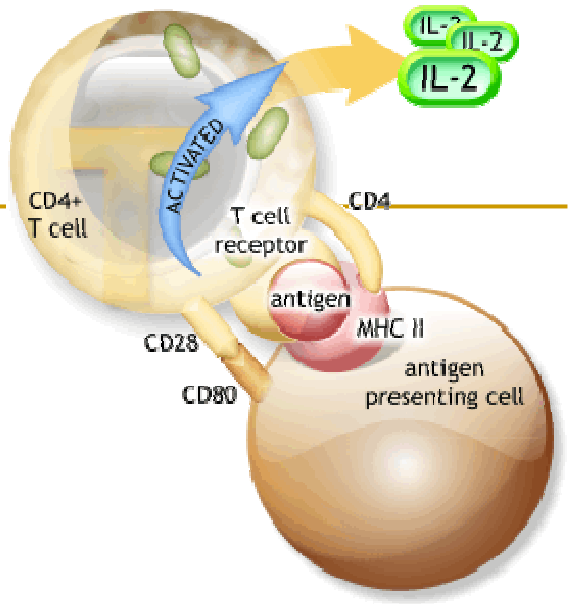
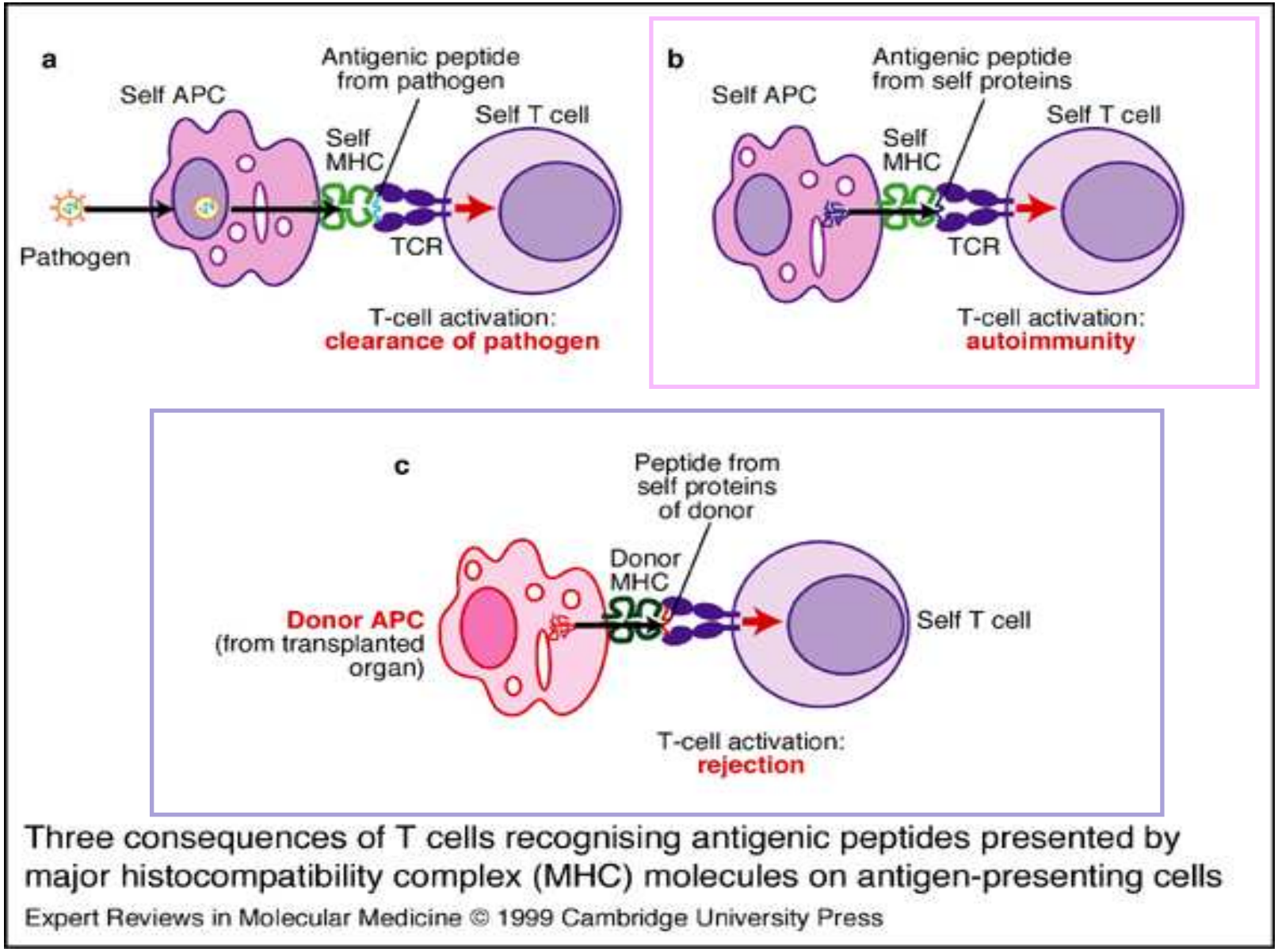
Inmunología Clínica 2009

Bioq Graciela R Svibel de Mizdraji

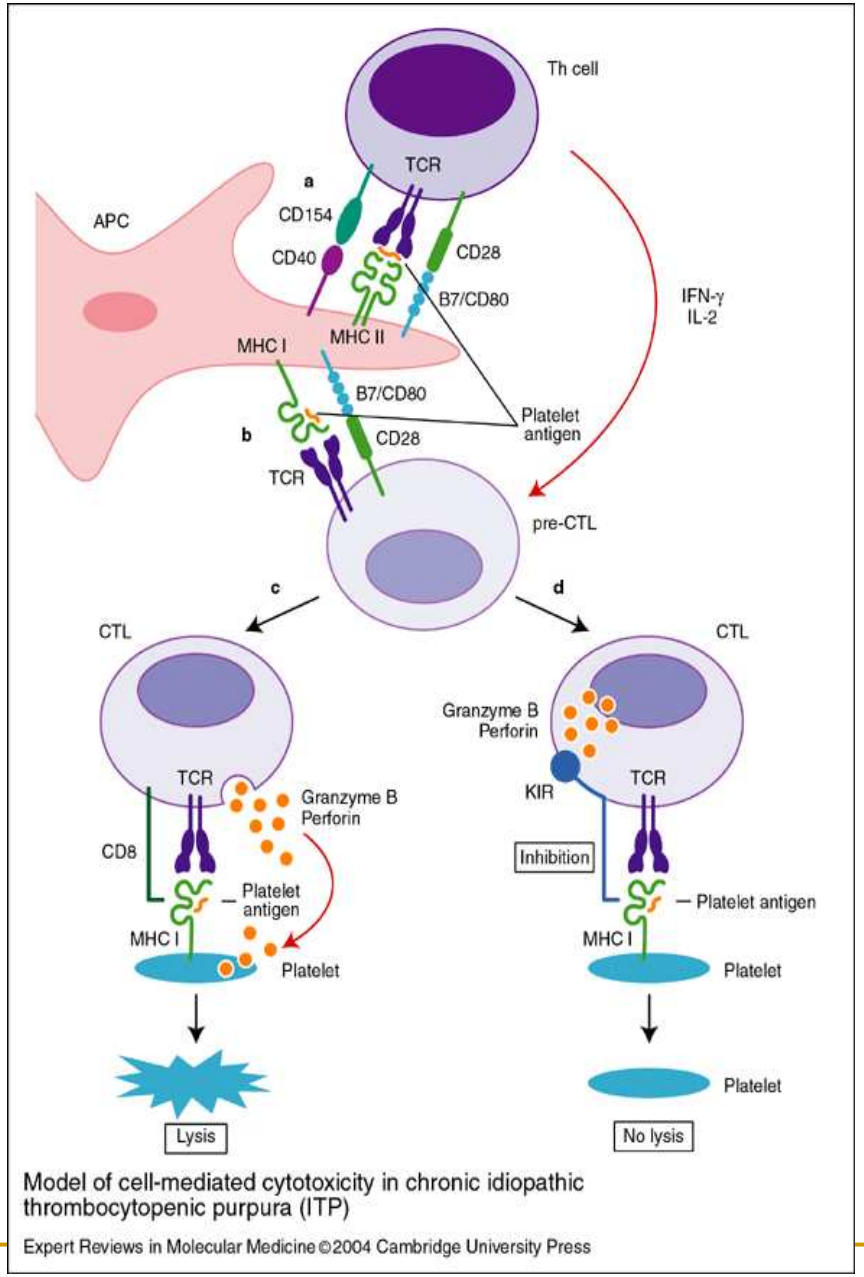


¿Cuáles son las consecuencias del reconocimiento del péptido antigénico-MHC por la célulaT?



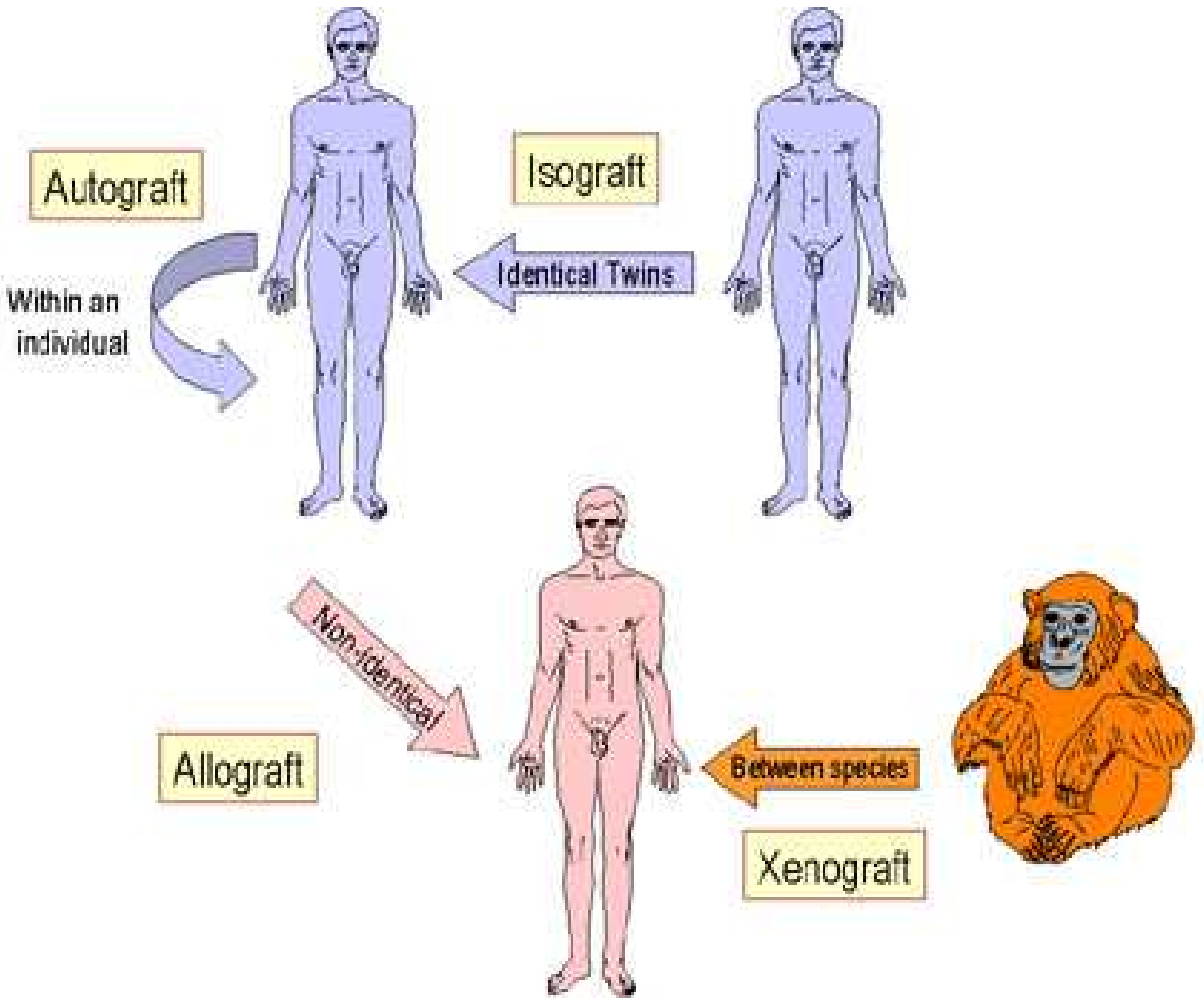
Three consequences of T cells recognising antigenic peptides presented by major histocompatibility complex (MHC) molecules on antigen-presenting cells

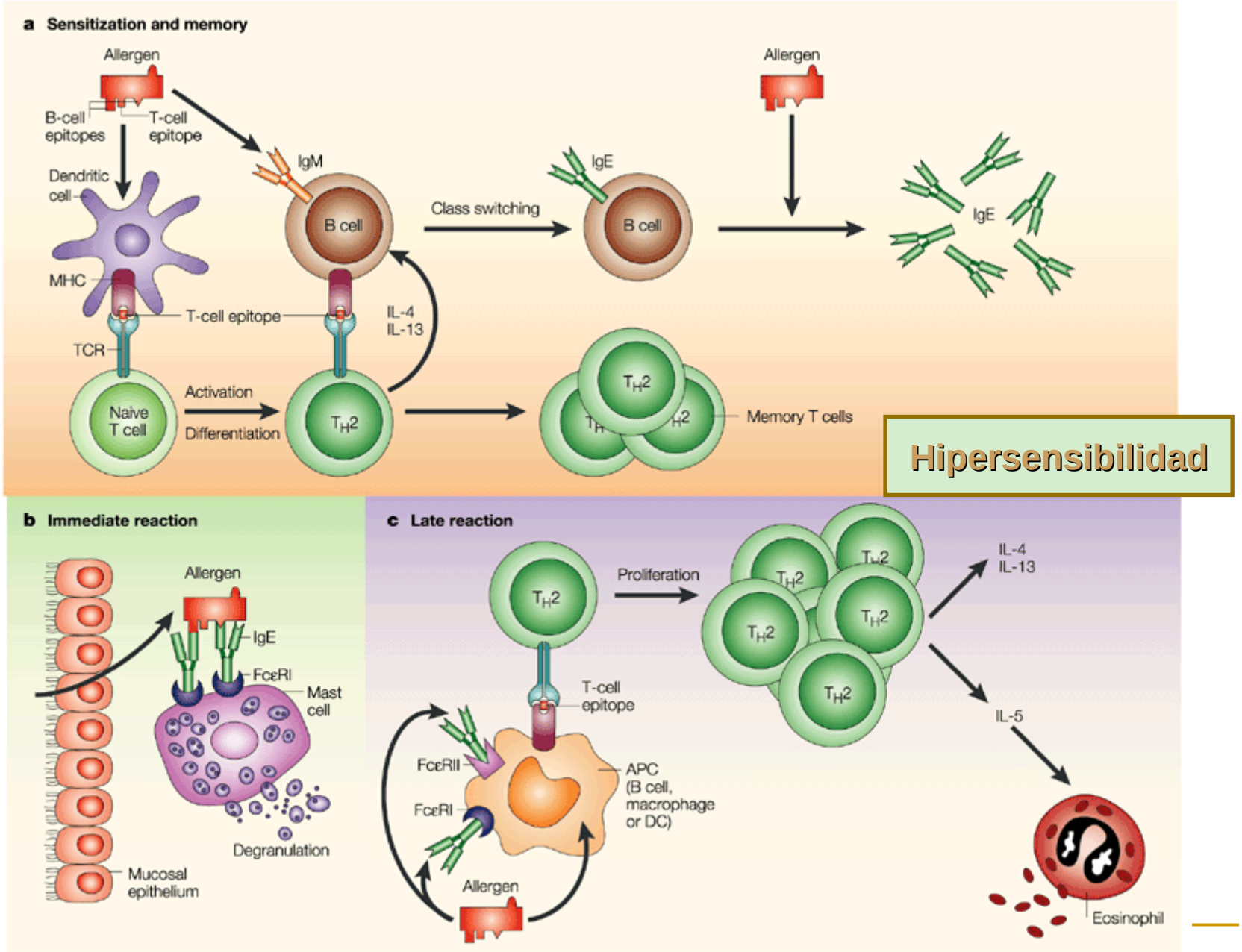
In the case of chronic Idiopathic Thrombocytopenic Purpura in the active phase



Model of cell-mediated cytotoxicity in chronic idiopathic thrombocytopenic purpura (ITP)

In the case of chronic ITP in remission phase


Autograft
Within an individual
Isograft
Identical Twins
Non-identical
Allograft
Between species
Xenograft

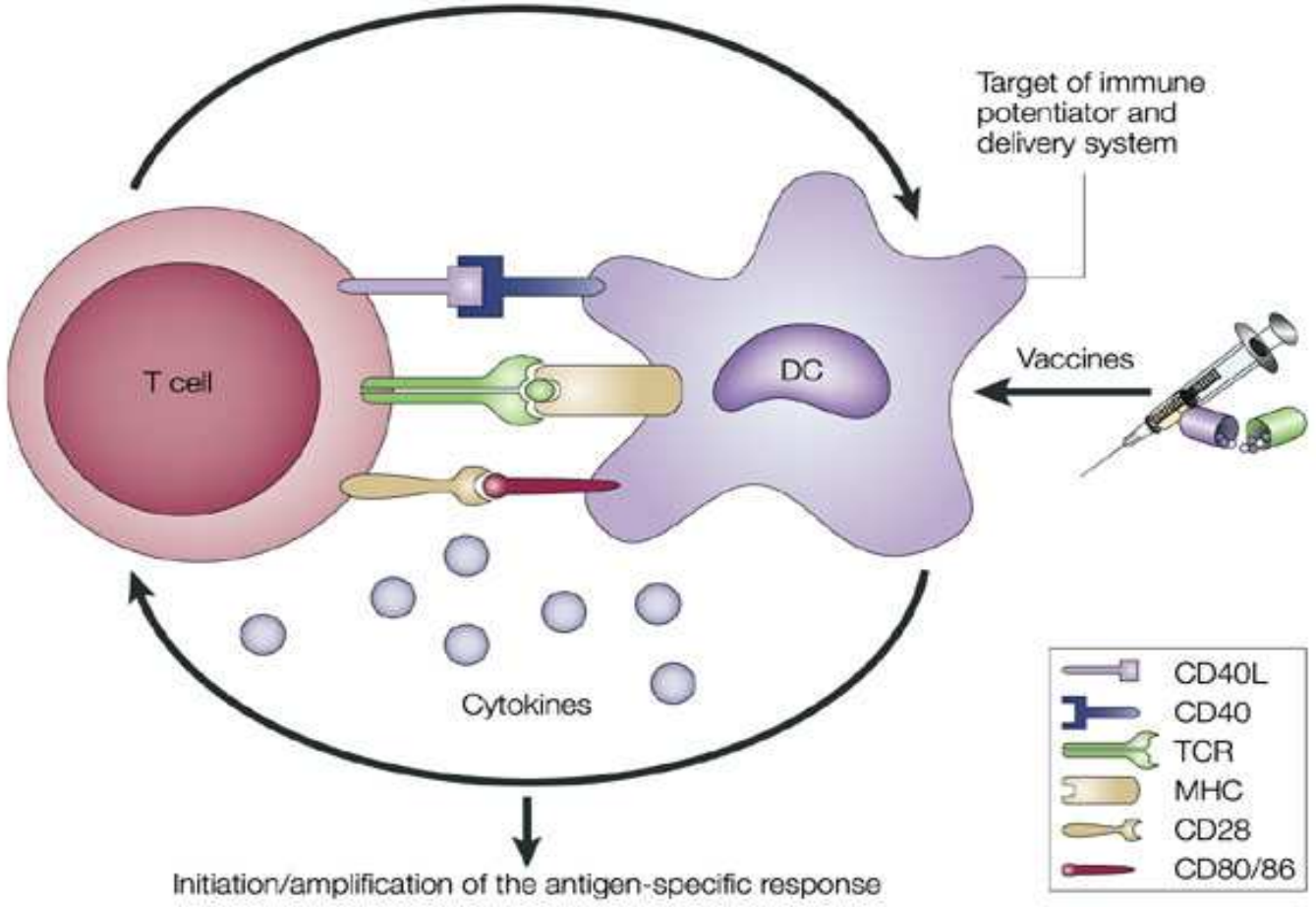


Hipersensibilidad

Nature Reviews Immunology 2, 446-453 (June 2002)

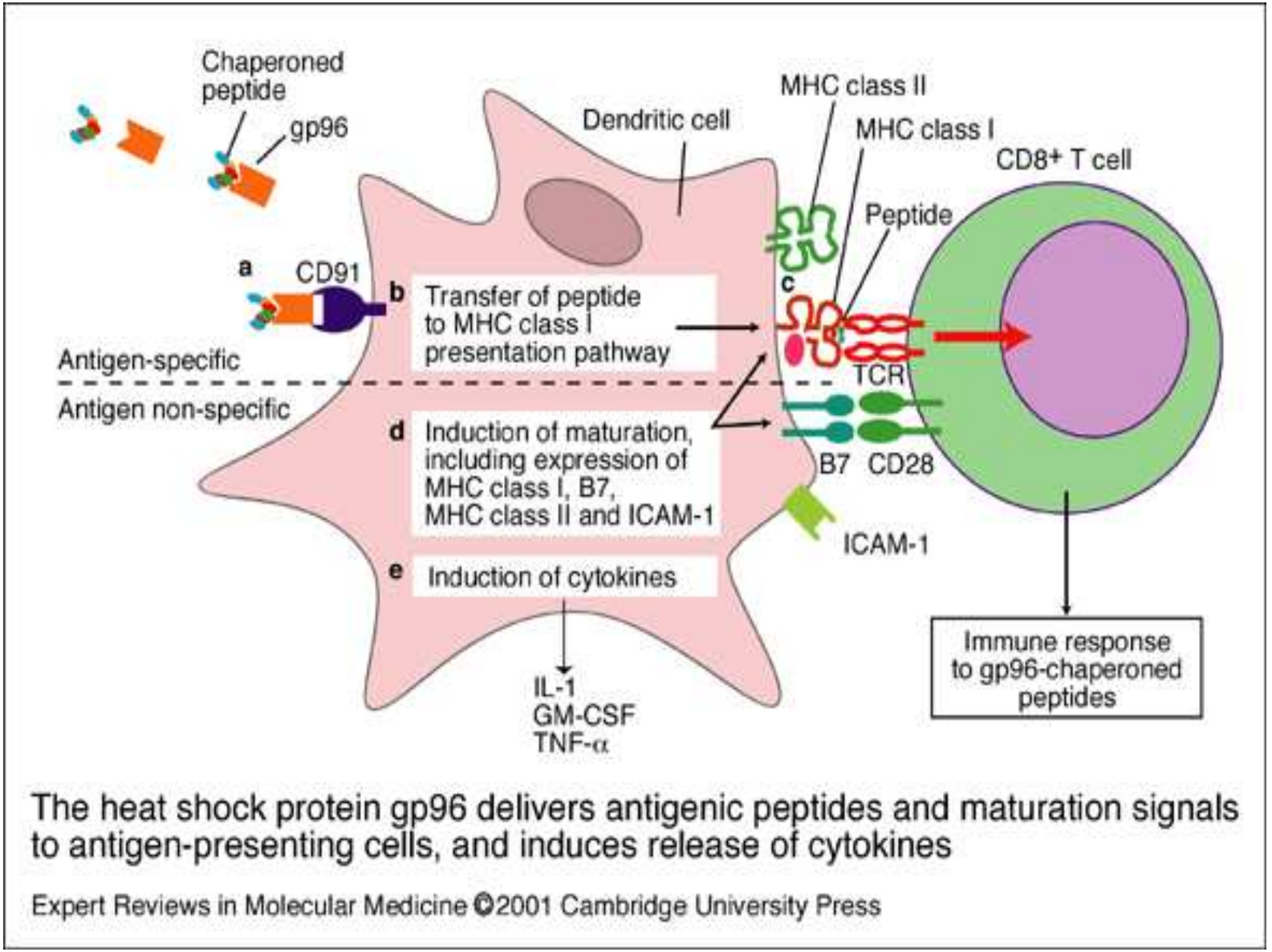
Nature Reviews | Immunology

La PRESENTACIÓN ANTIGÉNICA es el PUENTE entre la INMUNIDAD INNATA Y LAS REPUESTAS ANTÍGENO ESPECÍFICAS…..

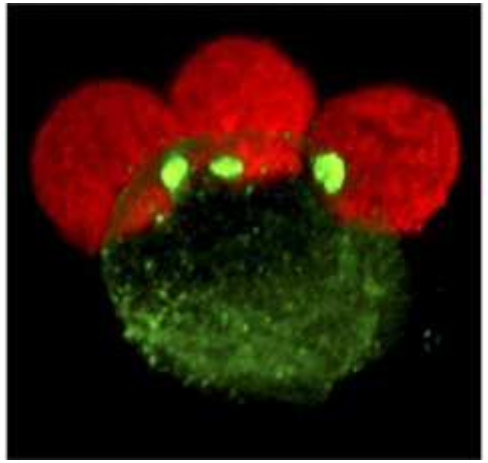


Nature Reviews Drug Discovery 2, 727-735 (September 2003)

Nature Reviews | Drug Discovery

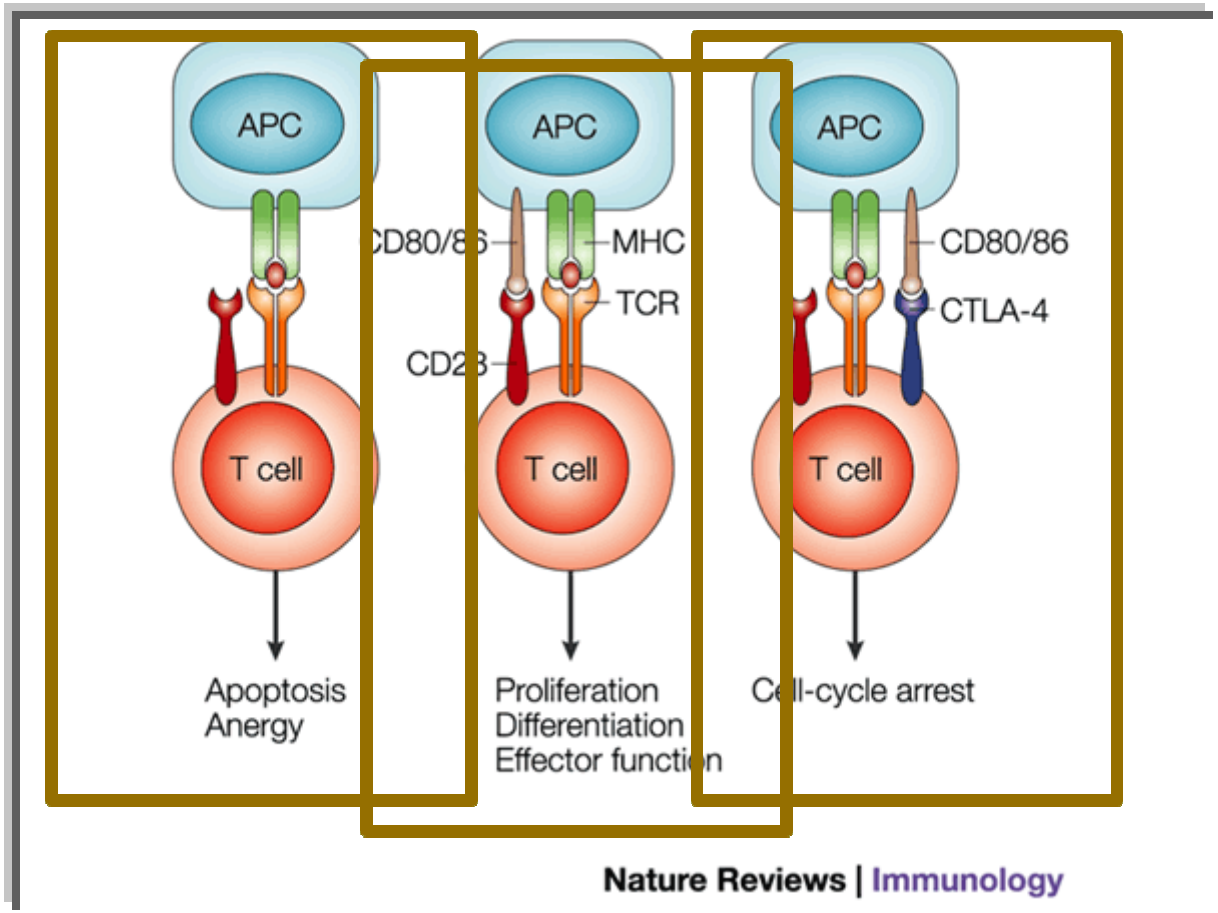


The heat shock protein gp96 delivers antigenic peptides and maturation signals to antigen-presenting cells, and induces release of cytokines

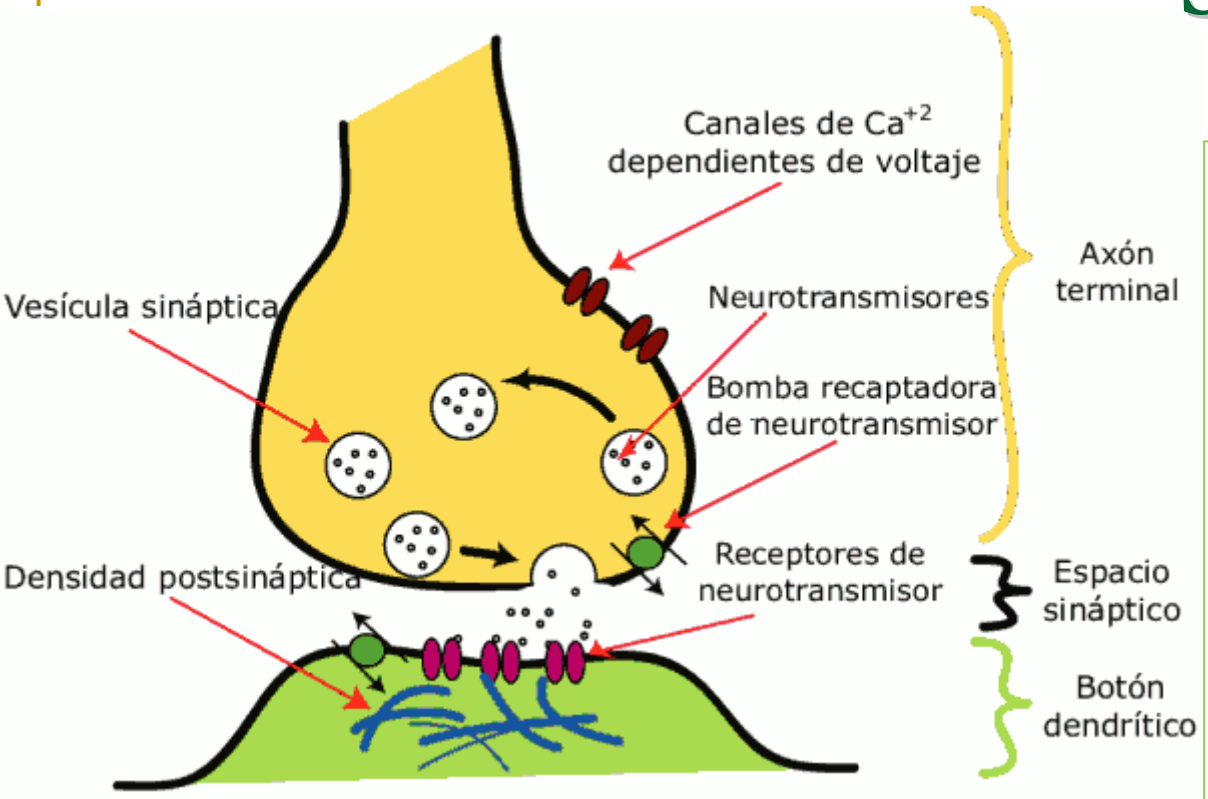


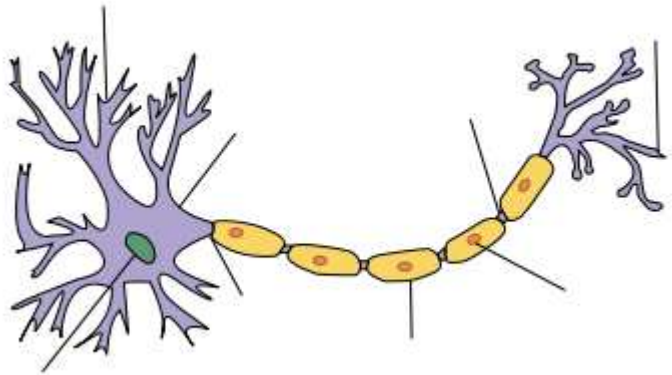
SINAPSIS INMUNOLÓGICA

La interacción entre la APC y célula T naive debe ser efectiva

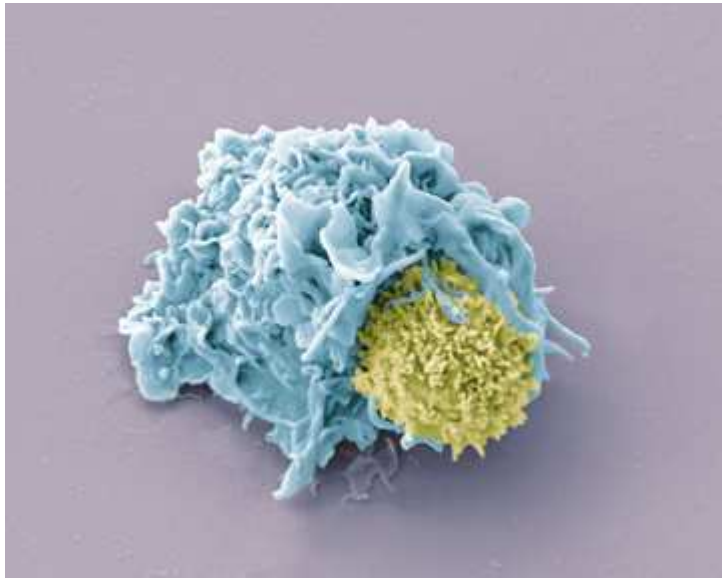


Sinapsis



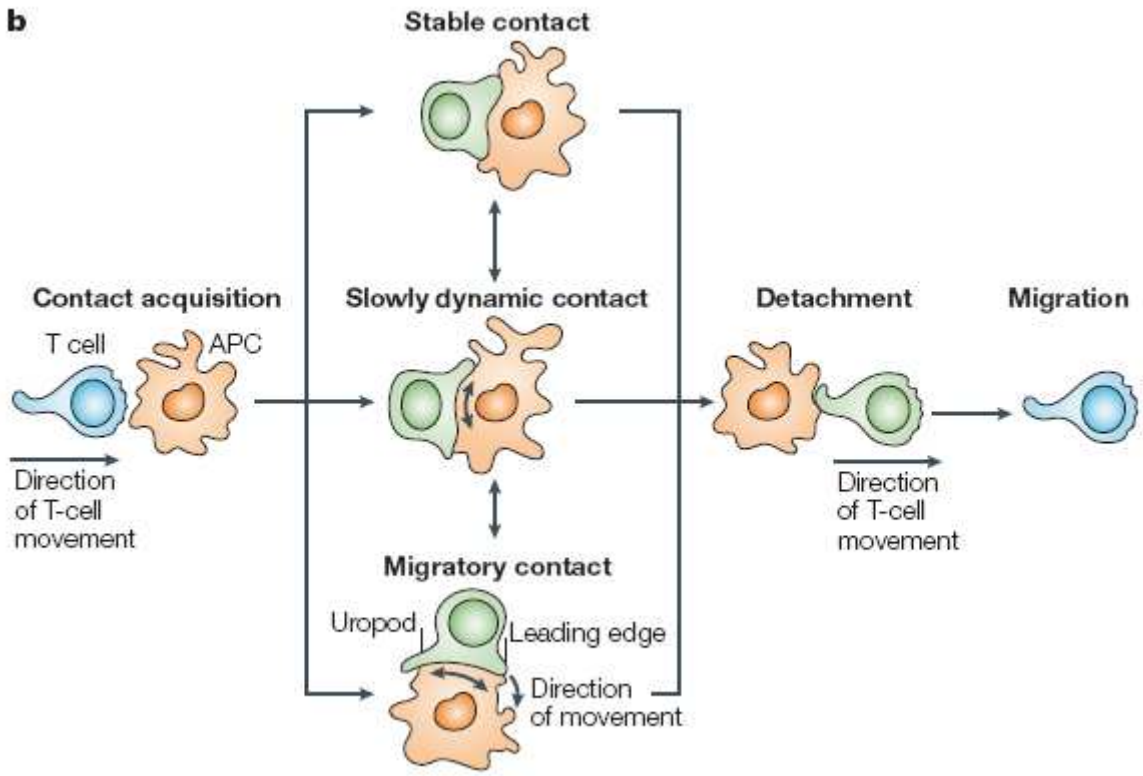


La sinapsis (del gr. σύναψις, "enlace") es un proceso que consta de descargas químico-eléctricas. Estas descargas se generan en la membrana celular de la neurona en un proceso de polarización-despolarización que libera unas sustancias químicas y un impulso eléctrico que estimula eléctricamente que van a la vesícula presináptica. Esta vesícula libera unas moléculas llamadas neurotransmisores que se acoplan en los receptores postsinápticos de la neurona destino. Este proceso se denomina **Sinapsis**.

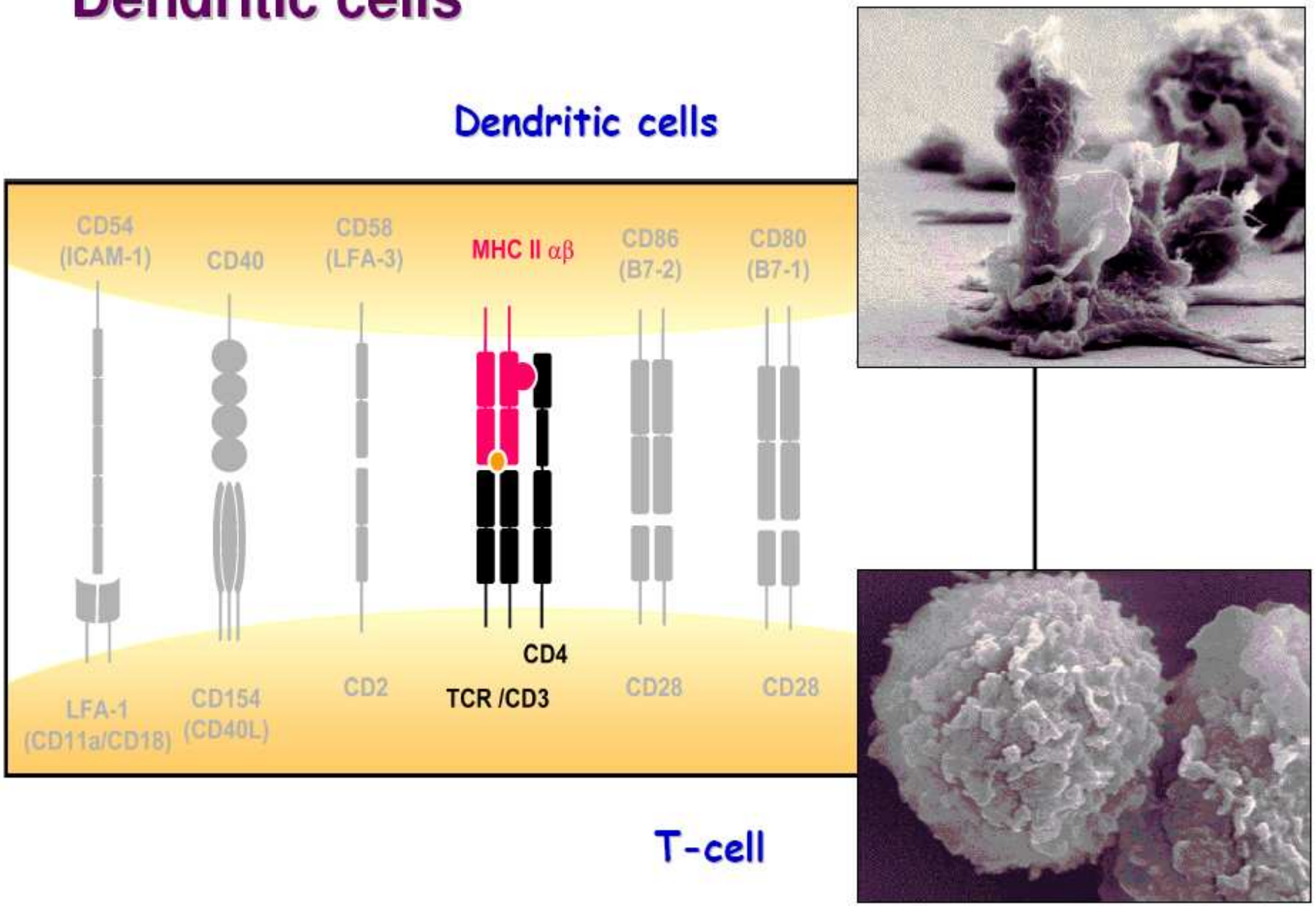


SINAPSIS INMUNOLÓGICA

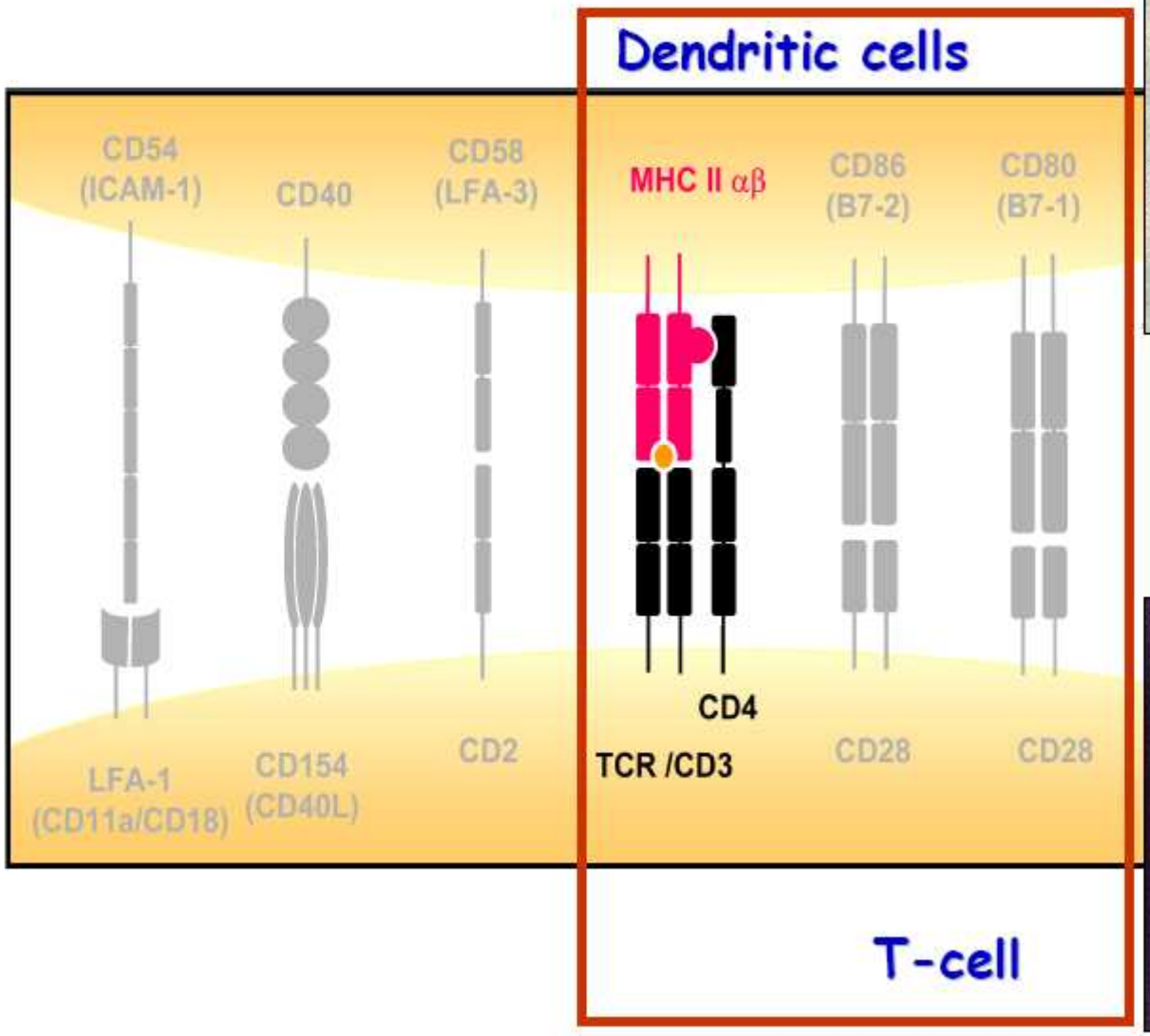
FASES DE LA INTERACCIÓN ENTRE LA APC Y EL LINFOCITO T

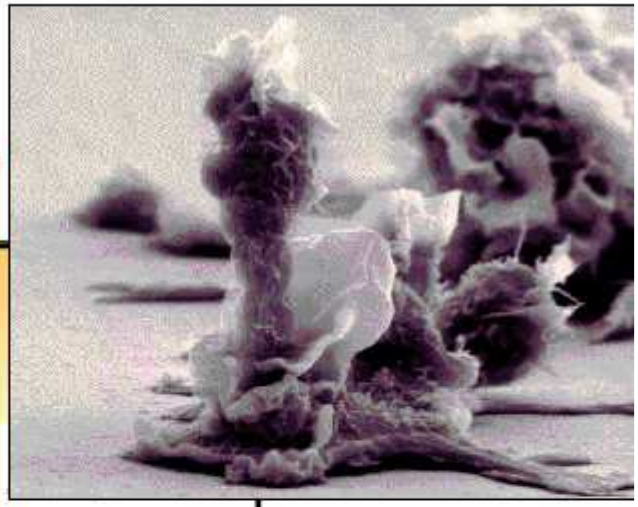


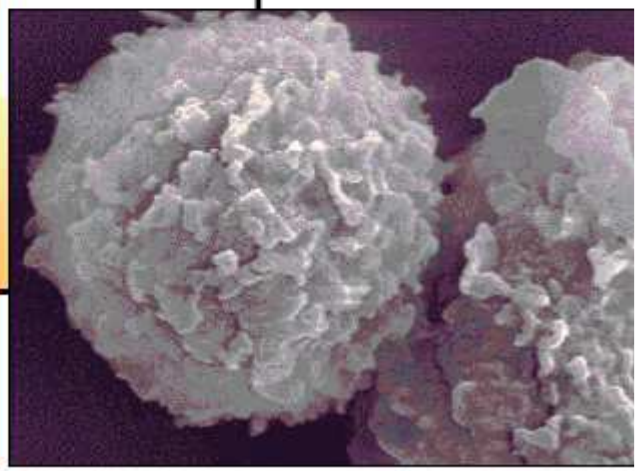
Dendritic cells



Naive T cell needs two signals for activation







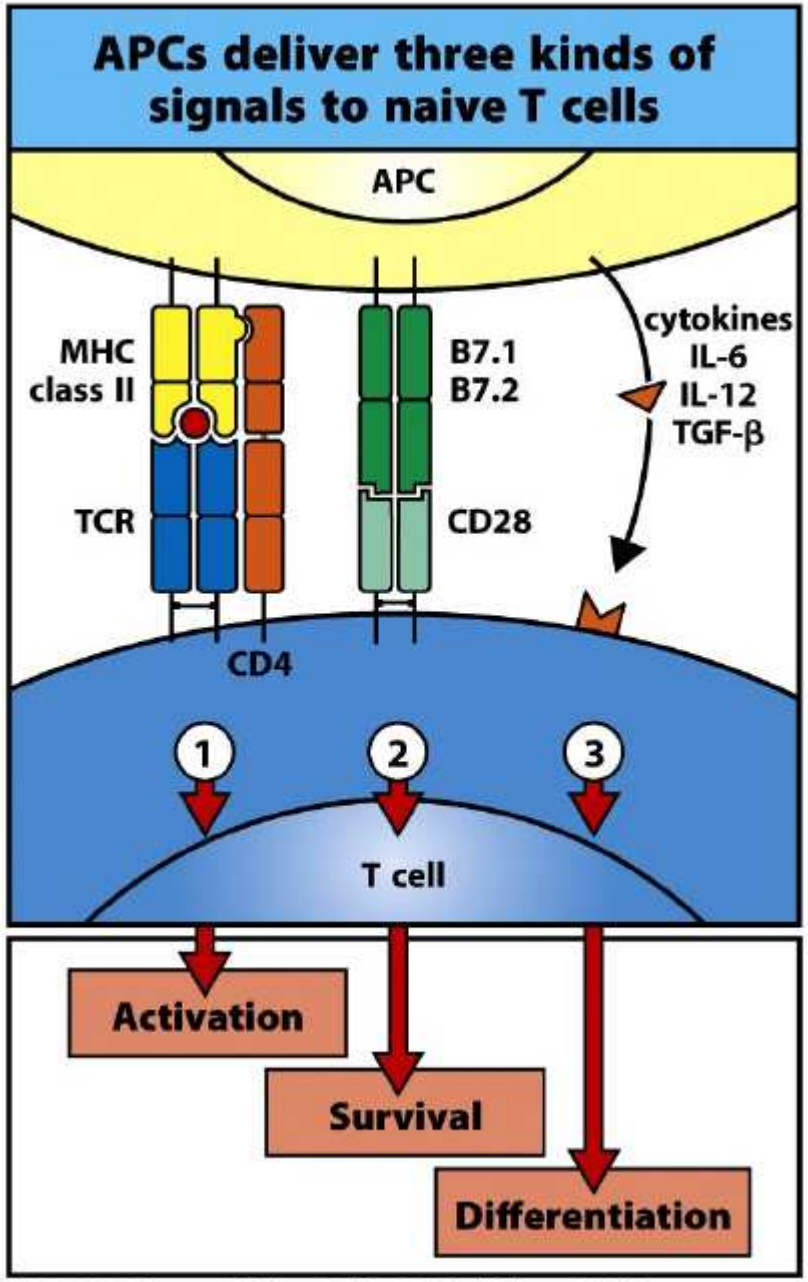
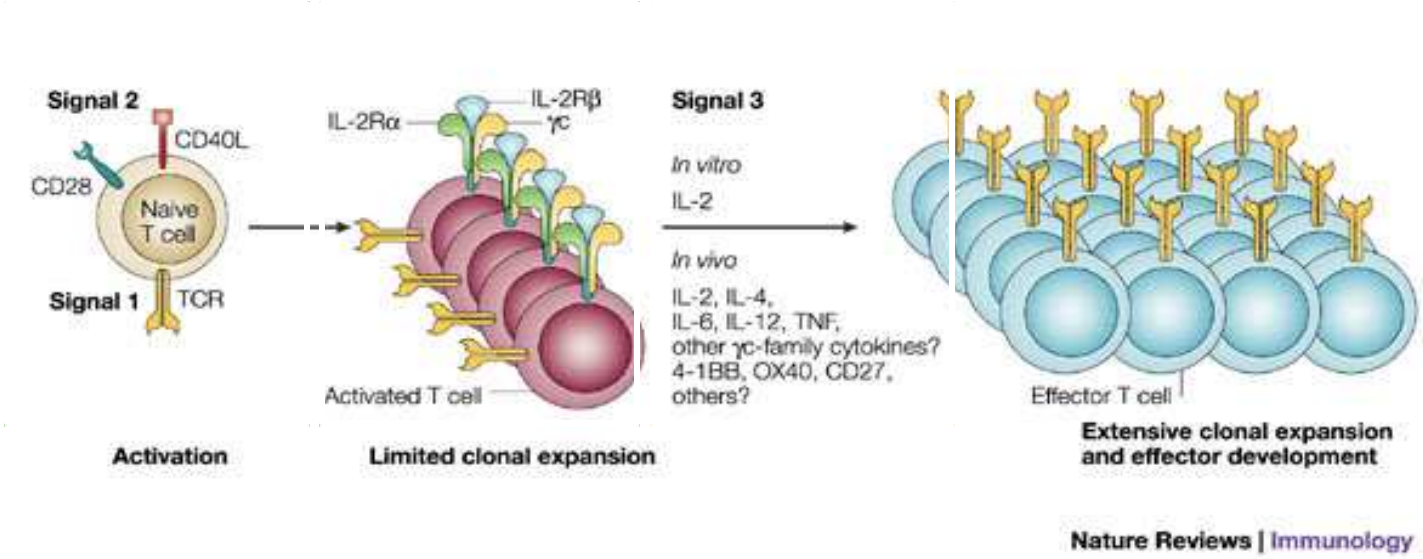
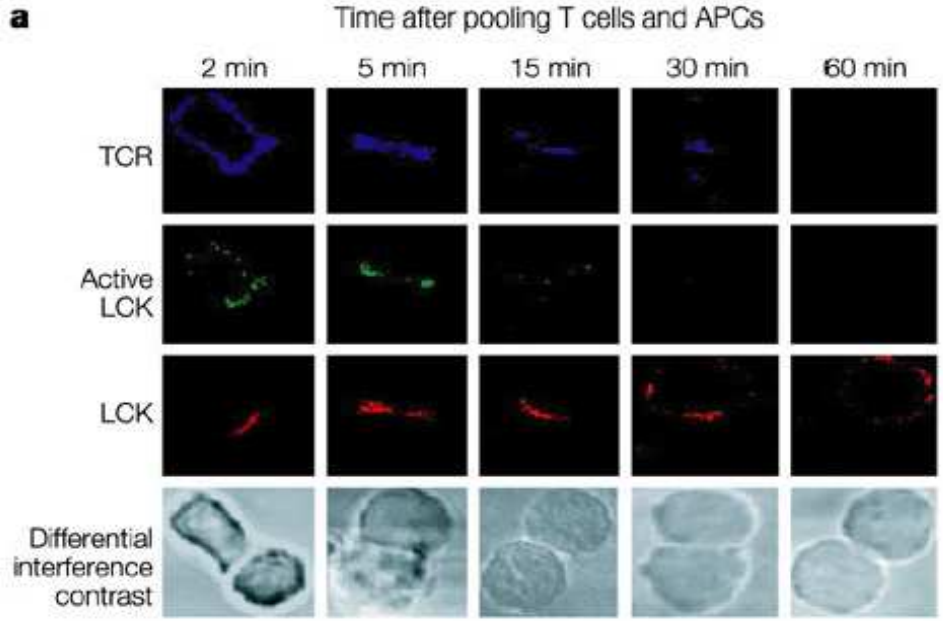


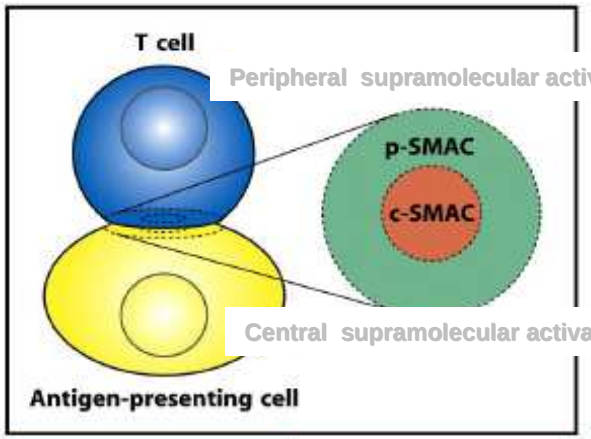
Figure 8-19 Immunobiology, 7ed. (© Garland Science 2008)



- A naive T cell is activated after ligation of its T-cell receptor (TCR) (signal 1) and engagement of the co-stimulatory molecules CD28 and CD40 ligand (CD40L) (signal 2) during antigen presentation by a dendritic cell (DC). This is sufficient to induce several rounds of T-cell proliferation; however, this interaction is not sufficient for an effective T-cell-dependent immune response. Signal 3 is a crucial checkpoint for substantial clonal expansion of antigen-specific T cells and development into effector cells. In tissue culture, engagement of the interleukin-2 receptor (IL-2R) is the main mechanism of passing the signal 3 checkpoint. However, there are several sources of signal 3 in vivo. It is probable that redundancy in the molecules that provide signal 3 is not limited to other common cytokine-receptor γ -chain (γc)-dependent cytokines. Candidates for signal 3 are shown. TNF, tumour-necrosis factor.

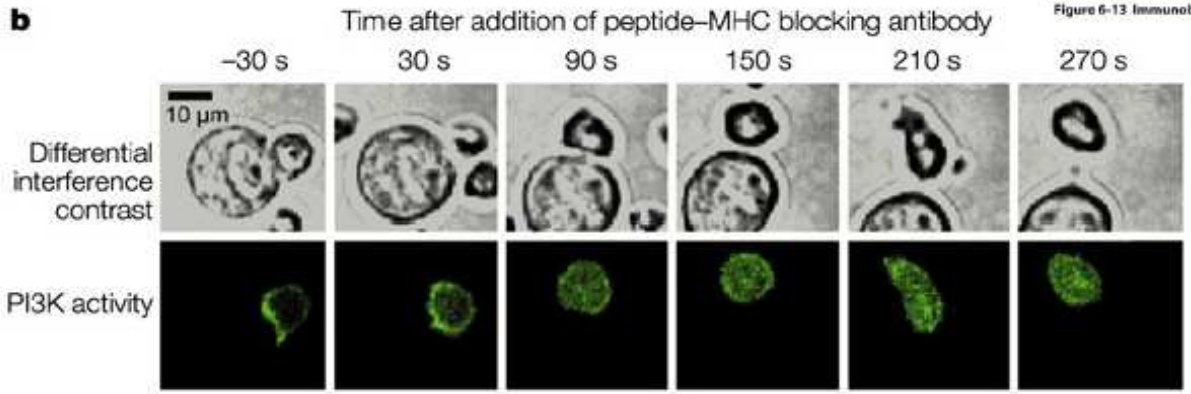
Signal 2 leads to formation of immunological synapsis





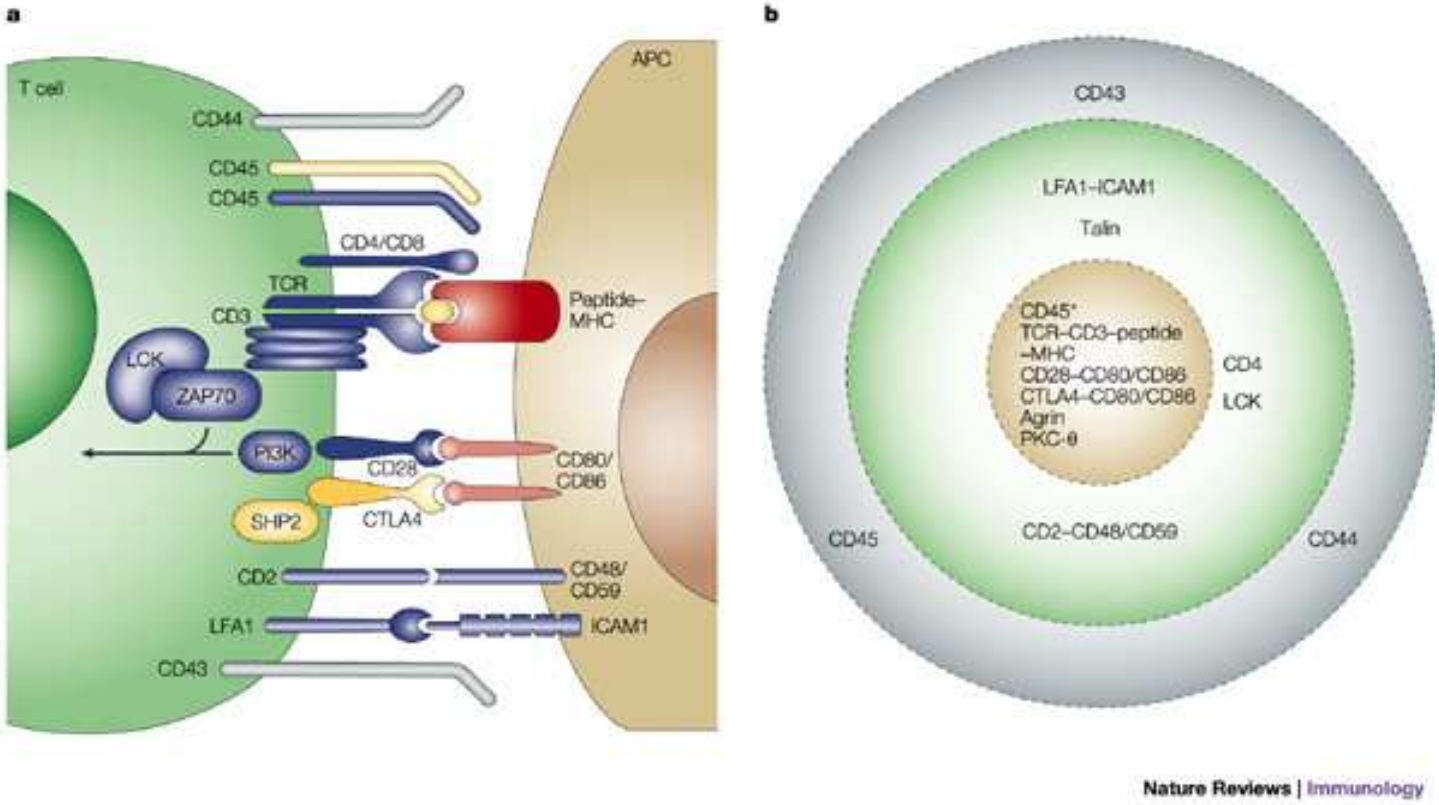
c-SMAC	p-SMAC
TCR CD2 CD4 CD8 CD28 PKC-θ	LFA-1 ICAM-1 talin

Figure 6-13 Immunobiology, 7ed. (© Garland Science 2008)



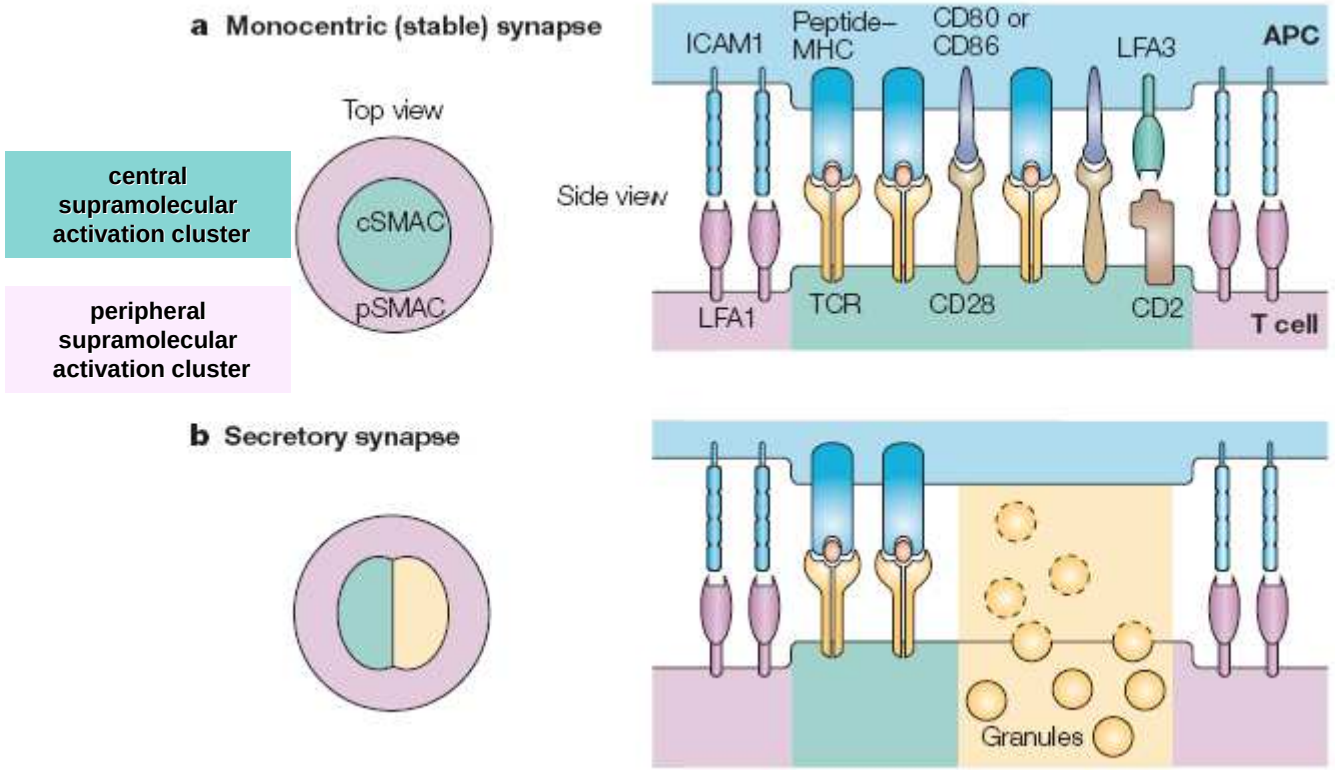
Nature Reviews | Immunology

La sinapsis madura…

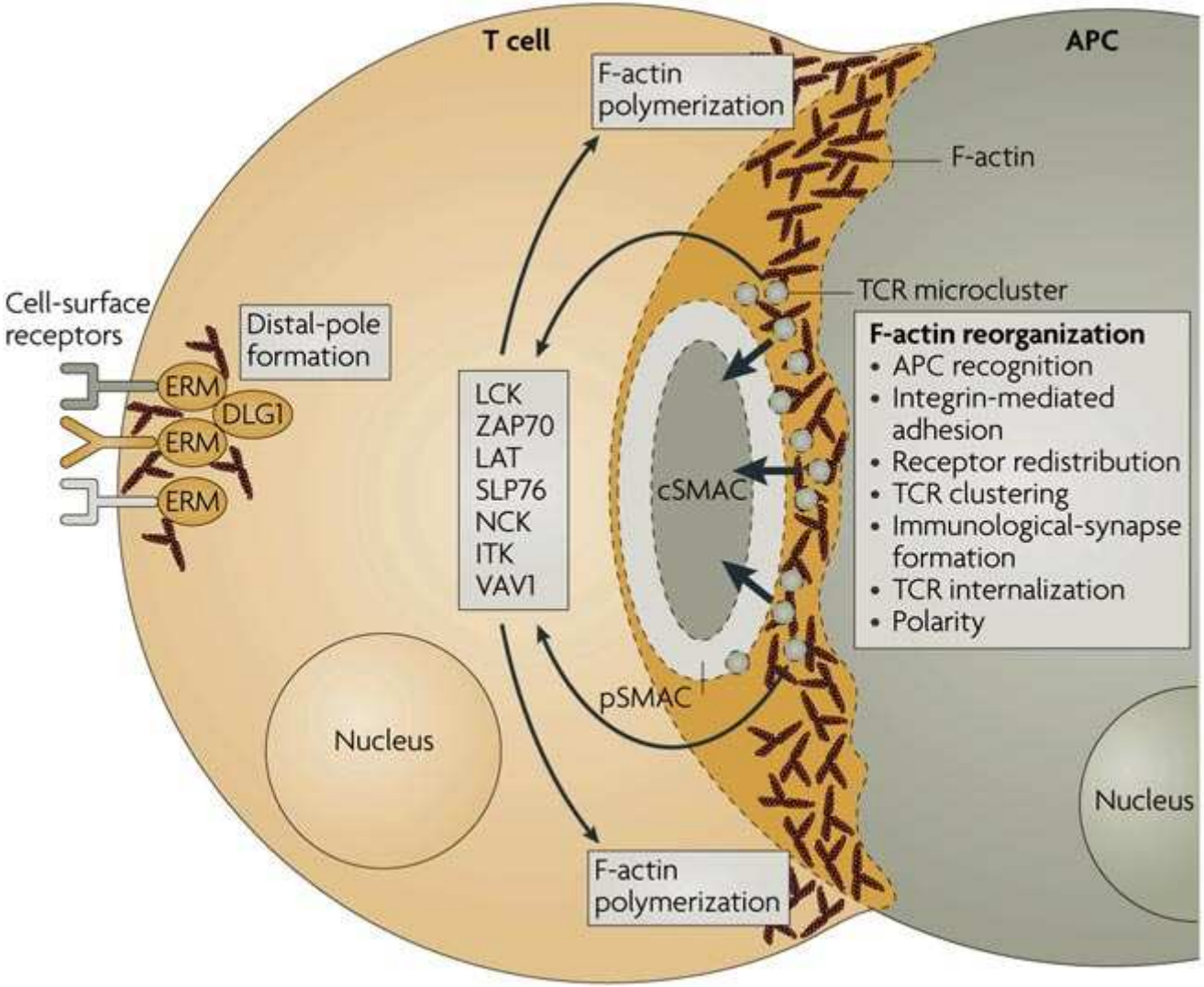


Nature Reviews Immunology 3, 973-983 (December 2003)

DOS TIPOS DE SINAPSIS INMUNOLÓGICA



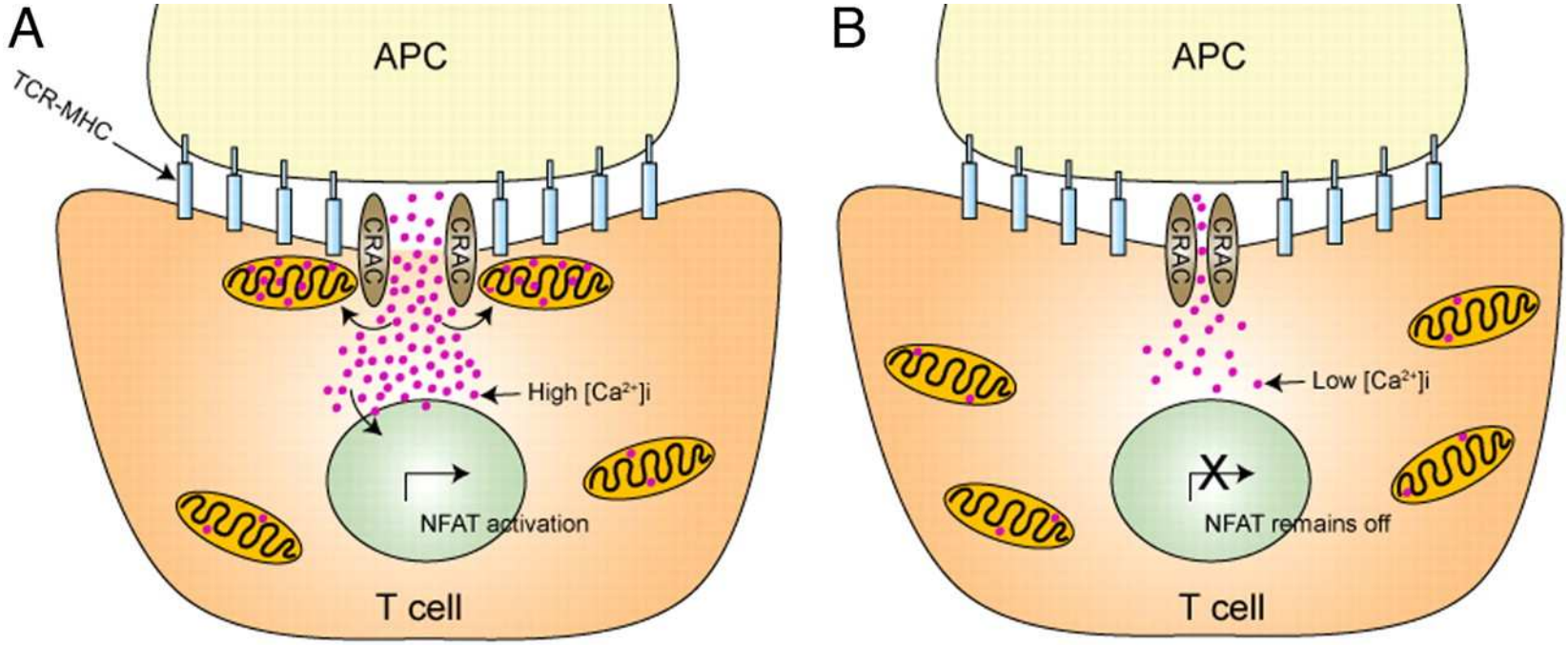
Two types of molecular arrangement at the immunological synapse are shown. a | A monocentric immunological synapse (also known as a stable immunological synapse) has a stably adhesive junction with a fully segregated **central supramolecular activation cluster** (cSMAC) and **peripheral SMAC** (pSMAC), which leads to T-cell priming, T-cell receptor (TCR) downregulation and sustained signalling. b | A secretory immunological synapse has a fully segregated junction that includes a secretory domain for exocytosis of cytokines and/or perforin and granzymes.



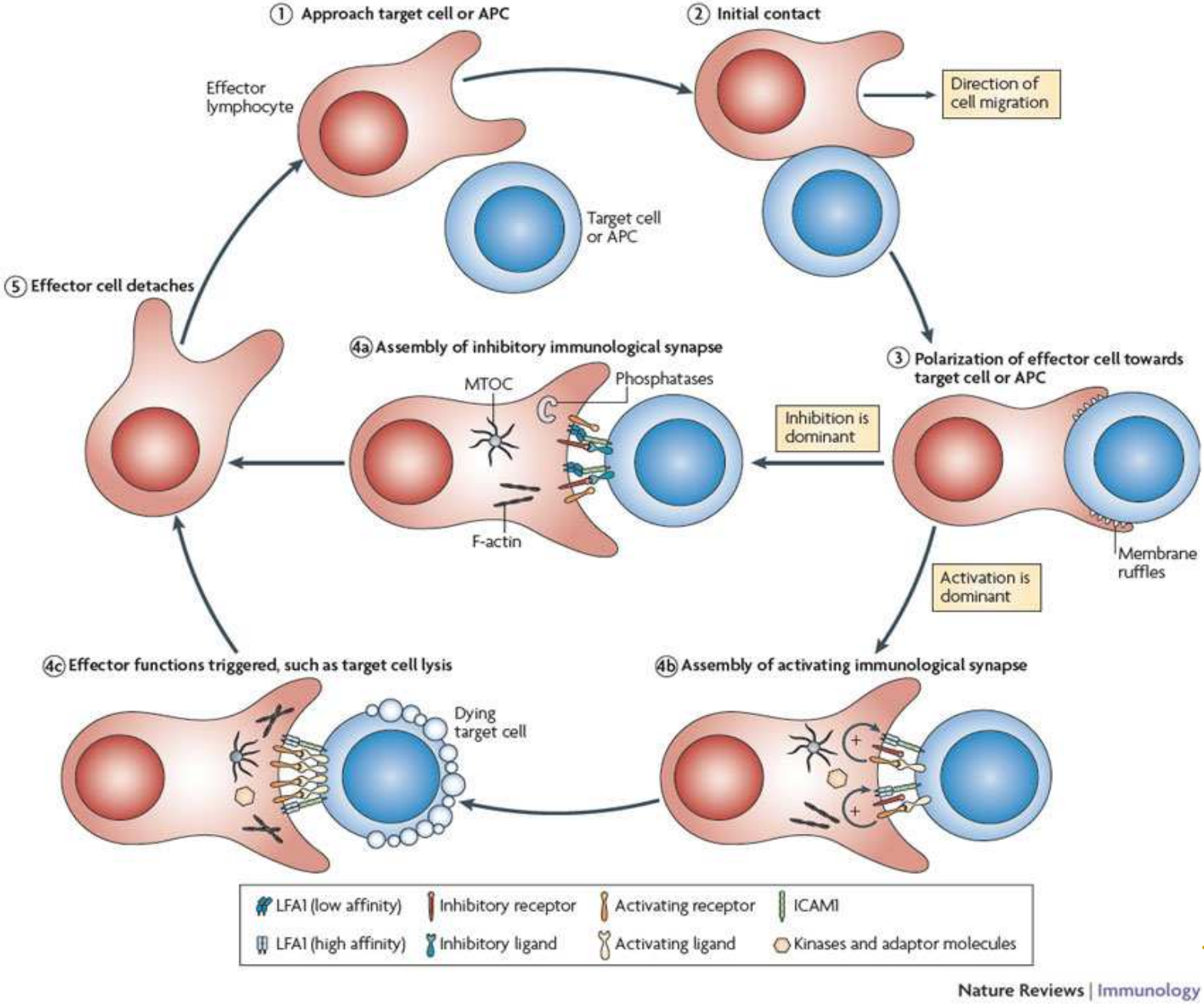
Nature Reviews Immunology 7, 131-143 (February 2007)

Cambios morfológicos y citoesqueléticos de la célula T

La eficiente activación de la célula T requiere la entrada de Ca^{2+} a la mitocondria en la sinapsis inmunológica

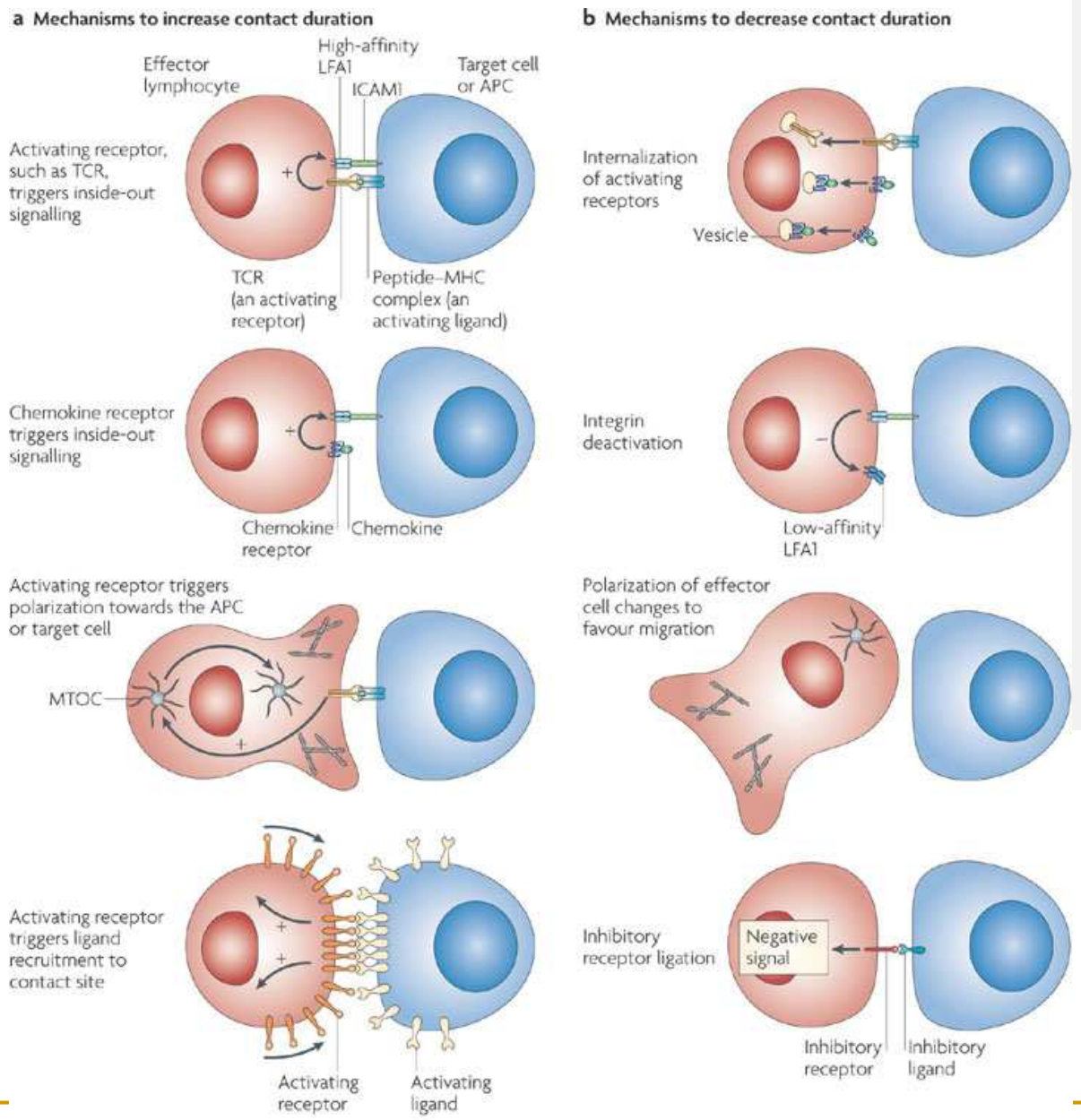


Oakes S. A. PNAS 2007;104:15171-15172



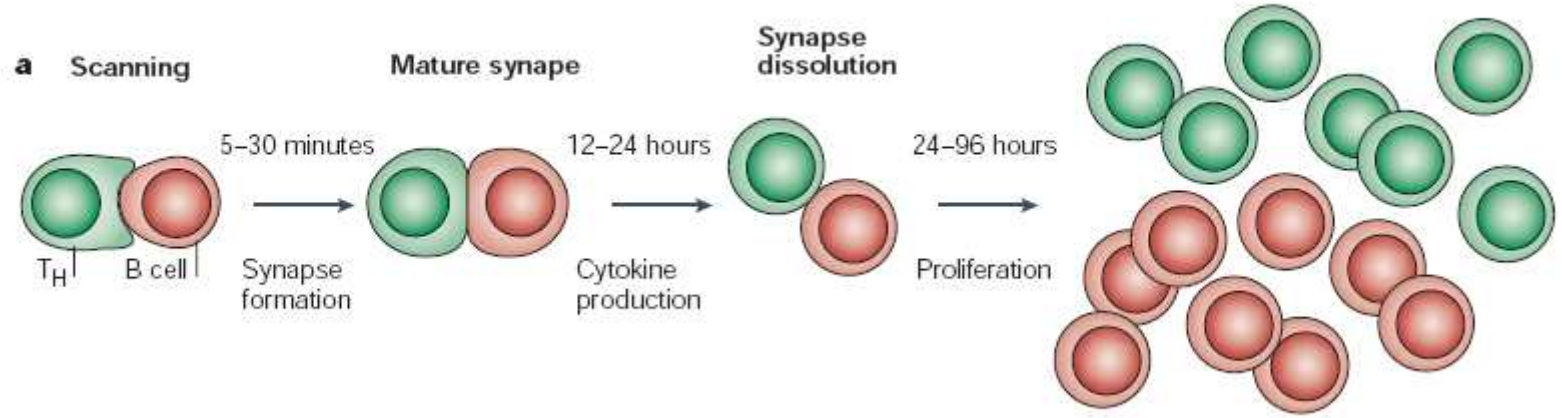
Nature Reviews Immunology 9, 543-555 (August 2009)

a | To increase the duration of intercellular contacts, activating receptors such as the T cell receptor (TCR), B cell receptor (BCR) or natural killer (NK) cell receptors can activate integrin adhesiveness by inside-out signalling. Chemokine receptor ligation can similarly activate integrins such as lymphocyte function-associated antigen 1 (LFA1). Activating receptors can also directly adjust cell polarity to face the target cell or antigen-presenting cell (APC). In addition, activating receptor signals can trigger the activation of cytoskeletal processes that recruit more receptors to the immunological synapse, thereby establishing a positive feedback amplification loop.



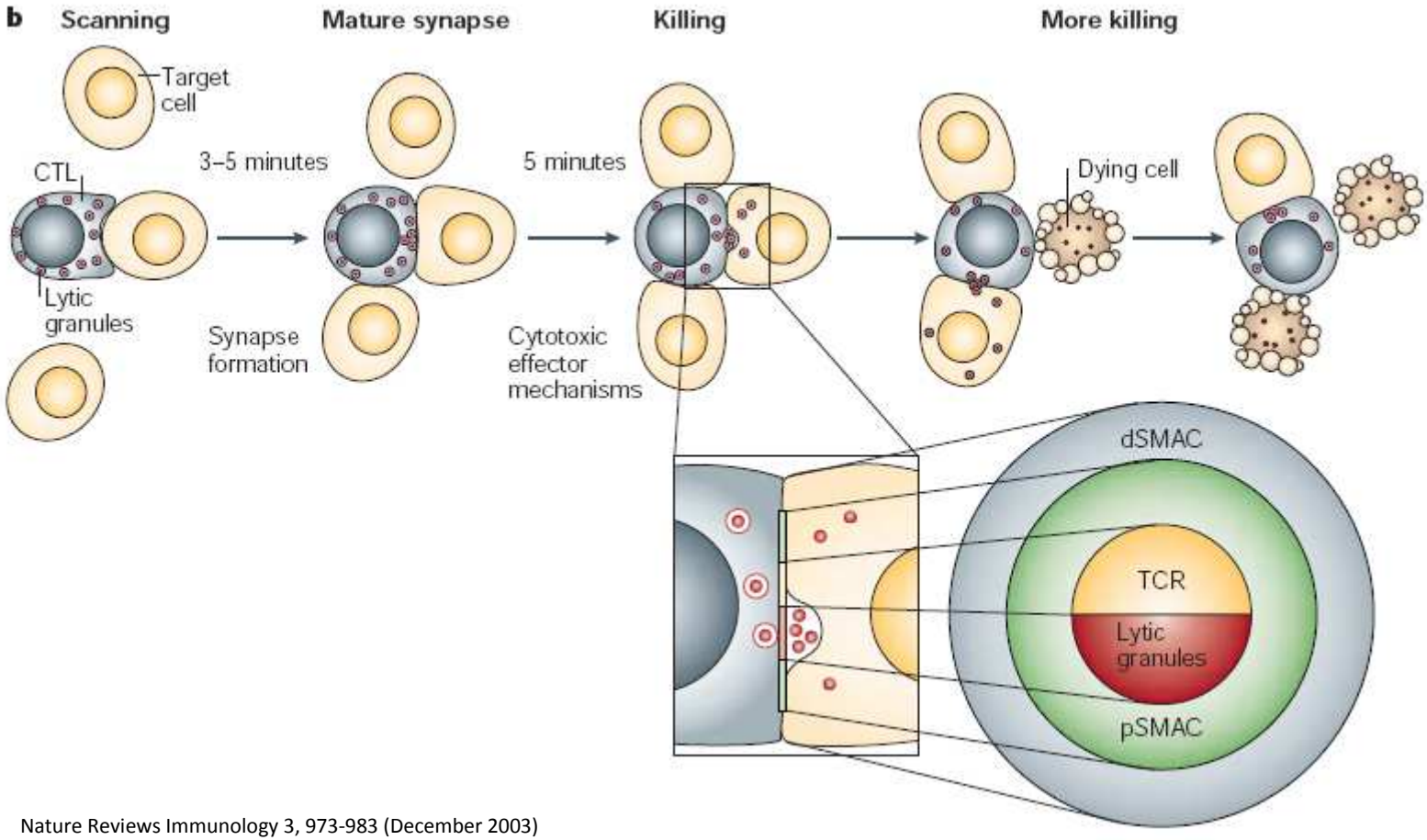
b | Activating receptors can be desensitized, for example, by internalization and degradation, which decreases the duration of intercellular contacts. In addition, integrins can be deactivated through processes that are not well defined (see main text for more detail). Cell polarity can change to favour migration away from the target cell or APC; such a change in polarity is perhaps facilitated by the recognition of another cell or adherent substrate. Finally, inhibitory receptors can function to reduce contact duration. The mechanism for this is not well defined but could involve maintaining or triggering a migratory effector cell configuration. Quantitatively, the extent to which each of these different mechanisms affect contact duration will vary with circumstance. ICAM1, intercellular adhesion molecule 1; MTOC, microtuble organizing centre.

Formación de la sinapsis entre Th y LB

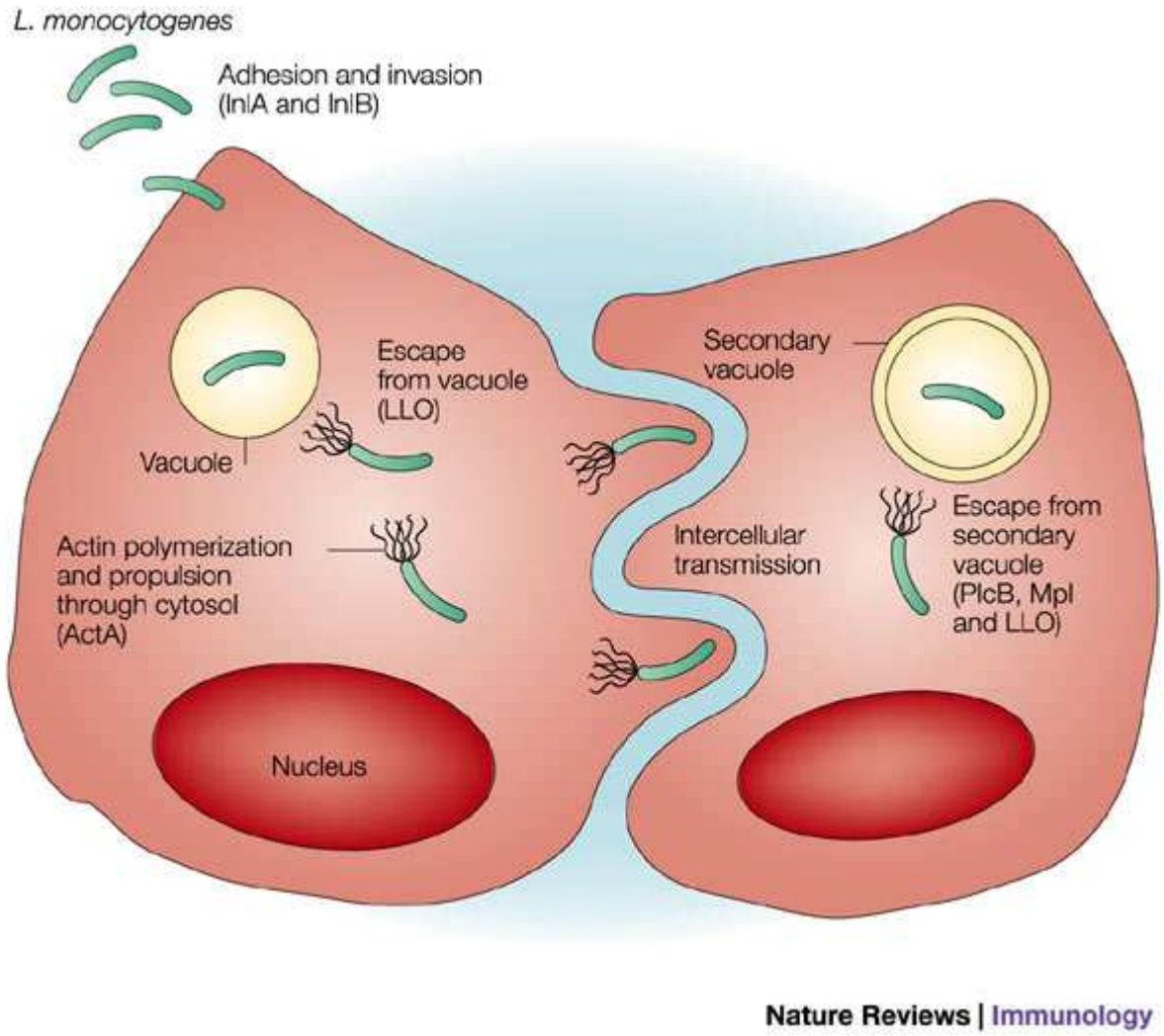


Nature Reviews Immunology 3, 973-983 (December 2003)

Formación de la sinapsis entre Tc y célula blanco

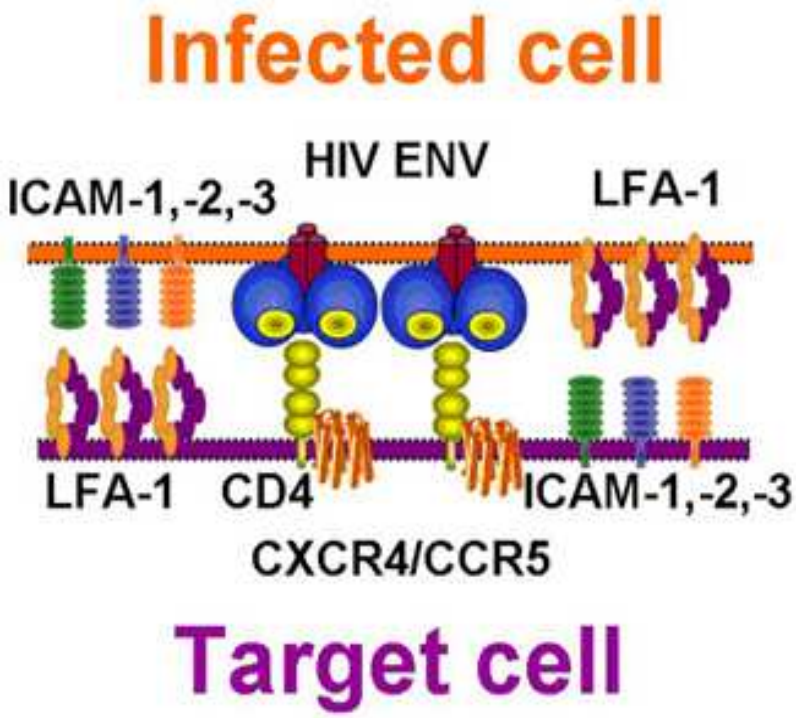


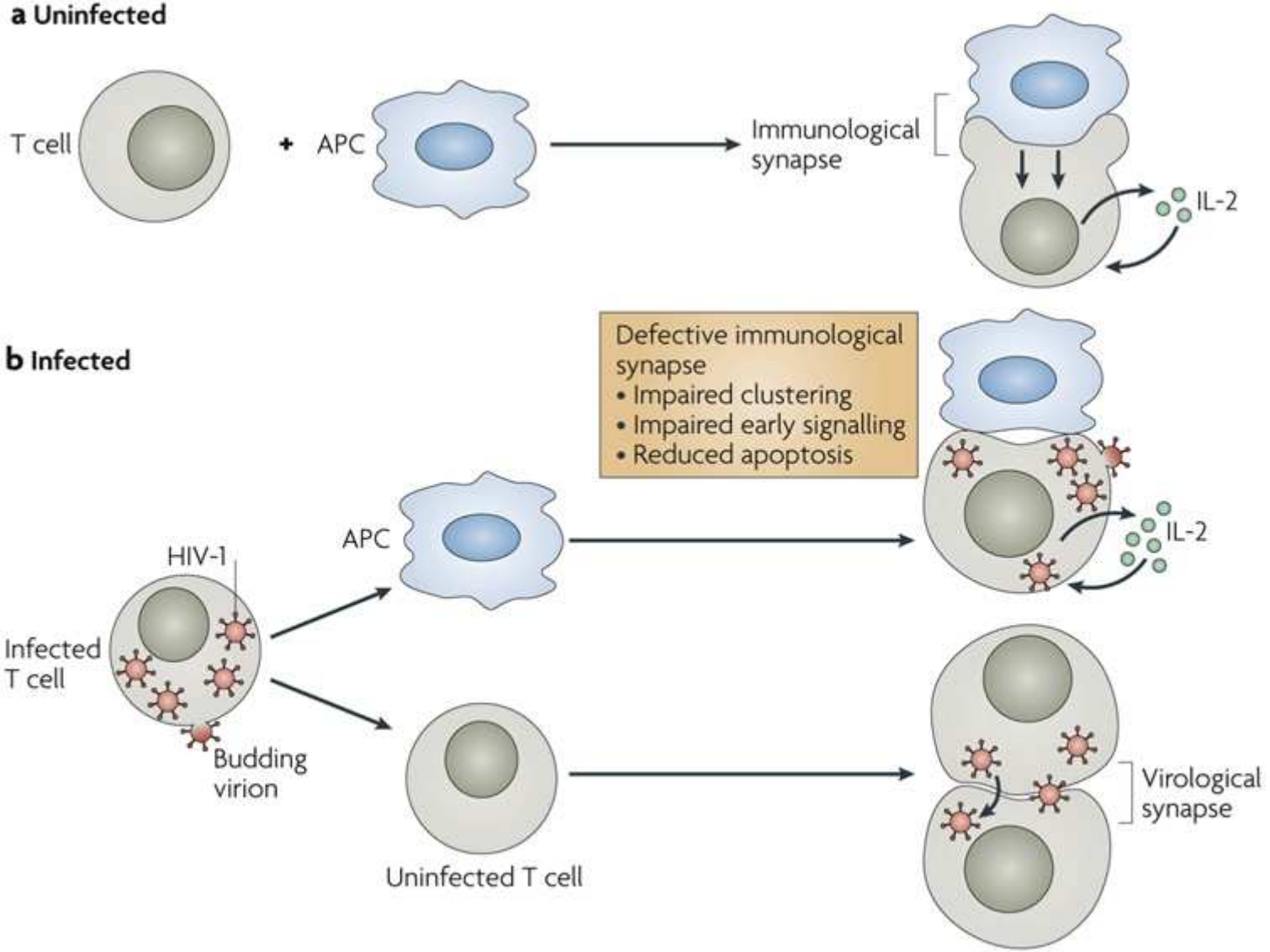
Nature Reviews Immunology 3, 973-983 (December 2003)



Listeria monocytogenes expresses cell-surface and secreted proteins that enable attachment to host cells, escape from the phagocytic vacuole and locomotion in the cytosol of the invaded cell. Internalin A (InlA) and InlB mediate the attachment of L. monocytogenes to the surface of host cells, and listeriolysin O (LLO) lyses the phagosomal membrane. The actin-assembly-inducing protein (ActA) is expressed in a polarized manner and catalyses actin polymerization, which propels bacteria through the cell and into neighbouring cells. To escape the secondary vacuole in the newly invaded cell, L. monocytogenes expresses the phosphatidylcholine-specific phospholipase PlcB, a secreted zinc metalloproteinase (Mpl) and LLO.

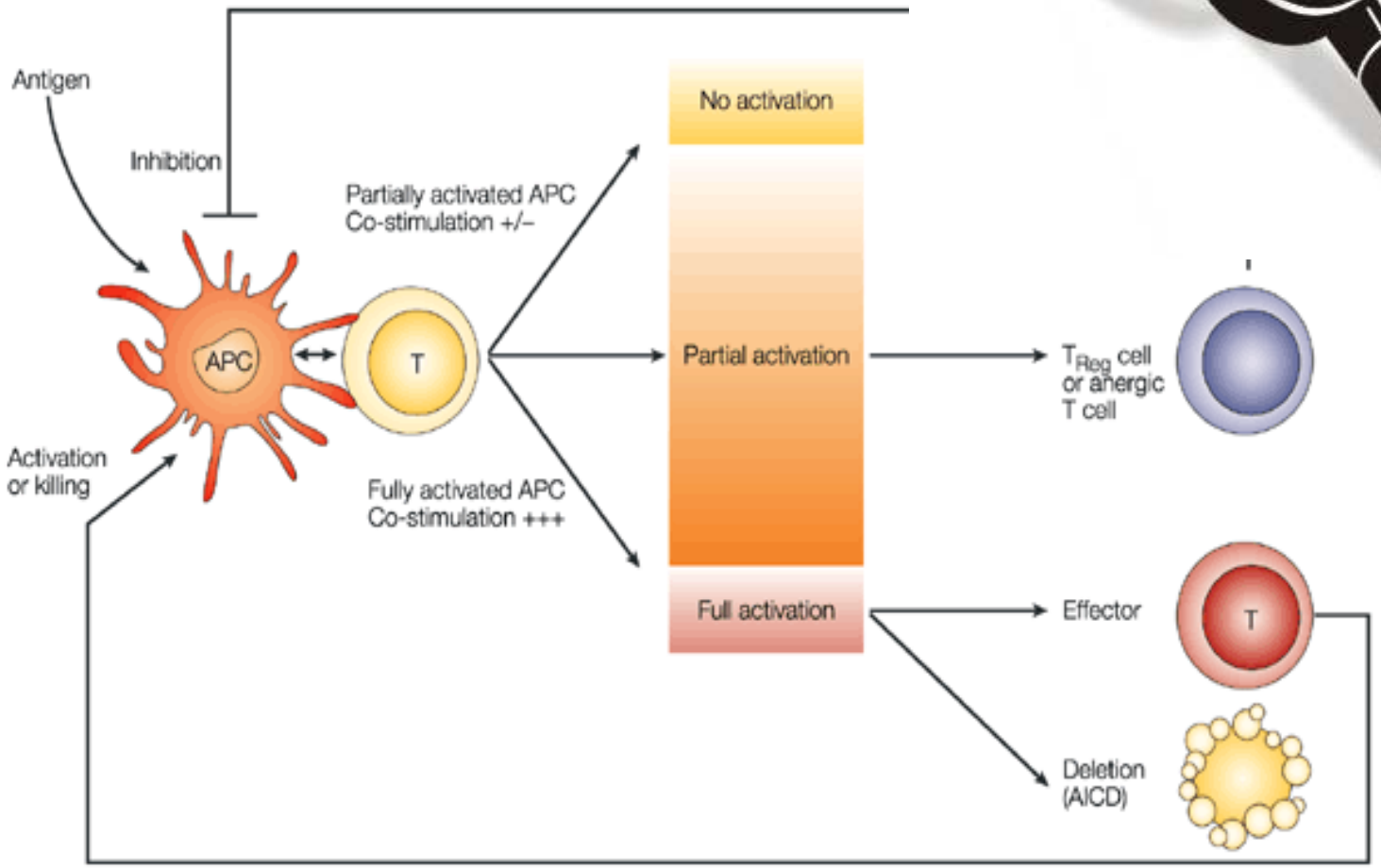
Sinapsis virológica



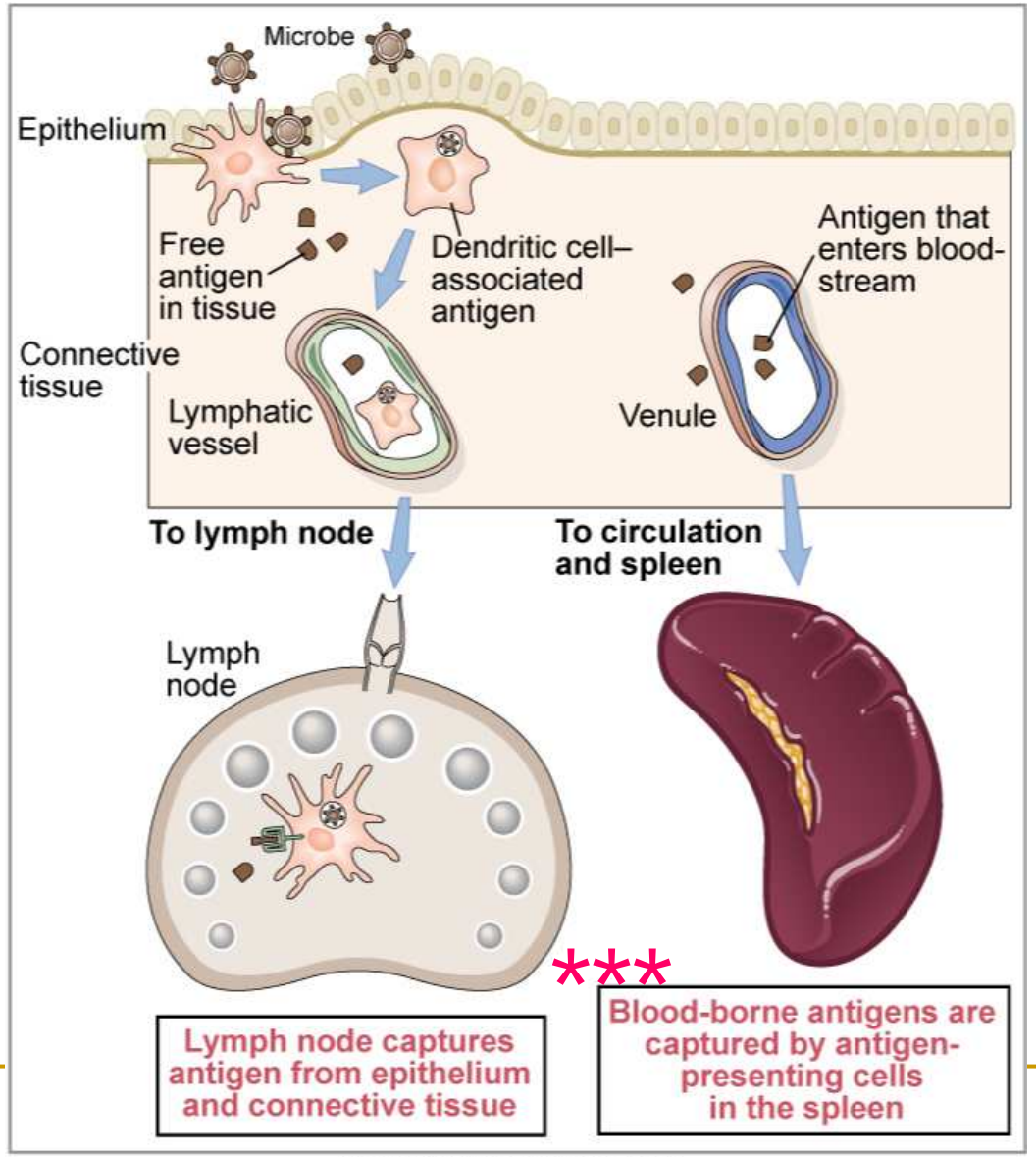


Nature Reviews Immunology 7, 310-317 (April 2007)

CONCLUSIÓN


Antigen
Inhibition
Partially activated APC
Co-stimulation +/–
No activation
APC
T
Partial activation
T_{Reg} cell
or anergic
T cell
Activation
or killing
Fully activated APC
Co-stimulation +++
Full activation
Effector
T
Deletion
(AICD)

Captura y distribución del antígeno



Células presentadoras de antígeno (APC)

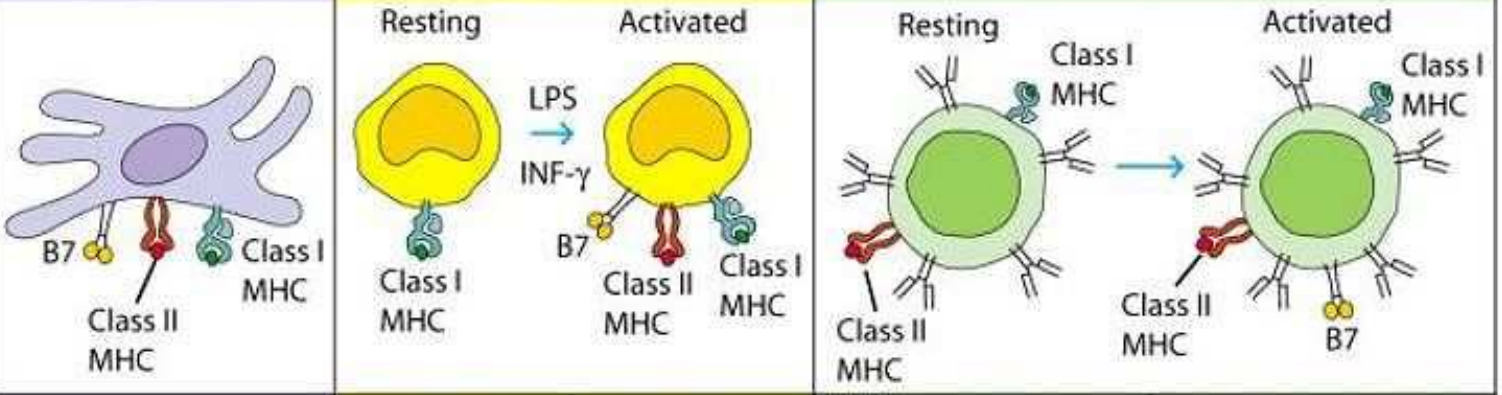
- **Son capaces de presentar péptidos en el contexto de MHC II …**
- **Llevar la señal coestimuladora necesaria para la activación completa de las células T, lo que conduce a la proliferación y diferenciación….**

TABLE 8-3 Antigen-presenting cells

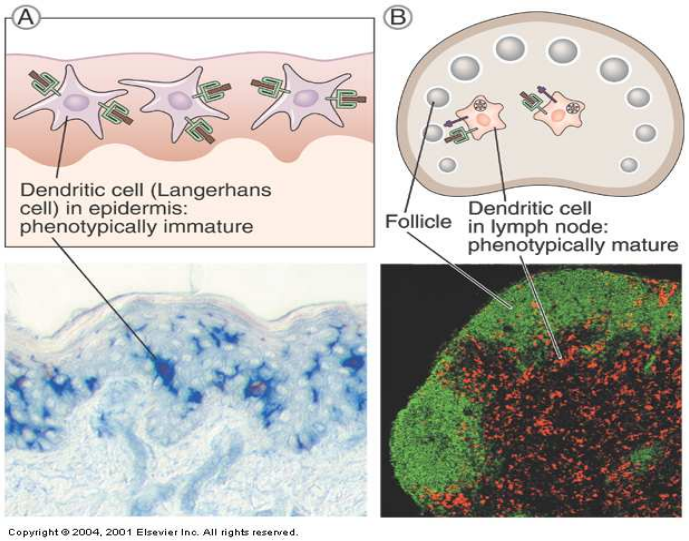
Professional antigen-presenting cells	Nonprofessional antigen-presenting cells	
Dendritic cells (several types)	Fibroblasts (skin)	Thymic epithelial cells
Macrophages	Glial cells (brain)	Thyroid epithelial cells
B cells	Pancreatic beta cells	Vascular endothelial cells

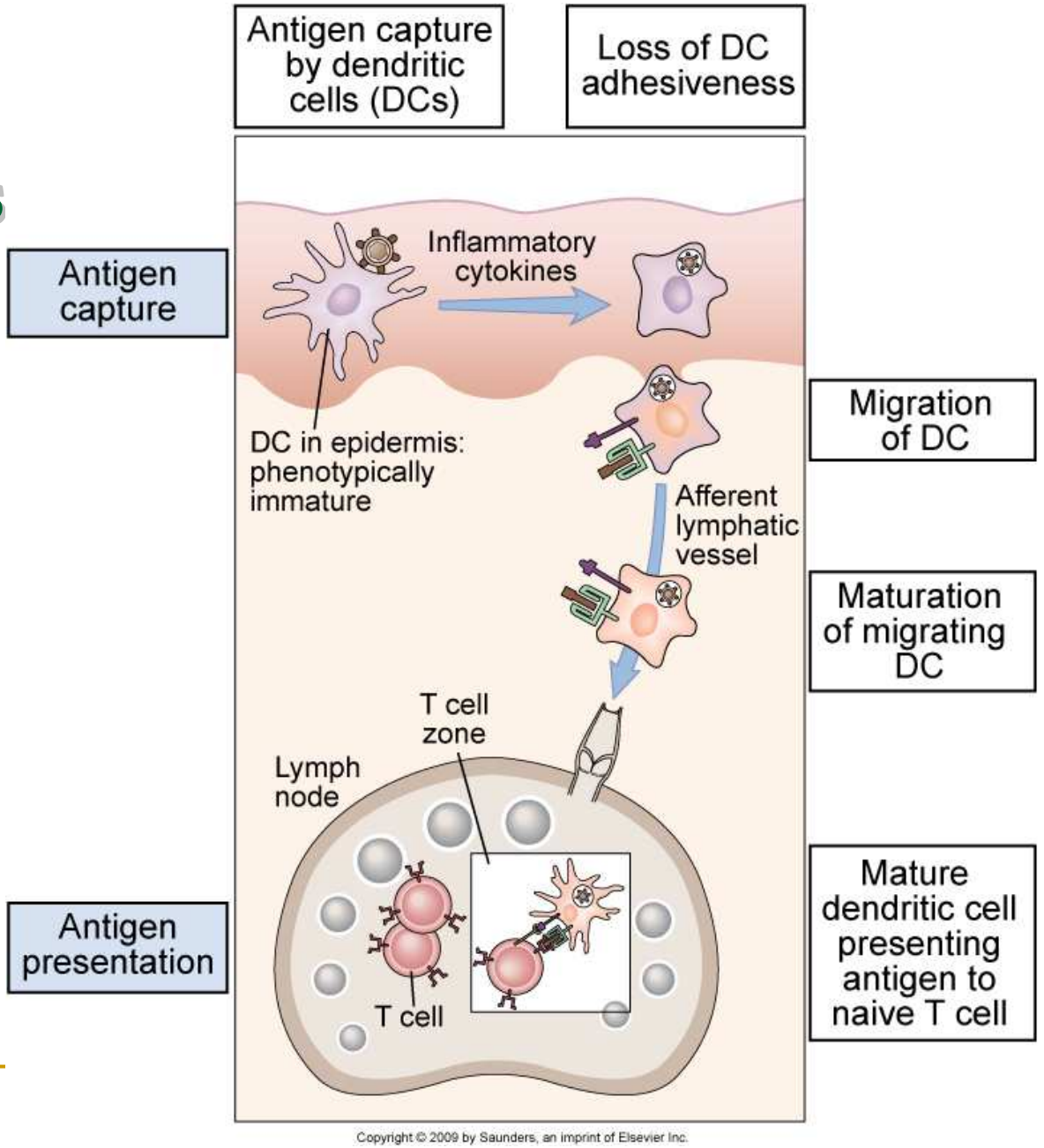
Table 8-3
Kuby IMMUNOLOGY, Sixth Edition

Propiedades de las APC

	Dendritic cell	Macrophage		B Lymphocyte	
					
Antigen uptake	Endocytosis phagocytosis (by Langerhans cells)	Phagocytosis	Phagocytosis	Receptor-mediated endocytosis	Receptor-mediated endocytosis
Class II MHC expression	Constitutive (+++)	Inducible (−)	Inducible (++)	Constitutive (++)	Constitutive (+++)
Co-stimulatory activity	Constitutive B7 (+++)	Inducible B7 (−)	Inducible B7 (++)	Inducible B7 (−)	Inducible B7 (++)
T-cell activation	Naive T cells Effector T cells Memory T cells	(−)	Effector T cells Memory T cells	Effector T cells Memory T cells	**Naive T cells** **Effector T cells** **Memory T cells**

Células dendríticas





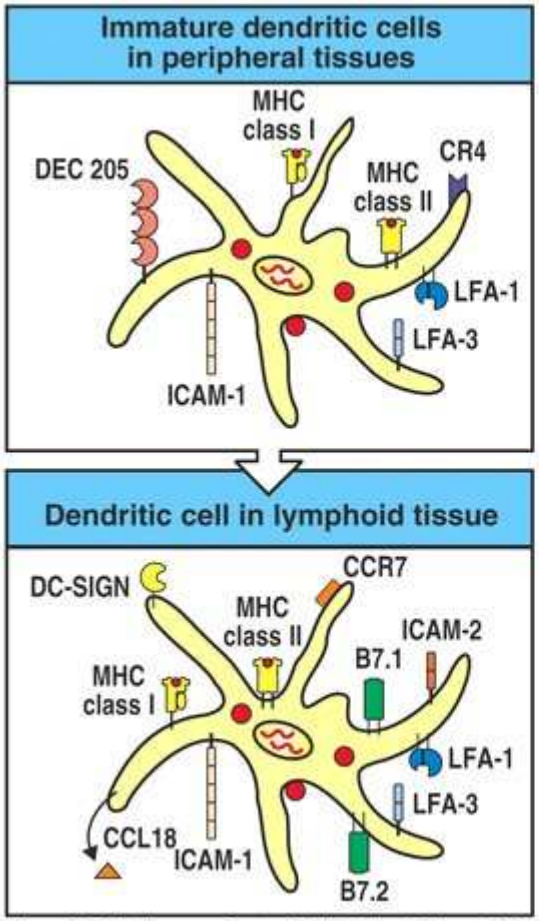
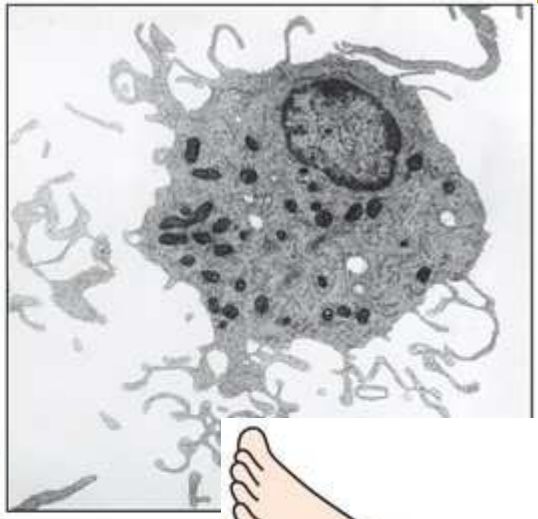


Figure 6-12 The Immune System, 2/e (© Garland Science 2005)



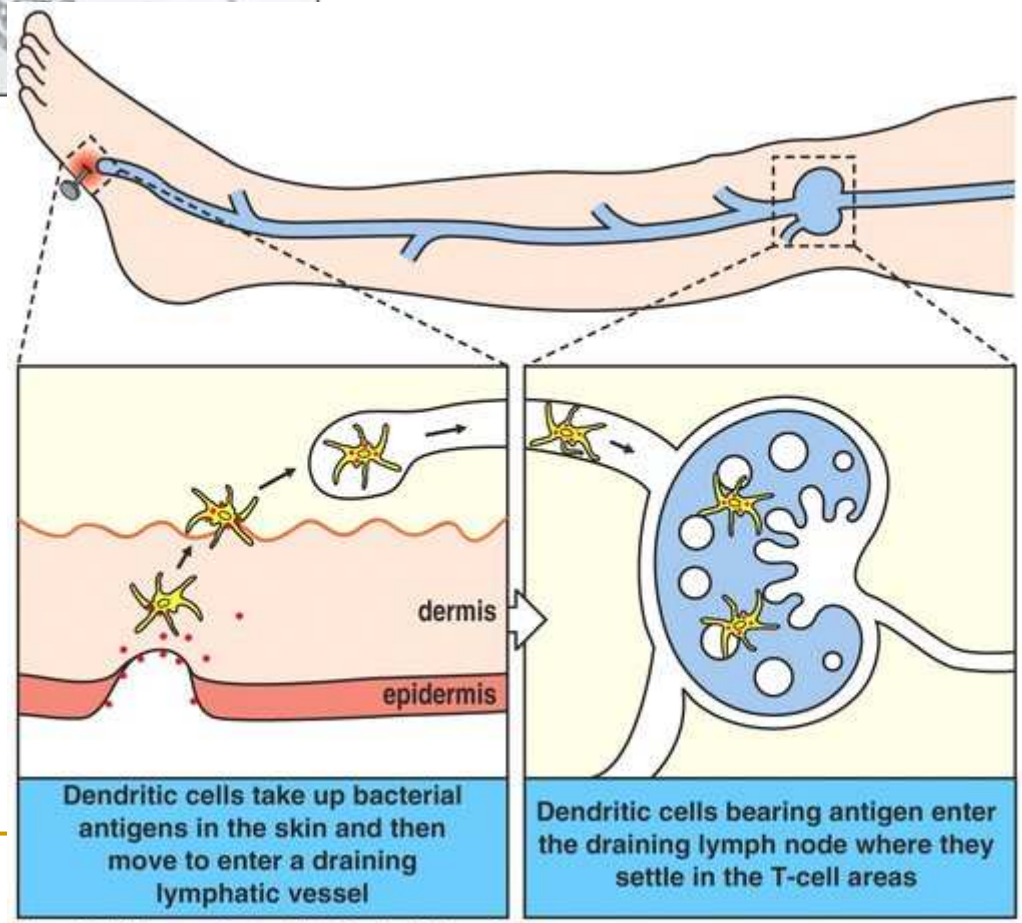
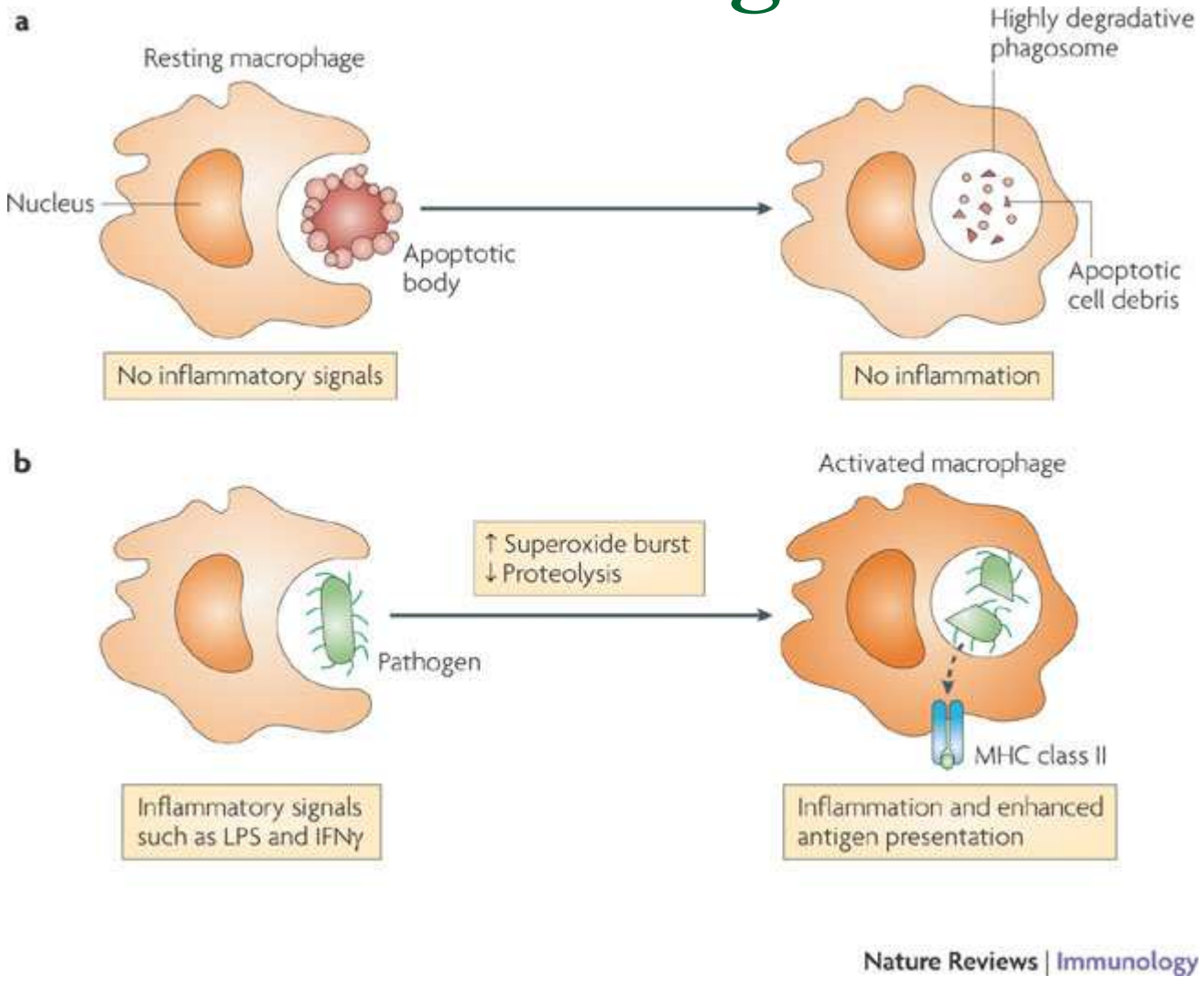


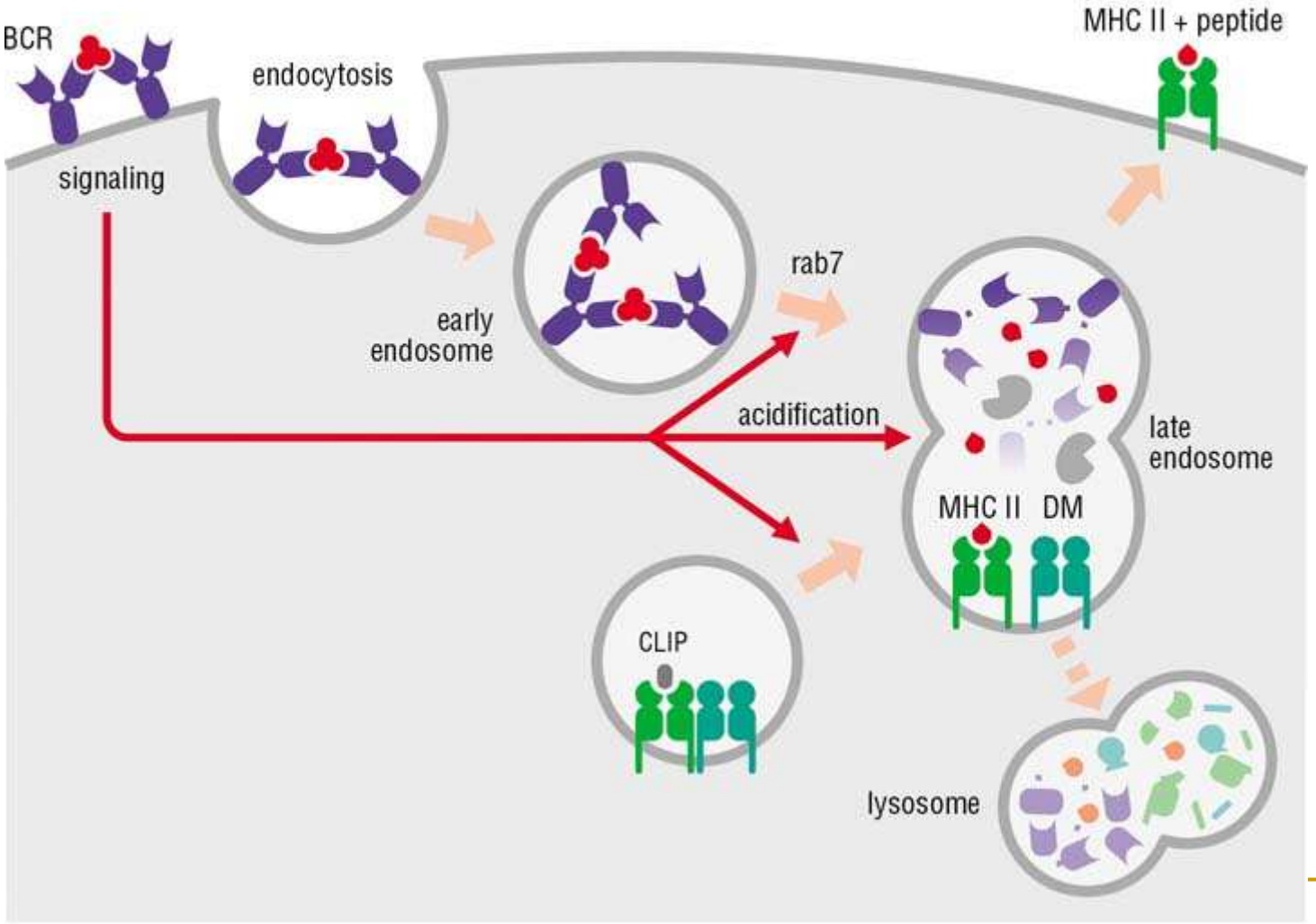
Figure 6-1 The Immune System, 2/e (© Garland Science 2005)

Macrófago

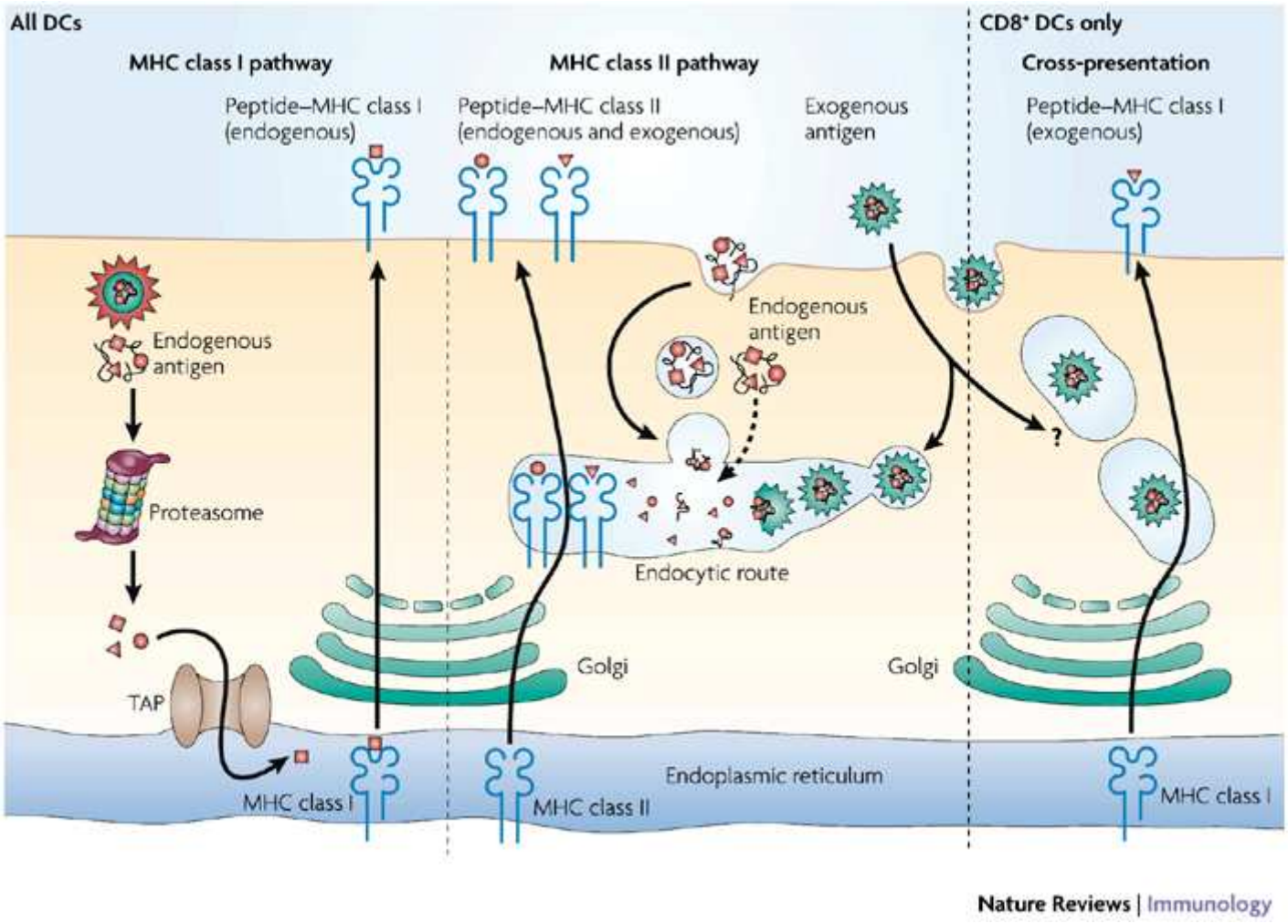


Nature Reviews Immunology 9, 594-600 (August 2009)

El linfocito B como APC

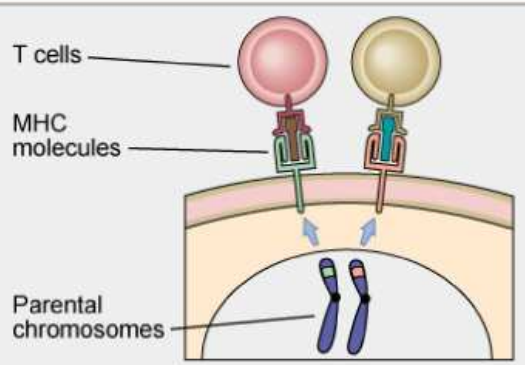
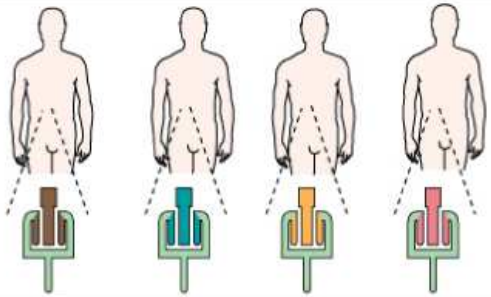
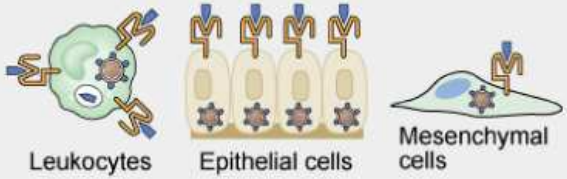


VÍAS DE PRESENTACIÓN ANTIGÉNICA

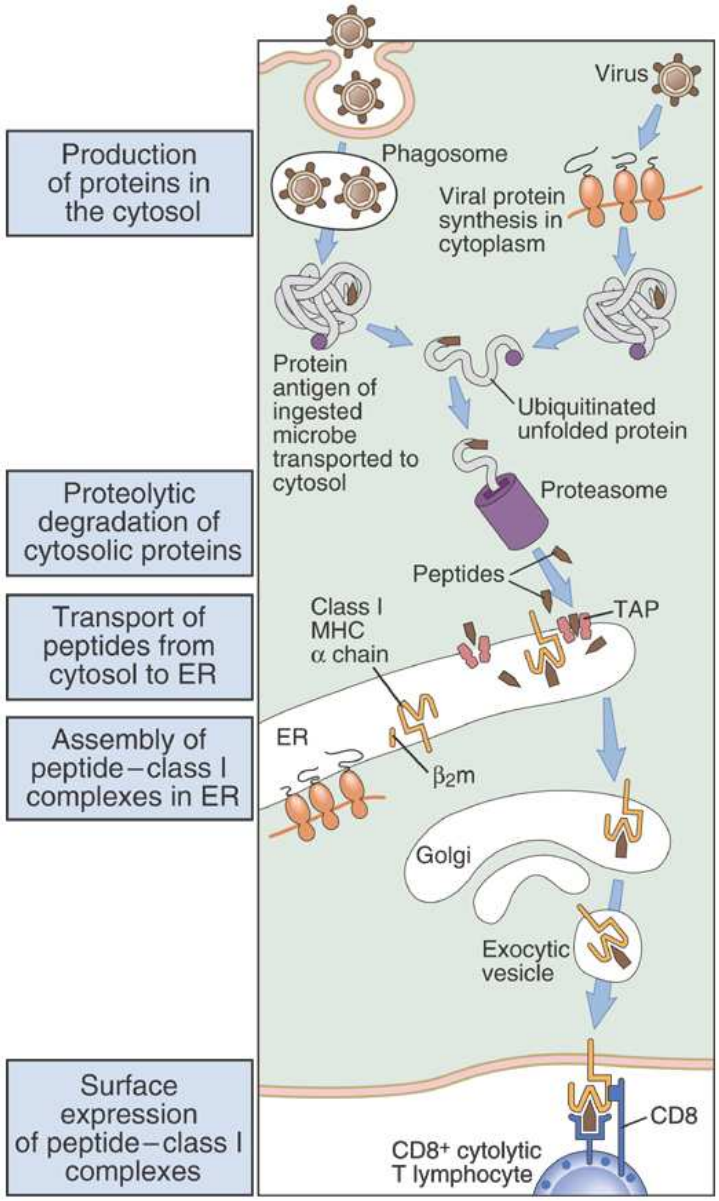


Nature Reviews Immunology **7**, 543-555 (July 2007)

Propiedades y Funciones del MHC

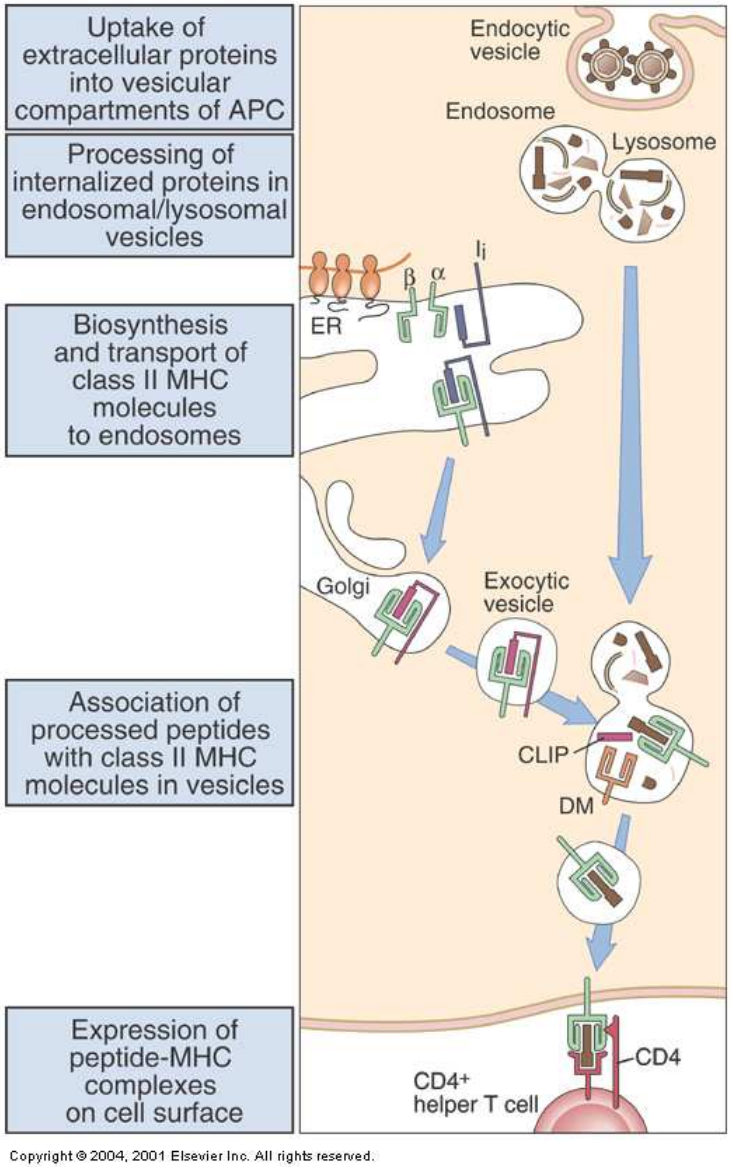
Feature	Significance	
Codominant expression: Both parental alleles of each MHC gene are expressed	Increases number of different MHC molecules that can present peptides to T cells	
Polymorphic genes: Many different alleles are present in the population	Ensures that different individuals are able to present and respond to different microbial peptides	
MHC-expressing cell types: Class II: Dendritic cells, macrophages, B cells	$CD4^+$ helper T lymphocytes interact with dendritic cells, macrophages, B lymphocytes	
Class I: All nucleated cells	$CD8^+$ CTLs can kill any virus-infected cell	

"Carga" del MHC I



- Cytosolic peptides – proteins from cytoplasmic viruses and from phagocytosed microbes that may break thru the vesicle and escape to the cytoplasm
  - proteolysis – ubiquitin binds to protein and leads to proteosomes for digestion
  - some cleaved peptides are small enough to fit into MHC I
- MHC I made in the ER while peptides are in cytoplasm – requires special transport proteins called TAP (transporters associated with Ag presentation) in the ER membrane
- TAP pumps peptides into ER so can get on MHC I – loose association between TAP and MHC on inner surface of ER
  - right fit of peptide and MHC will stabilize the complex and move it to the cytoplasm
  - no peptide leads to MHC degradation

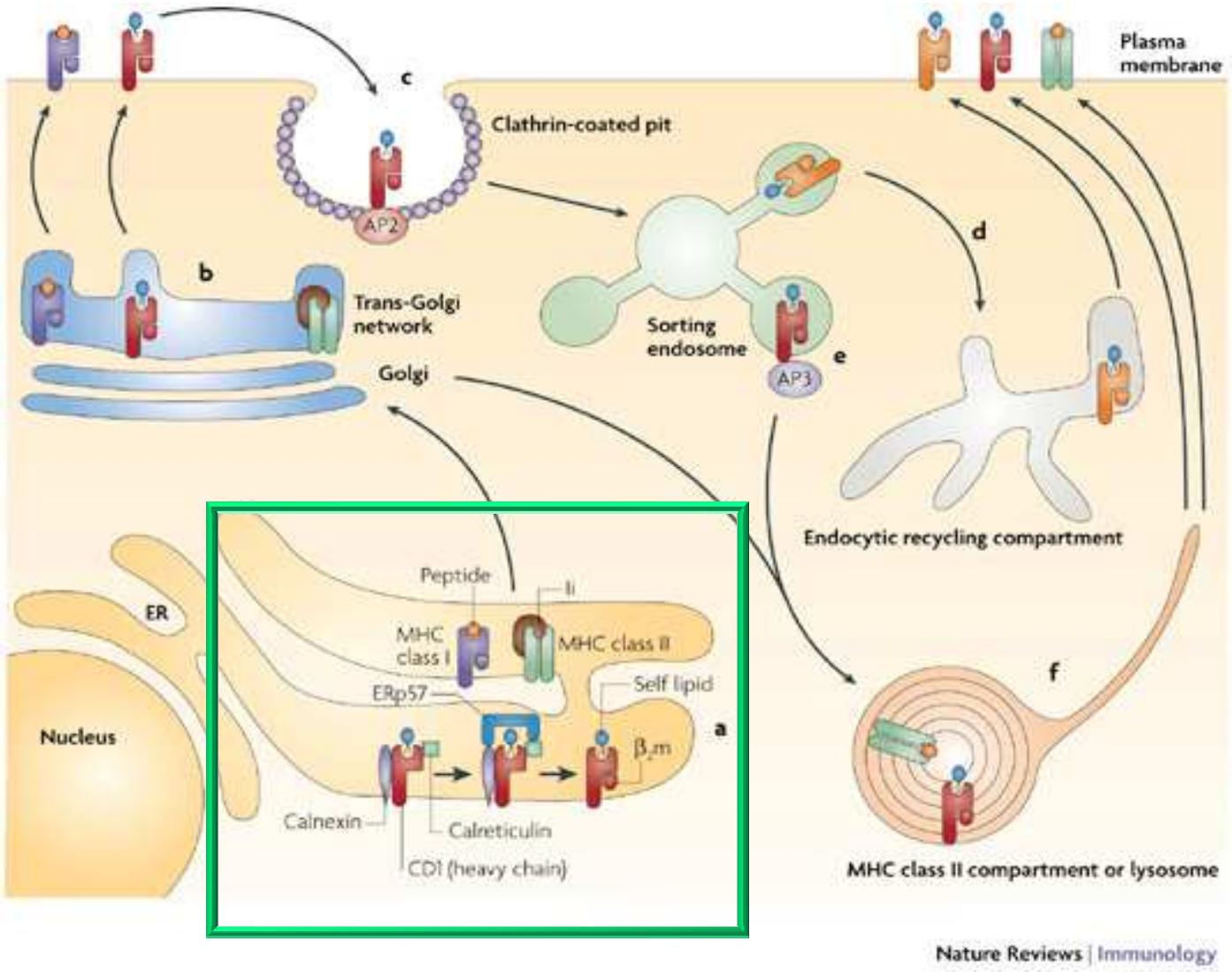
"Carga" del MHC II



- Endosomal peptides – proteins enter intracellular vesicles and may fuse with lysosome, proteins broken down by proteolytic enzymes to peptides
- APC synthesize MHC II in ER and each MHC II has a sequence called class II invariant chain peptide (CLIP) attached to the invariant chain which binds tightly to the cleft
- MHC II/CLIP complex begins way to cell surface in an exocytic vesicle which fuses with endosomal vesicle of peptides, also contains DM protein that removes CLIP so peptide can enter into cleft
  - if no peptide picked up, MHC II is degraded in endosome
- MHC II/peptide complex is now stable and can move to the surface
- Only the immunodominant epitopes of Ag enter MHC II – maybe 1-2 peptides

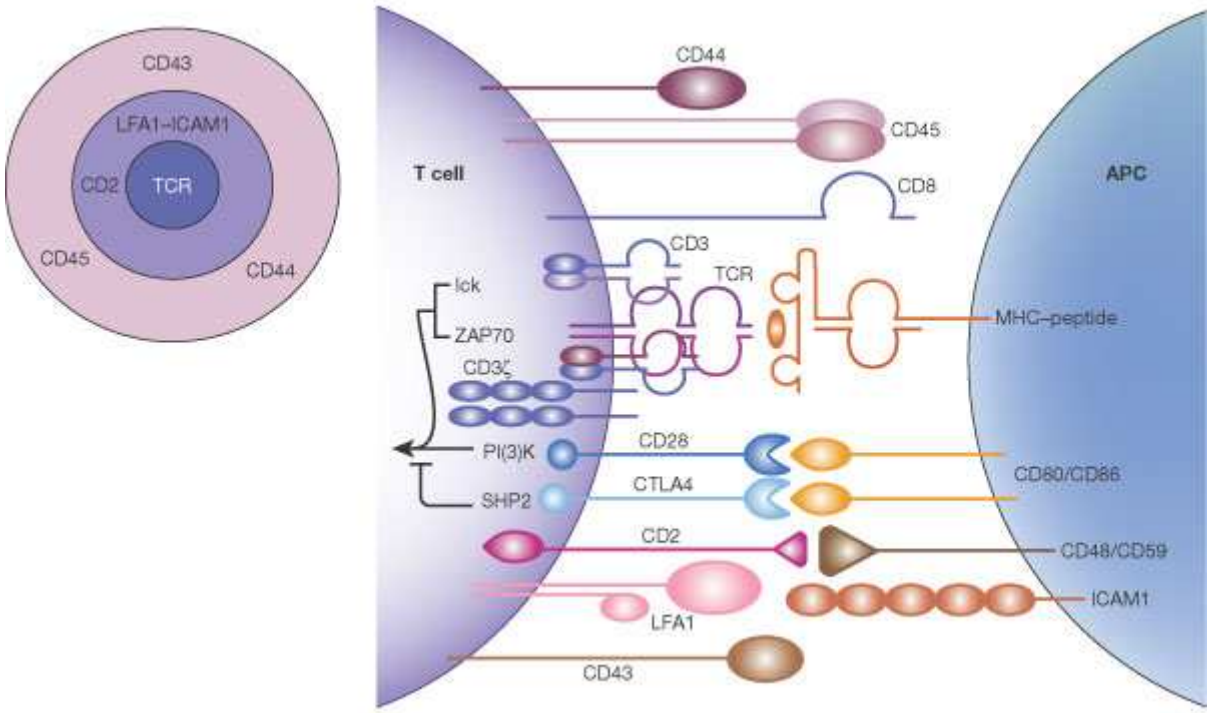
No hay carga cruzada de péptidos….

- Aunque MHC I y MHC II están en ER, NO HABRÁ CARGA CRUZADA DE PÉPTIDOS….
- EL CLIP presente en la MHC II la protege y solo permite la “carga” cuando llega al endosoma…..

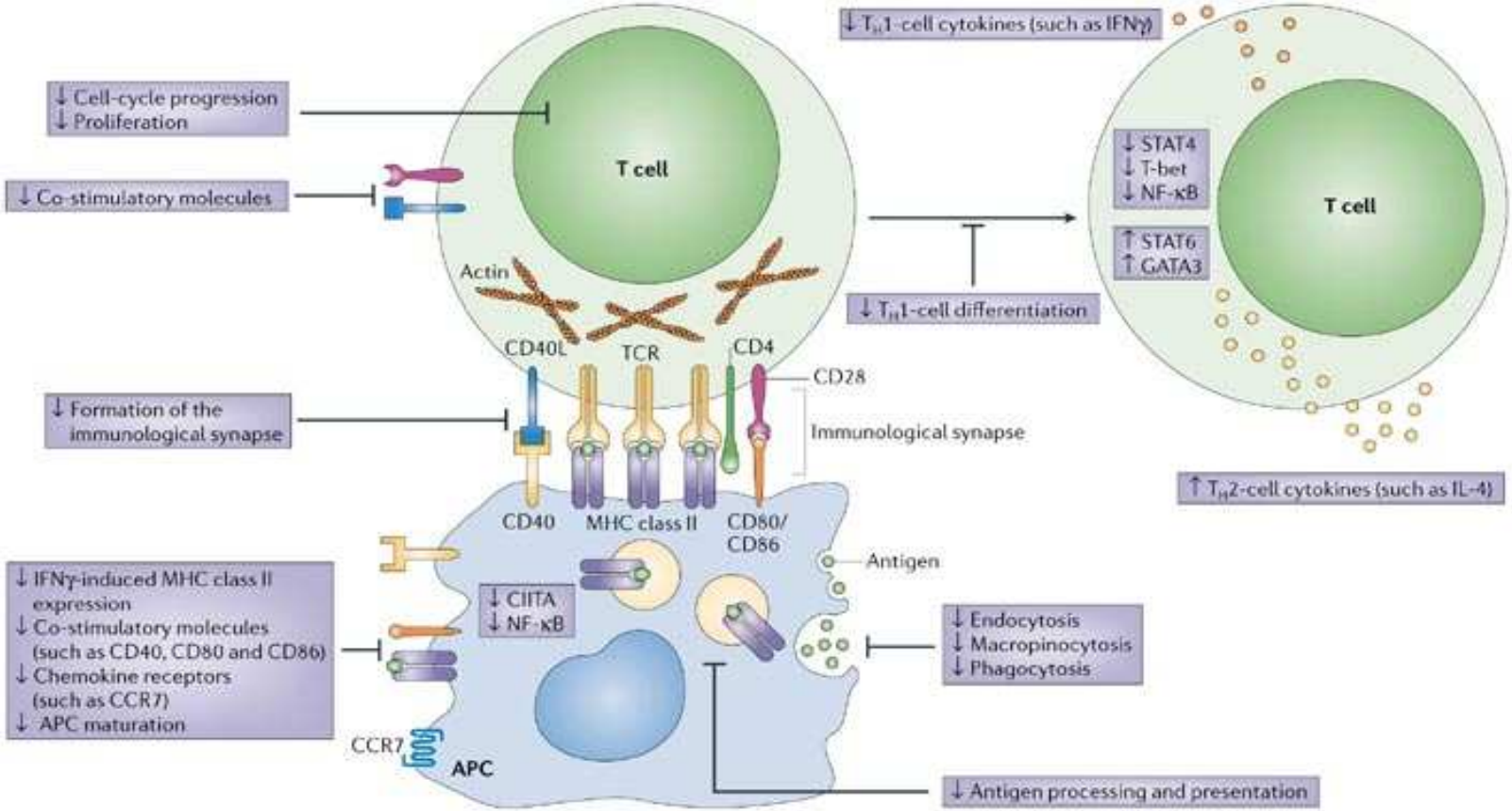

Plasma membrane
c
Clathrin-coated pit
AP2
b
Trans-Golgi network
Golgi
Sorting endosome
d
e
AP3
Endocytic recycling compartment
ER
Nucleus
Peptide
Ii
MHC class I
MHC class II
ERp57
Self lipid
a
β2m
Calnexin
Calreticulin
CD1 (heavy chain)
f
MHC class II compartment or lysosome
Nature Reviews | Immunology

PROCESAMIENTO Y PRESENTACIÓN ANTIGÉNICA

La sinapsis inmunológica permite la activación celular…



Bloqueo de la presentación antigénica

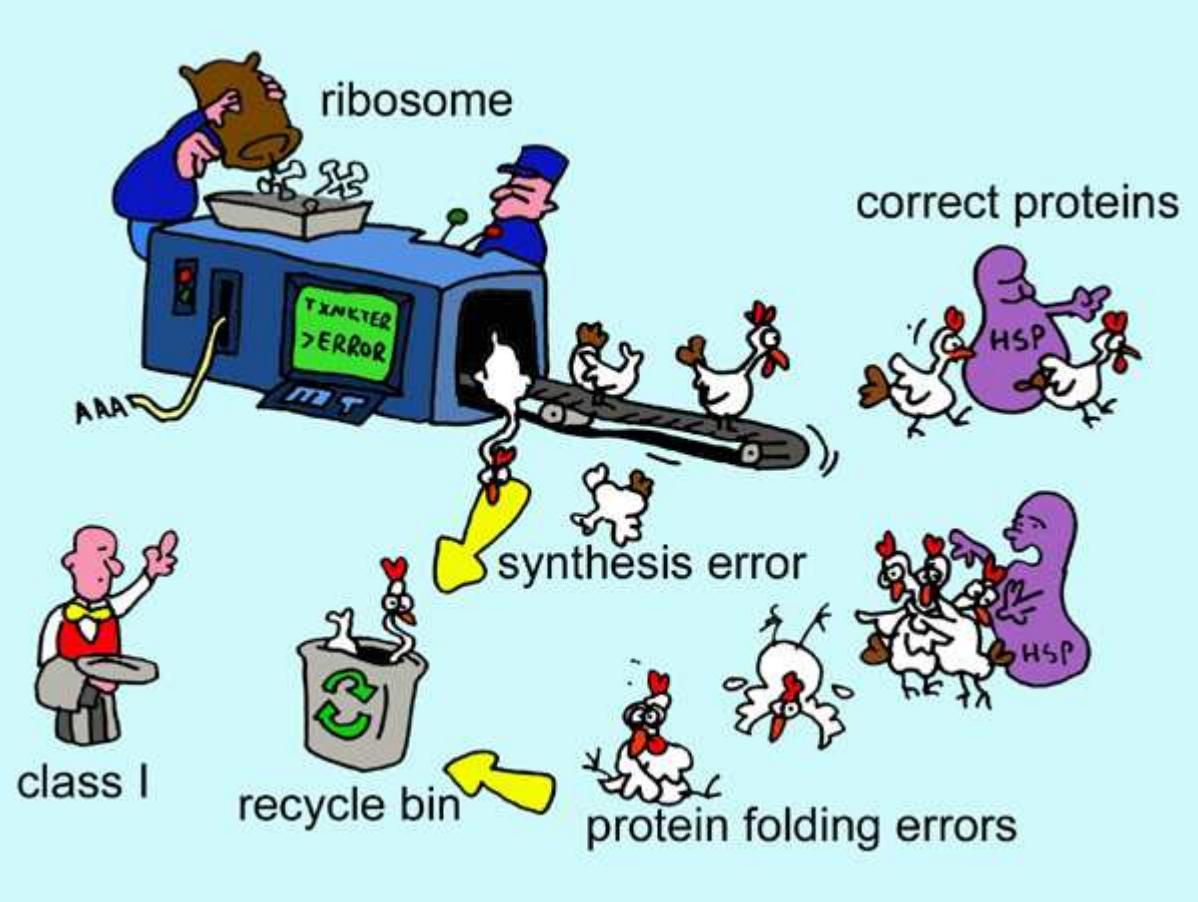


Nature Reviews Immunology **6**, 358-370 (May 2006)

Antígenos endógenos… producidos en el interior de las células del organismo…

- PROTEÍNAS VIRALES, producidas durante la replicación viral.
- PROTEÍNAS producidas por BACTERIAS INTRACELULARES, como , Rickettsias y Chlamydias durante su replicación.
- PROTEÍNAS QUE HAN ESCAPADO AL CITOSOL provenientes del fagosoma de la APC.
- ANTÍGENOS TUMORALES, producidos por células cancerosas.
- PÉPTIDOS PROPIOS provenientes de proteínas celulares humanas.

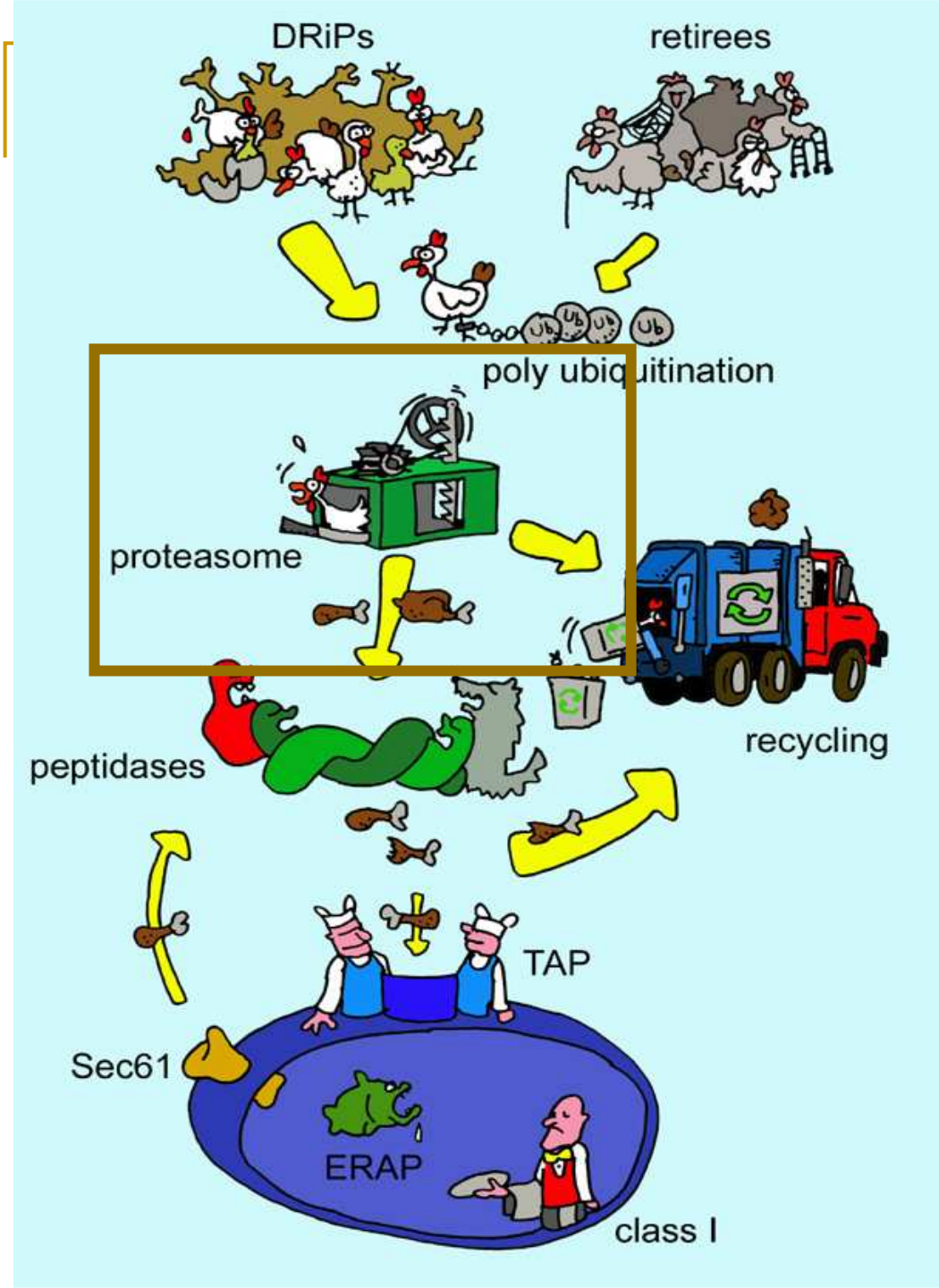
Síntesis de proteínas



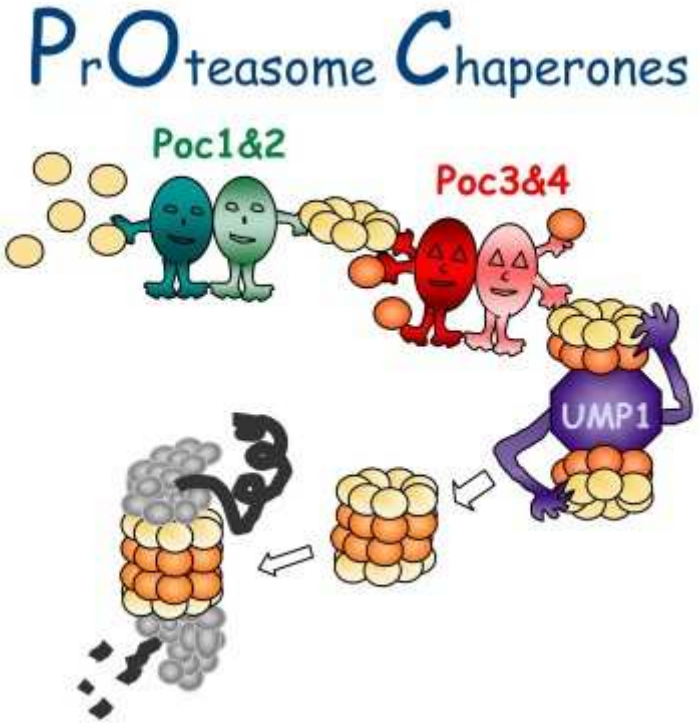
The perils of protein biogenesis. All proteins are made by the ribosome using messenger RNA as a template.

Nascent proteins are frequently stabilized by heat-shock proteins (HSPs), which probably facilitate correct folding and prevent aggregation.

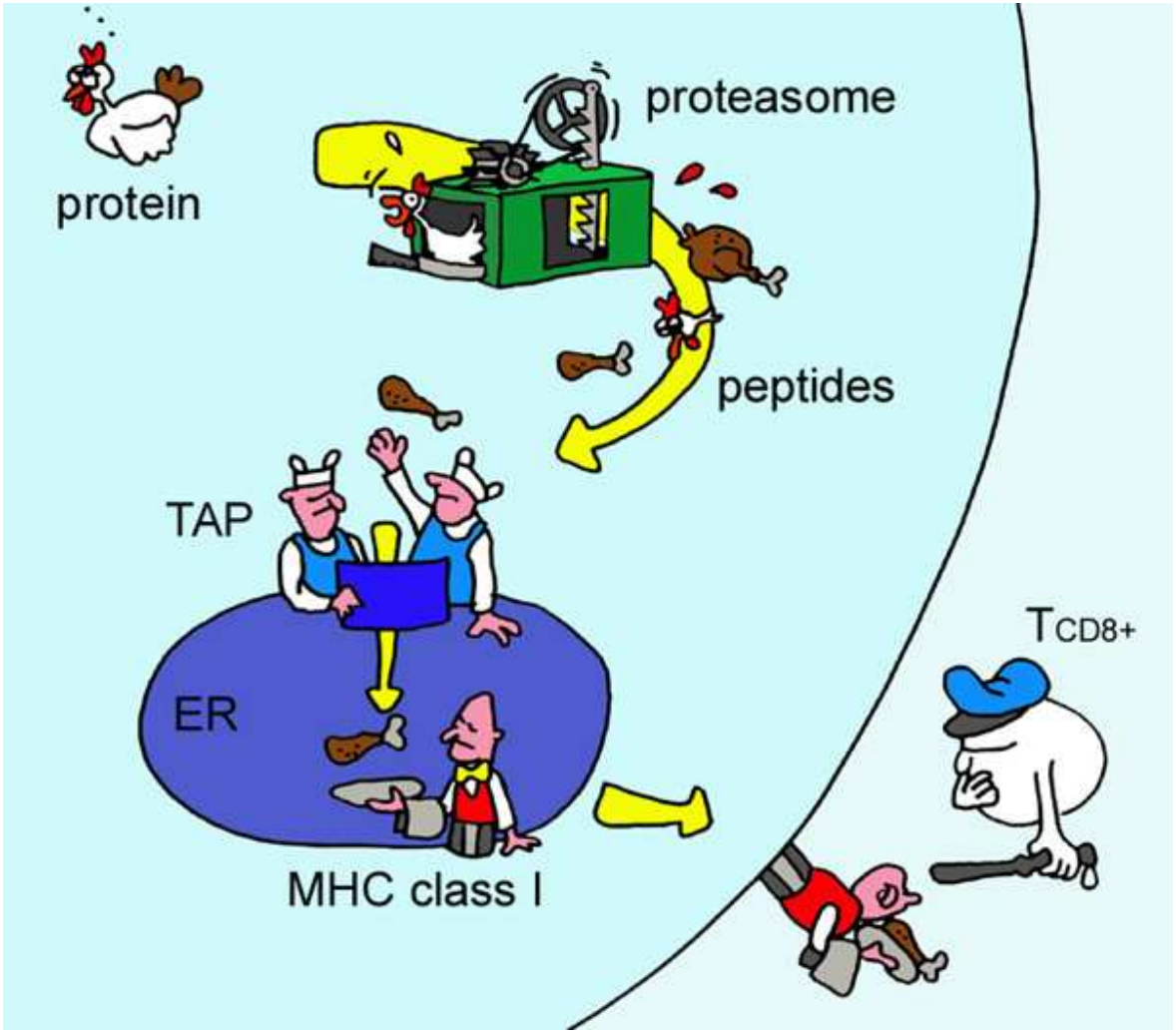
Despite this, a marked fraction of translation products is defective, resulting in incorrect (mistranslated or prematurely stopped), misfolded or misassembled proteins. These defective ribosomal products (DRiPs) are shunted to the proteasome for degradation, coupling protein production to MHC class I antigen presentation and enable a rapid T-cell response to new viral proteins.

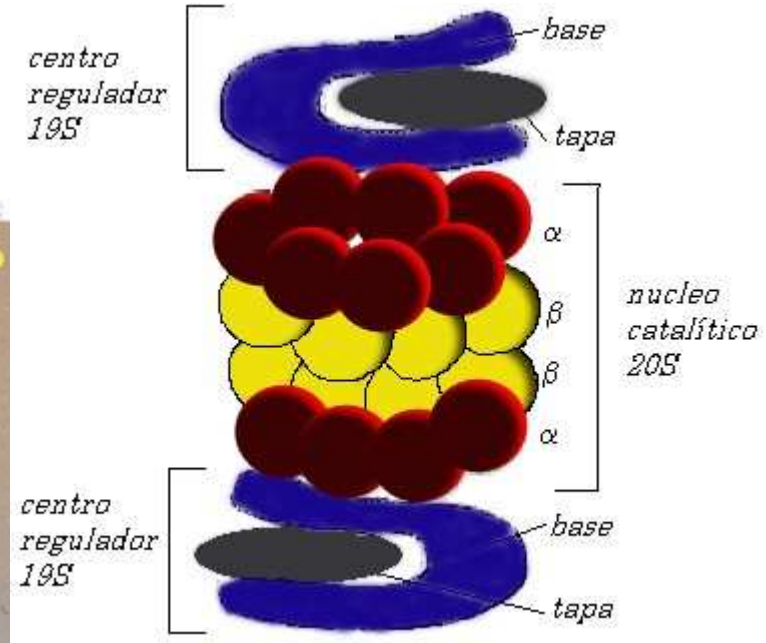


Complexities of MHC class I antigen presentation. Both defective ribosomal products (DRiPs) and mature proteins (retirees) are degraded by proteasomes, usually after polyubiquitylation. The proteasome digests proteins into peptides of various lengths. Many peptides are too small for presentation by MHC class I molecules and are recycled into amino acids that can be used for new proteins. Another fraction is appropriate or too long for MHC class I molecules. These, too, are substrates for various cytosolic peptidases that will degrade most to amino acids. Only a few (trimmed) peptides diffuse into the transporter for antigen processing (TAP). TAP translocates peptides into the lumen of the endoplasmic reticulum (ER), where they can associate with MHC class I molecules before or after trimming by ER aminopeptidases (ERAP). Peptides that fail to bind to MHC class I molecules are removed by the translocon SEC61 and enter the cytoplasm, where they will again be targets for the cytosolic peptidases.



PROTEASOMA

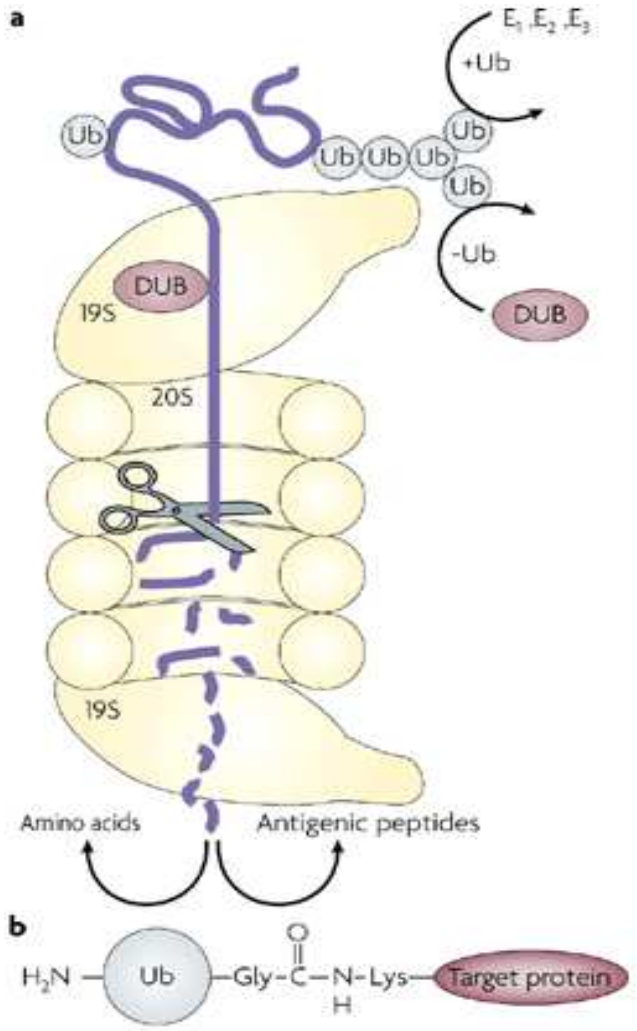

protein
proteasome
peptides
TAP
ER
MHC class I
TCD8+


centro
regulador
19S
base
tapa
α
β
β
α
nucleo
catalítico
20S
centro
regulador
19S
base
tapa


LA UBIQUITINA
MARCA LA
PROTEINA
El aspecto de un proteasoma característico. Consiste en un núcleo de forma tubular, con dos partículas posesionadas en cada uno de sus extremos, como formando un gorro. Estos últimos reconocen la proteína que debe ser destruida. La desenrollan y la inyectan dentro del tubo, donde es cortada en trozos.
El proceso de individualización de la proteína condenada comienza, siendo marcada por otra proteína llamada "ubiquitina". Luego sobre ella comienzan a actuar otras tres enzimas: E1, E2 y E3, completando así la marcación respectiva. En su interior, va siendo cortada en fragmentos y finalmente en aminoácidos
AMINOACIDOS
INDIVIDUALES
FRAGMENTOS DE
VARIAS LONGITUDES

- La ubicuitina (proviene del inglés ubiquitin que es la contracción de ubiquous protein) es la molécula responsable de dar este «beso de la muerte» a la proteína que se quiere degradar. Recibe este nombre por **su ubicua presencia en casi todos los tipos de células**. Además, es una de las proteínas más conservadas durante la evolución, con una secuencia de aminoácidos casi idéntica desde los insectos al hombre.

Ubiquitin is commonly found in a linkage through an isopeptide bond to the ε-amino moiety of a lysine residue of the target protein (shown) or to a lysine side chain of another Ub molecule. Alternatively, ubiquitin can be directly linked to the N terminus of a target protein or to the N terminus of another ubiquitin molecule.

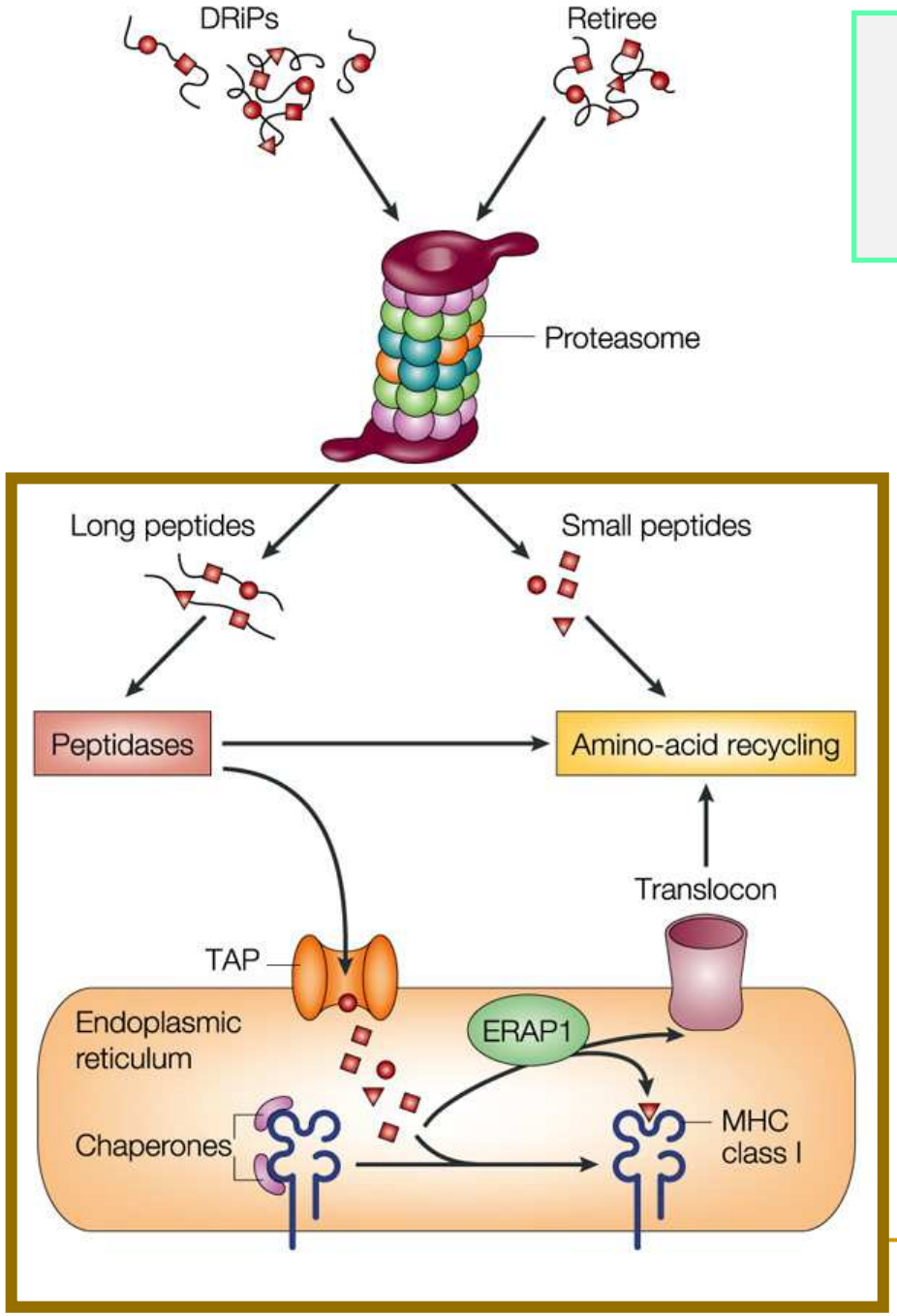


DUB, deubiquitylating enzyme.

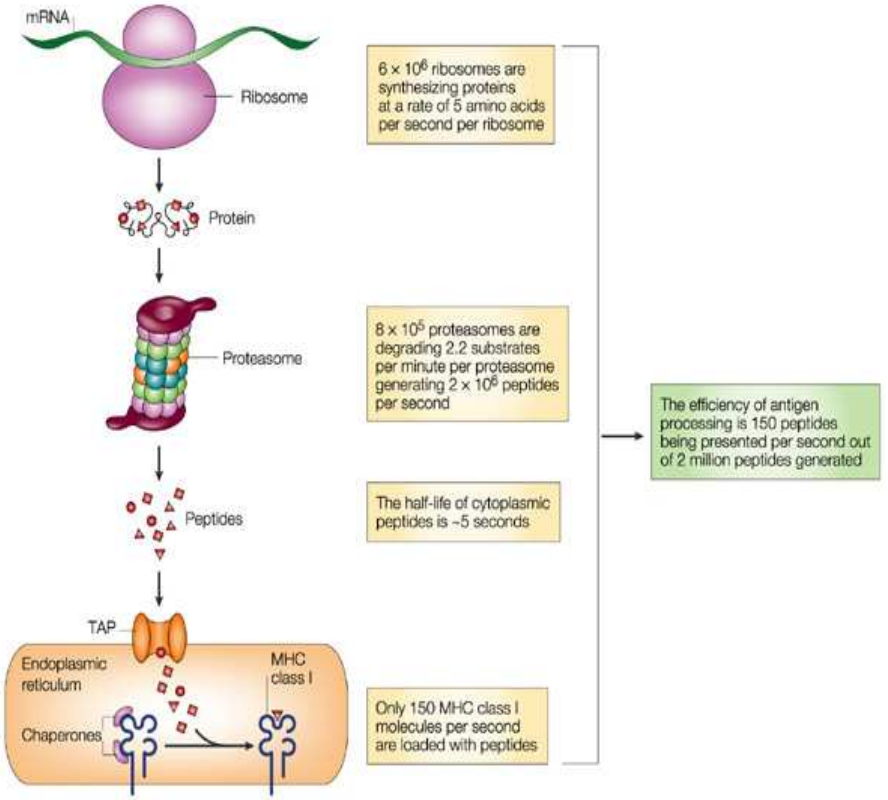
Nature Reviews | Cancer

Nature Reviews Cancer **7**, 613-620 (August 2007)

Se generan alrededor de 2 x 10^6 péptidos sin embargo sólo son presentados 150 péptidos por segundo!!!!!!!

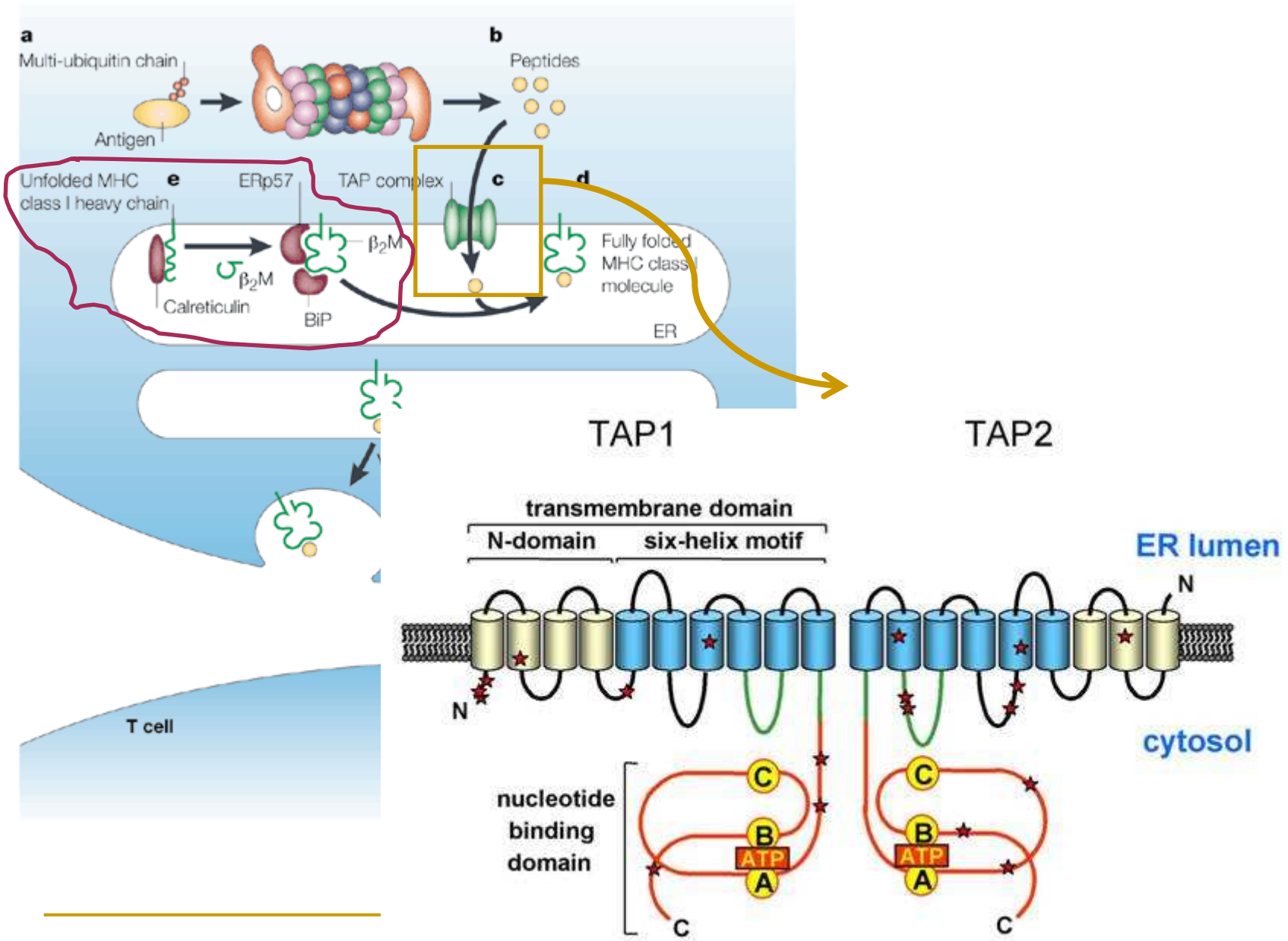


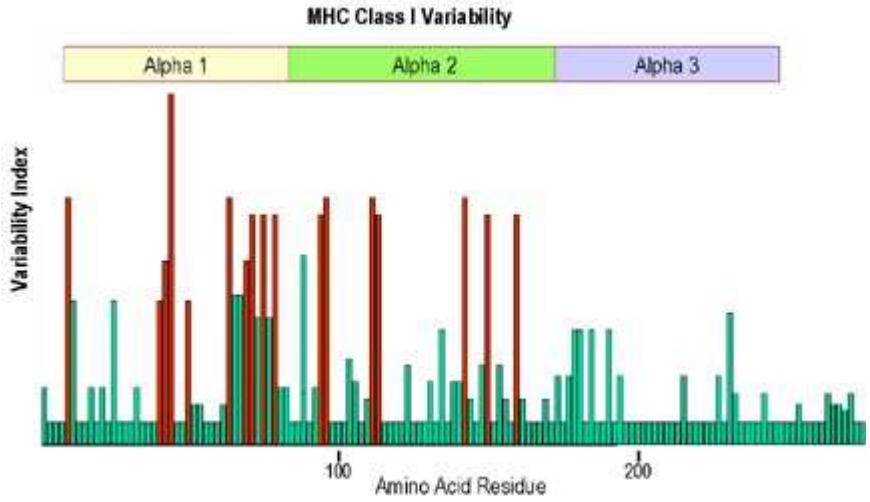
Nature Reviews | Immunology



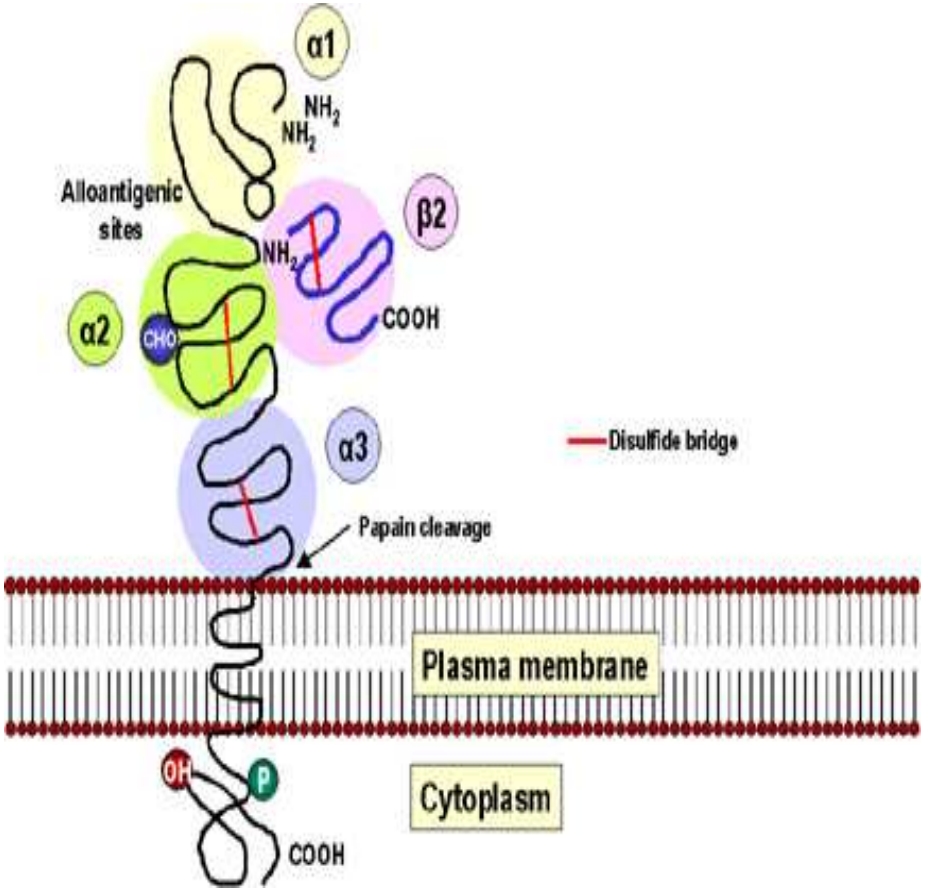
Nature Reviews | Immunology

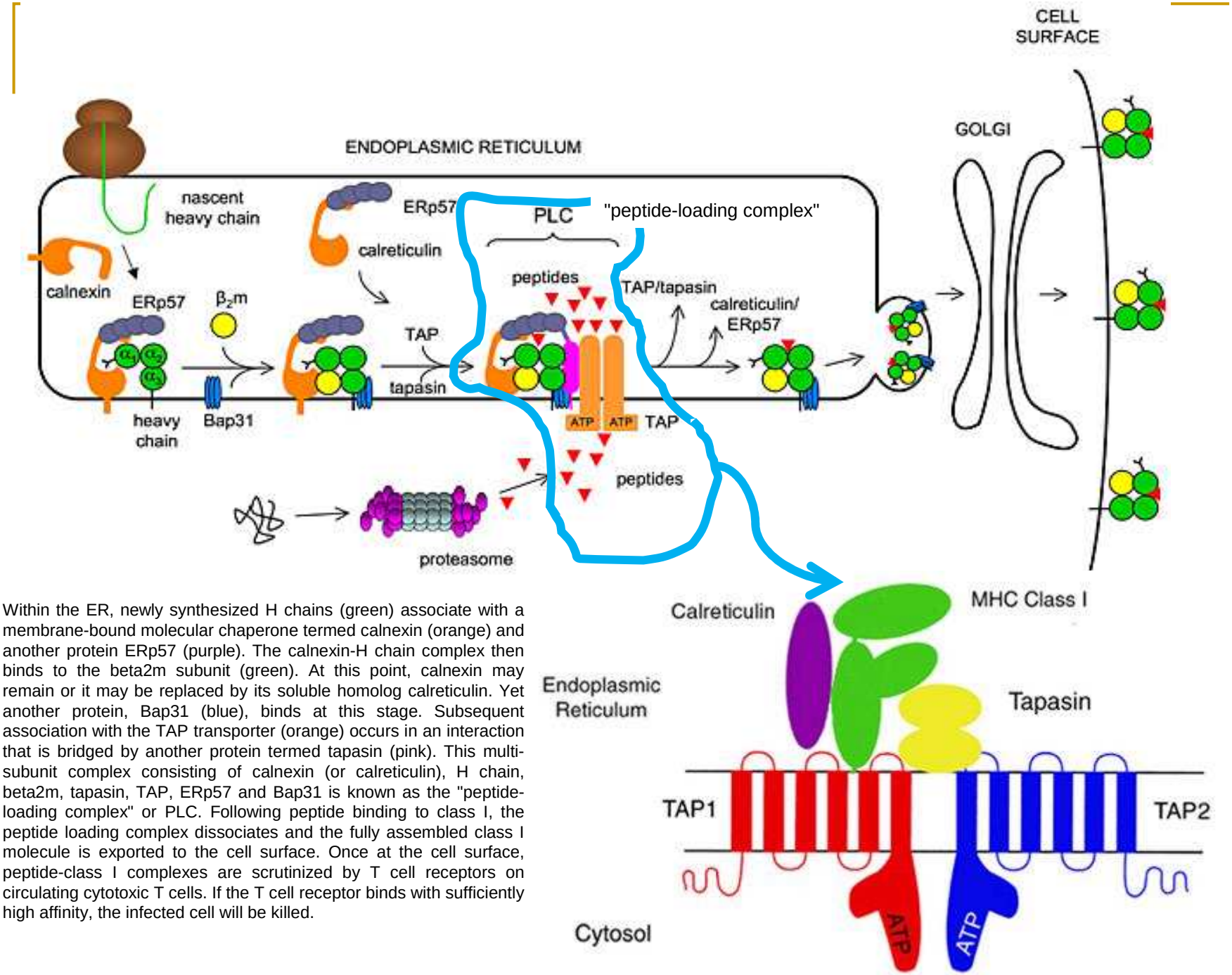
Solo 150 MHC I son cargadas con péptidos por segundo


a
Multi-ubiquitin chain
Antigen
b
Peptides
Unfolded MHC class I heavy chain
e
ERp57
TAP complex
c
d
β2M
β2M
Calreticulin
BiP
Fully folded MHC class I molecule
ER
T cell
TAP1
TAP2
transmembrane domain
N-domain
six-helix motif
ER lumen
N
N
cytosol
nucleotide binding domain
C
B
ATP
A
C
C
B
ATP
A
C


MHC Class I Variability
Alpha 1
Alpha 2
Alpha 3
Variability Index
100
200
Amino Acid Residue

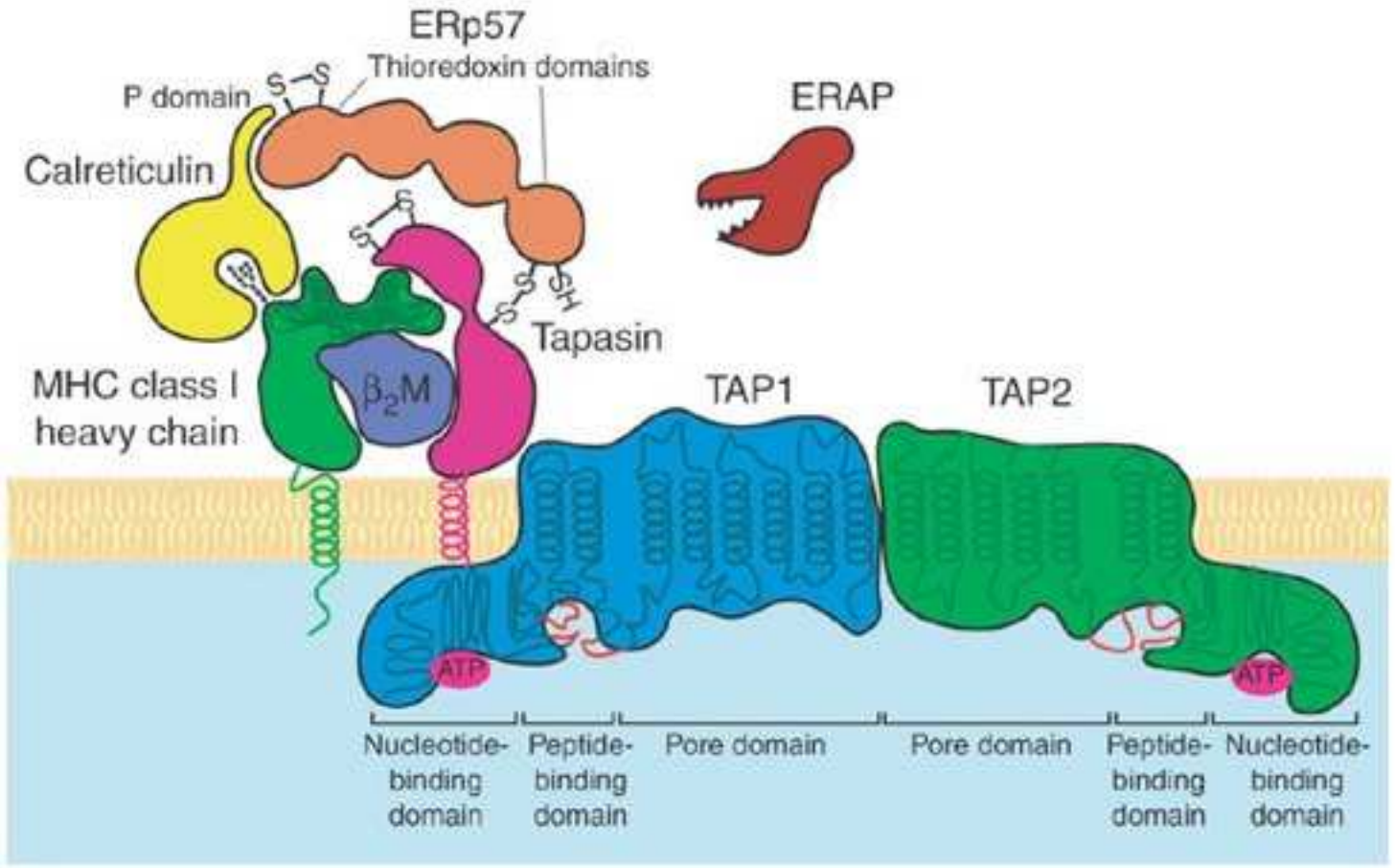
MHC I


α1
NH2
NH2
Alloantigenic sites
β2
NH2
COOH
α2
CHO
α3
Disulfide bridge
Papain cleavage
Plasma membrane
Cytoplasm
OH
P
COOH



Within the ER, newly synthesized H chains (green) associate with a membrane-bound molecular chaperone termed calnexin (orange) and another protein ERp57 (purple). The calnexin-H chain complex then binds to the beta2m subunit (green). At this point, calnexin may remain or it may be replaced by its soluble homolog calreticulin. Yet another protein, Bap31 (blue), binds at this stage. Subsequent association with the TAP transporter (orange) occurs in an interaction that is bridged by another protein termed tapasin (pink). This multi-subunit complex consisting of calnexin (or calreticulin), H chain, beta2m, tapasin, TAP, ERp57 and Bap31 is known as the "peptide-loading complex" or PLC. Following peptide binding to class I, the peptide loading complex dissociates and the fully assembled class I molecule is exported to the cell surface. Once at the cell surface, peptide-class I complexes are scrutinized by T cell receptors on circulating cytotoxic T cells. If the T cell receptor binds with sufficiently high affinity, the infected cell will be killed.

Peptide Loading Complex (PLC)

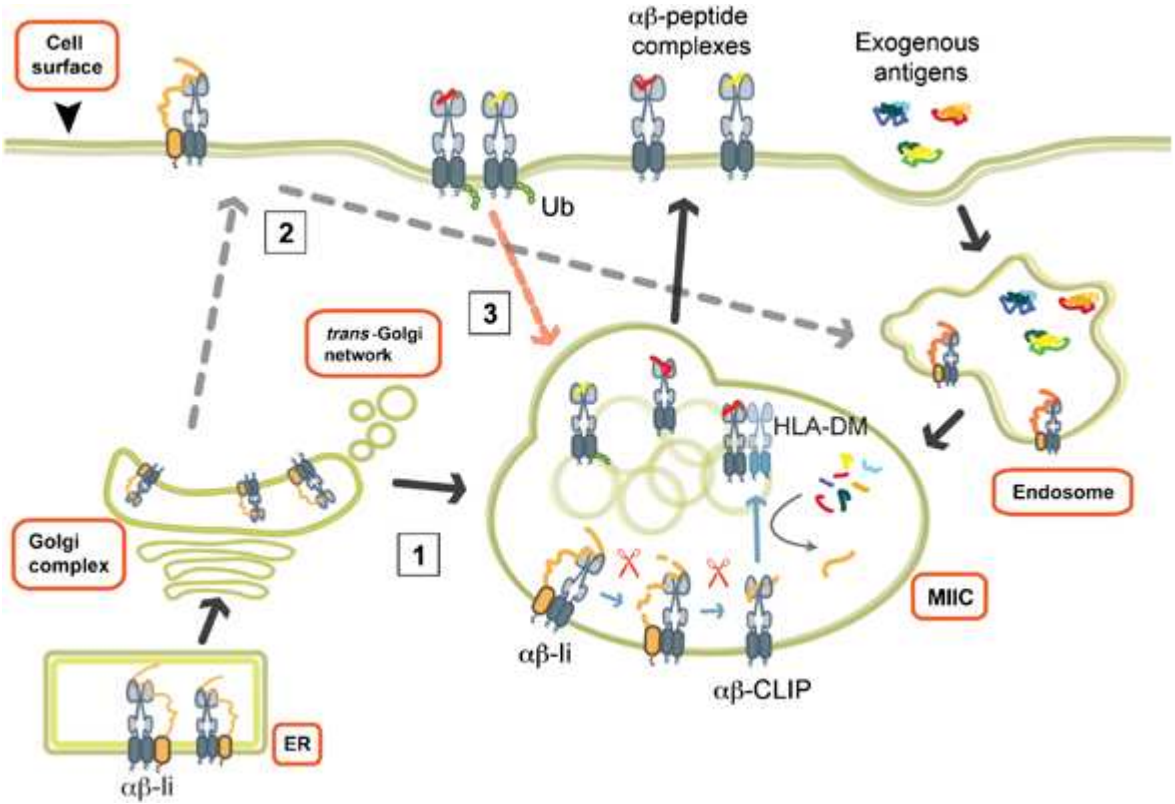


Ackerman and Cresswell, Nat. Immunol., 2004

Funciones de los componentes de la vía de presentación antigénica

- A major focus of my laboratory is to understand how the intracellular complex of peptide and class I molecule is assembled. We discovered a **novel molecular chaperone** known as **calnexin** that participates in the folding and assembly of many nascent proteins including class I. We have shown that calnexin, as well as a related protein termed **calreticulin**, function to prevent exit of incompletely assembled class I molecules from the ER and also protect assembly intermediates from rapid intracellular degradation. Furthermore, calnexin and calreticulin promote the assembly of class I-peptide complexes by as much as 5-fold.
- We have also shown that **newly synthesized class I molecules bind the TAP transporter** (via another protein termed **tapasin**), an interaction **that boosts the efficiency of peptide capture by class I.** The functions of tapasin remain enigmatic. Tapasin clearly is required to increase the efficiency of peptide capture but it remains an open question as to whether this is due to its role in bridging class I binding to TAP or to some other functions. Possibilities include maintaining class I in a peptide receptive state or acting as a "peptide editor", promoting the exchange of low affinity peptides for those that bind more tightly.
- **ERp57 is known to catalyze disulfide bond formation and isomerization and in fact we have recently shown that ERp57 enhances the rate of disulfide bond formation in the class I H chain by 5- to 7-fold.**
- **The Bap31 protein has been shown by others to promote the transport of some proteins out of the ER to the Golgi complex. Using RNA interference to reduce Bap31 levels we were able to demonstrate that Bap31 enhances the rate of class I export out of the ER and that Bap31 is required for class I molecules to cluster at ER "exit sites". It is likely that Bap31 serves as a "cargo receptor" for class I molecules.**

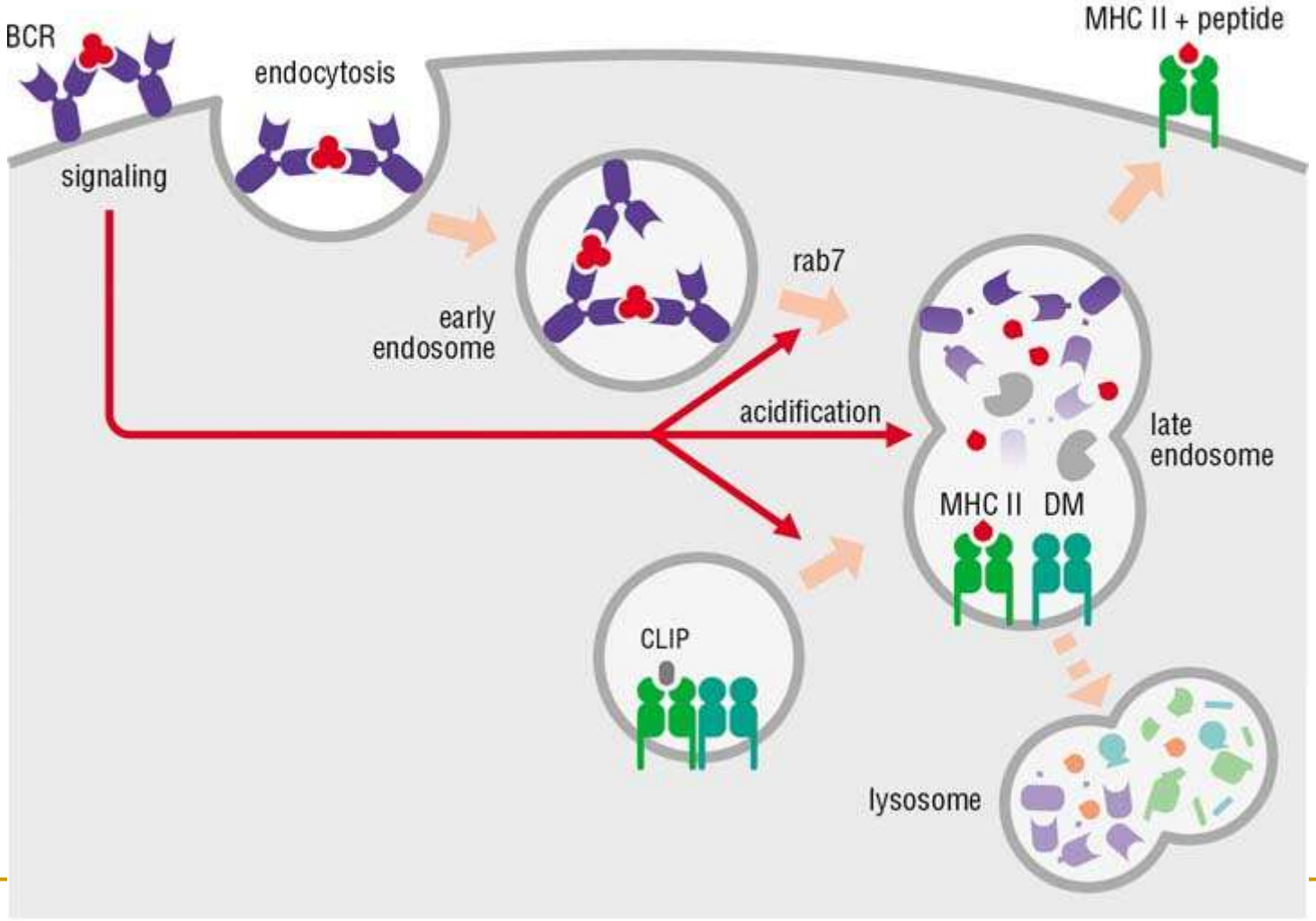
PRESENTACIÓN DE ANTÍGENOS EXÓGENOS



The cell biology of antigen presentation by MHC II. MHC II αβ heterodimers are assembled in the endoplasmic reticulum (ER) and form a peptide-binding groove that is occupied by Ii. Ii chaperones MHC II often directly (route 1; black solid arrows) and sometimes indirectly after internalization from the cell surface (route 2; gray dashed arrows) into MIIC where Ii is degraded by a series of endosomal proteases with the CLIP fragment remaining (orange). HLA-DM assists exchange of CLIP for relevant exogenous antigenic fragments (red or yellow) in subdomains of MIIC (the internal vesicles) prior to transport for stable integration in the plasma membrane (blue arrows in MIIC) unless internalization is induced by processes like ubiquitination (Ub) of the MHC II β-chain cytoplasmic tail (route 3; pink dashed arrow).

The EMBO Journal (2008) **27,** 1–5.

From **Immunity: The Immune Response in Infectious and Inflammatory Disease**
by DeFranco, Locksley and Robertson



HLA- DM Y HLA-DO

HLA-DM CATALIZA EL INTERCAMBIO DE CLIP POR PÉPTIDOS ANTIGÉNICOS (EDICIÓN DE PÉPTIDO).

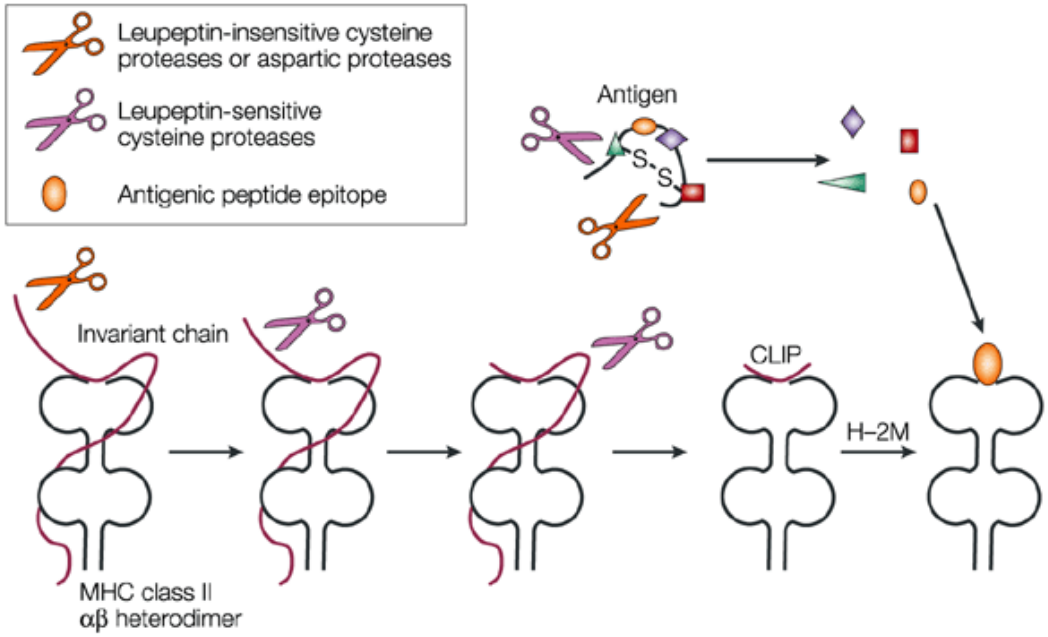
Es una molécula de HLA NO CLÁSICO, NO POLIMÓRFICA, QUE SE EXPRESA DENTRO DEL COMPARTIMENTO ENDOSÓMICO, EN CÉLULAS QUE EXPRESAN MOLÉCULAS CLASE II.

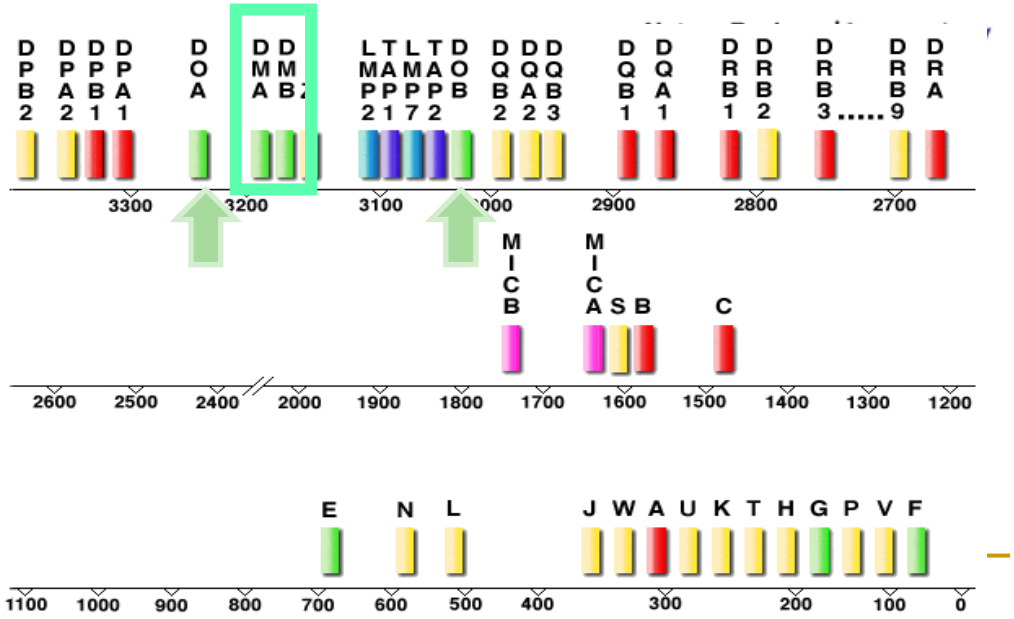
Los genes DMα y DMβ se localizan cerca de los genes TAP y LMP en el complejo MHC.

HLA-DO DISMINUYE LA EFICACIA DE INTERCAMBIO DE PÉPTIDO.

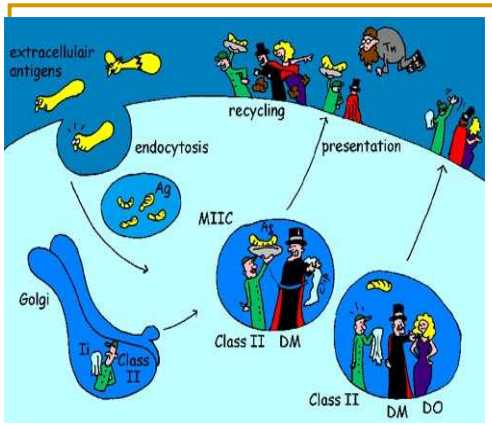
Es una molécula de HLA NO CLÁSICA, NO POLIMÓRFICA QUE SOLO SE EXPRESA EN CÉLULAS B Y EN TIMO, NO ES INDUCIDA POR INF-γ.

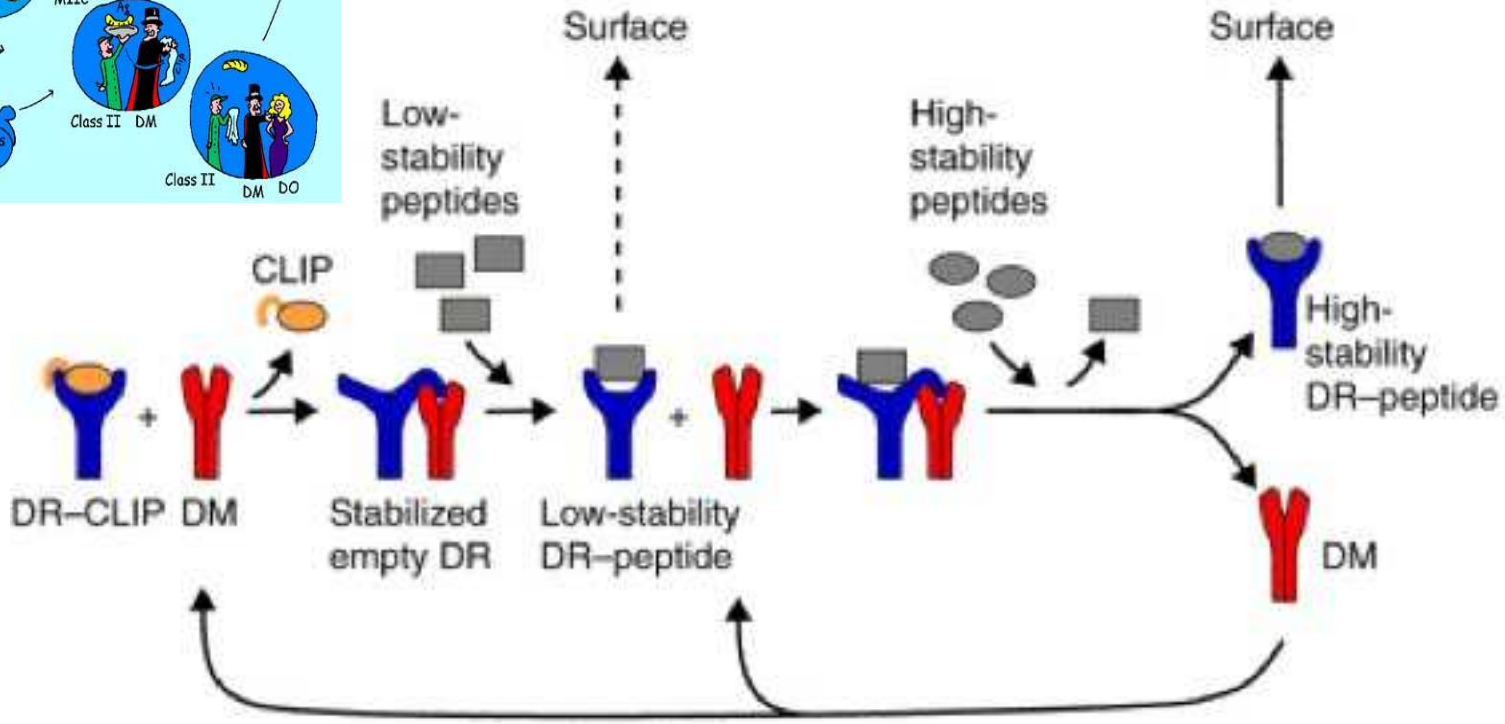
Los genes que codifican las cadenas α y β no son adyacentes en el MHC.





Rol de DM en la carga del péptido



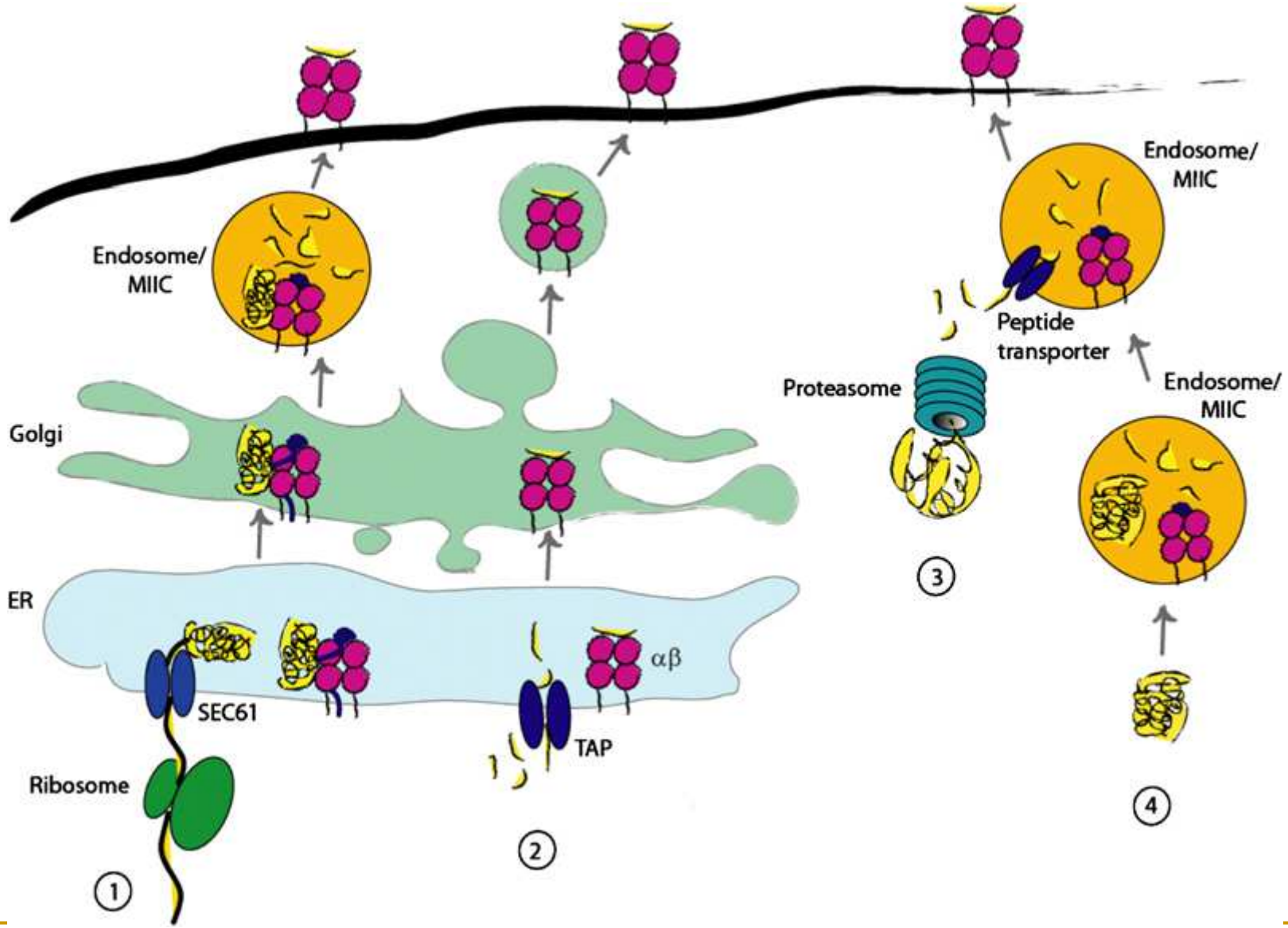


- Acts as a catalyst to enhance the release of CLIP
- Does not bind antigenic peptides so does not act as a peptide transfer molecule
- Most efficient at low pH
- Acts as a peptide editor, facilitating the exchange of low stability, high off rate peptides for high stability peptides with a low off rate

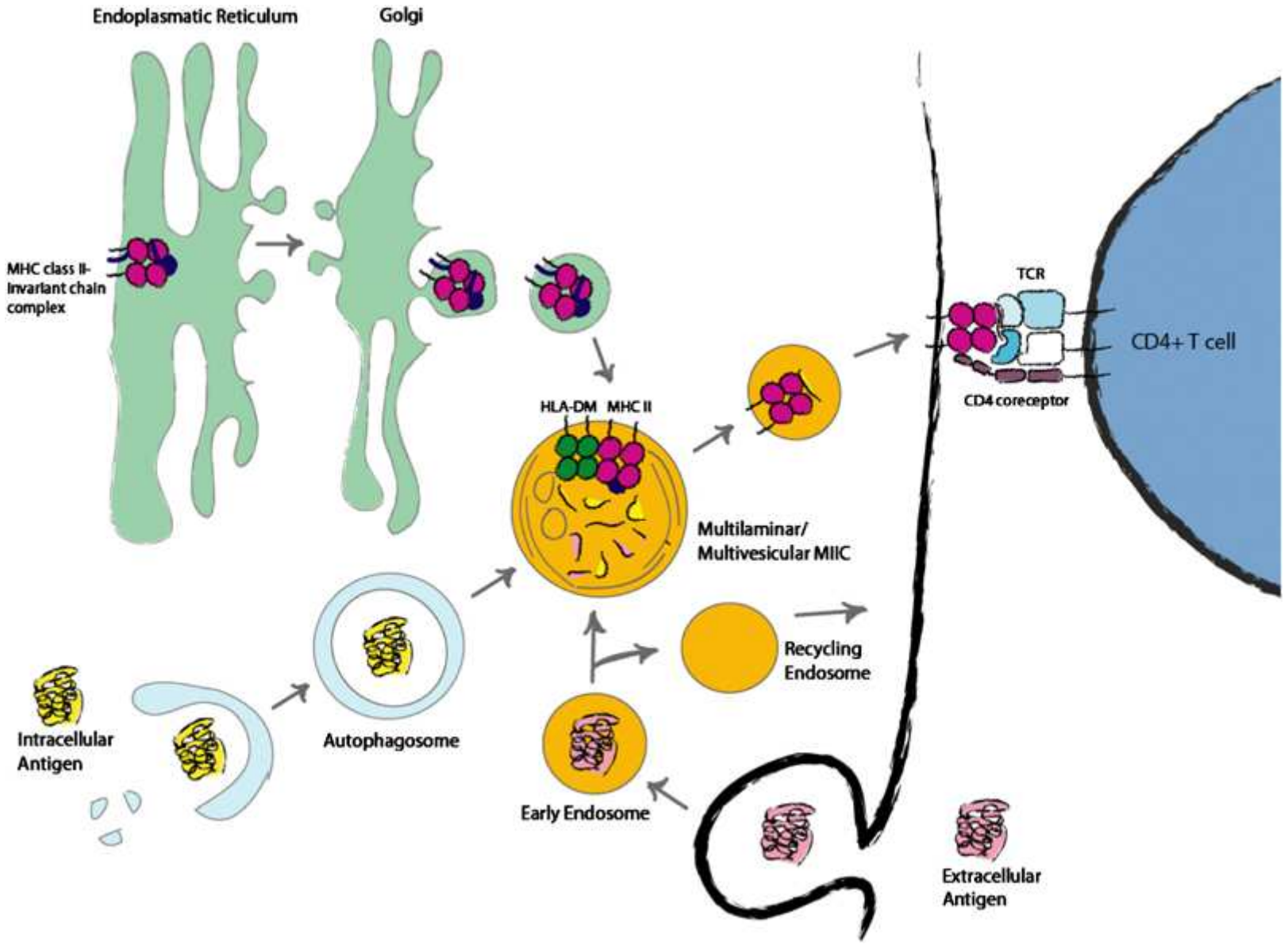
Brocke et al., 2002

PRESENTACIÓN DE PROTEÍNAS ENDÓGENAS EN MHC II

- Proposed processing pathways for endogenous presentation of intracellular antigens on MHC class II. Four different pathways have been postulated:
- (1) Secreted/transmembrane proteins (e.g. influenza A hemagglutinin) can associate with newly synthesized MHC class II molecules after their cotranslational synthesis into the ER via the Sec61 transporter. Complexes of antigen with MHC class II–I_i then traffic to endosomal compartments, where processing and peptide loading onto MHC class II occurs.
- (2) Similar to the classical MHC class I-processing pathway, cytosolic peptides (e.g. a 12-mer HA peptide) can be imported via TAP into the ER and then associate with MHC class II molecules. It is thought that peptides either bind into the peptide-binding groove of MHC class II molecules that failed to associate with invariant chain (I_i) or they comigrate with MHC class II–I_i complexes and get loaded onto MHC class II in the endosomal MIIC with the help of HLA-DM.
- (3) Other cytosolic proteins (e.g. GAD65) are degraded by the proteasome and then follow a TAP-independent pathway onto MHC class II. It is thought that peptides are directly imported into endosomal/lysosomal compartments via a peptide transporter, possibly Lamp-2a.
- (4) Cytosolic and nuclear proteins (e.g. the EBV nuclear antigen 1 (EBNA1) can be processed by lysosomal proteases after direct import into endosomal/lysosomal compartments

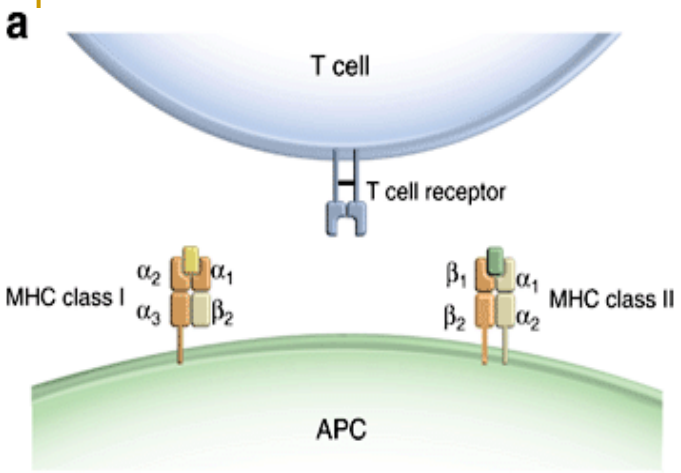

Endosome/
MIIC
Golgi
ER
SEC61
Ribosome
1
αβ
TAP
2
Proteasome
3
Peptide
transporter
Endosome/
MIIC
Endosome/
MIIC
4

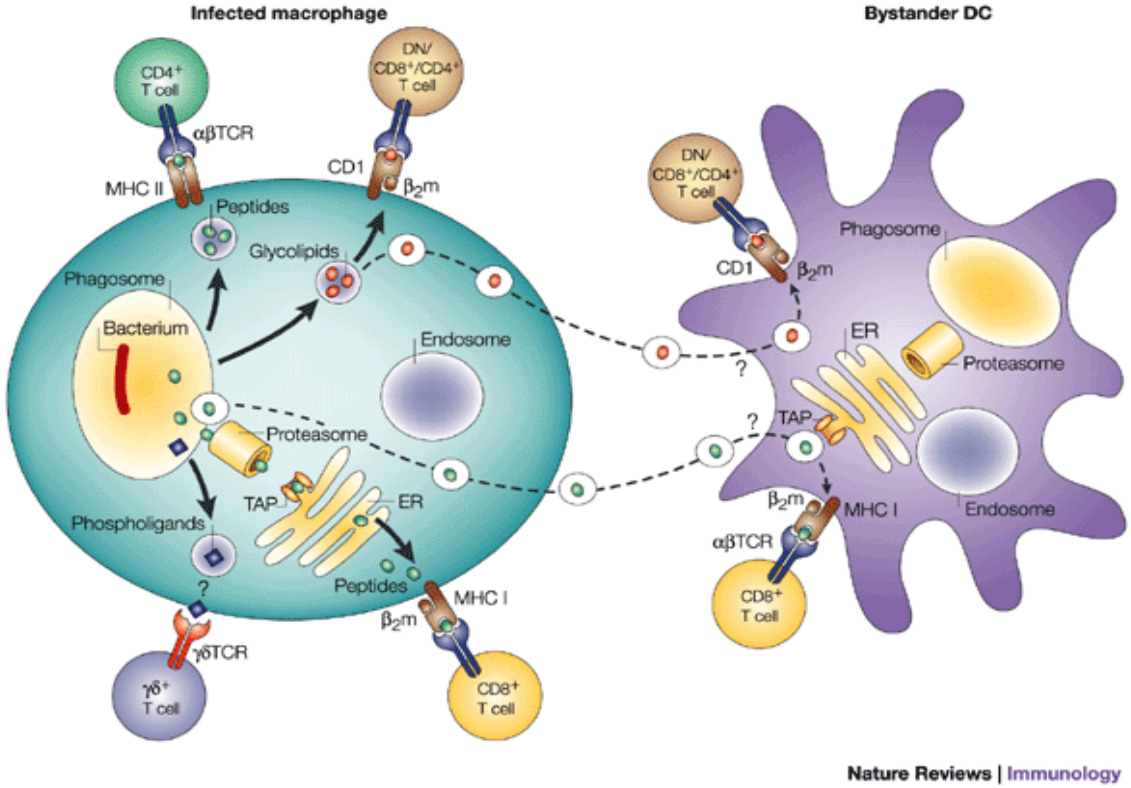
AUTOFAGIA Y PRESENTACIÓN ANTIGÉNICA EN MHC II


Endoplasmatic Reticulum
Golgi
MHC class II-
Invariant chain
complex
HLA-DM MHC II
Multilaminar/
Multivesicular MIIC
TCR
CD4+ T cell
CD4 coreceptor
Recycling
Endosome
Intracellular
Antigen
Autophagosome
Early Endosome
Extracellular
Antigen

- Autophagy as a novel pathway for endogenous MHC class II presentation. Classically, extracellular antigens were thought to be the sole source of peptides for MHC class II presentation. Extracellular antigens are taken up via endocytosis/phagocytosis into endosomal compartments and are degraded by lysosomal proteases. Antigenic peptides generated in this process get loaded onto MHC class II molecules in late endosomal MHC class II-loading compartments (MIICs) with the help of the peptide-loading chaperone HLA-DM, and MHC class II–peptide complexes are presented on the cell surface for recognition by $CD4^+$ T cells. MHC class II molecules reach the endosomal pathway after their synthesis into the ER and association with a glycoprotein called invariant chain (I_i) (shown in blue), which contains a targeting signal for endosomes. Recent evidence, discussed in this review, suggests that cytosolic and nuclear antigens can gain access to MHC class II-loading compartments via autophagy. Thus, autophagic degradation contributes to MHC class II presentation of intracellular antigens to $CD4^+$ T cells

Presentación antigénica en MHC II



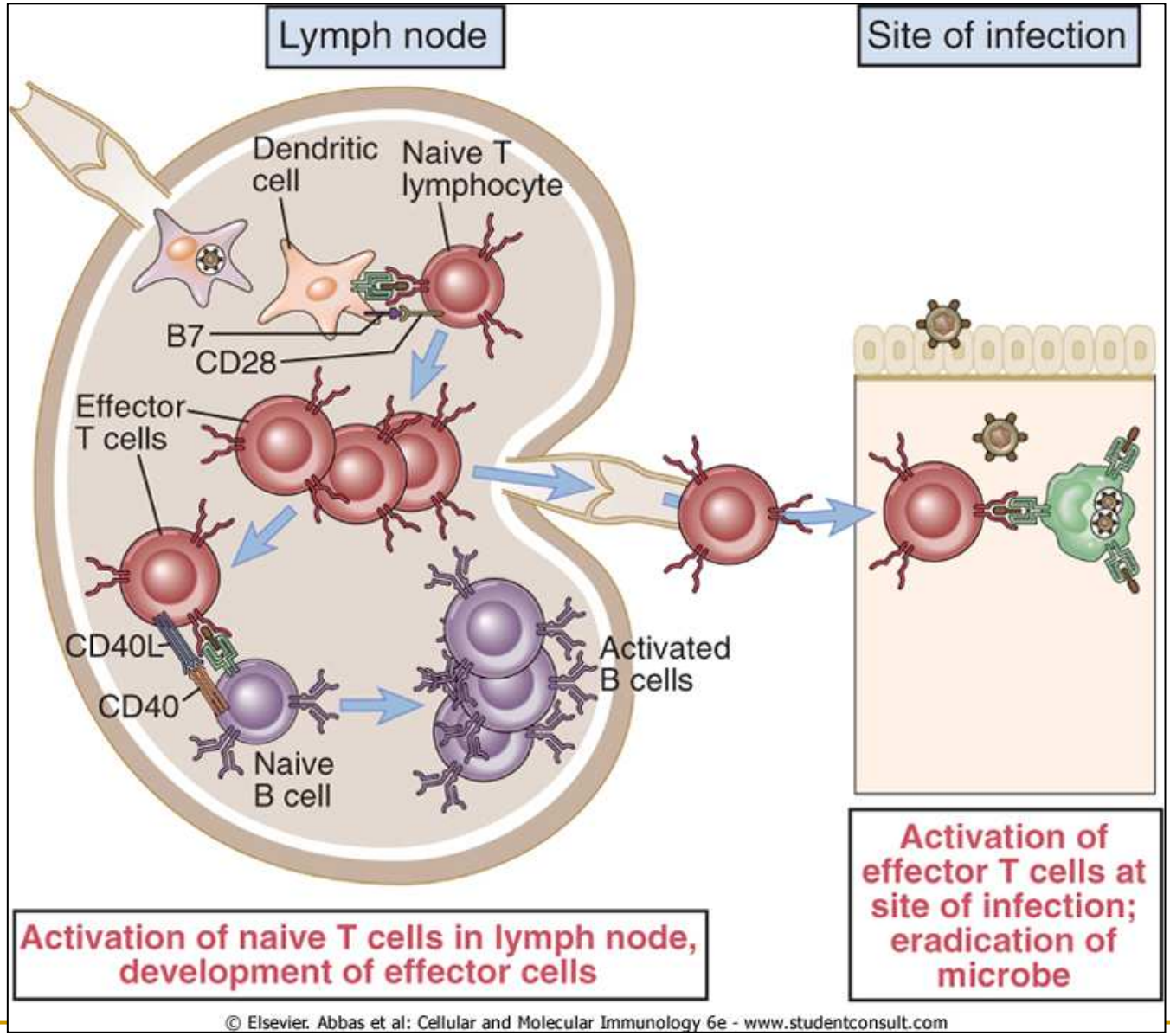


Presentación de antígenos por MICOBACTERIAS

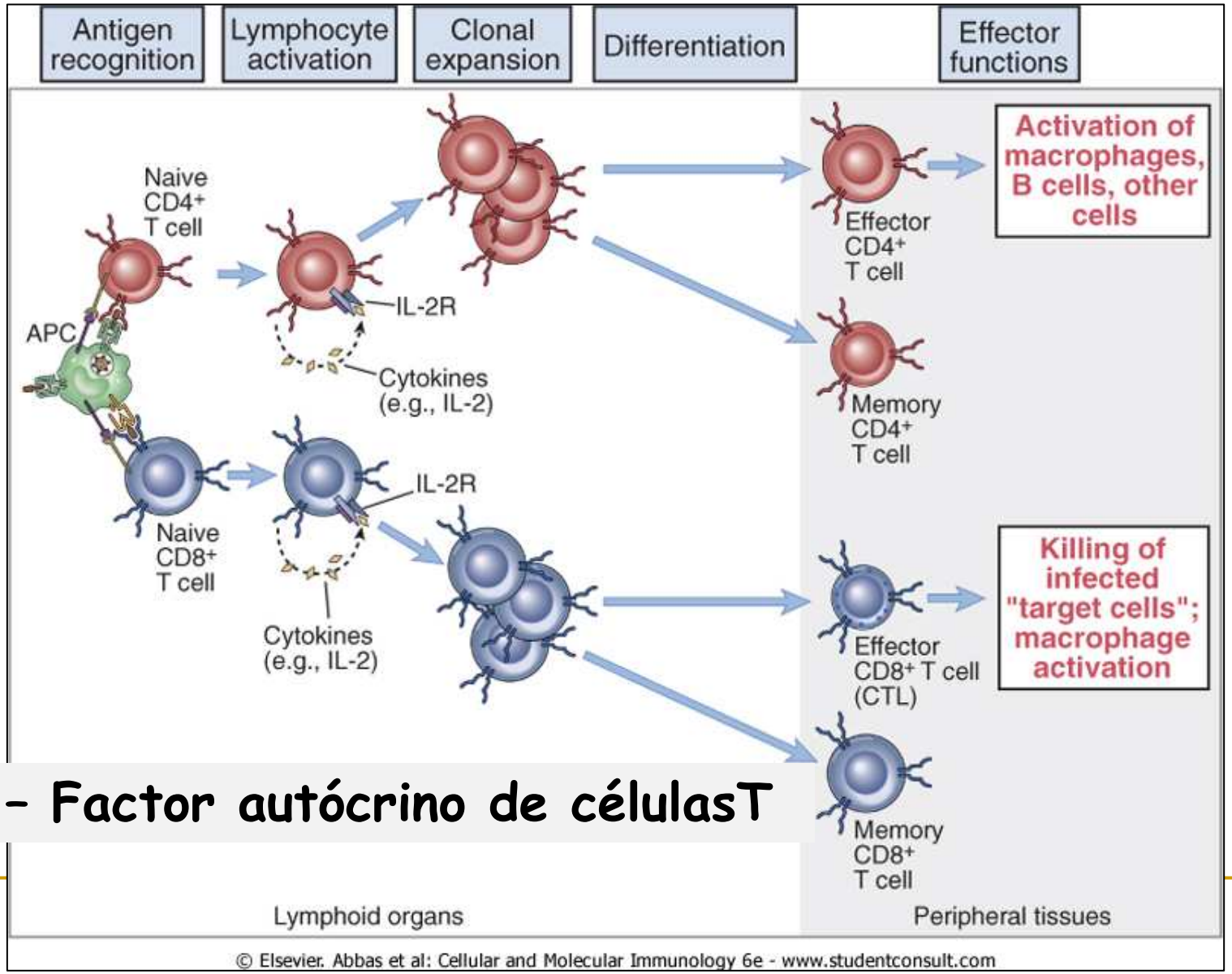
Cuando la célula T virgen reconoce el complejo péptido-MHC en una CPA o una célula blanco apropiada, se ACTIVA y precipita una reacción primaria. Tras varios ciclos de proliferación se genera una extensa clona de células progenitoras que se diferencia en CÉLULAS T DE MEMORIA Y EFECTORAS.

LA ACTIVACIÓN DE CÉLULAS T EFECTORAS Y DE MEMORIA NO REQUIERE LA MOLÉCULA B7

¿QUÉ OCURRE TRAS LA PRESENTACIÓN DEL ANTÍGENO????

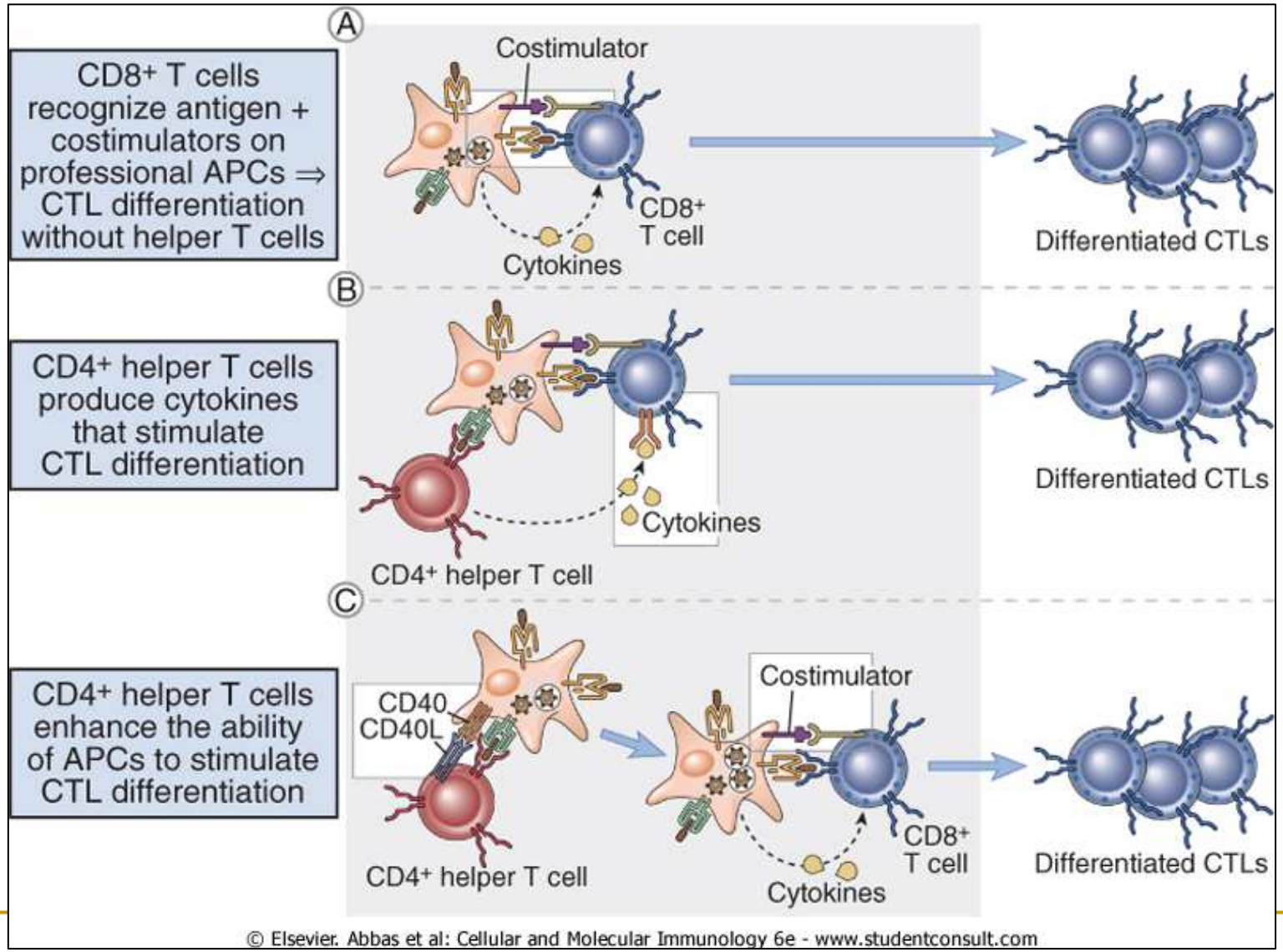

Lymph node
Site of infection
Dendritic cell
Naive T lymphocyte
B7
CD28
Effector T cells
CD40L
CD40
Naive B cell
Activated B cells
Activation of naive T cells in lymph node, development of effector cells
Activation of effector T cells at site of infection; eradication of microbe
© Elsevier. Abbas et al: Cellular and Molecular Immunology 6e - www.studentconsult.com

Fases de la respuesta T

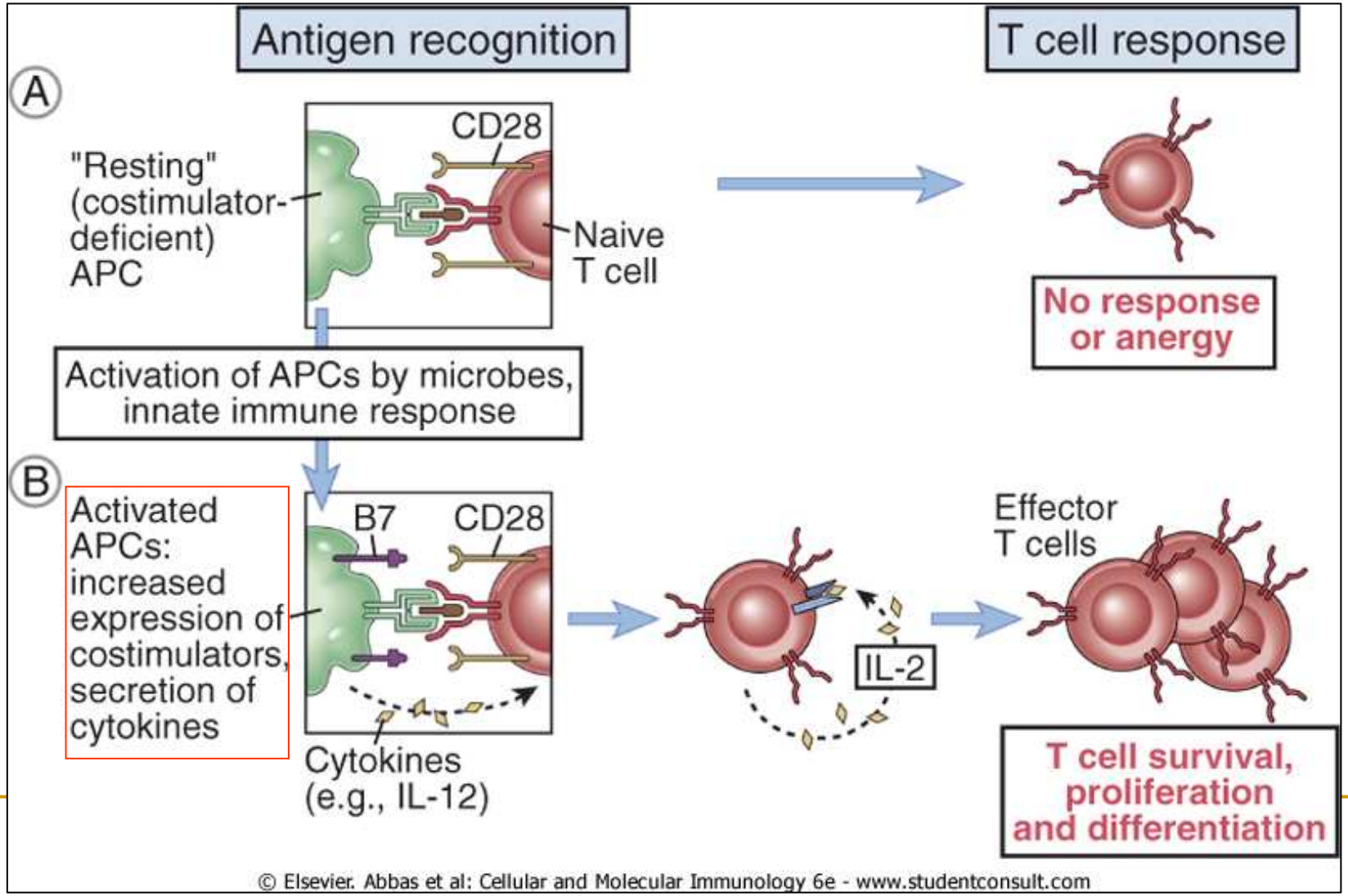


IL2 – Factor autócrino de célulasT

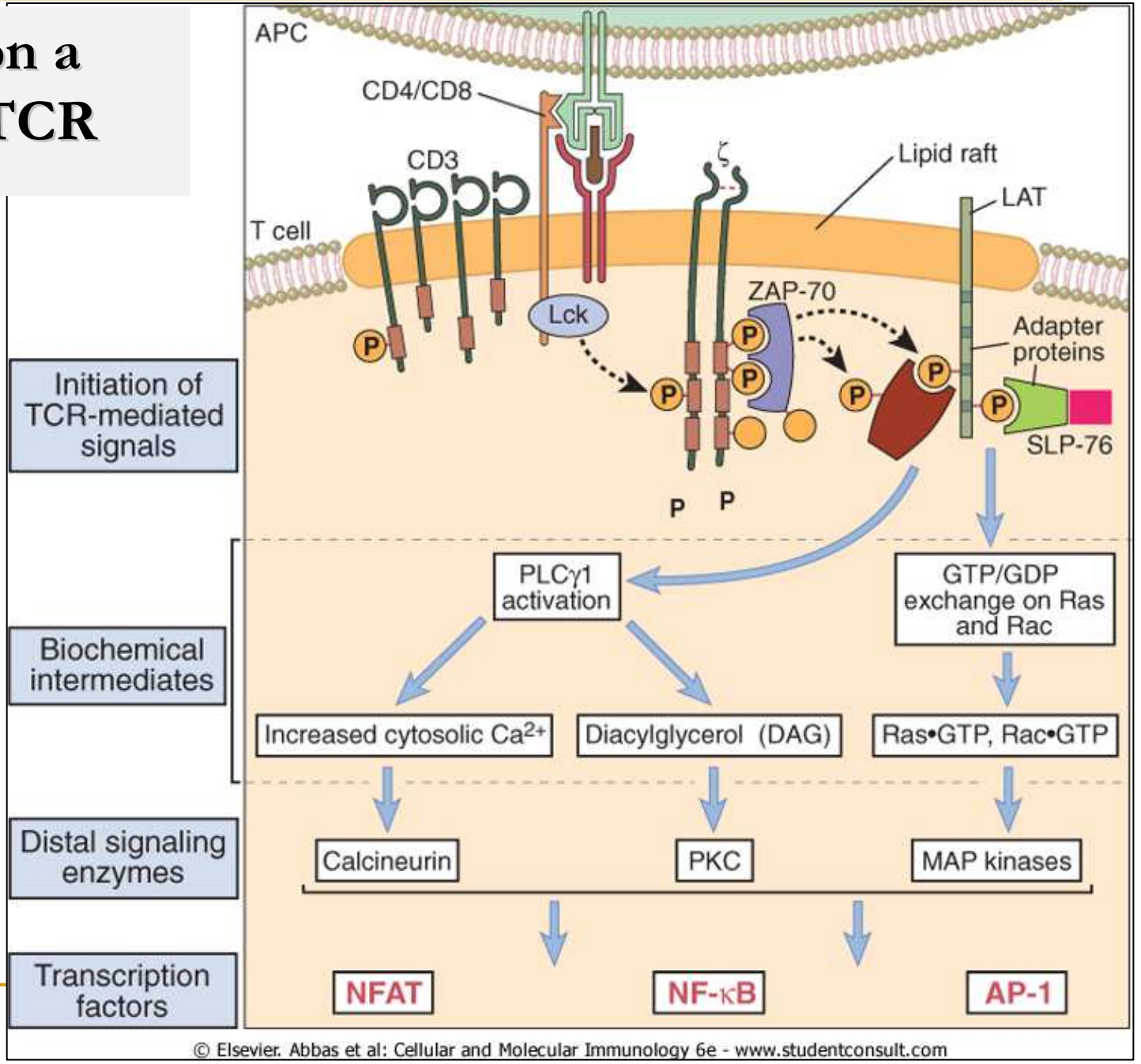
Rol de la célula Th en la diferenciación de células T CD8



Coestimulación en la activación de células T



Señalización a través del TCR

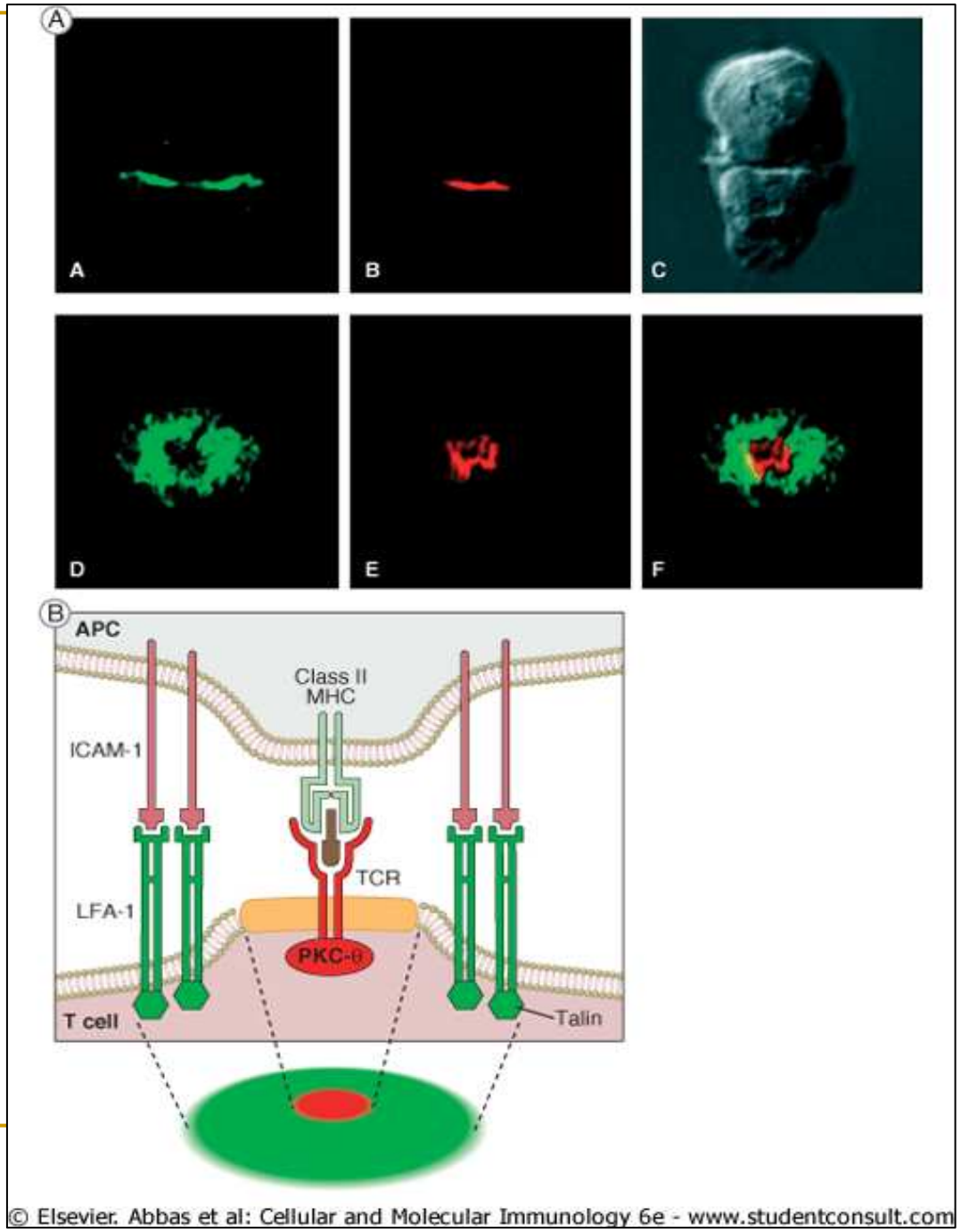


La sinapsis inmunológica

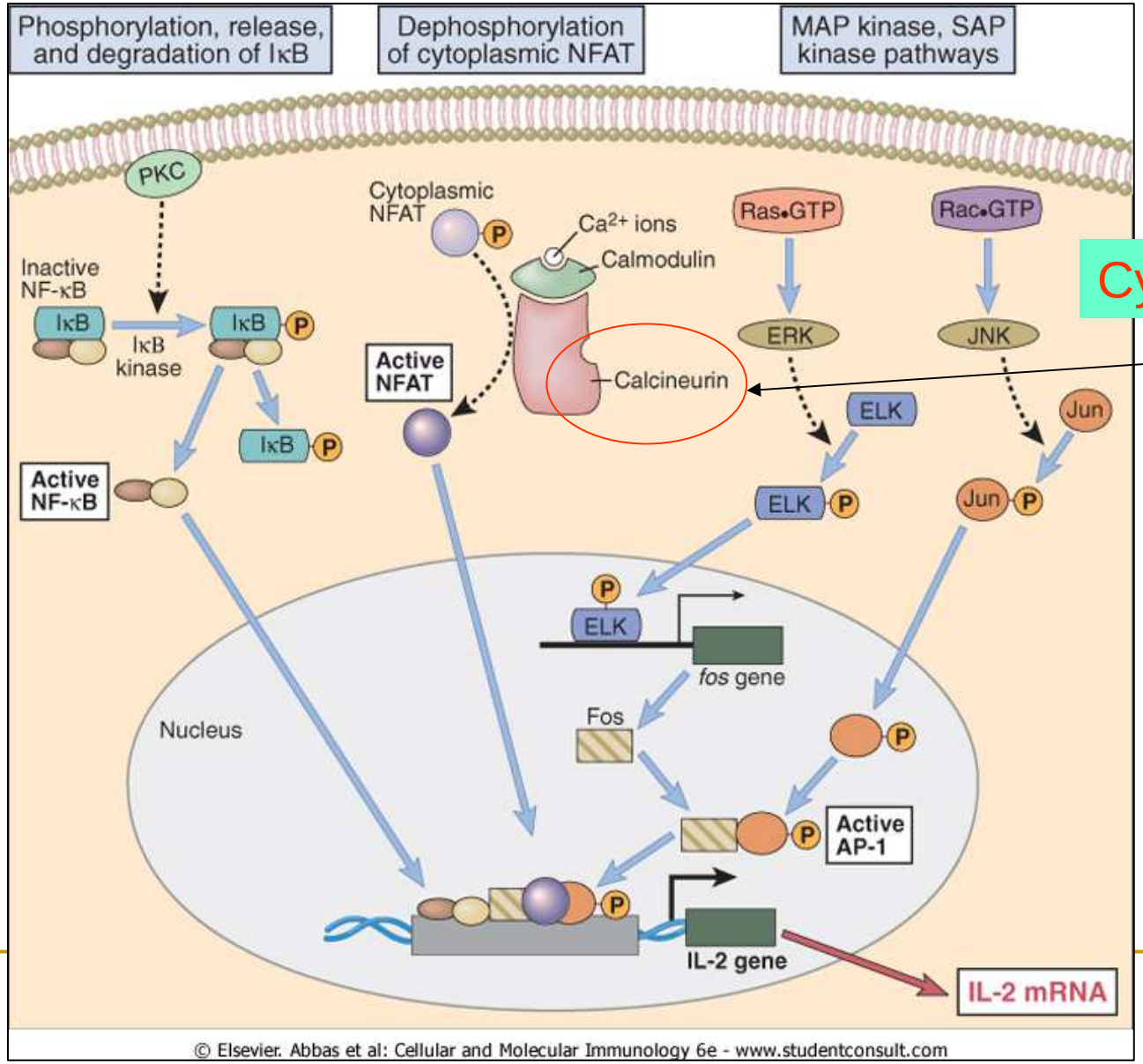
La interface entre **Células T** y **APC**

=> Prolonga interacción

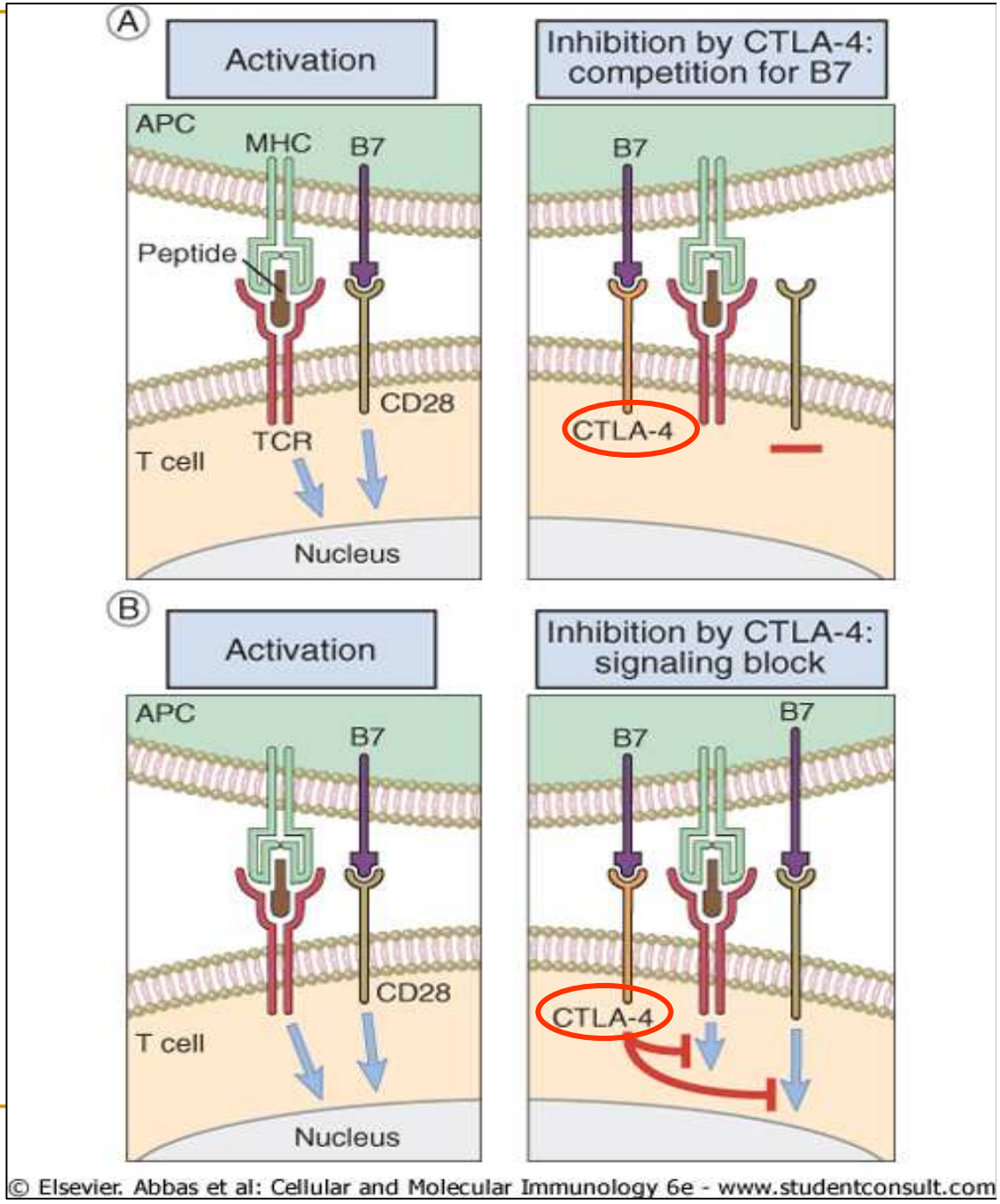
=> Incrementa la traducción de señal



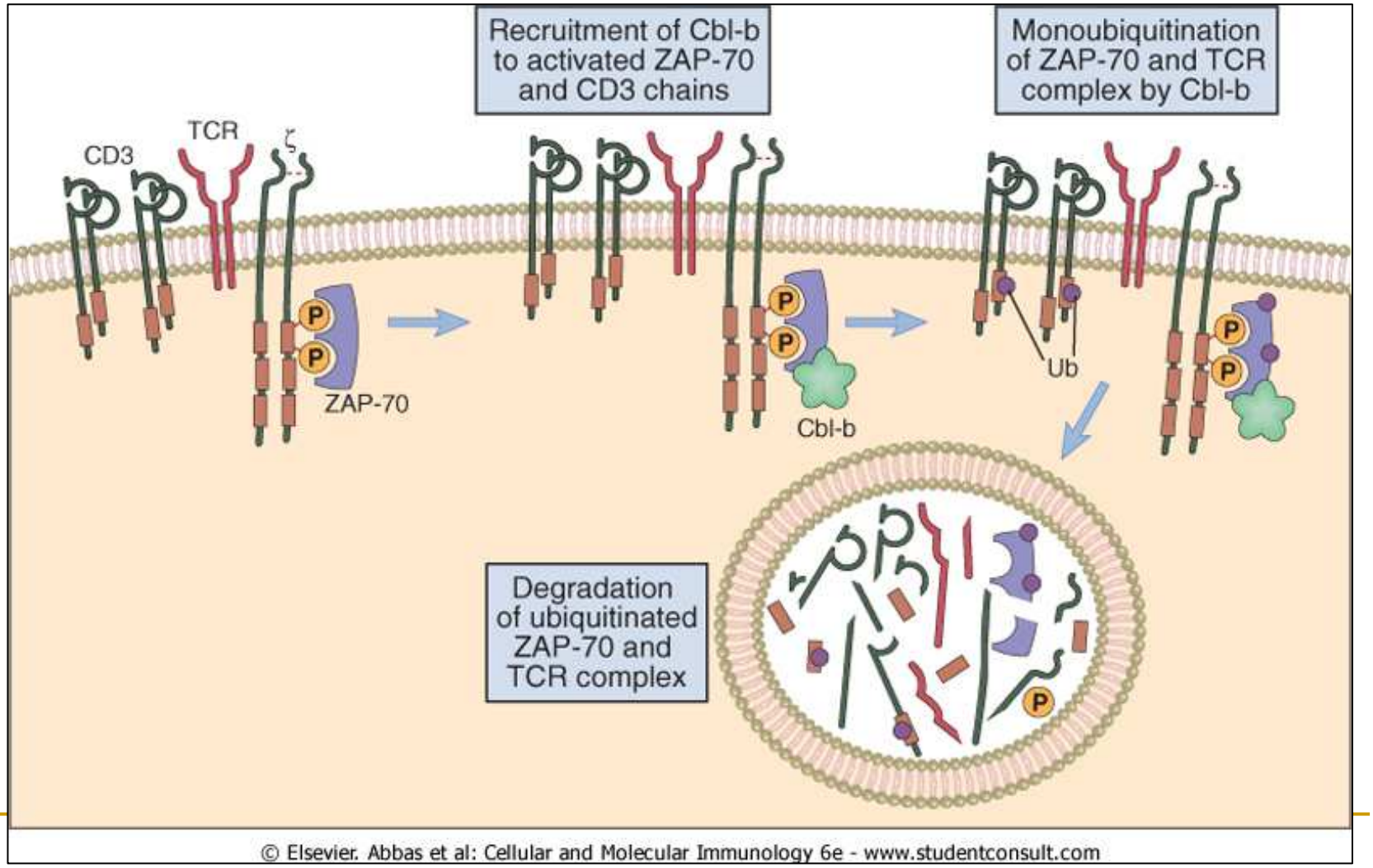
Expresión de IL-2 durante la señalización del TCR



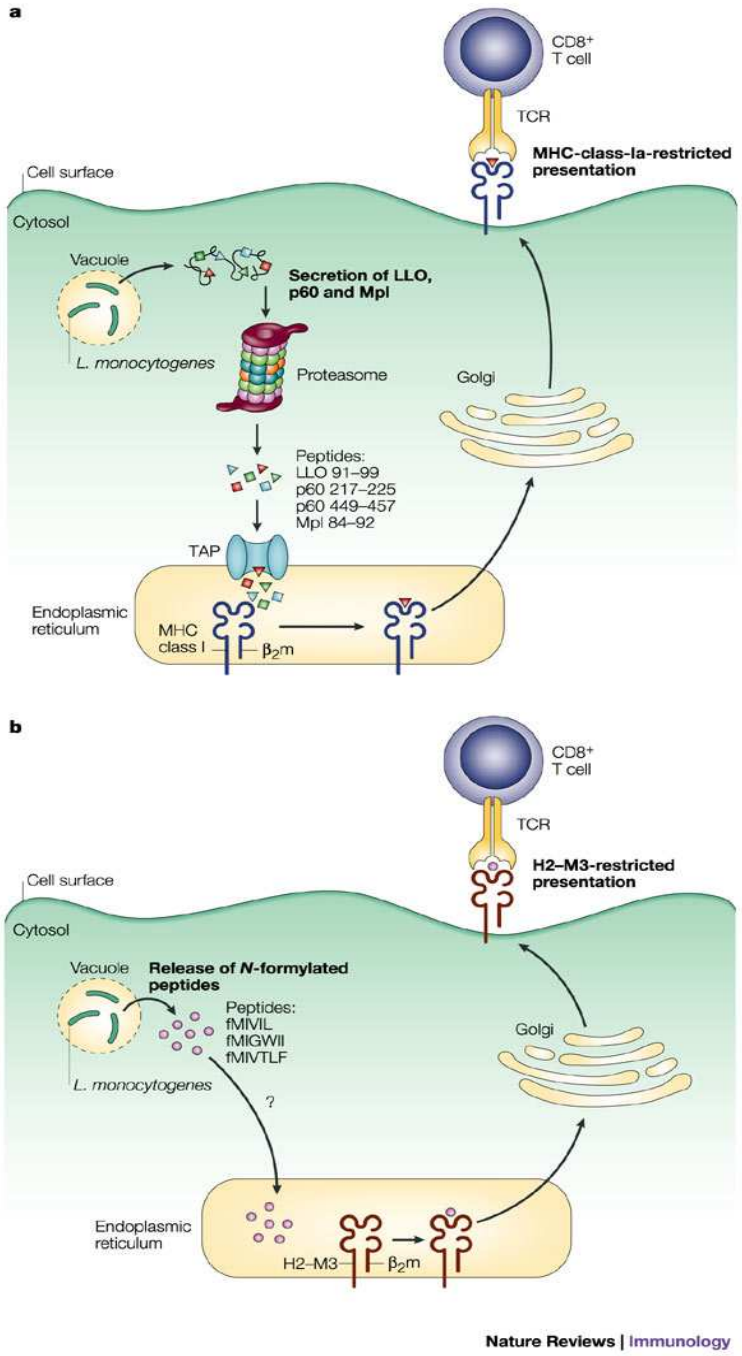
Señal de atenuación por el RECEPTOR INHIBITORIO (CTLA-4)



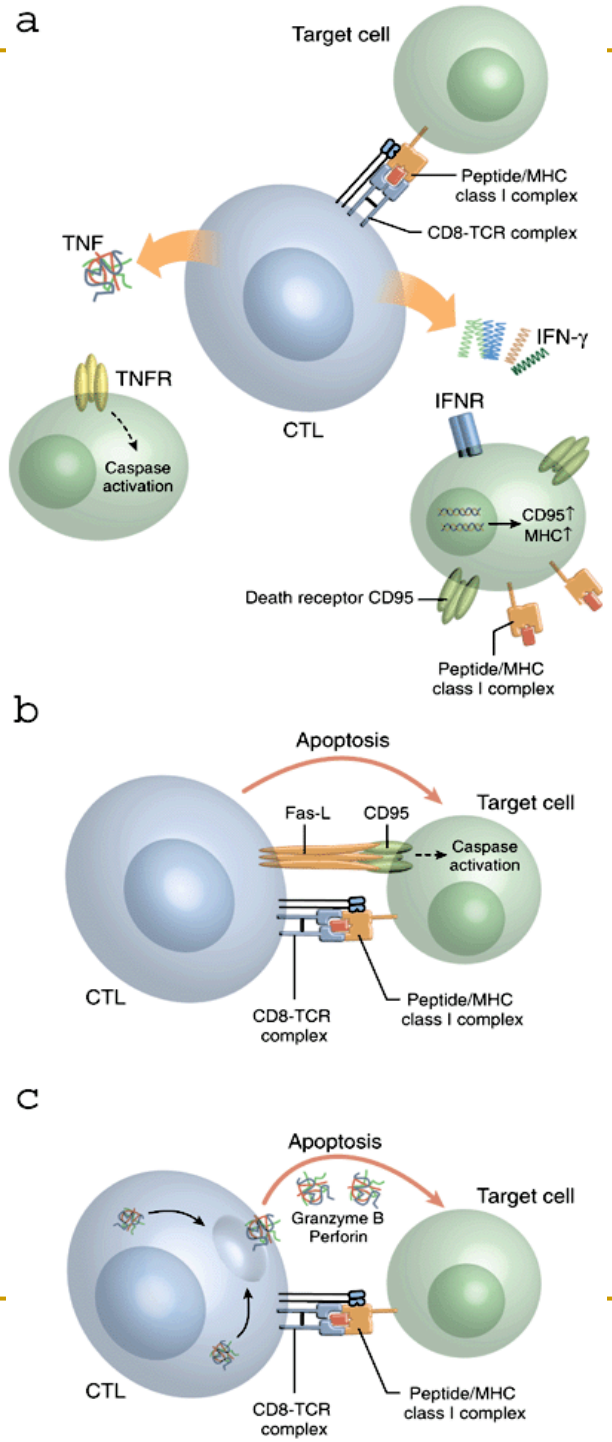
La señal a través del TCR termina al degradarse la proteína…



Infección por Listeria monocytogenes…. PRESENTACIÓN ANTIGÉNICA EN MHC I

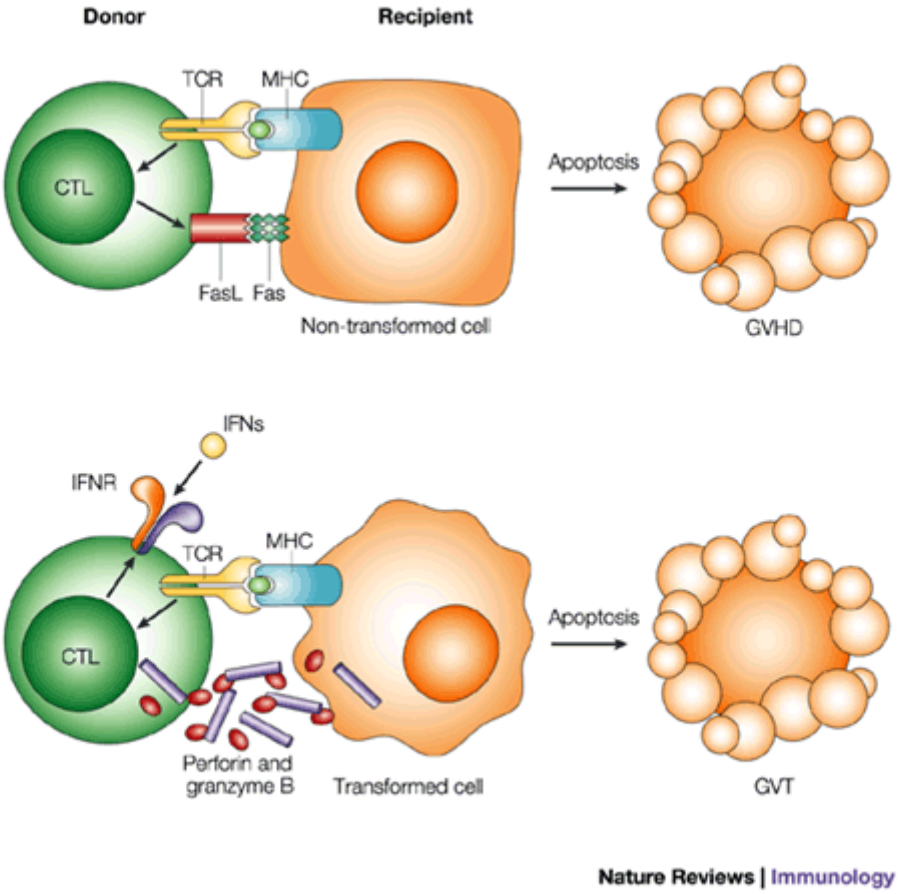


Nature Reviews Immunology 4, 812-823 (October 2004)

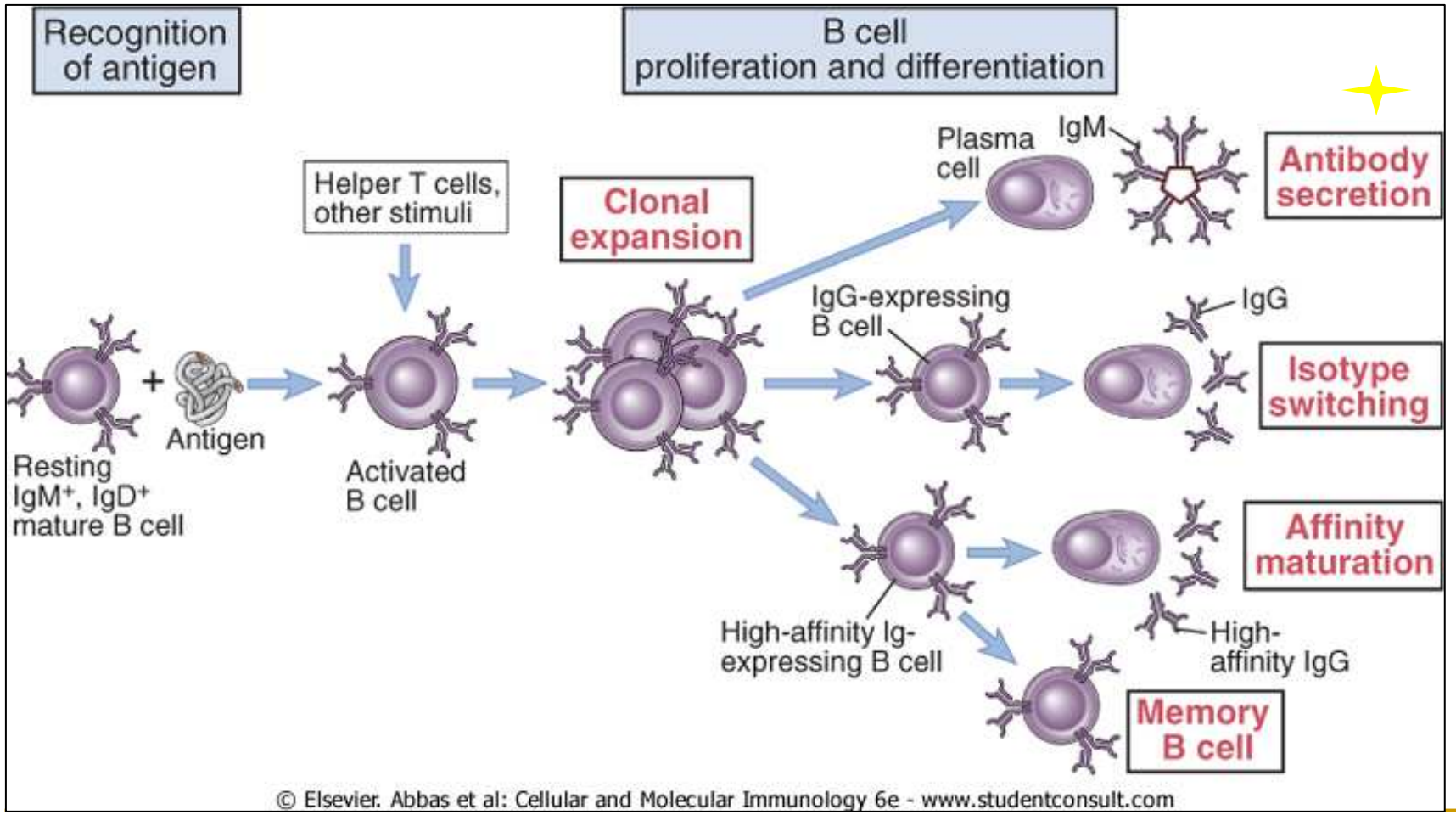


Diferentes formas de citotoxicidad

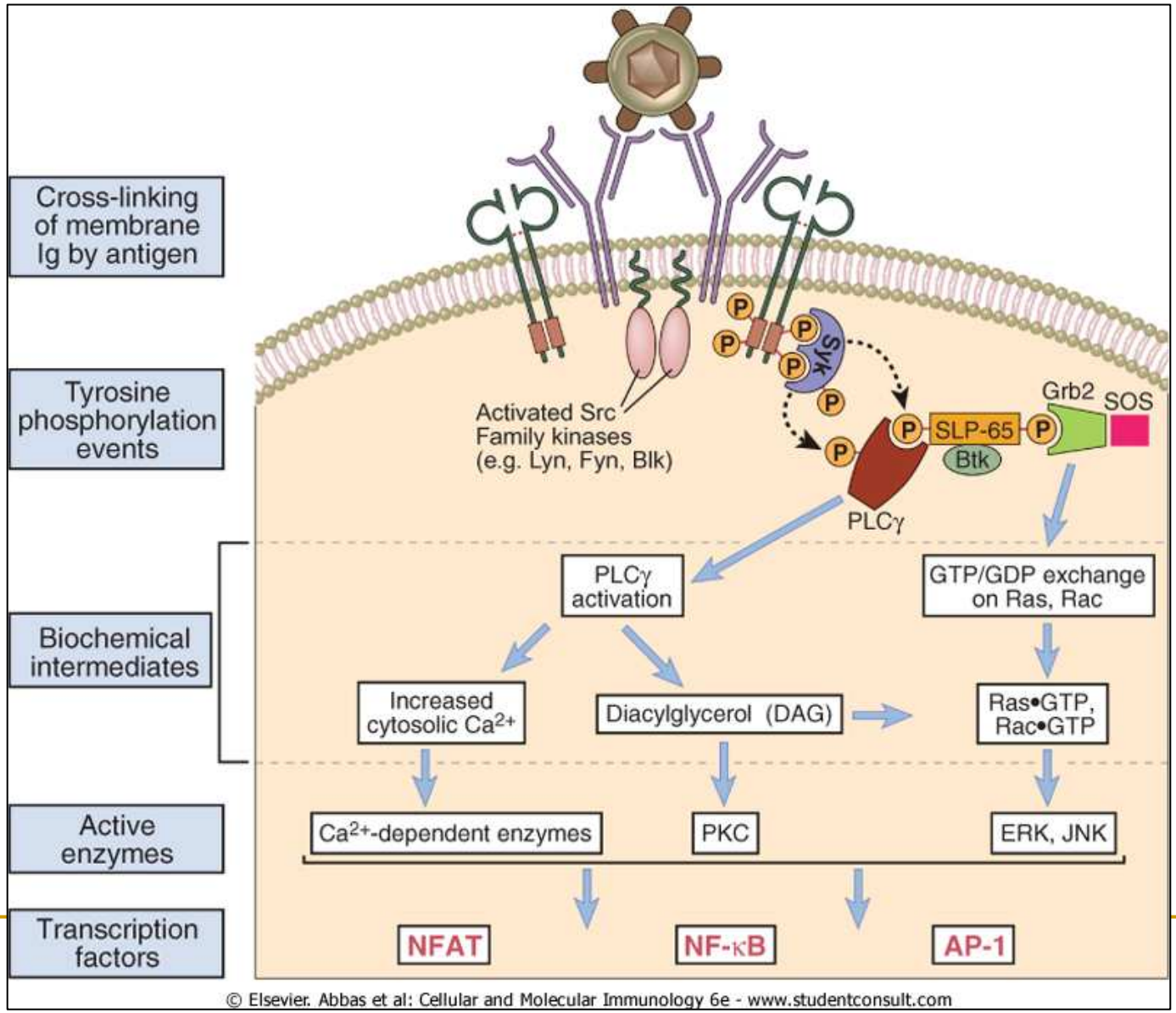
Actividad citotóxica



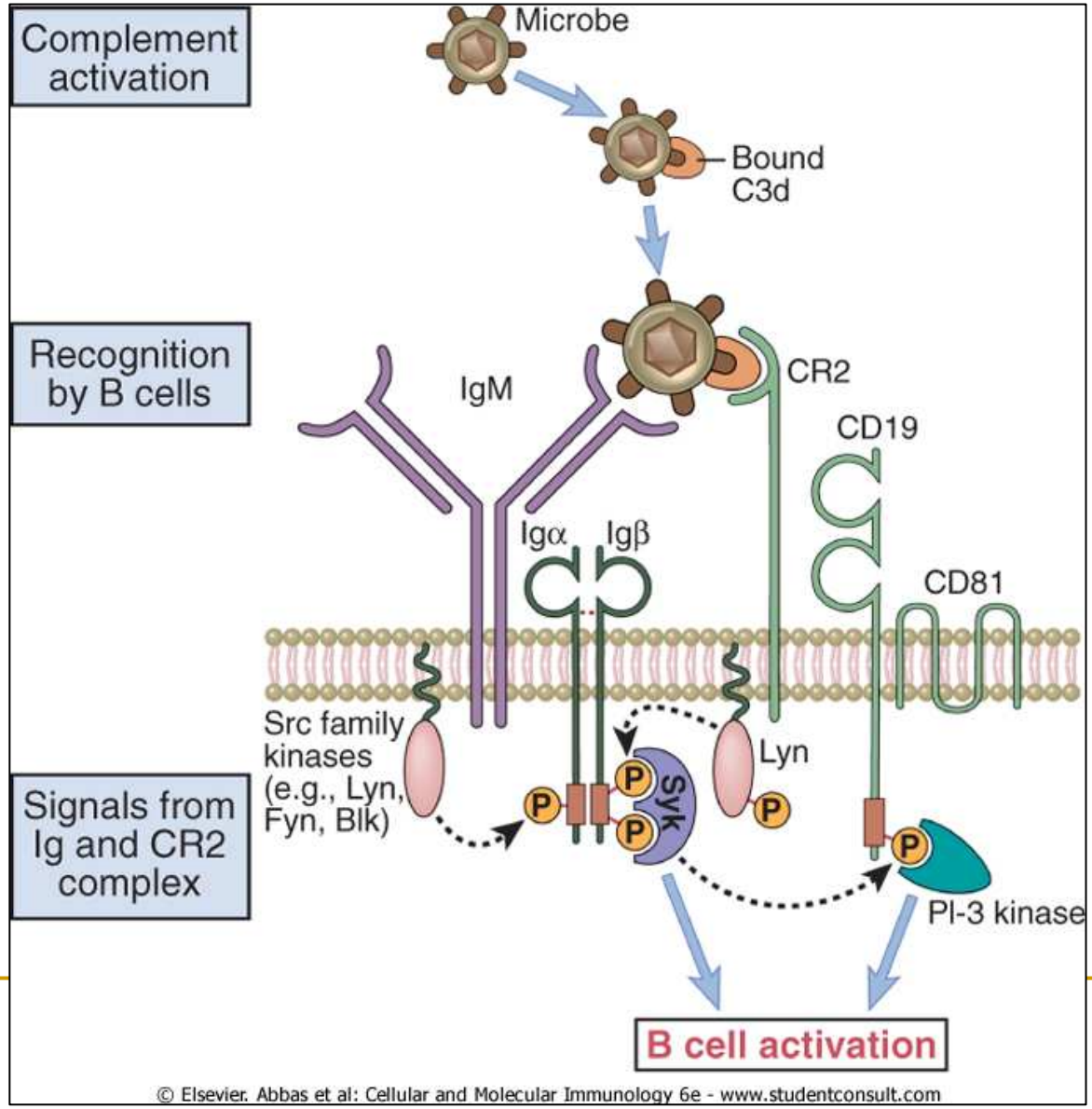
Fases de la respuesta de células B



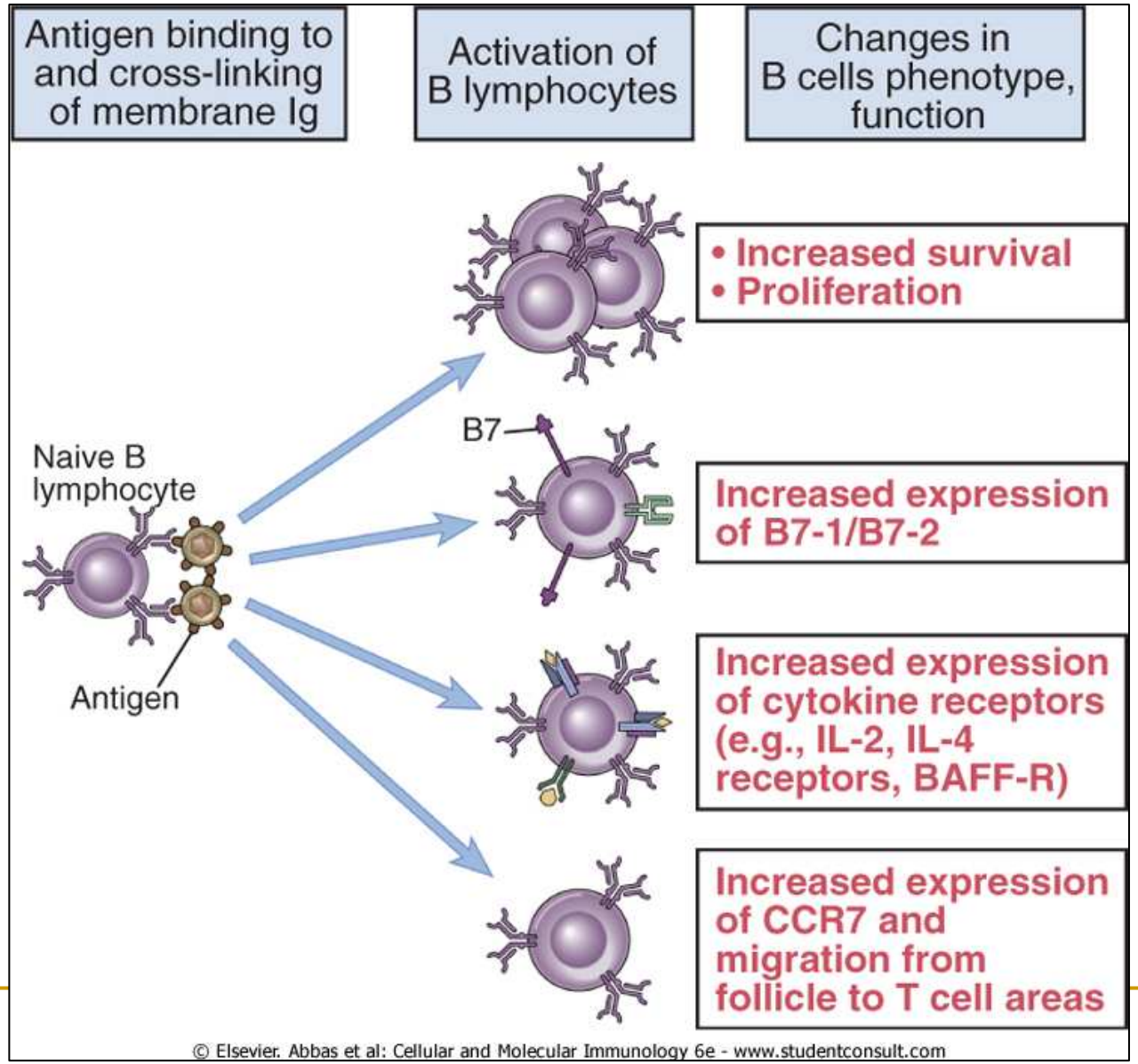
Señalización a través del BCR



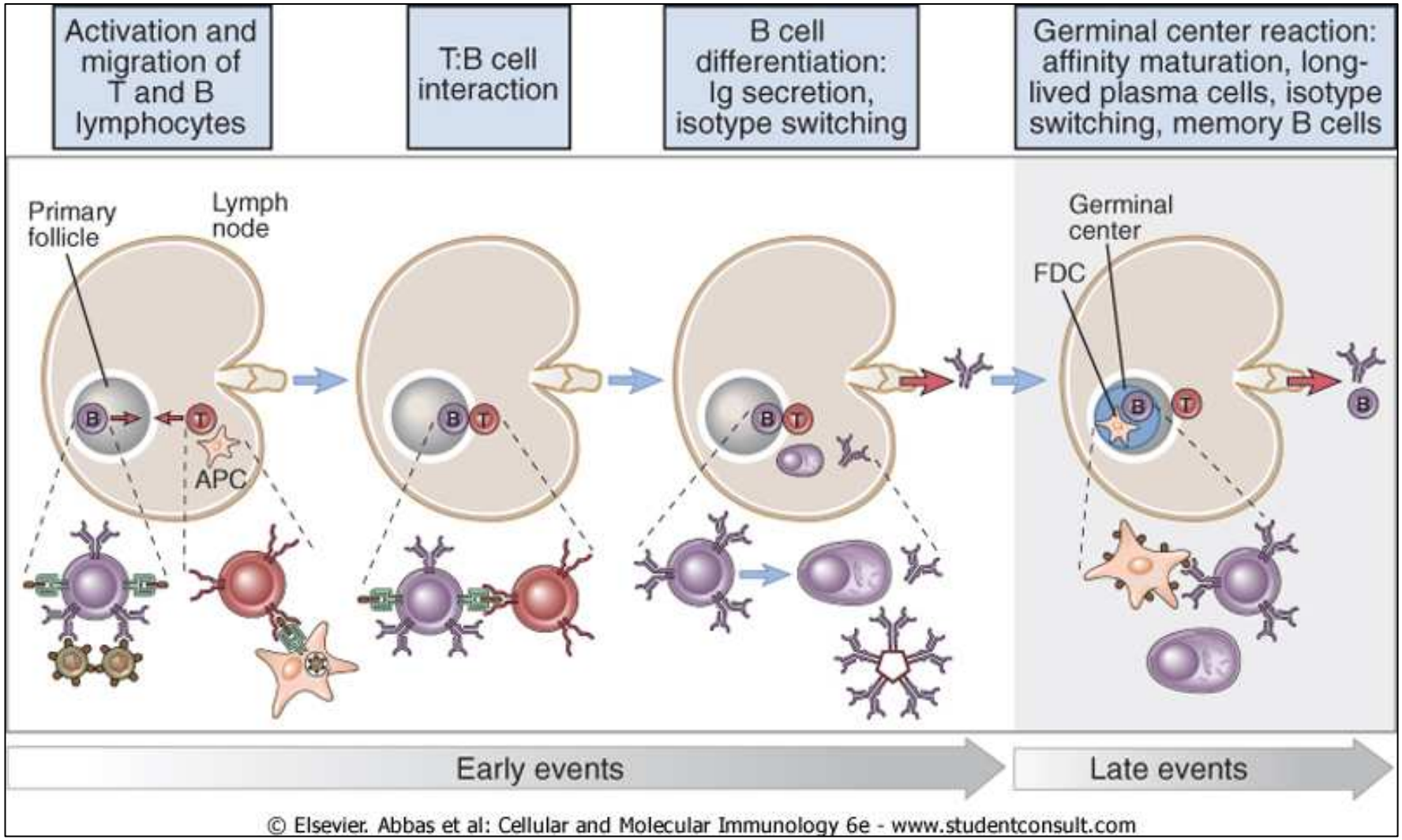
CD21/CR2 receptor complemento como correceptores de células B



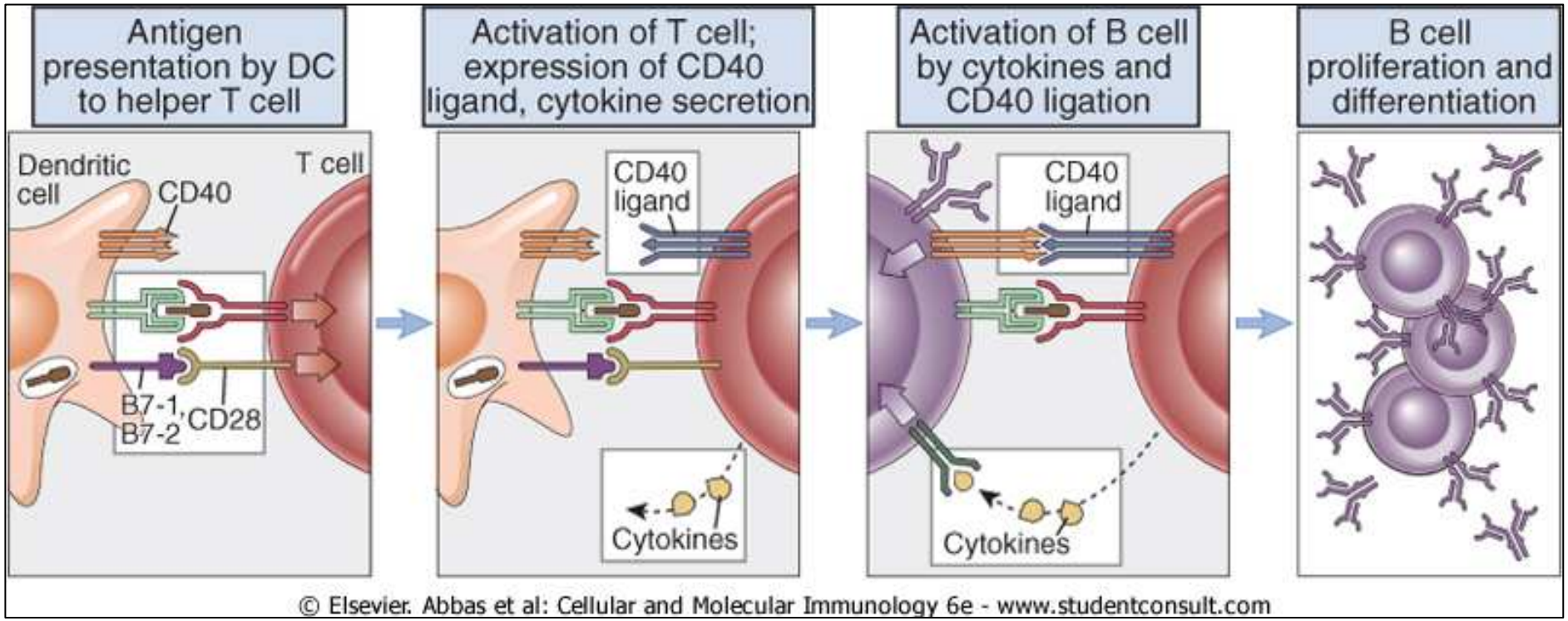
Las células B responden por entrecruzamiento de BCR



Eventos de la interacción T-B



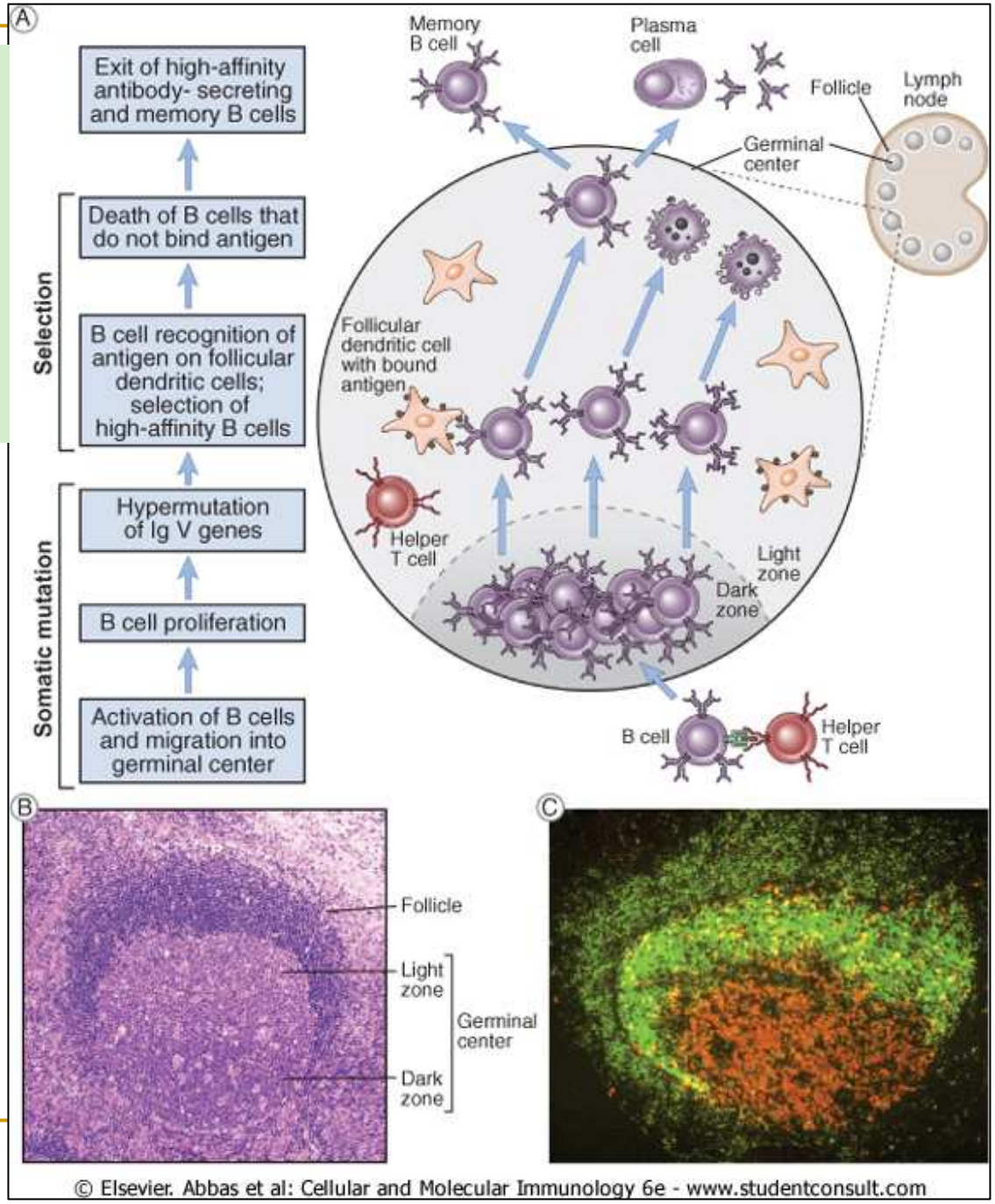
Activación de célula B inducida por Th



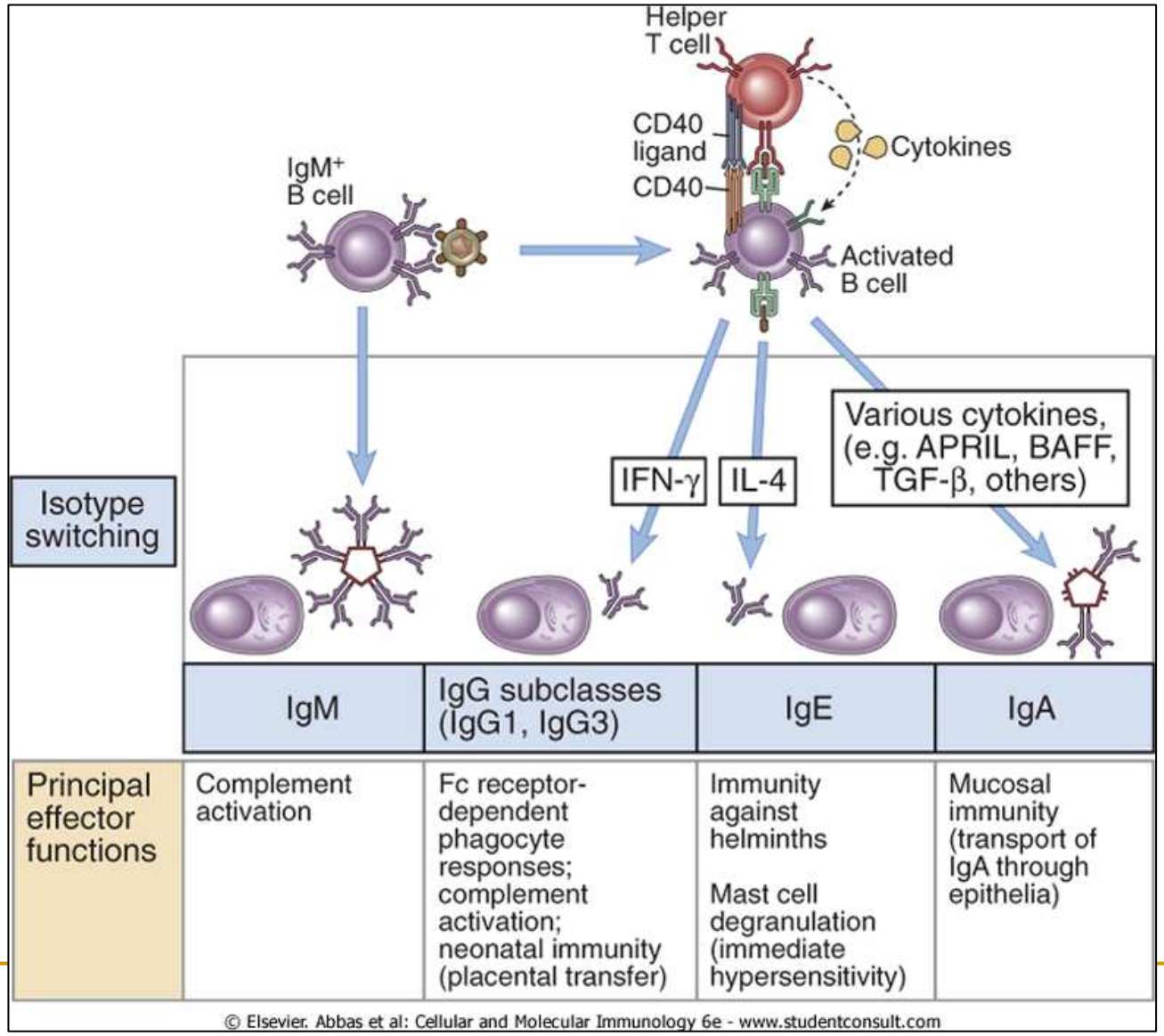
Reacciones en centro germinal, respuesta T-dependiente

Germinal centers (2nd follicle)

1. T-dep B cell activation
2. Somatic hypermutation
3. Isotype switching
4. Memory B cells



Cambio de isotipo



PRESENTACIÓN CRUZADA

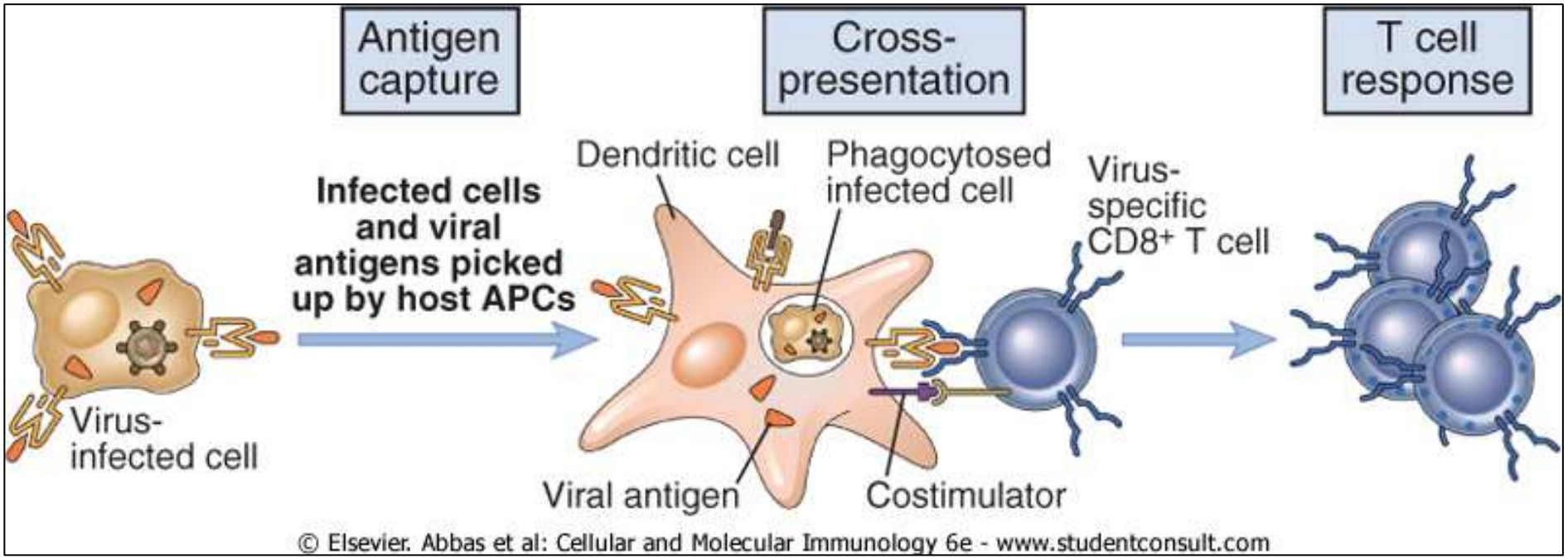
Presentación cruzada del antígeno a células T

DC has an unique feature:

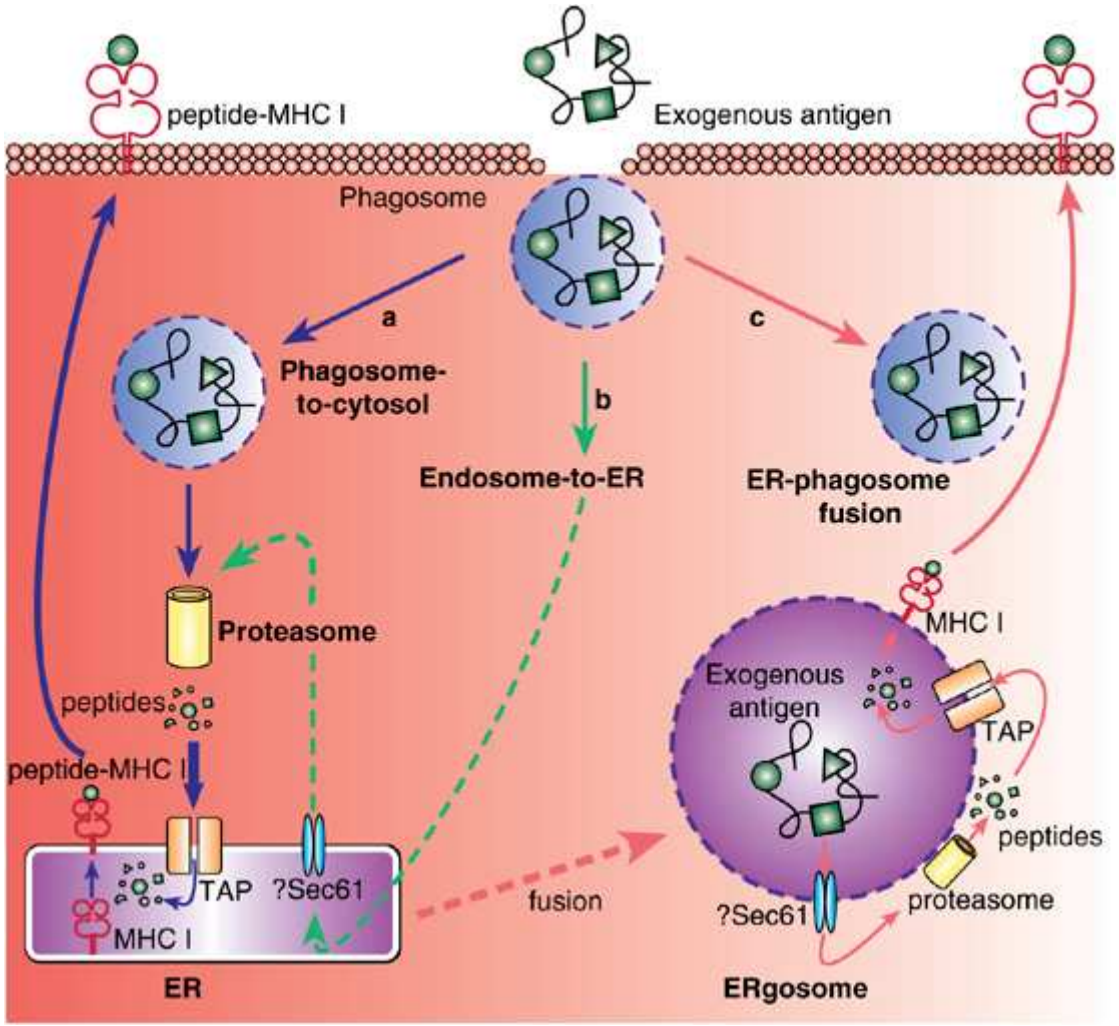
⇒ Allow protein traffic from endosomal vesicles to the cytosol

⇒ Ag-MHC-I presentation

⇒ Ingest virus-infected or tumor cells => CD8 T cells



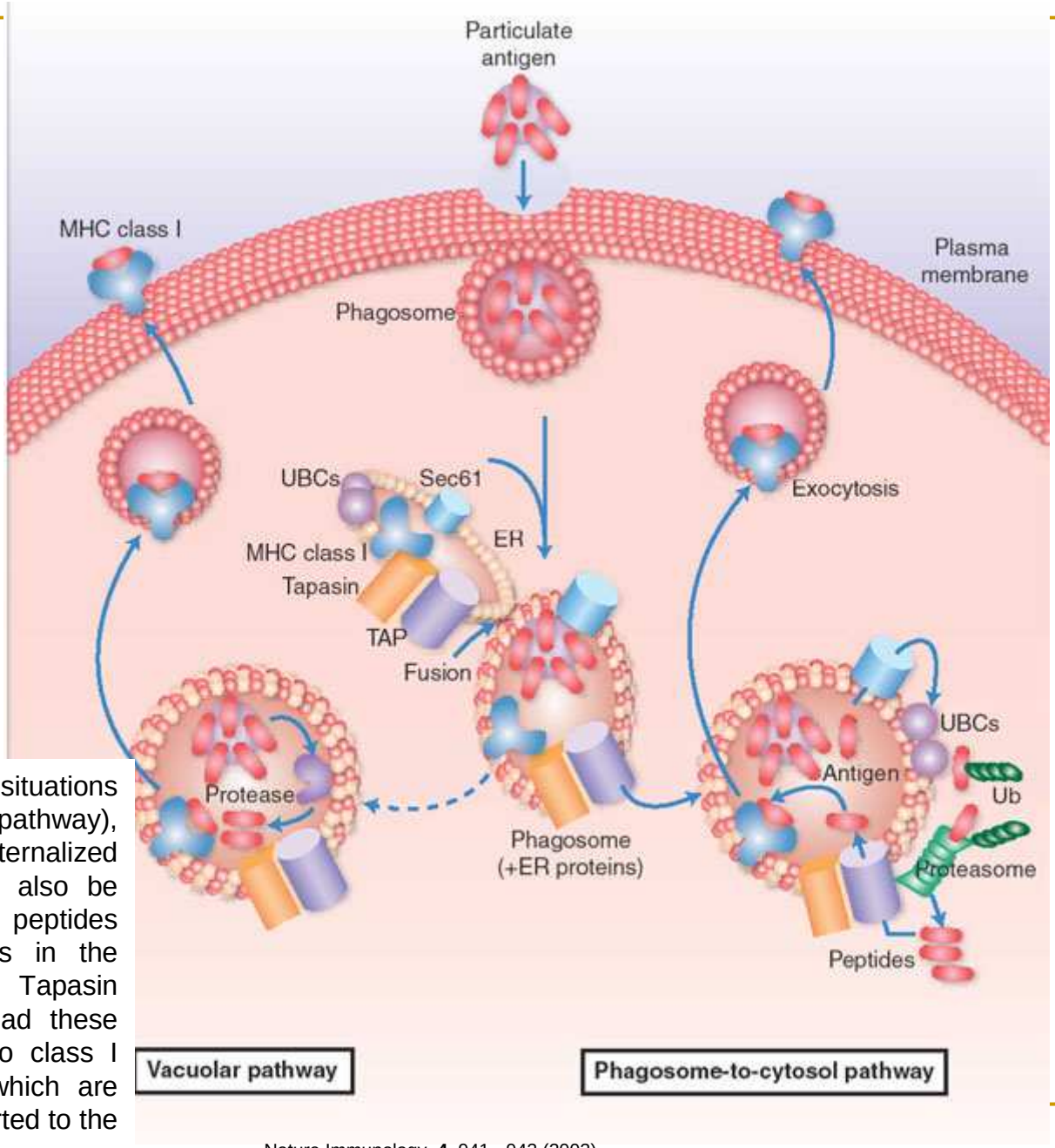
Modelos de Cross Presentation



•Immunology and Cell Biology, 2009 . ISSN: 0818-9641

Cross-Presentation

- Se refiere a la presentación de antígenos exógenos en el contexto de MHC clase I.
- Esencial para activar células TCD8 naïve.
- Importante mecanismo de activación de TCD8 en vacunación.
- El mecanismo exacto se desconoce pero se proponen diferentes modelos….
  - Antígenos particulados
  - Antigenos solubles
  - Transferencia directa intercelular

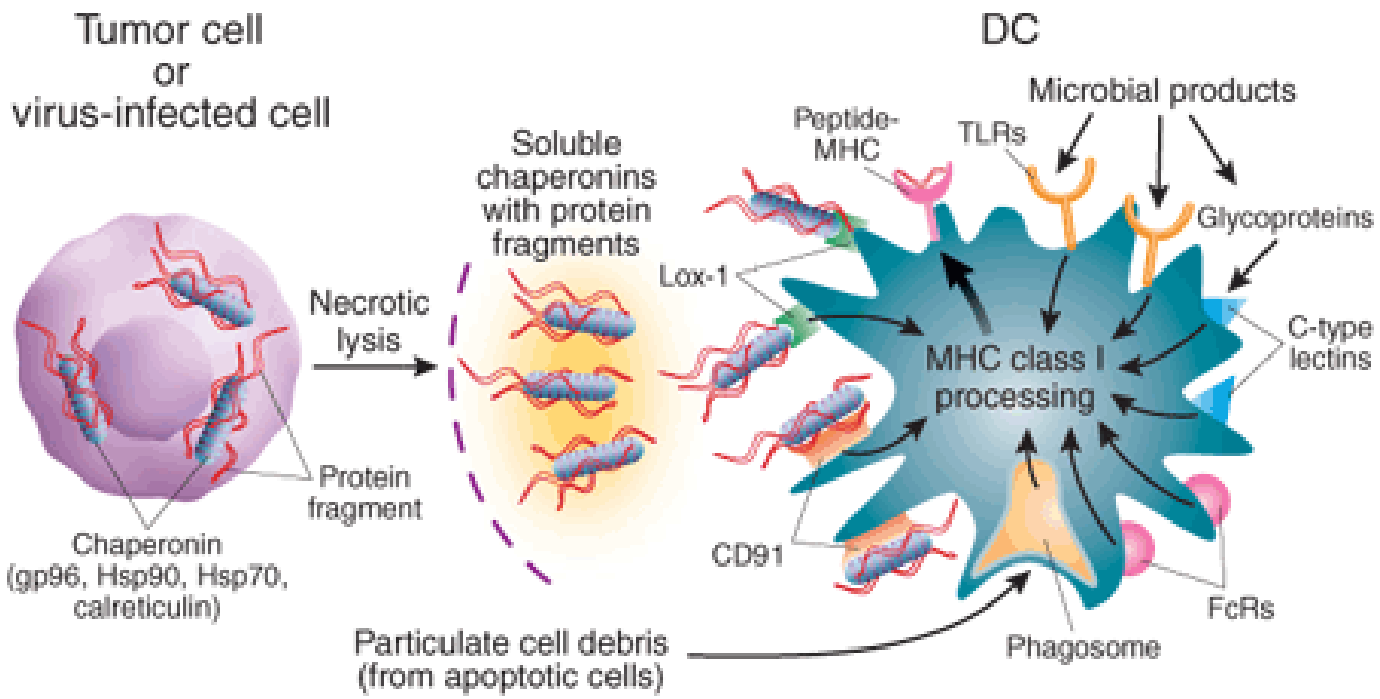


Particulate antigen is internalized into phagosomes. Early in this process, phagosomes fuse with the endoplasmic reticulum (ER) and thereby acquire the endoplasmic reticulum−resident antigen-presentation machinery (TAP, tapasin and MHC class I molecules) as well as the Sec61 translocon.

Some of the internalized antigen is transferred from the phagosome to the cytosol, possibly by retro-translocation through Sec61 and ubiqitination by ubiquitin (Ub)-conjugating enzymes (UBCs). This antigen is then cleaved by proteasomes that associate with the phagosome membrane, and some of the resulting peptides are transferred back into the phagosome by TAP.

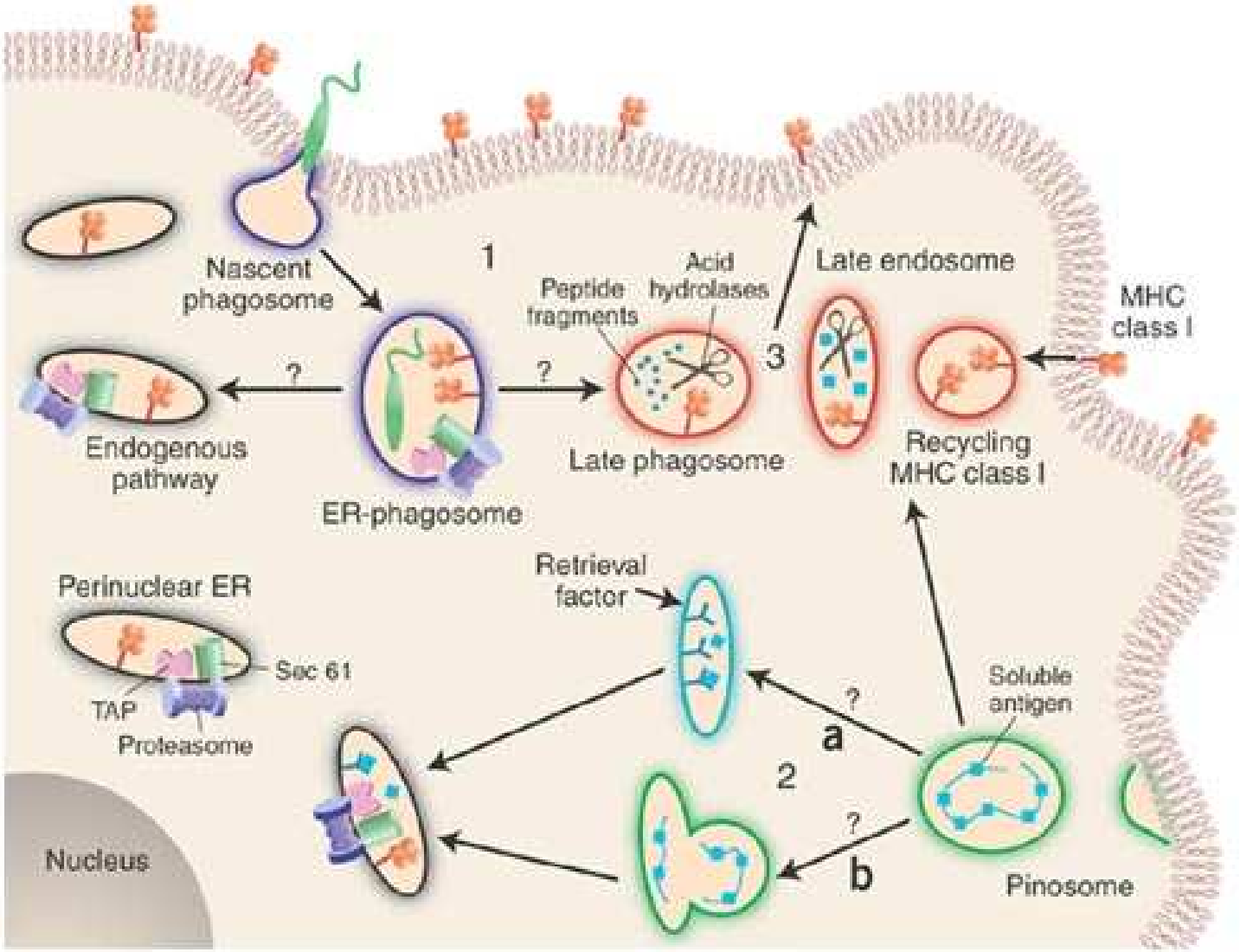
In some situations ('vacuolar' pathway), the internalized antigen may also be cleaved into peptides by proteases in the phagosome. Tapasin may help load these peptides onto class I molecules, which are then transported to the cell surface.

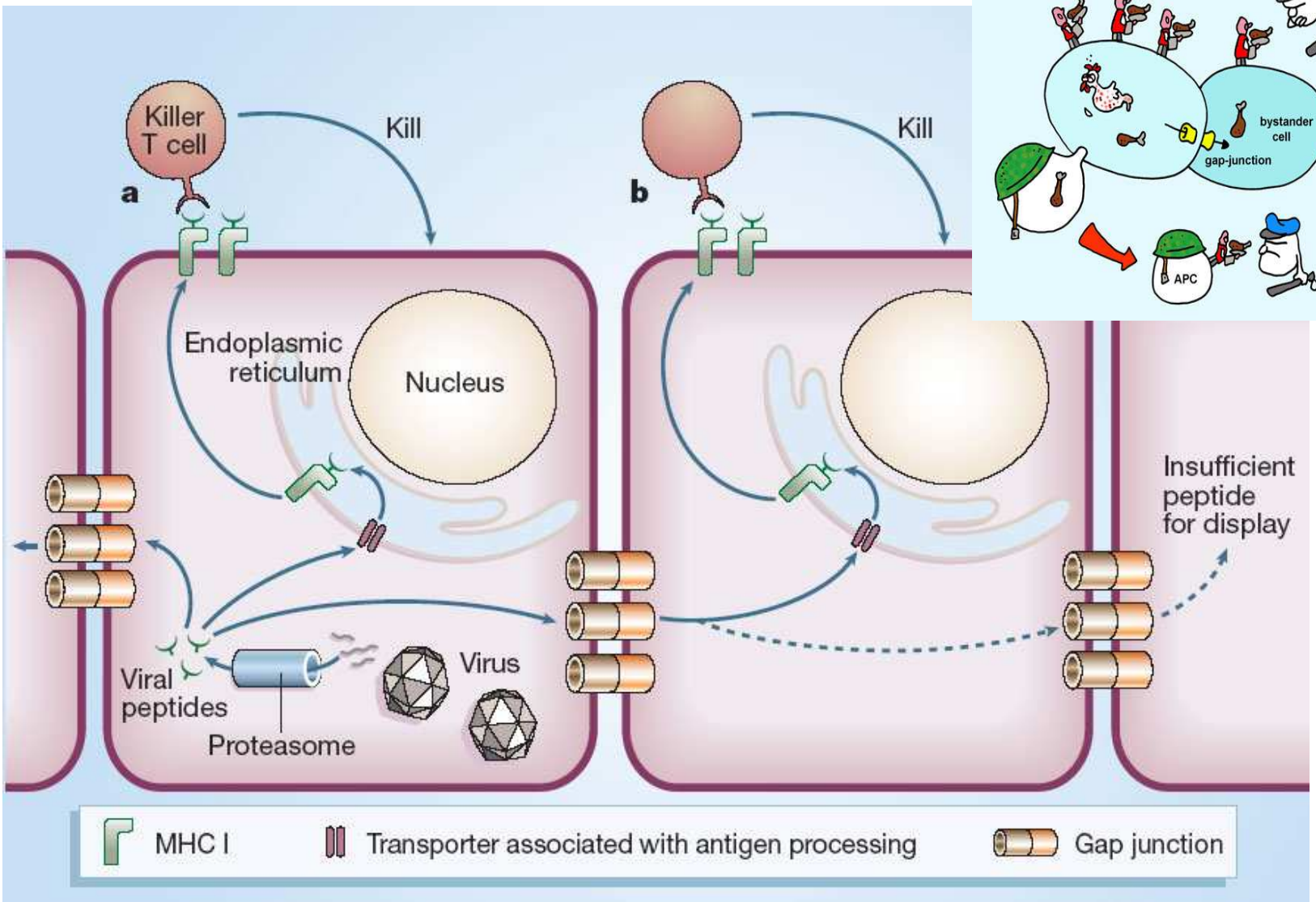
Nature Immunology **4**, 941 - 943 (2003)



Dead cell−derived protein antigens can be efficiently ingested and processed for MHC class I peptide presentation by either of two pathways. Soluble proteinaceous material can be targeted by attached chaperonins (gp96, Hsp90, Hsp70 and calreticulin) to scavenger receptors (such as LOX-1 and CD91), or it can directly bind to other receptors such as C-type lectins, Fc receptors (FcRs) or Toll-like receptors (TLRs). Alternatively, phagocytosis of particulate matter (from, for example, apoptotic cells) followed by phagosome fusion with endoplasmic reticulum membrane components can facilitate cytosolic access.

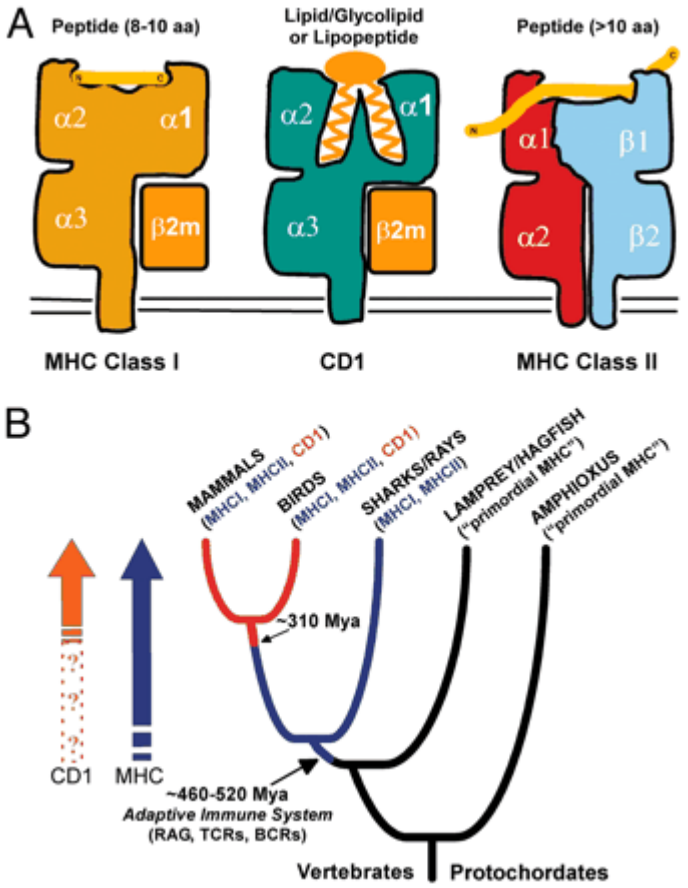
Nature Immunology **6**, 543 - 544 (2005)


Nascent phagosome
1
Peptide fragments
Acid hydrolases
Late endosome
MHC class I
3
?
?
Endogenous pathway
ER-phagosome
Late phagosome
Recycling MHC class I
Perinuclear ER
Retrieval factor
Sec 61
TAP
Proteasome
Soluble antigen
?
a
2
?
b
Nucleus
Pinosome


Killer
T cell
a
Kill
b
Kill
Endoplasmic
reticulum
Nucleus
Insufficient
peptide
for display
Viral
peptides
Proteasome
Virus
MHC I
Transporter associated with antigen processing
Gap junction

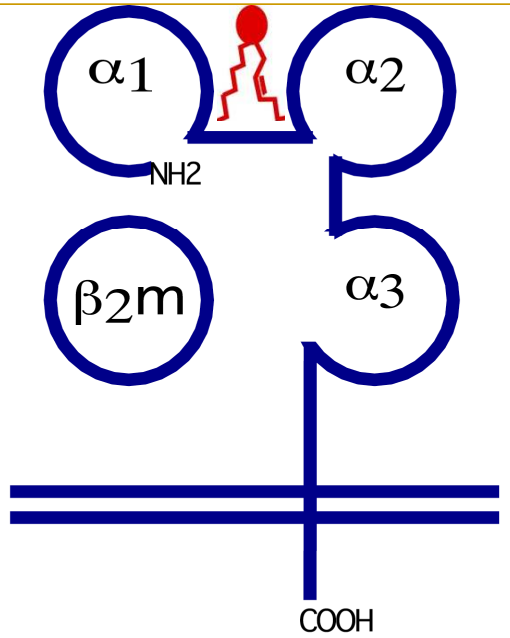
MHC class I
CTL
bystander
cell
gap-junction
APC

PRESENTACIÓN DE ANTÍGENOS NO PROTEICOS



PRESENTACIÓN EN CD1

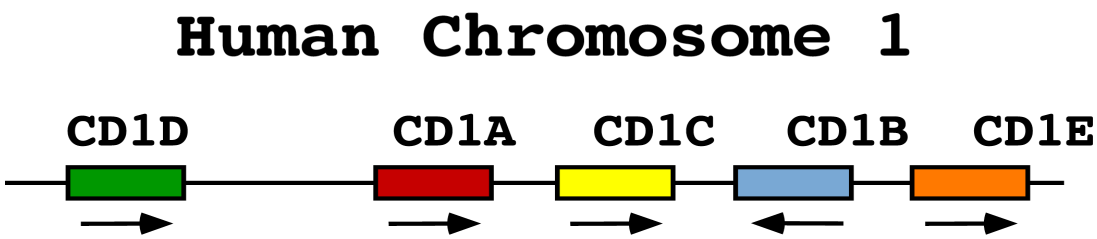
CD1

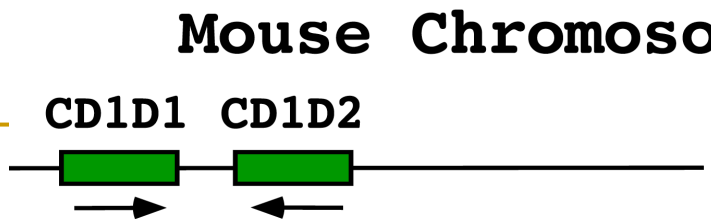


- Lípidos

Microbianos

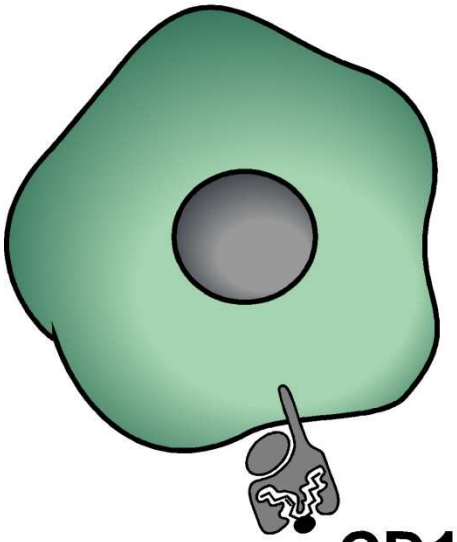
- Lípidos propios





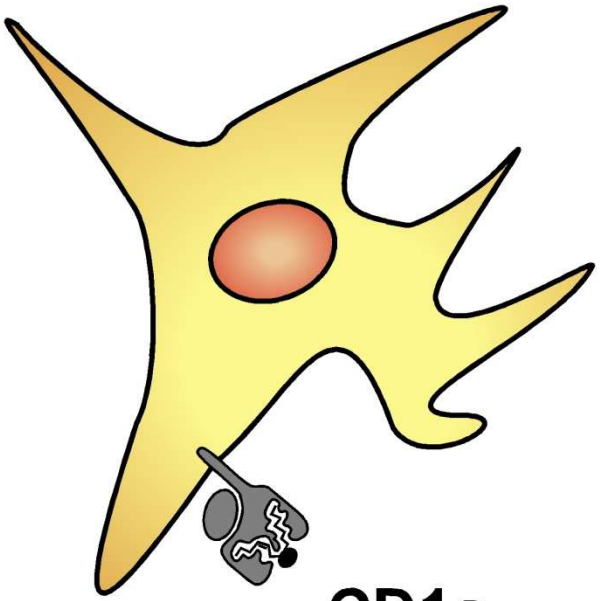
APC CD1^{+}

Monocyte



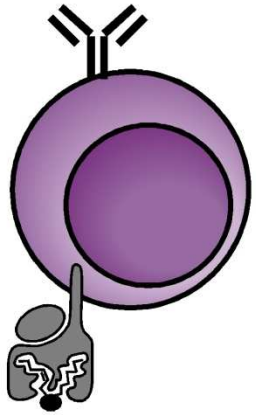
CD1d

Dendritic Cell



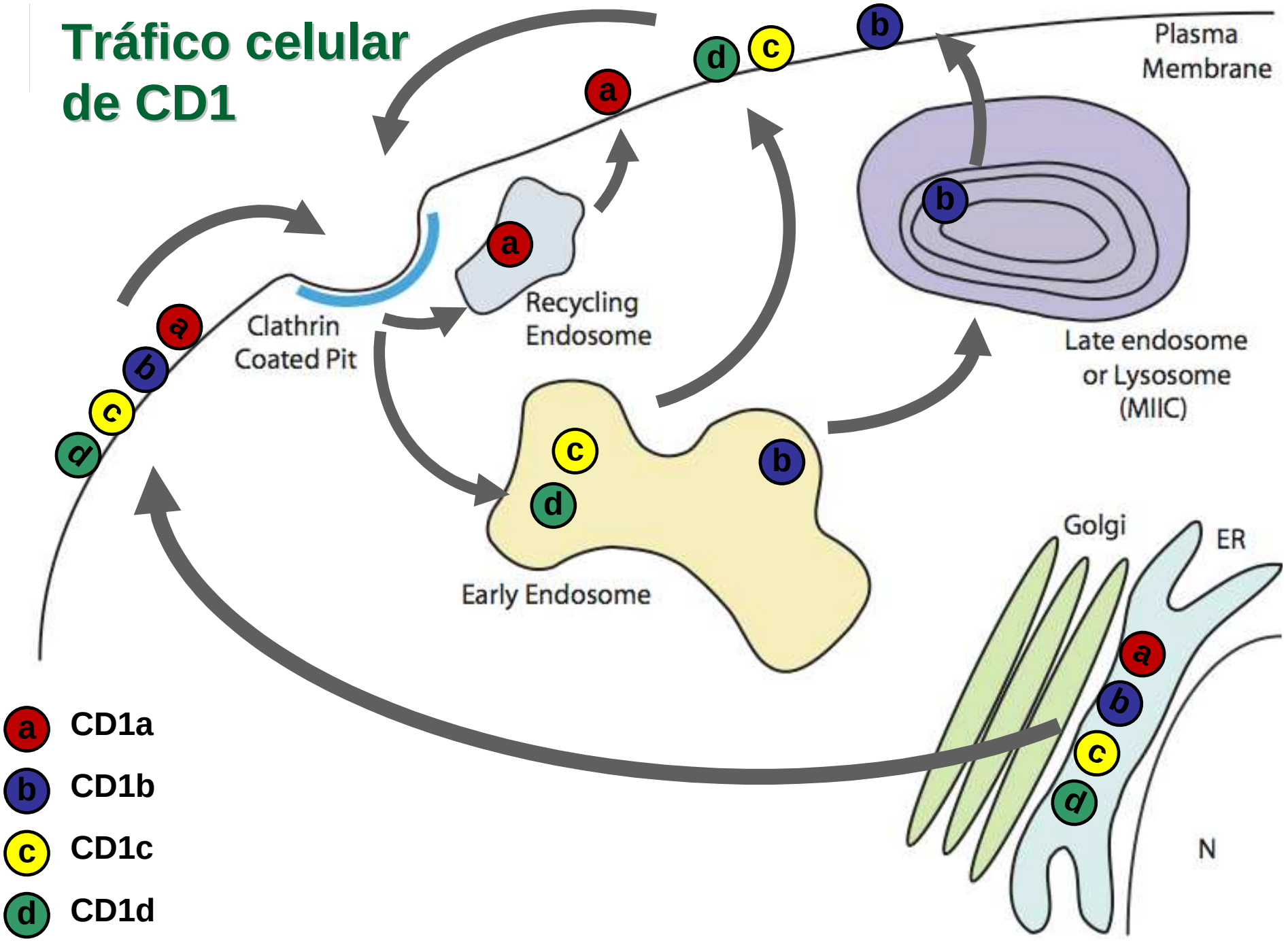
CD1a
CD1b
CD1c
CD1d

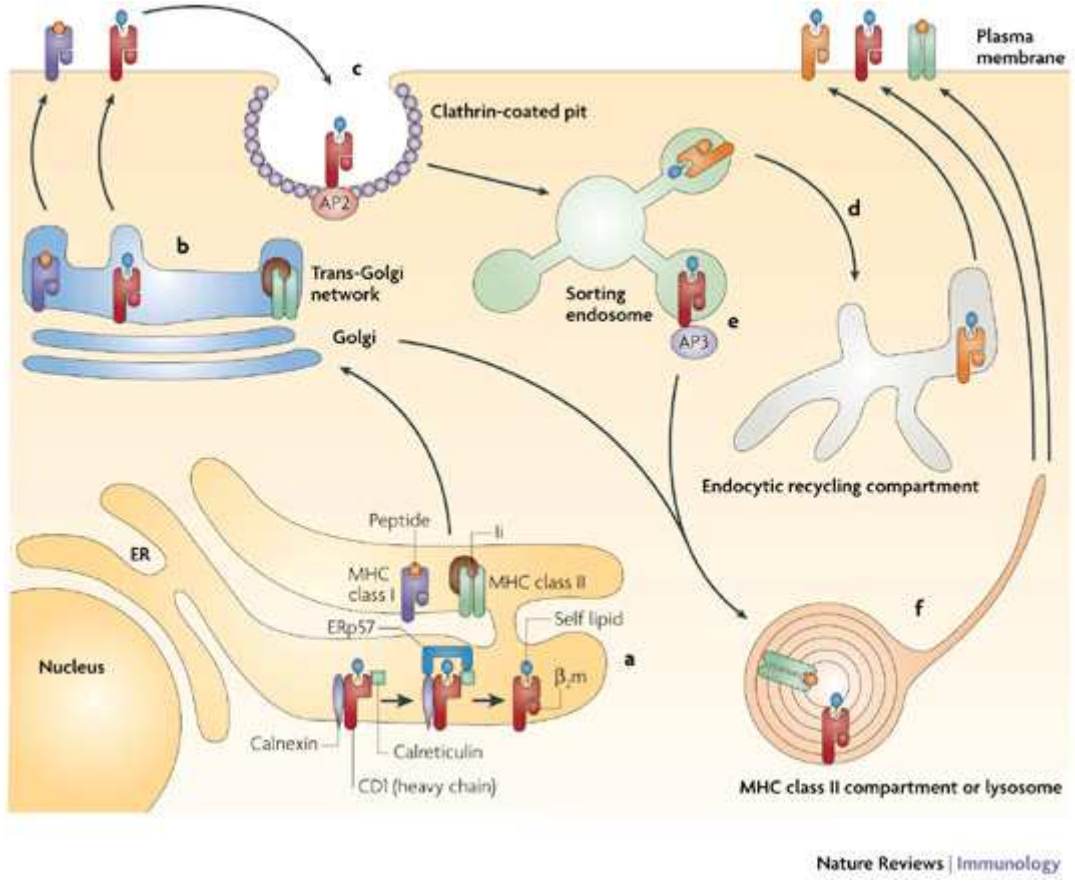
B cell



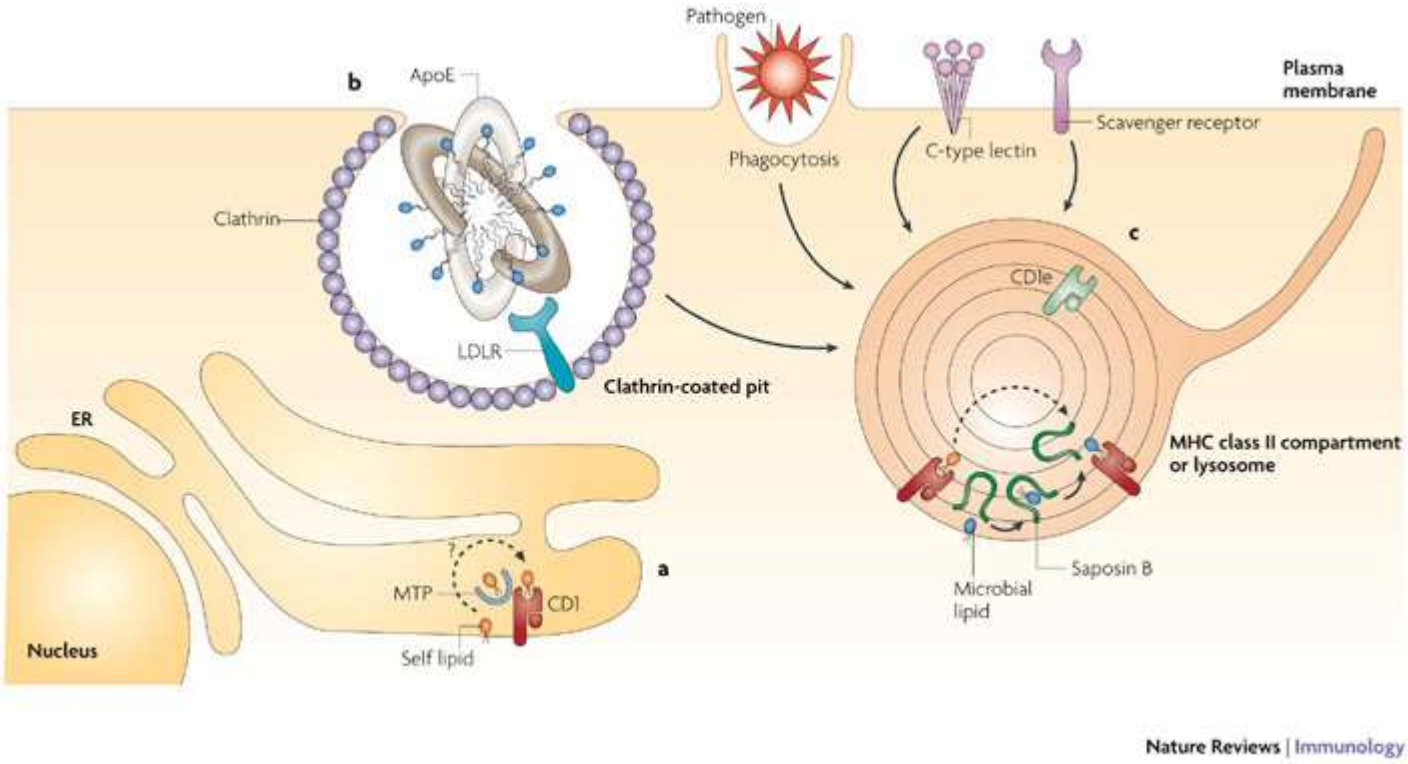
CD1c
CD1d

Tráfico celular de CD1

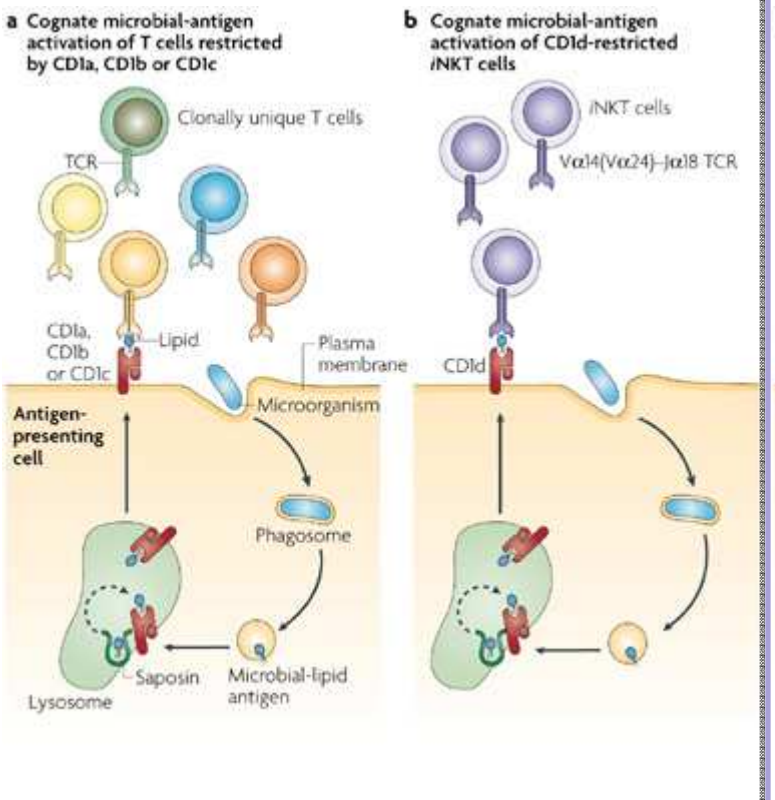




Nature Reviews Immunology 7, 929-941 (December 2007)



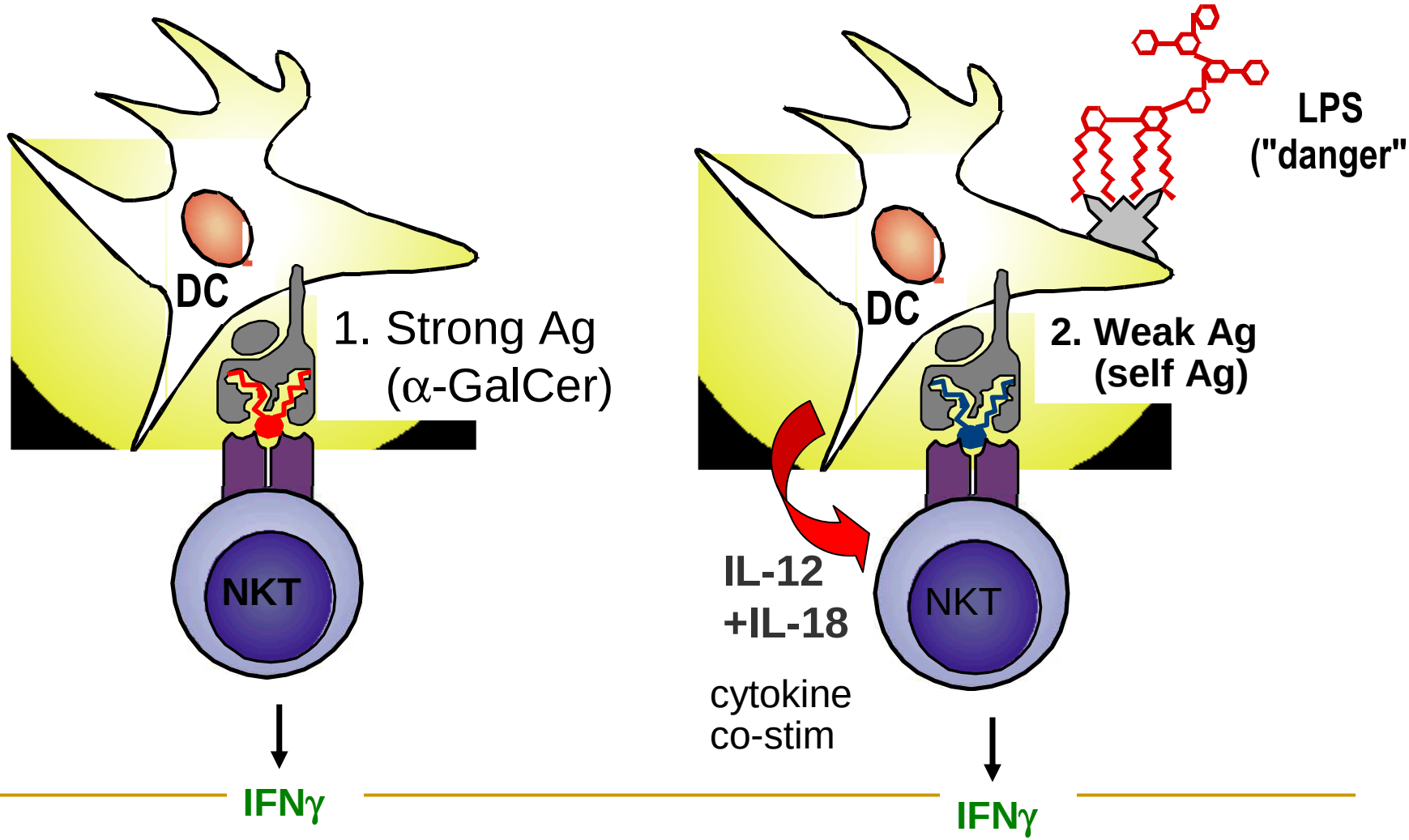
a | Self lipids (shown in orange) from the endoplasmic reticulum (ER) are loaded onto CD1 molecules. In the case of CD1d, this process is facilitated by a poorly characterized mechanism that involves microsomal triglyceride transfer protein (MTP). b | Four possible mechanisms for the uptake of foreign lipid antigens are shown: clathrin-dependent internalization of apolipoprotein E (apoE)–lipid complexes bound to the low-density lipoprotein receptor (LDLR); phagocytosis of particulate material or whole pathogens; C-type lectins, which can bind mannose residues on glycolipids; and internalization through scavenger receptors, which can bind modified forms of LDL and apoptotic cells. c | The exchange of endogenous lipids, loaded in the ER or the secretory pathway, by foreign lipids or different endogenous lipid antigens (in blue), takes place in endocytic compartments, such as lysosomes. Several accessory molecules, such as saposins and CD1e, have been implicated in the loading of lipids in these compartments. In the case of saposin B, the protein probably binds lipids, extracts them from membranes and transfers them onto CD1d molecules.



Cytokine-driven self-antigen activation of iNKT cells. Even in the absence of a cognate microbial lipid antigen for the iNKT-cell TCR, most microorganisms can activate iNKT cells by stimulating antigen-presenting cells to produce interleukin-12 (IL-12), which in combination with the self-lipid antigens presented by CD1d can stimulate potent iNKT-cell responses. This allows rapid activation of a large pool of iNKT cells without direct microbial lipid antigen recognition by the TCR.

Download file

ESTIMULACIÓN DE CÉLULAS NKT: SECRECIÓN DE IFNγ



Antígenos lipídicos presentados por CD1

Source	Antigen	CD1 isoform	Refs
Mycobacterium tuberculosis and other mycobacteria	Mycolic acids	CD1b	3
	Glucose monomycolate	CD1b	132
	Sulpholipid (diacylated sulphoglycolipid)	CD1b	8
	Phosphatidylinositol mannosides	CD1b, CD1d	5,133
	Mannosylated lipoarabinomannan	CD1b	5
	Mannosyl-β1-phosphomycoketides	CD1c	6,134
	Didehydroxymycobactin	CD1a	124
Sphingomonas spp.	α-Glucuronosylceramide	CD1d	9,10
Borrelia burgdorferi	α-Galactosyldiacylglycerol	CD1d	11
Leishmania donovani	Lipophosphoglycan	CD1d	12
Mammalian (self)	Phosphatidylinositol	CD1d	18
	Phosphatidylglycerol	CD1d	18
	Phosphatidylethanolamine	CD1d	18
	GM1	CD1b	20,21
	GD3	CD1d	22
	Sulphatide	CD1a, CD1b, CD1c	19
	Isoglobotrihexosylceramide	CD1d	10,23
Synthetic or marine sponge	α-Galactosylceramide	CD1d	125

Características de las células T restringidas por CD1

	Group-1-CD1-restricted T cells	CD1d-restricted iNKT cells	CD1d-restricted diverse NKT cells
Antigens	Microbial and self lipids	Microbial and self lipids	Unknown
T-cell population	Clonally diverse	Canonical TCRα but polyclonal	Clonally diverse
TCR	TCRα: diverse; TCRβ: diverse	TCRα: invariant Vα14 or Vα24 and Jα18; TCRβ: limited Vβ repertoire with diverse CDR3	TCRα: diverse; TCRβ:diverse
Precursor frequency	One per thousands, unique specificity for single antigen	<1% of T cells in humans; 2–50% of T cells in mice; pool of cells that responds *en masse* to a single antigen	Unknown
Memmory	Yes	No	Unknown
Immunity	Adaptive, slow	Innate-like, rapid (hours to few days)	Unknown

CDR3, complementarity-determining region 3; iNKT cell, invariant natural killer T cell; TCR, T-cell receptor.

GRACIAS POR SU ATENCIÓN!!!!