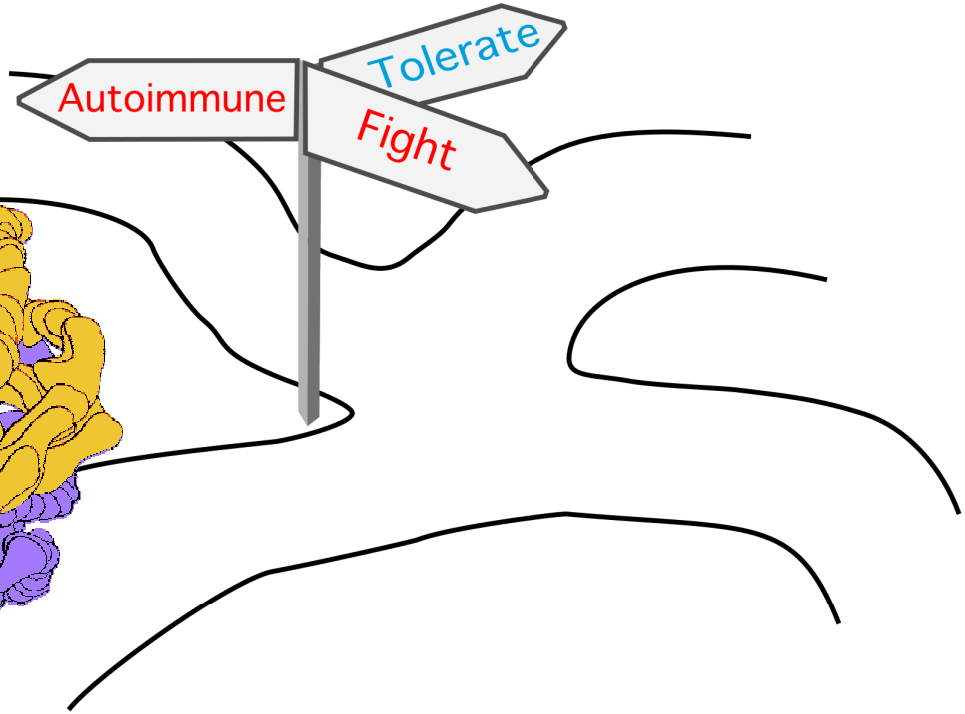
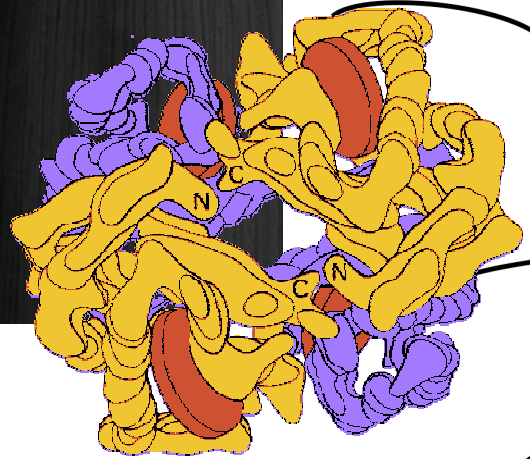
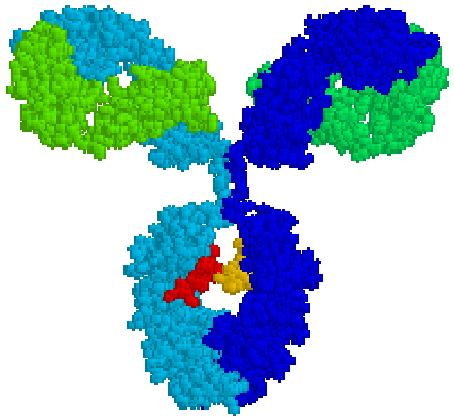
Inmunología Clínica 2009

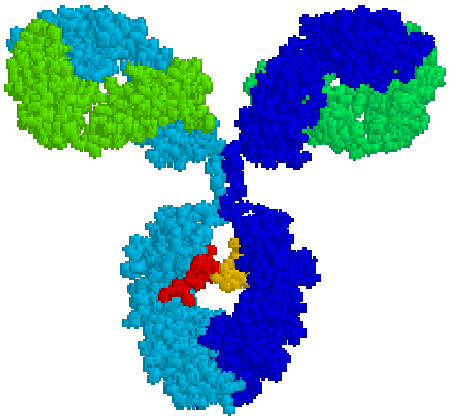
Bioq GRACIELA R SVIBEL DE MIZDRAJI







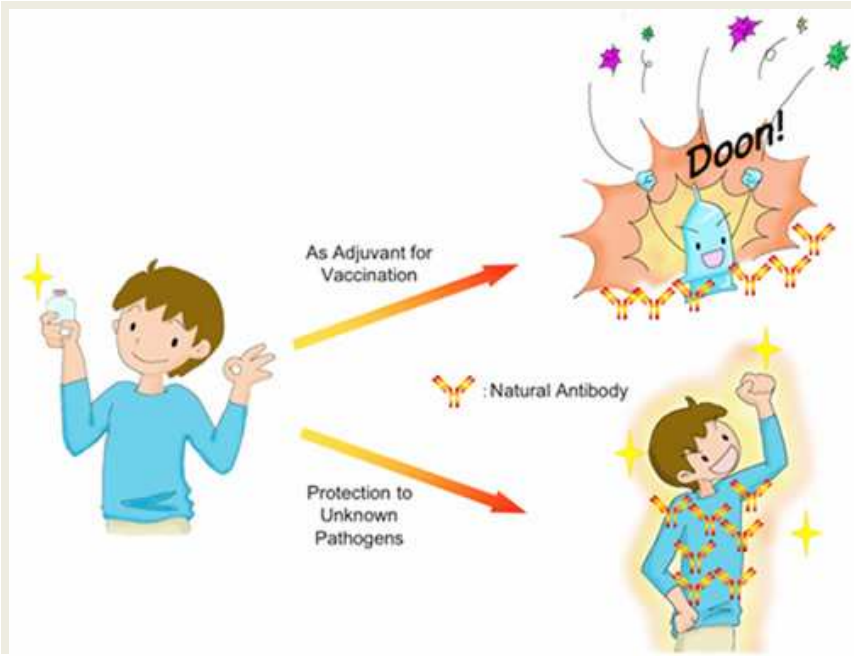
INMUNOGLOBULINAS-ANTICUERPOS



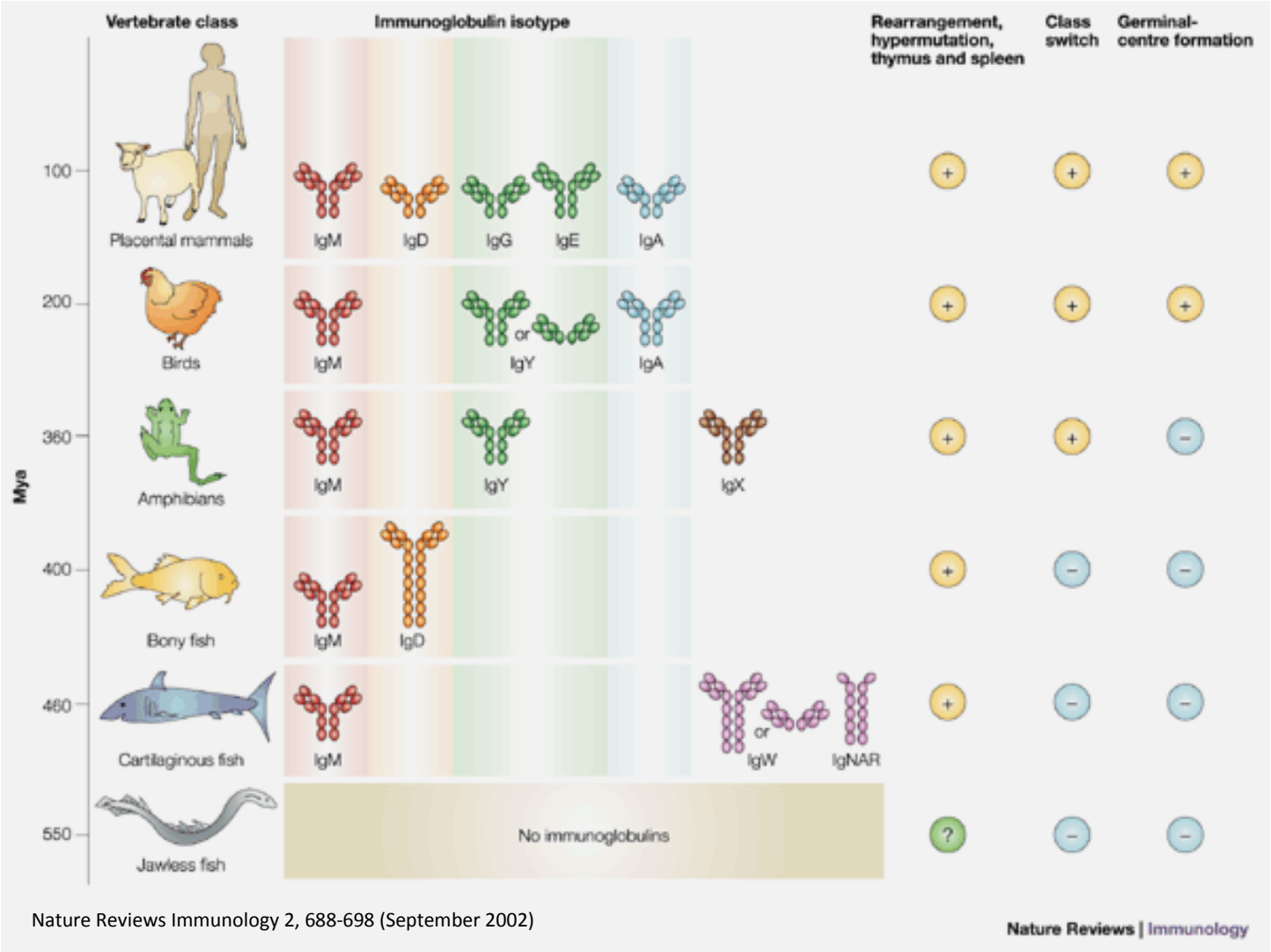
Definimos....

- Las INMUNOGLOBULINAS son Glicoproteínas presentes en el suero de un individuo y se generan en respuesta al ingreso de antígenos extraños ; su función más importante es proteger al huésped al erradicar los agentes patógenos.

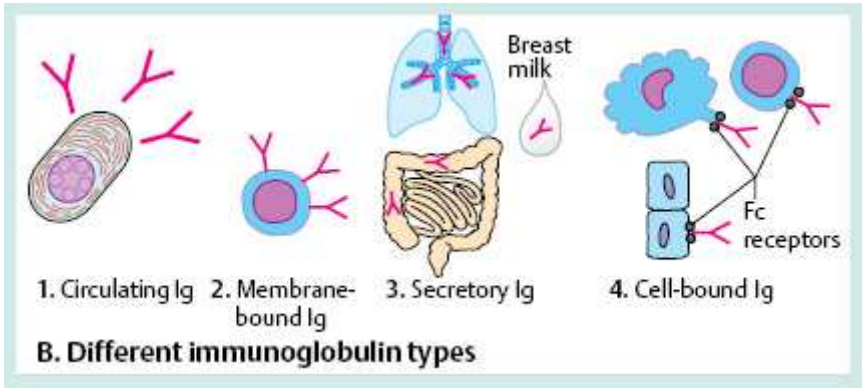
  Los **ANTICUERPOS** pertenecen a este grupo de proteínas y se caracterizan por su reactividad específica con el correspondiente antígeno



Las inmunoglobulinas en las distintas especies

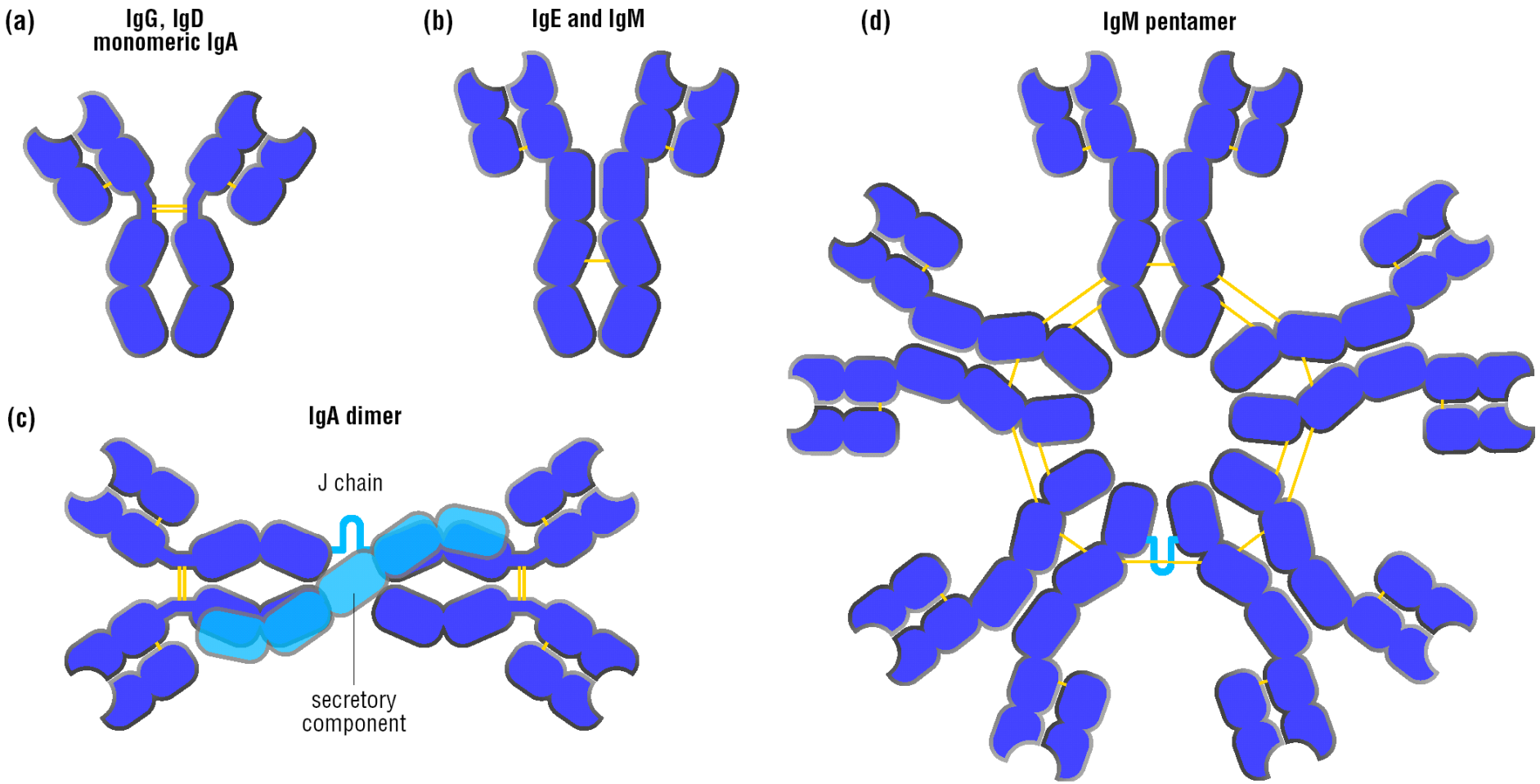


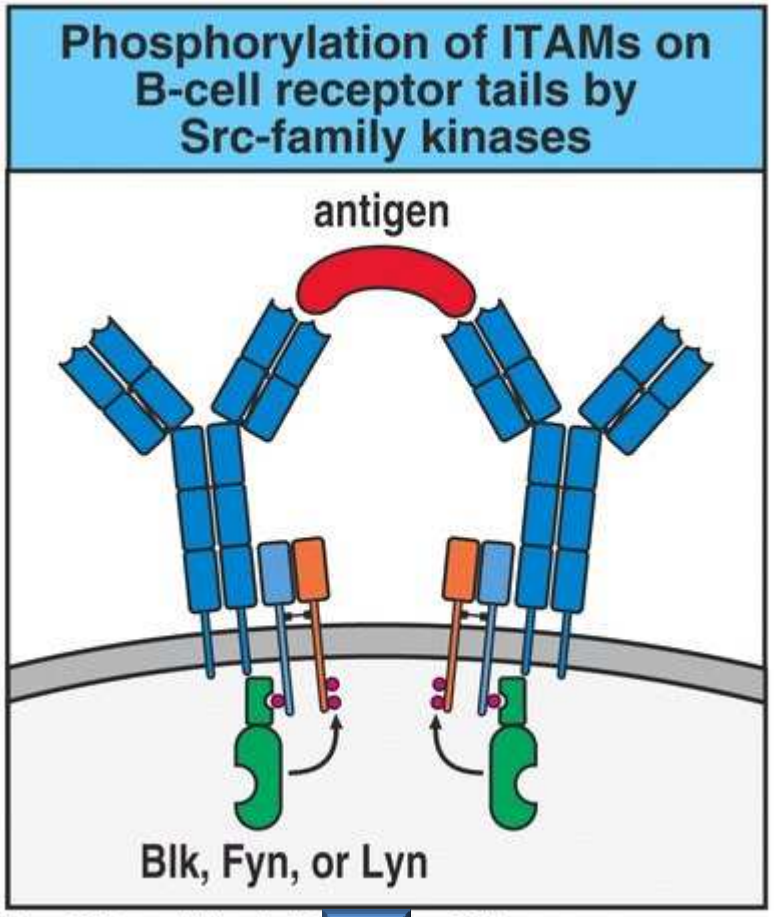
Nature Reviews Immunology 2, 688-698 (September 2002)



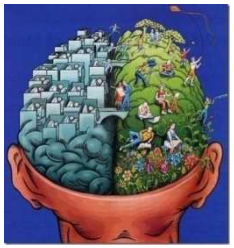
- **Libre en el suero (circulantes): MONÓMERO, DÍMERO, PENTÁMERO…..**
- **Unida a la membrana celular (BCR): MONOMÉRICA**
- **INMUNOGLULINA SECRETADA**
- **Unida al receptor celular específico (FcR)**

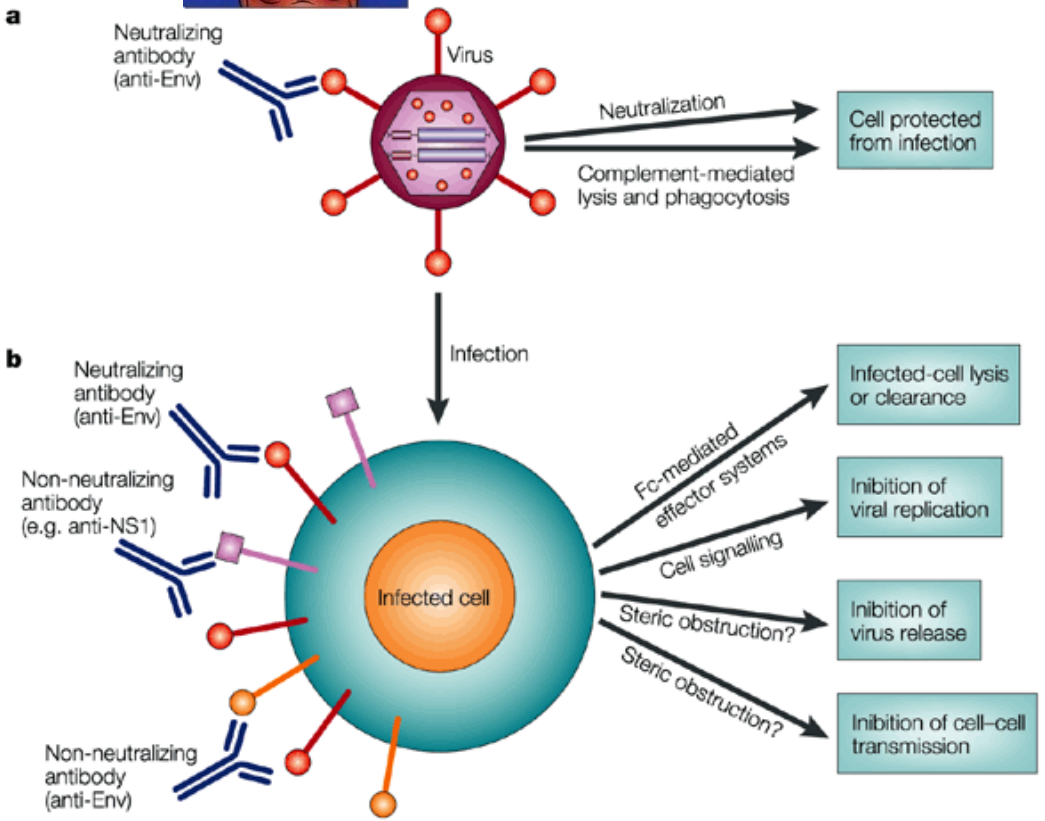
¿CÓMO PUEDE PRESENARSE LA INMUNOGLOBULINA/ANTICUERPO??


(a)
IgG, IgD
monomeric IgA
(b)
IgE and IgM
(d)
IgM pentamer
(c)
IgA dimer
J chain
secretory
component



Activación celular

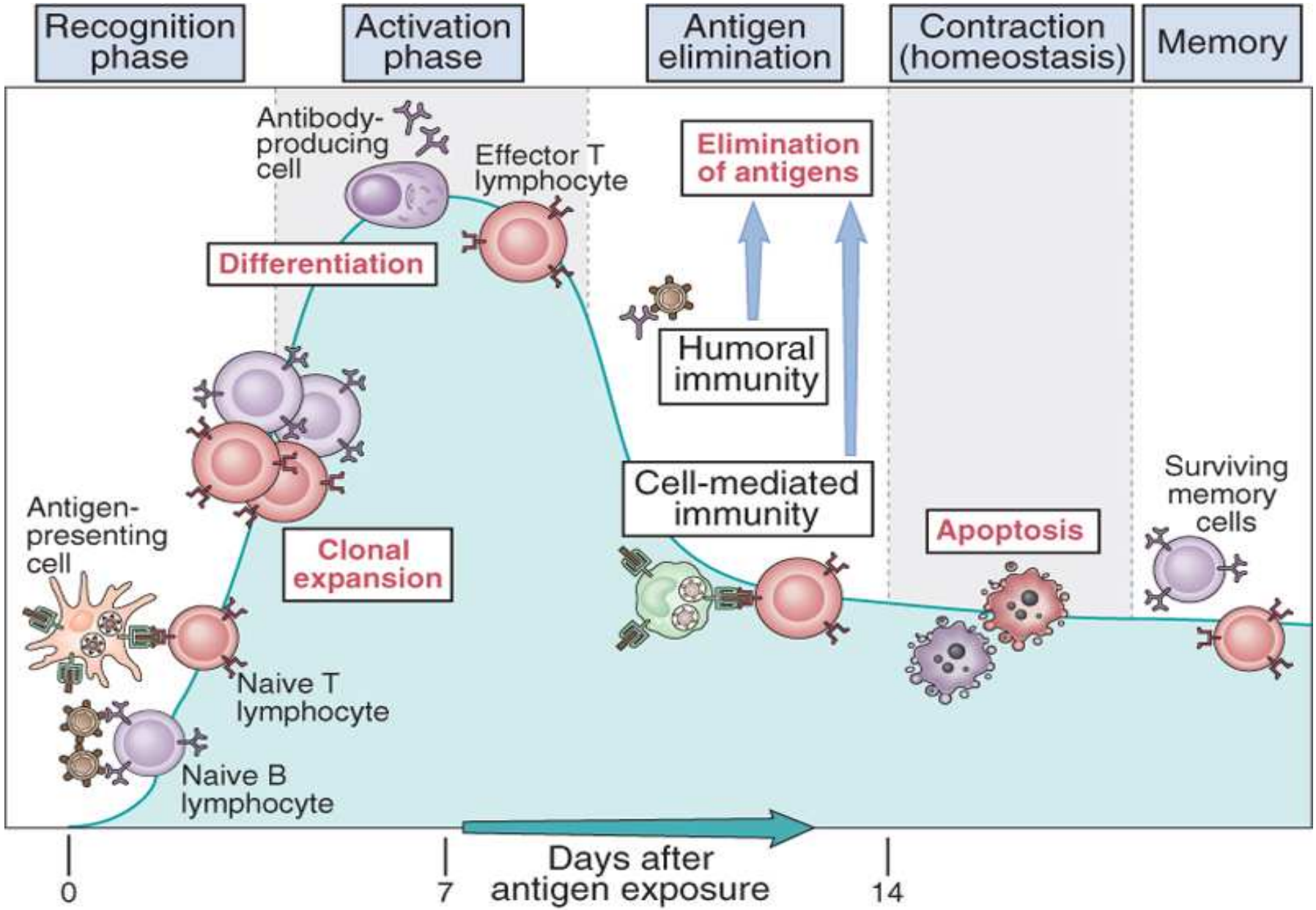


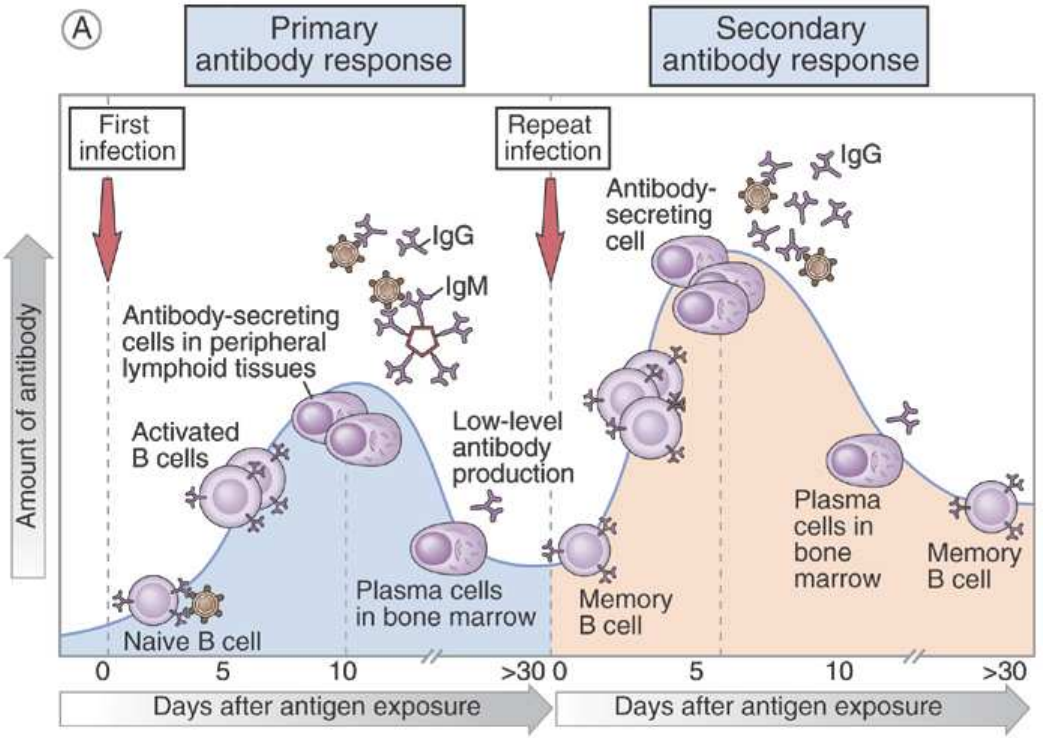


¿Por qué son importantes los anticuerpos???

1. La presencia de anticuerpos específicos protege contra patógenos a los que reaccionamos en el pasado: **MEMORIA.**
2. Su falta provoca **INMUNODEFICIENCIA**.

   Incluso deficiencias de algún isotipo (IgA) o déficits cuantitativos pueden comprometer la inmunocompetencia.
3. La presencia de **autoanticuerpos de isotipo IgG** contribuye a la **AUTOINMUNIDAD**.
4. La presencia de **IgE alergenoespecífica** contribuye a las **REACCIONES ALÉRGICAS (HS).**

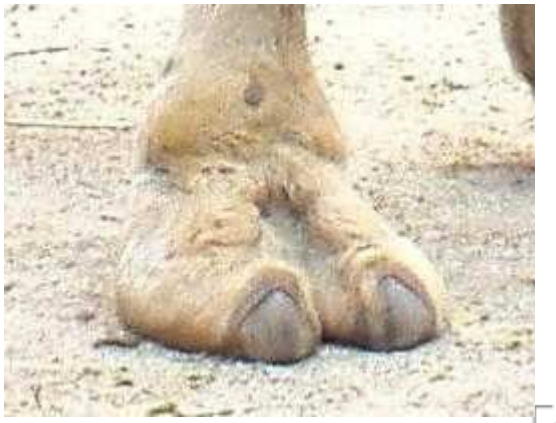


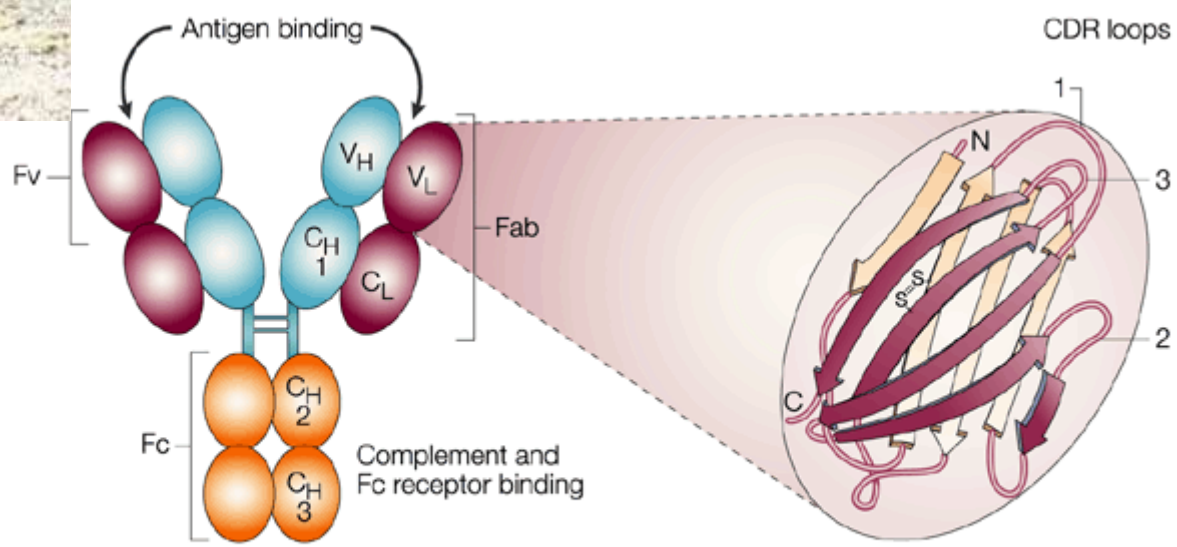


B

	Primary response	Secondary response
Lag after immunization	Usually 5-10 days	Usually 1-3 days
Peak response	Smaller	Larger
Antibody isotype	Usually IgM>IgG	Relative increase in IgG and, under certain situations, in IgA or IgE (heavy chain class switching)
Antibody affinity	Lower average affinity, more variable	Higher average affinity (affinity maturation)

ESTRUCTURA MOLECULAR DE LAS INMUNOGLOBULINAS





Nature Reviews Drug Discovery 2, 52-62 (January 2003)

Nature Reviews | Drug Discovery

Superfamilia de las INMUNOGLOBULINAS

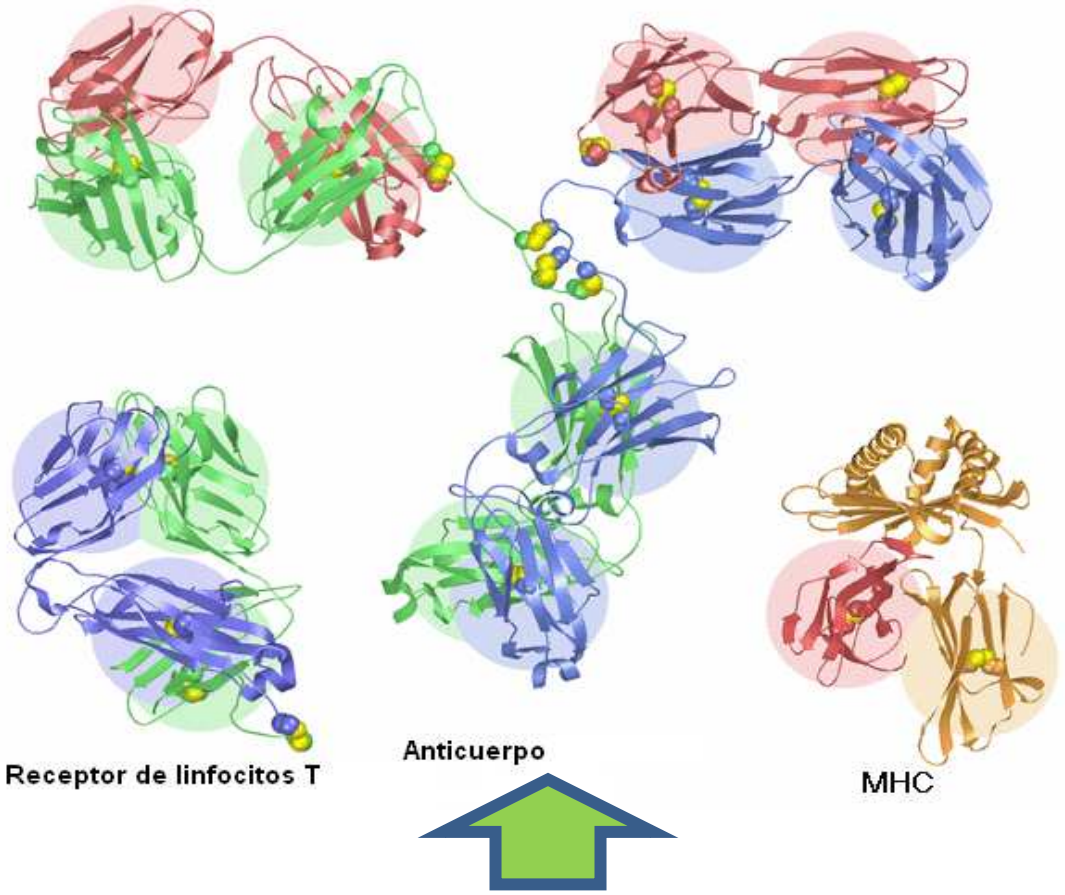
…..es un extenso grupo de proteínas solubles y de superficie celular que están implicadas en procesos de reconocimiento, unión o adhesión celular de las células.

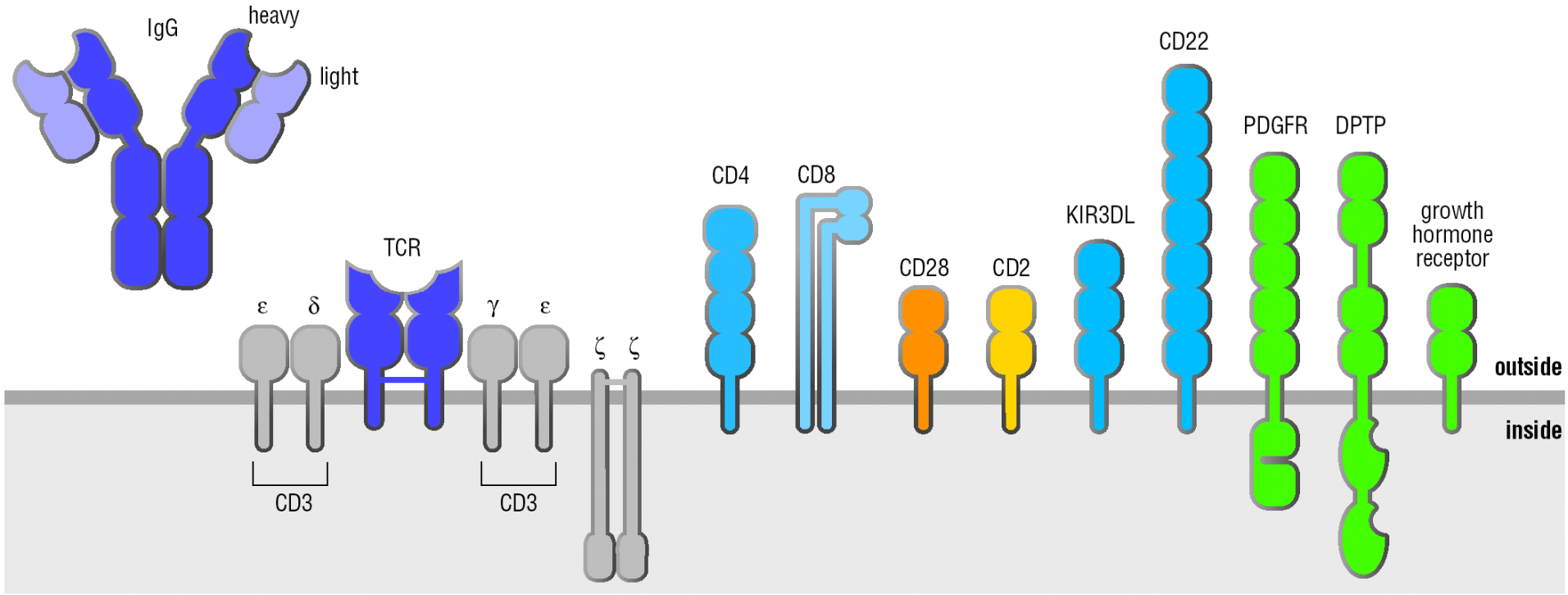
La asignación de una molécula a esta superfamilia se basa en que comparten rasgos estructurales con las inmunoglobulinas (también conocidas como anticuerpos).

Todas ellas poseen un dominio conocido como dominio o plegamiento inmunoglobulina.

Entre los miembros de la IgSF se incluyen receptores de antígenos en la superficie celular, correceptores y moléculas de coestimulación del sistema inmunitario, moléculas imlplicadas en la presentación de antígeno a los linfocitos, moléculas de adhesión celular y ciertos receptores de citocinas.

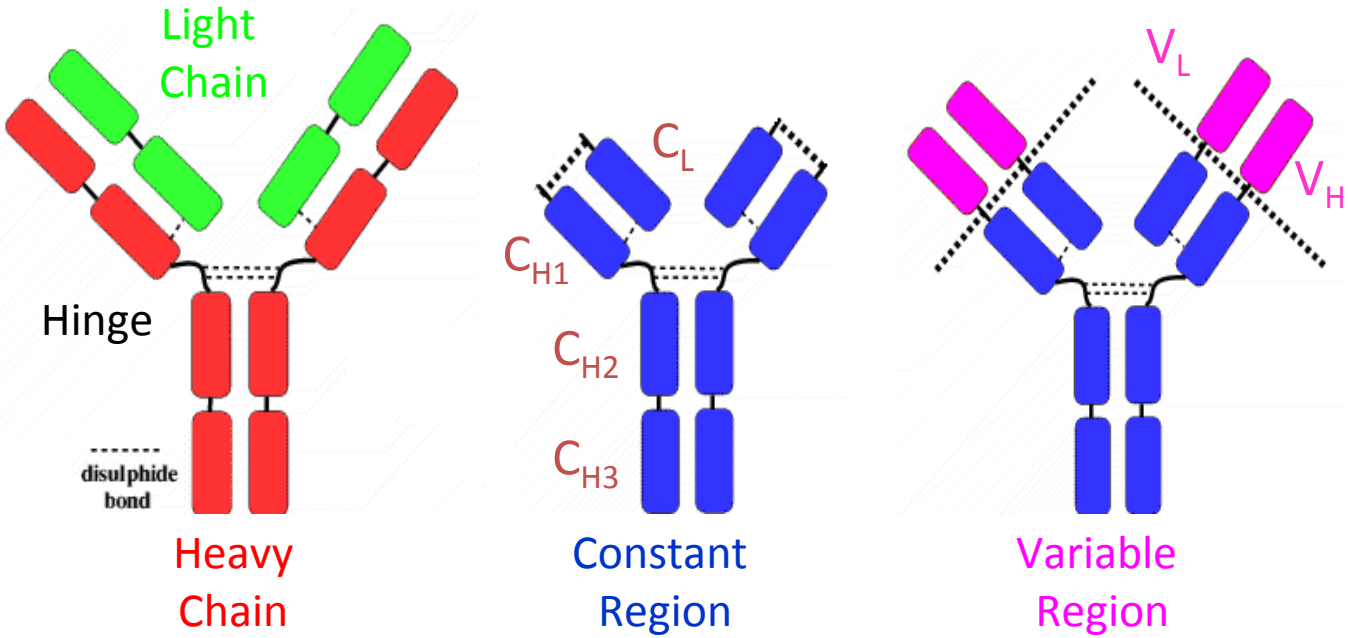
Habitualmente están asociadas con funciones del sistema inmunitario.

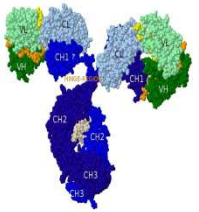



IgG
heavy
light
TCR
ε
δ
γ
ε
ζ
ζ
CD3
CD3
CD4
CD8
CD28
CD2
KIR3DL
CD22
PDGFR
DPTP
growth
hormone
receptor
outside
inside

GLICOPROTEÍNAS SINTETIZADAS POR LAS CÉLULAS PLASMÁTICAS EN RESPUESTA A UN ESTÍMULO ANTIGÉNICO……

Están formadas por cuatro cadenas polipeptídicas (IgG)

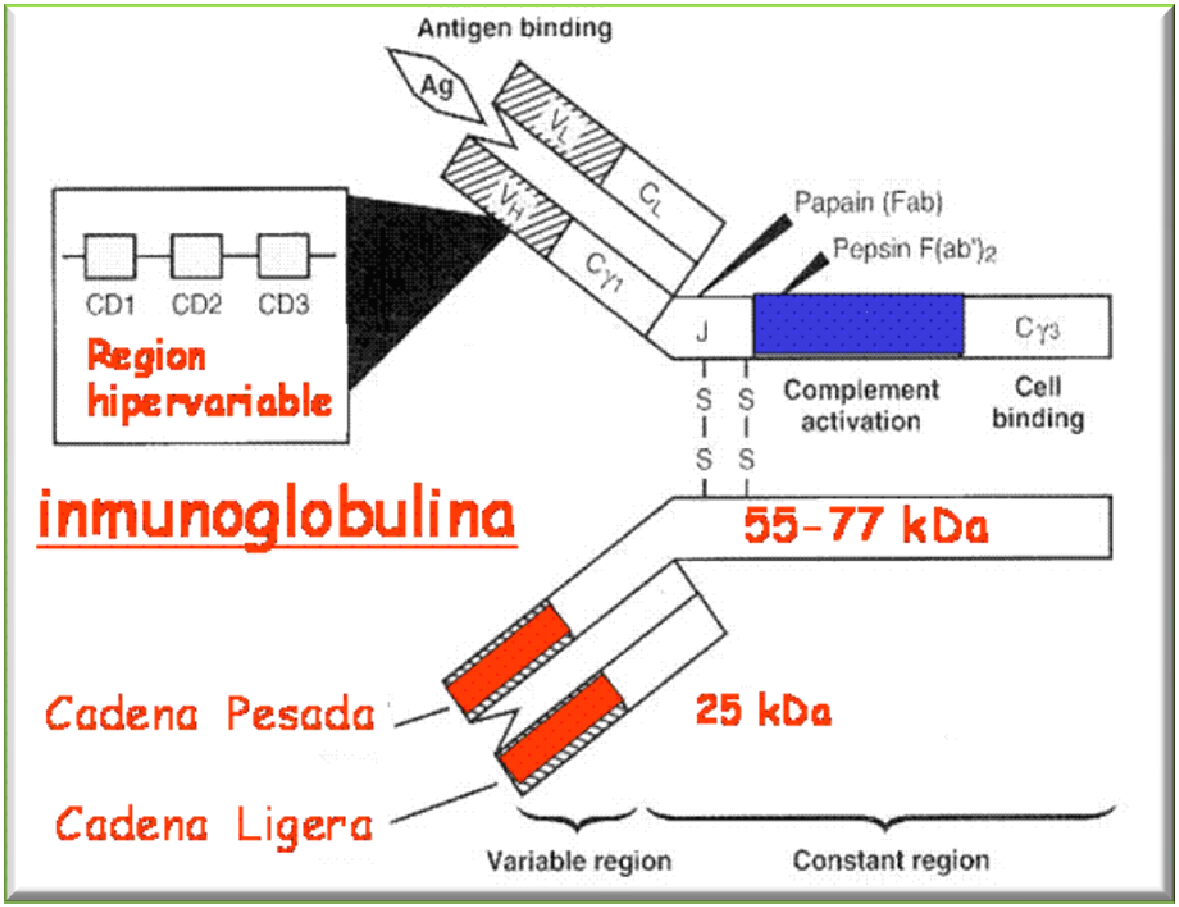


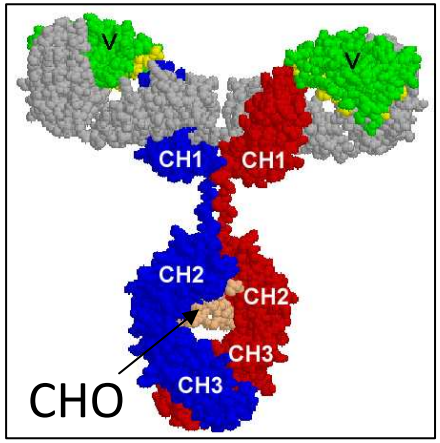


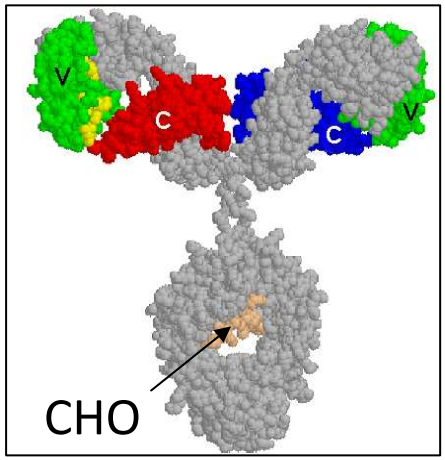
a) **Dos cadenas ligeras (25 Kd) y estructura común a todas las subclases** (Kappa y lambda), pero en una misma molécula de Ig, las dos cadenas son del mismo tipo. Se ha comprobado que está compuesta por dos regiones:

- **CL (extremo C-terminal):** región constante de la cadena ligera (107 aminoácidos), excepto para ciertas variaciones alotípicas e isotípicas.
- **VL (extremo N-terminal):** región variable (incluye variaciones idiotípicas).

b) Dos pesadas (55-70 Kd): estructura diferente para cada clase y subclase. Están **N-glicosiladas** y la cantidad de azúcares varía desde el 2% de la IgG al 12-14% de la IgM, IgD e IgE.



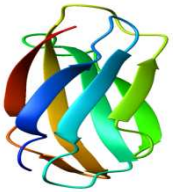


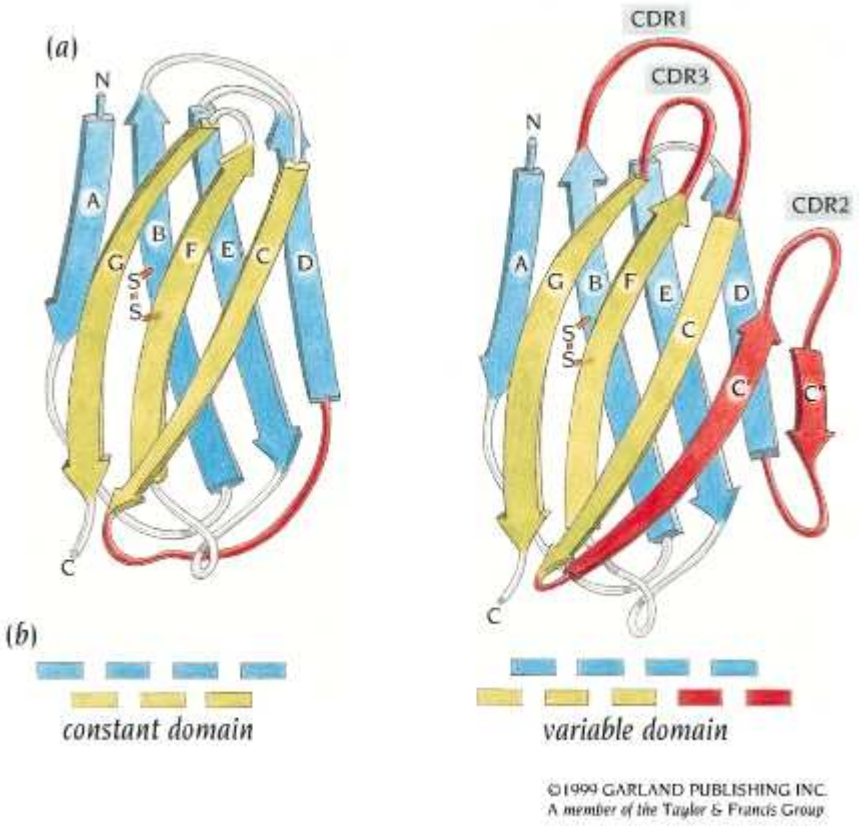


Las cadenas ligeras y pesadas están divididas en **DOMINIOS** .

Las cadenas pesadas tienen de cuatro dominios (**CH1, CH2, CH3, VH**) y las cadenas ligeras dos (**VL, CL**).

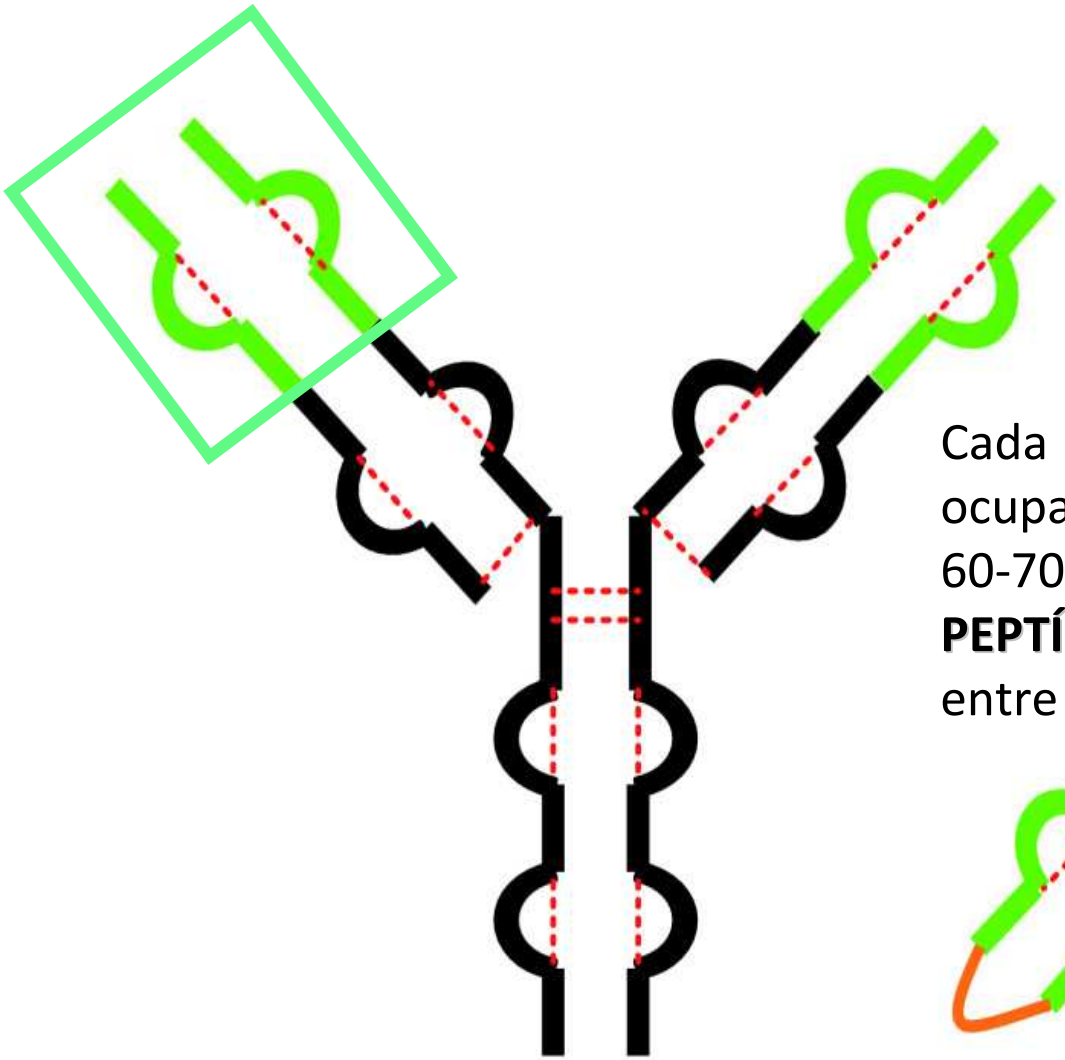
PLEGAMIENTO DE INMUNOGLOBULINA





Los **DOMINIOS DE INMUNOGLOBULINA** reciben su nombre de las moléculas de inmunoglobulina, en donde fueron descubiertos por primera vez.

- **Constan de entre 70-110 aminoácidos** y se clasifican en diferentes tipos de acuerdo a su tamaño y función.
- Los dominios Ig poseen un **PLEGAMIENTO** Ig característico que es **una estructura en forma de "sandwich" formada por dos láminas β antiparalelas.**
- Un extremo del dominio Ig alberga la sección llamada **REGIÓN DETERMINANTE DE COMPLEMENTARIDAD (CDR)** que es importante para la especificidad de los miembros de la superfamilia para sus respectivos ligandos.



IgG

Framework or scaffold
Variable regions
Linker
Disulfide bonds

Cada puente disulfuro intracatenario ocupa la región central del dominio (de 60-70 aminoácidos) llamado **ASA PEPTÍDICA** con una enorme homología entre los distintos Ac.

scFv

Peptide aptamer

La diversidad se localiza en la zona variables de las cadenas H y L

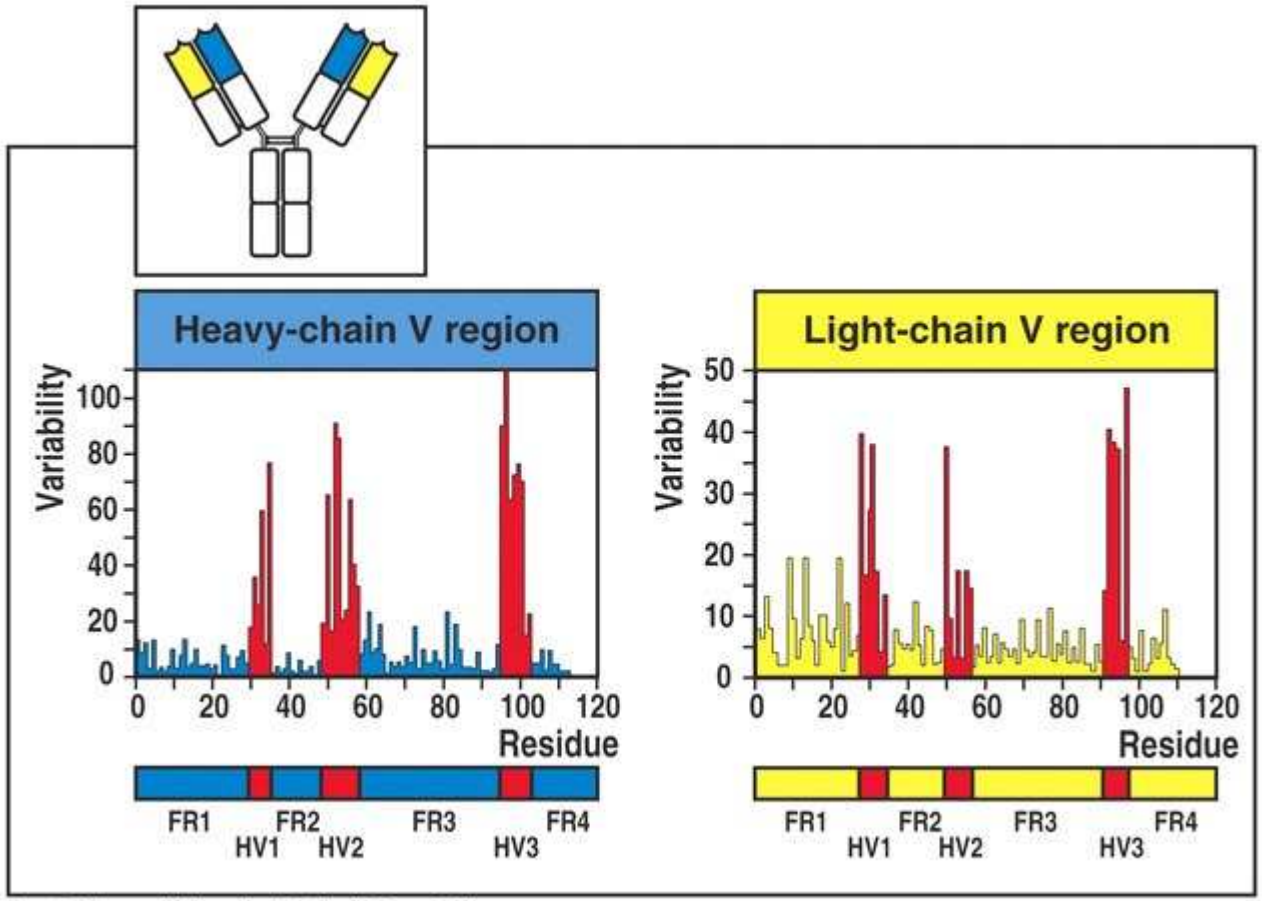
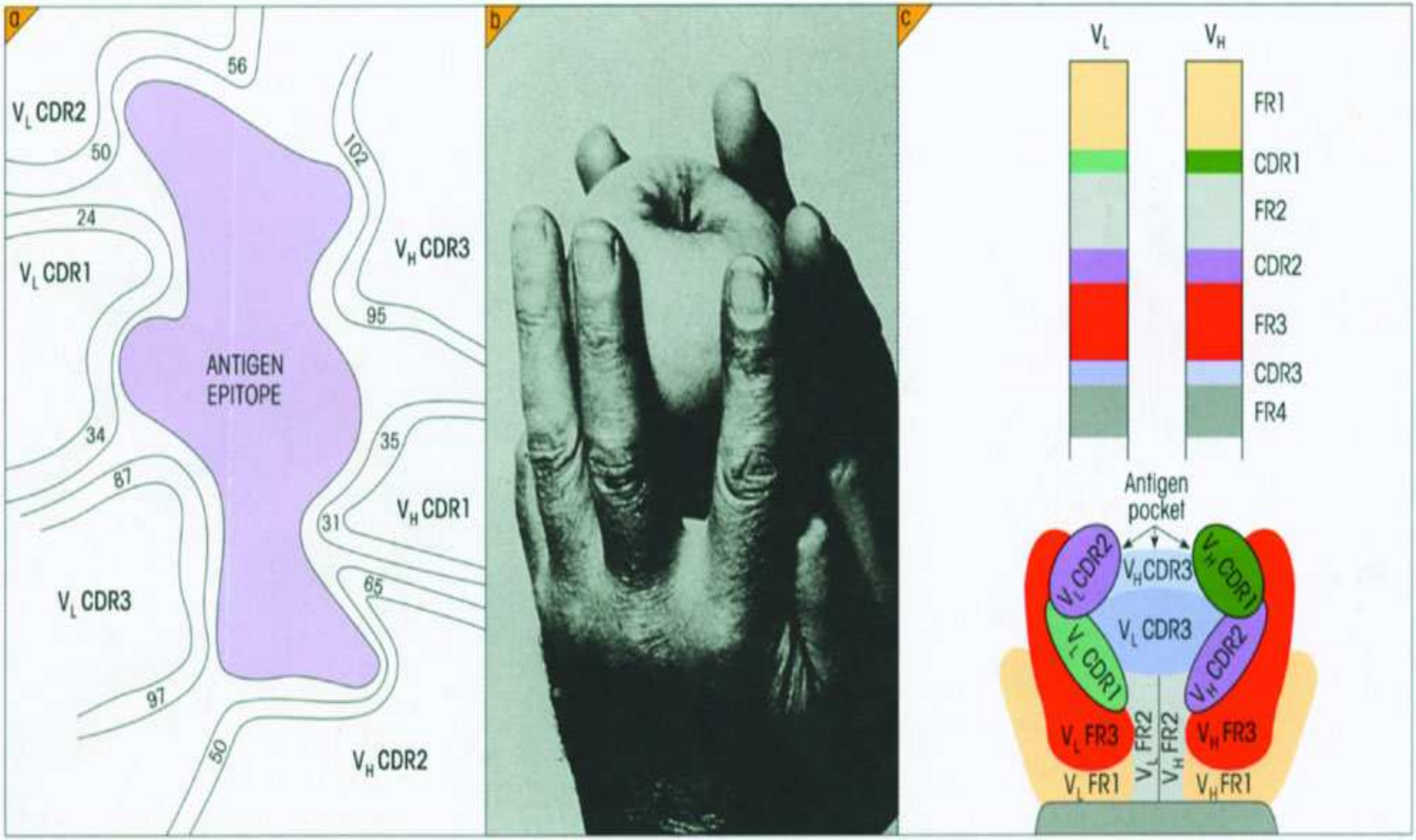
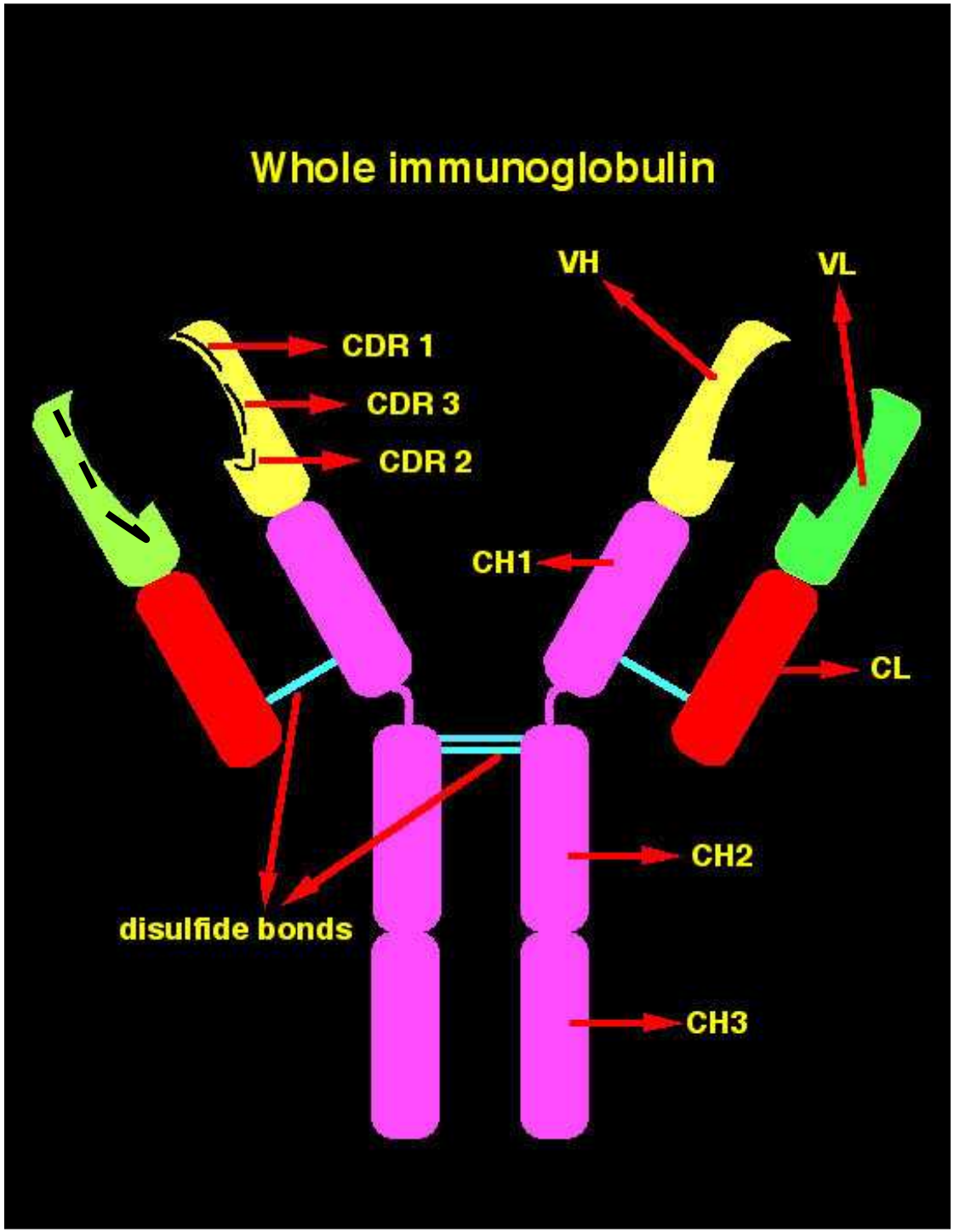


Figure 3-6 Immunobiology, 6/e. (© Garland Science 2005)

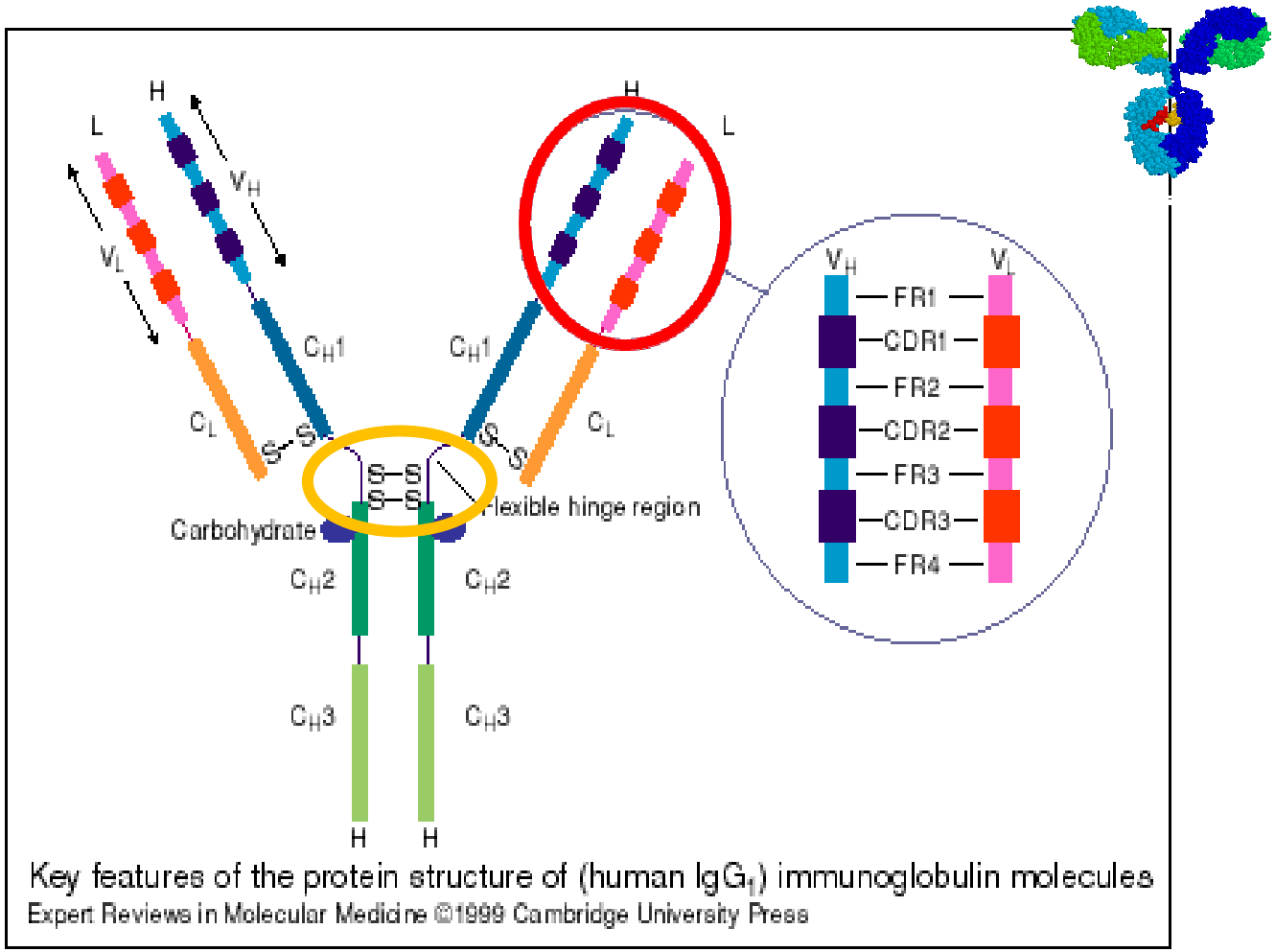

a
56
V_L CDR2
50
24
V_L CDR1
ANTIGEN EPITOPE
34
87
V_L CDR3
97
50
V_H CDR2
102
V_H CDR3
95
35
V_H CDR1
31
65
b
c
V_L
V_H
FR1
CDR1
FR2
CDR2
FR3
CDR3
FR4
Antigen pocket
V_HCDR3
V_L CDR2
V_H CDR1
V_L CDR3
V_L CDR1
V_H CDR2
V_L FR3
V_L FR2
V_H FR2
V_H FR3
V_L FR1
V_H FR1

- Complementarity Determining Regions
- **(CDRs),**
- **Región Hipervariable**



En la región variable se observan los **DOMINIOS HIPERVARIABLES CDR** flanqueados por los FR.

Los Ac son moléculas flexibles a nivel de la **REGIÓN BISAGRA**, que es un segmento situado entre los dominios CH1 y CH2 (en IgE no hay región bisagra), que permite al Ac acomodar su estructura para interaccionar con el Ag.



Key features of the protein structure of (human IgG_1) immunoglobulin molecules

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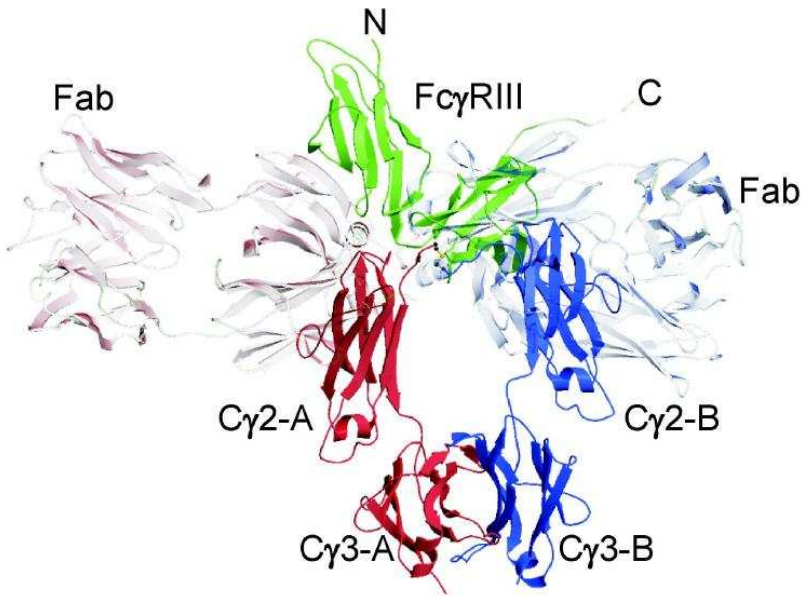
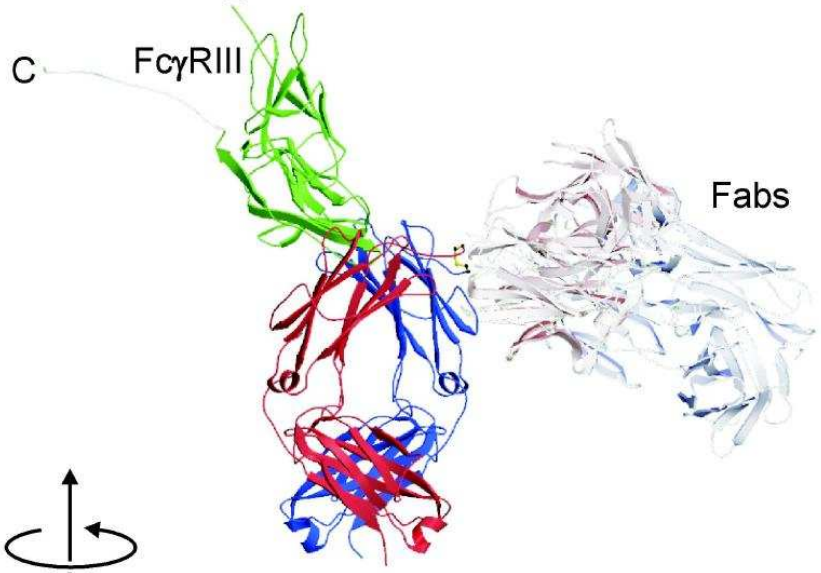
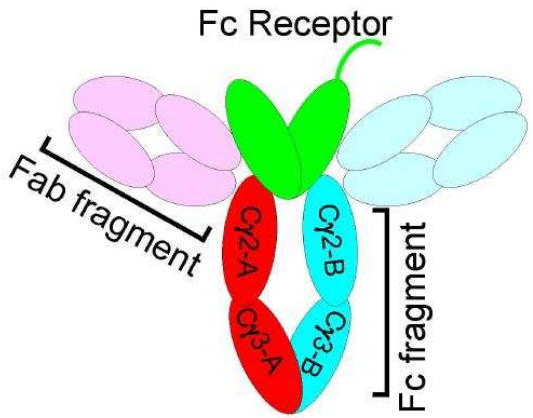
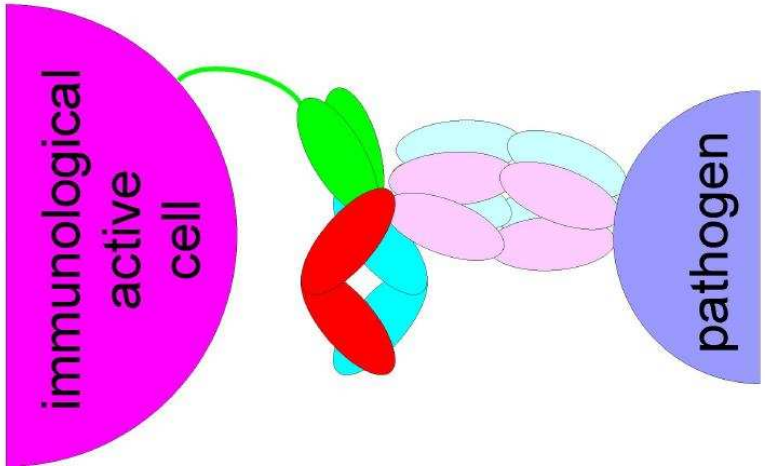
La inmunoglobulina:

un adaptador flexible

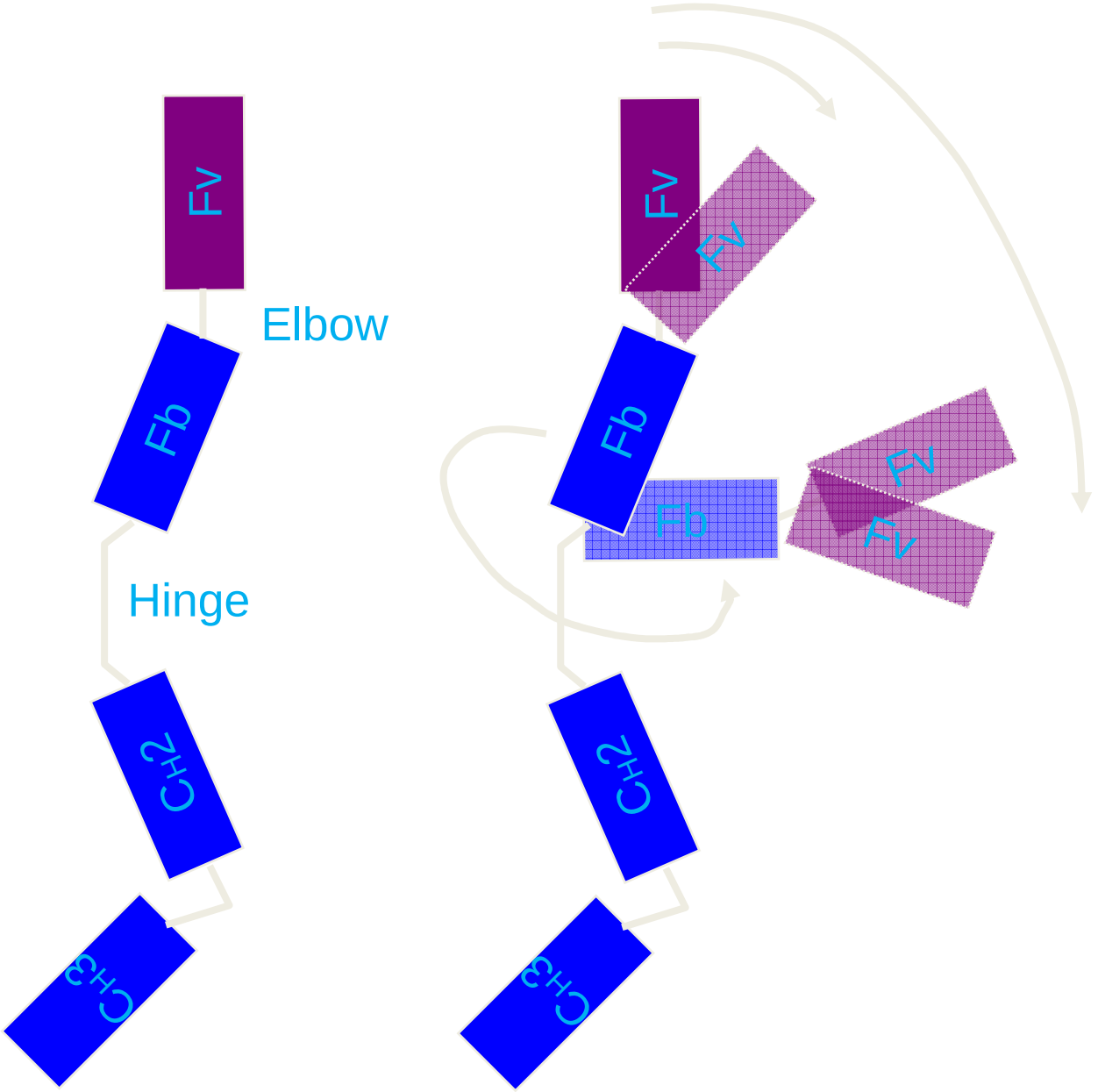








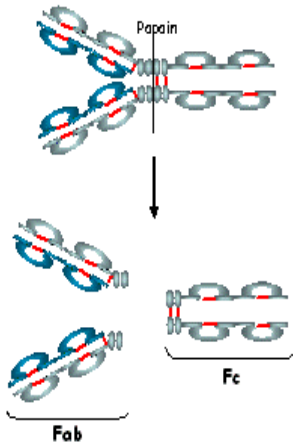
Flexibilidad y movimiento de las inmunoglobulinas



FRAGMENTACIÓN DE LA IGG CON PROTEASAS

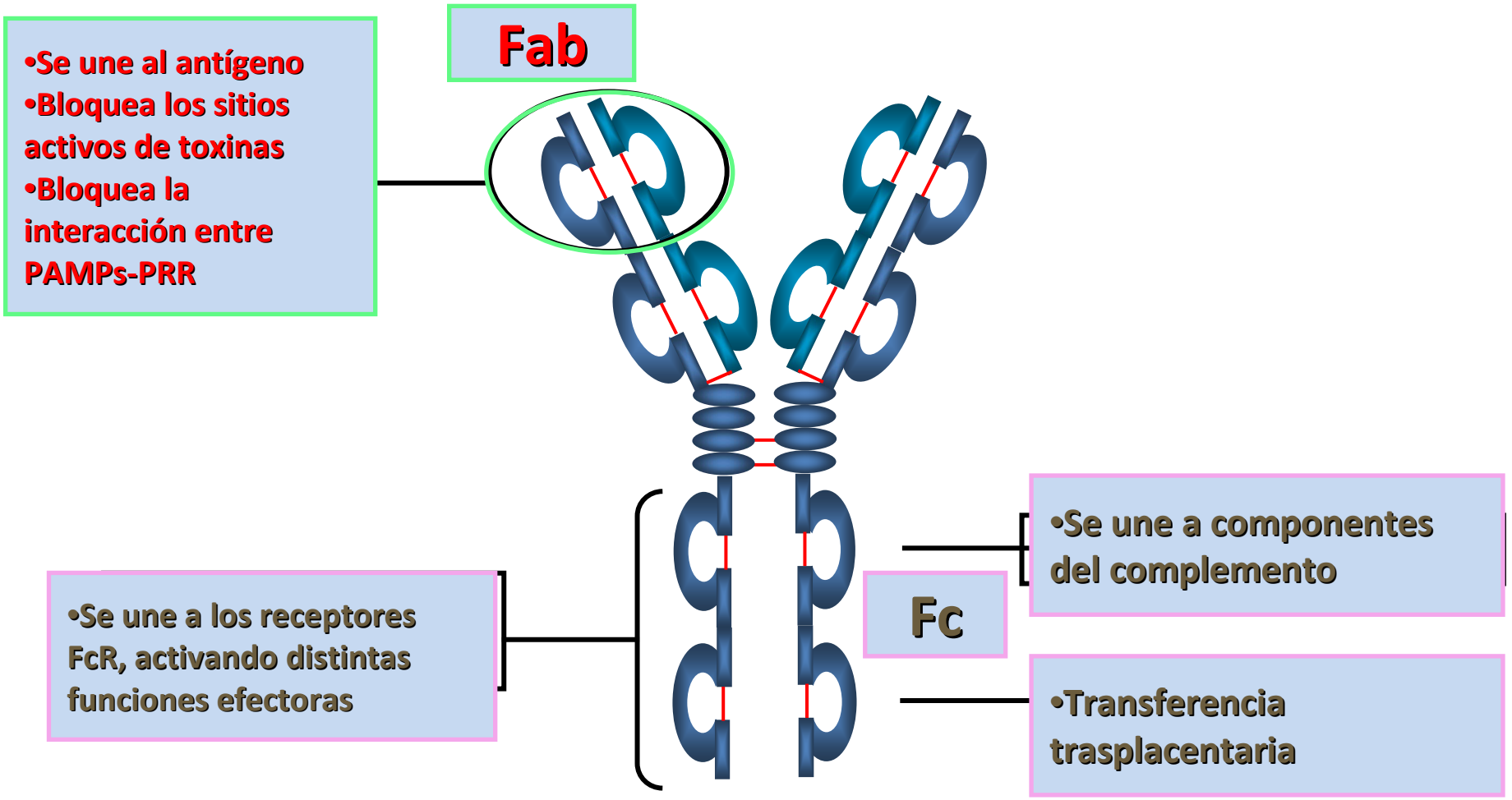
La papaína corta las cadenas pesadas de modo que se obtienen tres fragmentos peptídicos:

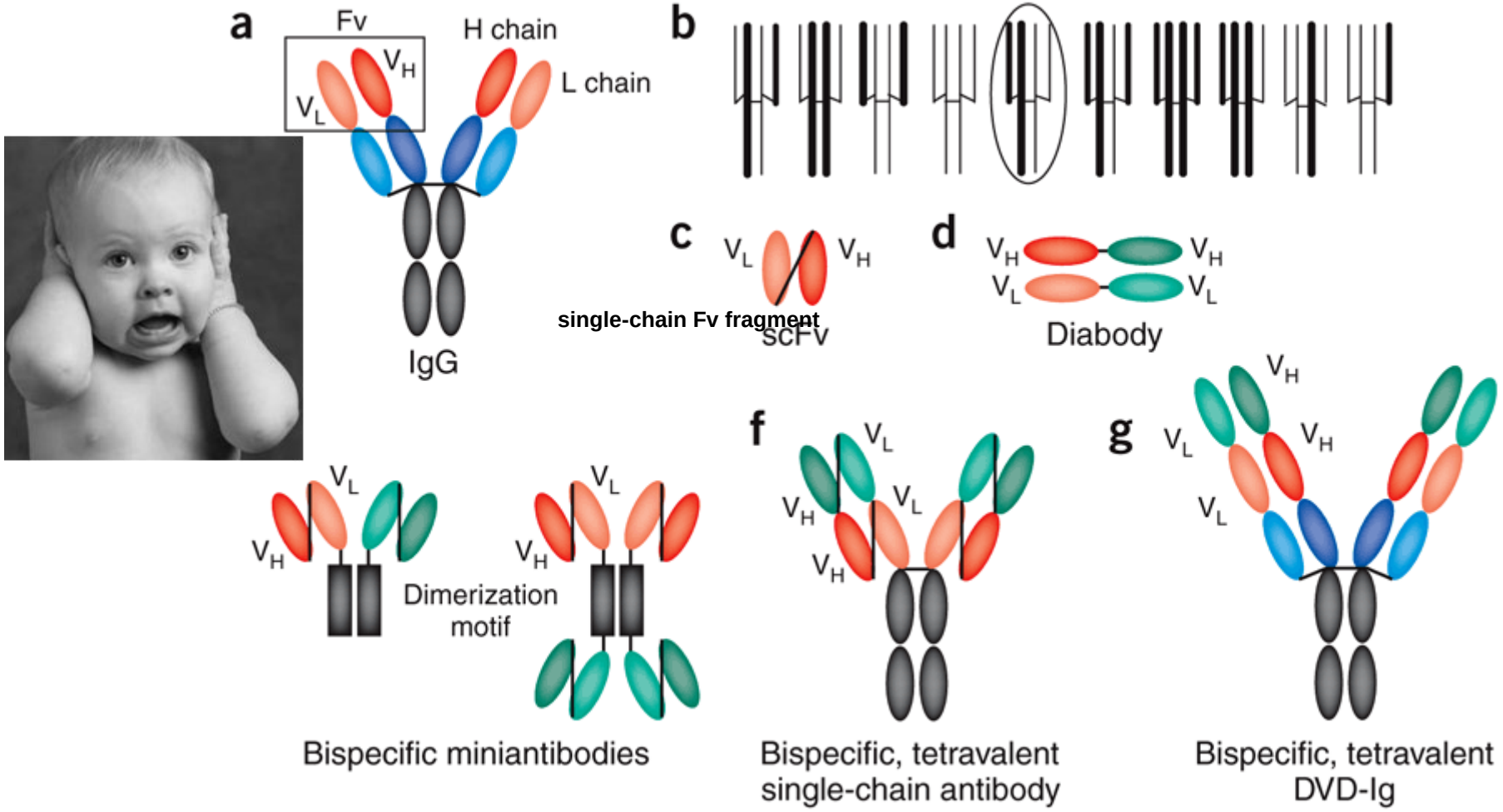
- **dos fragmentos F_{ab}** (el nombre procede de *fragment antigen binding*, fragmento ligante del antígeno; cada fragmento F_{ab} separado es aún capaz de unirse a una molécula de antígeno);
- **un solo fragmento F_c** (de *fragment crystallizable*), pues las dos cadenas pesadas se mantienen unidas gracias a enlaces disulfuro.



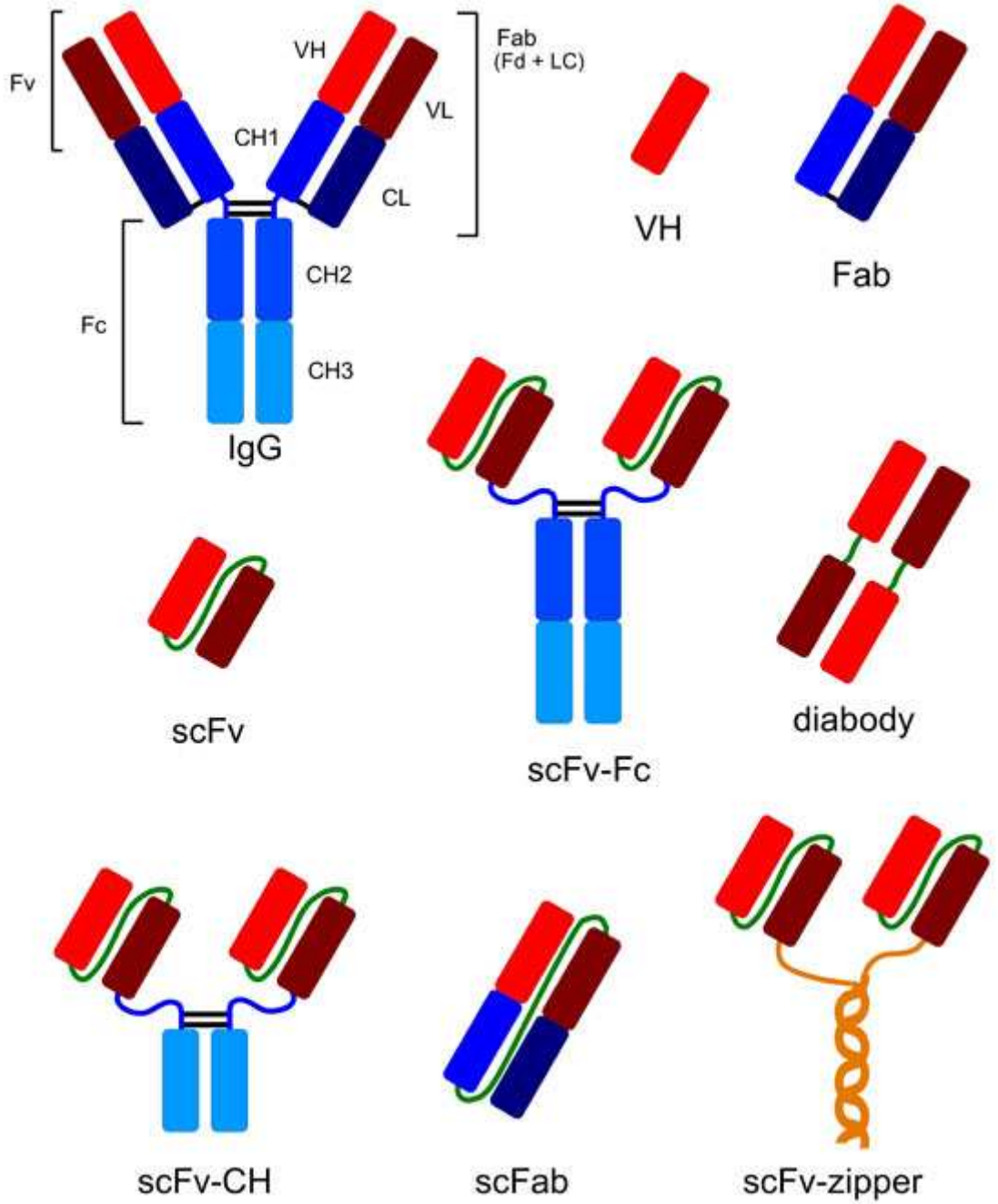
Esta enzima se extrae del jugo del fruto inmaduro de la papaya (*Carica papaya*).
Tiene aplicación:
•como ablandador de carne
•en medicina, como facilitador de la digestión
•para eliminar tejido muerto en heridas (llagas, úlceras, quemaduras, heridas quirúrgicas, quistes,...): mezclada con urea, en forma de pomada de uso tópico (marcas comerciales: Accuzyme, Ethezyme 830, Gladase, Kovia, Panafil, Ziox)
•para coagular la leche
•en la preparación de la lana
•en comida de mascotas, para reducir viscosidad y hacerla más apetecible
•como ingrediente en disoluciones de limpieza de lentes de contacto blandas

Función de los fragmentos de Ig



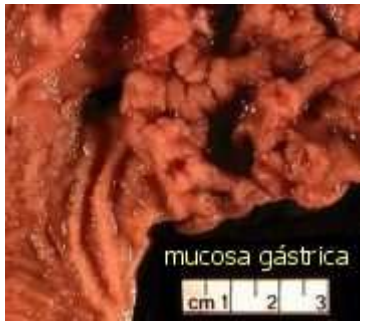


(**a**) IgG. (**b**) All possible antibodies produced by fusing two hybridomas. The circled antibody represents the bispecific molecule of interest. (**c**) scFv fragment. (**d**) Diabody. (**e**) Bispecific miniantibodies. (**f**) Bispecific, tetravalent single-chain antibody. (**g**) Bispecific, tetravalent dual–variable domain IgG.

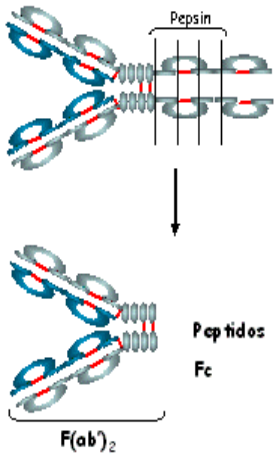

Fv
VH
Fab
(Fd + LC)
VL
CH1
CL
CH2
Fc
CH3
IgG
VH
Fab
scFv
scFv-Fc
diabody
scFv-CH
scFab
scFv-zipper

Sin embargo, si se trata la IgG con pepsina, los puntos de corte en las cadenas pesadas son ligeramente diferentes:

- **un solo fragmento denominado $F_{(ab')2}$** en el que los dos dominios F_{ab} permanecen unidos a través de la región bisagra,
- **otro fragmento $F_{c'}$,** ligeramente diferente al de la papaína (en realidad, éste no se obtiene íntegro como se muestra aquí, sino fragmentado en varios péptidos, pues la pepsina tiene varias dianas en la cadena H).

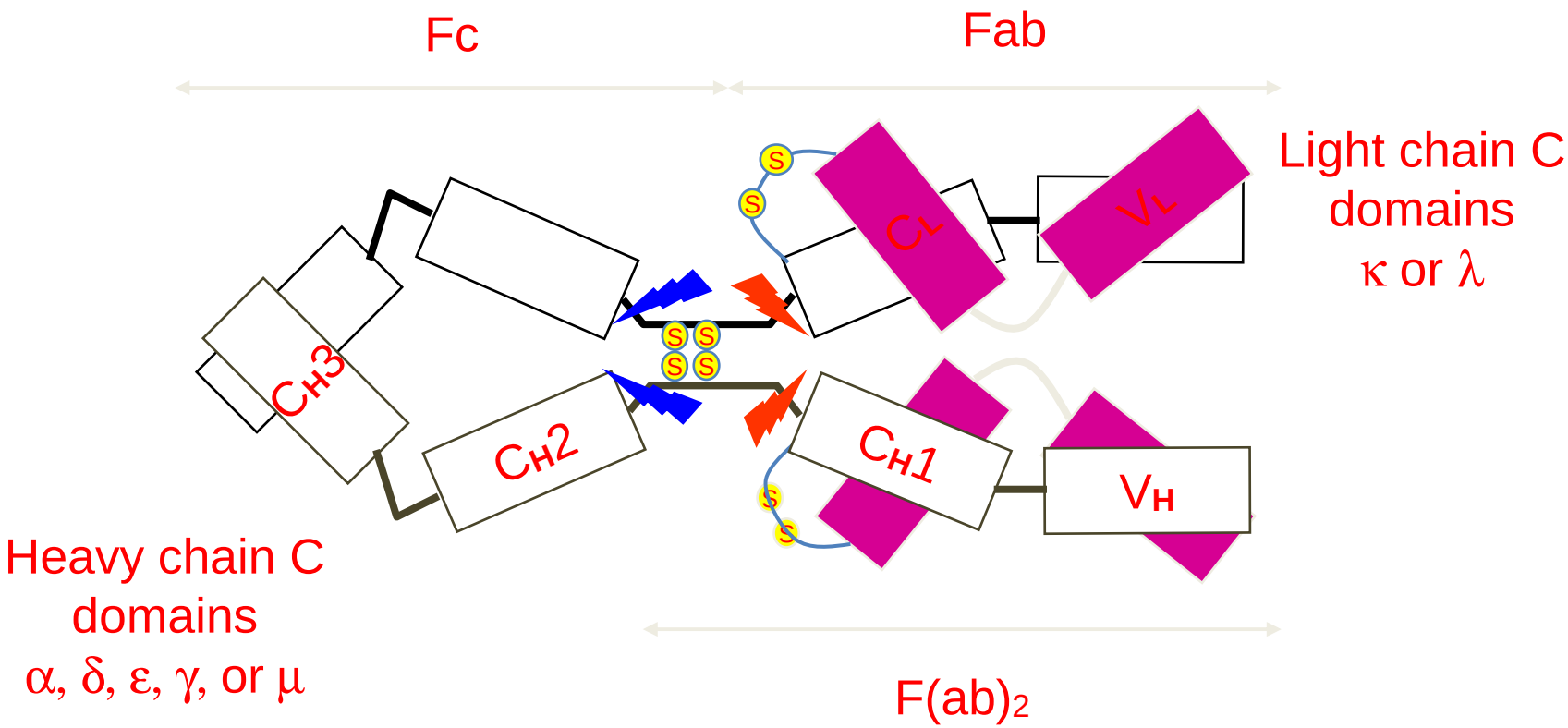


Esta enzima es sintetizada por las células de la pared del estómago y secretada como componente del jugo gástrico.
Etimológicamente procede del griego *pepsis*, digestión.
Tiene aplicación :
•como facilitador de la digestión (tras purificar la pepsina a partir de estómago de cerdo o ternero)



ESTRUCTURA DE DOMINIOS DE INMUNOGLOBULINA

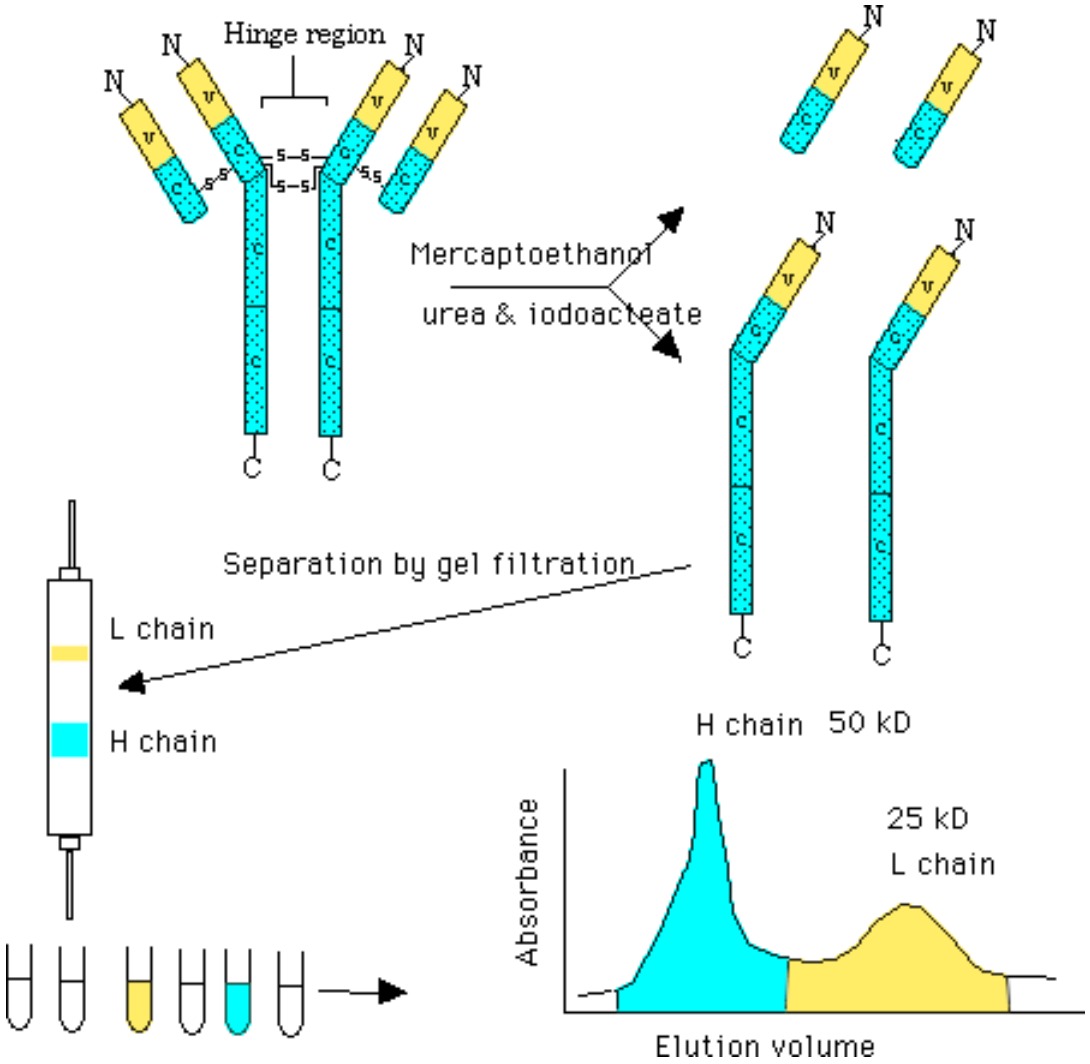
Los dominios son estructuras plegadas, compactas, resistentes a proteasas...



Pepsin cleavage sites - 1 x $(Fab')_2$ & 1 x Fc

Papain cleavage sites - 2 x Fab 1 x Fc

Separación de cadenas H y L



¿INMUNOGLOBULINAS ANTIGÉNICAS????


SERUM
Behring

Las inmunoglobulinas son glucoproteínas, por lo tanto, se pueden comportar como antígenos….

Determinantes antigénicos de las INMUNOGLOBULINAS

ISOTIPOS, ALOTIPOS, IDIOTIPOS

Isotipos

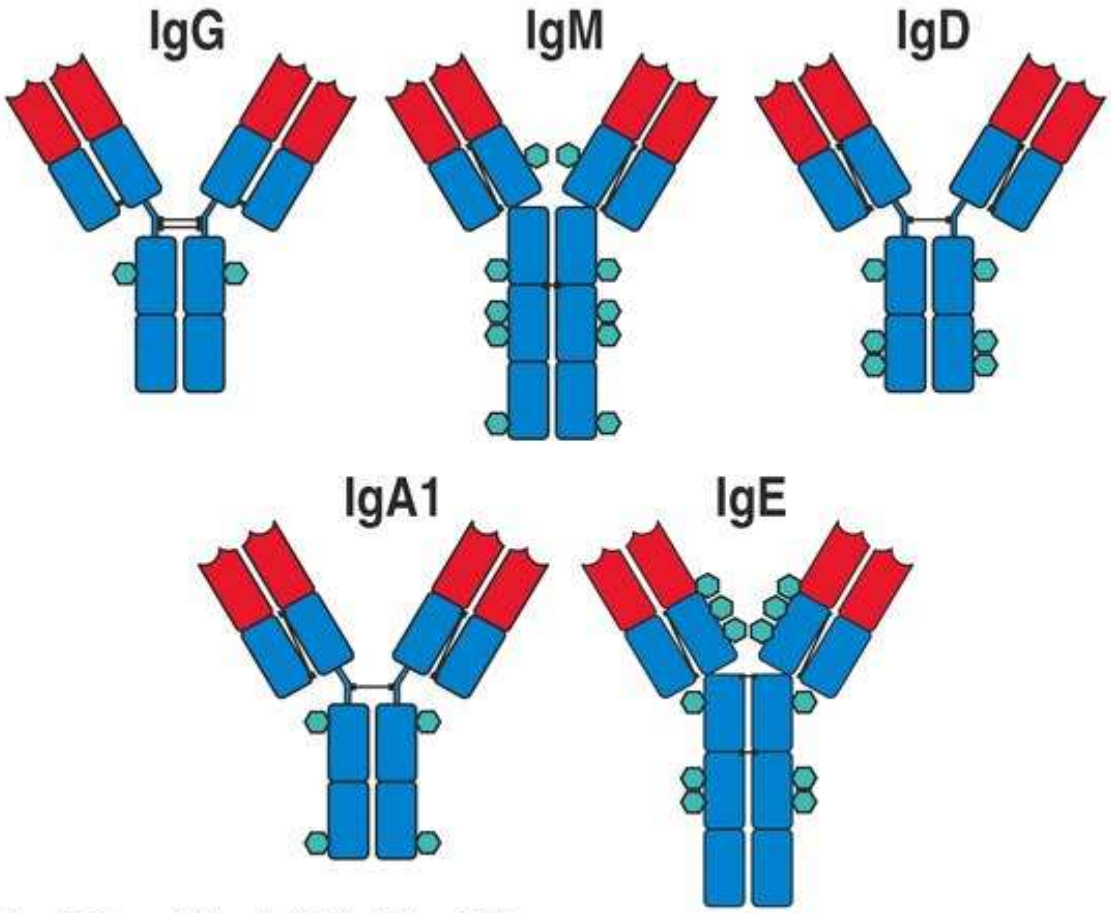
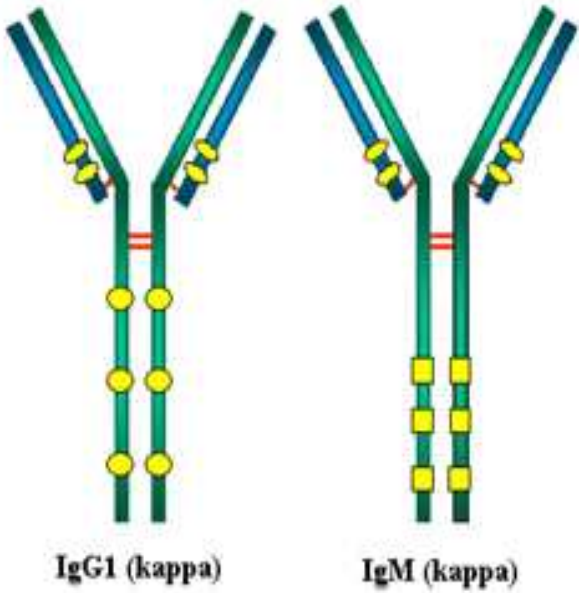


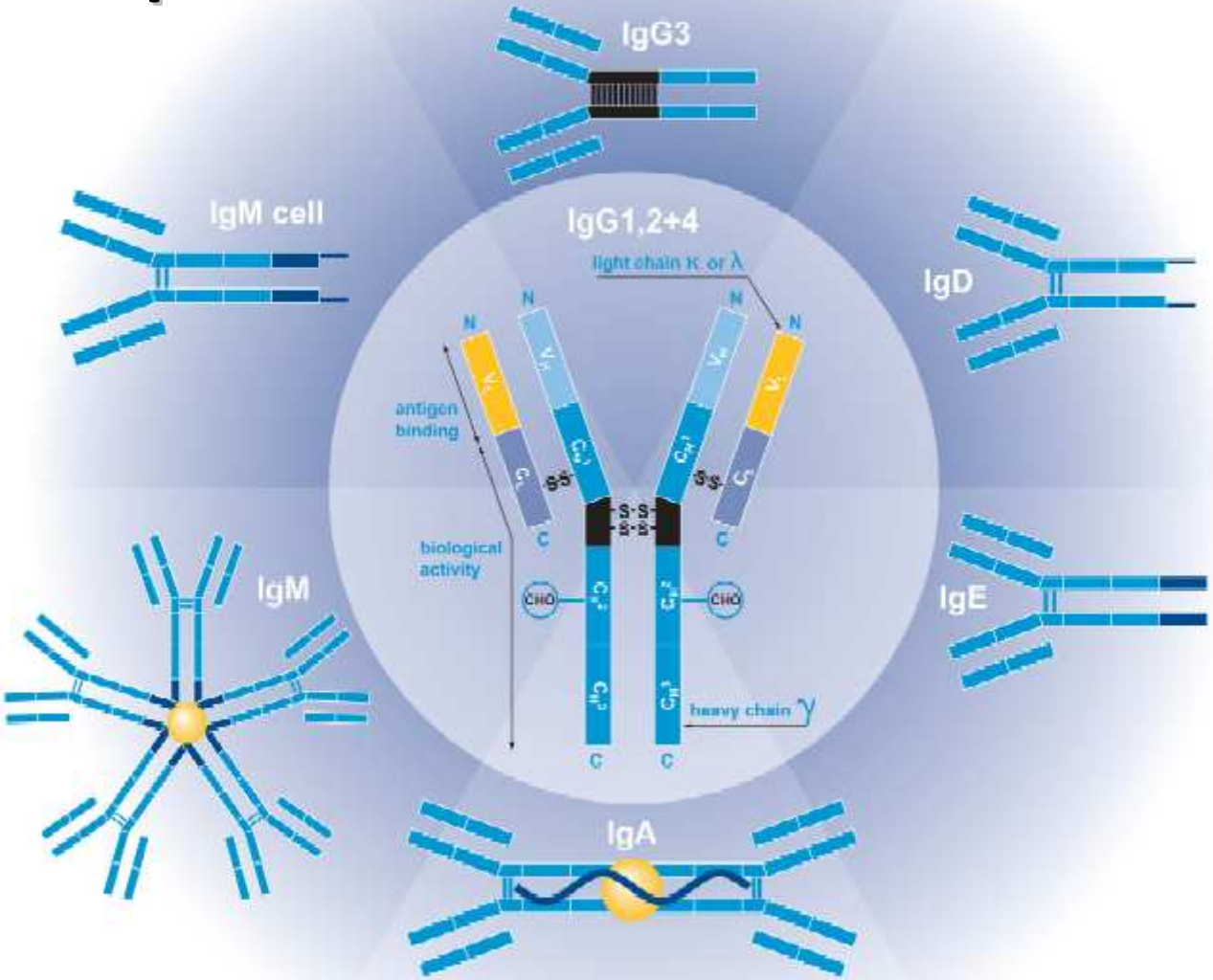
Figure 4-18 Immunobiology, 6/e. (© Garland Science 2005)



Se denominan isotipos al conjunto de variantes de inmunoglobulinas comunes a todos los miembros sanos de una determinada especie

- **A. Definition.**
  Isotypes are antigenic determinants that characterize classes and subclasses of heavy chains and types and subtypes of light chains.
- If human IgM is injected into a rabbit the rabbit will recognize antigenic determinants on the heavy chain and light chain and make antibodies to them. If that antiserum is absorbed with human IgG the antibodies to the light chain determinants and any determinants in common between human IgM and IgG will be removed and the resulting antiserum will be react only with human IgM. Indeed, the antibodies will only react with the constant region of the μ chain. Antibodies to the variable region are rare perhaps because only a few copies of each different variable region are represented in the IgM and thus effective immunization does not occur. The determinants that are recognized by such antibodies are called *isotypic determinants* and the antibodies to those determinants are called *anti-isotypic antibodies*. Each class, subclass, type and subtype of immunoglobulin has its unique set of isotypic determinants.
- **B. Location**
  Heavy chain isotypes are found on the Fc portion of the constant region of the molecule while light chain isotypes are found in the constant region.
- **C. Occurrence**
  Isotypes are found in ALL NORMAL individuals in the species. The prefix Iso means same in all members of the species. Some individuals with immunodeficiencies may lack one or more isotypes but normal individuals have all isotypes.
- **D. Importance**
  Antibodies to isotypes are used for the quantitation of Ig classes and subclasses in various diseases, in the characterization of B cell leukemia and in the diagnosis of various immunodeficiency diseases.

Isotipos


IgG3
IgM cell
IgG1,2+4
light chain κ or λ
IgD
antigen binding
biological activity
IgM
IgE
heavy chain γ
IgA

El cambio de isotipo depende de las citocinas secretadas por las Th

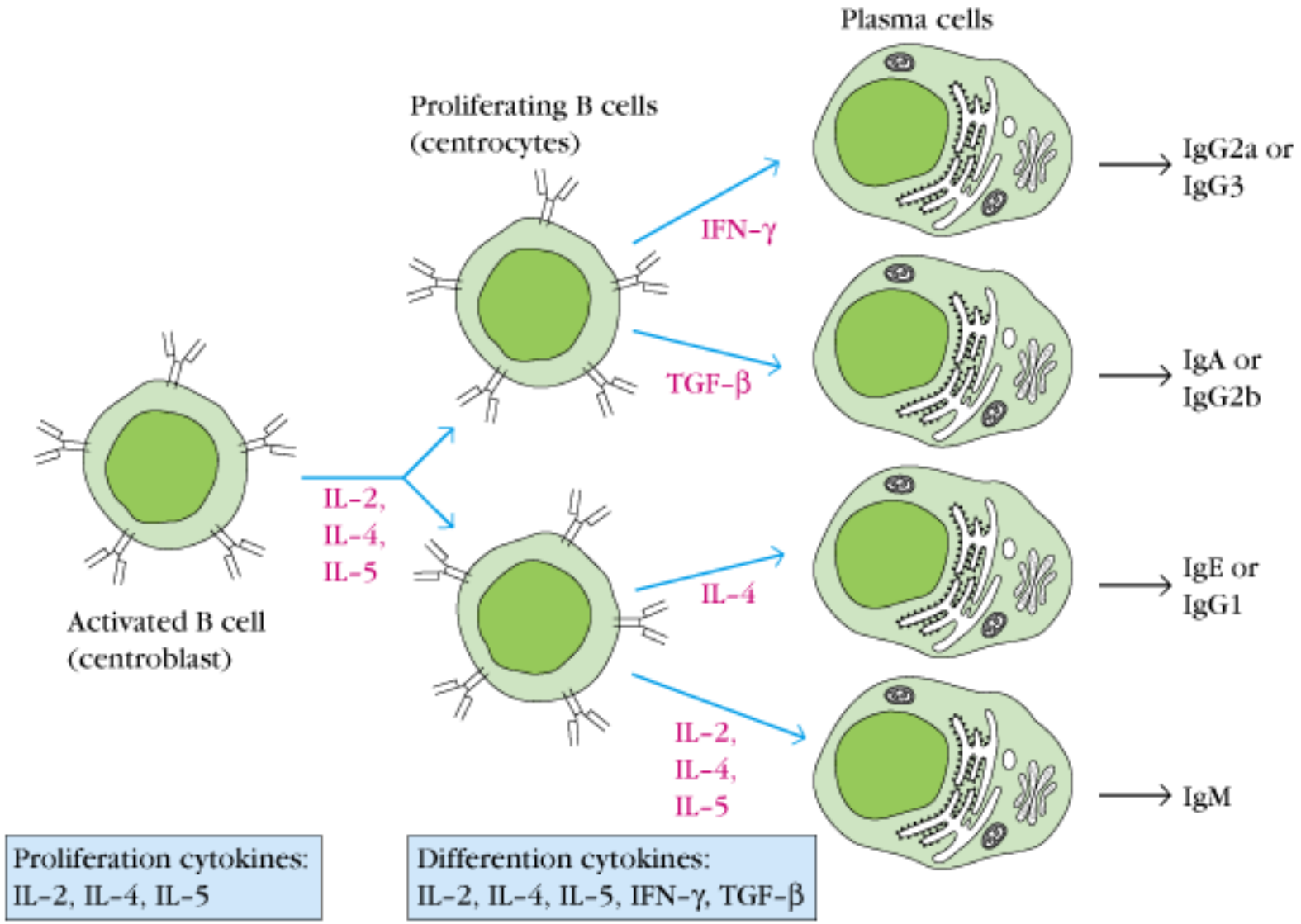
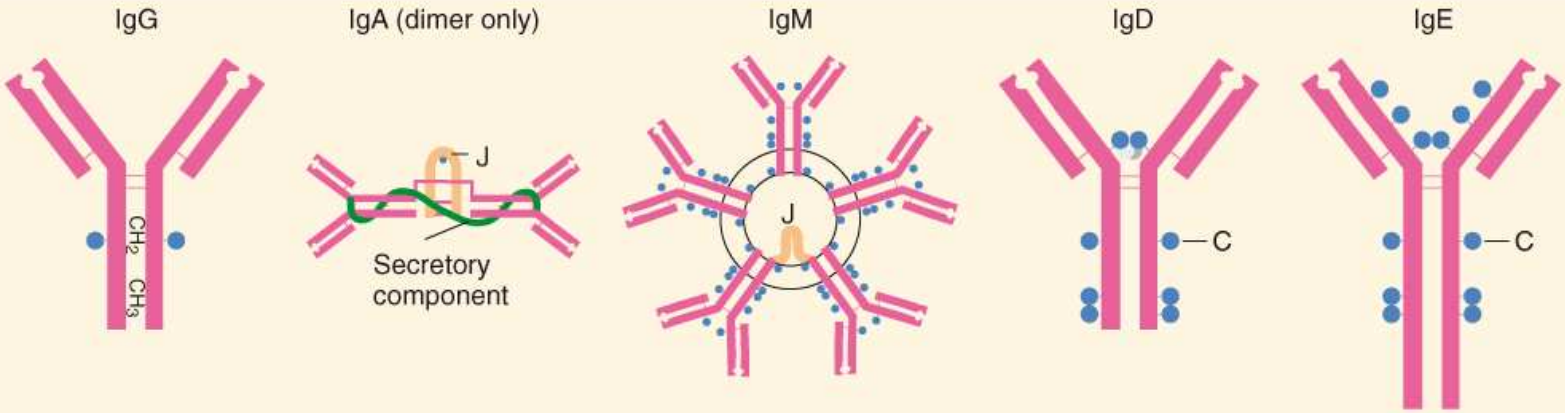


TABLE 15.2 Characteristics of the Immunoglobulin (Ig) Classes



	Monomer	Dimer, Monomer	Pentamer	Monomer	Monomer
Number of Antigen Binding Sites	2	4 2	10	2	2
Molecular Weight	150,000	170,000–385,000	900,000	180,000	200,000
Percentage of Total Antibody in Serum	80%	13%	6%	1%	0.002%
Average Half-Life in Serum (Days)	23	6	5	3	2.5
Crosses Placenta?	Yes	No	No	No	No
Fixes Complement?	Yes	No	Yes	No	No
Fc Binds To	Phagocytes				Mast cells and basophils
Biological Function	Long-term immunity; memory antibodies; neutralizes toxins, opsonizes, fixes complement	Secretory antibody; on mucous membranes	Produced at first response to antigen; can serve as B-cell receptor	Receptor on B cells	Antibody of allergy; worm infections

C = carbohydrate. J = J chain.

In addition to isotypes that identify H chains of a given species, antibodies **within an isotype have small amino acid sequence differences called allotypes.**

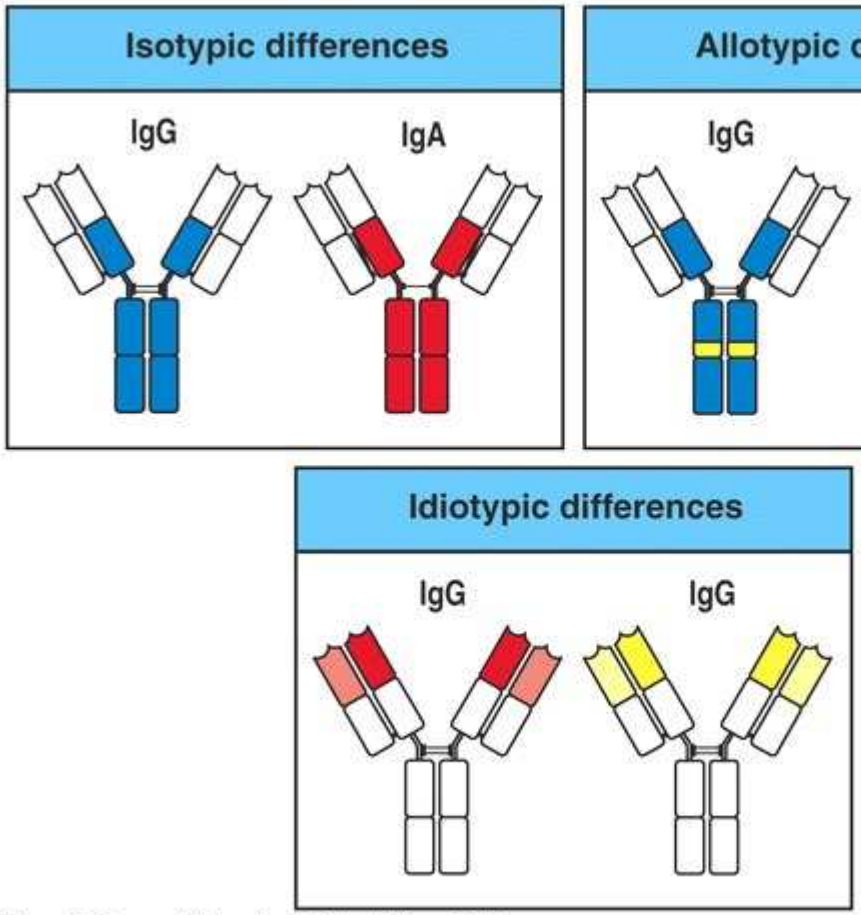
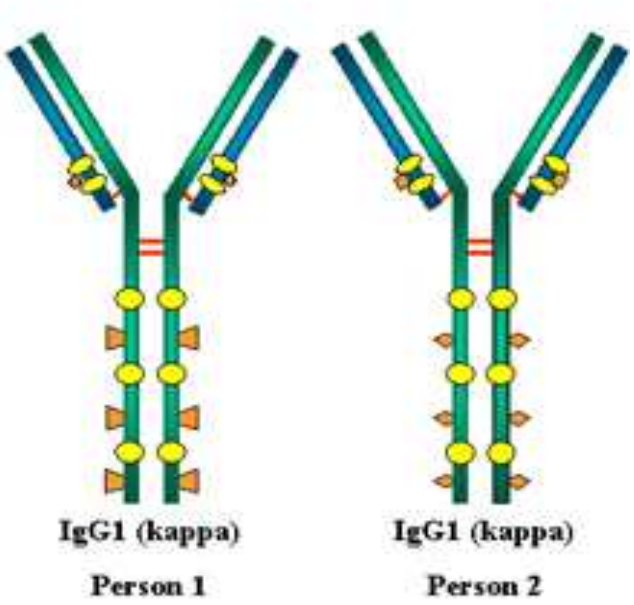


Figure 4-24 Immunobiology, 6/e. (© Garland Science 2005)

It is also possible to make antibodies that recognize the specific antigen-binding regions of the VH and VL domains = idiotypes.

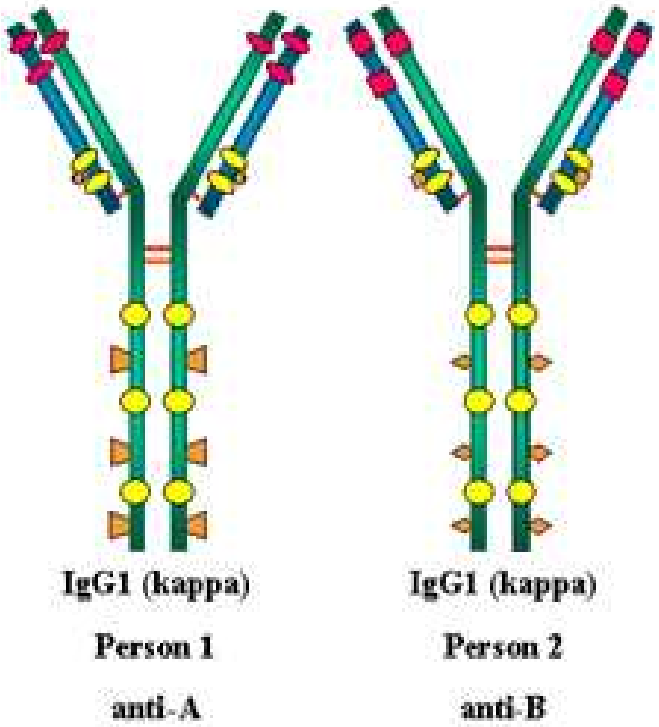
Los alotipos son el conjunto de variantes alélicas presentes en las poblaciones de una especie: individuos que para clase o subclase presentan una variante alélica distinta de otros individuos

Se deben a pequeñas diferencias que afectan a las regiones C_H y C_L



- **A. Definition**
  Allotypes are antigenic determinants specified by allelic forms of the Ig genes.
- Allotypes represent slight differences in the amino acid sequences of heavy or light chains of different individuals. Even a single amino acid difference can give rise to an allotypic determinant, although in many cases there are several amino acid substitutions that have occurred.
- Allotypic differences are detected by using antibodies directed against allotypic determinants. These antibodies can be prepared by injecting the Ig from one person into another. In practice however we obtain anti-allotype antisera from women who have had multiple pregnancies or from people who have received blood transfusions or from some patients with rheumatoid arthritis.
- **B. Location**
  In man the allotypic differences are localized to the constant region of the heavy and light chains as illustrated in the Figure 2.
- **C. Occurrence**
  Individual allotypes are found in individual members of a species. All allotypes are not found in all members of the species. The prefix Allo means different in individuals of a species
- **D. Human Ig Allotypes**
- Nomenclature - Human Ig allotypes are named on the basis of the heavy or light chain on which it is located. Thus, an allotype on a Gamma 1 heavy chain is given the name: G1m(3). An allotype on a Kappa light chain is given the name: Km(1).

- Los **idiotipos** son el conjunto de variantes antigénicas características de cada anticuerpo de un mismo individuo, debidas a las secuencias de aminoácidos de las porciones V_H y V_L
- A su vez, cada uno de los determinantes características de un anticuerpo concreto se denomina **idiotopo**
- Los Ac producidos por un determinado clon de linfocitos B y las células plasmáticas derivadas de ellos llevan el mismo idiotipo



- **A. Definition** - Unique antigenic determinants present on individual antibody molecules or on molecules of identical specificity.

  Identical specificity means that all antibodies molecules have the exact same hypervariable regions.

  Antigenic determinants created by the combining site of an antibody are called idiotypes and the antibodies elicited to the idiotypes are called anti-Id antibodies. Idiotypes are the antigenic determinants created by the hypervariable regions of an antibody and the anti-idiotypic antibodies are those directed against the hypervariable regions of an antibody.

- **B. Location** - Idiotypes are localized on the Fab fragment of the Ig molecules. Specifically, they are localized at or near the hypervariable regions of the heavy and light chains. In many instances the actual antigenic determinant (i.e. idiotype) may include some of the framework residues near the hypervariable region. Idiotypes are usually determinants created by both heavy and light chain HVR's although sometimes isolated heavy and light chains will express the idiotype.

- **C. Importance**

  1. V region marker - Idiotypes are a useful marker for a particular variable region.

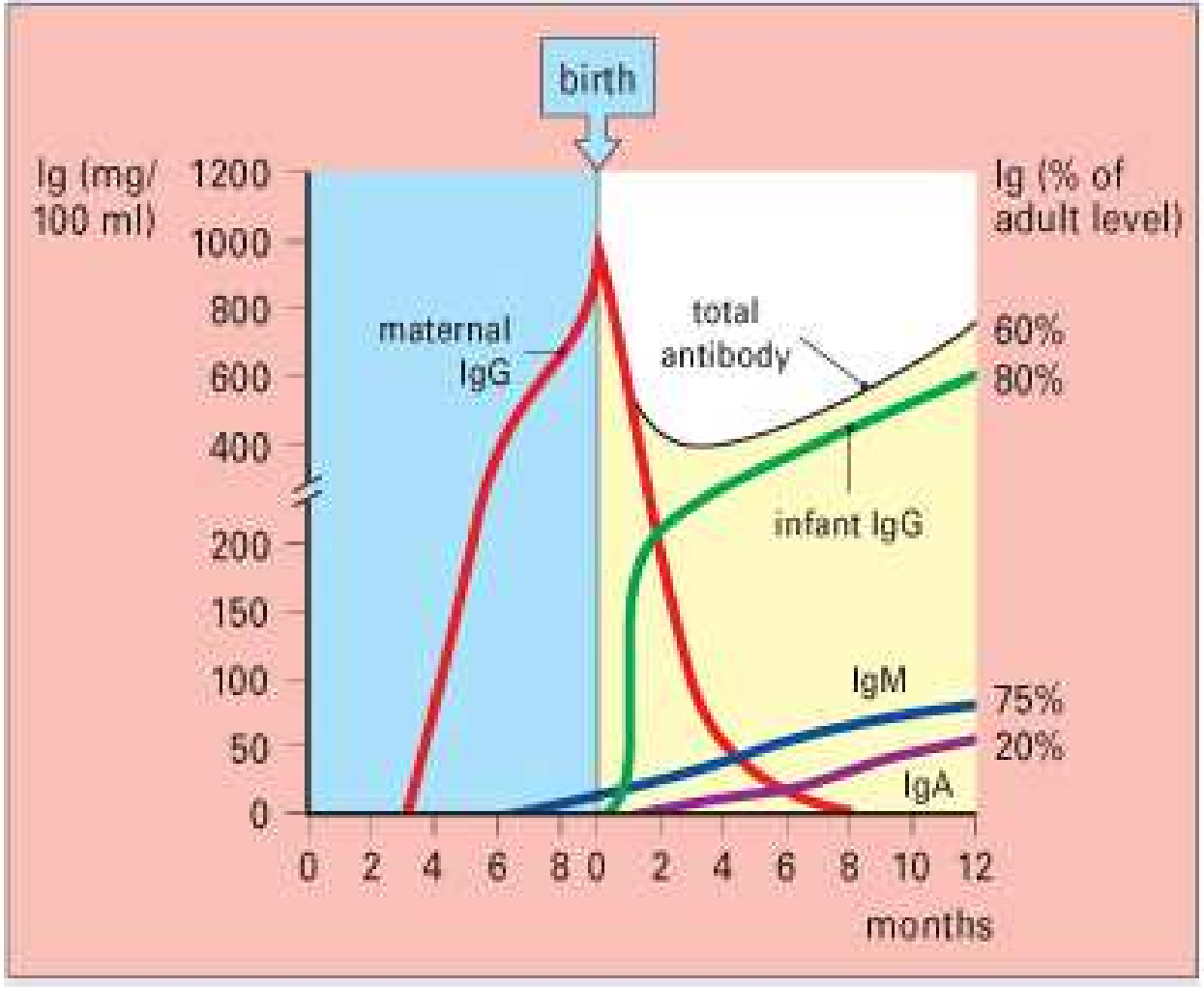
  2. Regulation of immune responses - there is evidence that immune responses may be regulated by anti-Id antibodies directed against our own Id's.

  3. Vaccines - In some cases anti-idiotypic antibodies actually stimulate B cells to make antibody and thus they can be used as a vaccine. This approach is being tried to immunize against highly dangerous pathogens that cannot be safely used as a vaccine.

- **D.Treatment of B cell tumors** - Anti-idiotypic antibodies directed against an idiotype on malignant B cells can be used to kill the cells. Killing occurs because of complement fixation or because toxic molecules are attached to the antibodies.

¿CÓMO SE DISTRIBUYEN LAS INMUNOGLOBULINAS????

Immunoglobulins in the serum of the fetus and newborn child



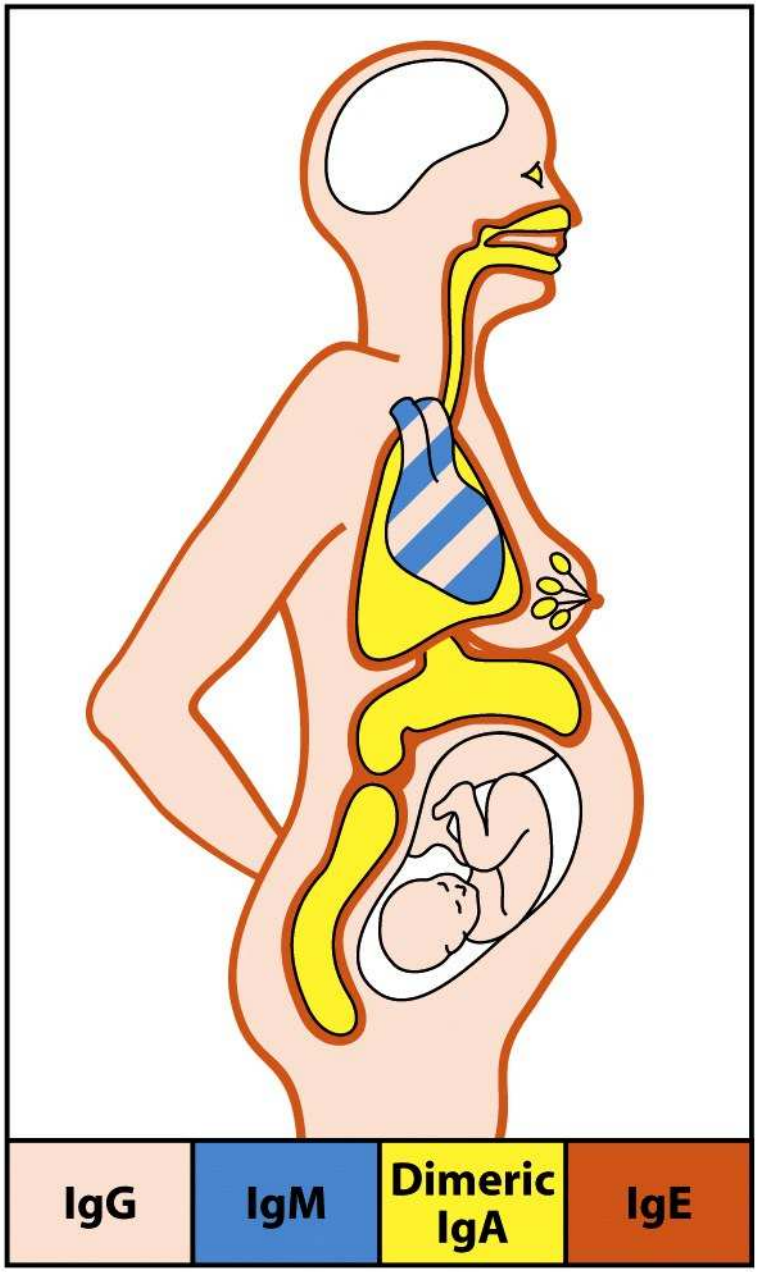
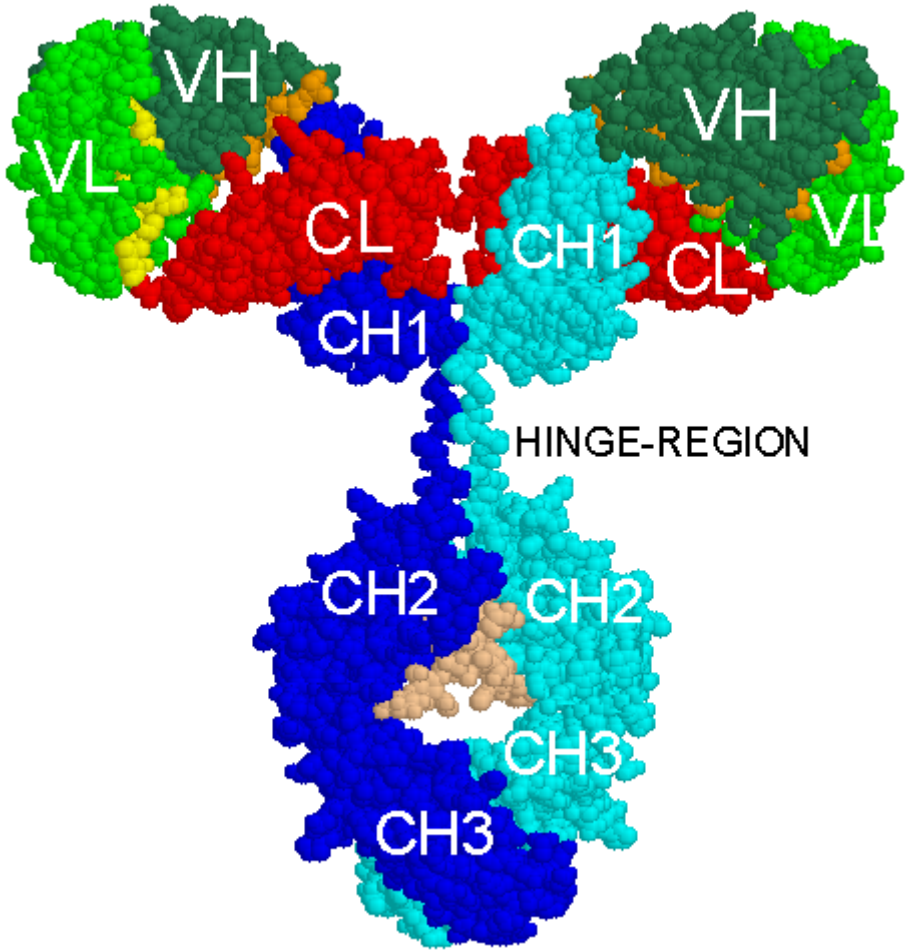


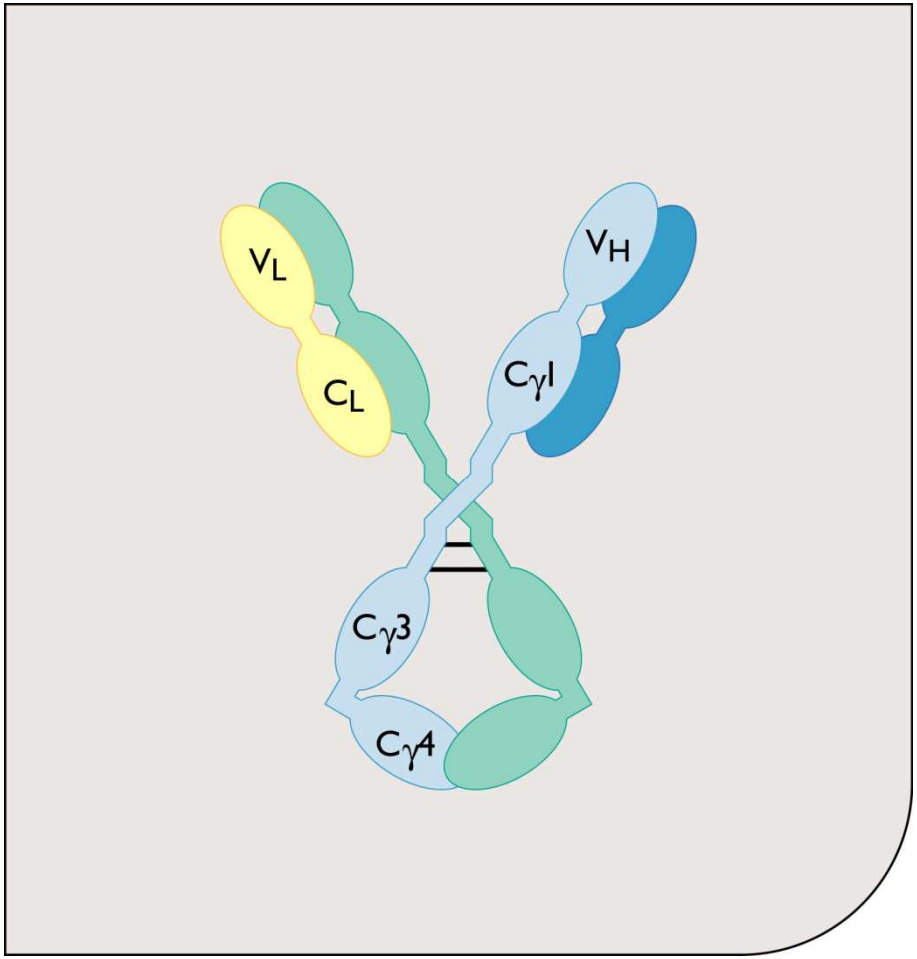
Figure 9-22 Immunobiology, 7ed. (© Garland Science 2008)

- **IgM e IgG** predominan en plasma, mientras que IgG e IgA monomérica son los isotipos mayoritarios en el fluido extracelular dentro del organismo.
- **IgA dimérica** predomina en secreciones a través de los epitelios, incluida la leche materna.
- **El feto recibe IgG** por transporte trasnplacental.
- **La IgE** se encuentra asociada a mastocitos, por debajo de las superficies epiteliales.
- El cerebro normalmente no tiene inmunoglobulinas.



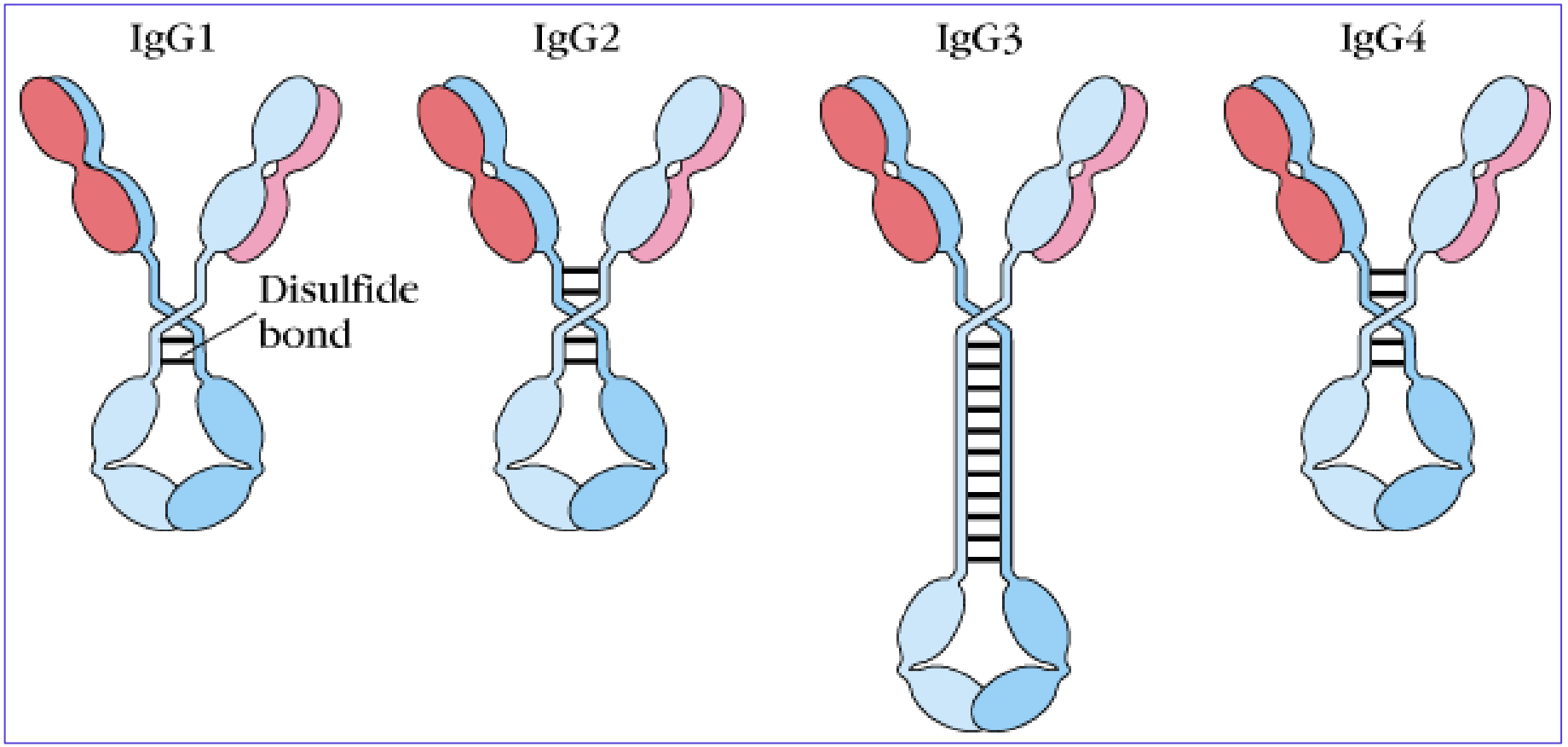
INMUNOGLOBULINA G

- Anticuerpo más prevalente (80% de los anticuerpos séricos)
  - **IgG_1 e IgG_3**
    - **Reconocen primariamente antígenos proteicos**
  - **IgG_2 e IgG_4**
    - **Se unen a antígenos carbohidratos**



Inmunoglobulina IgG

Ig más abundante, cuatro subclases, 90% homología



.- IgG1,IgG3 y IgG4 atraviesan placenta, protegen al feto.

.- Activan C´: IgG3 > IgG2 > IgG1. IgG4 no activa C´

.- IgG1 y IgG3 median opsonización. IgG4 menos e IgG2 baja afinidad.

Características de las subclases de IgG

	Immune response to:					
	Bacteria	Viruses	Proteins, toxins	Binding to Fc receptor	Complement activation	Binding to mast cells
IgG_1	+++	+++	+++	++	+++	-
IgG_2	+++	(+)	+	(+)	+	-
IgG_3	(+)	++	(+)	++	+++	-
IgG_4	(+)	(+)	(+)	(+)	-	++

- **La IgG2 es la responsable en gran parte de la respuesta a gérmenes como Streptococcus Pneumoniae y Haemophilus influenza. La disminución en la concentración sérica de IgG2 disminuye la formación de anticuerpos específicos contra estos agentes infecciosos a pesar de la administración de vacunas y predispone a presentar procesos infecciosos más severos.**

Receptores de INMUNOGLOBULINAS

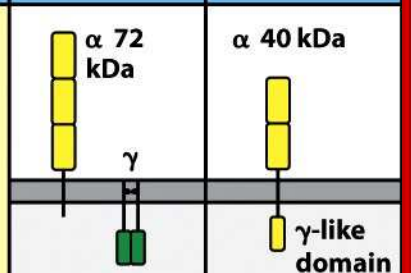
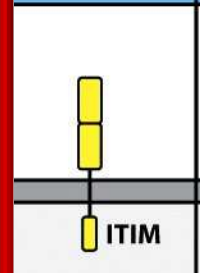
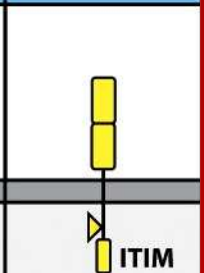
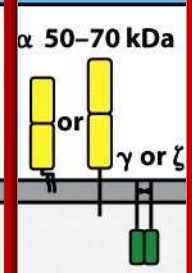
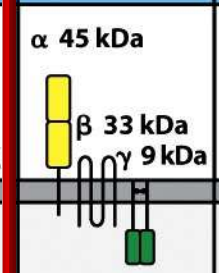
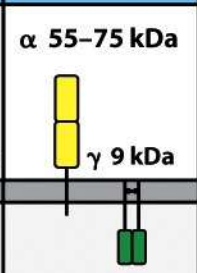
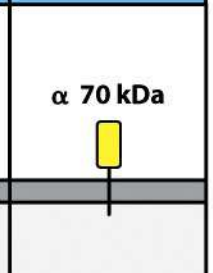
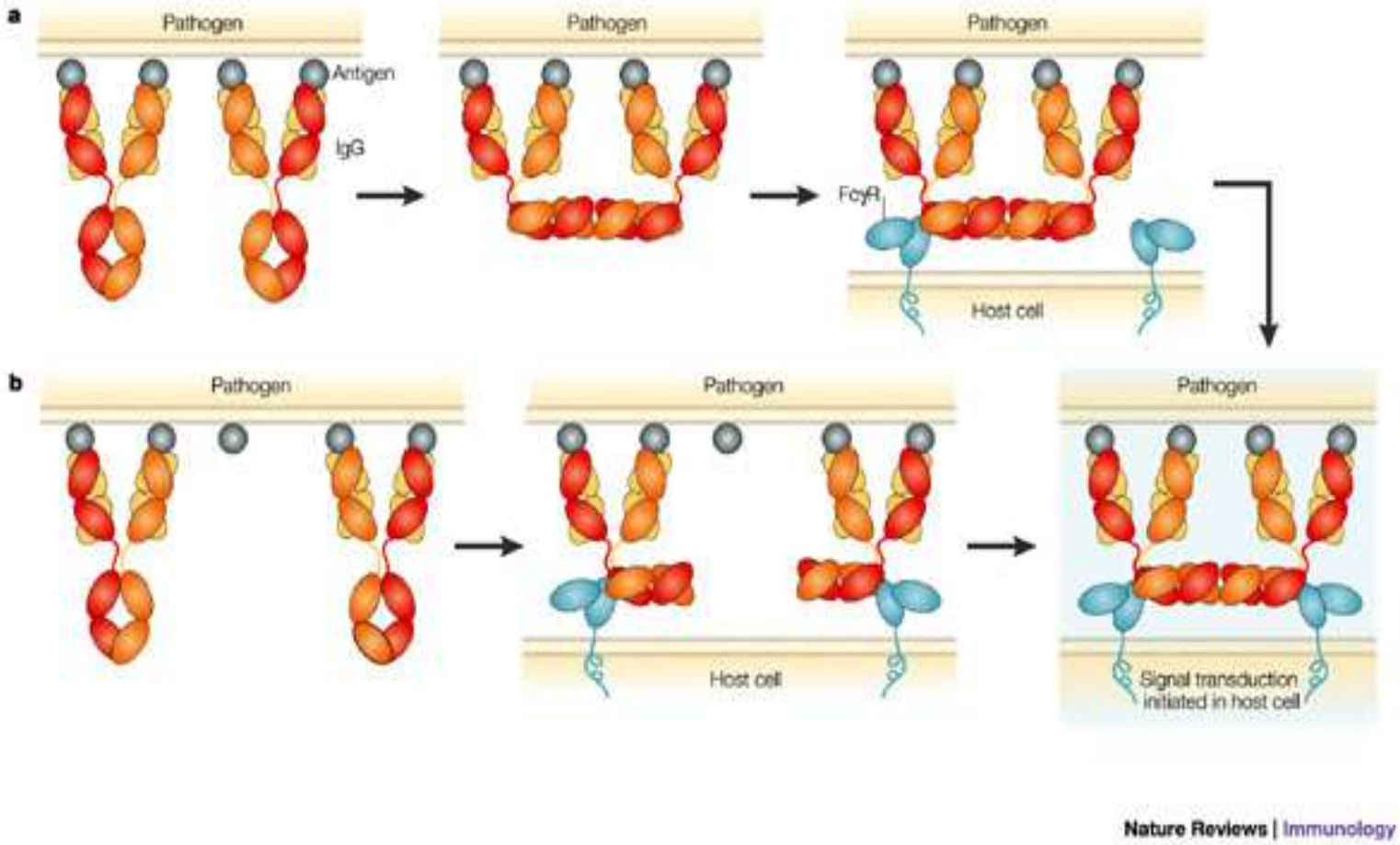
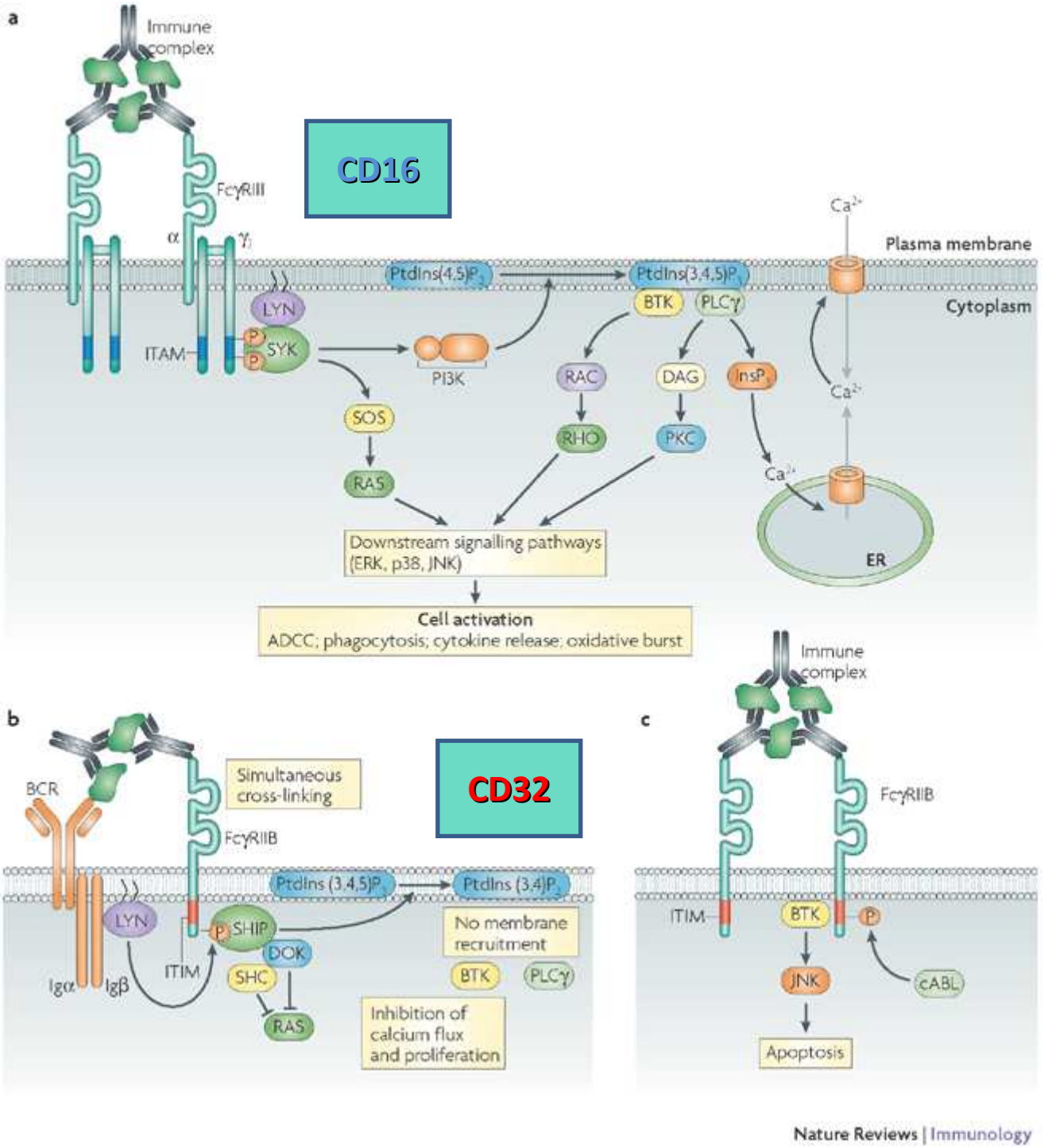
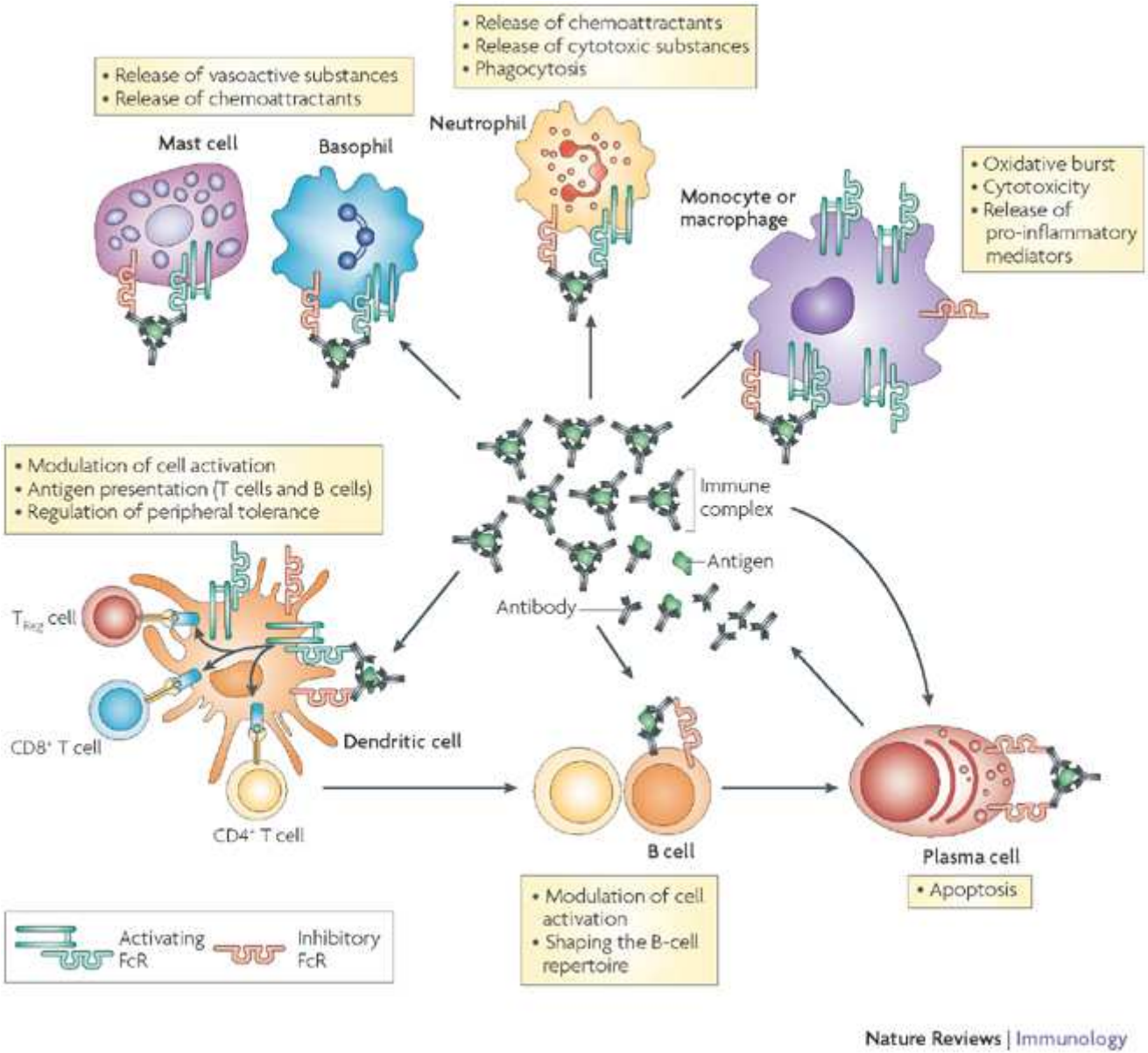
Receptor	FcγRI (CD64)	FcγRII-A (CD32)	FcγRII-B2 (CD32)	FcγRII-B1 (CD32)	FcγRIII (CD16)	FcεRI	FcαRI (CD89)	Fcα/μR
Structure								
Binding Order of affinity	IgG1 $10^8\ M^{-1}$ 1) IgG1=IgG3 2) IgG4 3) IgG2	IgG1 $2 \times 10^6\ M^{-1}$ 1) IgG1 2) IgG3=IgG2* 3) IgG4	IgG1 $2 \times 10^6\ M^{-1}$ 1) IgG1=IgG3 2) IgG4 3) IgG2	IgG1 $2 \times 10^6\ M^{-1}$ 1) IgG1=IgG3 2) IgG4 3) IgG2	IgG1 $5 \times 10^5\ M^{-1}$ IgG1=IgG3	IgE $10^{10}\ M^{-1}$	IgA1, IgA2 $10^7\ M^{-1}$ IgA1=IgA2	IgA, IgM $3 \times 10^9\ M^{-1}$ 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 Eosinophils‡ Neutrophils	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 Immunobiology, 7ed. (© Garland Science 2008)



Nature Reviews Immunology 4, 89-99 (February 2004)

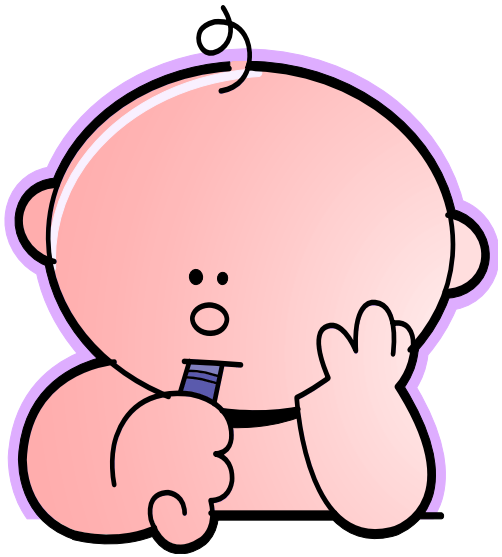

a
Immune complex
FcγRIII
α
γ
CD16
LYN
P
SYK
ITAM
PI3K
PtdIns(4,5)P2
PtdIns(3,4,5)P3
BTK
PLCγ
Plasma membrane
Cytoplasm
Ca2+
RAC
DAG
InsP3
SOS
RHO
PKC
RAS
Ca2+
ER
Downstream signalling pathways (ERK, p38, JNK)
Cell activation
ADCC; phagocytosis; cytokine release; oxidative burst
b
BCR
Simultaneous cross-linking
CD32
FcγRIIB
PtdIns (3,4,5)P3
PtdIns (3,4)P2
LYN
SHIP
DOK
SHC
RAS
ITIM
Igα
Igβ
No membrane recruitment
BTK
PLCγ
Inhibition of calcium flux and proliferation
c
Immune complex
FcγRIIB
ITIM
BTK
P
JNK
cABL
Apoptosis



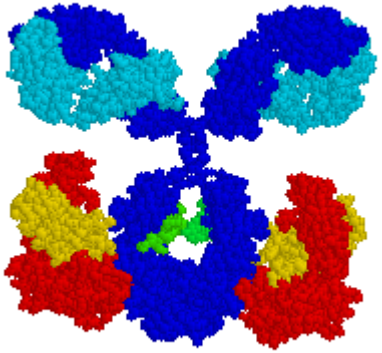
Nature Reviews Immunology 8, 34-47 (January 2008)

Immune complexes bind to activating Fc receptors (FcR) and inhibitory FcRs that are expressed by innate immune effector cells such as basophils, mast cells, neutrophils, monocytes and macrophages, in which they trigger the indicated effector responses.

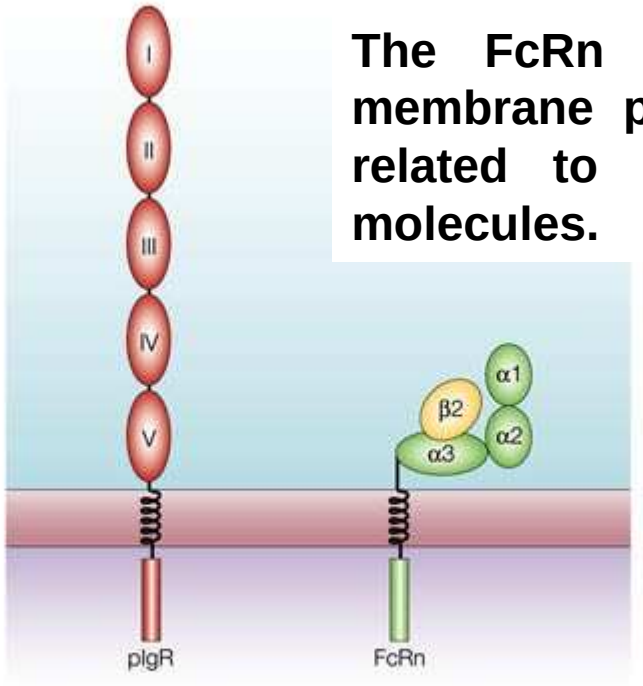
B cells only express the inhibitory low-affinity FcR for IgG (FcRIIB), which regulates activating signals transduced by the B-cell receptor (BCR). On plasma cells, which produce high levels of antigen-specific antibodies, BCR expression is very low or absent, resulting in exclusive triggering of inhibitory signalling pathways.



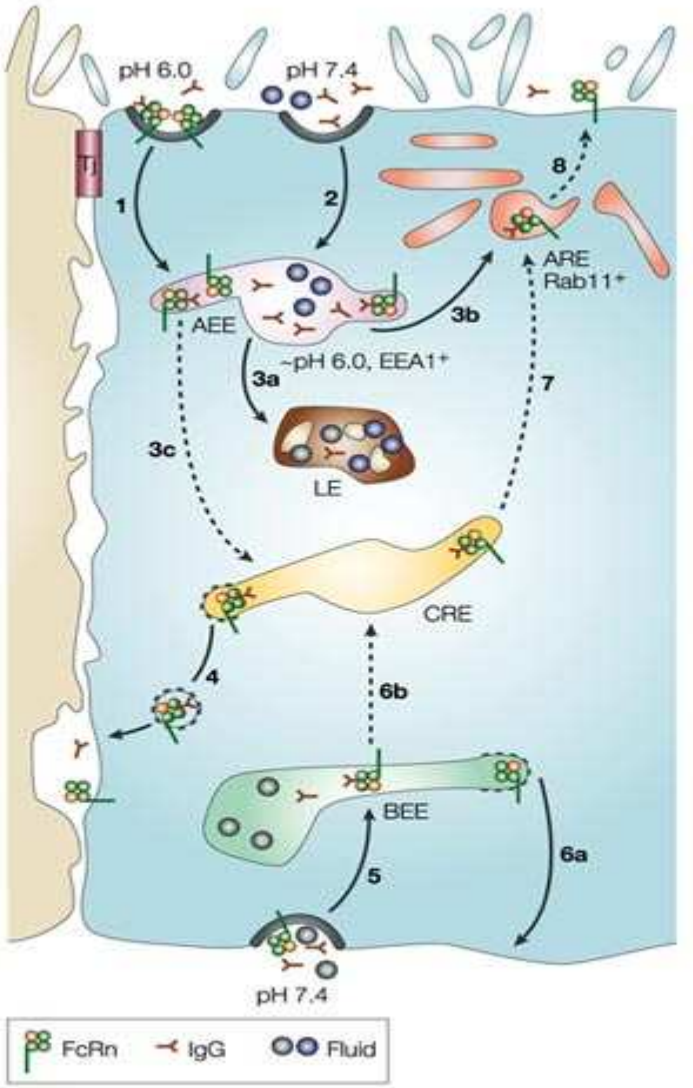
Receptor Fc neonatal



The pIgR is a type I membrane protein that has a large extracellular region arranged in five domains (that are homologous to the variable-like domains of the Ig superfamily)

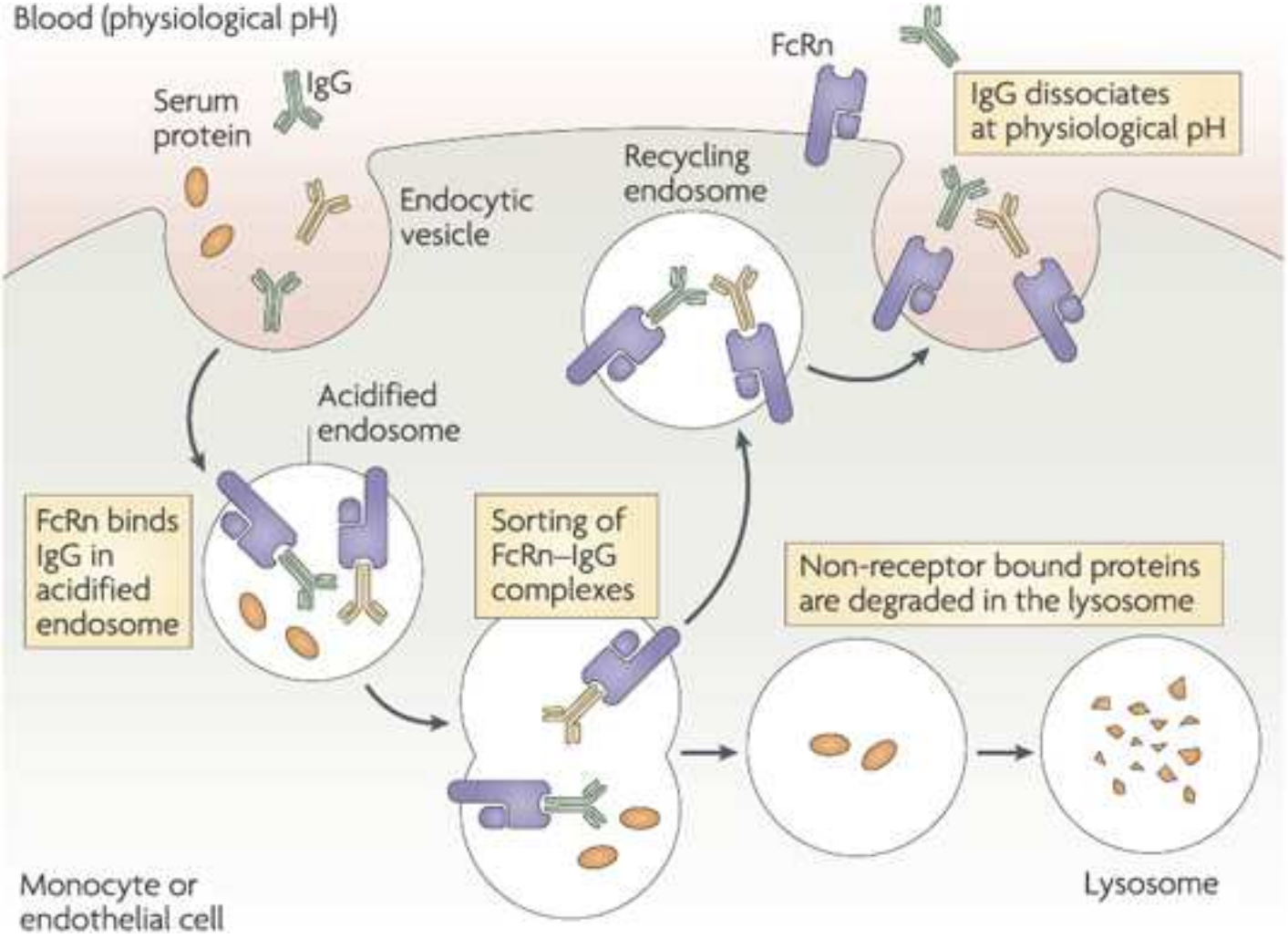


The FcRn is a type I membrane protein that is related to MHC class I molecules.

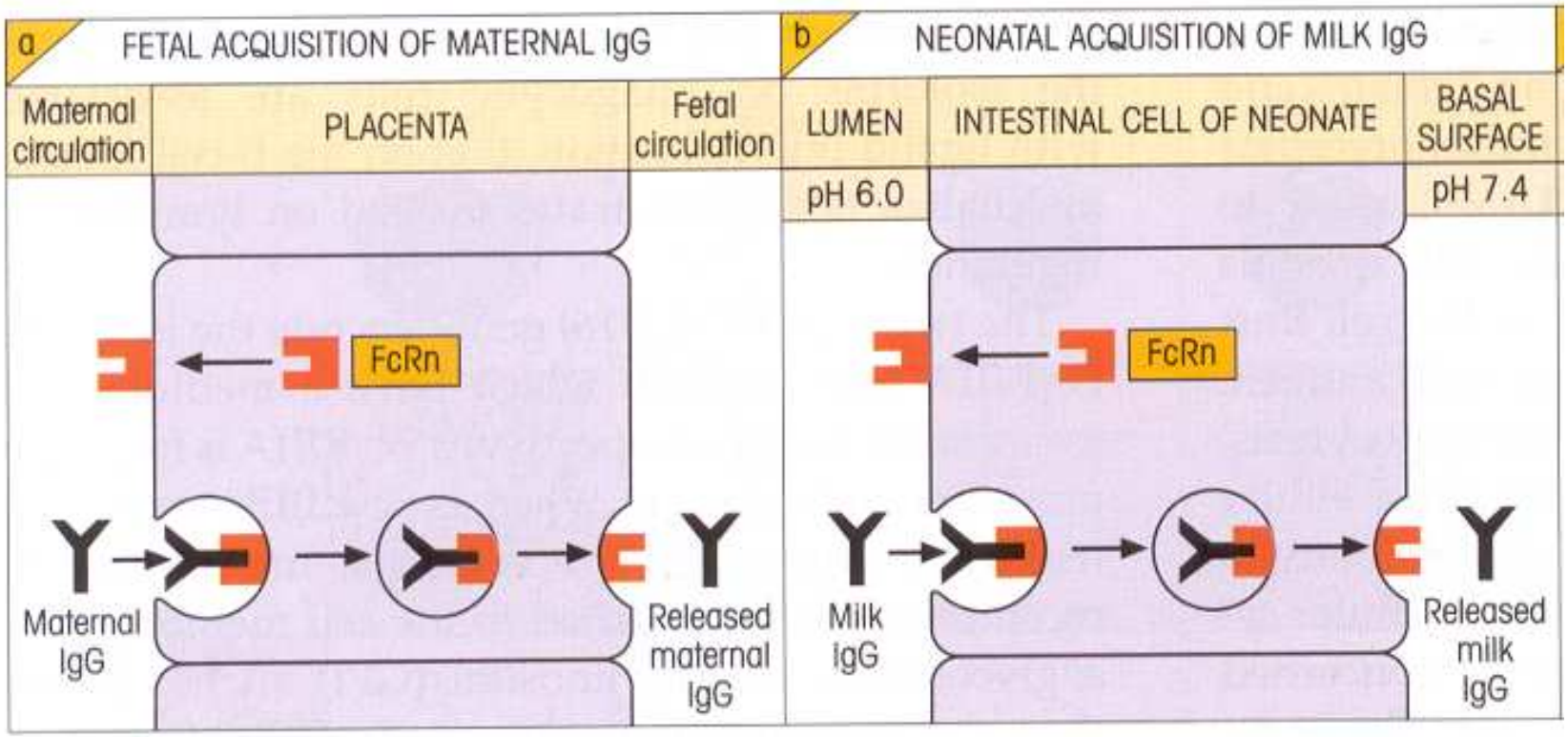


Nature Reviews | Molecular Cell Biology

The FcRn molecule (Fc receptor neonatal) is responsible for the transport of immunoglobulin from mother to neonate



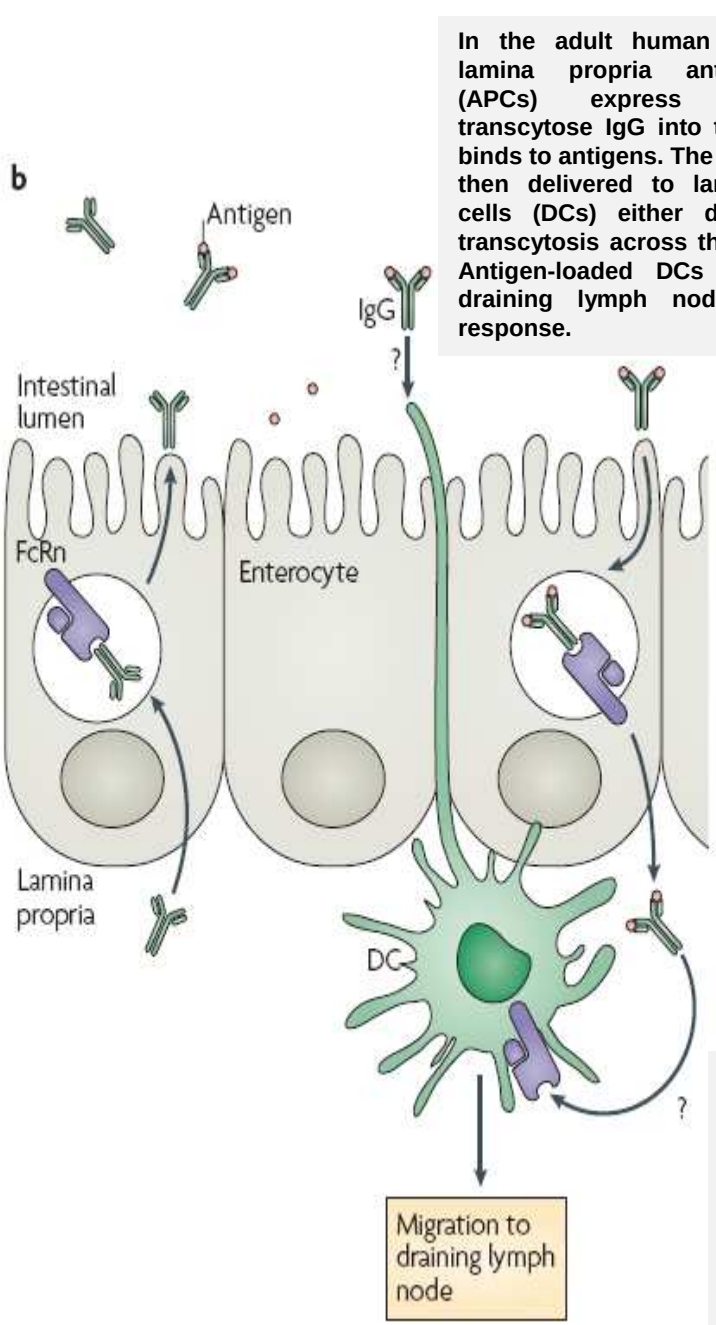
TRANSFERENCIA PASIVA DE IgG



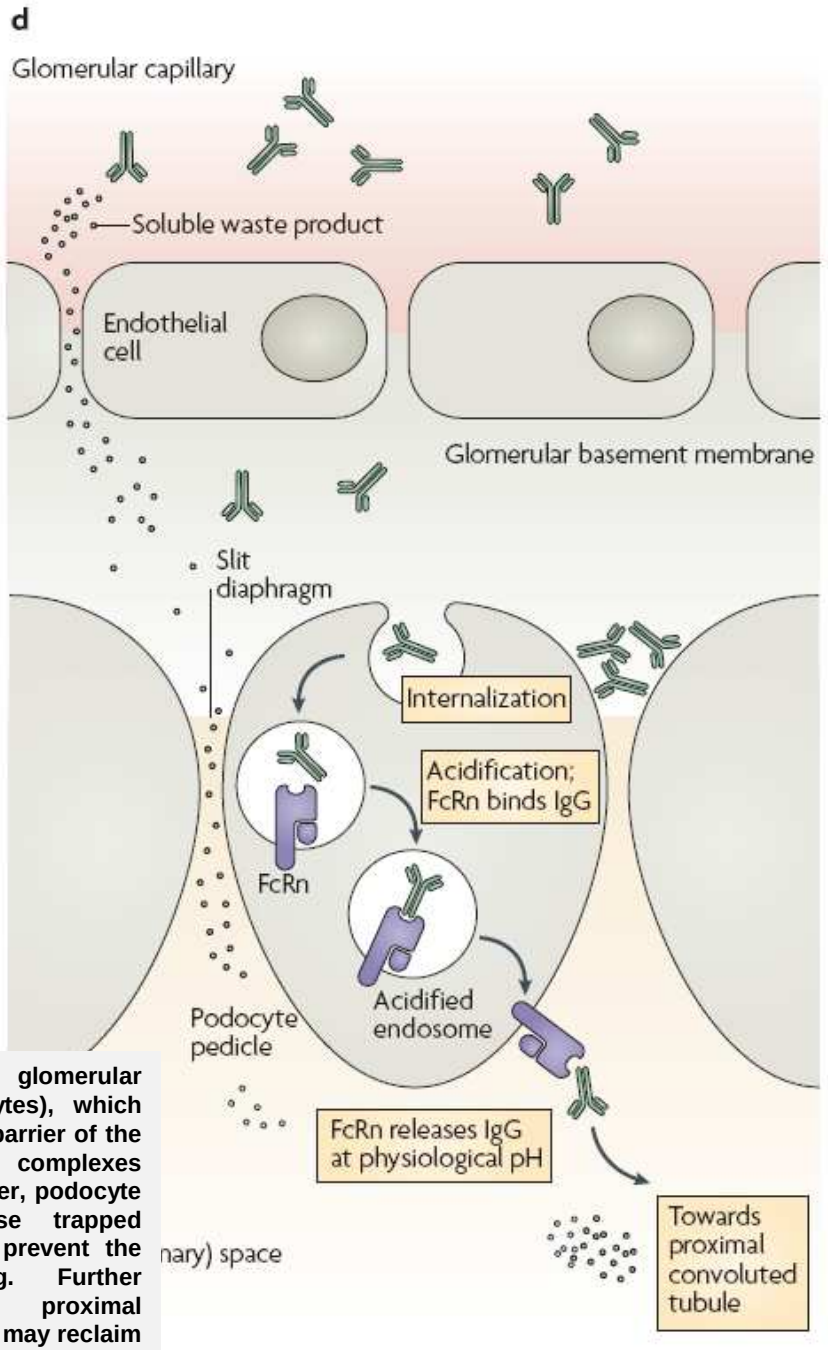
EL RECEPTOR Fc NEONATAL también se encuentra el intestino, podocitos, hígado , células endoteliales vasculares de los adultos….

REGULA LA CONCENTRACIÓN SÉRICA DE IgG EN EL ADULTO…..

SE UNE AL ANTICUERPO CIRCULANTE AL QUE ENDOCITA Y LUEGO RECICLA A LA SUPERFICIE CELULAR…..



In the adult human gut, enterocytes and lamina propria antigen-presenting cells (APCs) express FcRn. Enterocytes transcytose IgG into the gut lumen where it binds to antigens. The IgG–antigen complex is then delivered to lamina propria dendritic cells (DCs) either directly or by reverse transcytosis across the epithelial-cell barrier. Antigen-loaded DCs then migrate to the draining lymph node to prime a T-cell response.



FcRn is expressed in glomerular epithelial cells (podocytes), which form the main filtration barrier of the kidney. If IgG immune complexes deposit at the kidney filter, podocyte FcRn may transcytose trapped immune complexes to prevent the filter from clogging. Further downstream in the proximal convoluted tubule, FcRn may reclaim transcytosed IgG,

LOS GRUPOS SANGUÍNEOS EN EL EMBARAZO

TEORÍA DE LA ABUELA

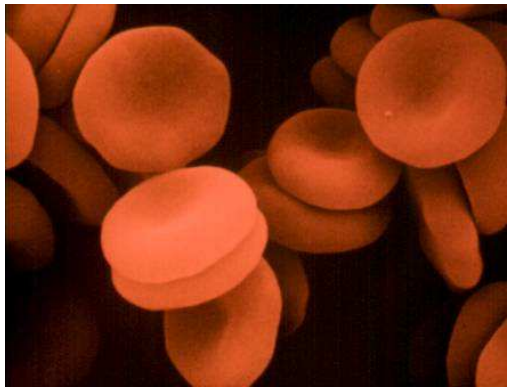
Una madre Rh(–) (2) puede inmunizarse en el momento del nacimiento si recibe sangre de su madre Rh(+) (1). Posteriormente puede darse una isoinmunización en sus descendientes (3). Tomada de Ramos de Almeida y col (Arch. Dis Child. 1972; 47: 609-612)

Figura 15. Sensibilización Rh en el momento del nacimiento. R.N. Rh(–), madre Rh(+)

GENERALIDADES

- Existen principalmente dos tipos de proteínas que determinan el tipo de sangre :
- A y B cuya presencia o ausencia dan lugar a 4 grupos sanguíneos : A , B , AB, O.

- El **Rh es una proteína** que se encuentra en la superficie de los eritrocitos .
- Así como también:
- Lewis, Duffy, Kell, Kidd, etc.

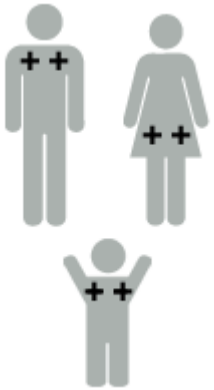


TIPIFICACIÓN DEL SISTEMA ABO Y Rh

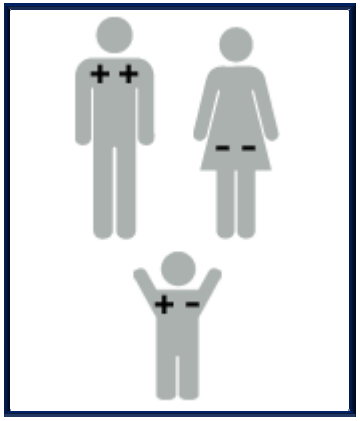
- En el sistema Rh (>50 Ags) se contemplan 5 Ags determinantes de la mayoría de los fenotipos: **D,C,c,E,e**

- **El antígeno D es el más inmunógeno y determina a las personas Rh(+)**

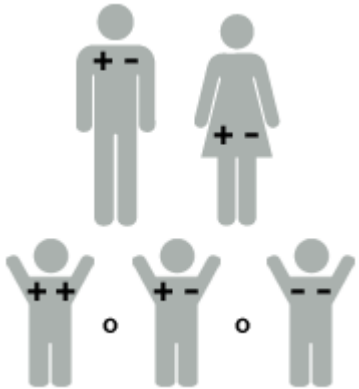
- **Algunos individuos Rh(+) presentan una *expresión débil del Ag D*: defecto cuantitativo (D débil) o incompleto (D parcial)**



Si los genes del **factor Rh** del padre son + + y los de la madre son + +, el bebé tendrá un gen + del padre y un gen + de la madre y será Rh positivo + +.



Si los genes del factor Rh del padre son + + y los de la madre son - -, el bebé tendrá un gen + del padre y un gen - de la madre y será Rh positivo + -.



Si los genes del padre son factor Rh positivo + - y los de la madre también, el bebé puede ser:

- Rh positivo + +
- Rh positivo + -
- Rh negativo - -

Si los genes del padre son - - y los de la madre son + -, el bebé puede ser:

- Rh negativo + -
- Rh positivo - -

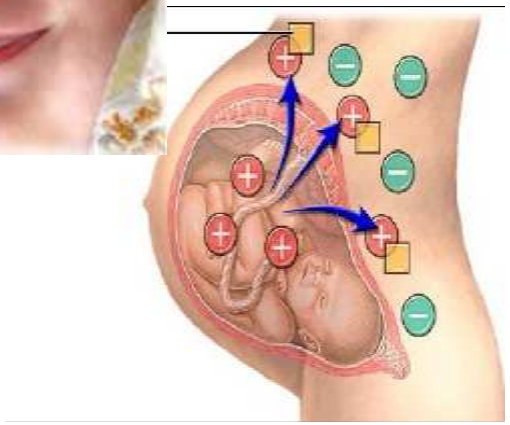
Si los genes del padre son - - y los de la madre son - -, el bebé será:

- Rh negativo - -

Los factores Rh se determinan genéticamente. Un bebé puede tener el grupo sanguíneo y el factor Rh de cualquiera de sus padres o bien una combinación de ambos. Los factores Rh siguen un patrón común de herencia genética. El gen Rh positivo es dominante (más fuerte) e incluso cuando se junta con un gen Rh negativo, el positivo prevalece.

- **Si una persona tiene los genes + +, el factor Rh en la sangre será positivo.**
- **Si tiene los genes + -, el factor Rh en la sangre también será positivo.**
- **Pero si una persona tiene los genes - -, el factor Rh en la sangre será negativo.**

ISOINMUNIZACIÓN



Los eritrocitos fetales acceden al torrente sanguíneo materno.

El sistema inmune materno trata las células fetales como sustancias extrañas, y forma Acs anti-Rh(D)

IgM

No pasan barrera placentaria

Depende de la dosis transferida desde el feto

(V>0.5 ml aumenta el riesgo de sensibilización)

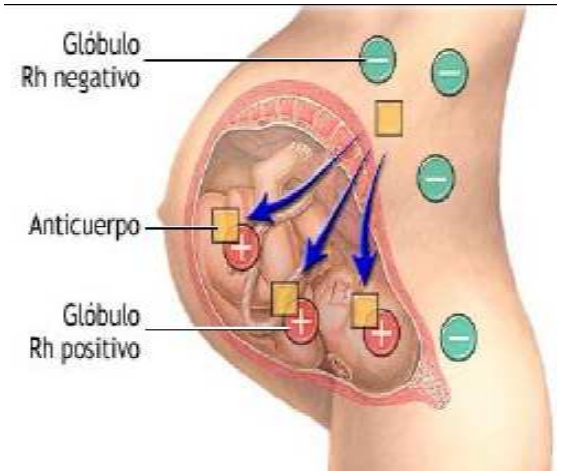
No sensibilización previa

Feto no afectado en 1er embarazo

ISOINMUNIZACIÓN

Embarazo posterior con feto Rh(+)

Sensibilización precoz



síntesis de **IgG** (menor PM)

↓

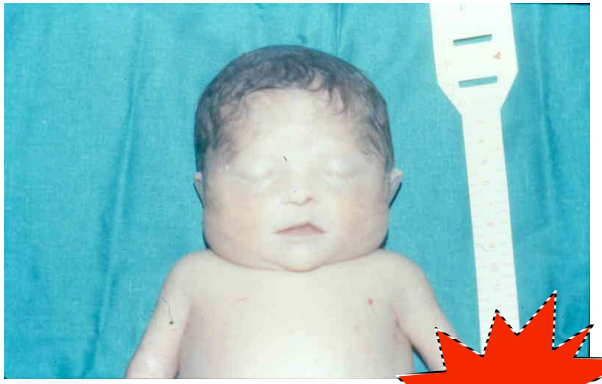
atraviesan la barrera placentaria
(>16º semana de gestación)

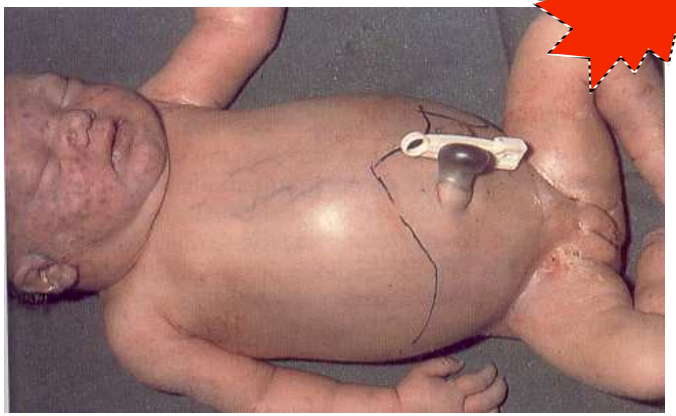
↓

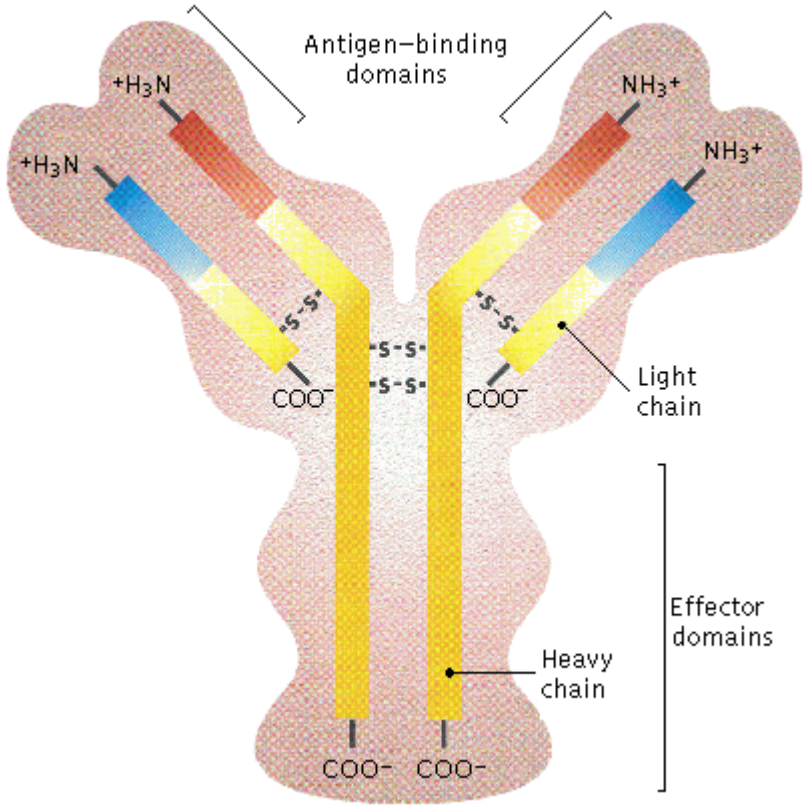
reacción contra los Ag Rh(D) y
destrucción de eritrocitos fetales

EHP

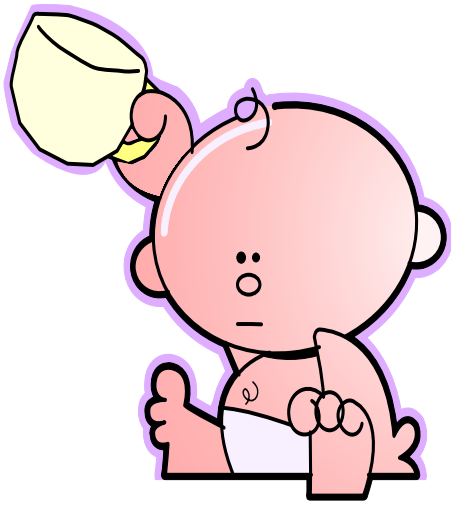
ENFERMEDAD HEMOLITICA PERINATAL



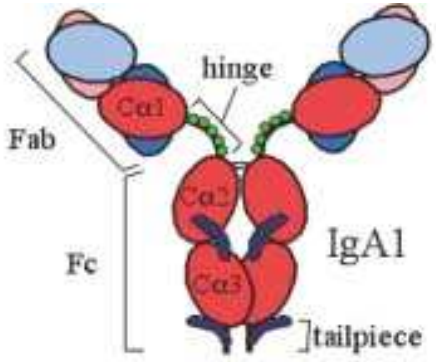




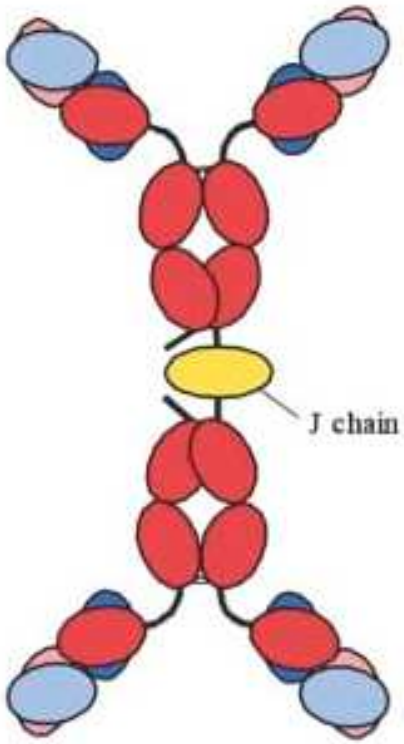
INMUNOGLOBULINA A



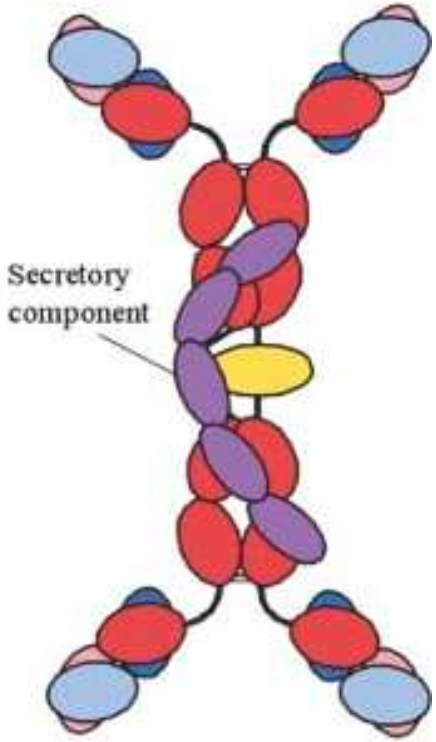
Estructura de la IgA



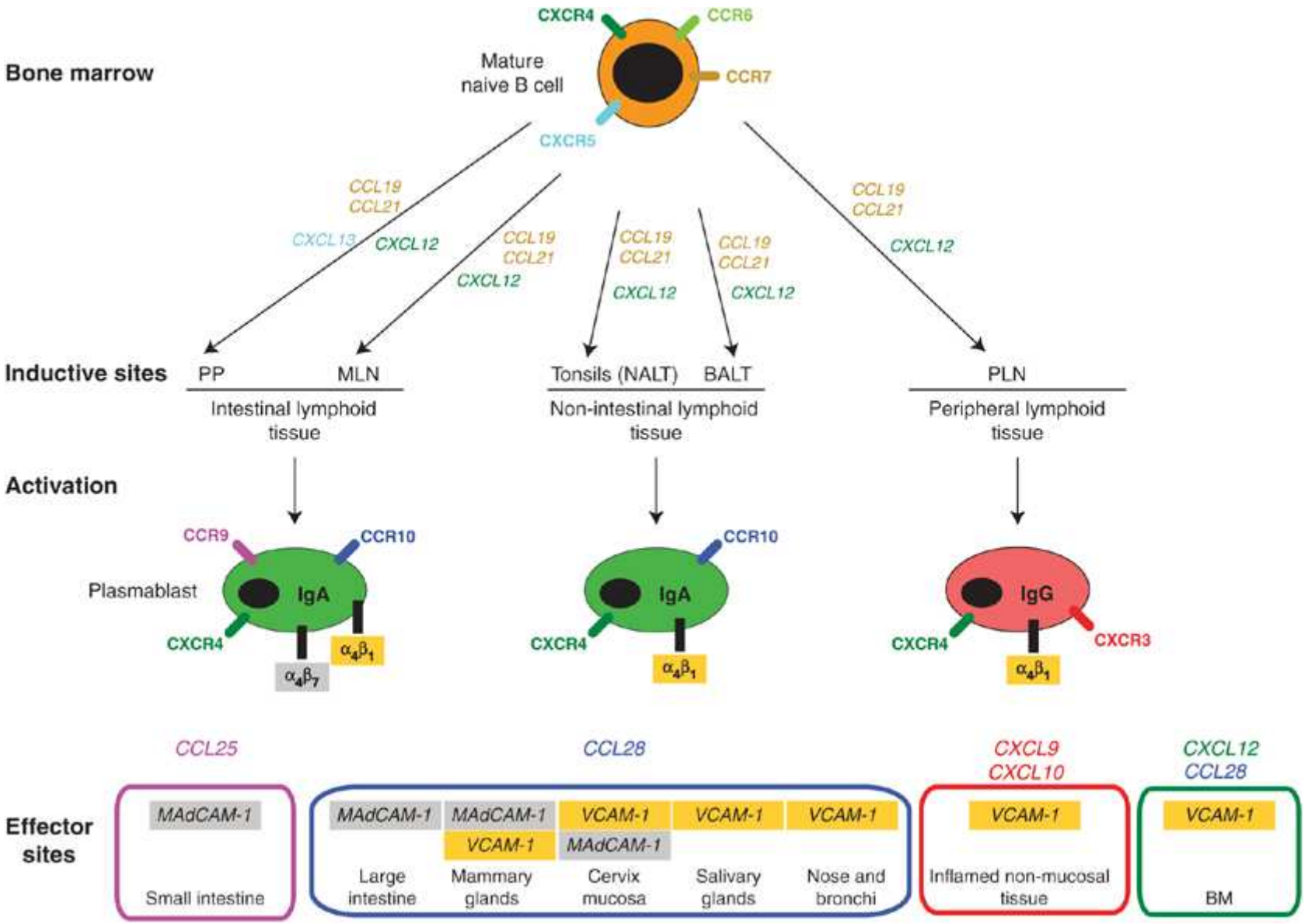
Monomérica IgA



Dimérica IgA

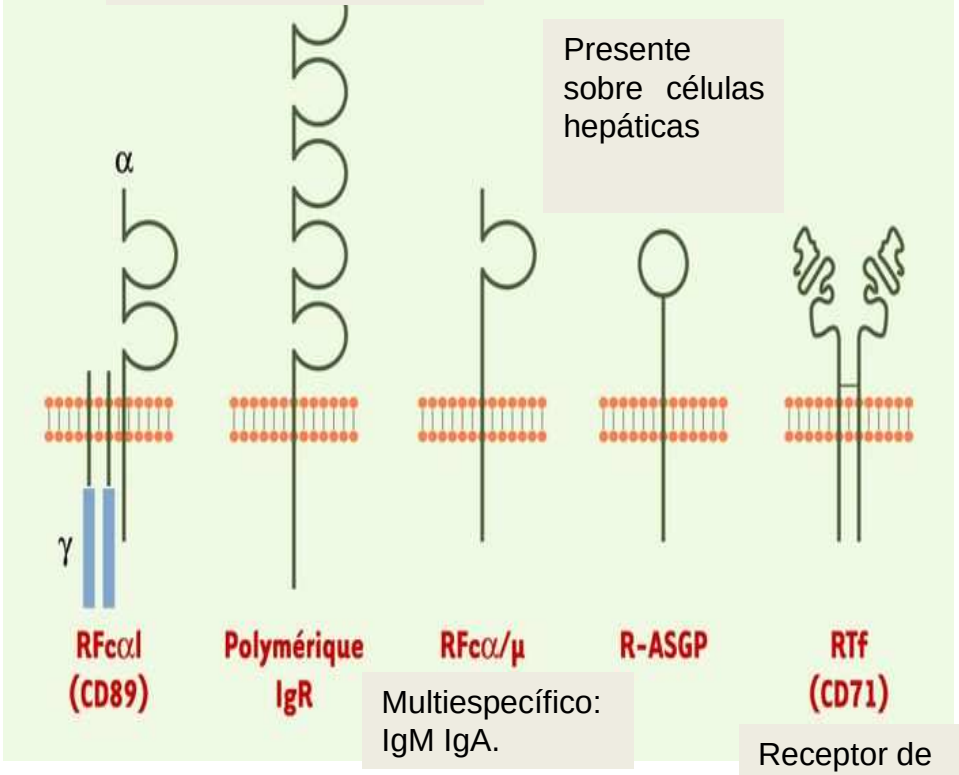


Secretoria IgA


Bone marrow
Mature naive B cell
CXCR4
CCR6
CCR7
CXCR5
CCL19
CCL21
CXCL13
CXCL12
Inductive sites
PP
MLN
Tonsils (NALT)
BALT
PLN
Intestinal lymphoid tissue
Non-intestinal lymphoid tissue
Peripheral lymphoid tissue
Activation
CCR9
CCR10
Plasmablast
IgA
IgG
CXCR3
$\alpha_4\beta_1$
$\alpha_4\beta_7$
CCL25
CCL28
CXCL9
CXCL10
CXCL12
CCL28
Effector sites
MAdCAM-1
VCAM-1
Small intestine
Large intestine
Mammary glands
Cervix mucosa
Salivary glands
Nose and bronchi
Inflamed non-mucosal tissue
BM

Receptores Fcα

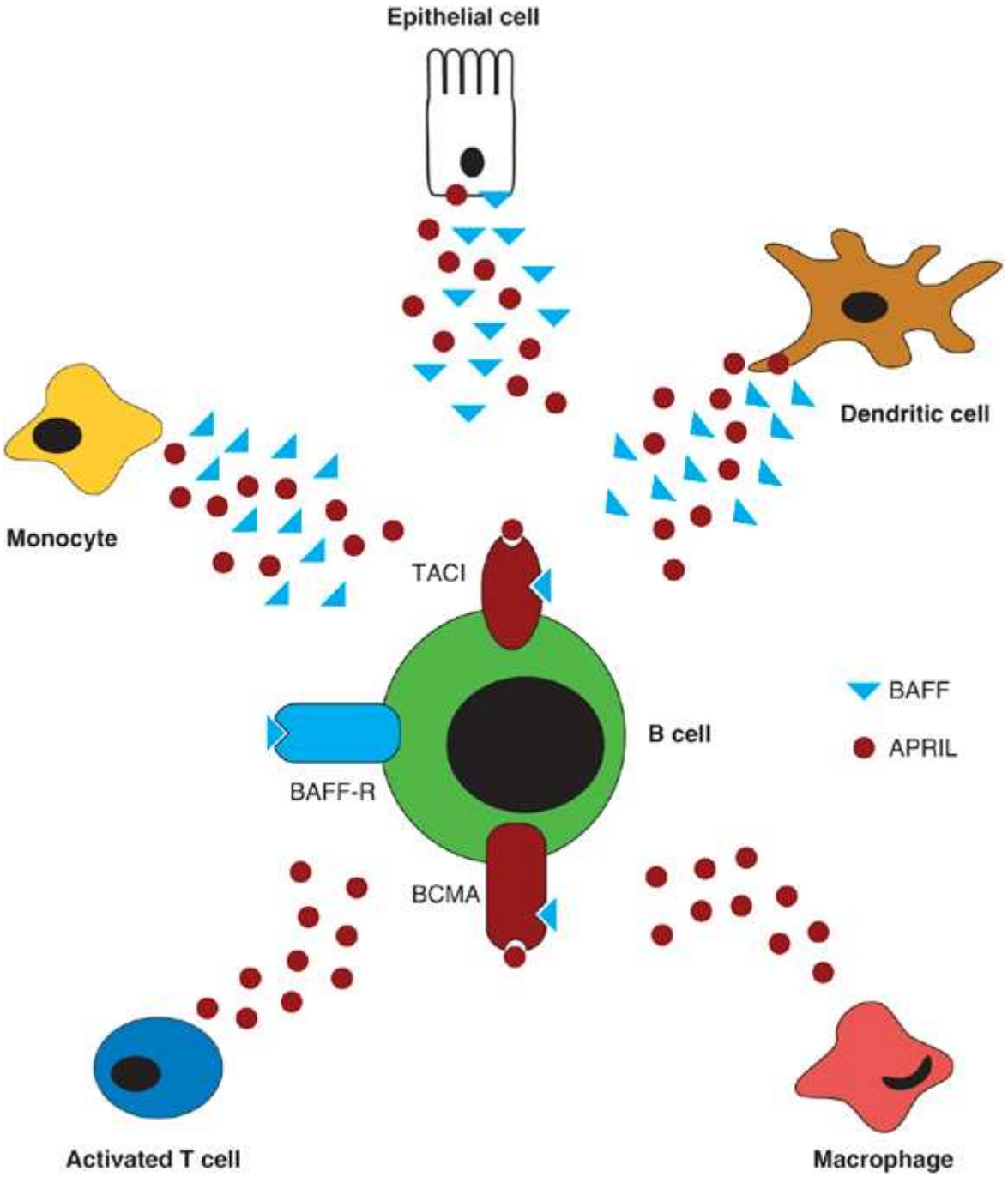
Presente en células epiteliales mucosas y glándulas exócrinas



Presente sobre células hepáticas

Multiespecífico: IgM IgA.

Receptor de transferrina



Costimulatory signals for class switch recombination (CSR) to IgA. BAFF and APRIL are expressed by dendritic cells, monocytes, and human colonic epithelial cells (following Toll-like receptor signaling, not shown), whereas APRIL can also be secreted by macrophages and activated T cells. These cytokines bind to their receptors, BAFF-R, TACI, or BCMA, which are all expressed by B cells.

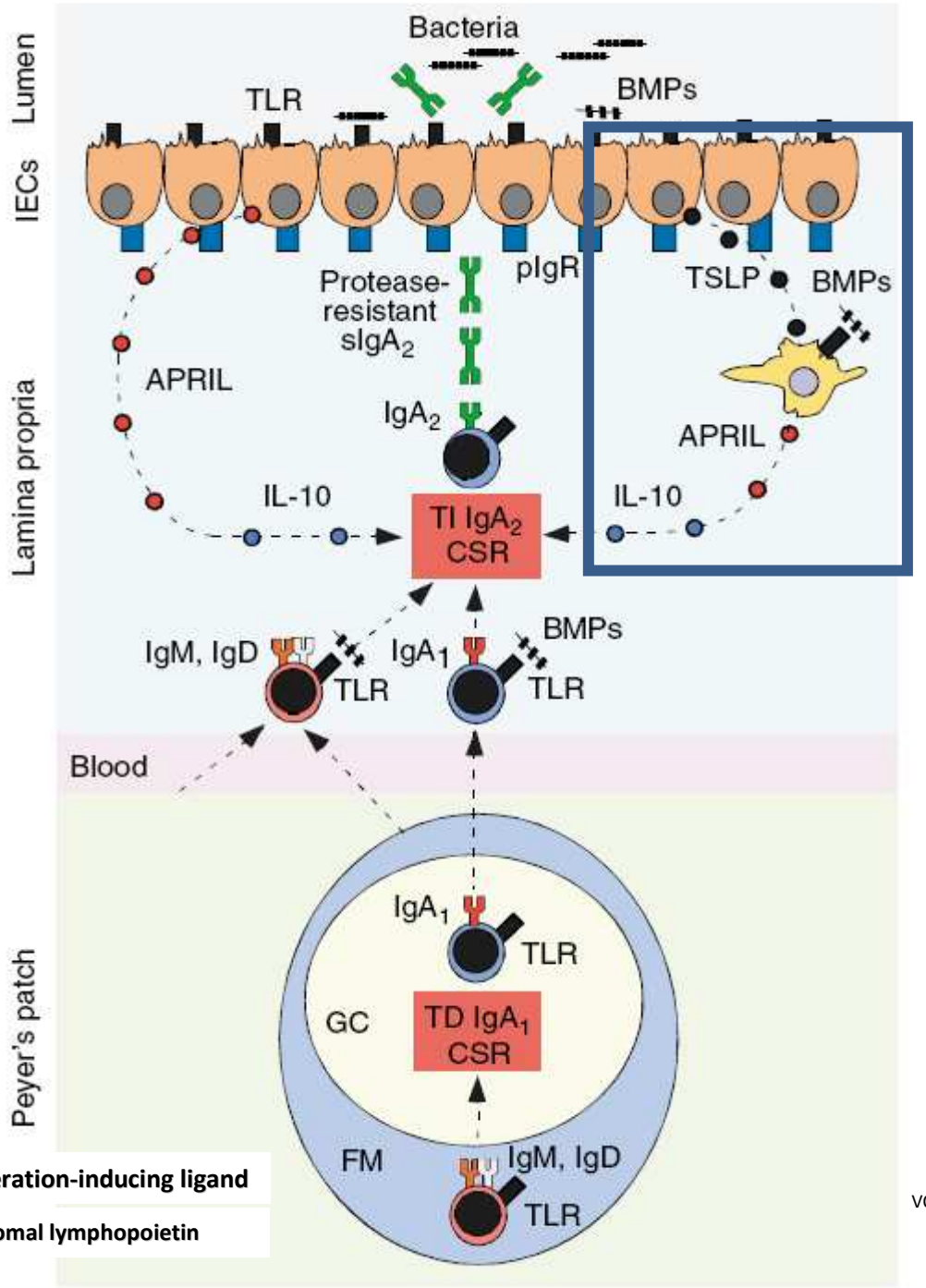
APRIL, A proliferation-inducing ligand;

BAFF, B-cell activating factor of the TNF family;

BCMA, B-cell maturation antigen;

TACI, transmembrane activator and CAML interactor.

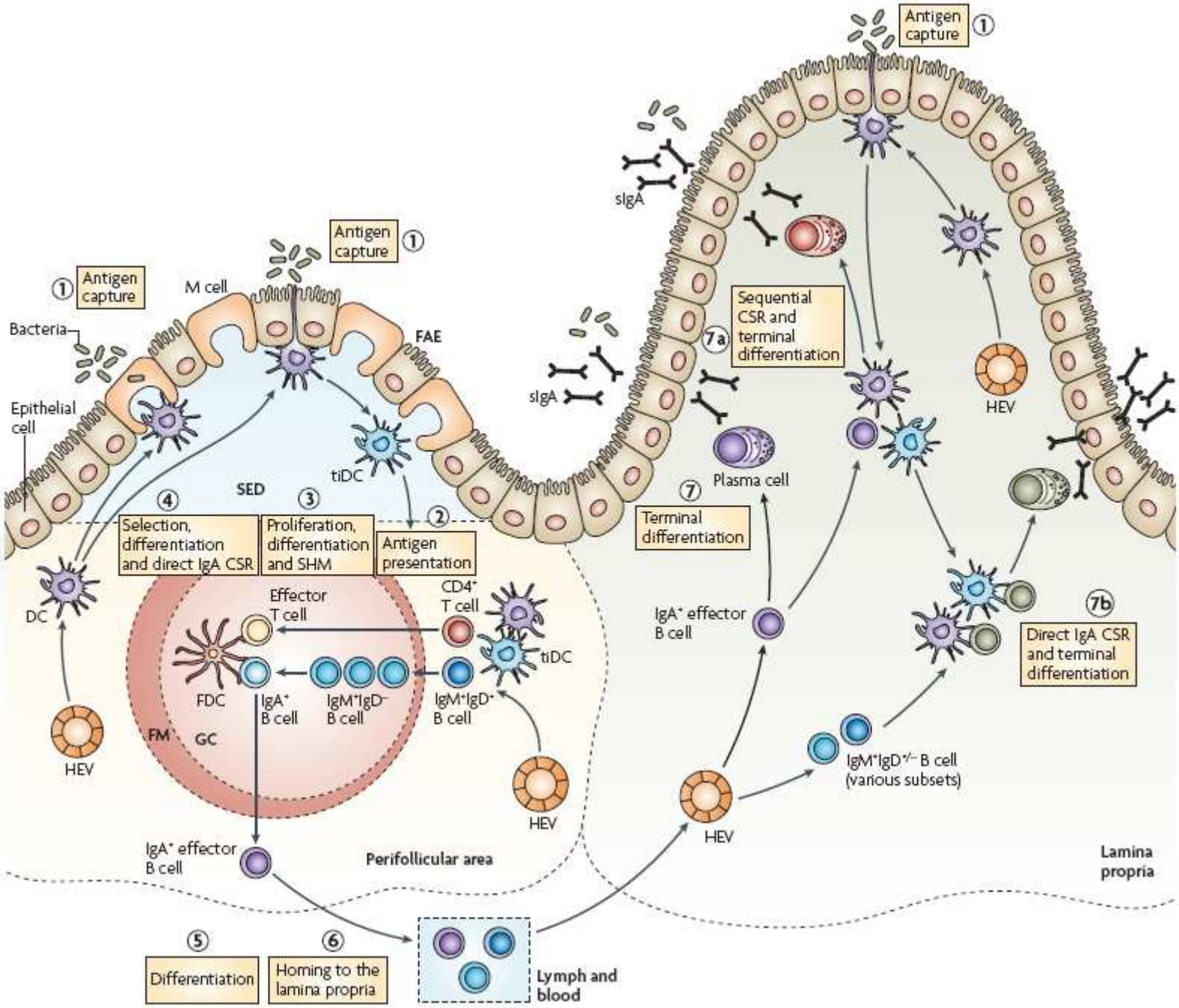
SÍNTESIS DE IGA en el intestino



APRIL, a proliferation-inducing ligand

TSLP, thymic stromal lymphopoietin

Proposed model of B-cell differentiation and IgA class switching in the human intestine.
Follicular mantle (FM) naive IgM + IgD + B cells undergo TD direct IgM-to-IgA1 CSR as well as SHM in the GC of PPs upon exposure to CD4 + T-helper cells expressing CD40L and cytokines, including (data not shown) IL-10 and TGF- β . The resulting mutated IgA1 + B cells migrate into the colon LP, where they undergo TI sequential IgA1-to-IgA2 CSR under the influence of APRIL and IL-10 released by intestinal epithelial cells (IECs). IECs produce these innate B-cell-stimulating cytokines after sensing bacterial molecular patterns (BMPs) through TLRs. IECs further amplify APRIL and IL-10 production by stimulating LP dendritic cells (DCs) through an IL-7-like cytokine known as thymic stromal lymphopoietin (TSLP). Then, protease-resistant IgA2 dimers released by LP B cells undergo pIgR-mediated transcytosis to prevent adhesion of commensal bacteria to IECs. Additional IgA2 would originate from PP- or bone marrow-derived IgM + IgD + B cells, which undergo TI IgM-to-IgA2 CSR in the APRIL-rich environment of the LP. These B cells likely include both mutated and unmutated subsets.
APRIL, a proliferation-inducing ligand; IgA, immunoglobulin A; CSR, class switch DNA recombination;
GC, germinal center; LP, lamina propria; pIgR, polymeric Ig receptor; PPs, Peyer ' s patches; SHM, somatic hypermutation; TD, T-cell-dependent; TI, T-cell-independent ; TLRs, Toll-like receptors.

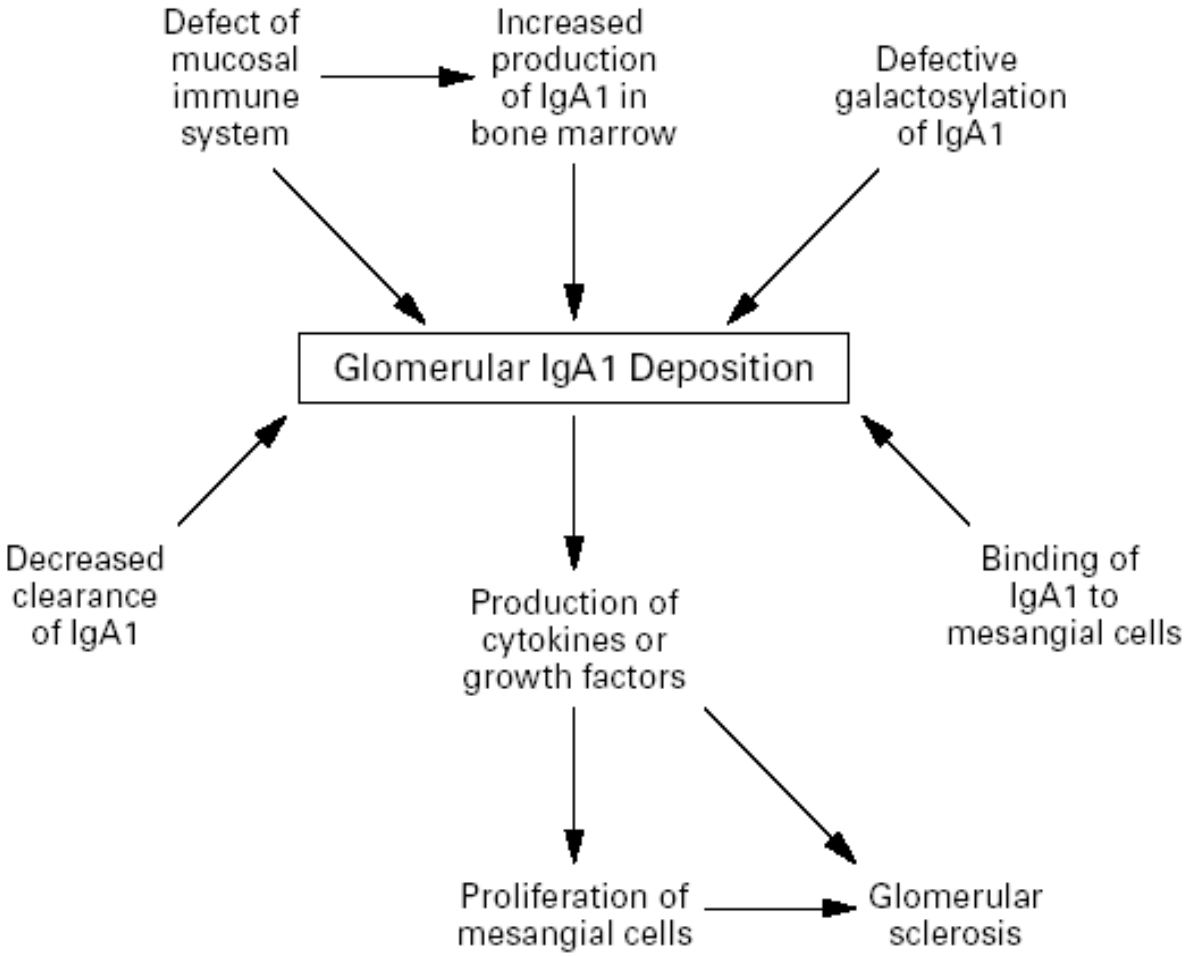

Antigen capture
1
sIgA
Antigen capture
1
Antigen capture
1
M cell
Bacteria
FAE
Epithelial cell
tiDC
SED
4
3
2
Selection, differentiation and direct IgA CSR
Proliferation, differentiation and SHM
Antigen presentation
DC
Effector T cell
CD4+ T cell
tiDC
FDC
IgA+ B cell
IgM+IgD− B cell
IgM+IgD+ B cell
FM
GC
HEV
HEV
sIgA
7a
Sequential CSR and terminal differentiation
HEV
Plasma cell
7
Terminal differentiation
IgA+ effector B cell
7b
Direct IgA CSR and terminal differentiation
IgM+IgD+/− B cell (various subsets)
HEV
IgA+ effector B cell
Perifollicular area
Lamina propria
5
Differentiation
6
Homing to the lamina propria
Lymph and blood

Map of I gA class switching in the gut. Dendritic cells (DCs) in the subepithelial dome (SED) of the Peyer's patches capture antigen by interacting with microfold (M) cells or by extending transepithelial projections into the lumen. During this process, DCs are induced to express tumour-necrosis factor (TNF) and inducible nitric oxide synthase (iNOS) (and are therefore referred to as tiDCs), which present antigen to perifollicular CD4+ T cells, thereby inducing them to differentiate into effector T cells releasing IgA-inducing cytokines. T cells also interact with antigen-specific IgM+IgD+ naive B cells. Together with follicular dendritic cells (FDCs), this interaction fosters a germinal centre (GC) reaction that includes somatic hypermutation (SHM) and IgA class-switch recombination (CSR). The resulting IgA+ effector B cells home to the gut lamina propria, where they differentiate into plasma cells that secrete high-affinity IgA. Human IgA1+ effector B cells can also undergo sequential IgA2 CSR on receiving T-cell-independent signals from bacteria-activated epithelial cells, DCs and tiDCs. Similar signals trigger direct IgA CSR in various B-cell subsets, including unmutated IgM+IgD+ B-1 cells from the peritoneum and mutated IgM+IgD– effector B cells from Peyer's patches. These local CSR events generate plasma cells secreting low- or high-affinity IgA. FAE, follicle-associated epithelium; FM, follicular mantle; HEV, high endothelial venule; sIgA, secreted IgA.

TRANSFERENCIA PASIVA DE IgA

Ig	Colostrum (g/L)	Milk (g/L)
IgA	**5 – 10**	**0.3 – 1**
IgM	0.06	0.06
IgG	0.1	0.01

Nefropatía por IgA

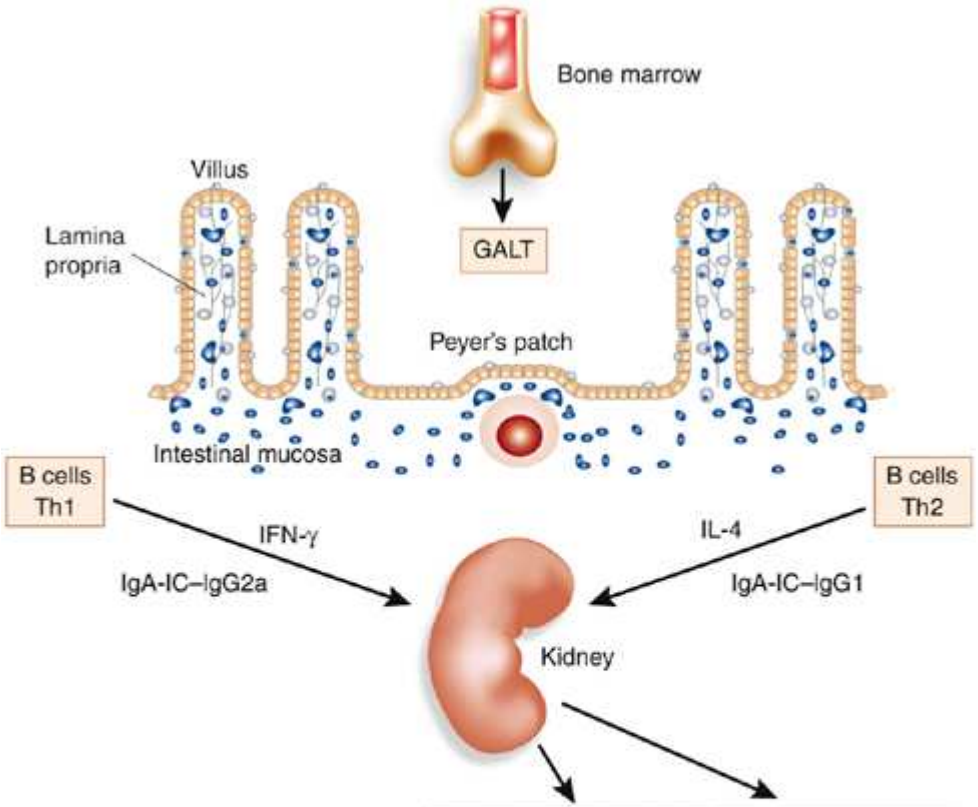


Modificación cuantitativa y estructural de la IgA en respuesta a antígenos:

Aumento de la concentración sérica de IgA polimérica (pIgA1) y anormalmente glicosilada (hipogalactosilada)

Inducen anomalías funcionales de los diferentes receptores de IgA de las células sanguíneas circulantes (CD89) y de las células mesangiales (CD71):

IgA anormales inducen liberación de CD89 soluble que participa en la formación de Complejos Inmunes circulantes que se depositan secundariamente en el mesangio por fijación a un segundo receptor sobreexpresado (CD71)



		Th 1		Th2	
Functional motif	Receptor	IgA-IC–IgG2a	IFN-γ	IgA-IC–IgG1	IL-4
ITAM	FcγRI	+		–	
ITAM	FcγRIII	++		+	
ITAM	FcγRIV	+++	↑↑↑	–	
ITIM	FcγRIIB	–	↓	++	↑↑↑
Macrophage activation		High		Low	
Glomular injury		Severe		Minimal	

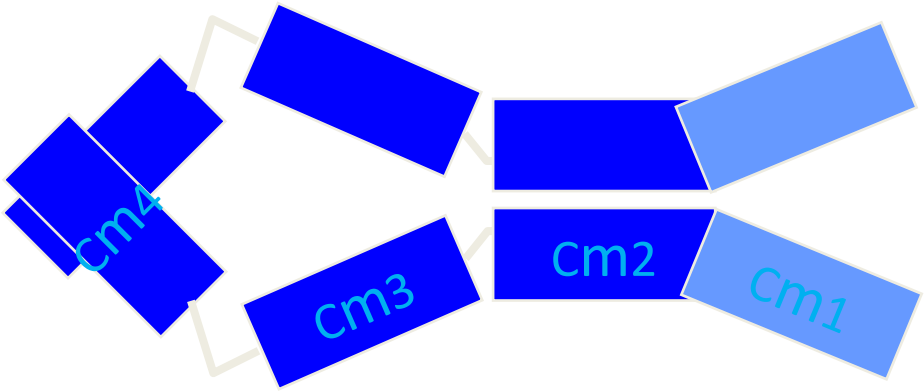
The simplified scheme illustrates how the pathogenic potential of an IgA immune complex (IgA-IC) glomerular immune deposit is influenced by the colocalized subclass IgA interaction with Fc receptors (Fc Rs) on infiltrating macrophages that affects the magnitude of their activation and consequently the extent of glomerular injury. In this model, stem cells in the bone serve as a reservoir of autoimmune B cells that home to the mucosa of the gut-associated lymphoreticular tissue (GALT) to generate polymeric IgA. T-helper 1 (Th1) polarization in the GALT will lead to B-cell immunoglobulin class switching favoring IgG2a that reacts with the antigenic component of the IgA-IC, generating a detrimental complex composite of IgA-IC-IgG2a. Conversely, a Th2 bias leads to production of IgG1 reactive with IgA-IC that generates complex composite of IgA-IC-IgG1 with low nephritogenic potential. Circulating interferon-γ (IFN-γ) and interleukin-4 (IL-4) produced, respectively, by Th1 and Th2 in the GALT modulate glomerular injury by affecting FcγR expression on macrophage infiltrates and consequently the magnitude of their activation by the IgA-IC–IgG deposit. ITAM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibition motif.

INMUNOGLOBLUNINA M

IgM Monomérica

IgM sólo existe como MONÓMERO en la superficie de células B

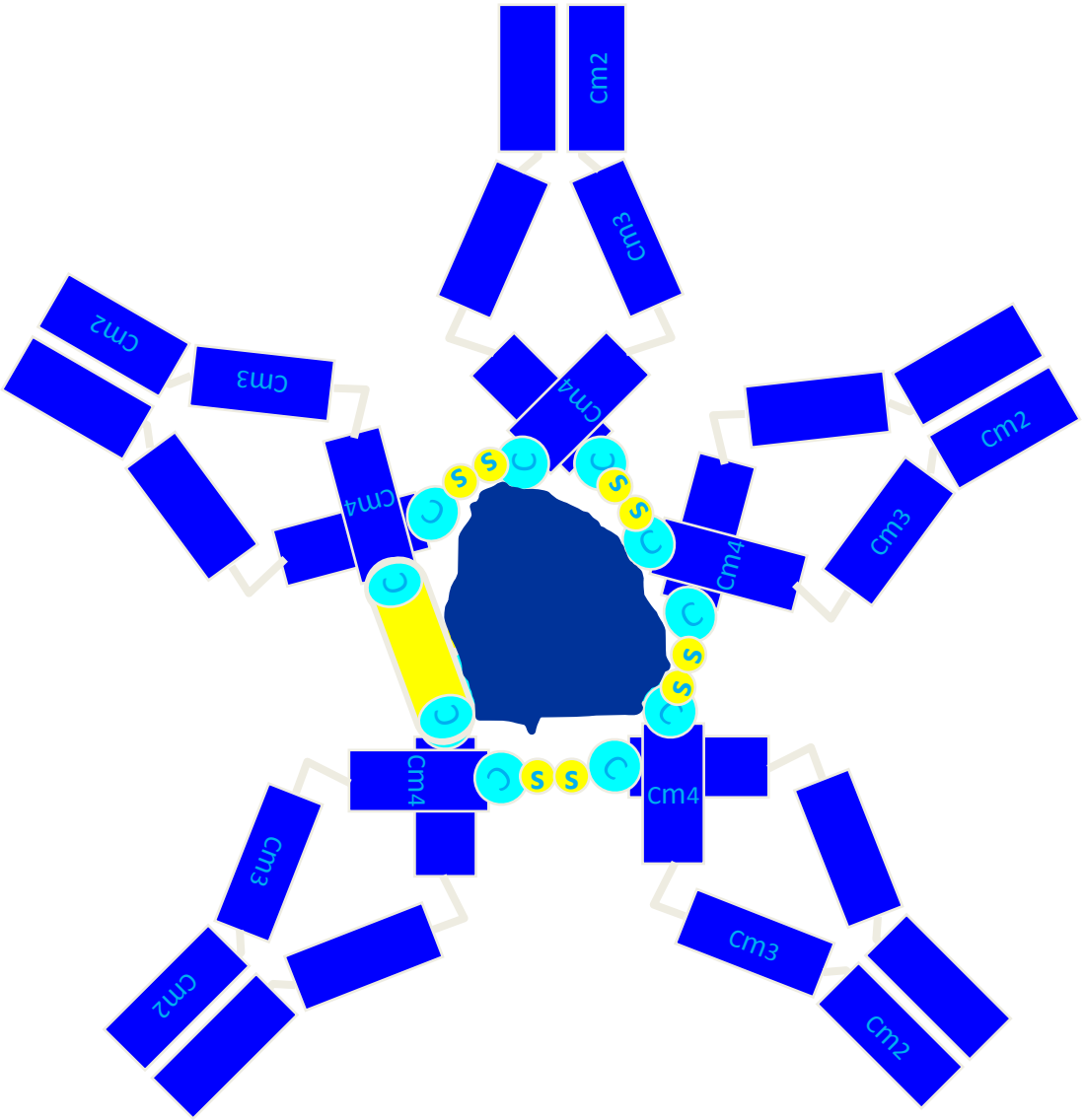
IgM mononérica tiene muy baja afinidad por el antígeno



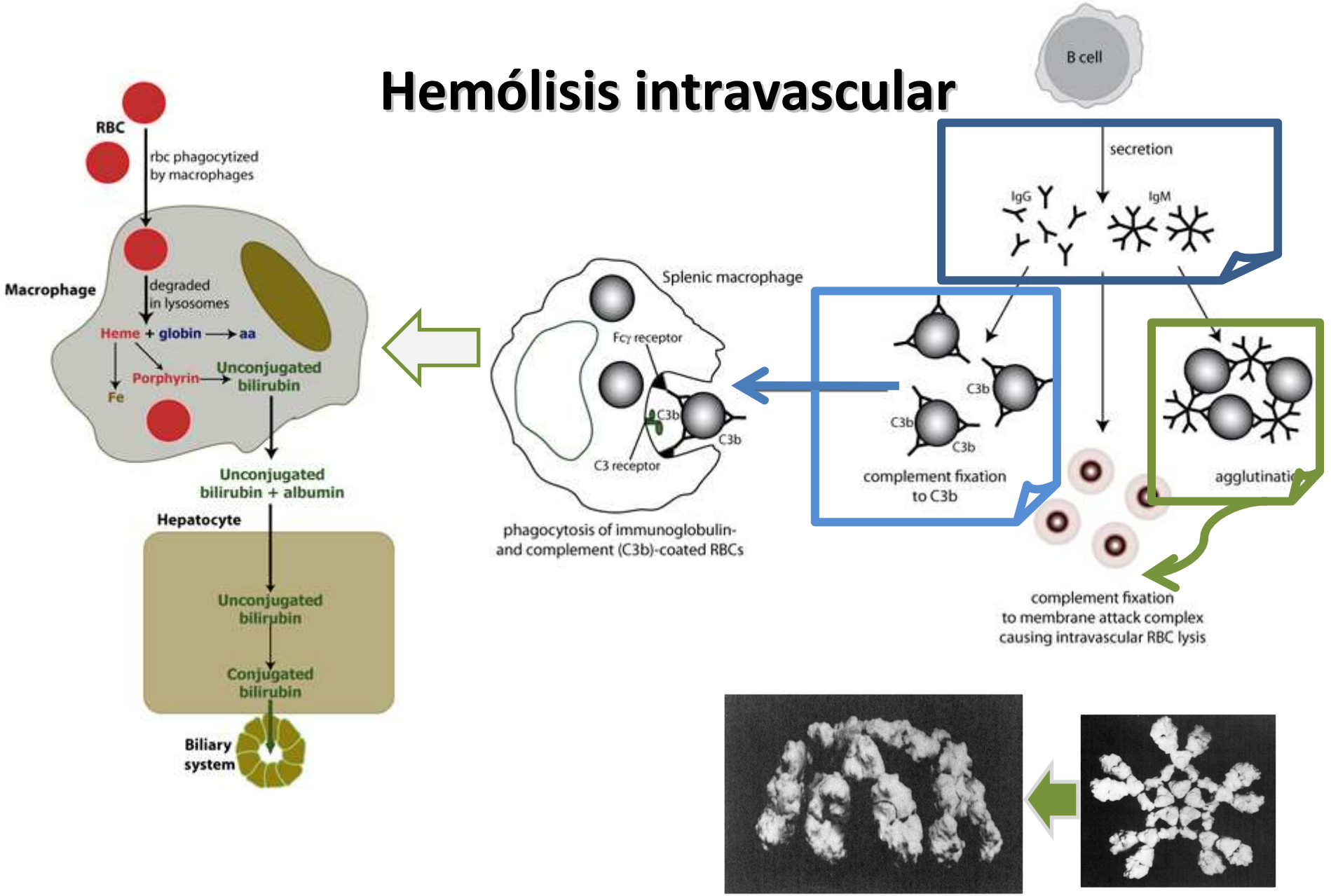
N.B. Only constant heavy chain domains are shown

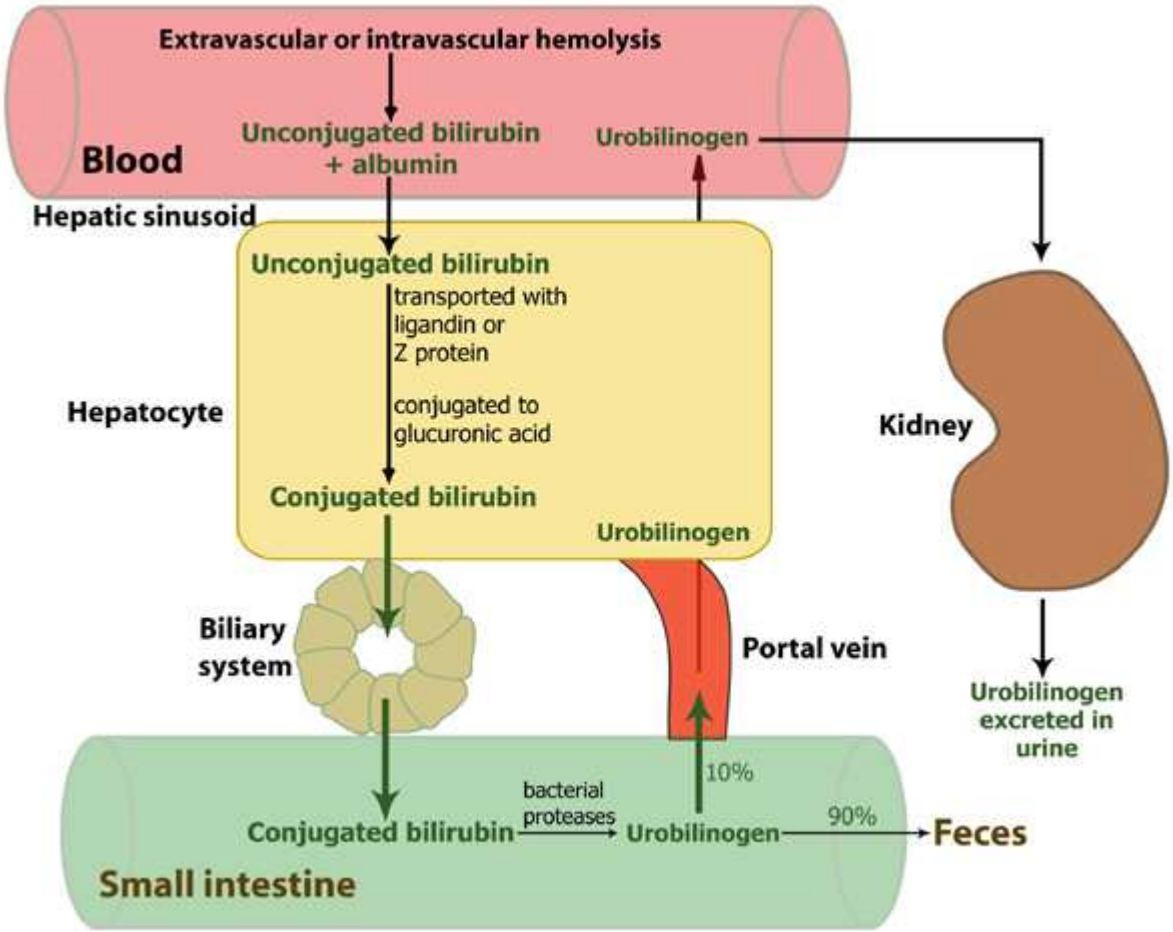
IgM forma pentámeros y hexámeros

Multimerización de IgM



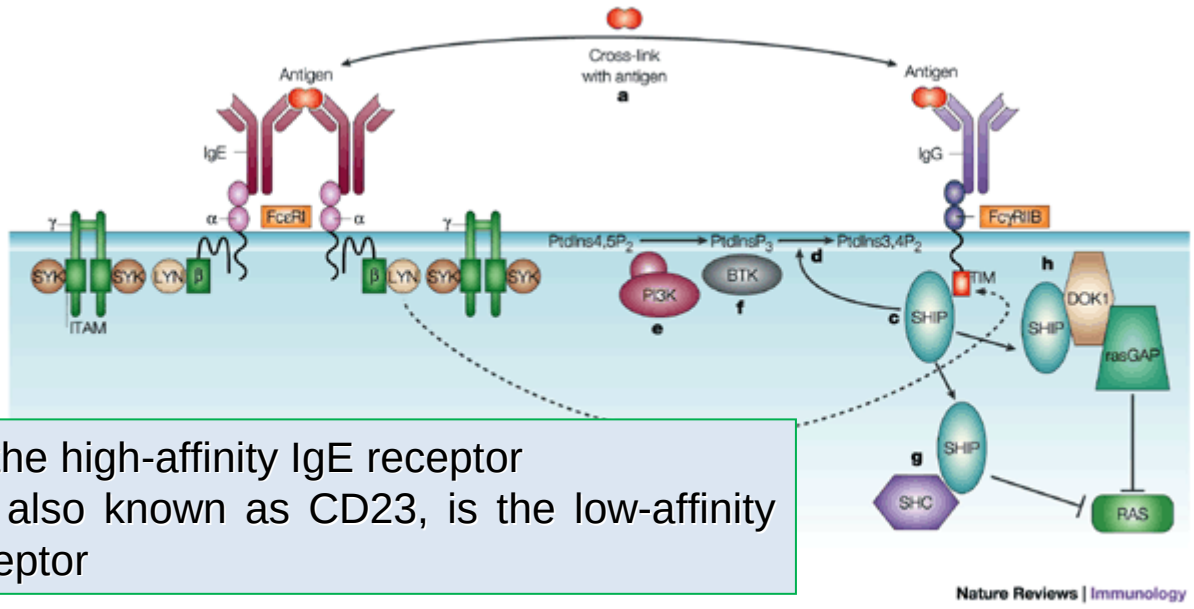
Hemólisis intravascular




Extravascular or intravascular hemolysis
Blood
Unconjugated bilirubin
+ albumin
Urobilinogen
Hepatic sinusoid
Unconjugated bilirubin
transported with
ligandin or
Z protein
Hepatocyte
conjugated to
glucuronic acid
Conjugated bilirubin
Urobilinogen
Kidney
Biliary
system
Portal vein
Urobilinogen
excreted in
urine
10%
bacterial
proteases
Conjugated bilirubin
Urobilinogen
90%
Feces
Small intestine

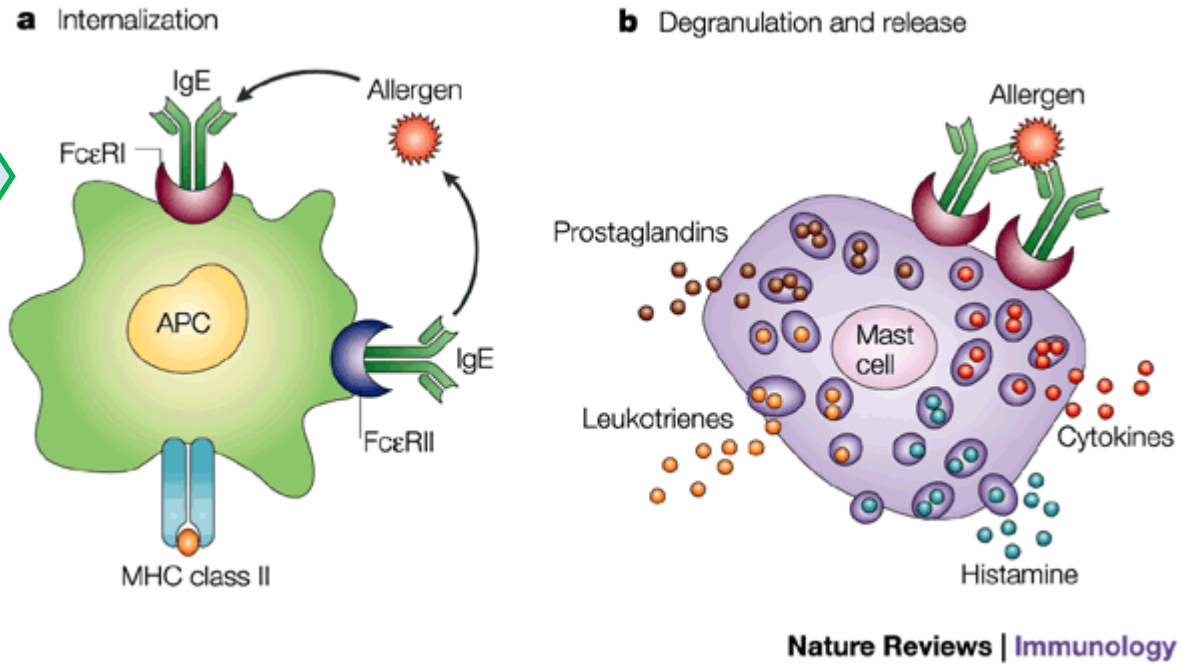
INMUNOGLOBULINA E

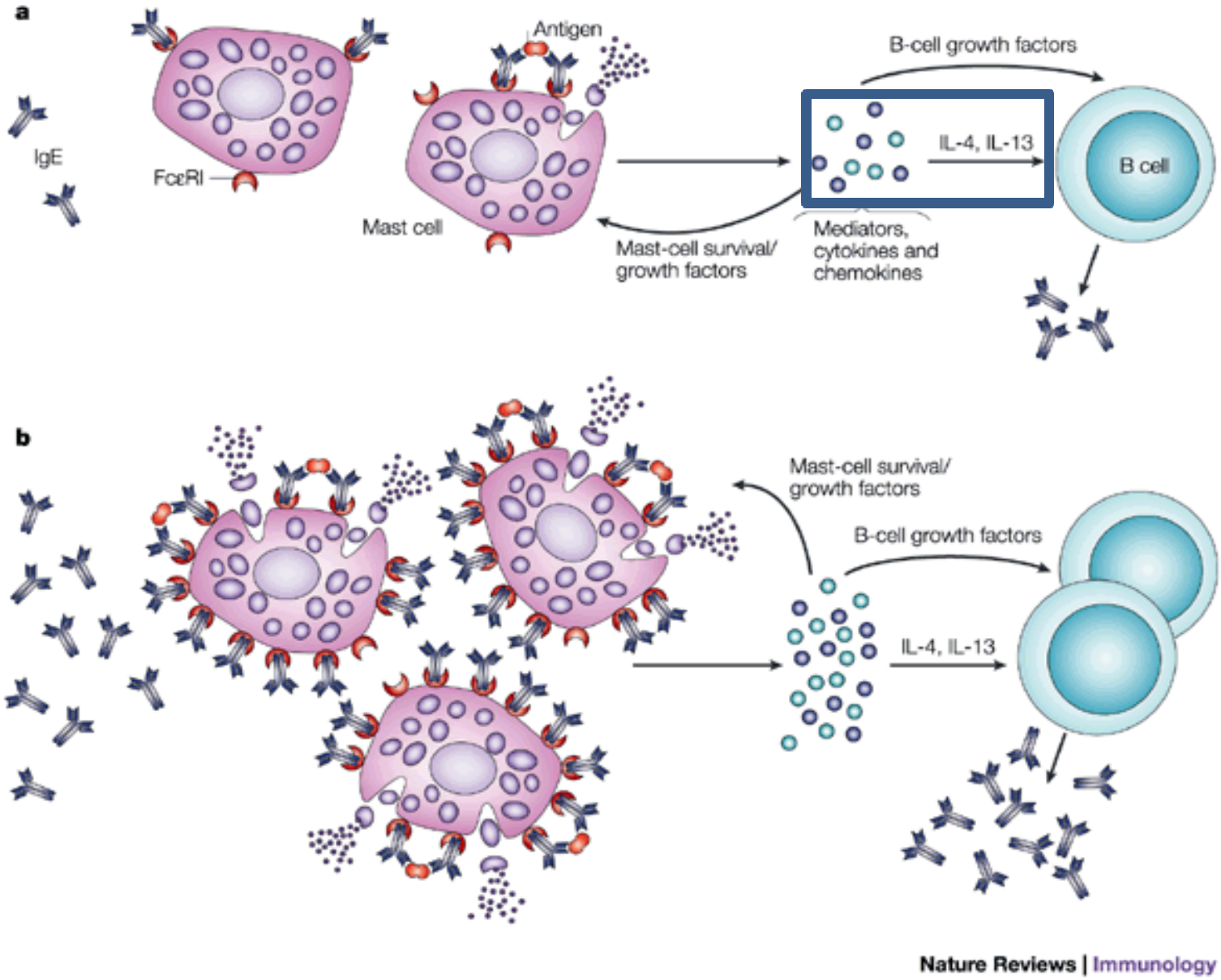
Receptores de IgE



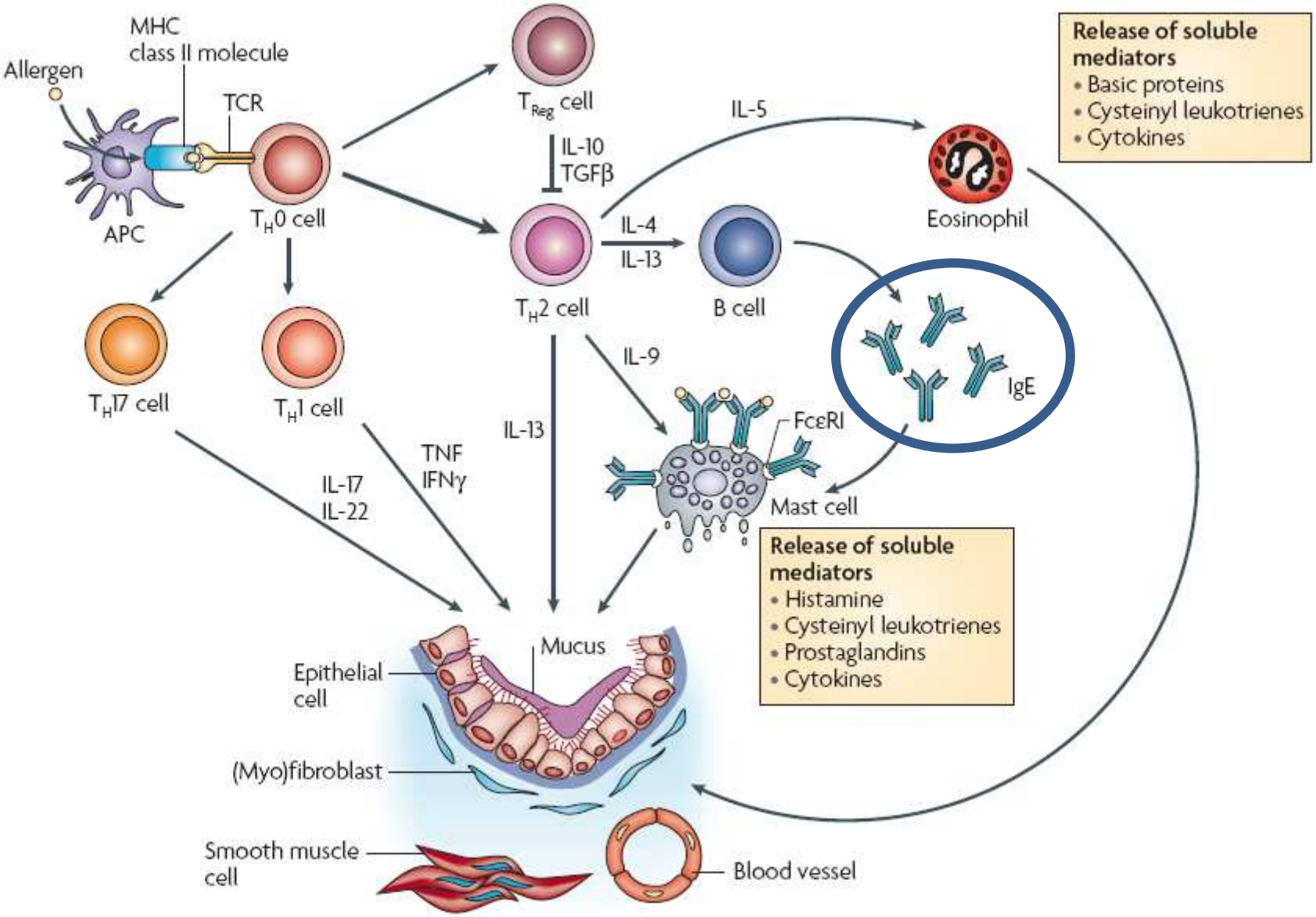
FcεRI, the high-affinity IgE receptor
FcεRII, also known as CD23, is the low-affinity IgE receptor

Activación



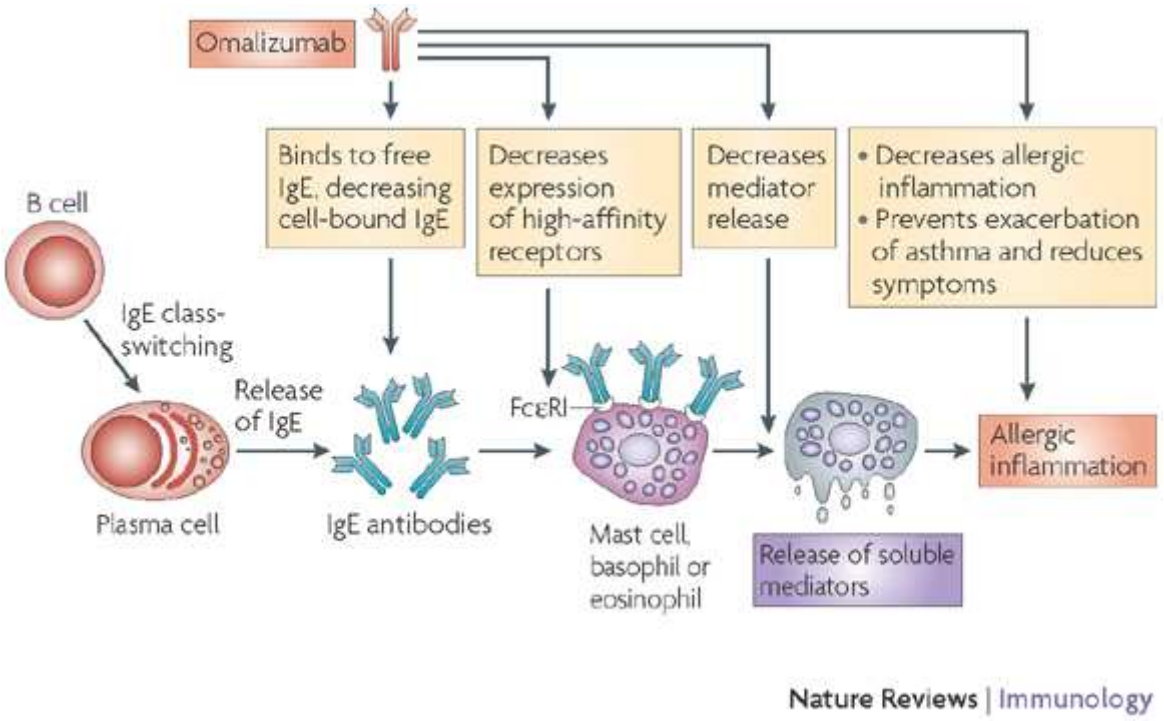


Nature Reviews Immunology 2, 773-786 (October 2002)

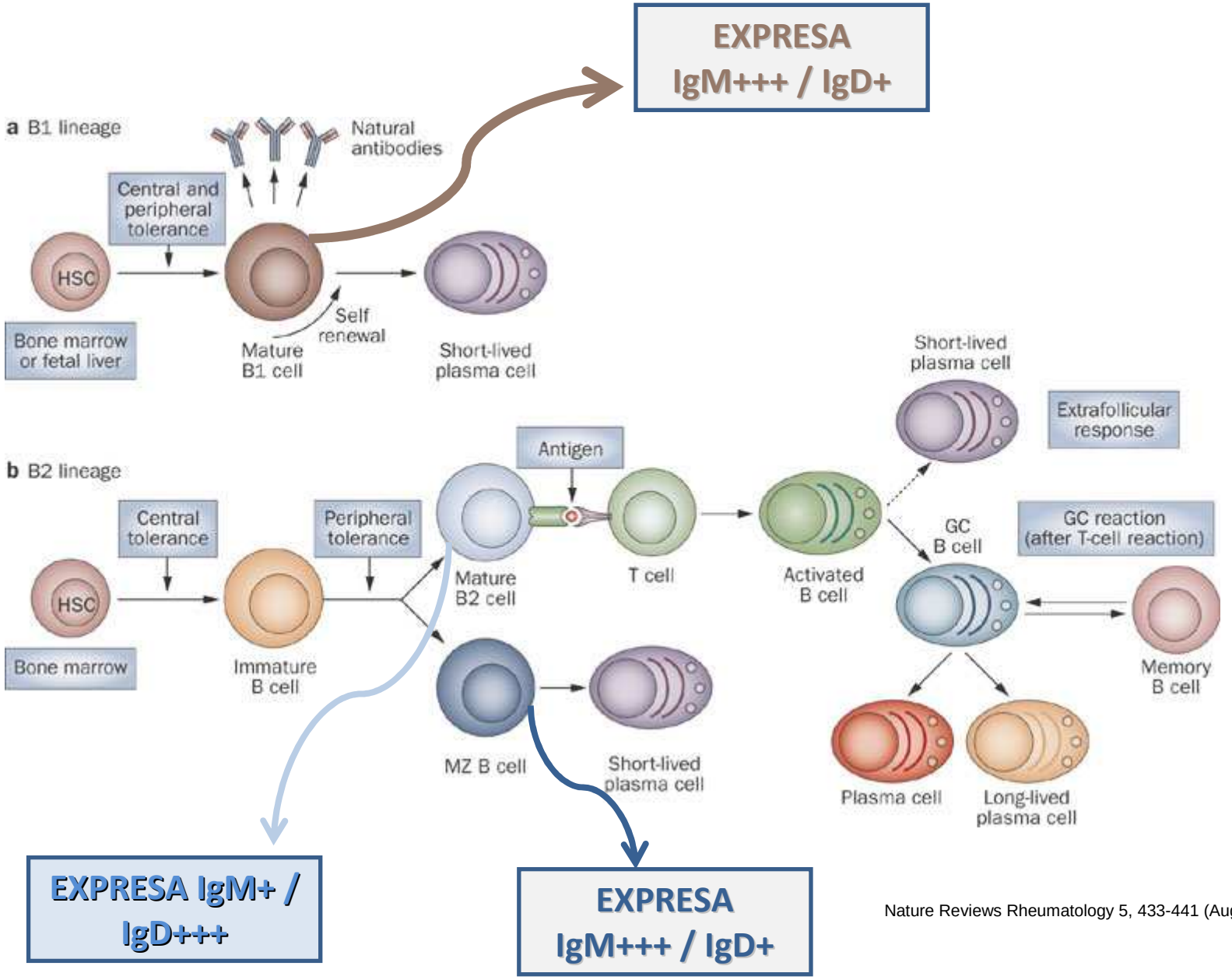


Nature Reviews Immunology 8, 218-230 (March 2008)

Tratamiento ….



INMUNOGLOBULINA D



Nature Reviews Rheumatology 5, 433-441 (August 2009)

Phenotypes of naïve mature B cell subtypes

	Type of B cell		
Surface molecule	**B-1**	**MZ**	**Follicular**
IgM	+++	+++	+
IgD	+/-	+/-	+++
CD45R	+/++	++	+++
CD21	+/-	+++	++
CD23	++or -	-	++
CD5	+	-	-
$\alpha_M\beta_2$ integrin	+ or -	-	-
CD9	+	+	-

Immunoglobulin D Enhances Antimicrobial Immunity by Activating Basophils

posted on 07/21/2009

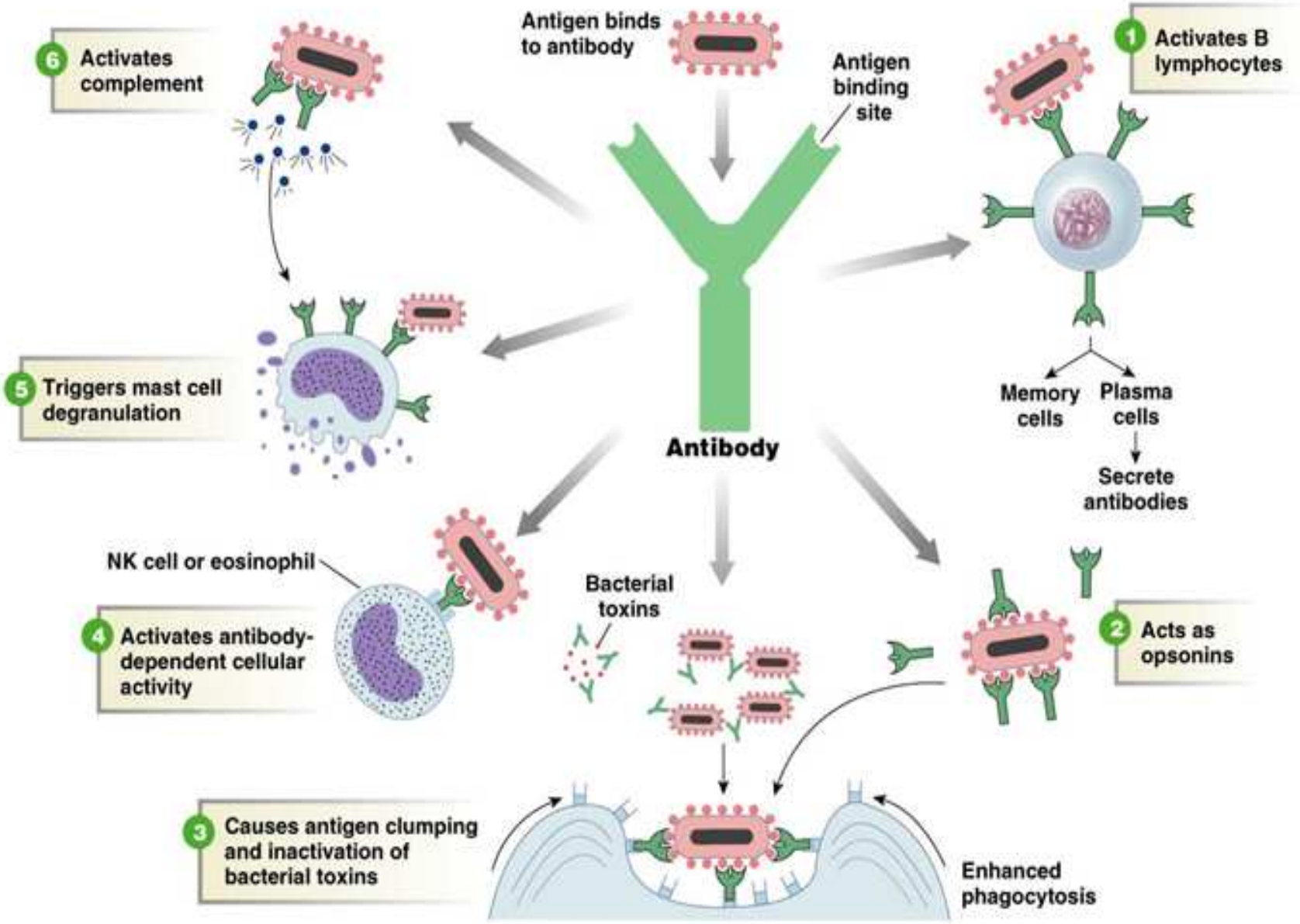
Detailed Description

- This invention discloses (1) a method to attenuate IgE-induced release of histamine by human basophils, and therefore, treat or prevent allergies using IgD itself or agents targeting the putative IgD receptor; (2) a method to generate antimicrobial agents by activating basophils with IgD and to screen novel antimicrobial agents from IgD-activated basophils; and (3) a method to produce IgD in vitro.

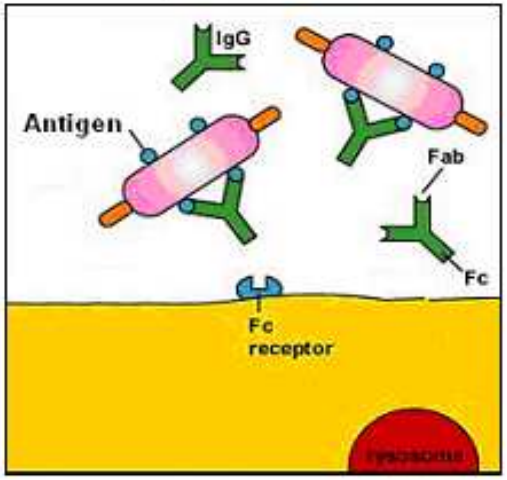
Technical Merits

- Humans produce five classes of immunoglobulins (Igs) known as IgM, IgD, IgG, IgA and IgE. While the functions of IgM, IgG, IgA and IgE are relatively well understood, the function of IgD remains unknown. This is particularly true for soluble IgD, which is secreted by a poorly characterized subset of human B cells. The inventors discovered new functions for immunoglobulin D (IgD). **They found that IgD cross-linking profoundly attenuates IgE-induced release of histamine by human basophils, indicating that IgD activates a basophil receptor with IgE-inhibitory properties. They also found that IgD shows strong reactivity for commensal and pathogenic respiratory bacteria and interacts with circulating basophils through a calcium-fluxing receptor different from canonical Fc receptors for IgG, IgA and IgE isotypes. In the presence of specific cross-linking agents such as a bead-conjugated anti-IgD monoclonal antibody, basophils up-regulate the production and release of antimicrobial, opsonizing, inflammatory and antibody-inducing factors, including cathelicidin, interleukin-1 (IL-2), IL-4, IL-13 and BAFF.**

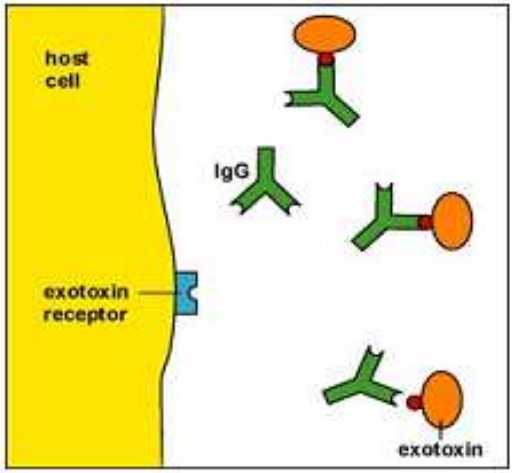
LOS ANTICUERPOS EN ACCIÓN



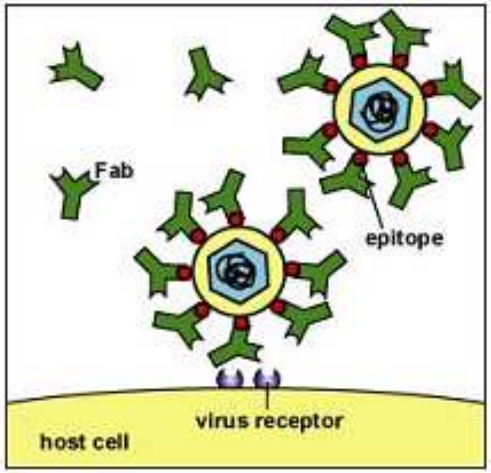
Oponization



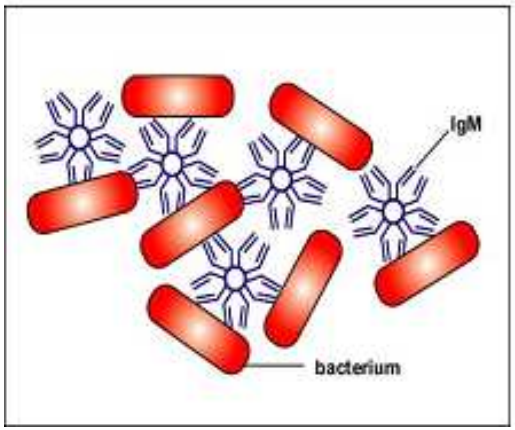
Endotoxin neutralization



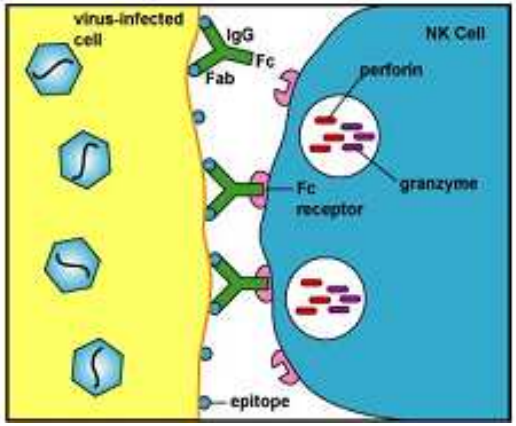
Viral neutralization



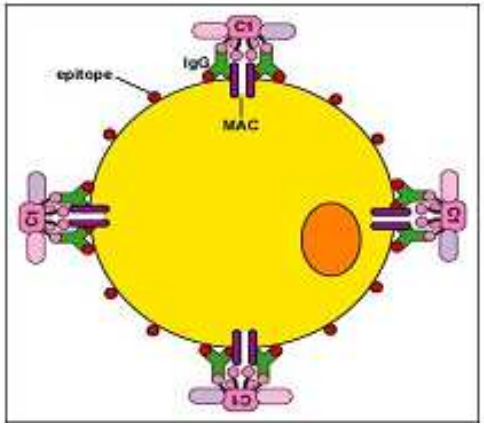
Agglutination



Cytotoxicity



Complement fixation



Affinity and avidity

Fab	IgG	IgG	IgM
			

antibody	Fab	IgG	IgG	IgM
effective antibody valence	1	1	2	up to 10
antigen valence	1	1	n	n
equilibrium constant (L/mol)	10^4	10^4	10^7	10^{11}
advantage of multivalence	–	–	10^3-fold	10^7-fold
definition of binding	affinity	affinity	avidity	avidity
	intrinsic affinity		functional affinity	

Physicochemical properties of human immunoglobulin classes

property	immunoglobulin type									
	IgG1	IgG2	IgG3	IgG4	IgM	IgA1	IgA2	sIgA	IgD	IgE
heavy chain	γ_1	γ_2	γ_3	γ_4	μ	α_1	α_2	α_1/α_2	δ	ϵ
mean serum conc. (mg/ml)	9	3	1	0.5	1.5	3.0	0.5	0.05	0.03	0.00005
sedimentation constant	7s	7s	7s	7s	19s	7s	7s	11s	7s	8s
mol. wt (kDa)	146	146	170	146	970	160	160	385	184	188
half-life (days)	21	20	7	21	10	6	6	?	3	2
% intravascular distribution	45	45	45	45	80	42	42	trace	75	50
carbohydrate (%)	2–3	2–3	2–3	2–3	12	7–11	7–11	7–11	9–14	12

NEUTRALIZAN TOXINAS

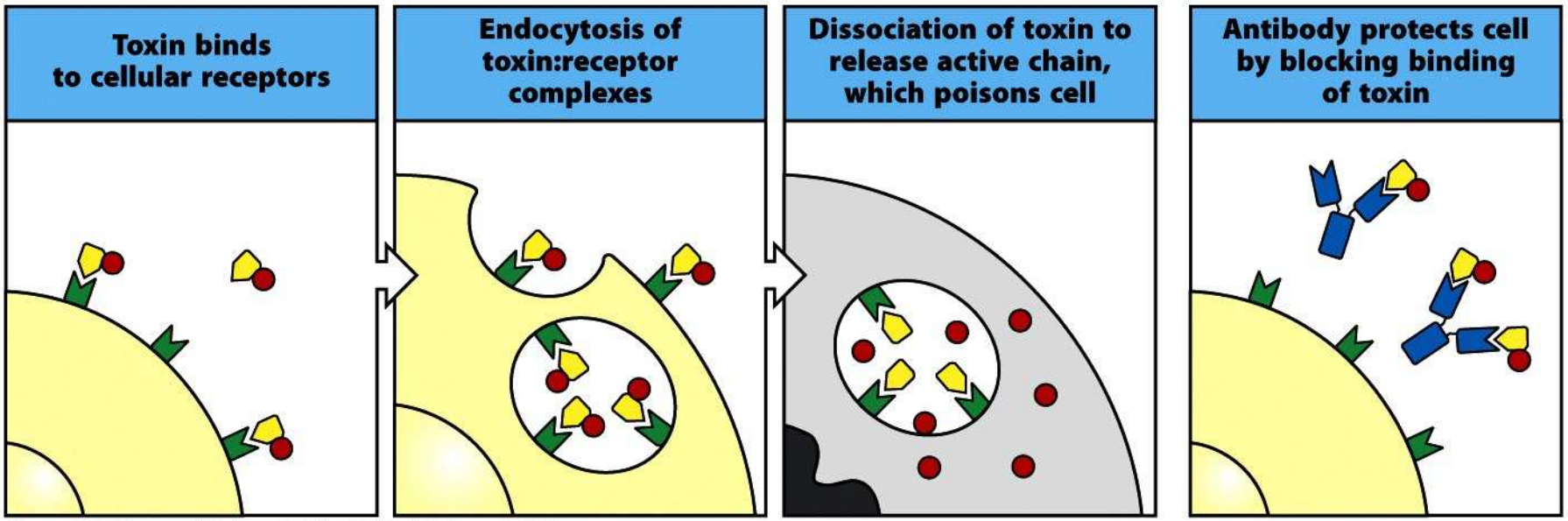


Figure 9-24 Immunobiology, 7ed. (© Garland Science 2008)

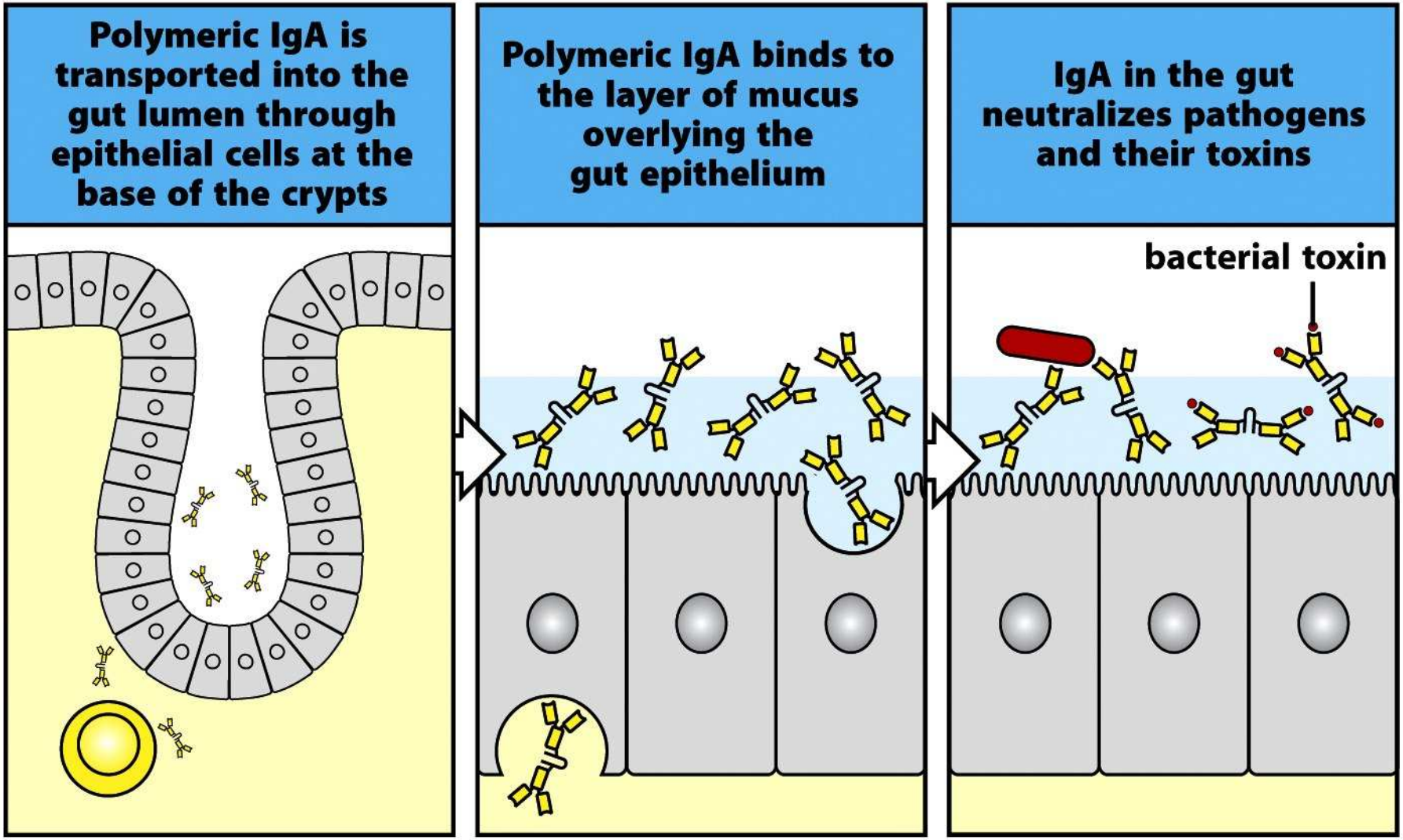


Figure 9-20 Immunobiology, 7ed. (© Garland Science 2008)

NEUTRALIZAN PARTÍCULAS VIRALES LIBRES

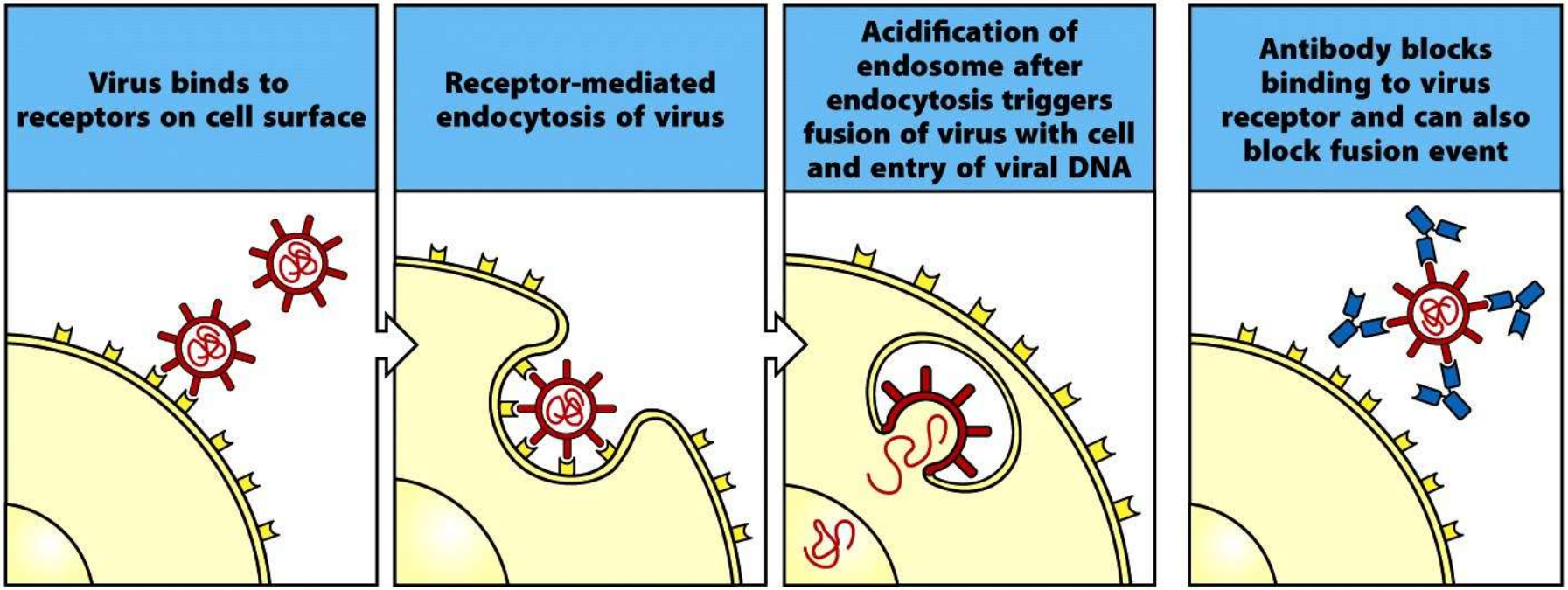


Figure 9-25 Immunobiology, 7ed. (© Garland Science 2008)

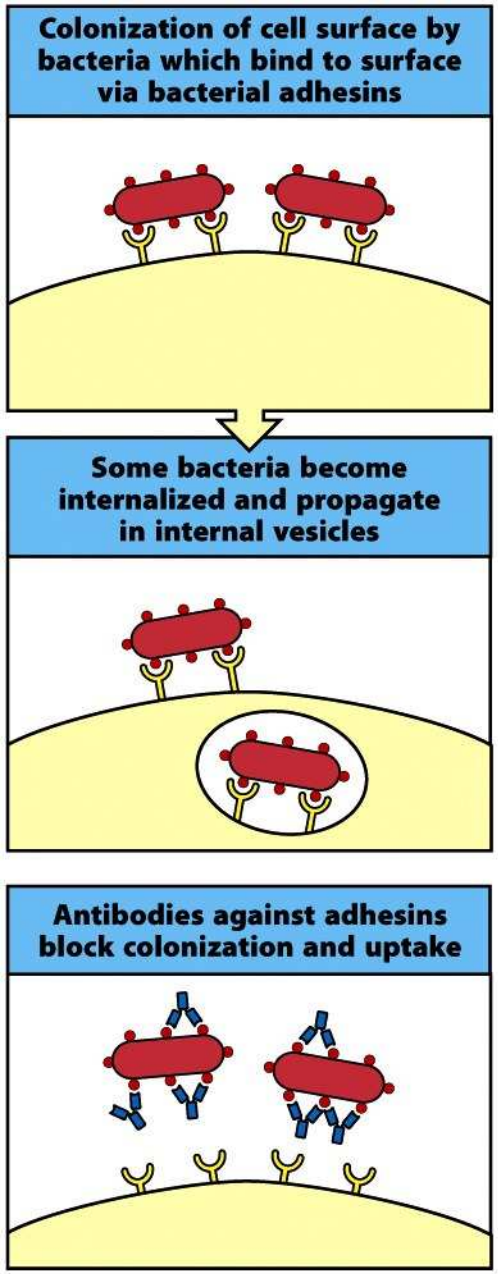


Figure 9-26 Immunobiology, 7ed. (© Garland Science 2008)

BLOQUEAN LA COLONIZACIÓN DE BACTERIAS

¿Qué pasa con los INMUNOCOMPLEJOS CIRCULANTES????

INDUCEN ACTIVACIÓN DEL COMLEMENTO Y ENDOCITOSIS

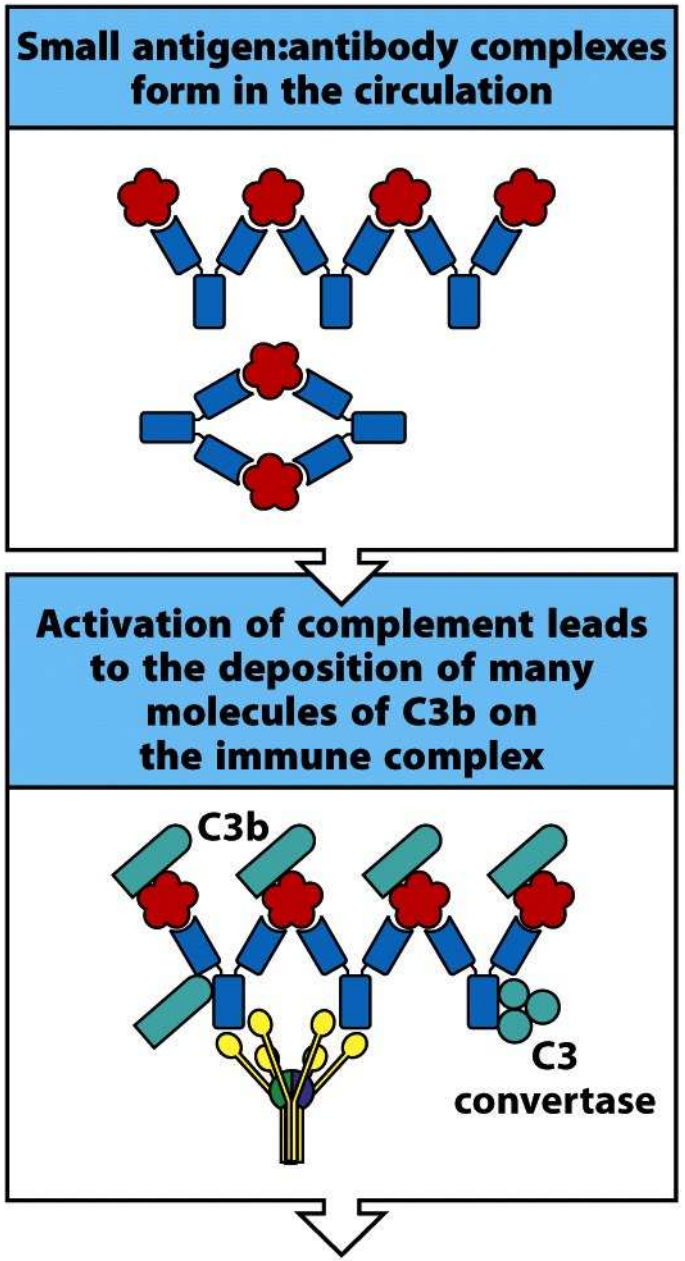


Figure 9-29 part 1 of 3 Immunobiology, 7ed. (© Garland Science 2008)

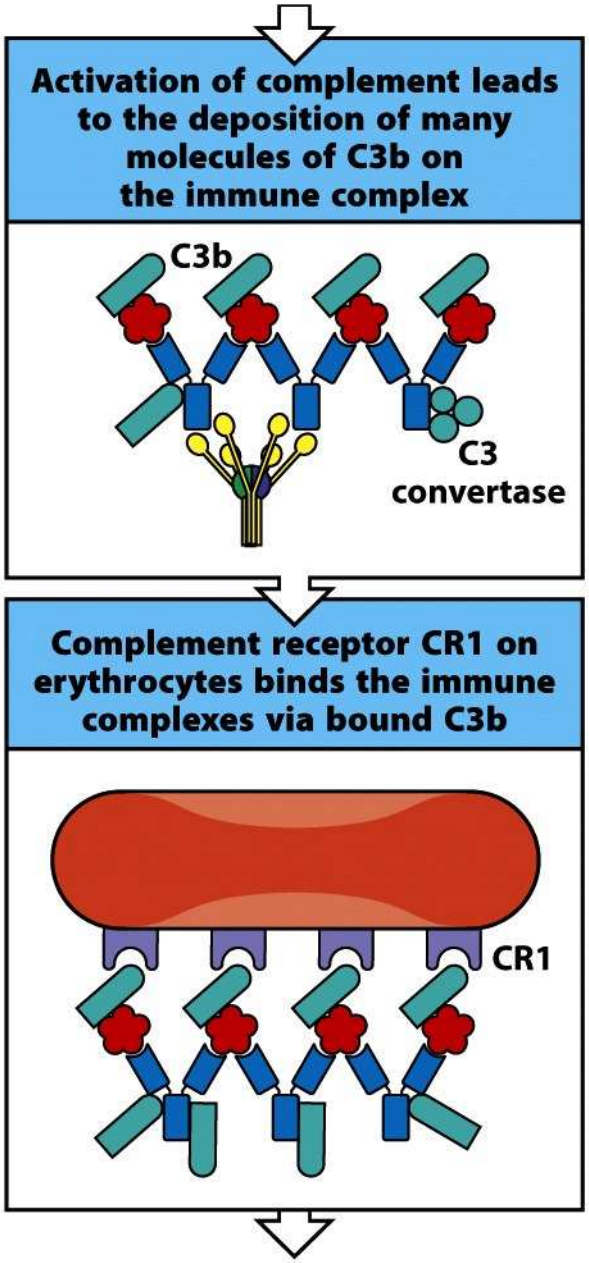


Figure 9-29 part 2 of 3 Immunobiology, 7ed. (© Garland Science 2008)

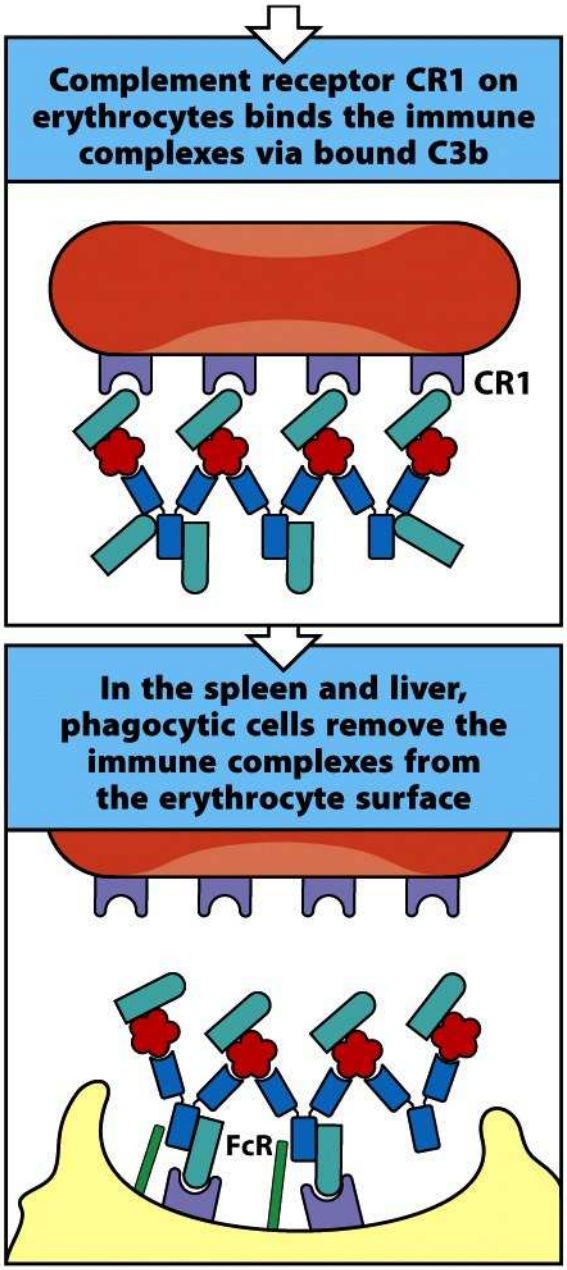


Figure 9-29 part 3 of 3 Immunobiology, 7ed. (© Garland Science 2008)

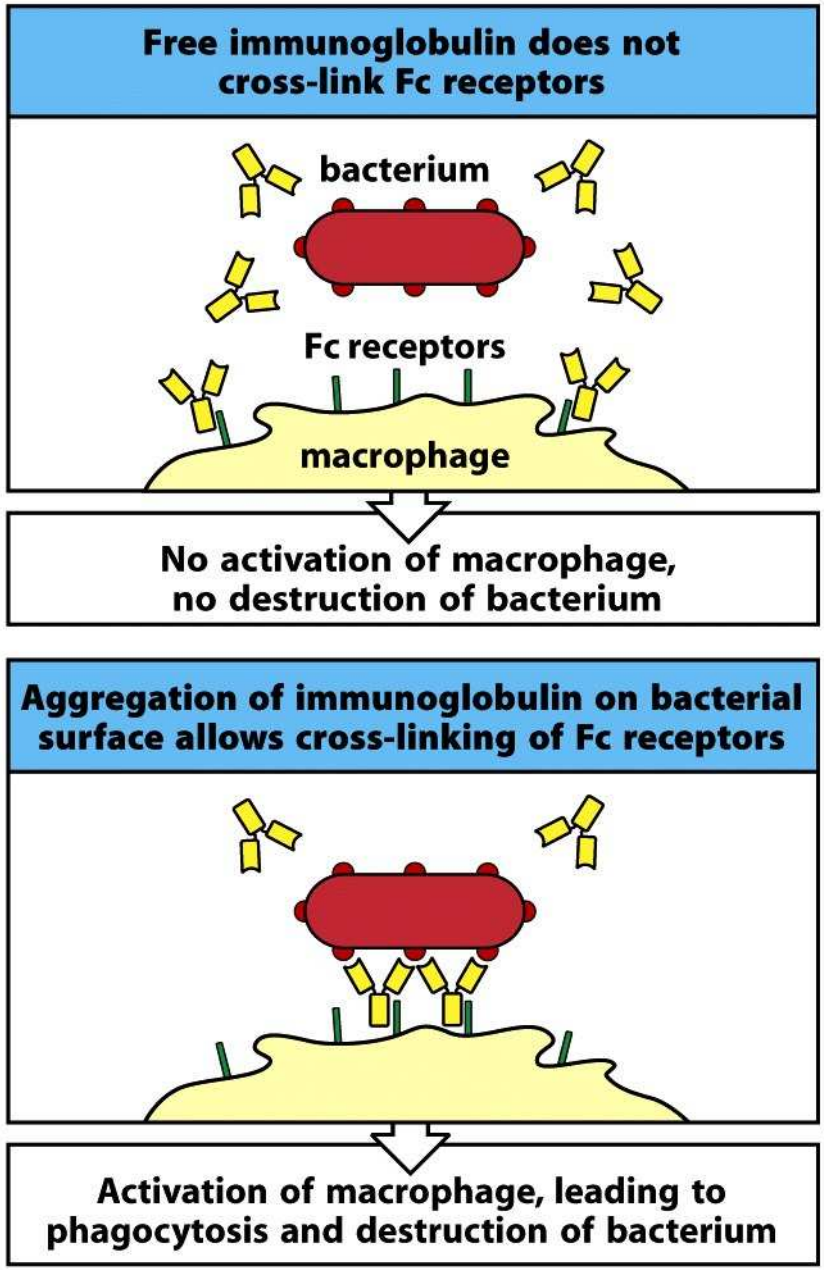


Figure 9-31 Immunobiology, 7ed. (© Garland Science 2008)

INDUCEN ADCC

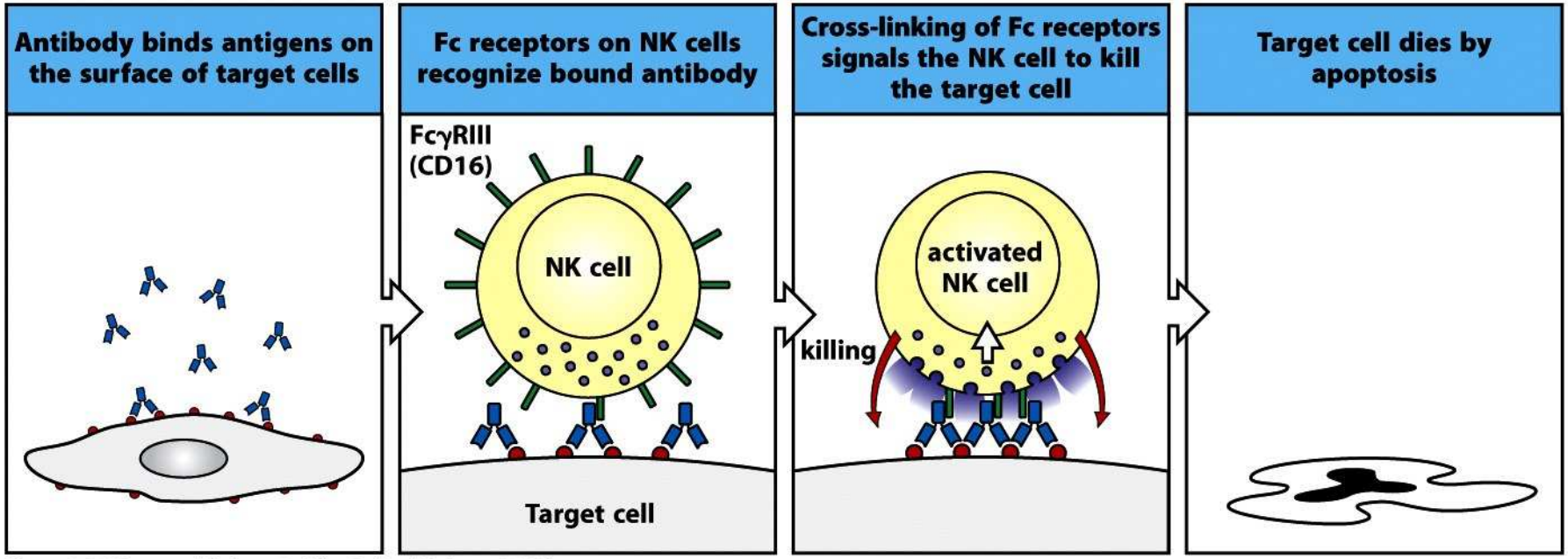
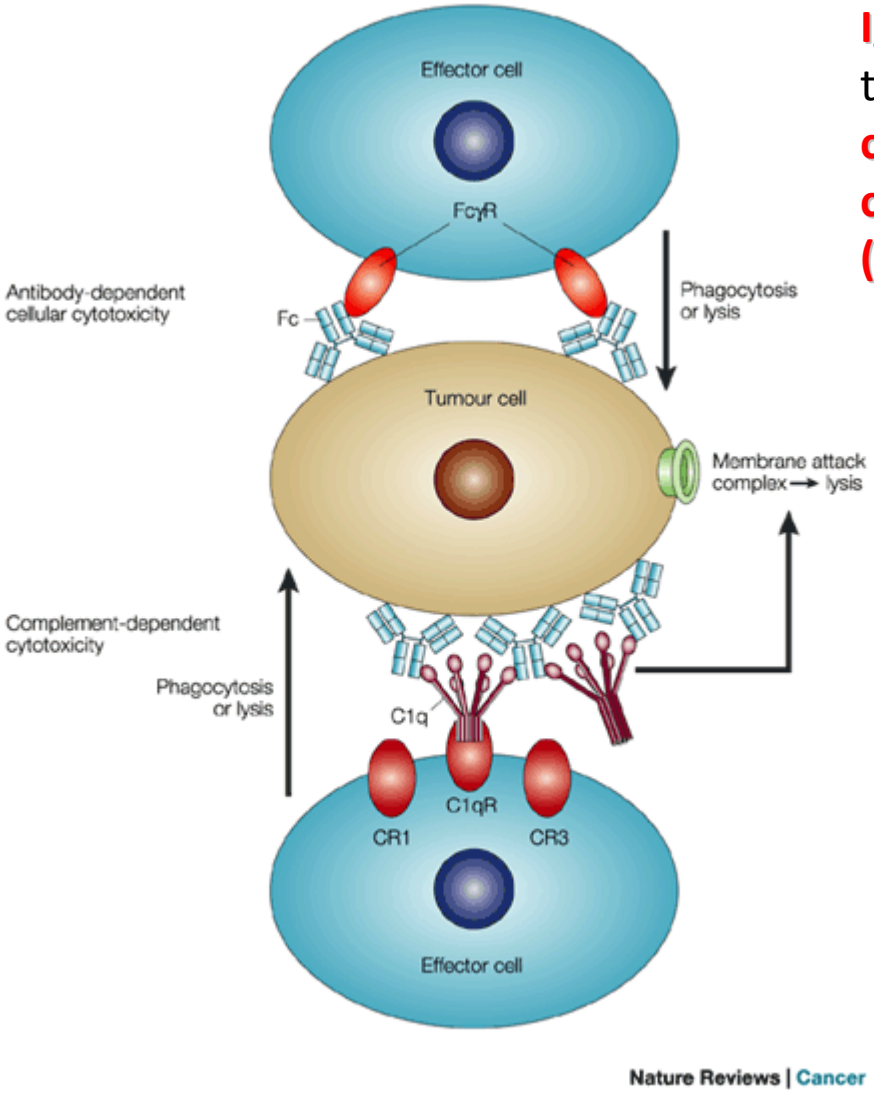


Figure 9-34 Immunobiology, 7ed. (© Garland Science 2008)



Human antibodies, particularly **IgG_1 and IgG_3,** can potentially direct the killing of tumour cells by **antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC)**

Alternatively, tumour-cell-bound C1q can bind to complement receptors, such as C1qR, CR1 (CD35) and CR3 (CD11b/CD18), on effector cells, such as neutrophils, macrophages and natural killer cells. This can trigger cell-mediated tumour-cell lysis or phagocytosis, depending on the type of effector cell.

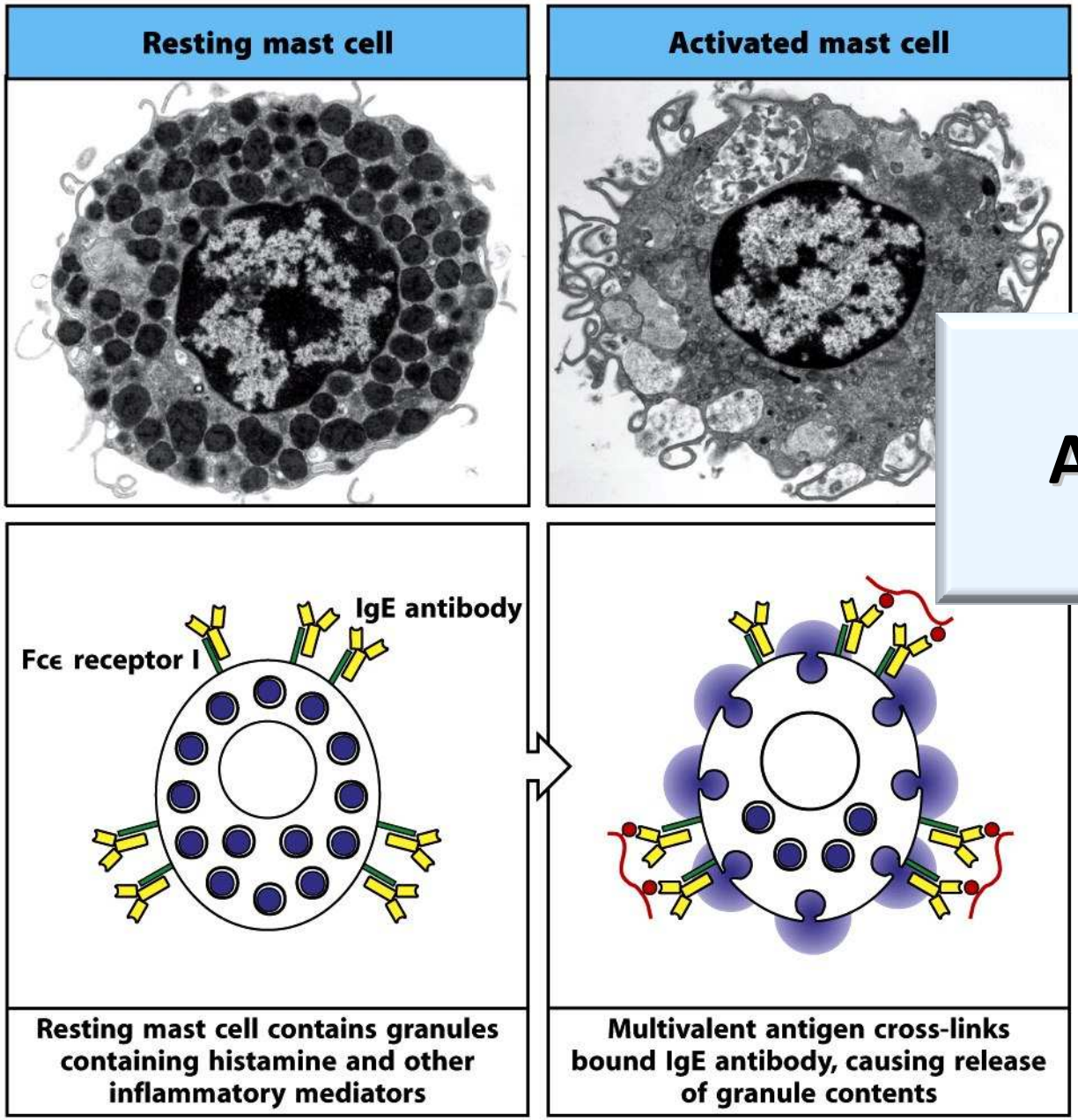
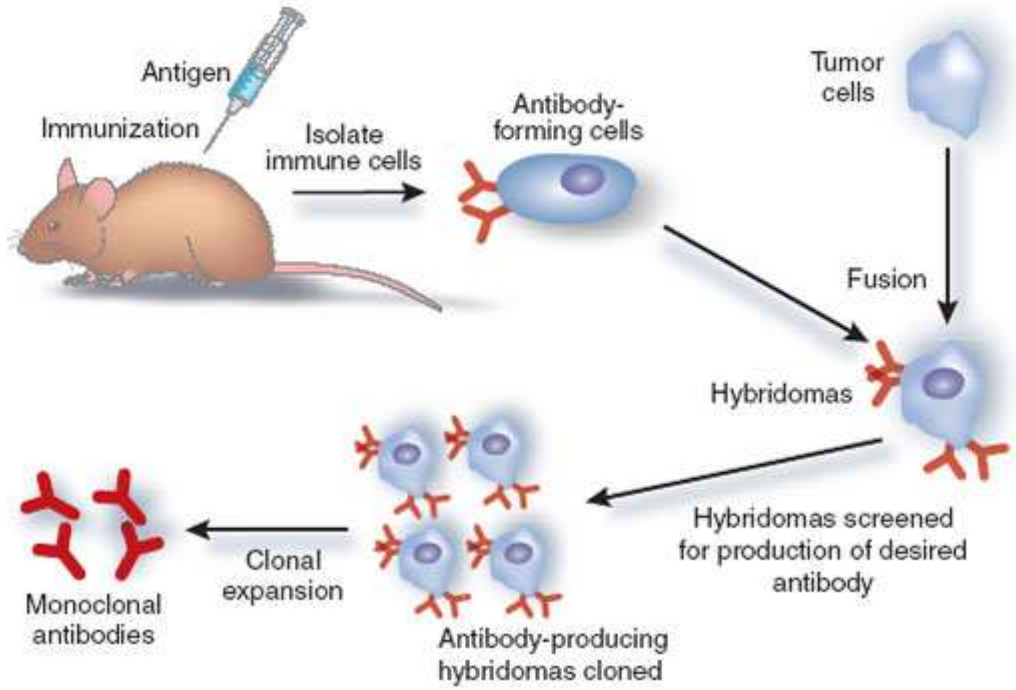


Figure 9-35 Immunobiology, 7ed. (© Garland Science 2008)

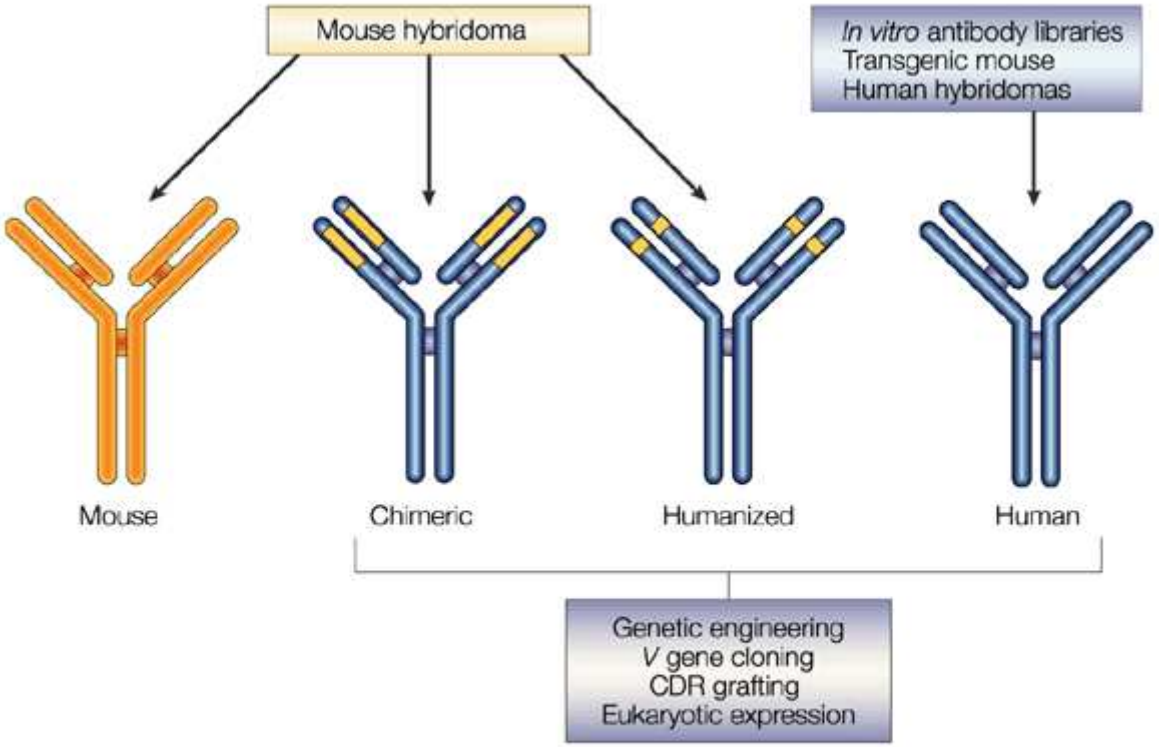
INDUCEN ACTIVACIÓN CELULAR

ANTICUERPOS EN TERAPÉUTICA

Anticuerpos monoclonales

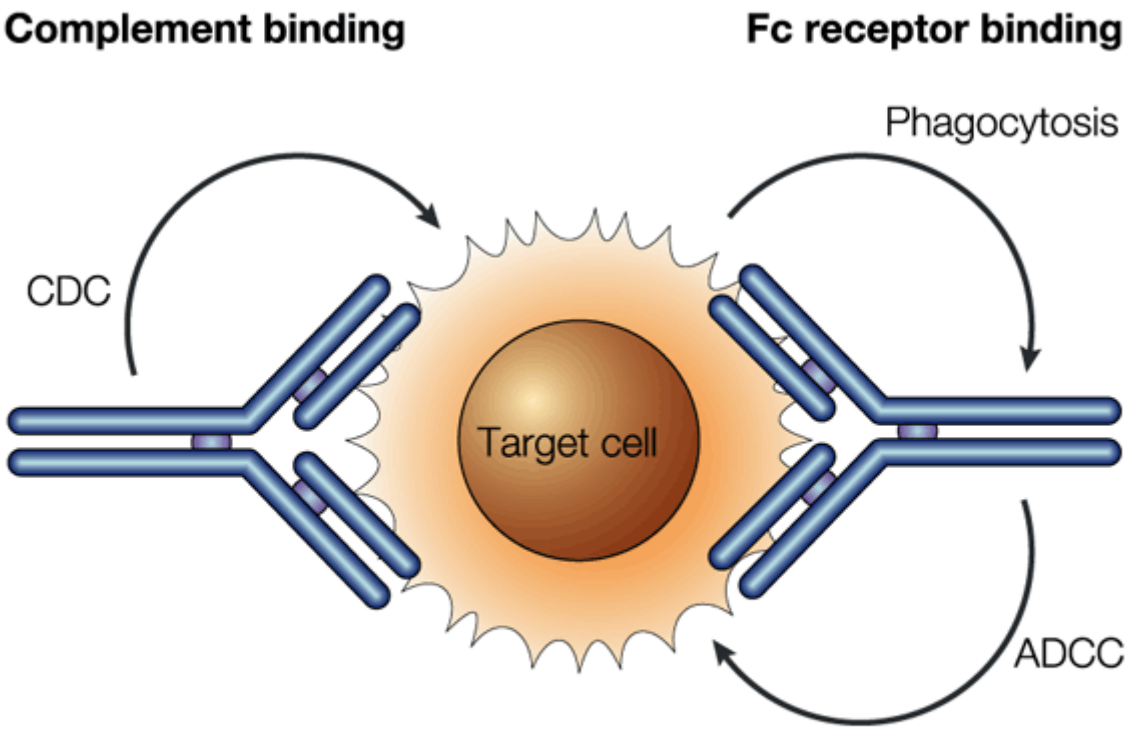


Ingeniería de anticuerpos

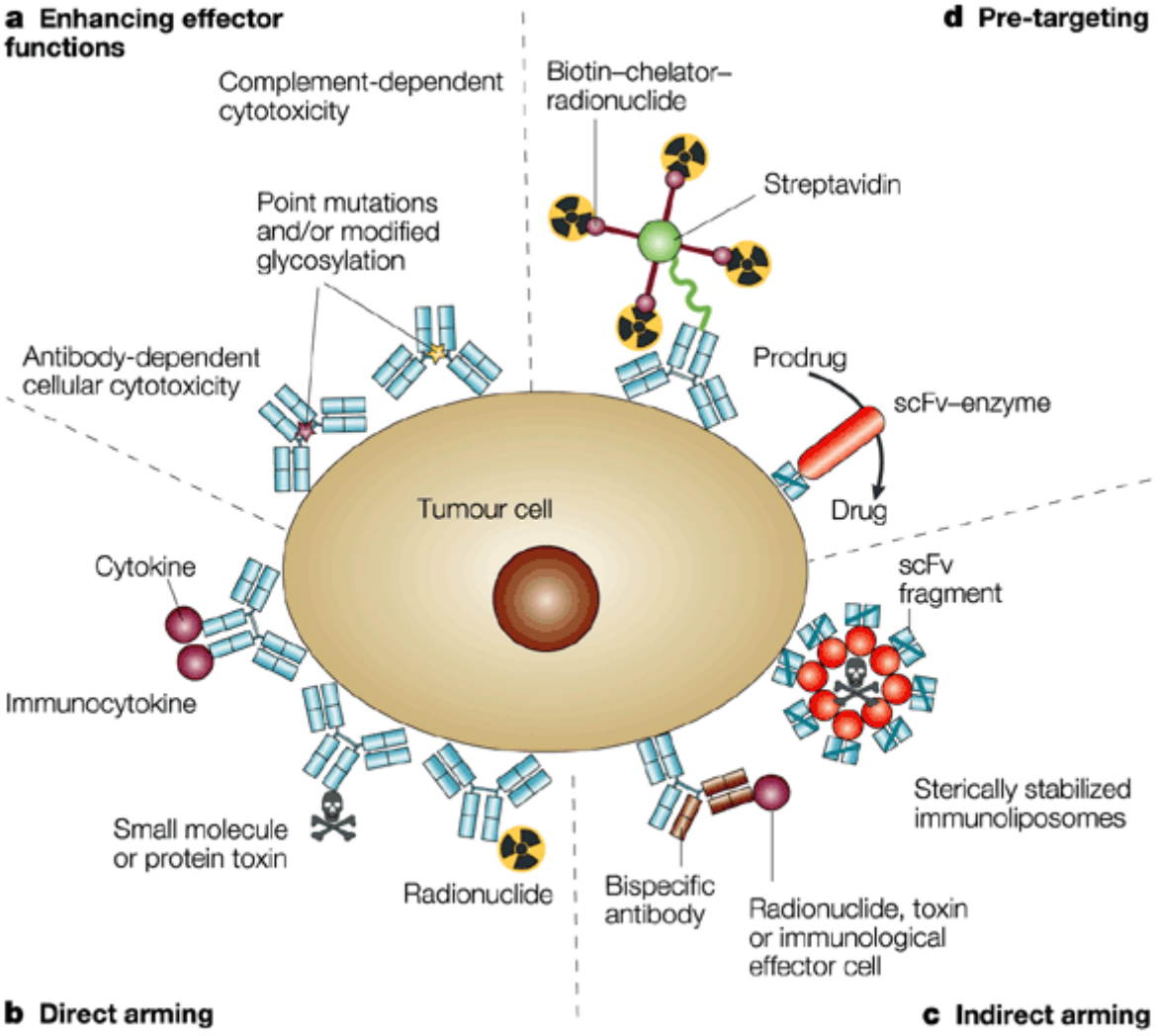


Nature Reviews | Drug Discovery

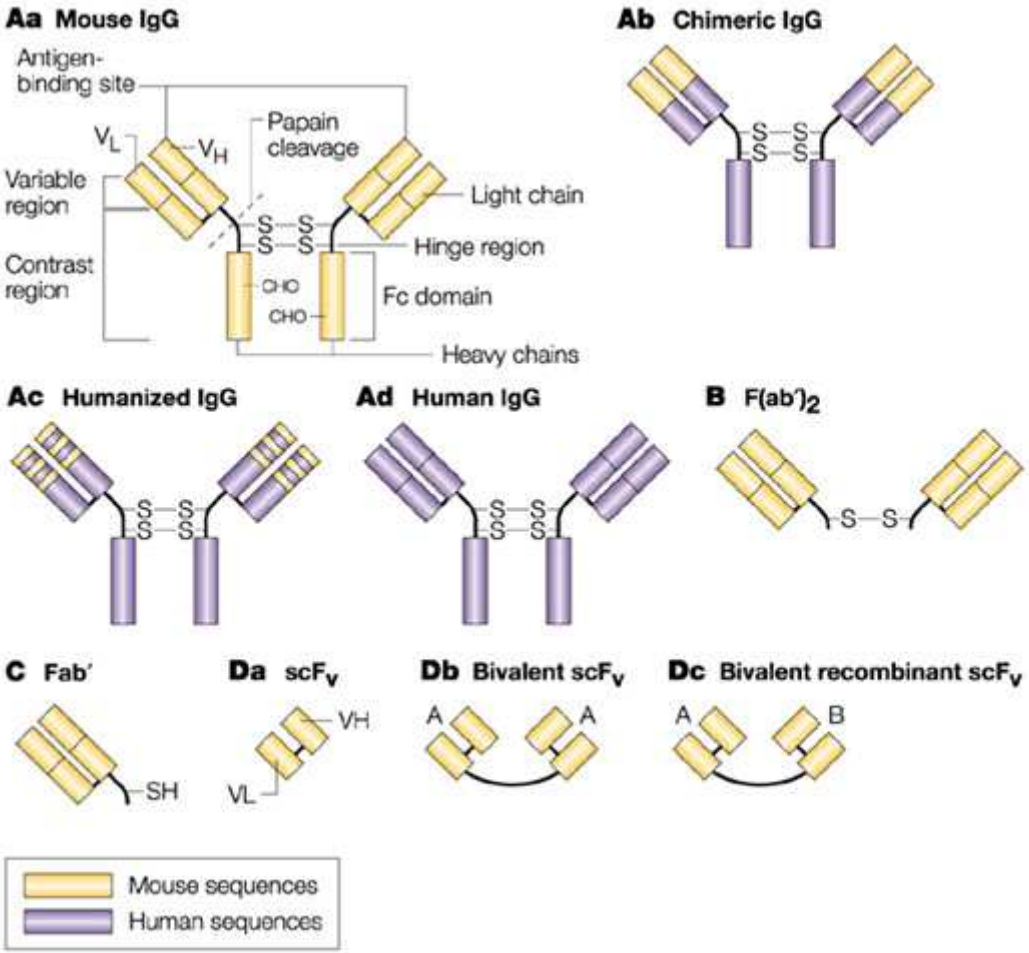
Anticuerpos terapeúticos



Nature Reviews Drug Discovery 2, 52-62 (January 2003) Nature Reviews | Drug Discovery


a Enhancing effector functions
Complement-dependent cytotoxicity
Point mutations and/or modified glycosylation
Antibody-dependent cellular cytotoxicity
d Pre-targeting
Biotin–chelator–radionuclide
Streptavidin
Prodrug
scFv–enzyme
Drug
Tumour cell
Cytokine
Immunocytokine
scFv fragment
Sterically stabilized immunoliposomes
Small molecule or protein toxin
Radionuclide
Bispecific antibody
Radionuclide, toxin or immunological effector cell
b Direct arming
c Indirect arming

Anticuerpos y fragmentos de anticuerpos

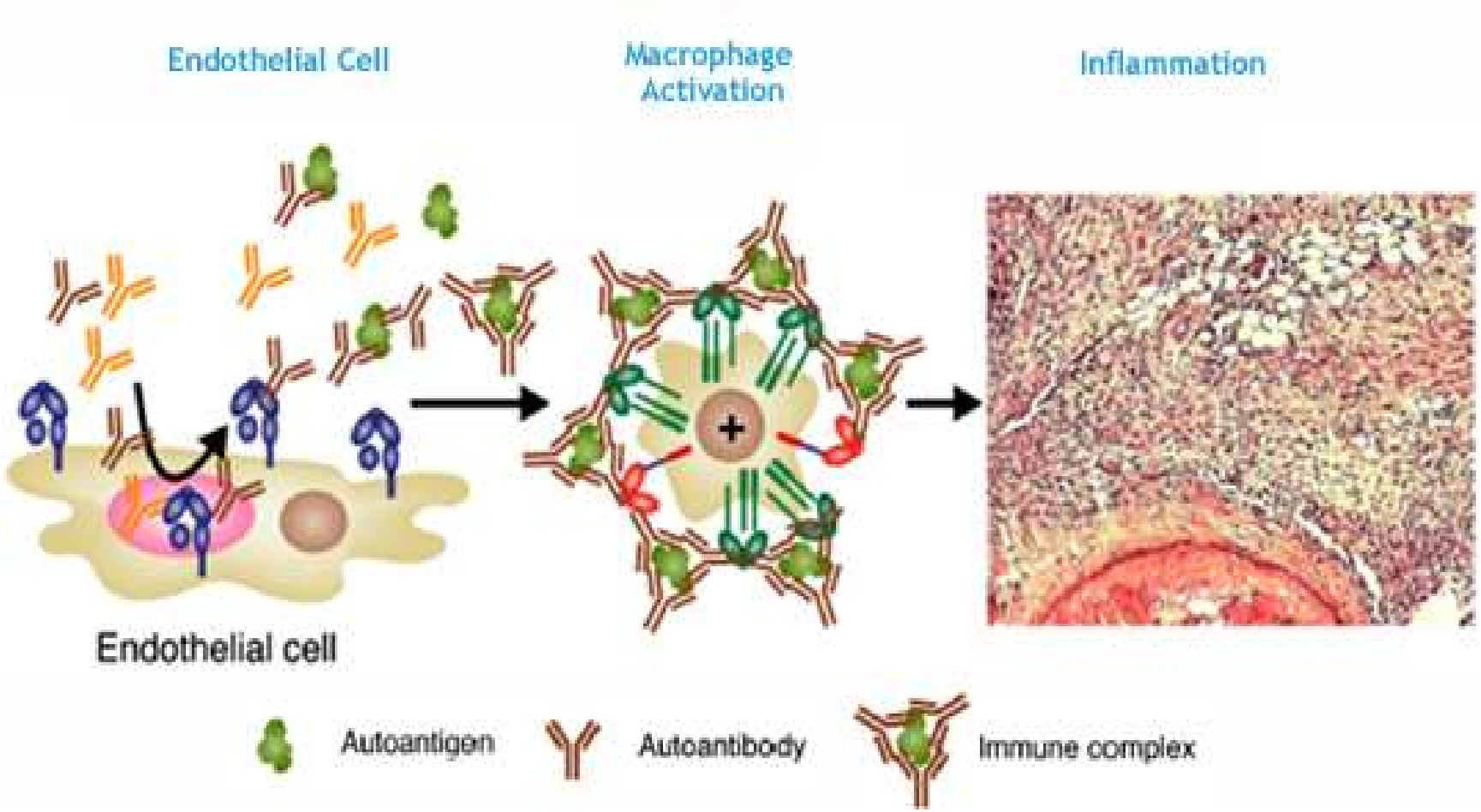


Nature Reviews Cancer 2, 750-763 (October 2002)

Nature Reviews | Cancer

Si, por ejemplo para obtener inmunoglobulinas más seguras y efectivas para el tratamiento de enfermedades autoinmunes….

¿PODEMOS MODIFICAR A LA INMUNOGLOBULINA?????



During an inflammatory response immune complexes consisting of auto-antibodies (brown) and self antigens (green) activate innate immune effector cells (e.g., macrophages) by cross-linking cell surface FcRs, which can lead to the destruction of self-tissues.

Receptores de INMUNOGLOBULINAS

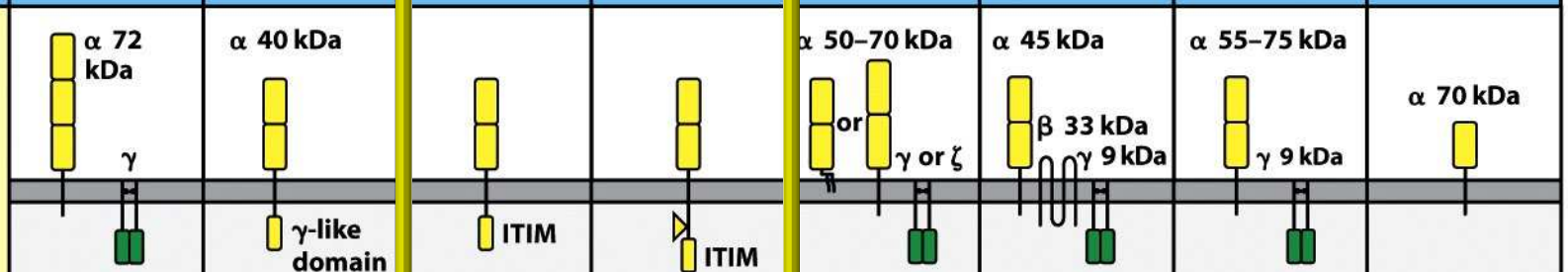
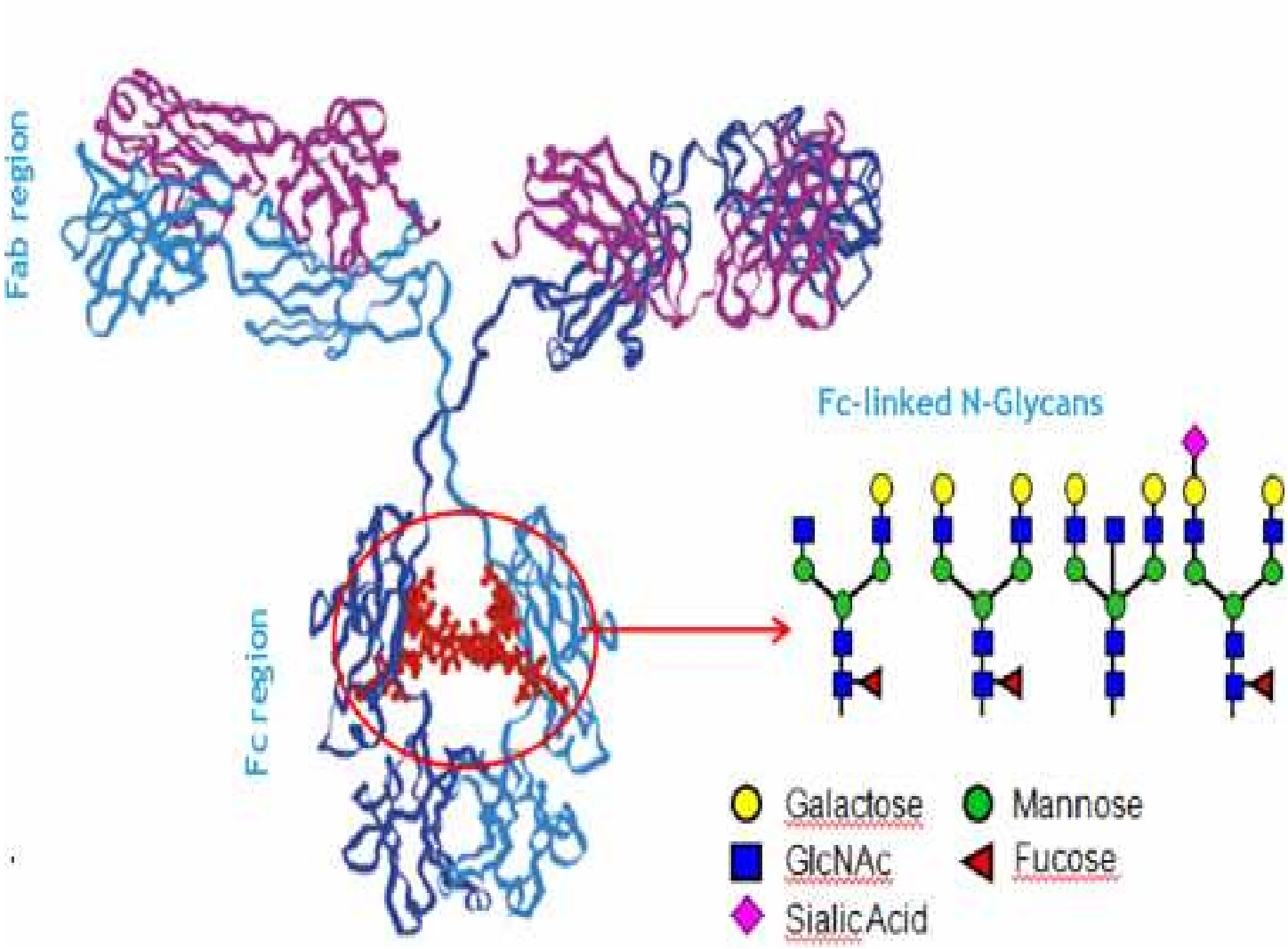
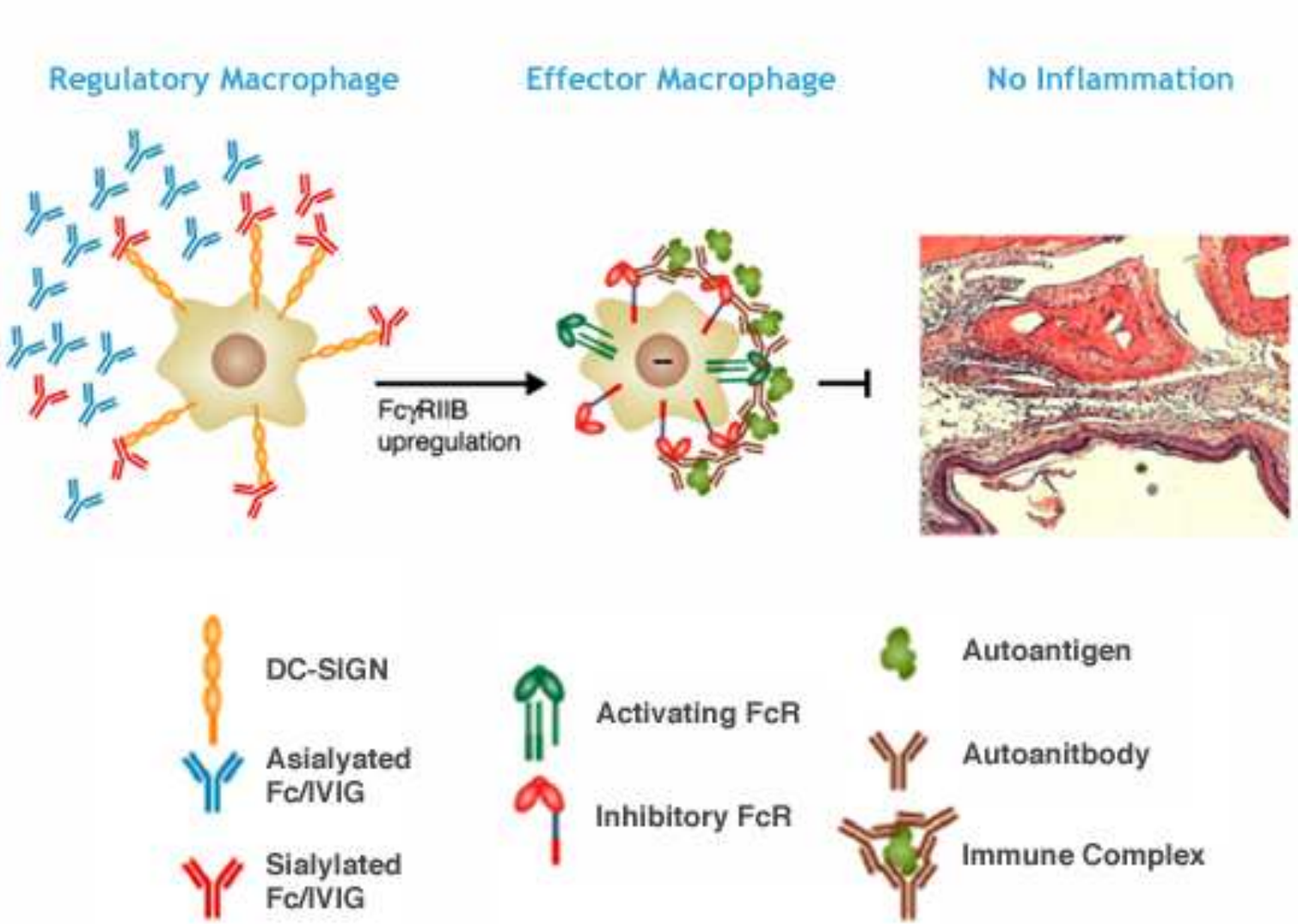
Receptor	FcγRI (CD64)	FcγRII-A (CD32)	FcγRII-B2 (CD32)	FcγRII-B1 (CD32)	FcγRIII (CD16)	FcεRI	FcαRI (CD89)	Fcα/μR
Structure								
Binding Order of affinity	IgG1 $10^8\ M^{-1}$ 1) IgG1=IgG3 2) IgG4 3) IgG2	IgG1 $2 \times 10^6\ M^{-1}$ 1) IgG1 2) IgG3=IgG2* 3) IgG4	IgG1 $2 \times 10^6\ M^{-1}$ 1) IgG1=IgG3 2) IgG4 3) IgG2	IgG1 $2 \times 10^6\ M^{-1}$ 1) IgG1=IgG3 2) IgG4 3) IgG2	IgG1 $5 \times 10^5\ M^{-1}$ IgG1=IgG3	IgE $10^{10}\ M^{-1}$	IgA1, IgA2 $10^7\ M^{-1}$ IgA1=IgA2	IgA, IgM $3 \times 10^9\ M^{-1}$ 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 Eosinophils‡ Neutrophils	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

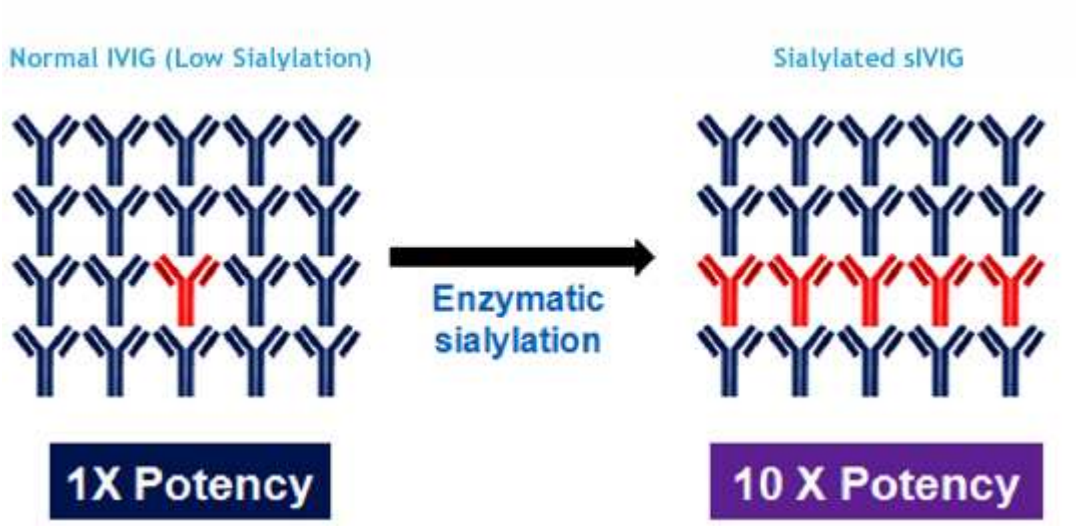
Figure 9-30 Immunobiology, 7ed. (© Garland Science 2008)

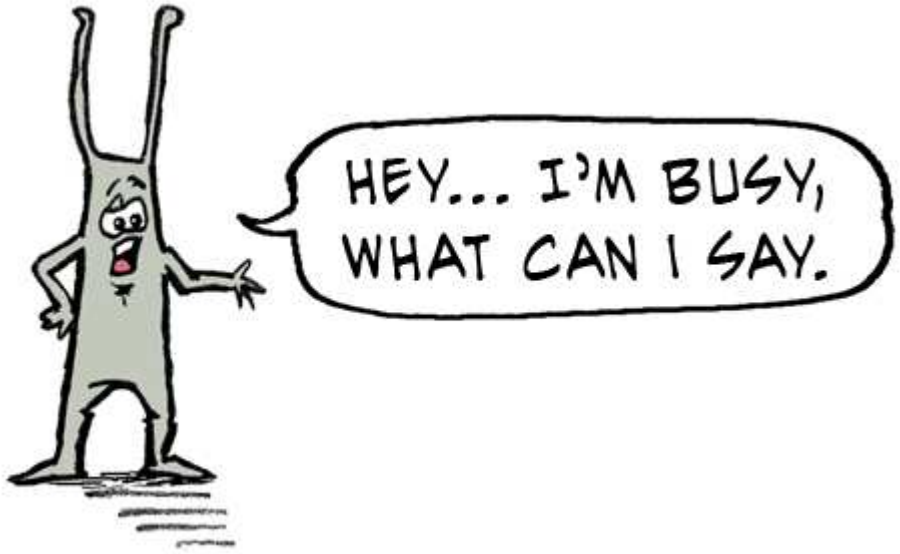


appropriately **sialylated IgG Fc fragments**, and has recently shown that these sialylated Fcs specifically **bind to a C-type lectin, DC-SIGN**


Regulatory Macrophage
Effector Macrophage
No Inflammation
FcγRIIB
upregulation
DC-SIGN
Asialyated
Fc/IVIG
Sialylated
Fc/IVIG
Activating FcR
Inhibitory FcR
Autoantigen
Autoanitbody
Immune Complex

- Sialic acid–rich antibodies (red) in the IVIG preparation engages a lectin (DC-SIGN) on the surface of a regulatory macrophage population (dendritic cells in humans).
- Engagement of this lectin induces a cellular program that results in the secretion of anti-inflammatory, soluble mediators that target effector macrophages found at the site of tissue inflammation where pathogenic immune complexes are deposited.
- These effector macrophages respond to the anti-inflammatory mediators by increasing surface expression of the inhibitory FcgRIIB receptor, thereby altering the threshold concentration of immune complexes necessary to trigger macrophage activation and subsequent inflammation. The net result of this pathway then is to attenuate autoantibody mediated inflammation and tissue pathology.


Normal IVIG (Low Sialylation)
Sialylated sIVIG
Enzymatic sialylation
1X Potency
10 X Potency



Gracias....