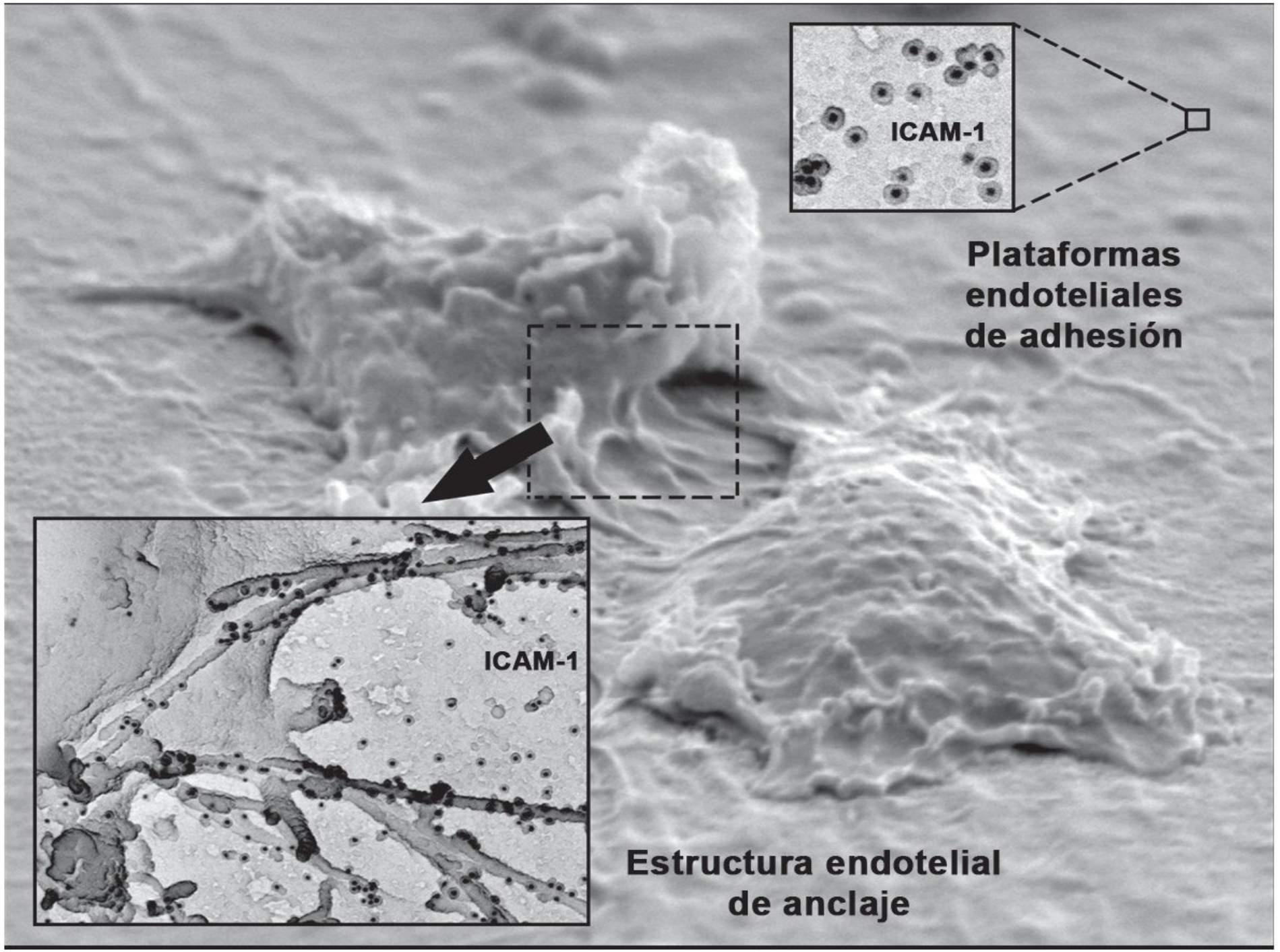
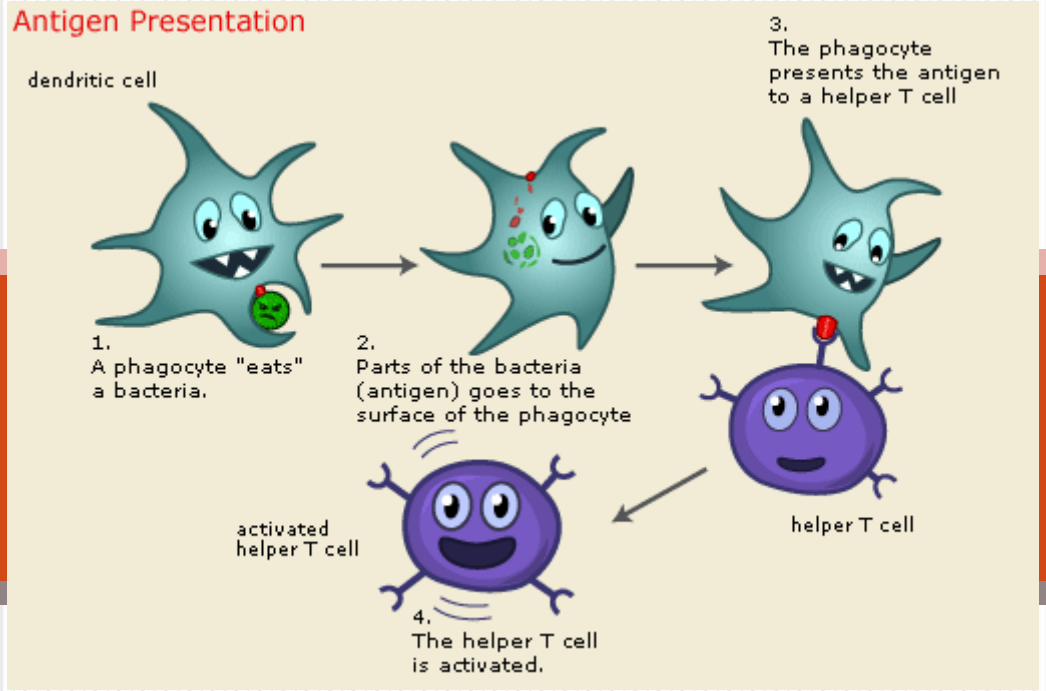
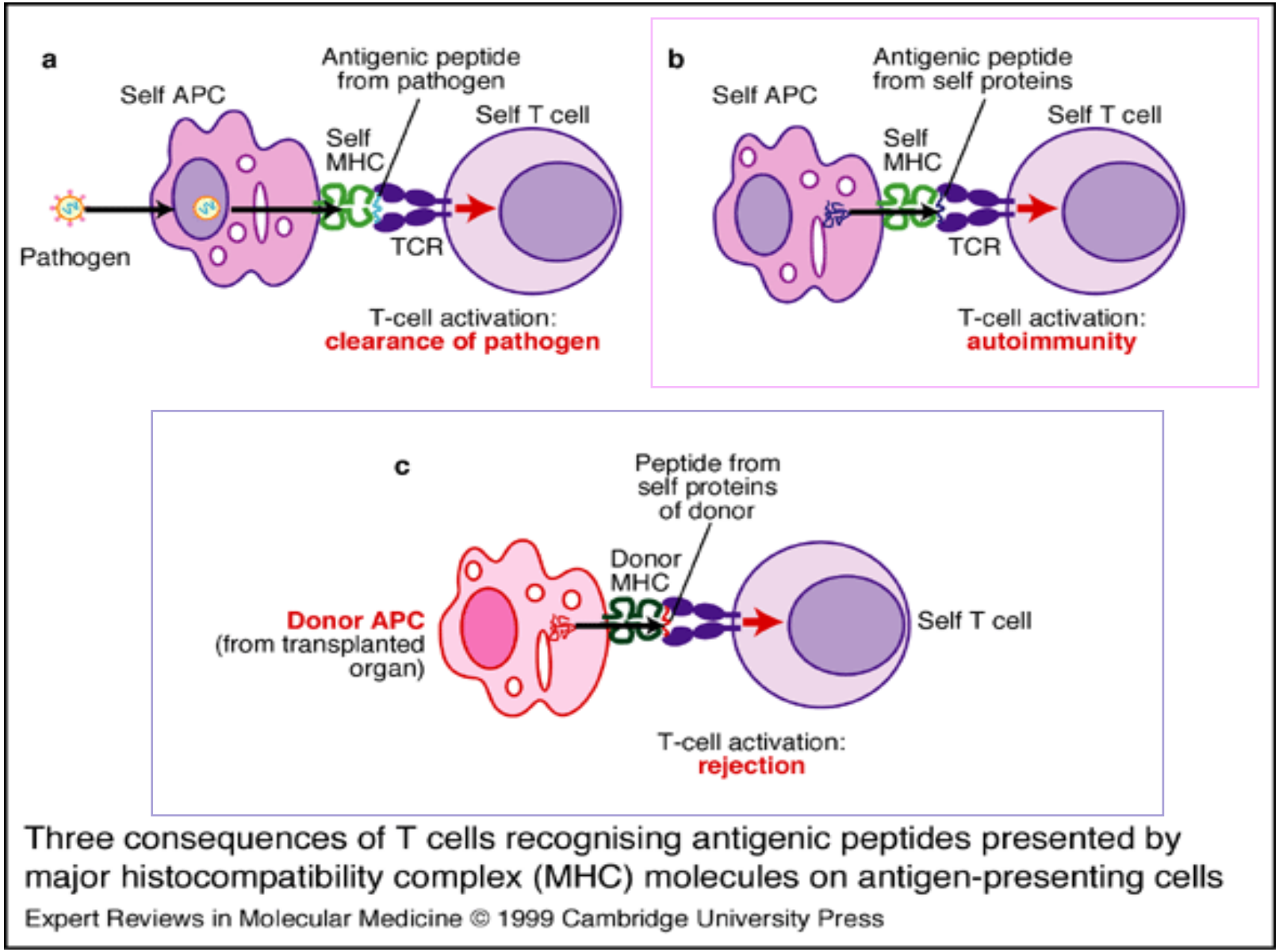

Inmunología Clínica
2010
Bioq Graciela Svibel


ICAM-1
Plataformas endoteliales de adhesión
ICAM-1
Estructura endotelial de anclaje

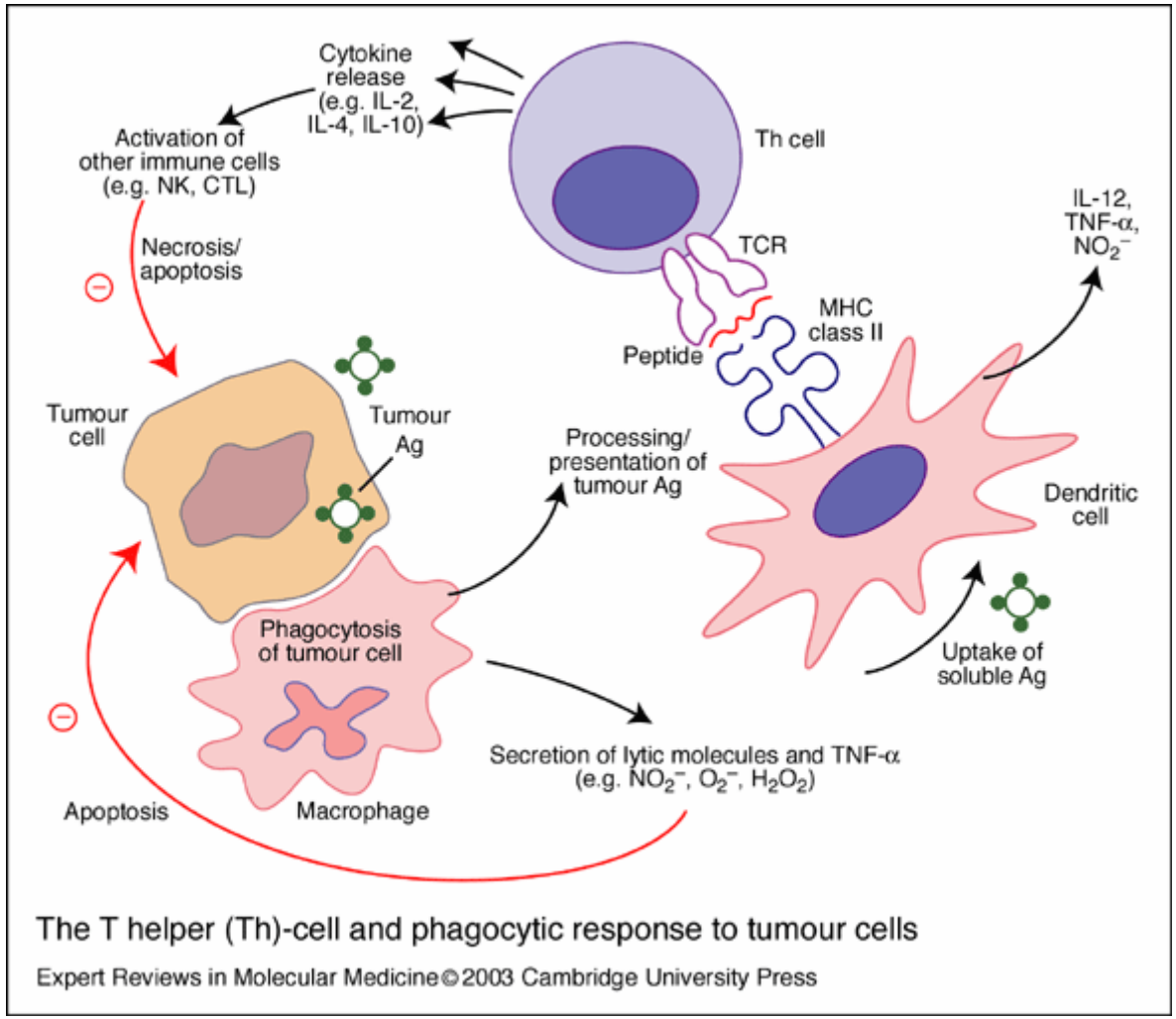


¿Cuáles son las consecuencias del reconocimiento del MHC -péptido antigénico por la célula T?



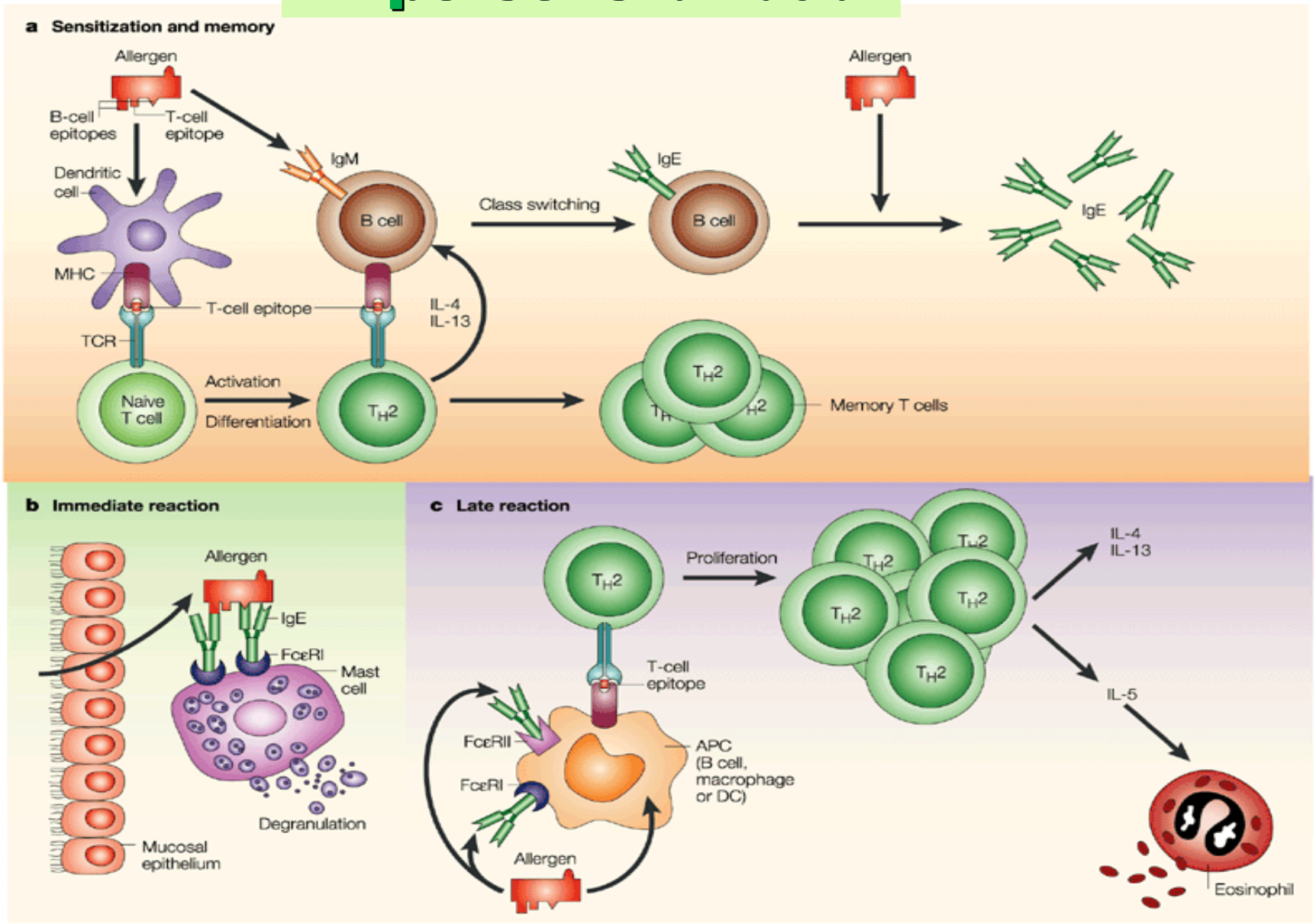
Three consequences of T cells recognising antigenic peptides presented by major histocompatibility complex (MHC) molecules on antigen-presenting cells

Presentación antigénica y tumores



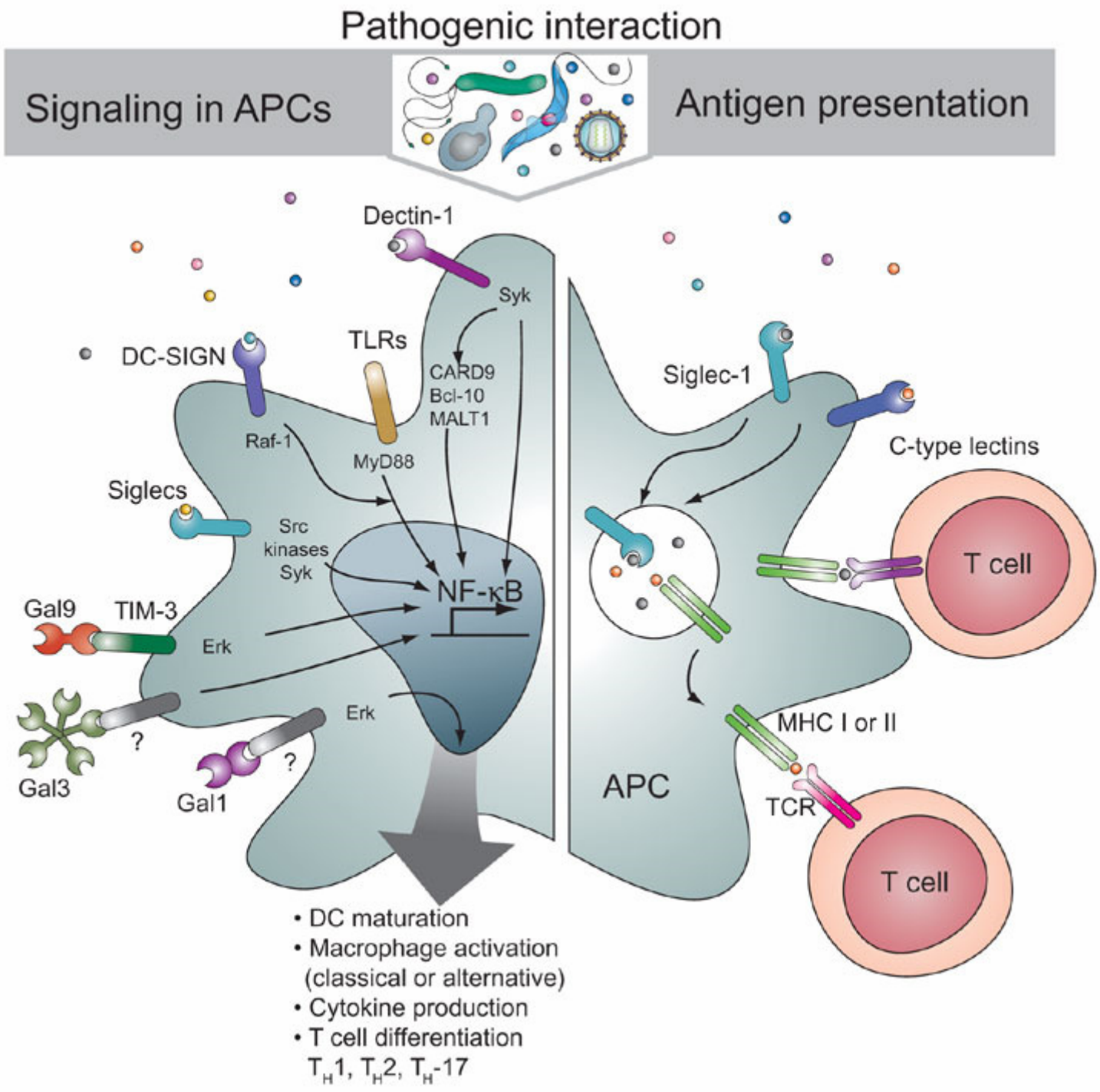
The T helper (Th)-cell and phagocytic response to tumour cells

Hipersensibilidad

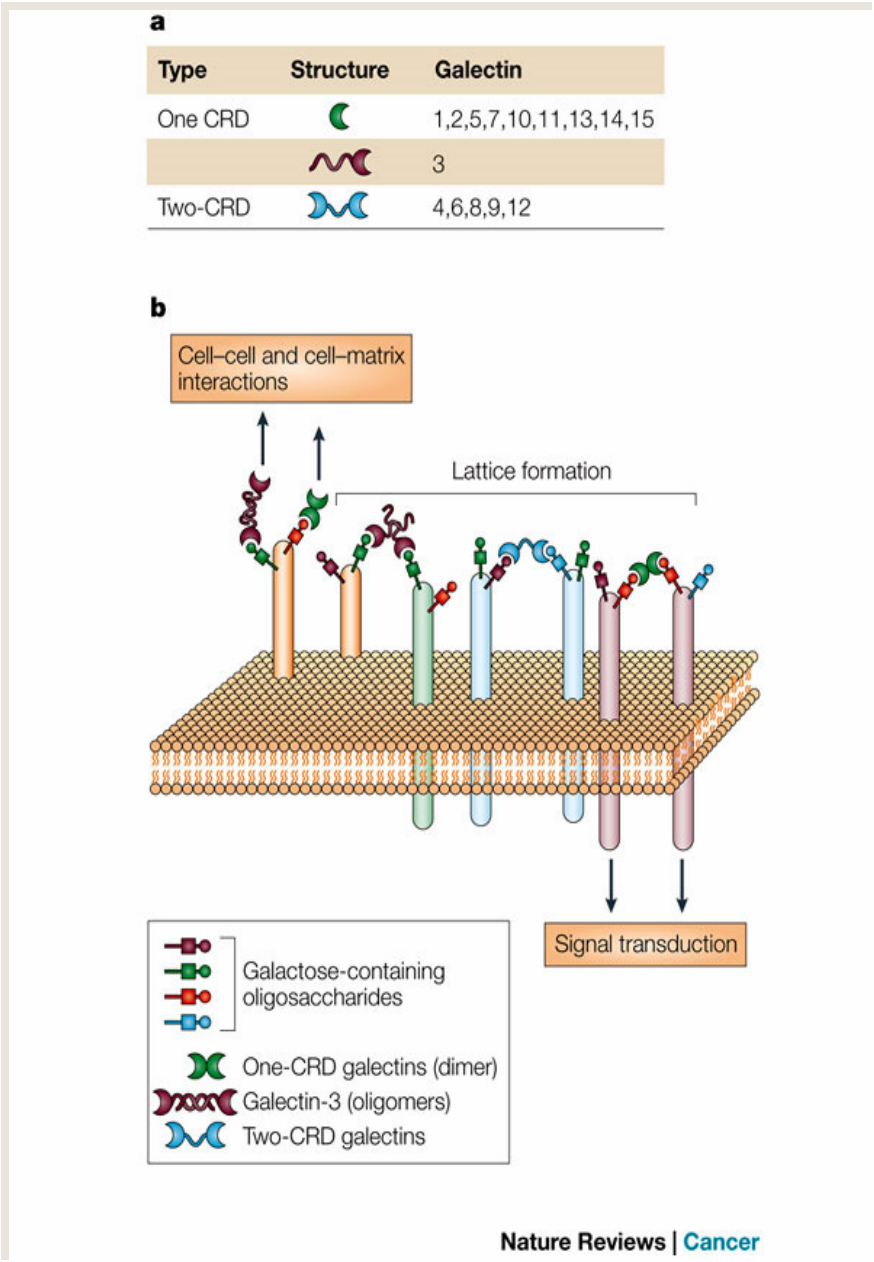


Nature Reviews Immunology 2, 446-453 (June 2002)

INTERACCIONES PROTEIN-GLICANO EN LA REGULACIÓN DE LA RESPUESTA INMUNE INNATA Y ADAPTATIVA

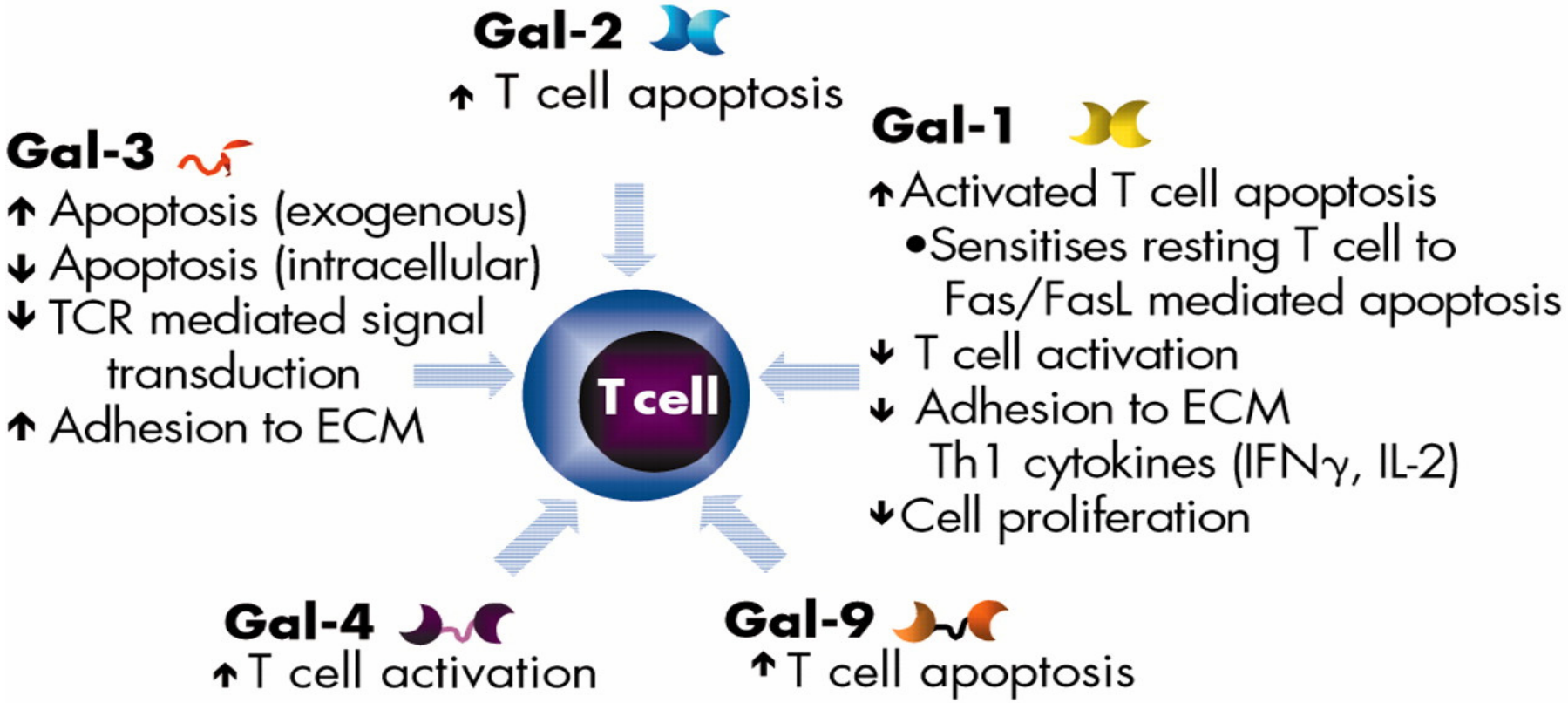

Pathogenic interaction
Signaling in APCs
Antigen presentation
Dectin-1
Syk
TLRs
DC-SIGN
CARD9
Bcl-10
MALT1
Raf-1
MyD88
Siglecs
Src
kinases
Syk
NF-κB
Gal9
TIM-3
Erk
Erk
?
?
Gal3
Gal1
• DC maturation
• Macrophage activation
(classical or alternative)
• Cytokine production
• T cell differentiation
T_H1, T_H2, T_H-17
Siglec-1
C-type lectins
T cell
MHC I or II
APC
TCR
T cell

GALECTINAS

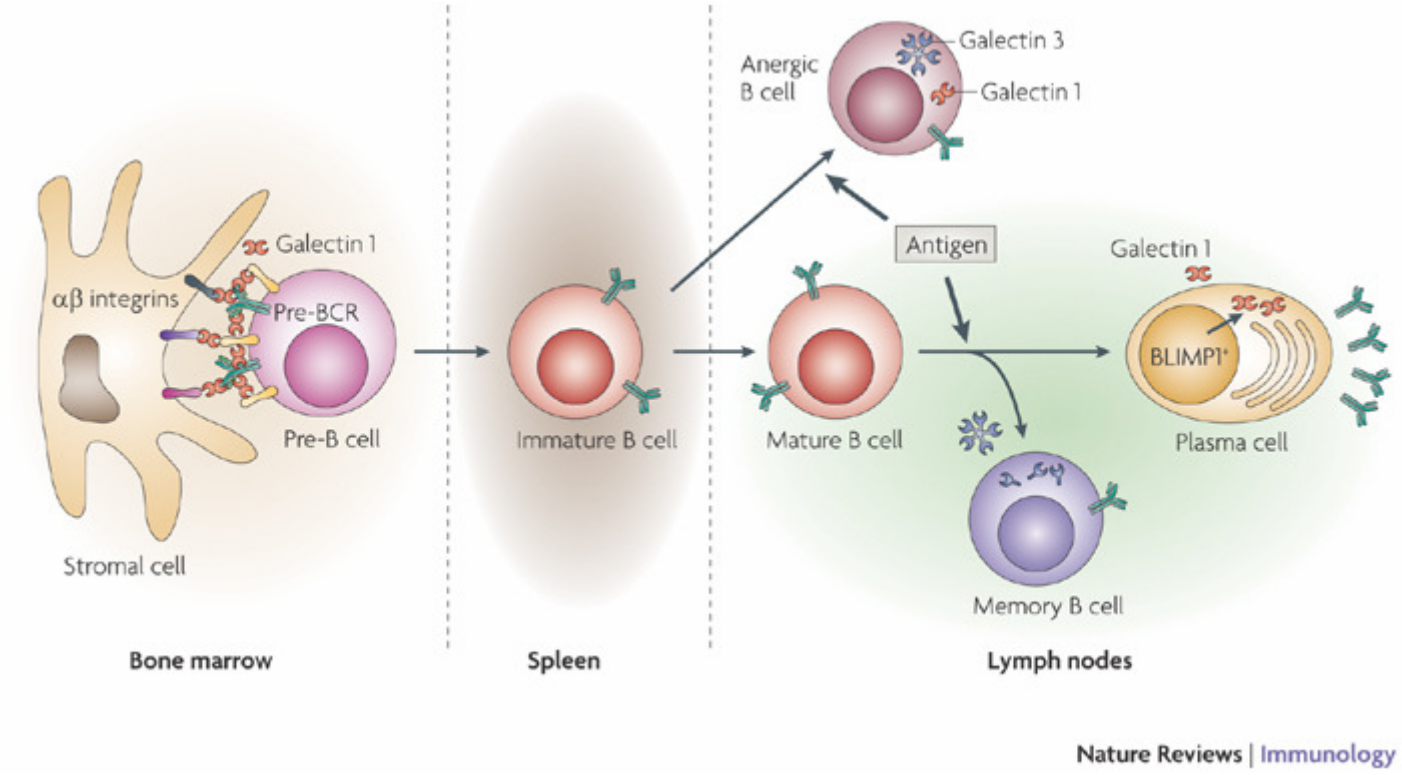


- **Las galectinas son una familia de proteínas con alta afinidad por residuos β□galactósidos altamente conservadas a lo largo de la evolución.**
- **Reconocen residuos sacarídicos presentes en glicoproteínas de la membrana plasmática y la matriz extracelular.**
- **A través de esta interacción, pueden modular interacciones entre células y la matriz extracelular.**
- **Activar vías de transducción de señales que regulan la proliferación, diferenciación y muerte.**

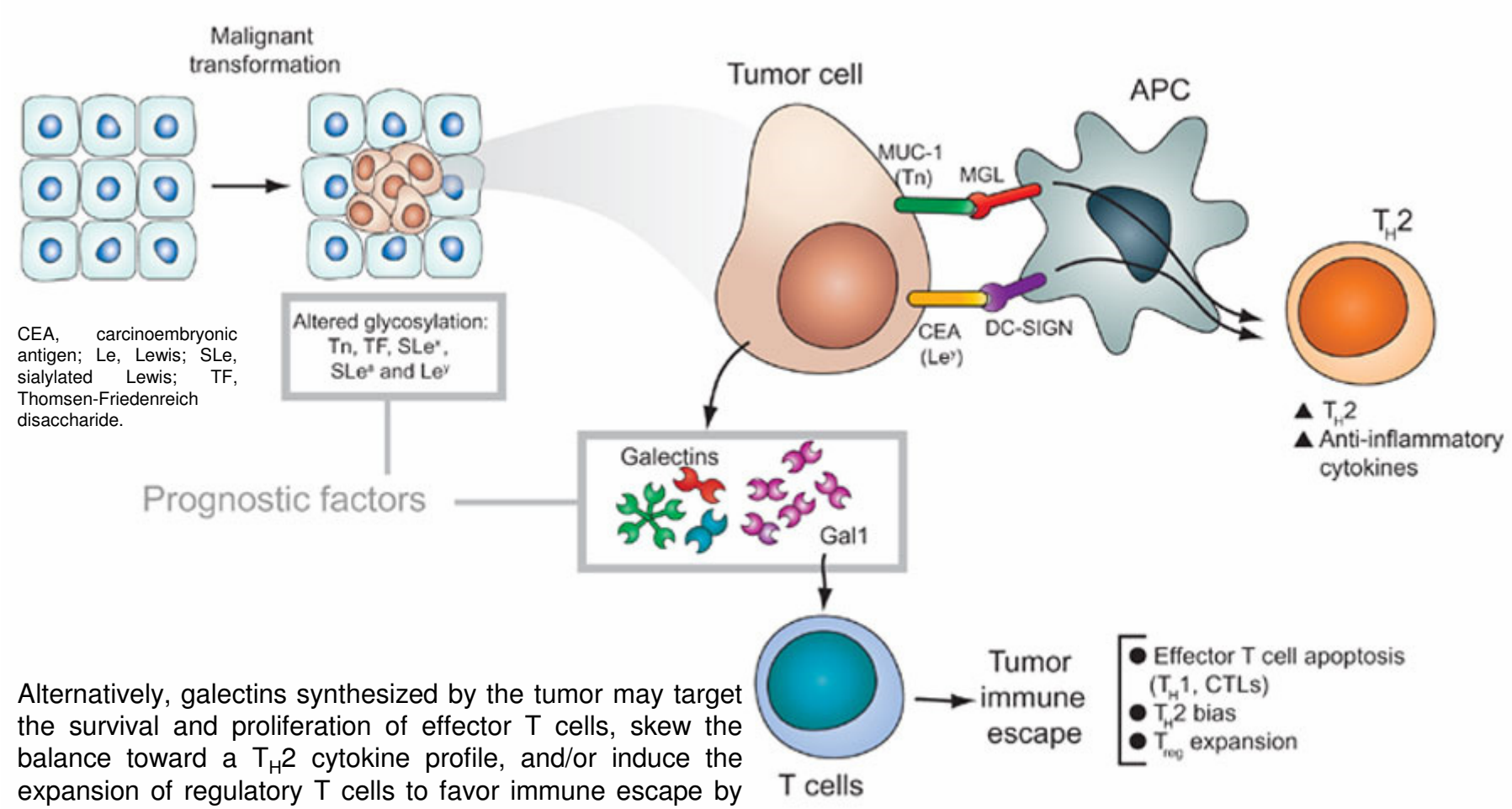
Liu & Rabinovich, Nature Rev Cancer 2005; 5: 29-41


Gal-2
↑ T cell apoptosis
Gal-3
↑ Apoptosis (exogenous)
↓ Apoptosis (intracellular)
↓ TCR mediated signal transduction
↑ Adhesion to ECM
T cell
Gal-1
↑ Activated T cell apoptosis
• Sensitises resting T cell to Fas/FasL mediated apoptosis
↓ T cell activation
↓ Adhesion to ECM
Th1 cytokines (IFNγ, IL-2)
↓ Cell proliferation
Gal-4
↑ T cell activation
Gal-9
↑ T cell apoptosis

Galectinas en la ontogenia de células B

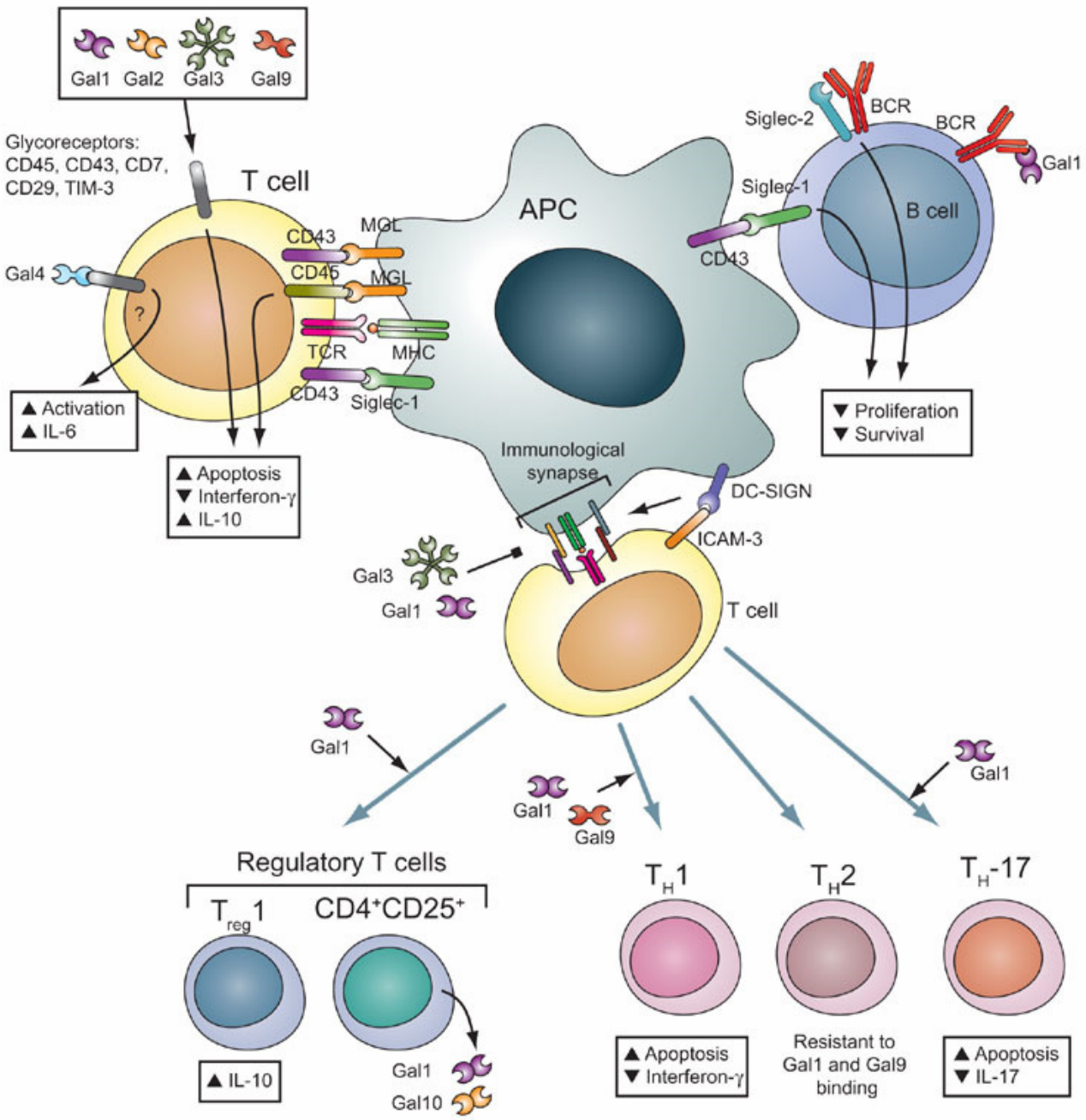


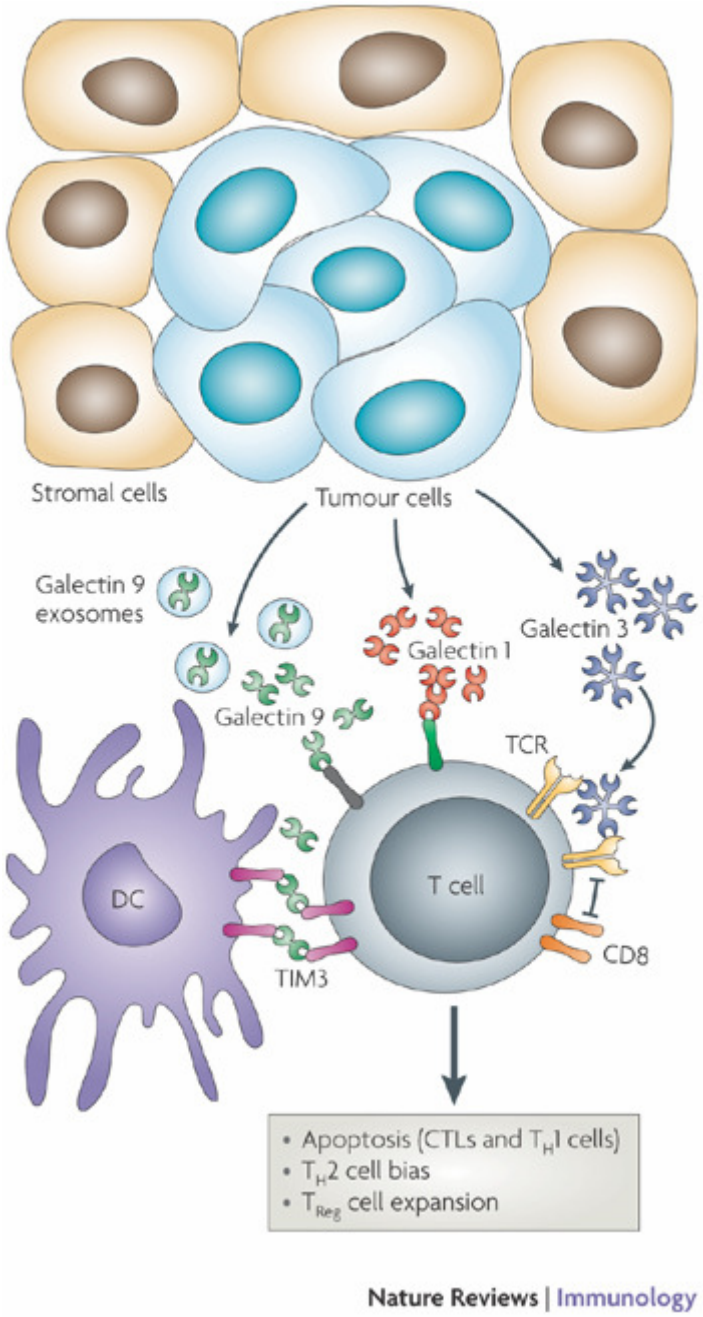
Malignant transformation often correlates with altered glycosylation of glycoproteins on the surface of tumor cells. These glycosylation changes, which have been widely used as prognostic markers of disease progression, can be detected by several galectins and C-type lectins (MGL and DC-SIGN).). The binding of these lectins to altered glycoproteins may affect APC function, leading to anti-inflammatory responses.



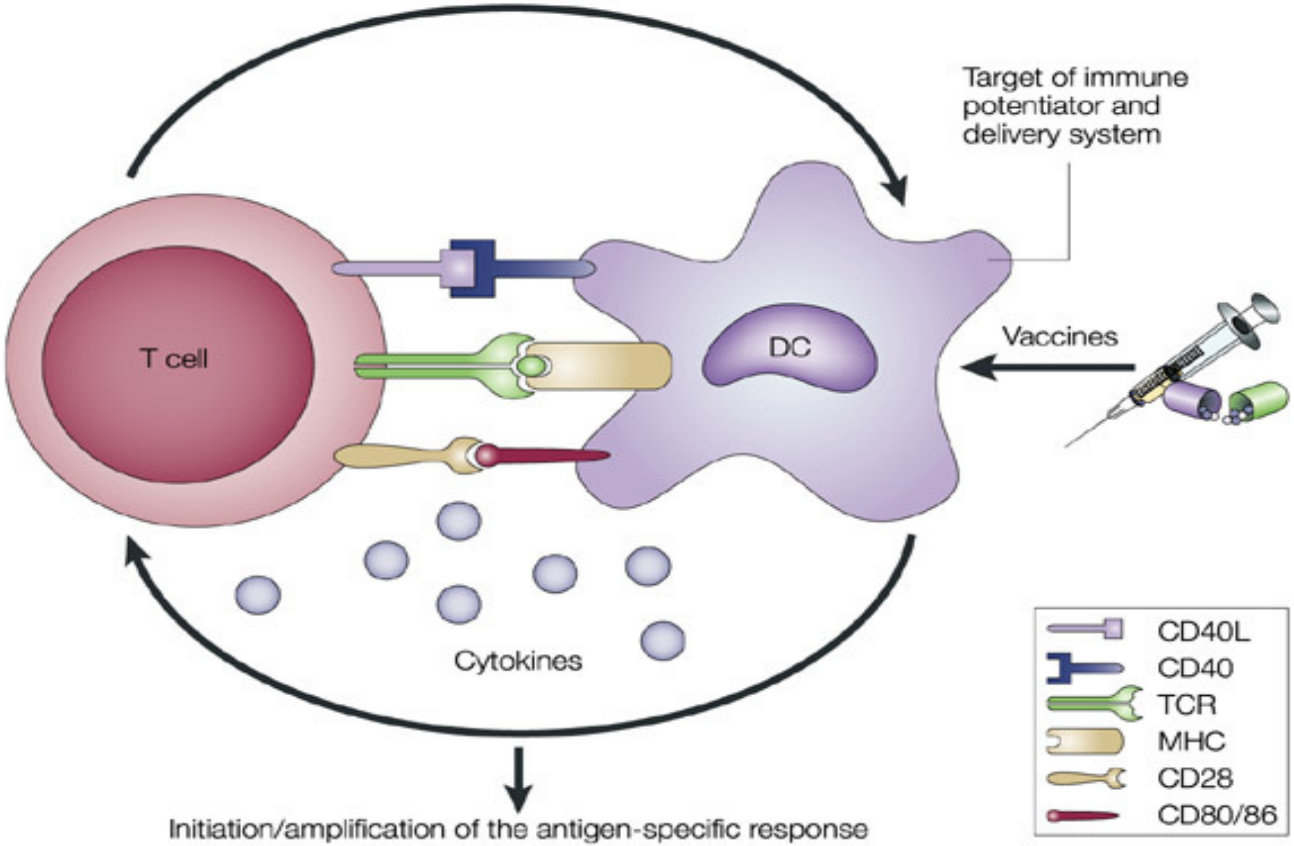
Alternatively, galectins synthesized by the tumor may target the survival and proliferation of effector T cells, skew the balance toward a T_H2 cytokine profile, and/or induce the expansion of regulatory T cells to favor immune escape by the tumor.

Lymphocyte homeostasis



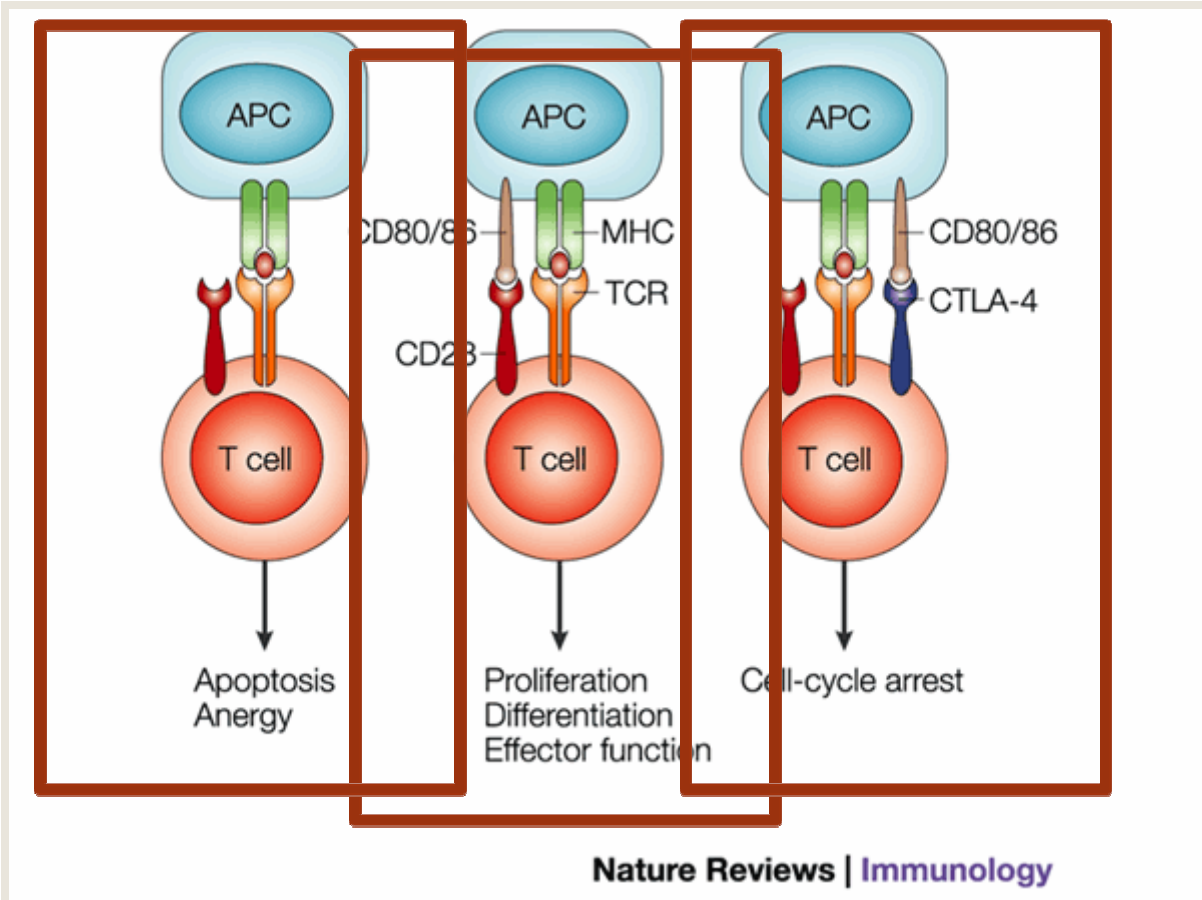

Stromal cells
Tumour cells
Galectin 9
exosomes
Galectin 9
Galectin 1
Galectin 3
TCR
DC
T cell
CD8
TIM3
• Apoptosis (CTLs and T_H1 cells)
• T_H2 cell bias
• T_{Reg} cell expansion
Nature Reviews | Immunology

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

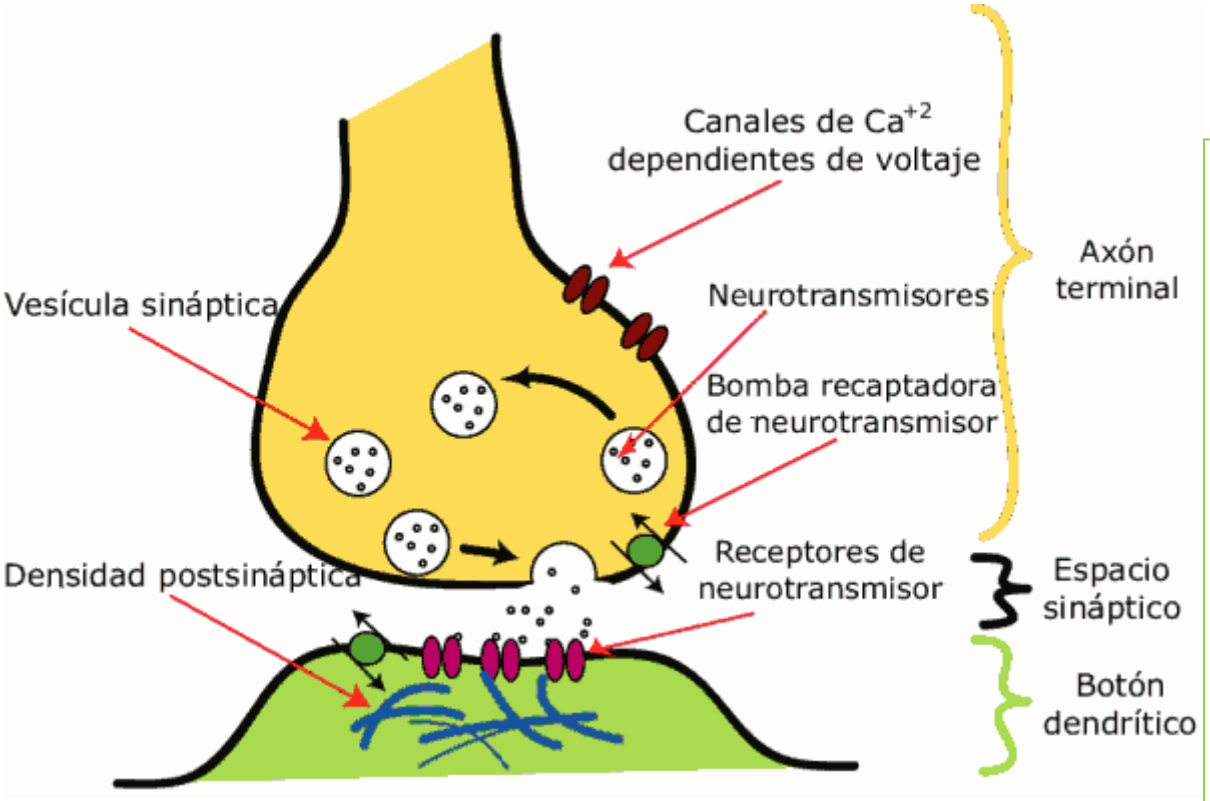


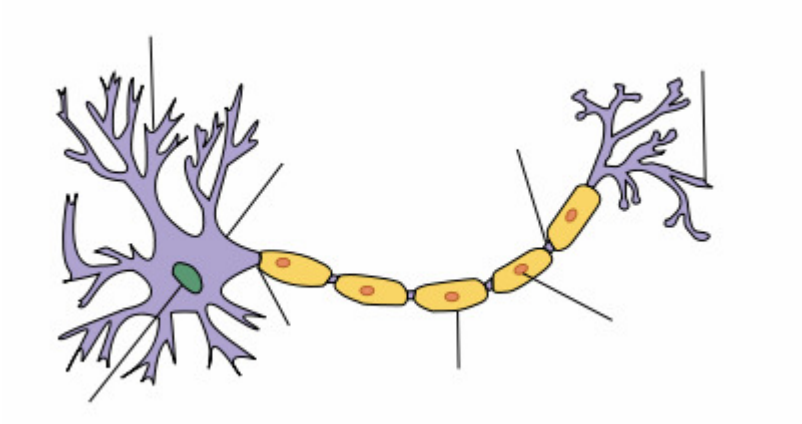
Nature Reviews | Drug Discovery
Nature Reviews Drug Discovery 2, 727-735 (September 2003)

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



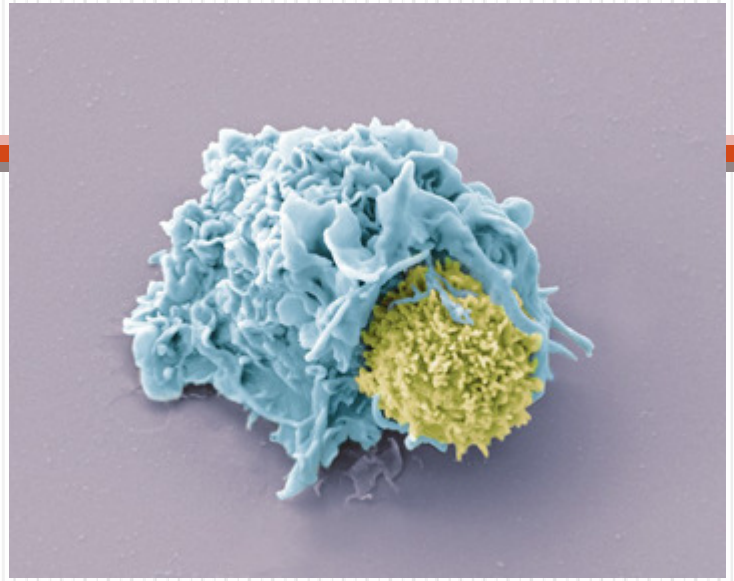
Sinapsis

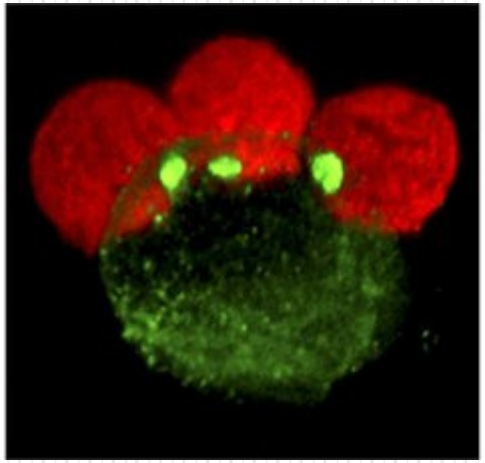




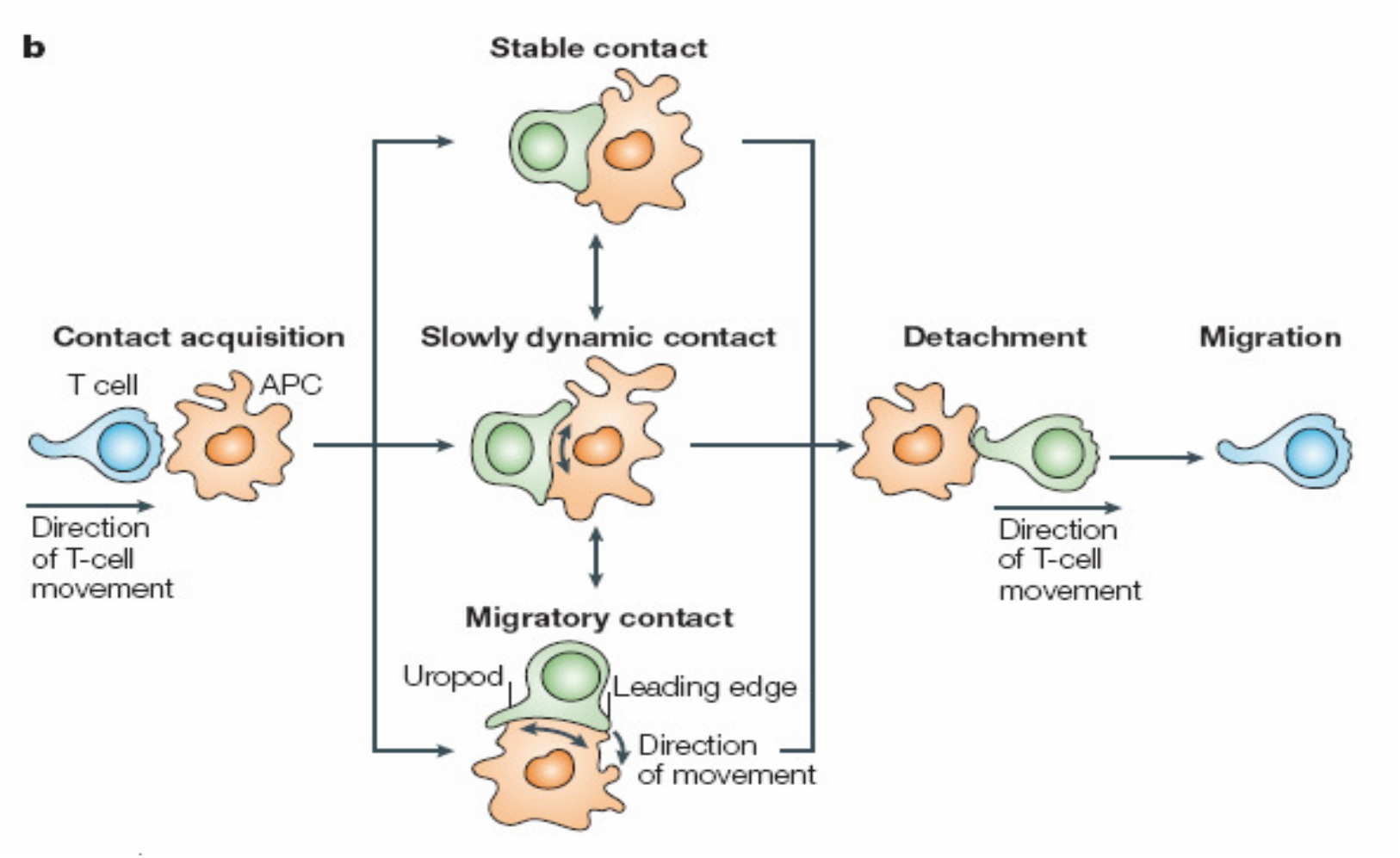
La sinapsis (del gr. σύναψις, "enlace") es un proceso que consta de descargas químico-eléctricas. Estas descargas se generan en la membrana celular de la neurona en un proceso de polarización-despolarización que libera unas sustancias químicas y un impulso eléctrico que estimula eléctricamente que van 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**.

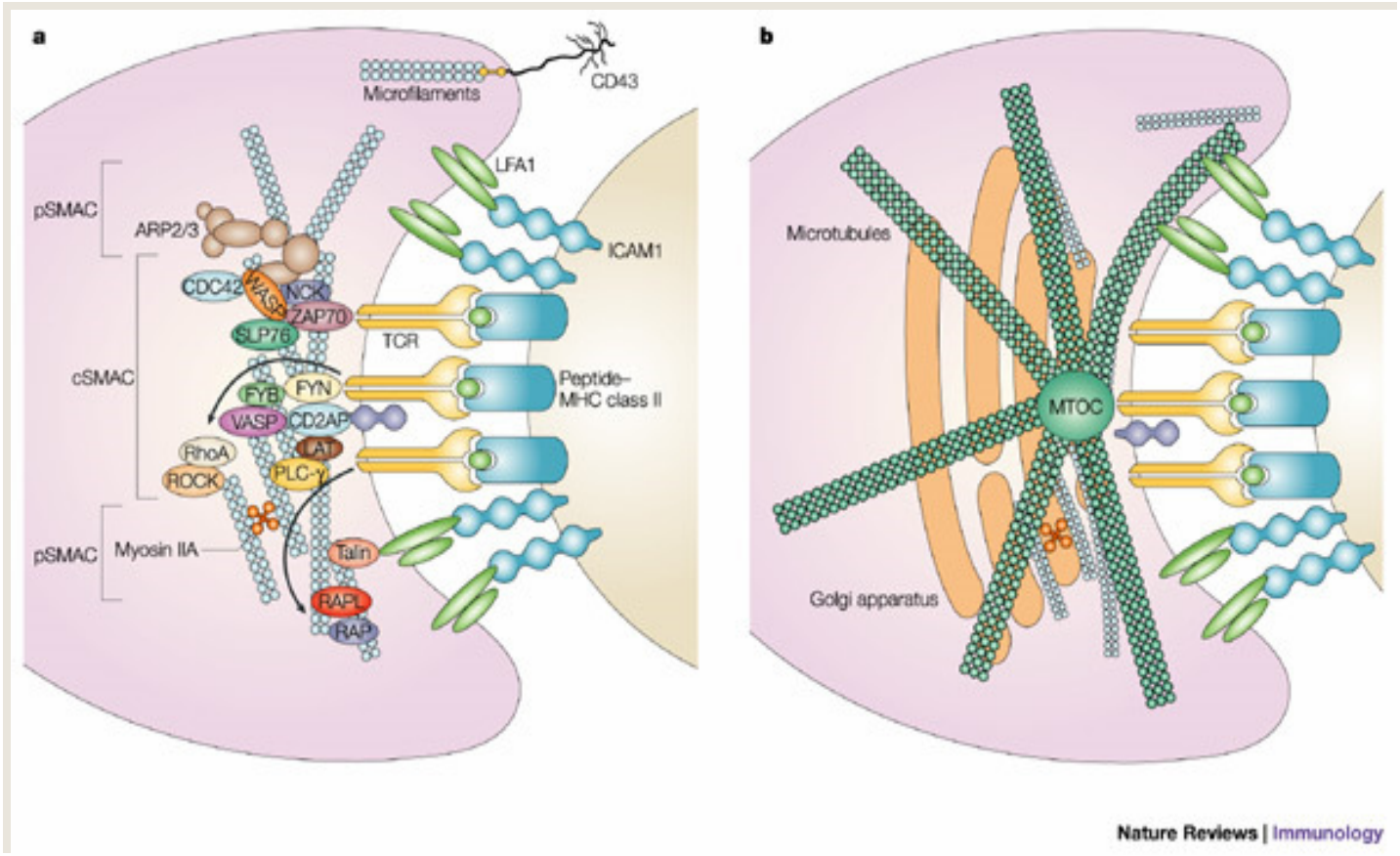
Sinapsis inmunológica





FASES DE LA INTERACCIÓN ENTRE LA APC Y EL LINFOCITO T





microtubule-organizing centres (MTOCs)

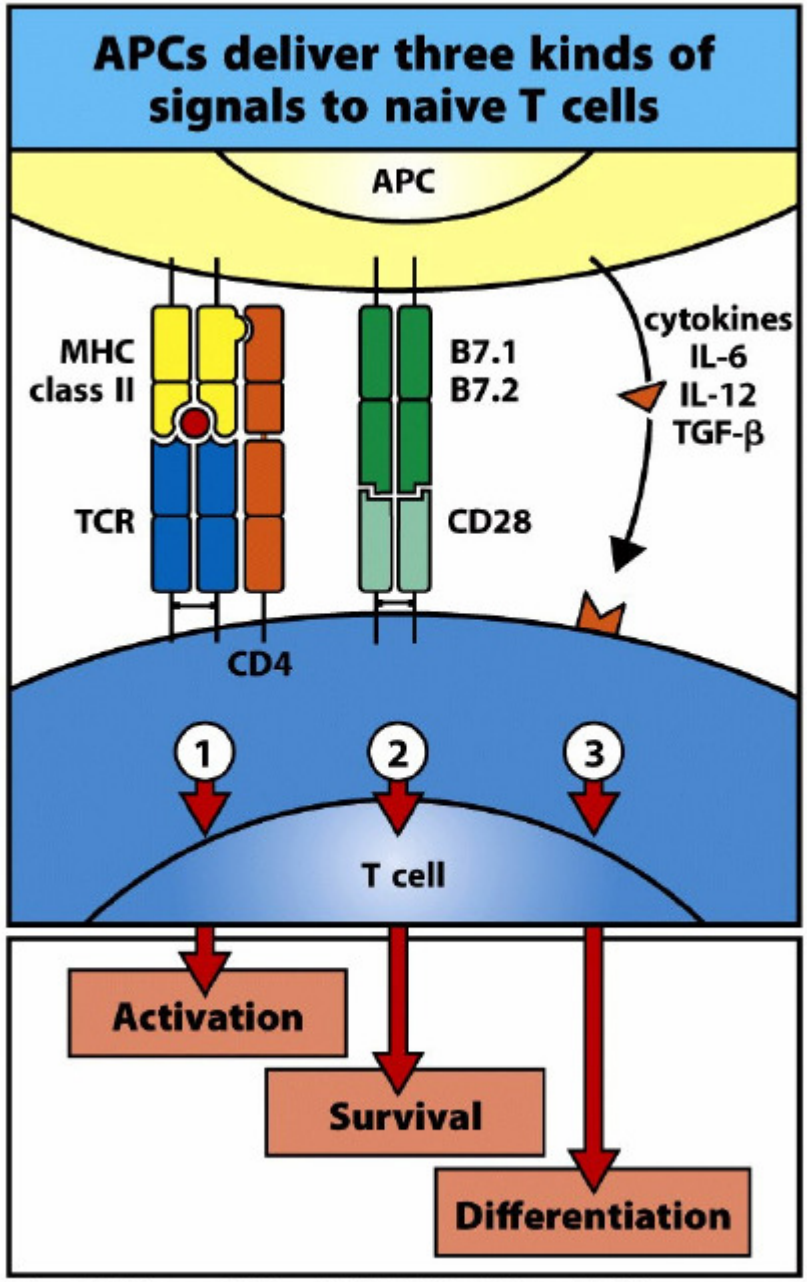
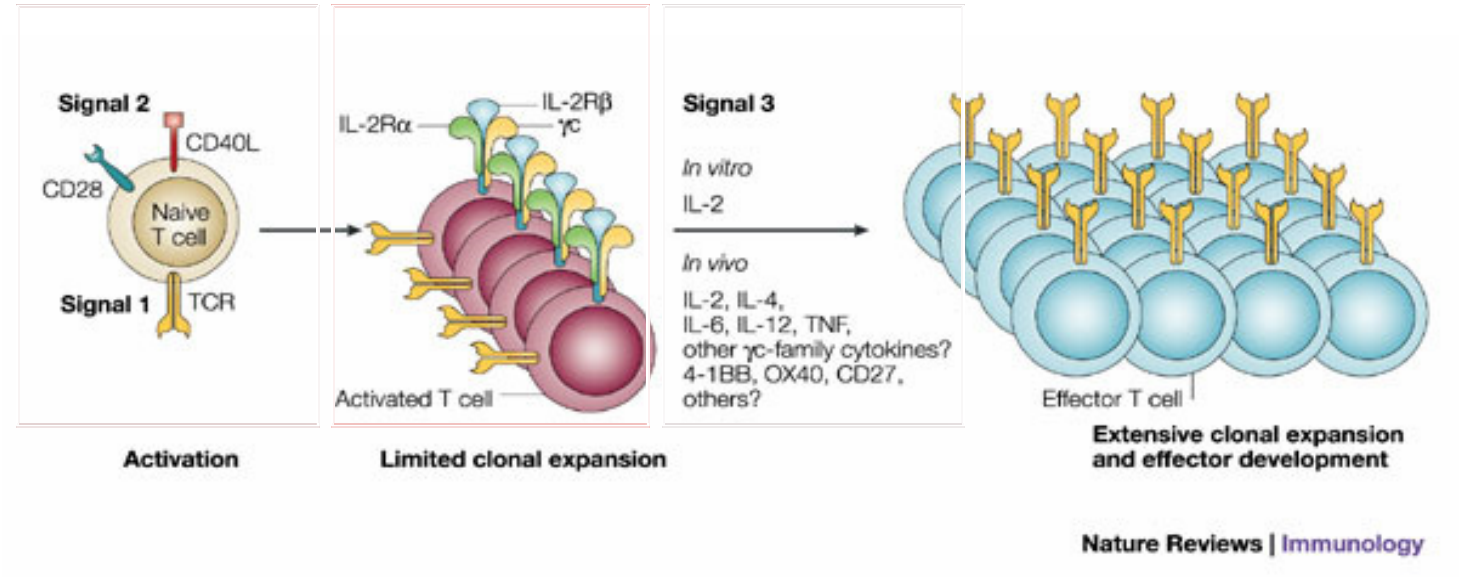
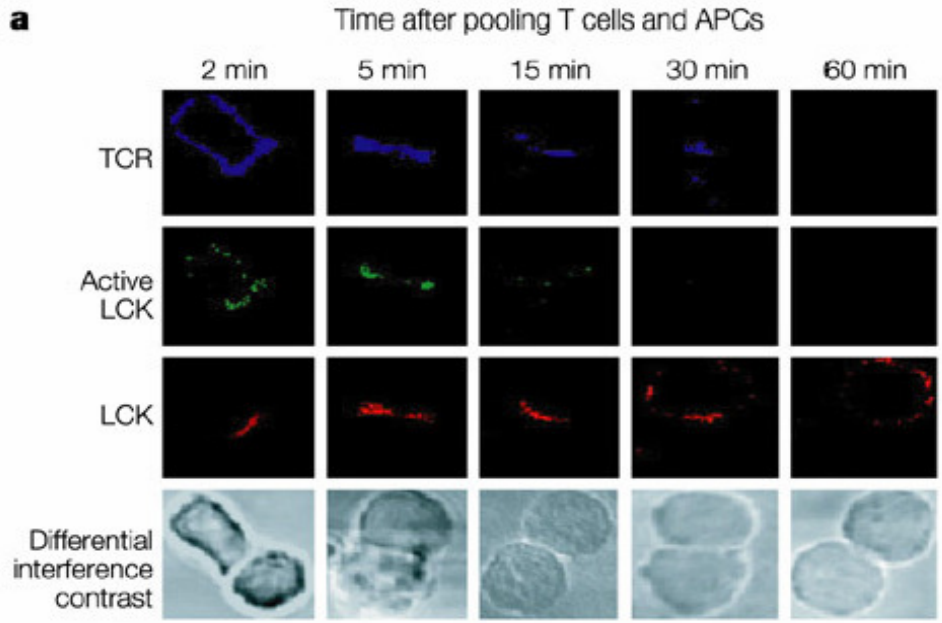


Figure 8-19 Immunobiology, 7ed. (© Garland Science 2008)



- 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.

LA SEÑAL 2 INDUCE LA FORMACIÓN DE LA SINAPSIS INMUNOLÓGICA



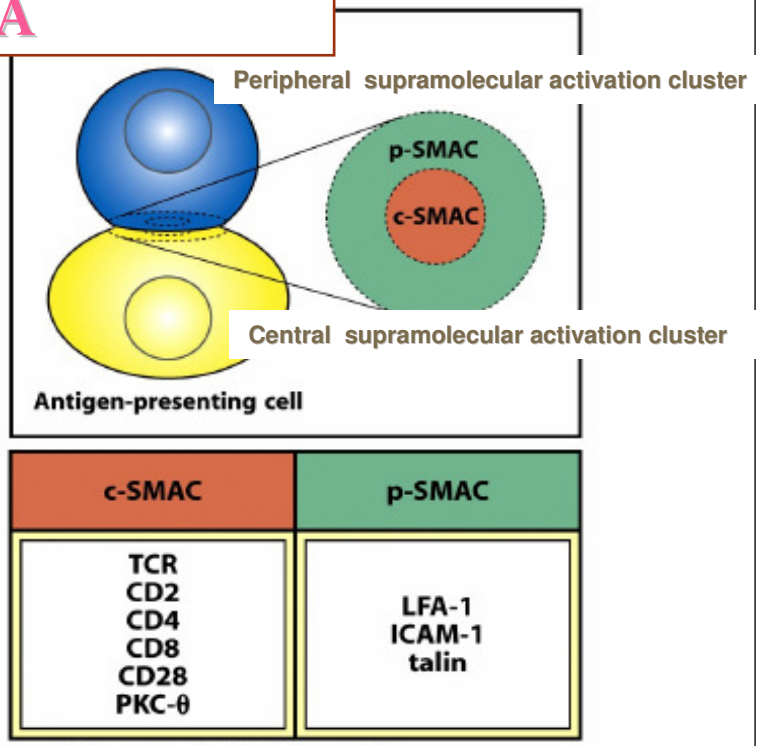
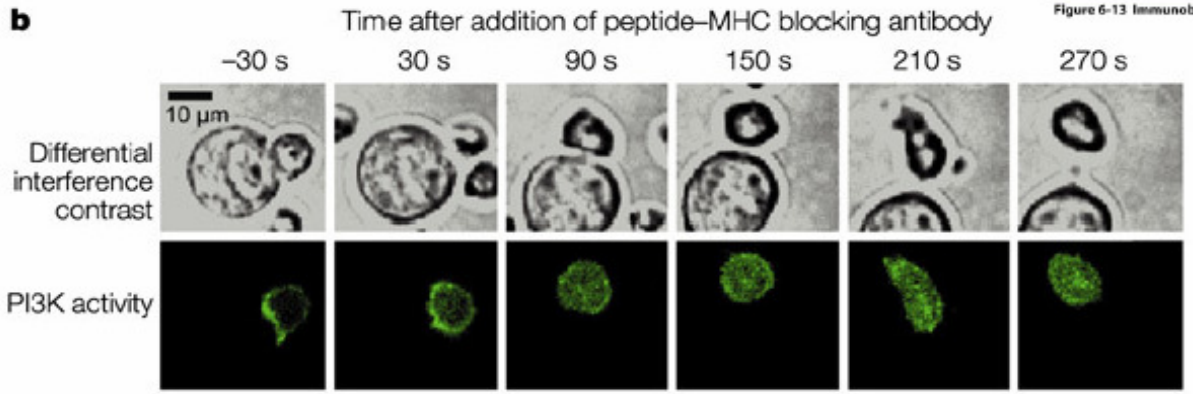
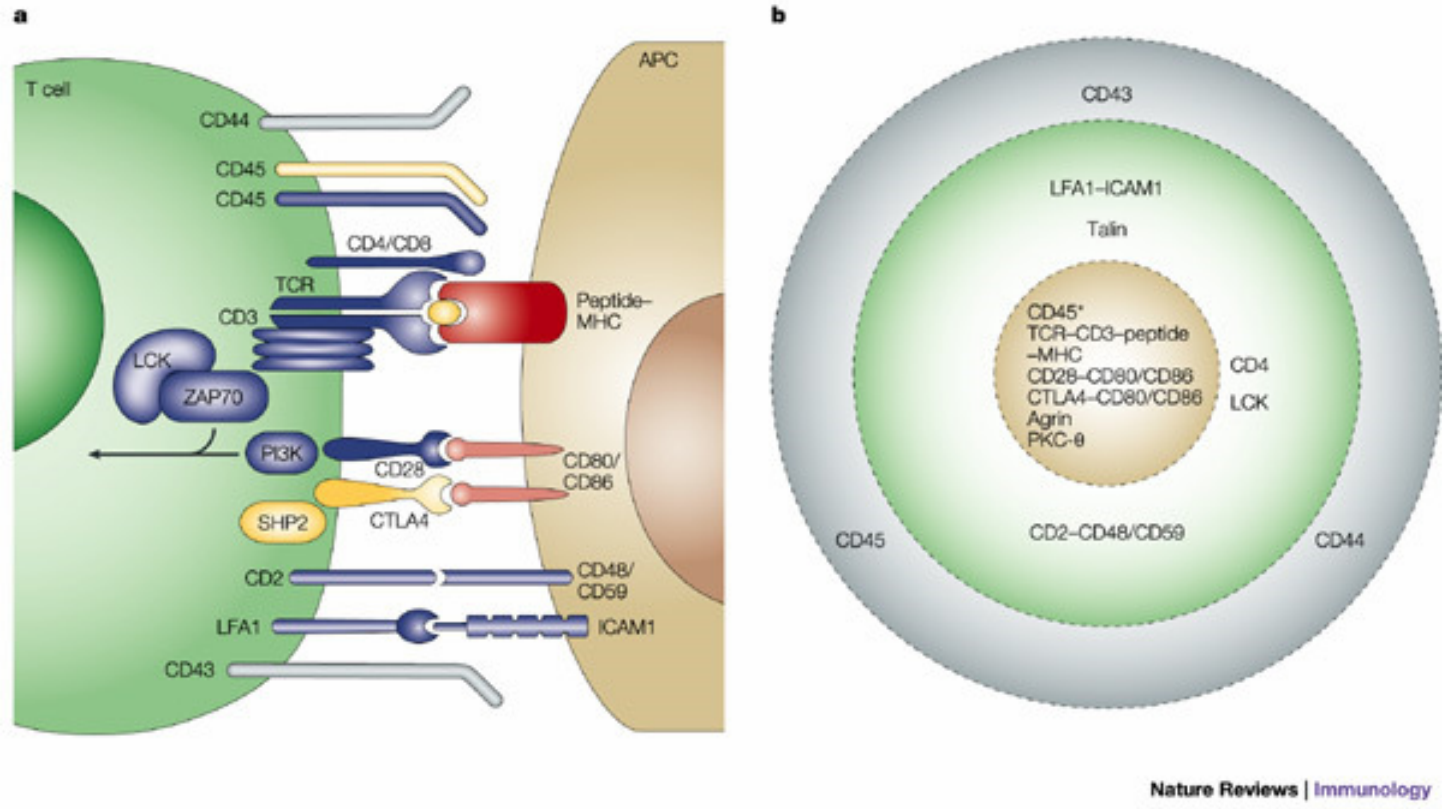


Figure 6-13 Immunobiology, 7ed. (© Garland Science 2008)



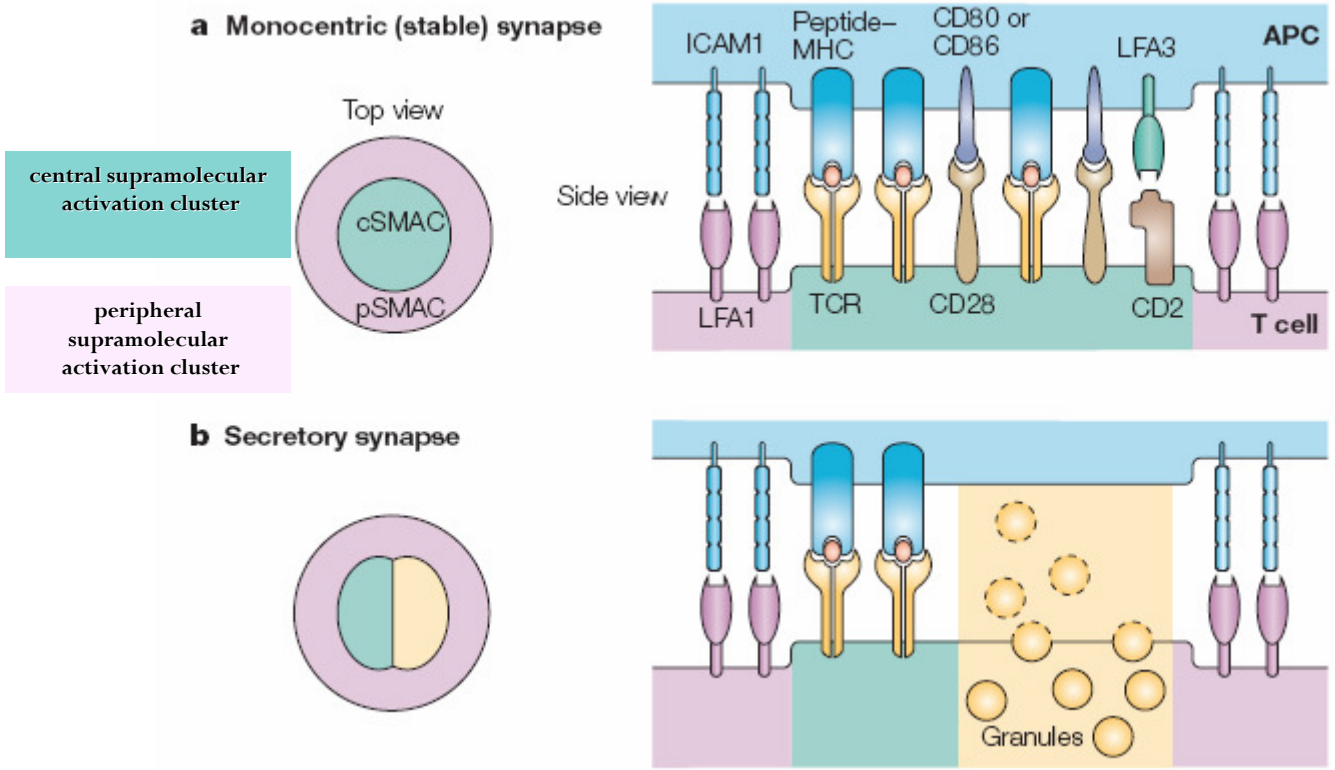
Nature Reviews | Immunology

La sinapsis madura...

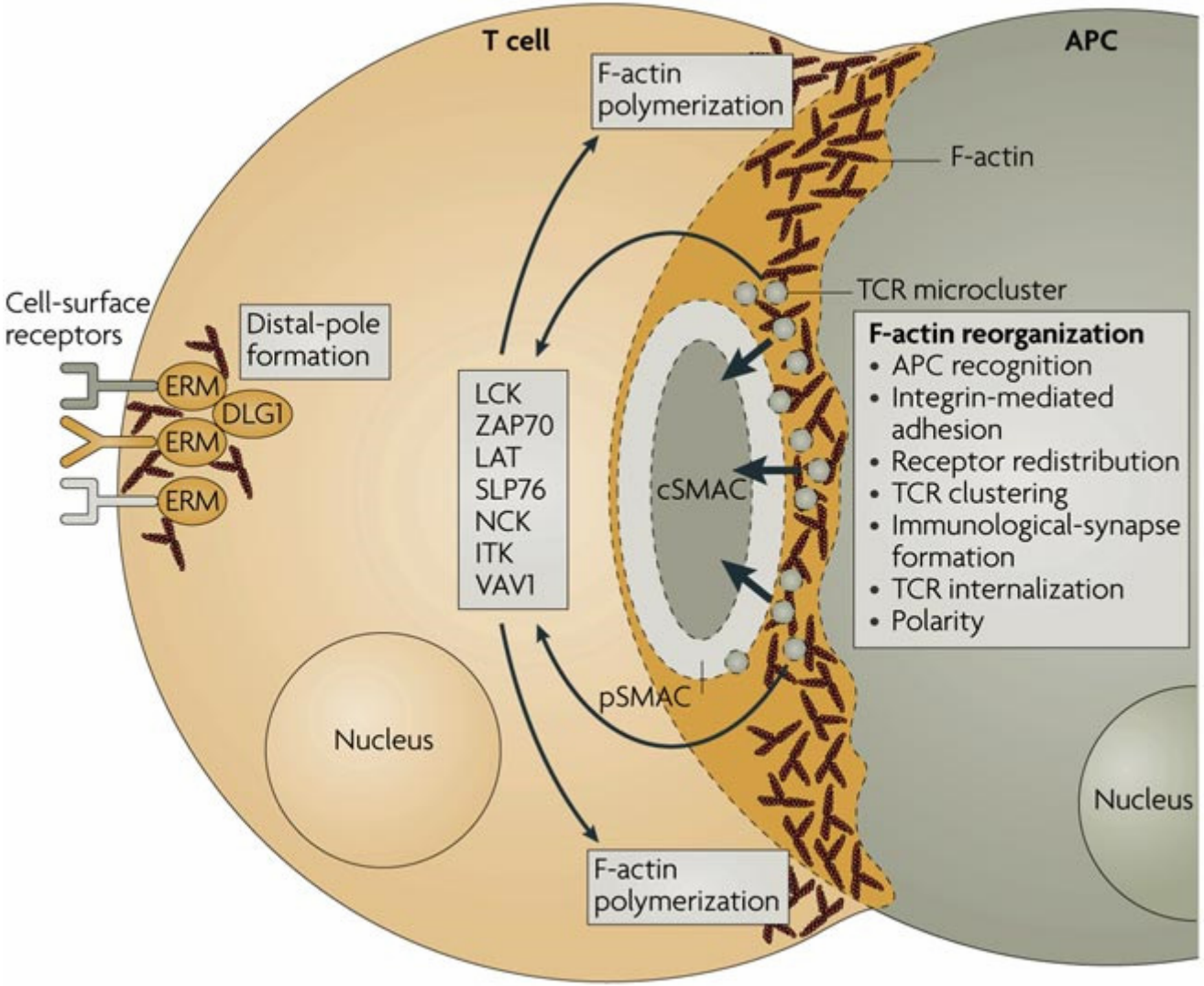


Nature Reviews Immunology 3, 973-983 (December 2003)

DOS TIPOS DE SINAPSIS INMUNOLÓGICA



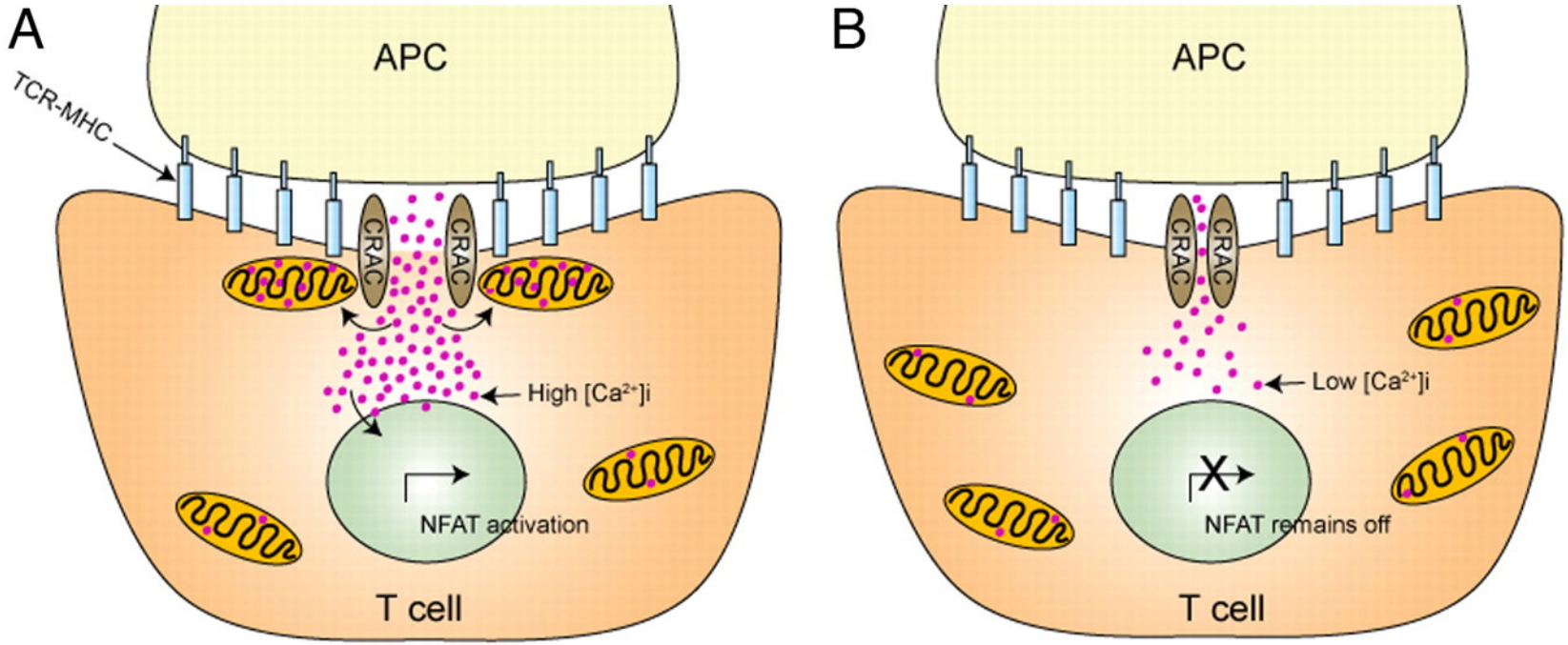
Two types of molecular arrangement at the immunological synapse are shown. a | A monocentric immunological synapse (also known as a stable immunological synapse) has a stably adhesive junction with a fully segregated **central supramolecular activation cluster** (cSMAC) and **peripheral SMAC** (pSMAC), 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)

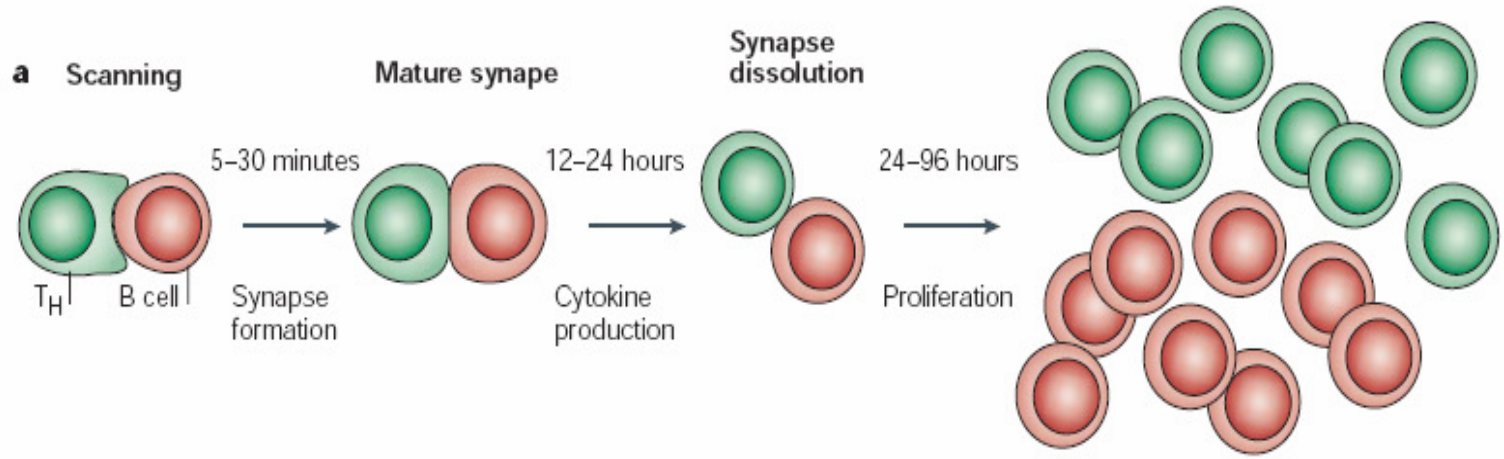
Cambios morfológicos y citoesqueléticos de la célula T

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



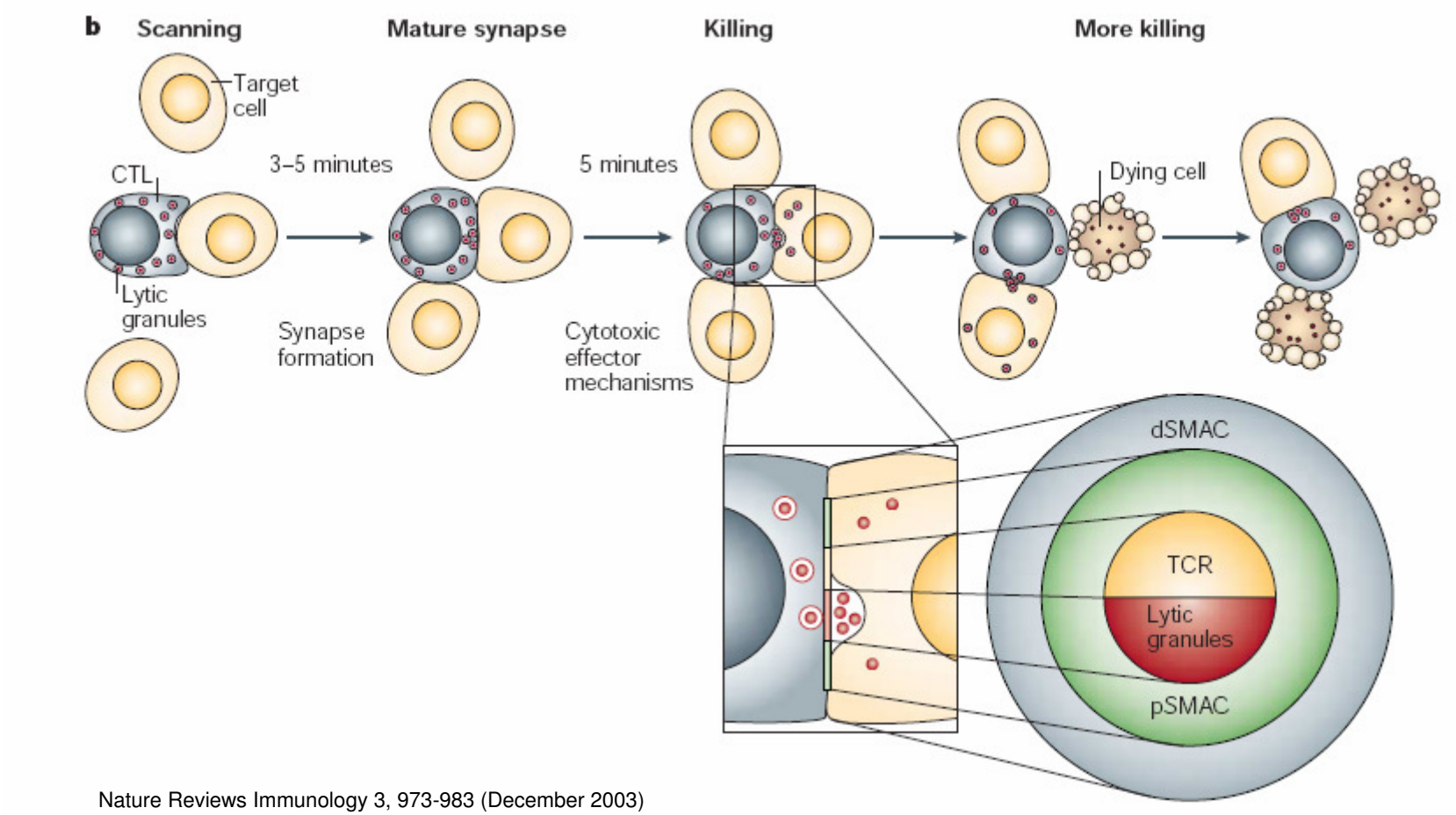
Oakes S. A. PNAS 2007;104:15171-15172

Formación de la SI entre Th y LB



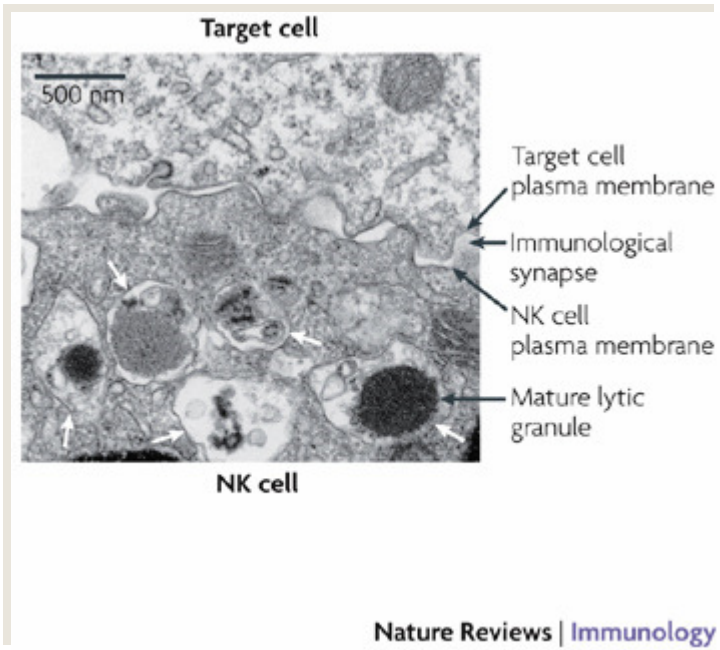
Nature Reviews Immunology 3, 973-983 (December 2003)

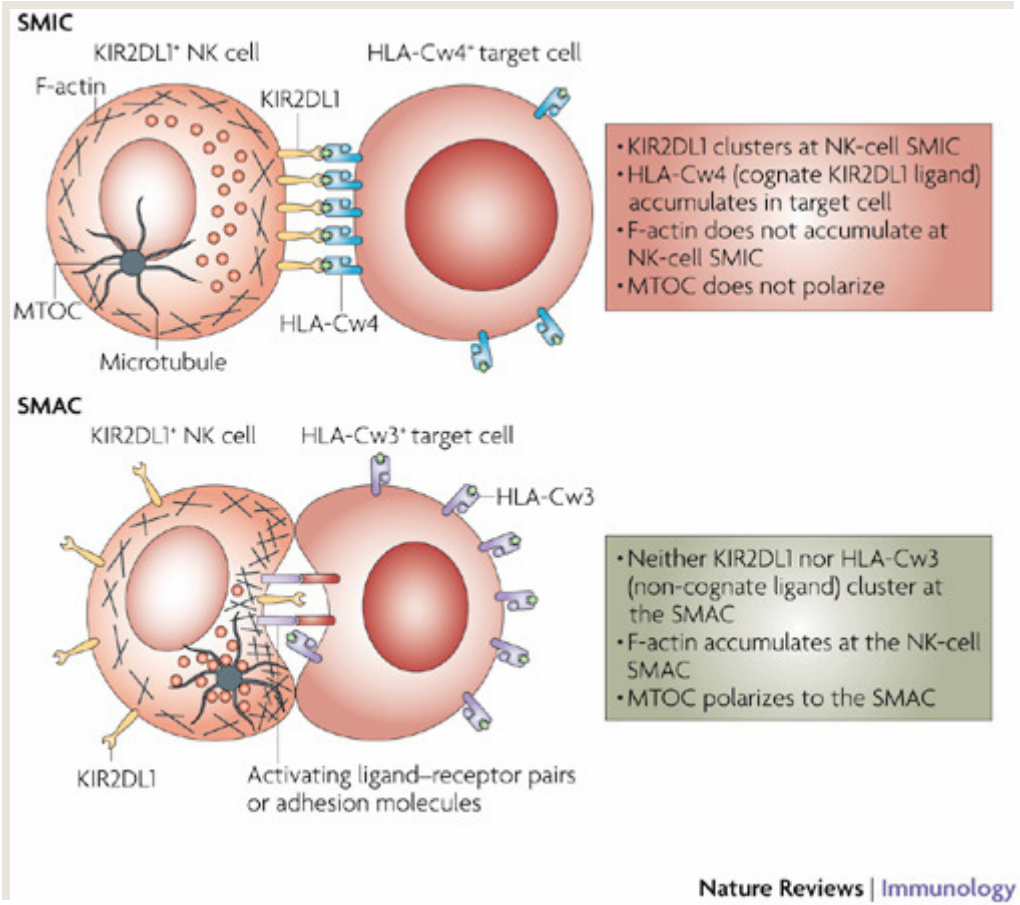
Formación de la SI entre Tc y célula blanco



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

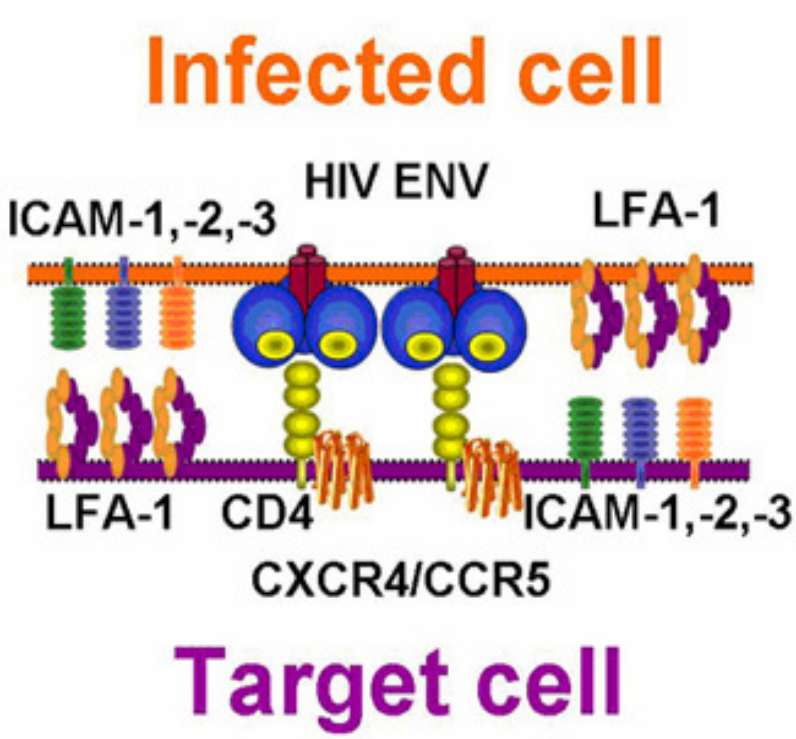
Formación de la SI entre célula NK y célula blanco

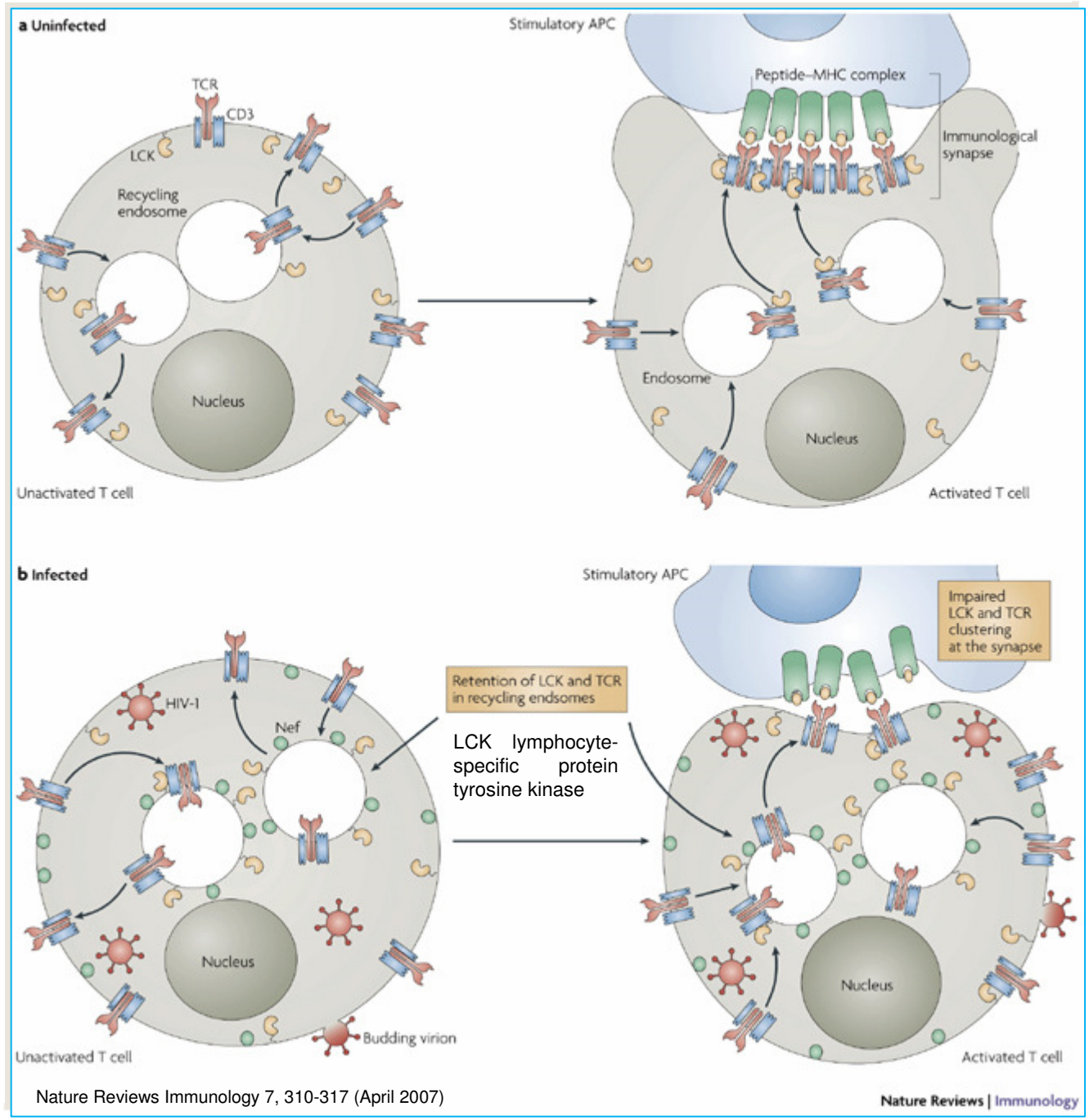




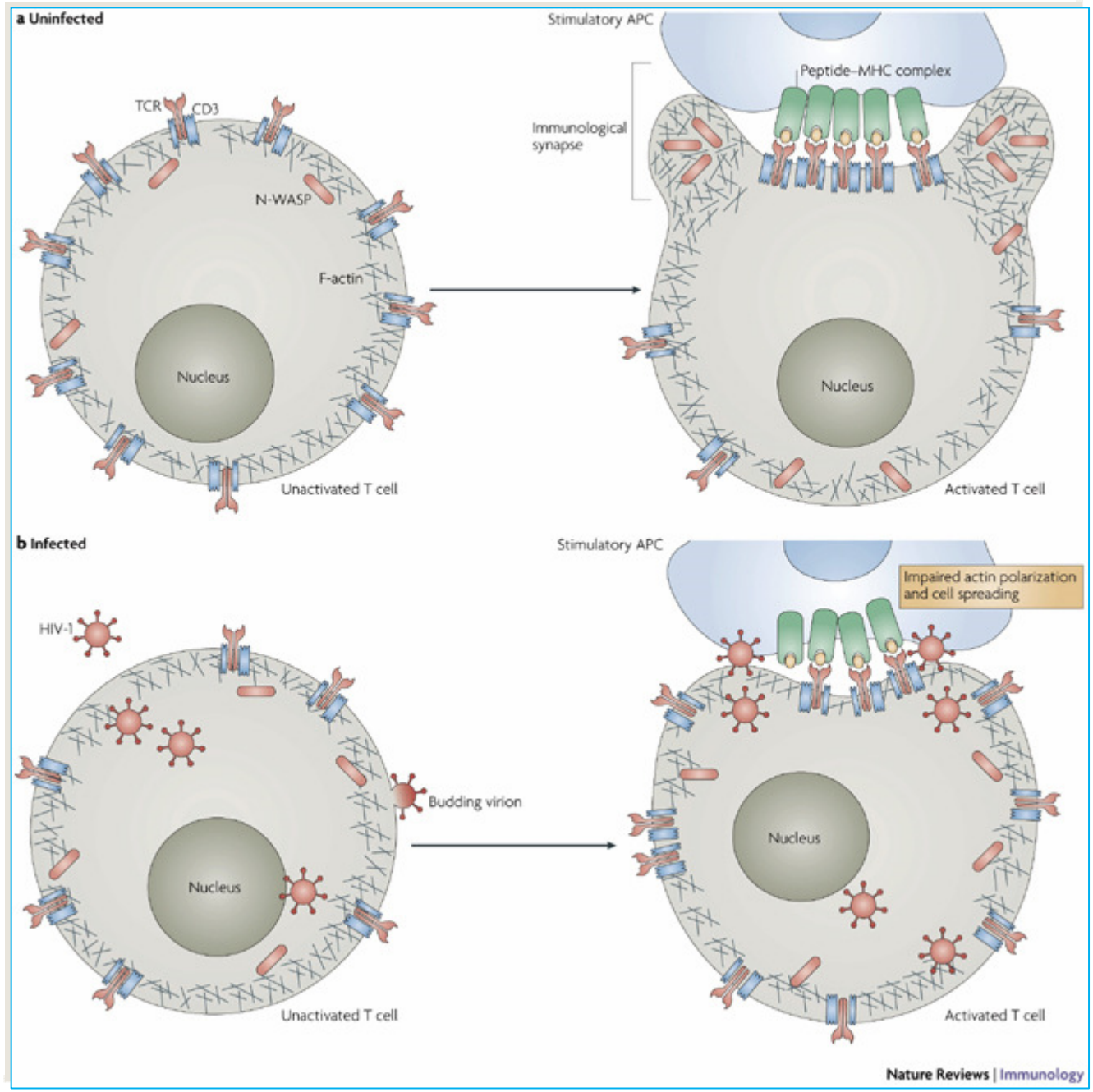
Nature Reviews Immunology 8, 713-725 (September 2008)

Sinapsis virológica





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


a Uninfected
Stimulatory APC
Peptide–MHC complex
Immunological synapse
TCR
CD3
N-WASP
F-actin
Nucleus
Unactivated T cell
Nucleus
Activated T cell
b Infected
Stimulatory APC
Impaired actin polarization and cell spreading
HIV-1
Budding virion
Nucleus
Unactivated T cell
Nucleus
Activated T cell
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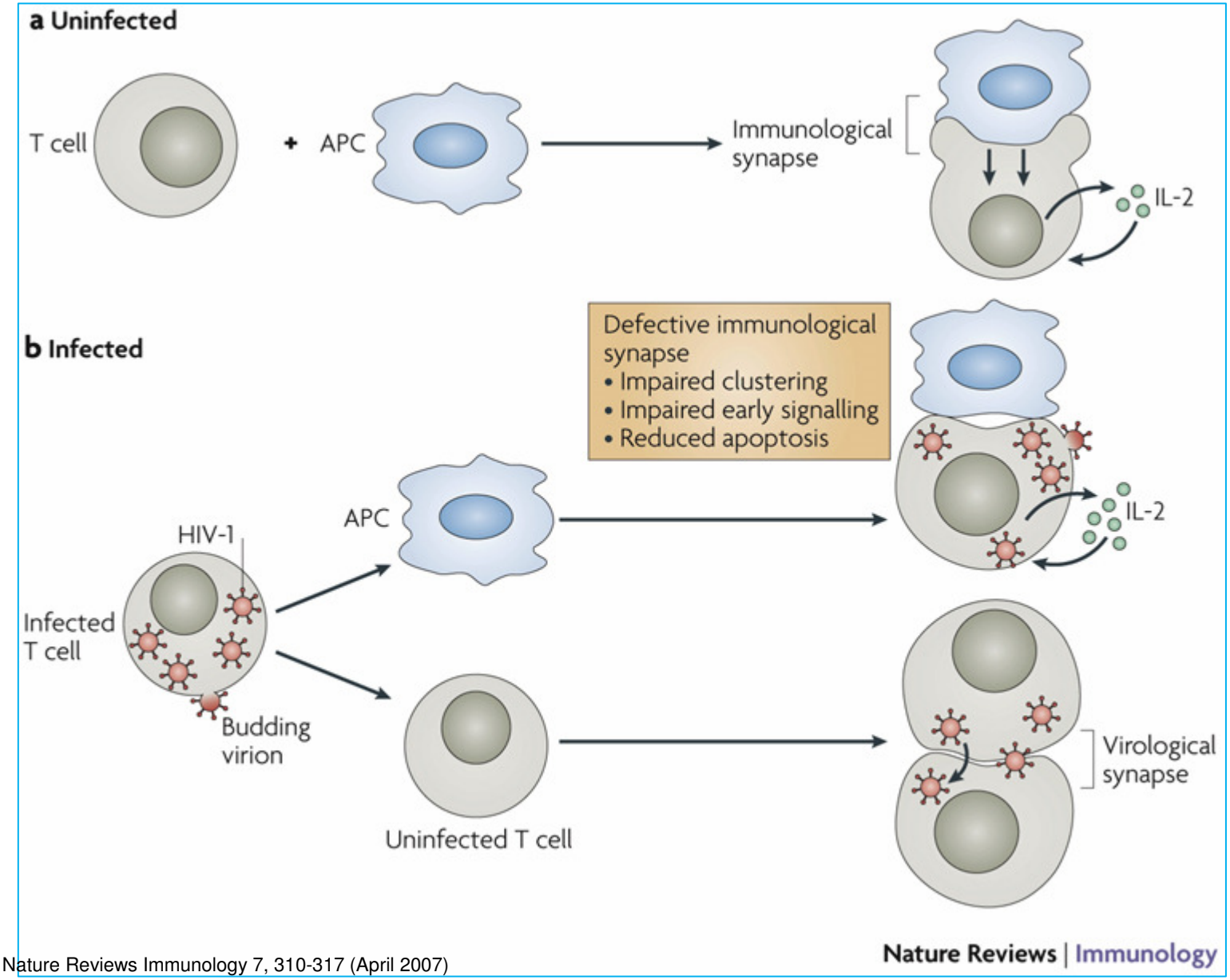
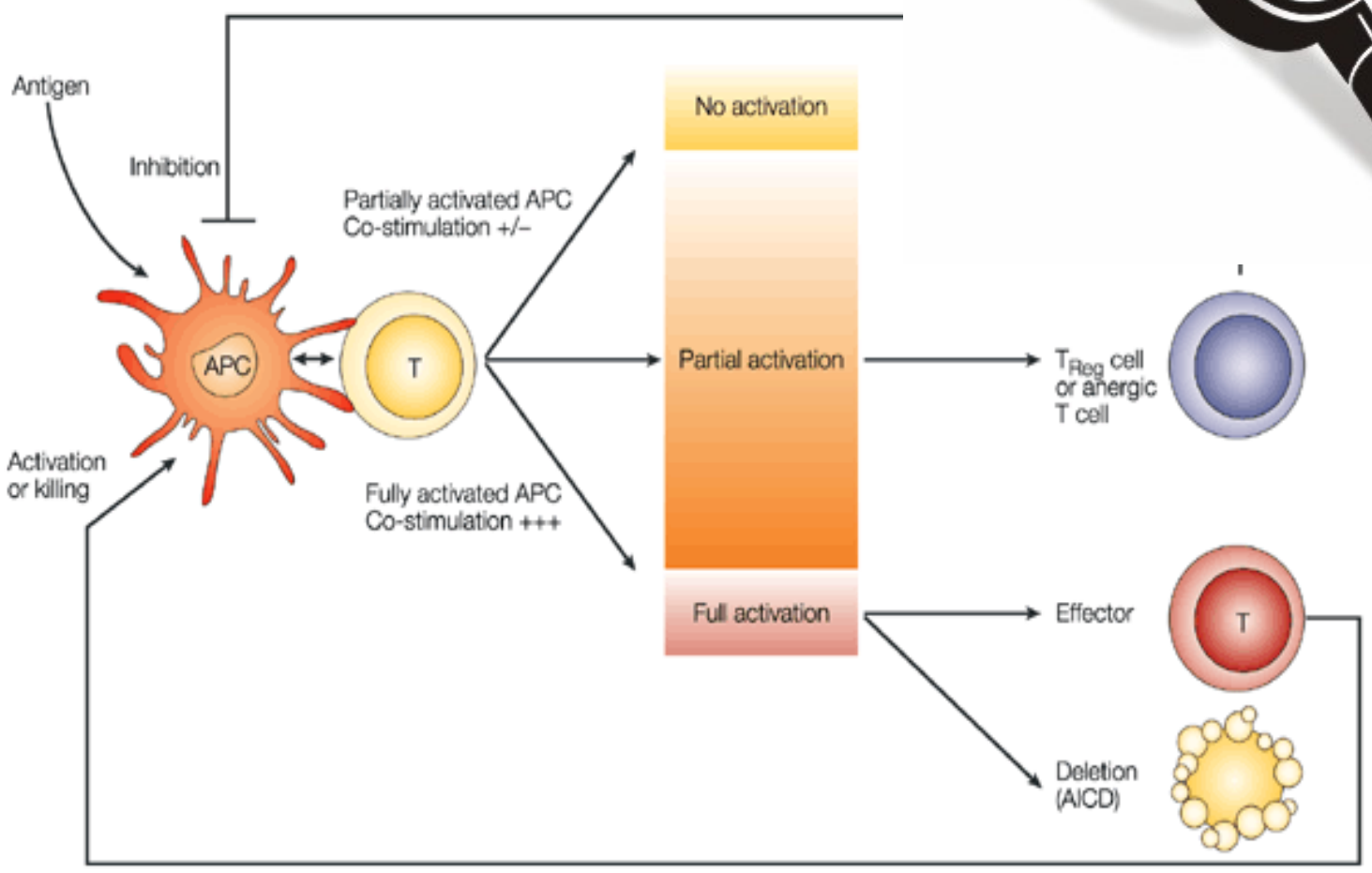


Nature Reviews Immunology 7, 310-317 (April 2007)

CONCLUSIÓN


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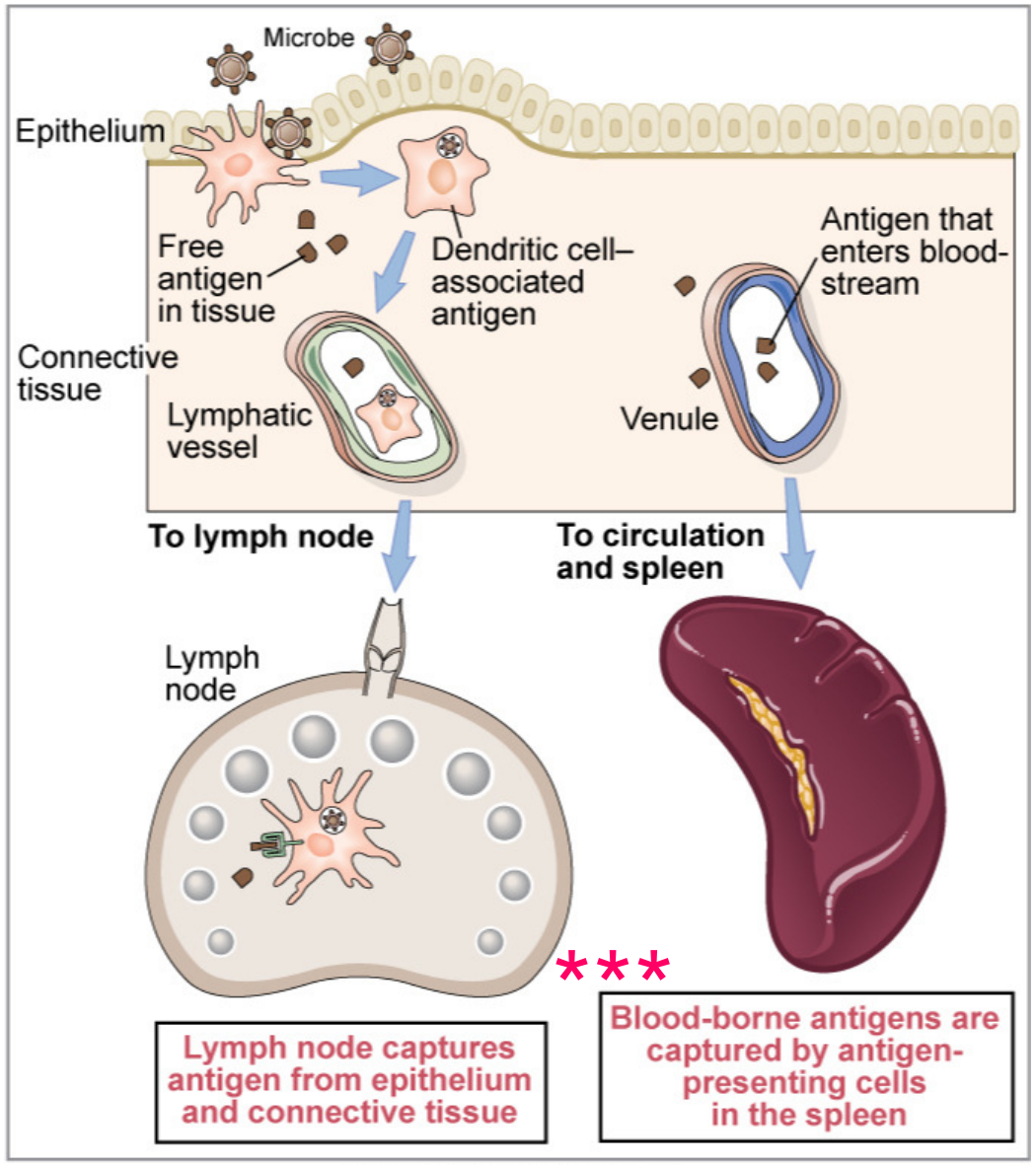
Captura y distribución del antígeno



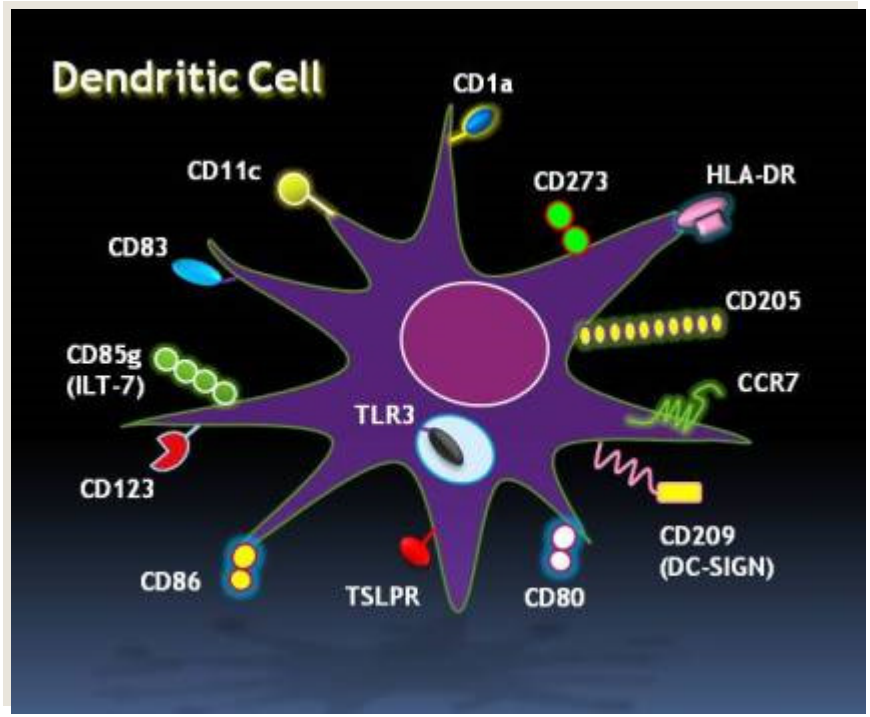
Células Presentadoras de Antígeno (APC)

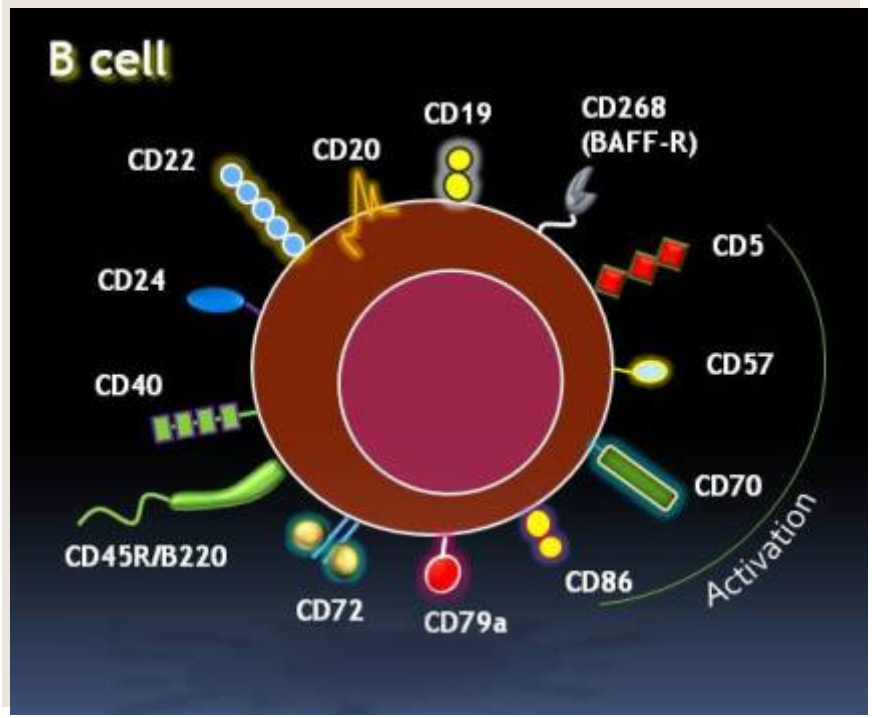
- Son capaces de presentar péptidos en el contexto de MHC II ...
- Llevar la señal coestimuladora necesaria para la activación completa de las células T, lo que conduce a la proliferación y diferenciación....

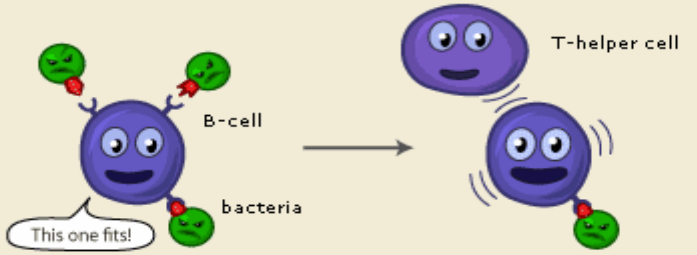
TABLE 8-3 Antigen-presenting cells

Professional antigen-presenting cells
Dendritic cells (several types)
Macrophages
B cells

Table 8-3
Kuby IMMUNOLOGY, Sixth Edition

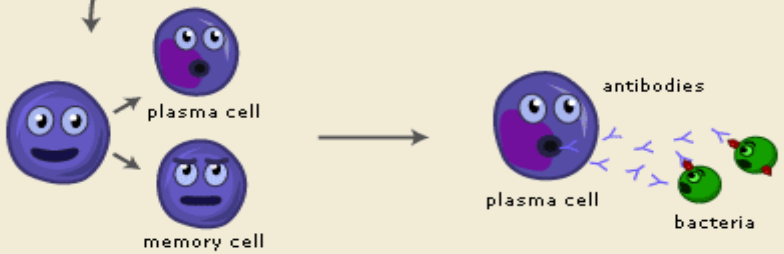

Dendritic Cell
CD1a
CD11c
CD273
HLA-DR
CD83
CD205
CD85g
(ILT-7)
CCR7
TLR3
CD123
CD209
(DC-SIGN)
CD86
TSLPR
CD80


B cell
CD19
CD268
(BAFF-R)
CD22
CD20
CD5
CD24
CD57
CD40
CD70
CD45R/B220
CD86
Activation
CD72
CD79a



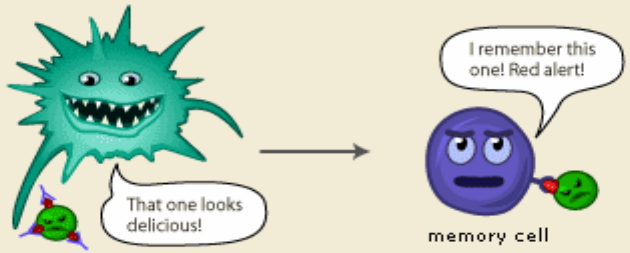
1.
The B-cell finds an antigen which matches its receptors.

2.
It waits until it is activated by a T-helper cell.



3.
Then the B-cell divides to produce plasma and memory cells.

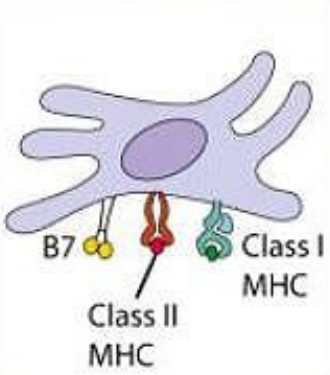
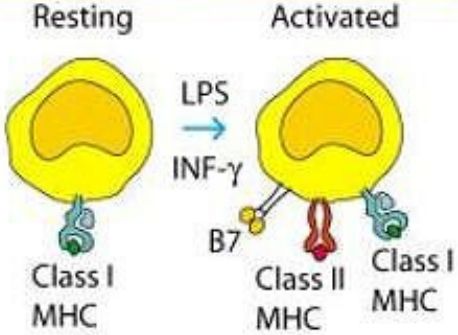
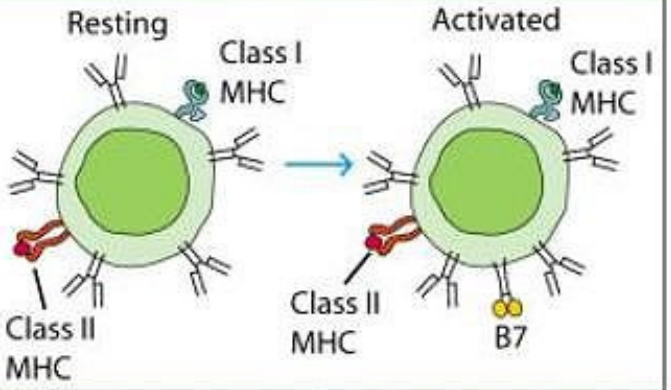
4.
Plasma cells produce antibodies that attach to the current type of invader.



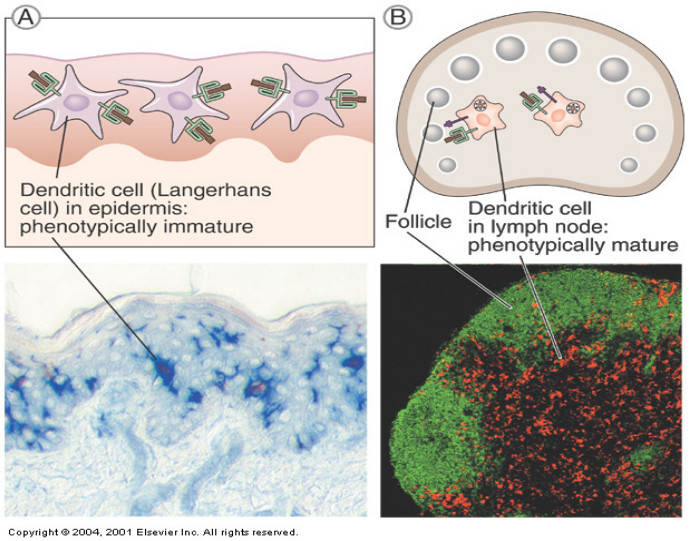
5.
"Eater cells," prefer intruders marked with antibodies and "eats" loads of them.

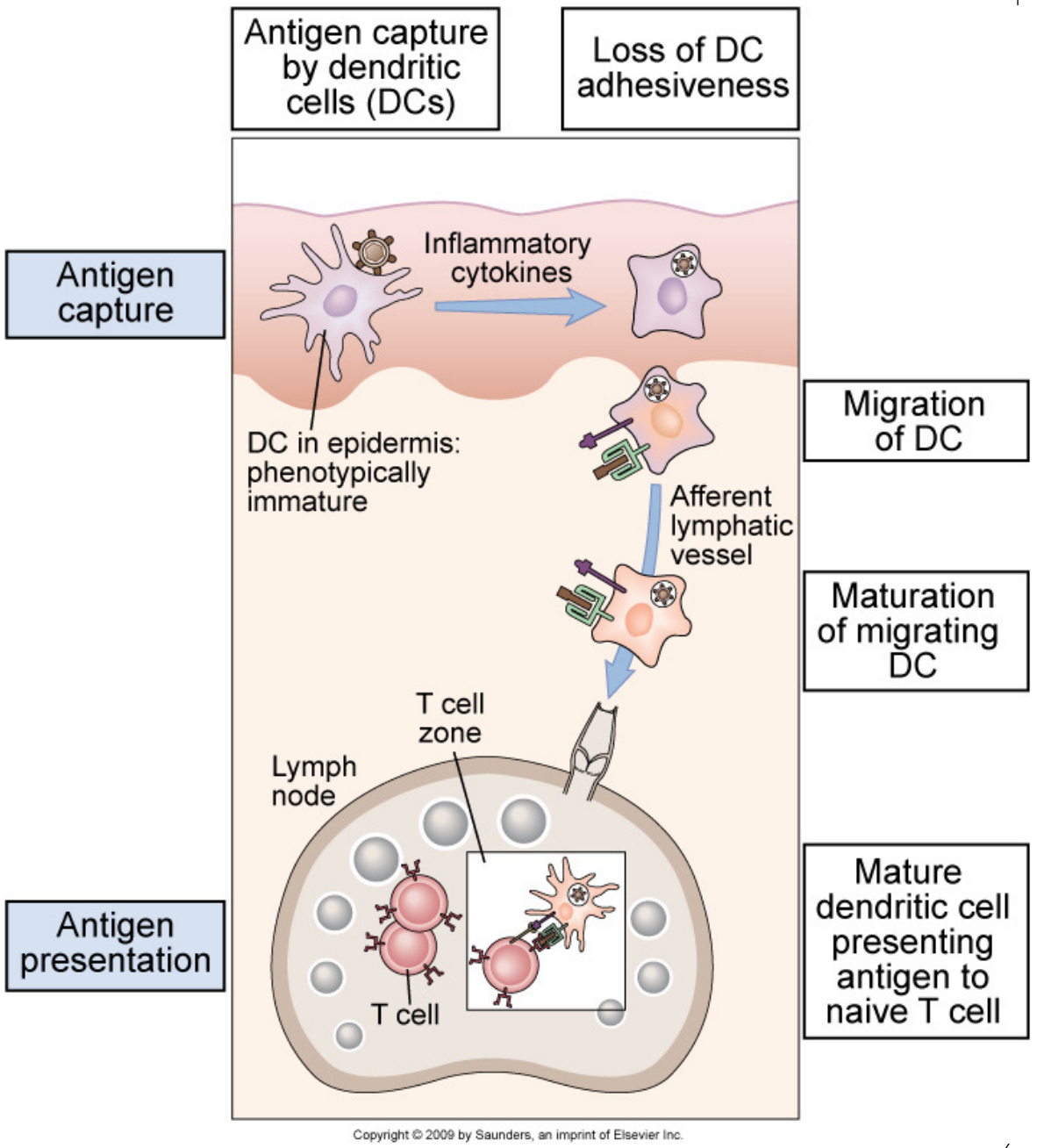
6.
If the same intruder invades again, memory cells help to activate the immune system to activate much faster

Propiedades de las APC

	Dendritic cell	Macrophage		B Lymphocyte	
					
Antigen uptake	Endocytosis phagocytosis (by Langerhans cells)	Phagocytosis	Phagocytosis	Receptor-mediated endocytosis	Receptor-mediated endocytosis

Células Dendríticas





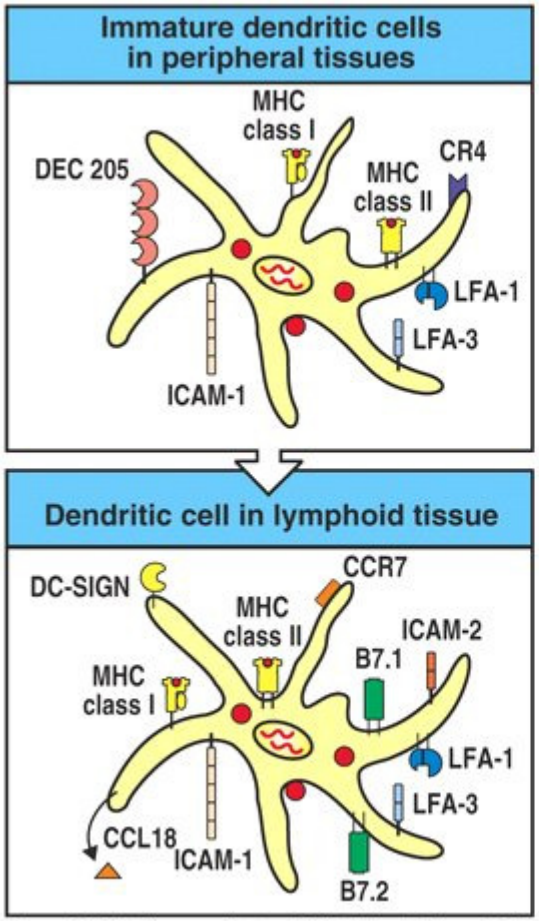
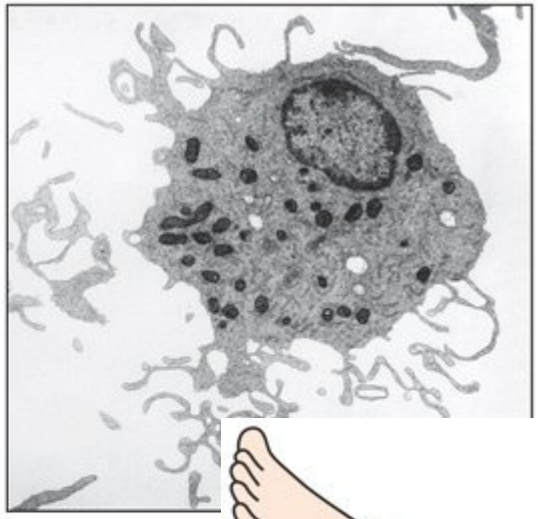


Figure 6-12 The Immune System, 2/e (© Garland Science 2005)



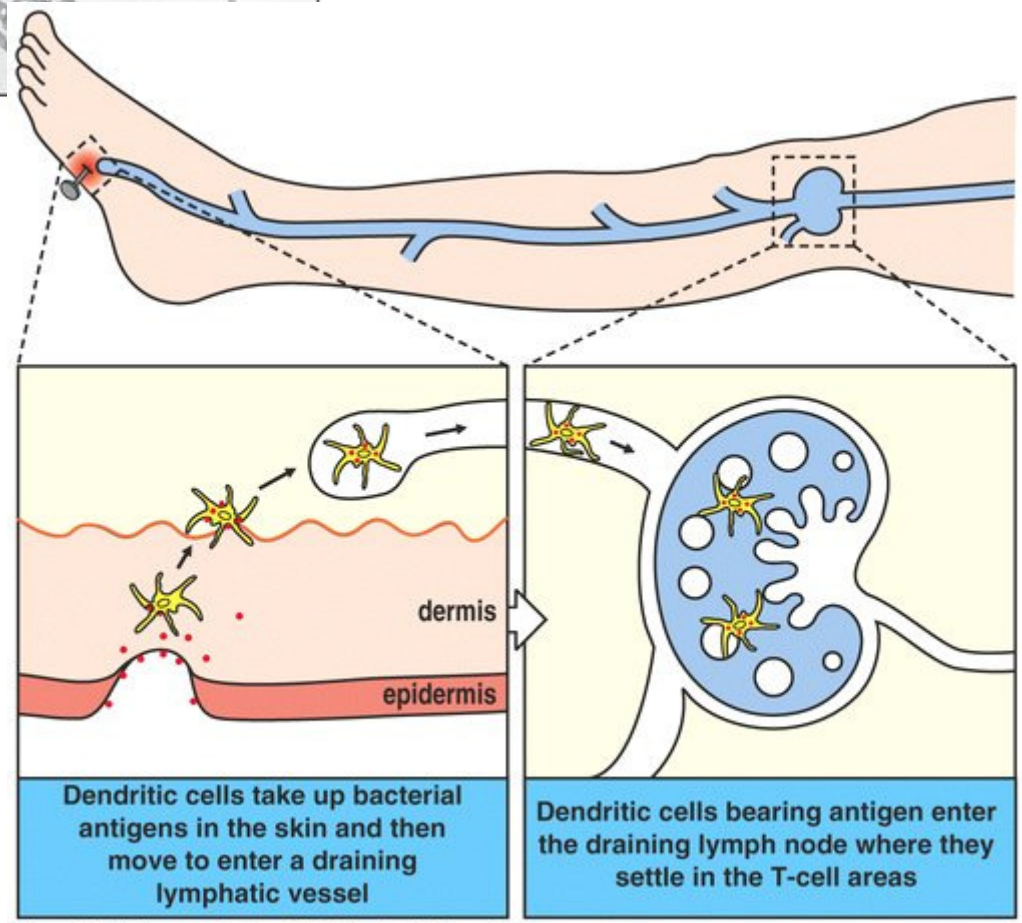
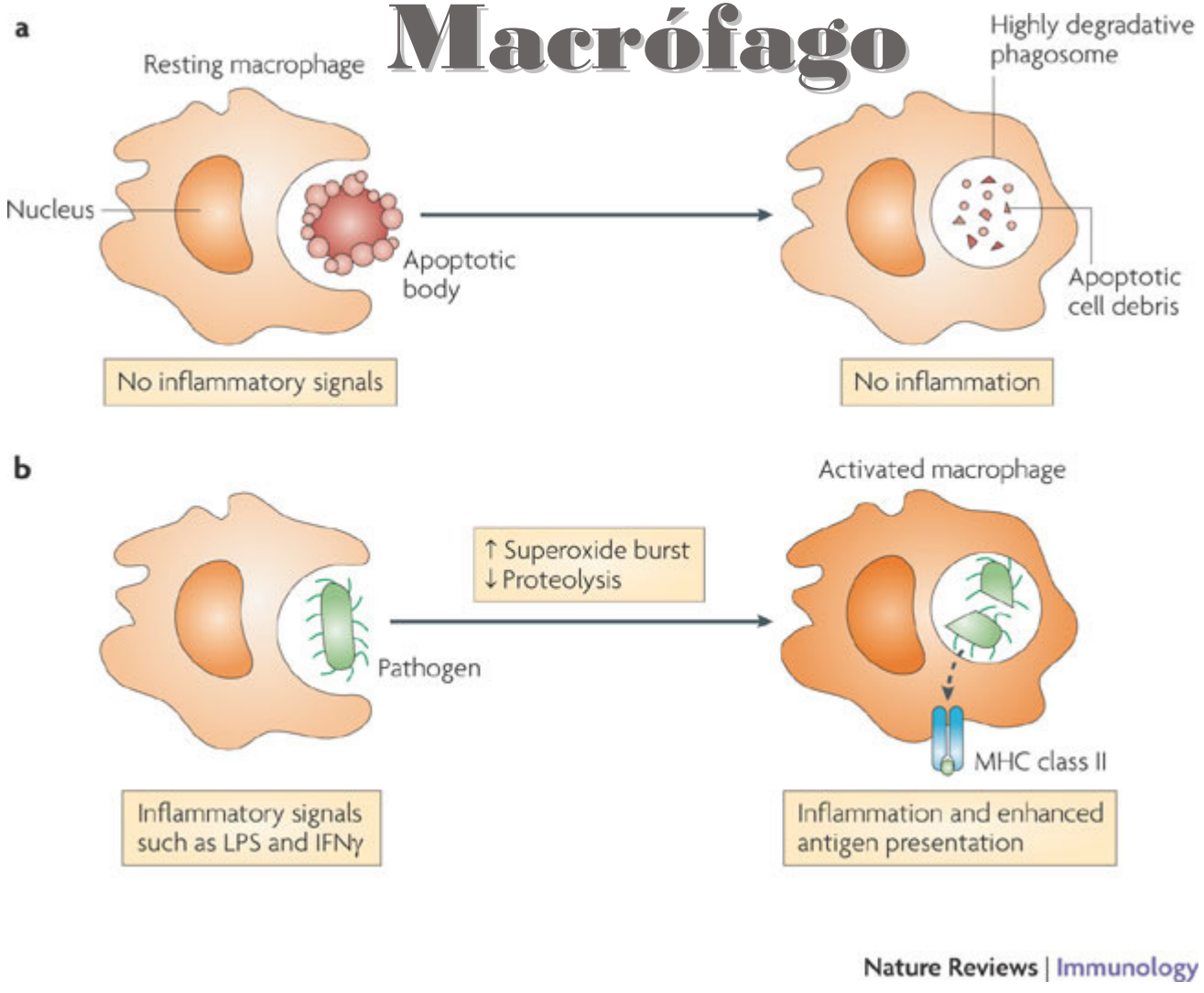


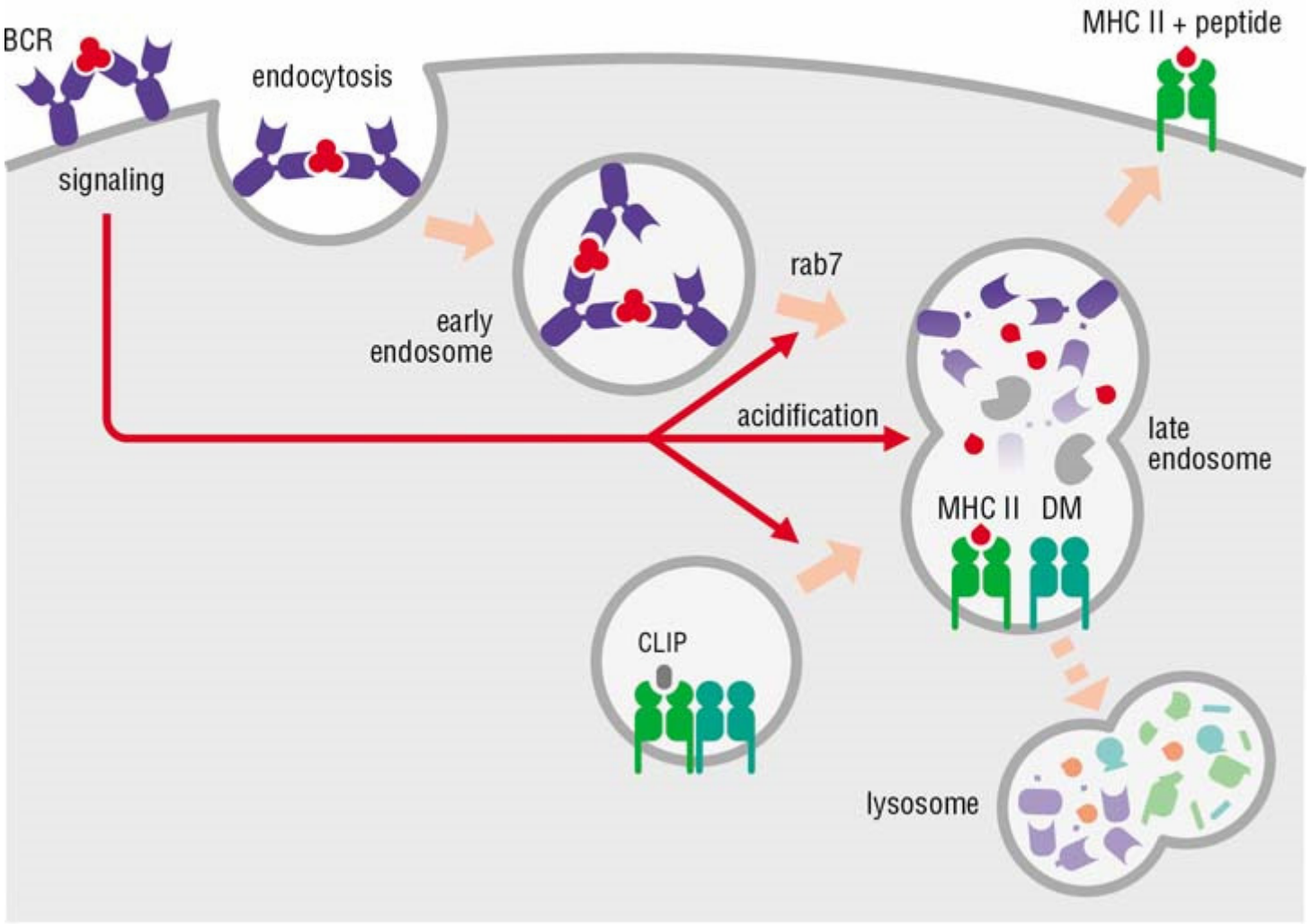
Figure 6-1 The Immune System, 2/e (© Garland Science 2005)

Macrófago

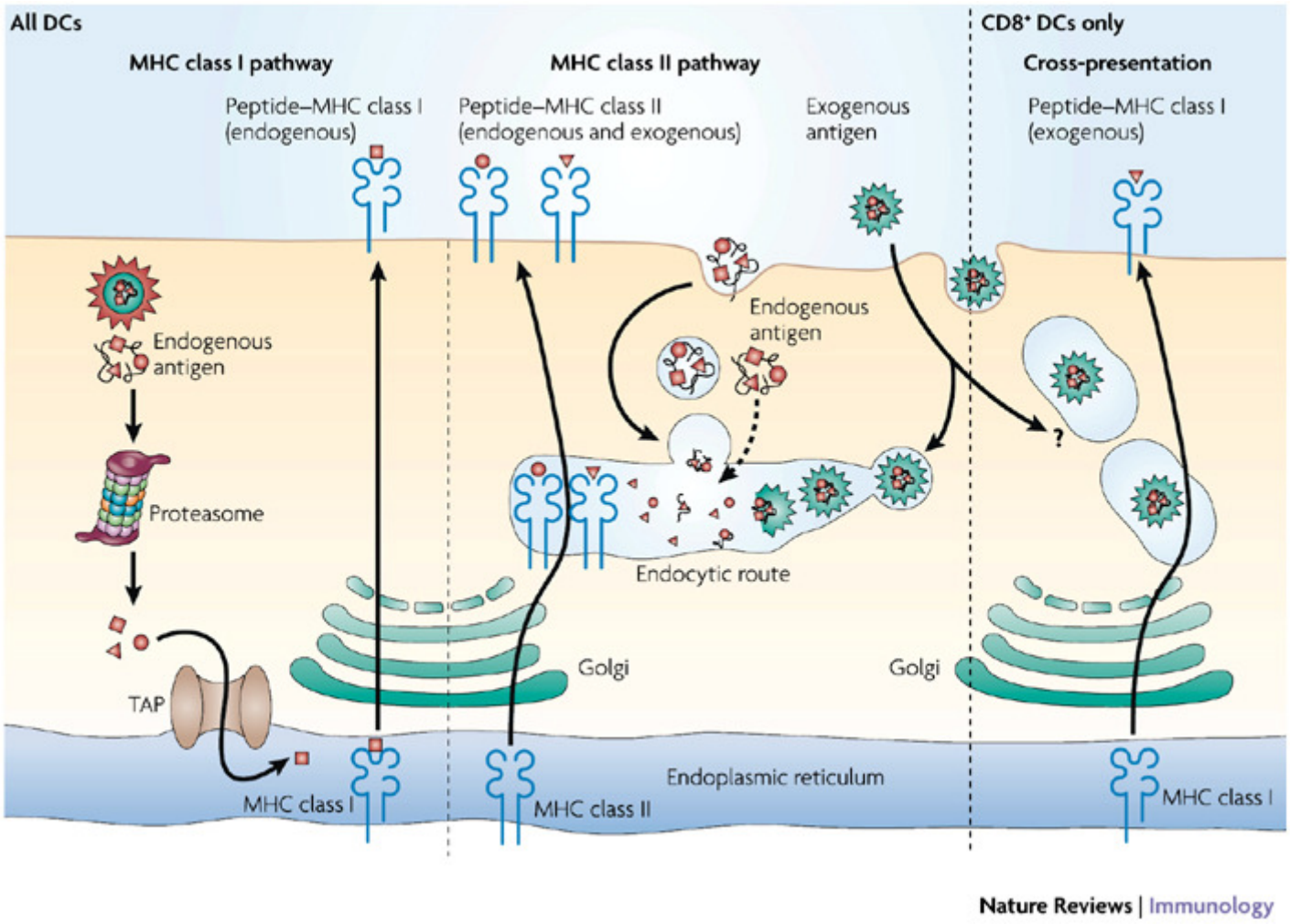


Nature Reviews Immunology 9, 594-600 (August 2009)

El linfocito B como APC

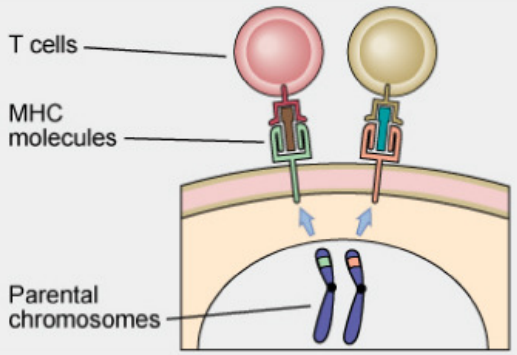
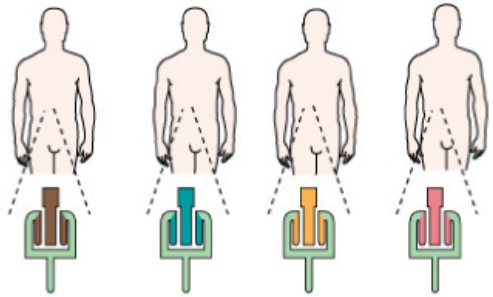
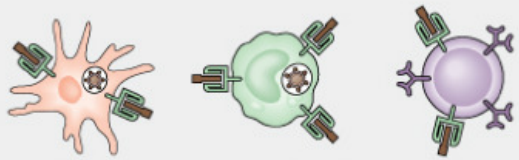
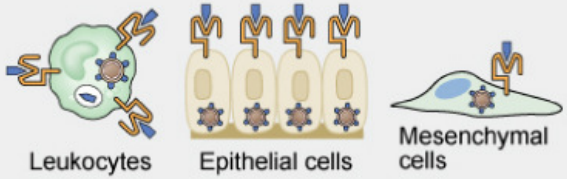


Vías de presentación antigénica

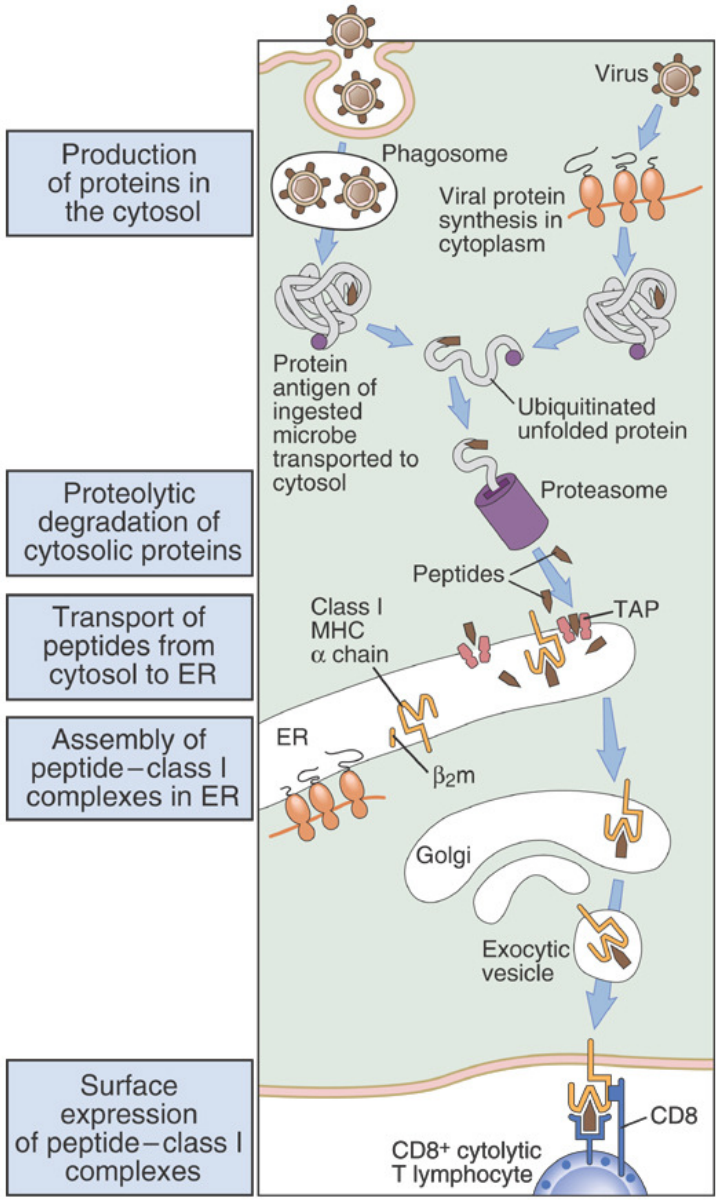


Nature Reviews Immunology **7**, 543-555 (July 2007)

Propiedades y Funciones del MHC

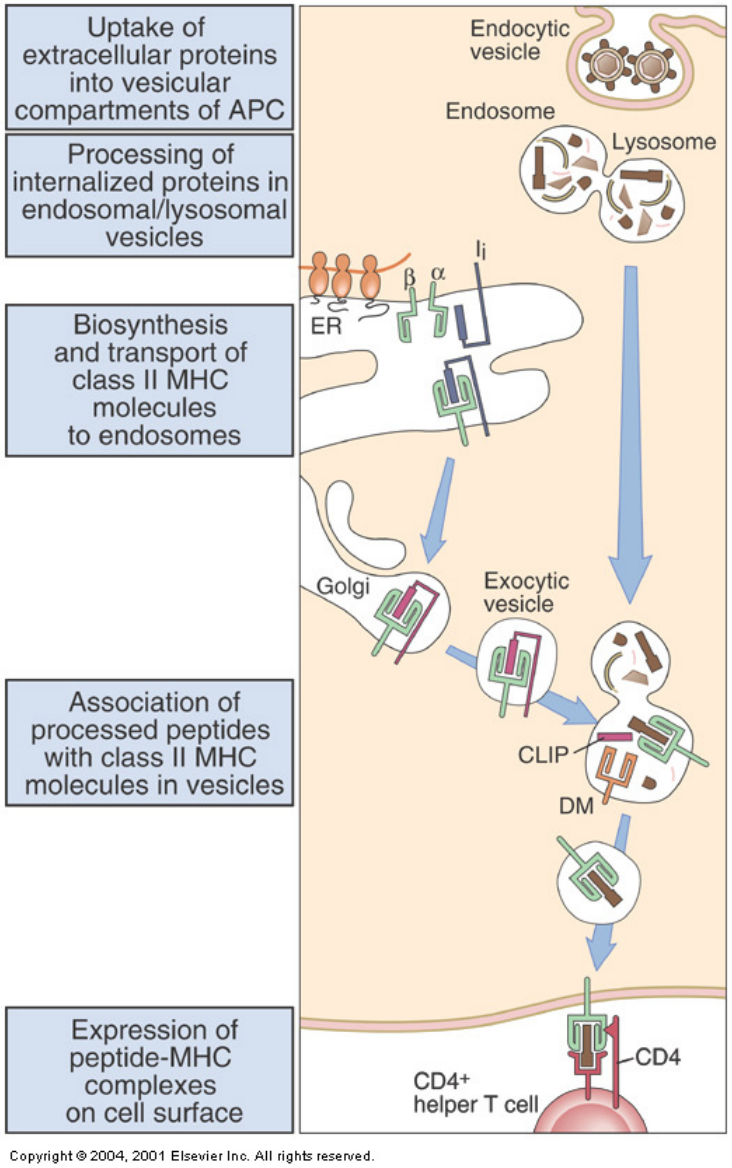
Feature	Significance	
Codominant expression: Both parental alleles of each MHC gene are expressed	Increases number of different MHC molecules that can present peptides to T cells	
Polymorphic genes: Many different alleles are present in the population	Ensures that different individuals are able to present 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

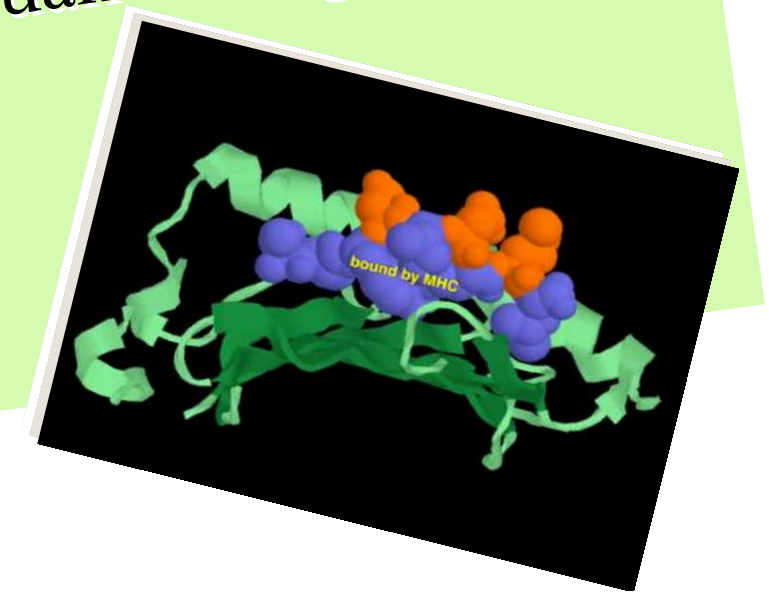
"Carga" del MHC II

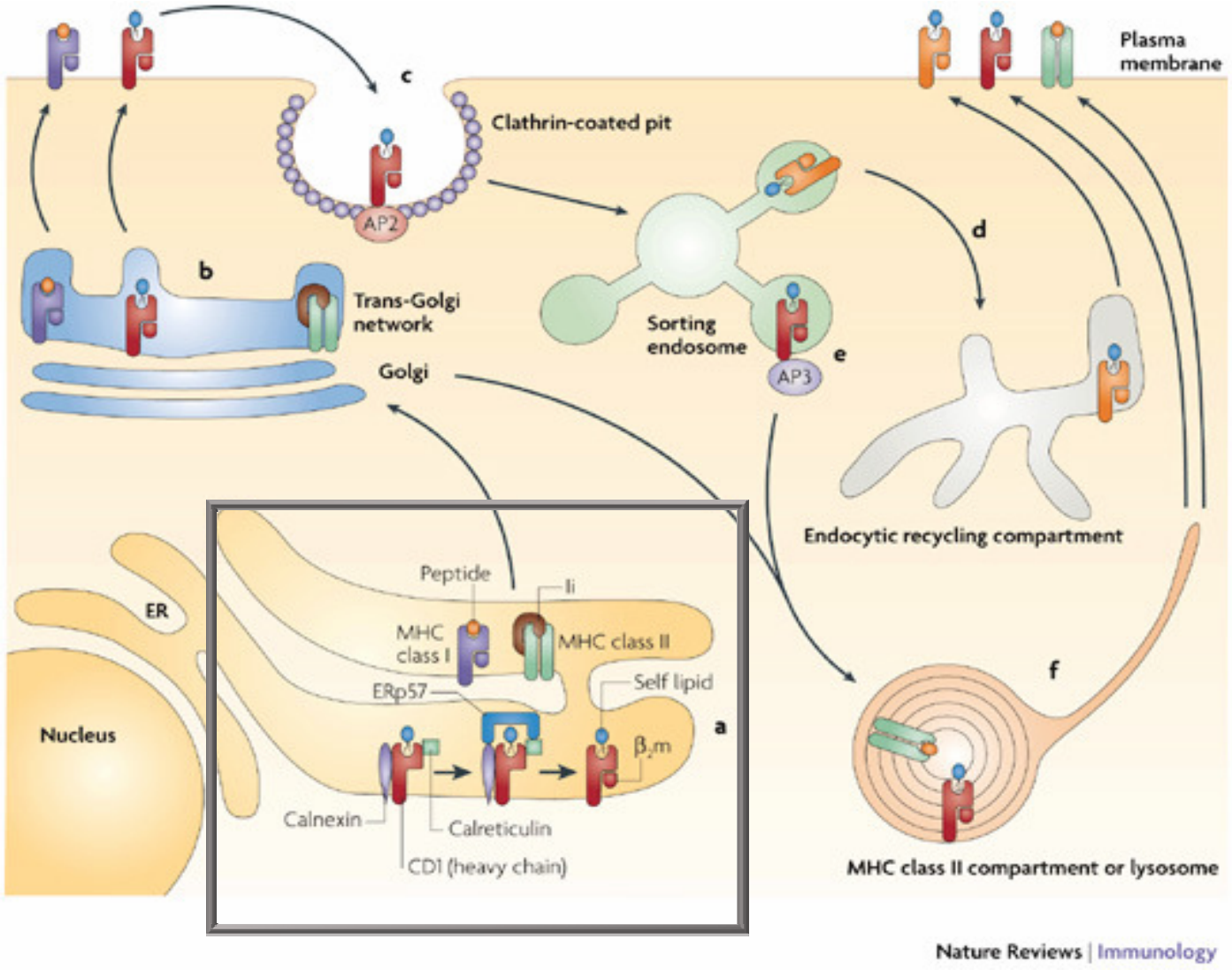


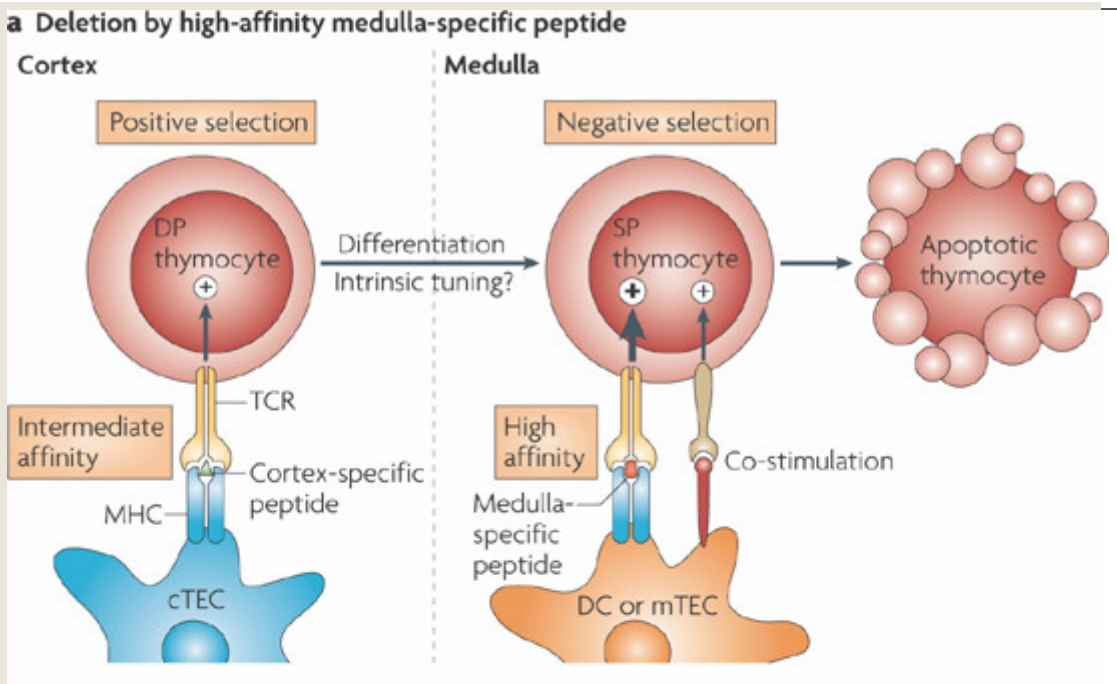
- Endosomal peptides – proteins enter intracellular vesicles and may fuse with lysosome, proteins broken down by proteolytic enzymes to peptides
- APC synthesize MHC II in ER and each MHC II has a sequence called class II invariant chain peptide (CLIP) attached to the invariant chain which binds tightly 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…..

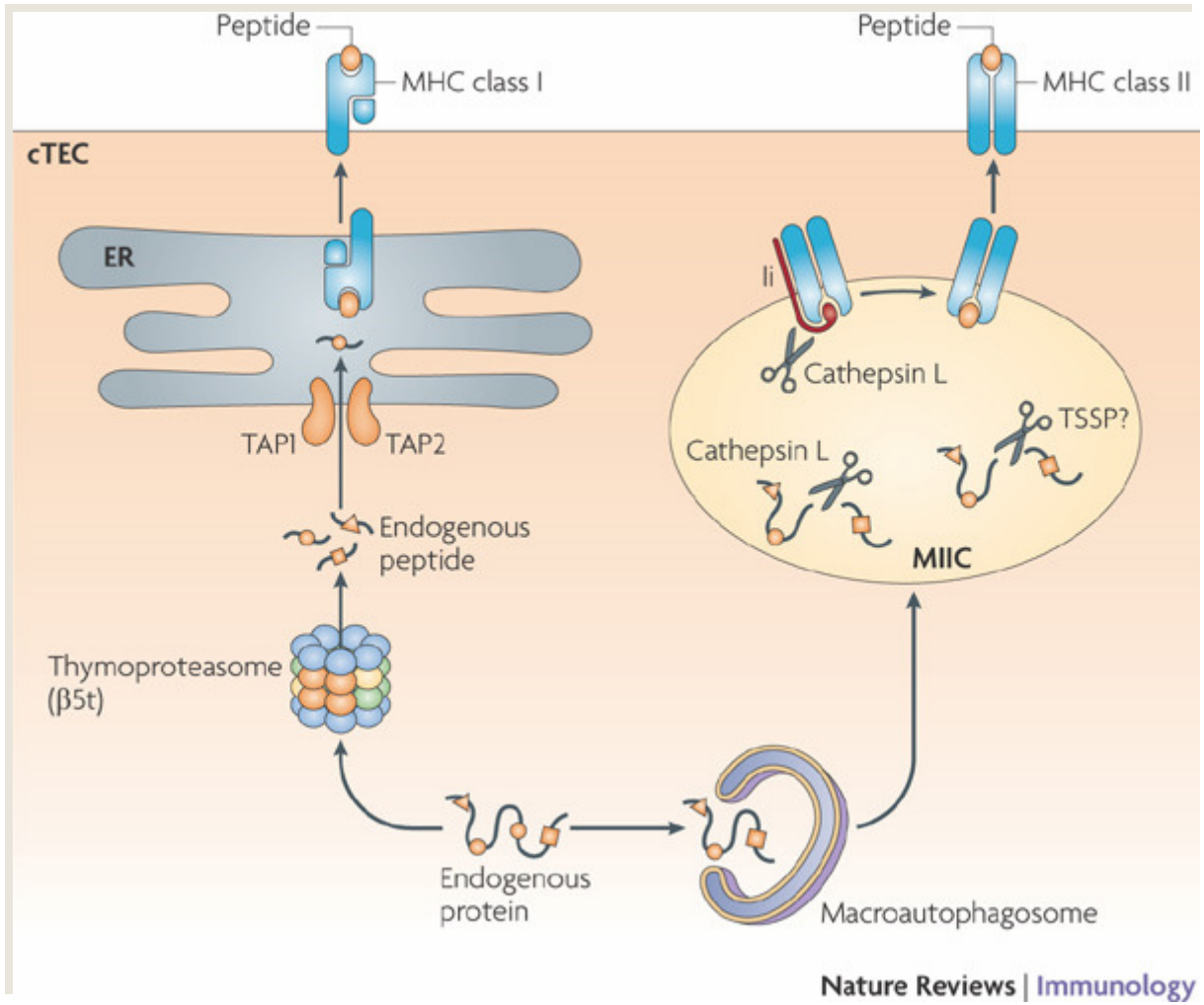



Plasma membrane
c
Clathrin-coated pit
AP2
b
Trans-Golgi network
Golgi
Sorting endosome
AP3
e
d
Endocytic recycling compartment
ER
Nucleus
Peptide
Ii
MHC class I
MHC class II
ERp57
Self lipid
a
β2m
Calnexin
Calreticulin
CD1 (heavy chain)
f
MHC class II compartment or lysosome
Nature Reviews | Immunology



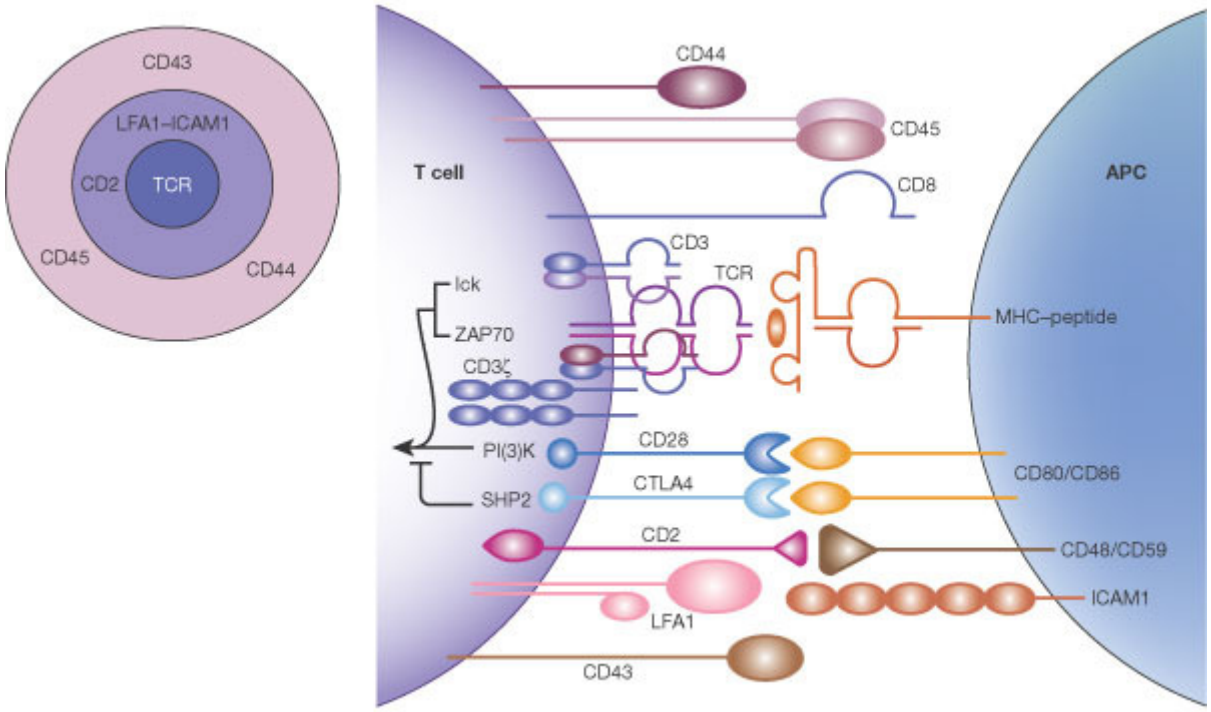
Presentación antigénica durante la ontogenia T....

Nature Reviews Immunology 9, 833-844 (December 2009)

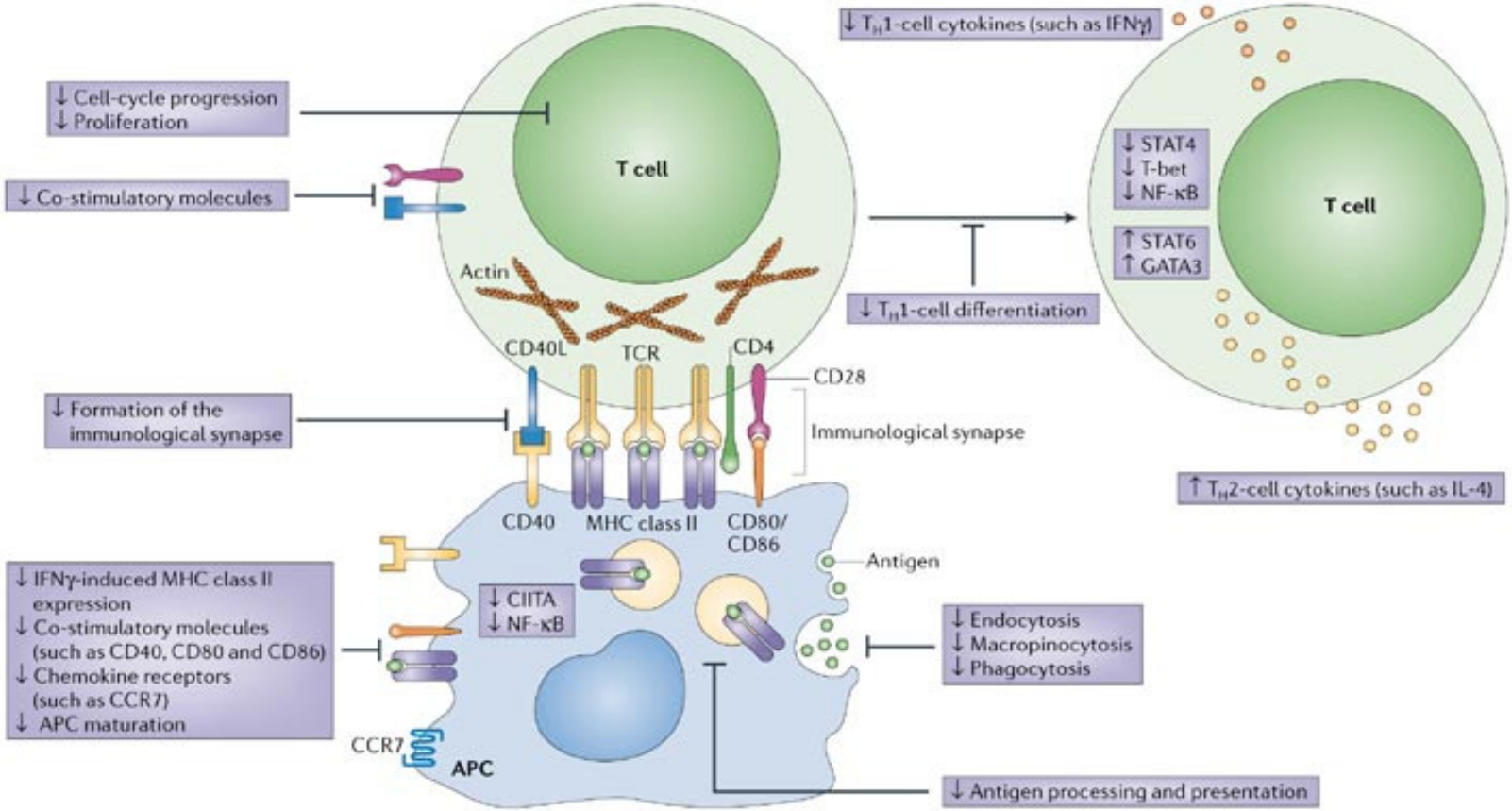

Peptide
MHC class I
Peptide
MHC class II
cTEC
ER
Ii
Cathepsin L
TSSP?
Cathepsin L
TAP1
TAP2
Endogenous peptide
MIIC
Thymoproteasome (β5t)
Endogenous protein
Macroautophagosome
Nature Reviews | Immunology


PROCESAMIENTO Y
PRESENTACIÓN ANTIGÉNICA

La sinapsis inmunológica permite la activación celular...



Bloqueo de la presentación antigénica

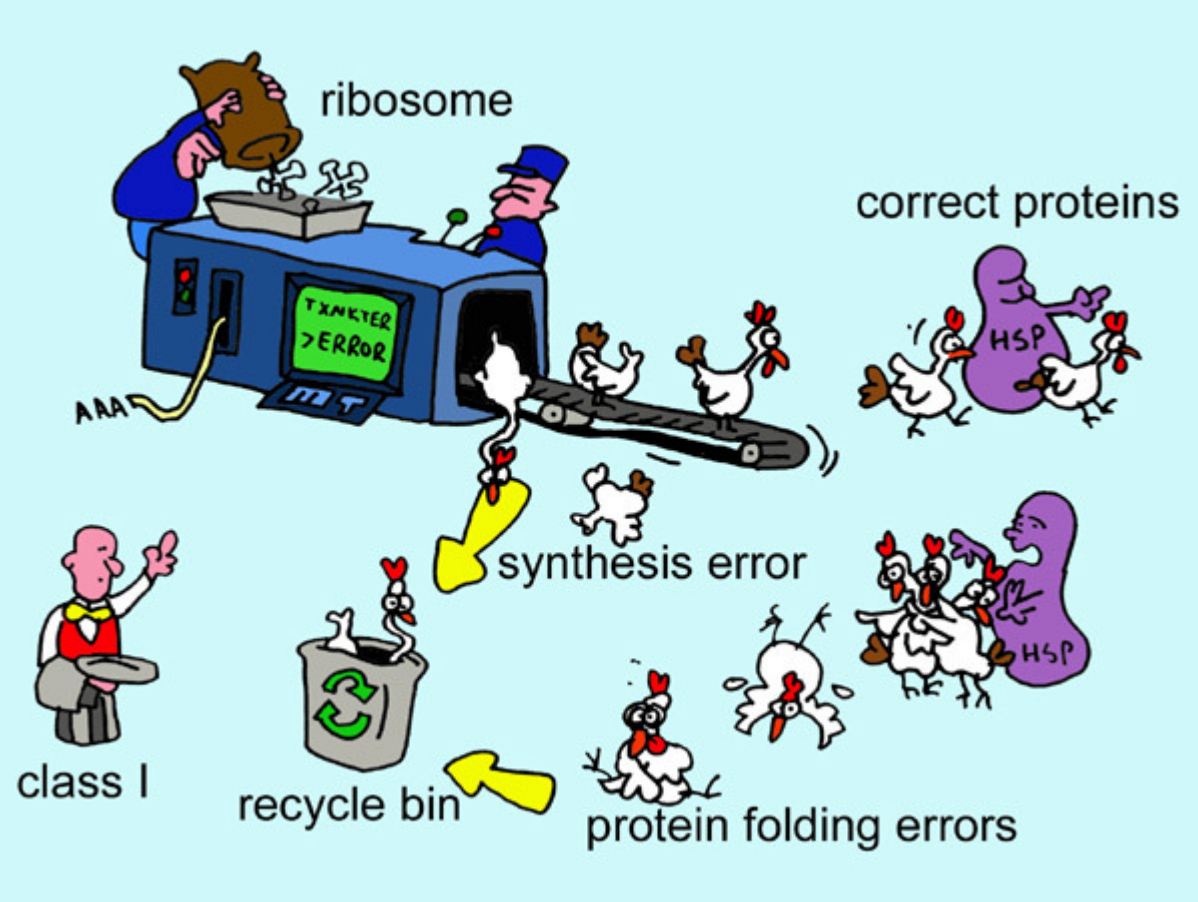


Nature Reviews Immunology **6**, 358-370 (May 2006)

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.

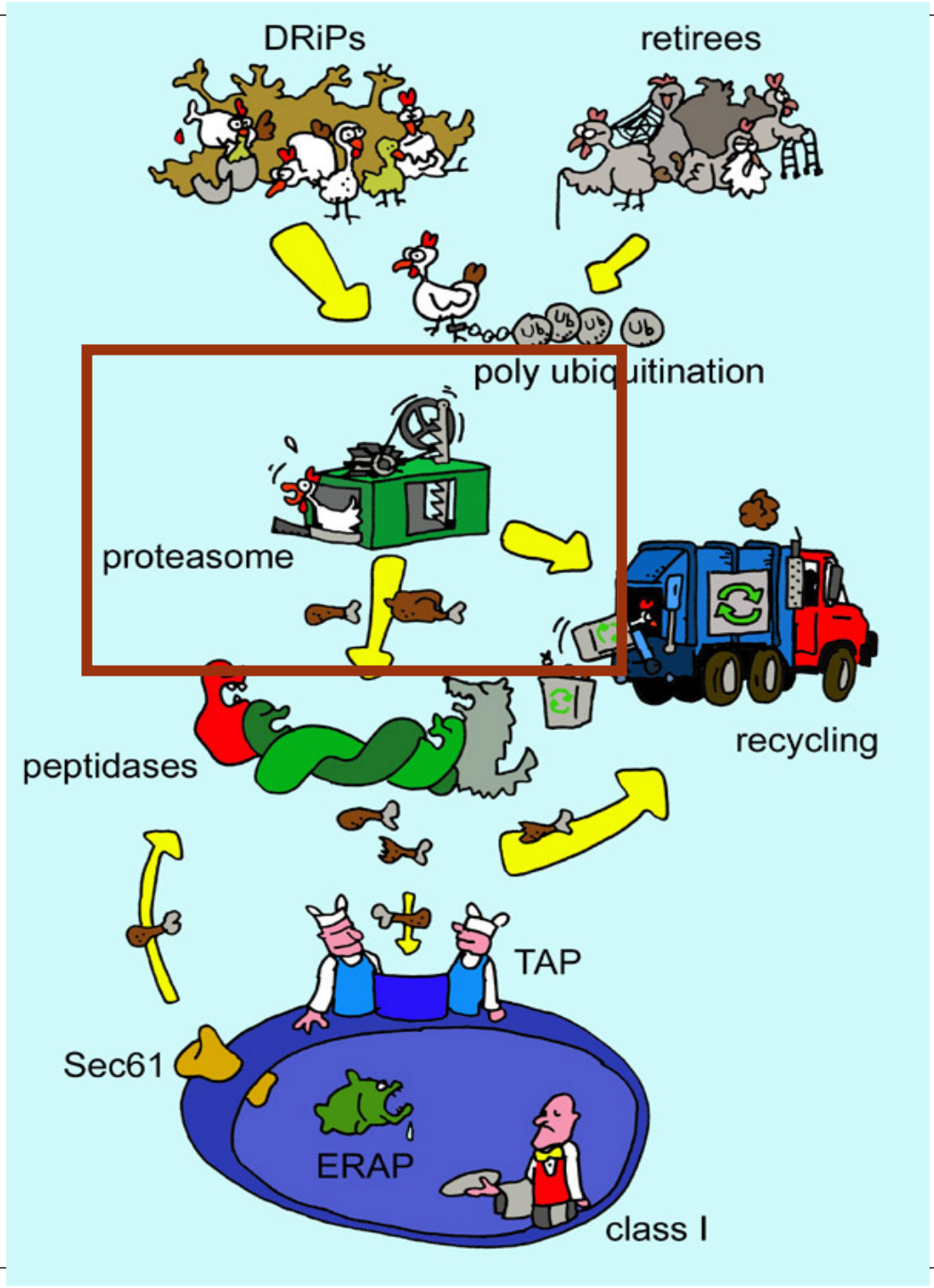
Síntesis de proteínas



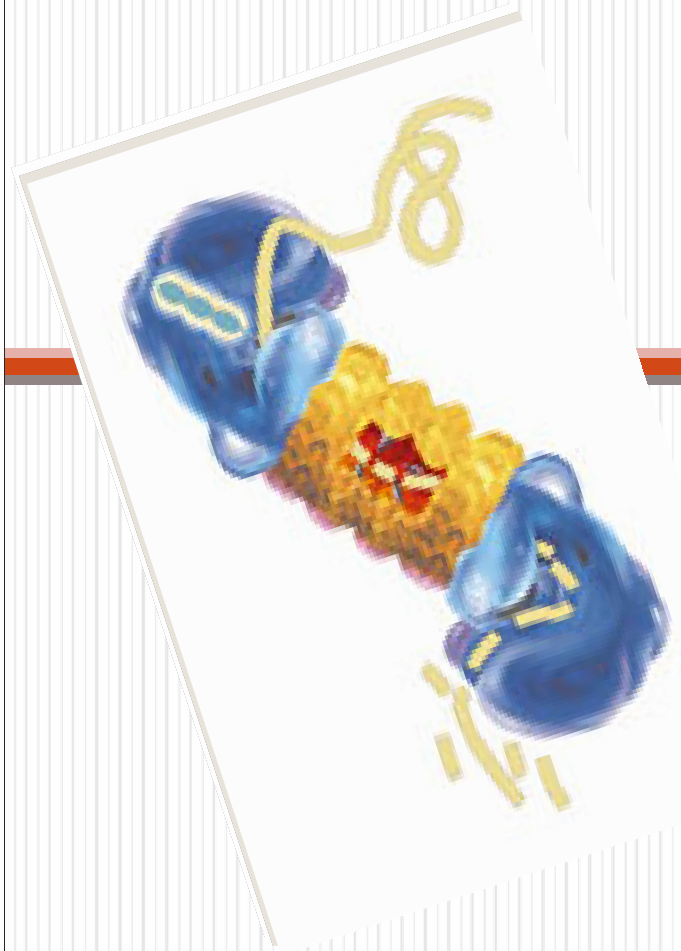
The perils of protein biogenesis. All proteins are made by the ribosome using messenger RNA as a template.

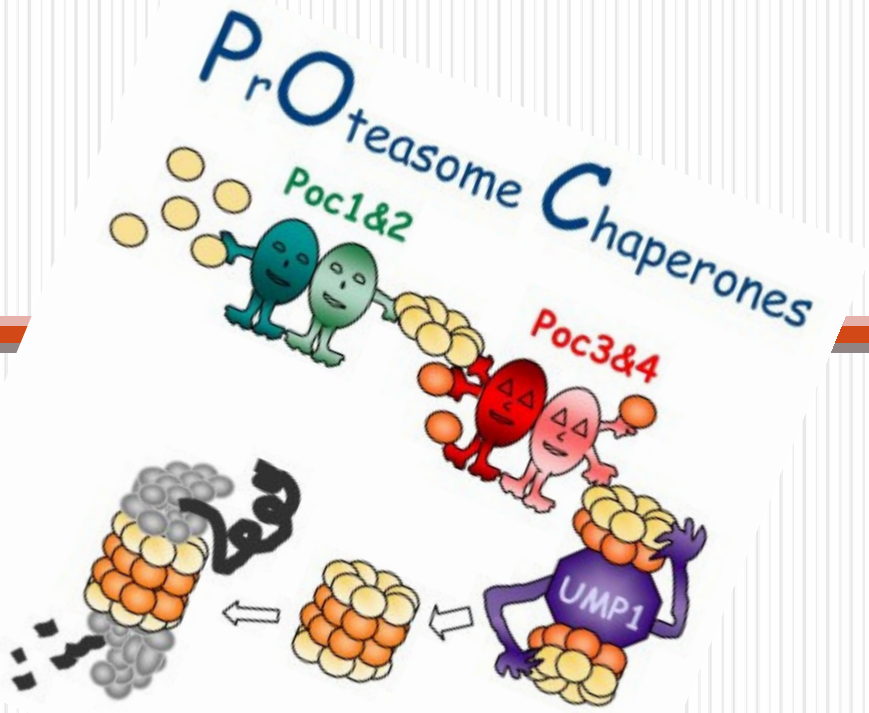
Nascent proteins are frequently stabilized by heat-shock proteins (HSPs), which probably facilitate correct folding and prevent aggregation.

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.

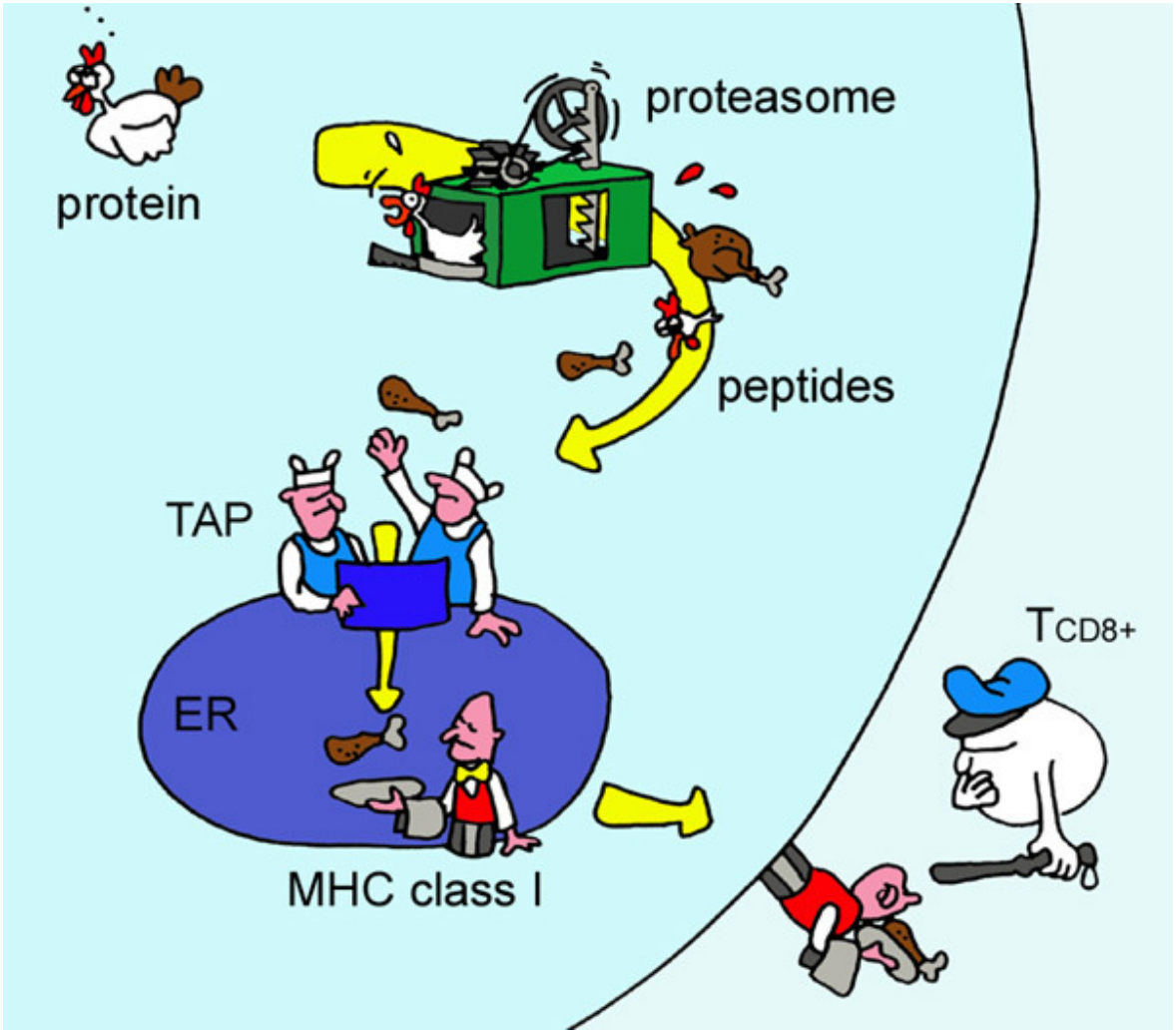


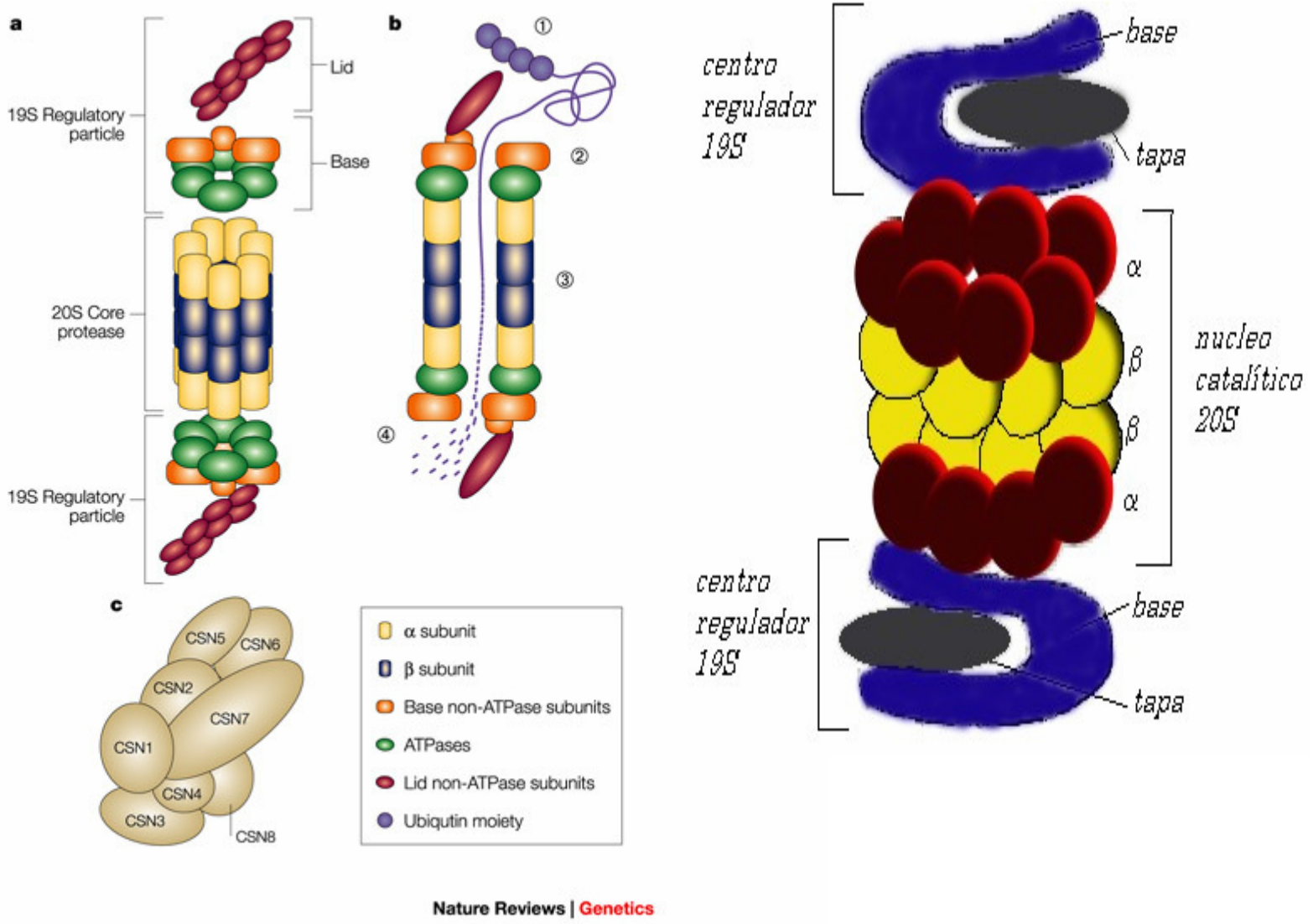
Complexities of MHC class I antigen presentation. Both **defective ribosomal products (DRiPs)** and mature proteins (retirees) are degraded by proteasomes, usually after polyubiquitylation. The proteasome digests proteins into peptides of various lengths. Many peptides are too small for presentation 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.





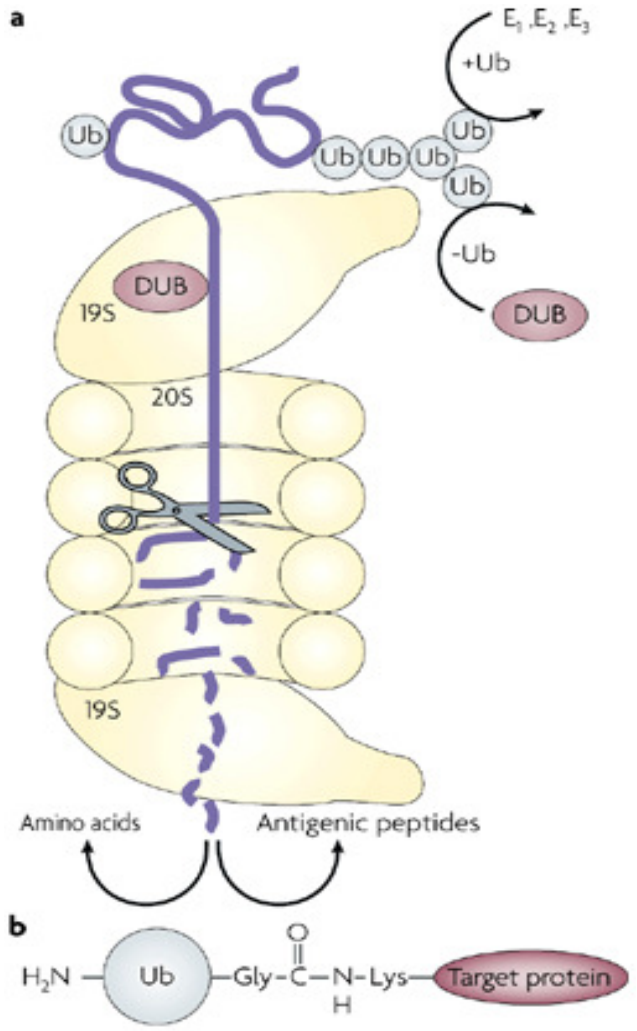
Proteasoma


protein
proteasome
peptides
TAP
ER
MHC class I
TCD8+


a
Lid
19S Regulatory particle
Base
20S Core protease
19S Regulatory particle
b
①
②
③
④
c
CSN5
CSN6
CSN2
CSN7
CSN1
CSN4
CSN3
CSN8
α subunit
β subunit
Base non-ATPase subunits
ATPases
Lid non-ATPase subunits
Ubiqutin moiety
Nature Reviews | Genetics
centro regulador 19S
base
tapa
α
β
β
α
nucleo catalítico 20S
centro regulador 19S
base
tapa

- 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.

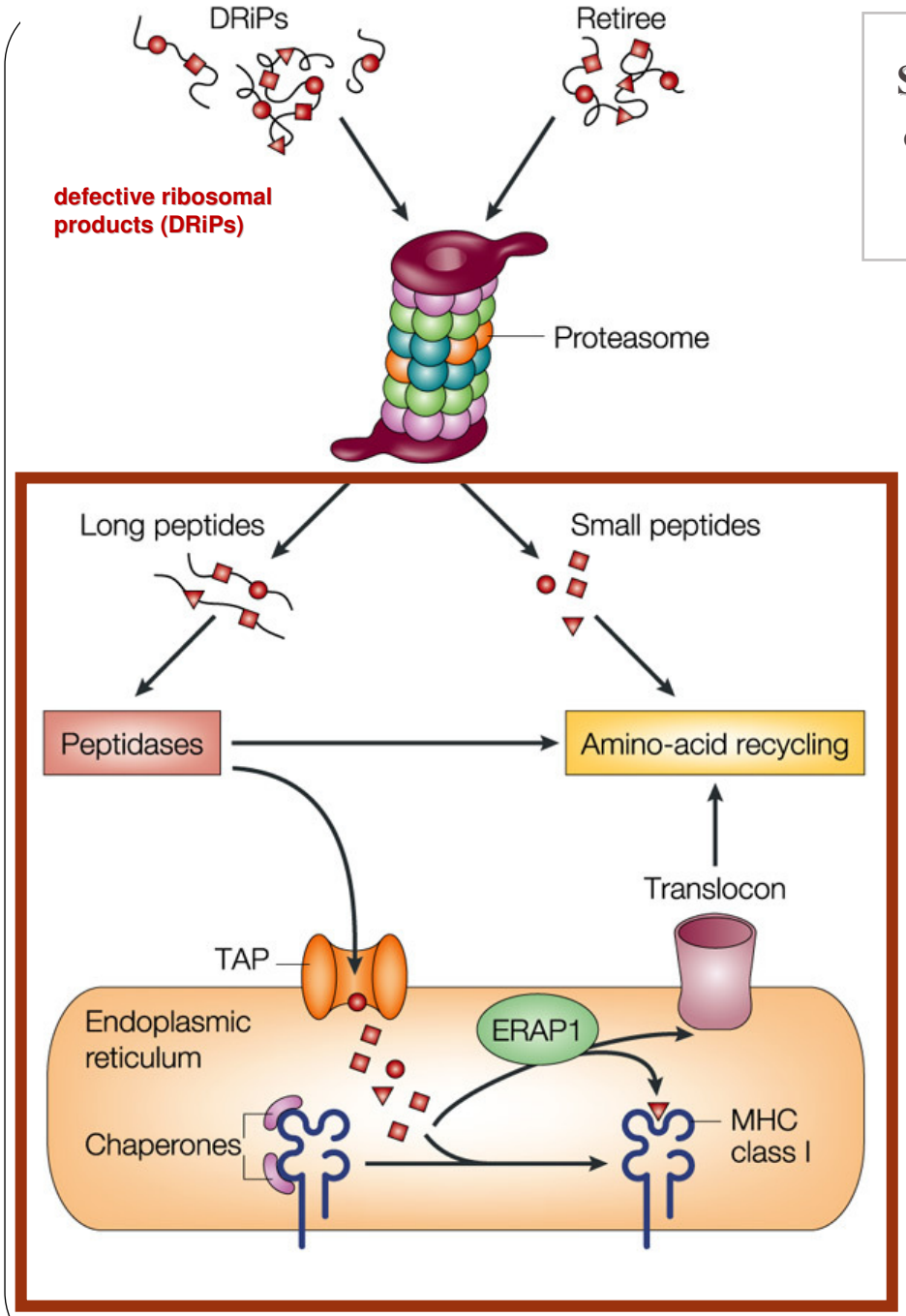
Ubiquitin is commonly found in a linkage through an isopeptide bond to the ε-amino moiety of a lysine residue of the target protein (shown) or to a lysine side chain of another Ub molecule. Alternatively, ubiquitin can be directly linked to the N terminus of a target protein or to the N terminus of another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



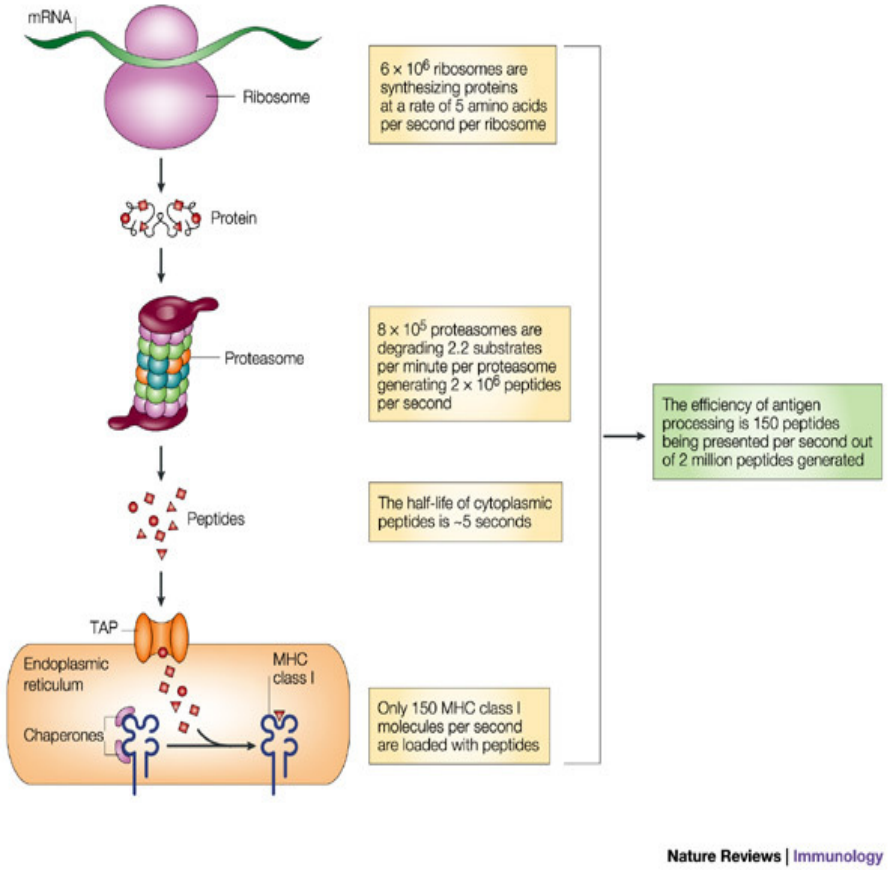
DUB, deubiquitylating enzyme.

Nature Reviews | Cancer

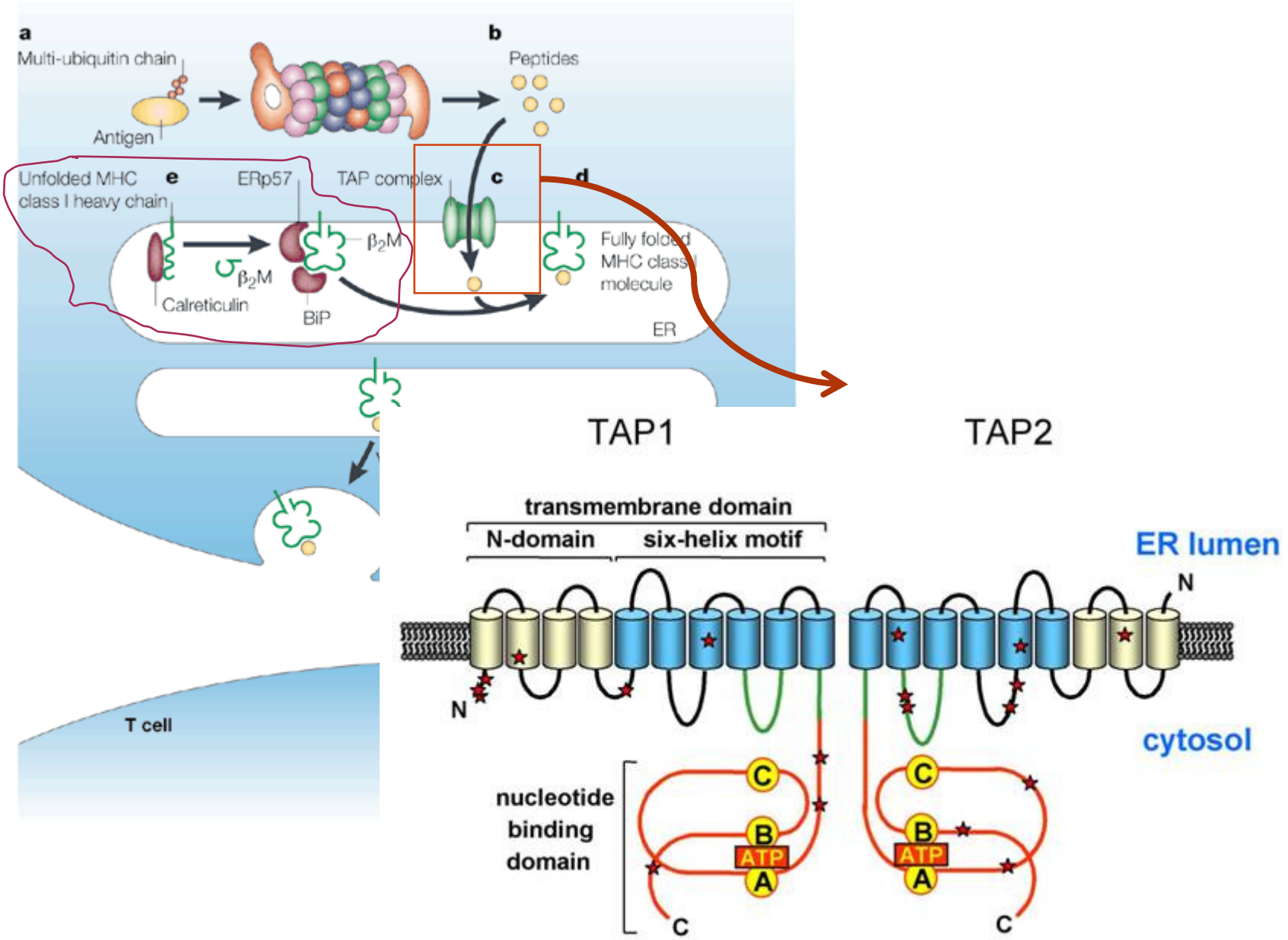
Nature Reviews Cancer **7**, 613-620 (August 2007)

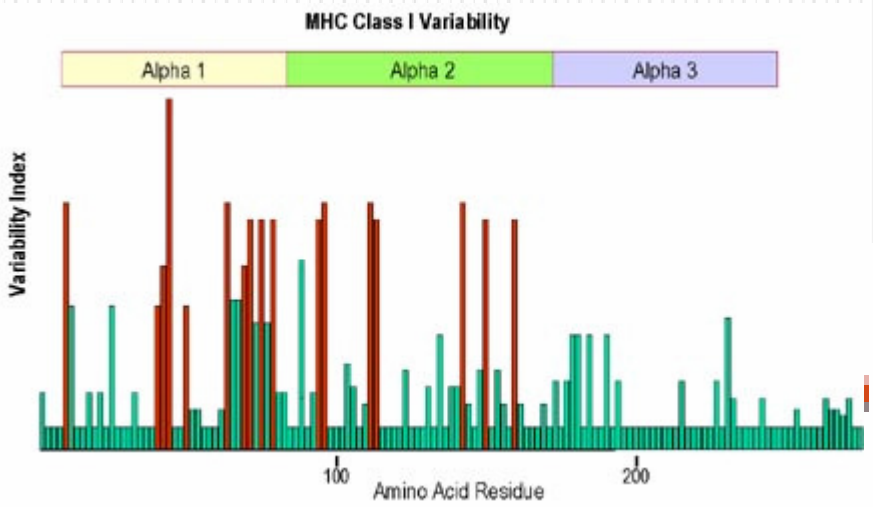


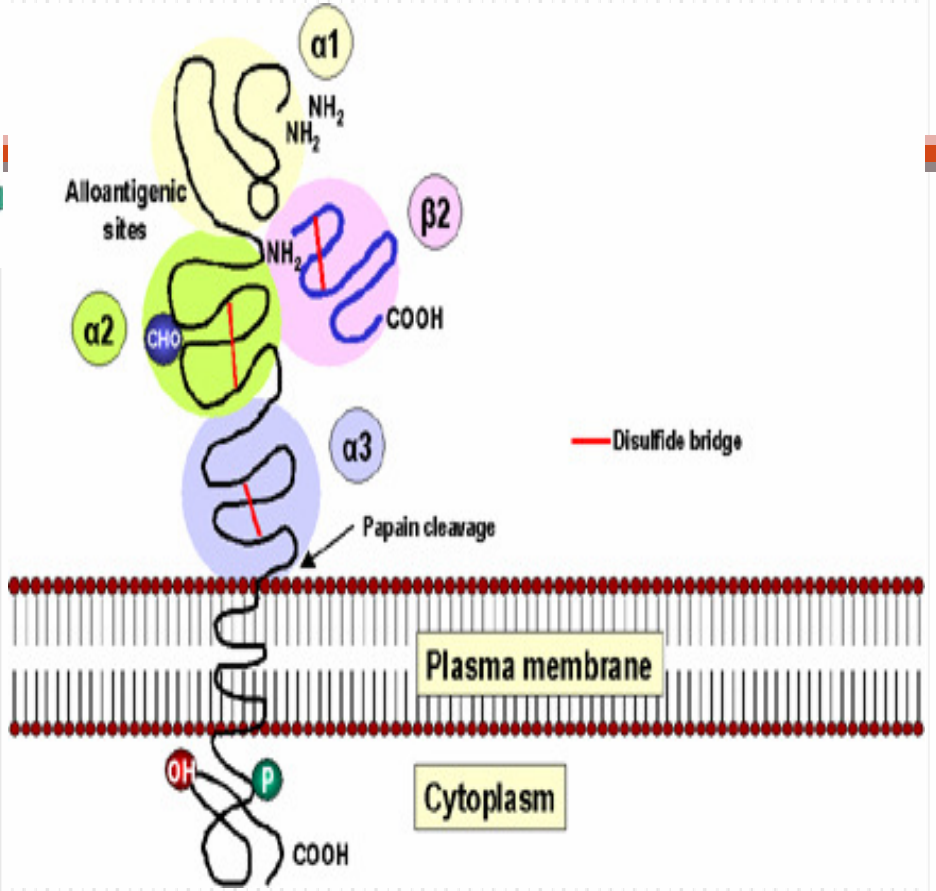
Se generan alrededor de 2 x 10^6 péptidos sin embargo sólo son presentados 150 péptidos por segundo!!!!!!

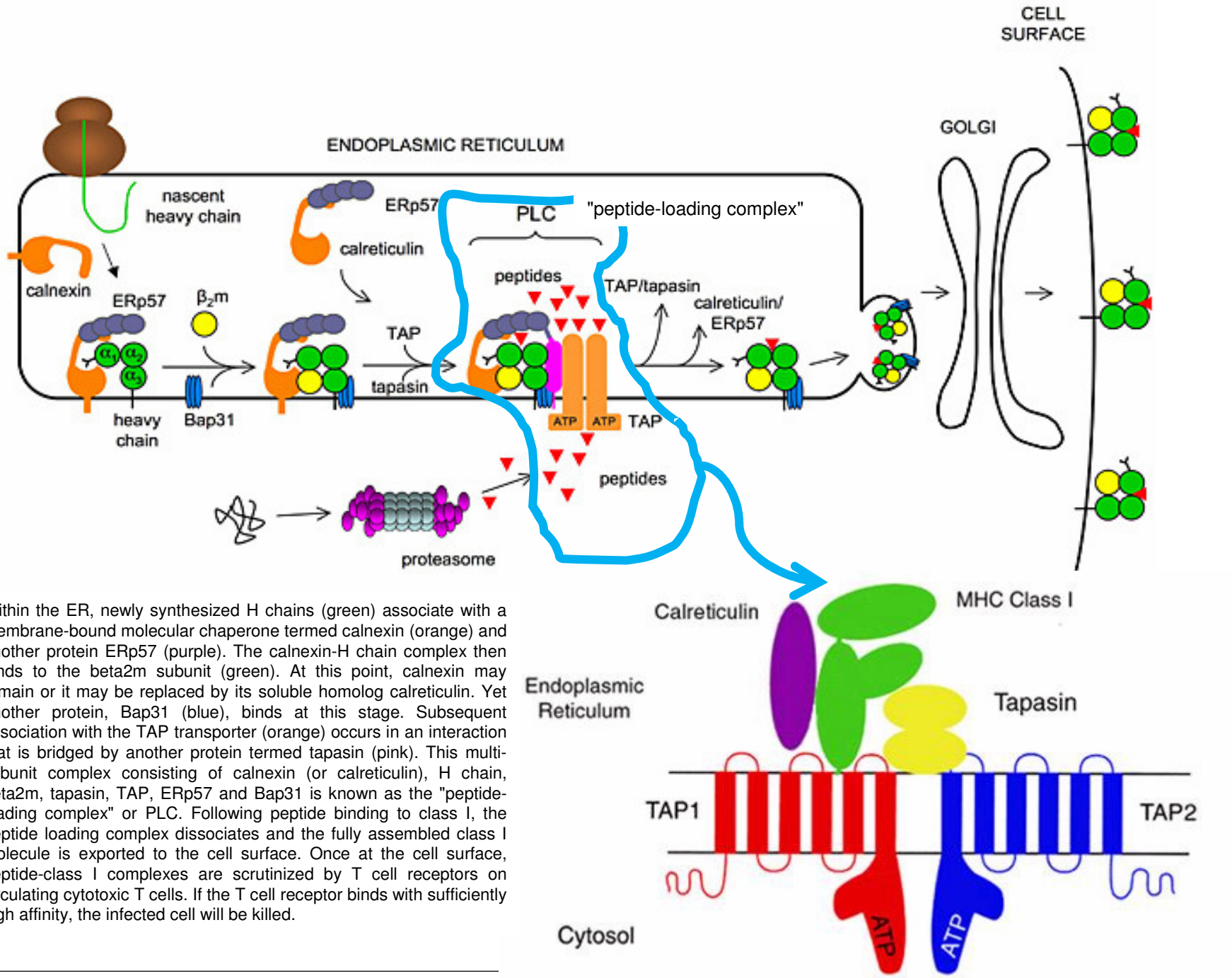


Solo 150 MHC I son cargadas con péptidos por segundo


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

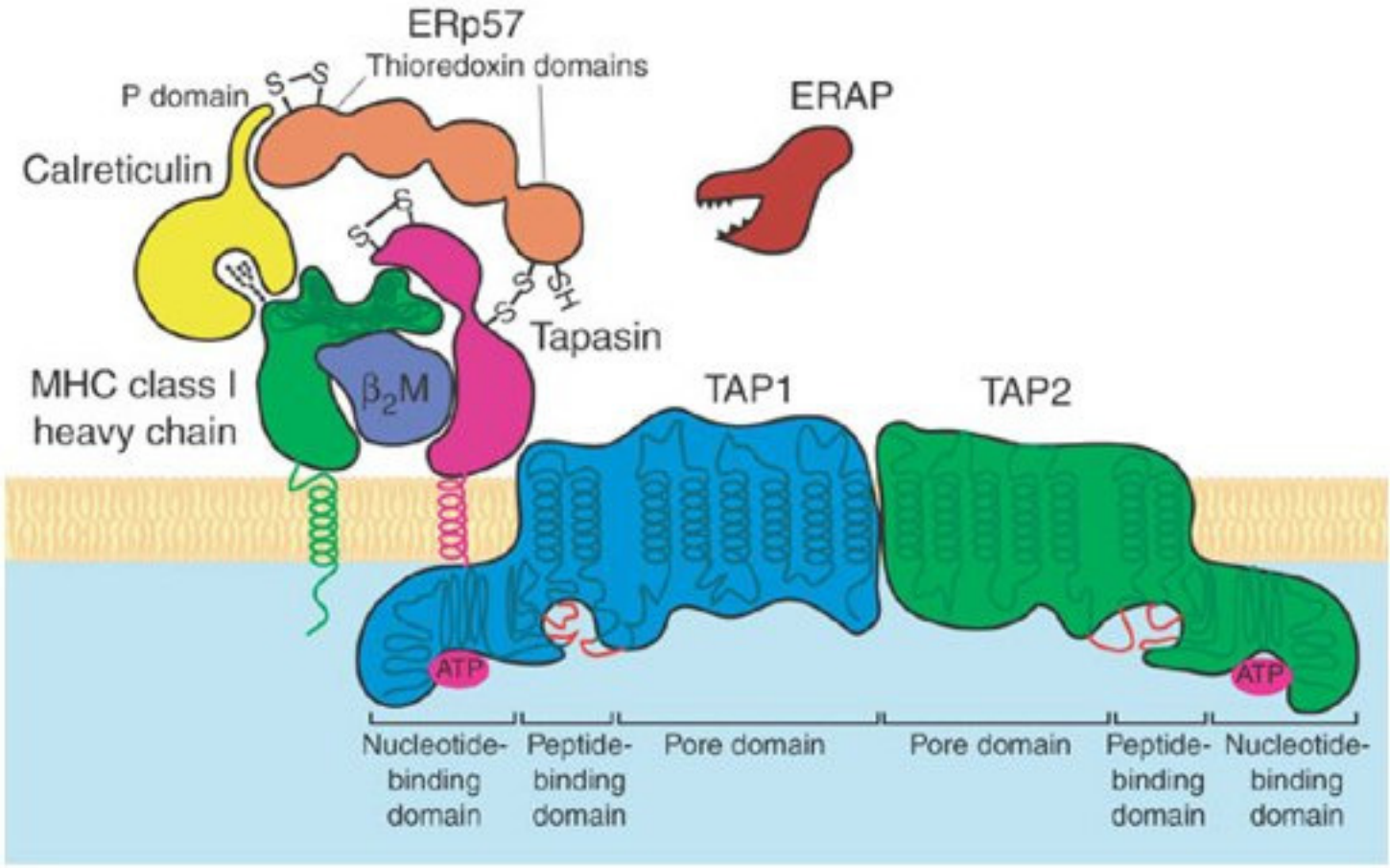

MHC Class I Variability
Alpha 1
Alpha 2
Alpha 3
Variability Index
100
200
Amino Acid Residue


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

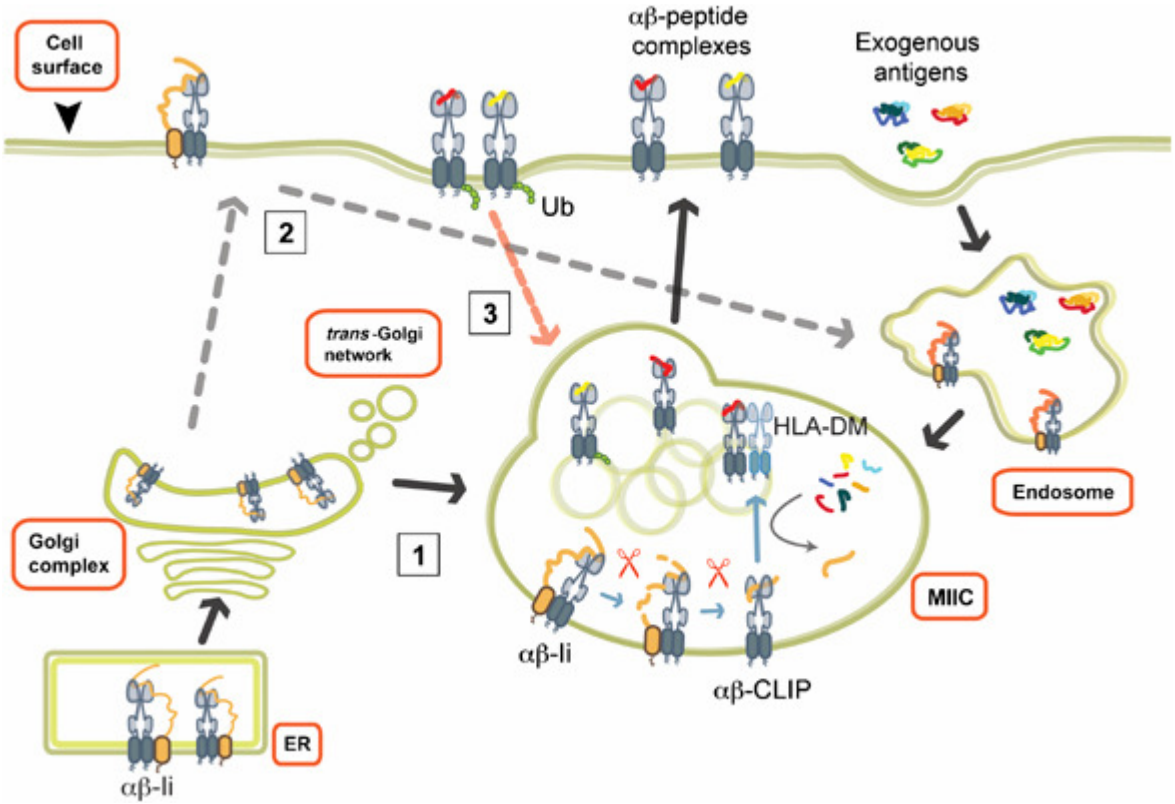


Ackerman and Cresswell, Nat. Immunol., 2004

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.**

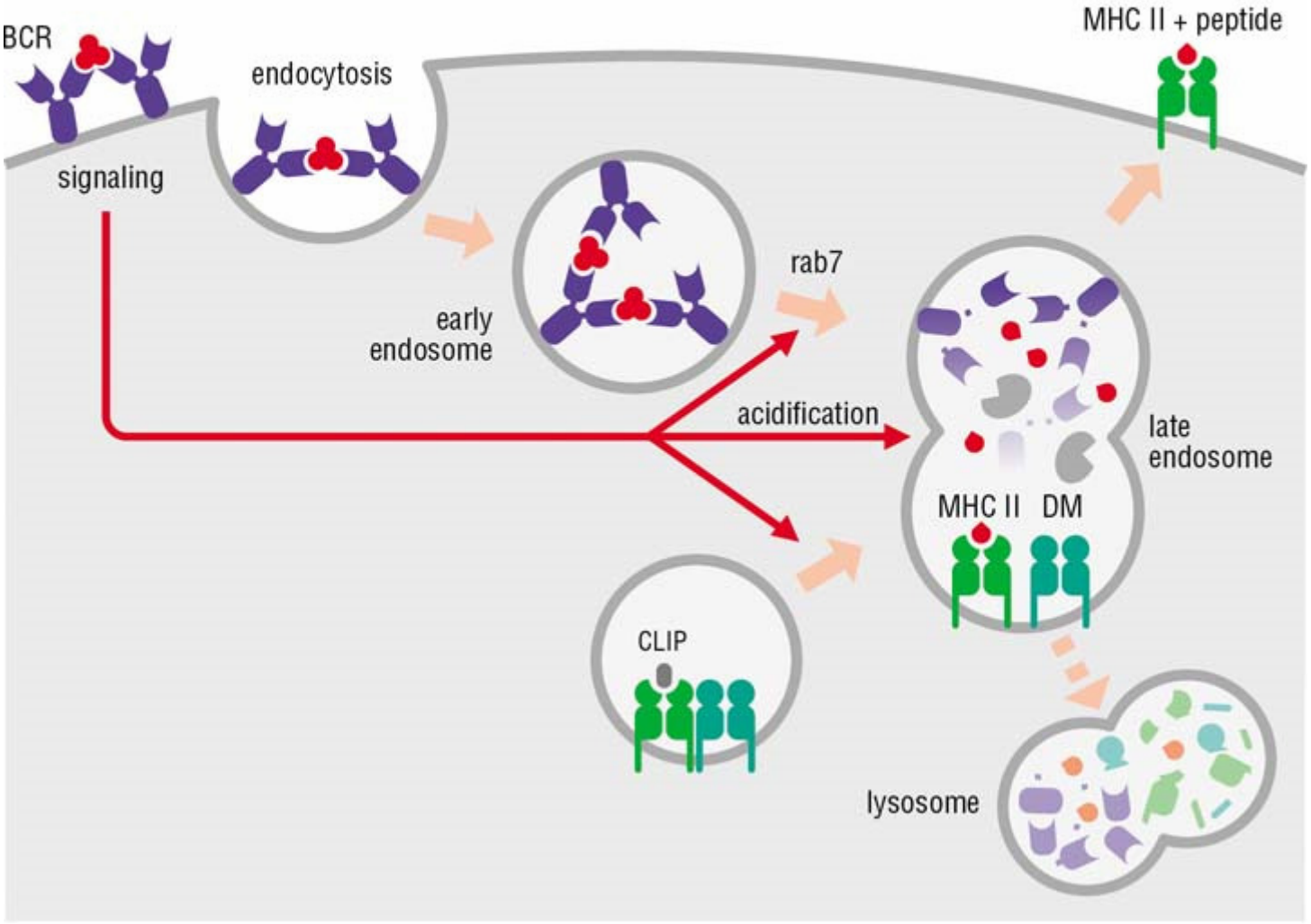
Presentación de antígenos exógenos



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).

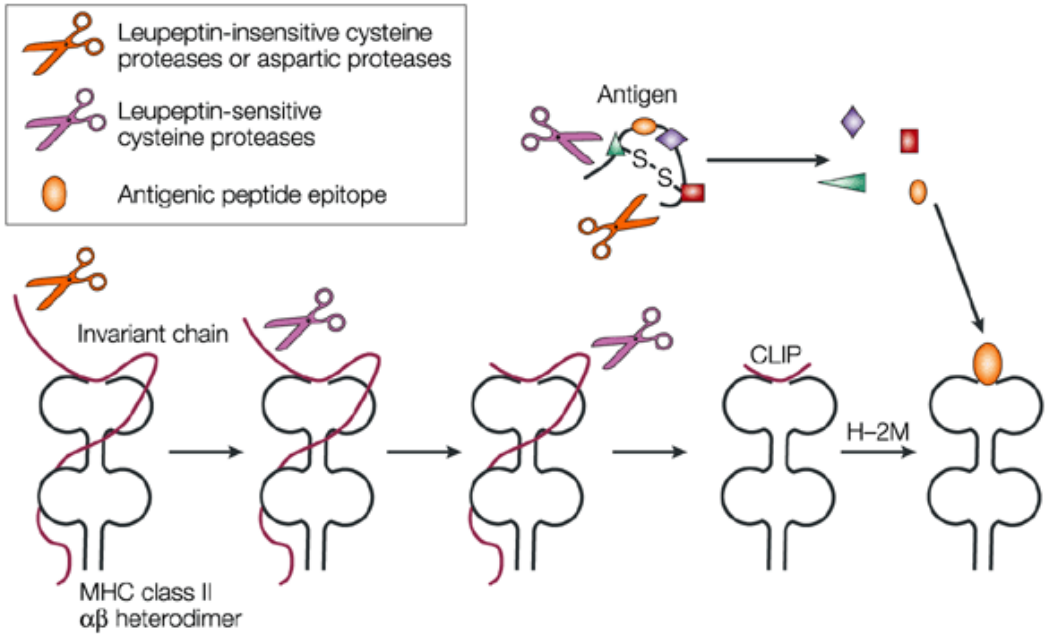
Es una molécula de HLA NO CLÁSICO, NO POLIMÓRFICA, QUE SE EXPRESA DENTRO DEL COMPARTIMENTO ENDOSÓMICO, EN CÉLULAS QUE EXPRESAN MOLÉCULAS CLASE II.

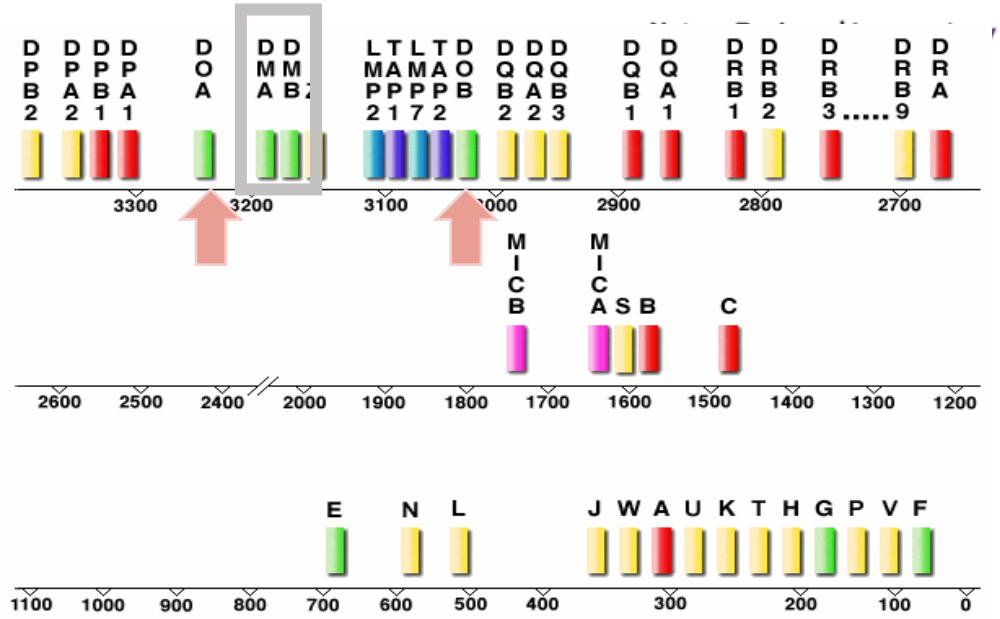
Los genes DMα y DMβ se localizan cerca de los genes TAP y LMP en el complejo MHC.

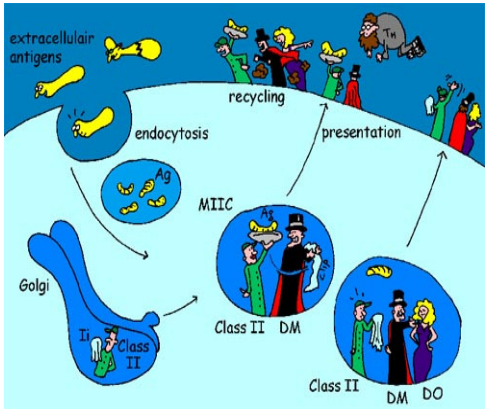
HLA-DO DISMINUYE LA EFICACIA DE INTERCAMBIO DE PÉPTIDO.

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.

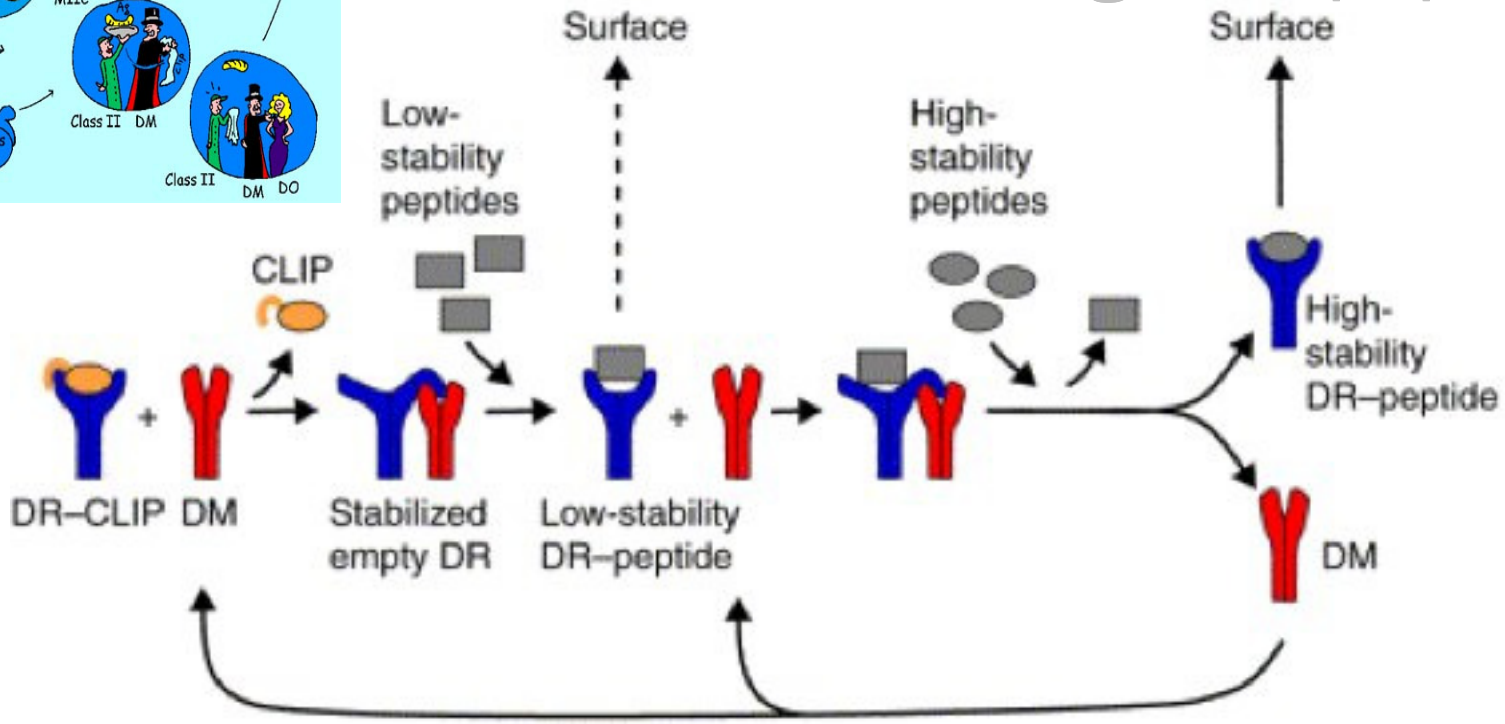
Los genes que codifican las cadenas α y β no son adyacentes en el MHC.







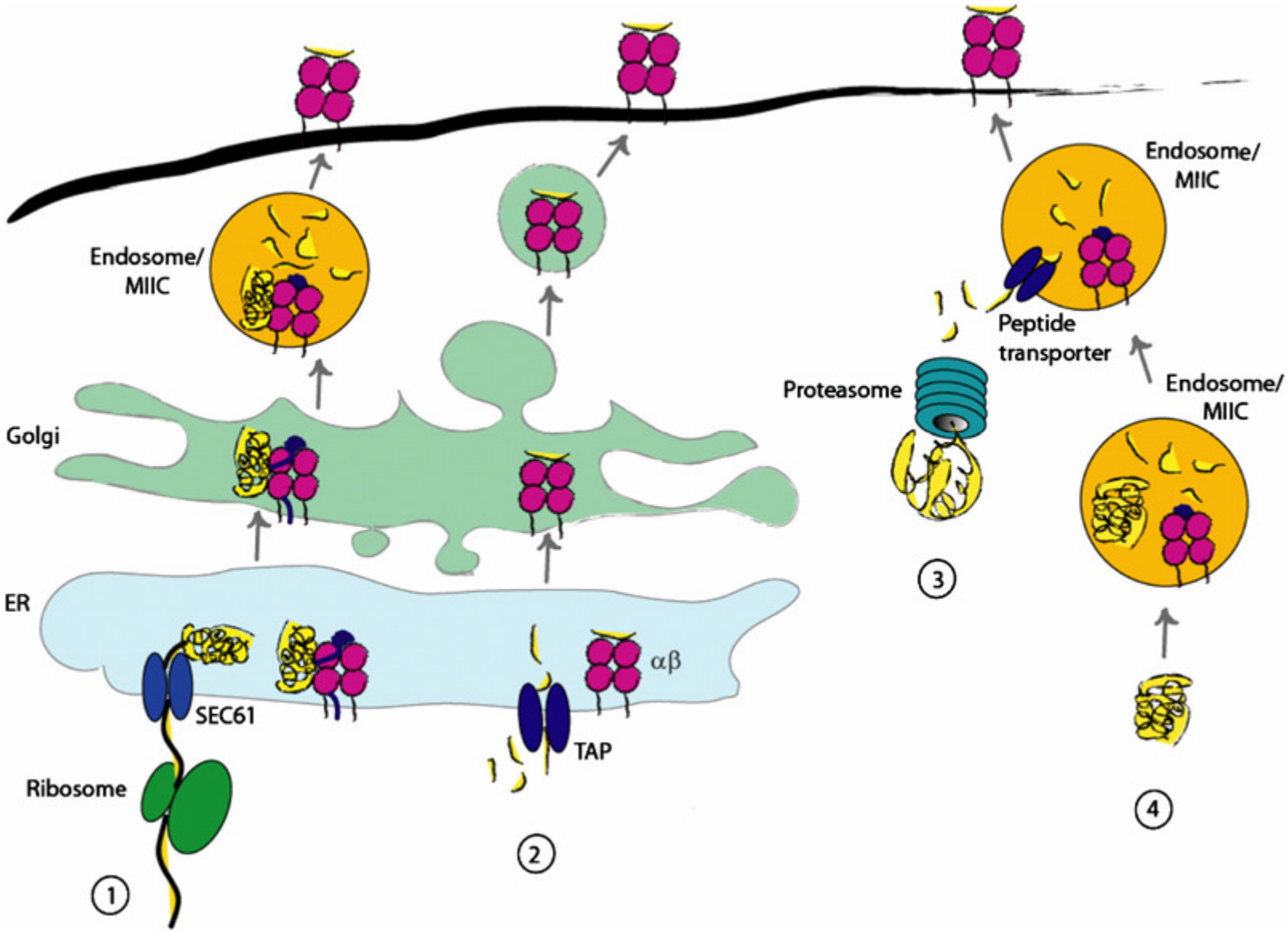
Rol de DM en la carga del péptido



- 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

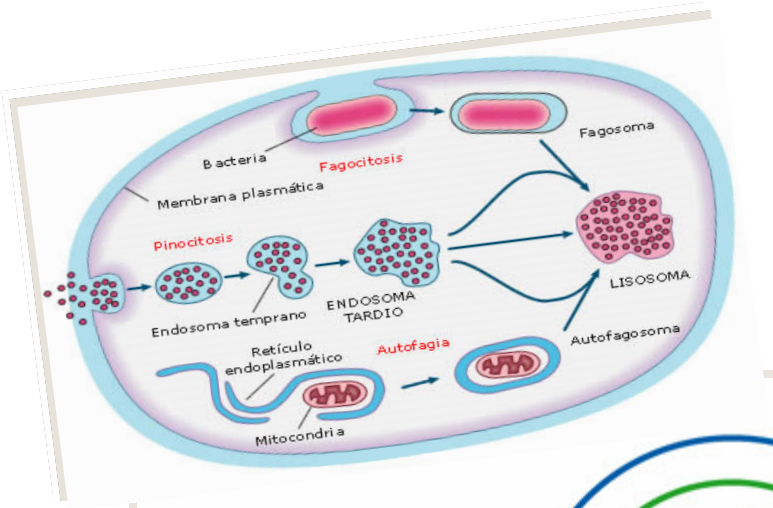

Endosome/
MIIC
Golgi
ER
SEC61
Ribosome
1
αβ
TAP
2
Proteasome
Peptide
transporter
3
Endosome/
MIIC
Endosome/
MIIC
4

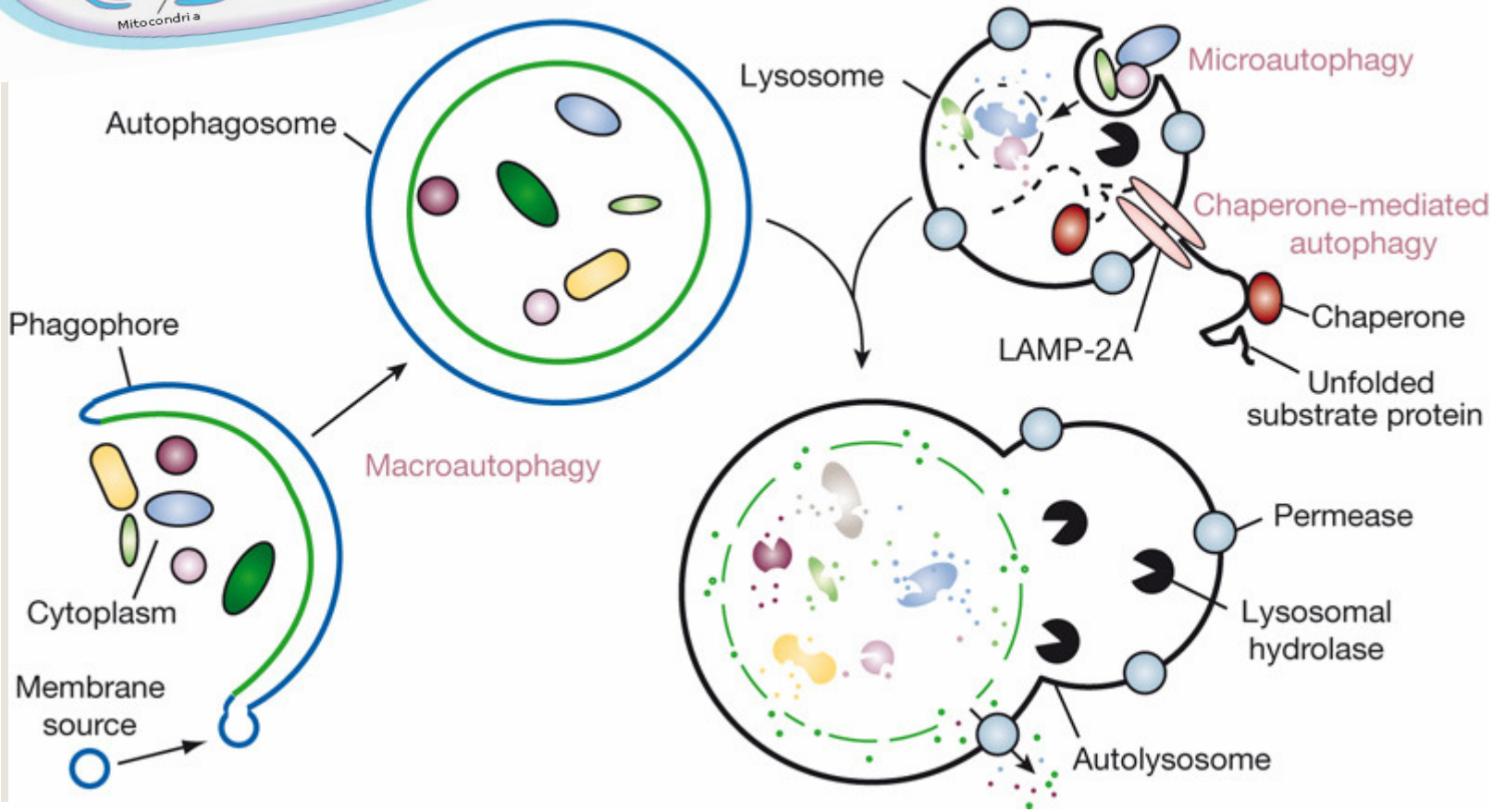
- Proposed processing pathways for endogenous presentation of intracellular antigens on MHC class II. Four different pathways have been postulated:
- (1) Secreted/transmembrane proteins (e.g. influenza A hemagglutinin) can associate with newly synthesized MHC class II molecules after their cotranslational 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

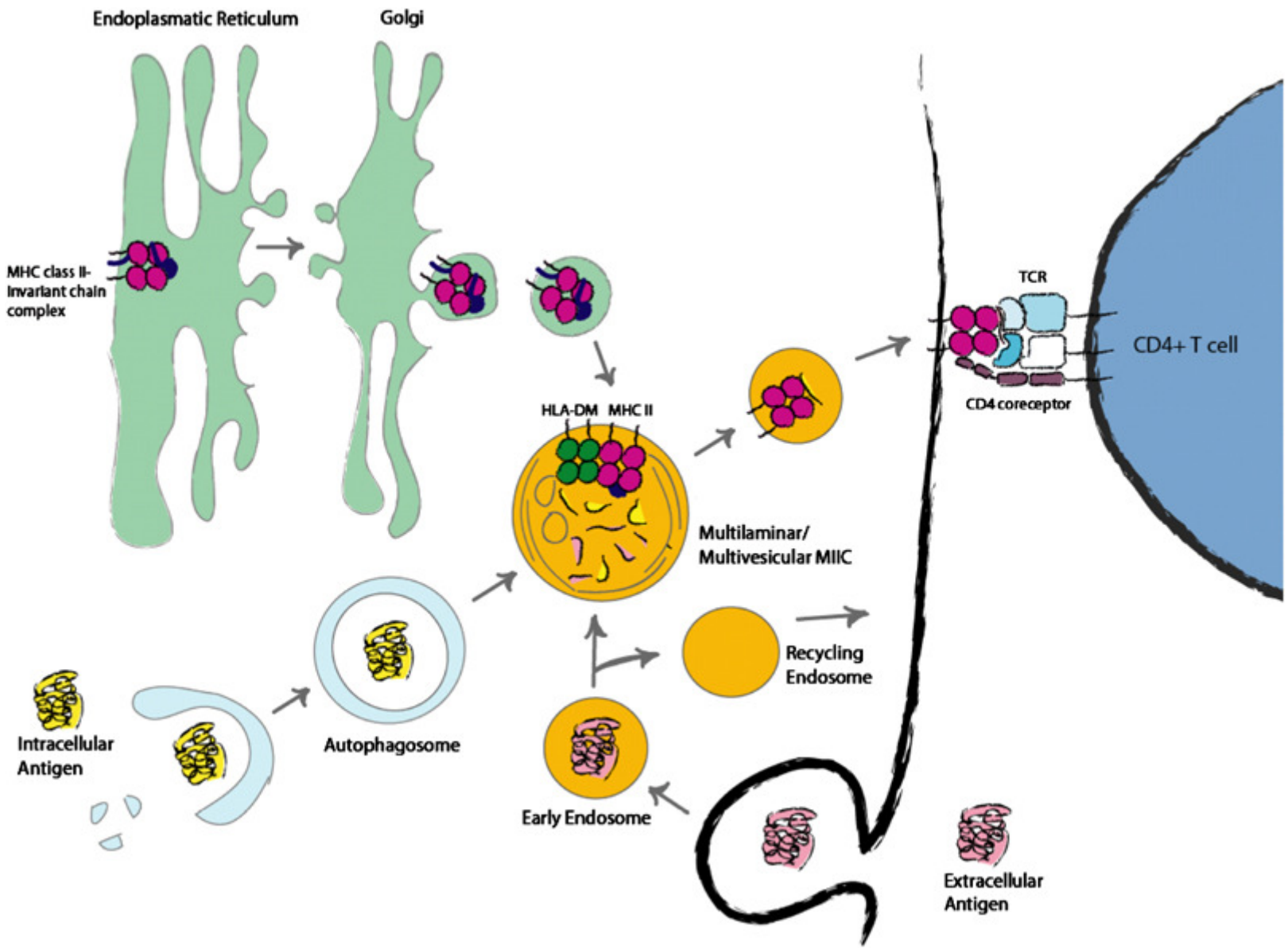
La **autofagia** es un proceso catabólico altamente conservado en eucariotas, en el cual el citoplasma, incluyendo el exceso de orgánulos o aquellos deteriorados o aberrantes, son secuestrados en vesículas de doble membrana y liberados dentro del lisosoma/vacuola para su descomposición y eventual reciclado de las macromoléculas resultantes.

Autofagia y presentación antigénica

Autofagia se ha relacionado con proliferación, diferenciación, respuesta inmune contra patógenos, cáncer, apoptosis y recientemente se ha propuesto como una herramienta que permite a la célula obtener energía, ácidos grasos y aminoácidos permitiendo su supervivencia en condiciones adversas. Un mecanismo de autofagia deficiente es también causante de distintas enfermedades neurodegenerativas.

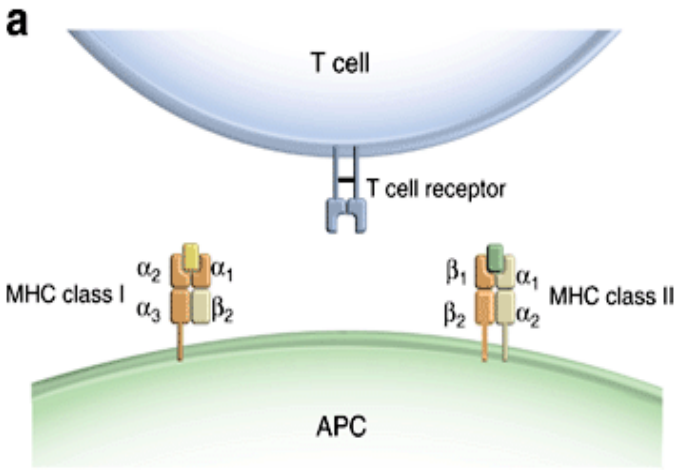

Bacteria
Fagocitosis
Fagosoma
Membrana plasmática
Pinocitosis
Endosoma temprano
ENDOSOMA TARDIO
LISOSOMA
Retículo endoplasmático
Autofagia
Autofagosoma
Mitocondria

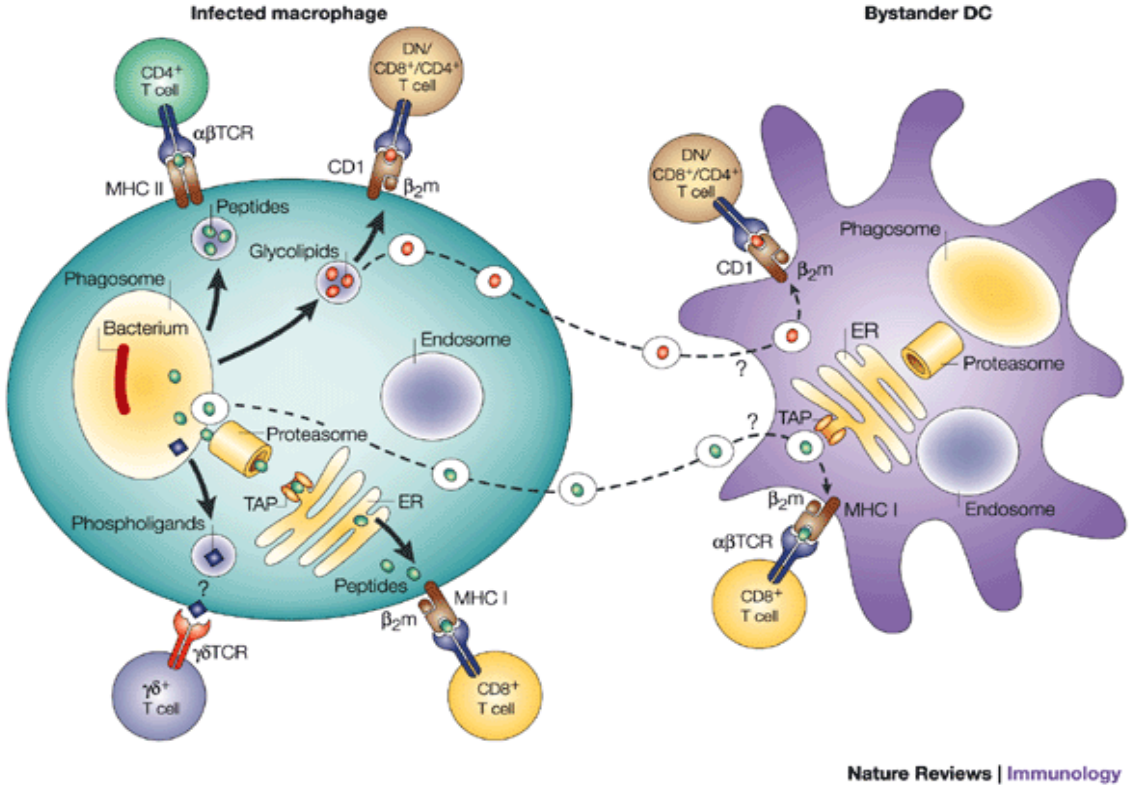

Autophagosome
Phagophore
Cytoplasm
Membrane source
Macroautophagy
Lysosome
Microautophagy
Chaperone-mediated autophagy
LAMP-2A
Chaperone
Unfolded substrate protein
Permease
Lysosomal hydrolase
Autolysosome


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



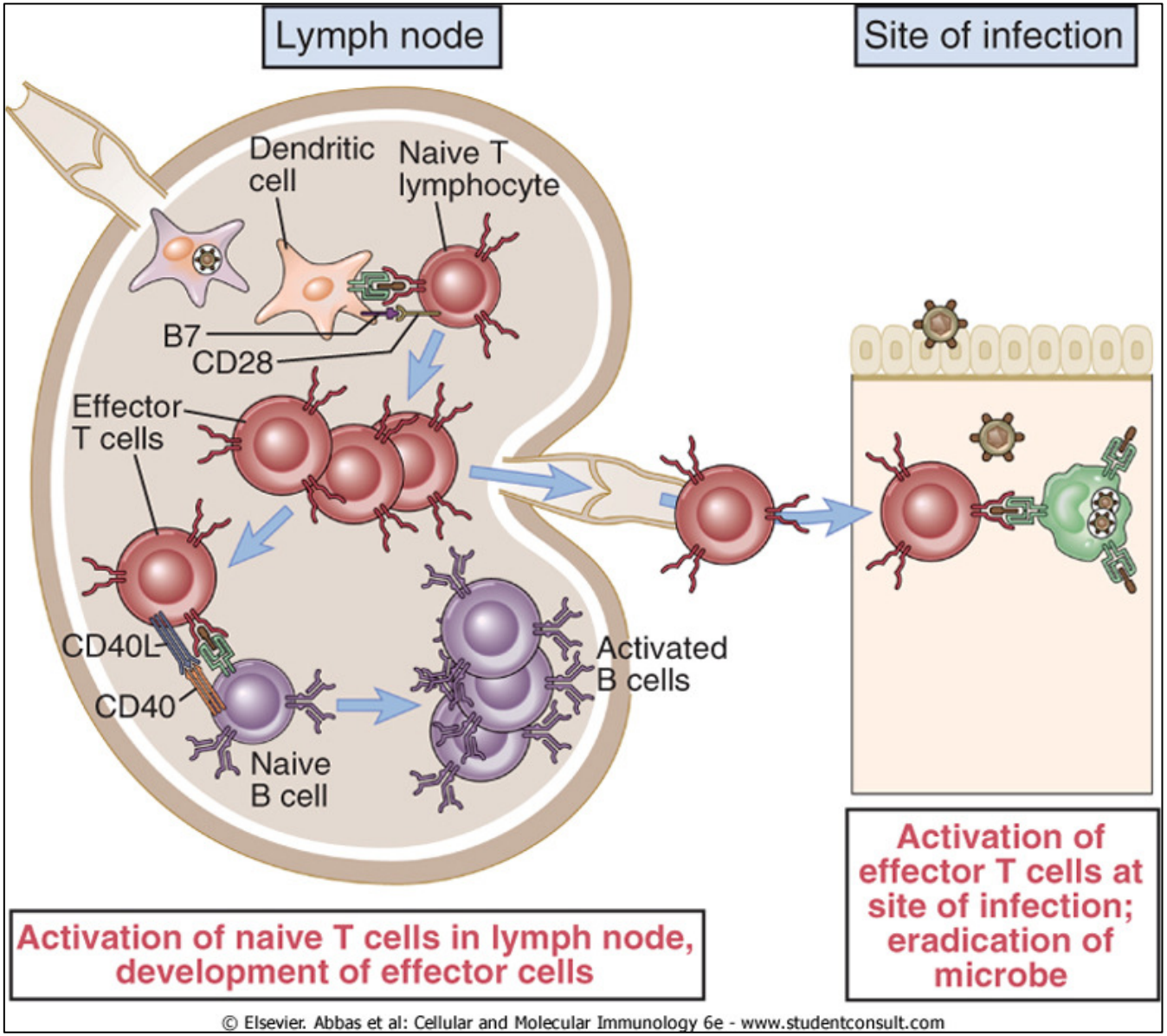


Presentación de antígenos por MICOBACTERIAS

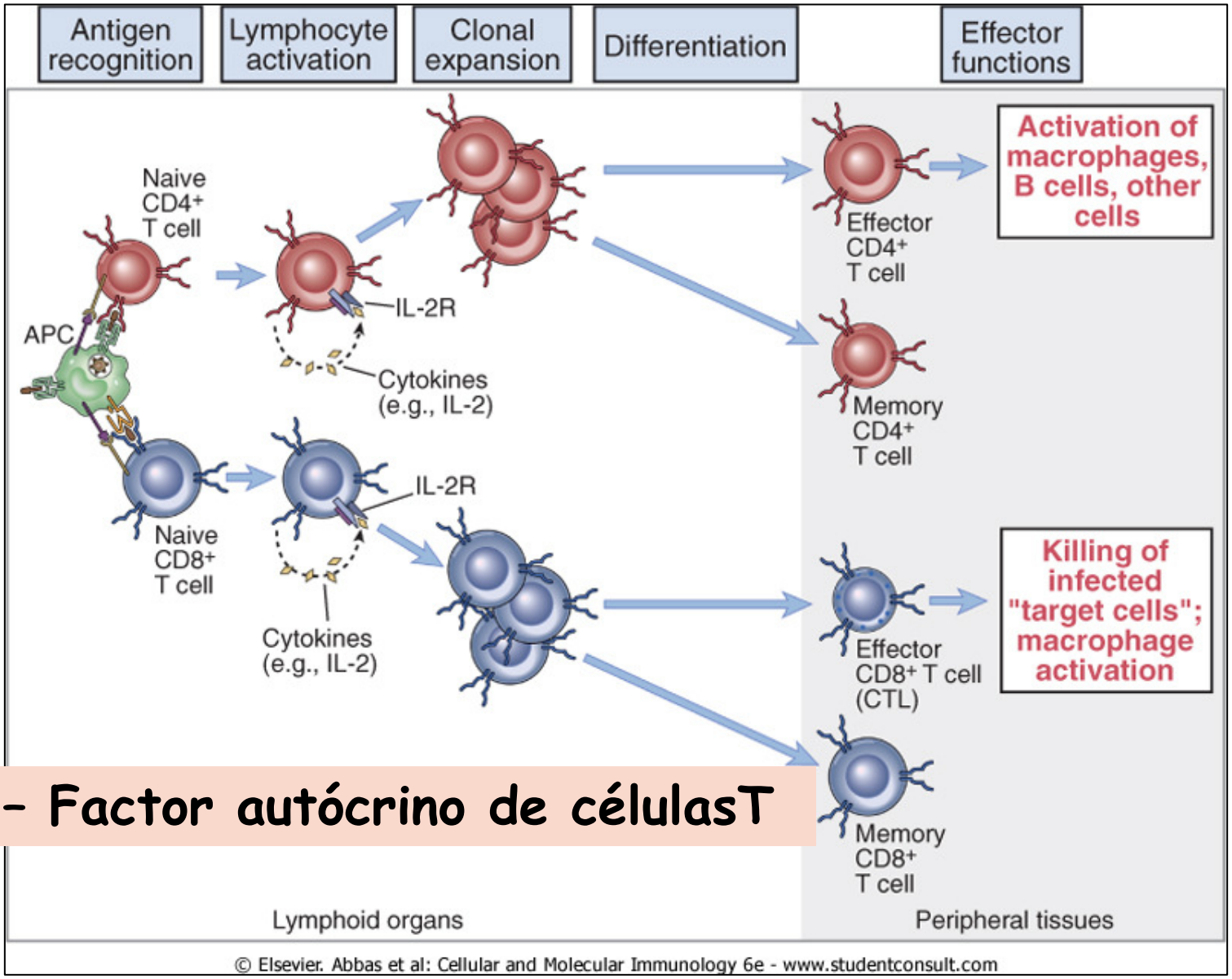
¿Qué ocurre tras la presentación del antígeno????

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

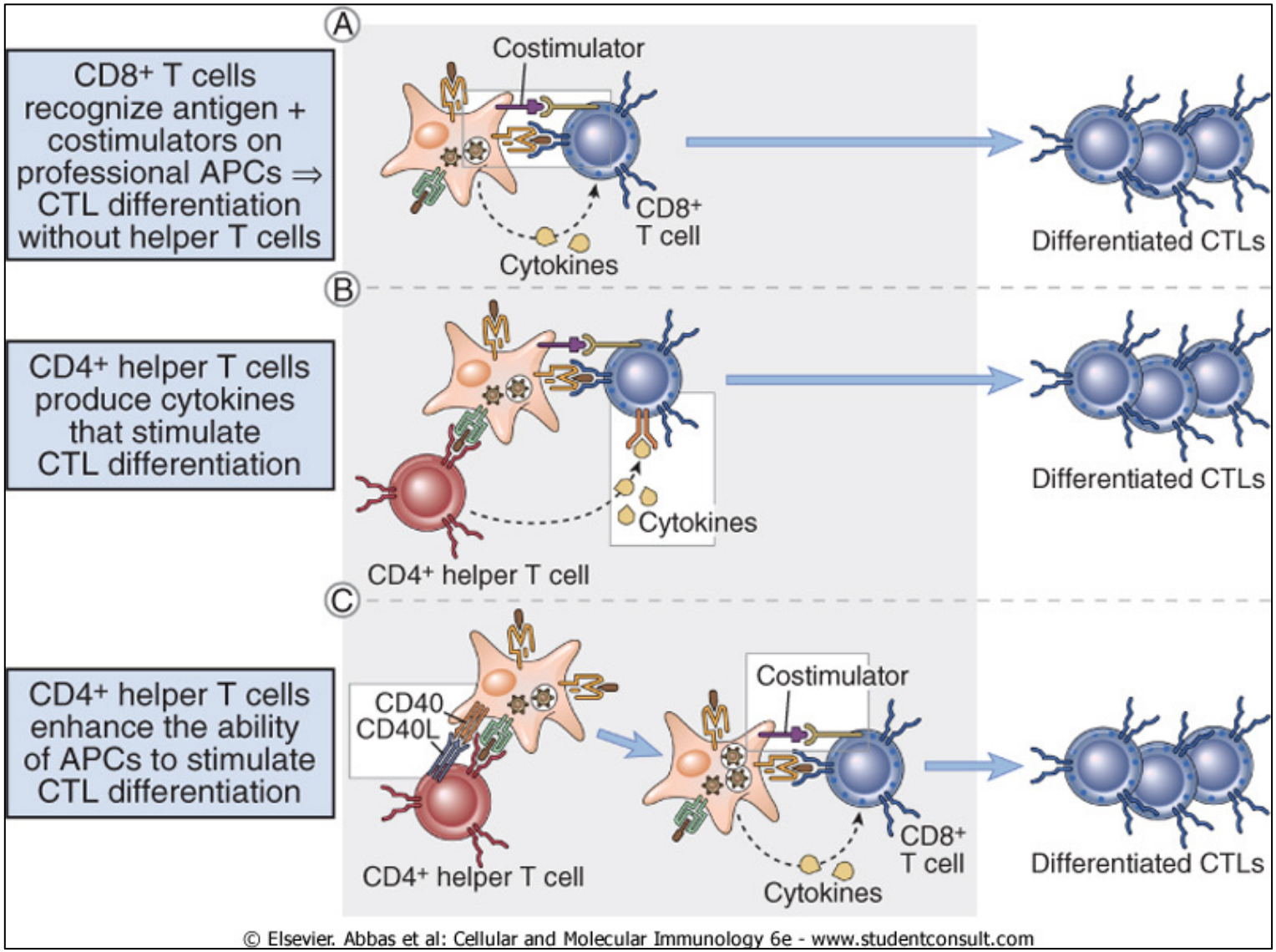

Lymph node
Site of infection
Dendritic cell
Naive T lymphocyte
B7
CD28
Effector T cells
CD40L
CD40
Naive B cell
Activated B cells
Activation of naive T cells in lymph node, development of effector cells
Activation of effector T cells at site of infection; eradication of microbe
© Elsevier. Abbas et al: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

Fases de la respuesta T

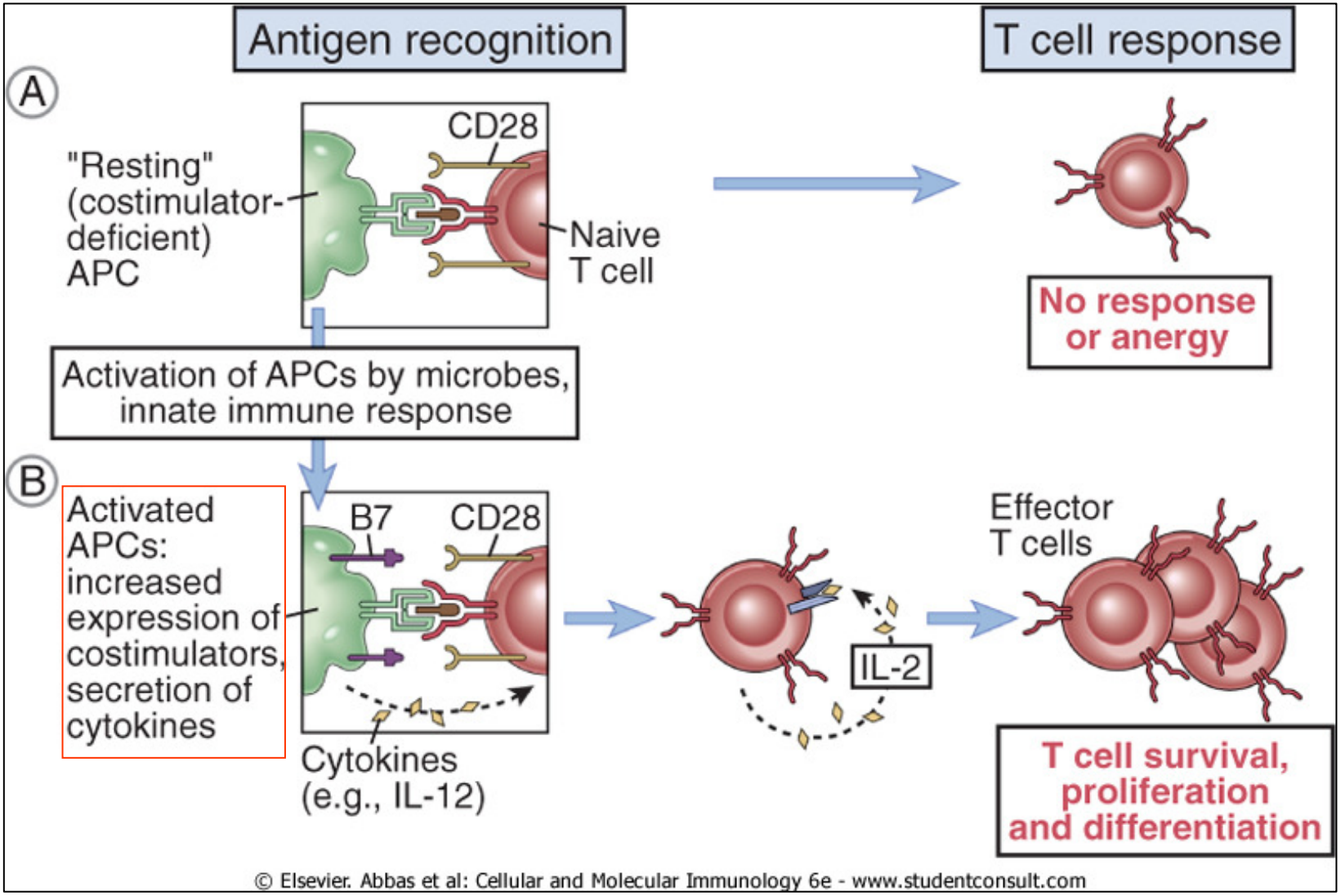


IL2 – Factor autócrino de célulasT

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

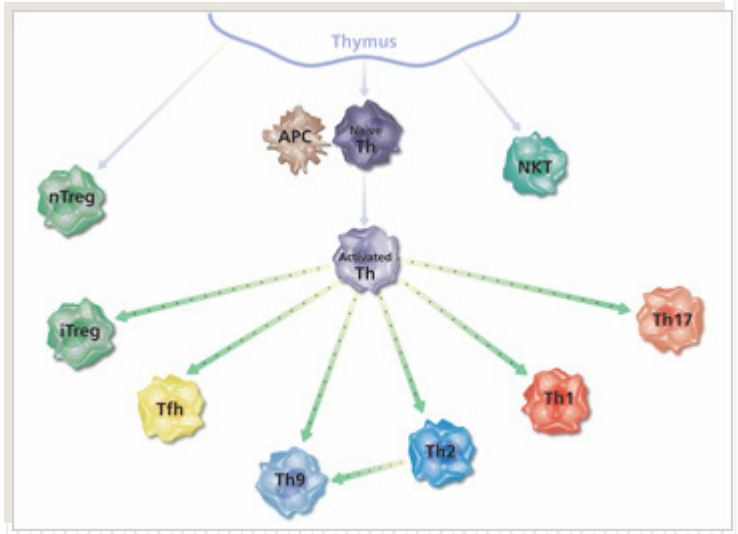


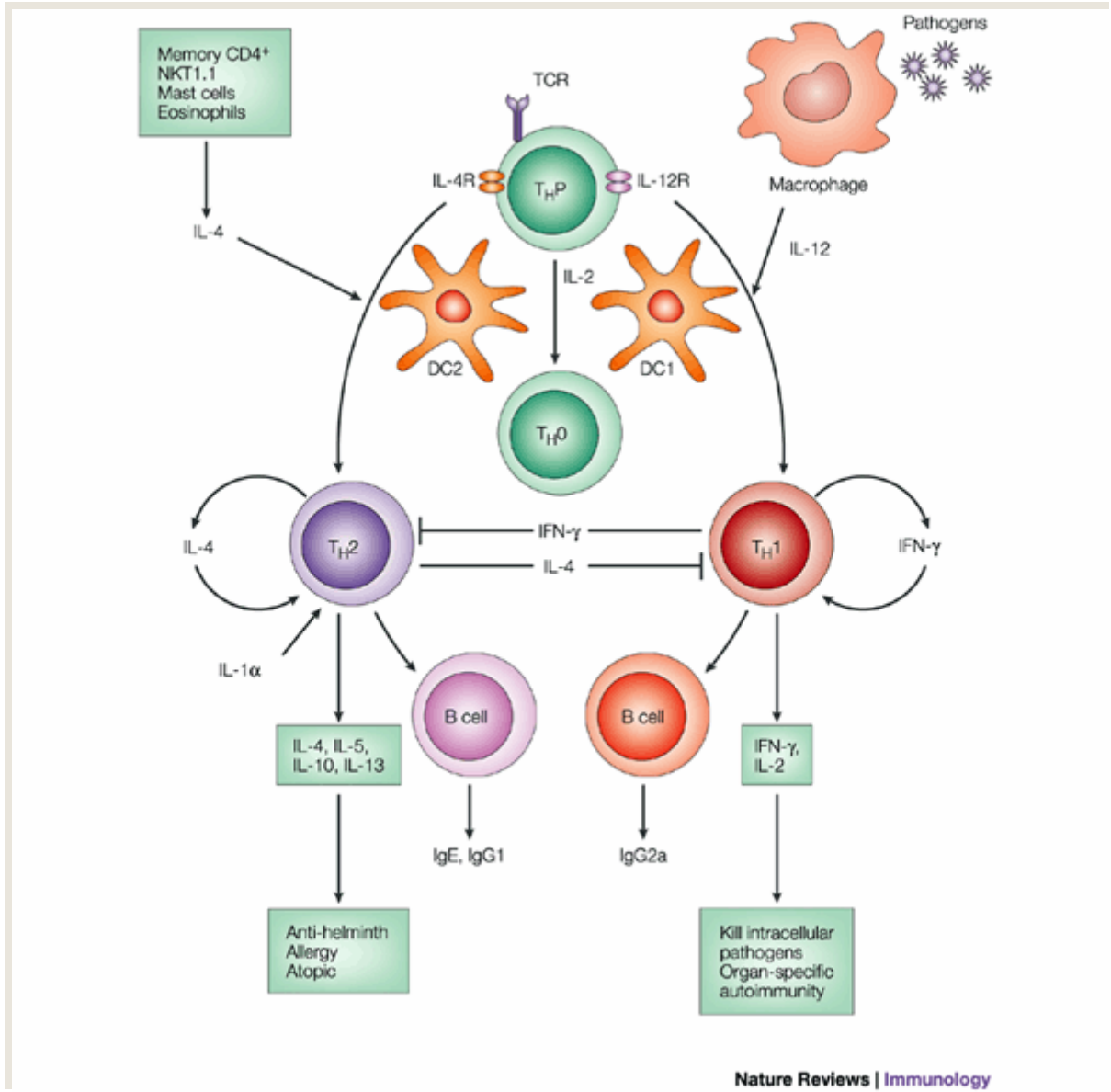
Coestimulación en la activación de células T



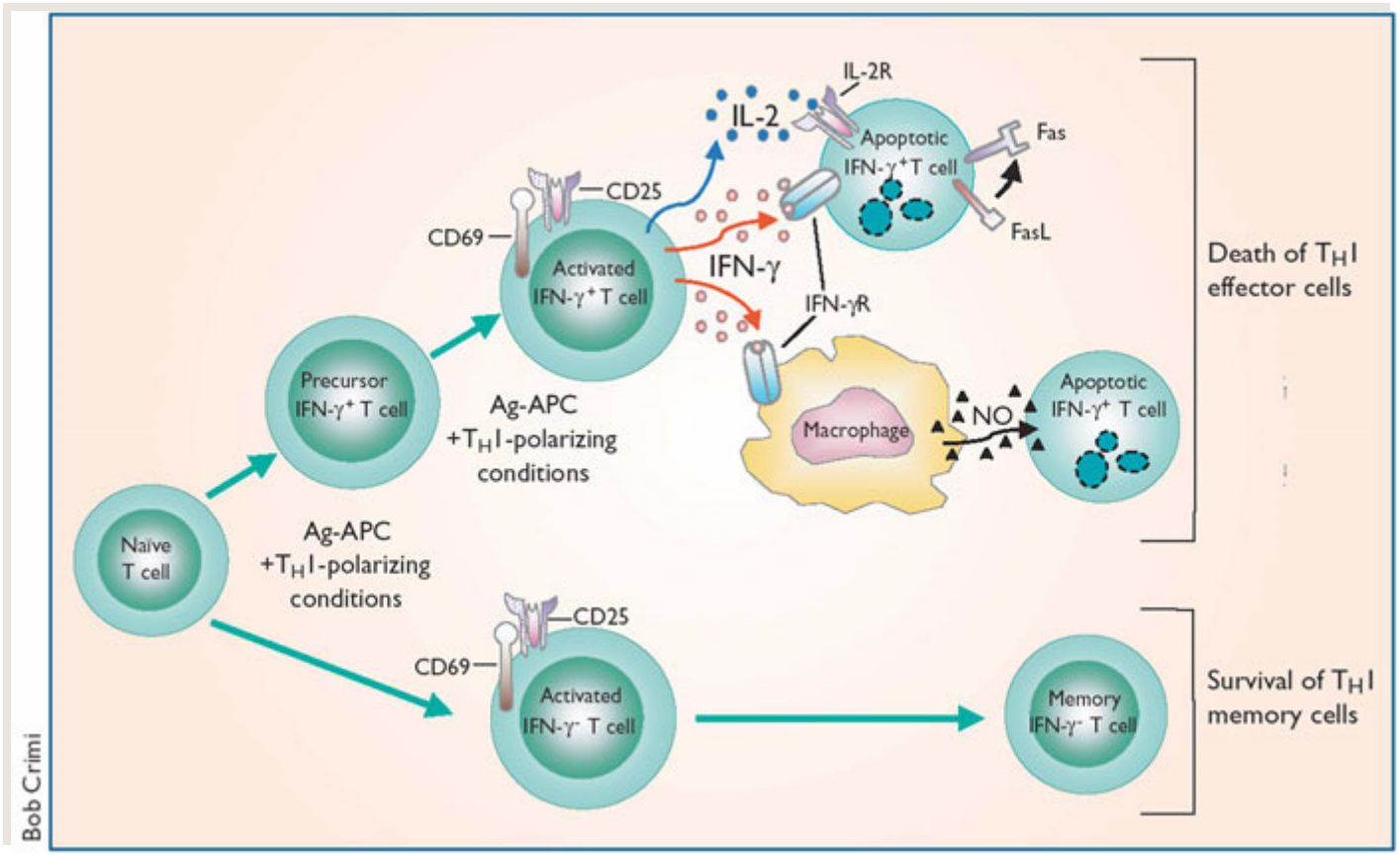
Generación de subpoblaciones celulares.....

La hipótesis de T helper (Th)1-Th2 fue descripta en 1986.

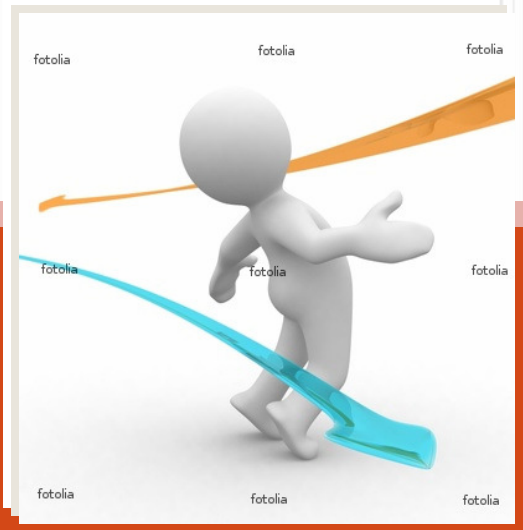




Nature Reviews Immunology 2, 55-60 (January 2002)

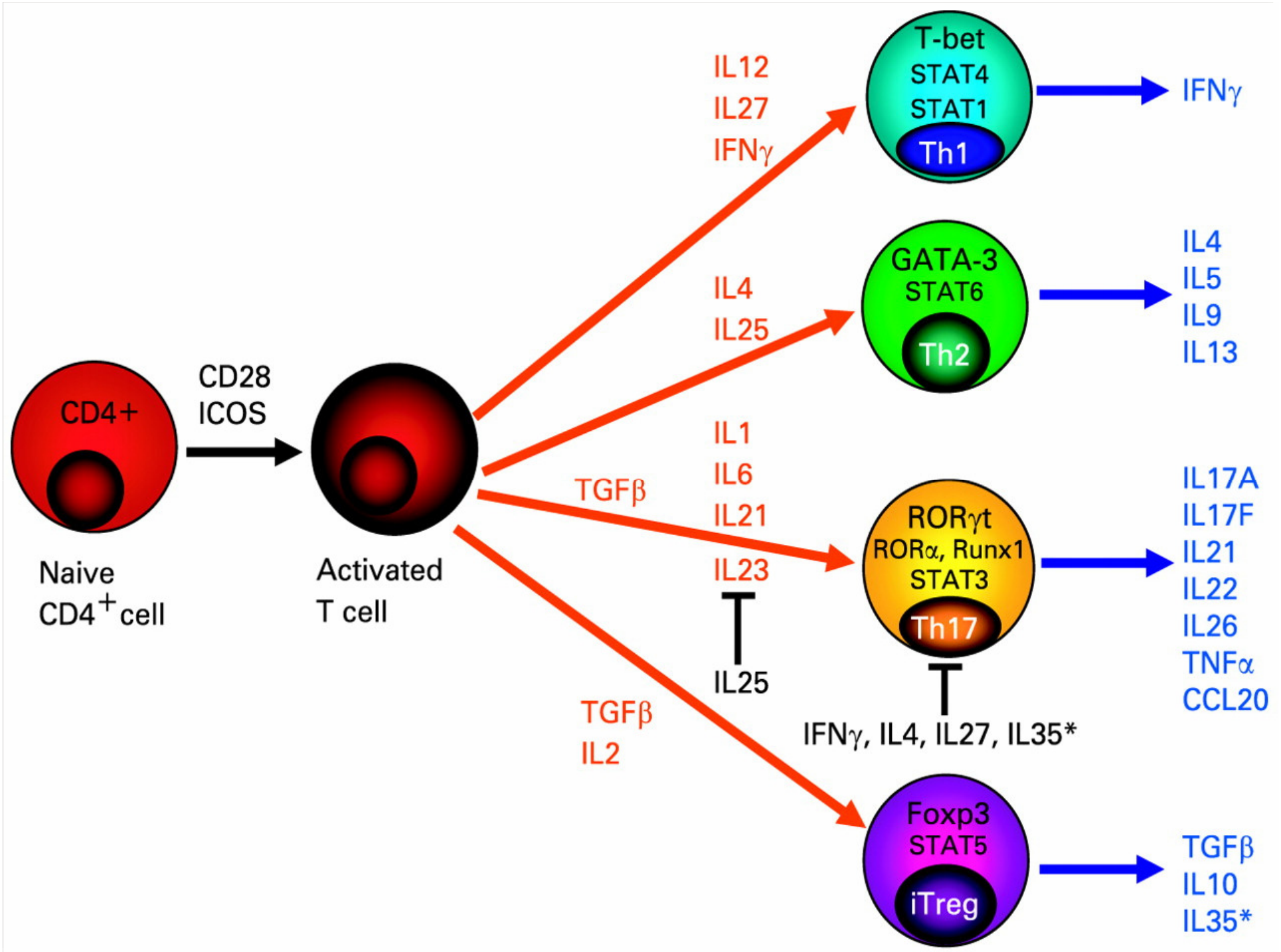


The development of two subpopulations of T_H1 cells. Naïve T cells stimulated with antigen under T_H1-polarizing conditions develop into two subpopulations of T_H1 cells: an IFN-γ^+ effector population and an IFN-γ^- population that is a dedicated T_H1 cell, as evaluated by other parameters (see text). IFN-γ – secreting cells are short-lived *in vivo* and are potentially eliminated by autocrine IFN-γ and IL-2 signals that lead to Fas-mediated apoptosis or by paracrine induction of NO production in macrophages. IFN-γ^- cells are resistant to apoptosis and develop into long-lived memory cells. Ag, antigen; APC, antigen-presenting cell; FasL, Fas ligand.



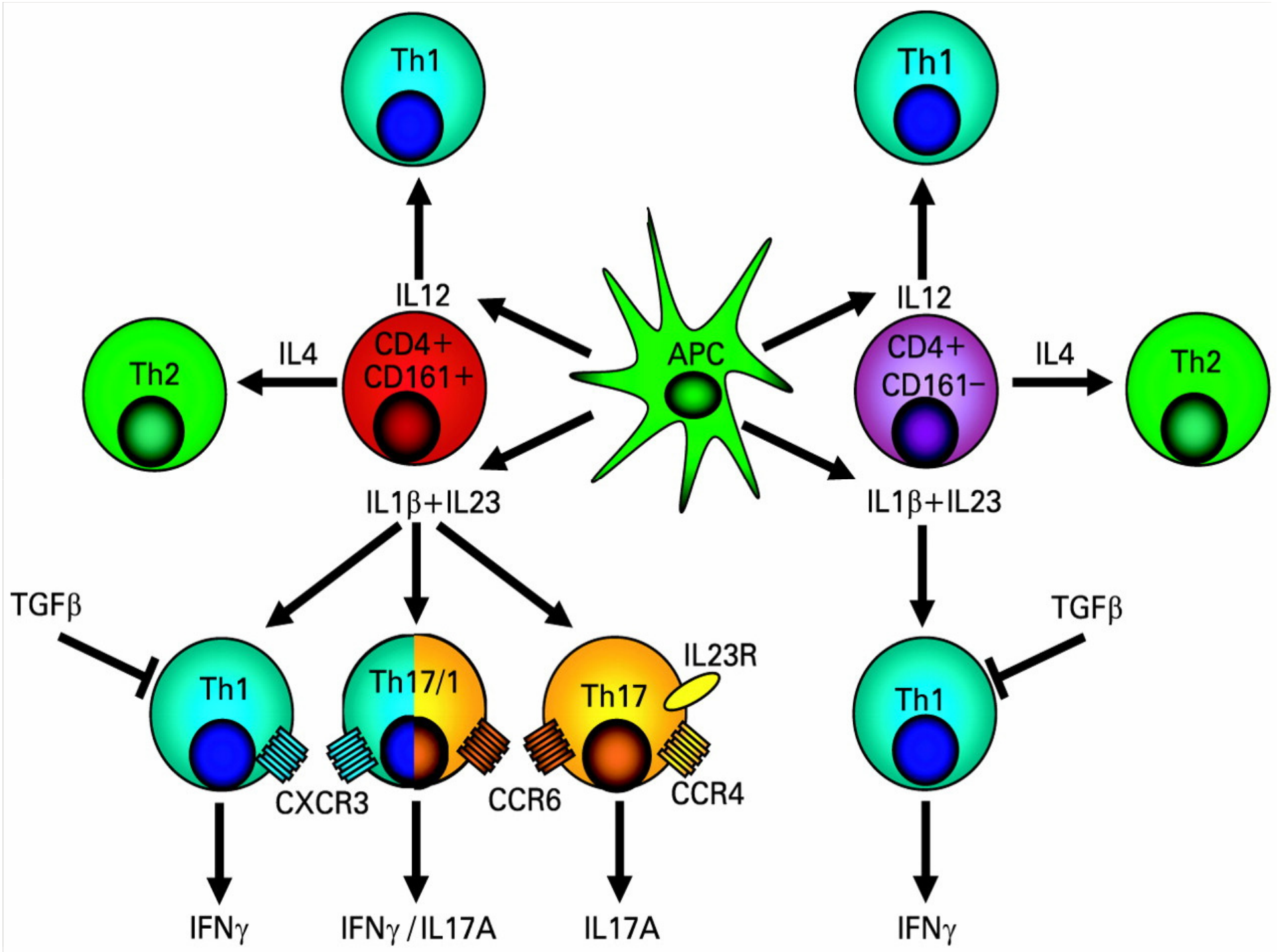
T regulatory cells (Tregs)

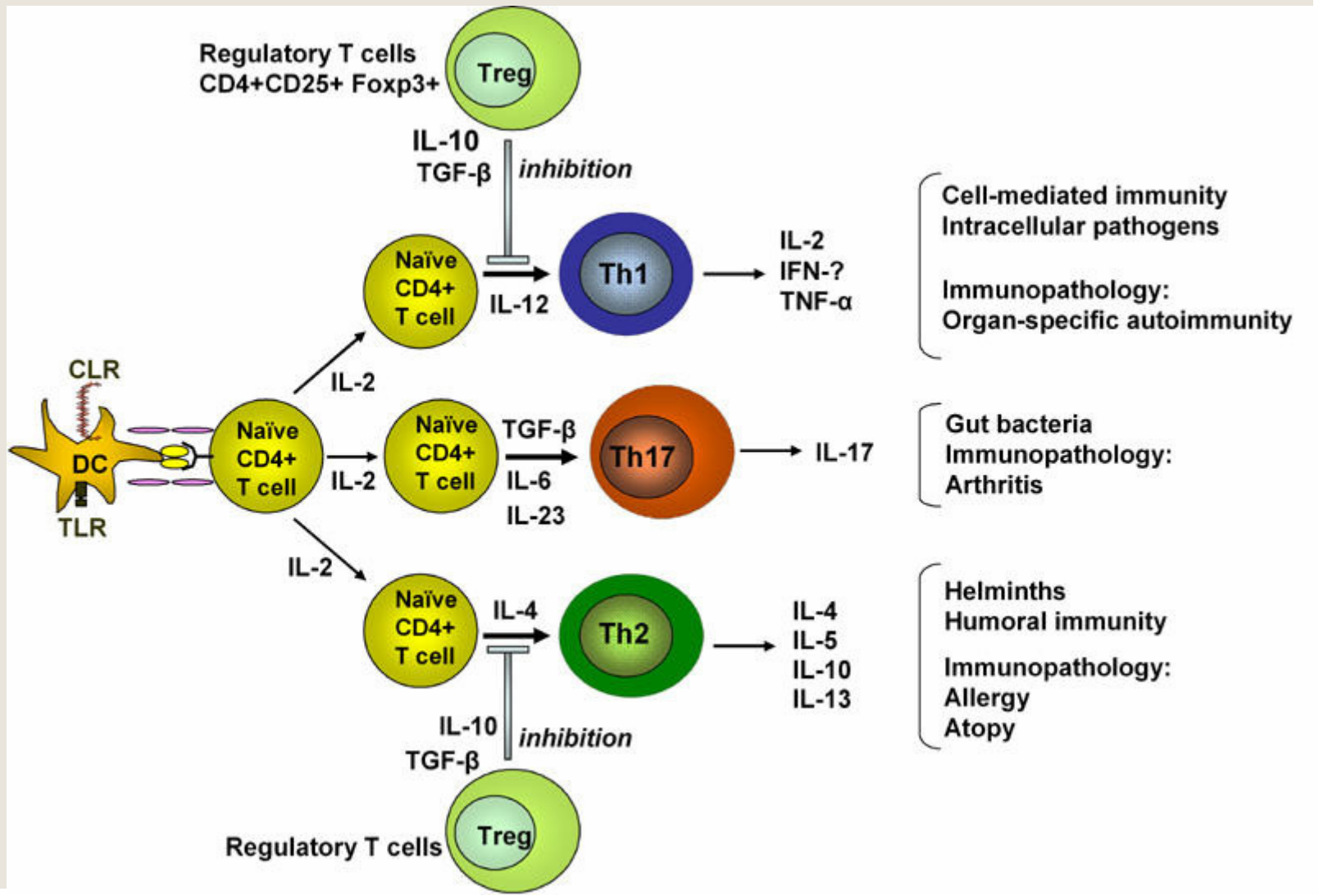
In 1970 Gershon and Kondo described the role of T-lymphocytes in the induction of tolerance . Much later true regulatory activity was recognized in a subpopulation of CD4+ cells characterized by high levels of CD25, the alpha-chain of IL-2 receptor . This novel population is usually referred to as **T regulatory cells (Tregs).**

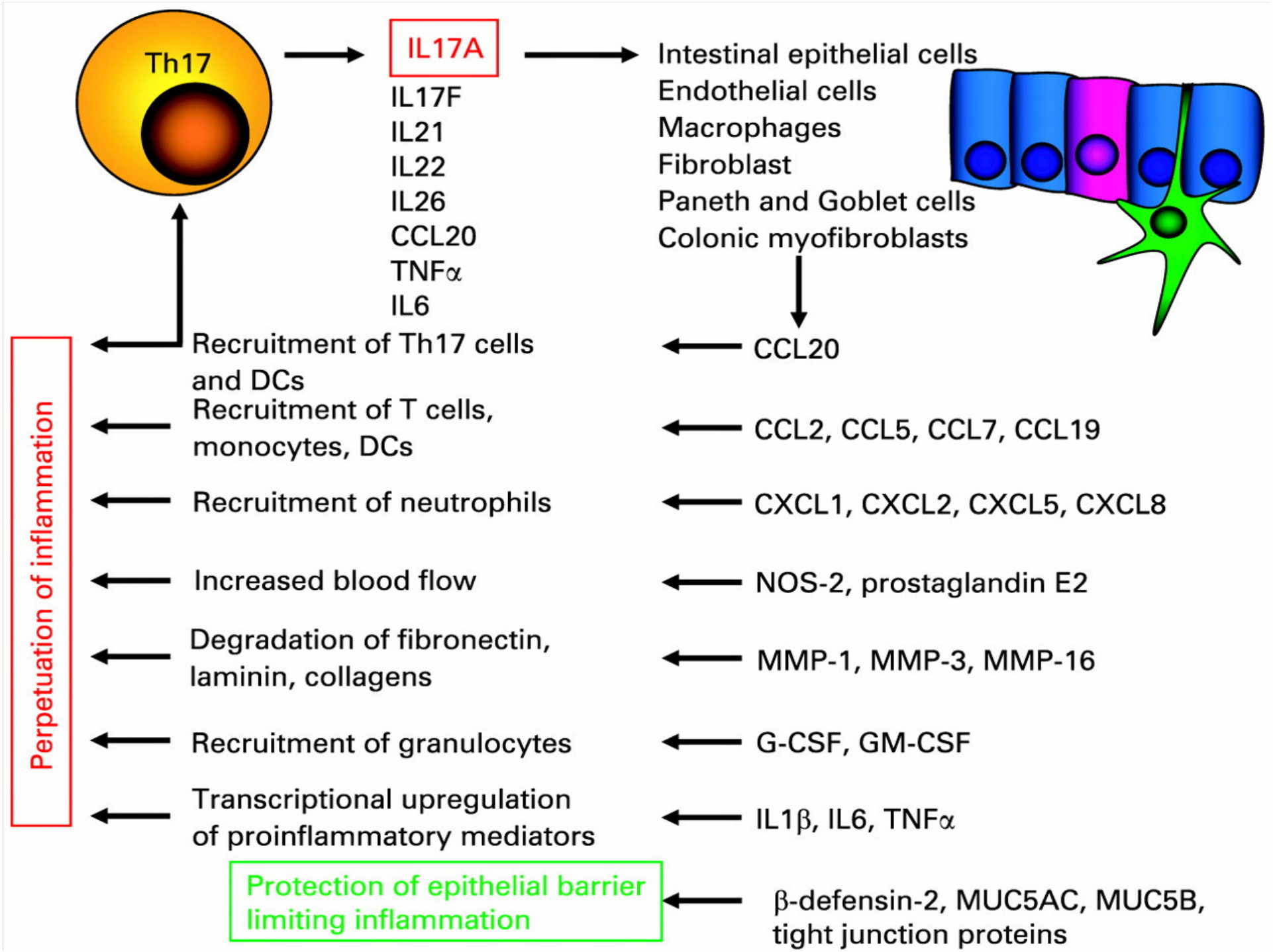

CD4+
Naive
CD4+ cell
CD28
ICOS
Activated
T cell
IL12
IL27
IFNγ
T-bet
STAT4
STAT1
Th1
IFNγ
IL4
IL25
GATA-3
STAT6
Th2
IL4
IL5
IL9
IL13
TGFβ
IL1
IL6
IL21
IL23
RORγt
RORα, Runx1
STAT3
Th17
IL17A
IL17F
IL21
IL22
IL26
TNFα
CCL20
IL25
IFNγ, IL4, IL27, IL35*
TGFβ
IL2
Foxp3
STAT5
iTreg
TGFβ
IL10
IL35*

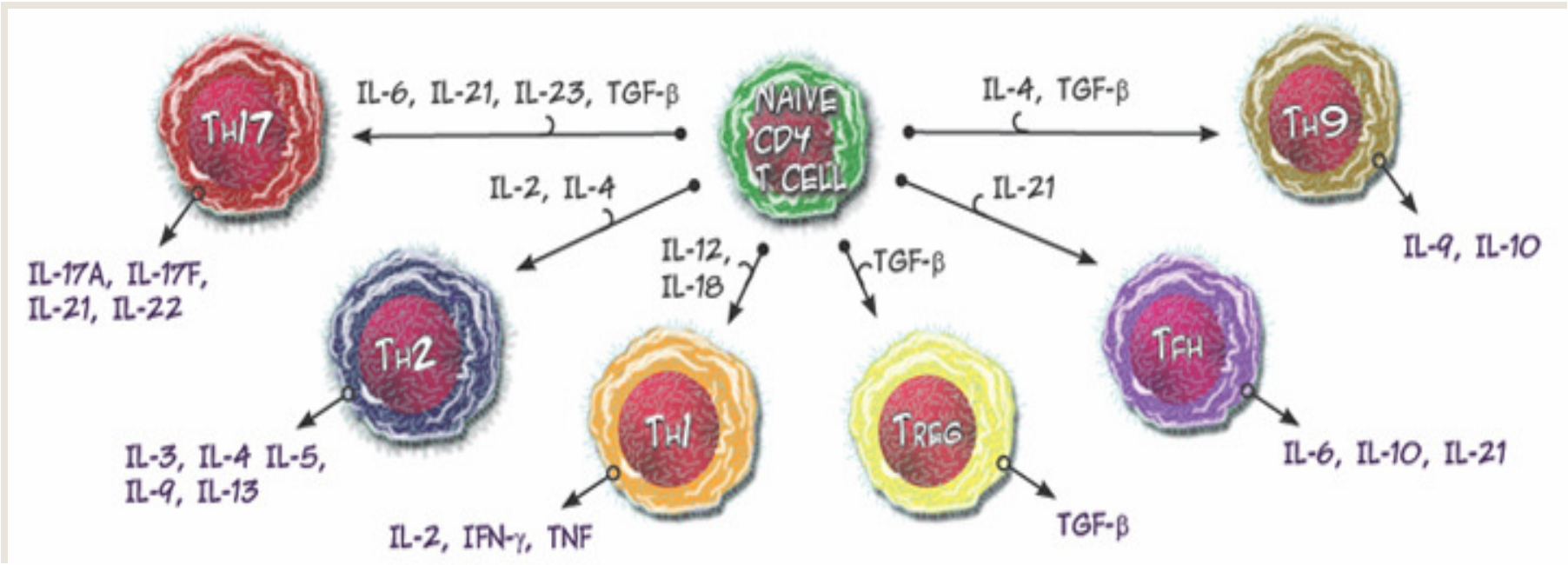
TH17

Trego and TH17 cells are related because they could derive from a common progenitor, depending on the presence of certain cytokines……

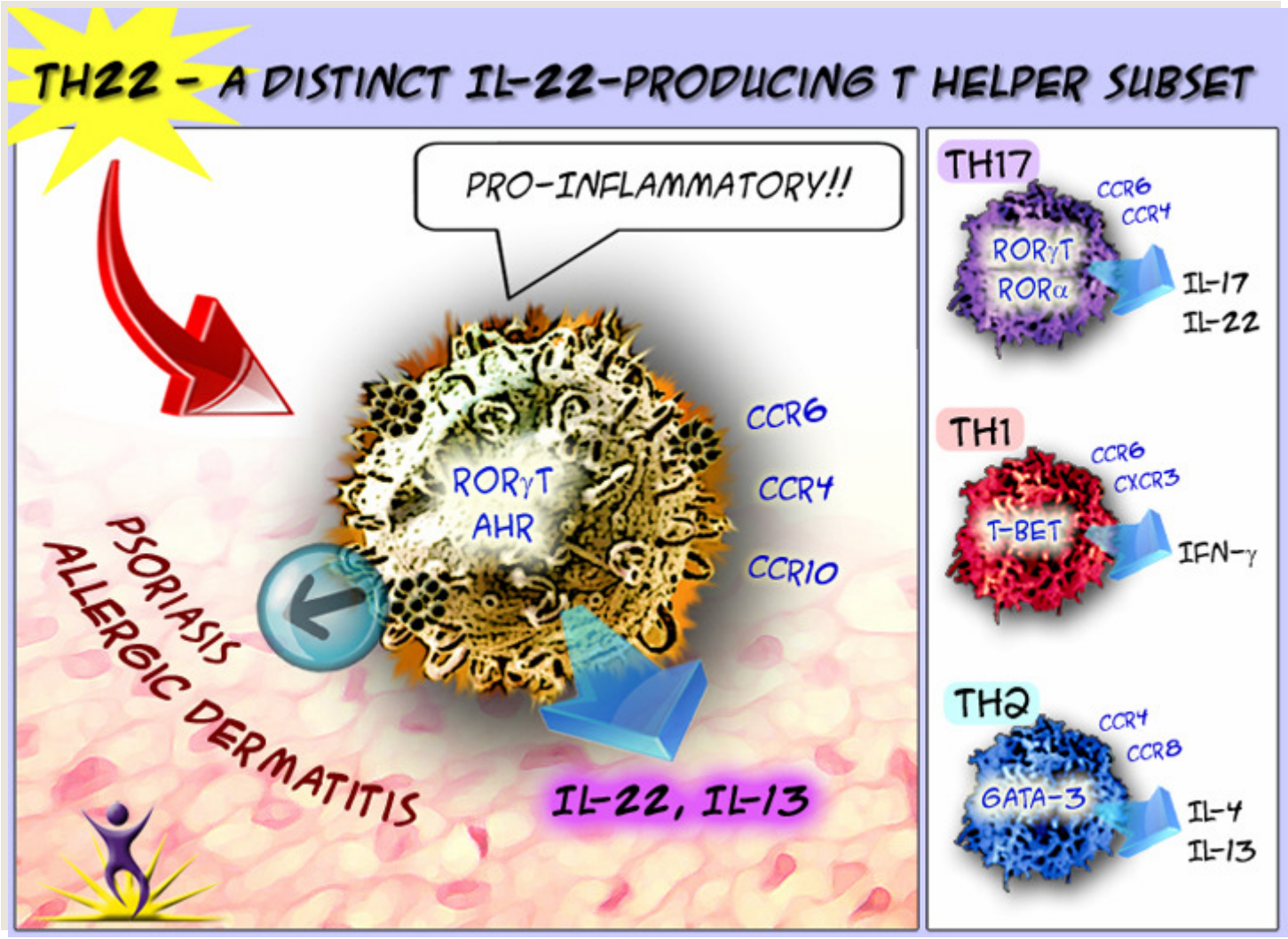

Th1
Th1
IL12
IL12
Th2
IL4
CD4+
CD161+
APC
CD4+
CD161−
IL4
Th2
IL1β+IL23
IL1β+IL23
TGFβ
TGFβ
Th1
Th17/1
Th17
IL23R
Th1
CXCR3
CCR6
CCR4
IFNγ
IFNγ / IL17A
IL17A
IFNγ

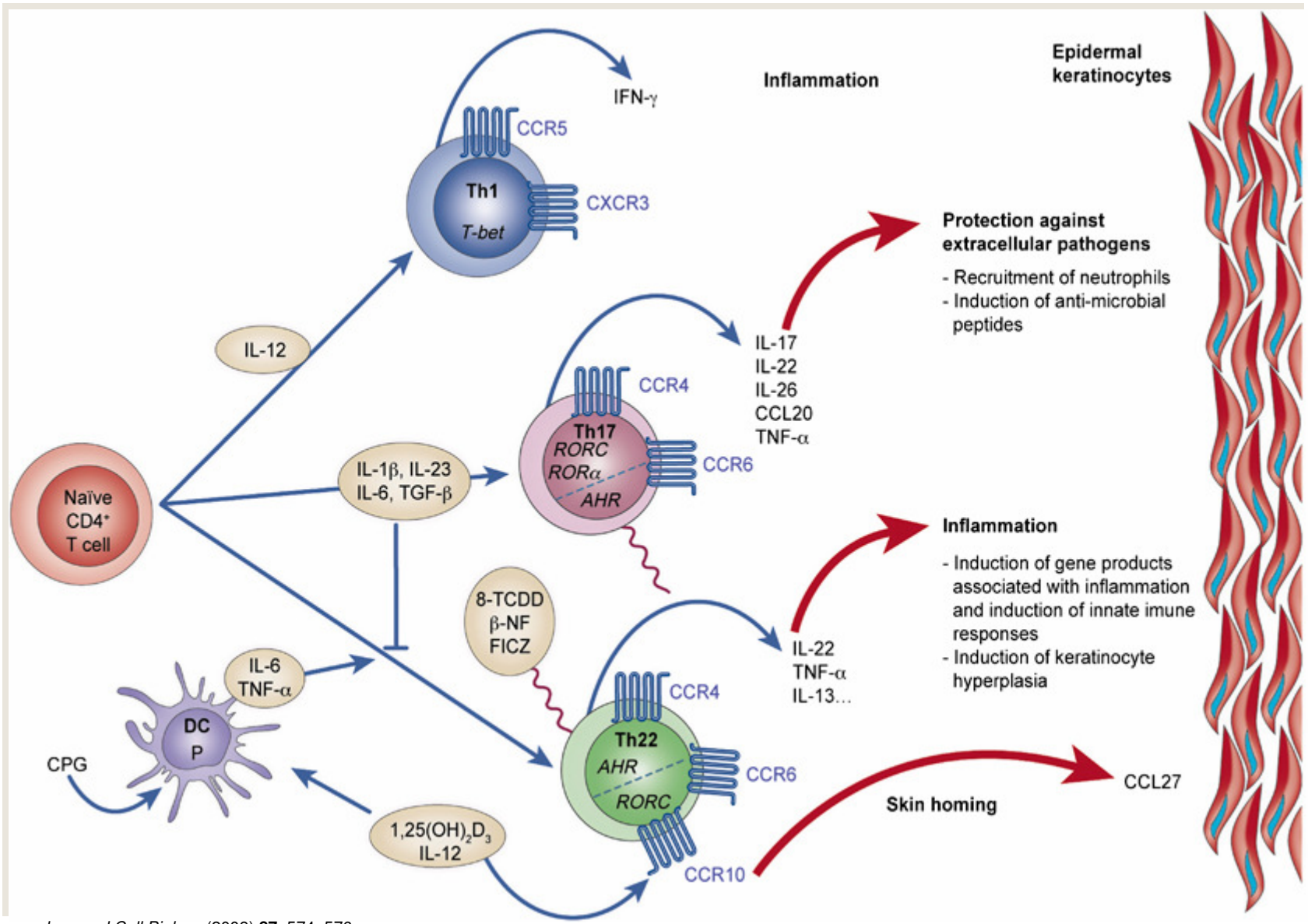

Regulatory T cells
CD4+CD25+ Foxp3+
Treg
IL-10
TGF-β
inhibition
Naïve
CD4+
T cell
IL-12
Th1
IL-2
IFN-?
TNF-α
Cell-mediated immunity
Intracellular pathogens
Immunopathology:
Organ-specific autoimmunity
CLR
DC
TLR
IL-2
Naïve
CD4+
T cell
IL-2
Naïve
CD4+
T cell
TGF-β
IL-6
IL-23
Th17
IL-17
Gut bacteria
Immunopathology:
Arthritis
IL-2
Naïve
CD4+
T cell
IL-4
Th2
IL-4
IL-5
IL-10
IL-13
Helminths
Humoral immunity
Immunopathology:
Allergy
Atopy
IL-10
TGF-β
inhibition
Regulatory T cells
Treg


Th17
IL17A
IL17F
IL21
IL22
IL26
CCL20
TNFα
IL6
Intestinal epithelial cells
Endothelial cells
Macrophages
Fibroblast
Paneth and Goblet cells
Colonic myofibroblasts
CCL20
Recruitment of Th17 cells and DCs
Recruitment of T cells, monocytes, DCs
CCL2, CCL5, CCL7, CCL19
Recruitment of neutrophils
CXCL1, CXCL2, CXCL5, CXCL8
Increased blood flow
NOS-2, prostaglandin E2
Degradation of fibronectin, laminin, collagens
MMP-1, MMP-3, MMP-16
Recruitment of granulocytes
G-CSF, GM-CSF
Transcriptional upregulation of proinflammatory mediators
IL1β, IL6, TNFα
Perpetuation of inflammation
Protection of epithelial barrier limiting inflammation
β-defensin-2, MUC5AC, MUC5B, tight junction proteins

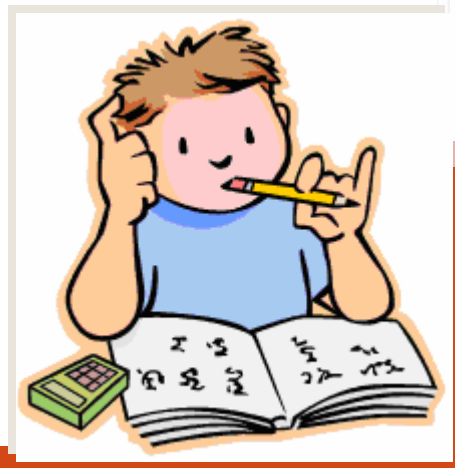

NAIVE CD4 T CELL
IL-6, IL-21, IL-23, TGF-β
TH17
IL-17A, IL-17F, IL-21, IL-22
IL-4, TGF-β
TH9
IL-9, IL-10
IL-2, IL-4
TH2
IL-3, IL-4 IL-5, IL-9, IL-13
IL-12, IL-18
TH1
IL-2, IFN-γ, TNF
TGF-β
TREG
TGF-β
IL-21
TFH
IL-6, IL-10, IL-21

Th22

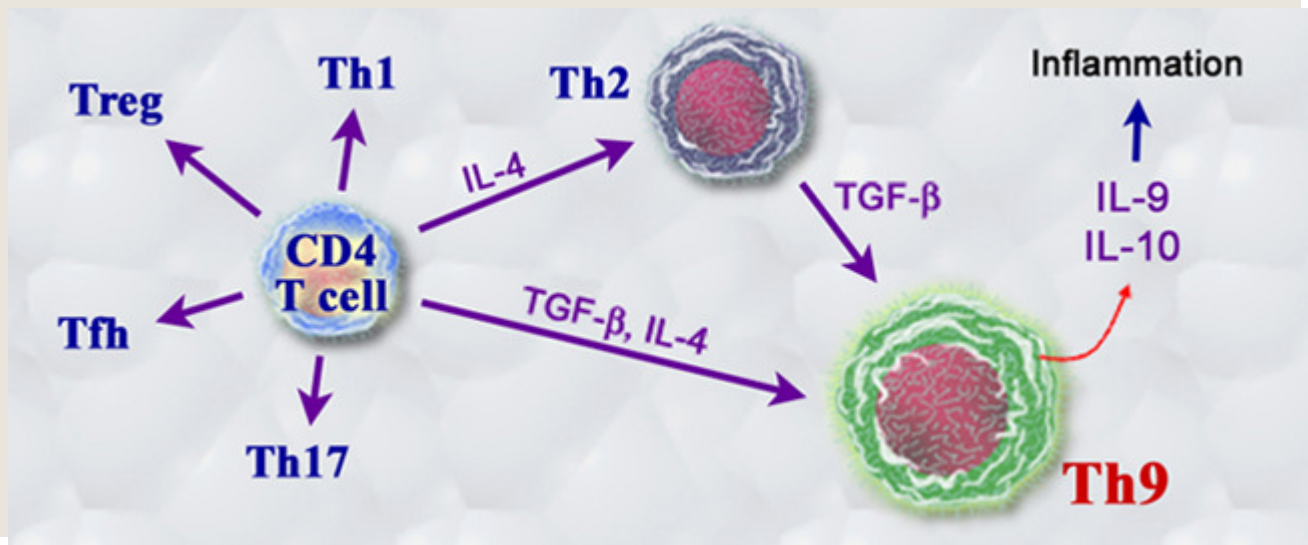

TH22 - A DISTINCT IL-22-PRODUCING T HELPER SUBSET
PRO-INFLAMMATORY!!
RORγT
AHR
CCR6
CCR4
CCR10
PSORIASIS
ALLERGIC DERMATITIS
IL-22, IL-13
TH17
CCR6
CCR4
RORγT
RORα
IL-17
IL-22
TH1
CCR6
CXCR3
T-BET
IFN-γ
TH2
CCR4
CCR8
GATA-3
IL-4
IL-13



Immunology and Cell Biology (2009) **87,** 574–576;

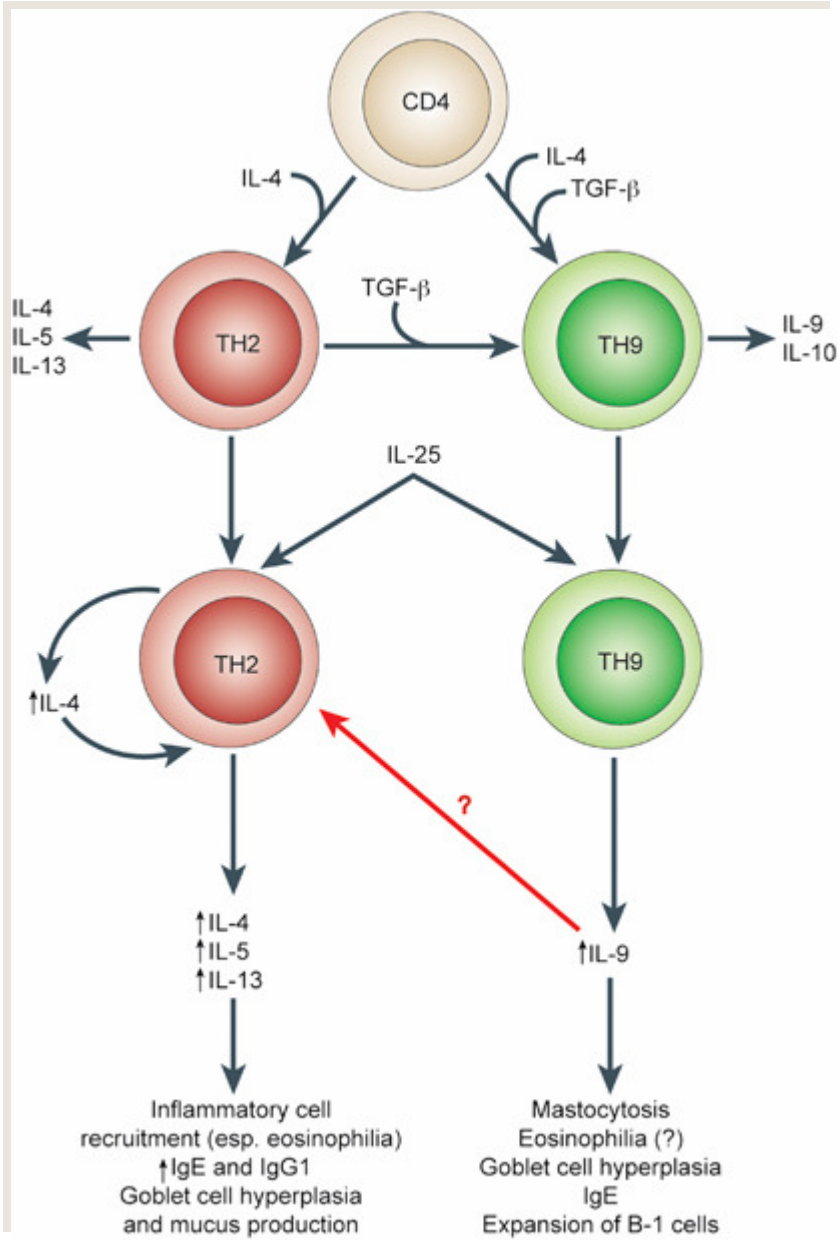


Th9



In late 2008, two groups showed that the combination of transforming growth factor-β (TGF-β) and IL-4 induced the differentiation of naive murine CD4⁺ T cells into a unique IL-9-producing subset termed Th9 cells. This confirmed the observations made 15 years earlier by Schmitt *et al.* that IL-4/TGF-β could induce IL-9 production from CD4⁺ T cells.

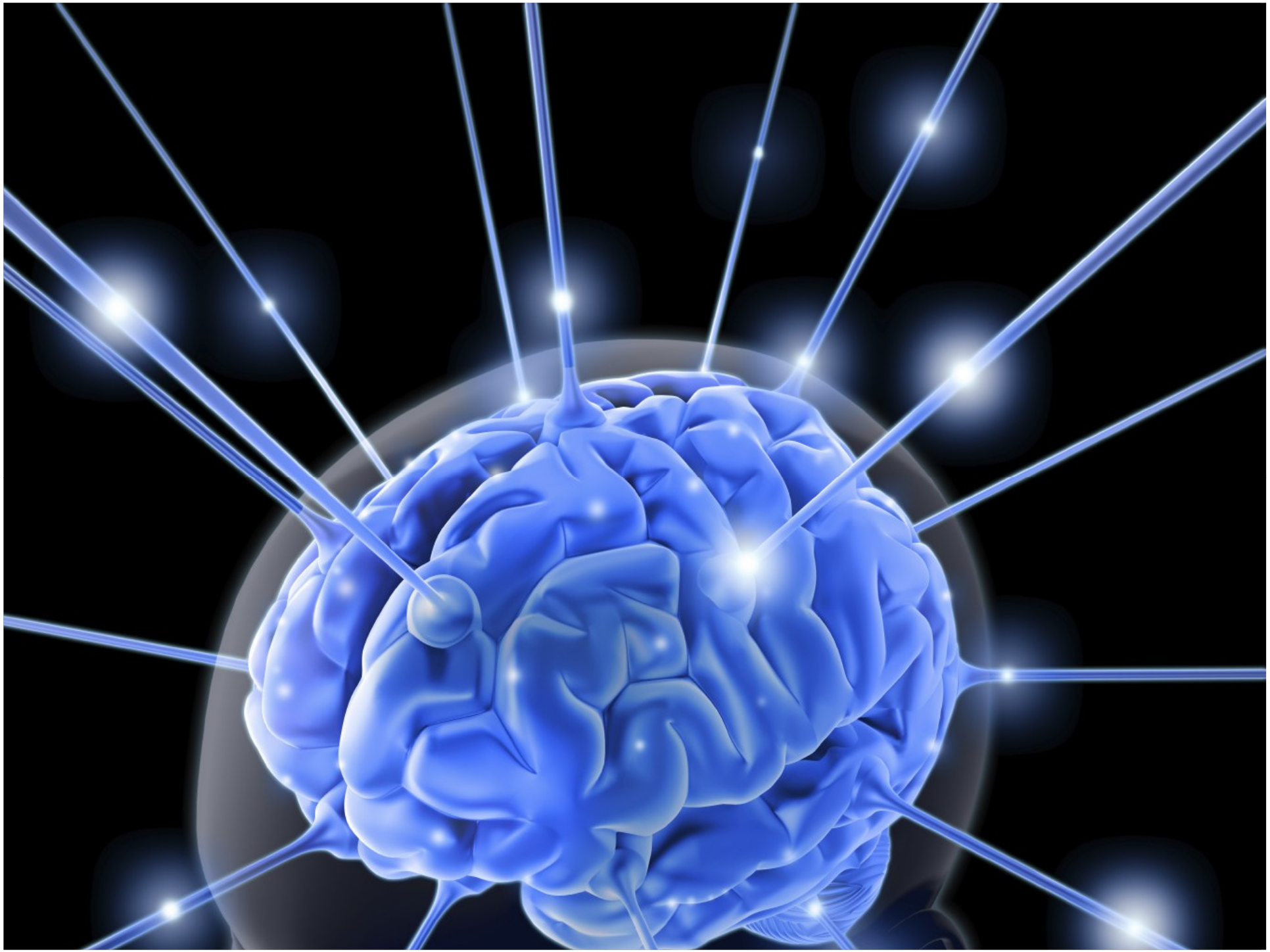
Factores que regulan el desarrollo y expansión de las células Th2 y Th9



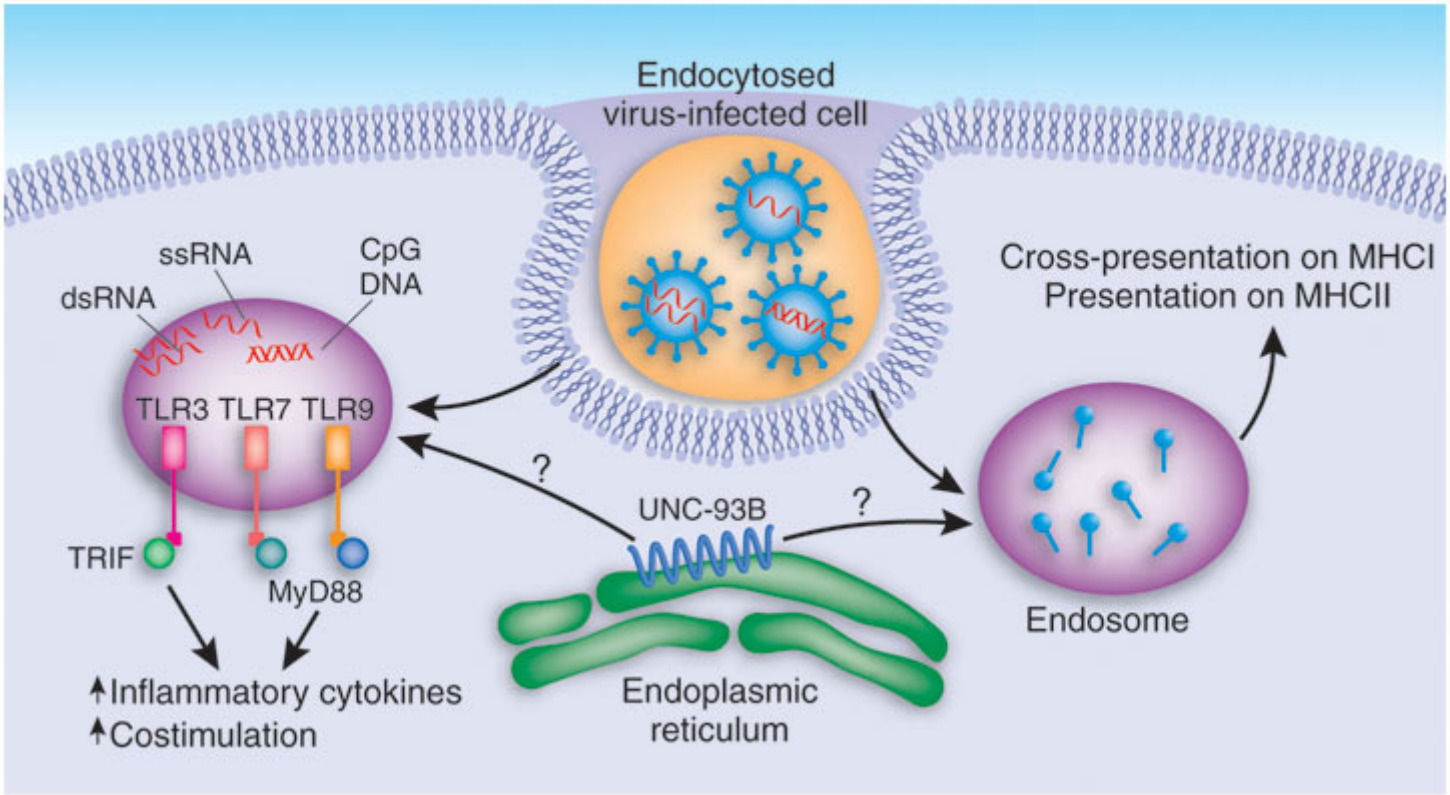
Immunology and Cell Biology (2010) **88,** 502–504;

Resumiendo.....

	Th1	Th2	Th9	Th17	Tfh	Treg
Signature cytokines lineage-specific transcription factors	IFN-γ TNF-α; TNF-β STAT4; T-bet; Hlx	IL-4; IL-5; IL-10; IL-13 STAT6; GATA3; c-maf; IRF4; Gfi-1	IL-9	IL-17; IL-21; IL-22 ROR-α ROR-γt	IL-21	TGF-β IL-10 Foxp3
Inducing cytokines	IL-12; IL-18; IL-27; IFN-γ	IL-4	TGF-β/IL-4	IL-6/TGF-β IL-21/TGF-β IL-23	IL-21	TGF-β IL-10; IL-2; TSLP
Pathogens cleared	Intracellular bacteria; protozoal parasites; fungi; viruses	Extracellular pathogens including helminthes and nematodes	Helminthes	Similar to Th1, but with certain specific functions		Negatively regulate pathogen clearance
Immune pathology involved	IBD; GVHD; IDDM (T1D); RA	atopic asthma; allergies		MS (EAE); RA; psoriasis; IBD; allergies		Maintain self-tolerance and homeostasis



Presentación cruzada

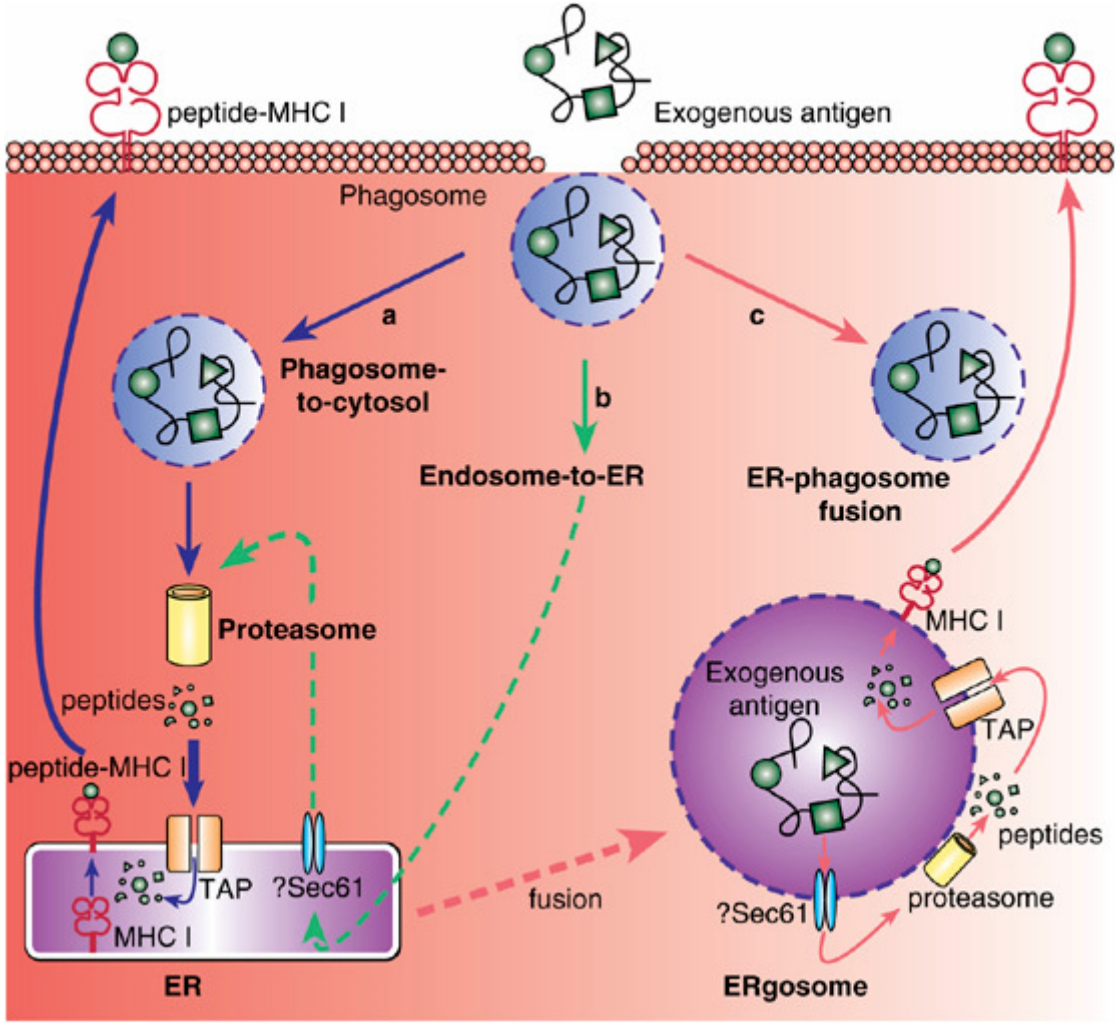


Nature Immunology **7**, 127 - 128 (2006)

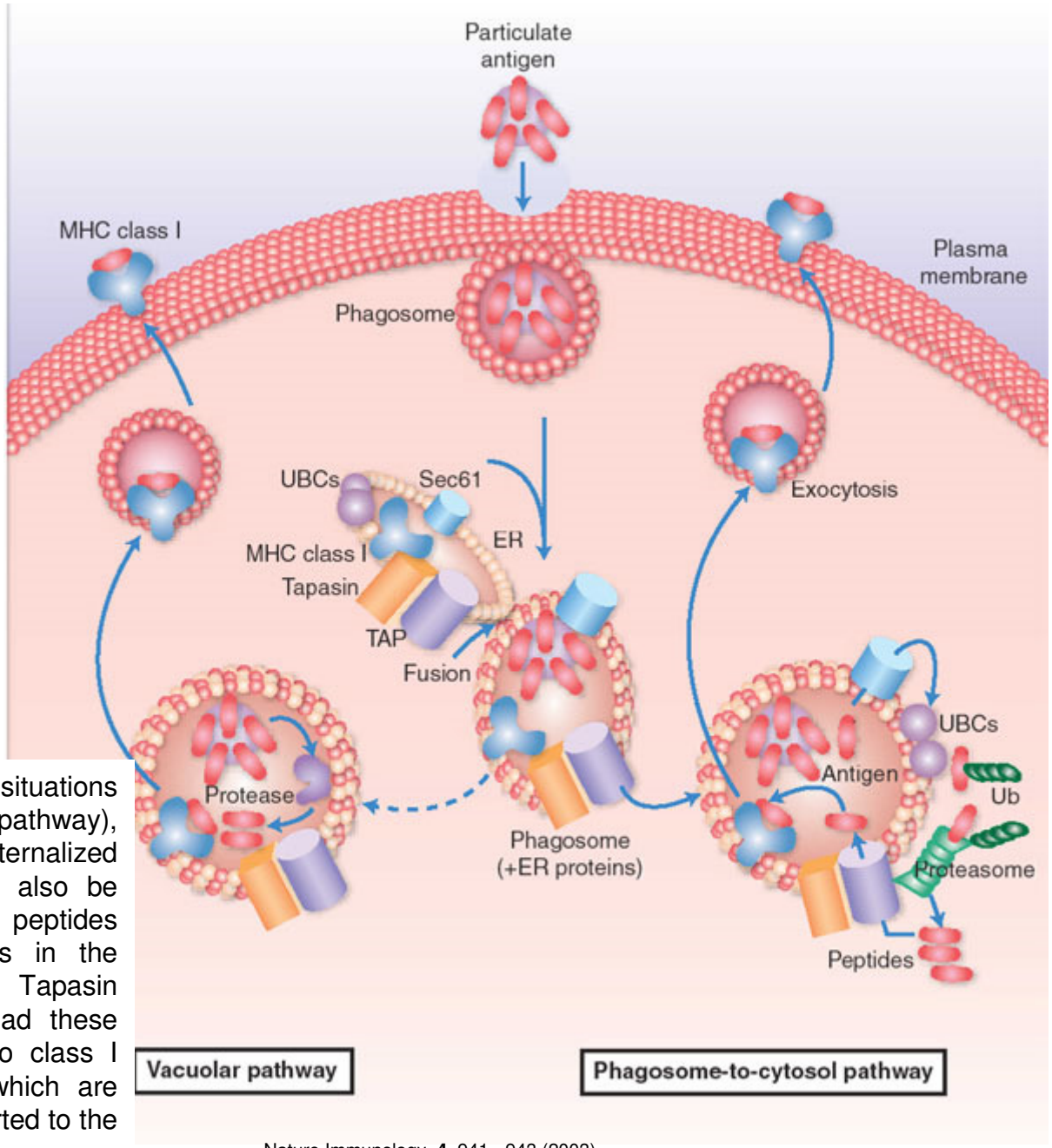
Presentación cruzada

- 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
  - Antígenos solubles
  - Transferencia directa intercelular

Modelos de PRESENTACIÓN CRUZADA



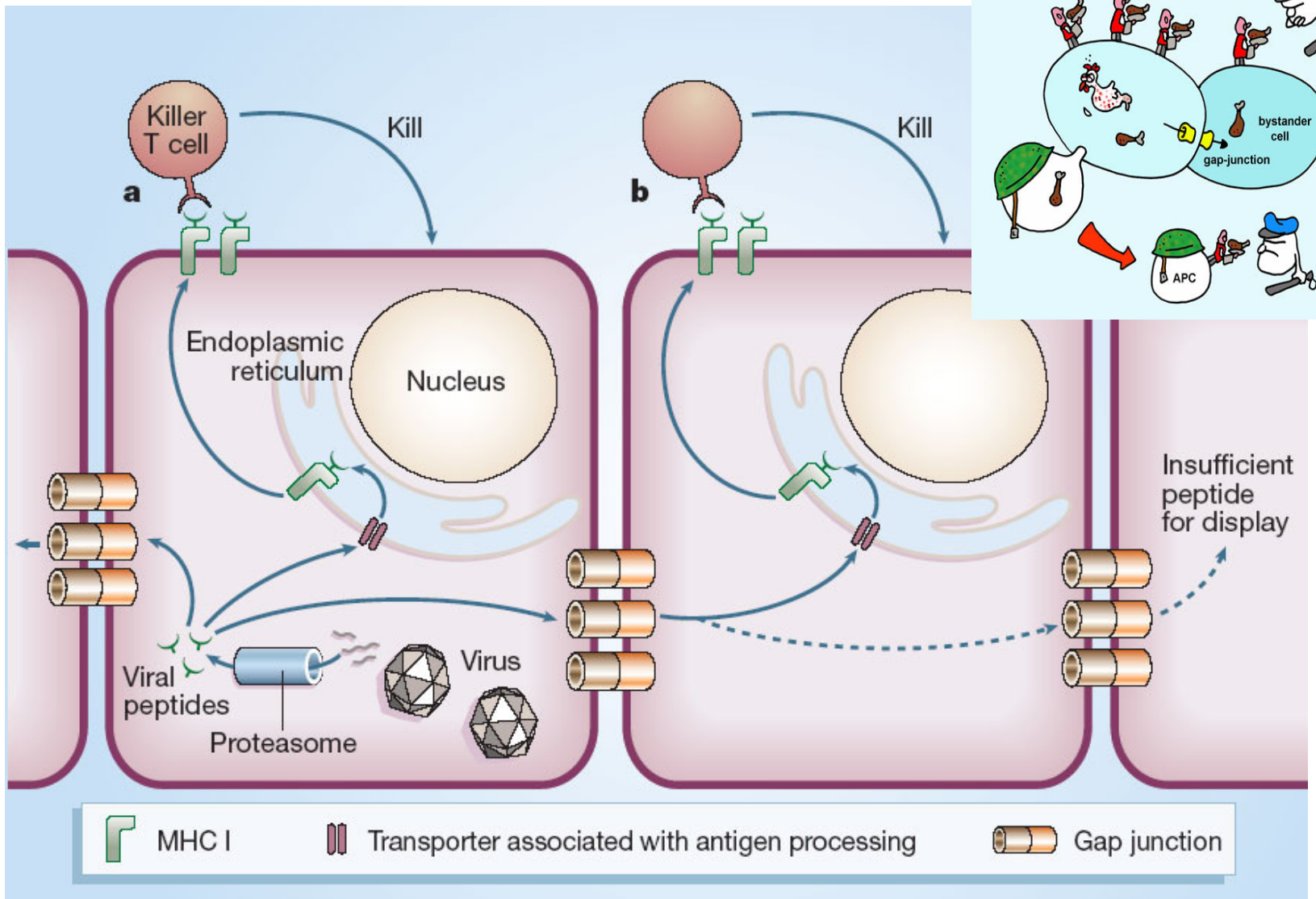
•Immunology and Cell Biology, 2009 . ISSN: 0818-9641



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

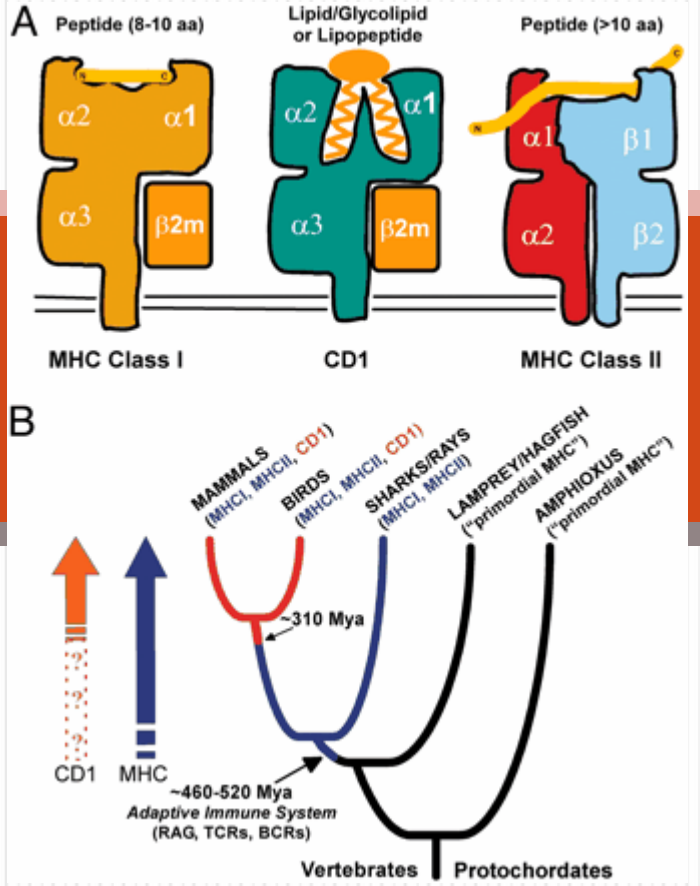
In some situations ('vacuolar' pathway), the internalized antigen may also be cleaved into peptides by proteases in the phagosome. Tapasin may help load these peptides onto class I molecules, which are then transported to the cell surface.

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.


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

MHC class I
CTL
bystander
cell
gap-junction
APC

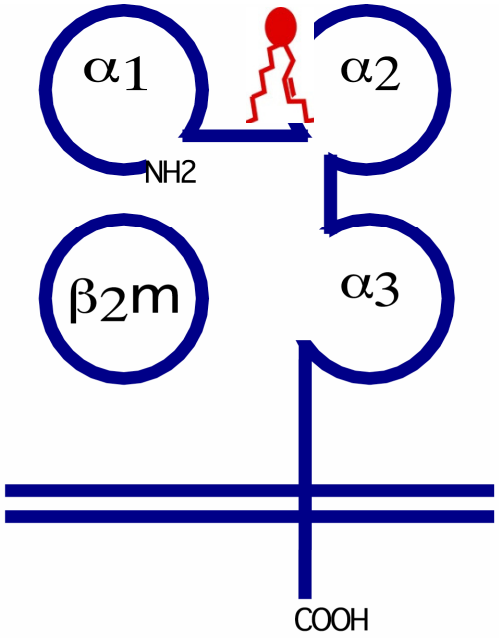
Presentación en CD1

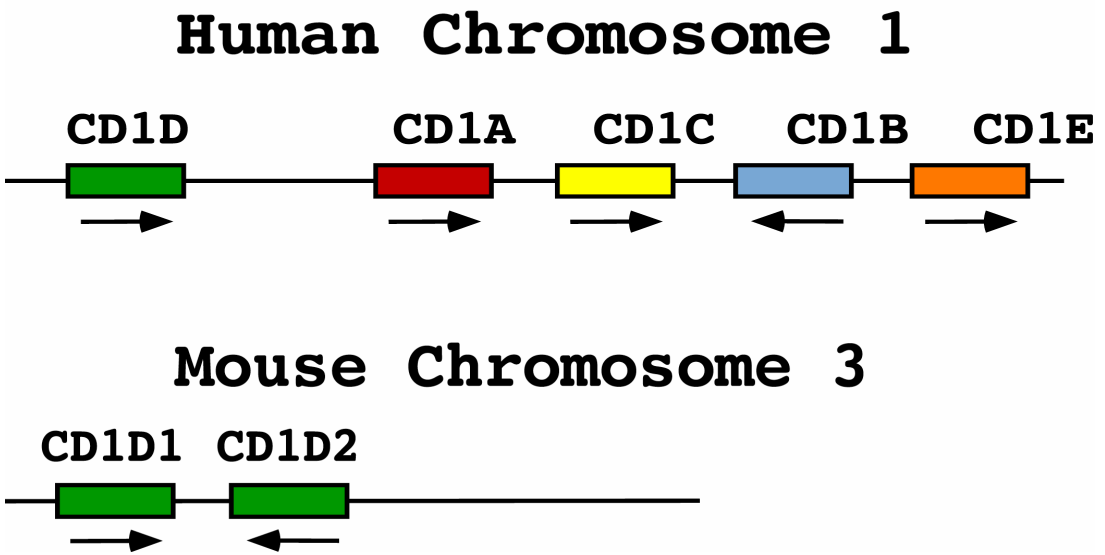


PRESENTACIÓN DE ANTÍGENOS NO PROTEICOS

CD1

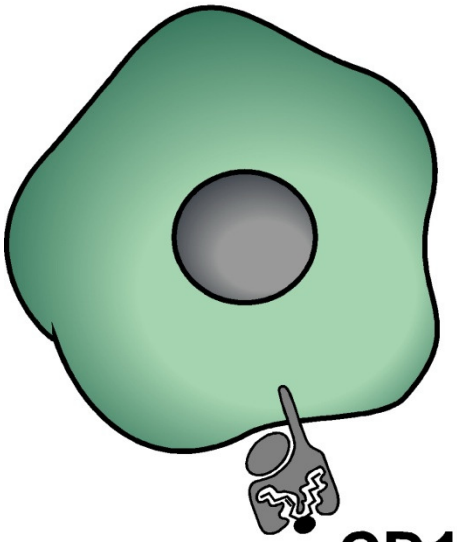
- Lípidos Microbianos
- Lípidos propios





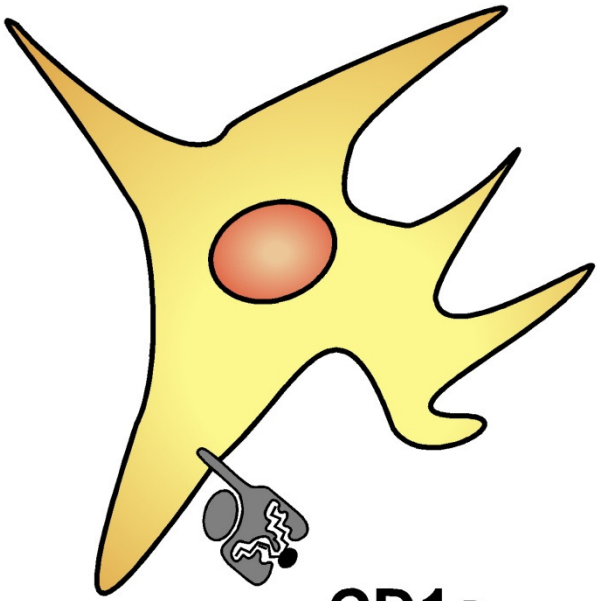
APC CD1^{+}

Monocyte



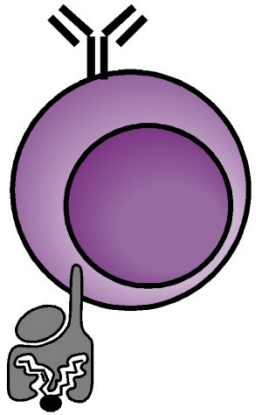
CD1d

Dendritic Cell



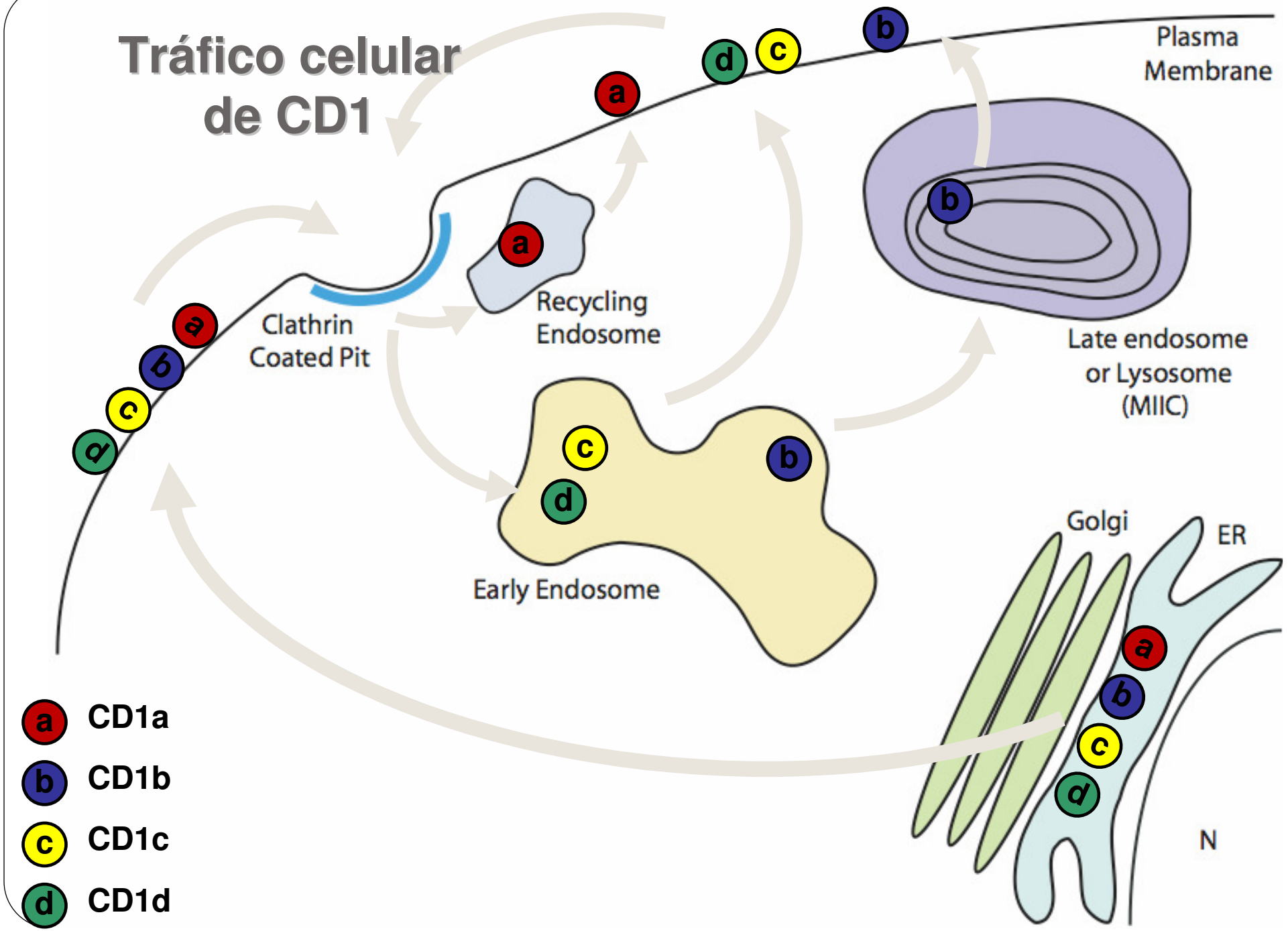
CD1a
CD1b
CD1c
CD1d

B cell

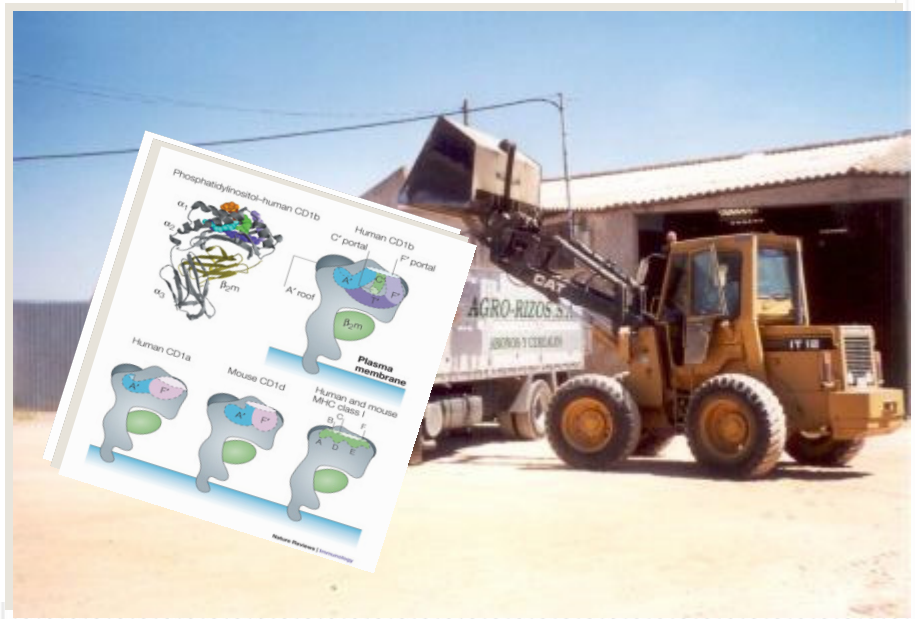


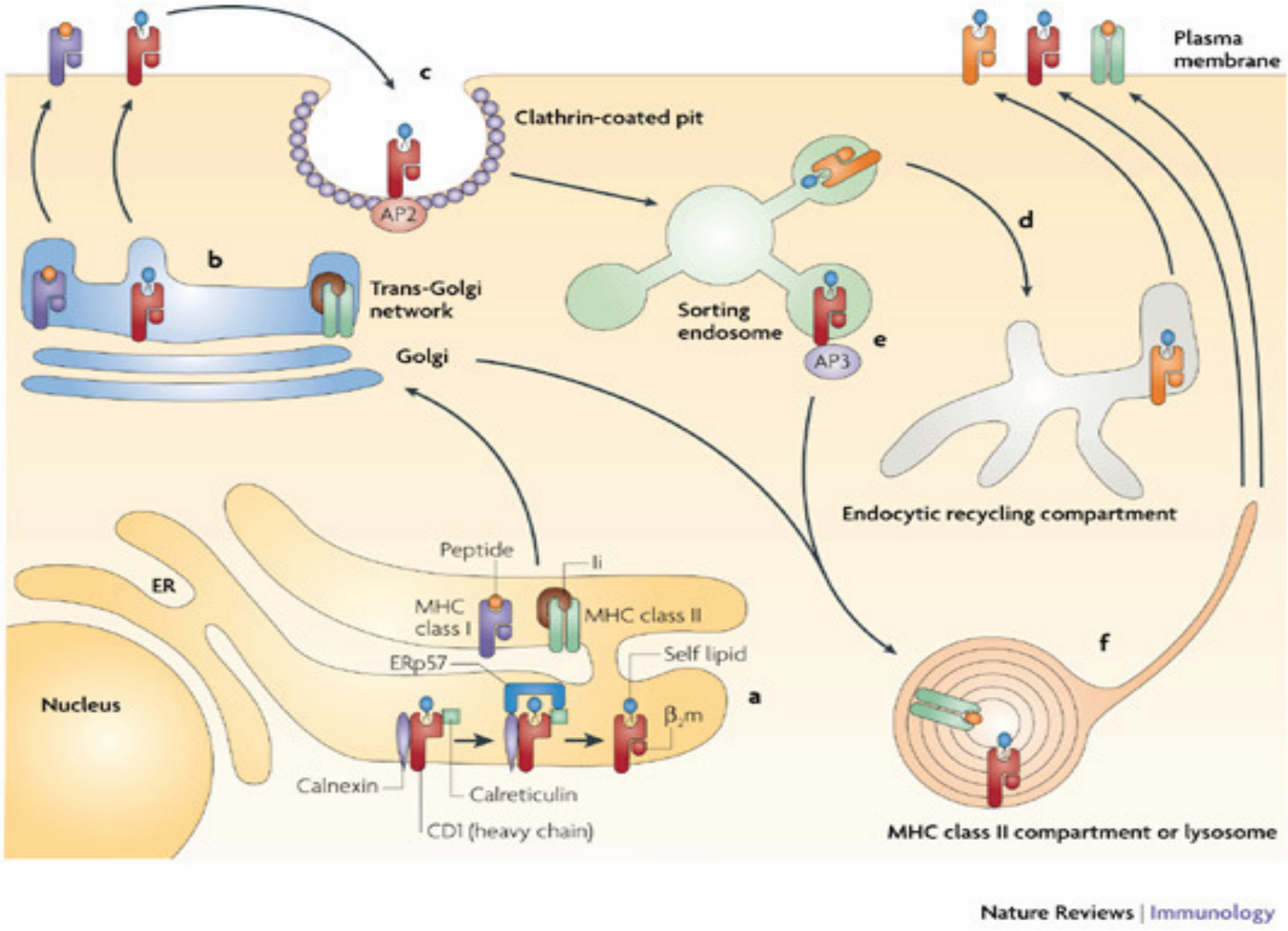
CD1c
CD1d

Tráfico celular de CD1

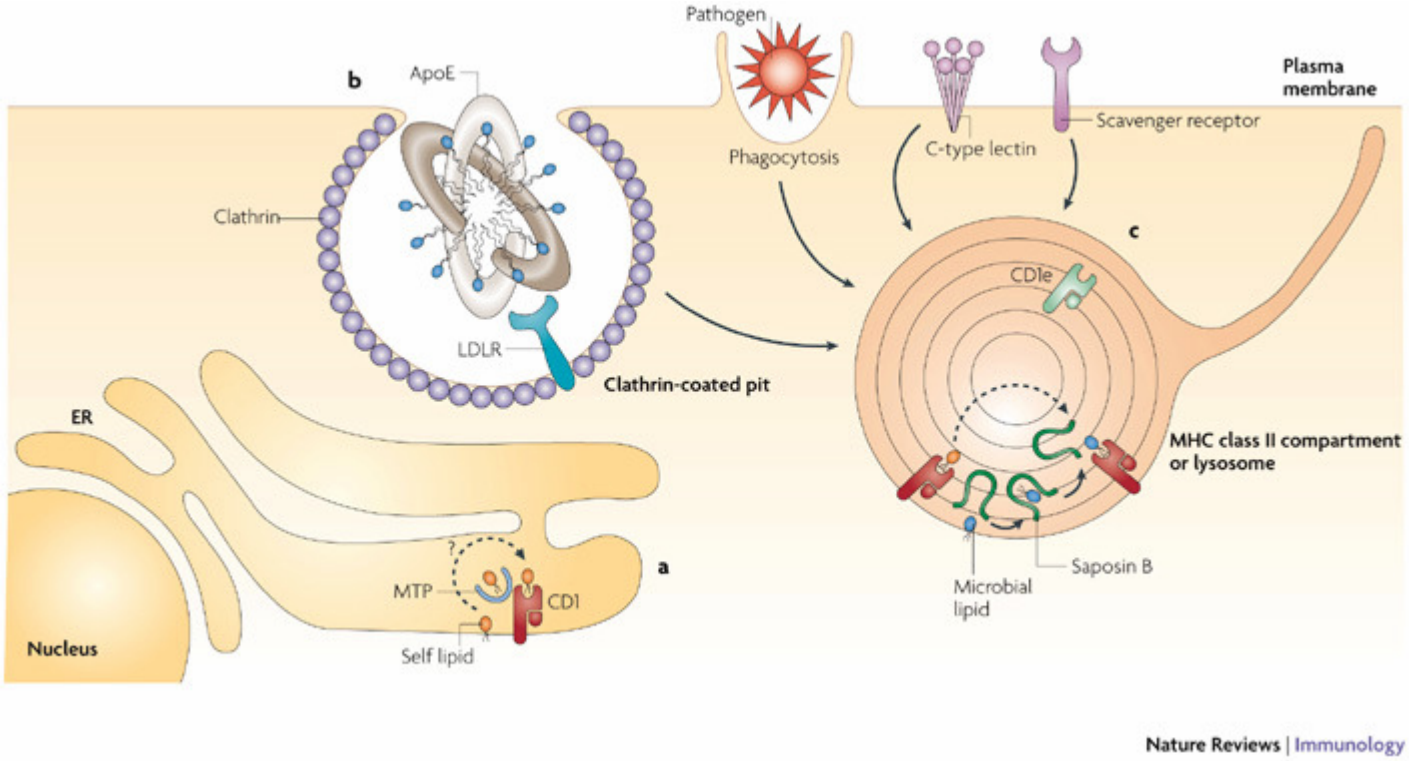


¿Cómo se carga la molécula de CD1?

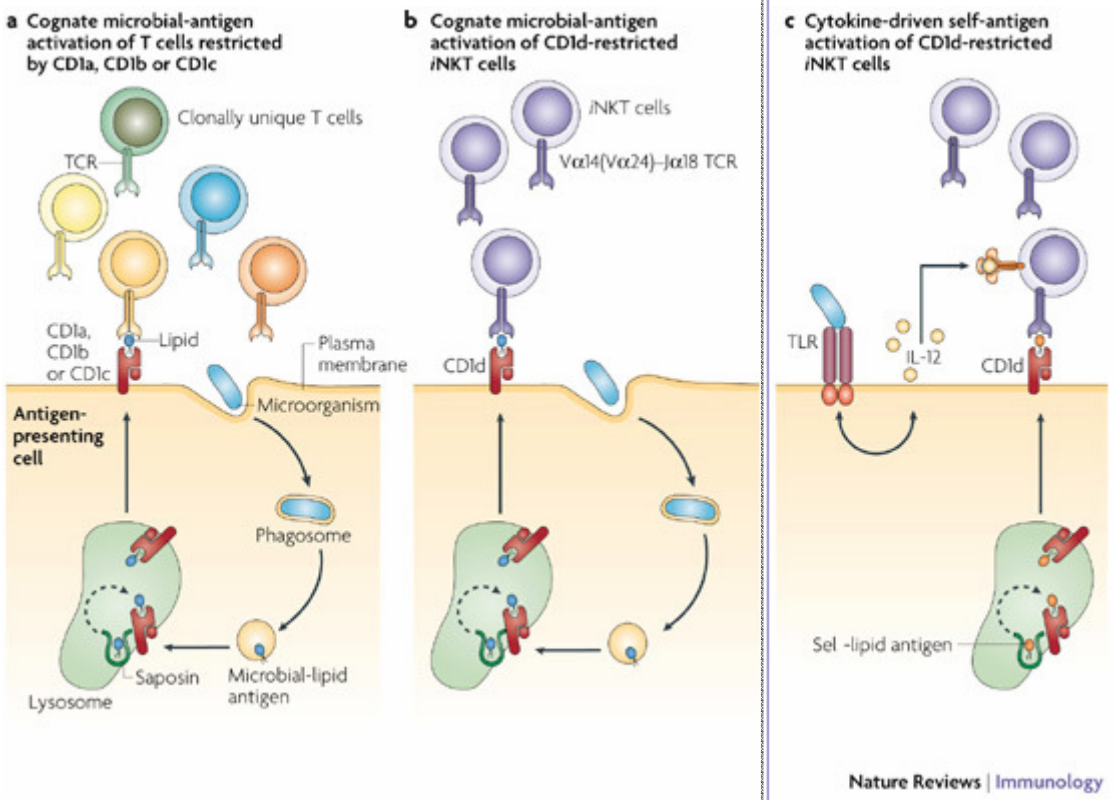




Nature Reviews Immunology 7, 929-941 (December 2007)

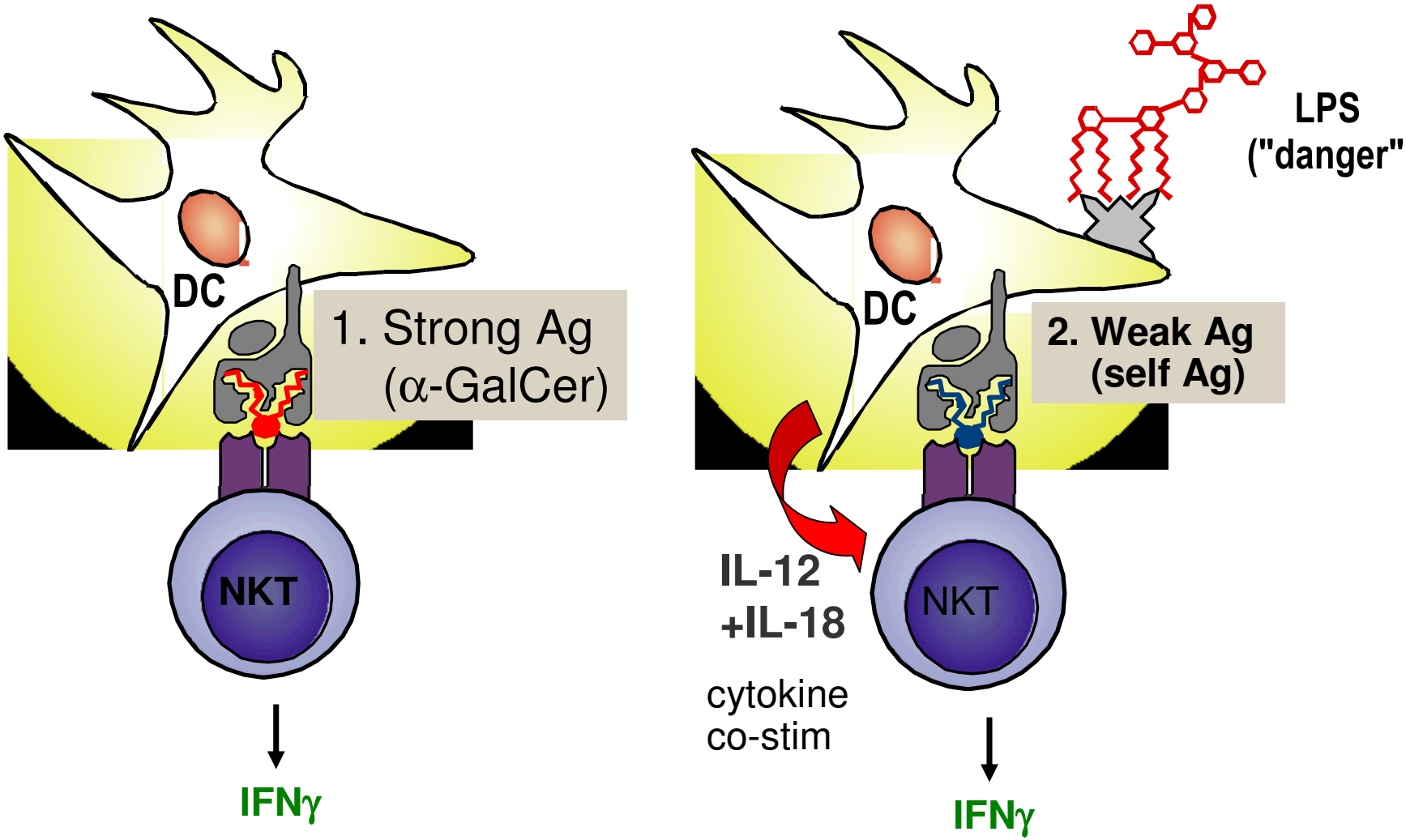


a | Self lipids (shown in orange) from the endoplasmic reticulum (ER) are loaded onto CD1 molecules. In the case of CD1d, this process is facilitated by a poorly characterized mechanism that involves microsomal triglyceride transfer protein (MTP). b | Four possible mechanisms for the uptake of foreign 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.

ESTIMULACIÓN DE CÉLULAS NKT: SECRECIÓN DE IFNγ



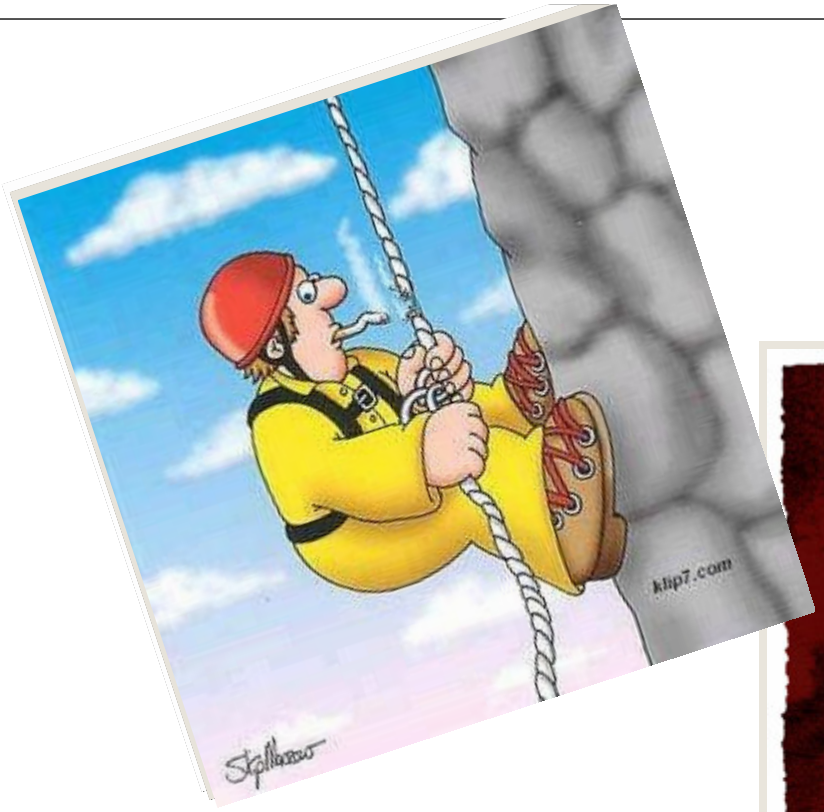
Antígenos lipídicos presentados por CD1

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 *i*NKT 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; *i*NKT cell, invariant natural killer T cell; TCR, T-cell receptor.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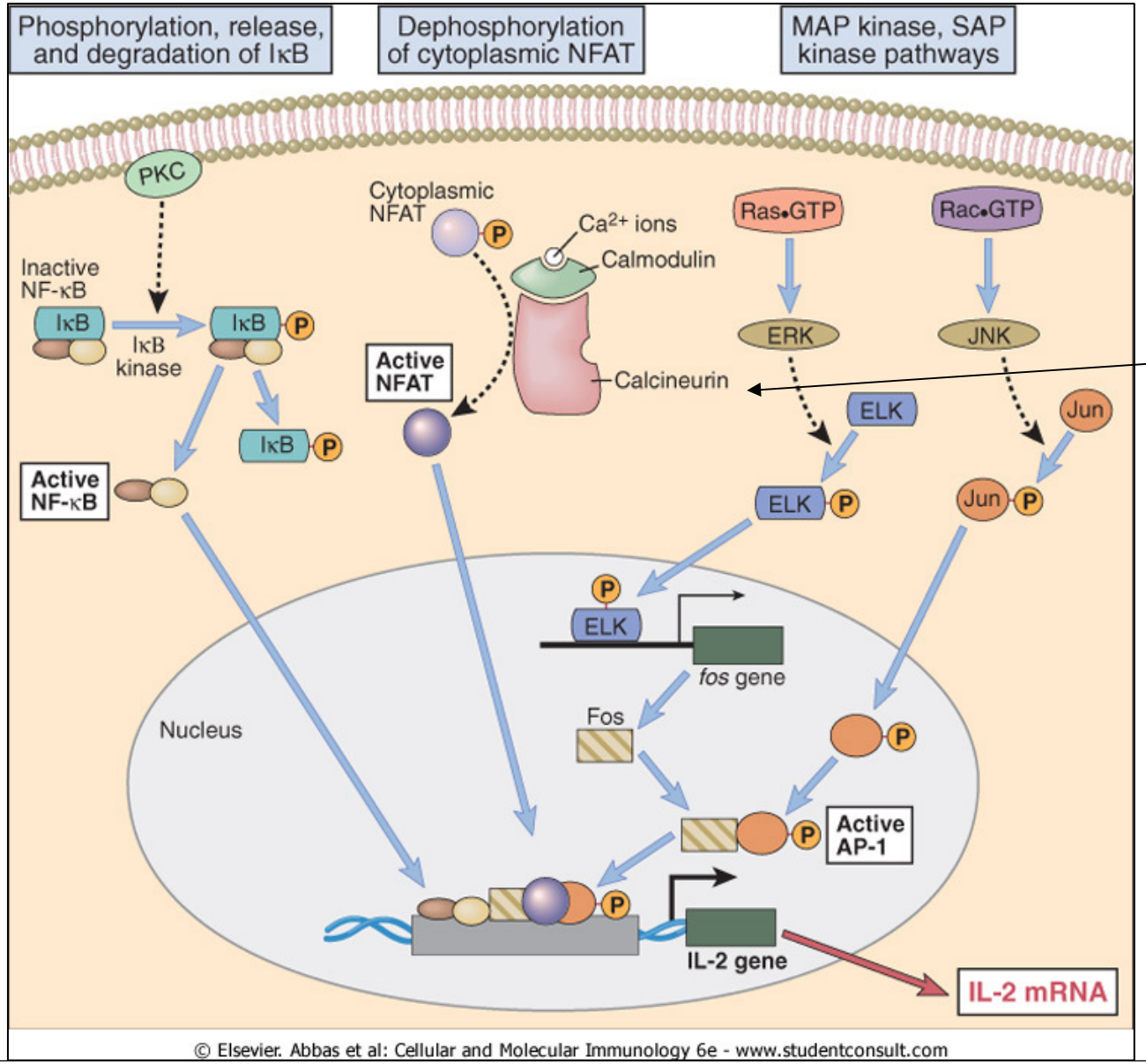
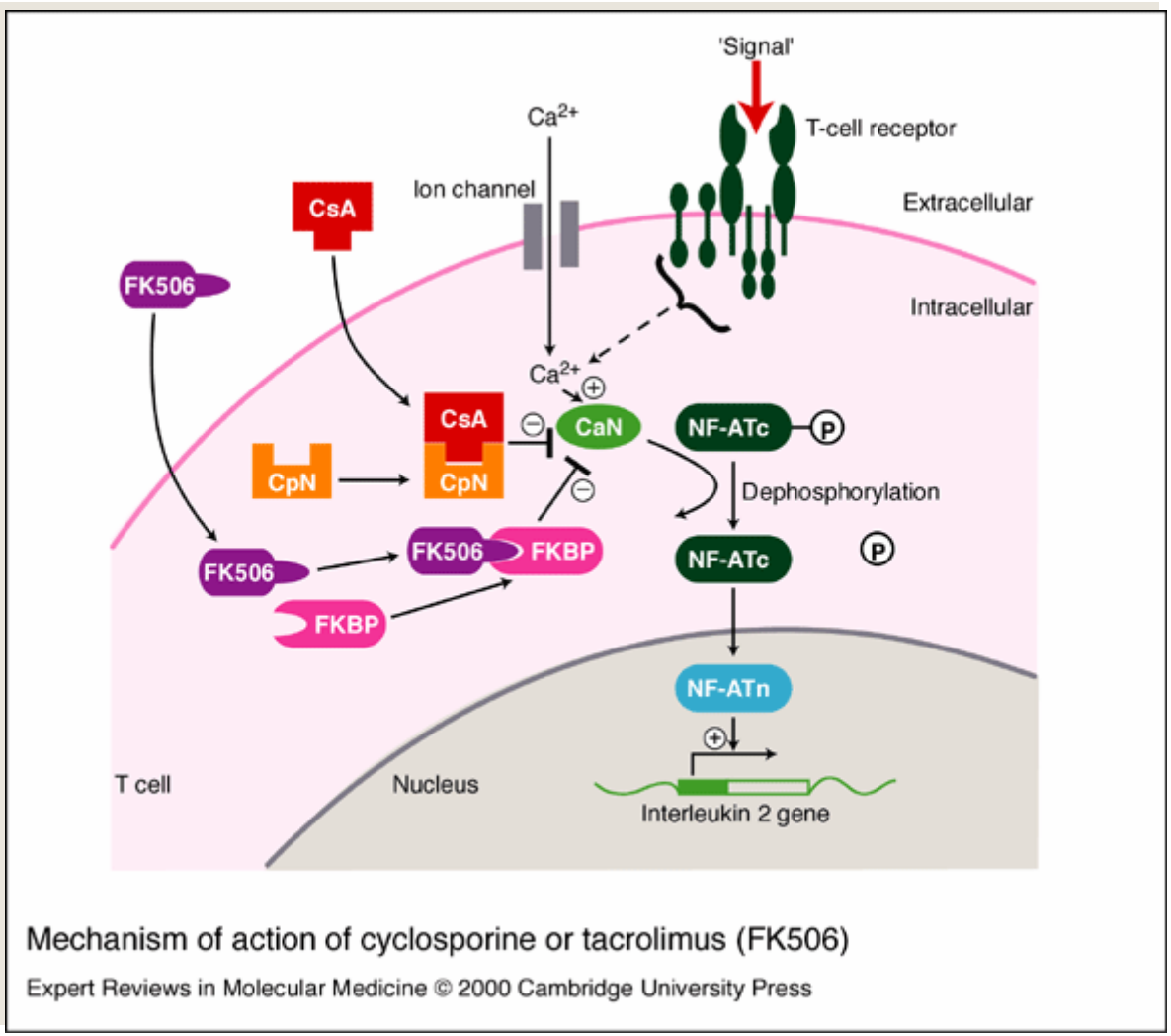
Recordemos

Expresión de IL-2 durante la señalización del TCR



Inhiben la secreción de IL-2.....

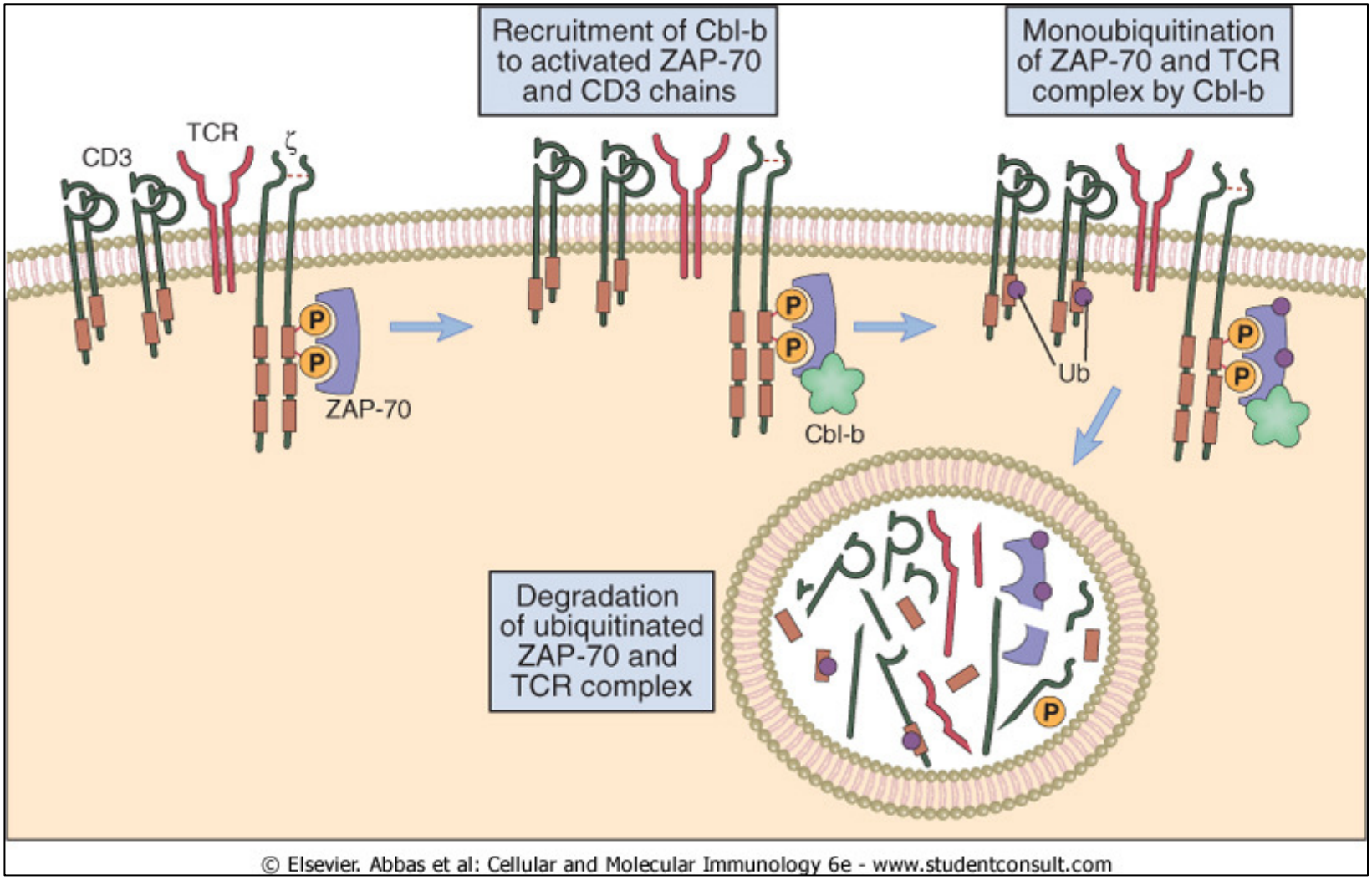


Mechanism of action of cyclosporine or tacrolimus (FK506)

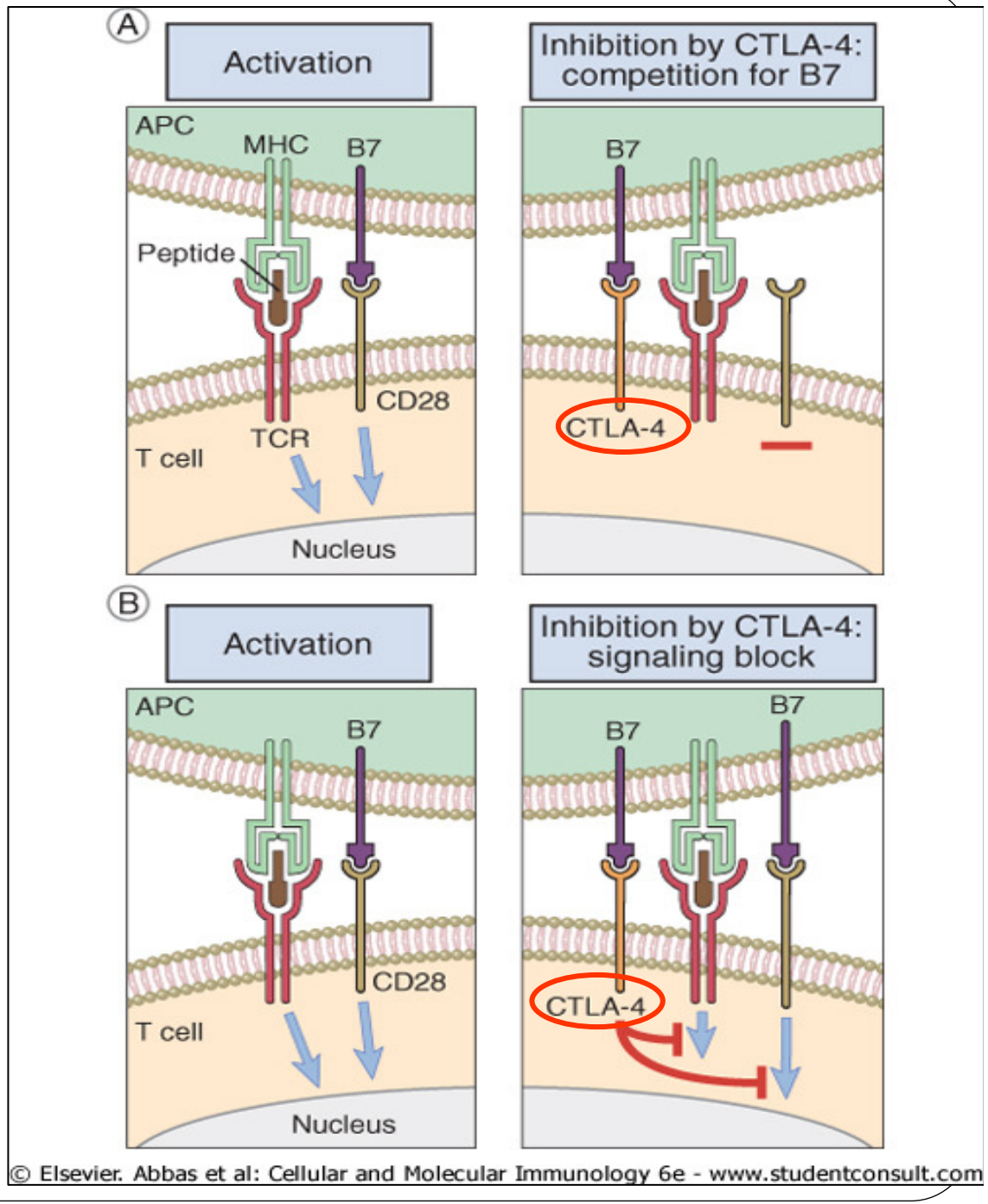
Ciclosporina / Tacrolimus

Mechanism of action of cyclosporine or tacrolimus (FK506). In the cytoplasm, cyclosporine (CsA) binds to its immunophilin, cyclophylin (CpN), forming a complex between cyclosporine and CpN. The cyclosporine–CpN complex binds and blocks the function of the enzyme calcineurin (CaN), which has a serine/threonine phosphatase activity. As a result, CaN fails to dephosphorylate the cytoplasmic component of the nuclear factor of activated T cells (NF-ATc), and thereby the transport of NF-ATc to the nucleus and the binding of NF-ATc to the nuclear component of the nuclear factor of activated T cells (NF-ATn). The NF-ATc–NF-ATn complex binds to the promoter of the interleukin 2 (IL-2) gene and initiates IL-2 production. Consequently, T cells do not produce IL-2, which is necessary for full T-cell activation. Tacrolimus (FK506) binds to FK506-binding protein (FKBP), forming a FK506–FKBP complex, which binds to and blocks CaN. The FK506–FKBP–CaN complex inhibits the activation of NF-ATc, thus preventing its entrance into the nucleus. Although the pre-drugs cyclosporine and FK506 bind to different target molecules, both drugs inhibit T-cell activation in the same fashion

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



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

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POR
INTENTARLO


Gracias!! que tengas un lindo dia
HON