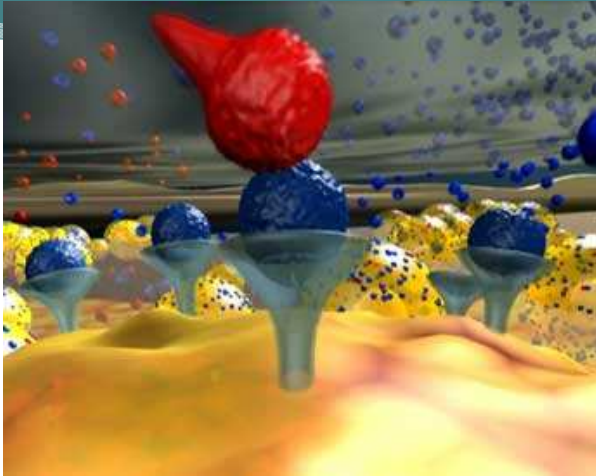
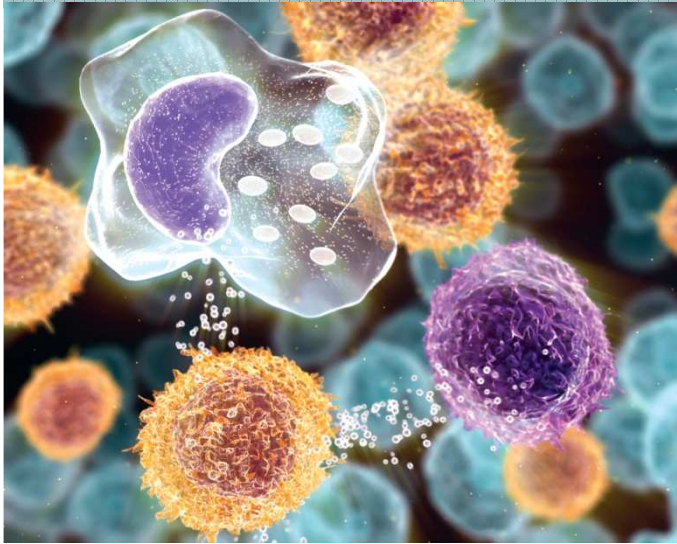


CITOQUINAS



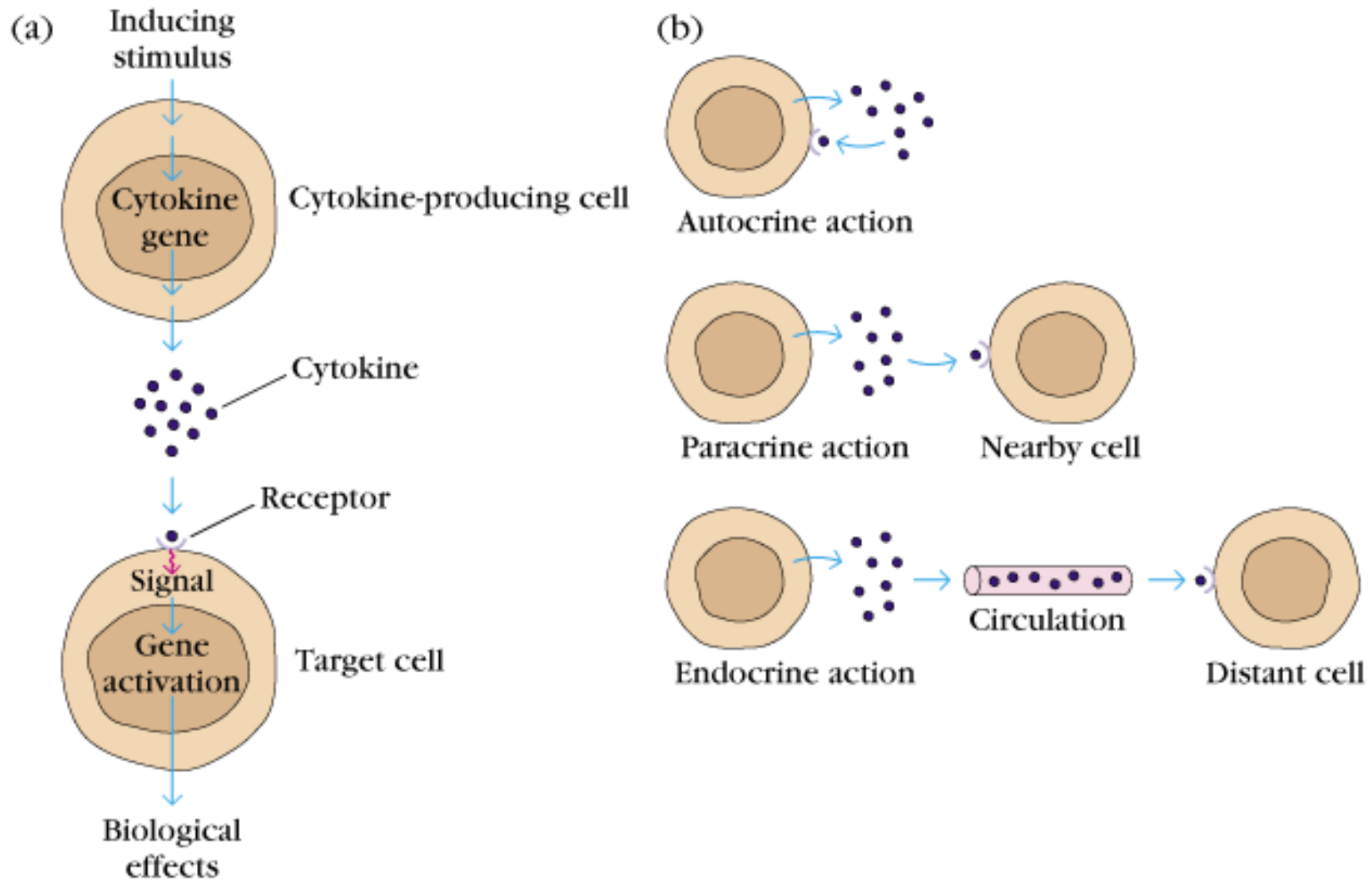


- Las citoquinas son proteínas secretadas por las células de la inmunidad innata y adaptativa que median muchas funciones de estas células.

Propiedades generales

- La secreción de citoquinas es un acontecimiento breve y autolimitado.
- Las acciones de las citoquinas a menudo son pleiotropica y redundantes.
- Las citoquinas a menudo influyen en la síntesis y las acciones de otras citoquinas.
- Las acciones pueden ser autocrina , paracrina o endocrina.
- Las citoquinas , al igual que otras hormonas polipeptídicas ,inician sus acciones uniéndose con alta afinidad a receptores de membrana específicos presentes en las células diana.

Modo de acción de las citoquinas.



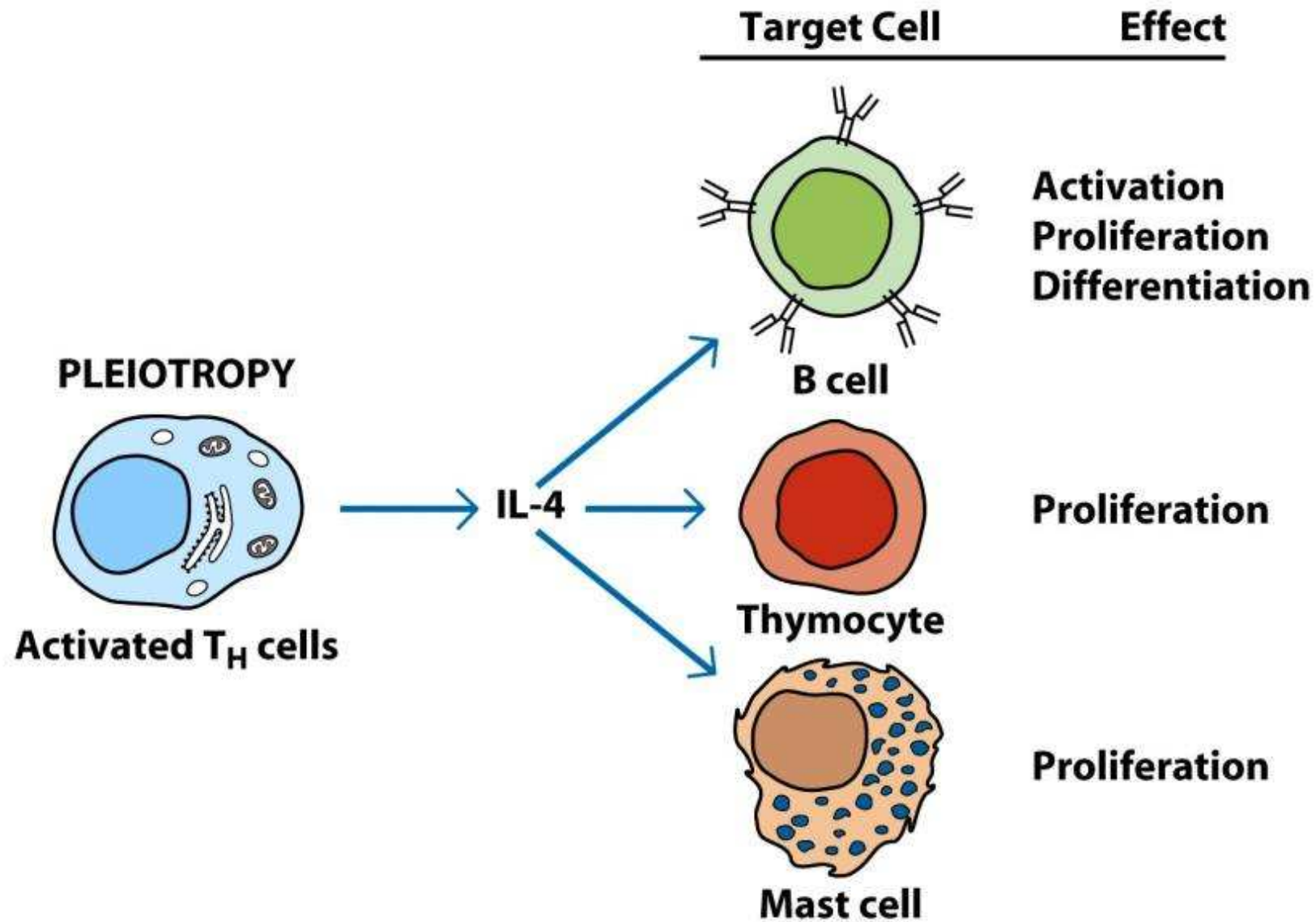
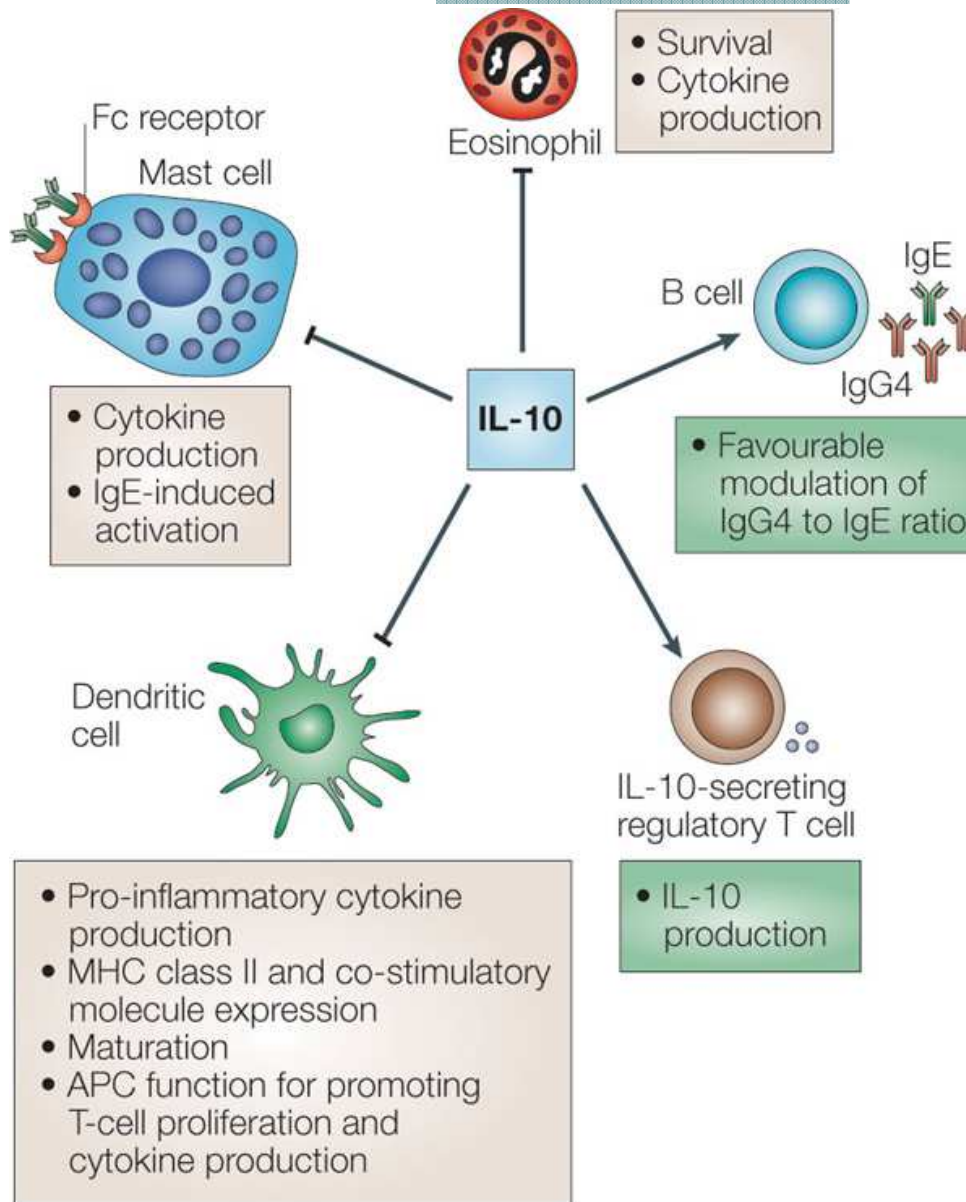
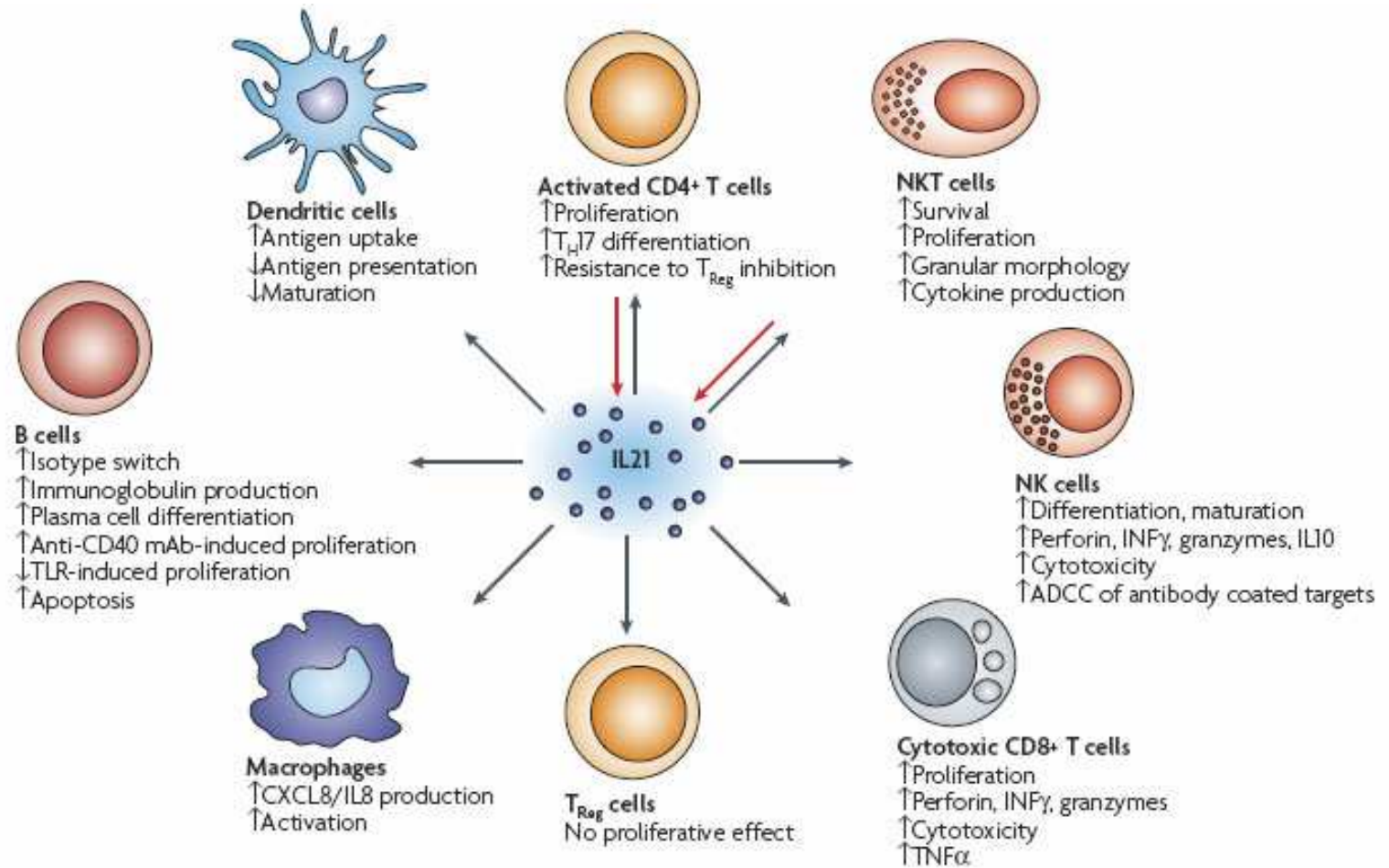


Figure 12-2a part 1
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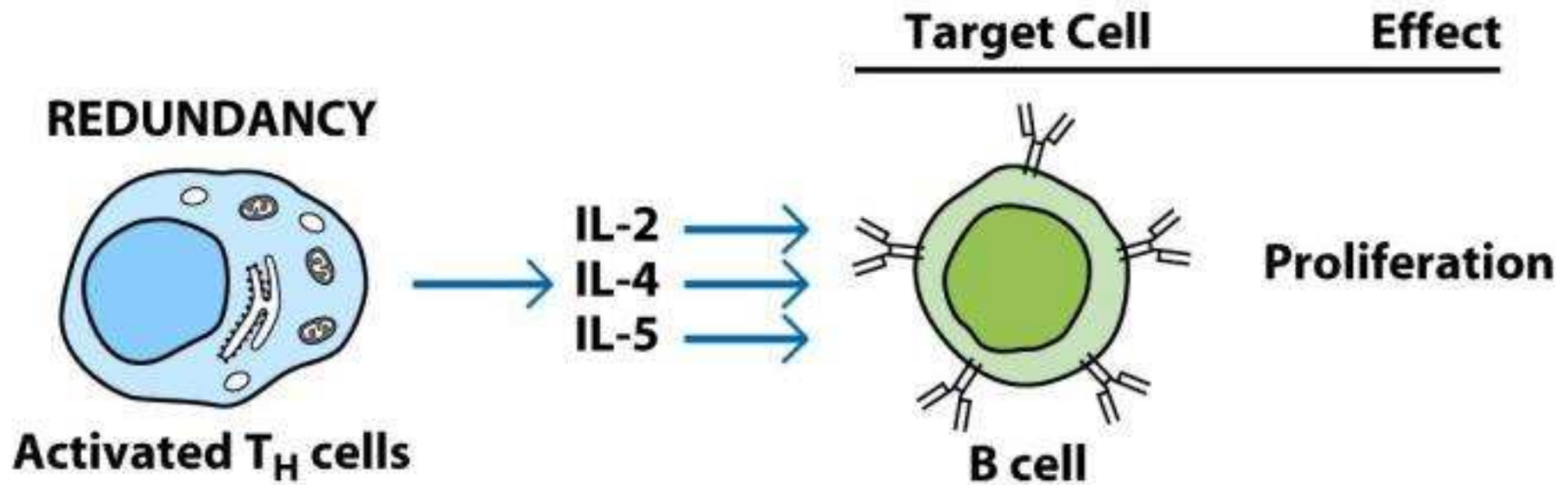
Pleiotropismo



Pleiotropismo



Redundancia



Sinergia y Antagonismo

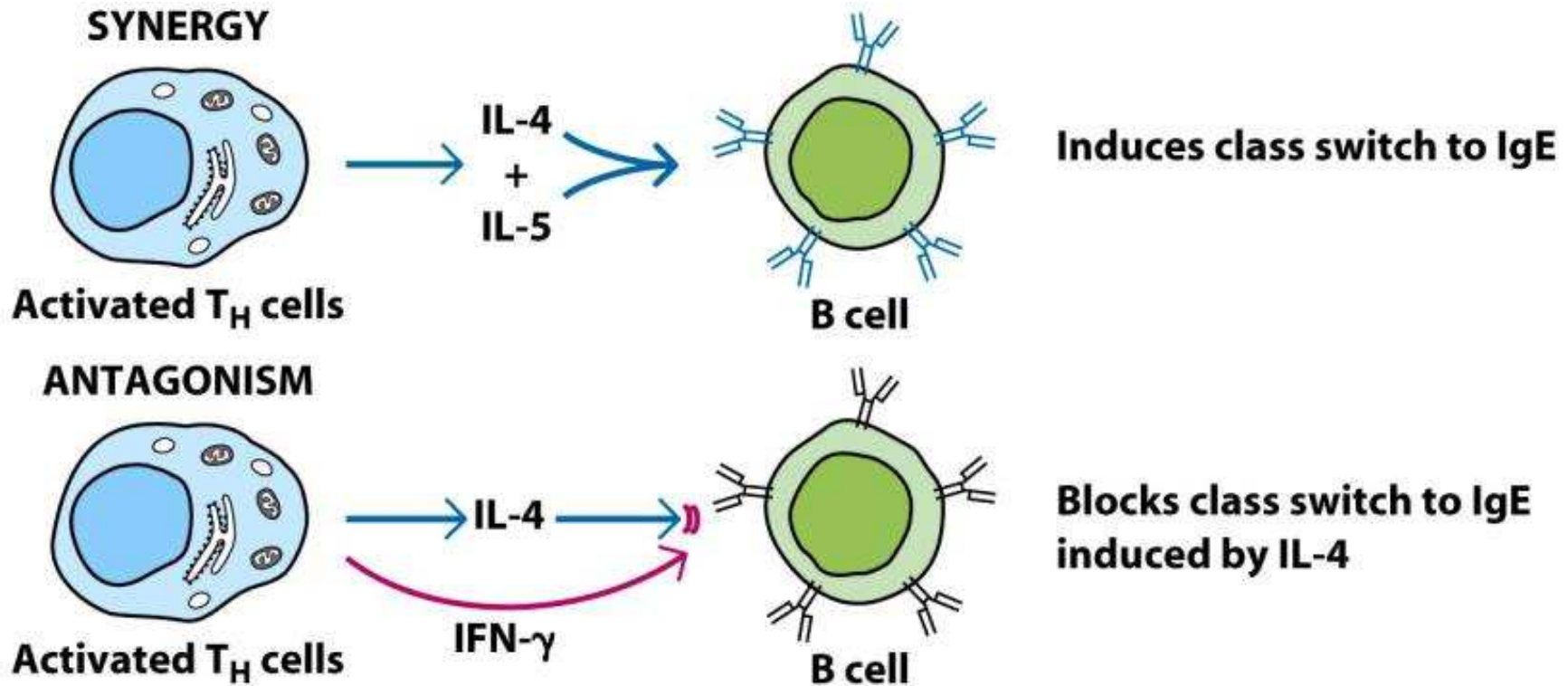
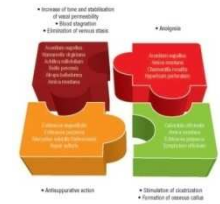


Figure 12-2a part 2
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Acción en cascada

CASCADE INDUCTION



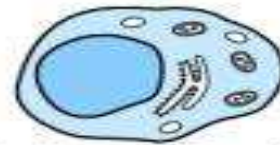
Activated T_H cells

IFN- γ



Macrophage

IL-12



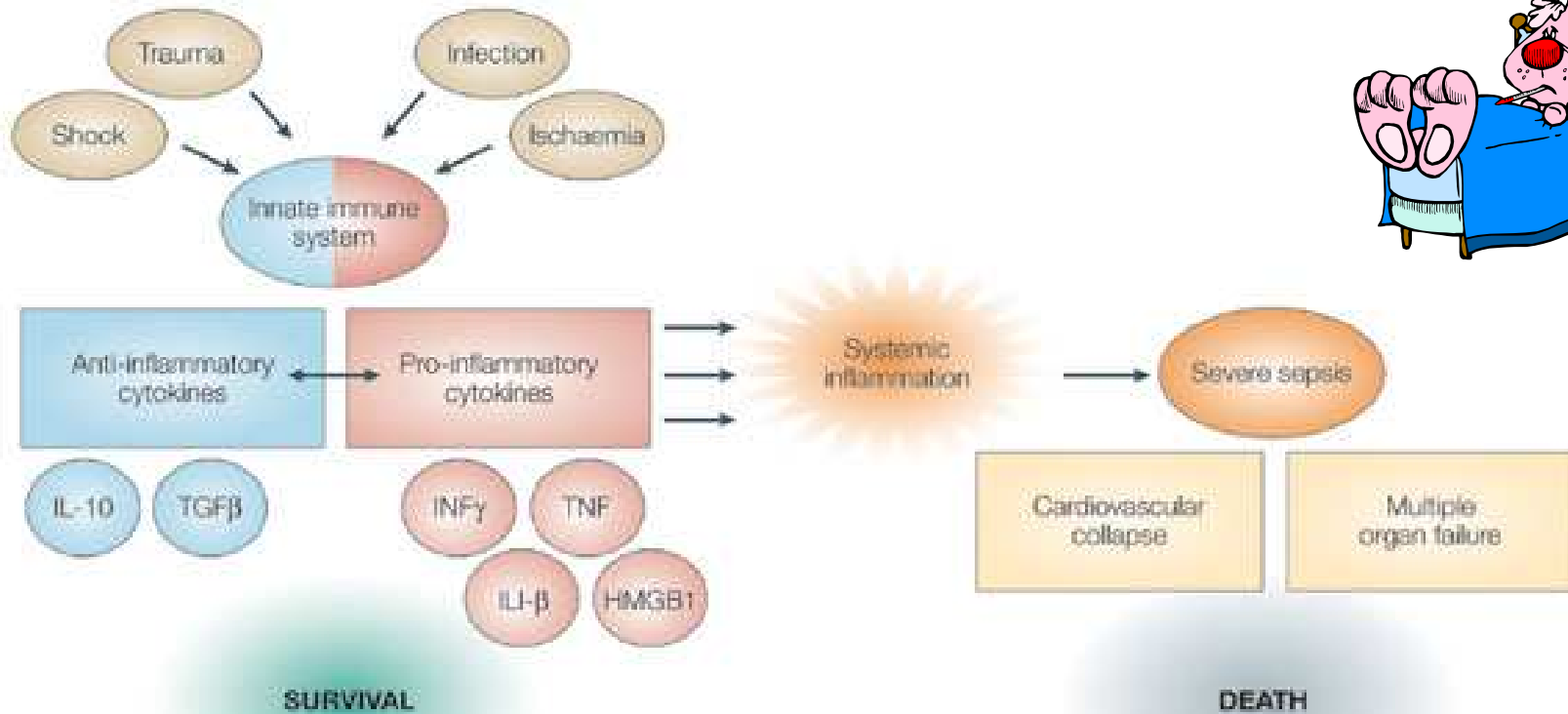
Activated T_H cells

IFN- γ , TNF, IL-2, and other cytokines

Figure 12-2b
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Interleukins	CSFS and others	Interferons
IL-1 α	GM-CSF	IFN- α
IL-1 β	G-CSF	IFN- β
IL-2	M-CSF	IFN- γ
IL-3	EPO	
IL-4	TNF- α	Growth factors
IL-5	TNF- β (LT)	
IL-6	LIF	EGF
IL-7	Steel factor	TGF- α
IL-9 (p40 TCGF)		aFGF
IL-10 (CSIF)	TGF- β Family	bFGF
IL-11		KGF
	TGF- β 1	PDGF-A
Chemotactic factors	TGF- β 2	PDGF-B
	TGF- β 3	NGF- β
	Inhibin	IGF-I
IL-8 (NAP-1)	Actibin	IGF-II
MCP-I		

Influyen en la síntesis y las acciones de otras citoquinas.



Receptores de citoquinas

- Receptores tipo I.
- Receptores de citoquinas tipo II.
- Receptores de TNF.
- Receptores de Inmunoglobulinas.
- Receptores siete hélice α transmembrana.

Receptores de citoquinas Tipo I

RECEPTOR FAMILY

**Class I cytokine receptors
(hematopoietin)**

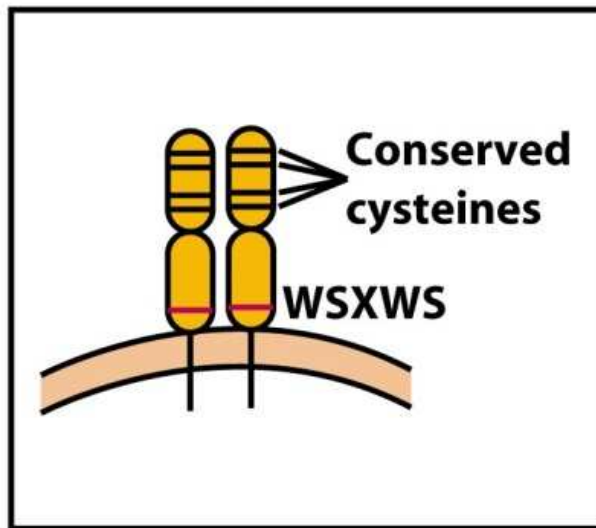
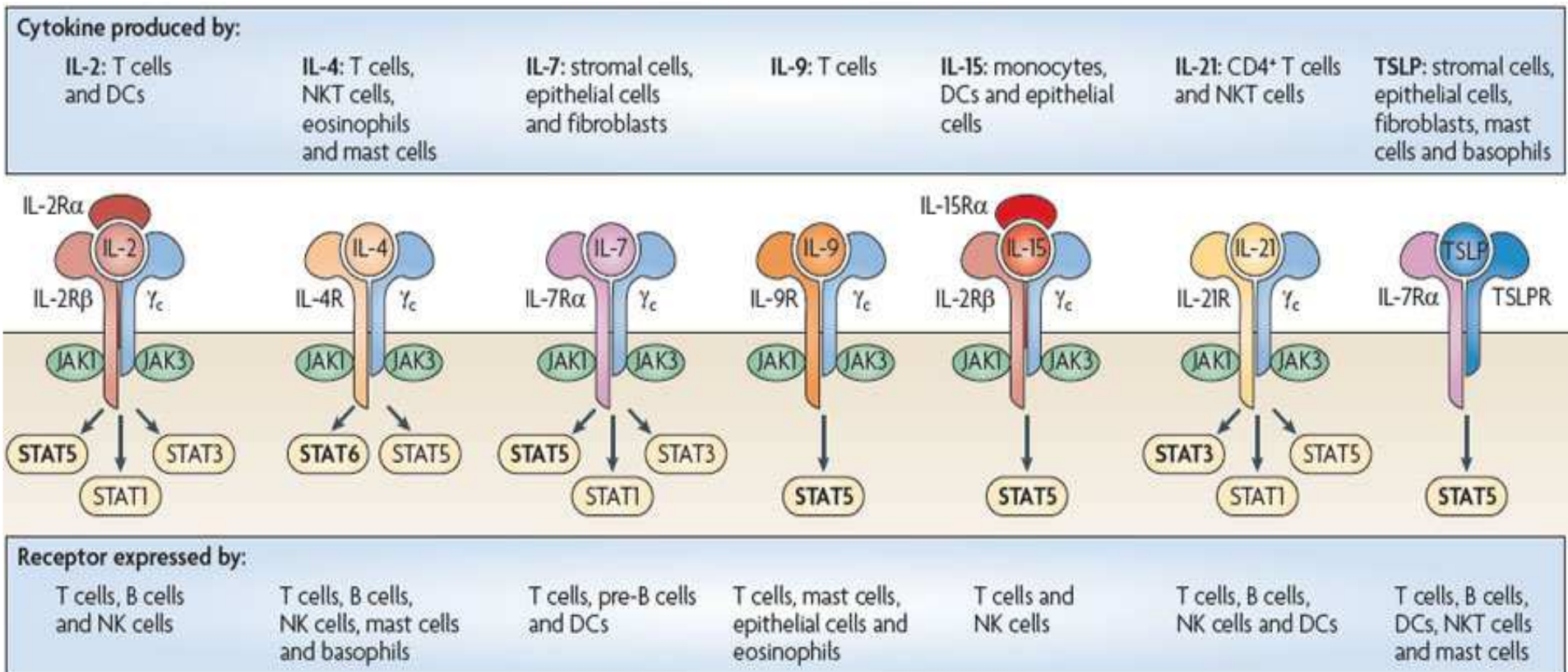


Figure 12-6b
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LIGANDS

IL-2	IL-21
IL-3	IL-23
IL-4	IL-27
IL-5	GM-CSF
IL-6	G-CSF
IL-7	OSM
IL-9	LIF
IL-11	CNTF
IL-12	Growth hormone
IL-13	Prolactin
IL-15	

Receptores de citoquinas Tipo I



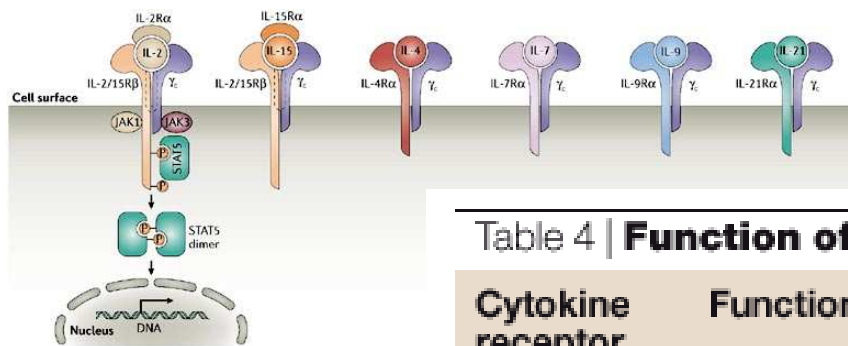


Table 4 | **Function of γ_c cytokines**

Cytokine receptor

Function

IL-2	Clonal expansion and differentiation of T-helper cells and cytotoxic T lymphocytes; <i>in vitro</i> expansion and differentiation of antigen-selected T and NK cells; regulation of self-tolerance and development of regulatory T cells (T_{Reg})
IL-4	Promotion of T-helper 2 (T_H2) cell differentiation; antagonism of T_H1 differentiation and macrophage activation; regulation of B-cell function and immunoglobulin class switching together with IL-21; stimulation of mast cells
IL-7	Growth and survival of T and B cell progenitors; thymic development and survival of T cells; homeostasis of peripheral lymphocytes
IL-9	Goblet-cell hyperplasia and mucus production
IL-15	Development, differentiation, survival and activation of NK cells; homeostasis of peripheral T cells; expansion of CD8 ⁺ memory cells
IL-21	Regulation of B-cell function and immunoglobulin class switching in conjunction with IL-4; proliferation and activation of NK cells

This list briefly summarizes the main actions of the cytokines as they relate to the potential functions of the JAK3 inhibitor. It should be noted that the actions of these cytokines, especially IL-7, are not identical in humans and mice; the actions in humans are emphasized here. IL, interleukin; JAK, Janus kinase; NK, natural killer.

Inmunodeficiencia combinada grave ligada al cromosoma X

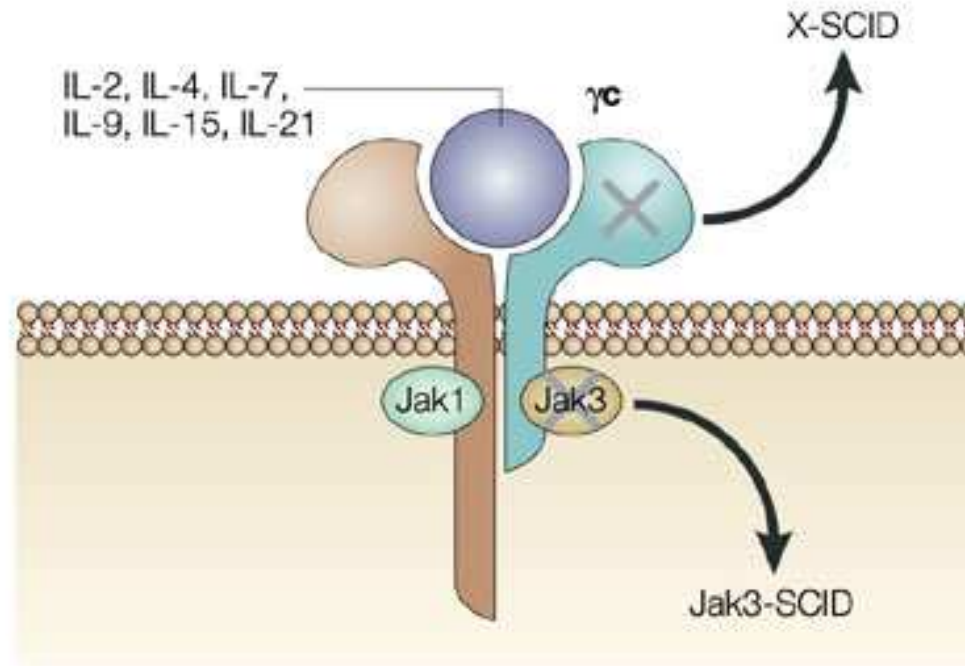
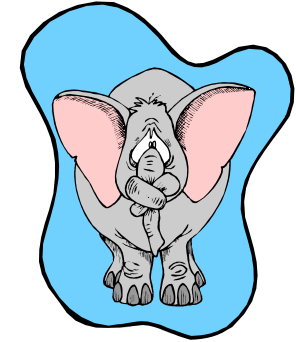


Table 1 | **Defects in γ_c -dependent cytokine- or receptor-deficient mice**

Cytokine or cytokine-receptor mutant	Phenotype	References
IL-2 deficient	Normal T-cell development; autoimmunity with increased serum immunoglobulin concentrations; inflammatory bowel disease	83–85
IL-4 deficient	Defective T_H2 -cytokine production; defective IgG1 and IgE production	36,86
IL-7 deficient	Markedly defective T- and B-cell development	87
IL-9 deficient	Defective pulmonary goblet-cell function	88
IL-15 deficient	Defective CD8 ⁺ memory T-cell and NK-cell development	58
IL-2 receptor α -chain deficient	Polyclonal T- and B-cell proliferation in adults; autoimmune-disease development	90,91
IL-2 receptor β -chain deficient	Severe autoimmunity with early death; dysregulated T- and B-cell proliferation; high IgG1 and IgE serum concentrations	57
γ_c deficient	Defective thymic development; cause of XSCID in humans, which accounts for ~50% of SCID cases	3,40,41
IL-4 receptor α -chain deficient	Defective T_H2 -cell development and cytokine production; decreased IgG1 and IgE production	92
IL-7 receptor α -chain deficient	Markedly defective T- and B-cell development in mice; loss of TSLP responses (because of shared receptor subunit); cause of T ⁺ B ⁺ NK ⁺ form of SCID in humans	1,2,42,93
IL-15 receptor α -chain deficient	Defective CD8 ⁺ memory T-cell and NK-cell development	58
IL-21R deficient	Normal lymphoid development; high IgE and low IgG1 serum concentrations in naive mice	27
IL-21R and IL-4 deficient	Normal lymphoid development; markedly deficient immunoglobulin production, of all classes including IgE	27

γ_c , common cytokine-receptor γ -chain; IL, interleukin; IL-21R, IL-21-receptor subunit; NK, natural killer; SCID, severe combined immunodeficiency; T_H2 , T helper 2; TSLP, thymic stromal lymphopoietin; XSCID, X-linked SCID.

Receptores de citoquinas Tipo II

RECEPTOR FAMILY

**Class II cytokine receptors
(interferon)**

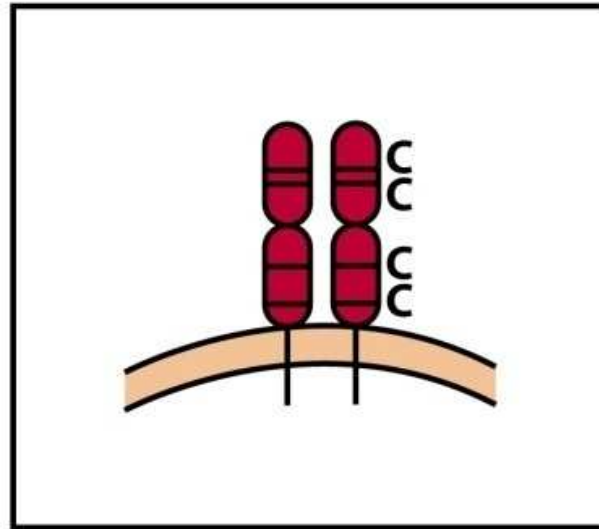


Figure 12-6c
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LIGANDS

IFN- α

IFN- β

IFN- γ

IL-10

IL-19

IL-20

IL-22

IL-24

IL-26

IL-28

IL-29

RECEPTOR FAMILY

TNF receptors

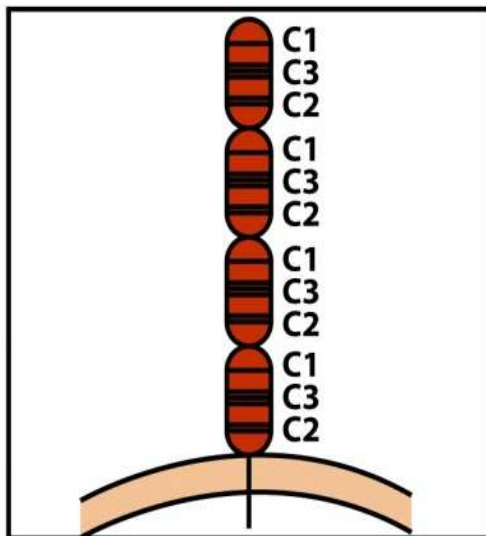
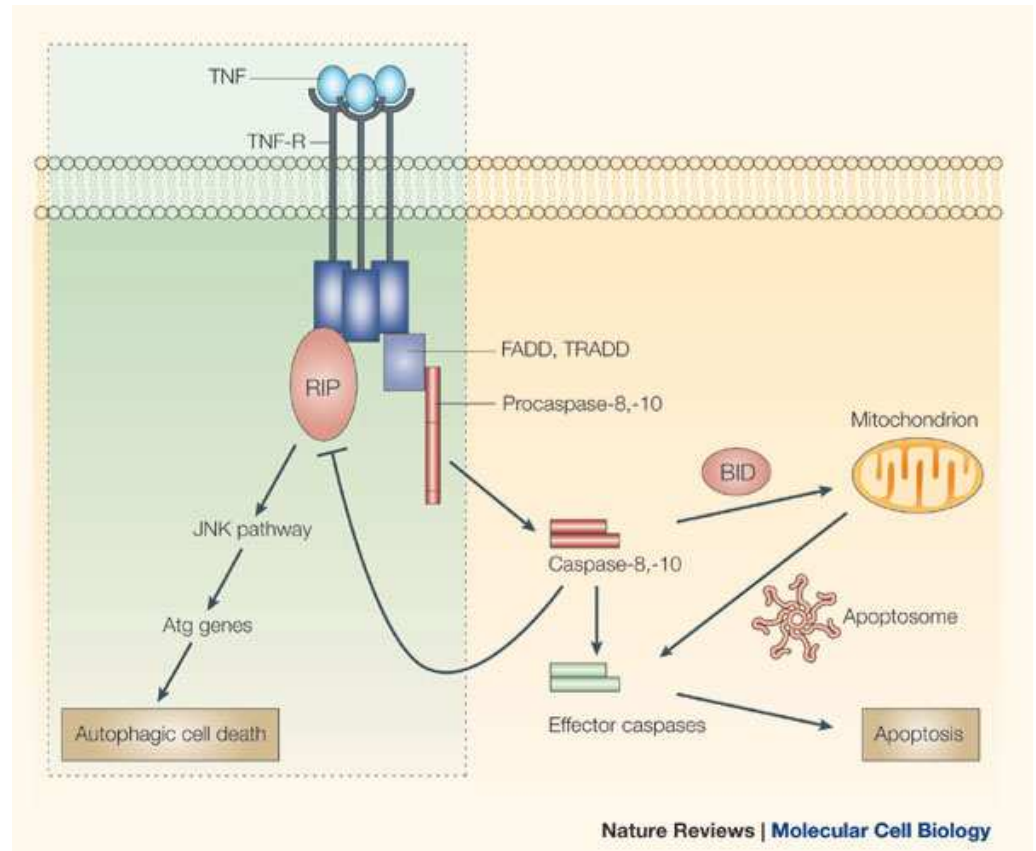


Figure 12-6d
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LIGANDS

- TNF- α
- TNF- β
- CD27L
- CD30L
- CD40L
- Nerve growth factor (NGF)
- FAS



RECEPTOR FAMILY

Immunoglobulin superfamily receptors

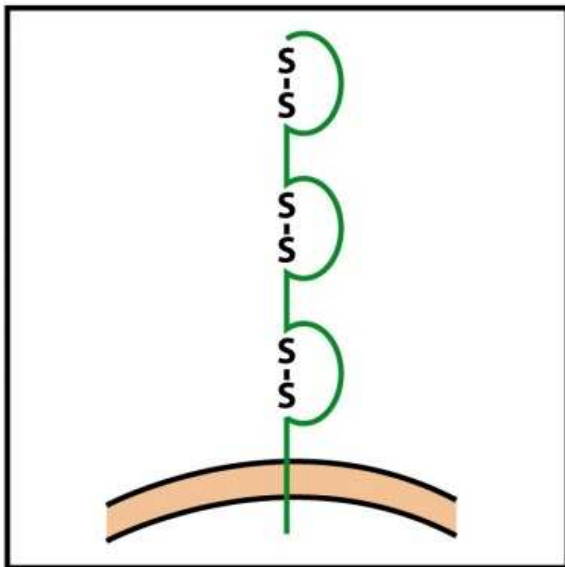
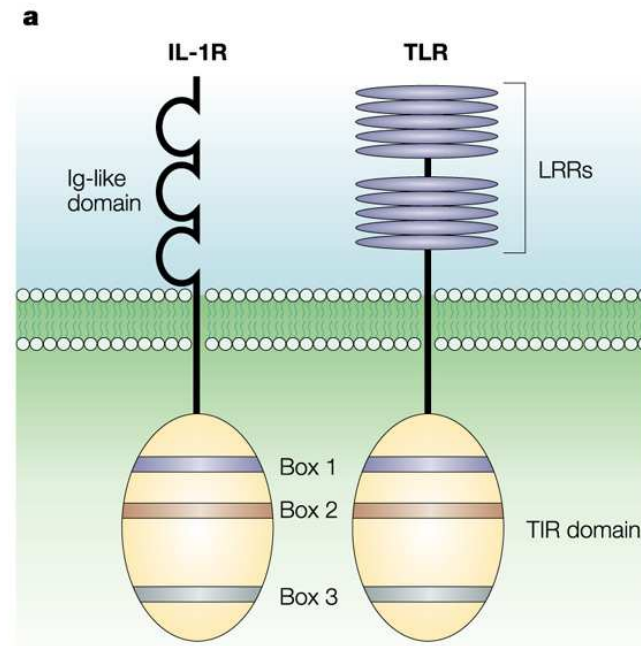


Figure 12-6a
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LIGANDS

IL-1
M-CSF
C-Kit
IL-18



Receptor de la superfamilia de las inmunoglobulinas

Receptor de quimioquinas

RECEPTOR FAMILY

Chemokine receptors

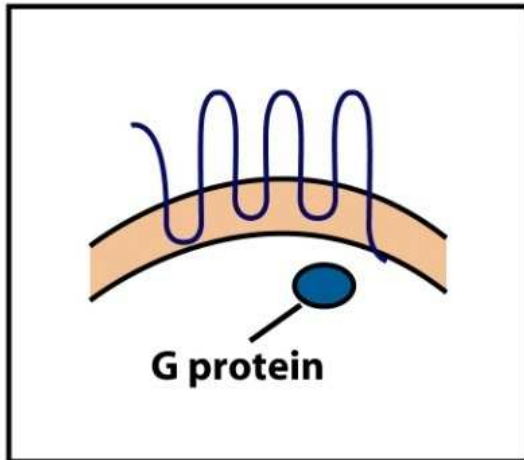


Figure 12-6e
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LIGANDS

- IL-8
- RANTES
- MIP-1
- PF4
- MCAF
- NAP-2

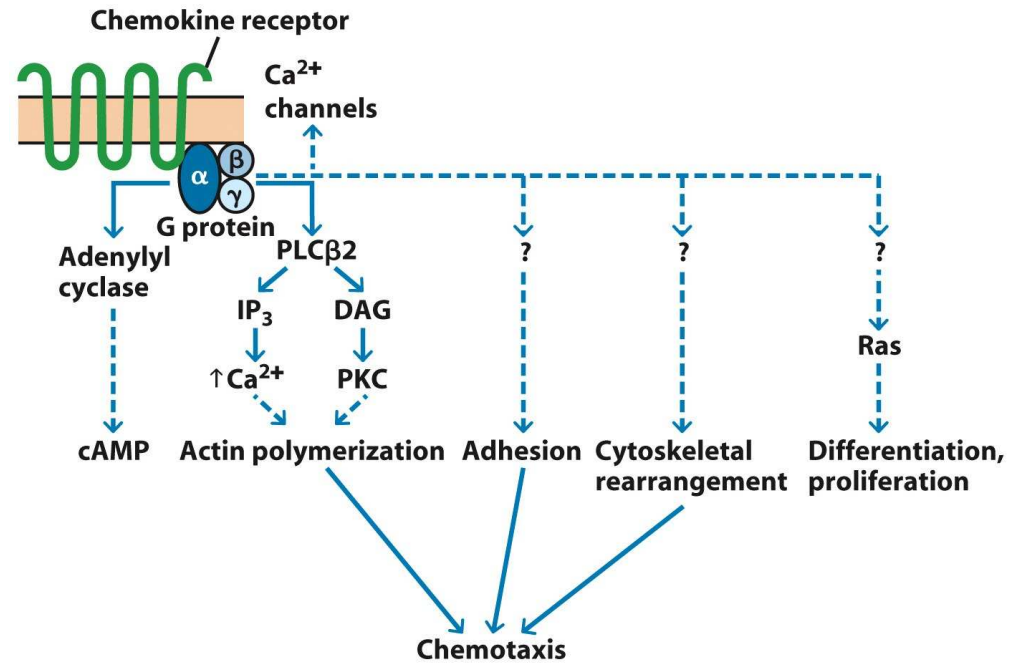


Figure 13-2
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Overview of the transcriptional pathways in natural killer cells

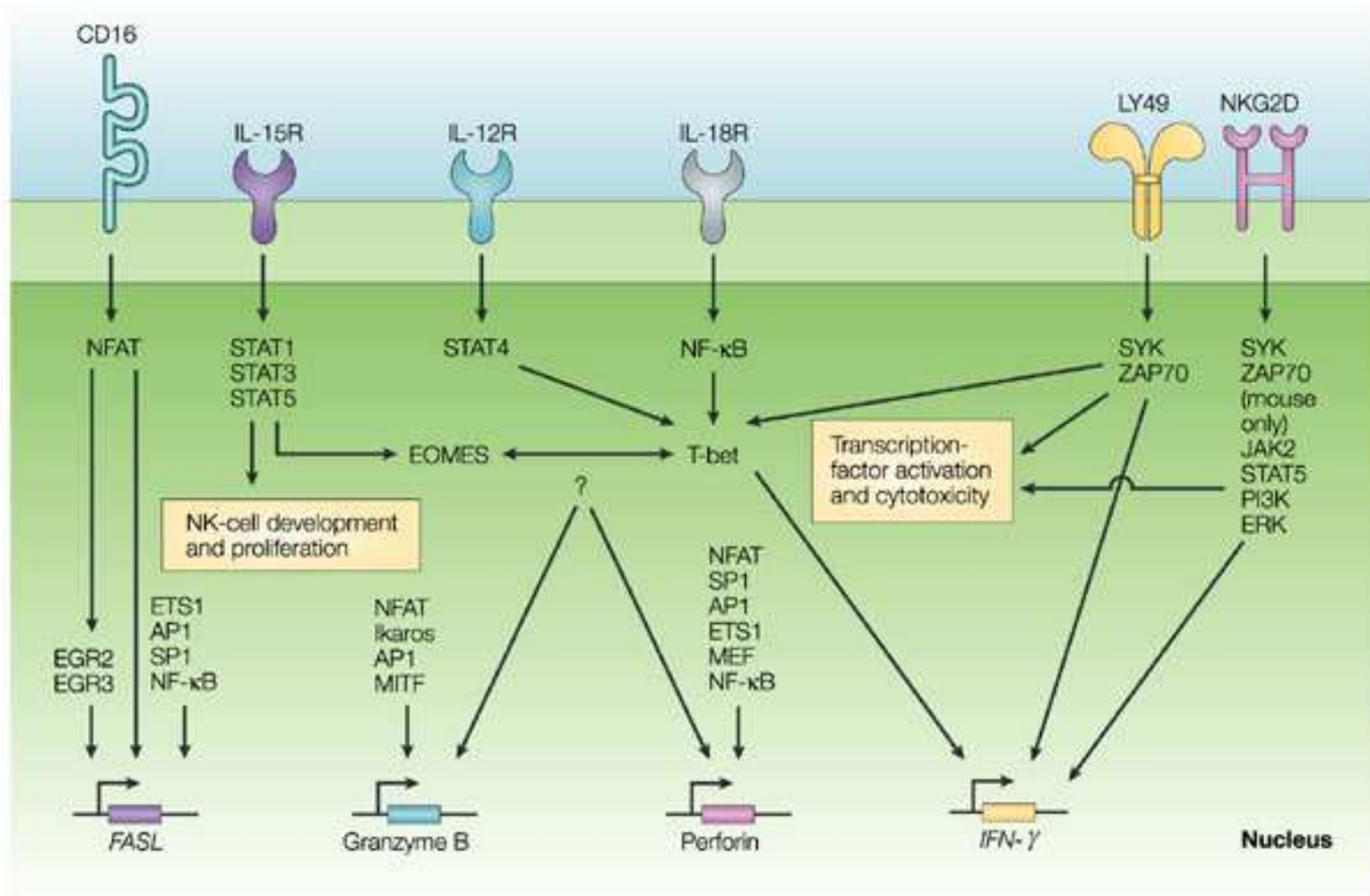


TABLE 12-1 Functional groups of selected cytokines*

Cytokine†	Secreted by‡	Targets and effects
SOME CYTOKINES OF INNATE IMMUNITY		
Interleukin 1 (IL-1)	Monocytes, macrophages, endothelial cells, epithelial cells	Vasculature (inflammation); hypothalamus (fever); liver (induction of acute phase proteins)
Tumor necrosis factor- α (TNF- α)	Macrophages	Vasculature (inflammation); liver (induction of acute phase proteins); loss of muscle, body fat (cachexia); induction of death in many cell types; neutrophil activation
Interleukin 12 (IL-12)	Macrophages, dendritic cells	NK cells; influences adaptive immunity (promotes T _H 1 subset)
Interleukin 6 (IL-6)	Macrophages, endothelial cells	Liver (induces acute phase proteins); influences adaptive immunity (proliferation and antibody secretion of B cell lineage)
Interferon α (IFN- α) (this is a family of molecules)	Macrophages	Induces an antiviral state in most nucleated cells; increases MHC class I expression; activates NK cells
Interferon β (IFN- β)	Fibroblasts	Induces an antiviral state in most nucleated cells; increases MHC class I expression; activates NK cells
SOME CYTOKINES OF ADAPTIVE IMMUNITY		
Interleukin 2 (IL-2)	T cells	T-cell proliferation; can promote AICD. NK cell activation and proliferation; B-cell proliferation
Interleukin 4 (IL-4)	T _H 2 cells, mast cells	Promotes T _H 2 differentiation; isotype switch to IgE
Interleukin 5 (IL-5)	T _H 2 cells	Eosinophil activation and generation
Transforming growth factor β (TGF- β)	T cells, macrophages, other cell types	Inhibits T-cell proliferation and effector functions; inhibits B-cell proliferation; promotes isotype switch to IgA; inhibits macrophages
Interferon γ (IFN- γ)	T _H 1 cells, CD8 ⁺ cells, NK cells	Activates macrophages; increases expression MHC class I and class II molecules; increases antigen presentation
<p>*Many cytokines play roles in more than one functional category. †Only the major cell types providing cytokines for the indicated activity are listed; other cell types may also have the capacity to synthesize the given cytokine. ‡Also note that activated cells generally secrete greater amounts of cytokine than unactivated cells.</p>		

Table 12-1

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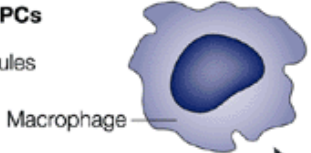
Factor de Necrosis Tumoral

- Es el mediador principal de la respuesta inflamatoria aguda frente a las bacterias gram negativas y a otros microorganismos infecciosos.
- En infecciones graves ,el TNF se produce en grandes cantidades y causa alteraciones histológicas y clínicas sistémicas.

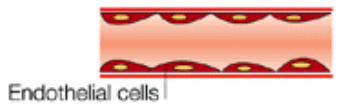
Immunostimulatory

Immunosuppressive

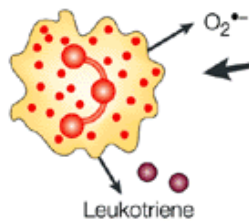
Activation of APCs
↑ MHC
↑ Adhesion molecules



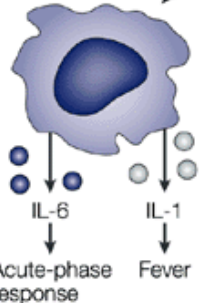
Activation of endothelial cells



Shock
iNOS
Activation of neutrophils



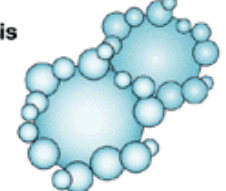
Cytokine induction



Inhibition of T-cell signalling



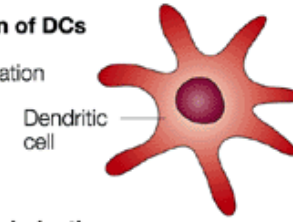
Apoptosis



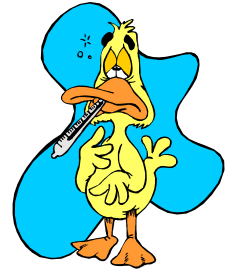
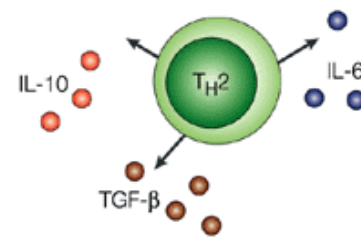
Lymphopaenia
Suppression of proliferation



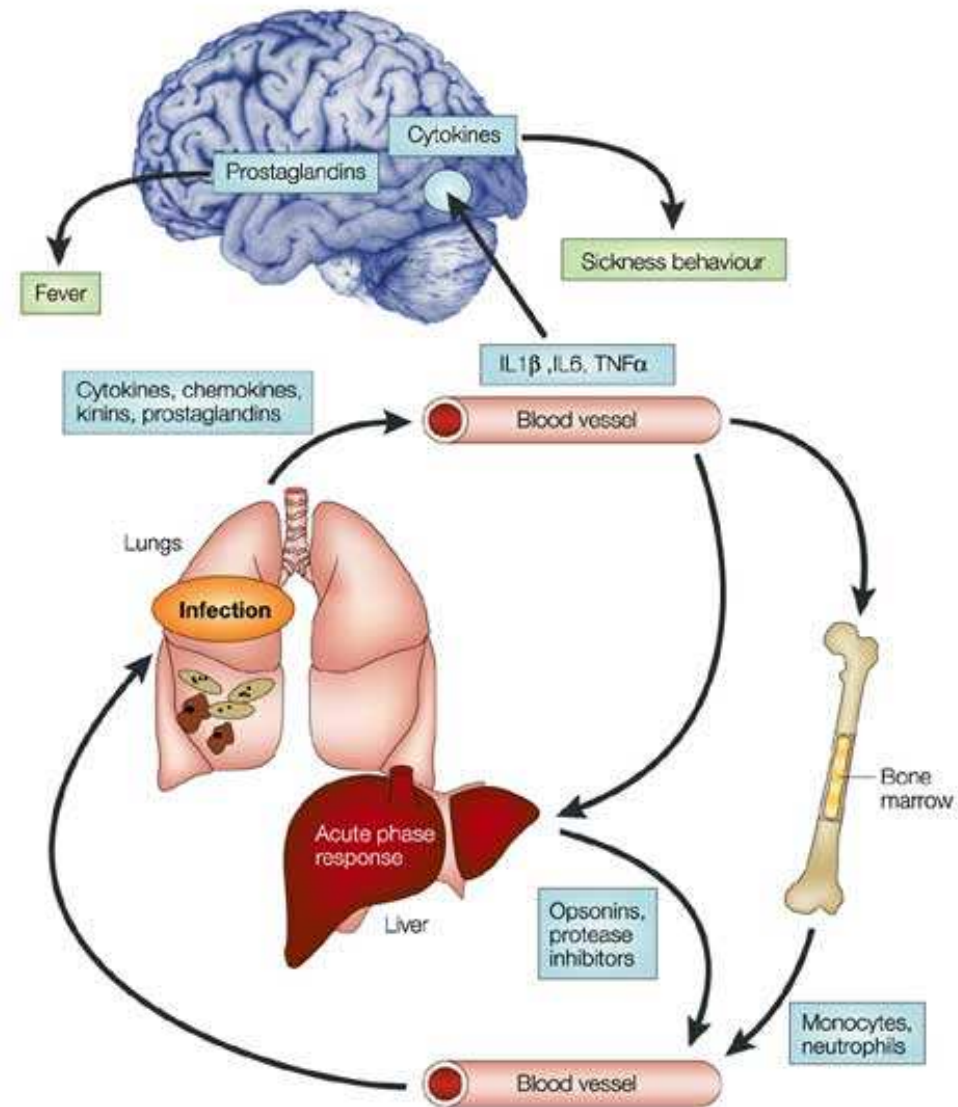
Inhibition of DCs
Defective co-stimulation



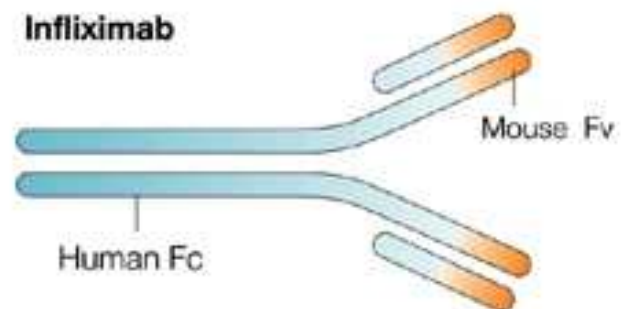
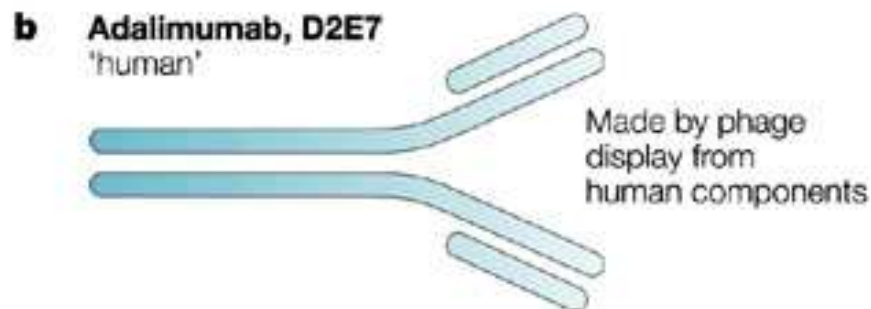
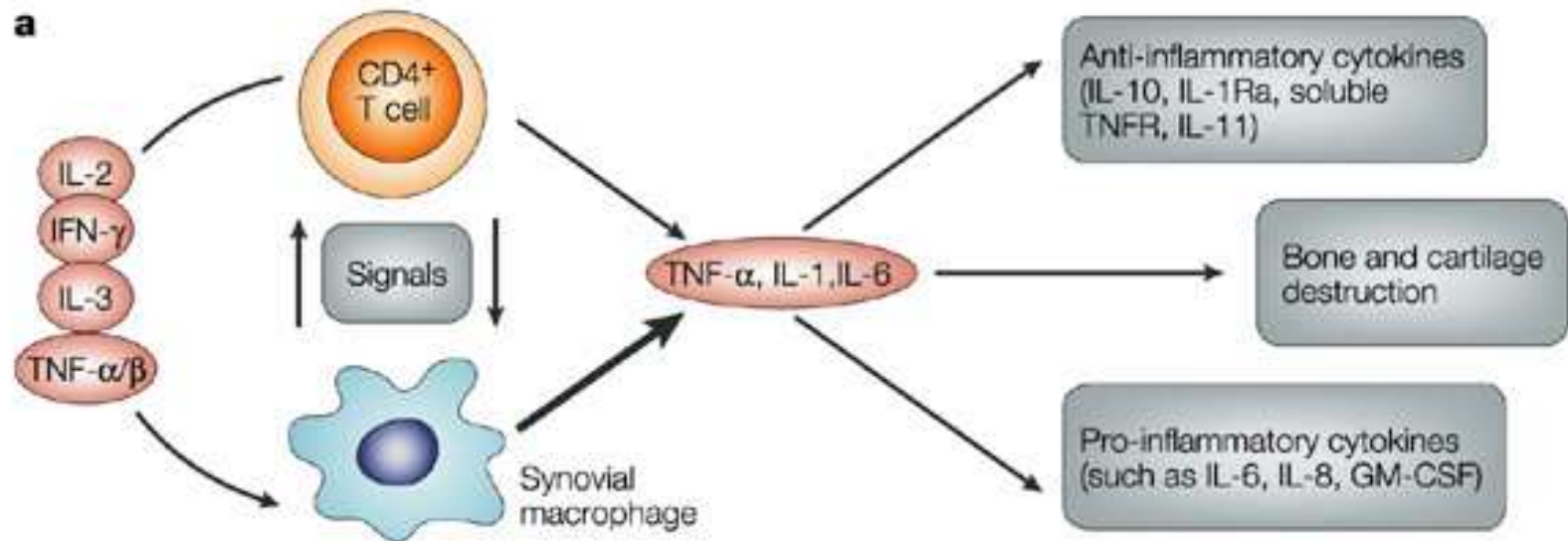
Cytokine induction



IL-1, TNF α , IL-6 Acción endocrina

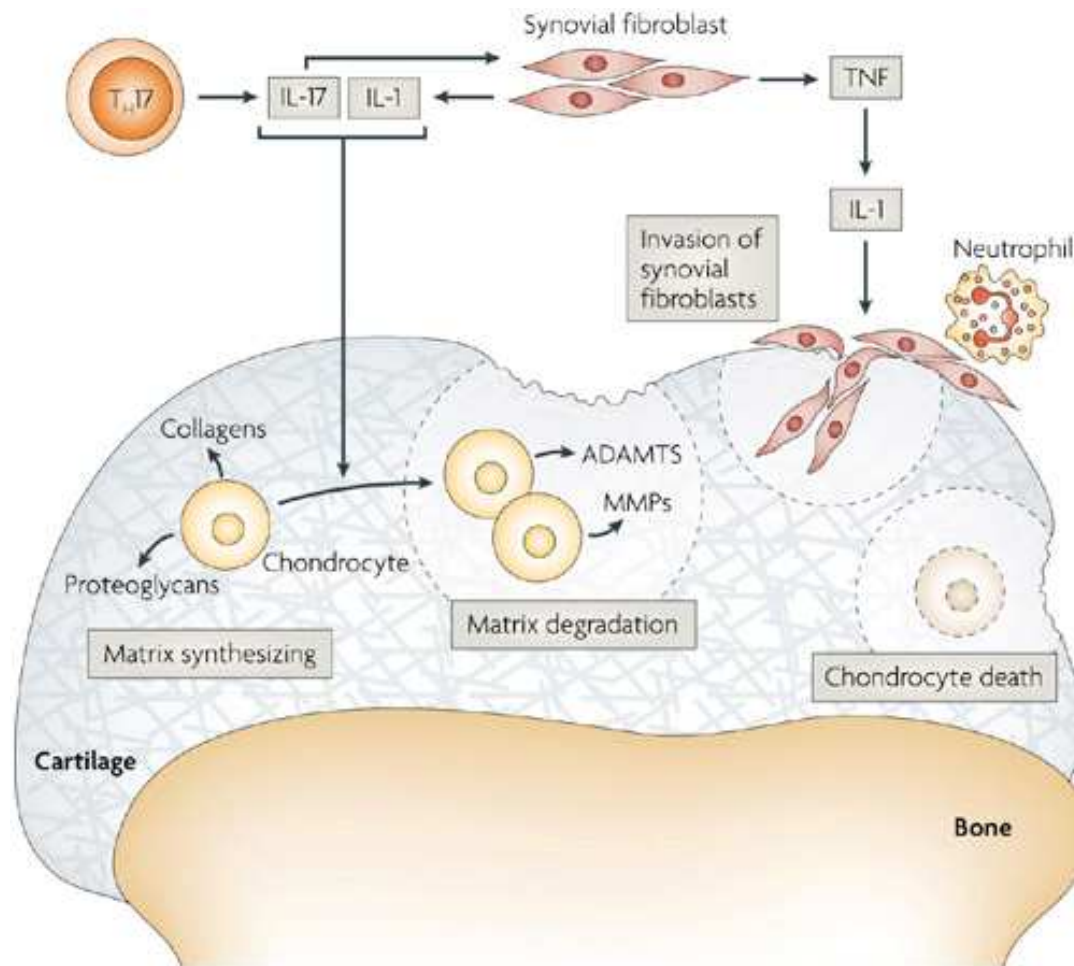


Arthritis



Citoquinas en patogénesis

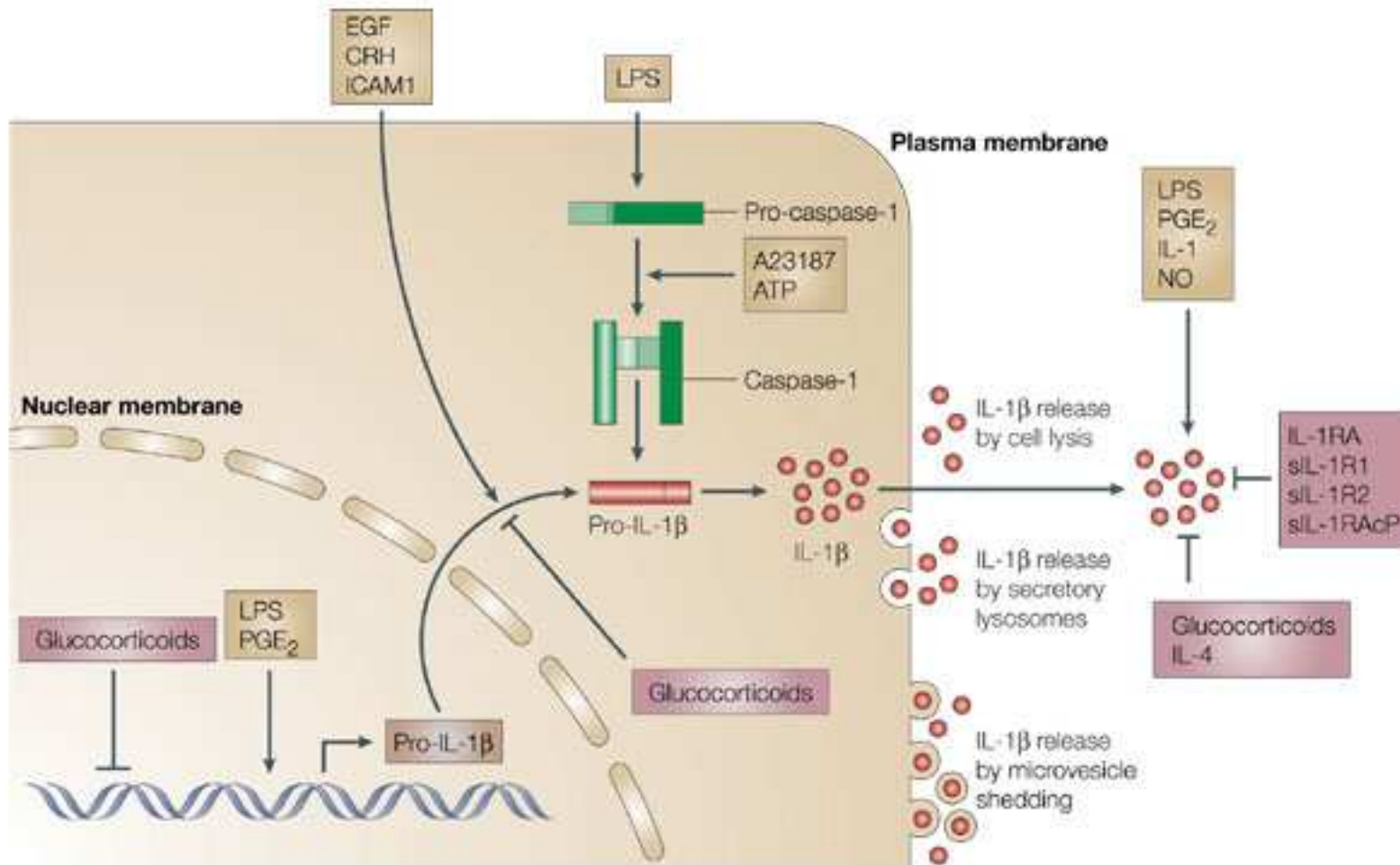
Pathways regulating chondrocyte activation and cartilage degradation in rheumatoid arthritis.



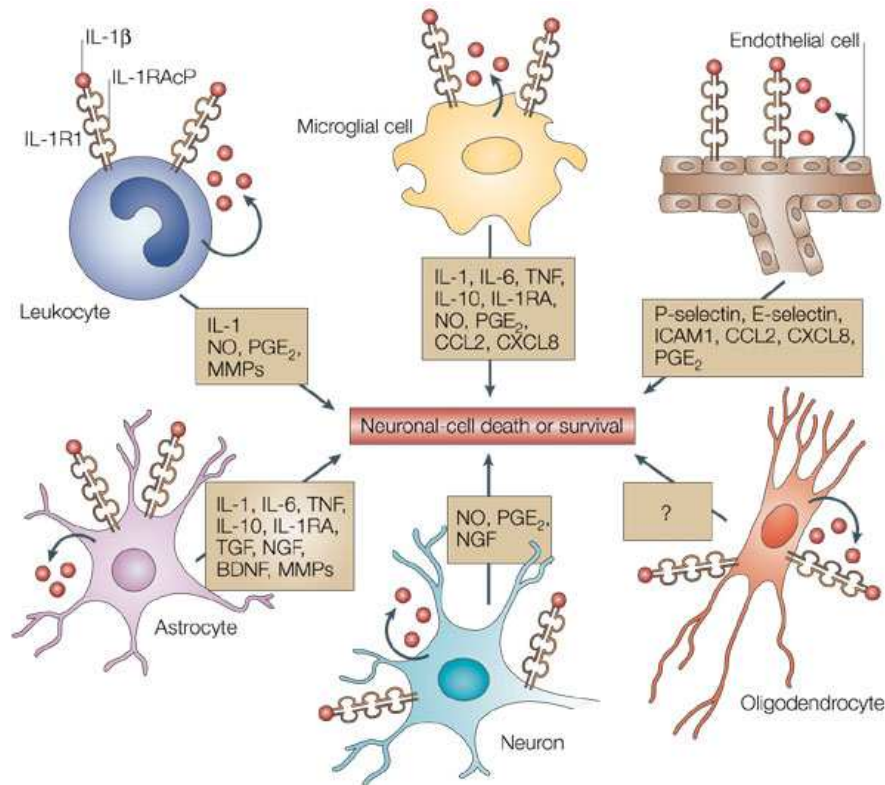
IL-1

- Producida por macrófagos activados
- Efectos similares al TNF- α , mediando la respuesta inflamatoria del huésped a las infecciones y otros estímulos inflamatorios.
- En bajas concentraciones actúa como mediador de la inflamación local pero a altas concentraciones la IL-1 entra en circulación y ejerce efectos endocrinos.

IL-1: regulación y liberación celular.



IL-1 – Desordenes neurológicos



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Table 2 | Neurological diseases to which interleukin-1 might contribute

Disease	Clinical evidence of a role for IL-1	Proposed role of IL-1
Alzheimer's disease	Increased expression of IL-1 is associated with plaques and tangles in brain parenchyma; polymorphisms in genes encoding IL-1 influence susceptibility	Excessive production and processing of β -amyloid precursor protein and phosphorylation of tau protein, the main components of plaques and tangles
Traumatic brain injury	Increased intracerebral expression of IL-1 early after injury, and increased concentration of IL-1 in cerebrospinal fluid	Increases neuronal excitability, induces neurotoxin production, increases leukocyte infiltration, activates microglial cells and promotes astrogliosis
Epilepsy	Increased expression of IL-1 in brain parenchyma; polymorphisms in genes encoding IL-1 might influence susceptibility	Increases neuronal excitability through modification of the balance between excitatory and inhibitory synaptic transmission
Parkinson's disease	Increased concentration of IL-1 in cerebrospinal fluid; polymorphisms in genes encoding IL-1 might influence susceptibility	Contributes to the degeneration of neurons in the substantia nigra
Stroke	Increased concentration of IL-1 in cerebrospinal fluid; polymorphisms in genes encoding IL-1 might influence susceptibility	Increases neuronal excitability, induces neurotoxin production, increases leukocyte infiltration, activates microglial cells and promotes astrogliosis

IL-1, interleukin-1.



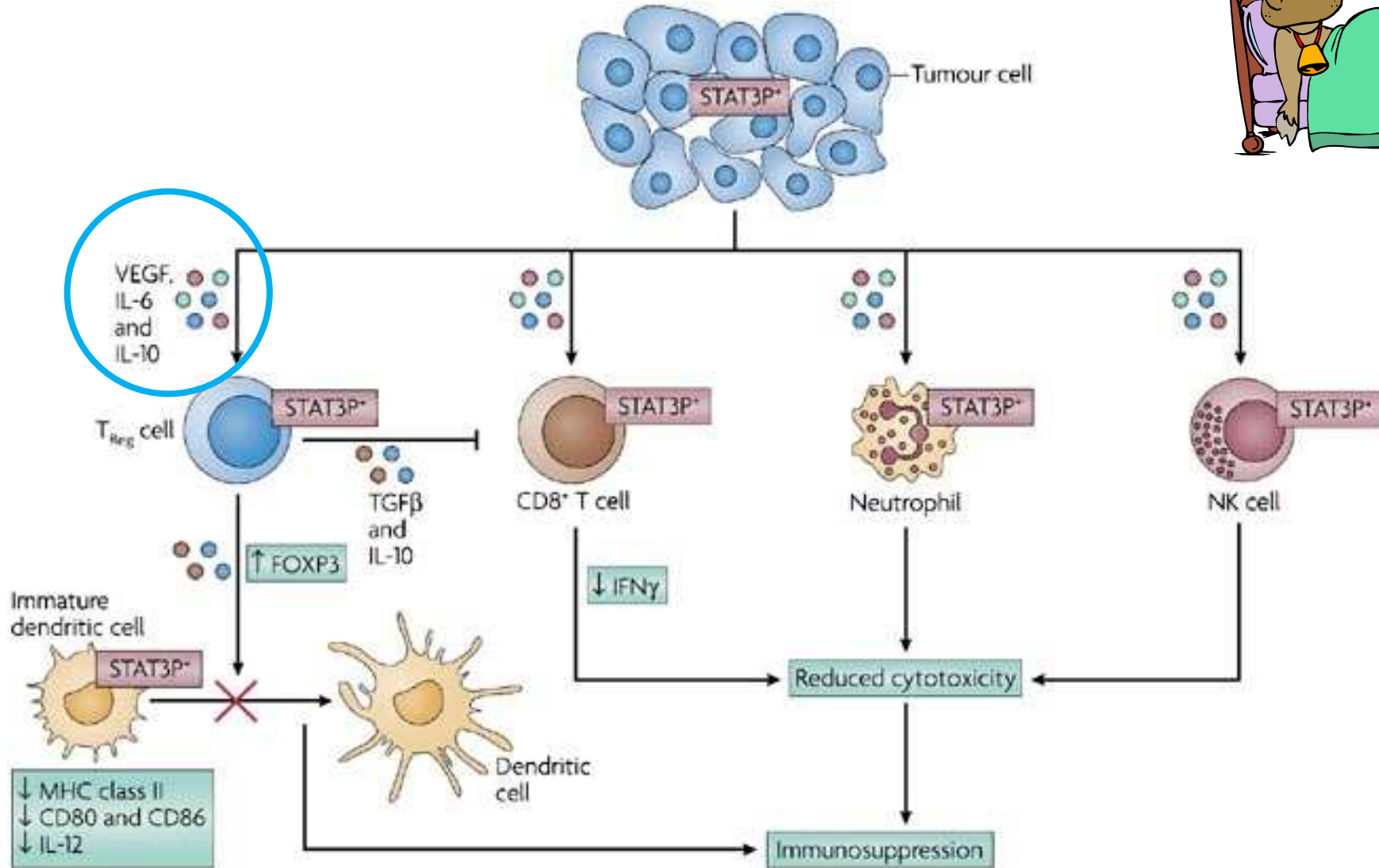
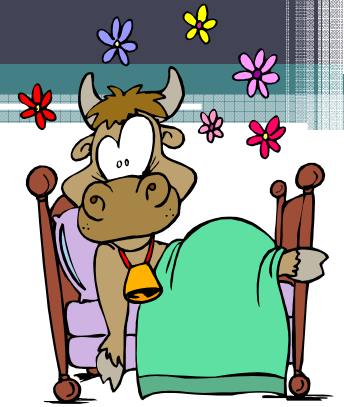
IL-10

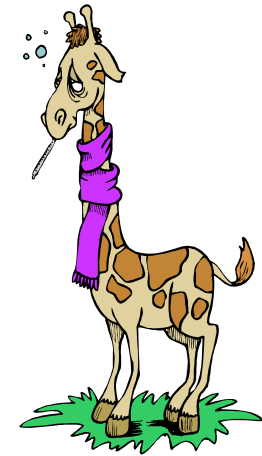
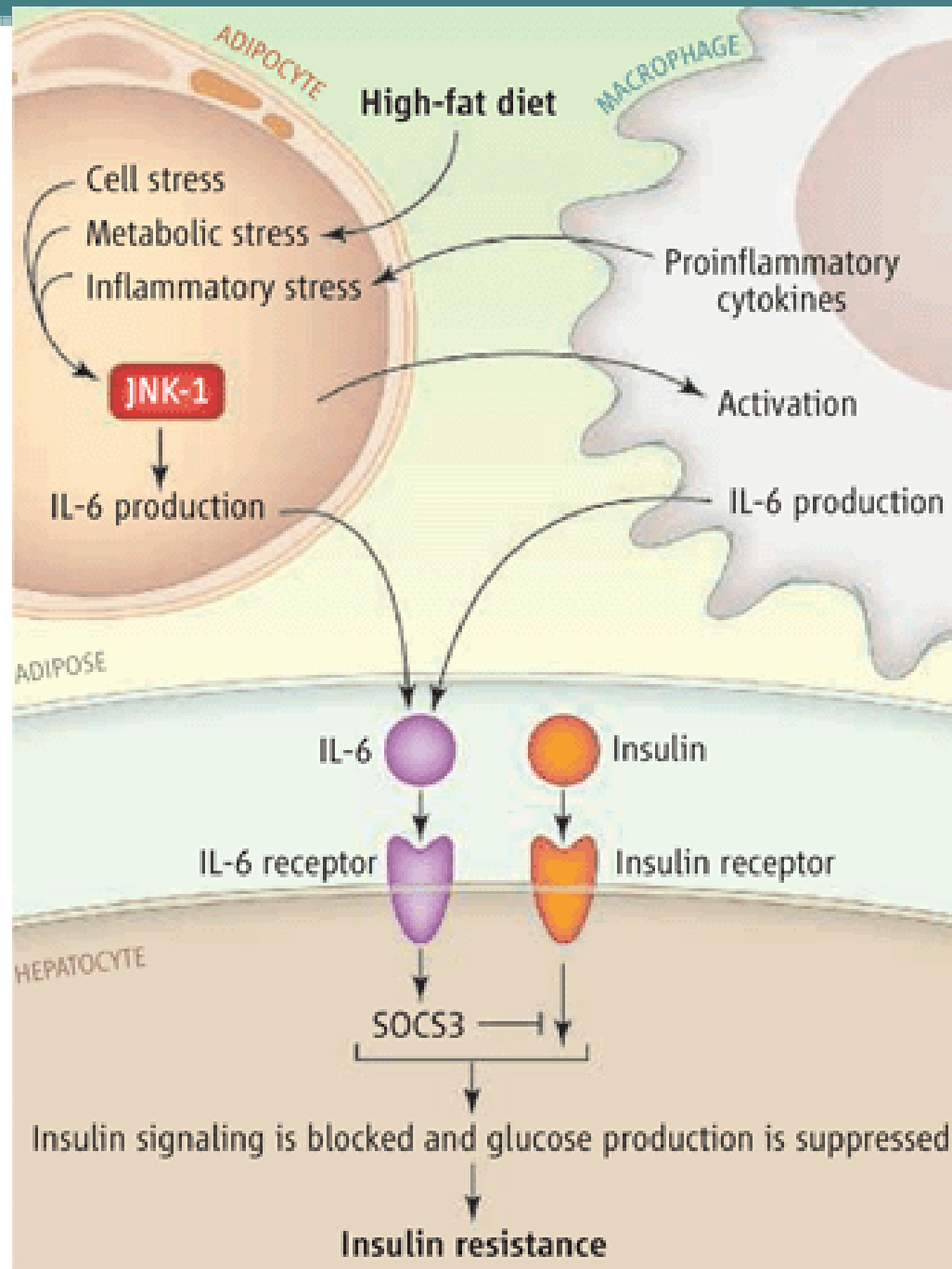
- Es un inhibidor de los macrófagos activados y ,por tanto ,interviene en el control homeostático de las reacciones de la inmunidad innata y de la celular.
- La IL-10 inhibe la producción de las citoquinas IL-12 y TNF de los macrófagos activados.
- Inhibe la expresión de coestimuladoras y moléculas MHC II en los macrófagos.

IL-6

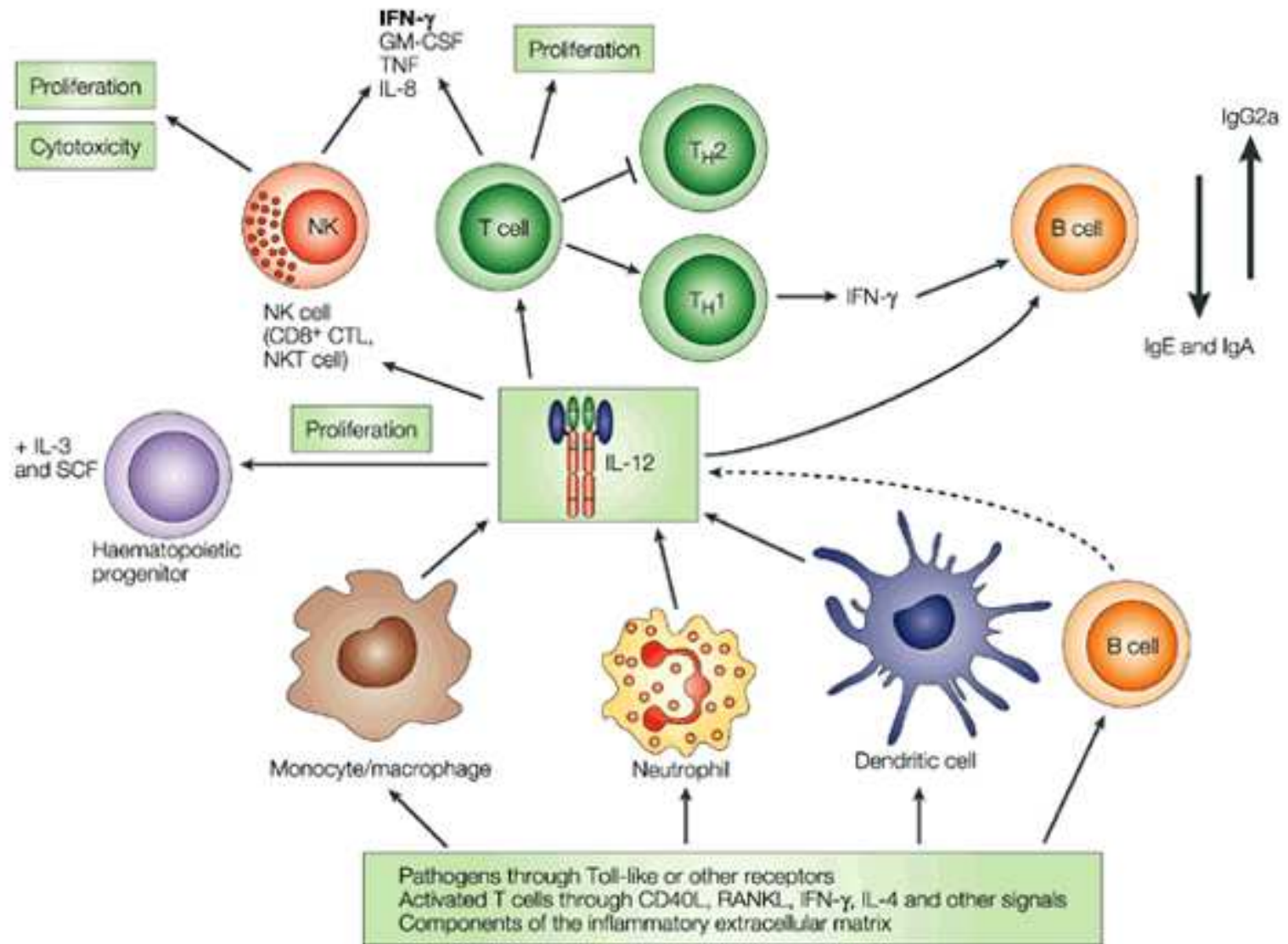
- Actua en la inmunidad innata y la adaptativa.
- Es sintetizada principalmente por macrófagos y células endoteliales.
- En la inmunidad innata estimula la síntesis de proteínas de fase aguda en hepatocitos.
- En la inmunidad adaptativa estimula el crecimiento de los linfocitos B que se han diferenciado .
- Actua como factor de crecimiento para las células plasmáticas neoplásicas, y muchas células de mieloma que crecen de forma autónoma secretan IL-6 como factor de crecimiento autocrino.

IL-10, IL-6 y tumores

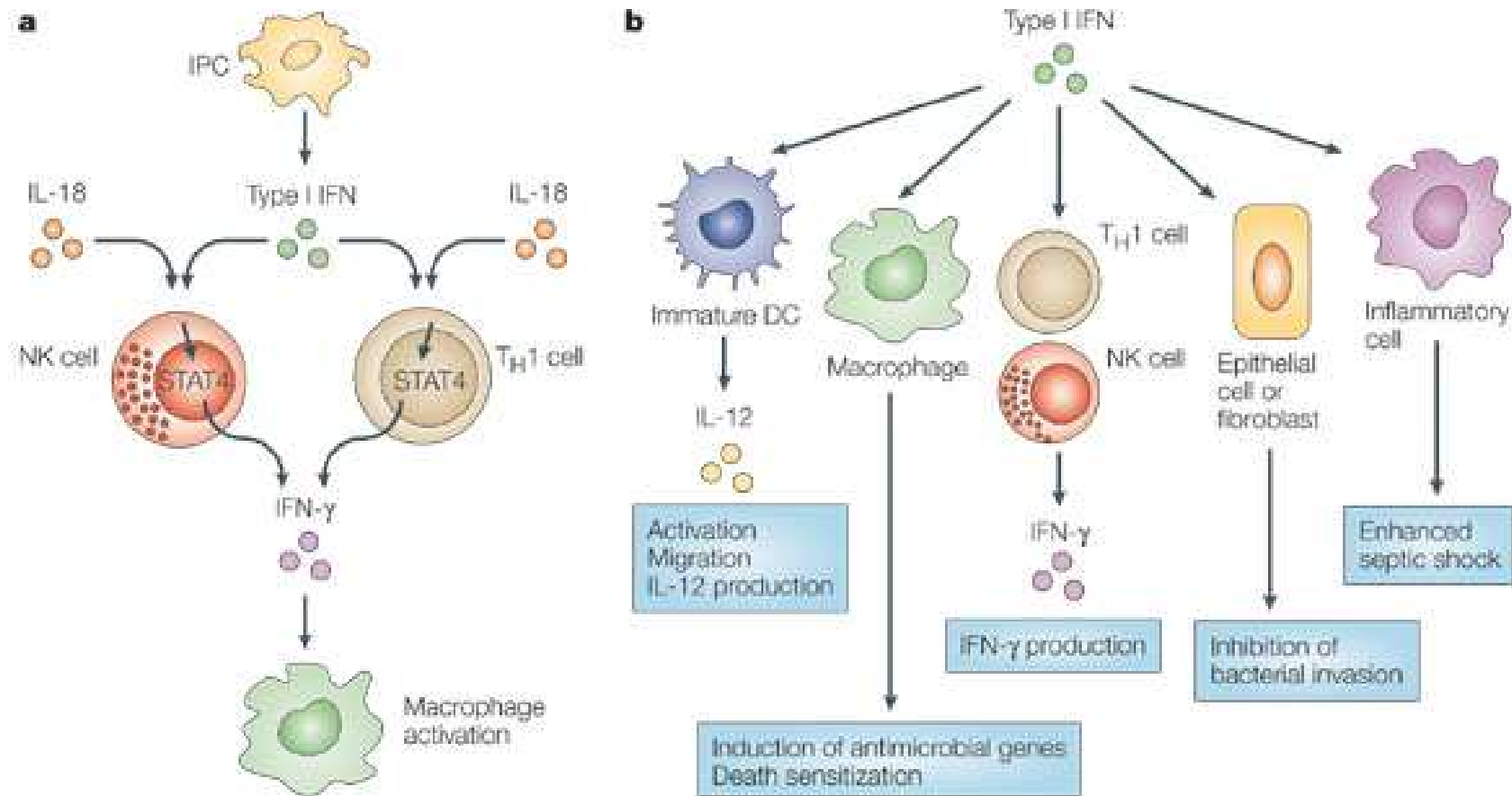




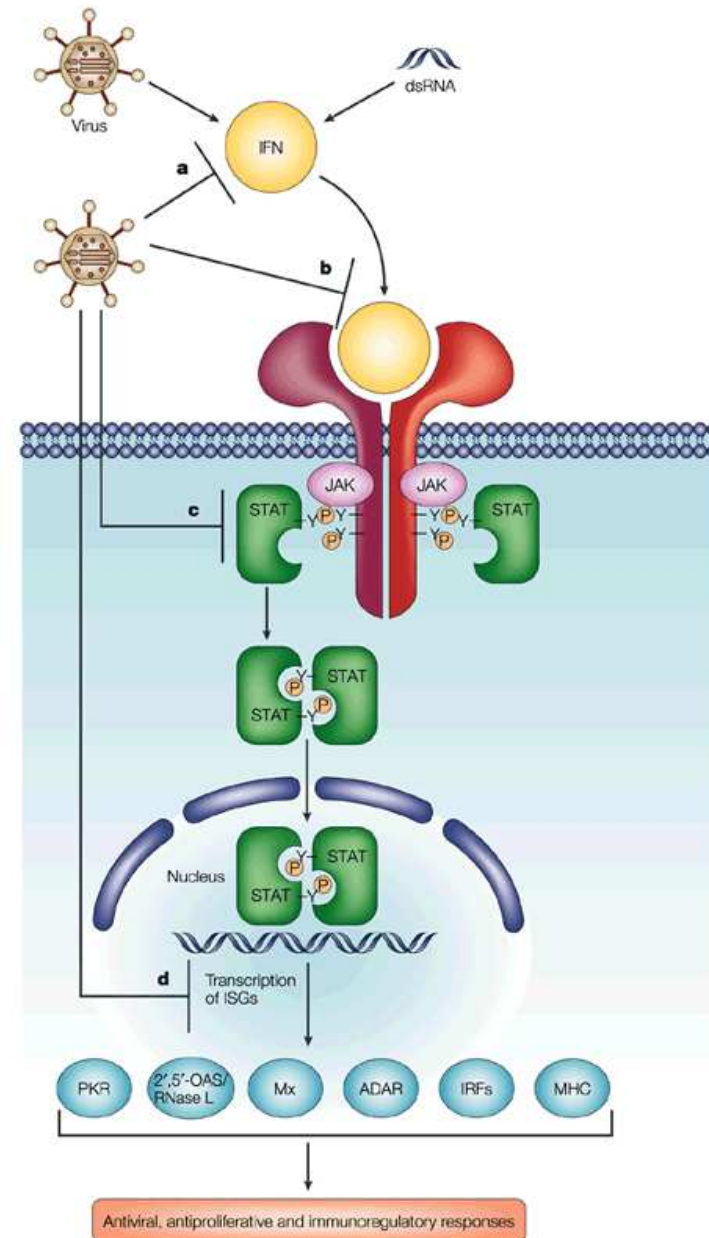
IL-12



INF Tipo I (IFN- α , IFN- β)



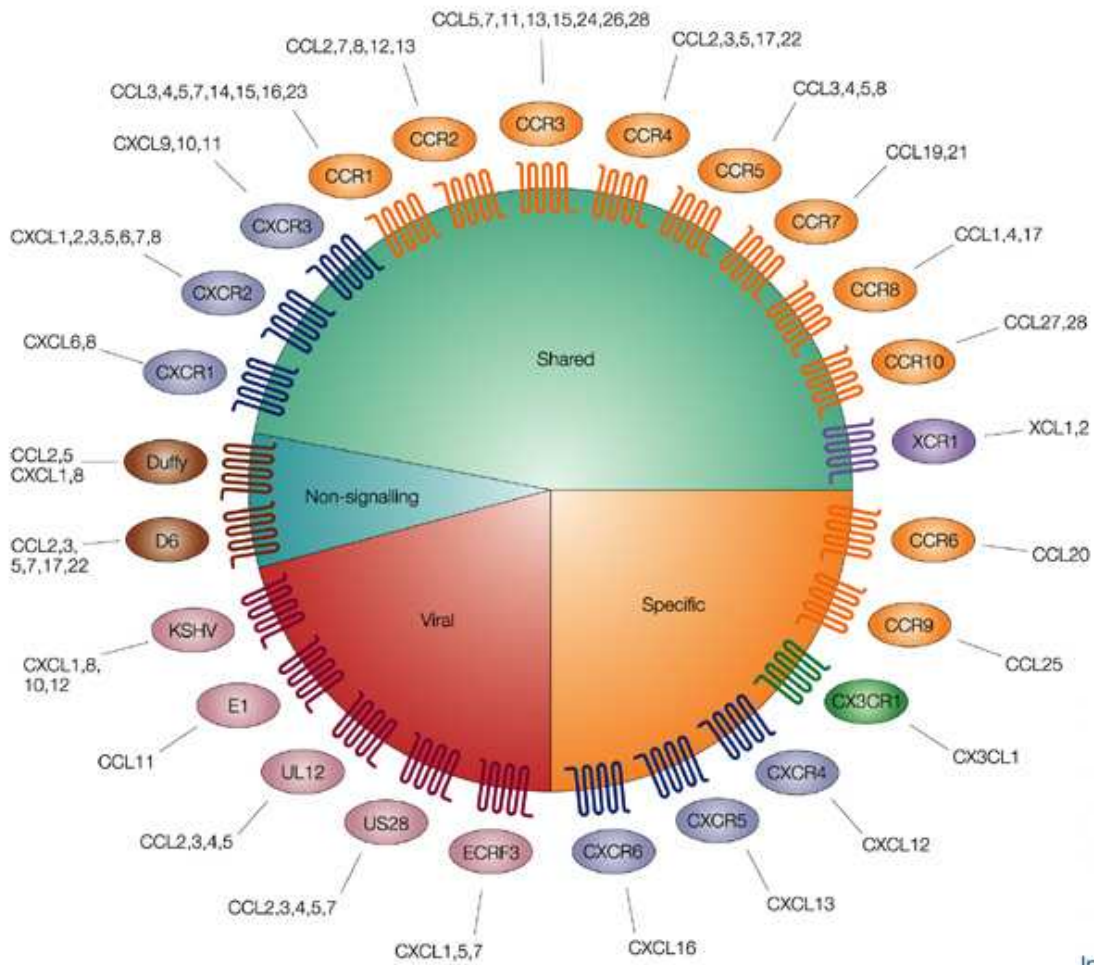
Overview of the IFN pathway and viral-counteracting strategies



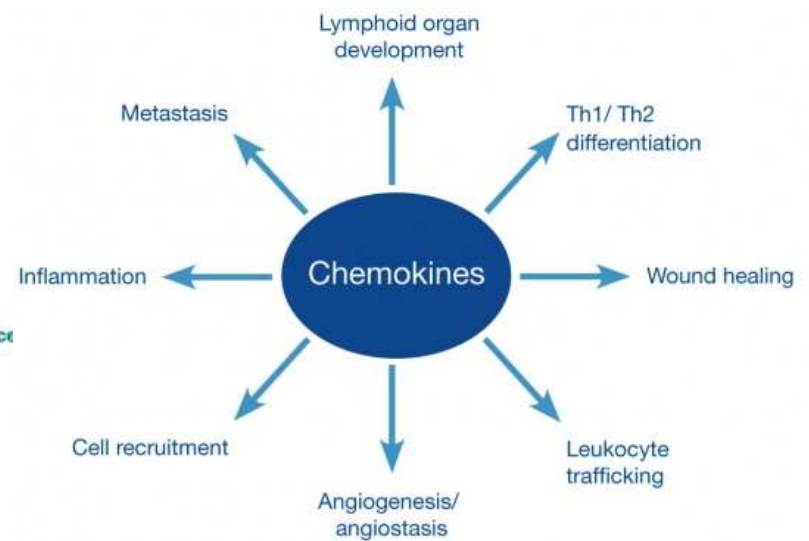
Quimiocinas



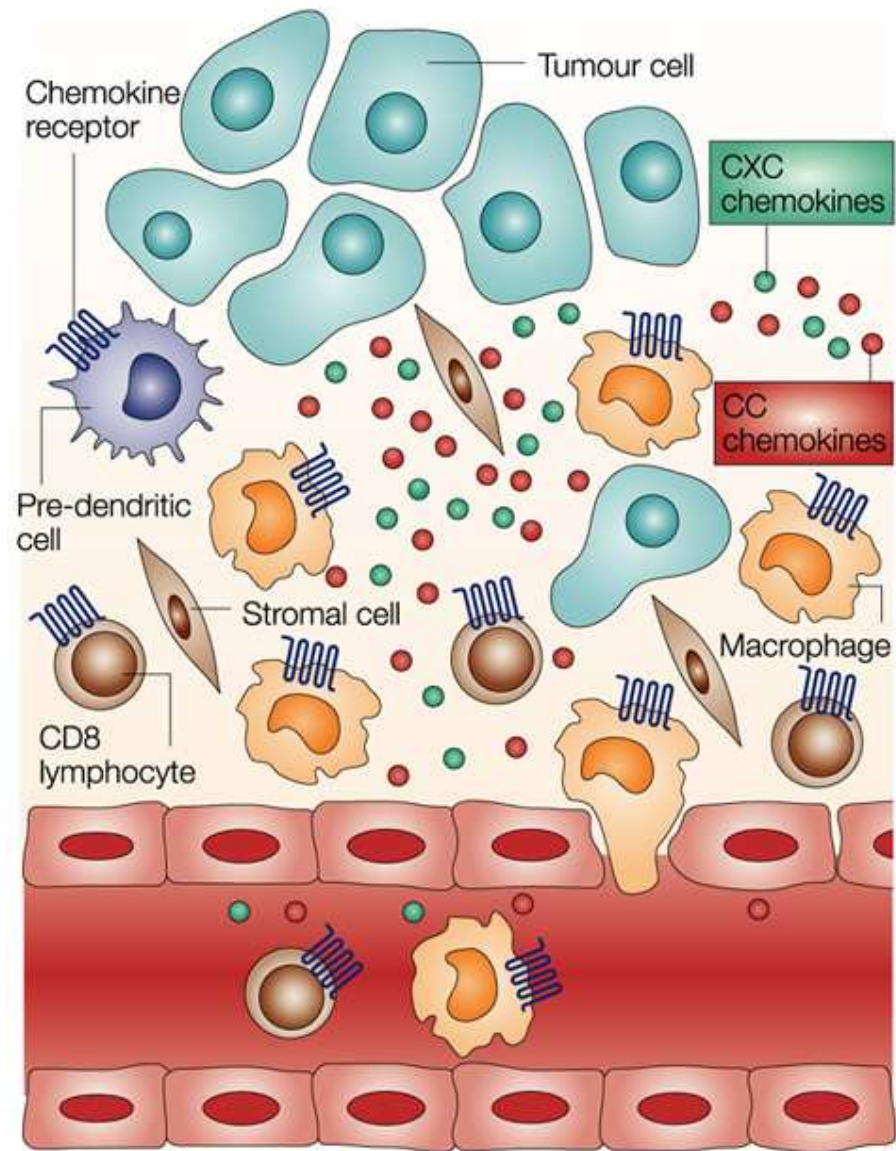
Chemokine	Original name	Chemokine receptor	Major function
CC chemokines			
CCL1	I-309	CCR8	Monocyte recruitment and endothelial cell migration
CCL2	MCP-1	CCR2	Mixed leukocyte recruitment
CCL3	MIP-1 α	CCR1, CCR5	Mixed leukocyte recruitment
CCL4	MIP-1 β	CCR5	T cell, dendritic cell, monocyte, and NK cell recruitment; HIV coreceptor
CCL5	RANTES	CCR1, CCR3, CCR5	Mixed leukocyte recruitment
CCL7	MCP-3	CCR1, CCR2, CCR3	Mixed leukocyte recruitment
CCL8	MCP-2	CCR3, CCR5,	Mixed leukocyte recruitment
CCL9/CCL10		CCR1	
CCL11	Eotaxin	CCR3	Eosinophil, basophil, and T _H ² recruitment
CCL12	Unknown	CCR2	Mixed leukocyte recruitment
CCL13	MCP-4	CCR2, CCR3	Mixed leukocyte recruitment
CCL14	HHC-1	CCR1, CCR5	
CCL15	MIP-1 δ	CCR1, CCR3	Mixed leukocyte recruitment
CCL16	HHC-4	CCR1, CCR2	
CCL17	TARC	CCR4	T cell and basophil recruitment
CCL18	DC-CK1	?	
CCL19	MIP-3 β /ELC	CCR7	T cell and dendritic cell migration into parafollicular zones of lymph nodes
CCL20	MIP-3 α	CCR6	
CCL21	SLC	CCR7	T cell and dendritic cell migration into parafollicular zones of lymph nodes
CCL22	MDC	CCR4	T cell and basophil recruitment
CCL23	MPIF-1	CCR1	
CCL24	Eotaxin-2	CCR3	Eosinophil, basophil, and T _H ² recruitment
CCL25	TECK	CCR9	Astrocyte migration
CCL26	Eotaxin-3	CCR3	Eosinophil, basophil, and T _H ² recruitment
CCL27	CTACK	CCR10	Dermal cell migration
CCL28	MEC	CCR10	Dermal cell migration
CXC chemokines			
CXCL1	GRO α	CXCR2	Neutrophil recruitment
CXCL2	GRO β	CXCR2	Neutrophil recruitment
CXCL3	GRO γ	CXCR2	Neutrophil recruitment
CXCL4	PF4	CXCR3B	Platelet aggregation
CXCL5	ENA-78	CXCR2	Neutrophil recruitment
CXCL6	GCP-2	CXCR1, CXCR2	Neutrophil recruitment
CXCL7	NAP-2	CXCR2	Neutrophil recruitment
CXCL8	IL-8	CXCR1, CXCR2	Neutrophil recruitment
CXCL9	Mig	CXCR3	Effector T cell recruitment
CXCL10	IP-10	CXCR3, CXCR3B	Effector T cell recruitment
CXCL11	I-TAC	CXCR3	Effector T cell recruitment
CXCL12	SDF-1 α/β	CXCR4	Mixed leukocyte recruitment; HIV coreceptor
CXCL13	BCA-1	CXCR5	B cell migration into follicles
CXCL14	BRAK		
CXCL16	-	CXCR6	
C chemokines			
XCL1	Lymphotactin	XCR1	T cell and NK cell recruitment
XCL2	SCM-1 β	XCR1	
CX₃C chemokines			
CX ₃ CL1	Fractalkine	CX ₃ CR1	T cell, NK cell, and macrophage recruitment; CTL and NK cell activation



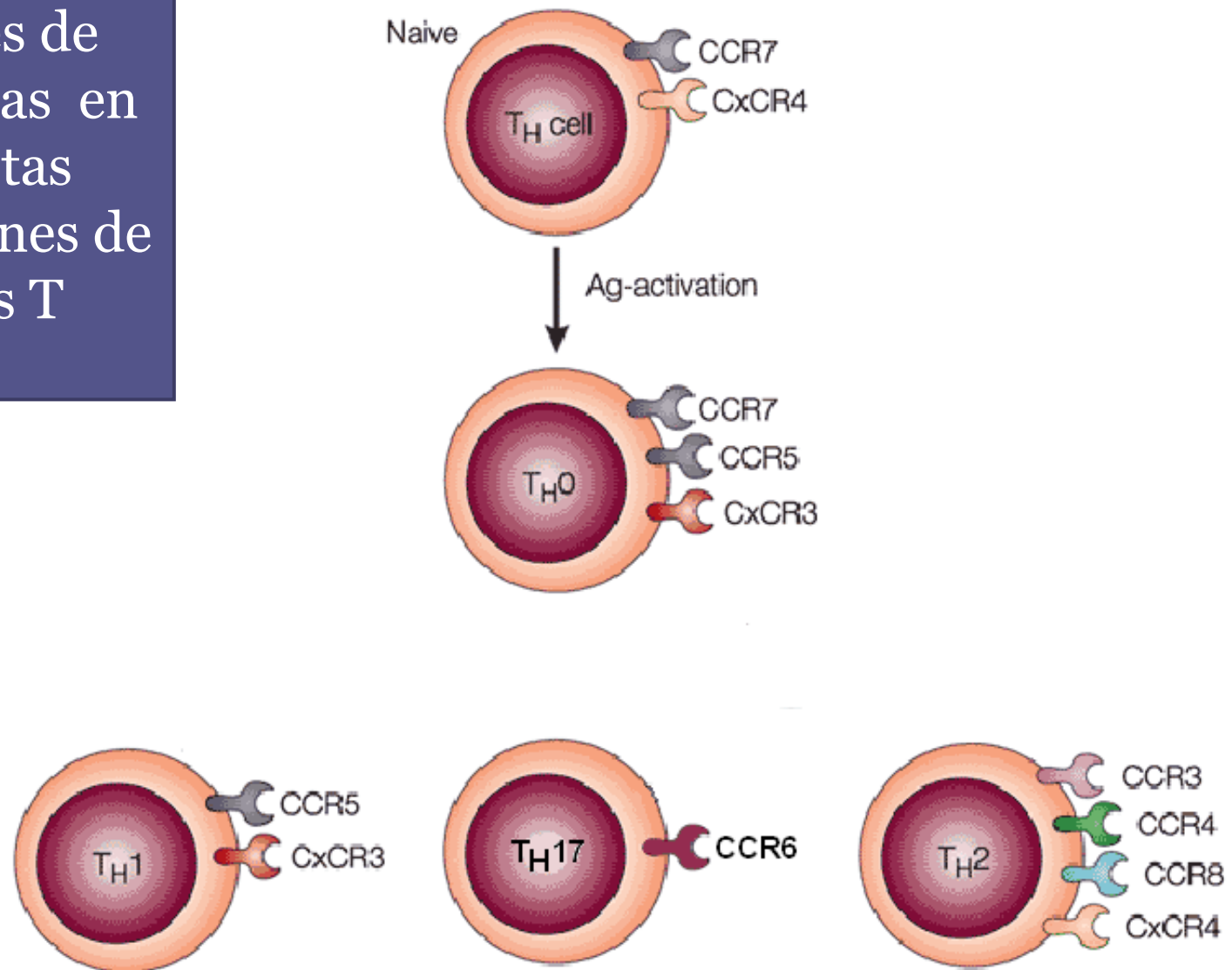
Nature Reviews | Cancer



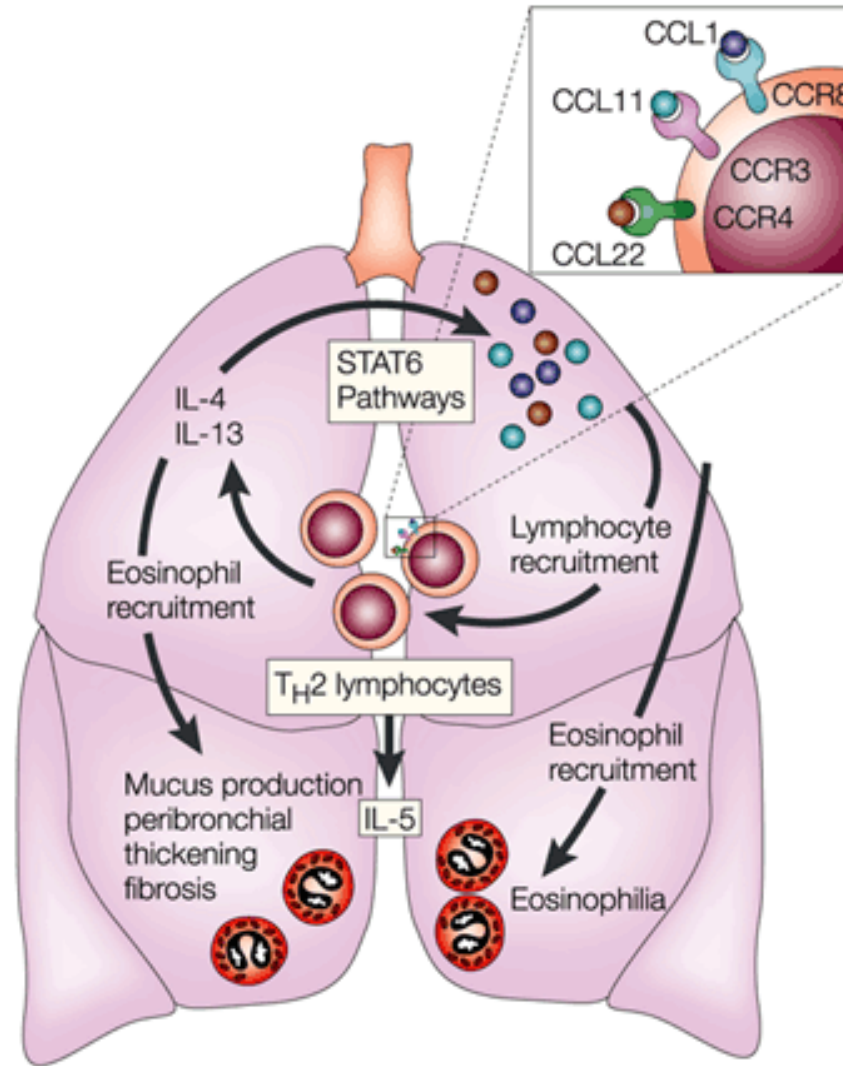
The chemokine network of human epithelial ovarian cancer.



Receptores de quimioquinas en las distintas subpoblaciones de linfocitos T



Asma



Mediadores en la inmunidad adaptativa

SOME CYTOKINES OF ADAPTIVE IMMUNITY		
Interleukin 2 (IL-2)	T cells	T-cell proliferation; can promote AICD. NK cell activation and proliferation; B-cell proliferation
Interleukin 4 (IL-4)	T _H 2 cells, mast cells	Promotes T _H 2 differentiation; isotype switch to IgE
Interleukin 5 (IL-5)	T _H 2 cells	Eosinophil activation and generation
Transforming growth factor β (TGF- β)	T cells, macrophages, other cell types	Inhibits T-cell proliferation and effector functions; inhibits B-cell proliferation; promotes isotype switch to IgA; inhibits macrophages
Interferon γ (IFN- γ)	T _H 1 cells, CD8 ⁺ cells, NK cells	Activates macrophages; increases expression MHC class I and class II molecules; increases antigen presentation
<p>*Many cytokines play roles in more than one functional category.</p> <p>†Only the major cell types providing cytokines for the indicated activity are listed; other cell types may also have the capacity to synthesize the given cytokine.</p> <p>‡Also note that activated cells generally secrete greater amounts of cytokine than unactivated cells.</p>		

Table 12-1
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Mediators of adaptive Immunity

TABLE 12-4	Cytokine secretion and principal functions of mouse T _H 1 and T _H 2 subsets	
	T _H 1	T _H 2
CYTOKINE SECRETION		
IL-2	+	-
IFN- γ	++	-
TNF- β	++	-
GM-CSF	++	+
IL-3	++	++
IL-4	-	++
IL-5	-	++
IL-10	-	++
IL-13	-	++
FUNCTIONS		
Help for total antibody production	+	++
Help for IgE production	-	++
Help for IgG2a production	++	+
Eosinophil and mast-cell production	-	++
Macrophage activation	++	-
Delayed-type hypersensitivity	++	-
T _C -cell activation	++	-
SOURCE: Adapted from F. Powrie and R. L. Coffman, 1993, <i>Immunology Today</i> 14:270.		

Table 12-4
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IL-4

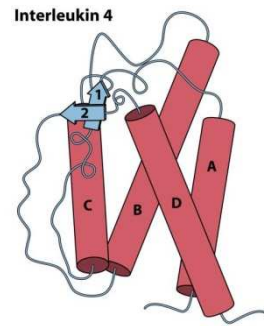
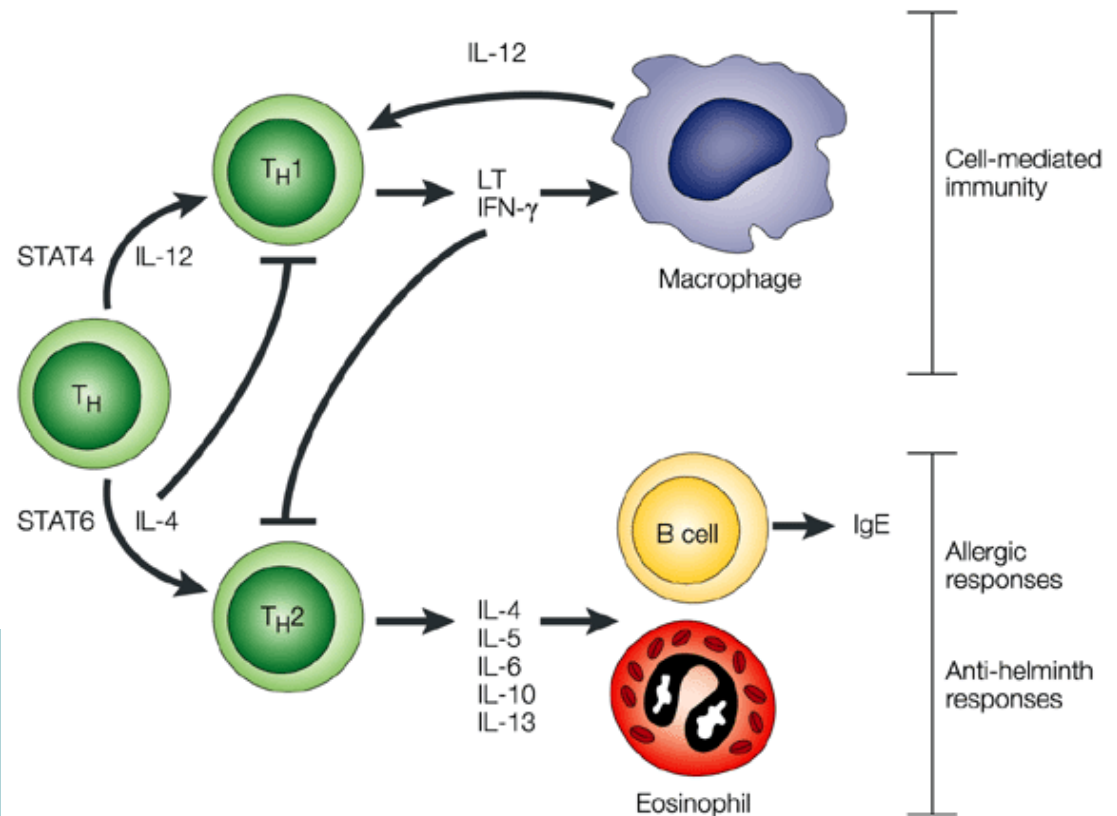
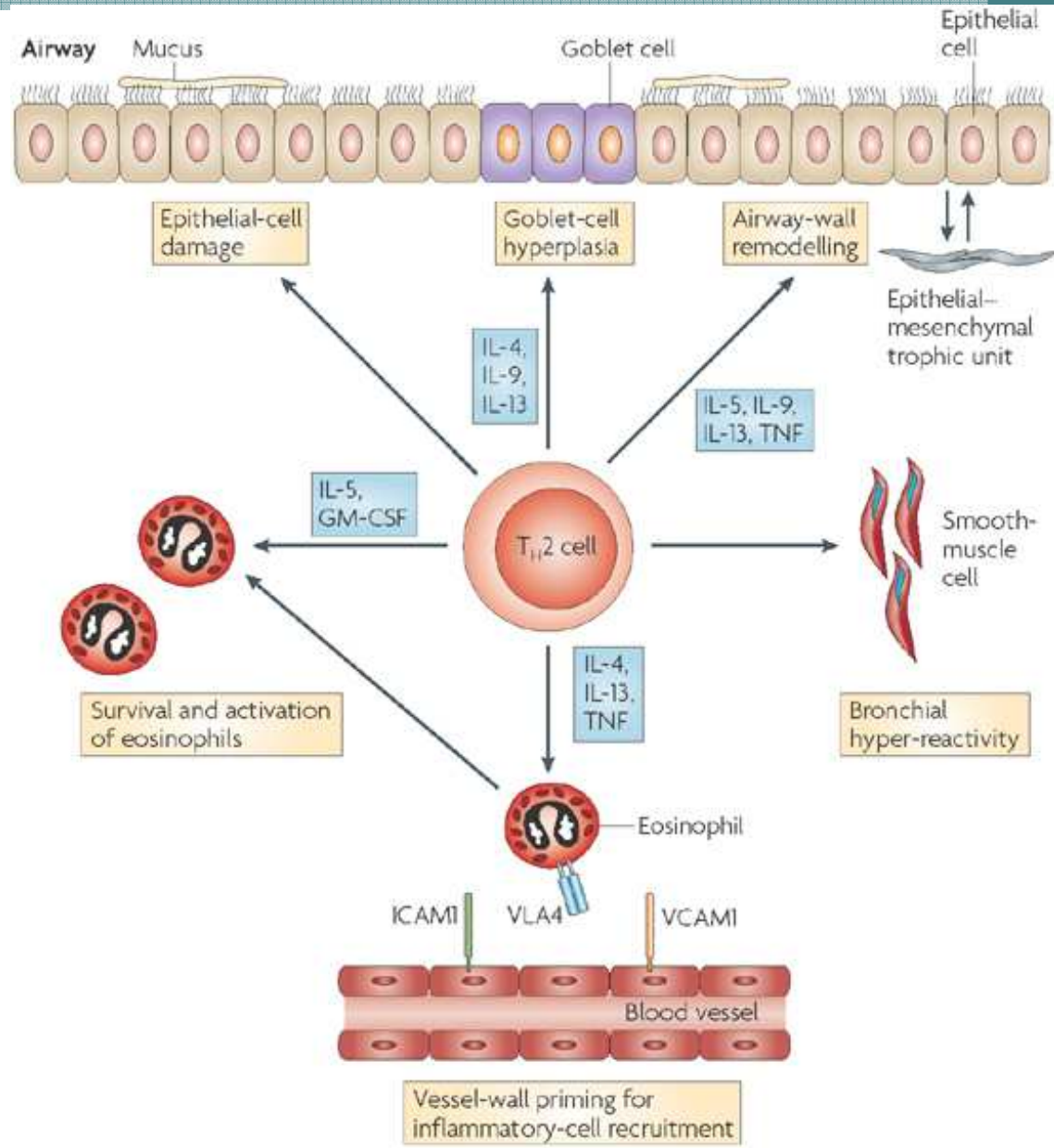


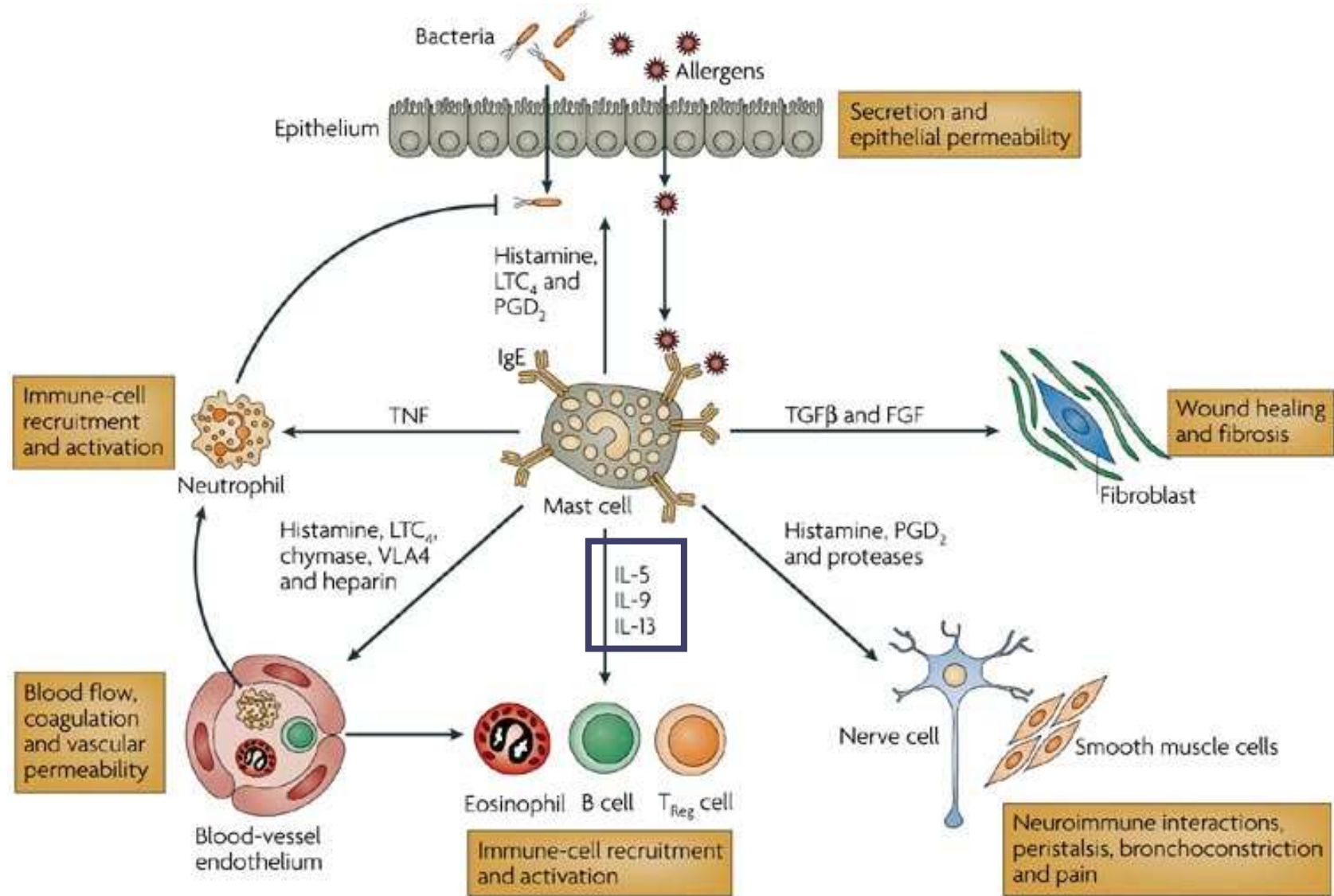
Figure 12-4b
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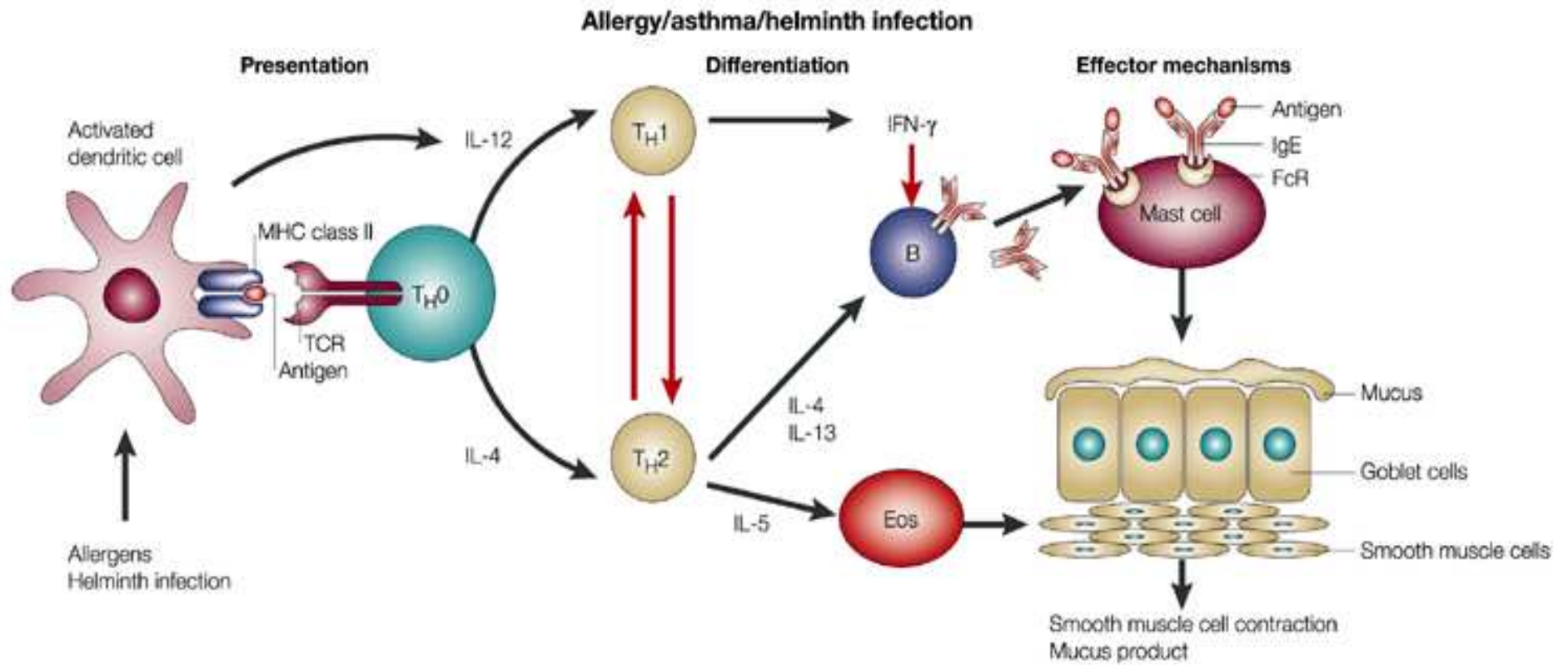
Produced by macrophages and Th2 cells
Stimulates development of TH2 cells from naïve Th cells
Promotes growth of differentiated Th2 cells
Stimulates Ig class switching to IgE isotype

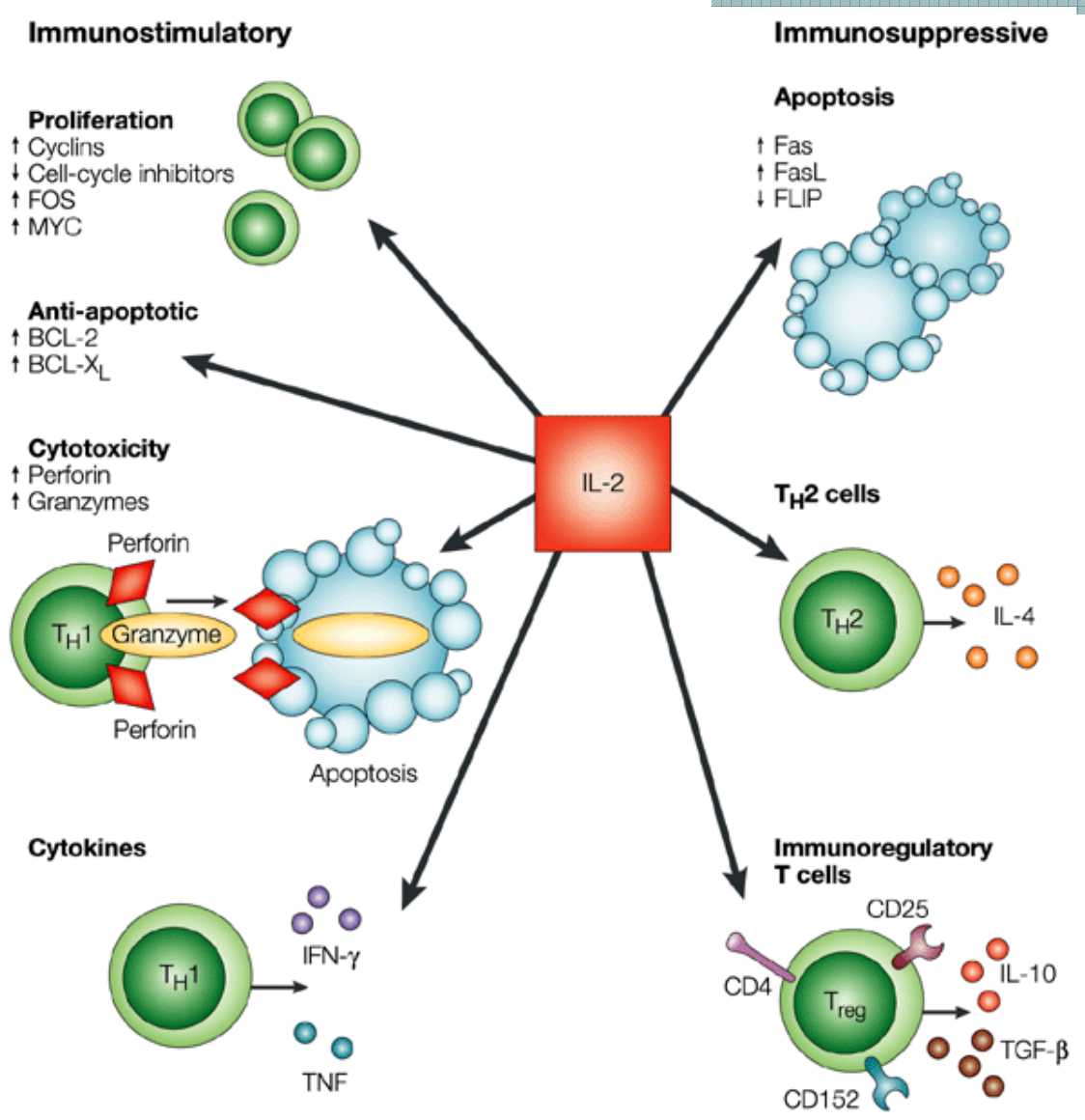




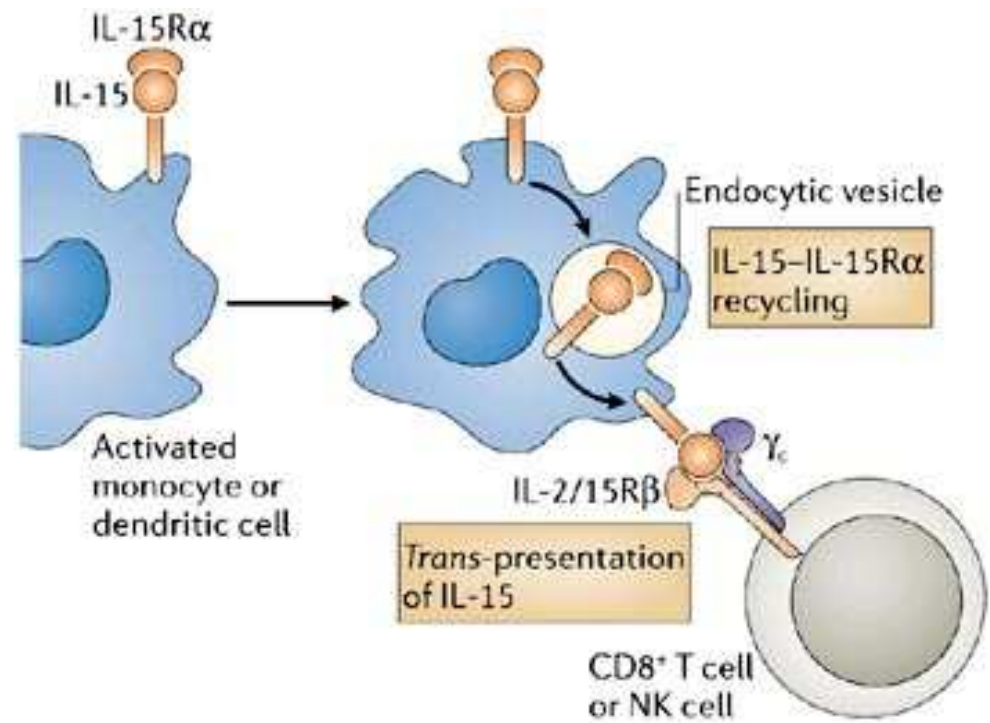
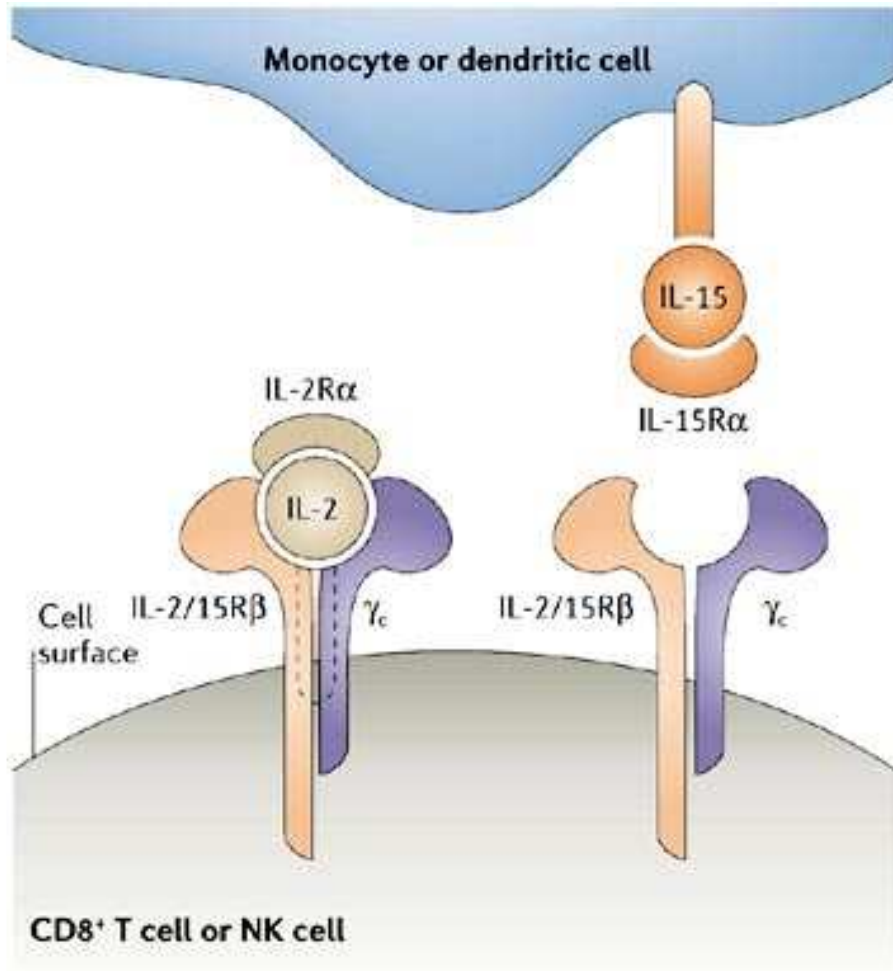
IL-5







IL-15



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Properties	IL-2	IL-15
Structure	15.5 kDa; 133 amino acids; four-helix bundle	14–15 kDa; 114 amino acids; four-helix bundle
Gene structure and location	Four exons; chromosome 4q26	Eight exons; chromosome 4q31
Main site of synthesis	Activated T cells	Dendritic cells and monocytes
Mechanism of regulation of expression	Transcriptional regulation, and stabilization of mRNA	Transcriptional regulation, but mainly post-transcriptional regulation during translation and intracellular trafficking
Receptor	IL-2R α , IL-2/15R β and γ_c are co-expressed by activated T and B cells	IL-15R α on the surface of monocytes and dendritic cells trans-presents IL-15 to NK cells and CD8 ⁺ memory T cells expressing IL-2/15R β and γ_c
Function	Proliferation and differentiation of NK cells, and T and B cells; elimination of self-reactive T cells, mediated by AICD and maintenance of T _{reg} cells	Proliferation and differentiation of NK cells, and T and B cells; maintenance of CD8 ⁺ CD44 ^{hi} memory T cells
Features of mice with knockout of gene encoding cytokine or cytokine-receptor α -chain	Marked enlargement of peripheral lymphoid organs and polyclonal expansion of T- and B-cell populations; associated with autoimmune diseases	Marked reduction in number of NK and NKT cells, and CD8 ⁺ CD44 ^{hi} memory T cells

Data taken from REFS 3–5,9,10,26,68. AICD, activation-induced cell death; γ_c , common cytokine-receptor γ -chain; IL, interleukin; IL-2R α , IL-2 receptor α -chain; IL-2/15R β , the β -chain of the IL-2 receptor and IL-15 receptor; IL-15R α , IL-15 receptor α -chain; NK cell, natural killer cell; NKT cell, natural killer T cell; T_{reg} cell, CD4⁺CD25⁺ regulatory T cell.

Waldmann *Nature Reviews Immunology* **6**, 595–601 (August 2006)
| doi:10.1038/nri1901

Feature	T _H 1 cells	T _H 2 cells	T _H 17 cells	Inducible regulatory T cells
Unique cytokine products	IFN γ	IL-4, IL-5 and IL-13	IL-17, IL-17F, IL-21 and IL-22	TGF β ?
Priming cytokines	IL-12	IL-25 (IL-17E)	TGF β and IL-6	TGF β and IL-2?
Autocrine cytokines	IFN γ	IL-4	IL-21	TGF β ?
STAT regulators	STAT1 and STAT4	STAT6	STAT3	STAT5
Lineage-specific transcriptional regulators	T-bet and HLX	GATA3 and MAF	ROR γ t and ROR α	FOXP3
Cytokine receptors	IL-12R β 2	IL-17RB	IL-23R and IL-1R1	ND

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

Citoquinas estimuladoras de la hematopoyesis



Stimulators of hematopoiesis

Granulocyte-macrophage colony stimulating factor (GM-CSF) promotes differentiation of bone marrow progenitors

Macrophage colony stimulating factor (M-CSF) promotes growth and differentiation of monocytes and macrophages

Granulocyte colony stimulating factor (G-CSF) promotes production of PMNs

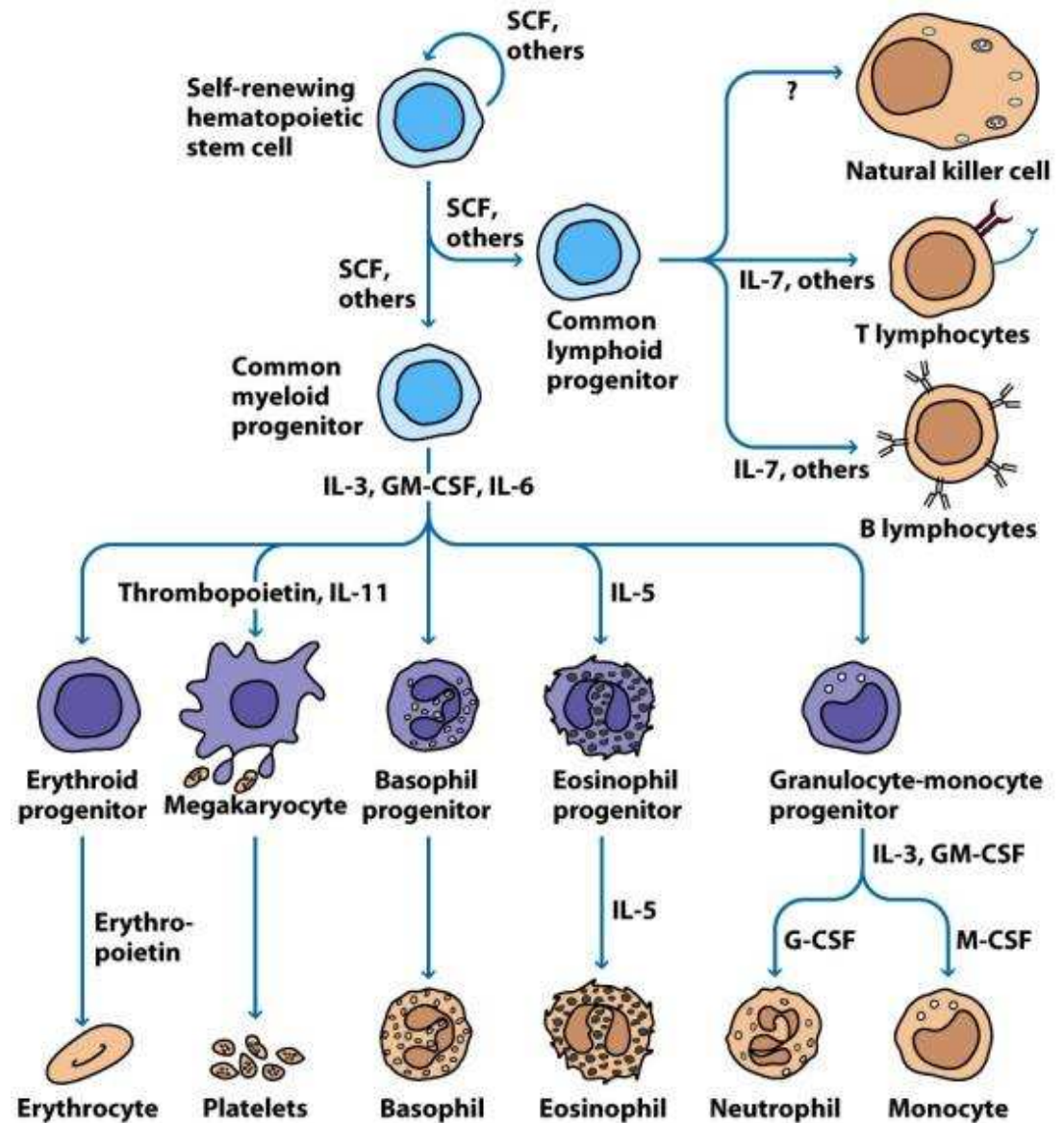
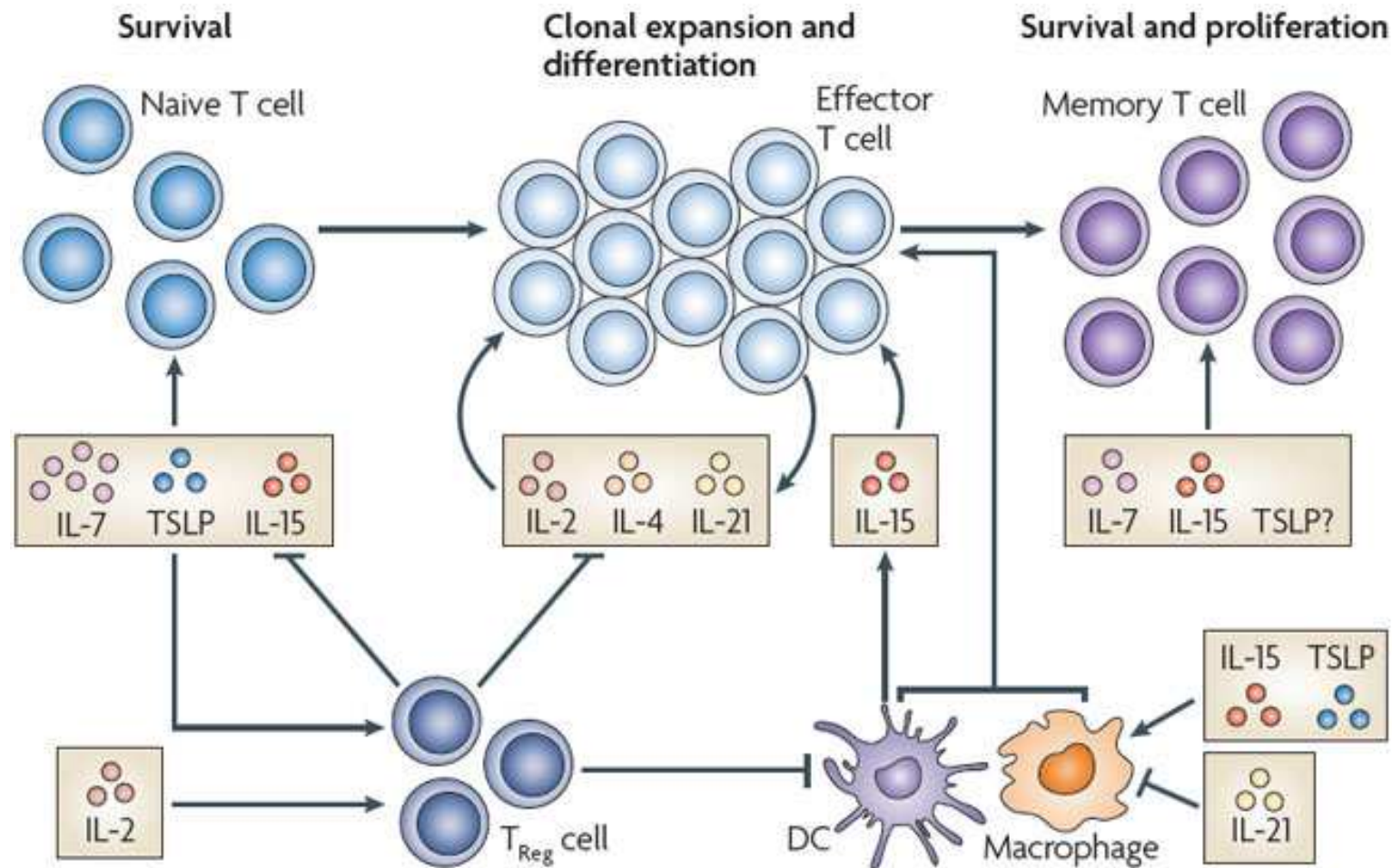
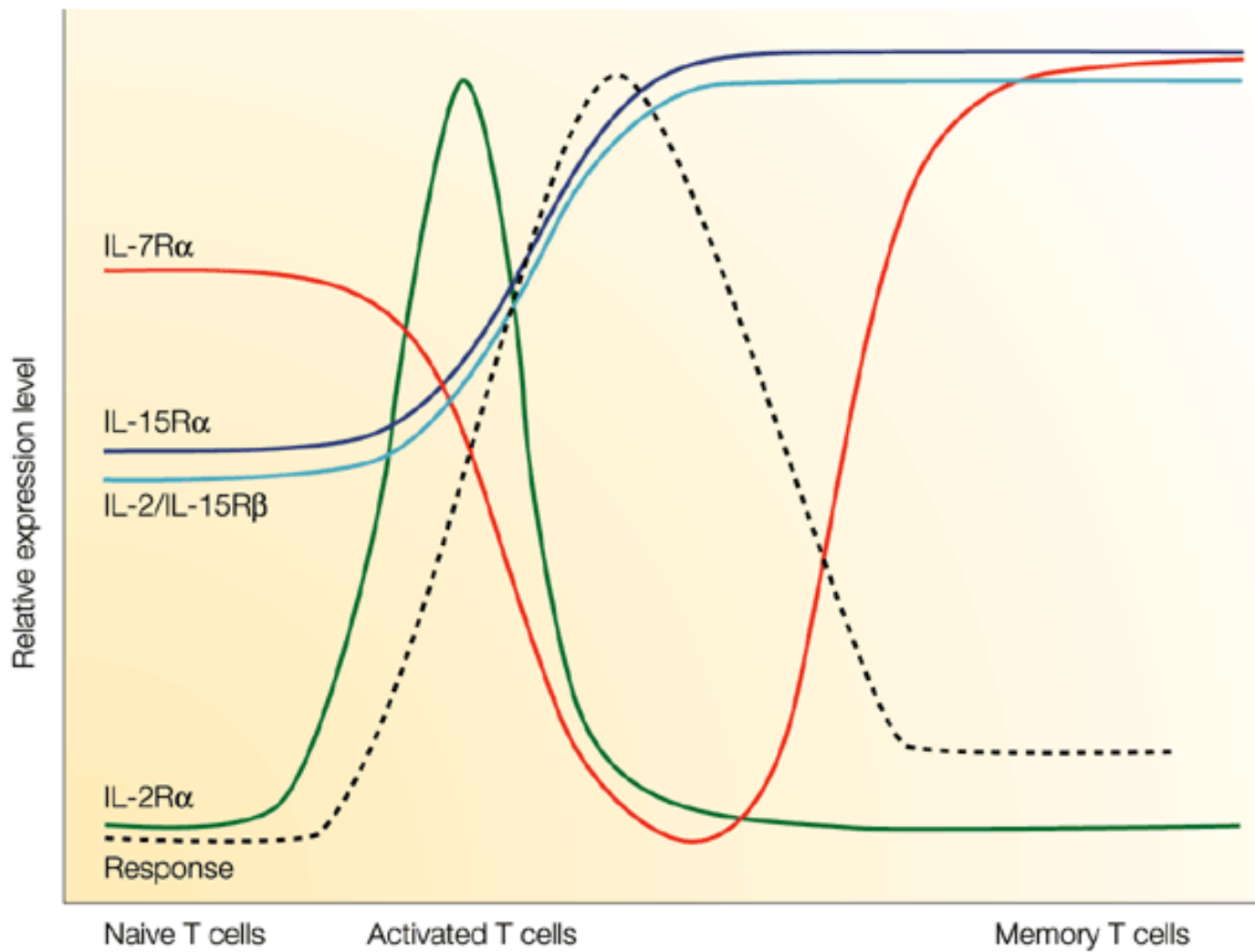


Figure 12-16
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Citoquinas que influyen en la supervivencia, activación, proliferación y diferenciación de células T.







IL-10

