INMUNOLOGIA MOLECULAR

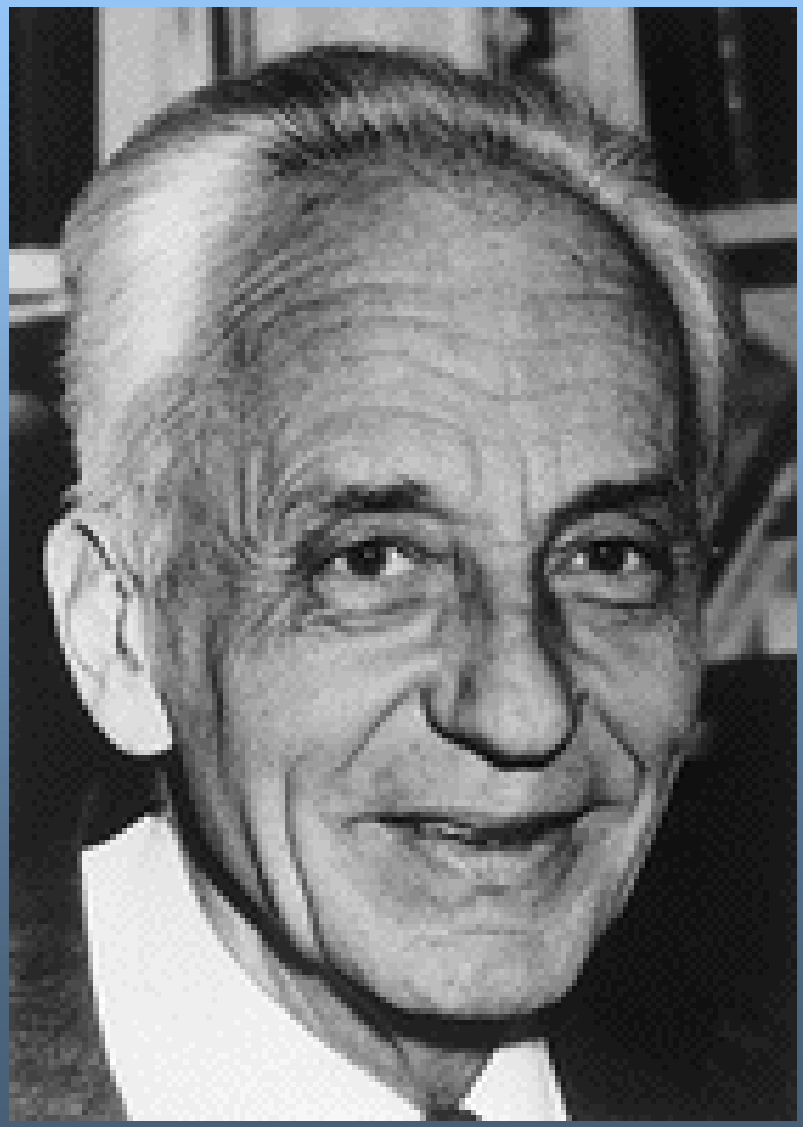
INMUNIDAD CELULAR

COMPLEJO MAYOR DE HISTOCOMPATIBILIDAD

(HLA, MHC)

Jean Dausset

Premio Nobel de Medicina 1980



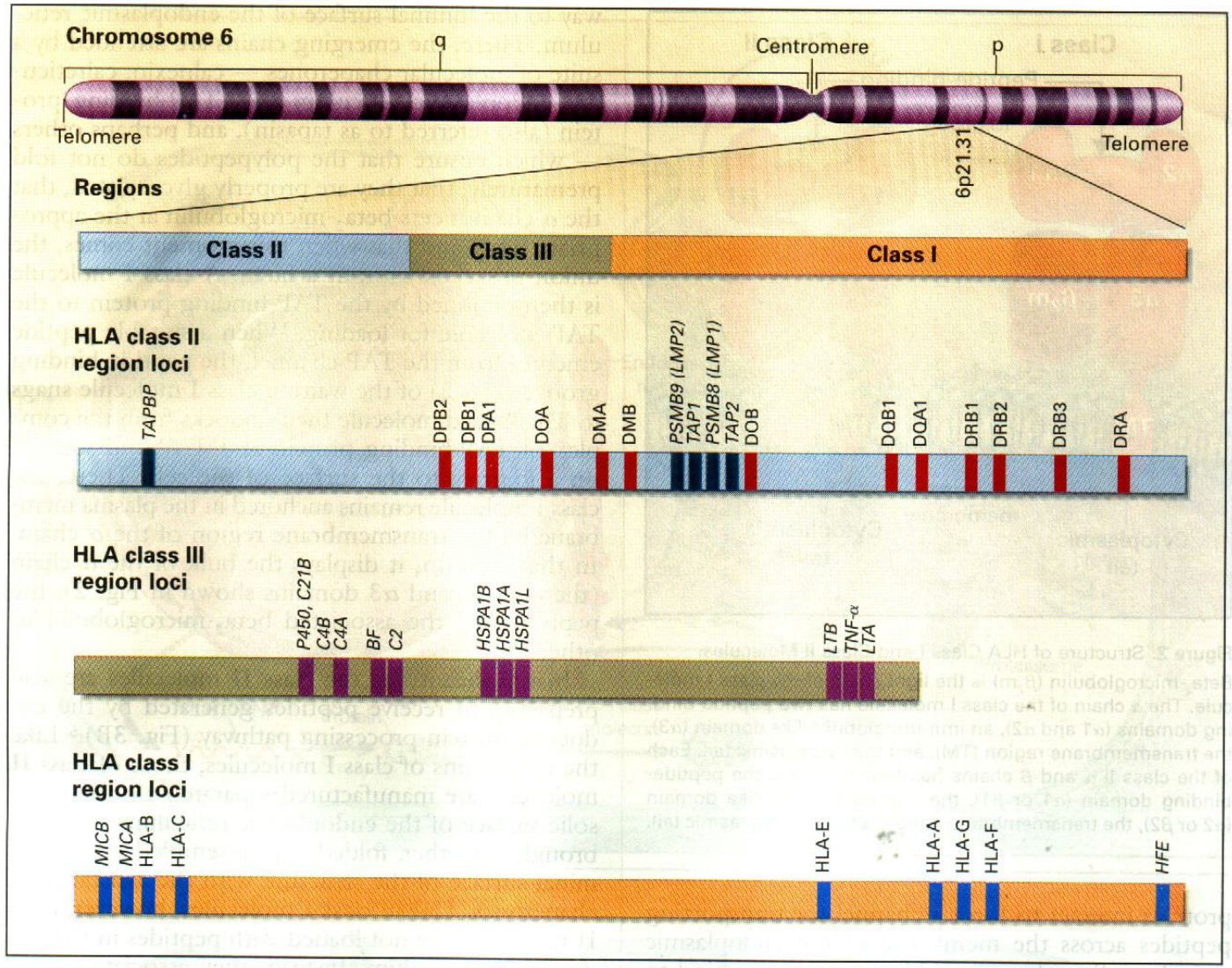


Figure 1. Location and Organization of the HLA Complex on Chromosome 6.

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.

ORGANIZACIÓN DE MHC (HLA)

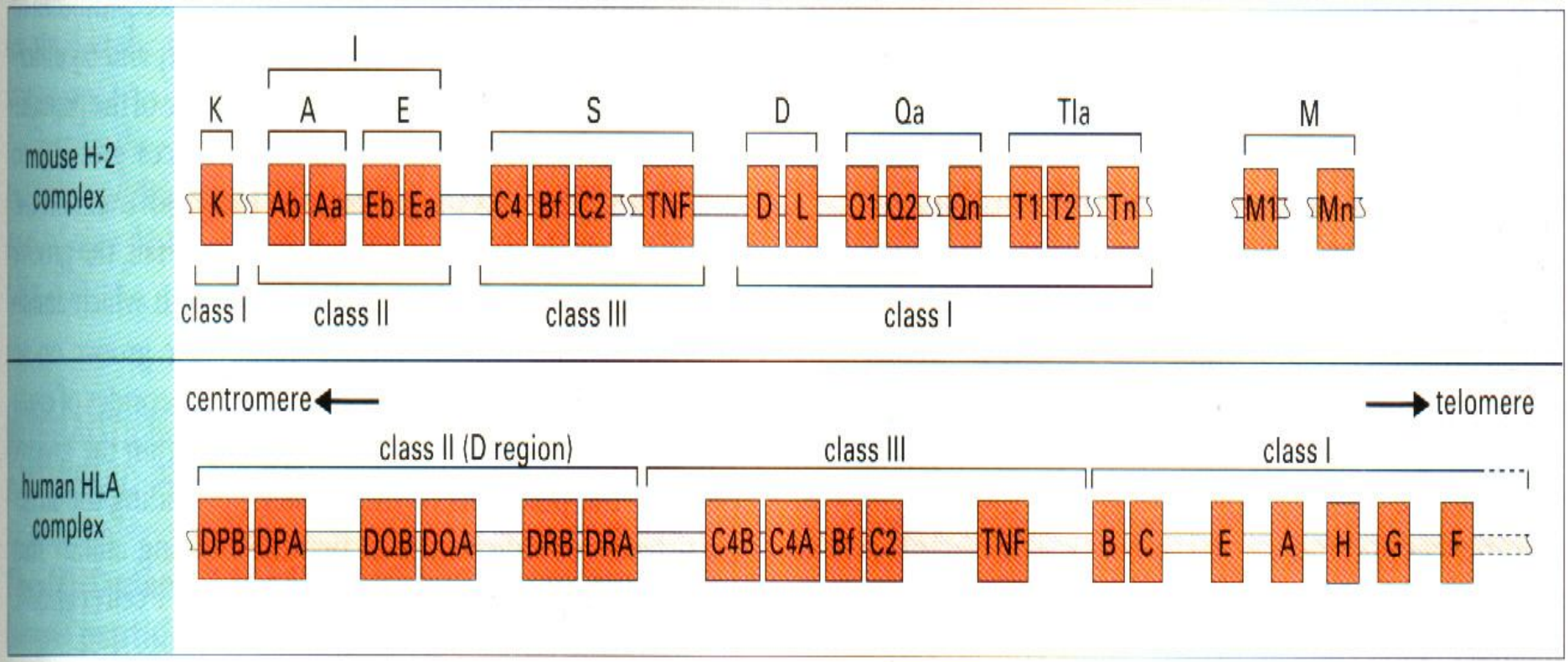


Fig. 5.4 Diagram showing the locations of subregions of the murine and human MHCs and the positions of the major genes within these subregions. The human organization pattern, in which the class II loci are positioned between the centromere and the class I loci, occurs in every other mammalian species so far examined. The regions span 3–4 Mbp of DNA.

GENES EN MHC CLASE II

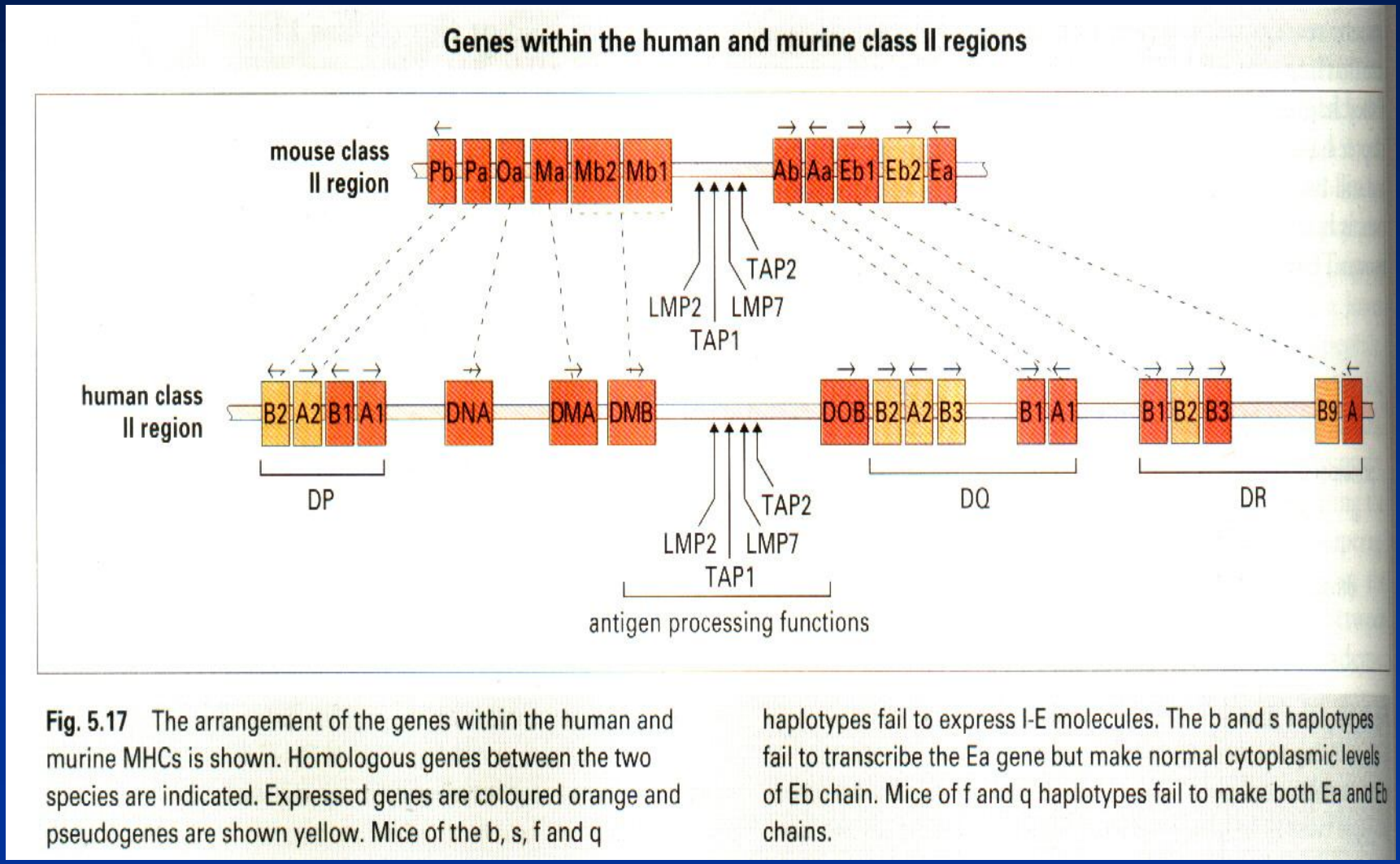
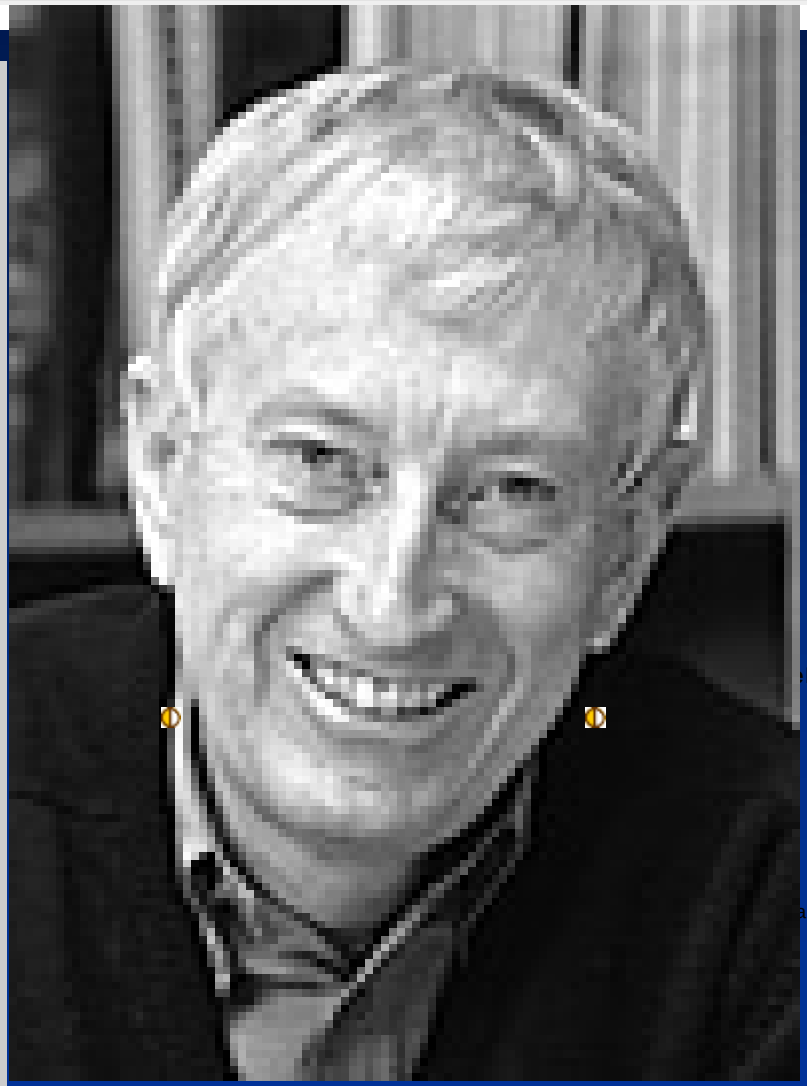
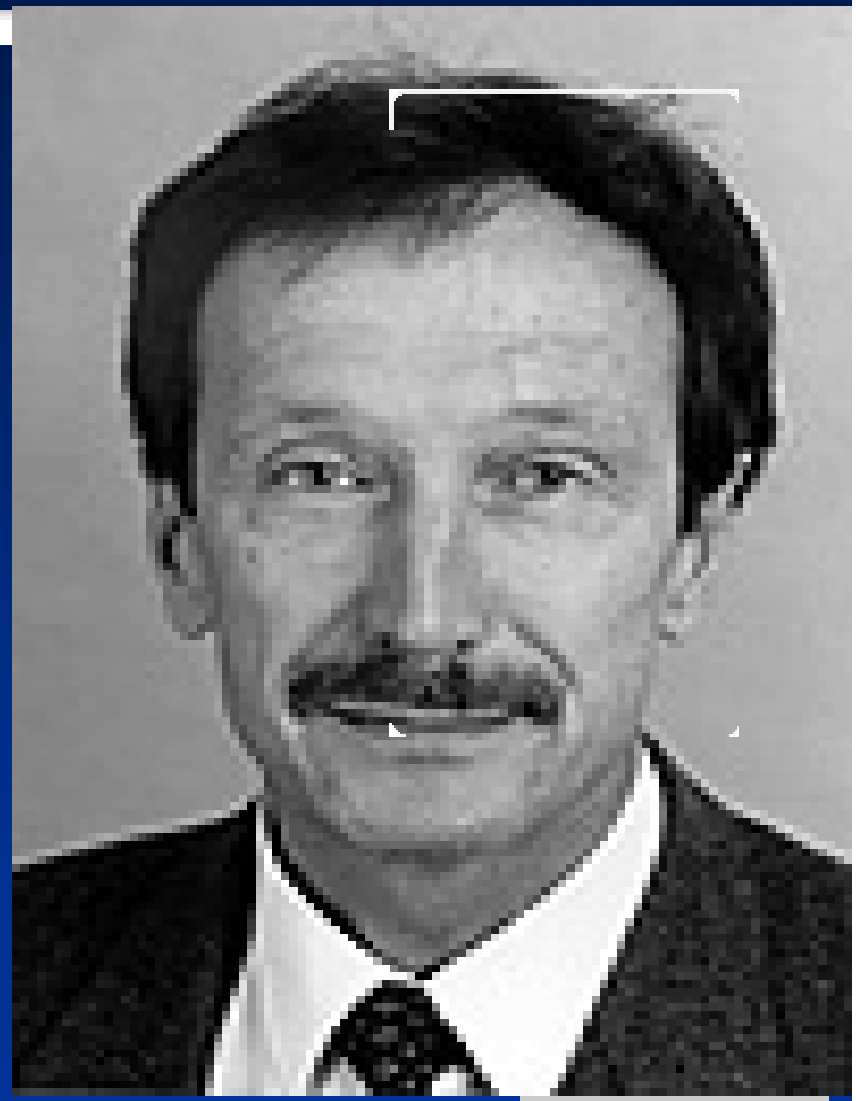


Fig. 5.17 The arrangement of the genes within the human and murine MHCs is shown. Homologous genes between the two species are indicated. Expressed genes are coloured orange and pseudogenes are shown yellow. Mice of the b, s, f and q haplotypes fail to express I-E molecules. The b and s haplotypes fail to transcribe the Ea gene but make normal cytoplasmic levels of Eb chain. Mice of f and q haplotypes fail to make both Ea and Eb chains.



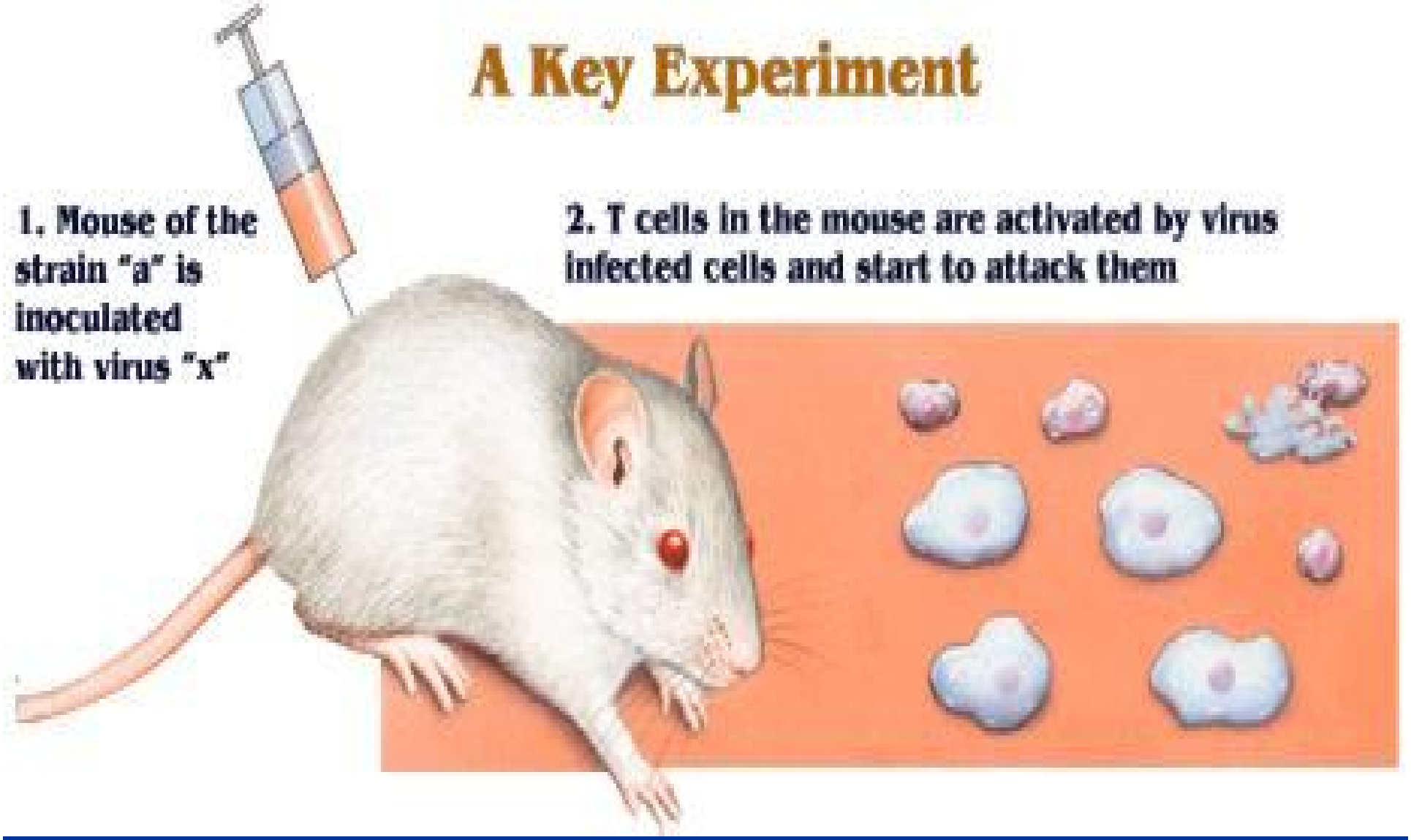


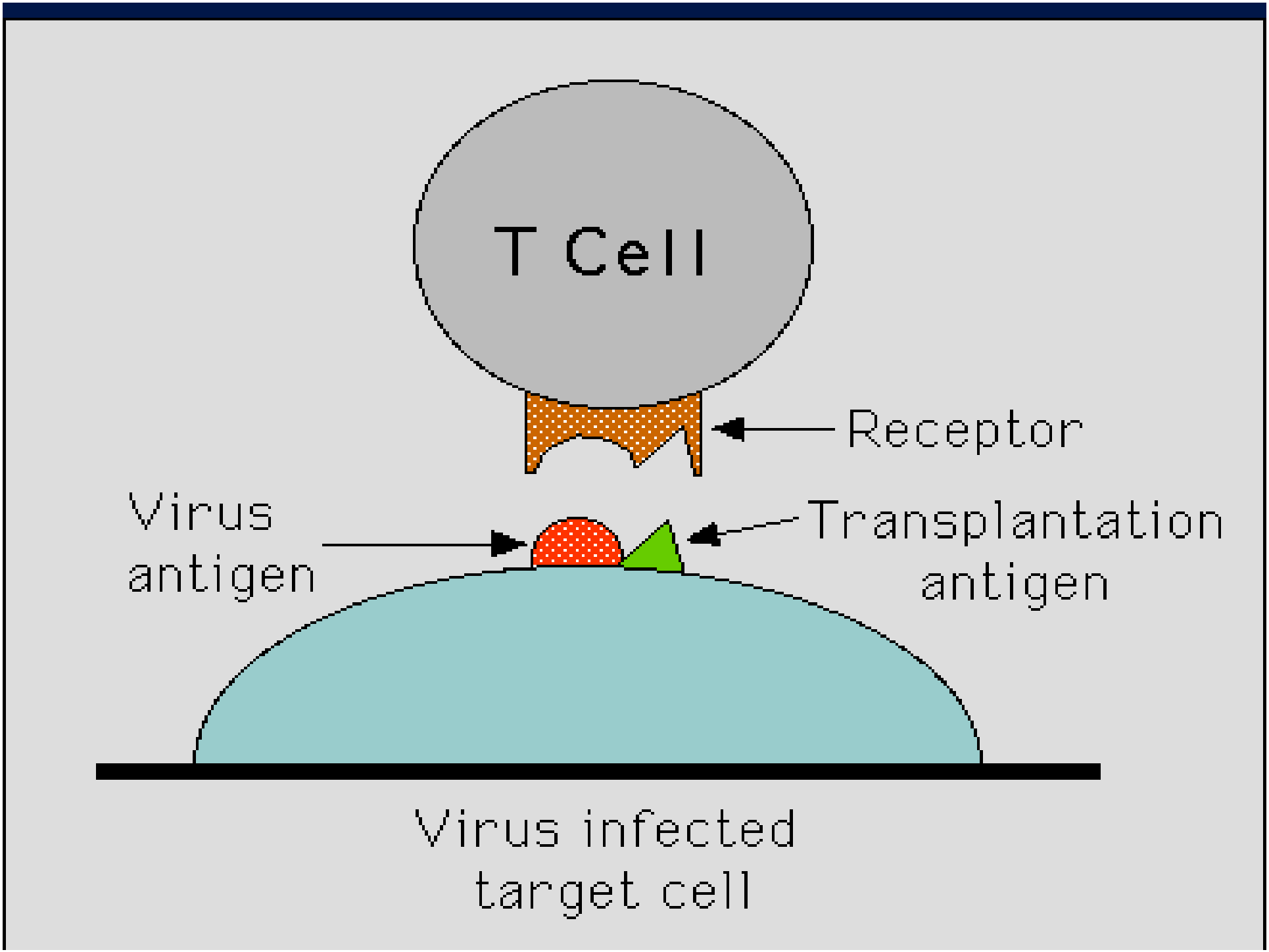
al Immunology,

A Key Experiment

1. Mouse of the strain "a" is inoculated with virus "x"

2. T cells in the mouse are activated by virus infected cells and start to attack them




T Cell
Receptor
Virus
antigen
Transplantation
antigen
Virus infected
target cell


The Kiss of Death
T cell receptor
Virus antigen (x)
MHC molecule (a)

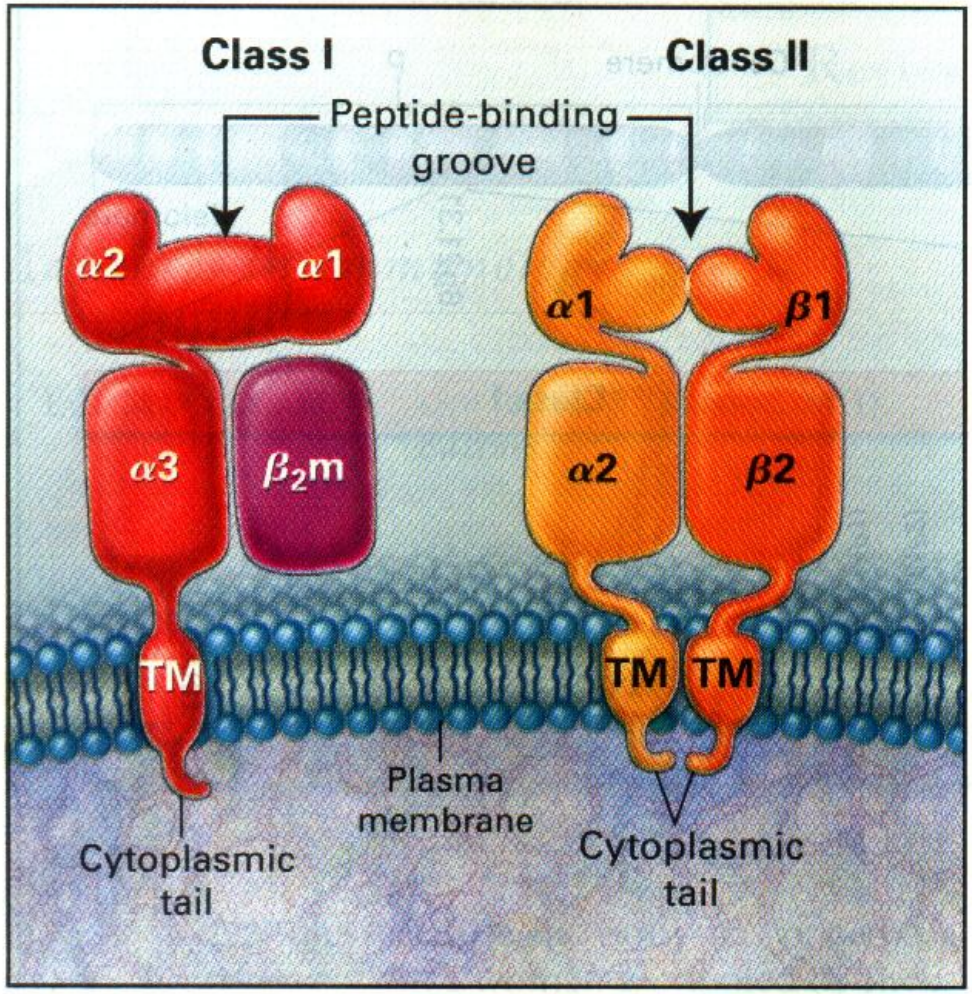


Figure 2. Structure of HLA Class I and Class II Molecules.

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

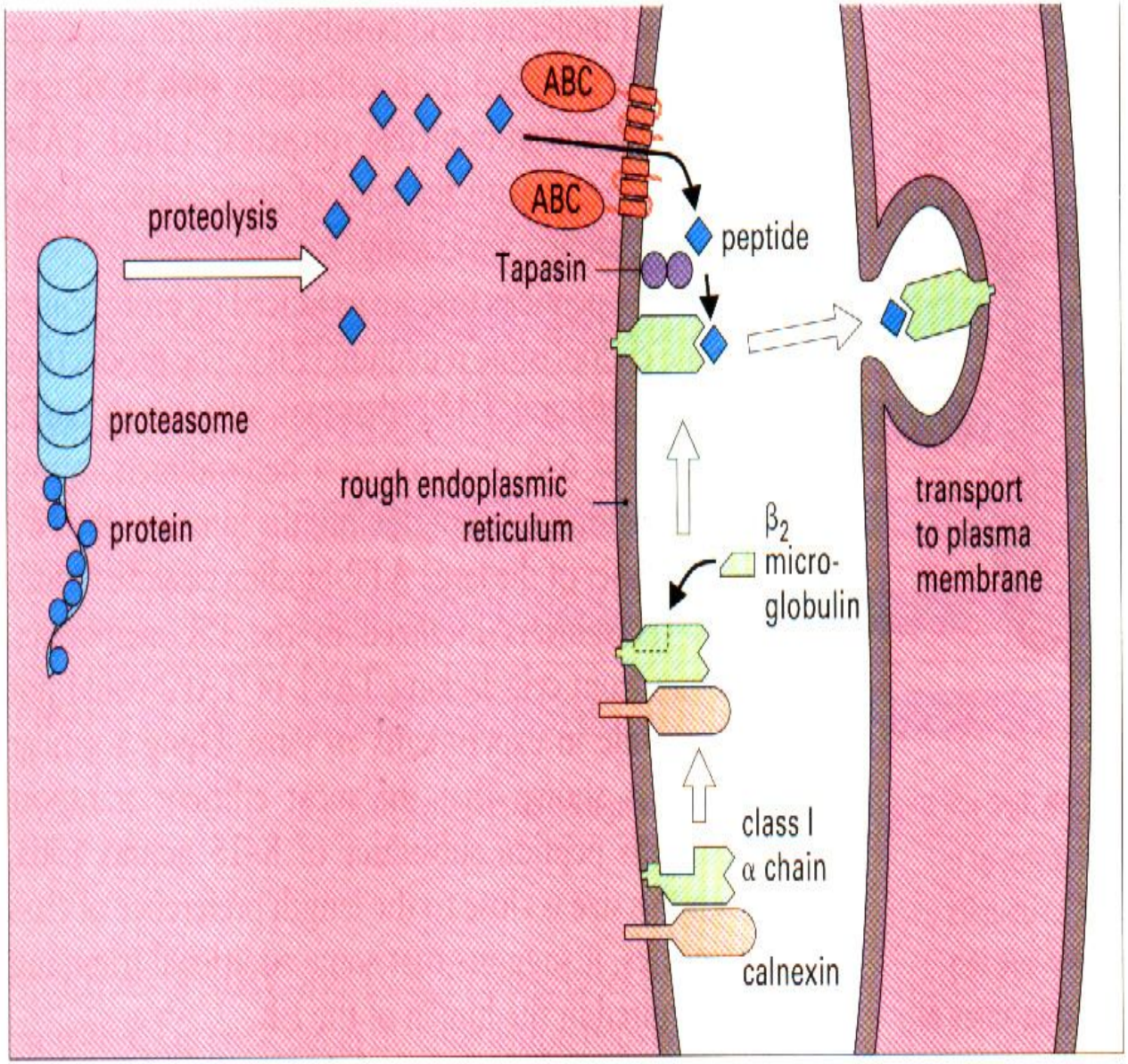


Fig. 6.10 Proposed assembly pathway of antigen–MHC complex. Cytoplasmic antigens are processed by proteasomes. Peptides are transported by two members of the 'ABC' superfamily of transporters, also encoded within the MHC (TAP1 and TAP2). Antigenic peptides associate with class I heavy chains and β_2-microglobulin (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

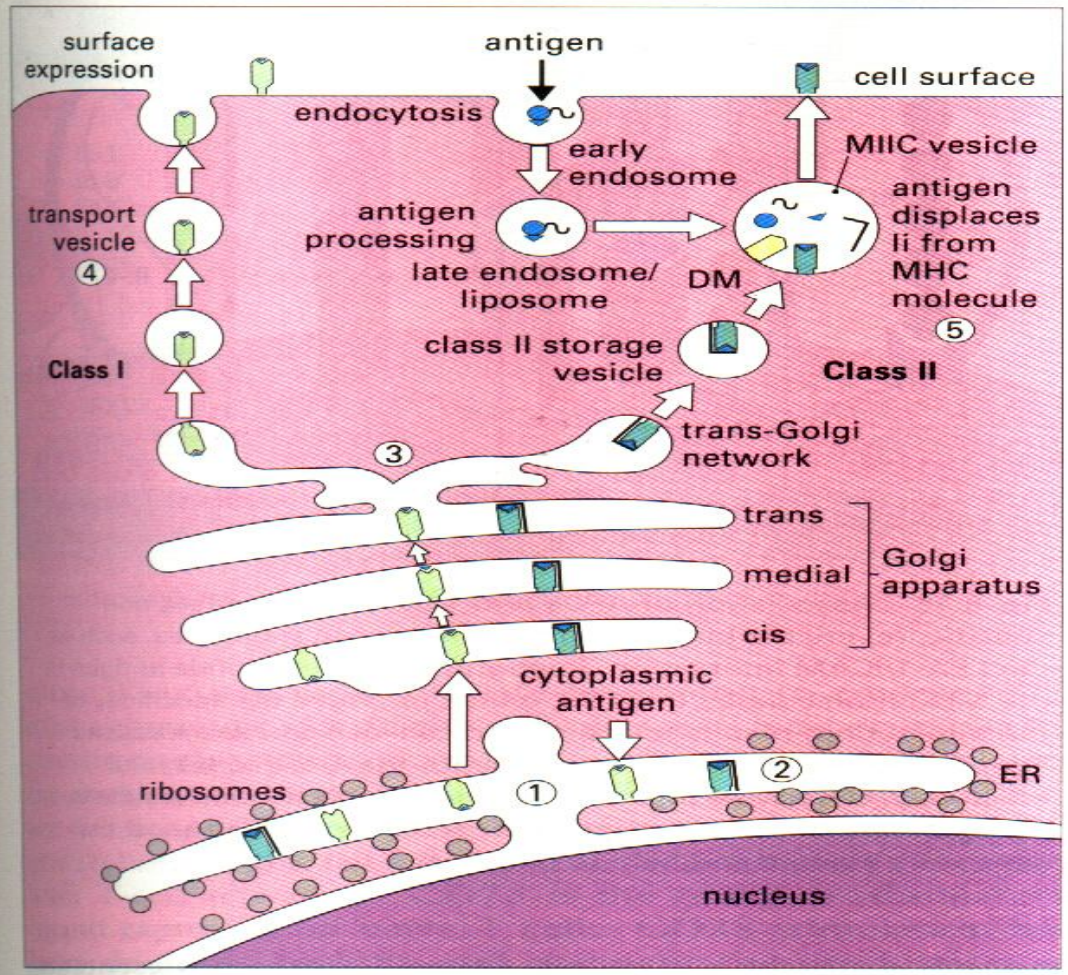


Fig. 6.12 Newly synthesized class I molecules are loaded with peptide (**1**). Class II molecules associate with Ii in the ER (**2**). Ii prevents loading with peptide and contains sequences that enable the class II molecule to exit from the rough endoplasmic reticulum (RER). Class I and class II molecules 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

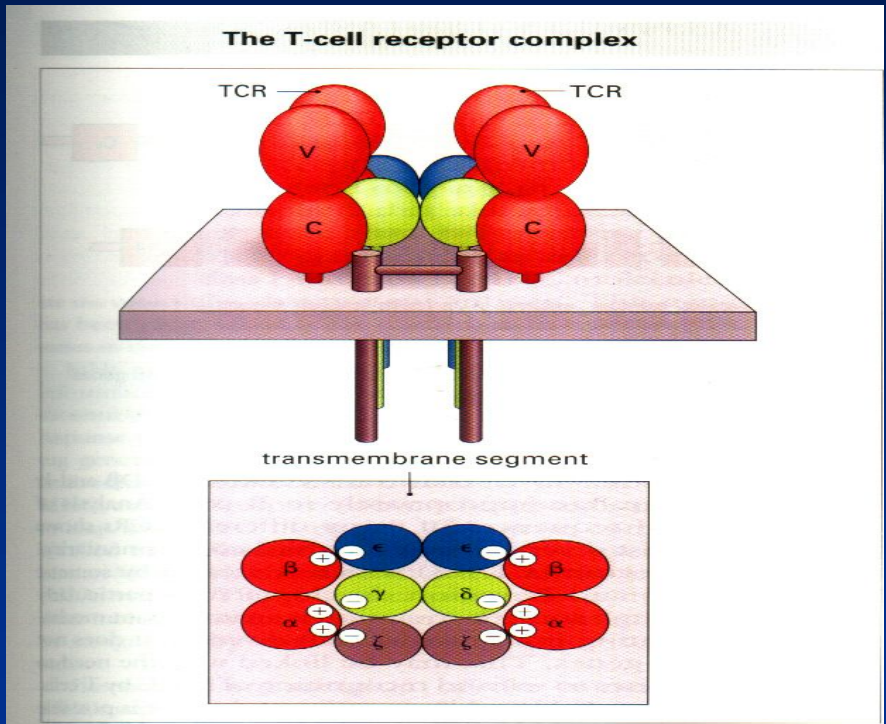
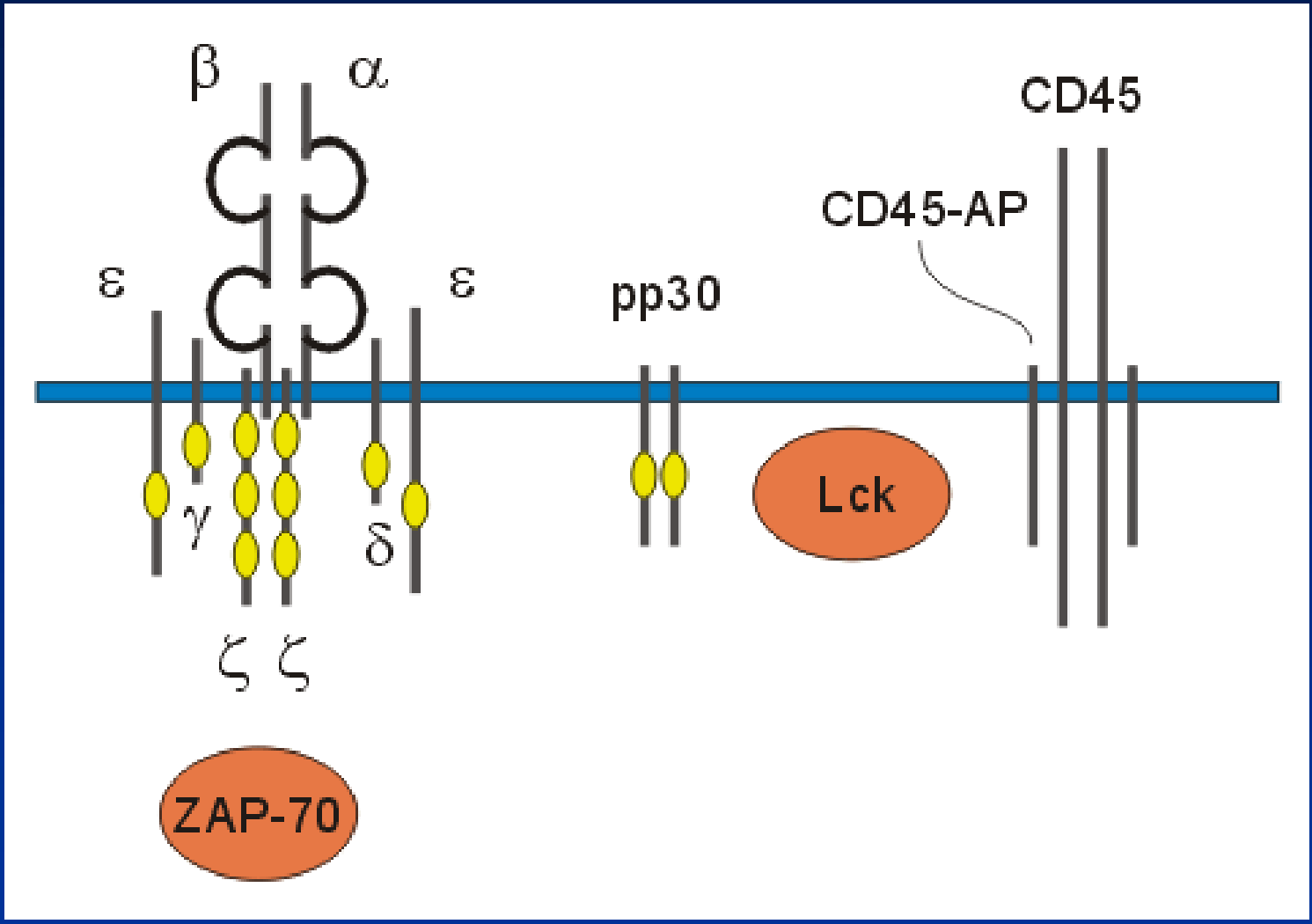


Fig. 5.2 The TCR α and β (or γ and δ) chains each comprise an external V and C domain, a transmembrane segment containing positively charged amino acids and a short cytoplasmic tail. The two chains are disulphide linked on the membrane side of their C domains. The CD3 γ, δ and ε chains comprise an external 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



T CELL RECEPTOR (TCR)

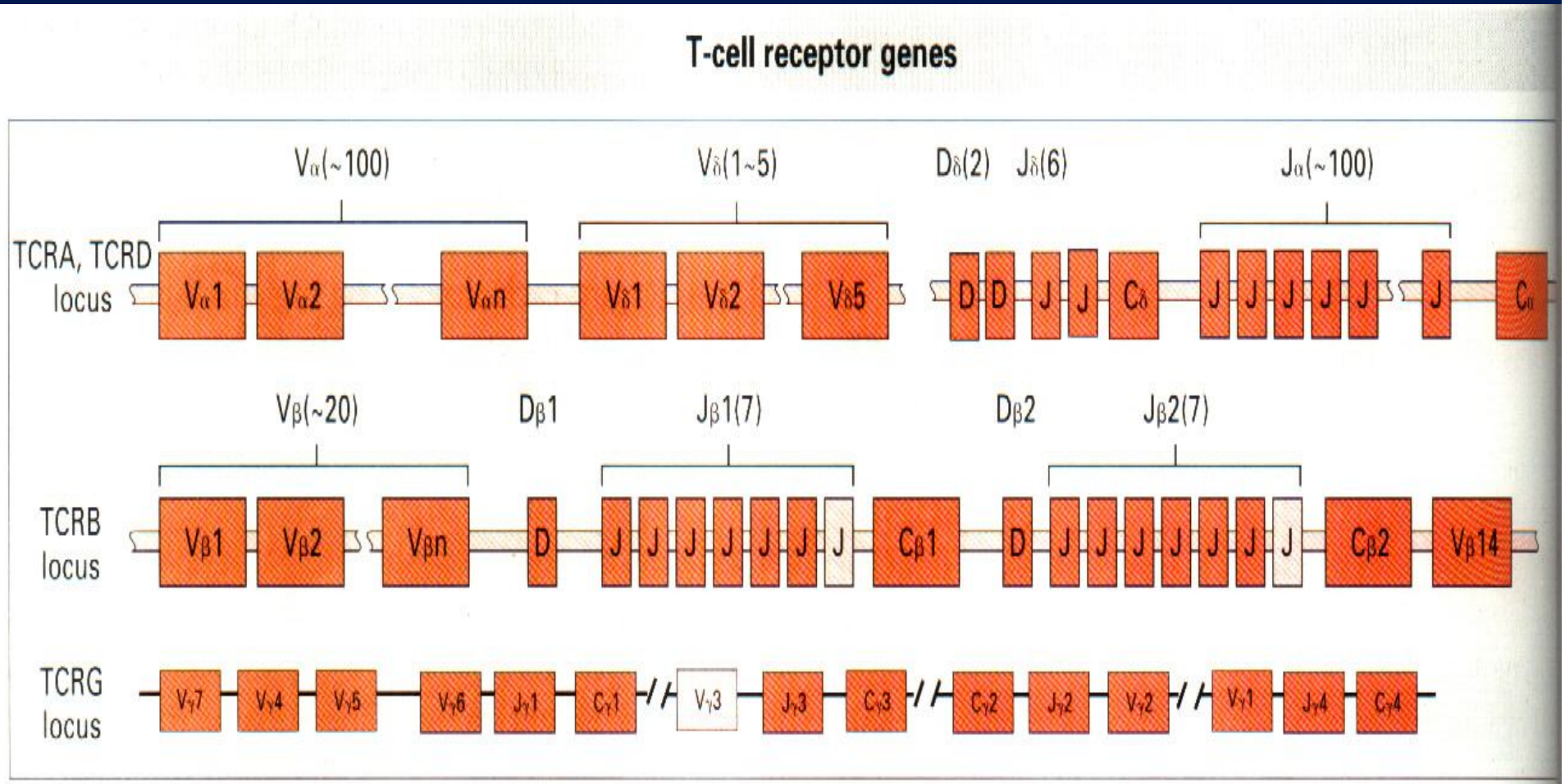
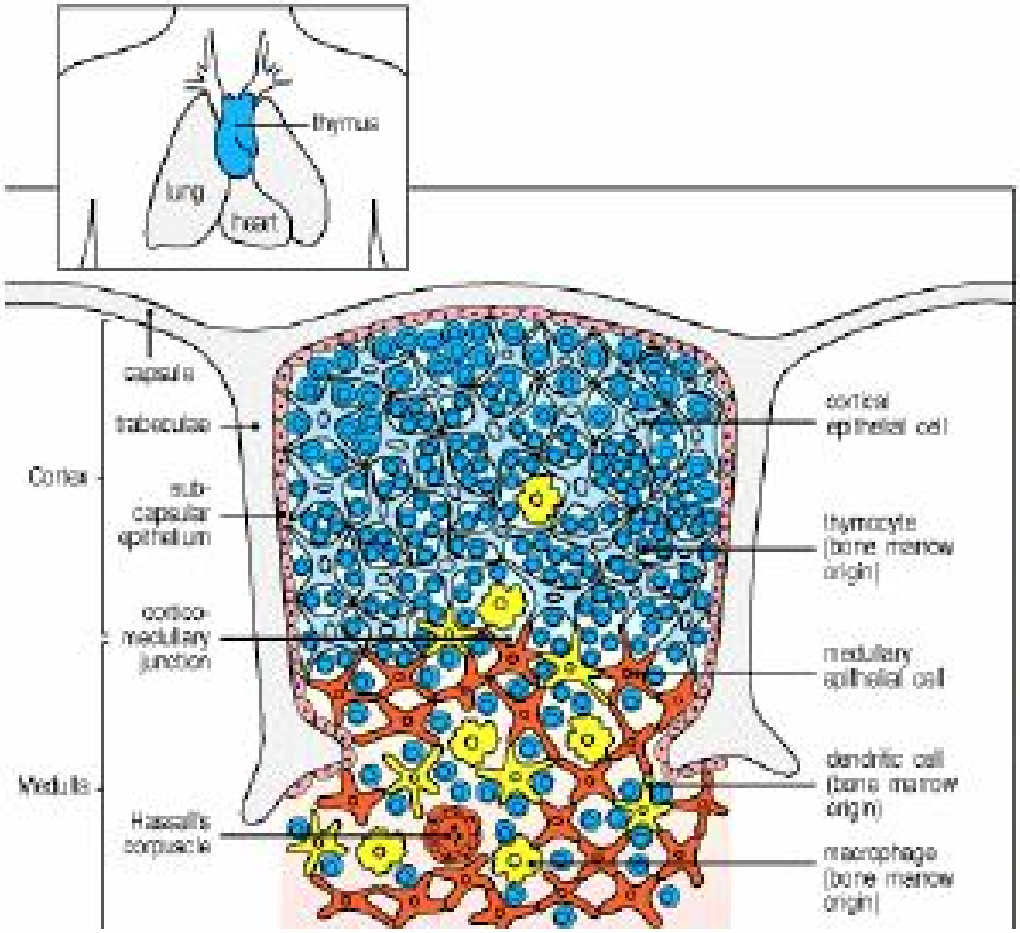
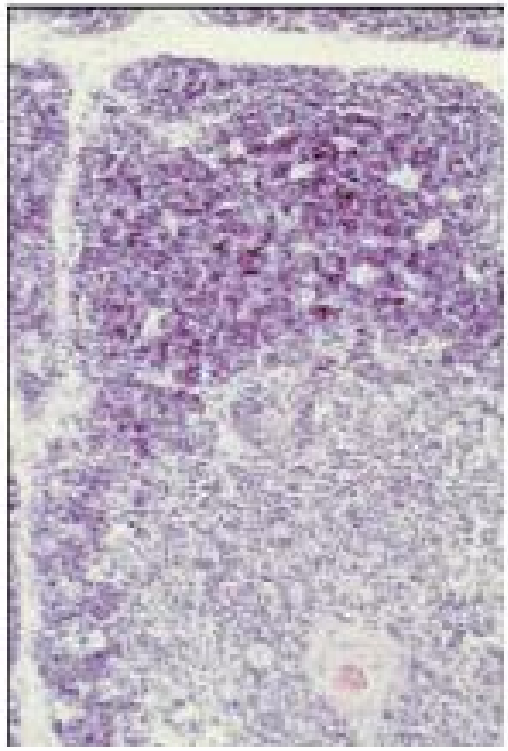


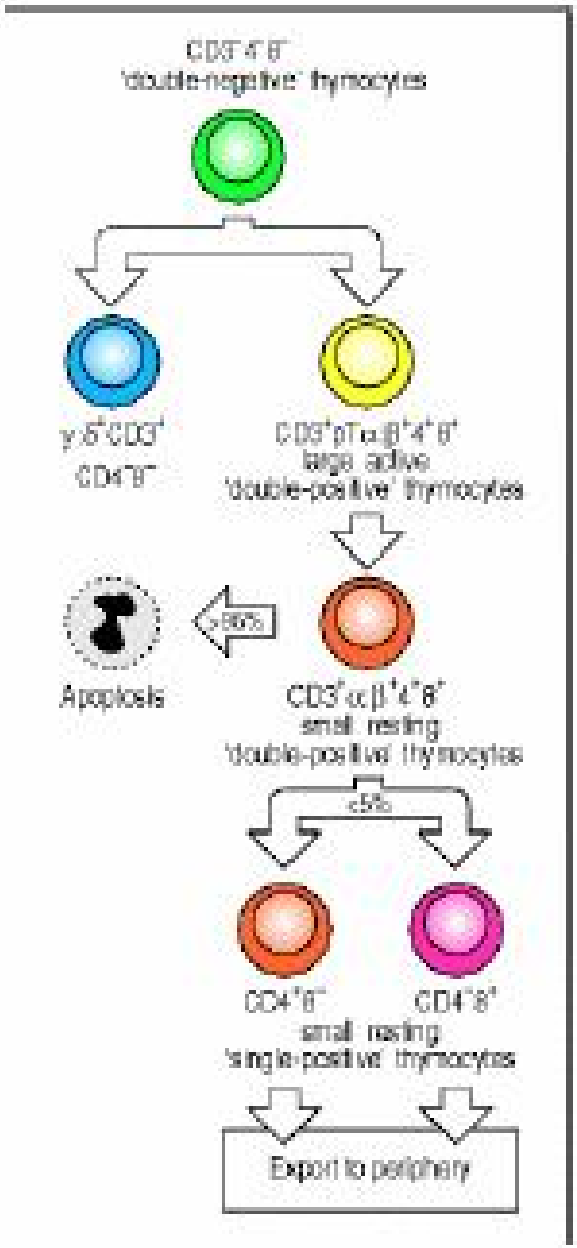
Fig. 5.3 The genes of the murine TCR chains are shown. The δ chain loci are embedded within the α loci and tandem duplication has occurred in the β chain loci. The last of each set of Jβ genes and the Vγ3 gene are pseudogenes.

Maduración y educación T

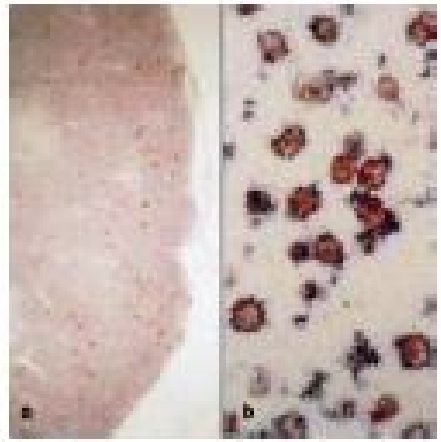


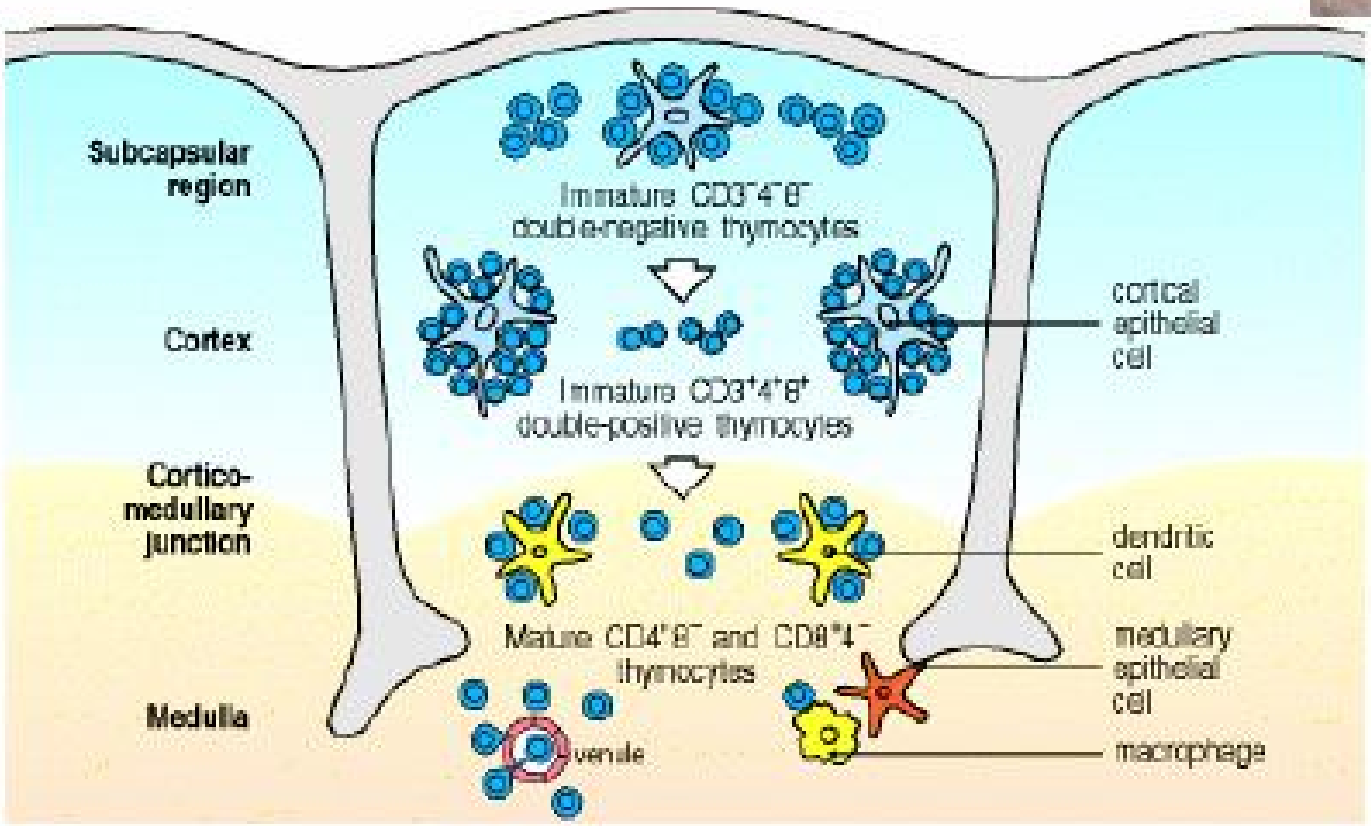


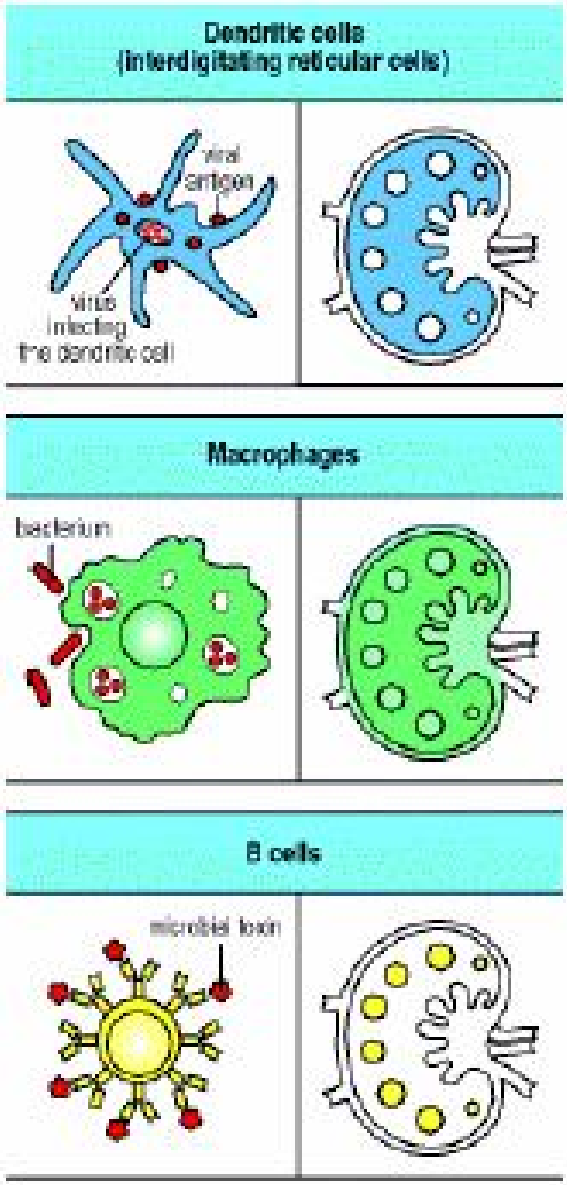
Rearreglos de TCR



Selección positiva y negativa







Captación por CPA

The role of CD4 and CD8 in T-cell activation

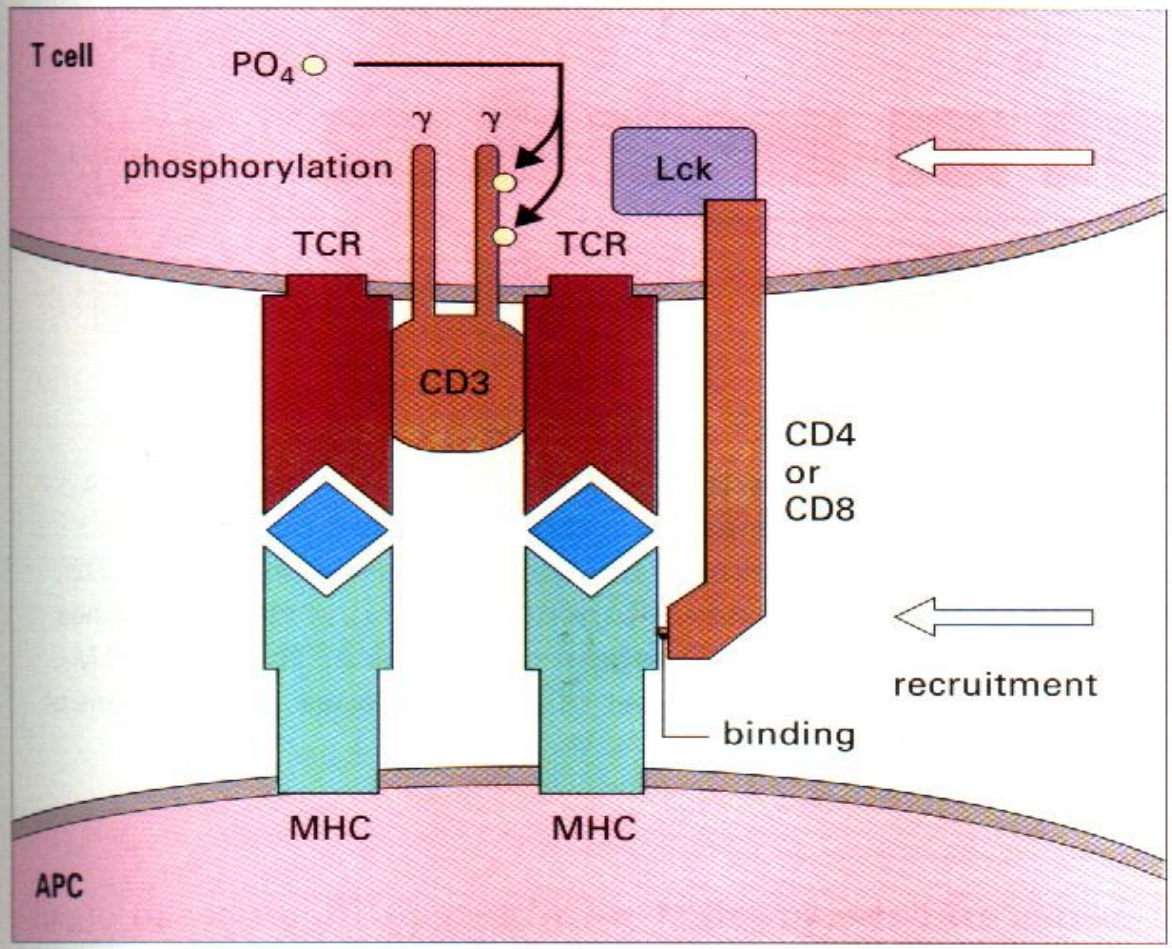


Fig. 5.14 After aggregation of MHC–peptide on the antigen-presenting cell with the T-cell's receptor, either CD4 or CD8 can join the complex. CD4 binds to MHC class II molecules and CD8 to class I. The kinase lck is attached to the intracytoplasmic portion of CD4 or CD8. Binding of these molecules to 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.

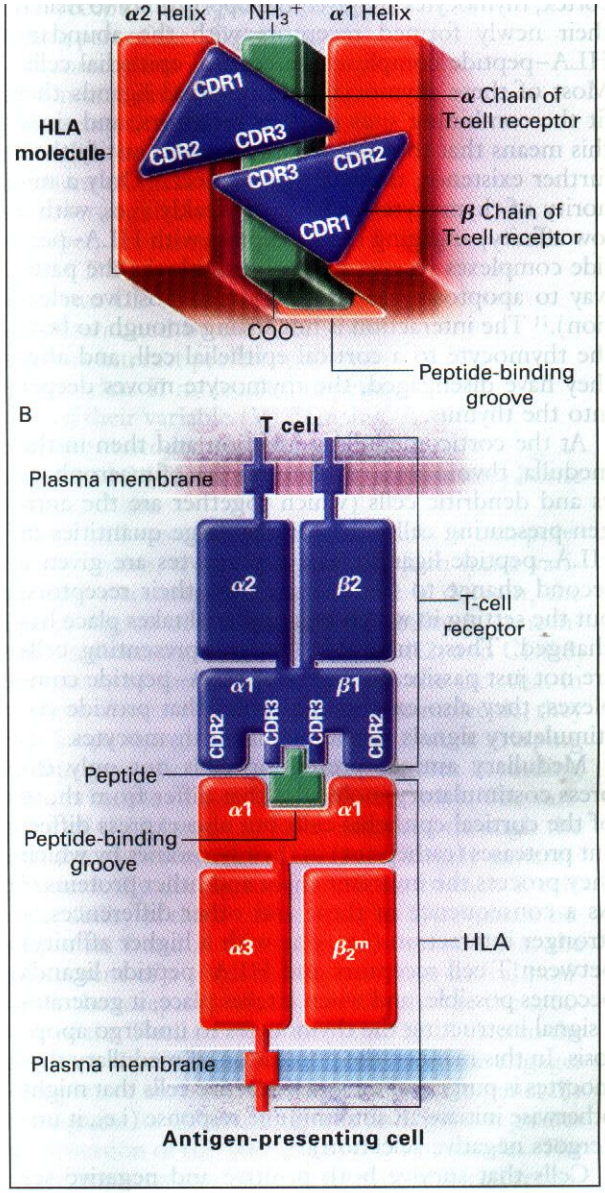
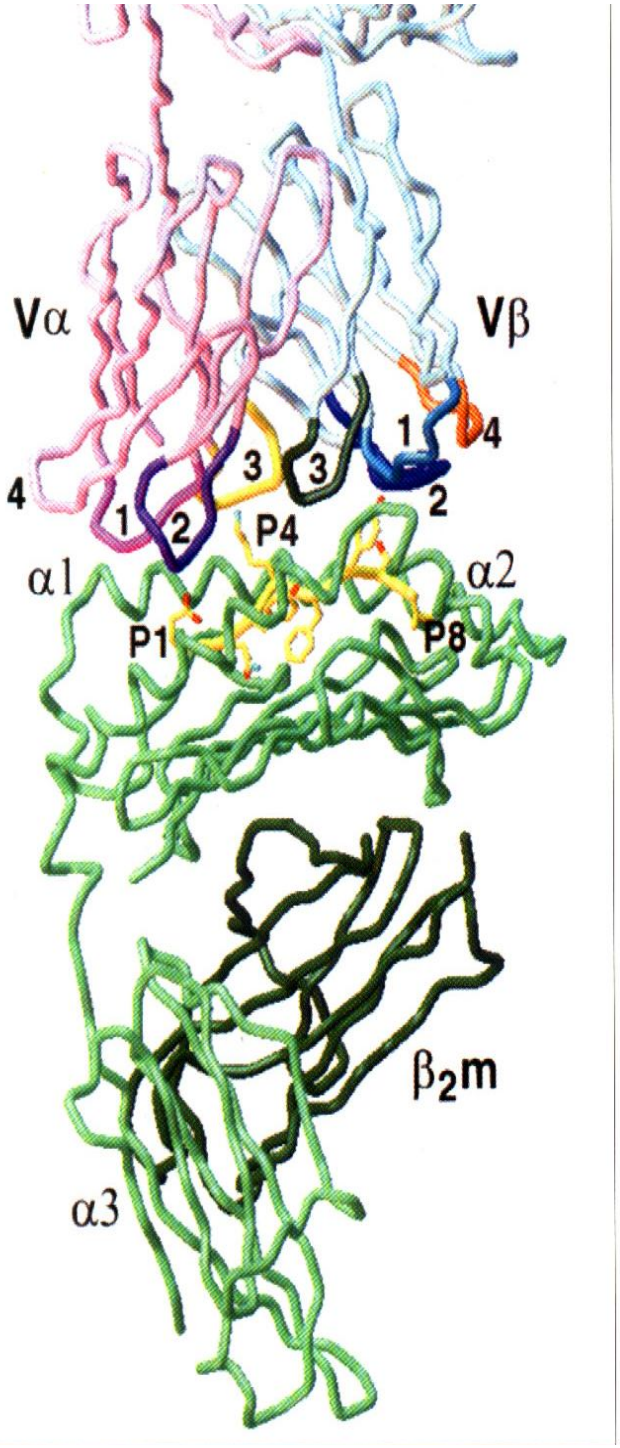
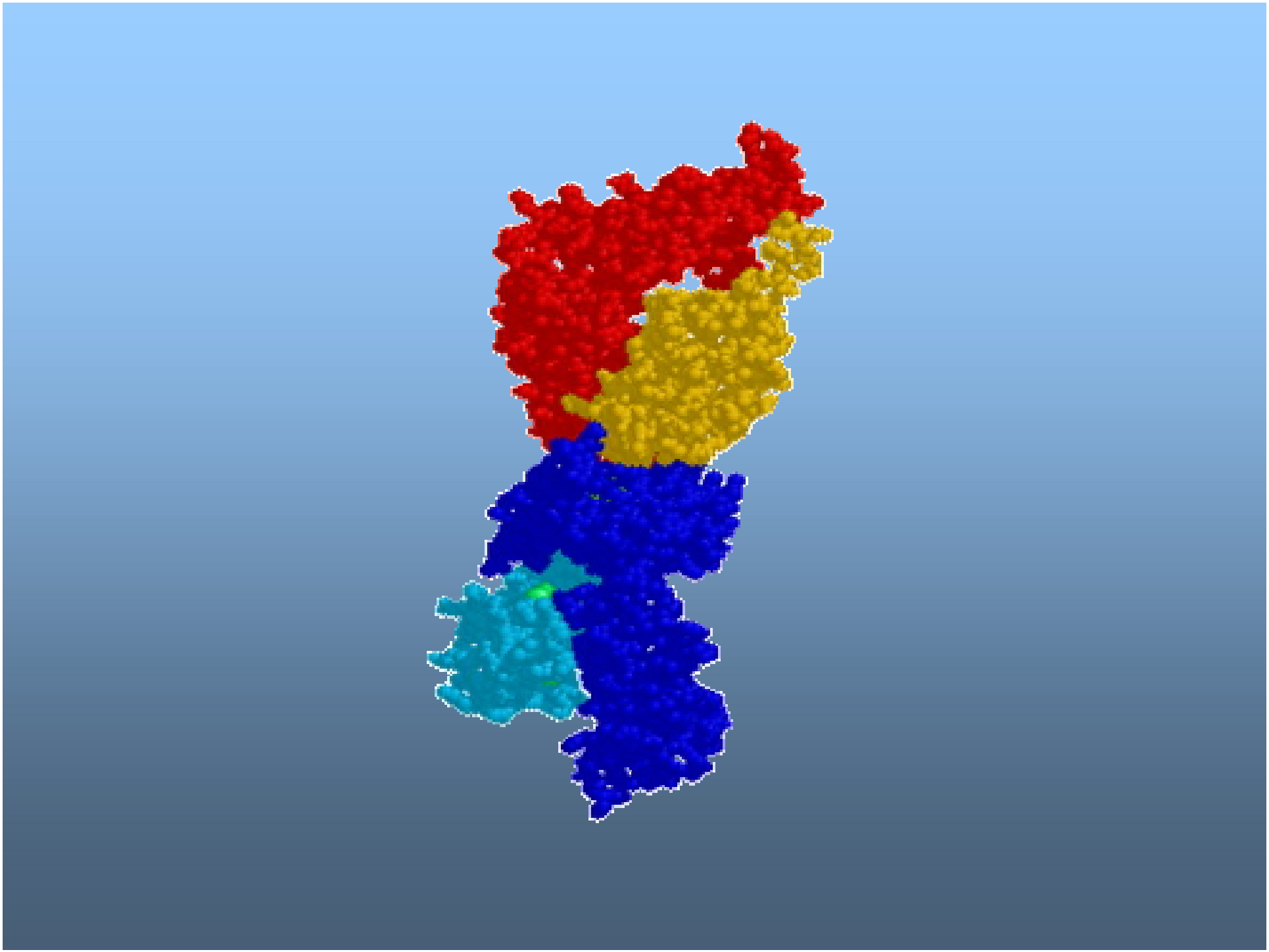


Figure 6. Interactions between a T-Cell Receptor and the HLA–Peptide Complex.

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


Vα
Vβ
4
1
2
3
3
1
4
2
P4
α1
α2
P1
P8
β2m
α3



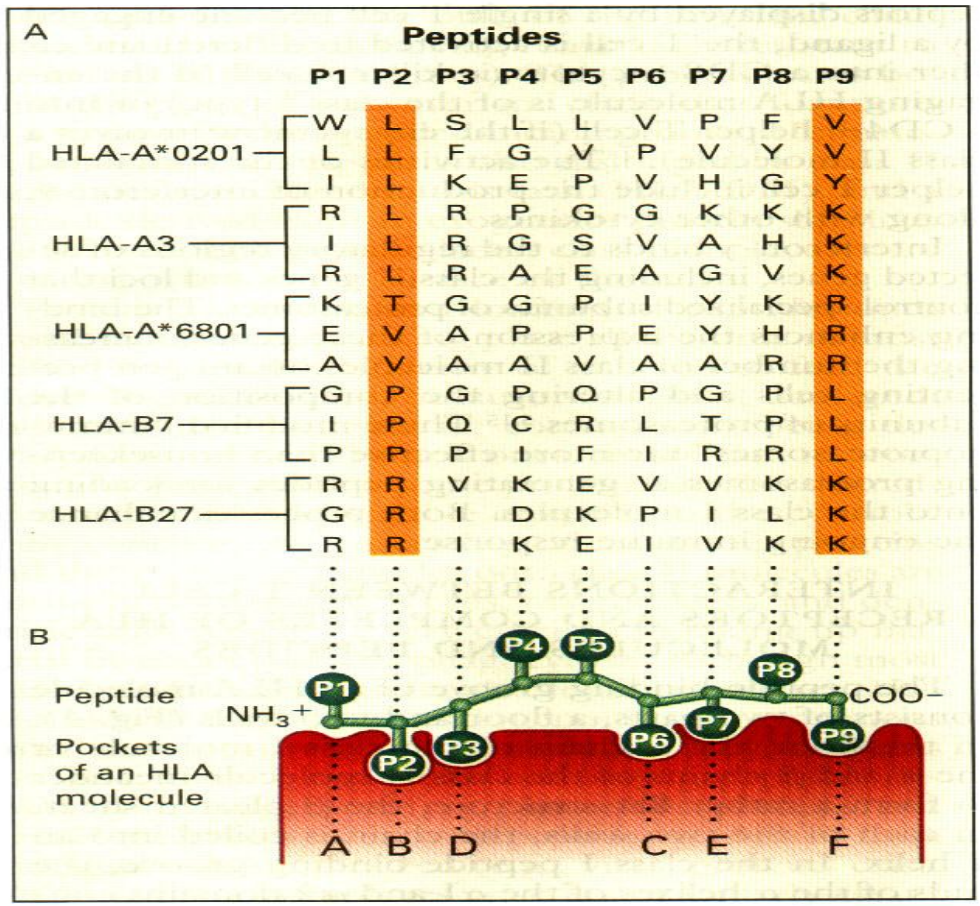


Figure 5. Interactions between HLA Molecules and Peptides.

Panel A shows examples of peptide motifs. The listed nonamers, as well as many others,[7] have been found in complexes with the indicated HLA class I molecules. The anchor residues are highlighted in yellow. In Panel B, a longitudinal section through the peptide-binding groove of an HLA class I molecule, the side chains of amino acid residues composing the bound peptide (P1 through P9) are oriented either down into the pockets of the HLA molecule or up. The following amino acids are shown: alanine (A), cysteine (C), aspartic acid (D), glutamic acid (E), phenylalanine (F), glycine (G), histidine (H), isoleucine (I), lysine (K), leucine (L), proline (P), glutamine (Q), arginine (R), serine (S), threonine (T), valine (V), tryptophan (W), and tyrosine (Y).

PRESENTACION ANTIGENOS TUMORALES

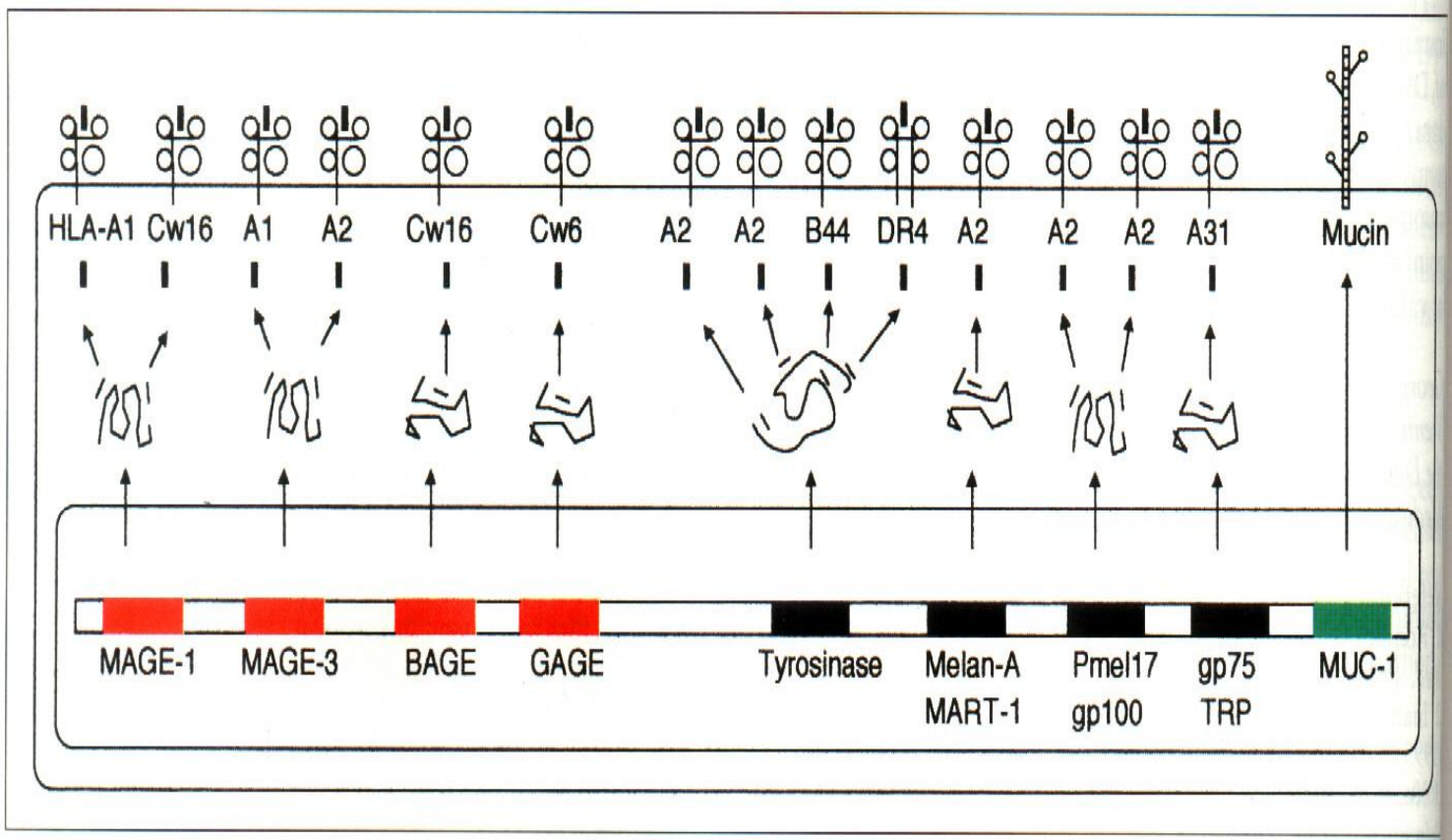
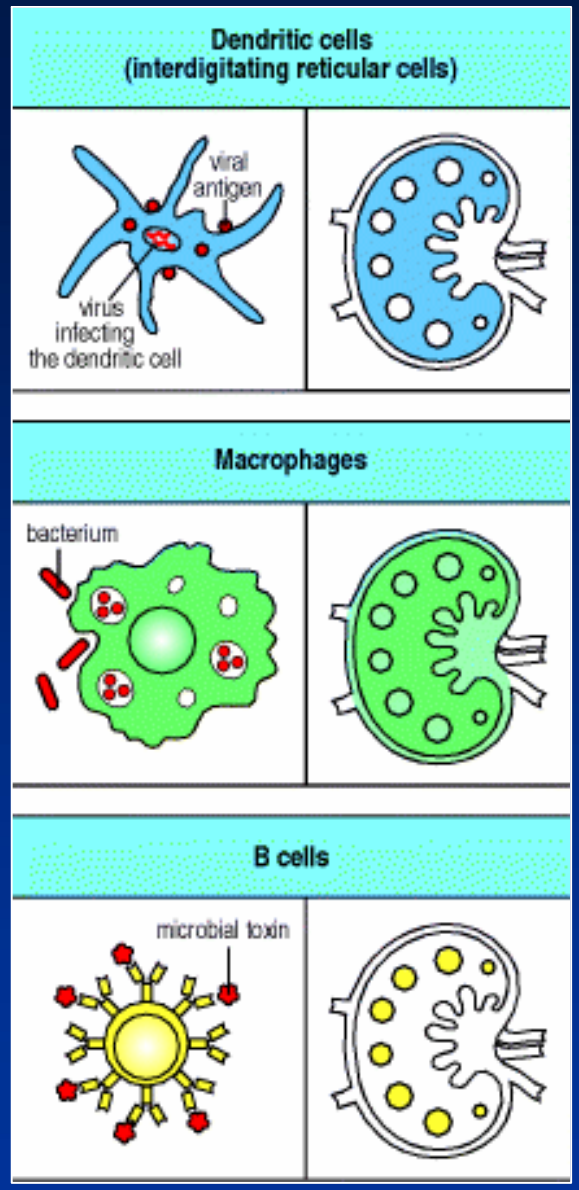
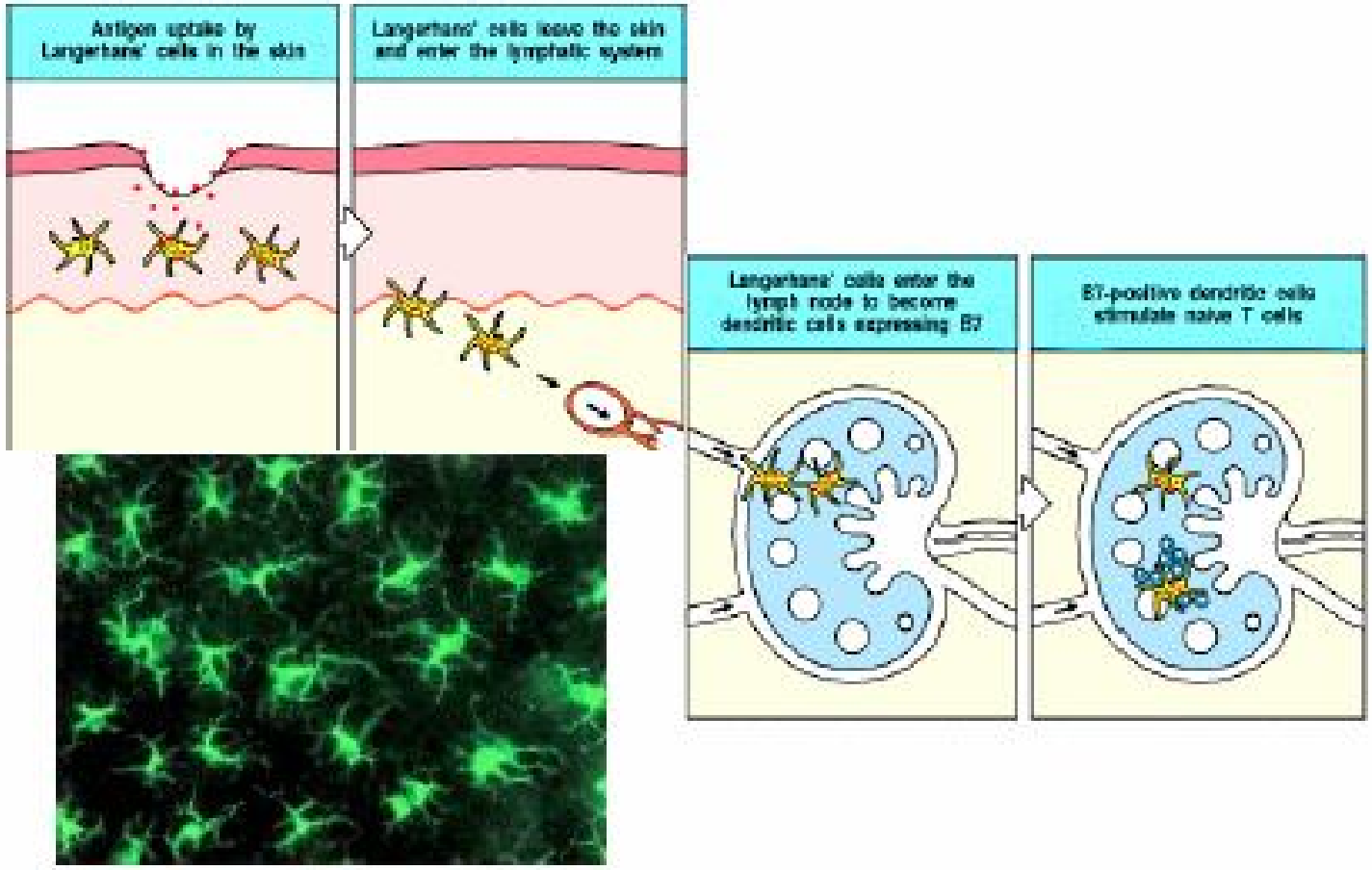


Fig. 1. *Genes encoding tumor antigens presented to autologous T lymphocytes by major histocompatibility complex (MHC) class I or class I molecules. Several of these genes encode proteins that generate multiple peptides, each of which binds to a distinct MHC molecule (shown at the top of the figure). In addition, altered mucin molecules can act as tumor-specific antigens.*



Captación por CPA

Migración de DC de tejidos periféricos a ganglios linfáticos



TOLL-LIKE RECEPTORS

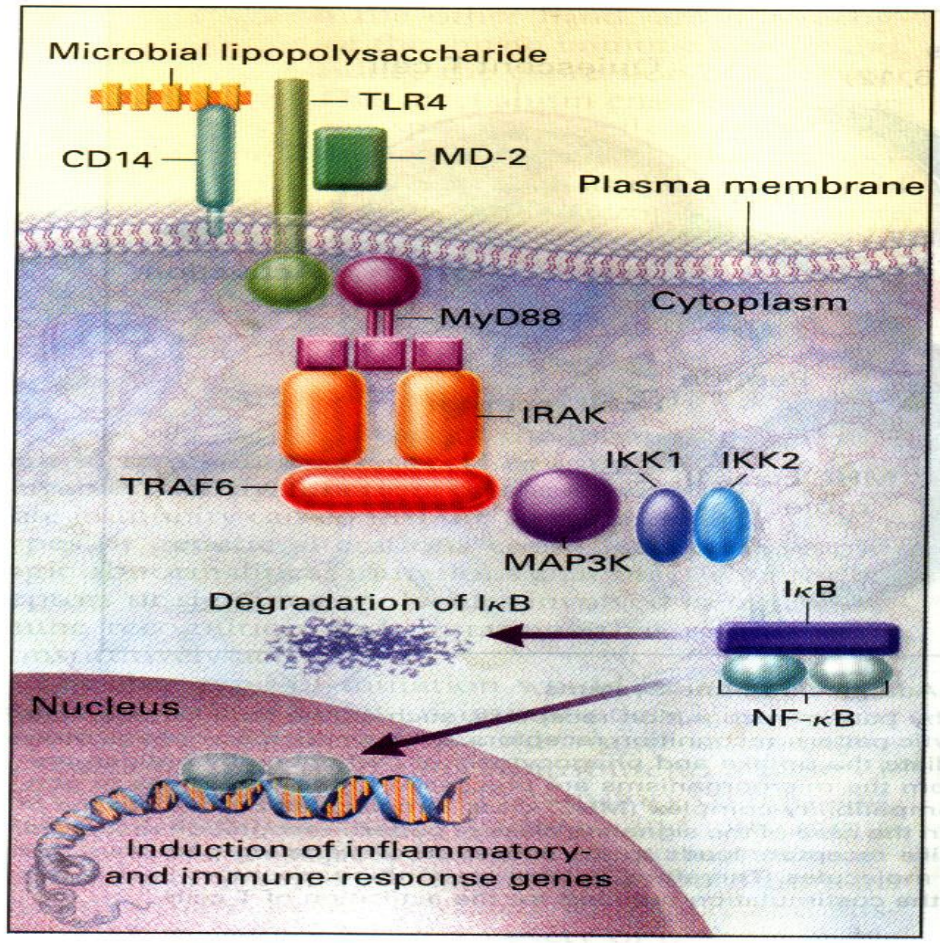
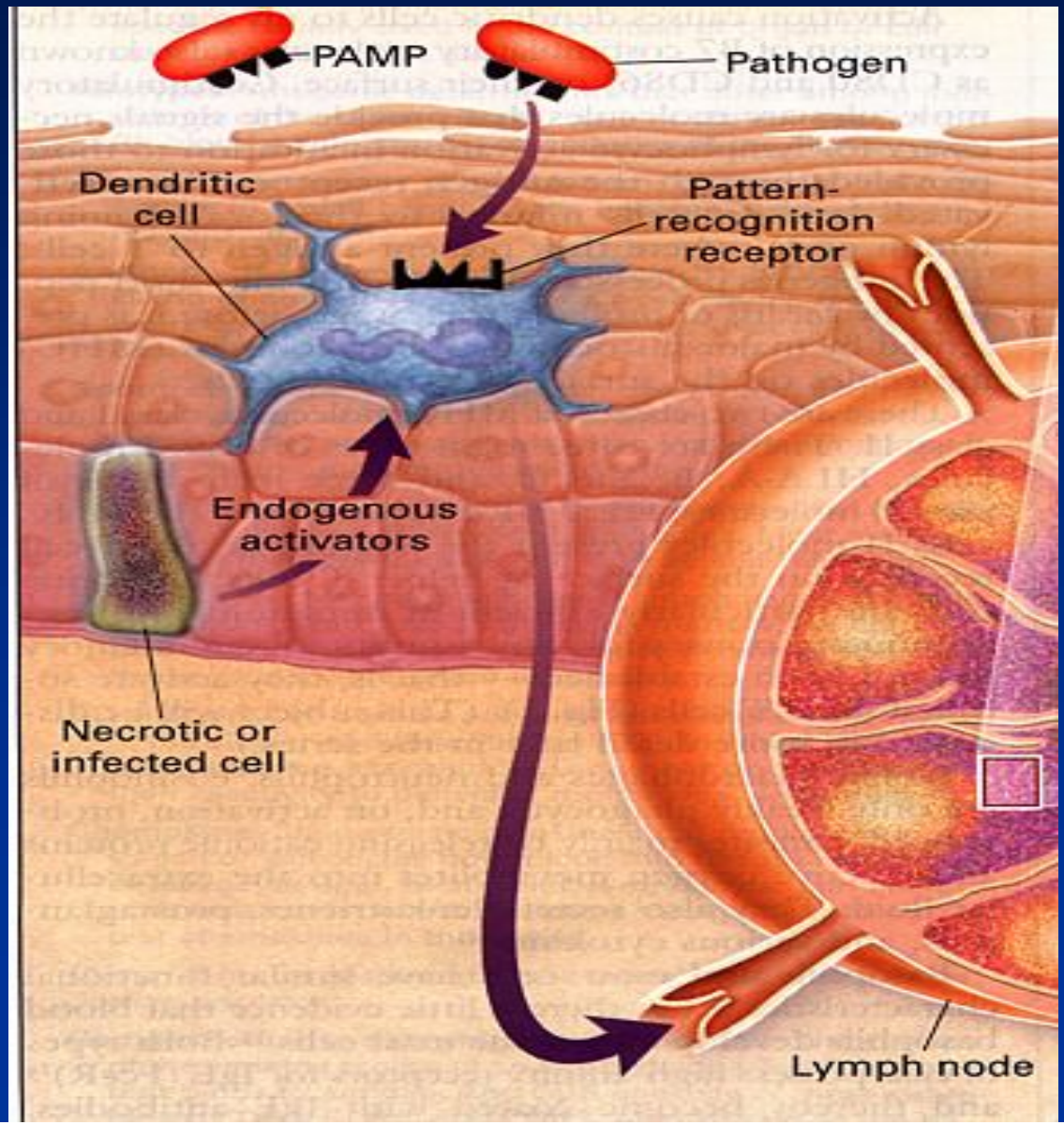


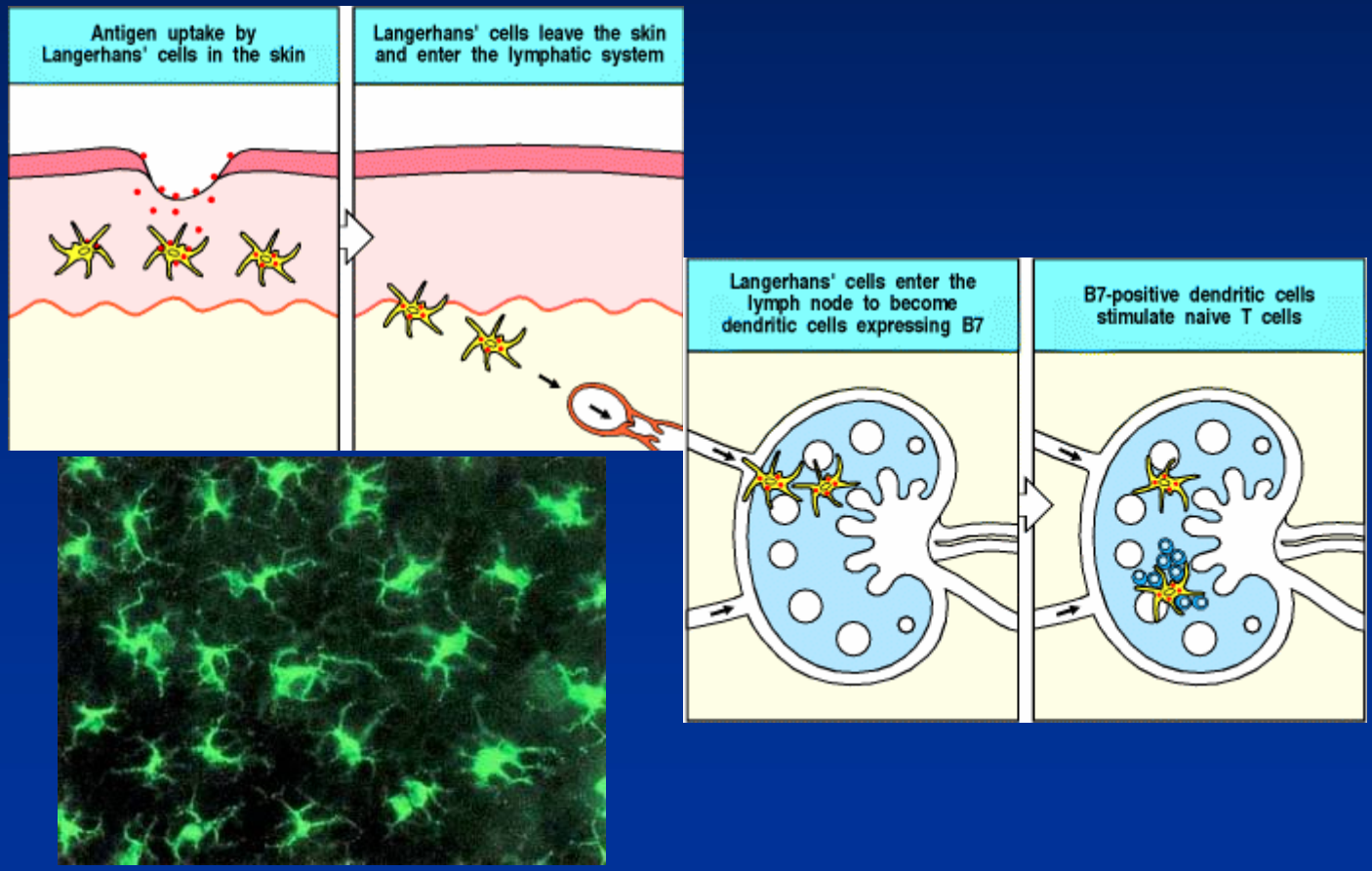
Figure 2. The Signaling Pathway of Toll-like Receptors.

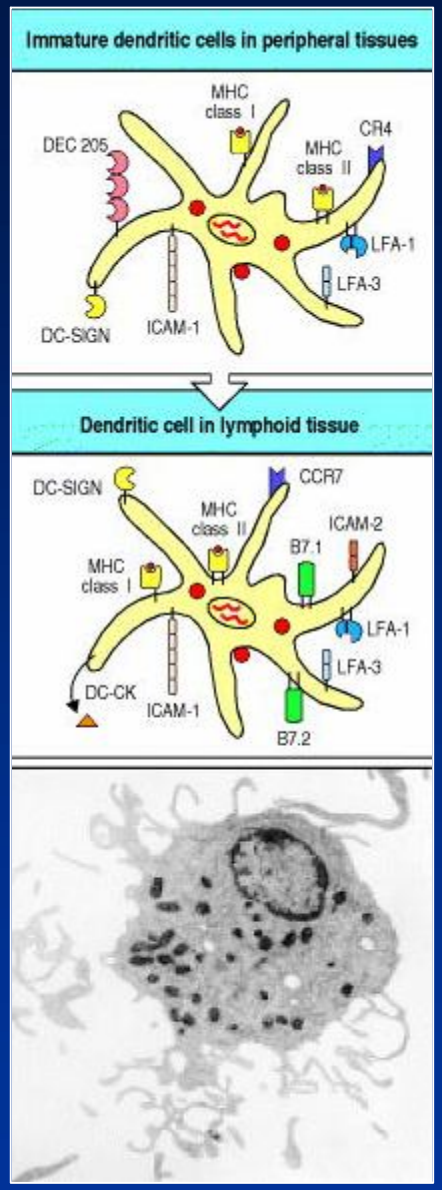
Some of the toll-like receptors (TLRs) function as pattern-recognition receptors of the innate immune system. Their recognition of microbial products leads to the activation of the nuclear factor-κB (NF-κB) signaling pathway. In this example, the recognition of lipopolysaccharide is mediated by three 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

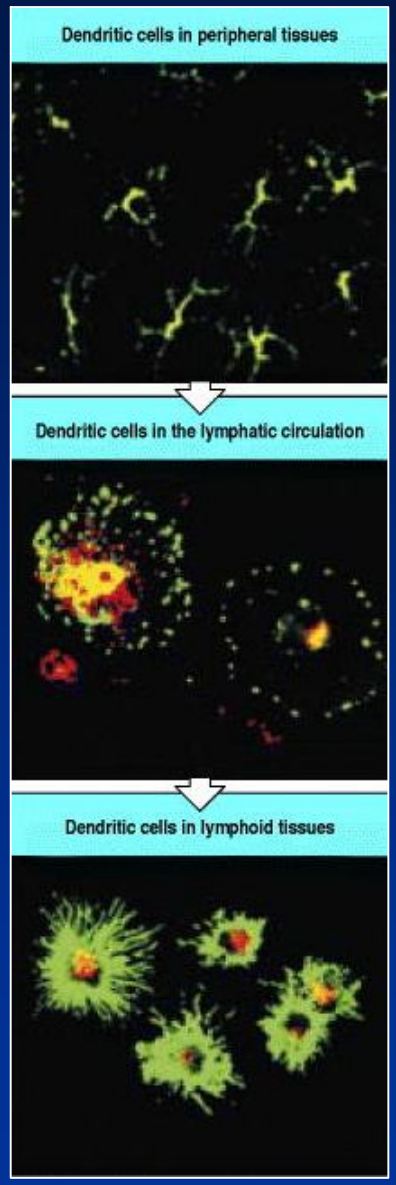
ACTIVACION CELULAS DENDRITICAS



Migración de DC de tejidos periféricos a ganglios linfáticos







Maduración de DC

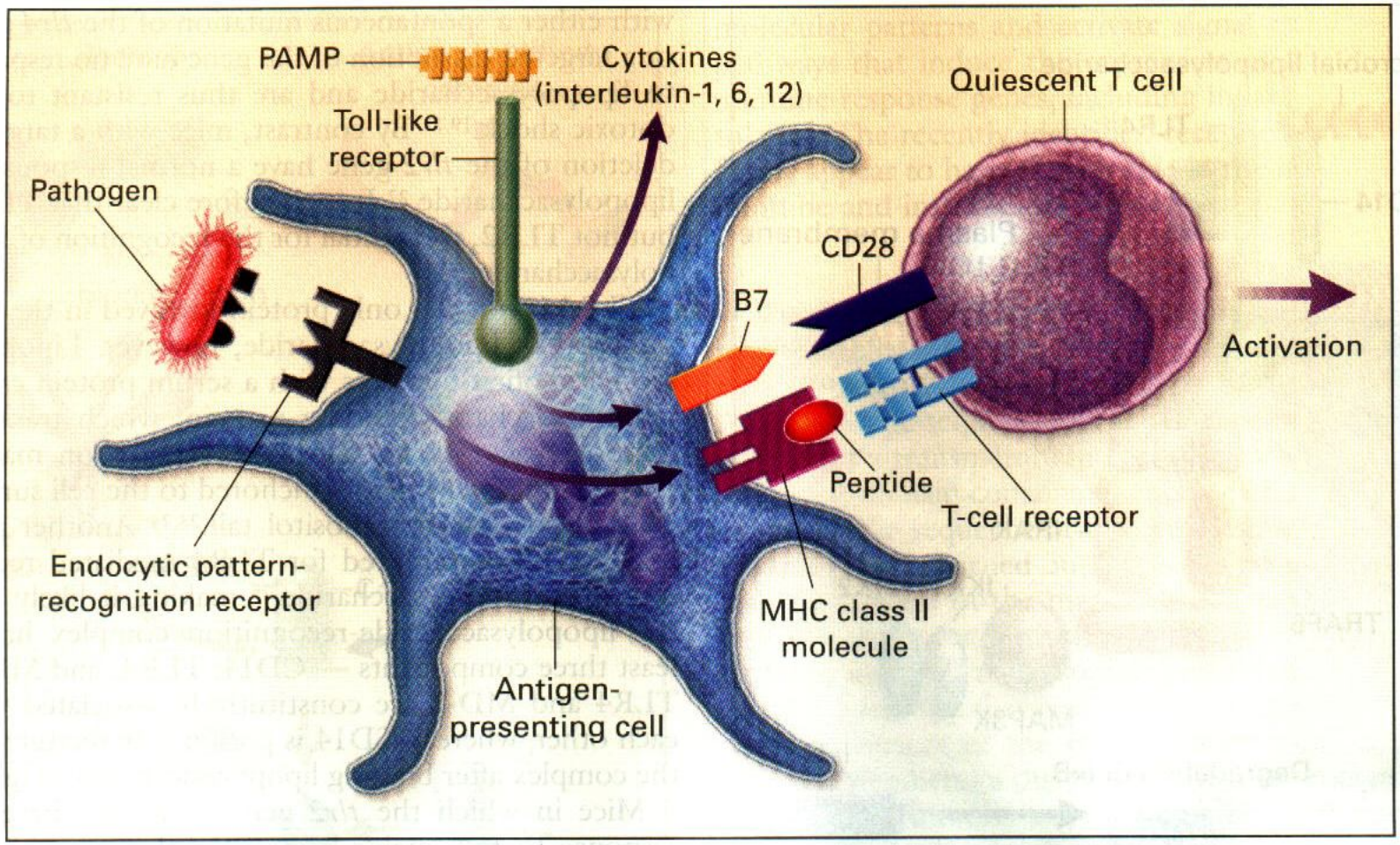
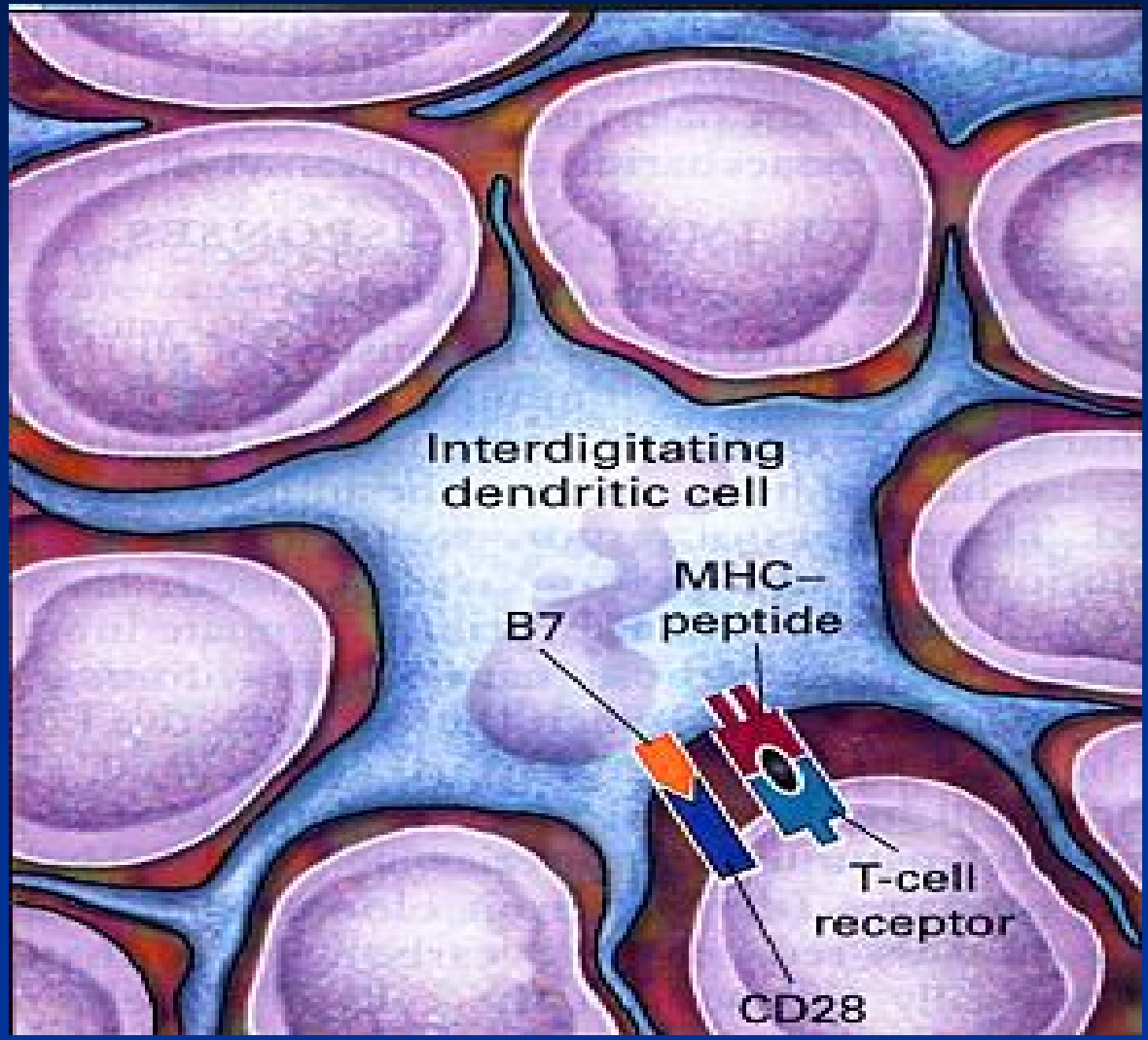
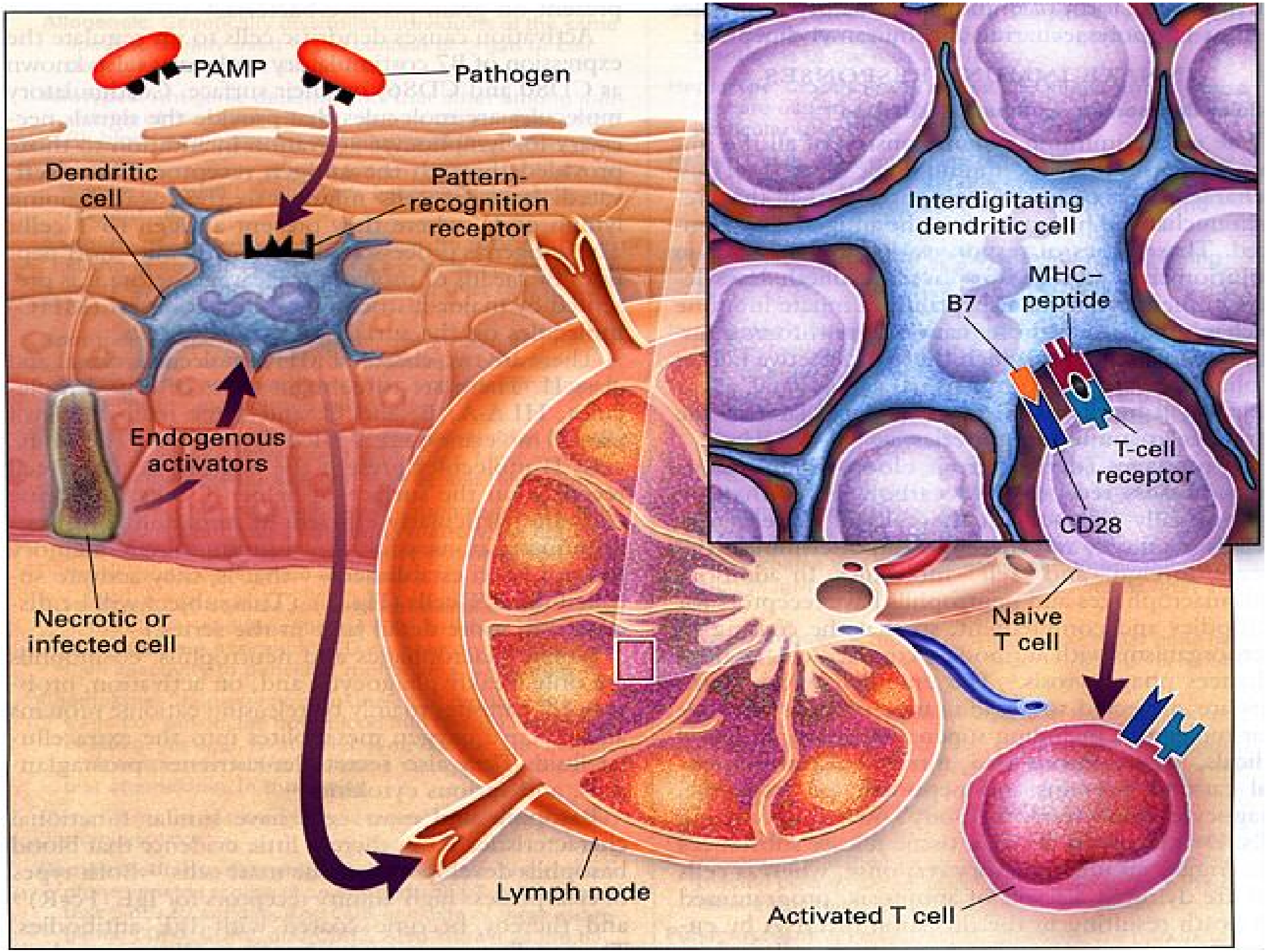


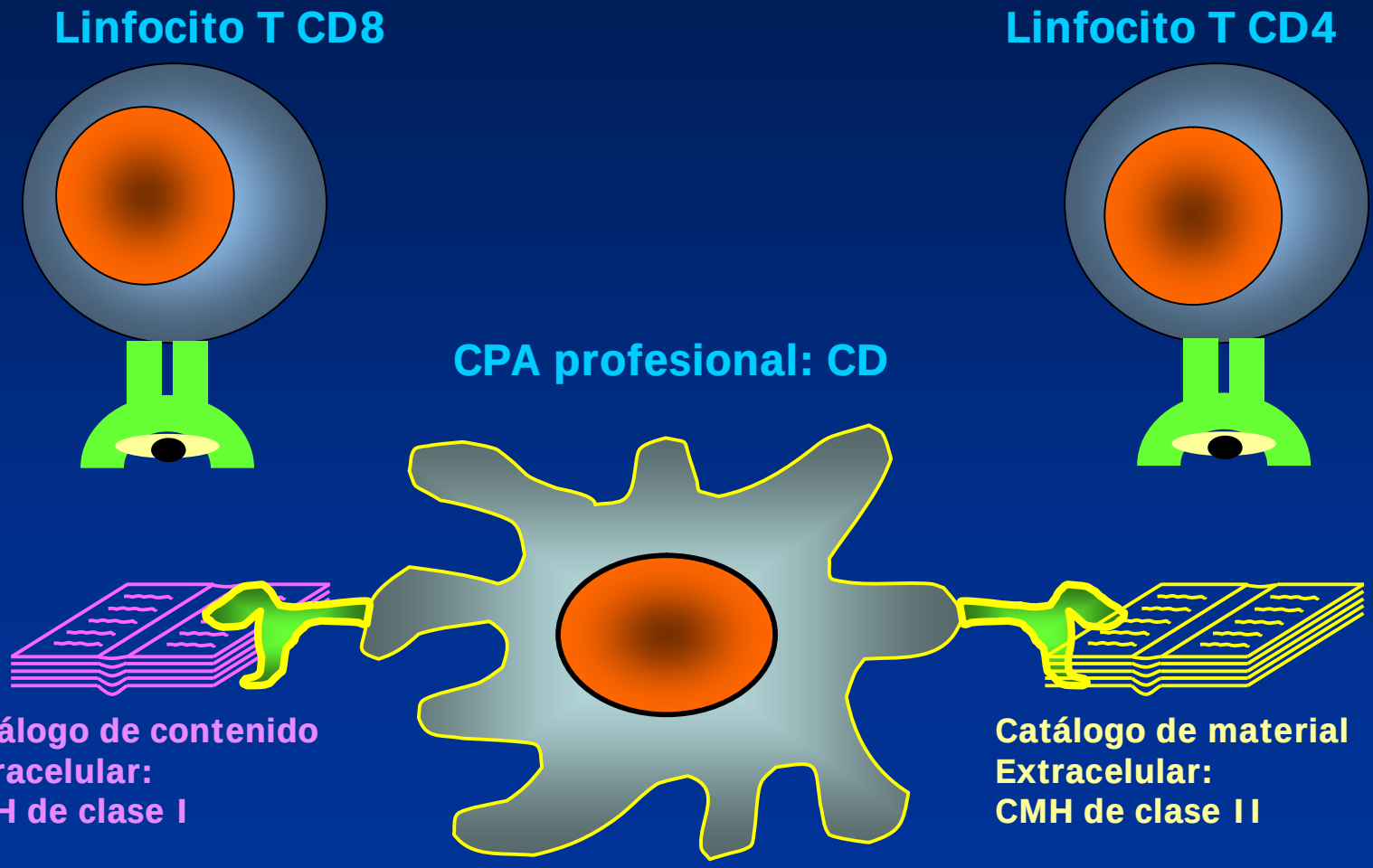
Figure 3. The Receptors Involved in the Interplay of the Innate and Adaptive Immune Systems.

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.


Interdigitating
dendritic cell
MHC–
peptide
B7
T-cell
receptor
CD28


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



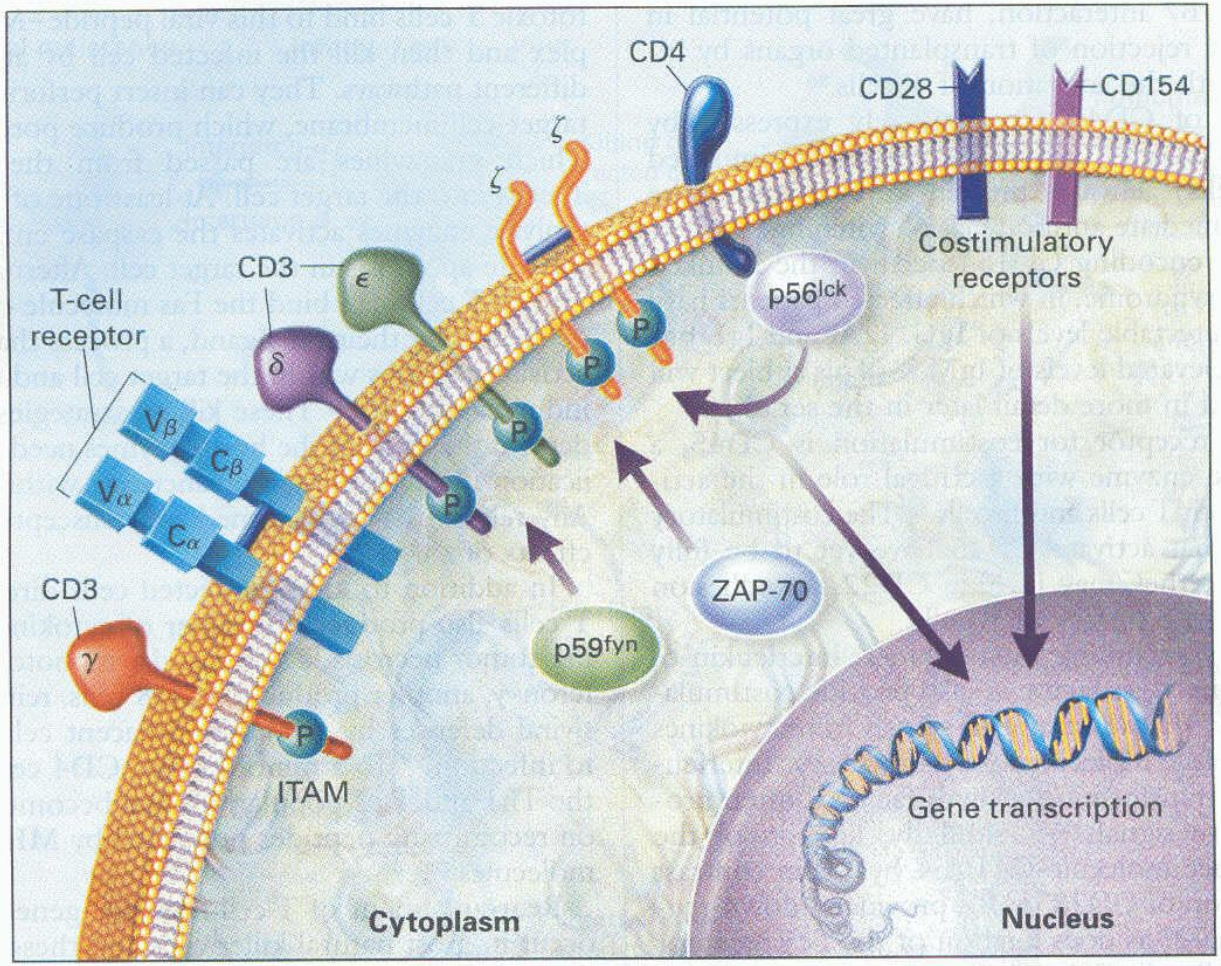
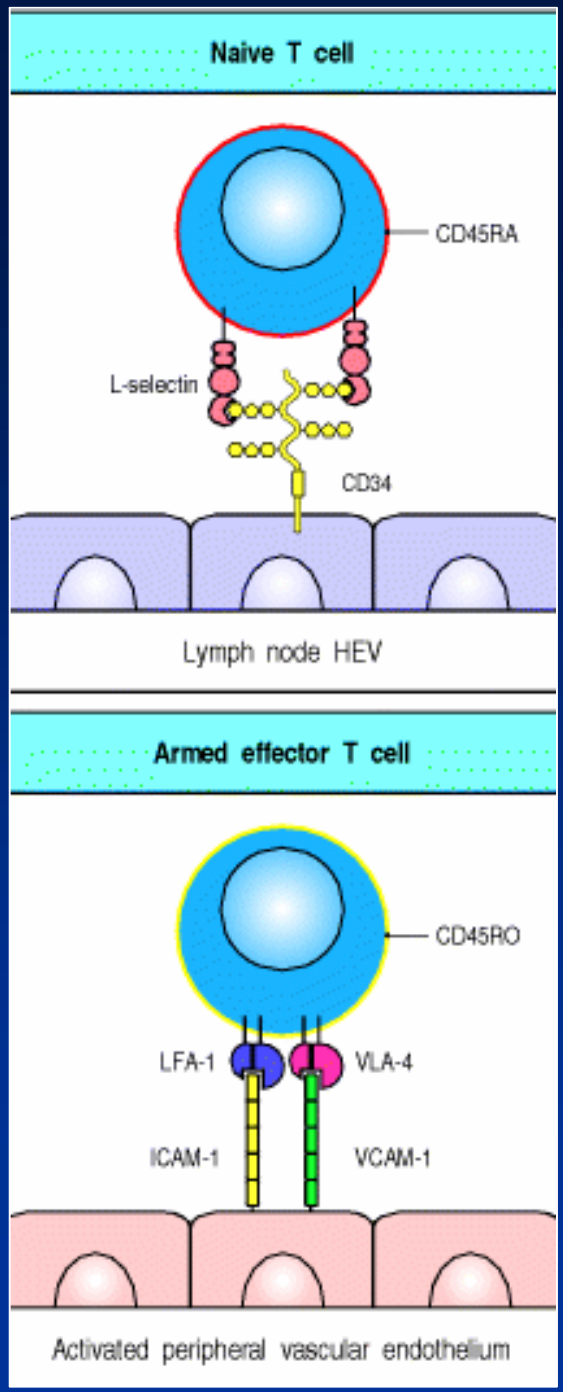


Figure 9. Activation of T Cells.

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

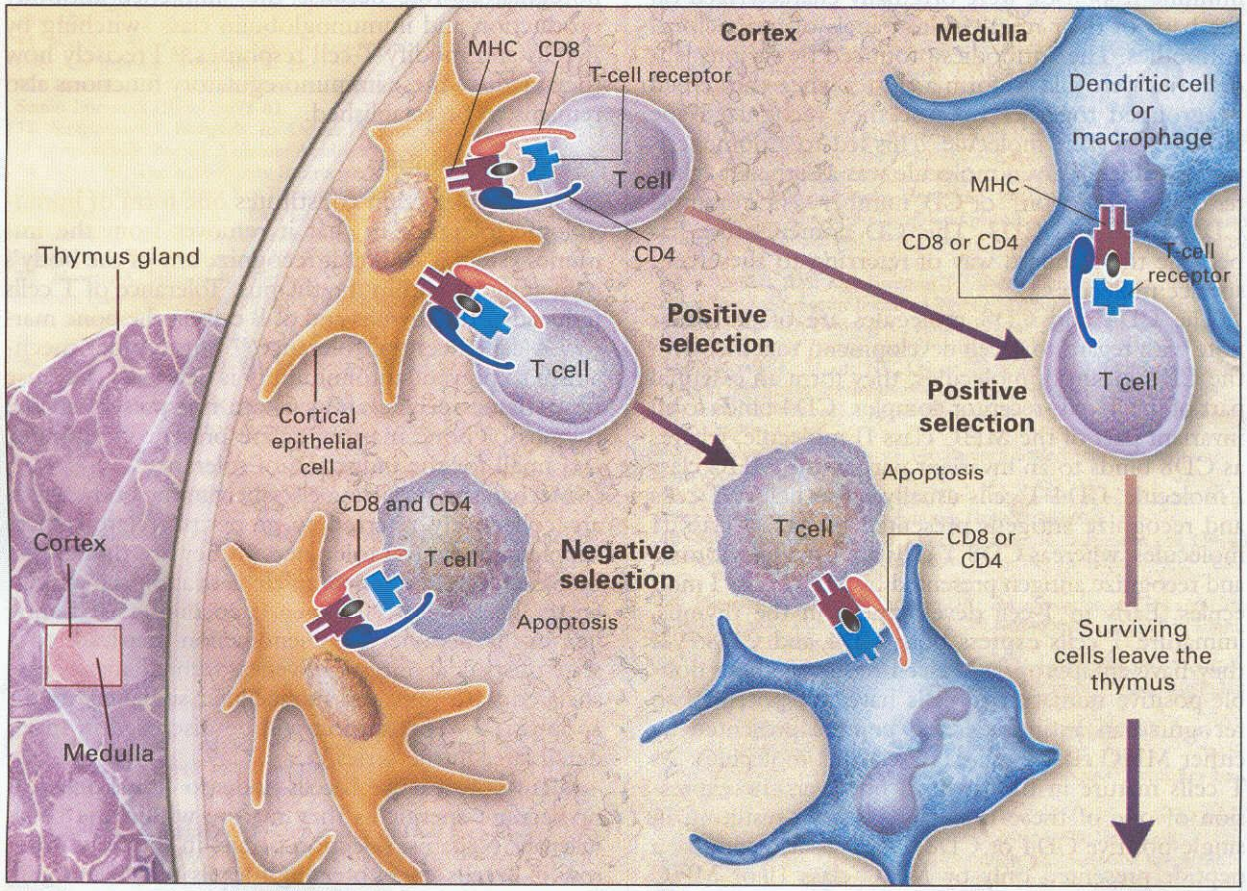


Figure 7. Positive and Negative Selection in the Thymus.

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.

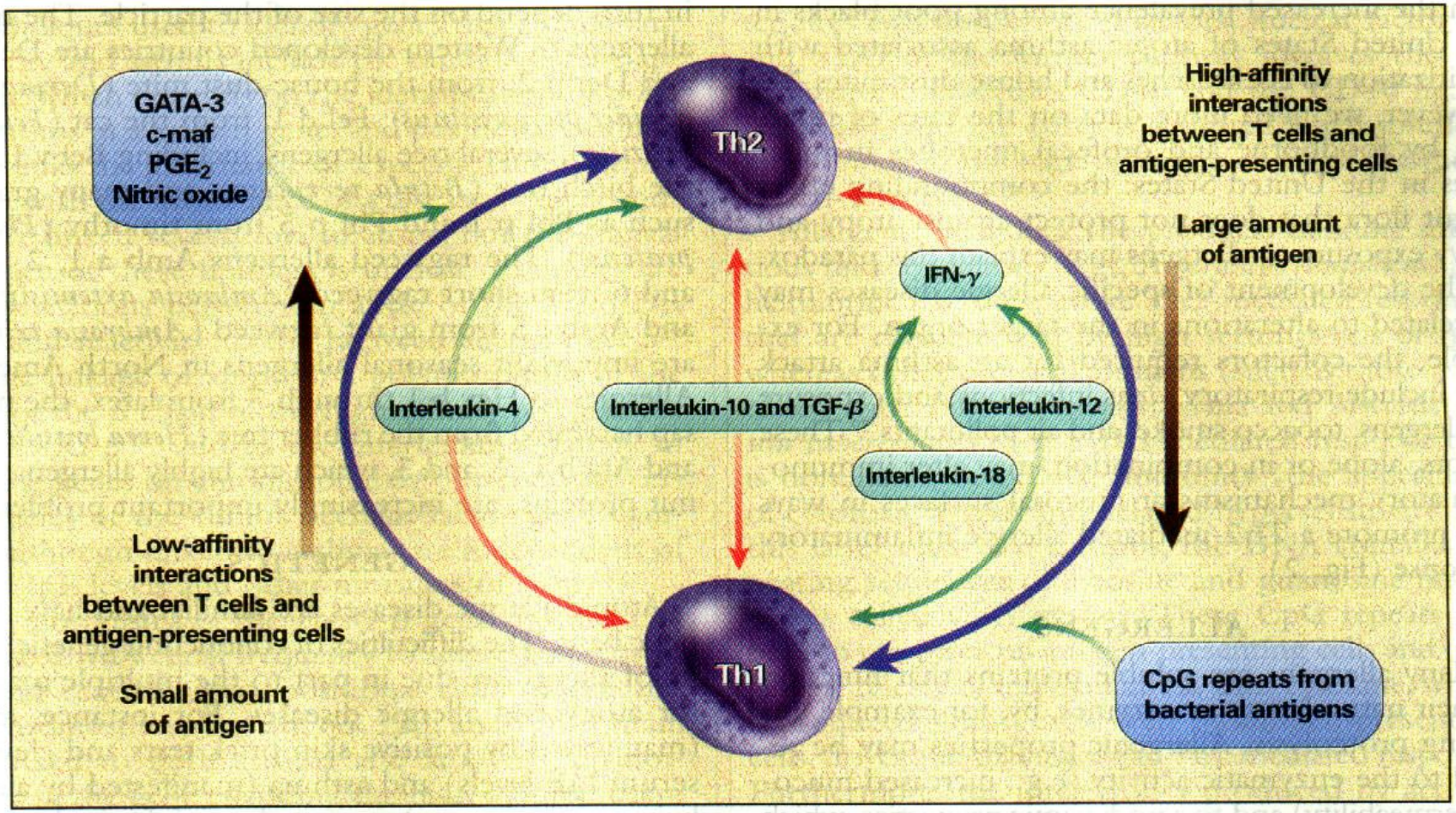
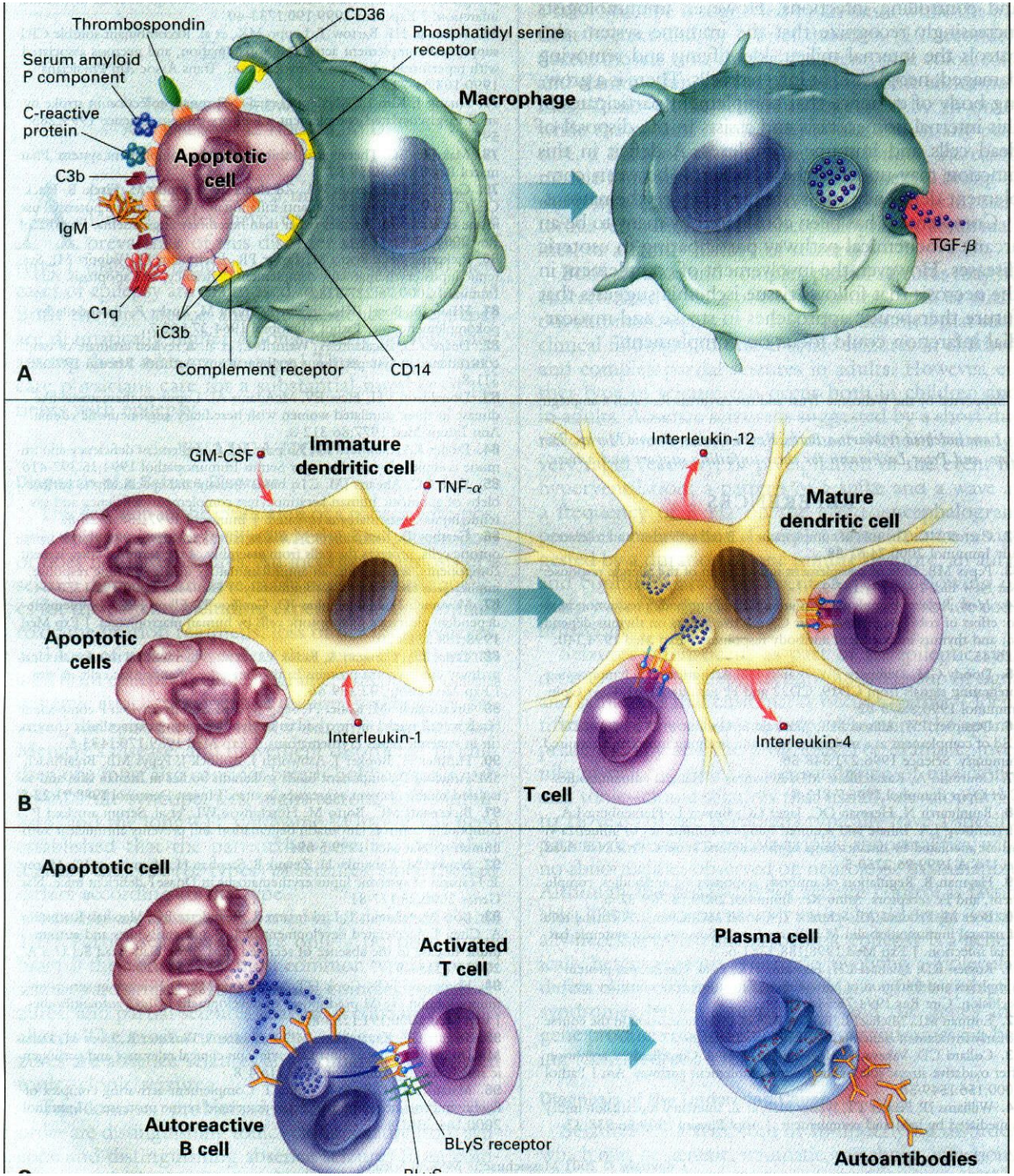


Figure 1. Immunologic and Cellular Factors Regulating the Expression of Th1 and Th2 Cells.

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

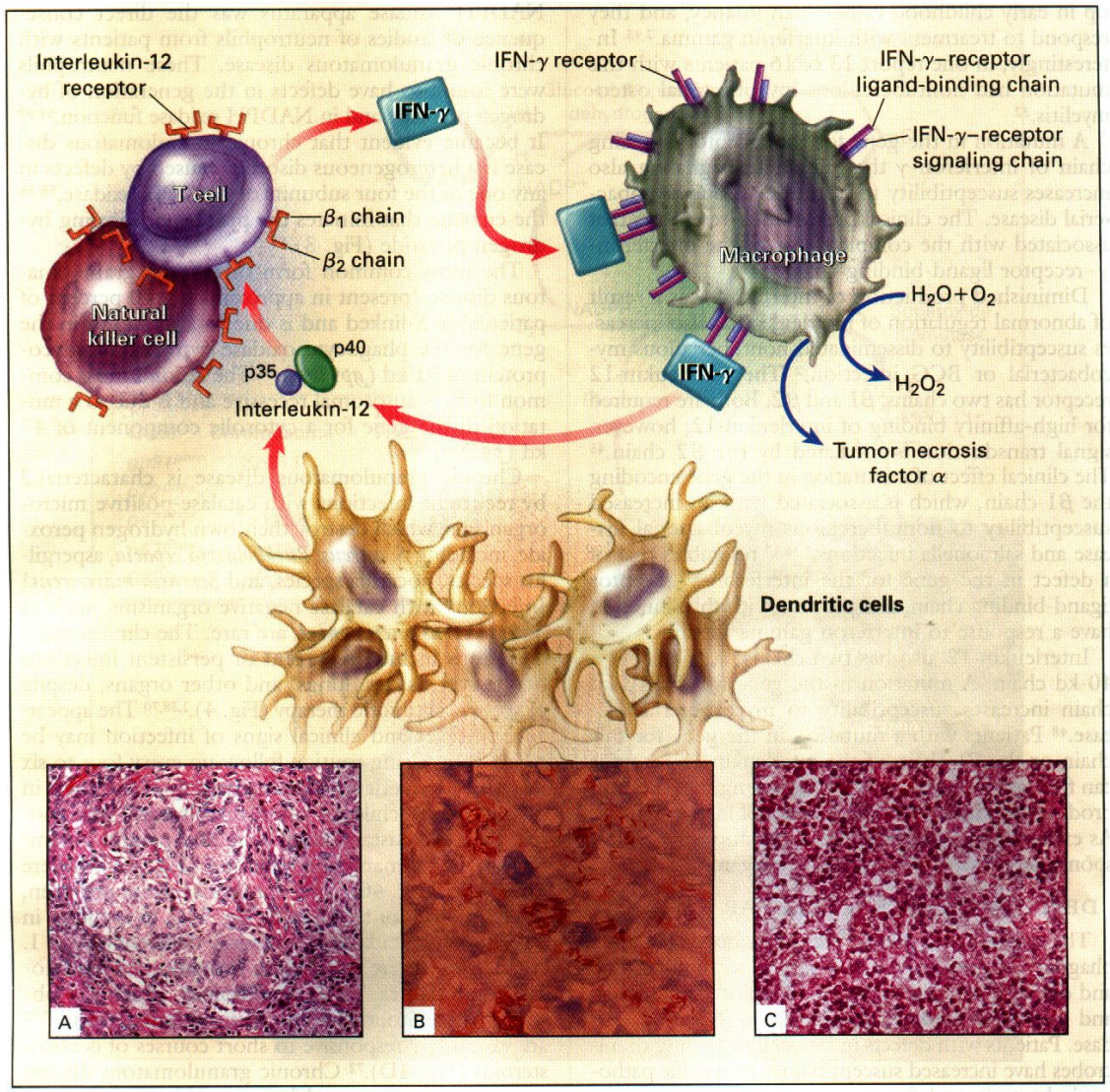
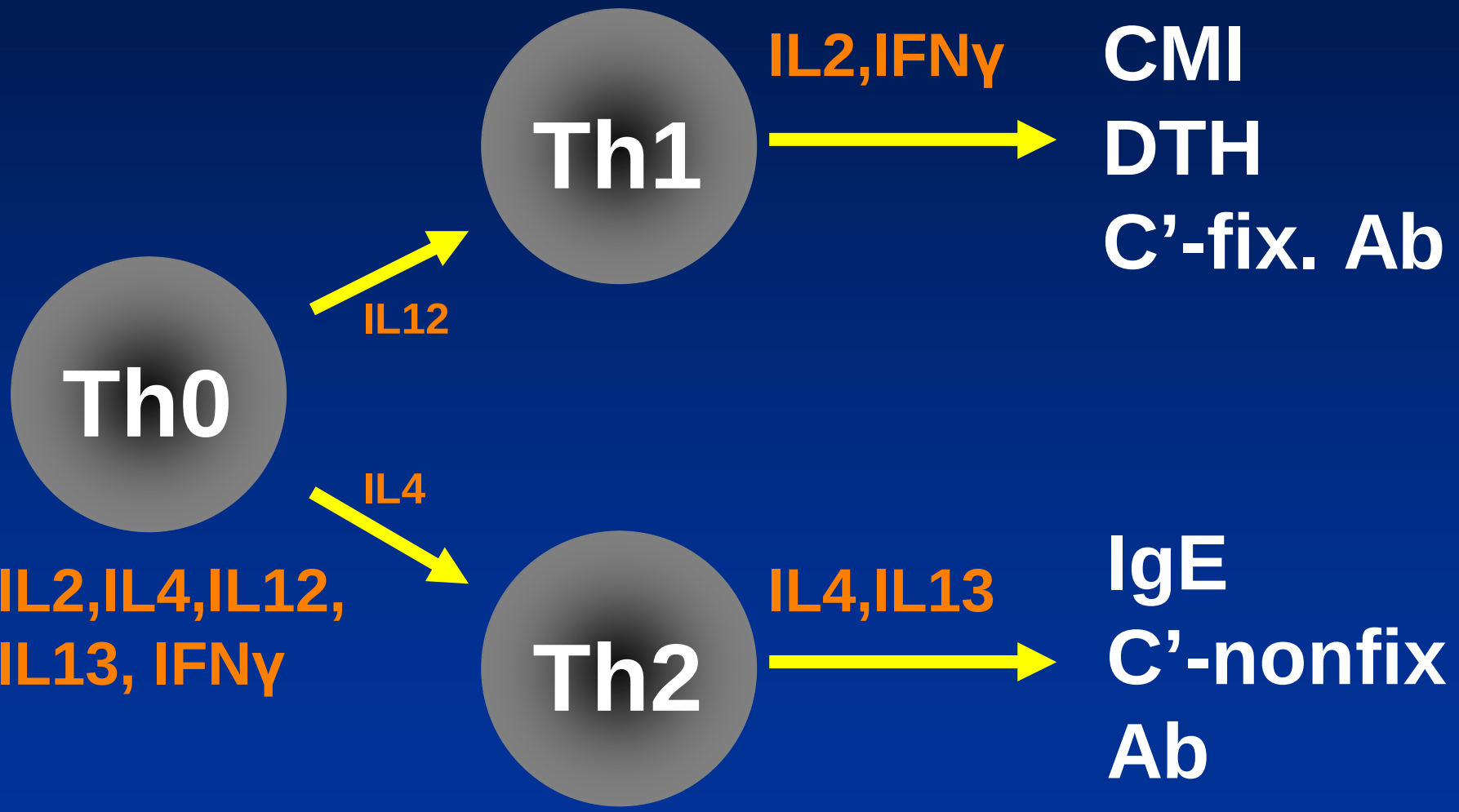


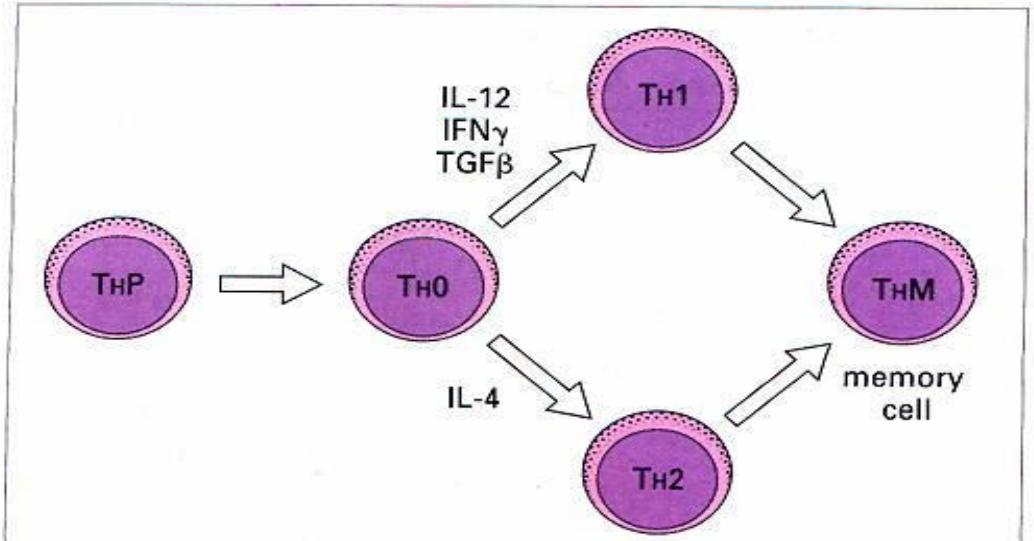
Figure 2. Interferon-γ–Interleukin-12 Signal-Transduction Cascade.

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).

CD4 T cell cytokine effects:



Differentiation of CD4⁺ TH cells



THP	TH0	TH1	TH2	THM
IL-2	IL-2	IL-2		IL-2
	IFNγ	IFNγ		
	TNFβ	TFNβ		
	IL-3	IL-3		
	IL-4		IL-4	
	IL-5		IL-5	
	IL-6		IL-6	
	IL-9		IL-9	
	IL-10		IL-10	
	IL-13		IL-13	
	GM–CSF	GM–CSF	GM–CSF	
	TNFα	TNFα	TNFα	

Fig. 7.12 The diagram illustrates the differentiation of murine TH cells into subsets with distinctive patterns of cytokine release. IL-12, IFNγ and TGFβ favour differentiation of TH1 cells and IL-4 favours TH2 cells. The cytokine patterns influence the effector functions that are activated.

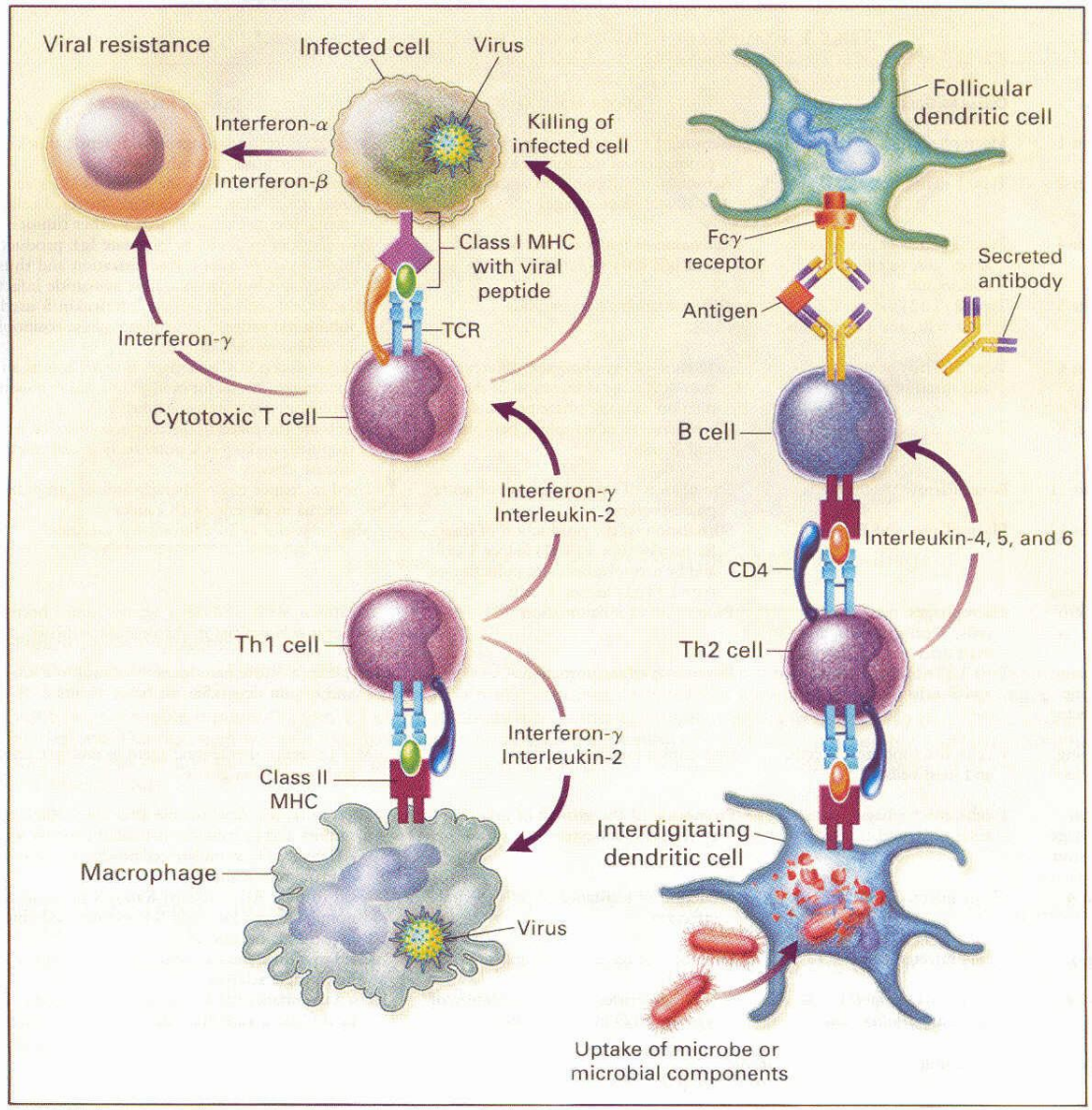


Figure 10. An Overview of Lymphocyte Responses.

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.

Selection of effector mechanisms by TH1 and TH2 cells

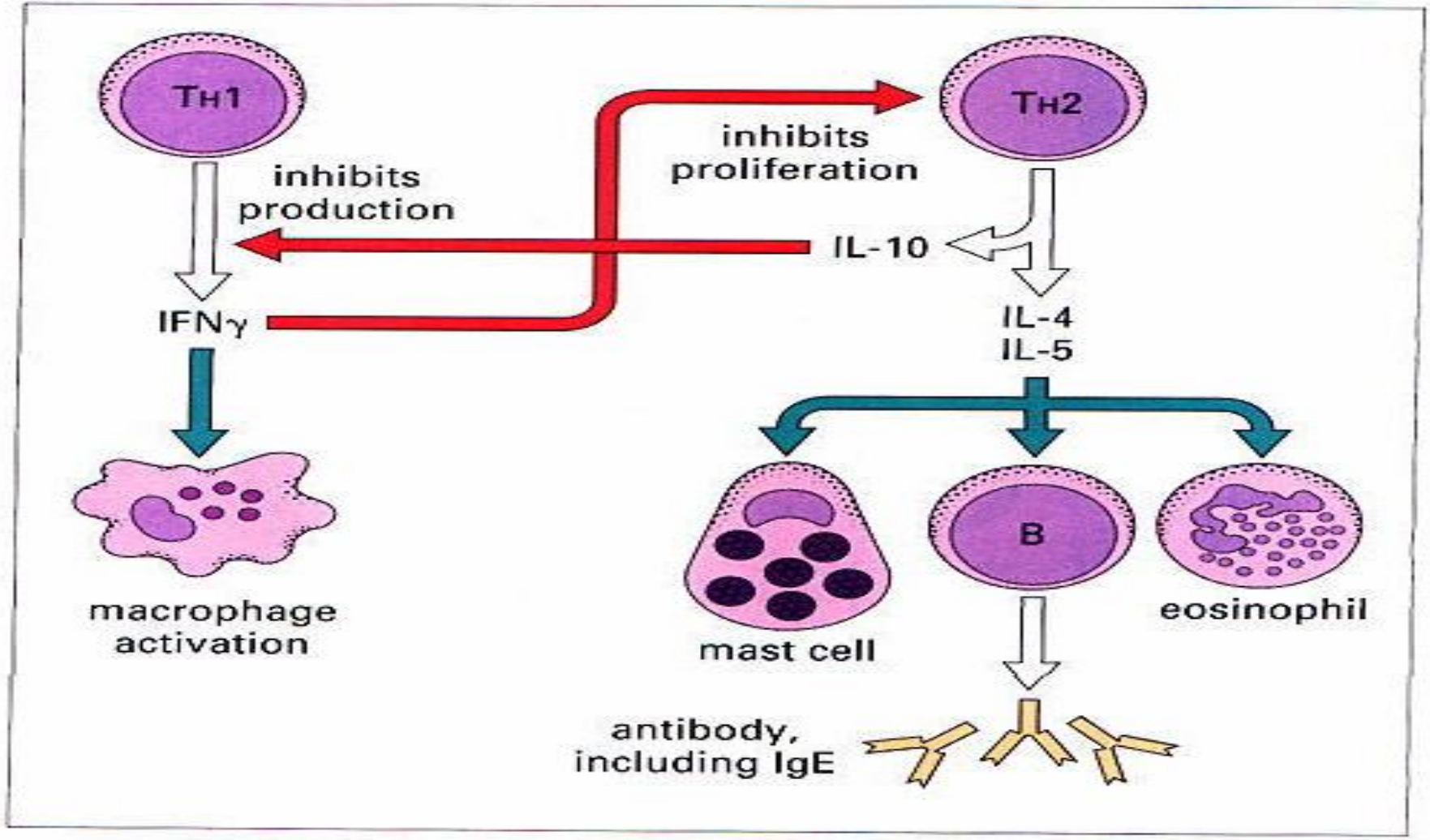


Fig. 7.13 Not only does their cytokine output drive different effector pathways, but TH1 cells tend to switch off TH2 cells, and vice versa.

LINFOCITO CD8

LINFOCITO CD4

EL SEPTIMO SELLO , INGMANR BERMAN

Ingmar Bergman, “EL SEPTIMO SELLO”

http://science.nhmccd.edu/biol/animatio.hml