

Basic Immunology

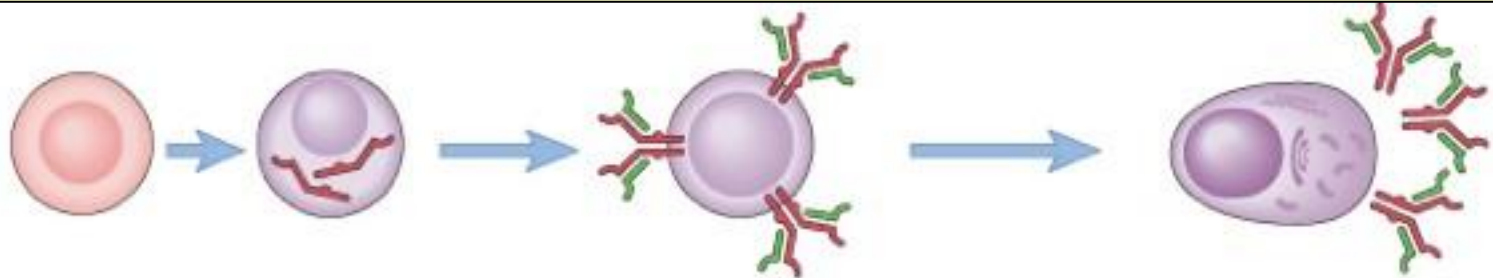
15. lecture

Effector functions of immunoglobulins.

Antigen-antibody reactions.

IgE mediated immunoreactions.

B cell development and immunoglobulin expression



Stage of maturation	Stem cell	Pre-B cell	Immature B cell	Mature B cell	Activated B cell	Antibody-secreting cell
Pattern of immunoglobulin production	None	Cytoplasmic μ heavy chain	Membrane IgM	Membrane IgM, IgD	Low-rate Ig secretion; heavy chain isotype switching; affinity maturation	High-rate Ig secretion; reduced membrane Ig

Phases of the humoral immune response

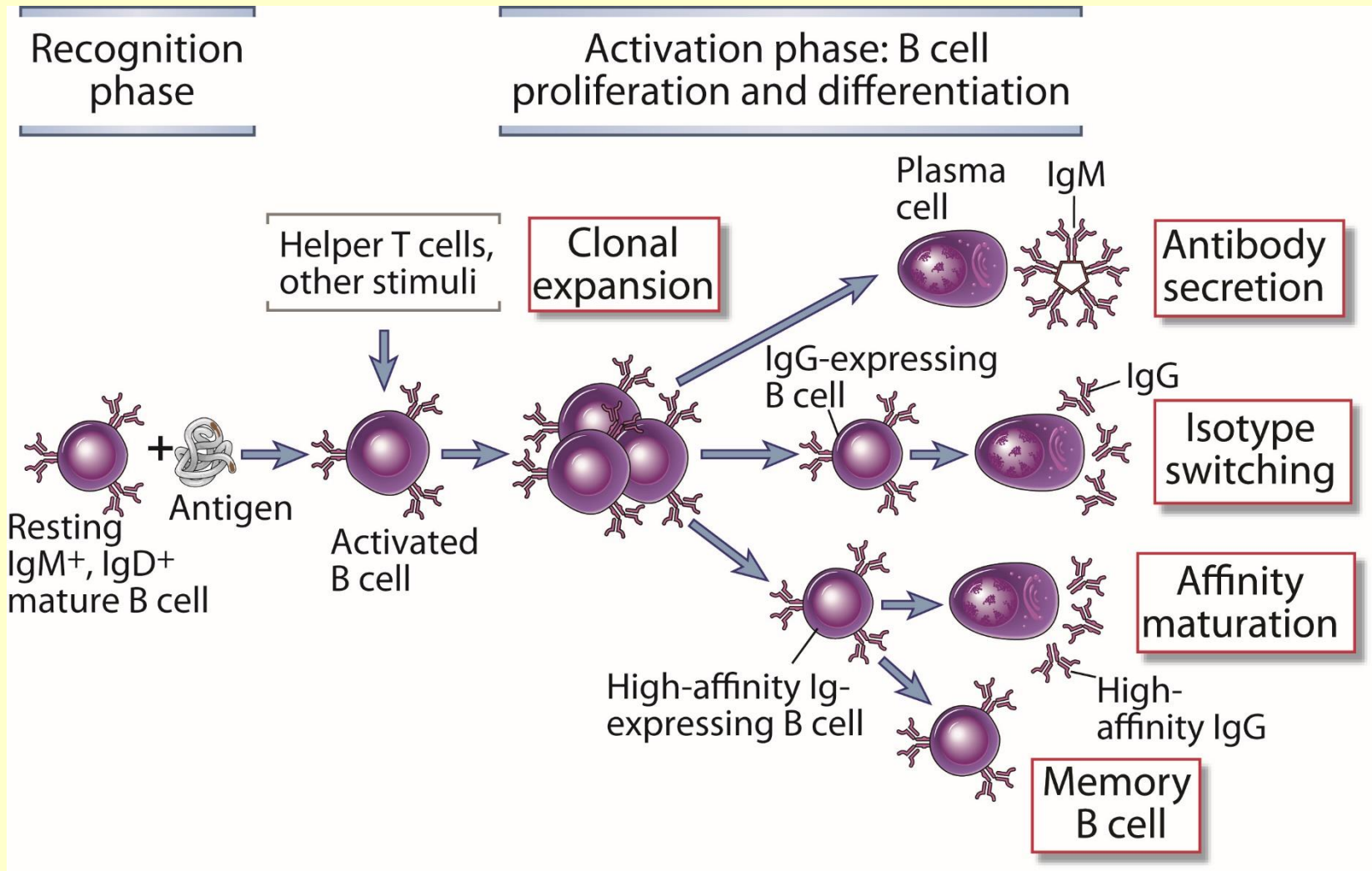


Fig. 11-1

Antitest termelés

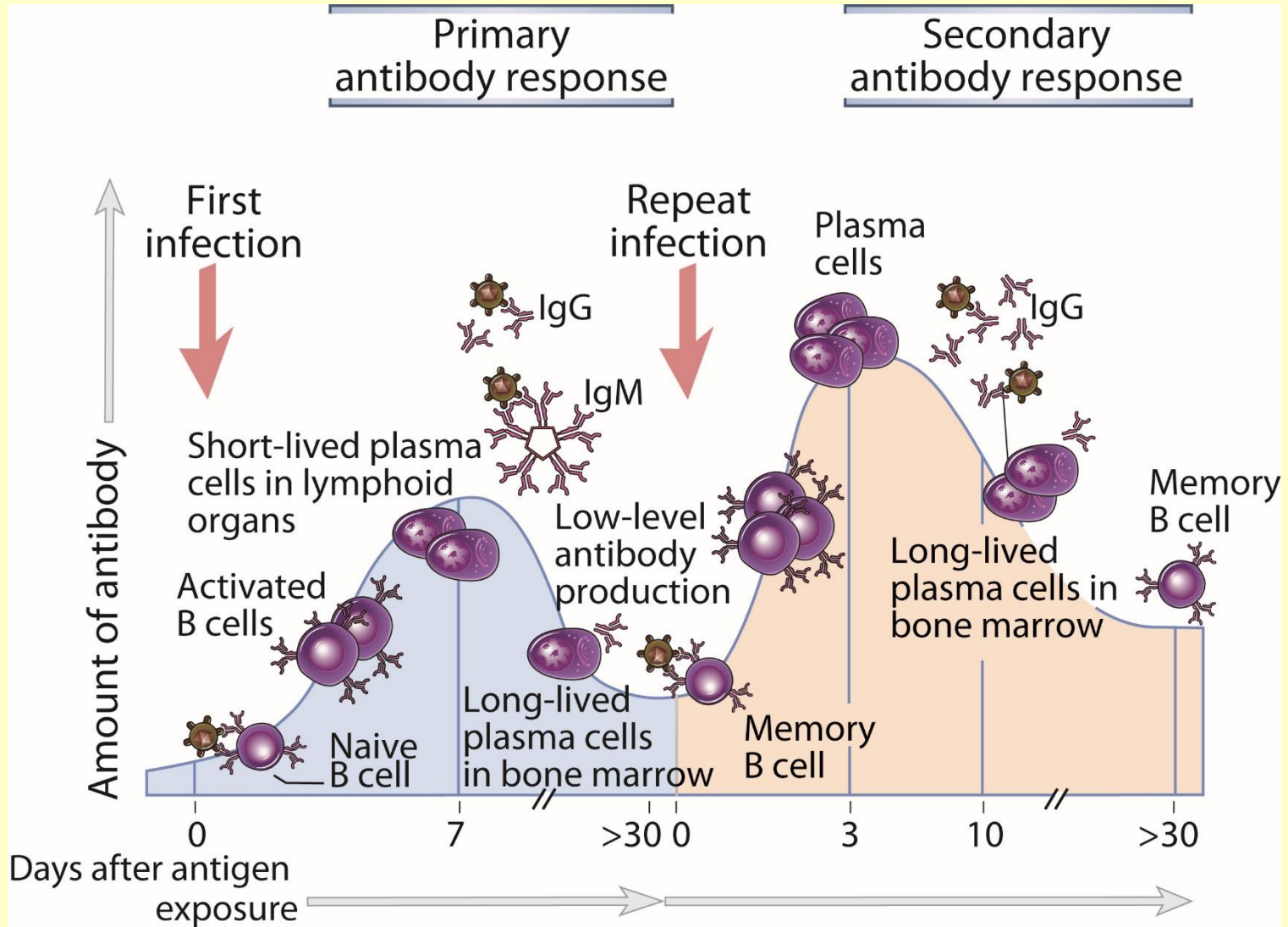
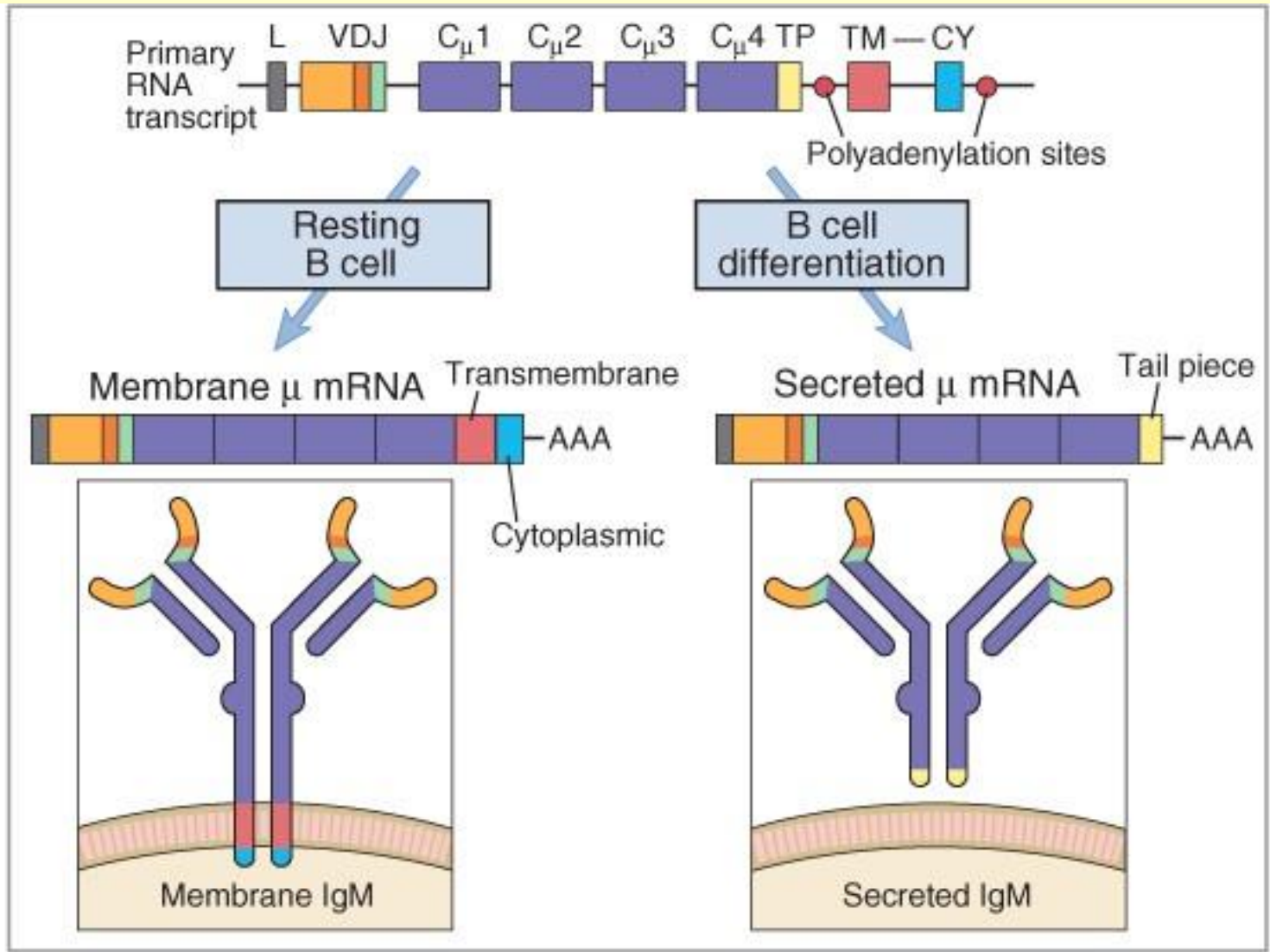
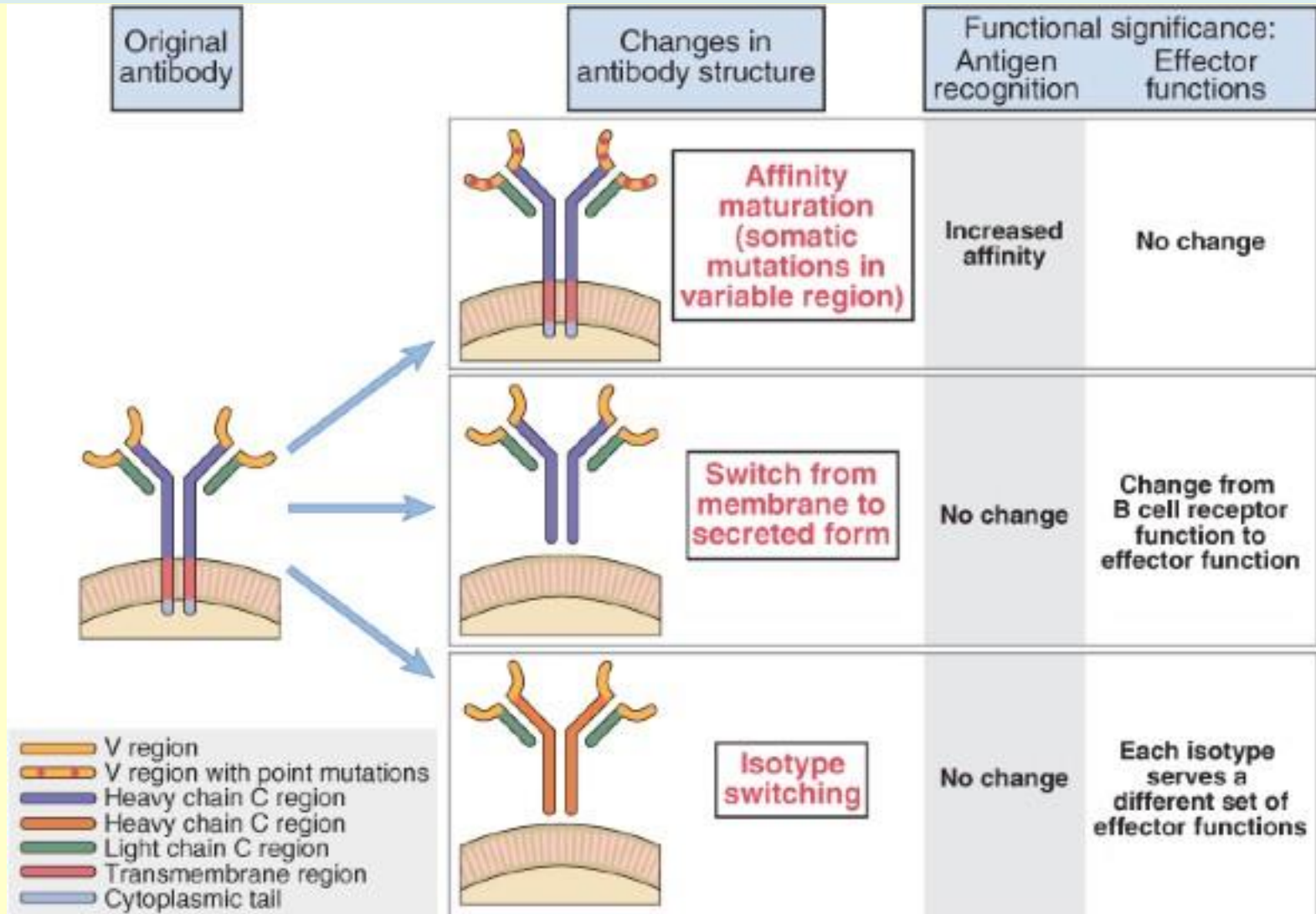


Fig. 11-2

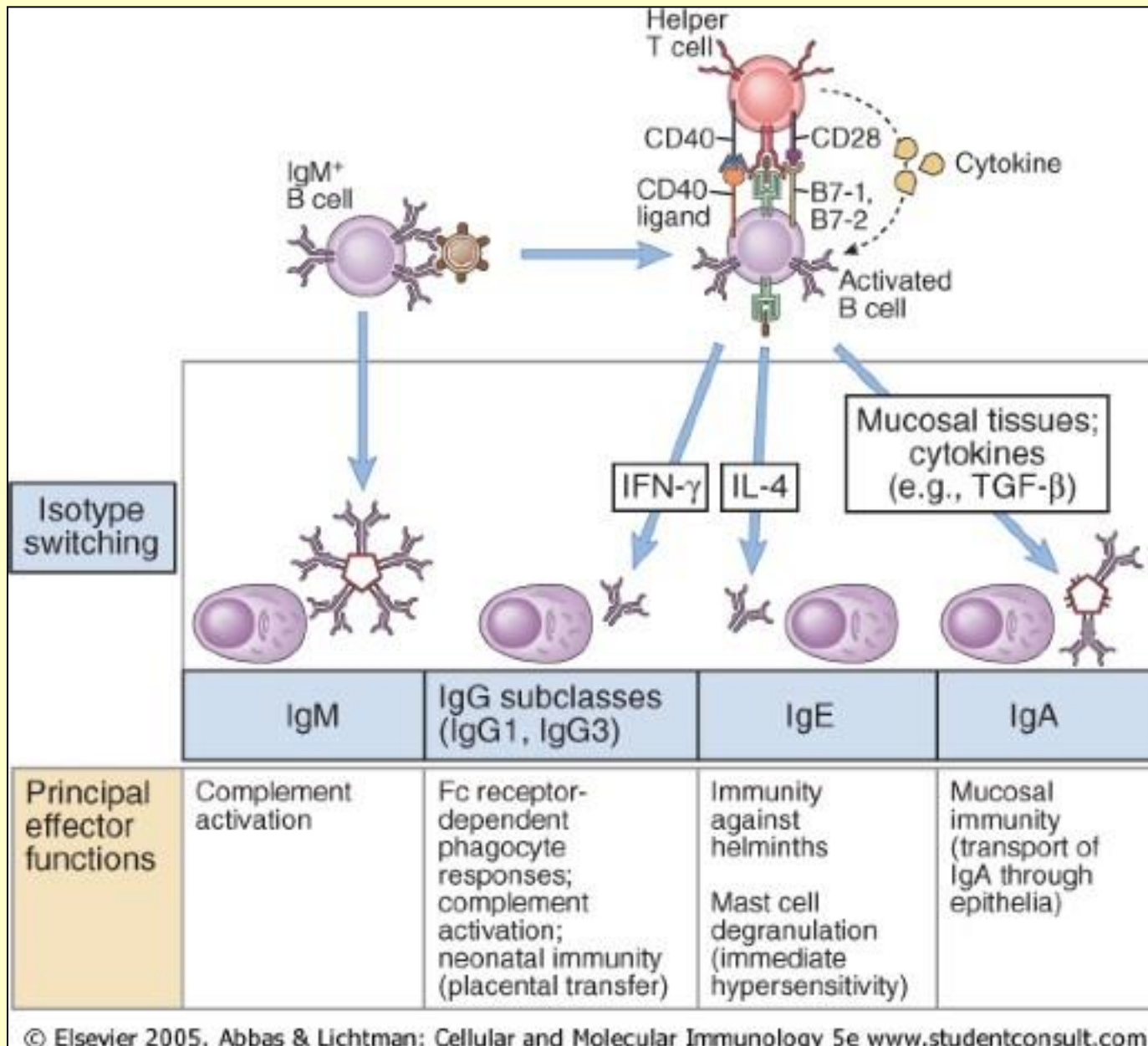
Membrane bound (mIg) and secreted (sIg) immunoglobulin 2.



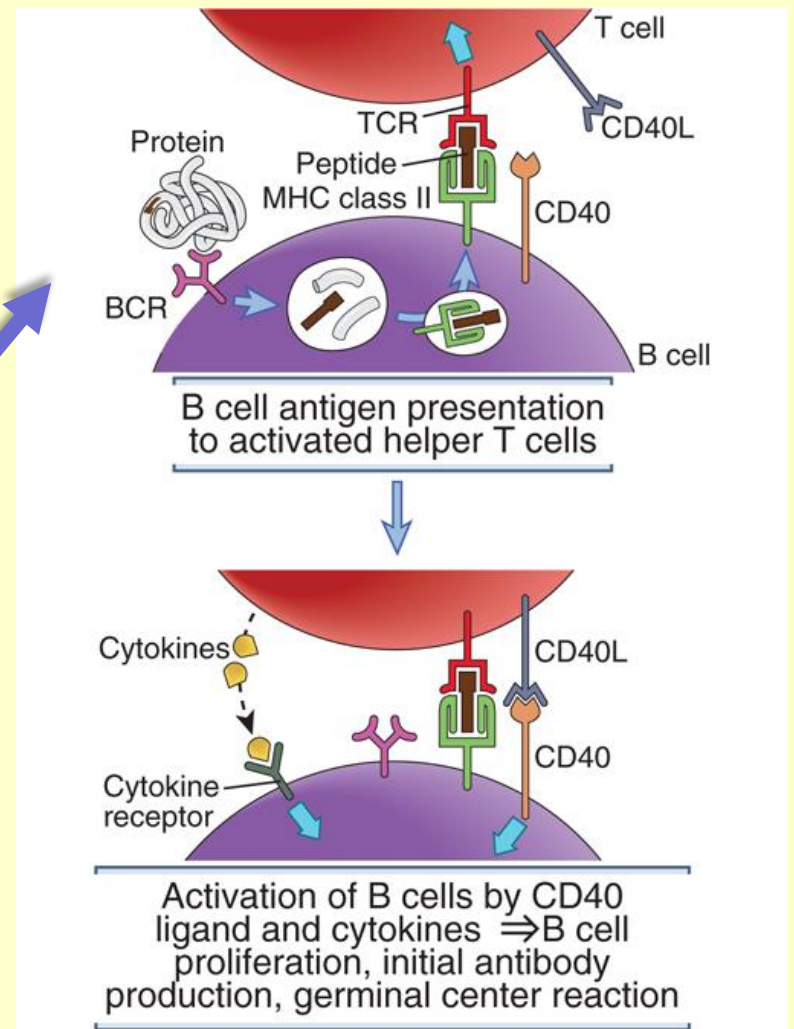
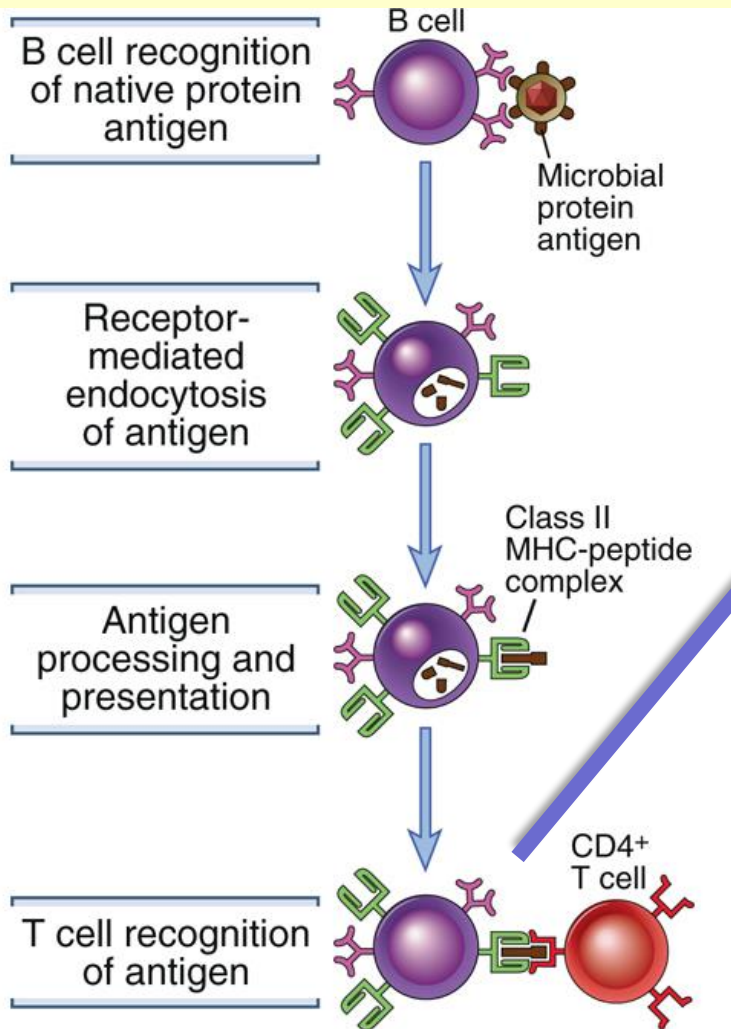
Changes in the immunoglobulin molecule during the immune response



Isotype switch – development of functional diversity



Helper T cell - B cell interaction



Functions of immunoglobulins

Monofunctional cell surface Ig (BcR) →
specific antigen recognition and binding
Before the antigen appears.

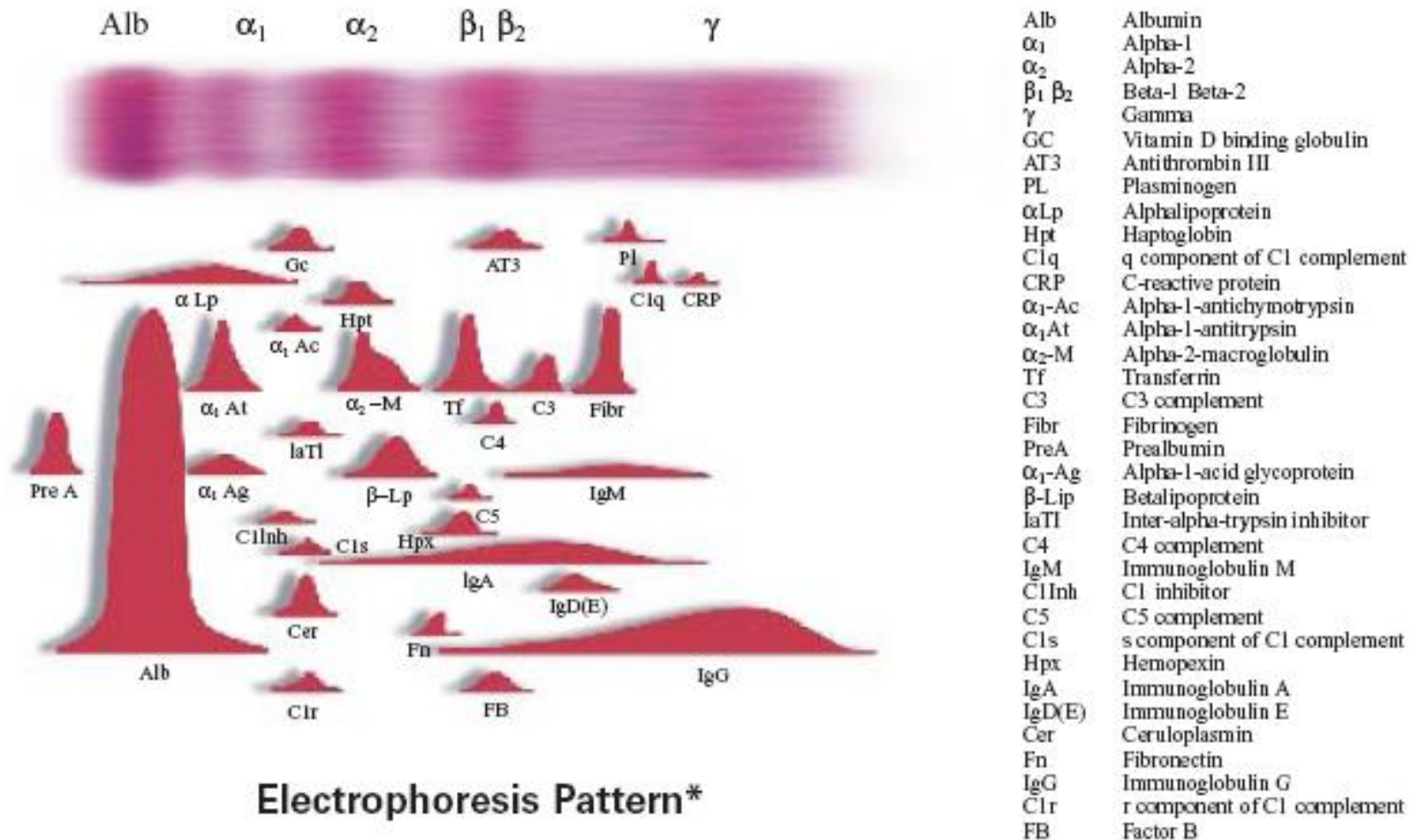
Polyfunctional secreted Ig →
After the antigen entry in effector functions: immunocomplex
formation → neutralization, opsonization, complement
binding and activation, Fc receptor binding, agglutination,
etc. → helps to eliminate pathogens before an infection
could begin

Immunoglobulins of various isotypes act at different places in the body

Distribution	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Transport across epithelium	+	-	-	-	-	-	+++ (dimer)	-
Transport across placenta	-	-	+++	+	++	+/-	-	-
Diffusion into extravascular sites	+/-	-	+++	+++	+++	+++	++ (monomer)	+
Mean serum level (mg ml ⁻¹)	1.5	0.04	9	3	1	0.5	2.1	3×10 ⁻⁵

Figure 9-19 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Serum ELFO



*Adapted from Laurell, C-B (11).

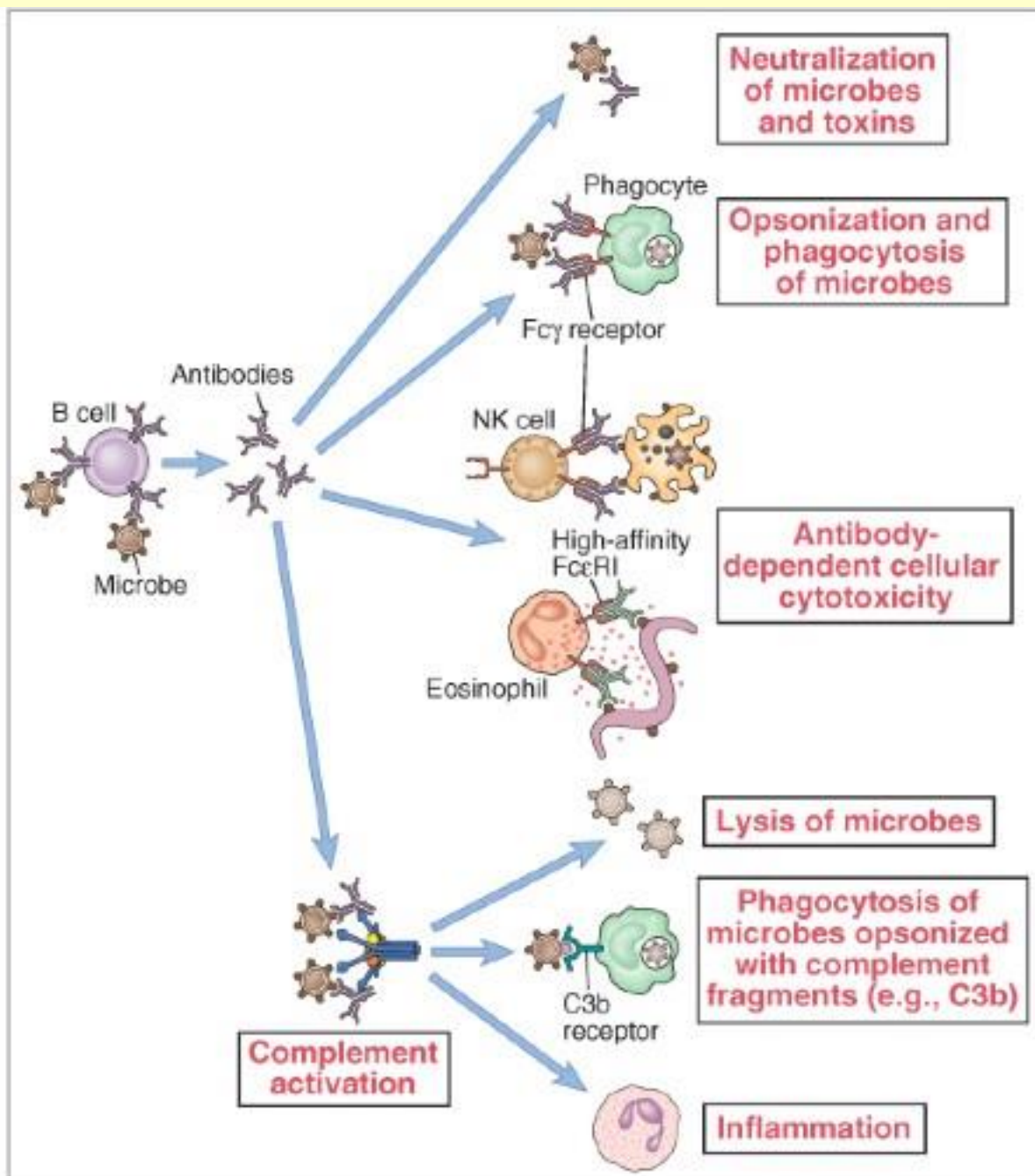
Immunglobulin effector functions

I. Neutralization of the antigen

II. Complement activation

III. Immunocomplex binding to Fc receptor and enhancing phagocytosis (opsonization)

IV. Antibody dependent cell-mediated cytotoxicity (ADCC)



Immunoglobulins of various isotypes have different functions

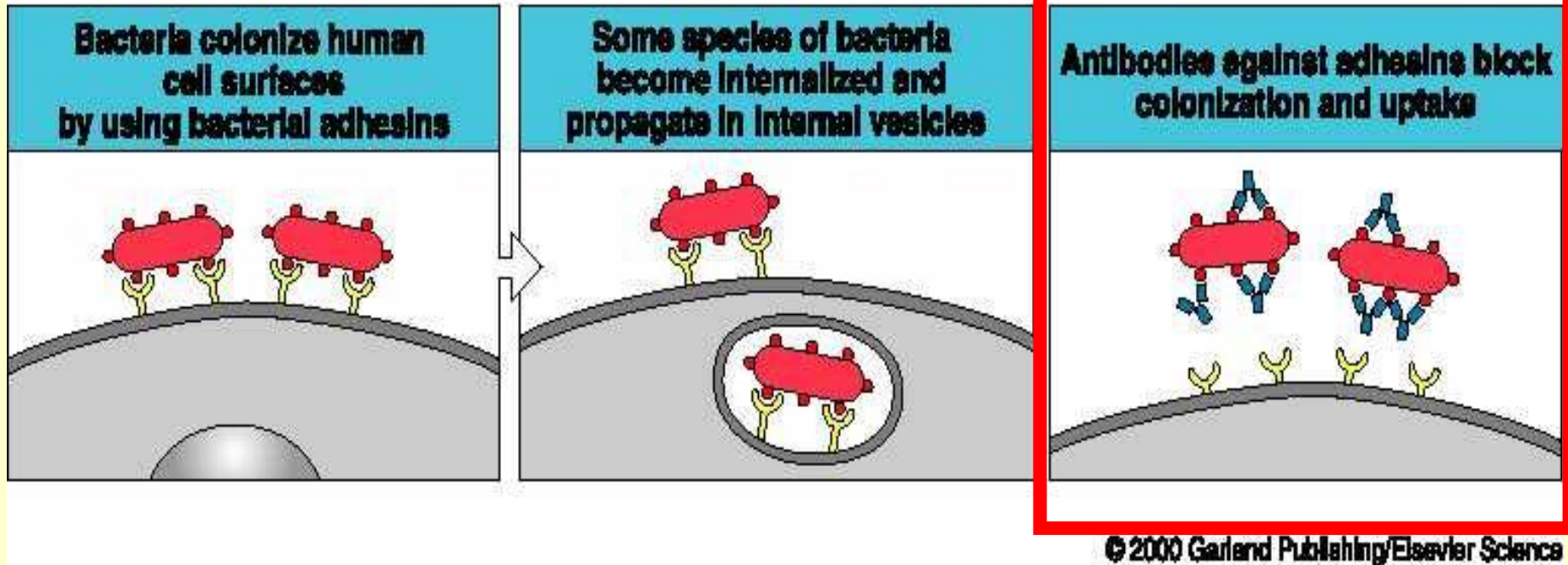
Functional activity	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Neutralization	+	-	++	++	++	++	++	-
Opsonization	+	-	+++	*	++	+	+	-
Sensitization for killing by NK cells	-	-	++	-	++	-	-	-
Sensitization of mast cells	-	-	+	-	+	-	-	+++
Activates complement system	+++	-	++	+	+++	-	+	-

Figure 9-19 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

NEUTRALIZATION

Neutralization: the antibody can inhibit the binding of bacteria to the host cells

Figure 7.21b



Secretory IgA inhibits binding to mucous membranes

Opsonization by IgG → enhanced phagocytosis

IgG & IgM → complement activation → lysis

Antibody-mediated agglutination → inhibits entrance into the host tissues

Neutralization of bacterial toxins

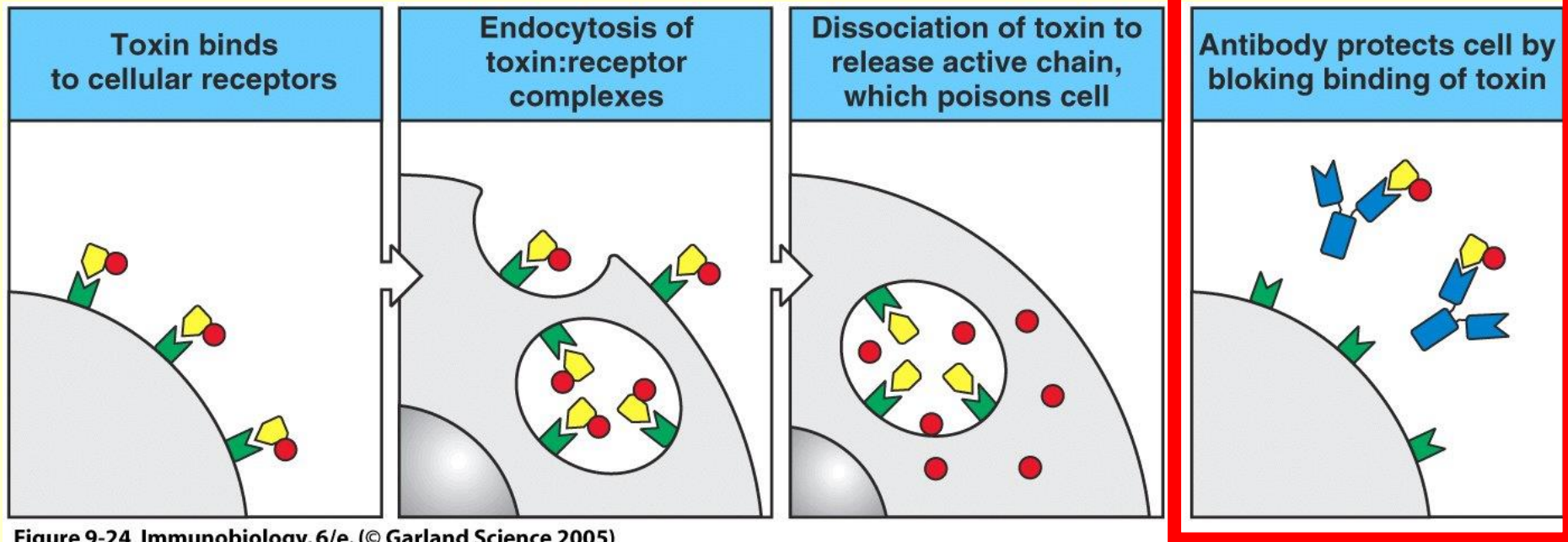


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Diphtheria, Tetanus exotoxin → Toxoid (inactivated exotoxin) for vaccination

Diseases caused by bacterial toxins

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

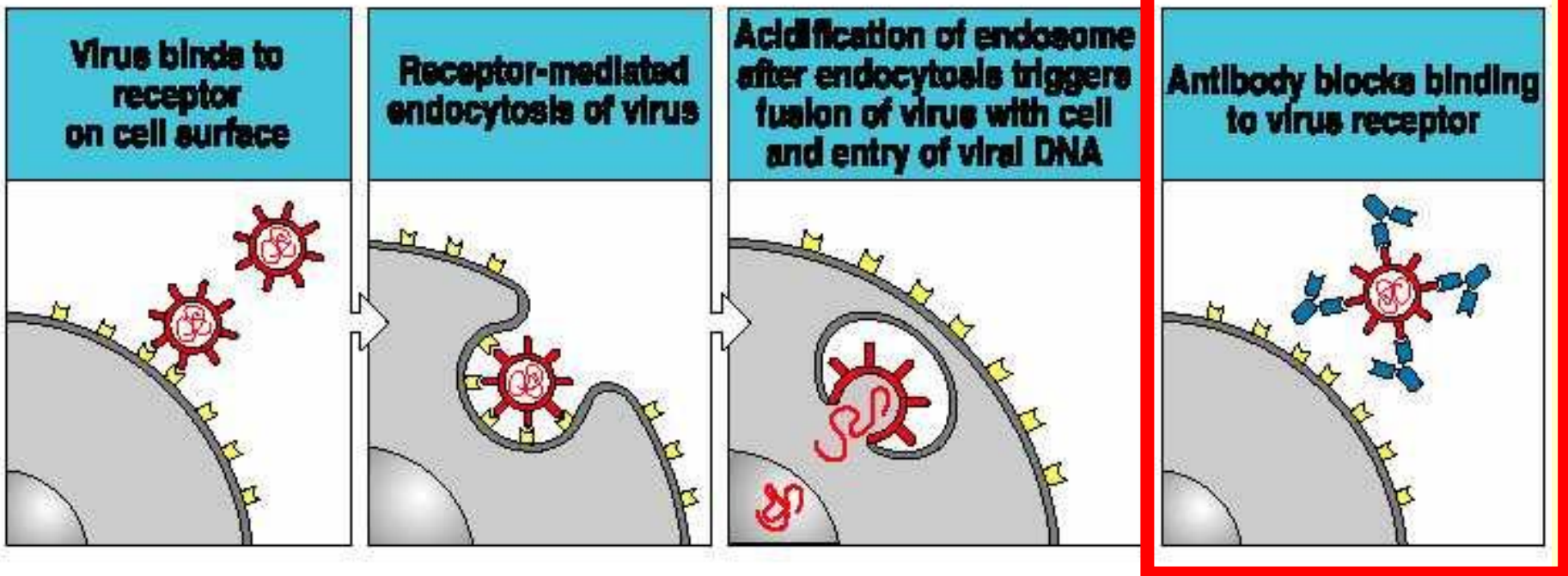
Figure 9-23 Immunobiology, 6/e. (© Garland Science 2005)

Virus neutralization

Antibody inhibits the binding of the virus to the host cell and the infection:

- Influenza virus binds to sialic acid residues of cell membrane glycoproteins
- Rhinovirus bind to ICAM-1
- Epstein-Barr virus binds to CR2

Figure 7.21a

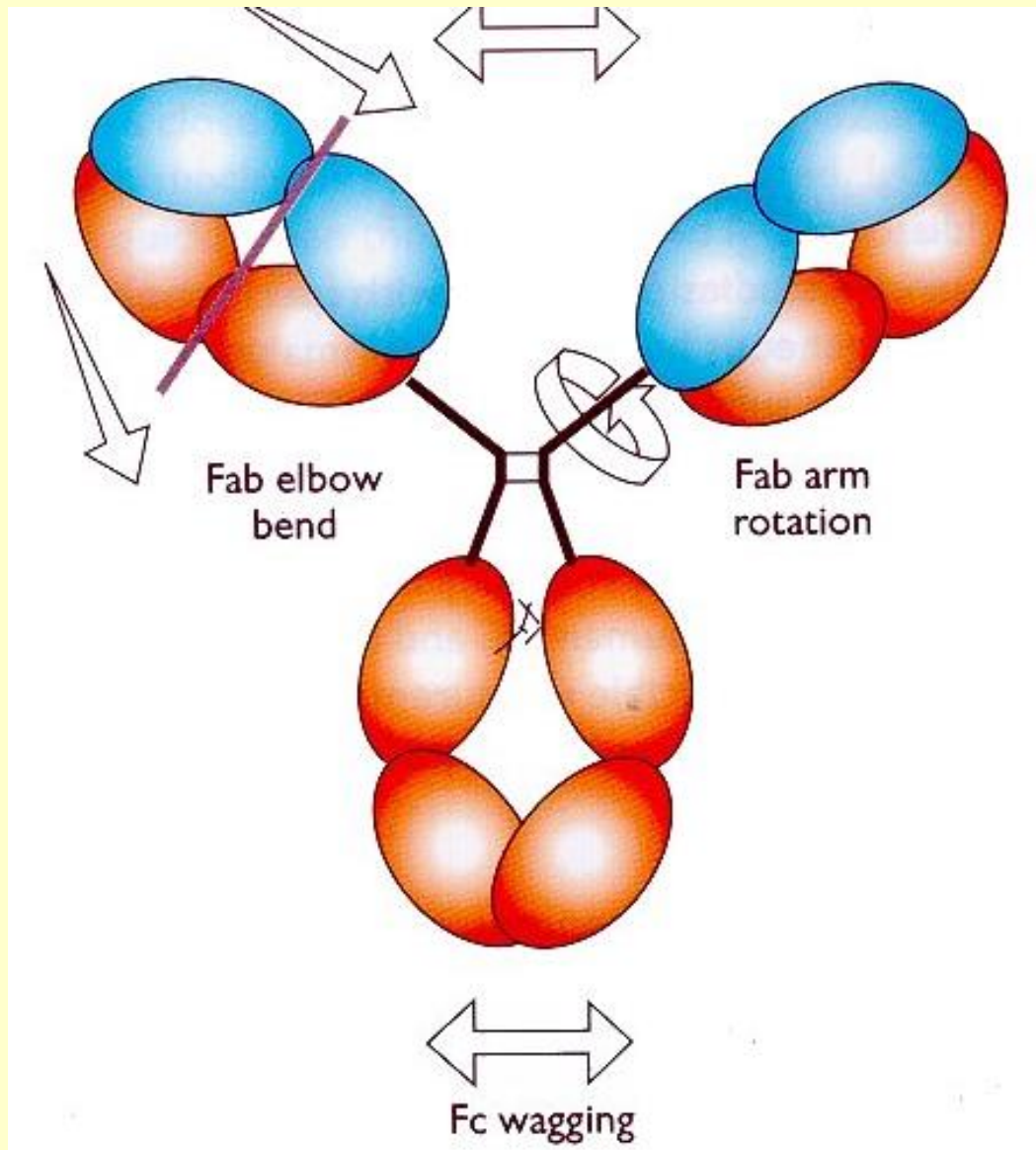


Antiviral mechanisms of the humoral immune response:

- Secretory IgA – inhibits binding of the virus to the host cell and inhibits infection or reinfection
- IgG, IgM & IgA – inhibits the fusion of the viral envelope with the host cell
- IgG and IgM – opsonization → helps the phagocytosis of virus particles
- IgM – agglutination of virus particles
- Complement-activating IgG & IgM - further opsonization with C3b, then lysis by MAC

Fc-RECEPTOR BINDING

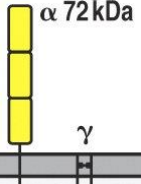
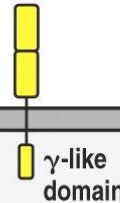
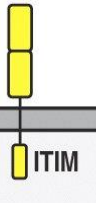

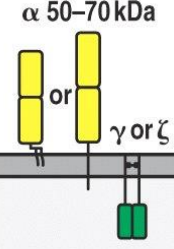
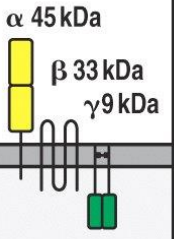
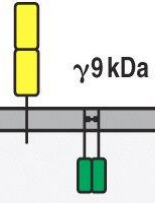
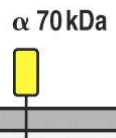
IgG is a flexible molecule



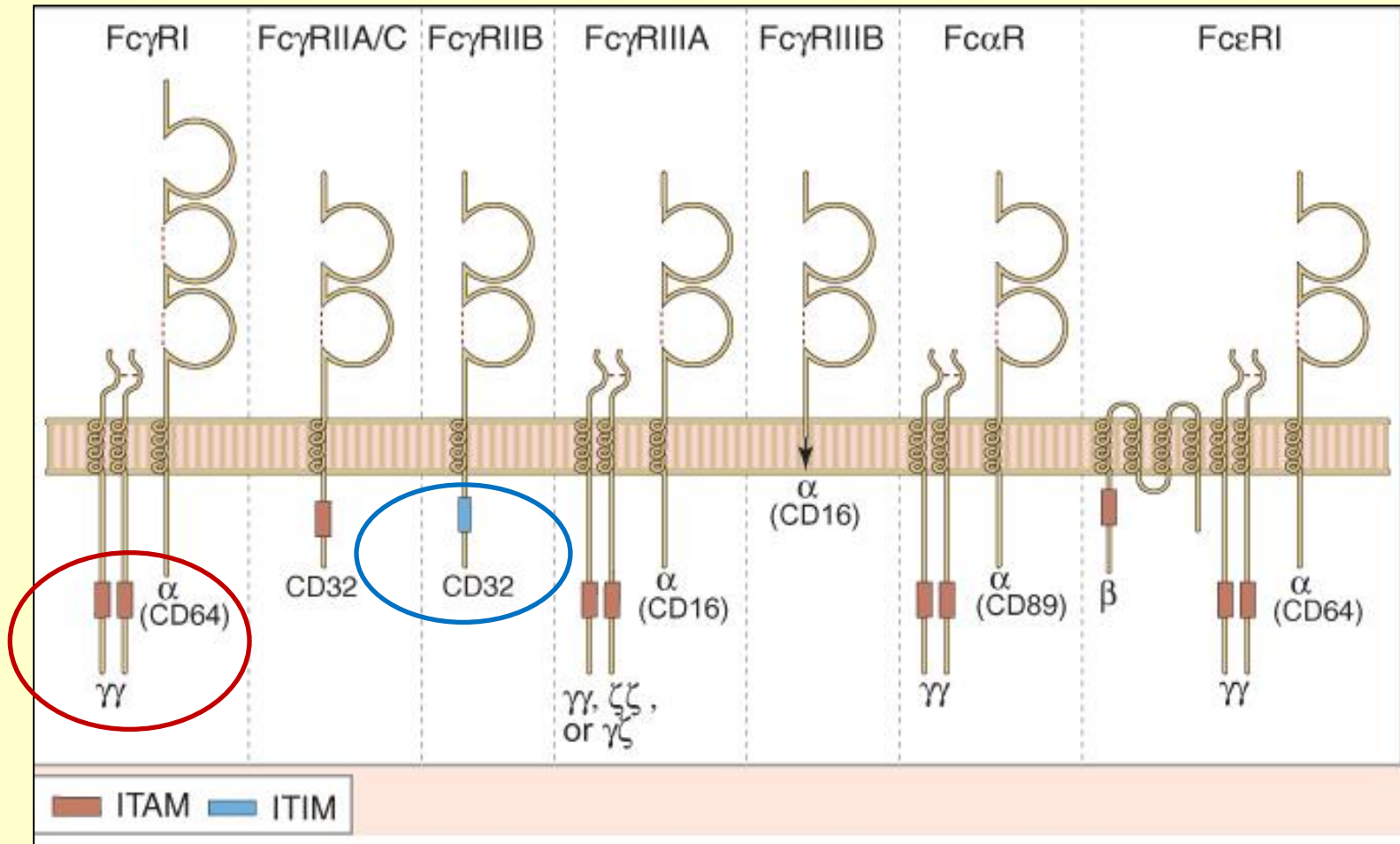
**Antigen binding >
Conformation change >
Complement activation,
FcR binding**

**Flexibility of
immunoglobulins
with various isotypes
is different.**

Fc receptors (FcR)

Receptor	FcγRI (CD64)	FcγRII-A (CD32)	FcγRII-B2 (CD32)	FcγRII-B1 (CD32)	FcγRIII (CD16)	FcεRI	FcαRI (CD89)	Fc α/μR
Structure	 <p>α 72 kDa γ</p>	 <p>α 40 kDa γ-like domain</p>	 <p>ITIM</p>	 <p>ITIM</p>	 <p>α 50-70 kDa γ or ζ</p>	 <p>α 45 kDa β 33 kDa γ 9 kDa</p>	 <p>α 55-75 kDa γ 9 kDa</p>	 <p>α 70 kDa</p>
Binding	IgG1 $10^8 M^{-1}$	IgG1 $2 \times 10^6 M^{-1}$	IgG1 $2 \times 10^6 M^{-1}$	IgG1 $2 \times 10^6 M^{-1}$	IgG1 $5 \times 10^5 M^{-1}$	IgE $10^{10} M^{-1}$	IgA1, IgA2 $10^7 M^{-1}$	IgA, IgM $3 \times 10^9 M^{-1}$
Order of affinity	1) IgG1=IgG3 2) IgG4 3) IgG2	1) IgG1 2) IgG3=IgG2* 3) IgG4	1) IgG1=IgG3 2) IgG4 3) IgG2	1) IgG1=IgG3 2) IgG4 3) IgG2	IgG1=IgG3		IgA1=IgA2	1) IgM 2) IgA
					NK cells Eosinophils Macrophages Neutrophils Mast cells	Mast cells Eosinophils [†] Basophils	Macrophages Neutrophils Eosinophils [†]	Macrophages B cells
					Induction of killing (NK cells)	Secretion of granules	Uptake Induction of killing	Uptake

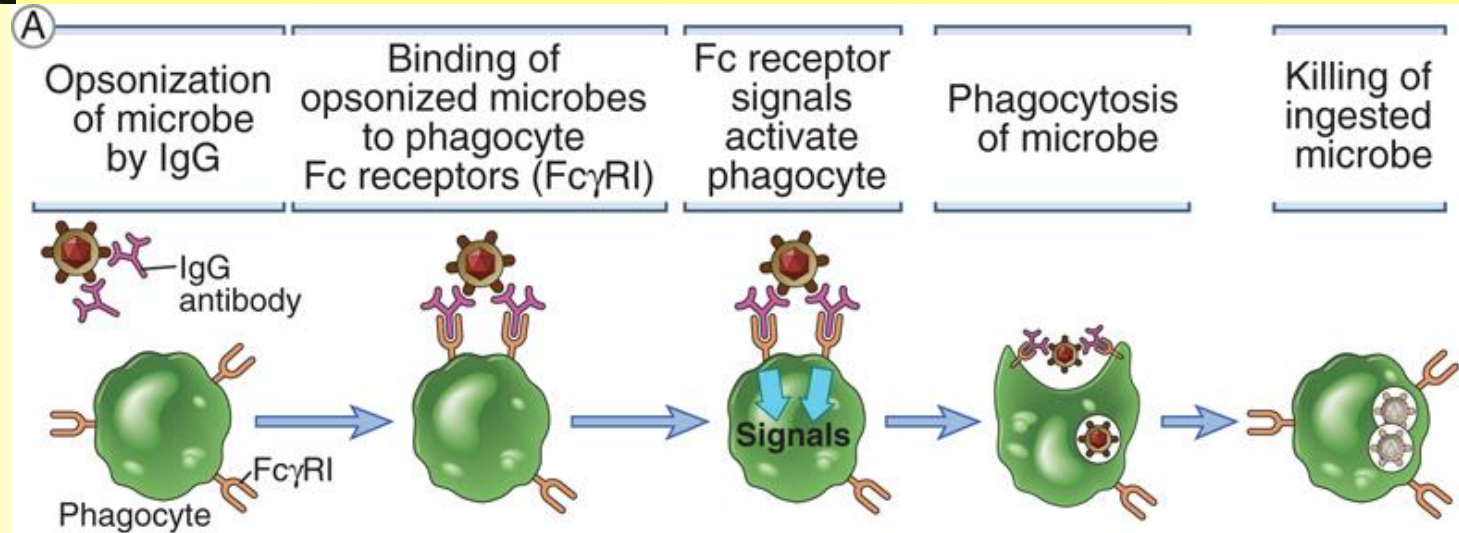
Activatory and inhibitory role of Fc γ Receptors



The role of Ig constant domains in the effector functions

Receptor	Ig domen
C1q binding sites	Cγ2 or Cμ3
FcγRI (CD64)	Cγ2
FcγRII (CD32)	Cγ2 and Cγ3
FcγRIII (CD16)	Cγ2 and Cγ3
FcαRI (CD89)	Cα
FcϵRI	Cϵ3
FcϵRII (CD23)	Cϵ3

Opsonization and Phagocytosis by Antibodies

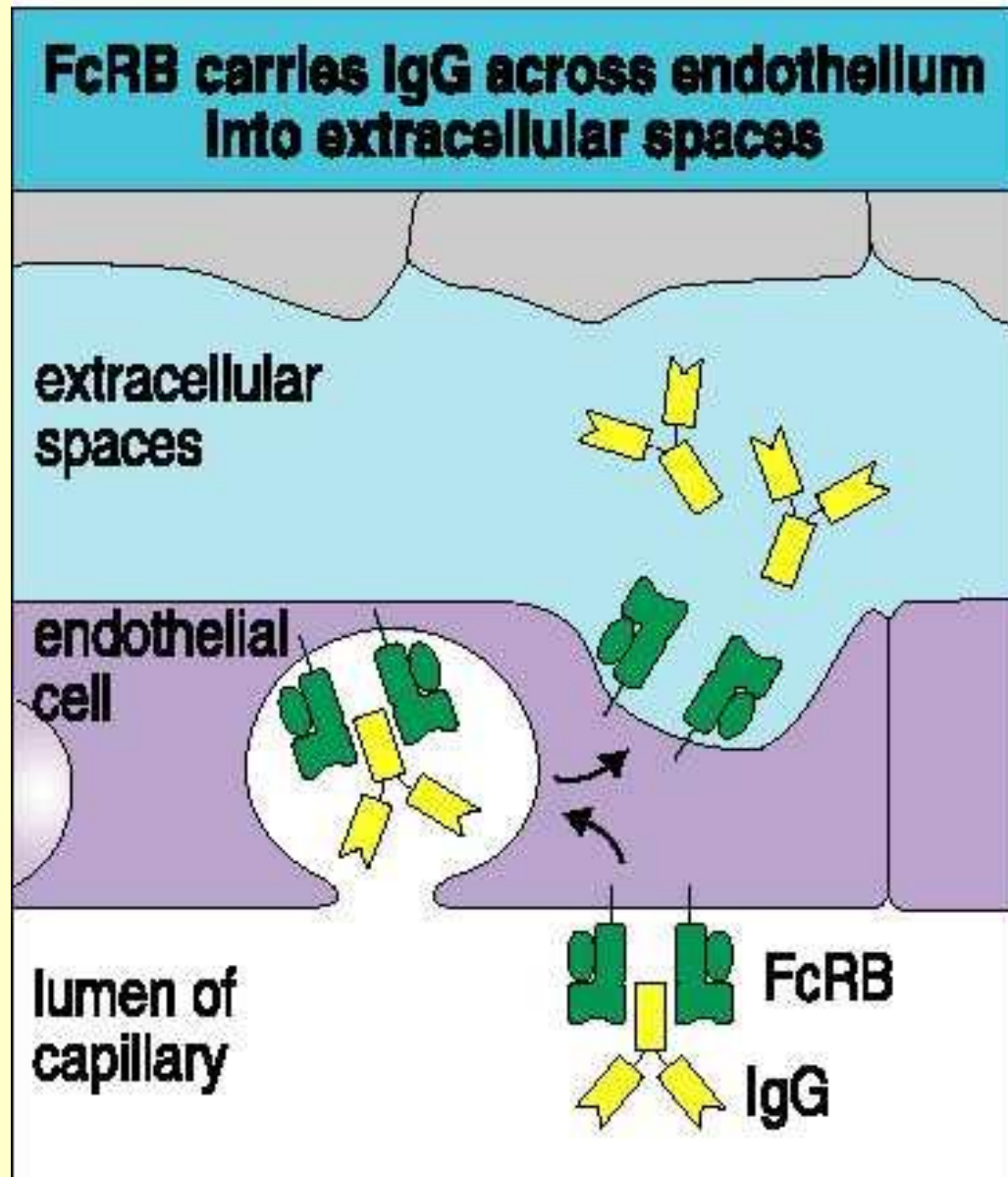


B

Fc Receptor	Affinity for Ig	Cell distribution	Function
Fc γ RI (CD64)	High ($K_d \sim 10^{-9}$ M); binds IgG1 and IgG3; can bind monomeric IgG	Macrophages, neutrophils; also eosinophils	Phagocytosis; activation of phagocytes
Fc γ RIIA (CD32)	Low ($K_d \sim 0.6\text{--}2.5 \times 10^{-6}$ M)	Macrophages, neutrophils; eosinophils, platelets	Phagocytosis; cell activation (inefficient)
Fc γ RIIB (CD32)	Low ($K_d \sim 0.6\text{--}2.5 \times 10^{-6}$ M)	B lymphocytes, DCs, mast cells, neutrophils, macrophages	Feedback inhibition of B cells, attenuation of inflammation
Fc γ RIIIA (CD16)	Low ($K_d \sim 0.6\text{--}2.5 \times 10^{-6}$ M)	NK cells	Antibody-dependent cellular cytotoxicity (ADCC)
Fc ϵ RI	High ($K_d \sim 10^{-10}$ M); binds monomeric IgE	Mast cells, basophils, eosinophils	Activation (degranulation) of mast cells and basophils

Fig. 12-4

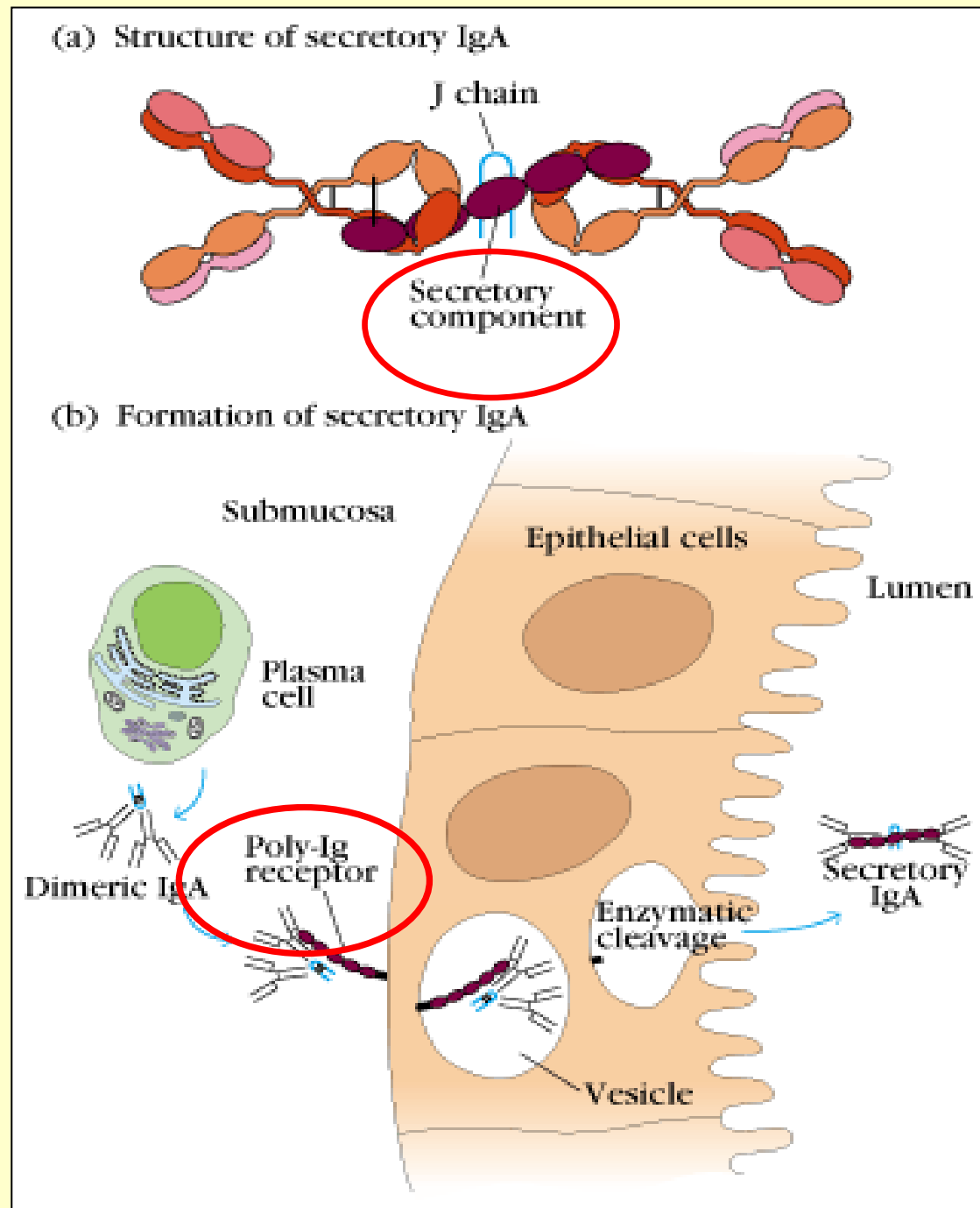
Figure 7.16



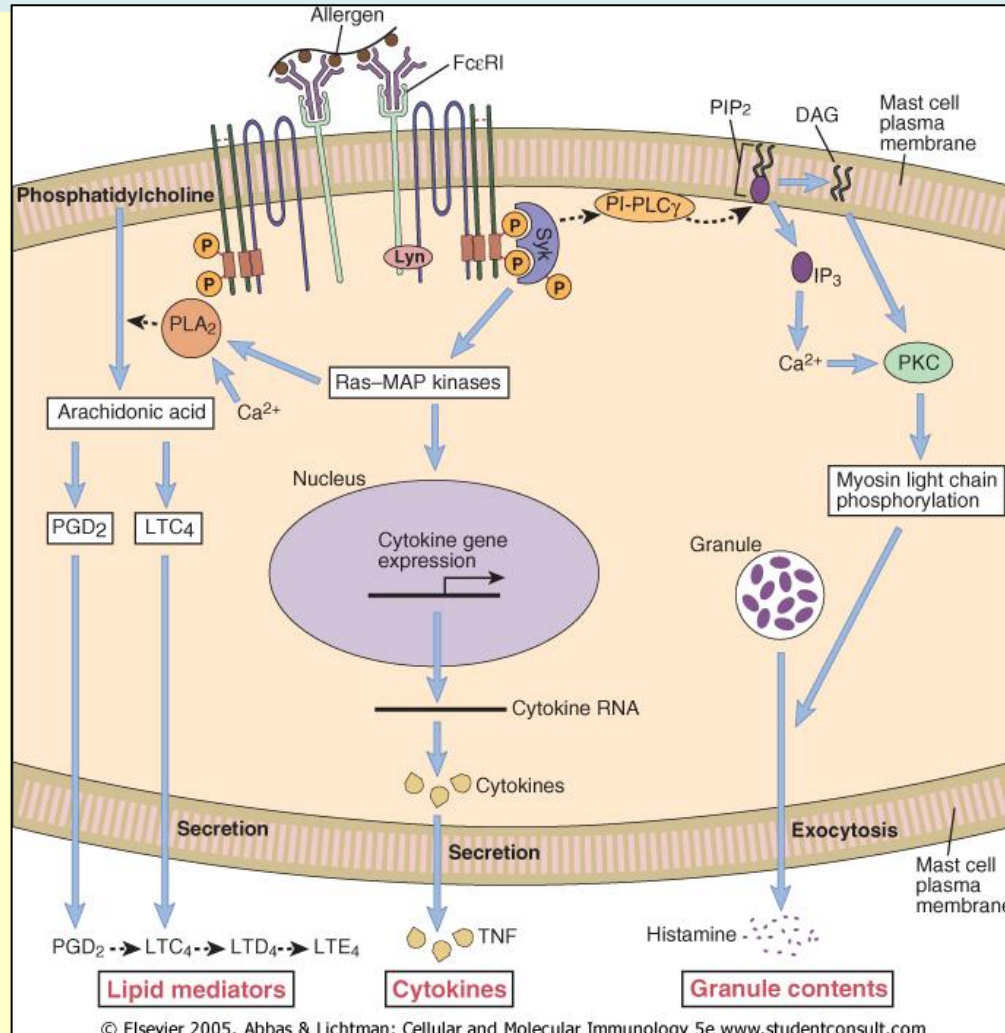
Fc α R

IgA/IgM transport

secretory
component



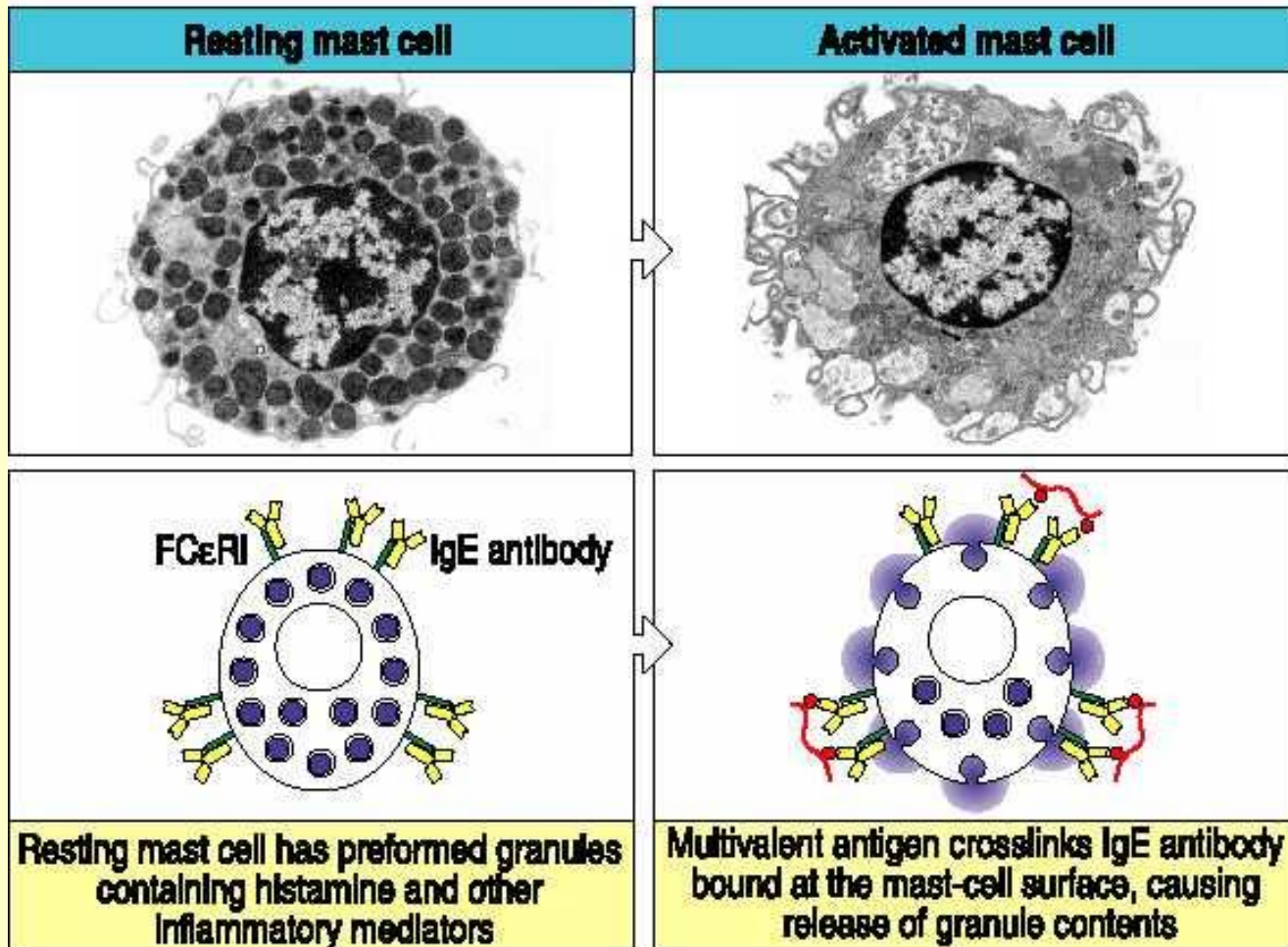
Antigen crosslinking of the receptor activate the signal transduction → mast cell activation



Syk is critical for FcεR-mediated Ca²⁺ mobilization, degranulation, production of cytokines, and arachidonic acid metabolites.

IgE-mediated mast cell activation

Figure 7.24



**ADCC = antibody dependent
cellular cytotoxicity**

ADCC

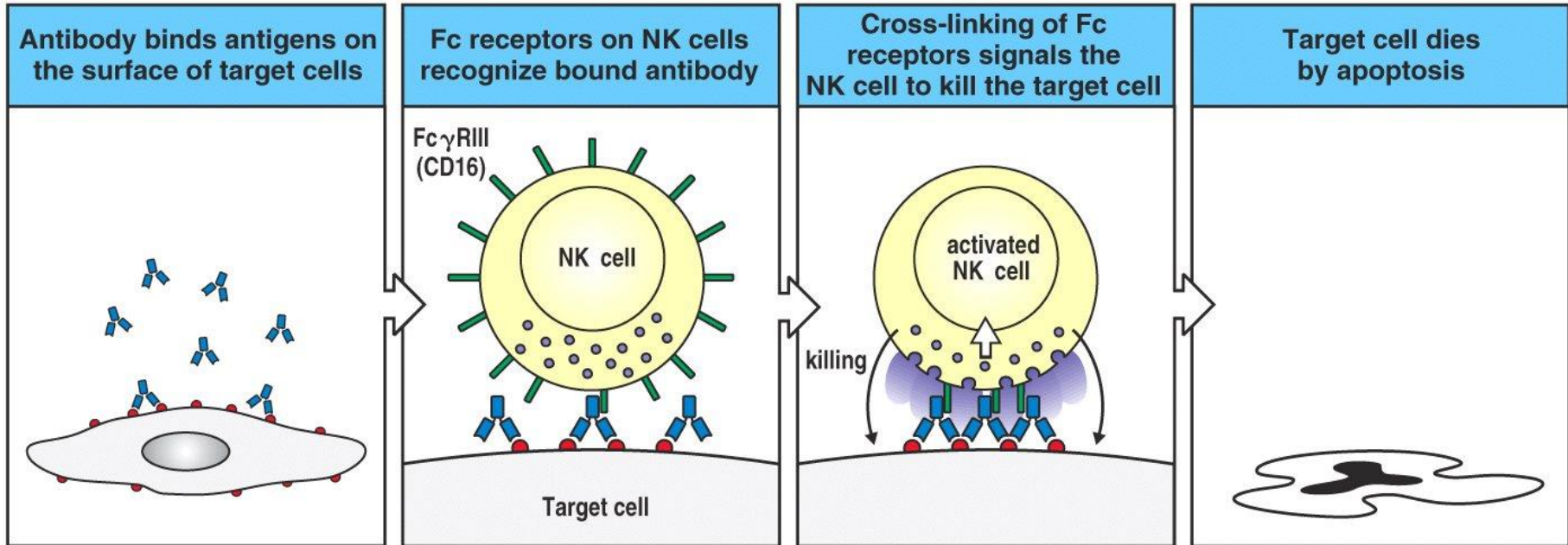
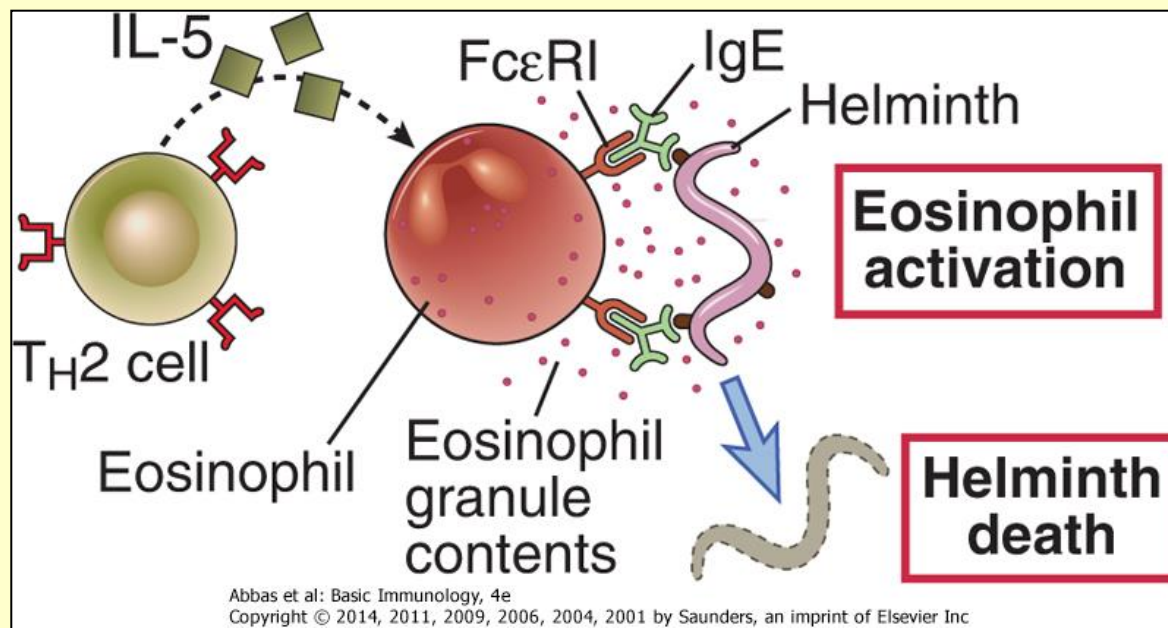
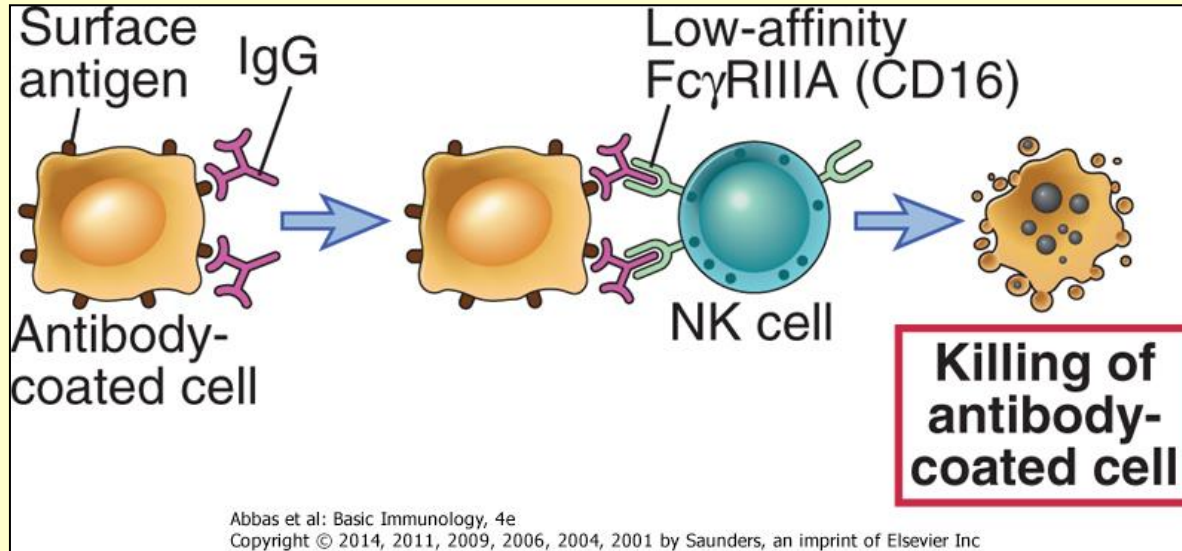


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ADCC



ADCC

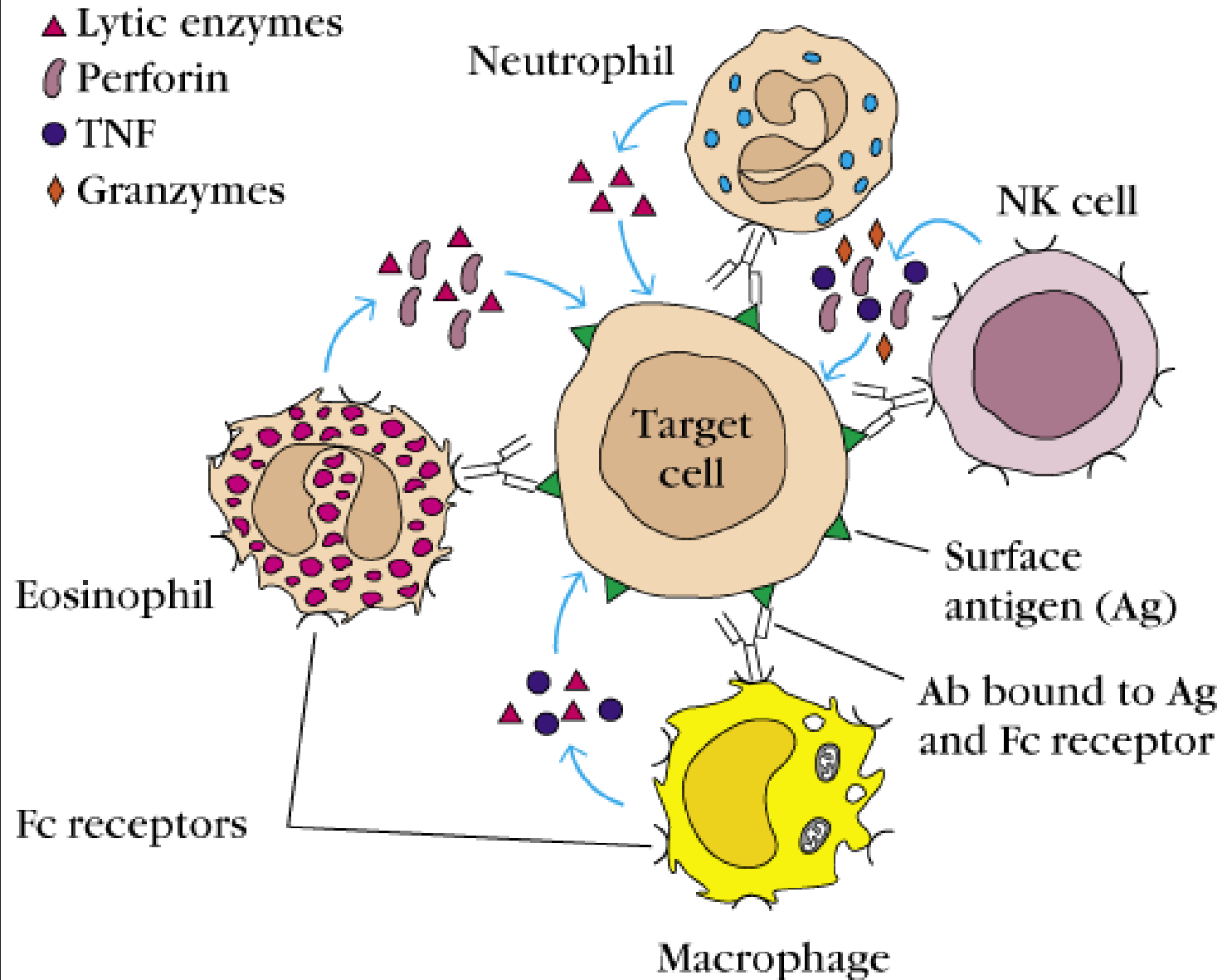
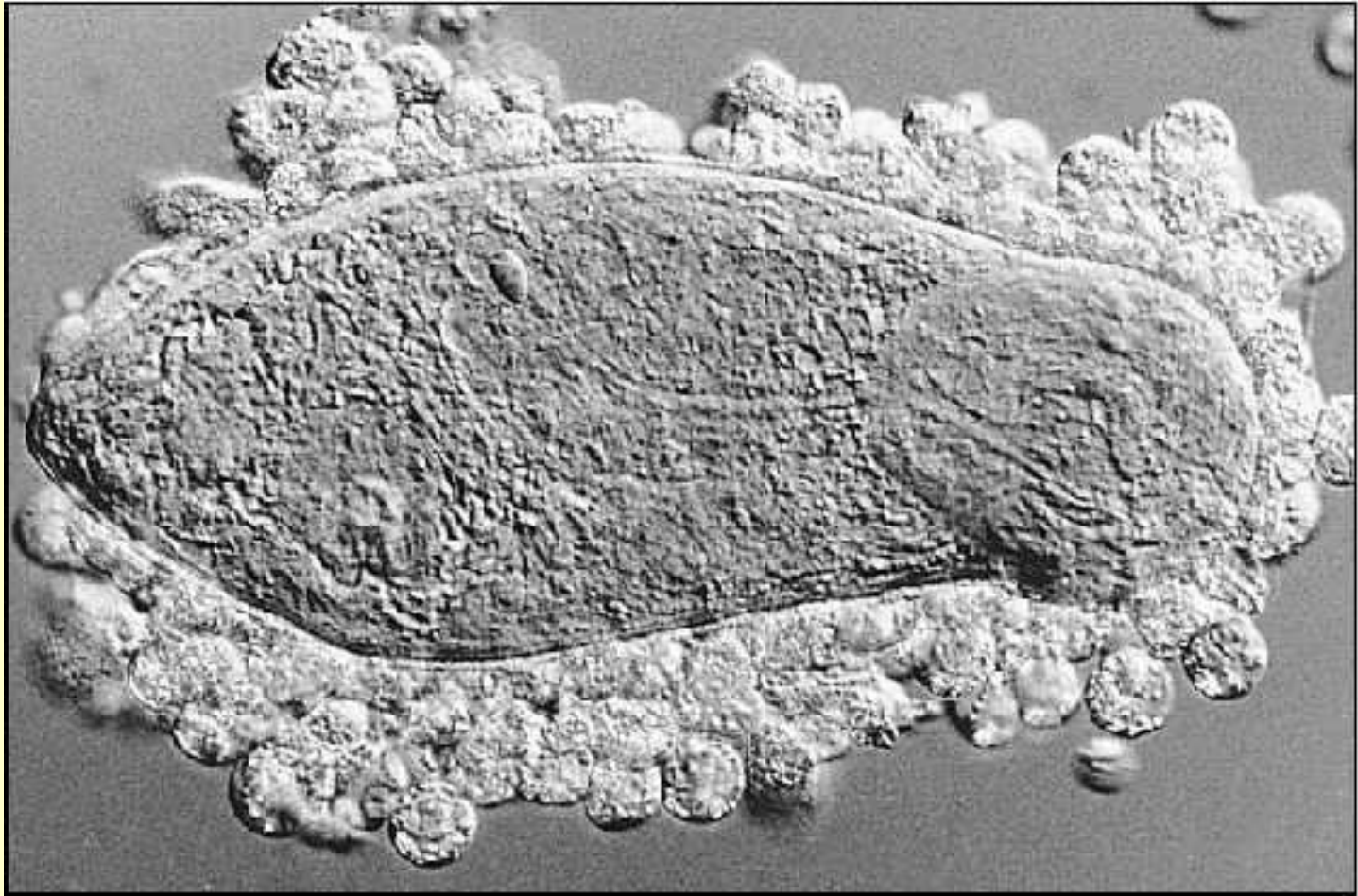


Figure 7.25



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Parasite covered by IgE > eosinophil activation > release of toxic granules

COMPLEMENT ACTIVATION

IgG & IgM antigen-antibody complexes activate complement

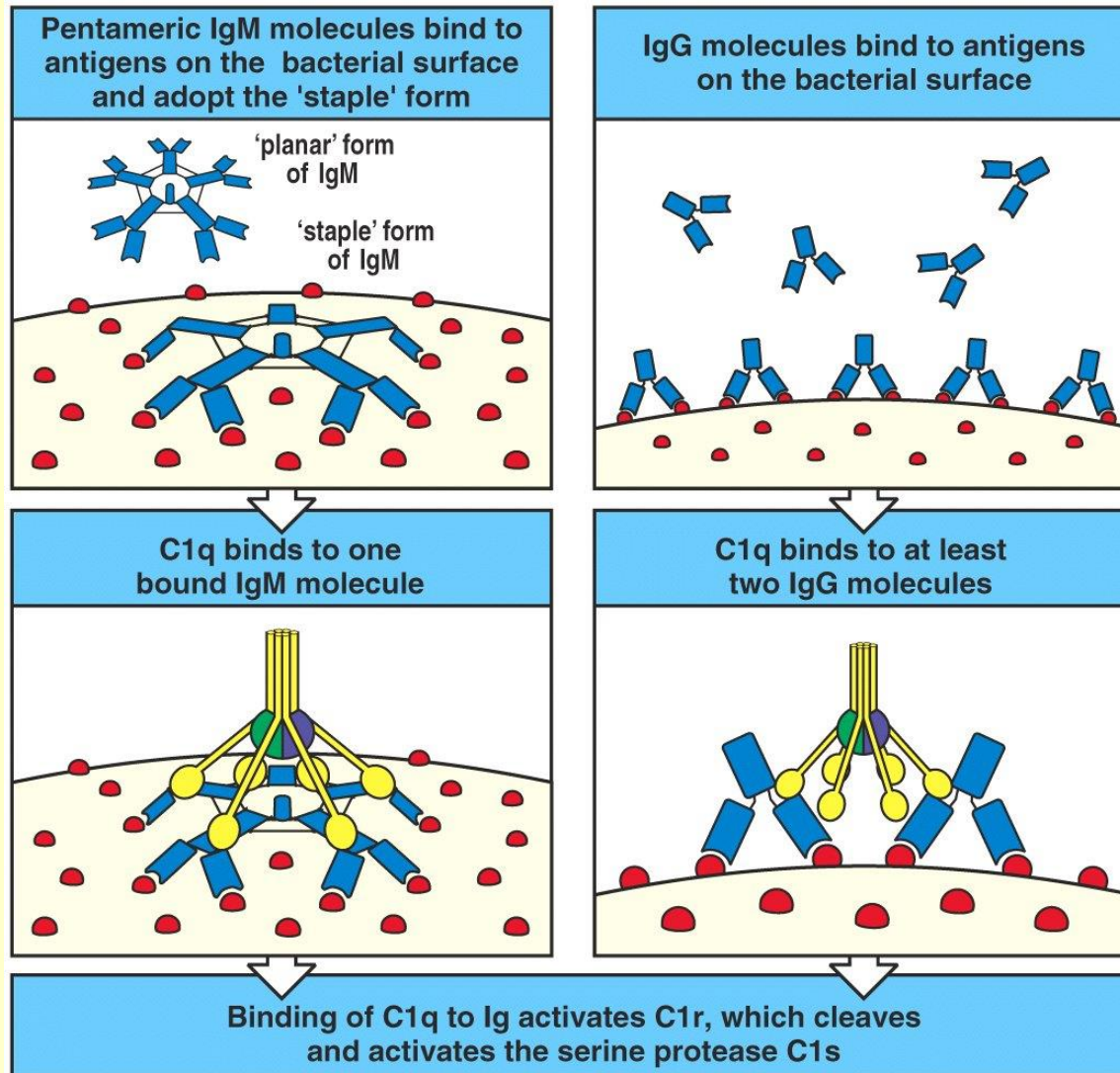


Figure 9-28 Immunobiology, 6/e. (© Garland Science 2005)