

Basic Immunology

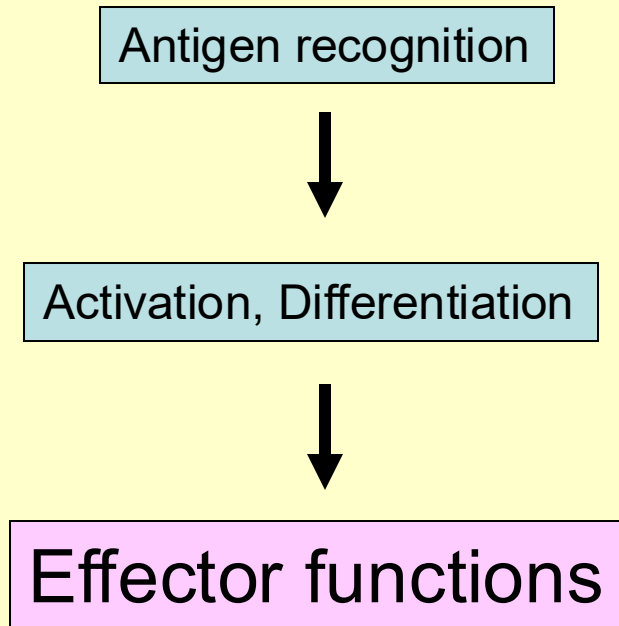
15. lecture

Effector functions of immunoglobulins

Antigen-antibody reactions

IgE mediated immunoreactions

Main stages of the adaptive immune response



Humoral effector mechanisms

- **Immunoglobulin-mediated – specific**
- **Complement-mediated - innate**

Phases of the Humoral Immune Response

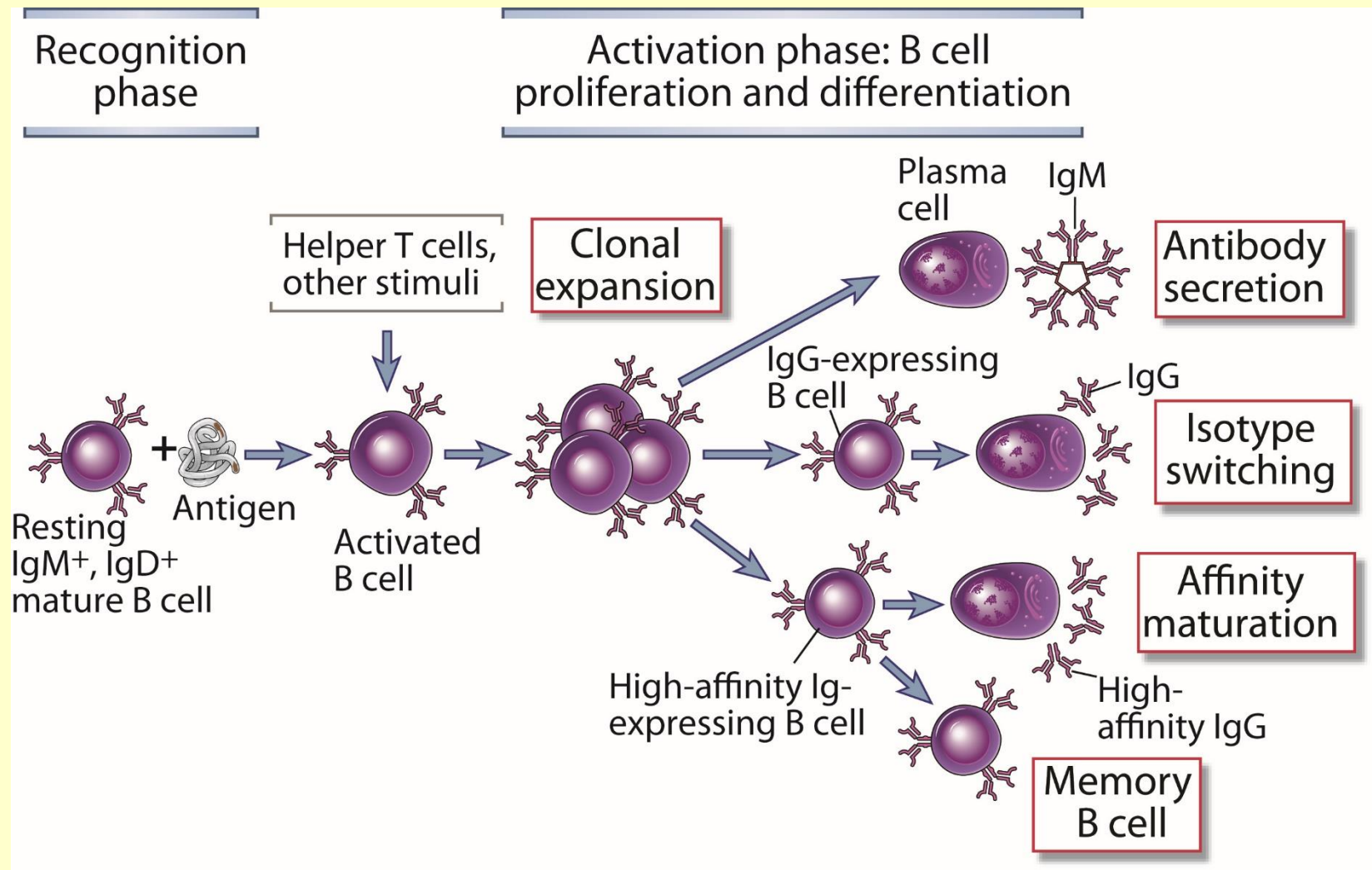


Fig. 11-1

Antibody production

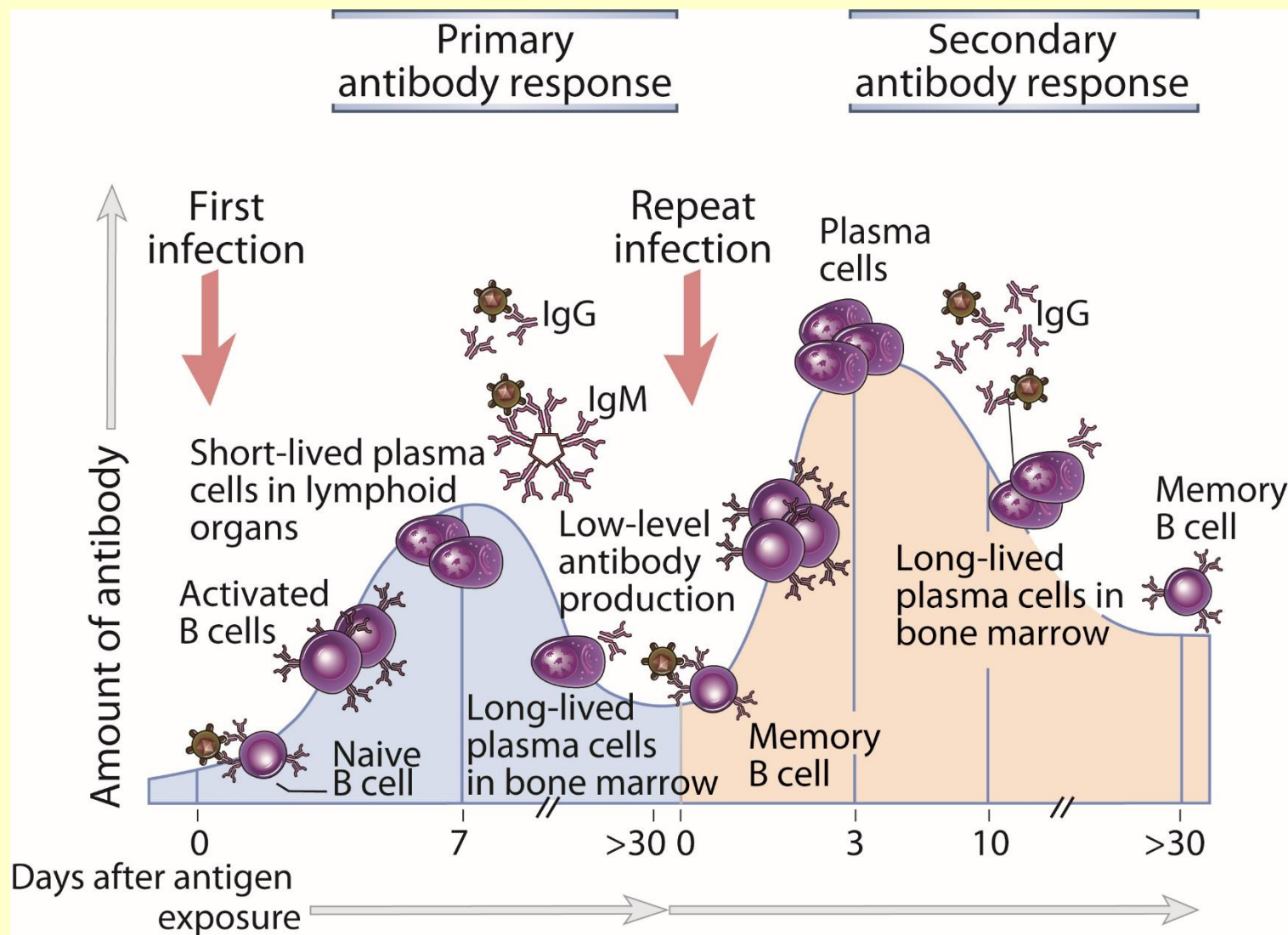
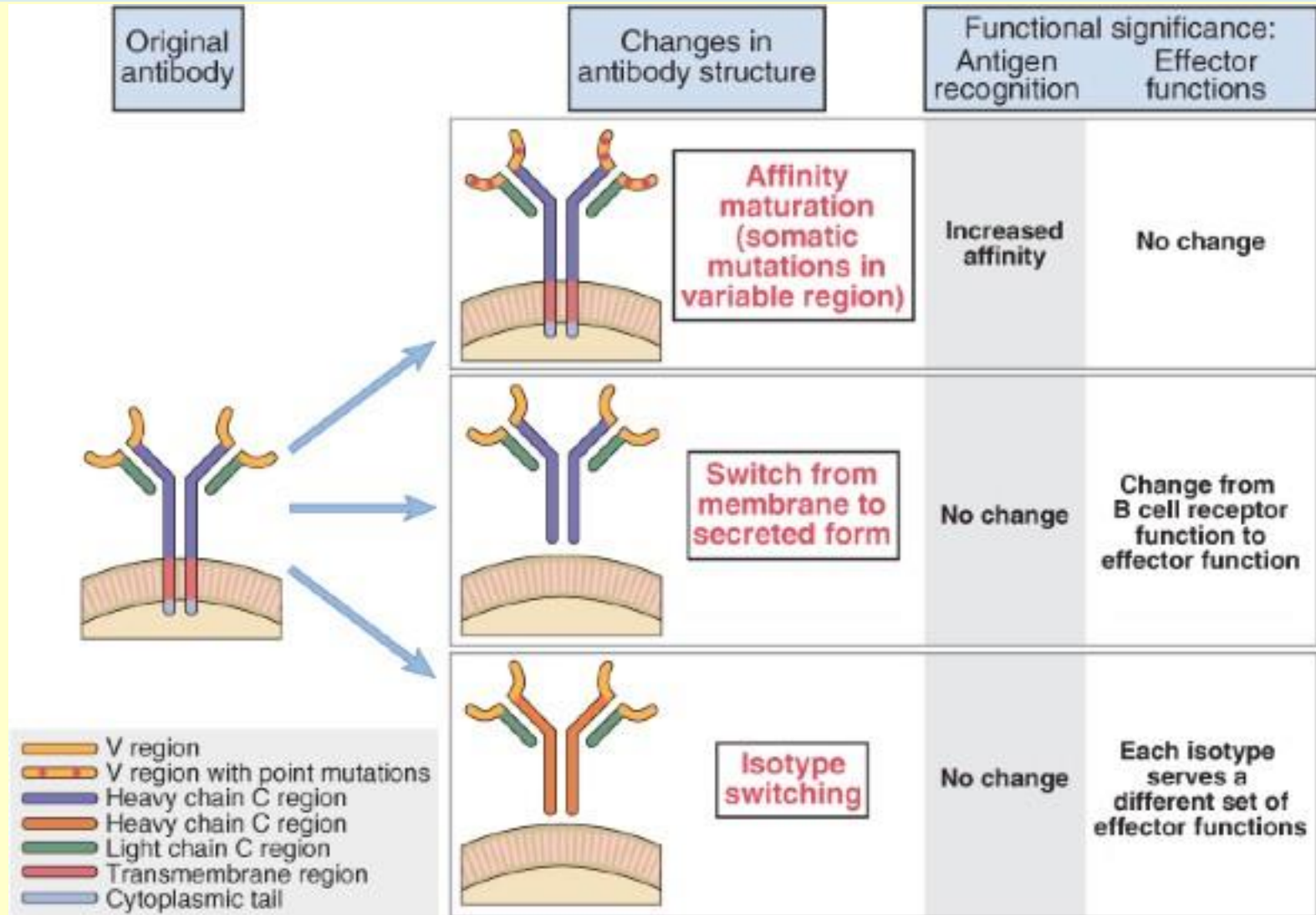
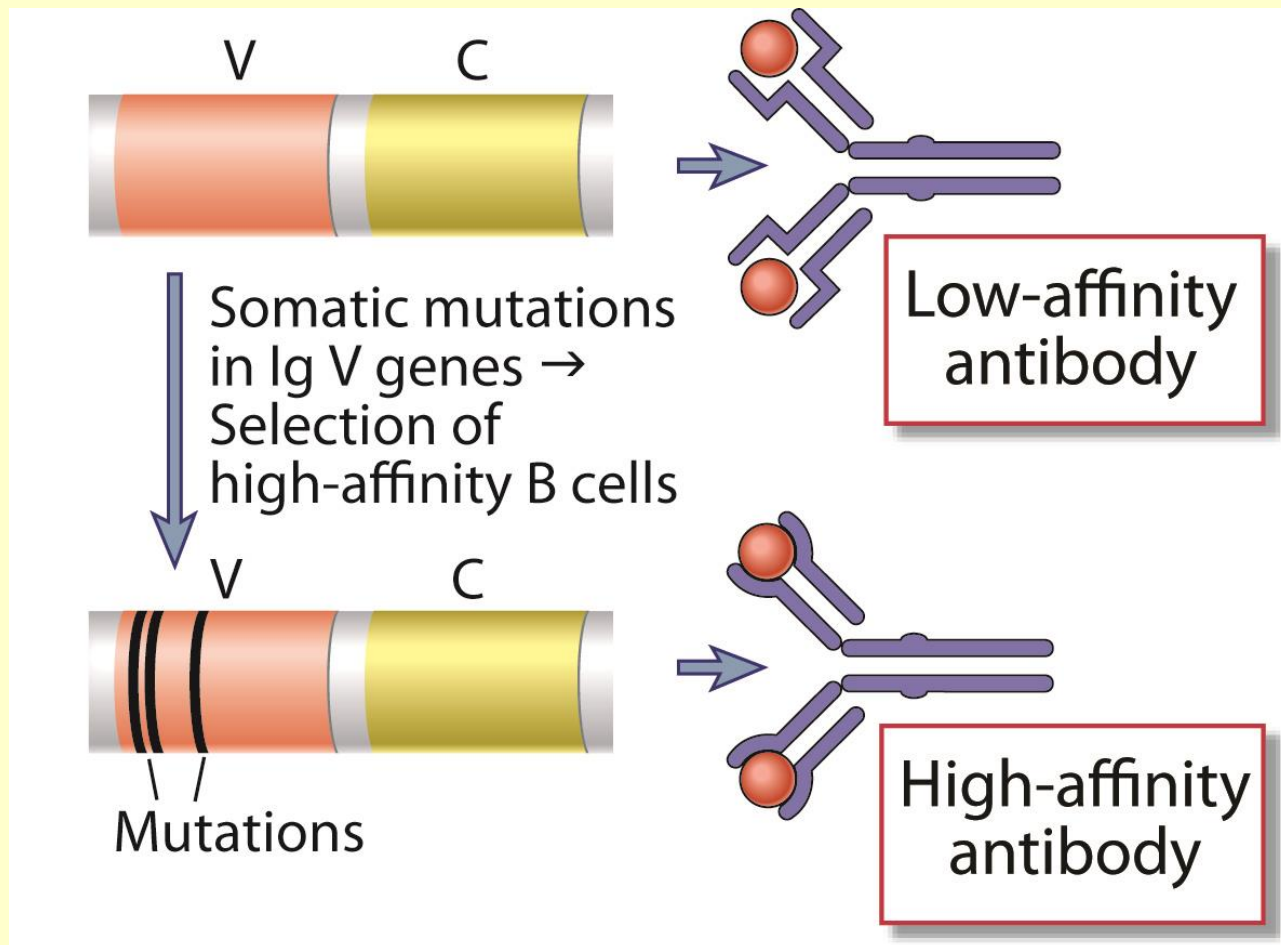


Fig. 11-2

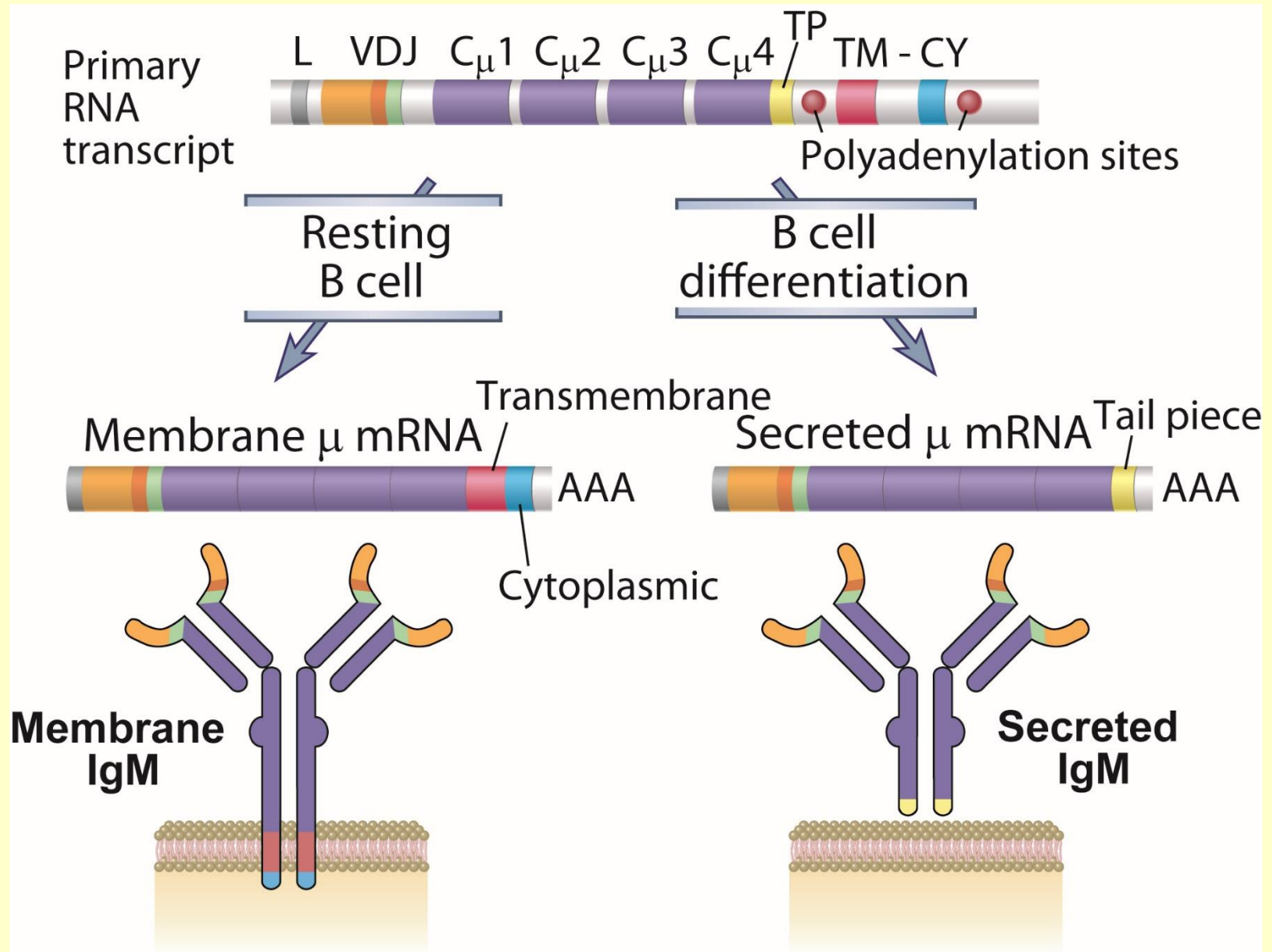
Changes in the immunoglobulin molecule during the immune response



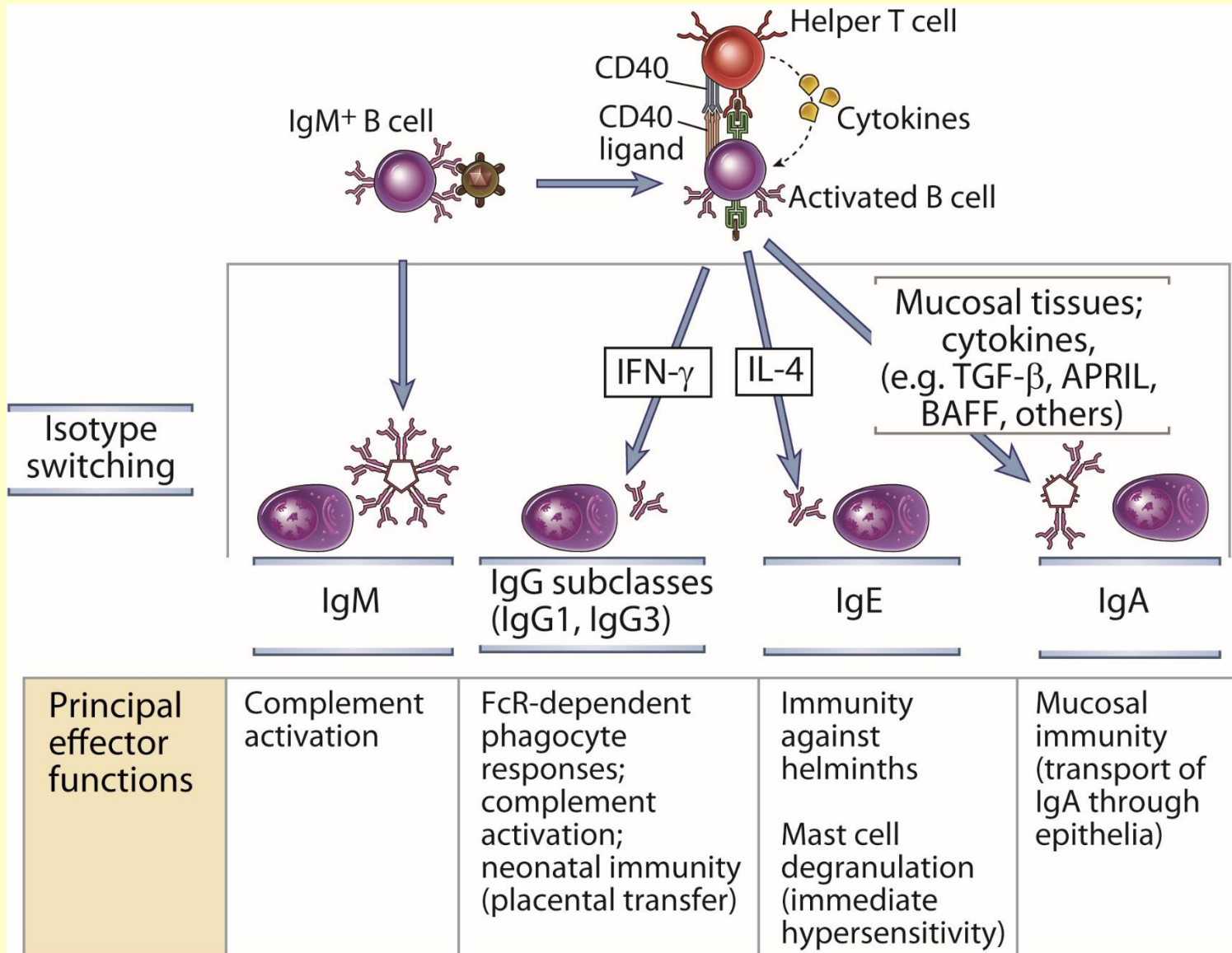
Somatic Mutations in Ig V genes → affinity maturation



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



Ig heavy chain isotype switching → development of functional diversity



Helper T cell Activation of B Cells

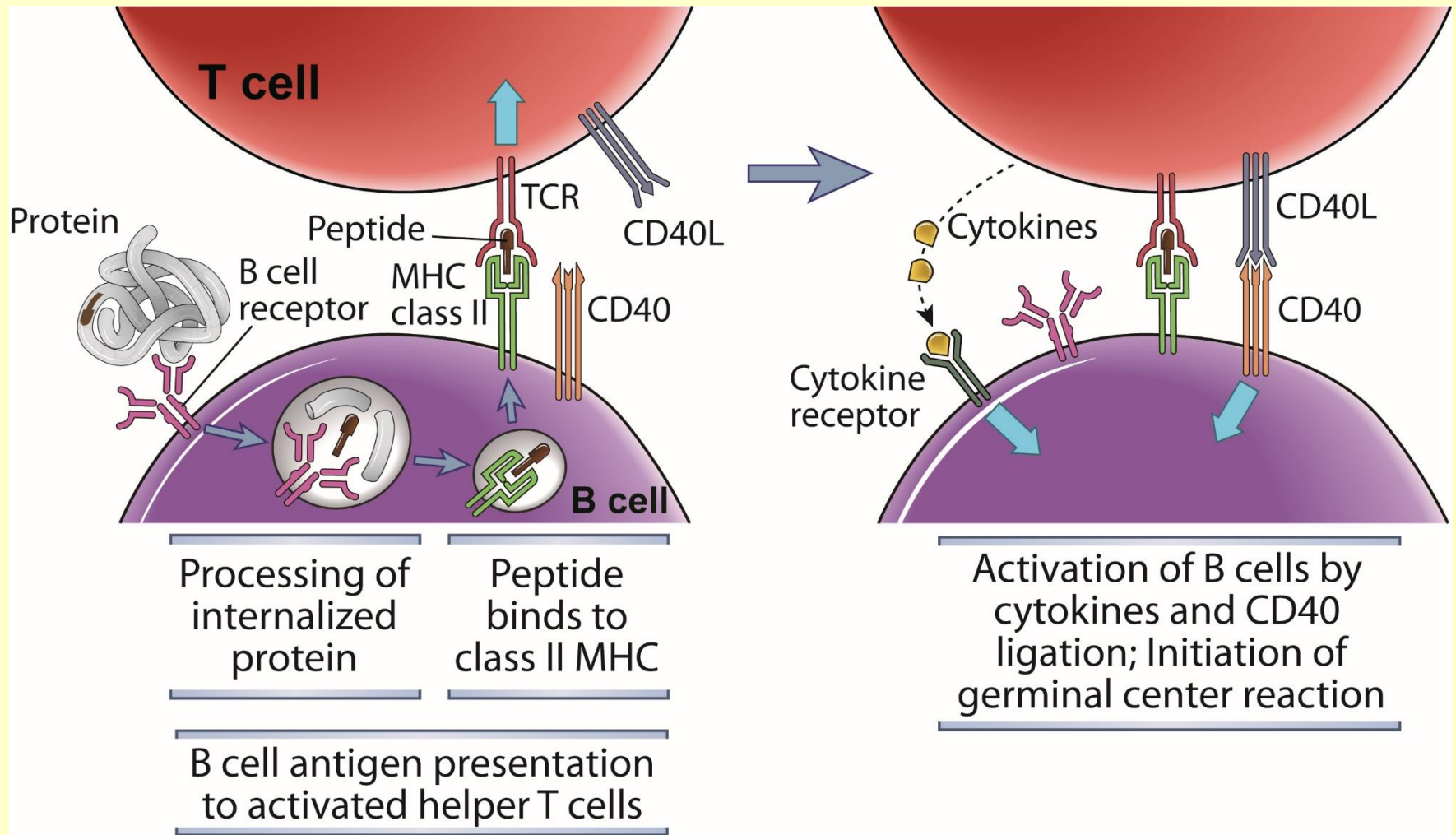


Fig. 11-10

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

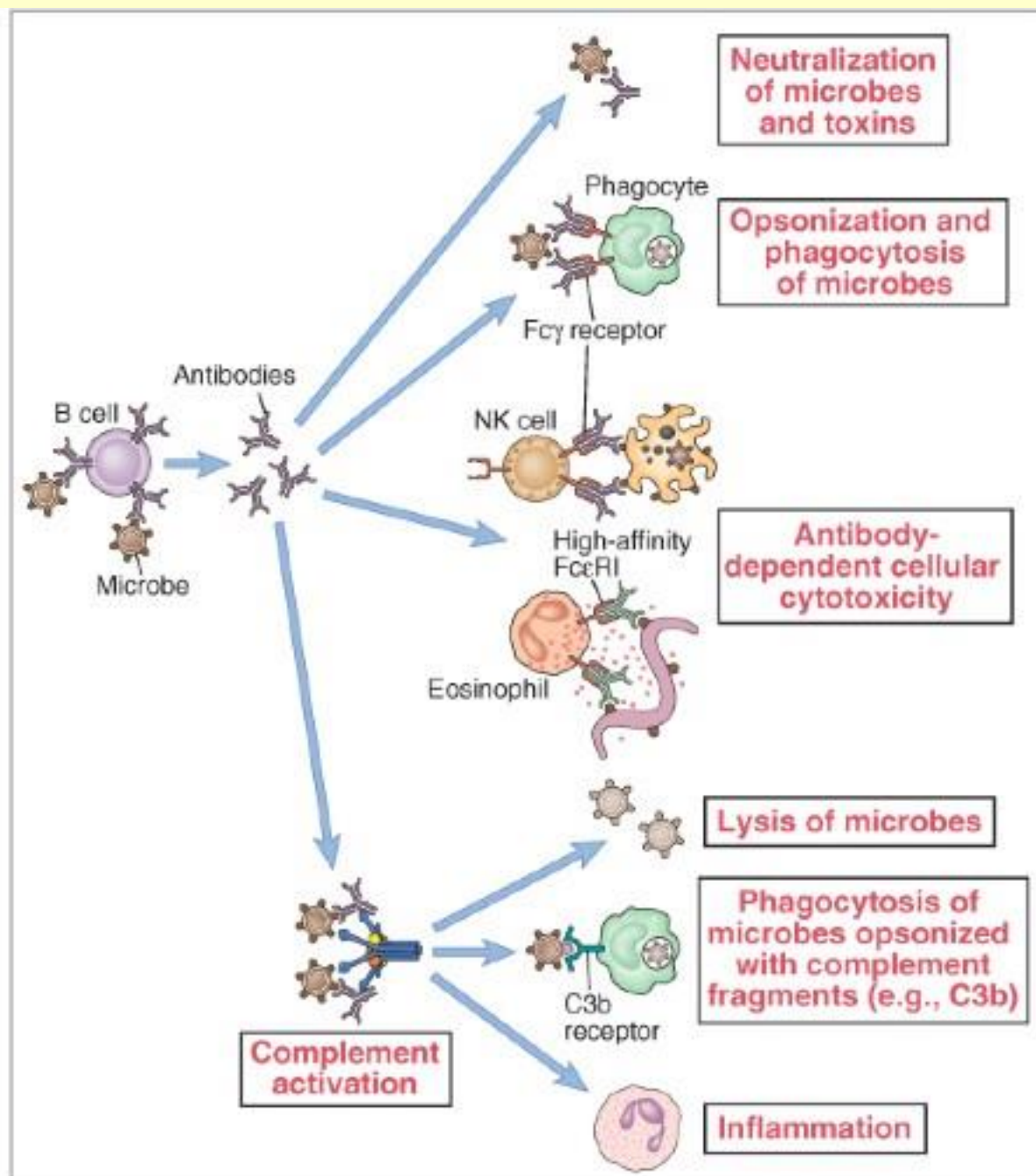
Immunoglobulins of various isotypes act at different places in the body

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

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Immunoglobulin 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

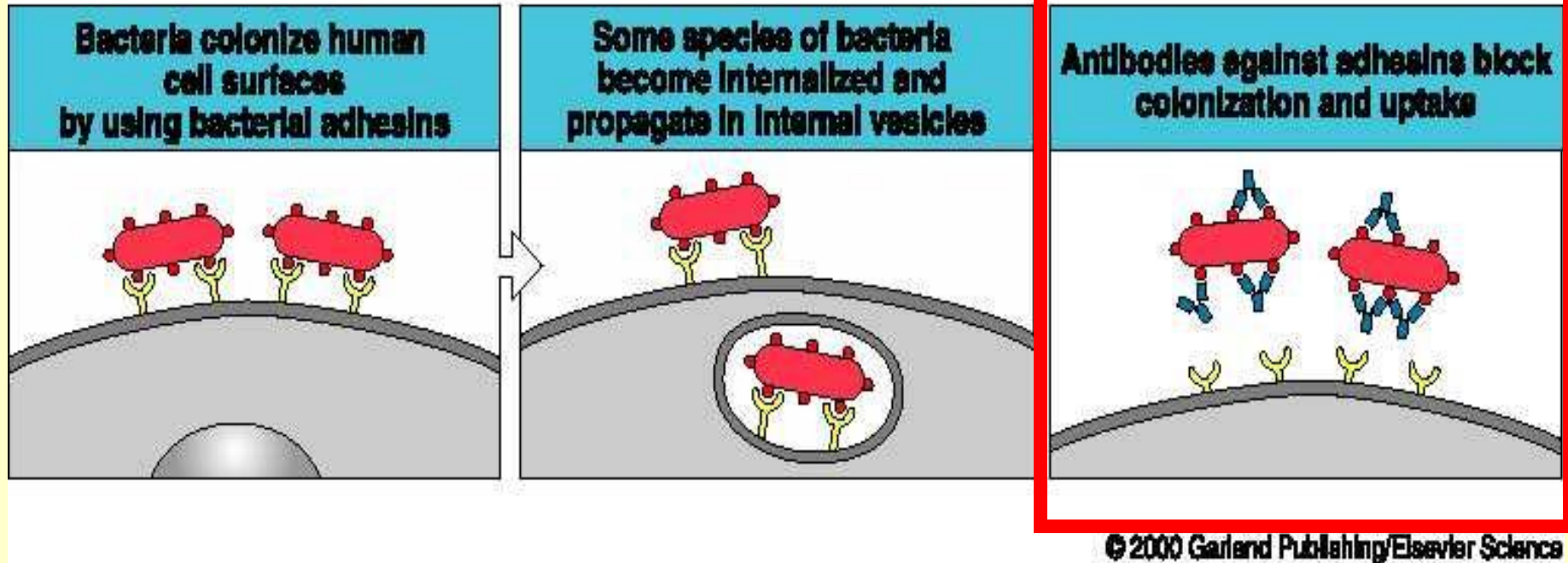
Functional activity	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Neutralization	+	-	++	++	++	++	++	-
Opsonization	+	-	+++	*	++	+	+	-
Sensitization for killing by NK cells	-	-	++	-	++	-	-	-
Sensitization of mast cells	-	-	+	-	+	-	-	+++
Activates complement system	+++	-	++	+	+++	-	+	-

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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

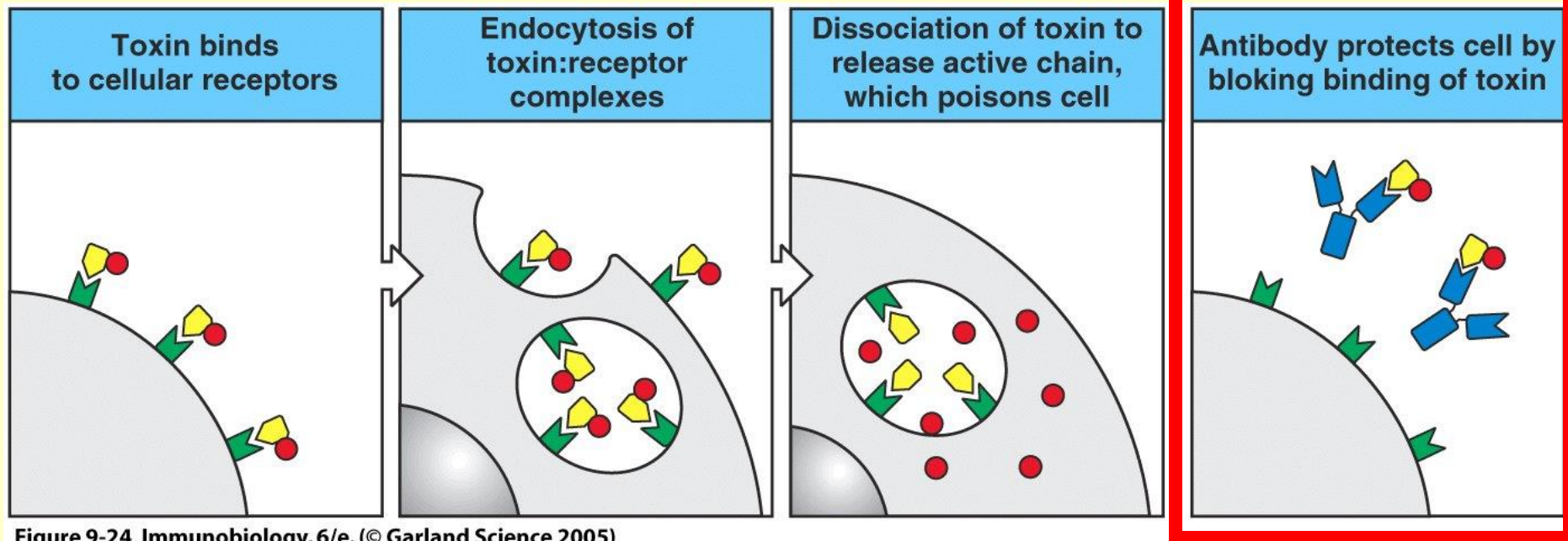


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Diphtheria, Tetanus exotoxin → Toxoid (inactivated exotoxin) for vaccination

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)

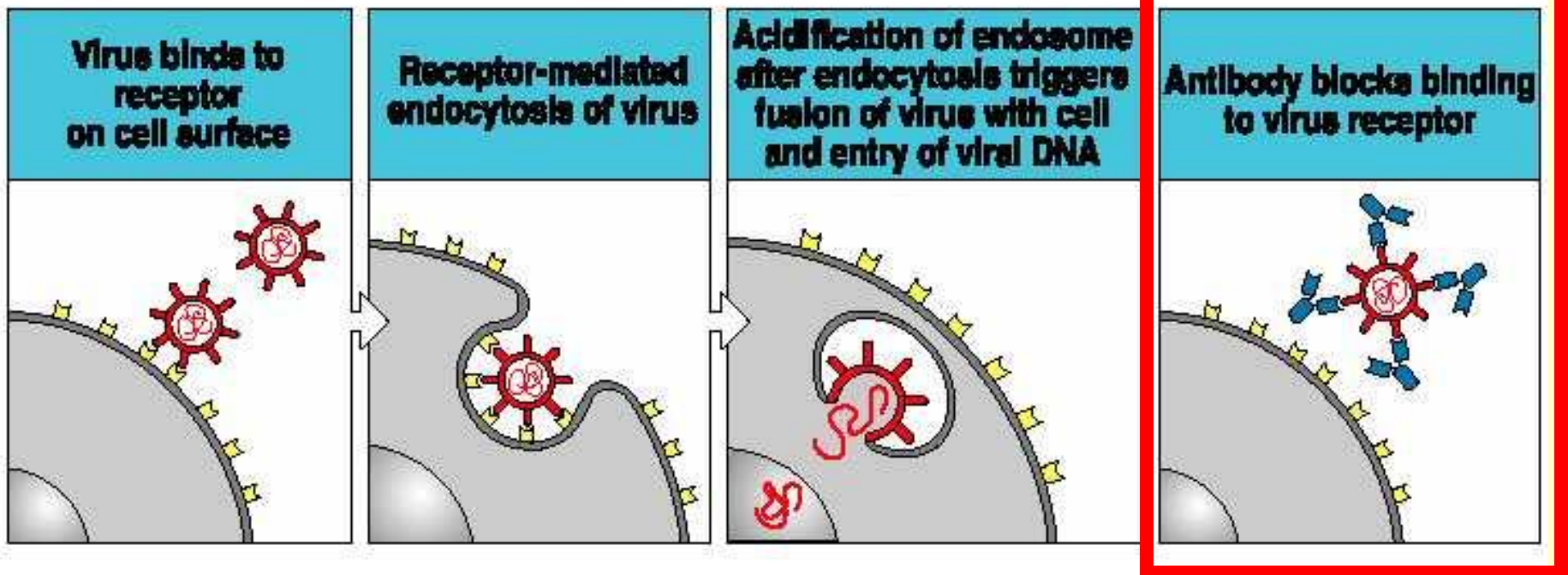
Figure 9-23 Immunobiology, 6/e. (© Garland Science 2005)

Virus neutralization

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

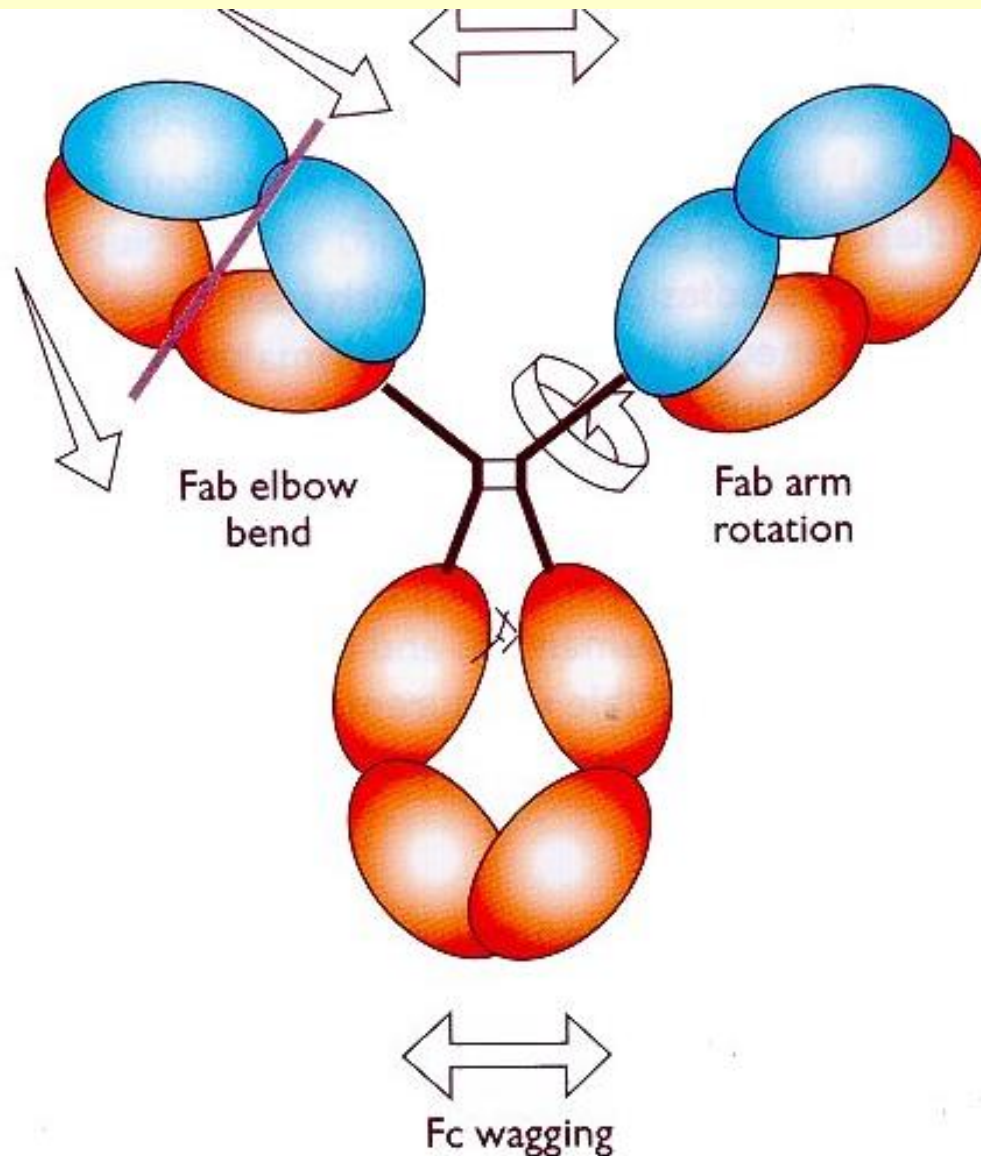
- Influenza virus binds to sialic acid residues of cell membrane glycoproteins
- Rhinovirus bind to ICAM-1
- Epstein-Barr virus binds to CR2

Figure 7.21a



Fc-RECEPTOR BINDING

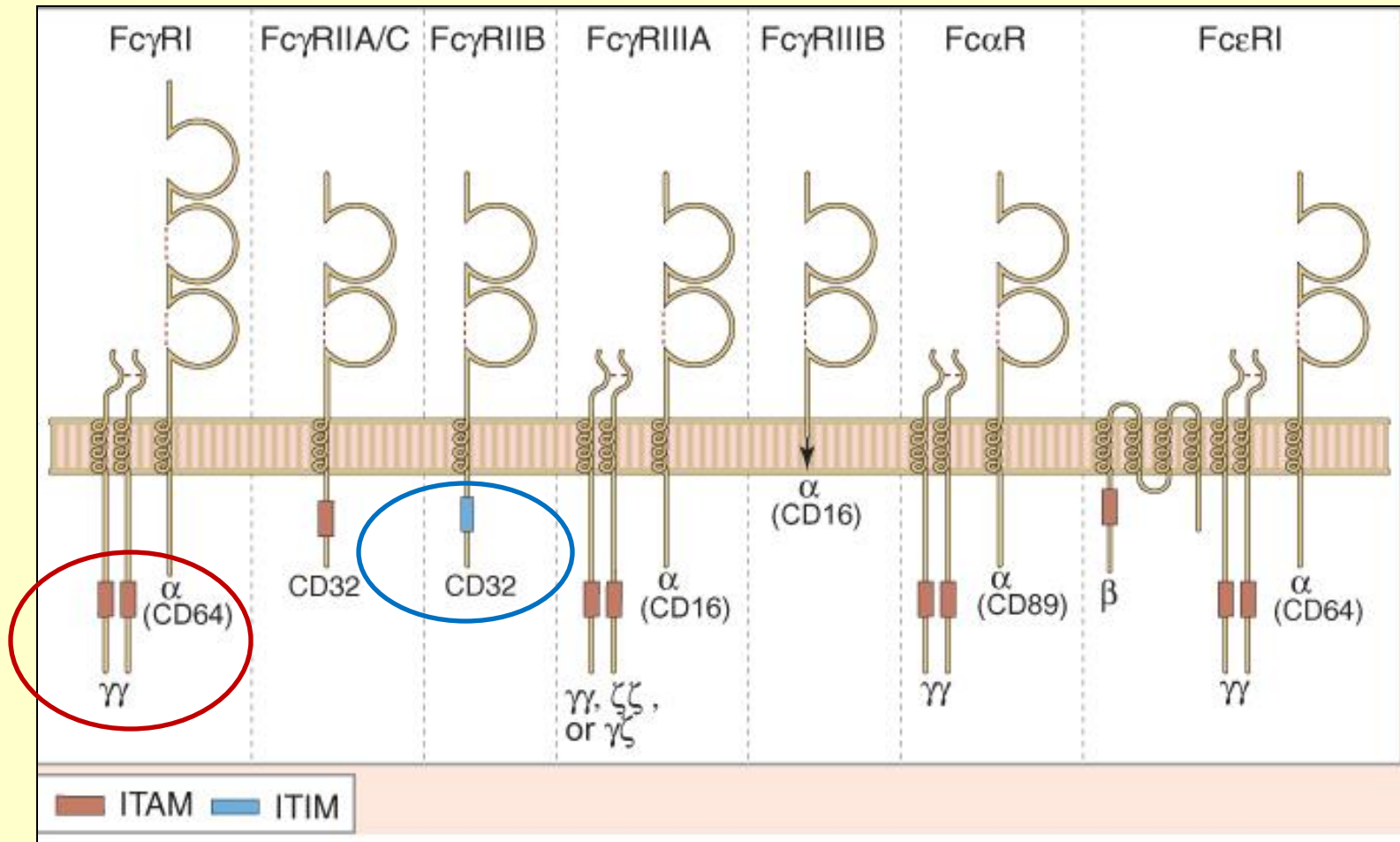
IgG is a flexible molecule



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

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

Activatory and inhibitory role of Fc γ Receptors



Fc receptors (FcR)

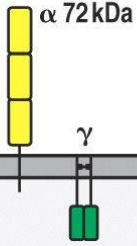
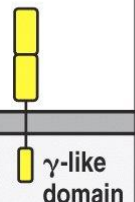
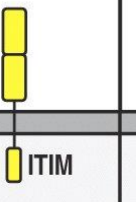
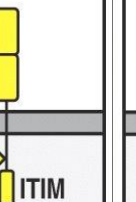
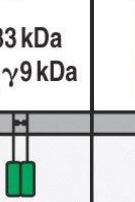
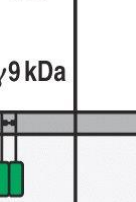
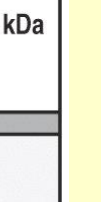
Receptor	FcγRI (CD64)	FcγRII-A (CD32)	FcγRII-B2 (CD32)	FcγRII-B1 (CD32)	FcγRIII (CD16)	FcεRI	FcαRI (CD89)	Fc α/μR
Structure								
Binding	IgG1 10^8 M^{-1}	IgG1 $2 \times 10^6 \text{ M}^{-1}$	IgG1 $2 \times 10^6 \text{ M}^{-1}$	IgG1 $2 \times 10^6 \text{ M}^{-1}$	IgG1 $5 \times 10^5 \text{ M}^{-1}$	IgE 10^{10} M^{-1}	IgA1, IgA2 10^7 M^{-1}	IgA, IgM $3 \times 10^9 \text{ M}^{-1}$
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
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 [†]	Macrophages B cells
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	Uptake

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Opsonization and Phagocytosis by Antibodies

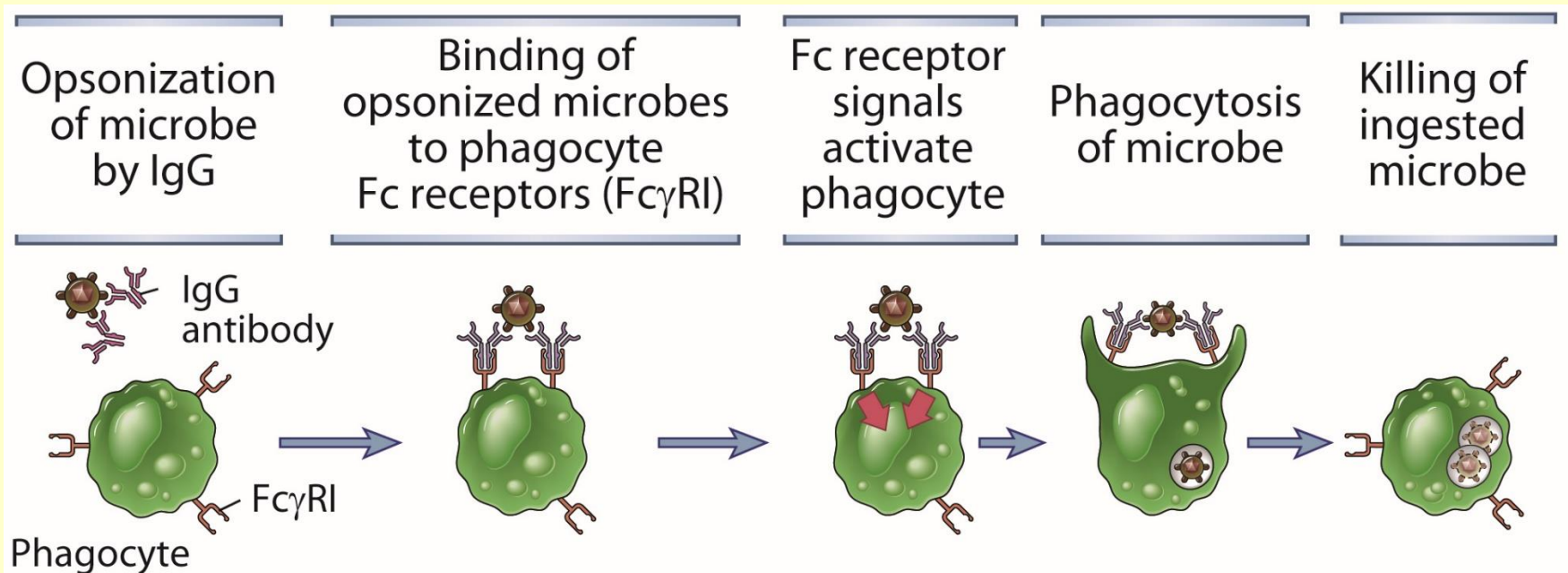


Fig. 12-4

Opsonization by antibody and complement C3b → FcR and CR mediated phagocytosis

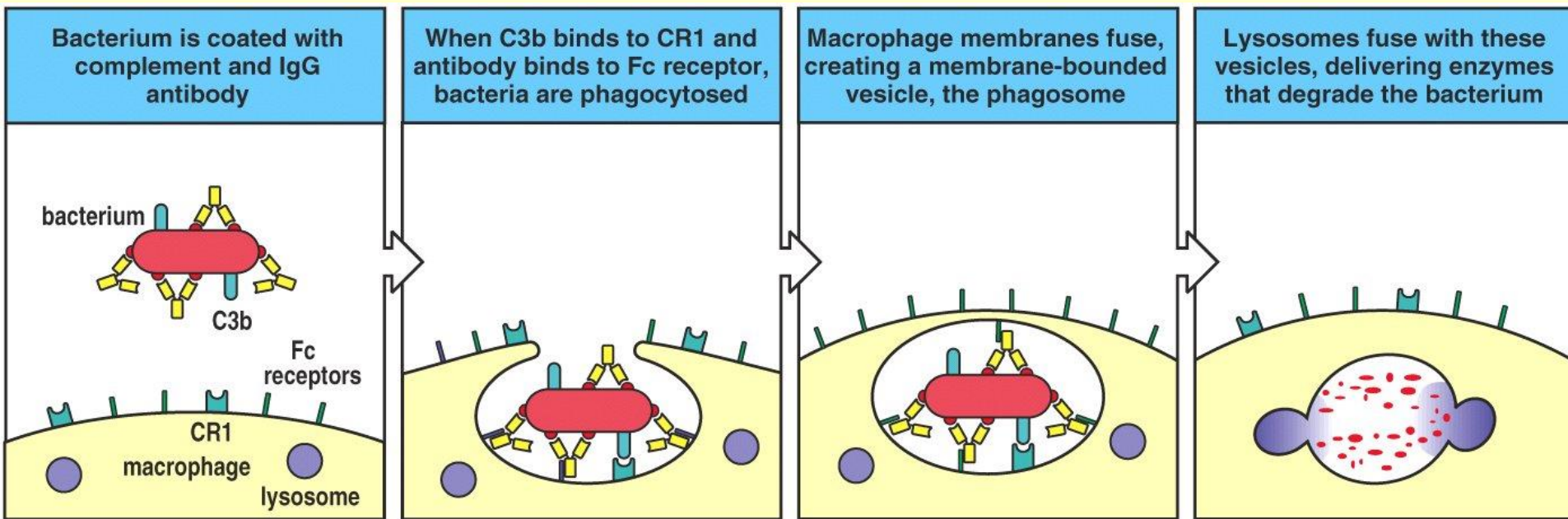


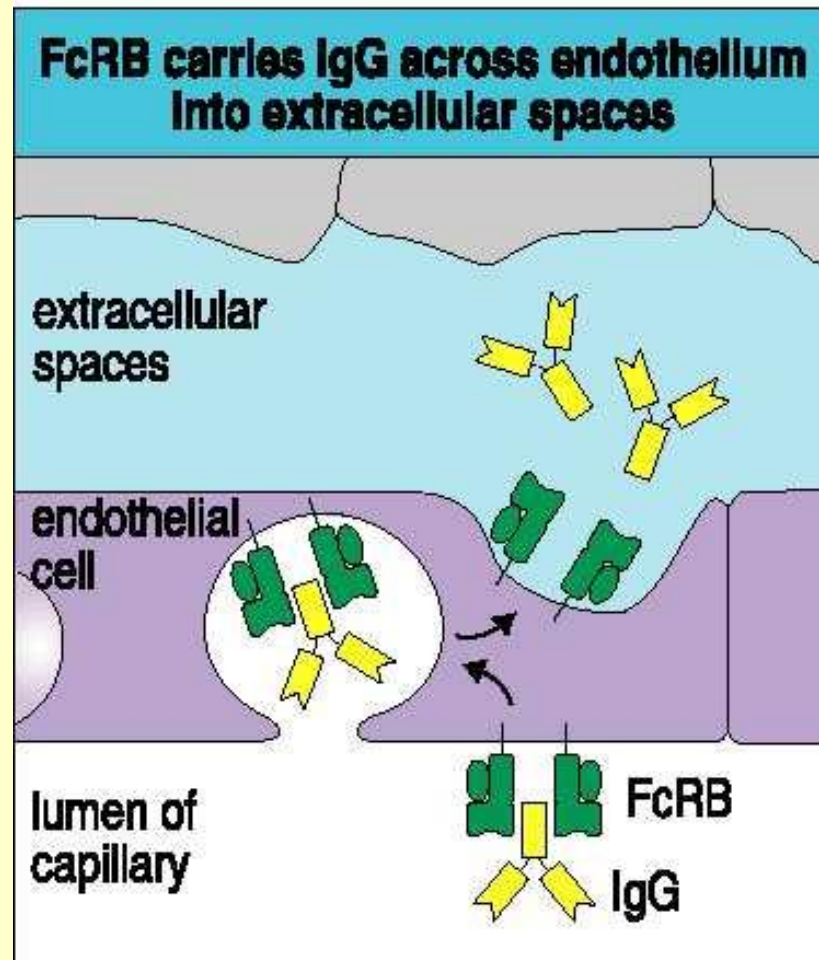
Figure 9-32 Immunobiology, 6/e. (© Garland Science 2005)

Free immunoglobulins cannot bind to Fc receptor and enhance phagocytosis

Antigen bound antibody is capable of binding to FcR

IgG transport from blood to tissues

Figure 7.16

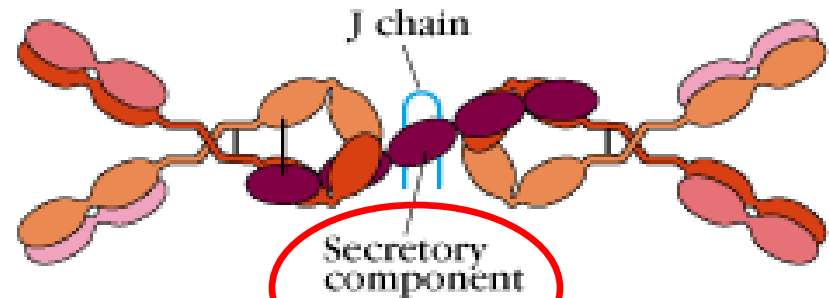


Poly-Ig receptor

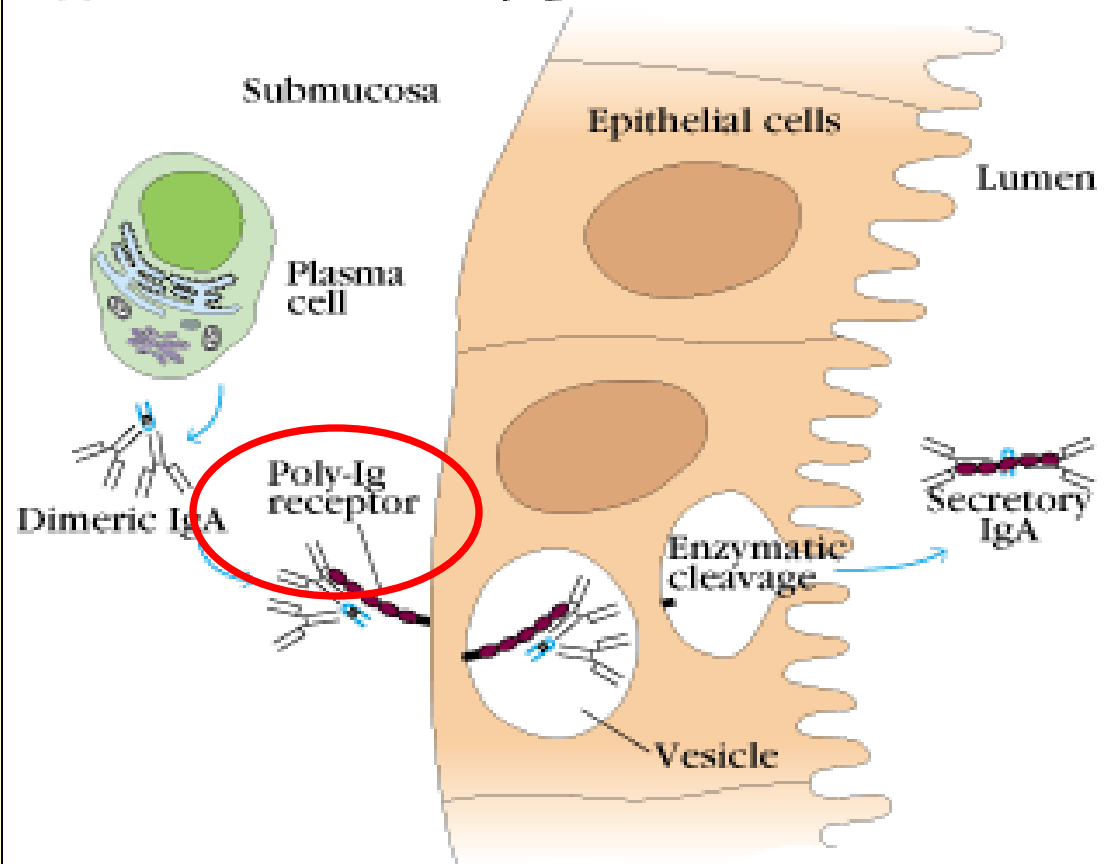
IgA/IgM transport

secretory
component

(a) Structure of secretory IgA



(b) Formation of secretory IgA



Regulation of the B cell activation by Fc γ RIIB

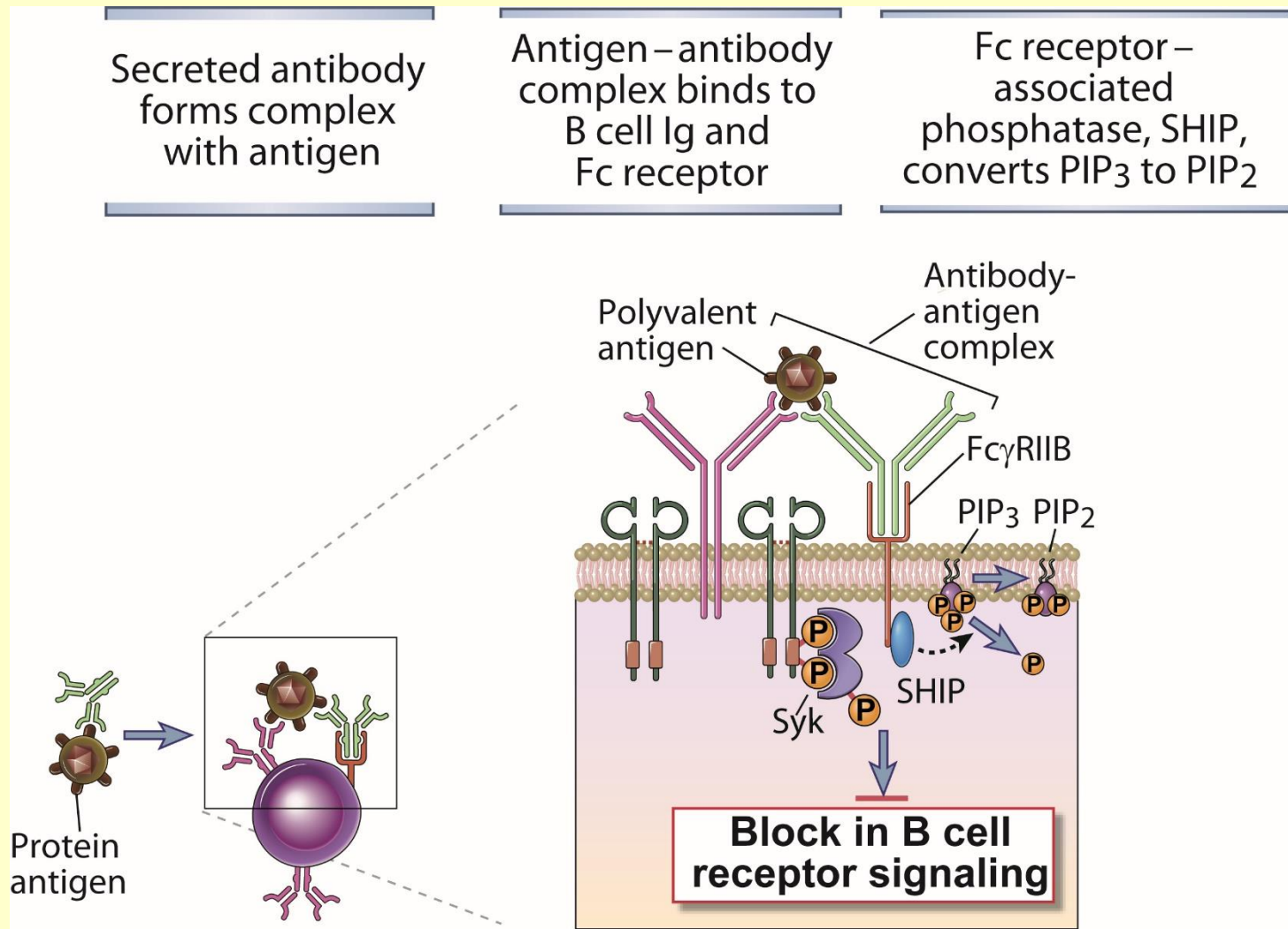
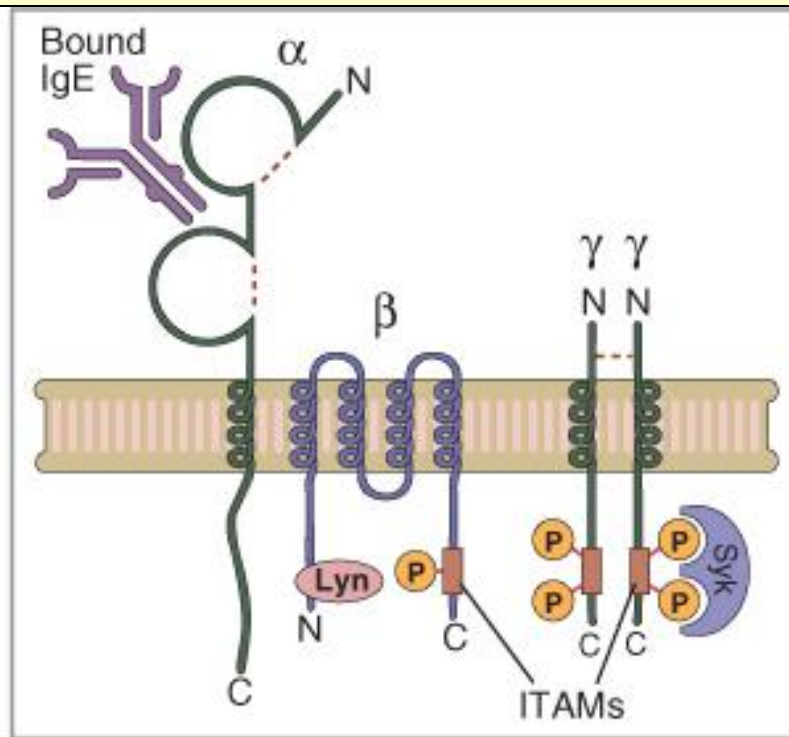


Fig. 11-21

Fc ϵ R -high affinity IgE receptor binds free IgE

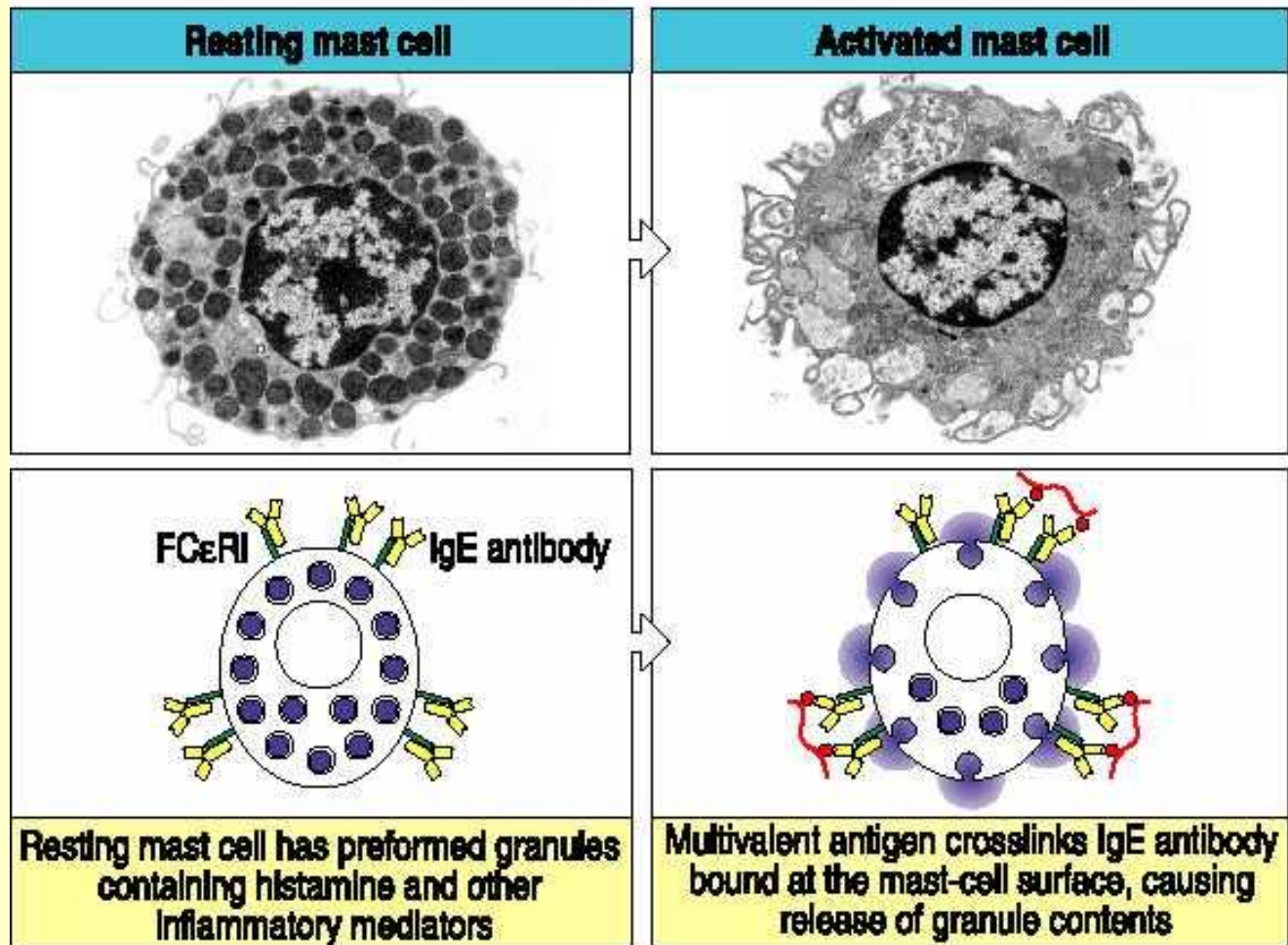


Mast cells, basophils, eosinophils
Langerhans cells, macrophages

IgE upregulate its expression on
Mast cells

IgE-mediated mast cell activation

Figure 7.24



ADCC = antibody dependent
cellular cytotoxicity

ADCC

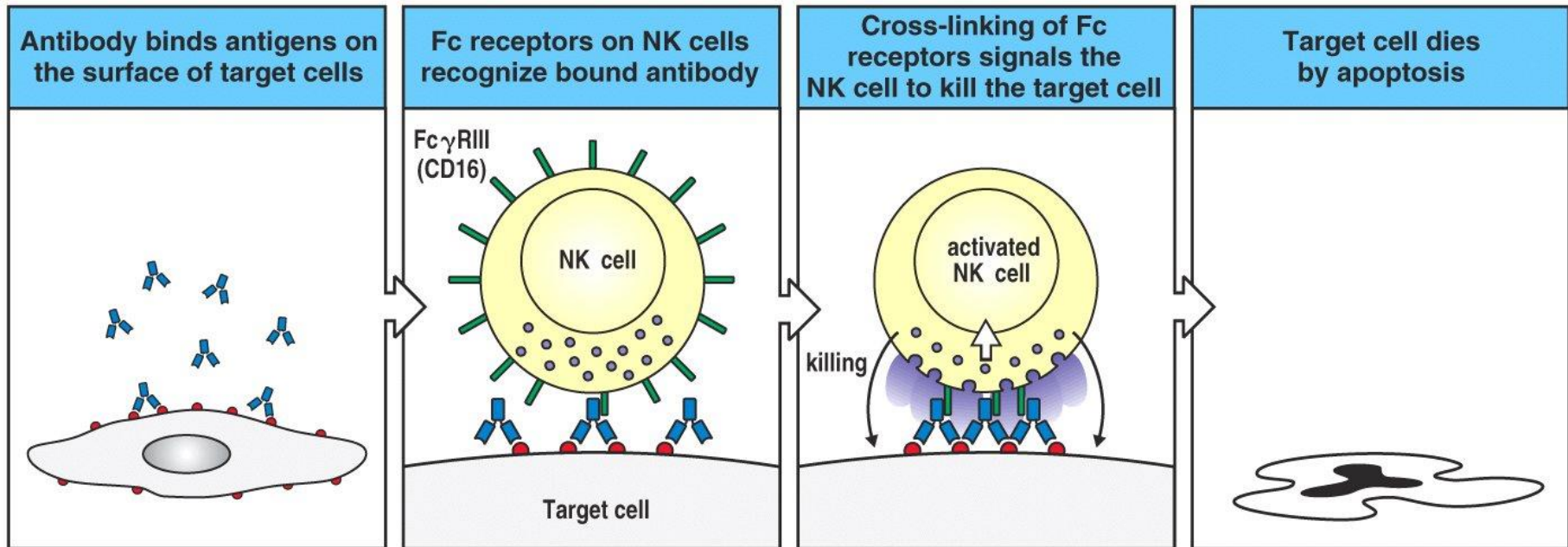
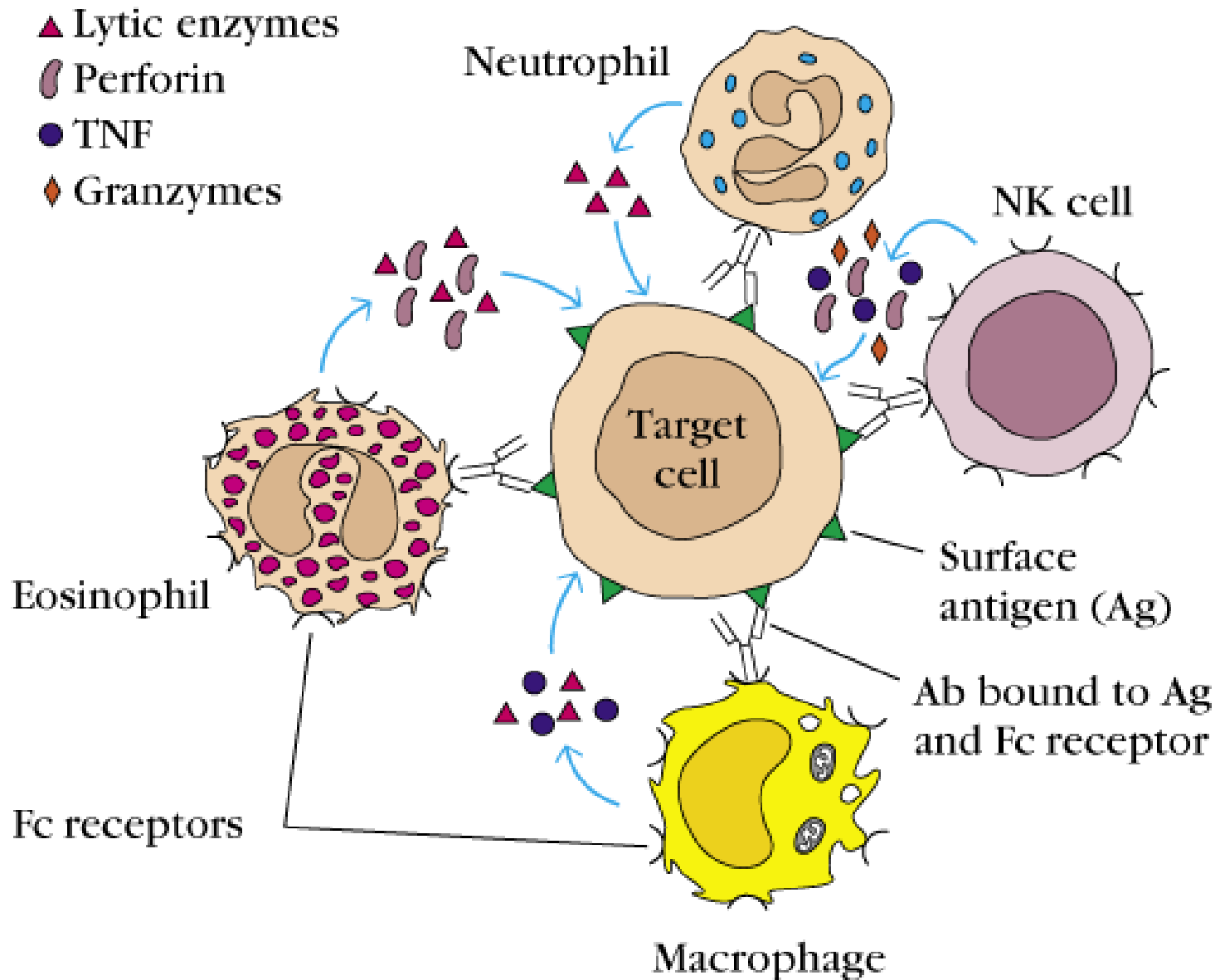


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ADCC



COMPLEMENT ACTIVATION

IgG & IgM antigen-antibody complexes activate complement

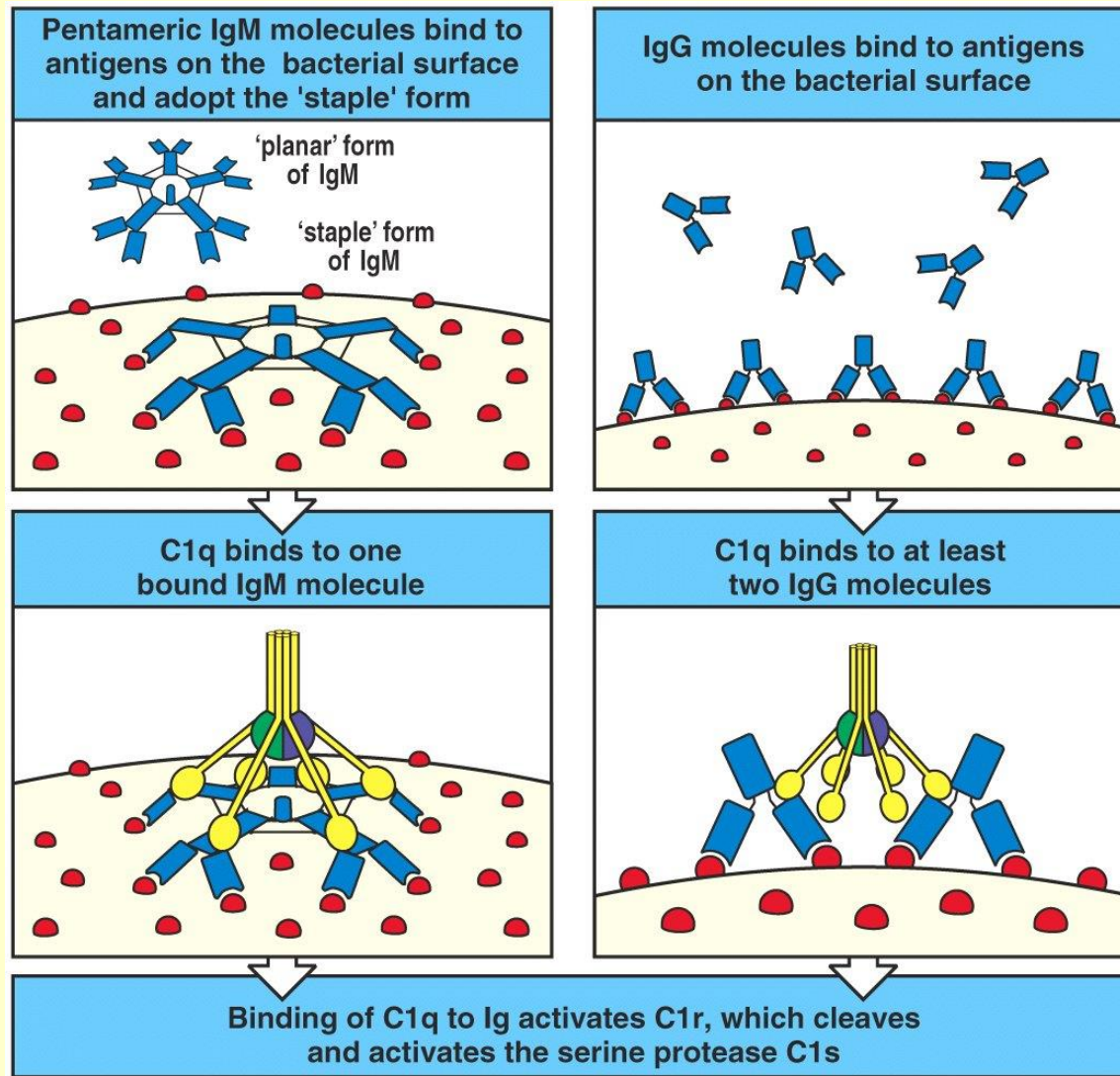


Figure 9-28 Immunobiology, 6/e. (© Garland Science 2005)

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