Basic Immunology

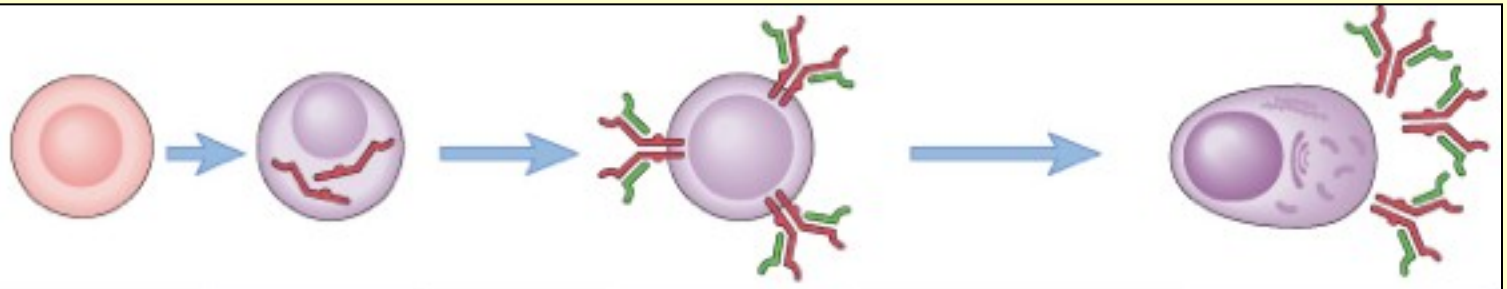
15. lecture

Effector functions of immunoglobulins

Antigen-antibody reactions

IgE mediated immunreactions

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

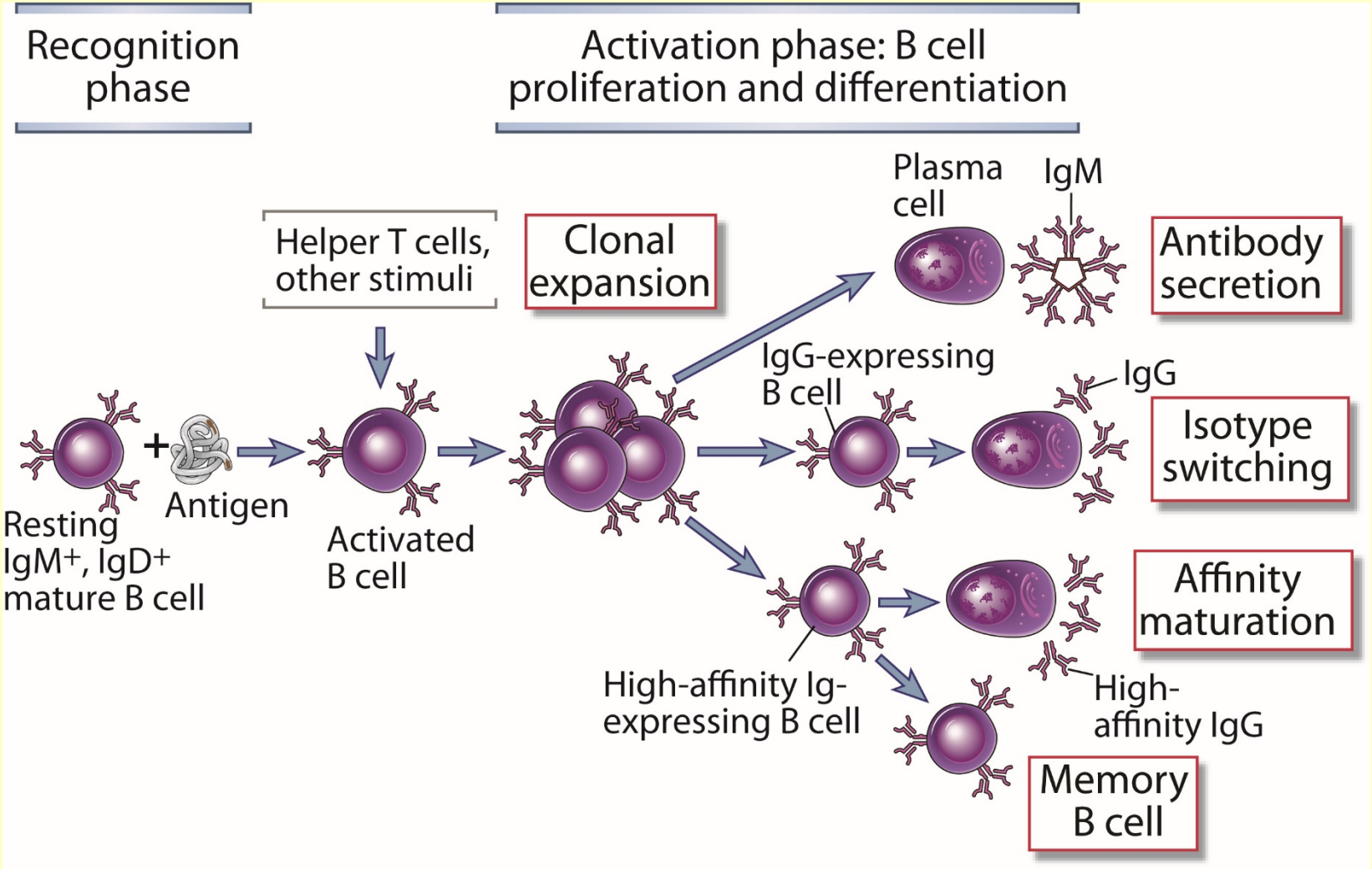


Fig. 11-1

Antibody production

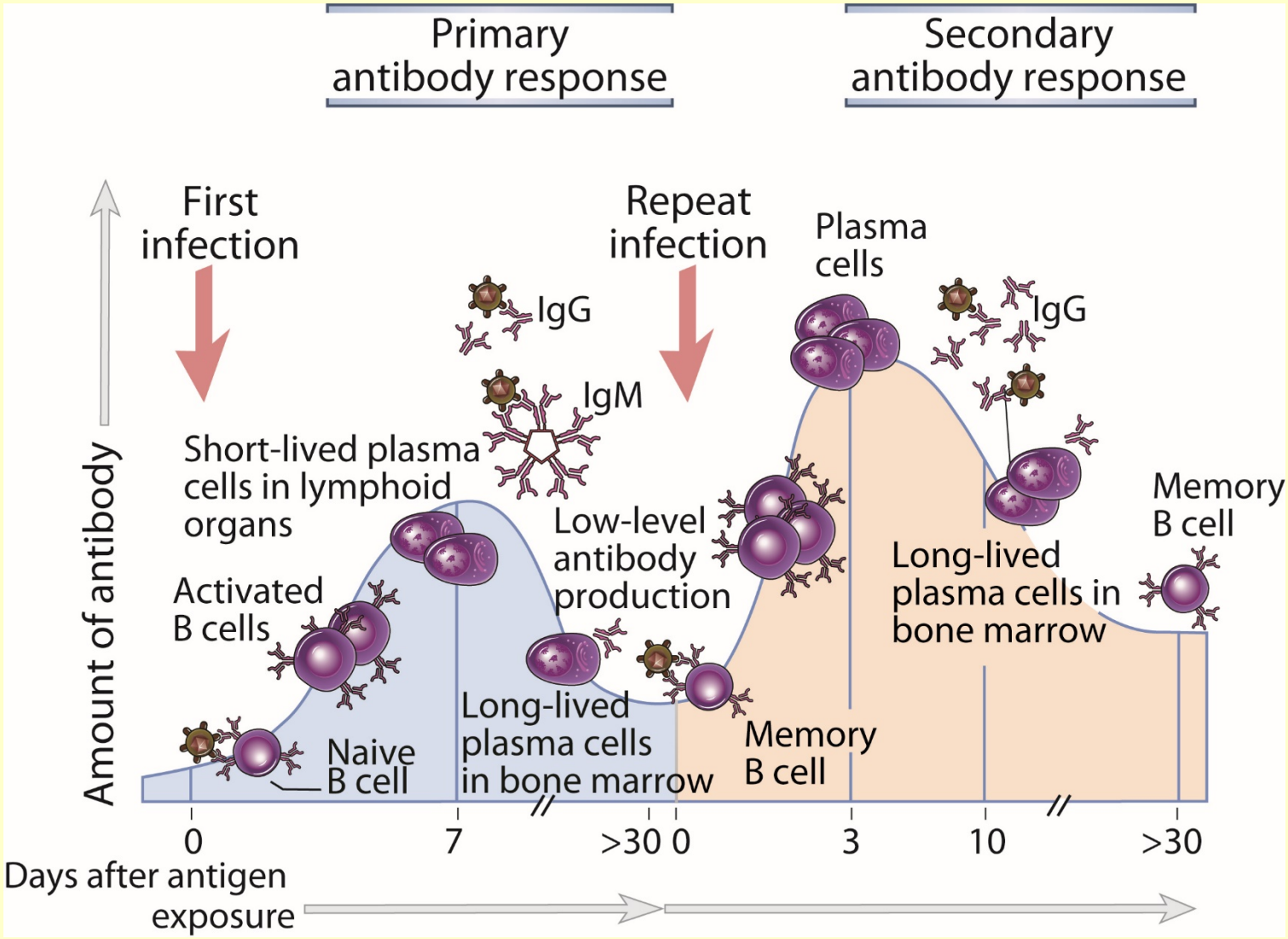
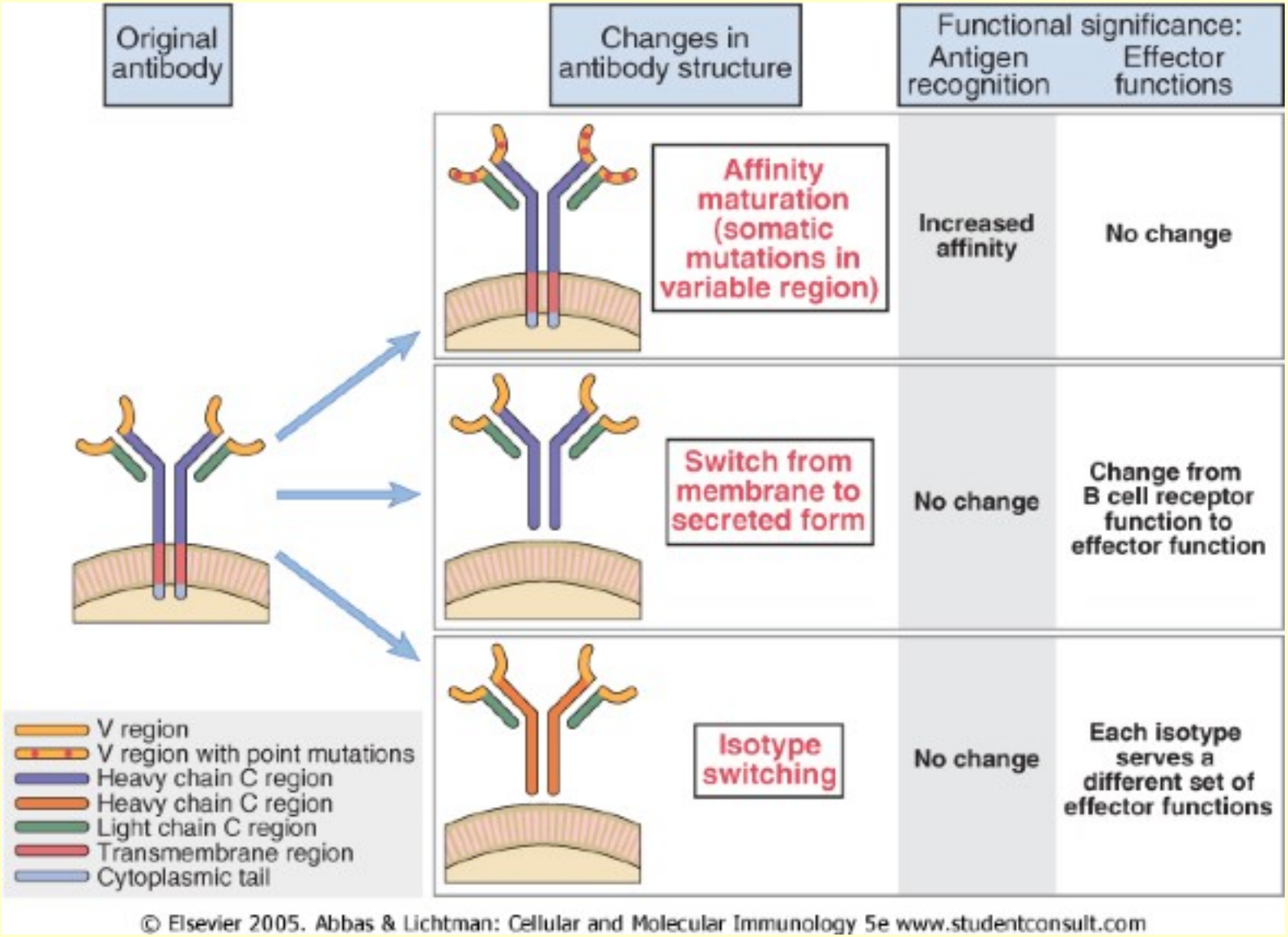
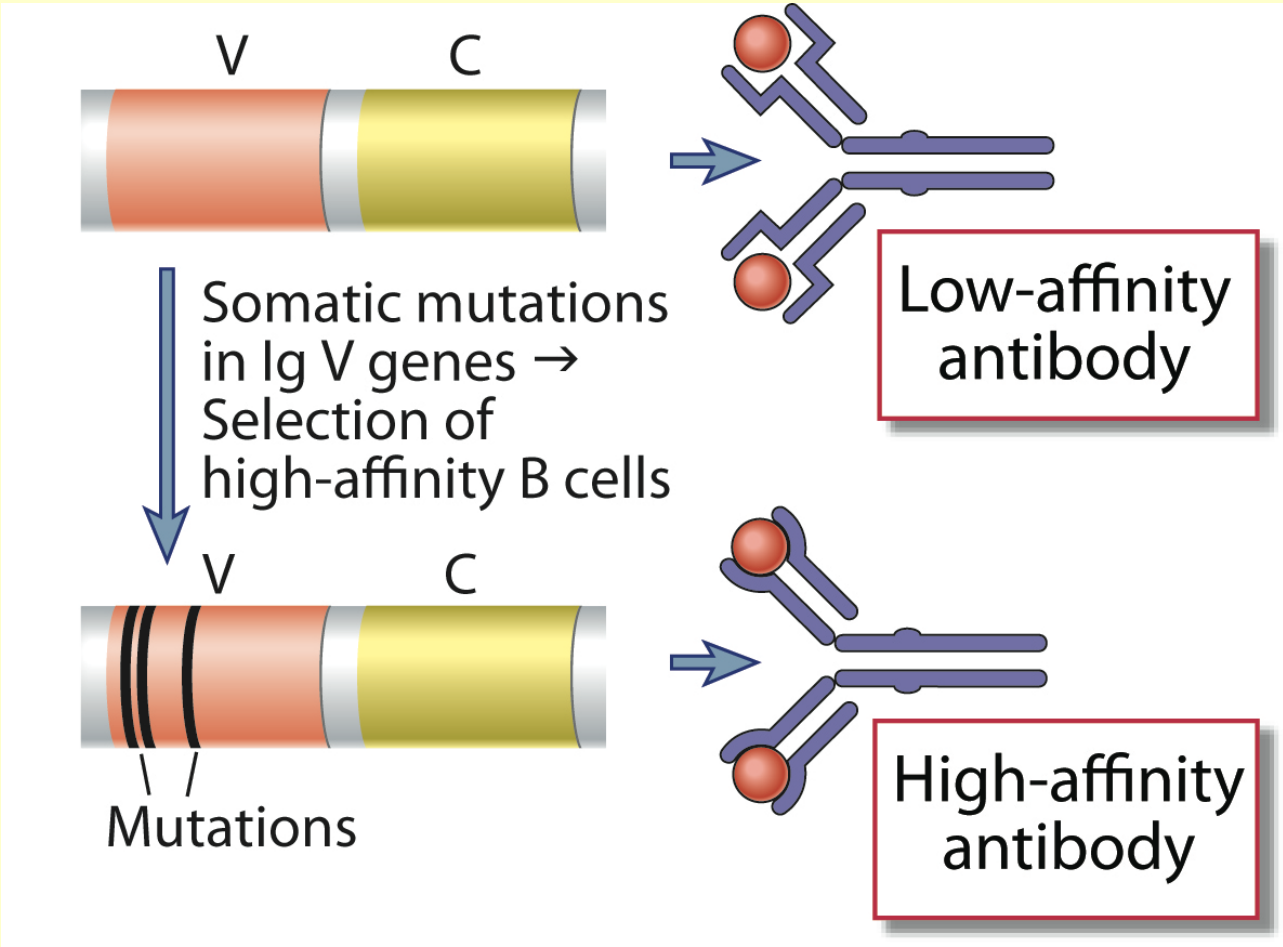


Fig. 11-2

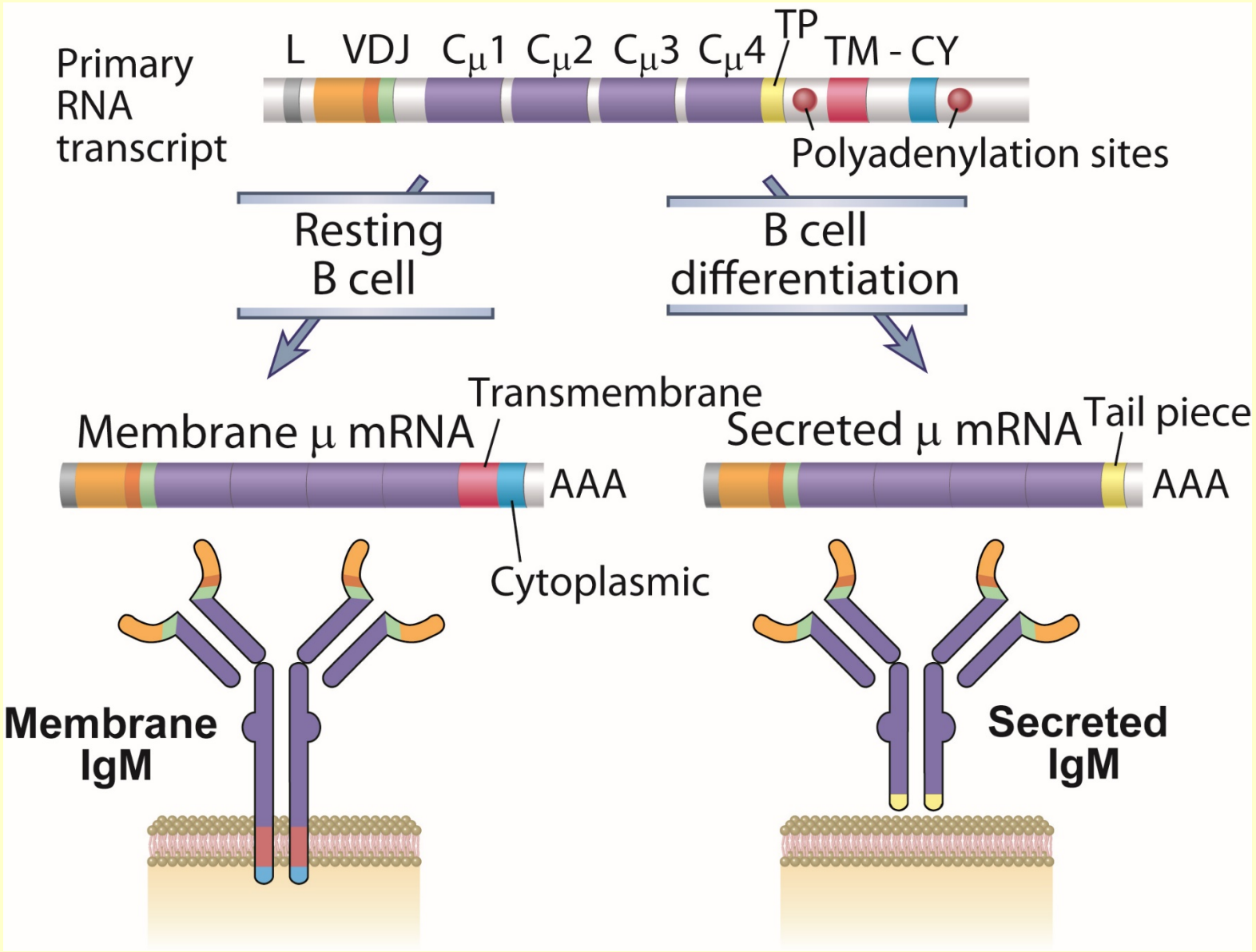
Changes in the immunoglobulin molecule during the immune response



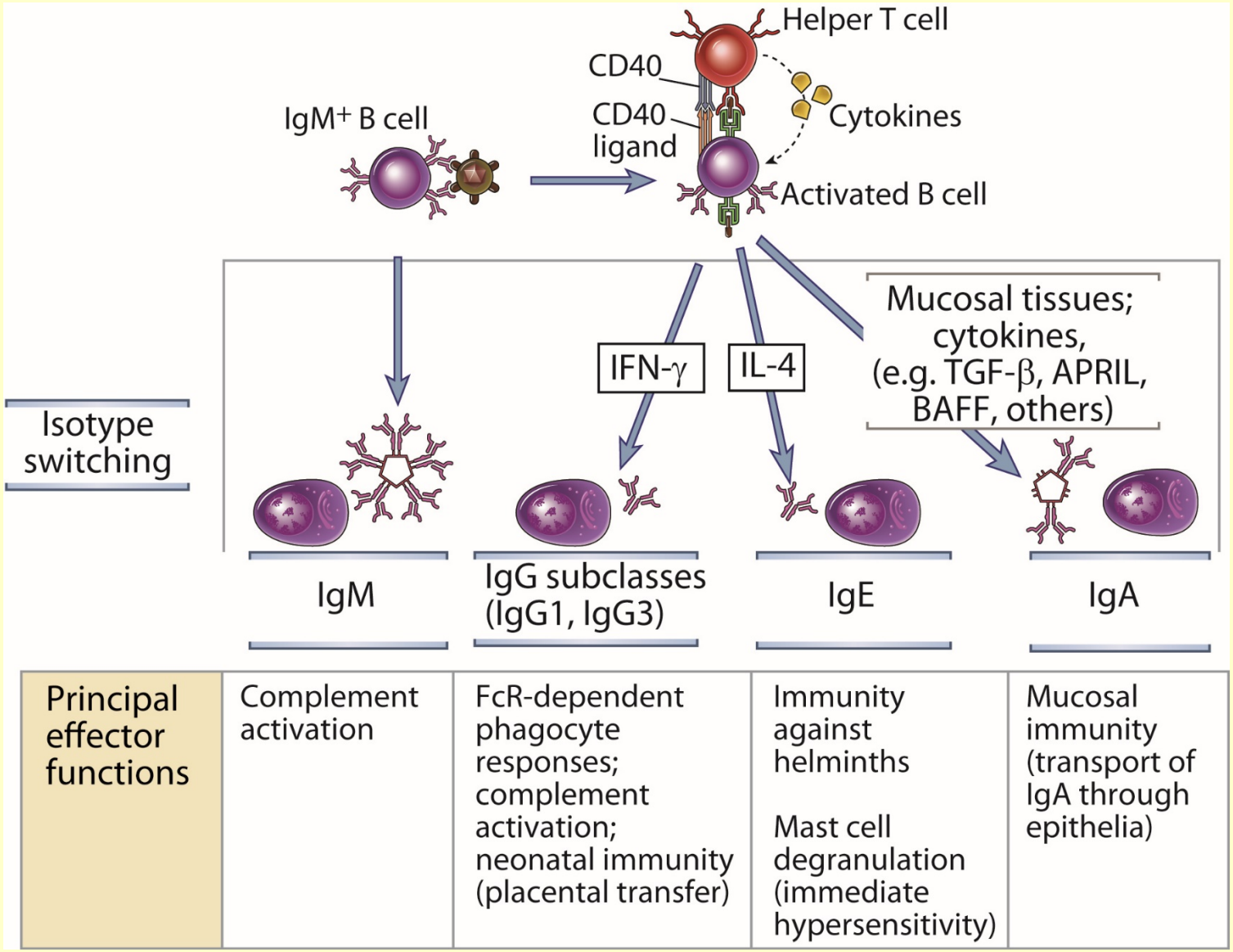
Somatic Mutations in Ig V genes → affinity maturation



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



Ig heavy chain isotype switching → development of functional diversity



Principal effector functions	Complement activation	FcR-dependent phagocyte responses; complement activation; neonatal immunity (placental transfer)	Immunity against helminths Mast cell degranulation (immediate hypersensitivity)	Mucosal immunity (transport of IgA through epithelia)

Helper T cell Activation of B Cells

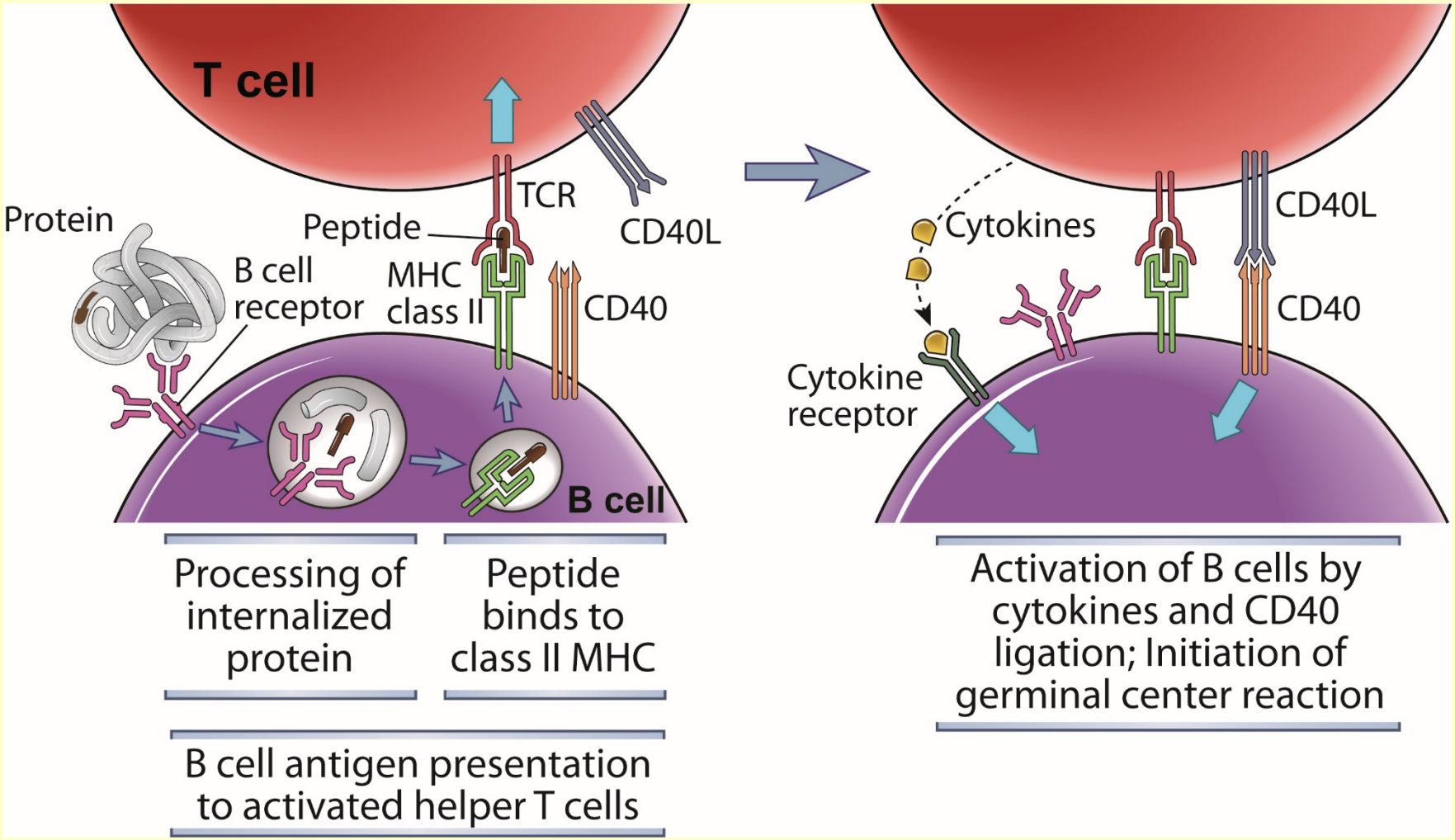


Fig. 11-10

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}

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

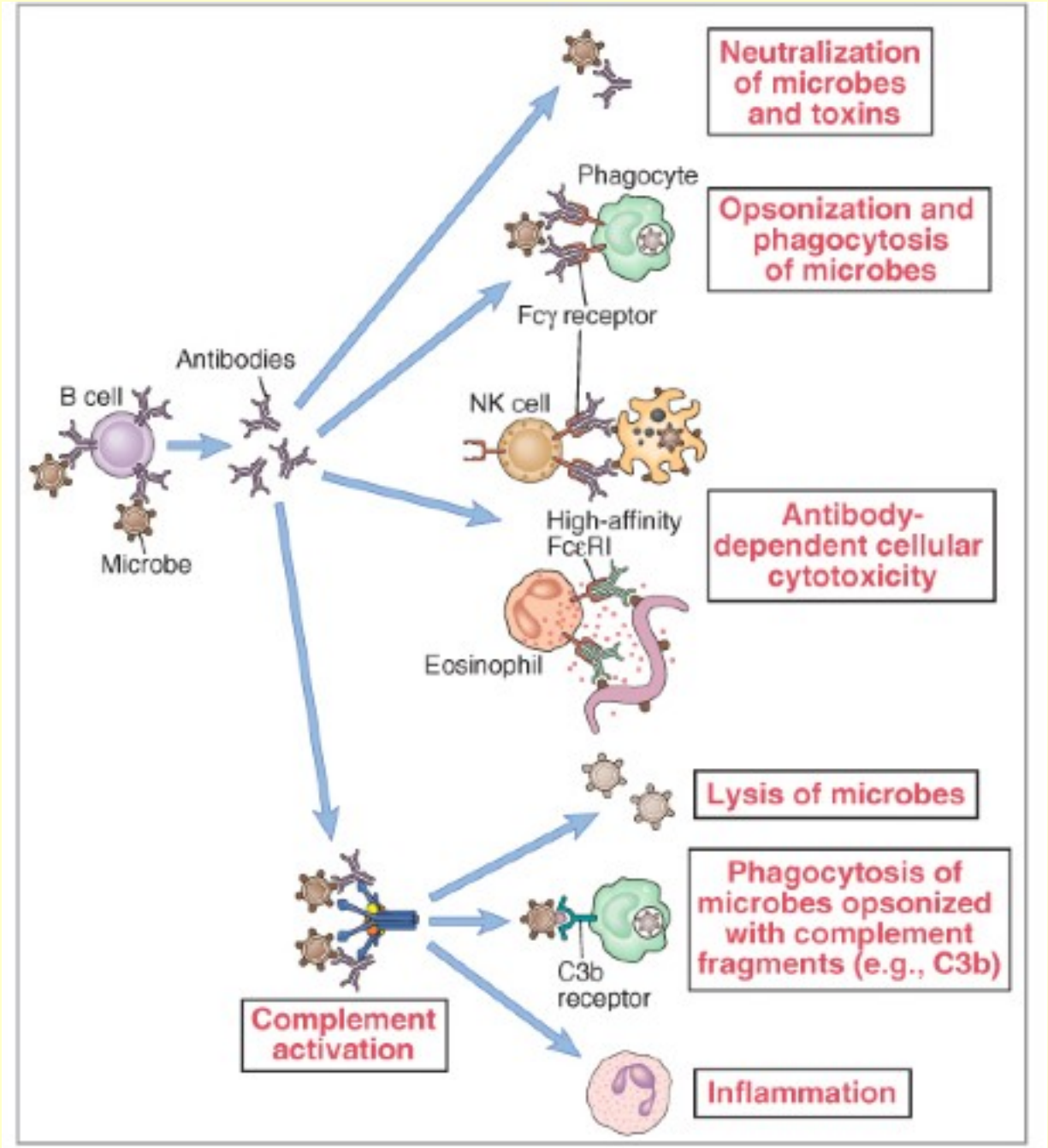
Immungolobulin effector functions

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)



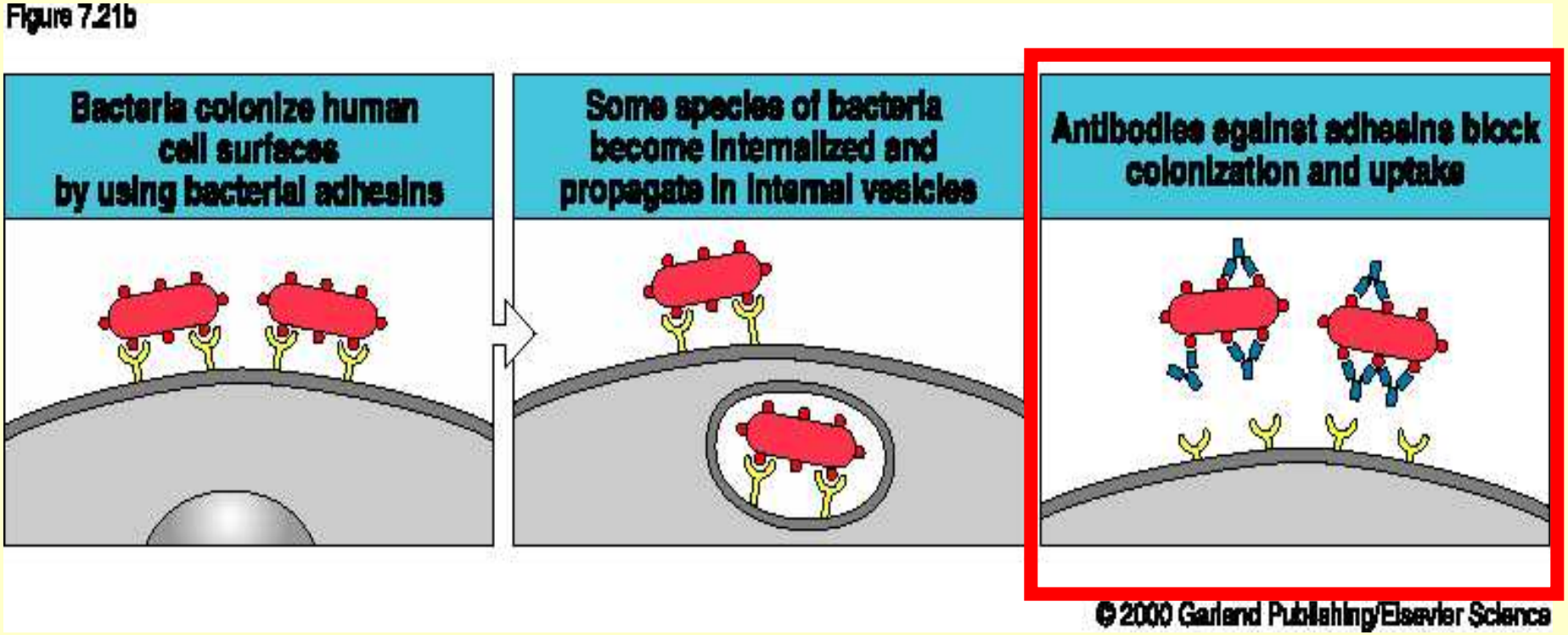
Immunoglobulins of various isotypes have different functions

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

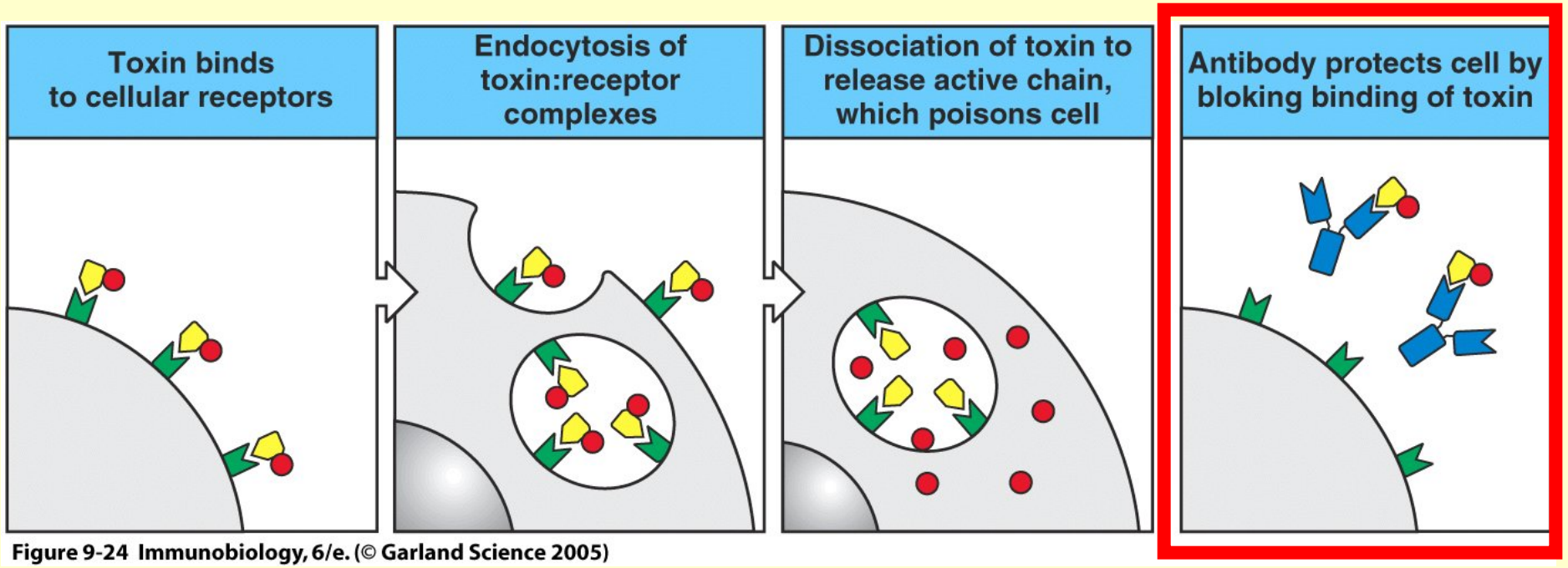


Secretory IgA inhibits binding to mucous membranes

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

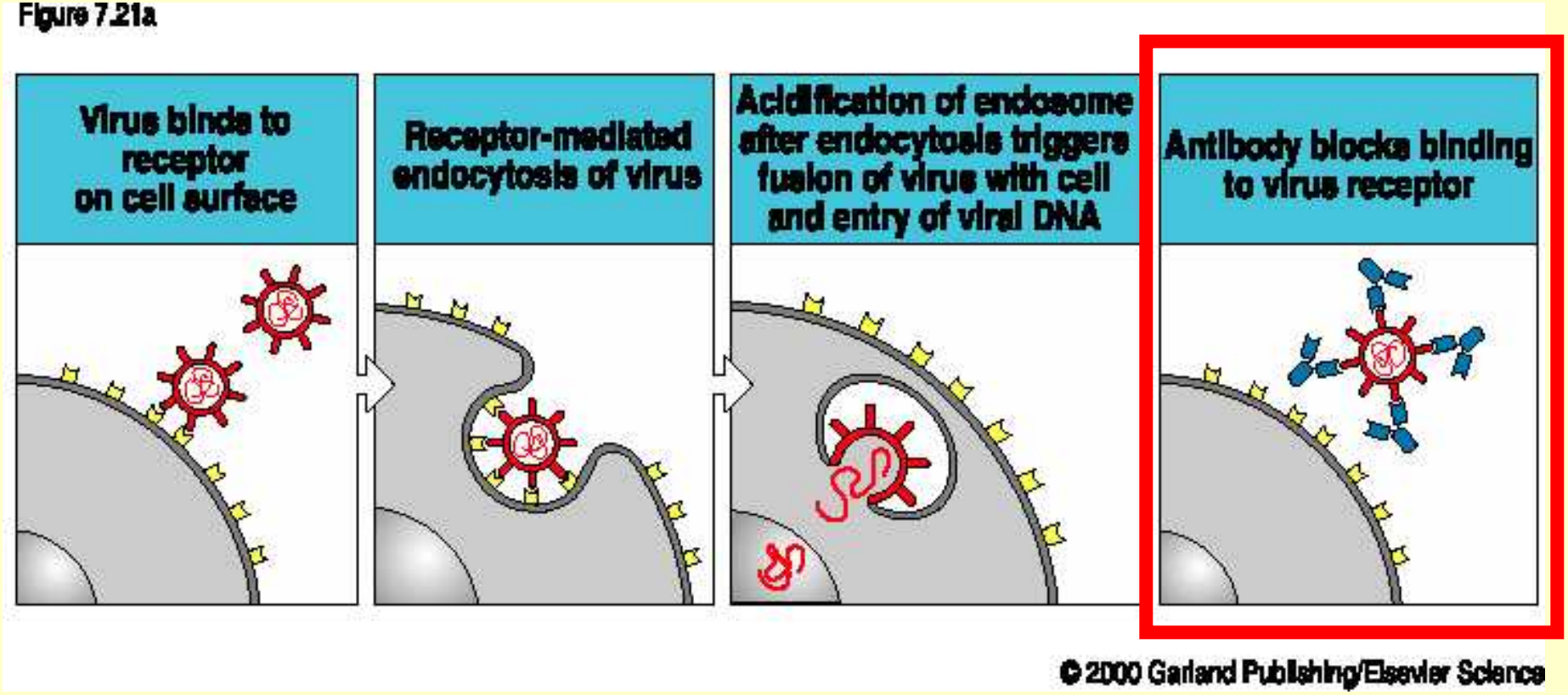
Disease	Organism	Toxin	Effects *in vivo*
Tetanus	*Clostridium tetani*	Tetanus toxin	Blocks inhibitory neuron action, leading to chronic muscle contraction
Diphtheria	*Corynebacterium diphtheriae*	Diphtheria toxin	Inhibits protein synthesis, leading to epithelial cell damage and myocarditis
Gas gangrene	*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)

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

Virus neutralization

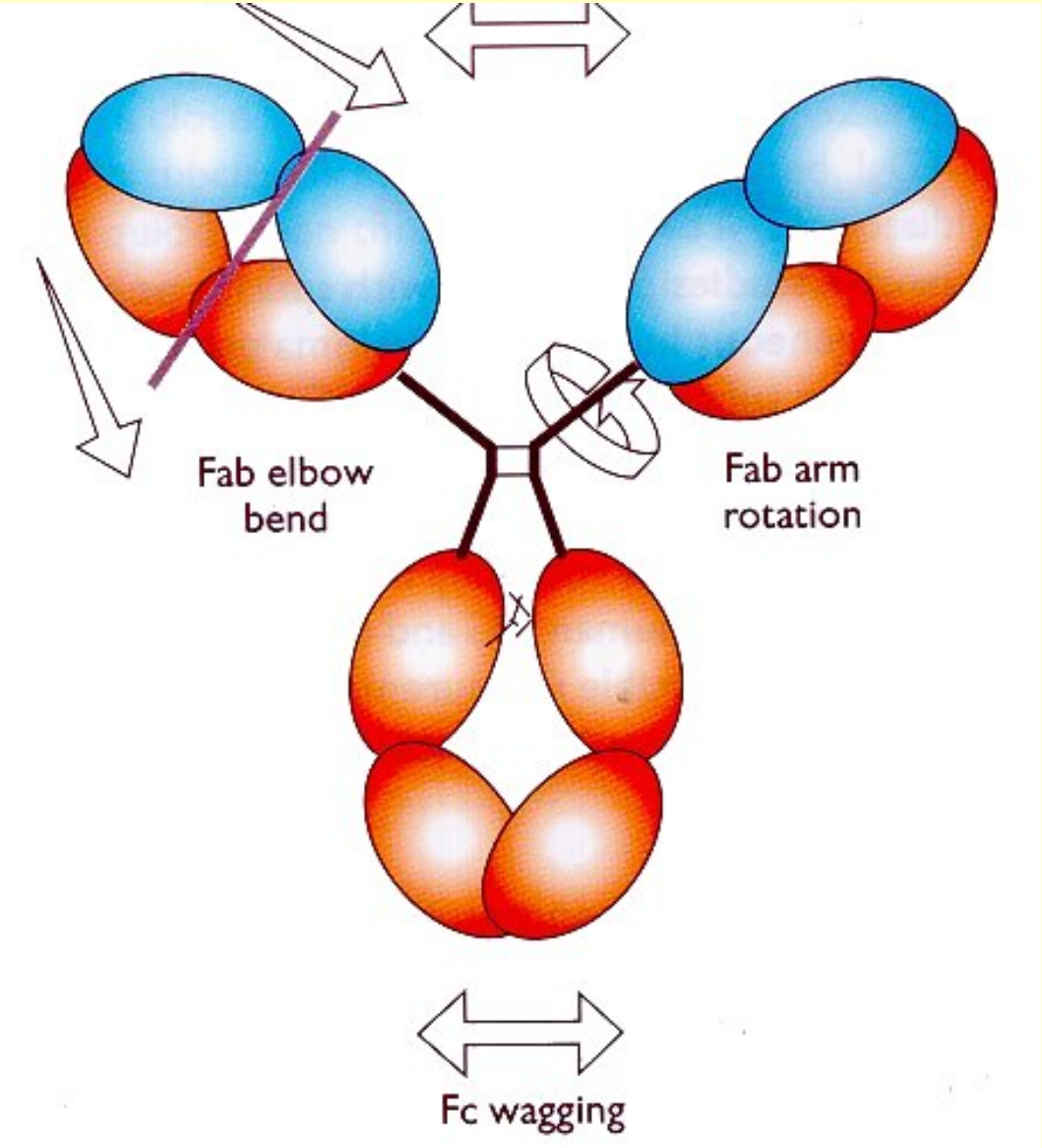
Antibody inhibits the binding of the virus to the host cell and the infection:

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



Fc-RECEPTOR BINDING

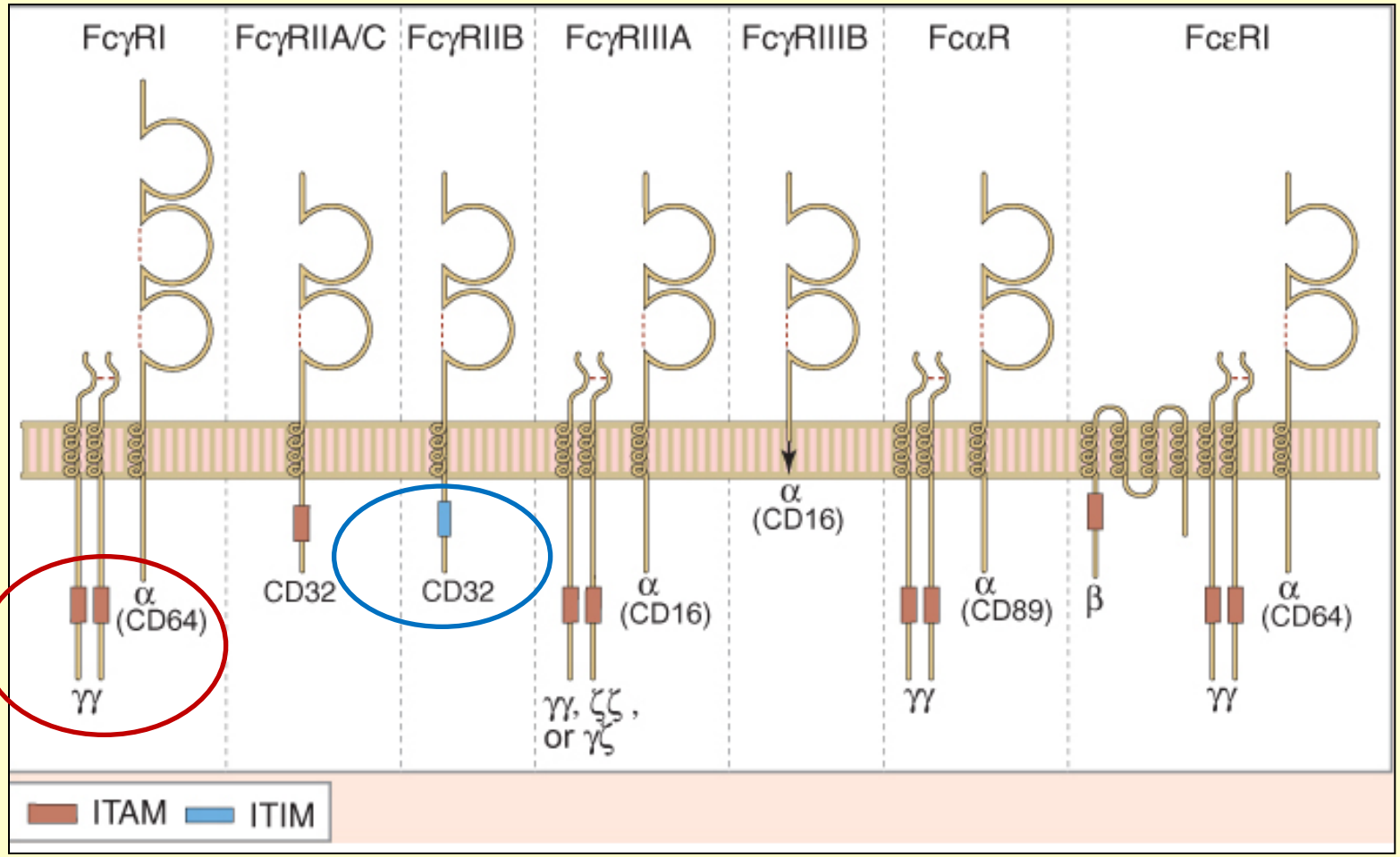
IgG is a flexible molecule



Antigen binding > Conformation change > Complement activation, FcR binding

Flexibility of immunoglobulins with various isotypes Is different.

Activatory and inhibitory role of FcγReceptors



Fc receptors (FcR)

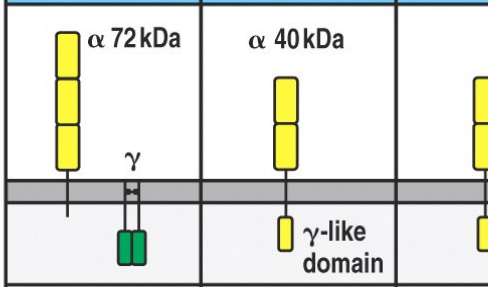
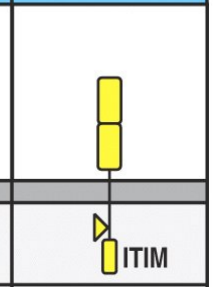
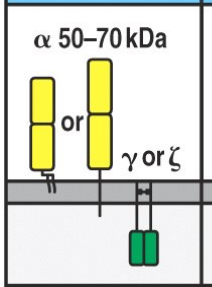
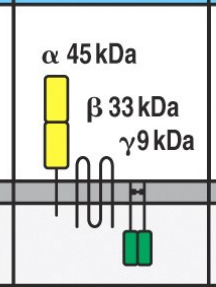
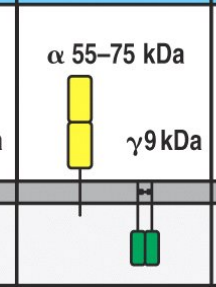
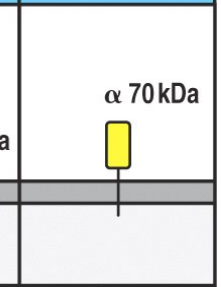
Receptor	FcγRI (CD64)	FcγRII-A (CD32)	FcγRII-B2 (CD32)	FcγRII-B1 (CD32)	FcγRIII (CD16)	FcεRI	FcαRI (CD89)	Fcα/μR
Structure								
Binding Order of affinity	IgG1 10^8 M^{-1} 1) IgG1=IgG3 2) IgG4 3) IgG2	IgG1 2×10^6 M^{-1} 1) IgG1 2) IgG3=IgG2* 3) IgG4	IgG1 2×10^6 M^{-1} 1) IgG1=IgG3 2) IgG4 3) IgG2	IgG1 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	IgA, IgM 3×10^9 M^{-1} 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

Figure 9-30 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

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Opsonization and Phagocytosis by Antibodies

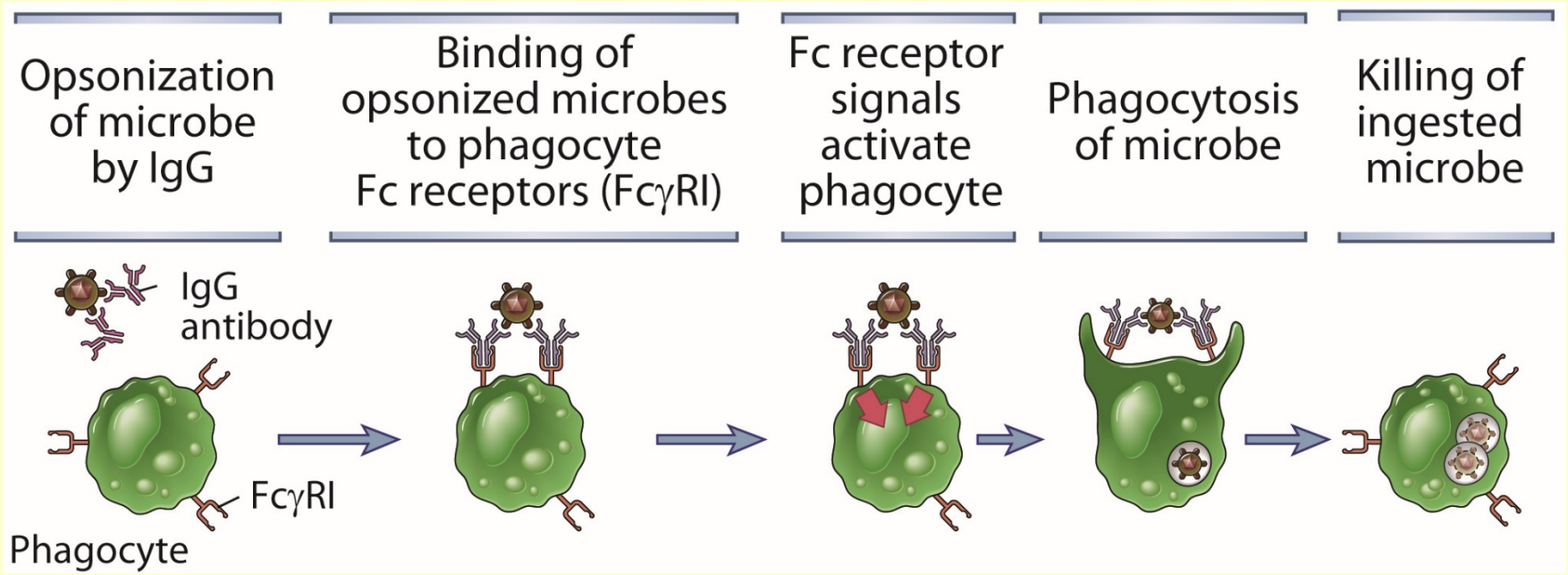


Fig. 12-4

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

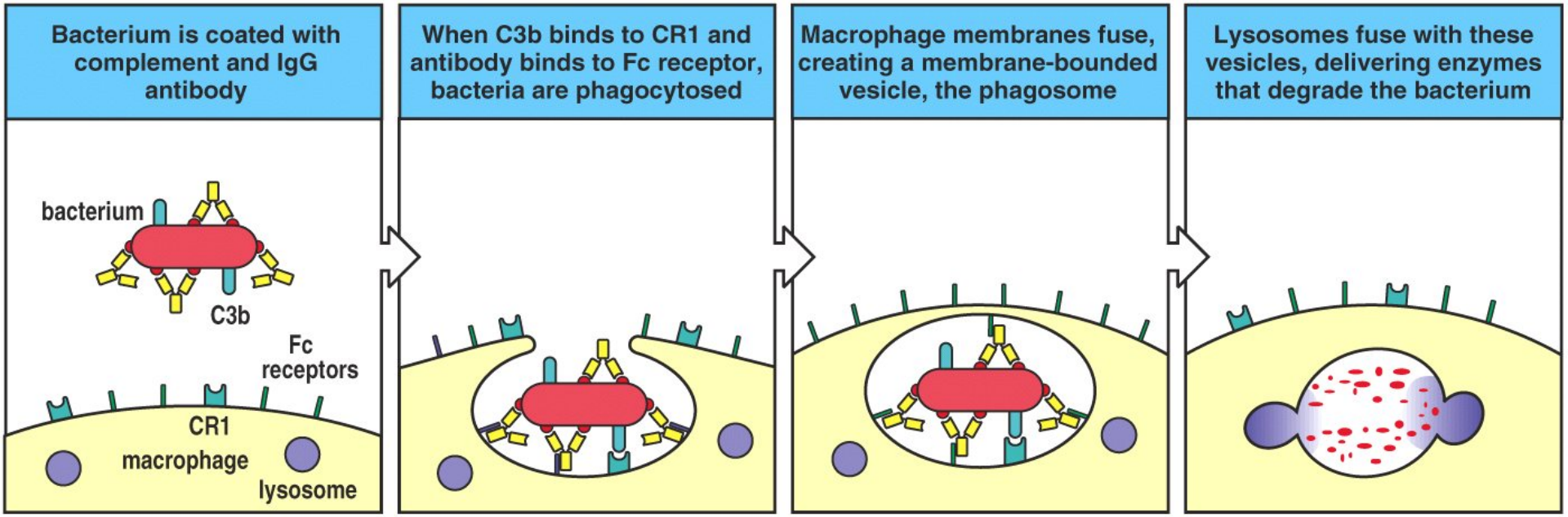
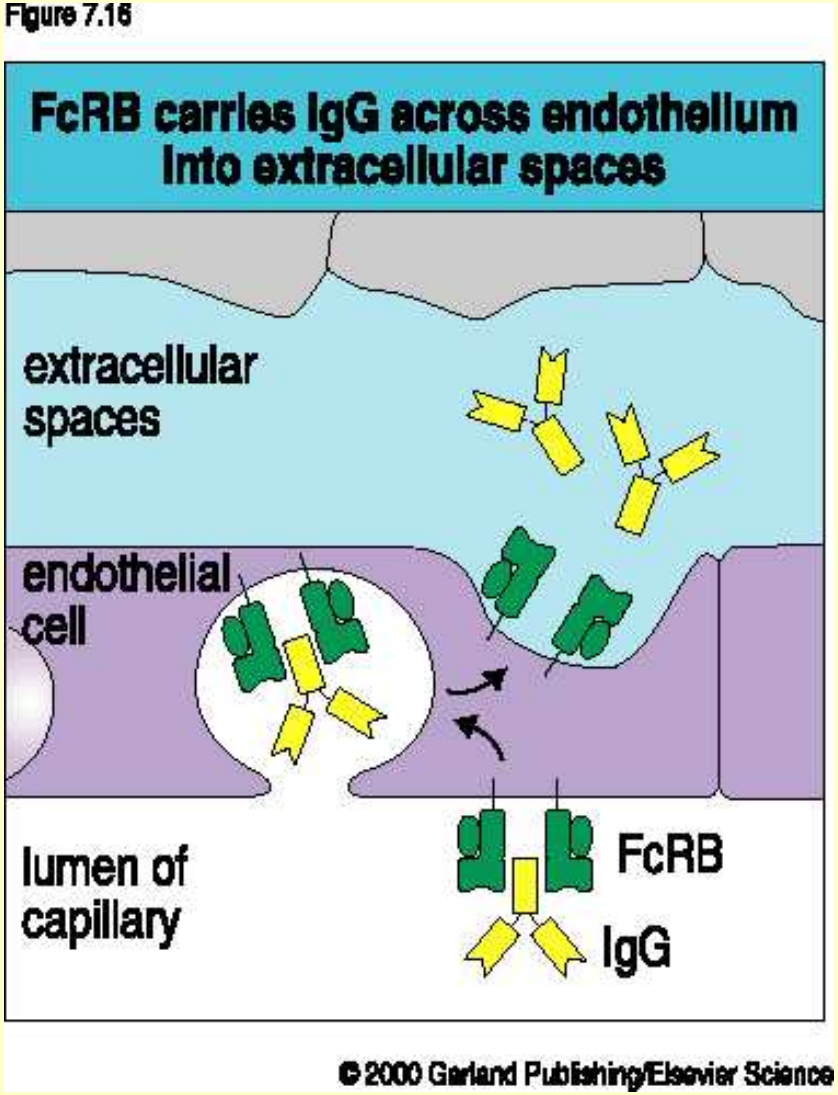


Figure 9-32 Immunobiology, 6/e. (© Garland Science 2005)

Free immunoglobulins cannot bind to Fc receptor and enhance phagocytosis

Antigen bound antibody is capable of binding to FcR

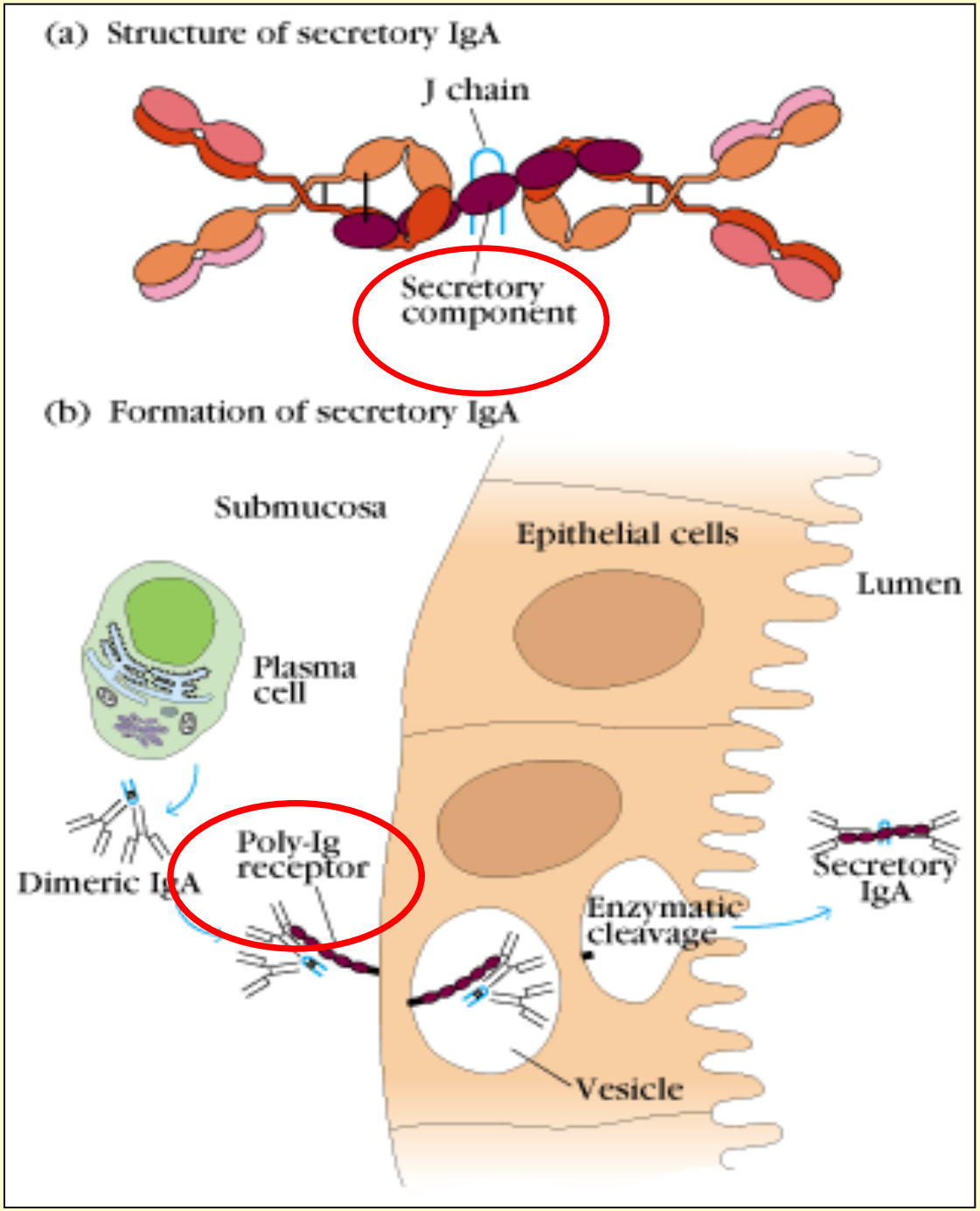
IgG transport from blood to tissues



Poly-Ig receptor

IgA/IgM transport

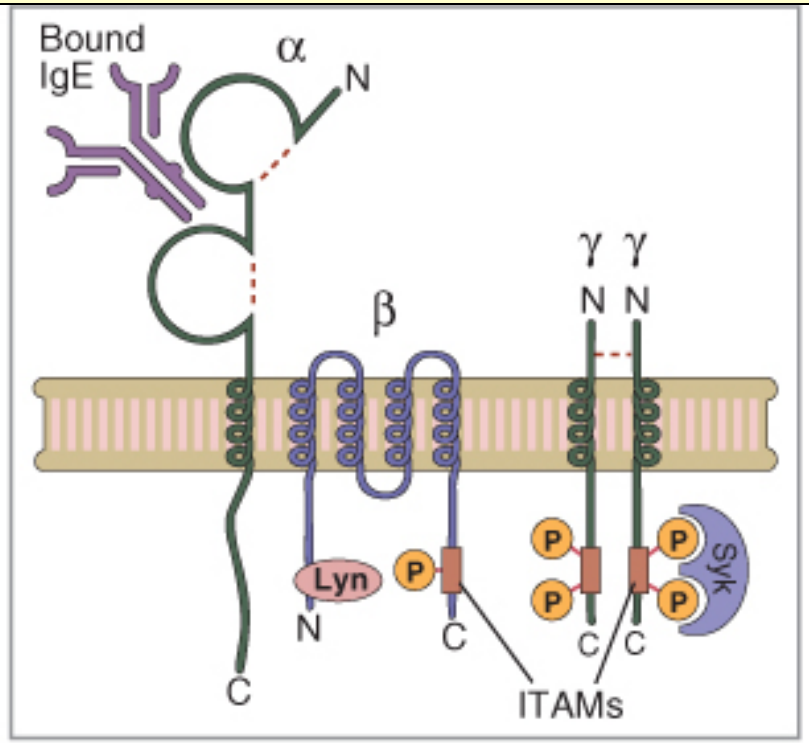
secretory component



The role of Ig constant domains in the effector functions

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

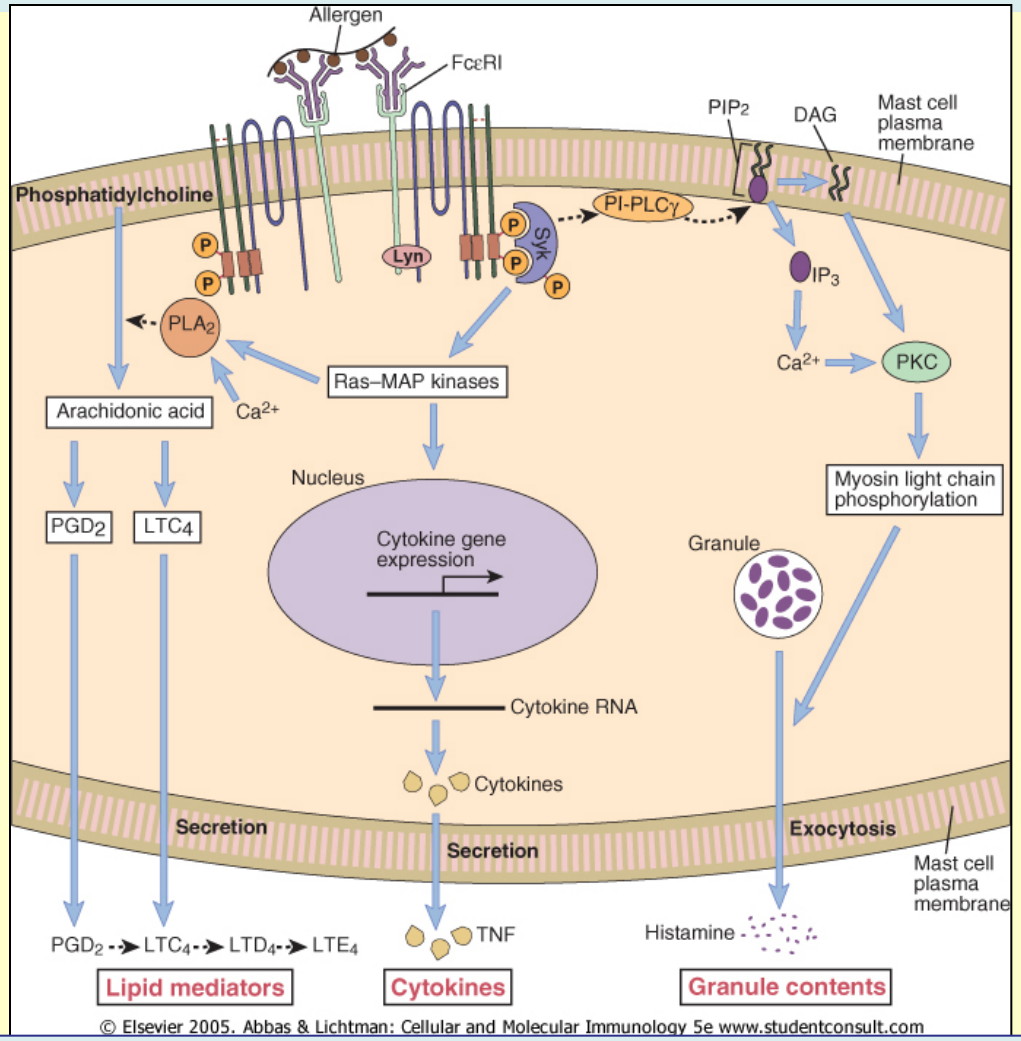
FcεR -high affinity IgE receptor binds free IgE



Mast cells, basophils, eosinophils Langerhans cells, macrophages

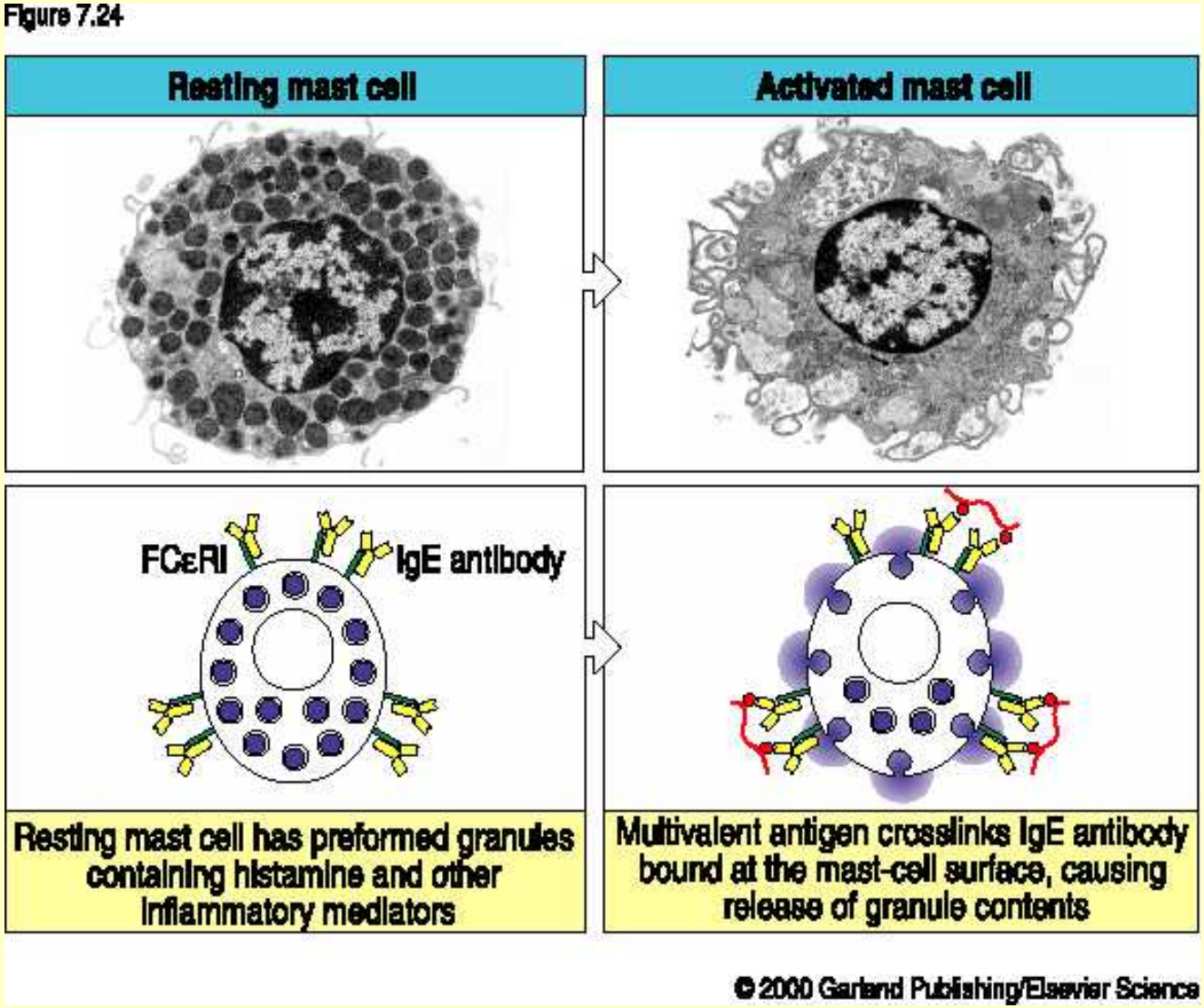
IgE upregulate its expression on Mast cells

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



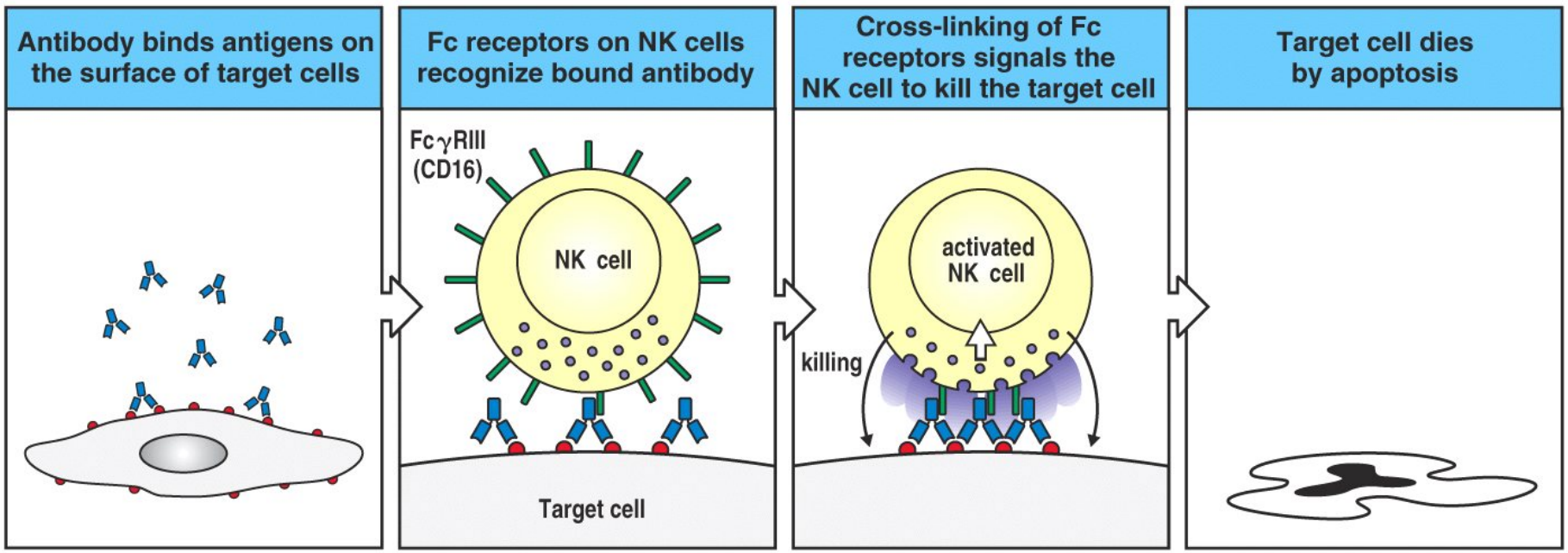
Syk is critical for FceR-mediated Ca2+ mobilization, degranulation, production of cytokines, and arachidonic acid metabolites.

IgE-mediated mast cell activation



ADCC = antibody dependent cellular cytotoxicity

ADCC



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ADCC

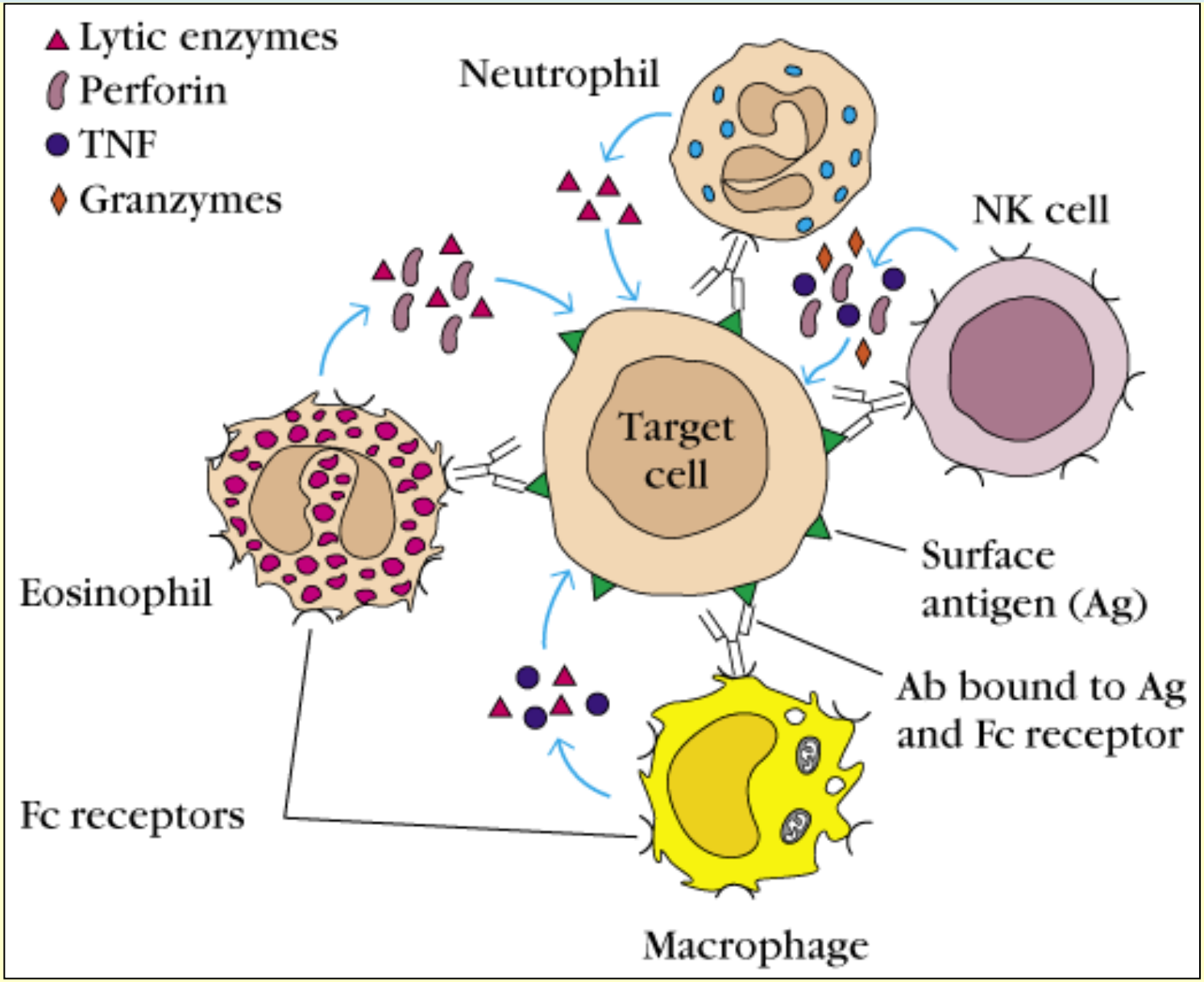
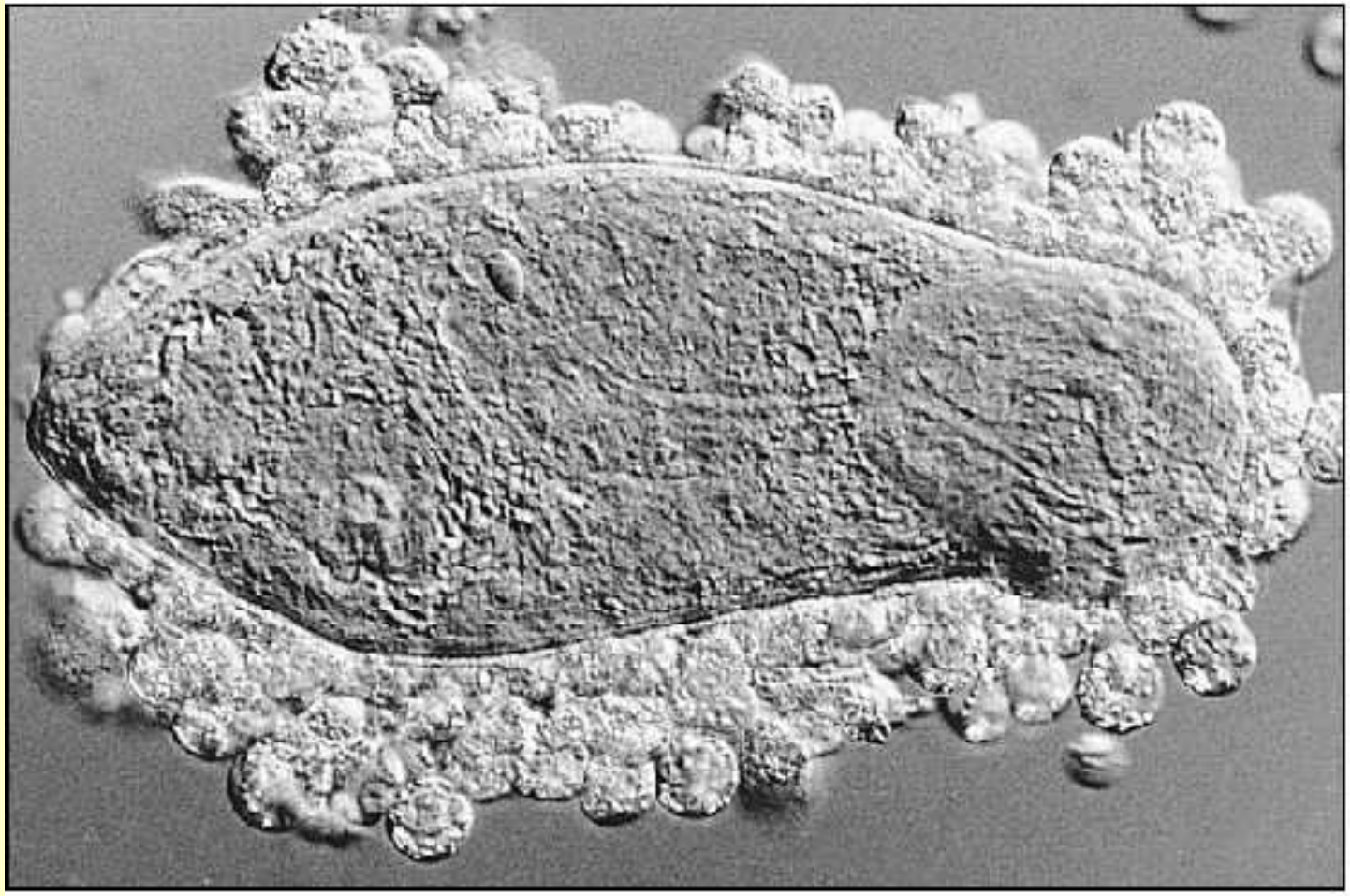

Lytic enzymes
Perforin
TNF
Granzymes
Neutrophil
NK cell
Target cell
Eosinophil
Surface antigen (Ag)
Ab bound to Ag and Fc receptor
Fc receptors
Macrophage

Figure 7 .25



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

COMPLEMENT ACTIVATION

IgG & IgM antigen-antitbody complexes activate complement

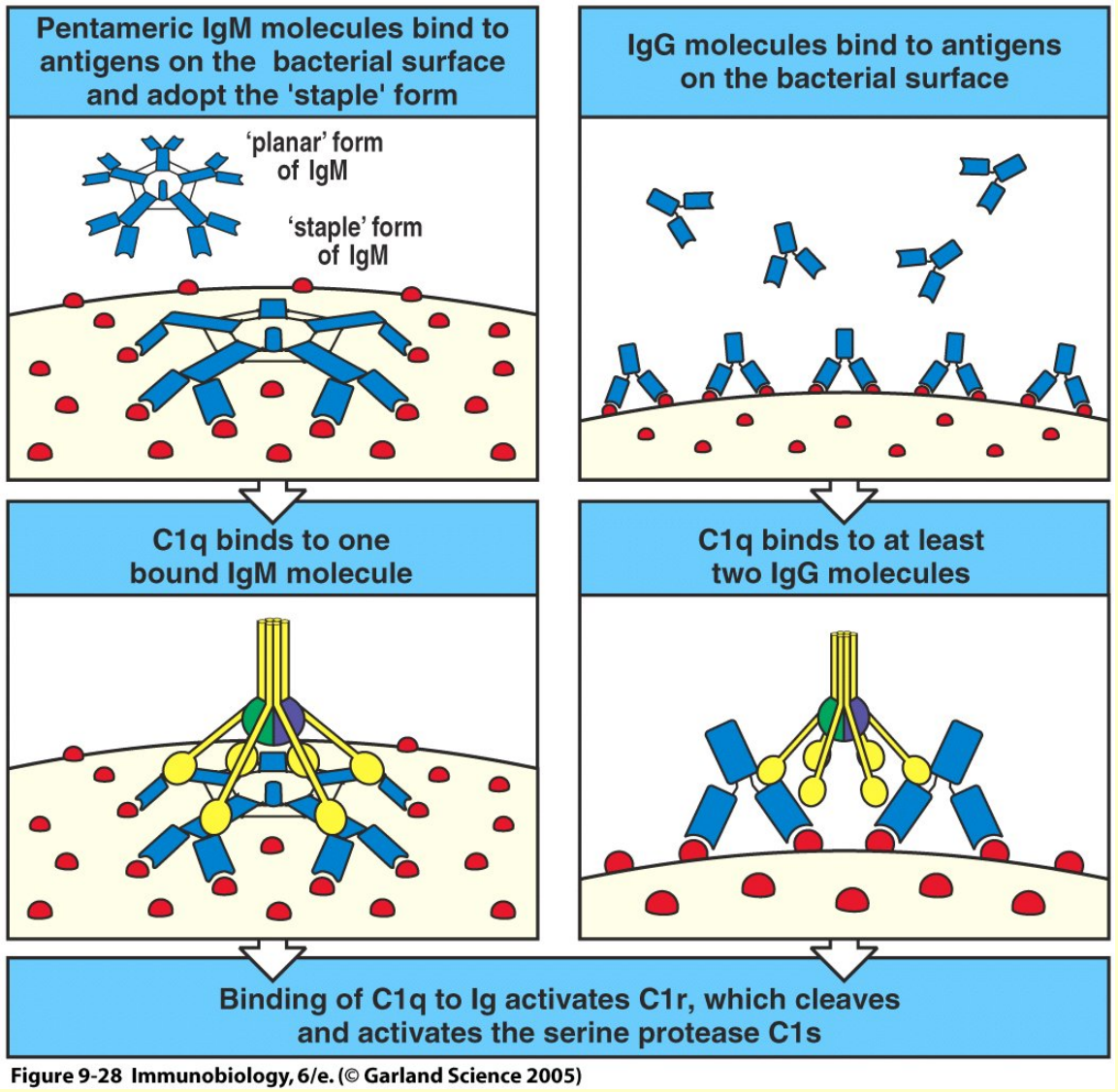


Figure 9-28 Immunobiology, 6/e. (© Garland Science 2005)

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