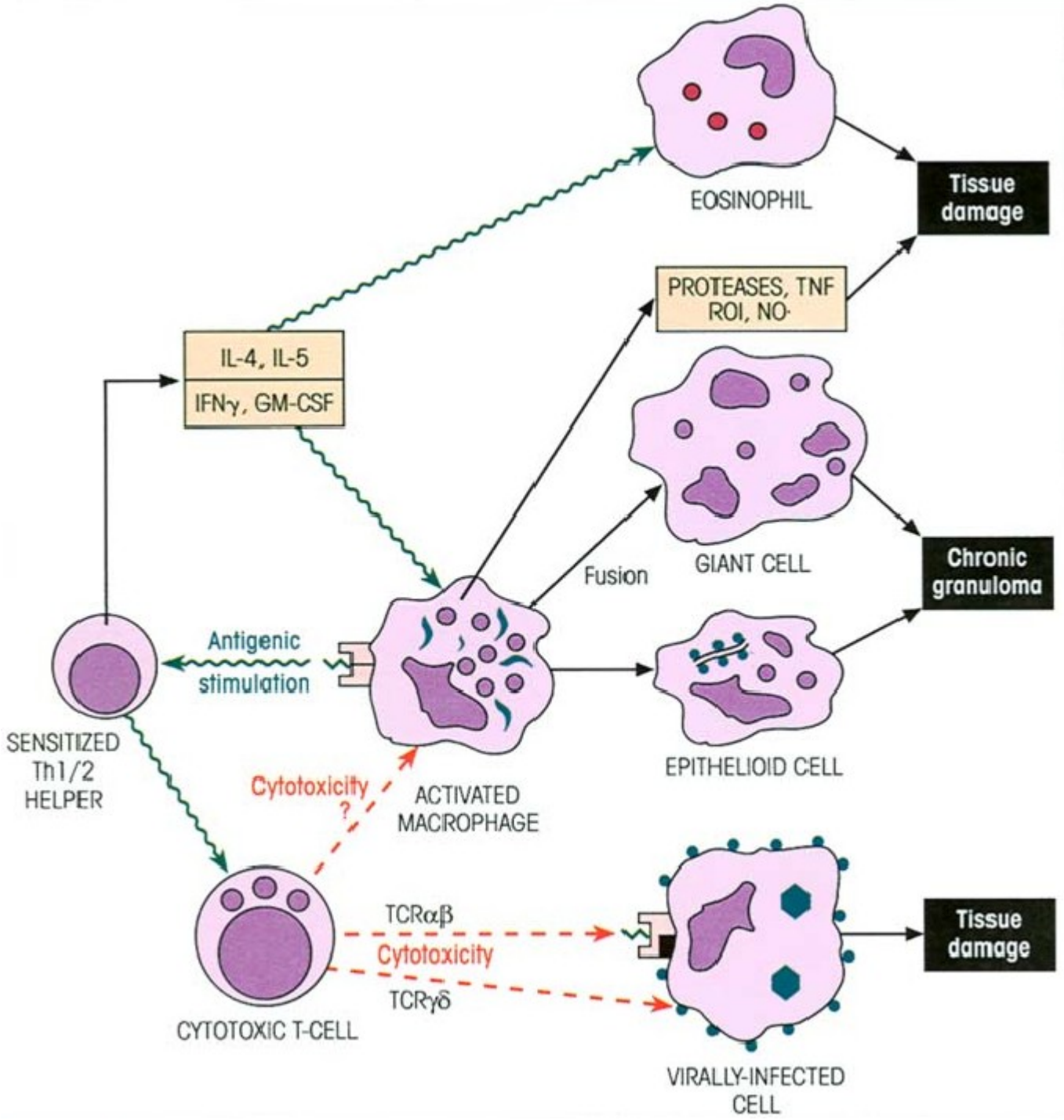
Drug Reactions

Allergies to penicillin and sulfonamides

Infectious Diseases

Poststreptococcal glomerulonephritis
Meningitis
Hepatitis
Mononucleosis
Malaria
Trypanosomiasis

Hücresel tip hipersensitivite – Tip IV


EOSINOPHIL
Tissue damage
PROTEASES, TNF
ROI, NO·
IL-4, IL-5
IFNγ, GM-CSF
GIANT CELL
Fusion
Chronic granuloma
Antigenic stimulation
SENSITIZED Th1/2 HELPER
ACTIVATED MACROPHAGE
EPITHELIOID CELL
Cytotoxicity ?
TCRαβ
Cytotoxicity
TCRγδ
Tissue damage
CYTOTOXIC T-CELL
VIRALLY-INFECTED CELL

Tüberkülin reaksiyonu...

Hücresel tip hipersensitiviteye neden olan hücre içi antijenler...

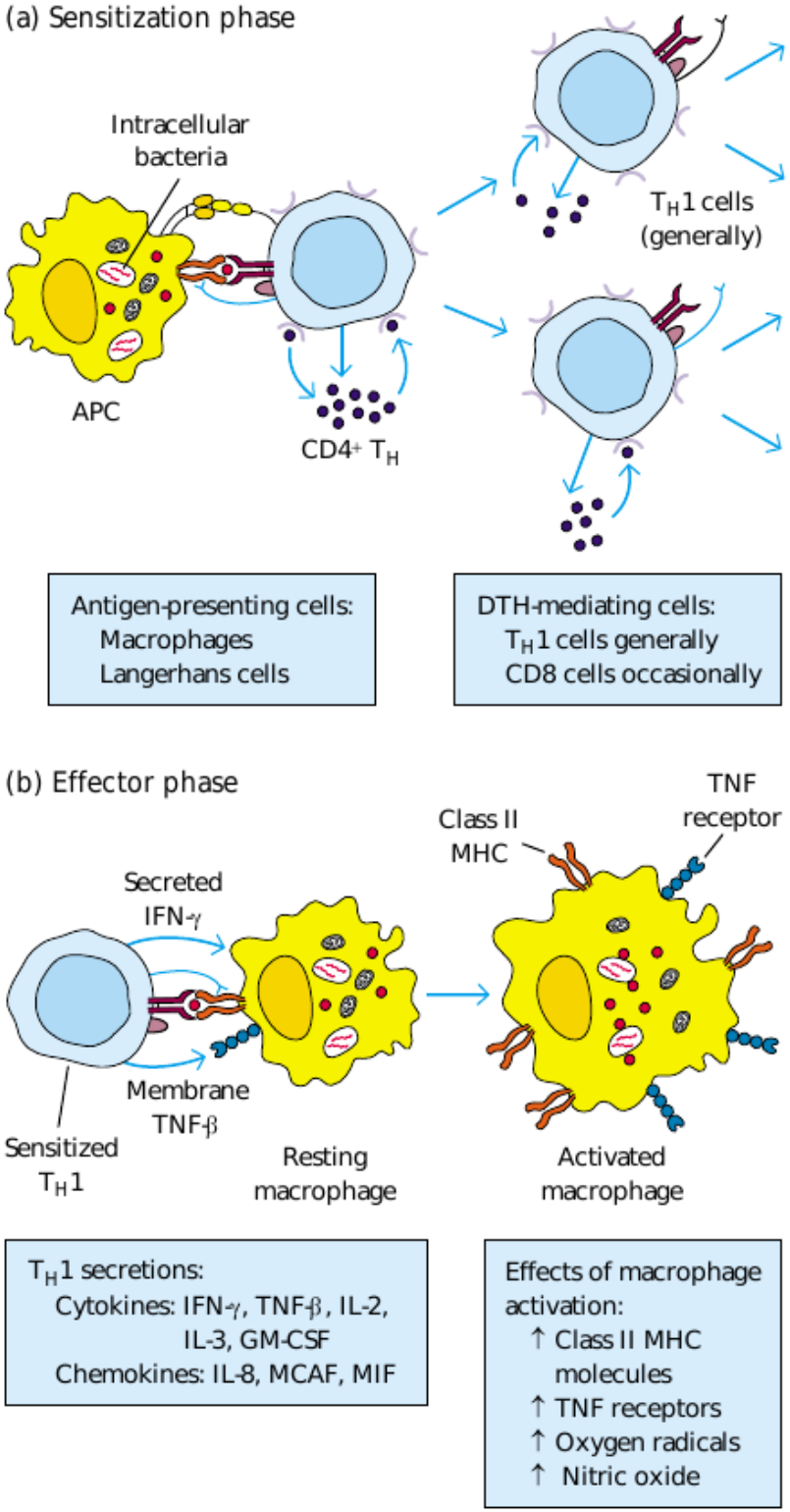
Intracellular bacteria
- *Mycobacterium tuberculosis*
- *Mycobacterium leprae*
- *Listeria monocytogenes*
- *Brucella abortus*

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

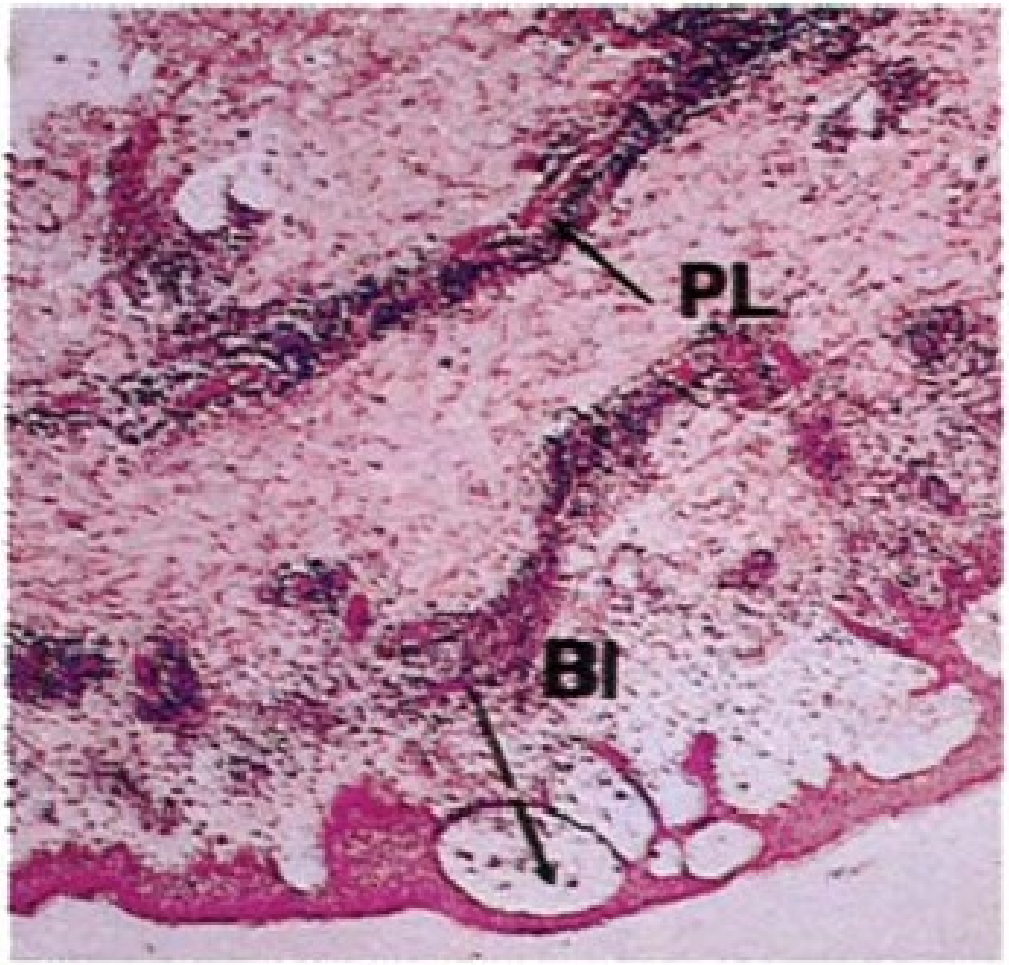
Intracellular parasites
- *Leishmania* sp.

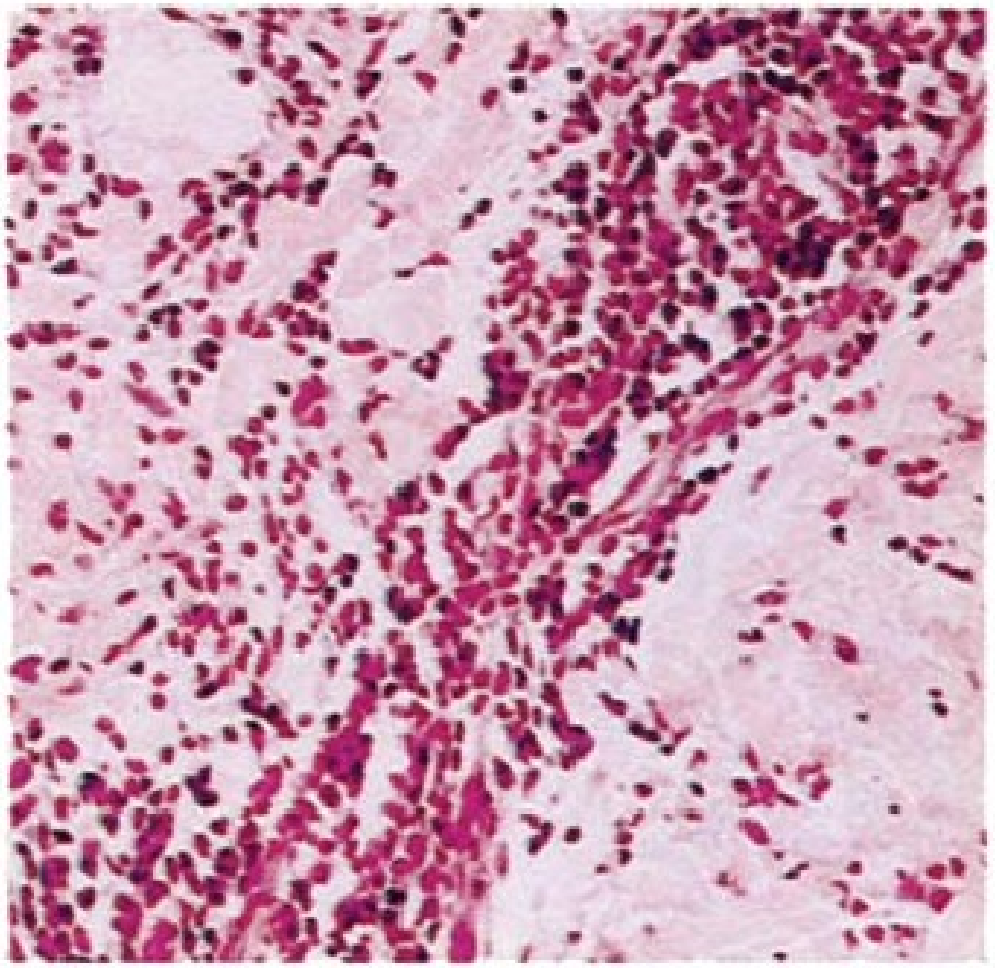
Intracellular viruses
- Herpes simplex virus
- Variola (smallpox)
- Measles virus

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

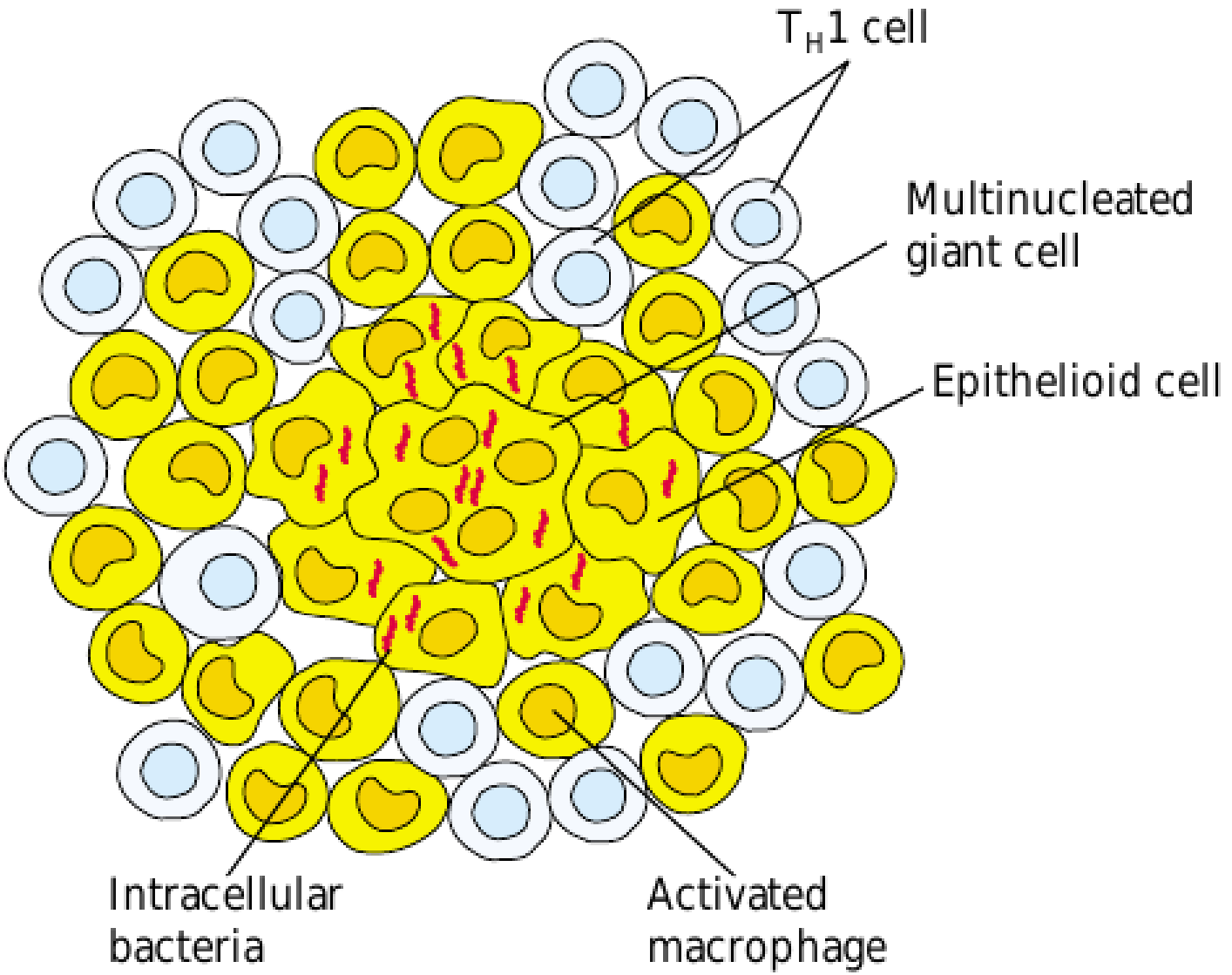

(a) Sensitization phase
Intracellular bacteria
APC
CD4+ TH
TH1 cells (generally)
Antigen-presenting cells:
Macrophages
Langerhans cells
DTH-mediating cells:
TH1 cells generally
CD8 cells occasionally
(b) Effector phase
Secreted IFN-γ
Membrane TNF-β
Sensitized TH1
Resting macrophage
Class II MHC
TNF receptor
Activated macrophage
TH1 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

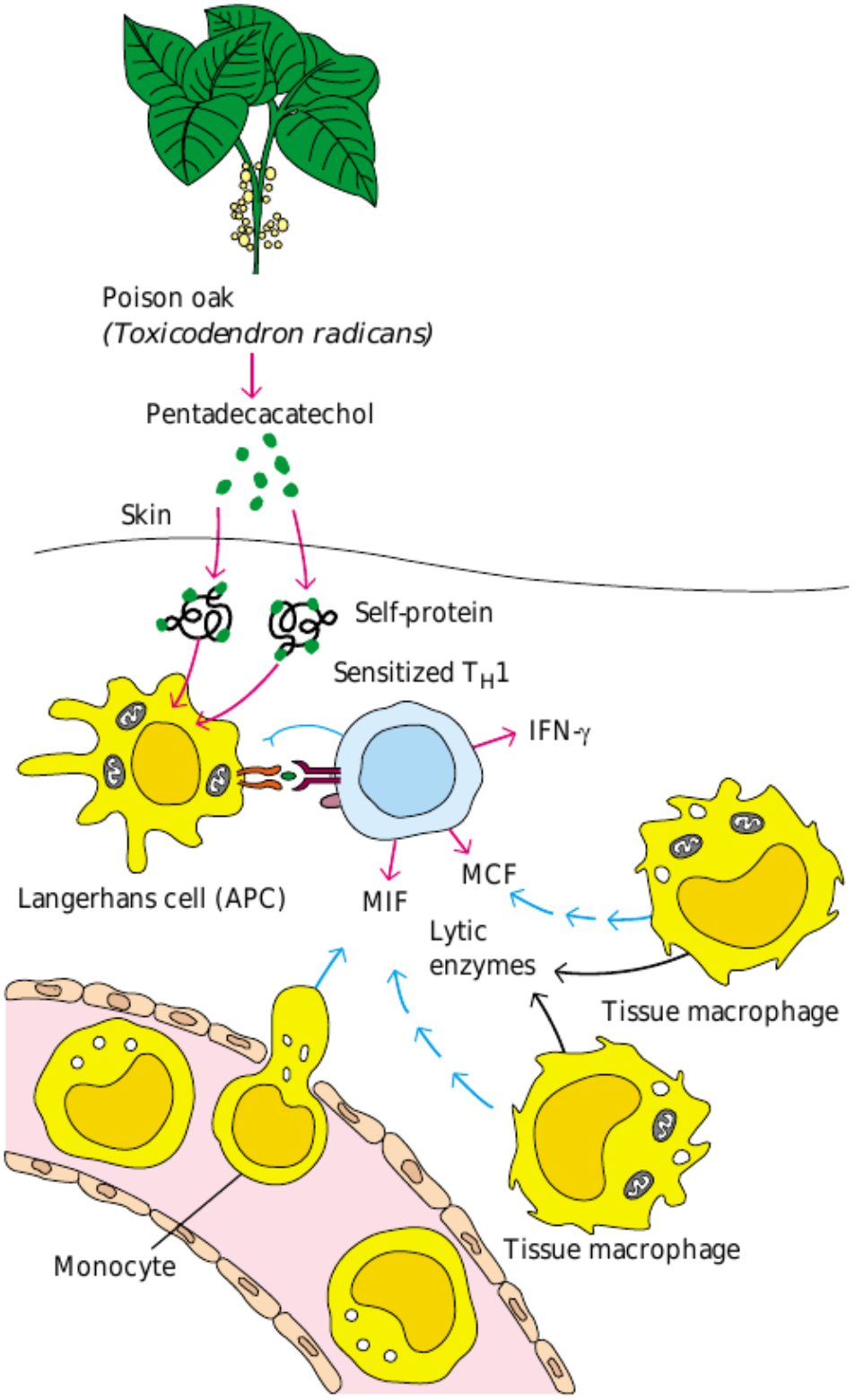
Kontakt dermatit





Granülom oluşumu: Uzuuuuun süren uyarımlar sonucu




Poison oak
(Toxicodendron radicans)
Pentadecacatechol
Skin
Self-protein
Sensitized T_H1
IFN-γ
MCF
MIF
Langerhans cell (APC)
Lytic
enzymes
Tissue macrophage
Tissue macrophage
Monocyte