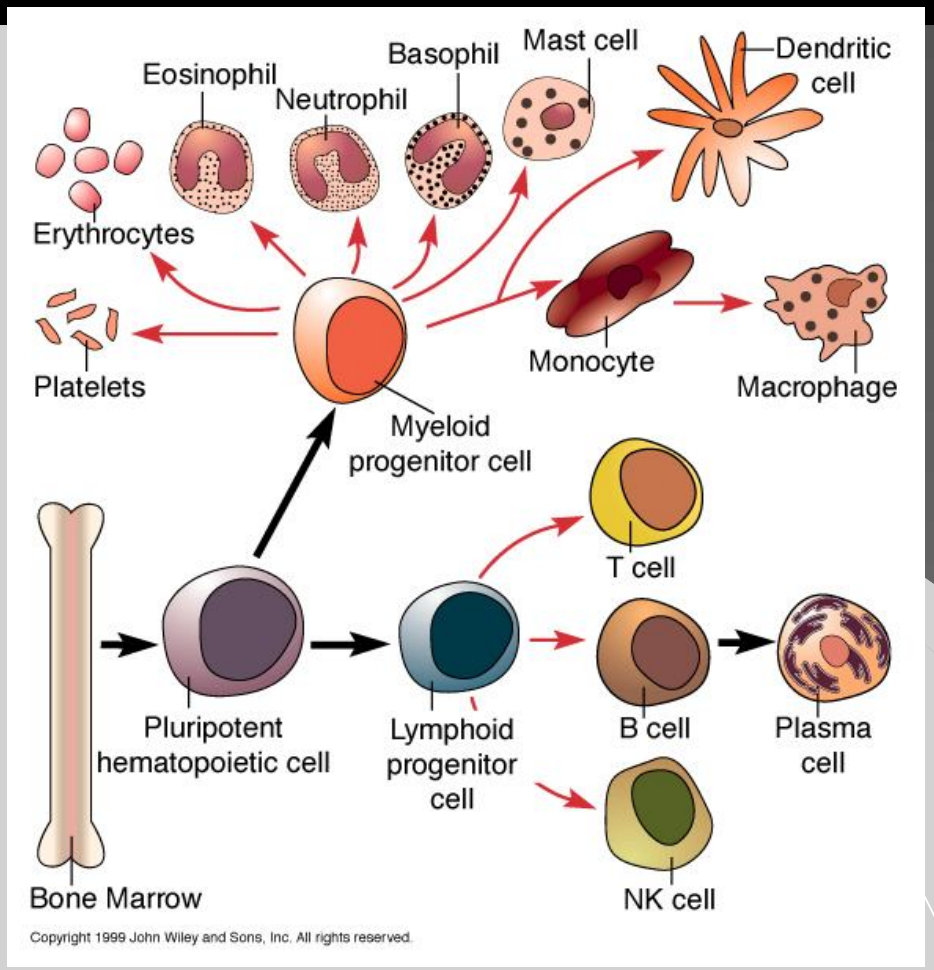
INMUNOLOGIA
ADAPTATIVA

	HUMORAL	CELULAR
INMUNIDAD NATURAL (sin memoria)	IgM	Macrófagos Células NK Neutrófilos
INMUNIDAD ADAPTATIVA (con memoria)	IgG	Linfocitos CD4+ (TH1, Th2,supresores) Linfocitos CD8+ (CTL)

Pathways of differentiation of a pluripotent hematopoietic stem cell of the bone marrow



differentiate in the thymus

Stem cells

differentiate in the bone marrow

ANTIGENOS

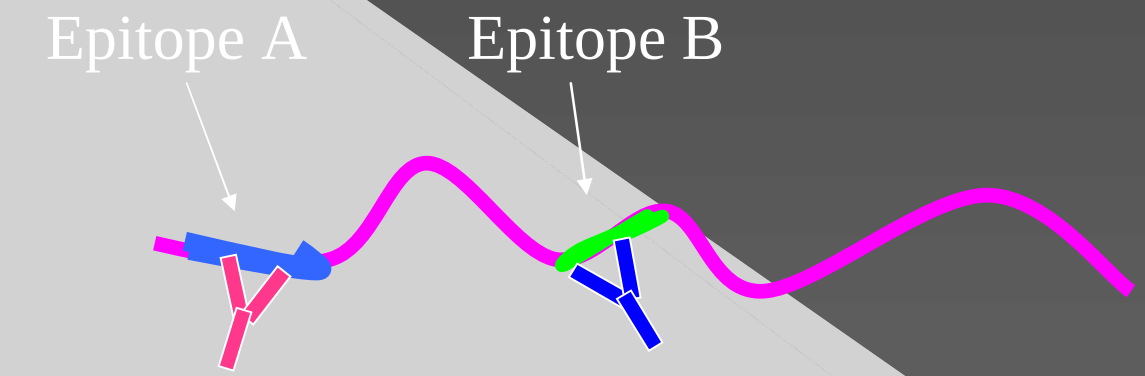
Moléculas reconocidas por receptores en células B (B cell receptor) o T (T cell receptor).

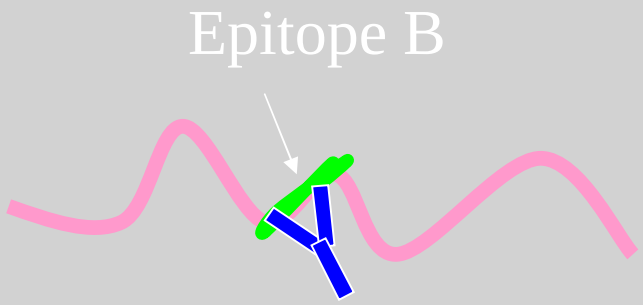
Hapteno : antígeno que para ser reconocido debe ser unido a un carrier (hidratos de carbono)

How many environmental antigens are we exposed to during our lifetime?

The immune system responds to hundreds of thousands of foreign antigens introduced from the environment

Examples of antigen, immunogen and epitopes





Immunogen

Adjuvant:

A substance that, when mixed with an antigen and injected with it, serves to enhance the immune response to the antigen.

Possible mechanisms of action of adjuvants:

- prolong the persistence of the antigen, thus giving the immune system more time to respond

- increase the “size” of the antigen by causing aggregation, perhaps facilitating phagocytosis and antigen presentation

- stimulate lymphocyte proliferation and/or activation

- stimulate a local inflammatory response, thus recruiting cells to the site of the antigen and causing production of factors that may stimulate the immune response.

Commonly used adjuvants

Alum - aluminum potassium sulfate - precipitates the antigen, resulting in increased persistence of the antigen and increased size of the antigen-containing complex.

Incomplete Freund's adjuvant - mineral oil-based - increases persistence of the antigen.

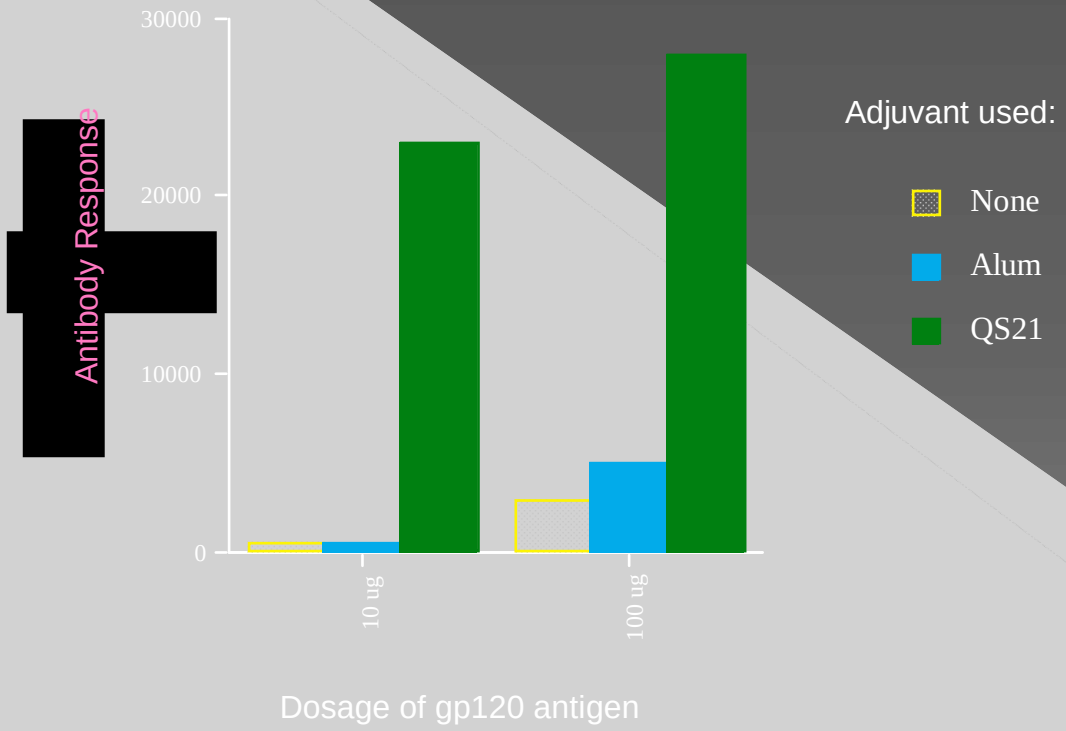
Complete Freund's Adjuvant - mineral oil-based adjuvant containing dead bacteria - increases persistence of the antigen and also stimulates a chronic inflammatory response.

Bacterial Lipopolysaccharides - stimulate nonspecific lymphocyte activation and proliferation.

The effectiveness of an adjuvant must be empirically determined for each individual antigen.

From: Powell, M.F. et al (1994) Immunogenicity and HIV-1 virus neutralization of MN recombinant glycoprotein 120/HIV-1 QS21 vaccine in baboons. *AIDS Research and Human Retroviruses 10(S2):S105.*

Immunization of baboons with gp120 - either alone or with alum adjuvant or QS21 adjuvant.



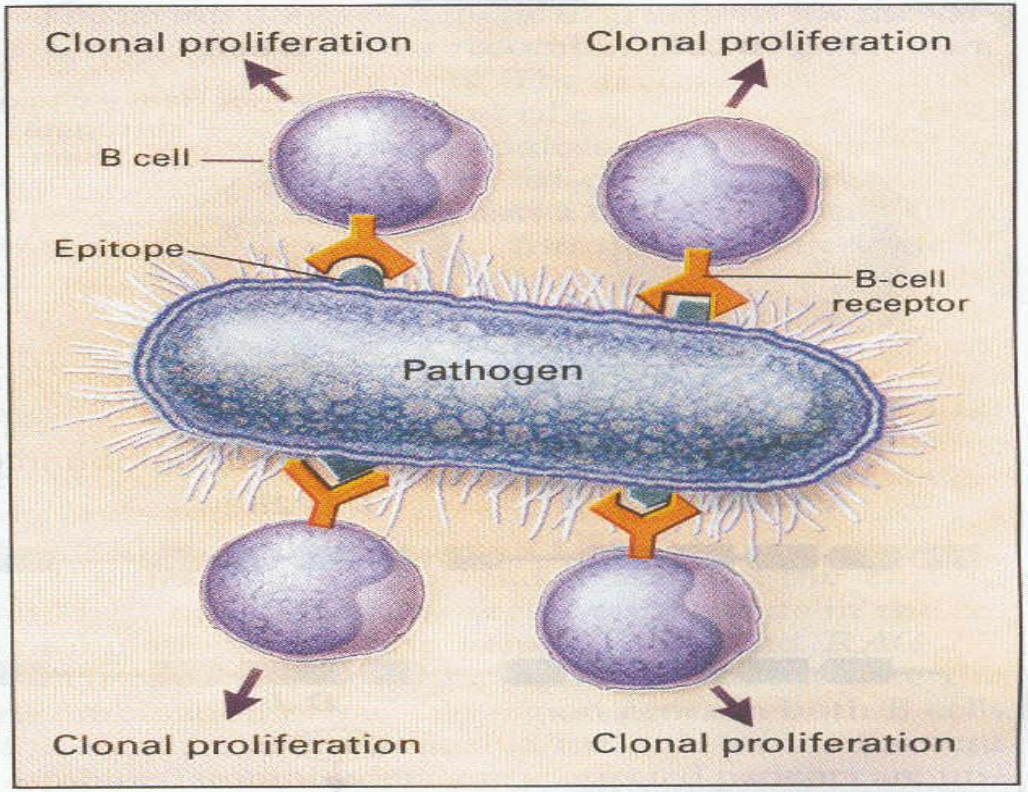


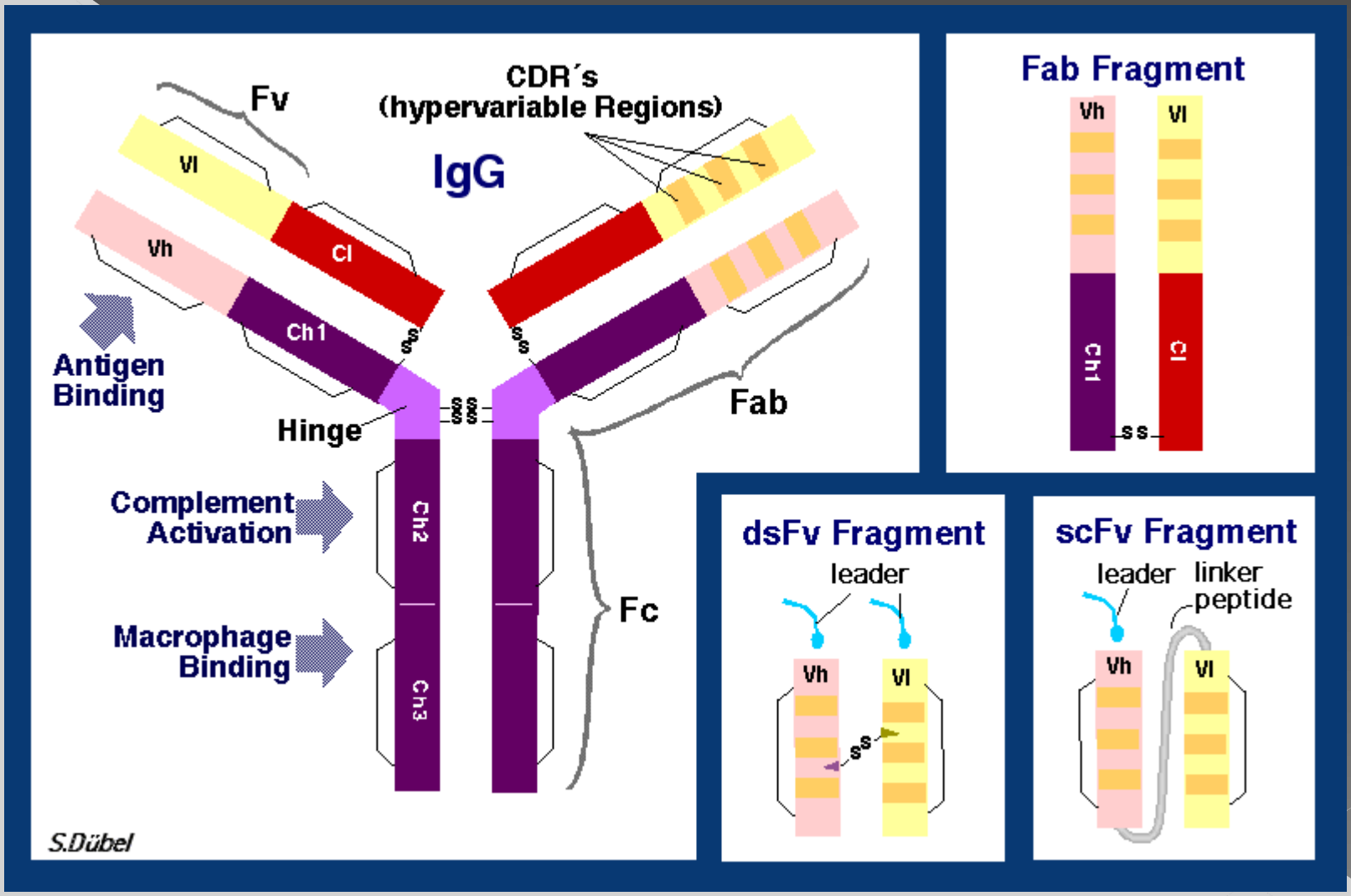
Figure 6. Recognition of Epitopes by B Cells.

Using the antibody molecule as its receptor, the B cell recognizes epitopes on the surface of the antigen. If it is stimulated by this contact, the B cell proliferates, and the resulting clones can secrete antibody whose specificity is the same as that of the cell-surface receptor that bound the epitope. Responses usually involve several different clones of lymphocytes and are therefore referred to as polyclonal. Although not shown here, for each epitope there may be several different lymphocyte clones with different B-cell receptors, each of which recognizes the epitope in a slightly different way and therefore with a different binding strength (affinity).

ANTIGENO CON MULTIPLES EPITOPES

SUERO CON MULTIPLES ANTICUERPOS

ANTICUERPOS


Fv
CDR´s
(hypervariable Regions)
IgG
Vl
Cl
Vh
Ch1
Antigen
Binding
Hinge
Fab
Complement
Activation
Ch2
Macrophage
Binding
Ch3
Fc
S.Dübel
Fab Fragment
Vh
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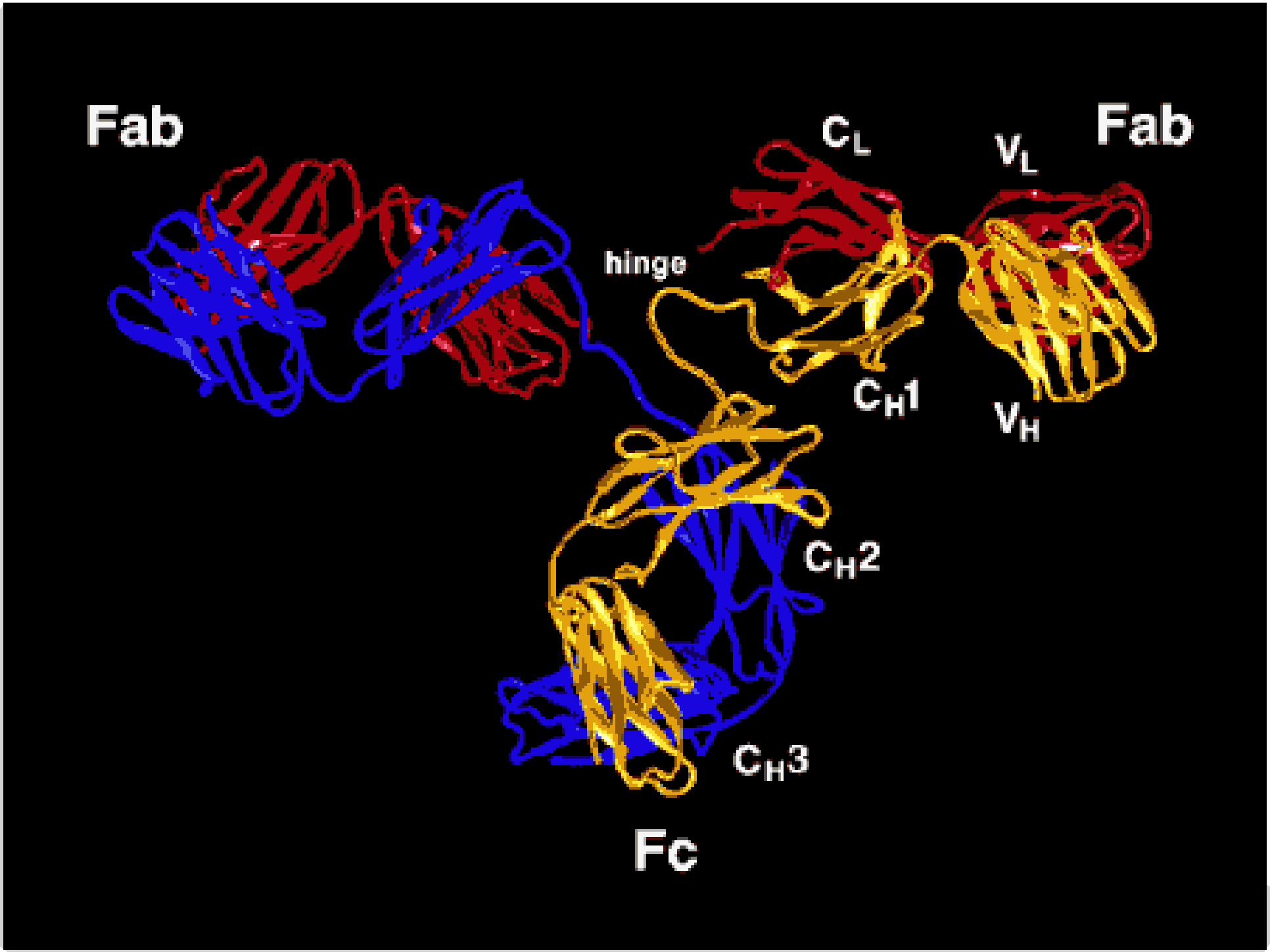
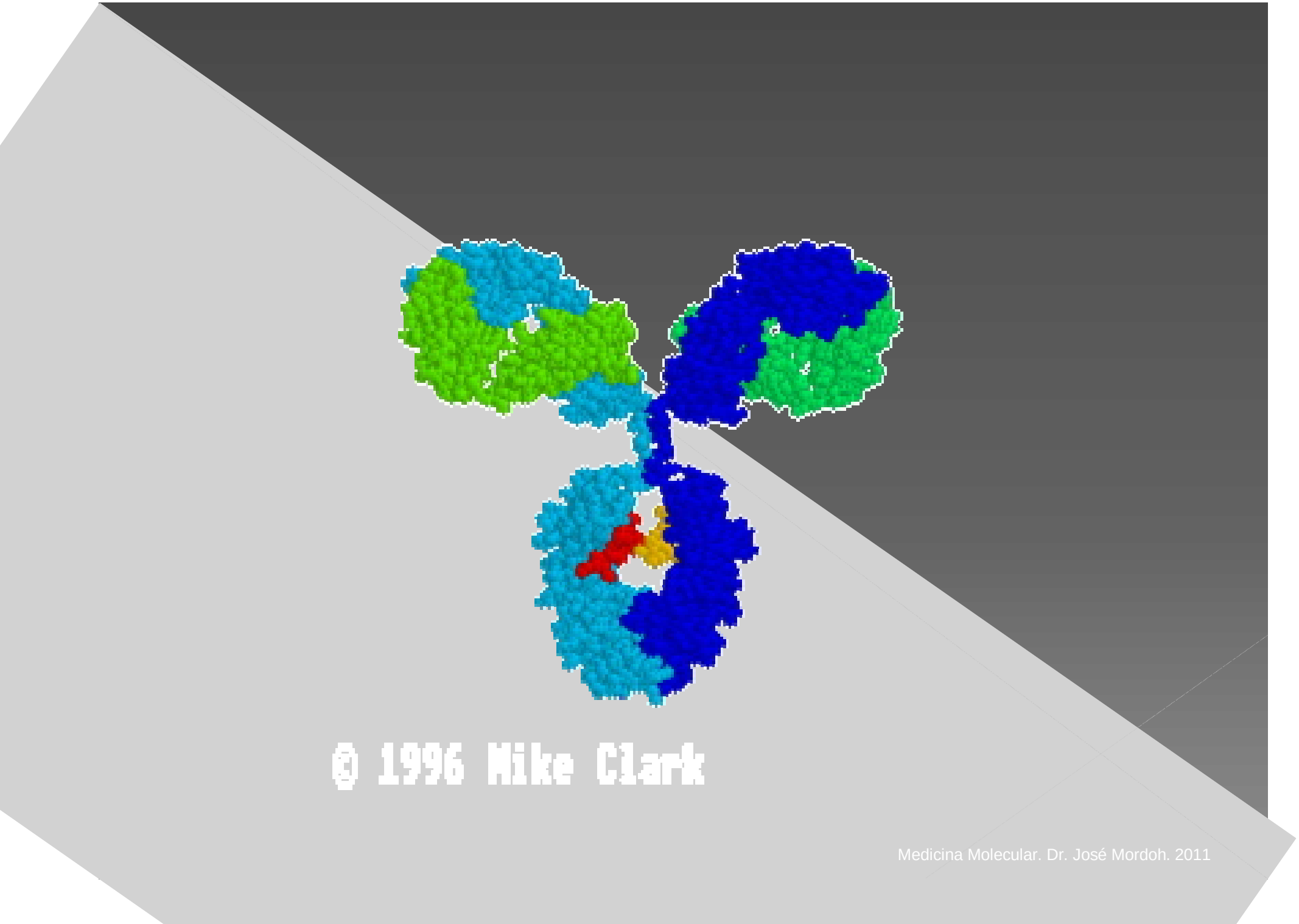
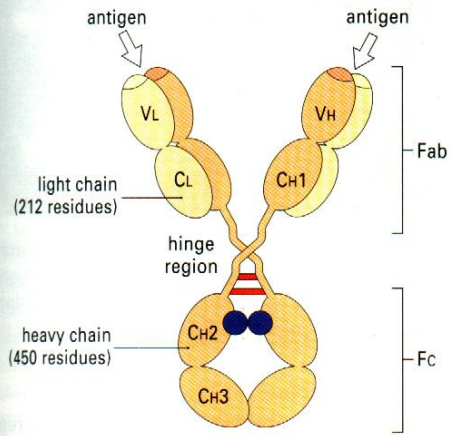
Vl
scFv Fragment
leader
linker
peptide
Vh
Vl


Fab
C_L
V_L
Fab
hinge
C_{H1}
V_H
C_{H2}
C_{H3}
Fc

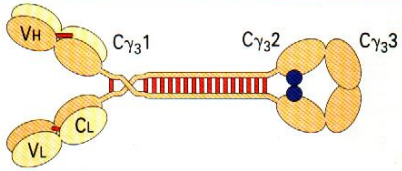

© 1996 Mike Clark

Structural characteristics of various human immunoglobulins

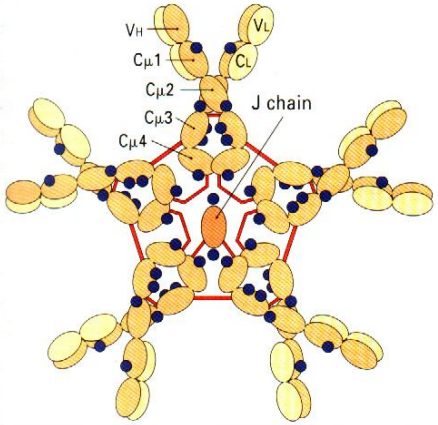
1. IgG1



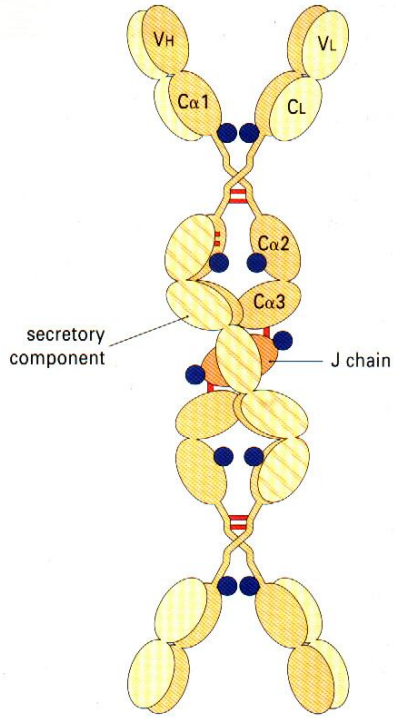
2. IgG3



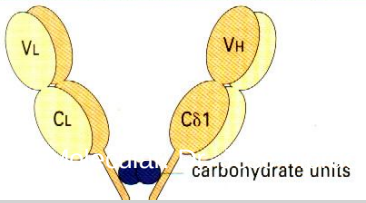
3. IgM



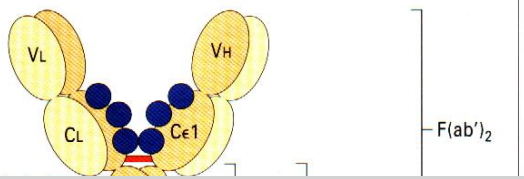
4. IgA (sIgA)



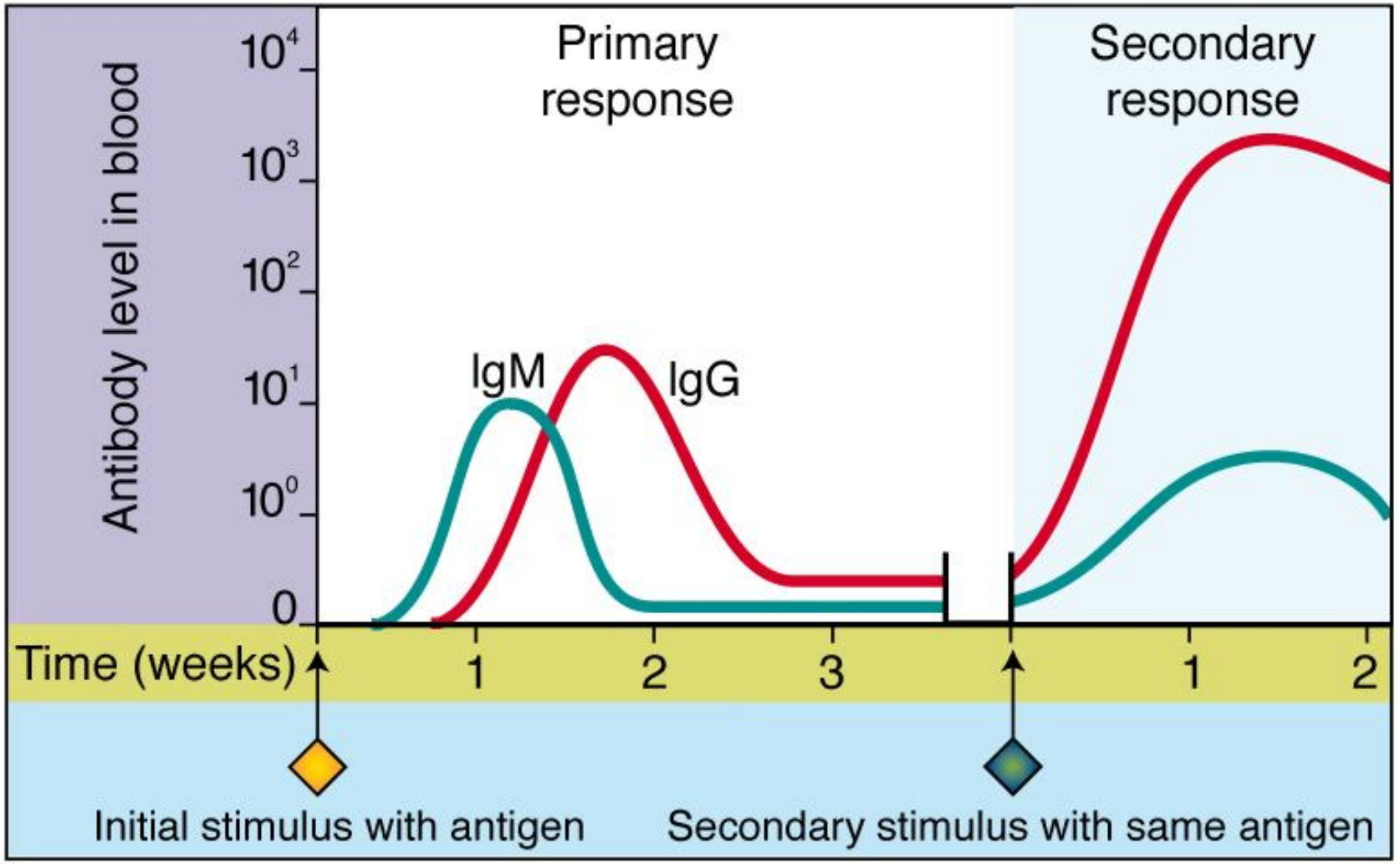
5. IgD



6. IgE



Primary and secondary antibody responses.



RECEPTORES ANTIGENICOS

- B cell receptor (linfocitos B) = reconoce Ag nativo
- T cell receptor (linfocitos T) = reconoce Ag procesado

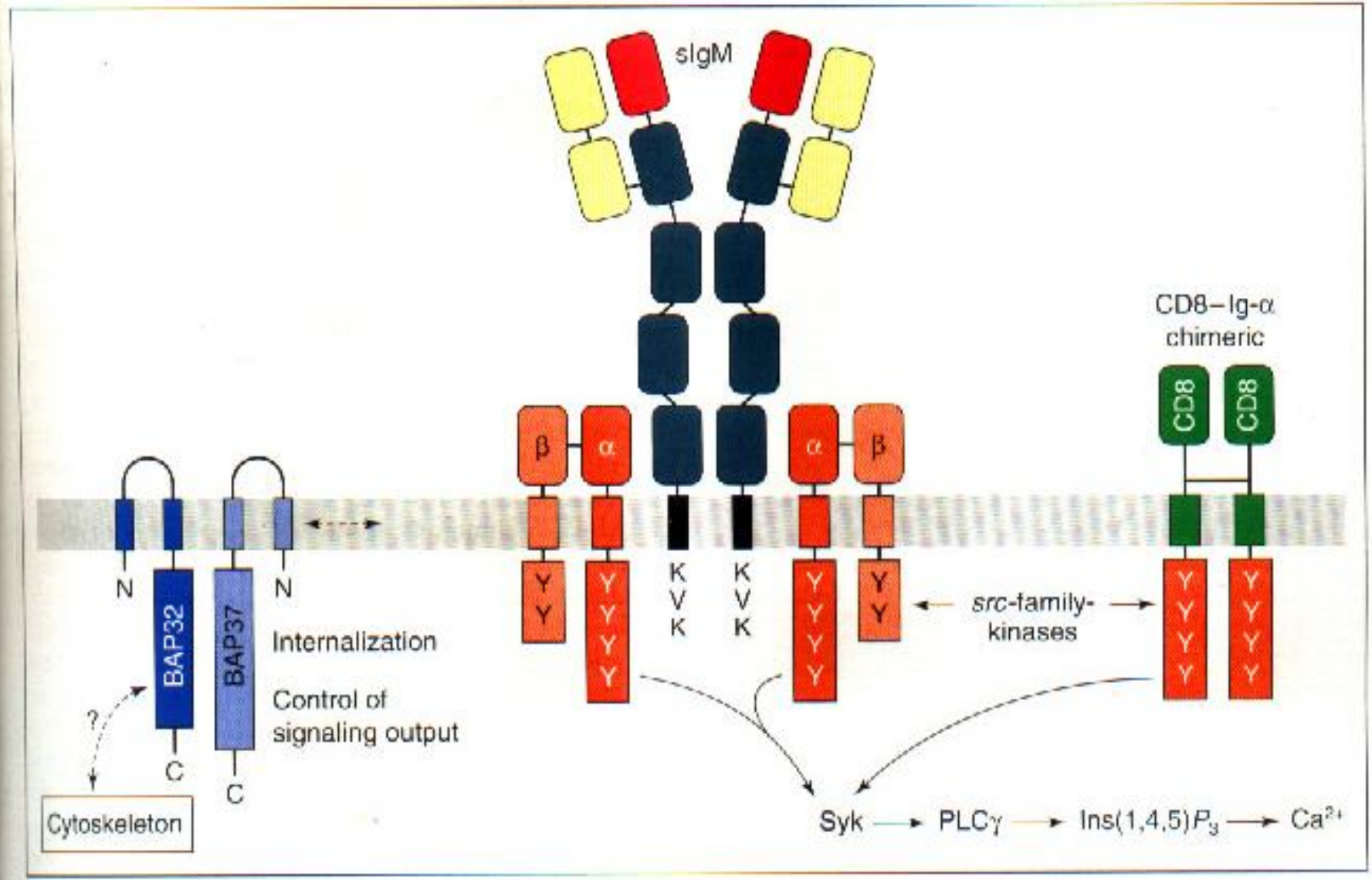
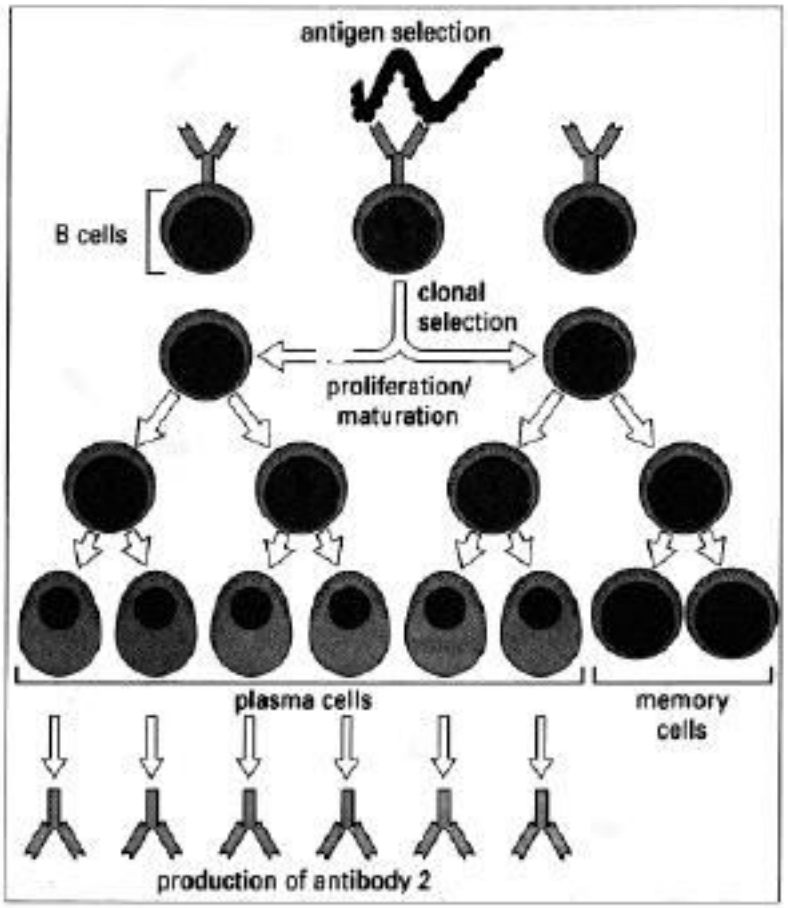


Fig. 1. *Structural model of the B-cell antigen receptor complex (BCR), the chimeric CD8–Ig-α molecule and the BCR-associated proteins BAP32 and BAP37. BAPs and the surface (s)IgM molecule interact with each other in the membrane via their transmembrane domains. BAPs may control activation of the BCR and its association with cytoskeletal elements. Upon crosslinking of the BCR or CD8–Ig-α chimeric receptor, src-family kinases are activated, tyrosine residues (Y) in the immunoreceptor tyrosine-based activation motif (ITAM) are phosphorylated and the spleen tyrosine kinase Syk is recruited to the activated receptors. These events induce activation of phospholipase Cγ (PLCγ), production of inositol (1,4,5)-trisphosphate (Ins(1,4,5)P_3) and Ca^{2+} release.*

Only B-cells with a complementary antibody receptor proliferate and mature.



The B-lymphocytes expressing antibody receptor with the best fit to the **epitope** (antibody-binding domain on the antigen) are the ones that proliferate and give rise to antibody in serum

¿Cómo se produce la gran diversidad de anticuerpos?

Susumu Tonegawa
Premio Nobel 1987

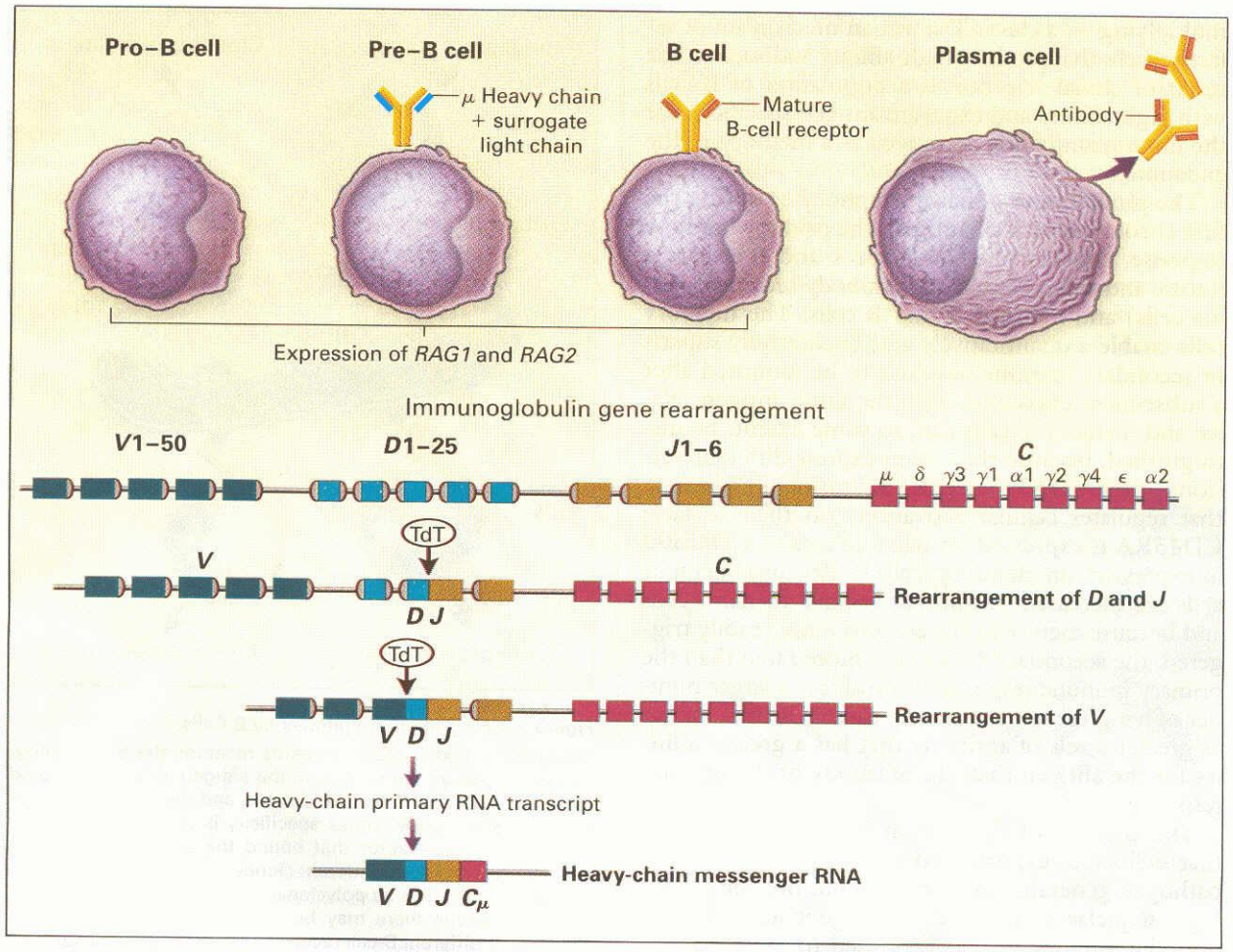


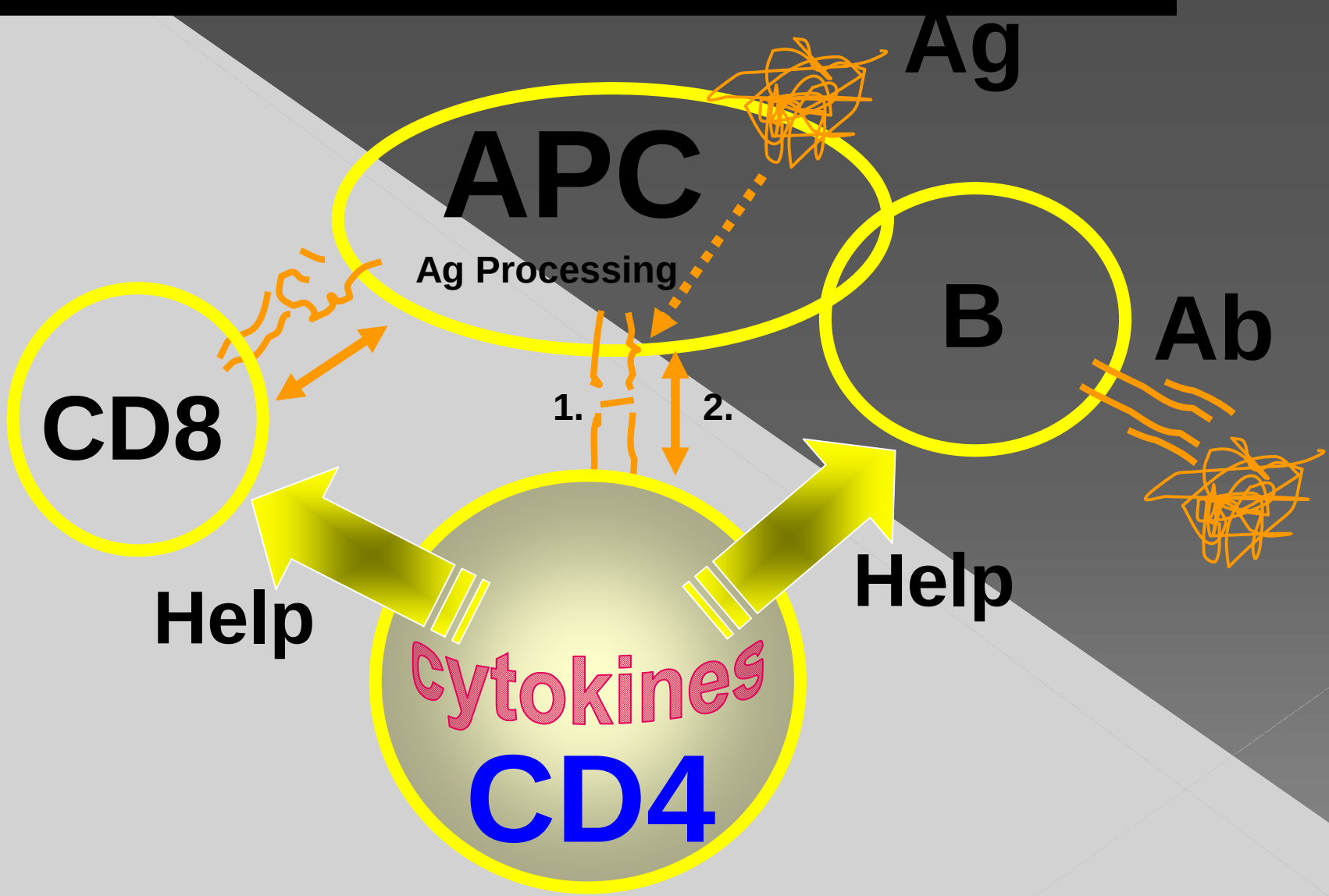
Figure 5. Diversity of Antigen Receptors.

The enormously diverse specificities of the antigen receptors are produced by gene rearrangements during the early developmental stages of the lymphocyte. The events involved in generating a coding sequence for the immunoglobulin heavy chain are shown. Early in B-cell development, pro–B cells mature into pre–B cells, at which stages they express the recombination-activating genes *RAG1* and *RAG2*. The recombinases encoded by these genes mediate the random rearrangement of 1 of 25 diversity (*D*) gene segments next to any 1 of 6 joining (*J*) gene segments. This is followed by the rearrangement of any 1 of 50 variable (*V*) gene segments next to the already rearranged *DJ* segment. Different B cells will rearrange a different segment in each pool, thereby creating one level of diversity. Further diversity is brought about by splicing inaccuracies and by the incorporation of nucleotides mediated by the enzyme terminal deoxyribonucleotidyltransferase (TdT). The heavy-chain primary RNA transcript is processed into messenger RNA (mRNA), with splicing of the rearranged *VDJ* segment next to the constant (*C*) region gene. This mRNA will encode a heavy chain that appears on the surface of the pre–B cell together with the surrogate light chain, which is encoded by genes that do not undergo rearrangement. As the pre–B cell continues to mature, the immunoglobulin light-chain genes undergo rearrangement; the resulting light chain replaces the surrogate light chain, and thereby produces a mature IgM B-cell receptor on the cell surface. The B-cell receptors at this stage also usually include IgD antibodies with the same specificity as the IgM molecule, produced by alternative splicing of the rearranged *VDJ* to either the C_μ or the C_δ gene. The expression of *RAG1* and *RAG2* is then switched off. After encountering an antigen, and in the presence of costimulatory signals, the B cell further differentiates into a plasma cell, which secretes high levels of the specific antibody (or into a memory B cell). The same general principles regarding the rearrangement process apply to the generation of α/β and γ/δ T-cell receptors. The gene segments in the figure are not drawn to scale.

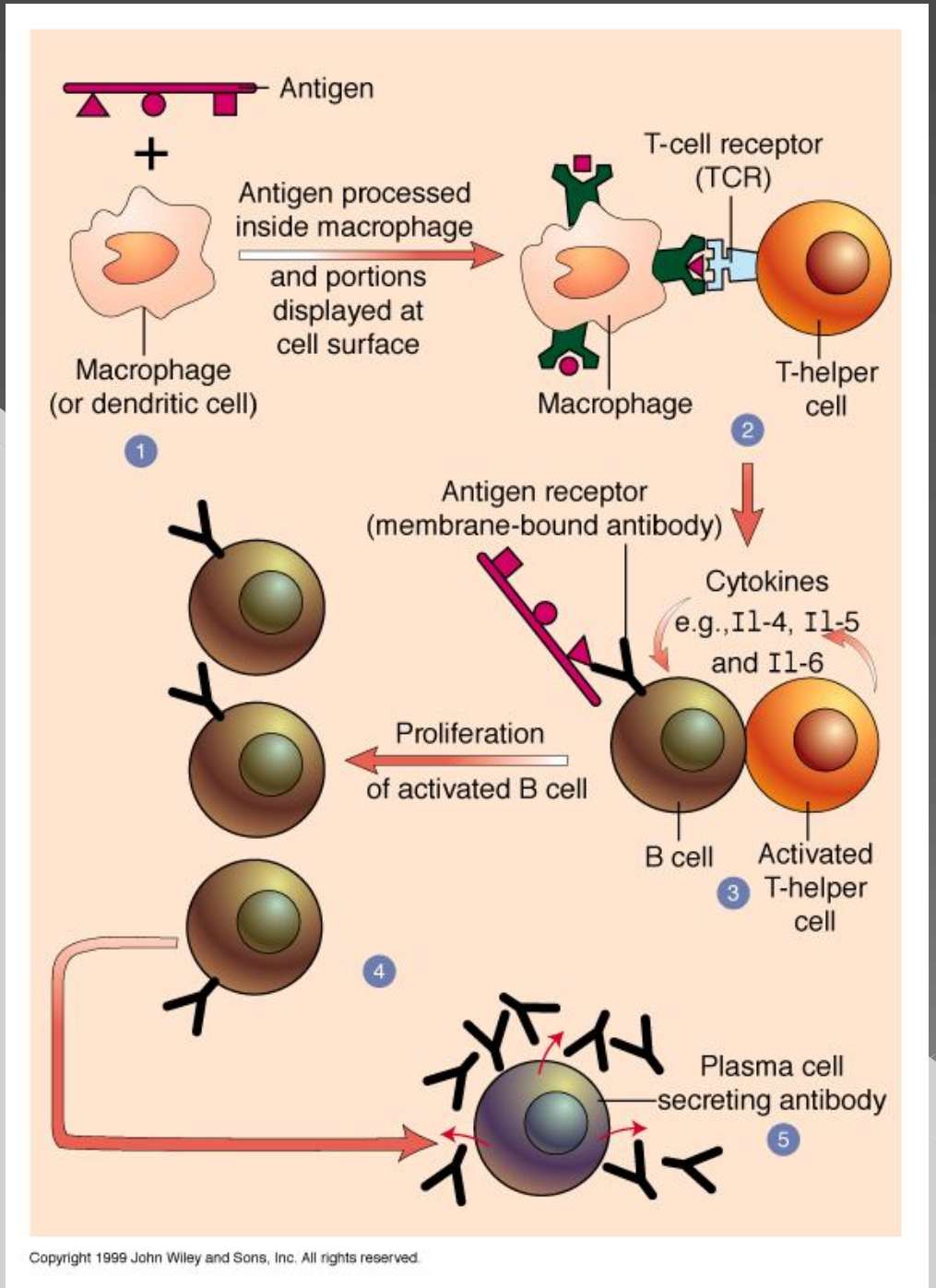
GENES CODIFICANTES PARA INMUNOGLOBULINAS

- Cluster IGH: cadena H; crom.14;V,D,J,C.
- Cluster IGK: cadena K; crom.2; V,J,C.
- Cluster IGL(λ): cadena λ; crom. 22; V,J,C.

The Immune Response:



Role of T-Helper cells in antibody formation.



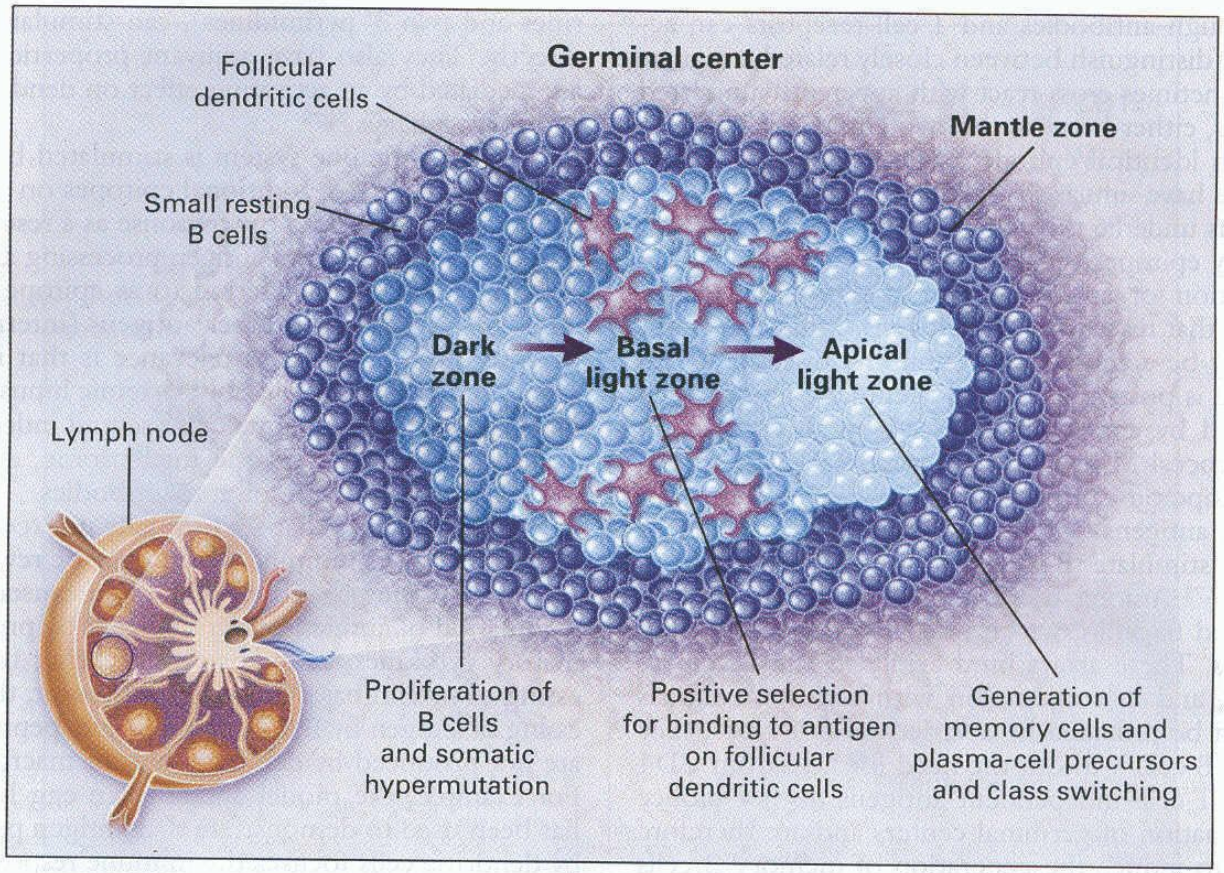
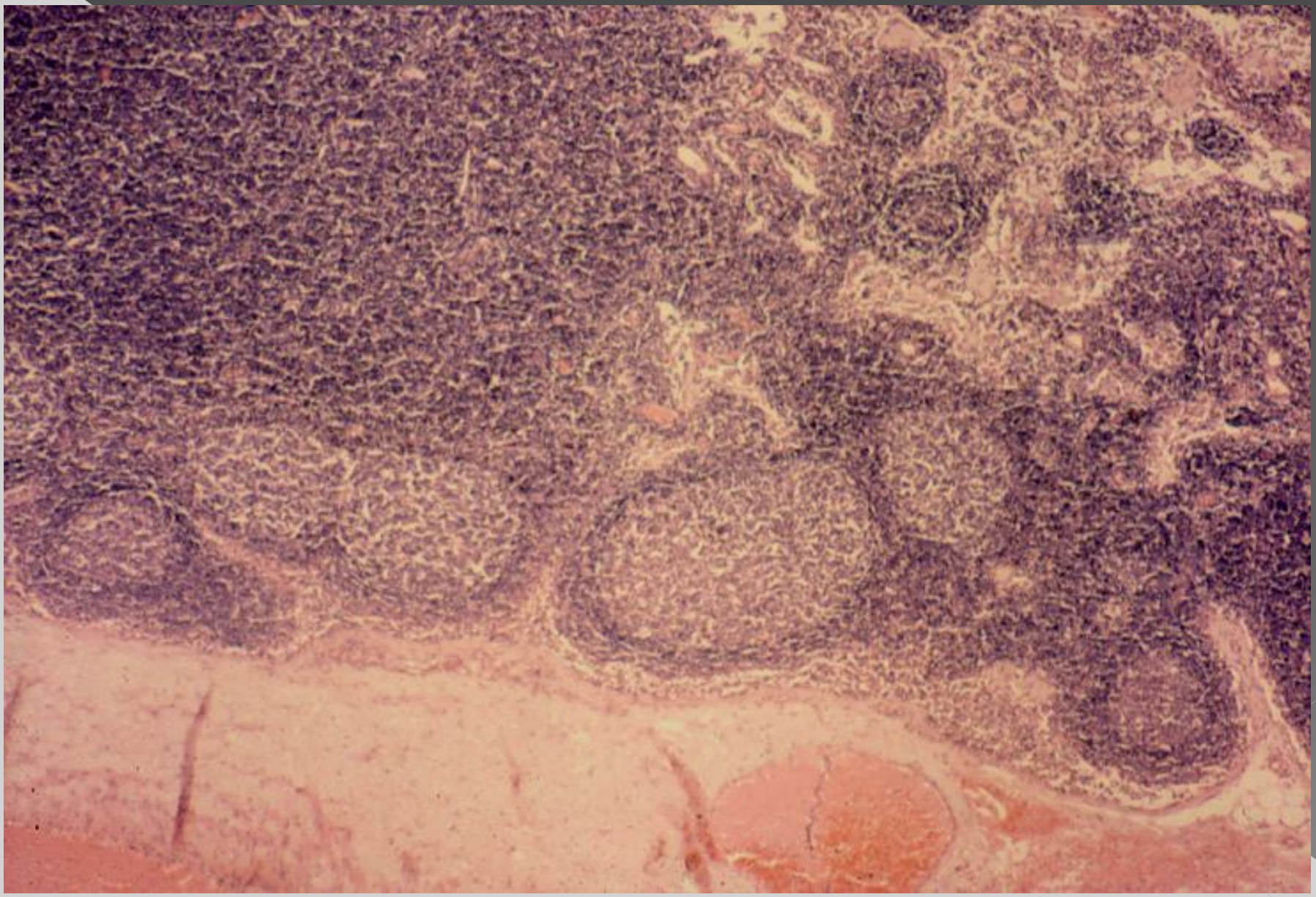


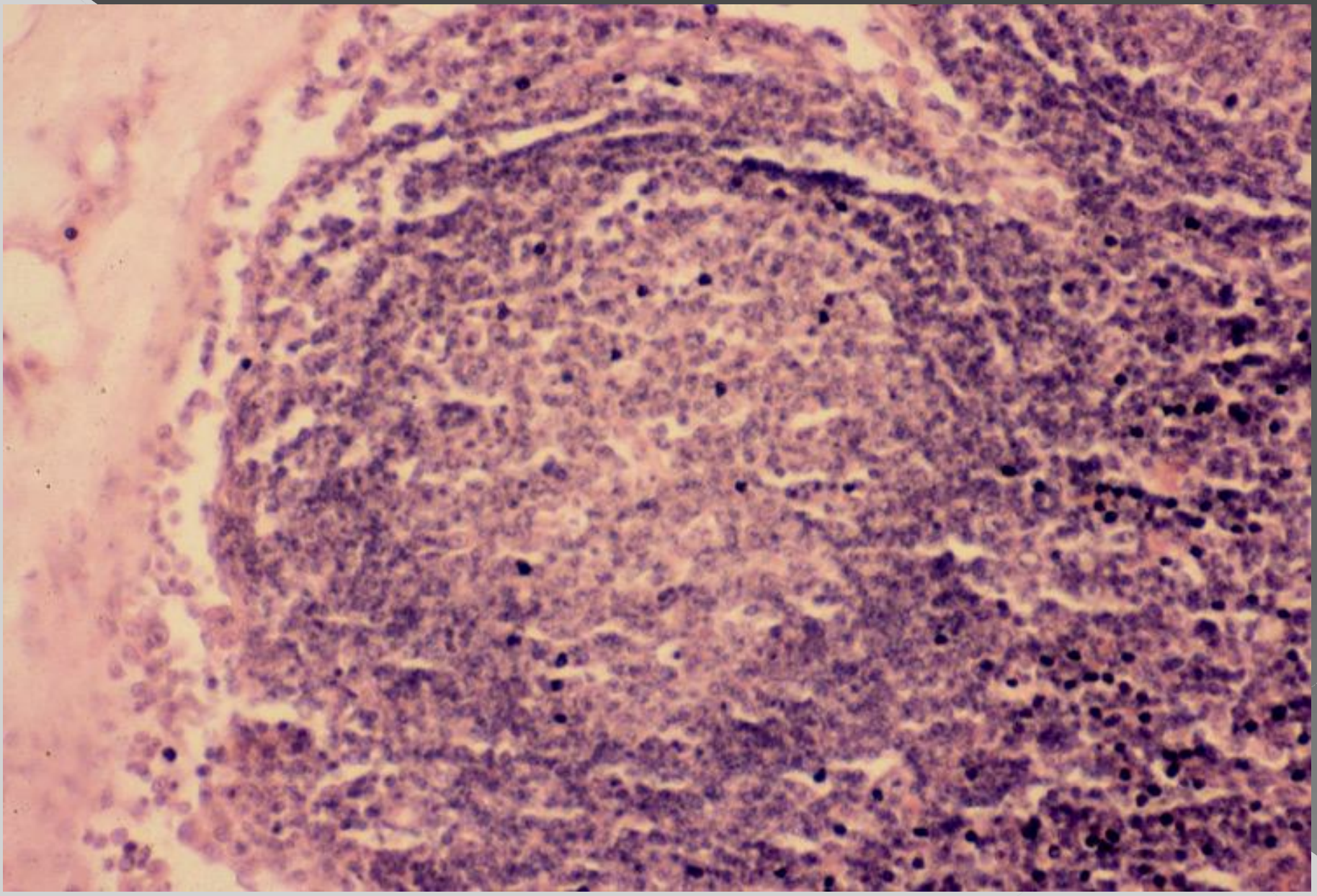
Figure 8. The Germinal Center.

During the initiation of the acquired immune response, germinal centers form in the secondary lymphoid tissues in order to create a microenvironment where all the necessary antigen-specific and innate antigen-presenting cells can interact. Several cytokines, such as interleukin-2, 4, 6, and 10 and transforming growth factor β, and various cell-surface molecules, including CD40, CD19, CD21, and B7, are critically important for these interactions. Antigen-stimulated proliferation of B cells occurs in the dark zone and is accompanied by the fine-tuning of specificity resulting from somatic hypermutation of the immunoglobulin variable-region genes. On reaching the basal light zone, high-affinity antigen-specific B cells are positively selected as a result of their interaction with antigen–antibody complexes on the surface of follicular dendritic cells. B cells that are not positively selected undergo apoptosis and are phagocytosed by tingible-body macrophages. The positively selected cells migrate to the apical light zone, where proliferation continues, class switching occurs, and memory cells and plasma-cell precursors are generated.

Lymph node



Germinal center in lymph node



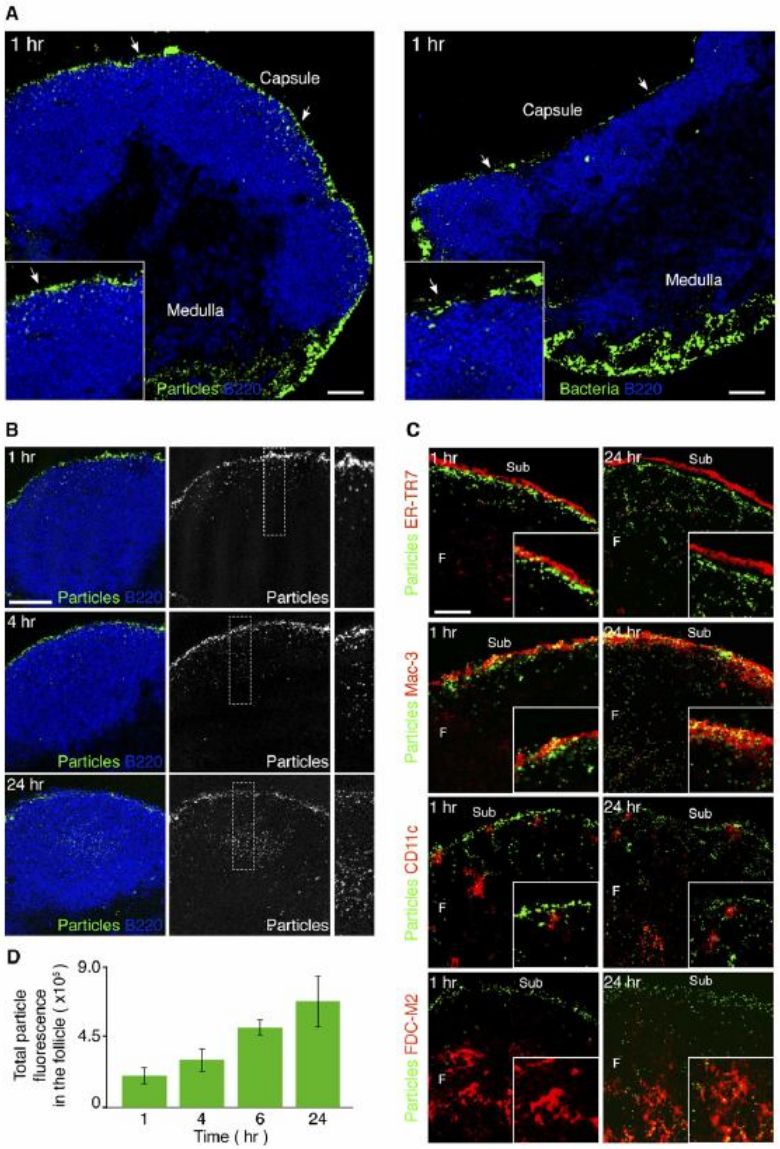
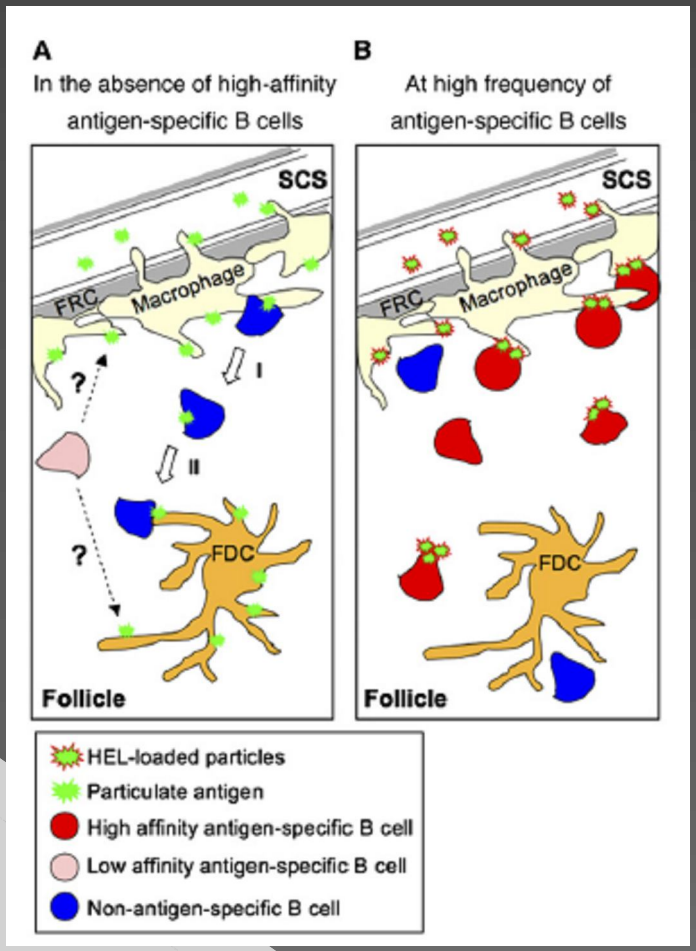


Figure 1. Detection of Particulate Antigen within the Follicle at Early Time Points after Footpad Injection

C57BL/6 recipient mice were injected in the footpad with avidin-coated fluorescent particles or Alexa-488-conjugated bacteria (*E.coli*) prepared as specified in the Experimental Procedures. At different time points after antigen administration, popliteal lymph nodes were isolated, frozen, and prepared for serial cryosection. Finally, lymph node tissue sections were stained as described in the Experimental Procedures.

(A) Representative tissue sections of popliteal lymph nodes from recipient mice, showing the distribution of avidin-coated fluorescent particles (left panel) and fluorescent bacteria (right panel) (green) 1 hr after injection. Tissue sections were stained with B220 (blue) to identify the B cell follicles. Inner panels show a higher magnification of the SCS area, where particulate antigen accumulates (white arrows).

(B) The entrance and accumulation of avidin fluorescent particles inside the follicular area are shown in the tissue sections of representative B cell follicles (identified by B220 staining, blue) of popliteal lymph nodes at different time points after injection. Magnification of a small section of each follicle (pictured in the middle panels) is shown on the right panels.



Carrasco and Batista, Immunity 27, 160-171, 2007

LINFOCITO B EN REPOSO

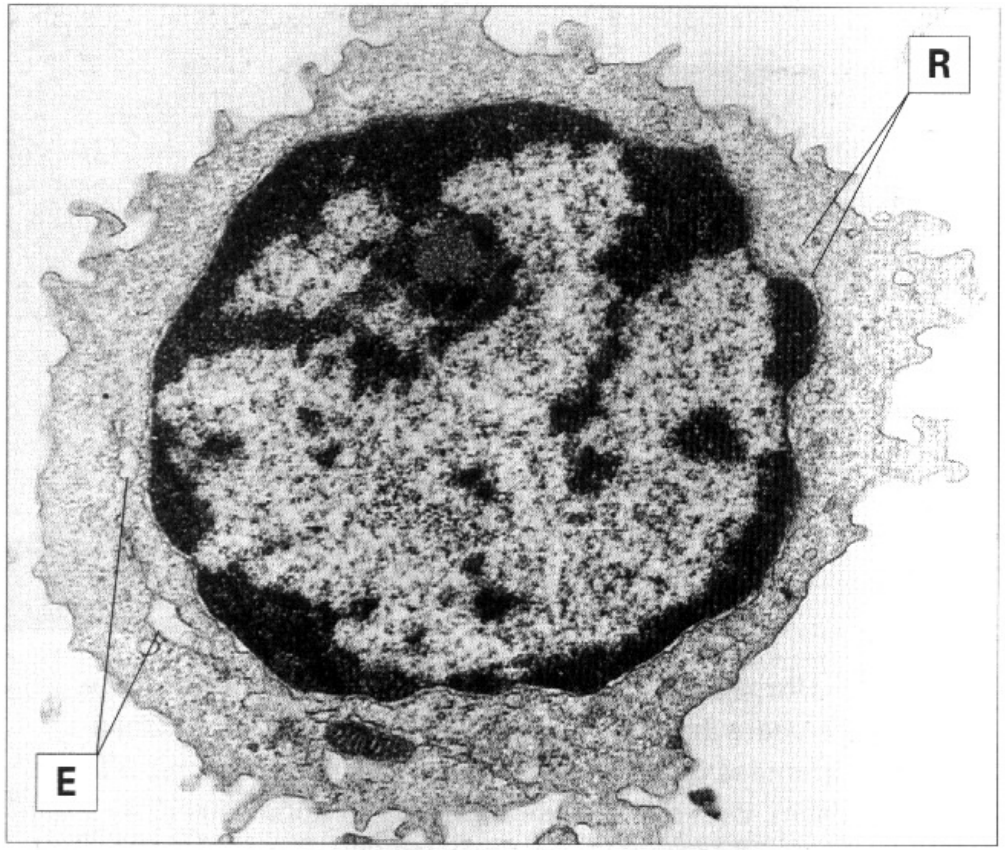


Fig. 2.27 Ultrastructure of resting B cells. These cells have no Gall body or granules. Scattered ribosomes (R) and isolated strands of rough endoplasmic reticulum (E) are seen in the cytoplasm. Development of the Golgi-lysosomal system in the B cell occurs on activation. ×11 500.

LINFOBLASTOS B

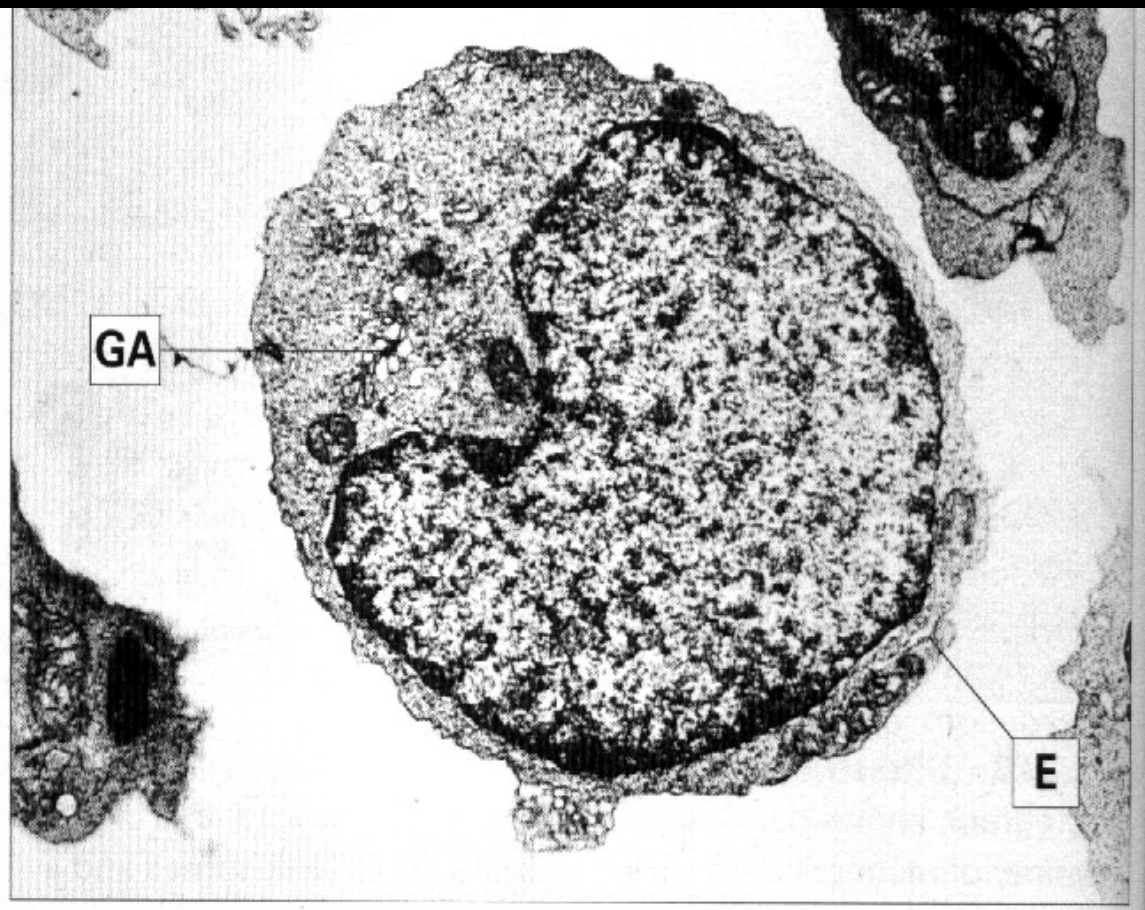


Fig. 2.28 Ultrastructure of B-cell blasts. The main feature of activated B cells is the development of the machinery for immunoglobulin synthesis. This includes rough endoplasmic reticulum (E), free polyribosomes and the Golgi apparatus (GA), which is involved in glycosylation of the immunoglobulins. ×7500.

PLASMOCITO

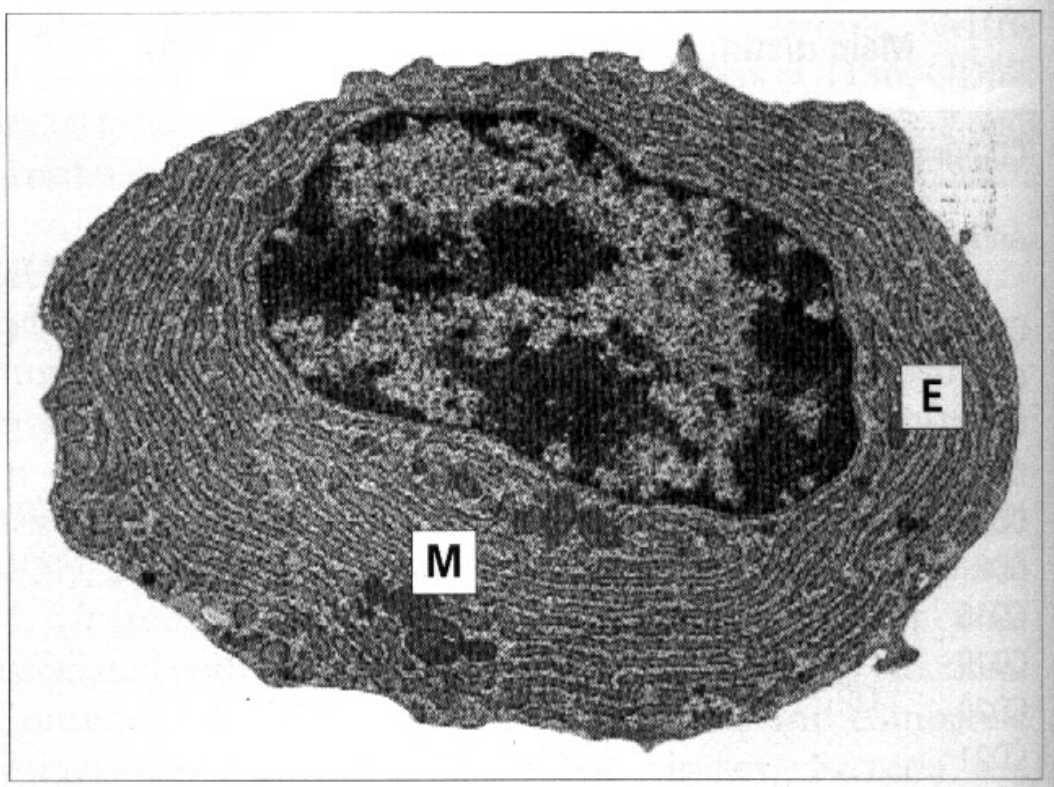


Fig. 2.33 Ultrastructure of the plasma cell. The plasma cell is characterized by parallel arrays of rough endoplasmic reticulum (E). In mature cells, these cisternae become dilated with immunoglobulins. Mitochondria (M) are also seen. ×5000. (Adapted from Zucker-Franklin D, Greaves MF, Grossi CE, *et al. Atlas of Blood Cells: Function and Pathology*. Vol II. 2nd edn. Milan: EE Ermes, Philadelphia: Lea and Febiger, 1988.)

PLASMOCITO APOPTOTICO

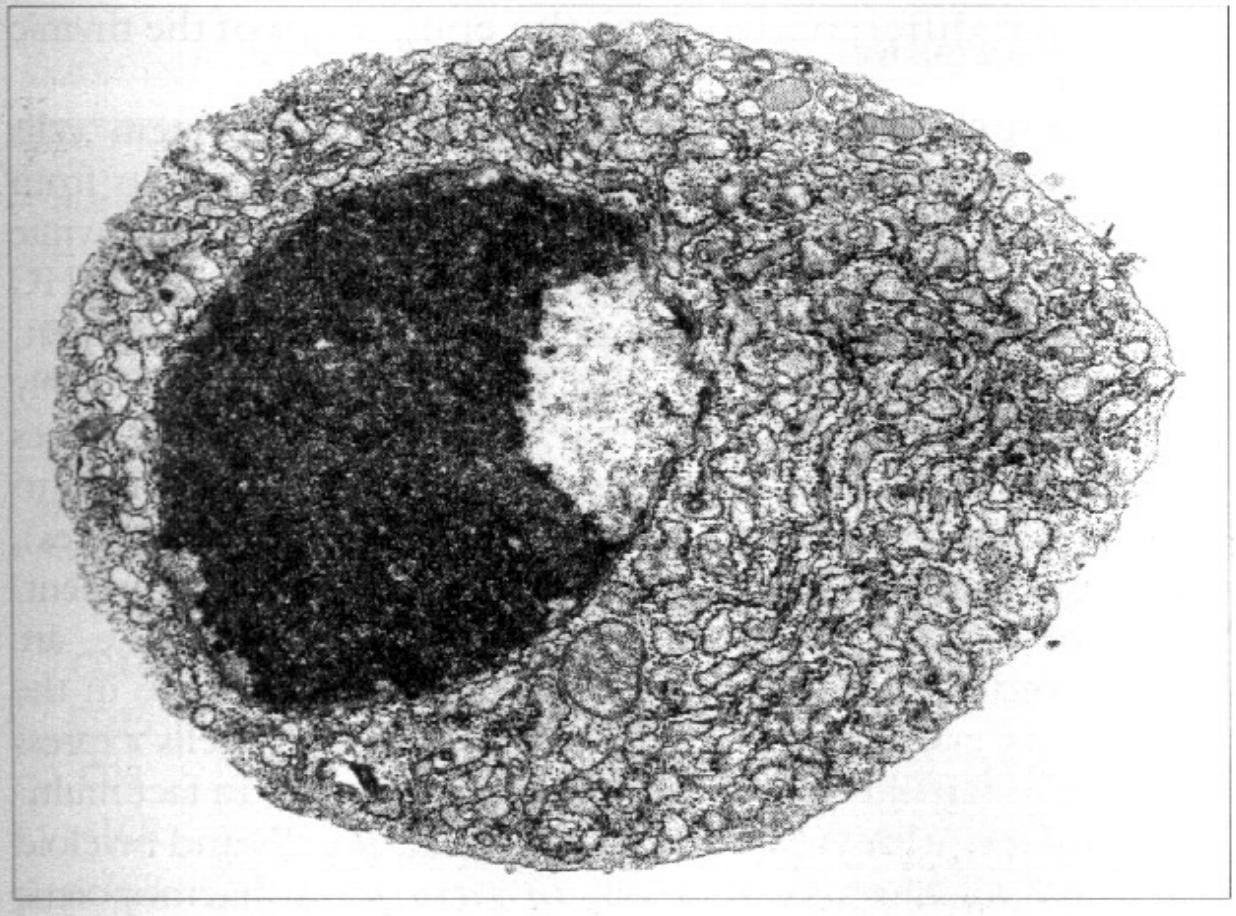
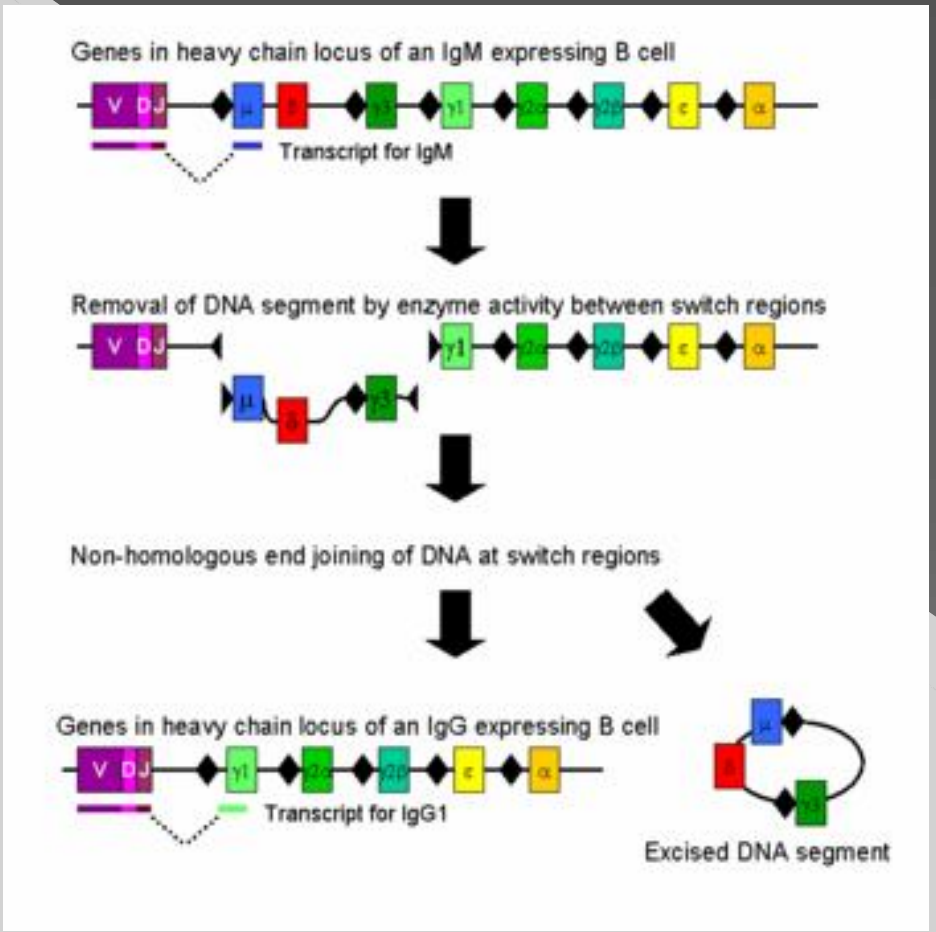


Fig. 2.35 Plasma cell death by apoptosis. Plasma cells are shortlived and die by apoptosis (cell suicide). Note the nuclear chromatin changes, which are characteristic of apoptosis. ×5000.


Genes in heavy chain locus of an IgM expressing B cell
V D J
μ
δ
γ3
γ1
α2
α1
ε
α
Transcript for IgM
Removal of DNA segment by enzyme activity between switch regions
Non-homologous end joining of DNA at switch regions
Genes in heavy chain locus of an IgG expressing B cell
Transcript for IgG1
Excised DNA segment

MECANISMO DE ACCION DE LOS ANTICUERPOS

Via Complemento

ADCC (antibody-dependent-cellular-cytotoxicity

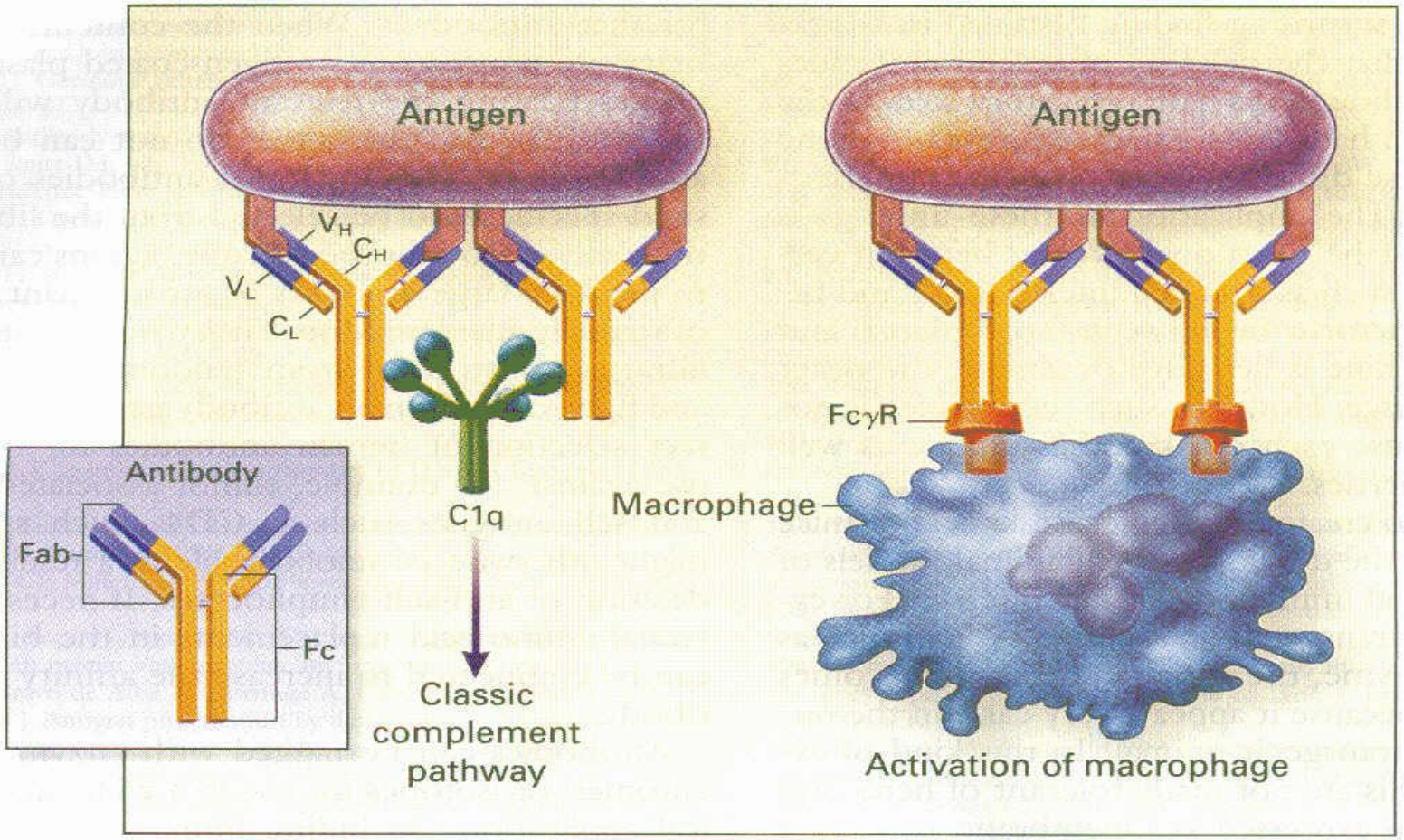


Figure 11. Role of Antibodies.

Antibodies rarely act in isolation. Their usual role is to focus components of the innate immune system on the pathogen, and the activation of these destructive forces normally requires coordinating events that occur after Fab heavy- and light-chain variable regions (V_H and V_L) of the antibody are bound to antigen, leading to the display of multiple exposed Fc regions. The figure shows two examples of this process: the activation of the classic complement pathway after binding of C1q to Fc, and the activation of phagocytosis after the cross-linking of Fc receptors and binding of the FcγR on the macrophage.

◉ COMPLEMENTO

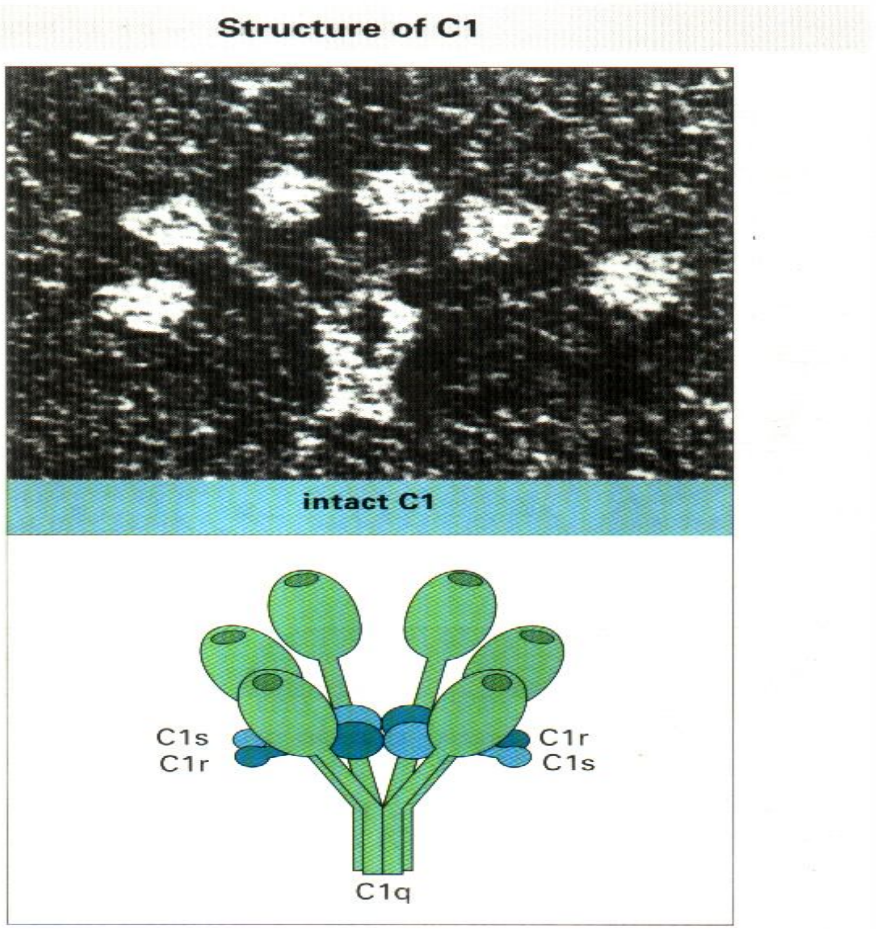


Fig. 3.21 Electronmicrograph of a human C1q molecule demonstrates six subunits. Each subunit contains three polypeptide chains, giving 18 in the whole molecule. The receptors for the Fc regions of IgG and IgM are in the globular heads. The connecting stalks contain regions of triple helix and the central core region contains collagen-like triple helix. The lower panel shows a model of intact C1 with two C1r and two C1s proenzymes positioned within the ring. The catalytic heads of C1r and C1s are closely apposed and conformational change induced in C1q following binding to complexed immunoglobulin causes mutual activation/cleavage of each C1r unit followed by cleavage of the two C1s units. The cohesion of the entire complex is dependent on Ca^{2+}. (Electronmicrograph, reproduced by courtesy of Dr N. Hughes-Jones.)

MAC (complejo ataque complemento)

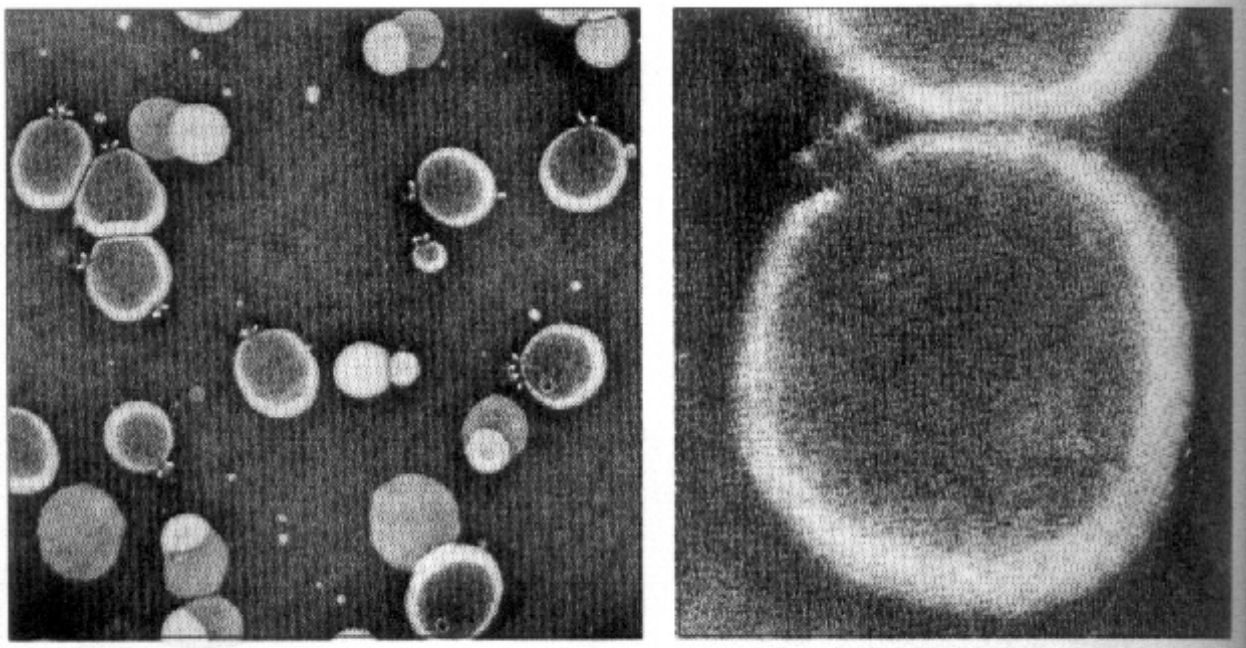


Fig. 3.19 Electronmicrographs of the membrane attack complex (MAC). The complex consists of a cylindrical pore, in which the walls of the cylinder, formed by C9, traverse the cell membrane. In these micrographs the human C5b–9 complex has been reincorporated into a lecithin liposomal membrane. ×234 000. (Courtesy of Professor J. Tranum-Jensen and Dr S. Bhakdi.)

Selected phagocyte receptors interacting with IgG

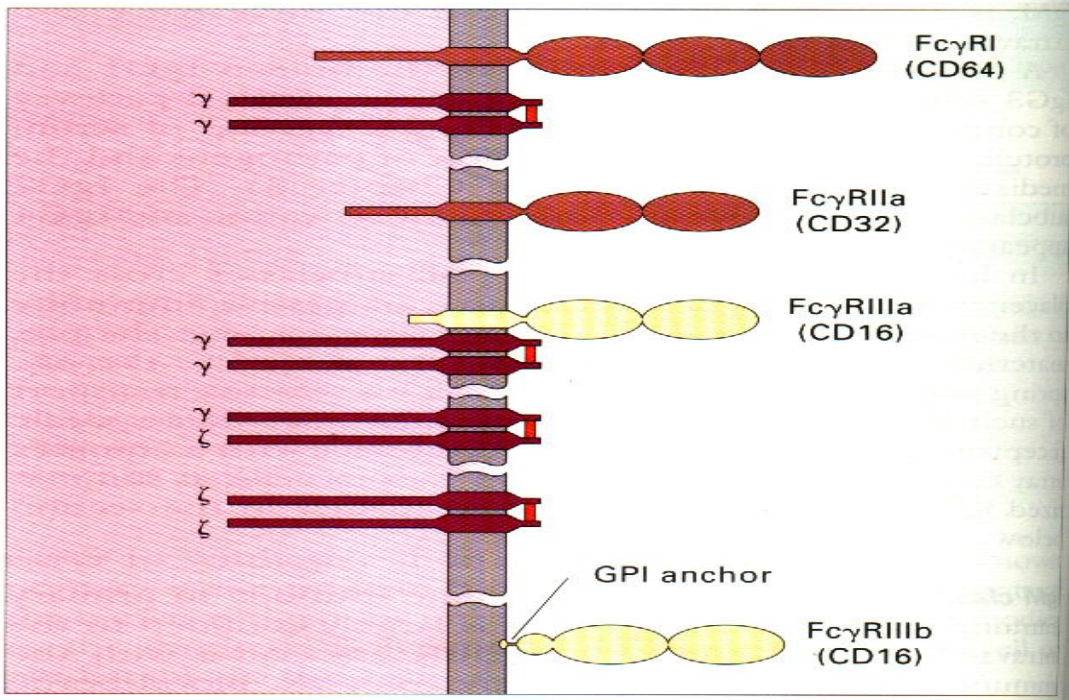


Fig. 4.22 The human Fcγ receptor structures shown are those for FcγRI (expressed by monocytes), FcγRIIa (expressed by monocytes and neutrophils), FcγRIIIa (expressed by monocytes and attached as a normal transmembrane protein) and FcγRIIIb (expressed by neutrophils and attached by a phosphatidyl inositol glycan [GPI] membrane anchor). Each receptor belongs to the immunoglobulin superfamily and expresses two or three extracellular immunoglobulin-like domains. Several of the receptors are now known to exist as complexes with various disulphide-linked subunits. FcγRI and FcγRIIIa both associate with dimers of the γ chain originally described as part of the high-affinity FcεRI complex (see *Fig 4.23*). FcγRIIIa has also been shown to associate with dimers of the ζ chain found in the TCR–CD3 complex. In the case of FcγRIIIa these subunits can associate as either homodimers (γ–γ or ζ–ζ) or as heterodimers (γ–ζ). They appear to be essential for surface expression and signal transduction. In FcγRI interactions, the receptor appears to bind a structural motif centred around Leu 235 in the C_H2 domain, present in IgG1, IgG3 and IgG4.

INMUNOLOGIA MOLECULAR

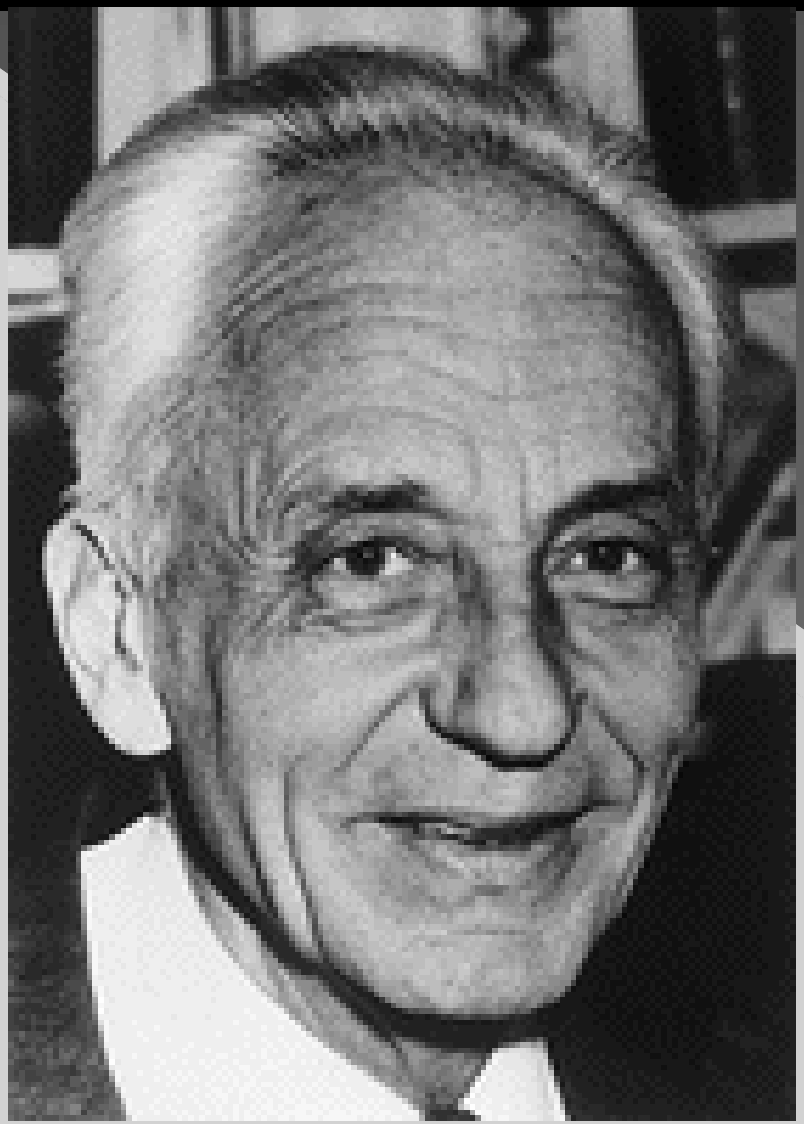
INMUNIDAD CELULAR

COMPLEJO MAYOR DE HISTOCOMPATIBILIDAD

(HLA, MHC)

Medicina Molecular. Dr. José Mordoh. 2011

Jean Dausset
Premio Nobel de Medicina 1980



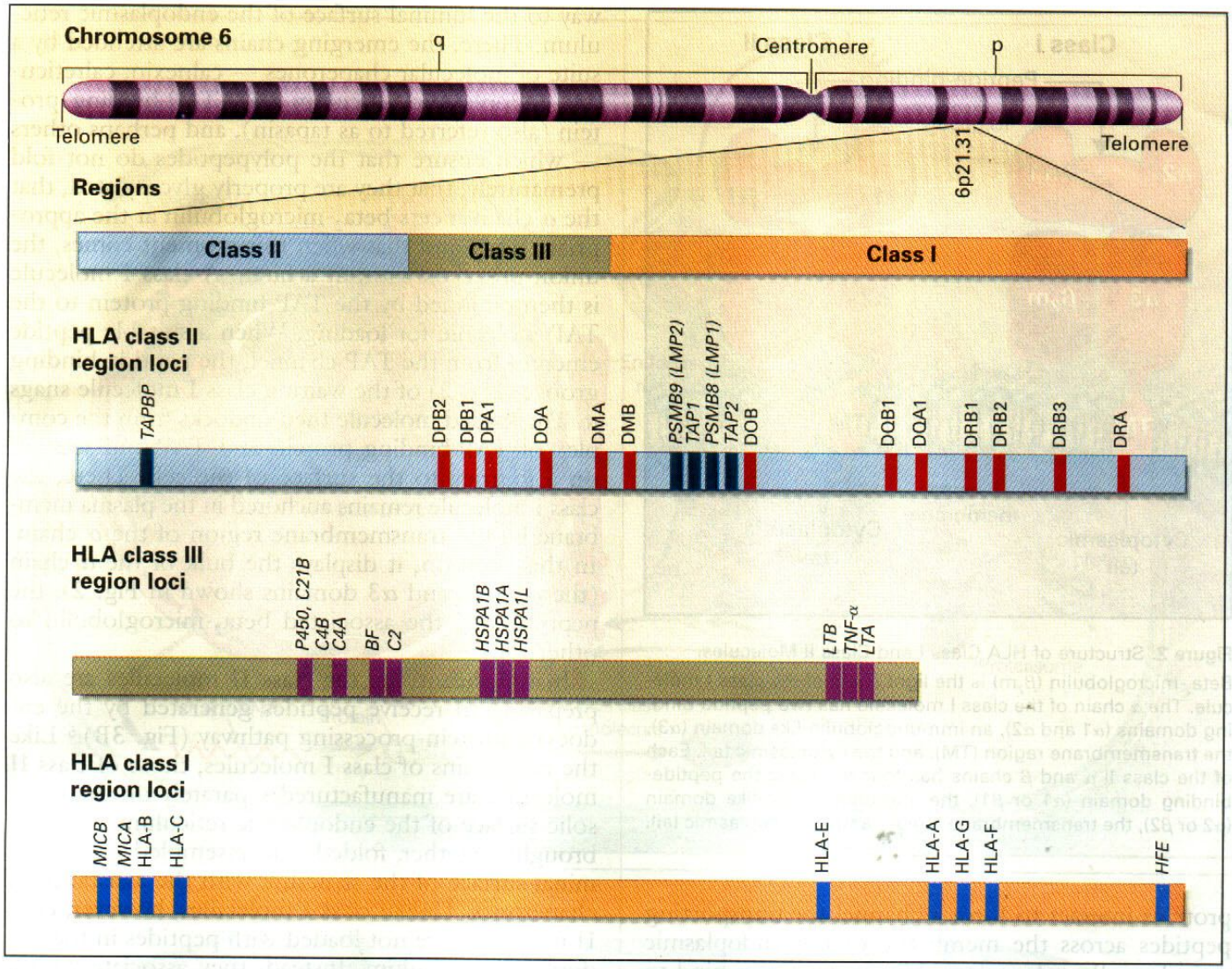
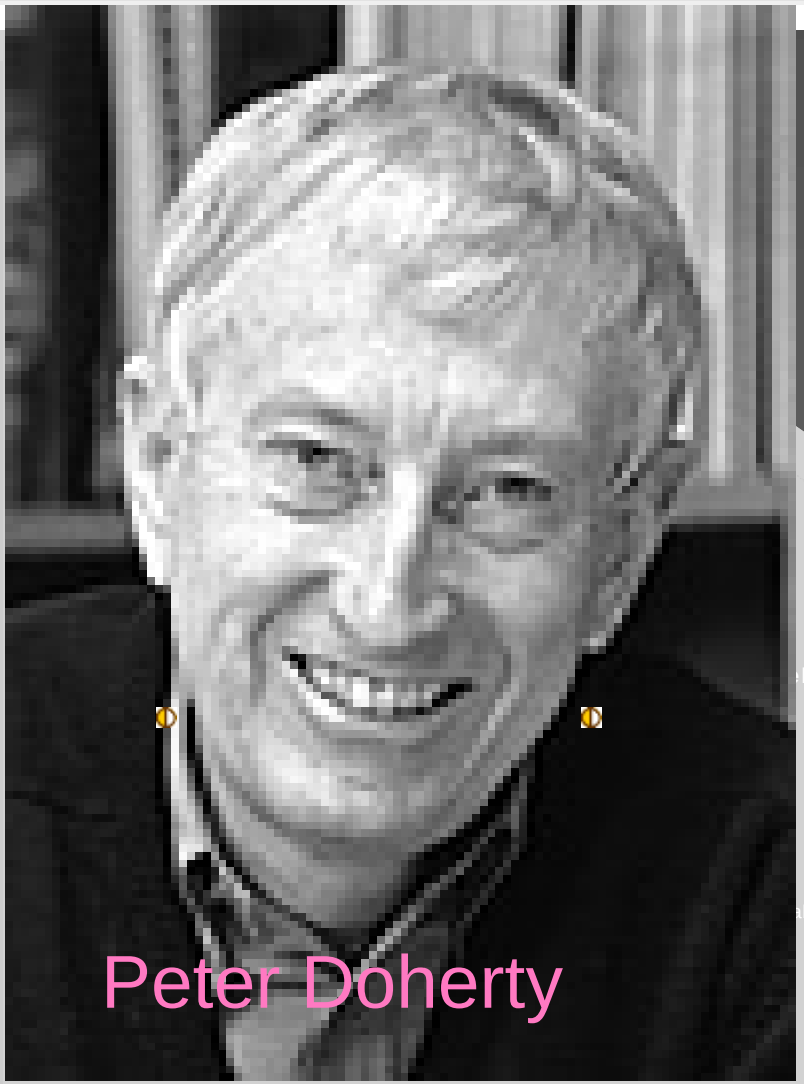


Figure 1. Location and Organization of the HLA Complex on Chromosome 6.

The complex is conventionally divided into three regions: I, II, and III. Each region contains numerous loci (genes), only some of which are shown. Of the class I and II genes, only the expressed genes are depicted. Class III genes are not related to class I and class II genes structurally or functionally. *BF* denotes complement factor B; *C2* complement component 2; *C21B* cytochrome P-450, subfamily XXI; *C4A* and *C4B* complement components 4A and 4B, respectively; *HFE* hemochromatosis; *HSP* heat-shock protein; *LMP* large multifunctional protease; *LTA* and *LTB* lymphotoxins A and B, respectively; *MICA* and *MICB* major-histocompatibility-complex class I chain genes A and B, respectively; *P450* cytochrome P-450; *PSMB8* and *9* proteasome β 8 and 9, respectively; *TAP1* and *TAP2* transporter associated with antigen processing 1 and 2, respectively; *TAPBP* TAP-binding protein (tapasin); TNF-α tumor necrosis factor α; and *HSPA1A, HSPA1B,* and *HSPA1L* heat-shock protein 1A A-type, heat-shock protein 1A B-type, and heat-shock protein 1A–like, respectively.

NOBEL e-MUSEUM

LAUREATES ARTICLES EDUCATIONAL



Peter Doherty

Rolf Zinkernagel

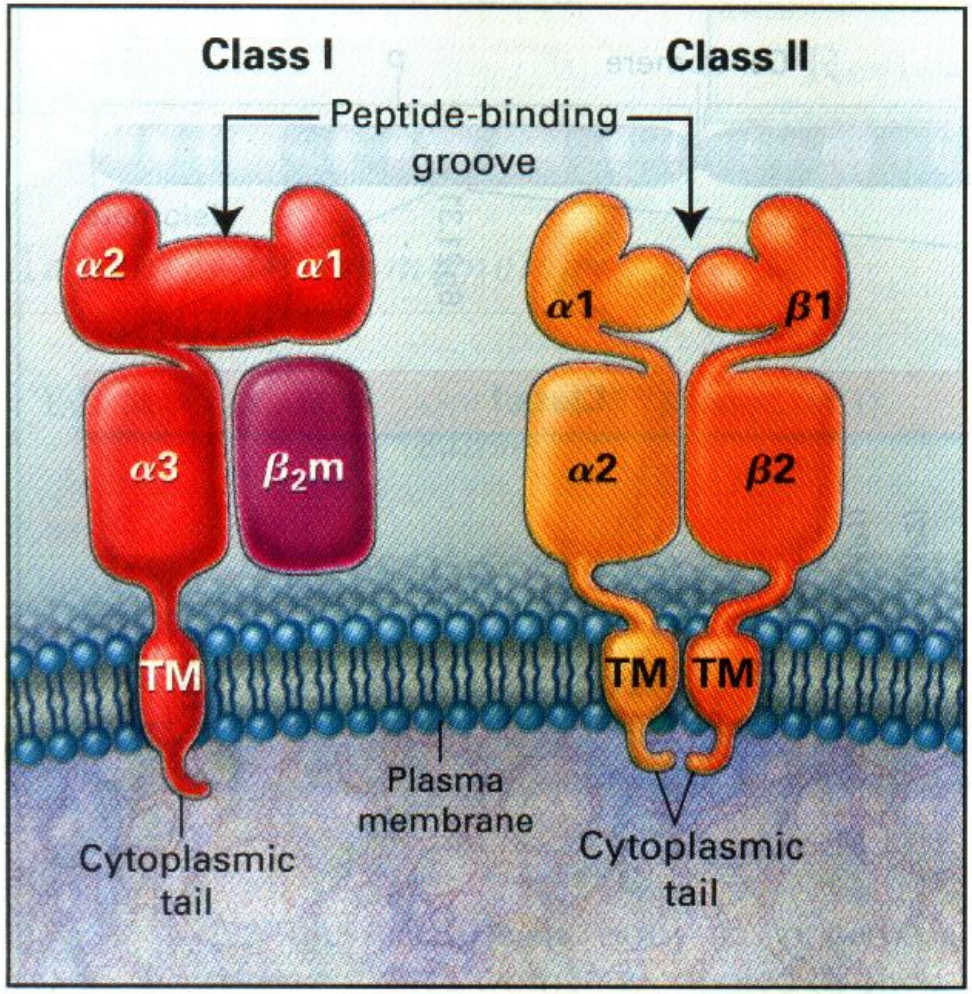


Figure 2. Structure of HLA Class I and Class II Molecules.

Beta$_2$-microglobulin (β_2m) is the light chain of the class I molecule. The α chain of the class I molecule has two peptide-binding domains (α1 and α2), an immunoglobulin-like domain (α3), the transmembrane region (TM), and the cytoplasmic tail. Each of the class II α and β chains has four domains: the peptide-binding domain (α1 or β1), the immunoglobulin-like domain (α2 or β2), the transmembrane region, and the cytoplasmic tail.

Assembly of endogenous peptides with MHC class I antigens

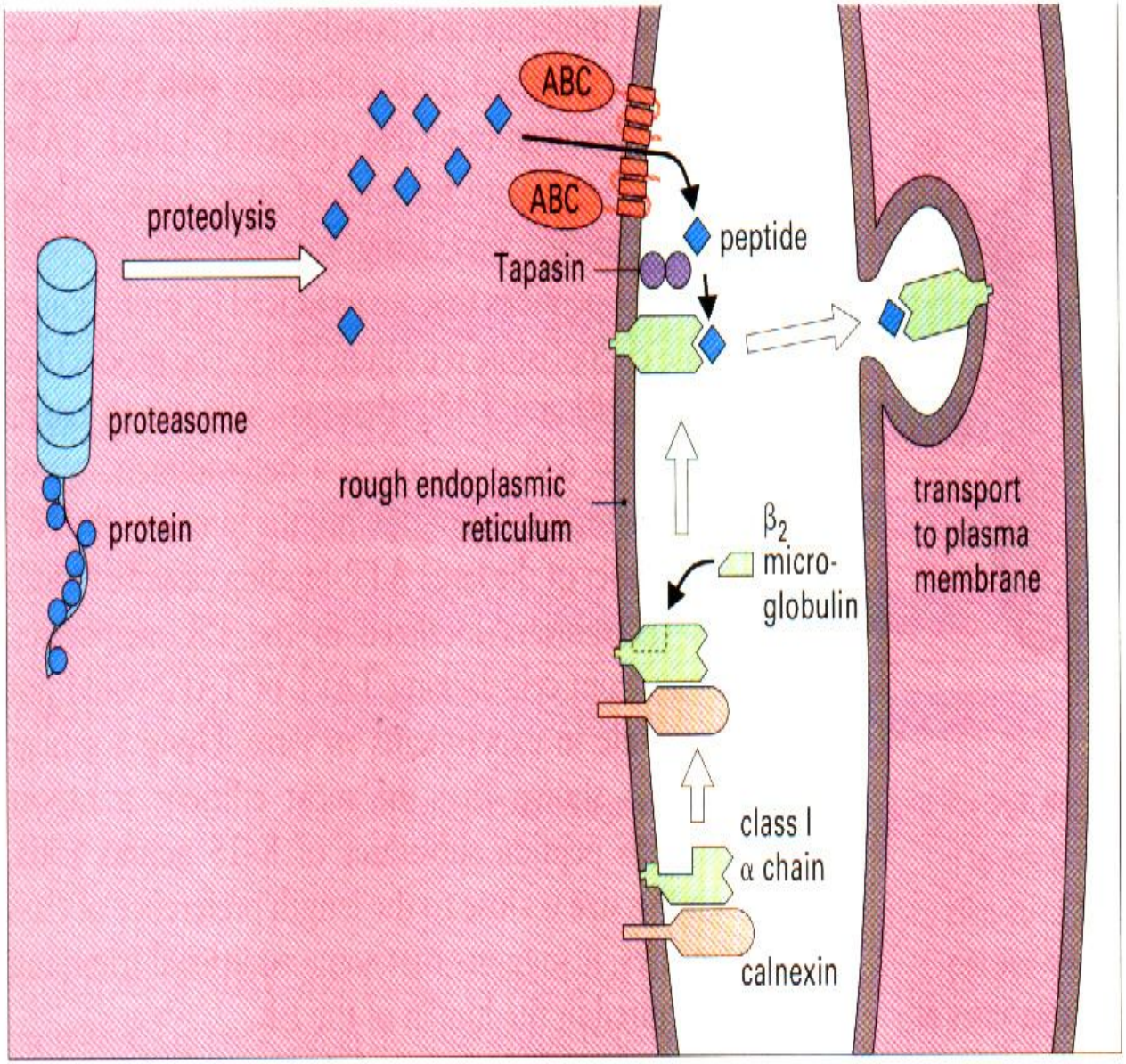


Fig. 6.10 Proposed assembly pathway of antigen–MHC complex. Cytoplasmic antigens are processed by proteasomes. Peptides are transported by two members of the 'ABC' superfamily of transporters, also encoded within the MHC (TAP1 and TAP2). Antigenic peptides associate with class I heavy chains and β_2-microglobulin (β_2m) in the ER. Molecular chaperones, such as calnexin, associate with partially assembled class I complexes. The Ig-superfamily molecule Tapasin forms a bridge between TAP and the class I molecule waiting to be loaded with peptide. Fully assembled class I molecules are then transported to the cell surface.

Proposed routes of intracellular trafficking of MHC molecules involved in antigen presentation

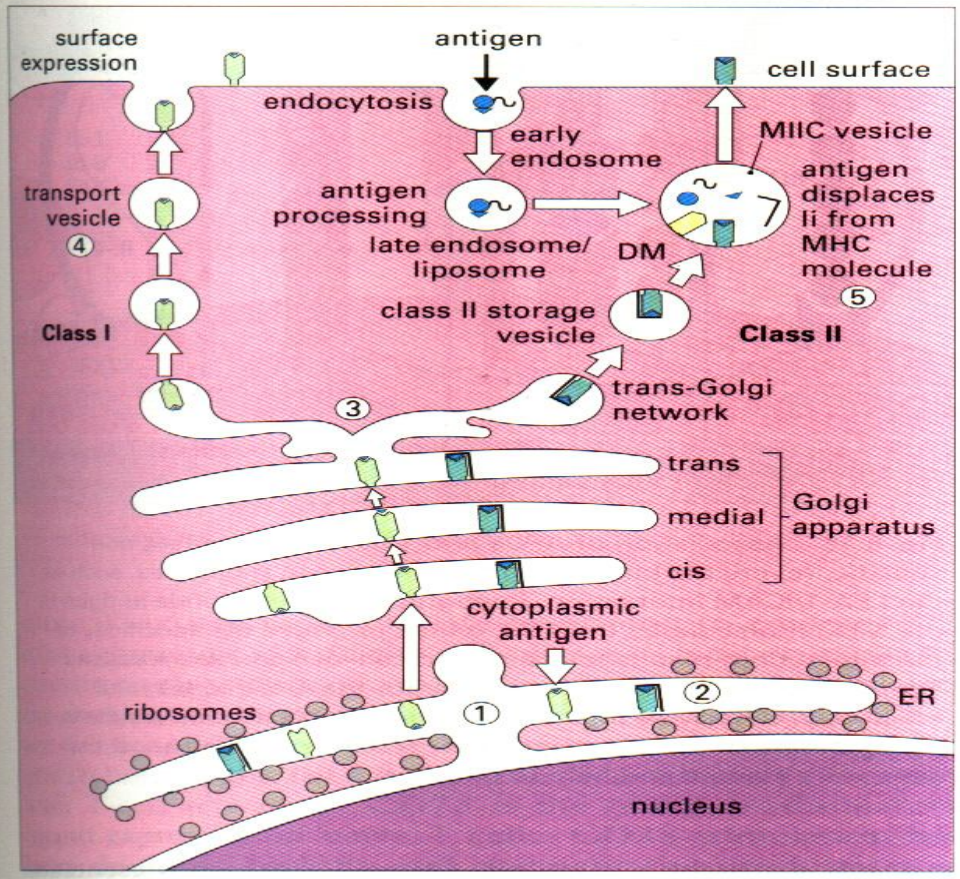


Fig. 6.12 Newly synthesized class I molecules are loaded with peptide (**1**). Class II molecules associate with Ii in the ER (**2**). Ii prevents loading with peptide and contains sequences that enable the class II molecule to exit from the rough endoplasmic reticulum (RER). Class I and class II molecules segregate after transit through the Golgi (**3**). Class I molecules go directly to the cell surface (**4**). Class II molecules enter an acidic compartment called MIIC, where they are loaded with peptide derived from exogenous antigen, and the CLIP peptide that occupies the binding groove dissociates (**5**).

T CELL RECEPTOR

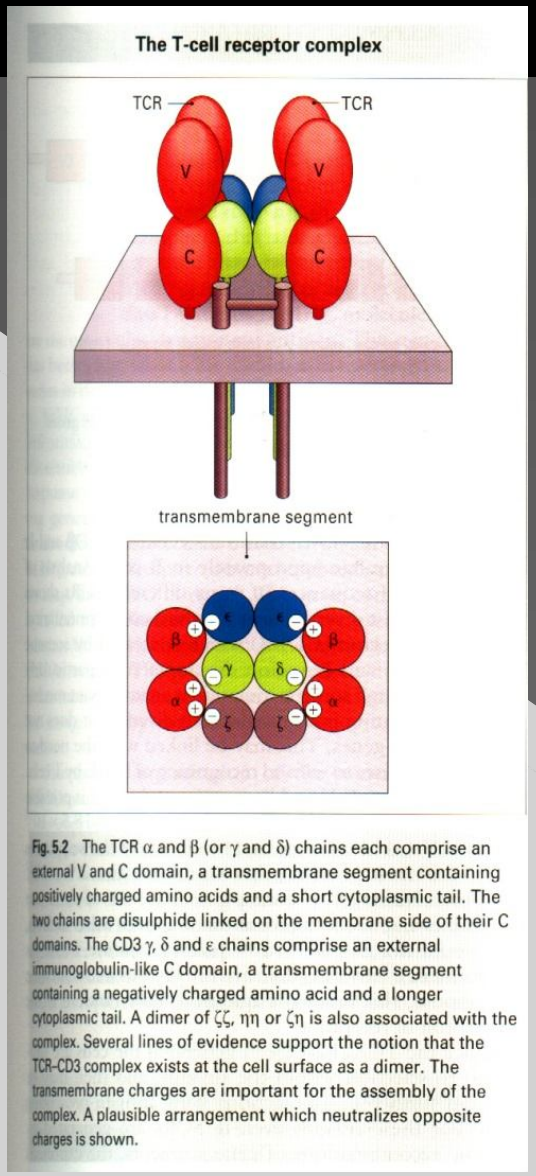
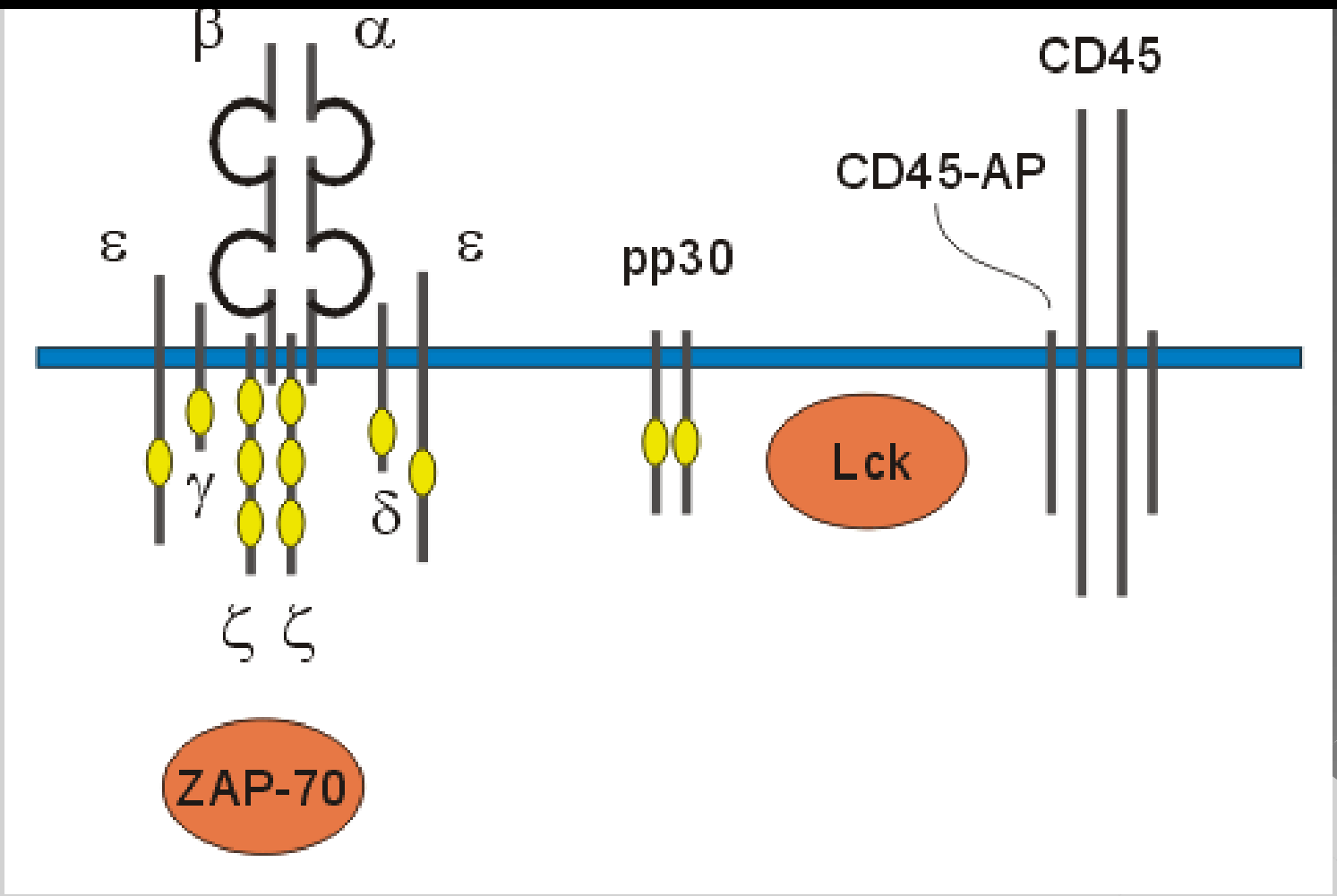


Fig. 5.2 The TCR α and β (or γ and δ) chains each comprise an external V and C domain, a transmembrane segment containing positively charged amino acids and a short cytoplasmic tail. The two chains are disulphide linked on the membrane side of their C domains. The CD3 γ, δ and ε chains comprise an external immunoglobulin-like C domain, a transmembrane segment containing a negatively charged amino acid and a longer cytoplasmic tail. A dimer of ζζ, ηη or ζη is also associated with the complex. Several lines of evidence support the notion that the TCR–CD3 complex exists at the cell surface as a dimer. The transmembrane charges are important for the assembly of the complex. A plausible arrangement which neutralizes opposite charges is shown.

T cell receptor



The role of CD4 and CD8 in T-cell activation

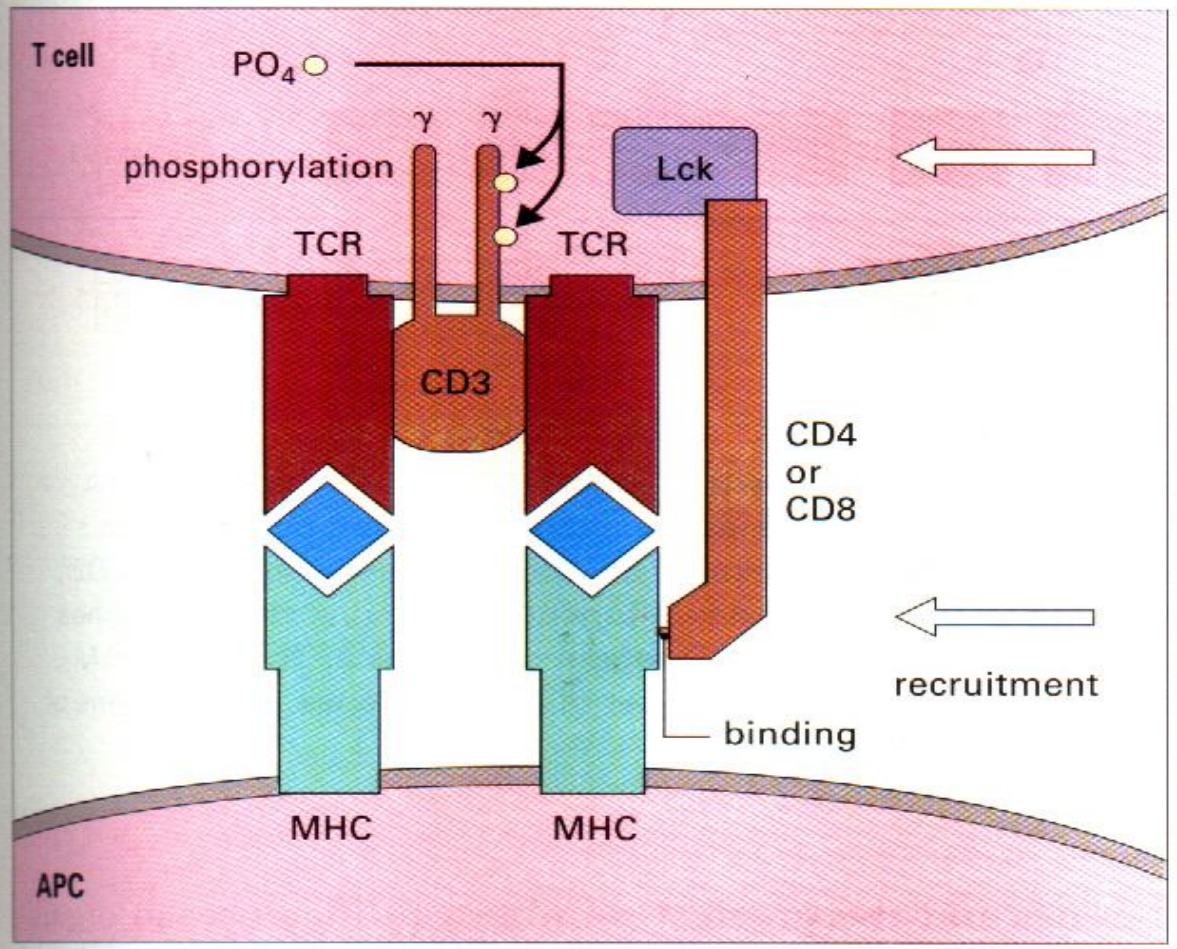


Fig. 5.14 After aggregation of MHC–peptide on the antigen-presenting cell with the T-cell's receptor, either CD4 or CD8 can join the complex. CD4 binds to MHC class II molecules and CD8 to class I. The kinase lck is attached to the intracytoplasmic portion of CD4 or CD8. Binding of these molecules to specific sites in the MHC brings the kinase into proximity with the ITAMs on the CD3 ζζ dimer. The kinase phosphorylates the motifs, as the first step in T-cell activation.

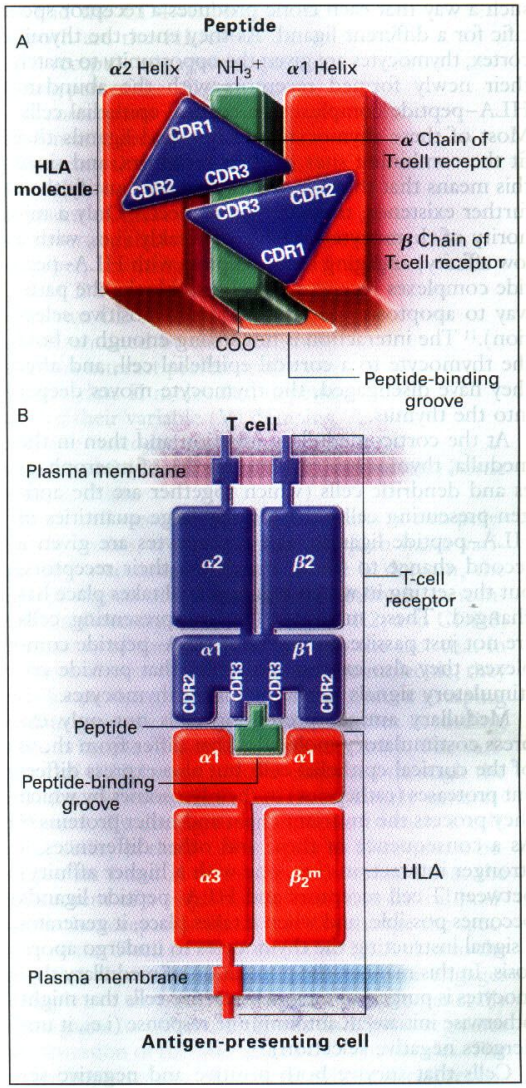


Figure 6. Interactions between a T-Cell Receptor and the HLA–Peptide Complex.

Panel A shows the diagonal orientation of the T-cell receptor on the surface of the HLA–peptide complex. Panel B shows the bridge between a T cell and the antigen-presenting cell created by the interaction between the T-cell receptor and the HLA–peptide complex. Complementarity-determining region 1 of the α and β chains of the T-cell receptor is not visible in this depiction because one is positioned behind and the other in front of the part shown. Beta$_2$-microglobulin (β_2m) is the light chain of the class I molecule. The three complementarity-determining regions (CDR1, CDR2, and CDR3) are shown.

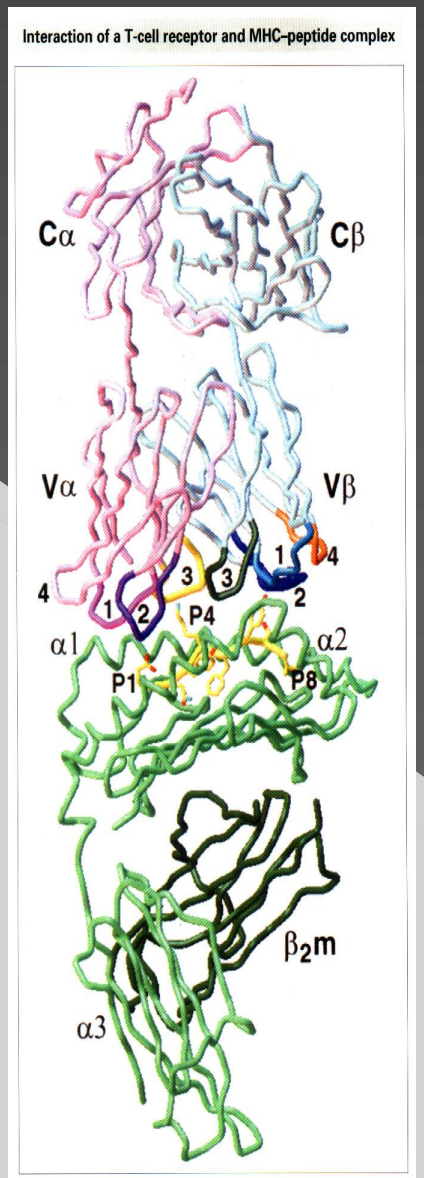
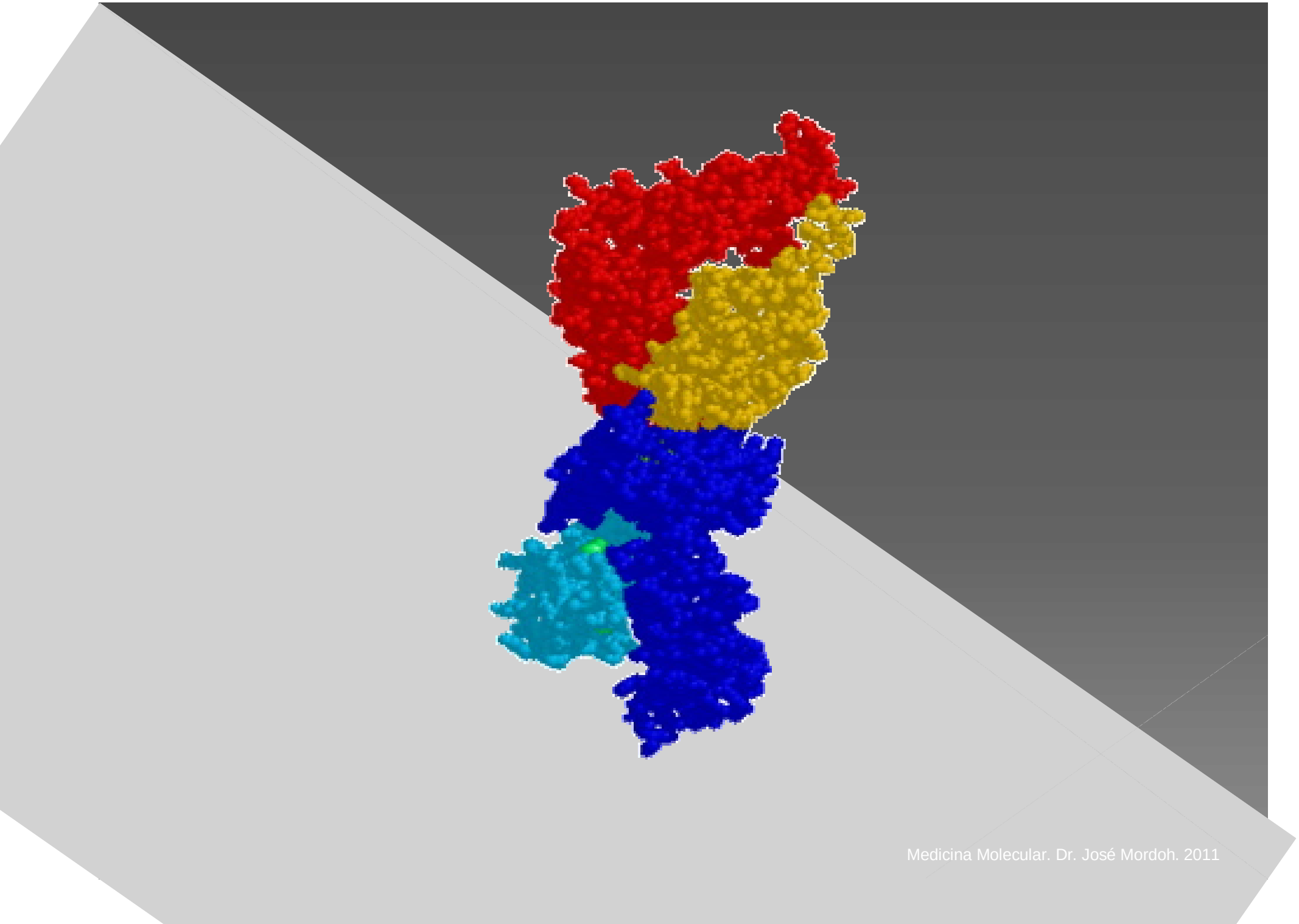
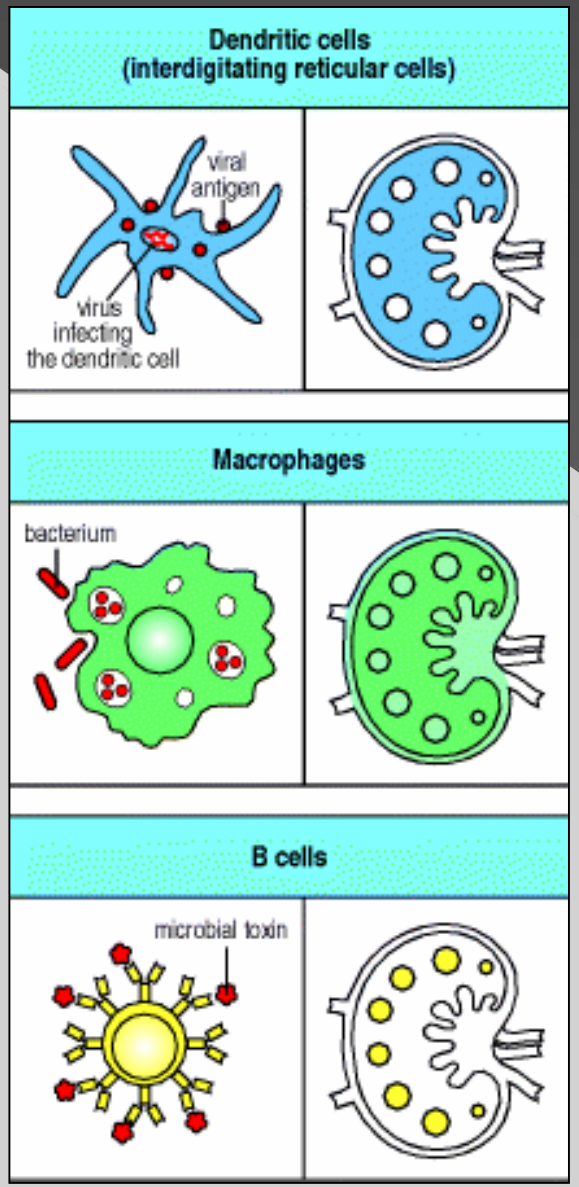


Fig. 5.13 The structure of an MHC class I molecule (H–2K^b), complexed to an octapeptide (yellow tube) is shown bound to an αβ TCR. The six CDRs which contact the peptide (1, 2, 3, 1, 2) are highlighted in deeper colours. Residues from αHV4 (pink) and βHV4 (orange) are not positioned to take part in the intermolecular interactions. (Illustration was kindly provided by Dr Christopher Garcia, and is reproduced with permission: *Science* 1996;**274**:209–19.)



Captación por CPA



TOLL-LIKE RECEPTORS

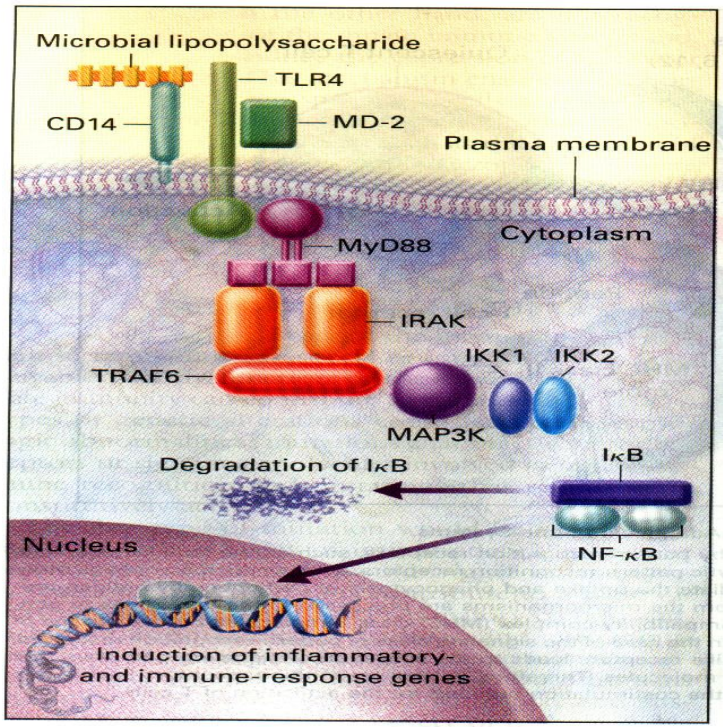
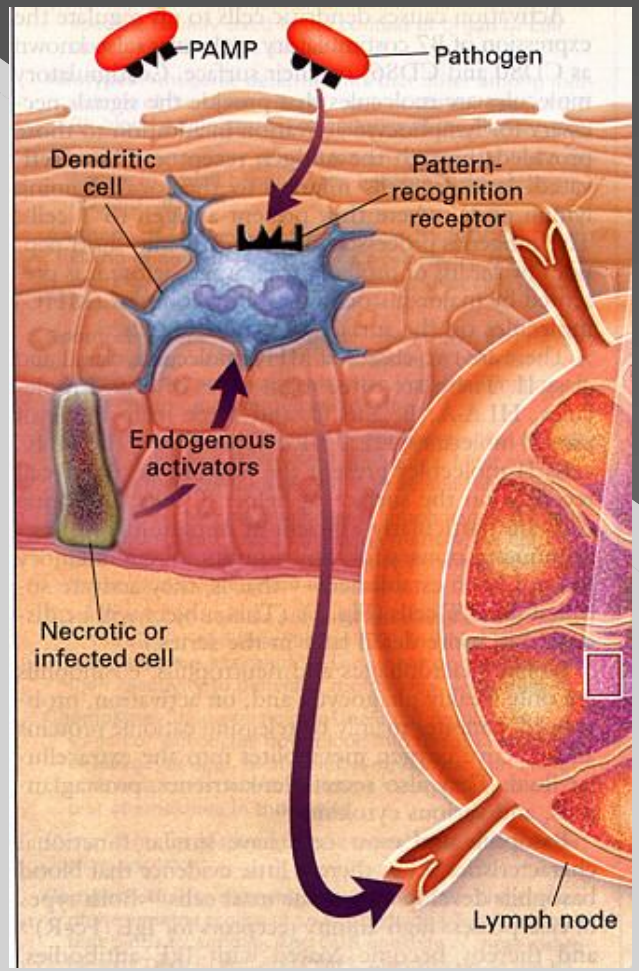


Figure 2. The Signaling Pathway of Toll-like Receptors.
Some of the toll-like receptors (TLRs) function as pattern-recognition receptors of the innate immune system. Their recognition of microbial products leads to the activation of the nuclear factor-κB (NF-κB) signaling pathway. In this example, the recognition of lipopolysaccharide is mediated by three different gene products: CD14, toll-like receptor 4 (TLR4), and MD-2. The binding of lipopolysaccharide to CD14 presumably leads to the association of CD14 with the TLR4–MD-2 complex and is thought to induce the dimerization of TLR4. Once TLR4 is activated, it recruits the adapter protein MyD88, which is associated with the serine–threonine protein kinase interleukin-1 receptor–associated kinase (IRAK). IRAK is then phosphorylated and associated with the tumor necrosis factor–associated factor 6 (TRAF-6) adapter protein. Oligomerization of TRAF-6 is thought to activate a member of the mitogen-activated protein kinase kinase kinase (MAP3K) family, which directly or indirectly leads to the activation of IκB kinase 1 (IKK1) and IκB kinase 2 (IKK2). These kinases phosphorylate IκB on serine residues, thus targeting IκB for degradation and releasing NF-κB, which moves into the nucleus and induces the transcriptional activation of a wide variety of inflammatory- and immune-response genes.

ACTIVACION CELULAS DENDRITICAS



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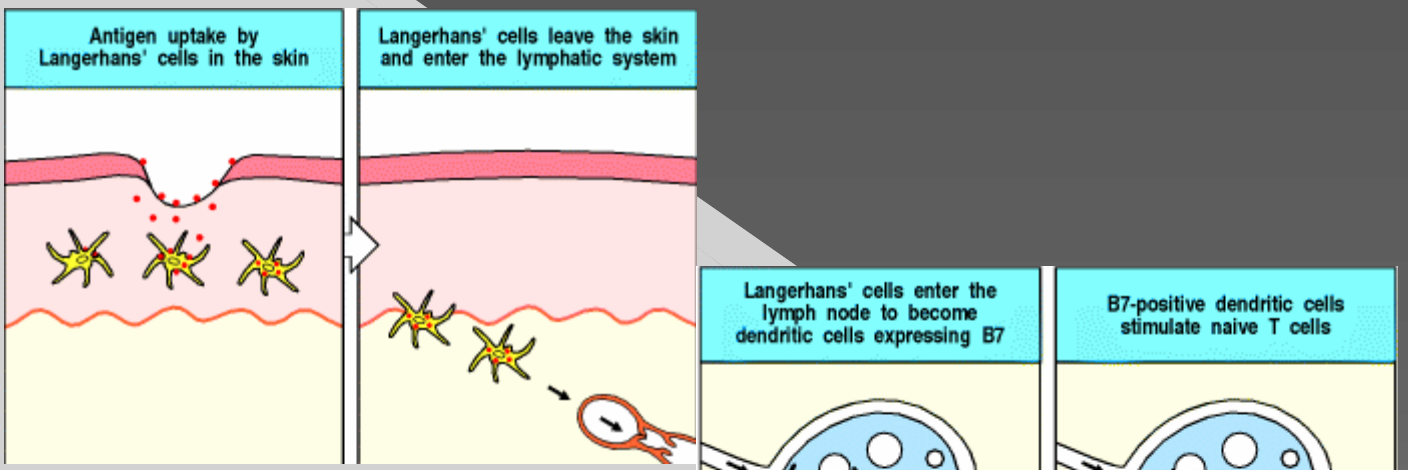
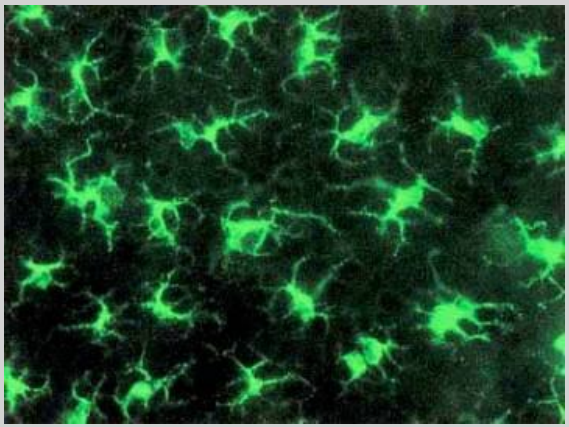
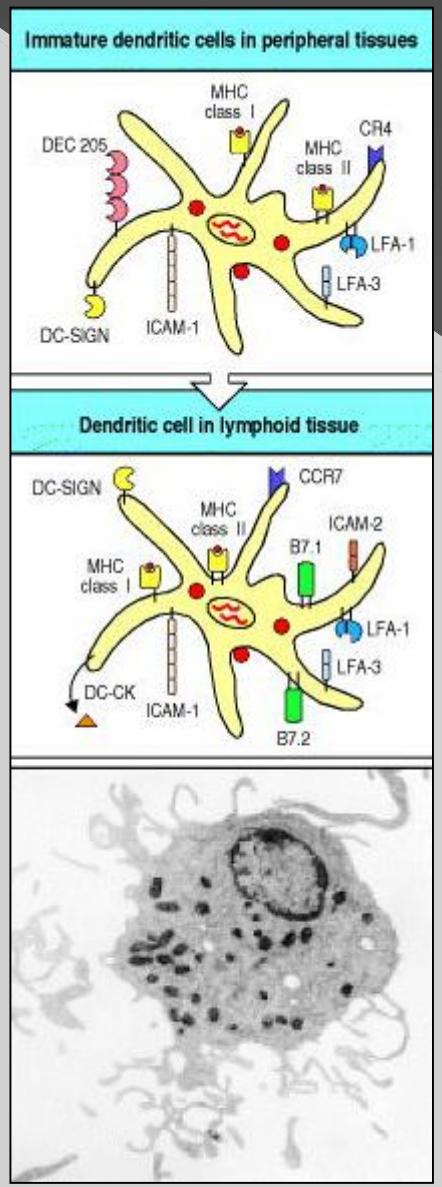
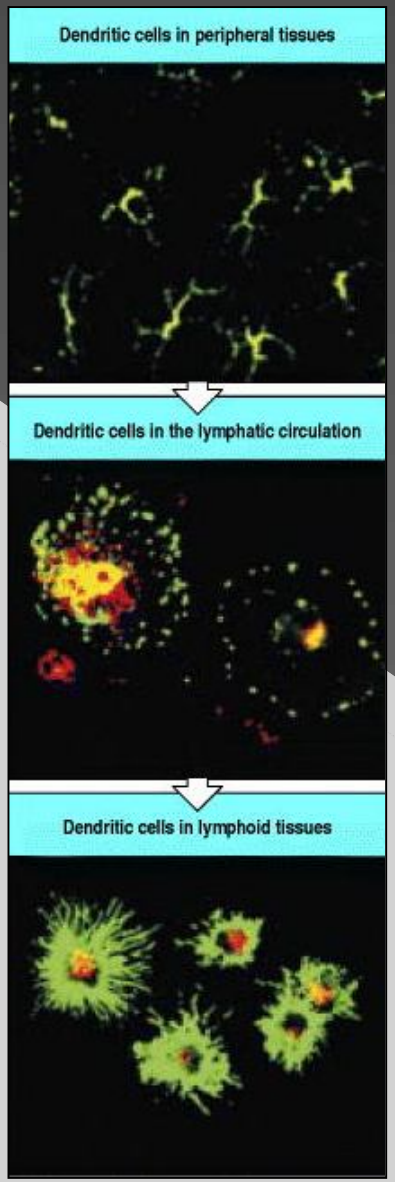
Migración de DC de tejidos periféricos a ganglios linfáticos









Maduración de DC

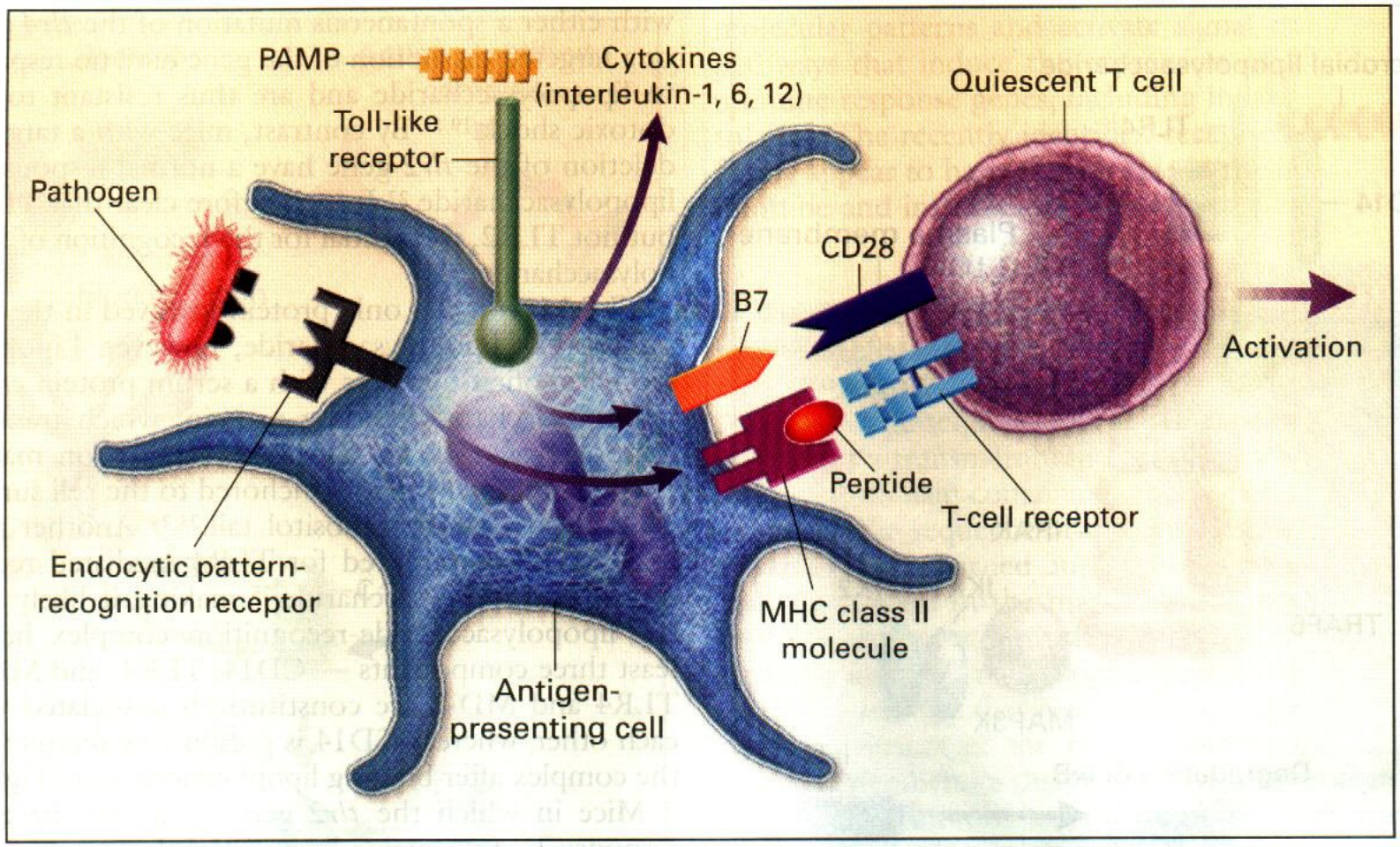
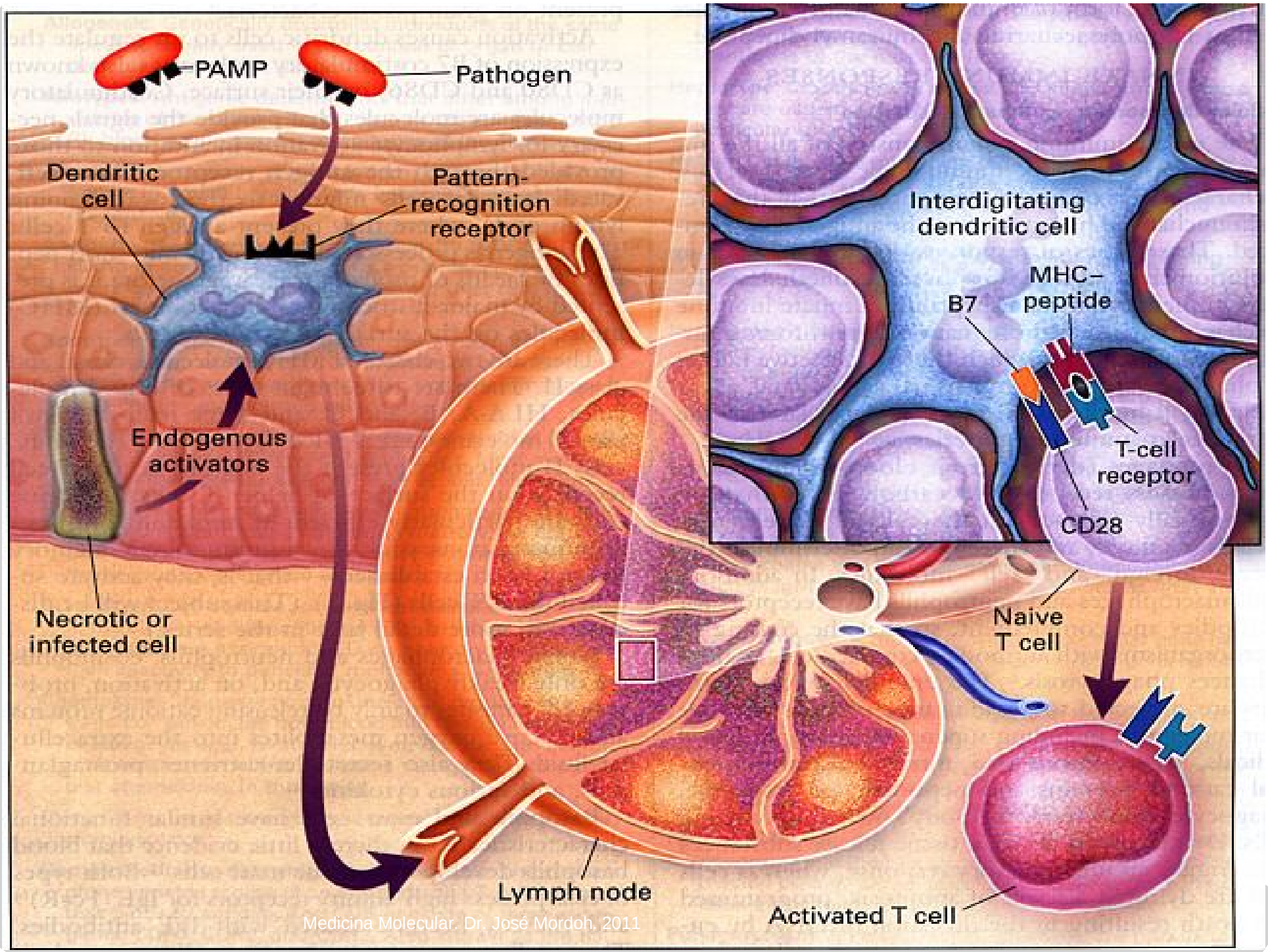
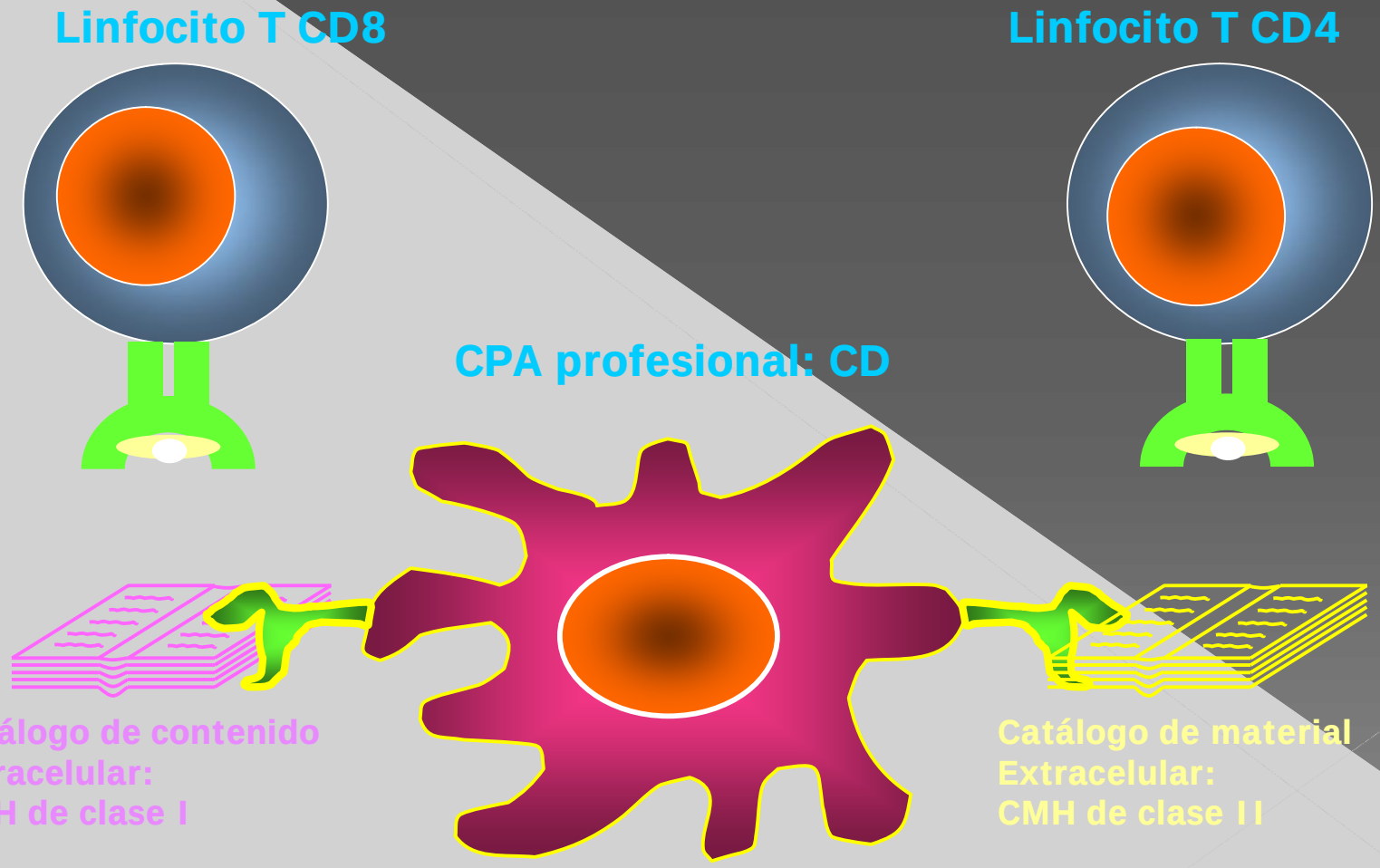


Figure 3. The Receptors Involved in the Interplay of the Innate and Adaptive Immune Systems.

Recognition of the pathogen-associated molecular pattern (PAMP) by pattern-recognition receptors, such as the toll-like receptors, generates signals that activate the adaptive immune system. Endocytic pattern-recognition receptors, such as the macrophage mannose receptor, bind to components of microbial cell walls and mediate the uptake and phagocytosis of pathogens by antigen-presenting cells (macrophages and dendritic cells). Proteins derived from the microorganisms are processed in the lysosomes to generate antigenic peptides, which form a complex with major-histocompatibility-complex (MHC) class II molecules on the surface of the macrophage. These peptides are recognized by T-cell receptors. In the case of the signaling class of pattern-recognition receptors, the recognition of pathogen-associated molecular patterns by toll-like receptors leads to the activation of signaling pathways that induce the expression of cytokines, chemokines, and costimulatory molecules. Therefore, pattern-recognition receptors have a role in the generation of both the peptide–MHC-molecule complex and the costimulation required for the activation of T cells.


PAMP
Pathogen
Dendritic cell
Pattern-recognition receptor
Endogenous activators
Necrotic or infected cell
Interdigitating dendritic cell
MHC–peptide
B7
T-cell receptor
CD28
Naive T cell
Lymph node
Activated T cell

Moléculas del CMH como muestreo



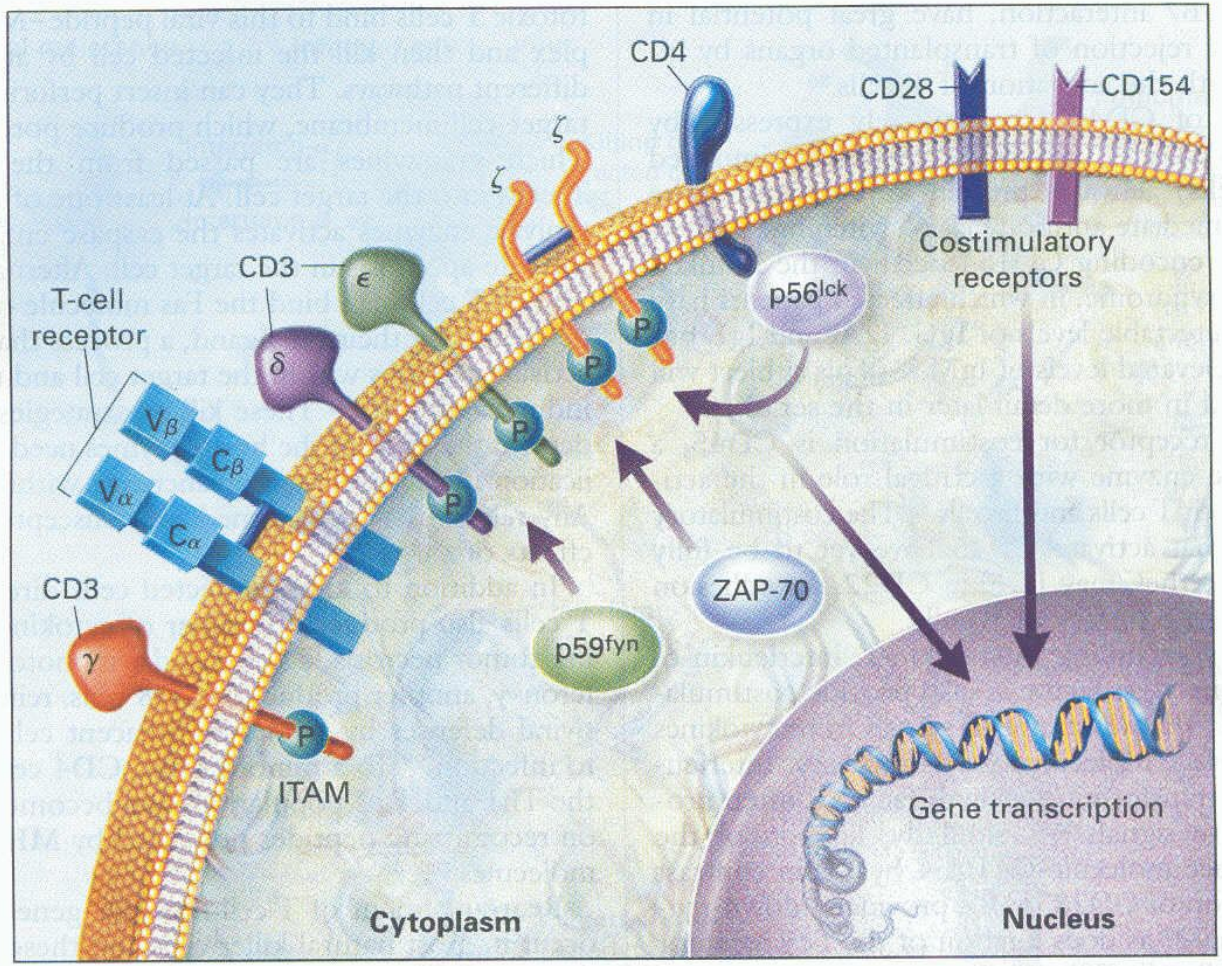
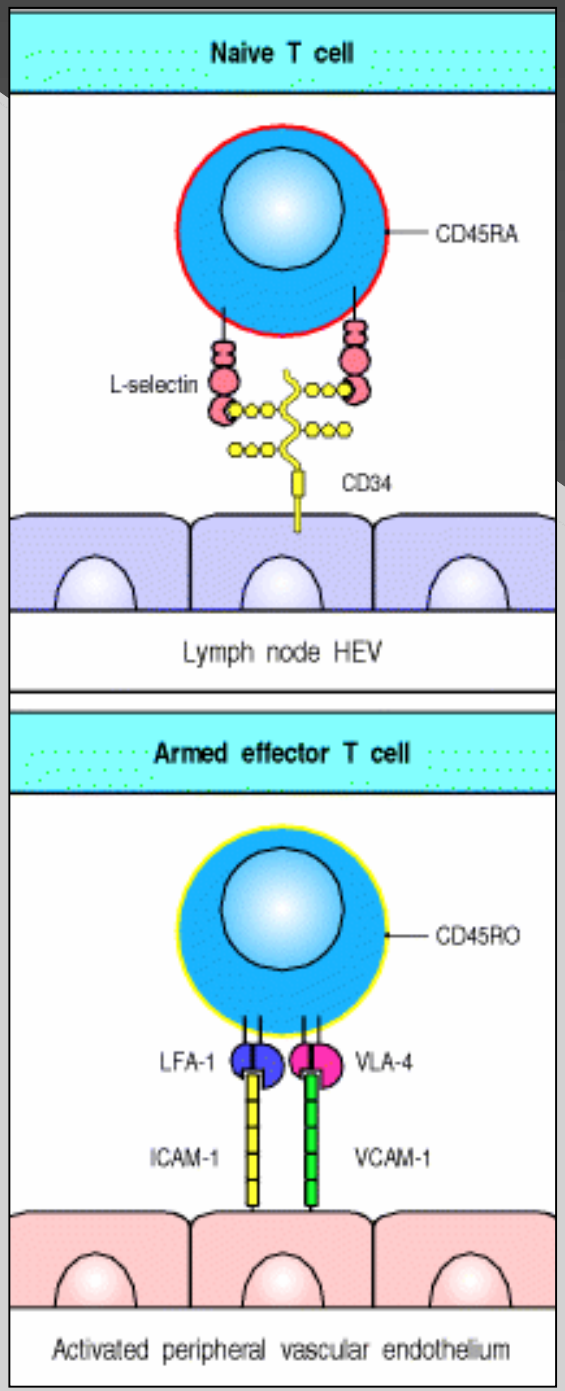


Figure 9. Activation of T Cells.

The activation of T cells involves a highly complex series of integrated events that result from the cross-linking of the antigen receptor on the cell surface. Because the antigen receptors have extremely short cytoplasmic tails, they are associated (in T cells) with the CD3 and ζ chain signal-transduction molecules bearing cytoplasmic immunoreceptor tyrosine-based activation motifs (ITAMs), which are subject to phosphorylation (P) by protein kinases such as $p56^{lck}$, $p59^{fyn}$, and ZAP-70 (for simplicity, only one of the CD3ε molecules is shown). The initial stages of activation also involve the binding of $p56^{lck}$ to the cytoplasmic tail of CD4 (in helper T cells) or CD8 (in cytotoxic T cells). These events lead to downstream signaling involving a number of different biochemical pathways and ultimately to the transcriptional activation of genes involved in cellular proliferation and differentiation. Signals from costimulatory receptors such as CD28 and CD154 must also be present in order to activate the lymphocyte; in the event that signals are sent only from the antigen-receptor signal-transducing molecules, anergy or apoptosis will occur.



Diferencias fenotípicas entre un linfocito vírgen y uno efector

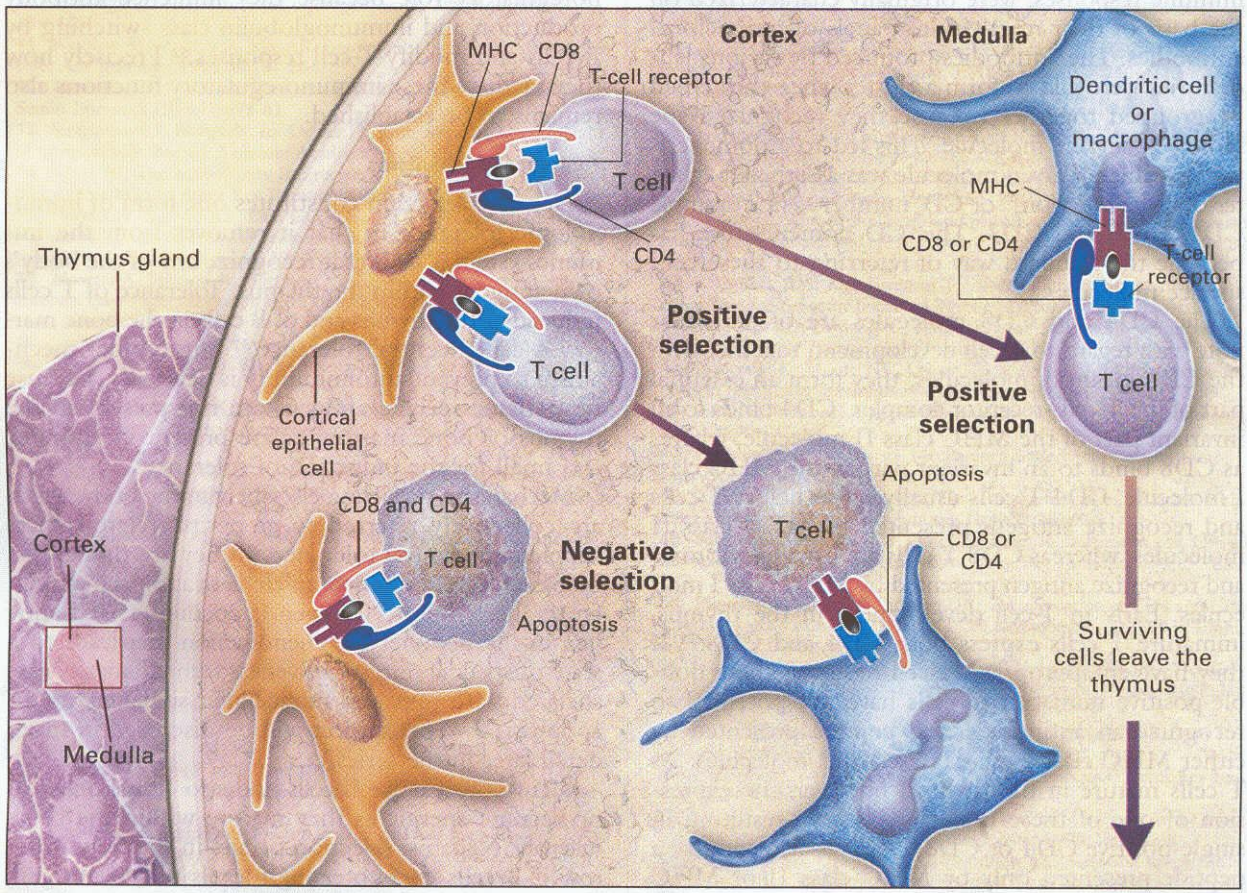


Figure 7. Positive and Negative Selection in the Thymus.

T cells need to detect foreign antigens presented by self major-histocompatibility-complex (MHC) molecules. Part of the T-cell receptor recognizes the foreign peptide, and part of it recognizes the self MHC molecule. The random nature of T-cell–receptor gene rearrangements means that only a minority of T cells are capable of performing this task. Many of the immature CD4 and CD8 double-positive T cells are useless because their T-cell receptors do not recognize self MHC molecules at all. These T cells eventually undergo apoptosis. Cells whose T-cell receptors have various affinities for binding self MHC molecules (usually containing a self peptide) are positively selected on cortical epithelial cells. However, many of these cells are potentially harmful because their T-cell receptors have a high affinity for a complex of self peptide and a self MHC molecule (or even an MHC molecule alone). These autoimmune T cells are eliminated by the induction of apoptosis when they interact with dendritic cells and macrophages in the thymic medulla (negative selection). This leaves T cells with only a weak affinity for self MHC molecules. These cells form the pool of T cells that are exported from the thymus as single-positive (CD4 or CD8) cells. In the periphery they have the potential to recognize a complex of foreign peptide plus self MHC molecules and to become activated if the affinity of the interaction exceeds a certain threshold.

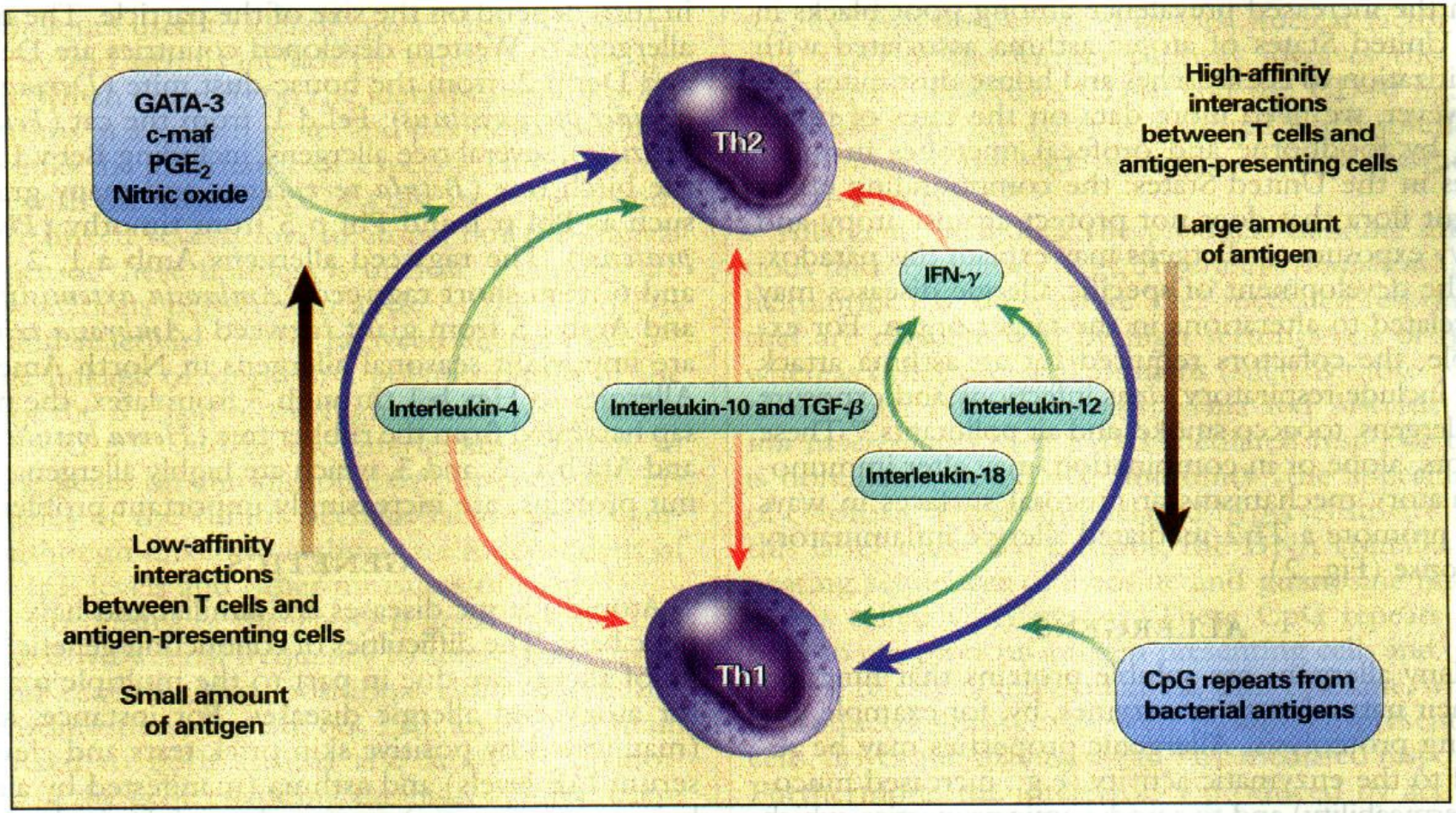
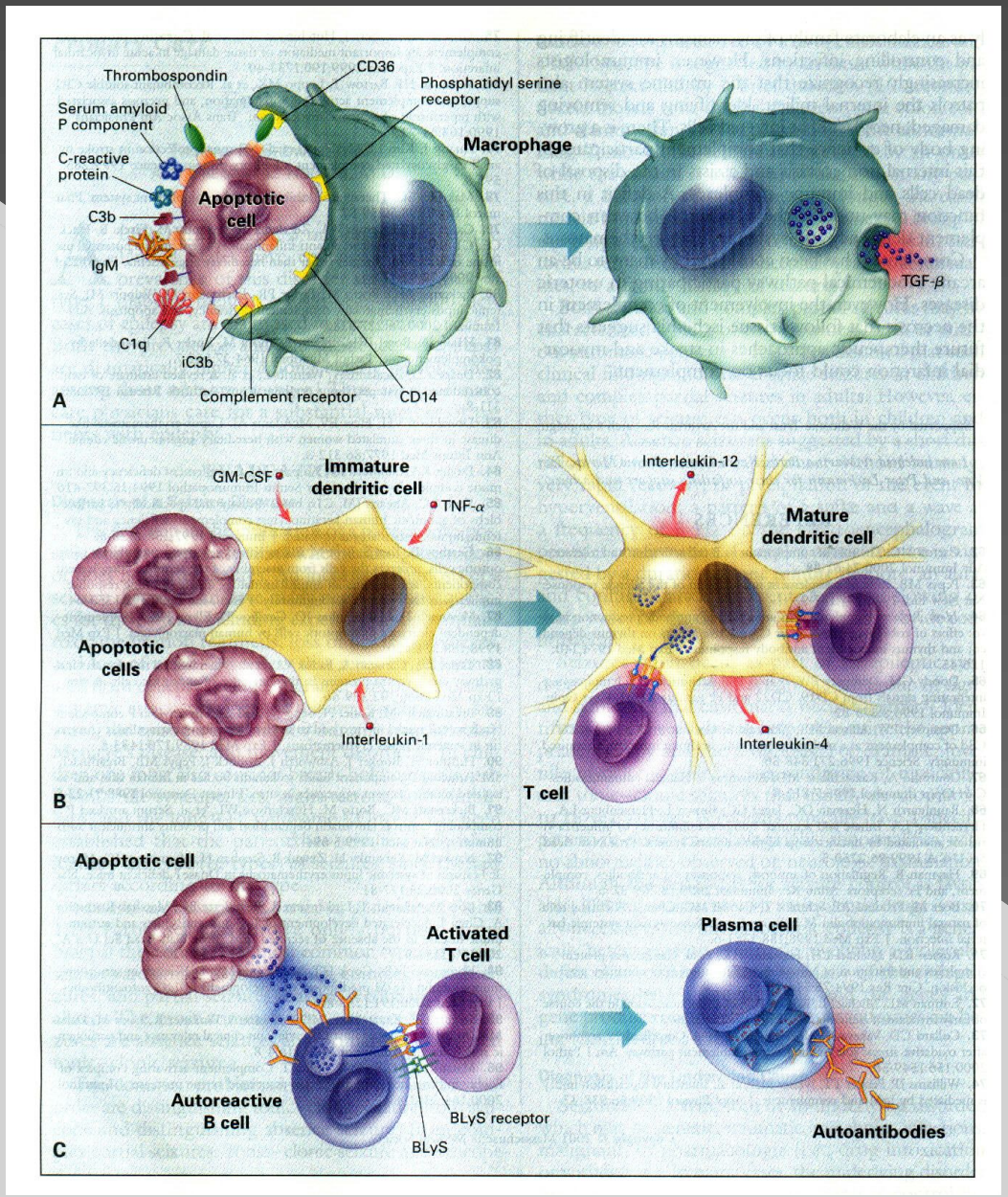


Figure 1. Immunologic and Cellular Factors Regulating the Expression of Th1 and Th2 Cells.

Whether the immune response is dominated by Th1 or Th2 cells is dependent on interleukin-12 and interleukin-4, respectively, as well as on the avidity of interactions between T cells and antigen-presenting cells and the amount of allergen to which the immune system is exposed (antigen).[13,14] In addition, the presence of cytidine–phosphate–guanosine (CpG) repeats derived from bacteria favors the Th1 phenotype, whereas the presence of transcription factors such as GATA-3 favors the Th2 phenotype,[15] as does the presence of c-maf and prostaglandin E_2 (PGE_2). Nitric oxide favors the expression of Th2 cells by being less inhibitory to Th2 cells than Th1 cells, whereas in humans interleukin-10 and transforming growth factor β (TGF-β) generally dampen the responses of both types of cells. Interferon-γ (IFN-γ) inhibits Th2-mediated responses; both interleukin-12 and interleukin-18 release interferon-γ from T cells. Interleukin-4 inhibits the expression of Th1 cells and promotes Th2-mediated responses. Green arrows indicate stimulatory effects, and red arrows inhibitory effects, of the cytokines.


Thrombospondin
Serum amyloid P component
C-reactive protein
C3b
IgM
C1q
iC3b
Apoptotic cell
CD36
Phosphatidyl serine receptor
Macrophage
Complement receptor
CD14
TGF-β
A
GM-CSF
Immature dendritic cell
TNF-α
Apoptotic cells
Interleukin-1
Interleukin-12
Mature dendritic cell
Interleukin-4
T cell
B
Apoptotic cell
Activated T cell
Autoreactive B cell
BLyS receptor
BLyS
Plasma cell
Autoantibodies
C

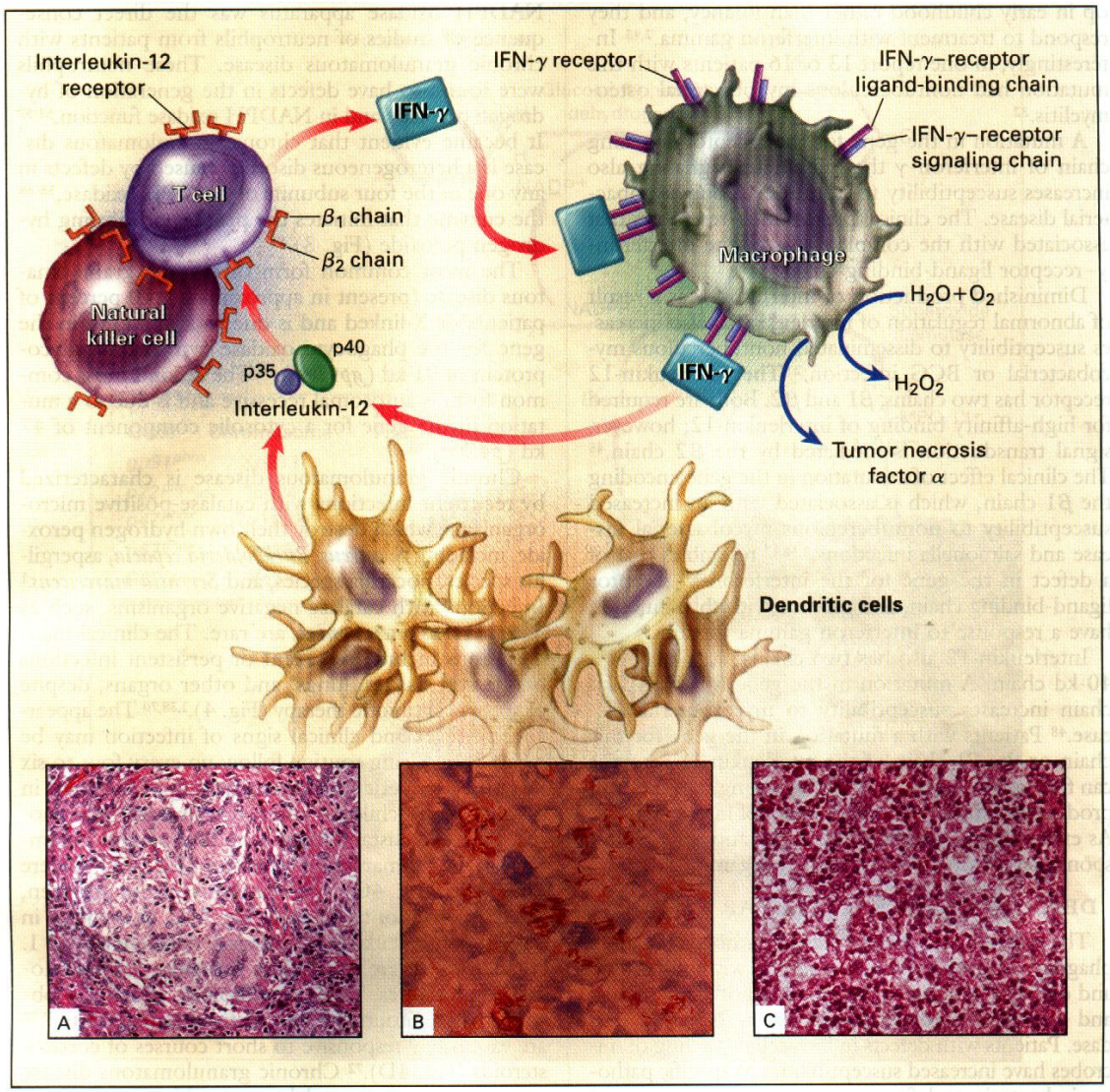


Figure 2. Interferon-γ–Interleukin-12 Signal-Transduction Cascade.

Interleukin-12, which is produced by macrophages and dendritic cells in response to the presence of a pathogen, binds to its receptors on T cells and natural killer cells, inducing the release of interferon-γ (IFN-γ). Monocytes and macrophages bind interferon-γ, resulting in the cross-linking of the interferon-γ receptor; activation of the cells, with the production of hydrogen peroxide (H_2O_2); and the synthesis and release of tumor necrosis factor α and interleukin-12 (dimer of subunits p35 and p40). Mutations resulting in increased susceptibility to nontuberculous mycobacteria have been identified in the genes for both ligand-binding chain and the signaling chain of the interferon-γ receptor, the β1 chain and the β2 chain of the interleukin-12 receptor (the β2 chain is the signal transducer), and the p40 subunit of interleukin-12. Panel A shows a resolving mycobacterial infection with normal granuloma formation in a lung-biopsy specimen from a patient with no known mutation in the interferon-γ–interleukin-12 axis (hematoxylin and eosin, ×20). Panel B shows a lung-biopsy specimen from a patient with an autosomal recessive mutation of the interferon-γ–receptor ligand-binding chain who was infected with nontuberculous mycobacteria (acid-fast Fite's stain, ×600). There are numerous mycobacteria (red) within macrophages (blue). Panel C shows a contiguous section of lung from the same patient in which there is no granuloma formation (hematoxylin and eosin, ×200).

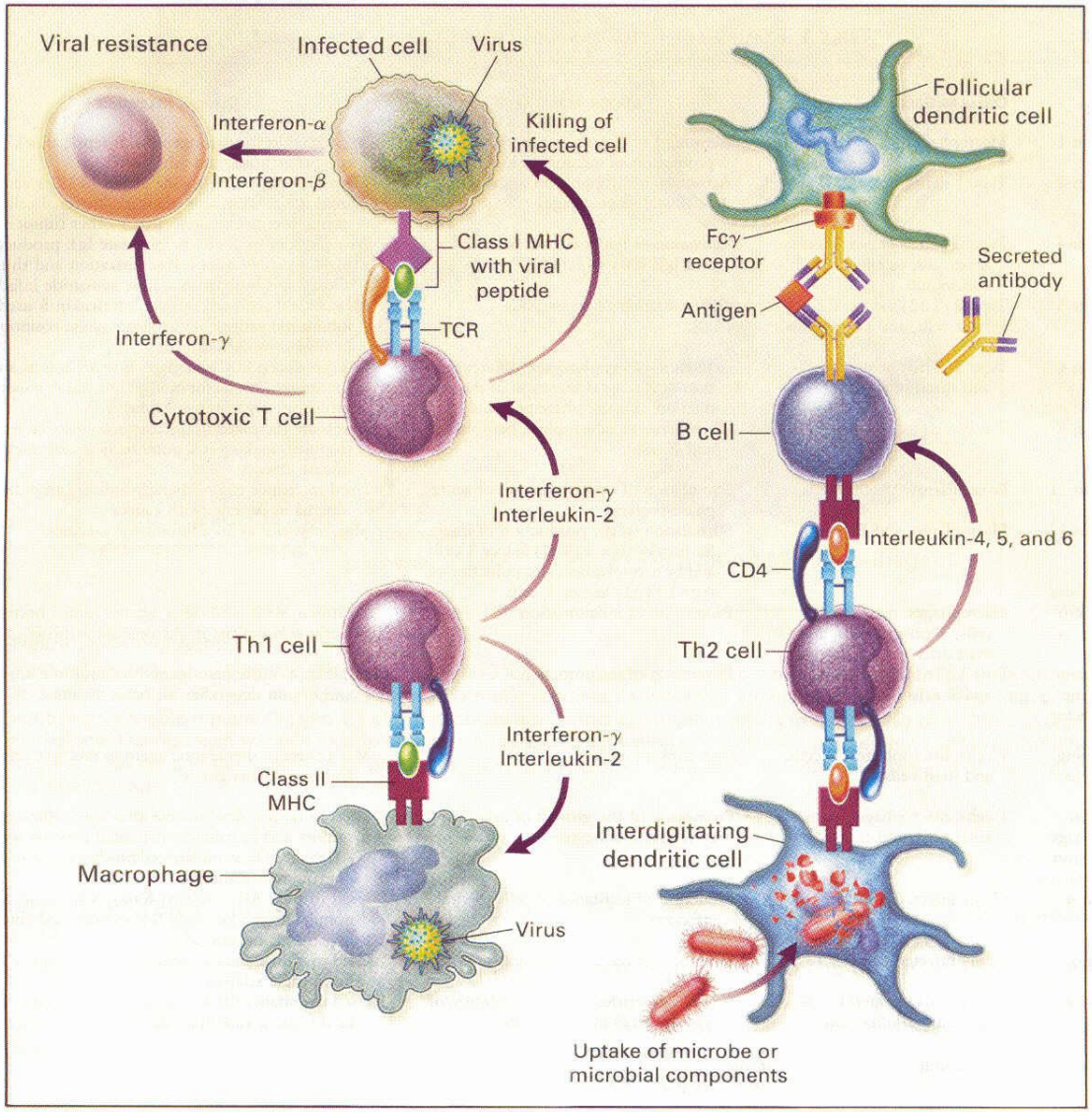
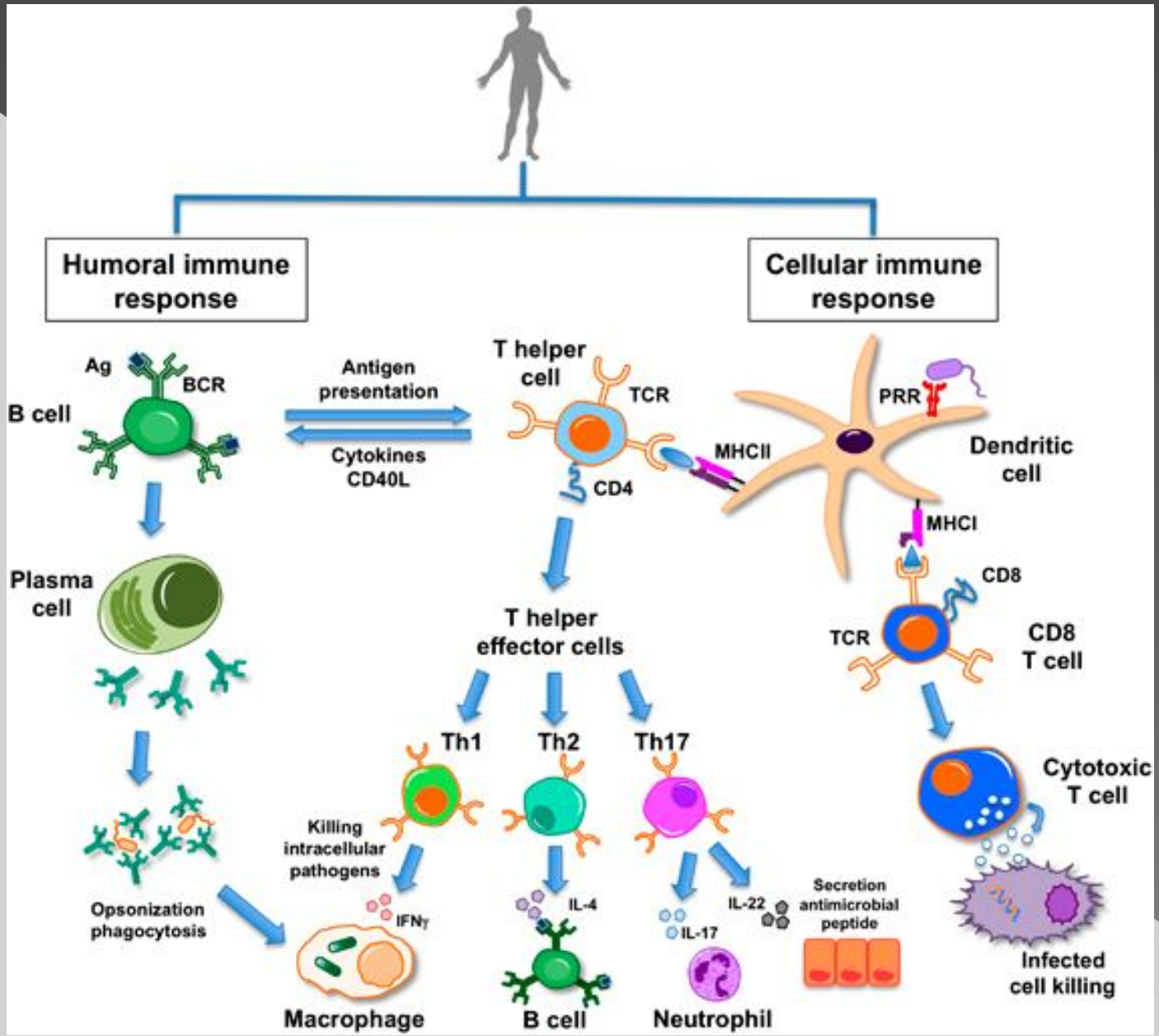


Figure 10. An Overview of Lymphocyte Responses.

T cells characteristically possess T-cell receptors (TCRs) that recognize processed antigen presented by major-histocompatibility-complex (MHC) molecules, as shown on the left-hand side of the figure. Most cytotoxic T cells are positive for CD8, recognize processed antigen presented by MHC class I molecules, and kill infected cells, thereby preventing viral replication. Activated cytotoxic T cells secrete interferon-γ that, together with interferon-α and interferon-β produced by the infected cells themselves, sets up a state of cellular resistance to viral infection. As shown on the right-hand side of the figure, helper T cells are generally positive for CD4, recognize processed antigen presented by MHC class II molecules, and can be divided into two major populations. Type 1 (Th1) helper T cells secrete interferon-γ and interleukin-2, which activate macrophages and cytotoxic T cells to kill intracellular organisms; type 2 (Th2) helper T cells secrete interleukin-4, 5, and 6, which help B cells secrete protective antibodies. B cells recognize antigen either directly or in the form of immune complexes on follicular dendritic cells in germinal centers.

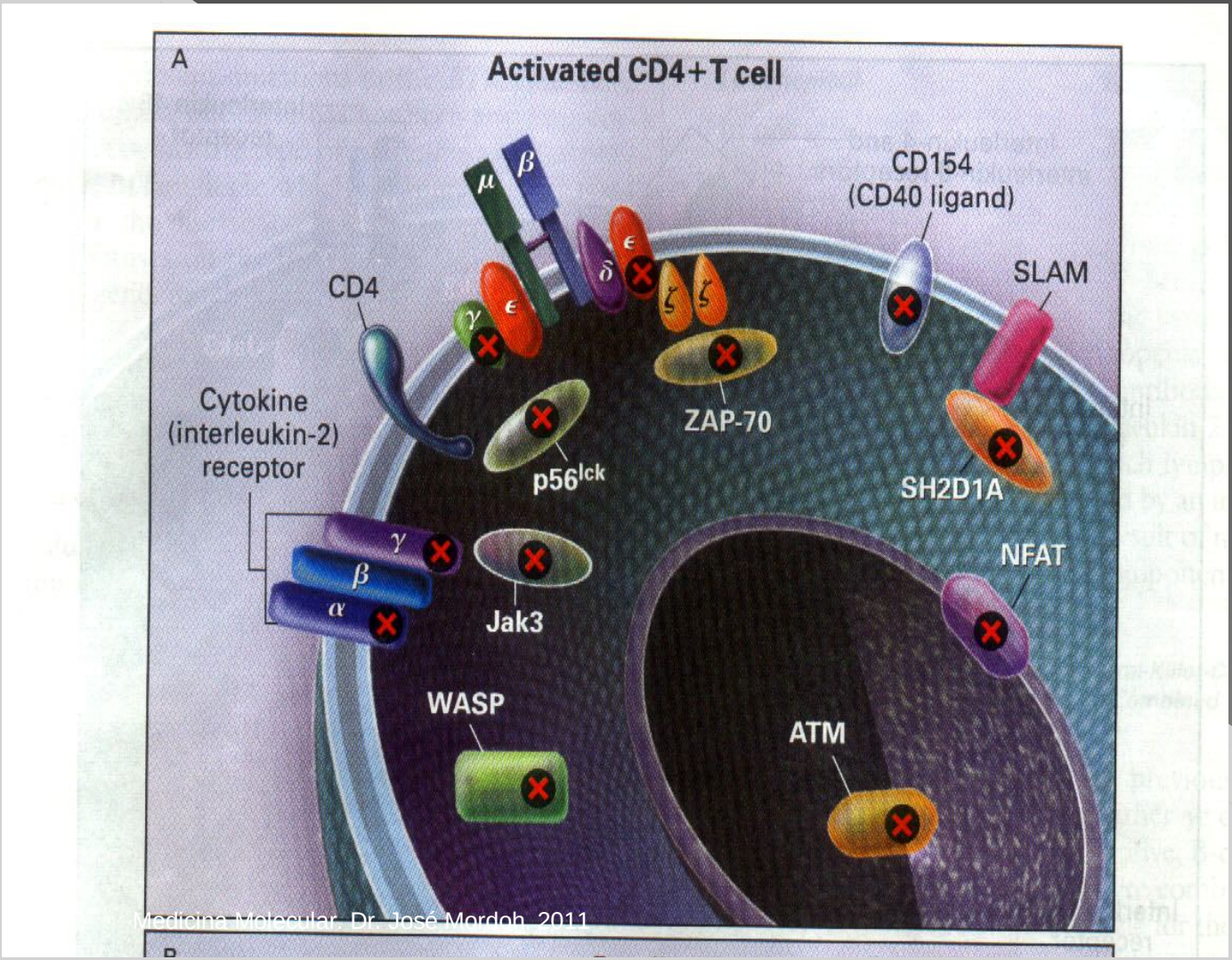
LINFOCITO CD4

LINFOCITO CD8



Alessandra Mortellaro and Paola Ricciardi-Castagnoli, Nature, 2011

LINFOCITO CD4 ACTIVADO



INMUNODEFICIENCIAS

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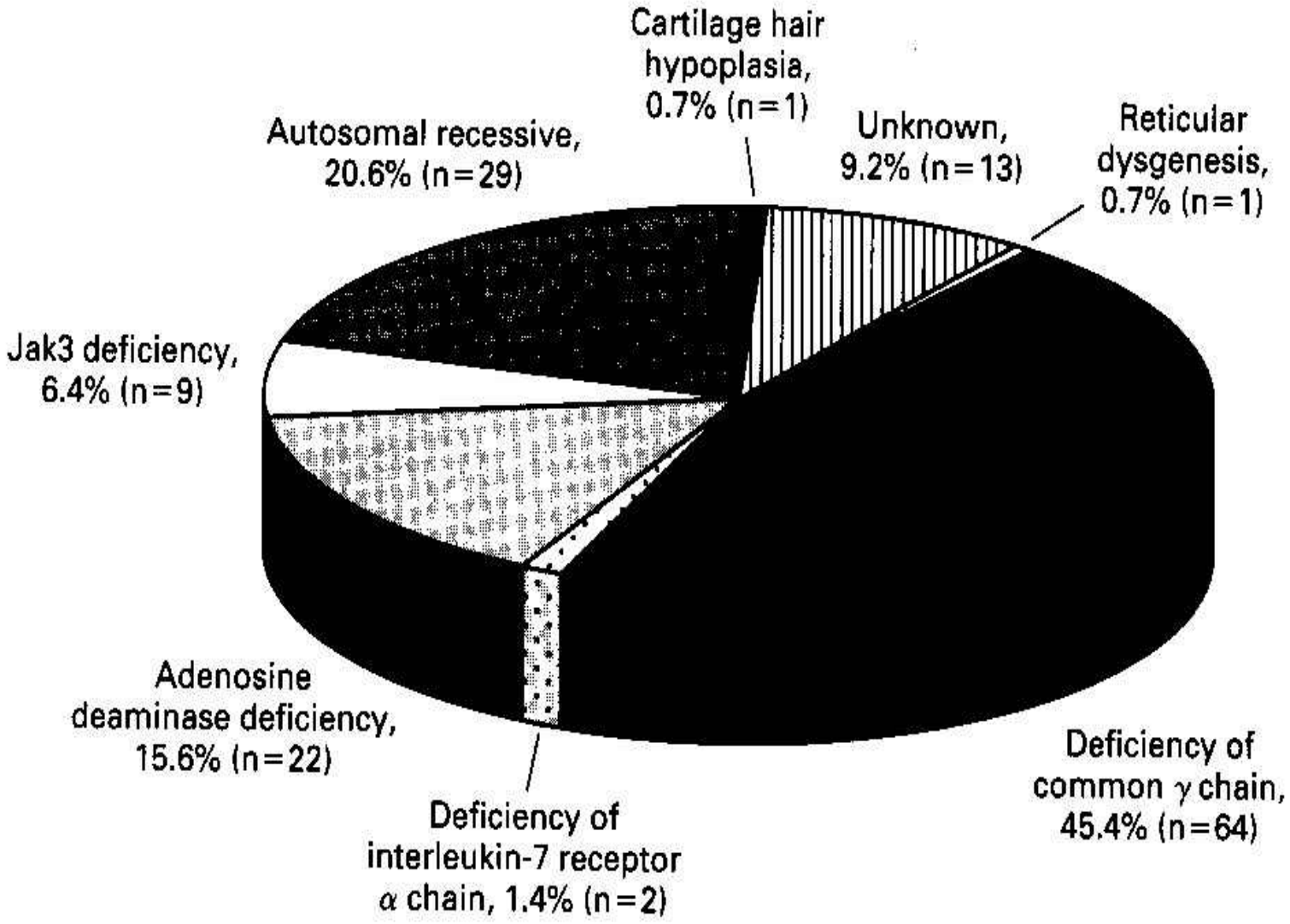


Figure 2. Relative Frequencies of the Various Types of Severe Combined Immunodeficiency among 141 Consecutive Patients.

"Autosomal recessive" refers to 23 patients with autosomal recessive severe combined immunodeficiency in whom the molecular defect has not been identified. Jak3 denotes Janus kinase 3.

DEFECTOS GENETICOS QUE PRODUCEN DEFICIENCIAS CELULARES O COMBINADAS

- Ligada al X: deficiencia en cadena gama del receptor IL-2 es la mas frecuente
- Deficiencia en Jak 3
- Mutaciones en RAG1 y RAG2
- Defectos metabólicos: ADA

SCI X linked

- <Fenotipo T-, NK-, B+
- Mutación en gen *IL2R gamma (CD132)*

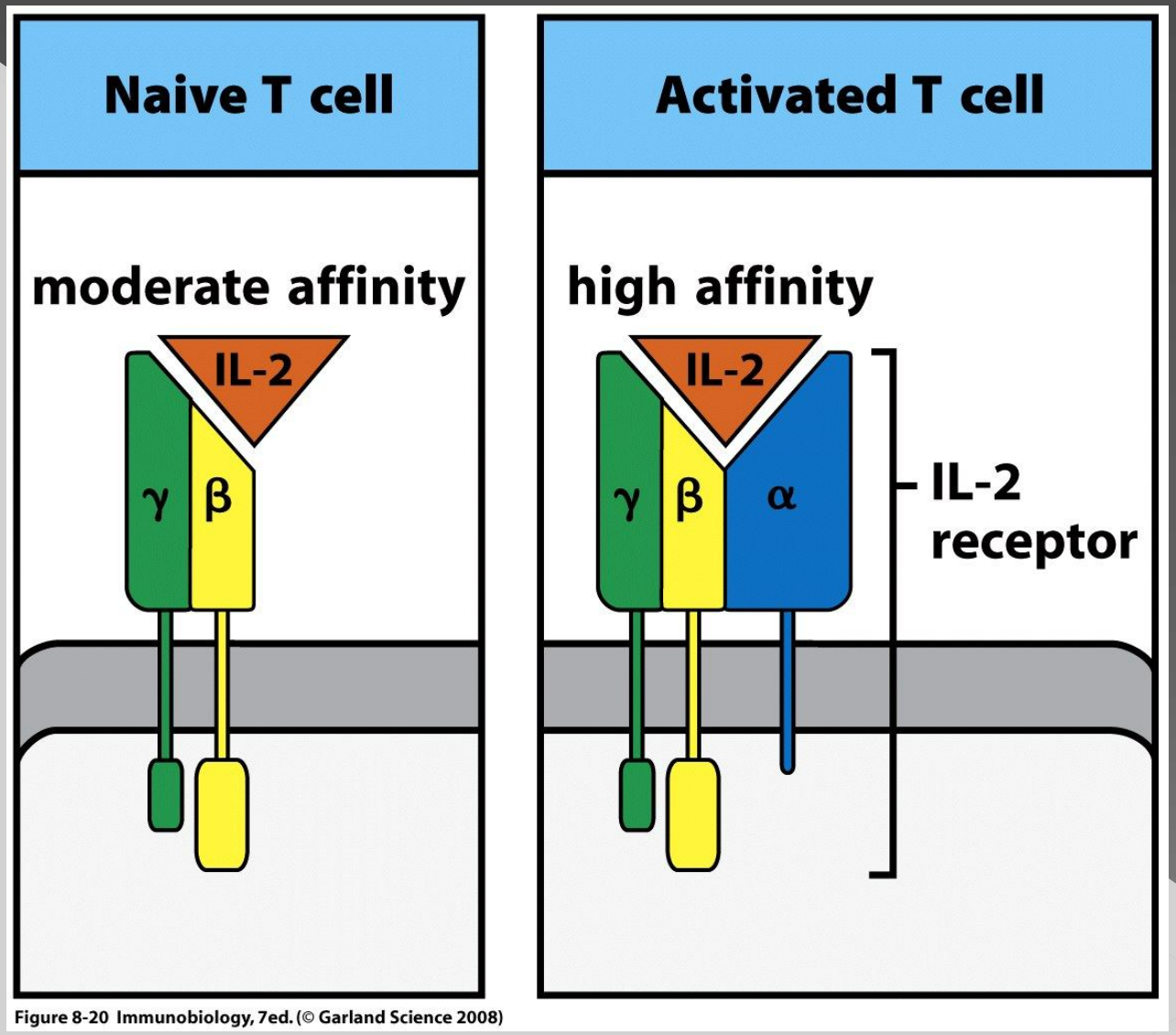
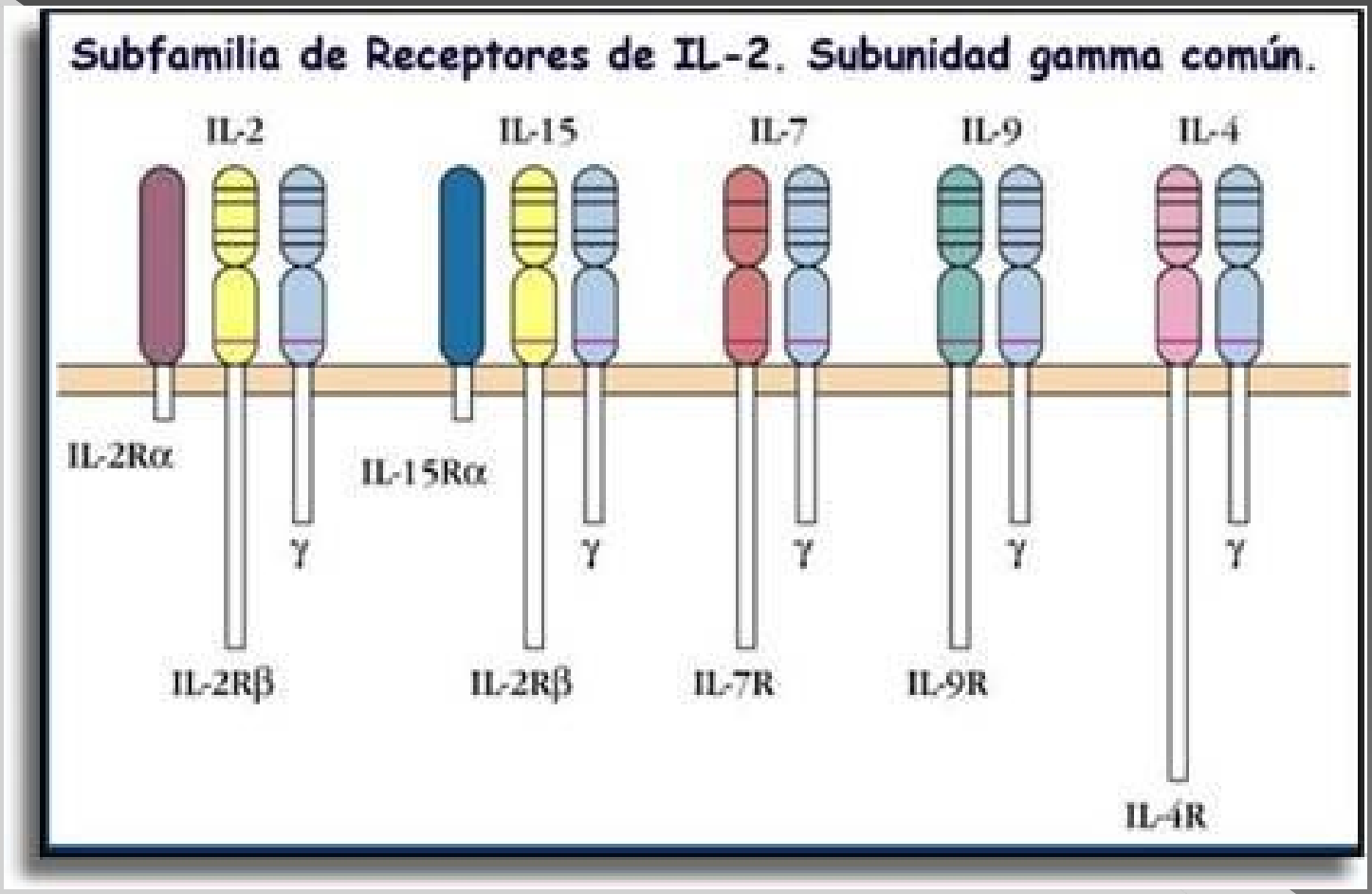
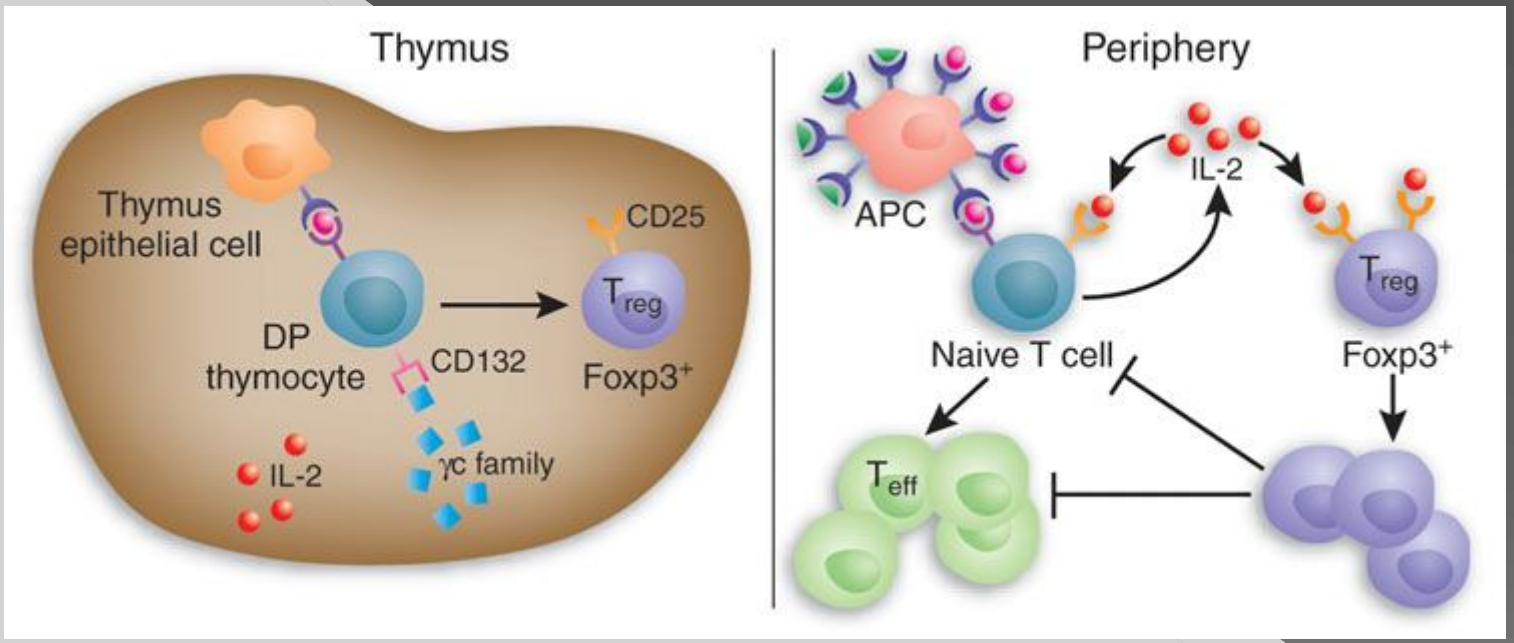


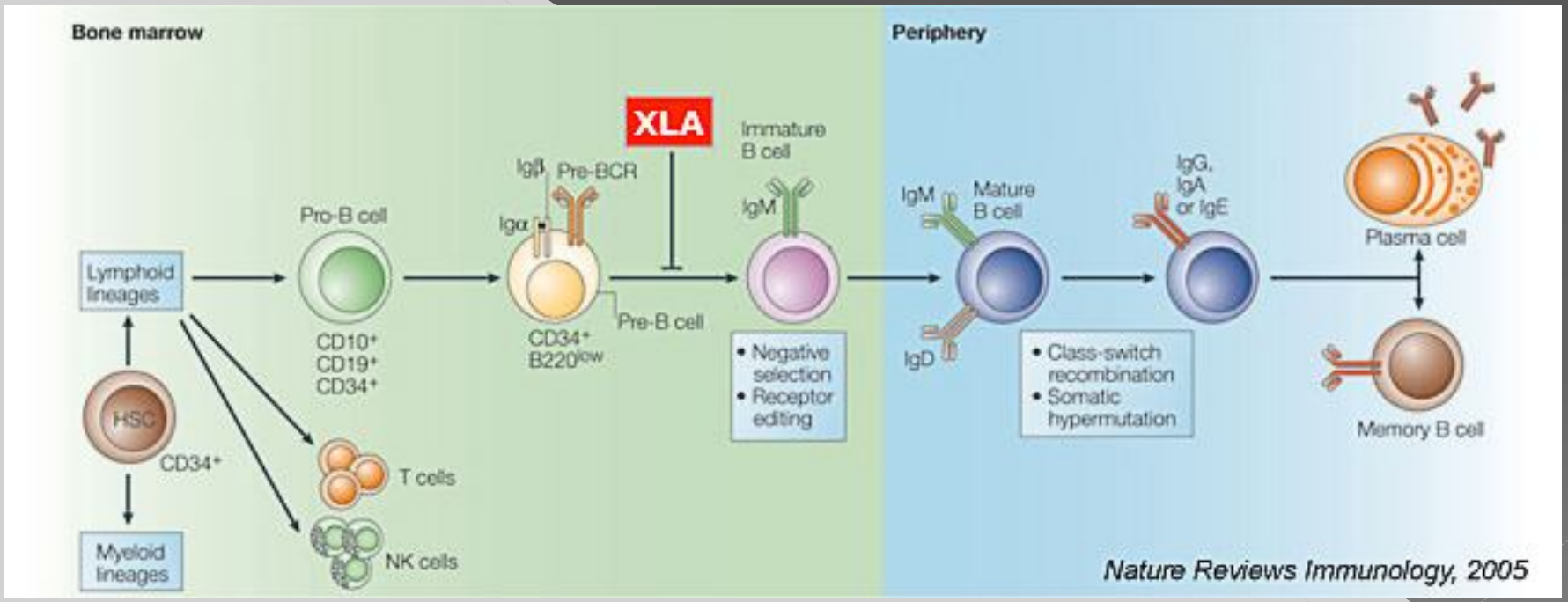
Figure 8-20 Immunobiology, 7ed. (© Garland Science 2008)


Subfamilia de Receptores de IL-2. Subunidad gamma común.
IL-2
IL-15
IL-7
IL-9
IL-4
IL-2Rα
IL-15Rα
γ
γ
γ
γ
γ
IL-2Rβ
IL-2Rβ
IL-7R
IL-9R
IL-4R


Thymus
Thymus epithelial cell
DP thymocyte
CD25
CD132
T_{reg}
Foxp3+
IL-2
γc family
Periphery
APC
IL-2
T_{reg}
Naive T cell
Foxp3+
T_{eff}

◉INMUNODEFICIENCIAS PRIMARIAS POR DEFECTOS EN LINFOCITOS

INMUNODEFICIENCIA DE BRUTTON



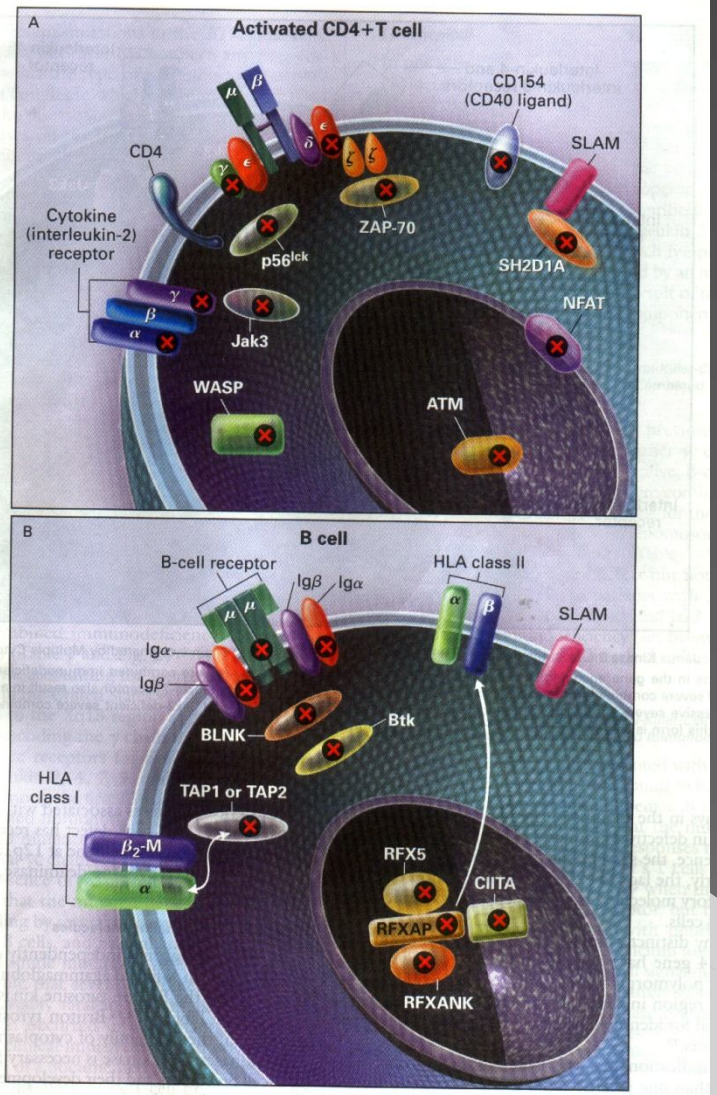


Figure 3. Locations of Mutant Proteins in CD4+ T Cells (Panel A) and B Cells (Panel B) Identified in Primary Immunodeficiency Diseases.

Each mutant protein is identified by a red X. ZAP-70 denotes zeta-associated protein 70; SLAM signaling lymphocyte activation molecule; SH2D1A SLAM-associated protein; ATM ataxia telangiectasia mutation; NFAT nuclear factor of activated T cells; Jak3 Janus kinase 3; WASP Wiskott–Aldrich syndrome protein; TAP1 and TAP2 transporter associated with antigen processing 1 and 2, respectively; Btk Bruton tyrosine kinase; BLNK B-cell linker adapter protein; β_2-M beta$_2$-microglobulin; and RFX, RFXAP, and CIITA transcription factors.

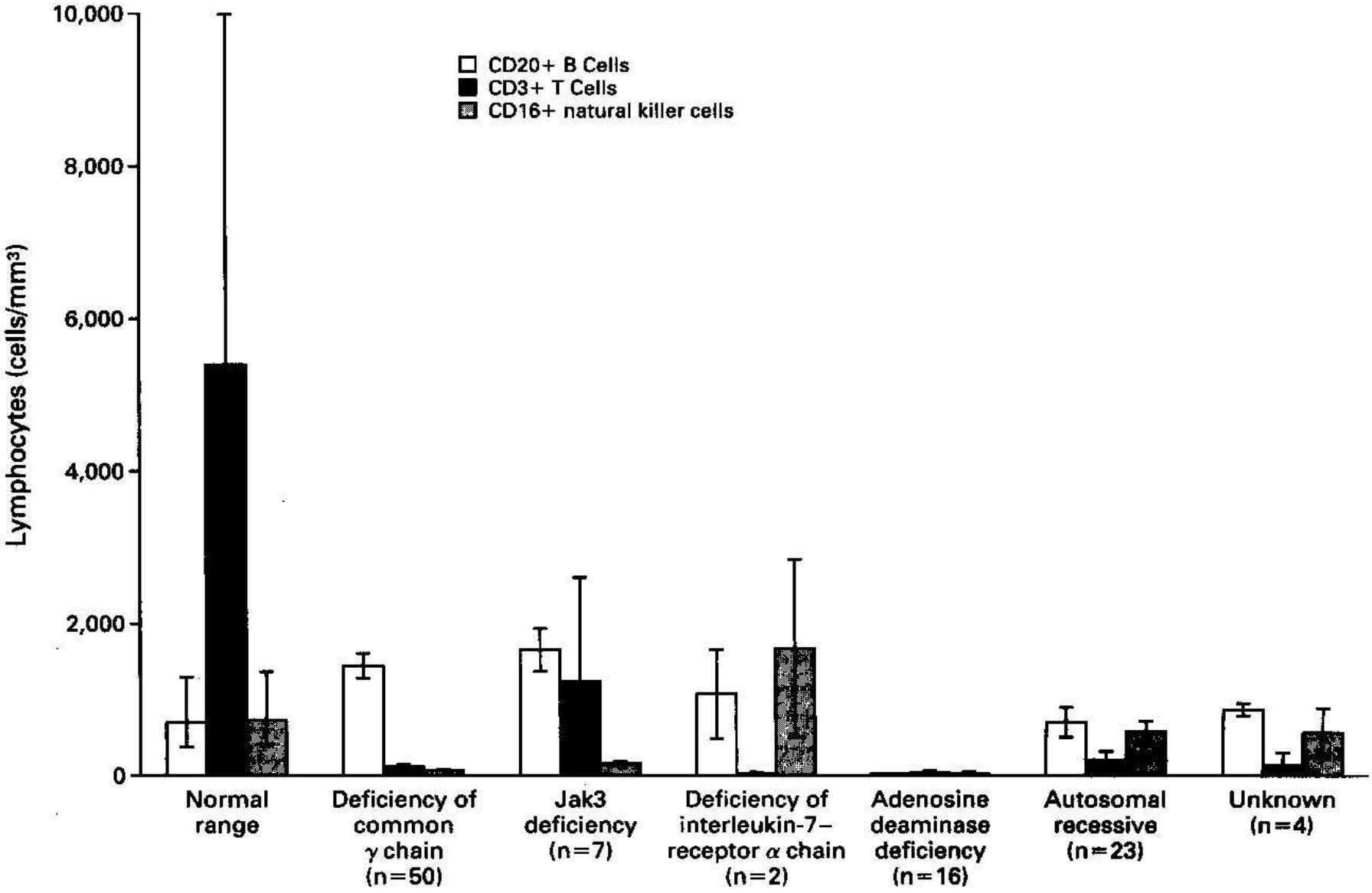


Figure 1. Mean (±SE) Numbers of CD20+ B Cells, CD3+ T Cells, and CD16+ Natural Killer Cells at Presentation in 102 Patients with Severe Combined Immunodeficiency, According to the Cause of the Disorder.

The lymphopenia characteristic of all forms of severe combined immunodeficiency is apparent, as are the differences in the lymphocyte phenotypes in the various forms of the syndrome. The normal ranges at my institution are shown for comparison. Jak3 denotes Janus kinase 3. "Autosomal recessive" refers to 23 patients with autosomal recessive severe combined immunodeficiency in whom the molecular defect has not been identified.

DEFECTOS GENETICOS QUE PRODUCEN DEFICIT IG

- **Defectos en BCR**
- **Defectos en un miembro de un par de ligandos (sindrome X-linked hiper IgM)**
- **Defectos en moléculas de señalizacion**
- **(agamaglobulinemia ligada al X)**

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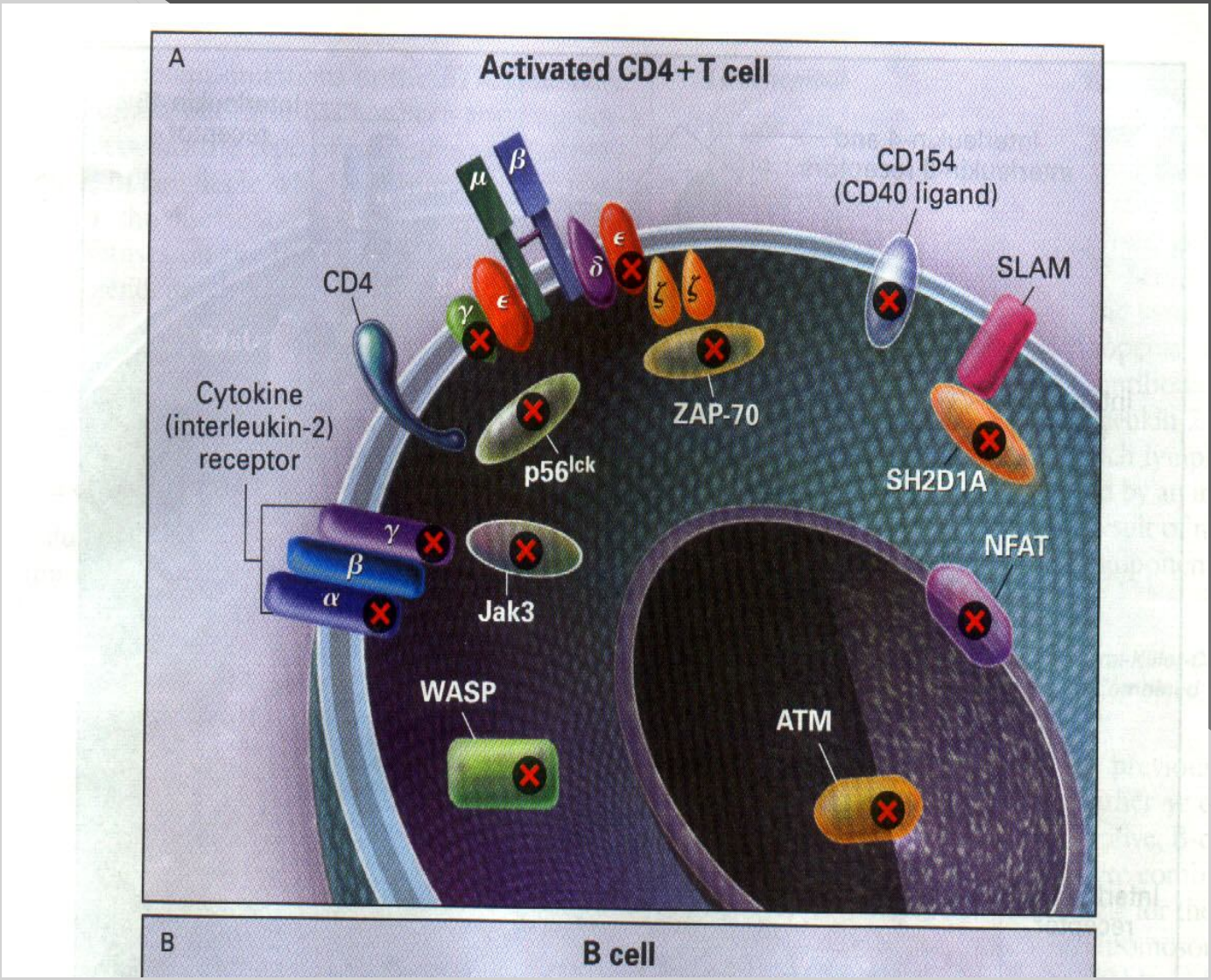
- (agamaglobulinemia ligada al X)

Hyper IgM syndrome

- **Defect in CD40 ligand**

- Absent IgG, IgA; normal/raised IgM
- Antenatal diagnosis possible
- Features of T cell immunodeficiency

LINFOCITO CD4 ACTIVADO



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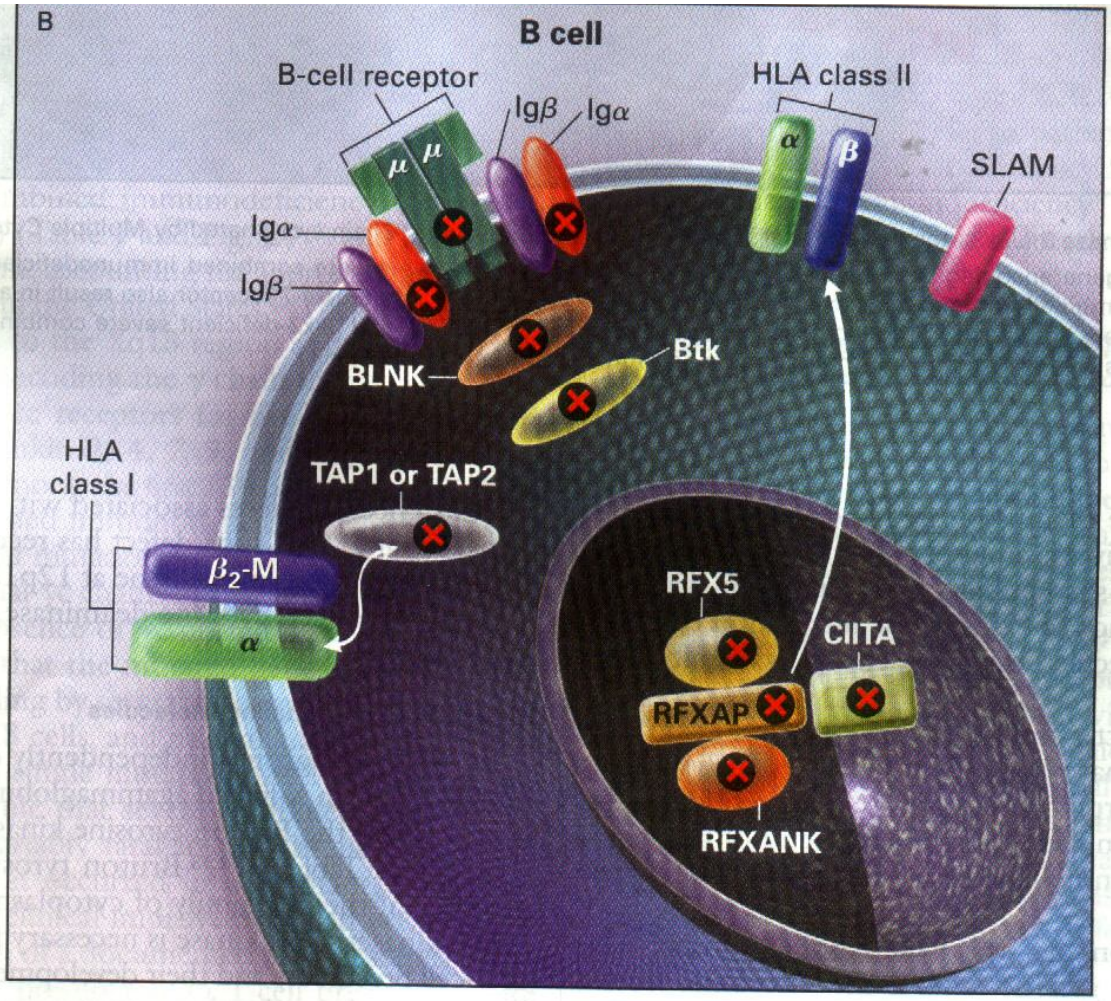

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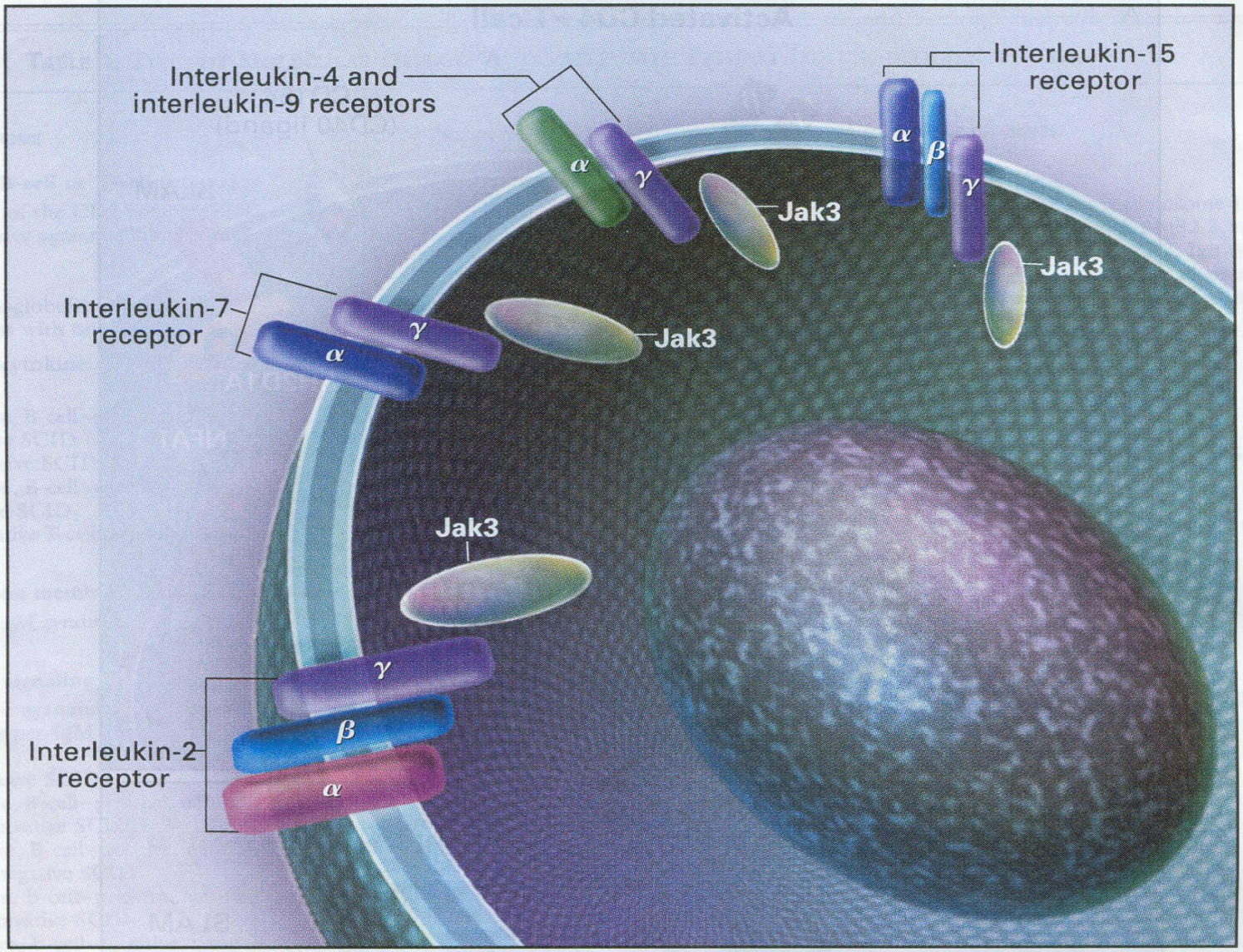

Figure 4. Janus Kinase 3 (Jak3), the Main Signal Transducer for the Common γ Chain (γc) Shared by Multiple Cytokine Receptors. Mutations in the gene encoding Jak3 result in a form of autosomal recessive severe combined immunodeficiency that mimics X-linked severe combined immunodeficiency. Mutations in the α chain of the interleukin-7 receptor also result in a form of autosomal recessive severe combined immunodeficiency, but in contrast to X-linked and Jak3-deficient severe combined immunodeficiency, this form is characterized by normal numbers and function of natural killer cells.

Los niños de la burbuja