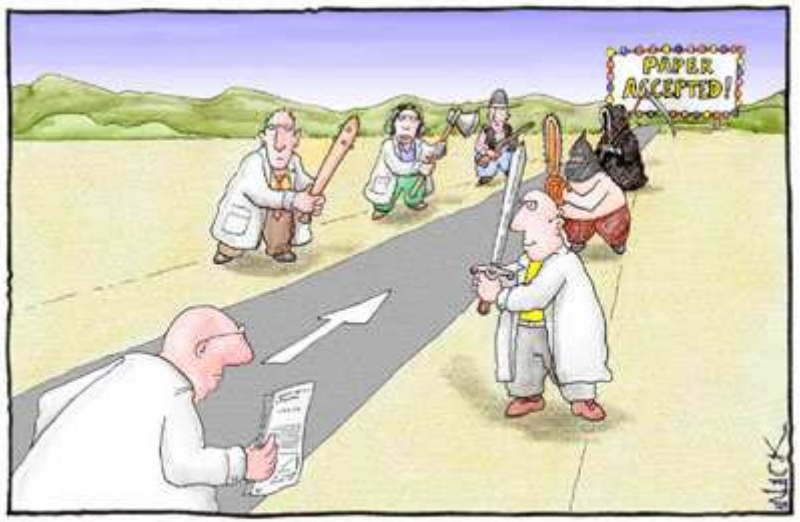
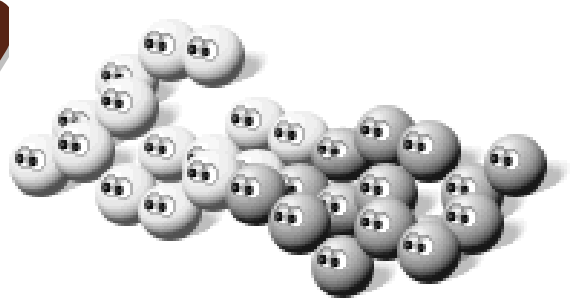


Most scientists regarded the new streamlined peer-review process as 'quite an improvement.'

INMUNOLOGÍA CLÍNICA 2009

Bioq Graciela R Svibel de Mizdraji



Para comunicarnos:

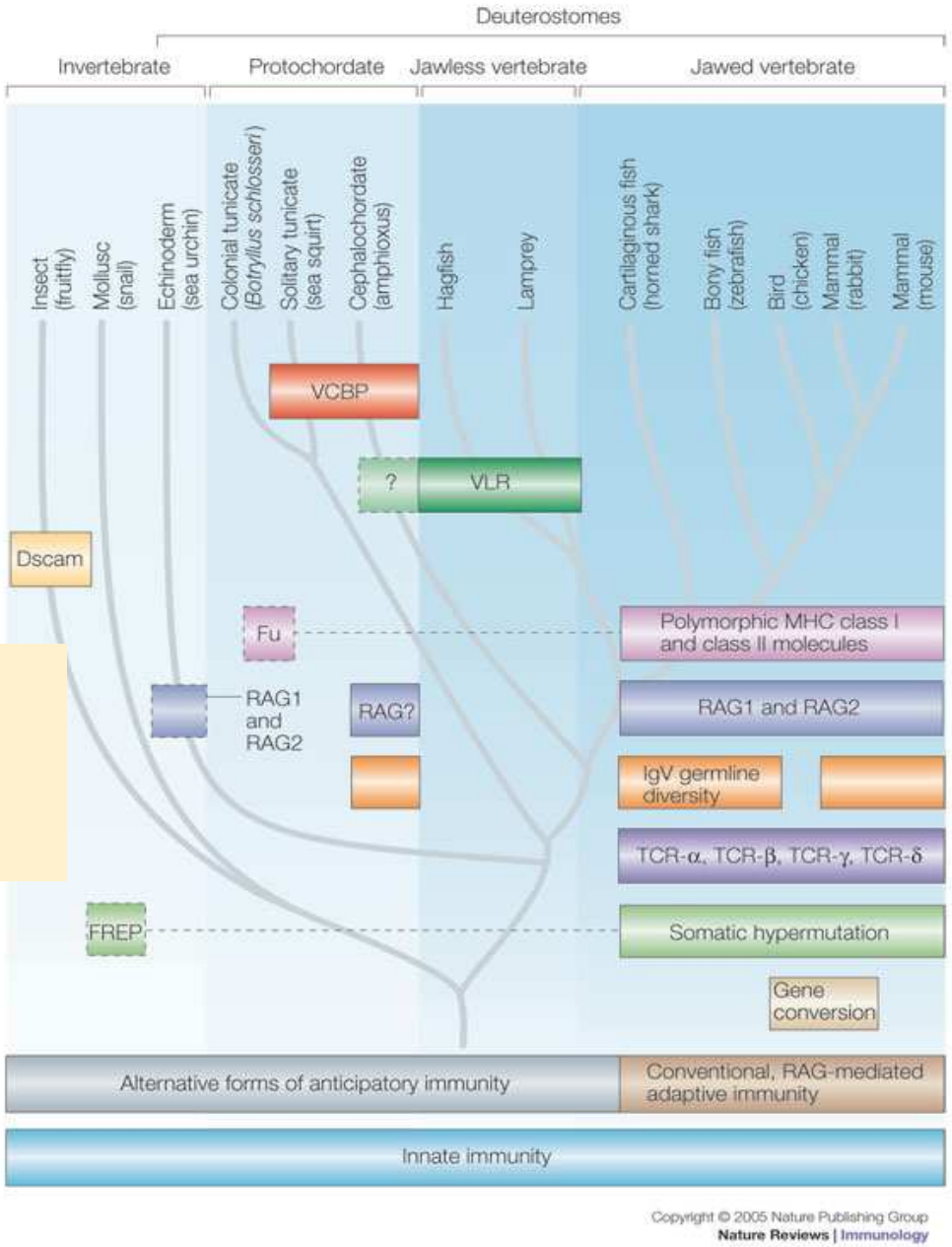
E-mail:

inmunologia.2009@hotmail.com

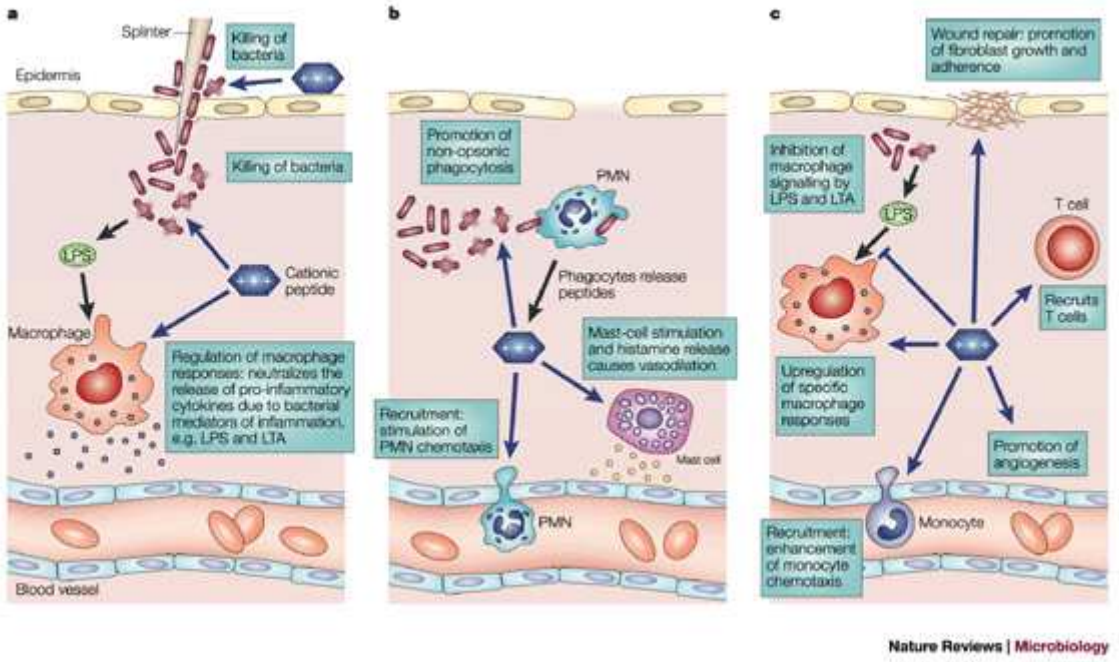
Contraseña: 135791

SISTEMA INMUNE INNATO

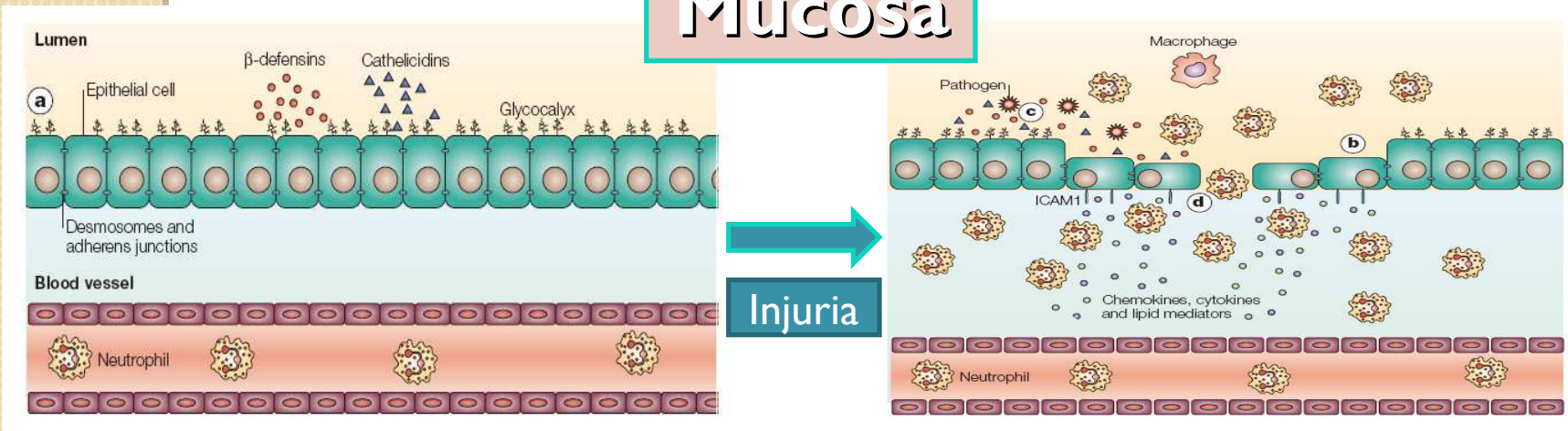
Filogenia del sistema inmune innato

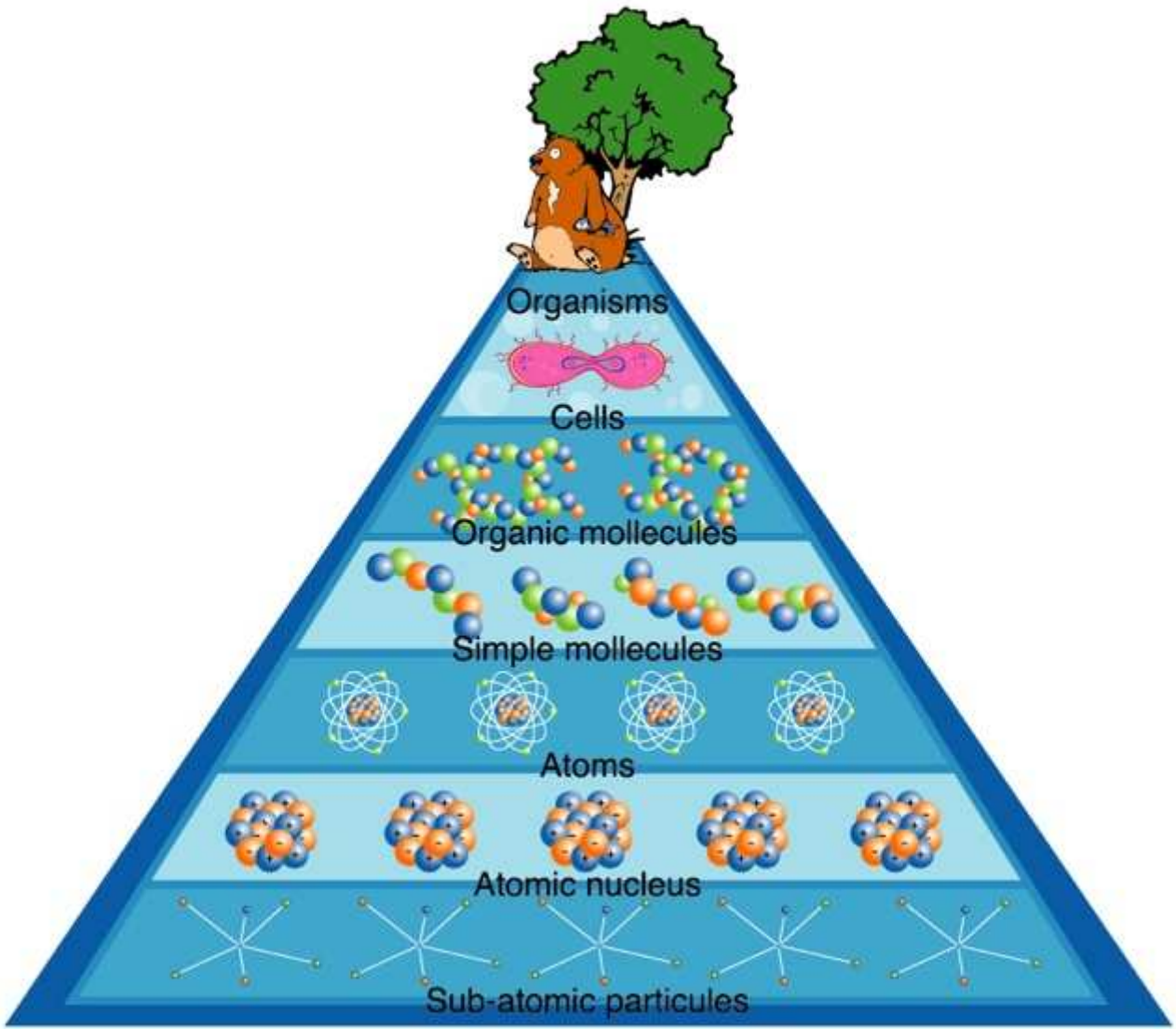


Piel


a
Splinter
Killing of bacteria
Epidermis
Killing of bacteria
LPS
Cationic peptide
Macrophage
Regulation of macrophage responses: neutralizes the release of pro-inflammatory cytokines due to bacterial mediators of inflammation, e.g. LPS and LTA
Blood vessel
b
Promotion of non-opsonic phagocytosis
PMN
Phagocytes release peptides
Mast-cell stimulation and histamine release causes vasodilation
Recruitment: stimulation of PMN chemotaxis
Mast cell
PMN
c
Wound repair: promotion of fibroblast growth and adherence
Inhibition of macrophage signalling by LPS and LTA
LPS
T cell
Recruits T cells
Upregulation of specific macrophage responses
Promotion of angiogenesis
Monocyte
Recruitment: enhancement of monocyte chemotaxis
Nature Reviews | Microbiology

Mucosa

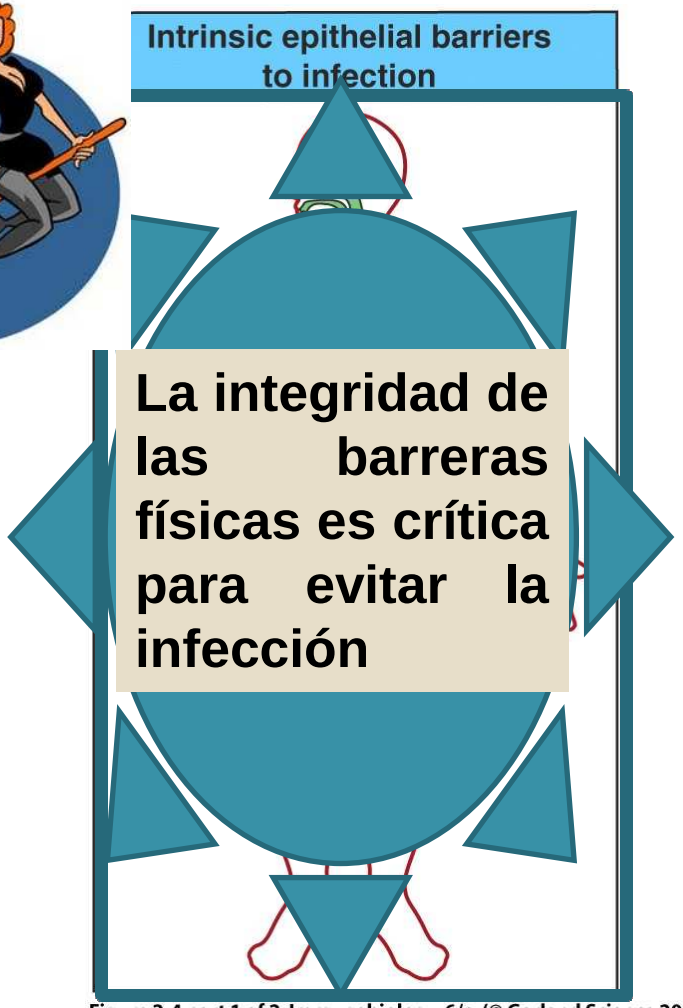

Lumen
β-defensins
Cathelicidins
a
Epithelial cell
Glycocalyx
Desmosomes and adherens junctions
Blood vessel
Neutrophil
Injuria
Macrophage
Pathogen
c
b
ICAM1
d
Chemokines, cytokines and lipid mediators
Neutrophil


Organisms
Cells
Organic mollecules
Simple mollecules
Atoms
Atomic nucleus
Sub-atomic particules

Defensa Innata

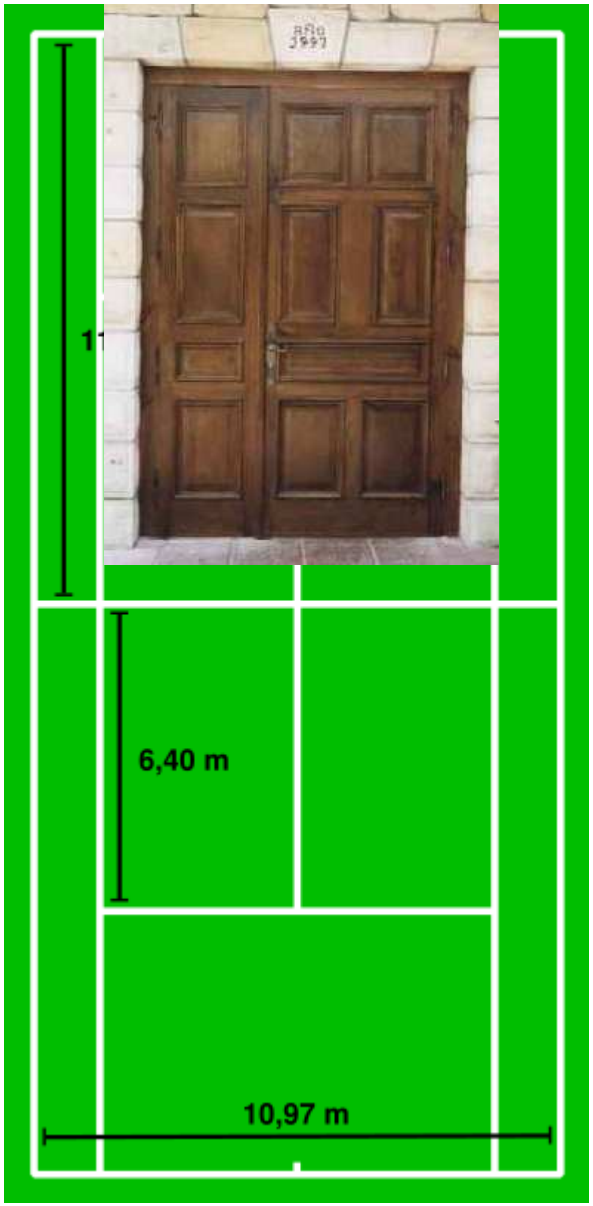
- Primera línea de defensa ante cualquier microorganismo exógeno.
- No es específica

- ***Barreras mecánicas,químicas y microbiológicas***
- ***Células de la respuesta inmune***
- **Moléculas solubles y receptores de membrana**



La integridad de las barreras físicas es crítica para evitar la infección

Figure 2-4 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)



Las superficie de las mucosas es equivalente a una cancha de tenis. A diferencia de la piel esta capa es más fina y esta especializada en intercambiar nutrientes y compuestos de descarte, lo cual la hace más susceptible a ser invadida por patógenos.

Sitios protegidos por el SISTEMA INMUNE

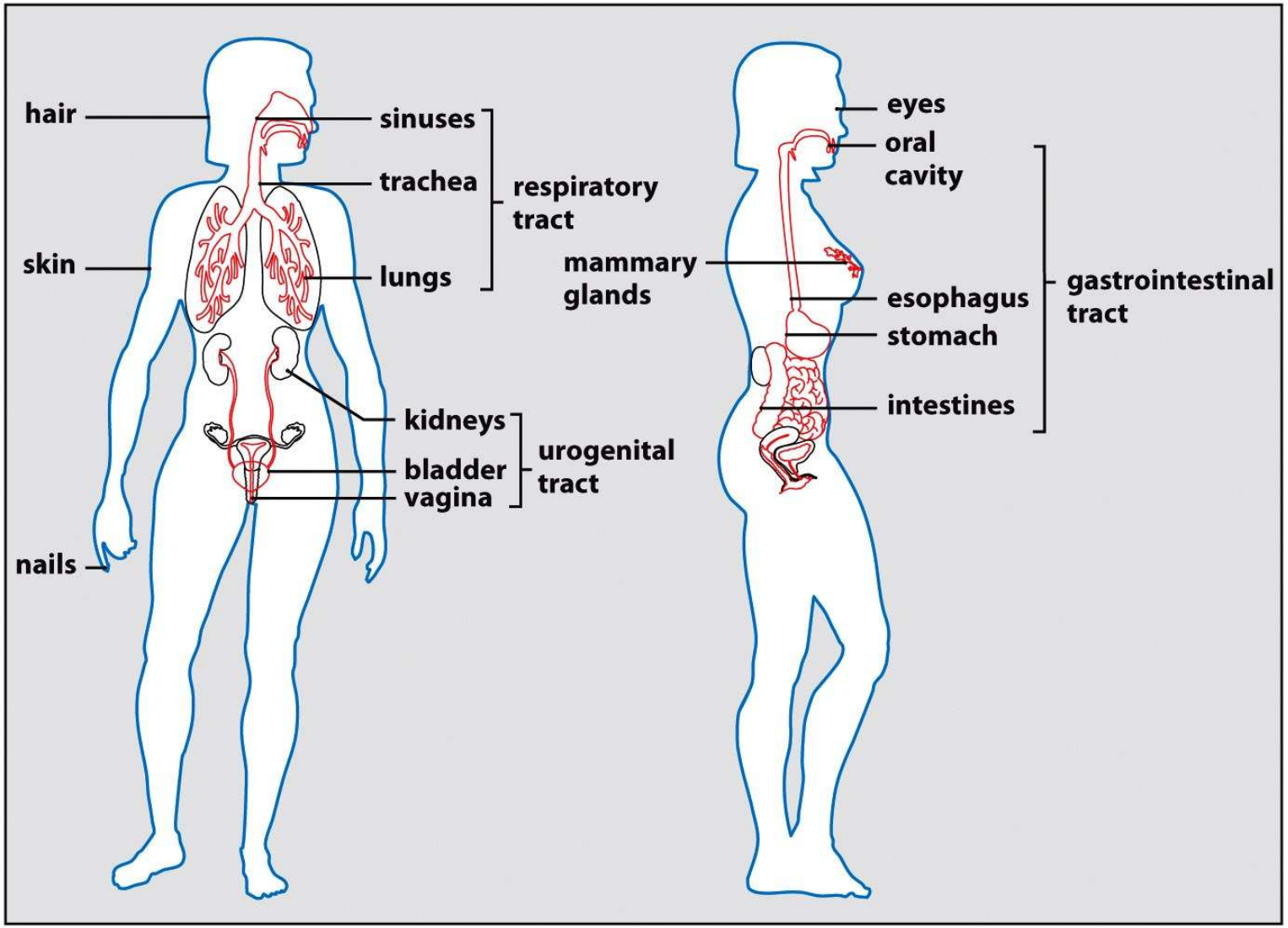


Figure 1.5 The Immune System, 3ed. (© Garland Science 2009)

Barreras naturales: clasificación

	Skin	Gastrointestinal tract	Respiratory tract	Urogenital tract	Eyes
Mechanical	Epithelial cells joined by tight junctions				
	Flow of fluid, perspiration, sloughing off of skin	Flow of fluid, mucus, food, and saliva	Flow of fluid and mucus, e.g., by cilia Air flow	Flow of fluid, urine, mucus, sperm	Flow of fluid, tears
Chemical	Sebum (fatty acids, lactic acid, lysozyme)	Acidity, enzymes (proteases)	Lysozyme in nasal secretions	Acidity in vaginal secretions Spermine and zinc in semen	Lysozyme in tears
	Antimicrobial peptides (defensins)				
Microbiological	Normal flora of the skin	Normal flora of the gastrointestinal tract	Normal flora of the respiratory tract	Normal flora of the urogenital tract	Normal flora of the eyes

Figure 1.6 The Immune System, 3ed. (© Garland Science 2009)

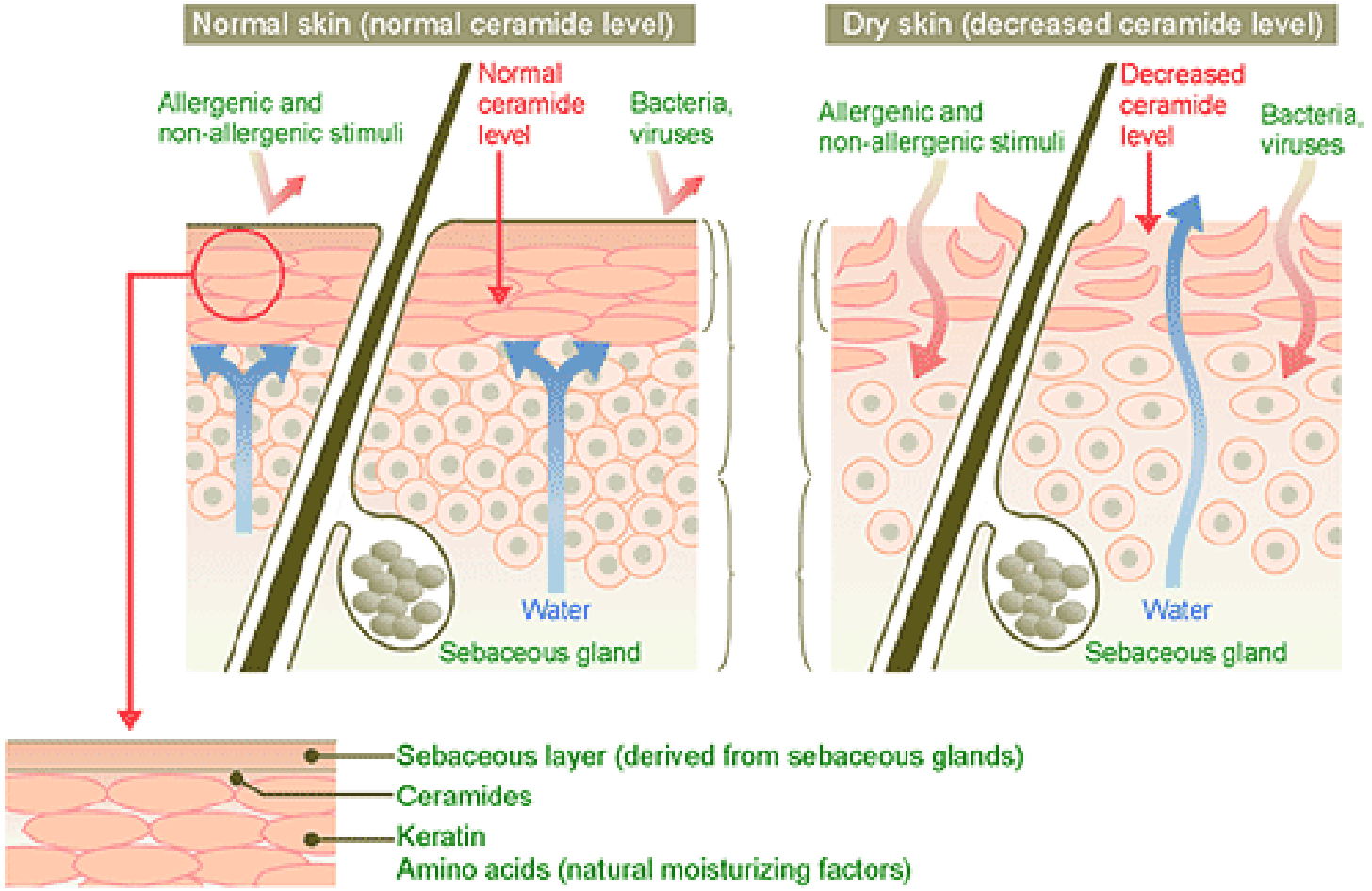
DEFENSAS DE PIEL Y MUCOSAS

SITIO	DEFENSA	FUNCIÓN
Piel	Acidez	Bacteriostasis
	Descamación celular	Remueve bacterias
	Flora NORMAL	Competencia
Folículos pilosos y glándulas sudoríparas	Lisozima, lípidos tóxicos	Bactericida
Por debajo de la piel	Tejido linfoide asociado a piel	Bactericida

DEFENSAS DE PIEL Y MUCOSAS

SITIO	DEFENSA	FUNCIÓN
Superficie mucosa	Mucina	Lubricación y protección celular; impermeabilidad; inhibición adherencia microbiana y toxinas; eliminación mecánicas de M.O.
	sIgA	Impide la adhesión bacteriana; neutraliza bacterias y virus; impide la absorción de antígenos por células epiteliales.
	Lactoferrina	Une hierro, bacteriostasis
	Lactoperoxidasa	Genera radicales superóxido tóxicos
Membrana mucosa	Descamación celular	Remueve bacterias
	Continuidad	Evita la invasión entre célula y célula
Por debajo de la mucosa	Tejido linfoide asociado a mucosa	Produce sIgA, células fagocíticas

Comparación entre PIEL NORMAL Y PIEL SECA



Yoshiki Miyachi and Toshikazu Nagakura (eds.): Atopic dermatitis –Consensus update–. Medical Review Co., Ltd. 2000.

Flora normal o habitual

Población de microorganismos que habitualmente coloniza la piel y las mucosas de las personas sanas.

La flora normal se adquiere con rapidez durante y poco después del nacimiento y cambia de constitución en forma permanente a lo largo de la vida. Muchos de estos microorganismos también coexisten en algunos animales o bien pueden desarrollar una vida libre. Es por lo tanto bastante difícil definir la flora normal, puesto que depende en gran parte del medio en que nos desenvolvemos.

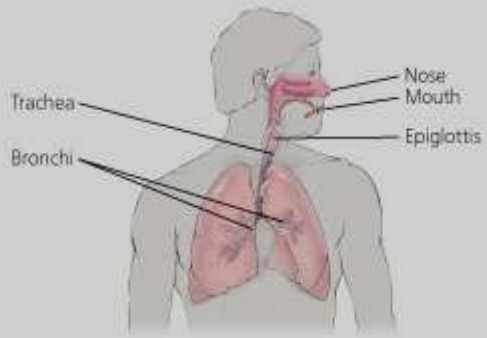
La flora normal la podemos dividir en dos poblaciones:

- **FLORA RESIDENTE**: Nº fijo de especies de microorganismos que se encuentran habitualmente en una zona definida.
- **FLORA TRANSITORIA**: Microorganismos no patógenos en principio que colonizan la piel o mucosas durante un período de tiempo corto.

- **Si la flora residente se altera, la transitoria puede multiplicarse y producir infecciones.**

- La presencia de microorganismos comensales de la flora residente no es esencial para la vida, pero suele se **beneficiosa**:
  - Síntesis de vitamina K (*Bacteroides* spp. Y **E. coli**)
  - Ayuda a la absorción de nutrientes
  - Ocupar un nicho ecológico que impide la colonización por microorganismos potencialmente patógenos.
- No obstante, también se pueden comportar como **patógenos oportunistas**. Por ejemplo cuando acceden a lugares normalmente estériles o en inmunodeprimidos. Ej.:
  - *S. viridans* : Boca a sangre y válvula cardíaca dañada = Endocarditis
  - *Bacteroides* spp: Intestino grueso a cavidad peritoneal = Peritonitis

Table 14.2 Resident Microbiota[a]



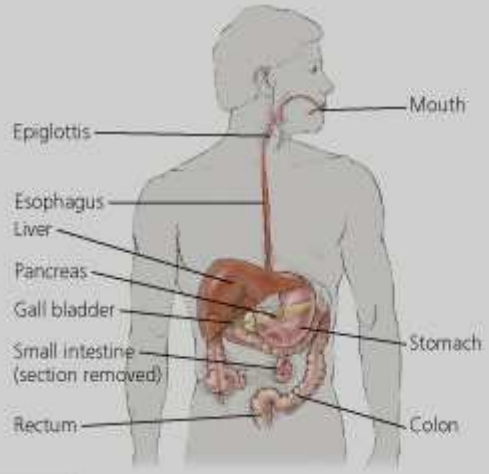
Upper Respiratory Tract

Genera

Staphylococcus, Streptococcus, Moraxella, Haemophilus, Lactobacillus, Veillonella, Fusobacterium, Candida (fungus)

Notes

The nose is cooler than the rest of the respiratory system and has some unique microbiota. The trachea and bronchi have a sparse microbiota compared to the nose and mouth. The alveoli of the lungs, which are too small to see at this magnification, have no natural microbiota.



Upper Digestive Tract

Genera

Lactobacillus, Haemophilus, Actinomyces, Bacteroides, Treponema, Neisseria, Streptococcus, Corynebacterium, Entamoeba (protozoan), *Trichomonas* (protozoan)

Notes

Microbes colonize surfaces of teeth, gingiva, lining of cheeks, and pharynx, and are found in saliva in large numbers. Dozens of species have never been identified.

Lower Digestive Tract

Genera

Bacteroides, Fusobacterium, Escherichia, Lactobacillus, Clostridium, Bifidobacterium, Enterococcus, Proteus, Shigella, Candida (fungus), *Entamoeba* (protozoan), *Trichomonas* (protozoan)

Notes

Bacteria are mostly strict anaerobes, though some facultative anaerobes are also resident.

[a]Genera are bacteria unless noted.

Table 14.2 Resident Microbiota[a]

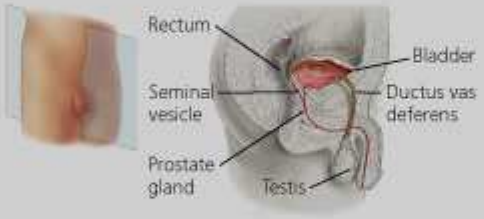
Female Urinary and Reproductive Systems

Genera

Lactobacillus, Streptococcus, Staphylococcus, Bacteroides, Clostridium, Candida (fungus), *Trichomonas* (protozoan)

Notes

Microbiota change as acidity in the vagina changes during menstrual cycle. The flow of urine prevents extensive colonization of the urethra.



Male Urinary and Reproductive Systems

Genera

Staphylococcus, Streptococcus, Mycobacterium, Bacteroides, Fusobacterium, Peptostreptococcus

Notes

The flow of urine prevents extensive colonization of the urethra.

Eyes and Skin

Genera

Skin: *Propionibacterium, Staphylococcus, Corynebacterium, Micrococcus, Malassezia* (fungus), *Candida* (fungus)

Conjunctiva: *Staphylococcus*

Notes

Microbiota live on the outer, dead layers of the skin and in hair follicles and pores of glands. The deeper layers (dermis and hypodermis) are axenic.

Tears wash most microbiota from the eyes, so there are few compared to the skin.

[a]Genera are bacteria unless noted.

Pero……

LA PERFECCIÓN NO EXISTE ….

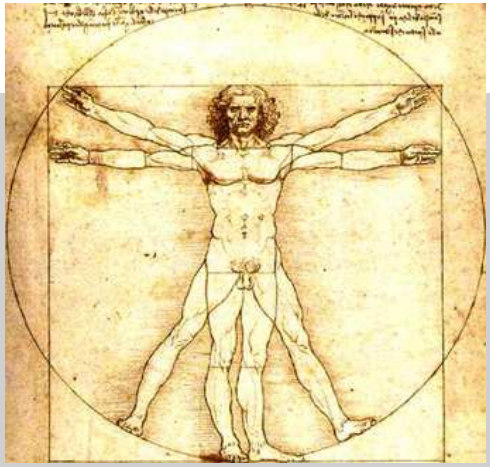


Table 14.3 Some Pathogens That Cross the Placenta

Type	Pathogen	Condition in the Adult	Effect on Embryo or Fetus
Protozoan	*Toxoplasma gondii*	Toxoplasmosis	Abortion, epilepsy, encephalitis, microcephaly, mental retardation, blindness, anemia, jaundice, rash, pneumonia, diarrhea, hypothermia, deafness
Bacteria	*Treponema pallidum*	Syphilis	Abortion, multiorgan birth defects, syphilis
	Listeria monocytogenes	Listeriosis	Granulomatosis infantiseptica (nodular inflammatory lesions and infant blood poisoning), death
DNA viruses	*Cytomegalovirus*	Usually asymptomatic	Deafness, microcephaly, mental retardation
	Parvovirus B19	Erythema infectiosum	Abortion
RNA viruses	*Lentivirus* (HIV)	AIDS	Immunosuppression (AIDS)
	Rubivirus rubella	German measles	Severe birth defects or death

Factores que afectan al mantenimiento de la flora normal:

1. Nutrientes
2. pH
3. Temperatura
4. Humedad
5. Potencial redox
6. Resistencia a sustancias naturales
7. Presencia de receptores celulares
8. Interferencia bacteriana

Efectos beneficiosos de la flora microbiana

1. Activación del sistema inmune
2. Interferencia bacteriana
3. Producción de nutrientes esenciales

Flora normal y lavado de manos

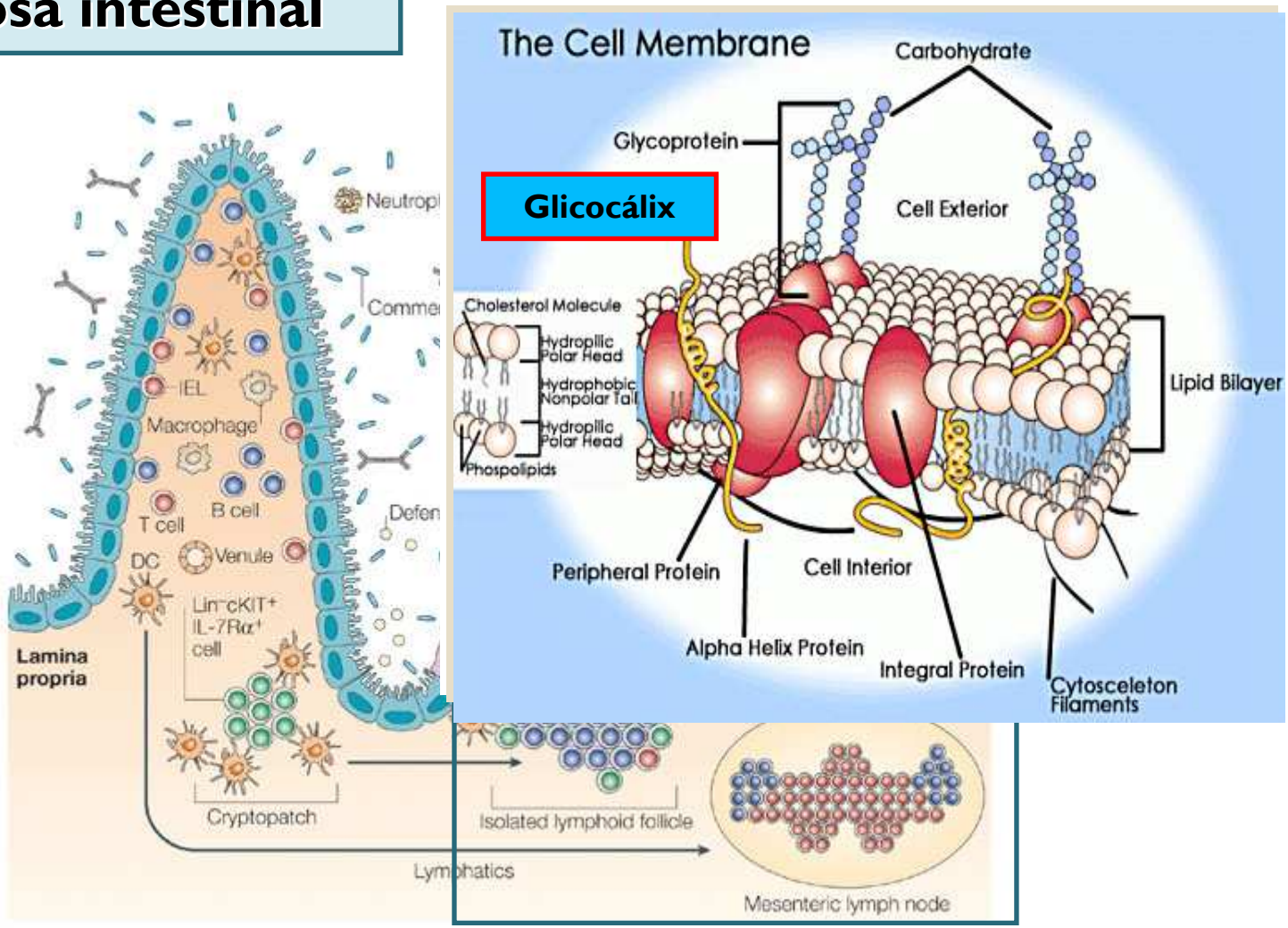
Flora residente

- Se ubica bajo el estrato córneo, en la zona más profunda de la epidermis, coloniza las glándulas sebáceas, de ahí que resulta más difícil su eliminación. Varía de acuerdo al sitio del cuerpo, edad, salud y tipo de trabajo.
- **Es difícil removerla con el lavado común con agua y jabón (reducción 50%).** Estos M.O. corresponden a **Estafilococo coagulasa negativa, Acinetobacter spp y levaduras del género Cándida.** En general estos M.O. son de baja virulencia y se comportan como oportunistas.

Flora transitoria

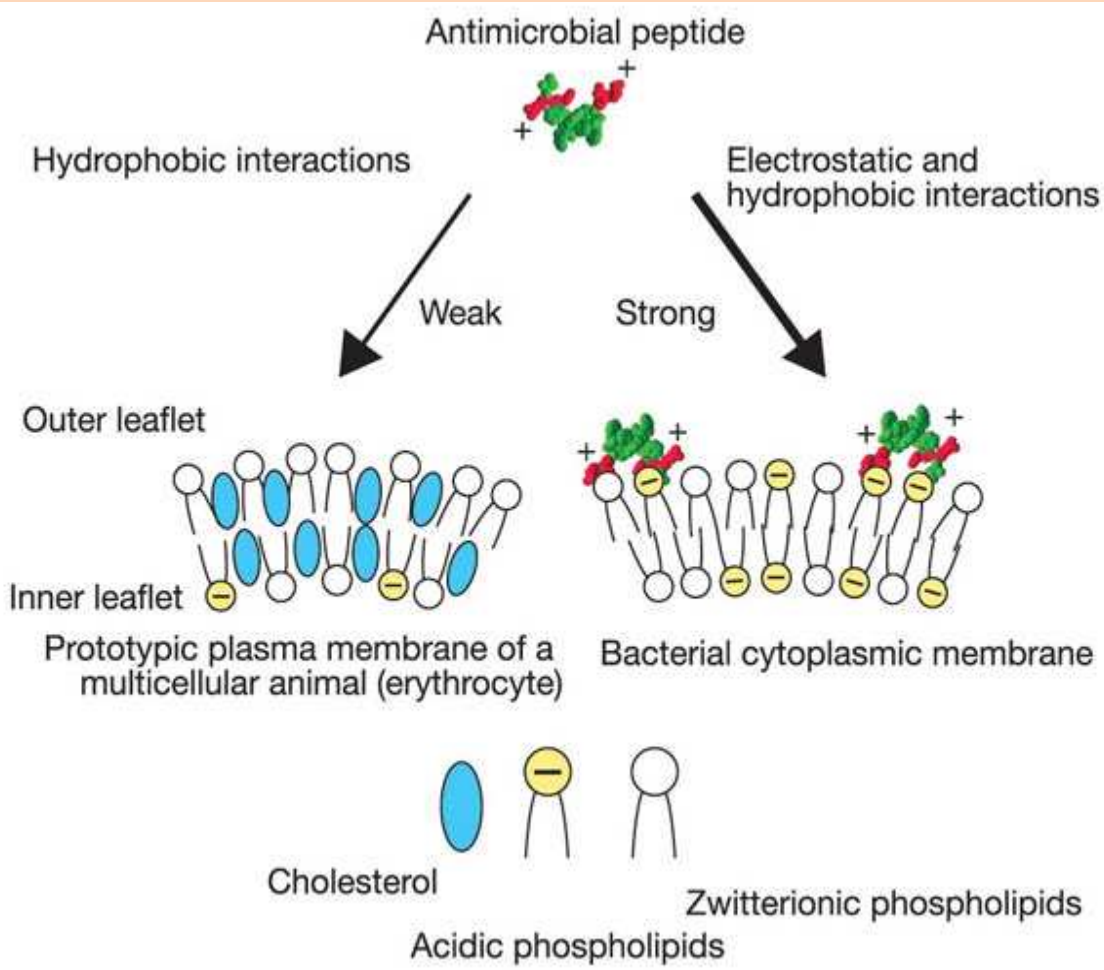
- Se ubica en la superficie de la piel.
- No pude multiplicarse en la piel.
- No sobrevive por tiempo prolongado.
- **Se elimina fácilmente, incluso con agua sola.**
- Es intercambiable entre personas.
- Depende de la actividad.
- Corresponden principalmente a **Staphylococcus aureus y bacilos gram negativos incluídos los no fermentadores.**

Mucosa intestinal



Nature Reviews Immnunology. June 2008

Péptidos antimicrobianos (AMP)



Human Antimicrobial Peptides

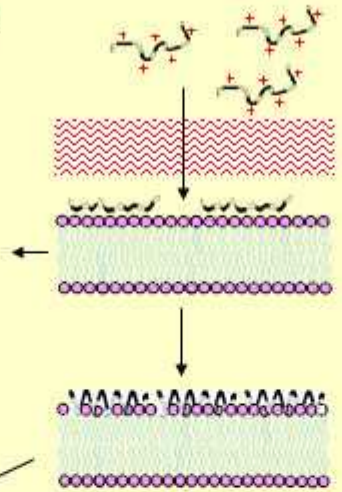
Family/member	Distribution
α-defensins	
HNP1-4	all present in neutrophils
HD5	Paneth cells of small intestine, airway epithelium, urogenital epithelium
HD6	Paneth cells of small intestine, airway epithelium
β-defensins	
HBD1	lung, other epithelia
HBD2	lung, other epithelia
HBD3	skin keratinocytes, airway epithelium
HBD4	neutrophils, epithelium of testes, stomach, uterus, lung, kidney
HBD5	male reproductive tract
HBD6	male reproductive tract
Cathelicidins	
LL37/hCAP-18	neutrophils, lung epithelium, mast cells, monocytes/ macrophages

AMPs are *Multimodal* & *Multifunctional*

Stimulate innate and adaptive immune responses

Cause autolytic enzyme release

Block cell envelope synthesis



Are attracted to the anionic microbial surface

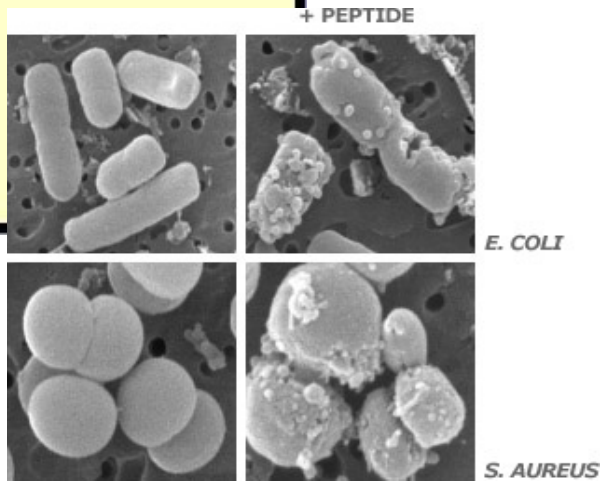
Assemble on the surface

Insert into the membrane

permeabilize/damage the membrane (pores, channels)

translocate

block internal metabolic processes



Barreras que encuentra el antígeno en el tracto gastrointestinal

Tubo digestivo	• Saliva
	• Ácido gástrico-pepsina
	• Enzimas pancreáticas e intestinales
	• Peristaltismo intestinal
Barreras físicas	• Glucocalix intestinal
	• Epitelio: microvellosidades intestinales
	• Submucosa
Barreras inmunológicas	• IgA secretora
	• Placas de Peyer: linfocitos T CD4,B, células plasmáticas, macrófagos y células M
	• Linfocitos intraepiteliales: mayoritariamente T CD8
	• Linfocitos B: productores de IgA localizados en la lámina propia y en los nódulos linfoides mesentéricos

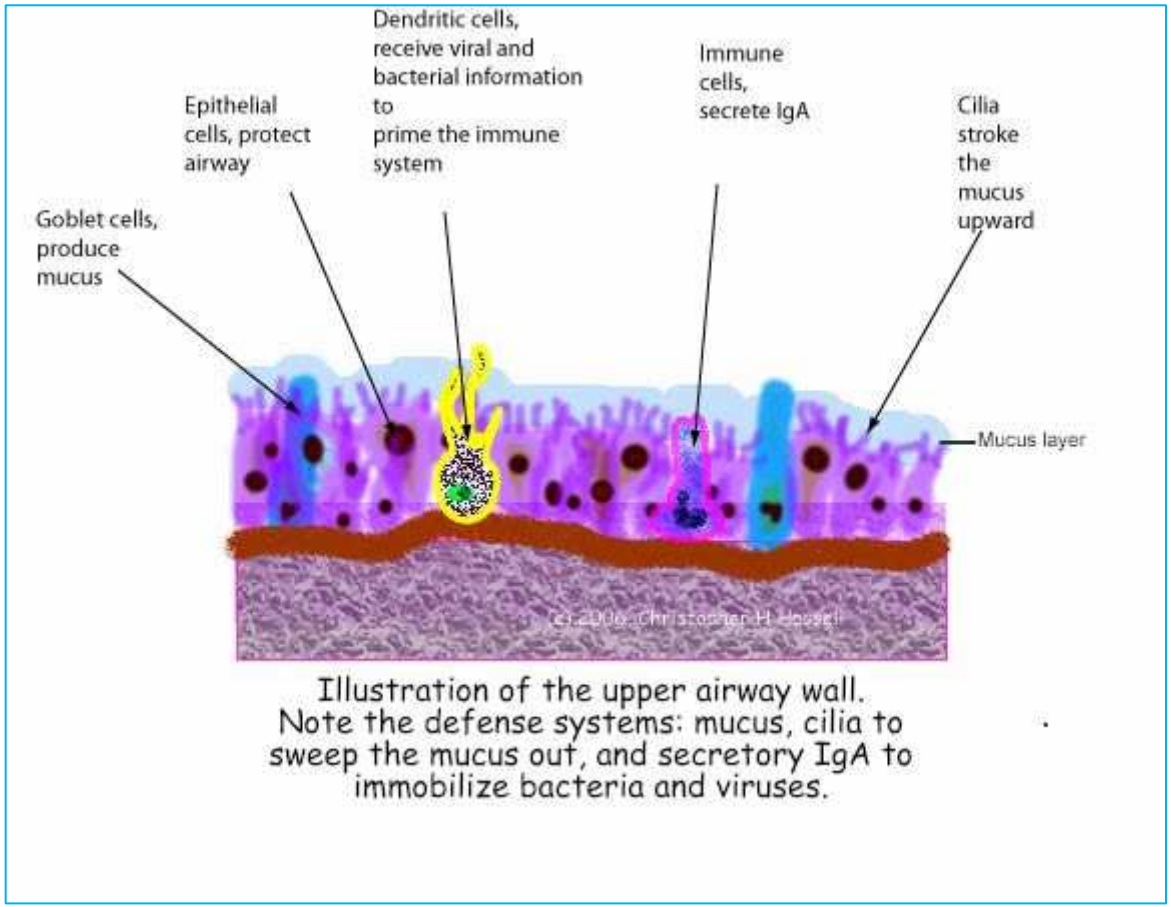
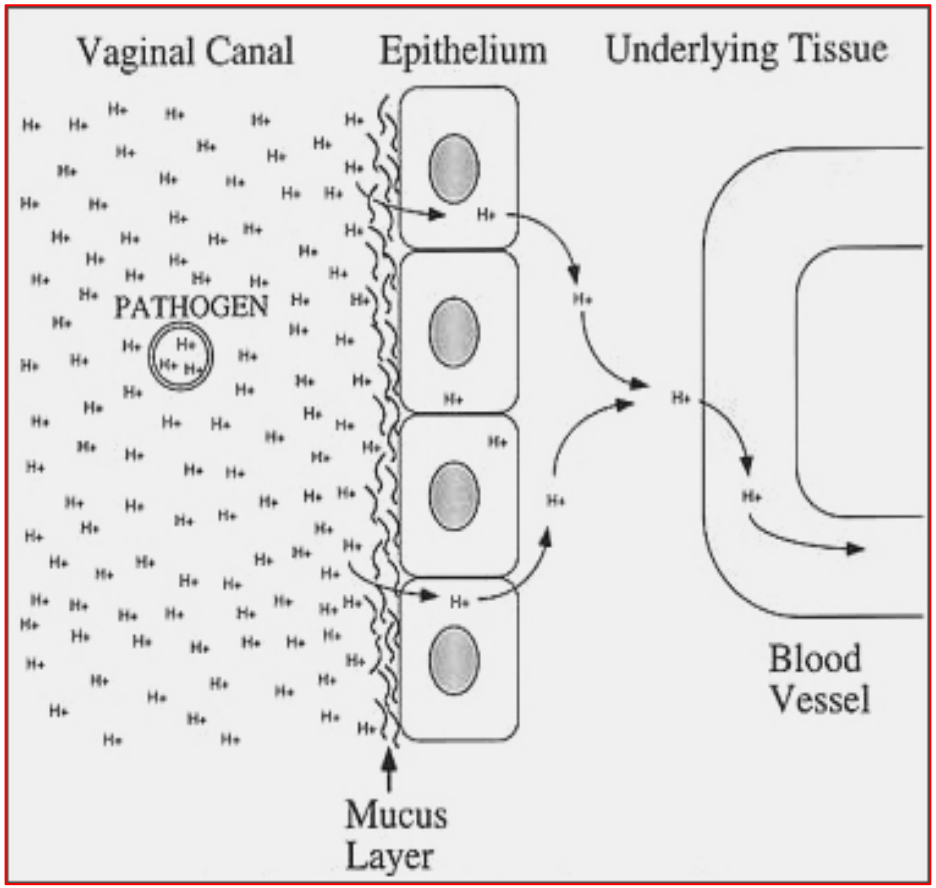


Illustration of the upper airway wall. Note the defense systems: mucus, cilia to sweep the mucus out, and secretory IgA to immobilize bacteria and viruses.

MUCOSA RESPIRATORIA

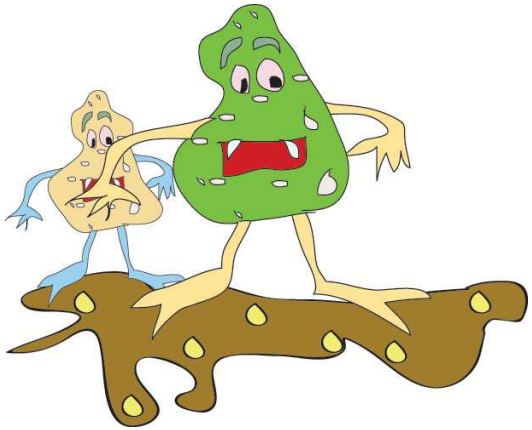
MUCOSA VAGINAL

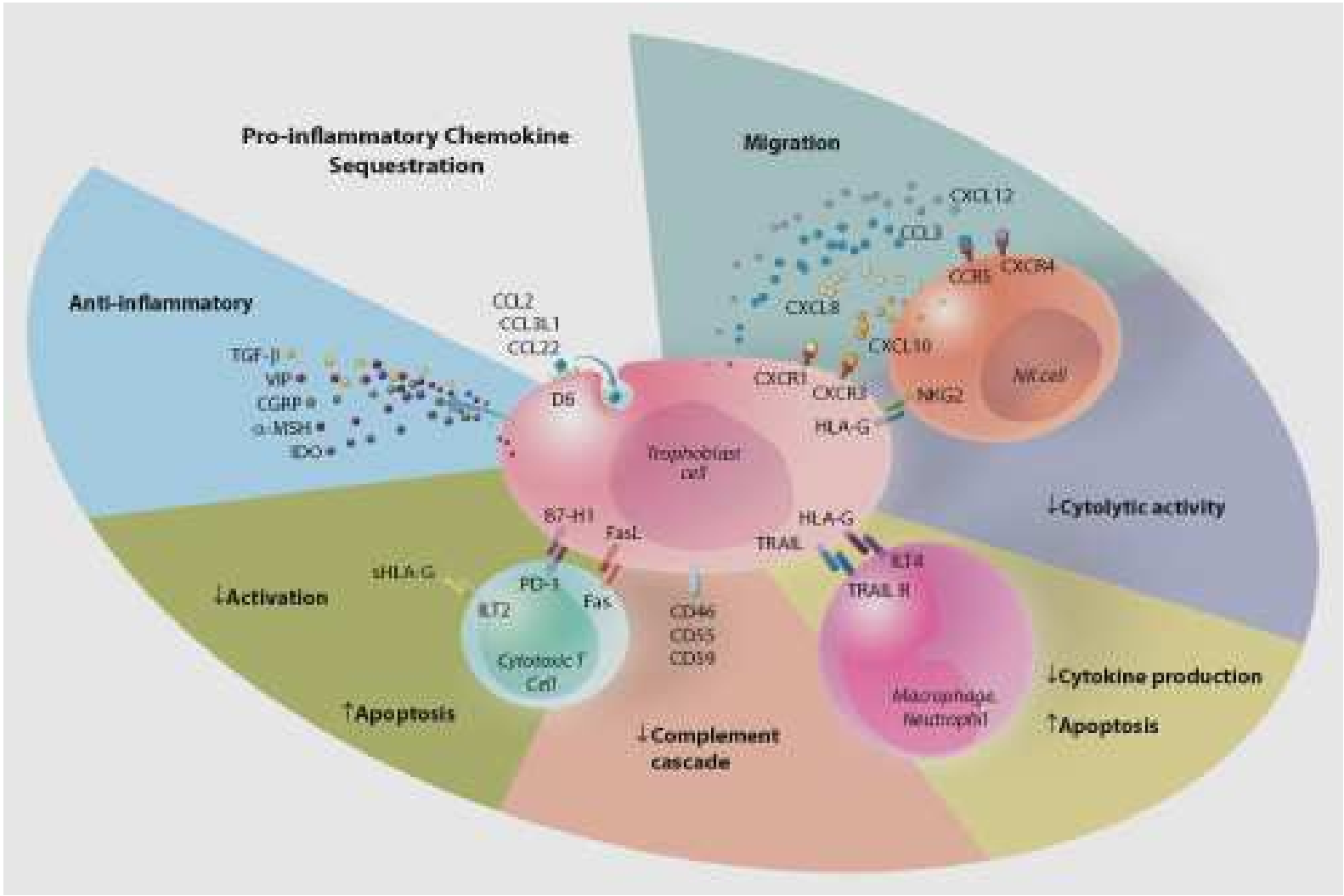


Acid-sensitive pathogens (viruses, bacteria or infected cells) are surrounded by vaginal acidity (hydrogen ions shown as H+ in diagram) and acidified and killed.

In contrast, epithelial cells are protected by a layer of mucus, and the small amount of acid that leaks in is easily passed on to the underlying tissue and carried away by the blood.

OTRAS BARRERAS NATURALES





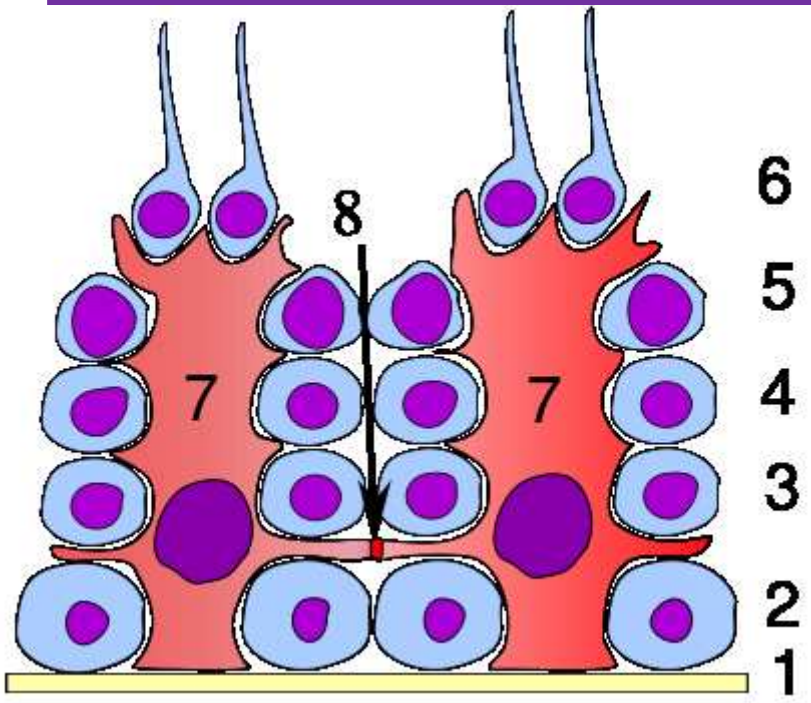
Las células trofoblásticas expresan numerosos receptores de membrana y moléculas solubles que contribuyen al privilegio inmune fetal y promueven el desarrollo de la interfase materno-fetal.

Testículo

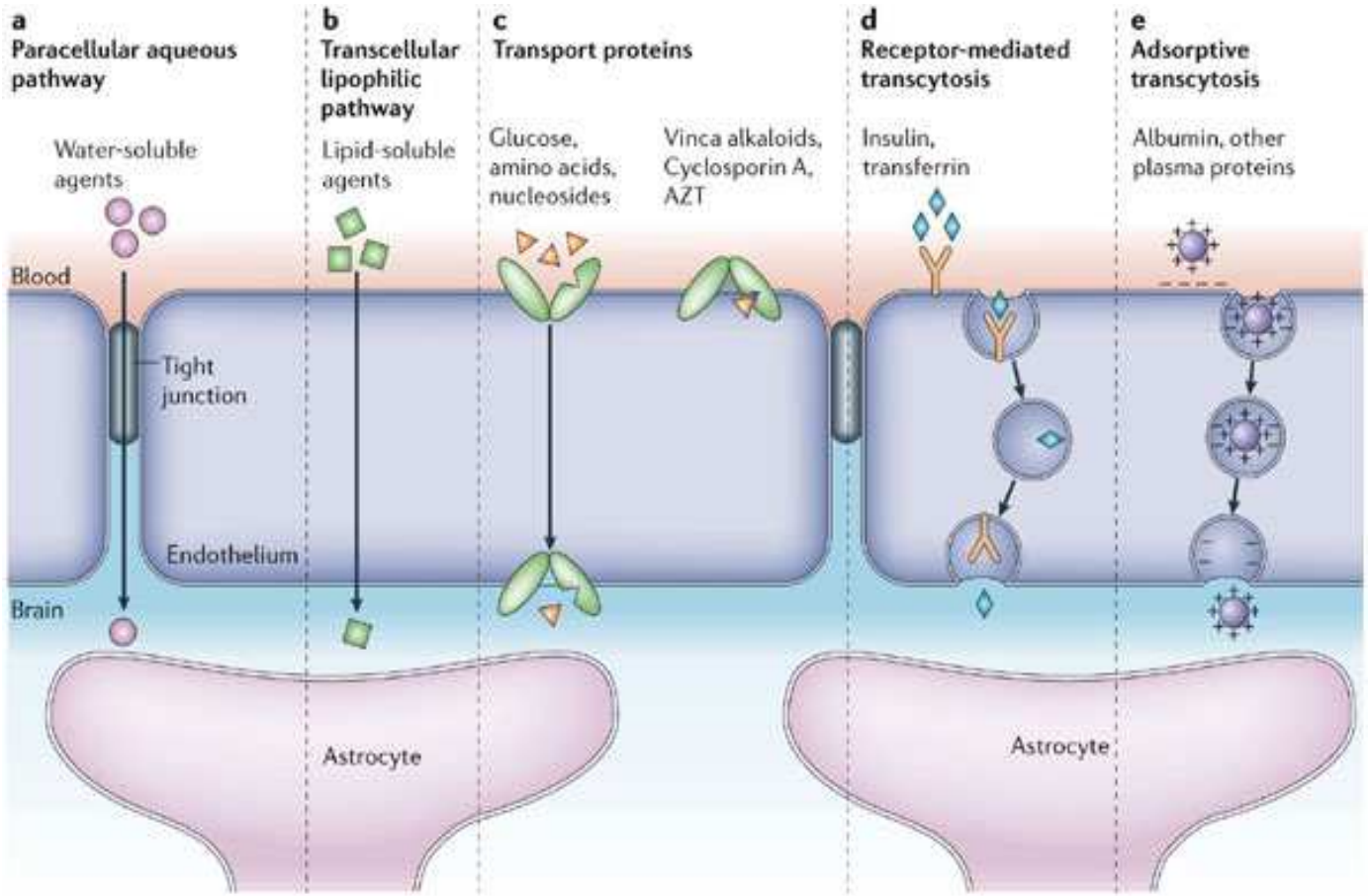
The blood-testis barrier (abbreviated as BTB) is a physical barrier between the blood vessels and the seminiferous tubules of the animal testes.

The barrier is formed by tight connections between the Sertoli cells, which are sustentacular cells (supporting cells) of the seminiferous tubules, and nourish the spermatogonia.

The barrier avoids passage of cytotoxic agents (bodies or substances that are toxic to cells) into the seminiferous tubules.



Germinal epithelium of the testicle. 1 basal lamina, 2 spermatogonia, 3 spermatocyte 1st order, 4 spermatocyte 2nd order, 5 spermatid, 6 mature spermatid, 7 Sertoli cell, 8 tight junction (blood testis barrier)



Nature Reviews Neuroscience 7, 41-53 (January 2006)

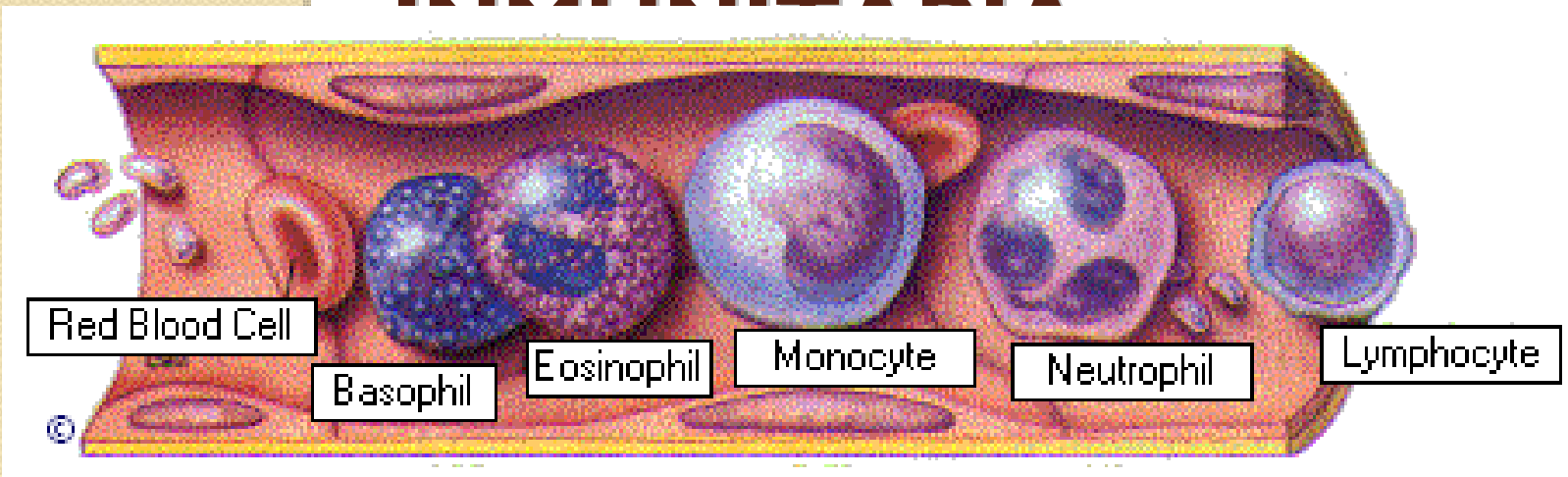
Tight junctions (TJ)

Adherens junctions (AJ),

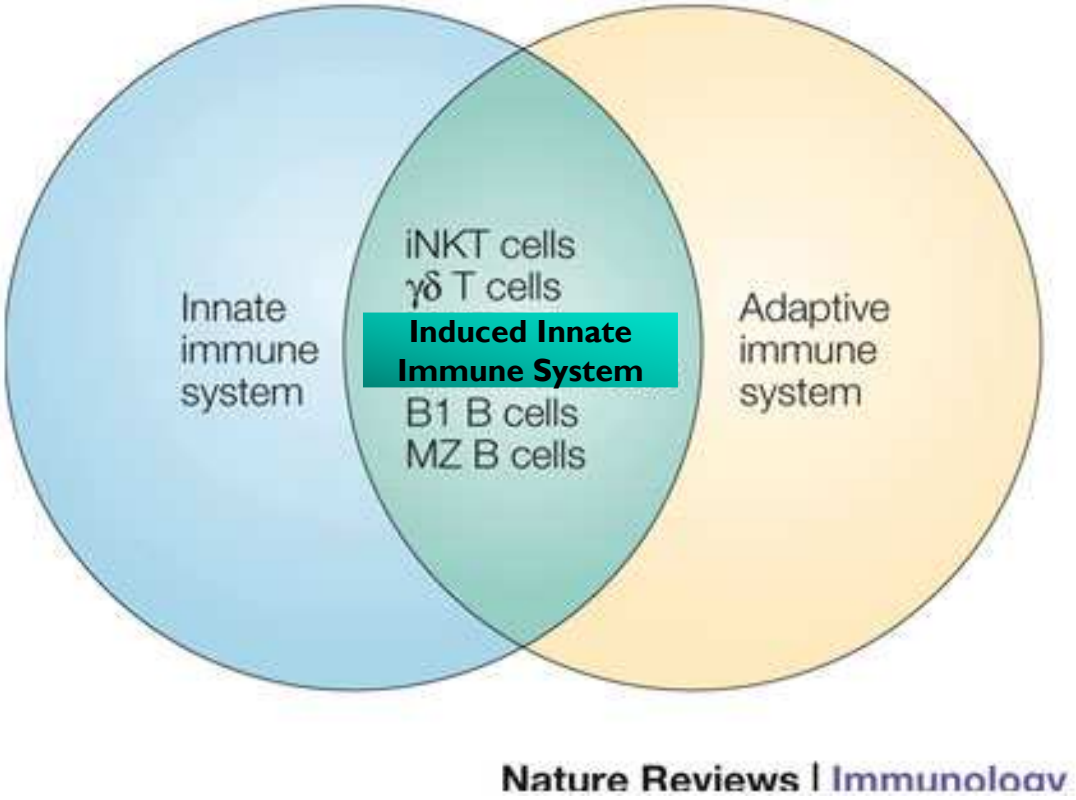
BARRERA HÉMATO-ENCEFÁLICA

- a | The blood–brain barrier (BBB) is formed by endothelial cells at the level of the cerebral capillaries. These endothelial cells interact with perivascular elements such as basal lamina and closely associated astrocytic end-feet processes, perivascular neurons (represented by an interneuron here) and pericytes to form a functional BBB. b | Cerebral endothelial cells are unique in that they form complex tight junctions (TJ) produced by the interaction of several transmembrane proteins that effectively seal the paracellular pathway. These complex molecular junctions make the brain practically inaccessible for polar molecules, unless they are transferred by transport pathways of the BBB that regulate the microenvironment of the brain. There are also adherens junctions (AJ), which stabilize cell–cell interactions in the junctional zone. In addition, the presence of intracellular and extracellular enzymes such as monoamine oxidase (MAO), -glutamyl transpeptidase (-GT), alkaline phosphatase, peptidases, nucleotidases and several cytochrome P450 enzymes endow this dynamic interface with metabolic activity. Large molecules such as antibodies, lipoproteins, proteins and peptides can also be transferred to the central compartment by receptor-mediated transcytosis or non-specific adsorptive-mediated transcytosis. The receptors for insulin, low-density lipoprotein (LDL), iron transferrin (Tf) and leptin are all involved in transcytosis. P-gp, P-glycoprotein; MRP, multidrug resistance-associated protein family.

CÉLULAS DE LA RESPUESTA

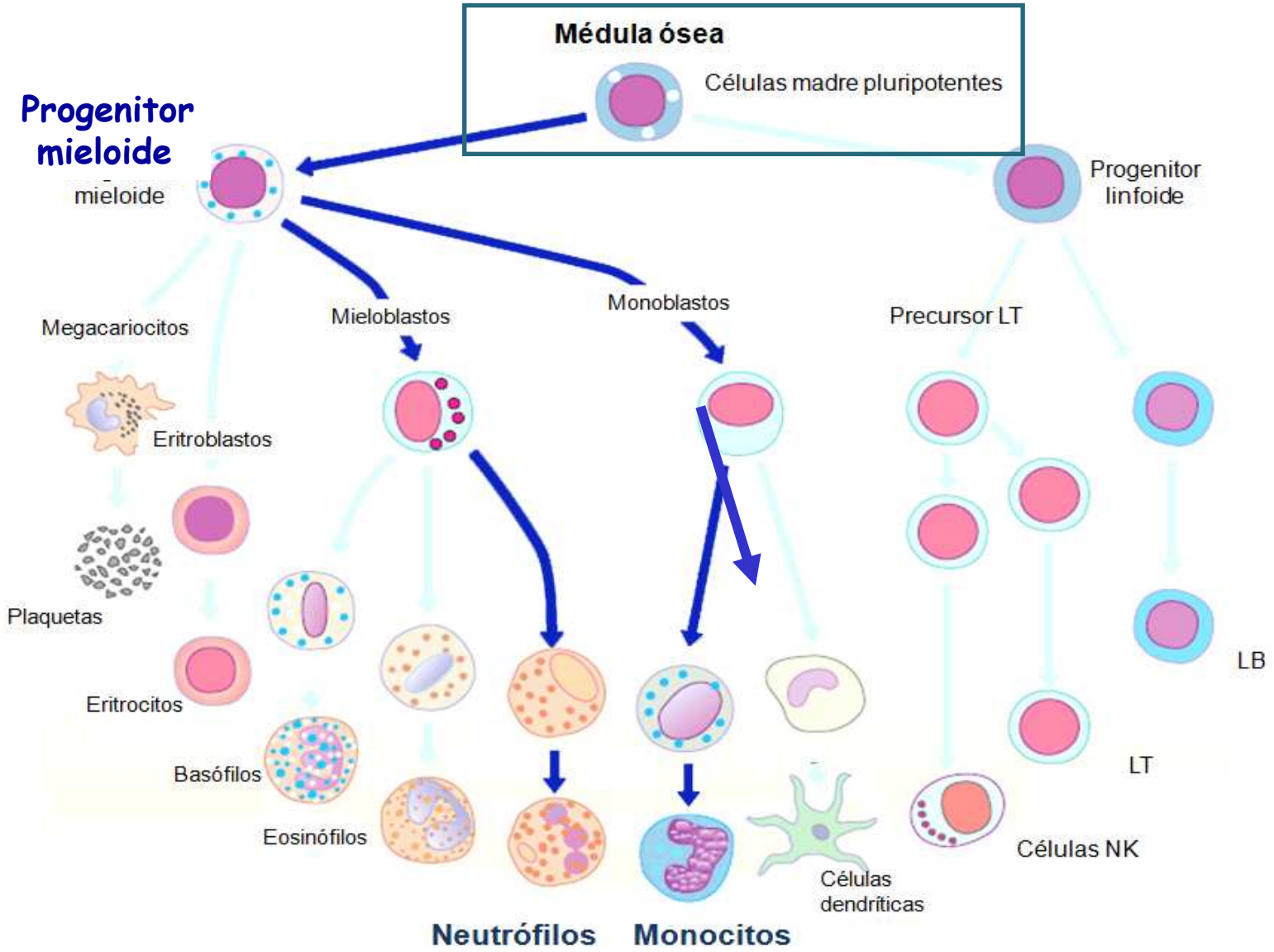


Sistema inmune innato

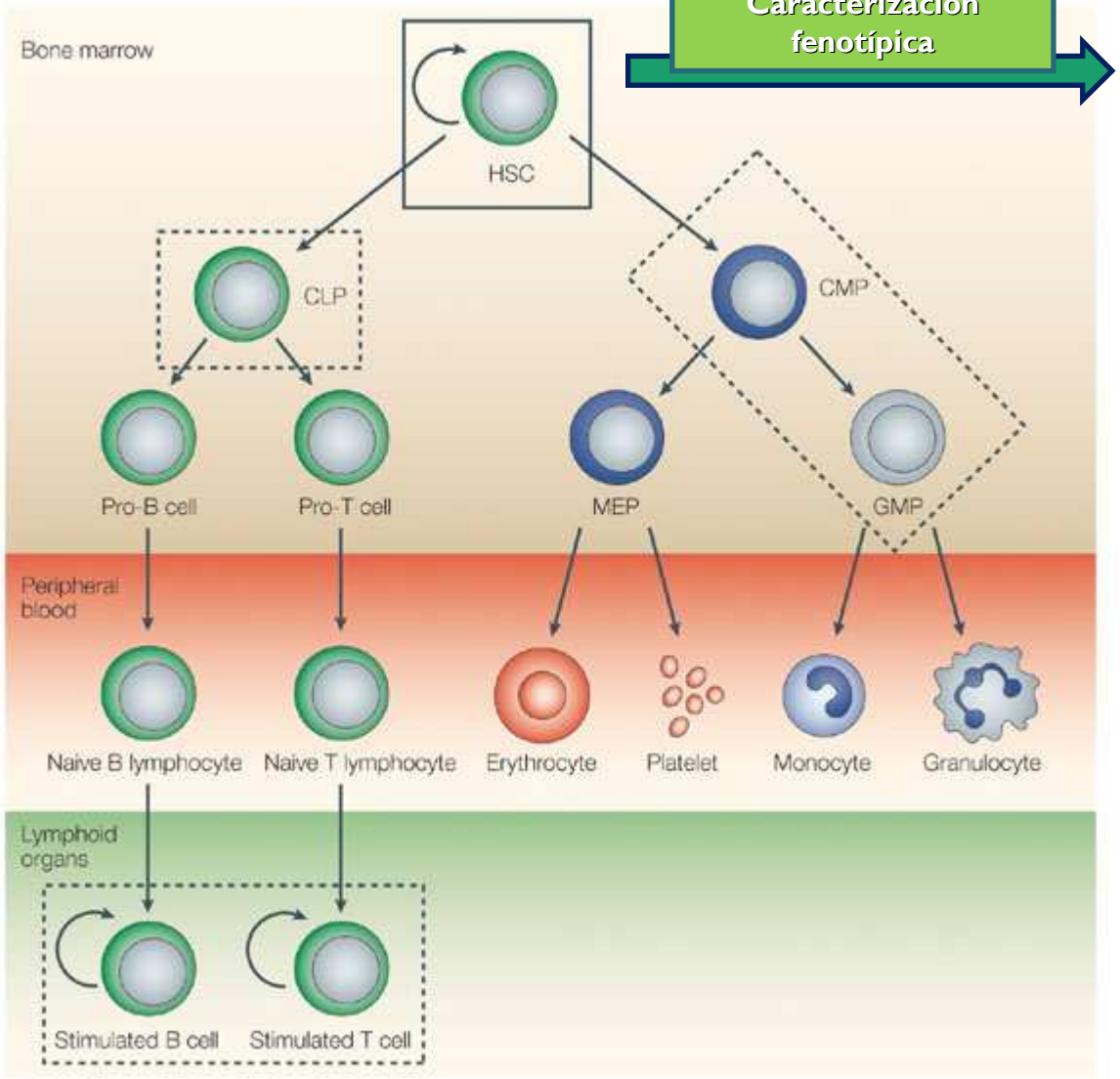


- Célula hematopoyética pluripotencial (STEM CELL)
- Fagocitos profesionales: Células dendríticas, Macrófagos, Neutrófilos
- Mastocitos y Basófilos
- Eosinófilos
- Células NK
- Células NKT
- Células T $\gamma\delta$
- Linfocitos B1
- Linfocitos MZB

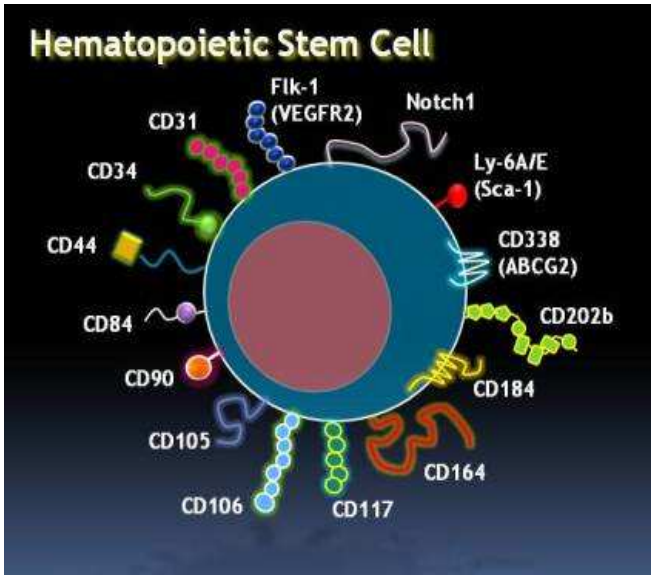
Macrófagos, neutrófilos y células dendríticas se generan en la médula ósea



Caracterización fenotípica



Nature Reviews | Cancer



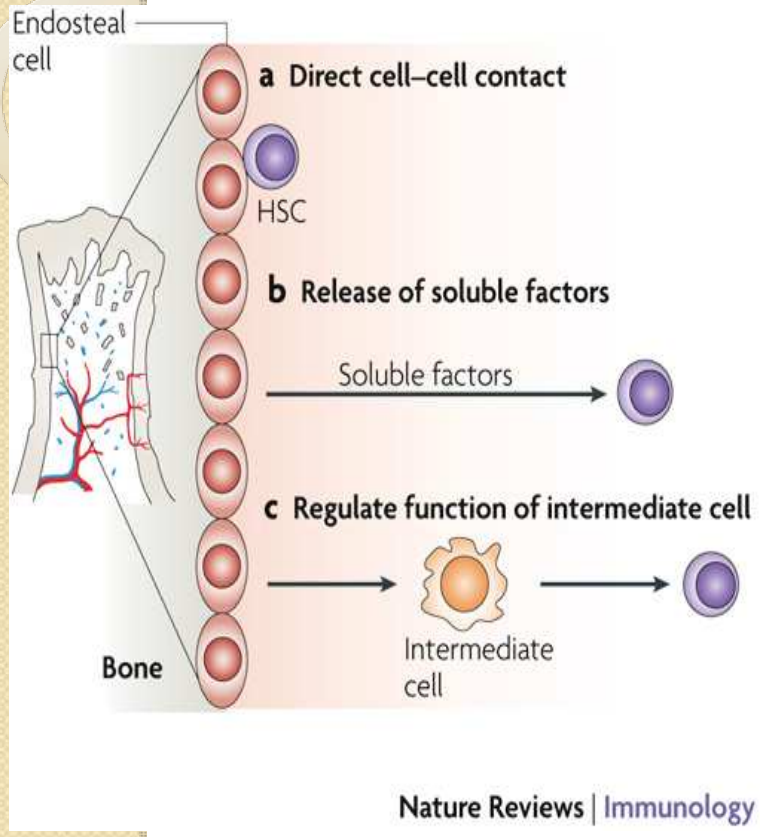
Common Lymphoid Progenitors (CLPs)
Common Myeloid Progenitors (CMPs)

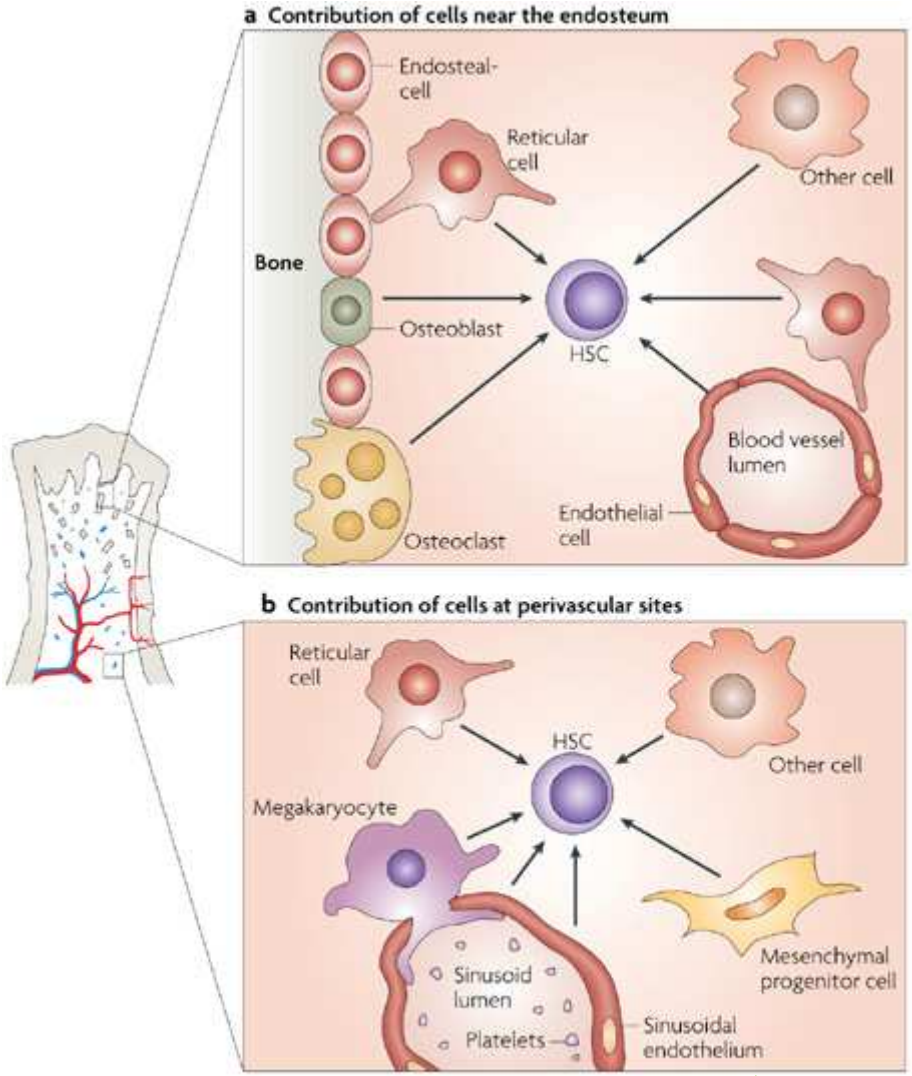
Megakaryocyte Erythroid Progenitors (MEPs)
Granulocyte Monocyte Progenitors (GMPs)

Nature Reviews Cancer 5, 311-321 (April 2005)

- Within the haematopoietic system, the haematopoietic stem cell (HSC) has self-renewal potential and multipotent differentiation potential. Its progeny include multipotent common lymphoid progenitors (CLPs) and common myeloid progenitors (CMPs). In turn, these progenitors give rise to progenitors that have more limited differentiation potential, Pro-B and Pro-T cells, megakaryocyte erythroid progenitors (MEPs) and granulocyte monocyte progenitors (GMPs). In the myeloid lineage, MEPs give rise to mature erythrocytes and platelets in the peripheral blood. GMPs give rise to monocytes and the various granulocyte lineages. In the lymphoid lineages Pro-B and Pro-T cells give rise to mature (naive) B and T lymphocytes and then stimulated B and T cells, respectively, following exposure to antigen. Cellular compartments that are known to be, or might be, potential targets for the generation of leukaemia stem cells (LSCs) are indicated by solid or dashed boxes, respectively. Not all of these cell types have self-renewal properties (which is indicated with a curved arrow). Mutations are therefore required to confer properties of self-renewal to these cell types, and to lead to LSC formation and leukaemogenesis.

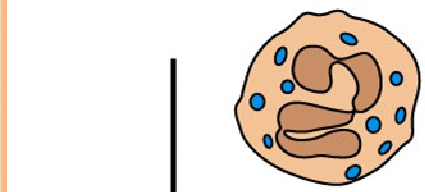
NICHOS de HSCs

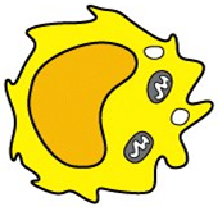


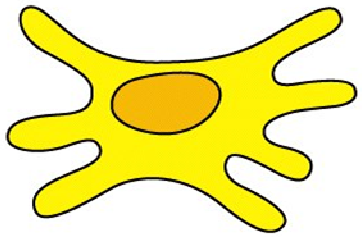


Perivascular sites are likely to maintain fetal HSCs in the placenta, spleen and liver.

Nature Reviews Immunology 8, 290-301 (April 2008)





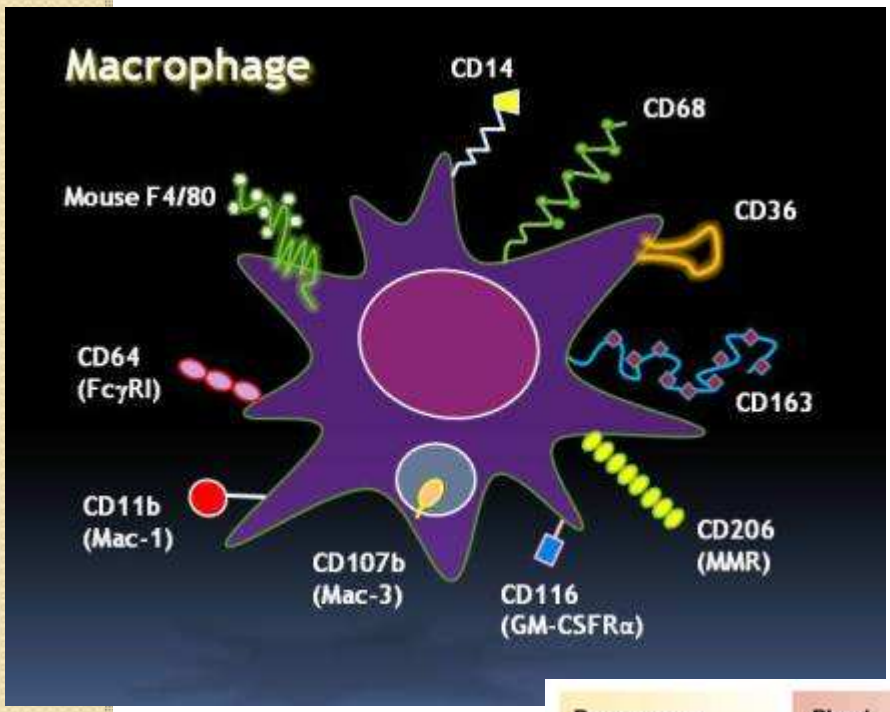


Cell type	Neutrophils	Macrophages	Dendritic cells
Function	Phagocytosis Reactive oxygen and nitrogen species Antimicrobial peptides	Phagocytosis Inflammatory mediators Antigen presentation Reactive oxygen and nitrogen species Cytokines Complement proteins	Antigen presentation Costimulatory signals Reactive oxygen species Interferon Cytokines

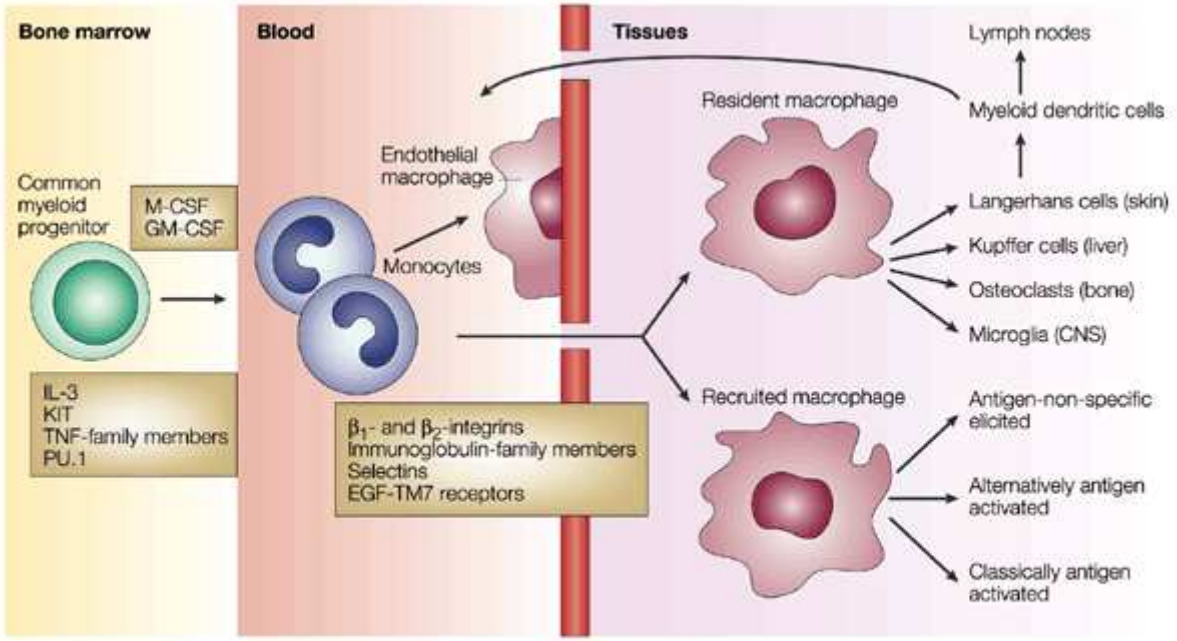
Figure 3-12
Kuby IMMUNOLOGY, Sixth Edition

FAGOCITOS PROFESIONALES

MACRÓFAGOS



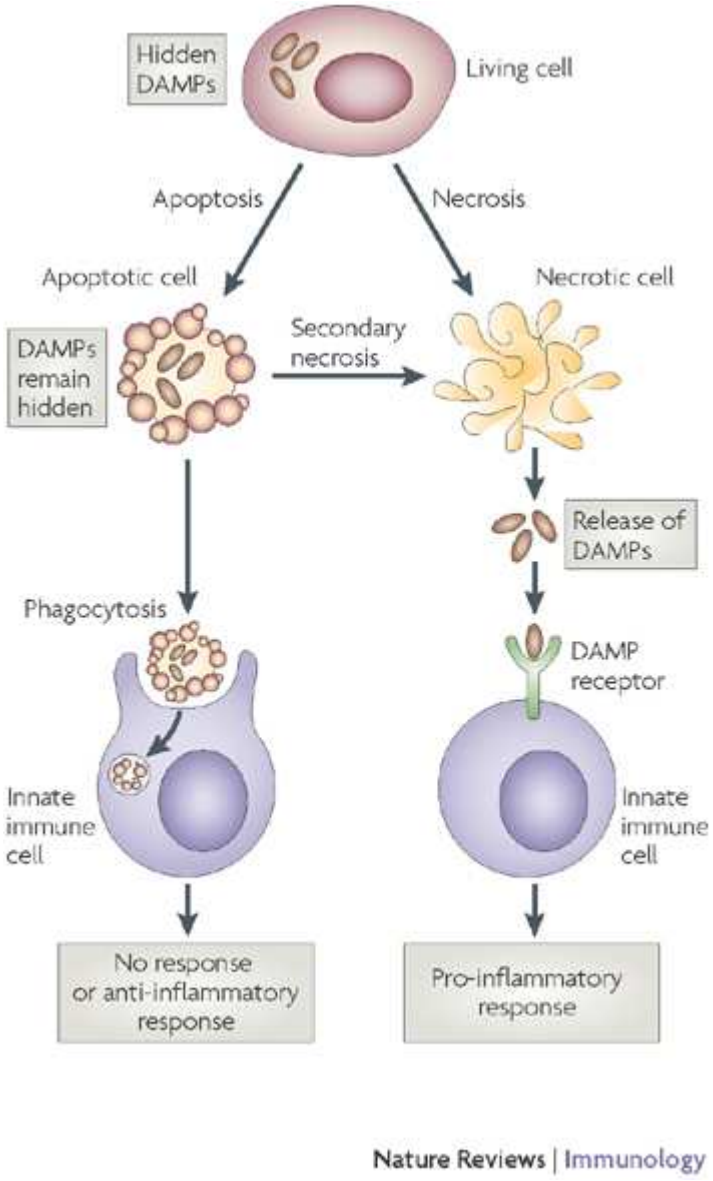
Tissue-resident macrophages undergo local activation in response to various inflammatory and immune stimuli; the enhanced recruitment of monocytes and precursors from bone-marrow pools results in the accumulation of tissue macrophages that have enhanced turnover and an altered phenotype. These macrophages are classified as being 'elicited', as in the antigen-non-specific response to a foreign body or sterile inflammatory agent, or as being 'classically activated' or 'alternatively activated' by an antigen-specific immune response. It is difficult to distinguish originally resident macrophages from more recently recruited, elicited or activated macrophages, because cells adapt to a particular microenvironment.



Nature Reviews Immunology 3, 23-35 (January 2003)

Nature Reviews | Immunology

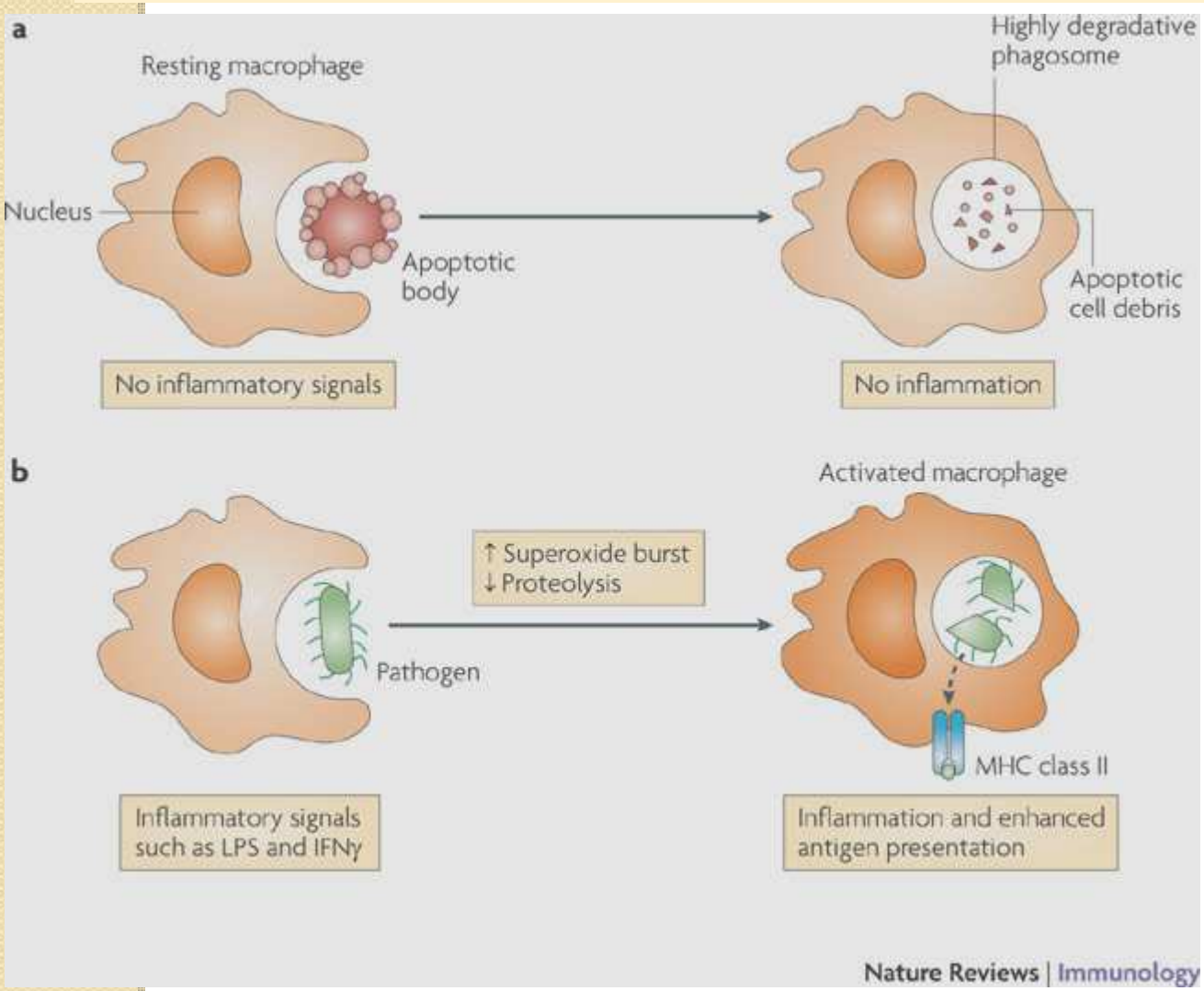
Modulación de las funciones del macrófago



Damage-Associated Molecular Patterns (DAMPs)

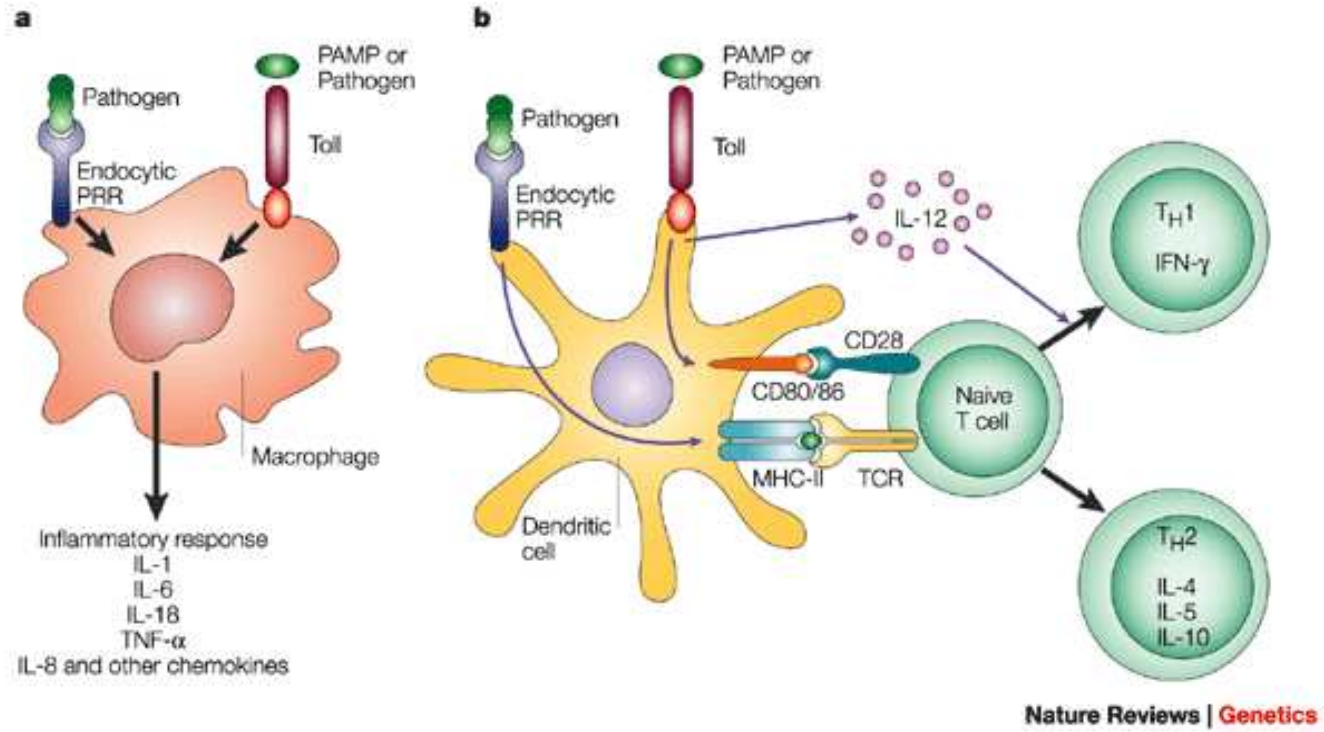
Nature Reviews Immunology 8, 279-289 (April 2008)

Modulación de las funciones del macrófago



The functions carried out by macrophages are modulated by their degree of stimulation by exogenous mediators, such as microorganism-derived Toll-like receptor (TLR) agonists, or endogenous activators, including cytokines and chemokines.

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



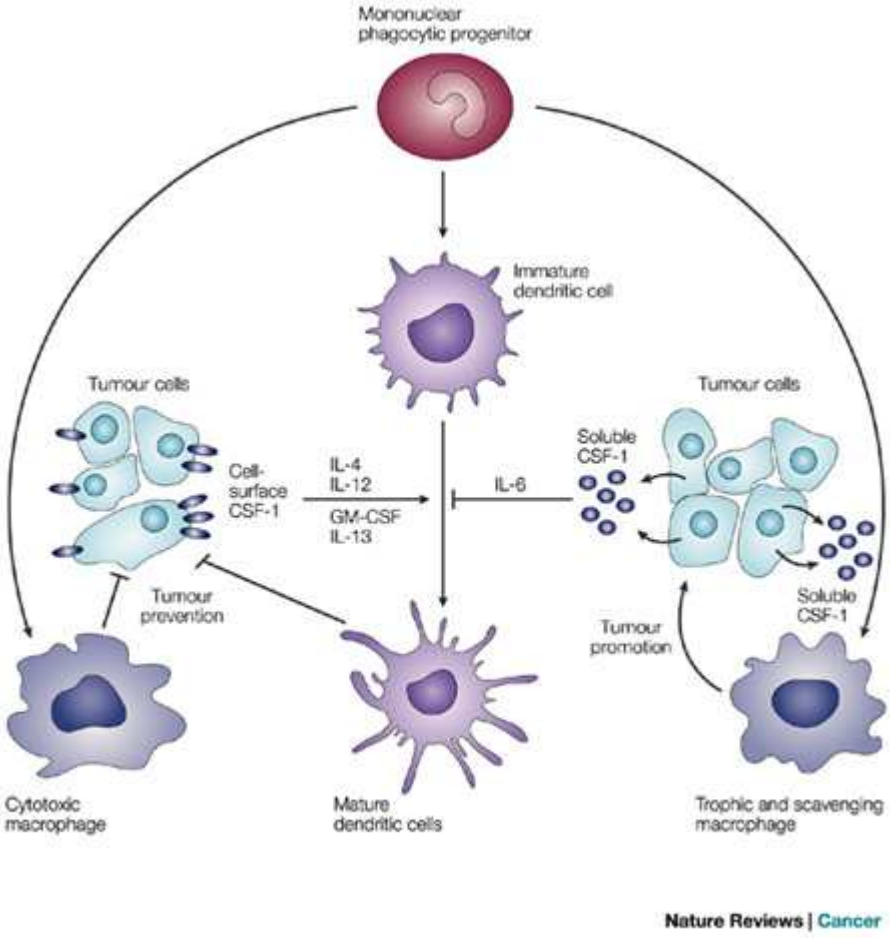
Macrophages (and neutrophils) engulf and destroy microbes after first encounter and — together with natural killer (NK) cells — secrete cytokines that orchestrate innate and adaptive immunity (panel a). The dendritic cells (DCs) — specialized relatives of macrophages — present antigens to LYMPHOCYTES (white blood cells) to stimulate adaptive immunity (panel b).

Nature Reviews Genetics 4, 195-205 (March 2003)

Macrófagos y tumores

Tumours are populated by macrophages and dendritic cells that are derived from mononuclear phagocytic progenitor cells.

CSF-1 presented in a transmembrane form on the tumour surface activates macrophages to kill tumour cells.



In many tumours, a high concentration of soluble colony-stimulating factor-1 (CSF-1) educates macrophages to be trophic to tumours and, together with interleukin-6 (IL-6), inhibits the maturation of dendritic cells. This creates a microenvironment that potentiates progression to metastatic tumours.

This — together with high concentrations of IL-4, IL-12, IL-13 and GM-CSF — causes dendritic cells to mature, allowing the presentation of tumour antigens to cytotoxic T cells, with the consequent rejection of the tumour.

Nature Reviews Cancer 4, 71-78 (January 2004)

CÉLULAS DENDRÍTICAS (DC)

IDENTIFICADAS EN 1868 POR PAUL LANGERHANS

DURANTE UN DETALLADO ESTUDIO ANATÓMICO

DE LA PIEL; FUERON LAS PRIMERAS CÉLULAS DEL

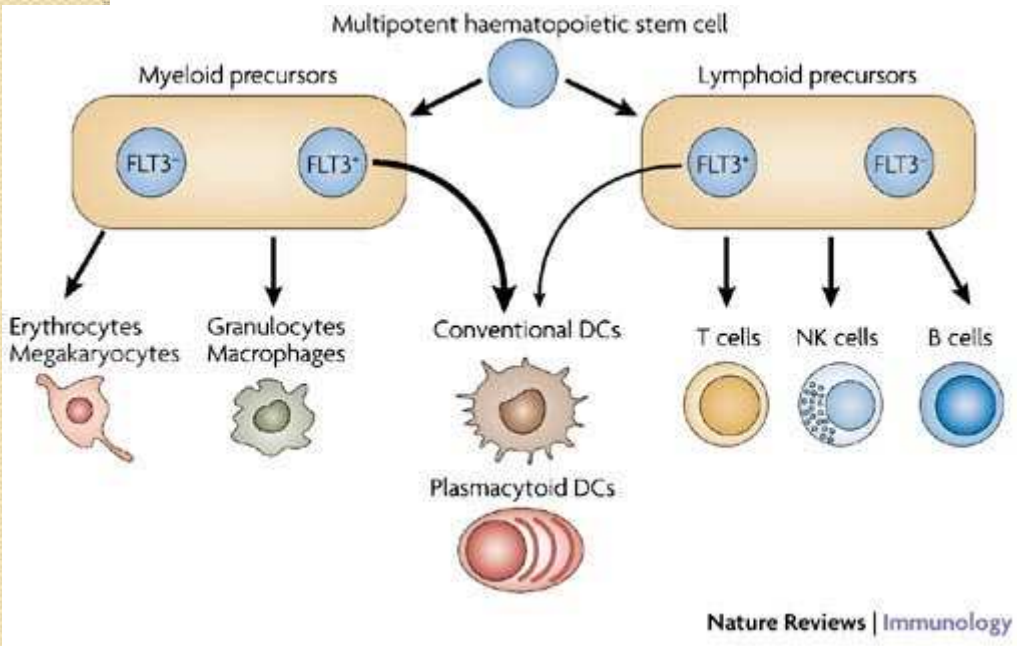
SISTEMA INMUNITARIOS EN SER DESCUBIERTAS

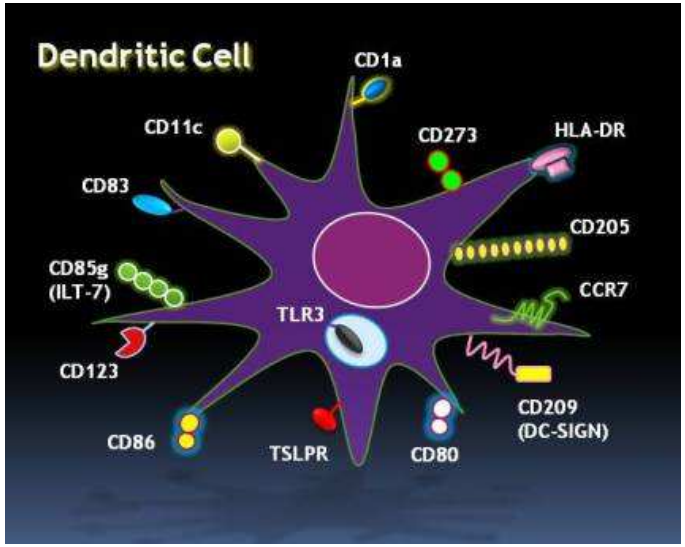
Células dendríticas

- 1.Población heterogénea
  2.Todas las DC son capaces de captar, procesar y presentar antígeno a LTnaive
- 3.Los distintos subtipos varían en:
- Localización
- Vía migratoria
- Función inmunológica
- Dependencia de infección o estímulo inflamatorio para su generación

Su origen…..

FLT-3:FMS-related tyrosine kinase 3

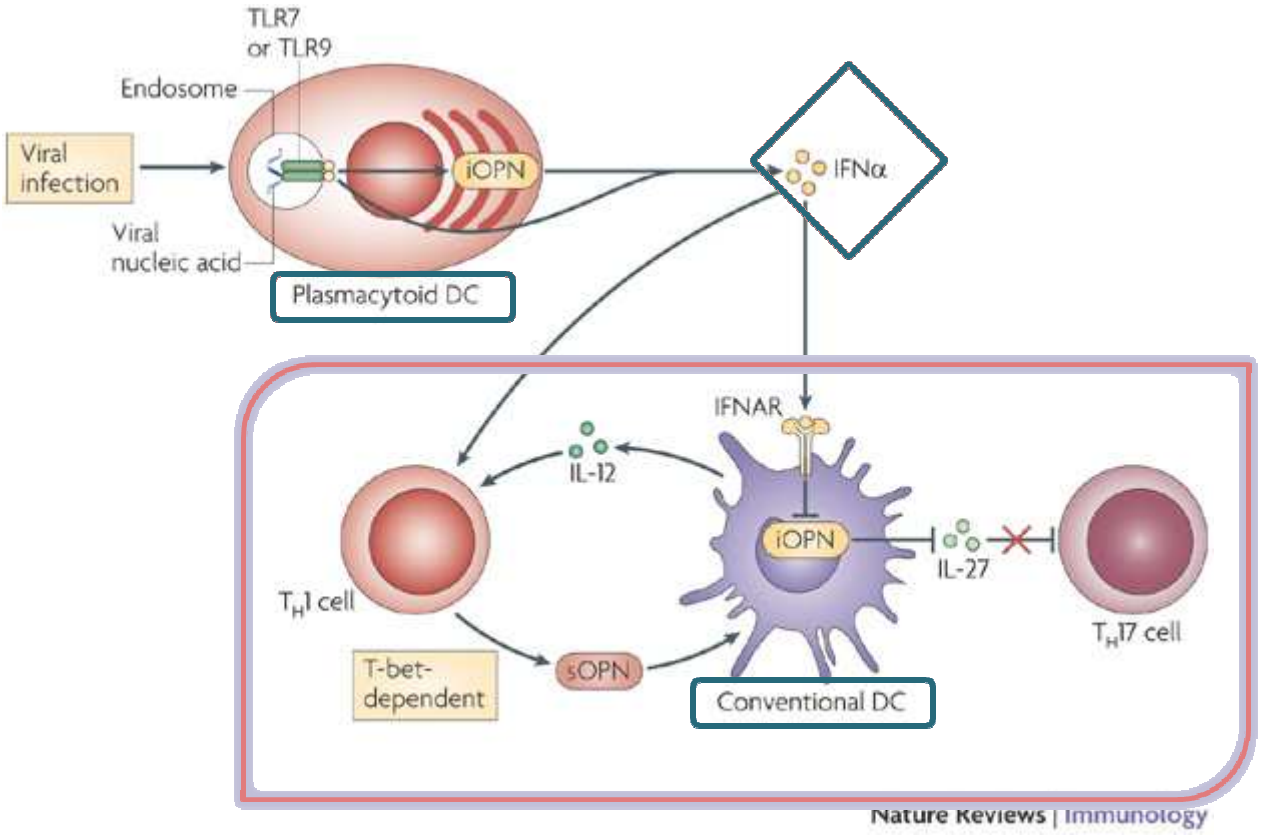




The myeloid precursors and the lymphoid precursors that express the FLT3 (FMS-related tyrosine kinase 3) receptor have the greatest capacity to form dendritic cells (DCs). Both the conventional tissue-resident DCs found in lymphoid organs and the plasmacytoid DCs can be generated from either FLT3⁺ precursor type. **Which precursor type will actually generate DCs in vivo will depend on the availability of precursors, the local environment and the tissue involved. Myeloid precursors are the main source of DCs in most circumstances.**

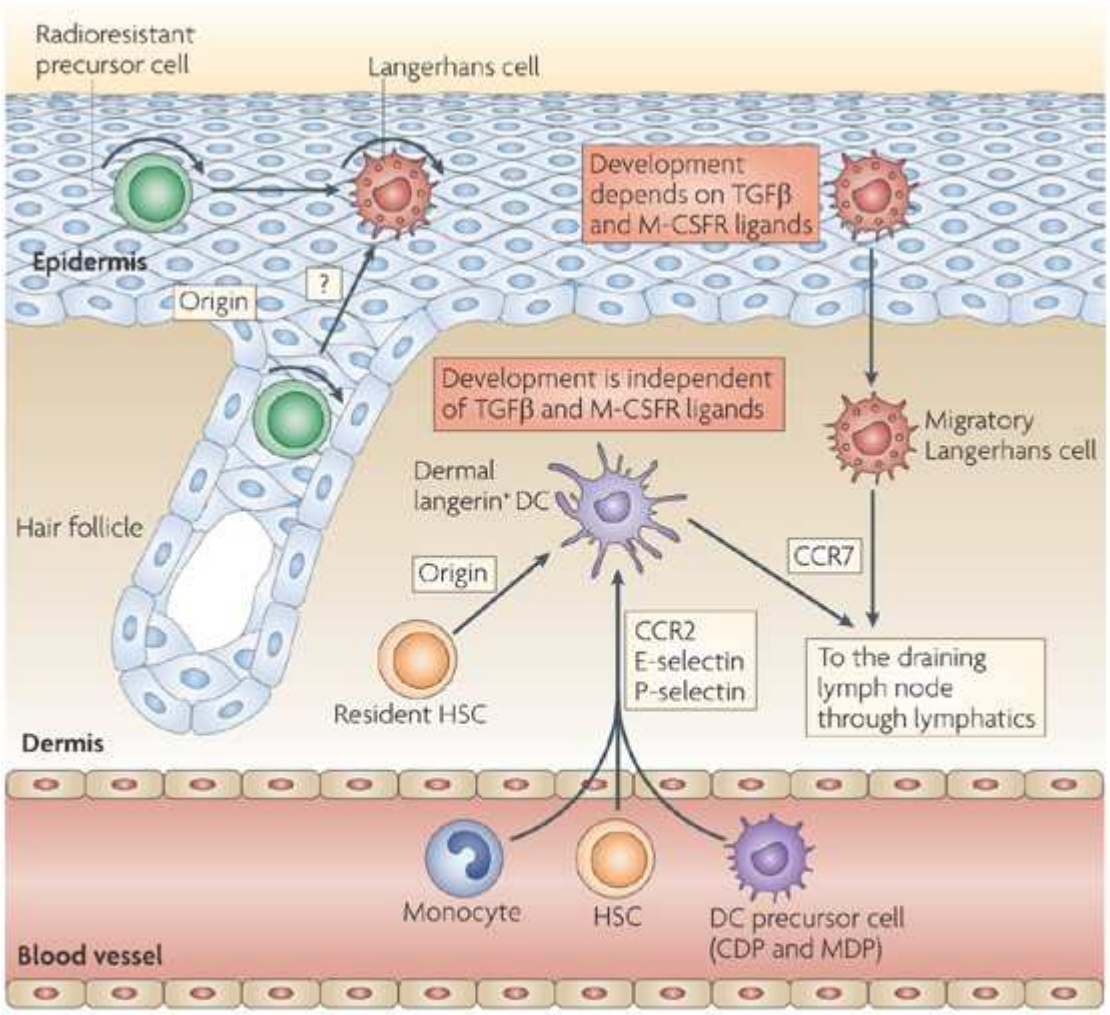
Nature Reviews Immunology 7, 19-30 (January 2007)

Células Dendríticas:
Funciones de los diferentes fenotipos



ACCIÓN COORDINADA

Células dendríticas en la piel



DC precursor (CDP) cells

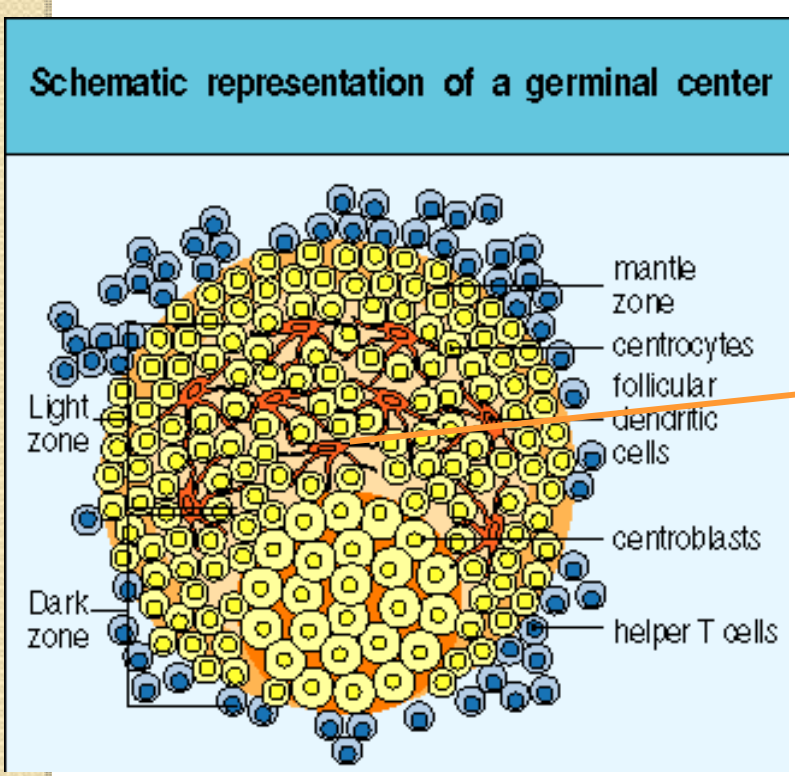
Macrophage DC precursor (MDP) cells

Nature Reviews | Immunology

Nature Reviews Immunology 8, 935-947 (December 2008)

- Langerhans cells (LCs) are derived from haematopoietic precursor cells that reside in the skin from embryonic development. LC development depends on an autocrine source of transforming growth factor-1 (TGF1) and on macrophage colony-stimulating factor receptor (M-CSFR) ligands. LCs that are lost during the steady state or after minor injuries are repopulated locally and independently of circulating precursor cells throughout the lifespan of the mouse. In lethally irradiated mice that have been reconstituted with congenic bone-marrow cells, 50% of LCs are eliminated in the first week post-transplantation and LCs repopulate locally within 3 weeks of transplantation. Some data also suggest that after exposure to ultraviolet B radiation, which affects the superficial layer of the epidermis but does not affect the dermis and the hair follicle, LCs repopulate from the follicle. Dermal langerin+ dendritic cells (DCs) differentiate from radiosensitive circulating precursor cells independently of TGF1 and M-CSFR ligands. Recruitment of blood-borne langerin+ DC precursor cells to the dermis depends on CC-chemokine receptor 2 (CCR2), E-selectin and P-selectin. The exact nature of the dermal langerin+ DC precursor cell remains to be determined. Potential precursor cells are the recently described common DC precursor (CDP) and macrophage DC precursor (MDP) cells, but also circulating monocytes and circulating haematopoietic stem cells (HSCs). LCs and dermal langerin+ DCs migrate to the skin-draining lymph node in the steady state in a CCR7-dependent manner.

Células dendríticas foliculares: Centro germinal



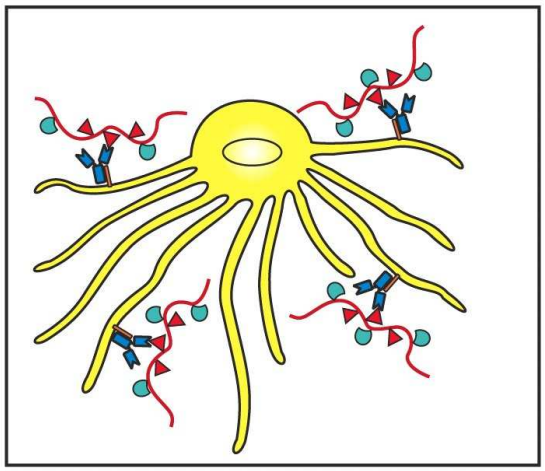
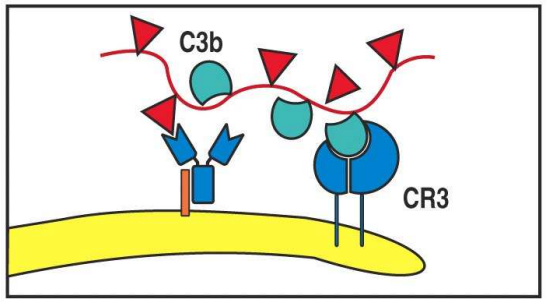


Figure 7-10 part 1 of 2 The Immune System, 2/e (© Garland Science 2005)



Follicular dendritic cells (FDCs) play a central role in controlling B-cell response maturation, isotype switching and the maintenance of B-cell memory.

Human follicular dendritic cells: function, origin and development.

Semin Immunol. 2002 Aug;14(4):251-7

They present native antigens to potential memory cells, of which only B cells with high affinity B cell receptors (BCR) can bind. These B lymphocytes survive, whereas nonbinding B cells undergo apoptotic cell death.

FDCs are present in follicles of any secondary lymphoid organ and belong to the stromal cells of these organs.

Ectopic FDC-formation can be found in a number of autoimmune diseases and/or chronic inflammatory situations. This indicates that the development of FDCs is not restricted to secondary lymphoid organs, but that it is rather a matter of local conditions that drives a precursor cell type into FDC-maturation.

A precursor of FDCs has presently not been identified, but phenotypic marker studies, in vitro experiments with fibroblast-like cell lines, and recent data on mesenchymal precursor cells from the peripheral blood suggest a close relation to fibroblast-like cells.

Follicular dendritic-like cells derived from human monocytes

Dagmar EH Heinemann and J Hinrich Peters . BMC Immunology 2005, 6:23

- **These functions are based on prolonged preservation of antigen and its presentation in its native form by FDCs. However, when entrapping entire pathogens, FDCs can turn into dangerous long-term reservoirs that may preserve viruses or prions in highly infectious form.**
- Despite various efforts, the ontogeny of FDCs has remained elusive. **They have been proposed to derive either from bone marrow stromal cells, myeloid cells or local mesenchymal precursors.** Still, differentiating FDCs from their precursors *in vitro* may allow addressing many unsolved issues associated with the (patho-) biology of these important antigen-presenting cells.
- **The aim of our study was to demonstrate that FDC-like cells can be deduced from monocytes, and to develop a protocol in order to quantitatively generate them *in vitro*.**

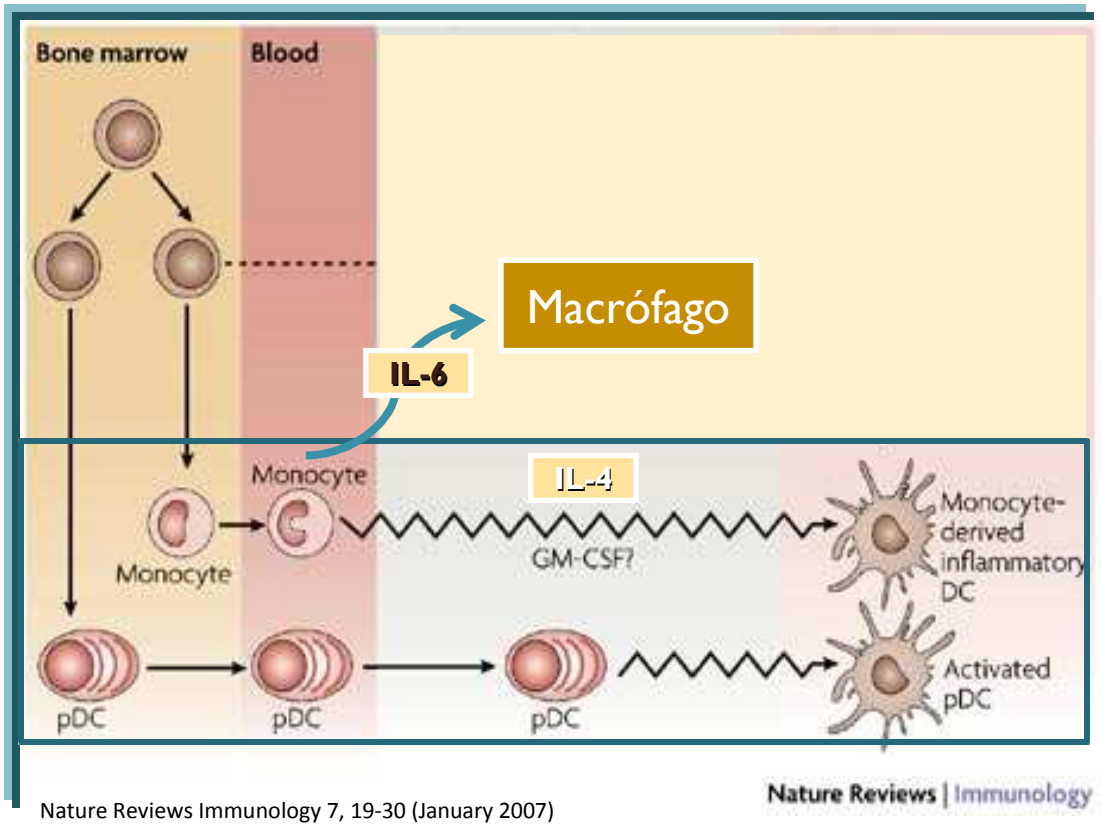
Tipos de DCs

1. **pre-DC: no presentan morfología ni función de DC, pero tras pocas divisiones, generalmente por un estímulo inflamatorio o microbiano se convierten en DC.** Ejemplos de ellas son los monocitos y pDC
2. **DC convencionales:**

- ✓ **DCs migratorias:** células de Langerhans (LC) y Dendríticas dérmicas
- ✓ **DCs tisulares:** DC tímicas y esplénicas

3. **DC inflamatorias: aparecen como consecuencia de la inflamación o estímulo microbiano; DC productoras de TNF-α e iNOs (tipDCs).** Los monocitos inflamatorios pueden transformarse en DC inflamatorias.

Pre-DCs

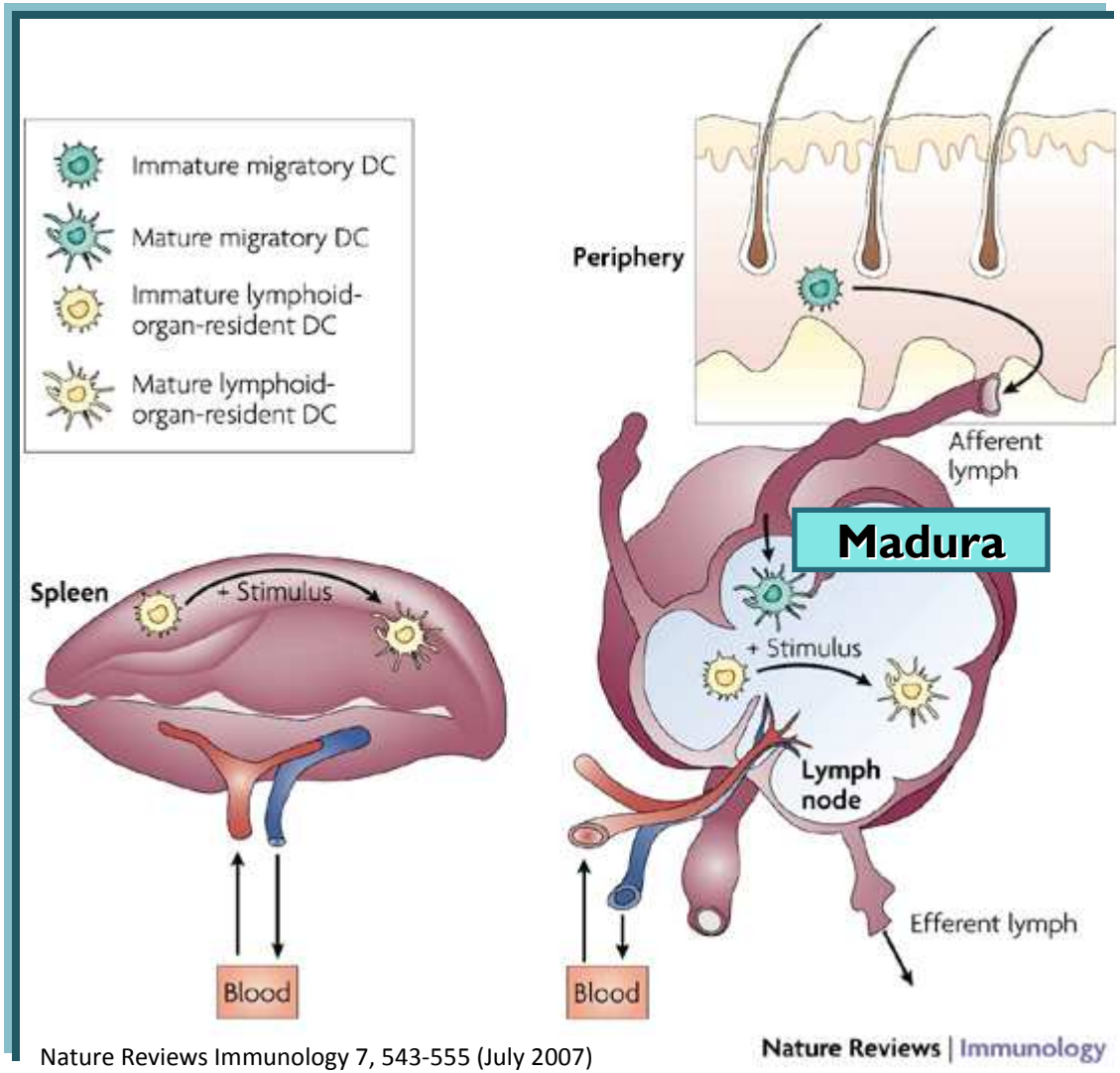


Nature Reviews Immunology 7, 19-30 (January 2007)

INF-I/II

DCs migratorias y residentes en tejidos

Resident DCs are also found in the spleen — the only DC type present here. Resident DCs develop within the lymphoid organs themselves, where they spend their entire lifespan in an immature state unless they encounter pathogen products or inflammatory signals, which cause their maturation in situ.



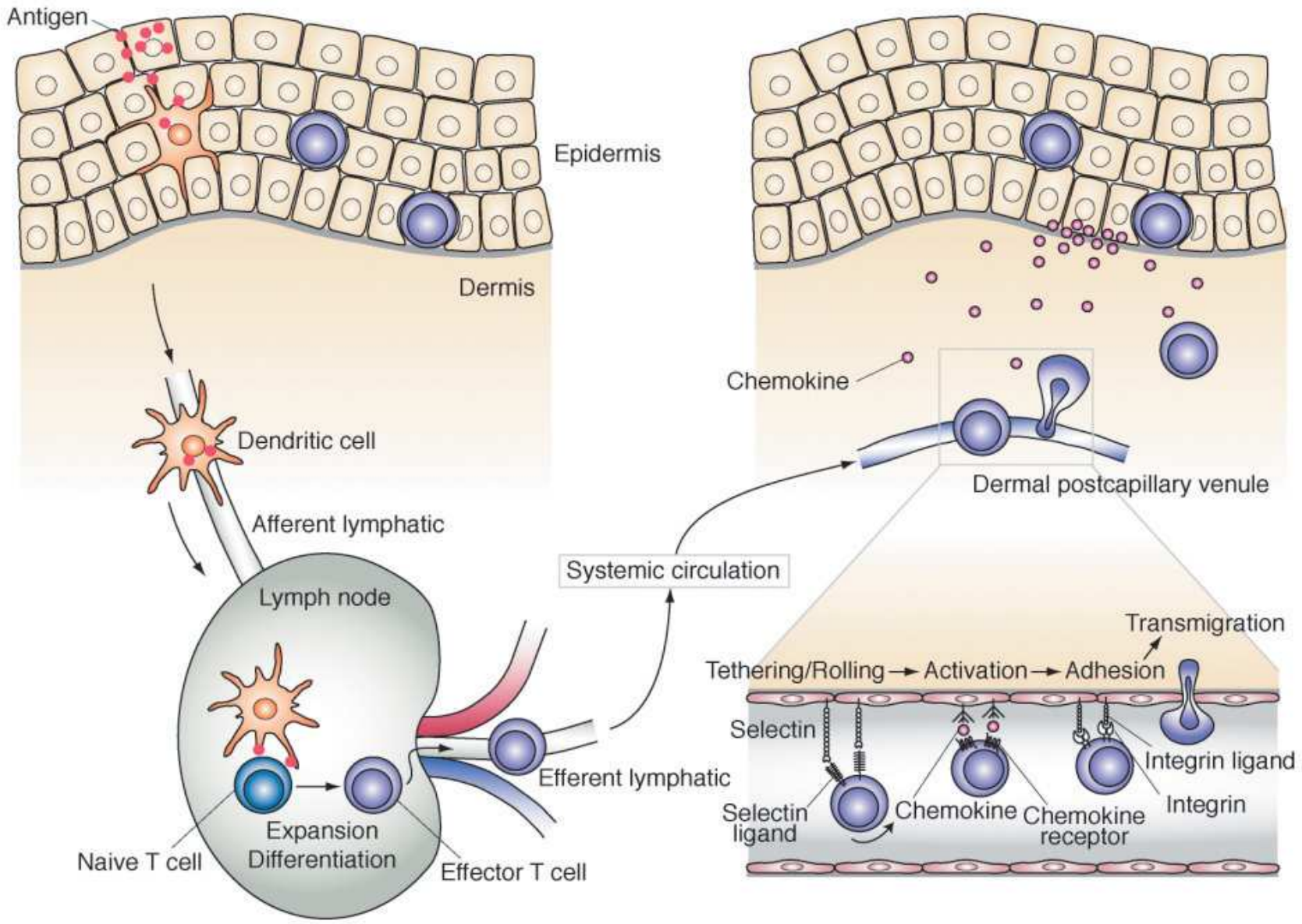
Nature Reviews Immunology 7, 543-555 (July 2007)

Células de Langerhans

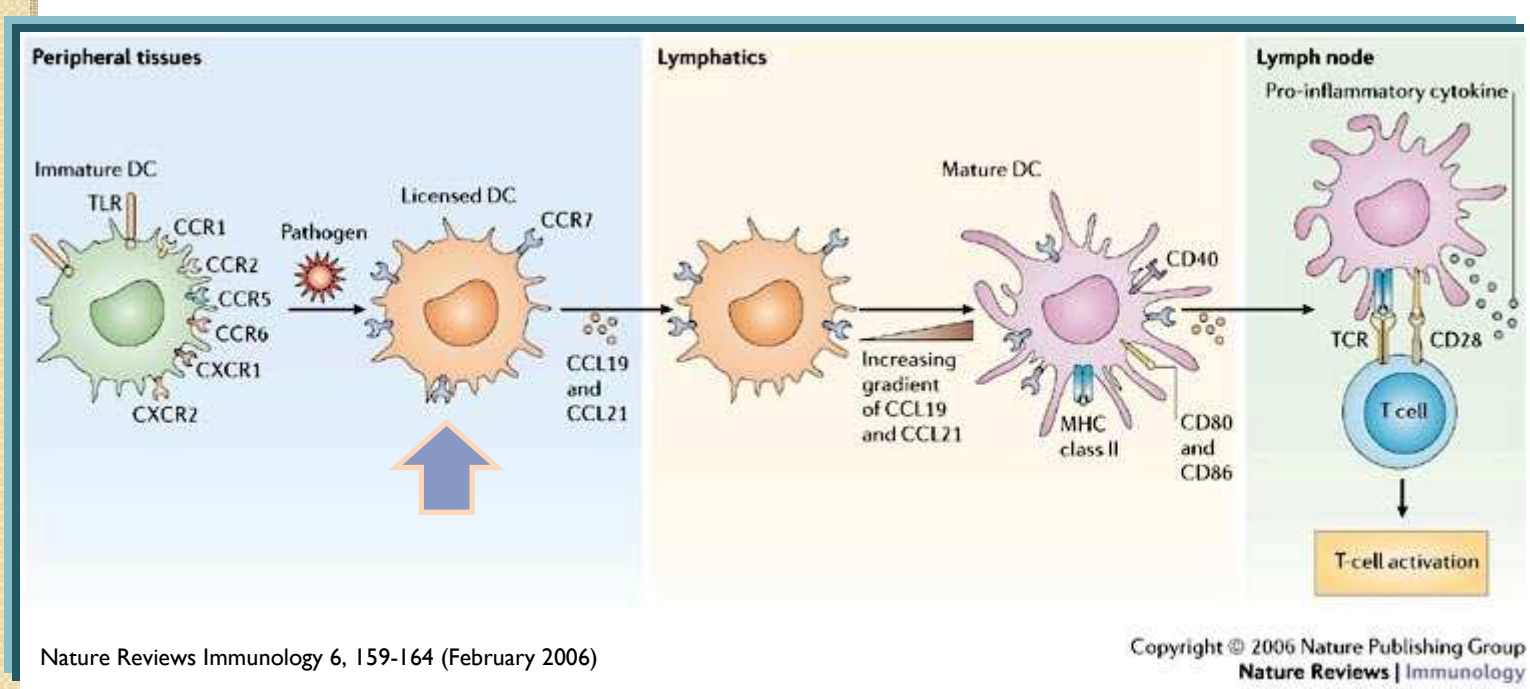
Inmadura

The migration and maturation of these DCs occur even in germ-free animals or in mice deficient in Toll-like receptor (TLR) signalling, indicating that this **process can be triggered by an inherent programme of DC differentiation or by the constant release of inflammatory compounds in the tissues.**

CÉLULAS DENDRÍTICAS: MIGRAN A LOS GANGLIOS LINFÁTICOS

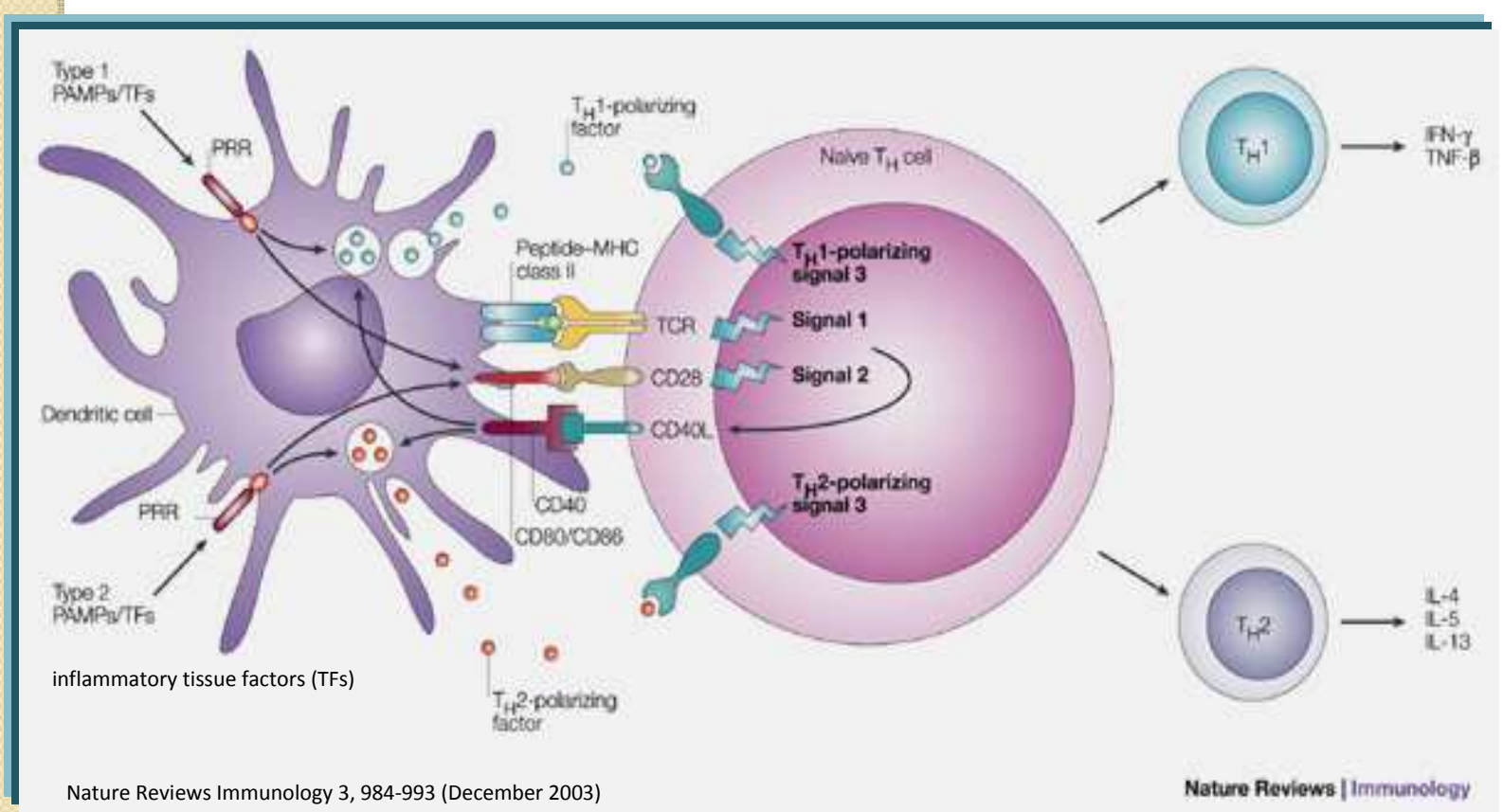


MADURACIÓN DE LA DC



Nature Reviews Immunology 6, 159-164 (February 2006)

Immature dendritic cells (DCs) express chemokine receptors that ensure their localization in peripheral tissues. Following exposure to antigen and pathogen-associated molecular patterns (PAMPs) (such as Toll-like receptor (TLR) ligands) the DCs become licensed and **undergo a maturation programme whereby they upregulate expression of CC-chemokine receptor 7 (CCR7) expression and become sensitive to the constitutively produced lymphoid-associated chemokines, CC-chemokine ligand 19 (CCL19) and CCL21.** In addition to directing these licensed DCs to the draining lymphoid tissue, CCL19 and CCL21 provide further maturation signals, which complete the DC-maturation process. The resulting, fully mature, DCs localize within the T-cell regions of the lymph node and drive T-cell activation. CXCR1, CXC-chemokine receptor 1.

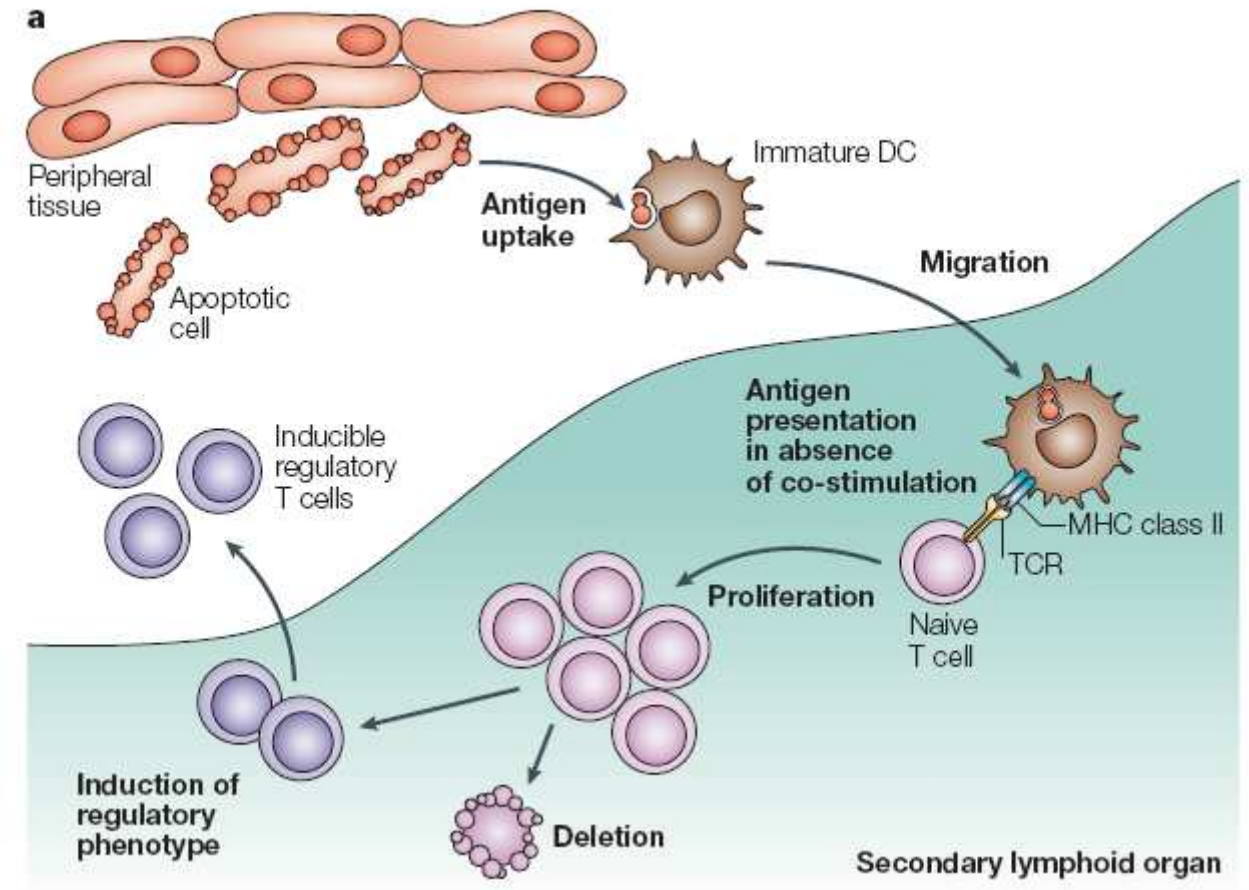


inflammatory tissue factors (TFs)

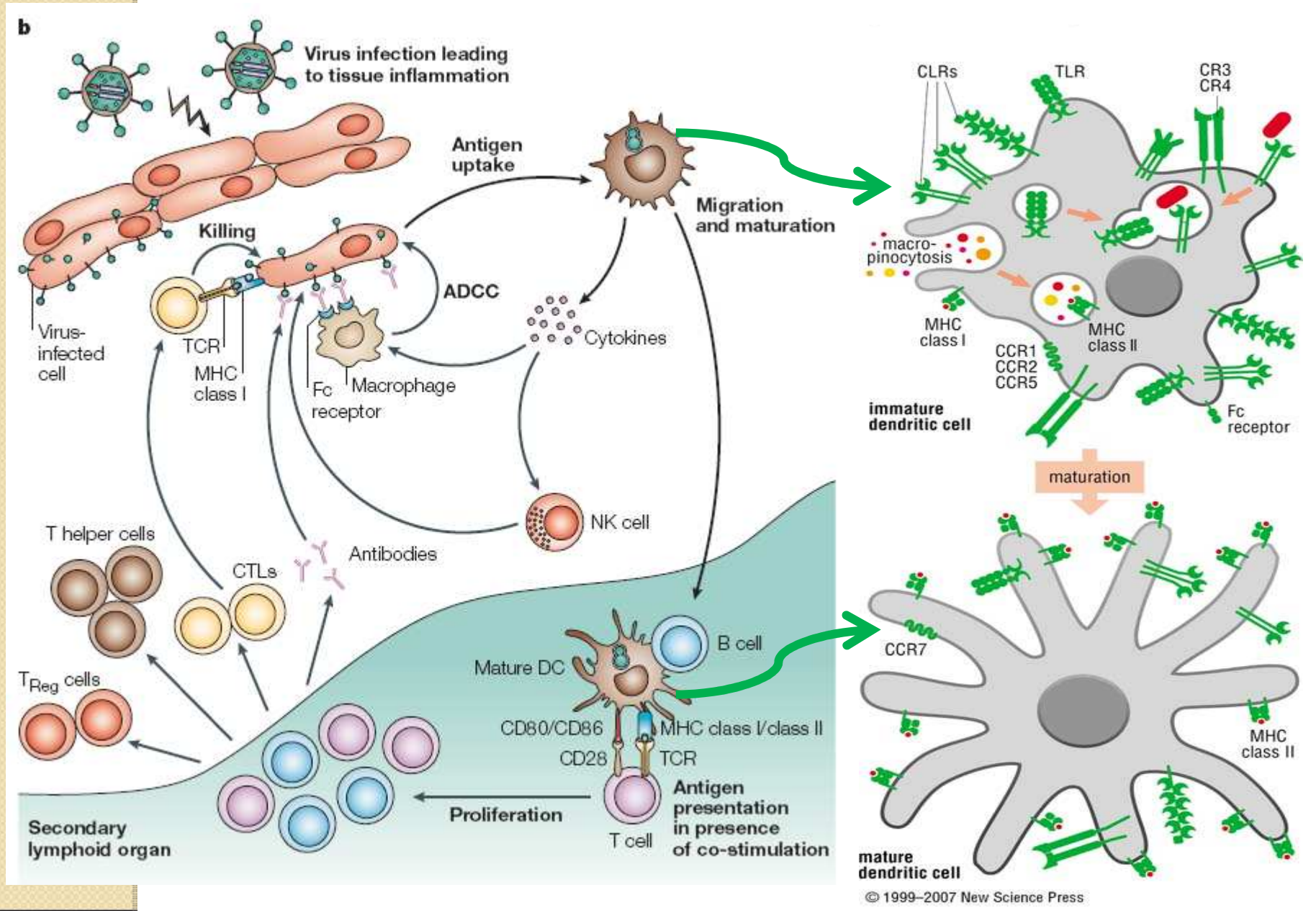
Nature Reviews Immunology 3, 984-993 (December 2003)

La maduración sólo se completa cuando la DC interacciona con el LTnaive

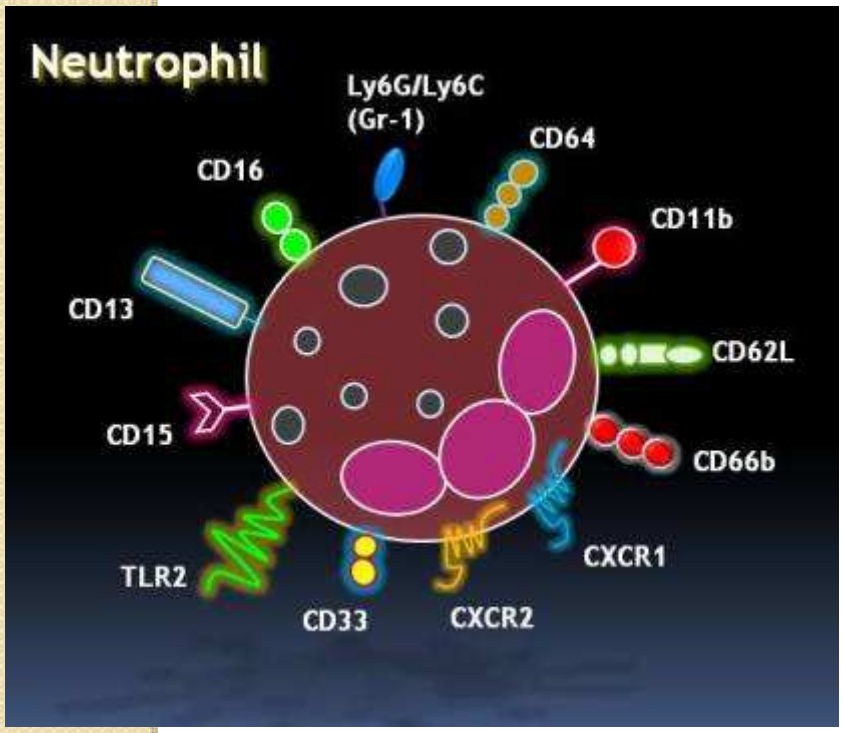
Célula Dendrítica inductora de tolerancia

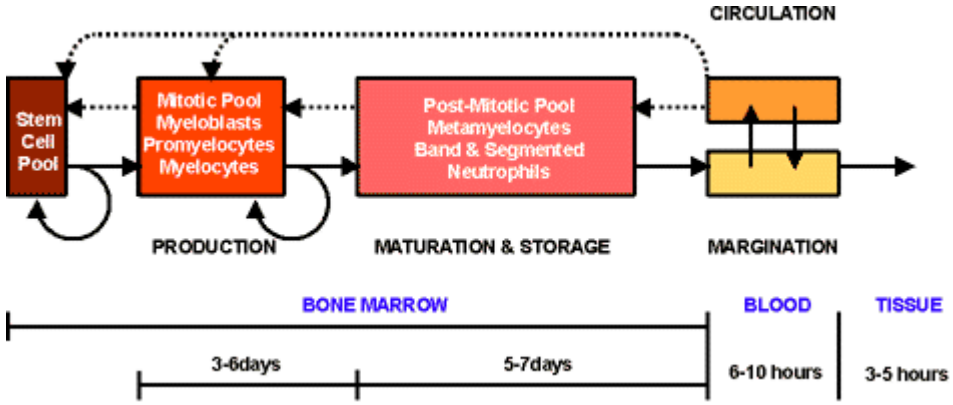


Célula Dendrítica efectora



NEUTRÓFILOS





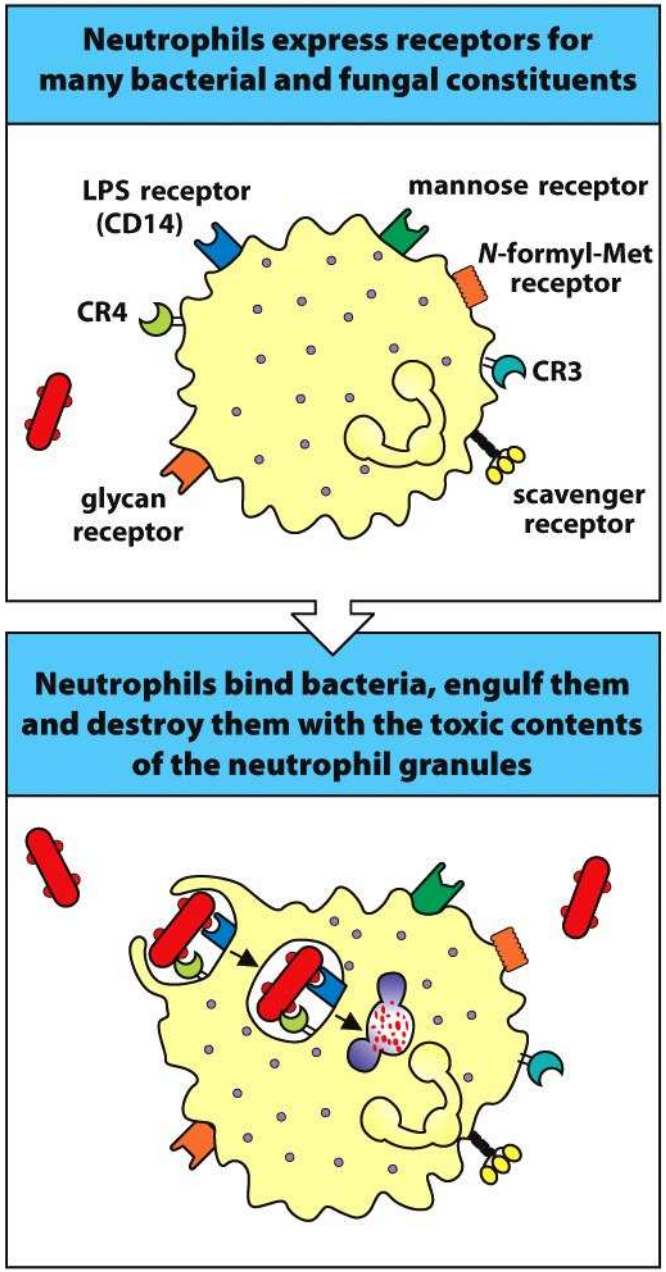
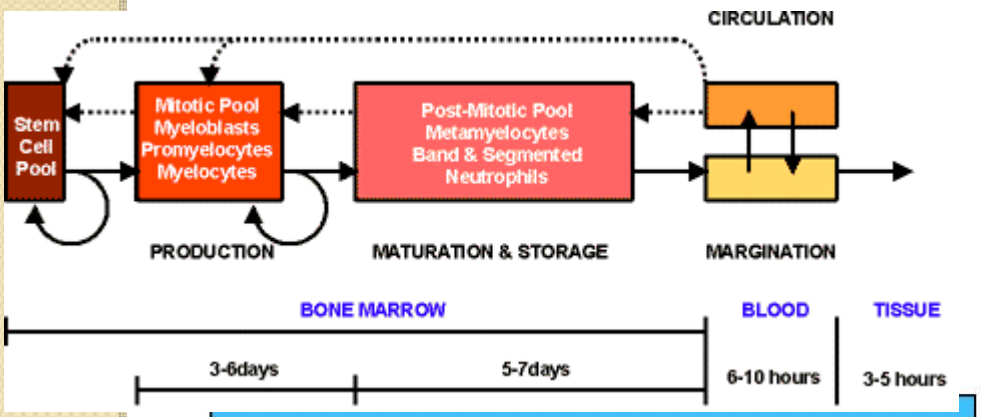


Figure 2.32 The Immune System, 3ed. (© Garland Science 2009)



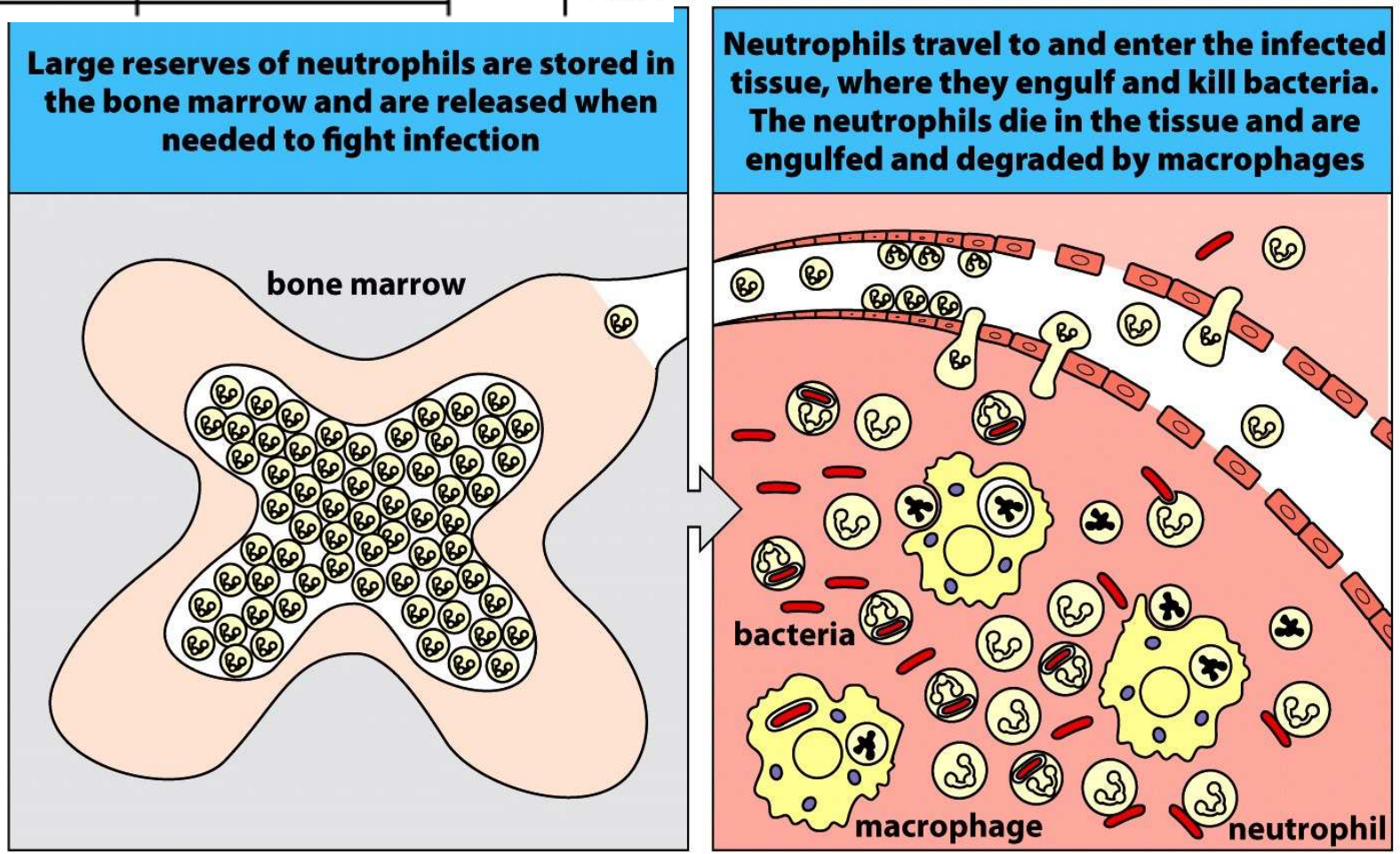


Figure 1.16 The Immune System, 3ed. (© Garland Science 2009)

RECLUTAMIENTO DE LOS LEUCOCITOS AL SITIO DE INFLAMACIÓN

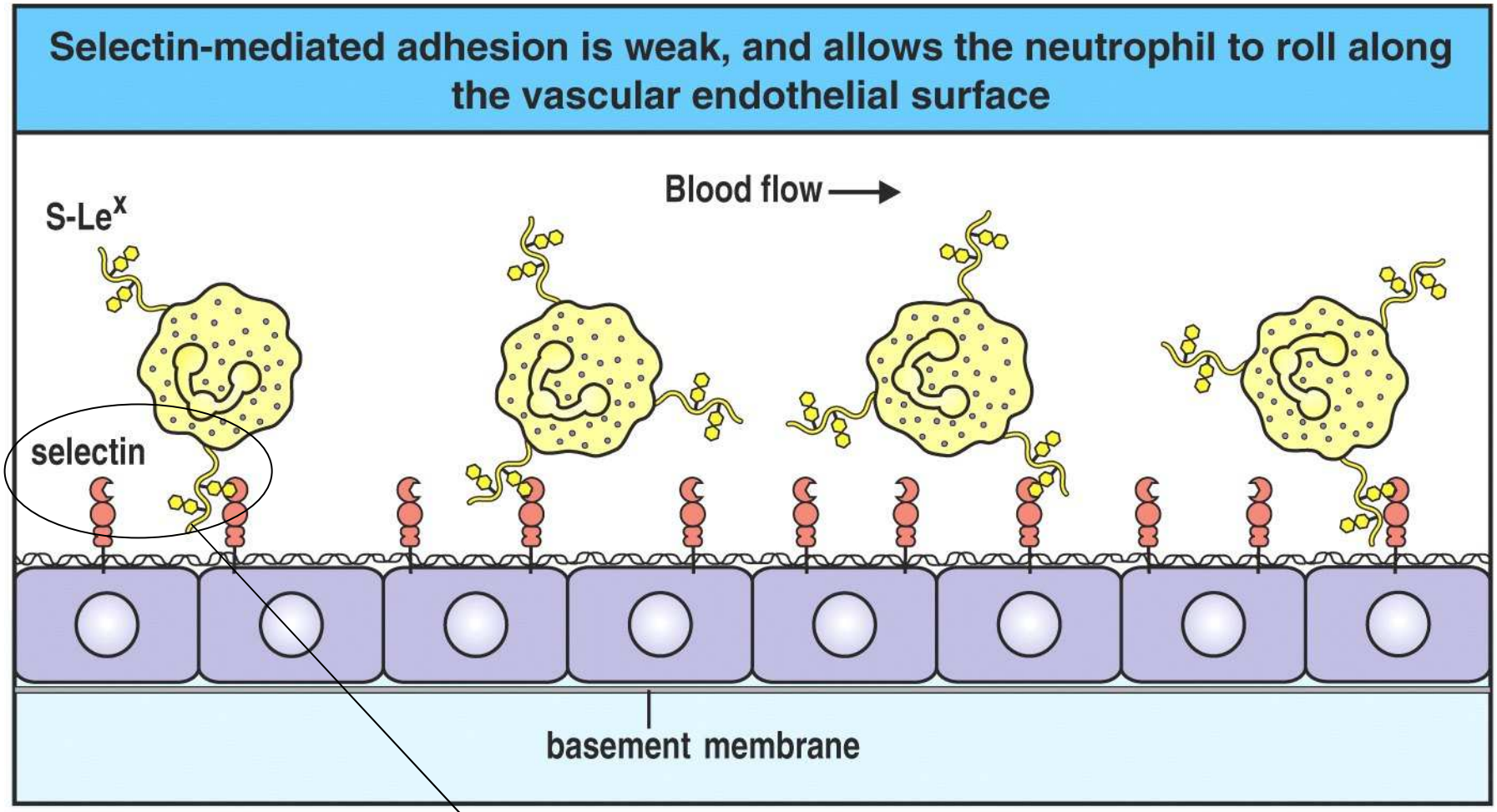


Figure 8-19 part 1 of 3 The Immune System, 2/e (© Garland Science 2005)

Importante para la infiltración de los tejidos en la inflamación

RECLUTAMIENTO DE LOS LEUCOCITOS AL SITIO DE INFLAMACIÓN

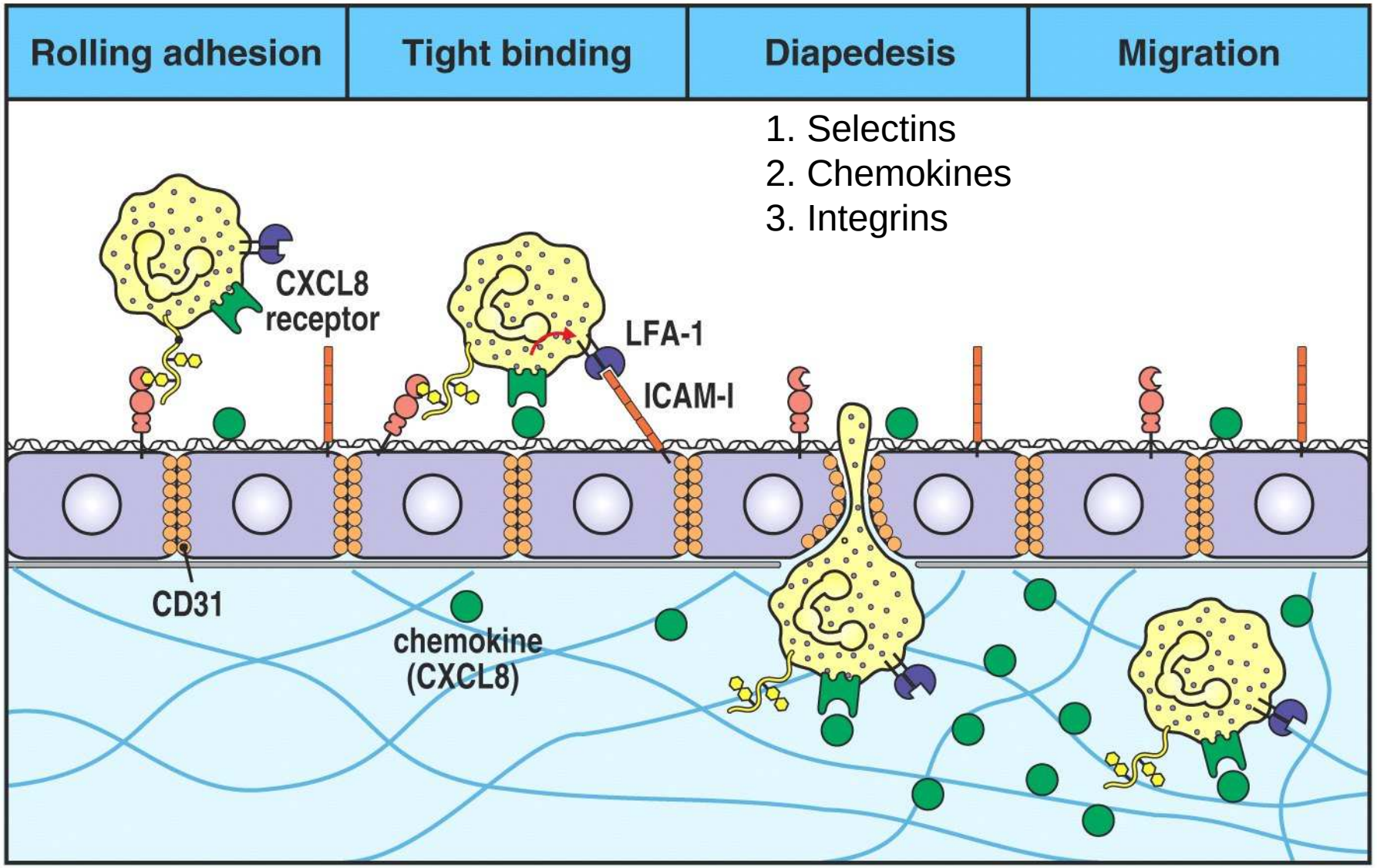


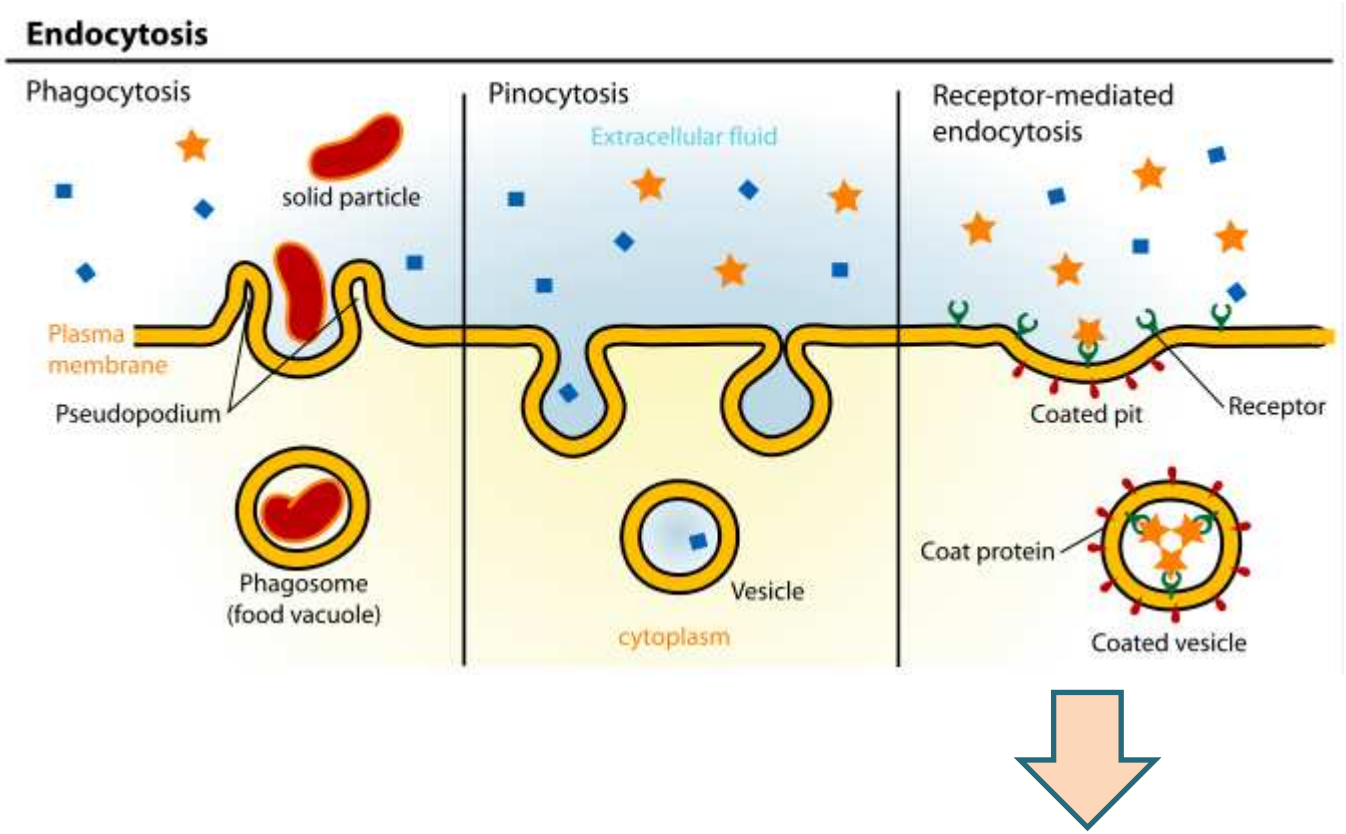
Figure 8-19 part 2 of 3 The Immune System, 2/e (© Garland Science 2005)

Fagocitosis

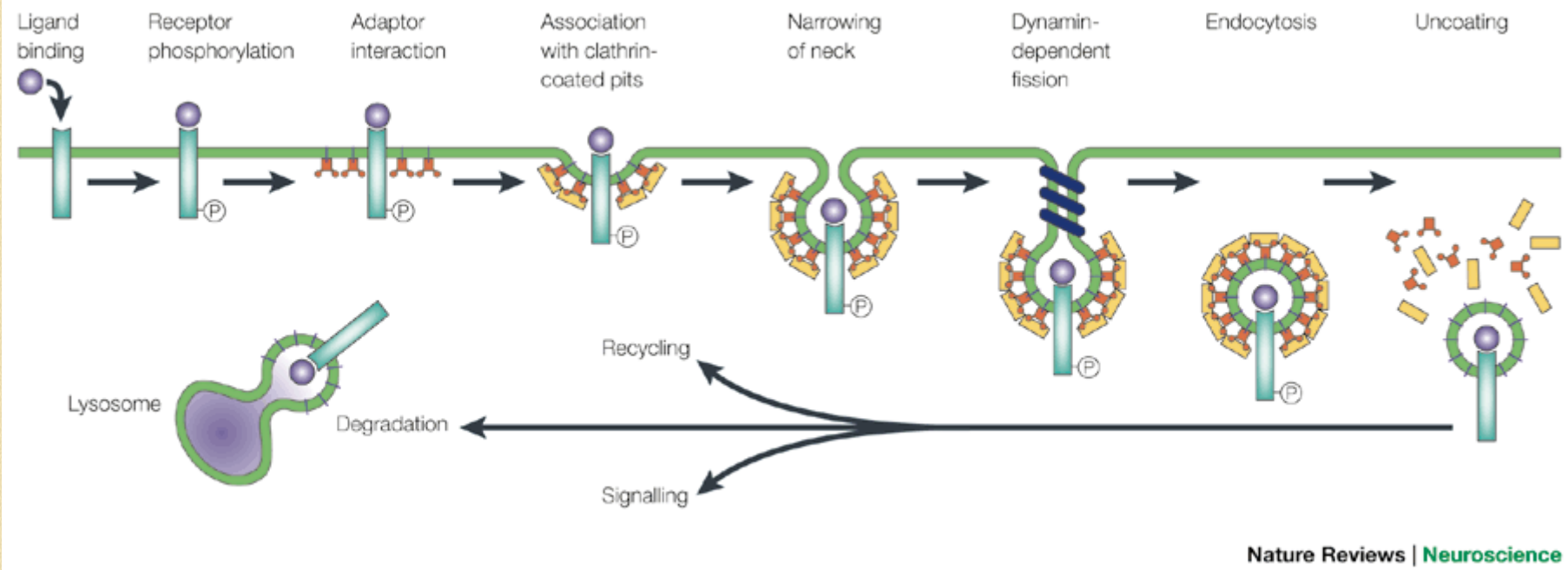
- Función por la cual células especializadas buscan, localizan, identifican e introducen a su citoplasma partículas o gérmenes extraños para matarlos y digerirlos

- Llevada a cabo por fagocitos:
  - **Macrófagos**
  - Granulocitos (**PMN**, eosinófilos, basófilos)

Endocitosis

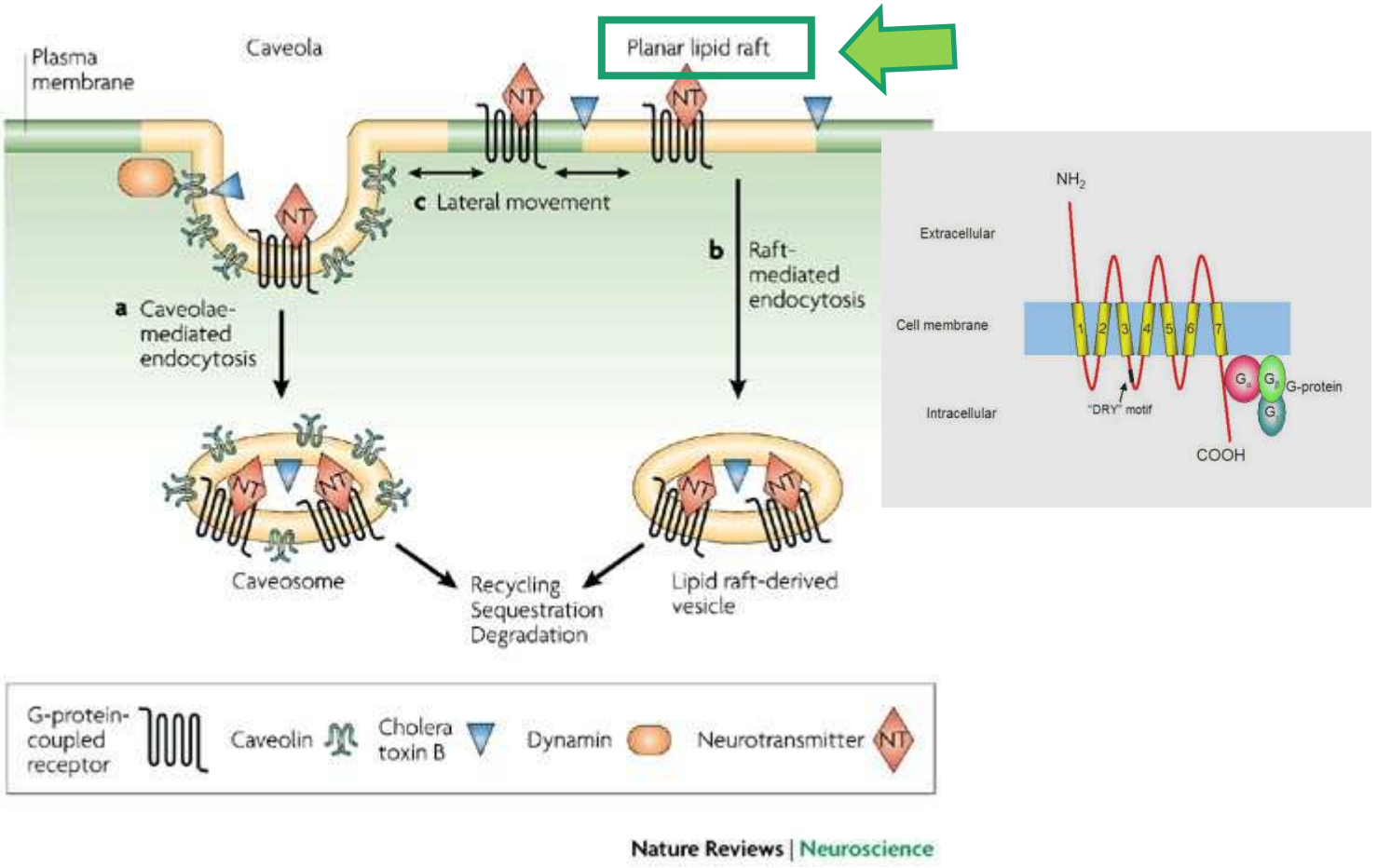


Endocitosis de receptores mediada por clatrina



Nature Reviews Neuroscience 2, 315-324 (May 2001)

Endocitosis de receptores de neurotransmisores

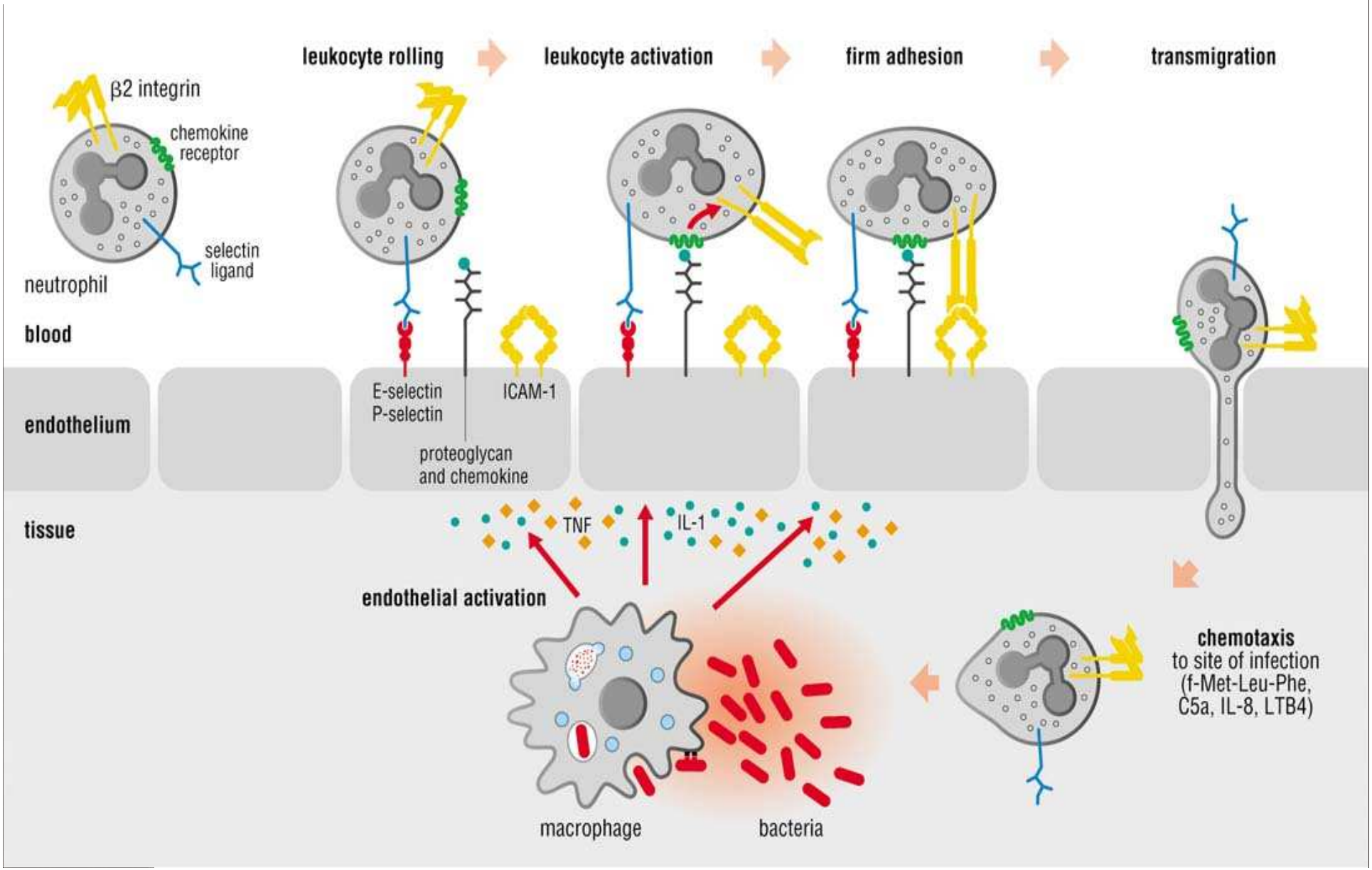


Nature Reviews Neuroscience 8, 128-140 (February 2007)

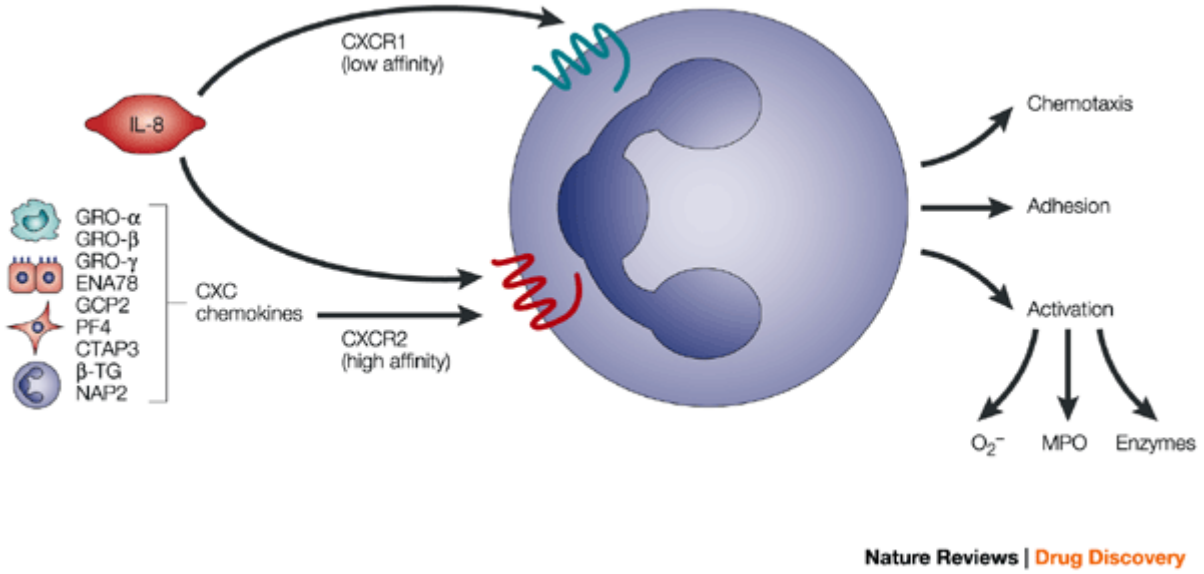
Fagocitosis

- Proceso
  - Búsqueda del antígeno
  - Respuesta quimiotáctica
  - Reconocimiento del antígeno
  - Ingestión
  - Degranulación
  - Muerte y digestión del antígeno

Búsqueda del antígeno y respuesta quimiotáctica



Respuesta quimiotáctica

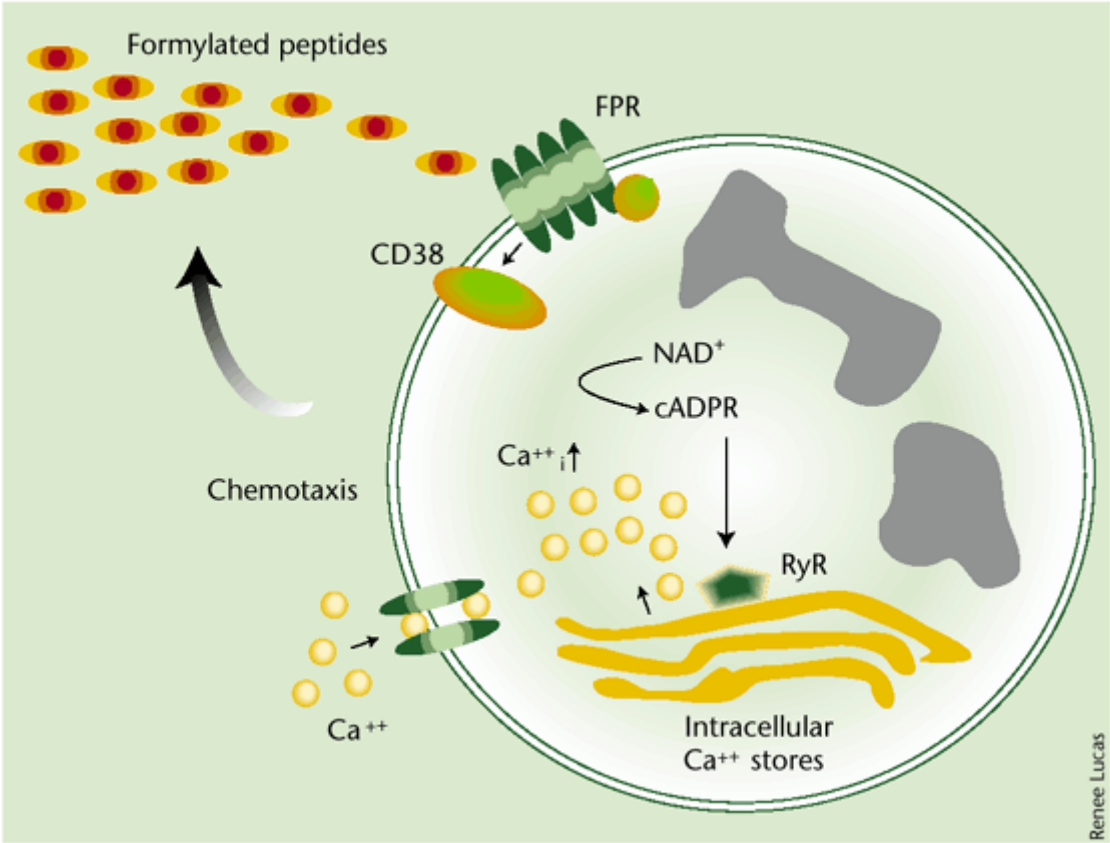


Nature Reviews Drug Discovery **1**; 437-446 (2002);

Interleukin-8 (IL-8) activates both the low-affinity chemokine receptor CXCR1, which mediates neutrophil activation, and the high-affinity receptor CXCR2, which mediates chemotaxis. CXCR2 is also activated by other CXC-chemokines that might also be involved in COPD. CTAP3, connective tissue-activating peptide III; ENA, epithelial neutrophil-activating protein; GCP2, granulocyte chemotactic protein 2; GRO, growth-related oncoprotein; NAP2, neutrophil-activating peptide2; PF4, platelet factor 4; β-TG, β -thromboglobin.

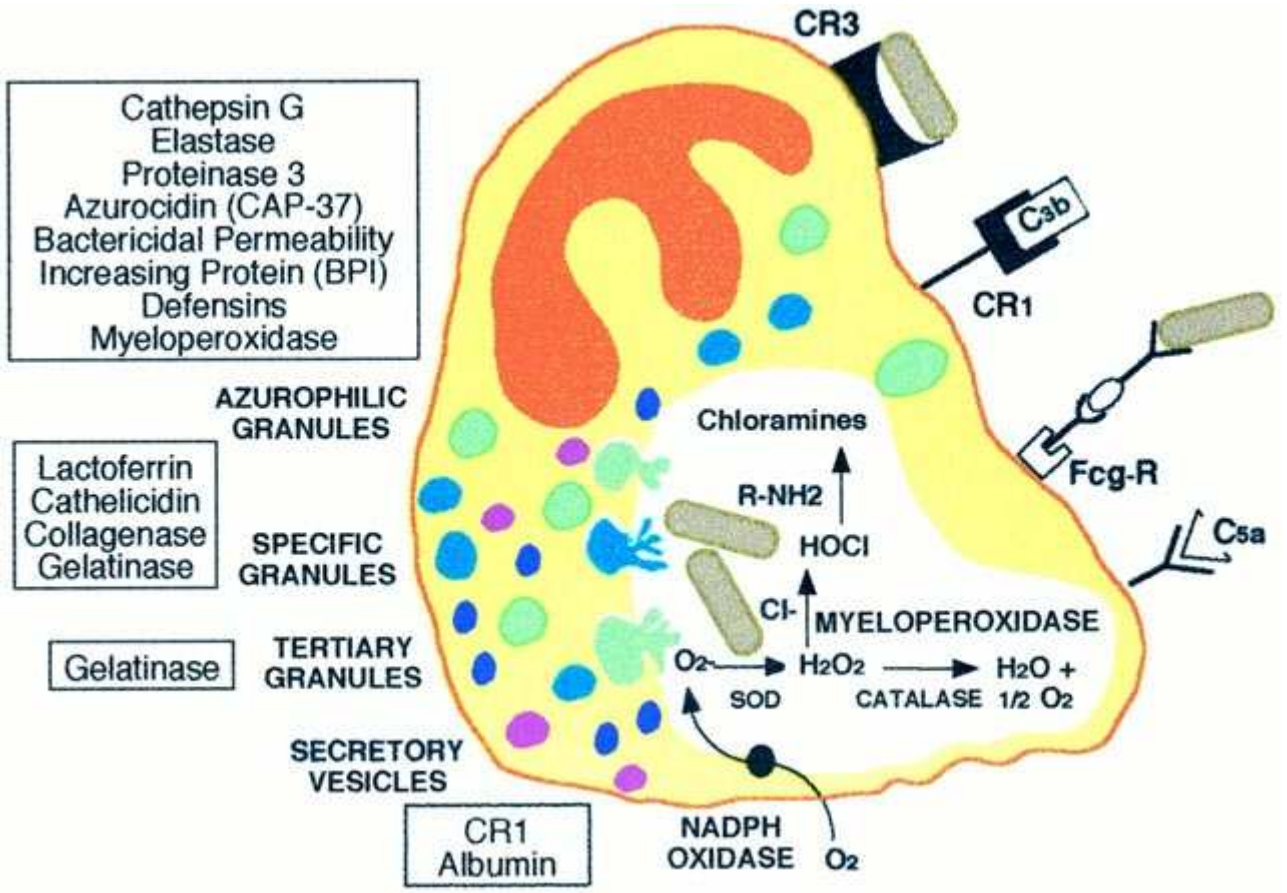
¿Cómo reconocen los neutrófilos las bacterias y se desplazan hacia el sitio de infección?????

***S. pneumoniae* releases formylated peptides which bind to FPR on a neutrophil.**
The binding activates CD38 which catalyses the transformation of NAD^+ to the active second messenger cADPR. Increase in cADPR levels inside the cell leads to the release of Ca^{++} from intracellular stores via the ryanodine receptor (RyR), which in turn increases Ca^{++} flow from the extracellular space. The sustained increase in $[Ca^{++}]_i$ is required for chemotaxis directed along the N-formylpeptide gradient to reach the site of infection.



Nature Medicine **7**, 1182 - 1184 (2001)

Reconocimiento del antígeno



Fagocitosis

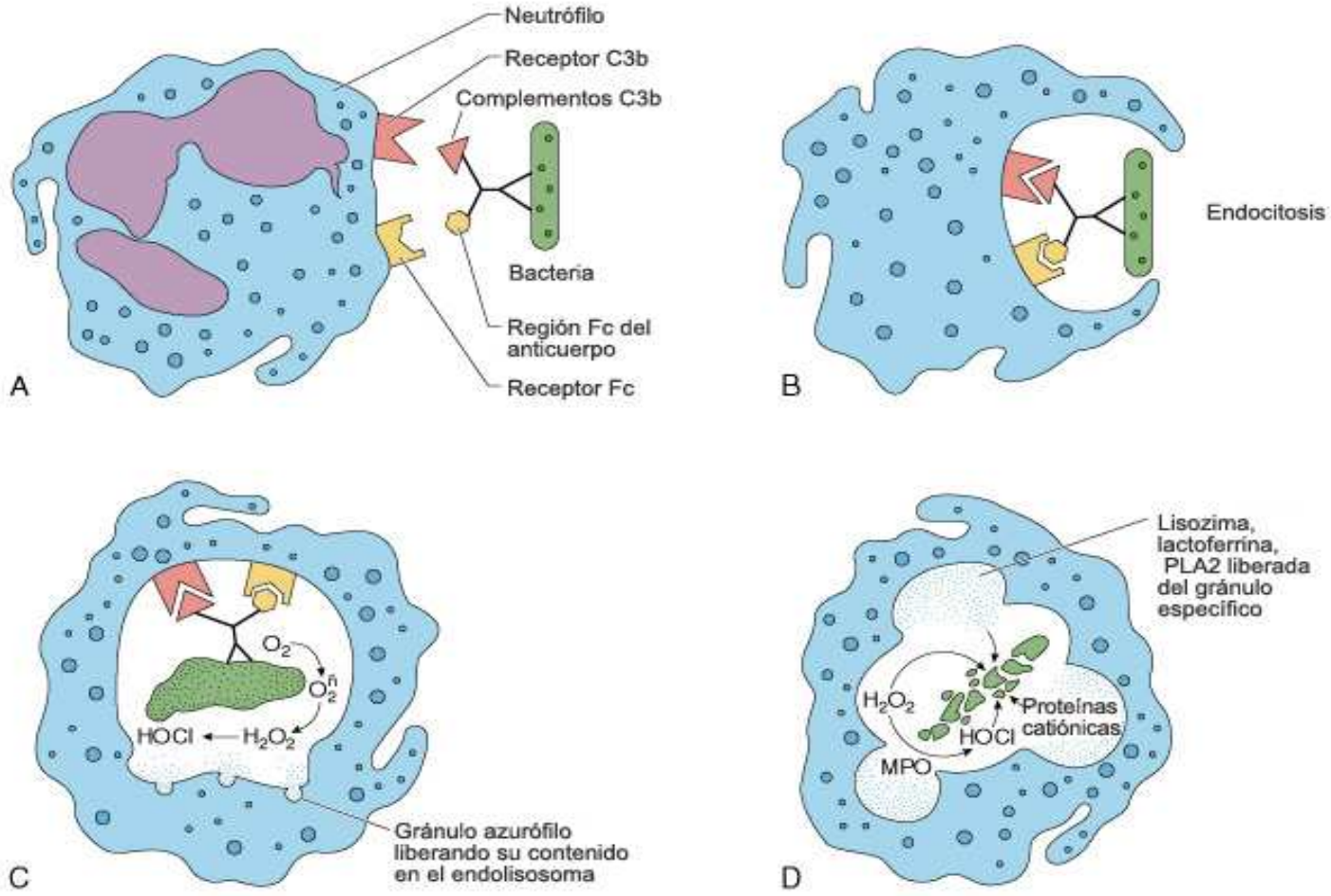


Fig. 10-7. Fagocitosis y destrucción bacterianas por un neutrófilo. O_2^-, superóxido; HOCl, ácido hipocloroso; MPO, mieloperoxidasa.

¿QUÉ OCURRE EN LOS FAGOSOMAS???????

Class of mechanism	Specific products
Acidification	pH=~3.5 – 4.0, bacteriostatic or bactericidal
Toxic oxygen-derived products	Superoxide (O_2^-), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2^{\bullet}$), hydroxyl radical ($OH^{\bullet}$), hypohalite (OCl)
Toxic nitrogen oxides	Nitric oxide (NO)
Antimicrobial peptides	Defensins and cationic proteins
Enzymes	NAPDH-dependent oxidases: generate toxic oxygen derivatives Lysozyme: dissolves cell walls of some Gram-positive bacteria Acid hydrolases: further digest bacteria
Competitors	Lactoferrin (binds Fe) and vitamin B_{12}-binding protein

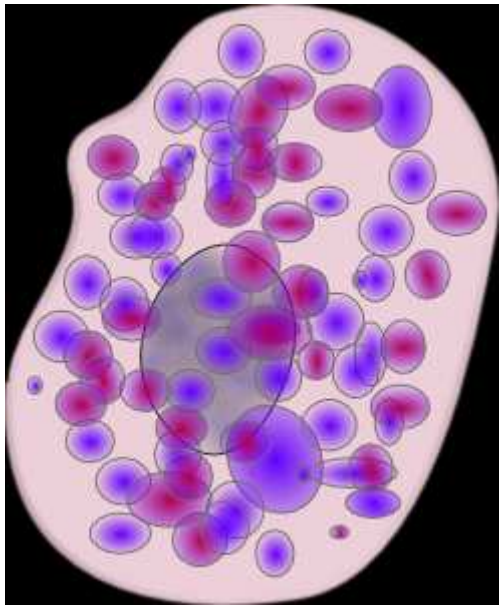
Figure 8-21 The Immune System, 2/e (© Garland Science 2005)

Fagocitosis

- **Mecanismos Citolíticos Independientes del O_2**
  - Proteínas de actividad antibiótica
  - Catepsina
  - Fagolisosoma
  - Lisozima
  - Lactoferrina

Fagocitosis

- **Mecanismos Citolíticos Dependientes del O_2**
  - Formación de Superóxido
  - Formación del Peróxido de Hidrógeno
  - Formación de radicales Hidroxílicos
  - Activación de halógenos
  - Descarboxilación de aminoácidos



BASÓFILOS Y MASTOCITOS

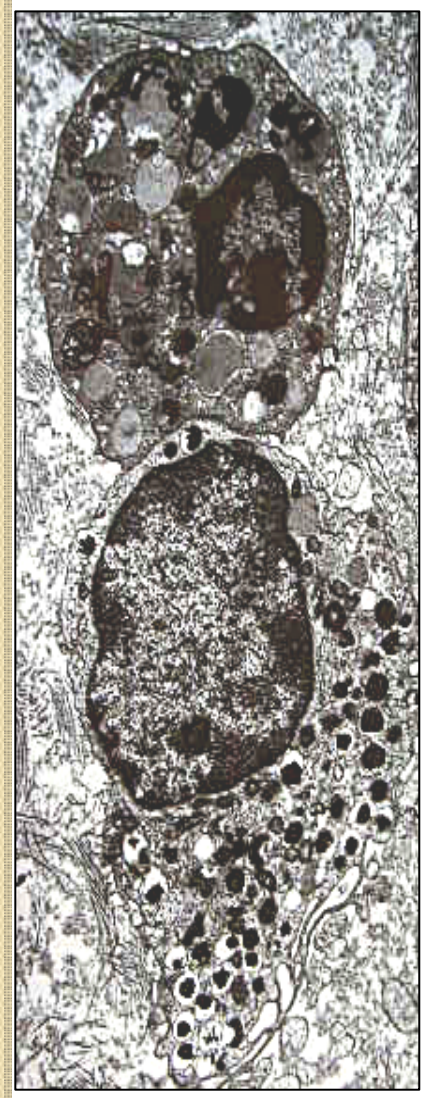
Básófilos

- Completan su maduración en la médula ósea antes de salir a circulación.
- Aumentados alrededor de los sitios de activación de las células Th.
- La vida media es de unos pocos días.
- Pueden identificarse por la presencia de marcadores como **CD200R3** (CD200 receptor 3, asociado a fagocitosis o citotoxicidad mediada por FcRγ), conocido como Ba103 y **MAR-1** (receptor de alta afinidad para IgE).
- Incrementados en enfermedades alérgicas y parasitarias.
- Presentan marcadores de activación**: CD203c and CD63.**

Mastocitos

- Salen de la médula ósea como células progenitoras y maduran en los tejidos periféricos donde residen mientras dura su vida media.
- La vida media es de semanas a meses.
- Incrementados en enfermedades fibróticas.
- Sin cambios en enfermedades alérgicas y parasitarias.

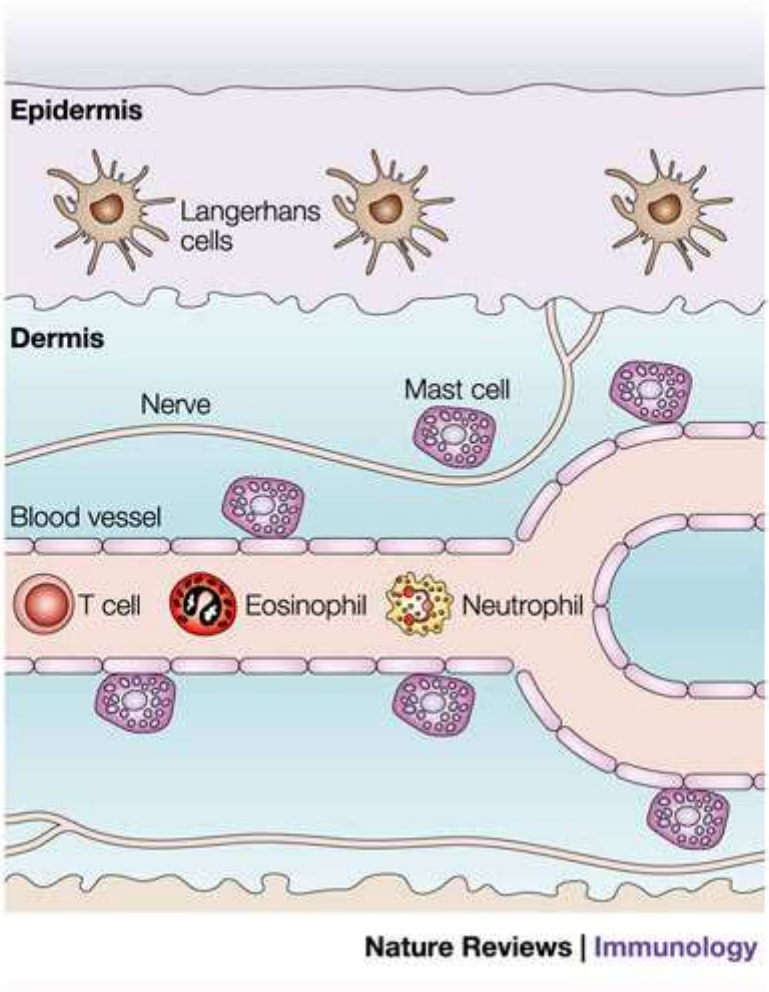
Funciones de basófilos y mastocitos



- ✓Mastocitos: Respuestas alérgicas inmediatas (célula principal de la respuesta inmediata)

- ✓Basófilos: respuesta alérgicas crónicas (célula principal de la respuesta tardía)

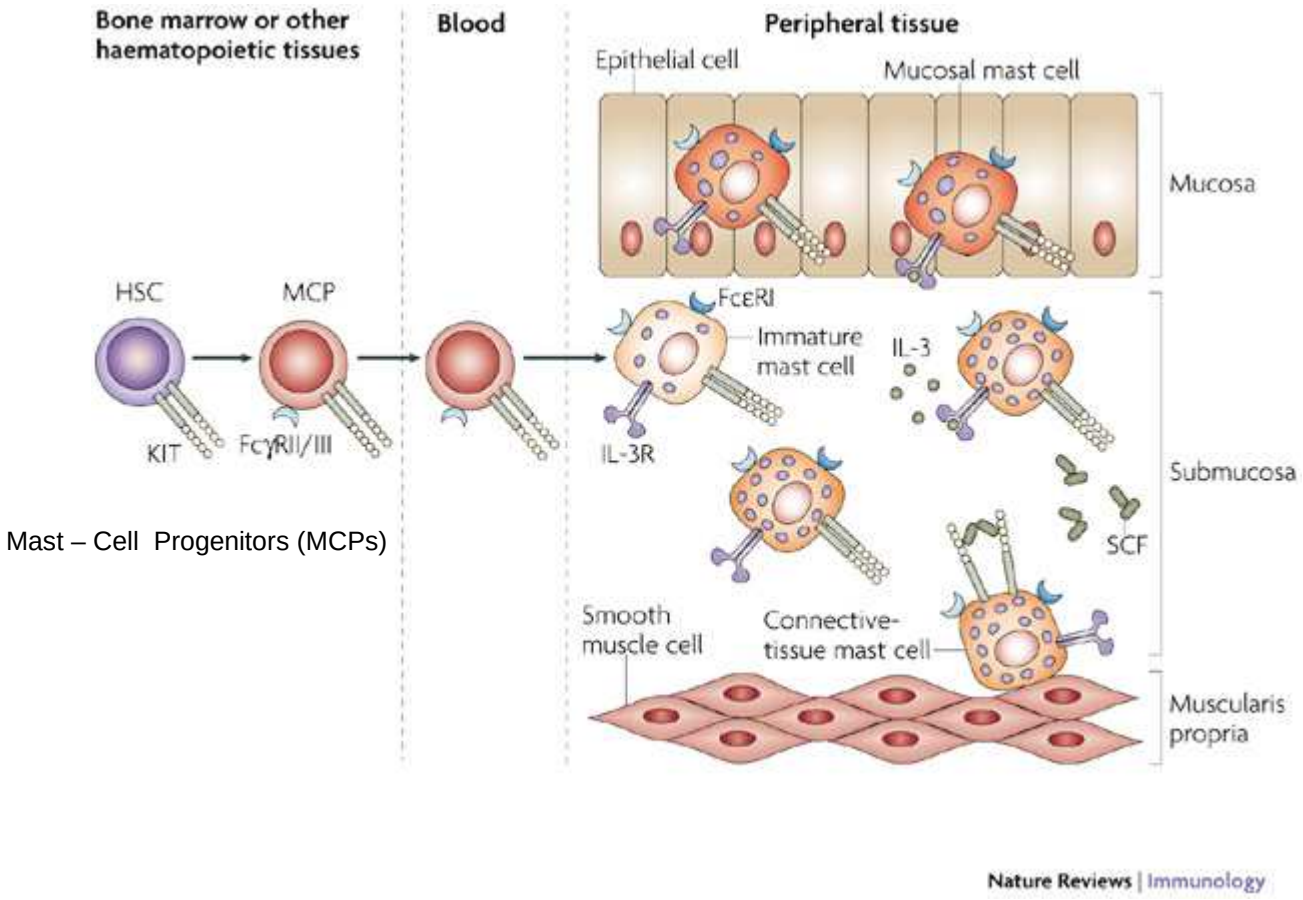
Los MASTOCITOS en acción…..



Localización estratégica

Mast cells are common at sites in the body that are exposed to the external environment, such as the skin. In these locations, they are found in close proximity to blood vessels, where they can regulate vascular permeability and effector-cell recruitment. Although they do not have direct cell–cell contact with local populations of antigen-presenting cells, such as the Langerhans cells in the skin, mast cells can modulate the behaviour of these and other neighbouring effector cells through the release of mediators.

Distribución de los mastocitos…



Mast – Cell Progenitors (MCPs)

Nature Reviews Immunology 8, 478-486 (June 2008)

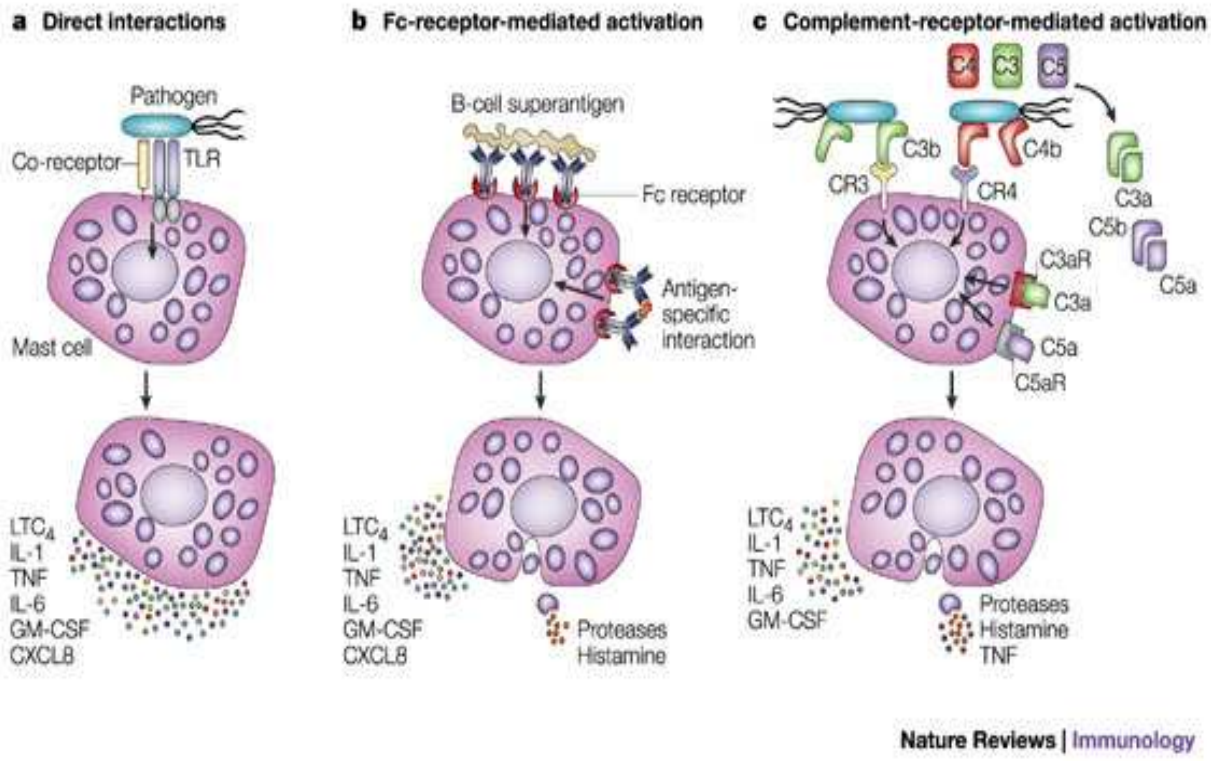
Mastocitos asociados a mucosas

- Distribución: **INTESTINO Y PULMÓN.**
- Diferenciación favorecida por IL-3 .
- Receptor Fcε: 2 x 10^5/célula.
- Tinción de los gránulos: azul y pardo.
- Ultraestructura: espiral.
- Proteasa: TRIPTASA.
- Proteoglicano: CONDROITINSULFATO.
- Liberación de HISTAMINA: +
- LTC_4:PGD_2: 25:1

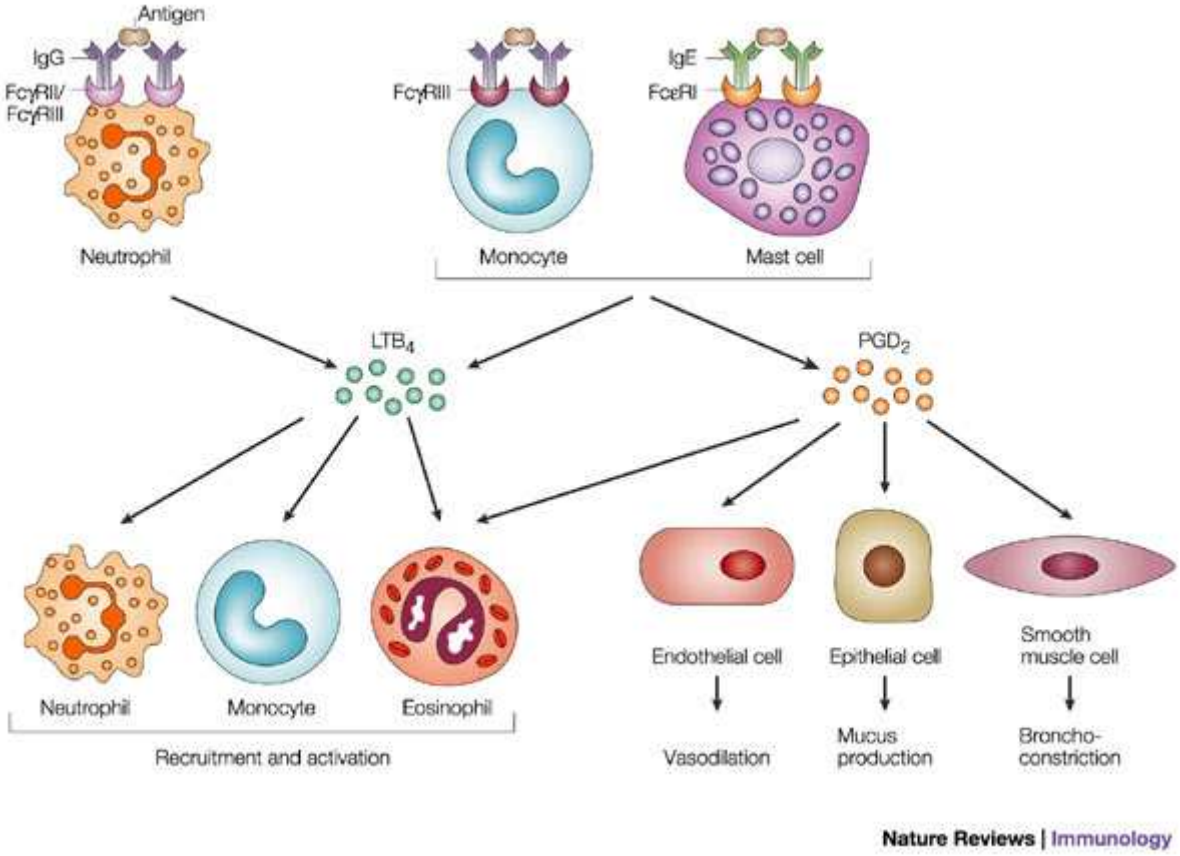
Mastocitos asociados al tejido conectivo

- Distribución: la mayoría de los tejidos **(PIEL Y SUBMUCOSA INTESTINAL).**
- Diferenciación favorecida por SCF.
- Receptor Fcε: 3 x 10^4/célula.
- Tinción de los gránulos: azul.
- Ultraestructura: reticular.
- Proteasa: TRIPTASA y QUIMASA.
- Proteoglicano: HEPARINA.
- Liberación de HISTAMINA: ++
- LTC_4:PGD_2: 1:40

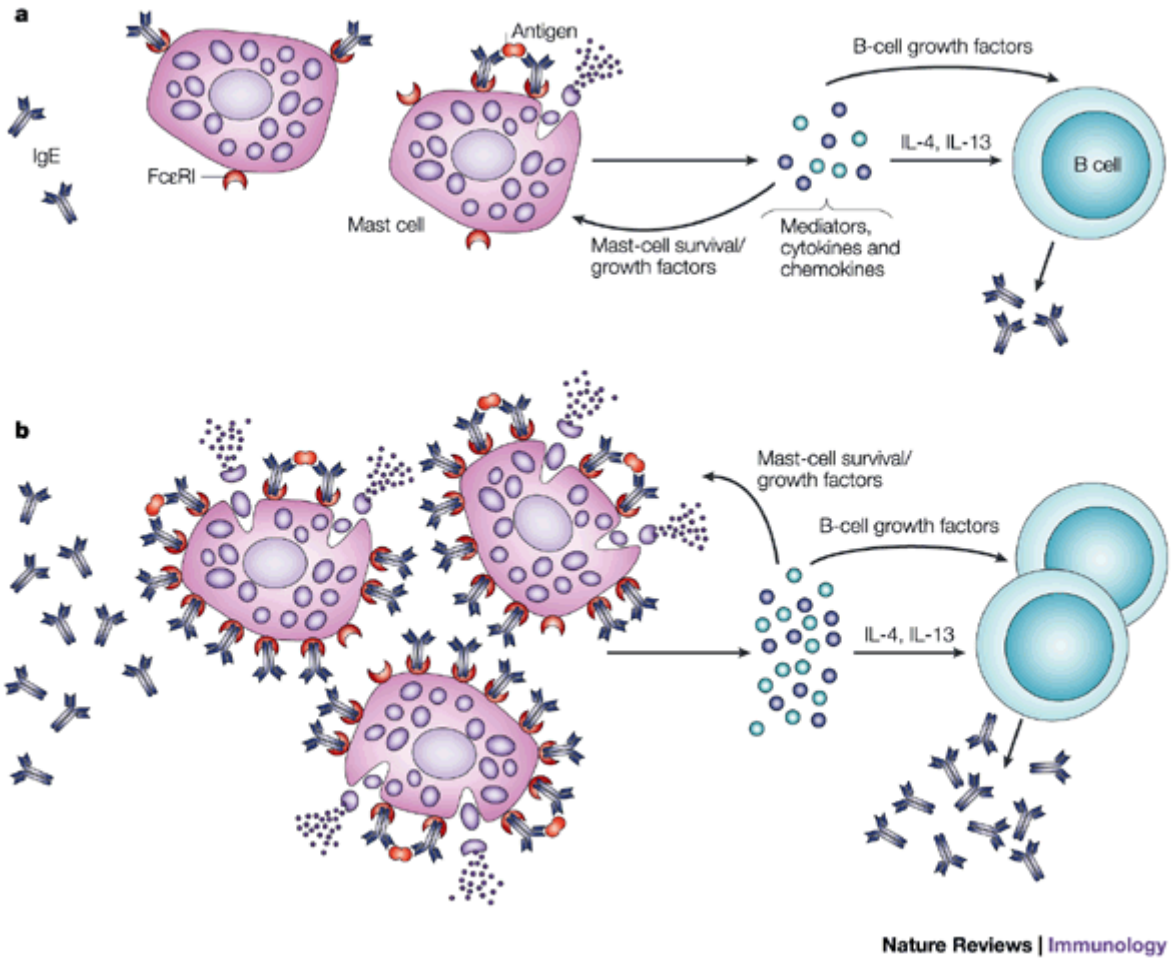
Receptores y activación....



Nature Reviews Immunology 4, 787-799 (October 2004)



Nature Reviews Immunology 4, 711-724 (September 2004)


a
IgE
FcεRI
Antigen
Mast cell
Mast-cell survival/
growth factors
Mediators,
cytokines and
chemokines
IL-4, IL-13
B-cell growth factors
B cell
b
Mast-cell survival/
growth factors
B-cell growth factors
IL-4, IL-13
Nature Reviews | Immunology

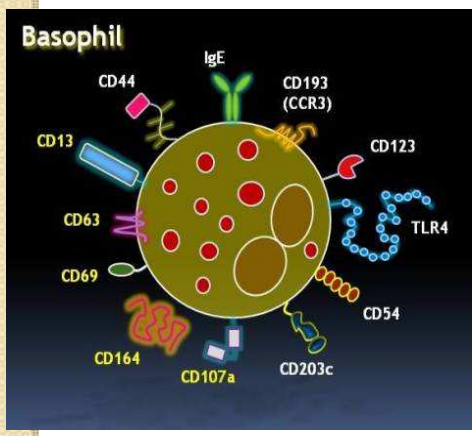
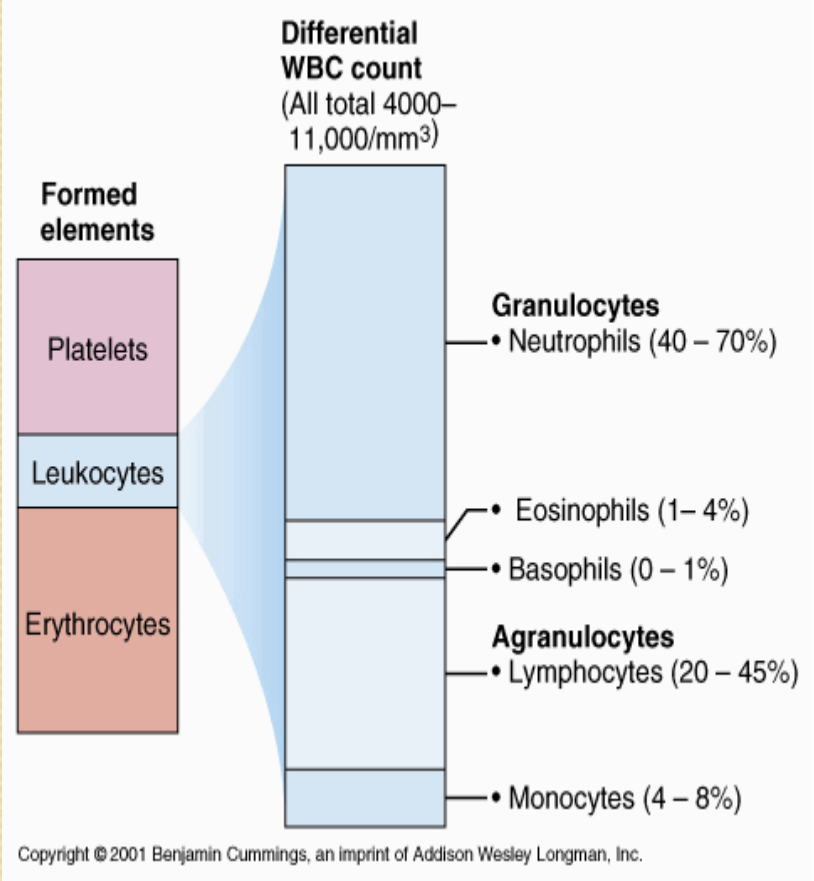


Table 1 | **Selected products of human mast cells and basophils**

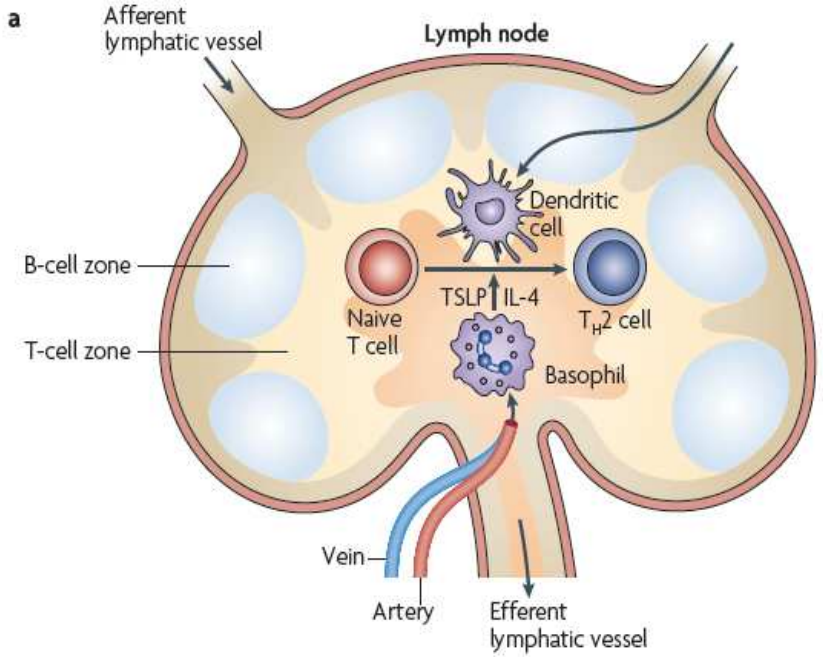
Feature	Basophils*	Mast cells*
Main mediators stored preformed in cytoplasmic granules	Histamine, chondroitin sulphates, neutral protease with bradykinin-generating activity, β-glucoronidase, elastase, cathepsin-G-like enzyme, major basic protein, Charcot–Leyden crystal protein, peroxidase, carboxypeptidase A‡	Histamine, heparin and/or chondroitin sulphates, neutral proteases (chymase and/or tryptase‡), major basic protein, many acid hydrolases, cathepsin, carboxypeptidases, peroxidase
Main lipid mediators produced after appropriate activation	Leukotriene C_4	Prostaglandin D_2, leukotriene C_4, platelet-activating factor
Cytokines released after appropriate activation¶	IL-4, IL-13	TNF, MIP1α, VPF/VEGF, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, IL-16, GM-CSF, MCP1 (and probably many more)

*Adapted from REF. 132. ‡Under certain conditions, tryptase-, chymase-, carboxypeptidase-A- and c-Kit-positive granulated cells that seem to be basophils by morphology and react with an antibody specific for BSP1 (which stains basophils, but not mast cells) can be observed in the peripheral blood. Adapted from REF. 133. ¶Several lines of evidence indicate that certain cytokines produced by mast cells, such as tumour-necrosis factor (TNF) and vascular permeability factor (VPF)/vascular endothelial growth factor (VEGF), are released in part from pre-formed stores, some of which might be associated physically with the cytoplasmic granules of the cell. GM-CSF, granulocyte–macrophage colony-stimulating factor; IL, interleukin; MCP1, monocyte chemotactic protein 1; MIP1α, macrophage inflammatory protein 1α (CCL3).

Nature Reviews Immunology 2, 773-786 (October 2002)



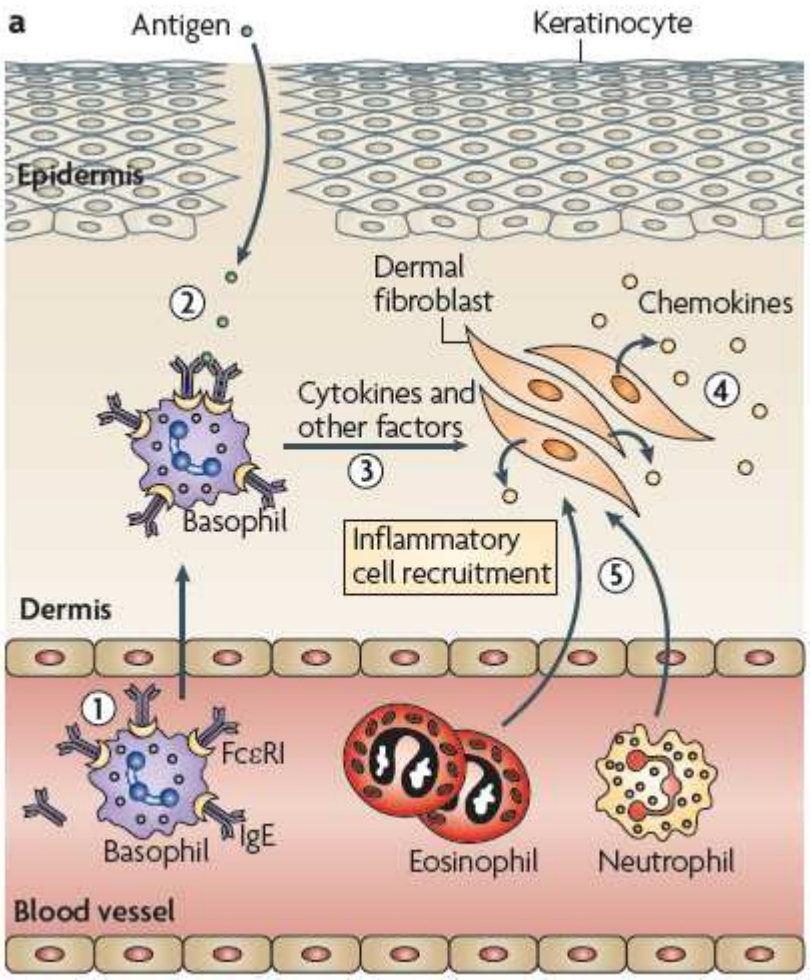
Inducción de Th2

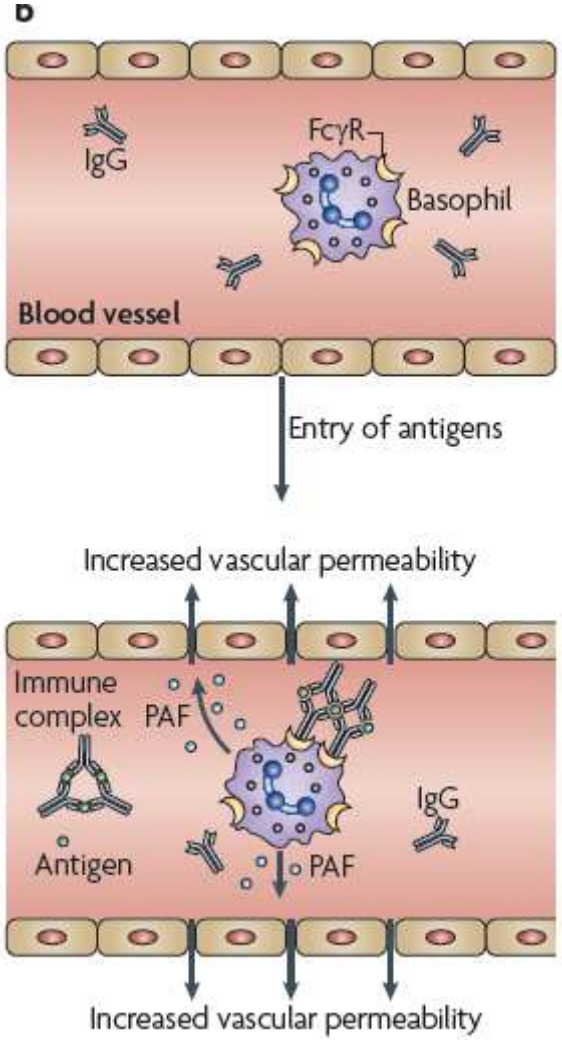


Thymic stromal lymphopoietin (TsLP)

Basófilos y funciones

Rol de los basófilos en la alergia y anafilaxia sistémica



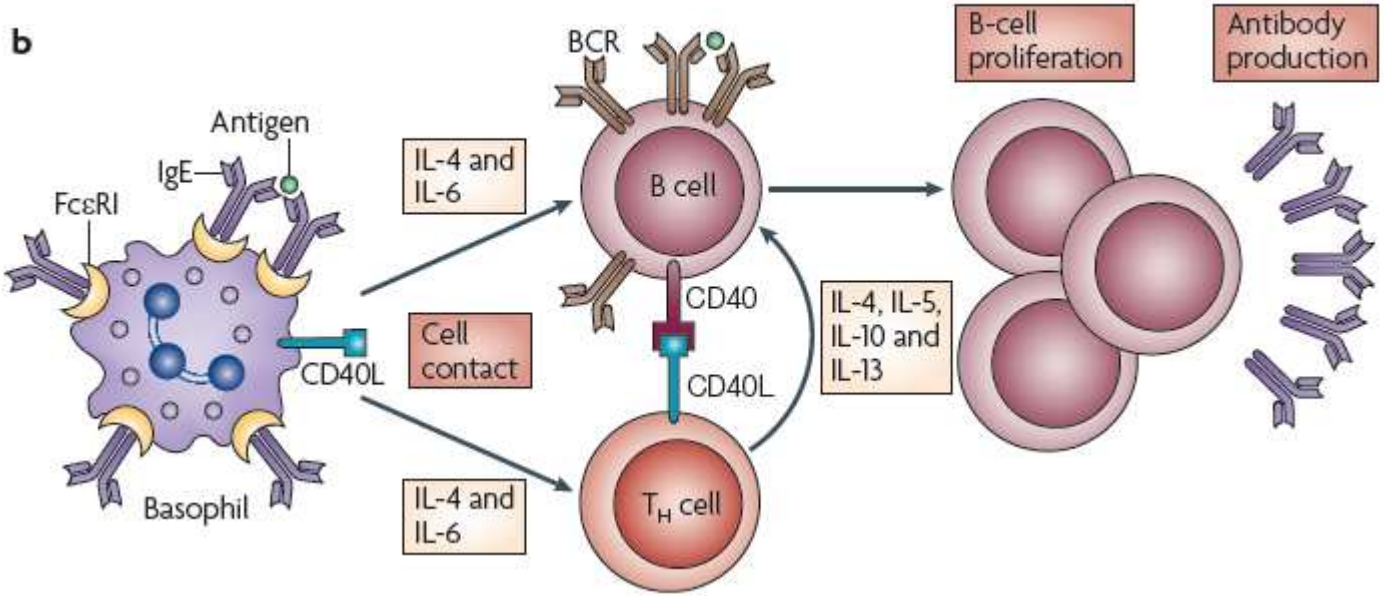


Nature Reviews Immunology 9, 9-13 (January 2009)

Inician inflamación alérgica crónica

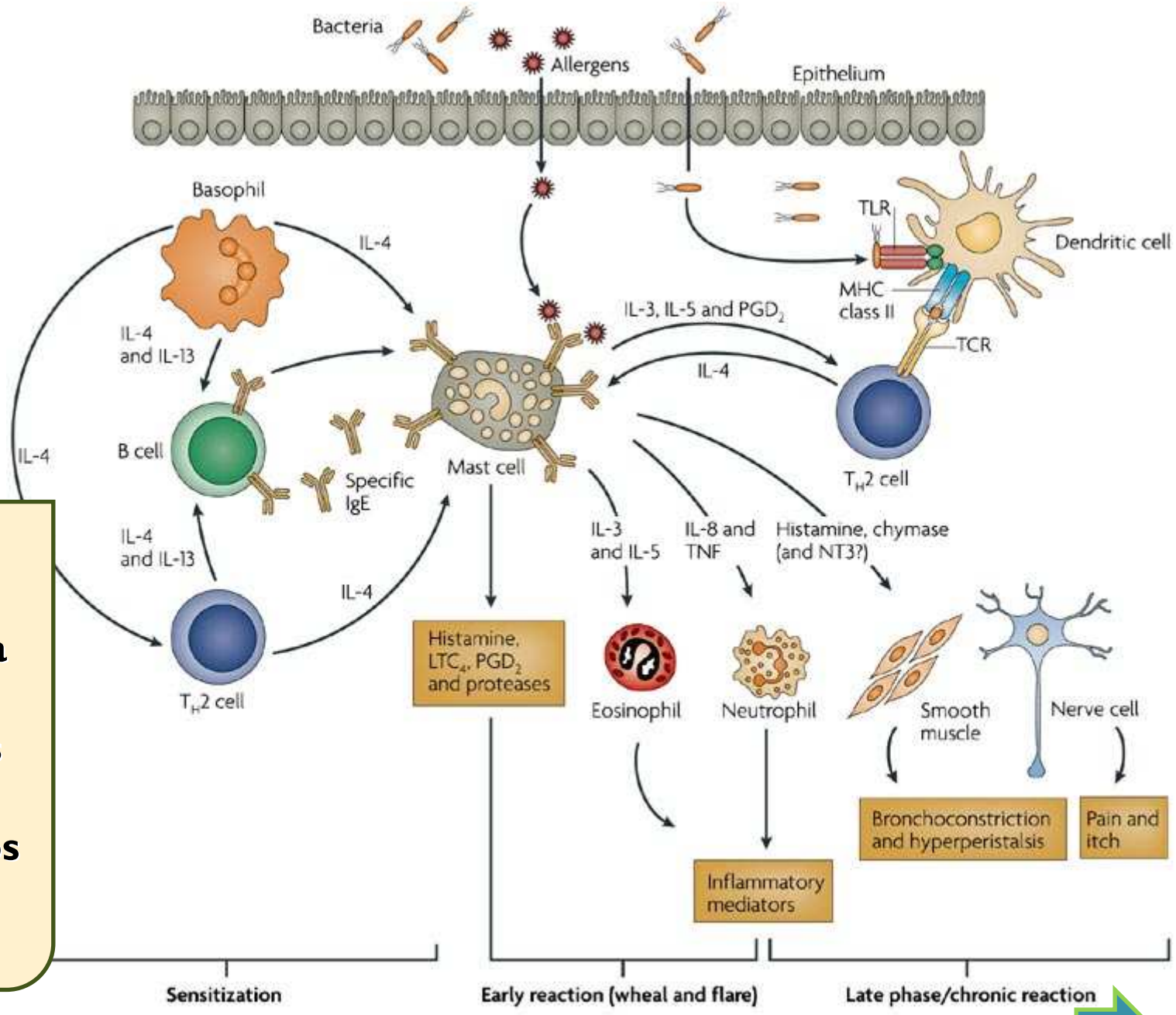
Inducen anafilaxia sistémica mediada por IgG en ratones

Incrementan la producción de anticuerpos en la respuesta inmune secundaria….



Nature Reviews Immunology 9, 9-13 (January 2009)

Acción Integrada entre basófilos y mastocitos ….



Nature Reviews Immunology 7, 93-104 (February 2007)

Nature Reviews | Immunology

EOSINÓFILOS

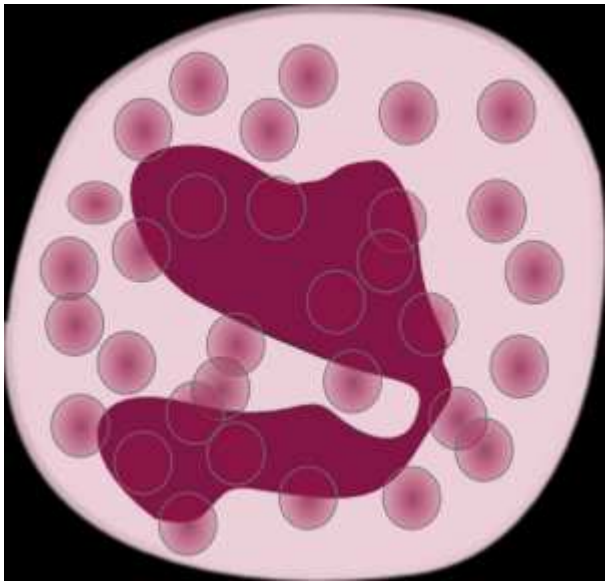
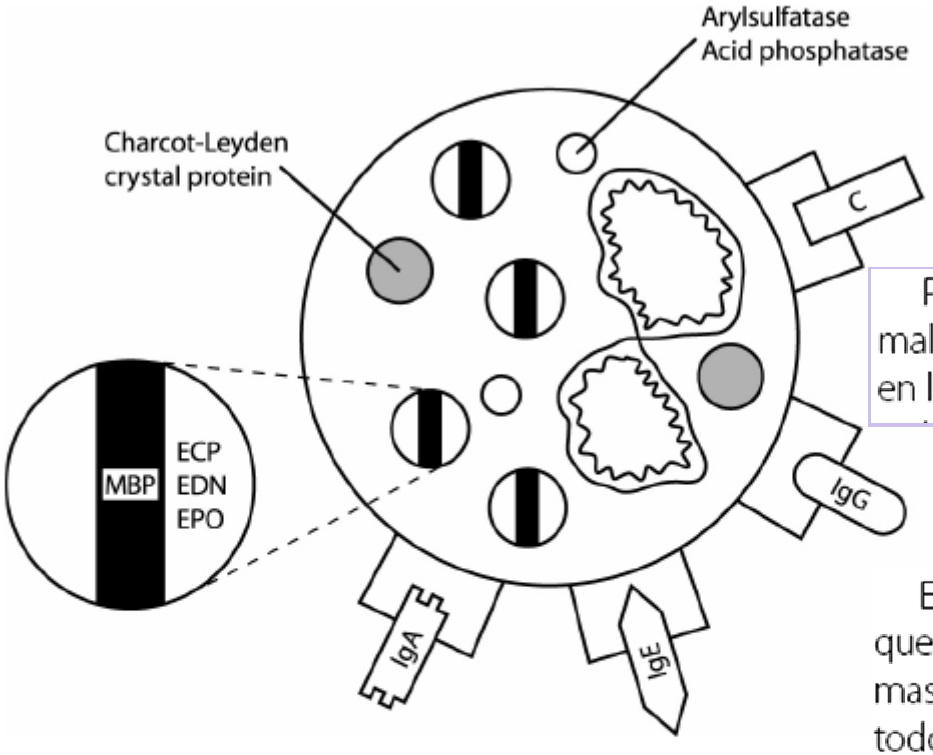


Fig. 1. Diagrama esquemático que muestra gránulos y proteínas de membrana



A. Proteína básica principal (MBP).
B. Proteína catiónica eosinofílica (ECP).
C. Neurotoxina derivada de eosinófilos (EDN).
D. Peroxidasa de eosinófilo (EPO) e hidrolasas lisosomales e histaminasa.

La primera de ellas está localizada en el core o envoltura granular y las últimas tres están localizadas en la matriz del gránulo

Dermatología Venezolana. Vol. 43, Nº 2, 2005.

Por cada eosinófilo presente en la circulación que normalmente es de 0-350 células/mL, hay 300-500 eosinófilos en los tejidos.

En la piel, la densidad de los eosinófilos es mucho menor que en el intestino, pulmón o útero, pero como posee mayor masa en conjunto, representa el principal centro de recambio; todo ello estudiado en ratas[1,5].

Moléculas derivadas de los eosinófilos

Proteína tóxica	Proteína básica principal	Tóxica para parásitos y células de mamíferos Provoca la liberación de histamina por los mastocitos
	Proteína catiónica de eosinófilos	Tóxica para parásitos Neurotoxina
	Neurotoxina derivada de eosinófilos	Neurotoxina
Citocina	IL-3, IL-5, GM-CSF	Amplifica la producción de eosinófilos por la médula ósea Causa la activación de los eosinófilos
Quimiocina	IL-8	Promueve el flujo de los leucocitos
Mediador lipídico	Leucotrienos C4 y D4	Contracción del músculo liso Permeabilidad vascular aumentada Secreción del moco
	Factor de activación de plaquetas	Quimiotáctico para los leucocitos Amplifica la producción de mediadores lipídicos Activación de neutrófilos, eosinófilos y plaquetas

Algunas características de los EOSINÓFILOS…..

- El desarrollo de eosinófilos en la médula ósea es estimulado por tres citocinas:

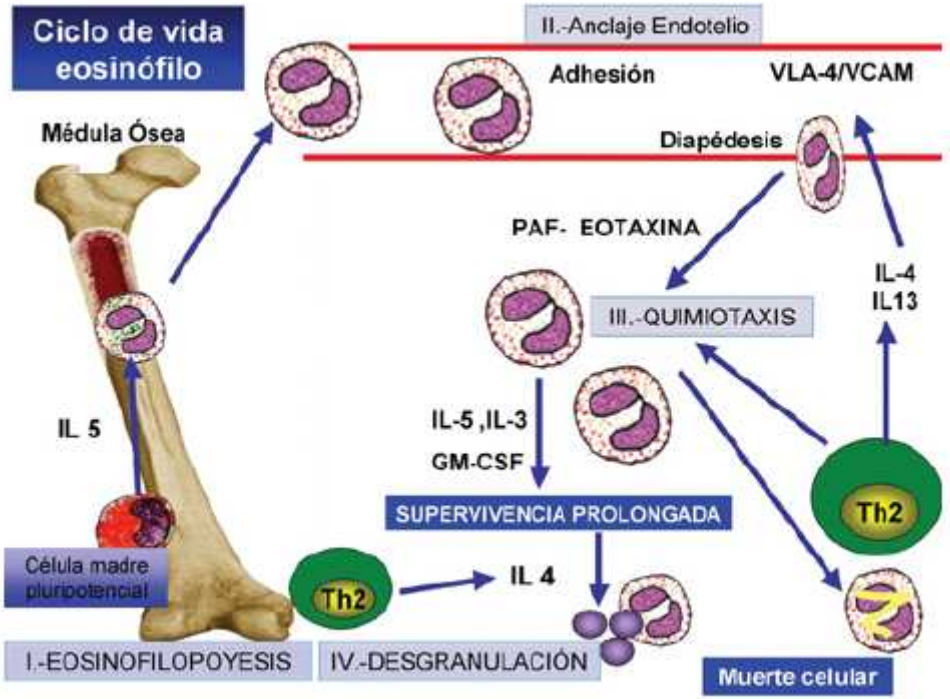
a. Factor estimulador de colonias de granulocitosmacrófagos (GM-CSF).

b. Interleuquina-3 (IL-3).

c. Interleuquina-5 (IL-5).

- La IL-5 promueve exclusivamente el desarrollo y diferenciación terminal de eosinófilos en la médula ósea, en contraste con IL-3 y GM-CSF que además de estimular la eosinófilopoyesis también estimulan otras líneas celulares.
- La IL-5 incrementa la función del eosinófilo maduro, así como la respuesta degranulatoria, la adhesión, la citotoxicidad y además prolonga la sobrevivencia del eosinófilo.

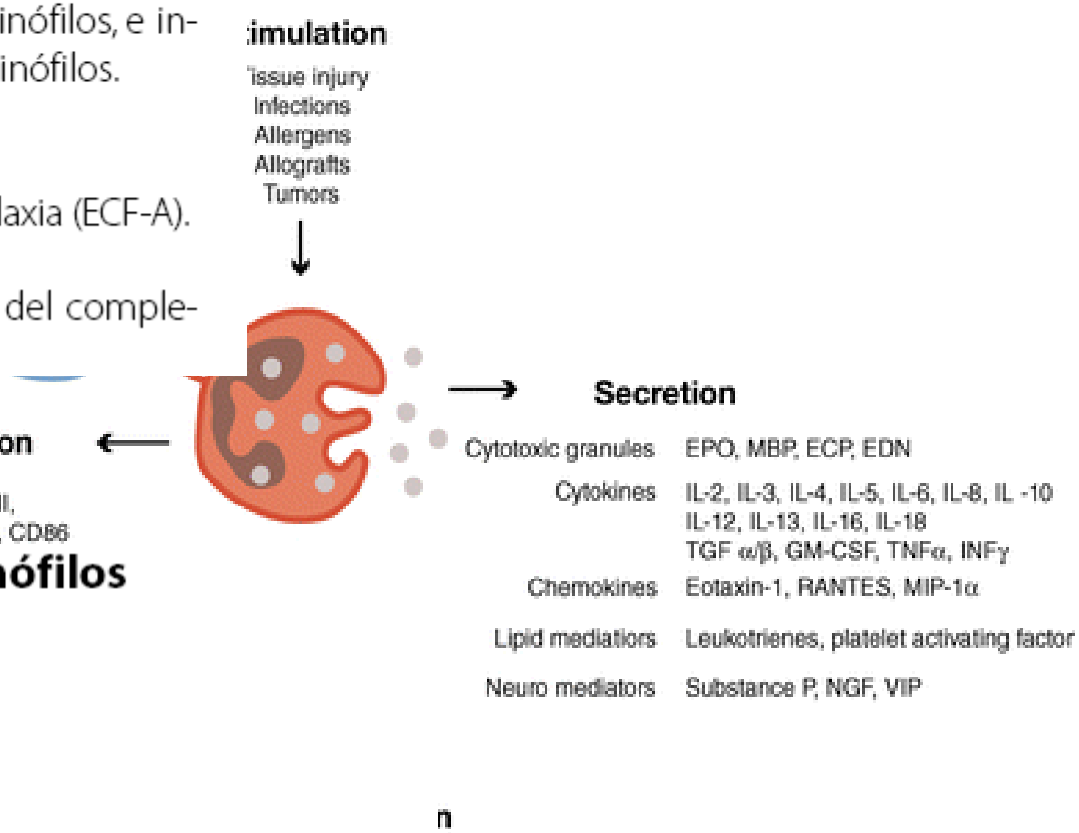
Fig. 2. Ciclo de vida del eosinófilo



Fuente: Brito F, Yamazaki M, Espinosa S, Vasquez O, Huerta J. Eosinófilos: Revisión de la literatura. Alergia, Asma e Inmunología Pediátrica. 2003;12(2):56-62.

Sustancias quimiotácticas de eosinófilos

1. Eotaxina: Es el único factor quimiotáctico específico de eosinófilos.
2. Factor activador de plaquetas (PAF) producido por varias células incluyendo eosinófilos, es uno de los quimoatrayentes más potentes para eosinófilos, e induce selectivamente la migración de eosinófilos.
3. Leucotrieno B4, leucotrieno D4.
4. Histamina.
5. Factor quimiotáctico eosinófilo de la anafilaxia (ECF-A).
6. IL-3, IL-5 y GM-CSF.
7. Productos procedentes de la activación del complemento C3, C5a, C6, C7.



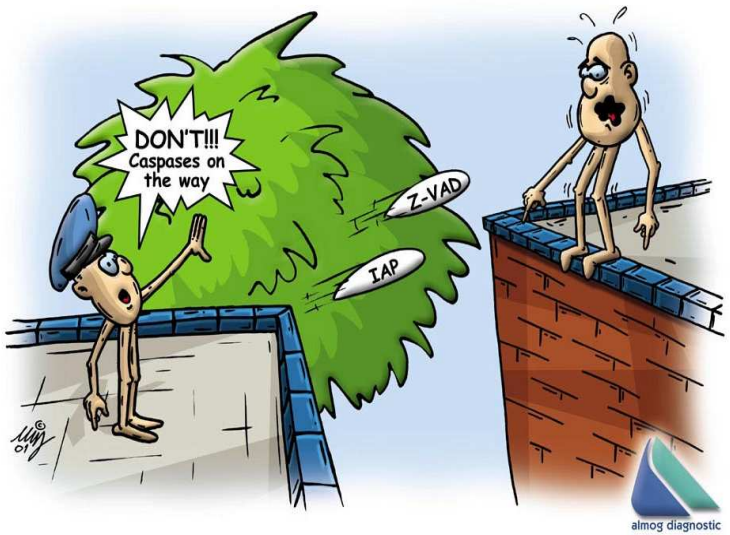
Función normal de eosinófilos

1. Quimiotaxis y quimocinesis.
2. Fagocitosis y endocitosis.
3. Citotoxicidad.
4. Actividad antiparasitaria.
5. Actividad bactericida.
6. Efector de hipersensibilidad inmediata.
7. Modulación de la respuesta inflamatoria.
8. Vigilancia inmune normal para neoantígenos y células neoplásicas.

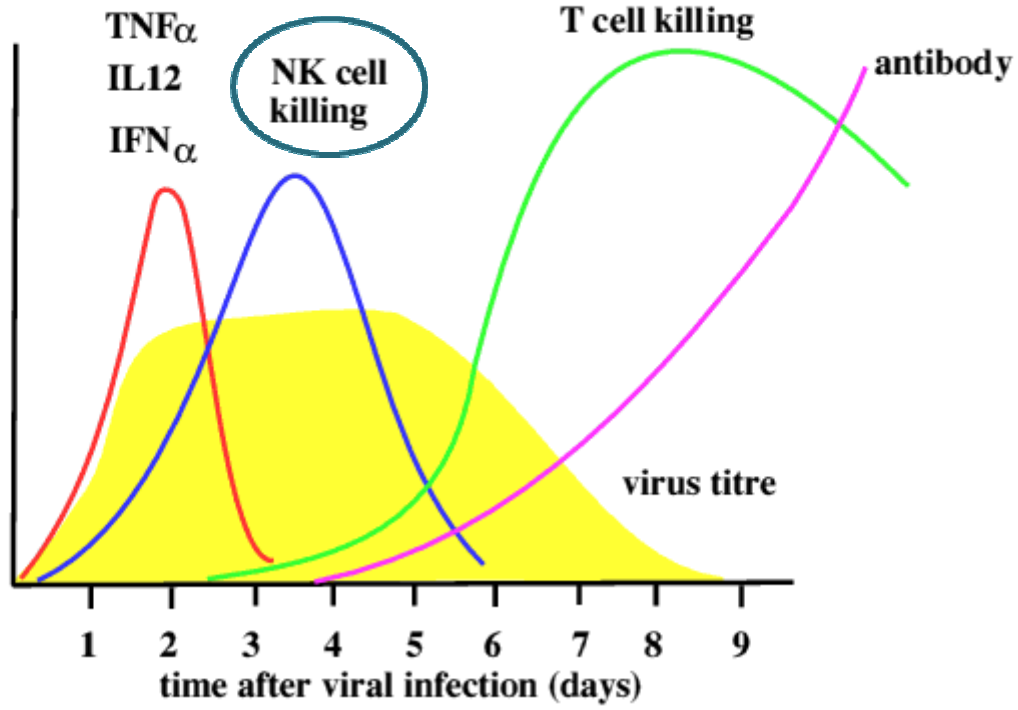
Hemograma Normal

	Valor normal	Unidades
Serie Roja		
Eritrocitos	4,5-5,5	$x10^6$
Hto	40-55	%
Hb	12-18	g/dL
Serie Blanca		
Leucocitos	5-10	$x10^3$
Neutrófilos	40-70	%
Linfocitos	12-46	%
Monocitos	1-13	%
Eosinófilos	0-7	%
Basófilos	0-3	%
Blastos	0	%
Plaquetas (PK's)	150-450	$x10^3$

NATURAL KILLER



Cytokines and NK cells combine to provide early defense against virus infections

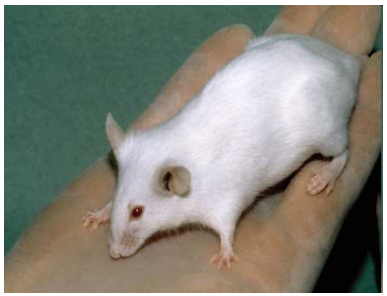


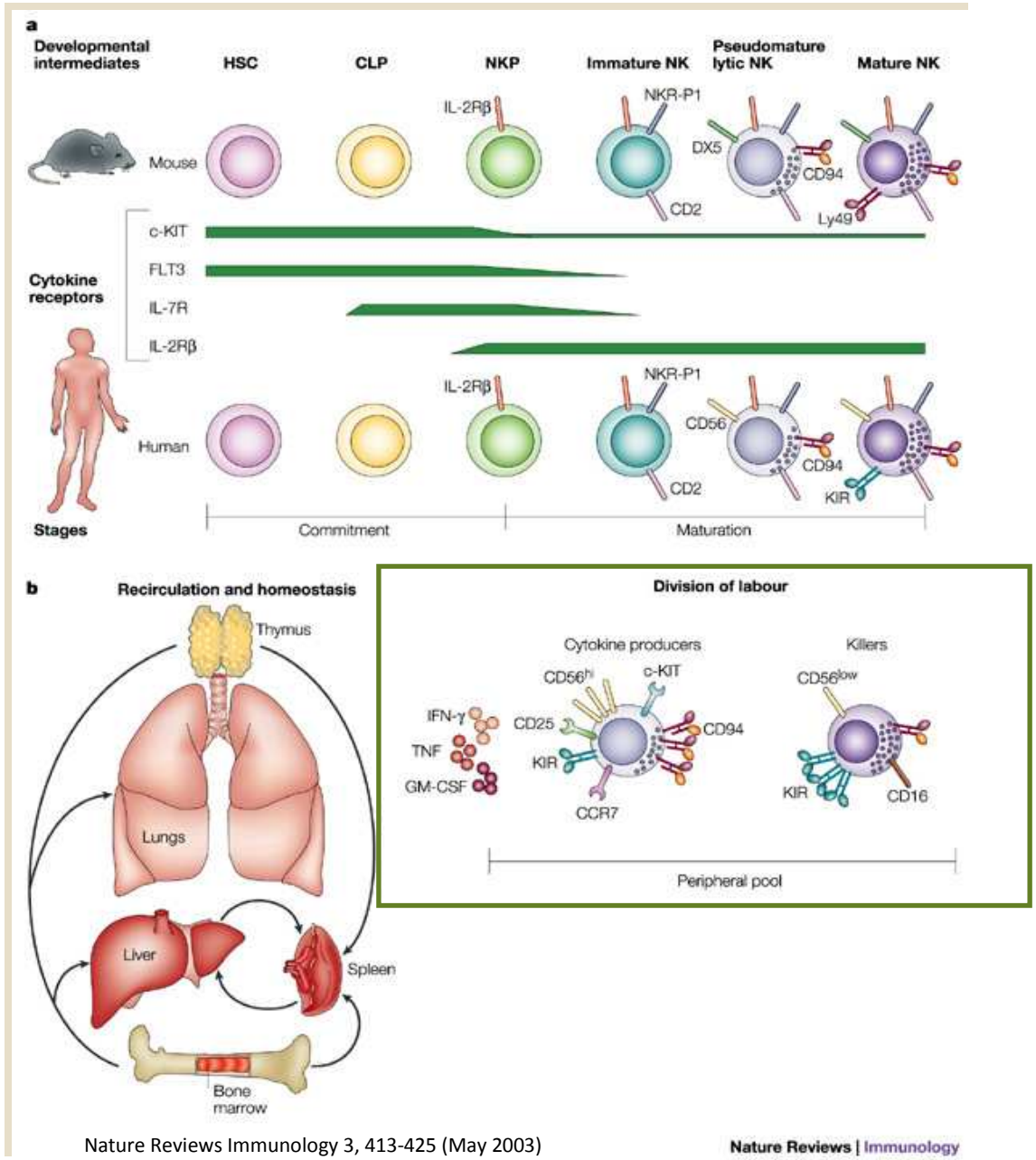
Células NK-
¿de dónde provienen?

- La célula progenitora de células NK se encuentra en la **médula ósea**

- El desarrollo de la célula NK es independiente del **TIMO**
  - ***ratones nude*** tienen células NK normales

- No existen rea-arreglos de las *cadenas α, β, γ o δ del TCR* o de las *cadenas H y L de las Ig*
  - células NK normales en ***ratones scid***





Nature Reviews Immunology 3, 413-425 (May 2003)

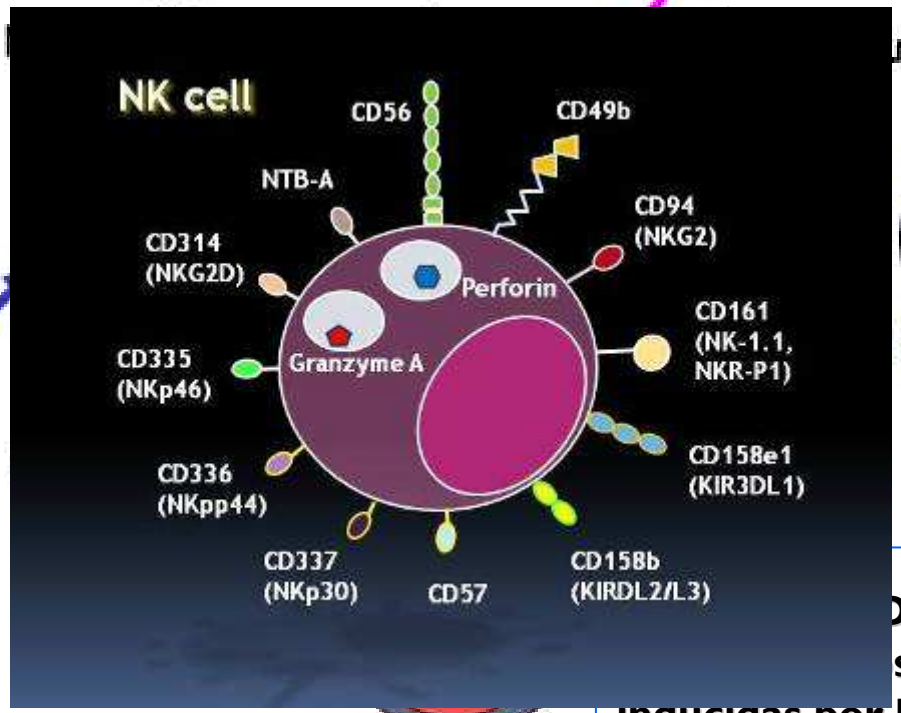
Origen de las células NK

Ontogenia

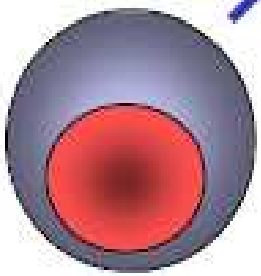
del estroma de M.O.

NKP: precursor de células NK

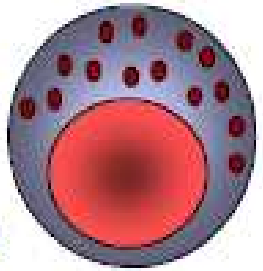
NKm:
ula NK madura



IL-7
(no indispensable)



PLC: progenitor
linfoide común
$CD34^+$, $Flt3^+$, $C\text{-}kit^+$



$CD56^{bright}$

$CD56^{dim}$

$CD56^{bright}$ maduran a
s GL por señales
inducidas por las DCs

Células NK-
¿dónde se encuentran?

- ~5-20% de los linfocitos de sangre periférica
- ~5% linfocitos en el bazo
- Abundantes en el hígado
- Baja frecuencia en el timo, médula ósea, nódulos linfáticos y linfáticos no infectados
- >90% de los linfocitos en el tejido decidual

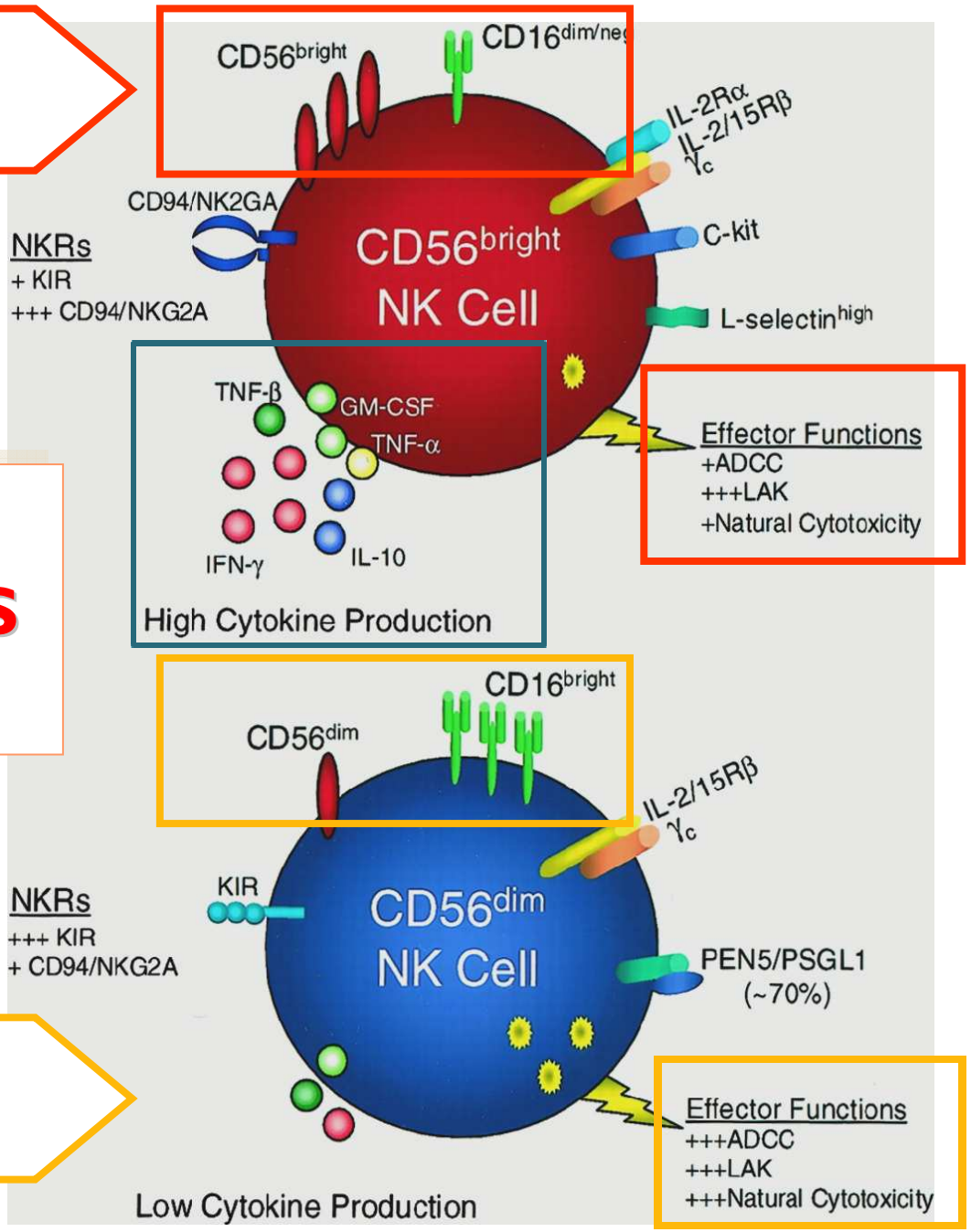
¿Qué papel cumplen las células NK?

- Defensa frente a bacterias y parásitos intracelulares
- Control de infecciones virales
- Eliminación de células tumorales
- Determinación del perfil de respuesta adaptativa que se montará contra un determinado patógeno

SUBPOBLACIONES NK

FENOTIPOS

CD56^{bright}
CD16^{dim}

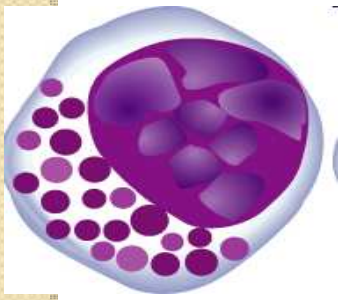


CD56^{dim}
CD16^{bright}

TRÁFICO Y MIGRACIÓN

CD56^{bright}
CD16^{dim}

CD62L+,CCR7+: TRÁFICO A OLS
CROSS TALK CON LINFOCITOS T Y CD
SECRECIÓN DE INF-γ: ¿SHIFT A Th1?



CD56^{dim}
CD16^{bright}

CD62L-,CCR7-: NO INGRESAN A OLS
REPRESENTA EL 90% DE CÉLULAS NK EN SANGRE PERIFERICA

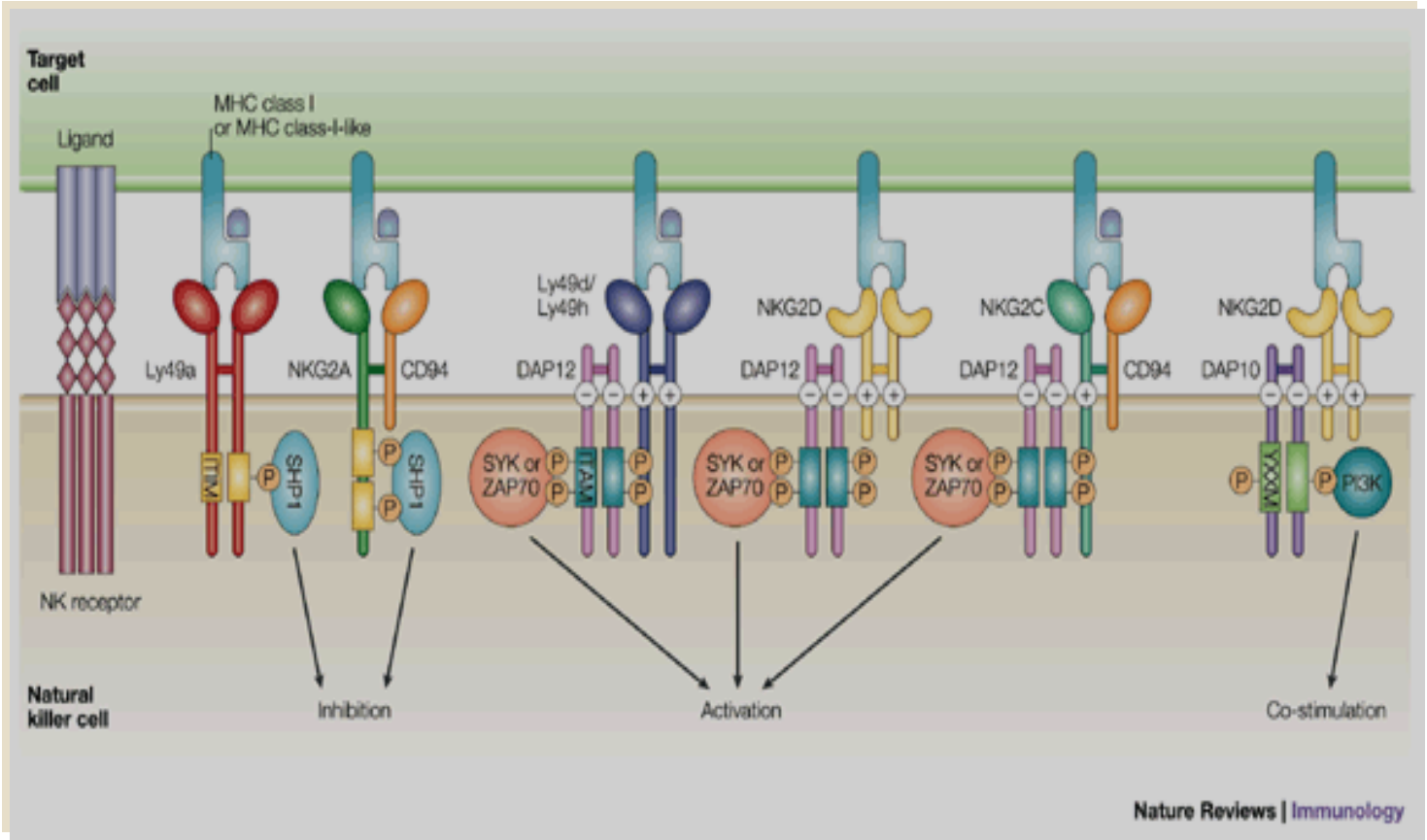
Citoquinas que regulan la actividad de las células NK

IL-2	**Estimula citotoxicidad, proliferación y producción de citoquinas**
IL-12	**Estimula citotoxicidad, proliferación y producción de citoquinas**
IL-15	**Estimula citotoxicidad, proliferación y producción de citoquinas**
IFN-γ	**Estimula citotoxicidad**
IFN-α/β	**Estimula citotoxicidad**
IL-10	Inhibe **producción de citoquinas**

Citoquinas secretadas por células NK

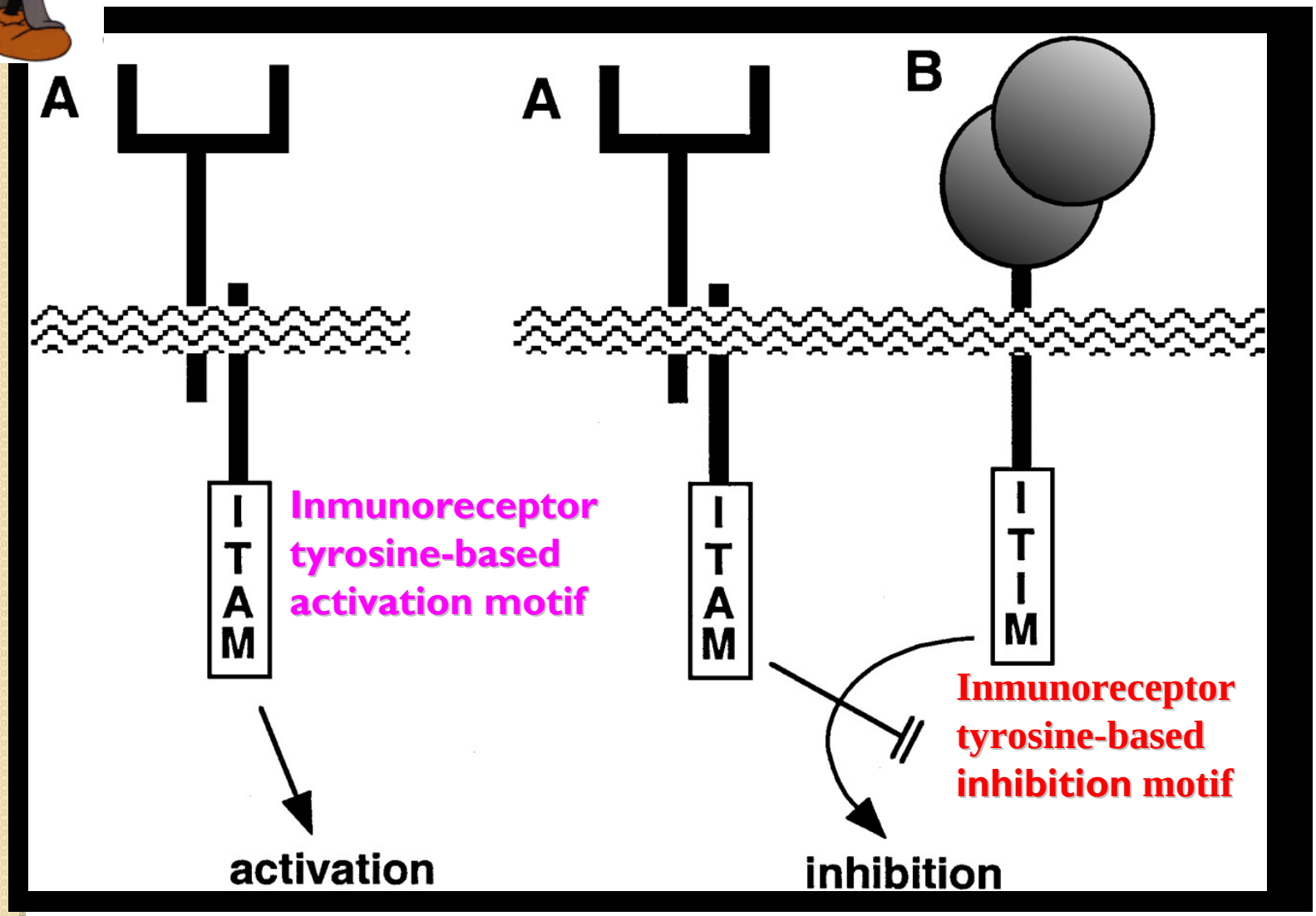
IFN-γ	**Inducción respuesta Th1. Activación de monocitos y macrófagos**
TNF	**Mediador de la respuesta inflamatoria. Activa monocito y LT. Acción lítica**
GM-CSF	**Factor estimulante de colonias de granulocitos/macrófagos**
TGF-β	**Inmunosupresión**
IL-3	**Induce proliferación y diferenciación de precursores hematopoyéticos**
IL-10	**Inmunosupresión**

Receptores NK

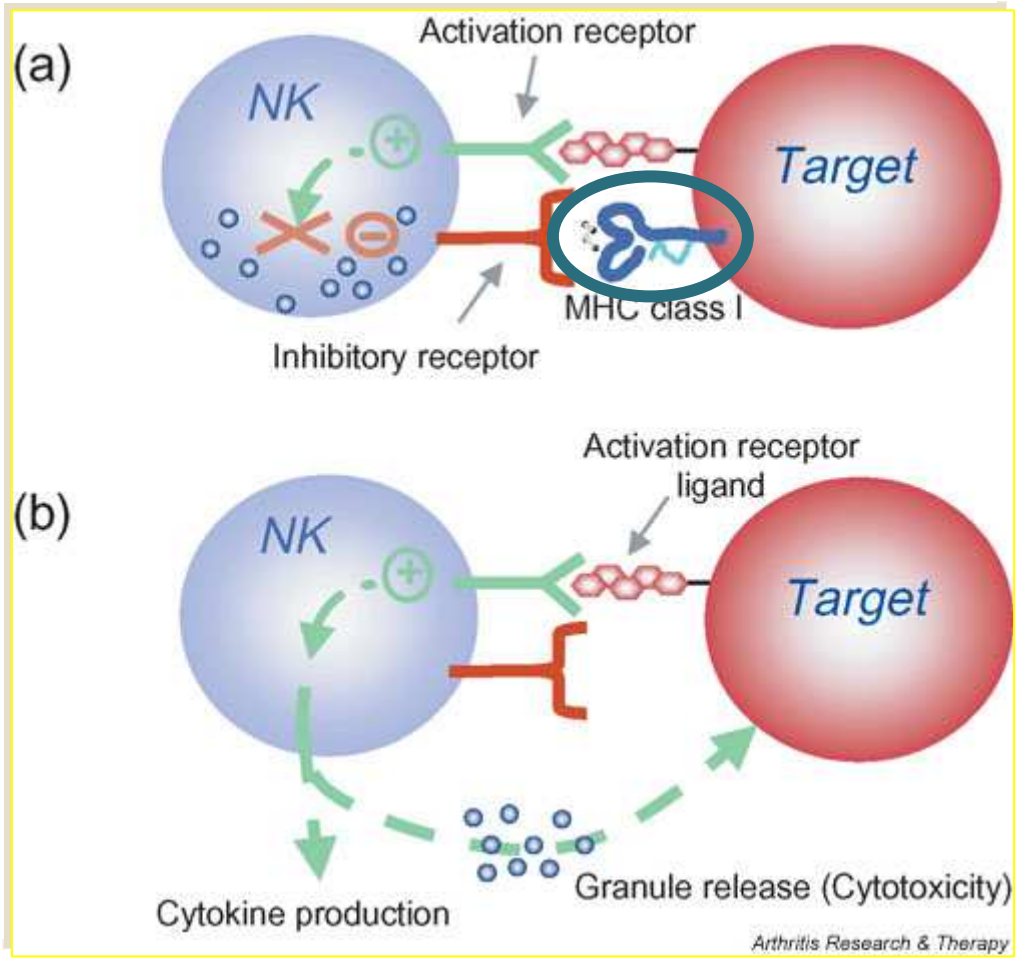


Nature Reviews Immunology 3, 304-316 (April 2003)

Señalización receptores NK
Inhibición-activación



Células NK en acción



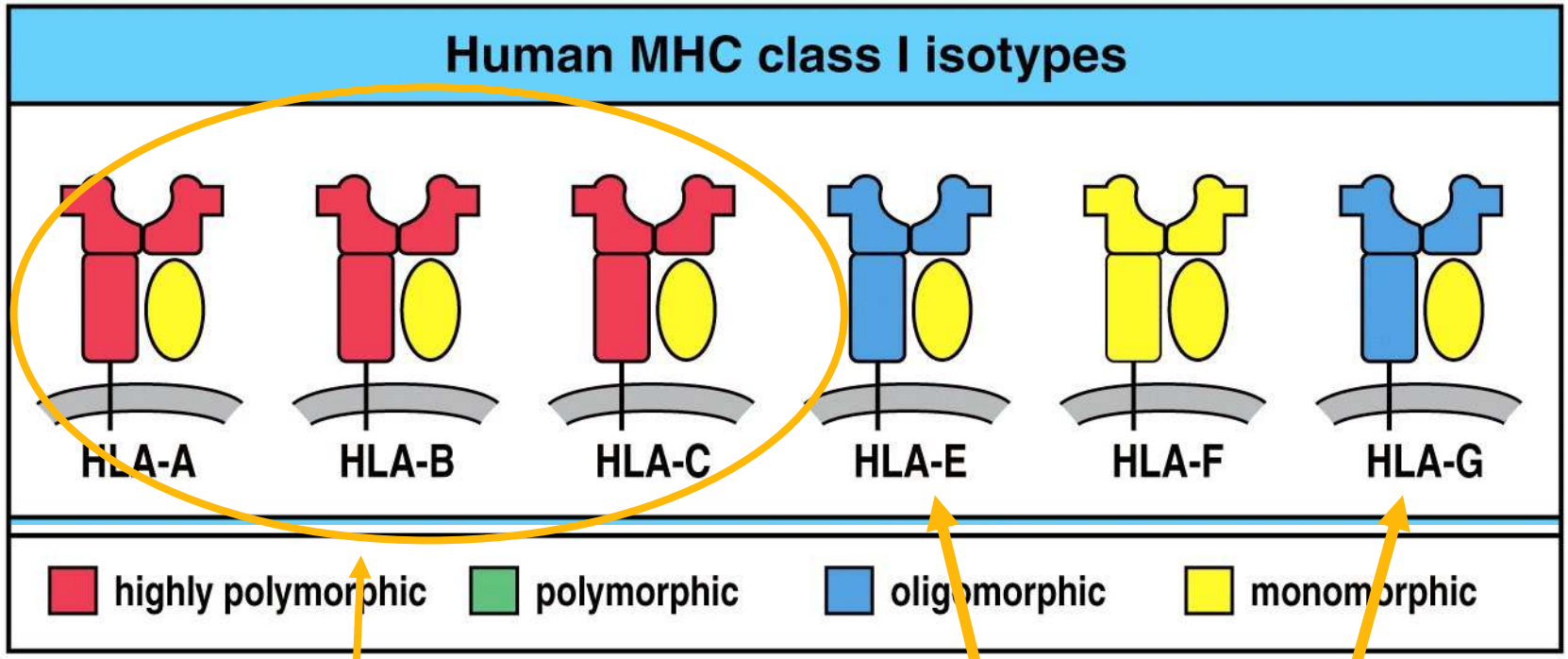


Figure 3-23 The Immune System, 2/e (© Garland Science 2005)

Estas moléculas son importantes en la presentación de antígenos a linfocitos TCD8⁺

Estas moléculas son importantes ligandos inhibidores de células NK

Table 1 | **Main receptors on human natural killer cells**

Receptor	Specificity
MHC-class-I-specific inhibitory receptors	
KIR2DL1	HLA-C allelic subgroup (Asn77, Lys80)
KIR2DL2/3	HLA-C allelic subgroup (Ser77, Asn80)
KIR3DL1	HLA-B allelic subgroup (HLA-BW4)
KIR3DL2	Some HLA-A alleles (HLA-A3 and HLA-A11)
CD94–NKG2A	HLA-E
Activating receptors	
NKp30	Unknown
NKp44	Unknown
NKp46	Unknown
NKG2D	MICA/MICB, and ULBP1, -2 and -3
Chemokine receptors	
CXCR1	CXCL8 (interleukin-8)
CX_3CR1	CX_3CL1 (fractalkine)
CXCR3	MIG (CXCL9), IP10 (CXCL10) and IP9 (CXCL11)
CXCR4	SDF1α and SDF1β (CXCL12)
CCR7	SLC (CCL21) and ELC (CCL19)

ELC, Epstein–Barr virus-induced molecule 1 ligand chemokine; IP, interferon-inducible protein; KIR, killer-cell immunoglobulin-like receptor; MICA/MICB, MHC class I polypeptide-related sequence A/B; MIG, monokine induced by γ-interferon; SDF1, stromal-cell-derived factor 1; SLC, secondary lymphoid tissue chemokine; ULBP, UL16-binding protein.

Funciones citotóxicas

Actividad NK (Natural Killer)

- Citotoxicidad espontánea. Se mide frente a células diana sensibles que carecen de expresión de moléculas de histocompatibilidad

Actividad LAK (Lymphokine Activated Killer)

- Citotoxicidad inducida por citocinas (IL-2, IFNα).

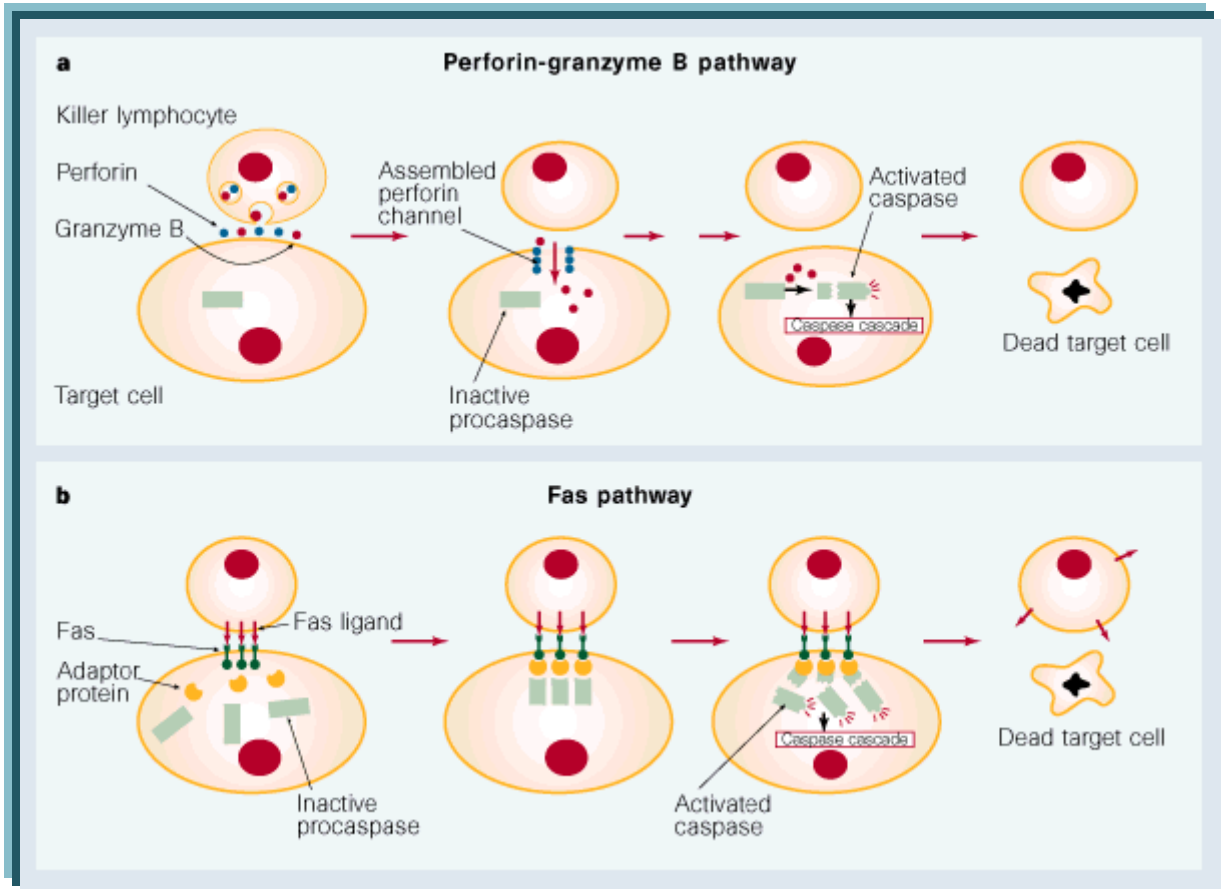
Actividad ADCC (Antibody dependent cell cytotoxicity)

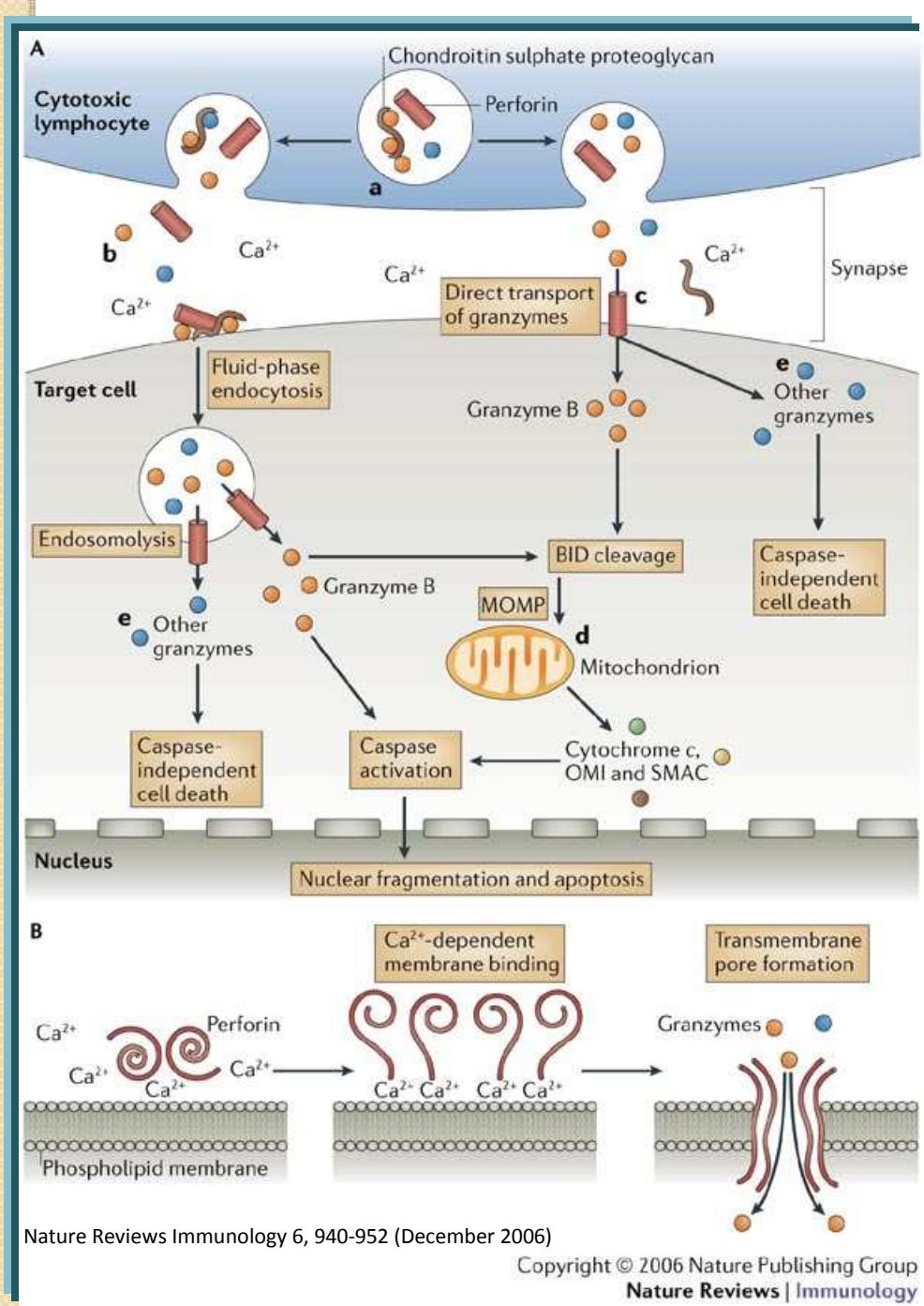
- Citotoxicidad dependiente de anticuerpos mediada por receptor FcγIIIb (CD16) Se mide en presencia de anticuerpos unidos a un antígeno en la superficie de la célula diana

NK $CD56^{bright}$ vs NK$CD56^{dim}$

Subpoblación	**$CD56^{bright}$ $CD16^{dim}$**	**$CD56^{dim}$ $CD16^{bright}$**
Produce citocinas immunoreguladoras	Si	Pocas
Citotoxicidad espontánea ADCC LAK	Baja Baja Potente	Potente Potente Potente

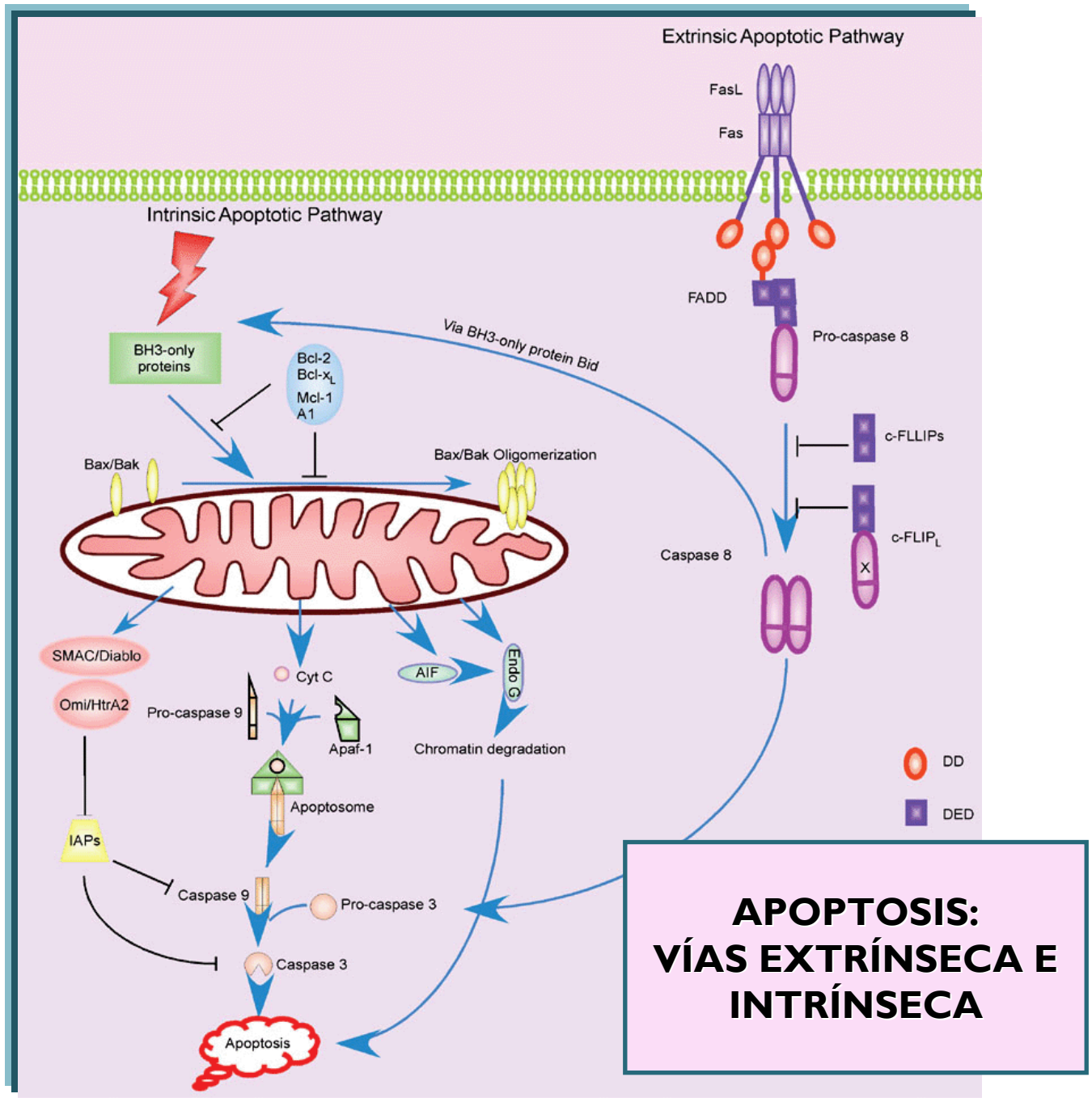
CITOTOXICIDAD NATURAL





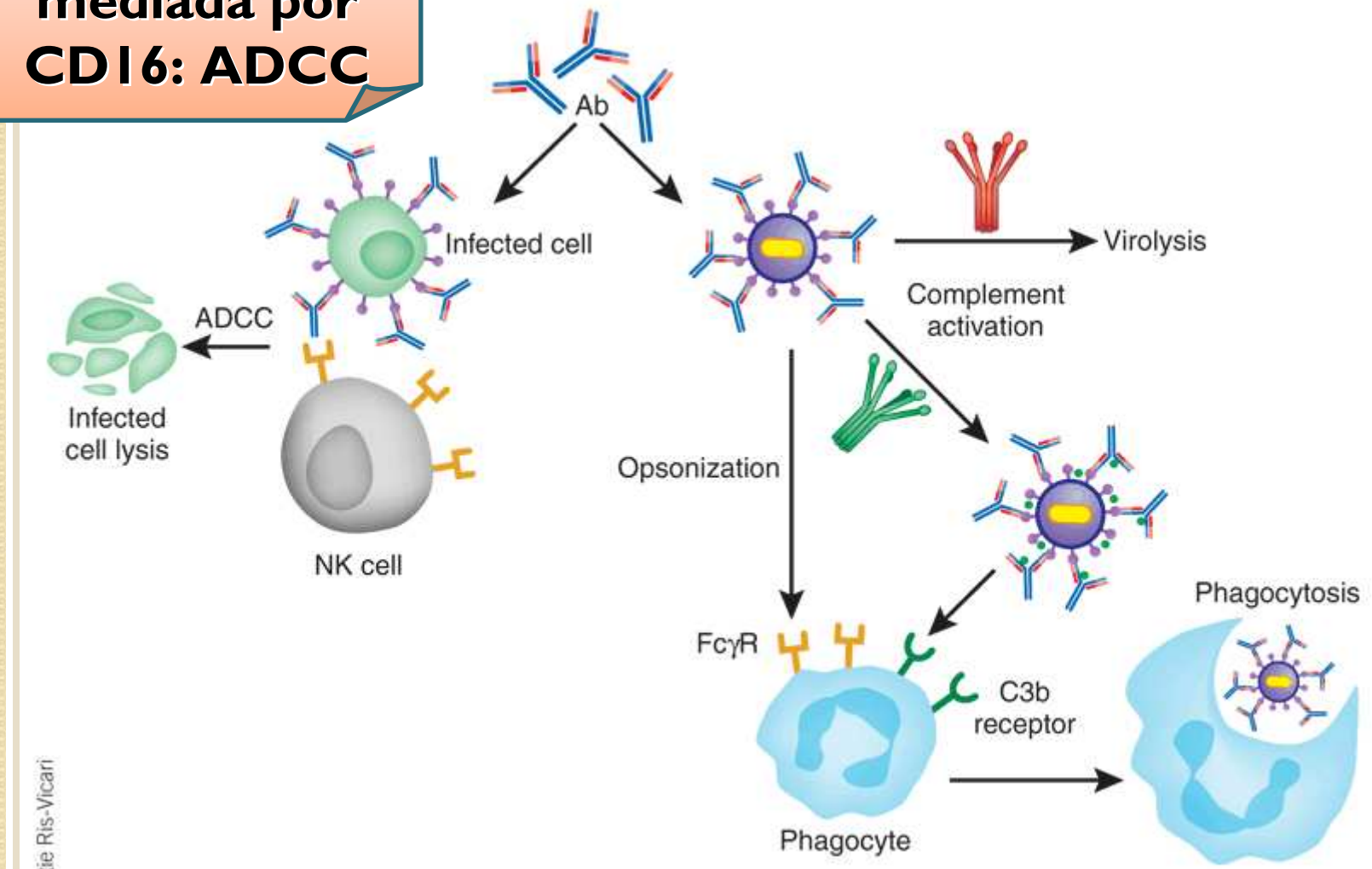
Nature Reviews Immunology 6, 940-952 (December 2006)

CITOTOXICIDAD NATURAL: VÍA PERFORINA-GRANZIMA B

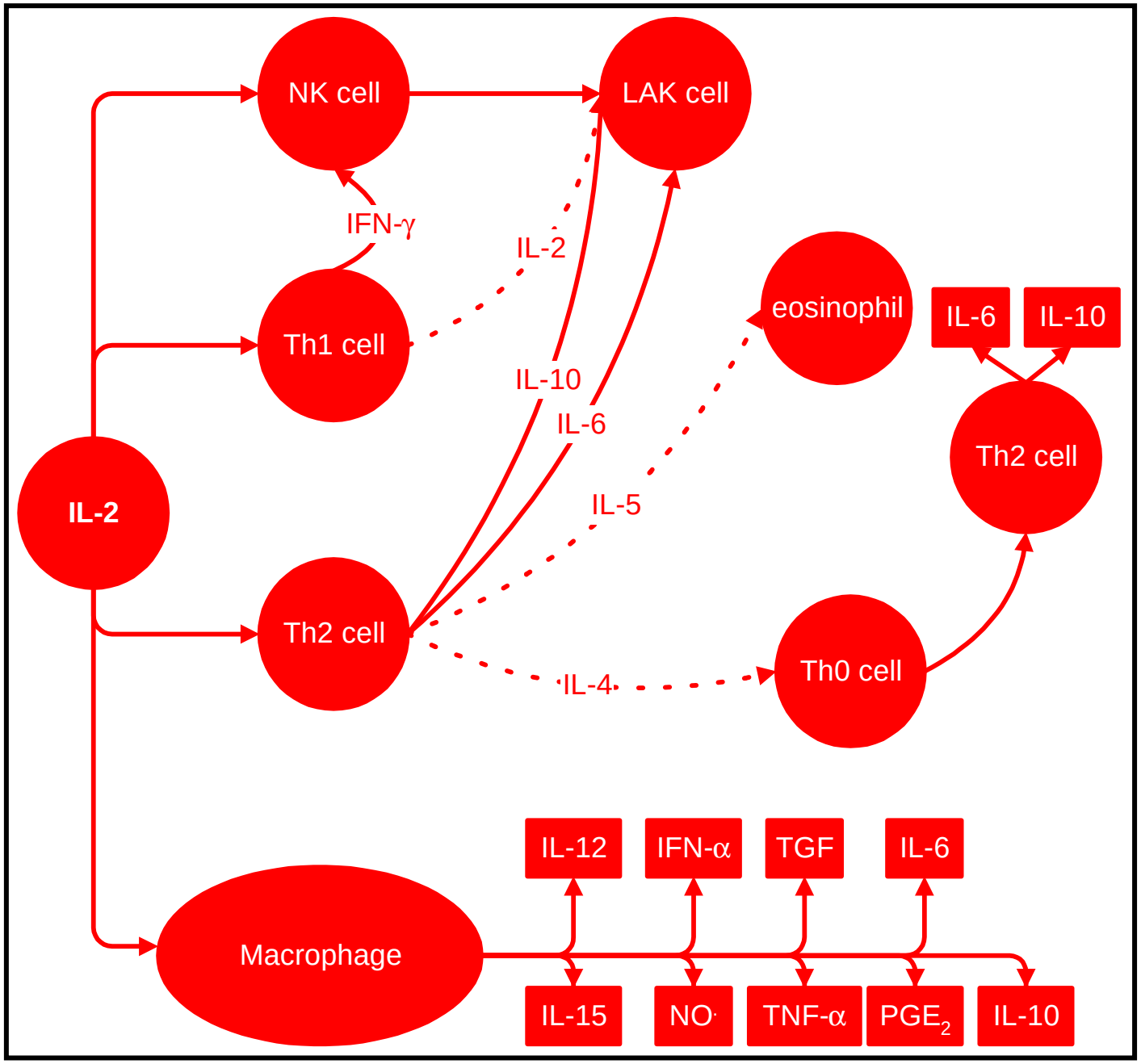


APOPTOSIS: VÍAS EXTRÍNSECA E INTRÍNSECA

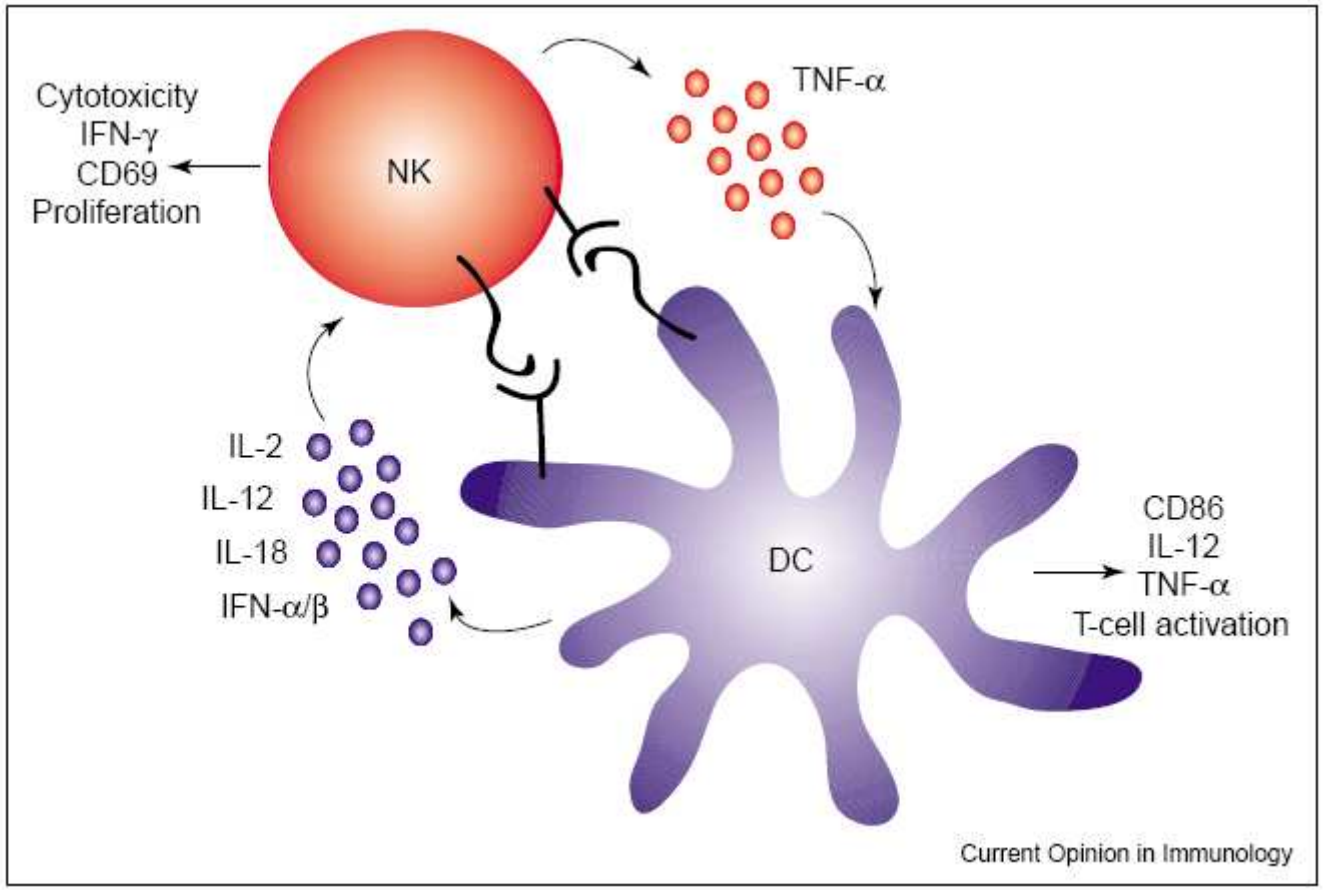
Función mediada por CD16: ADCC



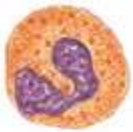
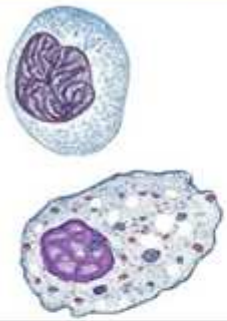
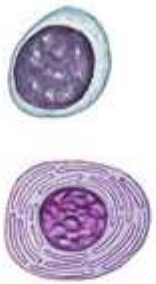
Nature Biotechnology 25, 1421 - 1434 (2007)


NK cell
LAK cell
IFN-γ
IL-2
Th1 cell
eosinophil
IL-6
IL-10
IL-10
IL-6
Th2 cell
IL-2
IL-5
Th2 cell
Th0 cell
IL-4
IL-12
IFN-α
TGF
IL-6
Macrophage
IL-15
NO·
TNF-α
PGE2
IL-10

Interacción entre DCs y Natural Killer



Resumiendo….

	Basophils and mast cells	*Neutrophils*	*Eosinophils*	*Monocytes and macrophages*	*Lymphocytes and plasma cells*	*Dendritic cells*
						
% of WBCs in blood	*Rare*	*50–70%*	*1–3%*	*1–6%*	*20–35%*	*NA*
Subtypes and nicknames		Called "polys" or "segs" Immature forms called "bands" or "stabs"		Called the mononuclear phagocyte system	B lymphocytes Plasma cells T lymphocytes Cytotoxic T cells Helper T cells Natural killer cells Memory cells	Also called Langerhans cells, veiled cells
Primary function(s)	Release chemicals that mediate inflammation and allergic responses	Ingest and destroy invaders	Destroy invaders, particularly antibody-coated parasites	Ingest and destroy invaders Antigen presentation	Specific responses to invaders, including antibody production	Recognize pathogens and activate other immune cells by antigen presentation

Tres cosas hay que son permanentes: la fe, la esperanza y el amor, pero la más importante de las tres es el amor
(1 Corintios 13:13)

“El sistema inmunitario tiene una gran belleza. Es extraordinario. Uno siempre descubre un misterio. Trata de resolverlo y cuando tiene toda la solución del problema, empieza todo de nuevo. Es fascinante.”

César Milstein
Premio Novel de Fisiología y Medicina - 1984