Inmunología Clínica 2009

Bioq Graciela R Svibel de Mizdraji

ONTOGENIA T

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

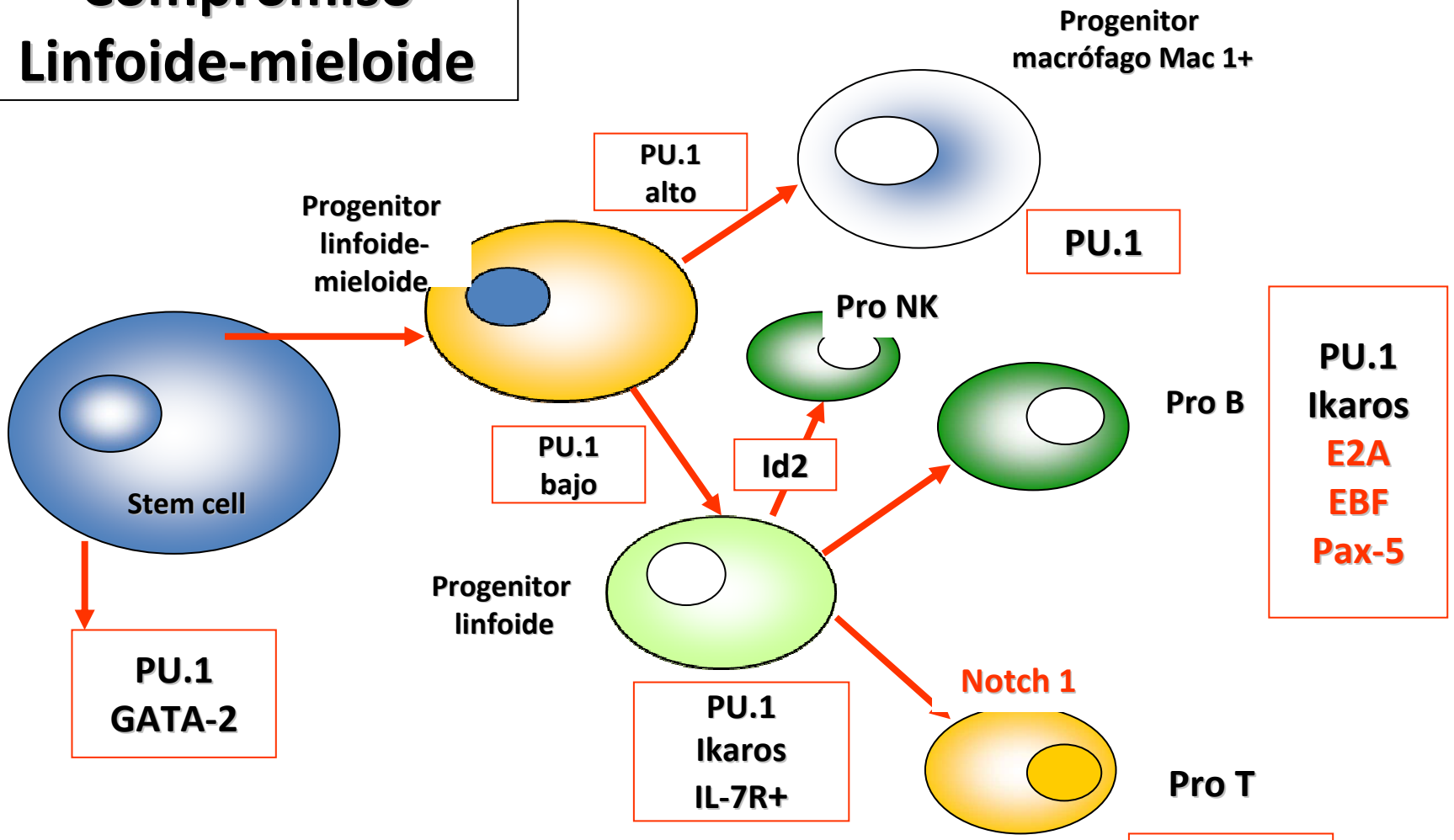
- Selección **NEGATIVA** de células autorreactivas

AUTOTOLERANCIA

- Diferenciación de los timocitos a distintos tipos celulares

Linfocitos NKT
Linfocitos Tγδ
Linfocitos T CD4+ (TH1/TH2/TH3/TH17/Thf)
Linfocitos T CD8+ (LTc)

Compromiso Linfoide-mieloide

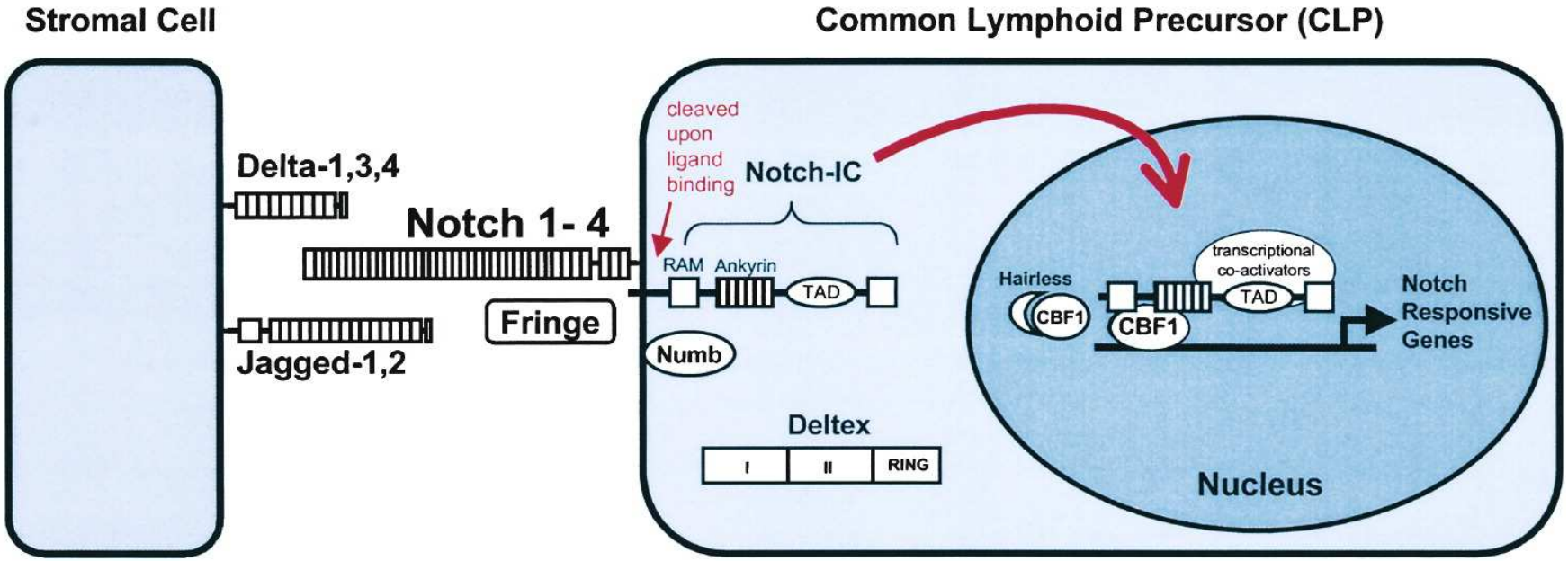


Factores de transcripción involucrados en el compromiso linfoide-mieloide en médula ósea

Para recordar

- **PU.1 (pertenece a la familia Ets) ha sido implicado recientemente en la determinación y compromiso temprano hacia linajes mieloides y linfoides**
- **E2A (perteneciente a la familia de factores *helix-loop-helix) y* EBF*(early-B cell factor)* están implicados en la iniciación de la linfopoyesis B. Estos dos factores regulan la expresión espacio temporal de las recombinasas RAG-1/RAG-2, esenciales en el proceso de recombinación V(D)J de los genes de inmunoglobulinas.**
- **Pax-5 es esencial junto a E2A y EBF para lograr un total compromiso hacia el linaje B**
- **La señalización vía Notch 1 permite el desarrollo temprano de células T.**
- **Id2 pertenece a la familia *helix-loop-helix* y está comprometido en el desarrollo de células NK; actuaría secuestrando E2A controlando así la maduración del linaje NK.**

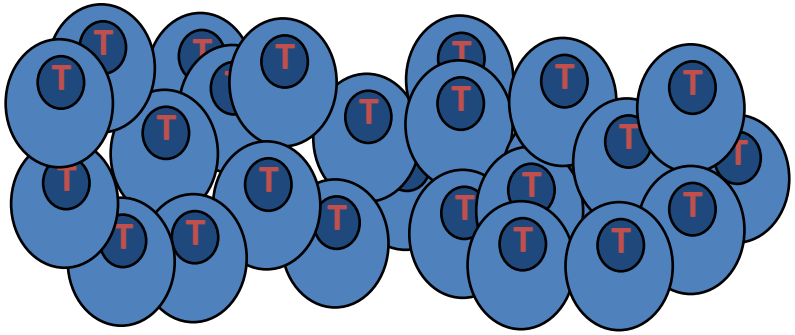
Rol de Notch en la "*elección*" del linaje T



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

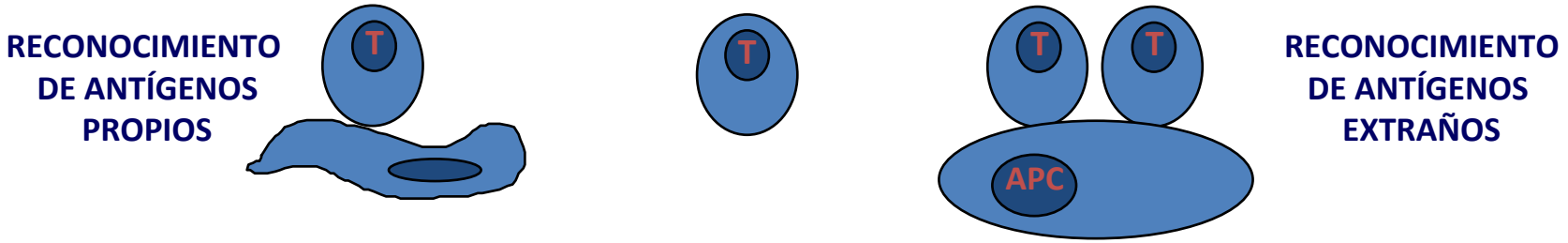
Lehar and Bevan, Immunity, 17:689, 2002

¿Por qué se necesita un MECANISMO DE SELECCIÓN DEL REPERTORIO y de TOLERANCIA A LO PROPIO?



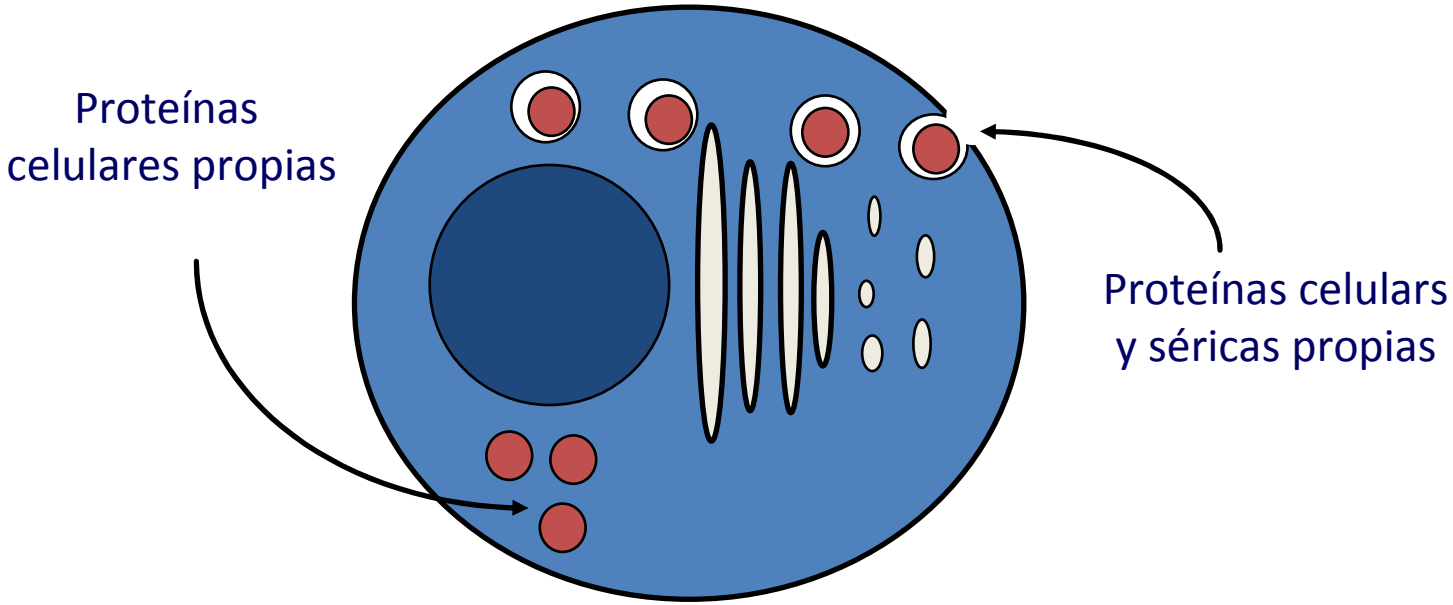
LA GENERACIÓN DEL REPERTORIO DE TCR INVOLUCRA MECANISMOS AL AZAR....

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



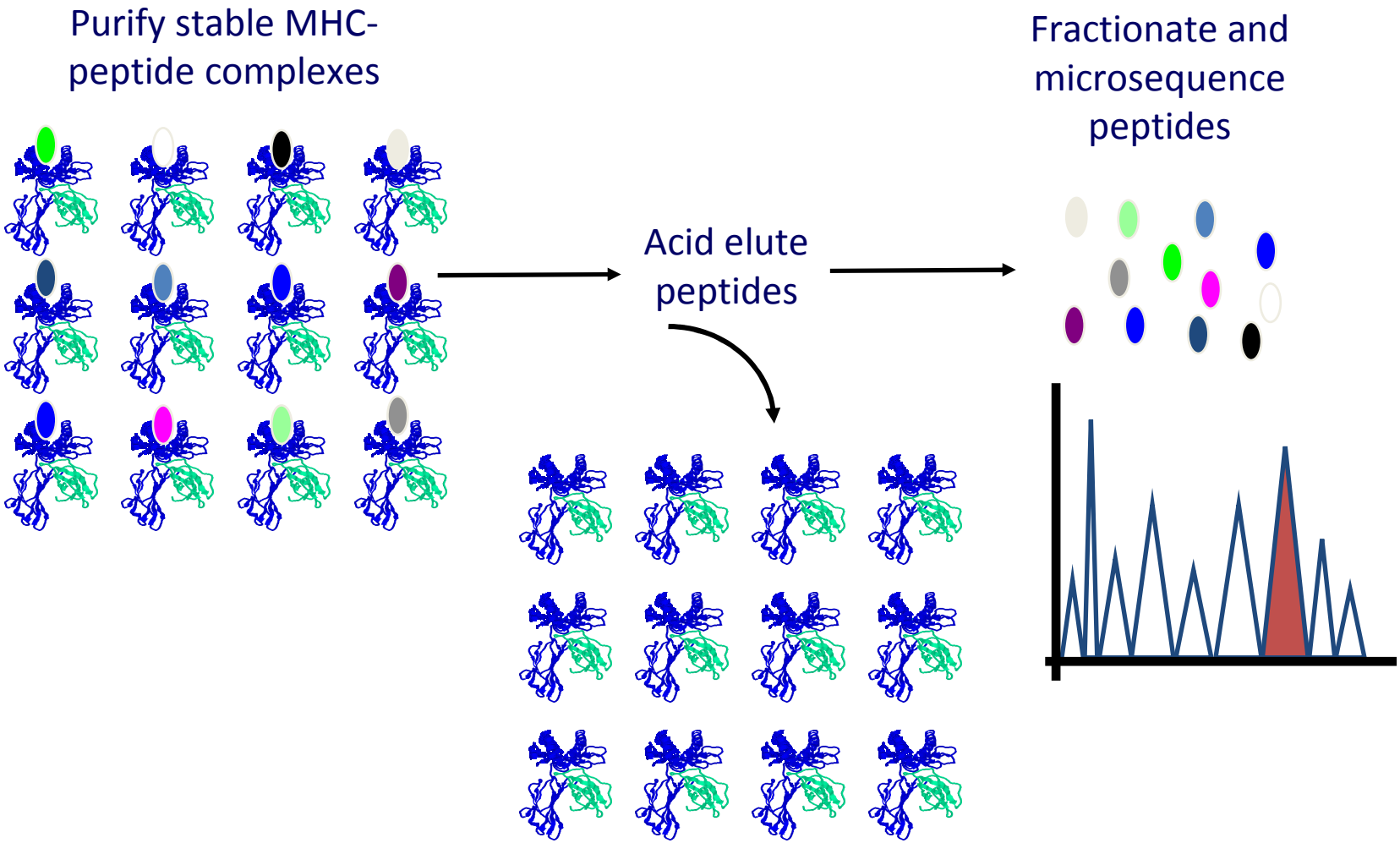
1. DAÑINOS 2. INÚTILES 3. ÚTILES

LAS PROTEÍNAS PROPIAS SON DEGRADADAS POR DISTINTAS VÍAS



LAS VÍAS DE PROCESMIENTO NO DISTINGUEN ENTRE PROPIO Y EXTRAÑO

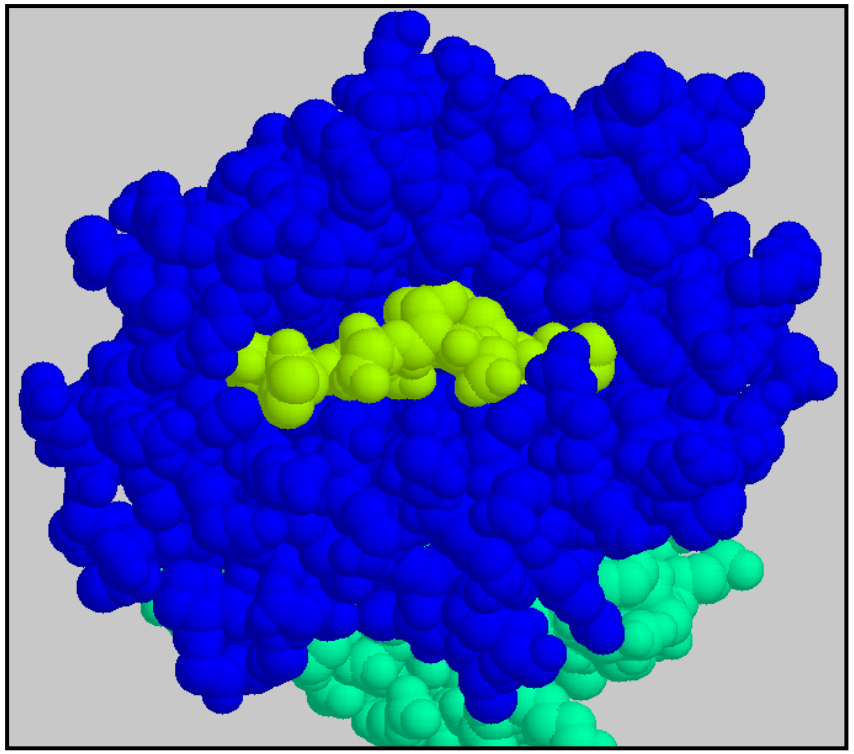
Los péptidos propios se “CARGAN” en MHC class I y II

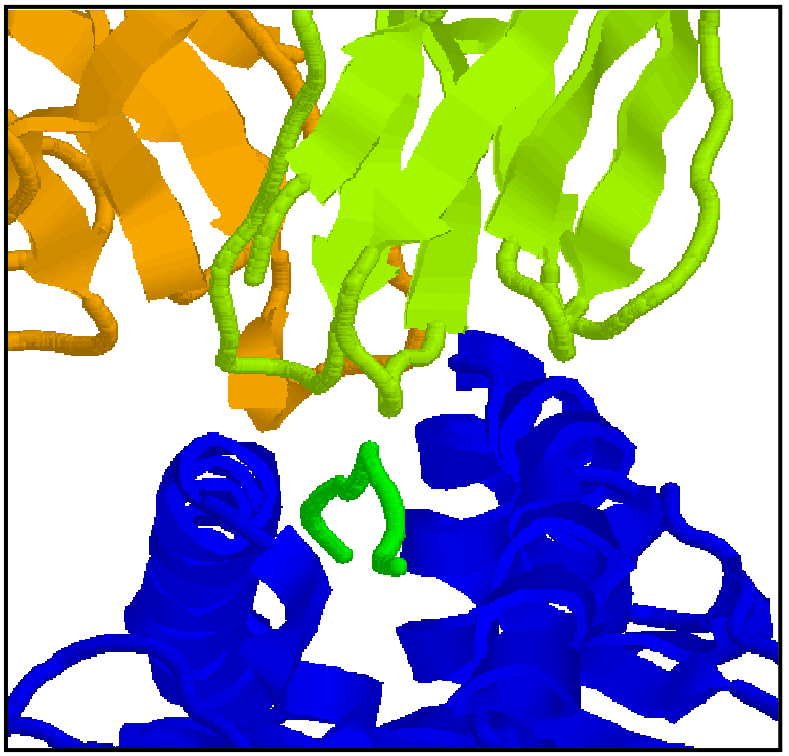


>90% de los péptidos eluidos provienen de proteínas propias.....

Los antígenos propios usualmente no activan células T.....

El sistema inmune permite un limitado grado de reconocimiento de lo propio....





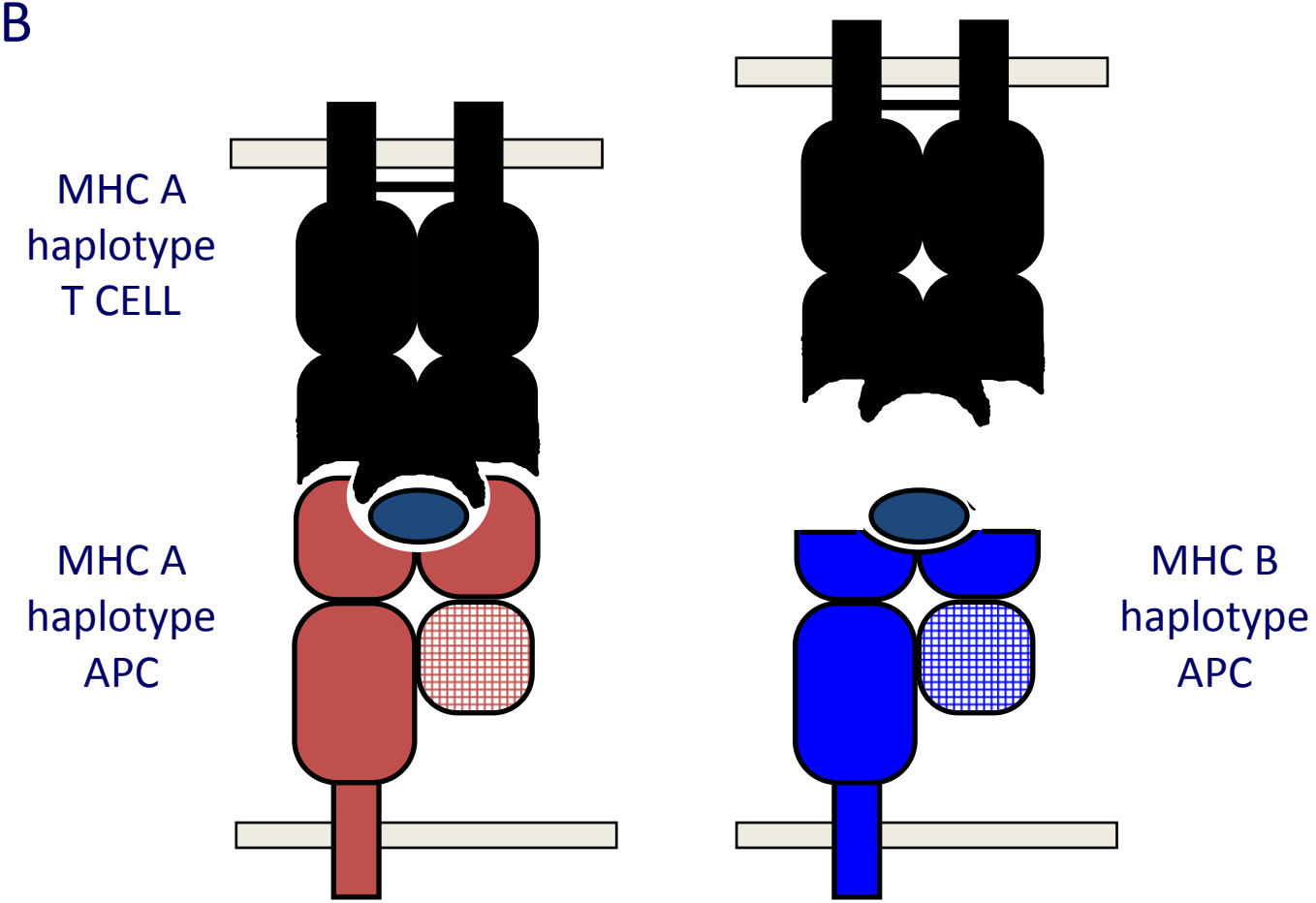
TCRs reconoce el péptido extraño y el MHC

Las moléculas MHC RESTRINGEN LA ACTIVACIÓN DE CÉLULA T

PERO.... ¿cómo las células T aprenden cuánto del renocimiento propio es aceptable???

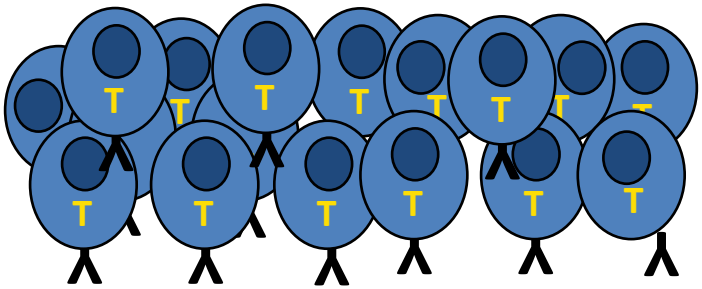
Las células T sólo podrán desarrollarse si sus TCR reconocen parte del MHC propio

Explica por qué las células T del haplotipo MHC A no reconocen el antígeno específico presentado por el haplotipo MHC B

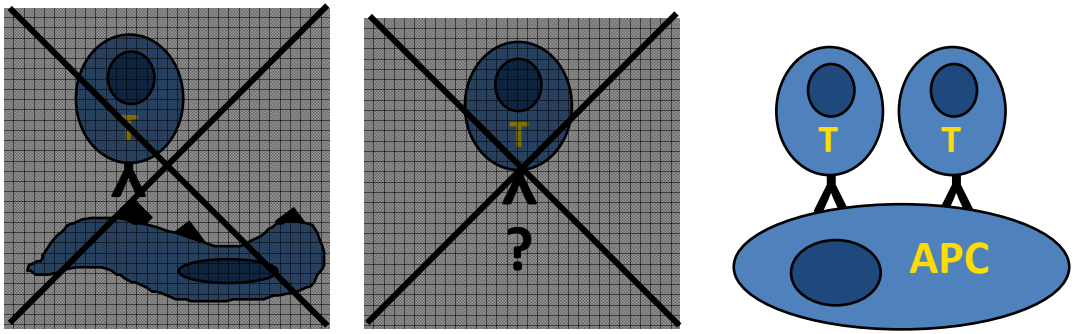


Todas las células autorreactivas o inútiles son removidas.....Sin embargo las MHC-restrictas son retenidas....

Random TcR repertoire ensures diversity



TiMo



Harmful

Selección NEGATIVA

Useless

MUERTE POR NEGLICENCIA

Useful

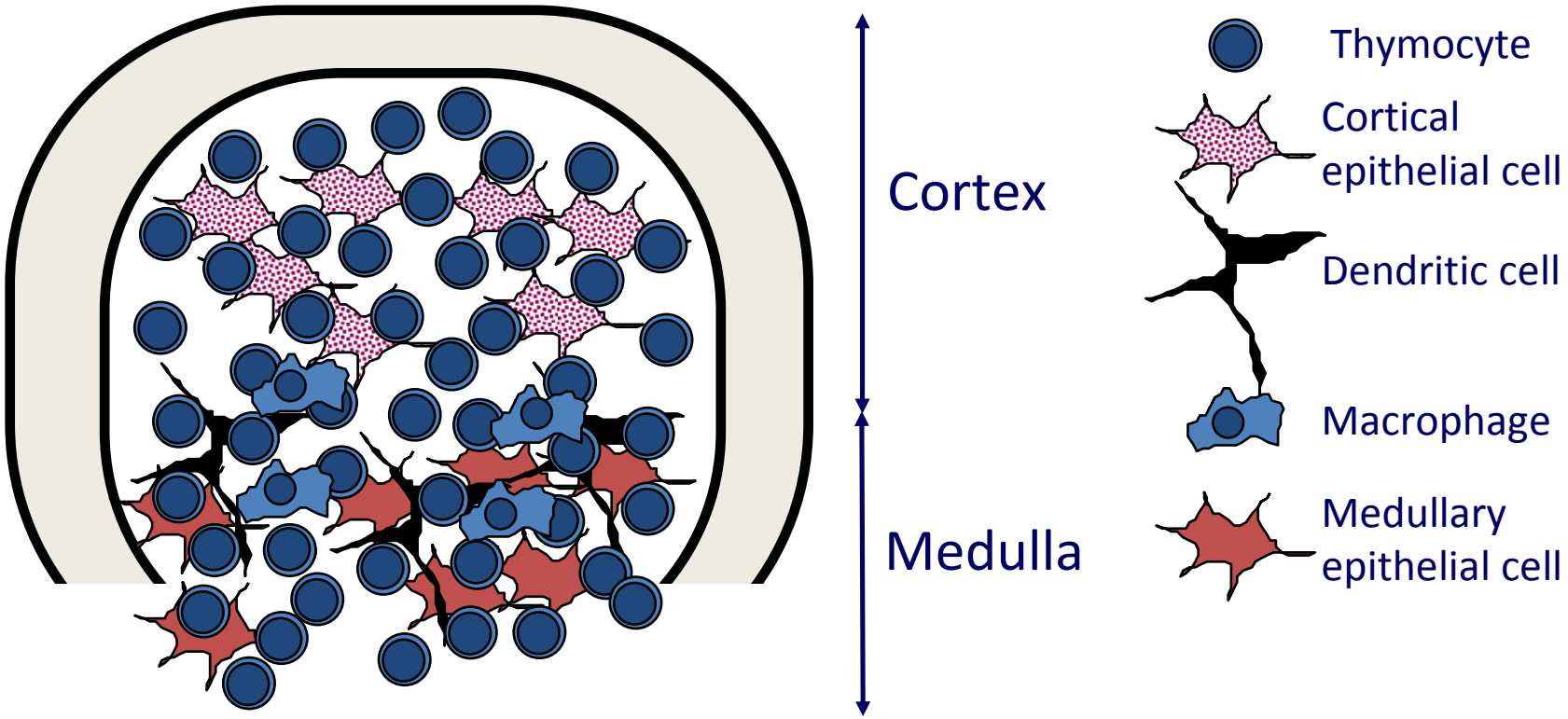
SELECCIÓN POSITIVA

EL TIMO

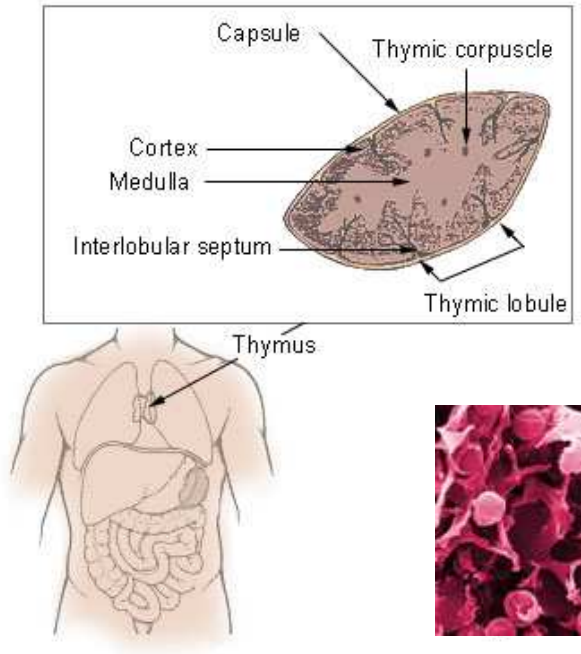
Lobulated structure with a STROMA of epithelial cells & connective tissue

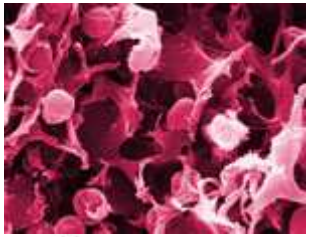
Stroma provides a microenvironment for T cell development & selection

Lobules differentiated into an outer CORTEX & inner MEDULLA, both filled with bone-marrow-derived THYMOCYTES



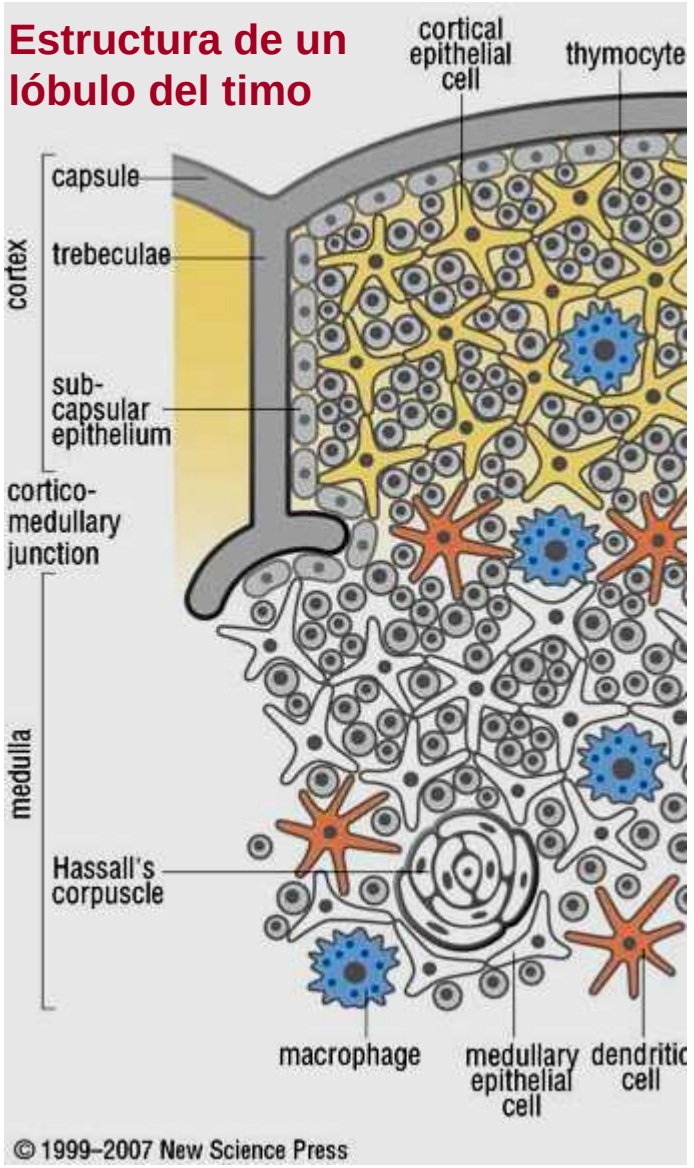
El desarrollo de los linfocitos T comienza en la médula ósea y pero los eventos más importantes ocurren en el timo



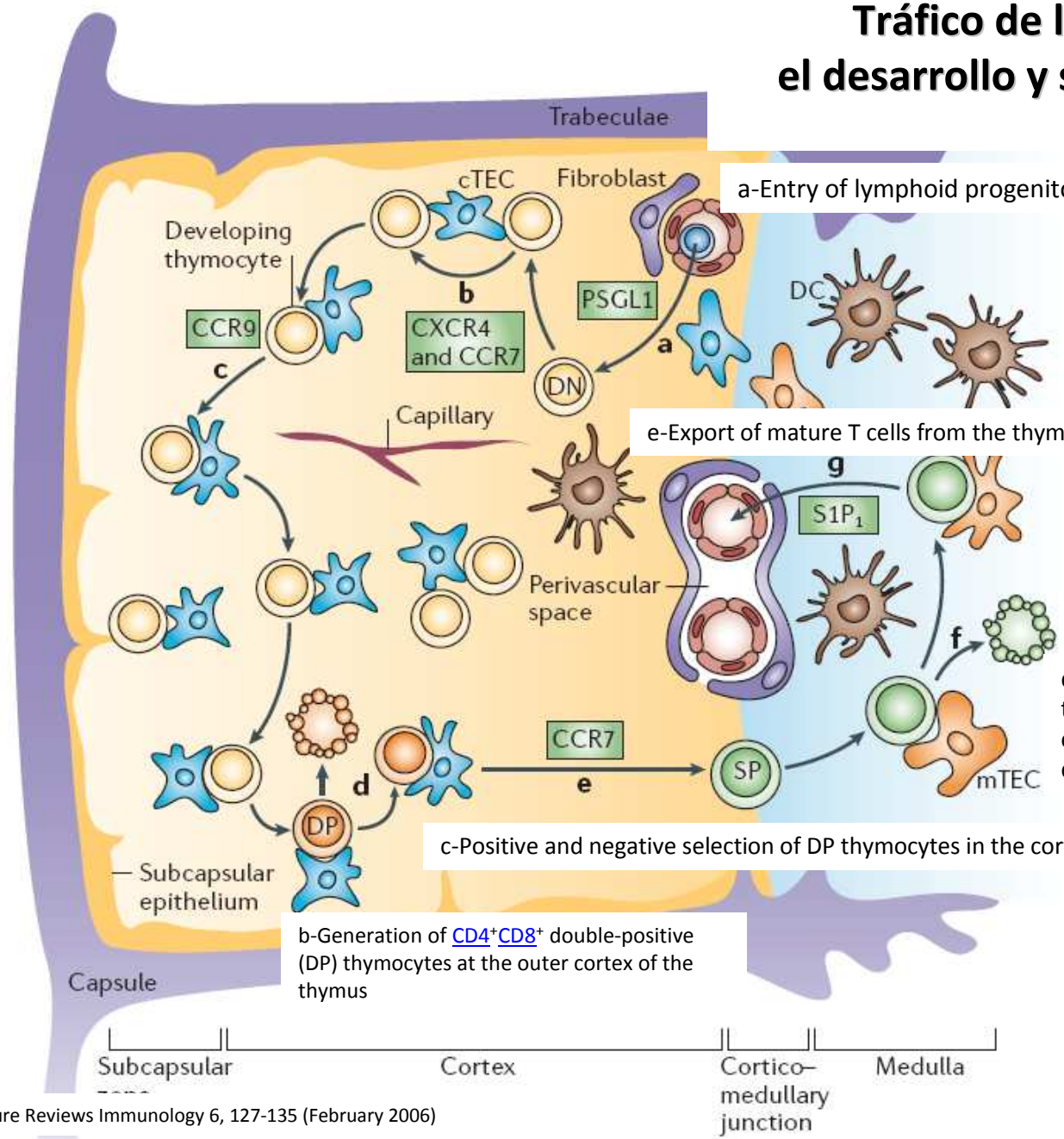


Síndrome de DiGeorge,
Carencia congénita de timo

Estructura de un lóbulo del timo



Tráfico de linfocitos durante el desarrollo y selección de células T



a-Entry of lymphoid progenitor cells into the thymus

The thymus is an organ that supports the differentiation and selection of T cells.

The thymic development of T cells consists of several processes that require the dynamic relocation of developing lymphocytes into, within and out of the multiple environments of the thymus .

d-Interaction of positively selected thymocytes with medullary thymic epithelial cells (mTECs) to complete thymocyte development and ensure central tolerance

PSGL1:platelet-selectin glycoprotein ligand 1.

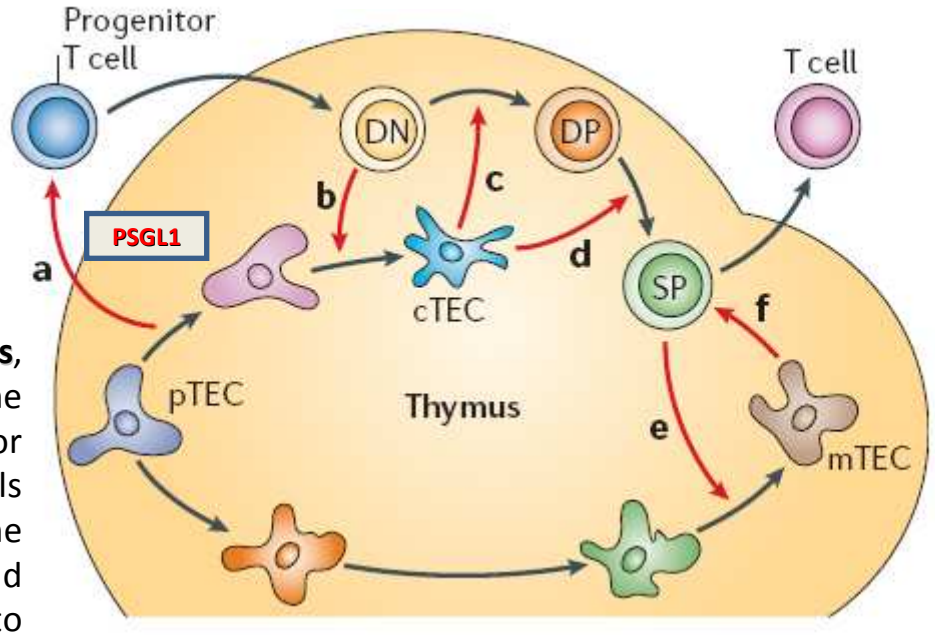
$S1P_1$: sphingosine-1-phosphate receptor 1 .

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

Rol de las células estromales tímicas

The developing double-negative (DN) thymocytes are required for pTECs to generate cortical thymic epithelial cells (cTECs) (signal b) that form the cortical environment that is needed to promote the generation of double-positive (DP) thymocytes (signal c) and the positive selection of DP thymocytes (signal d).

Thymic stromal cells, including the common progenitor thymic epithelial cells (pTECs), attract the entry of T-lymphoid progenitor cells to the thymus (signal a).



PSGL1:platelet-selectin glycoprotein ligand 1.

pTEC: common progenitor thymic epithelial cells

cTEC: cortical thymic epithelial cells

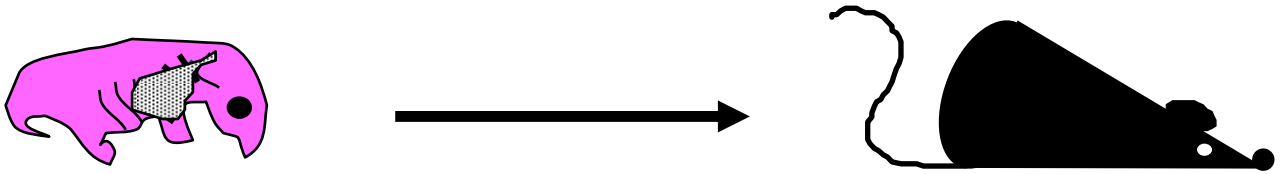
mTEC: medullary thymic epithelial cells

The generation of single-positive (SP) thymocytes by the positive selection of DP thymocytes is required for the development of mature medullary thymic epithelial cells (mTECs) (signal e) that form the medullary environment to support the maturation, further selection and export of mature SP thymocytes (signal f) to supply the peripheral T-cell pool. Red arrows indicate crosstalk signals.

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

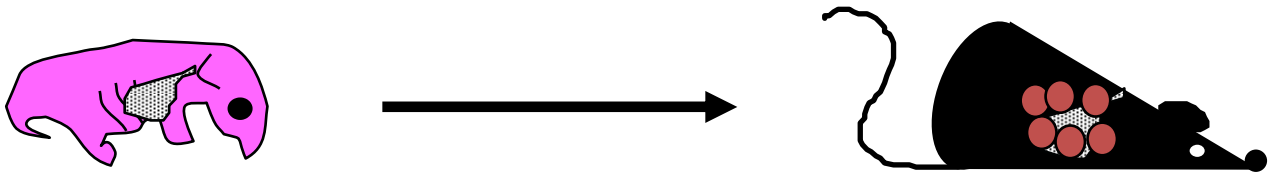
EL TIMO SE REQUIERE PARA LA MADURACIÓN DE CÉLULAS T

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



Neonatal thymectomy

No mature T cells
In adult

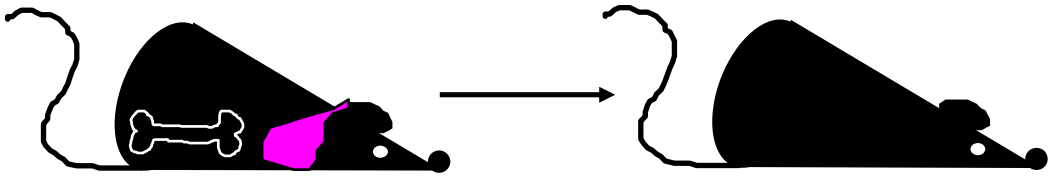


Thymus intact

Mature T cells
In adult

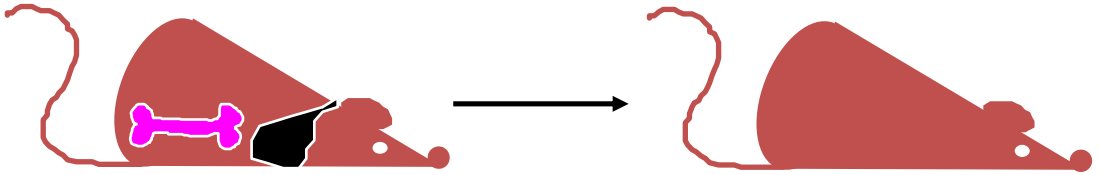
Roles DE LA MÉDULA ÓSEA Y EL TIMO EN LA MADURACIÓN DE CÉLULAS T

Defective lymphocyte production
Normal thymus
scid/scid



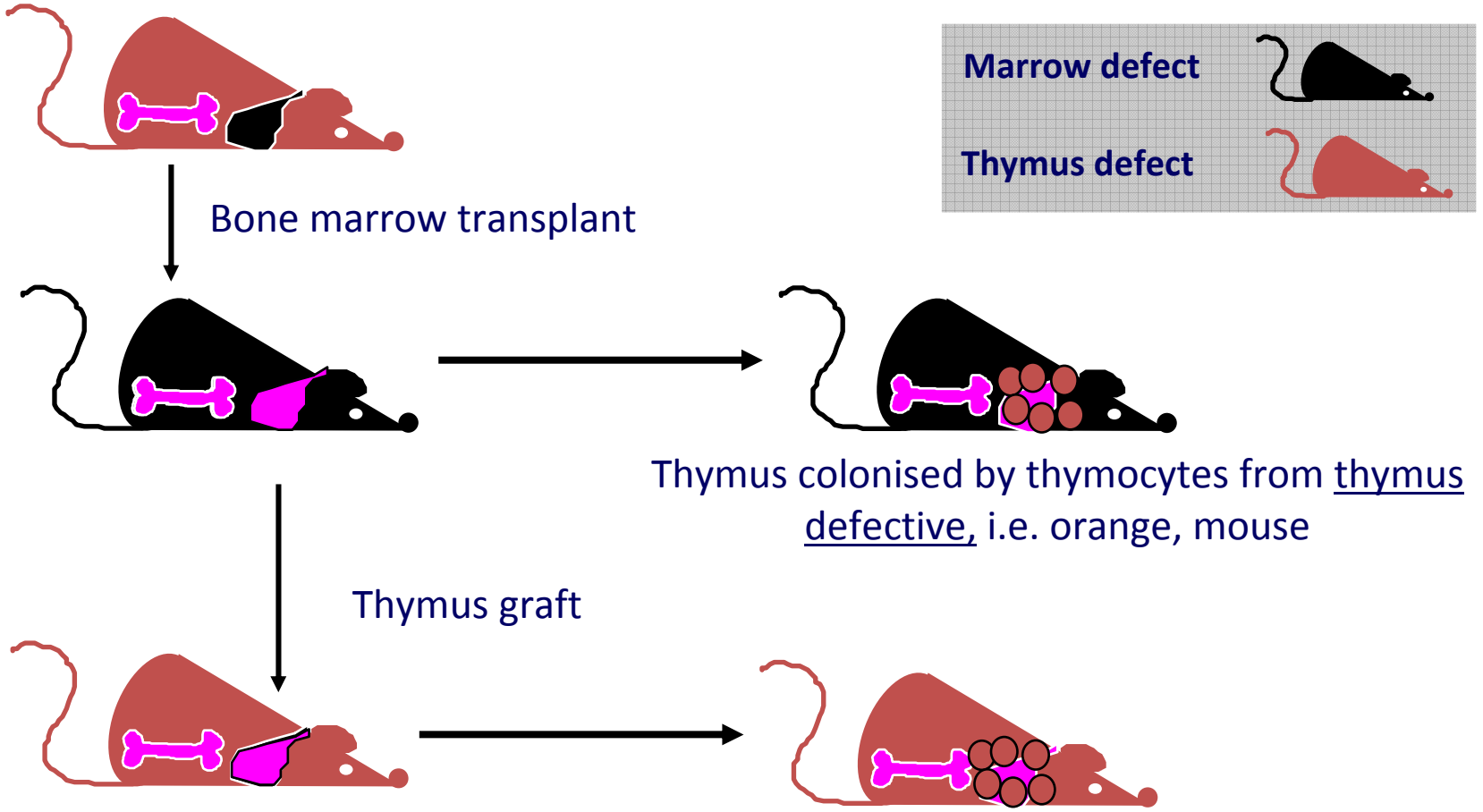
No mature T cells
In adults

Thymus defect
Normal bone marrow
nu/nu

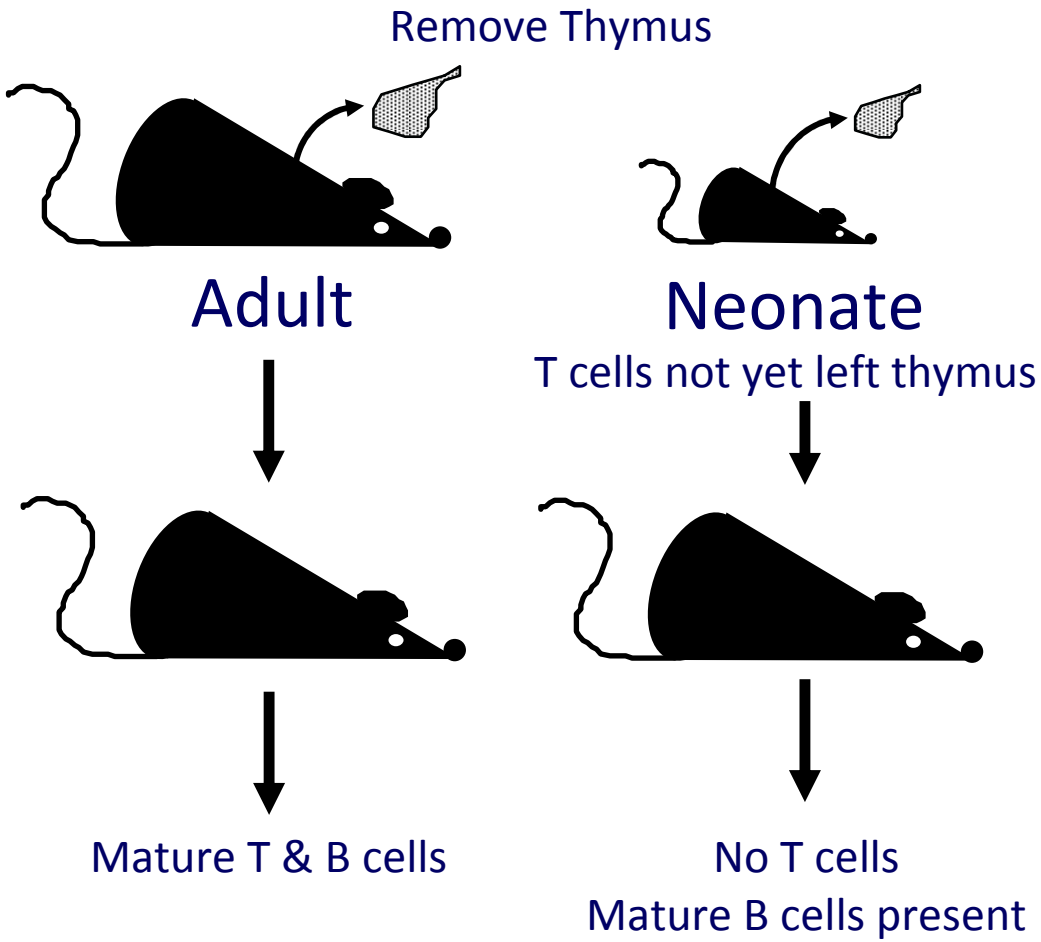


No mature T cells
In adults

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

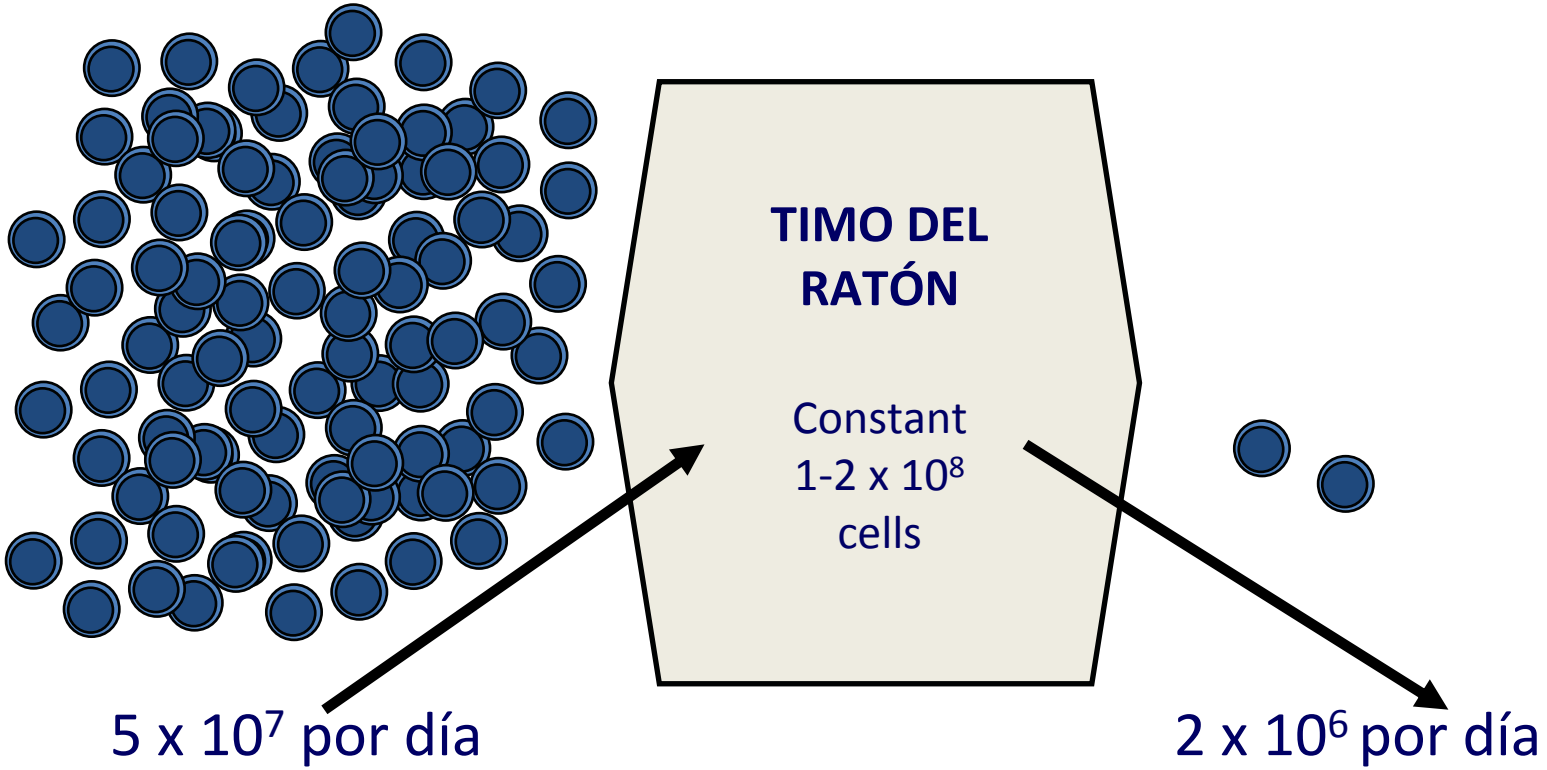


LAS CÉLULAS T MADURAN TEMPRANAMENTE EN LA VIDA....EN EL TIMO...



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

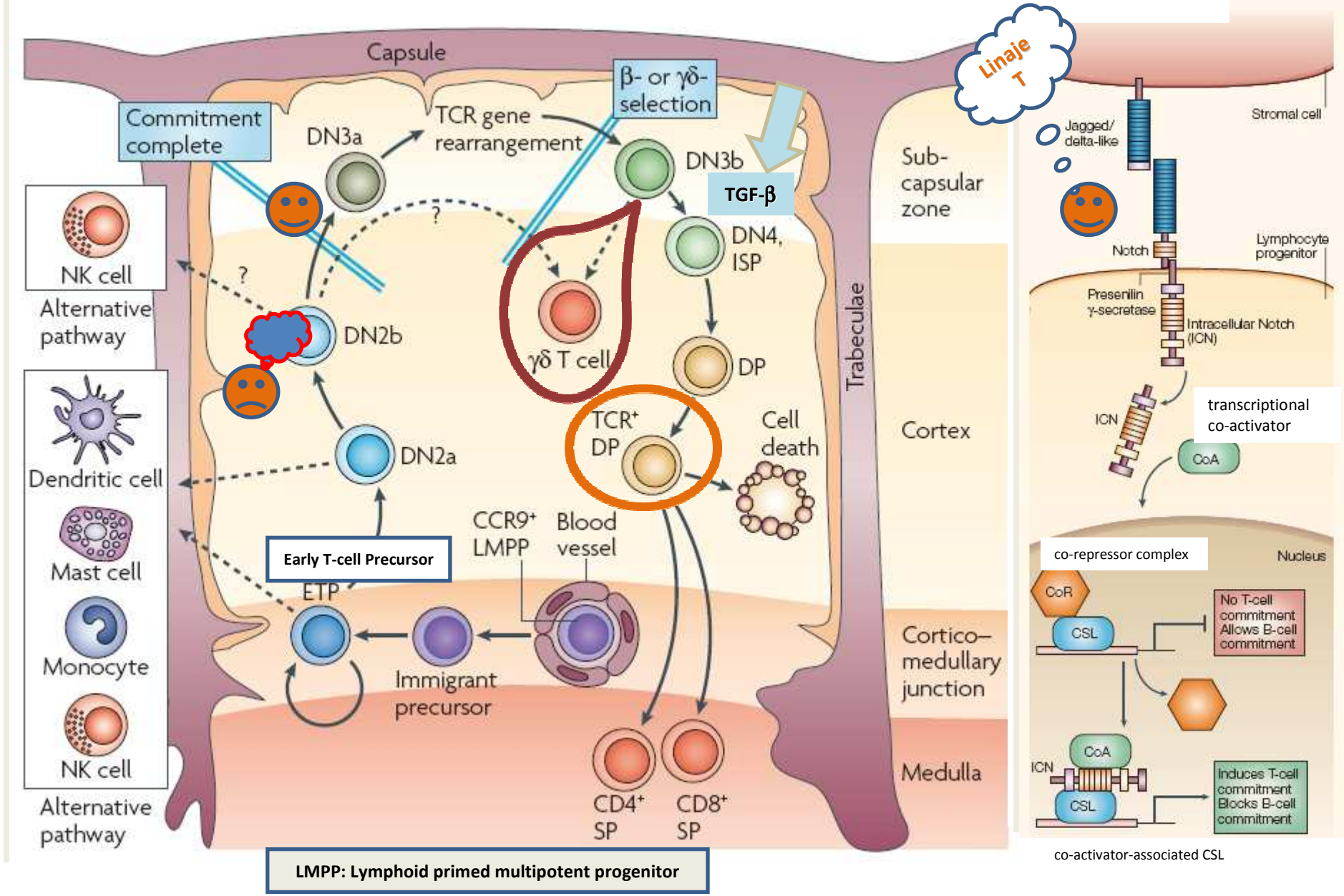
LAS CÉLULAS T MADURAN EN EL TIMO, PERO LA MAYORÍA DE ELLAS MUERE ALLÍ.....



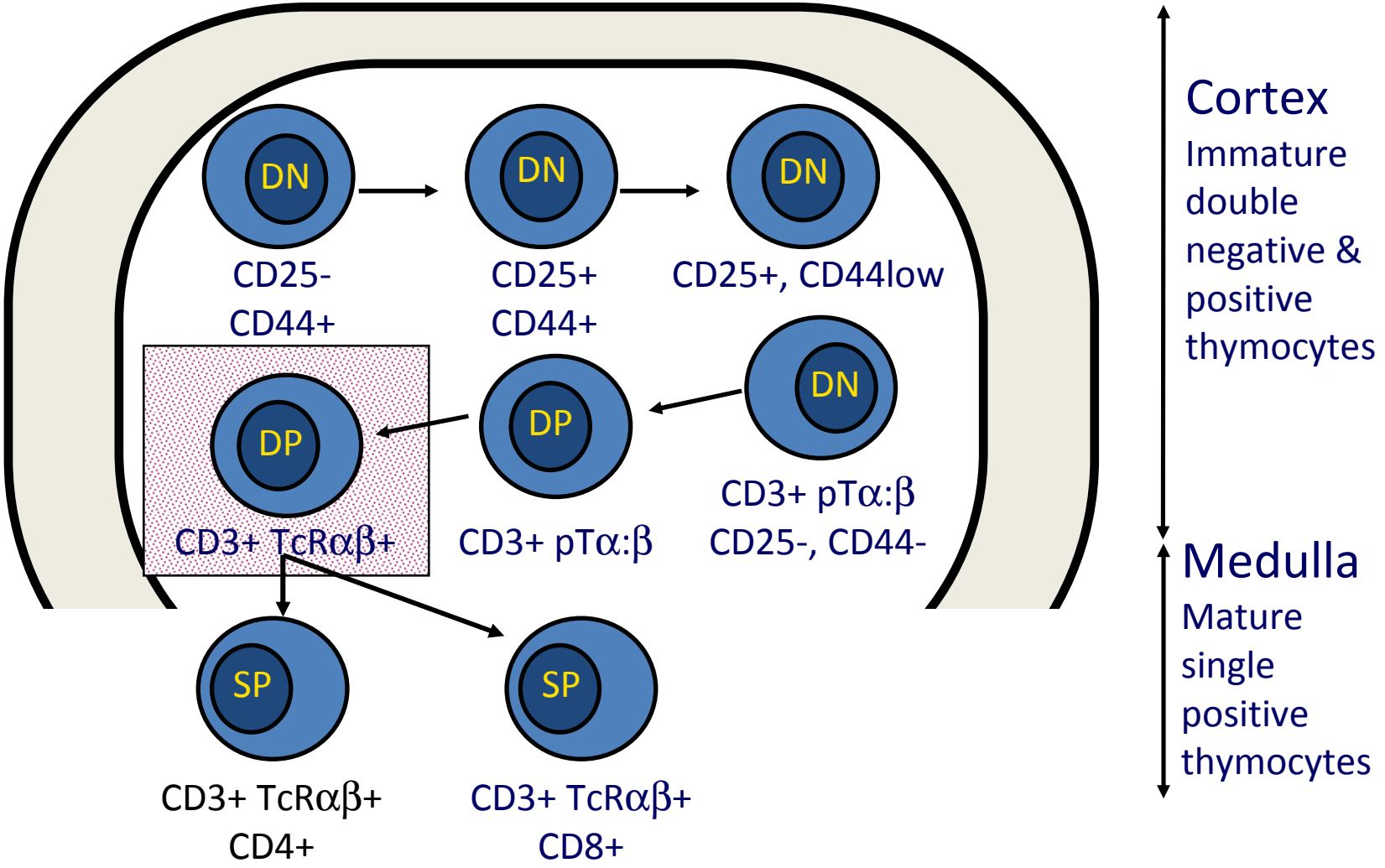
❖**98% de las células muere en el timo, sin inducir imflamación o cambios en el tamaño de la glándula....**

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

ESTAPAS EN EL DESARROLLO TEMPRANO DE CÉLULAS T

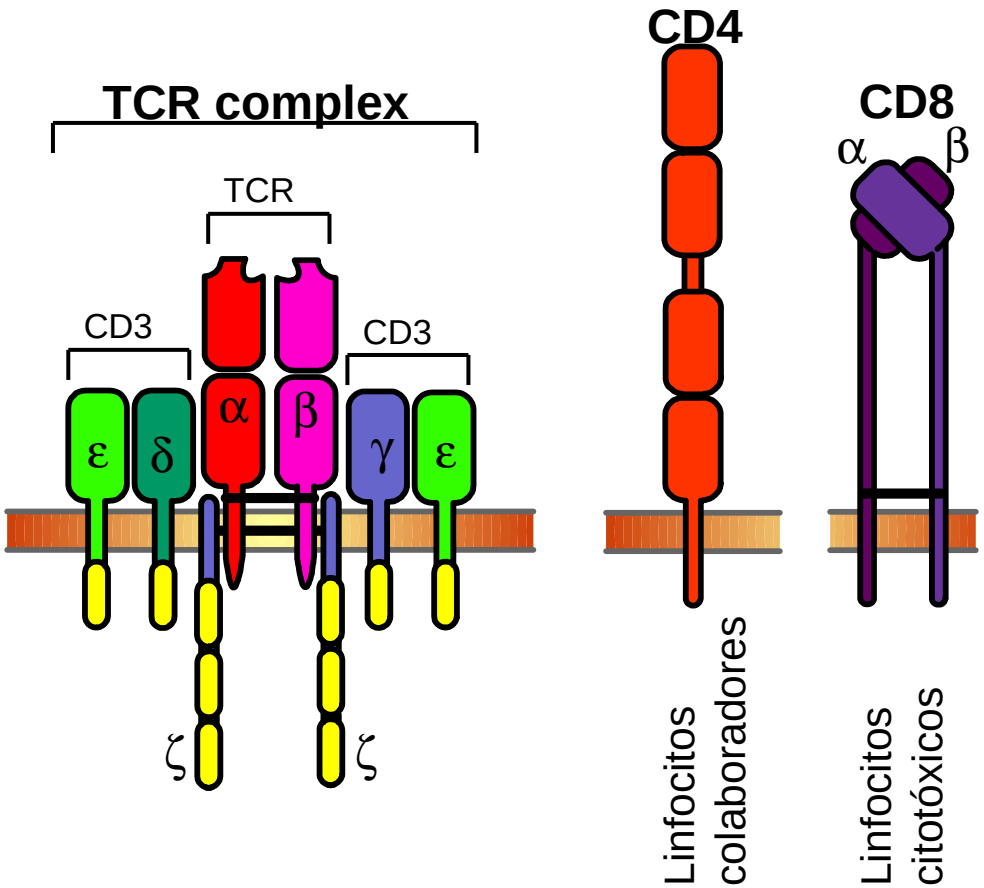


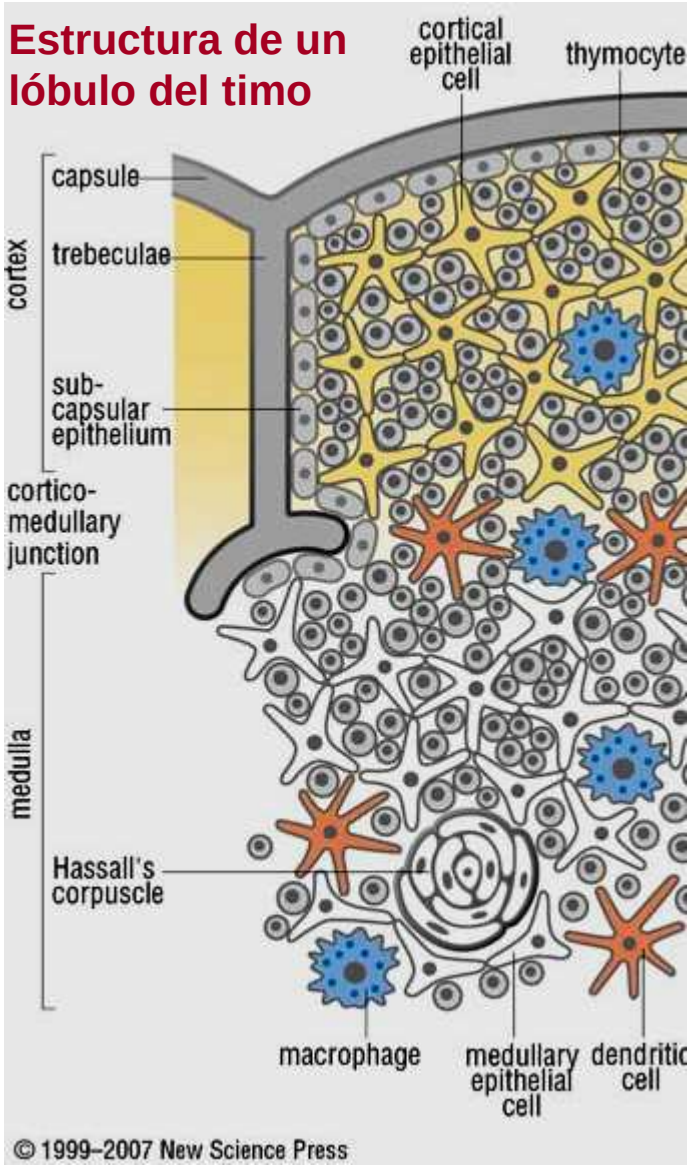
Etapas del desarrollo de timocitos en el TIMO



Durante el desarrollo los linfocitos adquieren los receptores característicos y se diferencian en distintos tipos de células T

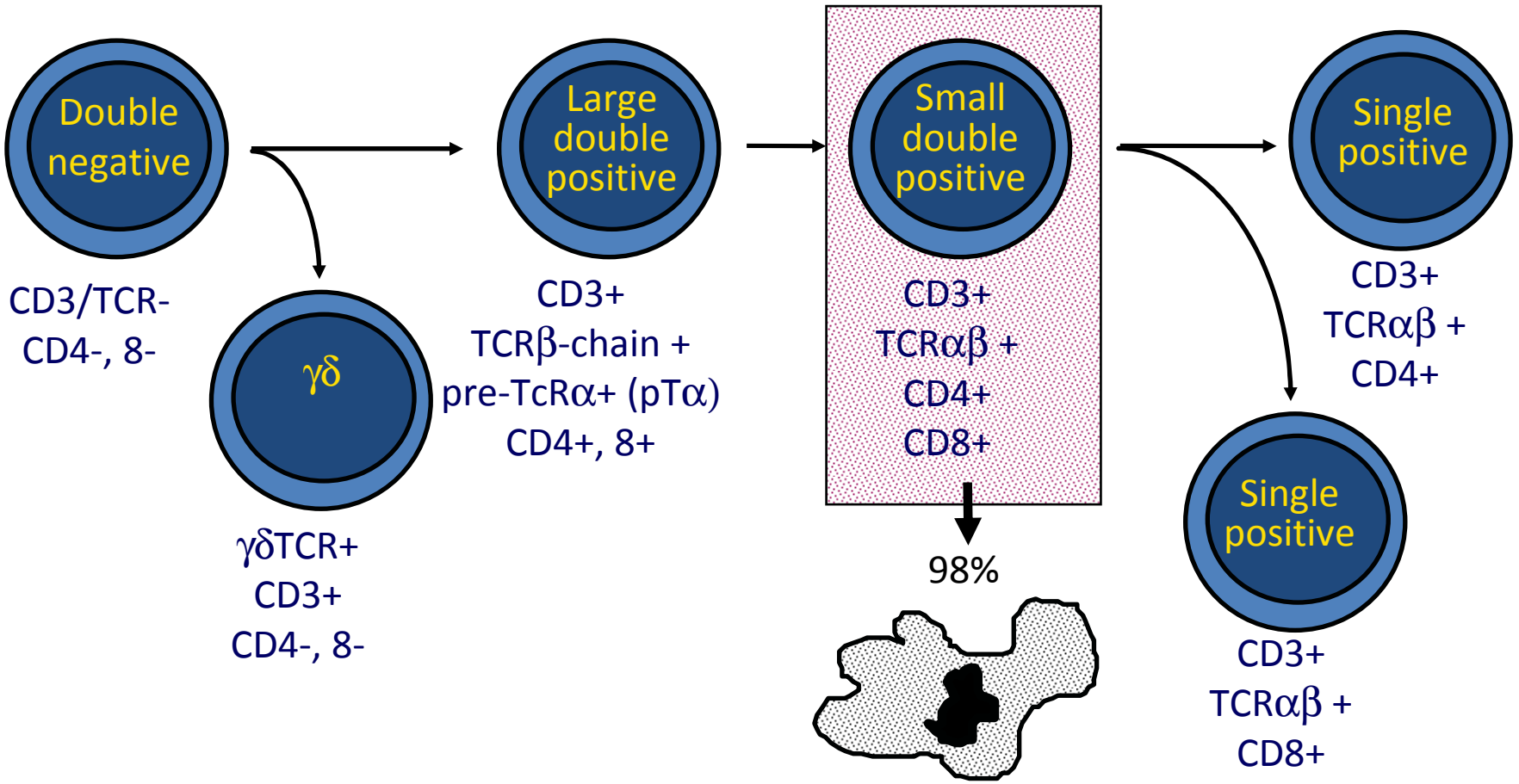
En el caso de los linfocitos T αβ ...





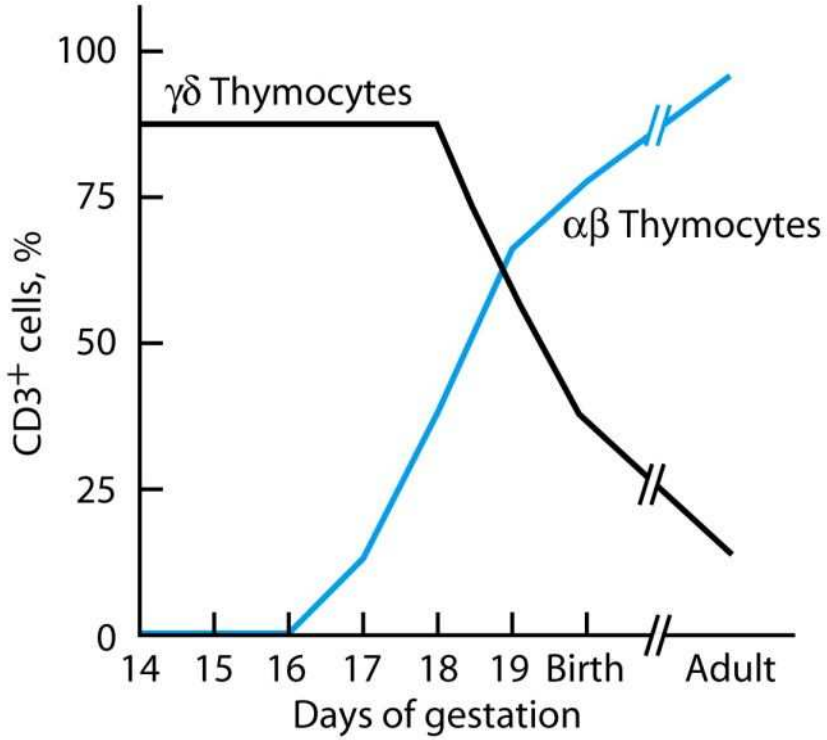
El desarrollo de la céllula T está marcado por el cambio de expresión de moléculas de superficie

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



Desarrollo de los LTγδ

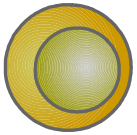
•En el ratón, la expresión del TCRγδ asociado a CD3 en la superficie celular, ocurre 3 o 4 días después de la llegada los precursores al timo, mientras que los TCRαβ se expresan 2 o 3 días más tarde.



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…….

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 ?

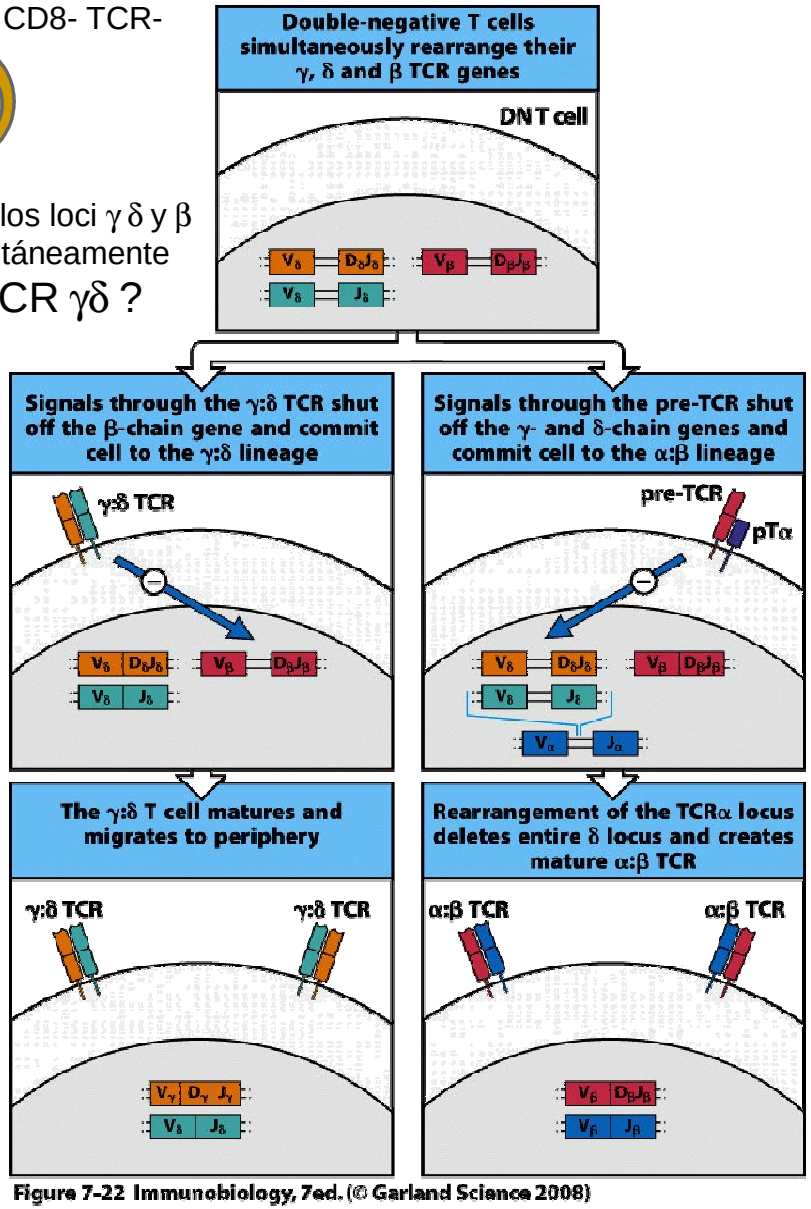
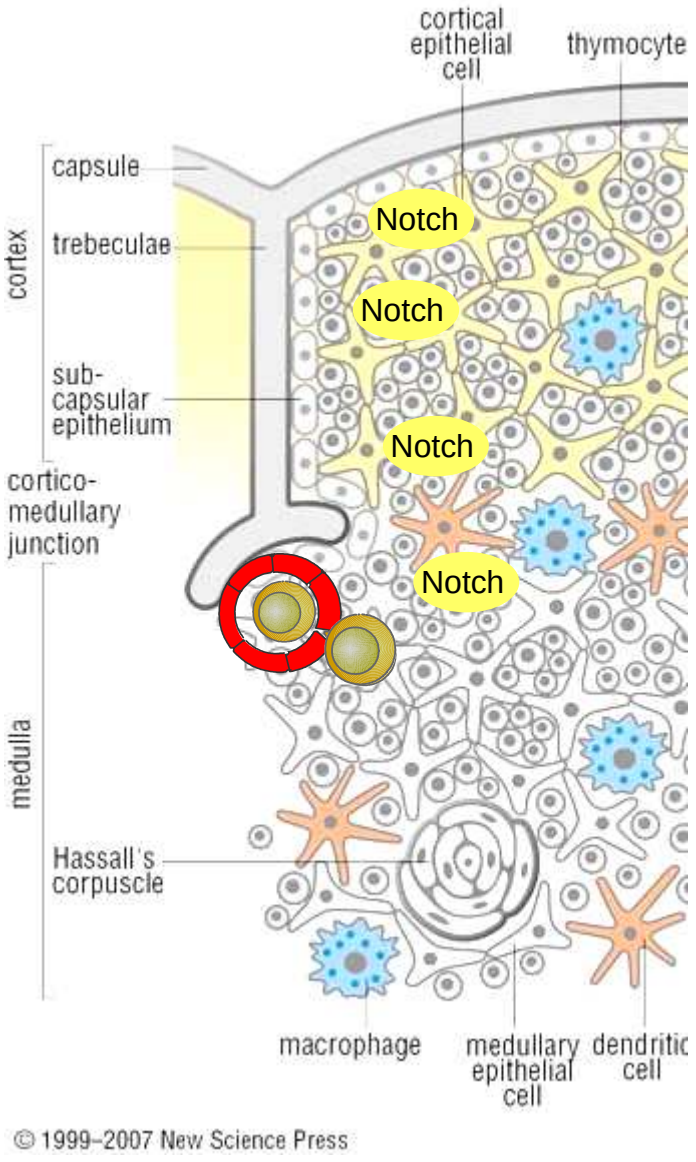
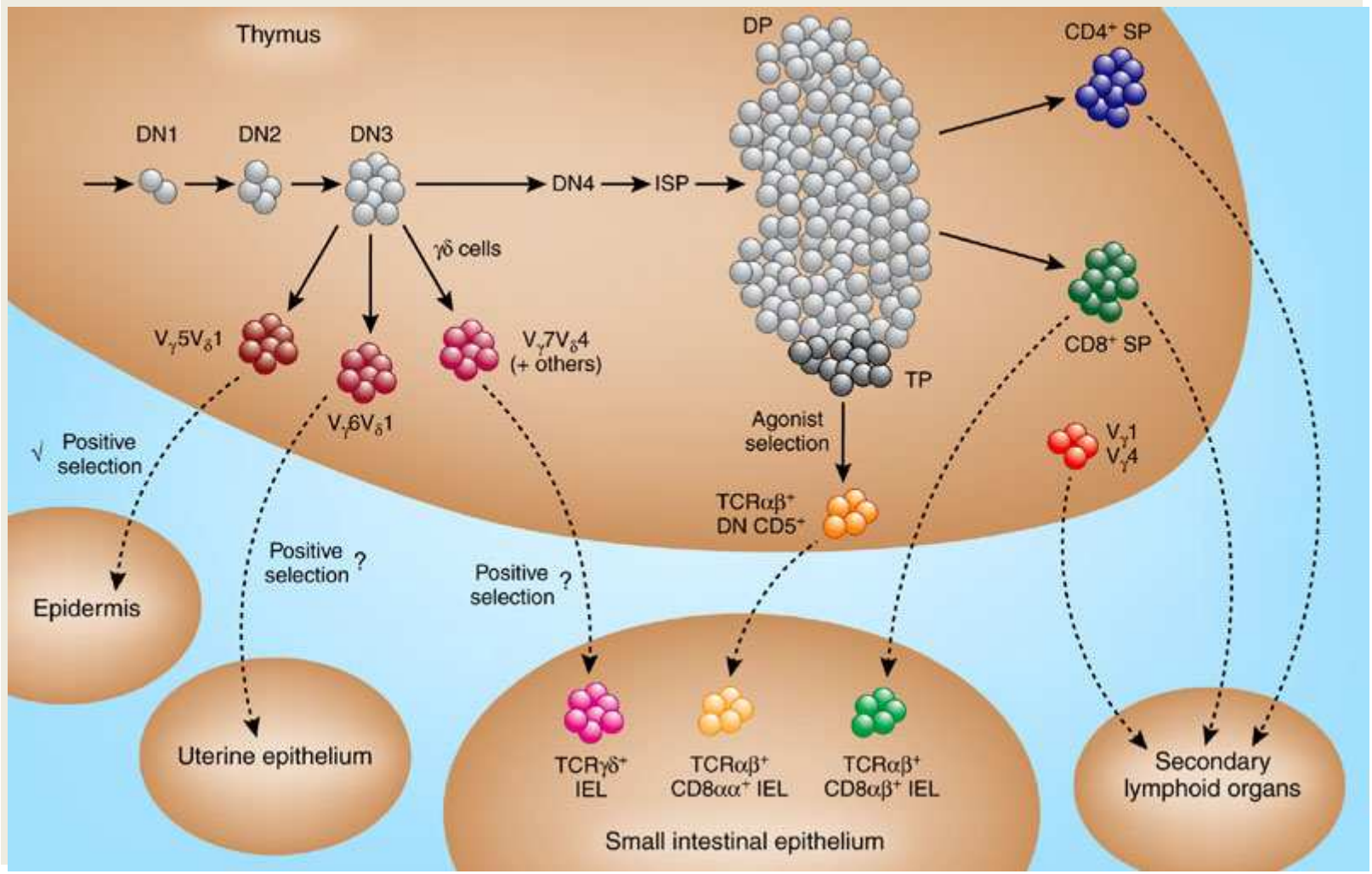


Figure 7-22 Immunobiology, 7ed. (© Garland Science 2008)





Nature Immunology 8, 137 - 144 (2007)

Generación del TCR: RECOMBINACIÓN SOMÁTICA

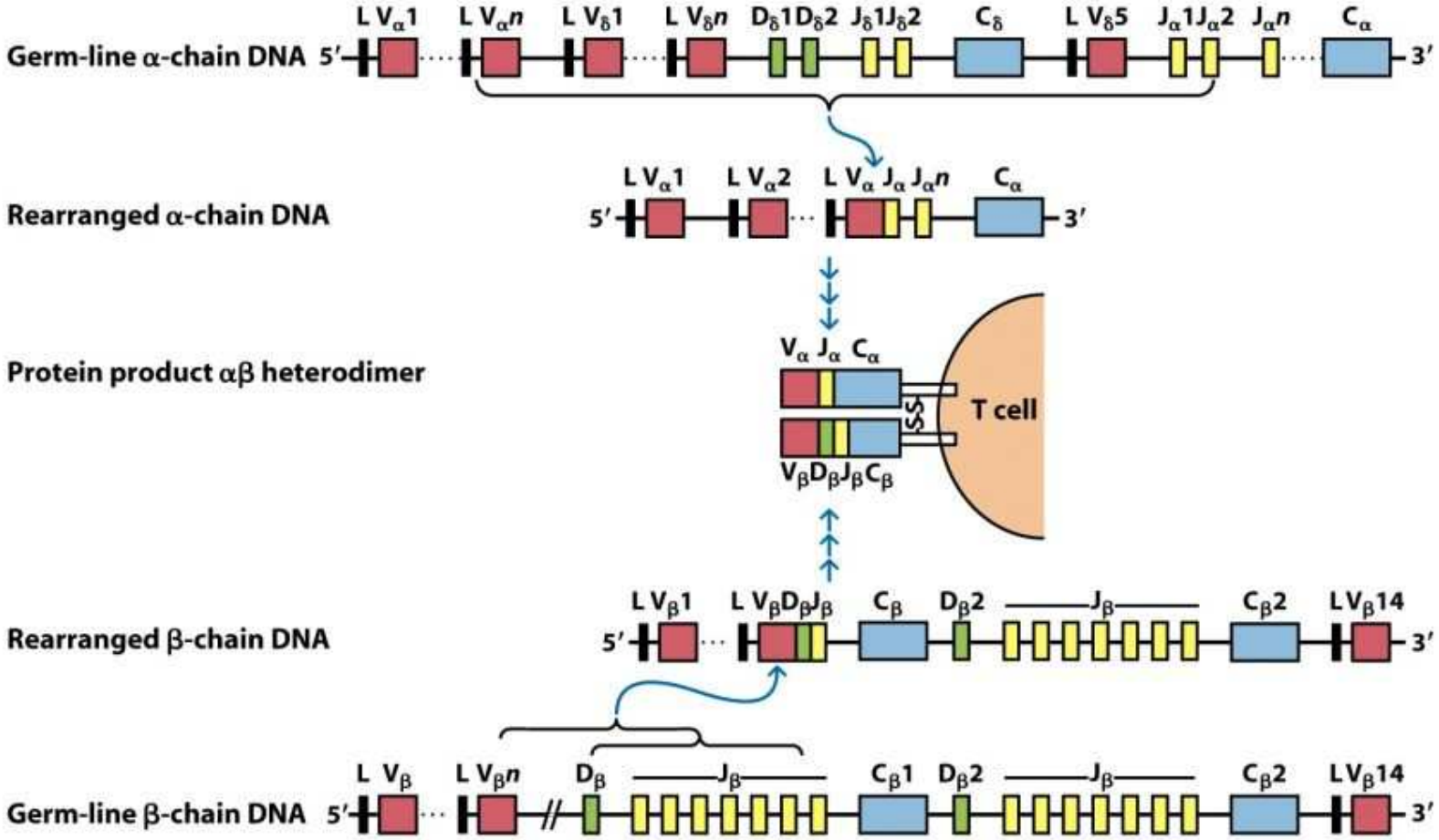


Figure 9-6
Kuby IMMUNOLOGY, Sixth Edition

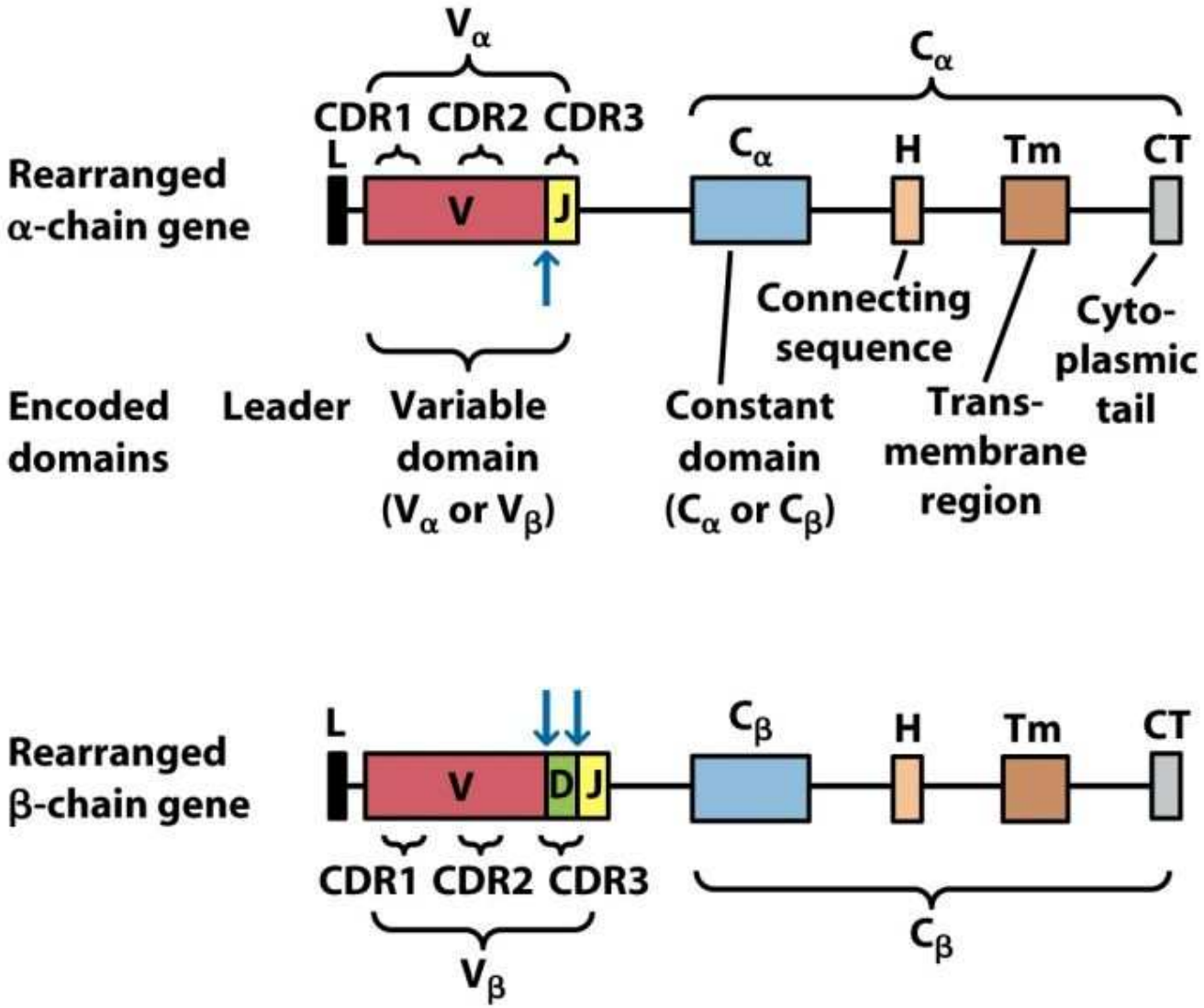


Figure 9-7
Kuby IMMUNOLOGY, Sixth Edition

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
Kuby IMMUNOLOGY, Sixth Edition

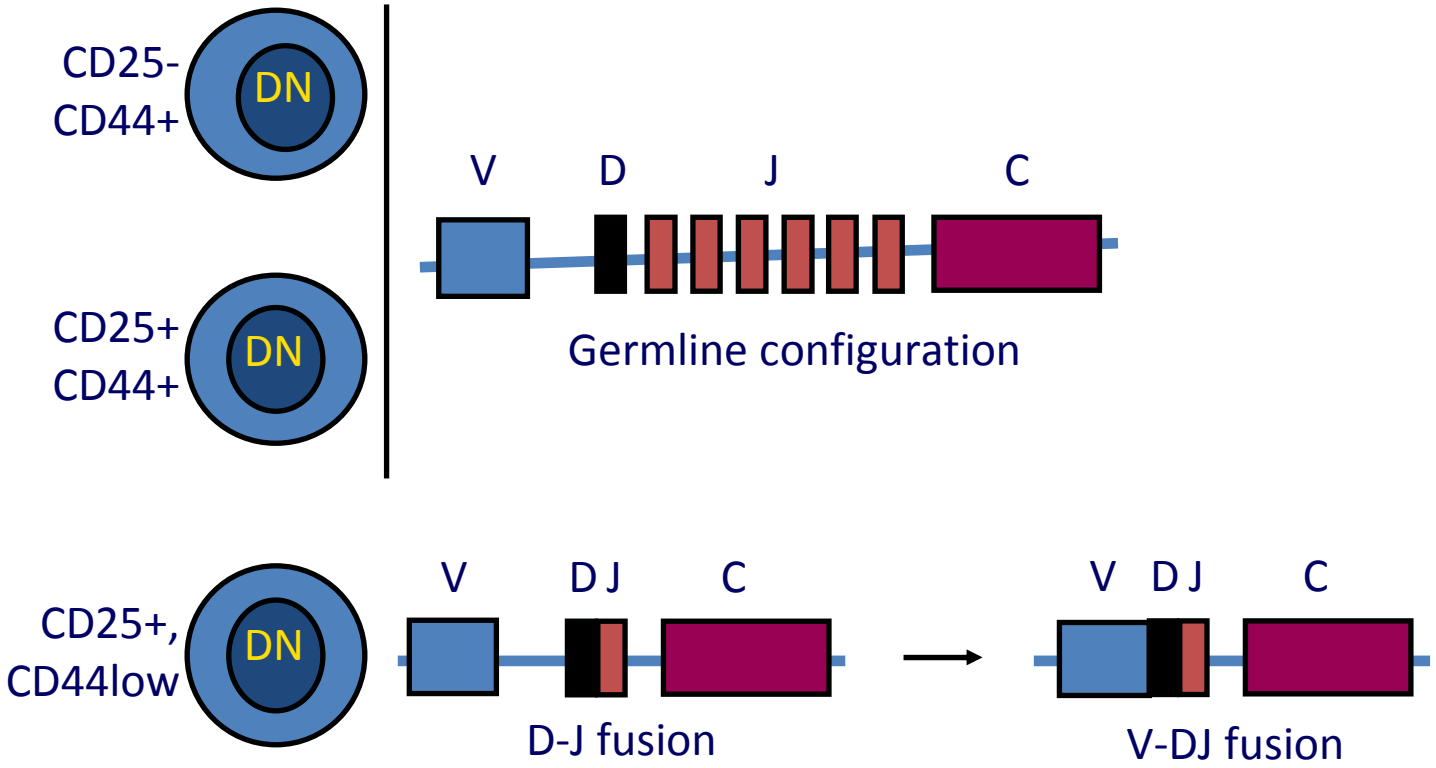
TABLE 9-3 Sources of possible diversity in mouse immunoglobulin and TCR genes

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.

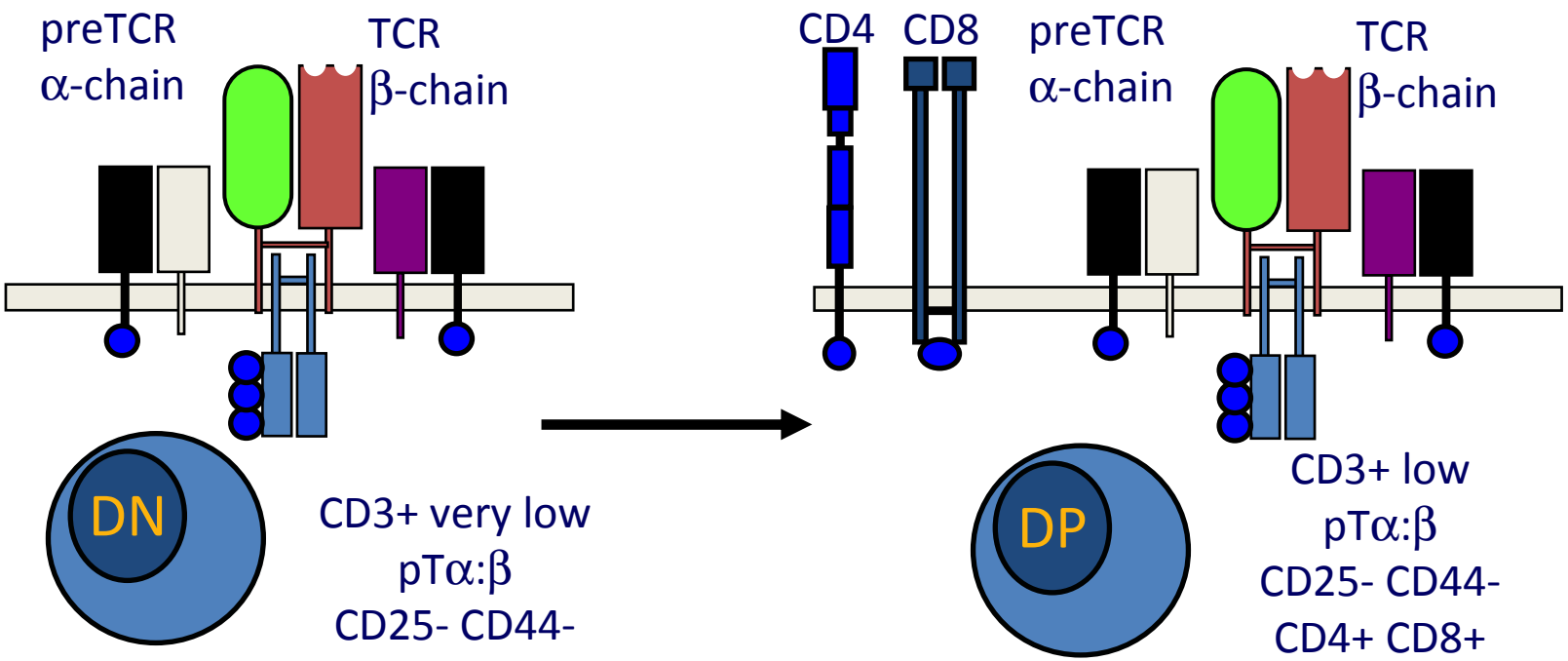
Table 9-3
Kuby IMMUNOLOGY, Sixth Edition

Rearreglo del TCRβ



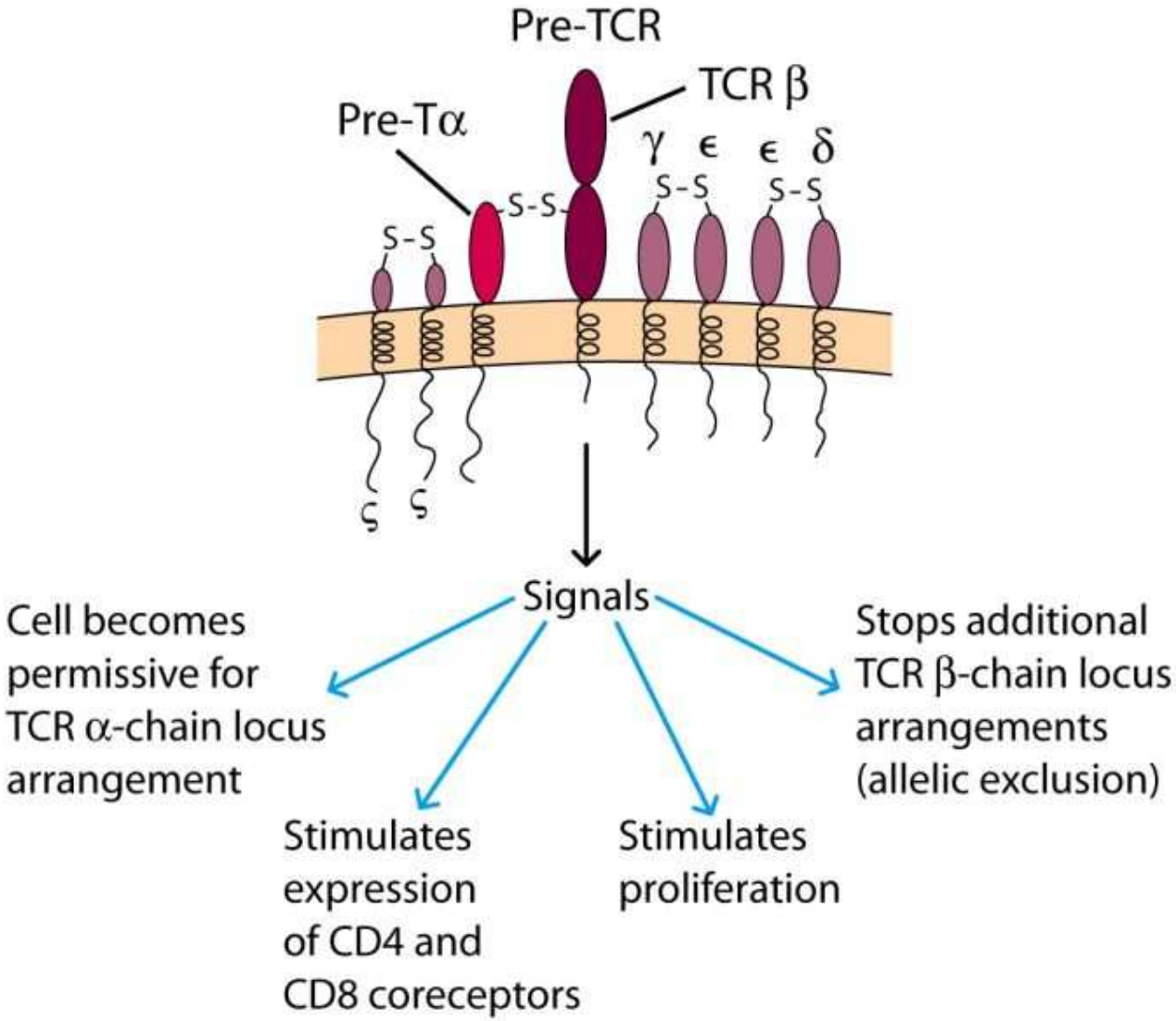
C region spliced to VDJ fusion and β-chain protein produced in cytoplasm
No TCR at cell surface

RECEPTOR Pre TCR

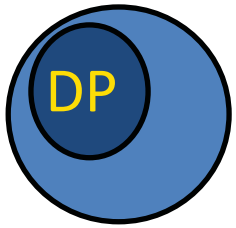


1. Cell proliferates rapidly to yield daughter cells with the same β chain
Expands only cells with in-frame TCR β chains

2. Successful β rearrangement shuts off β rearrangement on 2nd chromosome
Ensures only one specificity of TCR expressed per cell

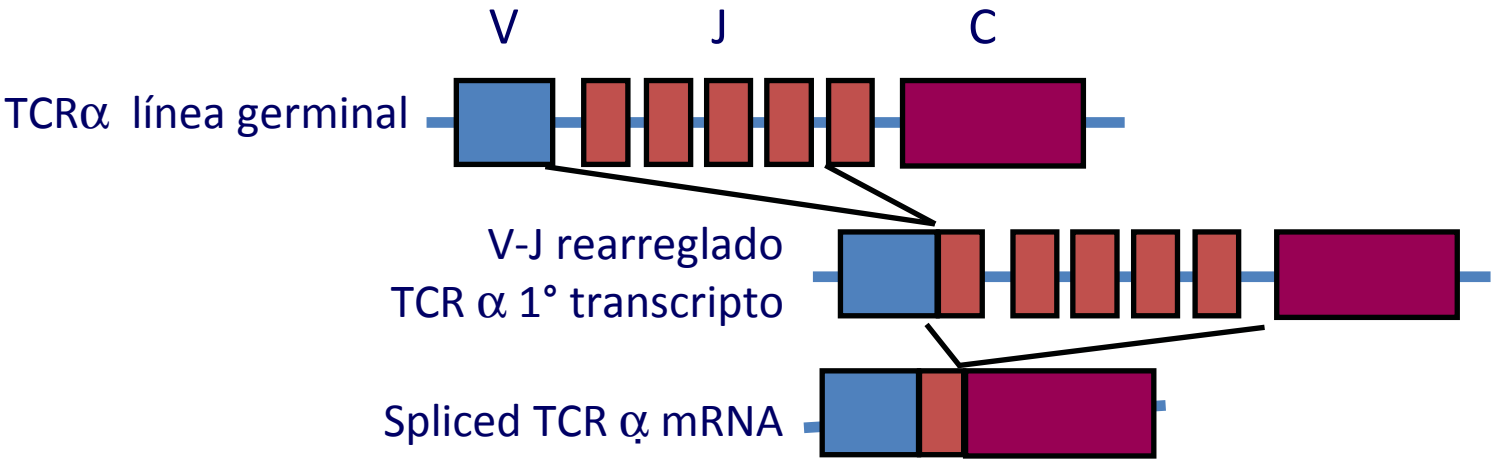

Pre-TCR
TCR β
Pre-Tα
γ ϵ ϵ δ
S-S
S-S
S-S
S-S
ς ς
Signals
Cell becomes permissive for TCR α-chain locus arrangement
Stimulates expression of CD4 and CD8 coreceptors
Stimulates proliferation
Stops additional TCR β-chain locus arrangements (allelic exclusion)

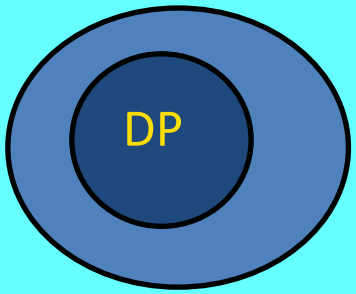
Rearreglo del TCRα



CD3+ low
pTα:β
CD25- CD44-
CD4+ CD8+

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





CD3+ TCRαβ+

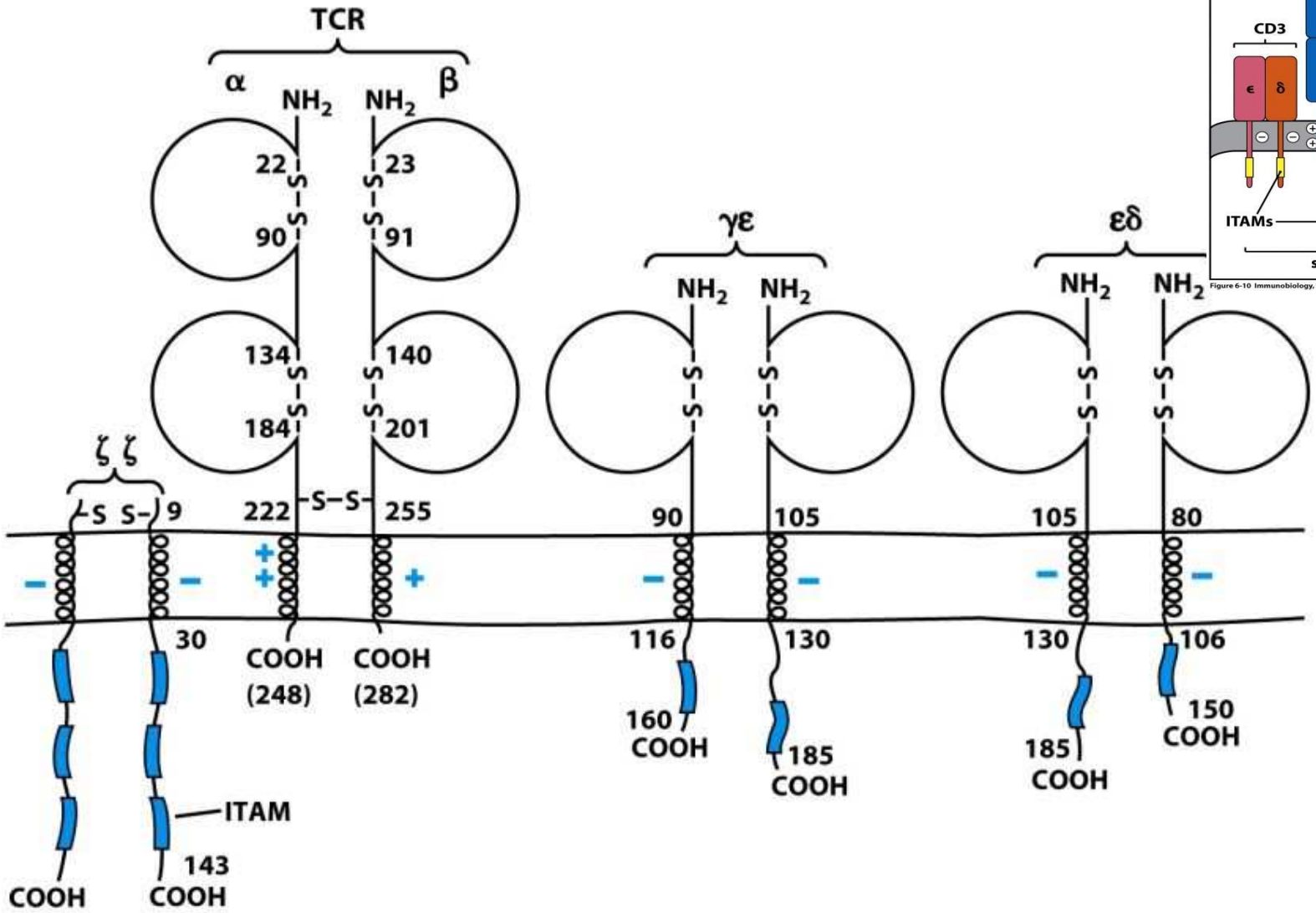
Las células T pueden ahora reconocer antígenos e interactuar con MHC class I y II a través de CD4 y CD8

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.**



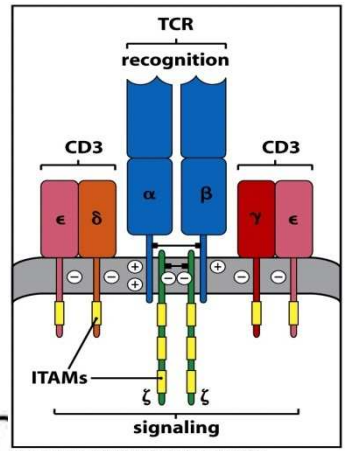


Figure 6-10 Immunobiology, 7ed. (© Garland Science 2008)

Figure 9-9a
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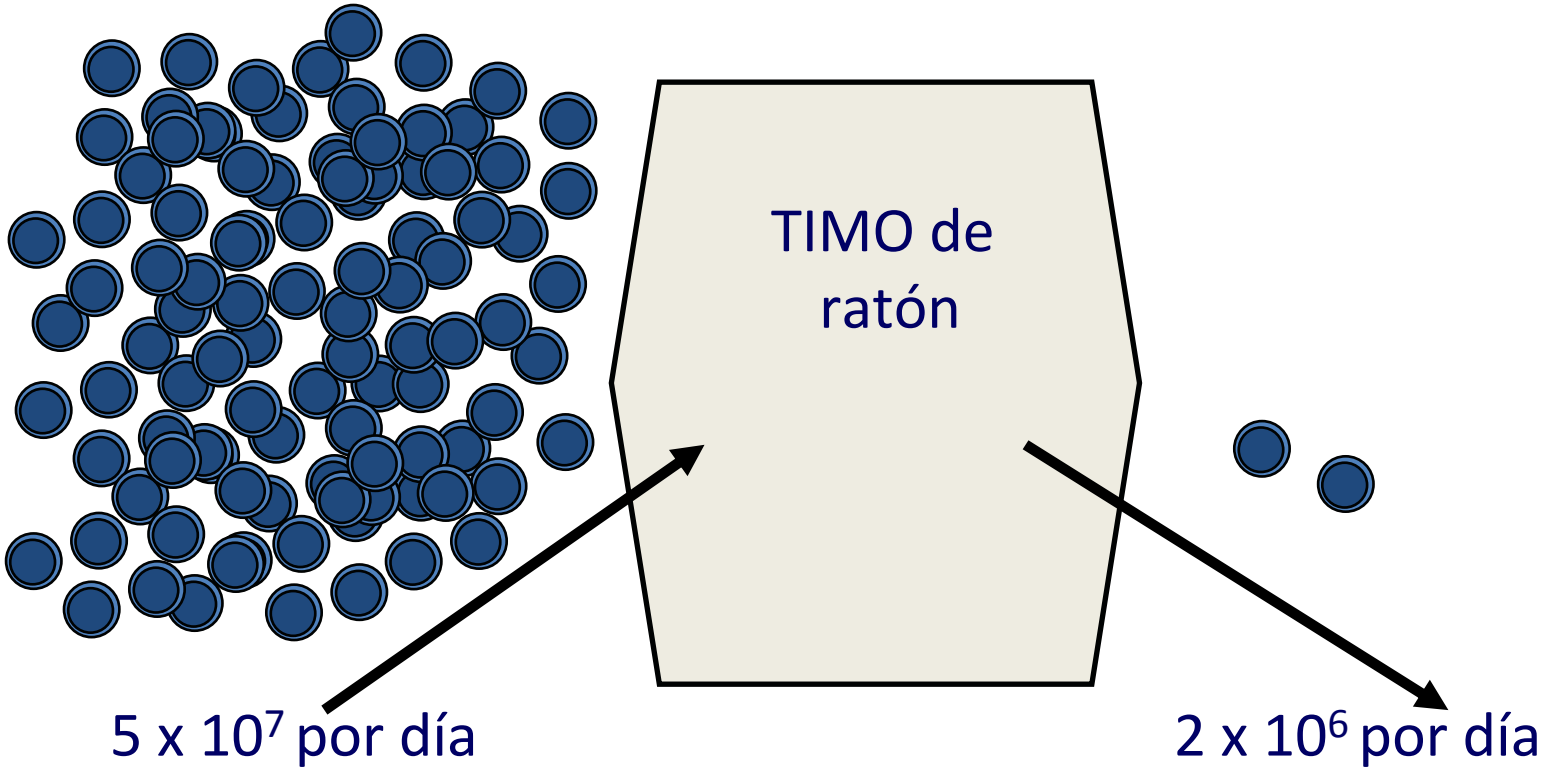


¿Cómo el TIMO elige aquellas células que son útiles????

SELECCIÓN.....

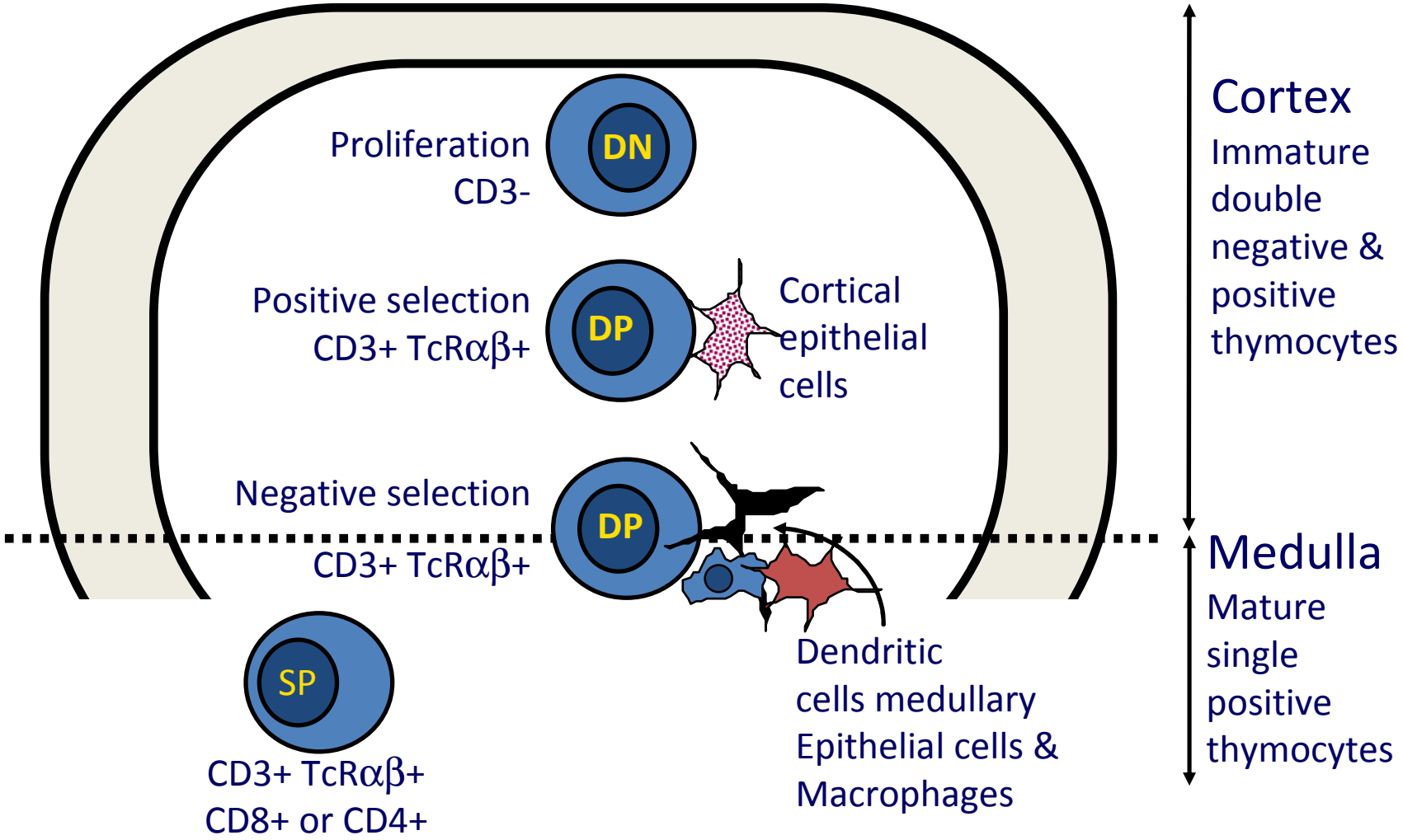
SELECCIÓN POSITIVA

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

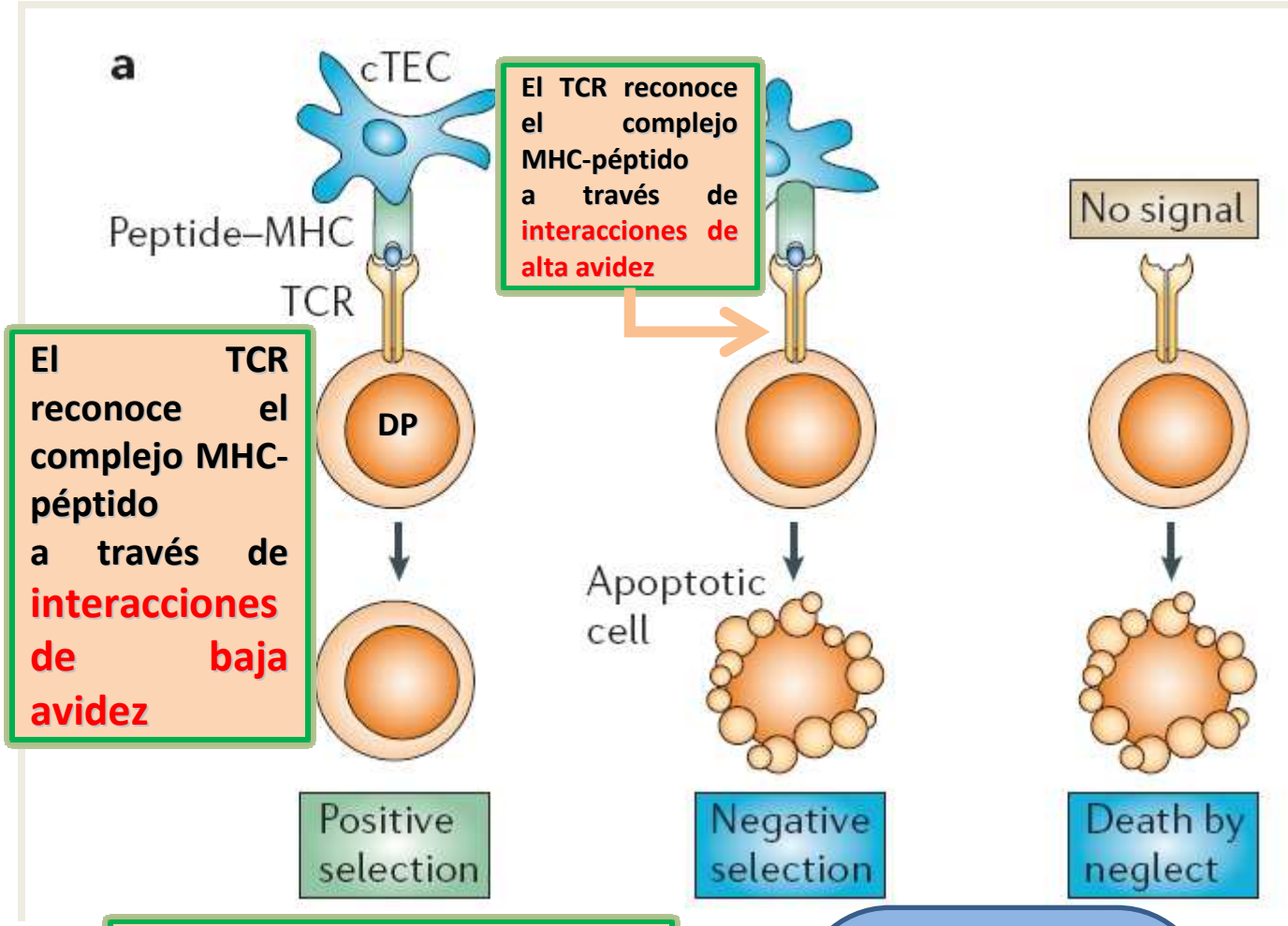
Selección NEGATIVA

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



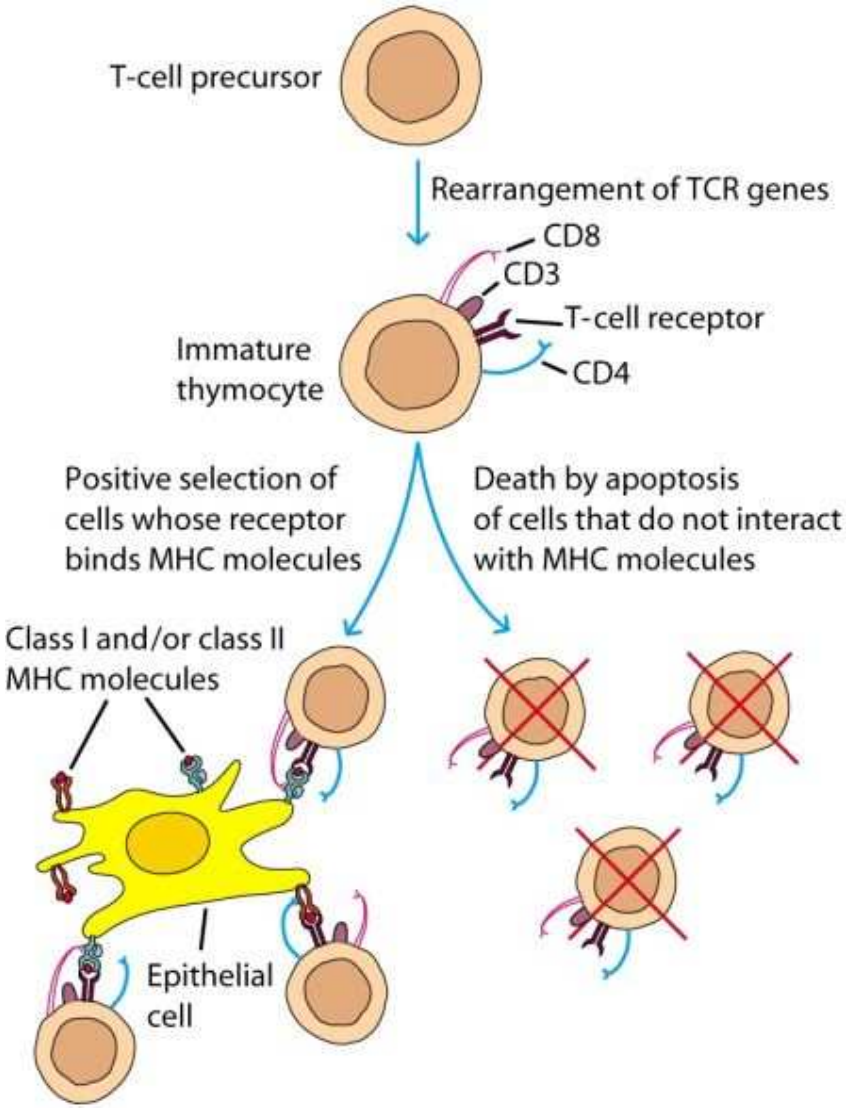
- Señales de supervivencia
- Diferenciación a timocito SP (solo el 3-5% de los timocitos)

Tolerancia central

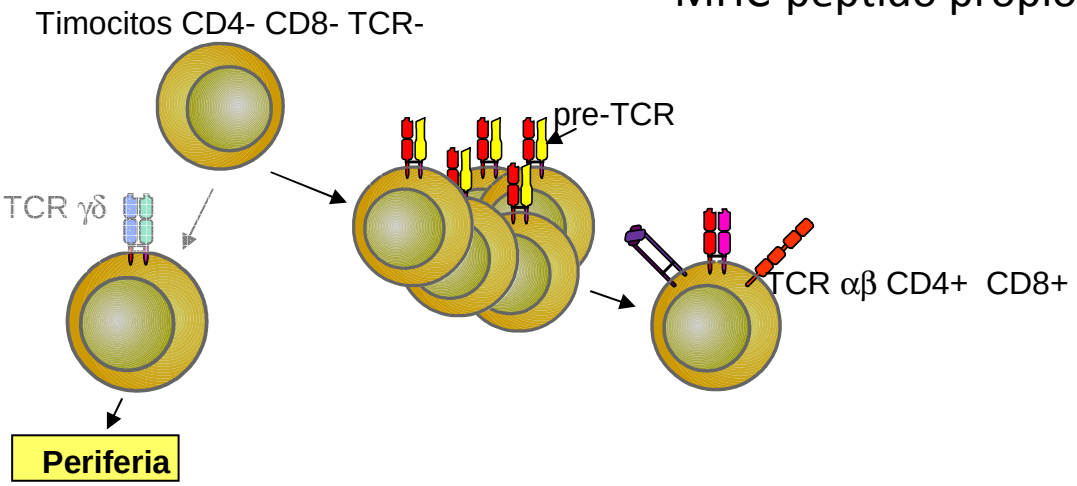
Nature Reviews Immunology 6, 127-135 (February 2006)

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**

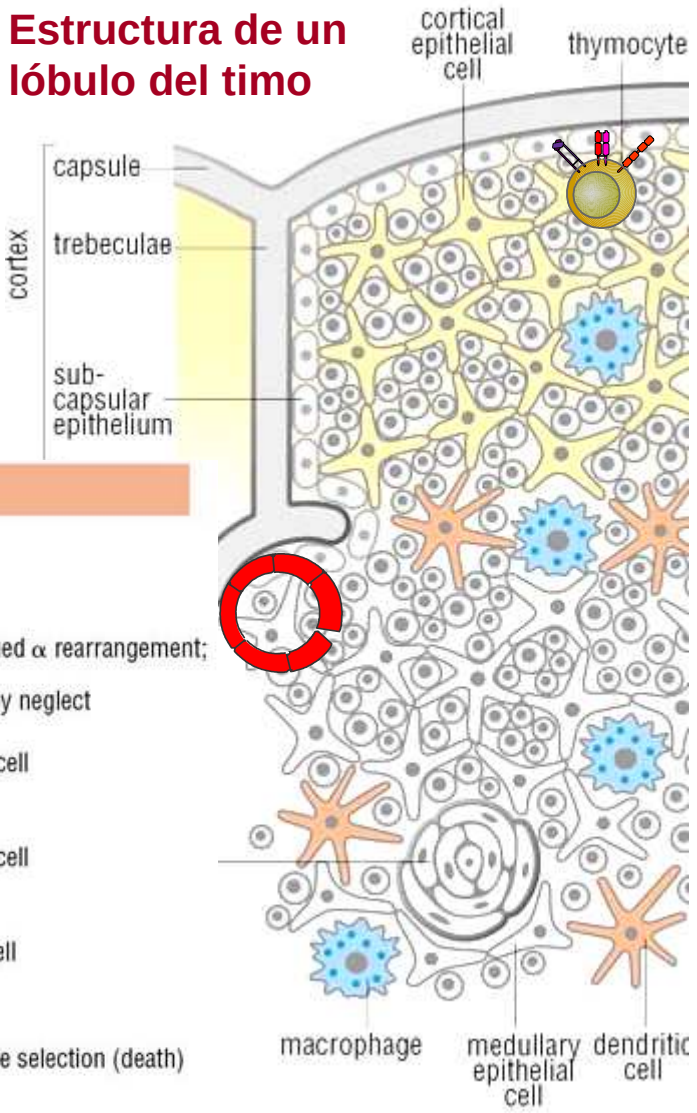
Selección positiva



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



Estructura de un lóbulo del timo

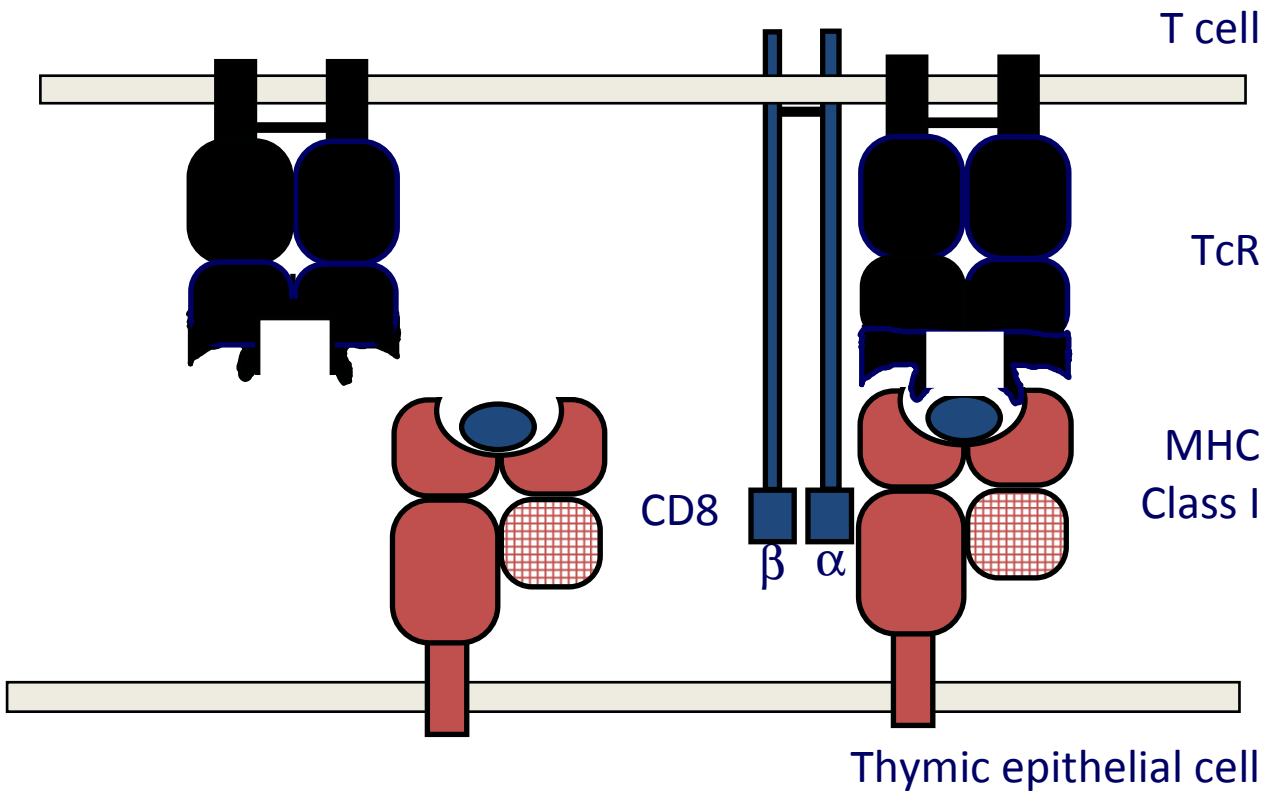


CD4 CD8 T cell	Reactivity to:			Cell fate
	self peptides plus		lipids plus	
	MHC class I	MHC class II	CD1d	
CD4 CD8 αβ TCR	none	none	none	continued α rearrangement; death by neglect
	intermediate			CD8 T cell
		intermediate		CD4 T cell
			intermediate?	NK T cell
	strong	strong		negative selection (death)

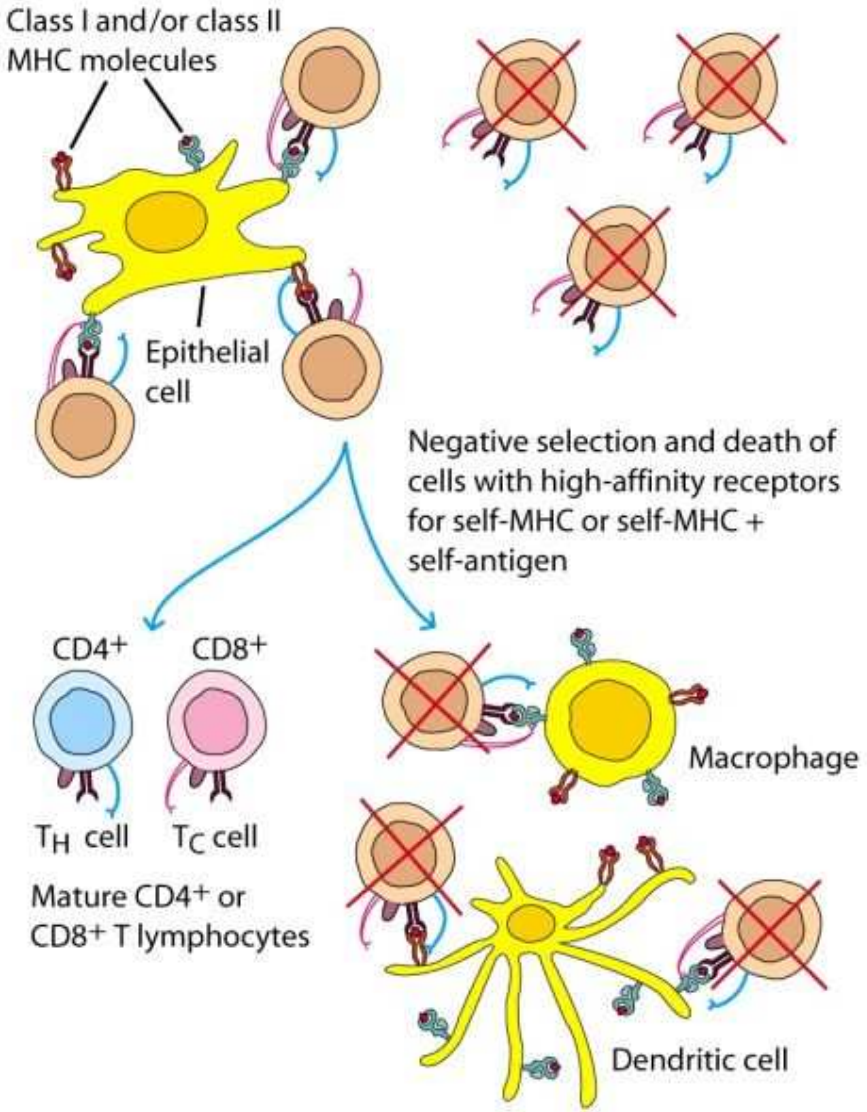
SELECCIÓN POSITIVA

Peptide is a partial agonist.
Thymocyte receives a partial signal and is rescued from apoptosis
i.e. the cell is positively selected to survive and mature.

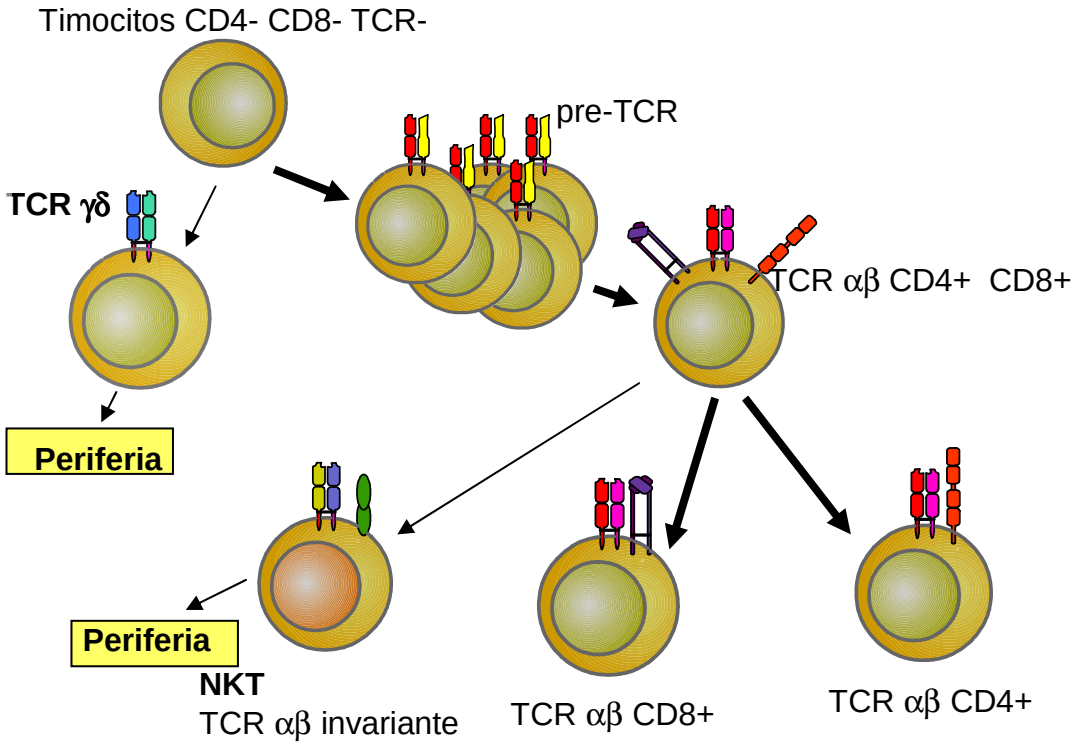
PARTIAL SIGNAL



Selección negativa



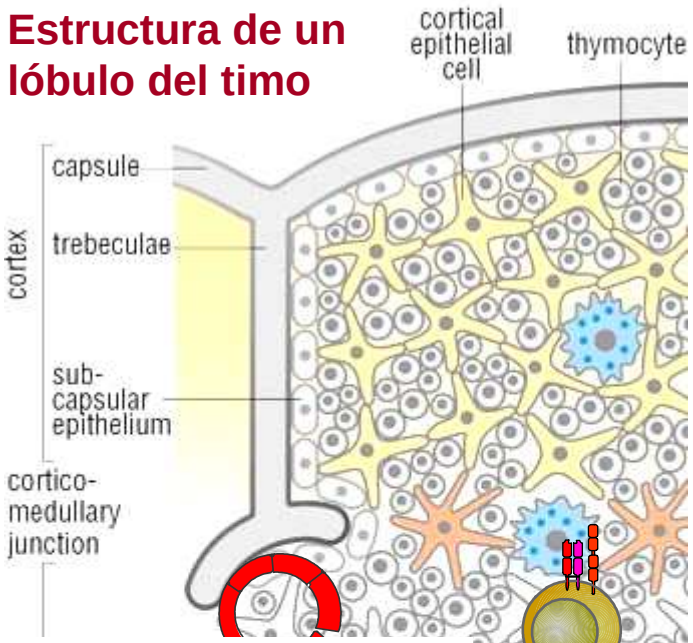
SELECCIÓN NEGATIVA:Los timocitos que reaccionan con alta afinidad con complejos MHC-péptido propios mueren rápidamente



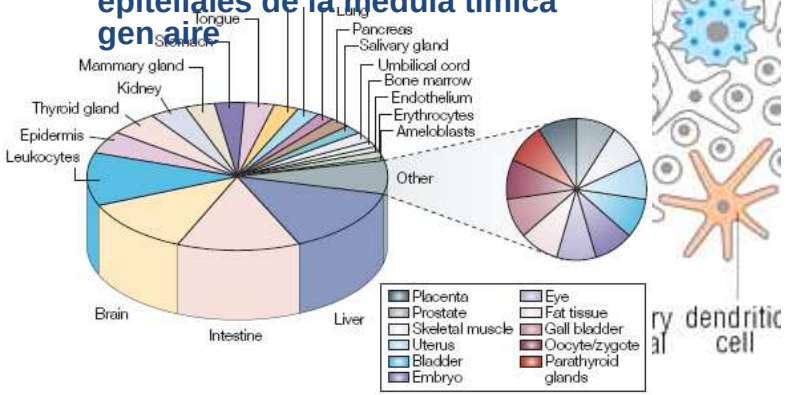
Los linfocitos T**αβ** que fueron seleccionados positivamente pasan a una estapa de **selección negativa** para evitar que reaccionen con lo propio
La médula del tímo es un sitio especializado para la **selección negativa**, las células presentadores principales son:

- **Células epiteliales de la médula tímica**
- **Macrófagos y células dendríticas**

Estructura de un lóbulo del timo



Expresión de genes extratímicos en las células **epiteliales de la médula tímica gen aire**

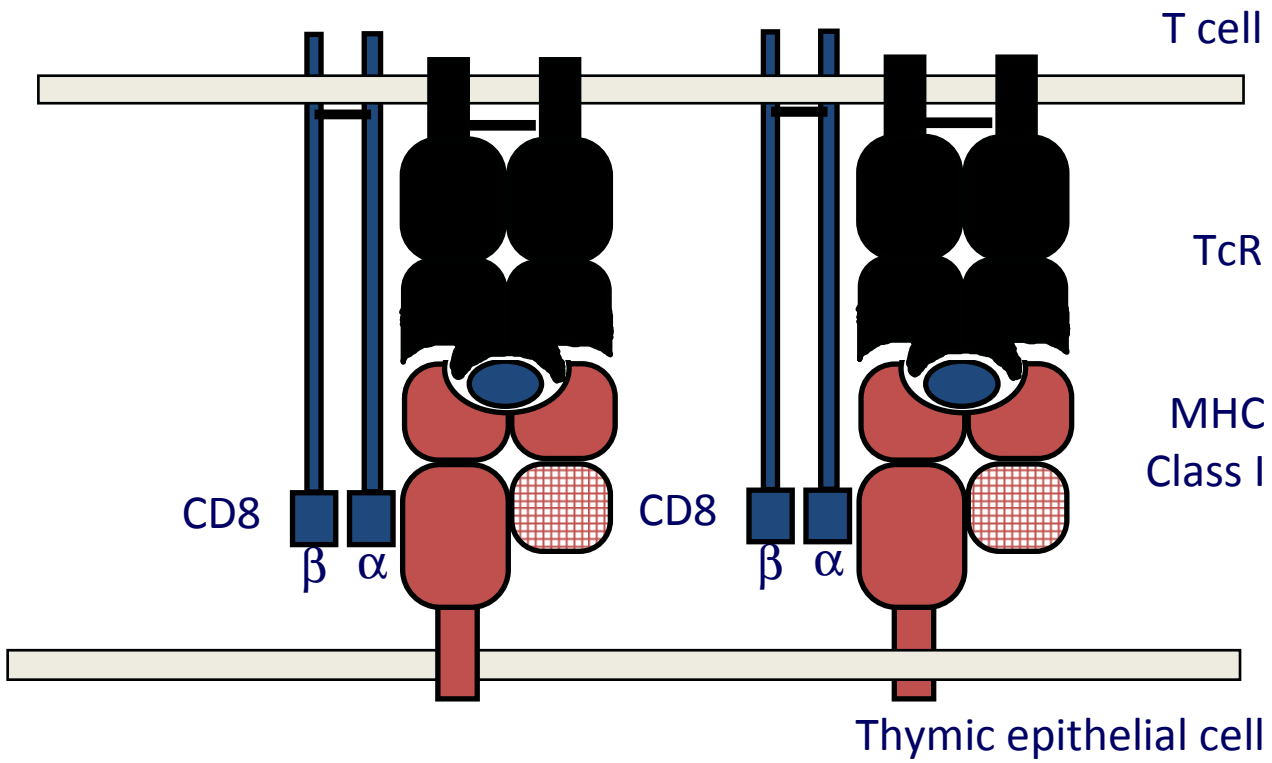


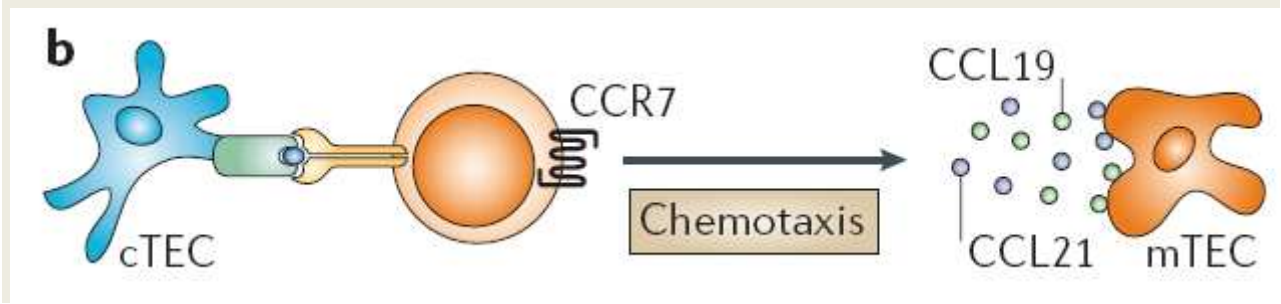
Expresión de proteínas tejido-específico en el timo => **gen AIRE**:
Deficiencia: Síndrome autoinmune poliglandular de tipo I

SELECCIÓN NEGATIVA

Peptide is an agonist
Thymocyte receives a powerful signal and undergoes apoptosis
i.e. the cell is negatively selected and dies.

FULL SIGNAL





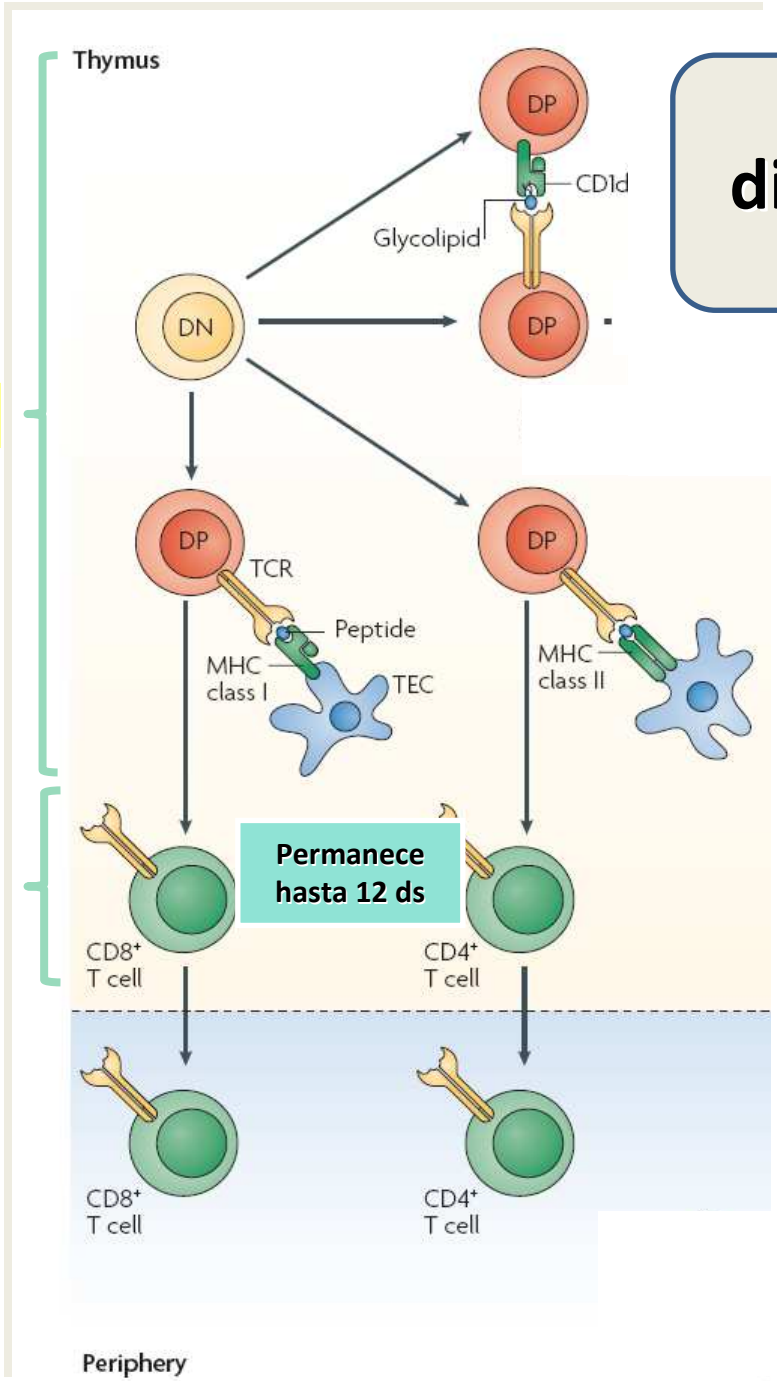
b | Positively selected thymocytes are induced to express CC-chemokine receptor 7 (CCR7) as well as to **undergo the programme of differentiation into single-positive (SP) thymocytes**, and CCR7-expressing thymocytes are attracted to the CCR7 ligands, CC-chemokine ligand 19 (CCL19) and CCL21, which are produced by medullary TECs (mTECs) and mainly localized in the medulla.

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

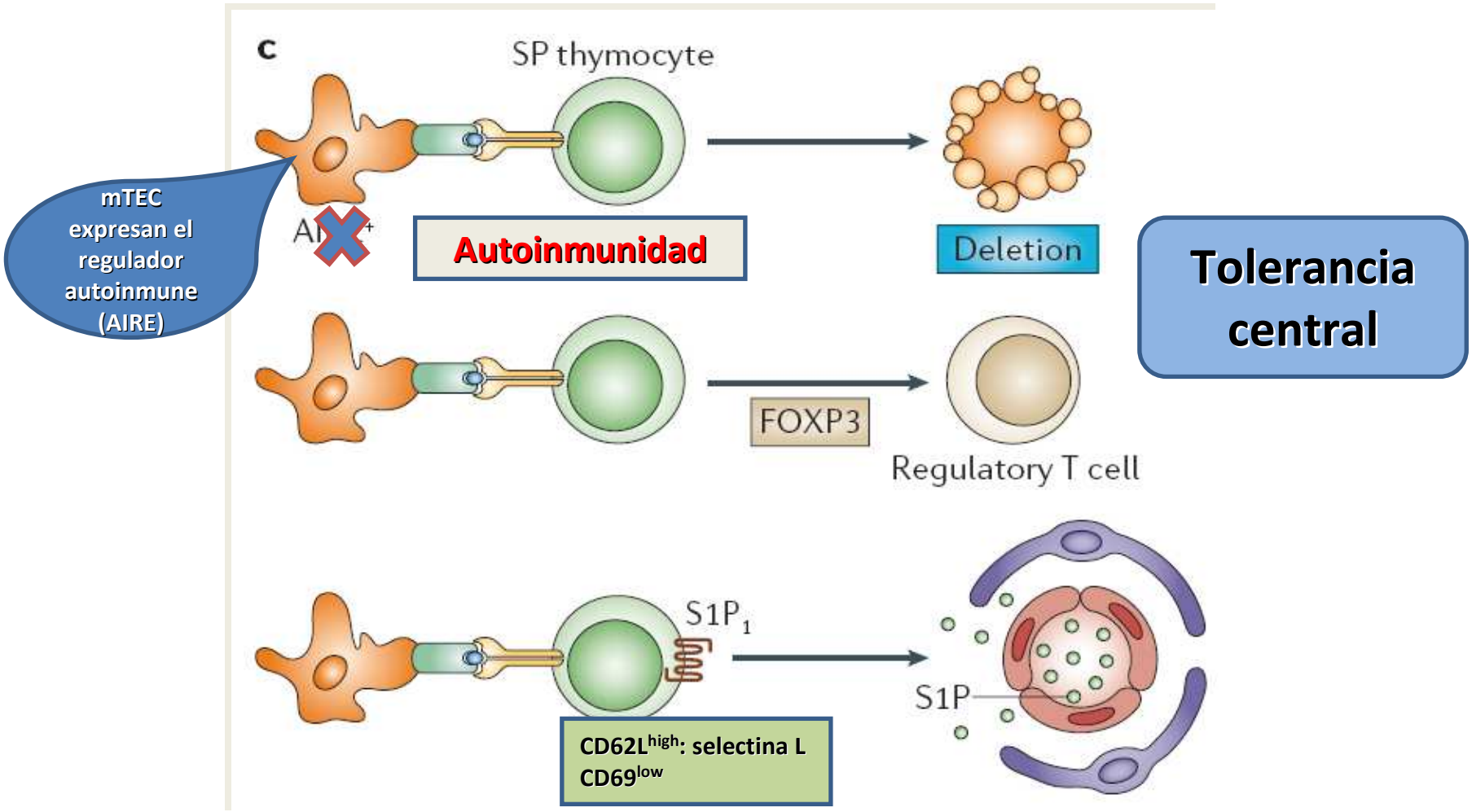
Programa de diferenciación a timocitos SP

CORTEZA

MÉDULA



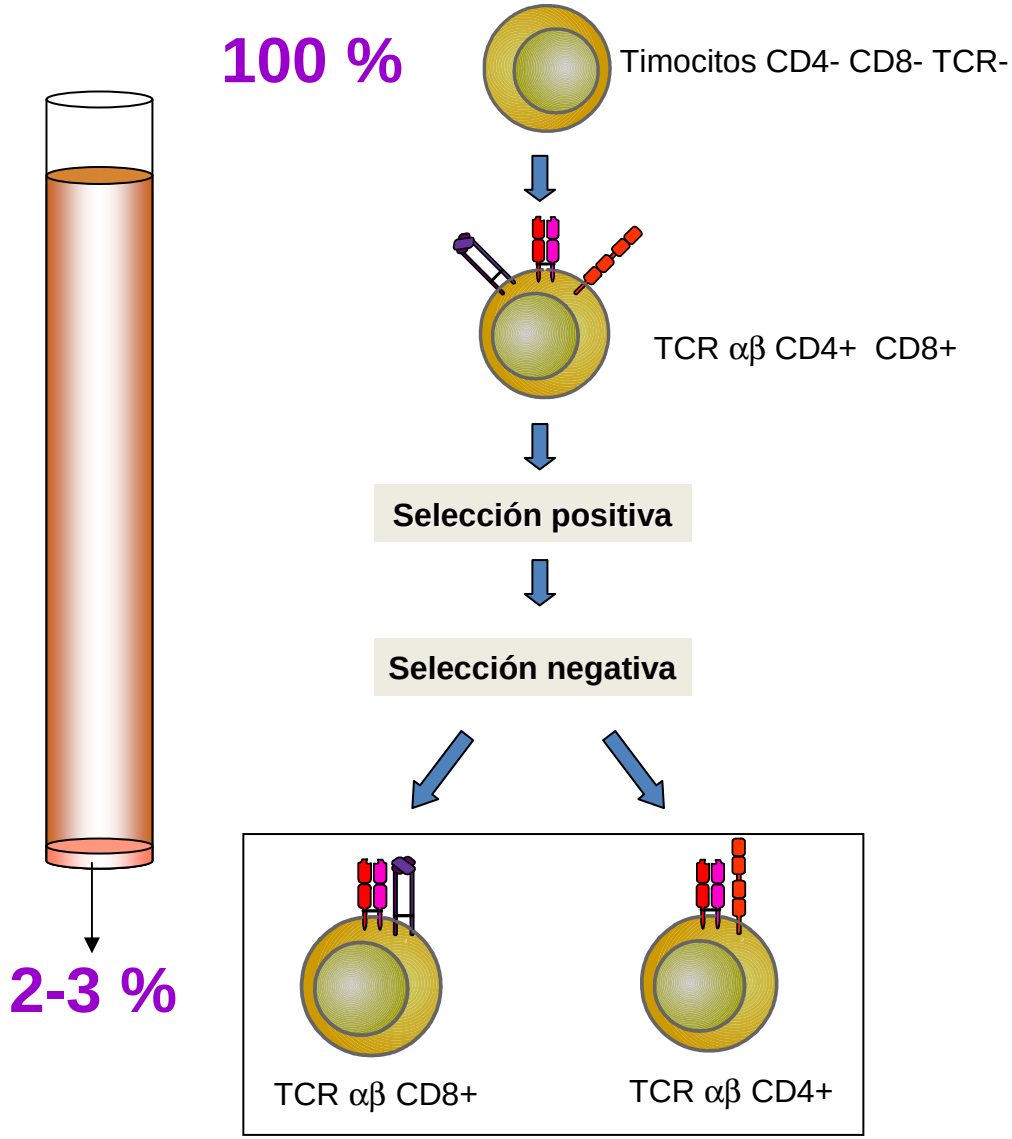
Si el TCR de un linfocito reconoce péptidos propios presentados por moléculas MHC I y al mismo tiempo la molécula CD8 interacciona con las moléculas MHC I, dicha célula recibe señales que evitan su muerte y favorecen que finalice su maduración…. Para continuar con el proceso madurativo, el linfocito 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



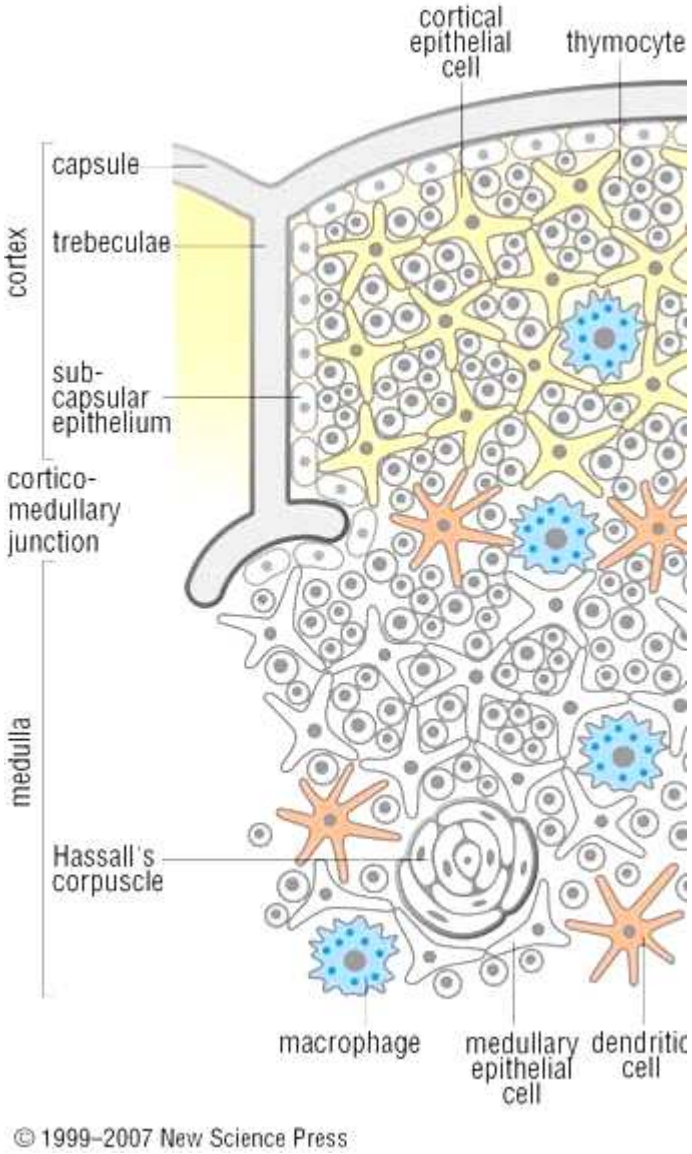


TABLE 9-1 Comparison of αβ and γδ T cells in peripheral blood

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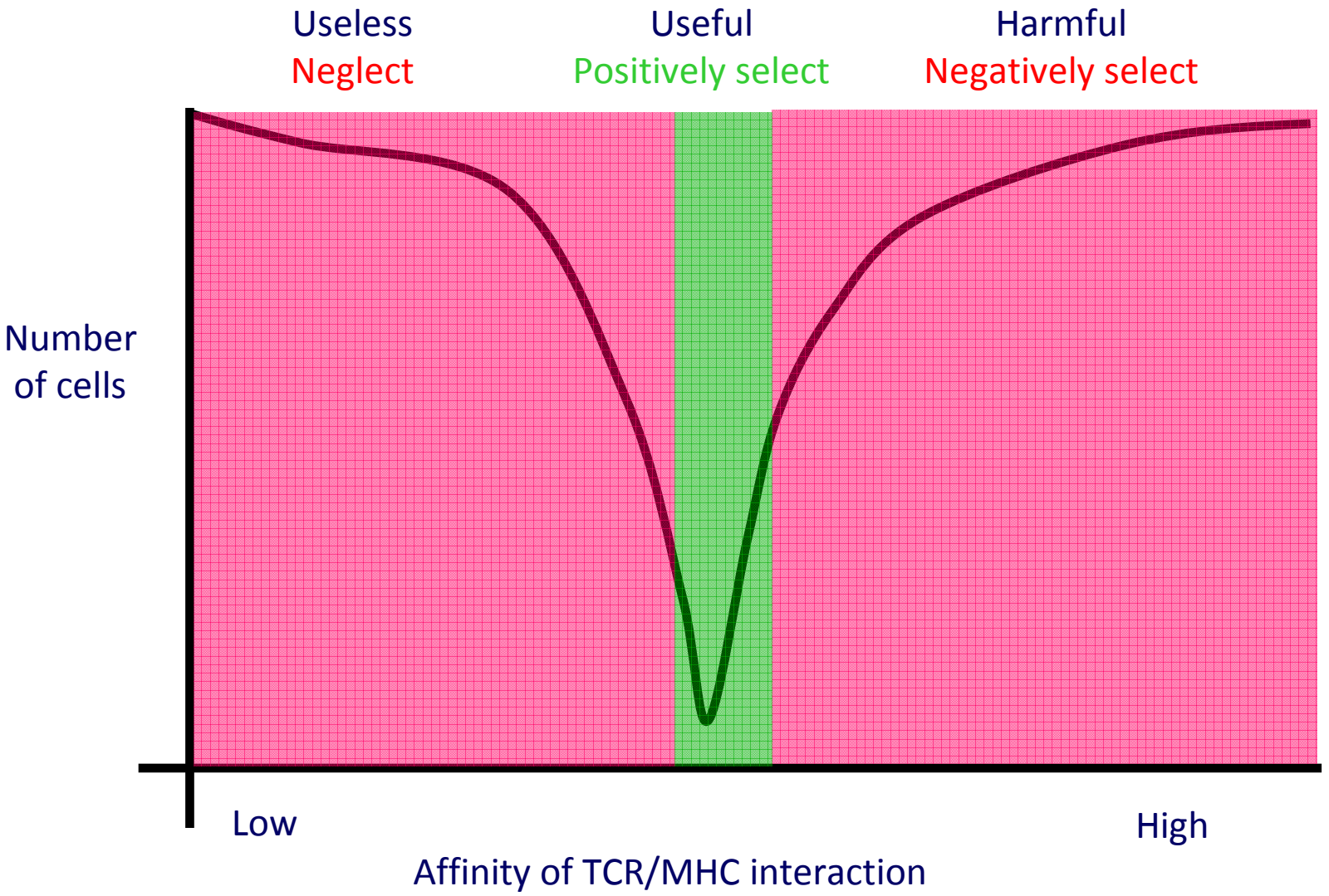
EL TIMO acepta aquellas células T que caen en una estrecha ventana de afinidad por moléculas MHC

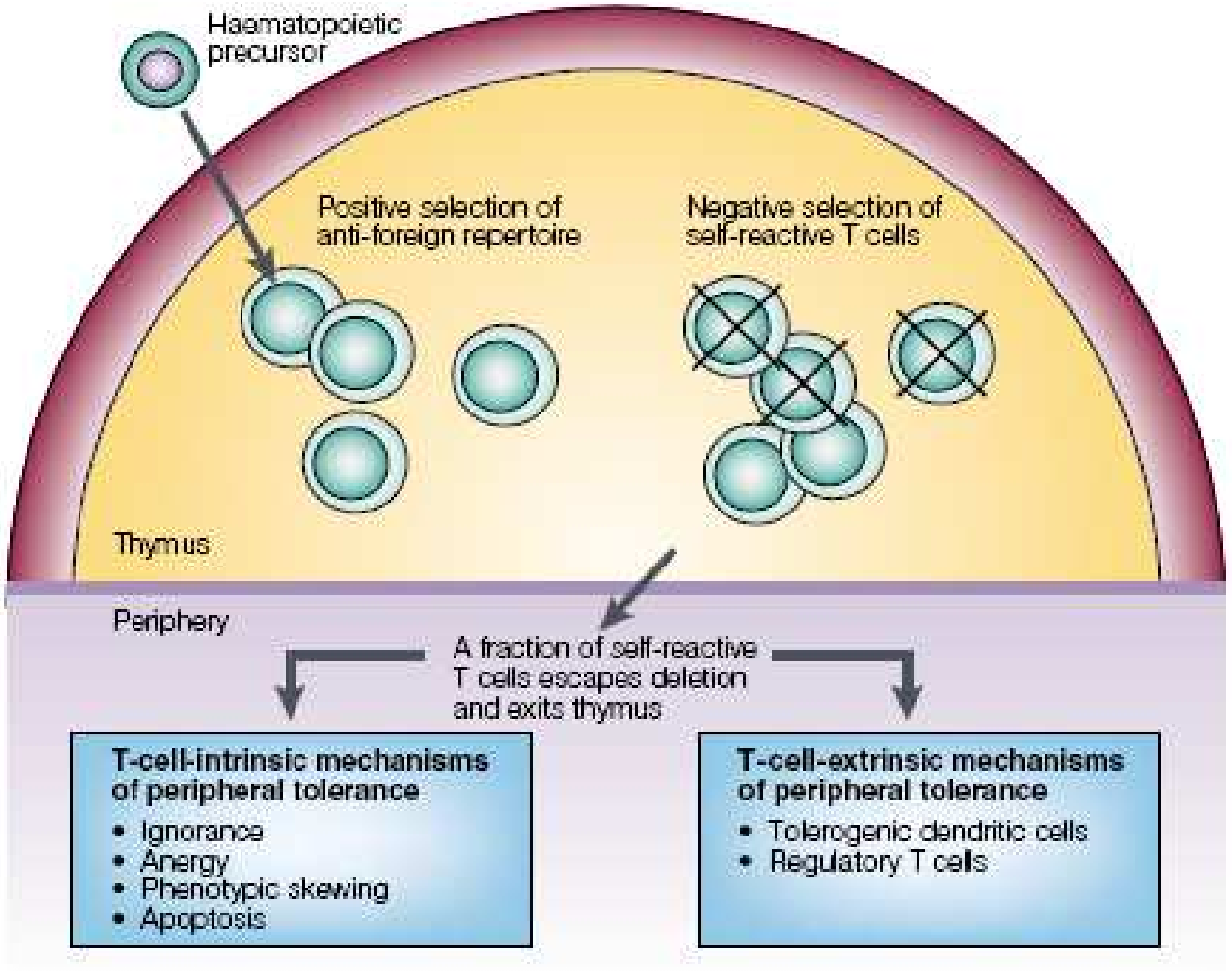


¿Cómo se establece la tolerancia frente a antígenos que no se expresan en el timo?

- T cells bearing TCR reactive with proteins expressed in the thymus are deleted.
- Some self proteins are not expressed in the thymus e.g. antigens first expressed at puberty
- Self tolerance can be induced outside the thymus

TOLERANCIA PERIFÉRICA O ANERGIA

A state of immunological inactivity caused by a failure to deliver appropriate signals to T or B cells when stimulated with antigen.
i.e. a failure of antigen presenting cells to deliver COSTIMULATION



Mecanismos de tolerancia periférica

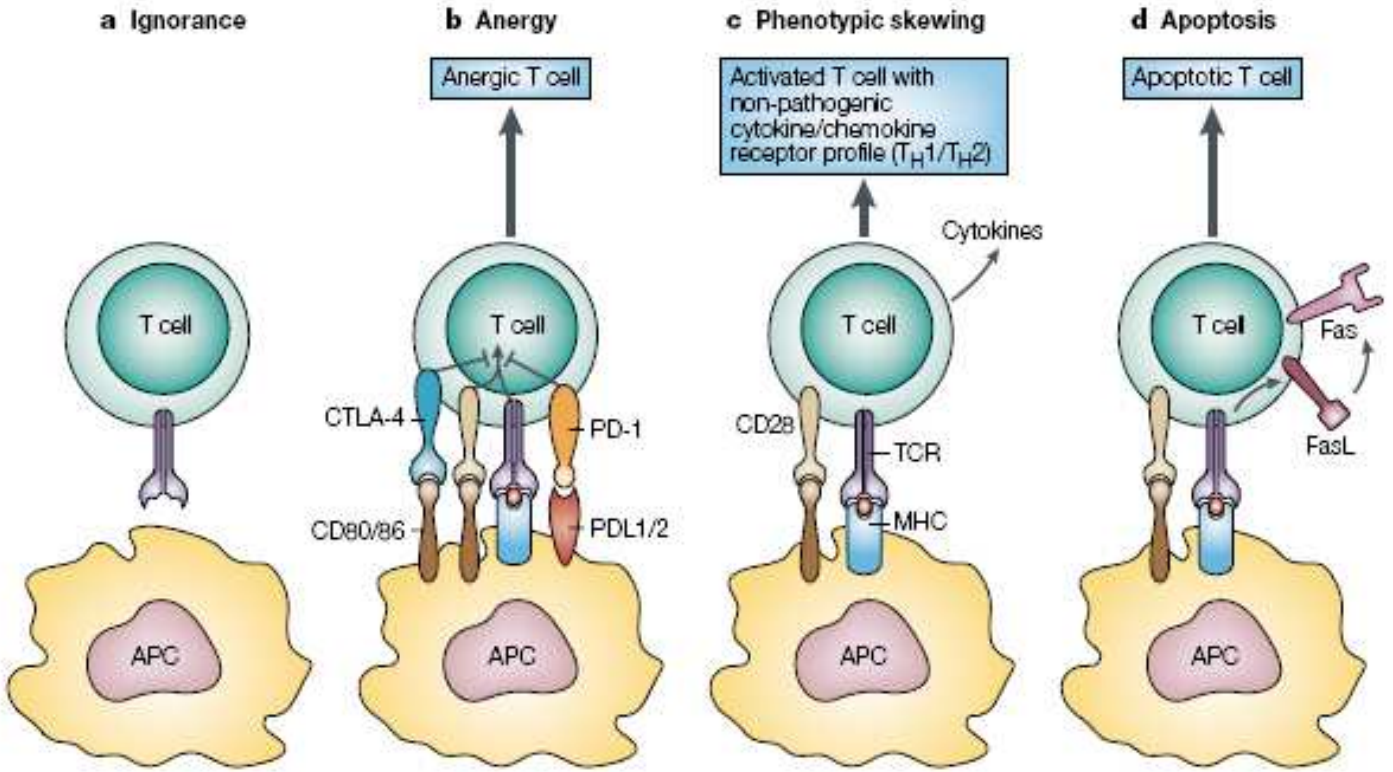
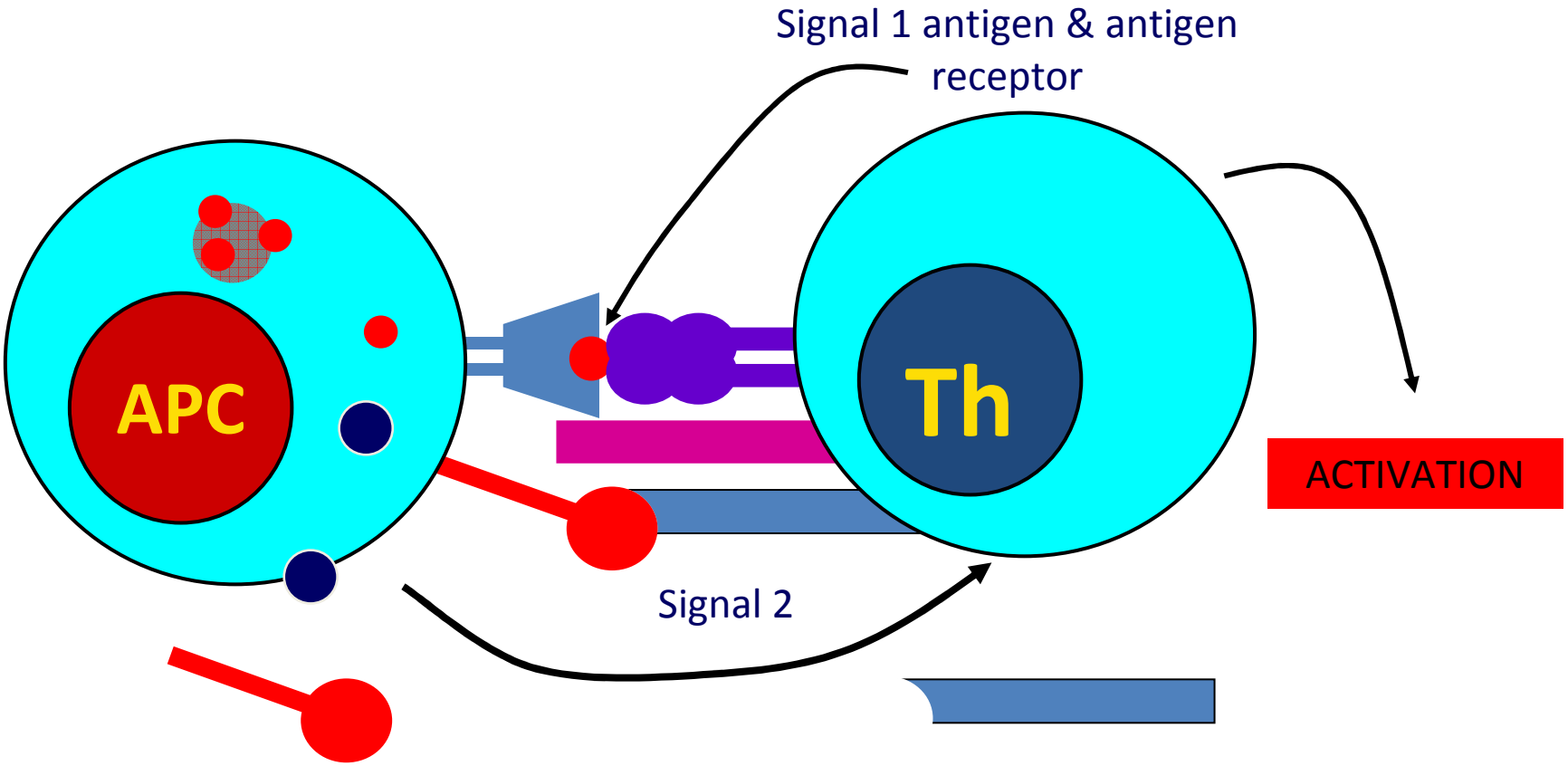


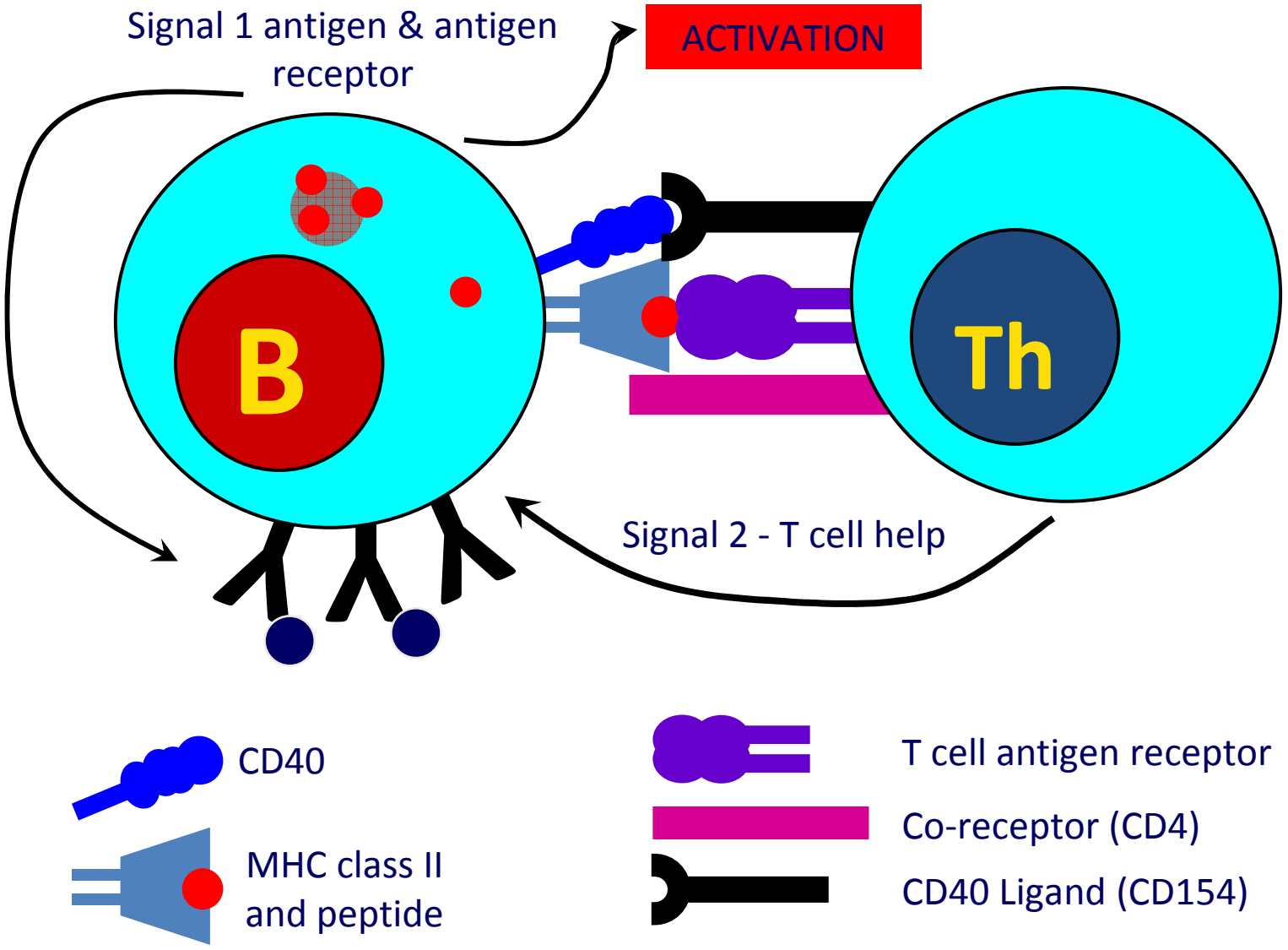
Figure 2 | **T-cell-intrinsic mechanisms of peripheral tolerance.** **a** | Self-reactive T cells might never encounter the self-protein they recognize and therefore exist in a state of ignorance. **b** | Encounter with self-protein might induce T-cell anergy, possibly involving interaction of the T-cell 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.

Presentación antigénica - 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, epithelial cells etc.

Células Th coestimulan células B
Modelos de activación



ACTIVACIÓN DE LA CÉLULA T

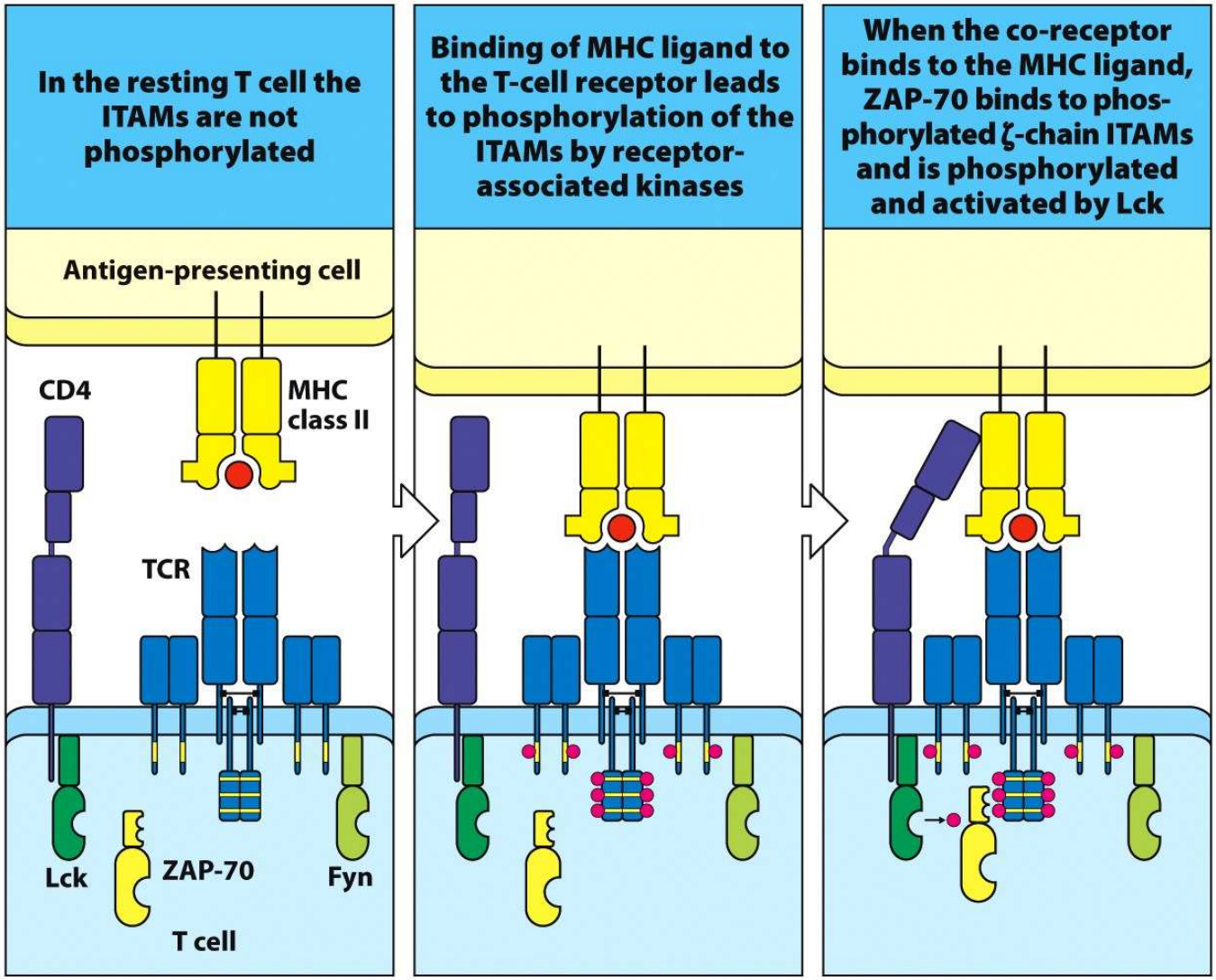


Figure 8.14 The Immune System, 3ed. (© Garland Science 2009)

Eventos intracelulares durante la activación celular

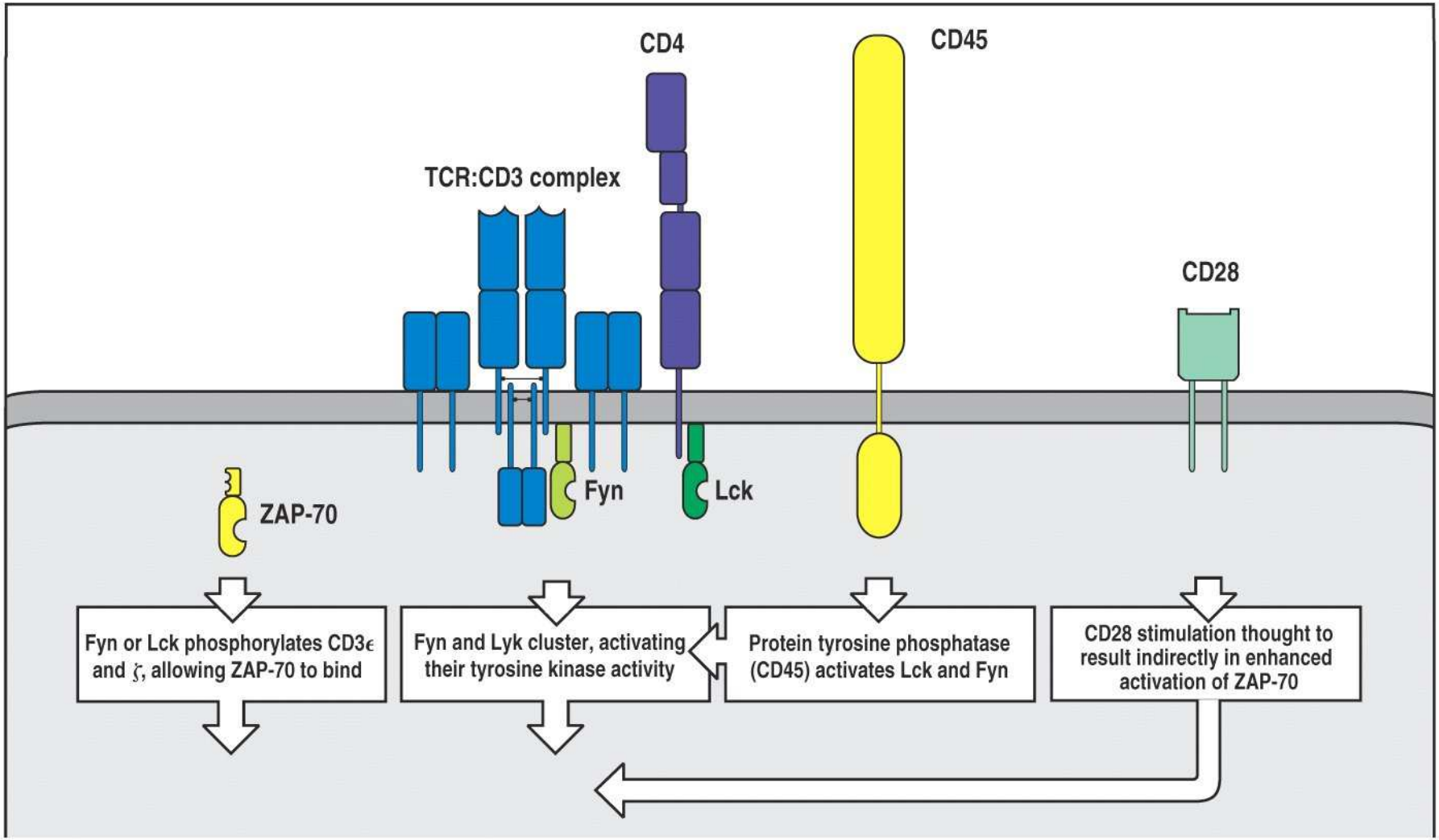


Figure 6-17 part 1 of 2 The Immune System, 2/e (© Garland Science 2005)

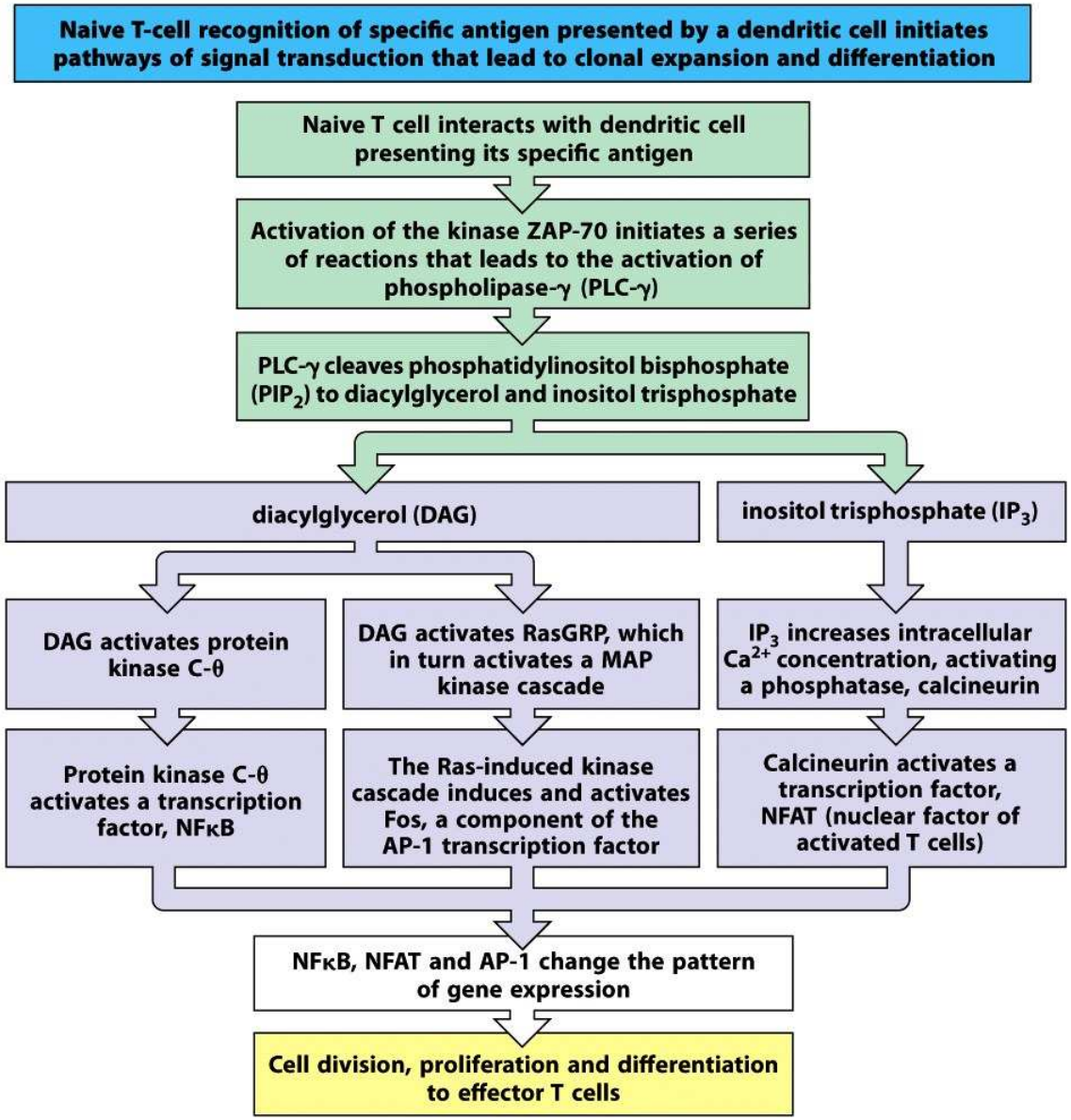
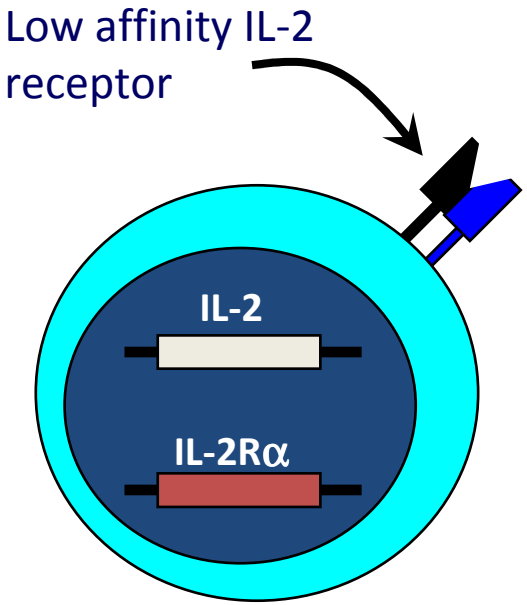


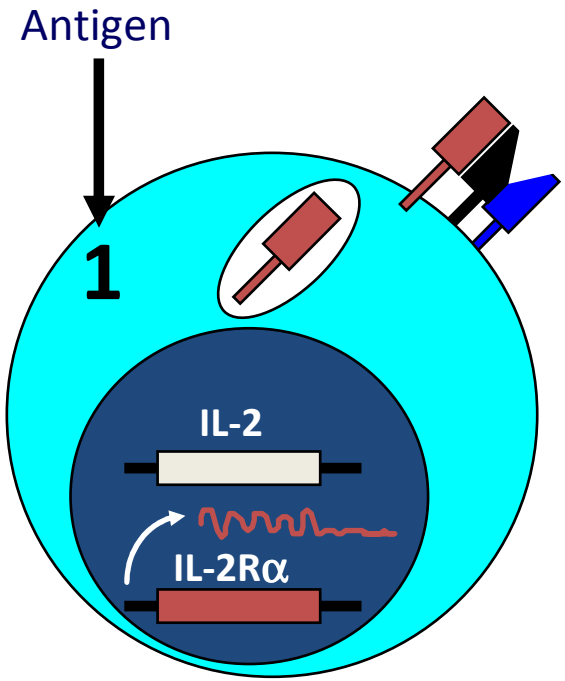
Figure 8.16 The Immune System, 3ed. (© Garland Science 2009)

Mecanismo de co-estimulación en células T



Resting T cells

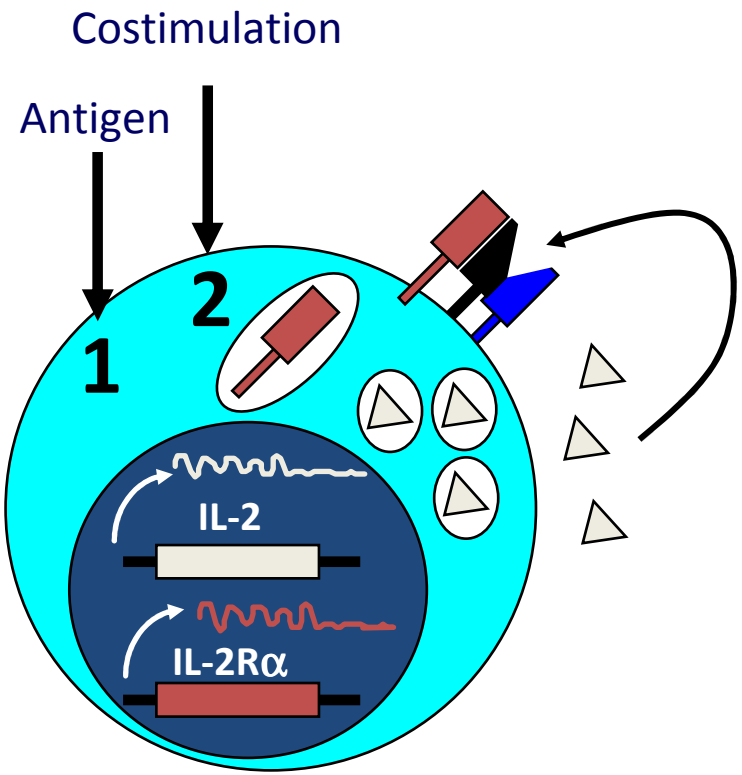
Express IL-2 receptor-
β and γ chains but no α
chain or IL-2



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

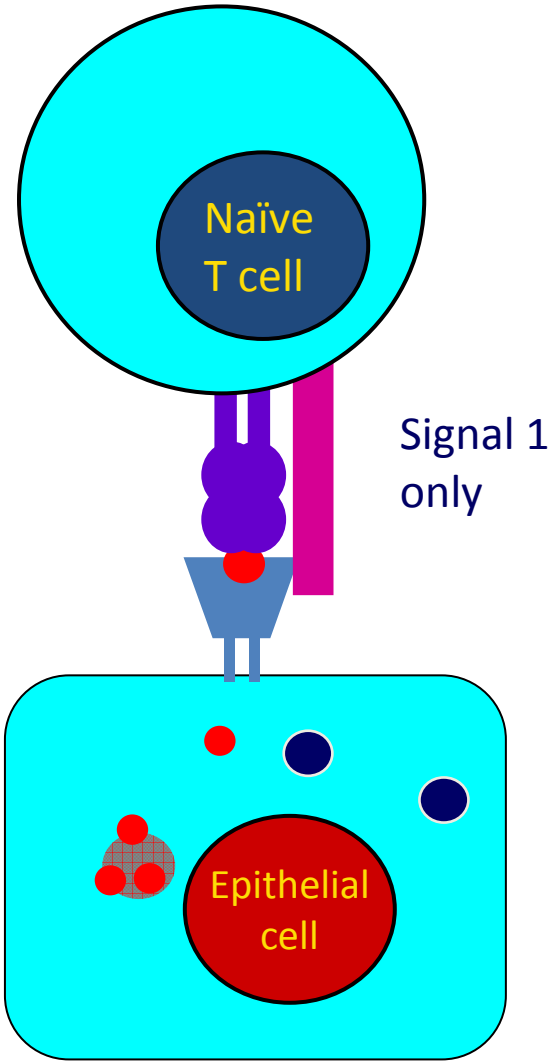
Stabilises and increases the half-life of IL-2 mRNA by 20-30 fold

IL-2 production increased by 100 fold overall

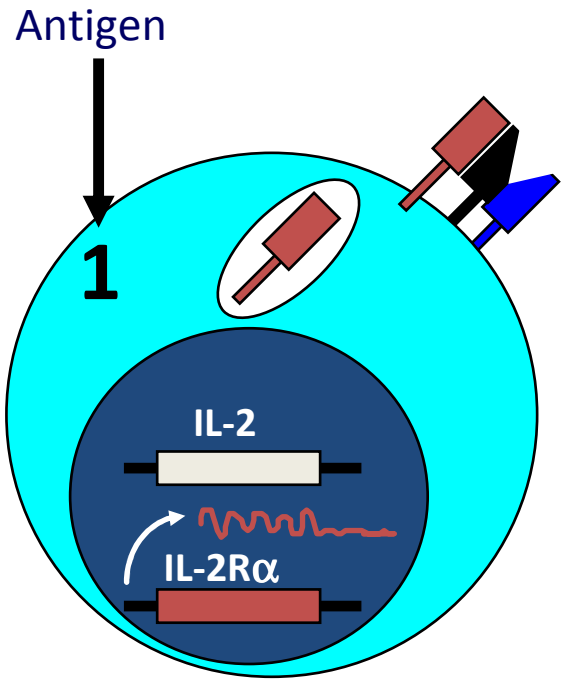
Immunosuppressive drugs illustrate the importance of IL-2 in immune responses

- Cyclosporin & FK506 inhibit IL-2 by disrupting TCR signalling
- Rapamycin inhibits IL-2R signalling

Anergia



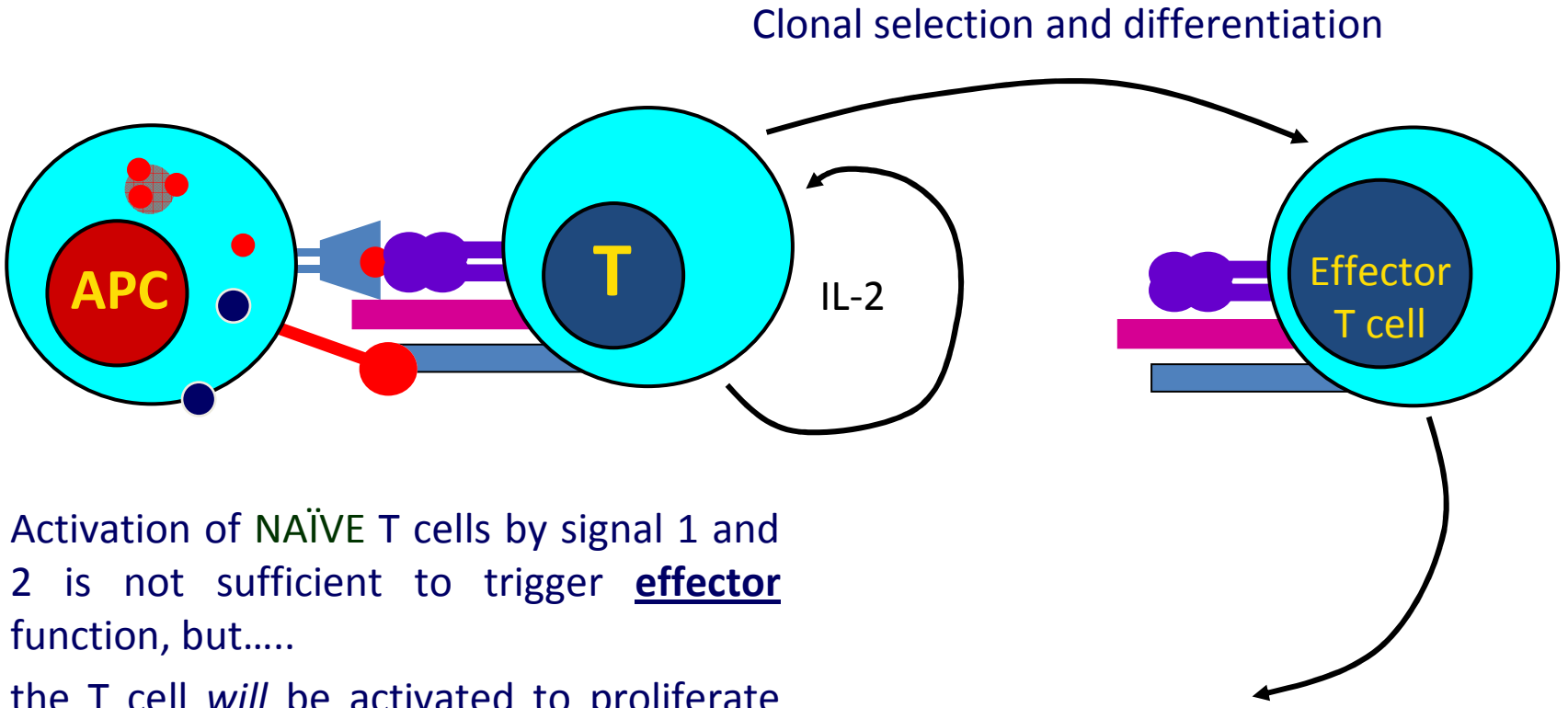
Self peptide epitopes presented by a non-classical APC e.g. an epithelial cell



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.

Generando células T efectoras....



Activation of NAÏVE T cells by signal 1 and 2 is not sufficient to trigger **effector** function, but.....

the T cell *will* be activated to proliferate and differentiate under the control of autocrine IL-2 to an effector T cell.

These T cells are ARMED

How can this cell give help to, or kill cells, that express low levels of B7 family costimulators?

Expresión de moléculas de superficie por las células TCD4^{+}

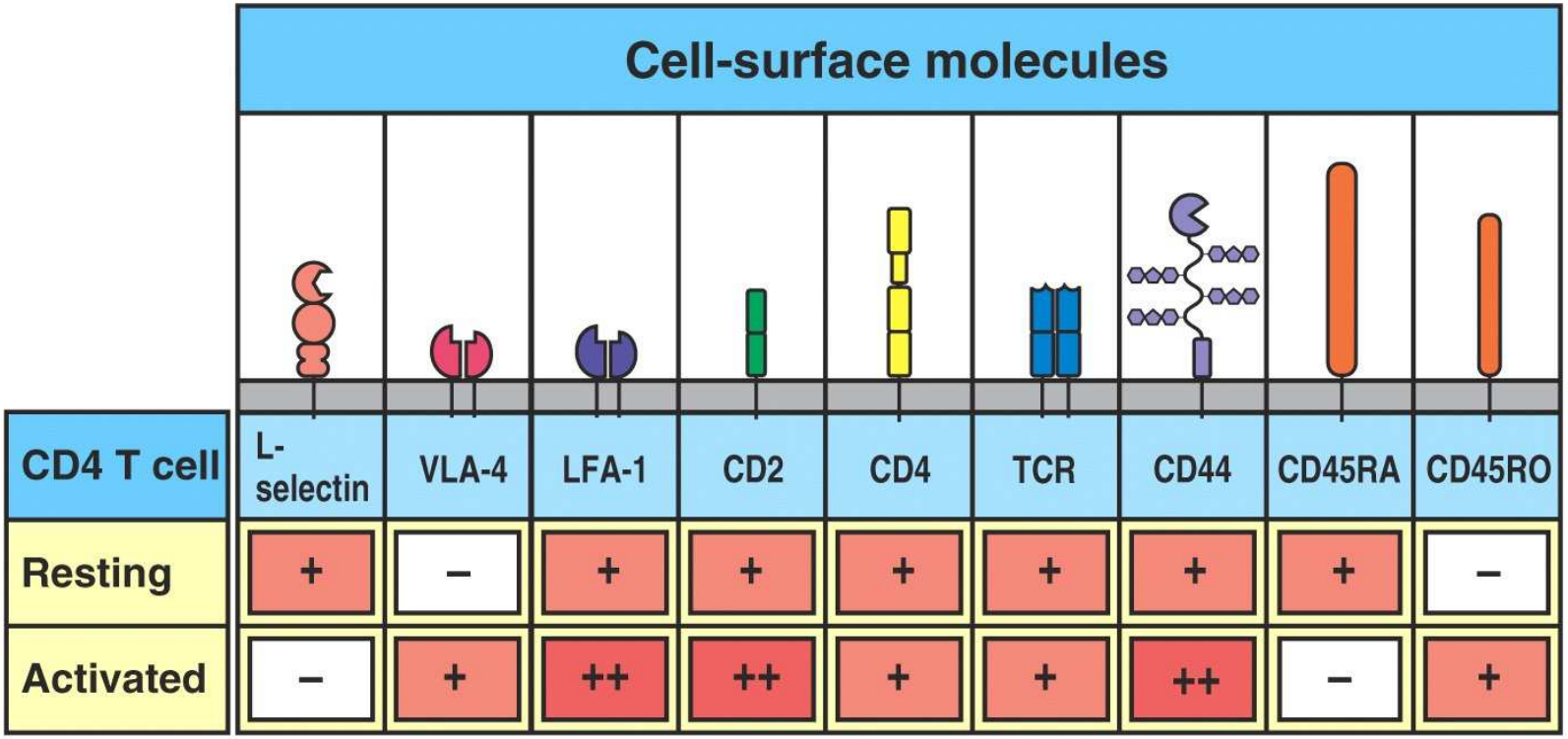


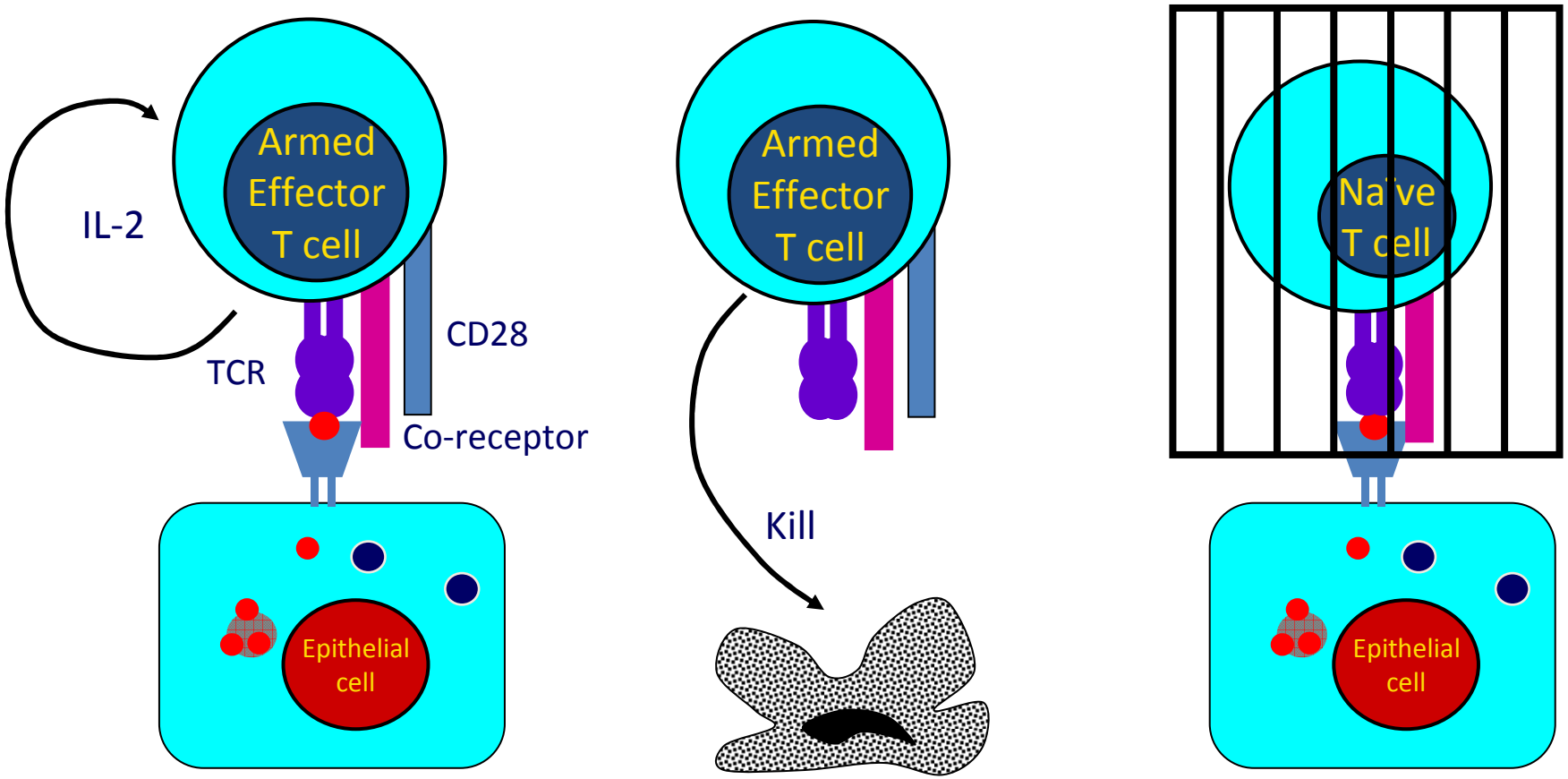
Figure 6-23 The Immune System, 2/e (© Garland Science 2005)

Función efectora o anergia?

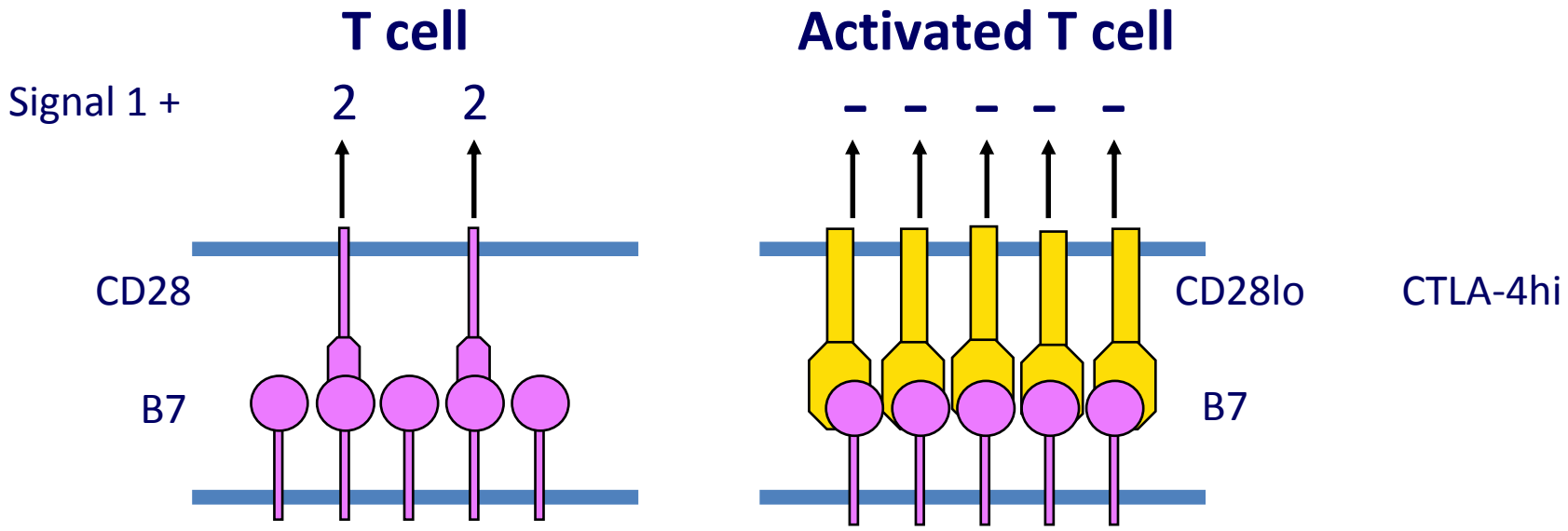
Clonally selected, proliferating and differentiated T cell i.e. ARMED sees antigen on a B7 -ve epithelial cell

The effector programme of the T cell is activated **without** costimulation

This contrasts the situation with naïve T cells, which are anergised without costimulation



Moléculas Coestimulatorias siempre están asociadas con receptores inhibidores...



CTLA-4 binds CD28 with a higher affinity than B7 molecules

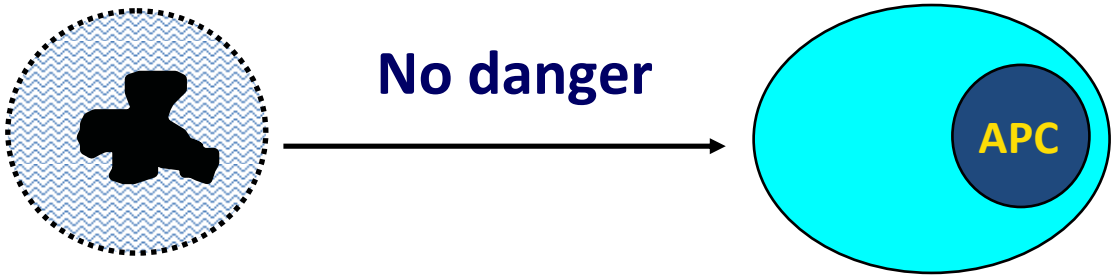
The lack of signal 2 to the T cell shuts down the T cell response.

La hipótesis de daño y coestimulación

Full expression of T cell function and self tolerance depends upon when and where co-stimulatory molecules are expressed.

Cell containing only self antigens

Apoptotic cell death.
A natural, often useful cell death.

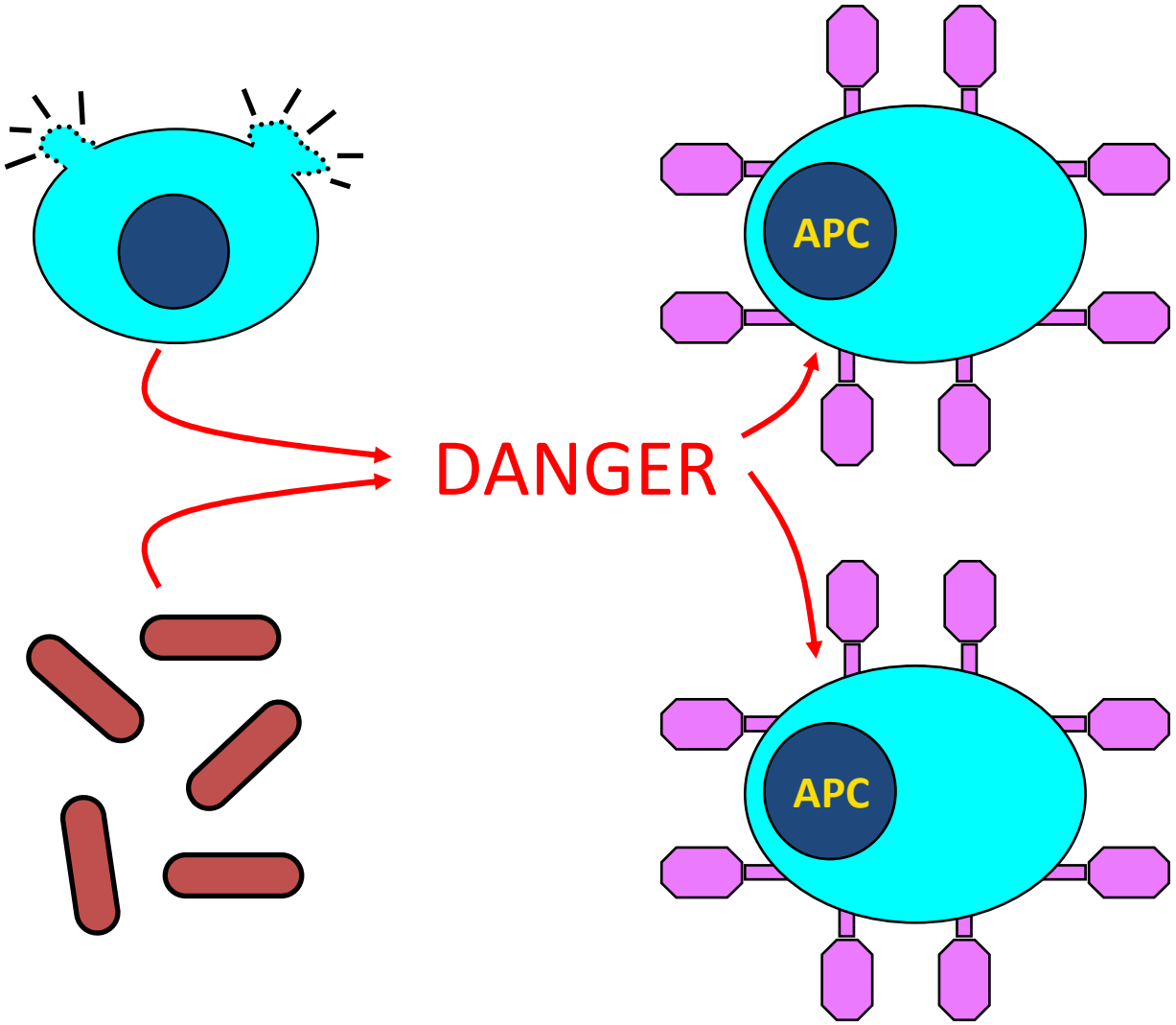


Innocuous challenge to the immune system fails to activate APC and fails to activate the immune system

Fuchs & Matzinger 1995

La hipótesis del daño...

Necrotic cell death
e.g. tissue damage,
virus infection etc



Pathogens recognised
by microbial patterns

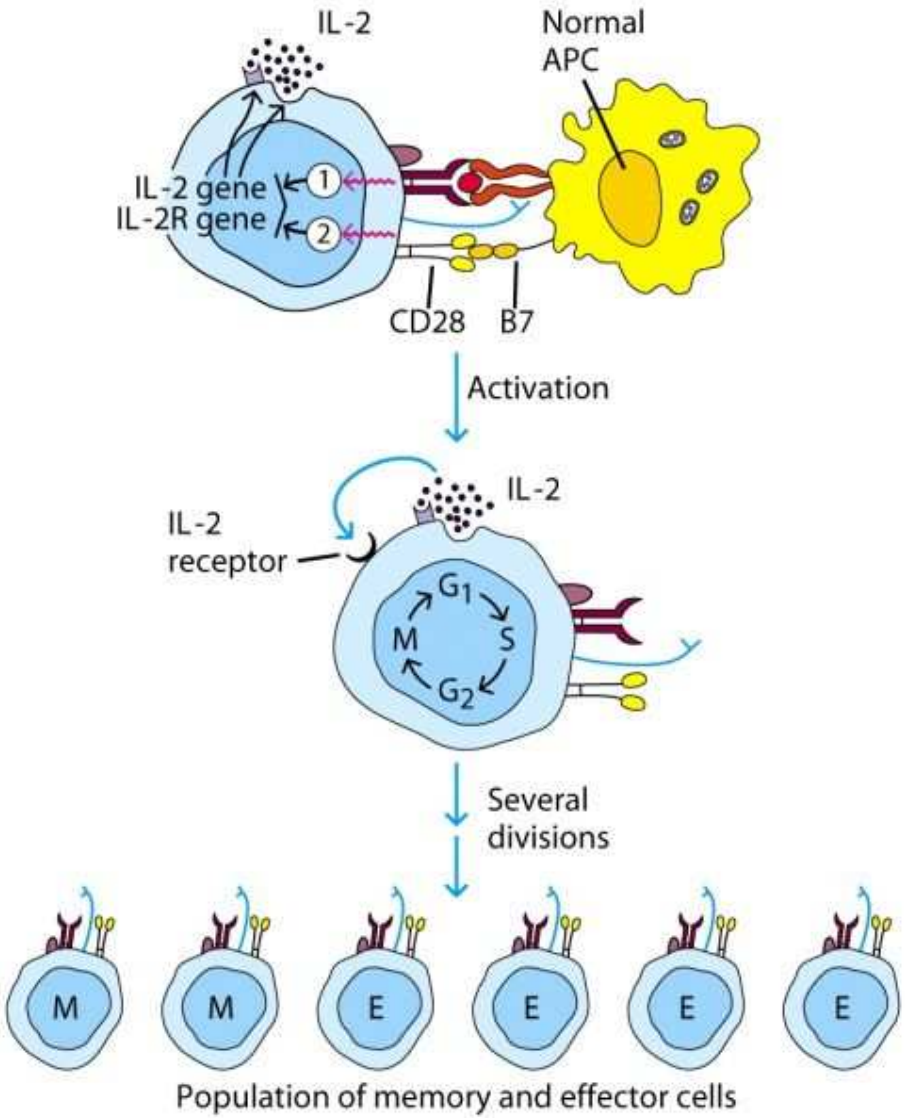
APC that detect ‘danger’ signals express costimulatory molecules, activate T cells and the immune response

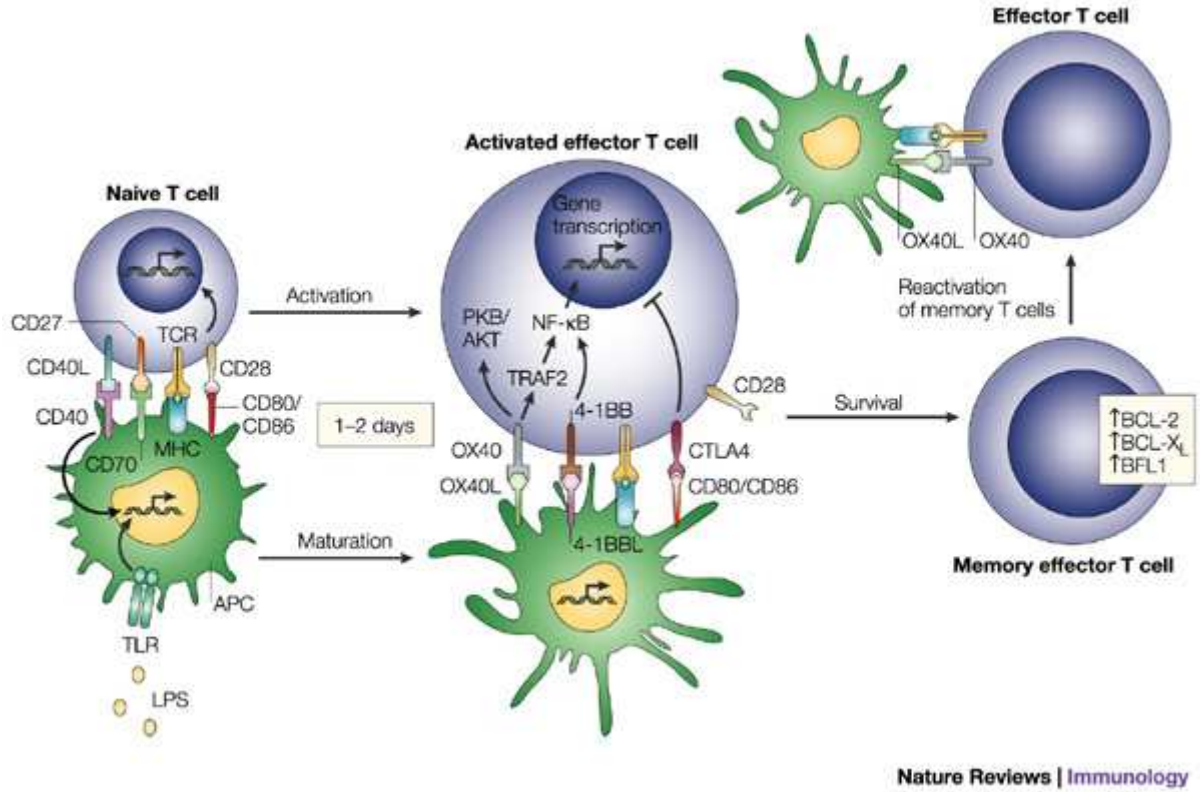
How the danger hypothesis suggests a review of immunological dogma

- Antigens induce tolerance or immunity depending upon the ability of the immune system to sense them as ‘dangererous’, and not by sensing whether they are self or ‘non-self’.
- There is no window for tolerance induction in neonates - if a ‘danger signal’ is received, the neonatal immune system will respond
- Neonatal T cells are not intrinsically tolerisable but the natural anti-inflammatory nature of the neonatal environment predisposes to tolerance
- Apoptosis, the ‘non-dangerous’ death of self cells may prevent autoimmunity when old or surplus cells are disposed of.
- Suggests that tolerance is the default pathway of the immune system on encountering antigens.
- Explains why immunisations require adjuvants to stimulate cues of danger such as cytokines or costimulatory molecule expression.

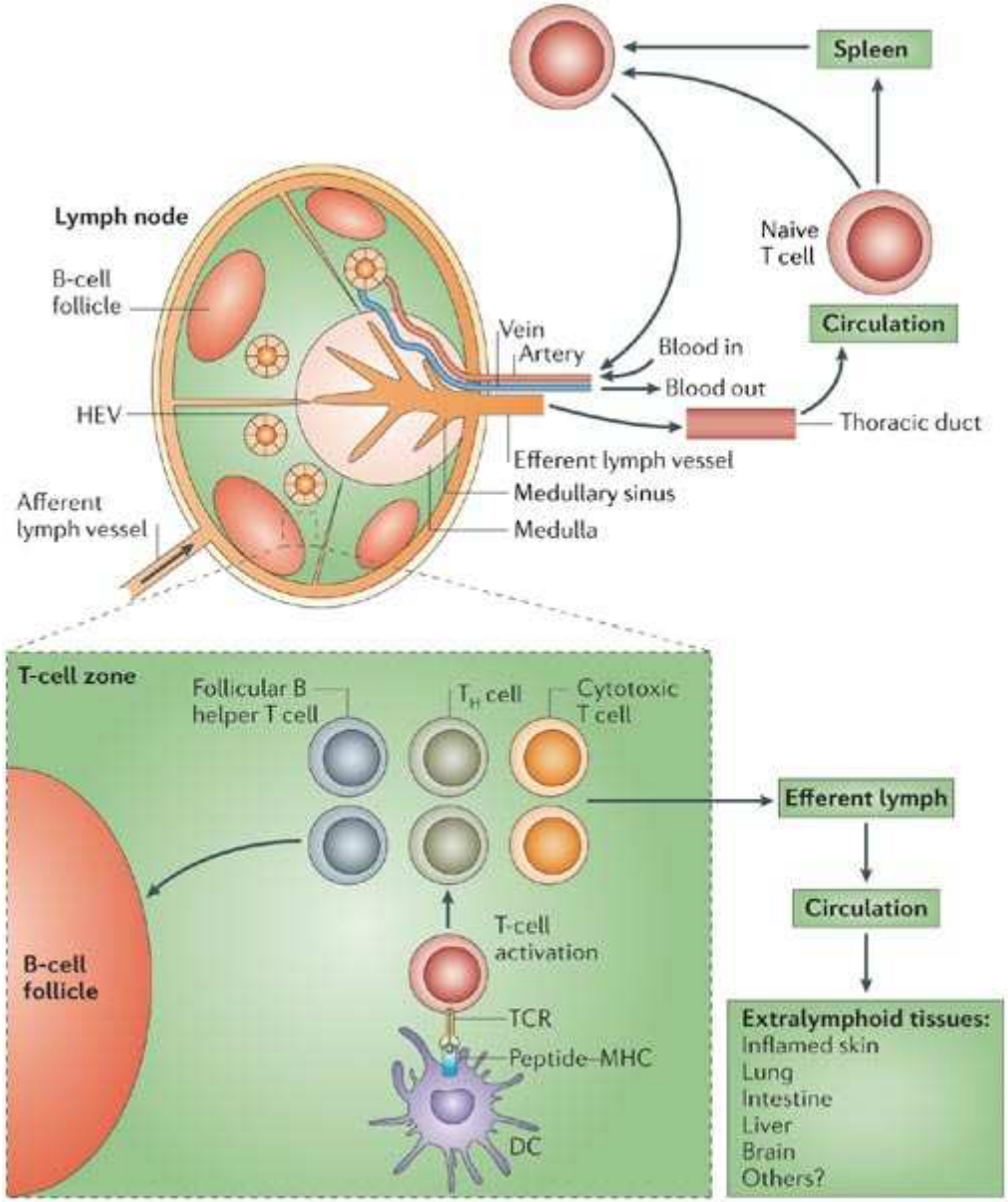
Doesn’t exclude self-nonself discrimination, but the danger hypothesis will be very hard to disprove experimentally.

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



Optimal activation of naive T cells after antigen recognition requires signals through early co-stimulatory molecules, such as CD28–CD80/CD86, CD27–CD70 and CD40L–CD40. After antigen stimulation together with signals through CD28, activated T cells express OX40, 4-1BB and cytotoxic T lymphocyte antigen 4 (CTLA4) on their cell surface. Similarly, stimulation of antigen-presenting dendritic cells with CD40L through CD40, or lipopolysaccharide (LPS) through Toll-like receptors (TLRs), induces optimal OX40L and 4-1BBL expression. So, efficient interaction between OX40 and OX40L probably occurs 1–2 days after antigen recognition. During the effector phase, as the affinity of CTLA4 for CD80/CD86 is much higher than that of CD28, CD80/CD86 on antigen-presenting cells (APCs) preferentially binds to CTLA4 on activated T cells, resulting in suppression of T-cell activation. Ligation of OX40 on T cells by OX40L on APCs can induce the activation of nuclear factor- κB (NF-κB). It has been shown that crucial OX40-specific signals for memory T-cell generation are transmitted through TRAF2 (tumour-necrosis factor receptor-associated factor 2). Sustained PKB/AKT activation in activated T cells has also been shown to be important for OX40-specific effector T-cell survival. OX40-induced survival of effector T cells might contribute to the generation of memory T cells, in which expression of the anti-apoptotic proteins BCL-2, BCL-X_L and BFL1 is maintained. Furthermore, OX40 signals through T-cell–APC interactions also contribute to the optimal reactivation of memory T cells. PKB, protein kinase B; TCR, T-cell receptor.



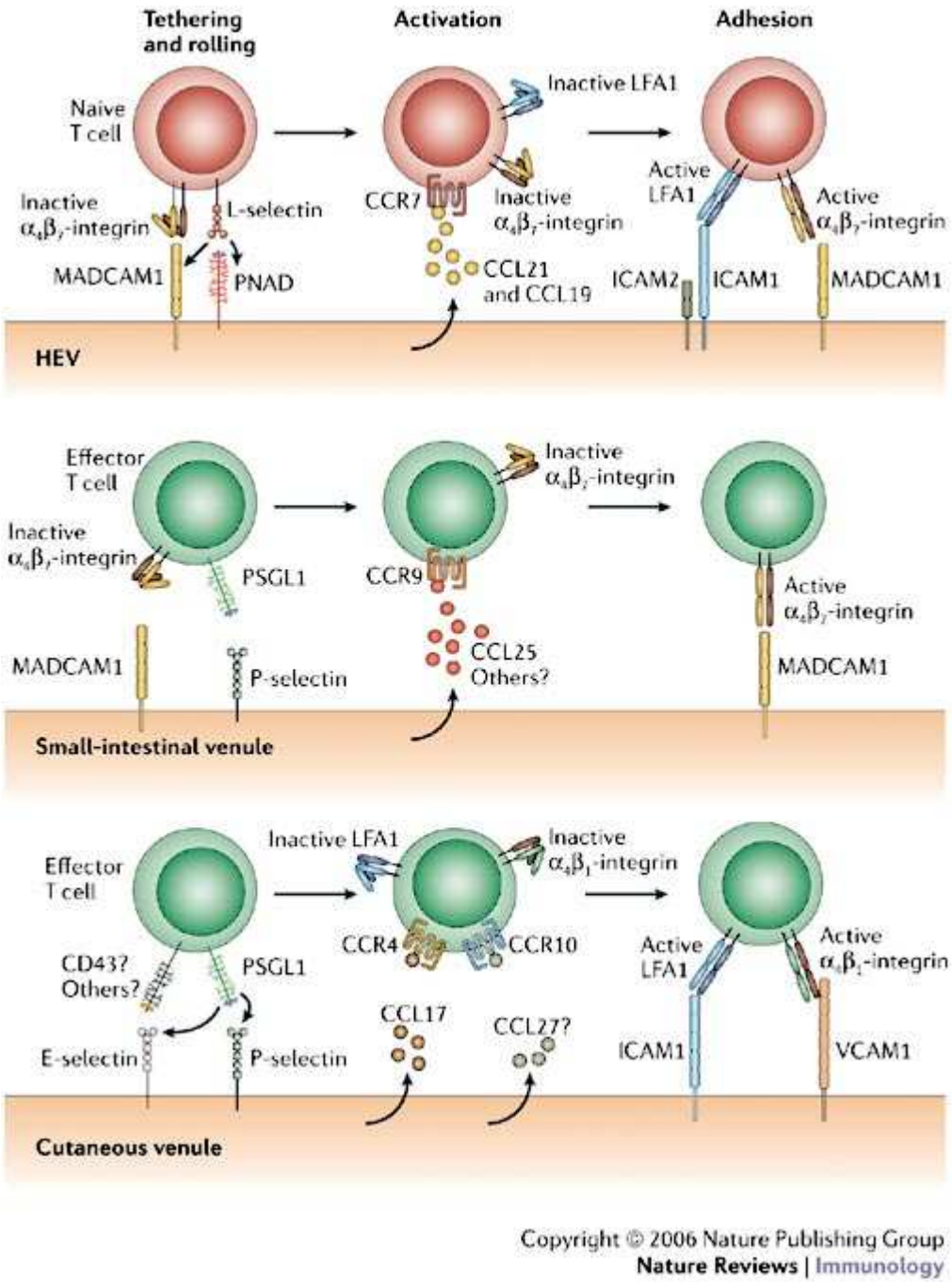
Naive T cells continually circulate through secondary lymphoid organs and the spleen in search of their cognate peptide–MHC complex on the surface of antigen-presenting cells.

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).

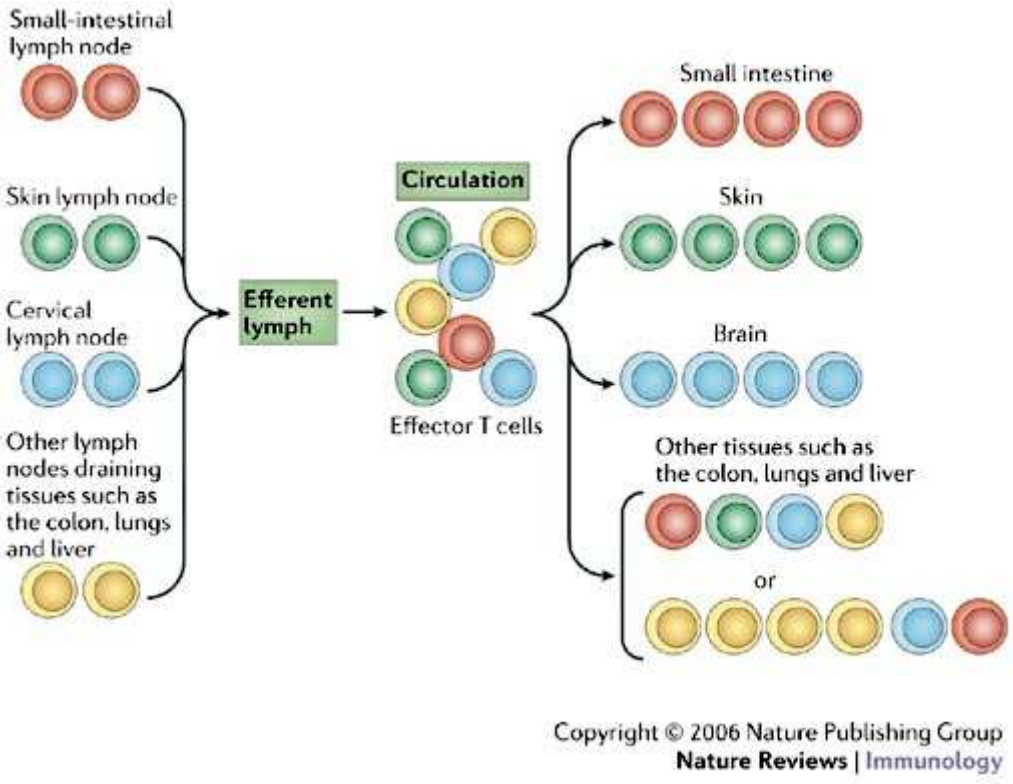
A subset of $CD4^+$effector T cells together with $CD8^+$ effector T cells leave the lymph node, return to the circulation through the lymph system, and might enter a wide range of extralymphoid tissues, where they help to coordinate immune responses in the periphery. DC, dendritic cell; TCR, T-cell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



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….

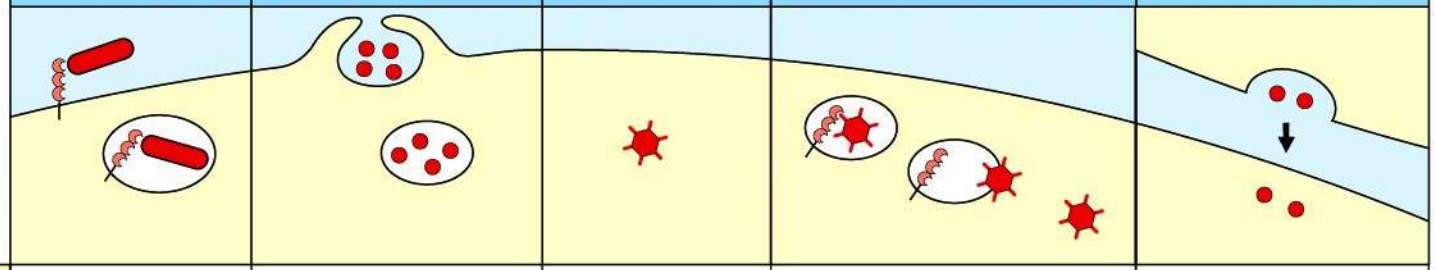
	Routes of antigen processing and presentation by dendritic cells				
	Receptor-mediated endocytosis	Macro-pinocytosis	Viral infection	Cross-presentation after phagocytic or macropinocytic uptake	Transfer from incoming dendritic cell to resident dendritic cell
					
Type of pathogen presented	Extracellular 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)

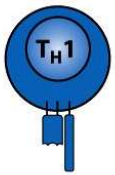
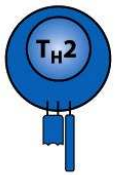
	CD8 cytotoxic T cells	CD4 T_H1 cells	CD4 T_H2 cells	CD4 T_H17 cells	CD4 regulatory T cells (various types)
Types of effector T cell					
Main functions in adaptive immune response	Kill virus-infected cells	Activate infected macrophages Provide help to B cells for antibody production	Provide help to B 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)

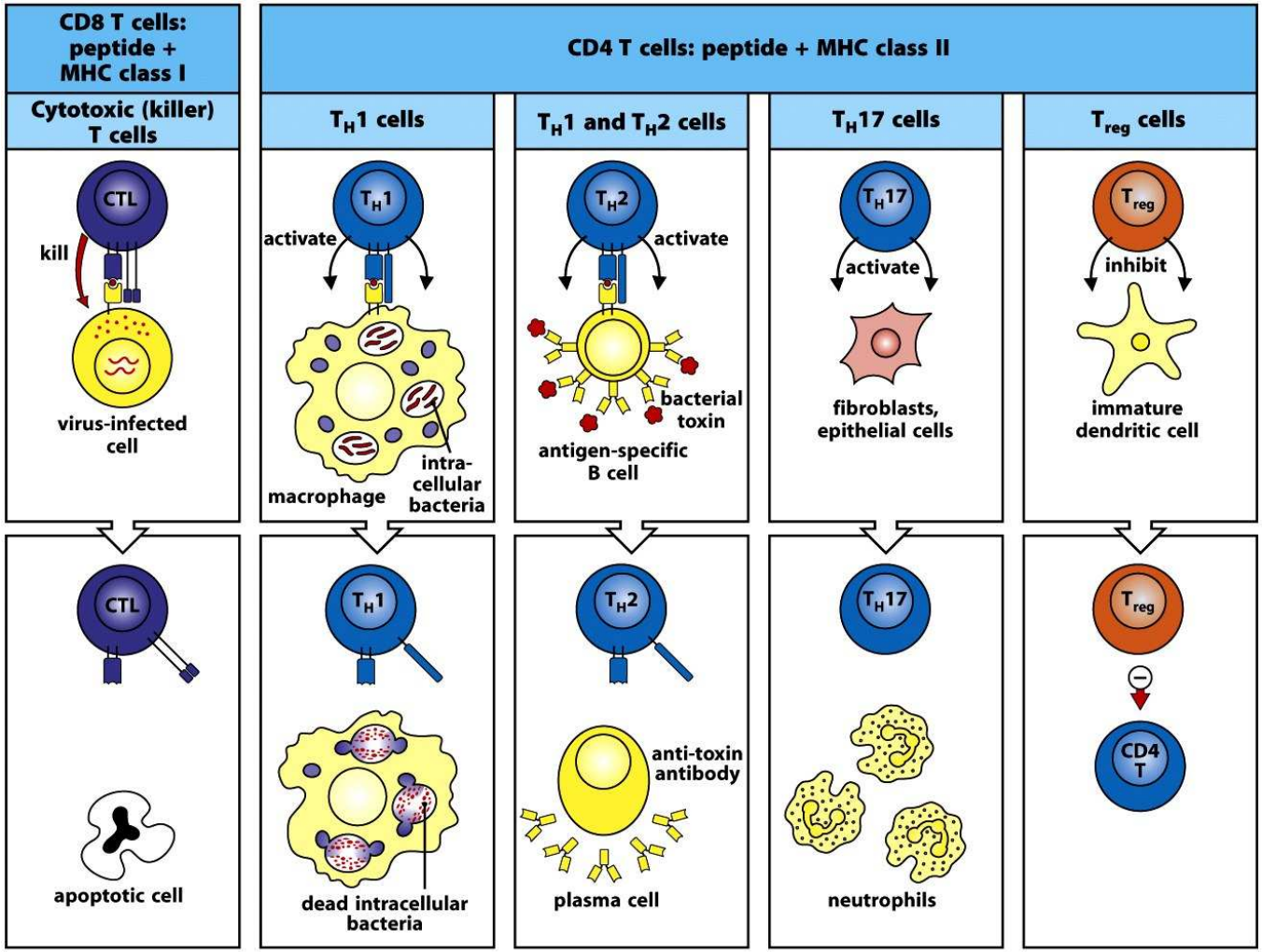
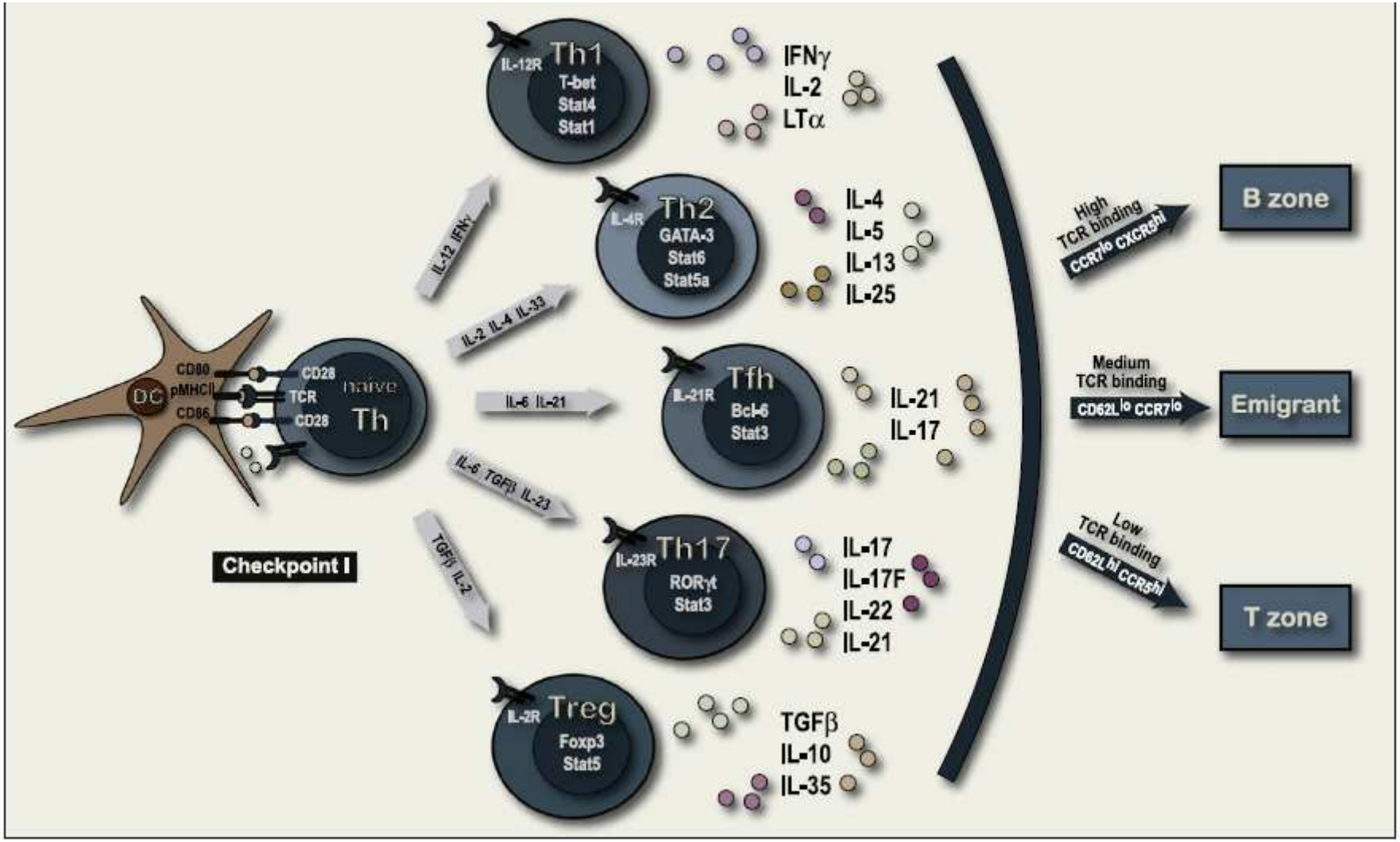


Figure 8-27 Immunobiology, 7ed. (© Garland Science 2008)



CÉLULAS T CD4^{+}

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

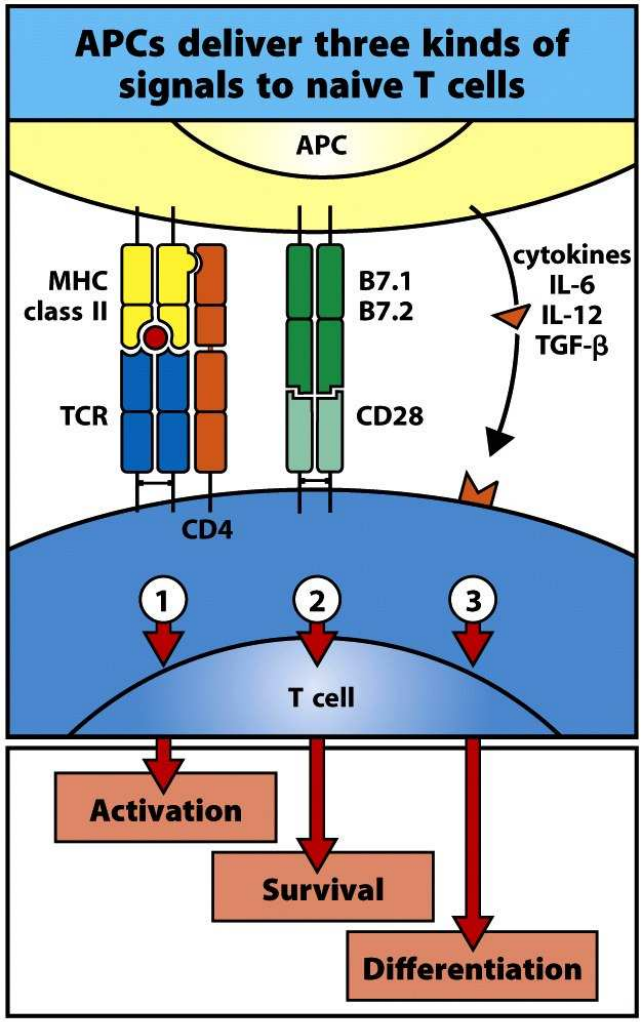


Figure 8-19 Immunobiology, 7ed. (© Garland Science 2008)

Diferenciación de células Th

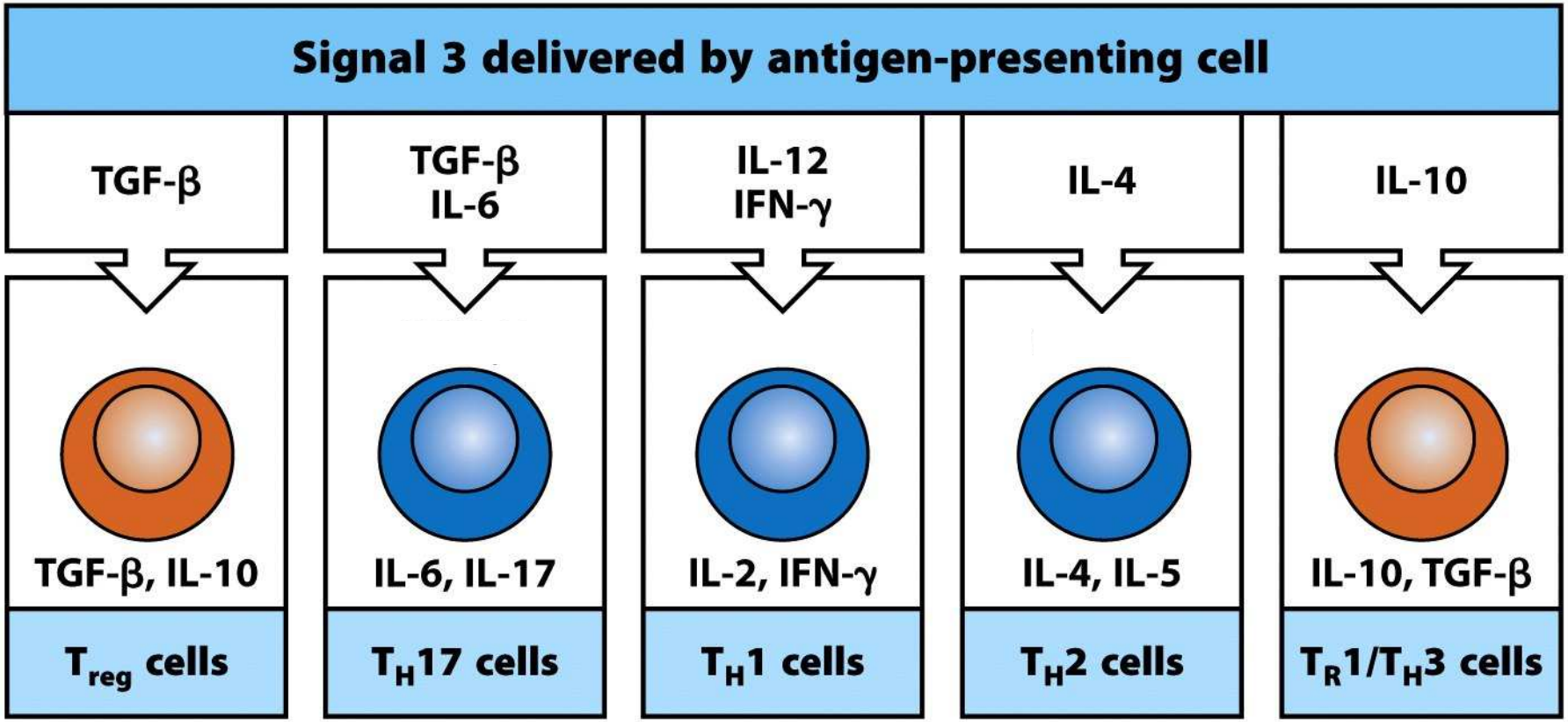
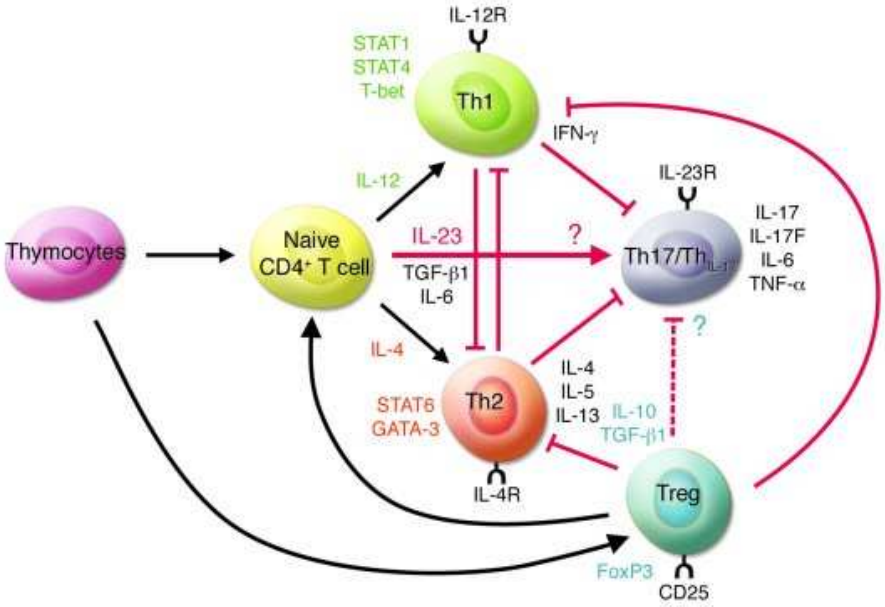
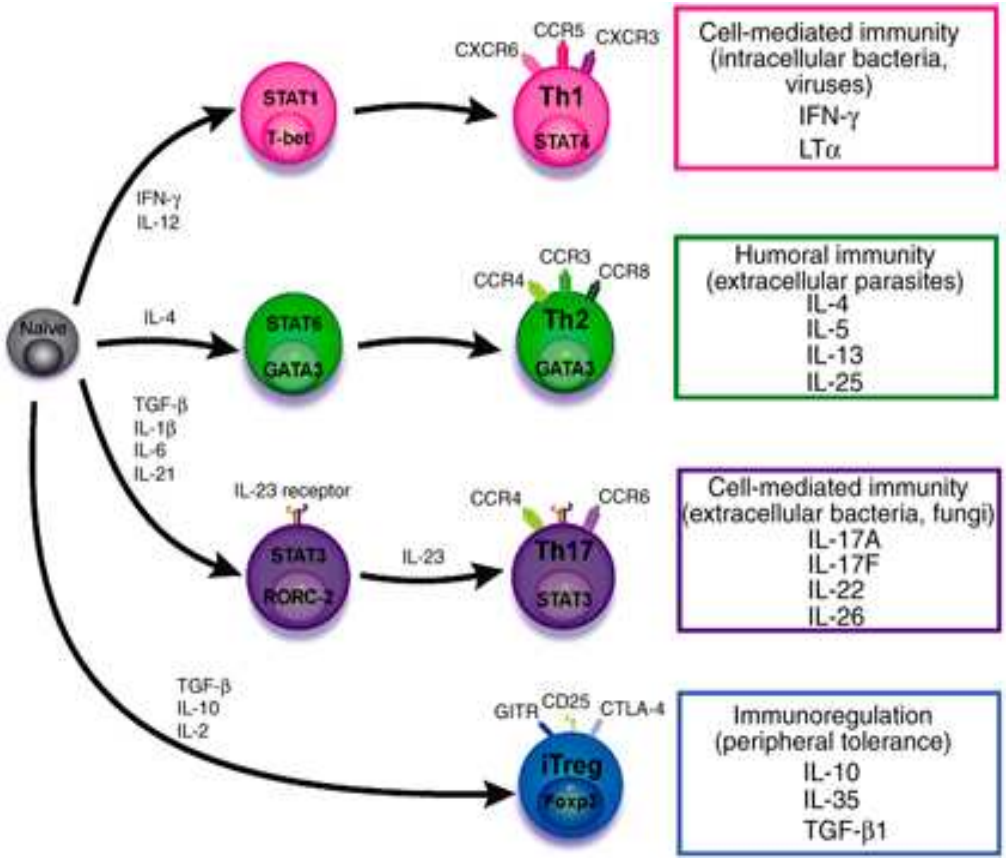


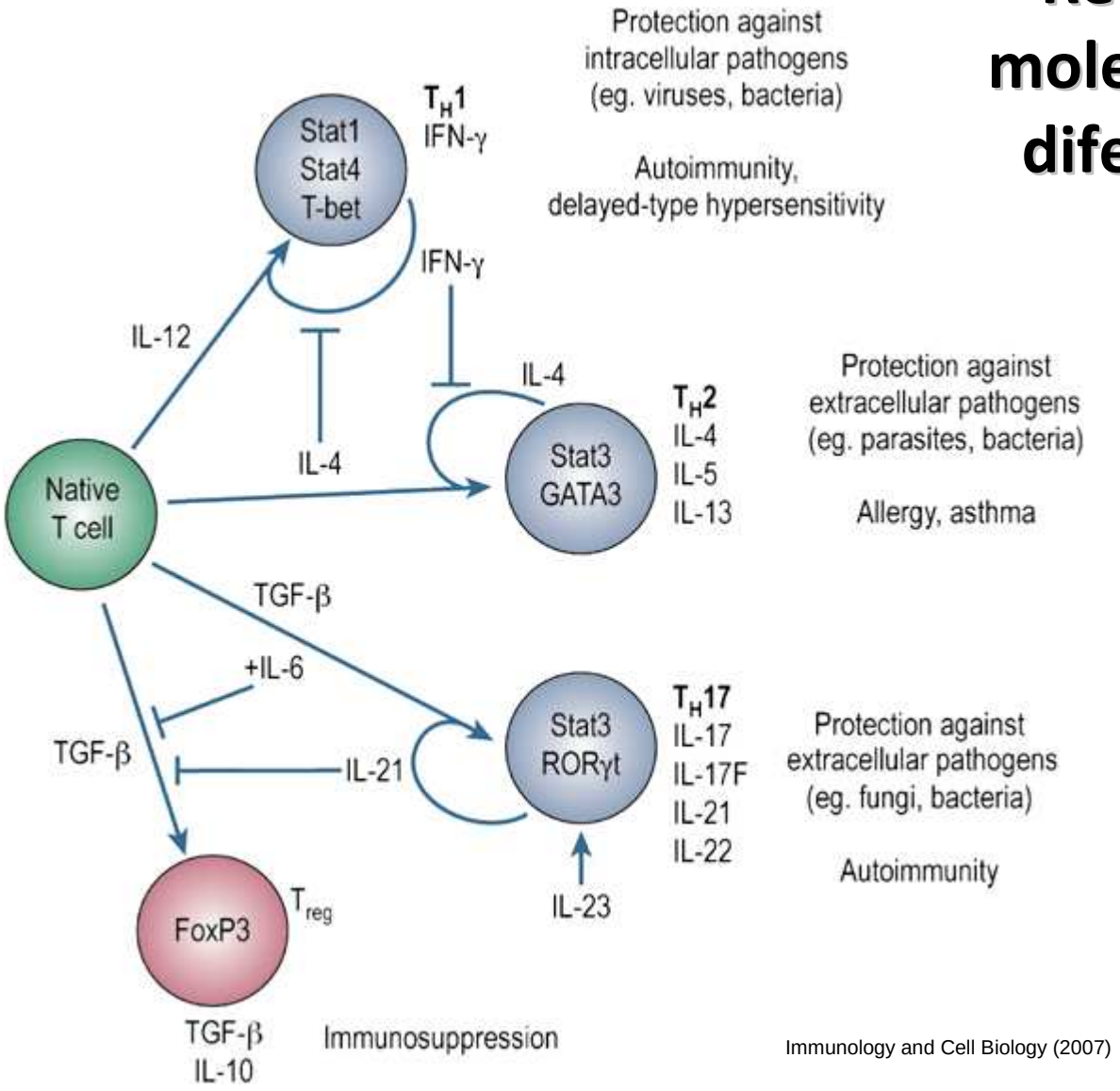
Figure 8-29 Immunobiology, 7ed. (© Garland Science 2008)





Nature Reviews Immunology **8**, 337-348 (May 2008)

Requerimientos moleculares para la diferenciación de células Th

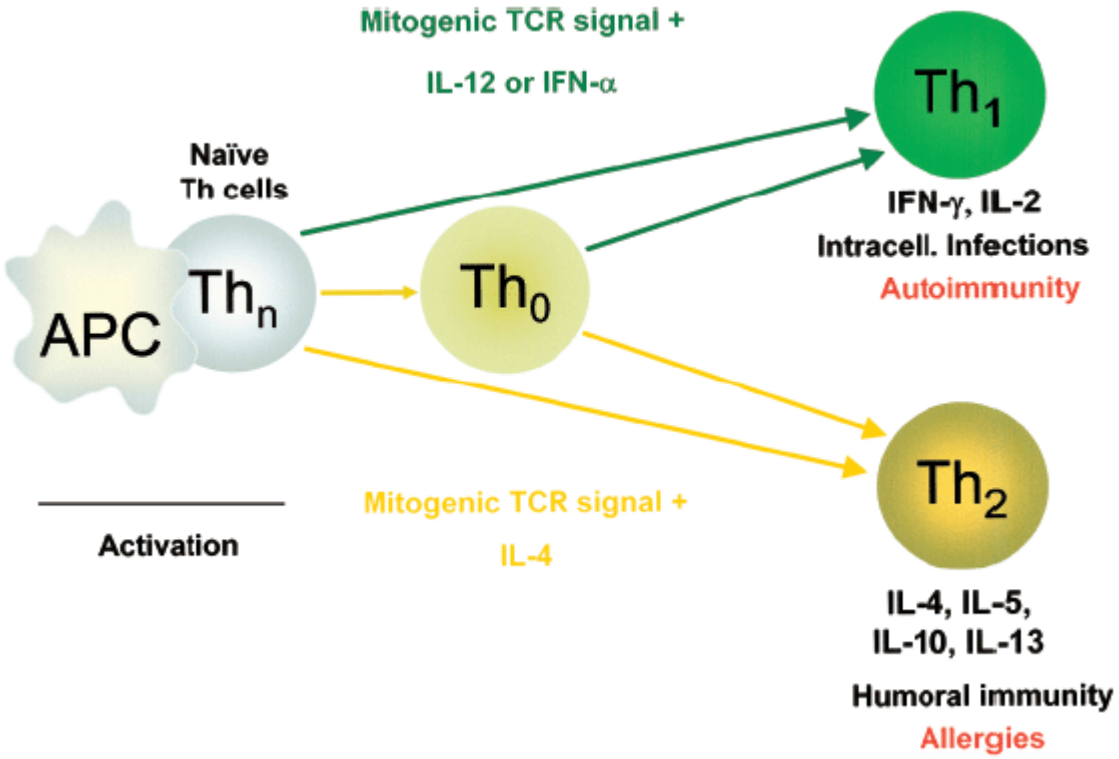


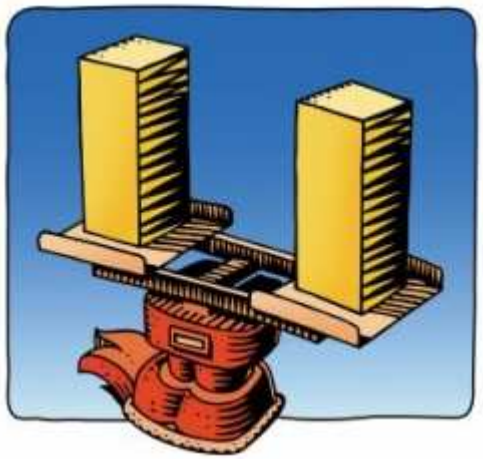
Immunology and Cell Biology (2007)

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

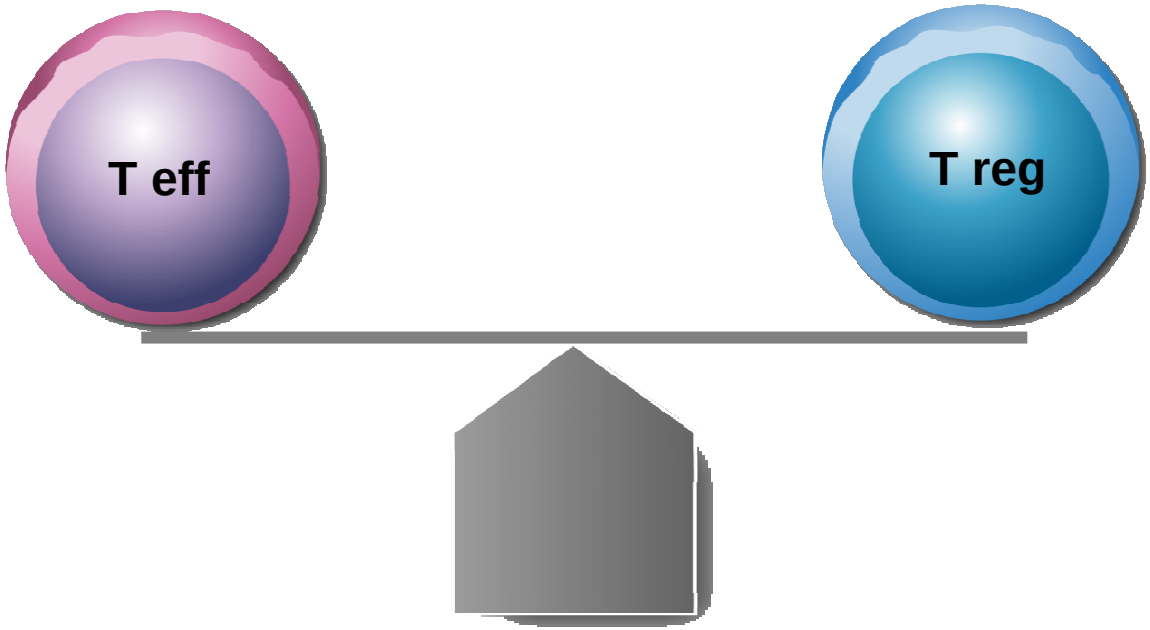
FOXP3, forkhead box P3; GATA3, GATA-binding protein 3; HLX, H2.0-like homeobox 1; IFNγ, interferon-γ; IL, interleukin; ND, not determined; ROR, retinoic-acid-receptor-related orphan receptor; STAT, signal transducer and activator of transcription; TGFβ, transforming growth factor-β; T_H, T helper.



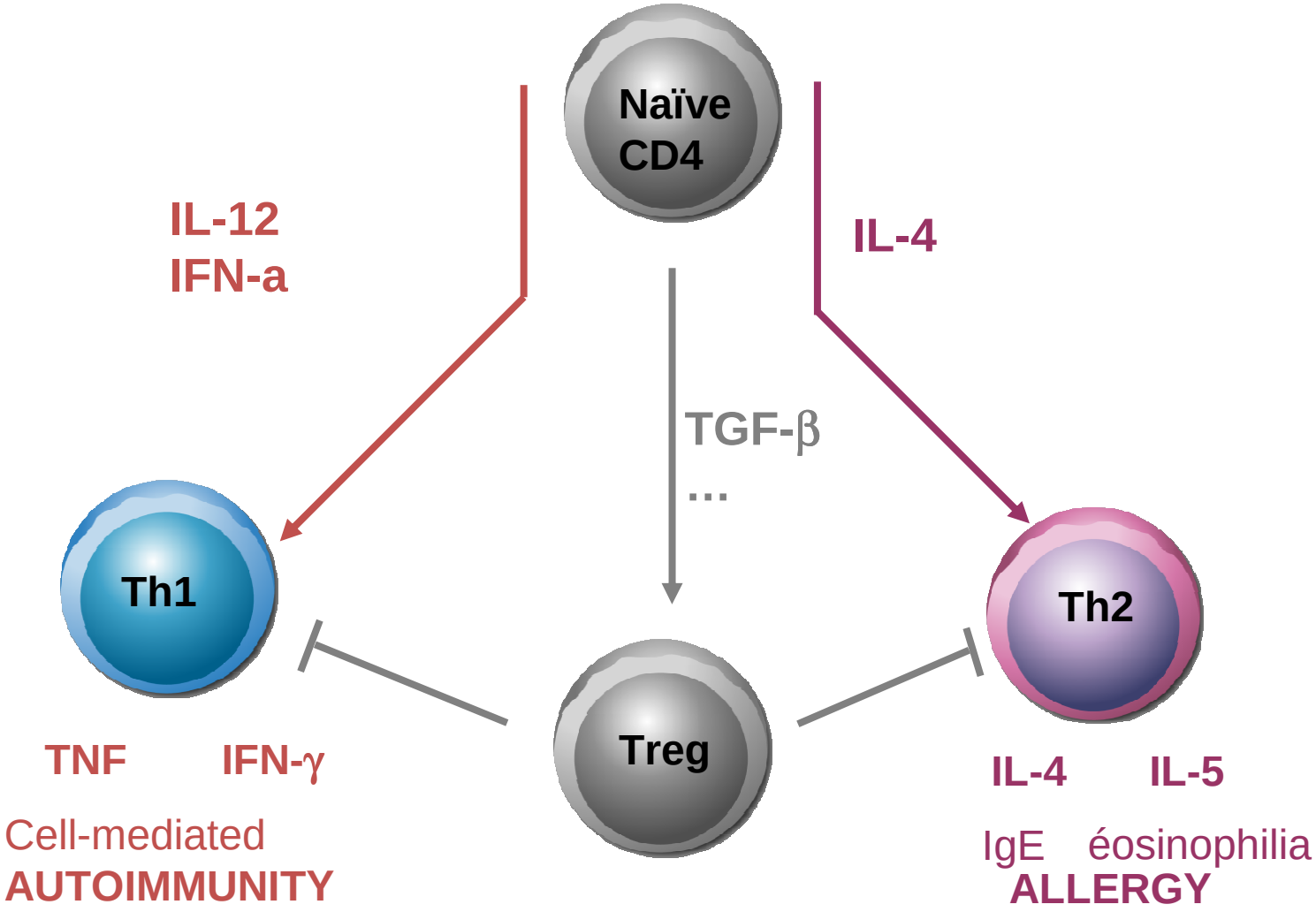


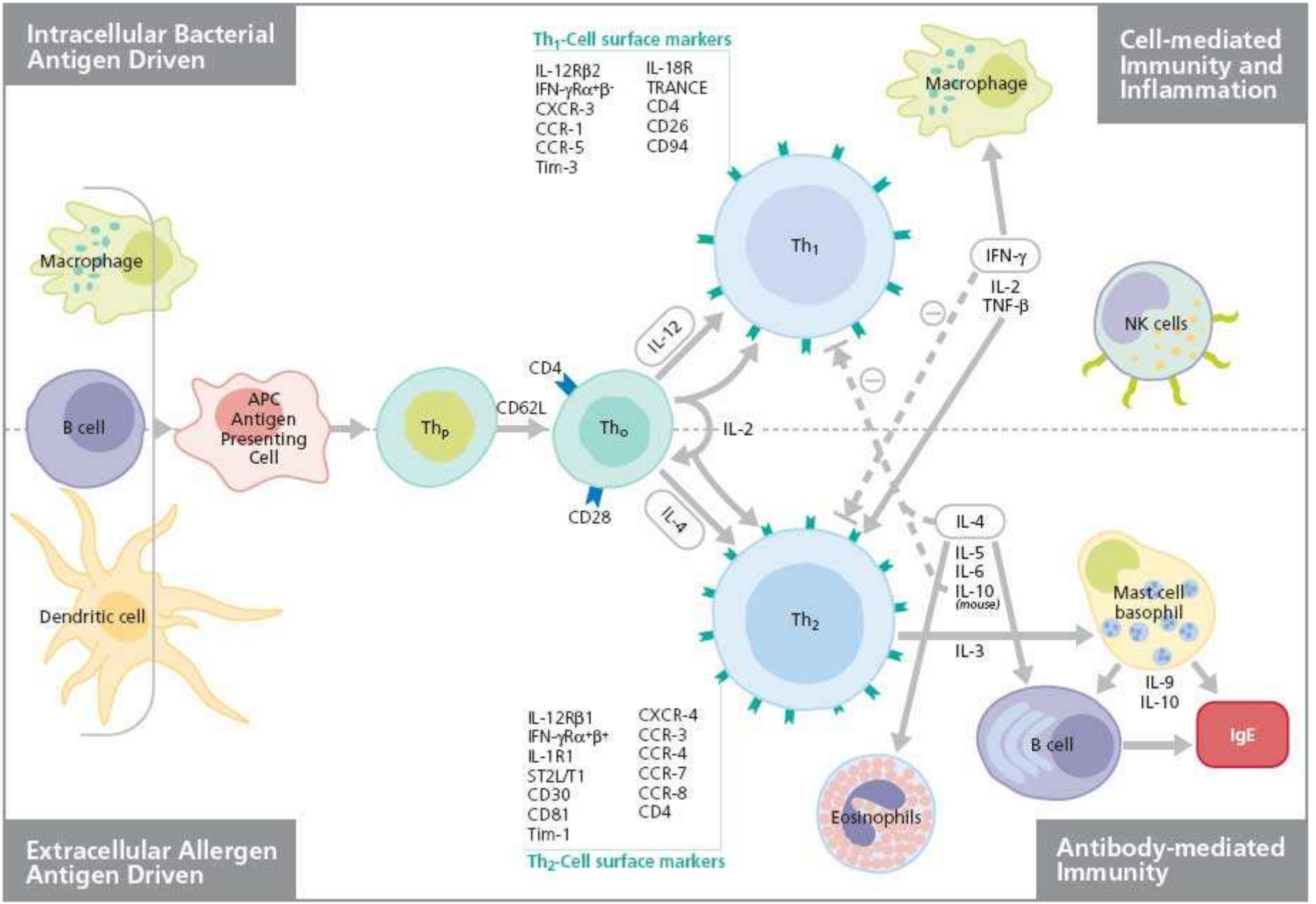
LINFOCITOS TH1-TH2

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

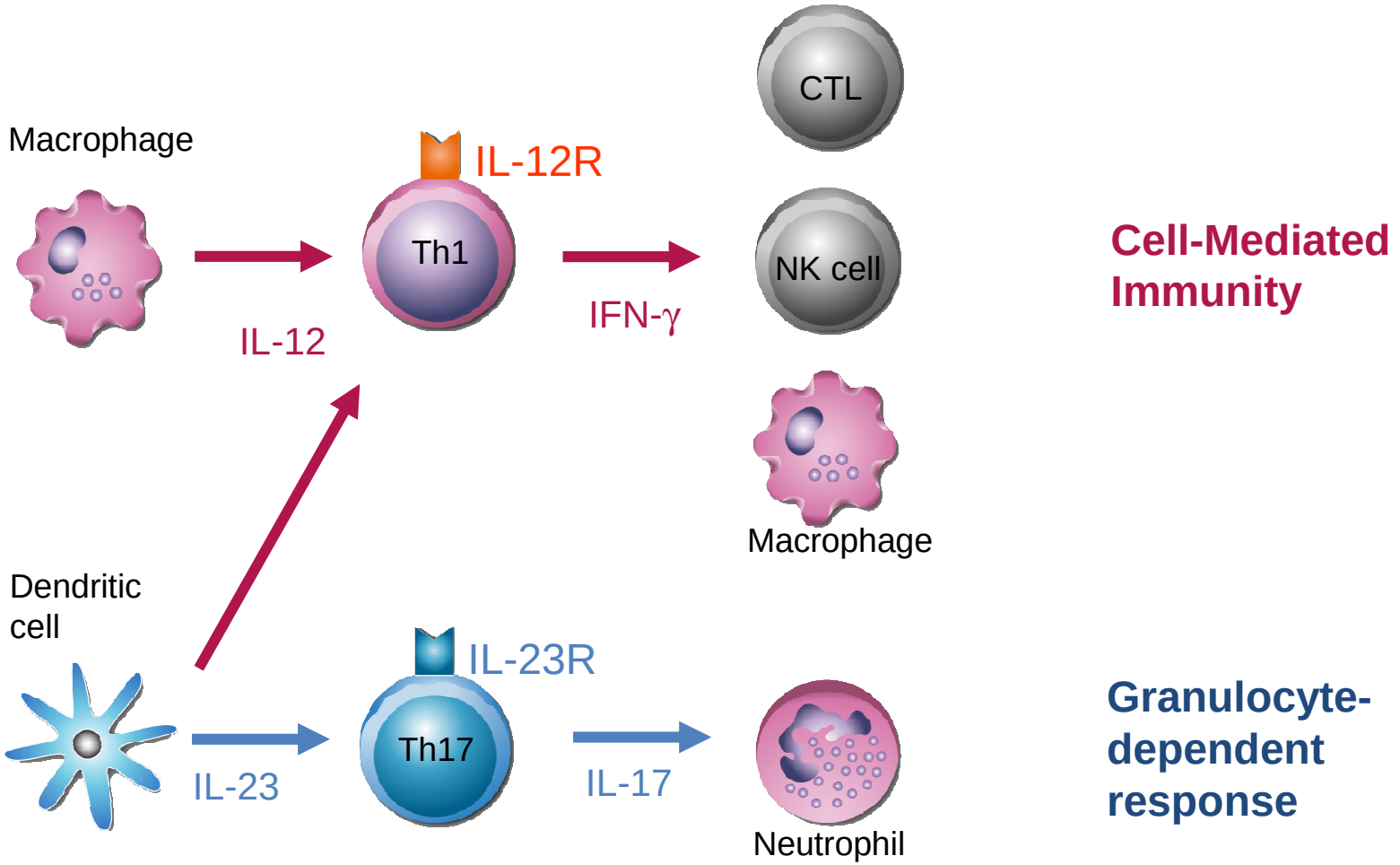


El paradigmaTh1-Th2



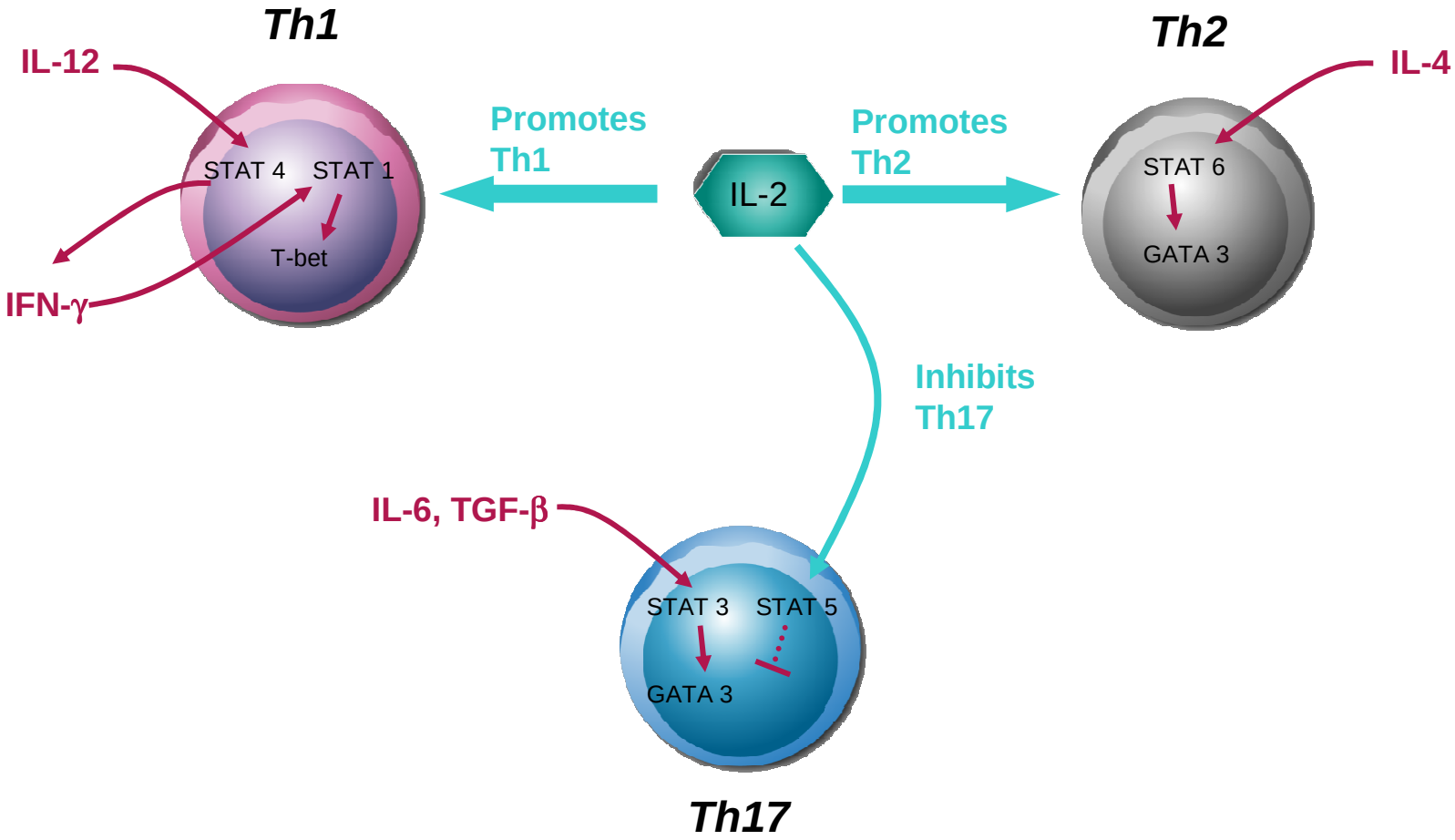

Intracellular Bacterial Antigen Driven
Th1-Cell surface markers
IL-12Rβ2
IFN-γRα+β-
CXCR-3
CCR-1
CCR-5
Tim-3
IL-18R
TRANCE
CD4
CD26
CD94
Macrophage
Cell-mediated Immunity and Inflammation
Th1
IFN-γ
IL-2
TNF-β
NK cells
Macrophage
IL-12
CD4
B cell
APC Antigen Presenting Cell
Thp
CD62L
Tho
IL-2
CD28
IL-4
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

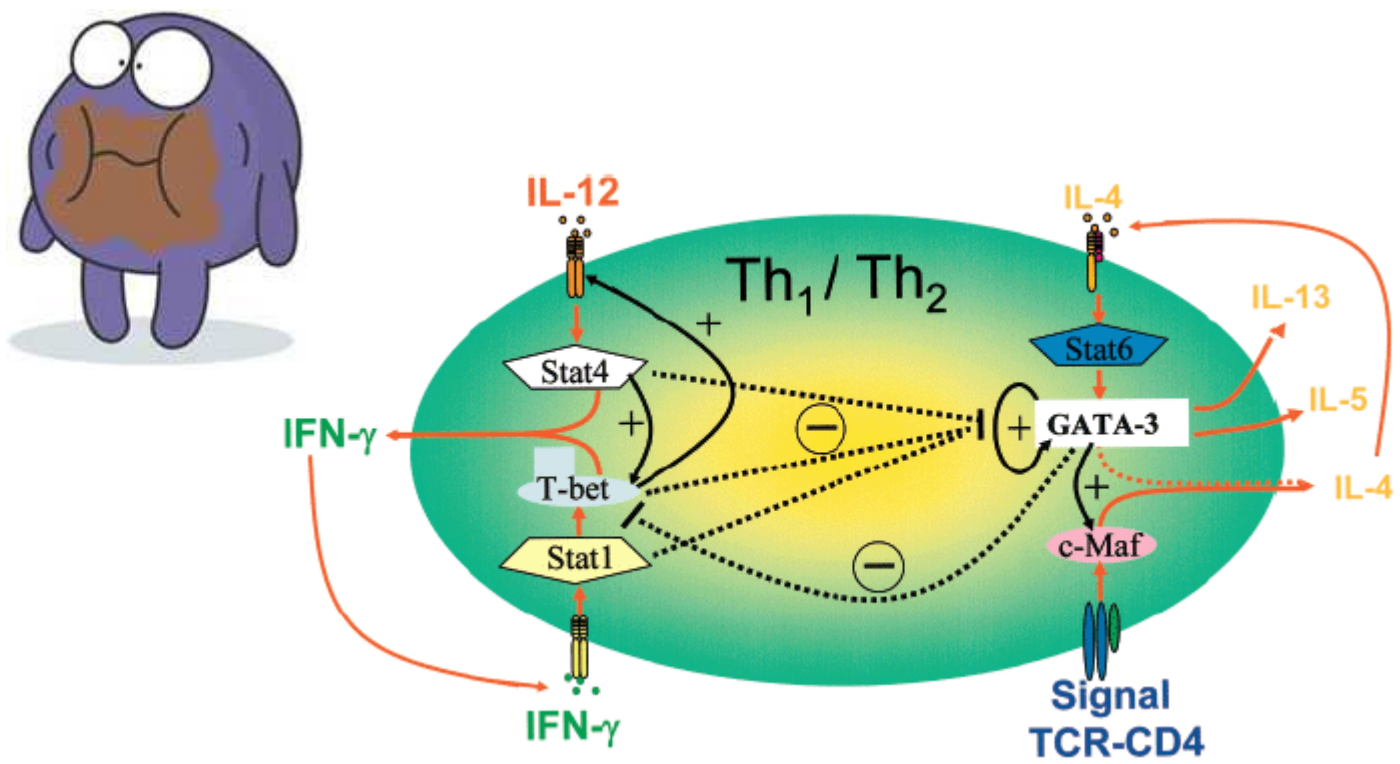


Adapted from Iwakura & Ishigame, J Clin Invest 116:1218-1222 (2006)

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



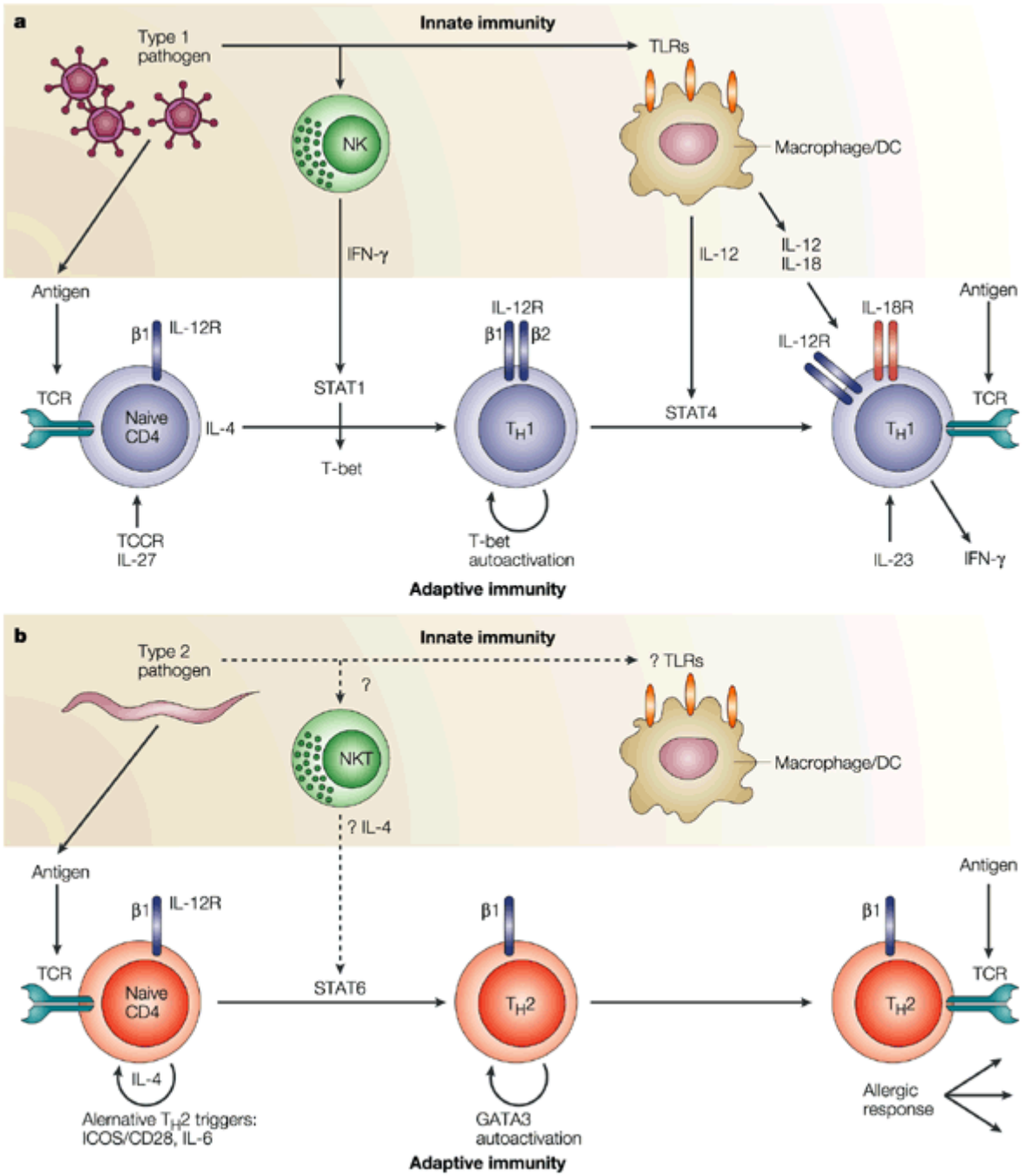
Adapted from Stockinger, Immunity, 26:278-279, 2007



Two major pathways for TH1 cytokine production have been identified. IL-12 signaling via its receptor activates Stat4, which upregulates IFN-γ transcription. IFN-γ, on the other hand, activates Stat1, which upregulates the leading TH1 transcription factor, T-bet, further enhancing IFN-γ production. Both pathways upregulate each other via positive feedback mechanisms (solid black arrows, +).

For TH2 cytokine production, two major pathways are identified: IL-4–mediated signaling through the IL-4 receptor activating Stat6 and GATA-3, leading to IL-5 and IL-13 production; and signaling through the TCR-CD4 complex upregulating c-Maf, which in turn initiates and enhances IL-4 transcription. The response controlled by GATA-3 is further enhanced by an autoactivation process and a positive feedback on c-Maf expression. All three factors for TH1 cytokine production (Stat4, Stat1, and T-bet) inhibit GATA-3, which in turn downmodulates T-bet (dotted black line; -).

Journal of Investigative Dermatology Symposium Proceedings ISSN: 1087-0024



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

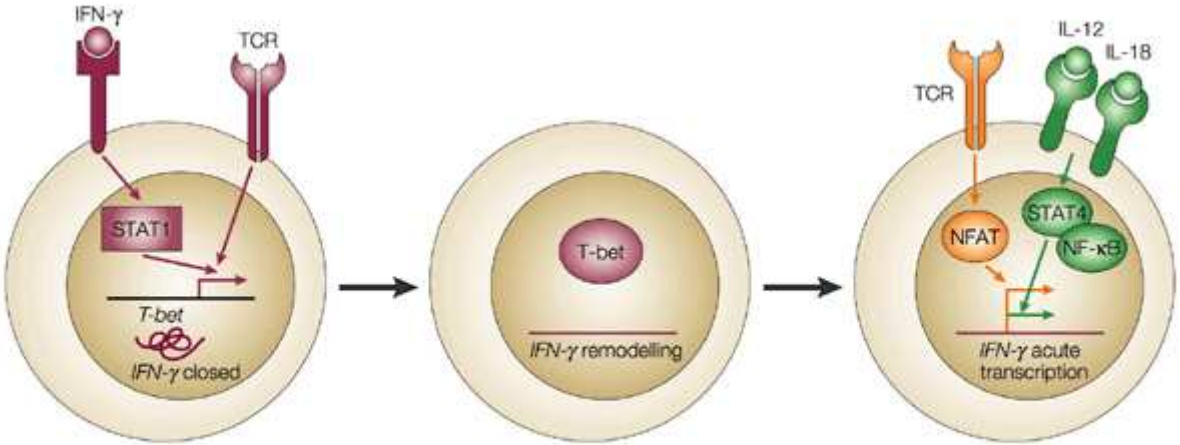
Th1 Related Markers

NAME	DESCRIPTION / FUNCTION	MW (KDA)
CCR1, MIP-1α-R, RANTES-R	Chemokine receptor for Th1. Binds to MIP-1-α, MIP-1-δ, RANTES, and MCP-3. Responsible for affecting stem cell proliferation.	63
CD4 (L3T4)	Co-receptor in antigen-induced T-cell activation; thymic differentiation; regulation of T-B lymphocyte adhesion; primary receptor for HIV.	55
CD26 (DPP IV, THAM)	Co-stimulatory molecule in T cell activation; associated marker of auto-immune diseases, adenosine deaminase-deficiency and HIV pathogenesis.	110
CD94	Assembled with other C-type lectins (NKG2) forms inhibitory or activating receptors for HLA class I.	43
CD119 (IFN-γ Rα)	IFN-γ regulates IL-18R α expression by preventing the negative effects of IL-4 and by inducing/maintaining IL-12 receptor β 2 expression.	35
CD183 (CXCR3)	Th1 cell surface marker. Cytokine that acts as a major participant in Th1-induced inflammation.	40
CD195 (CCR5, Cmkbr5)	Regulates lymphocyte chemotaxis activation and trans-endothelial migration during inflammation. Neutralizes HIV infection. Acts as a co-receptor for HIV-1. Expressed on immature dendritic cells.	45
CD212 (IL-12Rβ2)	Th1 cell surface marker. The expression of this gene is up-regulated by IFNγ in Th1 cells, and plays a role in Th1 cell differentiation. The up-regulation of this gene is found to be associated with a number of infectious diseases, such as Crohn's disease and leprosy, which is thought to contribute to the inflammatory response and host defense.	97
GM-CSF	Pleiotropic cytokine that stimulates proliferation, maturation and function of hematopoietic cells. Produced by both Th1 and Th2 cells.	22
Granzyme B	Serine protease involved in the perforation of target cells and initiation of proteolysis that leads to apoptosis.	28
IFN-α	Antiviral and anti-proliferative activity.	19-26
IL-2 (TCGF)	IL-2 is the most potent T cell growth factor produced by Th1 cells.	15-17
IL-12	Inducer of proliferation and differentiation of Th1 cells. Dominant cytokine in Th1 development. Secreted by APCs, neutrophils, and keratinocytes. IL-4 and IL-10 inhibit IL-12 production by dendritic cells and macrophages.	70
IL-15 (IL-T)	IL-15 is a recently discovered cytokine with the ability to stimulate the proliferation activity of Th1 and/or Th2 lymphocytes.	14-15
IL-18R	A co stimulatory factor for the induction of IL-12–mediated IFNγ production by Th1 cells, but also can induce IL-4 production and thus facilitate the differentiation of Th2 cells.	93, 160, 220
IL-23	IL-23 affects Th1 differentiation by directly stimulating proliferative responses of Th1 cells.	
IL-27	A member of the IL-12 family mainly produced by activated monocytes and dendritic cells. IL-27 induces expression of the IL-12 receptor that in turn allows the Th1 response to be maintained.	
IL-27R (TCCR, WSX-1)	The IL-27R (WSX-1) is required to suppress T cell hyperactivity during infection.	
Lymphotoxin (LT-α)	Plays a role in the recruitment and activation of neutrophils and in lymphoid organogenesis. Being chemically similar to TNF, LT-α is also a mediator of acute inflammatory responses. LT-α is made by T lymphocytes.	60-70
Perforin	Cytolytic mediator produced by killer lymphocytes.	70
t-bet	Transcription factor for Th1. Regulates the differentiation and function of lymphocytes.	58
Tim-3 (Havcr2, Timd3, Q8WW60)	Th1-specific cell surface protein. Tim-3 regulates macrophage activation and severity of an autoimmune disease.	16
TNF-β	Secreted by Th1 and cytotoxic T lymphocytes (Tc cells). It targets tumor cells, macrophages and neutrophils. Exerts inflammatory and cytotoxic effects.	19
TRANCE	Expressed on the surface of activated CD4+ Th1 cells. The ligand for TRANCE is RANK. TRANCE increases expression of inflammatory cytokines, such as IL-1 and IL-6, and secretion of IL-12, which can promote differentiation of CD4+ T cells into Th1 cells.	42

Th2 Related Markers

NAME	DESCRIPTION / FUNCTION	MW (KDA)
CCR3	Chemokine receptor for Th2. Binds to eotaxin, eotaxin-3, MCP-3, MCP-4, RANTES and MIP-1 δ. Alternative co receptor with CD4 for HIV-1 infection.	41
CCR4	Chemokine receptor for Th2. High affinity for TARC/SCYA17 and MDC/SCYA22.	41
CCR7 (CD197, EB/1, Cmkbr7)	Th2 cell surface marker. Receptor for the MIP-3β chemokine, probable mediator of EBV effects on B lymphocytes.	46-52
CCR8 (Cy6, Cmkbr8)	CCR8 may contribute to the proper positioning of activated T cells within the antigenic challenge sites and specialized areas of lymphoid tissues. Th2 cell surface marker that plays a role in the control of Th2 responses, and may represent a potential target for treatment of allergic diseases.	41
CD4 (L3T4, W3/25)	Co-receptor in antigen-induced T-cell activation; thymic differentiation; regulation of T-B lymphocyte adhesion; primary receptor for HIV. Th2 cell surface marker.	55
CD30 (Ber-H2, Ki-1)	Member of TNFR family, involved in negative selection of T cells in thymus and TCR mediated cell death; expressed on R-S cells in Hodgkin's lymphomas. Th2 cell surface marker.	120
CD81 (TAPA-1)	Th2 cell surface marker. CD81 directly enhances Th1 and Th2 cell activation, but preferentially induces proliferation of Th2 cells upon long-term stimulation.	26
CD184 (CXCR4)	Homing receptor of hematopoietic progenitor cells; co-stimulation of B cells; induces apoptosis; involved with the entry of HIV-1. Cell surface marker for Th2 cells.	
CD278 (ICOS, H4, AILIM, CRP-1)	ICOS costimulation leads to the induction of Th2 cytokines without augmentation of IL-2 production, suggesting a role for ICOS in Th2 cell differentiation and expansion.	40-70
c-maf	Transcription factor involved in the induction of production of IL-4.	
CRTH2	Th2 cell surface marker. Putative G protein-coupled receptor GPR44 (chemoattractant receptor-homologous molecule expressed on Th2 cells).	43
GATA-3	Transcription factor associated with induction of Th2 cells.	49
GM-CSF	Pleiotropic cytokine that stimulates proliferation, maturation and function of hematopoietic cells. Produced by both Th1 and Th2 cells.	22
IFN-γR	Th2 cell surface marker.	60-65
IgD	IgD production by normal B cells is regulated positively by Th2 cytokines and negatively by Th1 cytokines.	
IL-1R	Th2 cell surface marker.	
IL-4 (BCDF, BCDF-1, BSF-1)	Th2 cytokine that stimulates antibody production by B cells. IL-4 stimulates Th2 activity and suppresses Th1 activity.	20
IL-5 (EDF, BCGFII, TRF)	Th2 cytokine that stimulates antibody production by B cells. A potent factor that drives bone marrow progenitor cells into IL-4-producing eosinophils.	32-34
IL-6 (BCSF, BSF-2)	Th2 inducing cytokine.	21-28
IL-9	IL-9 is a pleiotropic cytokine that can induce Th2 cytokine expression. IL-9 is also a candidate gene for asthma and atrophy.	36
IL-10 (CSIF)	Th2 cytokine that inhibits IFN-γ, IL-2, and TNF-β. Inhibits IL-12 production by dendritic cells thus inhibiting pre-Th cells from entering the Th1 pathway.	17-21
IL-12Rβ1	Th2 cell surface marker.	
IL-13	IL-13 promotes the synthesis of IgE antibodies.	11-12
IL-15	IL-15 enhances a Th2 immune response.	14-15
ST2L/T1	ST2L is a stable cell surface marker that distinguishes Th2 from Th1 cells. It is also believed associated with Th2 cells function and is coexpressed with IL-4.	
Tim-1 (Havcr1, Timd1)	A novel allergy and asthma susceptibility gene expressed by Th2 but not Th1 cells.	

Activación de células Th1



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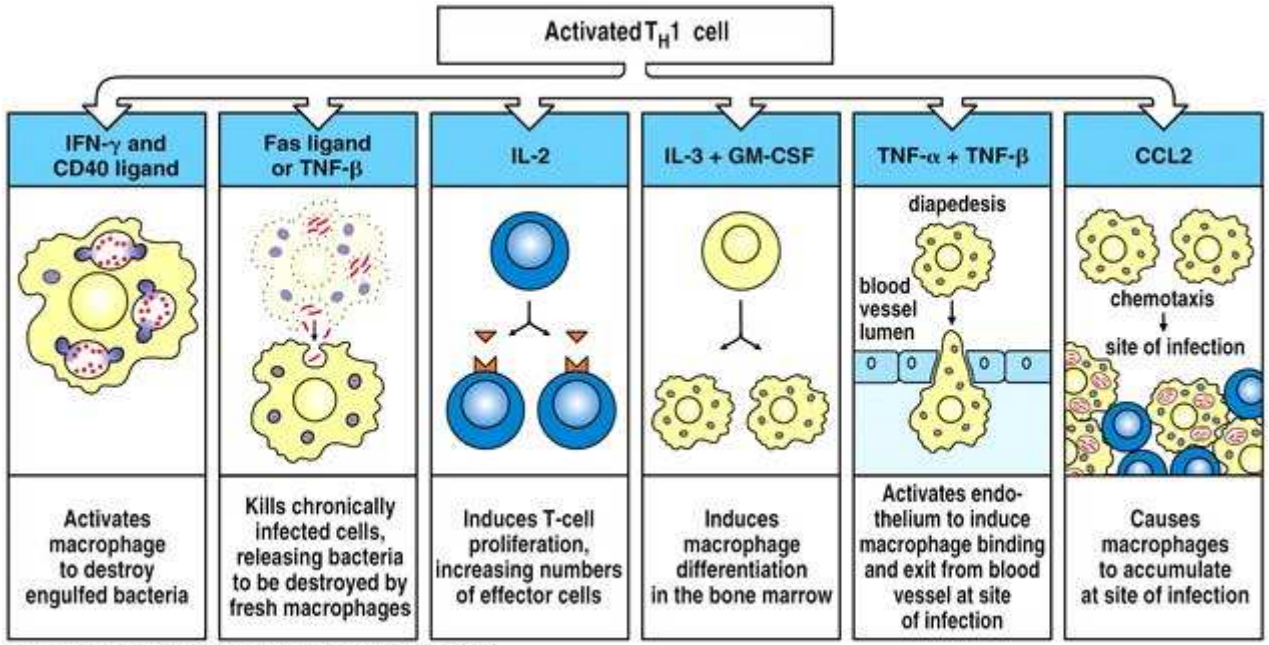


Figure 8-41 Immunobiology, 6/e. (© Garland Science 2005)

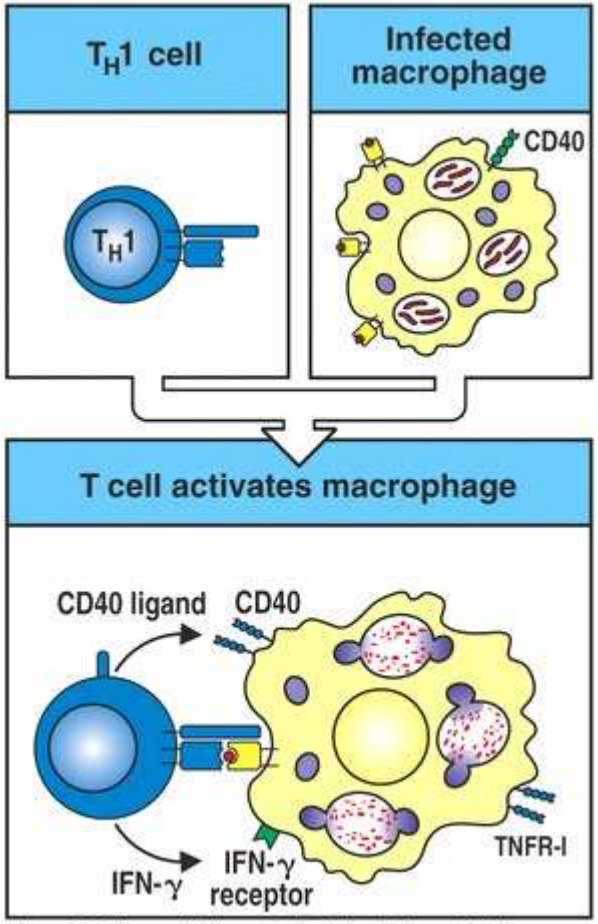


Figure 8-39 Immunobiology, 6/e. (© Garland Science 2005)

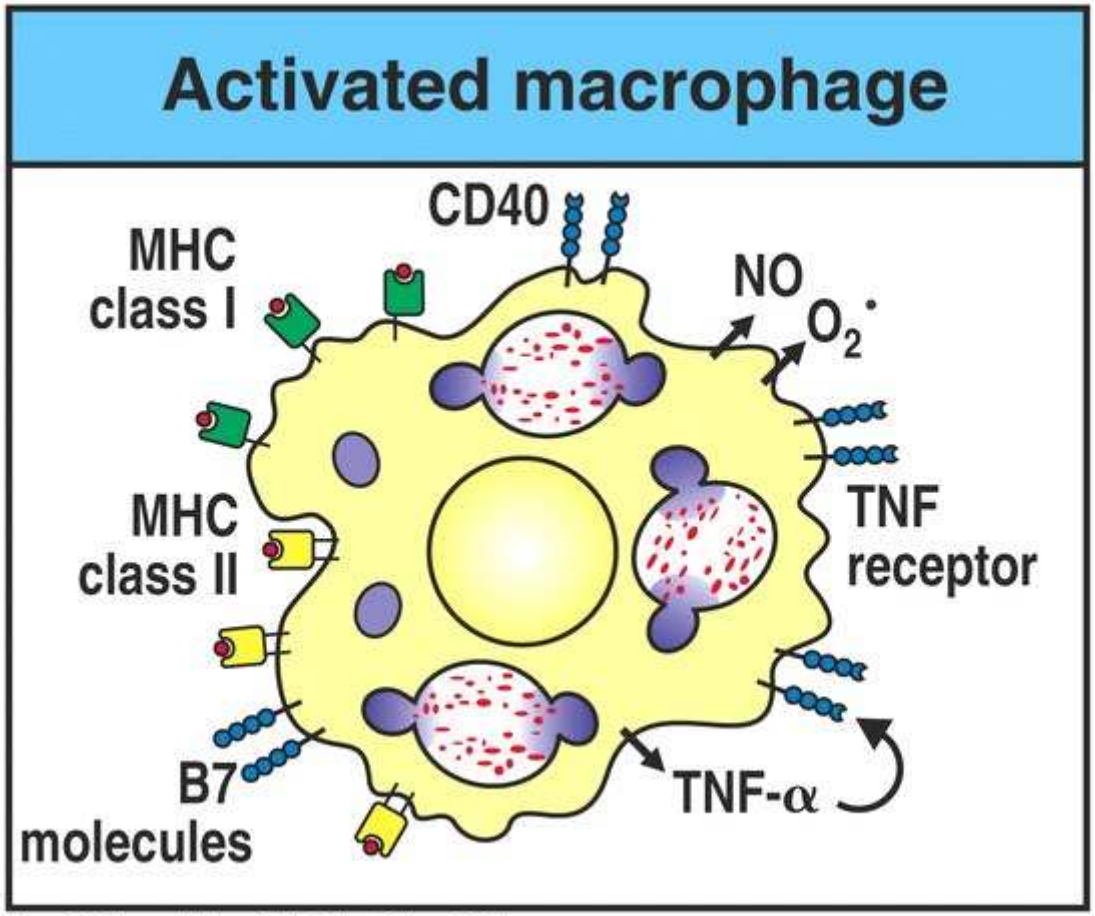
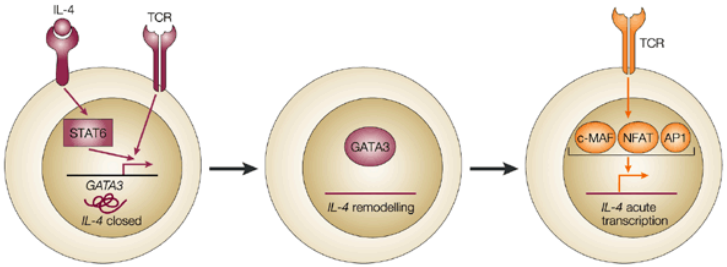
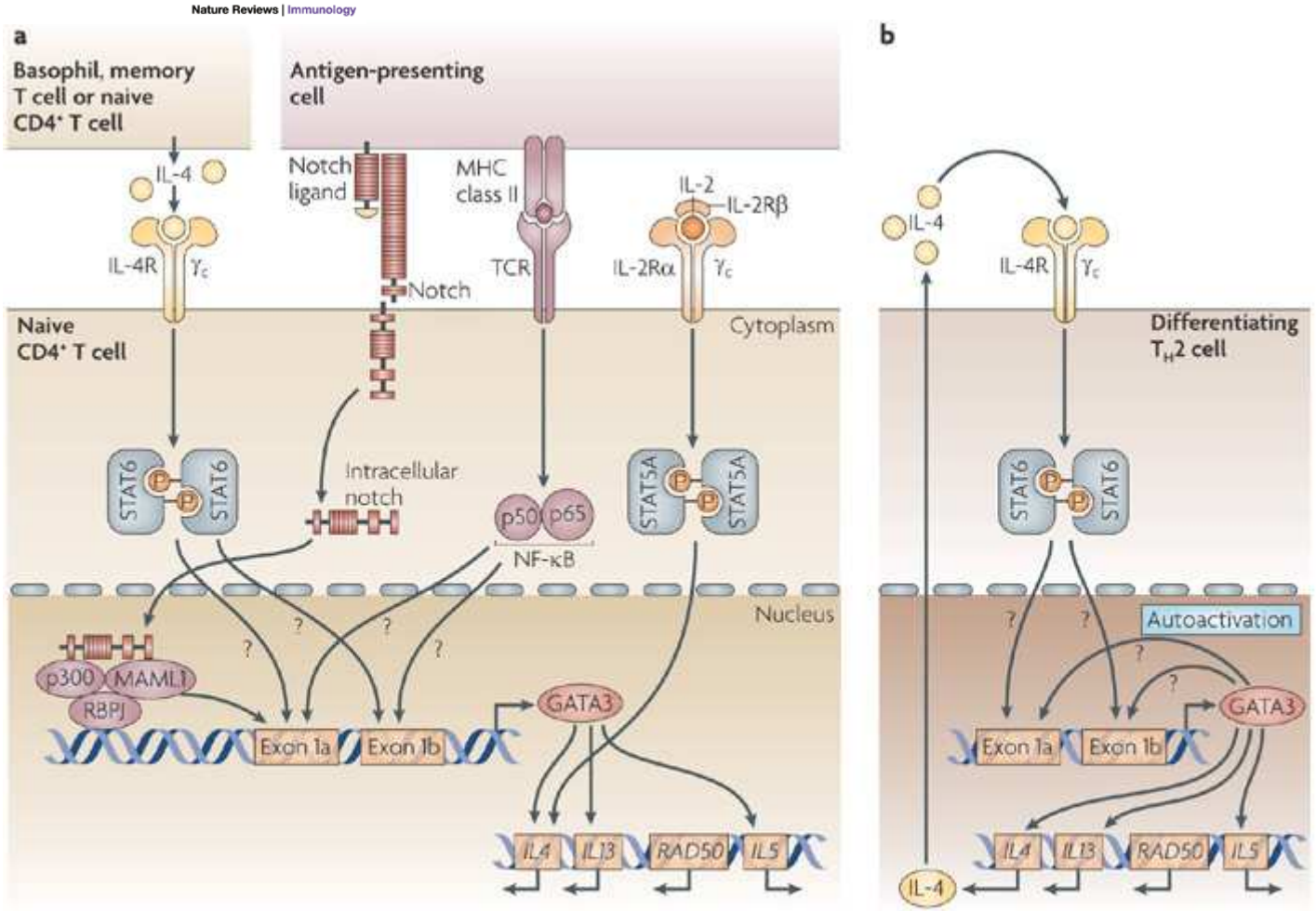


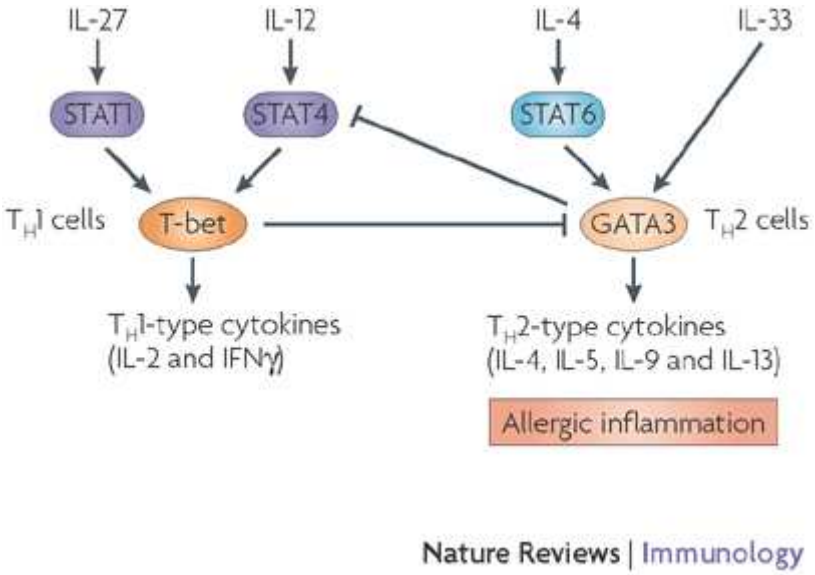
Figure 8-40 Immunobiology, 6/e. (© Garland Science 2005)

Diferenciación de células Th-2

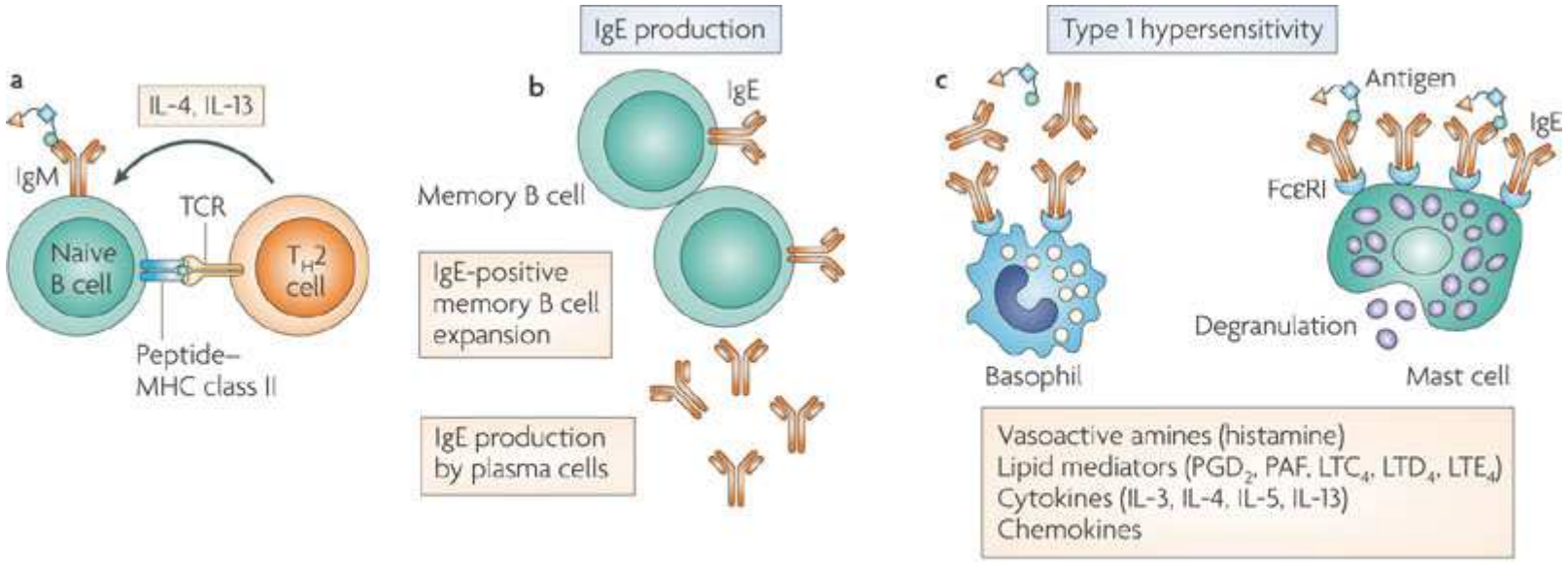




Nature Reviews Immunology 9, 125-135 (February 2009)

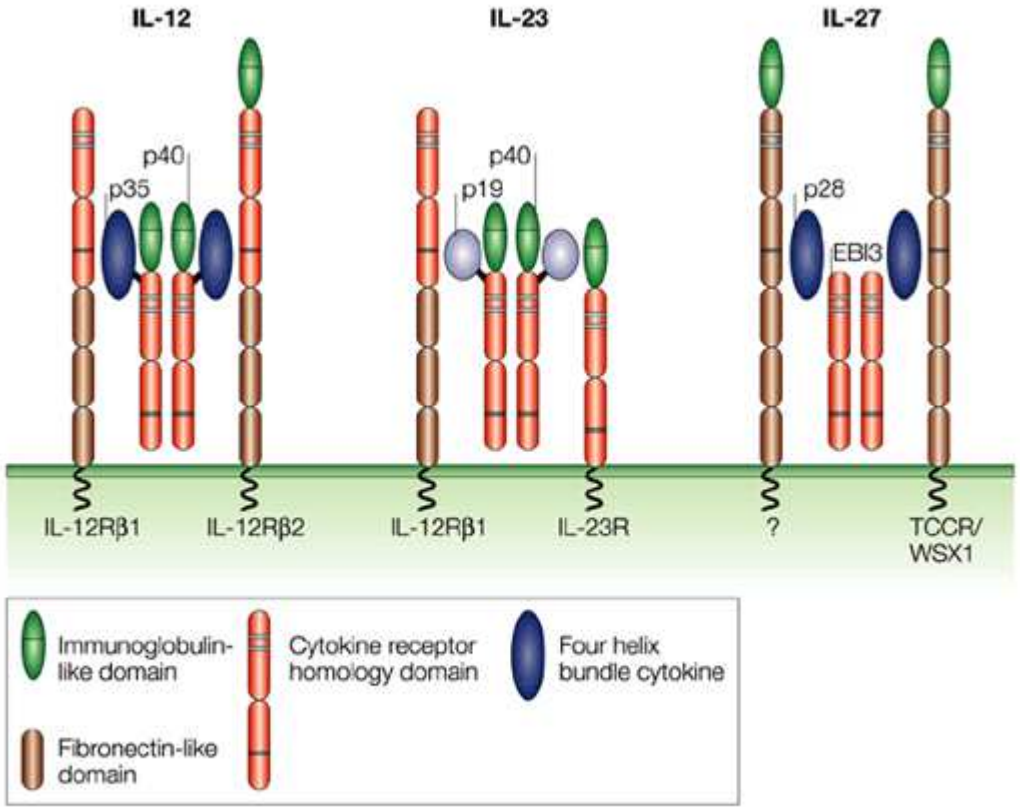


Th-2 en acción



- **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



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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.

IL-27: citocina inmunoduladora

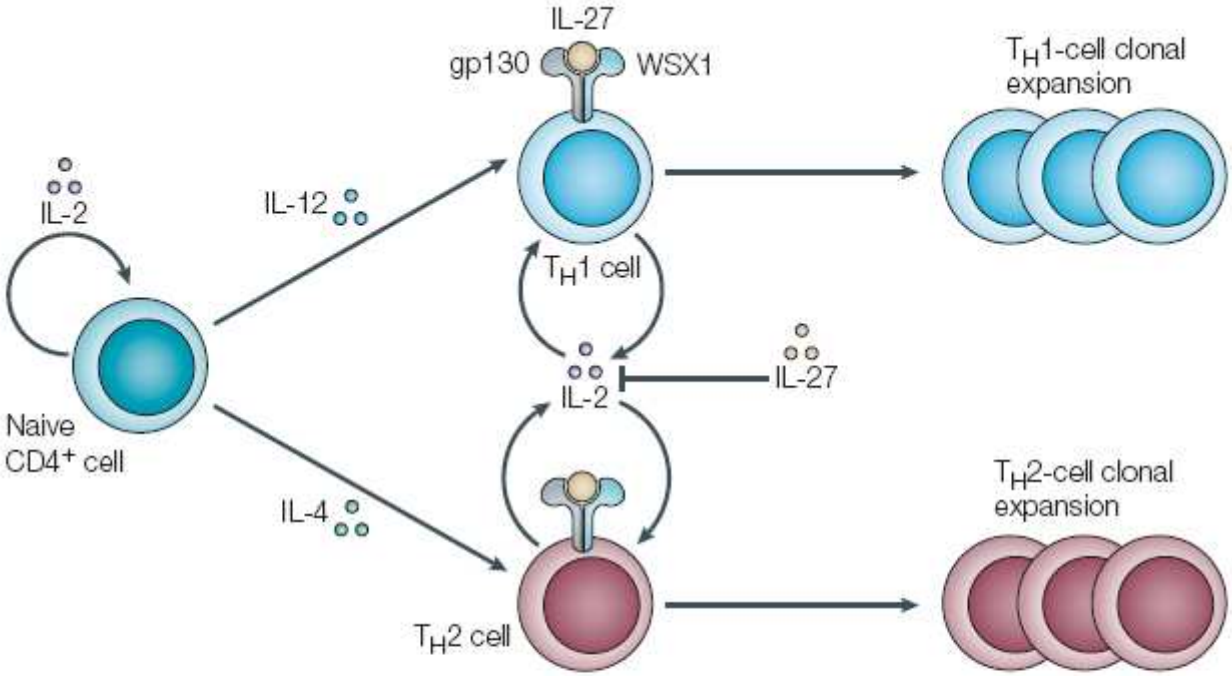
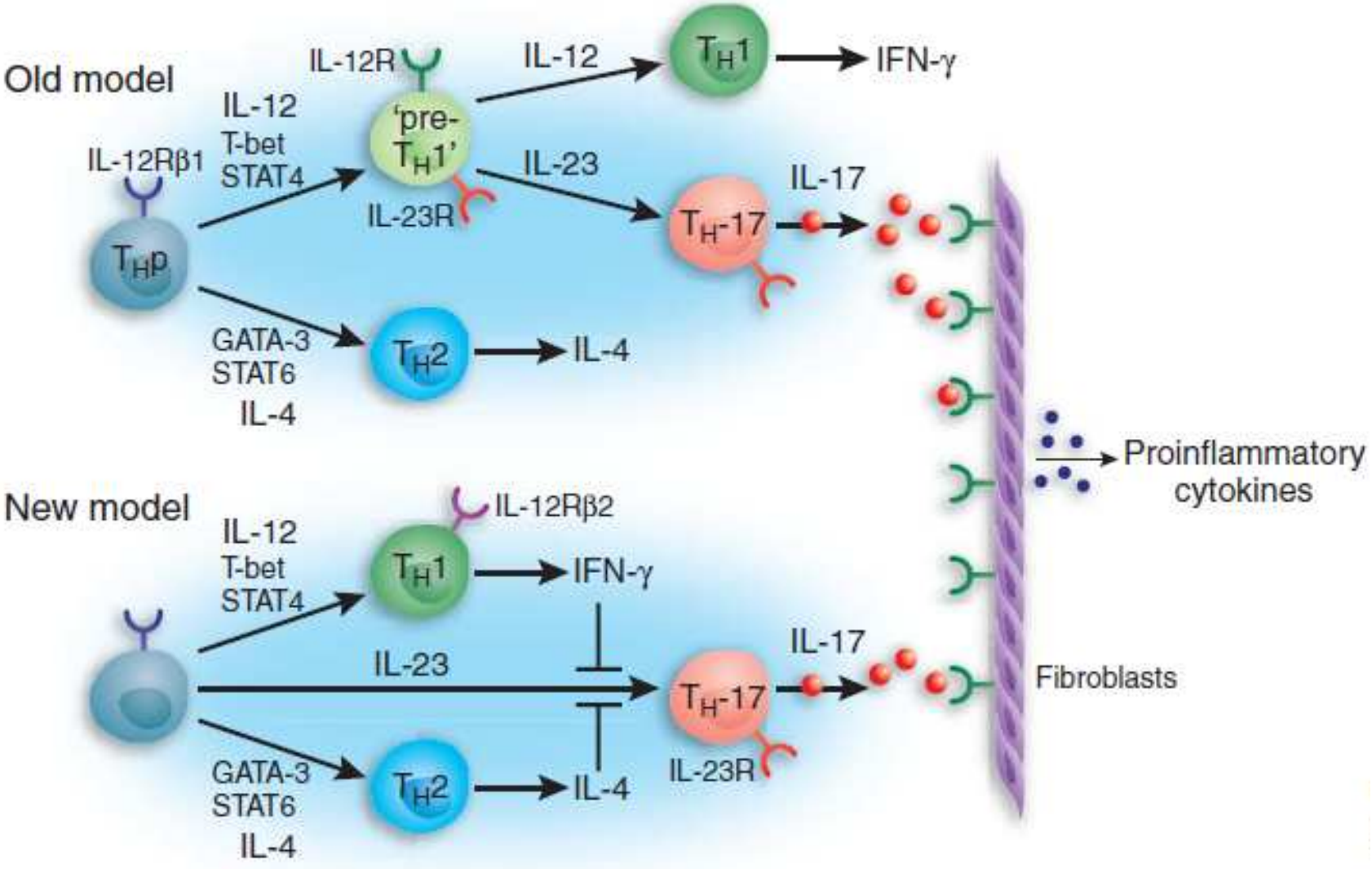


Figure 4 | **Interleukin-27 regulates the intensity and duration of T-helper-1 cell and T-helper-2 cell responses.** Under conditions that polarize CD4+ T cells towards either T helper 1 (T_H1) or T_H2 cells — that is, in the presence of high levels of interferon-γ or interleukin-4 (IL-4), respectively — 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.

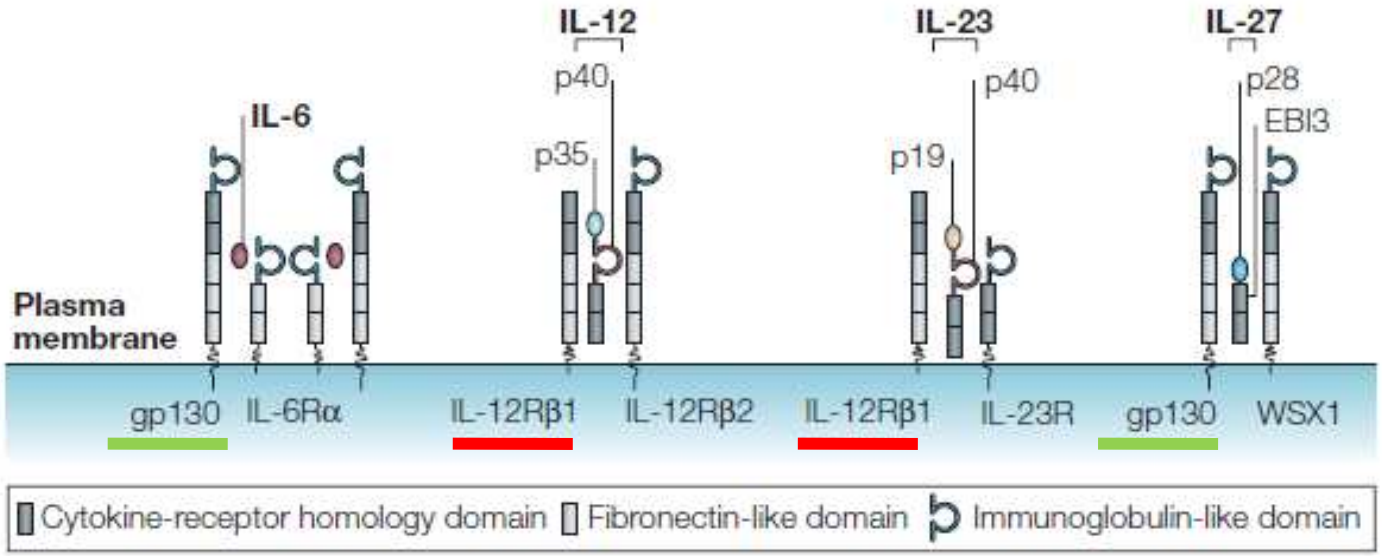
LINFOCITOS TH-17

Generación de Th17: 2 modelos



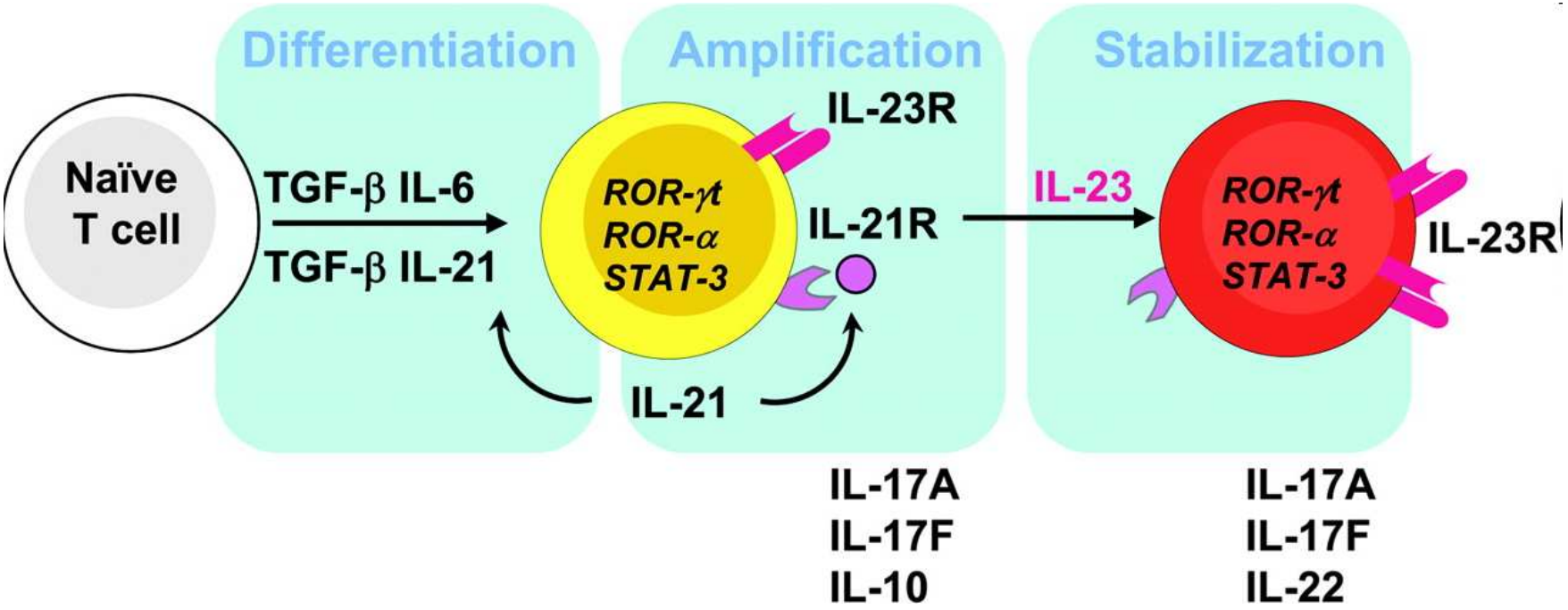
IL-23

- **The IL-6, IL-12, IL-23 and IL-27 family**
  - **Basically all are proinflammatory**
  - **Unique function for IL-23 in T-cell responses**
  - **IL-27: pro- and anti-inflammatory effects**



Nature Reviews Immunology 5, 521-531 (July 2005)

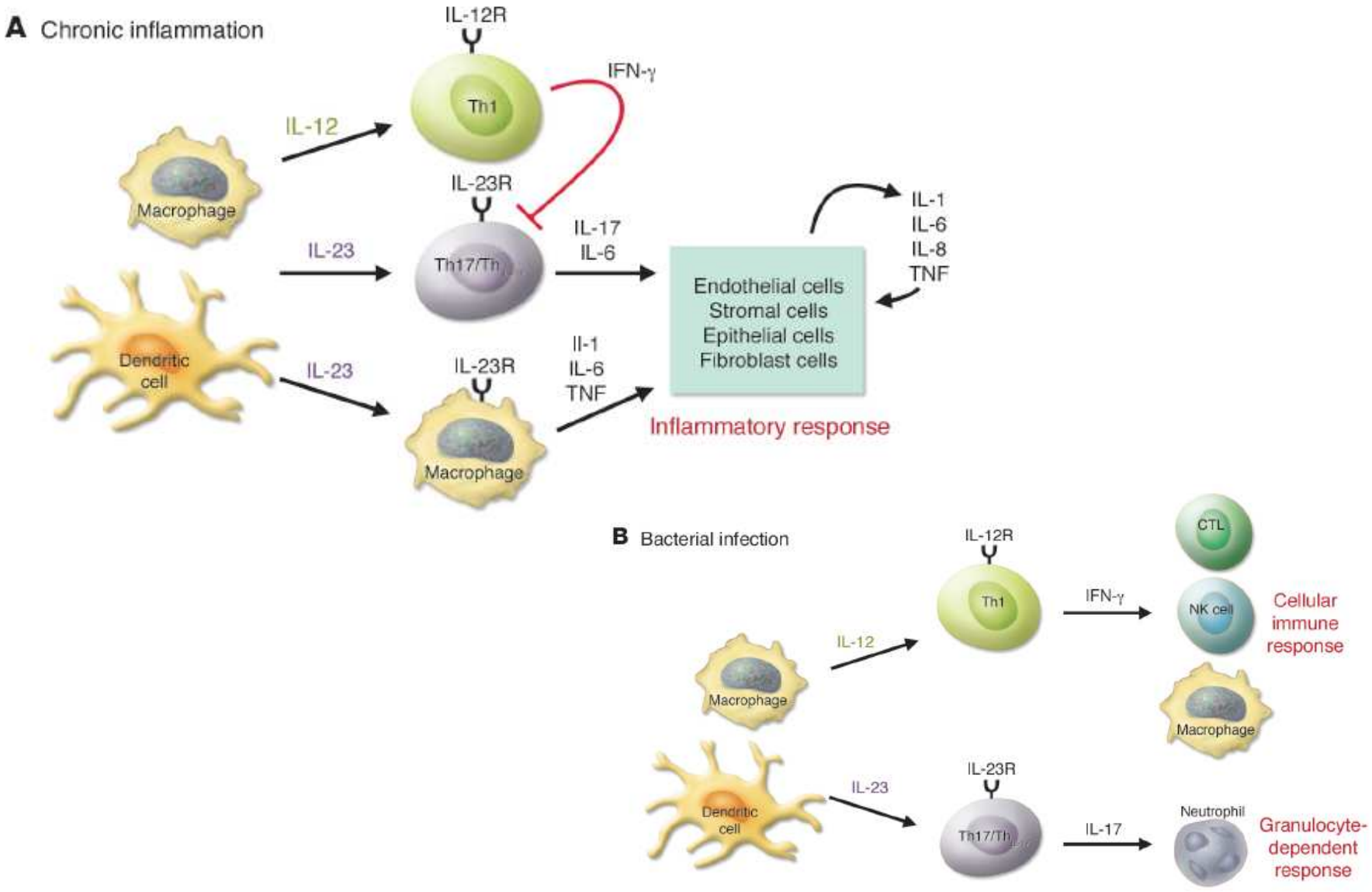
Etapas en la generación de células Th17

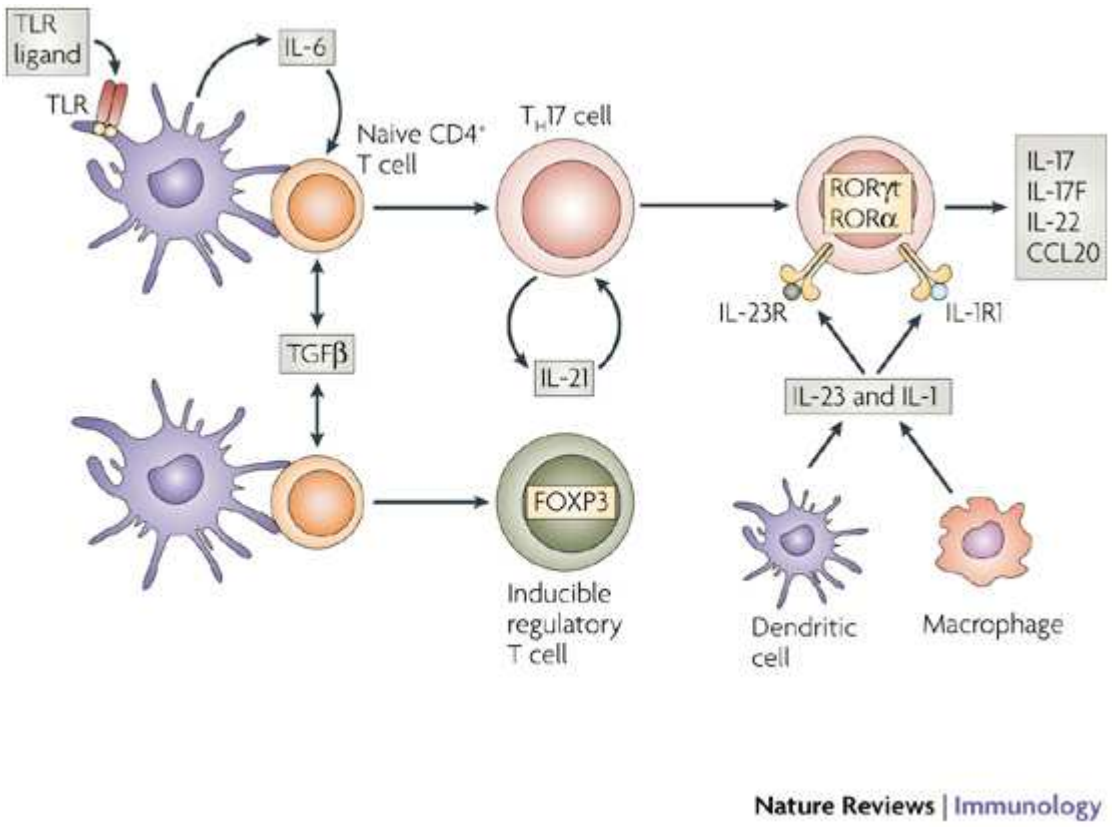


The activation of naive T cells in the presence of TGF-β and IL-6 initiates the Th17 differentiation pathway. Th17 cells produce IL-21, which further amplifies Th17 generation in an autocrine manner. IL-21 also induces the IL-23R on differentiated Th17 cells to make them responsive to IL-23 signaling. 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)

IL-23/IL-17

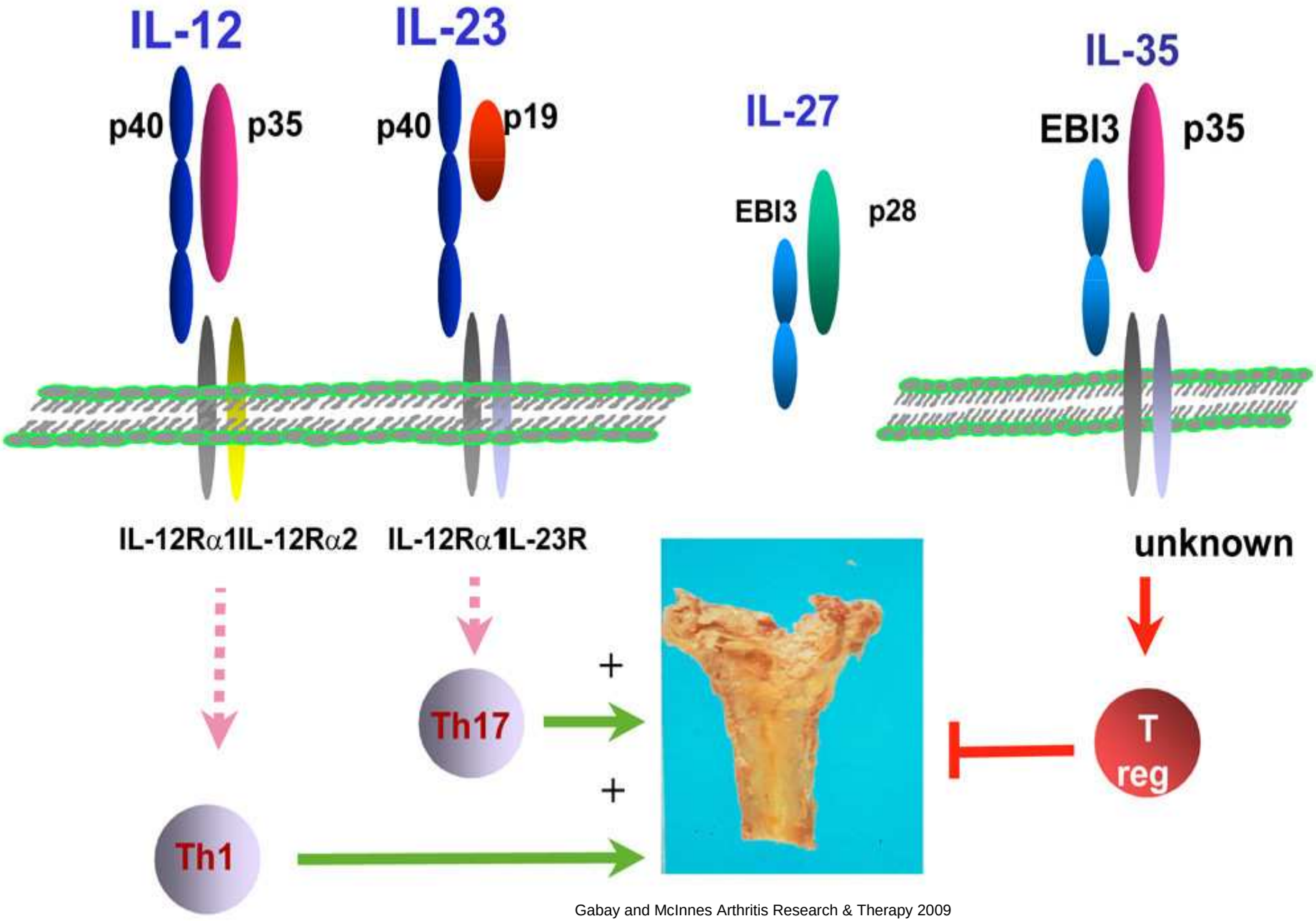

A Chronic inflammation
IL-12R
Th1
IFN-γ
IL-12
Macrophage
IL-23R
IL-23
Th17/Th
IL-17
IL-6
IL-1
IL-6
IL-8
TNF
Endothelial cells
Stromal cells
Epithelial cells
Fibroblast cells
Dendritic cell
IL-23
IL-23R
Il-1
IL-6
TNF
Macrophage
Inflammatory response
B Bacterial infection
IL-12R
Th1
IFN-γ
CTL
NK cell
Cellular immune response
IL-12
Macrophage
Macrophage
IL-23R
IL-23
Dendritic cell
Th17/Th
IL-17
Neutrophil
Granulocyte-dependent response



Naive CD4+ T helper (T_H) cells undergo initial T_H17-cell differentiation in the presence of transforming growth factor-β (TGF-β) and interleukin-6 (IL-6), which leads to the expression of IL-21. IL-21 further sustains T_H17-cell differentiation in an autocrine manner and establishes the transcriptional programme of T_H17 cells, including the expression of IL-23 receptor (Il-23R) and IL-1R1. IL-23 and IL-1, both of which are products of activated myeloid cells, possibly finalize the differentiation programme of T_H17 cells and help to maintain the differentiated T_H17 cells. CCL20, CC-chemokine ligand 20; FOXP3, forkhead box P3; ROR, retinoic-acid-receptor-related orphan receptor; TLR, Toll-like receptor.

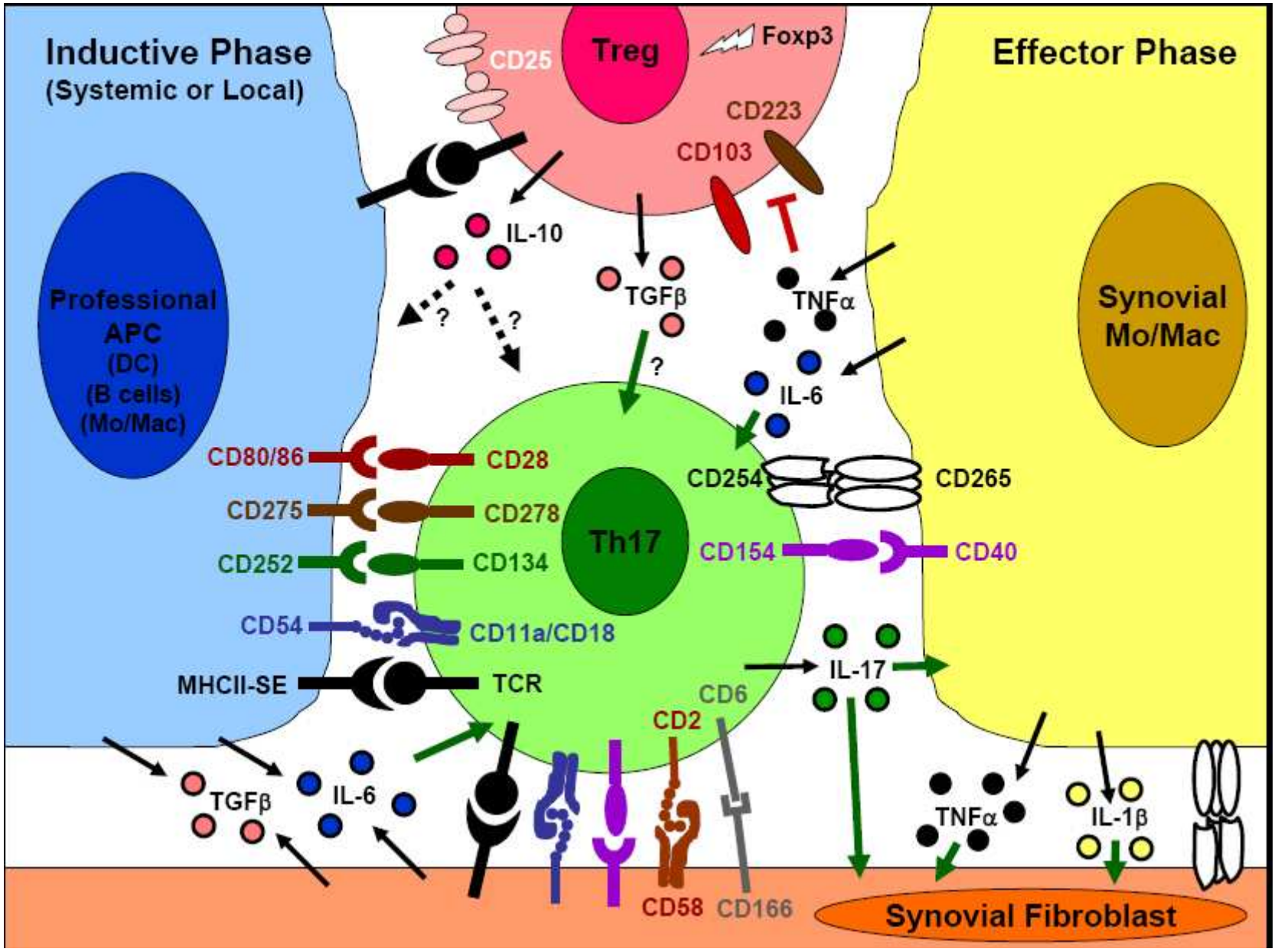
Nature Reviews Immunology **8**, 337-348 (May 2008)

Th-17 en acción



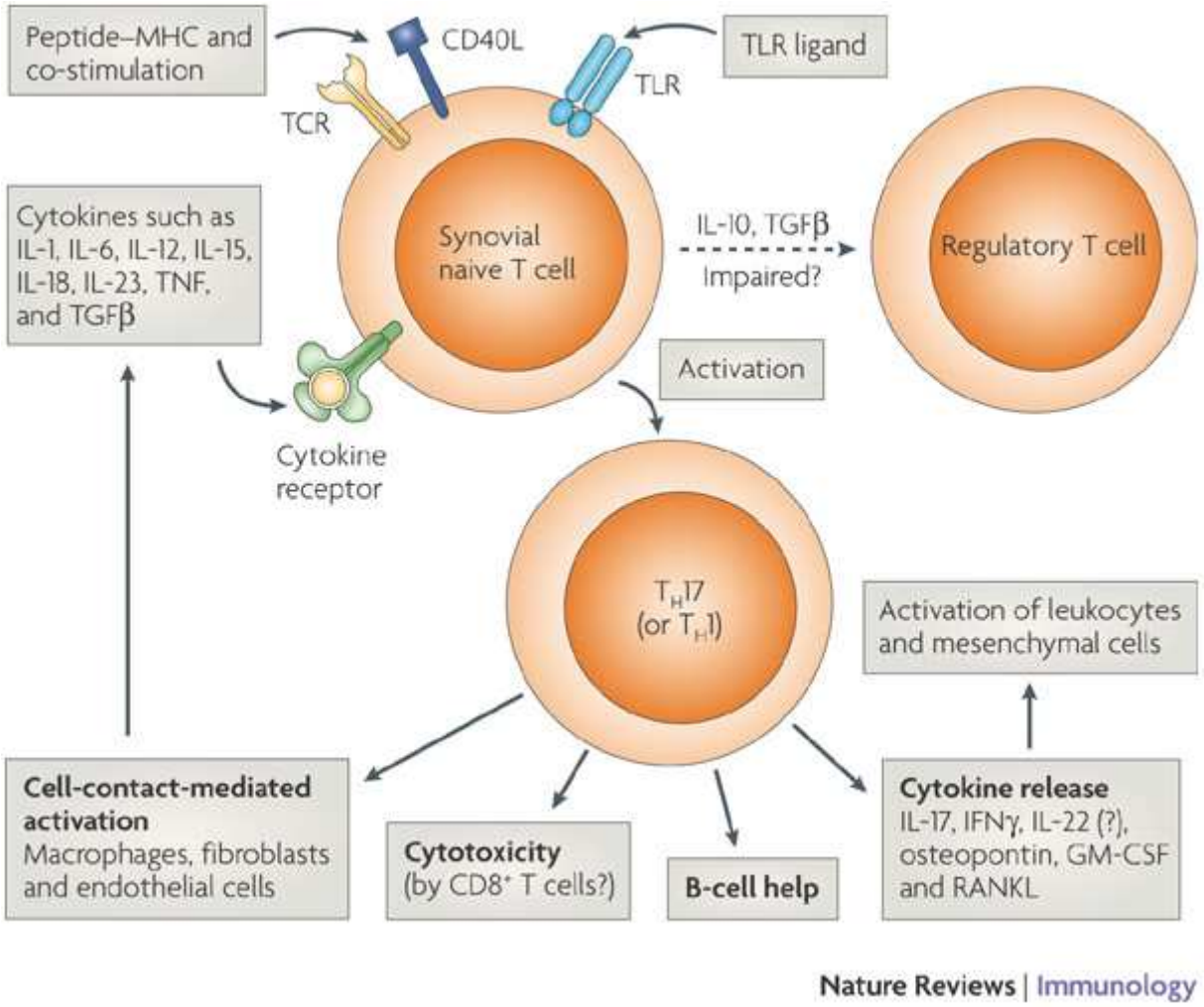
Gabay and McInnes Arthritis Research & Therapy 2009

- This cytokine superfamily contains at least four members: IL-12, IL-23, IL-27, and IL-35. They share peptides as indicated; note that EIB3 shares significant homology with p40.
- The key effects on T-cell subsets are depicted, showing IL-12 driving Th1 cells, IL-23 expanding Th17 cells, and IL-35 modulating regulatory T (T_{reg}) function.
- It is unclear at this time whether IL-35 is exclusively T_{reg}-derived or whether it can emanate from adjacent cell lineages to promote T_{reg} function. IL-27 has bimodal function in T-cell regulation dependent upon the maturity and differentiation status of the T cell.

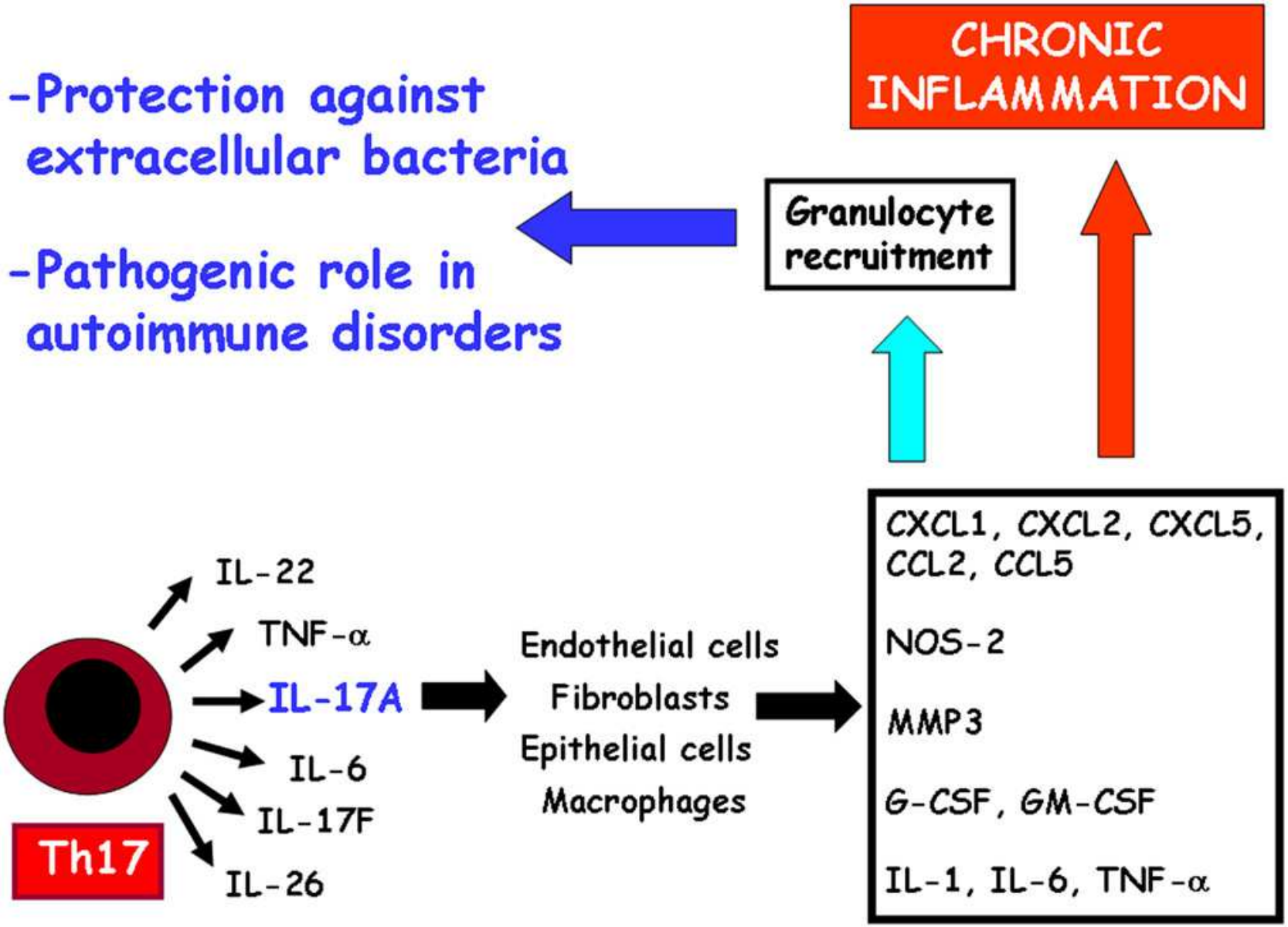


Lundy *et al. Arthritis Research & Therapy* 2007

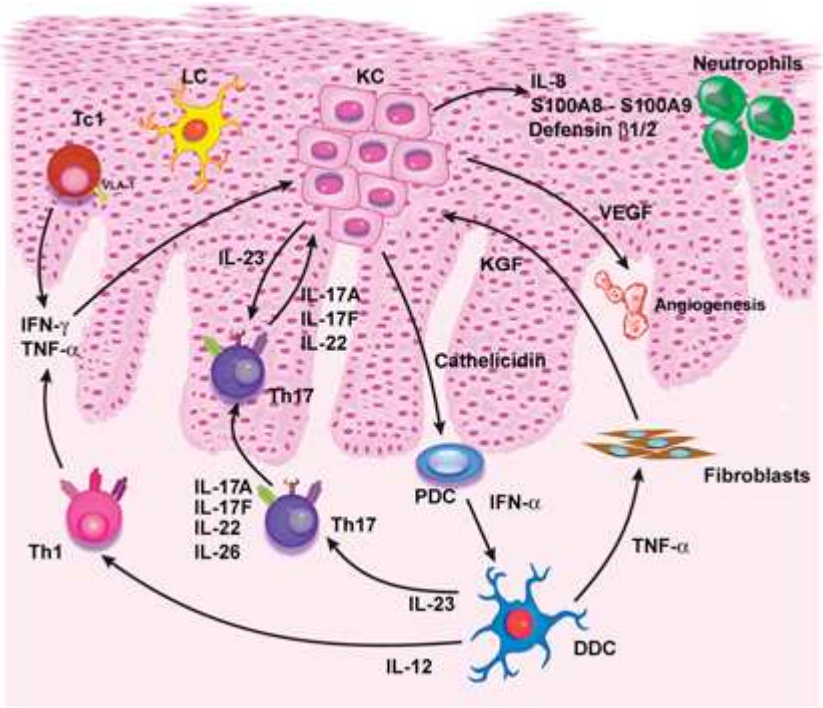
- Schematic diagram of the putative interactions of pathogenic Th17 cells in the synovial microenvironment. Induction of T-cell responses in rheumatoid arthritis (RA) is initiated by T-cell receptor (TCR) interaction with shared epitope major histocompatibility complex class II (MHCII-SE) and peptide 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.



Nature Reviews Immunology 7, 429-442 (June 2007)

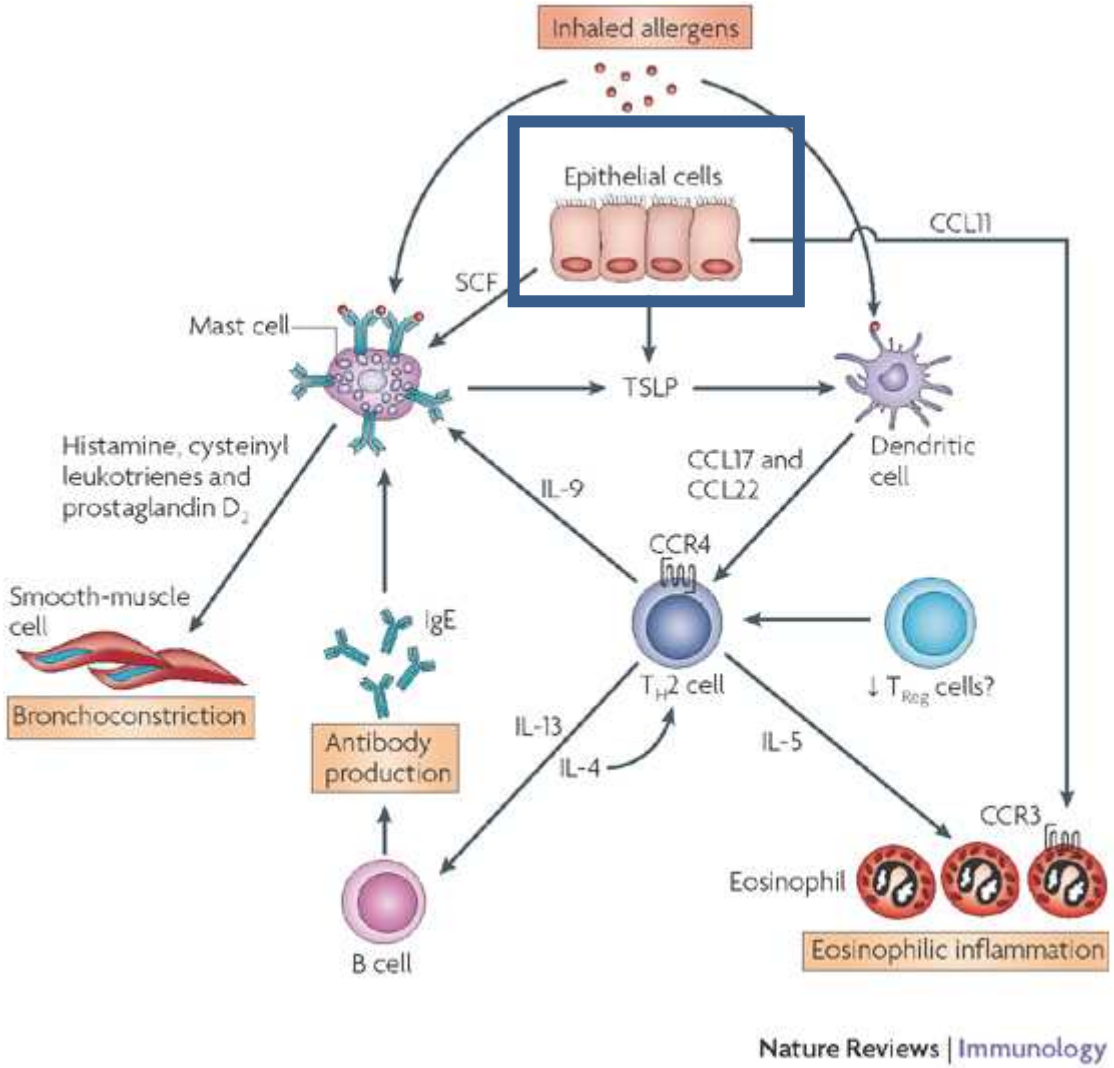

CHRONIC INFLAMMATION
-Protection against extracellular bacteria
-Pathogenic role in autoimmune disorders
Granulocyte recruitment
IL-22
TNF-α
IL-17A
IL-6
IL-17F
IL-26
Th17
Endothelial cells
Fibroblasts
Epithelial cells
Macrophages
CXCL1, CXCL2, CXCL5, CCL2, CCL5
NOS-2
MMP3
G-CSF, GM-CSF
IL-1, IL-6, TNF-α

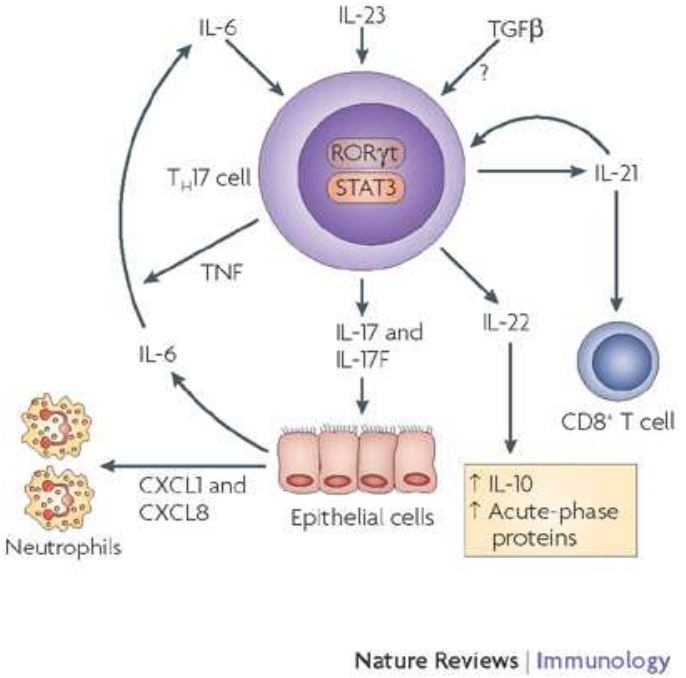
Th-17 y Psoriasis



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.

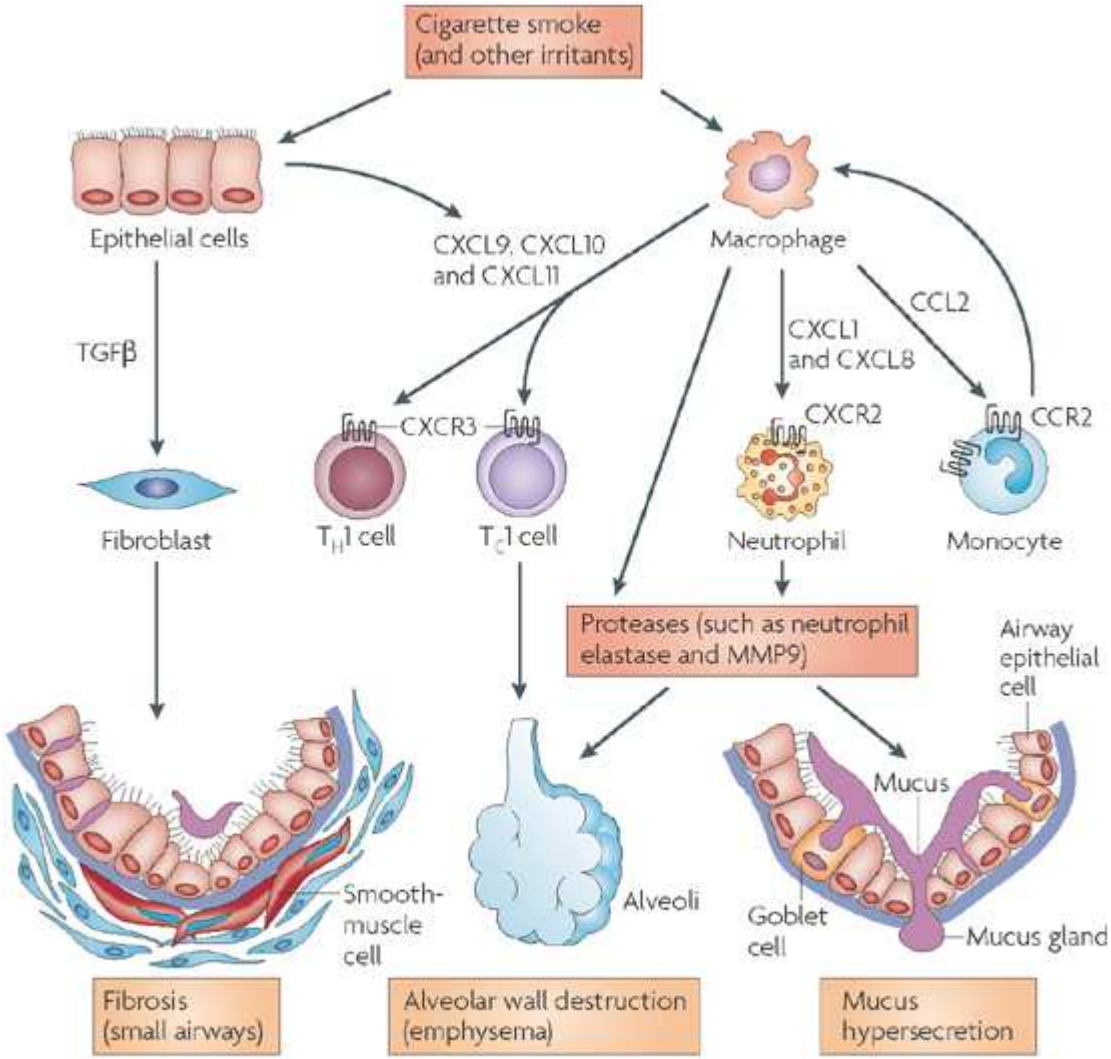
•Journal of Investigative Dermatology ISSN: 0022-202X

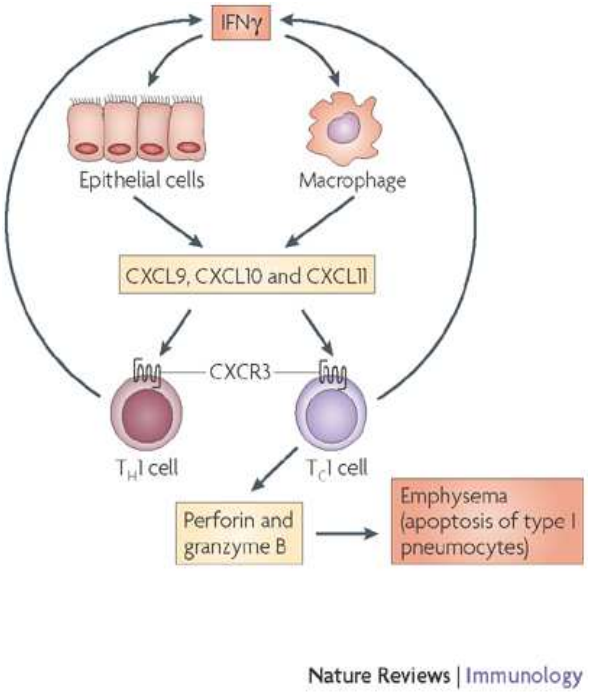




Th-1, Th-2, Th-17 y T CD8+ en enfermedad pulmonar

Nature Reviews Immunology 8, 183-192 (March 2008)

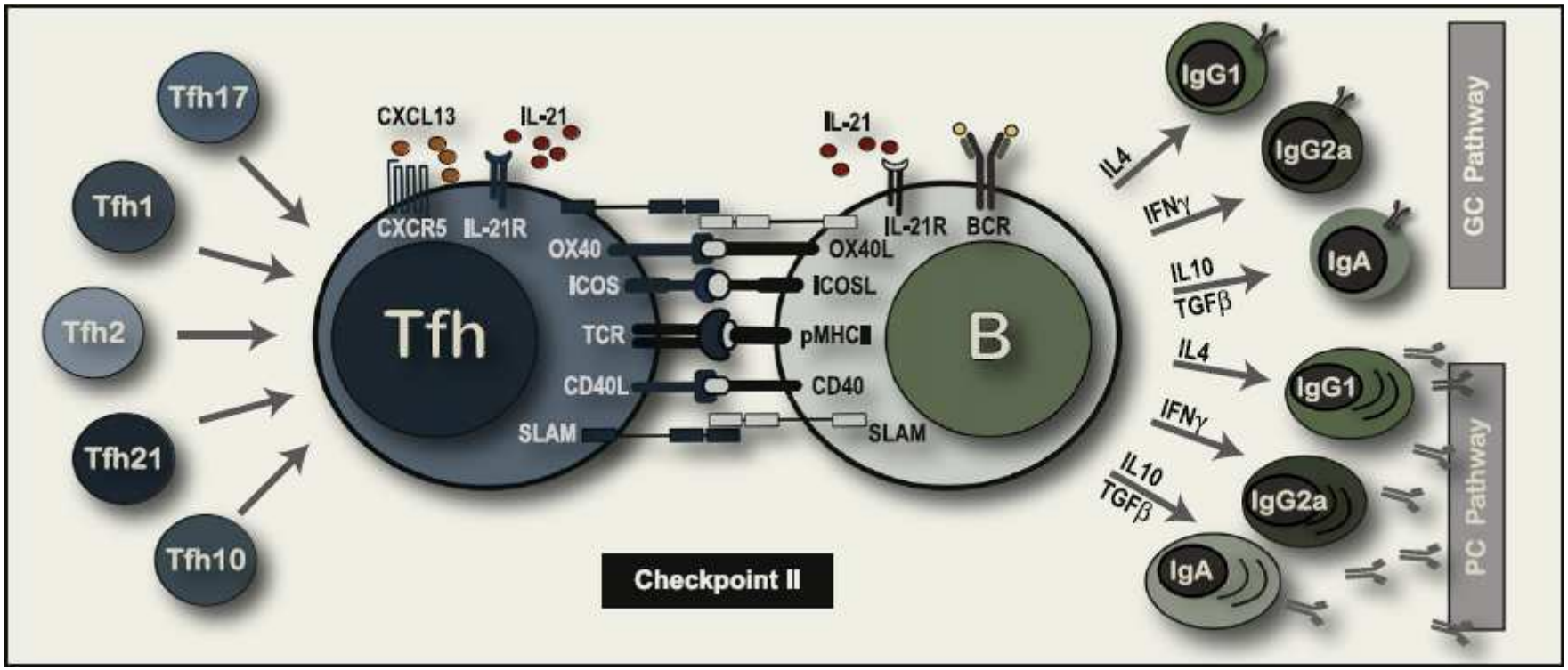




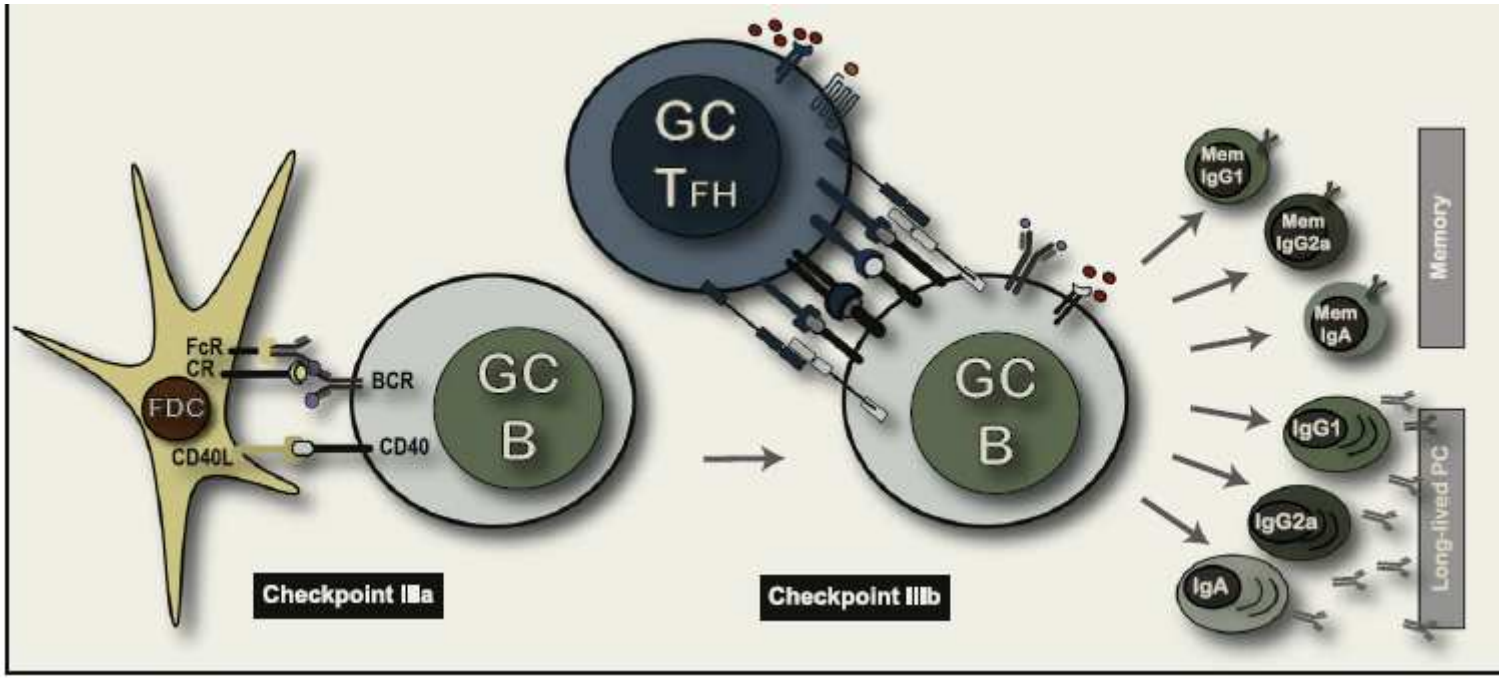
Nature Reviews Immunology 8, 183-192 (March 2008)

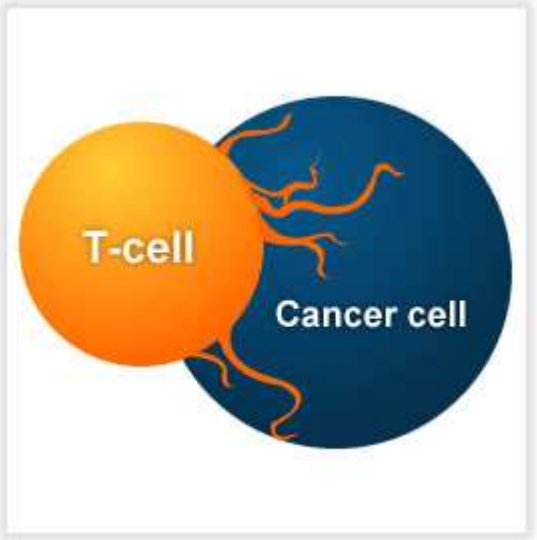
T HELPER FOLICULARES

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

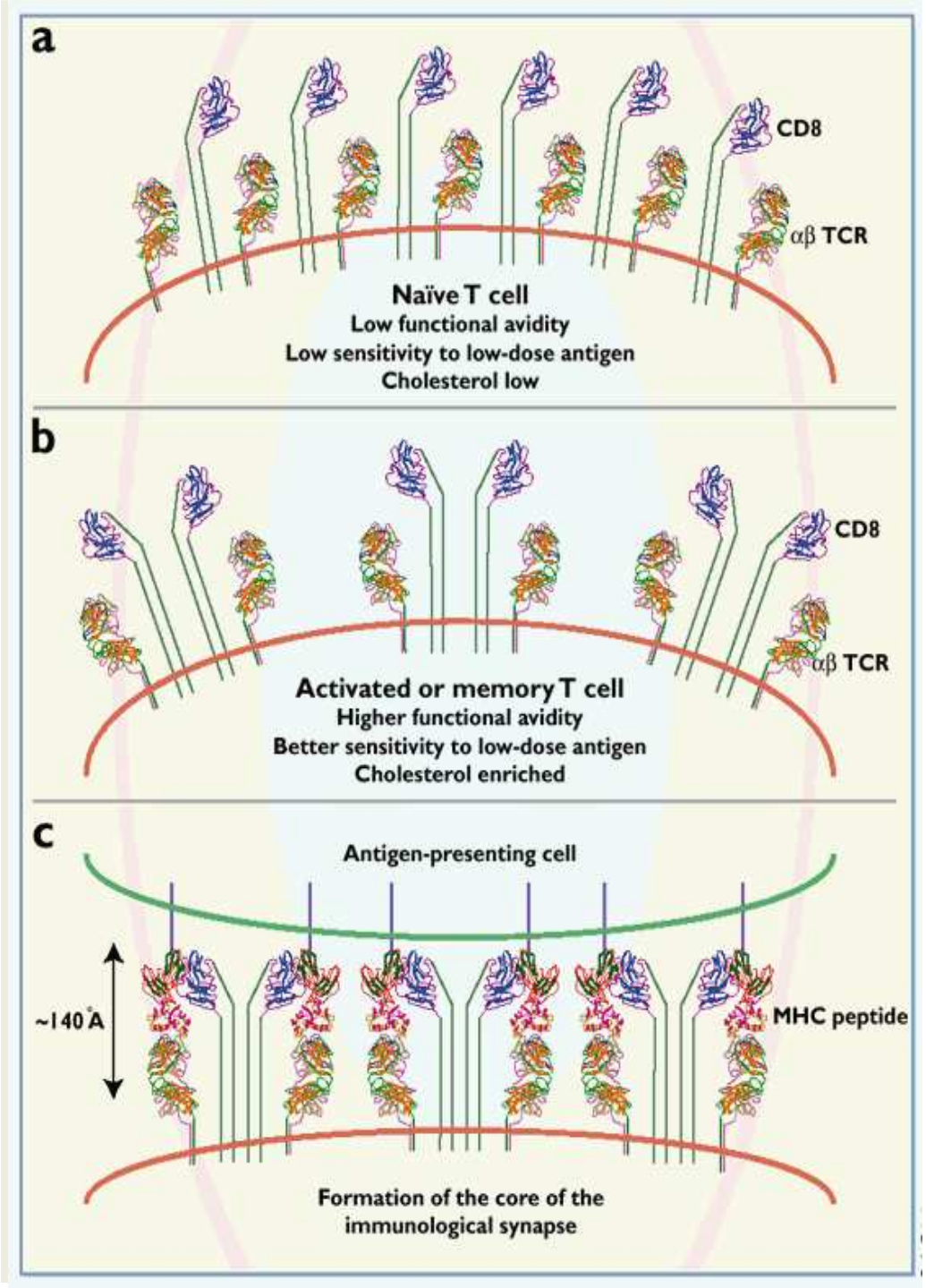


LINFOCITOS TCD8^{+}

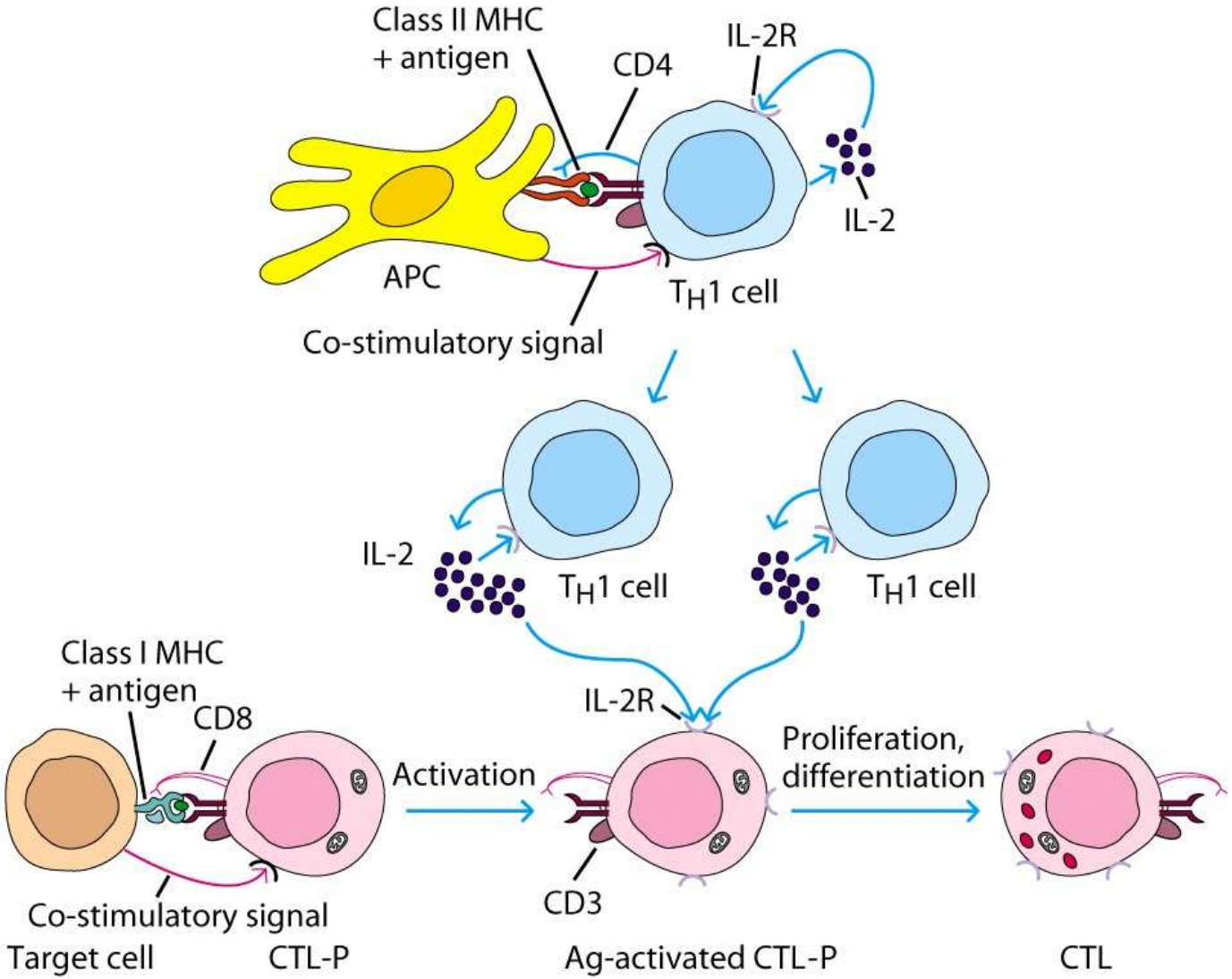
¿CÓMO SE ACTIVA LA CÉLULA TCD8^{+}?

LAS CÉLULAS TCD8^{+} NAÏVE REQUIEREN MÁS ACTIVIDAD COESTIMULADORA PARA SER CONDUCIDAS A CÉLULAS EFECTORAS QUE LAS CÉLULAS TCD4^{+} NAÏVE

Model for TCR and coreceptor rearrangements in the progression from naïve to activated T cells.

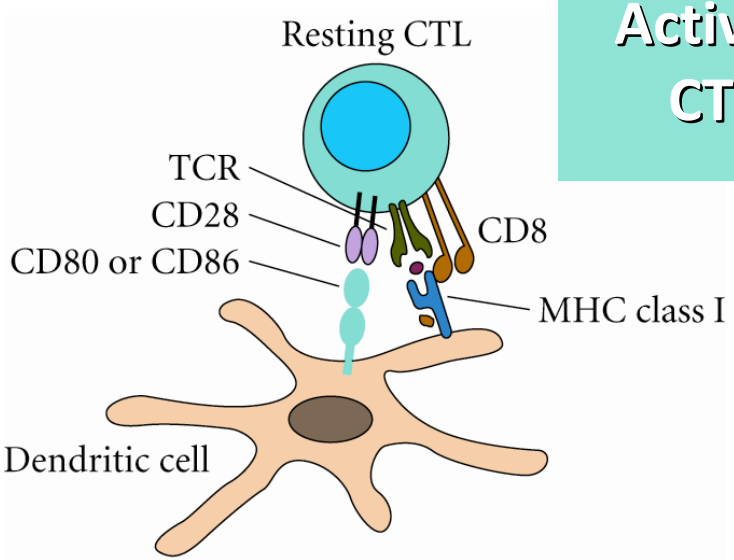


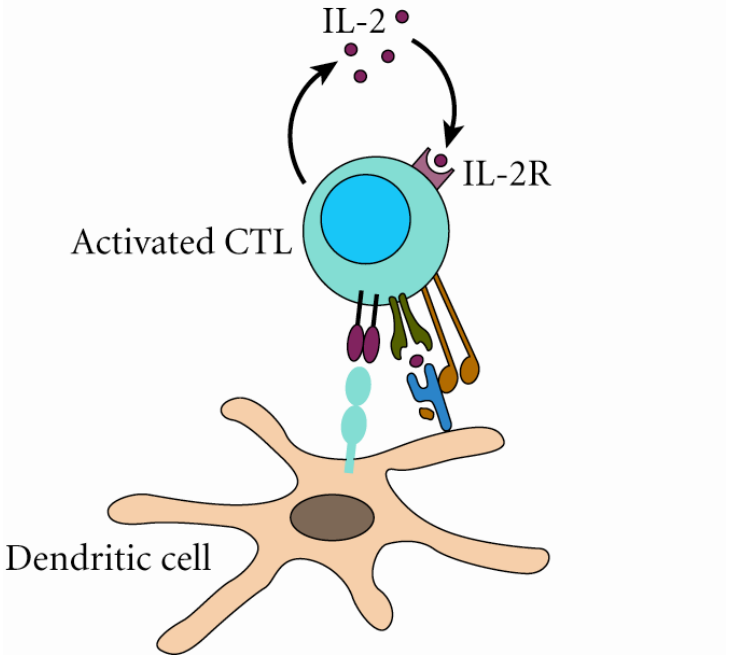
Nature Immunology 2, 669 - 670 (2001)



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

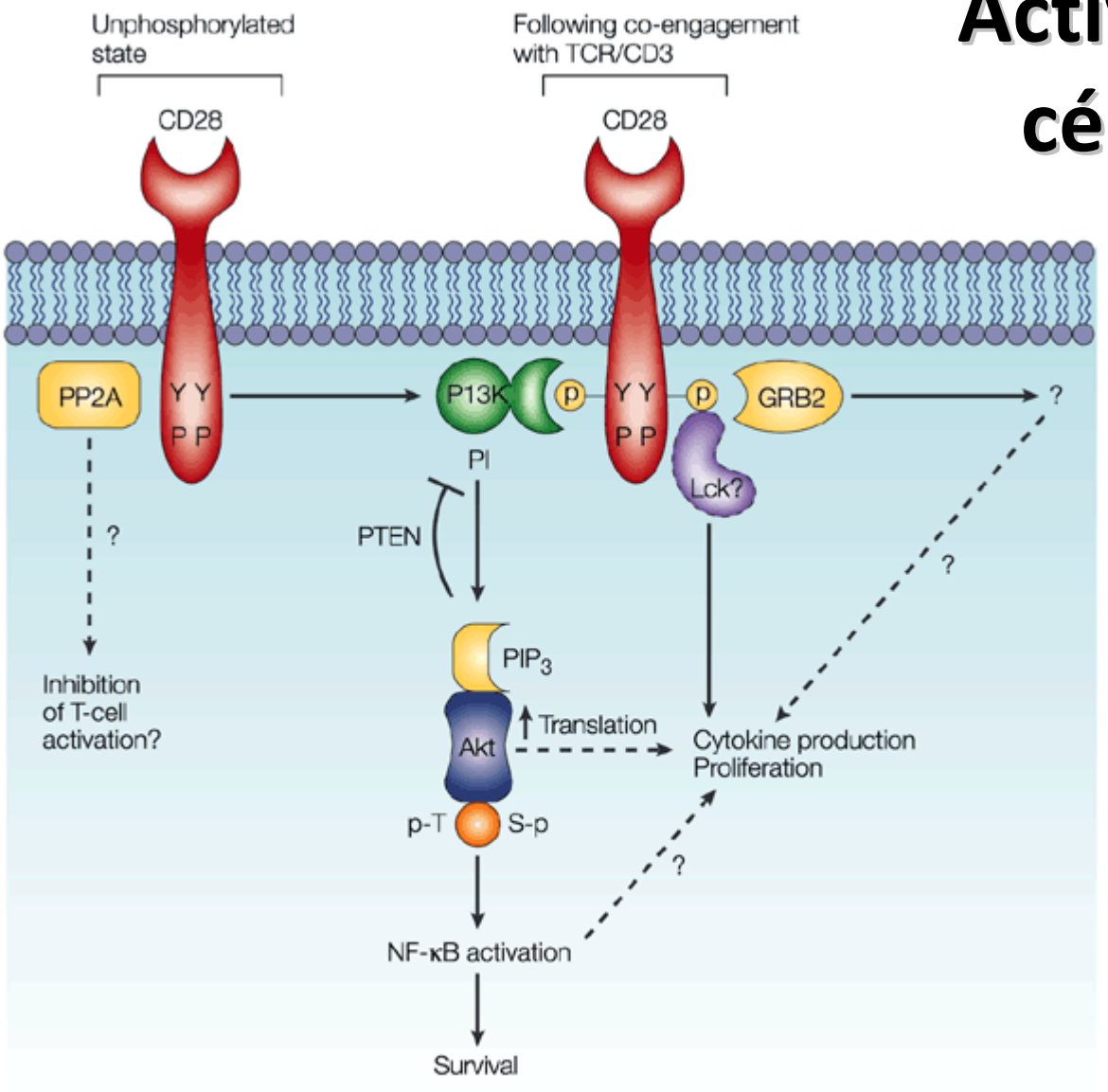
Activación DIRECTA del precursor de células CTL $CD8^+$ por una DC infectada por virus





- **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+



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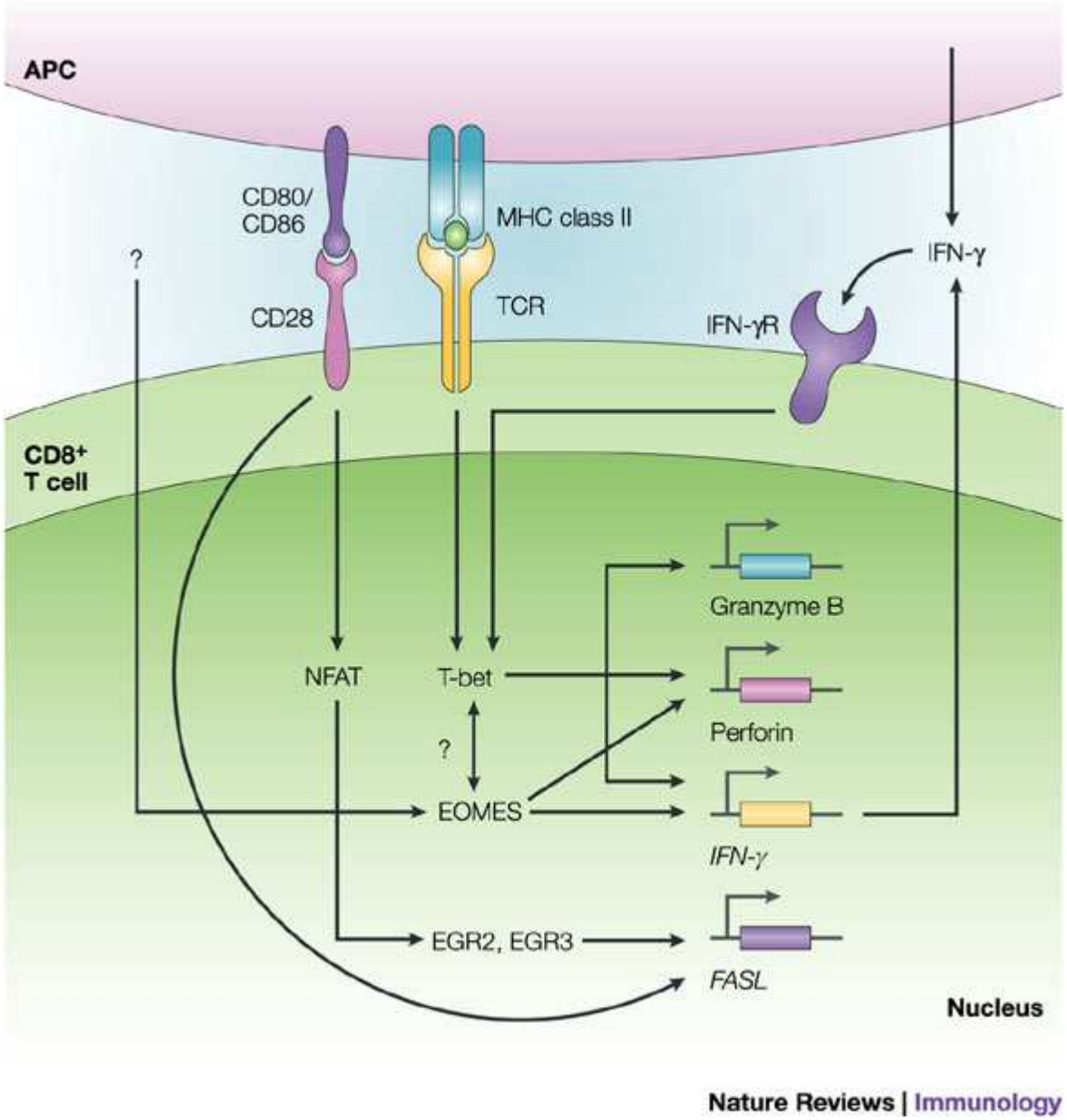
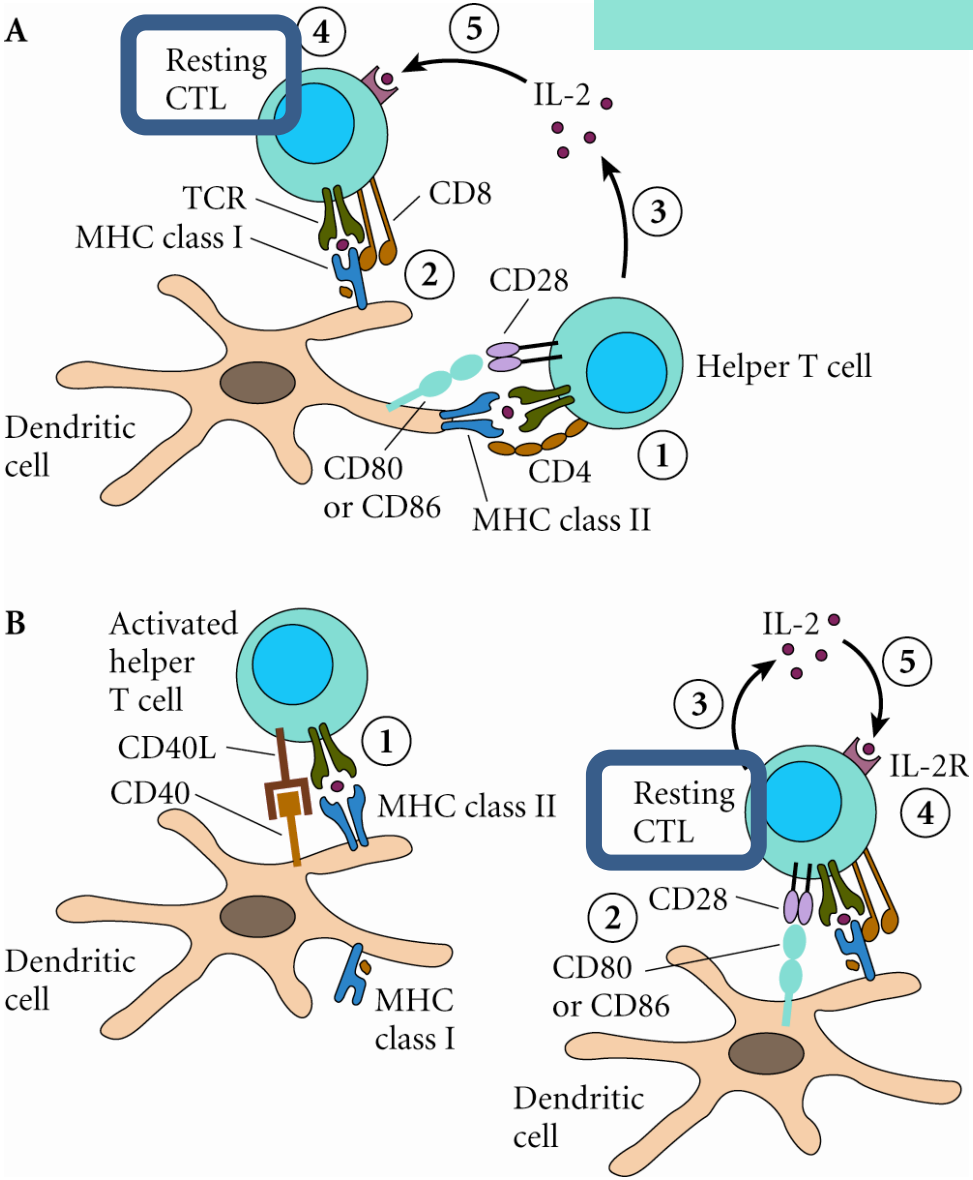


T-bet expression is induced by signalling through the T-cell receptor (TCR) and the interferon-γ (IFN- γ) receptor (IFN- γ R). T-bet then induces the expression of the effector molecules IFN-γ , perforin and granzyme B. Eomesodermin (EOMES) also induces the expression of IFN-γ and perforin. There is 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+

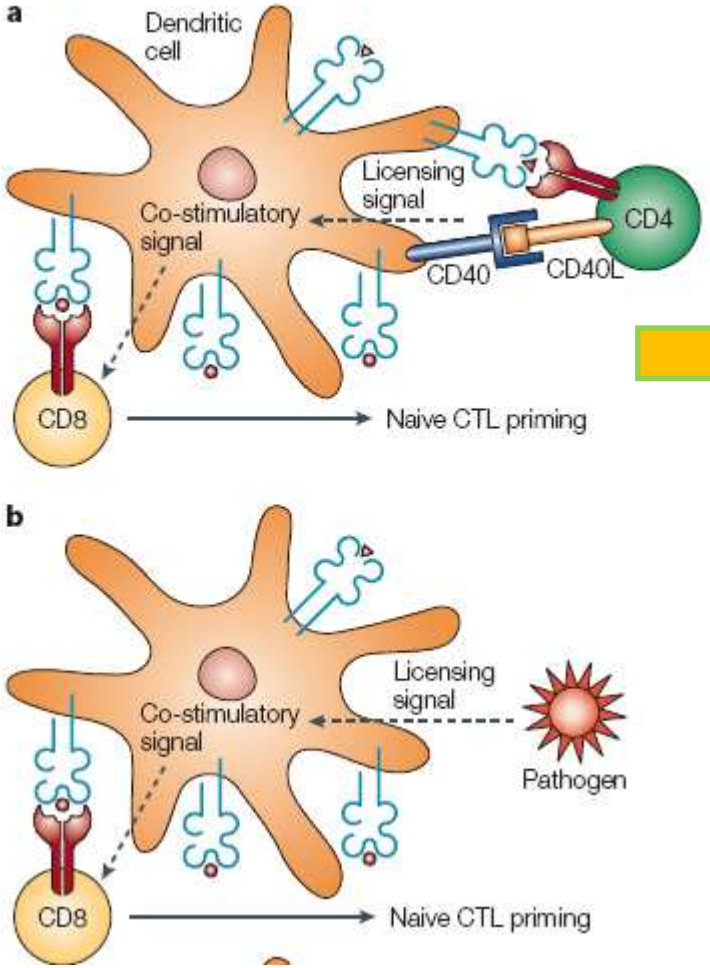


ACTIVACIÓN PARACRINA

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

Th1 coopera en la activación de TCD8+



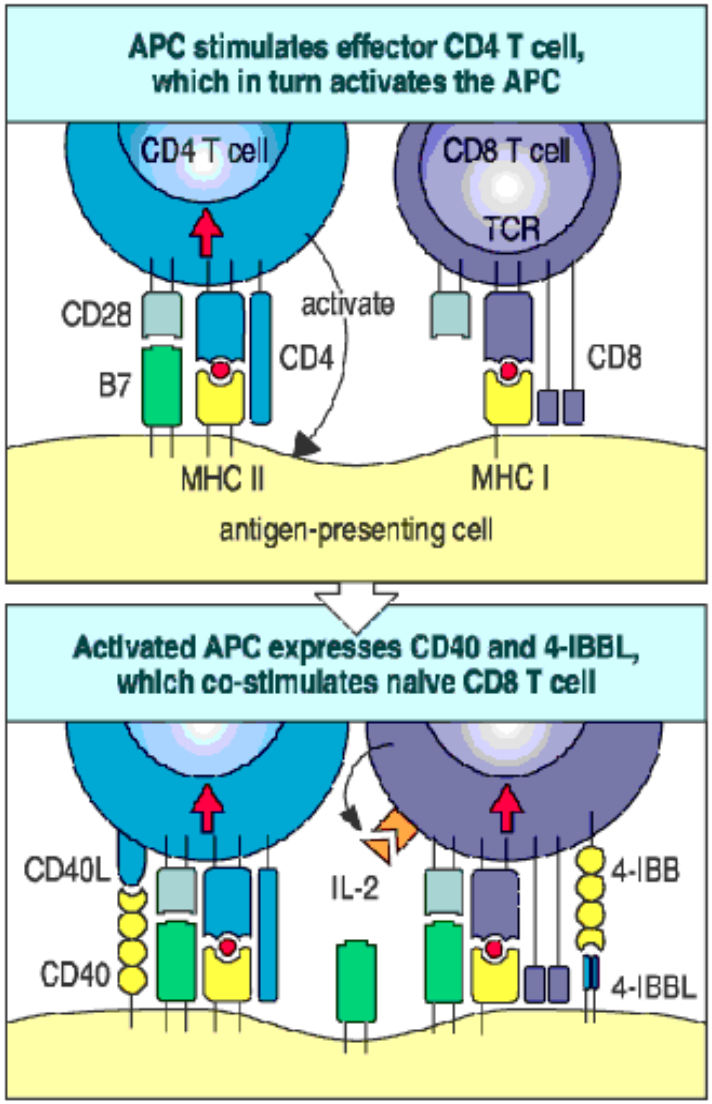
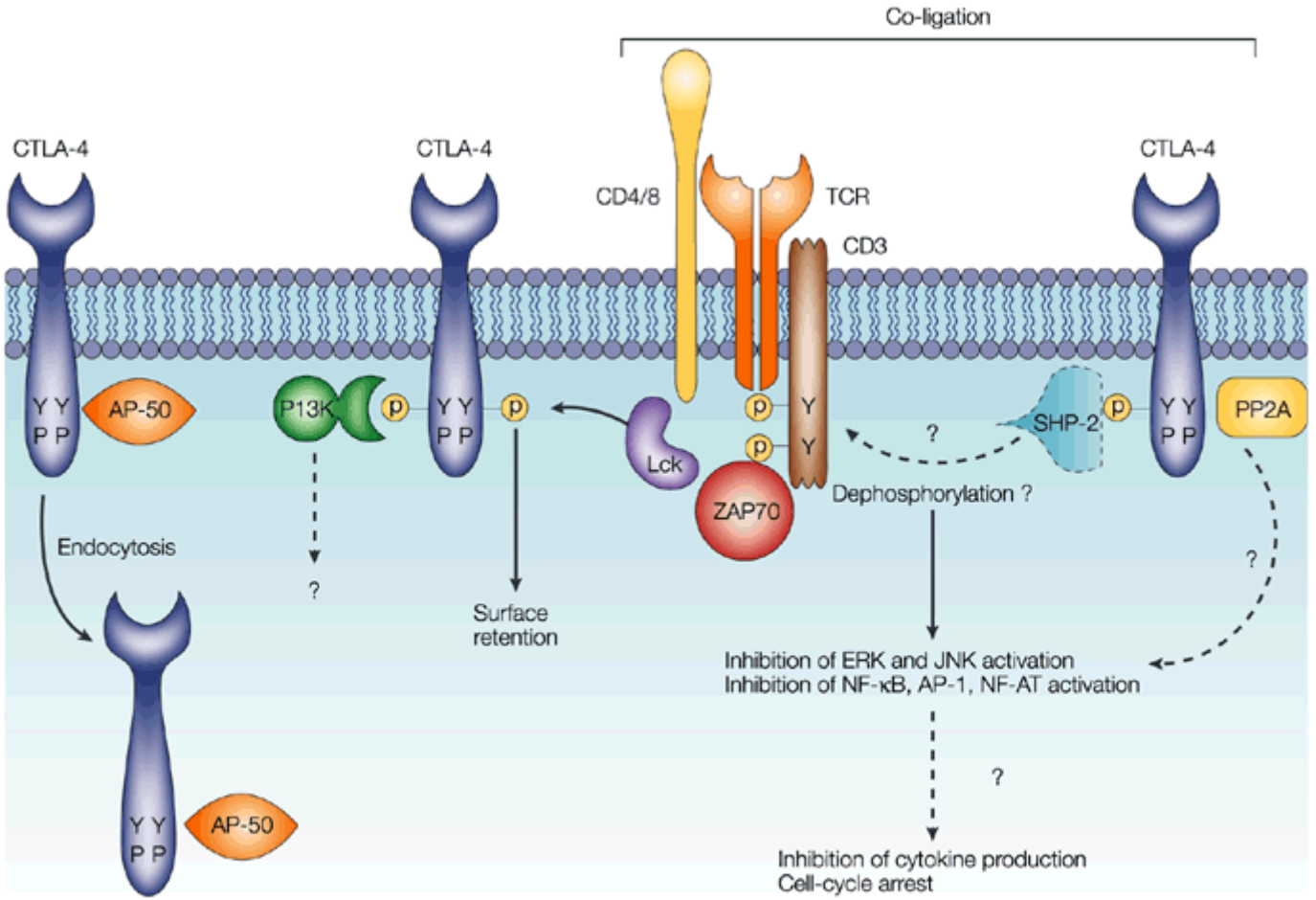


Fig 8.26 © 2001 Garland Science

Inhibición de la activación de TCD8+



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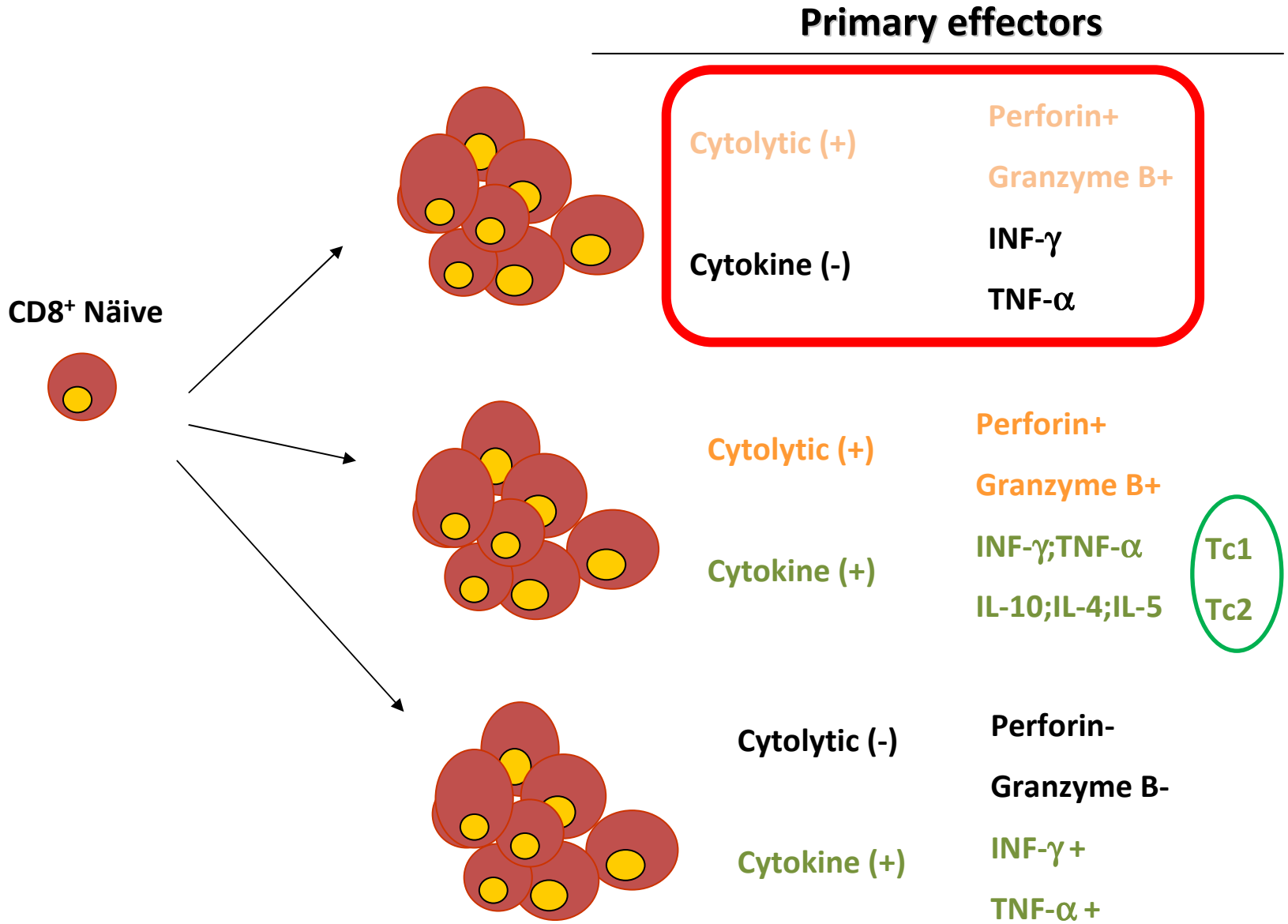
Generación de células CD8⁺ efectoras

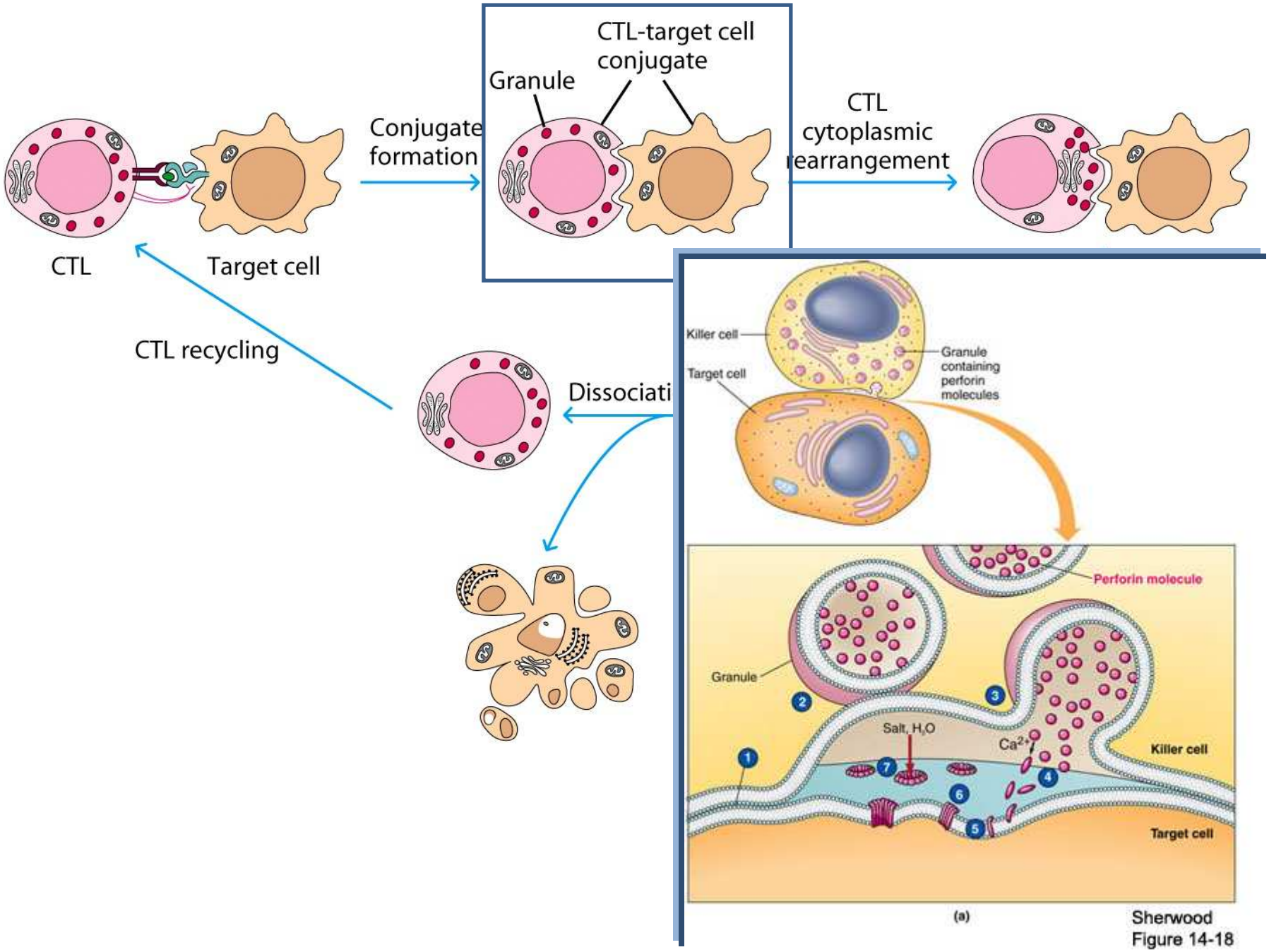


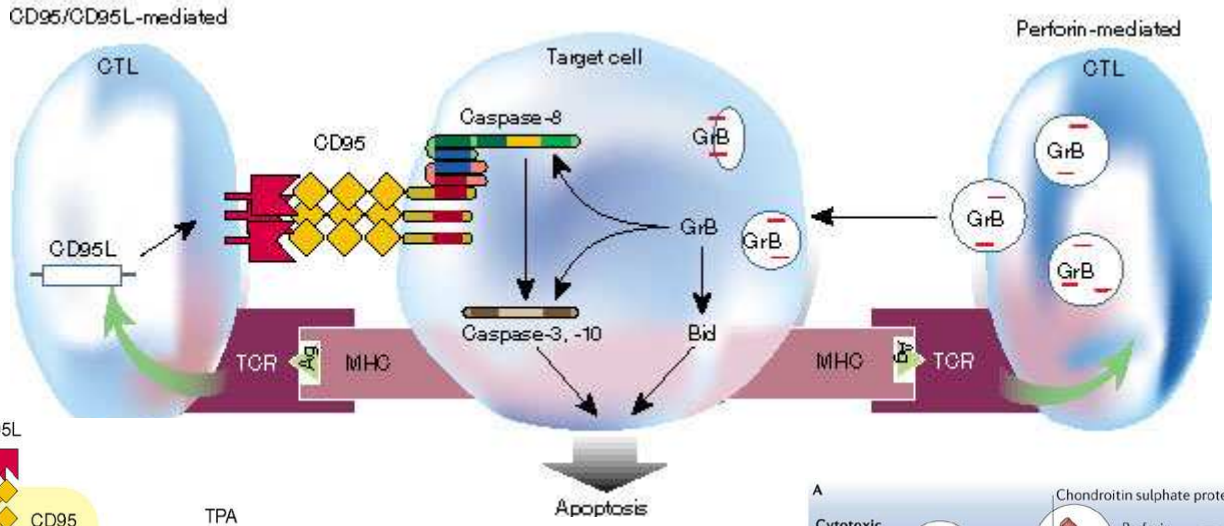
Mecanismos líticos

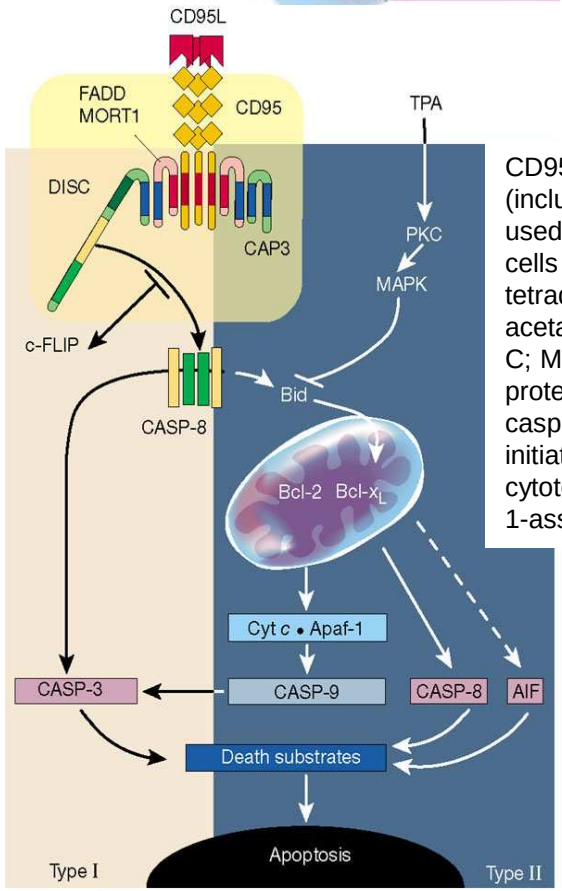
- **Exocitosis de gránulos - vía predominante (FAST KILLING)**
  - granzimas y perforinas

- **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

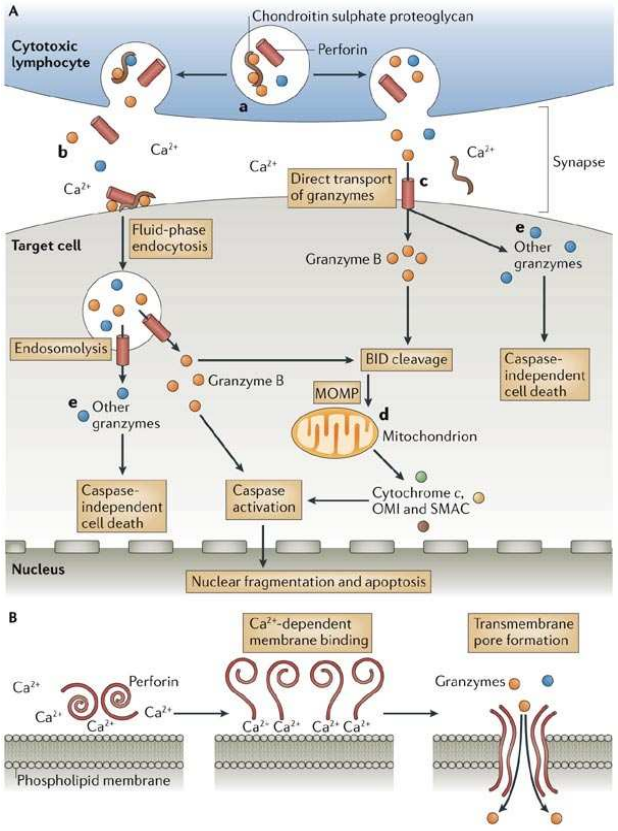

CTL-target cell conjugate
Granule
Conjugate formation
CTL cytoplasmic rearrangement
CTL
Target cell
CTL recycling
Dissociati
Killer cell
Target cell
Granule containing perforin molecules
Perforin molecule
Granule
Salt, H2O
Ca2+
Killer cell
Target cell
(a)
Sherwood
Figure 14-18





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).

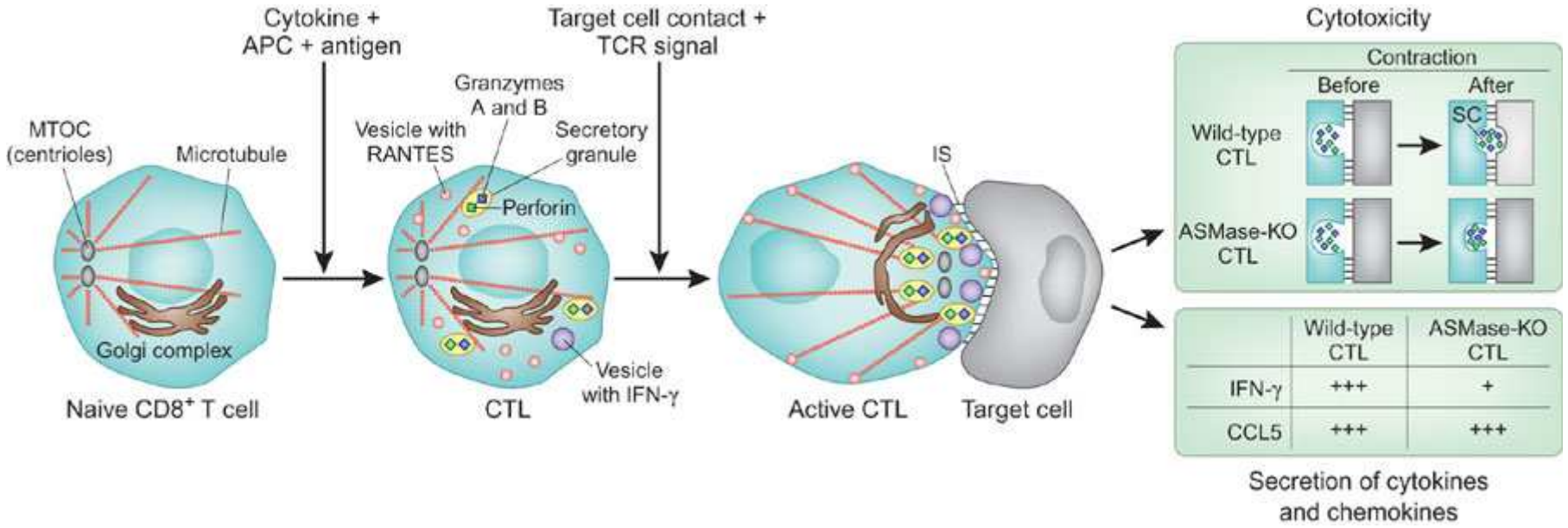
Nature 407, 789-795(12 October 2000)



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

microtubule-organizing center : MTOC

acidic sphingomyelinase: ASMase



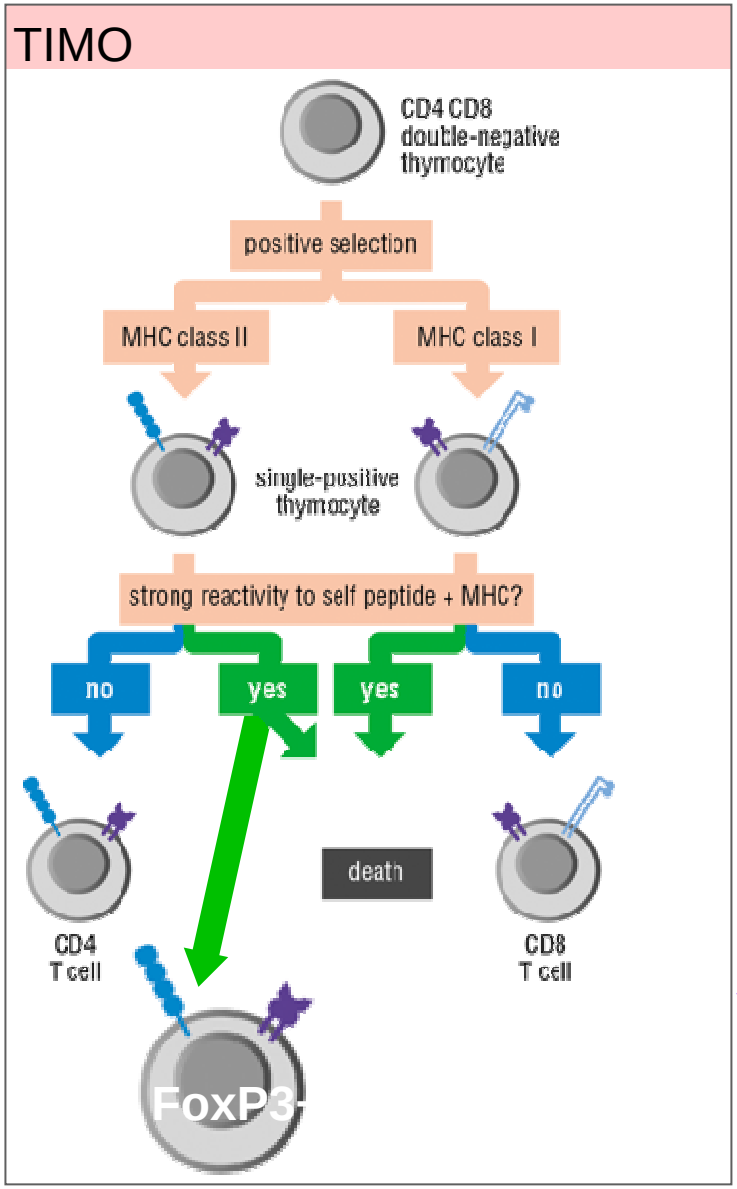
Naive CD8⁺ cytotoxic T cells differentiate into functionally competent CTLs when they receive the appropriate cytokine stimulation, such as IL-12, IL-18 or IL-21 from antigen-presenting cells (APC) or IL-2 from helper T cells, and TCR stimulation. After recognition of the target cell (such as a tumor 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)

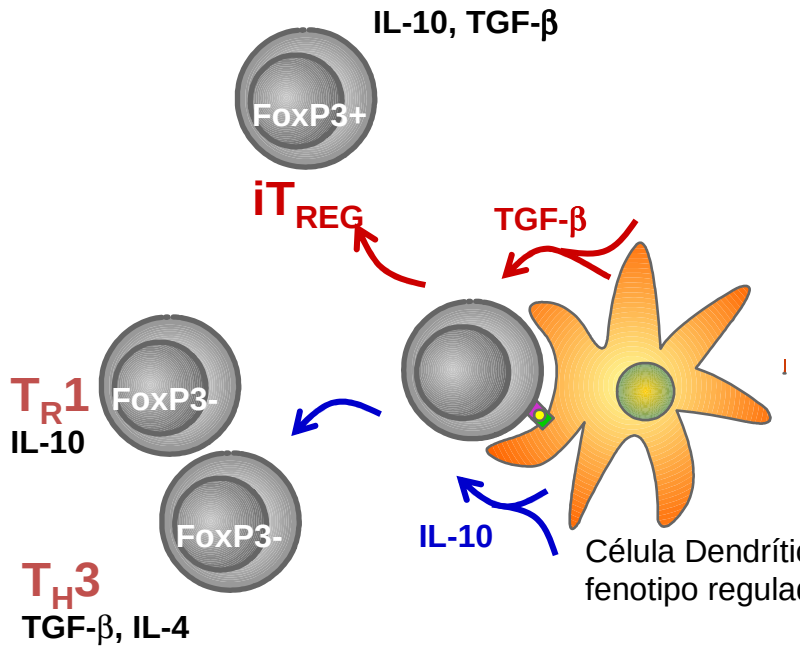
CÉLULAS T REGULADORAS

Las células T_{REG} se generan en timo y alternativamente en la periferia

TIMO



Células T reguladoras inducidas



PERIFERIA

La mayoría de la Treg se generan en el timo (**nTreg** = Treg naturales) a partir de timocitos CD4+ autoreactivos, como un destino alternativo a su muerte durante la selección negativa, y llegan a ser **10-15% de los T CD4 en circulación**

Células T reguladoras naturales (nTreg)

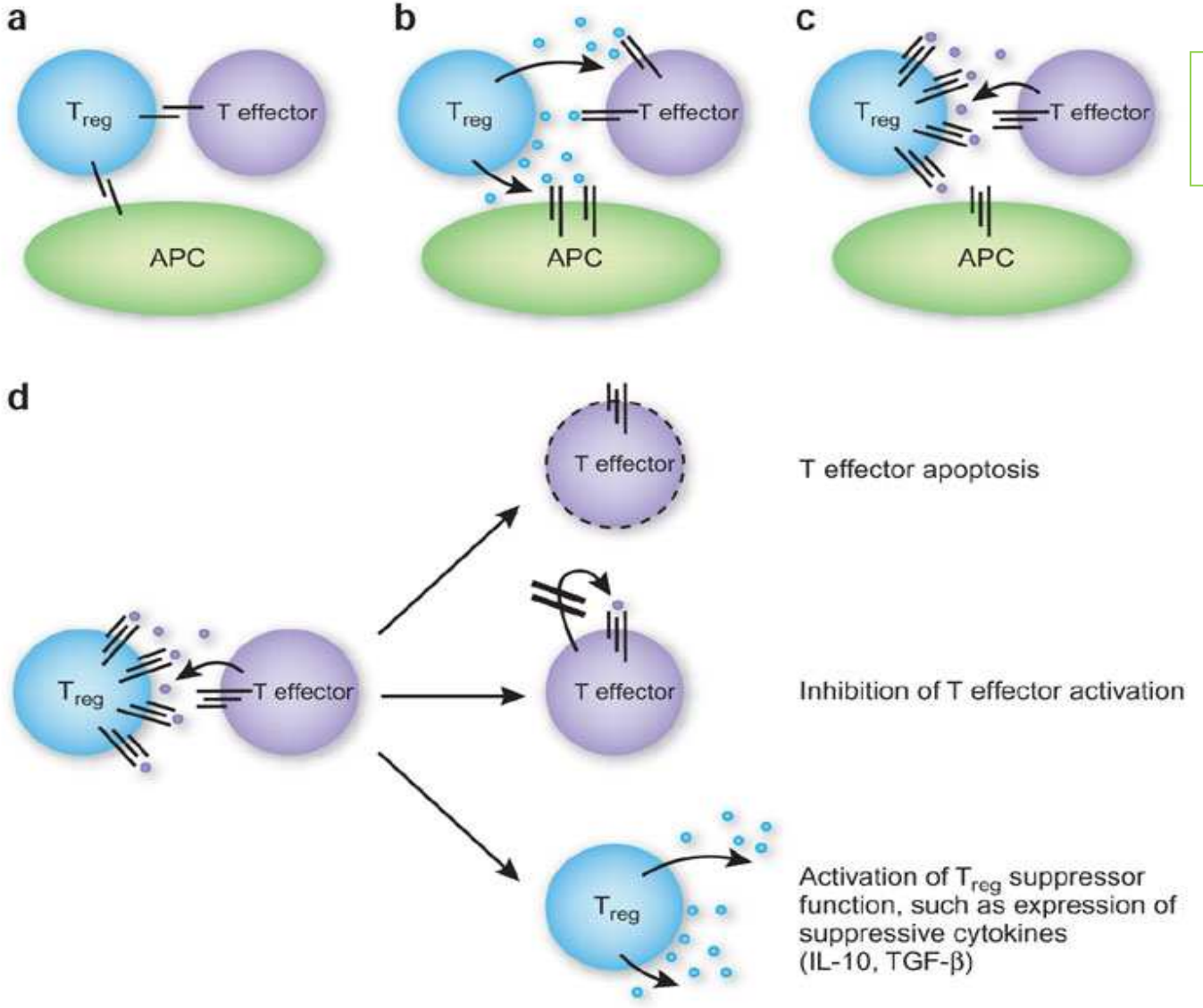
Marcadores de Treg naturales

Ratón: CD4 FoxP3 y CD25

Humanos: CD4, CD25, $CD127^{low}$
(CD127=IL-7R)

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).

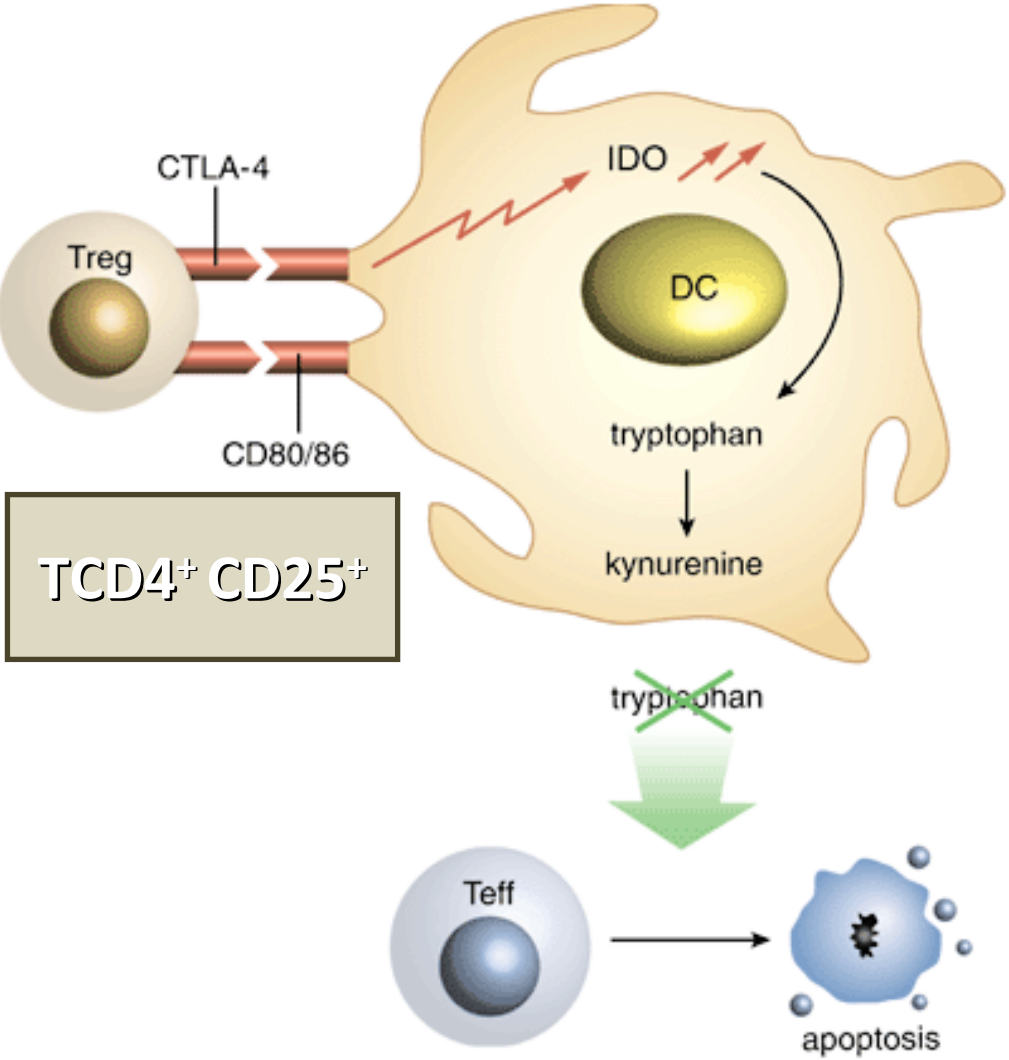


Competition (via consumption) by T_{reg} cells for resources for growth and/or survival factors such as IL-2.

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.

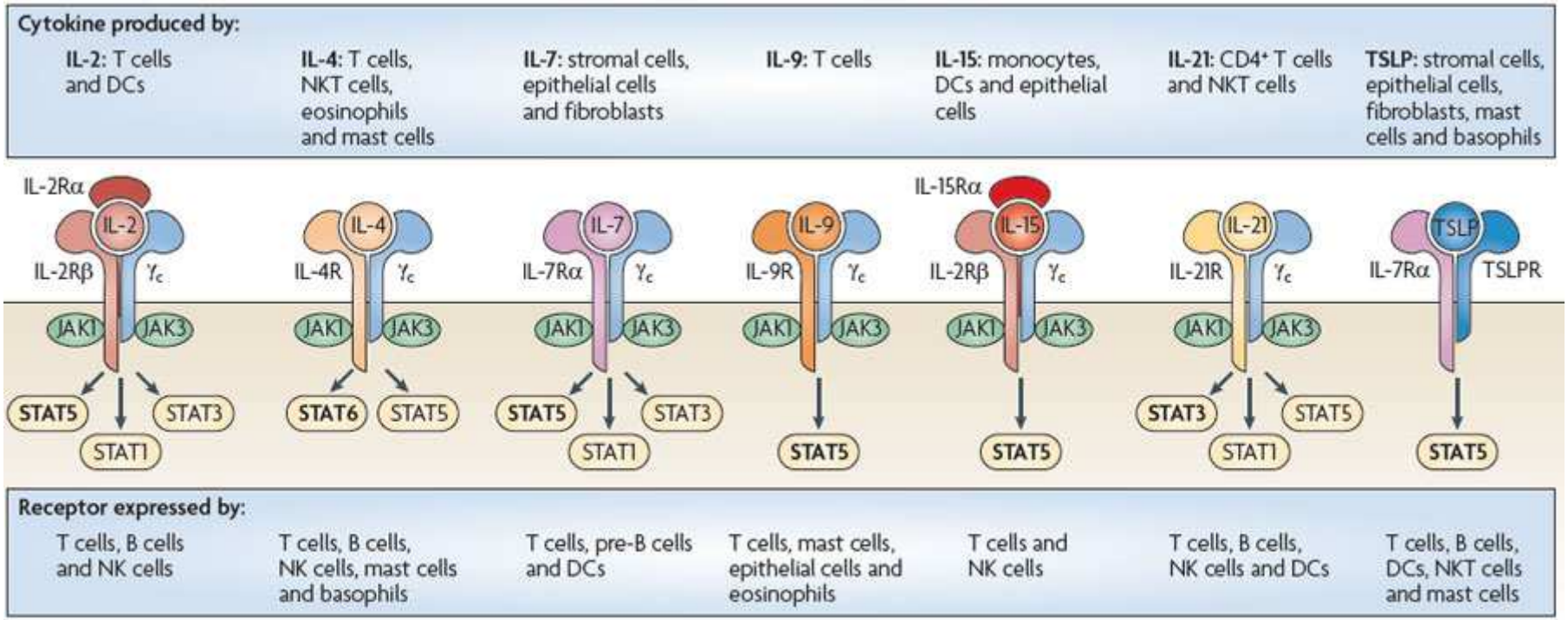
Nature Immunology **8**, 1285 - 1287 (2007)

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 environment.



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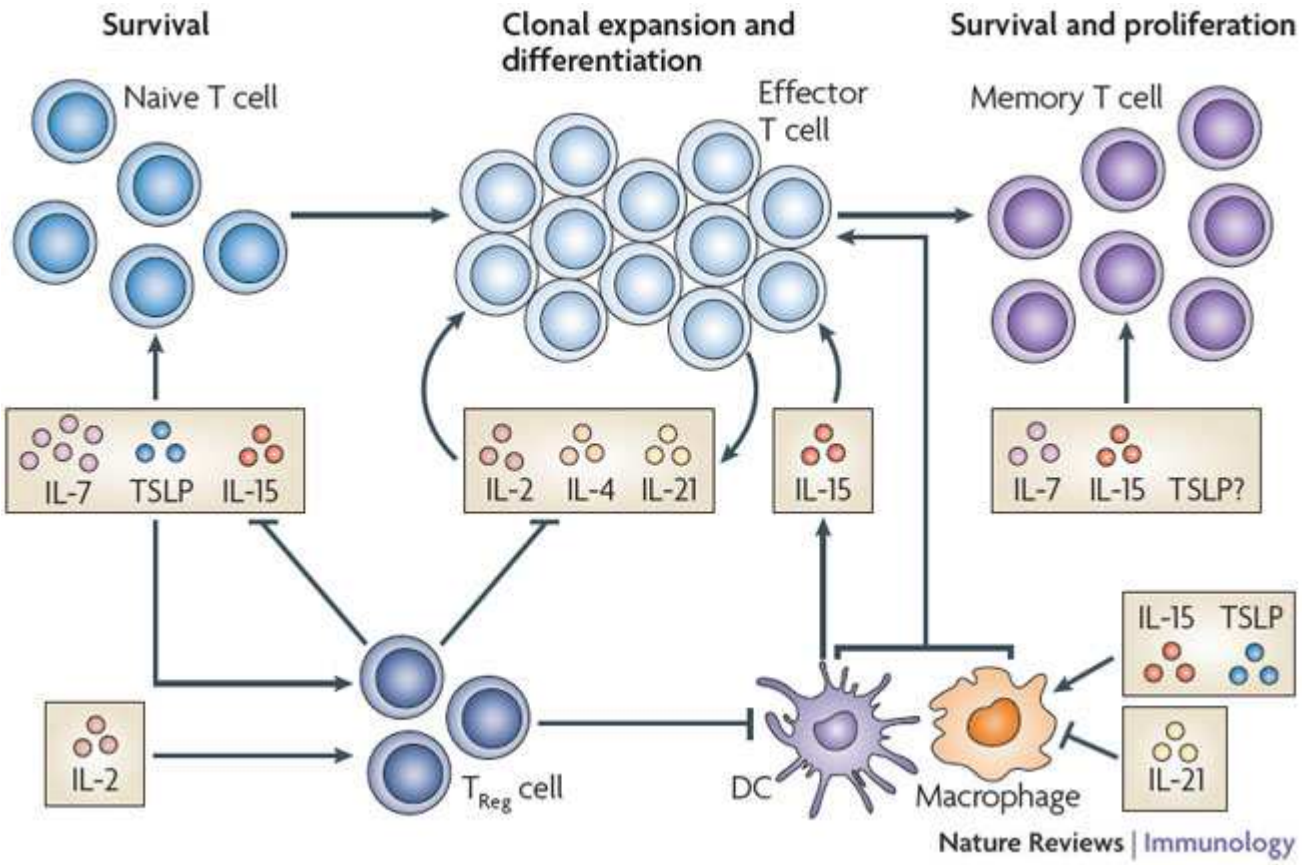
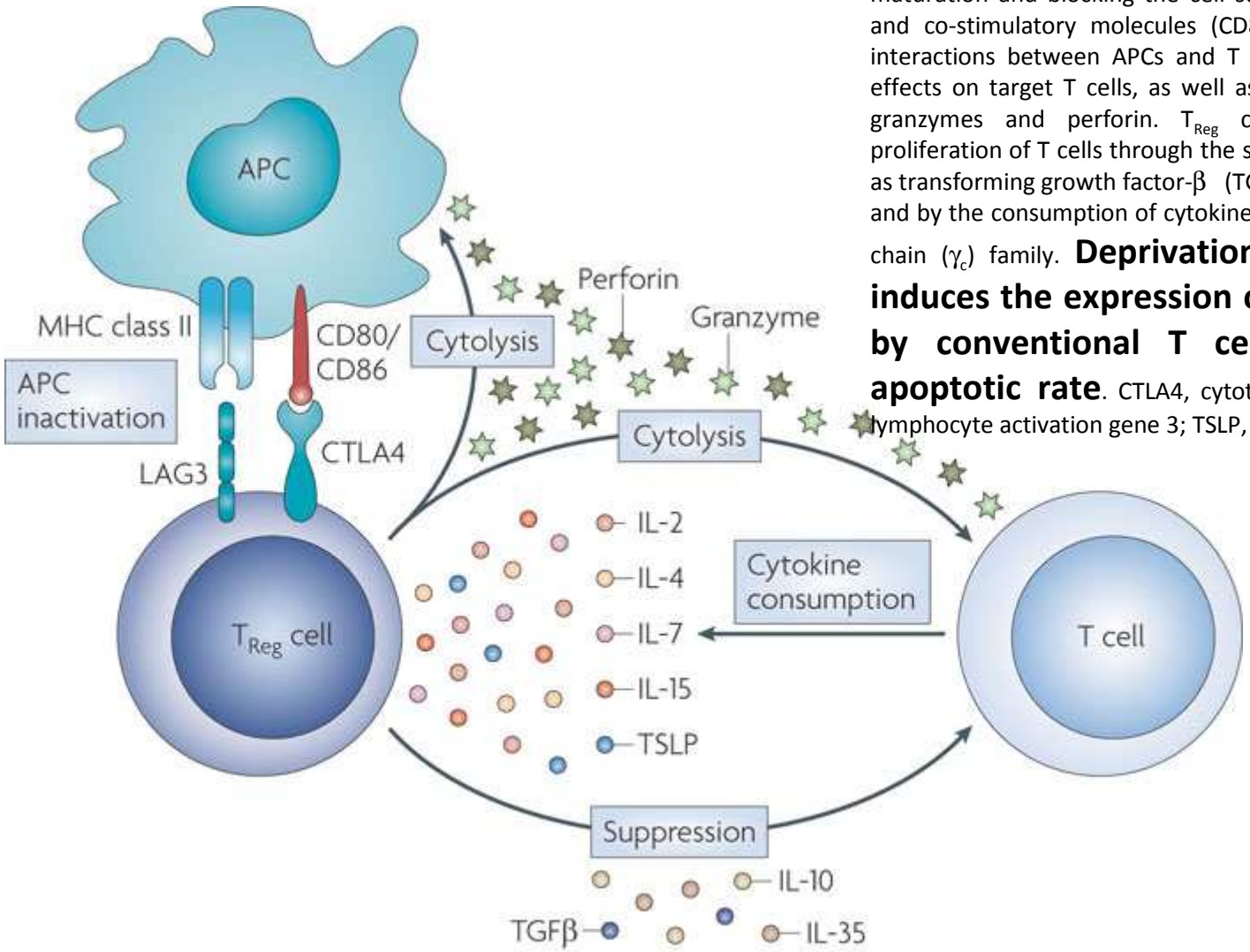
Nature Reviews Immunology 9, 480-490 (July 2009)


Survival
Clonal expansion and differentiation
Survival and proliferation
Naive T cell
Effector T cell
Memory T cell
IL-7 TSLP IL-15
IL-2 IL-4 IL-21
IL-15
IL-7 IL-15 TSLP?
IL-15 TSLP
IL-2
T_{Reg} cell
DC
Macrophage
IL-21
Nature Reviews | Immunology



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)

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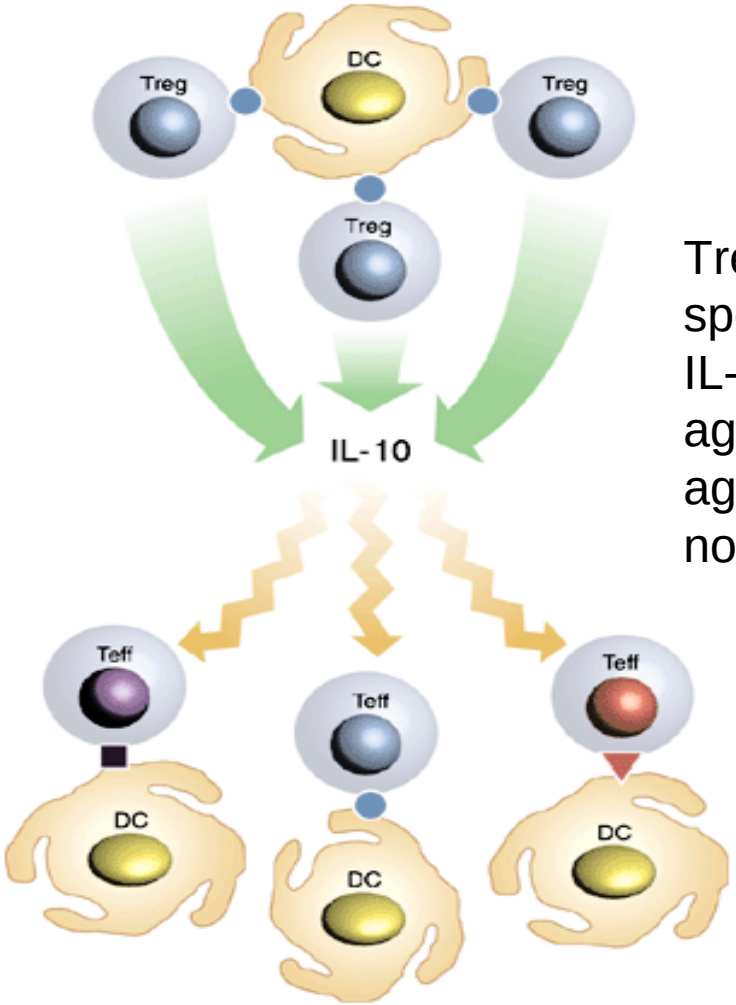
SUPRESIÓN “BY STANDER”



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 (?[2])

[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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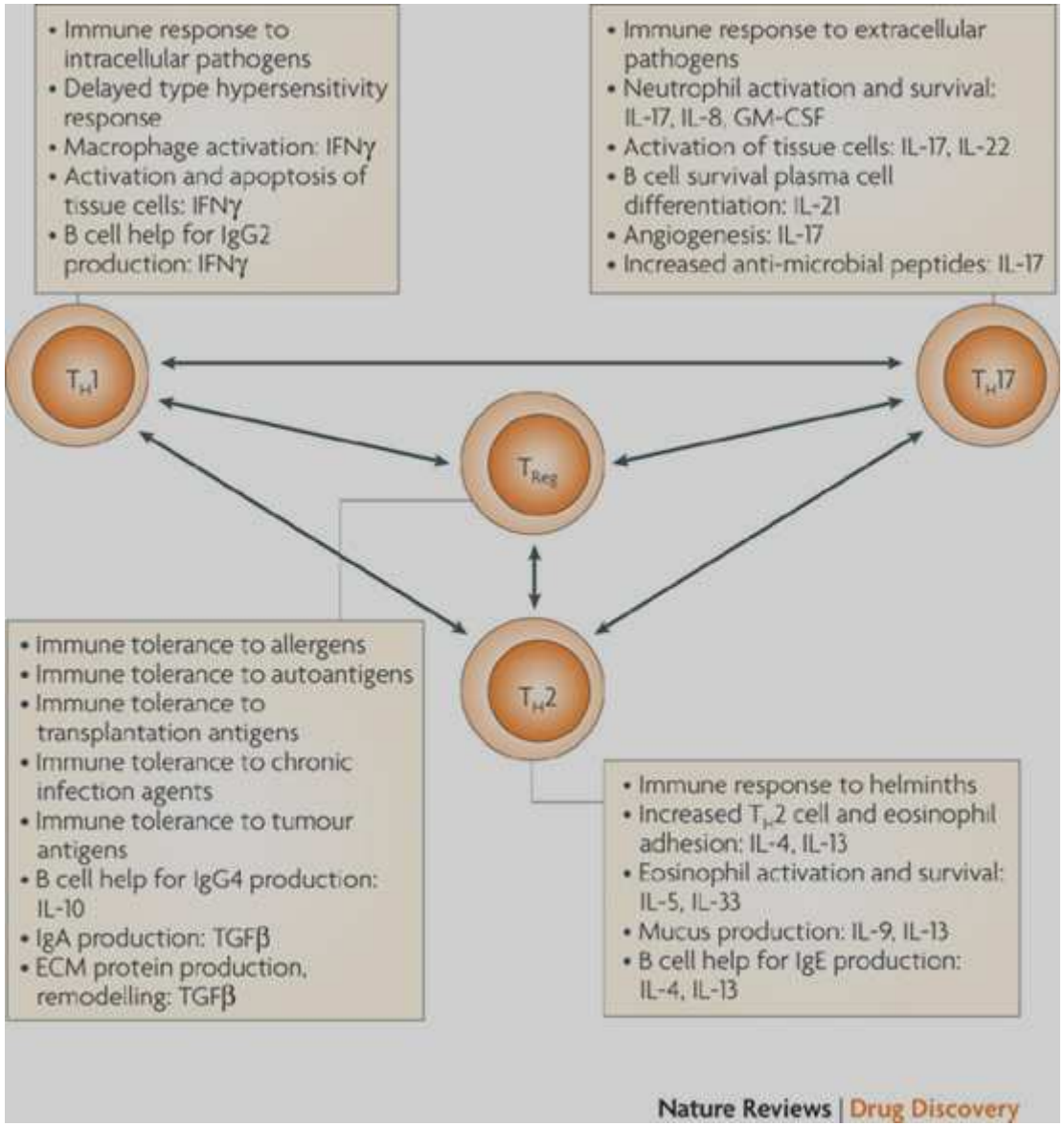

Nature Reviews Drug Discovery **8**, 645-660 (August 2009)


GRACIAS…
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