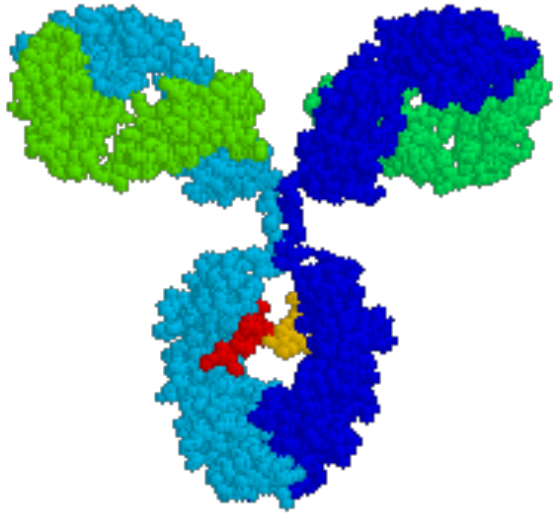
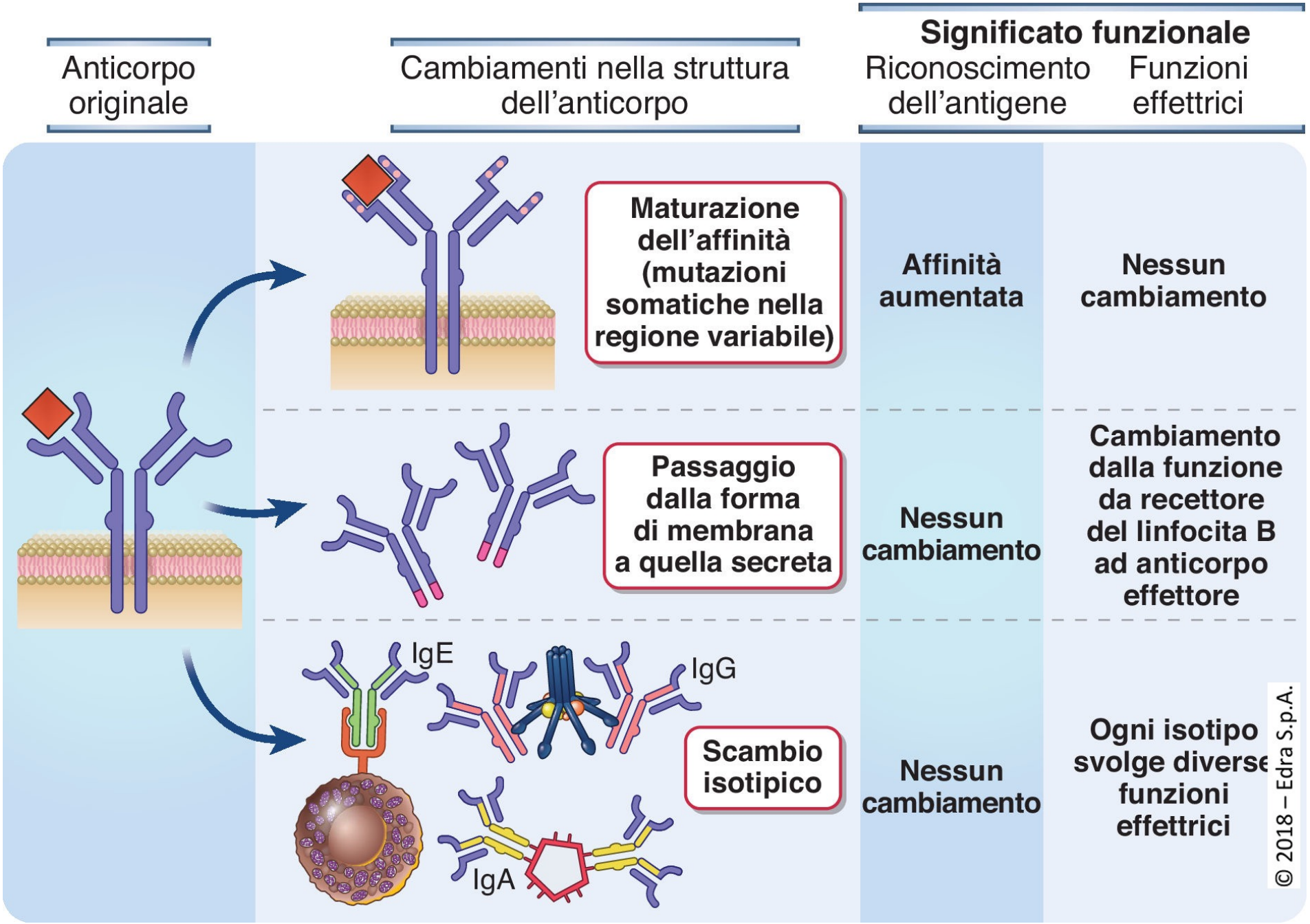
Corso di Immunologia - III anno
Prof. Paolini

Lezione 22/11/2024

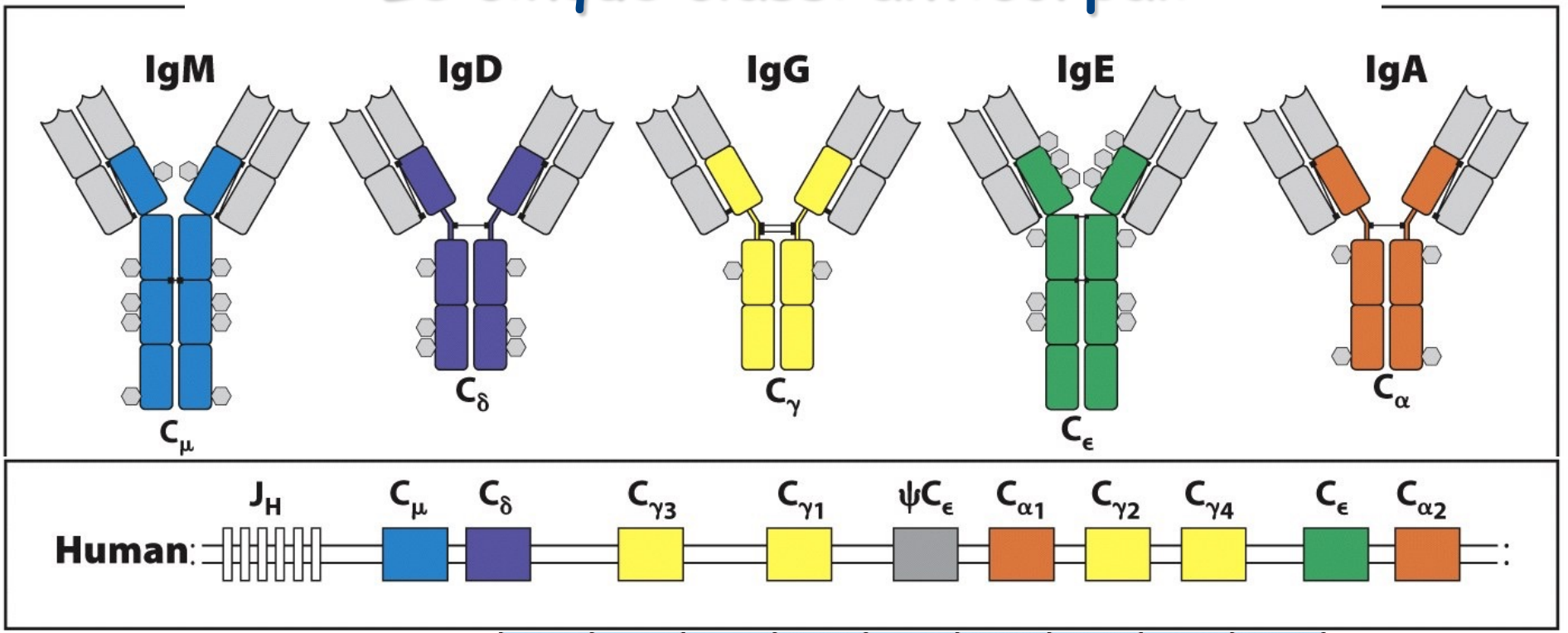
"Le funzioni effettrici degli anticorpi"



Durante la risposta umorale il recettore del linfocita B cambia



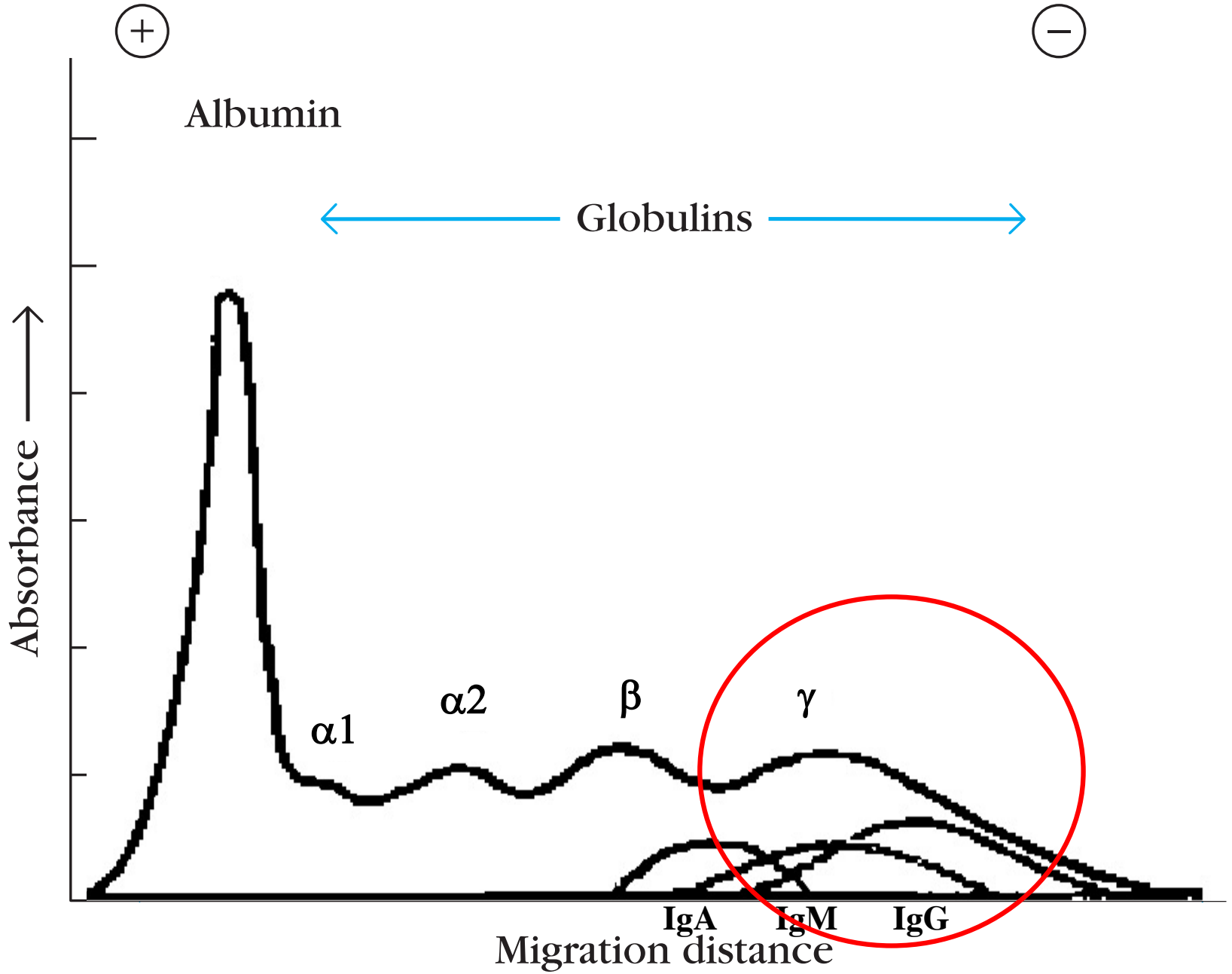
Le cinque classi anticorpali



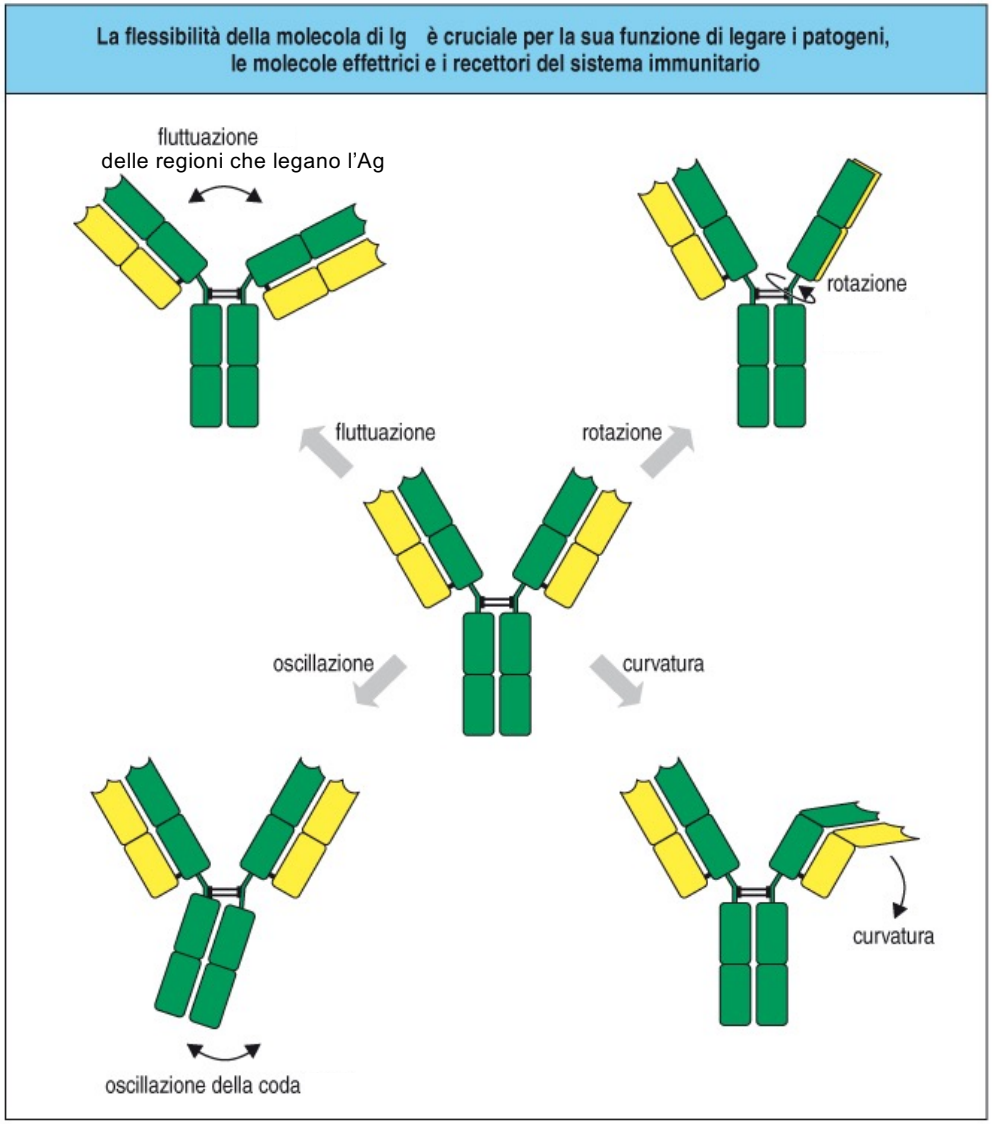
	IgG1	IgG2	IgG3	IgG4	IgM	IgA1	IgA2	IgD	IgE
Heavy chain	γ_1	γ_2	γ_3	γ_4	μ	α_1	α_2	δ	ϵ
Molecular weight (kDa)	146	146	165	146	970	160	160	184	188
Serum level (mean adult mg/ml)	9	3	1	0.5	1.5	3.0	0.5	0.03	5×10^{-5}
Half-life in serum (days)	21	20	7	21	10	6	6	3	2

Livelli sierici IgG>IgA>IgM>IgD>IgE

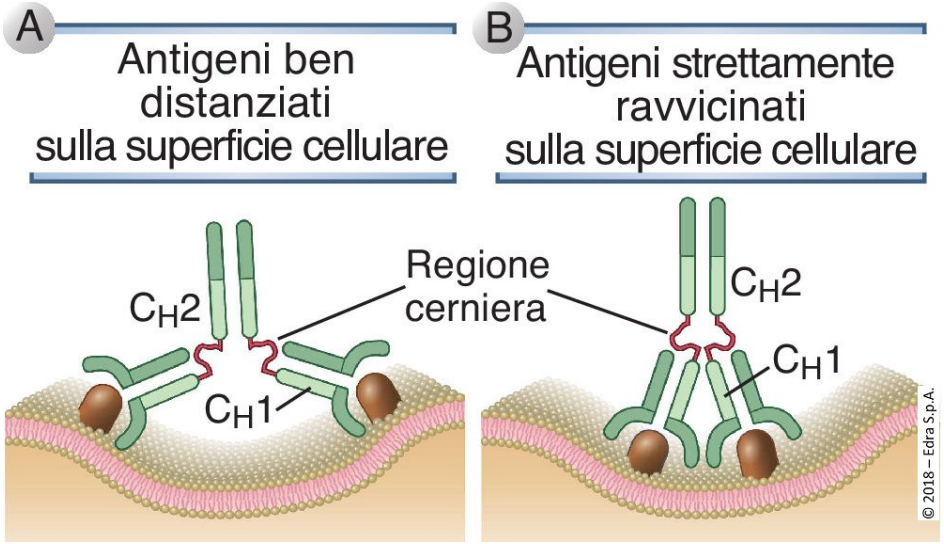
Elettroforesi delle proteine sieriche



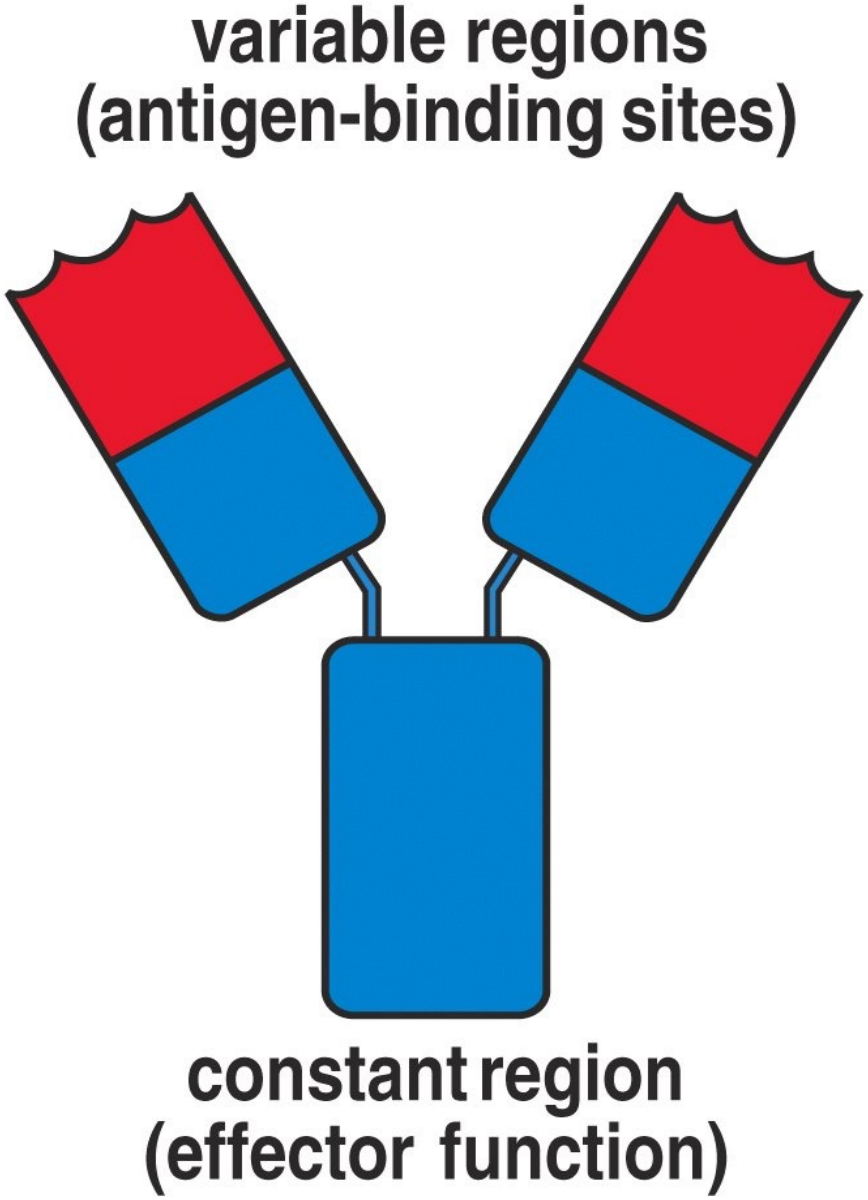
La regione cerniera conferisce flessibilità agli anticorpi…



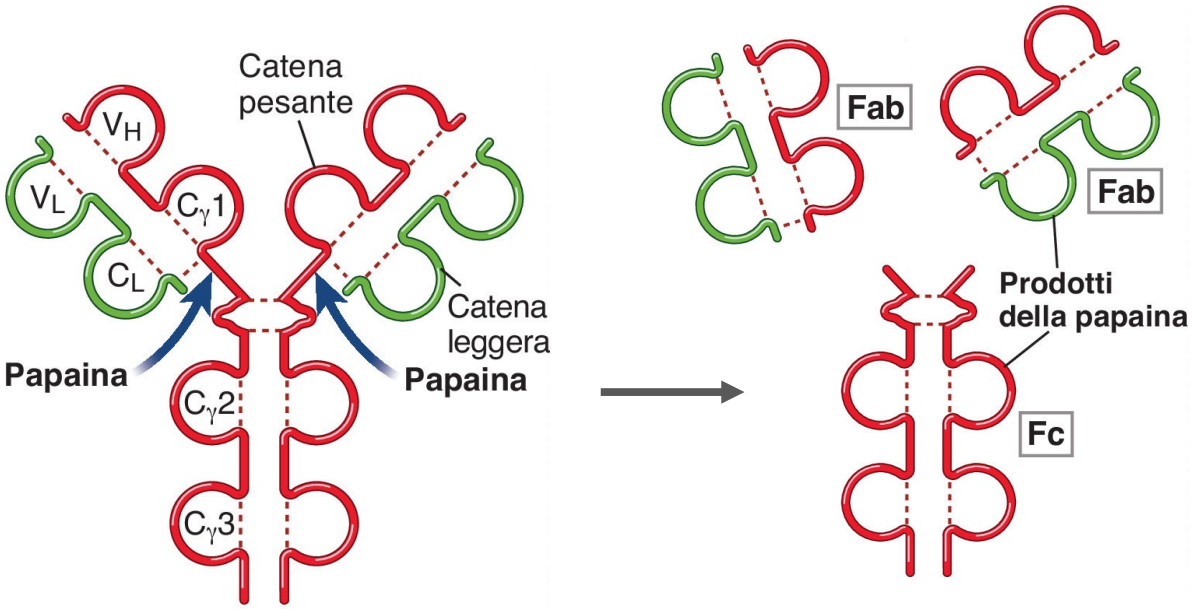
… che possono legare contemporaneamente due antigeni anche distanti tra loro



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

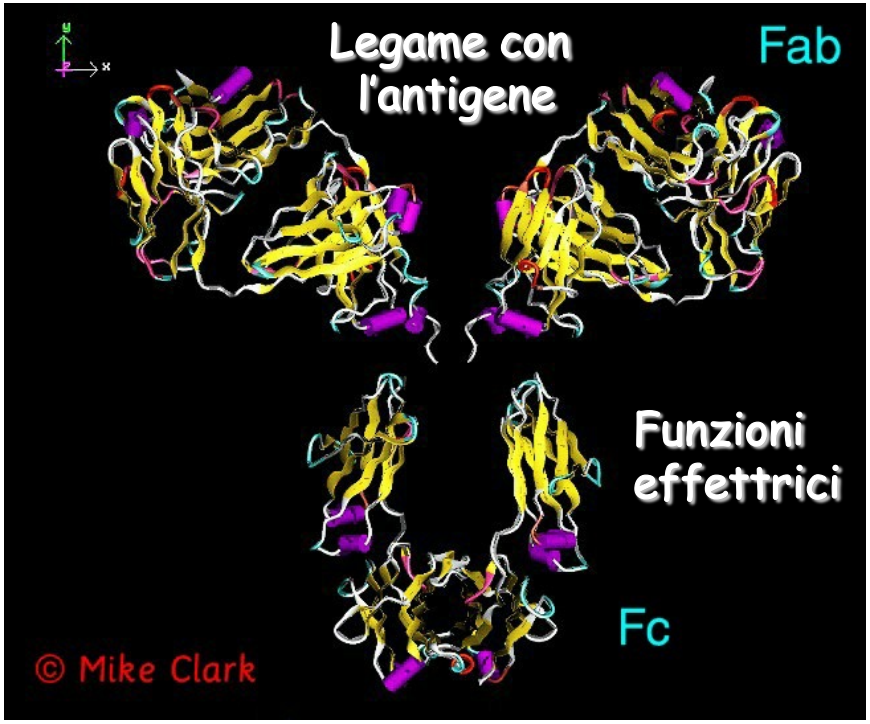


L'Ig può venire scissa in tre frammenti, due identici tra loro chiamati Fab ed un terzo frammento Fc

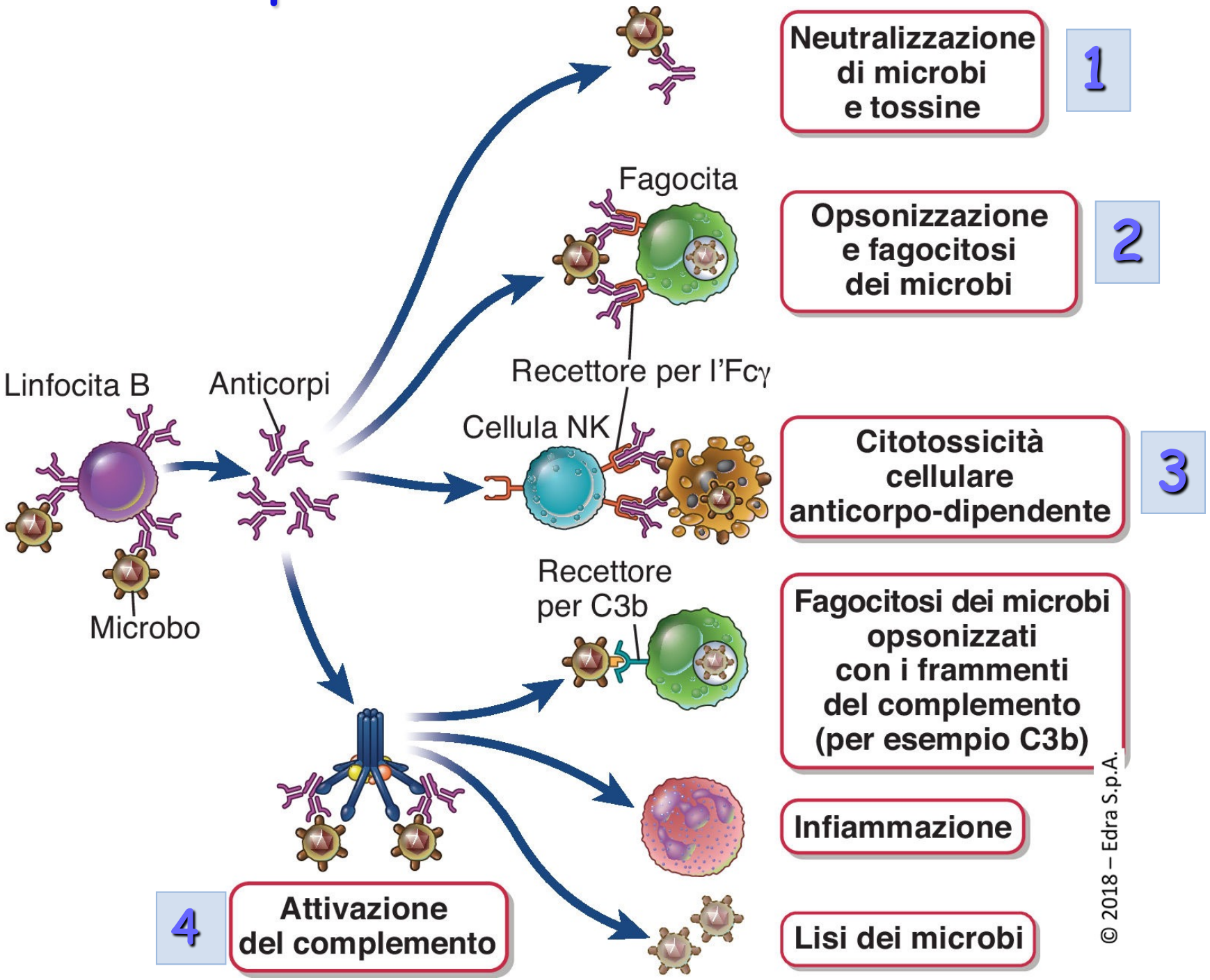


Fab = Fragment Antigen Binding

Fc = Frammento Cristallizzabile



Antibodies perform several effector functions



1. Antibodies can neutralize the infectious ability of pathogens

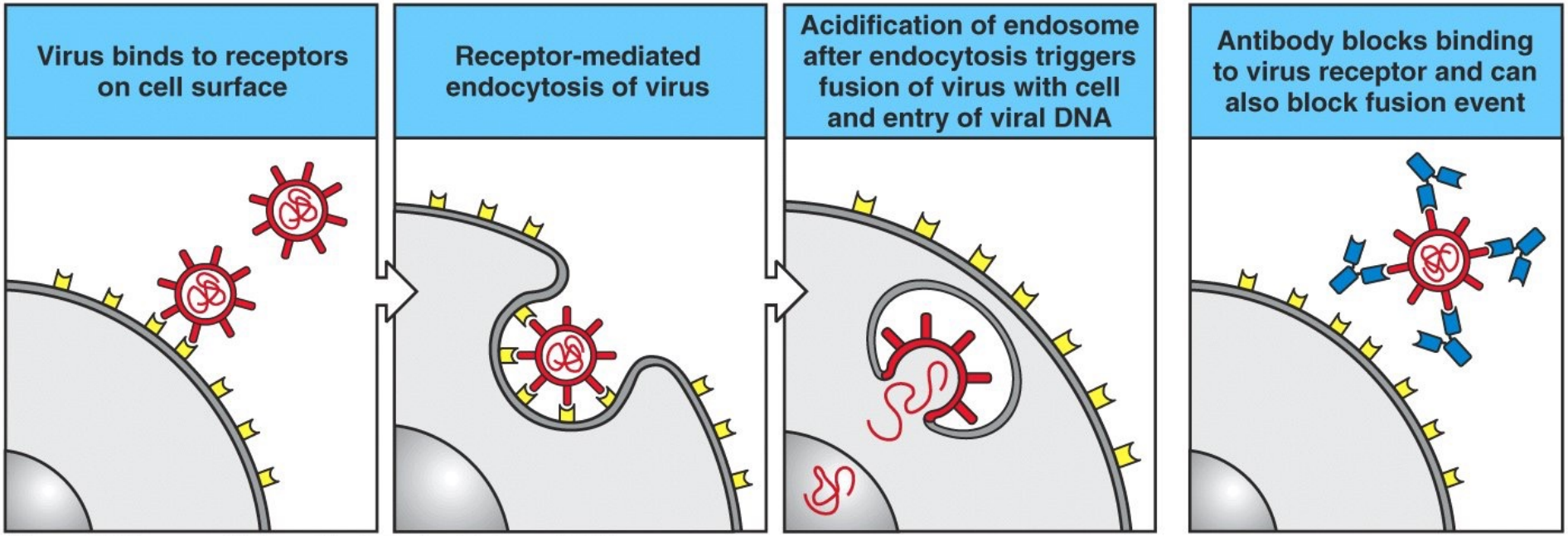
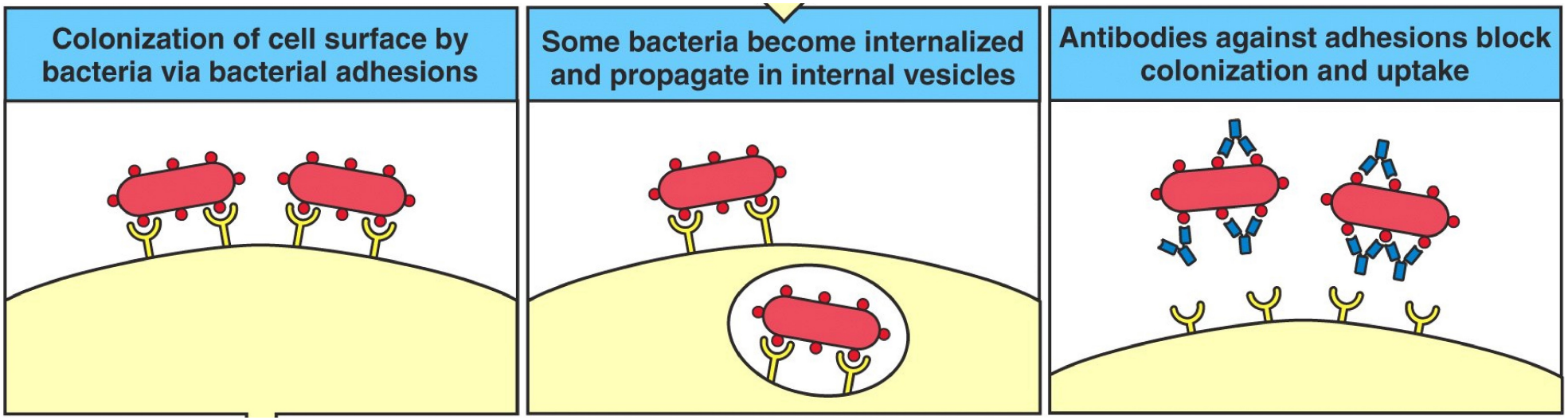
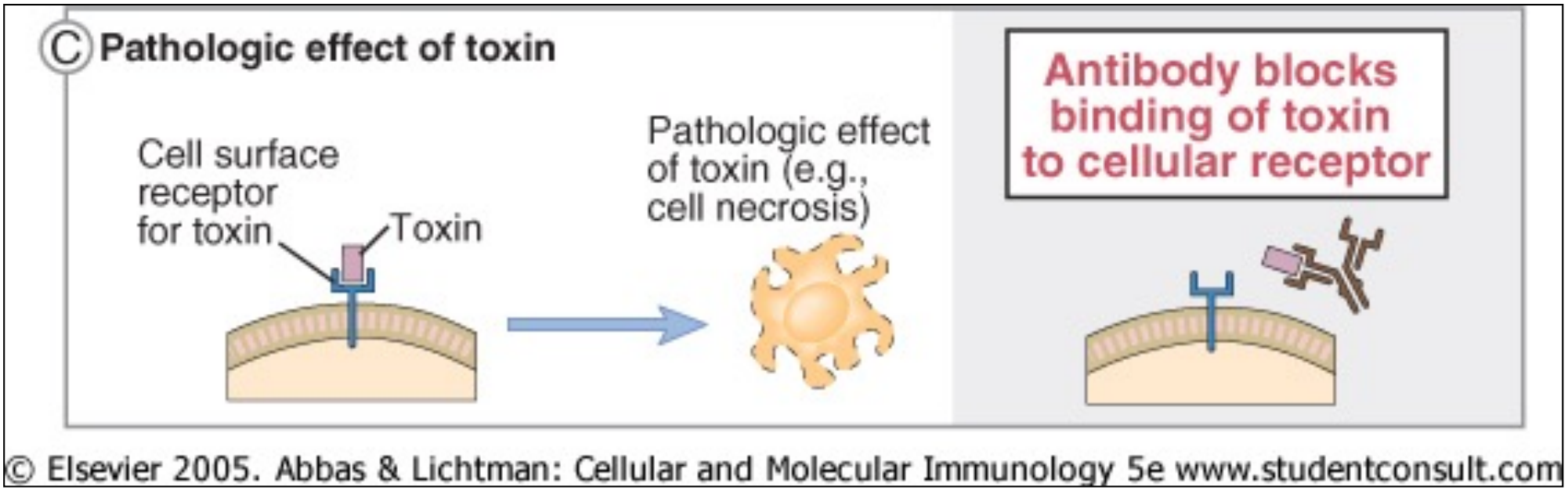


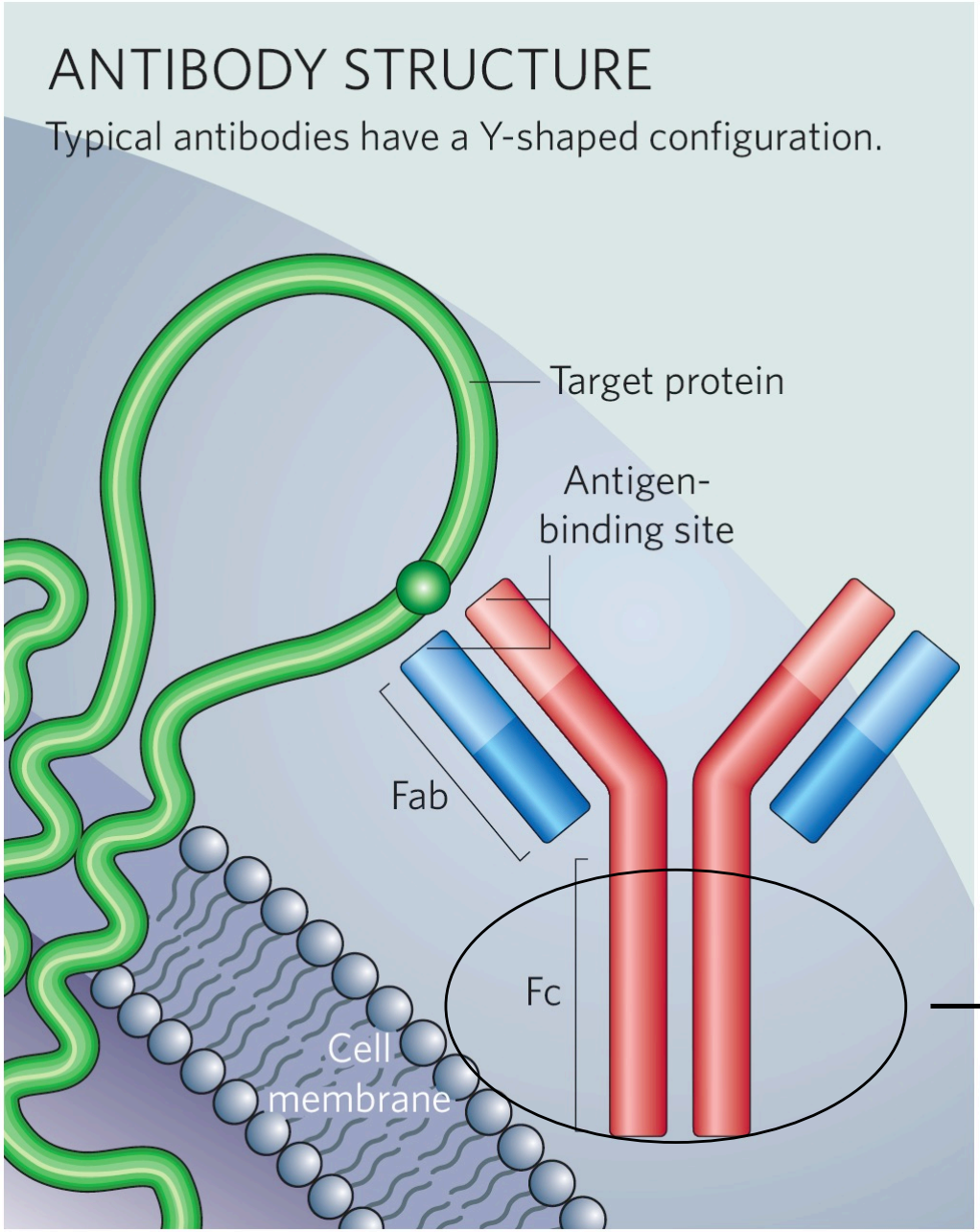
Figure 9-25 Immunobiology, 6/e. (© Garland Science 2005)



1. Antibodies can neutralize pathogen-derived toxins



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



→ Effector functions

I recettori Fc

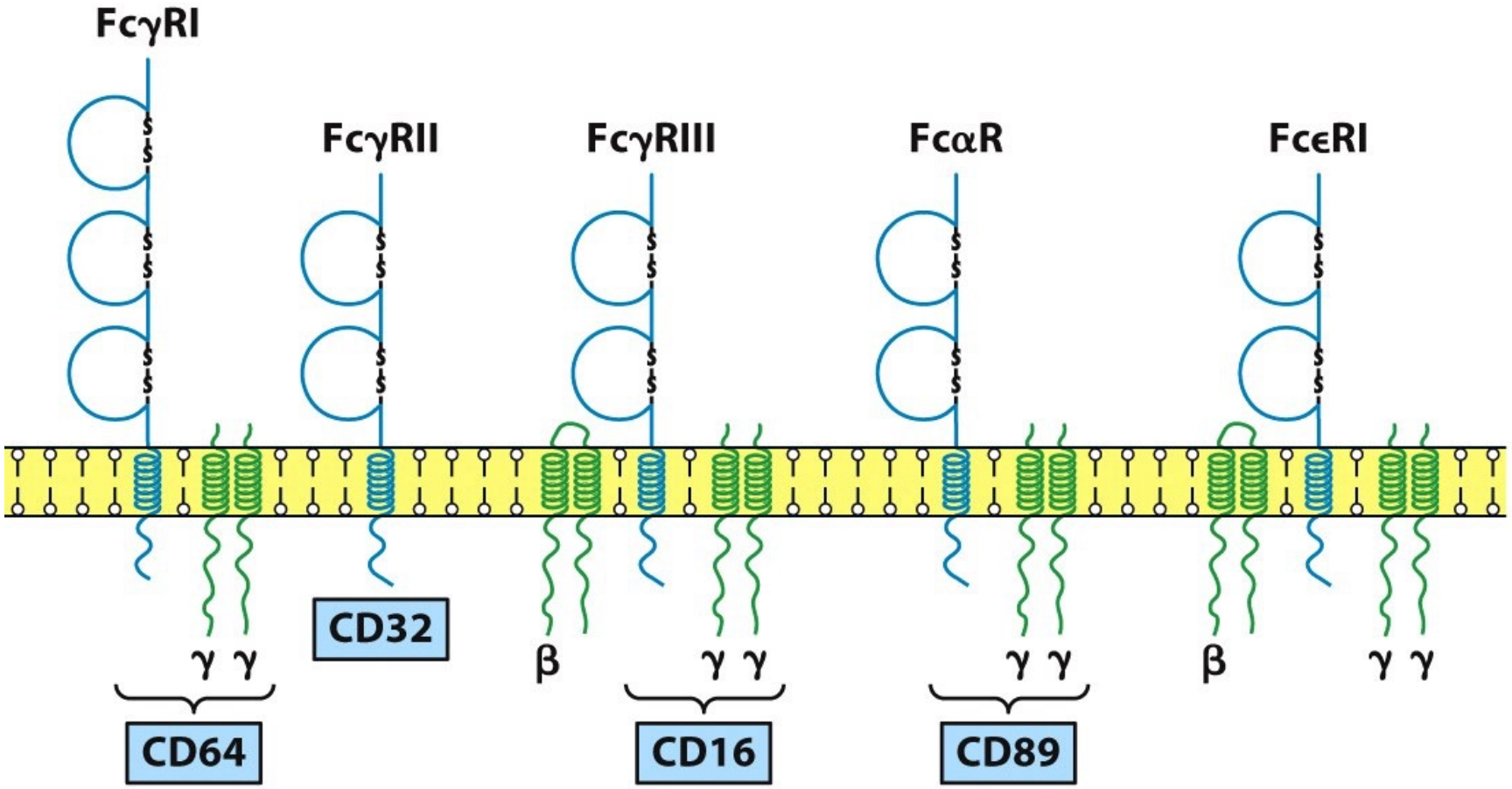
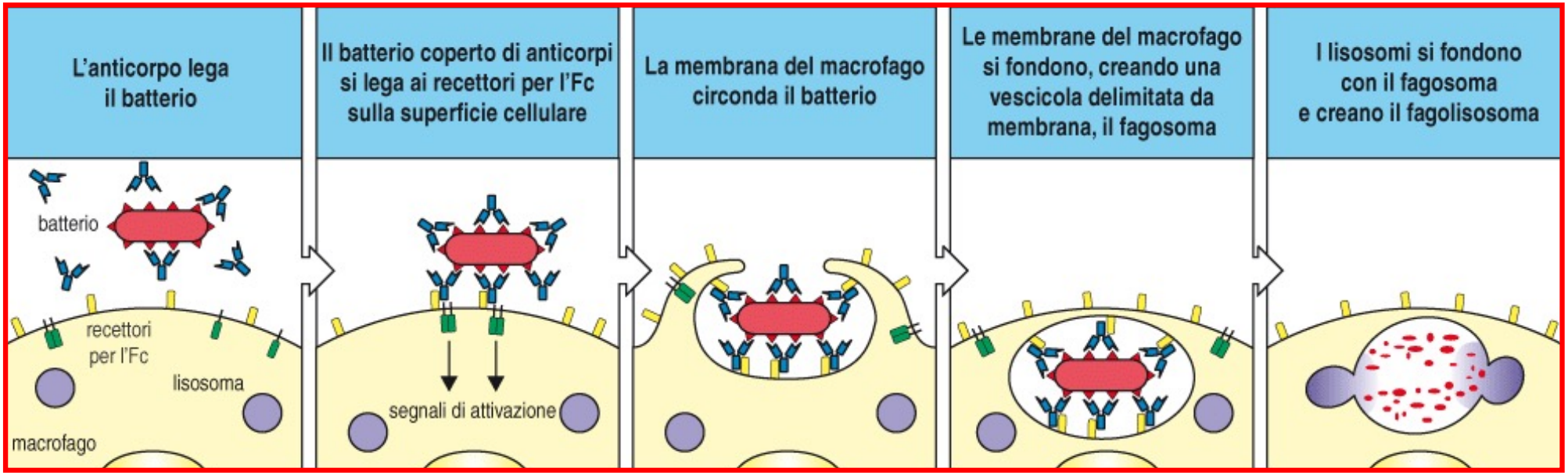


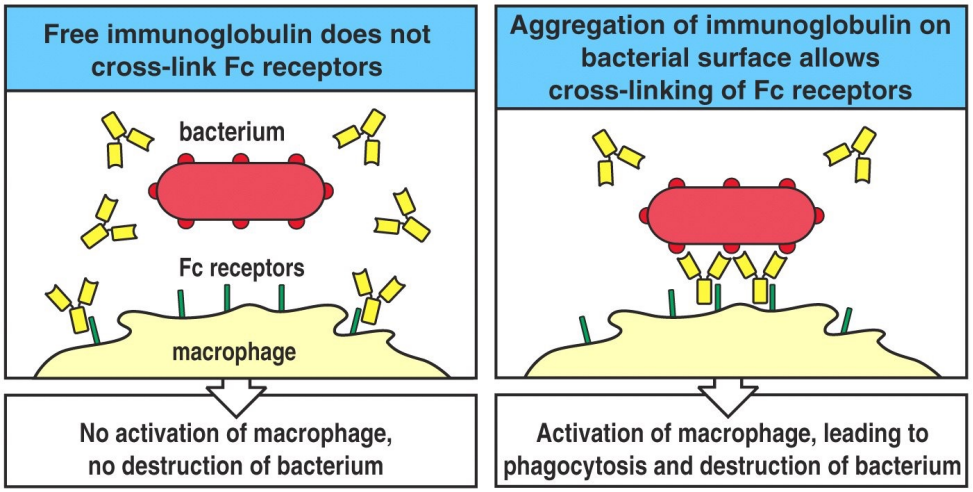
Figure 4-23
Kuby IMMUNOLOGY, Sixth Edition

MΦ, PMN

Mastociti, Basofili, Eosinofili

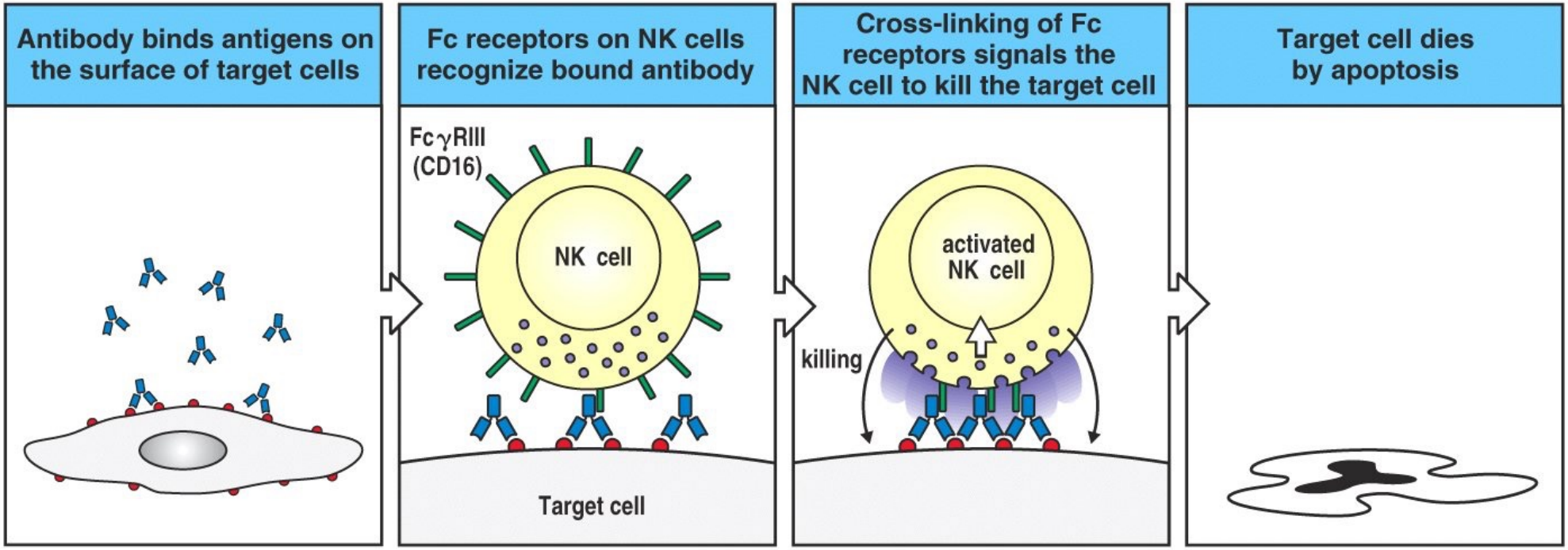
2. Antibodies can enhance phagocytosis of pathogens (OPSONIZATION)

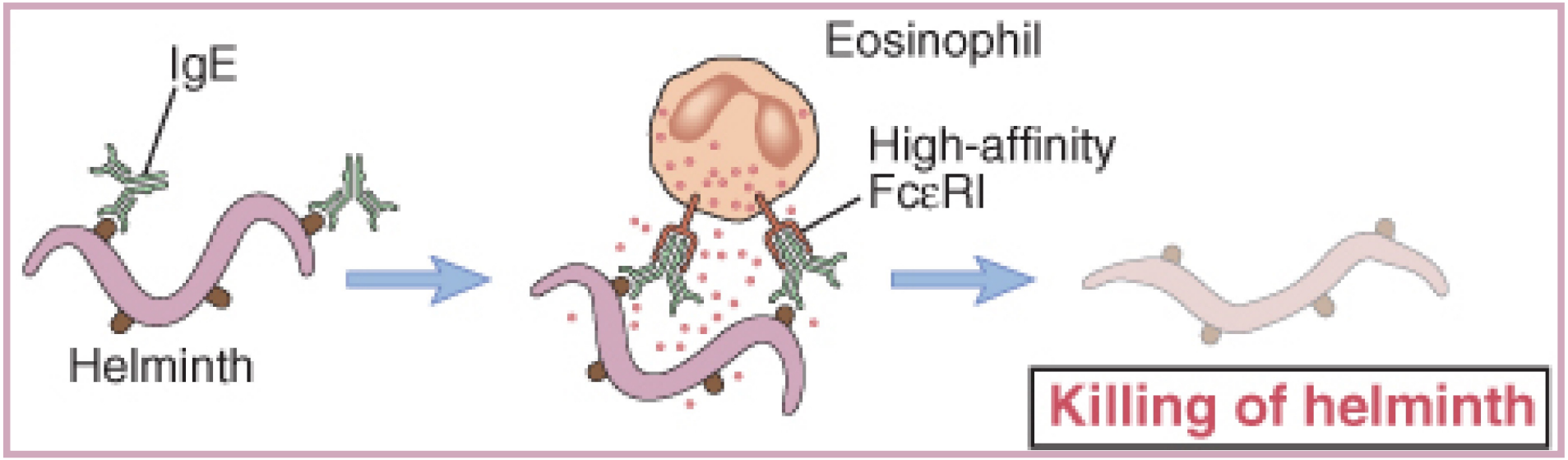




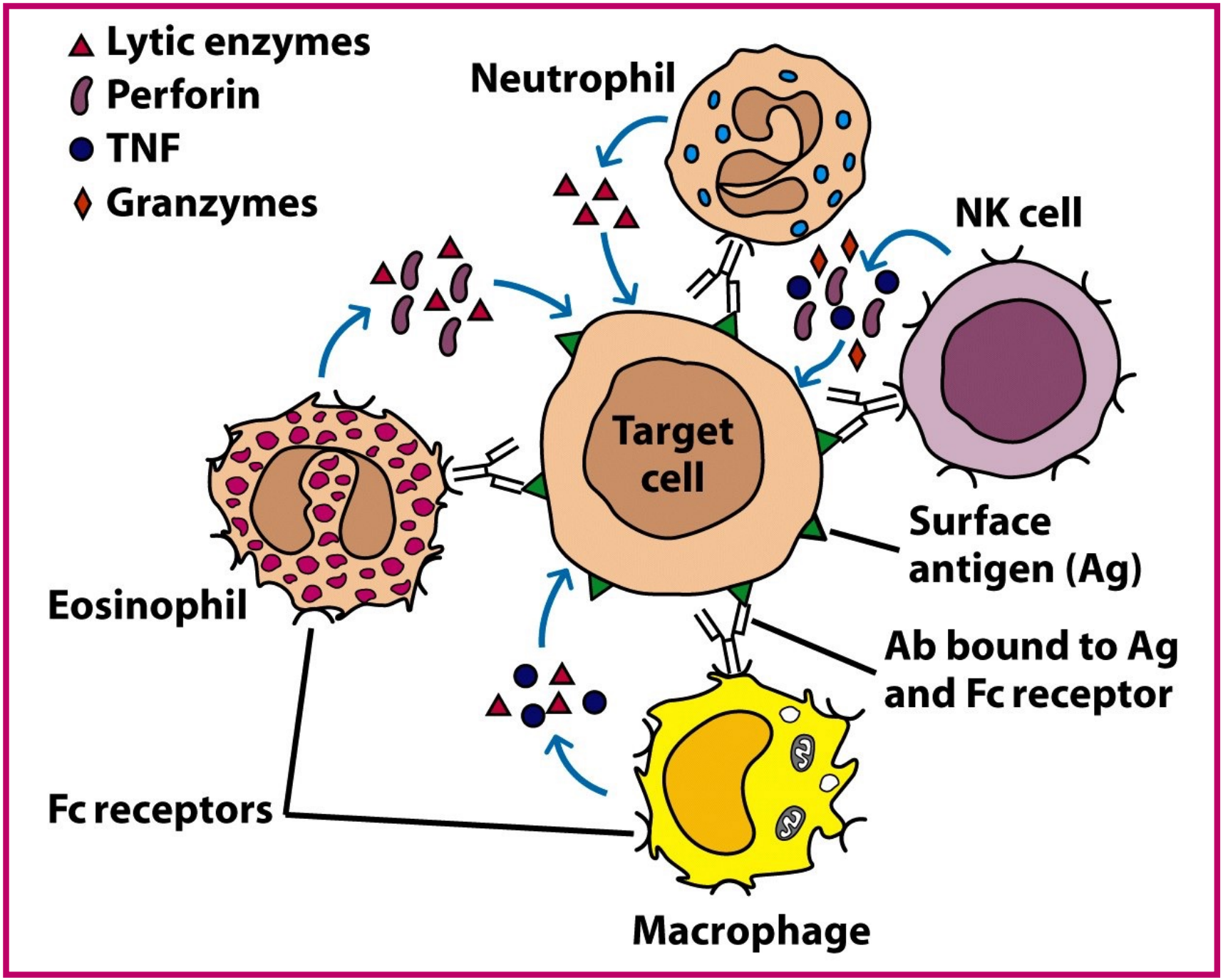
Antibody-mediated crosslinking of Fc receptors is necessary for phagocyte activation!

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

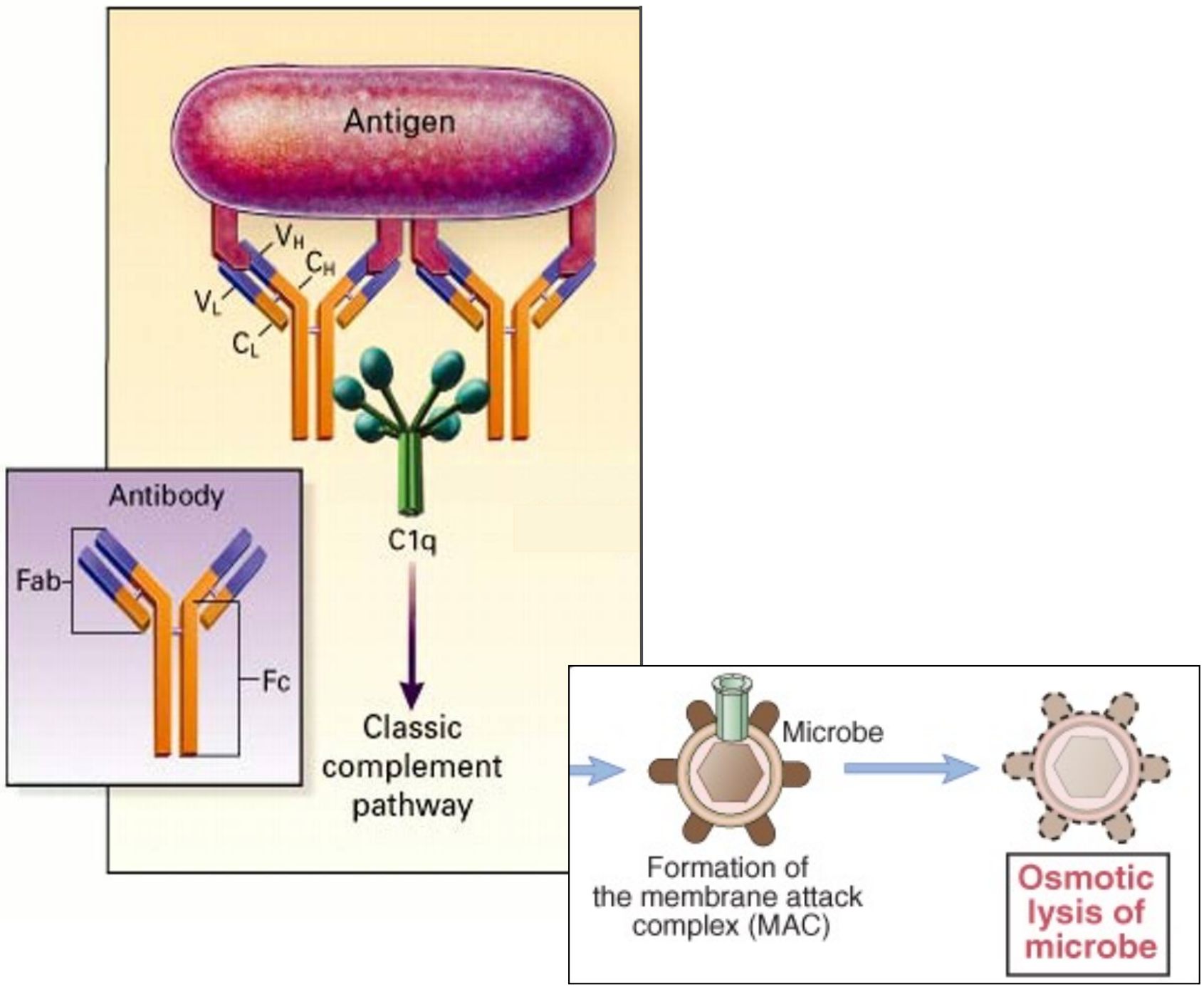




Many innate cell populations are capable of ADCC



4. Antibodies can induce the activation of COMPLEMENT



Five different Ig classes

(ISOTYPES)

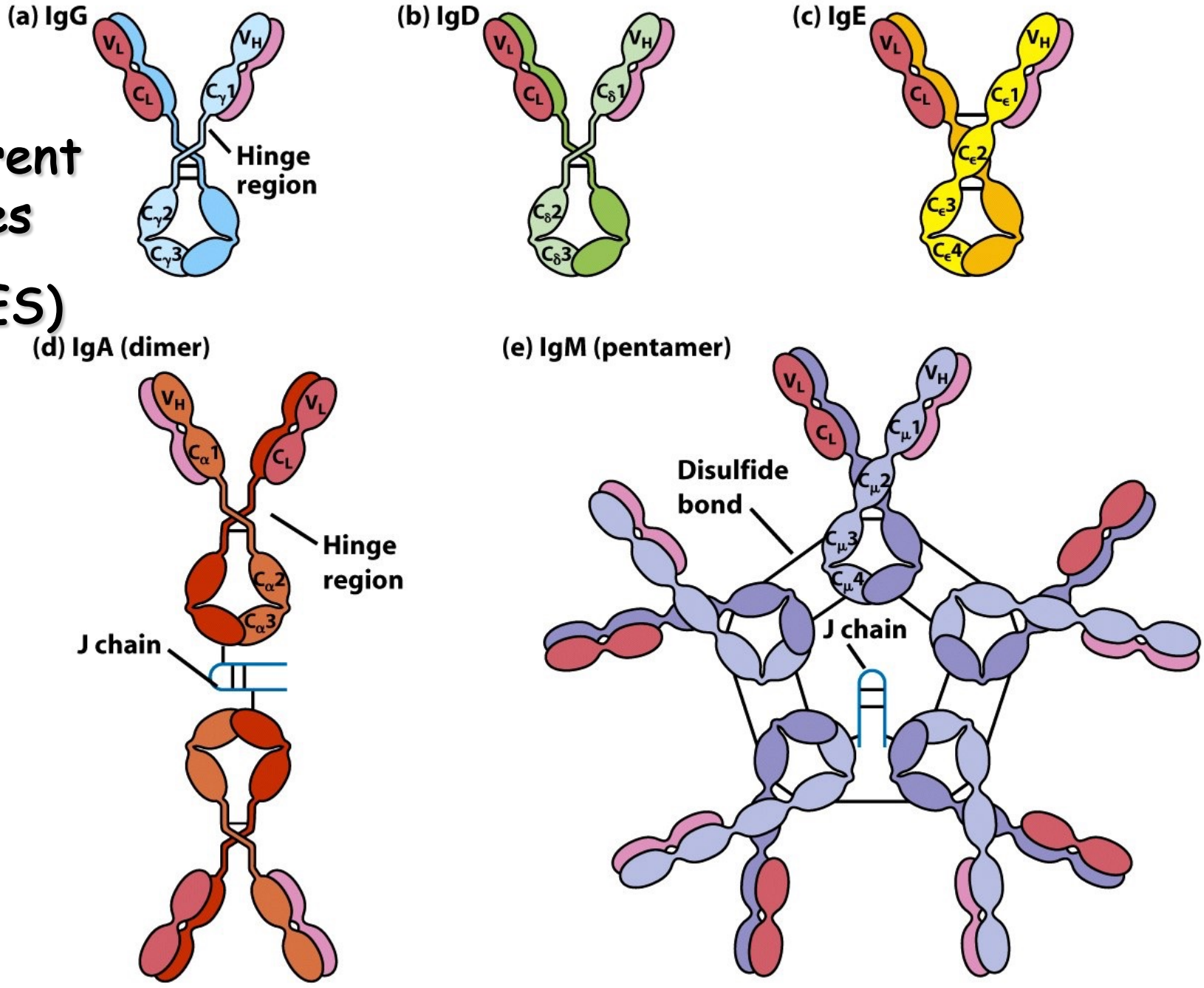
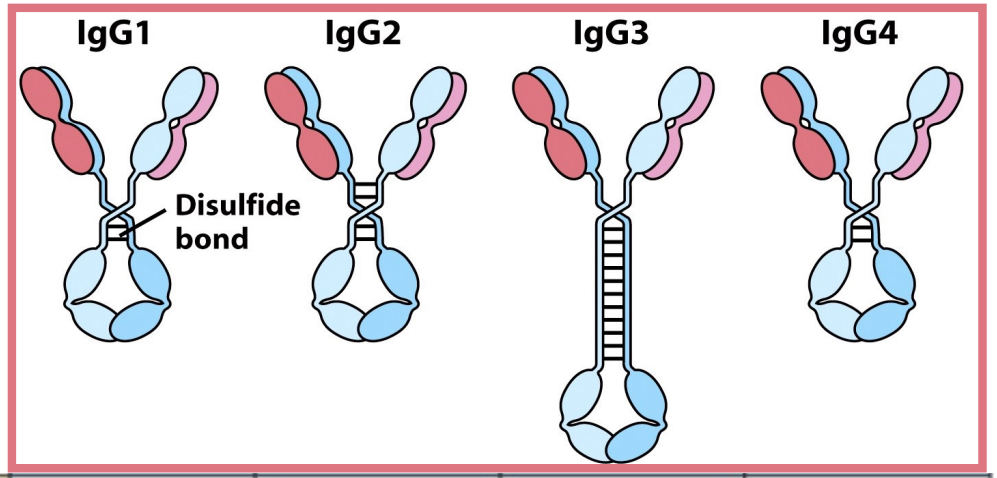


Figure 4-17
Kuby IMMUNOLOGY, Sixth Edition

IgG

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



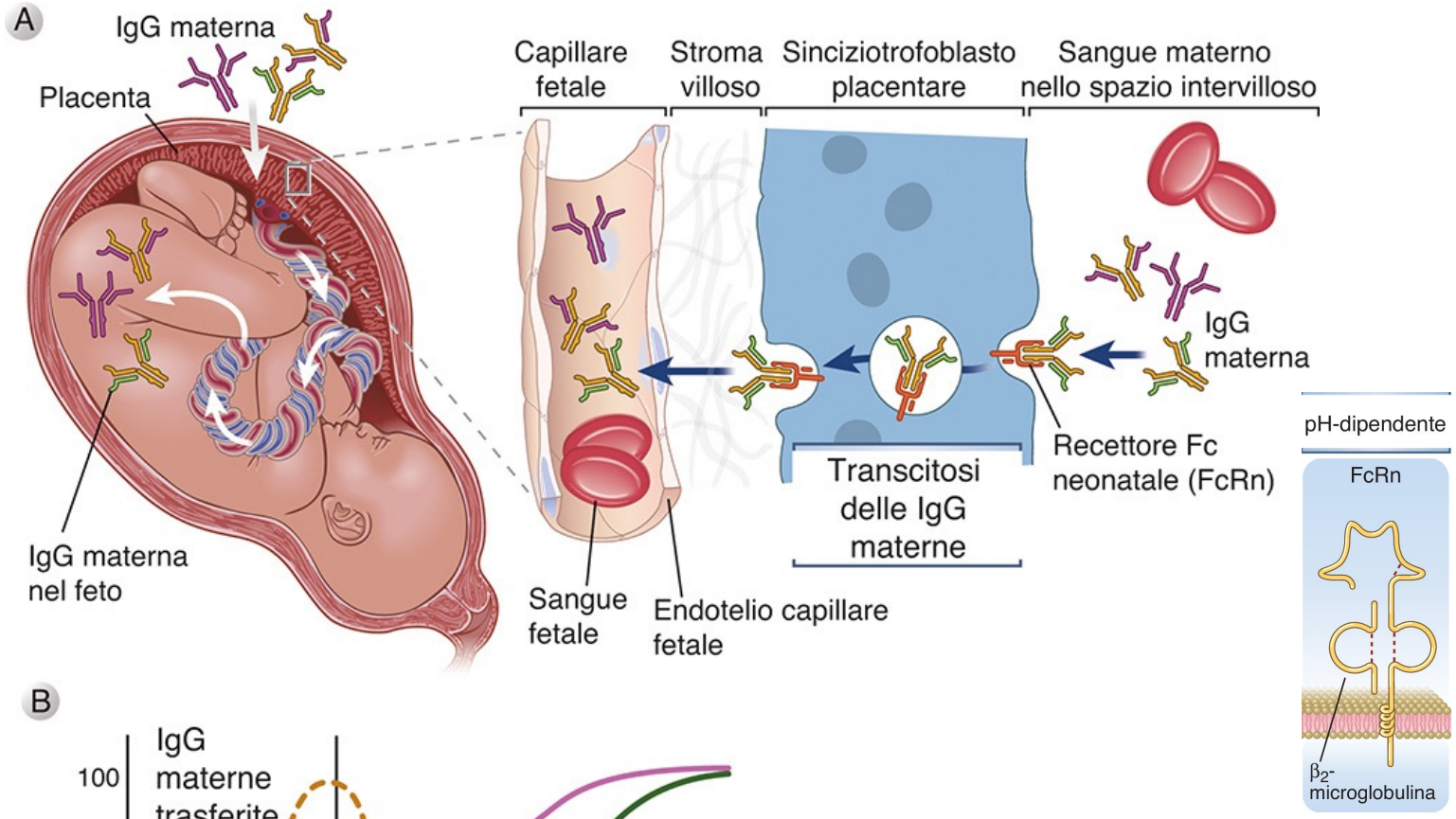
Proporzione delle IgG totali (%)	45–75	16–48	2–8	1–12
Lunghezza della cerniera della catena pesante (aminoacidi)	15	12	62	12
Numero di legami disolfuro nella cerniera	2	4	11	2
Suscettibilità della cerniera alla proteolisi	++	+	+++	+
Emivita nel siero (giorni)	21	21	7	21

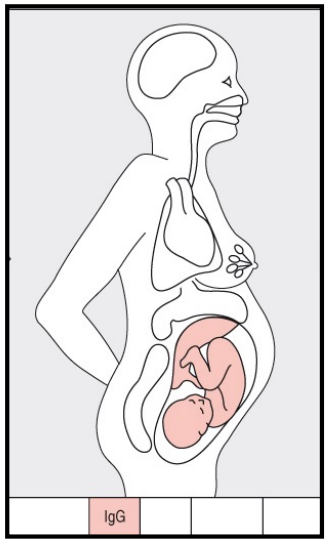
IgG

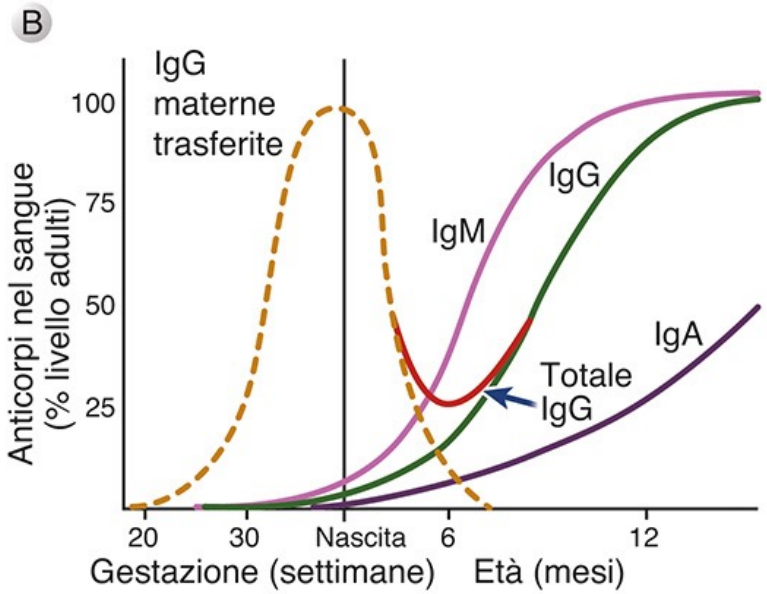
Proprietà e funzioni

- Possono attraversare la placenta
- Neutralizzano patogeni e tossine batteriche
- Attivano il complemento
- Legano recettori Fc
  - Fagocitosi - opsonizzazione
  - ADCC

Il recettore Fc neonatale (FcRn) media il trasferimento delle IgG dalla madre al feto

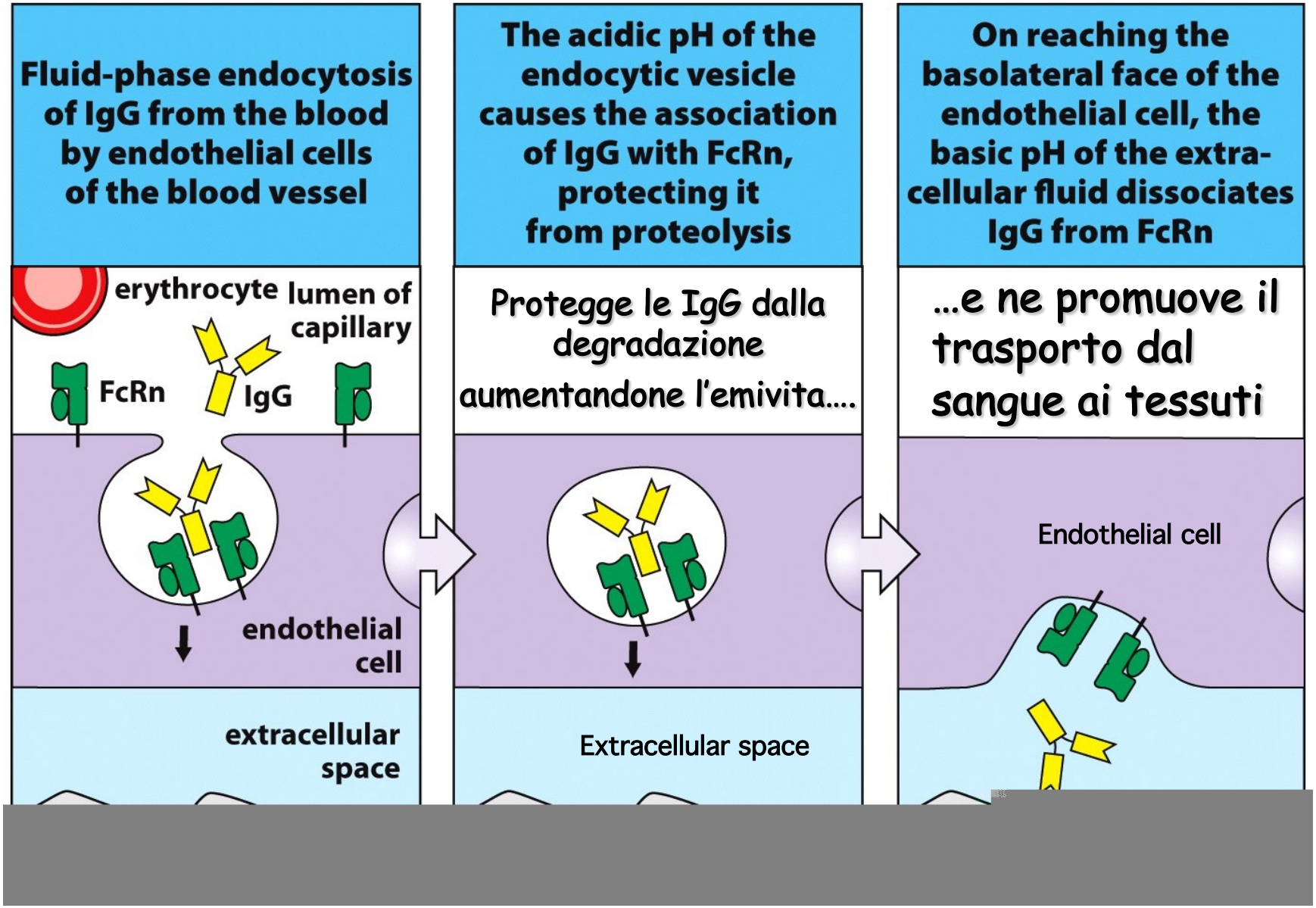






Le IgG materne trasferite proteggono il neonato nei primi mesi di vita!!

Il recettore FcRn è espresso anche nell'adulto a livello delle cellule endoteliali



Le IgG sono l'isotipo più abbondante negli spazi extracellulari !

IgG

Proprietà e funzioni

- Possono attraversare la placenta
- Neutralizzano patogeni e tossine batteriche
- Attivano il complemento
- Legano recettori Fc
  - Fagocitosi - opsonizzazione
  - ADCC

IgG

Proprietà e funzioni

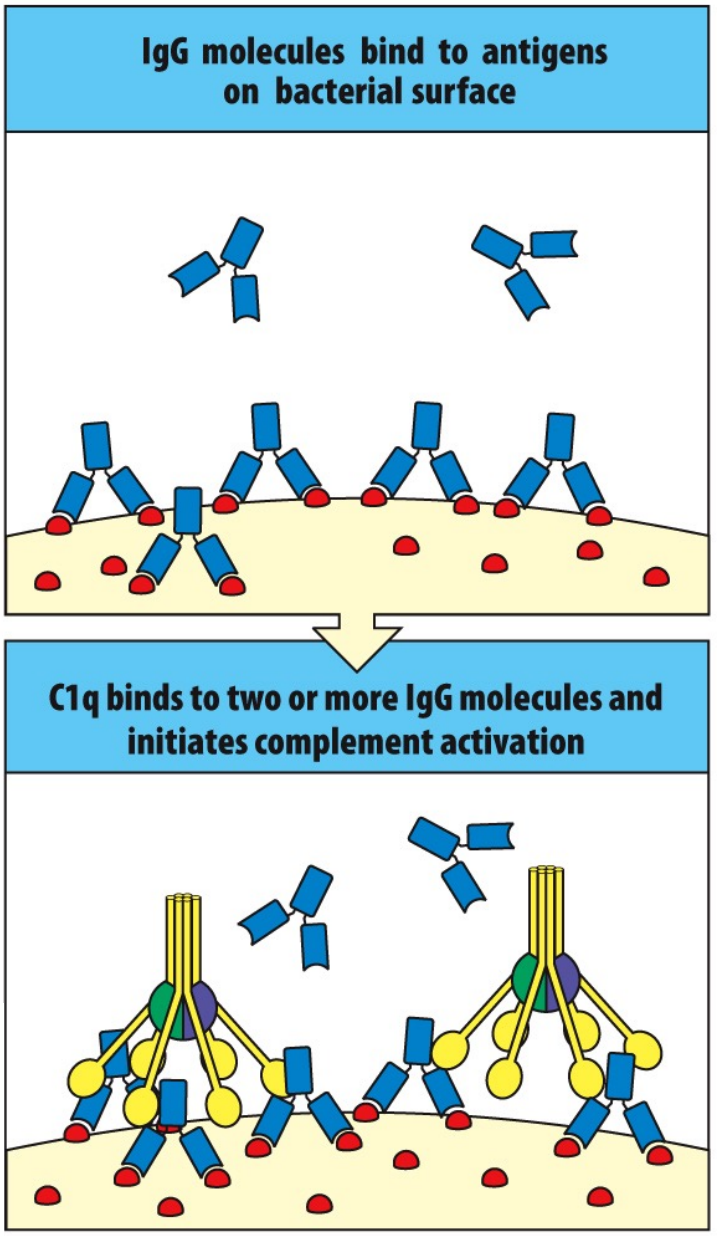
- Possono attraversare la placenta
- Neutralizzano patogeni e tossine batteriche
- Attivano il complemento

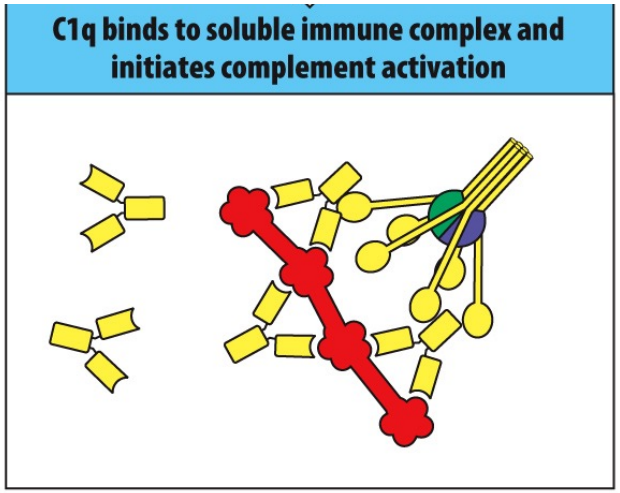
  IgG3>IgG1>IgG2
- Legano recettori Fc
  - Fagocitosi - opsonizzazione
  - ADCC

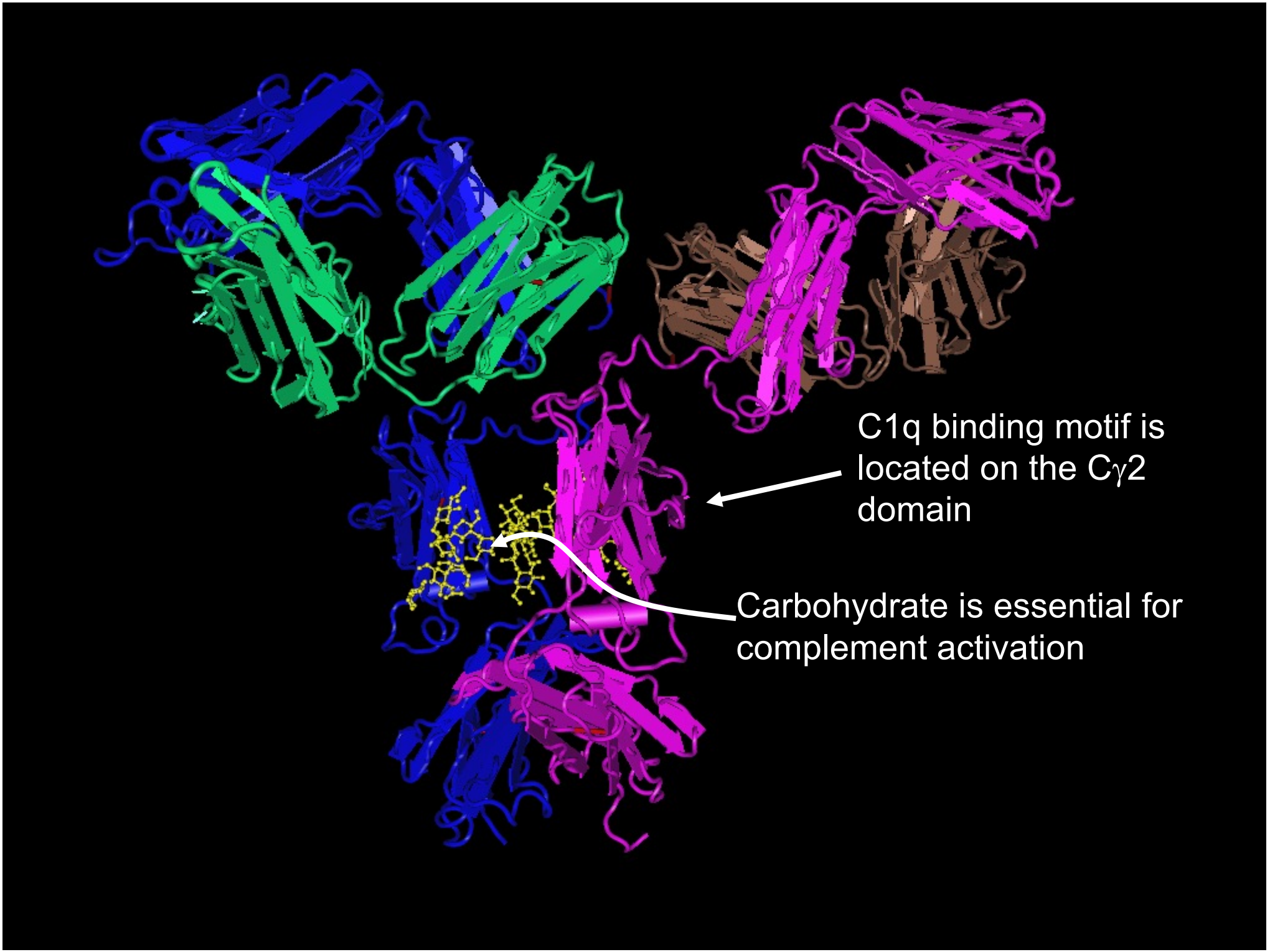
I frammenti Fab legano l'antigene e il frammento Fc rimane accessibile……

…ma per attivare la via classica sono necessarie due molecole di IgG che devono simultaneamente legare una molecola C1

Anche antigeni solubili possono attivare il complemento !





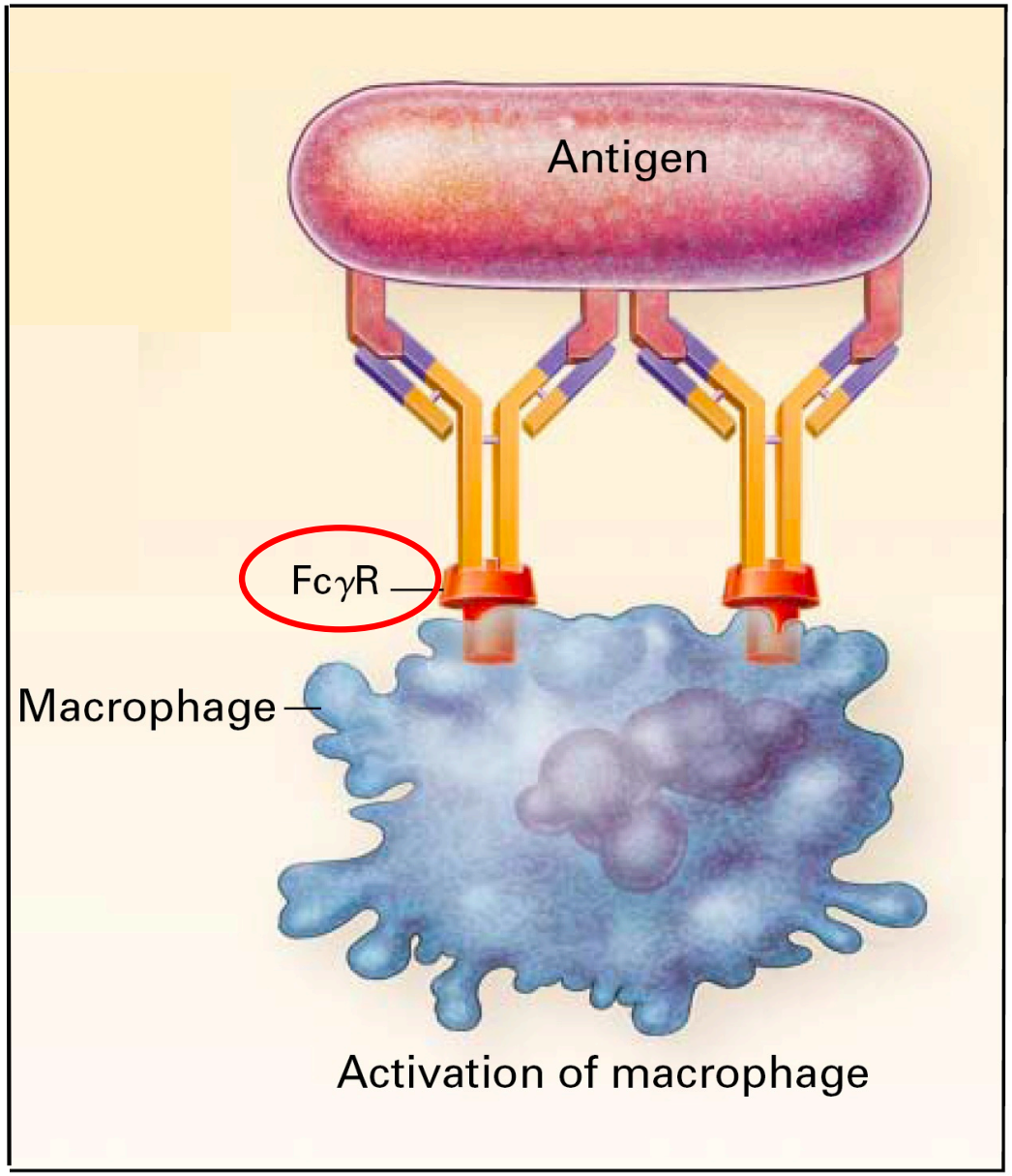

C1q binding motif is located on the Cγ2 domain
Carbohydrate is essential for complement activation

IgG

Proprietà e funzioni

- Possono attraversare la placenta
- Neutralizzano patogeni e tossine batteriche
- Attivano il complemento
- Legano recettori Fc
  - Fagocitosi - opsonizzazione IgG1>IgG3
  - ADCC IgG1, IgG3

La regione costante delle IgG è riconosciuta da recettori specifici: FcγR

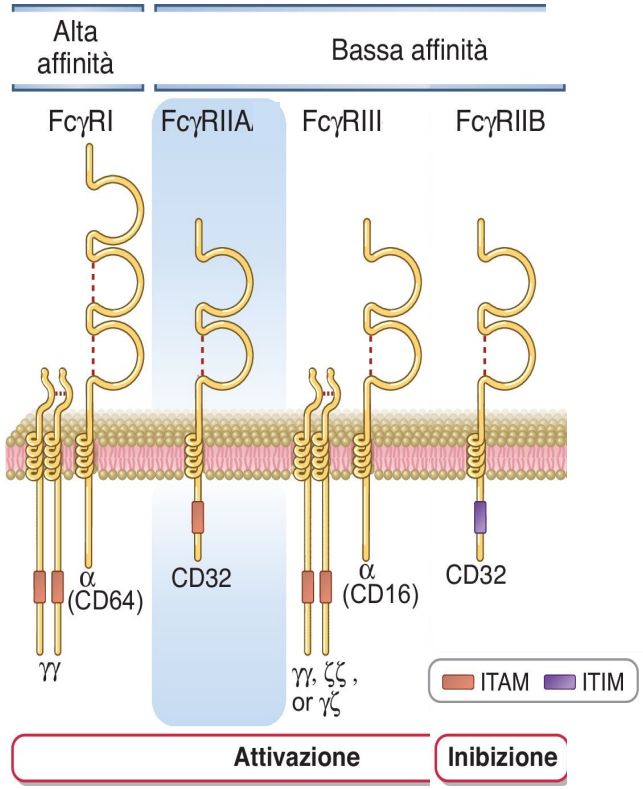


A family of Fcγ receptors

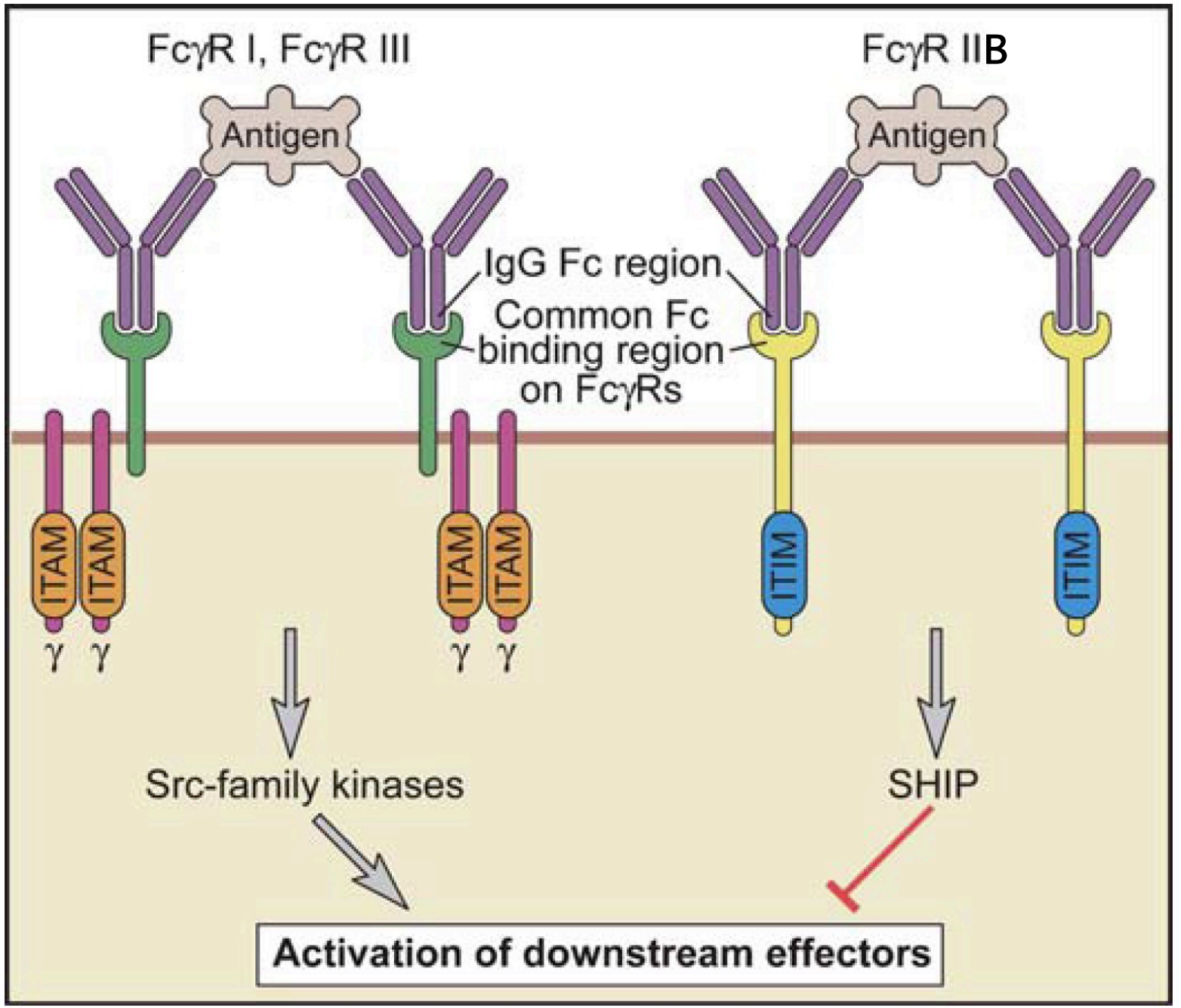
HIGH Affinity 10^{-9}M

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

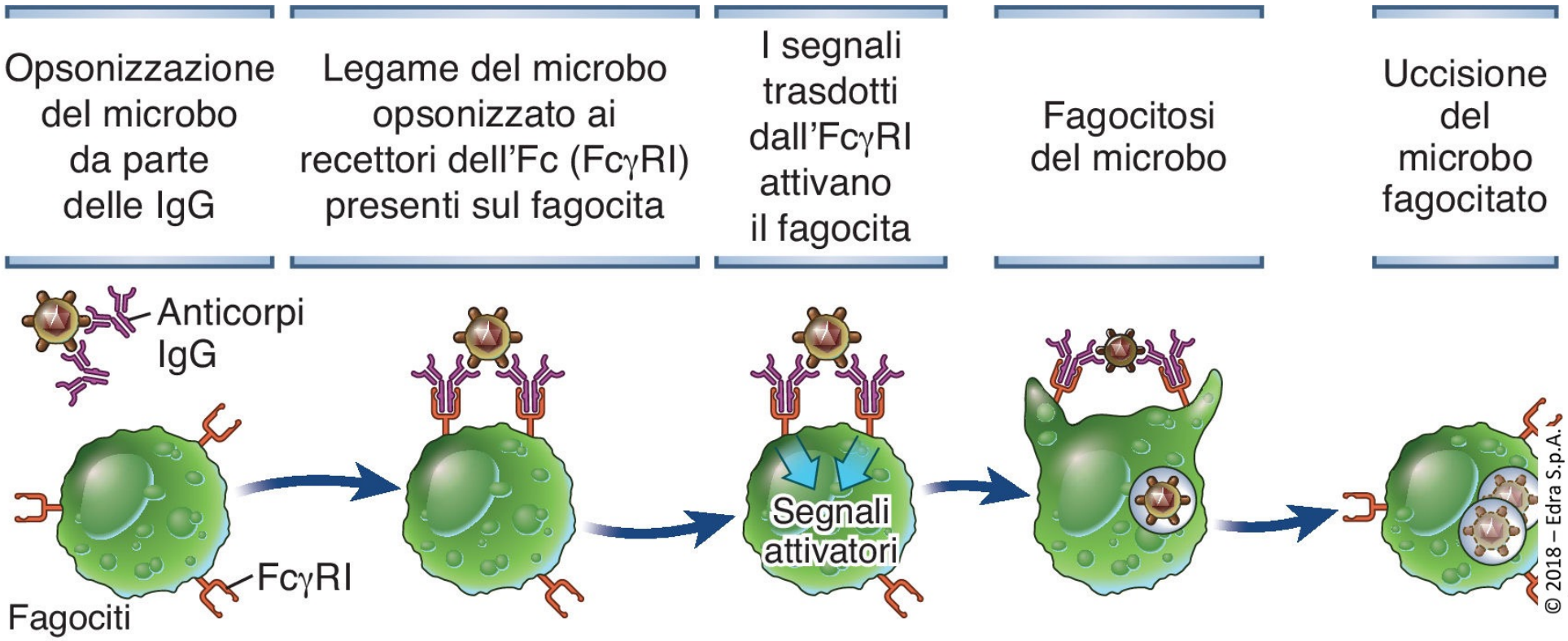
Receptor	FcγRI (CD64)	FcγRII-A (CD32)	FcγRII-B2 (CD32)	FcγRII-B1 (CD32)	FcγRIII (CD16)
Structure	α 72 kDa, γ	α 40 kDa, γ-like domain	ITIM	ITIM	α 50–70 kDa, or, γ or ζ
Binding	IgG1	IgG1	IgG1	IgG1	IgG1
	10^8 M^{-1}	2×10^6 M^{-1}	2×10^6 M^{-1}	2×10^6 M^{-1}	5×10^5 M^{-1}
Order of affinity	1) IgG1=IgG3 2)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



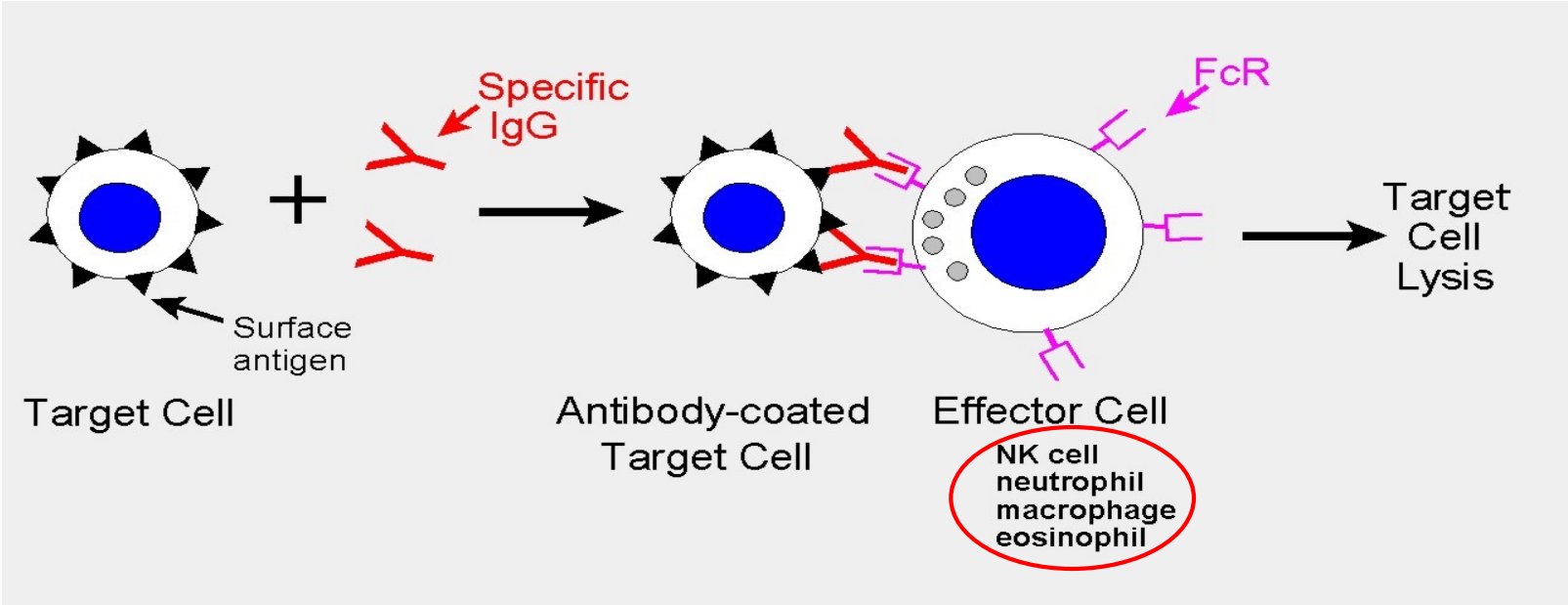
Recettori Fcγ attivatori e inibitori



Gli anticorpi IgG sono potenti opsonine: potenziano la fagocitosi dei patogeni extracellulari perché sono riconosciuti dai recettori Fcγ attivatori



Gli anticorpi IgG promuovono la citotossicità cellulare anticorpo dipendente (ADCC)



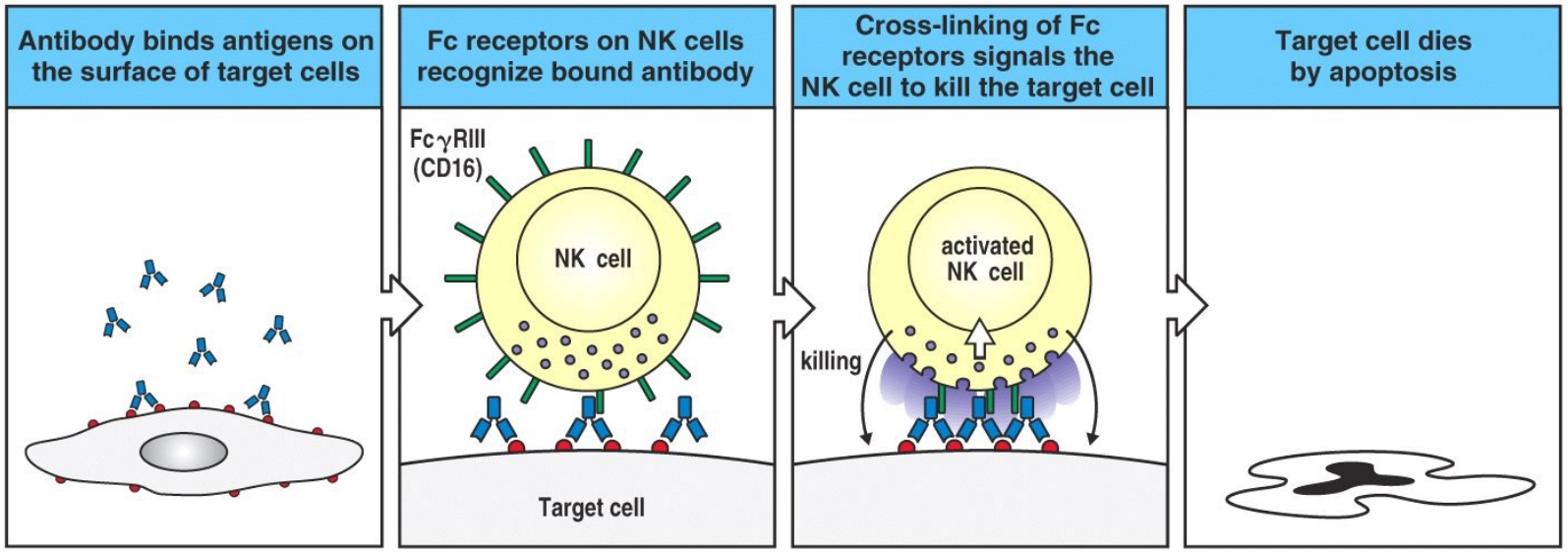
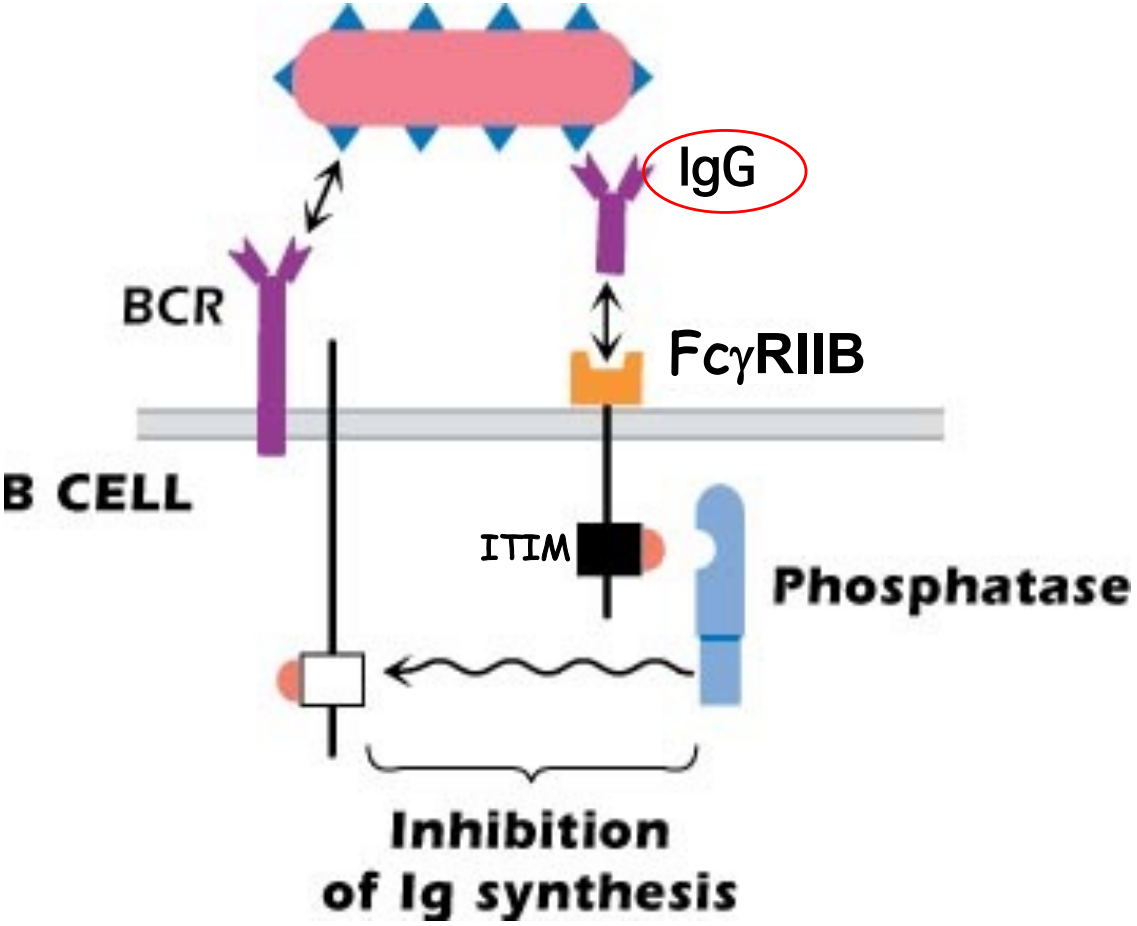
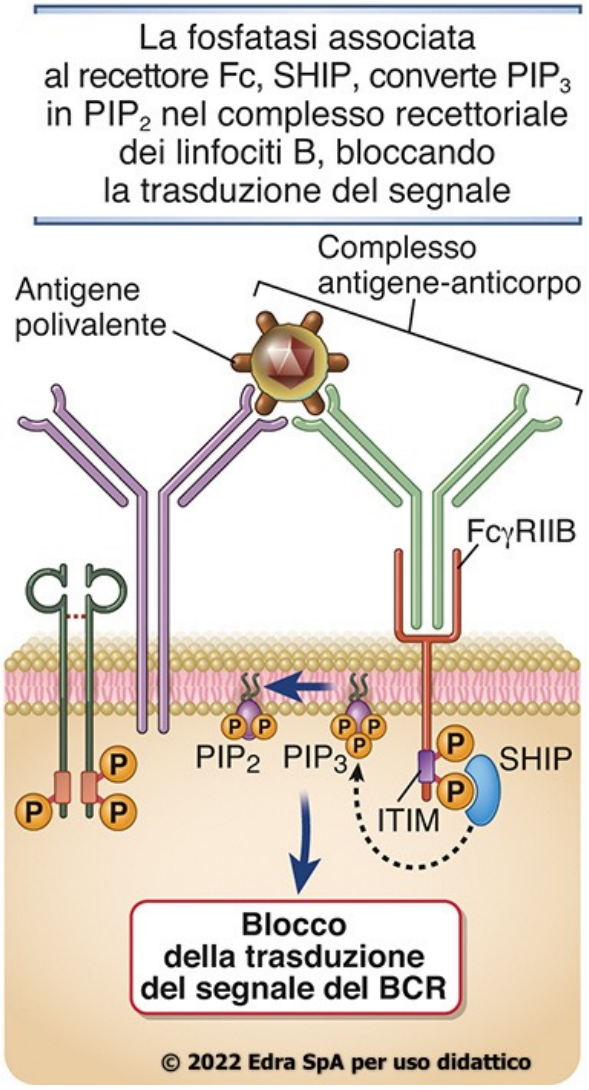


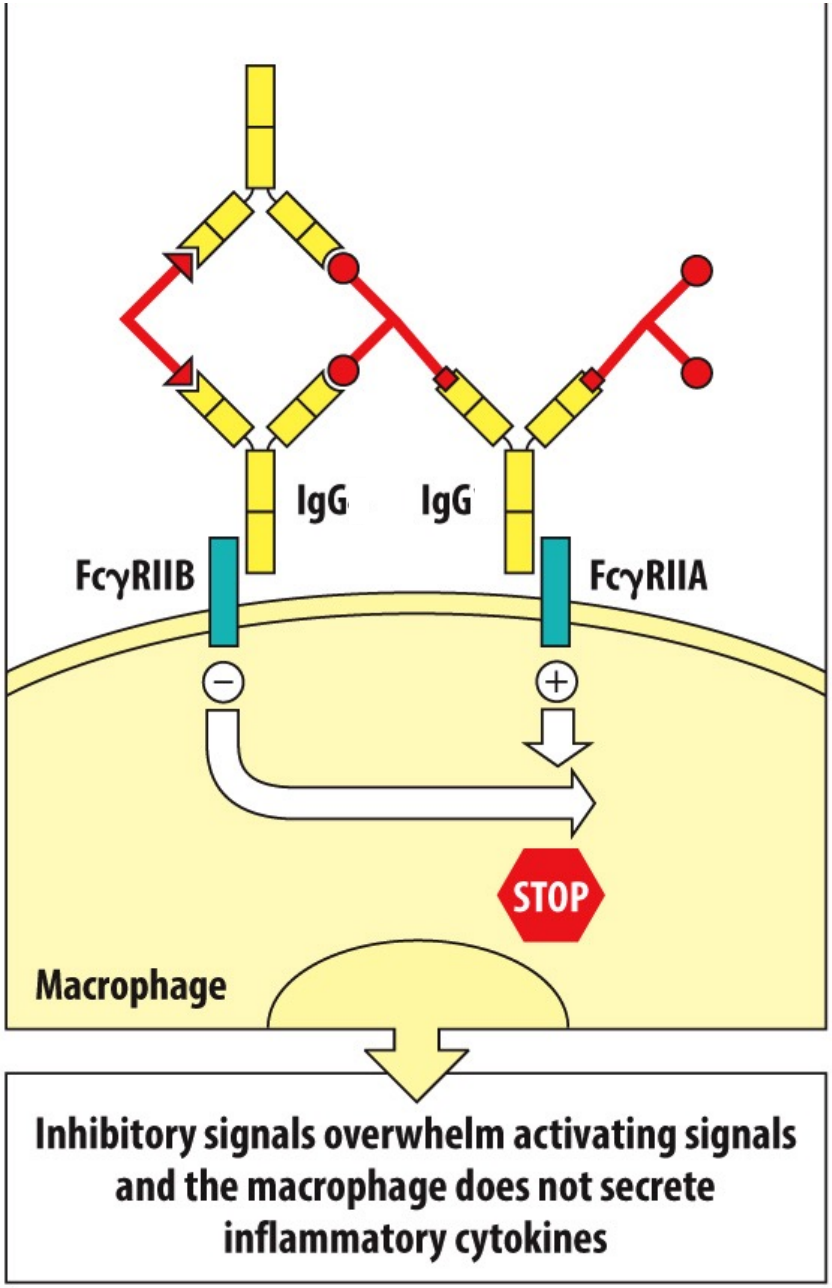
Figure 9-34 Immunobiology, 6/e. (© Garland Science 2005)

Le IgG contribuiscono allo spegnimento del segnale trasdotto dal BCR ingaggiando il recettore Fcγ inibitorio

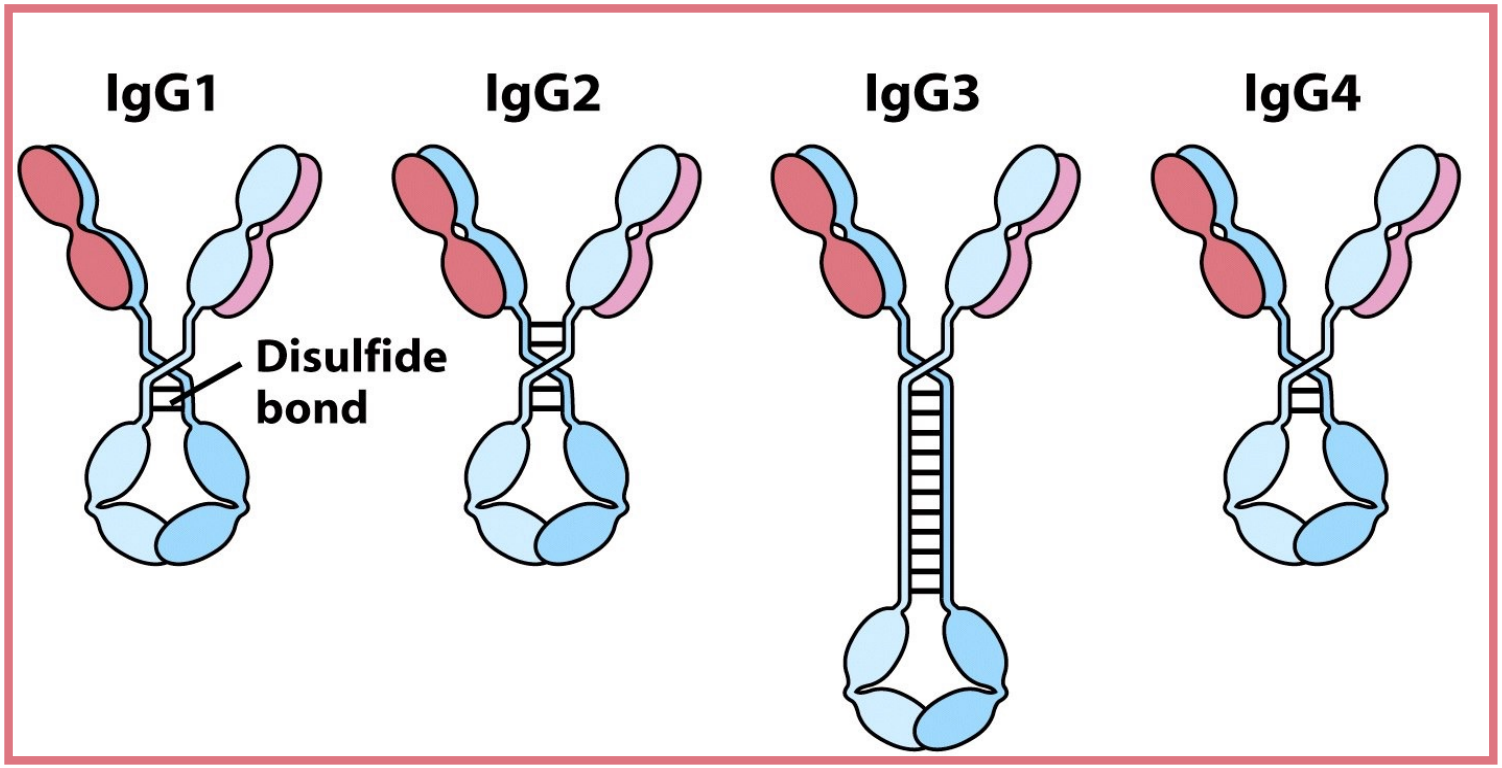




Nei macrofagi il recettore FcγRIIB blocca il segnale trasdotto dalla controparte attivatoria

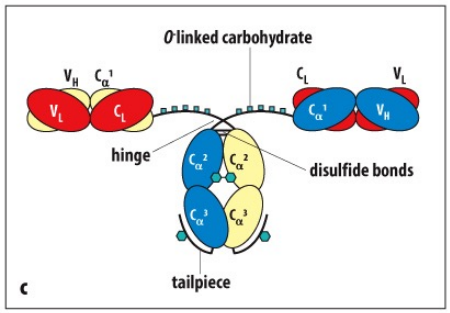


Functions of IgG subclasses



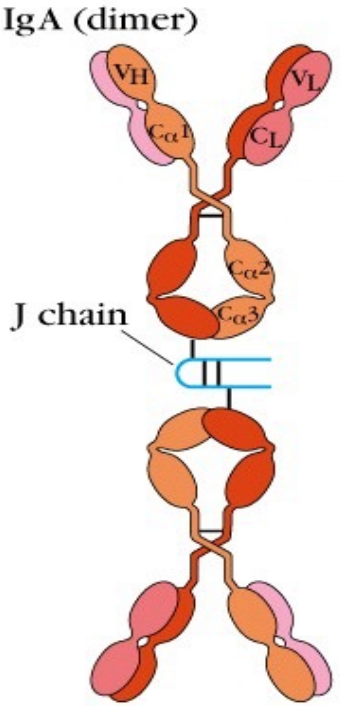
+++	+	++	+/-	Transport across placenta
++	+	+++	-	Complement activation
++	+/-	++	+	Binding to Fc receptors

IgA



Le IgA possono essere rilasciate sia in forma monomerica che in forma dimerica.

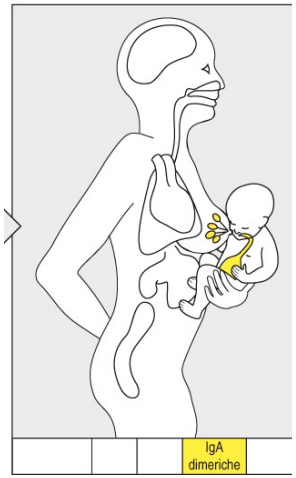
Il dimero è stabilizzato dalla presenza di una catena invariante aggiuntiva, la catena J.



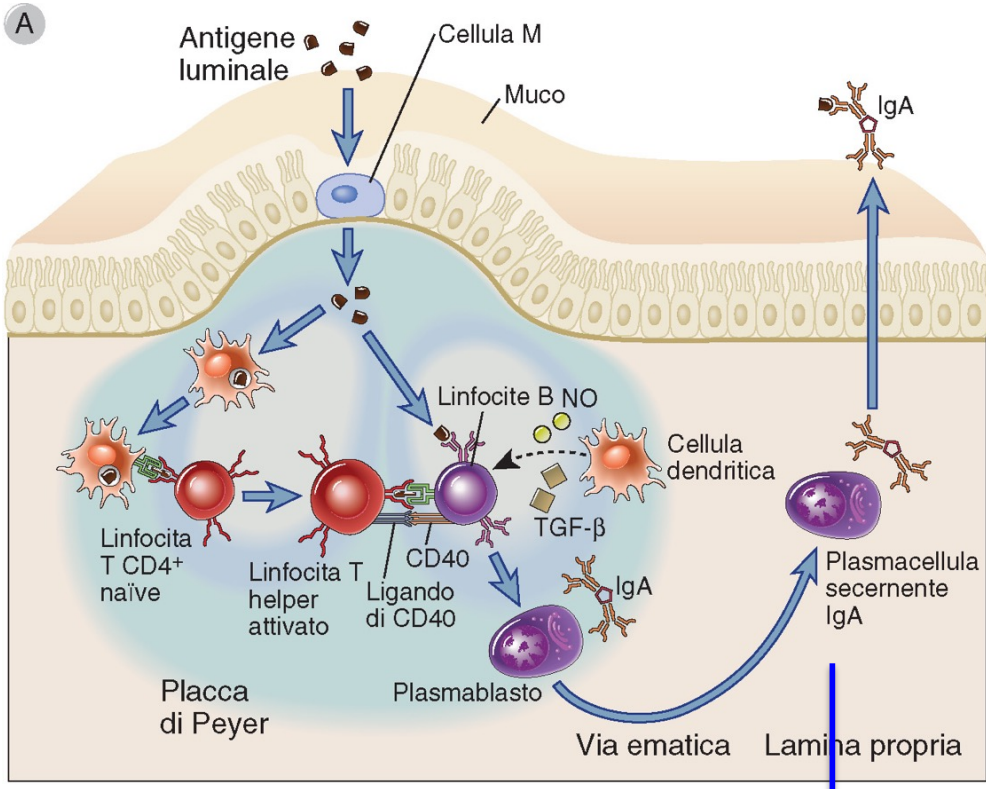
·**IgA1** è più abbondante nel sangue (90%)

IgA1:IgA2 10:1; principalmente monomero

·**IgA2** è molto abbondante nelle secrezioni in particolare nel colon (60%) dove i batteri sono presenti in gran quantità.



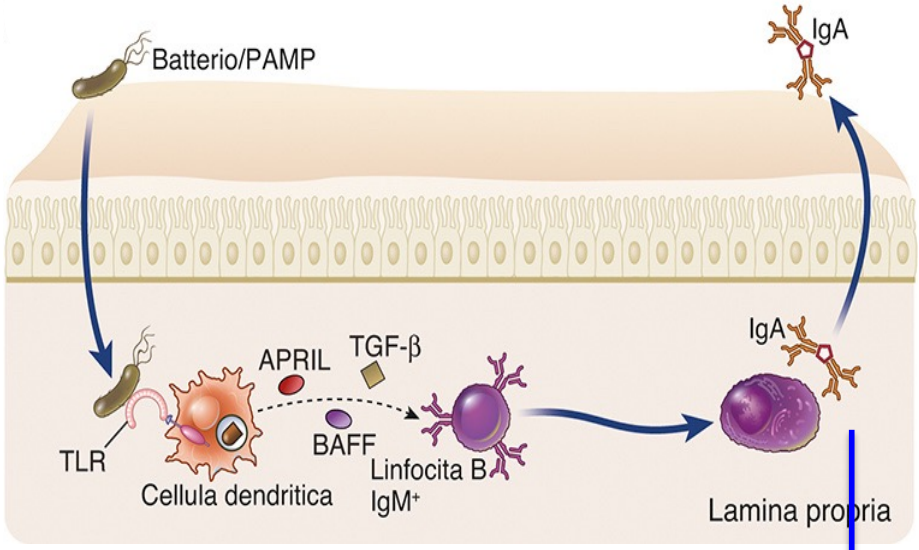
Scambio isotipico T-dipendente



CD40
TGF-β

IgA alta affinità
vs patogeni e tossine

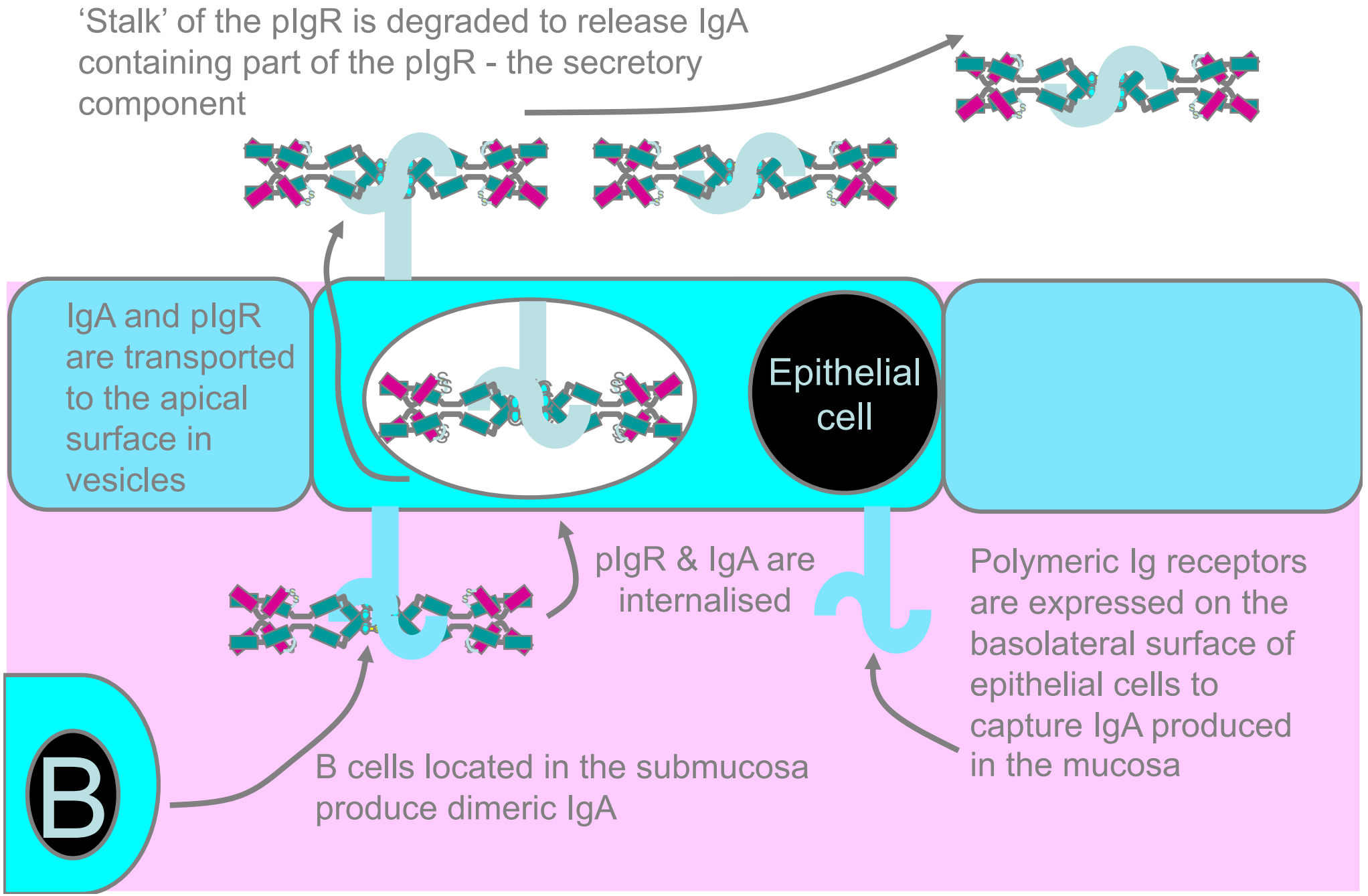
Scambio isotipico T-indipendente



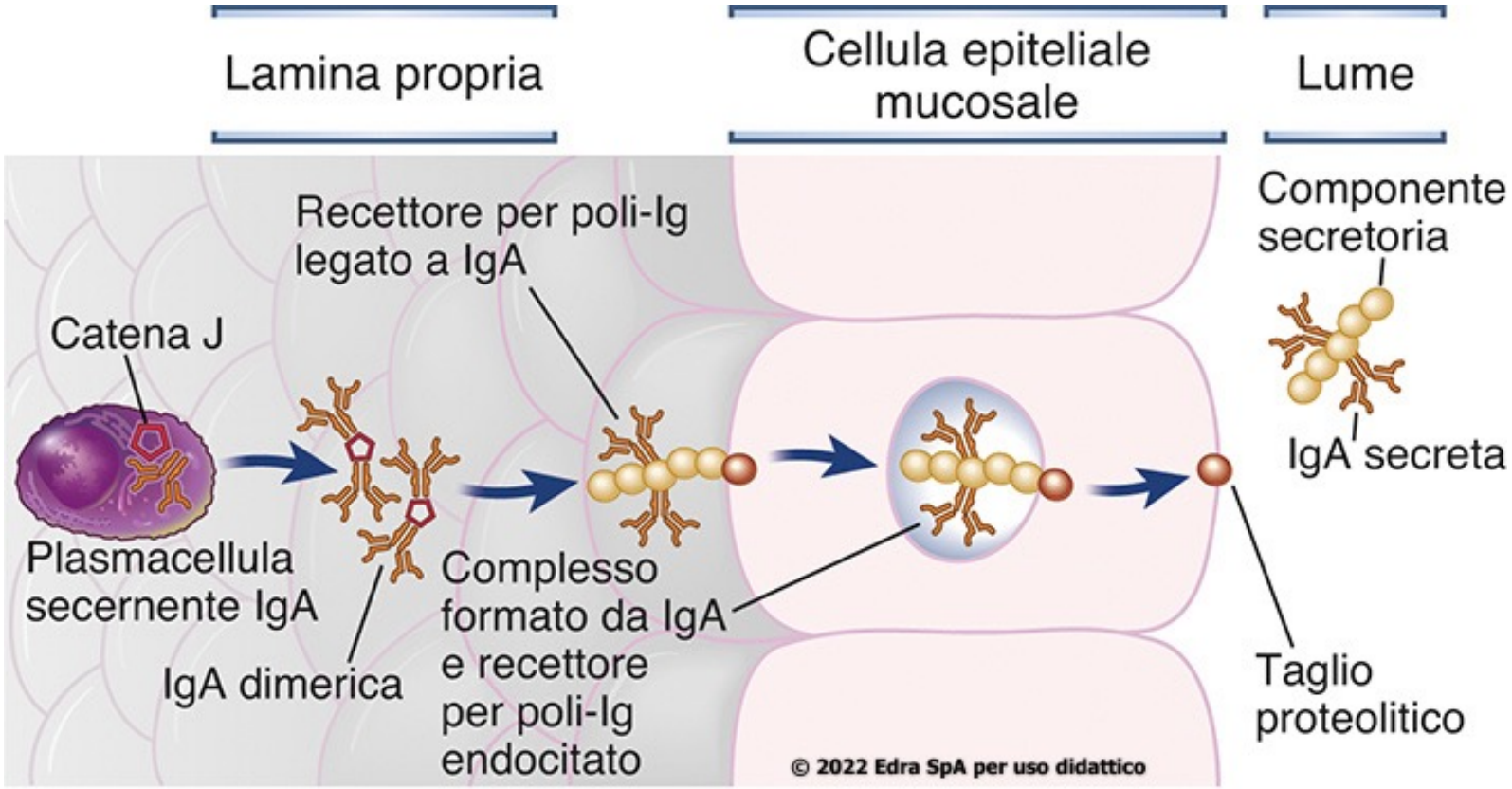
BAFF
APRIL

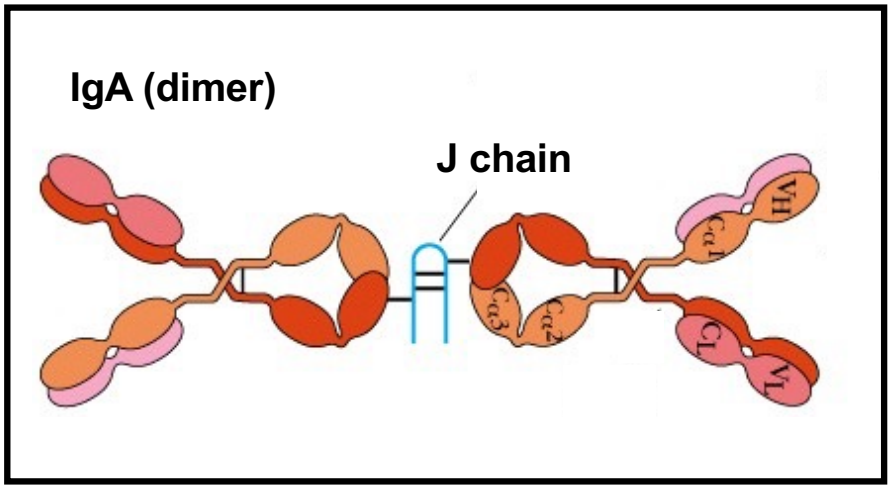
IgA bassa affinità

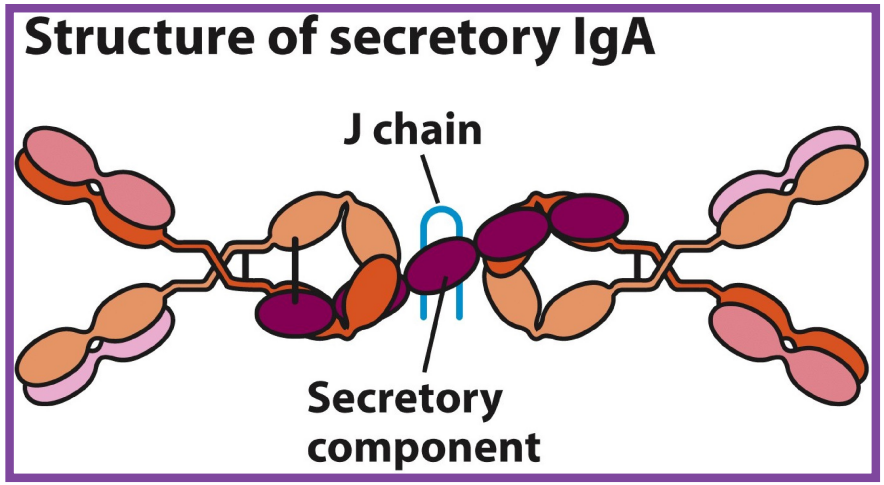
Secretory IgA and transcytosis



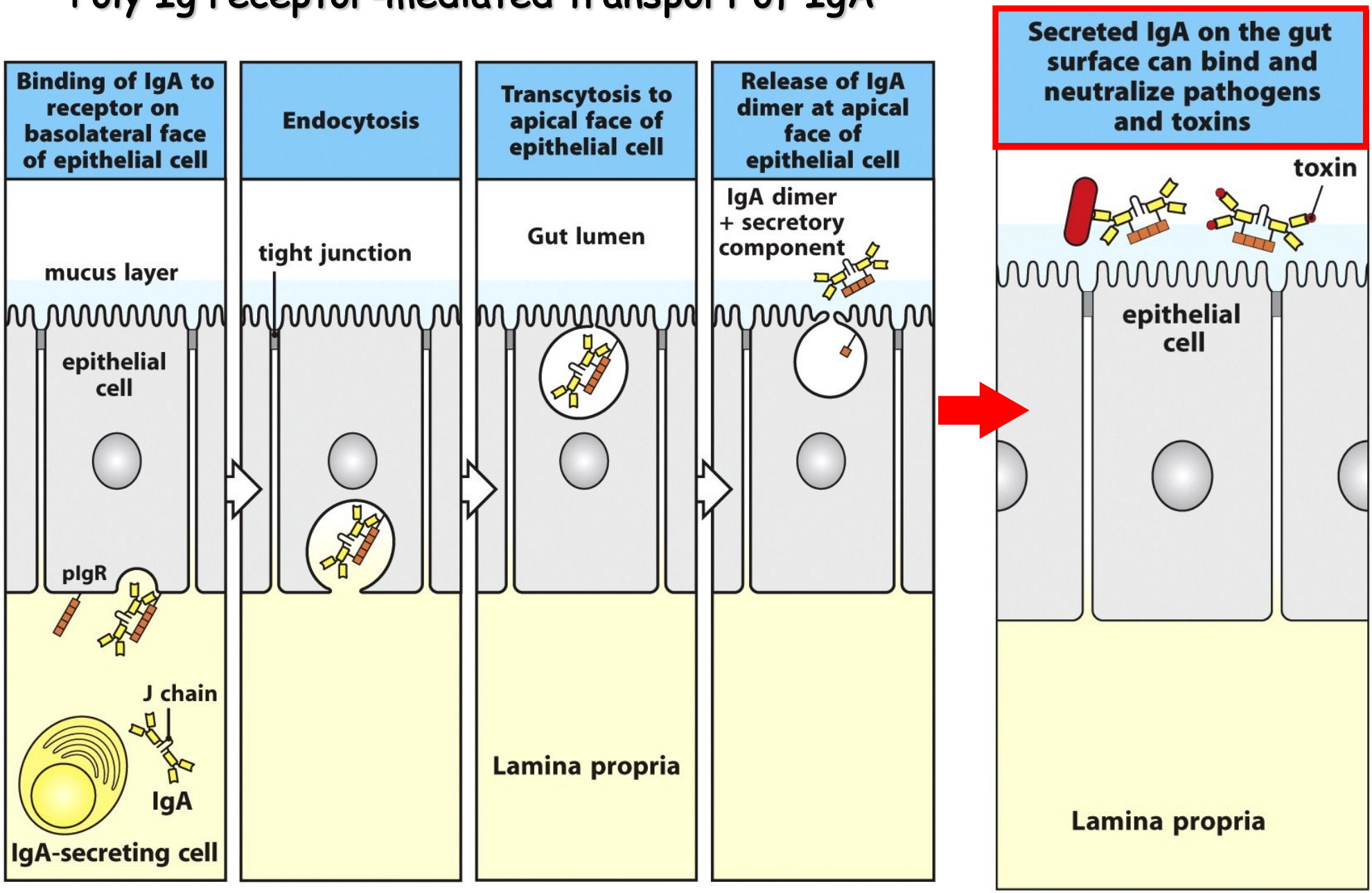
Poly Ig receptor-mediated transport of IgA through epithelial cells







Poly Ig receptor-mediated transport of IgA



IgA Functions

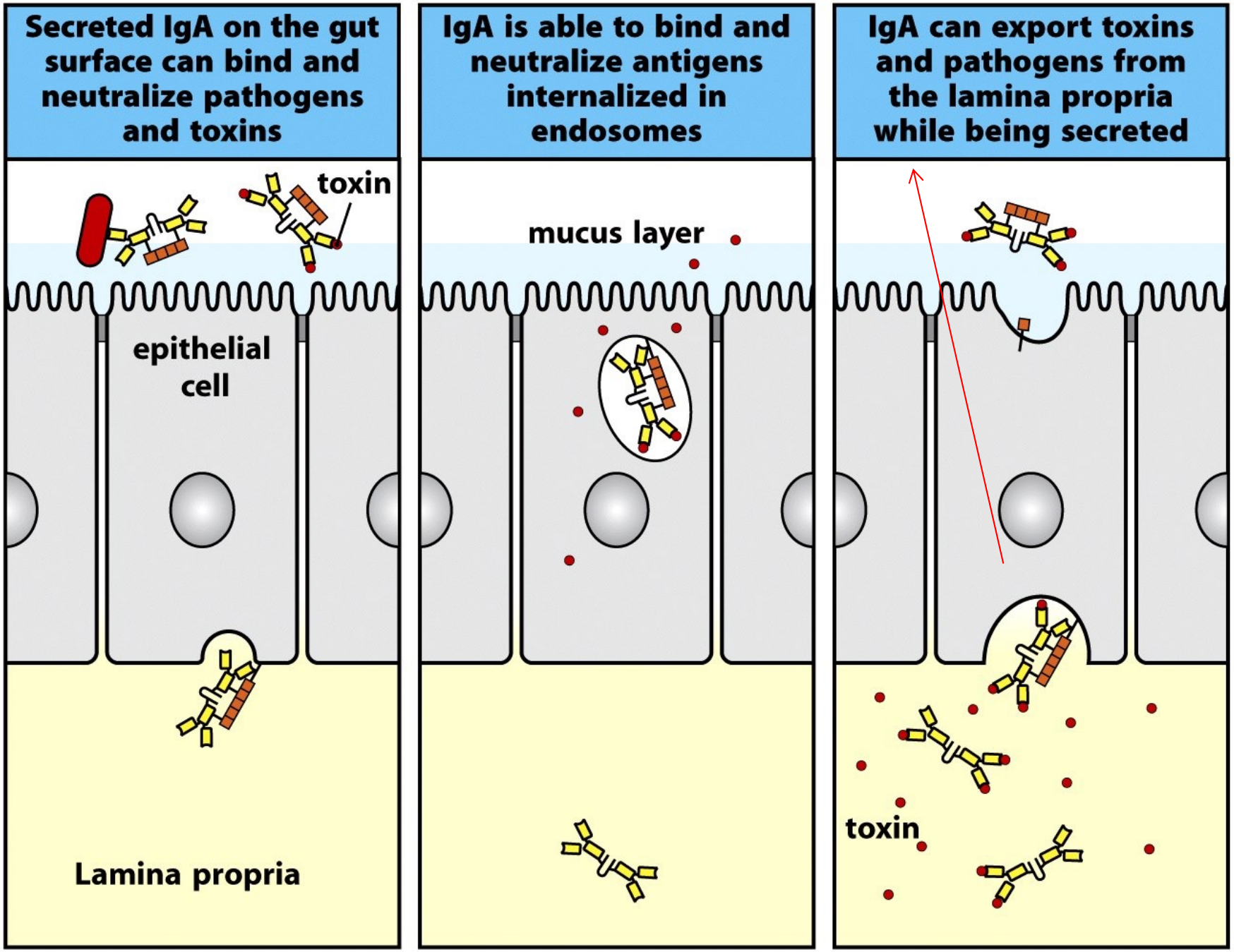


Figure 11-15 Immunobiology, 7ed. (© Garland Science 2008)

IgM

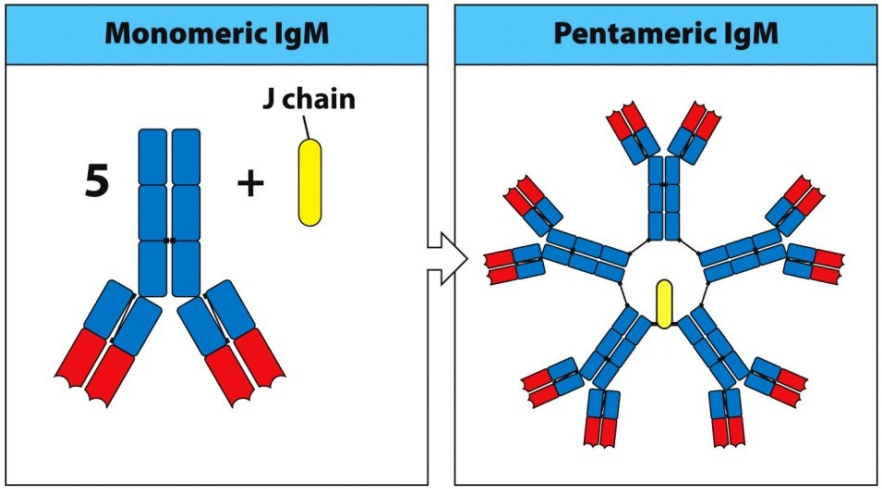
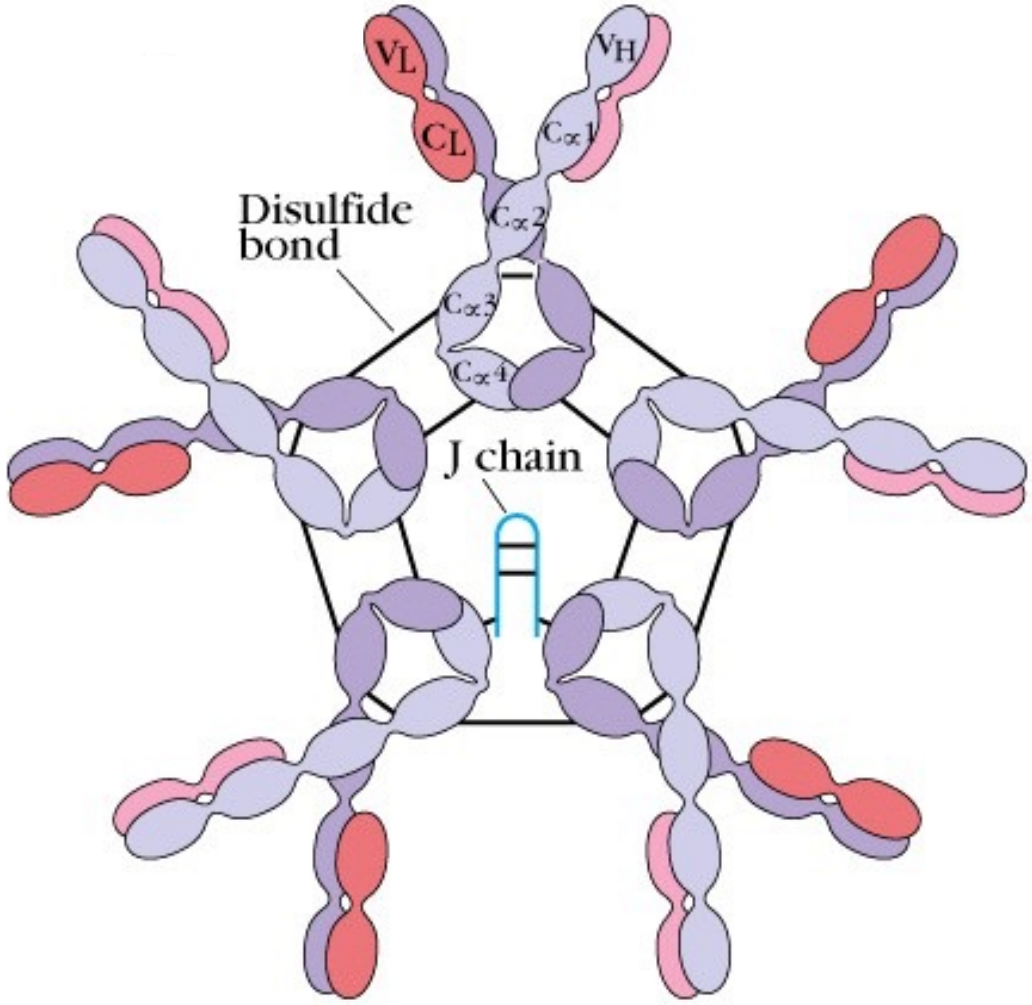
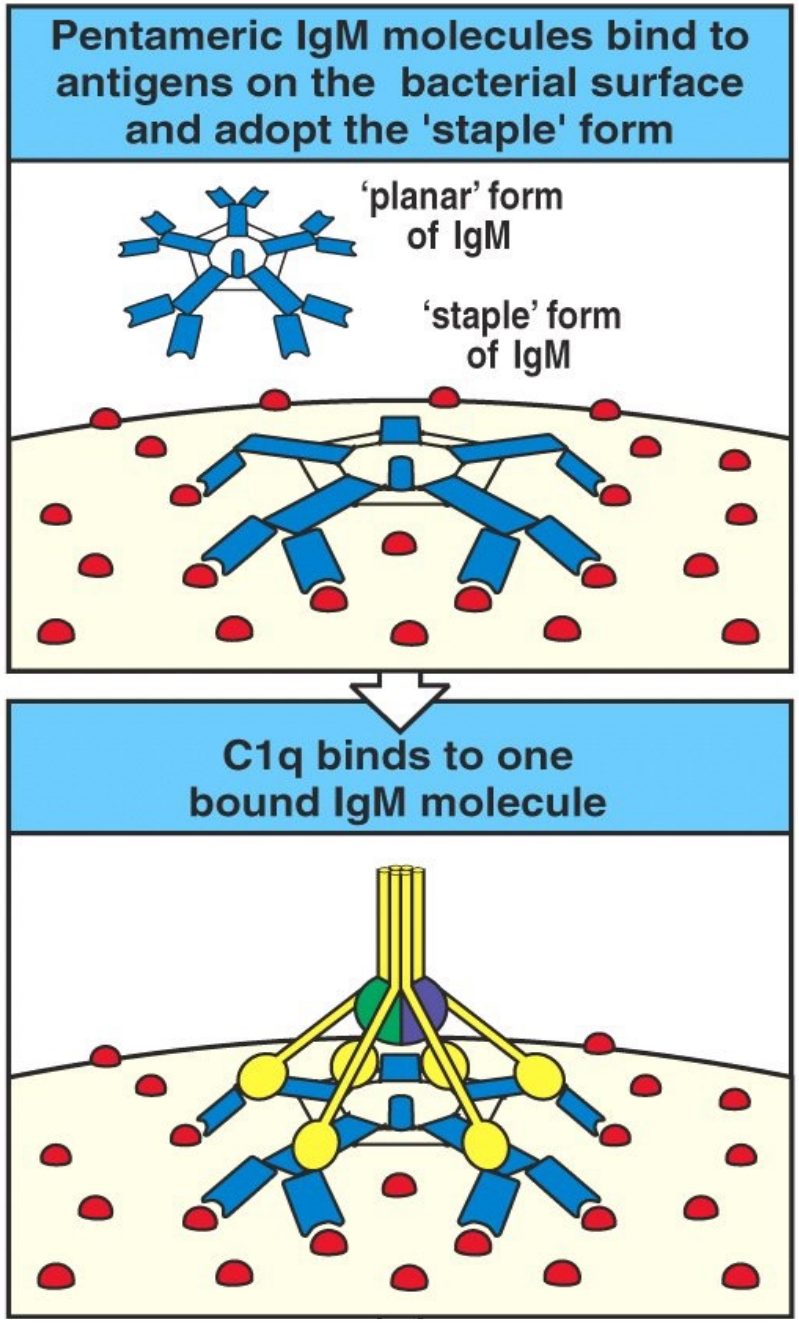


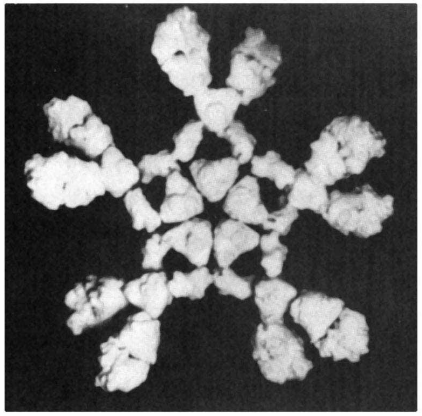
Figure 4.29 part 1 of 2 The Immune System, 3ed. (© Garland Science 2009)



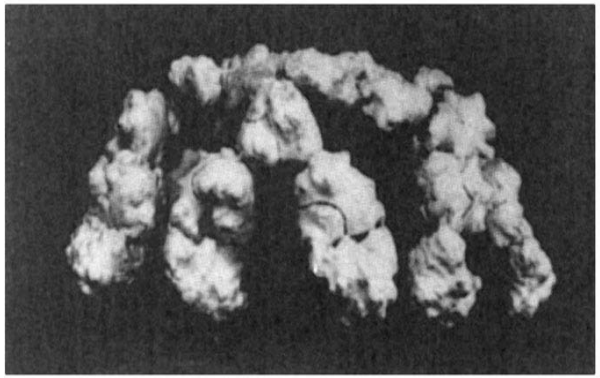
- E' sempre secreta in forma pentamerica
- E' l'isotipo più abbondante nella risposta primaria
- E' l'isotipo più efficiente nell'attivare il complemento

Il legame con l'antigene cambia la conformazione dell'IgM





Le IgM libere hanno una conformazione planare e non sono in grado di fissare il complemento.



Il legame con l'antigene induce un cambiamento conformazionale che rende accessibile la porzione costante.

L'IgM complessata lega il componente C1q del complemento attivandolo.

Le IgM complessate all'antigene attivano la via classica del complemento

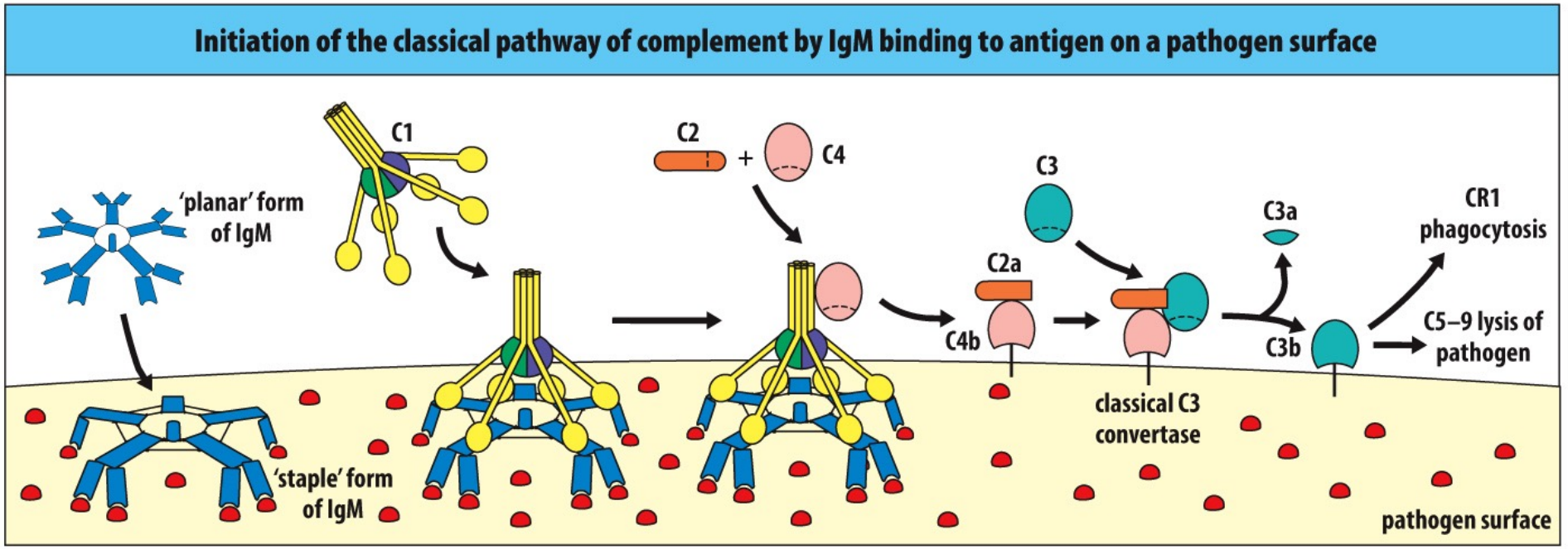
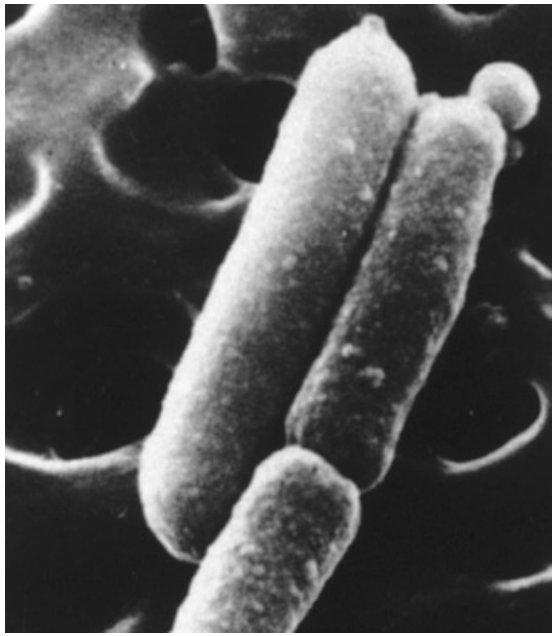
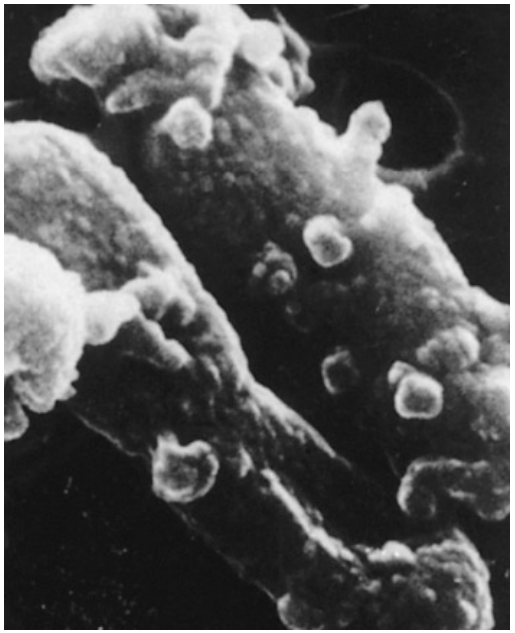


Figure 9.28 The Immune System, 4th ed. (© Garland Science 2015)

Electron micrographs of the effect of antibodies and complement upon bacteria



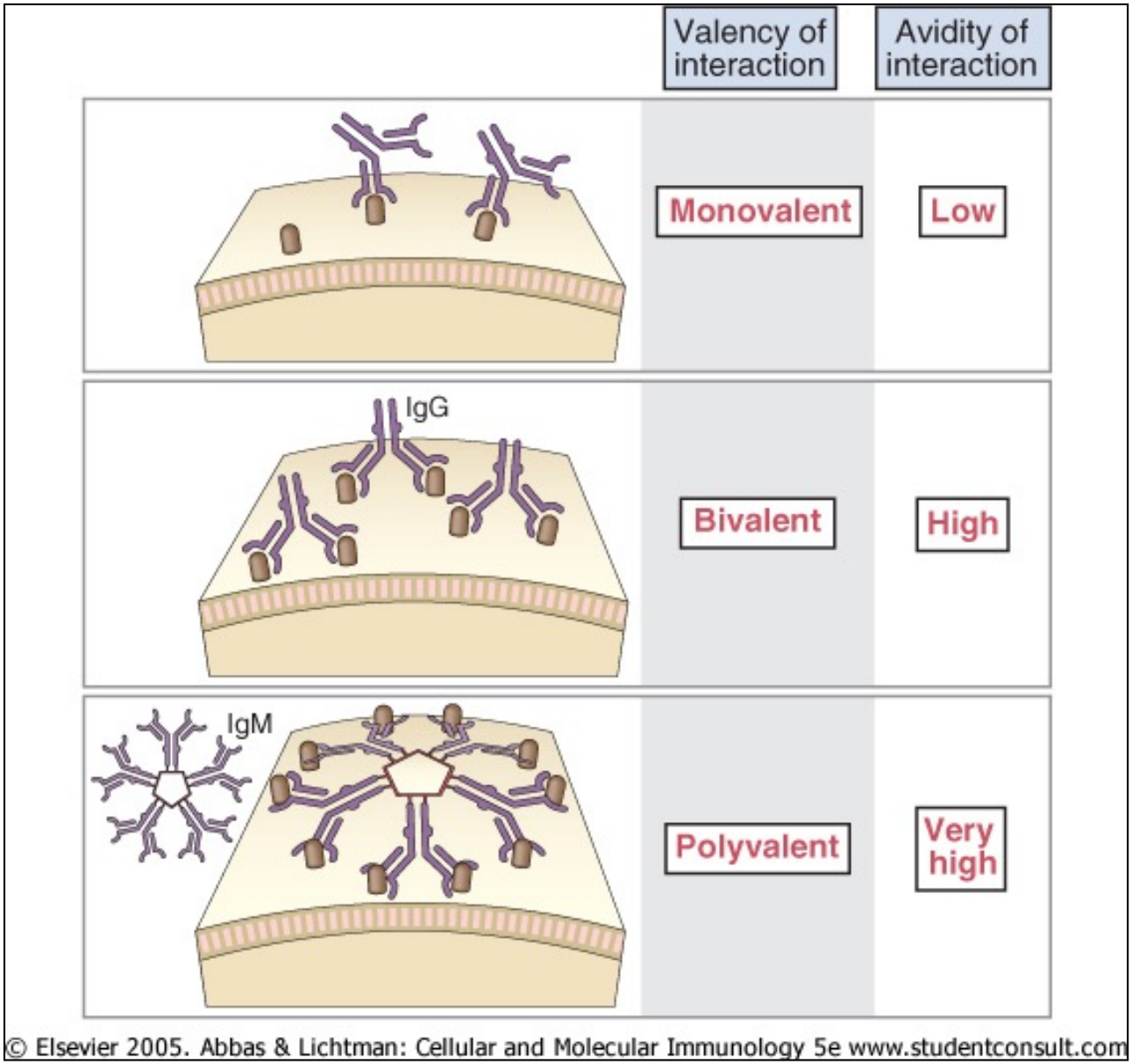
Healthy E. coli



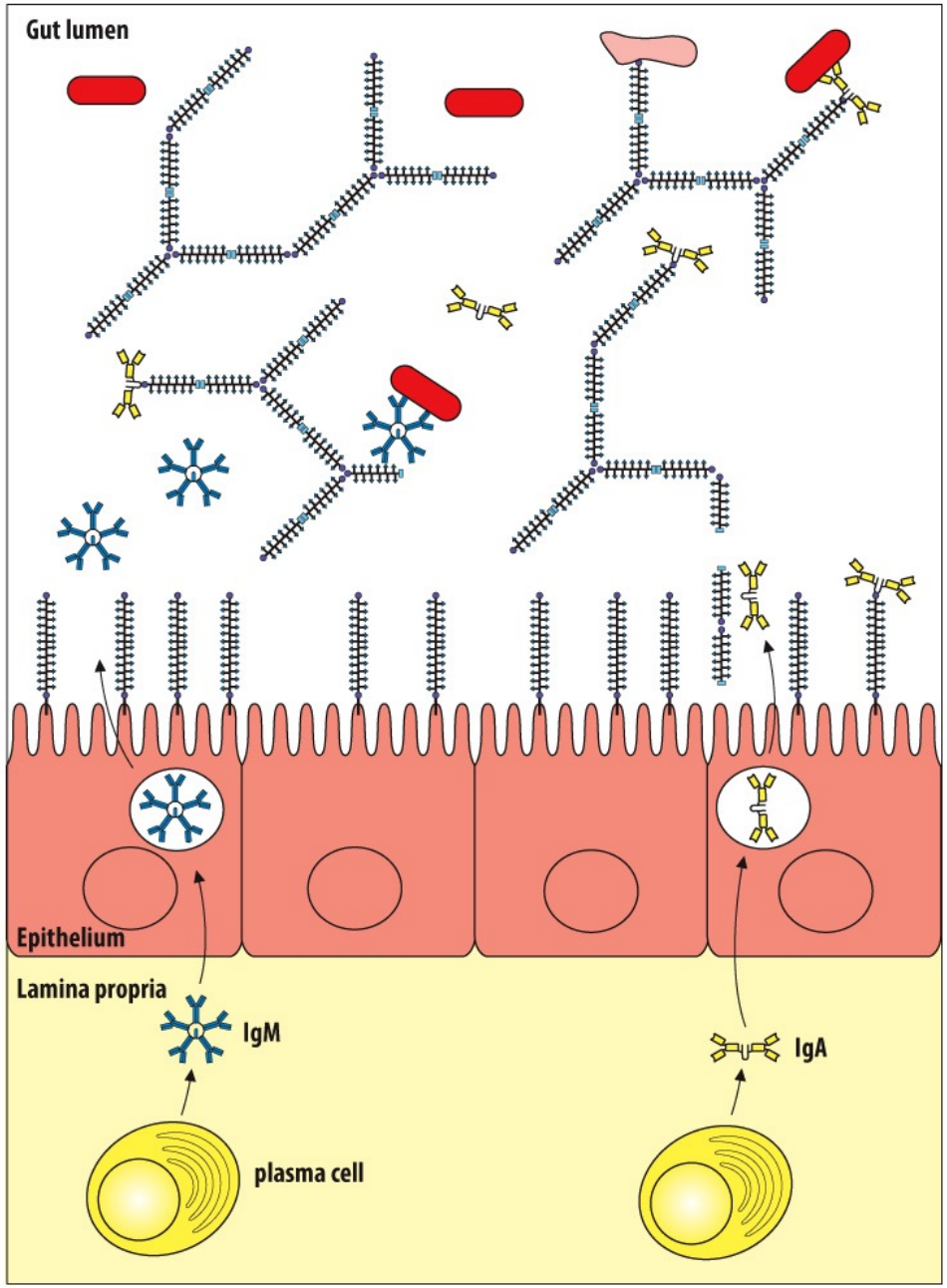
Antibody + complement- mediated damage to E. coli

The avidity of IgM interaction is very high!

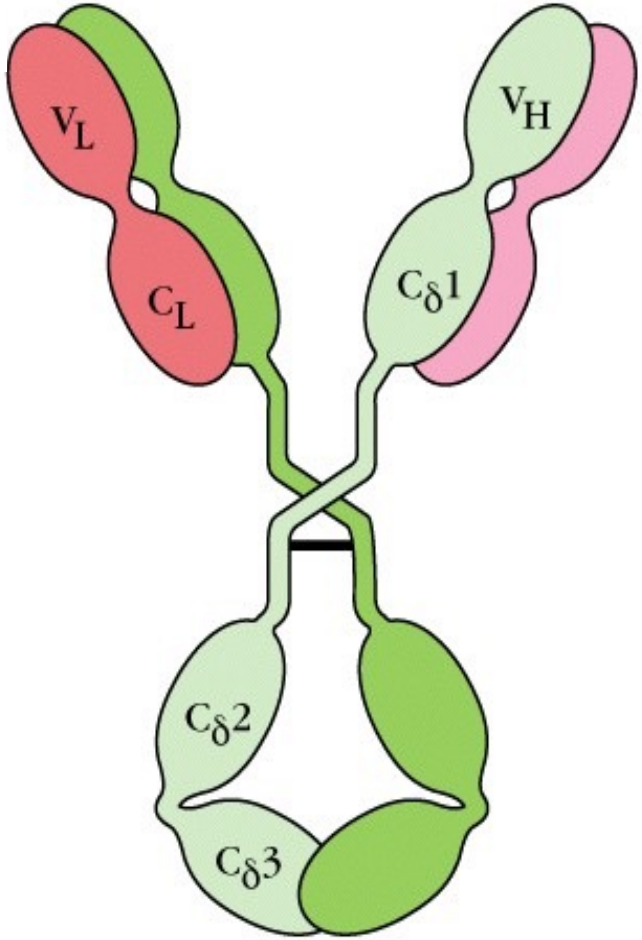
Affinity ≠ Avidity



Secretory IgM protects together with IgA mucosal surfaces from microbial invasion

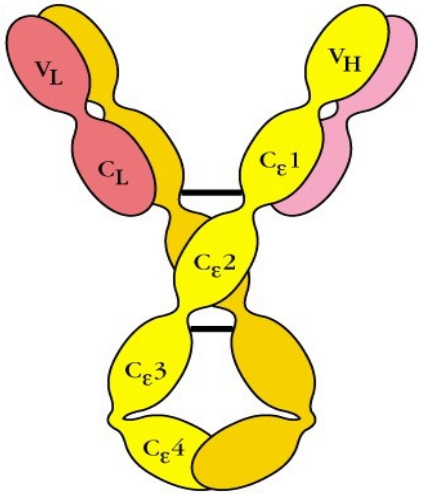


IgD



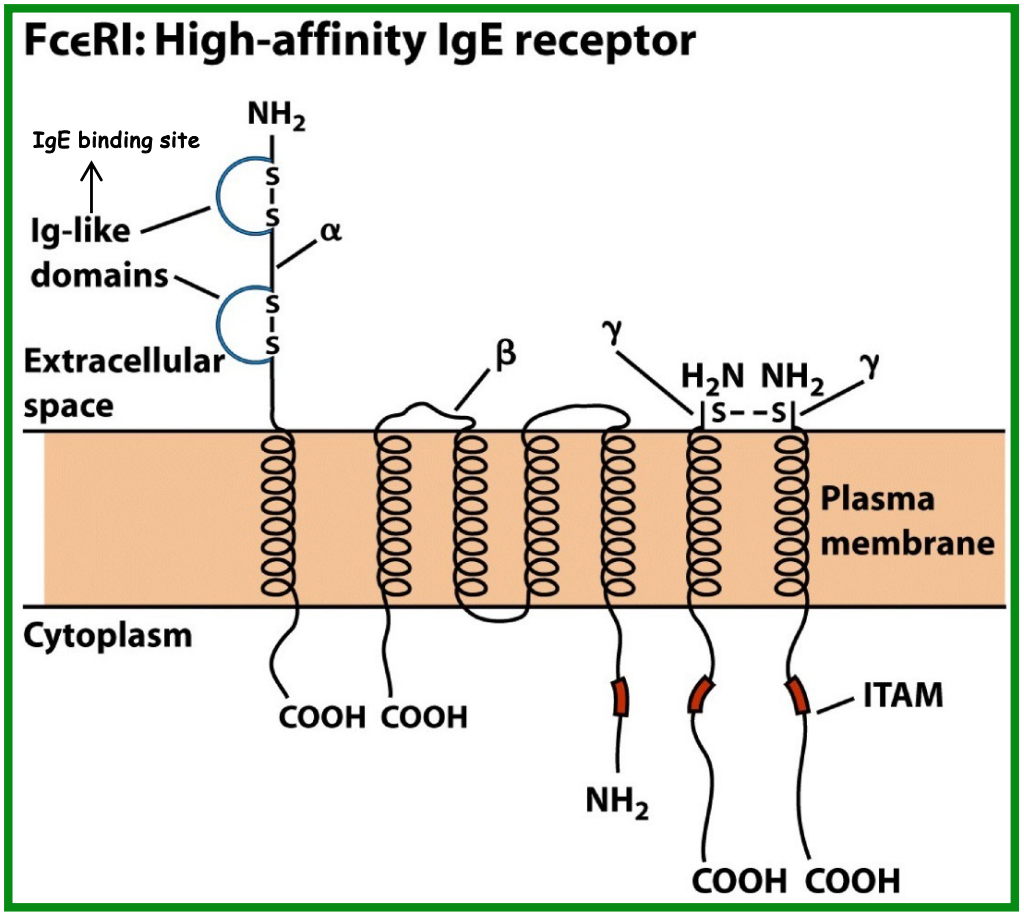
- E' co-espressa con le IgM sulla membrana dei linfociti B naive
- Non è nota la funzione delle IgD rilasciate in forma secreta

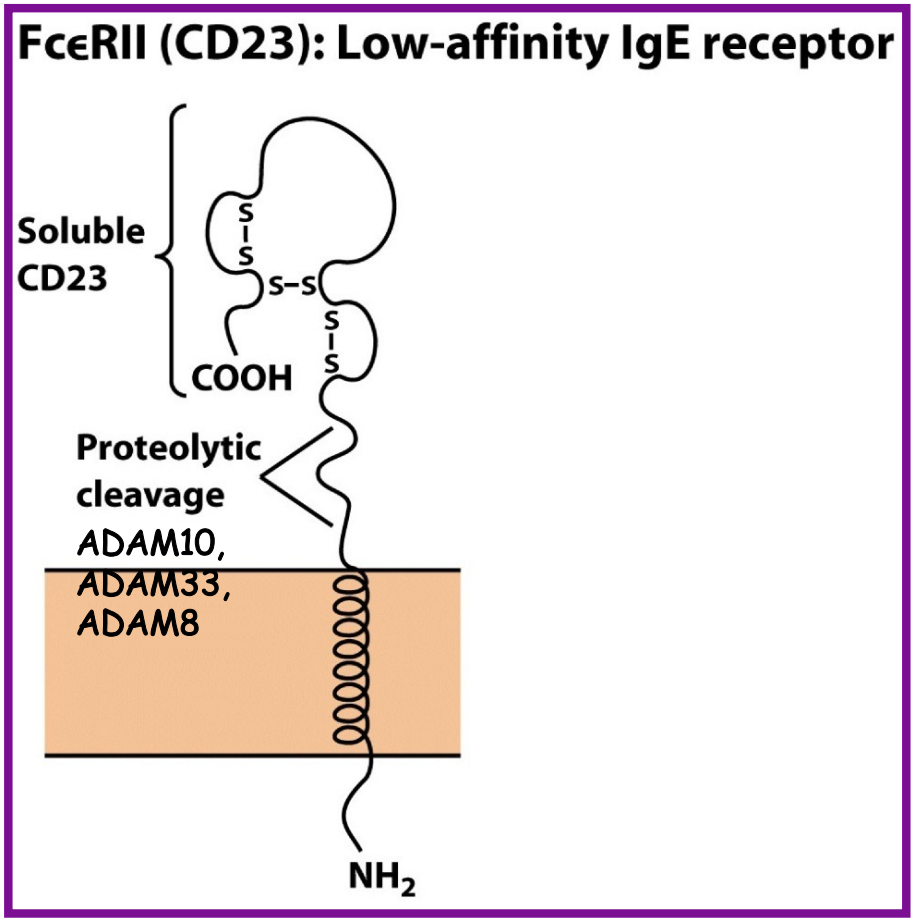
IgE



- Proteggono nei confronti di infezioni parassitarie (elminti)
  - Legano recettori Fcε espressi sui mastociti e granulociti

I recettori Fc per le IgE

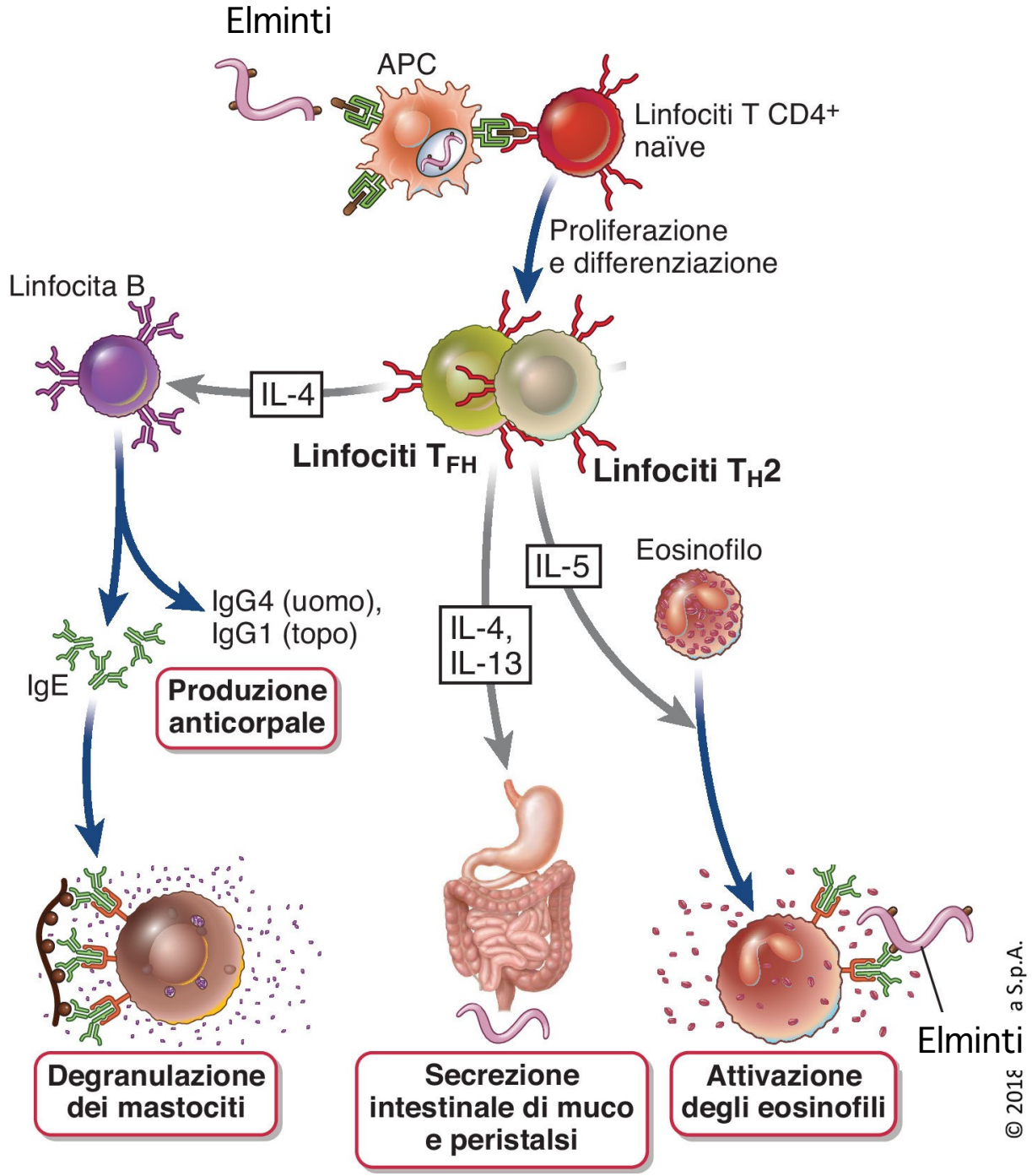




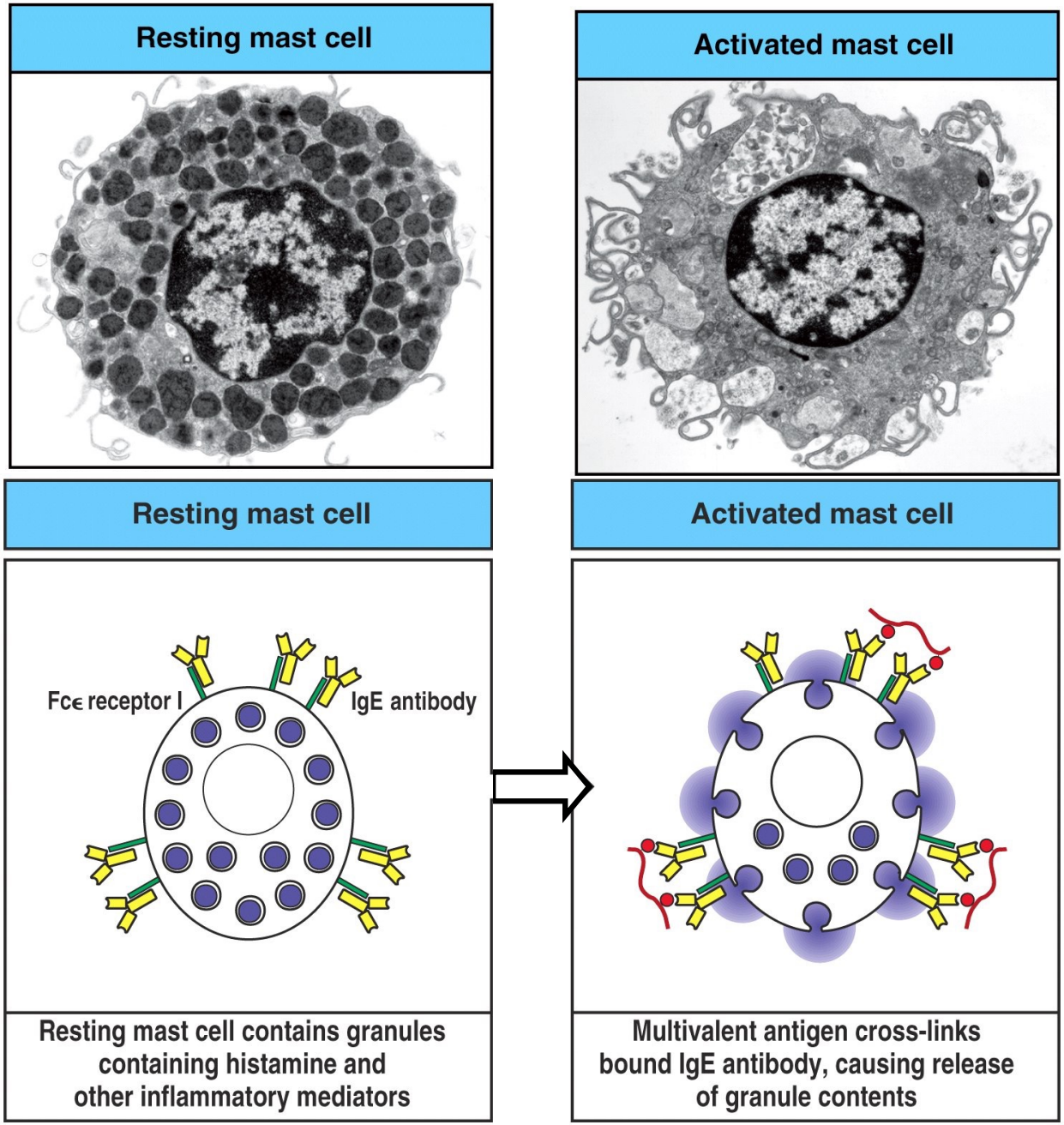
Mastociti, granulociti basofili,
cellule di Langerhans,
monociti attivati
eosinofili (bassi livelli)

Granulociti eosinofili,
altre cellule (linfociti B)

Effector functions in helmint infections

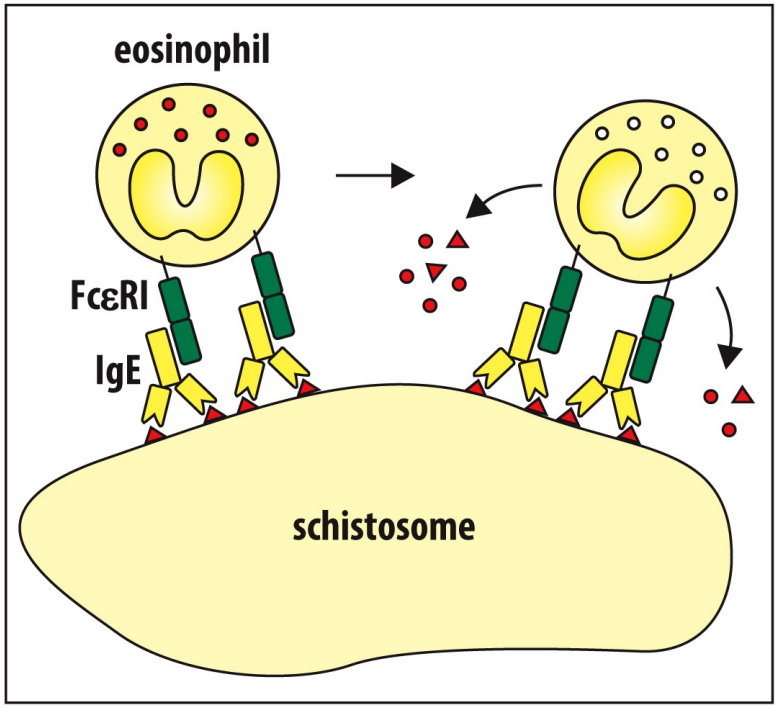


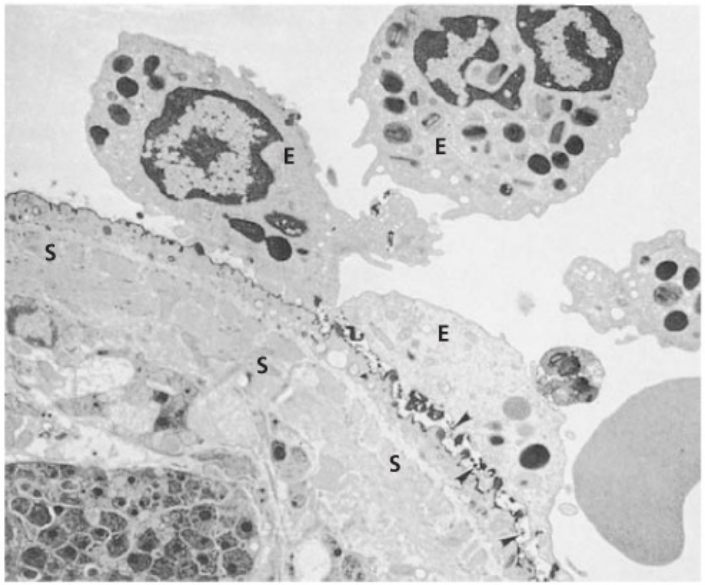
IgE antibody cross-linking on mast cell leads to a rapid relese of pro-inflammatory mediators

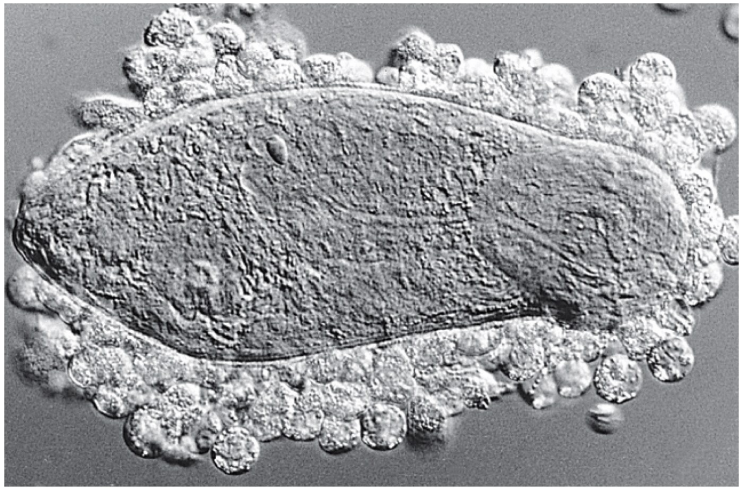


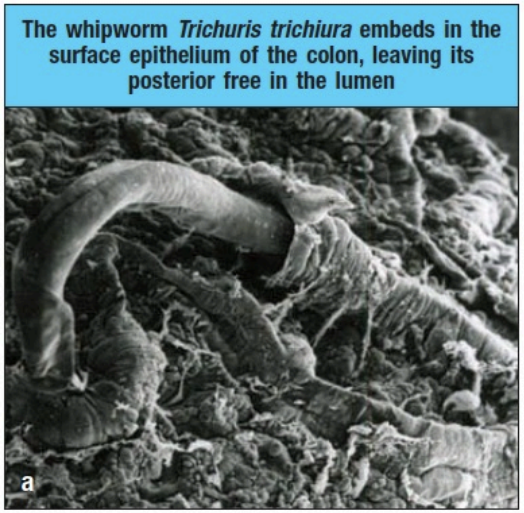
IgE provides a mechanism for the rapid ejection of parasites

I RECETTORI Fcε ESPRESSI SUGLI EOSINOFILI PROMUOVONO LA CITOTOSSICITA' CELLULARE ANTICORPO DIPENDENTE (ADCC)





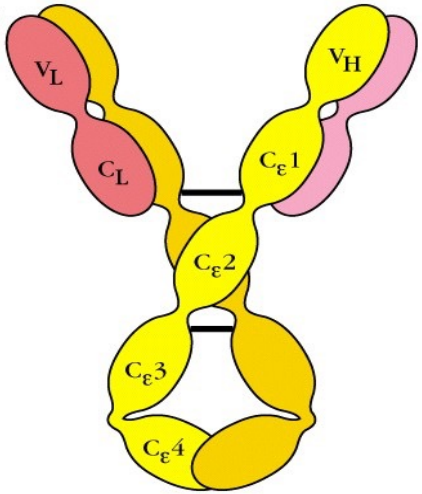




LE PRINCIPALI FUNZIONI EFFETTRICI DEGLI ANTICORPI

Function	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Neutralization	+	–	+++	+++	+++	+++	+++	–
Opsonization	–	–	+++	*	++	+	+	–
Sensitization for killing by NK cells	–	–	++	–	++	–	–	–
Sensitization of mast cells	–	–	+	–	+	–	–	+++
Activation of complement system	+++	–	++	+	+++	–	+	–

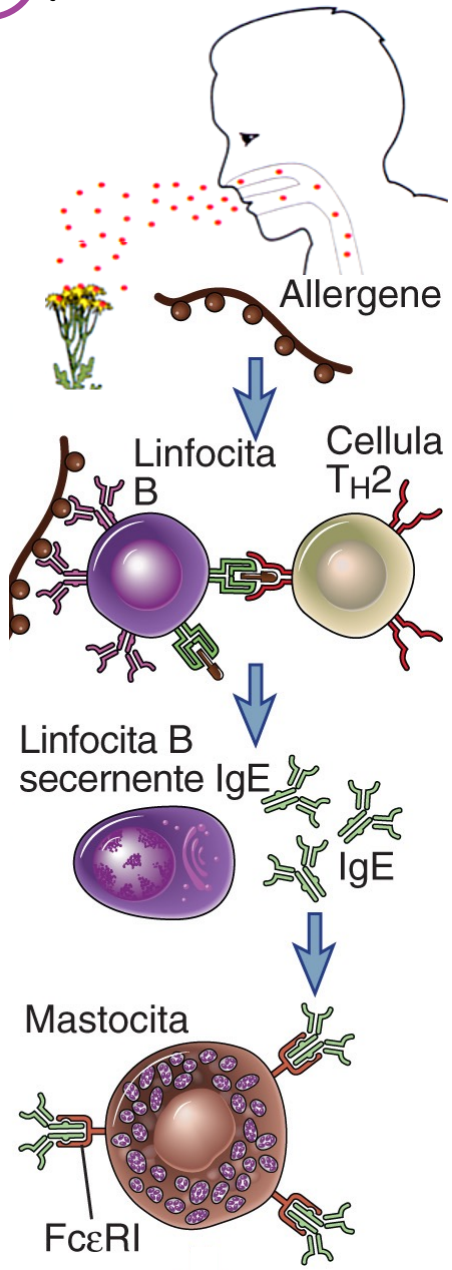
IgE



- Proteggono nei confronti di infezioni parassitarie (Elminti)
  - Legano recettori Fc espressi sui mastociti e granulociti eosinofili
- Mediano le reazioni allergiche

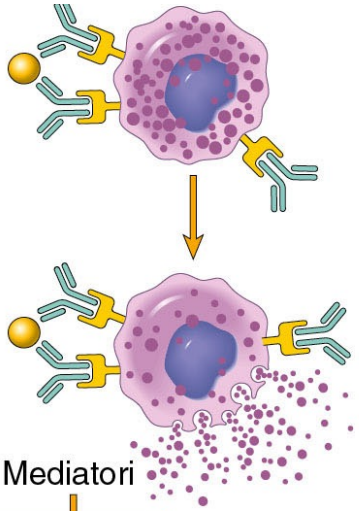
La reazione allergica: una visione integrata

1 fase di sensibilizzazione



2 fase di scatenamento

La seconda esposizione allo stesso allergene attiva il mastocita con conseguente rilascio dei mediatori proinfiammatori



Amine vasoattive, mediatori lipidici → **Reazione di ipersensibilità immediata (entro pochi minuti dall'esposizione all'antigene)**

Citochine → **Reazione tardiva (2-8 ore dopo l'esposizione ripetuta all'allergene)**