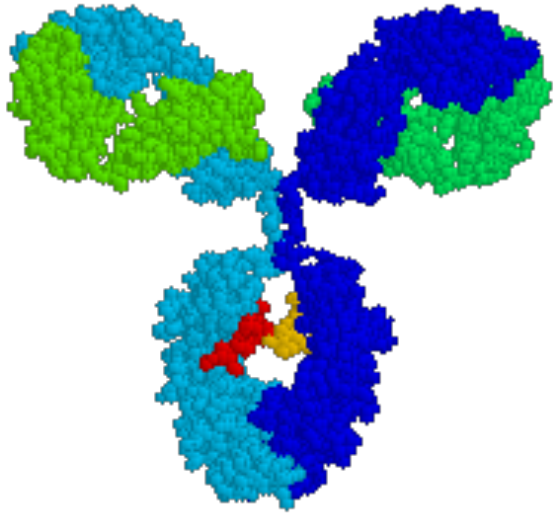
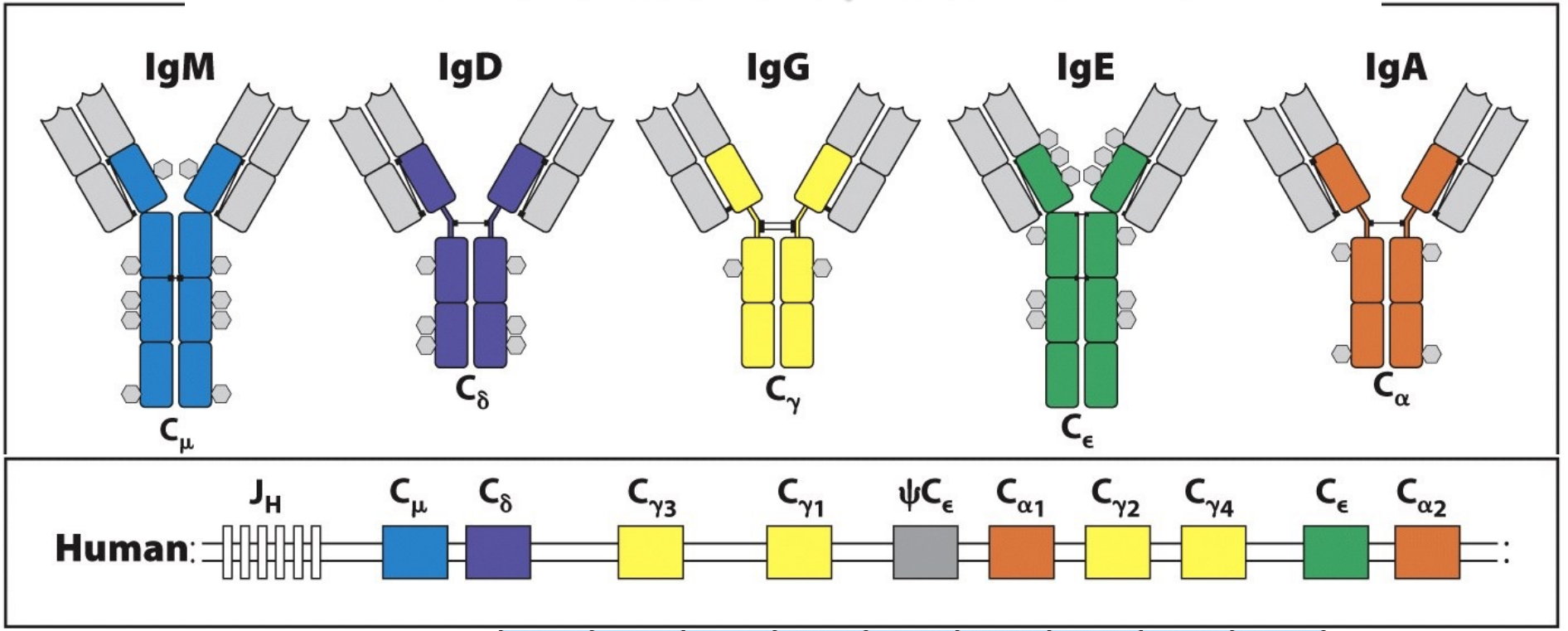
Corso di Immunologia - III anno
Prof. Paolini

Lezione 19/11/2025

"Le funzioni effettrici degli anticorpi"



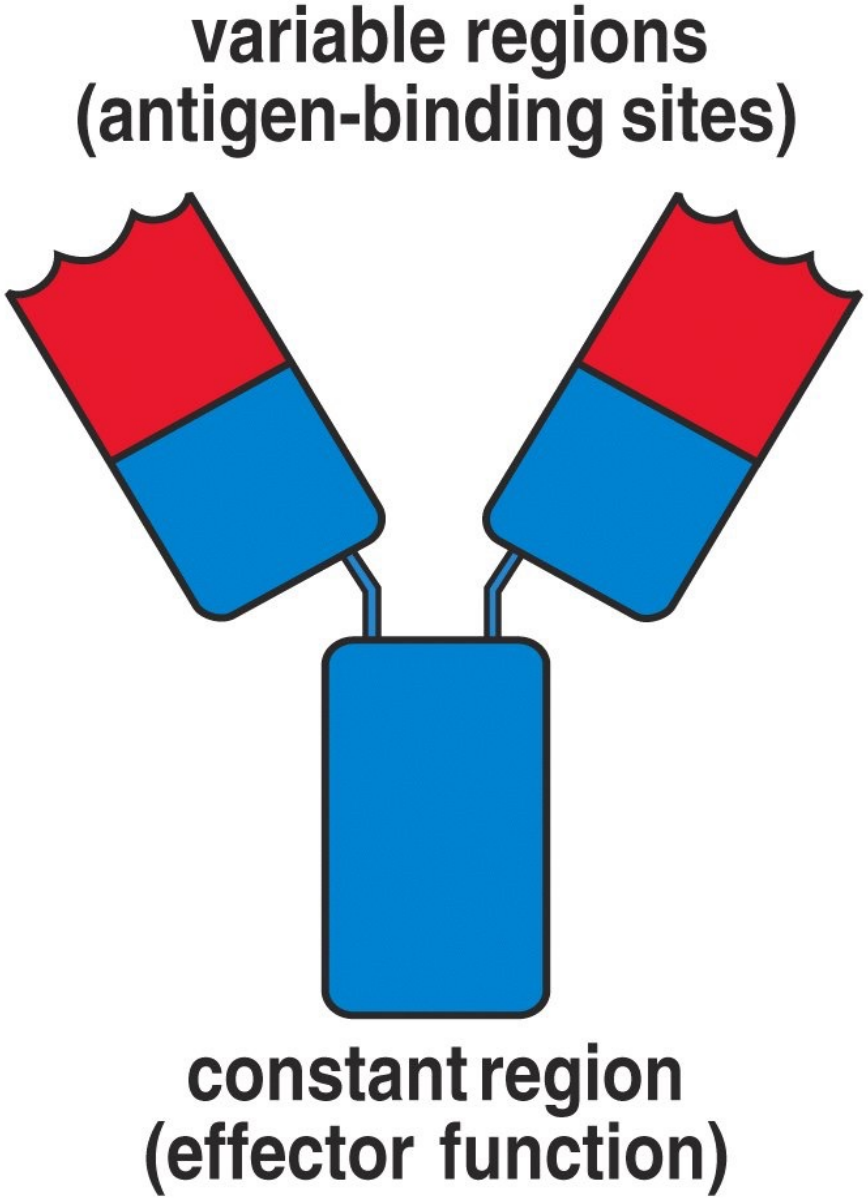
The 5 classes of antibodies



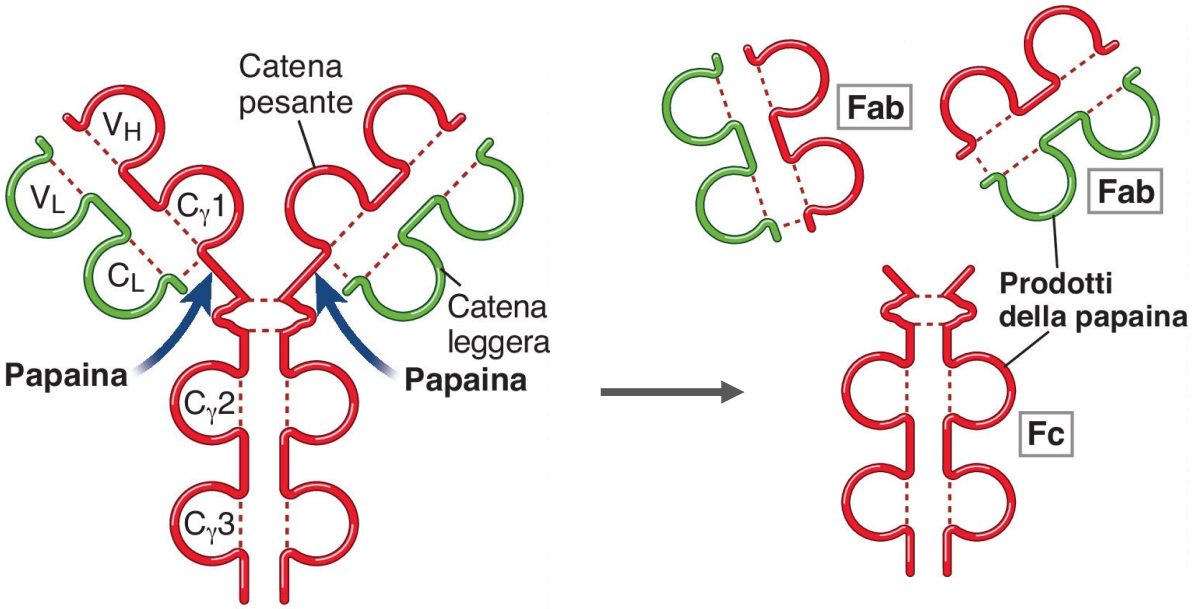
	IgG1	IgG2	IgG3	IgG4	IgM	IgA1	IgA2	IgD	IgE
Heavy chain	γ_1	γ_2	γ_3	γ_4	μ	α_1	α_2	δ	ϵ
Molecular weight (kDa)	146	146	165	146	970	160	160	184	188
Serum level (mean adult mg/ml)	9	3	1	0.5	1.5	3.0	0.5	0.03	5×10^{-5}
Half-life in serum (days)	21	20	7	21	10	6	6	3	2

Serum level IgG>IgA>IgM>IgD>IgE

The antibody couples the specific recognition of antigen to the activation of non-specific effector mechanisms

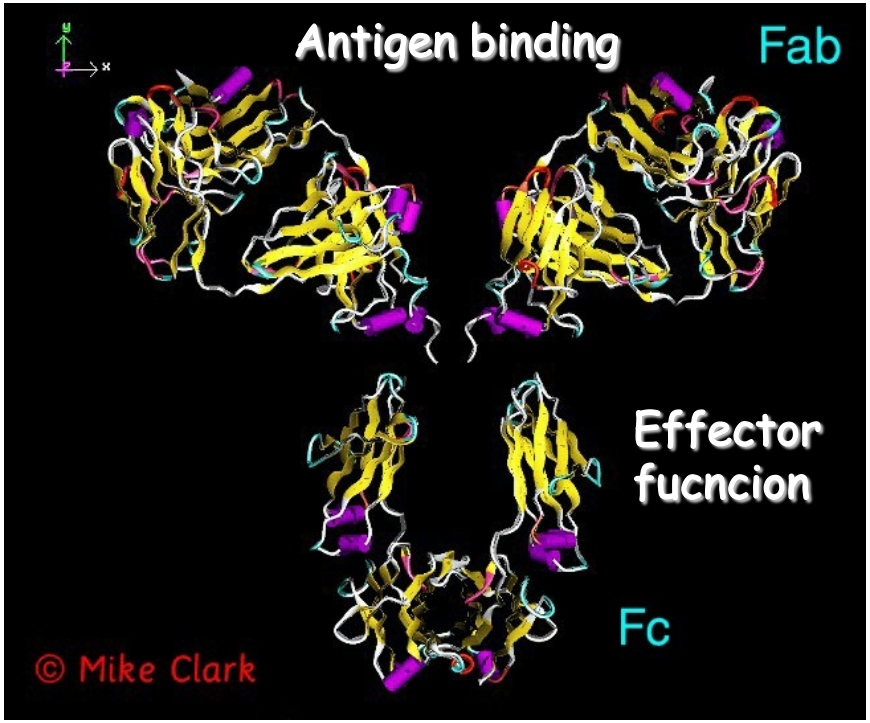


Ig can be split into three fragments, two identical to each other called Fab and a third Fc fragment

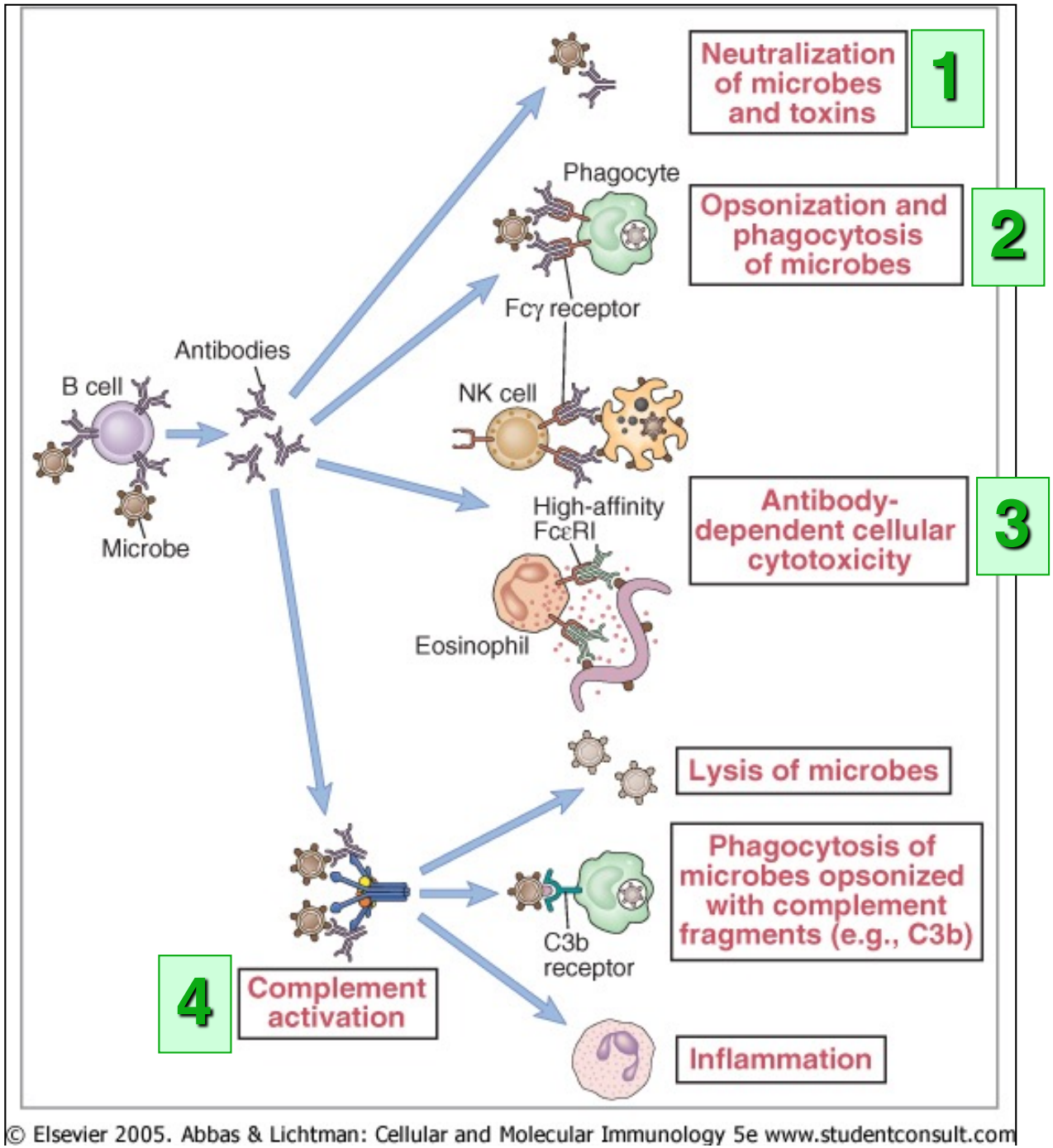


Fab = Fragment Antigen Binding

Fc = Frammento Cristallizzabile



Antibodies can perform several effector functions



1. Antibodies can neutralize the infectious ability of pathogens

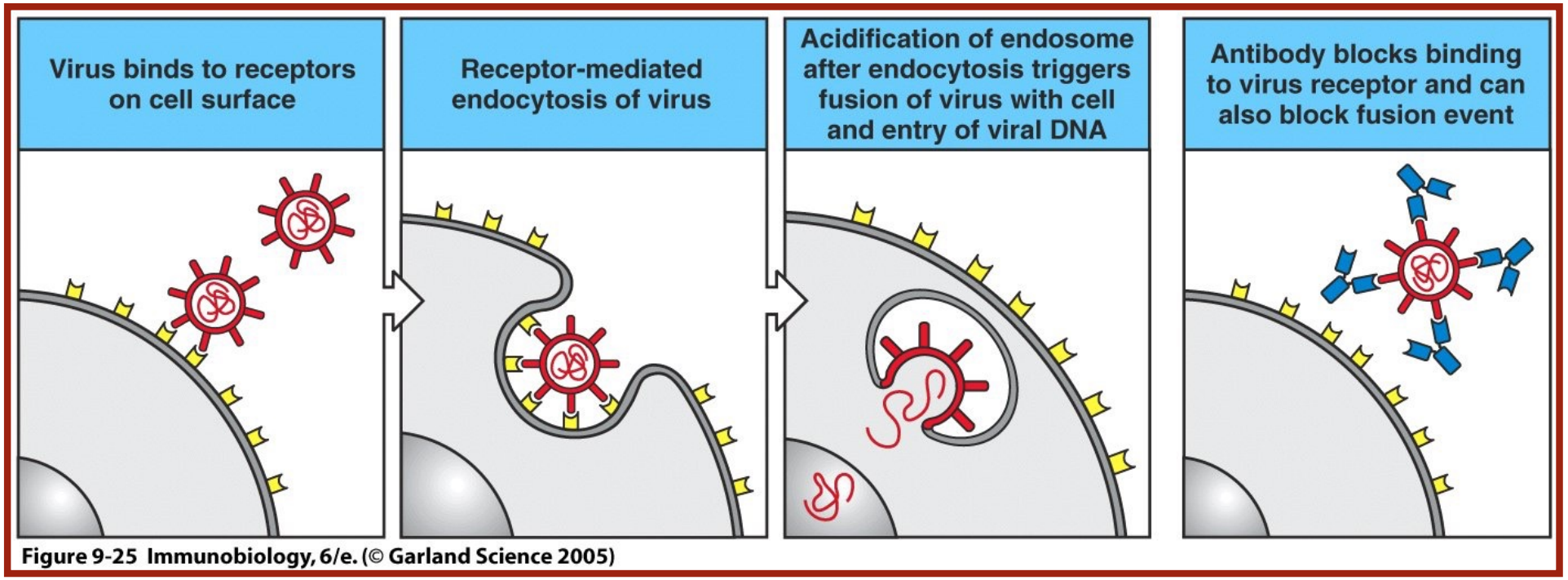
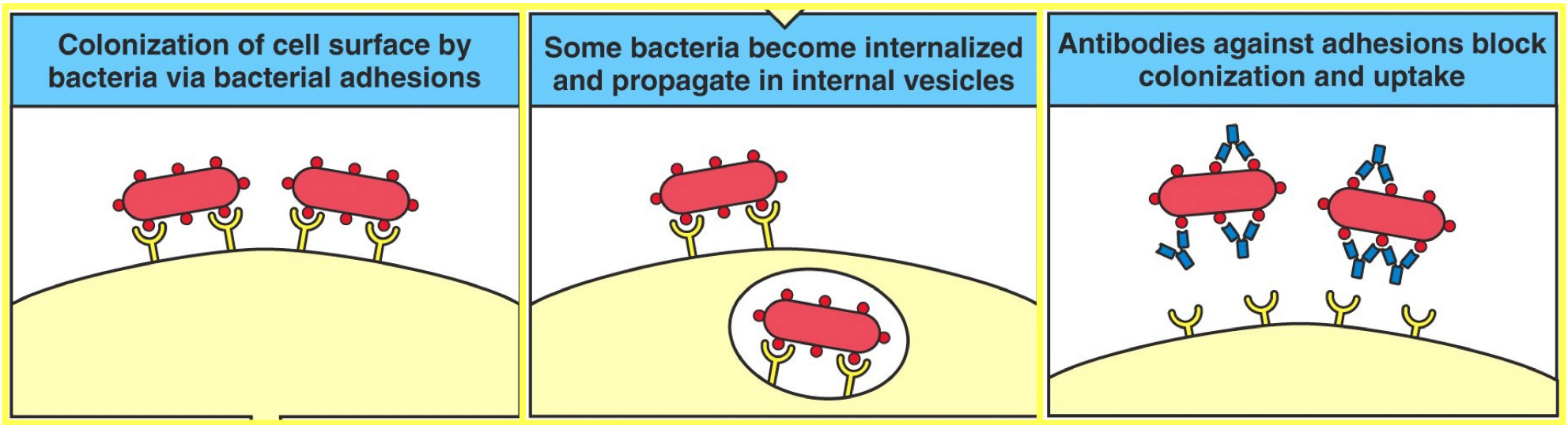
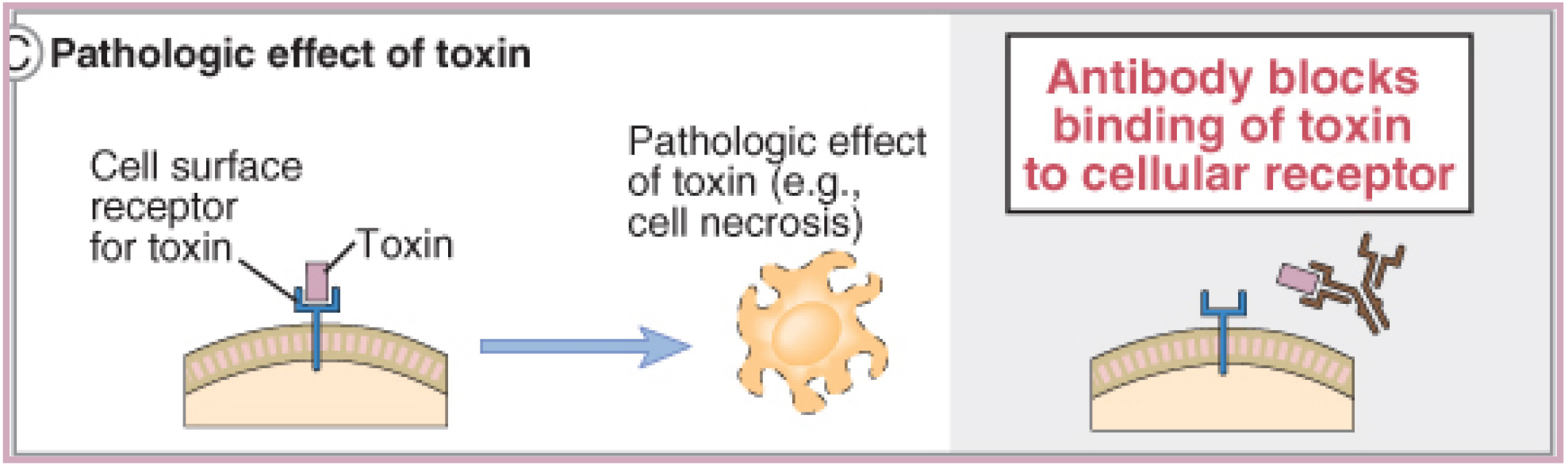


Figure 9-25 Immunobiology, 6/e. (© Garland Science 2005)



1. Antibodies can neutralize pathogen-derived toxins



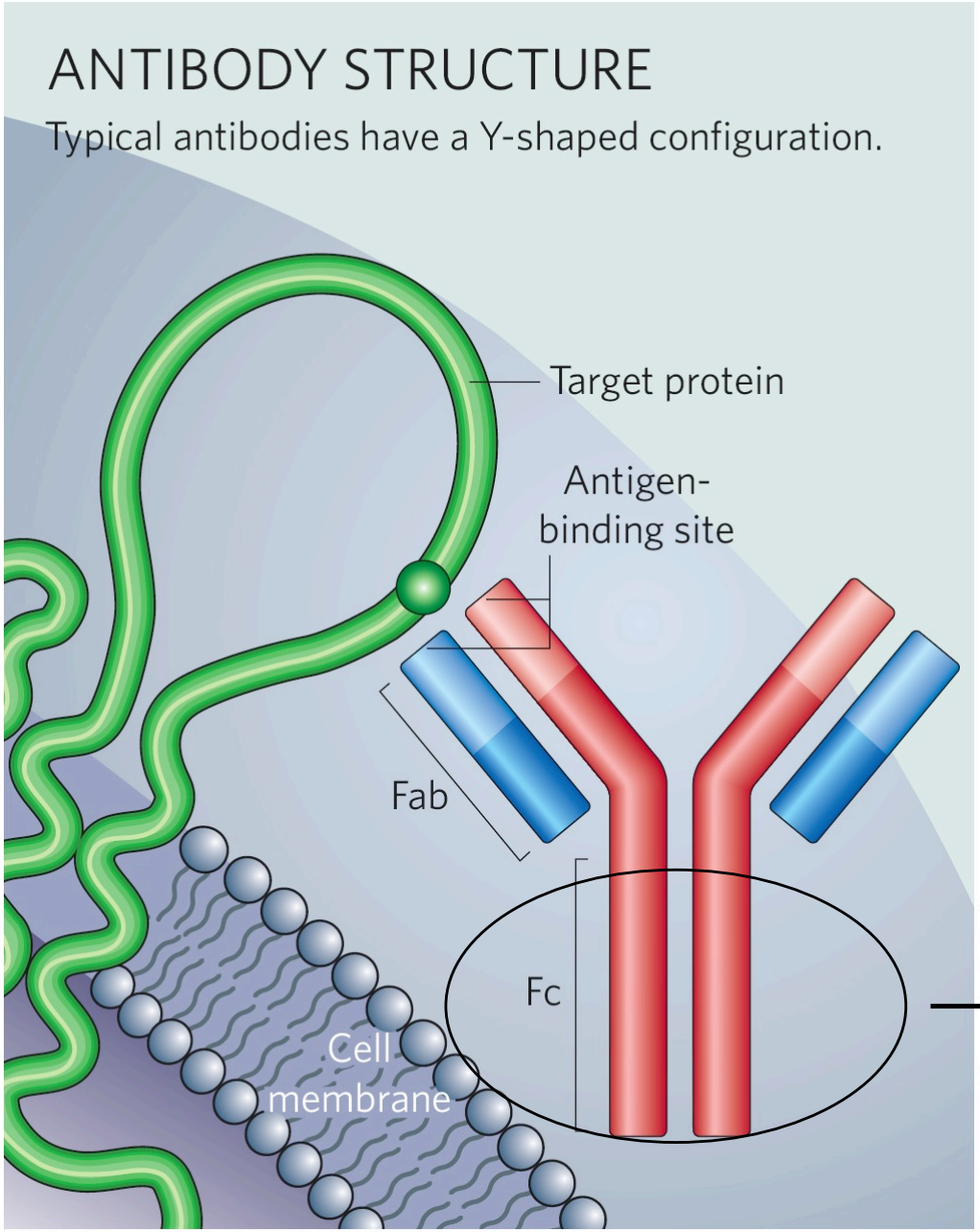
Disease	Organism	Toxin	Effects *in vivo*
Tetanus	*Clostridium tetani*	Tetanus toxin	Blocks inhibitory neuron action, leading to chronic muscle contraction
Diphtheria	*Corynebacterium diphtheriae*	Diphtheria toxin	Inhibits protein synthesis, leading to epithelial cell damage and myocarditis
Gas gangrene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

Figure 9-23 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Disease	Organism	Toxin	Effects *in vivo*
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)

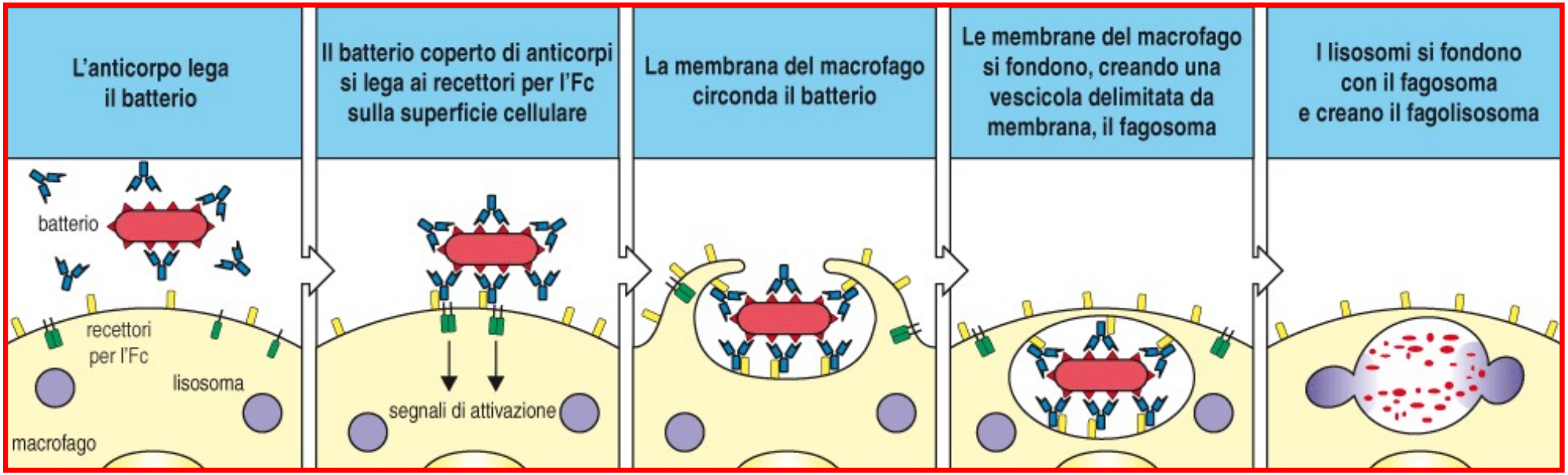
Figure 9-23 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

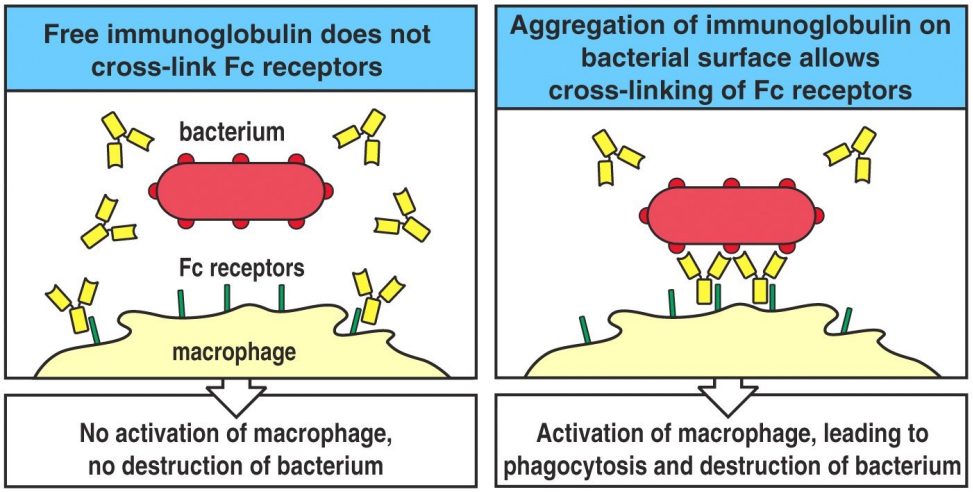
The antibody couples the specific recognition of antigen to the activation of non-specific effector mechanisms



→ Effector functions

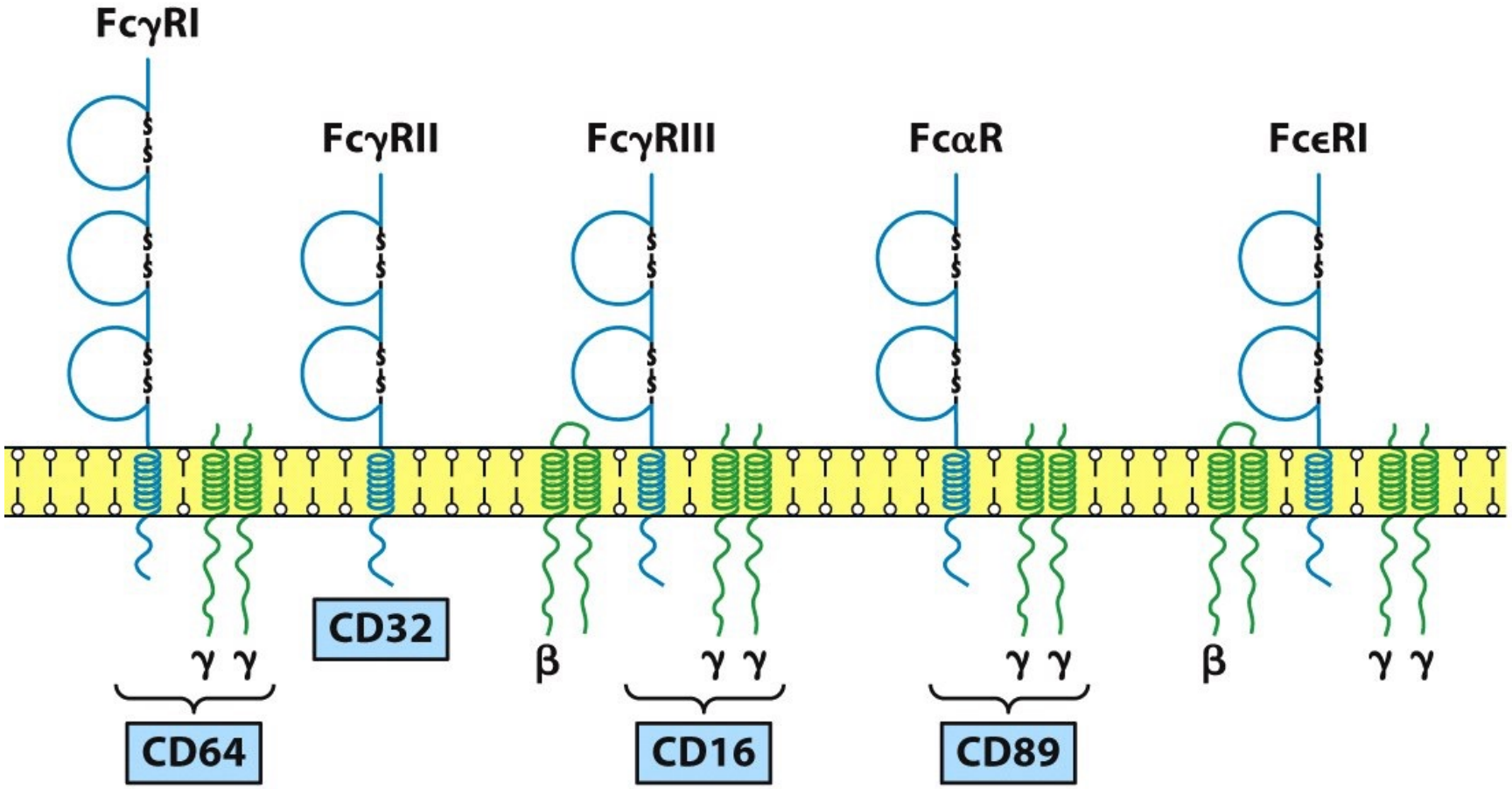
2. Antibodies can enhance phagocytosis of pathogens (OPSONIZATION)





Antibody-mediated crosslinking of Fc receptors is necessary for phagocyte activation!

Fc receptor family

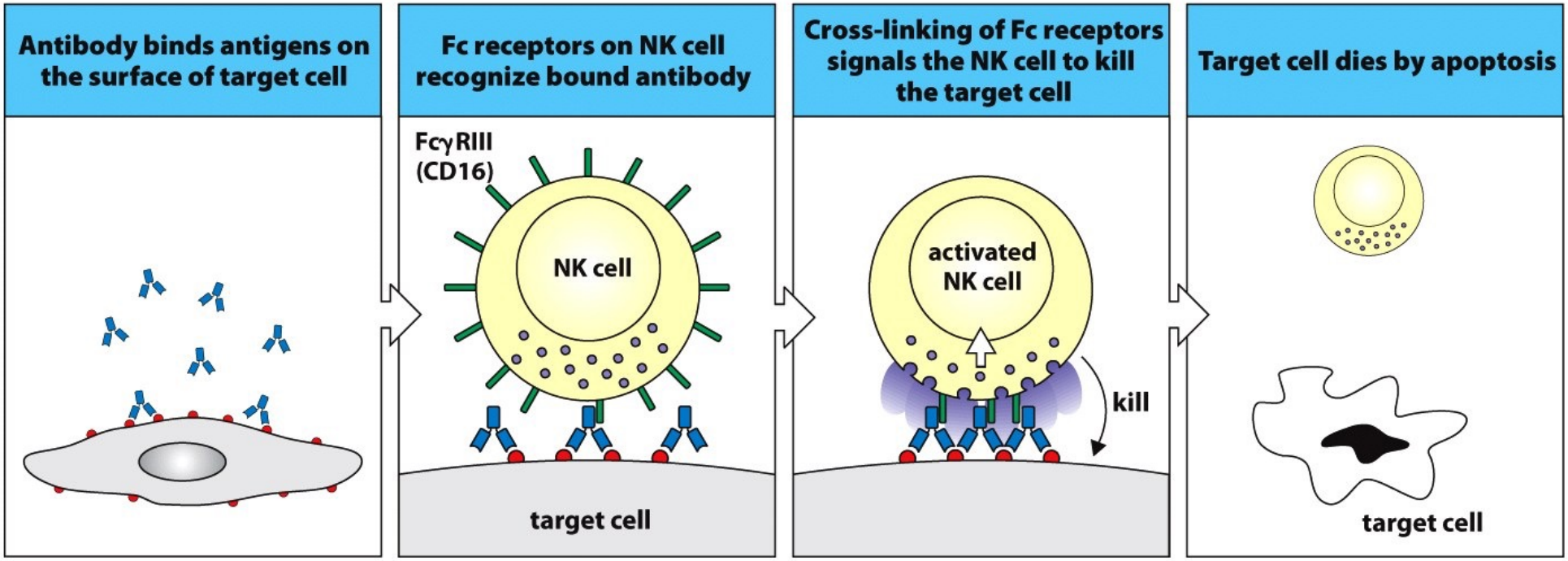


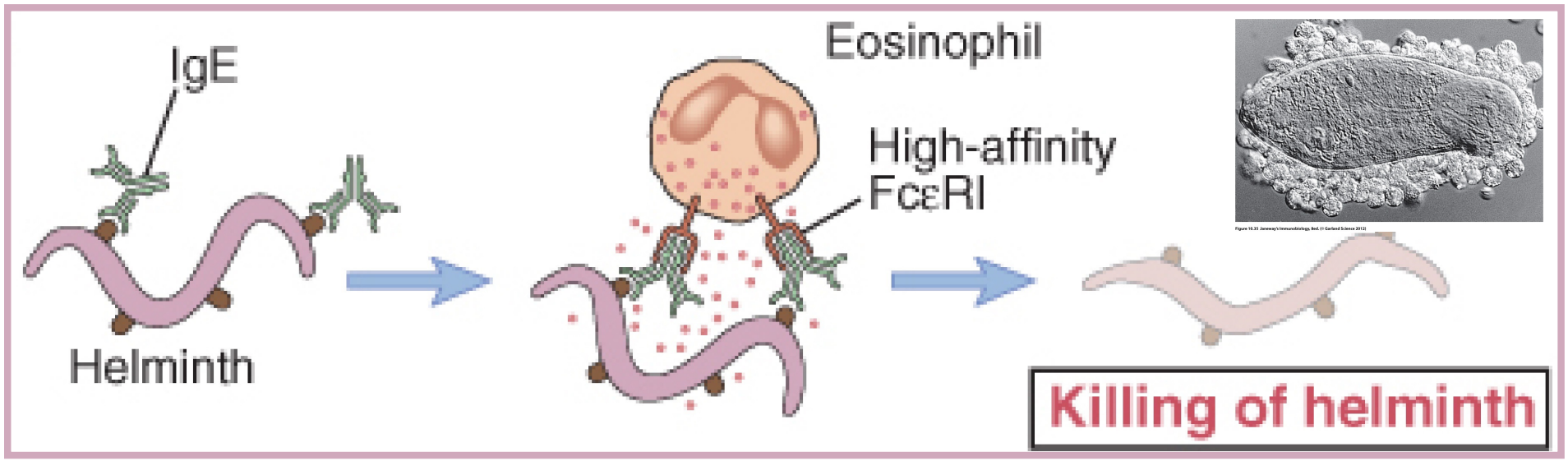
Mast cells, basophils, eosinophils

MΦ, PMN

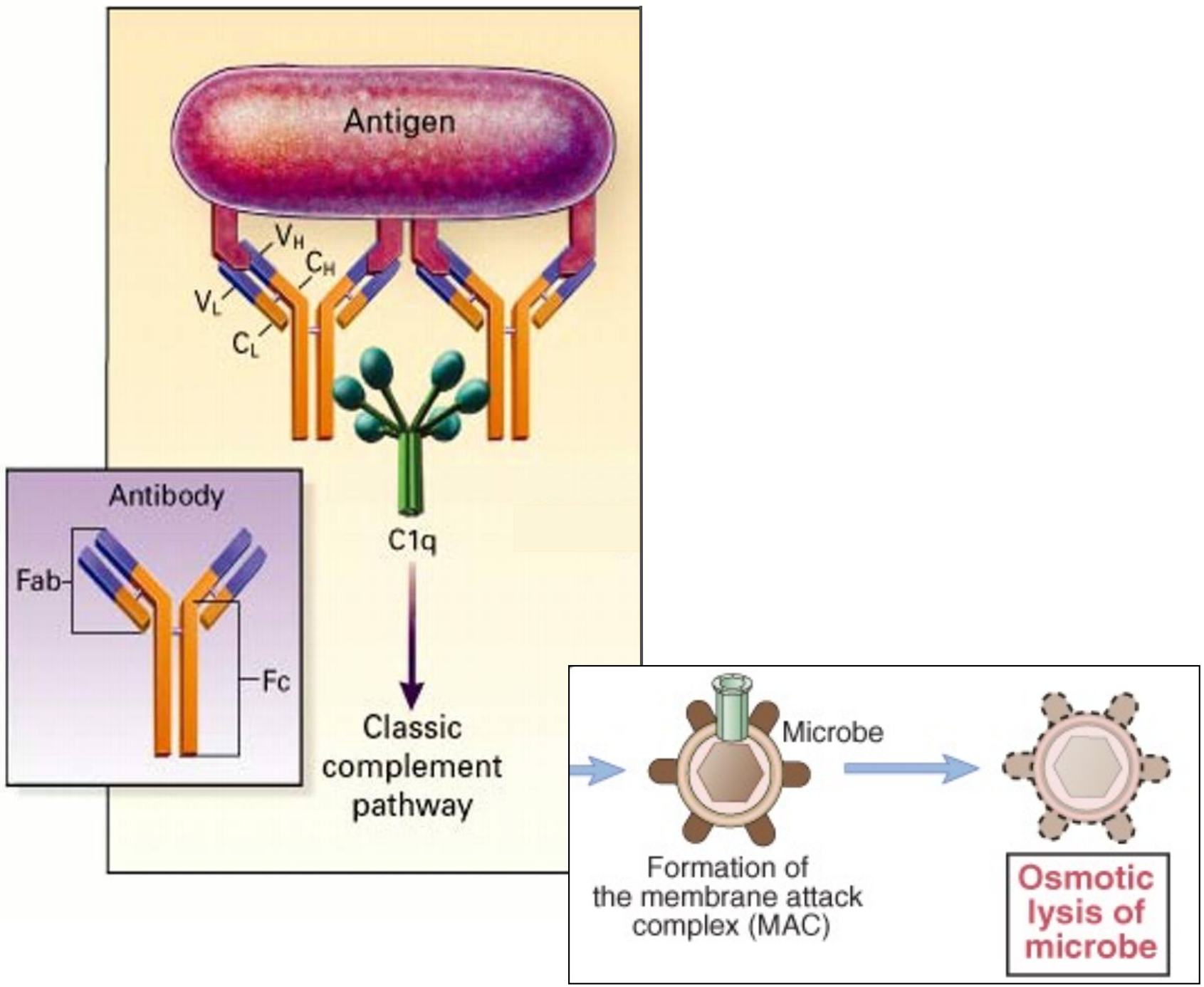
Figure 4-23
Kuby IMMUNOLOGY, Sixth Edition

3. Antibodies can induce cytotoxicity by innate immunity cells (Antibody Dependent Cytotoxicity-ADCC)

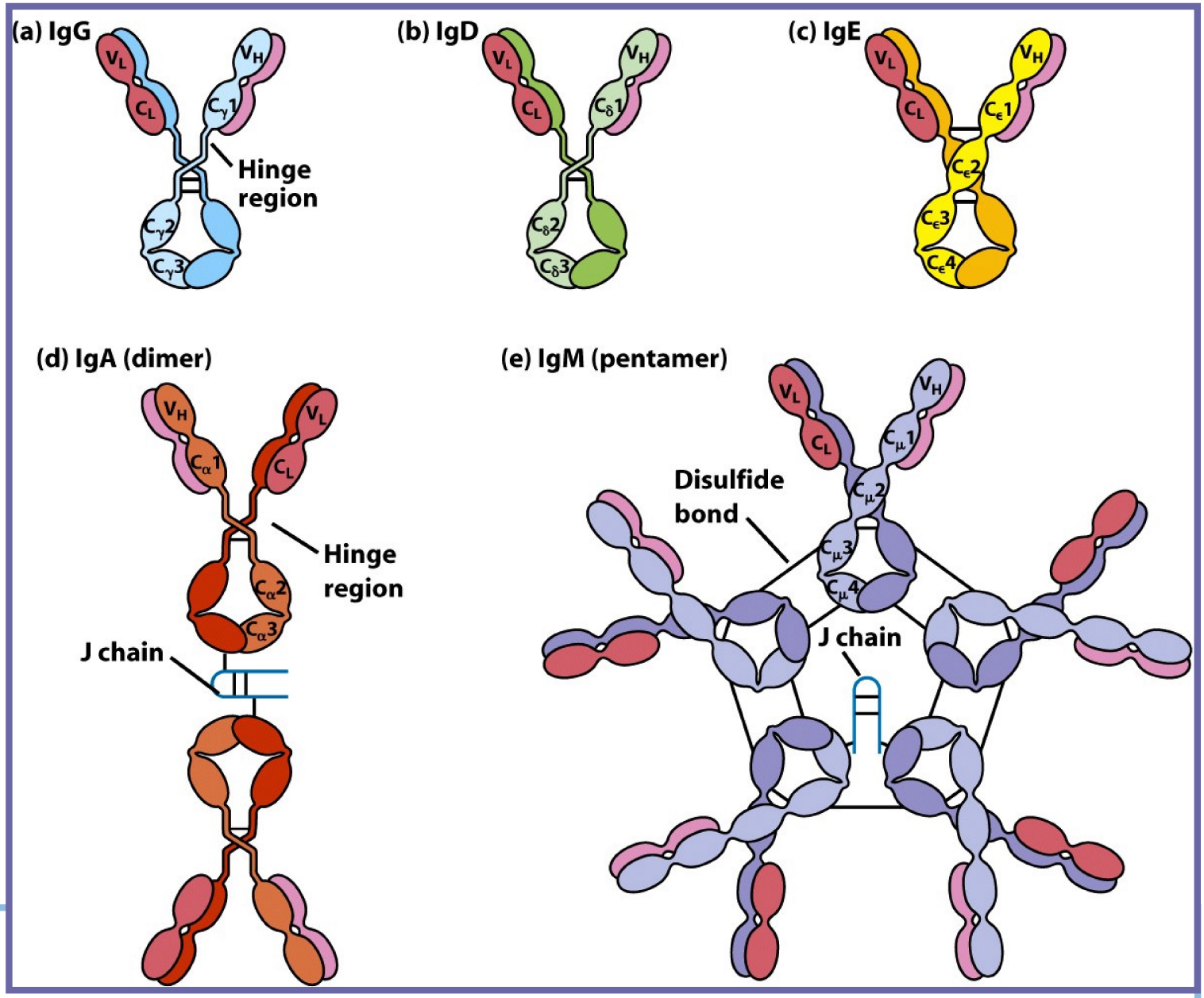




4. Antibodies can induce the activation of COMPLEMENT



Five different Ig classes (ISOTYPES)



The HINGE region

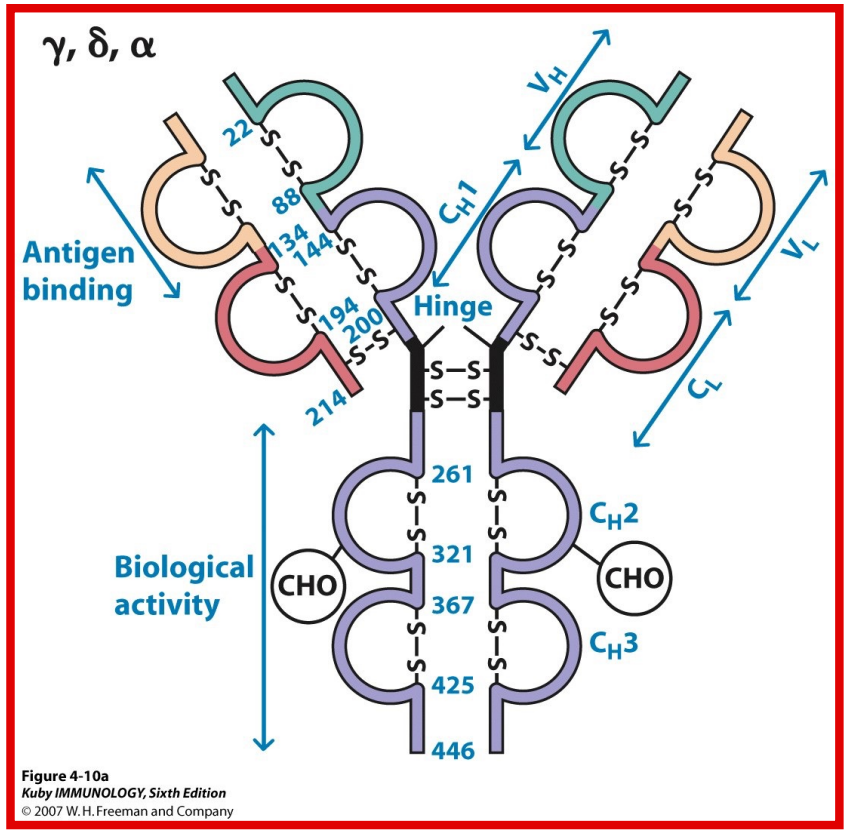


Figure 4-10a
Kuby IMMUNOLOGY, Sixth Edition

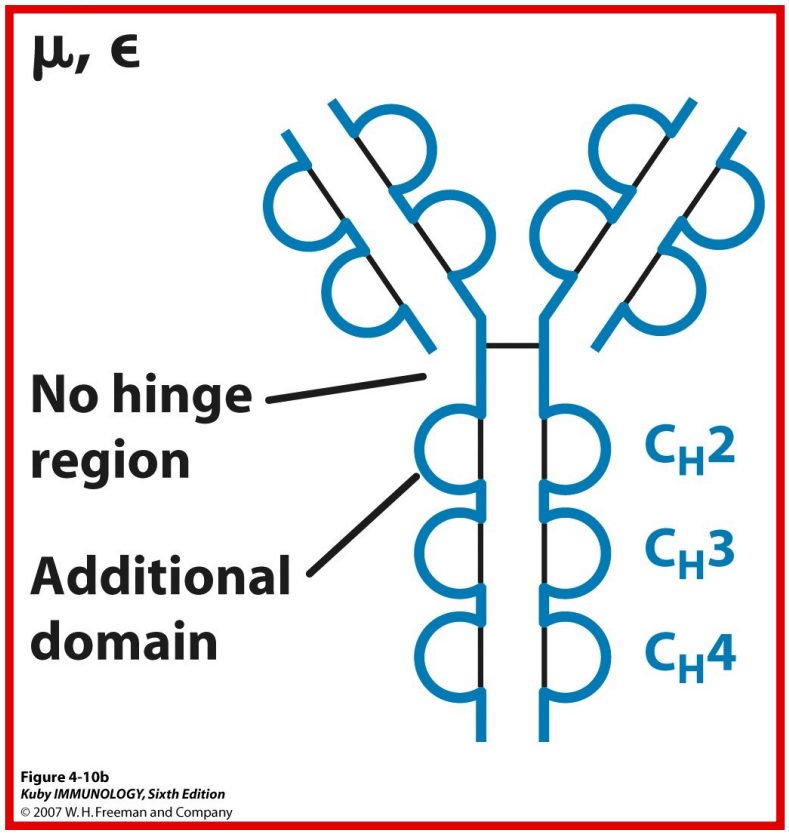
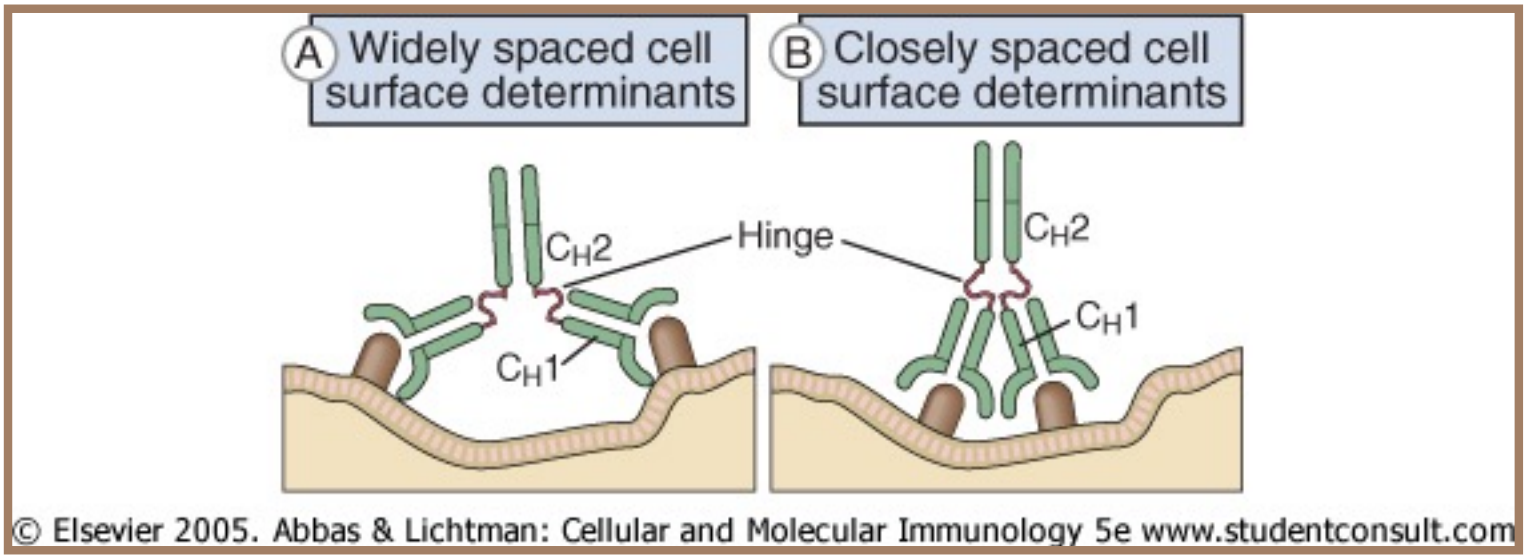
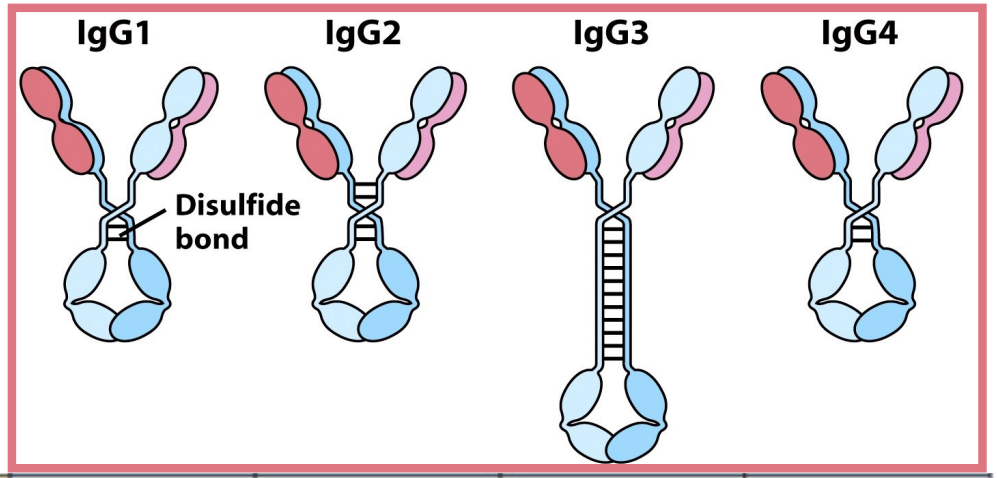


Figure 4-10b
Kuby IMMUNOLOGY, Sixth Edition



IgG

- Most abundant Ig in body
- Highest concentration in serum (75%)
- Major form produced in secondary response
- Four subclasses: IgG1-4



Proporzione delle IgG totali (%)	45–75	16–48	2–8	1–12
Lunghezza della cerniera della catena pesante (aminoacidi)	15	12	62	12
Numero di legami disolfuro nella cerniera	2	4	11	2
Suscettibilità della cerniera alla proteolisi	++	+	+++	+
Emivita nel siero (giorni)	21	21	7	21

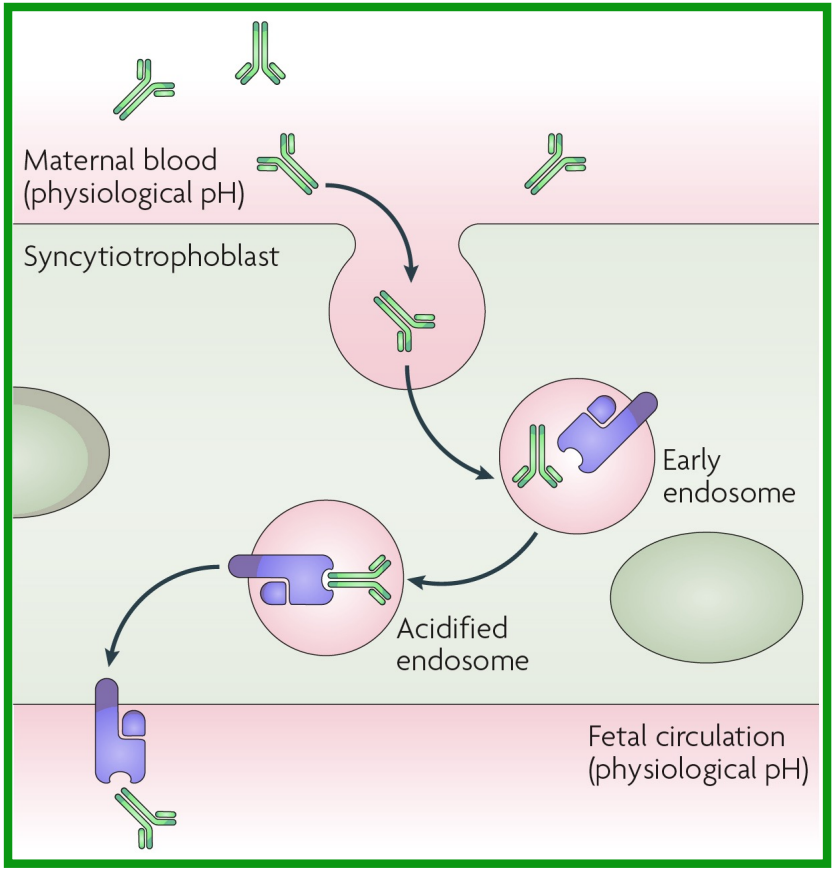
IgG

Properties and functions:

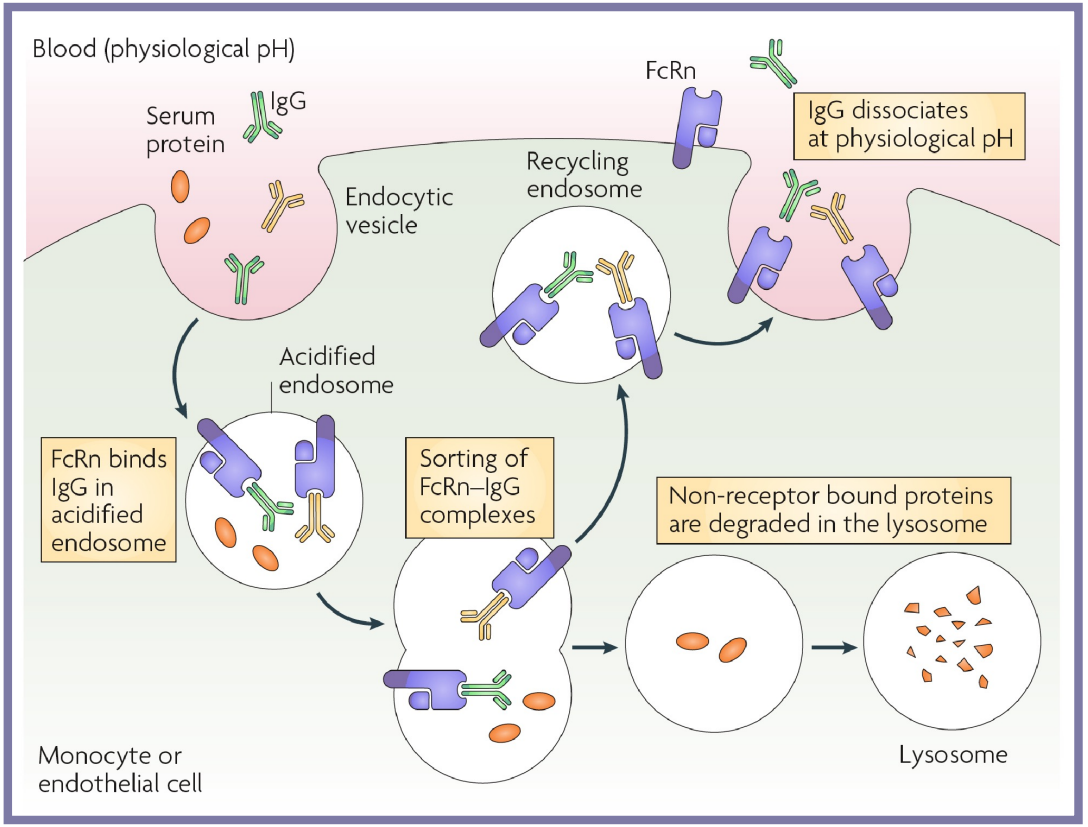
- They can cross the placenta
- They neutralize pathogens and bacterial toxins
- They activate complement
- They bind Fc receptors
  - Phagocytosis - opsonization
  - ADCC

FcRn mediates IgG transport at the materno-fetal barrier and into tissue interstitial space

FcRn-mediated transport of IgG at the materno-fetal interface



FcRn-dependent recycling of IgG extends their serum half-life and mediates their transport in the tissue interstitial space



IgG

Properties and functions:

- They can cross the placenta
- They neutralize pathogens and bacterial toxins
- They activate complement
- They bind Fc receptors
  - Phagocytosis - opsonization
  - ADCC

IgG

Properties and functions:

- They can cross the placenta
- They neutralize pathogens and bacterial toxins
- They activate complement

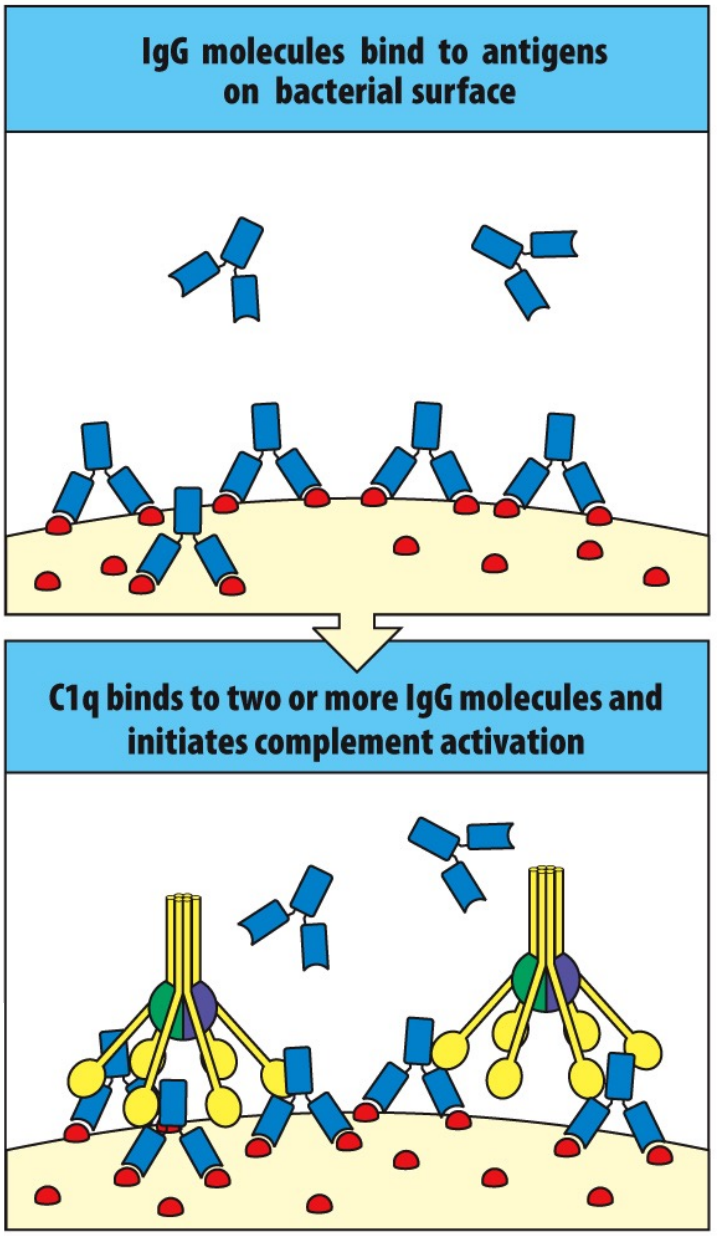
  IgG3>IgG1>IgG2

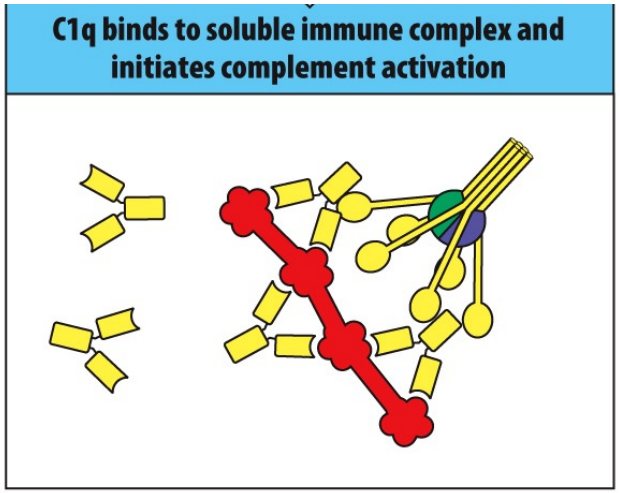
- They bind Fc receptors
  - Phagocytosis - opsonization
  - ADCC

The Fab fragments bind the antigen and the Fc fragment remains accessible……

…but to activate the classical pathway two IgG molecules are needed which must simultaneously bind a C1 molecule

Even soluble antigens can activat complement!





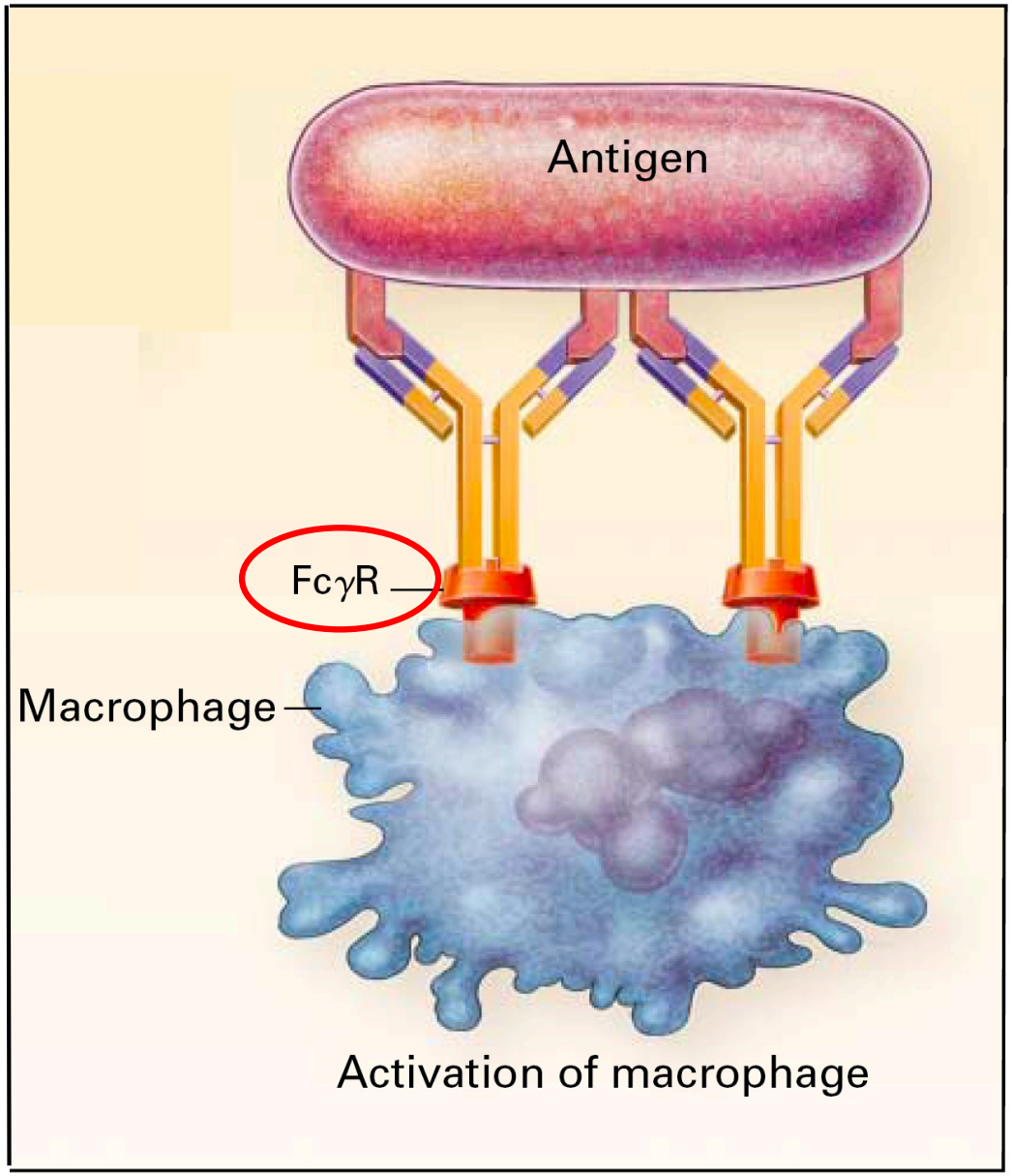
IgG

Properties and functions:

- They can cross the placenta
- They neutralize pathogens and bacterial toxins
- They activate complement

  IgG3>IgG1>IgG2
- They bind Fc receptors
  - Phagocytosis - opsonization
  - ADCC

The constant region of IgG is recognized by specific receptors: FcγR

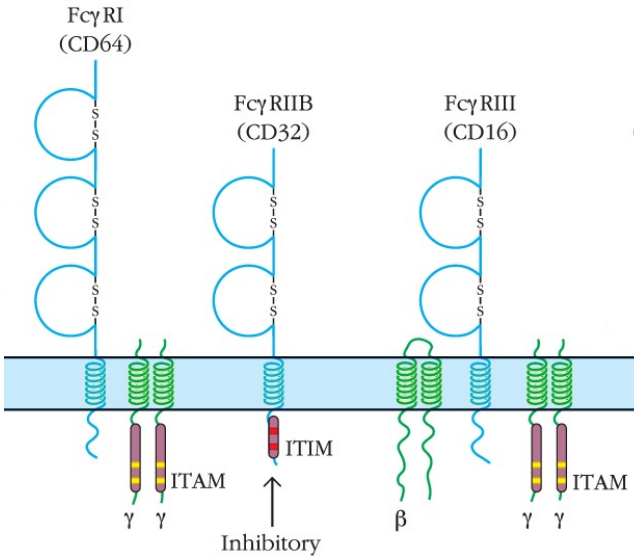


A family of Fcγ receptors

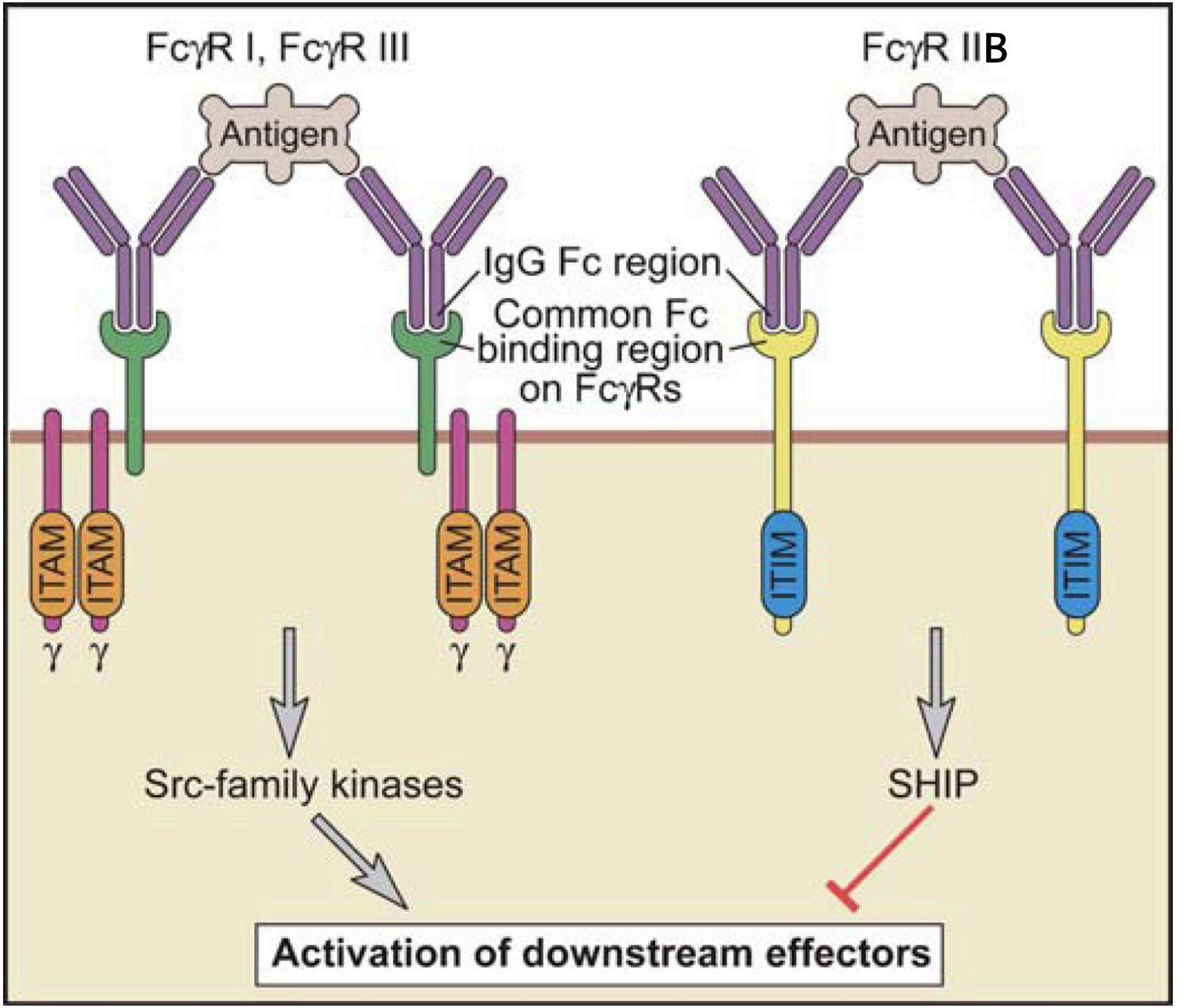
HIGH Affinity 10^{-9}M

Medium to low affinity (10^{-6}-10^{-5}M)

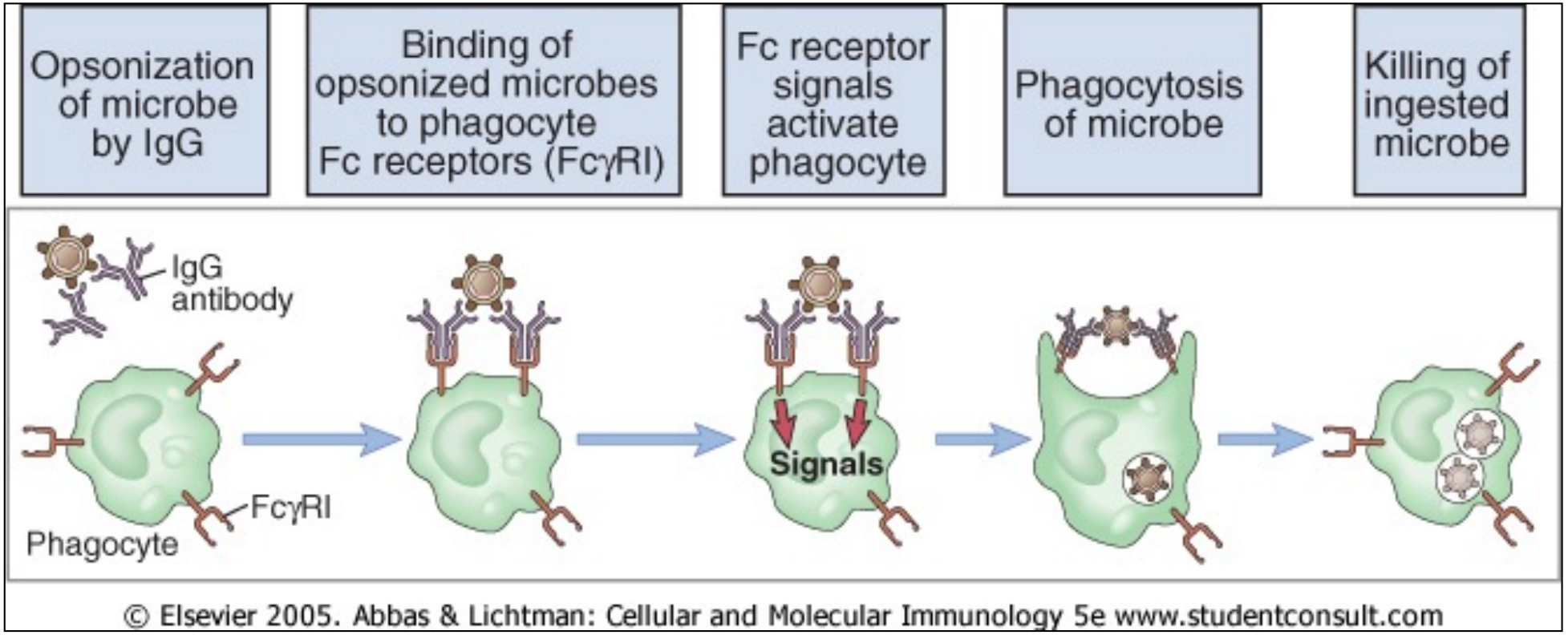
Receptor	FcγRI (CD64)	FcγRII-A (CD32)	FcγRII-B2 (CD32)	FcγRII-B1 (CD32)	FcγRIII (CD16)
Structure	α 72 kDa, γ	α 40 kDa, γ-like domain	ITIM	ITIM	α 50–70 kDa or, γ or ζ
Binding	IgG1	IgG1	IgG1	IgG1	IgG1
	10^8 M^{-1}	2×10^6 M^{-1}	2×10^6 M^{-1}	2×10^6 M^{-1}	5×10^5 M^{-1}
Order of affinity	1) IgG1=IgG3 2) 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
Cell type	Macrophages Neutrophils Eosinophils	Macrophages Neutrophils Eosinophils Platelets Langerhans cells	Macrophages Neutrophils Eosinophils	B cells Mast cells	NK cells Eosinophils Macrophages Neutrophils Mast 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)



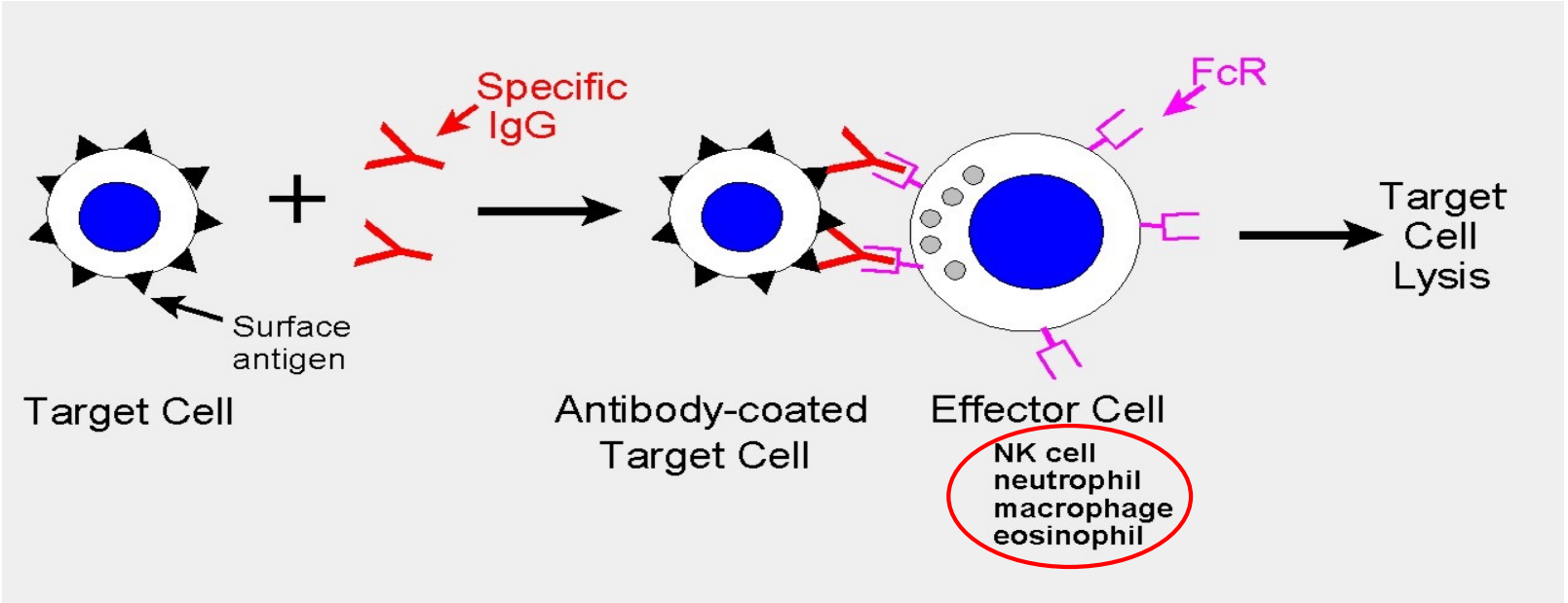
Fcγ receptors activators and inhibitors



IgG antibodies are potent opsonins: they enhance the phagocytosis of extracellular pathogens because they are recognized by activating Fcγ receptors



IgG antibodies promote antibody-dependent cellular cytotoxicity (ADCC) by engaging activatory Fcγ receptors



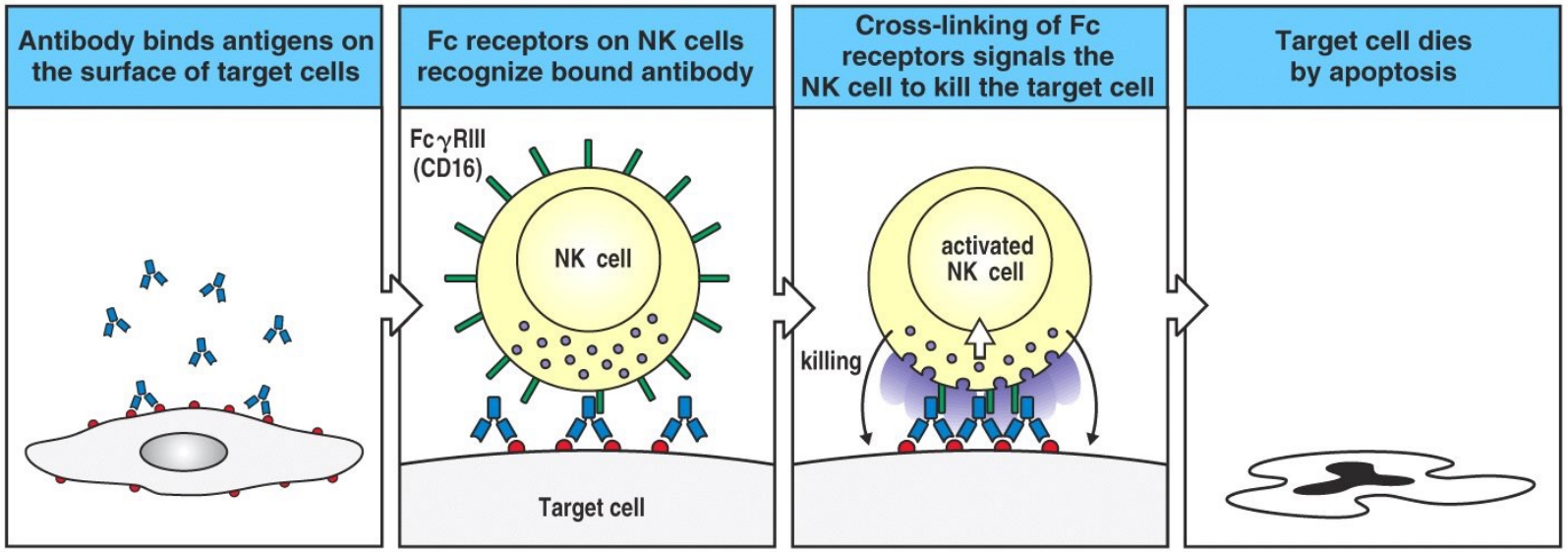
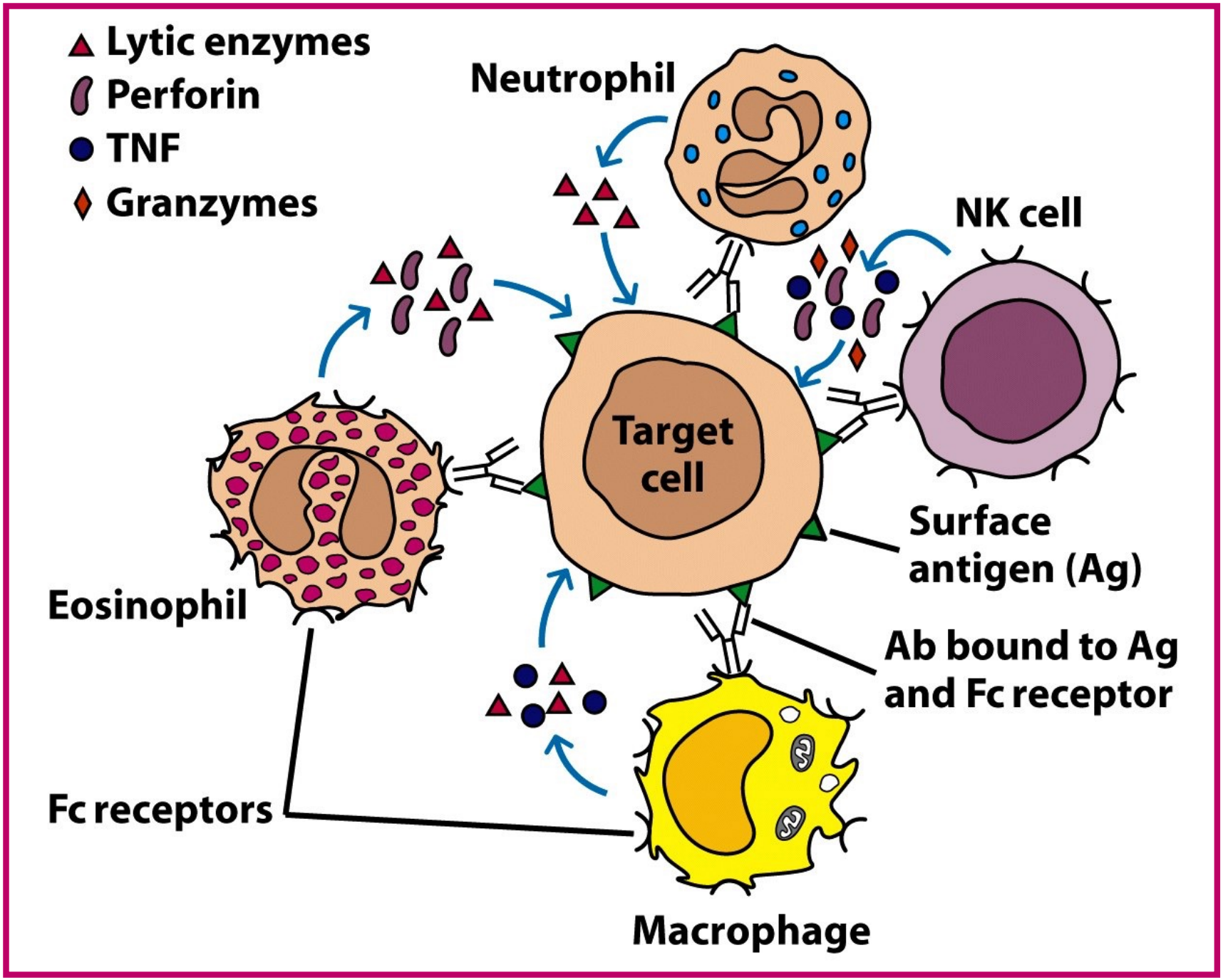
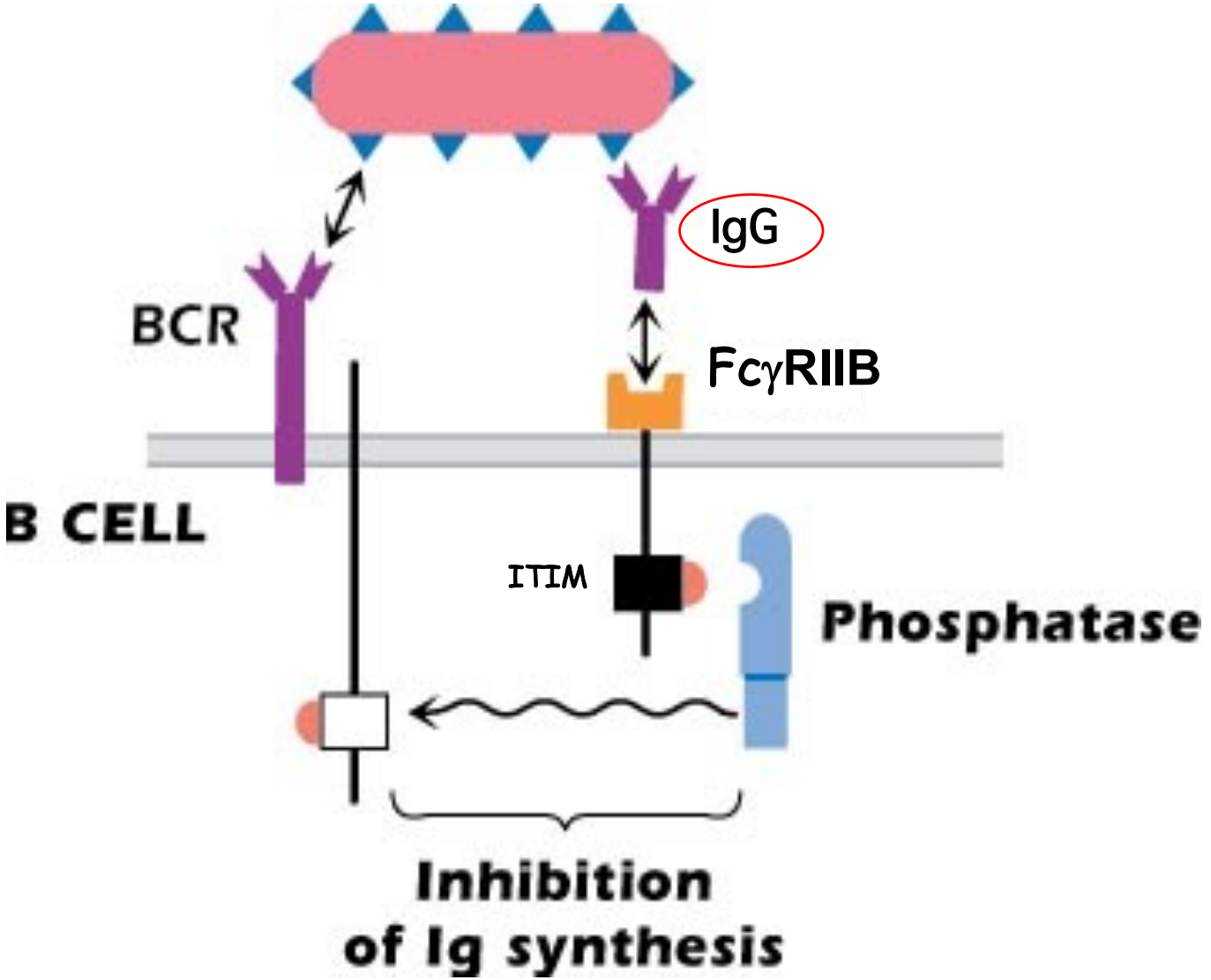


Figure 9-34 Immunobiology, 6/e. (© Garland Science 2005)

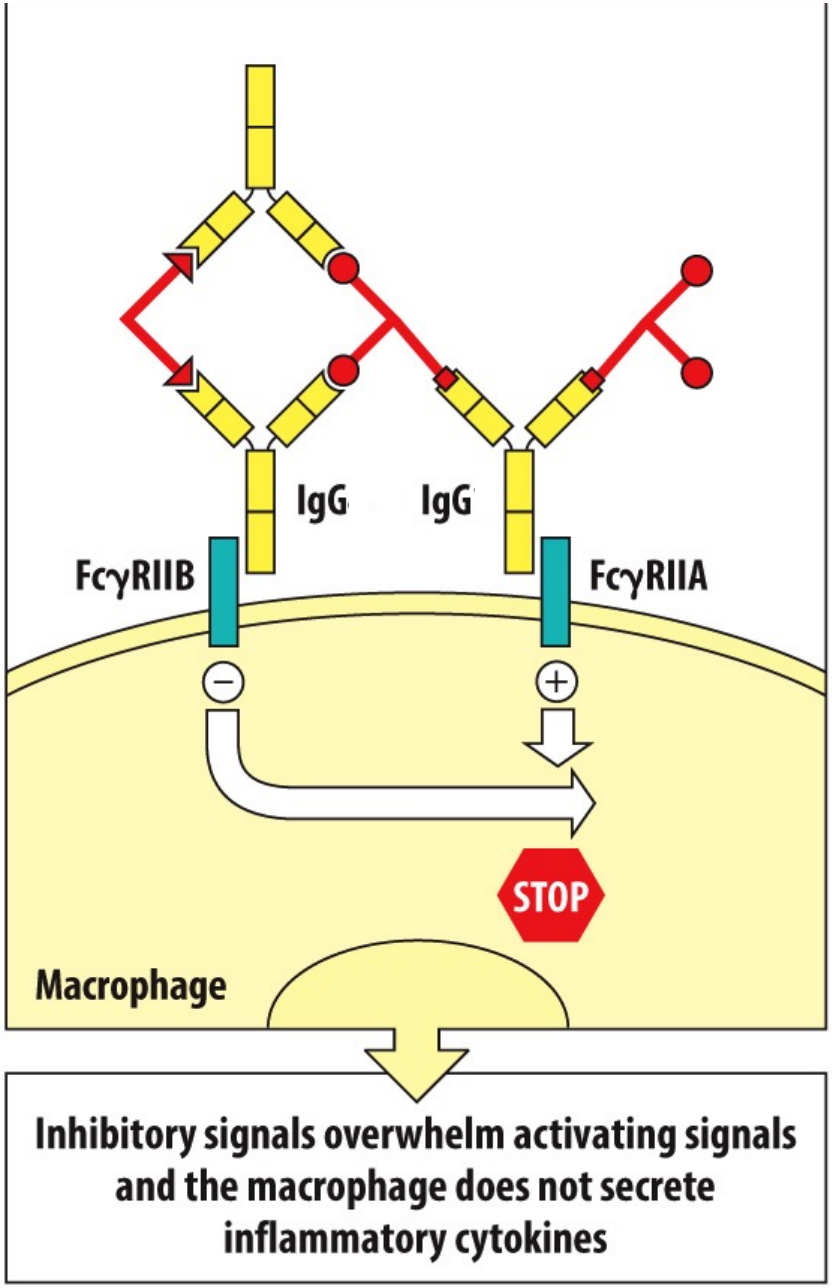
Many innate cell populations are capable of ADCC



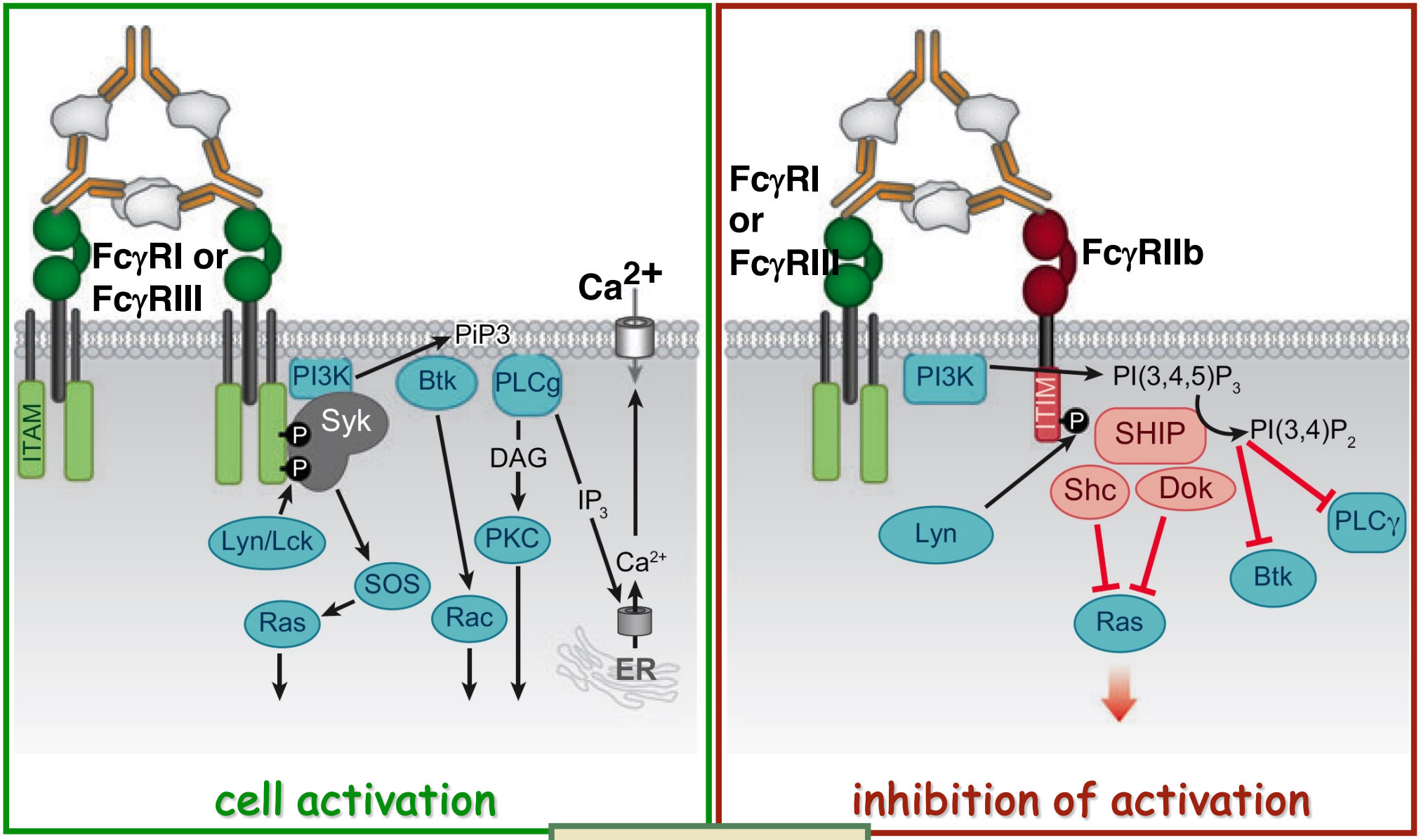
IgG contributes to the suppression of the signal transduced by the BCR by engaging the inhibitory Fcγ receptor



In macrophages, the FcγRIIB receptor blocks the signal transduced by the activating counterpart



Activating and inhibitory Fcγ receptors set a threshold for immune effector cell activation by immune complexes

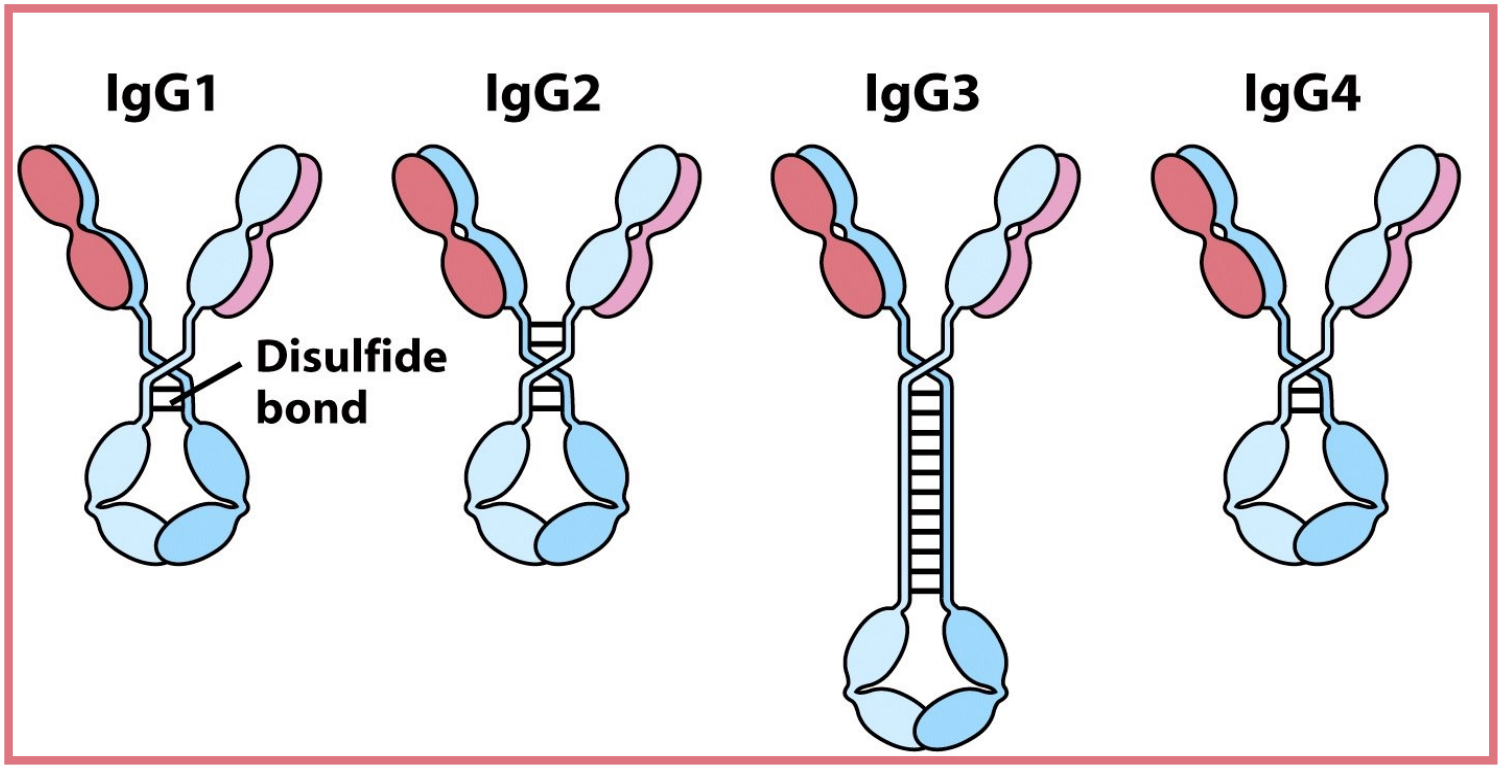


MΦ, DC, PMN

Which factors modulate the pro-inflammatory vs anti-inflammatory function of IgG-containing immune complexes?

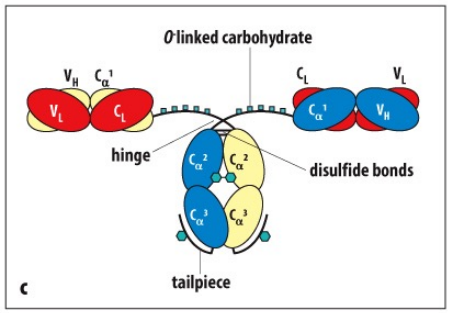
- Expression of activating and inhibitory Fc receptors
- Functional polymorphisms of Fcγ receptors
- Differential binding ability of IgG subclasses
- Post-translational modifications of IgG

Functions of IgG subclasses



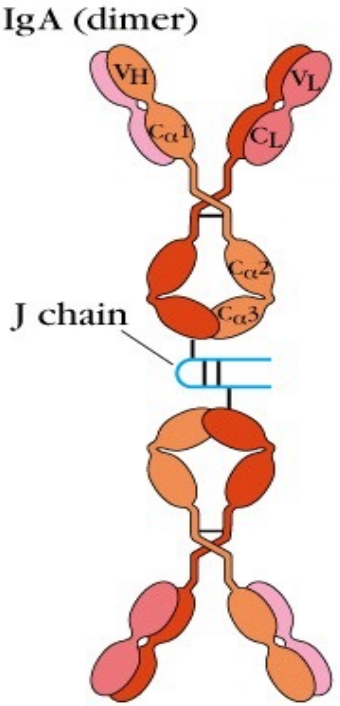
+++	+	++	+/-	Transport across placenta
++	+	+++	-	Complement activation
++	+/-	++	+	Binding to Fc receptors

IgA



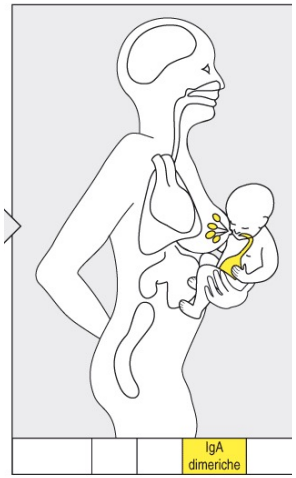
IgA can form monomers (blood), and dimers (mucosal tissues).body

The dimer is stabilized by the presence of an additional invariant chain, the J chain.

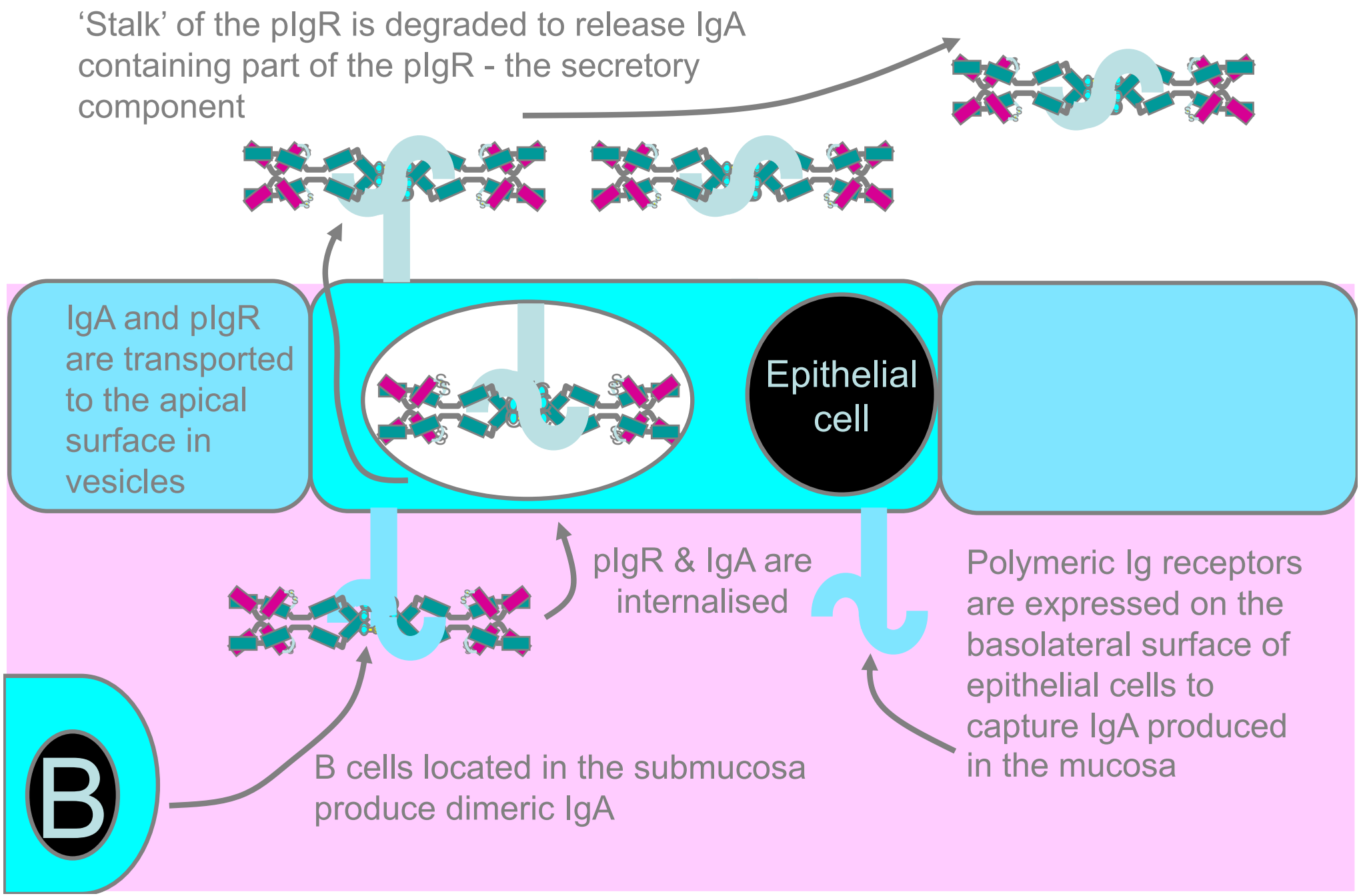


IgA can be found in circulation but is the major isotype found in secretions such as mucus in gut, milk from mammary glands, tears, and saliva.

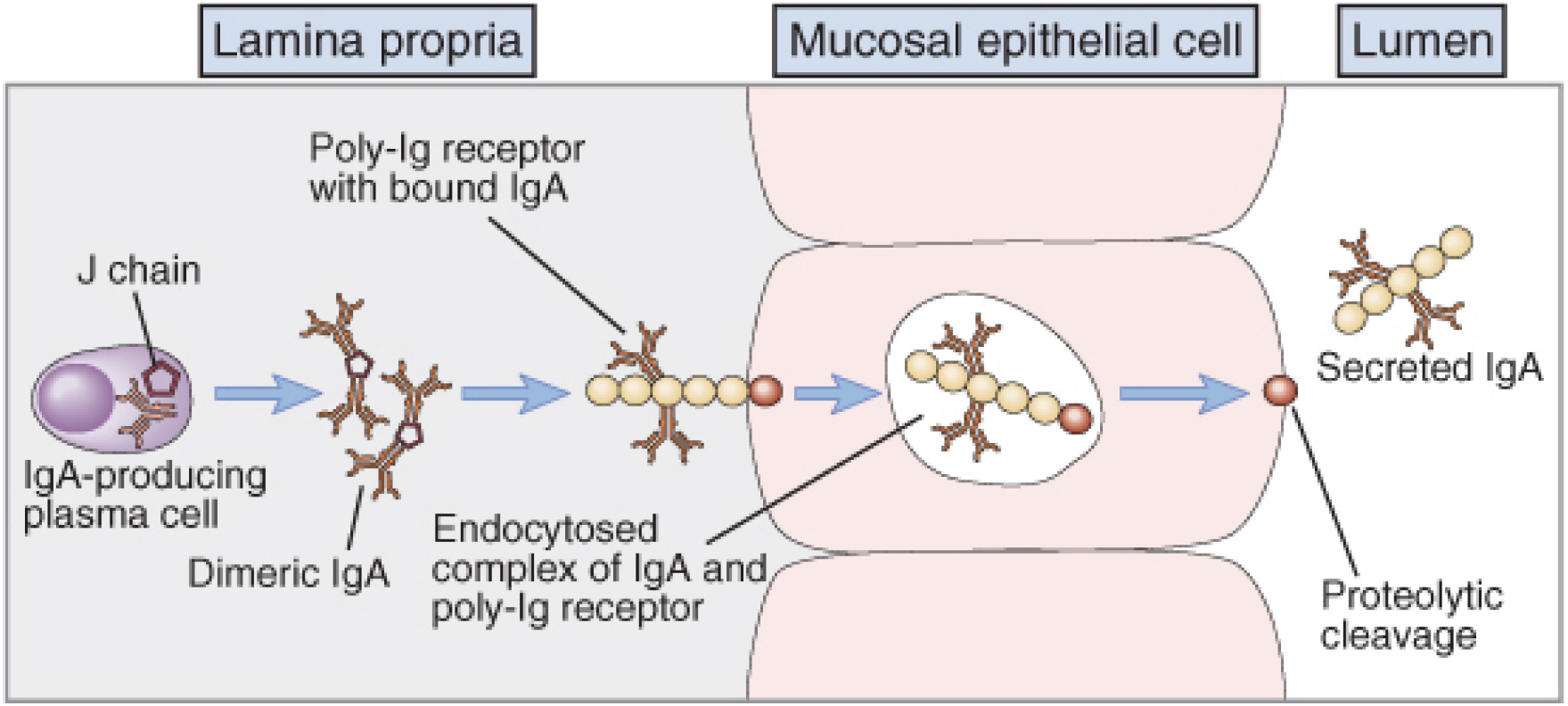
- IgA1 is more prevalent in serum (90%);
- IgA2 is more prevalent in secretions.

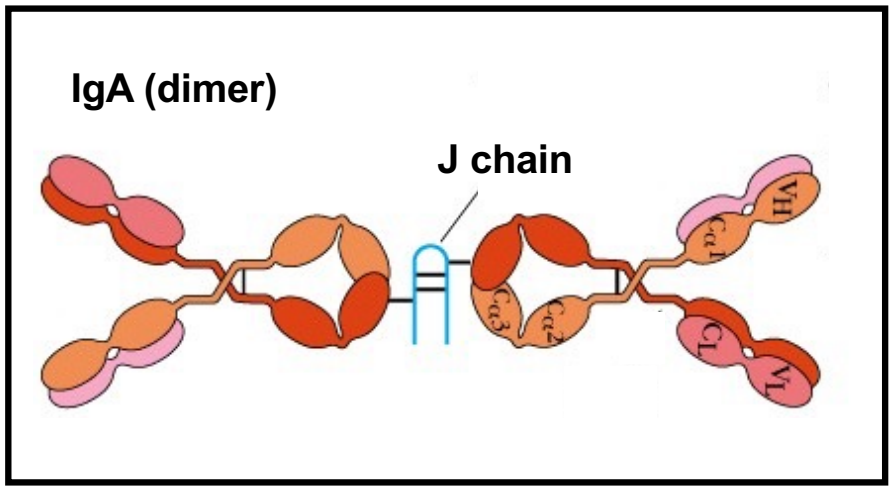


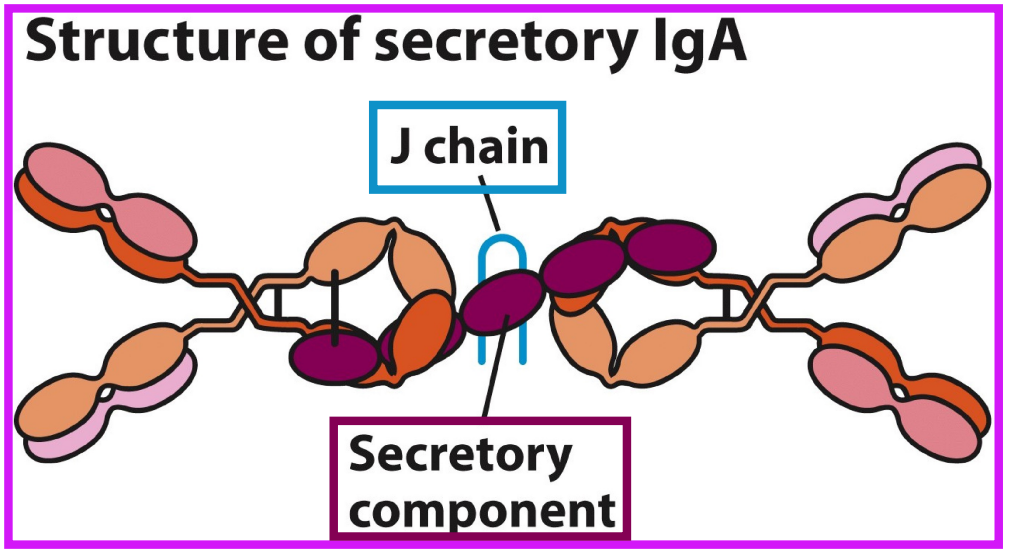
A specific transport mechanism for secretory IgA



A specific transport mechanism for secretory IgA







IgA Functions

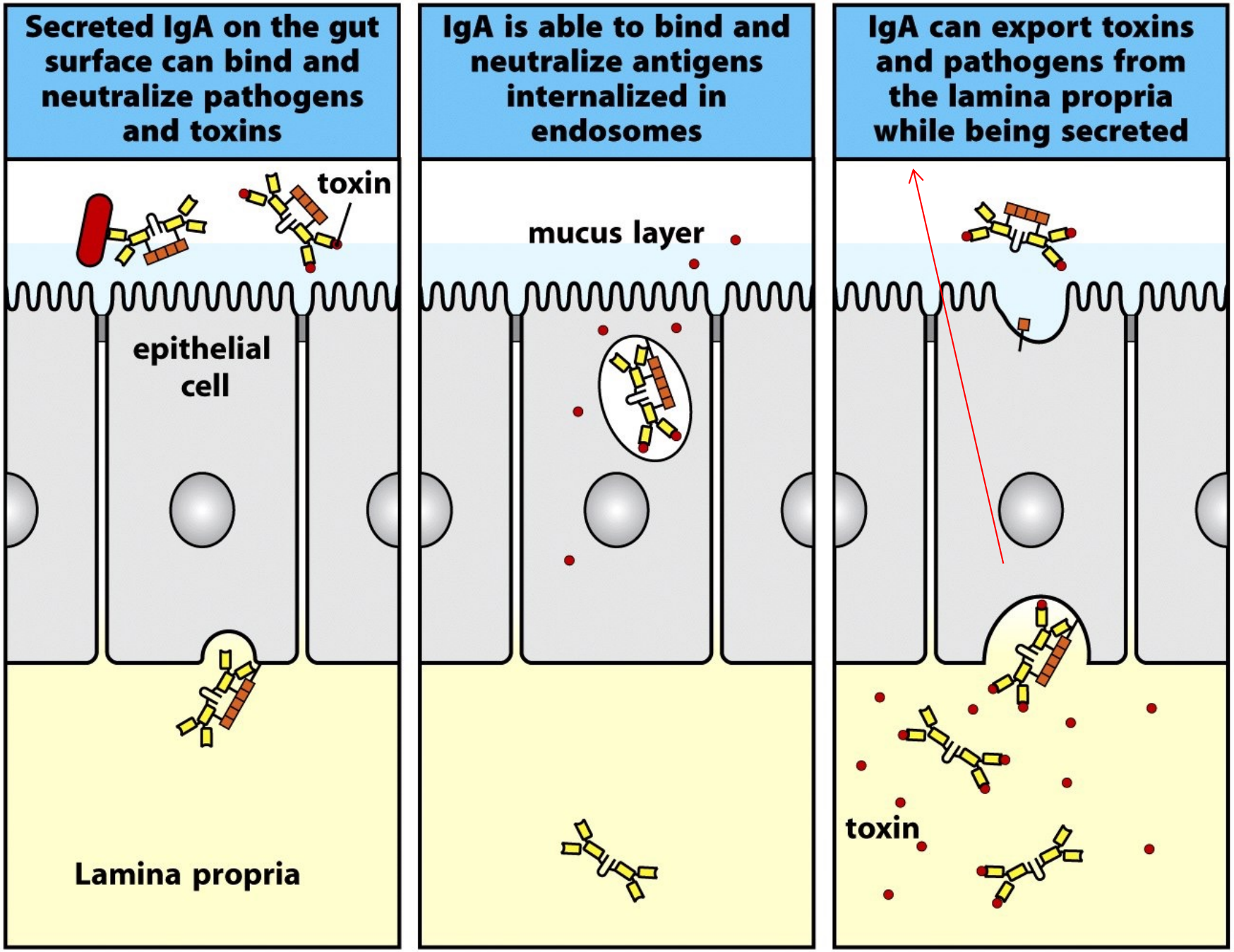
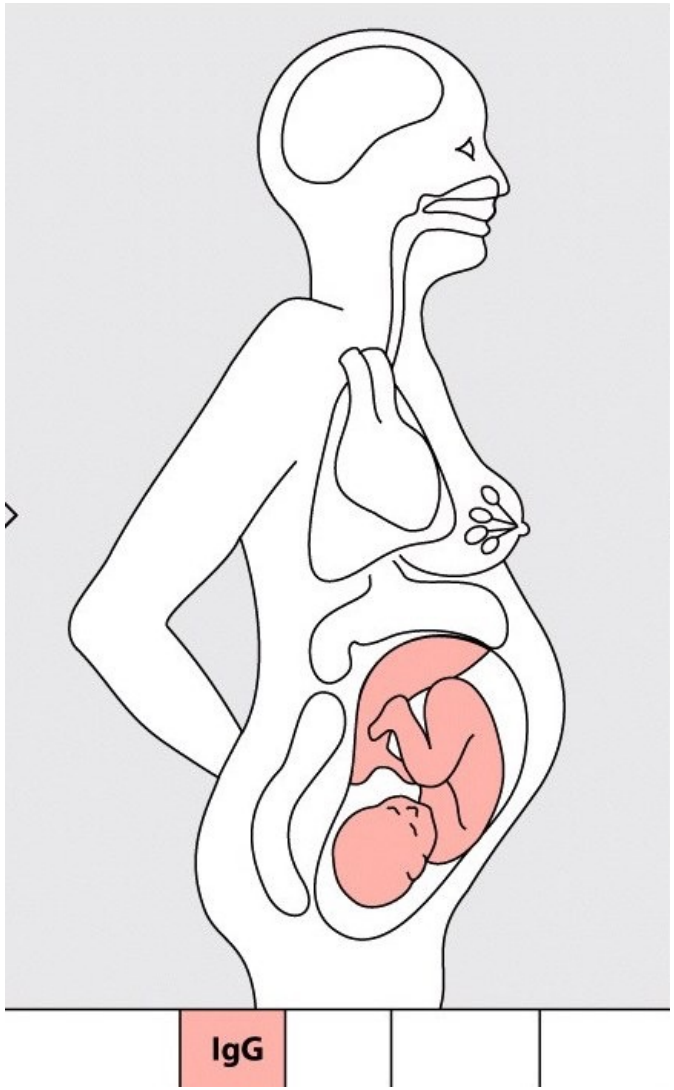


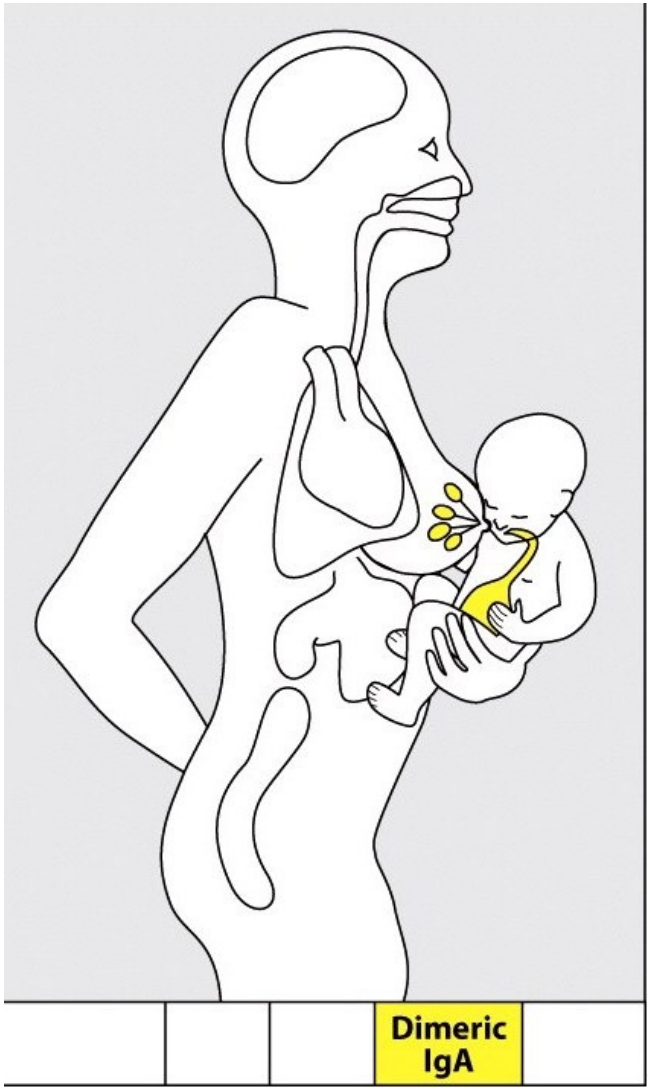
Figure 11-15 Immunobiology, 7ed. (© Garland Science 2008)

Neonatal humoral immunity

Antibodies can

6. **Cross the human placenta** from mother to fetus (IgG only)
7. Dimeric IgA also found in **breast milk** -> GI tract of a nursing infant





IgM

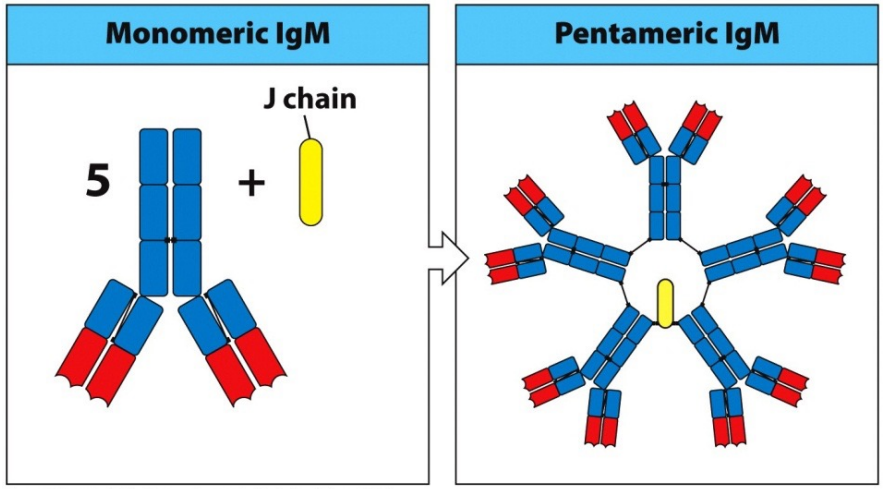
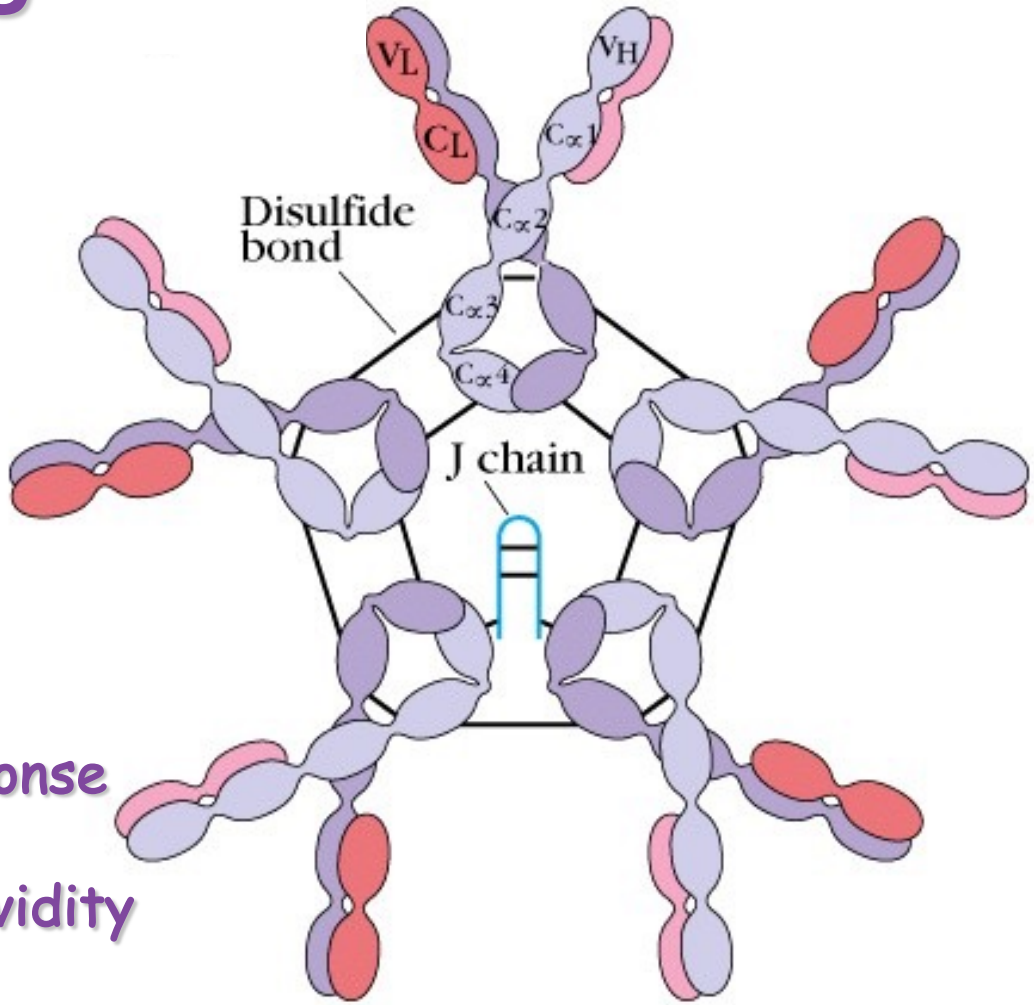


Figure 4.29 part 1 of 2 The Immune System, 3ed. (© Garland Science 2009)

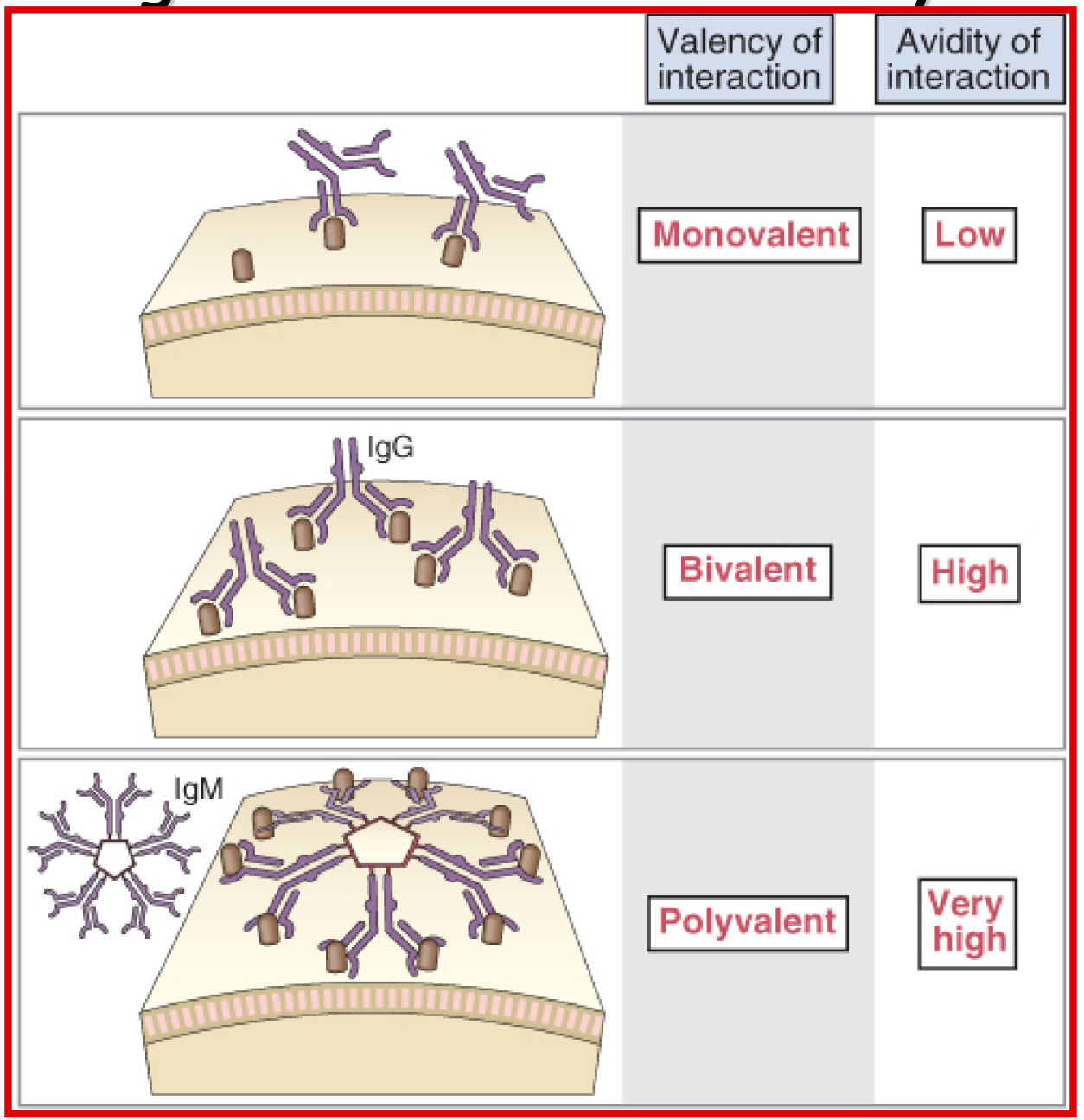


Effector functions:

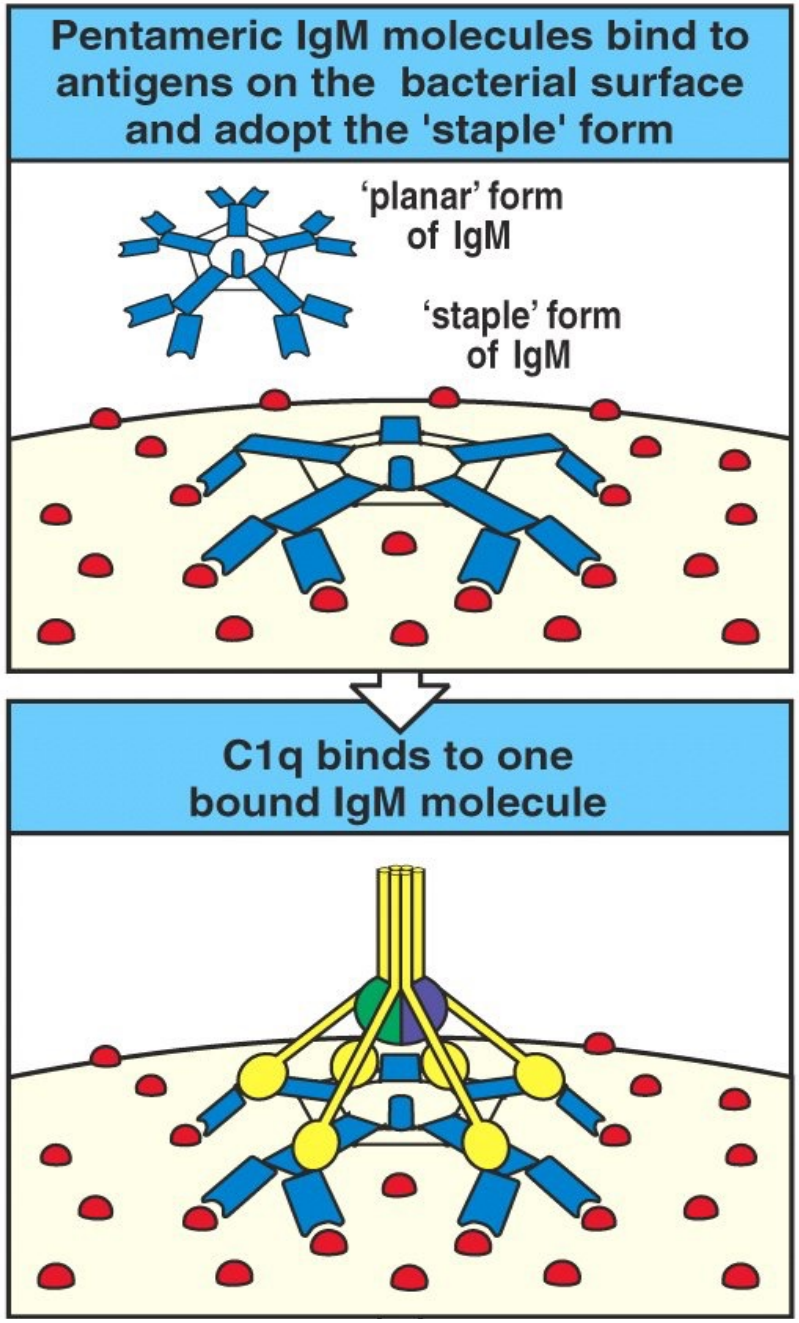
- first Ab produced in a primary response
- tend to be lower affinity but high avidity
- pentavalent (10 total Ag-binding sites)
- many are "natural antibodies" from B-1 B cells
- very good at complement fixation leading to target lysis

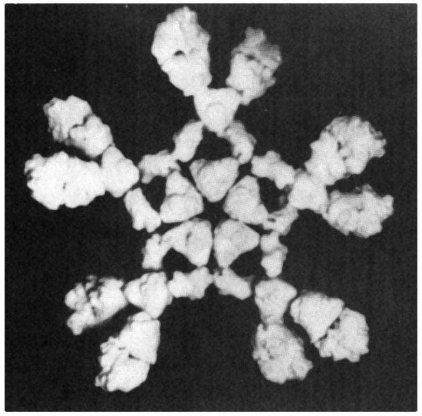
Avidity: The <u>overall strength</u> of binding between a multivalent Antigen and a whole Antibody

Affinity ≠ Avidity

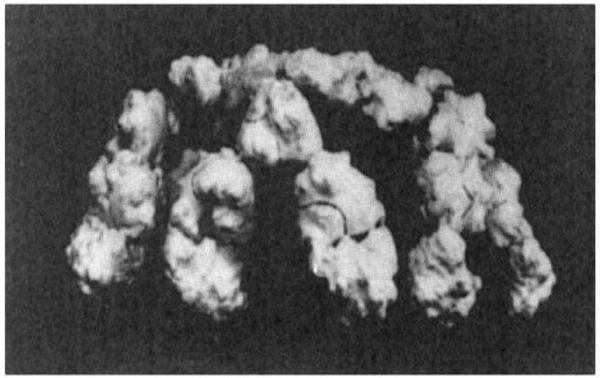


Binding to antigen changes the conformation of IgM





Free IgM has a planar conformation and is unable to fix complement



Binding to the antigen induces a conformational change that makes the constant portion accessible

Complexed IgM binds to the complement component C1q, activating it

IgM complexed to the antigen activates the classical complement pathway

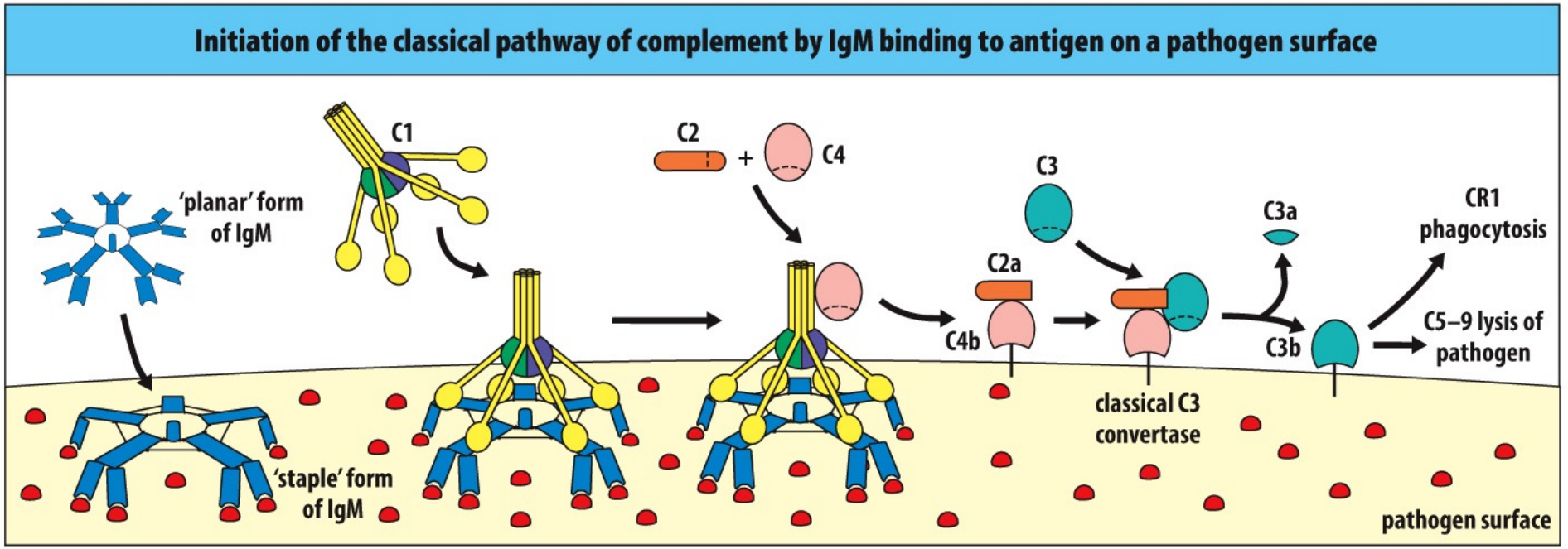
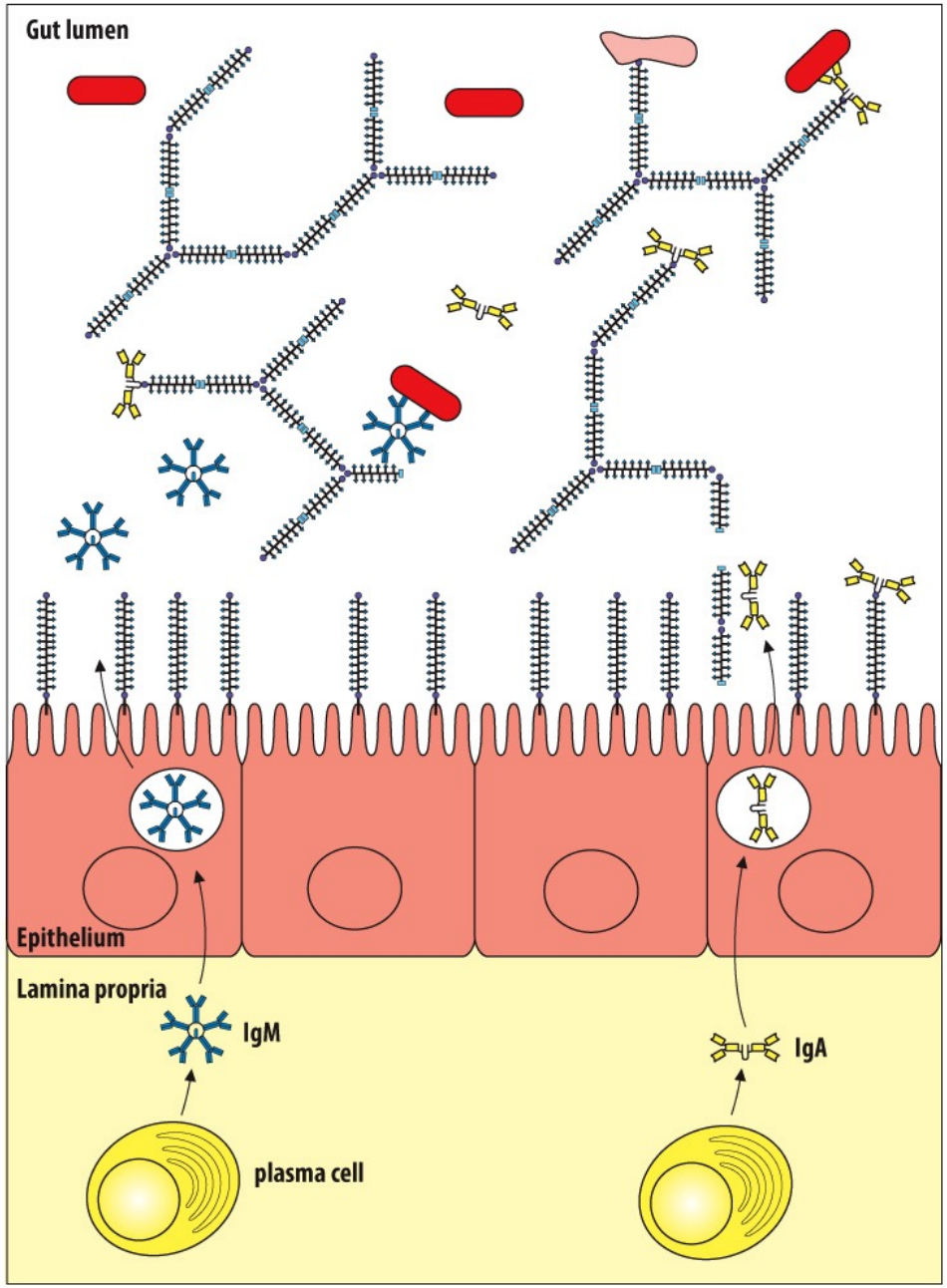
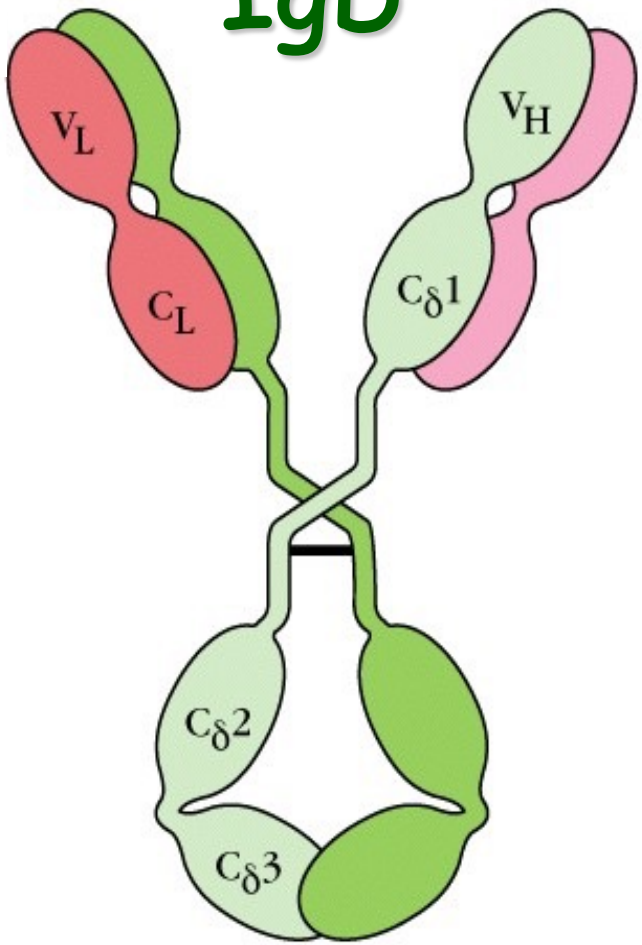


Figure 9.28 The Immune System, 4th ed. (© Garland Science 2015)

Secretory IgM protects together with IgA mucosal surfaces from microbial invasion

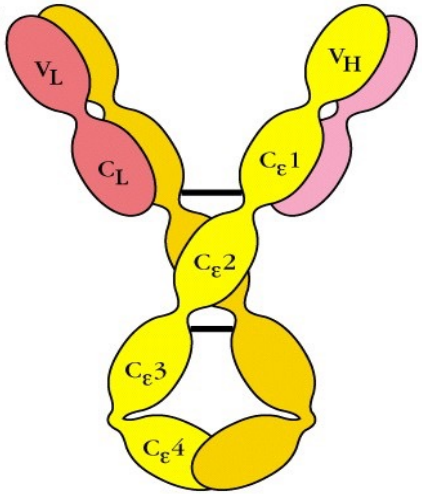


IgD



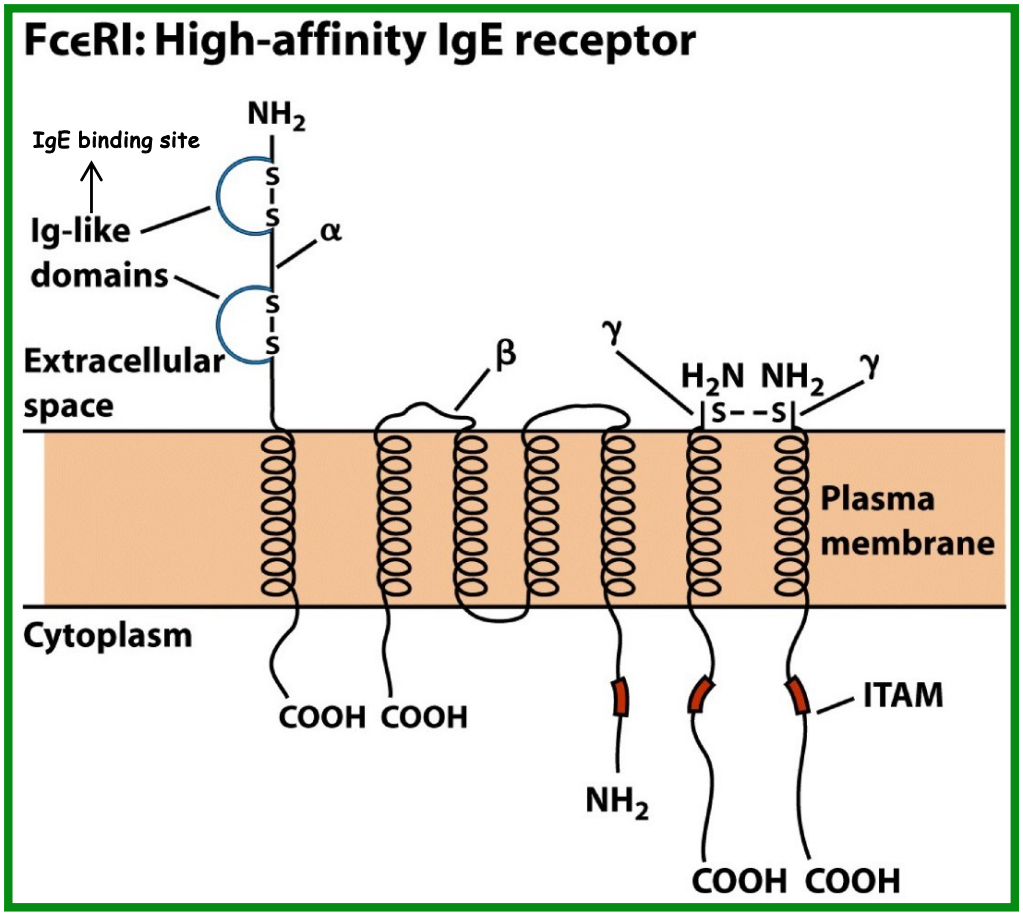
•IgD is a minor component of blood but is present at higher levels in secretions of the upper respiratory tract.

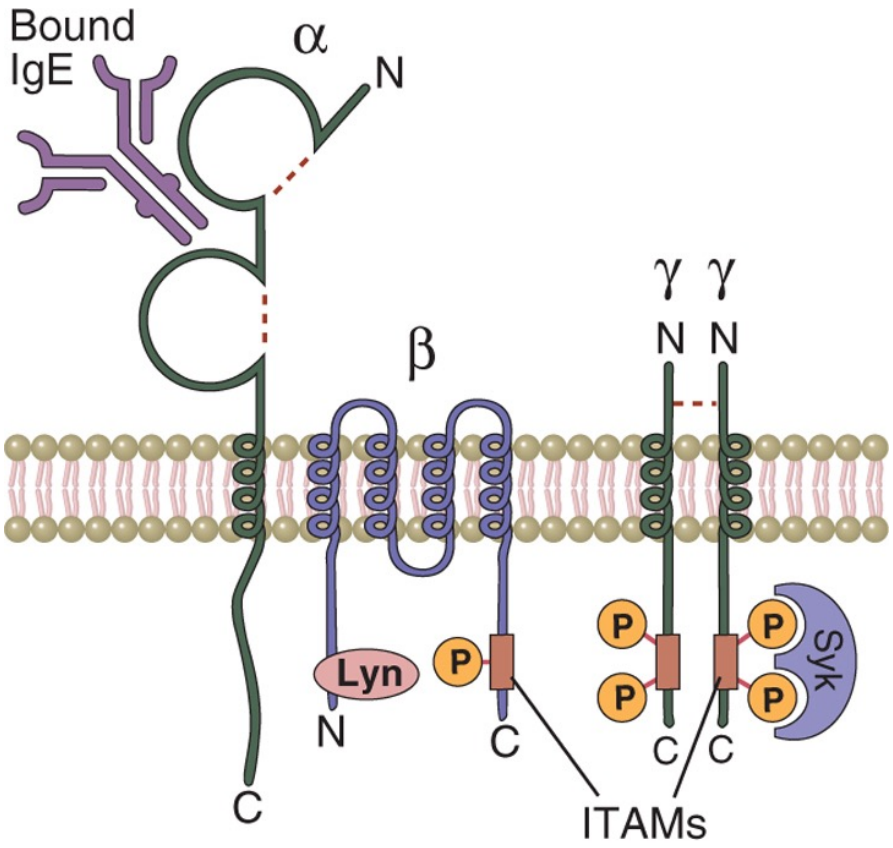
IgE



- IgE is best known for its role in allergy and asthma.
- IgE play a role in protection against parasitic helminths (worms), protozoa, and venoms.
- It is made in very small quantities but induces potent effects upon binding on FcεR

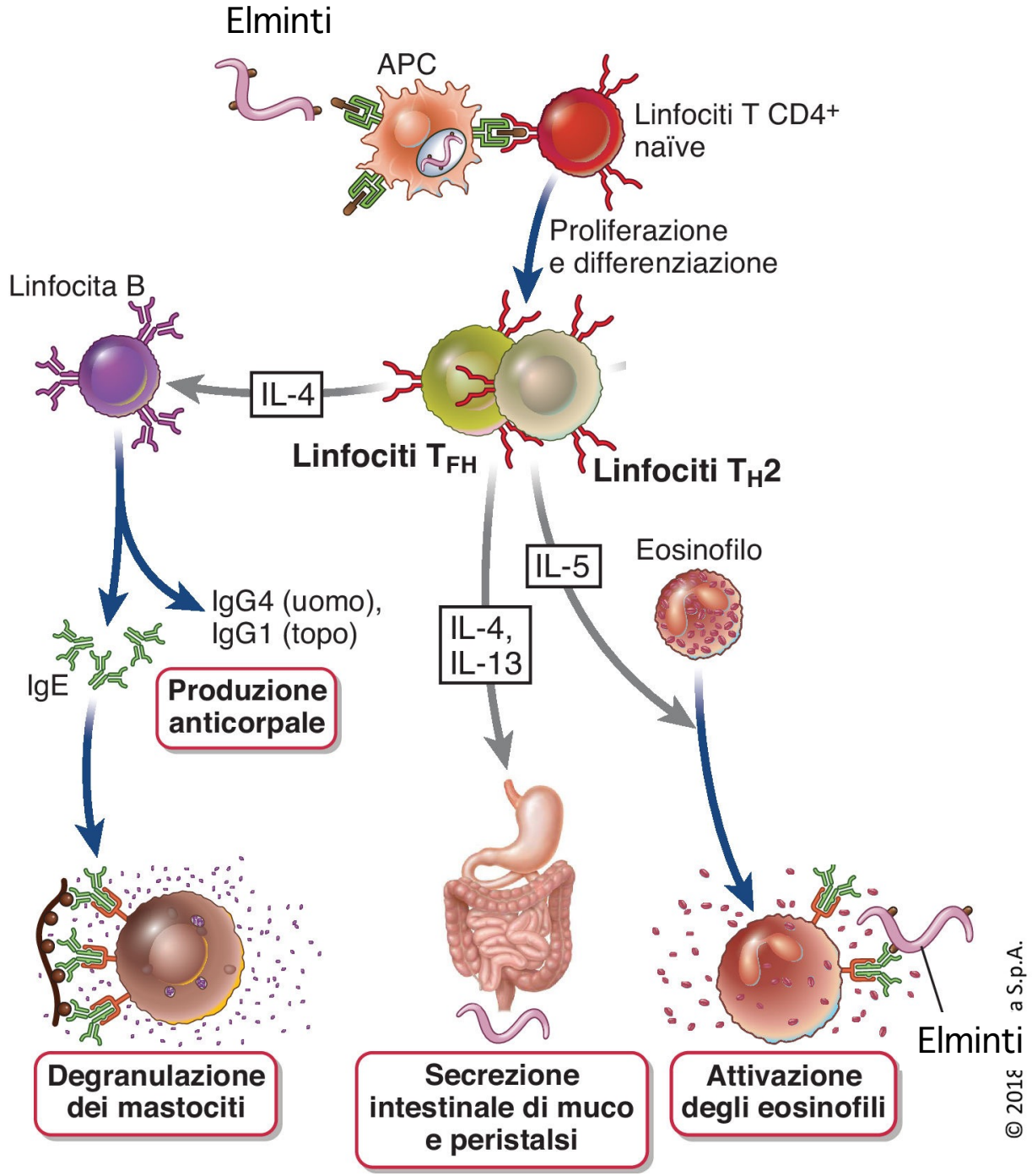
The high affinity receptor for IgE



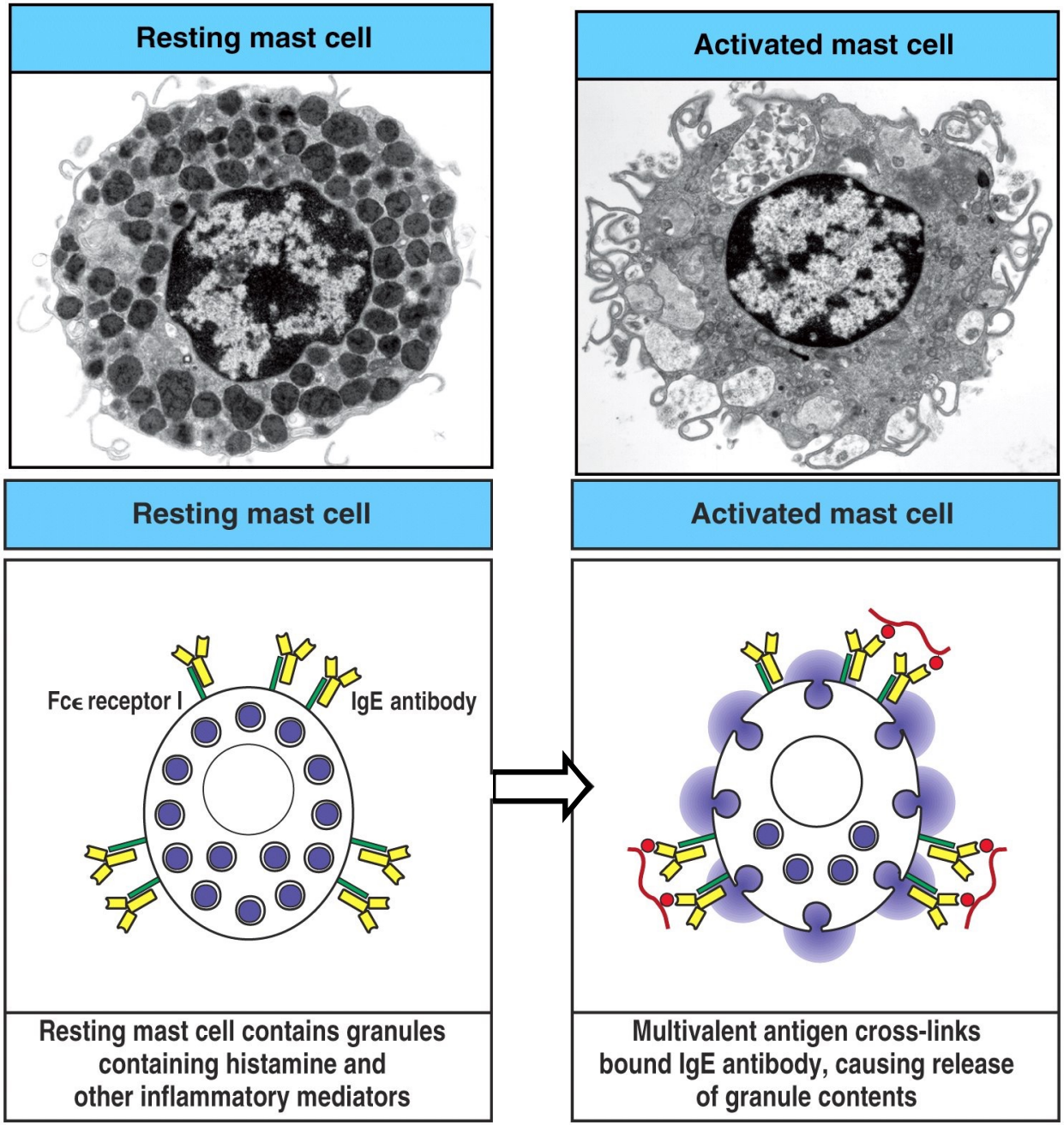


Mast cells, basophils,
eosinophils (low levels),
Langerhans cells,
activated monocytes.

Effector functions in helmint infections

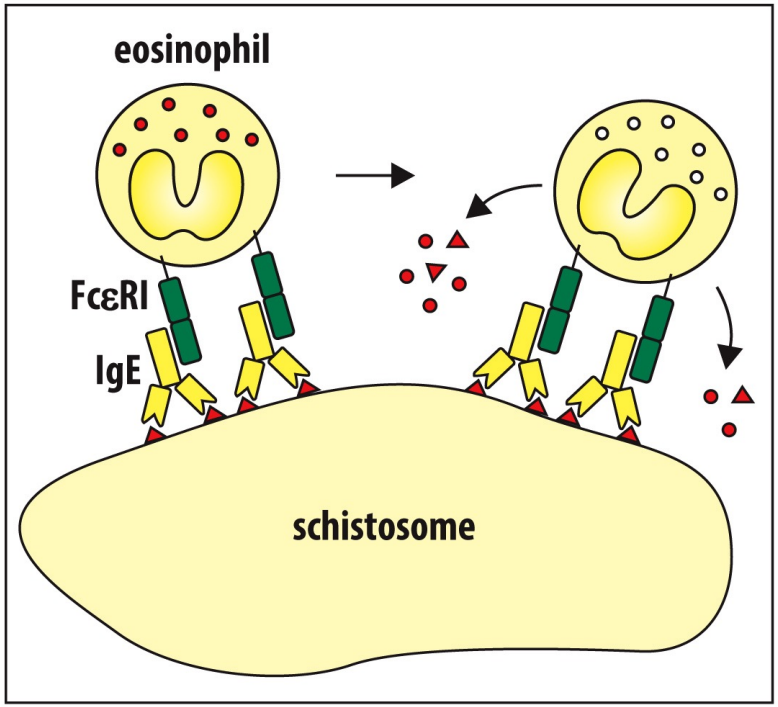


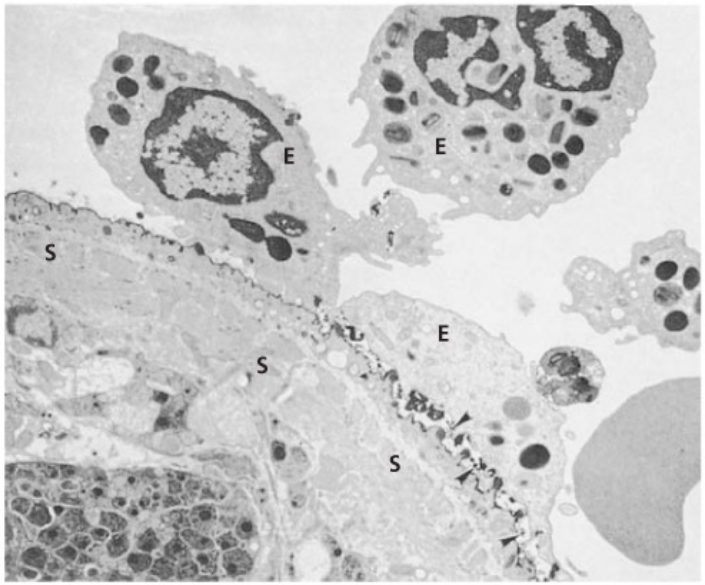
IgE antibody cross-linking on mast cell leads to a rapid relese of pro-inflammatory mediators

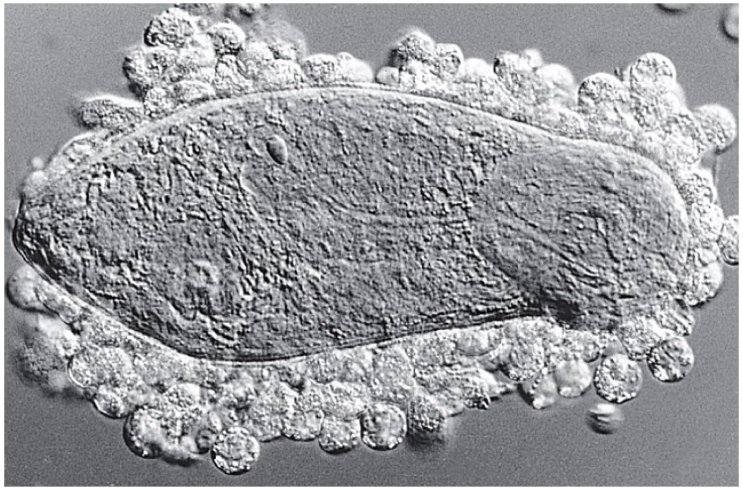


IgE provides a mechanism for the rapid ejection of parasites

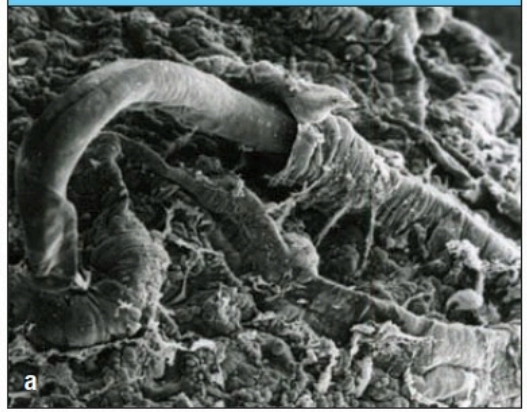
Fcε receptors expressed on eosinophils promote antibody-dependent cellular cytotoxicity (ADCC)







The whipworm *Trichuris trichiura* embeds in the surface epithelium of the colon, leaving its posterior free in the lumen

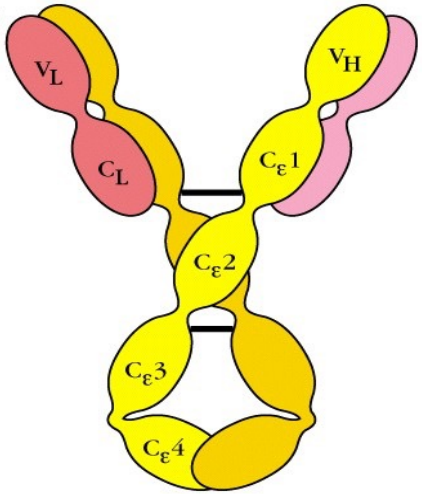


The different Ig isotypes can perform different effector functions

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

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

IgE



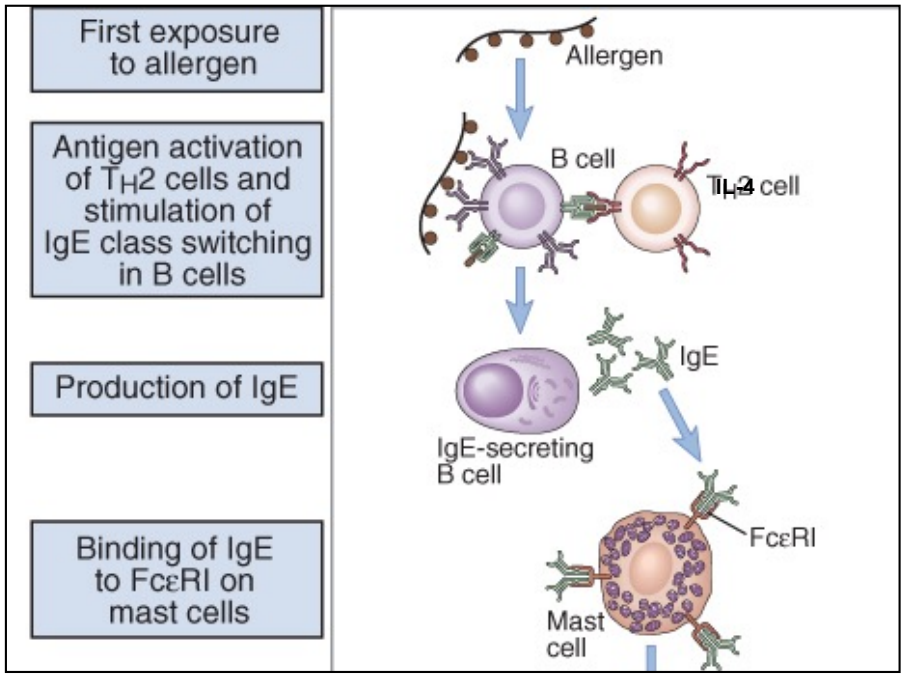
- **IgE and its role in allergy and asthma.**

- IgE play a role in protection against parasitic helminths (worms), protozoa, and venoms.

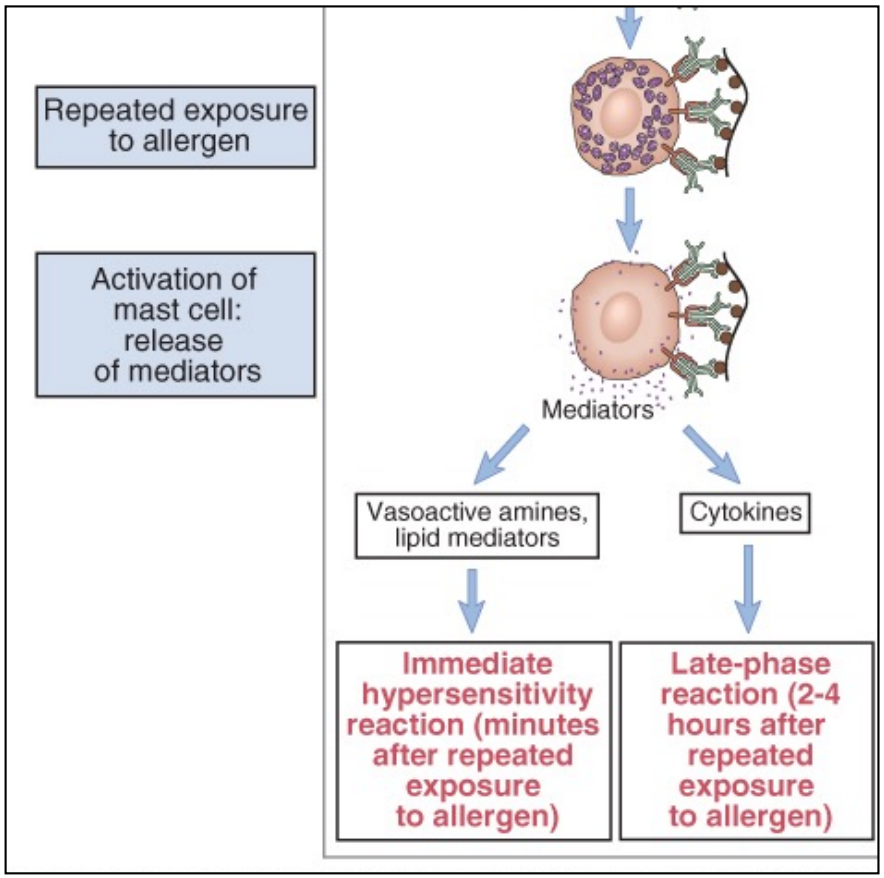
- It is made in very small quantities but induces potent effects upon binding on FcεR

The allergic reaction: an integrated view

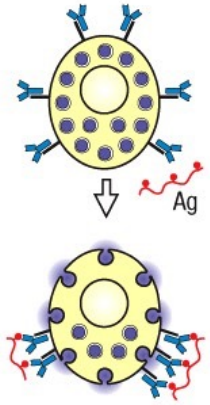
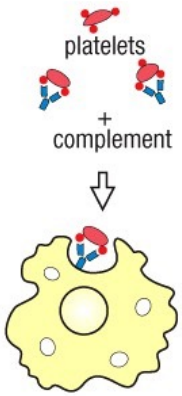
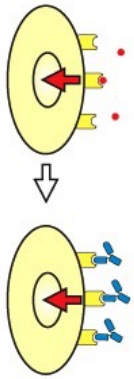
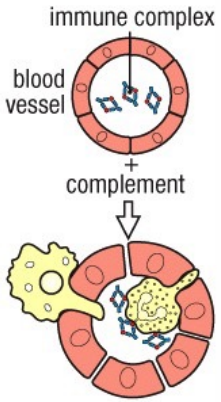
1 Sensitization phase



2 triggering phase



Antibodies are responsible for some hypersensitivity reactions

	Type I	Type II		Type III
Immune reactant	IgE	IgG		IgG
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Cell-surface receptor	Soluble antigen
Effector mechanism	Mast-cell activation	Complement, FcR^+ cells (phagocytes, NK cells)	Antibody alters signaling	Complement, phagocytes
				
Example of hypersensitivity reaction	Allergic rhinitis, allergic asthma, atopic eczema, systemic anaphylaxis, some drug allergies	Some drug allergies (e.g., penicillin)	Chronic urticaria (antibody against $Fc\varepsilon RI$ alpha chain)	Serum sickness, Arthus reaction