Basic Immunology

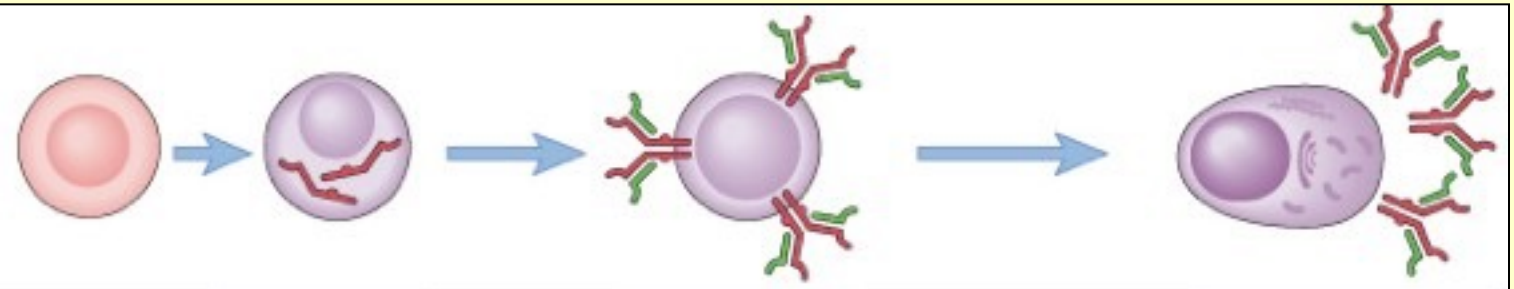
15. lecture

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

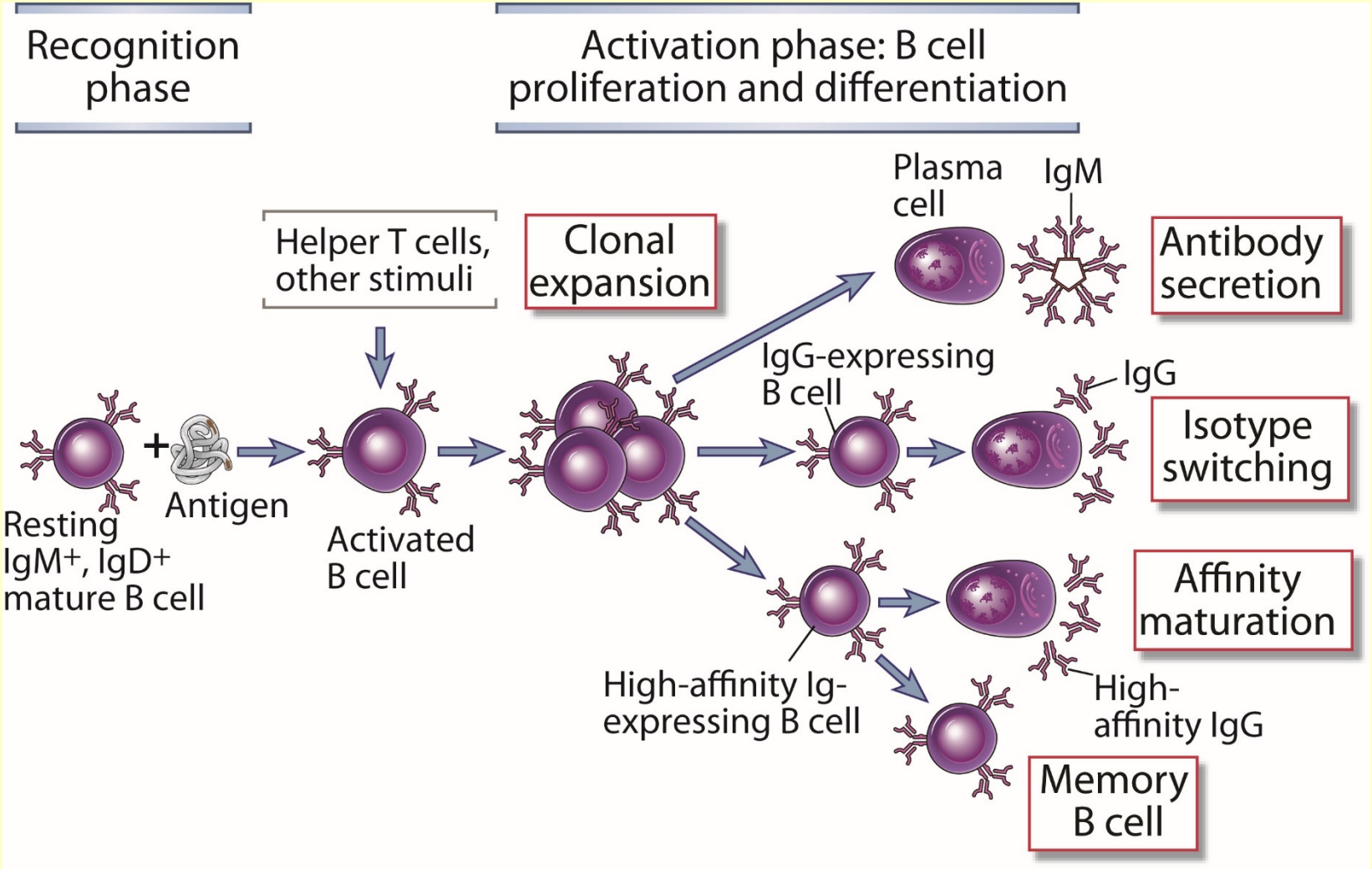


Fig. 11-1

Antitest termelés

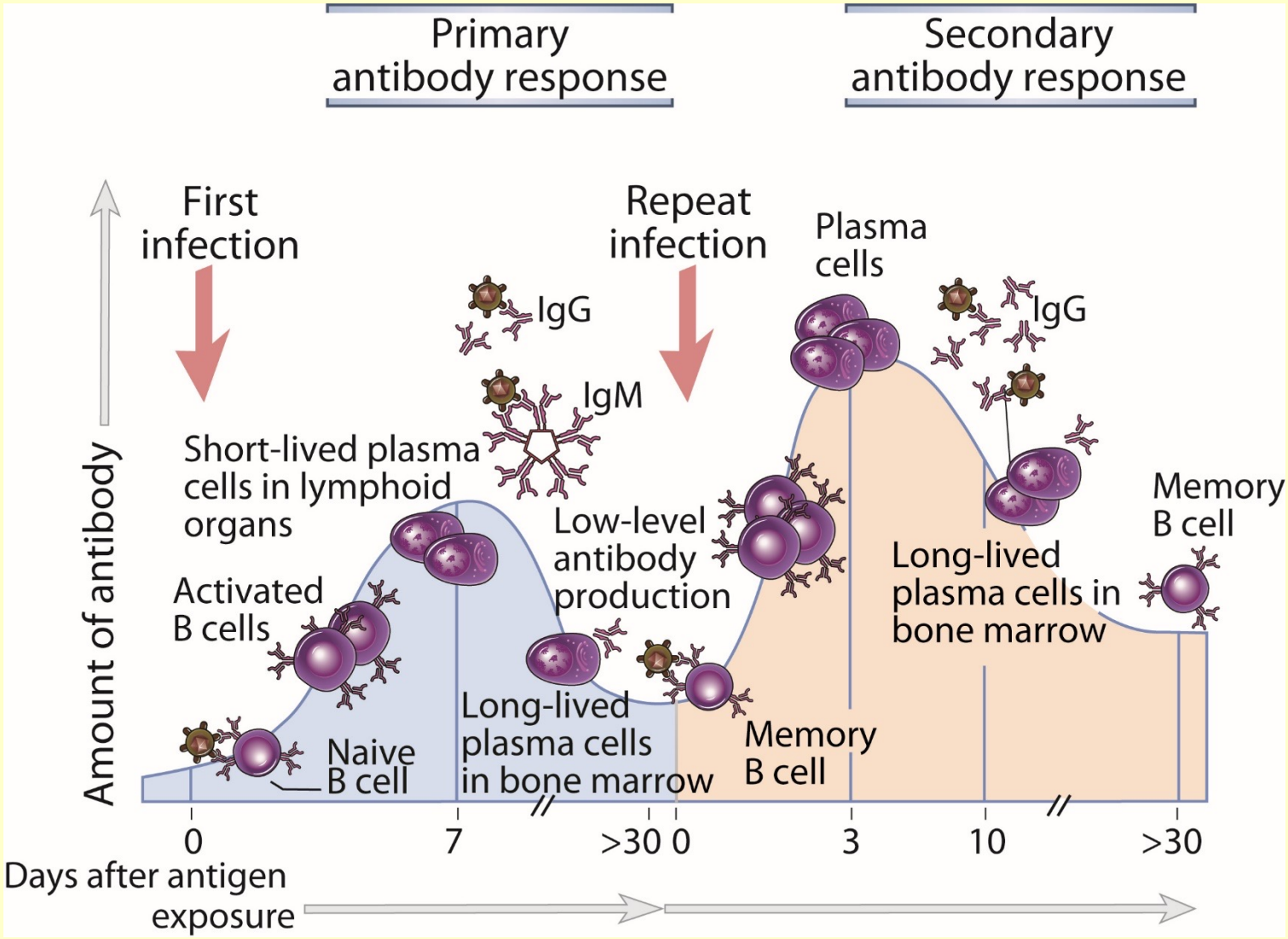
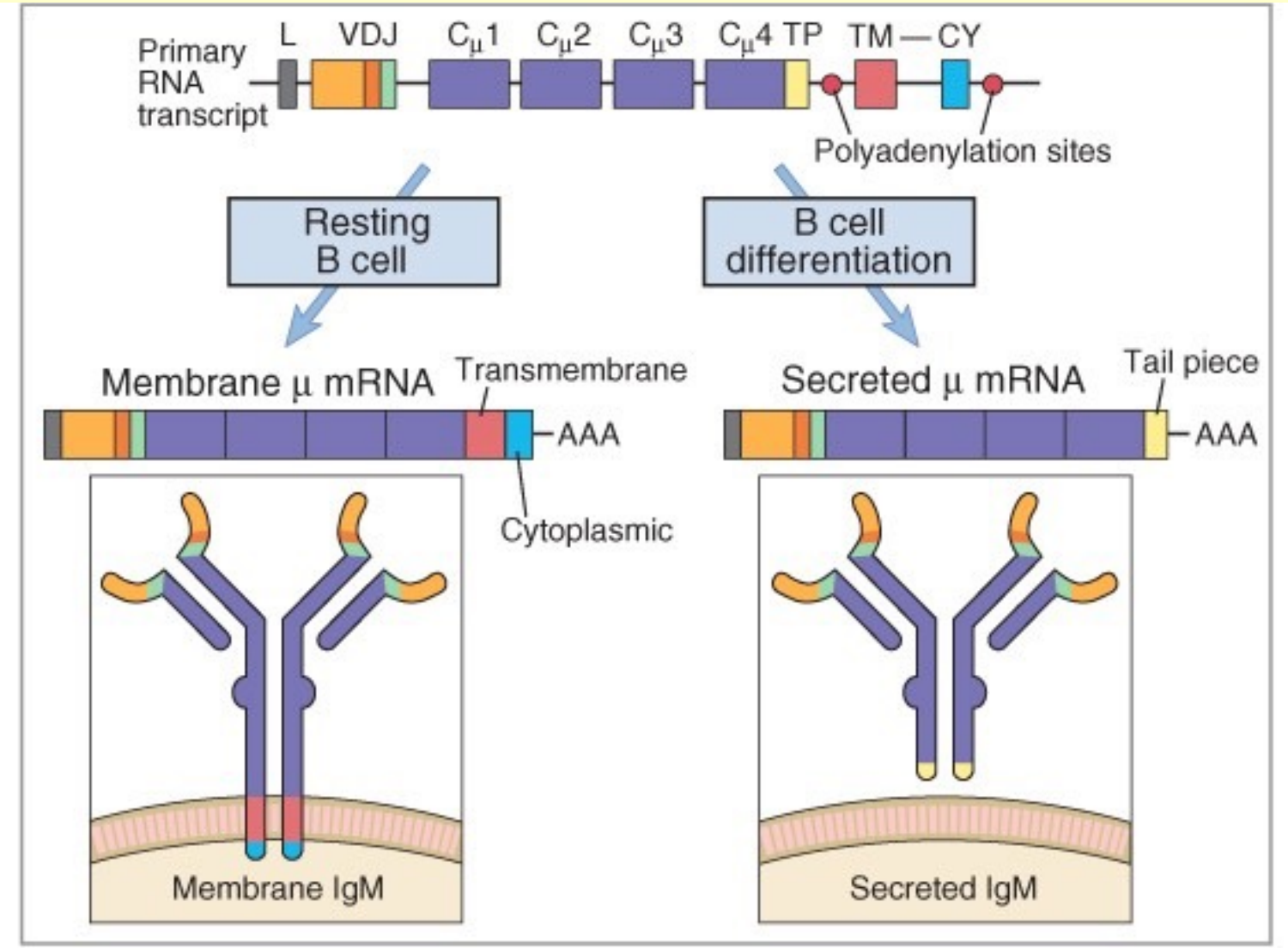
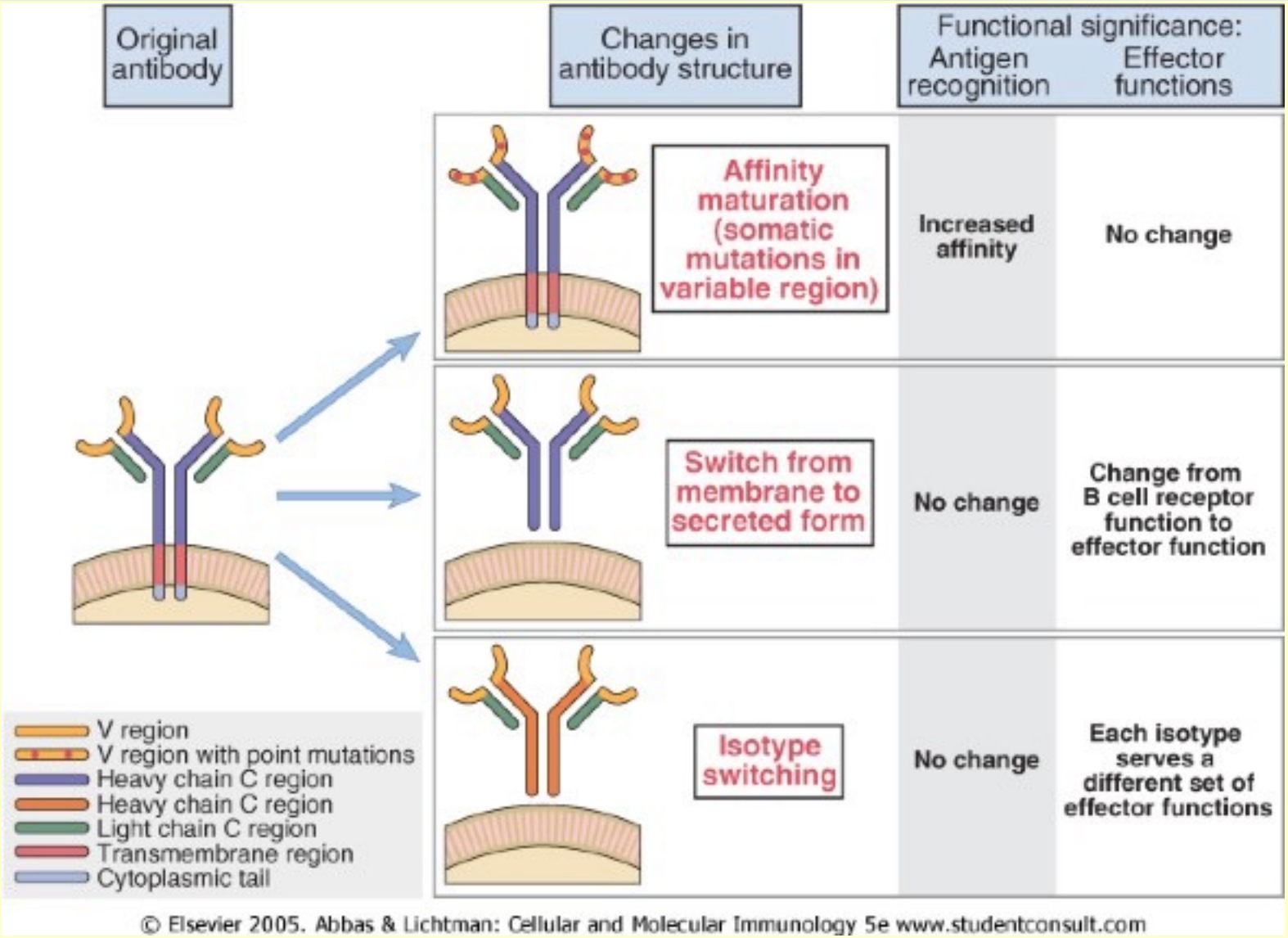


Fig. 11-2

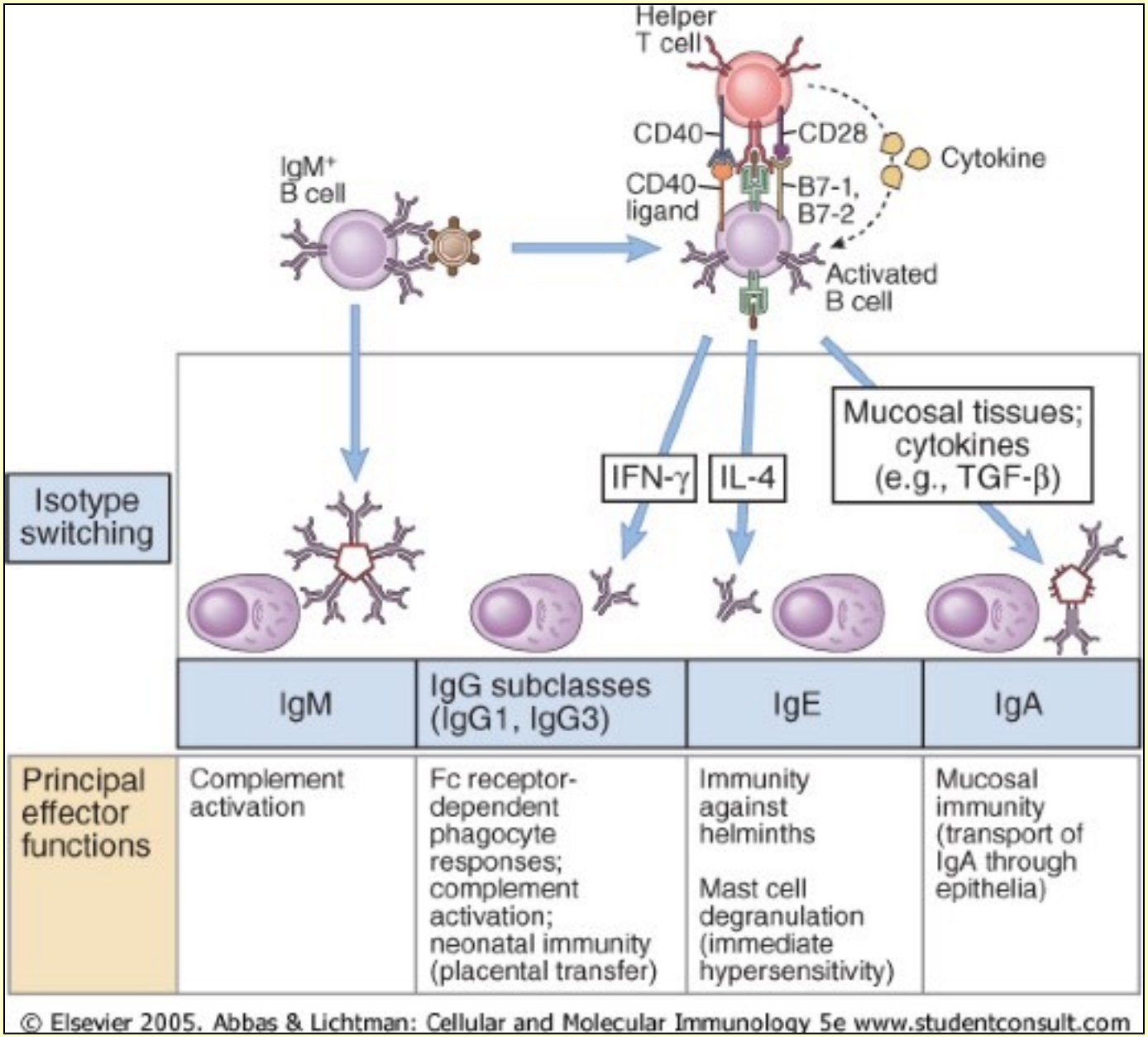
Membrane bound (mIg) and secreted (sIg) immunoglobulin 2.



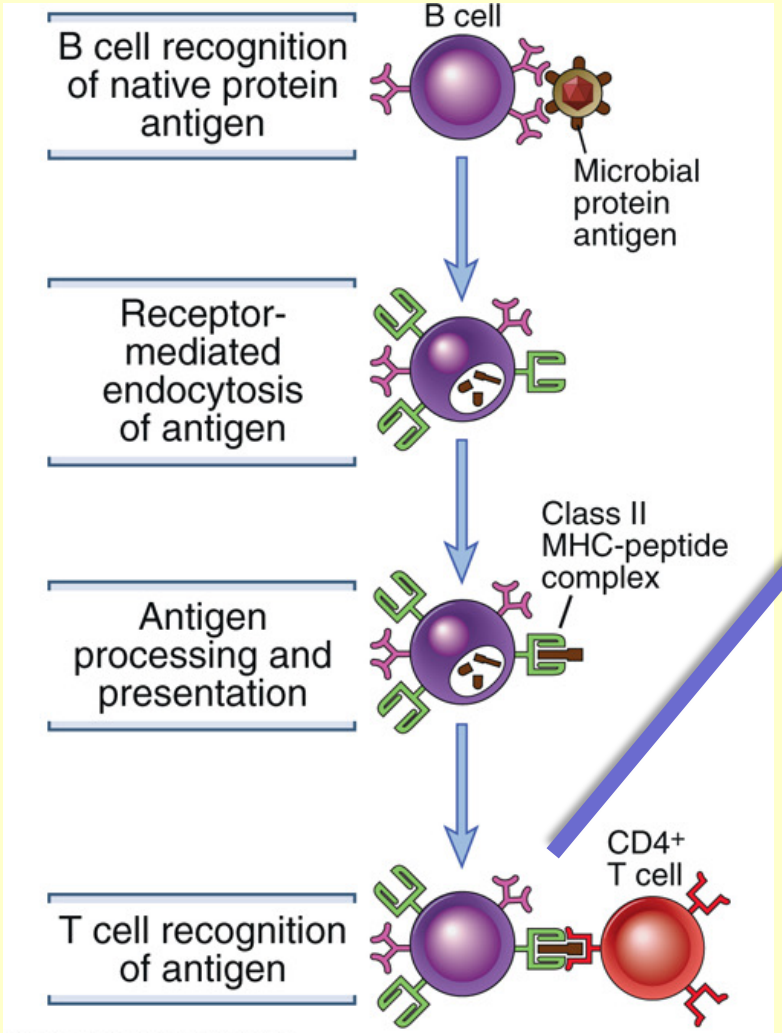
Changes in the immunoglobulin molecule during the immune response

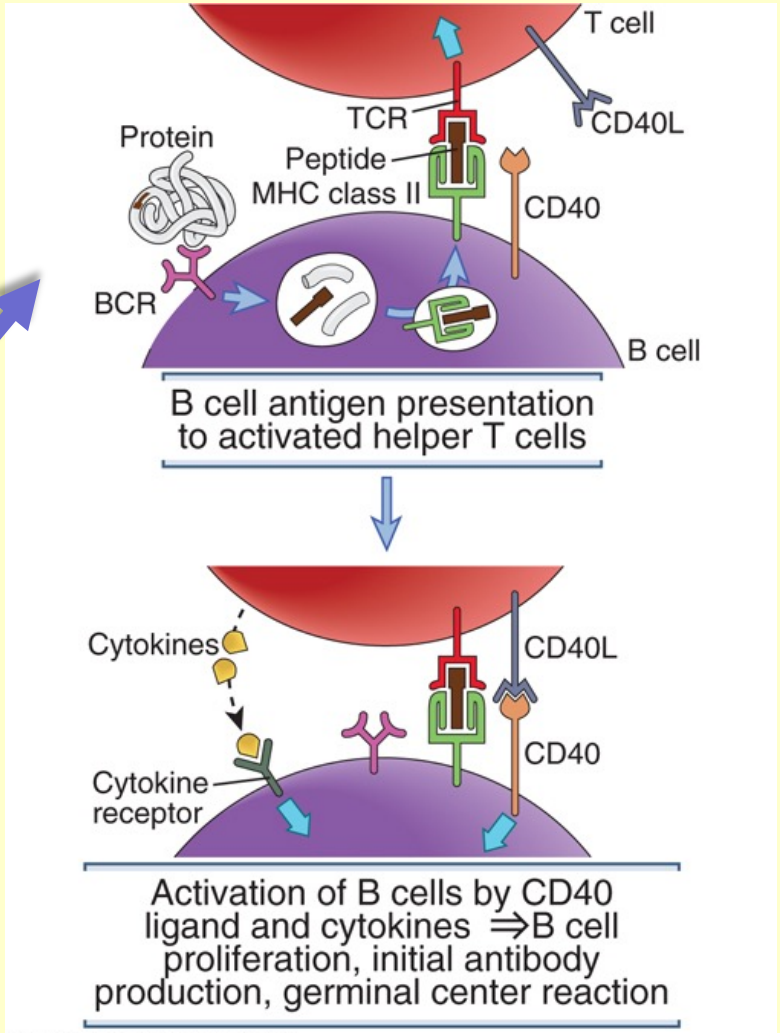


Isotype switch – development of functional diversity



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 →

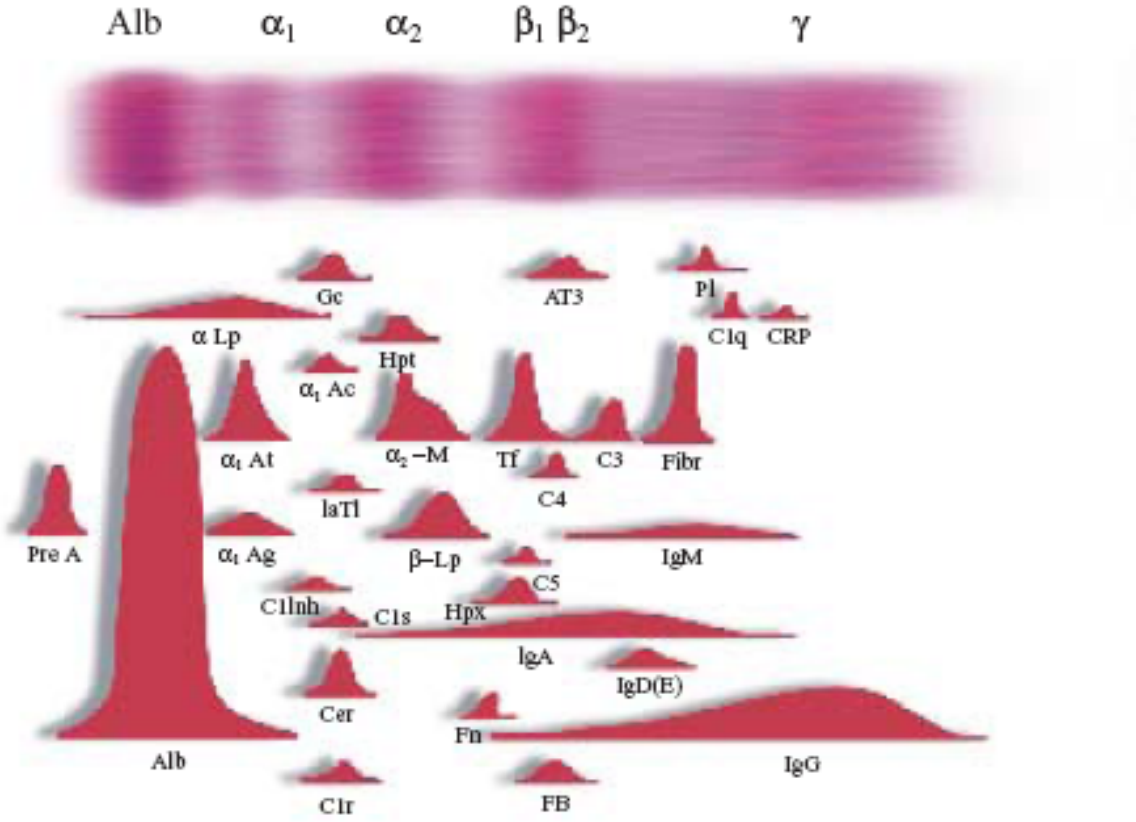
After the antigen entry in effector functions: immunocomplex formation → neutralization, opsonization, complement binding and activation, Fc receptor binding, agglutination, etc. → helps to eliminate pathogens before an infection could begin

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



Electrophoresis Pattern*

Alb	Albumin
α_1	Alpha-1
α_2	Alpha-2
β_1 β_2	Beta-1 Beta-2
γ	Gamma
GC	Vitamin D binding globulin
AT3	Antithrombin III
PL	Plasminogen
αLp	Alphalipoprotein
Hpt	Haptoglobin
C1q	q component of C1 complement
CRP	C-reactive protein
α_1-Ac	Alpha-1-antichymotrypsin
α_1At	Alpha-1-antitrypsin
α_2-M	Alpha-2-macroglobulin
Tf	Transferrin
C3	C3 complement
Fibr	Fibrinogen
PreA	Prealbumin
α_1-Ag	Alpha-1-acid glycoprotein
β-Lip	Betalipoprotein
IaTI	Inter-alpha-trypsin inhibitor
C4	C4 complement
IgM	Immunoglobulin M
C1Inh	C1 inhibitor
C5	C5 complement
C1s	s component of C1 complement
Hpx	Hemopexin
IgA	Immunoglobulin A
IgD(E)	Immunoglobulin E
Cer	Ceruloplasmin
Fn	Fibronectin
IgG	Immunoglobulin G
C1r	r component of C1 complement
FB	Factor B

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

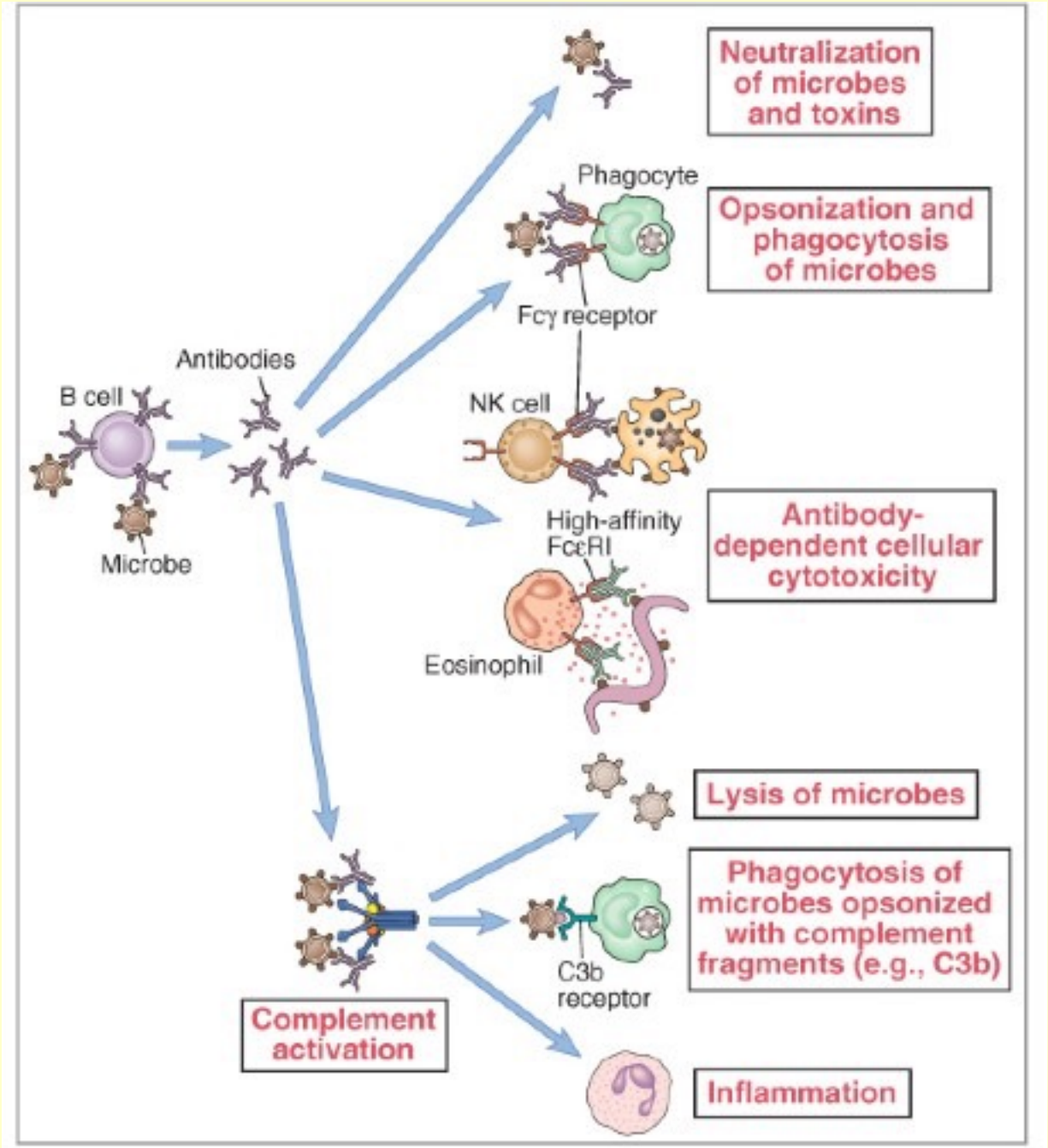
Immungolobulin effector functions

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)



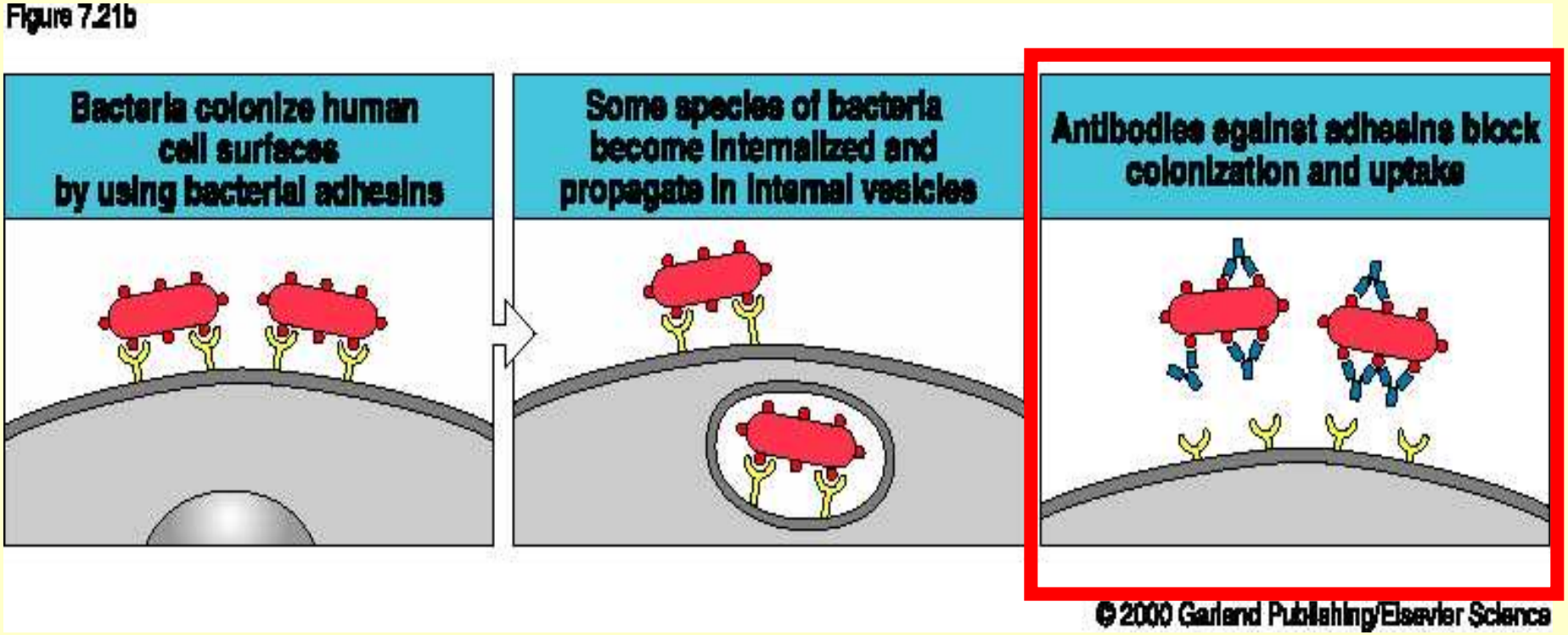
Immunoglobulins of various isotypes have different functions

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

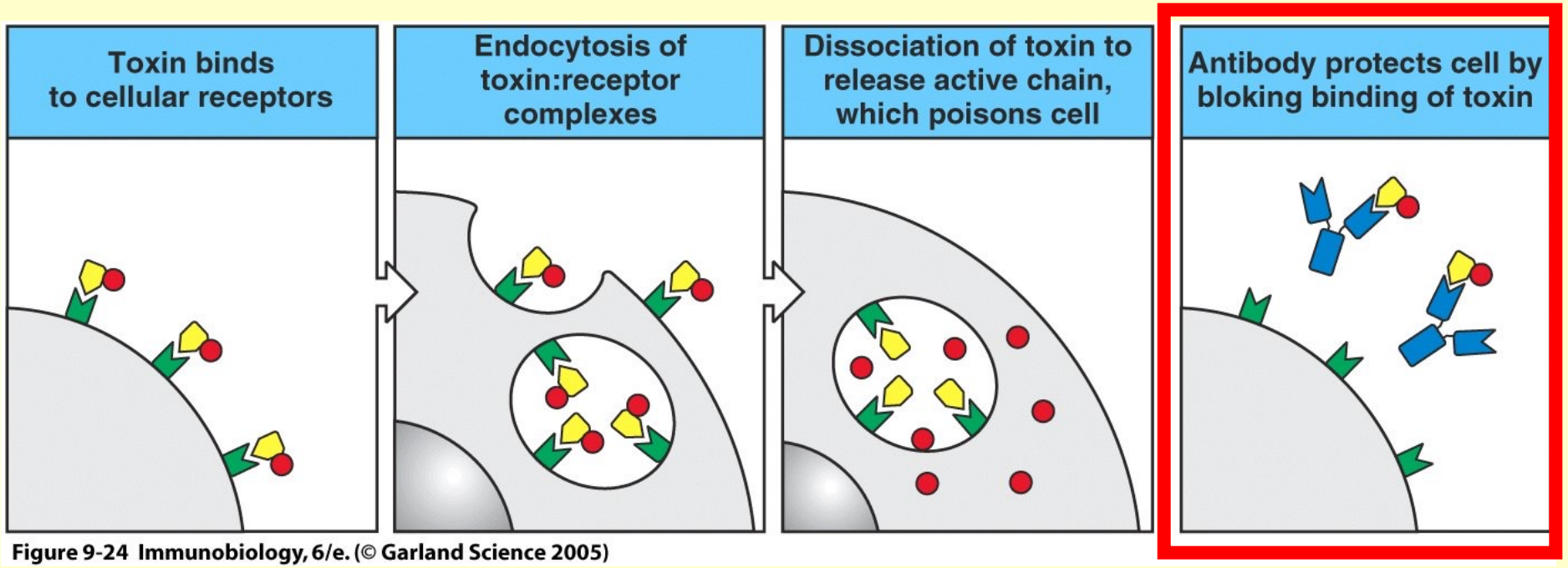


Figure 9-24 Immunobiology, 6/e. (© Garland Science 2005)

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

Diseases caused by bacterial toxins

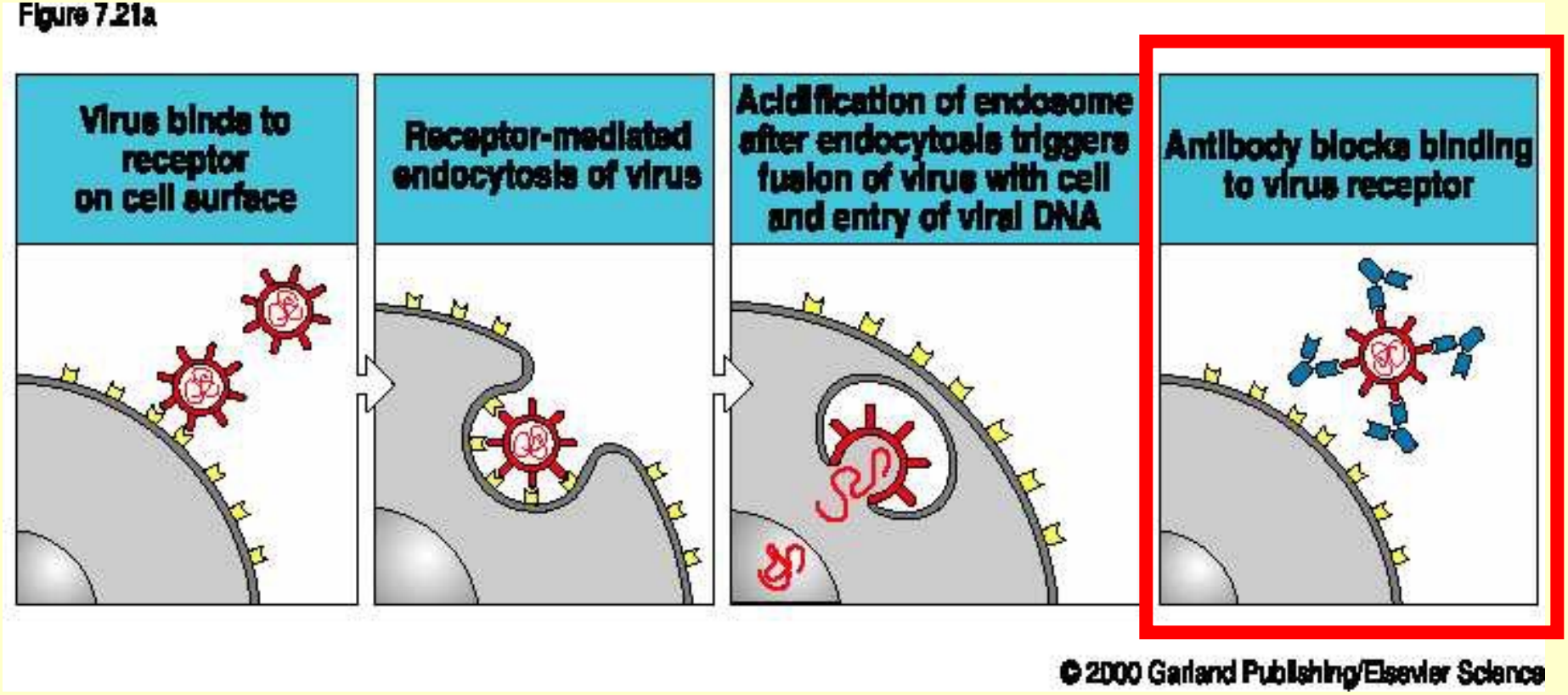
Disease	Organism	Toxin	Effects *in vivo*
Tetanus	*Clostridium tetani*	Tetanus toxin	Blocks inhibitory neuron action, leading to chronic muscle contraction
Diphtheria	*Corynebacterium diphtheriae*	Diphtheria toxin	Inhibits protein synthesis, leading to epithelial cell damage and myocarditis
Gas gangrene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

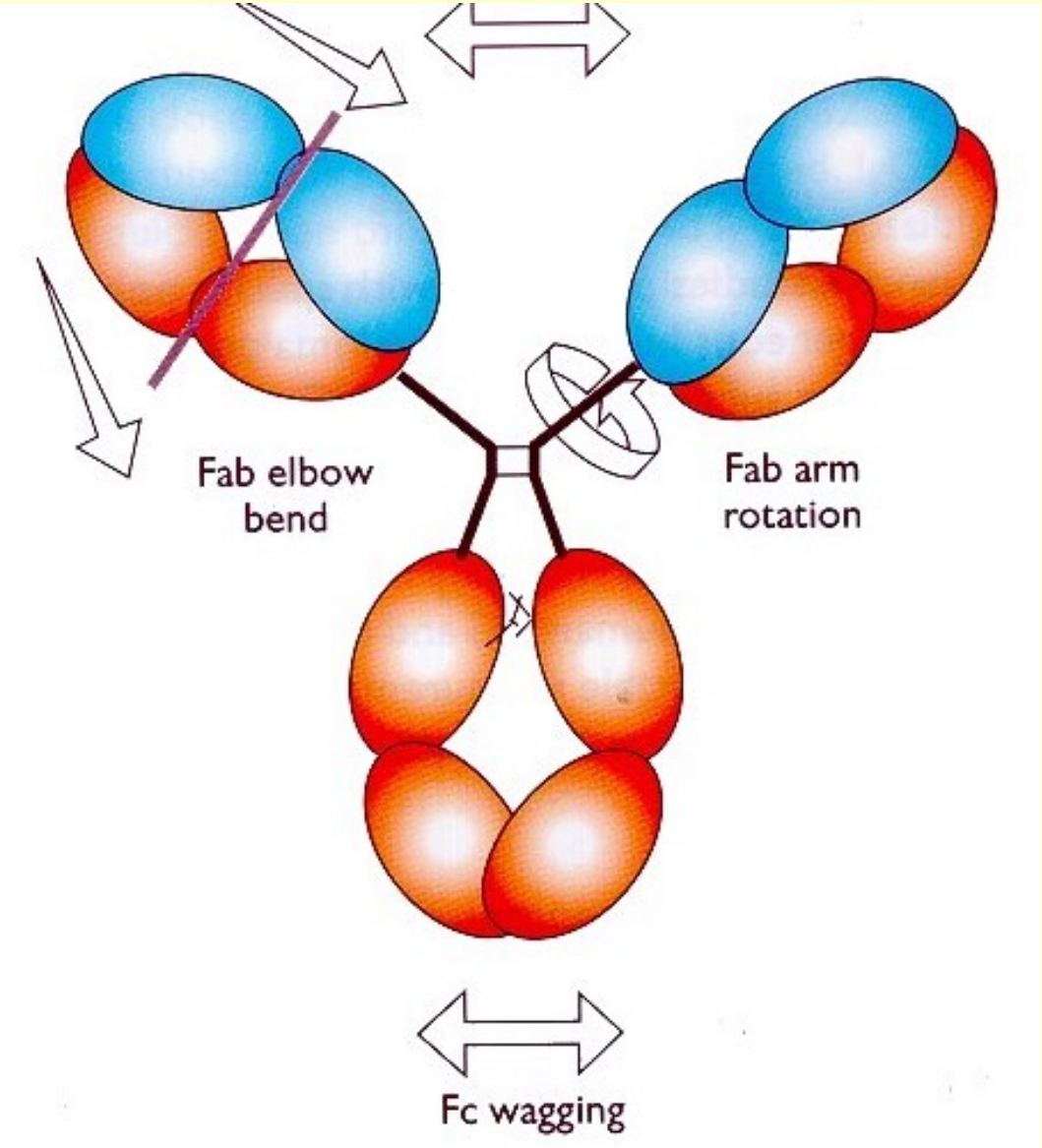


Antiviral mechanisms of the humoral immune response:

- 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

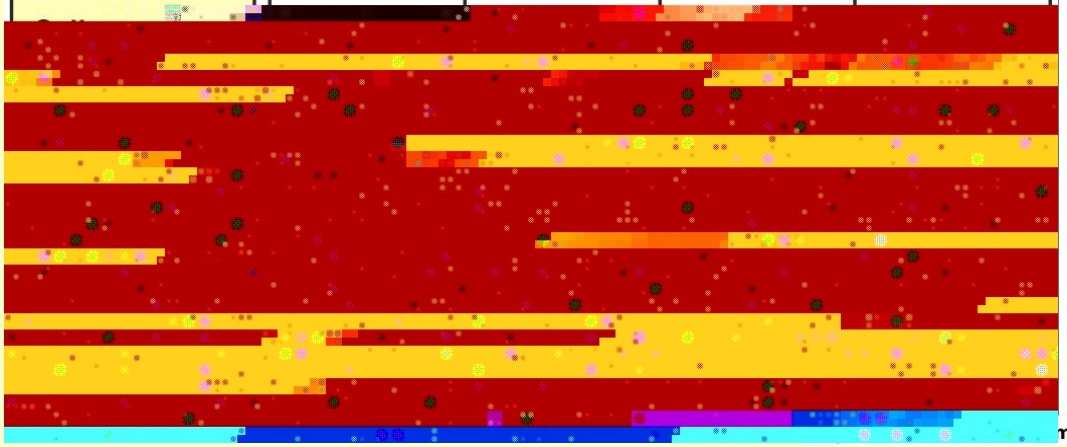


Antigen binding > Conformation change > Complement activation, FcR binding

Flexibility of immunoglobulins with various isotypes Is different.

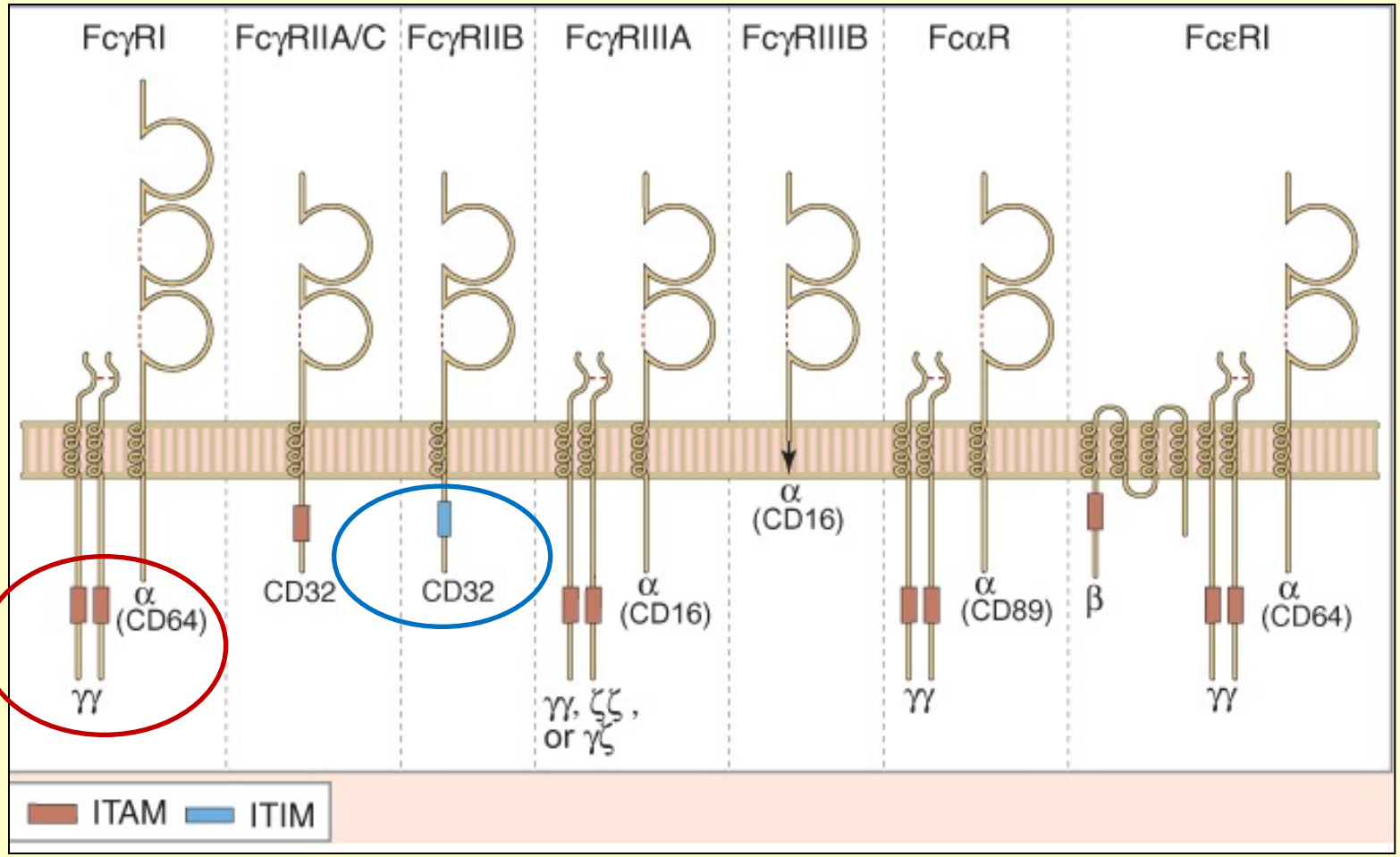
Fc receptors (FcR)

Receptor	FcγRI (CD64)	FcγRII-A (CD32)	FcγRII-B2 (CD32)	FcγRII-B1 (CD32)	FcγRIII (CD16)	FcεRI	FcαRI (CD89)	Fcα/μR
Structure	α 72 kDa, γ	α 40 kDa, γ-like domain	ITIM	ITIM	α 50–70 kDa, or, γ or ζ	α 45 kDa, β 33 kDa, γ 9 kDa	α 55–75 kDa, γ 9 kDa	α 70 kDa
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
	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



munobiology, 6/e. (© Garland Science 2005)

Activatory and inhibitory role of FcγReceptors

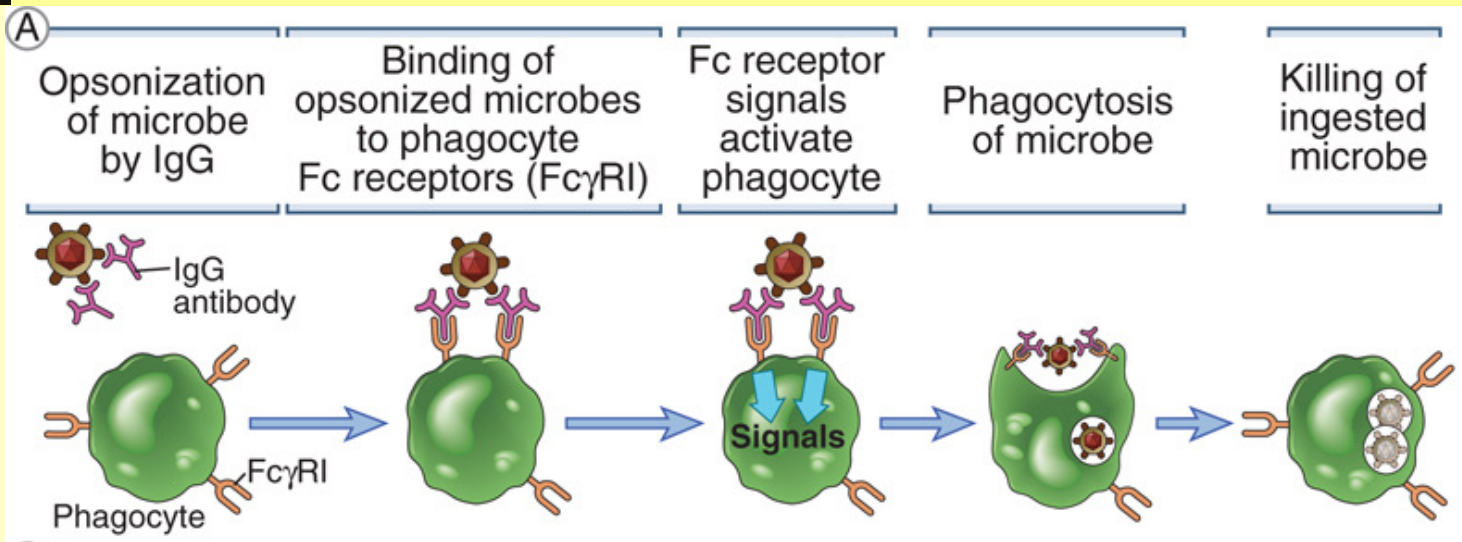


The role of Ig constant domains in the effector functions

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**

Opsonization and Phagocytosis by Antibodies

A

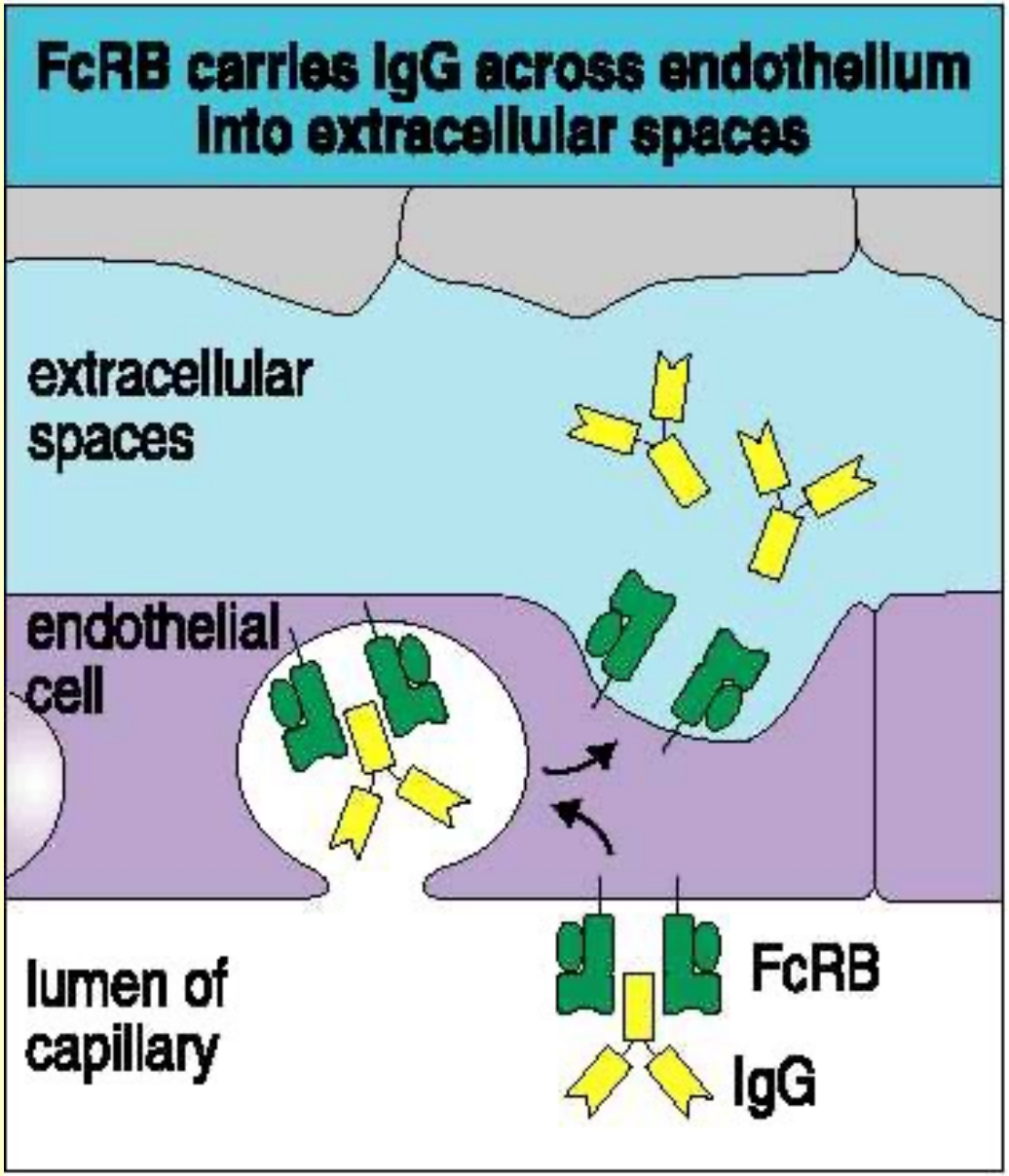


B

Fc Receptor	Affinity for Ig	Cell distribution	Function
FcγRI (CD64)	High (K_d ~10^{-9} M); binds IgG1 and IgG3; can bind monomeric IgG	Macrophages, neutrophils; also eosinophils	Phagocytosis; activation of phagocytes
FcγRIIA (CD32)	Low (K_d ~0.6–2.5×10^{-6} M)	Macrophages, neutrophils; eosinophils, platelets	Phagocytosis; cell activation (inefficient)
FcγRIIB (CD32)	Low (K_d ~0.6–2.5×10^{-6} M)	B lymphocytes, DCs, mast cells, neutrophils, macrophages	Feedback inhibition of B cells, attenuation of inflammation
FcγRIIIA (CD16)	Low (K_d ~0.6–2.5×10^{-6} M)	NK cells	Antibody-dependent cellular cytotoxicity (ADCC)
FcεRI	High (K_d ~10^{-10} M); binds monomeric IgE	Mast cells, basophils, eosinophils	Activation (degranulation) of mast cells and basophils

Fig. 12-4

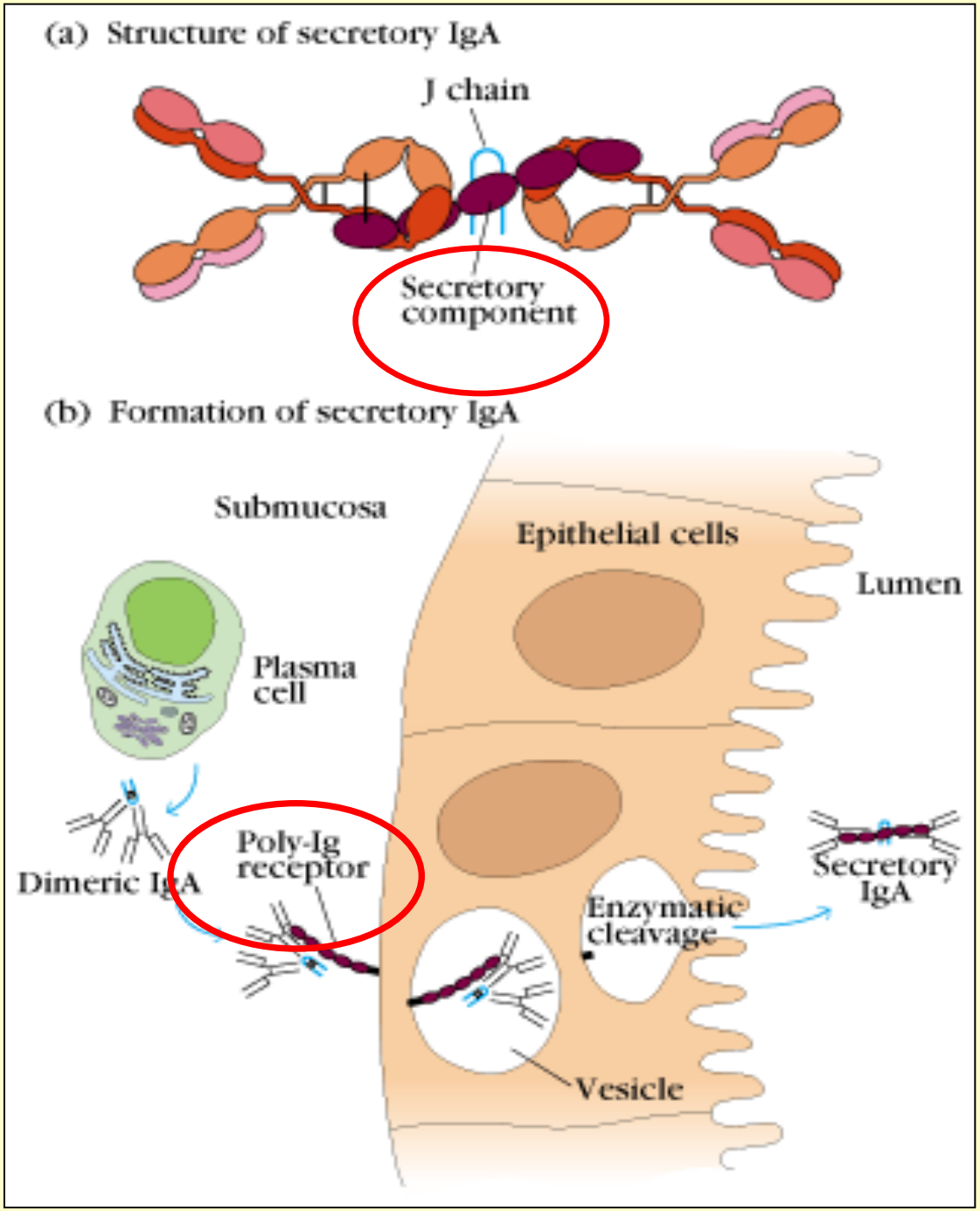
Figure 7.16



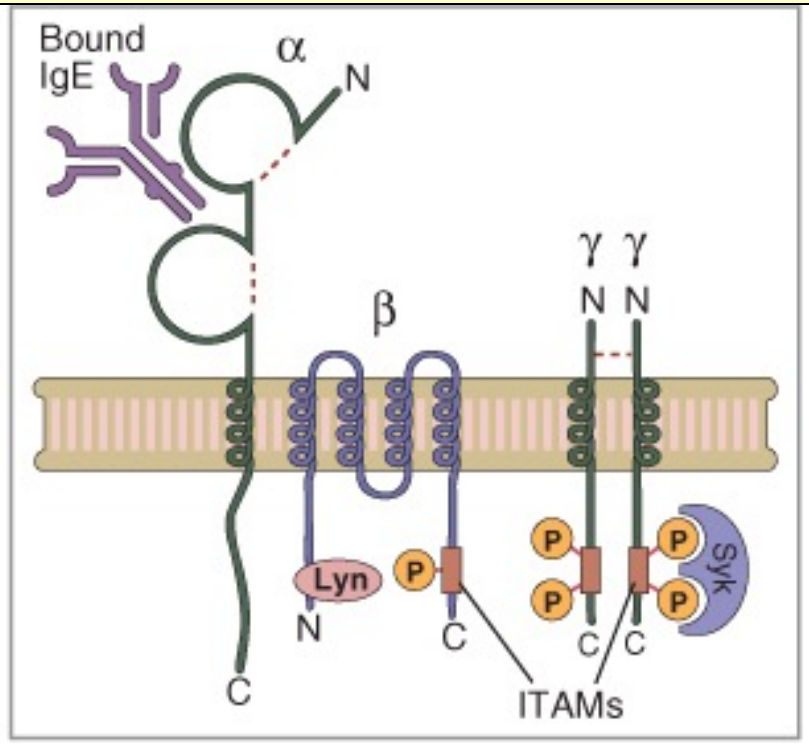
FcαR

IgA/IgM transport

secretory component



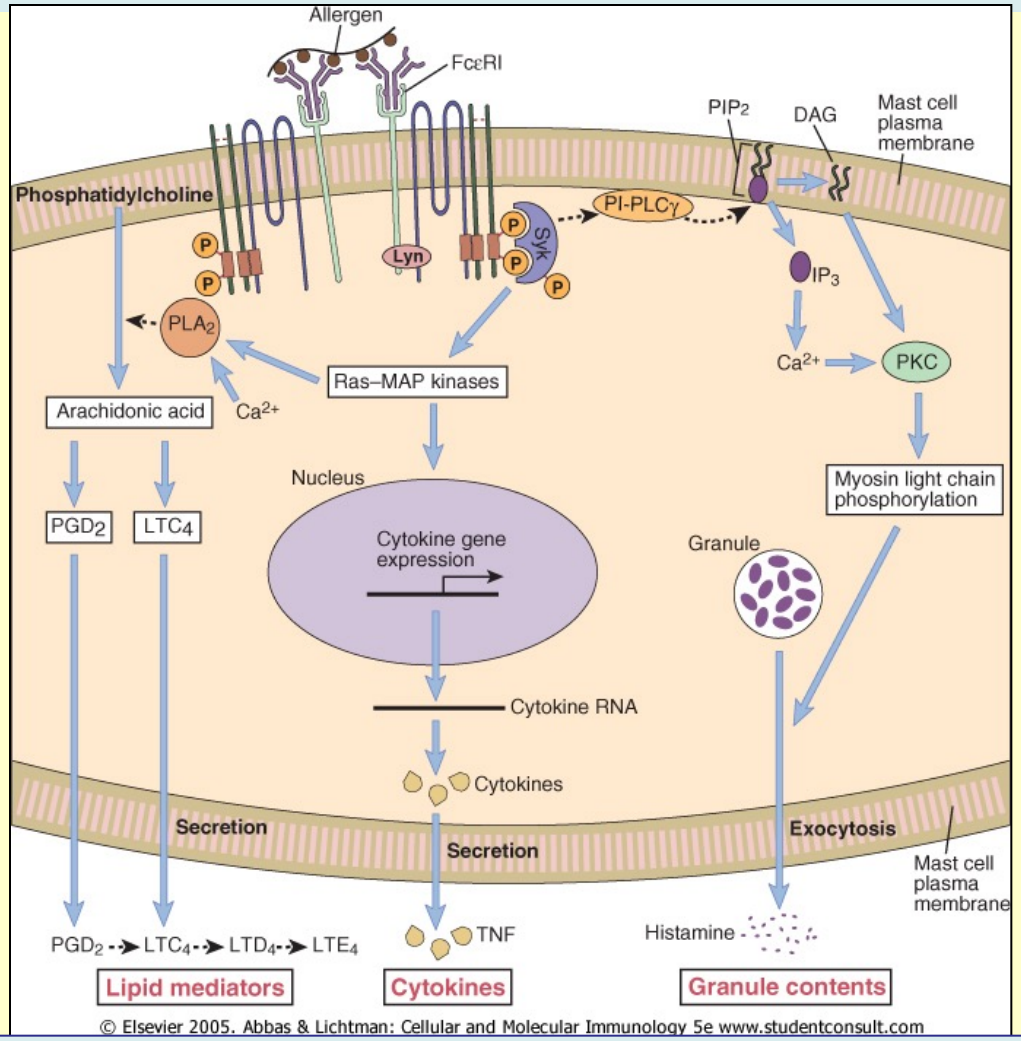
High affinity IgE receptor (FcεR) binds free IgE



Mast cells, basophils, eosinophils Langerhans cells, macrophages

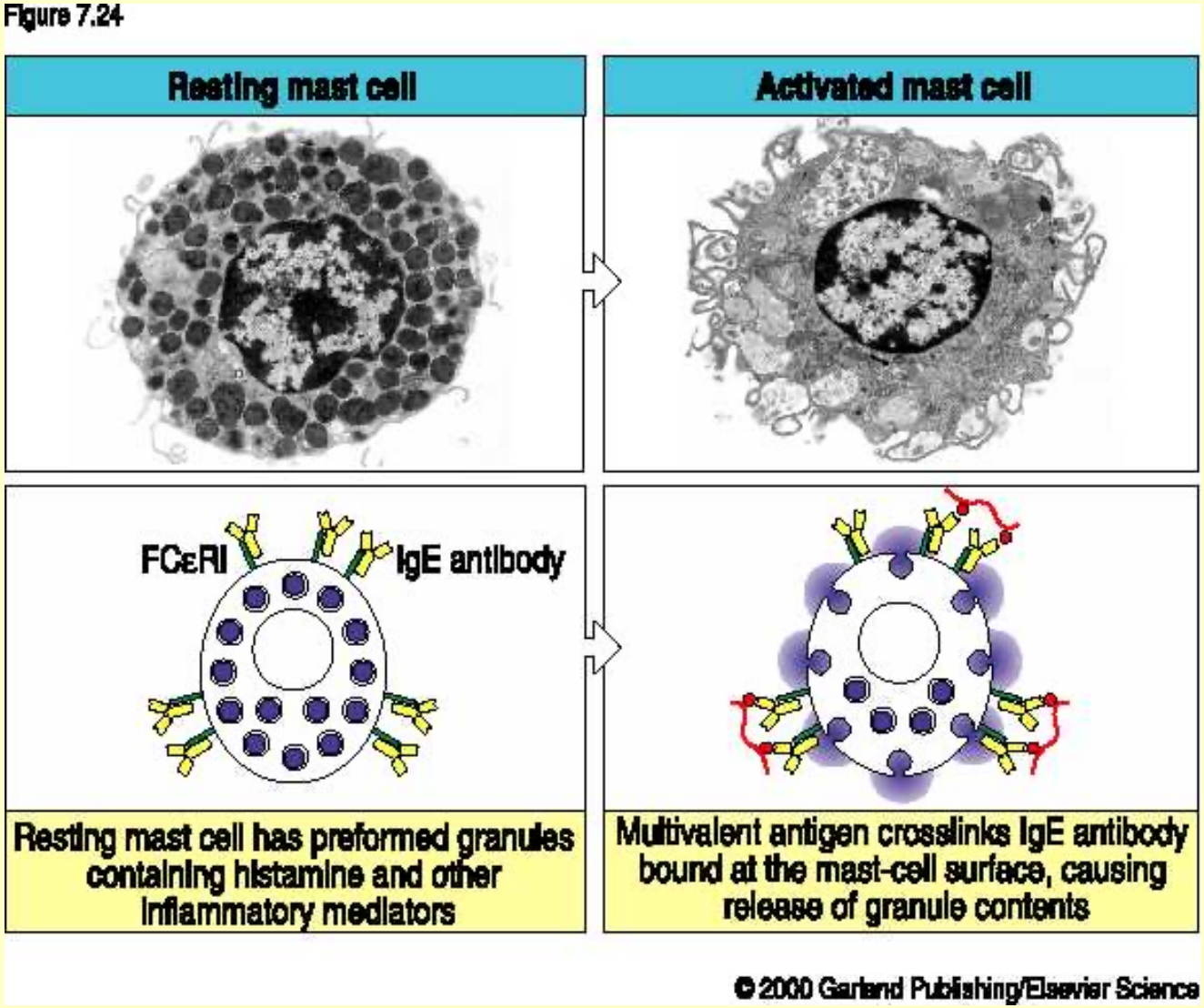
IgE upregulate its expression on Mast cells

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

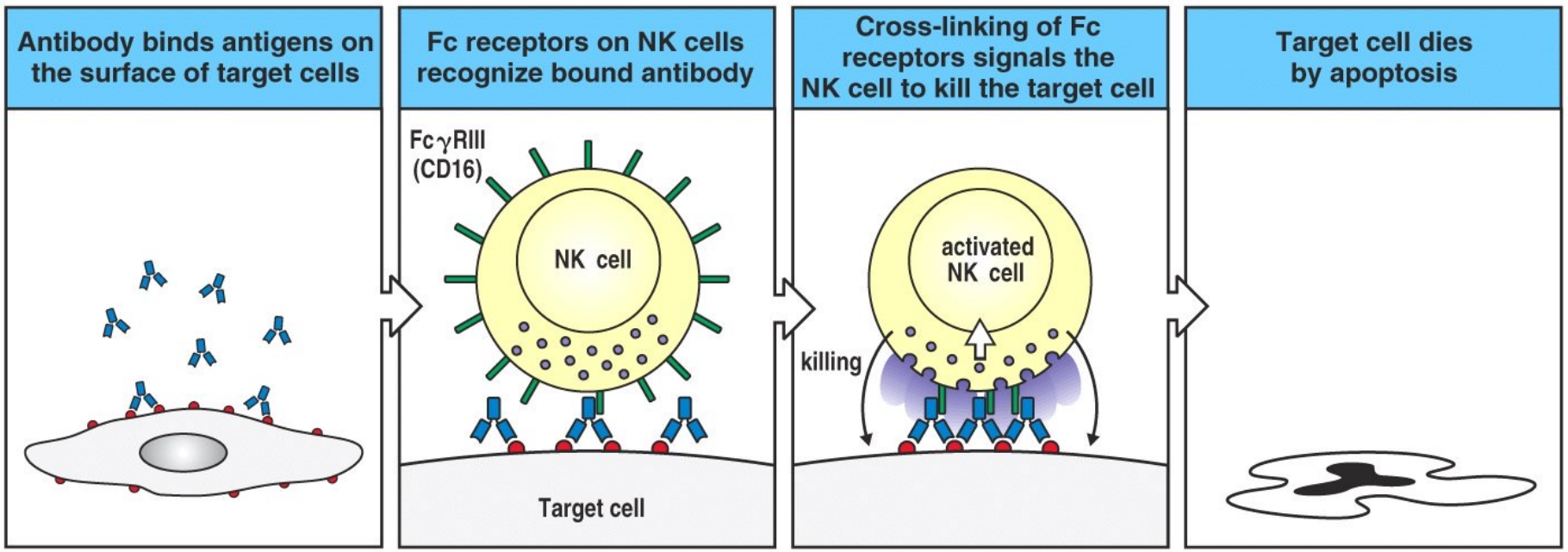
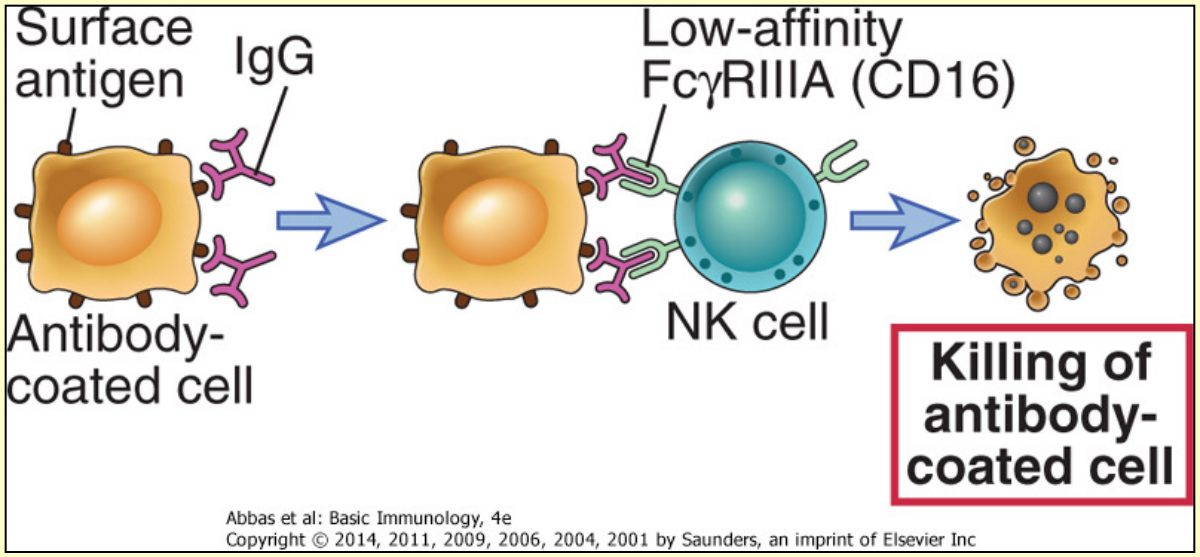
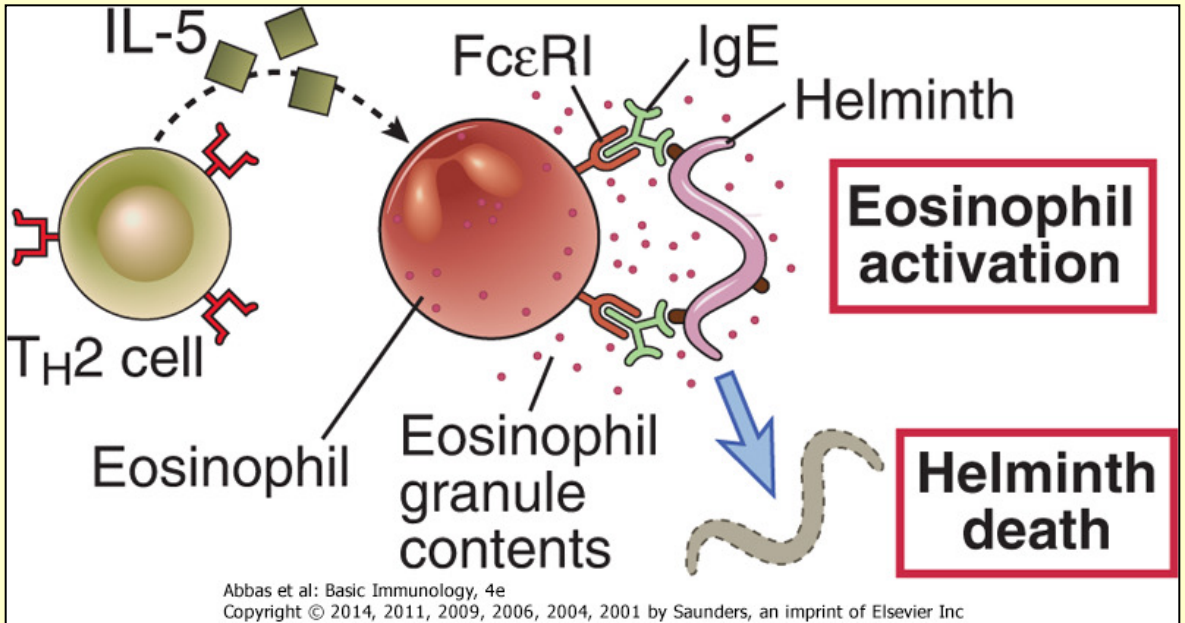


Figure 9-34 Immunobiology, 6/e. (© Garland Science 2005)

ADCC


Surface antigen
IgG
Low-affinity FcγRIIIA (CD16)
Antibody-coated cell
NK cell
Killing of antibody-coated cell
Abbas et al: Basic Immunology, 4e
Copyright © 2014, 2011, 2009, 2006, 2004, 2001 by Saunders, an imprint of Elsevier Inc


IL-5
FcεRI
IgE
Helminth
Eosinophil activation
TH2 cell
Eosinophil
Eosinophil granule contents
Helminth death
Abbas et al: Basic Immunology, 4e
Copyright © 2014, 2011, 2009, 2006, 2004, 2001 by Saunders, an imprint of Elsevier Inc

ADCC

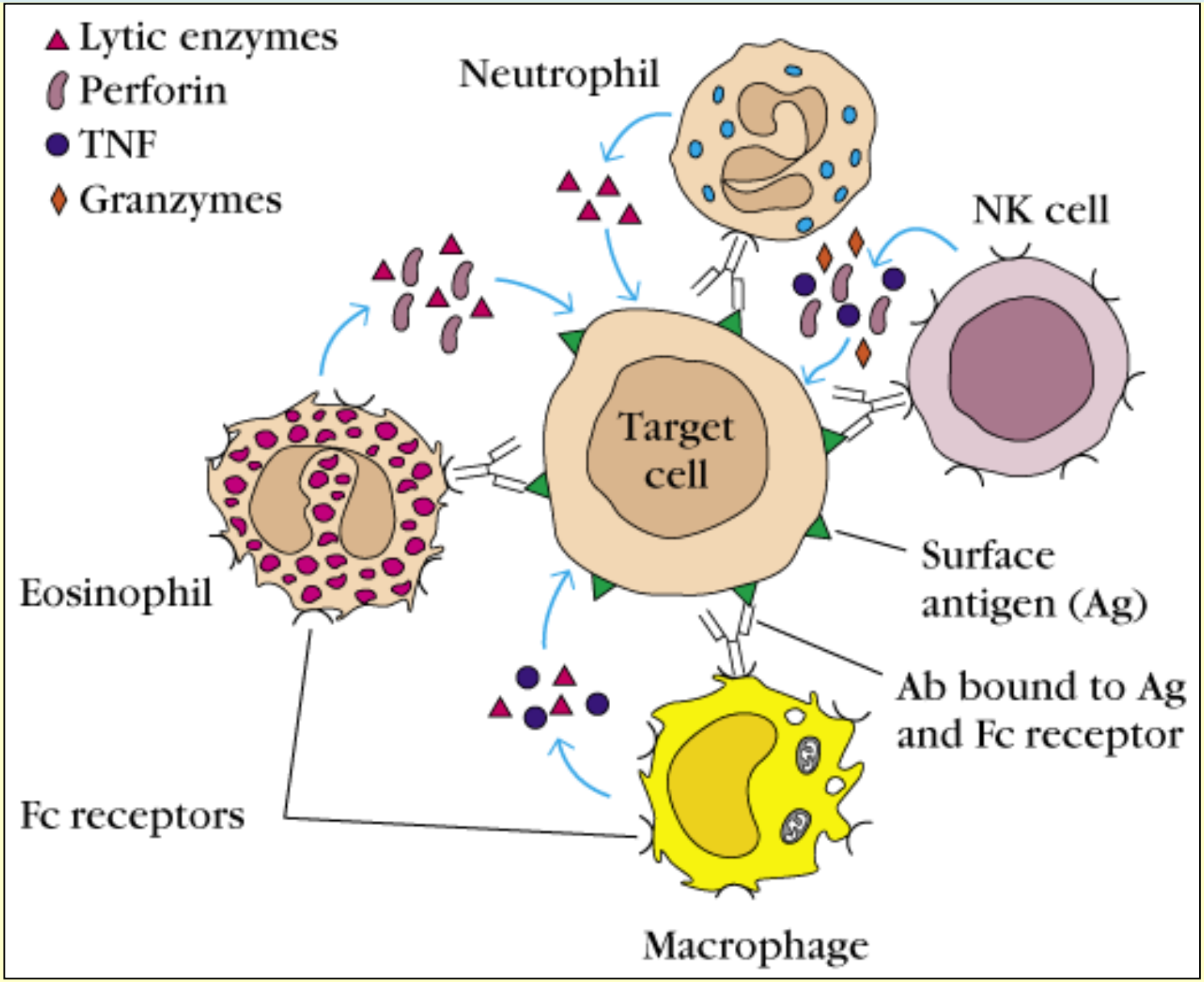
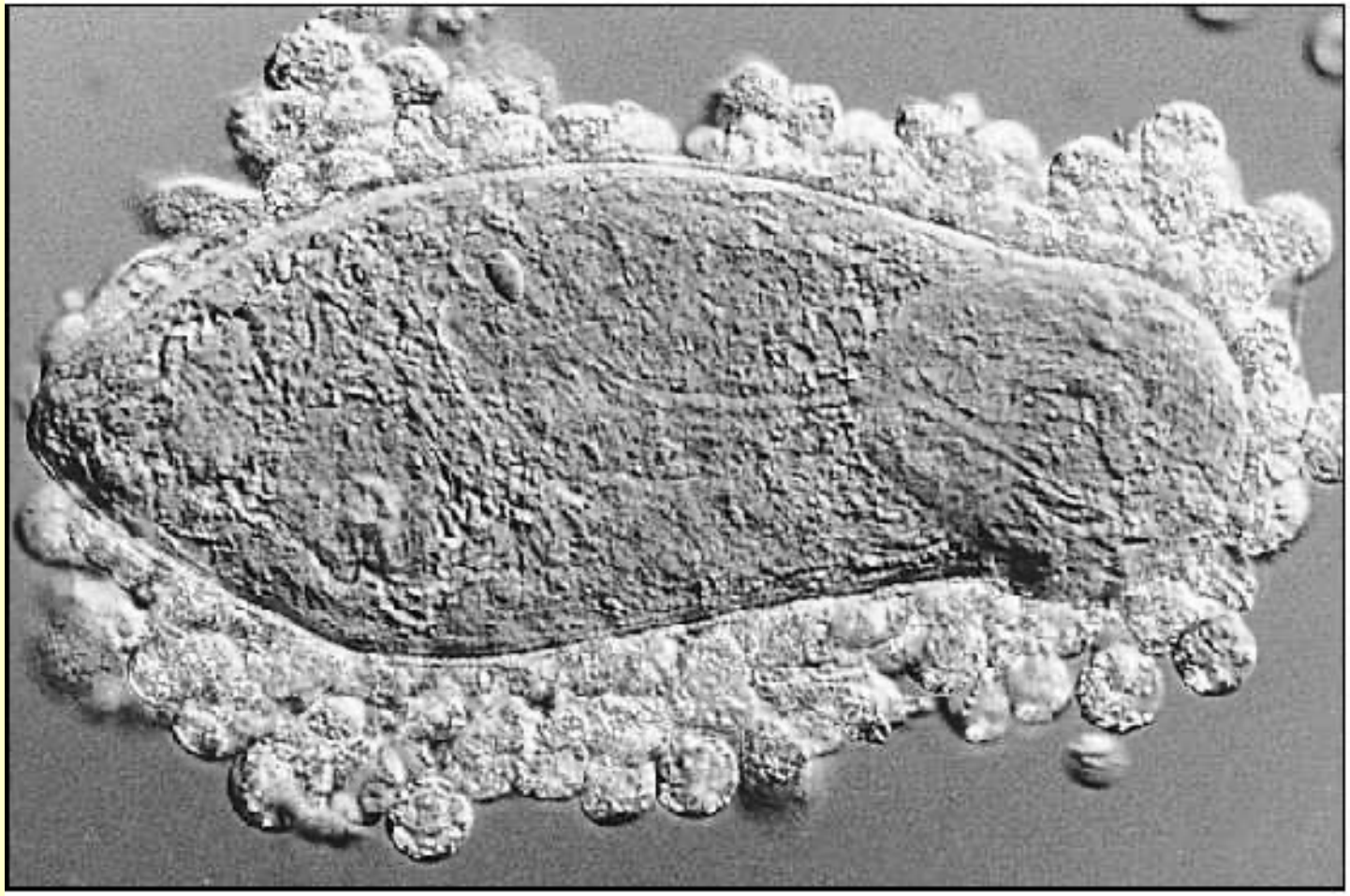

Lytic enzymes
Perforin
TNF
Granzymes
Neutrophil
NK cell
Target cell
Eosinophil
Surface antigen (Ag)
Ab bound to Ag and Fc receptor
Fc receptors
Macrophage

Figure 7 .25



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

COMPLEMENT ACTIVATION

IgG & IgM antigen-antitbody complexes activate complement

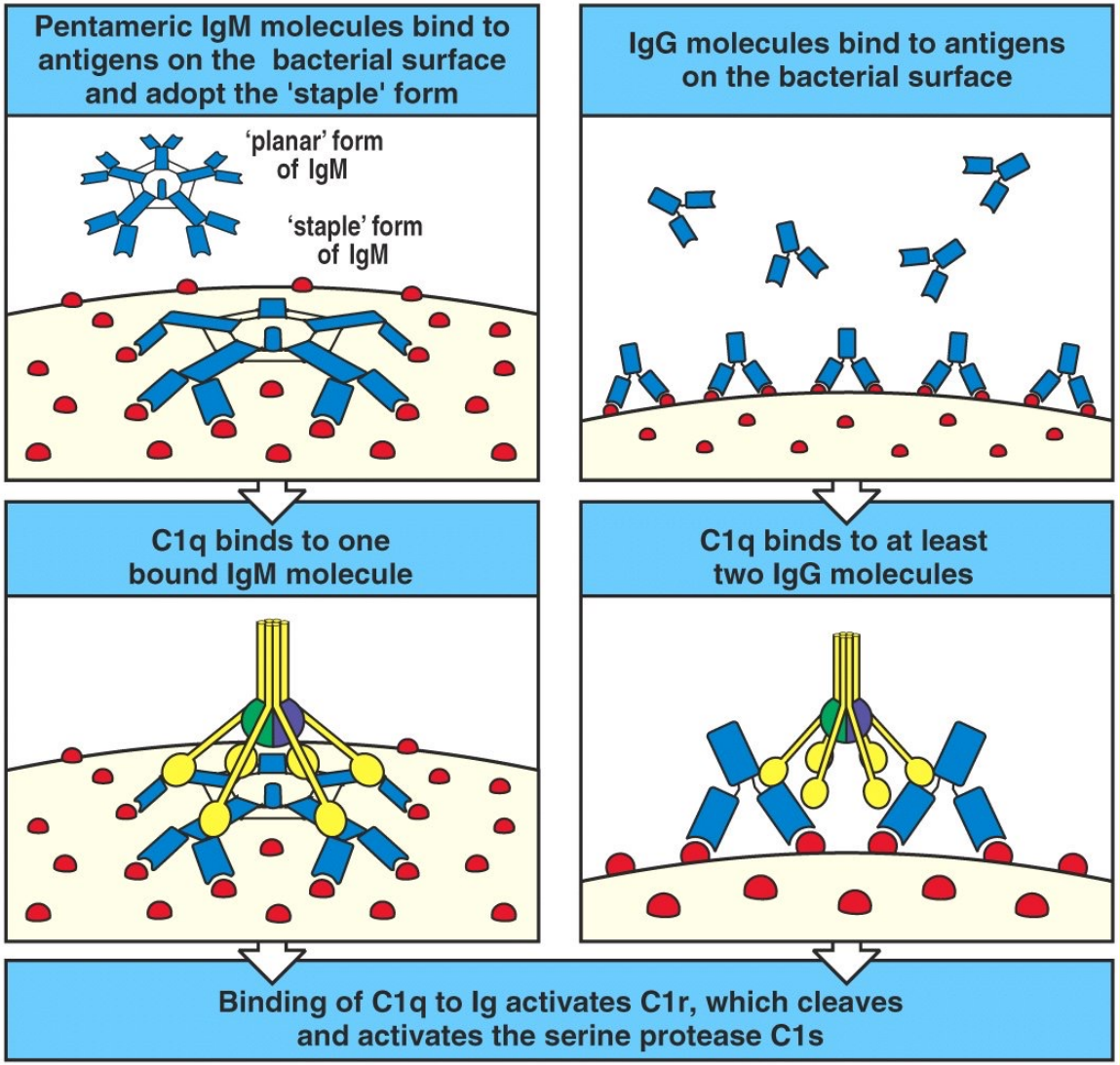


Figure 9-28 Immunobiology, 6/e. (© Garland Science 2005)