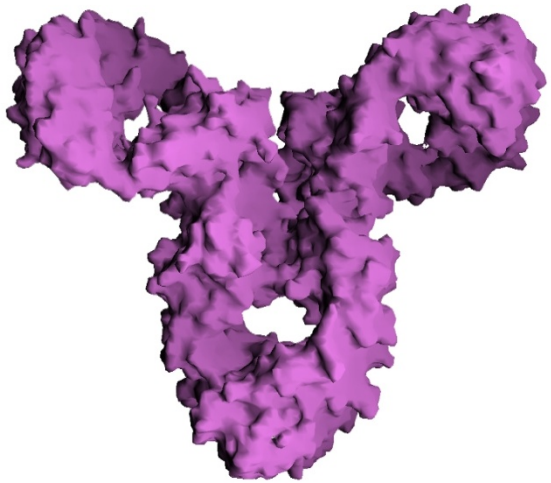
3. Az ellenanyagokra épülő immunválasz



Varga Lilian
Semmelweis Egyetem
III. Sz. Belgyógyászati Klinika

Az ellenanyag funkciói

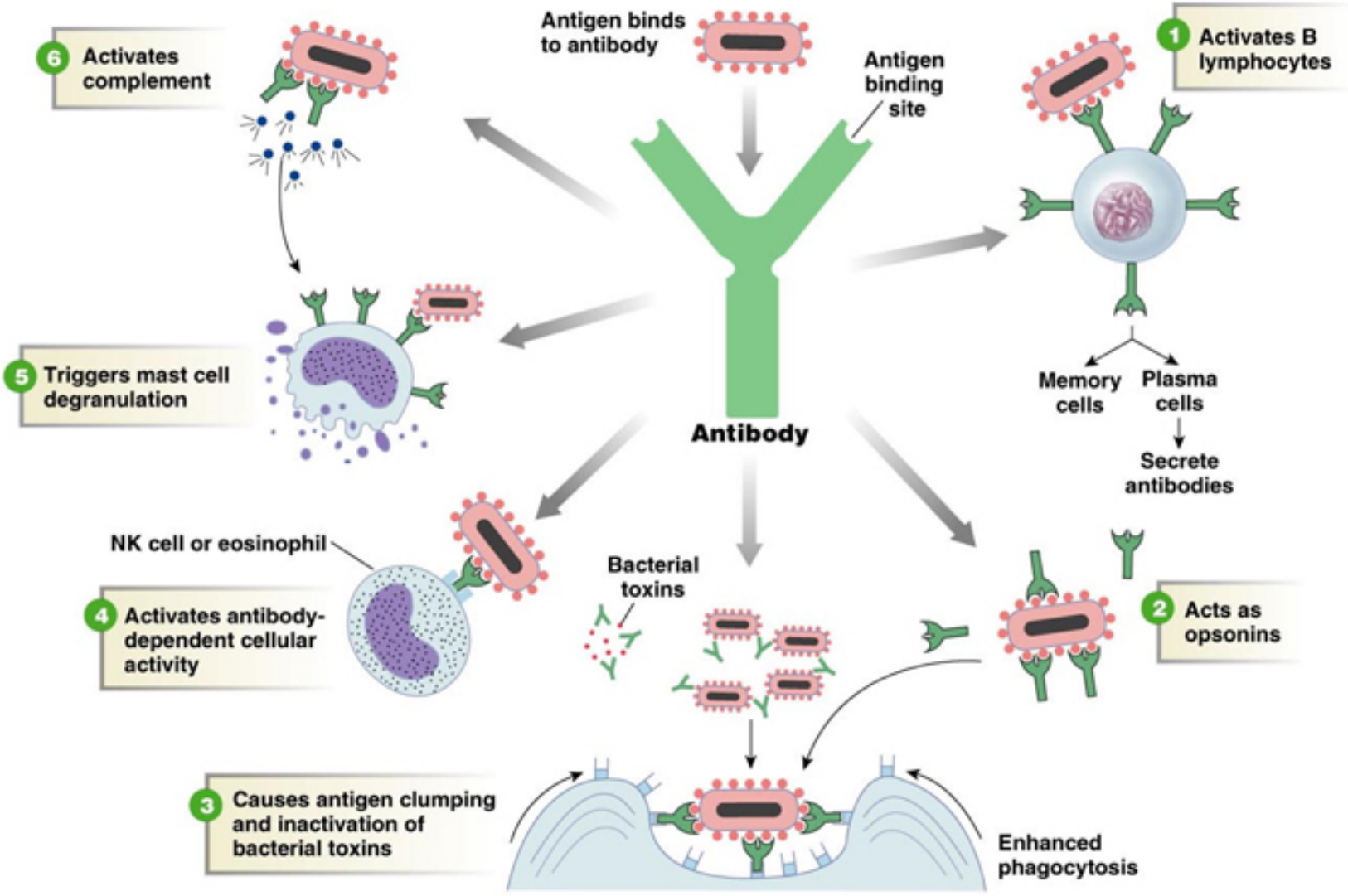
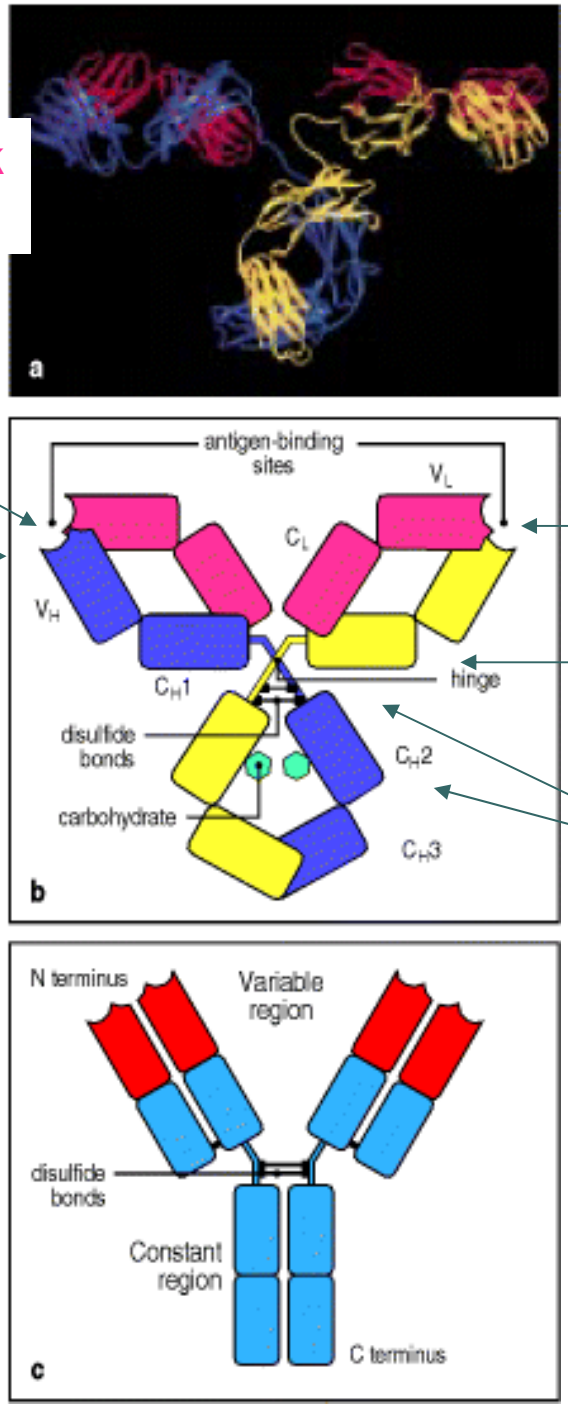


Fig. 24-13

Molekuláris kölcsönhatások helye az immunglobulinon



Paratop specifikus ab

Idiotípus specifikus ab

Antigén

C3b, C4b

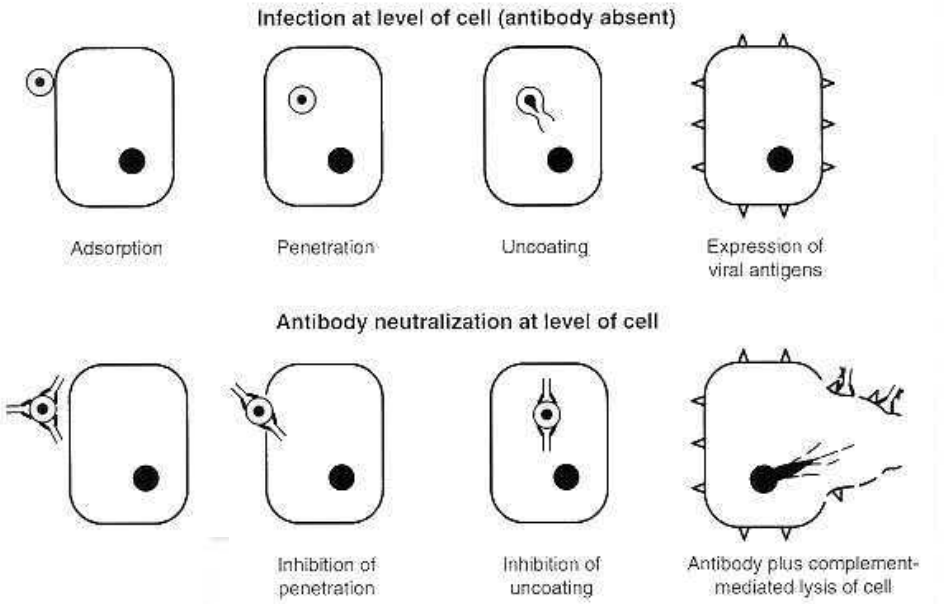
Fc receptorok

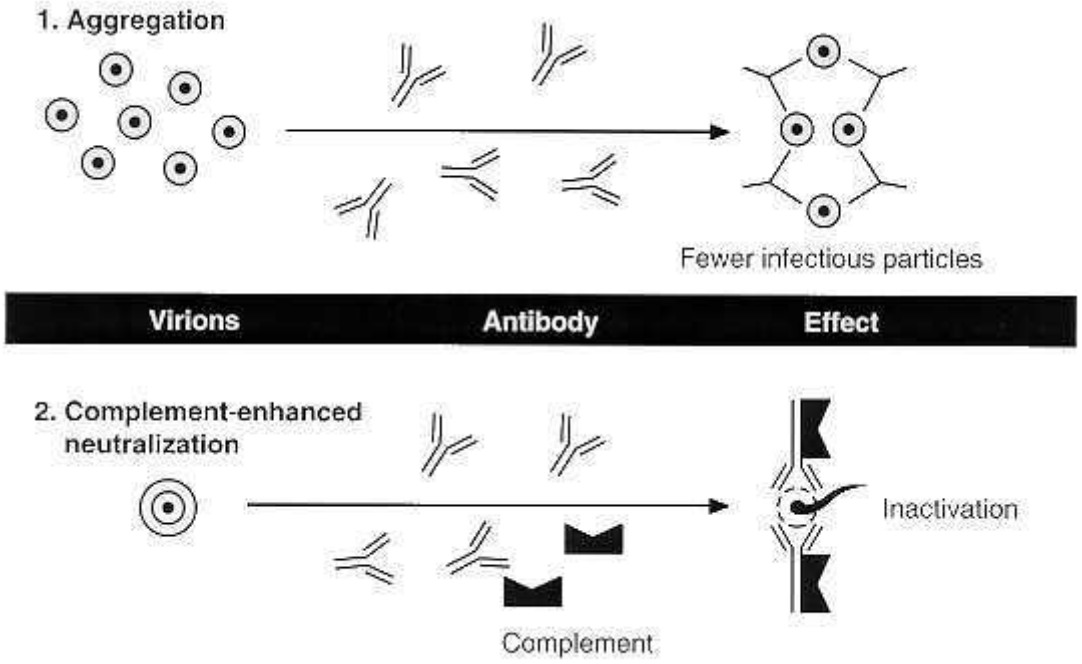
C1q globuláris rész

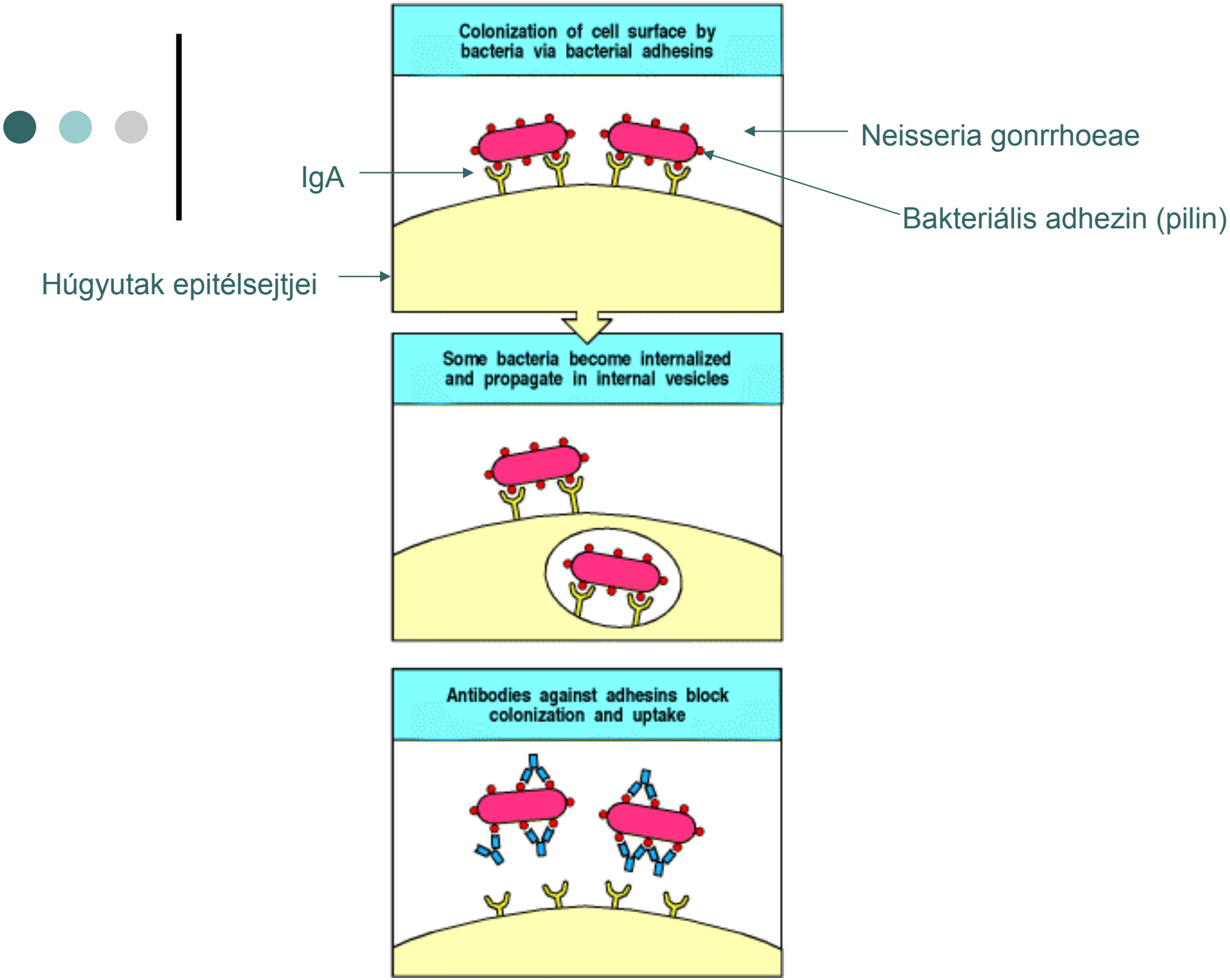
Az immunglobulinok: funkciók és eloszlás

Funkcionális aktivitás	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
neutralizáció	+	-	++	++	++	++	++	-
opszonizáció	-	-	+++	*	++	+	+	-
komplement aktiválás	+++	-	++	+	+++	-	+	-
ADCC	-	-	++	-	++	-	-	-
hízósejt aktiválás	-	-	+	-	+	-	-	+++
Eloszlás a szervezetben	**IgM**	**IgD**	**IgG1**	**IgG2**	**IgG3**	**IgG4**	**IgA**	**IgE**
átjutás epitéliumon	+	-	-	-	-	-	+++	-
átjutás placentán	-	-	+++	+	++	+/-	-	-
extravazális kijutás	+/-	-	+++	+++	+++	+++	++	+

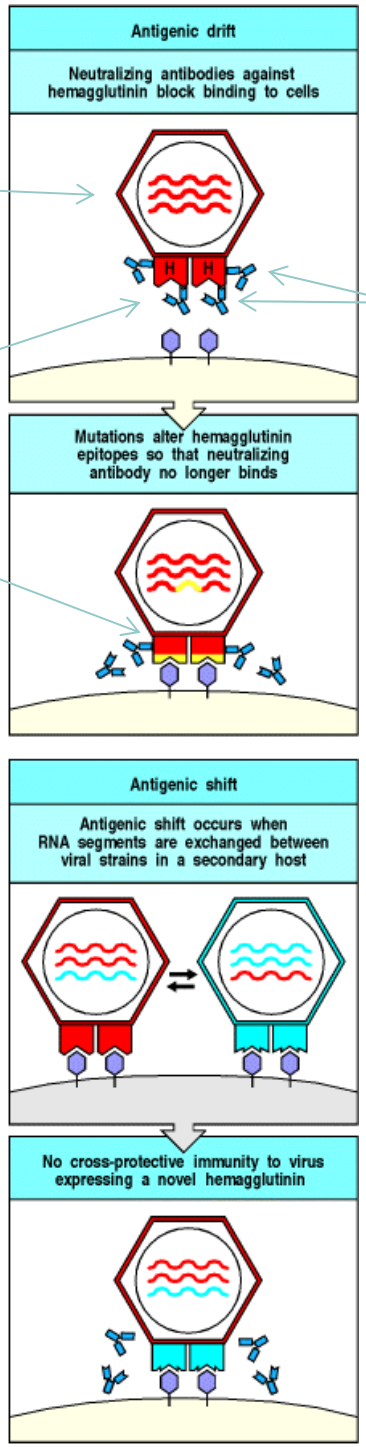
A neutralizáció






Colonization of cell surface by bacteria via bacterial adhesins
Some bacteria become internalized and propagate in internal vesicles
Antibodies against adhesins block colonization and uptake
IgA
Húgyutak epitélsejtjei
Neisseria gonrrhoeae
Bakteriális adhezin (pilin)

Influenza A vírus



Protektív ellenanyagok

hemagglutinin

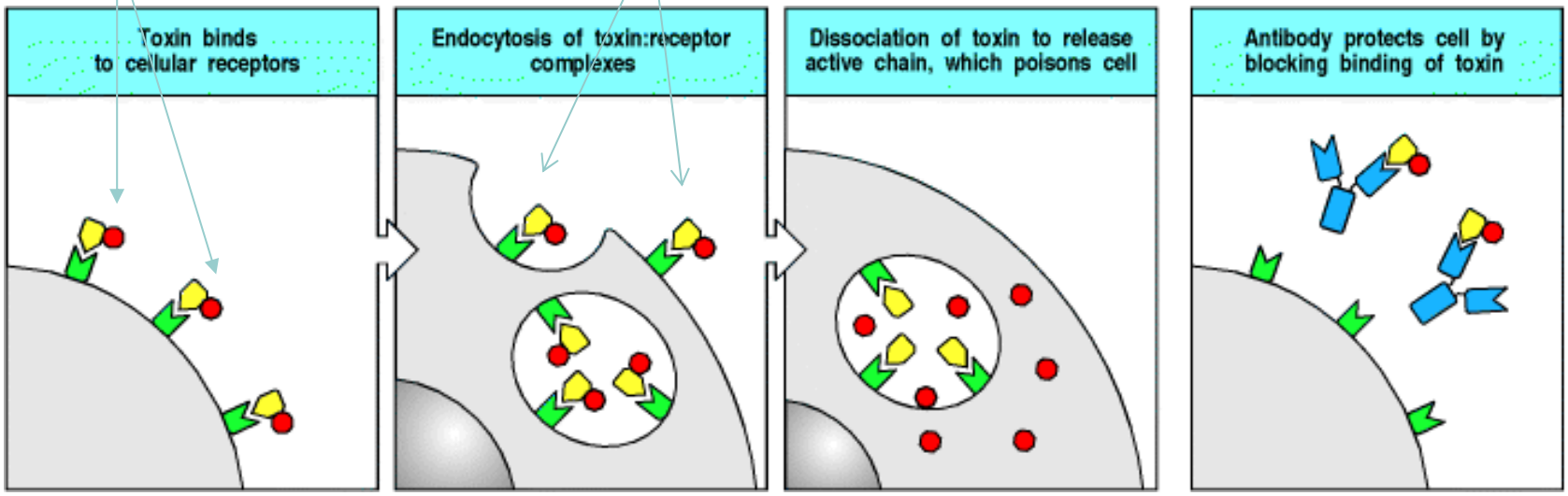
Mutációk a vírus genomban

Kétféle influenzavírus genetikai
Átrendeződése, pl. madárban

Megszűnik a védettség

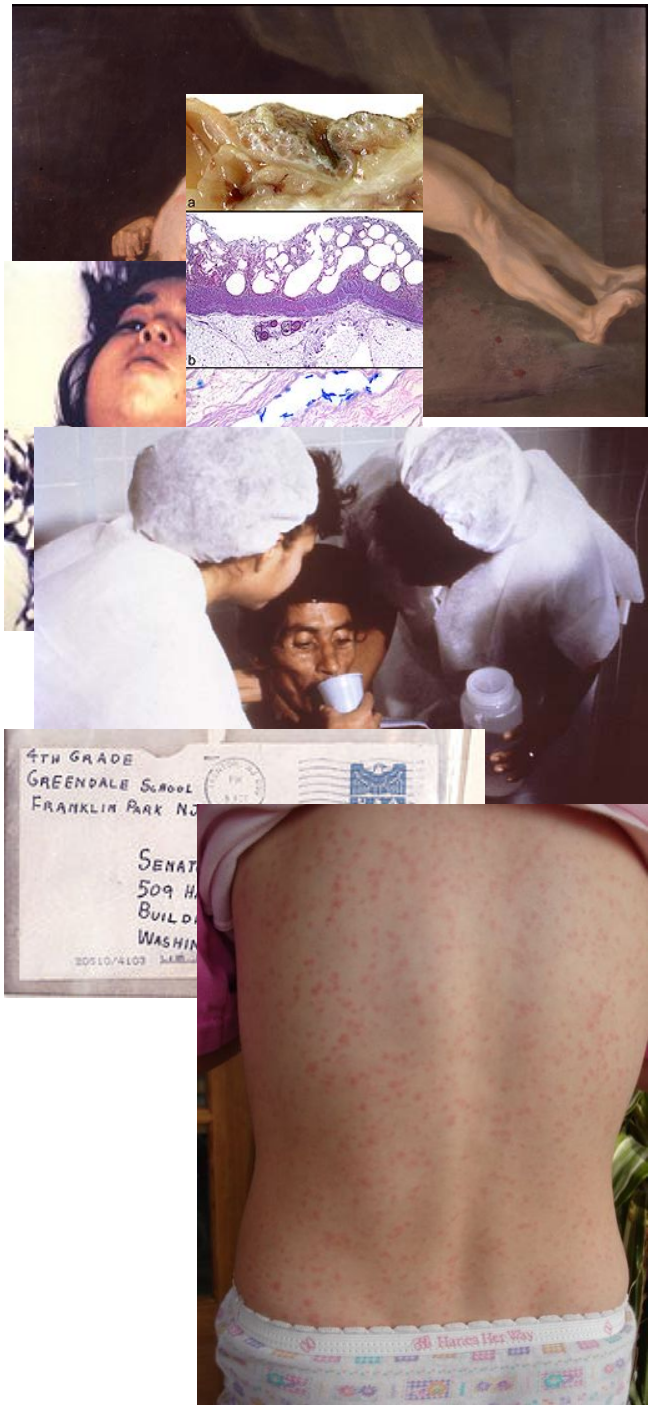
Diftéria és tetanusz toxinok

Toxikus komponens Bejutásért felelős receptorkötő rész

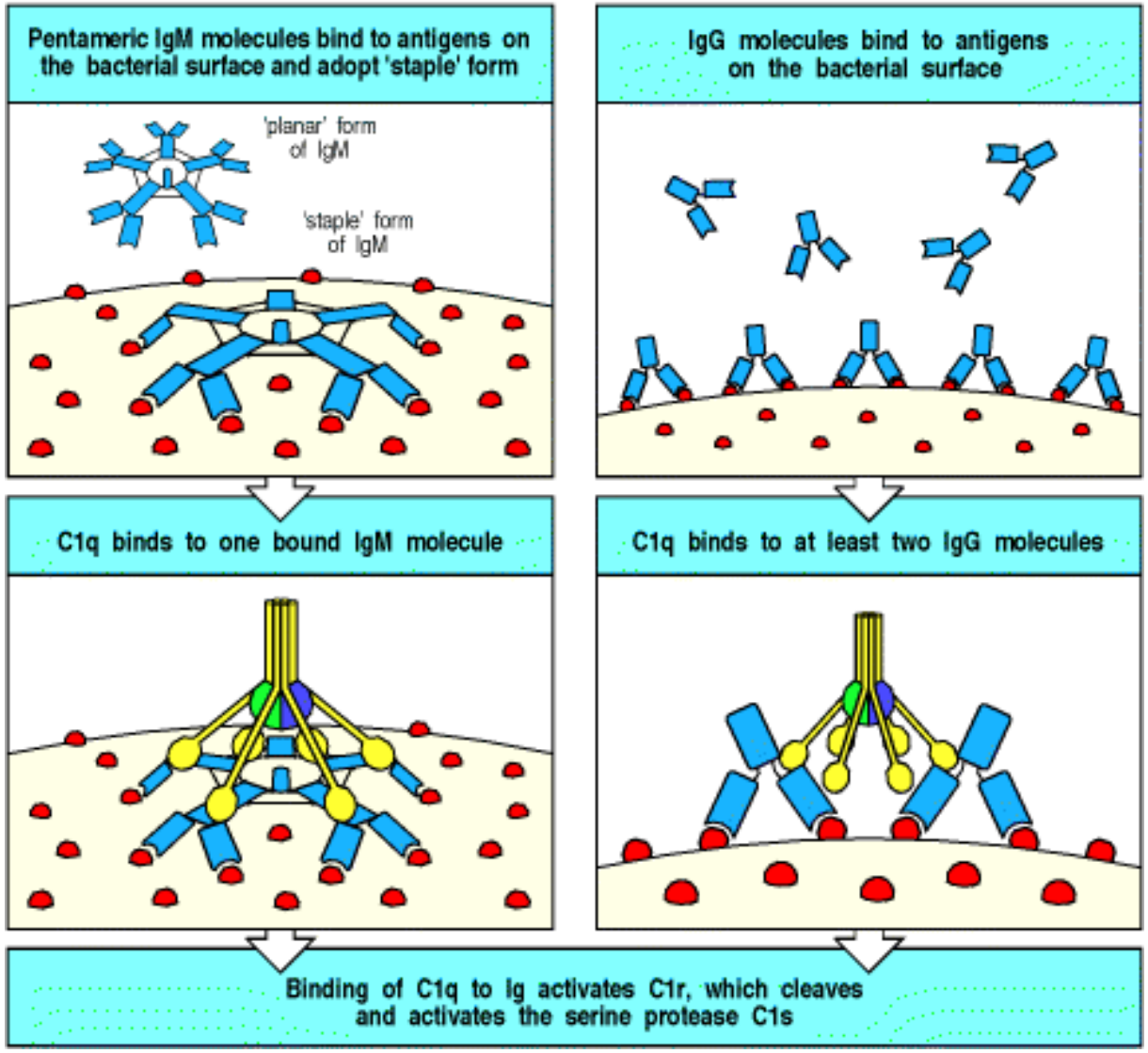


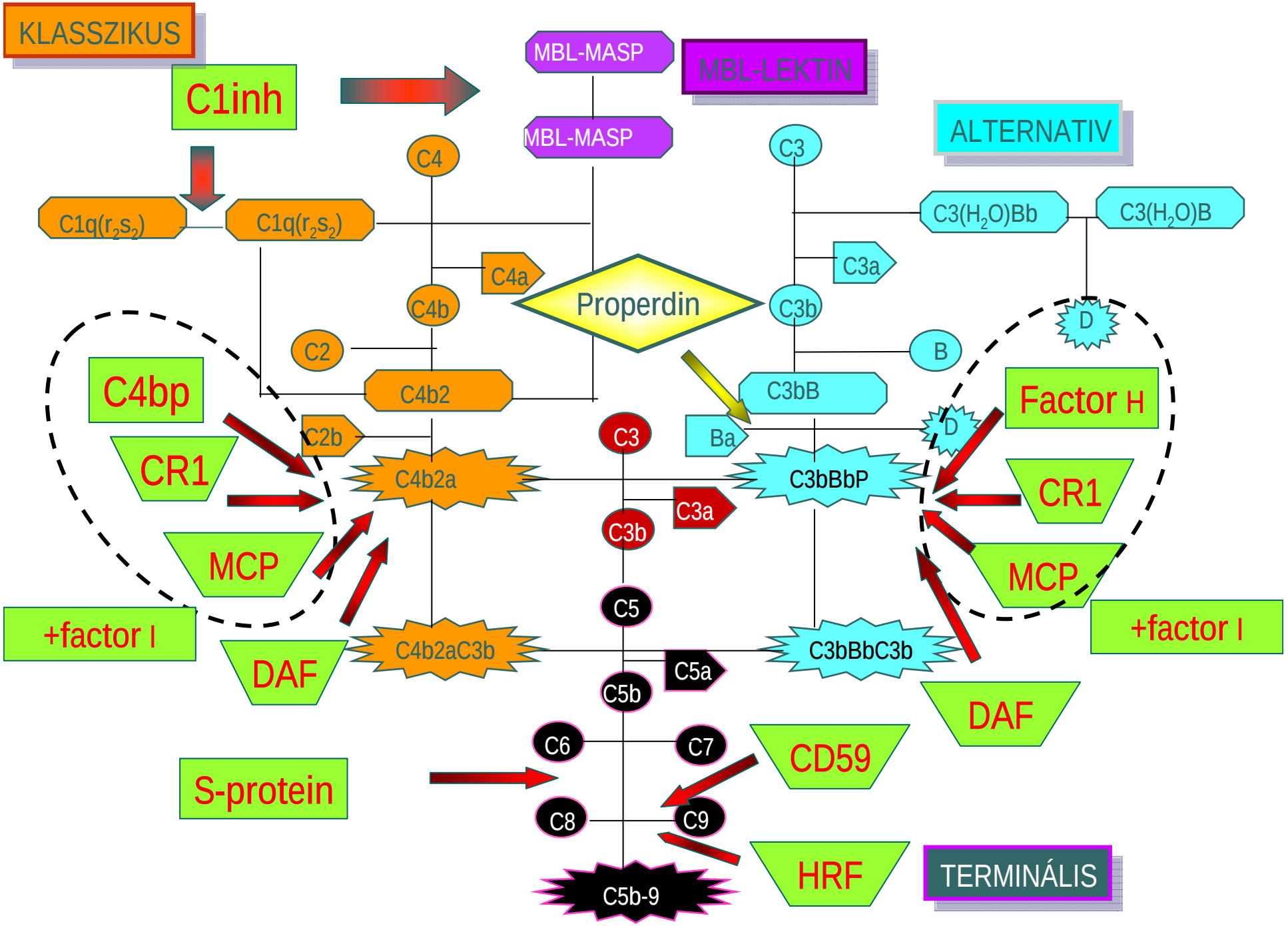
Immunizálás

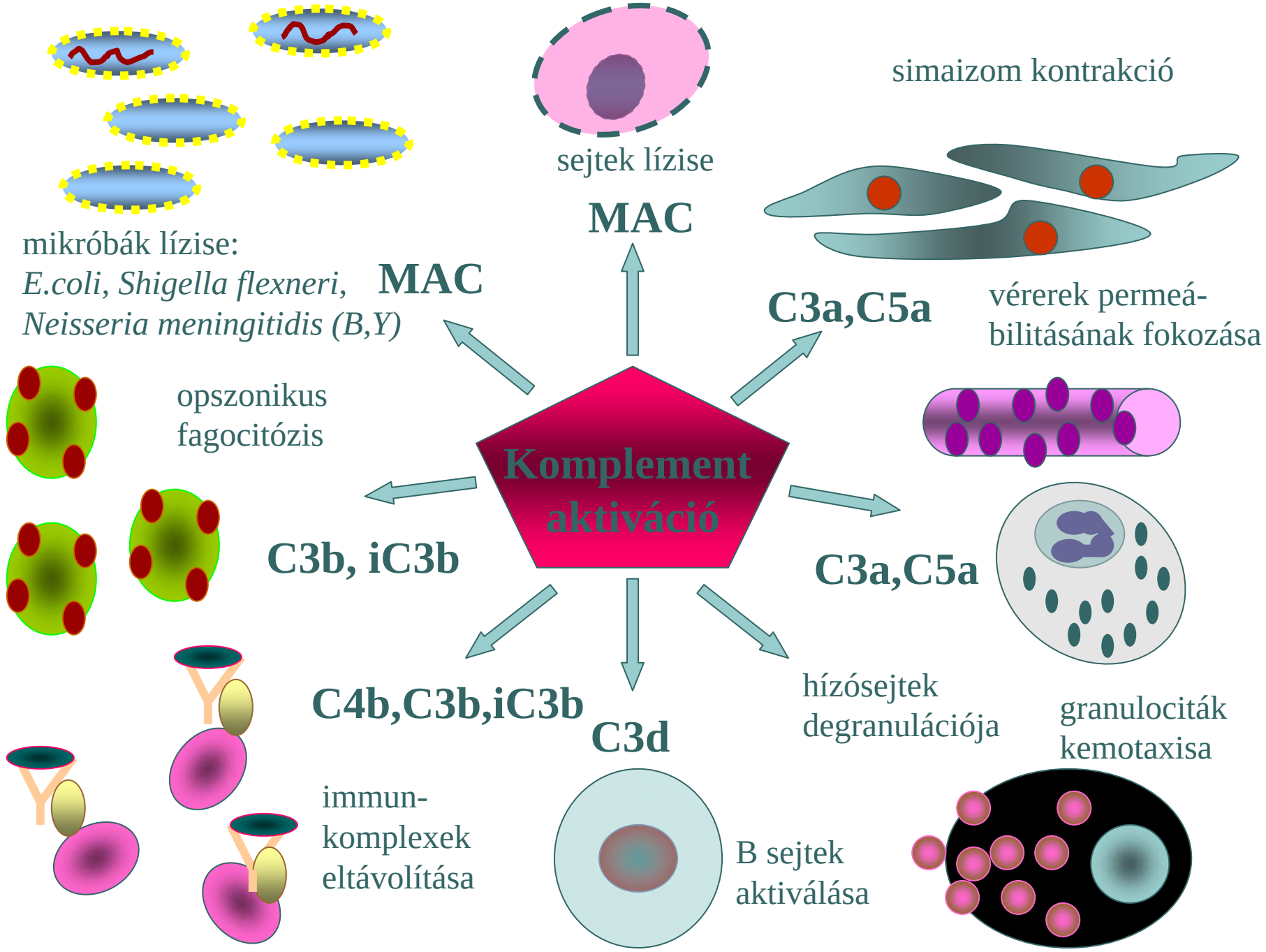
Disease	Organism	Toxin	Effects *in vivo*
Tetanus	*Clostridium tetani*	Tetanus toxin	Blocks inhibitory neuron action leading to chronic muscle contraction
Diphtheria	*Corynebacterium diphtheriae*	Diphtheria toxin	Inhibits protein synthesis leading to epithelial cell damage and myocarditis
Gas gangrene	*Clostridium perfringens*	Clostridial toxin	Phospholipase activation leading to cell death
Cholera	*Vibrio cholerae*	Cholera toxin	Activates adenylate cyclase, elevates cAMP in cells, leading to changes in intestinal epithelial cells that cause loss of water and electrolytes
Anthrax	*Bacillus anthracis*	Anthrax toxic complex	Increases vascular permeability leading to edema, hemorrhage, and circulatory collapse
Botulism	*Clostridium botulinum*	Botulinum toxin	Blocks release of acetylcholine leading to paralysis
Whooping cough	*Bordetella pertussis*	Pertussis toxin	ADP-ribosylation of G proteins leading to lymphoproliferation
		Tracheal cytotoxin	Inhibits cilia and causes epithelial cell loss
Scarlet fever	*Streptococcus pyogenes*	Erythrogenic toxin	Vasodilation leading to scarlet fever rash
		Leukocidin Streptolysins	Kill phagocytes, allowing bacterial survival
Food poisoning	*Staphylococcus aureus*	Staphylococcal enterotoxin	Acts on intestinal neurons to induce vomiting. Also a potent T-cell mitogen (SE superantigen)
Toxic-shock syndrome	*Staphylococcus aureus*	Toxic-shock syndrome toxin	Causes hypotension and skin loss. Also a potent T-cell mitogen (TSST-1 superantigen)

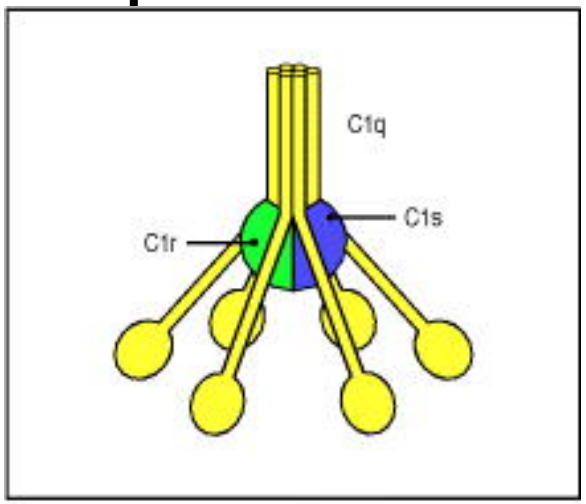


Komplementaktiváció

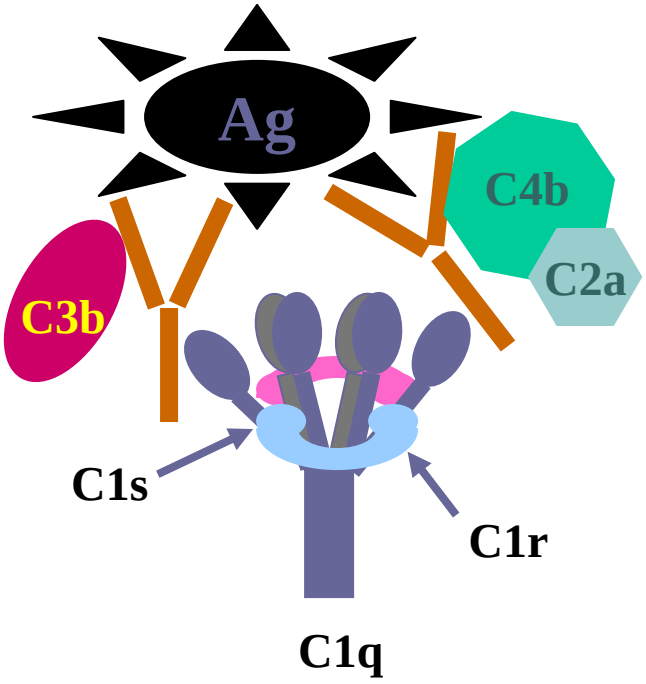



KLASSZIKUS
C1inh
MBL-MASP
MBL-LEKTIN
MBL-MASP
ALTERNATIV
C4
C3
C1q(r2s2)
C1q(r2s2)
C3(H2O)Bb
C3(H2O)B
C4a
C3a
Properdin
C4b
C3b
D
C2
B
C4bp
C4b2
C3bB
Factor H
C2b
C3
Ba
D
CR1
C4b2a
C3bBbP
CR1
C3a
C3b
MCP
MCP
C5
+factor I
+factor I
C4b2aC3b
C3bBbC3b
DAF
C5a
DAF
C5b
C6
C7
CD59
S-protein
C8
C9
HRF
TERMINÁLIS
C5b-9

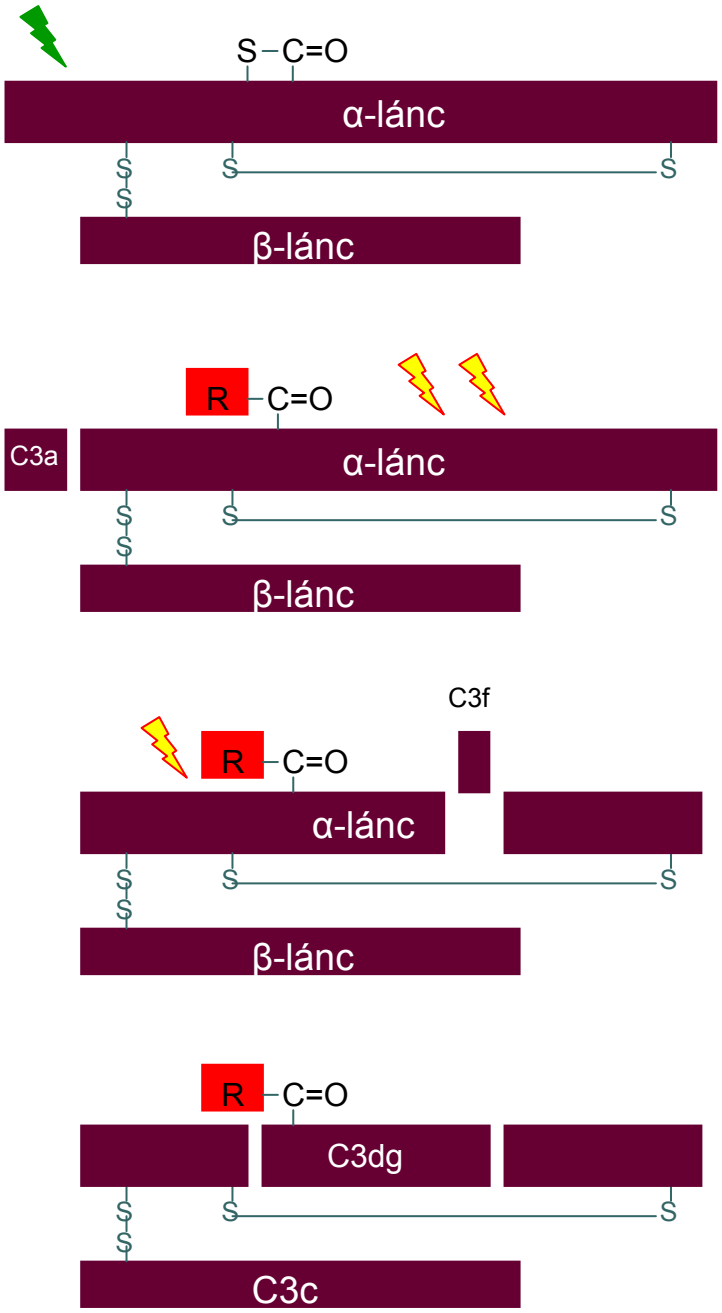

Komplement aktiváció
MAC
sejtek lízise
simaizom kontrakció
MAC
mikróbák lízise:
E.coli, Shigella flexneri,
Neisseria meningitidis (B,Y)
C3a,C5a
vérerek permeá-
bilitásának fokozása
opszonikus
fagocitózis
C3b, iC3b
C3a,C5a
C4b,C3b,iC3b
C3d
hízósejtek
degranulációja
granulociták
kemotaxisa
immun-
komplexek
eltávolítása
B sejtek
aktiválása



MBL,
Conglutinin,
SP-A



∞C1qRp/CD93 ↑ Fc és kompl. mediált Mf fagocitózist
∞cC1qR/calreticulin opszonizálja az apopt. Sejteket
∞gC1qR globuláris részt köti, PI3K aktiválás?
∞CD35 ismeretlen hatás



C3

C3b

iC3b

C3dg
+
C3c

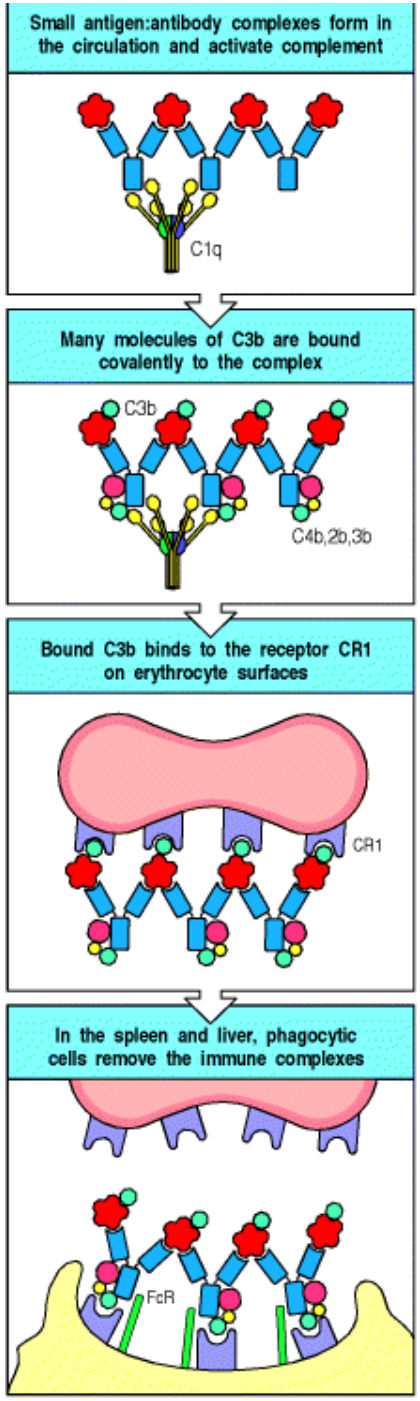
R = lehet IgG, IgA is

CR1 (CD35)
SCR
kofaktor, IC transzport,
C1q-t köt,
gátolja a B sejt aktivációt
Er, Mo, Neutr, Eos, B, ~T, FDC, Astro

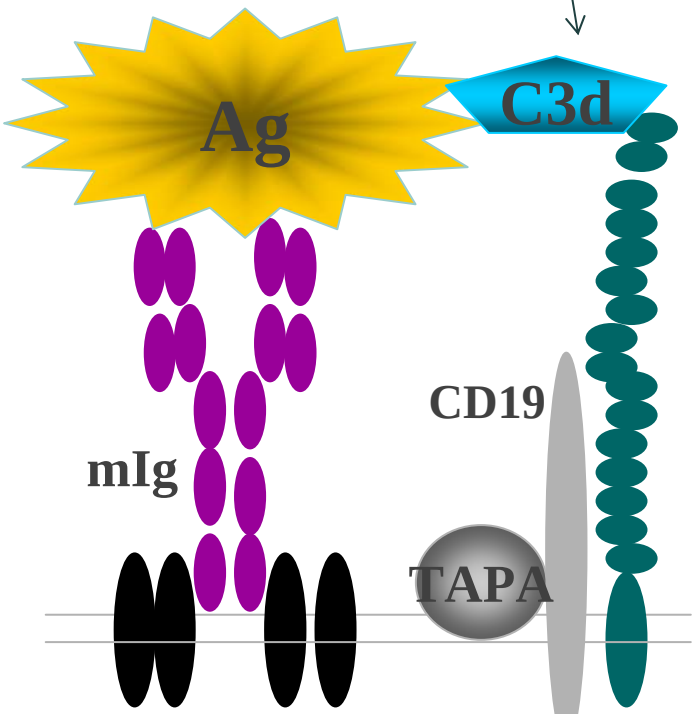
CR3 (Cd11c/CD18)
CR4 (CD11b/CD18)
integrin
fagocitózis,
ICAM-ot köt, adhézió
Leishmania, histoplasma bejutás
Mo, Gr, NK, Migl

CR2 (CD21)
SCR
EBV recepor
kofaktor, BCR koreceptor, elősegíti a B sejt aktivációt, B sejt memória elősegítése
B, FDC, ~T, Thymo, Astro

CR1



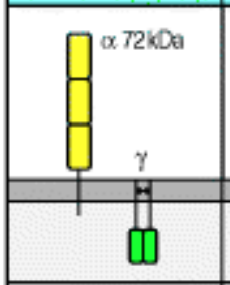
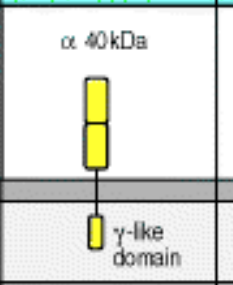
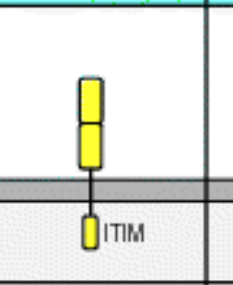
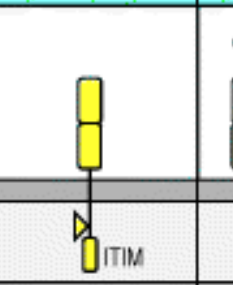
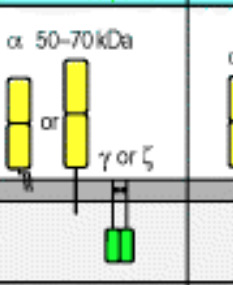
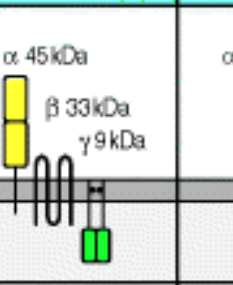
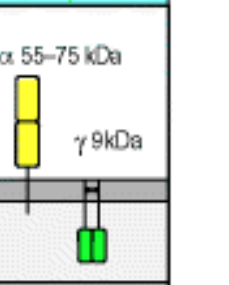
Molekuláris adjuváns



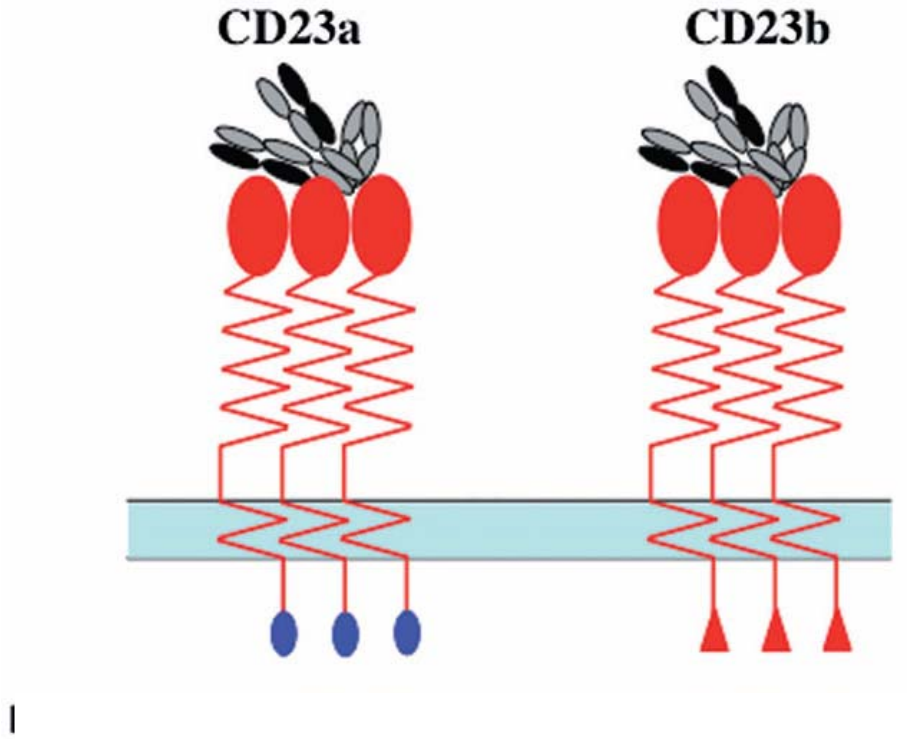
Fokozott jelátvitel, aktivációs küszöbérték csökken

molekula	aktivitás	receptor	sejt
C4a	kemotaxis?	?	?
C3a *$C3a_{desarg}$*	Kemotaxis, degranuláció, adhézió beindítás, NADPH oxidáz út aktiválás, ea termelést gátol	C3aR *-G-proteinhez kapcsolódik*	Mf, Eos, Neu, Baso, hízósejt, Tr, End, Epi,
C5a *$C5a_{desarg}$*	kemotaxis, degranuláció gyulladásos mediátorok felszabadítása, adhézió beindítás, NADPH oxidáz út aktiválás, arachidonsav metabolizmos, ea termelést fokoz	C5aR *-G-proteinhez kapcsolt* C5L2 *-nem kapcsolt G-proteinhez*	Mf, Eos, Neu, Baso, hizósejt, Tr, Si, End, Epi,
C5b-9 Sublitikus	lízis, érzékenyítés Sejtaktiválás Mf-ban: cyclooxigenase és lipoxygenase utak aktiválása, gyulladásos mediátorok felszabadítása	-	Célsejt, baktérium

Az immunglobulin szupercsaládba tartozó Fc receptorok*

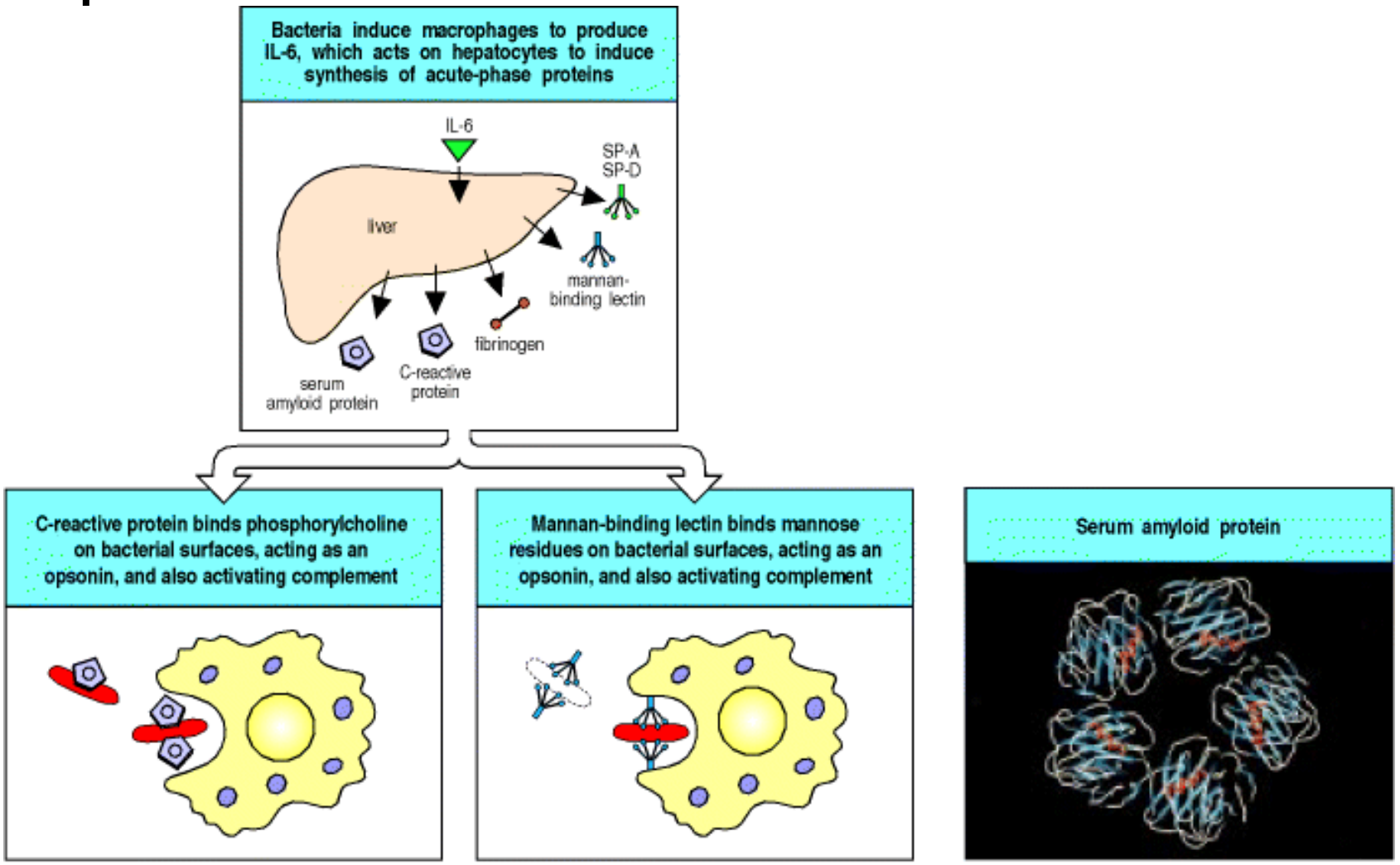
Receptor	FcγRI (CD64)	FcγRII-A (CD32)	FcγRII-B2 (CD32)	FcγRII-B1 (CD32)	FcγRIII (CD16)	FcεRI	FcαRI (CD89)
Structure							
Binding Order of affinity	IgG1 10^8 M^{-1} 1) IgG1=IgG3 2) IgG4 3) IgG2	IgG1 2×10^6 M^{-1} 1) IgG1 2) IgG3=IgG2* 3) IgG4	IgG1 2×10^6 M^{-1} 1) IgG1=IgG3 2) IgG4 3) IgG2	IgG1 2×10^6 M^{-1} 1) IgG1=IgG3 2) IgG4 3) IgG2	IgG1 5×10^5 M^{-1} IgG1=IgG3	IgE 10^{10} M^{-1}	IgA1, IgA2 10^7 M^{-1} IgA1=IgA2
Cell type	Macrophages Neutrophils† Eosinophils† Dendritic cells	Macrophages Neutrophils Eosinophils Platelets Langerhans' cells	Macrophages Neutrophils Eosinophils	B cells Mast cells	NK cells Eosinophils Macrophages Neutrophils Mast cells	Mast cells Eosinophils† Basophils	Macrophages Neutrophils Eosinophils‡
Effect of ligation	Uptake Stimulation Activation of respiratory burst Induction of killing	Uptake Granule release (eosinophils)	Uptake Inhibition of stimulation	No uptake Inhibition of stimulation	Induction of killing (NK cells)	Secretion of granules	Uptake Induction of killing

**Kivéve a pIgR és FcRn receptorokat*

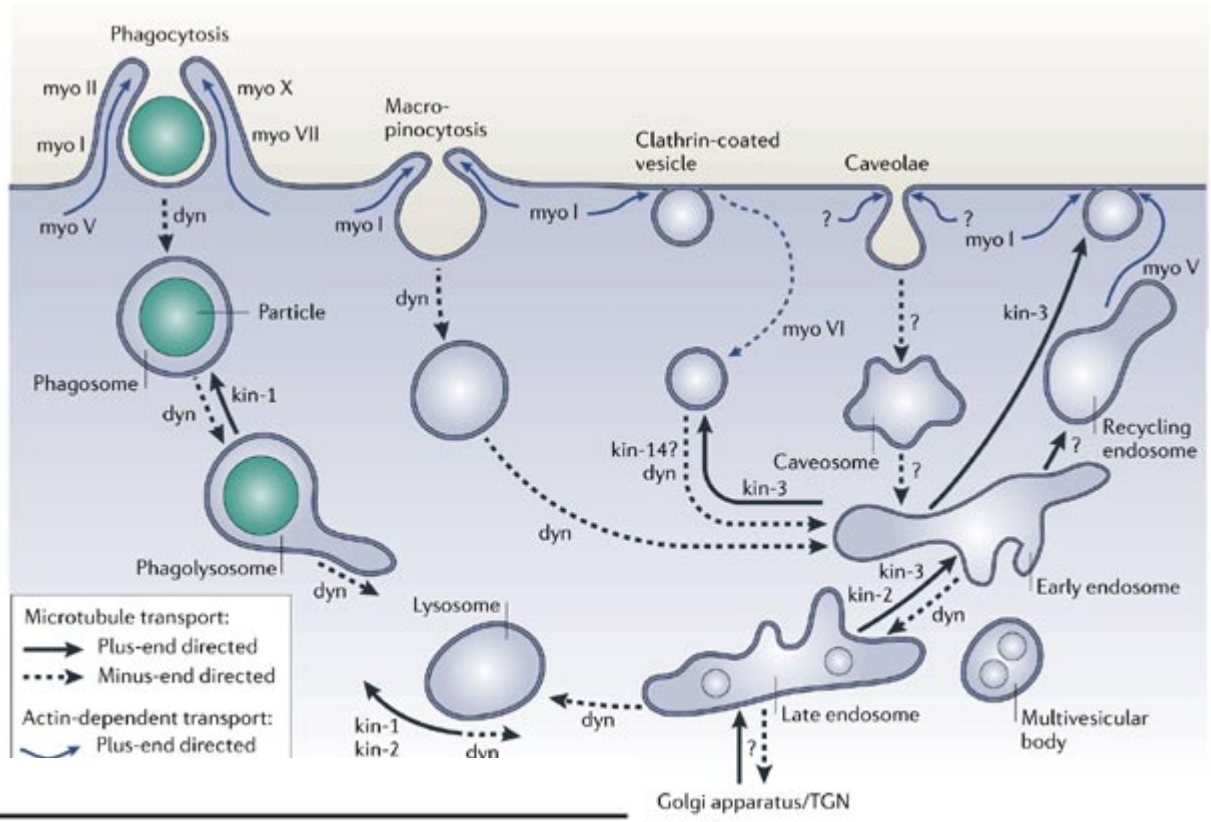


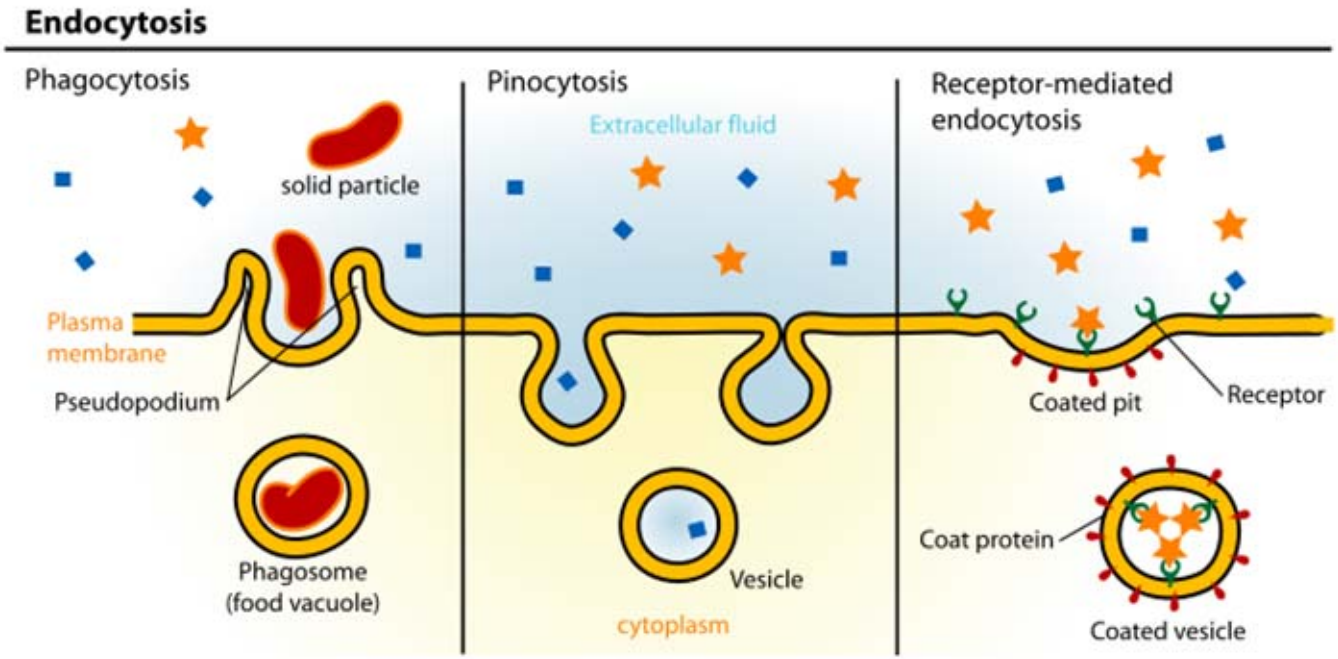
C-típusú lektin
IgE-kötés kis affinitással,
Ligandja az EBV receptor
Mf, B, T Eos, FDC, Langerhans, Epit
B sejteken a-forma konstitutivan, b-forma IL-4 indukáltan jelenik meg.
IgE termelés szabályozása B-sejteken a szolubilis fragmentumok által

Opszonizáció

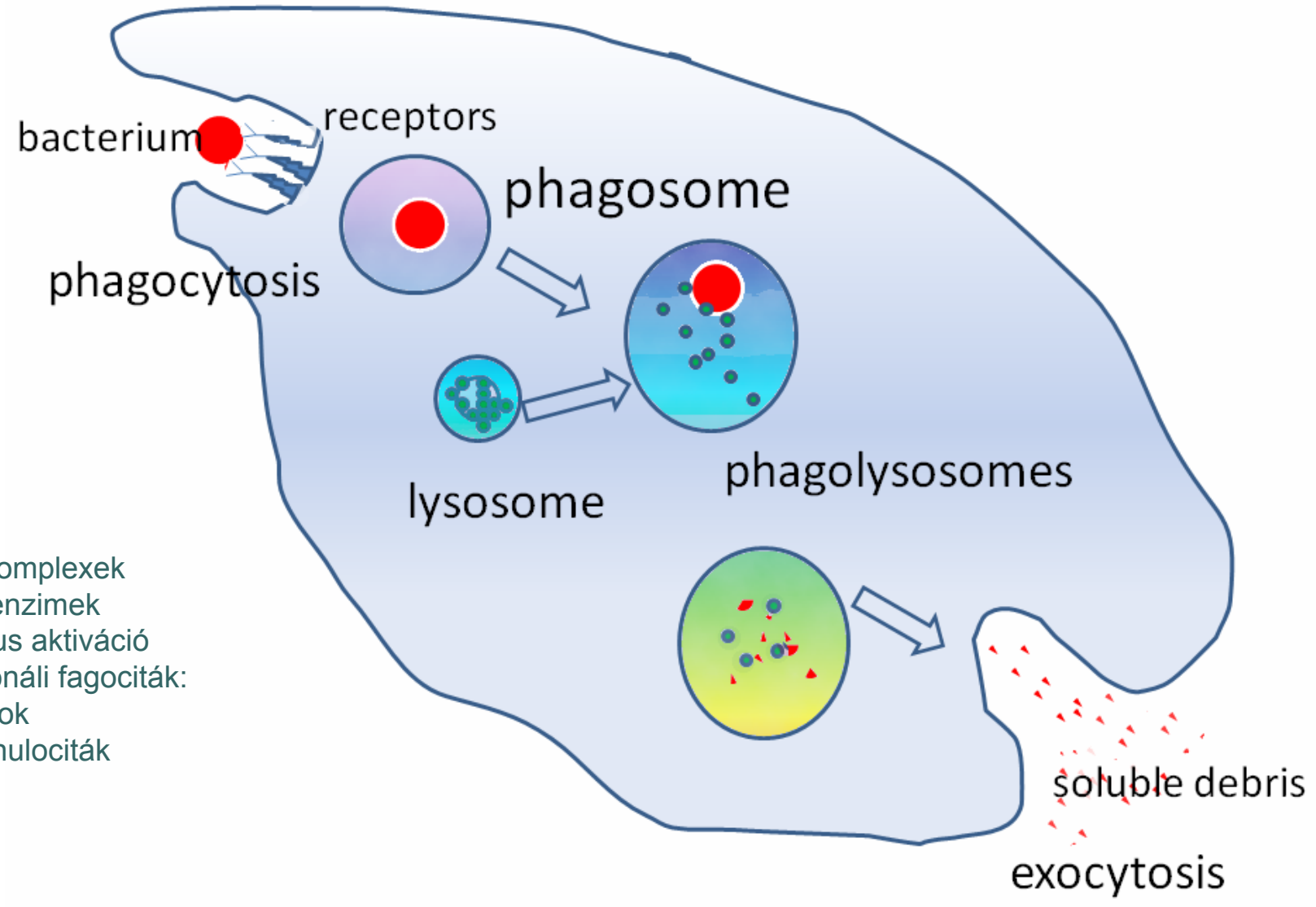


Az endocitózis

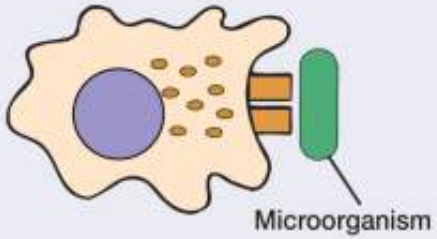
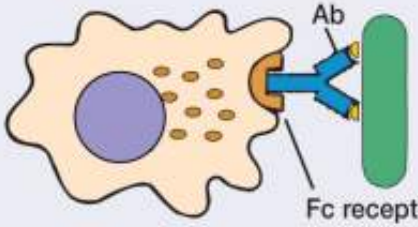
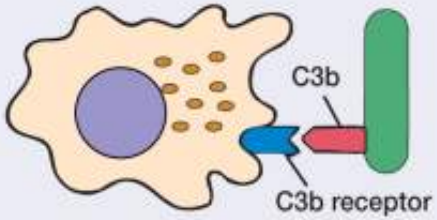
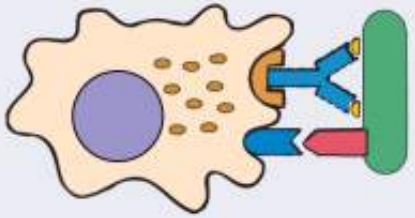




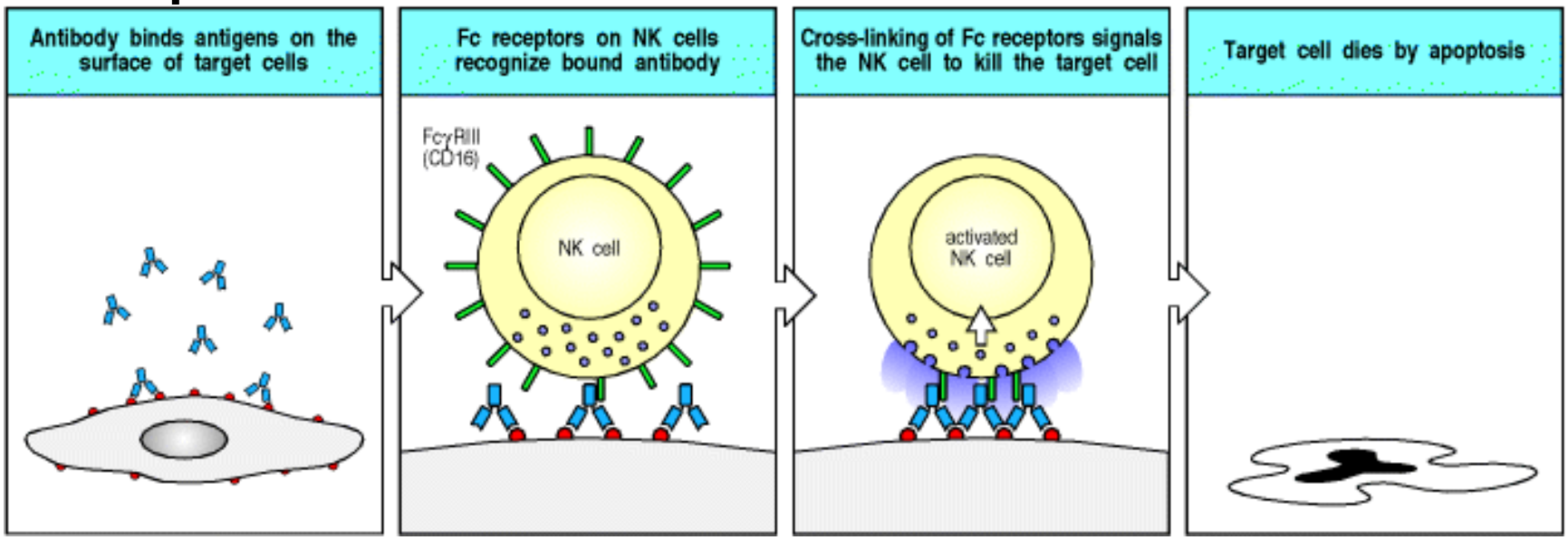
Fagocitózis



Oxidatív komplexek
Emésztő enzimek
Metabolikus aktiváció
Professzionáli fagociták:
-makrofágok
-PMN granulociták
-DC

Phagocytic cell	Degree of binding	Opsonin
 (a) Attachment by nonspecific receptors	±	–
 (b)	+	Antibody
 (c)	+ +	Complement C3b
 (d)	+ + + +	Antibody and complement C3b

Antitest-függő sejtes citotoxicitás: ADCC

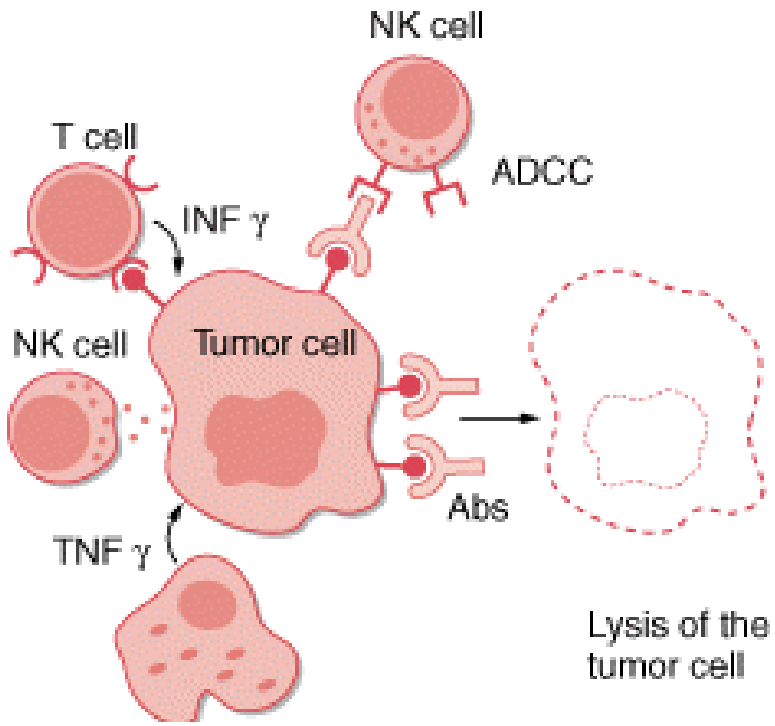


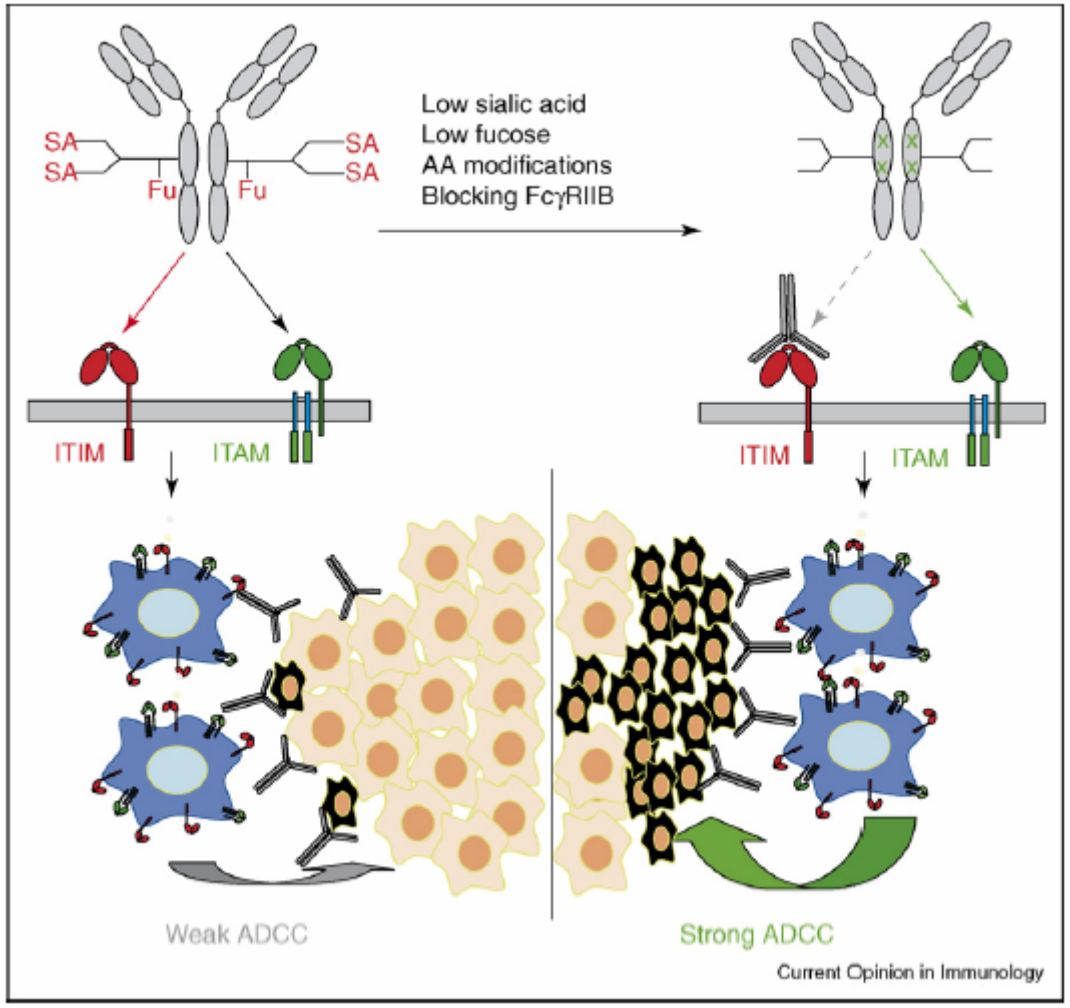
NK,
Makrofágok,
Eozinofil granulociták

KAR: killer funkció aktiválás
KIR: MHCI felismerés,
killer funkció gátlás
FcγRIII

Tumorsejtek (NK),
Virussal fertőzött sejtek (varicella, CMV) (Mf)
Férgek (Eos)

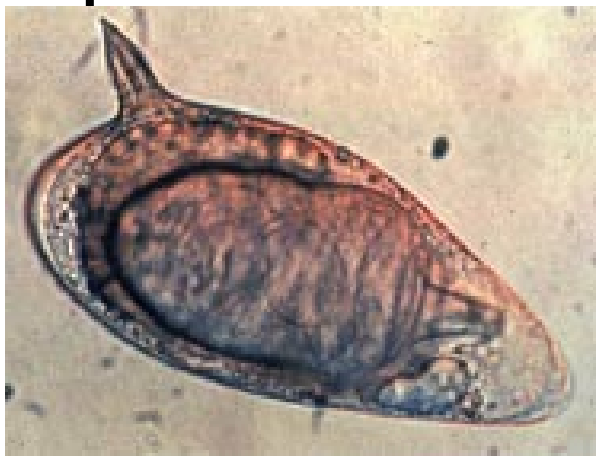
+ iC3b és CR3, CR4
Fokozza az adherenciát, de a citotoxicitást nem


NK cell
T cell
ADCC
INF γ
NK cell
Tumor cell
Abs
TNF γ
Lysis of the
tumor cell



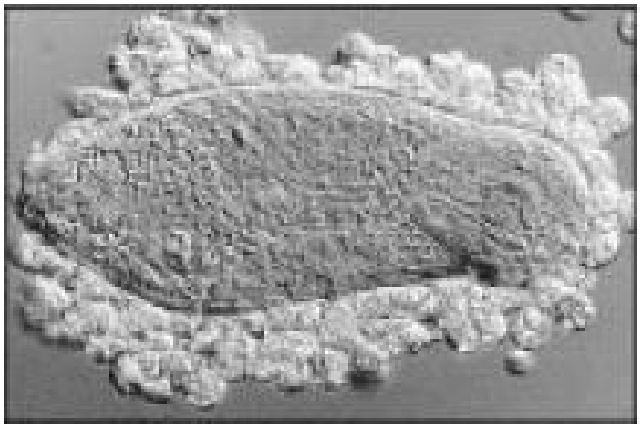
Nimmerjahn és Ravetch Cur Opin Immunol 2007

Schistosoma pete

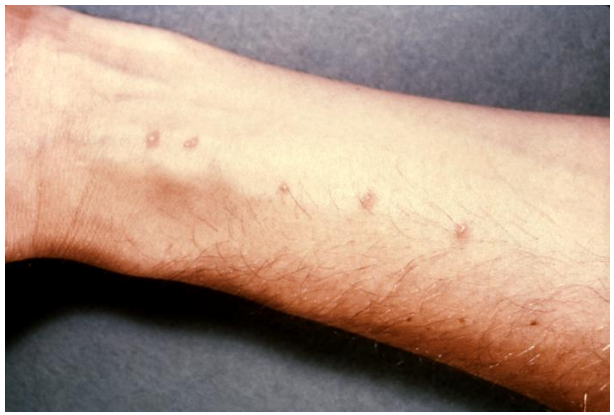


Fonalféreg a bél falán

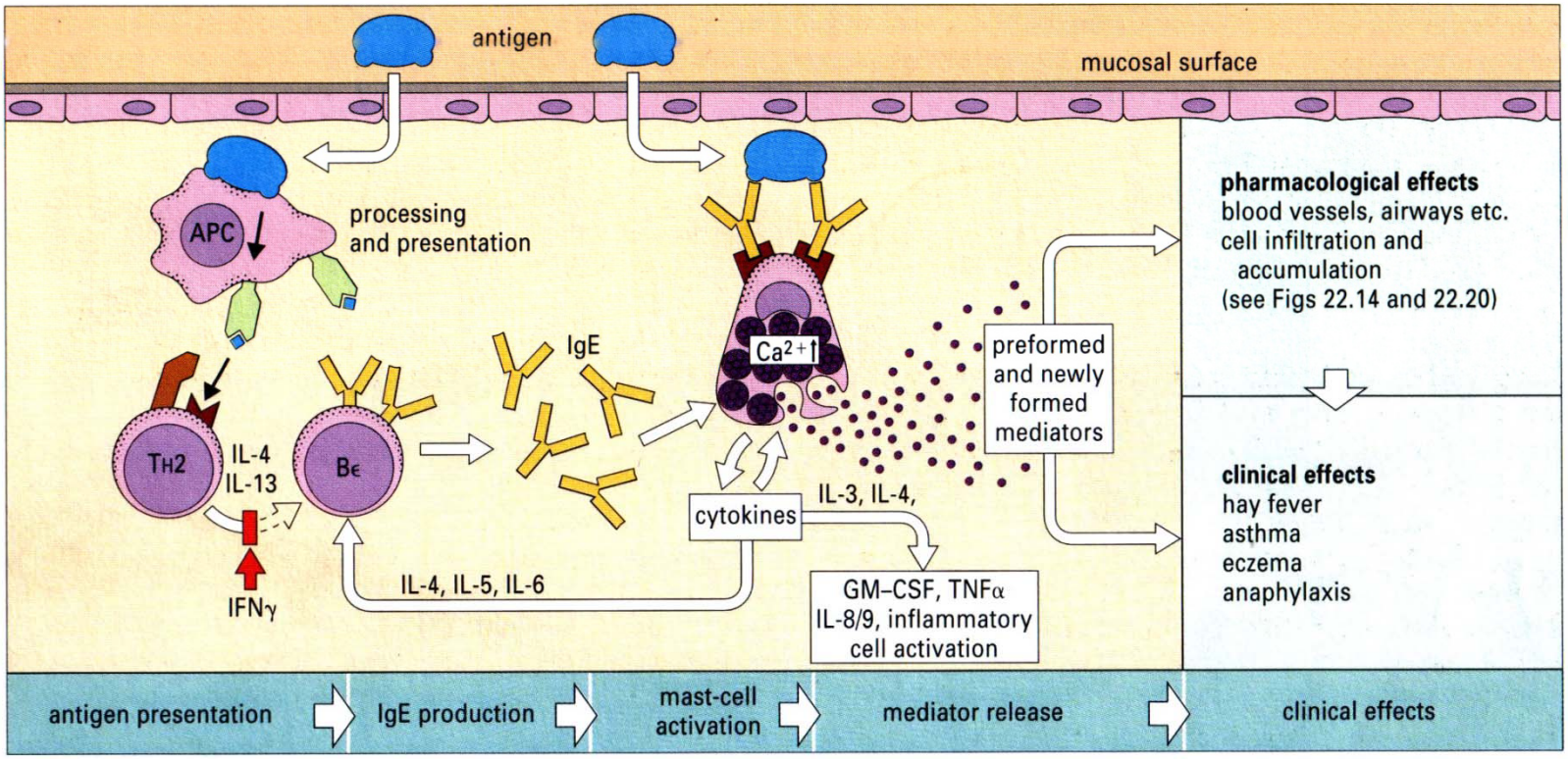
IgE-vel fedett Schistosoma pete, amint Eos gran. támadják

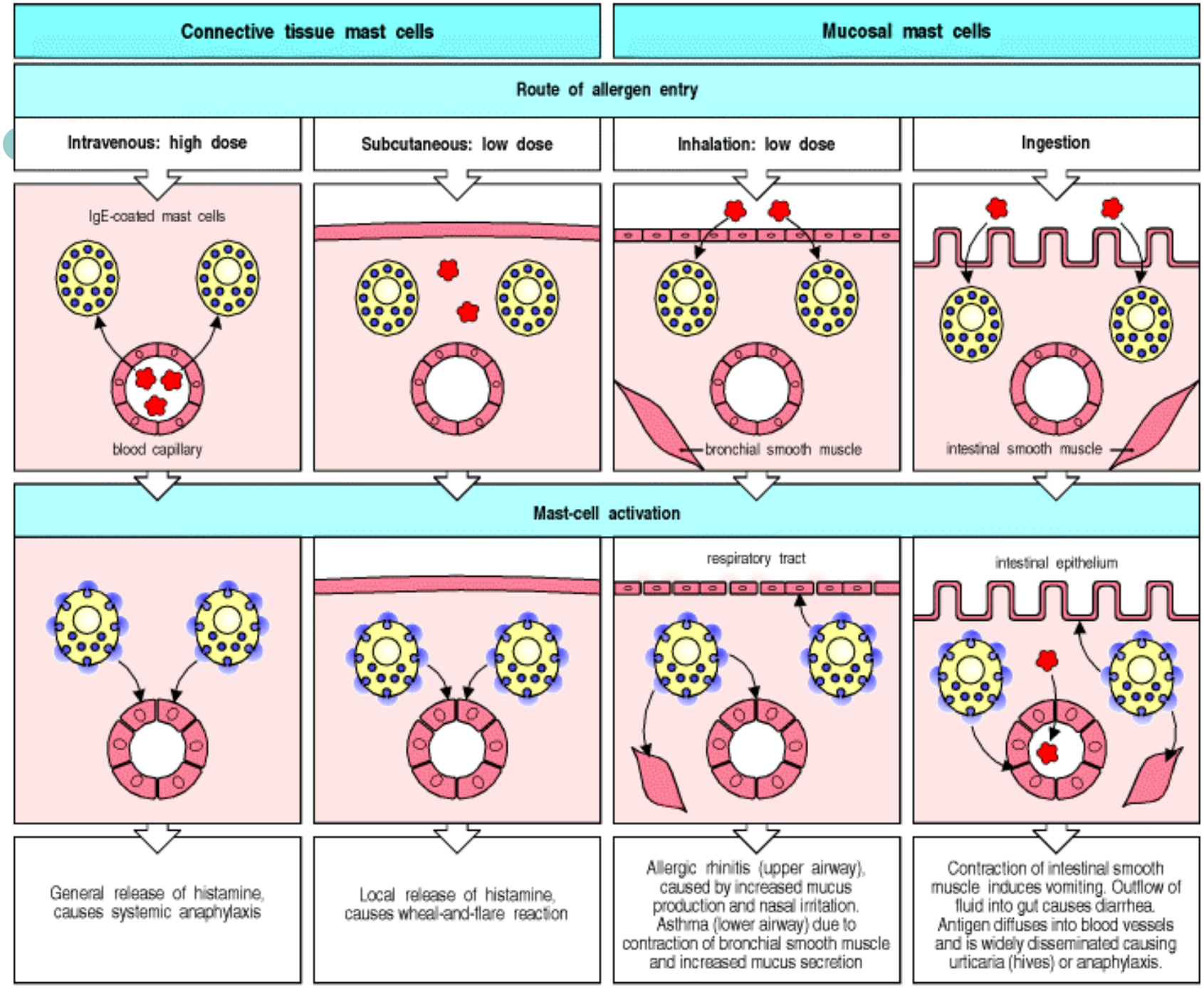


Schistosomiázis: hegek jelzik a bőrön való áthatolást



Hízósejt degranuláció




Connective tissue mast cells
Mucosal mast cells
Route of allergen entry
Intravenous: high dose
Subcutaneous: low dose
Inhalation: low dose
Ingestion
IgE-coated mast cells
blood capillary
bronchial smooth muscle
intestinal smooth muscle
Mast-cell activation
respiratory tract
intestinal epithelium
General release of histamine, causes systemic anaphylaxis
Local release of histamine, causes wheal-and-flare reaction
Allergic rhinitis (upper airway), caused by increased mucus production and nasal irritation. Asthma (lower airway) due to contraction of bronchial smooth muscle and increased mucus secretion
Contraction of intestinal smooth muscle induces vomiting. Outflow of fluid into gut causes diarrhea. Antigen diffuses into blood vessels and is widely disseminated causing urticaria (hives) or anaphylaxis.

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