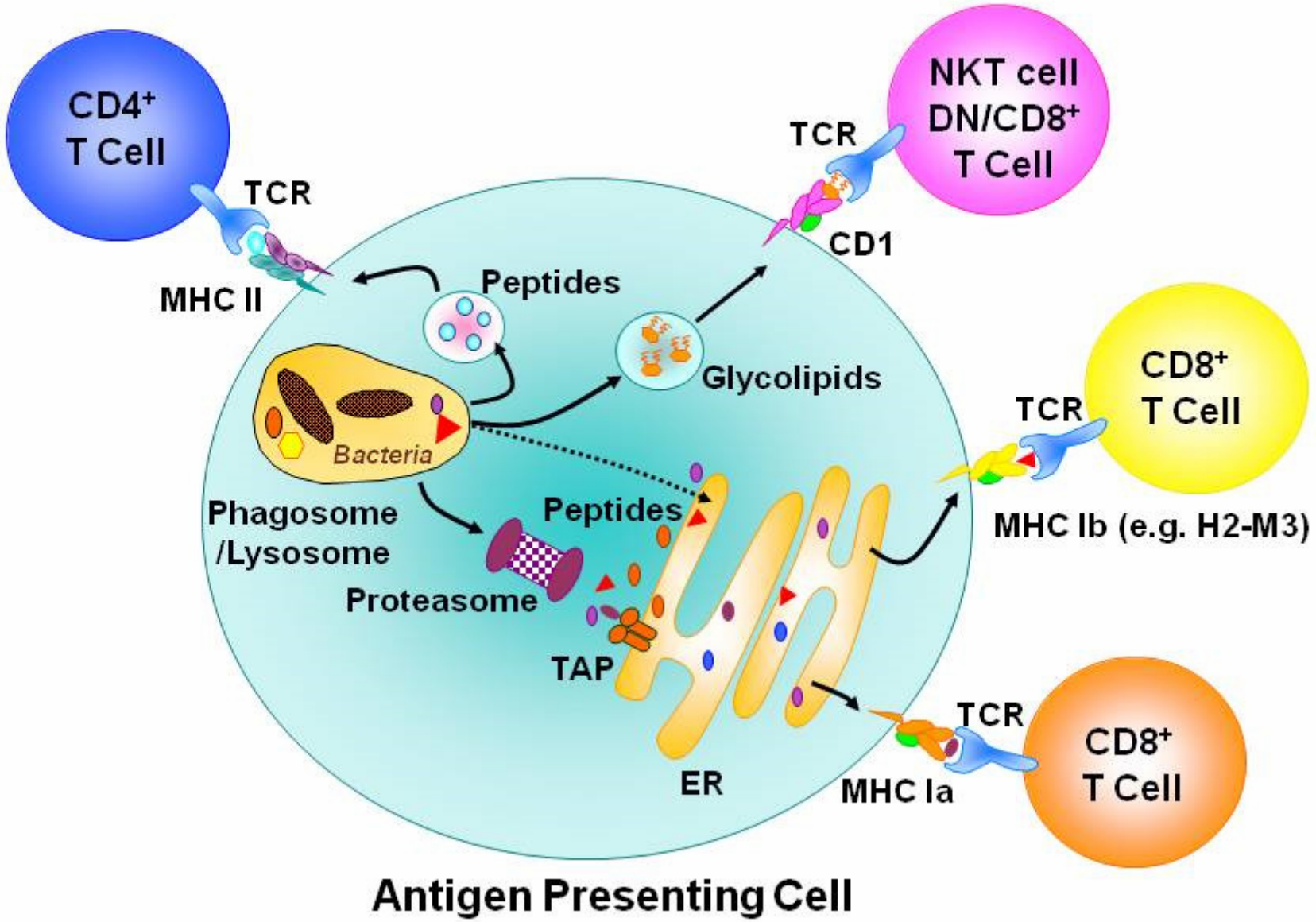
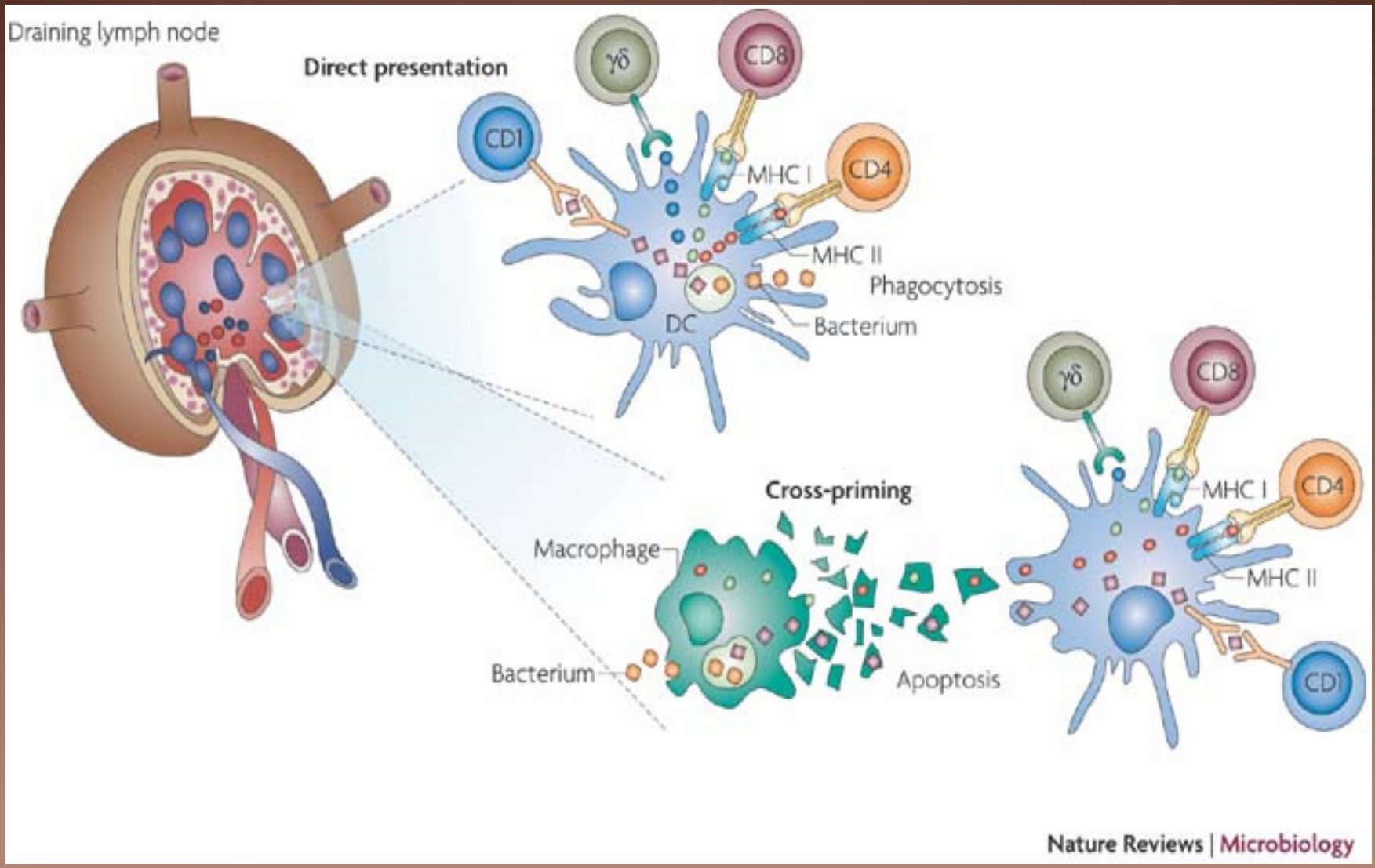
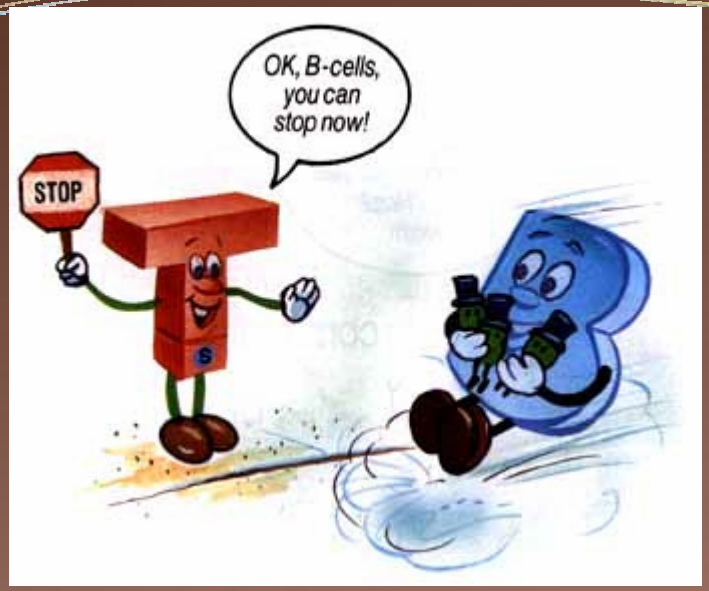
Inmunología Clínica 2010

Bioq Graciela Svibel

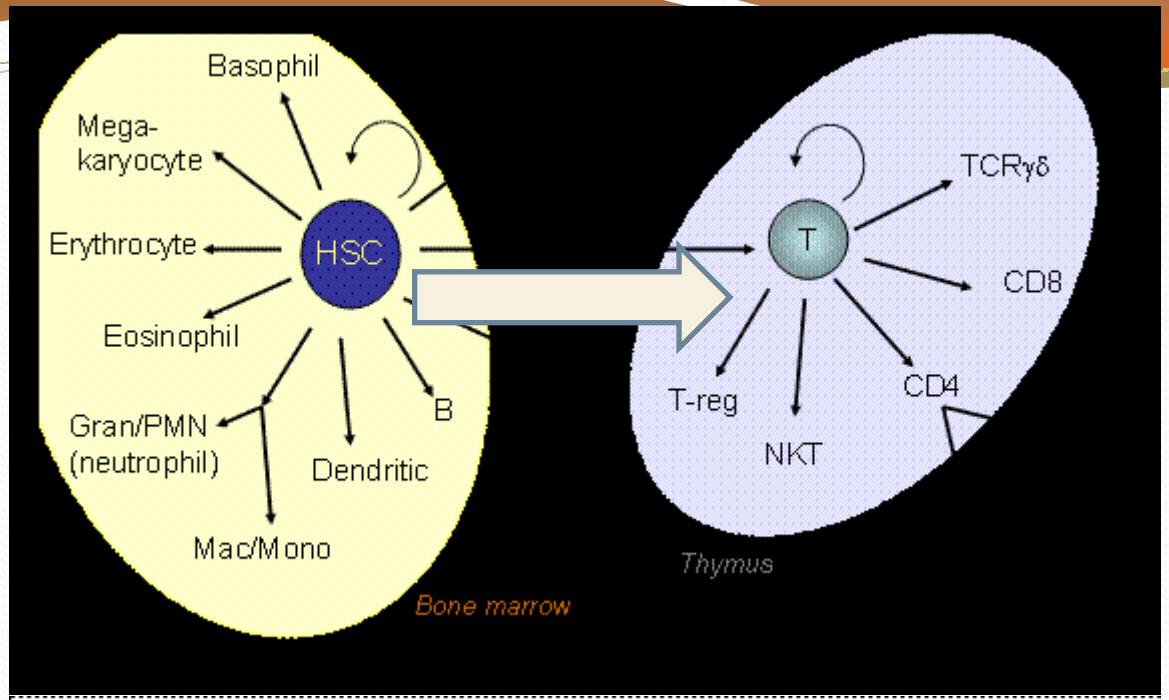
Knowledge about the function of different T cell populations during infection provides the basis for rational vaccine design

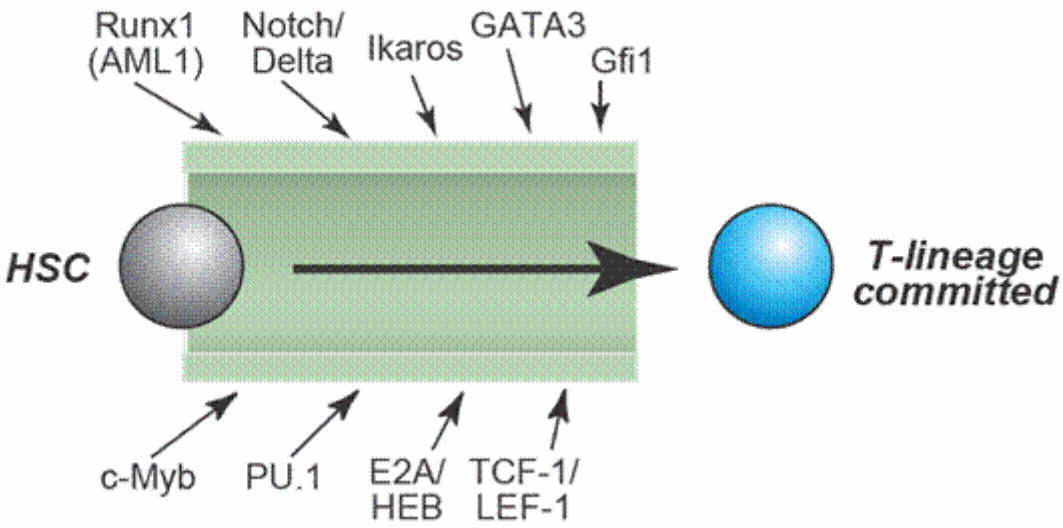



Draining lymph node
Direct presentation
γδ
CD8
CD1
MHC I
CD4
MHC II
Phagocytosis
DC
Bacterium
Cross-priming
Macrophage
Bacterium
Apoptosis
γδ
CD8
MHC I
CD4
MHC II
CD1
Nature Reviews | Microbiology

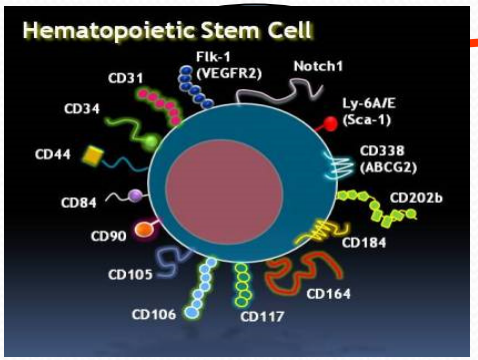


ONTOGENIA DE CÉLULAS T


Basophil
Mega-
karyocyte
Erythrocyte
HSC
Eosinophil
Gran/PMN
(neutrophil)
Dendritic
B
Mac/Mono
Bone marrow
T
TCRγδ
CD8
CD4
T-reg
NKT
Thymus


Runx1
(AML1)
Notch/
Delta
Ikaros
GATA3
Gfi1
HSC
T-lineage
committed
c-Myb
PU.1
E2A/
HEB
TCF-1/
LEF-1

Compromiso Linfoide-mieloide



PU.1 GATA-2

Progenitor linfoide-mieloide

PU.1 alto

Progenitor macrófago Mac 1+

PU.1

PU.1 bajo

Pro NK

Id2

Pro B

PU.1 Ikaros E2A EBF Pax-5

Progenitor linfoide

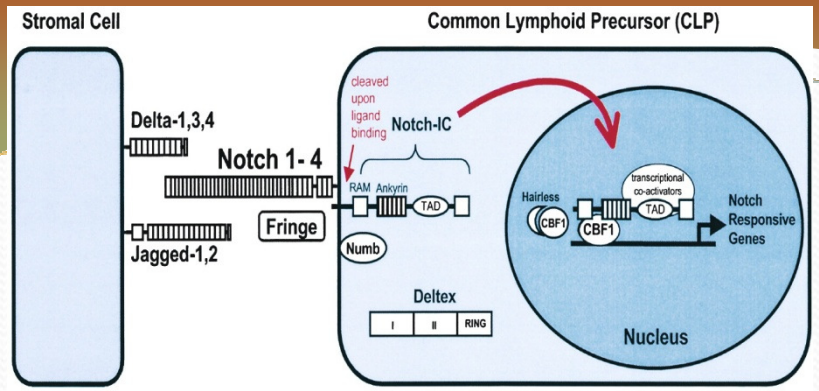
PU.1 Ikaros IL-7R+

Notch 1

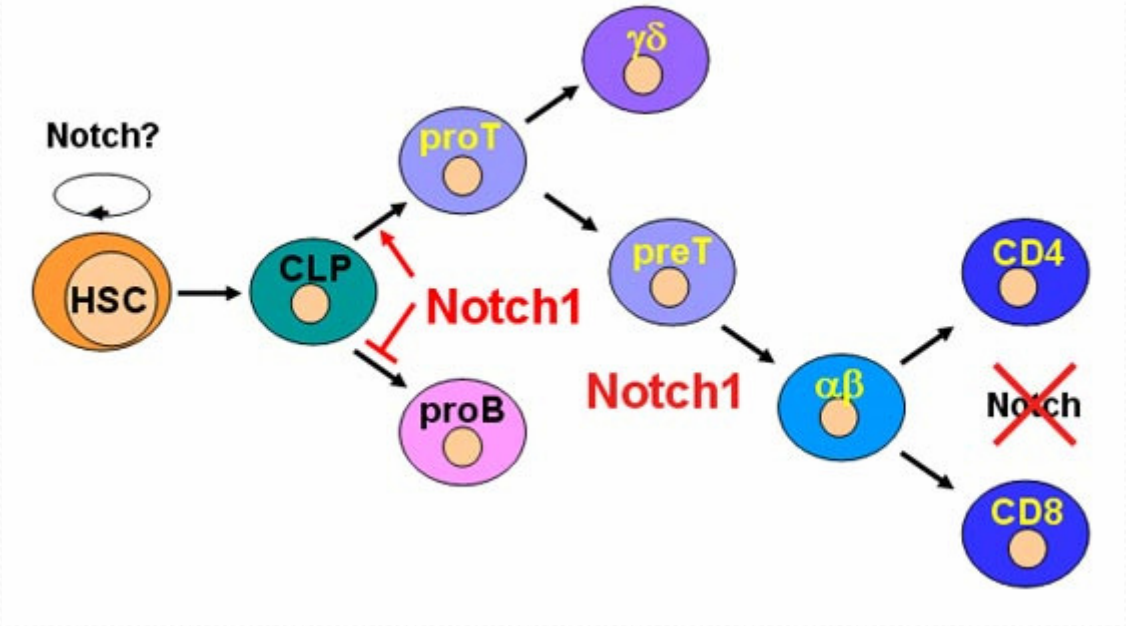
Pro T

Ikaros GATA-3

Factores de transcripción involucrados en el compromiso linfoide-mieloide en médula ósea



Rol de Notch en la "*elección*" del linaje T



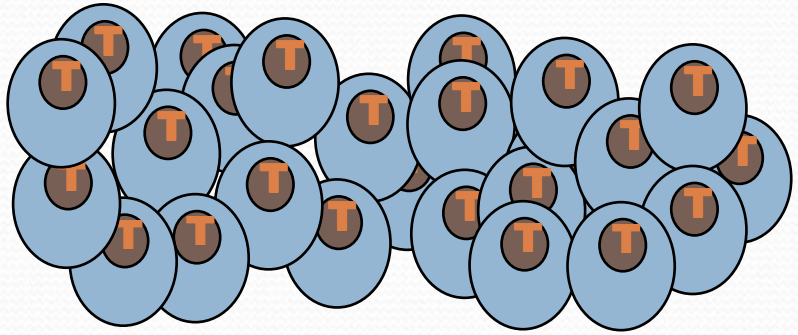
Notch (1,2,3) juega un rol importante al comprometer al CLP con el linaje T, pues interfiere con el Factor de transcripción E2A, importante en el compromiso hacia el linaje de células B

Lehar and Bevan, Immunity, 17:689, 2002

Ontogenia del Linfocito T

- Adquisición del receptor antigénico **REPERTORIO**
- Adquisición de moléculas de superficie CD : - Marcadores de **LINAJE**
  - Marcadores de **DIFERENCIACIÓN**
  - Marcadores de **FUNCIÓN**
- Selección **POSITIVA** de células que sean capaces de reconocer MHC propio **RESTRICCIÓN**
- Selección **NEGATIVA** de células autorreactivas **AUTOTOLERANCIA**
- Diferenciación de los timocitos a distintos tipos celulares

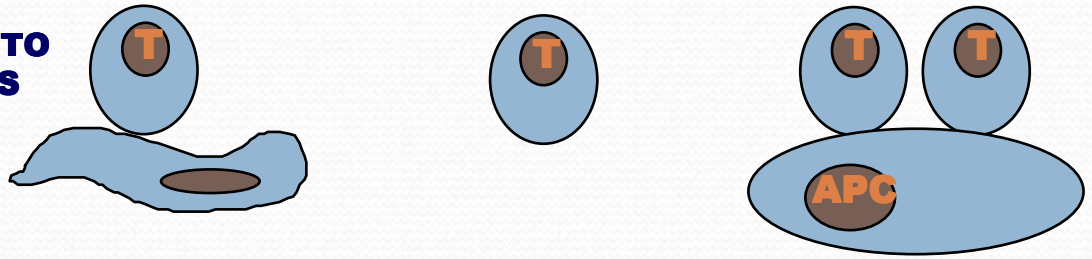
Linfocitos NKT
Linfocitos Tγδ
Linfocitos T CD4+ (Th1/Th2/Th3/Th17/Th9/Th22)
Linfocitos T CD8+ (LTc)



LA GENERACIÓN DEL REPERTORIO DE TCR INVOLUCRA MECANISMOS AL AZAR....

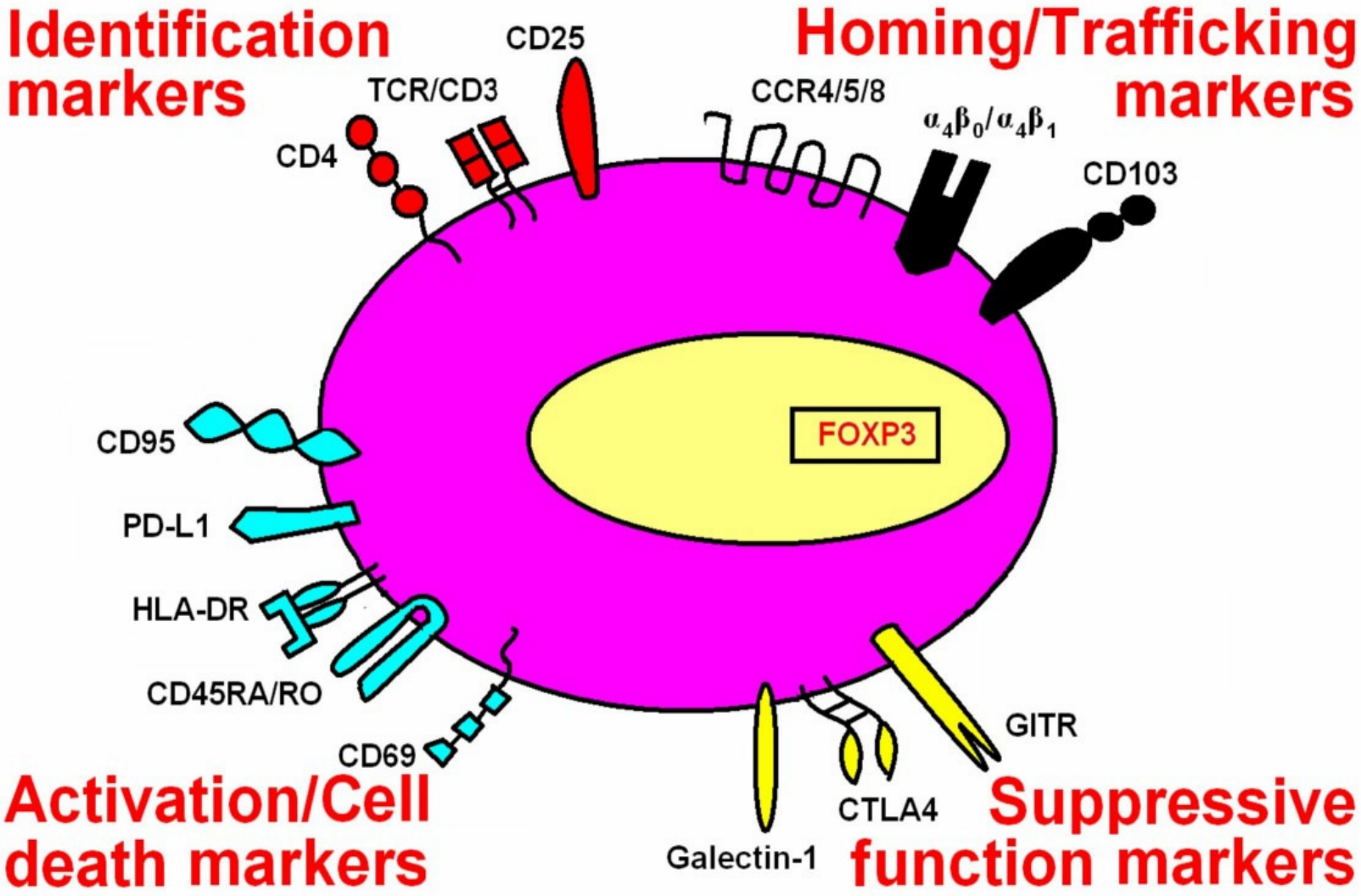
LA ESPECIFICIDAD DEL TCR EN EL REPERTORIO INMADURO ES TAMBIÉN AL AZAR E INCLUYE CÉLULAS CON RECEPTORES QUE SON:

RECONOCIMIENTO DE ANTÍGENOS PROPIOS

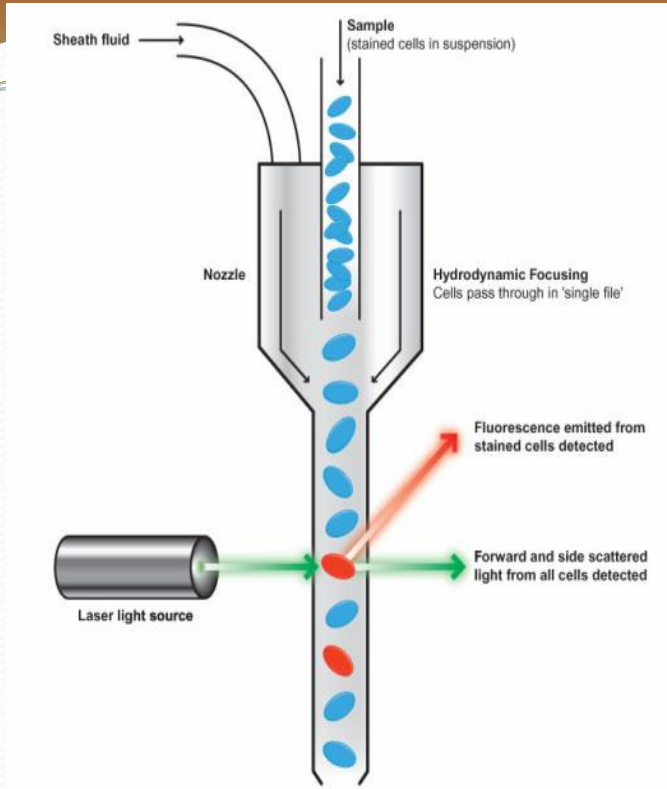


RECONOCIMIENTO DE ANTÍGENOS EXTRAÑOS

1. DAÑINOS 2. INÚTILES 3. ÚTILES

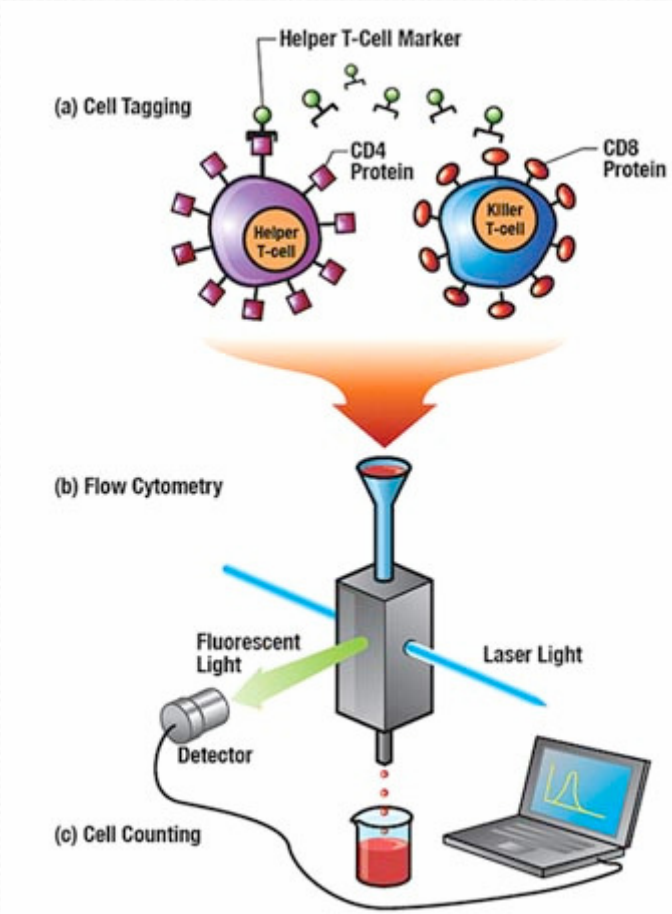


Milojevic *et al. Pediatric Rheumatology* 2008 **6**:20



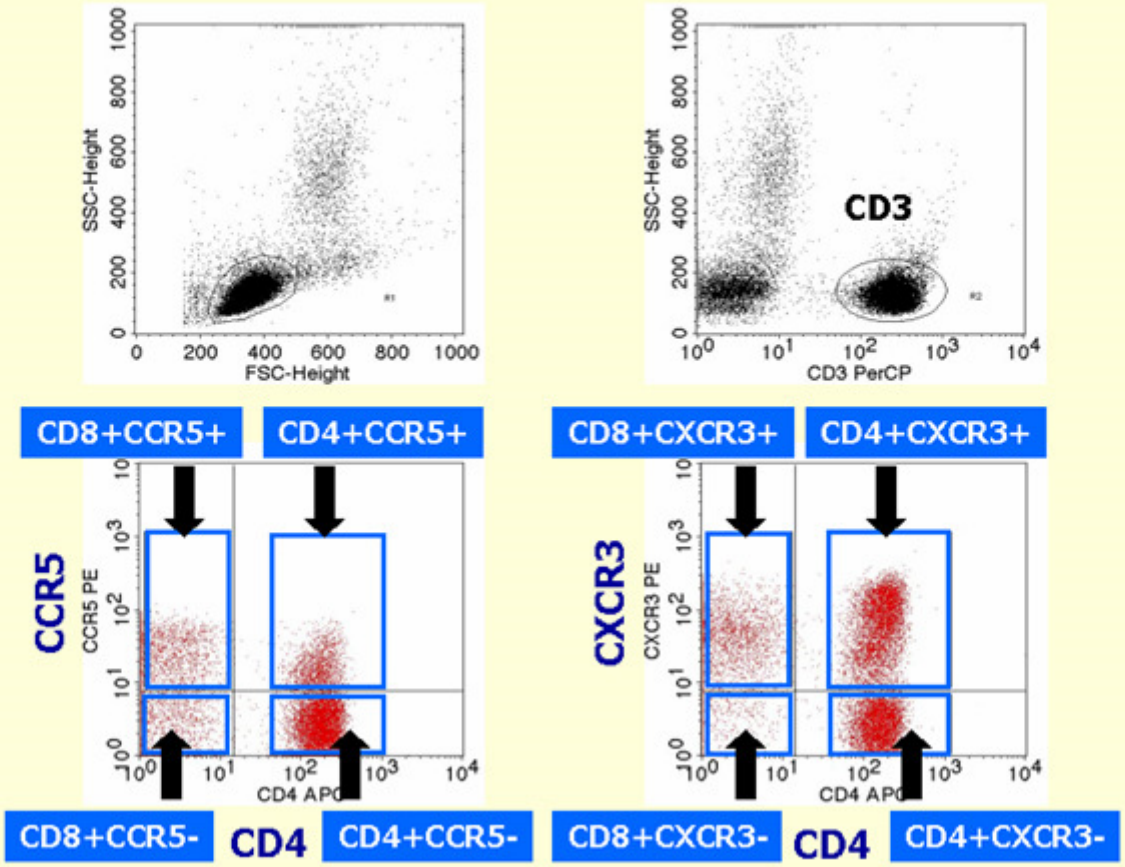
El conocimiento de las **moléculas de superficie** permite la identificación de los distintos tipos celulares.....

CITOMETRÍA DE FLUJO



Métodos

- Selección de las diferentes poblaciones de linfocitos T.



PARÁMETROS MEDIBLES POR CF

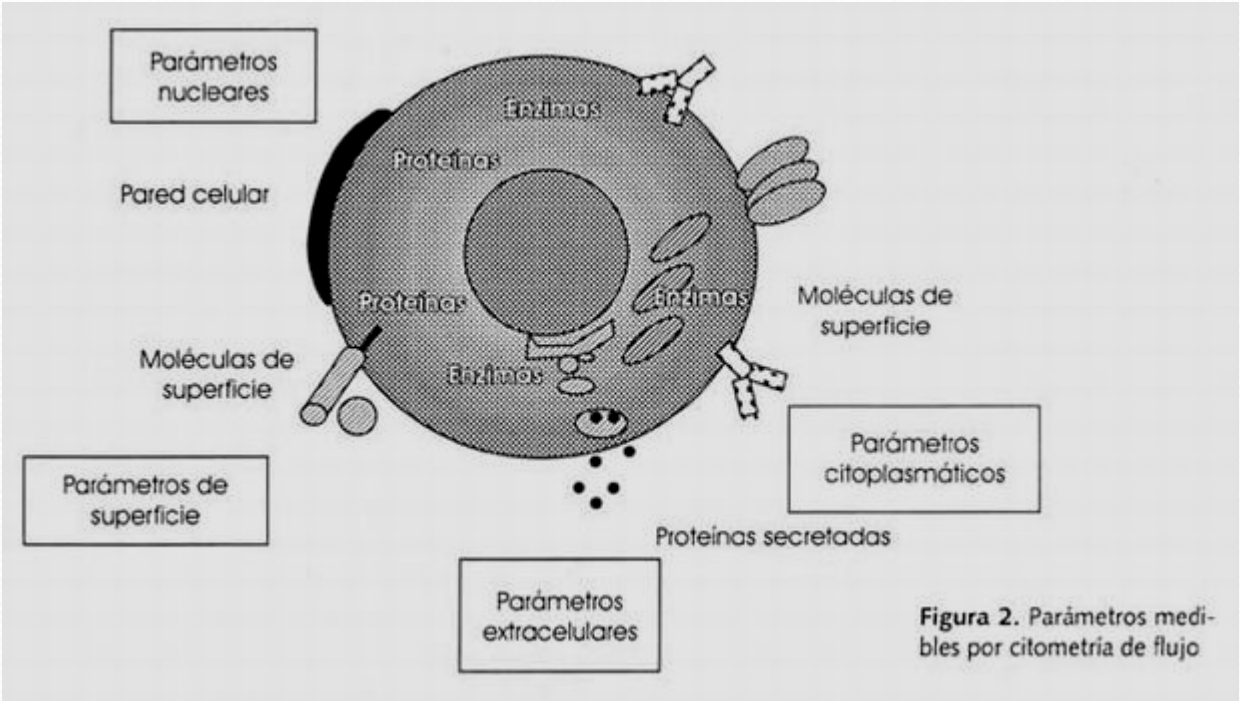
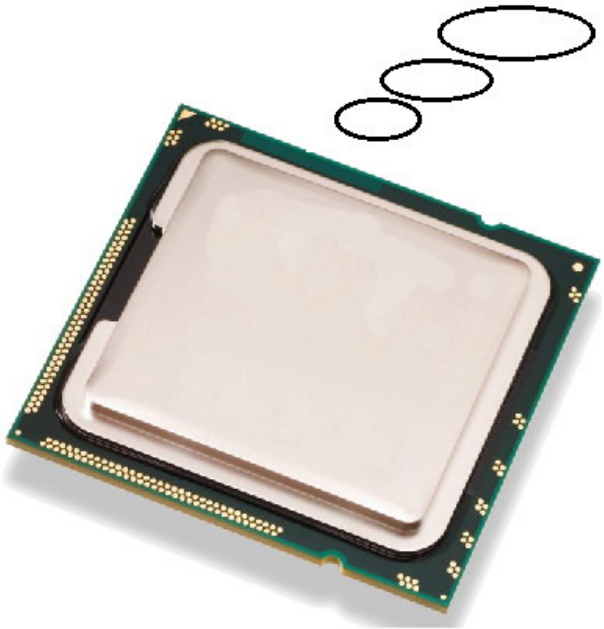
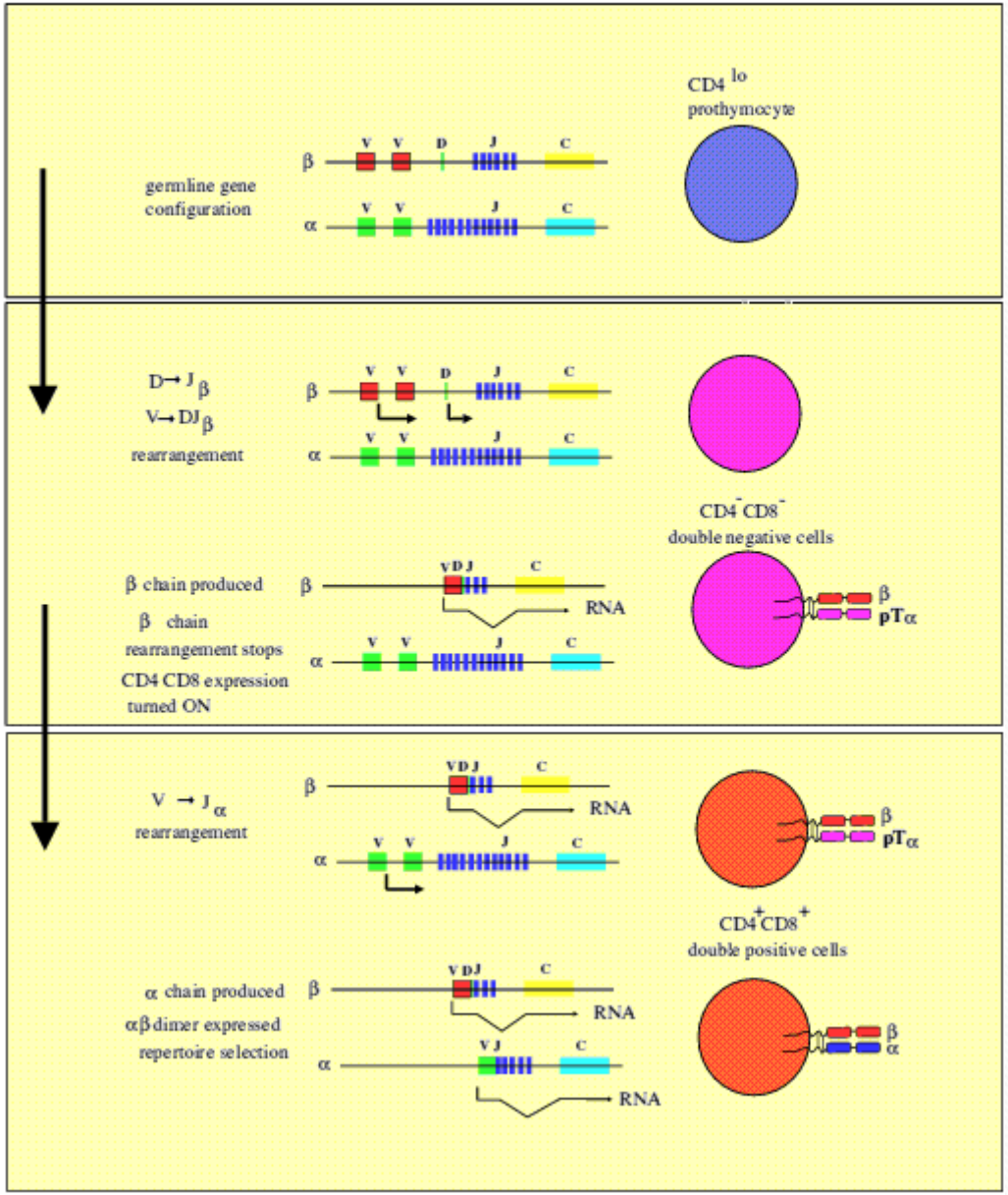
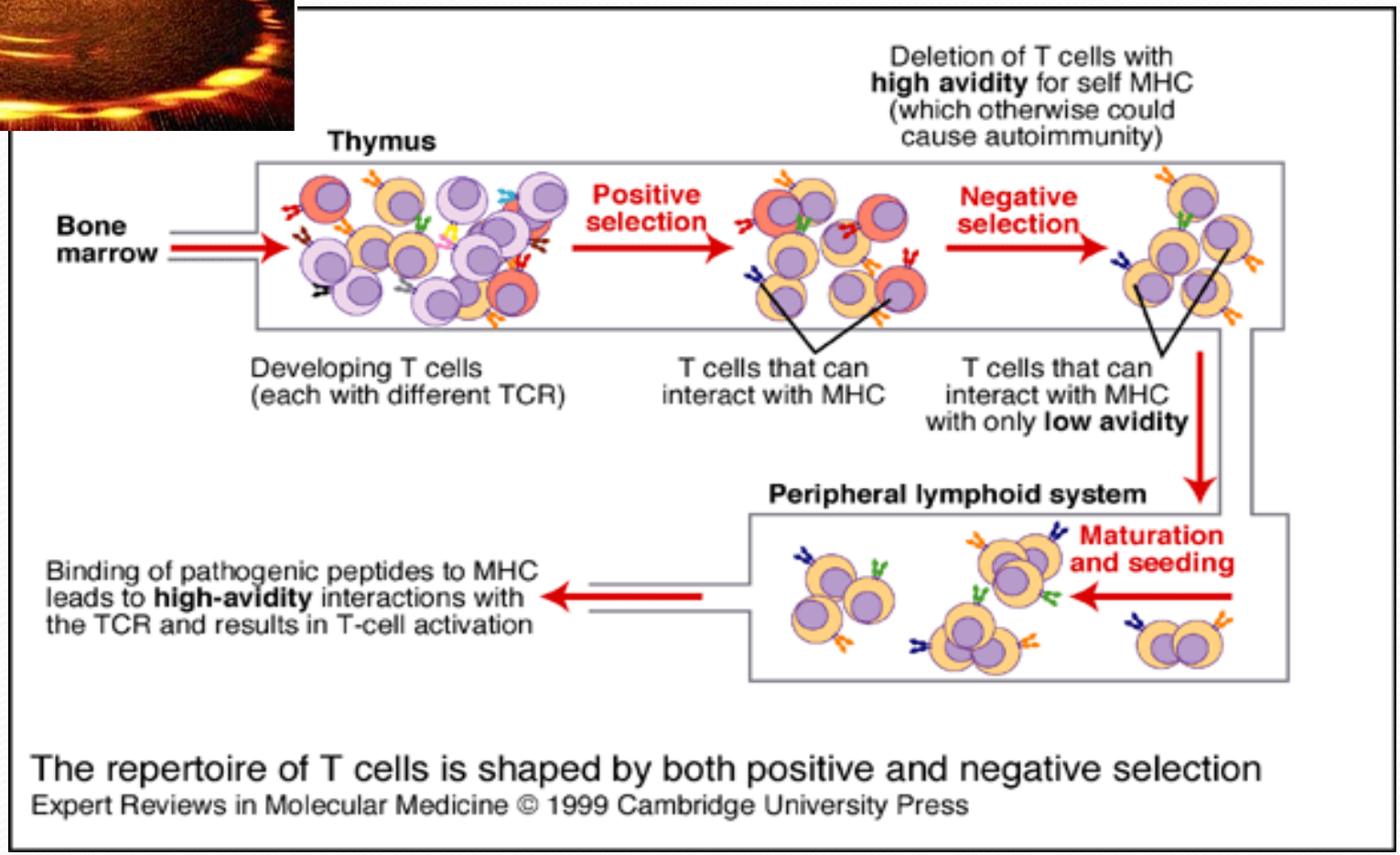


Figura 2. Parámetros medibles por citometría de flujo

Thymocyte development



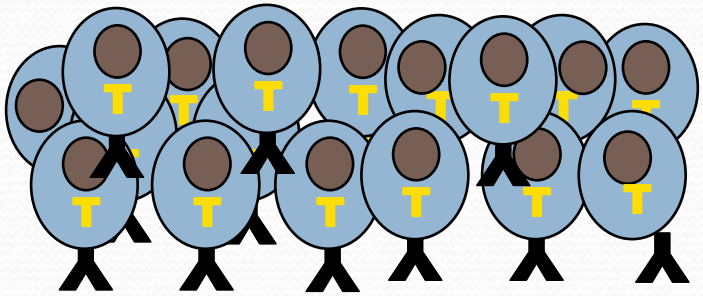




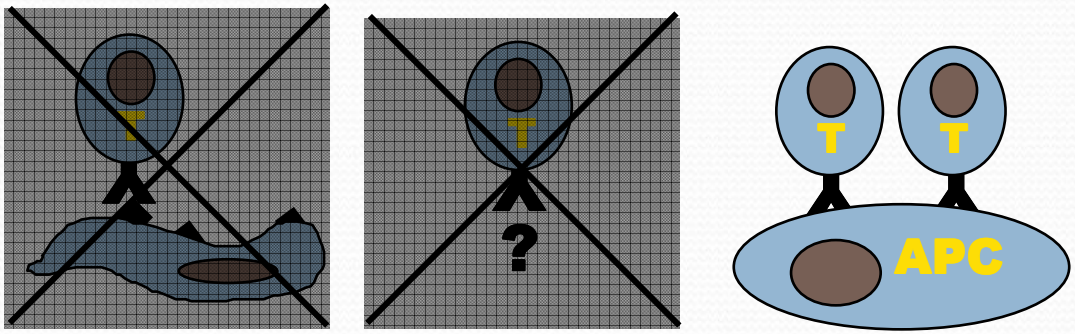
The repertoire of T cells is shaped by both positive and negative selection

Todas las células autorreactivas o inútiles son removidas.....Sin embargo las MHC-restrictas son retenidas....

Random TcR repertoire ensures diversity



TiMo



Harmful **Useless** **Useful**

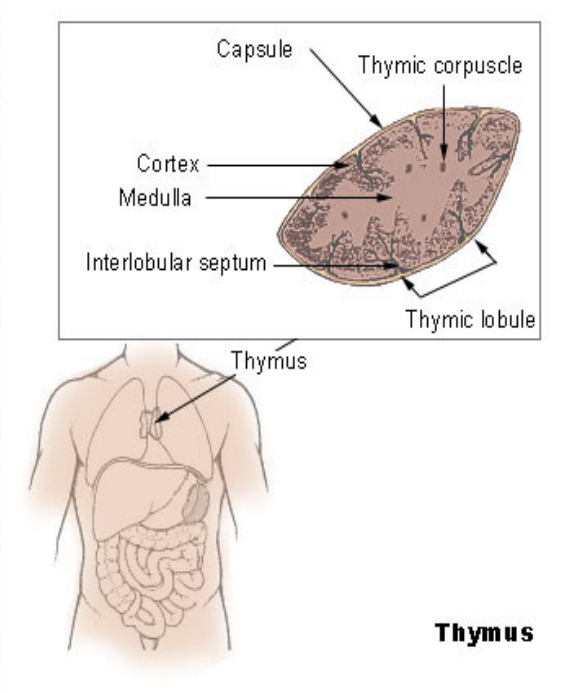
Selección NEGATIVA

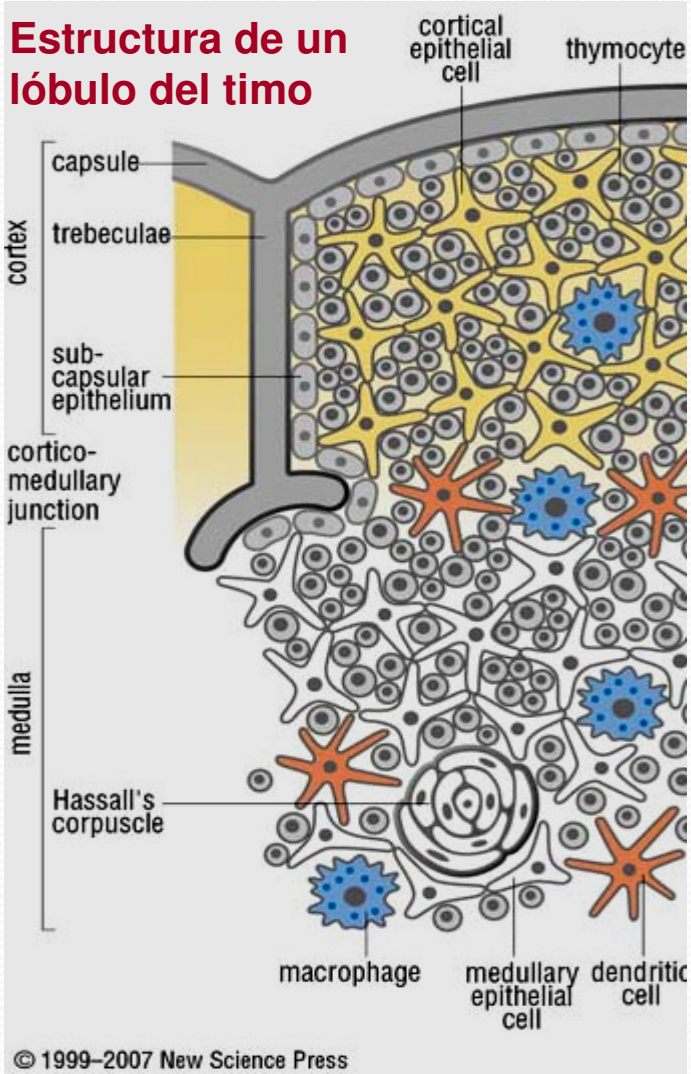
MUERTE POR NEGLICENCIA

SELECCIÓN POSITIVA

EL TIMO.....

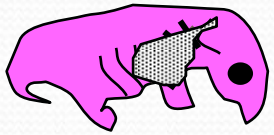
El desarrollo de los linfocitos T comienza en la médula ósea y pero los eventos más importantes ocurren en el timo





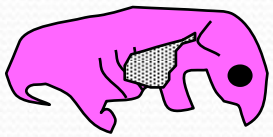
EL TIMO SE REQUIERE PARA LA MADURACIÓN DE CÉLULAS T

Athymic mice (*nude*) and humans (DiGeorge syndrome) are immunodeficient due to a lack of T cells

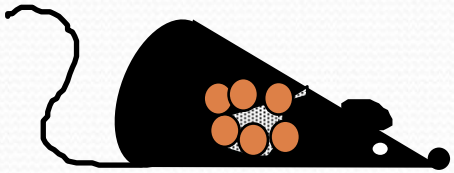


Neonatal thymectomy

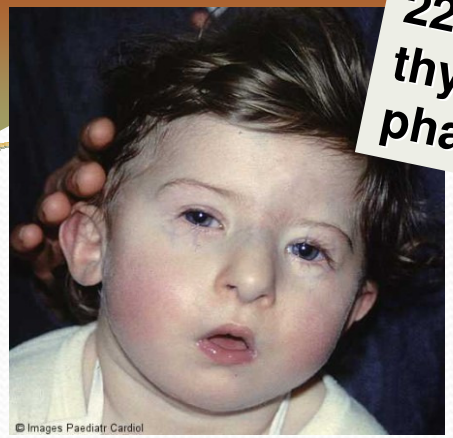
No mature T cells
In adult



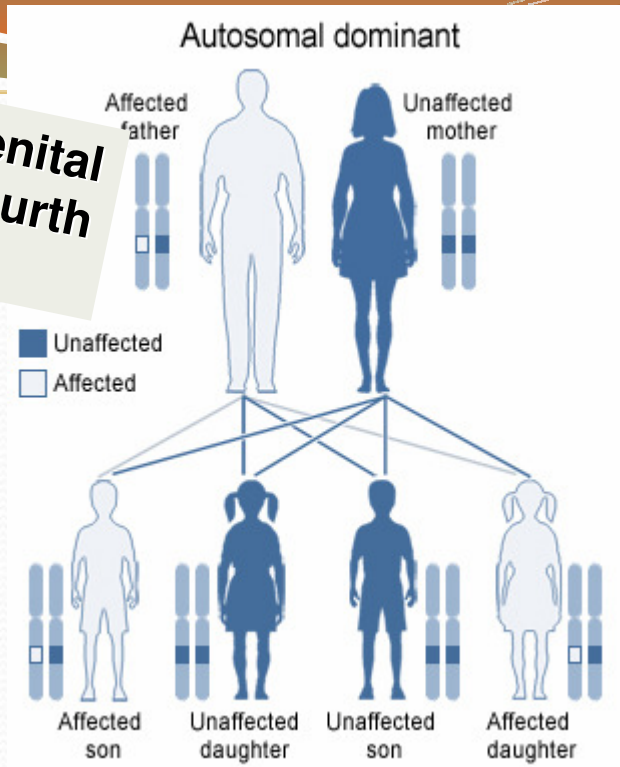
Thymus intact



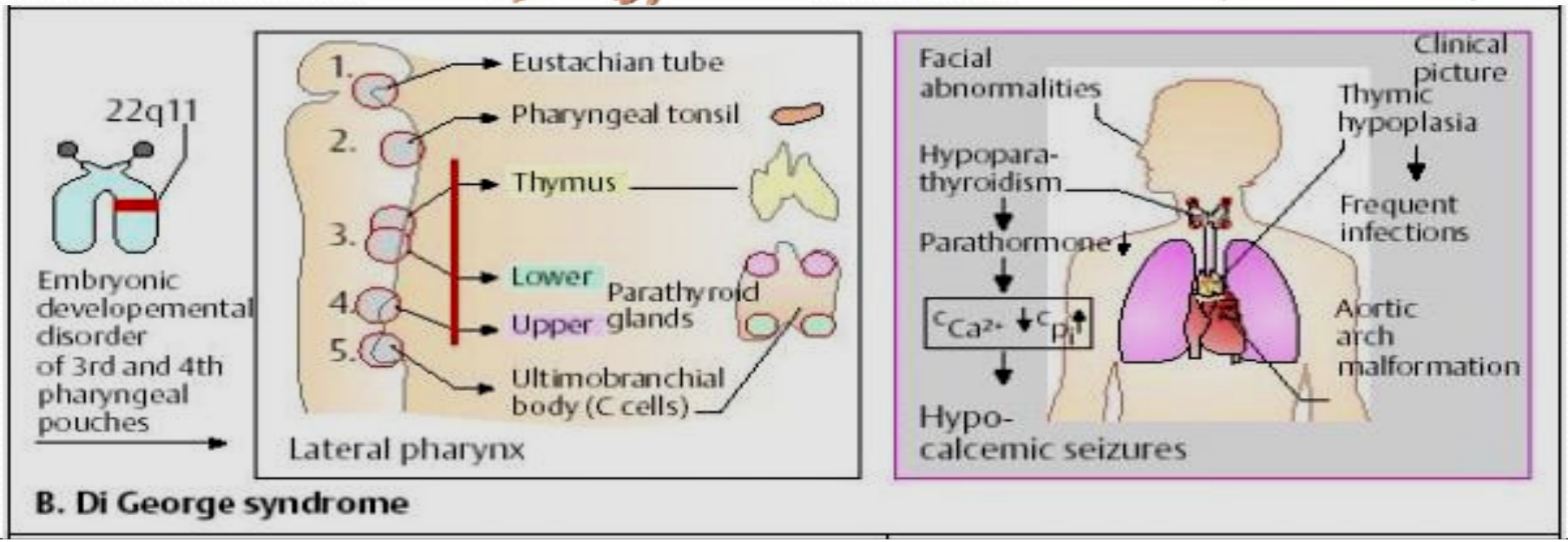
Mature T cells
In adult



22q11 deletion syndrome, congenital thymic hypoplasia, or third and fourth pharyngeal pouch syndrome



Síndrome de DiGeorge, Carencia congénita de timo

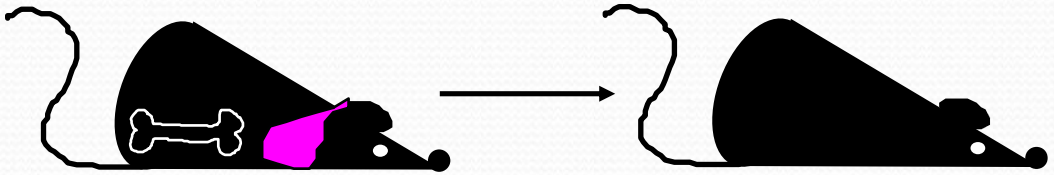


Roles DE LA MÉDULA ÓSEA Y EL TIMO EN LA MADURACIÓN DE CÉLULAS T

Marrow defect

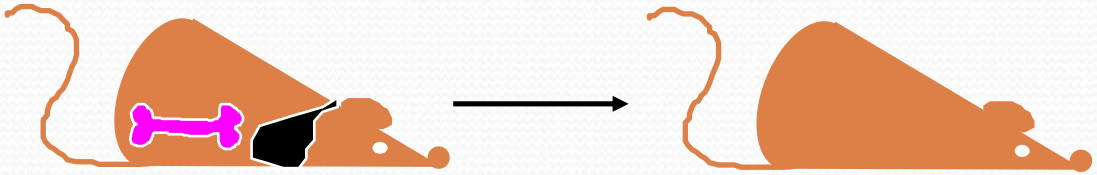
Thymus defect

Defective lymphocyte production
Normal thymus
scid/scid



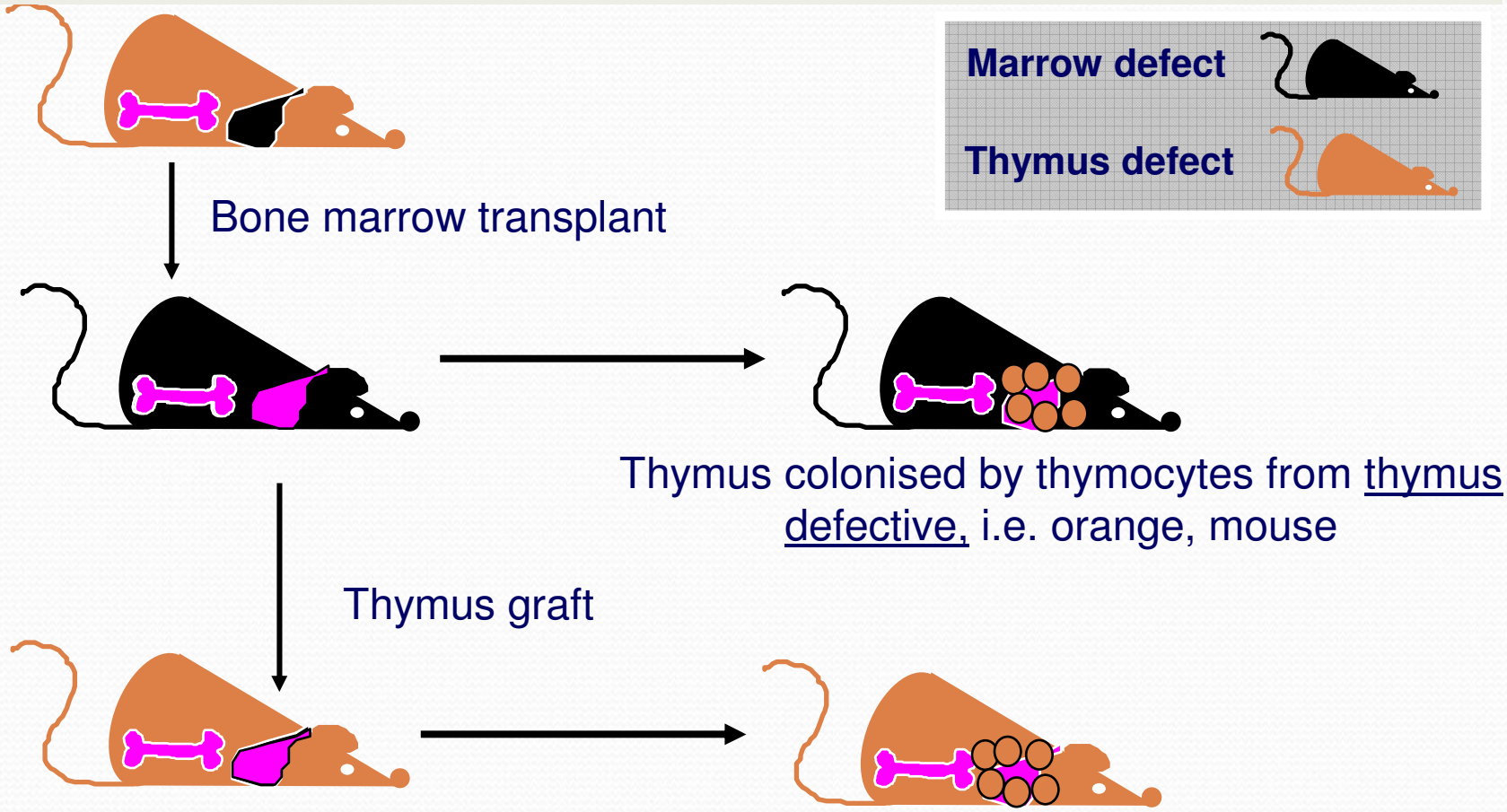
No mature T cells
In adults

Thymus defect
Normal bone marrow
nu/nu

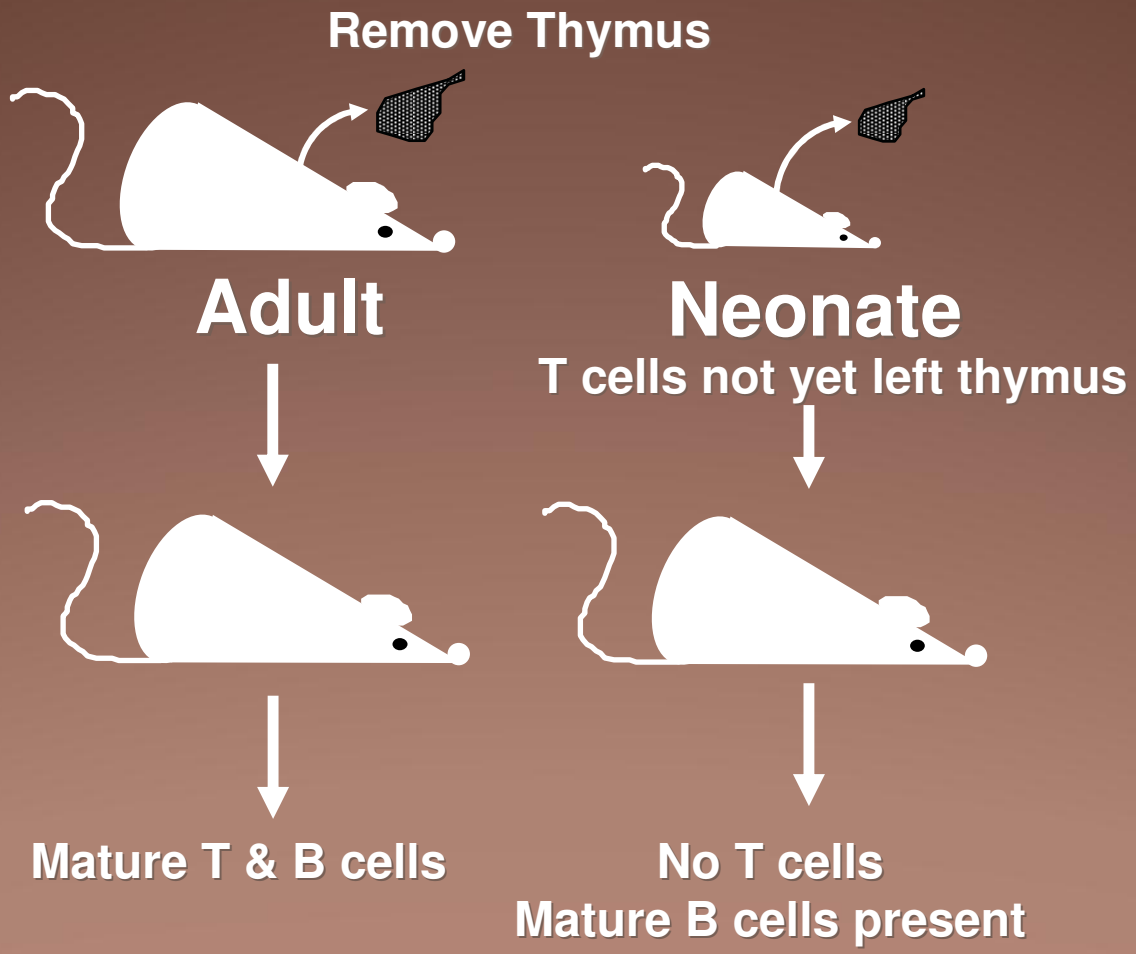


No mature T cells
In adults

LA MÉDULA ÓSEA PROPORCIONA CÉLULAS T... MADURAN EN EL TIMO.....

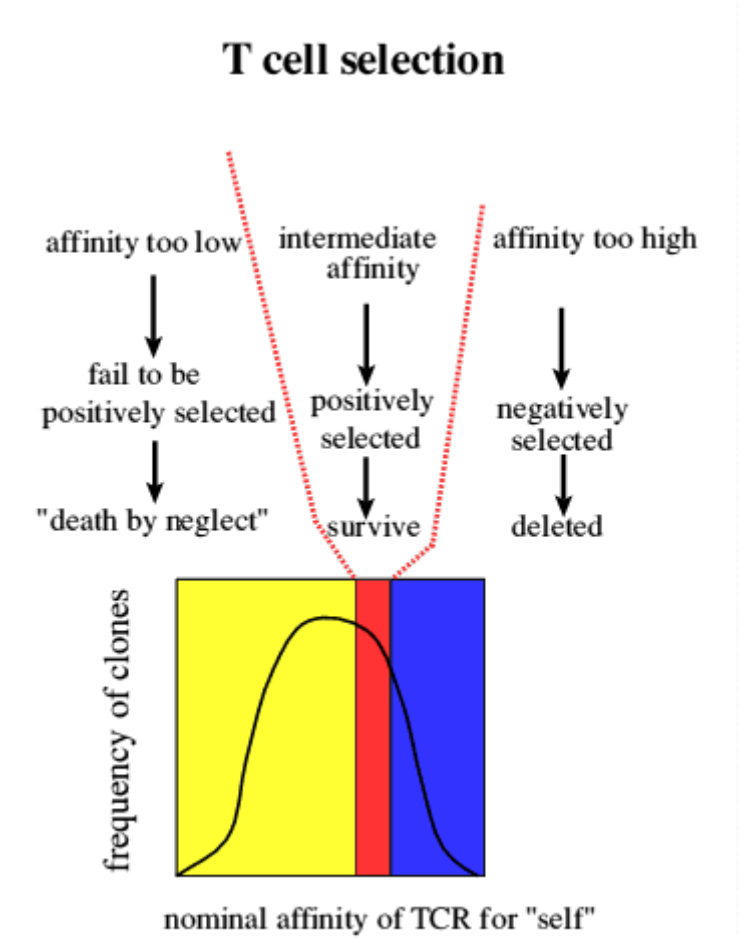


LAS CÉLULAS T MADURAN TEMPRANAMENTE EN LA VIDA....EN EL TIMO...



- EL TIMO ES NECESARIO PARA GENERAR CÉLULAS T MADURAS
- ES NECESARIO PARA GENERAR TOLERANCIA NEONATAL....

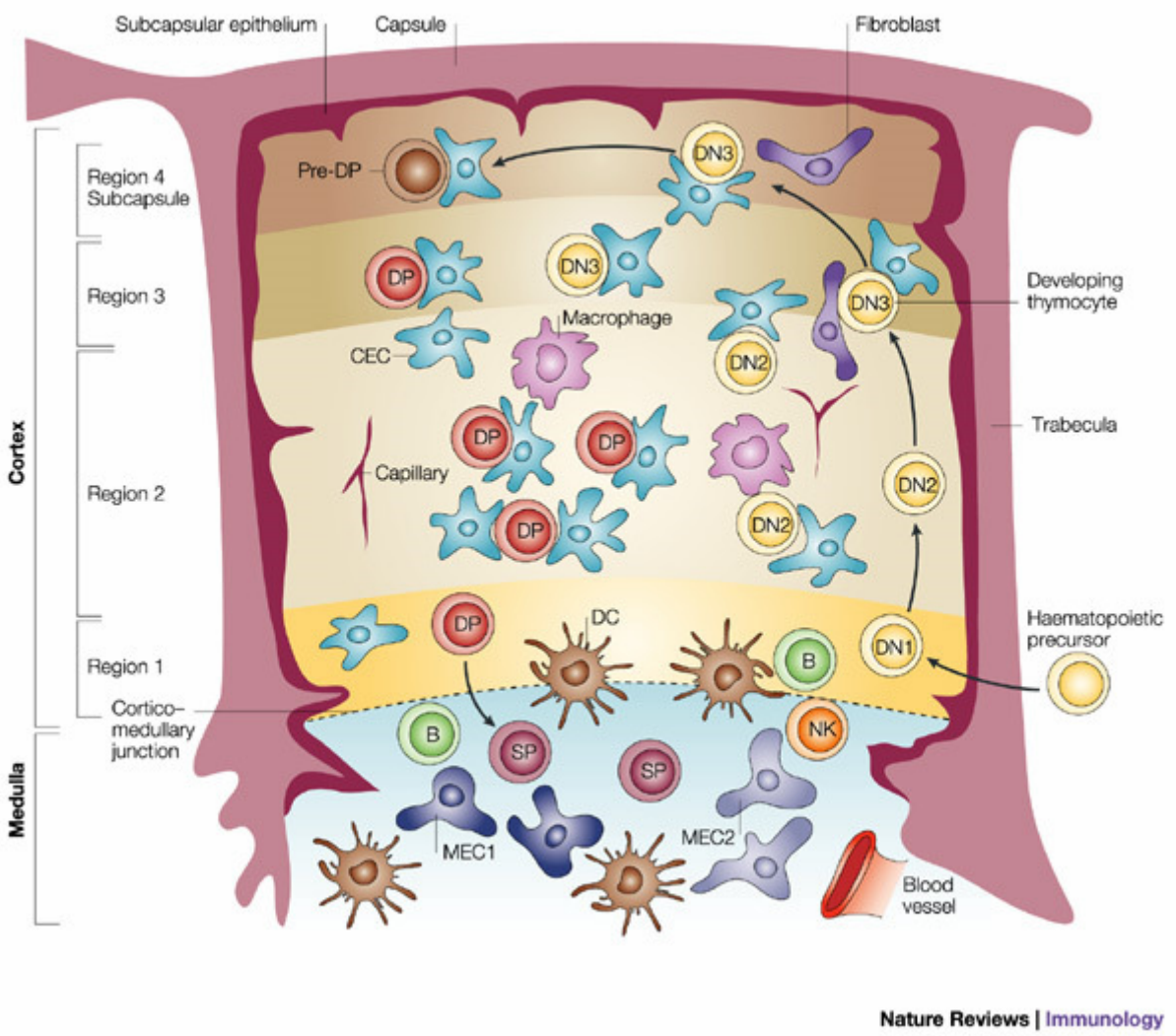
LAS CÉLULAS T MADURAN EN EL TIMO, PERO LA MAYORÍA DE ELLAS MUERE ALLÍ.....



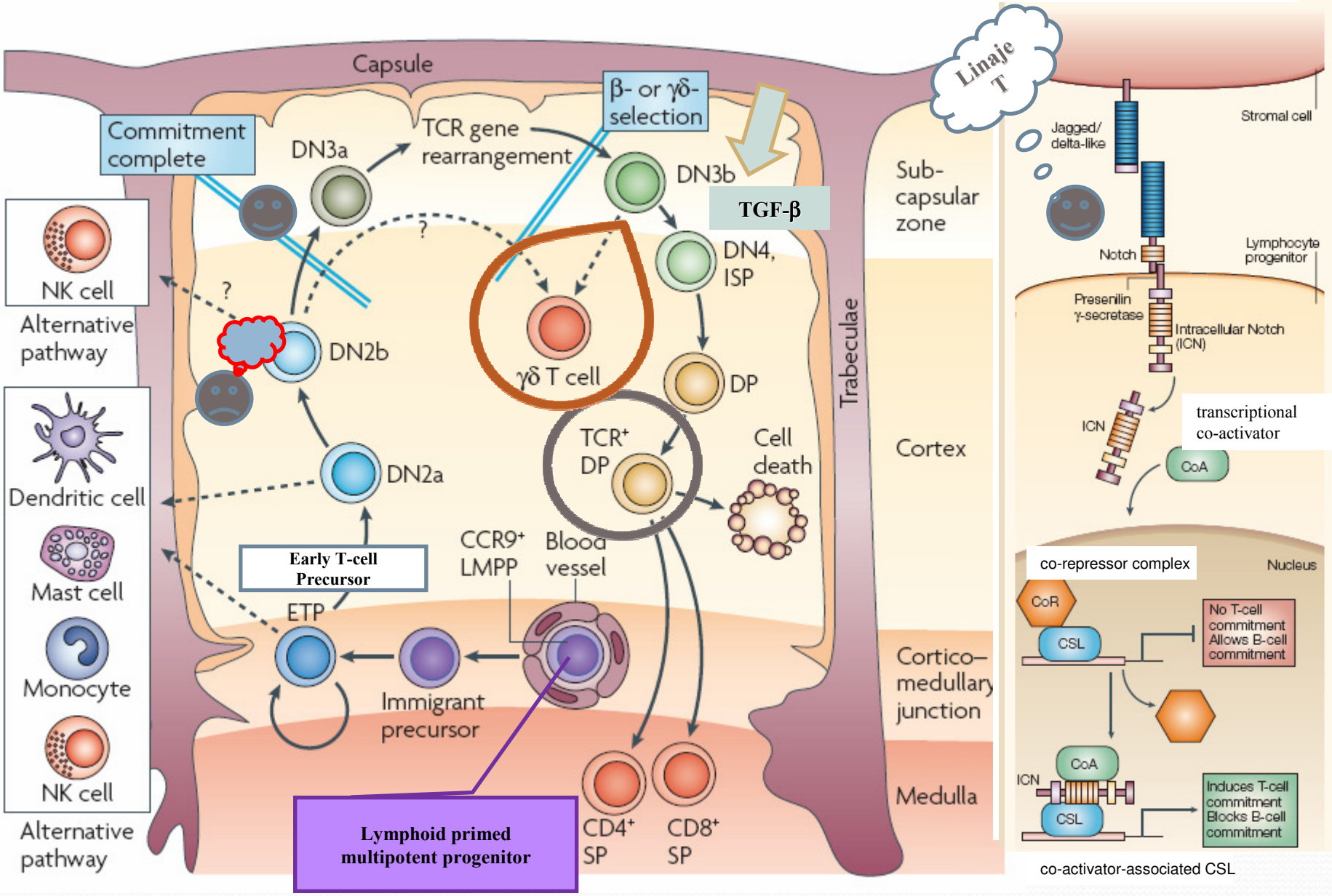
❖**98% de las células muere en el timo, sin inducir imflamación o cambios en el tamaño de la glándula....**

❖**Los MACRÓFAGOS TÍMICOS fagocitas los timocitos apoptóticos....**

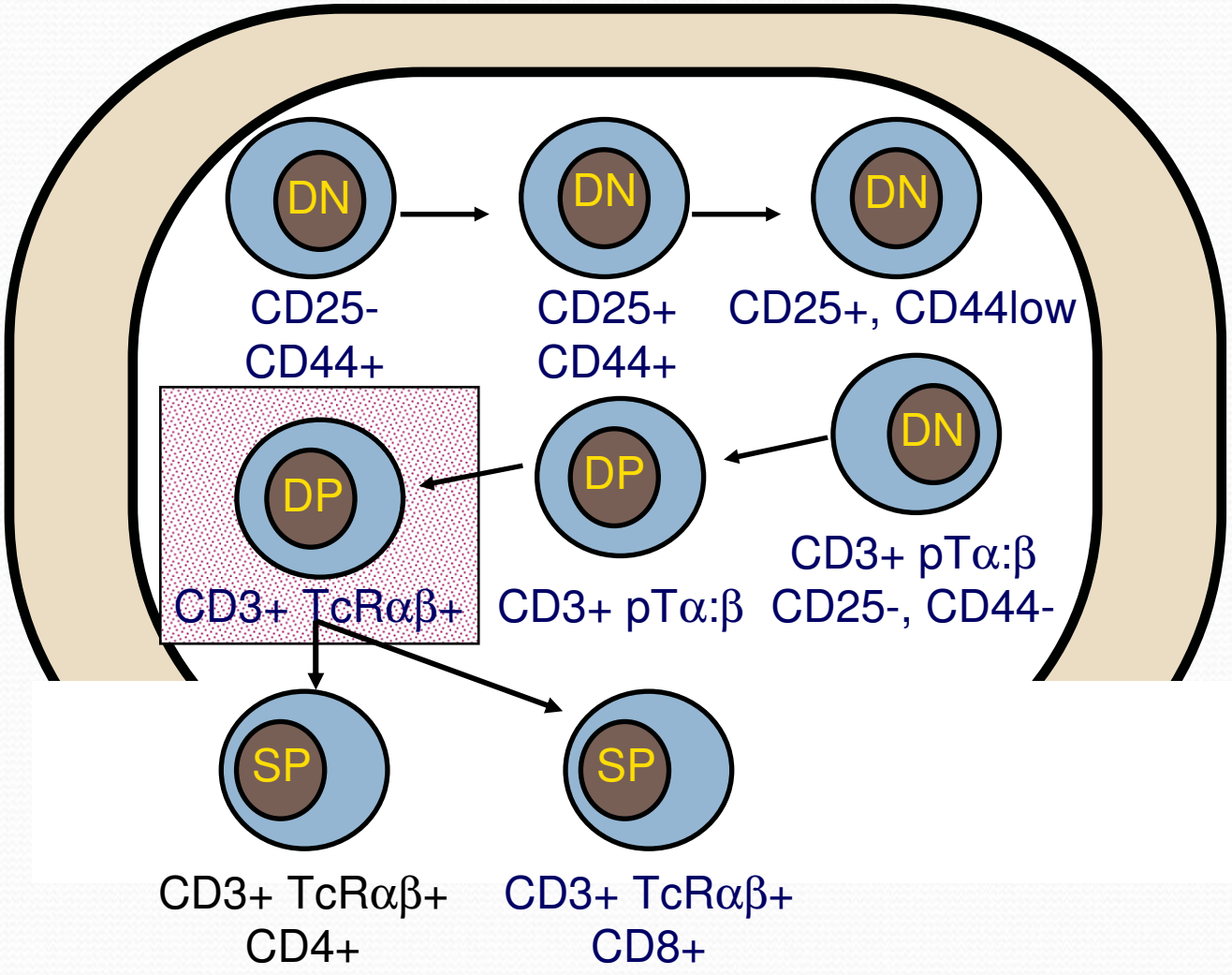
DISTRIBUCIÓN DE LOS DISTINTOS TIPOS CELULARES EN EL TIMO



ETAPAS EN EL DESARROLLO TEMPRANO DE CÉLULAS T



Etapas del desarrollo de timocitos en el TIMO

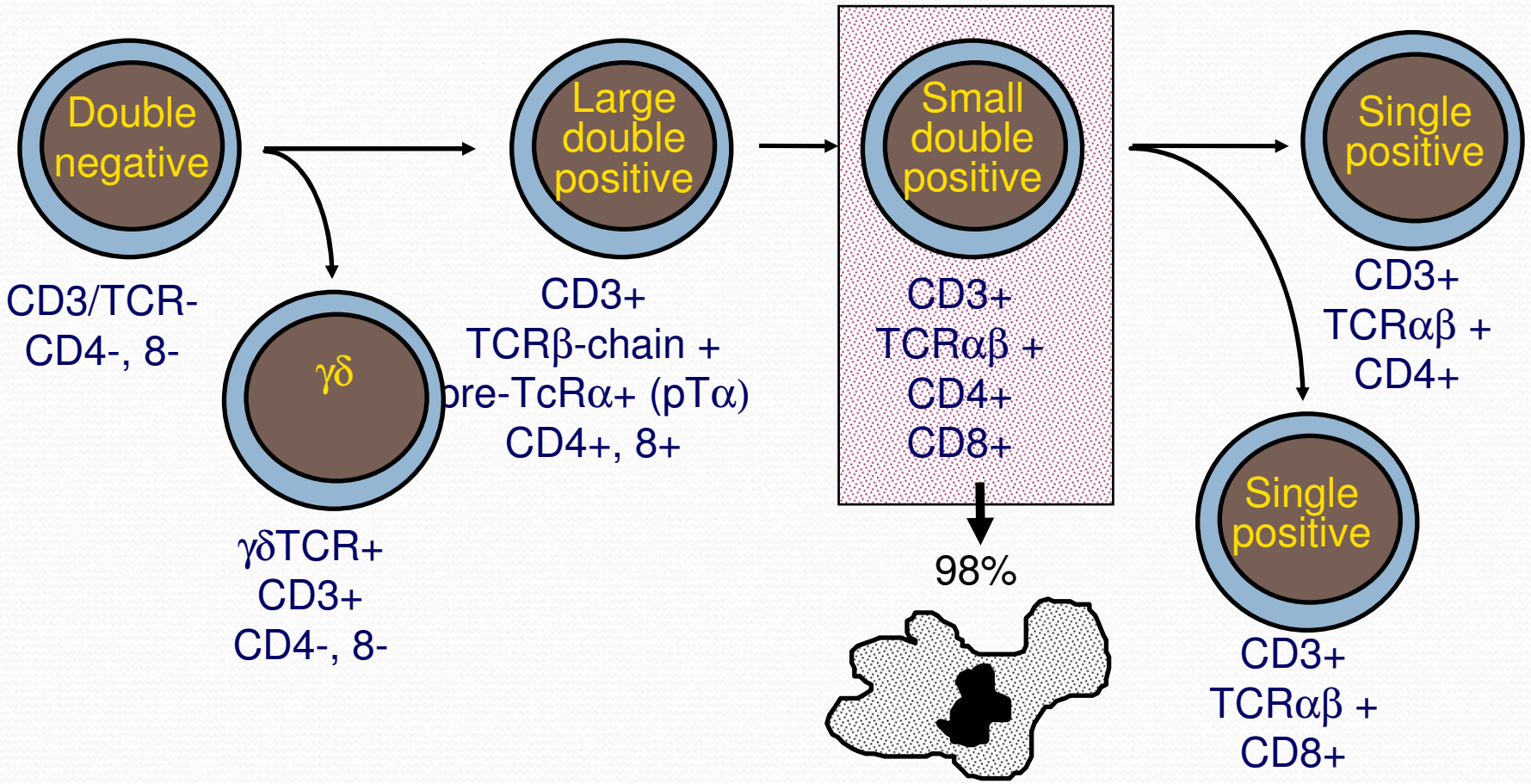


Cortex
Immature double negative & positive thymocytes

Medulla
Mature single positive thymocytes

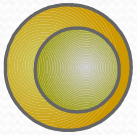
El desarrollo de la céllula T está marcado por el cambio de expresión de moléculas de superficie

As T cells mature in the thymus they change their expression of TCR-associated molecules and co-receptors.
These changes can be used as **markers of their stage of maturation**



La primer decisión que deben tomar los timocitos en desarrollo es entre su diferenciación hacia linfocitos T αβ o γδ

Timocitos CD4- CD8- TCR-



El rearreglo de los loci γ δ y β comienza simultáneamente

TCR αβ o TCR γδ ?

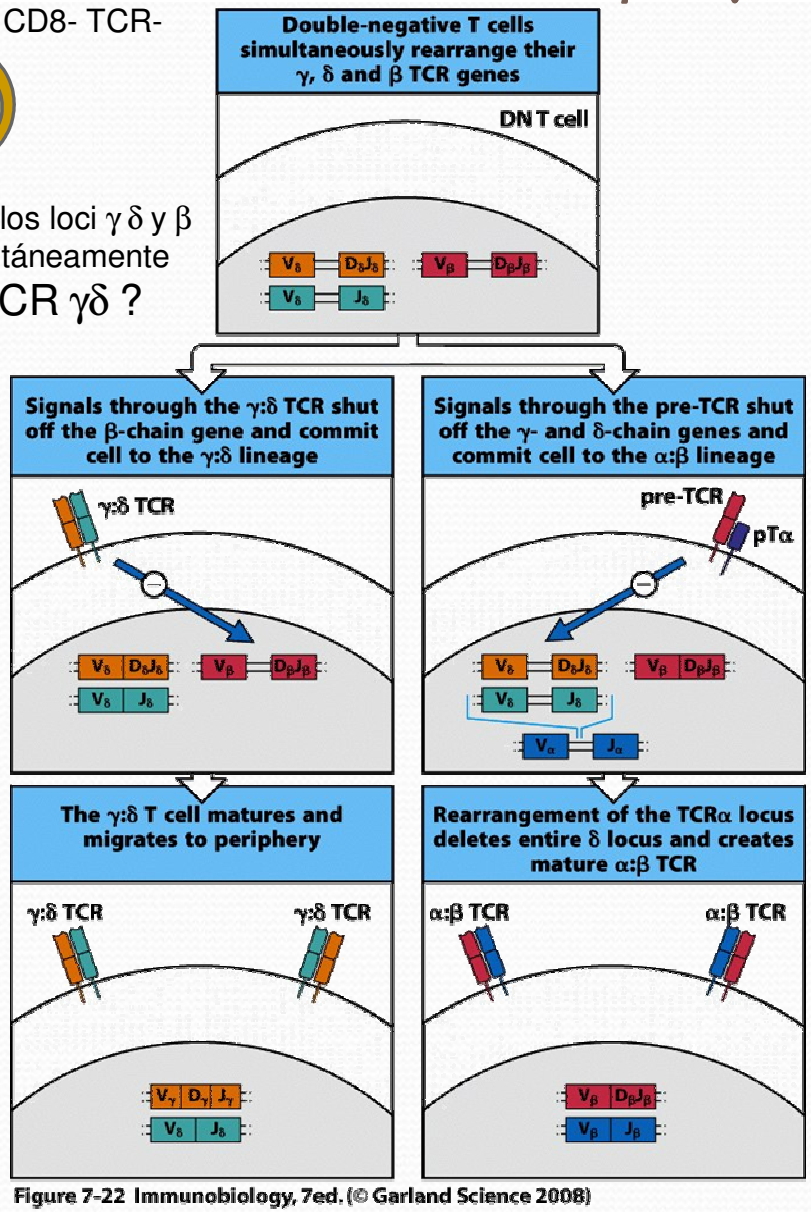
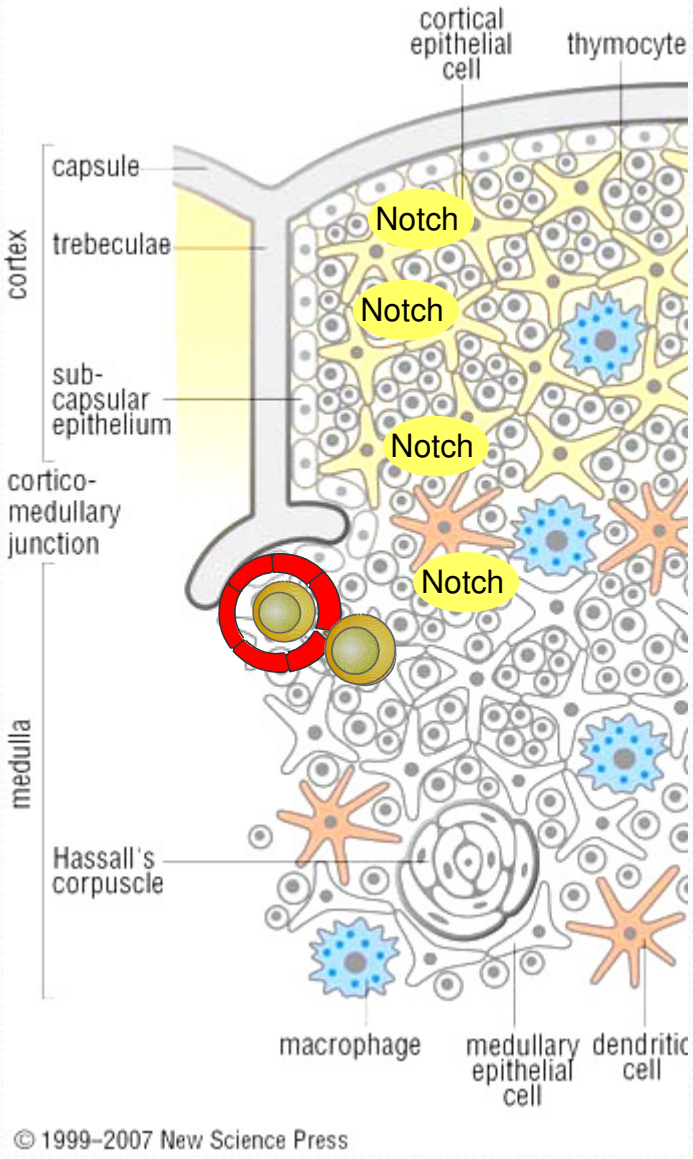
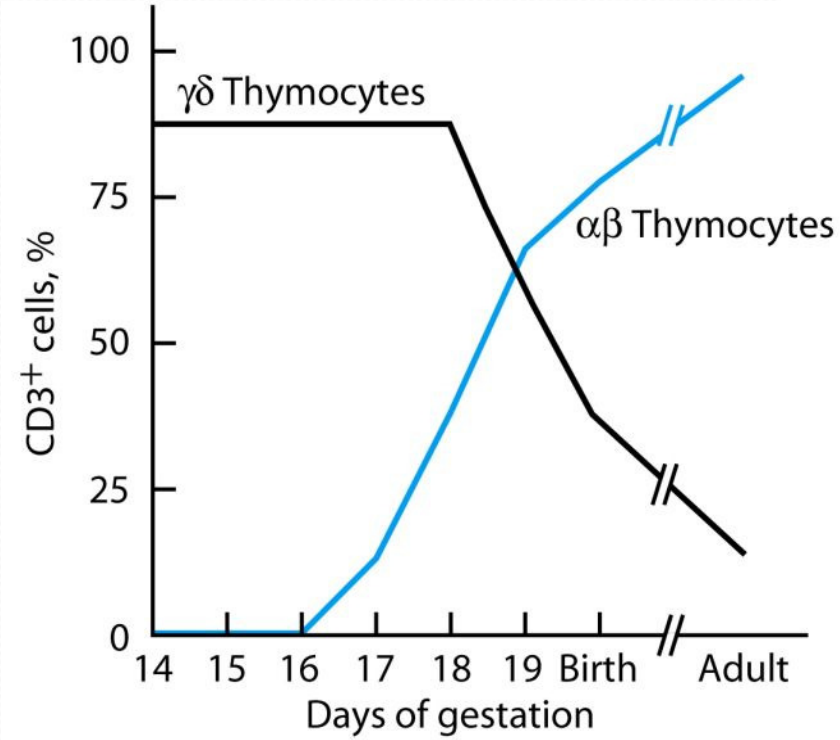


Figure 7-22 Immunobiology, 7ed. (© Garland Science 2008)



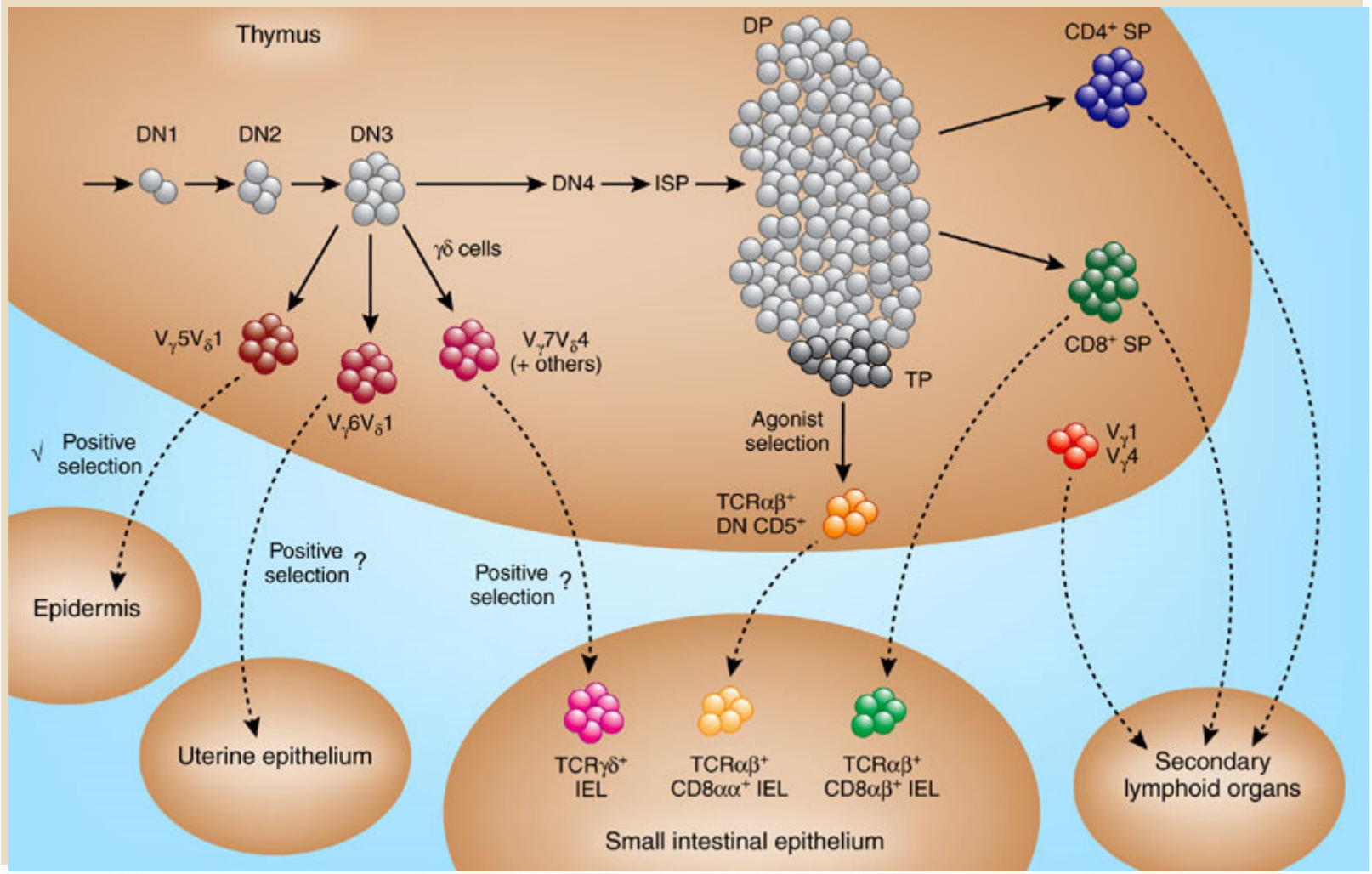
•En el ratón, la expresión del TCRγδ asociado a CD3 en la superficie celular, ocurre 3 o 4 días después de la llegada los precursores al timo, mientras que los TCRαβ se expresan 2 o 3 días más tarde.

Desarrollo de los LTγδ



En el timo fetal humano, la expresión de los TCRγδ comienza alrededor de la 9º semana de gestación, seguido de la expresión de los TCRαβ a las 10º semanas…….

Distribución de las células T



Nature Immunology 8, 137 - 144 (2007)

Generación del TCR: RECOMBINACIÓN SOMÁTICA

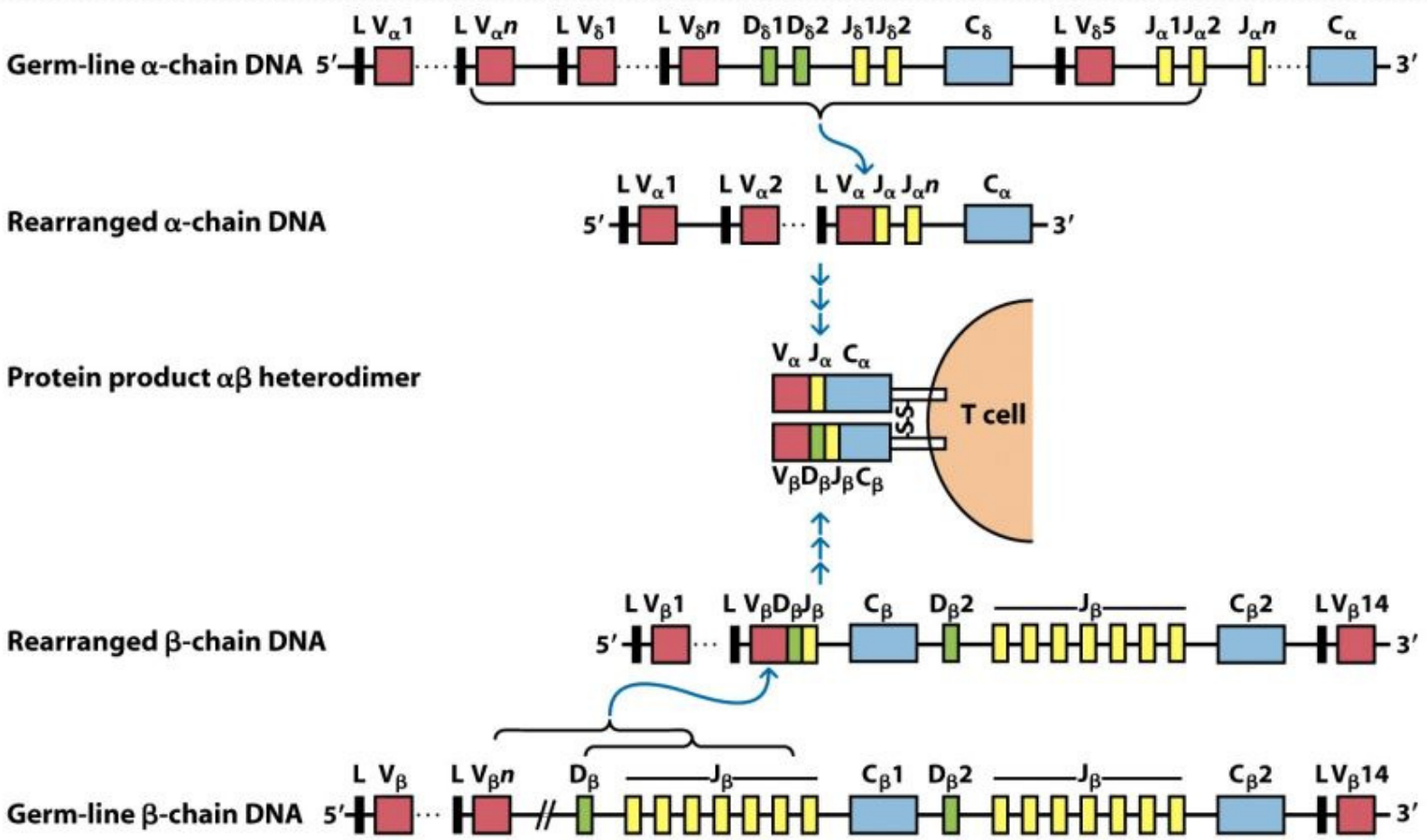


Figure 9-6
Kuby IMMUNOLOGY, Sixth Edition

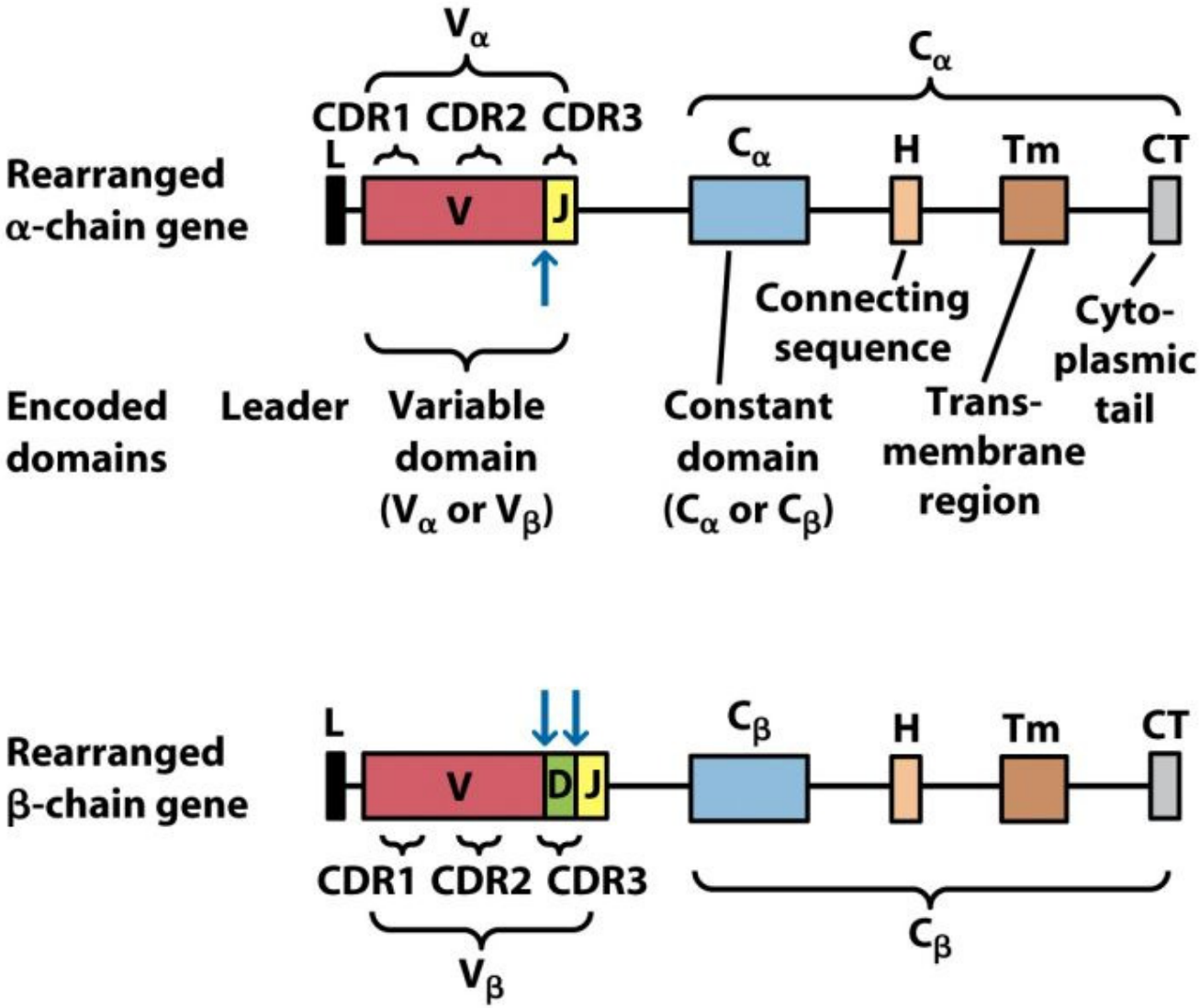


Figure 9-7
Kuby IMMUNOLOGY, Sixth Edition

TABLE 9-2 TCR multigene families in humans

Gene	Chromosome location	NO. OF GENE SEGMENTS* V	D	J	C
α Chain	14	54		61	1
δ Chain†	14	3	3	3	1
β Chain‡	7	67	2	14	2
γ Chain§	7	14		5	2

*Not all gene segments listed here give rise to TCR products; pseudogenes are included in this list.

†The δ-chain gene segments are located between the V_α and J_α segments.

‡There are two repeats, each containing one D_β, six or seven J_β, and one C_β.

§There are two repeats, each containing two or three J_γ and One C_γ.

Table 9-2
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TABLE 9-3 Sources of possible diversity in mouse immunoglobulin and TCR genes

Mechanism of diversity	IMMUNOGLOBULINS		αβ T-CELL RECEPTOR		γδ T-CELL RECEPTOR	
	H Chain	κ Chain	α Chain	β Chain	γ Chain	δ Chain
ESTIMATED NUMBER OF FUNCTIONAL GENE SEGMENTS*						
V	101	85	79	21	7	6
D	13	0	0	2	0	2
J	4	4	38	11	3	2
POSSIBLE NUMBER OF COMBINATIONS†						
Combinatorial V-J and V-D-J joining	$101 \times 13 \times 4$ 5.3×10^3	85×4 3.4×10^2	79×38 3.0×10^3	$21 \times 2 \times 11$ 4.6×10^2	7×3 21	$6 \times 2 \times 2$ 24
Alternative joining of D gene segments	–	–	–	+ (some)	–	+ (often)
Junctional flexibility	+	+	+	+	+	+
N-region nucleotide addition‡	+	–	+	+	+	+
P-region nucleotide addition	+	+	+	+	+	+
Somatic mutation	+	+	–	–	–	–
Combinatorial association of chains	+		+		+	

*Immunoglobulin data from Table 5-2; TCR data from Baum et al., 2004, *Nucleic Acids Research* **32**:D51.
†A plus sign (+) indicates mechanism makes a significant contribution to diversity but to an unknown extent.
A minus sign (−) indicates mechanism does not operate.
‡See Figure 9-8d for theoretical number of combinations generated by N-region addition.

Table 9-3
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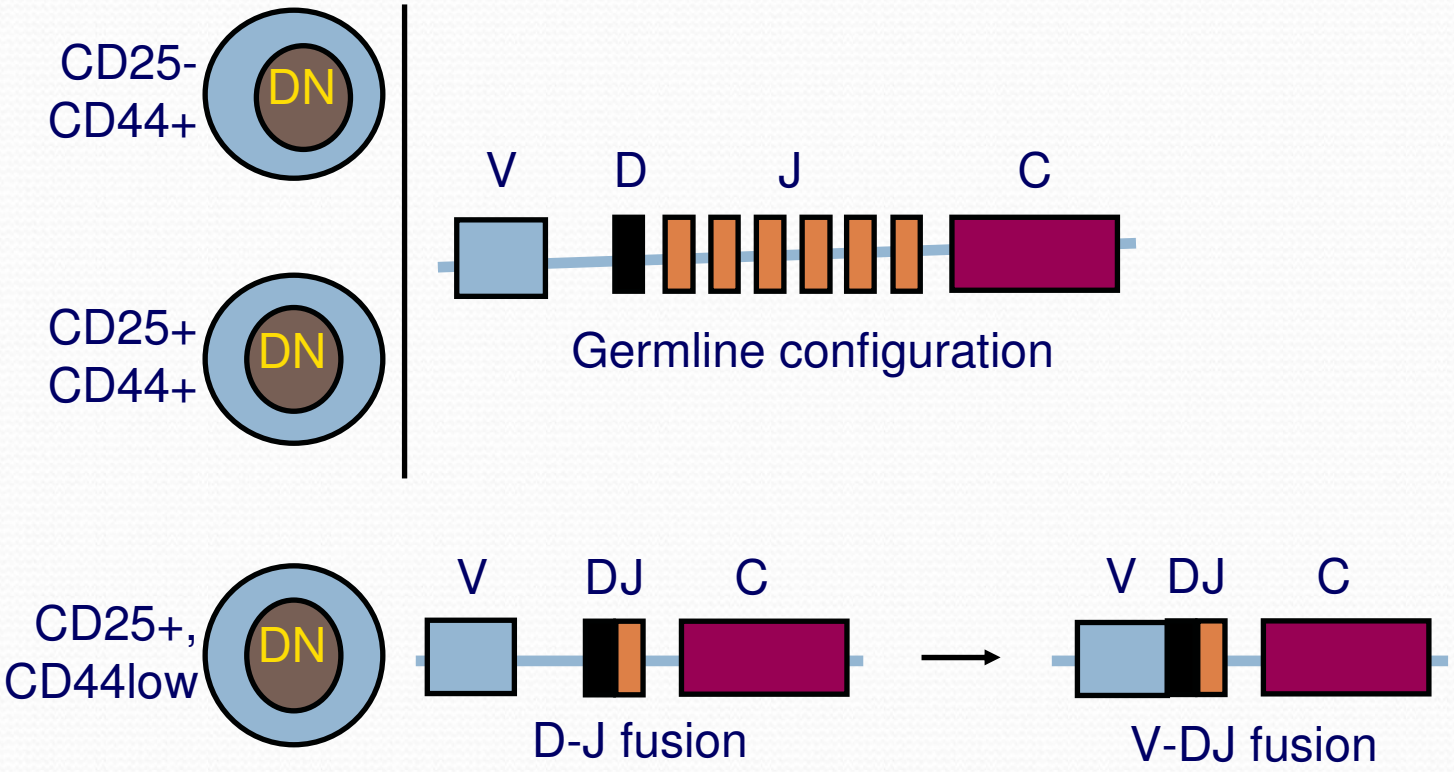
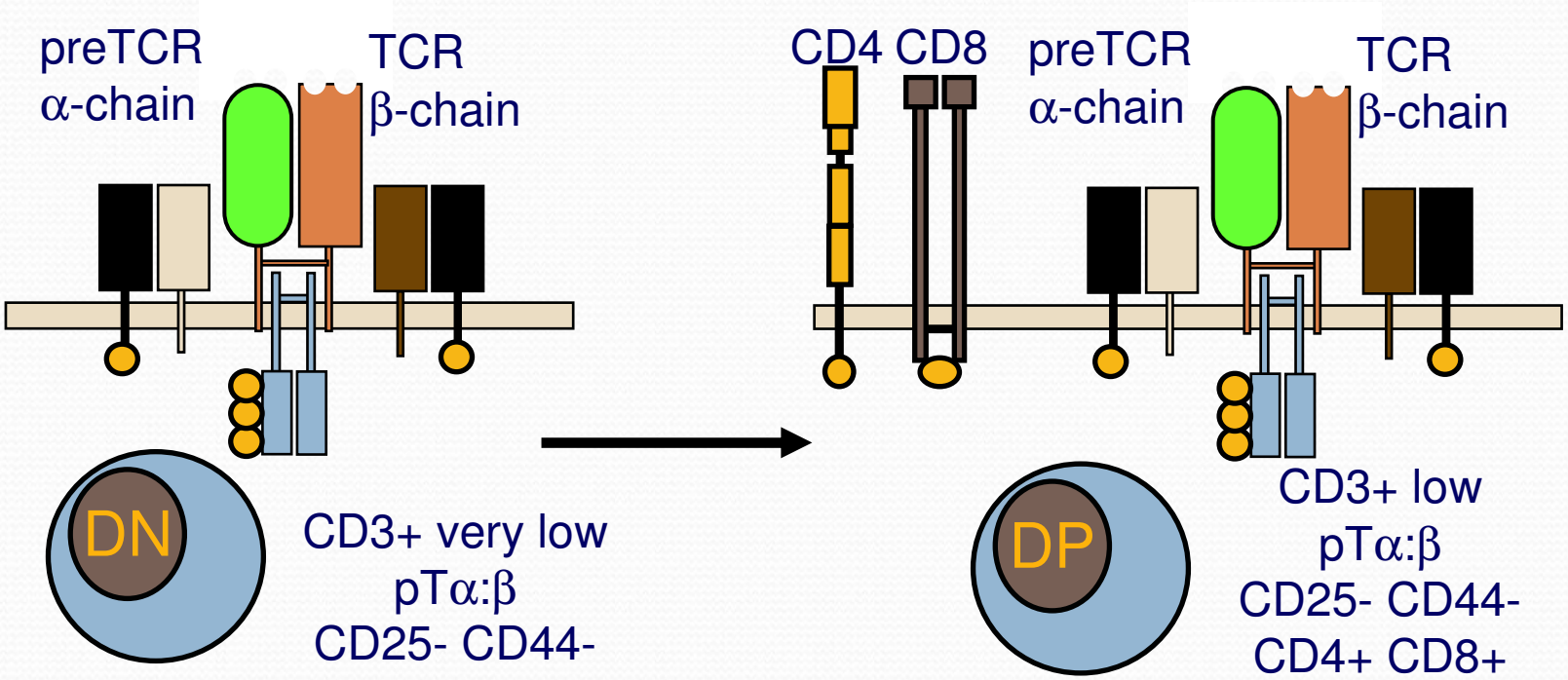
Rearreglo del TCR

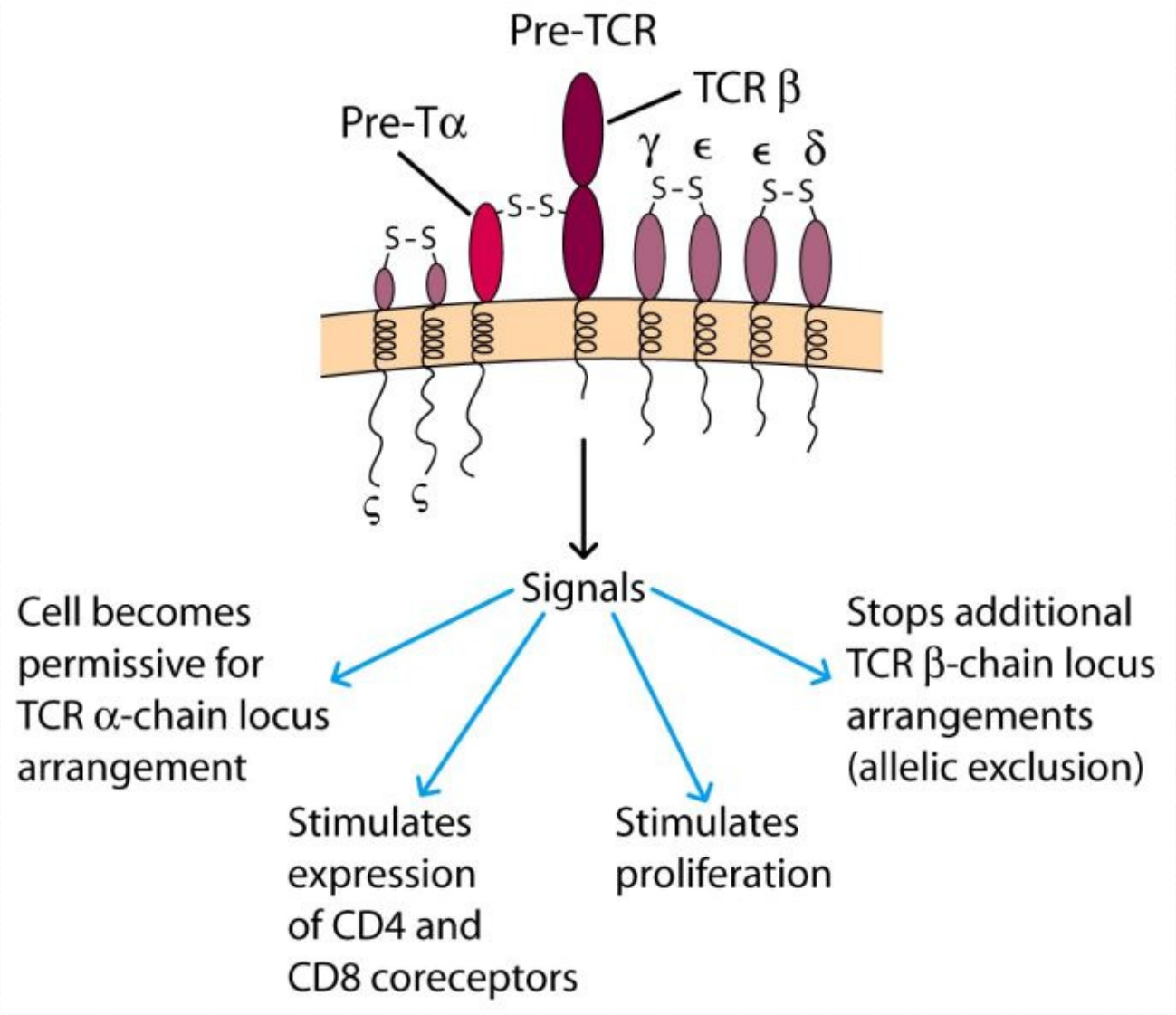


C region spliced to VDJ fusion and β-chain protein produced in cytoplasm
No TCR at cell surface

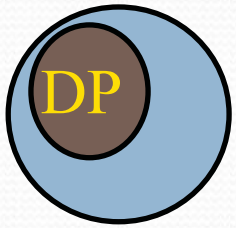
RECEPTOR Pre TCR



1. La célula prolifera rápidamente para permitir la expansión clonal. Las células hijas expresan la misma cadena β .
2. El rearreglo satisfactorio de la cadena β inhibe el rearreglo de la cadena β del 2º cromosoma (exclusión alélica)….

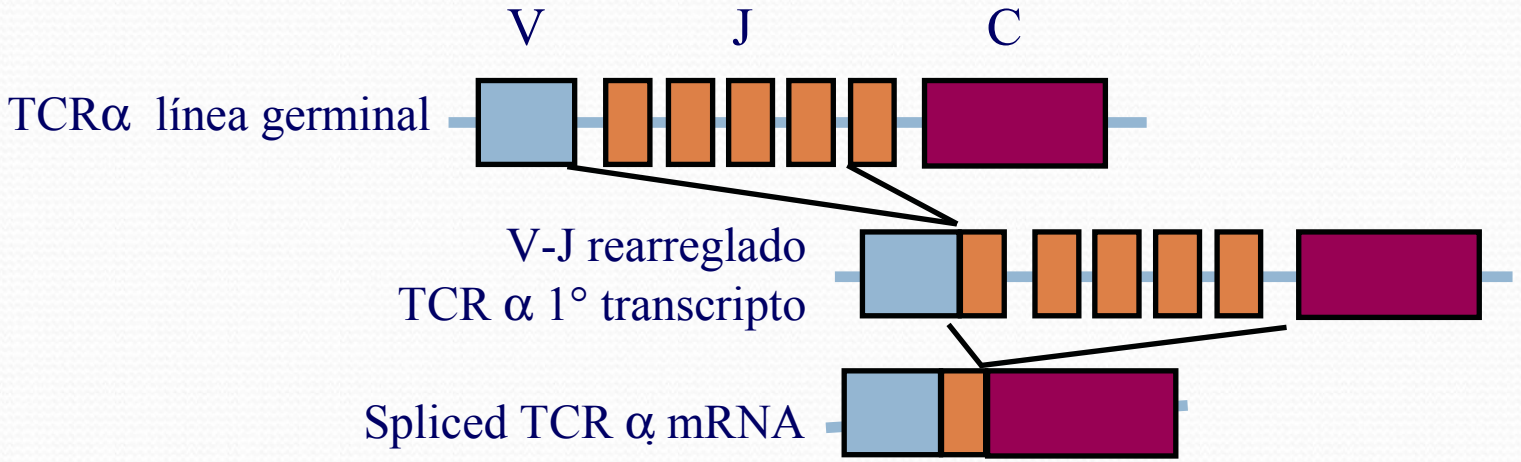

Pre-TCR
TCR β
Pre-Tα
γ ϵ ϵ δ
S-S
S-S
S-S
S-S
ς ς
Signals
Cell becomes permissive for TCR α-chain locus arrangement
Stimulates expression of CD4 and CD8 coreceptors
Stimulates proliferation
Stops additional TCR β-chain locus arrangements (allelic exclusion)

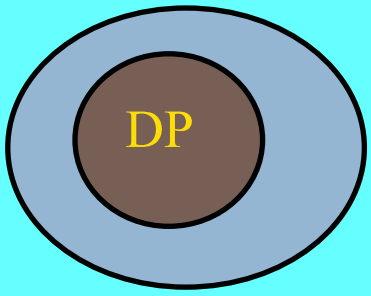
Rearreglo del TCRα



CD3+ low
pTα:β
CD25- CD44-
CD4+ CD8+

Cuando la proliferación cesa, se inicia el rearreglo de la cadena α…..





$CD3^+$ $TCR\alpha\beta^+$

Las células T pueden ahora reconocer antígenos propios e interactuar con MHC class I y II a través de CD4 y CD8….

La **SELECCIÓN** puede comenzar……

Rearreglo del gen α-TCR
RECOMBINACIÓN SOMÁTICA

- **La exclusión alélica es escasa o nula en el locus de la cadena α: pueden producirse reordenamientos funcionales en ambos cromosomas…..**

- **El 30% de los LTm expresan dos TCR distintos, con la misma cadena β pero con diferentes cadenas α, sin embargo uno de ellos carecería de función, ya que sólo se necesita un TCR para la selección positiva.**

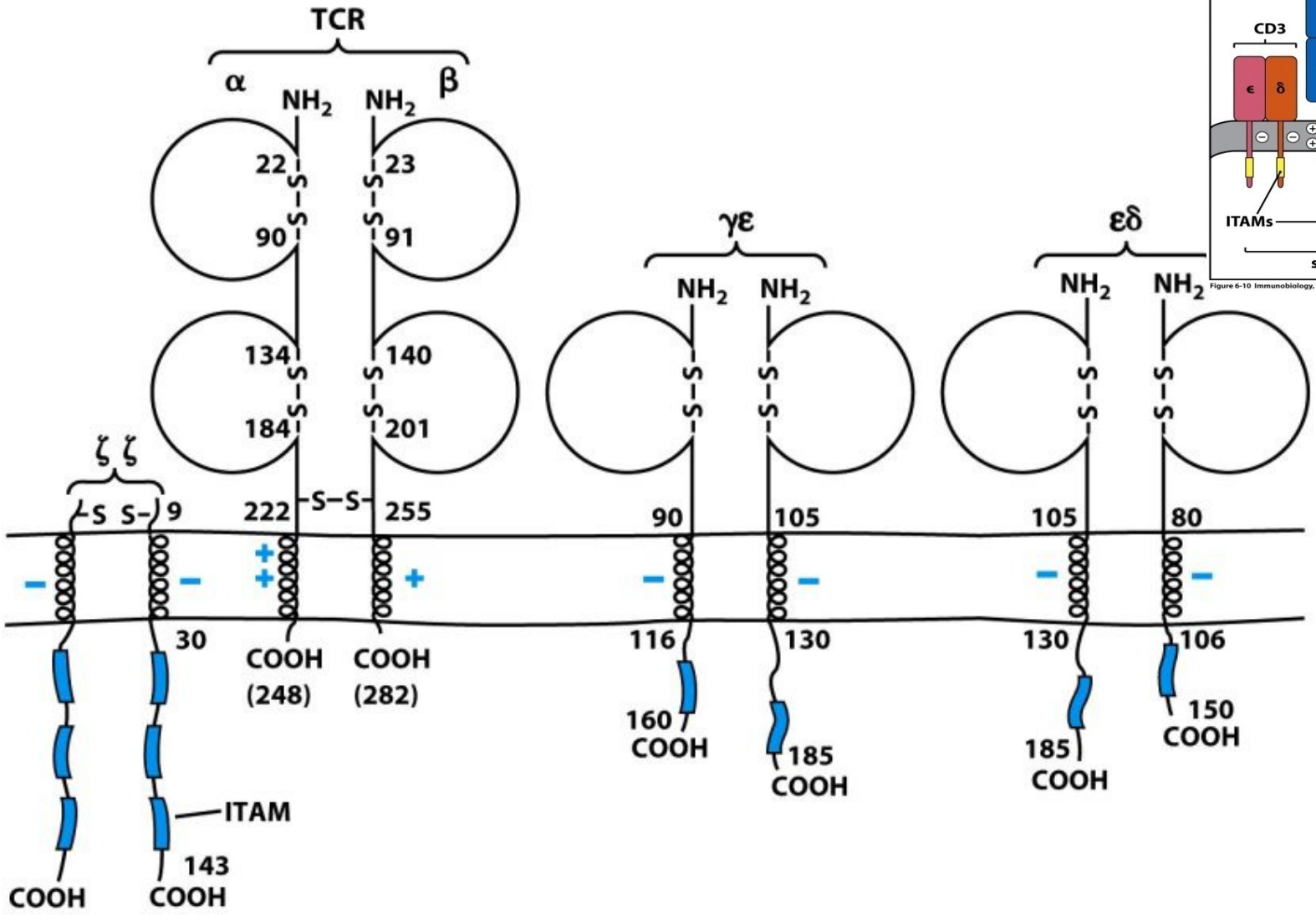


Figure 9-9a
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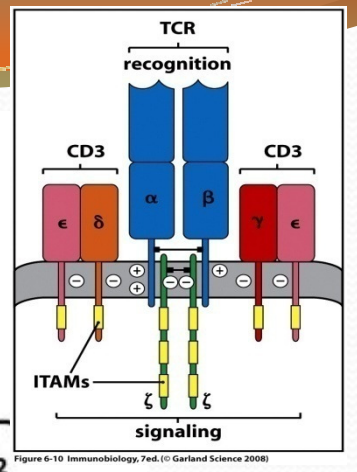
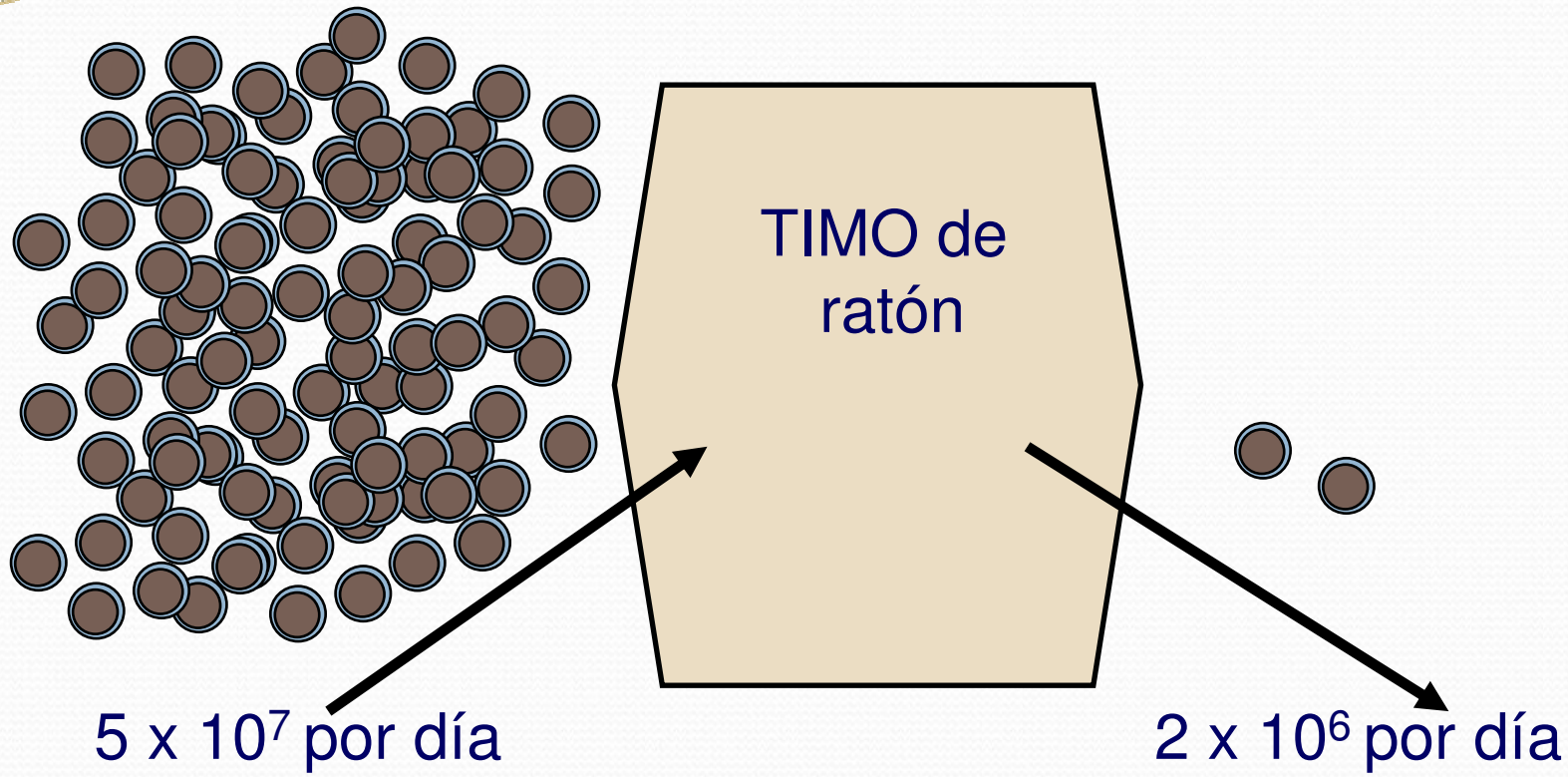


Figure 6-10 Immunobiology, 7ed. (© Garland Science 2008)



¿Cómo el TIMO elige aquellas células que son útiles????

SELECCIÓN.....

SELECCIÓN POSITIVA

Retención de timocitos que expresan TCRs que están RESTRICTOS en su reconocimiento por MHC propio...

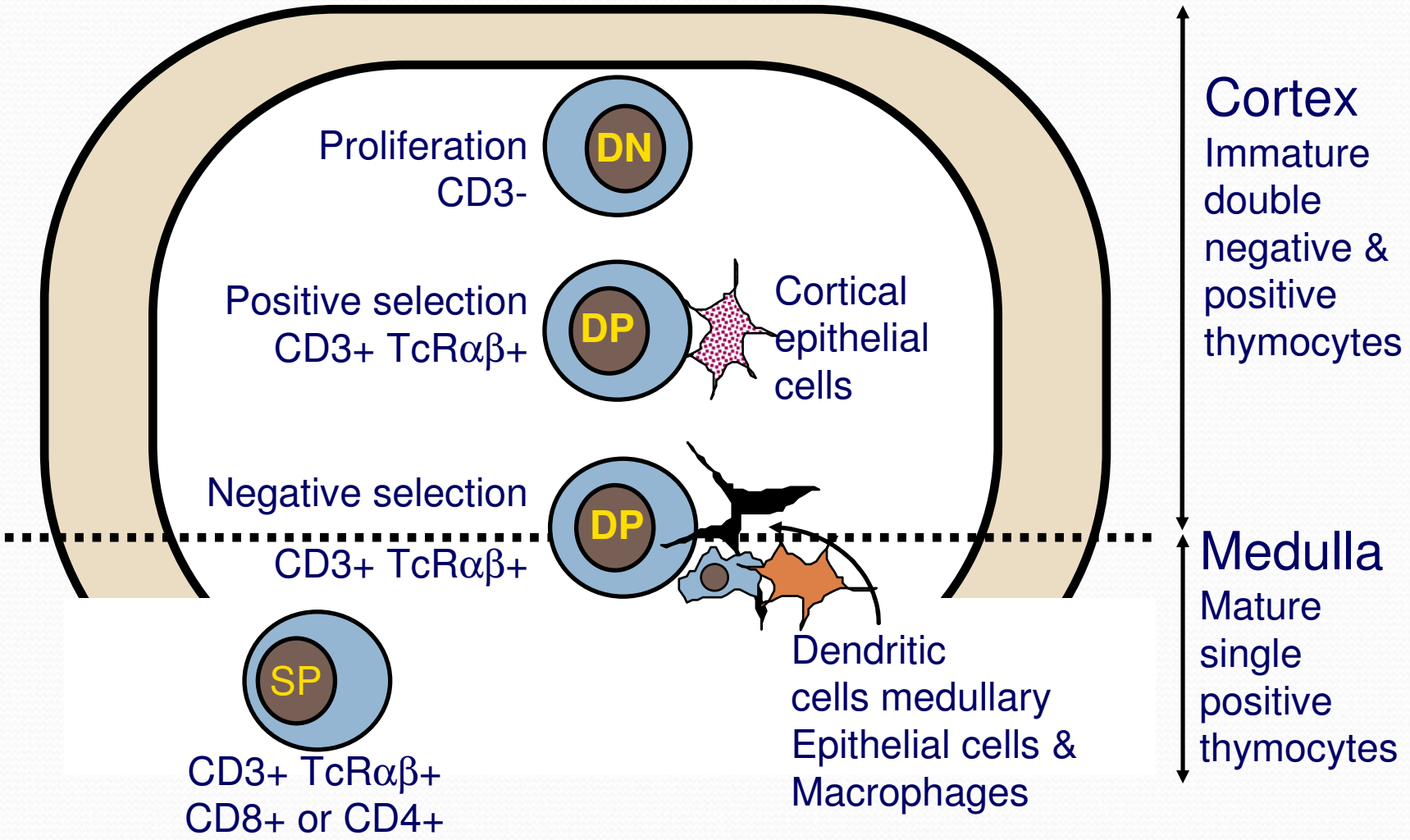
....Selección de lo ÚTIL....

Selección NEGATIVA

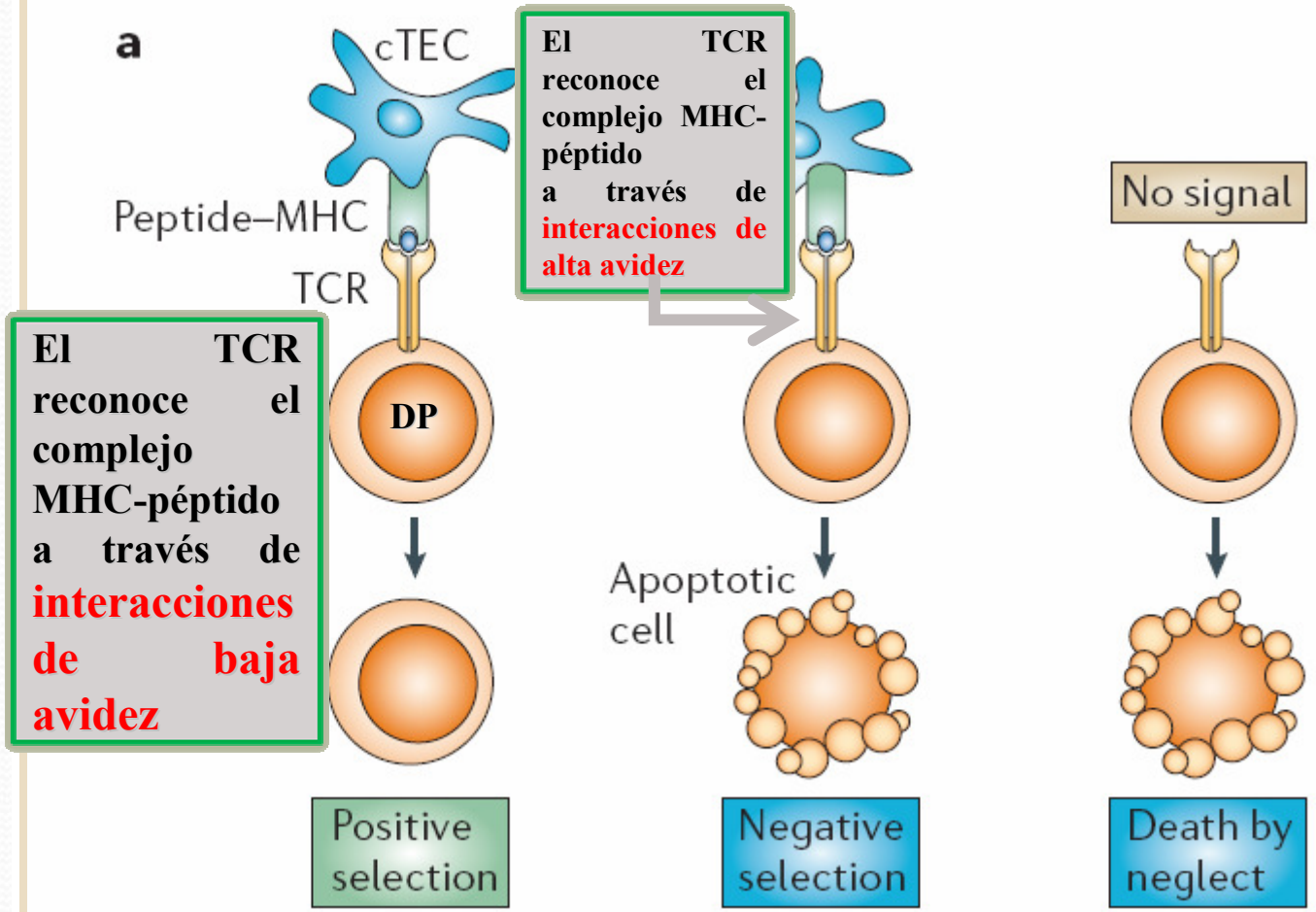
Remoción de timocitos que expresan TCRs que reconocen antígenos propios presentados por MHC propio con alta afinidad o que no tienen afinidad por el MHC propio.

..... Selección de lo DAÑIÑO E INÚTIL....

Selección positiva y negativa ocurren en distintos microambientes.....



Selección positiva y negativa



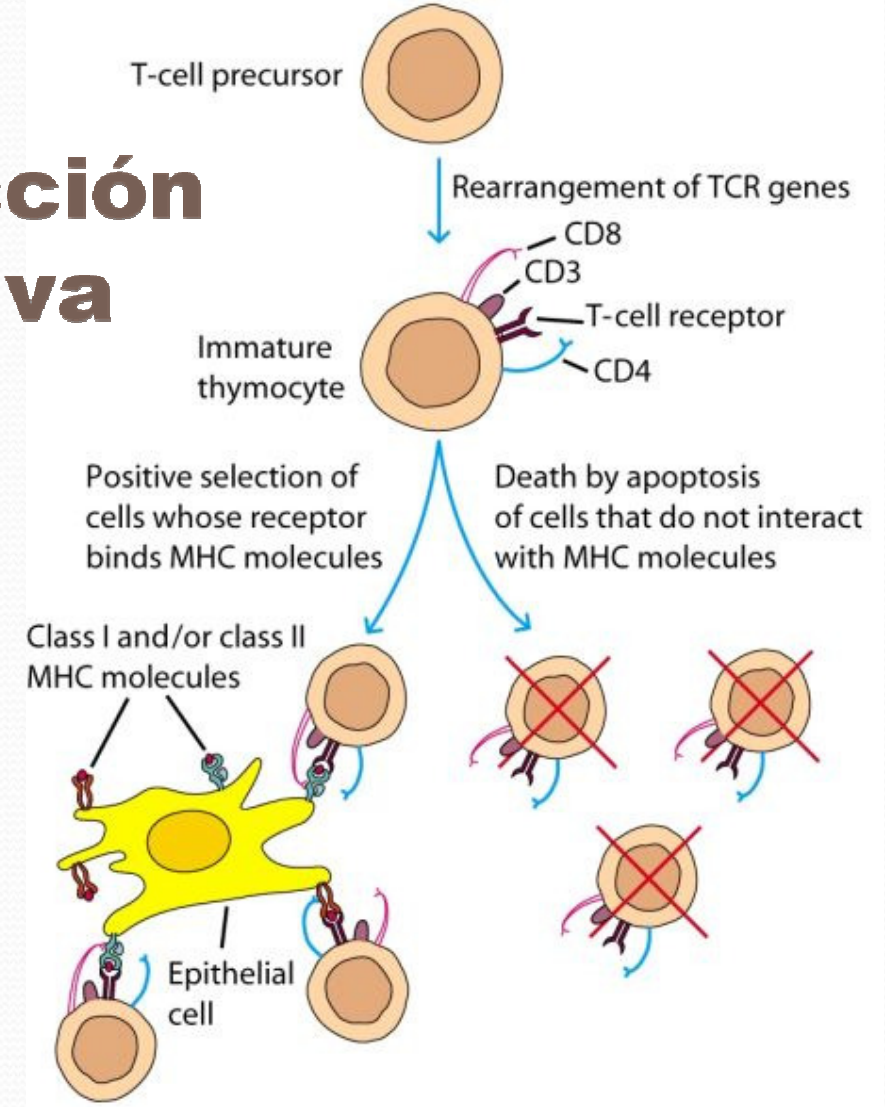
- Señales de supervivencia
- Diferenciación a timocito SP (solo el 2-3% de los timocitos)

Tolerancia central

Nature Reviews Immunology 6, 127-135 (February 2006)

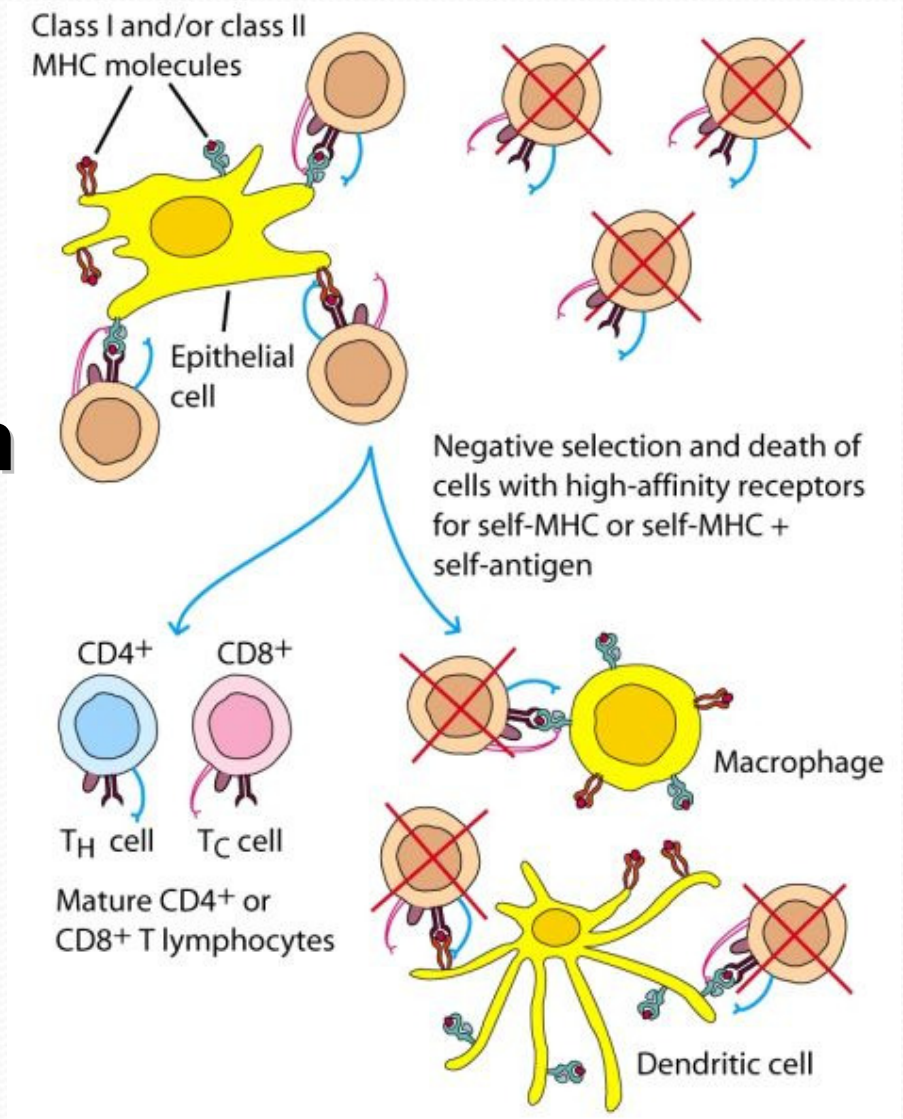
a | Double-positive (DP) thymocytes that are generated in the thymic cortex are selected for their T-cell receptor (TCR) recognition specificity by interacting with peptide–MHC complexes that are presented in the cortex by cortical thymic epithelial cells (cTECs) and dendritic cells

Selección positiva

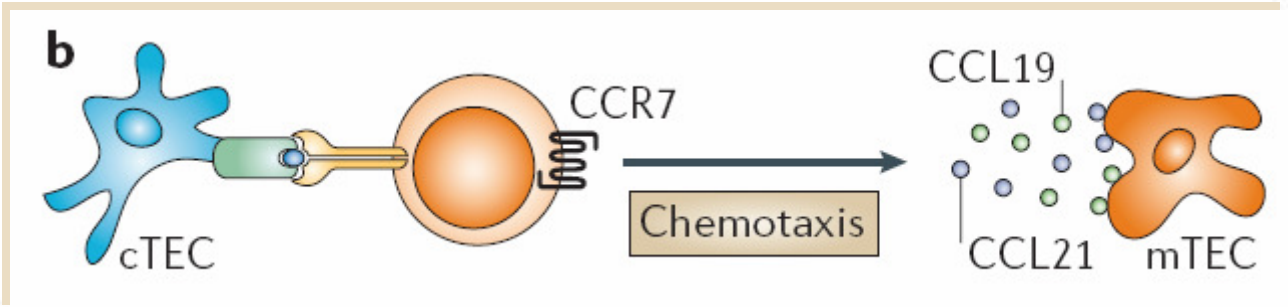


SELECCIÓN POSITIVA: En el estadío doble positivo, la cadena a del TCR del timocito experimenta sucesivos rearreglos hasta ser selecionada positivamente para reaccionar con el MHC-péptido propio o morir

Selección negativa



SELECCIÓN NEGATIVA: Los timocitos que reaccionan con alta afinidad con complejos MHC-péptido propios mueren rápidamente



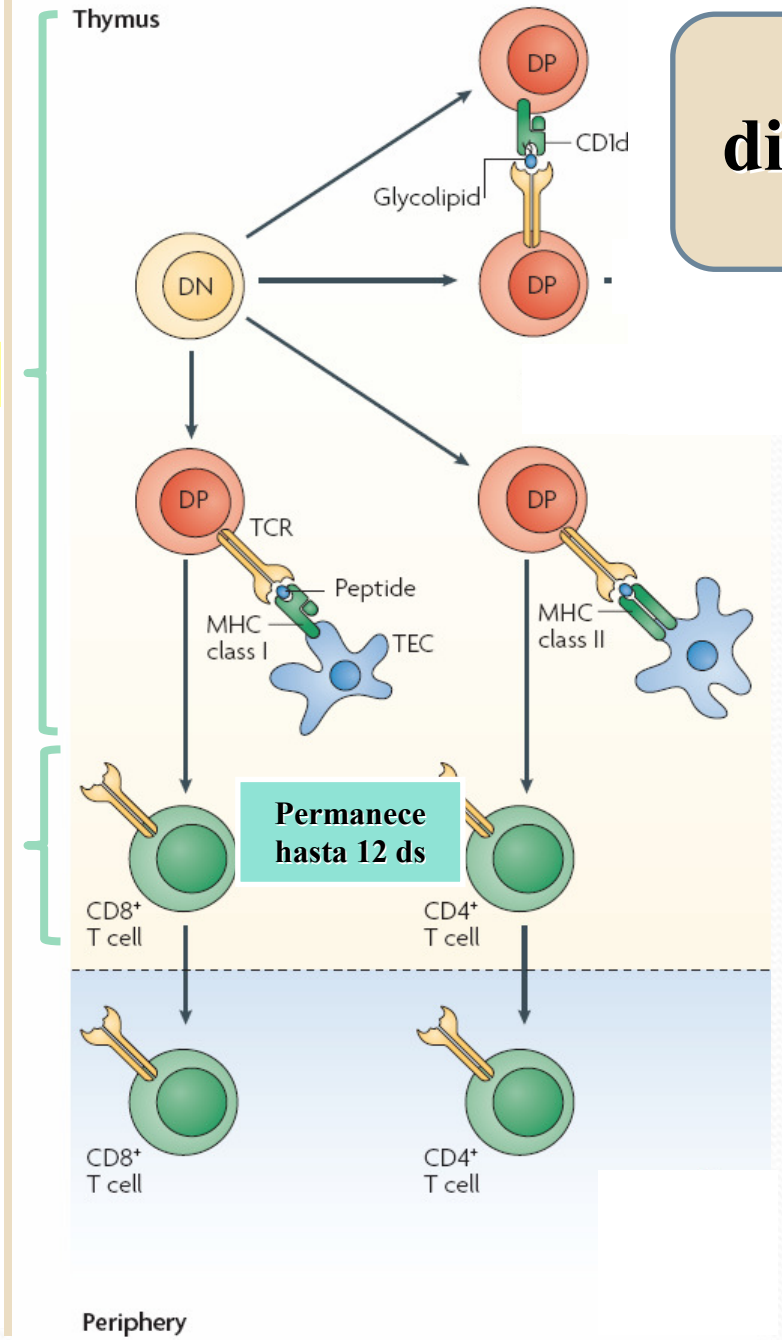
b | Positively selected thymocytes are induced to express CC-chemokine receptor 7 (CCR7) as well as to **undergo the programme of differentiation into single-positive (SP) thymocytes**, and CCR7-expressing thymocytes are attracted to the CCR7 ligands, CC-chemokine ligand19 (CCL19) and CCL21, which are produced by medullary TECs (mTECs) and mainly localized in the medulla.

Nature Reviews Immunology 6, 127-135 (February 2006)

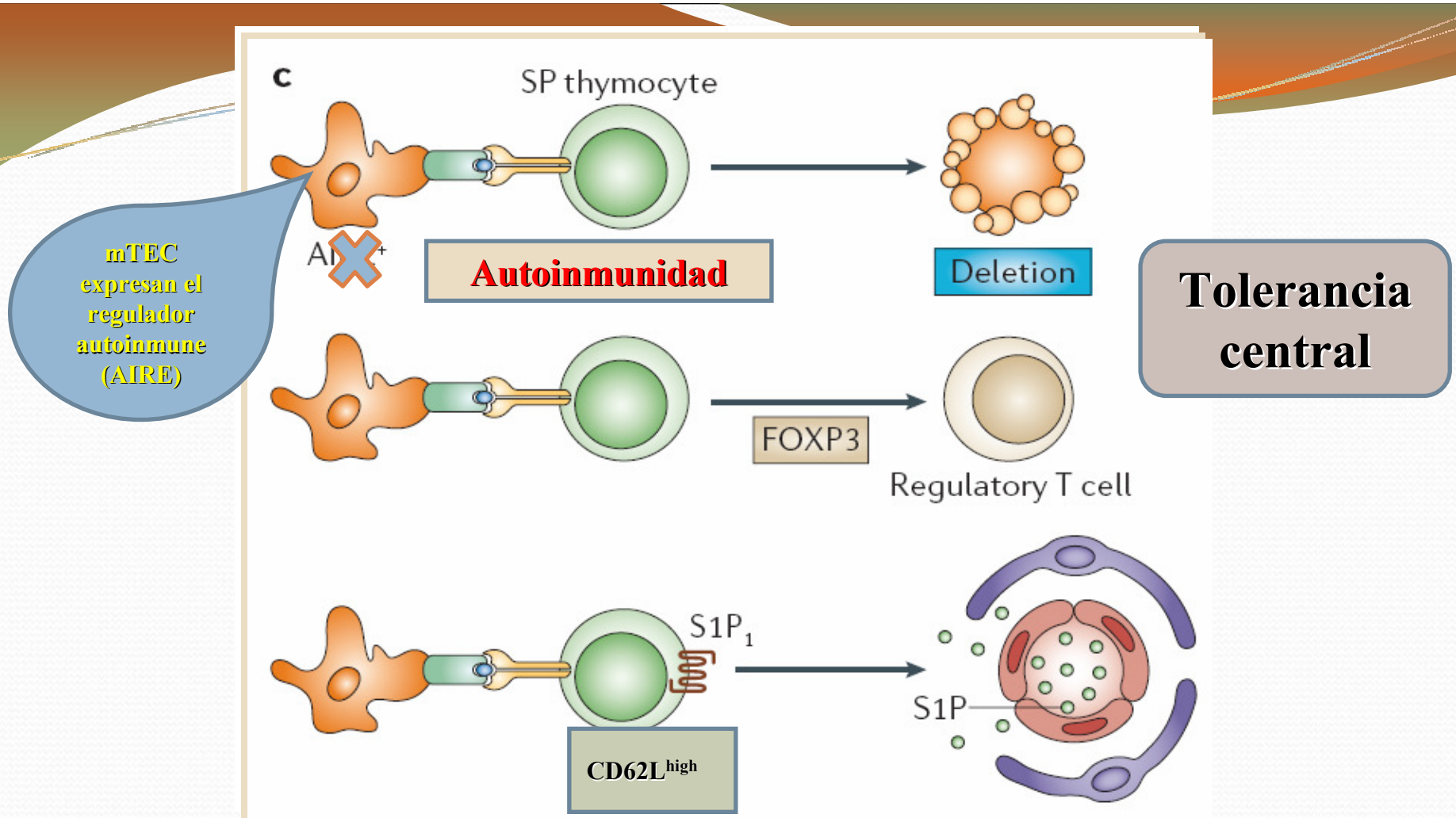
Programa de diferenciación a timocitos SP

CORTEZA

MÉDULA



Si el TCR de un linfocito reconoce péptidos propios presentados por moléculas MHC I y al mismo tiempo la molécula CD8 interacciona con las moléculas MHC I, dicha célula recibe señales que evitan su muerte y favorecen que finalice su maduración…. Para continuar con el proceso madurativo, el linfocito debe seguir expresando su TCR y CD8 aunque perderá la expresión de CD4. **El resultado final es la formación de un LTCD8$^+$ restringido por MHC I**. Del mismo modo se generan los LTCD4$^+$ restringidos por MHC II



c | In the medulla, newly generated SP thymocytes are further selected by the medullary stromal cells, **including autoimmune regulator (AIRE)-expressing mTECs,** so that the cells that are reactive to tissue-specific antigens can be deleted. The maturation of SP thymocytes in the medulla includes the production of regulatory T cells and the expression of sphingosine-1-phosphate receptor 1 ($S1P_1$).

$S1P_1$-expressing mature T cells seem to be attracted to the circulation, where the concentration of S1P is high. FOXP3, forkhead box P3.

La exigente selección que ocurre en el timo durante el desarrollo de los linfocitos T determina que solo un pequeño porcentaje termine siendo exportado a la periferia....

EL TIMO acepta aquellas células T que caen en una estrecha ventana de afinidad por moléculas MHC

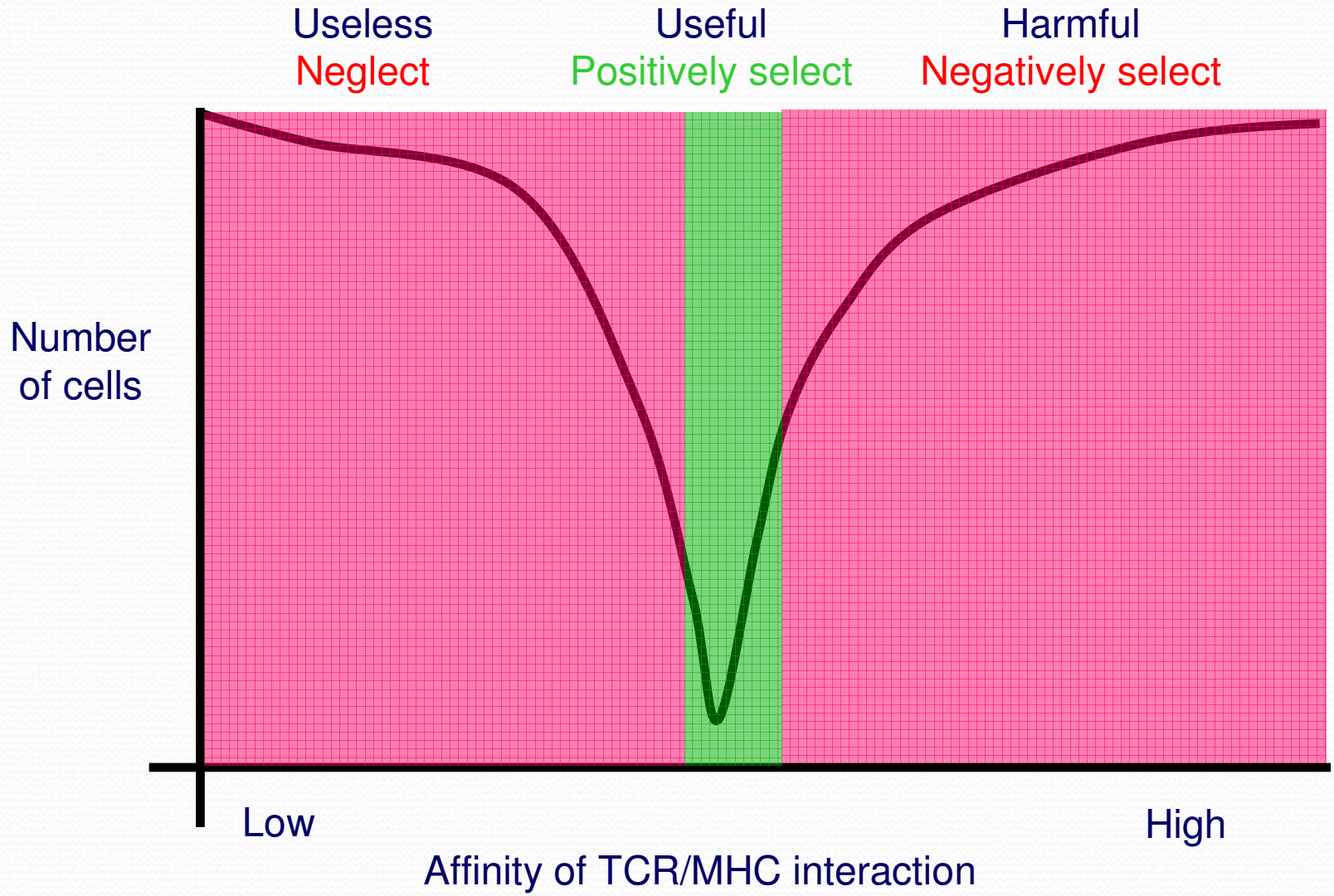


TABLE 9-1 Comparison of αβ and γδ T cells in peripheral blood

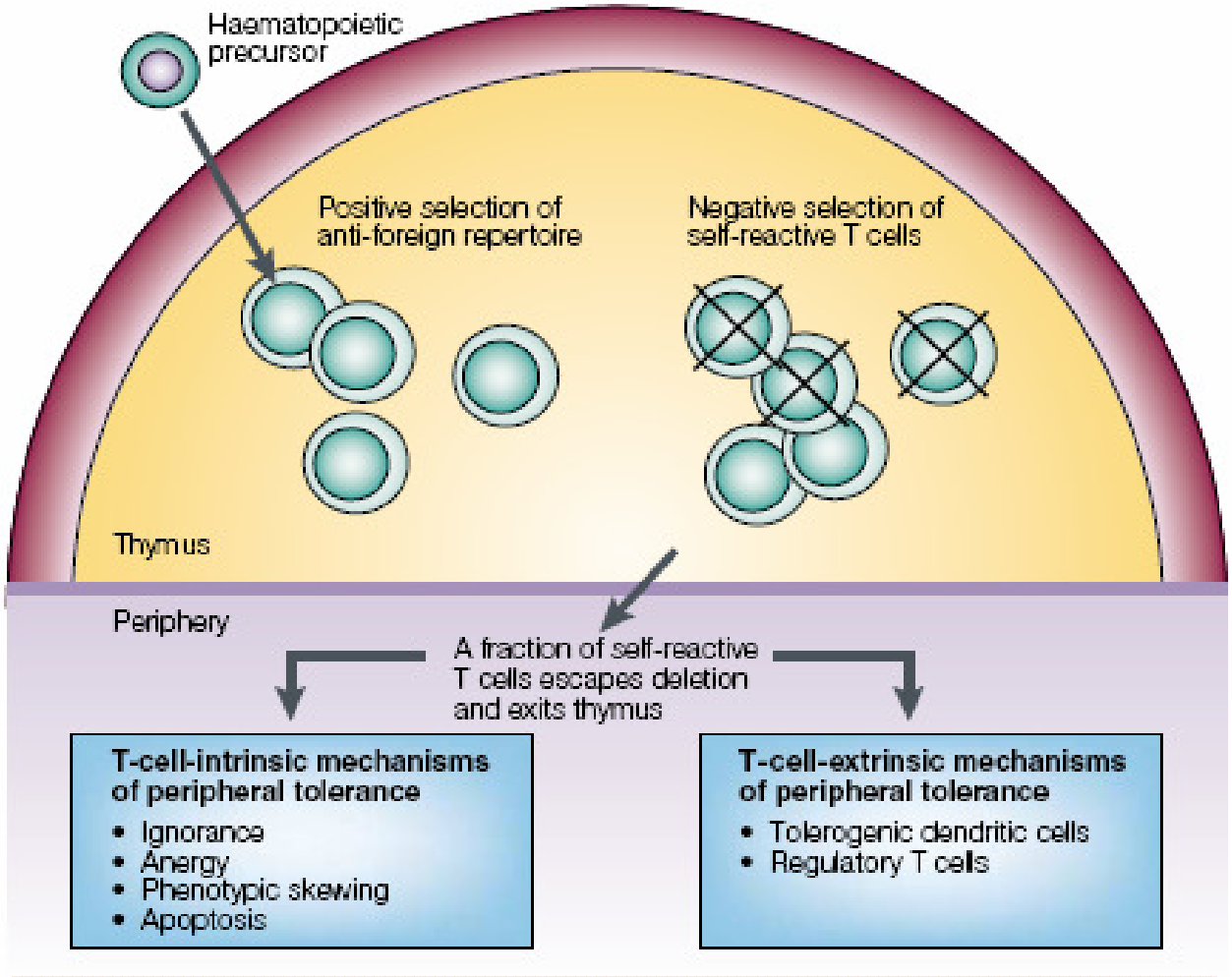
Feature	αβ T cells	γδ T cells
Proportion of $CD3^+$ cells	90–99%	1–10%
TCR V gene germ-line repertoire	Large	Small
CD4/CD8 phenotype		
$CD4^+$	~60%	<1%
$CD8^+$	~30%	~30%
$CD4^+$ $CD8^+$	<1%	<1%
$CD4^-$ $CD8^-$	<1%	~60%
MHC restriction	$CD4^+$: MHC class II $CD8^+$: MHC class I	No MHC restriction
Ligands	MHC + peptide antigen	Phospholipid, intact protein

SOURCE: D. Kabelitz et al., 1999, *Springer Seminars in Immunopathology* **21** (55): 36.

Table 9-1
Kuby IMMUNOLOGY, Sixth Edition

¿Cómo se establece la tolerancia frente a antígenos que no se expresan en el timo?

PERIFÉRICA O ANERGIA…



Mecanismos de tolerancia periférica

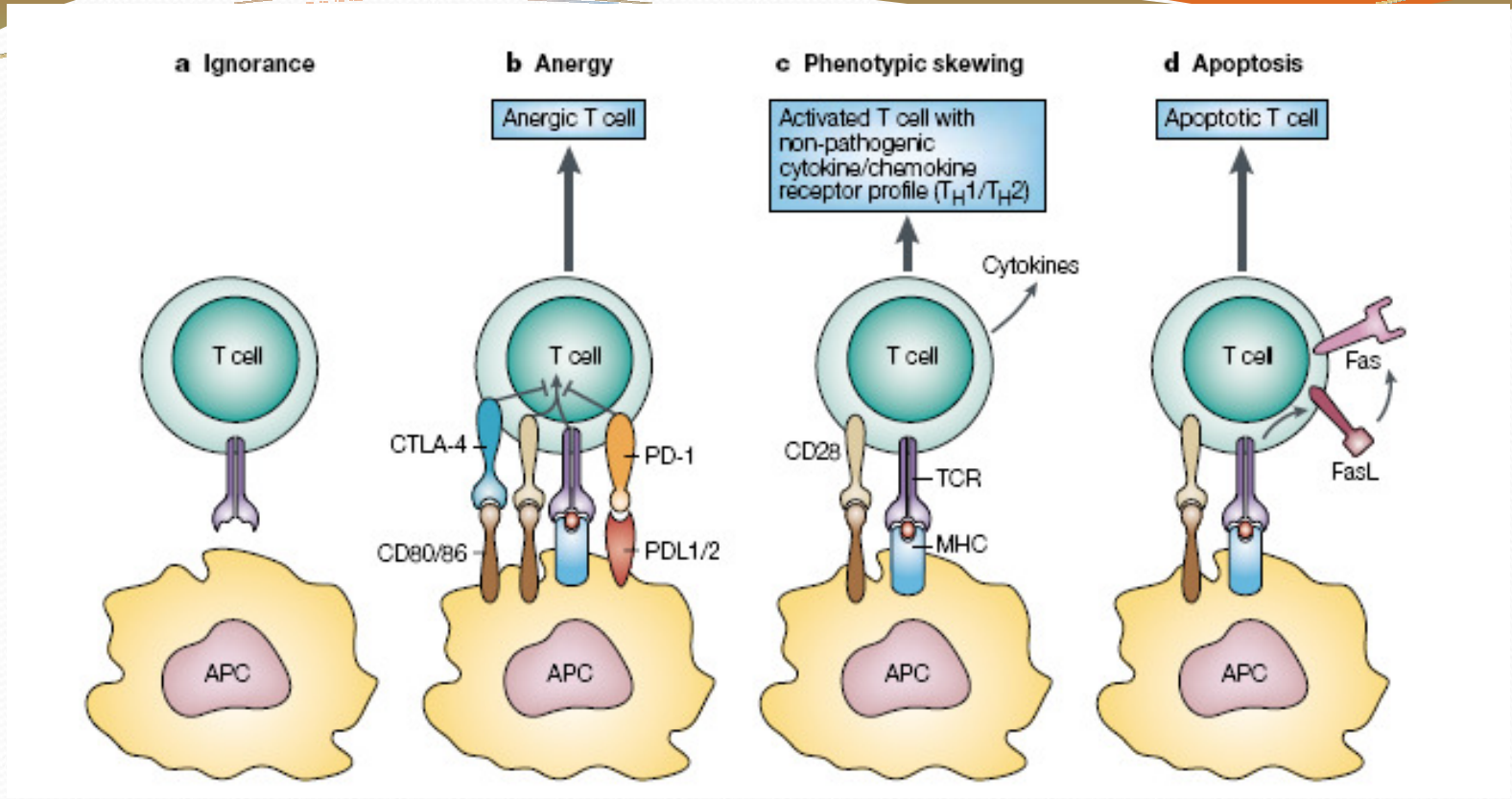
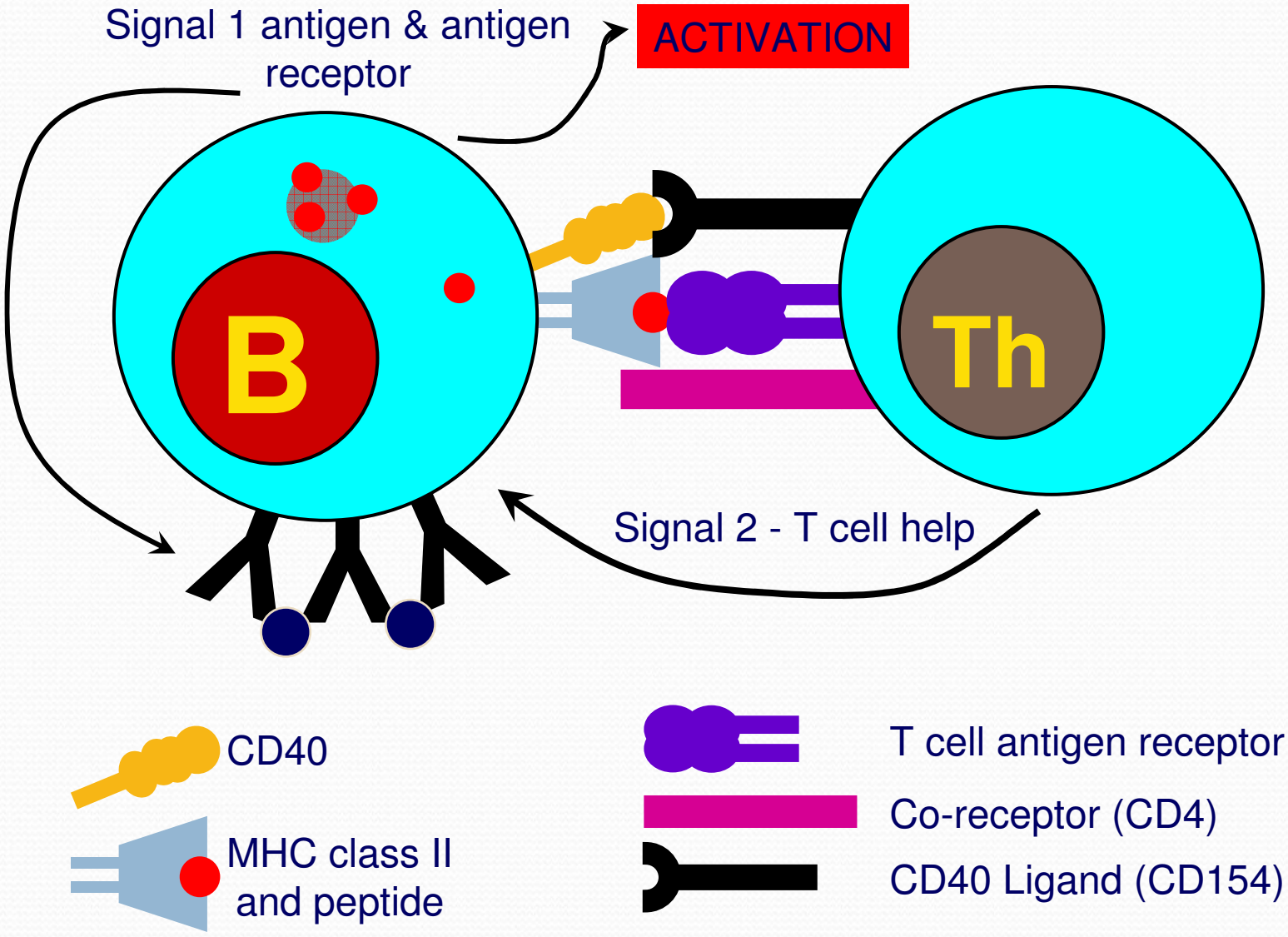


Figure 2 | **T-cell-intrinsic mechanisms of peripheral tolerance. a** | Self-reactive T cells might never encounter the self-protein they recognize and therefore exist in a state of ignorance. **b** | Encounter with self-protein might induce T-cell anergy, possibly involving interaction of the T-cell molecules CTLA-4 or PD-1 with their ligands (CD80/86, PDL1/2). **c** | T cells interacting with self-protein might undergo full activation, but might develop a non-pathogenic phenotype in terms of which cytokines and chemokine receptors they express. In this scenario, self-reactive T cells become activated yet fail to induce autoimmune tissue damage. **d** | Self-reactive T cells might be deleted following contact with self-protein by activation-induced cell death involving upregulation of T-cell Fas ligand and subsequent signalling through the death receptor Fas. APC, antigen-presenting cell; CTLA-4; cytotoxic T-lymphocyte-associated antigen 4; FasL, Fas ligand; MHC, major histocompatibility complex; PD-1; programmed cell death 1; PDL, PD-1 ligand; TCR, T-cell receptor; T_H cell, T helper cell.

Activación de la célula T

Células Th coestimulan células B
Modelos de activación



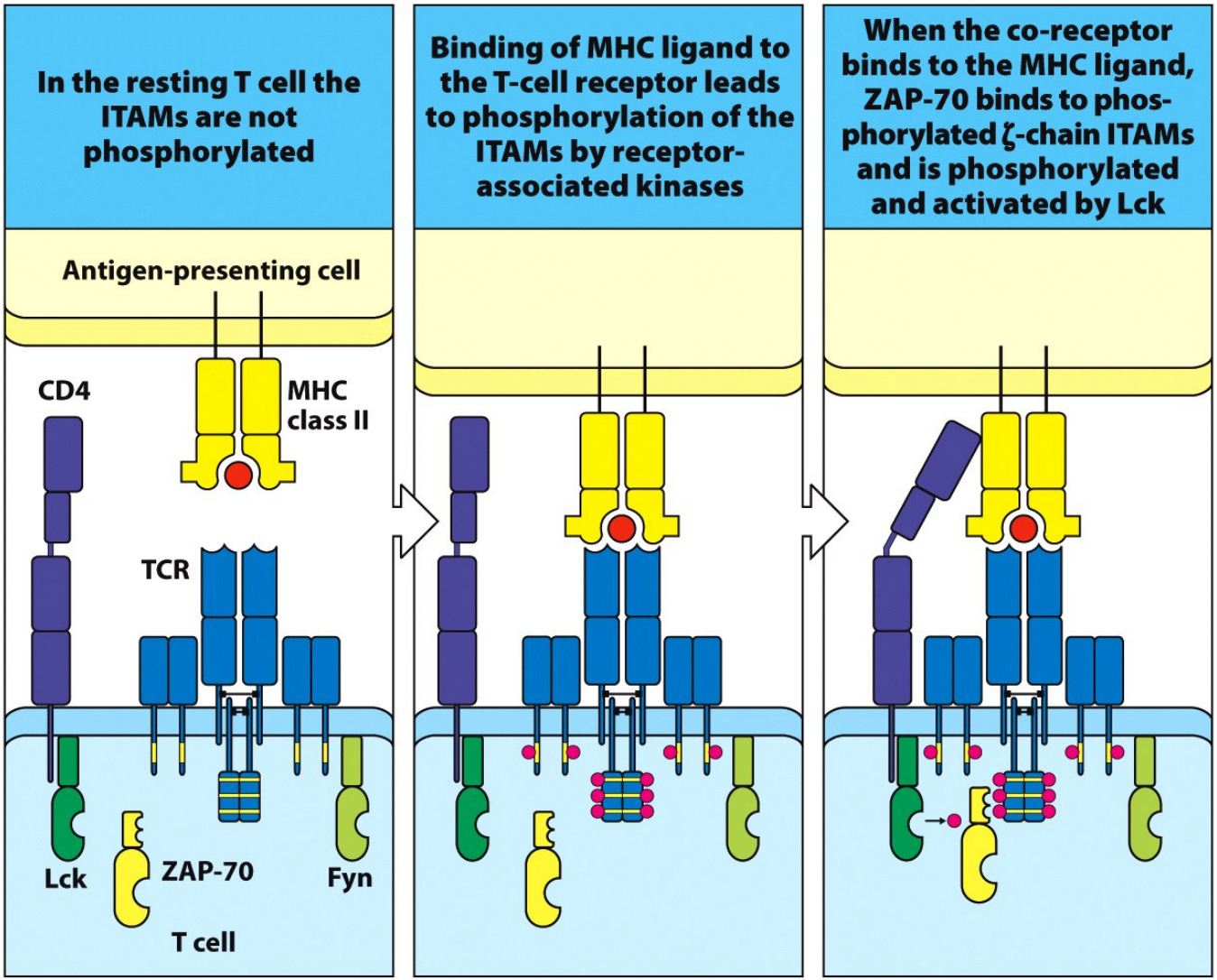


Figure 8.14 The Immune System, 3ed. (© Garland Science 2009)

Eventos intracelulares durante la activación celul

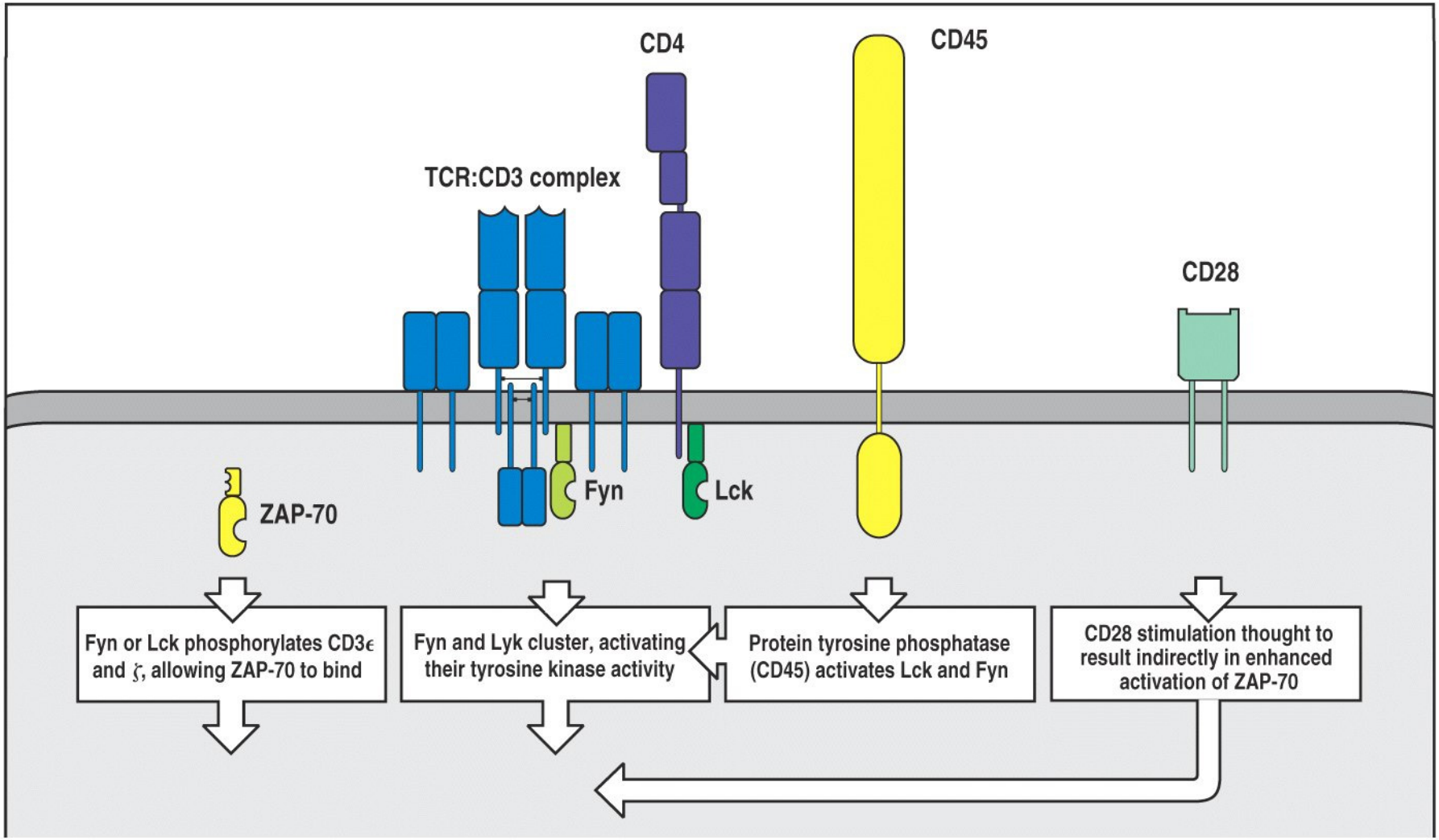


Figure 6-17 part 1 of 2 The Immune System, 2/e (© Garland Science 2005)

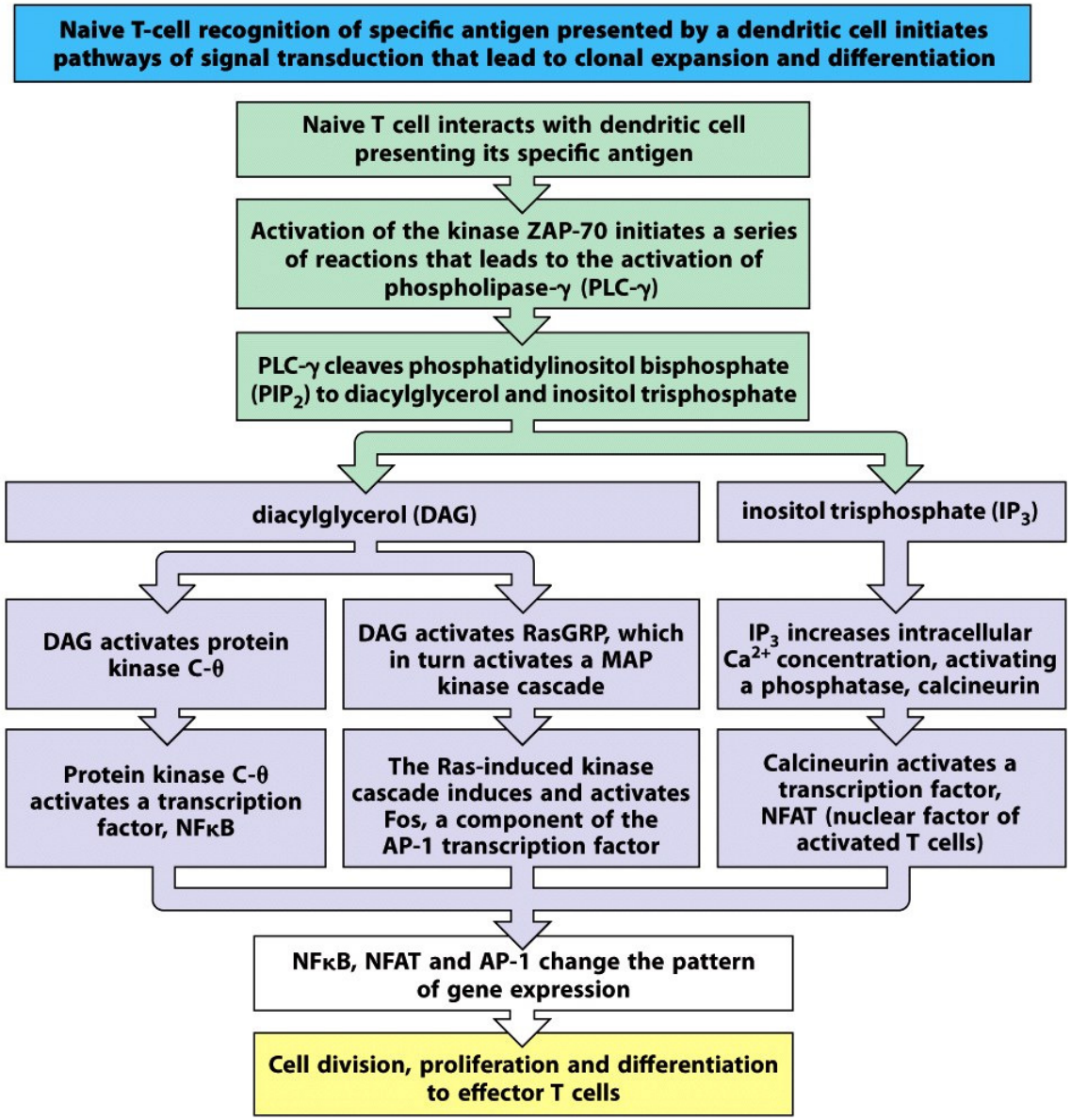
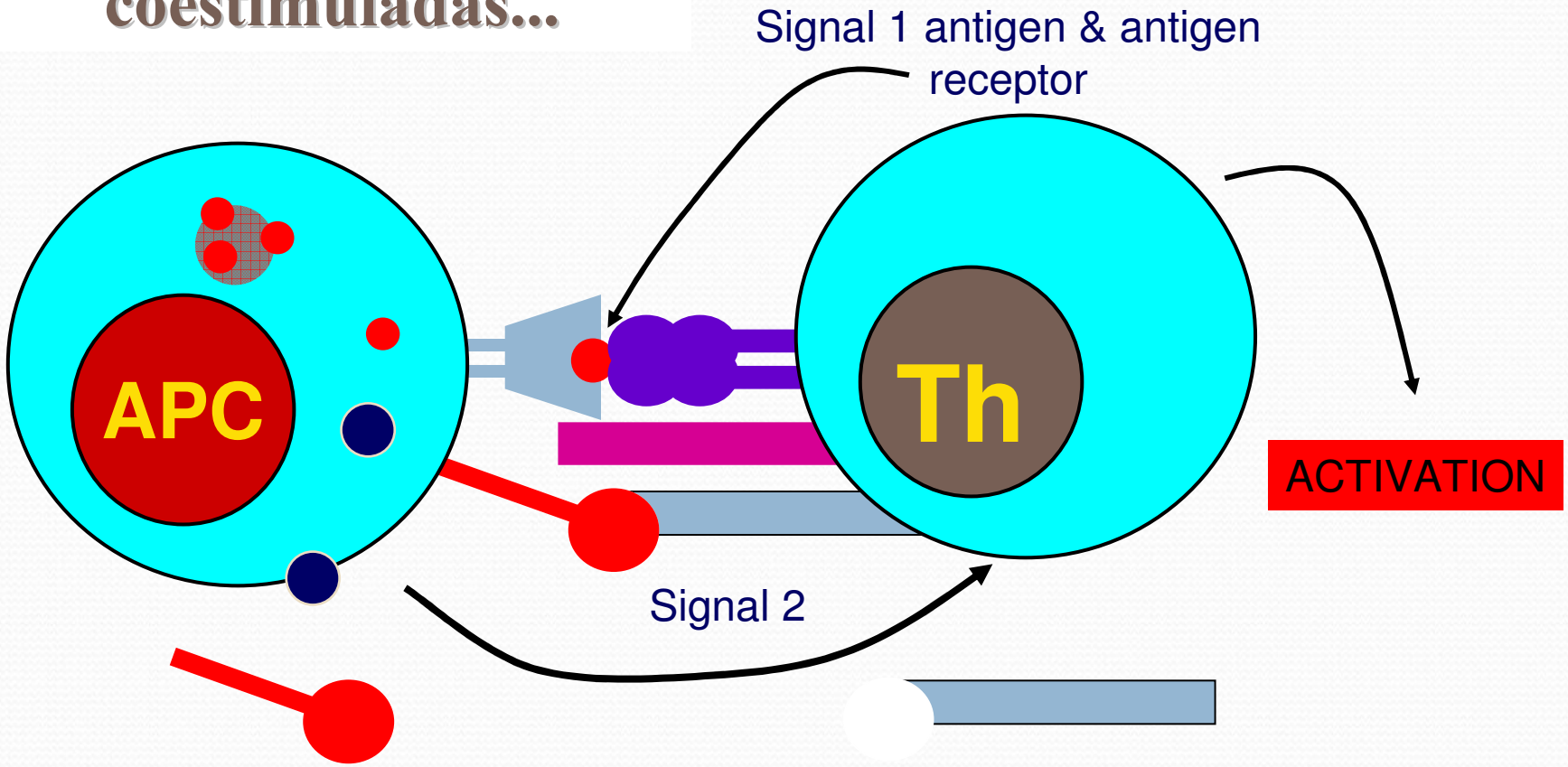


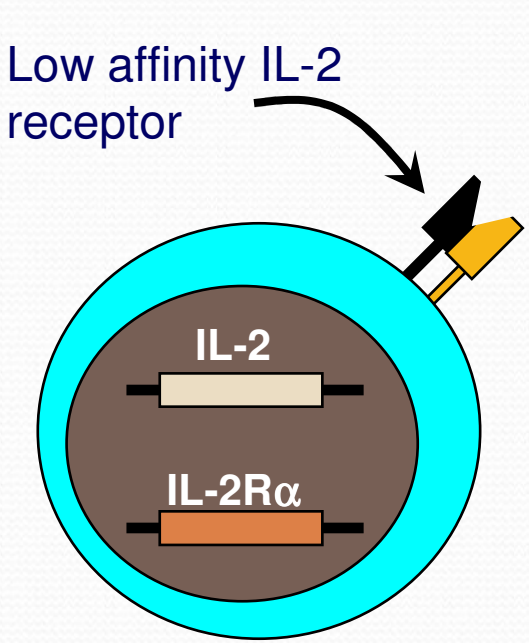
Figure 8.16 The Immune System, 3ed. (© Garland Science 2009)

Las células T son coestimuladas...



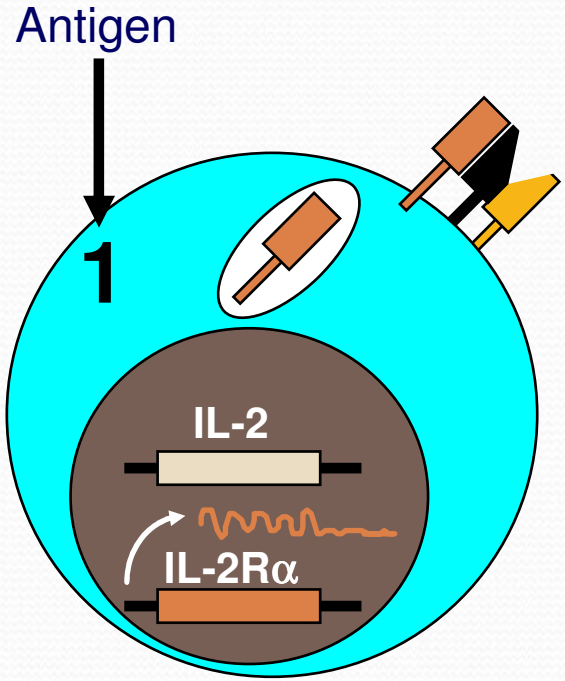
Costimulatory molecules are expressed by most APC including dendritic cells, monocytes, macrophages, B cells etc., but **not by cells that have no immunoregulatory functions such as muscle, nerves, hepatocytes,**

Expresión de la cadena α de IL-2R en células T



Resting T cells

Express IL-2 receptor-β and γ chains but no α chain or IL-2

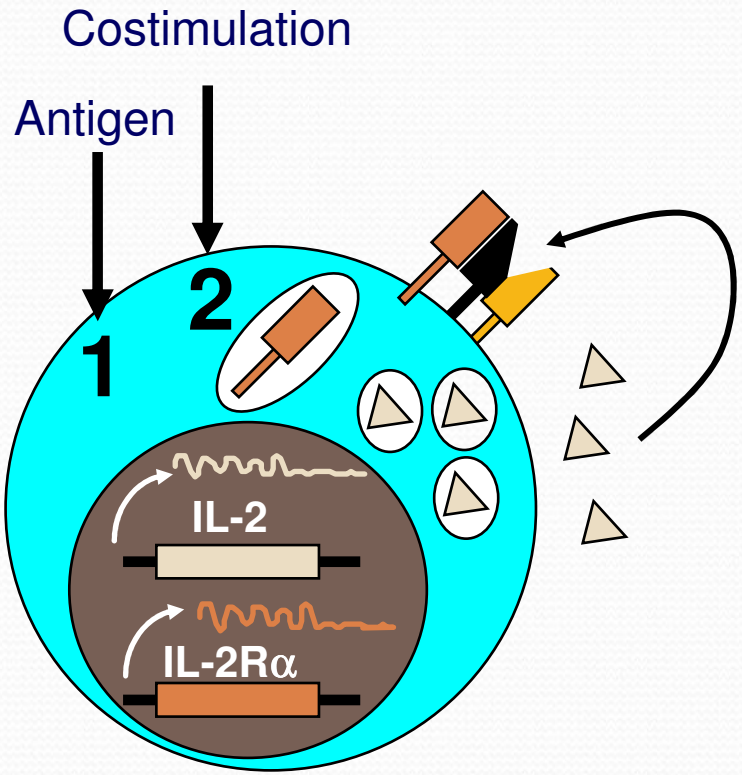


Signal 1

NFAT binds to the promoter of of the α chain gene of the IL-2 receptor

The α chain converts the IL-2R to a high affinity form

Mecanismo de co-estimulación en células T



Signal 2

Activates AP-1 and NFκ-B to increase IL-2 gene transcription by 3 fold

Stabilises and increases the half-life of IL-2 mRNA by 20-30 fold

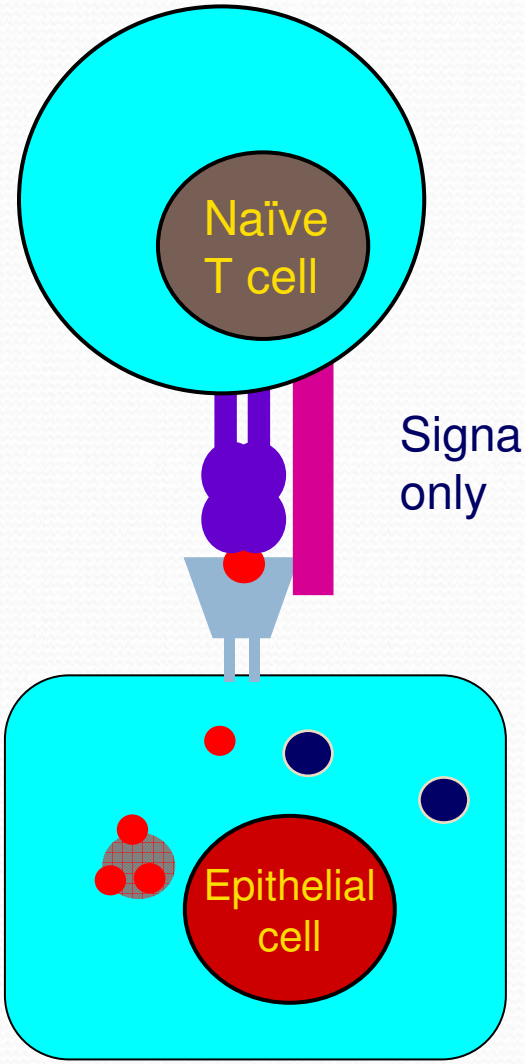
IL-2 production increased by 100 fold overall

Immunosuppressive drugs illustrate the importance of IL-2 in immune responses

Cyclosporin & FK506 inhibit IL-2 by disrupting TCR signalling

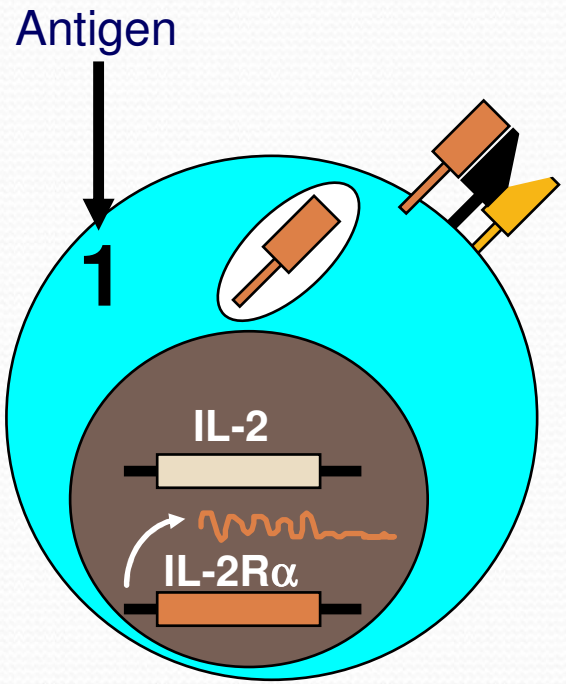
Rapamycin inhibits IL-2R signalling

Anergia



Signal 1 only

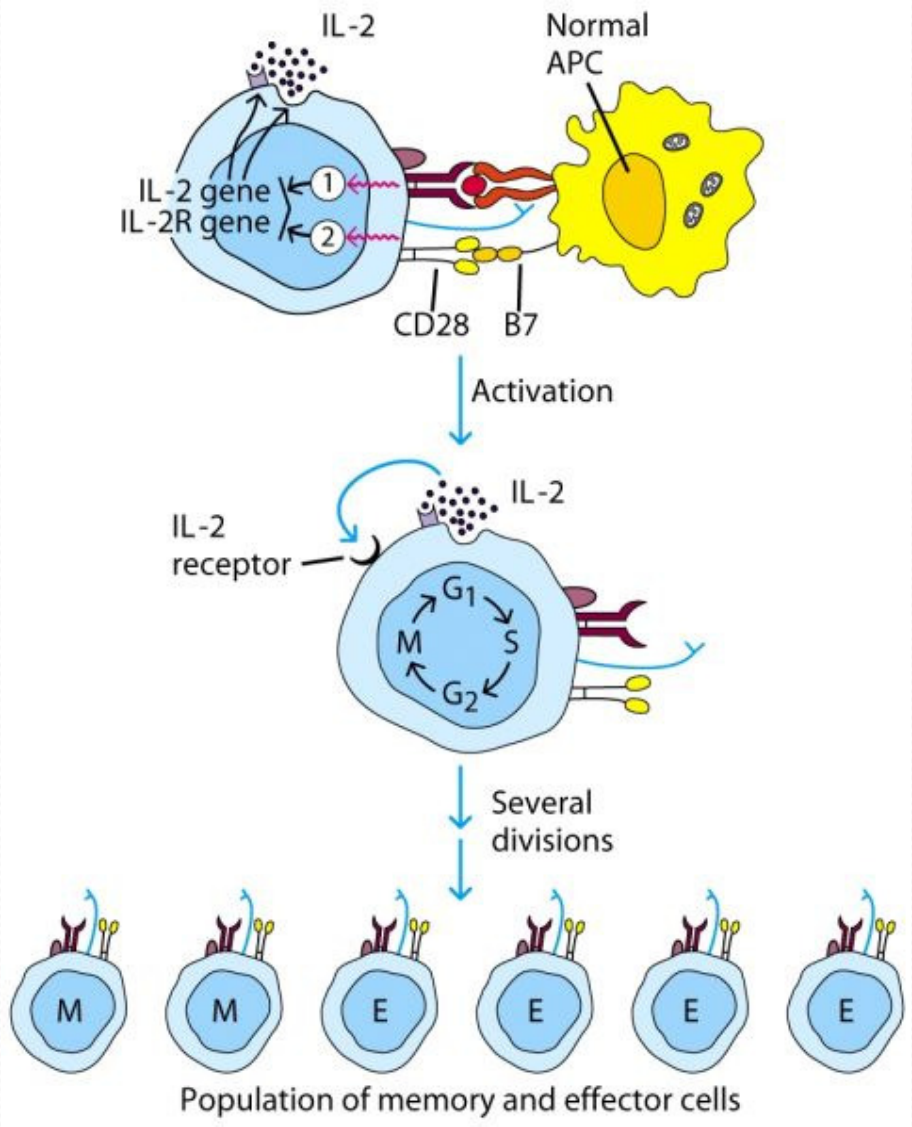
Self peptide epitopes presented by a non-classical APC e.g. an epithelial cell

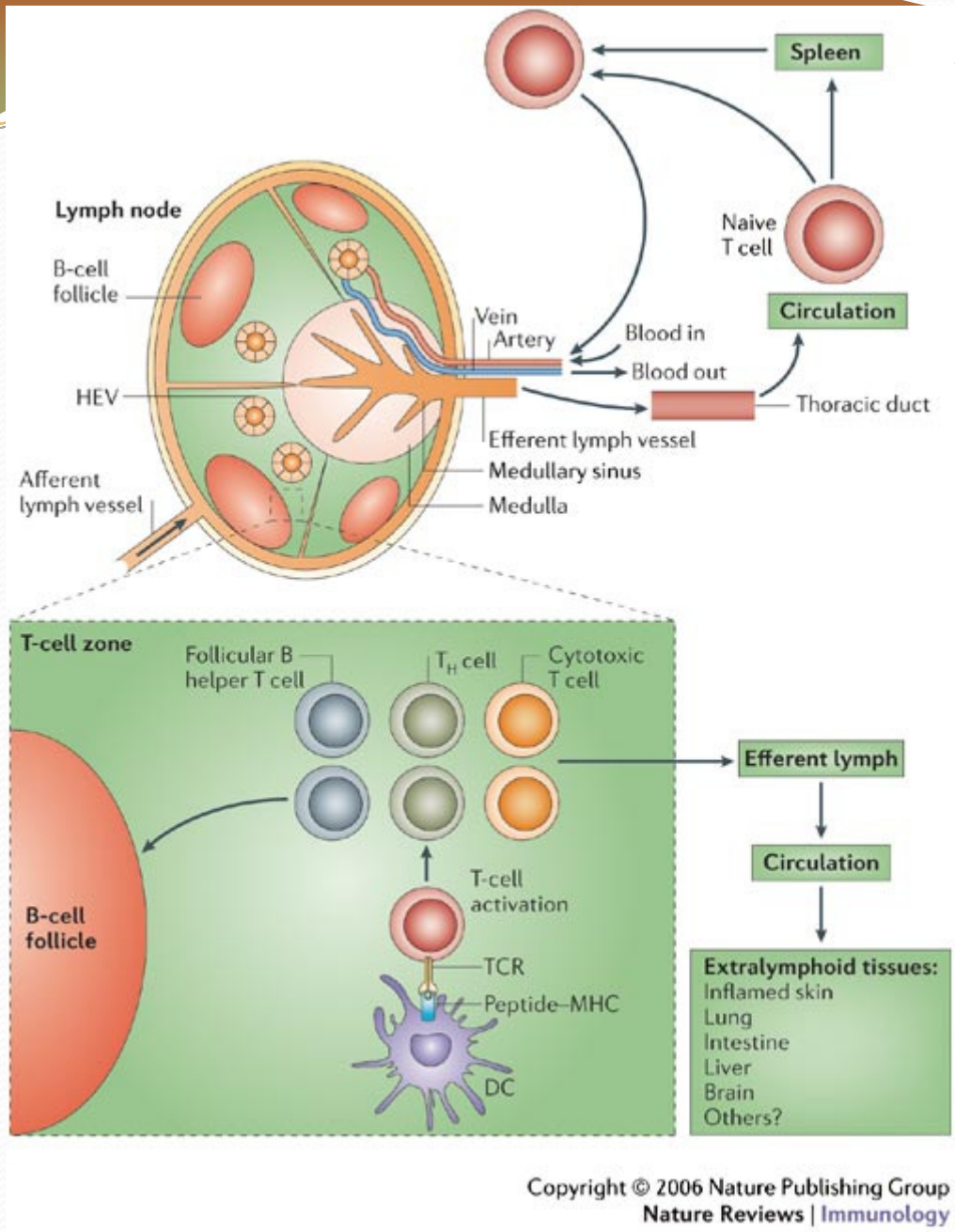


The T cell is unable to produce IL-2 and therefore is unable to proliferate or be clonally selected.

Unlike immunosupressive drugs that inhibit all specificities of T cell, signal 1 in the absence of signal 2 causes antigen specificT cell unresponsiveness.

Células T efectoras


IL-2
Normal
APC
IL-2 gene
IL-2R gene
1
2
CD28
B7
Activation
IL-2
IL-2
receptor
G1
S
G2
M
Several
divisions
M
M
E
E
E
E
Population of memory and effector cells



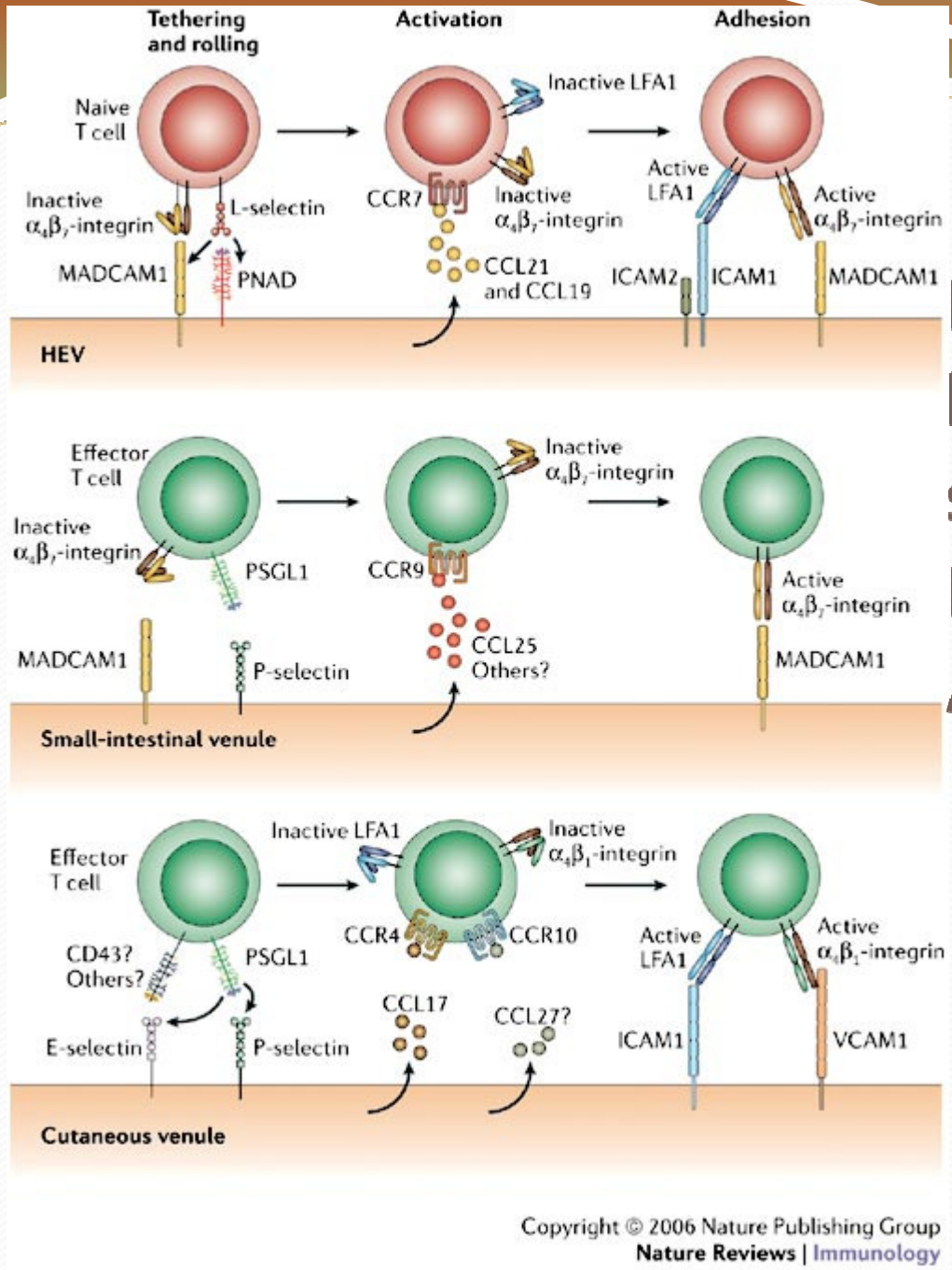
Naive T cells continually circulate through secondary lymphoid organs and the spleen in search of their cognate peptide–MHC complex on the surface of antigen-presenting cells.

They enter lymph nodes across specialized high endothelial venules (HEVs) and return to the circulation through efferent lymphatics and the thoracic duct.

Following activation in the lymph node, T cells differentiate into effector T cells (such as T helper (T_H) cells and cytotoxic T cells), some of which migrate towards the B-cell follicle to provide help to B cells (follicular B helper T cells).

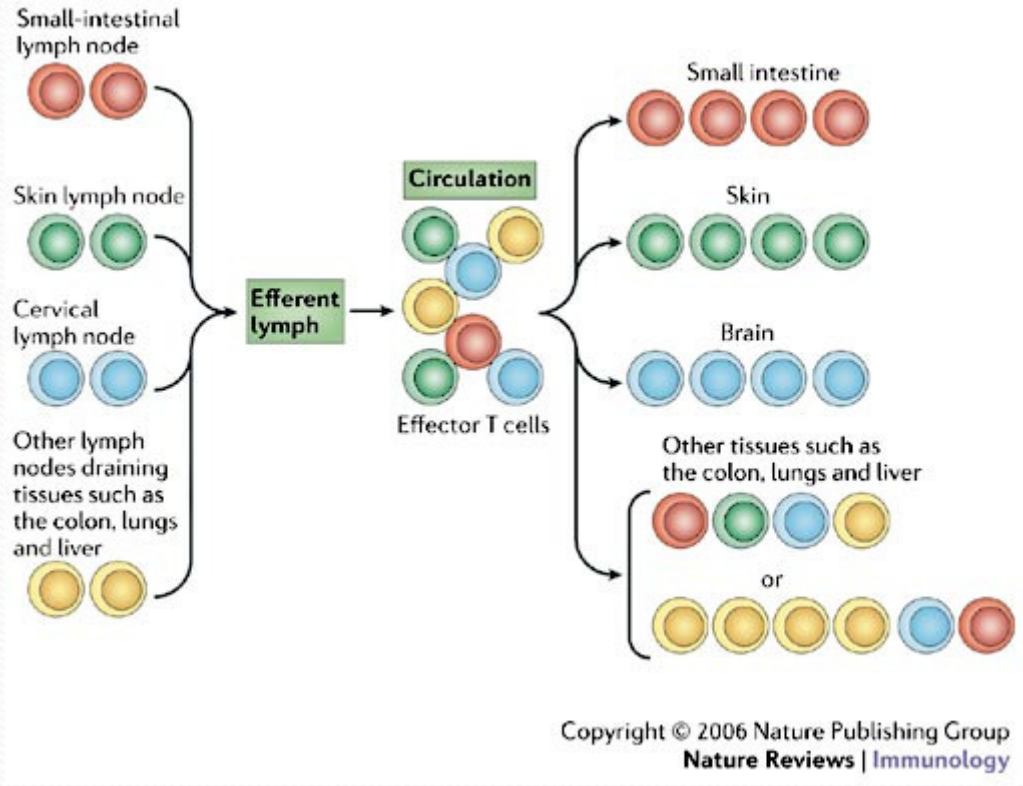
A subset of $CD4^+$effector T cells together with $CD8^+$ effector T cells leave the lymph node, return to the circulation through the lymph system, and might enter a wide range of extralymphoid tissues, where they help to coordinate immune responses in the periphery. DC, dendritic cell; TCR, T-cell receptor.

Nature Reviews Immunology **6**, 682-692 (September 2006)



La célula T efectora llega a distintos sitios…… EXPRESIÓN DE MOLÉCULAS DE ADHESIÓN….

El linfocito efector ingresa a tejidos extralinfoideos, después de su activación en OLS……



Following their activation in secondary lymphoid tissues, effector T cells gain the ability to enter a wide range of extralymphoid tissues. Certain lymphoid tissues (small-intestinal, skin and cervical lymph nodes) seem to generate effector T-cell populations with enhanced tropism for the tissues that they drain. So, the small intestine and skin seem to selectively recruit intestinal- and skin-lymph-node-primed T cells, respectively, from the circulating effector T-cell pool. For simplicity, the skin, small intestine and brain are depicted as collecting only those effector populations generated in the relevant draining lymph node. However, there is likely to be redundancy in the system so that effector T-cell populations generated in other lymph nodes can enter these sites, albeit to a lesser extent. It is currently unclear whether T cells primed in lymph nodes that drain extralymphoid tissues such as the colon, lungs, liver and kidney display enhanced tropism for the tissues that they drain; however, effector T-cell populations generated in non-draining lymph nodes can readily enter the lungs and liver.

Los microorganismos inducen distintos tipos de respuesta inmune....

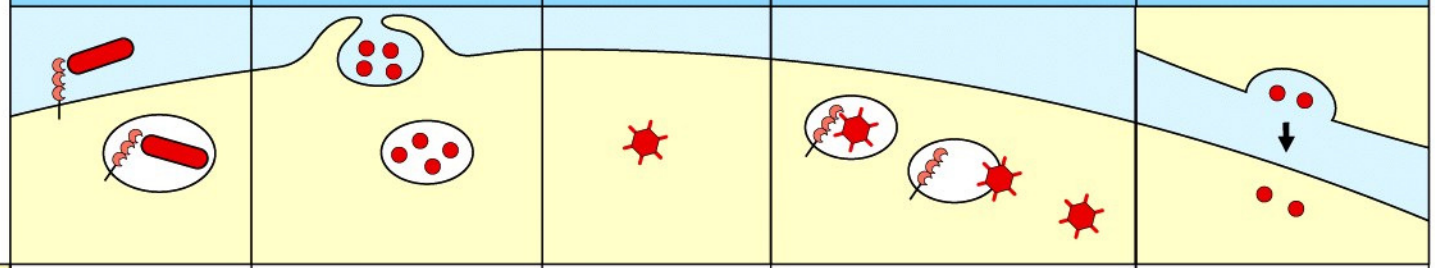
	Routes of antigen processing and presentation by dendritic cells				
	Receptor-mediated endocytosis	Macro-pinocytosis	Viral infection	Cross-presentation after phagocytic or macropinocytic uptake	Transfer from incoming dendritic cell to resident dendritic cell
					
Type of pathogen presented	Extracellular bacteria	Extracellular bacteria, soluble antigens, virus particles	Viruses	Viruses	Viruses
MHC molecules loaded	MHC class II	MHC class II	MHC class I	MHC class I	MHC class I
Type of naive T cell activated	CD4 T cells	CD4 T cells	CD8 T cells	CD8 T cells	CD8 T cells

Figure 8.3 The Immune System, 3ed. (© Garland Science 2009)

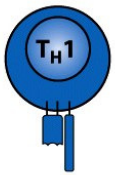
	CD8 cytotoxic T cells	CD4 T_H1 cells	CD4 T_H2 cells	CD4 T_H17 cells	CD4 regulatory T cells (various types)
Types of effector T cell					
Main functions in adaptive immune response	Kill virus-infected cells	Activate infected macrophages Provide help to B cells for antibody production	Provide help to B cells for antibody production, especially switching to IgE	Enhance neutrophil response	Suppress T-cell responses
Pathogens targeted	Viruses (e.g. influenza, rabies, vaccinia) Some intracellular bacteria	Microbes that persist in macrophage vesicles (e.g. mycobacteria, *Listeria*, *Leishmania donovani*, *Pneumocystis carinii*) Extracellular bacteria	Helminth parasites	Extracellular bacteria (e.g. *Salmonella enterica*)	

Figure 8-1 Immunobiology, 7ed. (© Garland Science 2008)

Moléculas efectoras secretadas por células efectoras activadas...

CD8 T cells: peptide + MHC class I		CD4 T cells: peptide + MHC class II							
Cytotoxic (killer) T cells		T_H1 cells		T_H2 cells		T_H17 cells		T_{reg} cells	
Cytotoxic effector molecules	Others	Macrophage-activating effector molecules	Others	B-cell-activating effector molecules	Others	Neutrophil recruitment	Others	Suppressive cytokines	Others
Perforin Granzymes Granulysin Fas ligand	IFN-γ LT-α TNF-α	IFN-γ GM-CSF TNF-α CD40 ligand Fas ligand	IL-3 LT-α CXCL2 (GROβ)	IL-4 IL-5 IL-13 CD40 ligand	IL-3 GM-CSF IL-10 TGF-β CCL11 (eotaxin) CCL17 (TARC)	IL-17A IL-17F IL-6	TNF CXCL1 (GROα)	IL-10 TGF-β	GM-CSF

Figure 8-33 Immunobiology, 7ed. (© Garland Science 2008)

Cytotoxicity

Macrophage enhancement

Allergy

Neutrophil recruitment Epithelial cell activation

Down regulation of immune response

Citocinas secretadas por las distintas poblaciones de linfocitos efectores

Cytokine	T-cell source	Effects on				
		B cells	T cells	Macrophages	Hemato-poietic cells	Other somatic cells
Interleukin-2 (IL-2)	Naive, T_H1, some CD8	Stimulates growth and J-chain synthesis	Growth	–	Stimulates NK cell growth	–
Interferon-γ (IFN-γ)	T_H1, CTL	Differentiation IgG2a synthesis (mouse)	Inhibits T_H2 cell growth	Activation, ↑ MHC class I and class II	Activates NK cells	Antiviral ↑ MHC class I and class II
Lymphotoxin (LT, TNF-β)	T_H1, some CTL	Inhibits	Kills	Activates, induces NO production	Activates neutrophils	Kills fibroblasts and tumor cells
Interleukin-4 (IL-4)	T_H2	Activation, growth IgG1, IgE ↑ MHC class II induction	Growth, survival	Inhibits macrophage activation	↑ Growth of mast cells	–
Interleukin-5 (IL-5)	T_H2	Mouse: Differentiation IgA synthesis	–	–	↑ Eosinophil growth and differentiation	–
Interleukin-10 (IL-10)	T_H2 (human: some T_H1), T_{reg}	↑ MHC class II	Inhibits T_H1	Inhibits cytokine release	Co-stimulates mast cell growth	–

Figure 8-34 part 1 of 2 Immunobiology, 7ed. (© Garland Science 2008)

Cytokine	T-cell source	Effects on				
		B cells	T cells	Macrophages	Hemato-poietic cells	Other somatic cells
Interleukin-3 (IL-3)	T_H1, T_H2 some CTL	–	–	–	Growth factor for progenitor hematopoietic cells (multi-CSF)	–
Tumor necrosis factor-α (TNF-α)	T_H1, some T_H2 some CTL	–	–	Activates, induces NO production	–	Activates microvascular endothelium
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	T_H1, some T_H2 some CTL	Differentiation	Inhibits growth?	Activation Differentiation to dendritic cells	↑ Production of granulocytes and macrophages (myelopoiesis) and dendritic cells	–
Transforming growth factor-β (TGF-β)	CD4 T cells (T_{reg})	Inhibits growth IgA switch factor	Inhibits growth, promotes survival	Inhibits activation	Activates neutrophils	Inhibits/ stimulates cell growth
Interleukin-17 (IL-17)	CD4 T cells (T_H17) macrophages	–	–	–	Stimulates neutrophil recruitment	Stimulates fibroblasts and epithelial cells to secrete chemokines

Figure 8-34 part 2 of 2 Immunobiology, 7ed. (© Garland Science 2008)

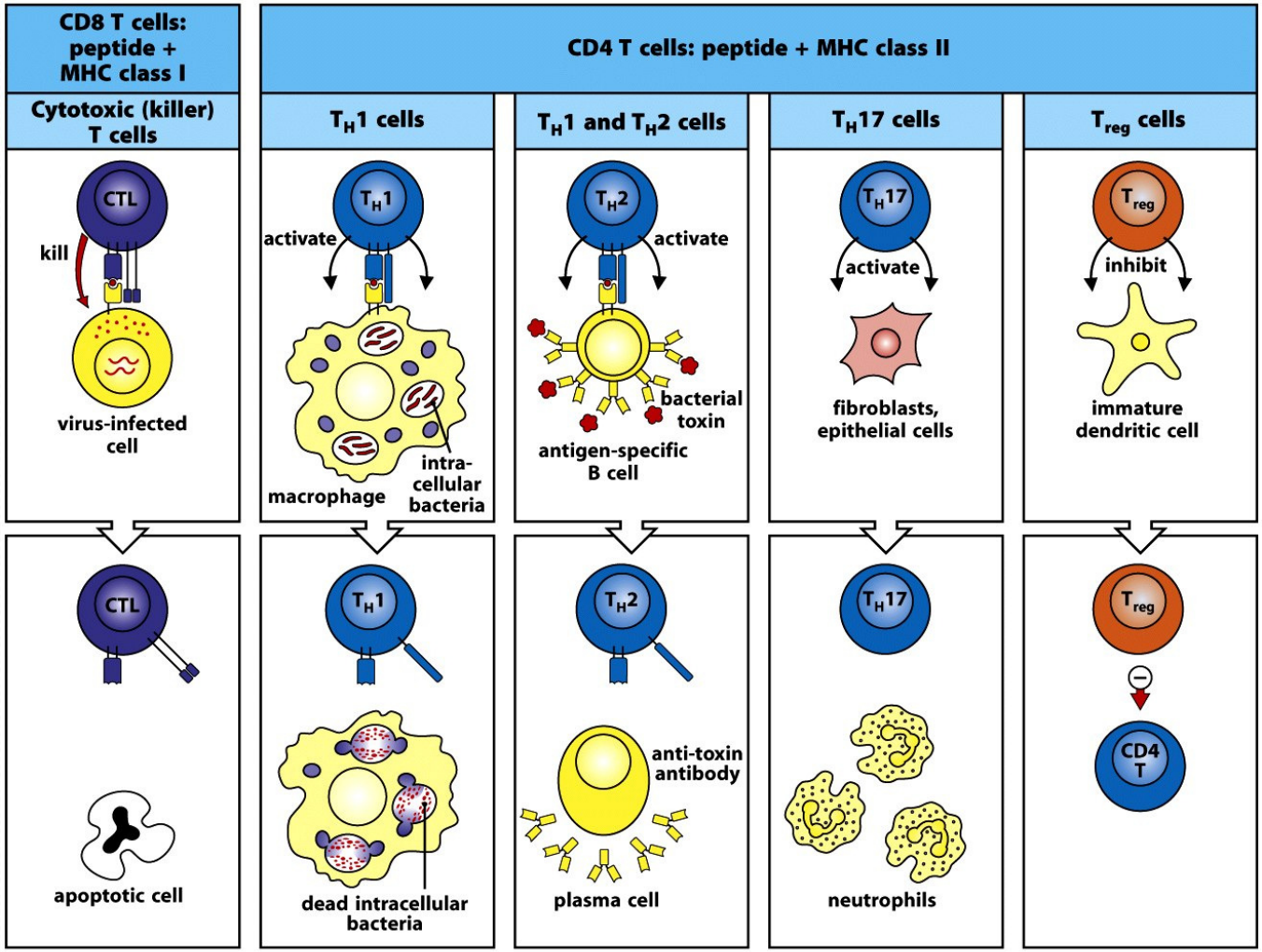


Figure 8-27 Immunobiology, 7ed. (© Garland Science 2008)

Células TCD4^{+}

Expresión de moléculas de superficie por las células TCD4+

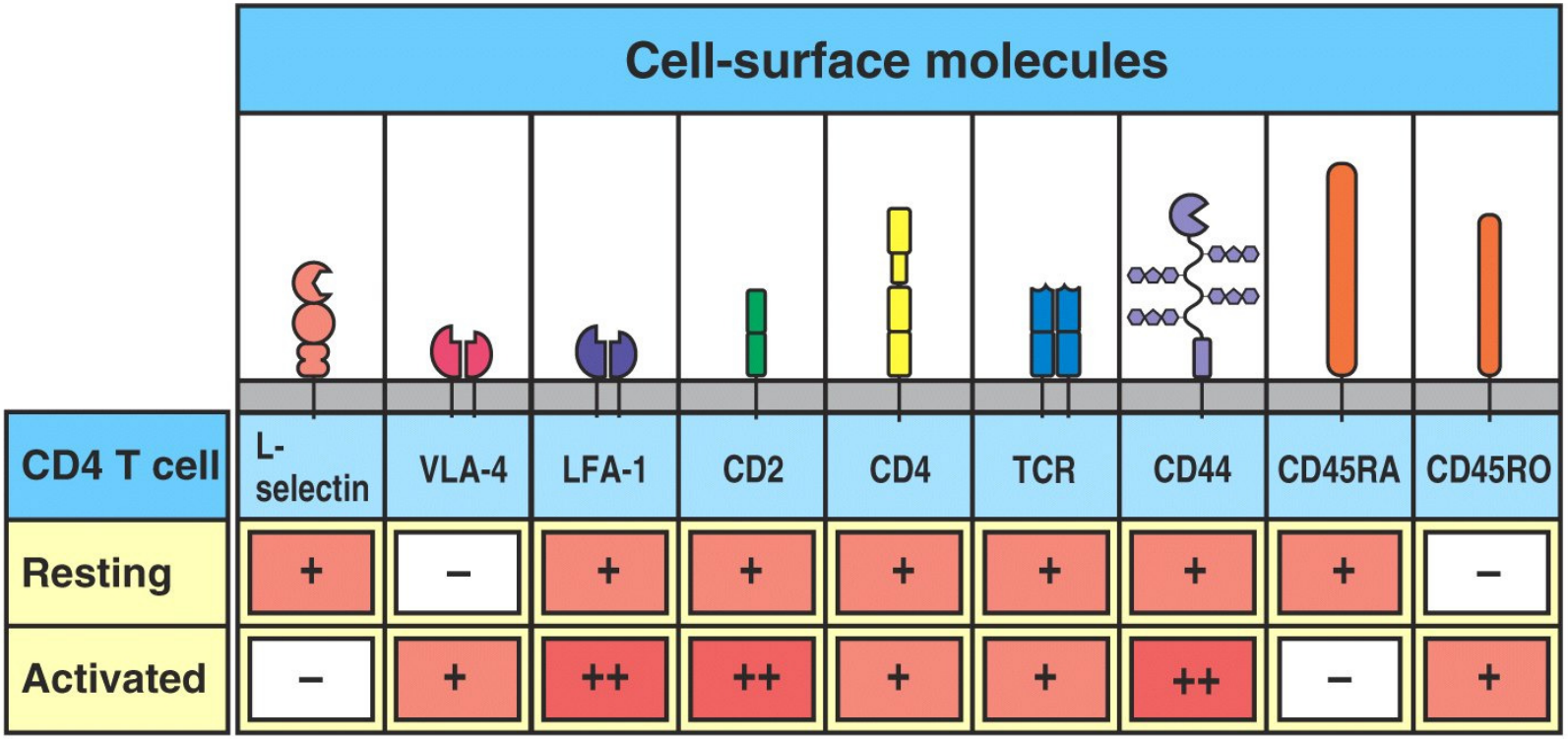


Figure 6-23 The Immune System, 2/e (© Garland Science 2005)

Las citocinas derivadas de APC influyen en la diferenciación de células Th

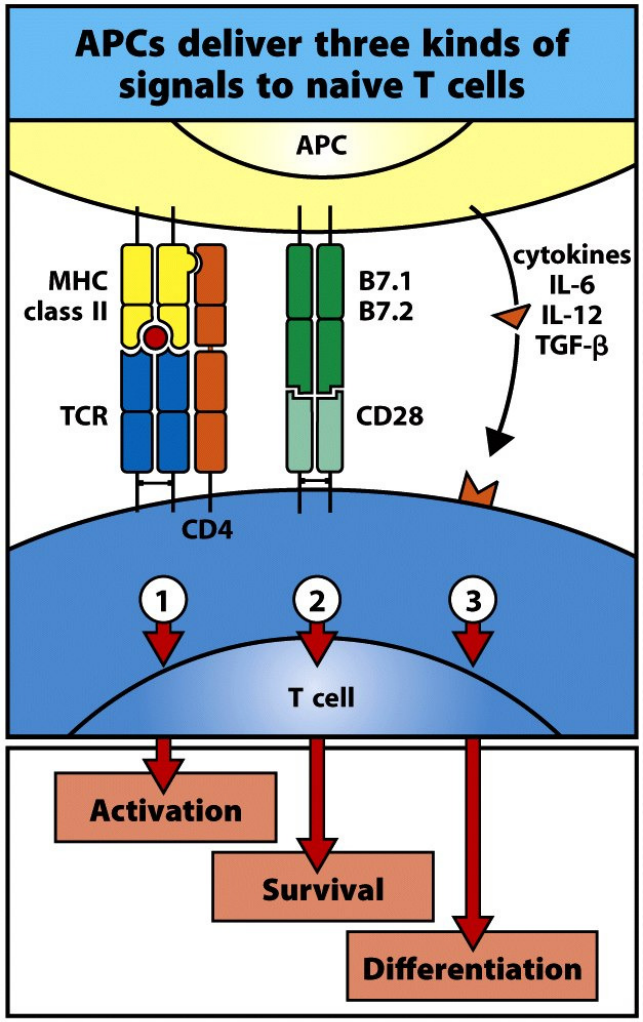


Figure 8-19 Immunobiology, 7ed. (© Garland Science 2008)

Diferenciación de células Th

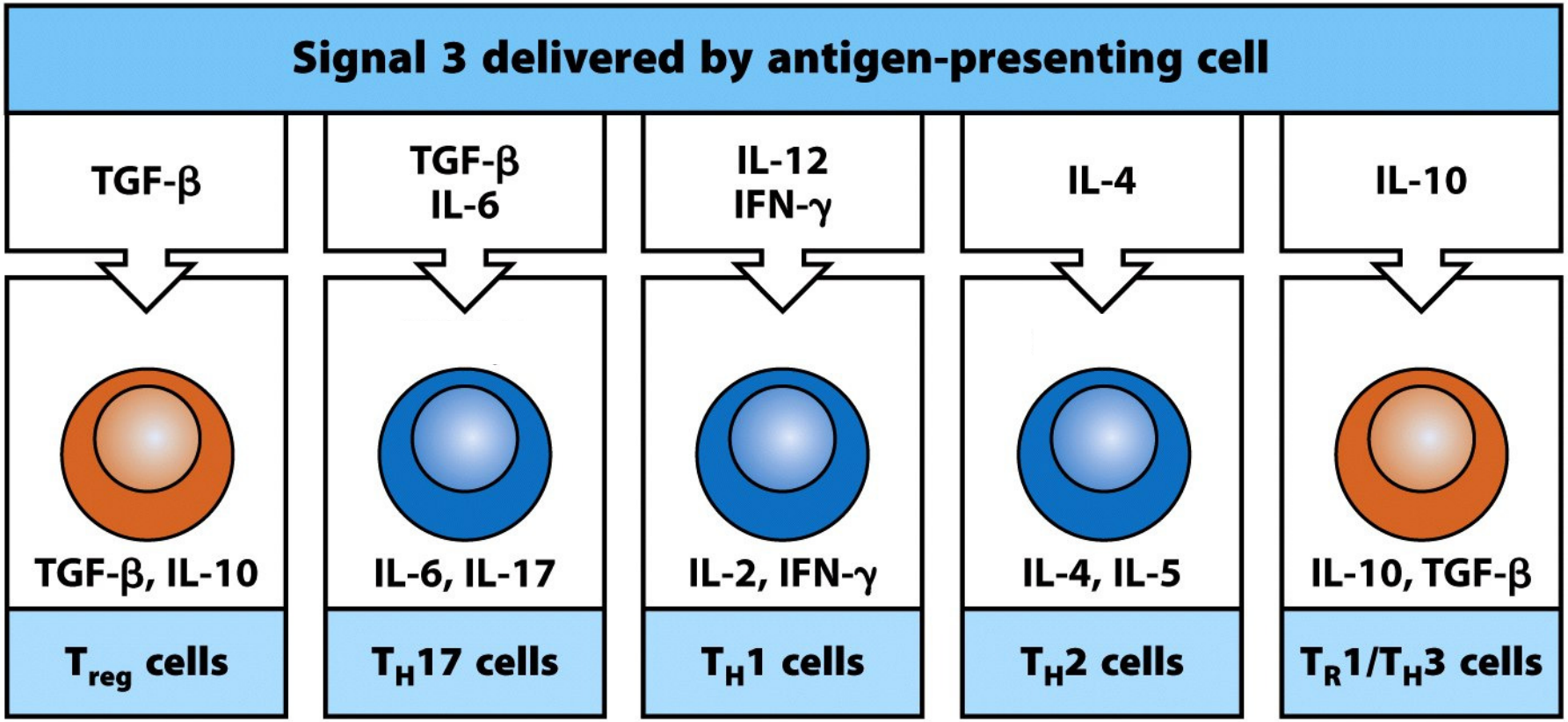
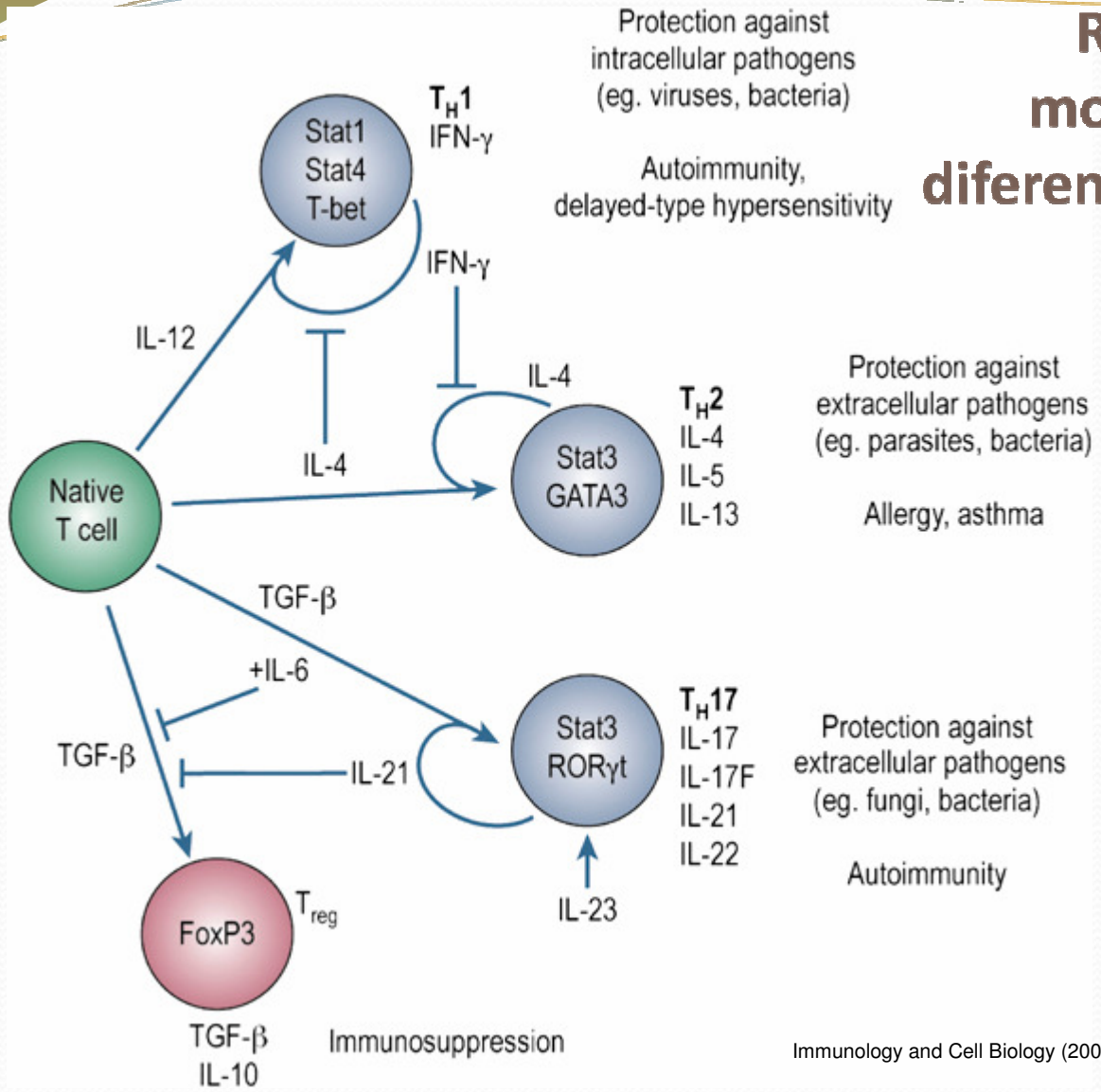


Figure 8-29 Immunobiology, 7ed. (© Garland Science 2008)

Requerimientos moleculares para la diferenciación de células Th



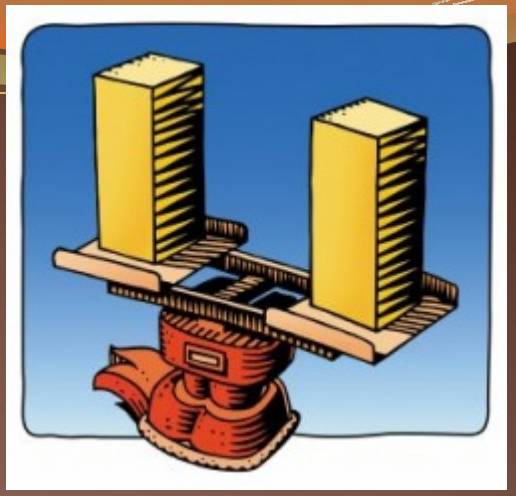
Immunology and Cell Biology (2007)

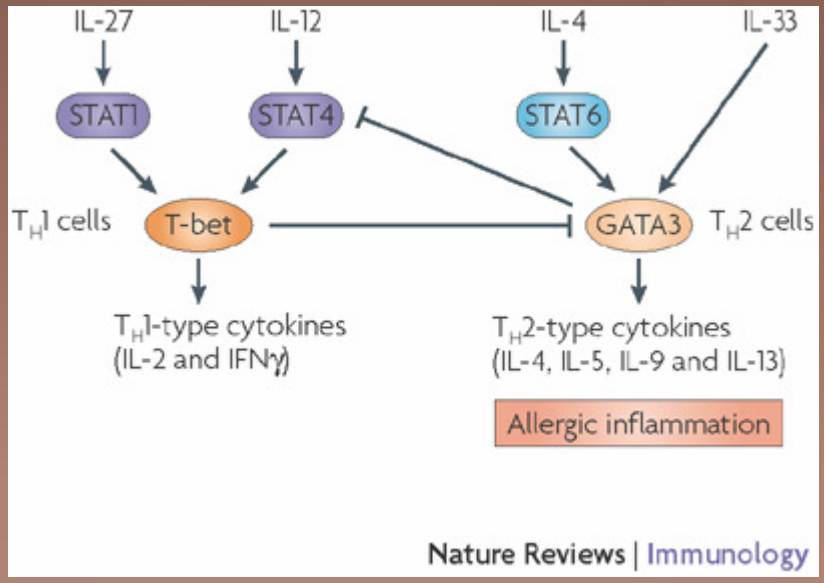
Células Th efectoras

Feature	T_H1 cells	T_H2 cells	T_H17 cells	Inducible regulatory T cells
Unique cytokine products	IFNγ	IL-4, IL-5 and IL-13	IL-17, IL-17F, IL-21 and IL-22	TGFβ?
Priming cytokines	IL-12	IL-25 (IL-17E)	TGFβ and IL-6	TGFβ and IL-2?
Autocrine cytokines	IFNγ	IL-4	IL-21	TGFβ?
STAT regulators	STAT1 and STAT4	STAT6	STAT3	STAT5
Lineage-specific transcriptional regulators	T-bet and HLX	GATA3 and MAF	RORγt and RORα	FOXP3
Cytokine receptors	IL-12Rβ2	IL-17RB	IL-23R and IL-1R1	ND

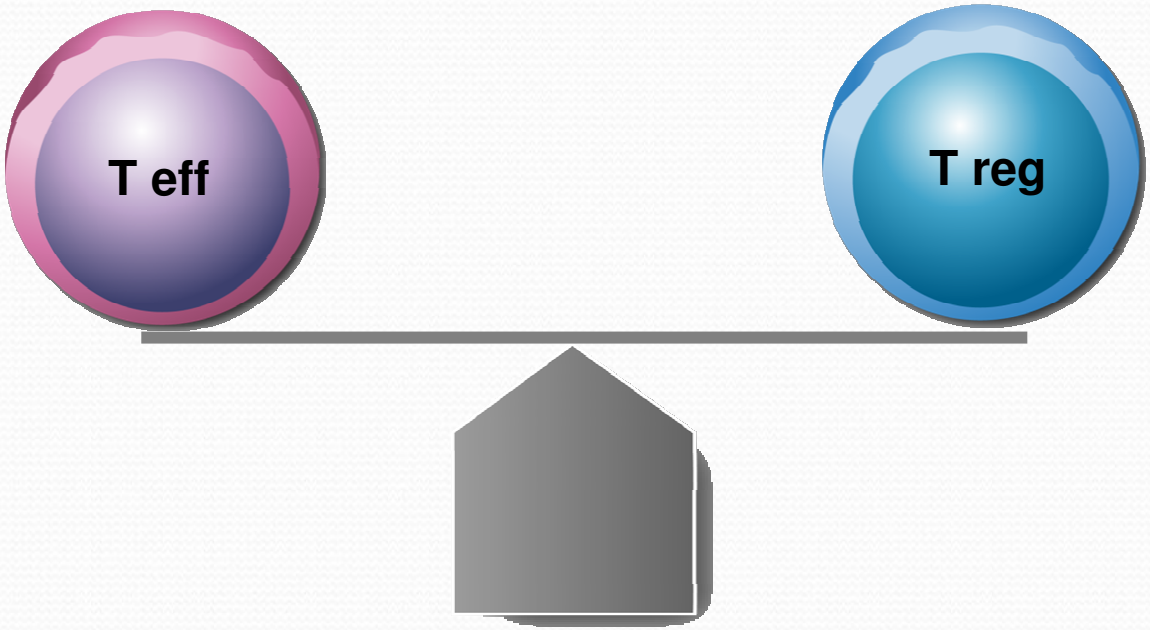
FOXP3, forkhead box P3; GATA3, GATA-binding protein 3; HLX, H2.0-like homeobox 1; IFNγ, interferon-γ; IL, interleukin; ND, not determined; ROR, retinoic-acid-receptor-related orphan receptor; STAT, signal transducer and activator of transcription; TGFβ, transforming growth factor-β; T_H, T helper.

Linfocitos Th1-Th2

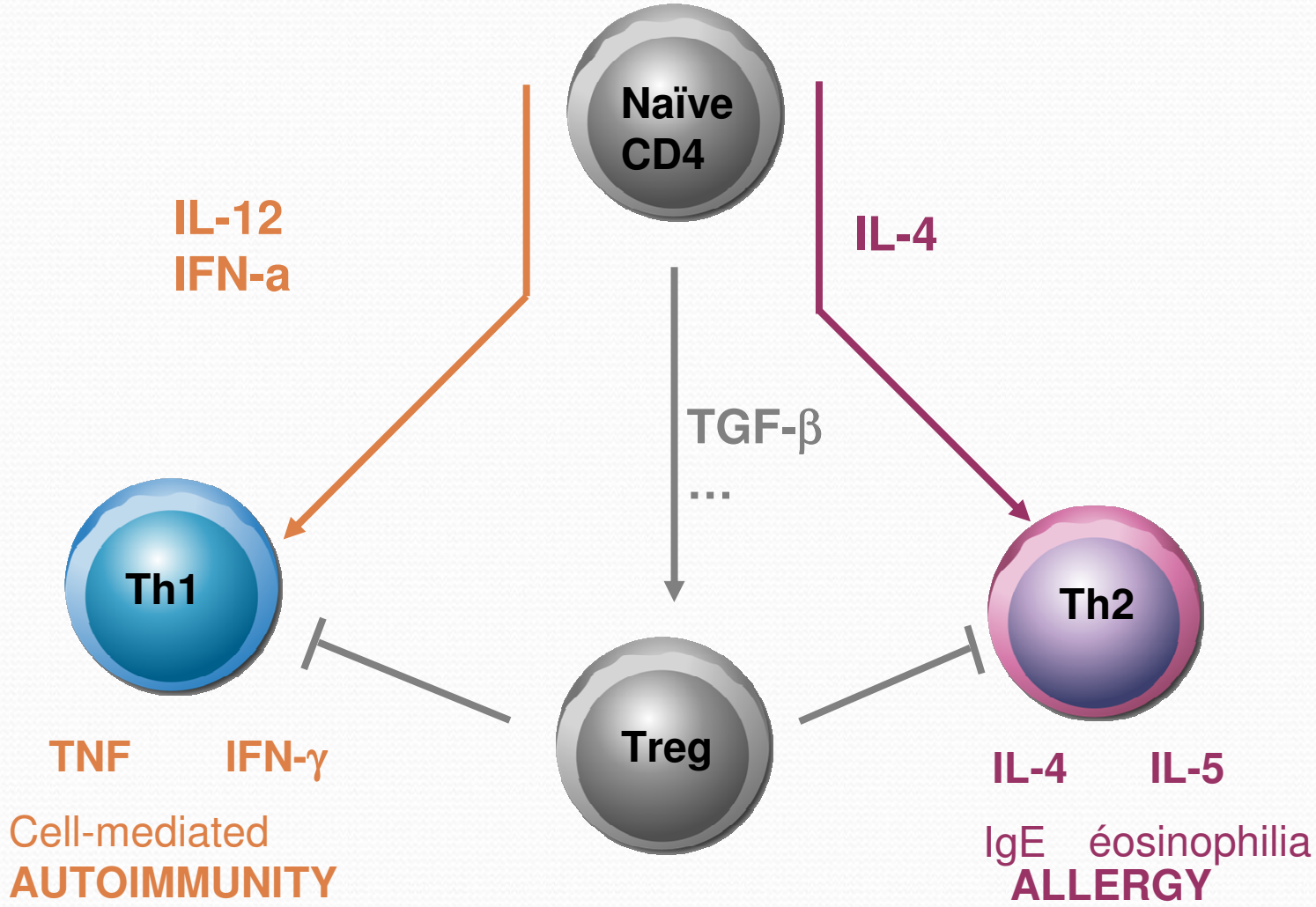


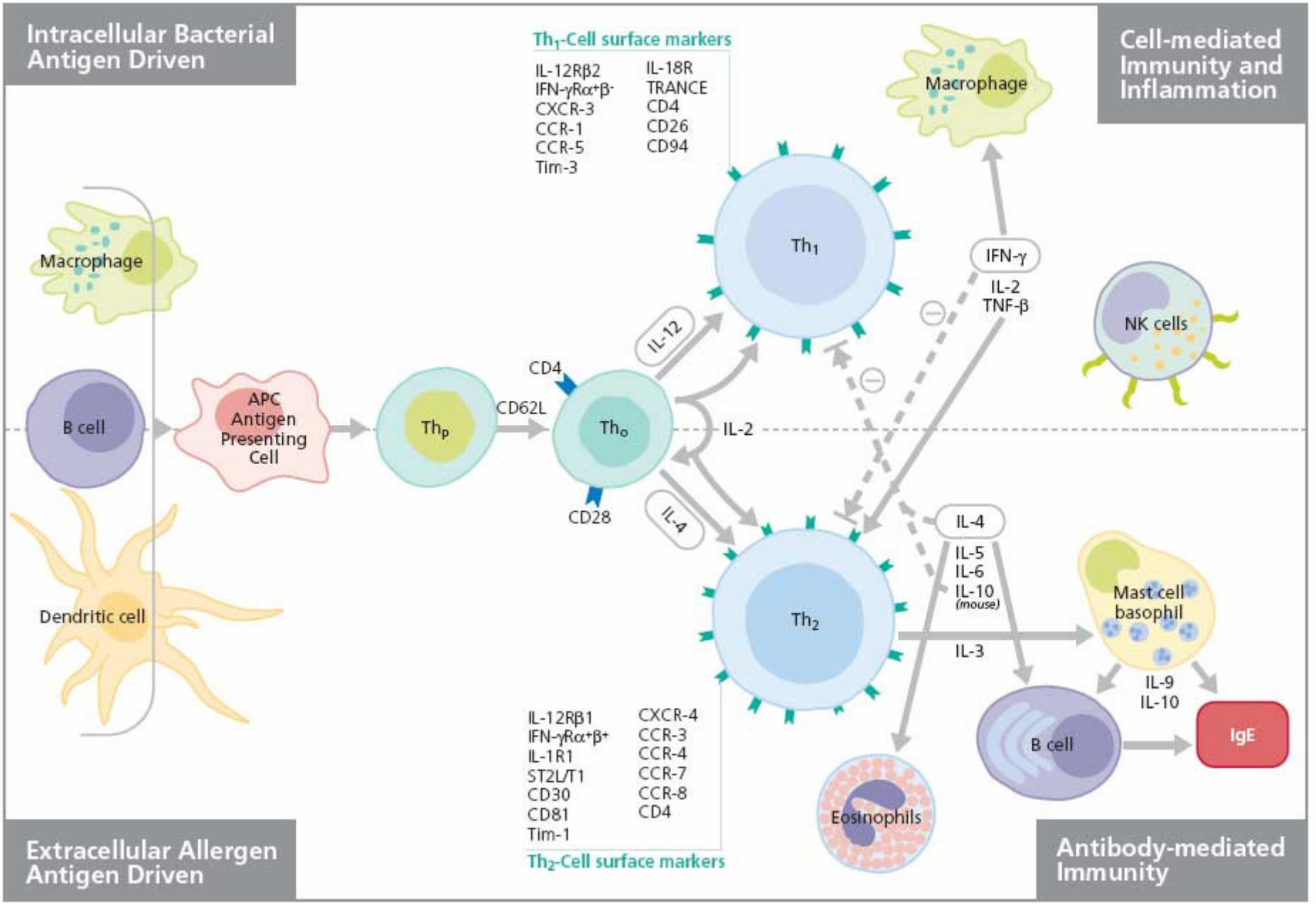


El tipo de respuesta inmune depende del balance entre células efectoras y reguladoras

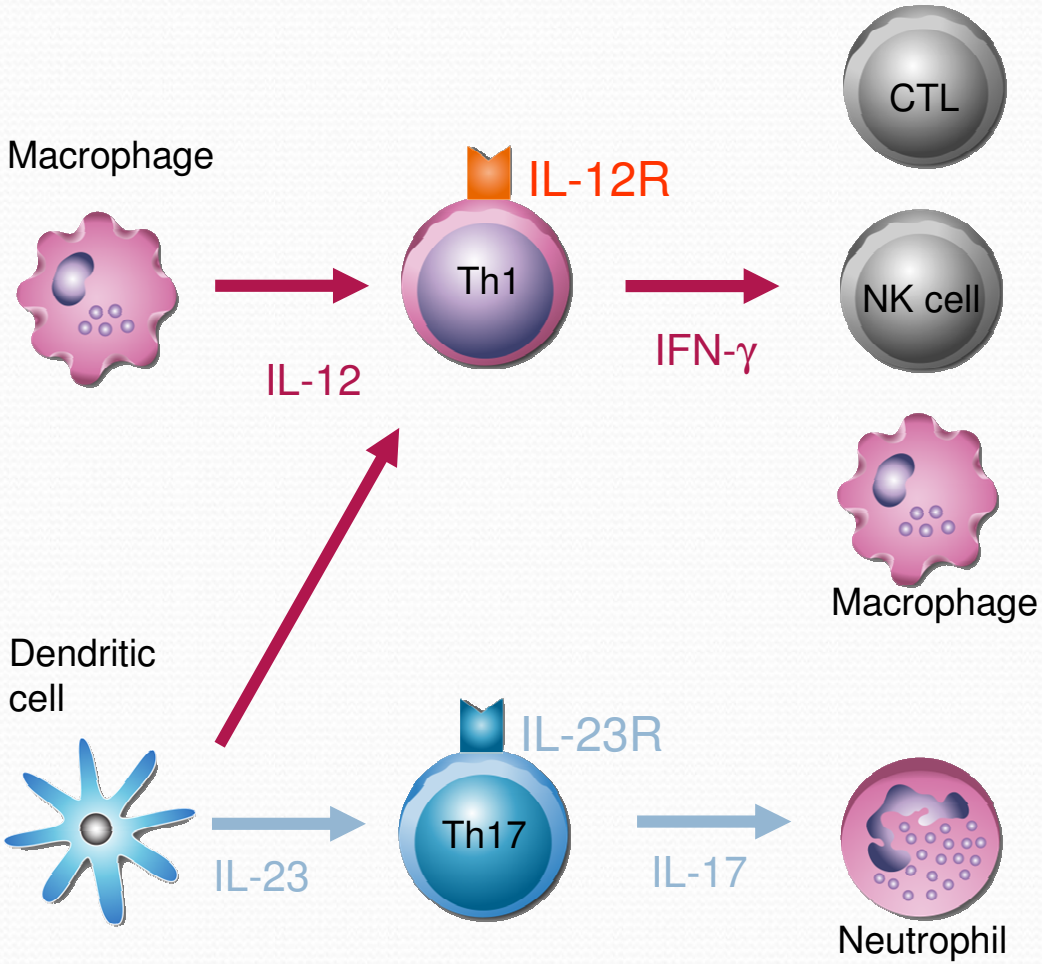


El paradigmaTh1-Th2




Intracellular Bacterial Antigen Driven
Th1-Cell surface markers
IL-12Rβ2
IFN-γRα+β-
CXCR-3
CCR-1
CCR-5
Tim-3
IL-18R
TRANCE
CD4
CD26
CD94
Macrophage
Cell-mediated Immunity and Inflammation
Macrophage
Th1
IFN-γ
IL-2
TNF-β
NK cells
IL-12
CD4
B cell
APC Antigen Presenting Cell
Thp
CD62L
Tho
IL-2
CD28
IL-4
Dendritic cell
IL-4
IL-5
IL-6
IL-10
(mouse)
Th2
Mast cell basophil
IL-3
IL-9
IL-10
IL-12Rβ1
IFN-γRα+β+
IL-1R1
ST2L/T1
CD30
CD81
Tim-1
CXCR-4
CCR-3
CCR-4
CCR-7
CCR-8
CD4
B cell
IgE
Eosinophils
Th2-Cell surface markers
Extracellular Allergen Antigen Driven
Antibody-mediated Immunity

Roles de IL-12 e IL-23 en la defensa anti-microbial

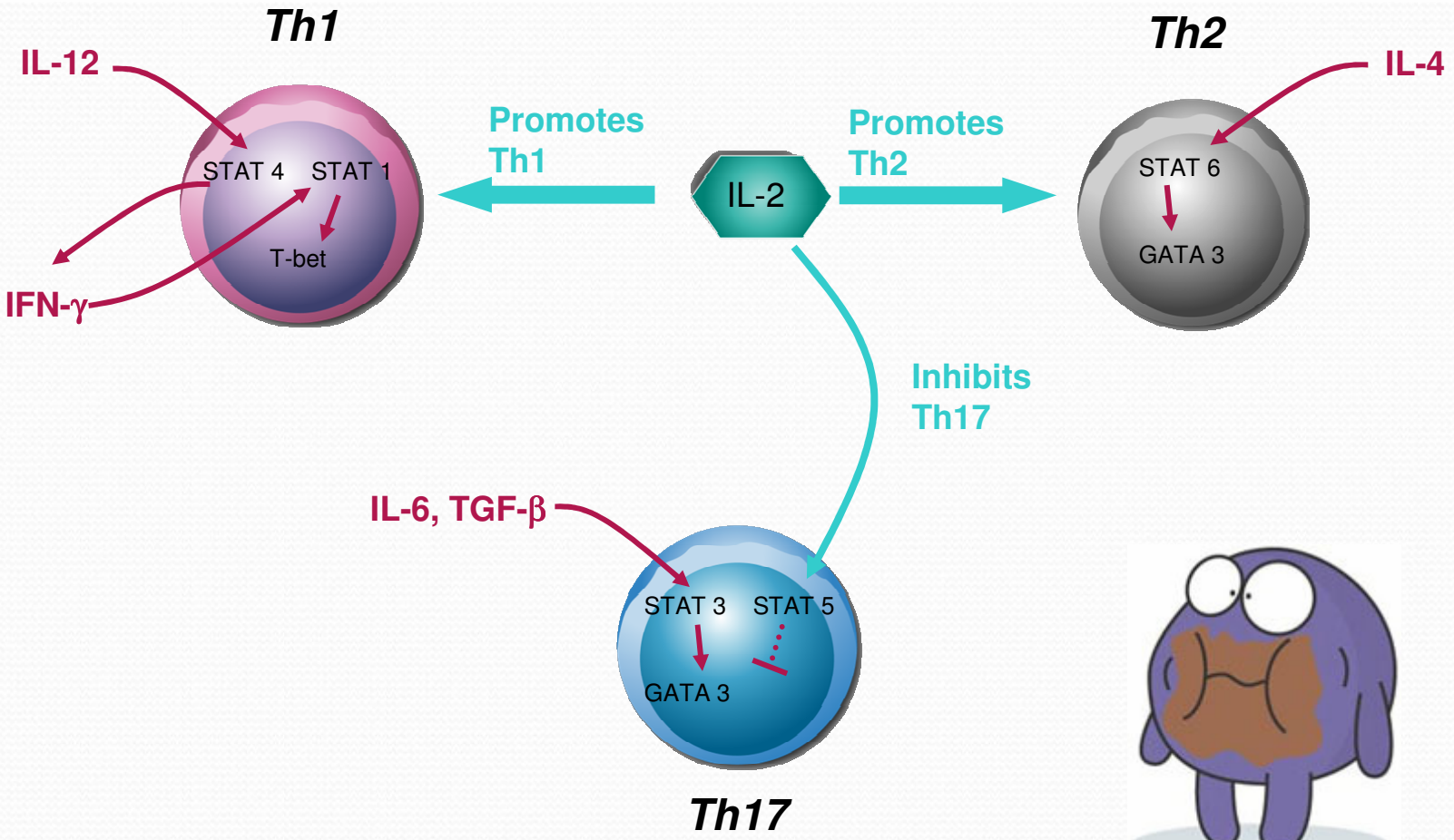


Cell-Mediated Immunity

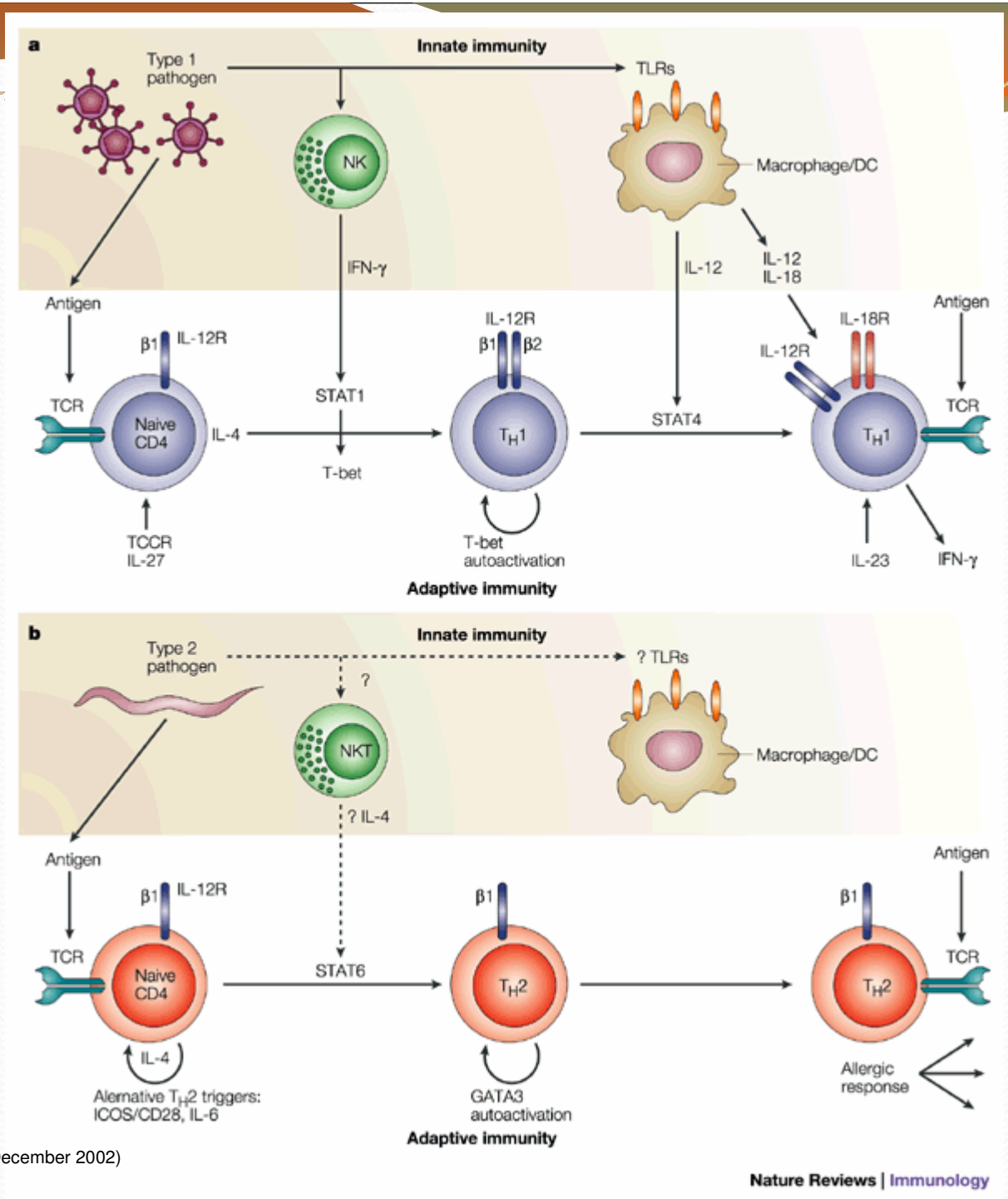
Granulocyte-dependent response

Adapted from Iwakura & Ishigame, J Clin Invest 116:1218-1222 (2006)

Efectos divergentes de IL-2 sobre las respuestas Th1, Th2 y Th17

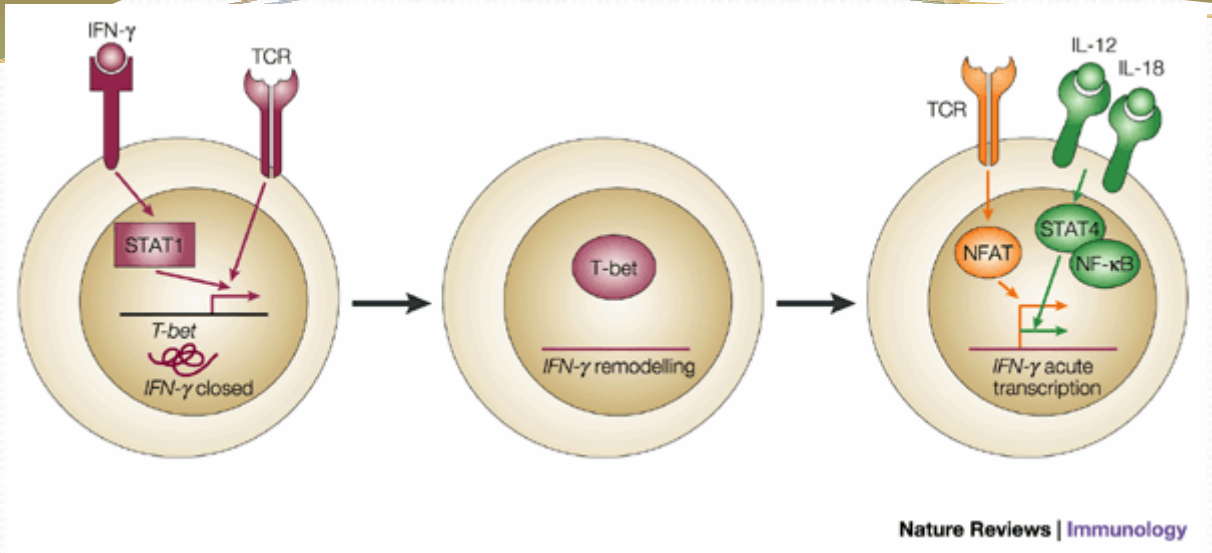


Adapted from Stockinger, Immunity, 26:278-279, 2007



Nature Reviews Immunology 2, 933-944 (December 2002)

Activación de células Th1



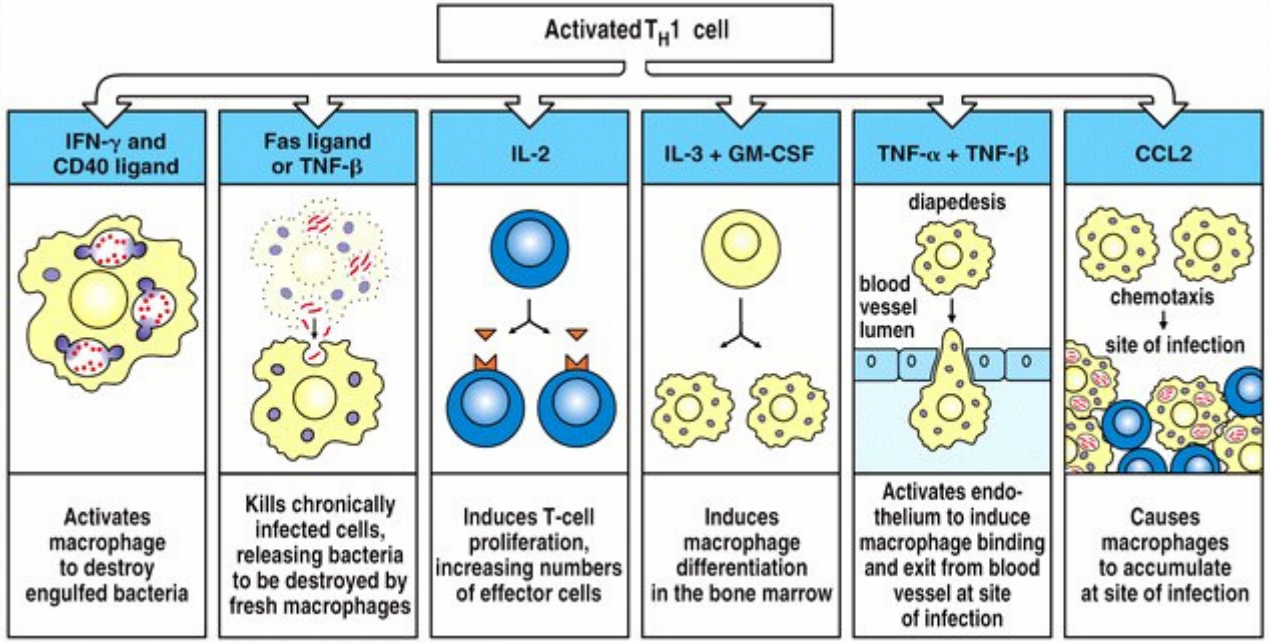


Figure 8-41 Immunobiology, 6/e. (© Garland Science 2005)

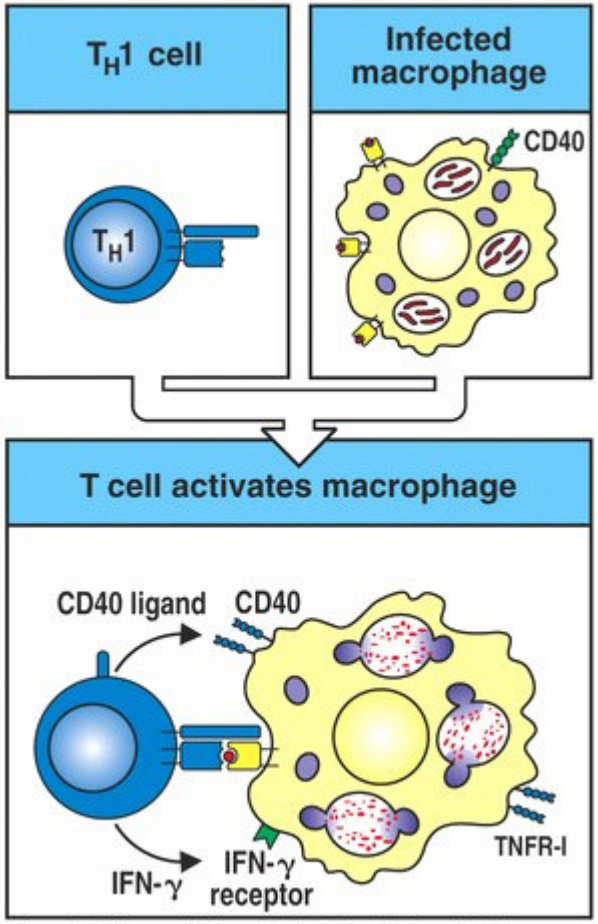


Figure 8-39 Immunobiology, 6/e. (© Garland Science 2005)

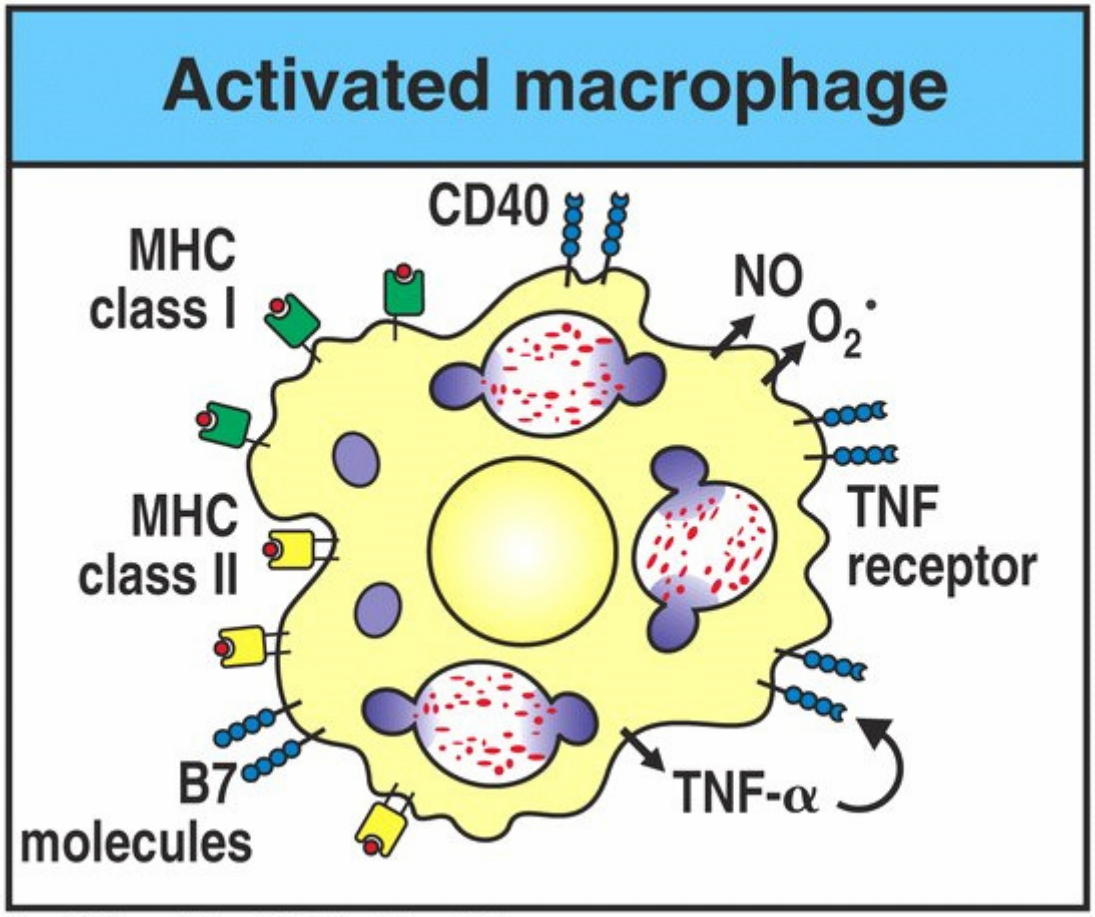
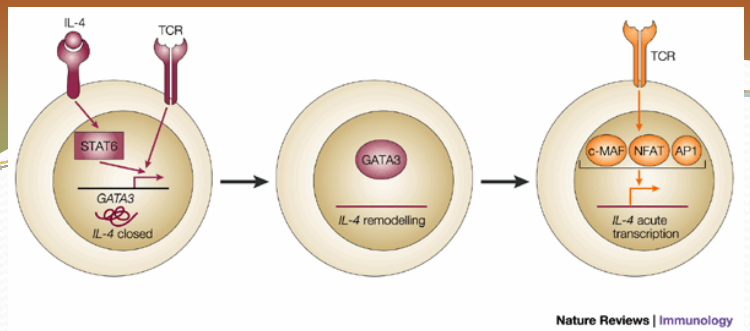
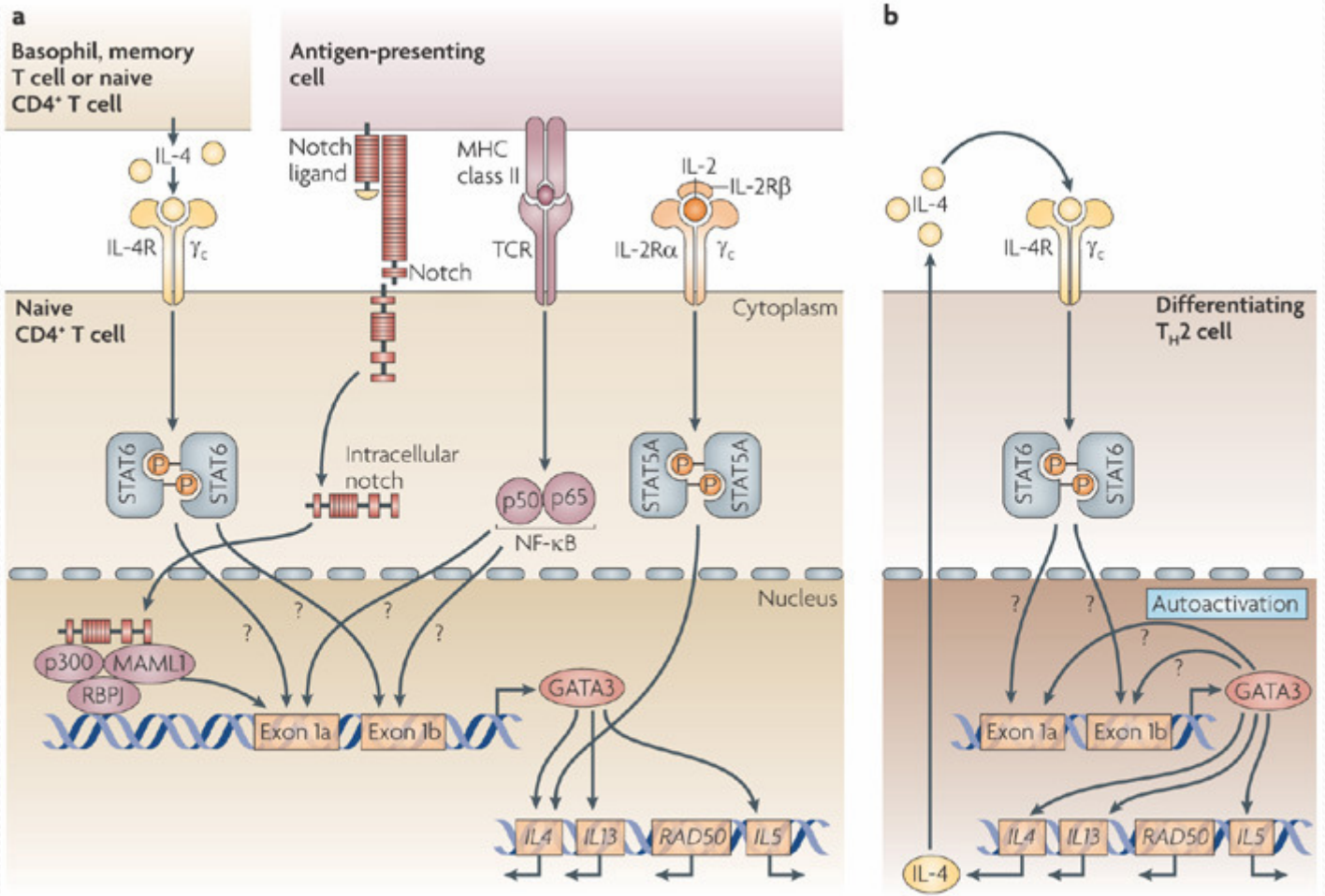


Figure 8-40 Immunobiology, 6/e. (© Garland Science 2005)

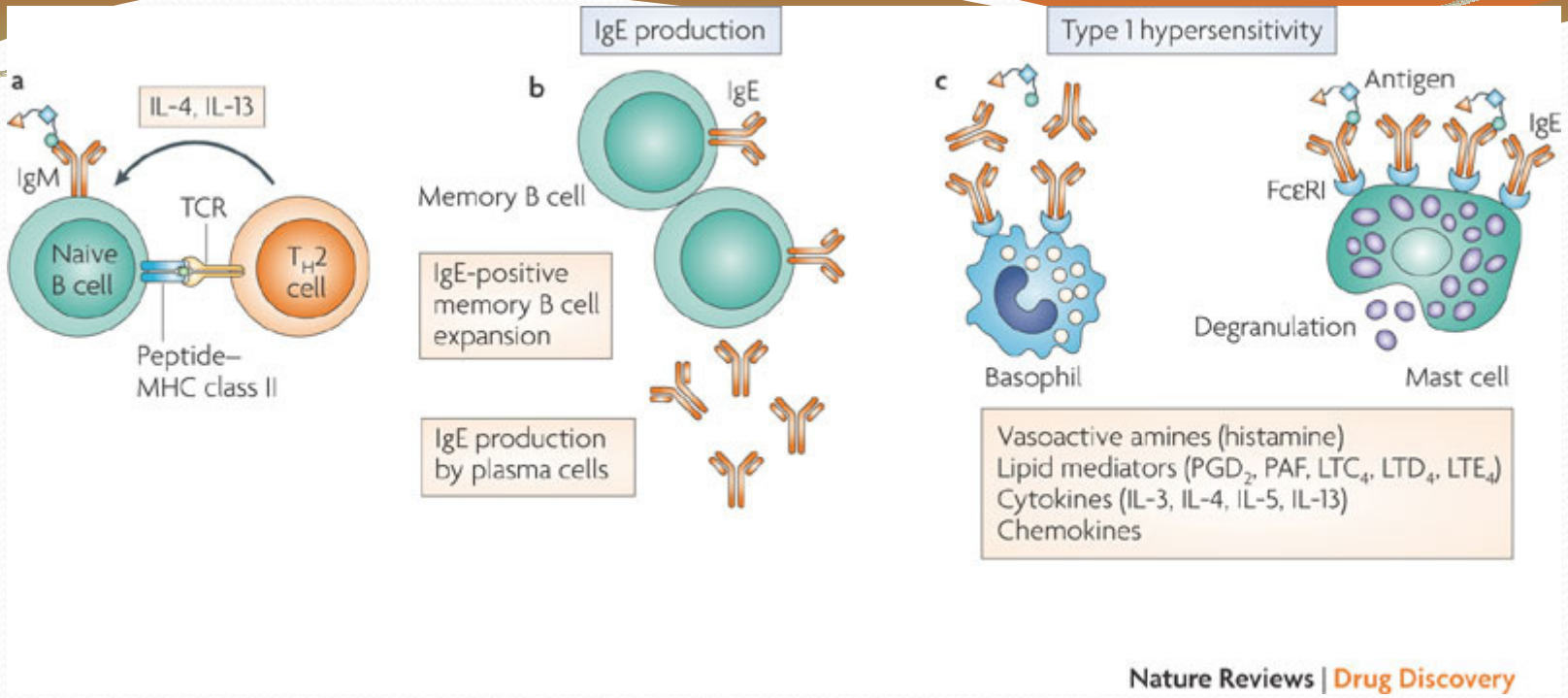
Diferenciación de células Th-2





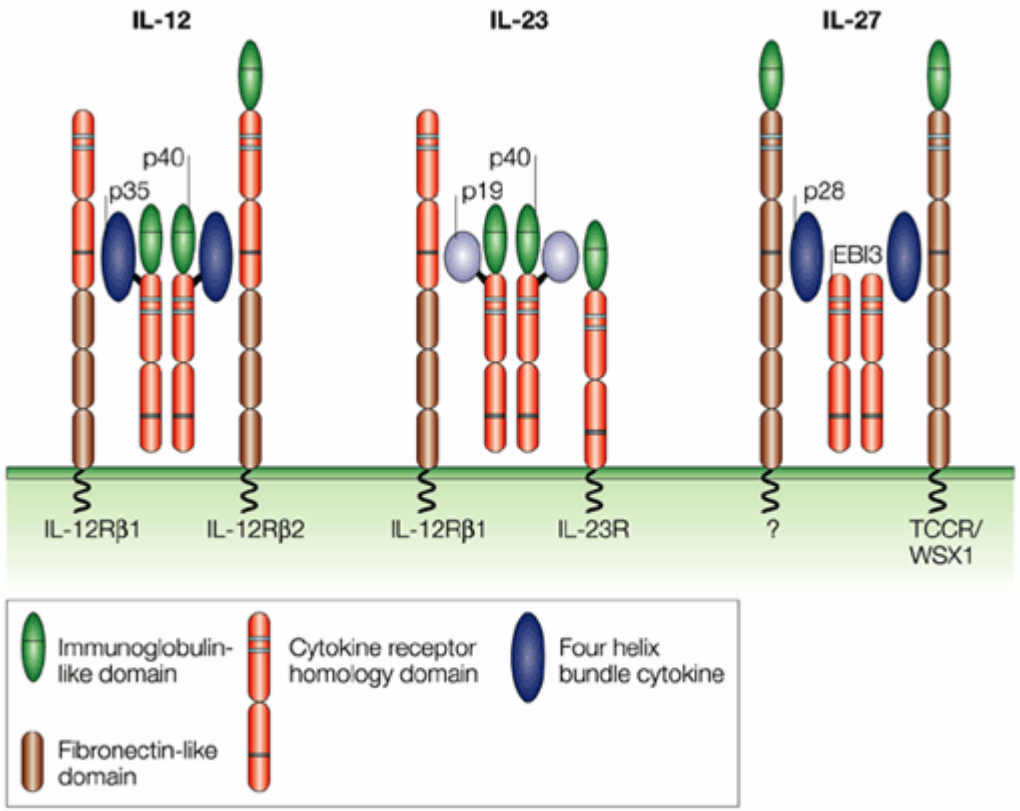
Nature Reviews Immunology 9, 125-135 (February 2009)

Nature Reviews | Immunology



- **a** | T_H2 cell interaction with naive B cells leads to immunoglobulin class switch to IgE and expansion of allergen-specific memory B cells. **b** | IgE produced by plasma cells sensitizes mast cells and basophils by binding to surface Fc RI. **c** | The crosslinking of basophil and mast-cell surface Fc RI-bound IgE by B-cell epitopes of allergens leads to the release of vasoactive amines (such as histamine), lipid mediators (such as prostaglandin D 2 (PGD_2), platelet-activating factor (PAF), leukotriene (LT) C4 (LTC_4), LTD_4 and LTE_4, cytokines and chemokines, and to the immediate symptoms of allergic disease (type I hypersensitivity), including pruritis, wheal and flare, nasal conjunctival discharge, angioedema, systemic anaphylaxis and bronchoconstriction. T regulatory (T_{Reg}) cells modulate type-1 hypersensitivity reactions by: suppression of IgE and induction of blocking antibodies by interleukin 10 (IL-10), suppression of mast-cell tissue infiltration by IL-10 and TGF β , and suppression of T_H2 cells by IL-10 and TGFb. MHC, major histocompatibility complex; TCR, T-cell receptor.

IL-27: citocina inmunomoduladora



Nature Reviews | Immunology

IL-27 induces proliferation of naive T cells and is a strong inducer of IFN-γ production, particularly in synergy with IL-12 and IL-18.

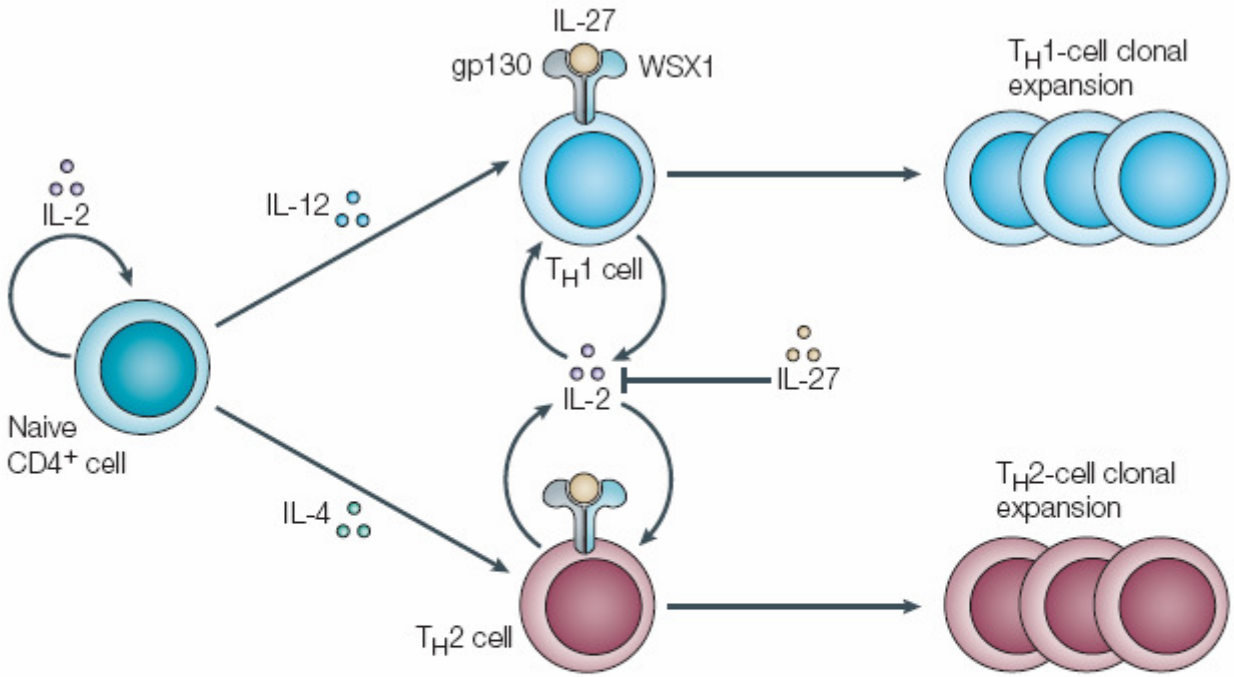
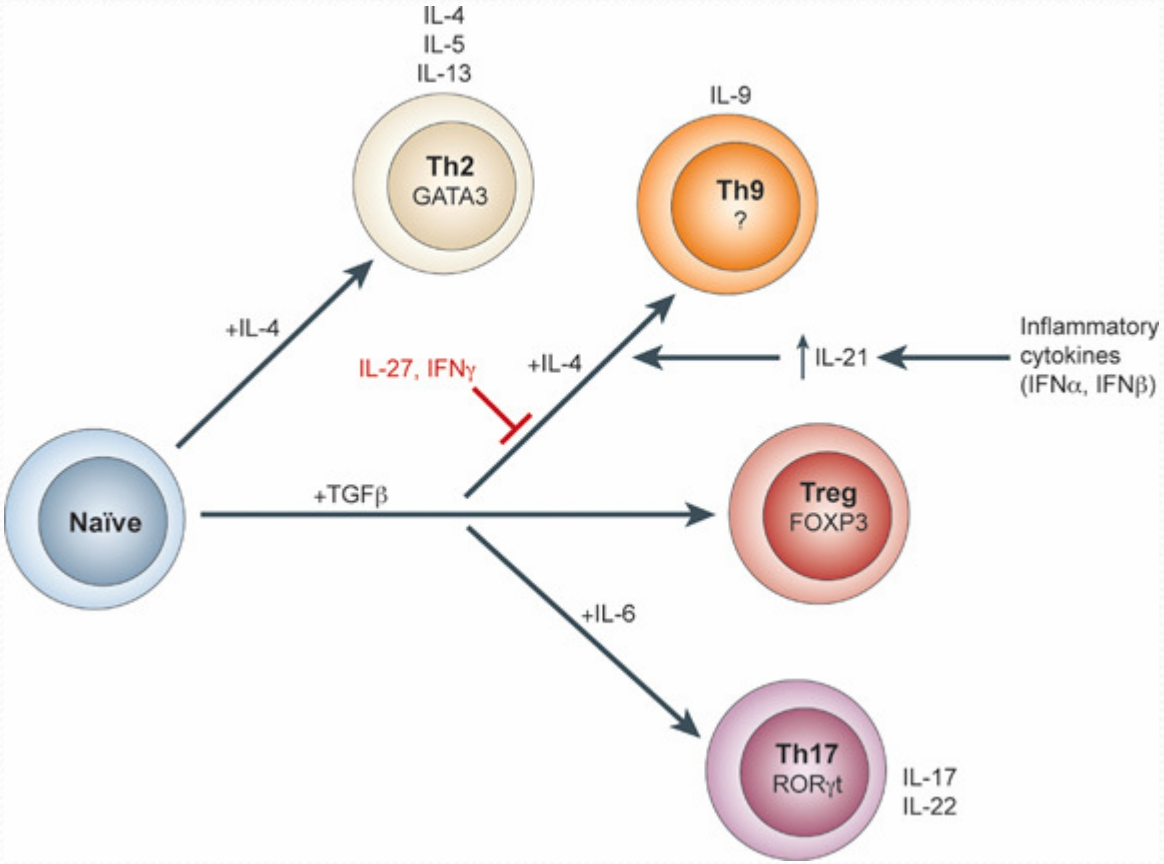


Figure 4 | **Interleukin-27 regulates the intensity and duration of T-helper-1 cell and T-helper-2 cell responses.** Under conditions that polarize CD4+ T cells towards either T helper 1 (T_H1) or T_H2 cells — that is, in the presence of high levels of interferon-γ or interleukin-4 (IL-4), respectively — the production of IL-2 is an important first step in T-cell activation and contributes to the success and magnitude of either response. Naive CD4+ T cells express low levels of the IL-27-receptor subunit WSX1, but following activation under conditions that polarize them towards T_H1 or T_H2 cells, they produce high levels of IL-2 before the upregulation of WSX1 expression. However, as they become sensitive to IL-27, this cytokine antagonizes the sustained production of IL-2, which might explain, in part, the ability of IL-27 to inhibit T_H1- and T_H2-cell responses.

IL-27: citocina reguladora de Th1-Th2

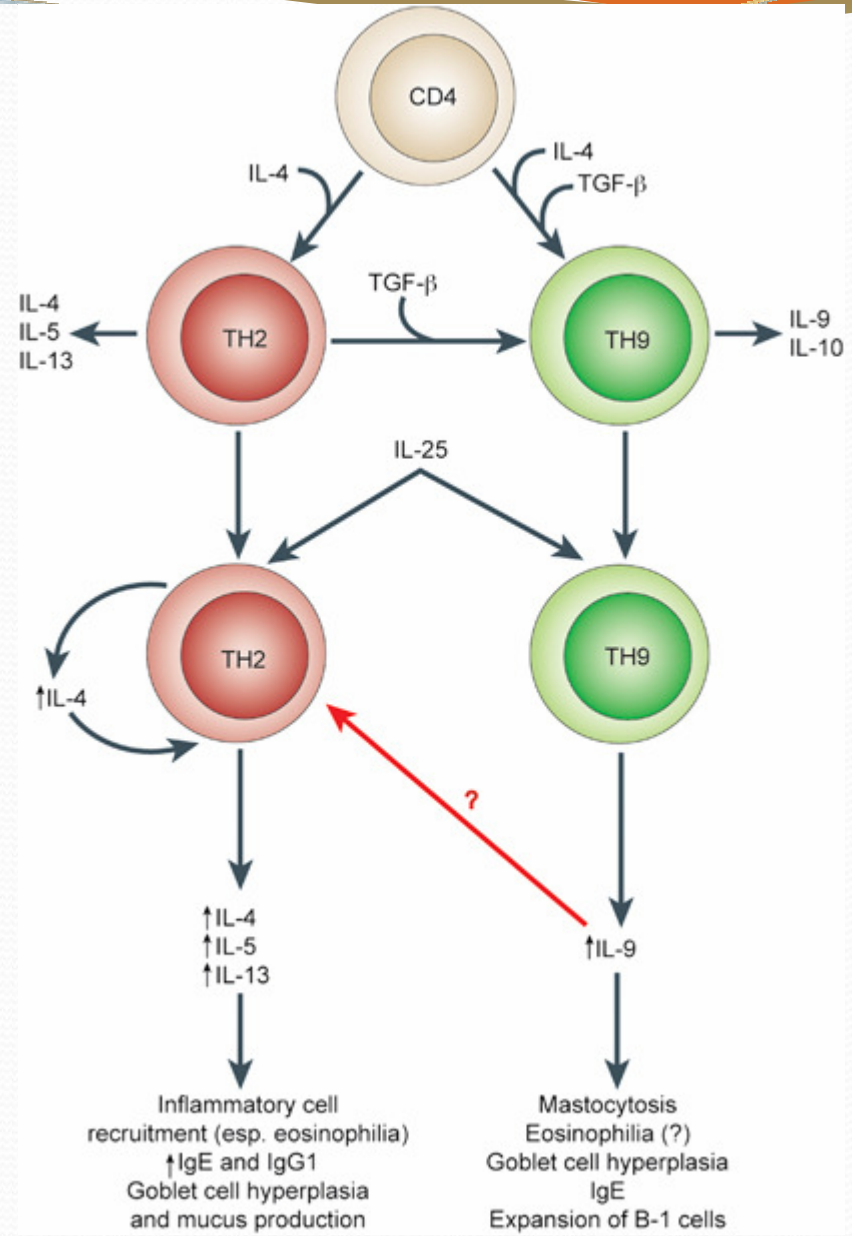
Linfocitos Th 9

Generación de las células Th9



Immunology and Cell Biology (2010) **88,** 621–623

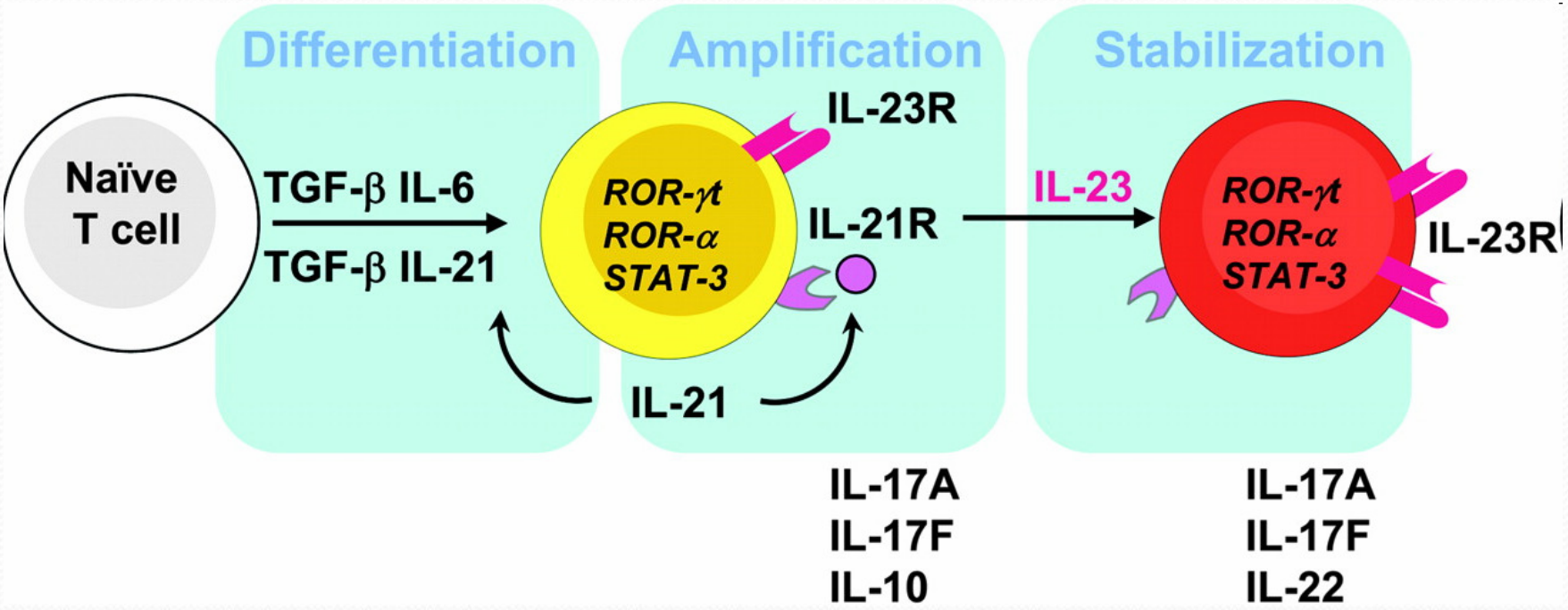
Regulación de las células Th2 / Th9



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

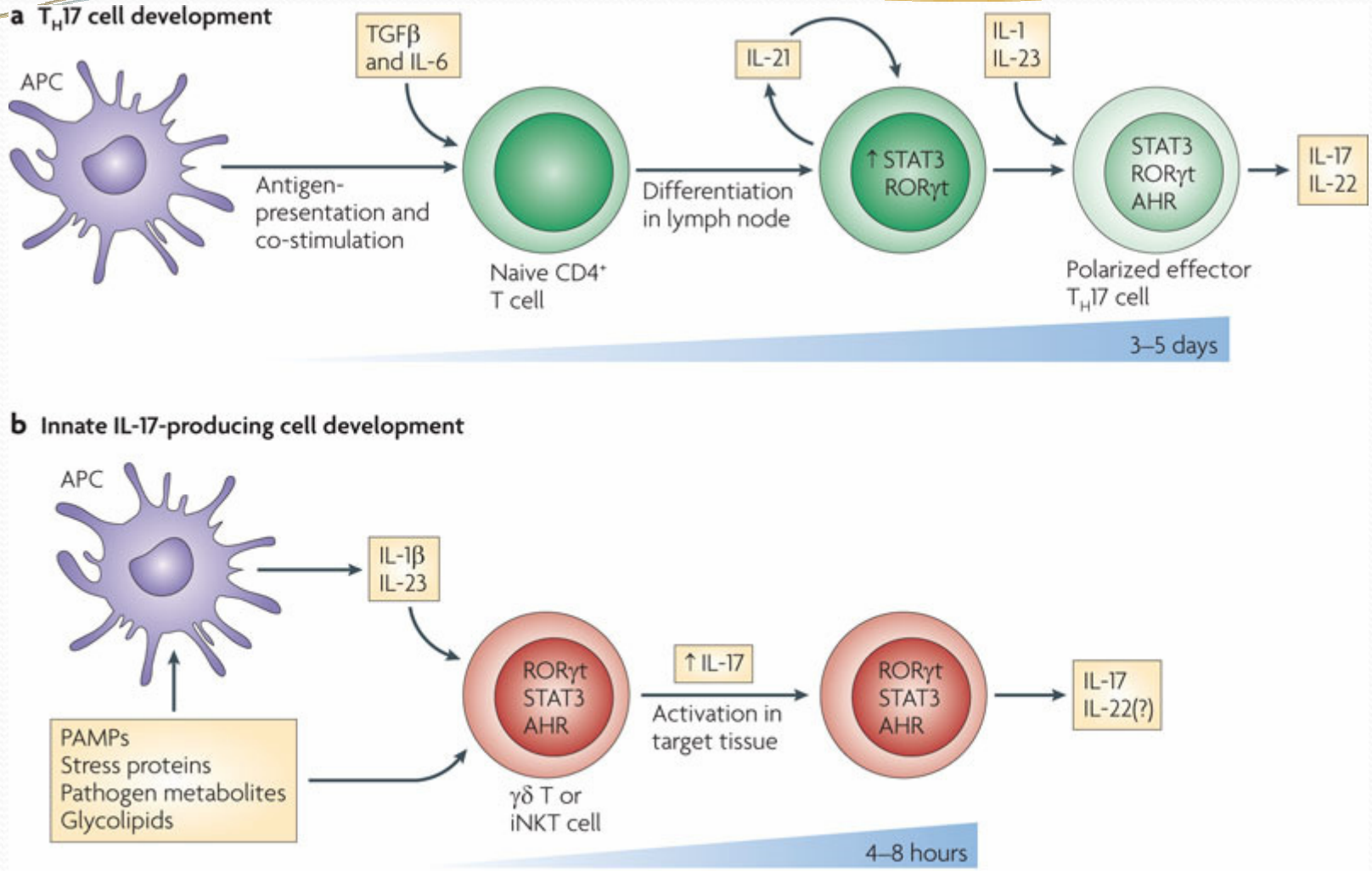
Linfocitos Th-17

Etapas en la generación de células Th17



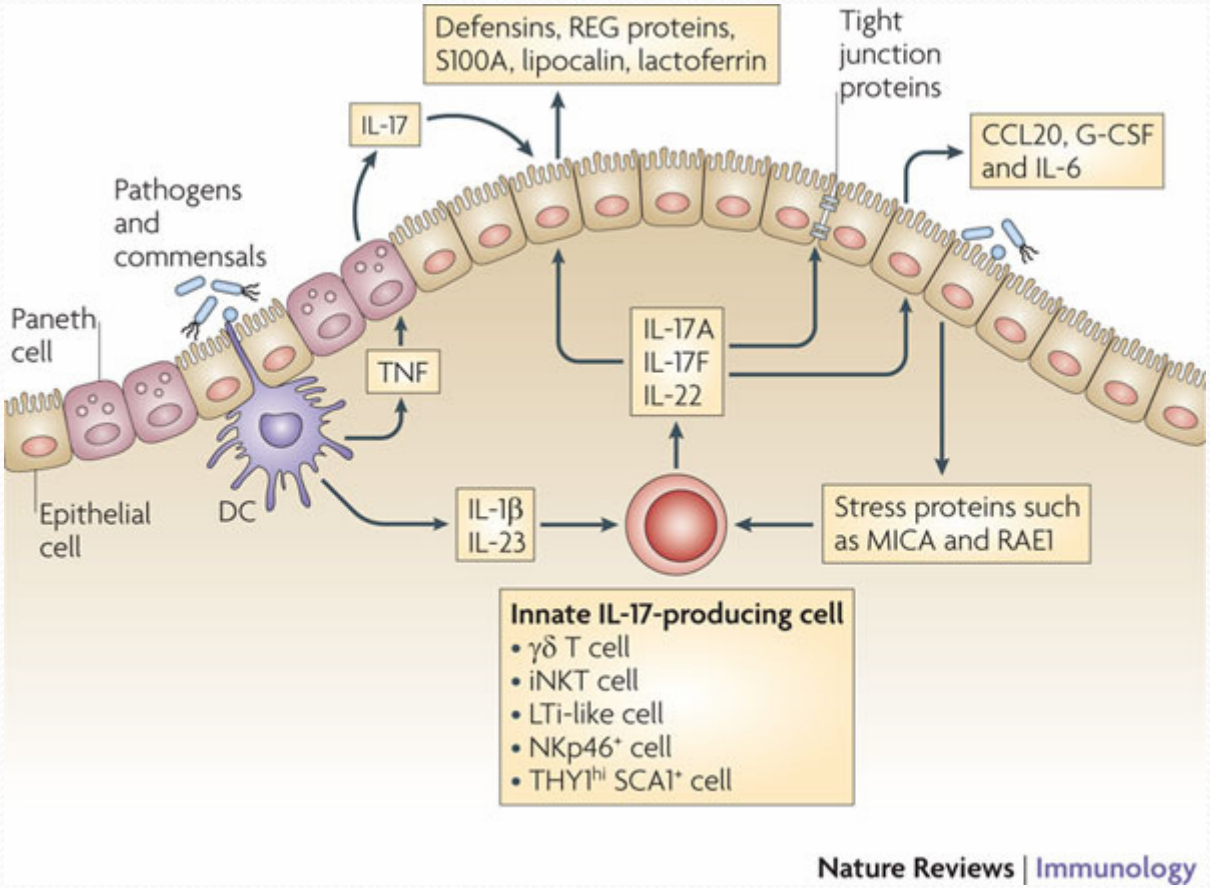
The activation of naive T cells in the presence of TGF-β and IL-6 initiates the Th17 differentiation pathway. Th17 cells produce IL-21, which further amplifies Th17 generation in an autocrine manner. IL-21 also induces the IL-23R on differentiated Th17 cells to make them responsive to IL-23 signaling. IL-23 stabilizes the Th17 phenotype by secreting IL-17A, IL-17F and IL-22 and helping Th17 cells to acquire effector functions. STAT-3 plays an important role in Th17 differentiation, amplification and stabilization as IL-6, IL-21 and IL-23 signals through STAT-3.

(Awasthi and Kuchroo, International Immunology, 2009)



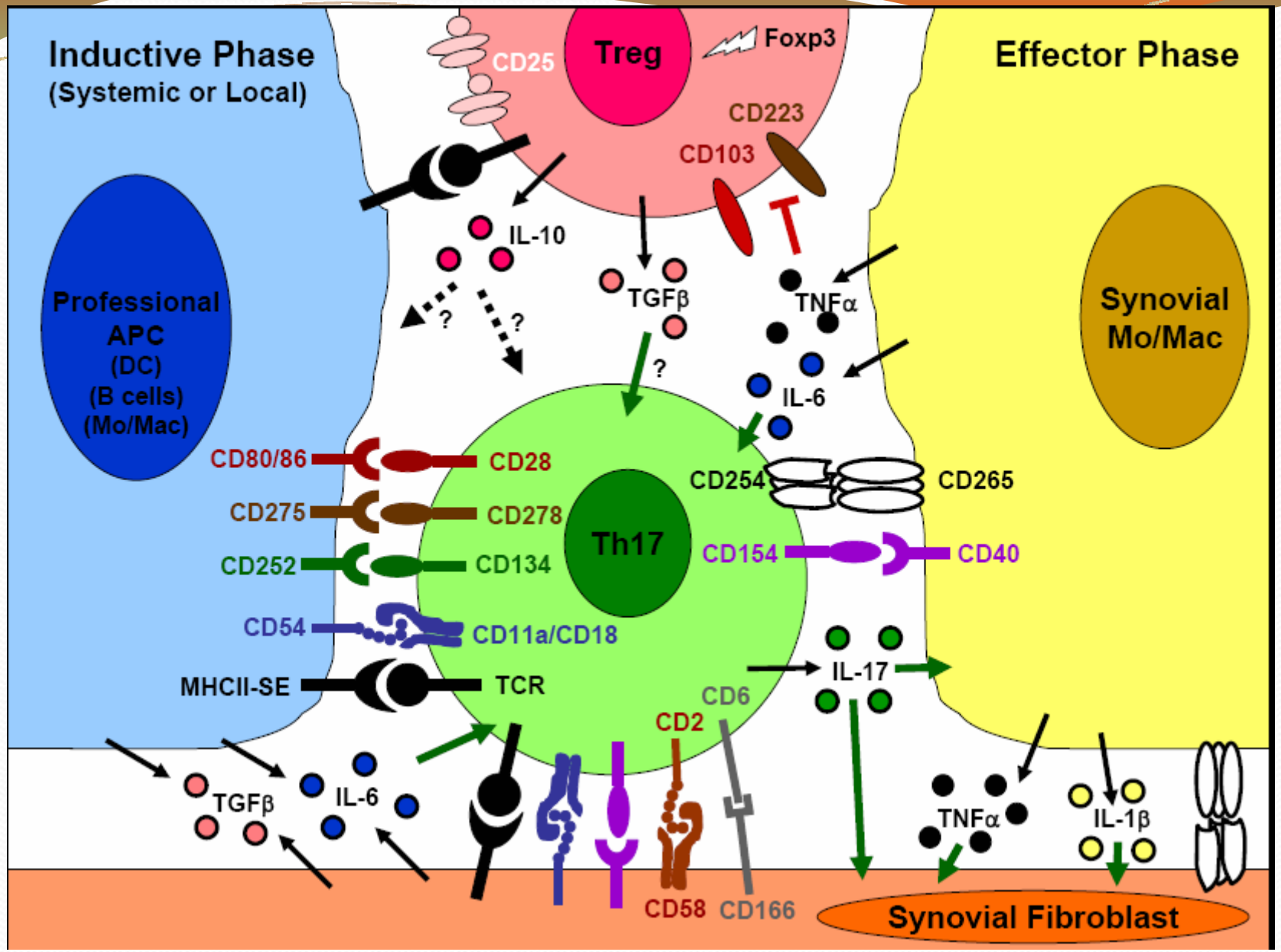
Nature Reviews Immunology 10, 479-489 (July 2010)

Th17 en la respuesta innata



Regenerating (REG) proteins

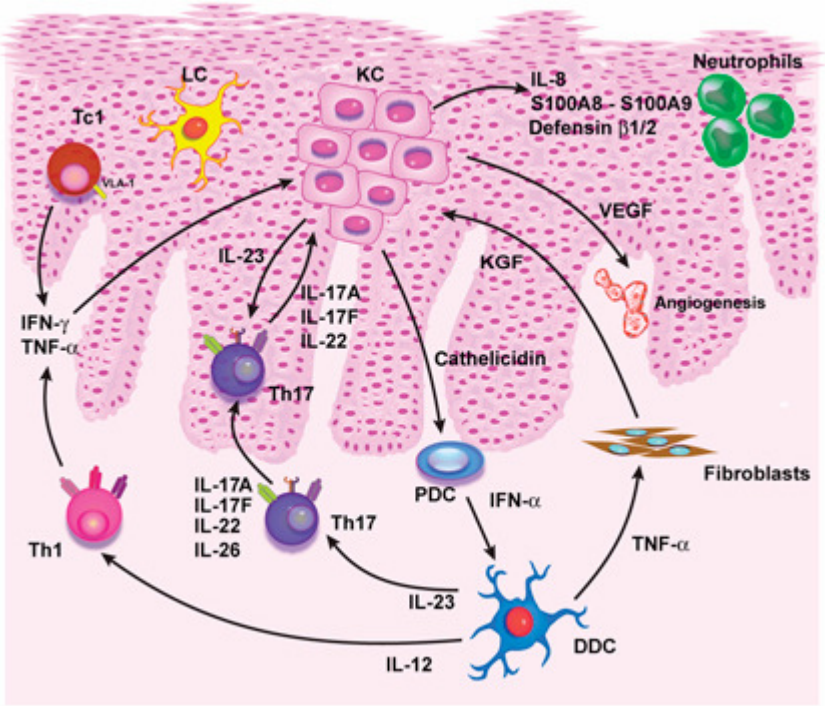
RAE1, retinoic acid early transcript 1
SCA1, stem cell antigen 1



Lundy *et al. Arthritis Research & Therapy* 2007

- Schematic diagram of the putative interactions of pathogenic Th17 cells in the synovial microenvironment. Induction of T-cell responses in rheumatoid arthritis (RA) is initiated by T-cell receptor (TCR) interaction with shared epitope major histocompatibility complex class II (MHCII-SE) and peptide on antigen-presenting cells (APCs) either systemically or in the synovium. Accessory molecules expressed by APCs, including ICAM-1 (intercellular adhesion molecule-1) (CD54), OX40L (CD252), inducible costimulator (ICOS) ligand (CD275), B7-1 (CD80), and B7-2 (CD86), participate in T-cell activation by binding lymphocyte function-associated antigen (LFA)-1 (CD11a/CD18), OX40 (CD134), ICOS (CD278), and CD28. Activated fibroblast-like synoviocytes (FLS) may also participate in antigen presentation and have additional accessory molecules such as LFA-3 (CD58) and ALCAM (activated leukocyte cell adhesion molecule) (CD166) which interact with T cell-expressed CD2 and CD6, respectively. Cytokines interleukin (IL)-6 and transforming growth factor-beta (TGF-β), most likely derived from activated APCs, signal the T cell to differentiate into IL-17-producing Th17 cells. IL-17 has independent and synergistic effects with other proinflammatory cytokines (tumor necrosis factor-alpha [TNF-α] and IL-1β) in the synovium to induce further cytokine release, matrix metalloproteinase production, RANK/RANK ligand (CD265/CD254) expression, and osteoclastogenesis. CD40L (CD154) interaction with CD40 also leads to activation of synovial monocytes/macrophages (Mo/Mac), FLS, and B cells. Although present in the synovia of most patients with RA, $CD4^{+}CD25^{hi}$ regulatory T (Treg) cells are ineffective at controlling inflammation and may be deactivated by synovial TNF-α. IL-10 is abundant in synovial fluid but its effect on Th17 regulation has yet to be determined. Expression of accessory molecules on Th17 cells, as denoted in the figure, are speculative and are inferred from expressions found on non-subdivided T-cell populations in animal models. Further investigation is necessary to directly demonstrate expression of these structures on the Th17 cell subset in human RA synovium. DC, dendritic cell; RANK, receptor activator of nuclear factor-kappa B.

Th-17 y Psoriasis

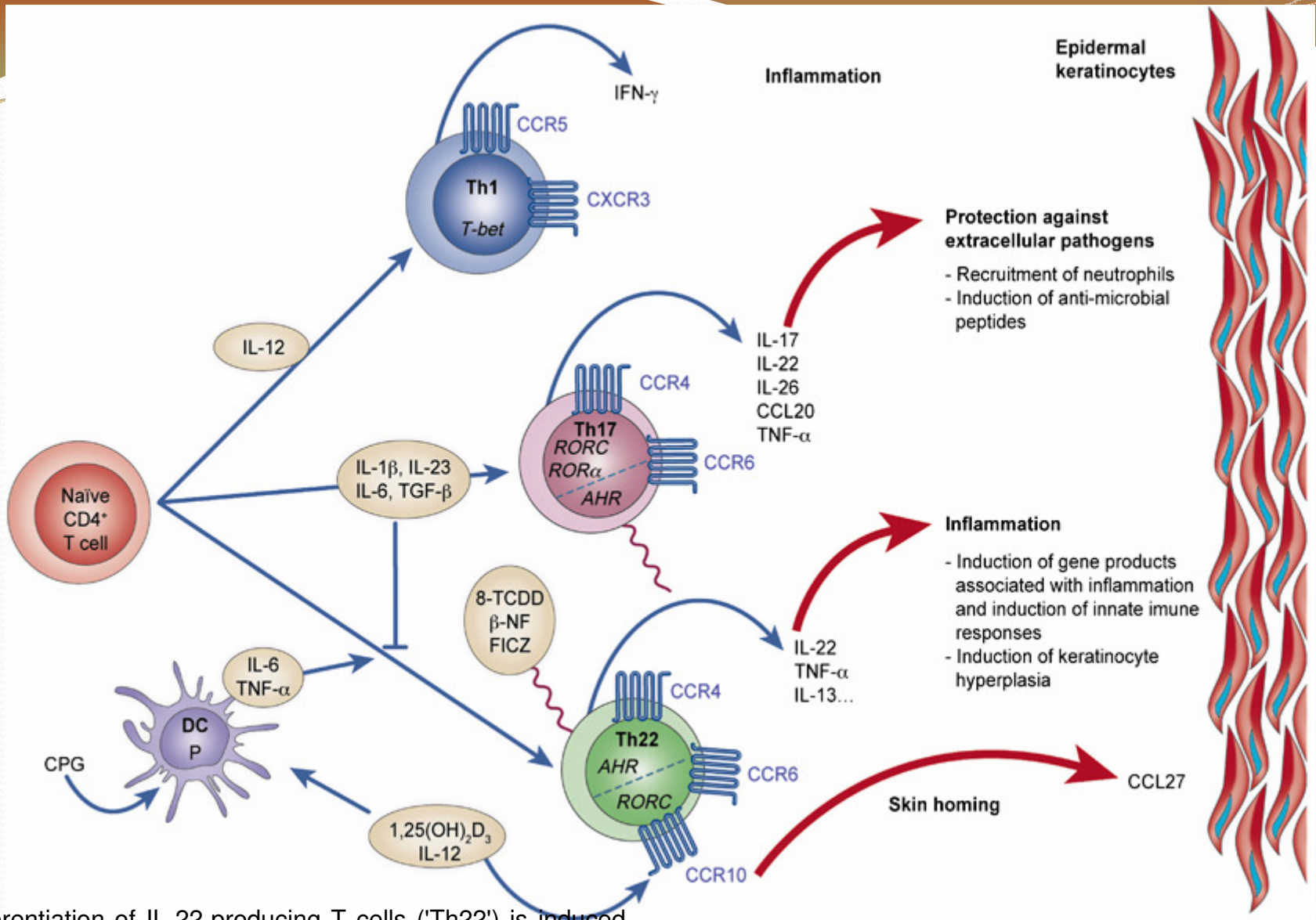


In the 'IL-23/Th17 axis' model for psoriasis, Th17 lymphocytes (Th17) interact with skin-resident cells, contributing to the psoriatic phenotype. In the dermis, IL-23, secreted by dermal dendritic cells (DDC), is able to induce Th17 lymphocyte activation with the consequent release of proinflammatory cytokines, such as IL-17A, IL-17F, IL-22, and IL-26. IL-17A, IL-17F, and IL-22 act on keratinocytes (KC) leading to epidermal hyperplasia, acanthosis, and hyperparakeratosis. Dermal CCR5+CXCR3+CXCR6+ Th1 and epidermal VLA-1+ Tc1 lymphocytes are activated by DDCs and produce TNF-α and IFN-γ , contributing to the pathogenesis of the disease. KC hyperproliferation might also be influenced by fibroblasts, which can release keratinocyte growth factor (KGF) through TNF-α stimulation. In the context of this proinflammatory milieu, activated KCs might produce IL-23, which could mediate a cross-talk with Th17 lymphocytes in synergy with IL-23 coming from DDC. Th17 cells induce KC to produce IL-8 and antimicrobial peptides (for example, S100A8, S100A9, and defensin β 1/2) for recruitment of neutrophils, cathelicidin for activation of plasmacytoid dendritic cells (PDC), and vascular endothelial growth factor (VEGF) with resulting angiogenesis.

•Journal of Investigative Dermatology ISSN: 0022-202X

Células Th22

Interleukin-22-producing T cells: a specialized population involved in skin inflammation?



Differentiation of IL-22-producing T cells ('Th22') is induced or enhanced by aryl hydrocarbon receptor (AHR) ligands, such as β-naphthoflavone (β-NF), 8-tetrachlorodibenzo-*p*-dioxin (TCDD) or 6-formylindolo[3,2-b]carbazole (FICZ), which promote IL-22 production while inhibiting the production of IL-17.

retinoid-related orphan receptor (RORC)

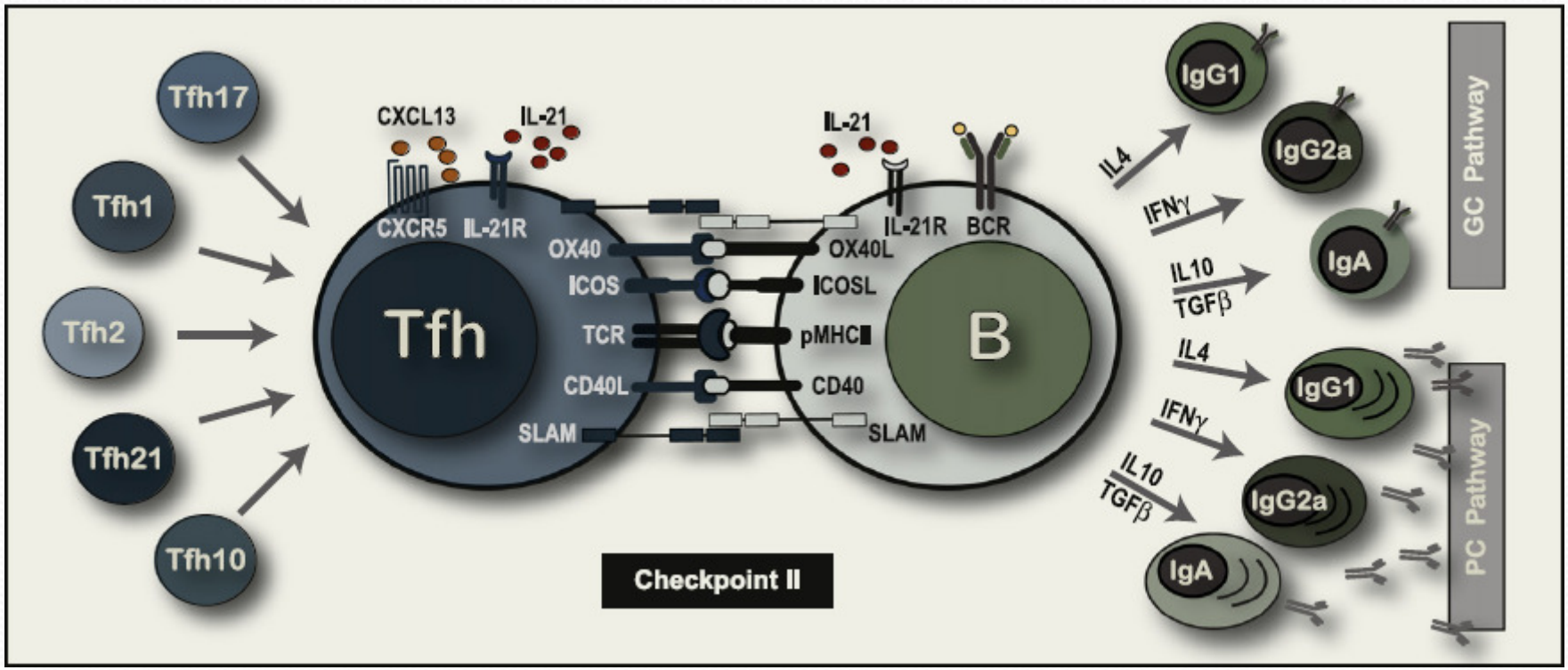
Immunology and Cell Biology (2009) **87,** 574–576

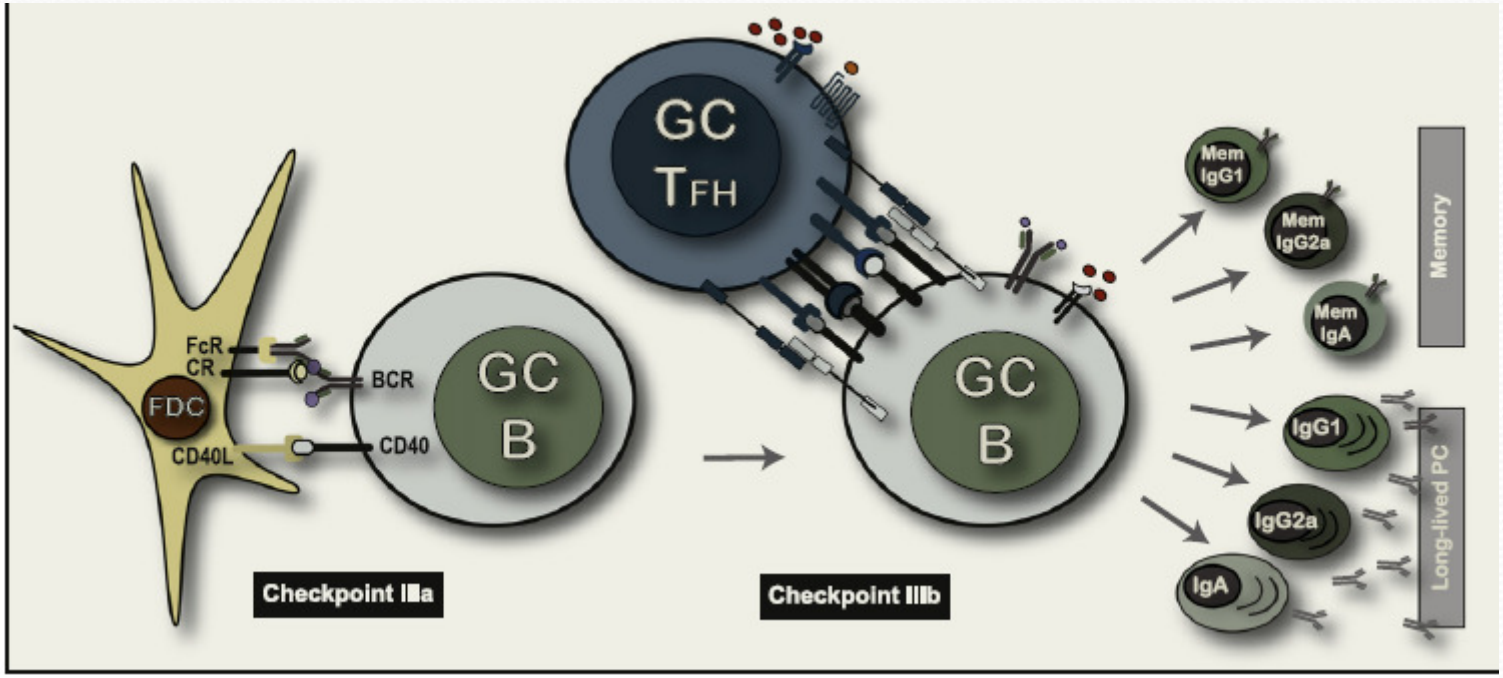
8-tetrachlorodibenzo-*p*-dioxin

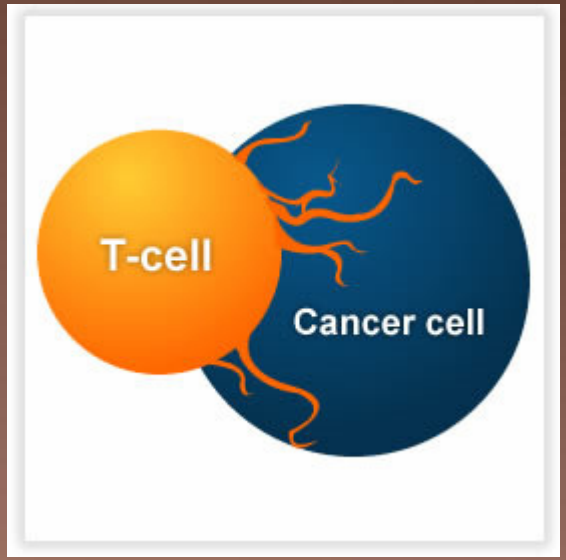
In humans, TCDD can produce the skin condition known as **chloracne;** the possibility that it also produces cancer, endocrine alterations, immunological changes, and/or birth defects (as it does in animals) is the subject of debate. Many individuals have been exposed to TCDD, primarily from dietary sources, although occupational and accidental exposures have also occurred.

Th foliculares

Follicular helper T (Tfh) cells can be considered a separable T helper cell subset specialized to regulate the evolution of effector and memory B cell responses (Fazilleau et al.,2007b; King et al., 2008;Vinuesa et al., 2005b).




GC
TFH
FcR
CR
FDC
CD40L
BCR
CD40
GC
B
GC
B
Checkpoint IIIa
Checkpoint IIIb
Mem
IgG1
Mem
IgG2a
Mem
IgA
Memory
IgG1
IgG2a
IgA
Long-lived PC

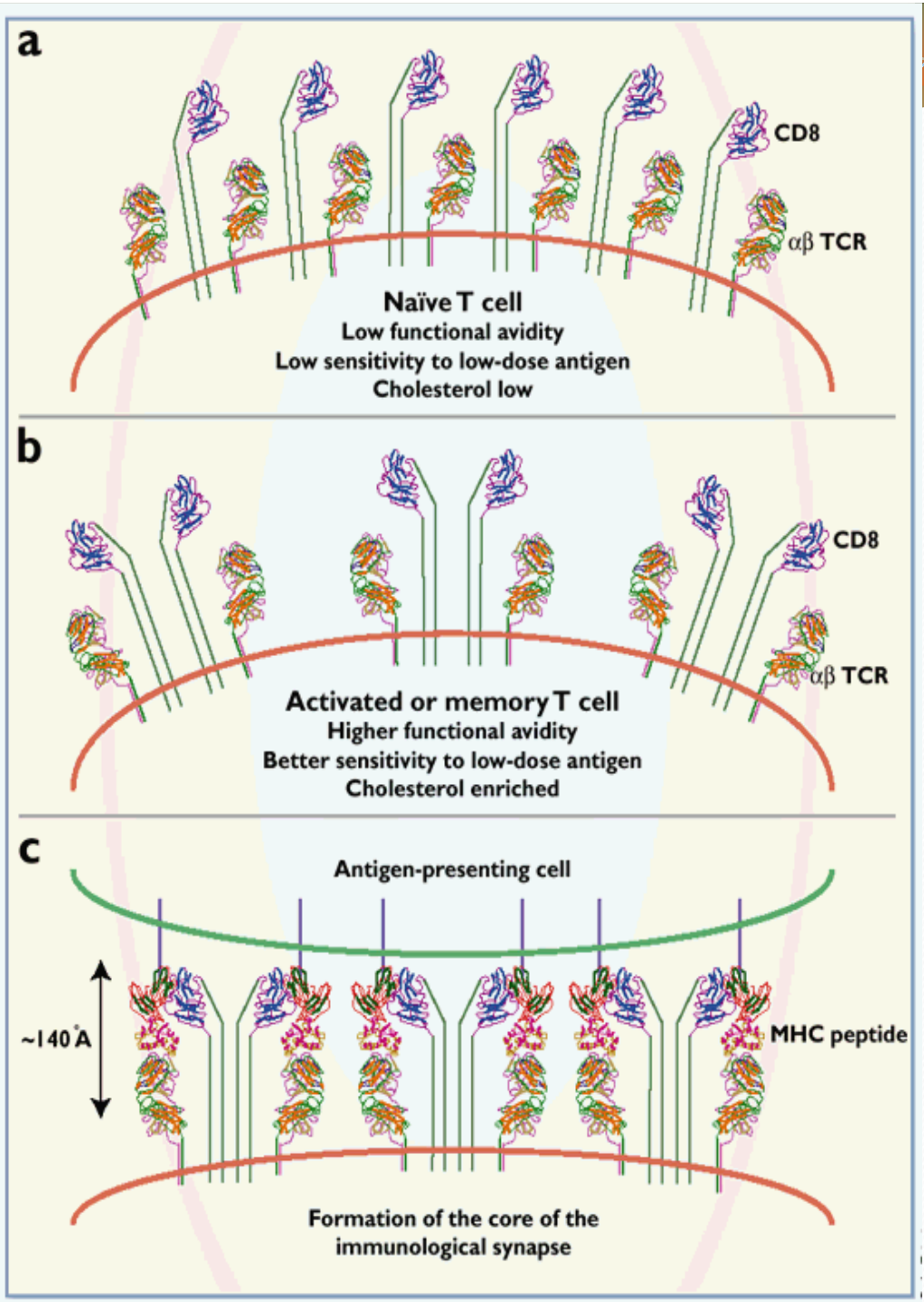


LINFOCITOS TCD8+

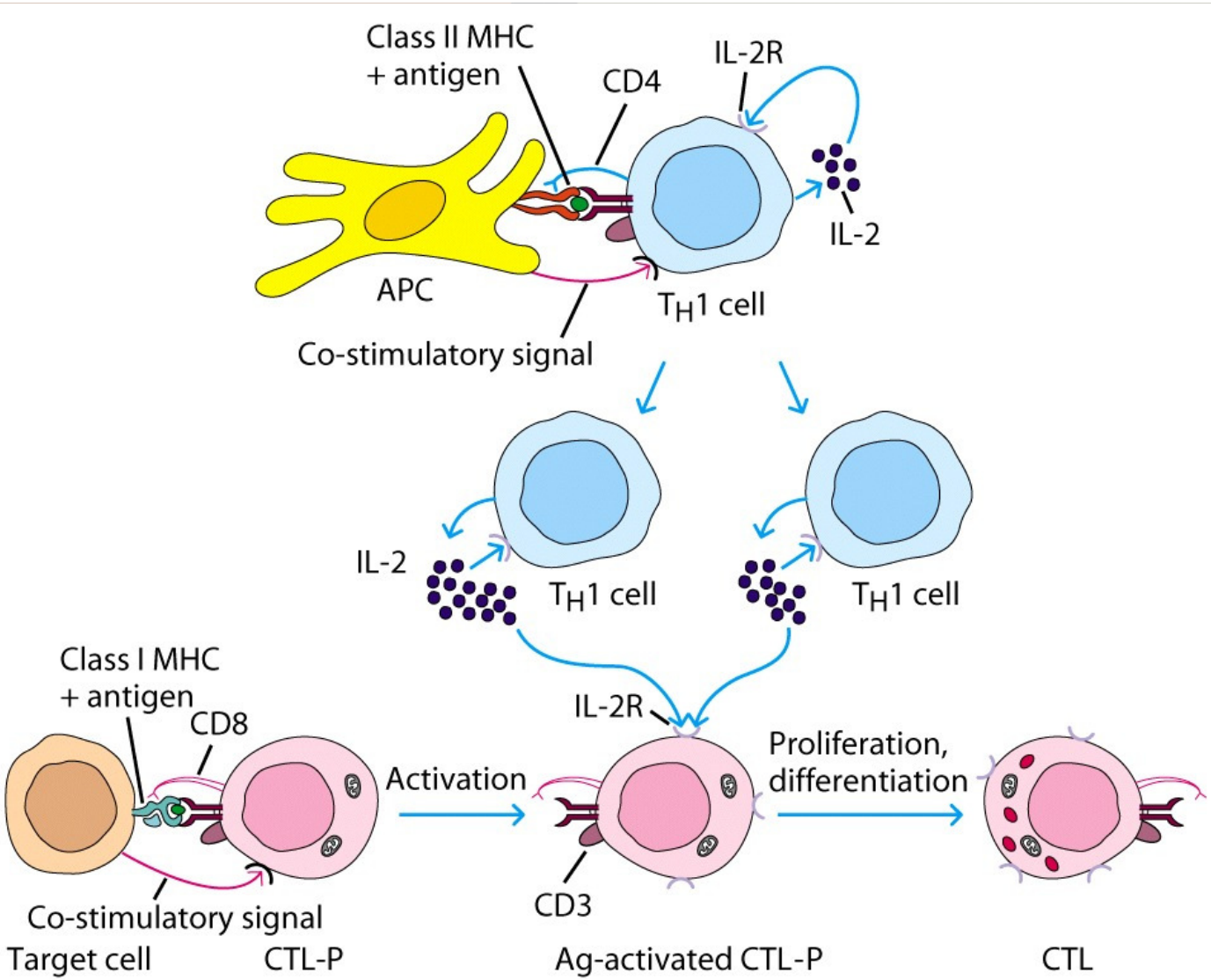
¿CÓMO SE ACTIVA LA CÉLULA TCD8^{+}?

Las células TCD8^{+} naïve requieren más actividad coestimuladora para ser conducidas a células efectoras que las células TCD4^{+} naïve

Re arreglos del TCR y correceptor al pasar de una célula T naïve a célula T activada……

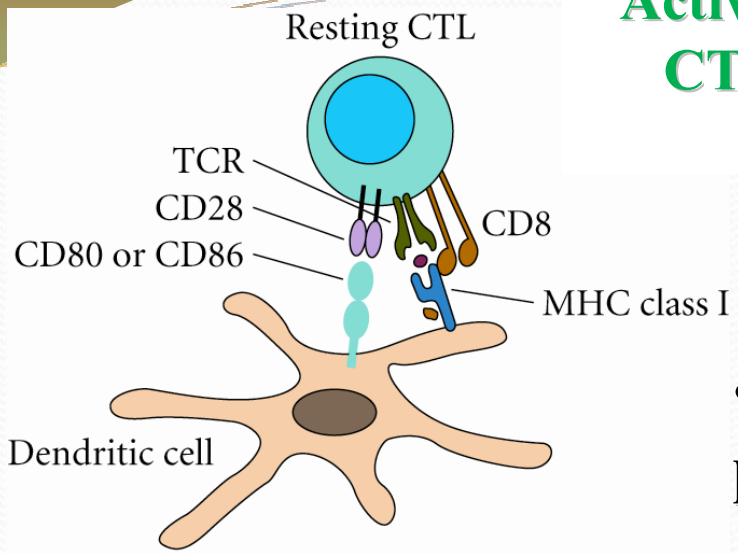


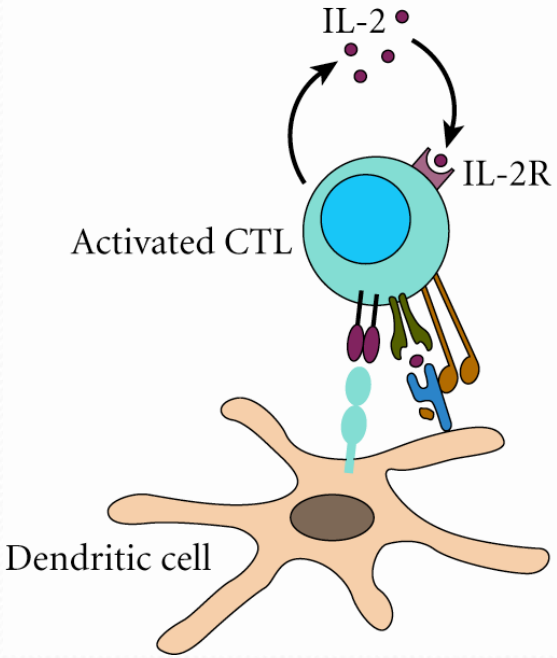
Nature Immunology 2, 669 - 670 (2001)



IL-2R expression	–	+	+
IL-2 expression	–	±	±
Proliferation	–	–	+
Effector cytotoxic function	–	–	+

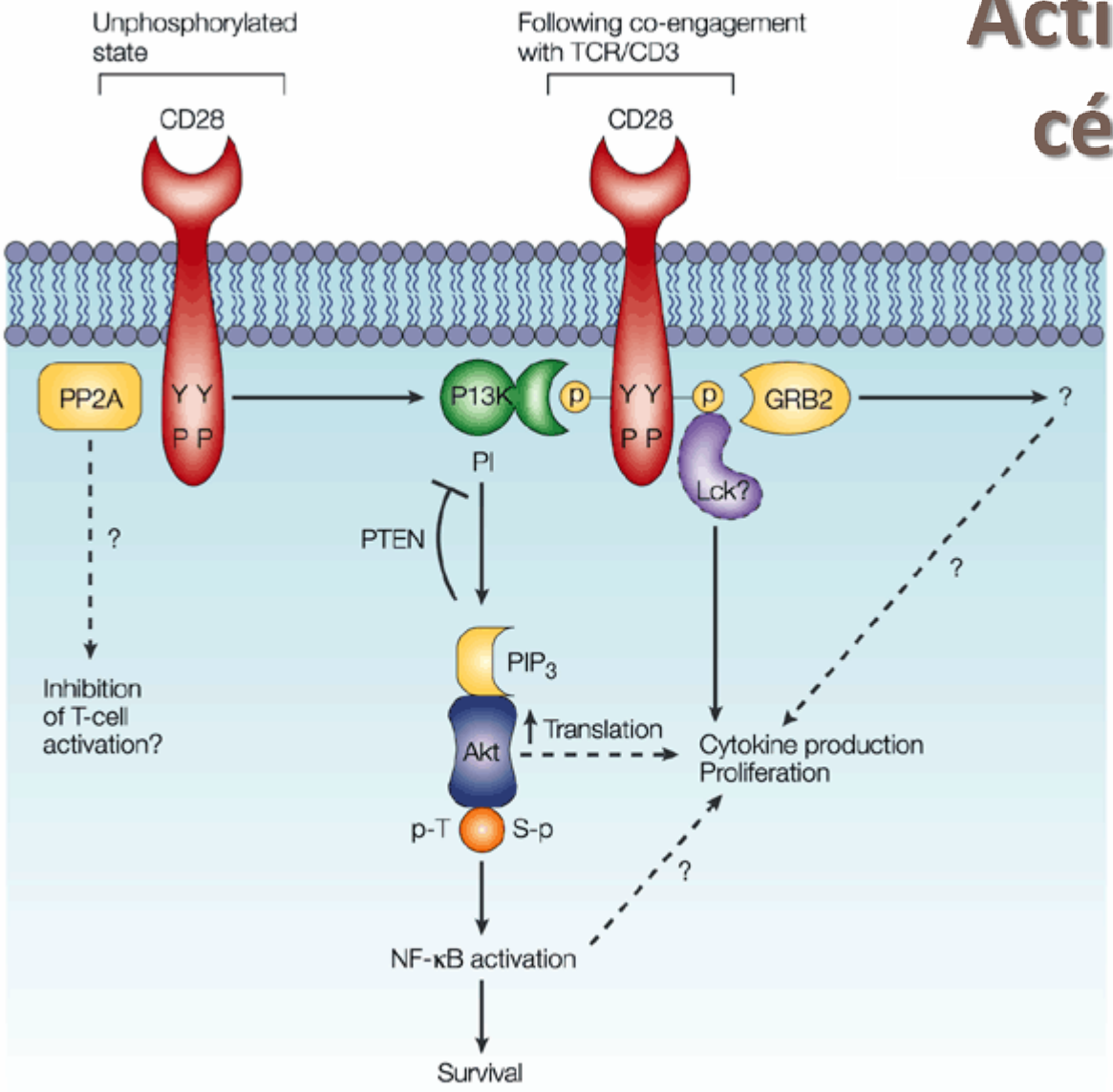
Activación DIRECTA del precursor de células CTL CD8^{+} por una DC infectada por virus



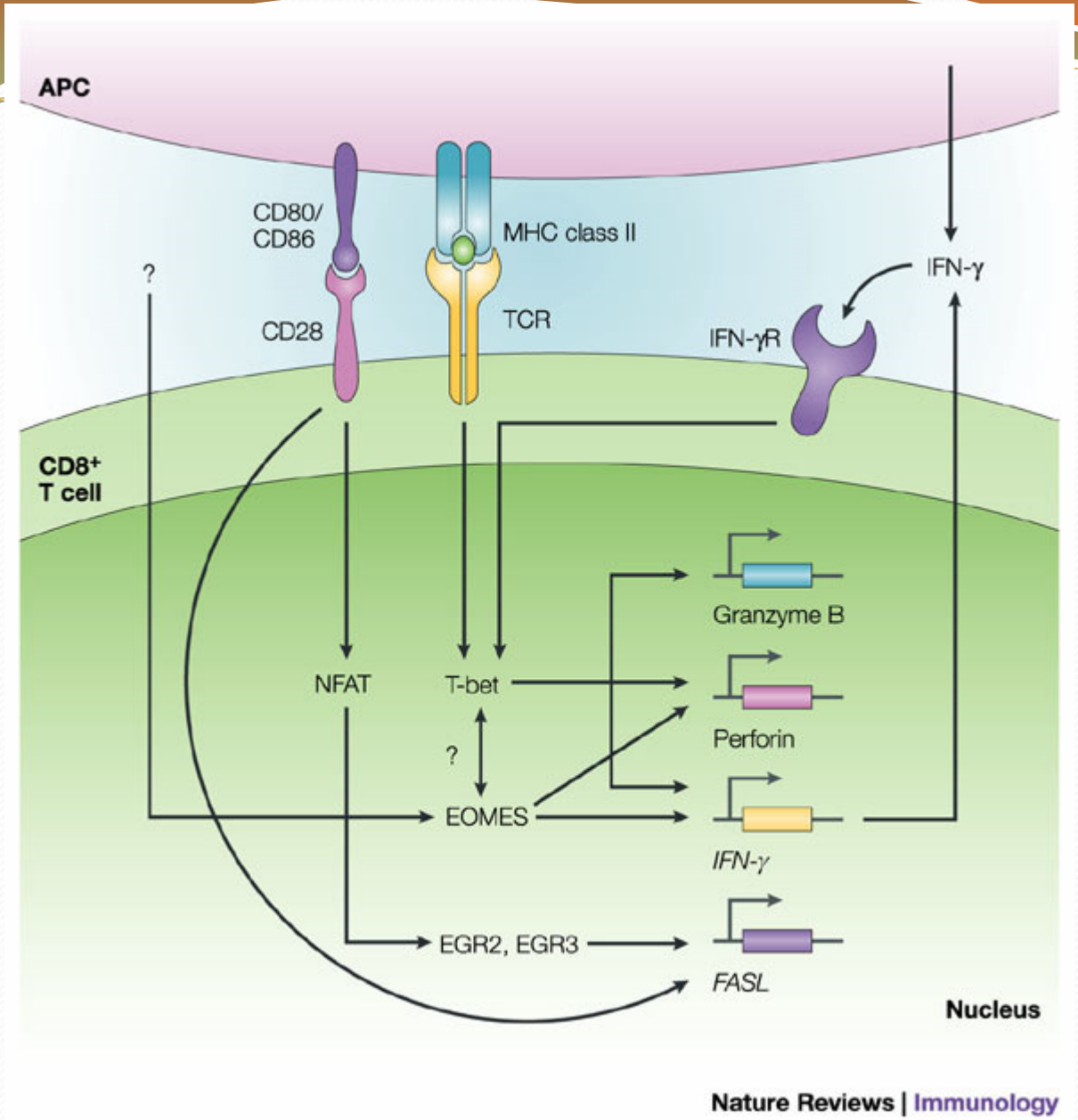


- **Signal 1 from TCR-MHC /viral peptide)**
- **Signal 2 from CD28-CD80/86 on DC**
- **CTL then produces both IL-2 and IL-2R**
- **Autocrine stimulated CTL activation**

Activación de la célula TCD8+



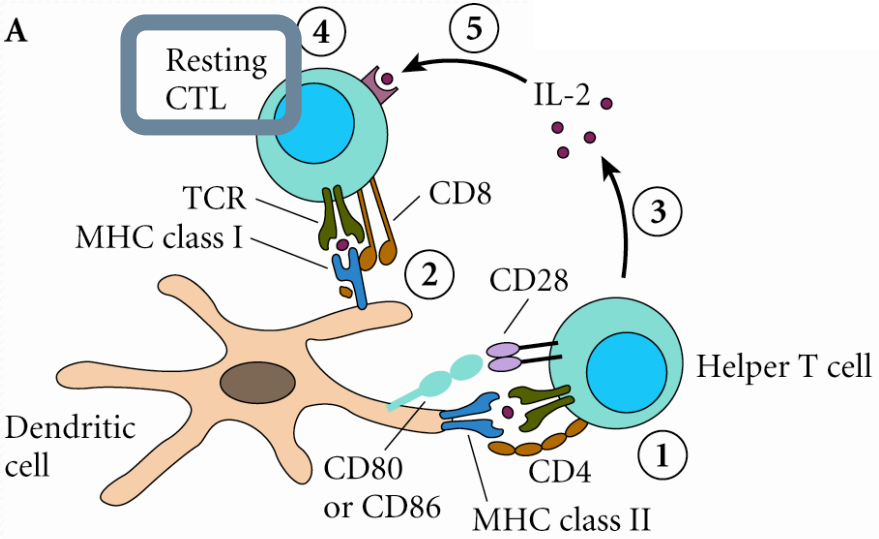
Nature Reviews | Immunology



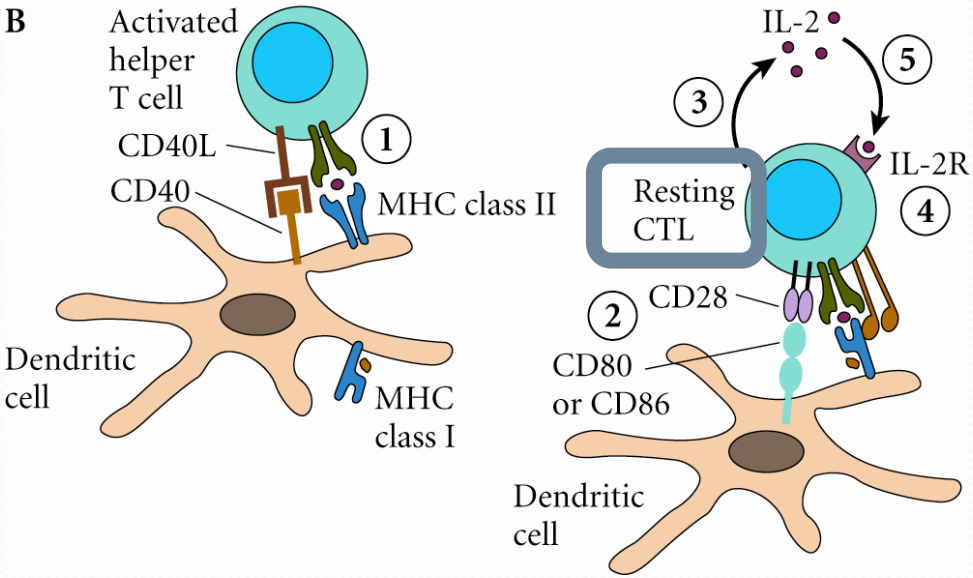
T-bet expression is induced by signalling through the T-cell receptor (TCR) and the interferon-γ (IFN- γ) receptor (IFN- γ R). T-bet then induces the expression of the effector molecules IFN-γ , perforin and granzyme B. Eomesodermin (EOMES) also induces the expression of IFN-γ and perforin. There is a CD28-dependent pathway that activates the expression of FAS ligand (FASL) either directly or through the transcription factors NFAT (nuclear factor of activated T cells), EGR2 (early growth response 2) and EGR3. At present, the signals that induce expression of EOMES and the possible interactions between T-bet and EOMES are unclear. APC, antigen-presenting cell.

Nature Reviews Immunology 4, 900-911 (November 2004)

Activación INDIRECTA del precursor de células CTL CD8$^+$ por una TCD4$^+$



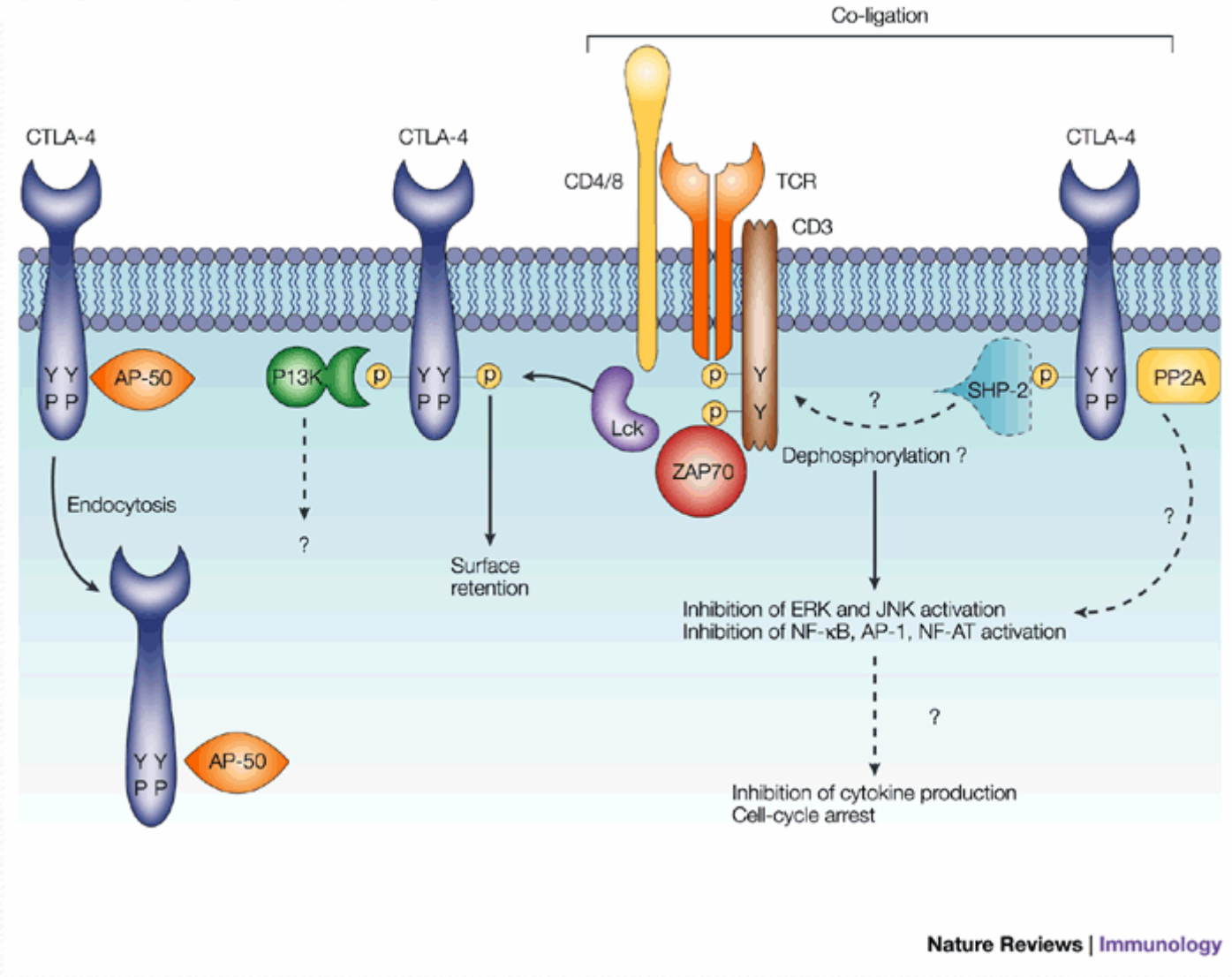
ACTIVACIÓN PARACRINA



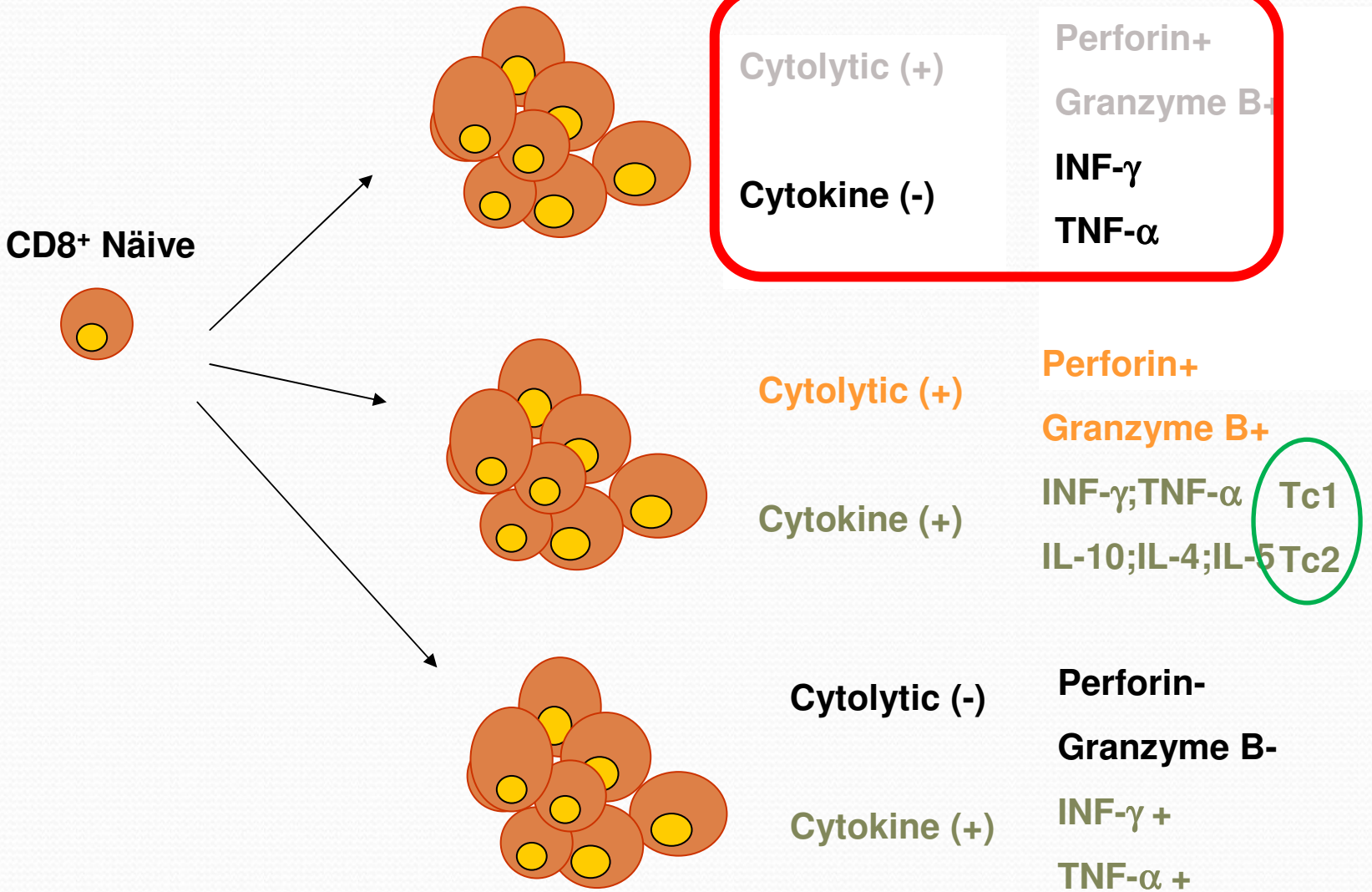
ACTIVACIÓN DE DC POR Th

La interacción CD40- CD40L induce la expresión de B7 en la CPA, capacitándola así para coestimular a la células TCD8 naïve

Inhibición de la activación de TCD8+

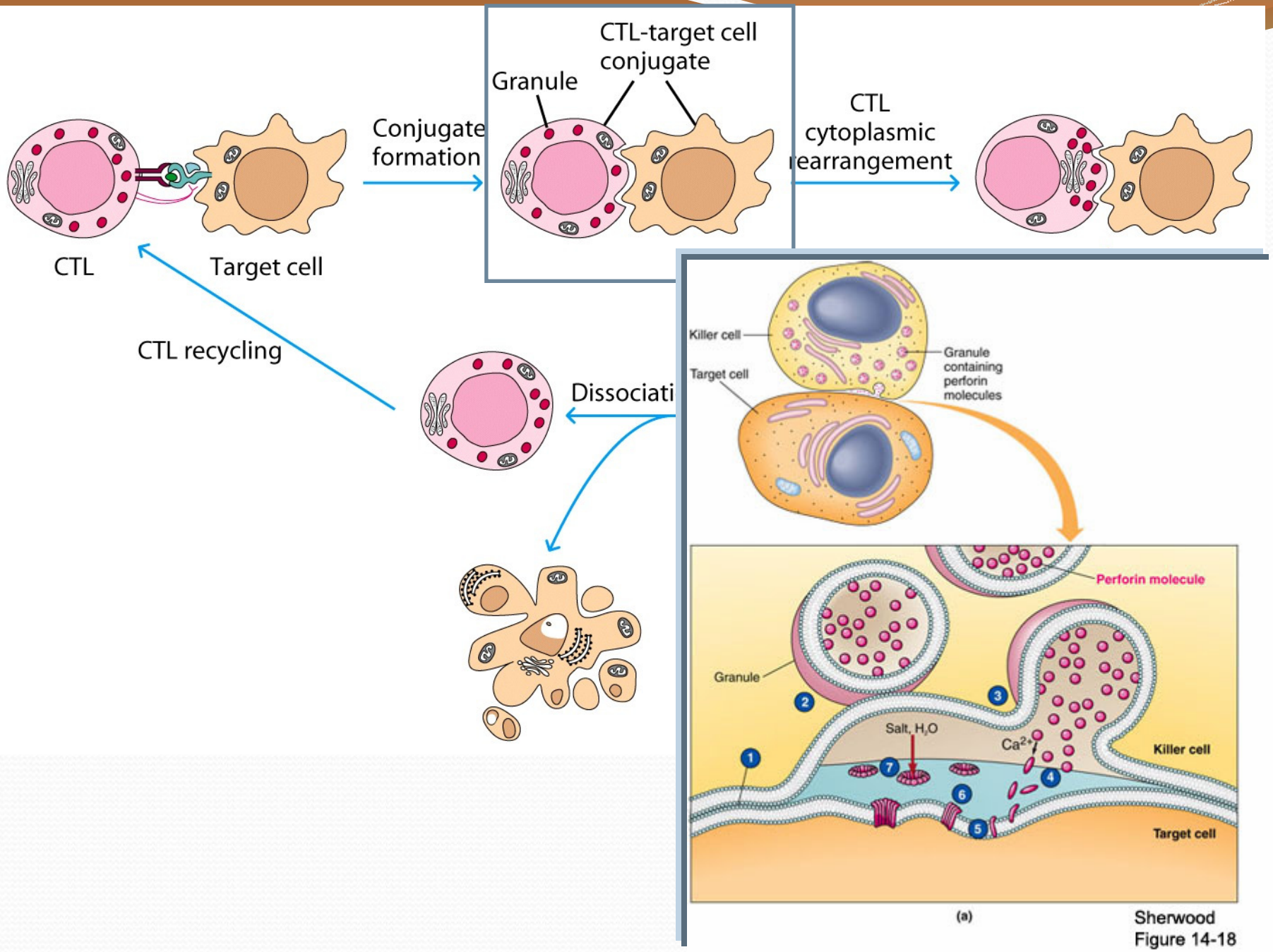


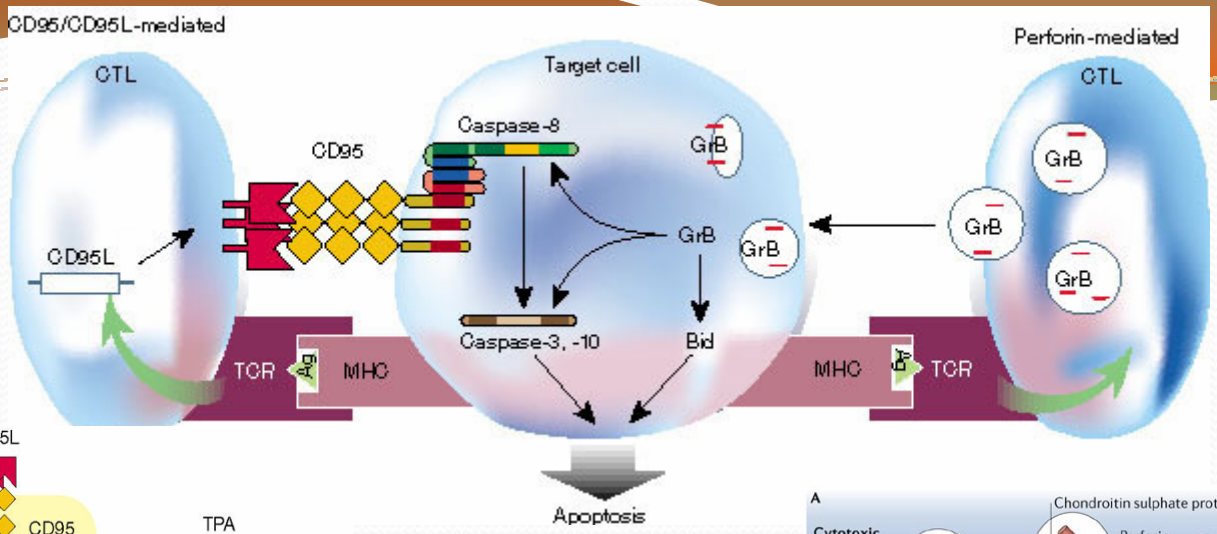
Generación de células CD8⁺ efectoras

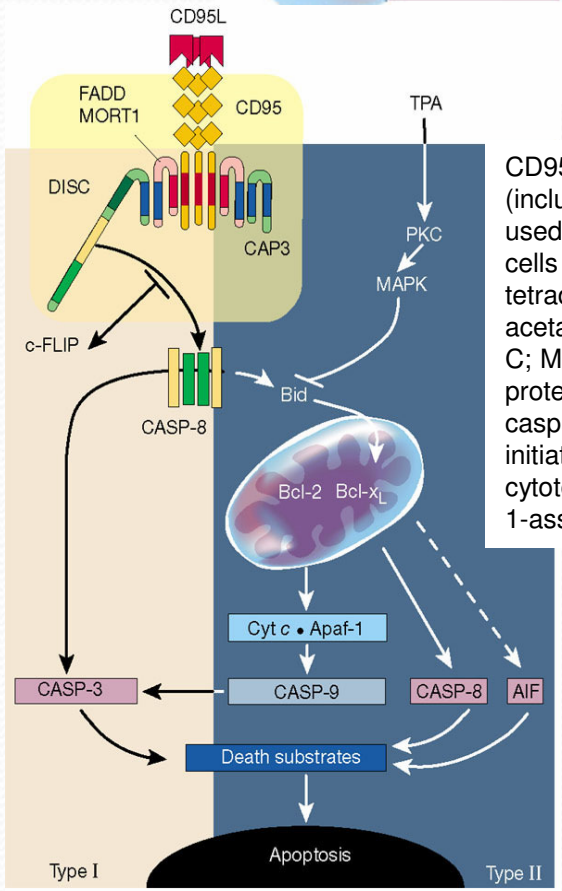


Mecanismos líticos

- **Exocitosis de gránulos - vía predominante (FAST KILLING)**
  - granzimas y perforinas
- **Expresión en la superficie celular de moléculas efectoras de la familia TNF (SLOW KILLING)**
  - TNF de Membrana, linfotoxina, Fas-L, Trail
- **Secreción de citocinas tóxicas solubles (SLOW KILLING)**
  - TNF e IFN-γ

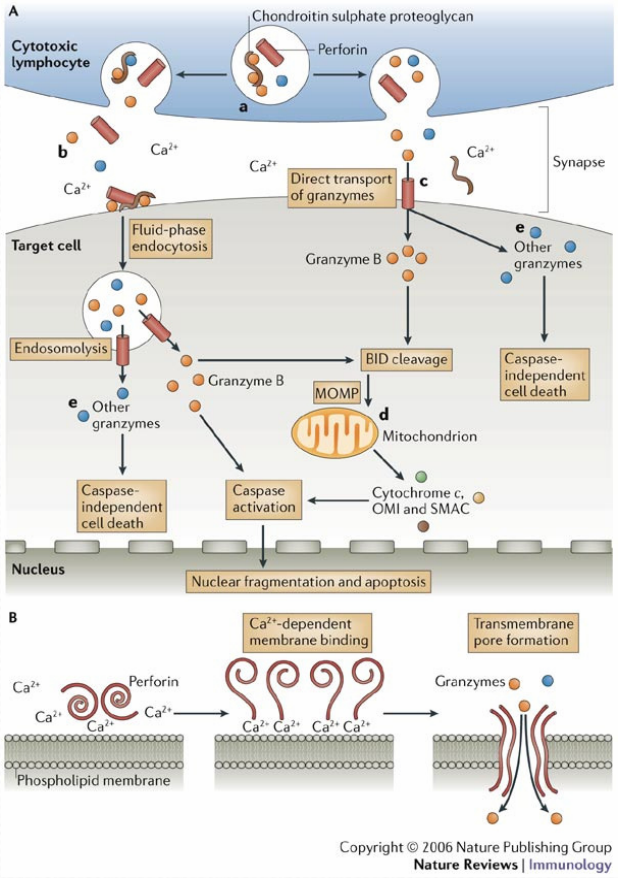

CTL-target cell conjugate
Granule
Conjugate formation
CTL cytoplasmic rearrangement
CTL
Target cell
CTL recycling
Dissociati
Killer cell
Target cell
Granule containing perforin molecules
Perforin molecule
Granule
Salt, H2O
Ca2+
Killer cell
Target cell
(a)
Sherwood
Figure 14-18





CD95 signalling pathway (including DISC formation) used in type I and type II cells (see text). TPA, 12-*O*-tetradecanoylphorbol-13-acetate; PKC, protein kinase C; MAPK, mitogen-activated protein kinase; CASP, caspase; AIF, apoptosis-initiating factor; CAP3, cytotoxicity-dependent Apo-1-associated protein 3).

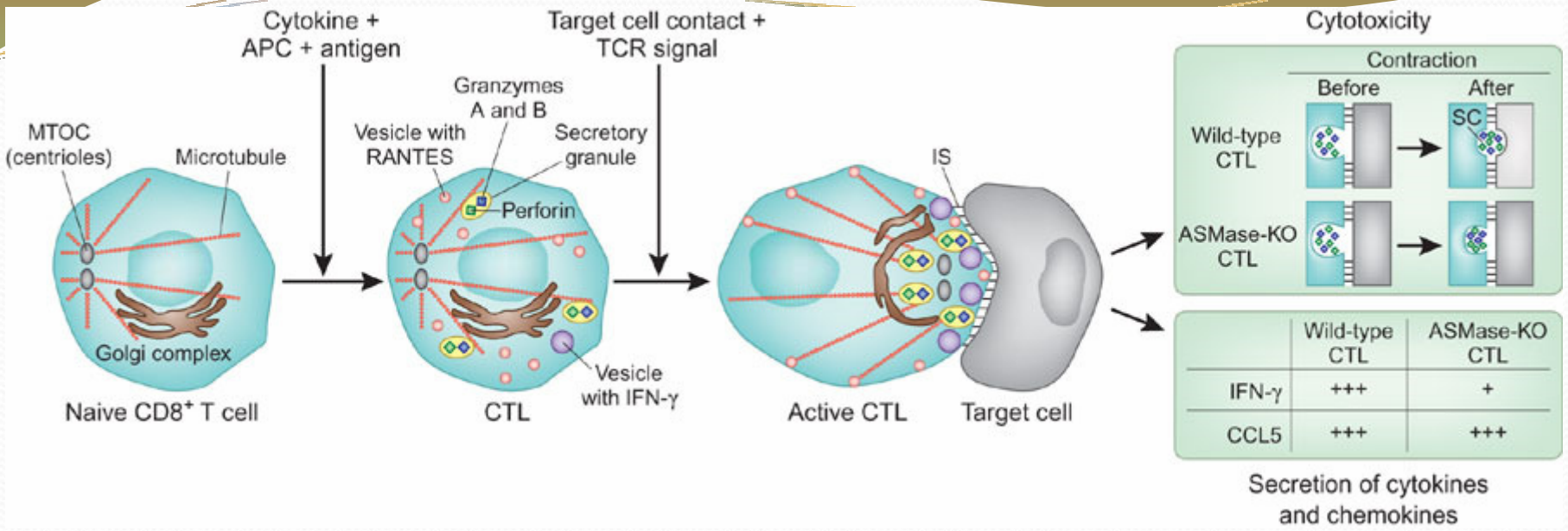
Nature 407, 789-795(12 October 2000)



Nature Reviews Immunology 6, 940-952 (December 2006)

microtubule-organizing center : MTOC

acidic sphingomyelinase: ASMase



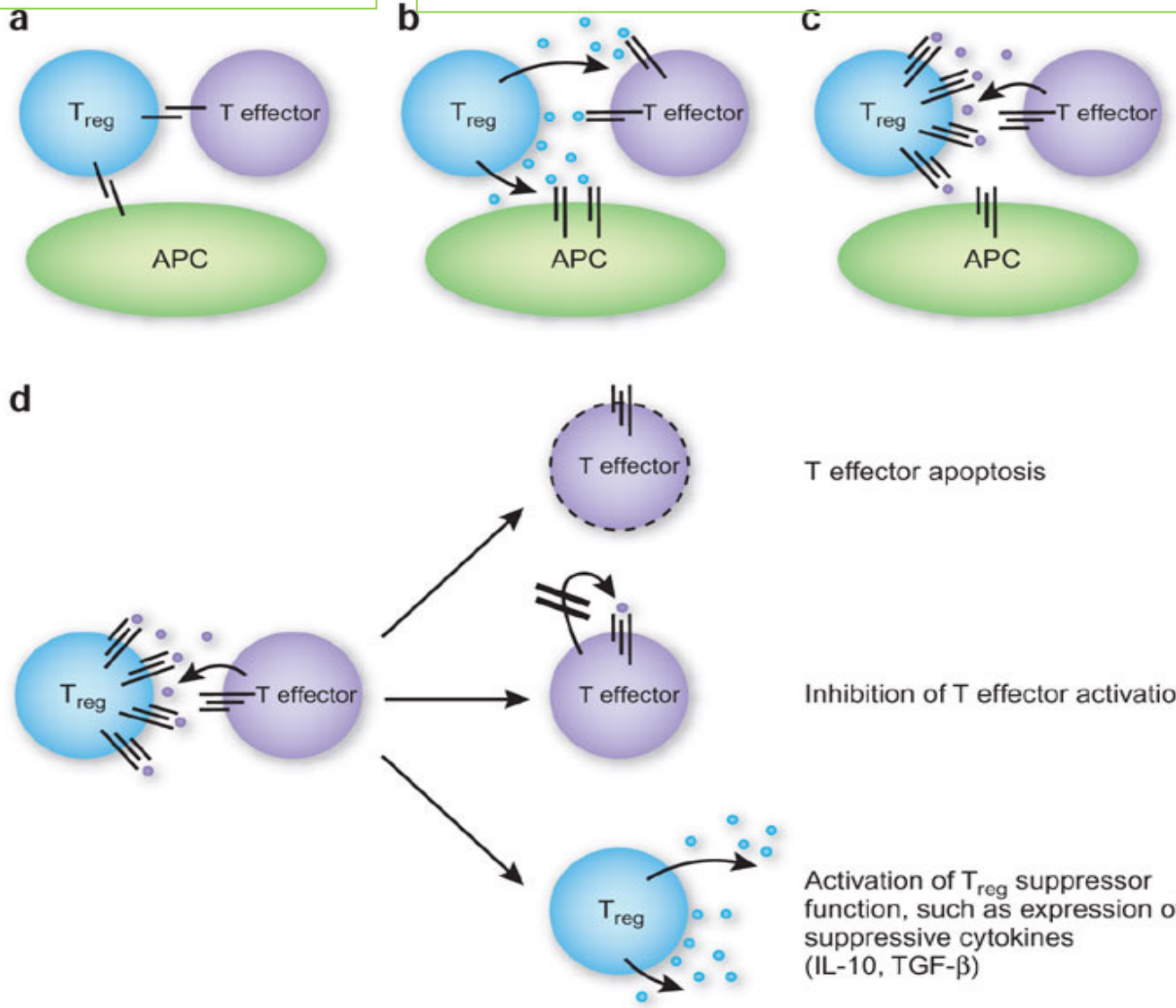
Naive CD8+ cytotoxic T cells differentiate into functionally competent CTLs when they receive the appropriate cytokine stimulation, such as IL-12, IL-18 or IL-21 from antigen-presenting cells (APC) or IL-2 from helper T cells, and TCR stimulation. After recognition of the target cell (such as a tumor cell, virus-infected cell or macrophage carrying intracellular bacteria) and the formation of an immunological synapse (IS), the microtubule-organizing center (MTOC), Golgi apparatus and secretory granules containing perforin and serine proteases (granzymes) are polarized toward the immunological synapse and target cell. The contraction of the granules and therefore the extrusion of their content into the synaptic cleft (SC) are facilitated by **ASMase**. Consequently, wild-type CTLs have much stronger cytotoxic activity against target cells ('vanishing' gray) than do ASMase-deficient CTLs (ASMase-KO). After contact with the target cell, differentiated CTLs also release certain cytokines (such as IFN- γ) and chemokines (such as CCL5 (RANTES)). There is evidence of new synthesis of IFN-γ protein by CTLs after TCR stimulation. The secretion (presumably in a synaptic direction) of IFN-γ is largely dependent on ASMase, but IFN-γ protein expression is not. In contrast, CCL5, which is reported to be preformed and stored in differentiated CTLs, is secreted in a multidirectional and ASMase-independent way.

Nature Immunology 10, 683 - 685 (2009)

Células T reguladoras

Cell contact–mediated action of membrane-bound suppressive or cytotoxic molecules.

Secretion by T_{reg} cells of diffusible molecules, such as transforming growth factor- β(TGF-β) or IL-10, that exert inhibitory actions on effector T cells or antigen-presenting cells (APC).

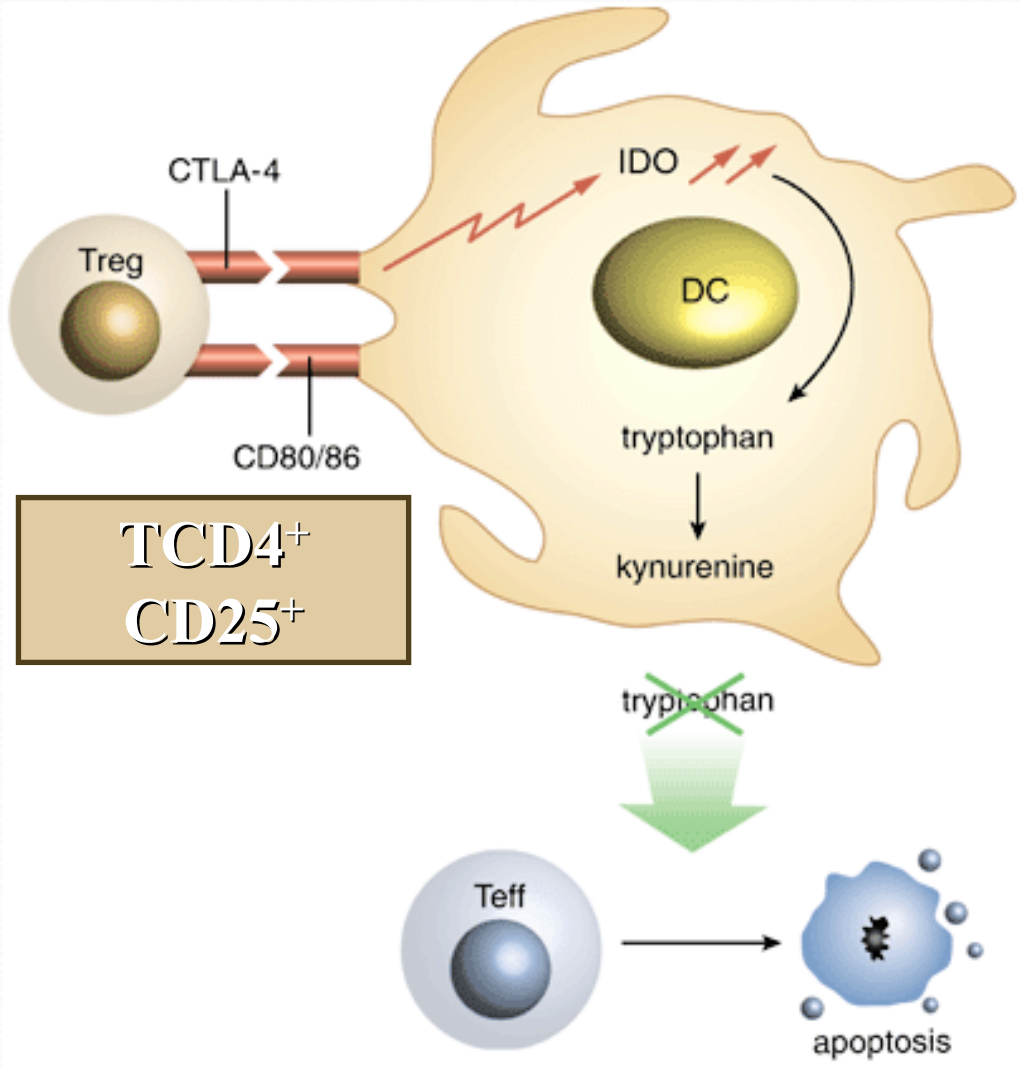


Competition (via consumption) by T_{reg} cells for resources for growth and/or survival factors such as IL-2.

The consequences of cytokine deprivation of effector T cells caused by T_{reg} cells include induction of apoptosis (top), interference with T cell activation (such as through the interruption of autocrine cytokine loops, as with IL-2; middle) or enhancement of T_{reg} cell suppressive activity (bottom). Combining these three effects provides a model for the known diversity of the suppressive activity of T_{reg} cells in various immunological settings.

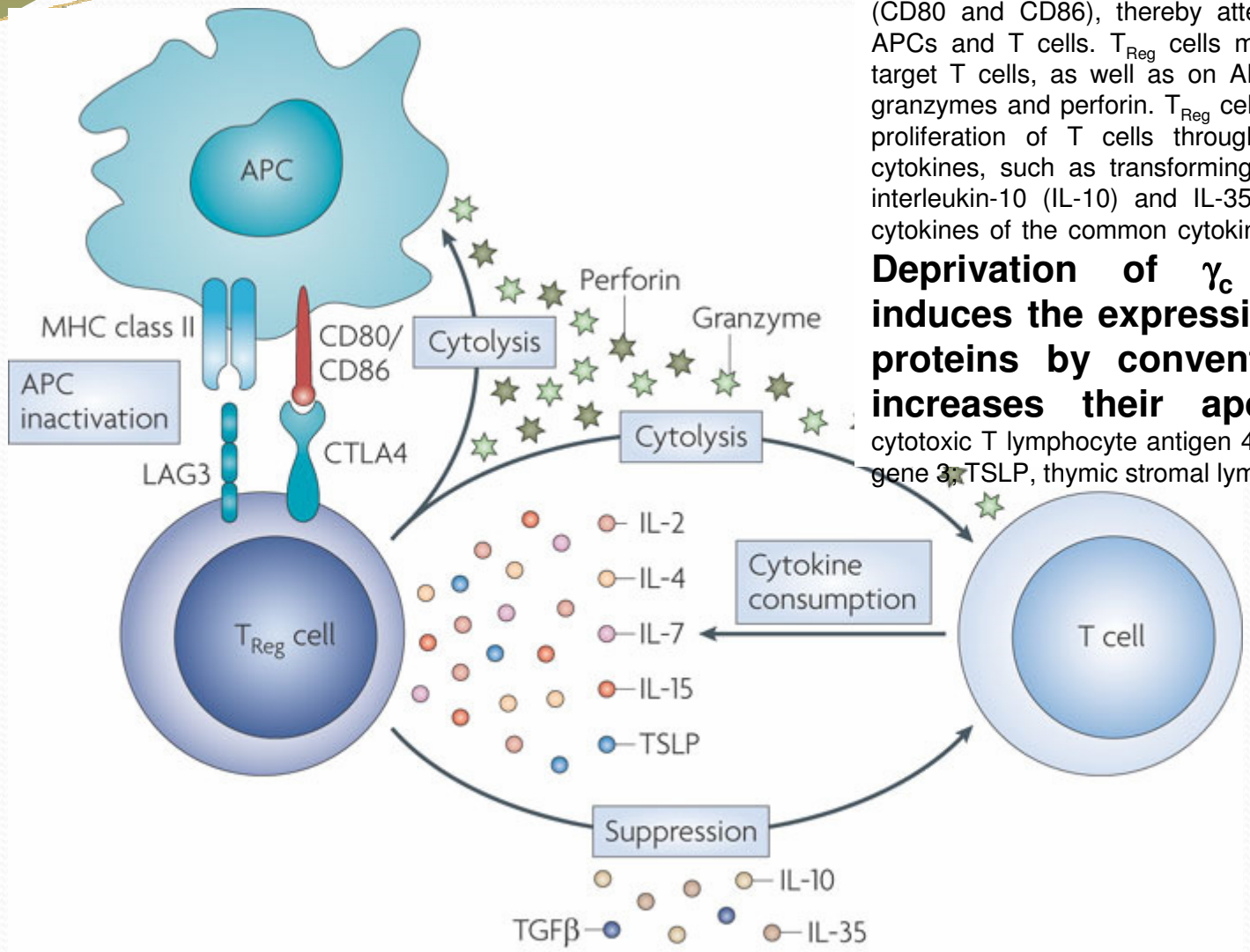
Nature Immunology **8**, 1285 - 1287 (2007)

Células T reguladoras inducen activación de indolamine 2,3-dioxygenase (IDO)



Regulatory T cells (Tregs) induce activation of indolamine 2,3-dioxygenase (IDO) in dendritic cells (DCs). This is partially mediated via the interaction of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) expressed on Tregs and CD80/86 expressed on DCs. IDO catalyzes the initial and rate-limiting step of tryptophan degradation, resulting in tryptophan deficiency.

Because tryptophan is an essential proliferative stimulus for effector T cells (Teff), these cells undergo apoptosis in a tryptophan-deprived

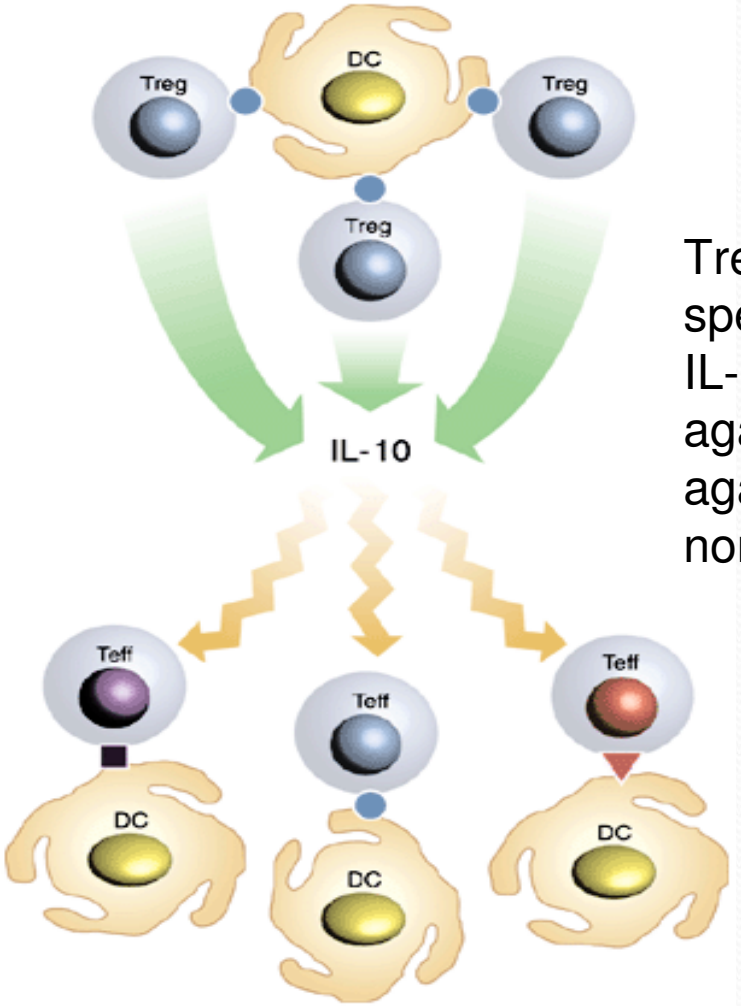


Regulatory T (T_{Reg}) cells use several mechanisms to suppress the activation and proliferation of conventional T cells. T_{Reg} cells modulate the functions of antigen-presenting cells (APCs) by inhibiting their maturation and blocking the cell surface expression of MHC molecules and co-stimulatory molecules (CD80 and CD86), thereby attenuating interactions between APCs and T cells. T_{Reg} cells might have cytolytic effects on target T cells, as well as on APCs, through the secretion of granzymes and perforin. T_{Reg} cells suppress the activation and proliferation of T cells through the secretion of inhibitory cytokines, such as transforming growth factor-β (TGF β), interleukin-10 (IL-10) and IL-35 and by the consumption of cytokines of the common cytokine receptor γ chain (γ_c) family. **Deprivation of γ_c family cytokines induces the expression of pro-apoptotic proteins by conventional T cells and increases their apoptotic rate**. CTLA4, cytotoxic T lymphocyte antigen 4; LAG3, lymphocyte activation gene 3; TSLP, thymic stromal lymphopoietin.

Nature Reviews Immunology 9, 480-490 (July 2009)

Nature Reviews | Immunology

SUPRESIÓN "BY STANDER"



Tregs that are activated by DCs in an antigen-specific fashion release IL-10. Once released, IL-10 inhibits immune reactions not only against the initial antigen (●) but also against other antigens (■ , ▼) in a nonspecific fashion.

Table 1. Subsets of natural and induced regulatory T cells[1]

Treg subset	Regulatory mechanisms	Transcription factor expressed	Target cells	Function
$CD4^+CD25^+$ Tregs	Cell contact-dependent, cytokines (IL-10?[2])	Foxp3	T cells, APCs	Suppression of autoimmunity; inhibition of allograft rejection and of immune responses induced by microbial infection; mediation of UV-induced immunosuppression
$CD4^+CD25^-$ Tregs	Mostly mediated by cytokines	Foxp3 (?[2])	T/B cells, APCs	Suppression of autoimmunity
Tr1 cells	Mediated by IL-10	Foxp3 (?[2])	T cells	Suppression of autoimmunity
Th3 cells	Mediated by TGF-β	?[2]	T cells	Suppression of autoimmunity
NKTregs	IL-4, IL-10, TGF-β, cytotoxicity	?[2]	T cells, APCs, tumor cells	Elimination of tumors and pathogens; suppression of autoimmunity; mediation of UV-induced suppression of protective tumor immunity
$CD8^+$ Tregs	Cell contact-dependent, cytotoxicity, cytokines (?[2])	Foxp3 (?[2])	T cells	Suppression of autoimmunity; regulation of peripheral TCR repertoire
$CD8^+CD28^-$ Tregs	Induction of ILT3/ILT4 in DCs	Foxp3 (?[2])	DCs/APCs	Regulation of autoimmunity (?[b])

[1]Subsets have been detected in humans and rodents. [2]Issue uncertain, not yet clear or not yet investigated. Abbreviations: APC, antigen-presenting cell; DC, dendritic cell; ILT, immunoglobulin transcript; NKTreg, regulatory cell of natural killer T cell phenotype; Th3, T helper type 3; Tr1 cell, type 1 regulatory T cell; Treg, regulatory T cell.

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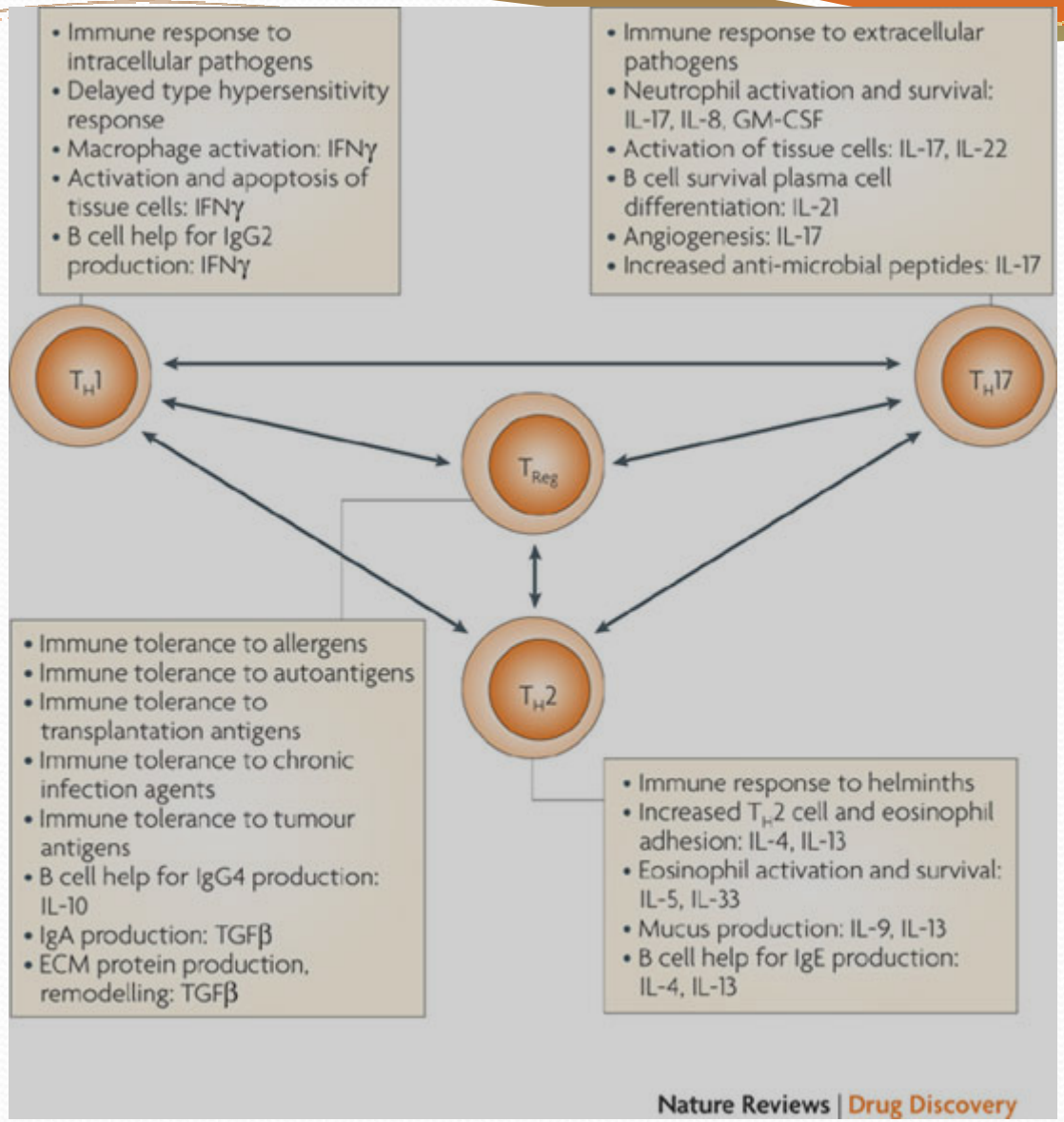
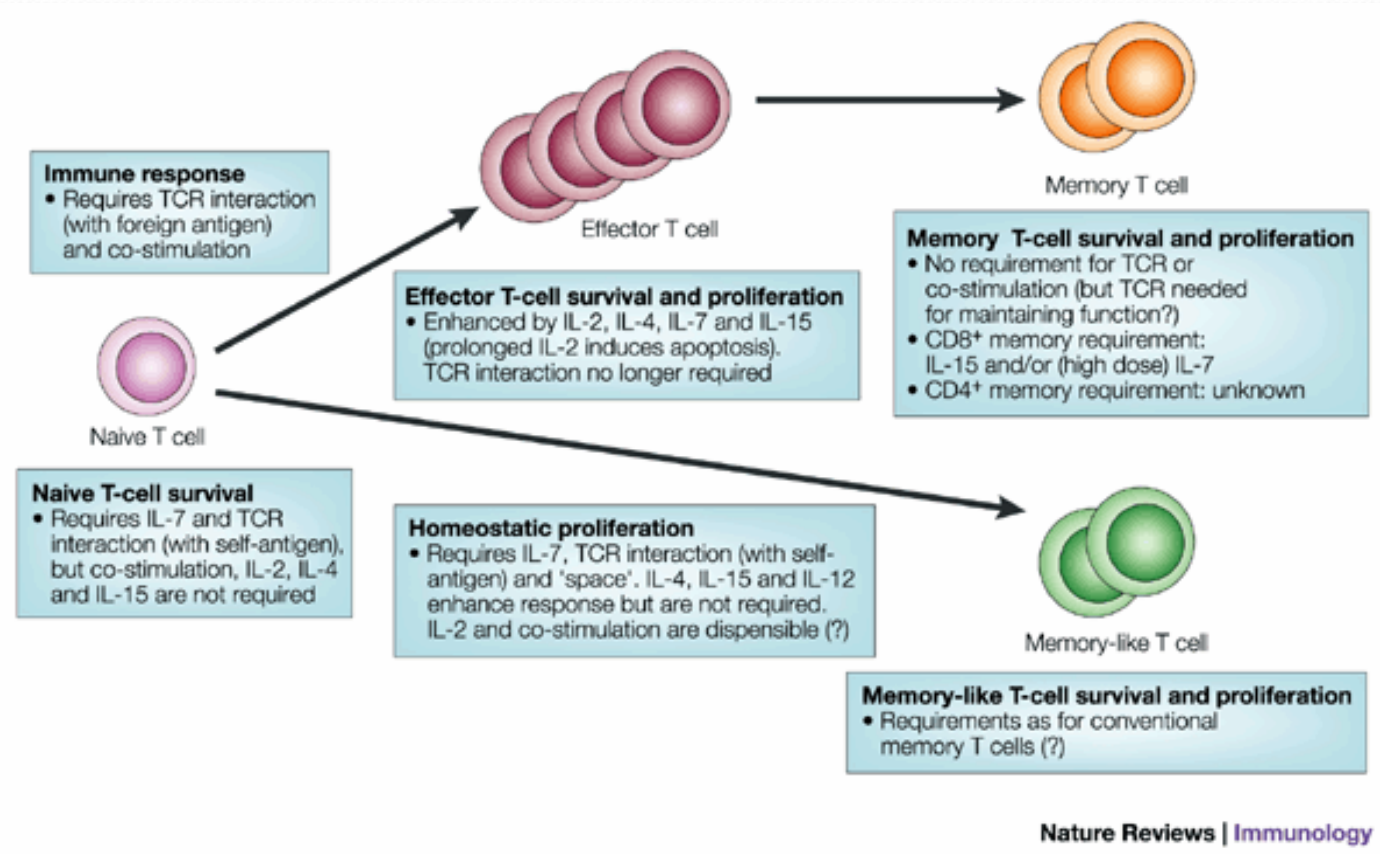
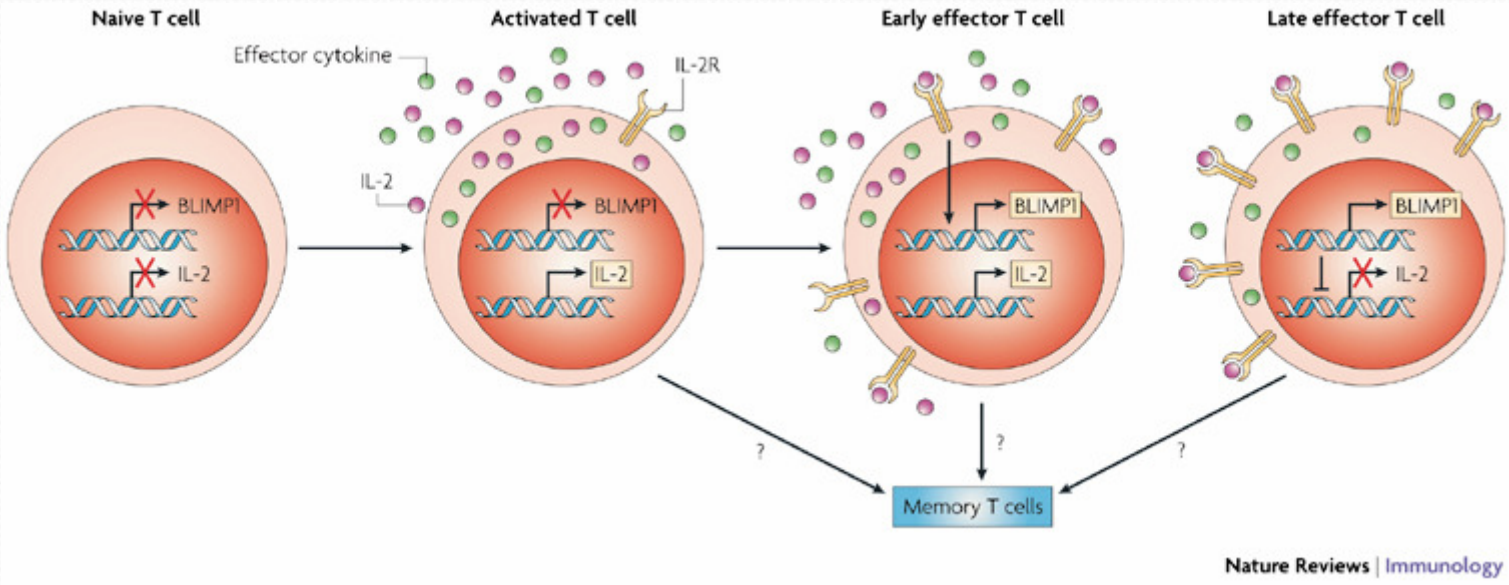


Nature Reviews Drug Discovery **8**, 645-660 (August 2009)

Células de memoria....


Immune response
• Requires TCR interaction (with foreign antigen) and co-stimulation
Effector T cell
Memory T cell
Effector T-cell survival and proliferation
• Enhanced by IL-2, IL-4, IL-7 and IL-15 (prolonged IL-2 induces apoptosis). TCR interaction no longer required
Memory T-cell survival and proliferation
• No requirement for TCR or co-stimulation (but TCR needed for maintaining function?)
• CD8+ memory requirement: IL-15 and/or (high dose) IL-7
• CD4+ memory requirement: unknown
Naive T cell
Naive T-cell survival
• Requires IL-7 and TCR interaction (with self-antigen), but co-stimulation, IL-2, IL-4 and IL-15 are not required
Homeostatic proliferation
• Requires IL-7, TCR interaction (with self-antigen) and 'space'. IL-4, IL-15 and IL-12 enhance response but are not required. IL-2 and co-stimulation are dispensible (?)
Memory-like T cell
Memory-like T-cell survival and proliferation
• Requirements as for conventional memory T cells (?)
Nature Reviews | Immunology

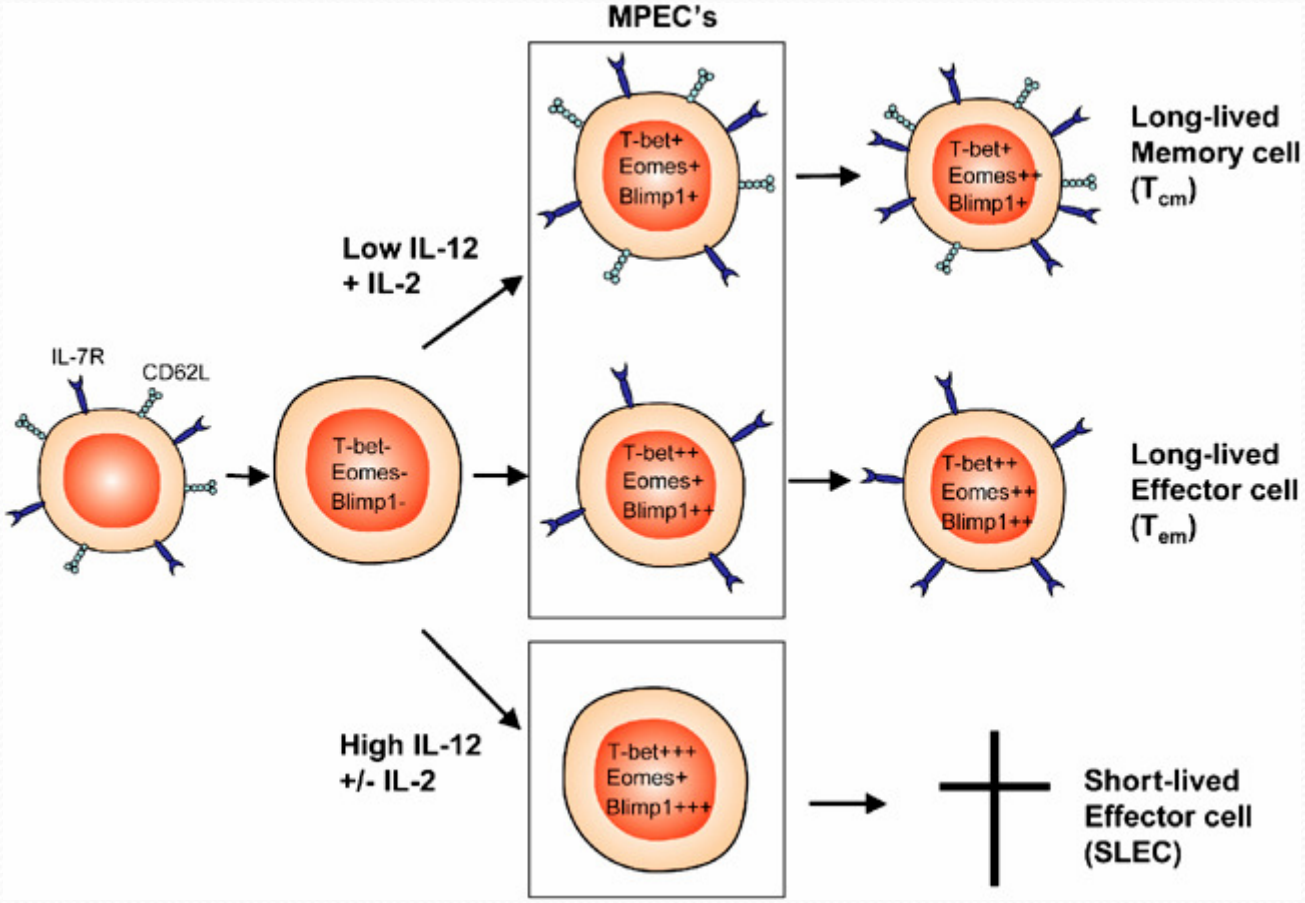
Activación de la célula T



B-lymphocyte-induced maturation protein 1 (BLIMP1)

Naive T cells express neither B-lymphocyte-induced maturation protein 1 (BLIMP1) nor interleukin-2 (IL-2). Following encounter with antigen, activated T cells secrete high quantities of IL-2 and upregulate the IL-2 receptor (IL-2R). Engagement of IL-2R by IL-2 results in BLIMP1 transcription in early effector cells. BLIMP1 expression increases in late effector cells and represses Il2 expression through an unknown mechanism. By contrast, most effector cytokines such as interferon-γ or tumour-necrosis factor appear to be unaffected by BLIMP1 expression.

Memory precursor effector cells (MPECs)



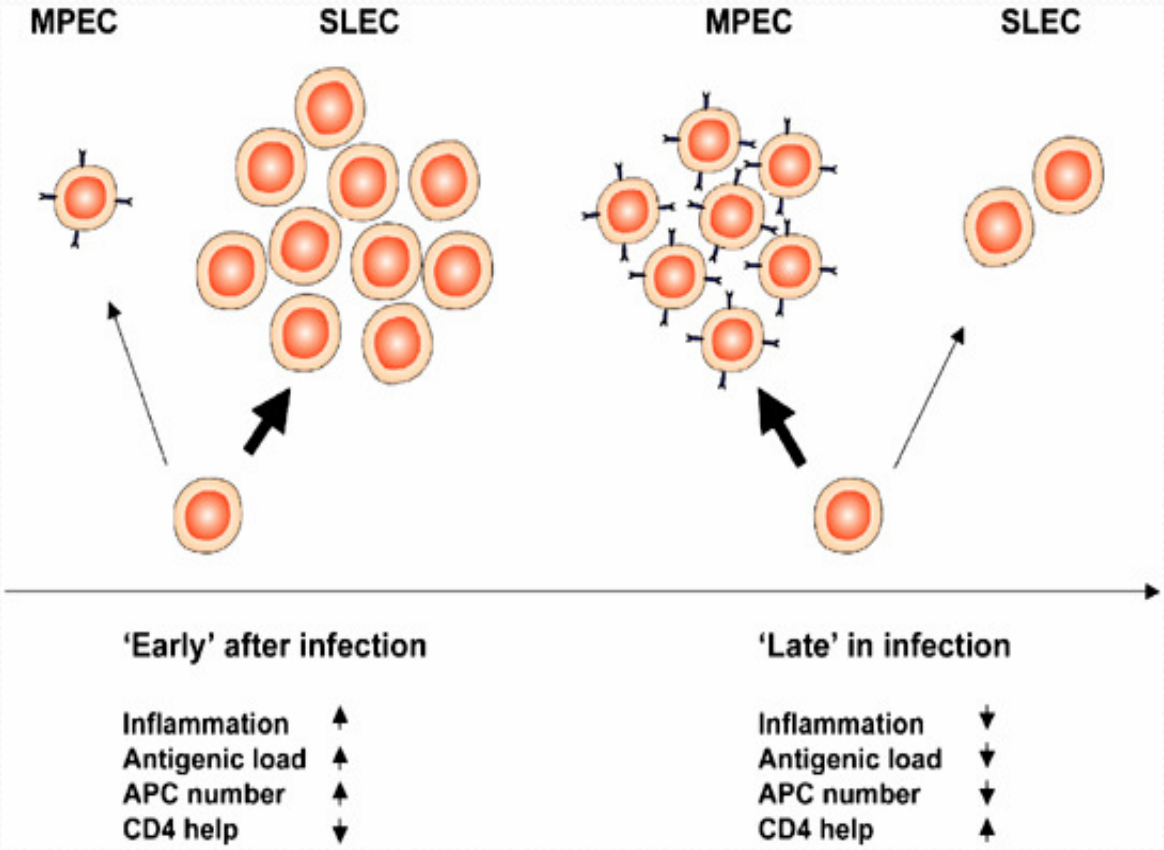
Células T de memoria central

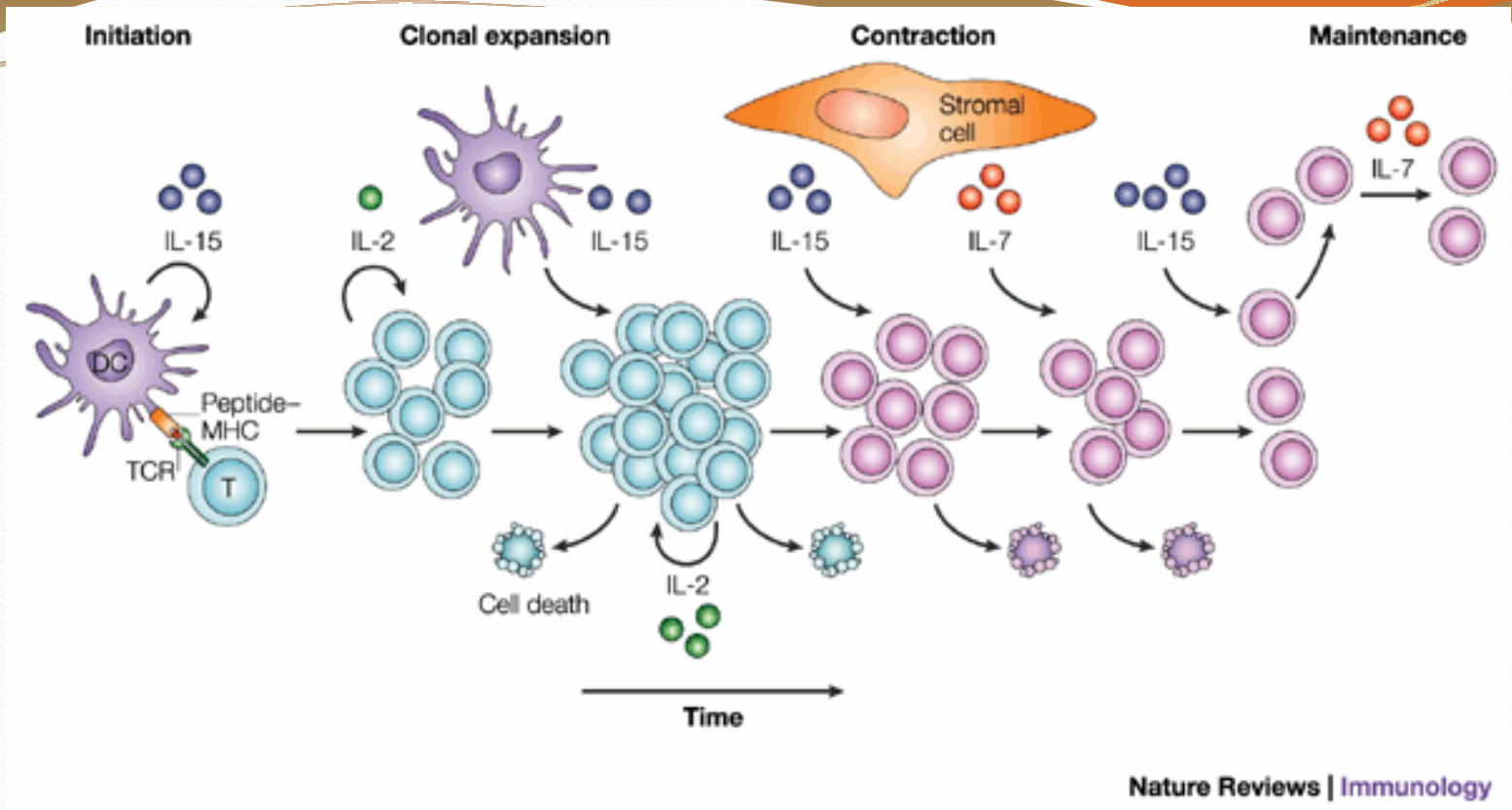
Células T de memoria efectoras

Eomesodermin (Eomes)

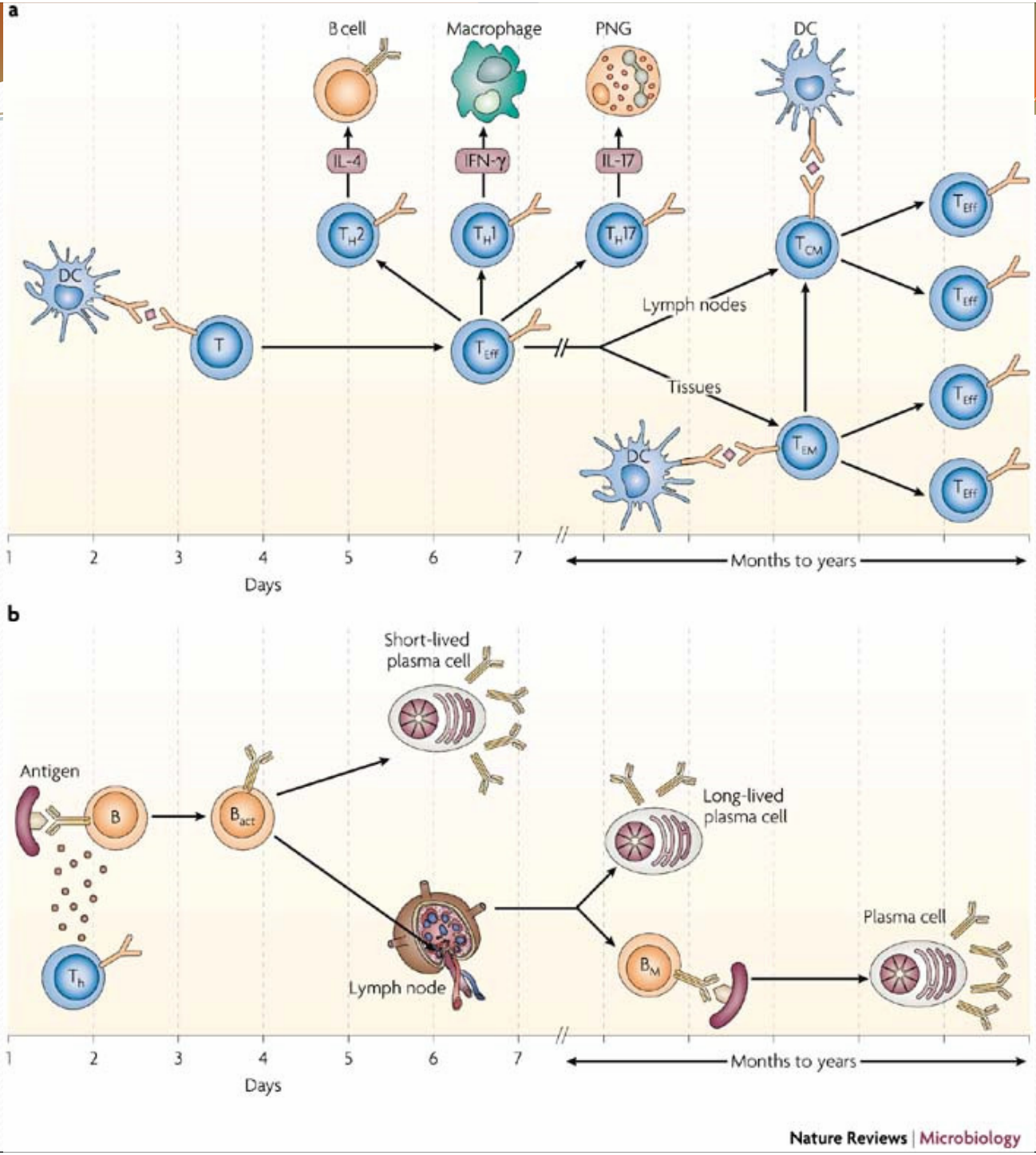
CD62 ligand (CD62L): L-selectin

Cambios en la diferenciación de células TCD8⁺ efectoras y de memoria durante la respuesta inmune

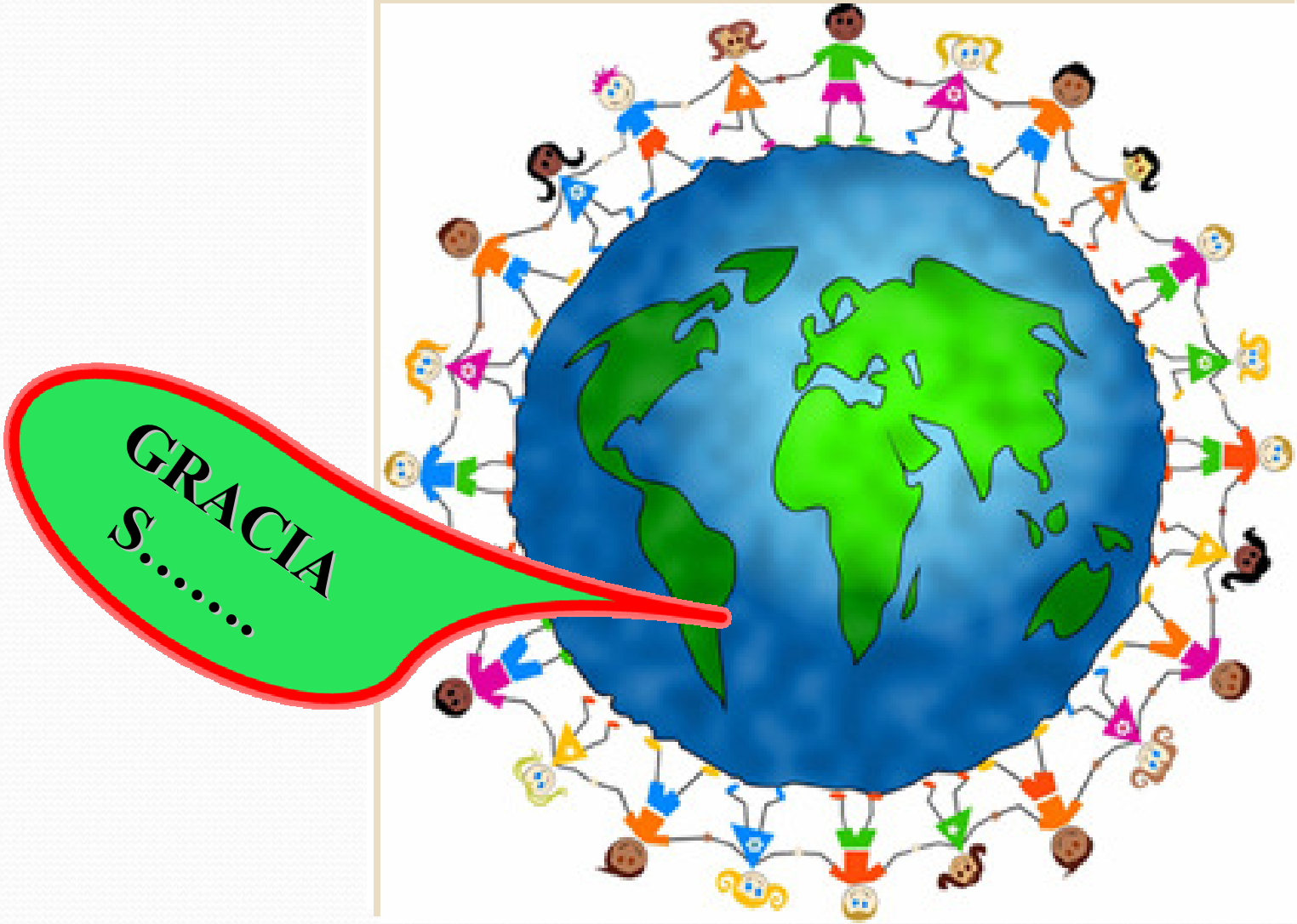




Cytokines can affect T-cell proliferation and survival at many stages of the immune response. During initiation of the T-cell response, interleukin-15 (IL-15) might be involved in dendritic-cell (DC) activation. After T-cell receptor (TCR) ligation of peptide–MHC, substantial T-cell clonal expansion occurs and might be driven, in part, by IL-2. IL-15 might also enhance the proliferation of antigen-specific T cells. IL-2 can also control the late clonal-expansion phase by inducing T-cell death. The massive cell death that occurs during the contraction phase results in the loss of most antigen-specific T cells. Both IL-15 and IL-7 might rescue T cells from cell death at this stage, thereby allowing memory T-cell generation. Memory T cells are maintained long term by undergoing a low level of proliferation, which depends on IL-15. IL-7 seems to be more important for promoting the survival, rather than the growth, of memory T cells.


a
B cell
Macrophage
PNG
DC
IL-4
IFN-γ
IL-17
T_H2
T_H1
T_H17
DC
T
T_{Eff}
Lymph nodes
T_{CM}
T_{Eff}
T_{Eff}
Tissues
T_{EM}
DC
T_{Eff}
T_{Eff}
1 2 3 4 5 6 7
Days
Months to years
b
Short-lived plasma cell
Antigen
B
B_{act}
Long-lived plasma cell
Plasma cell
T_h
Lymph node
B_M
1 2 3 4 5 6 7
Days
Months to years


BRED


GRACIA
S……