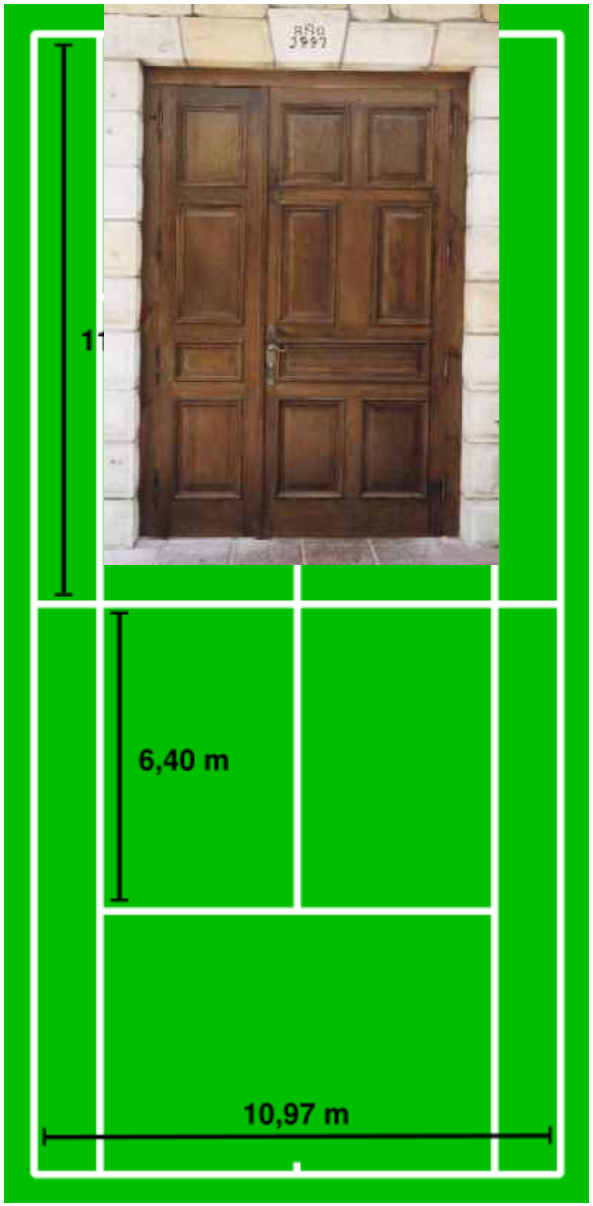
INMUNOLOGÍA CLÍNICA 2009

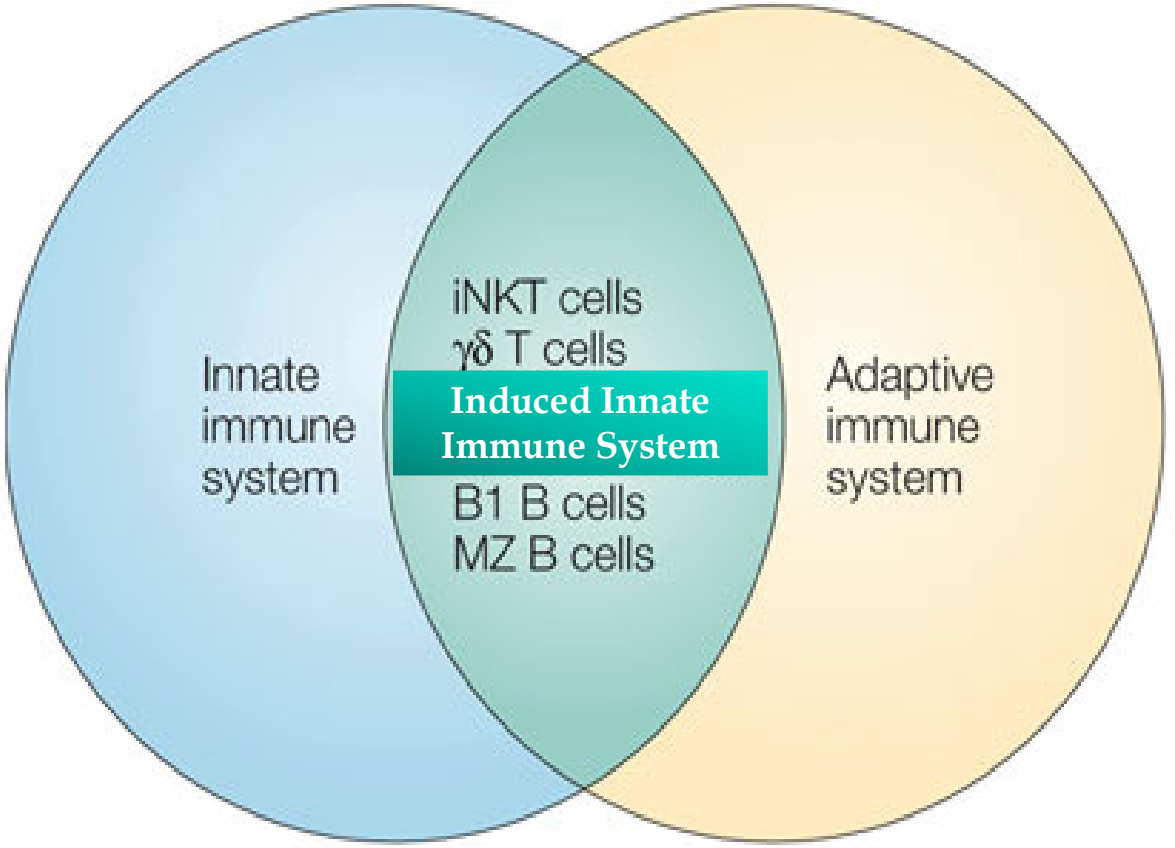
La integridad de las barreras físicas es crítica para evitar la infección

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.

Sistema inmune innato



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Defensa Innata

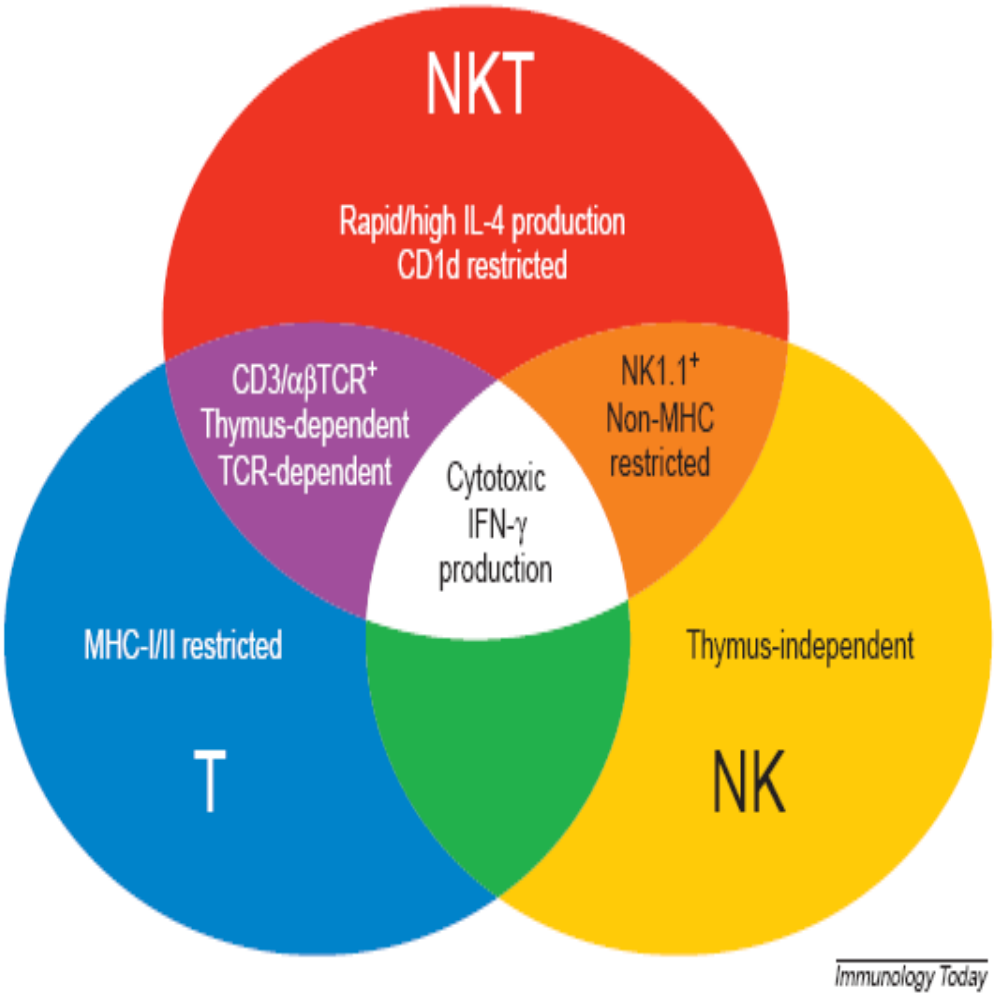
- Primera línea de defensa ante cualquier microorganismo exógeno.
- No es específica

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

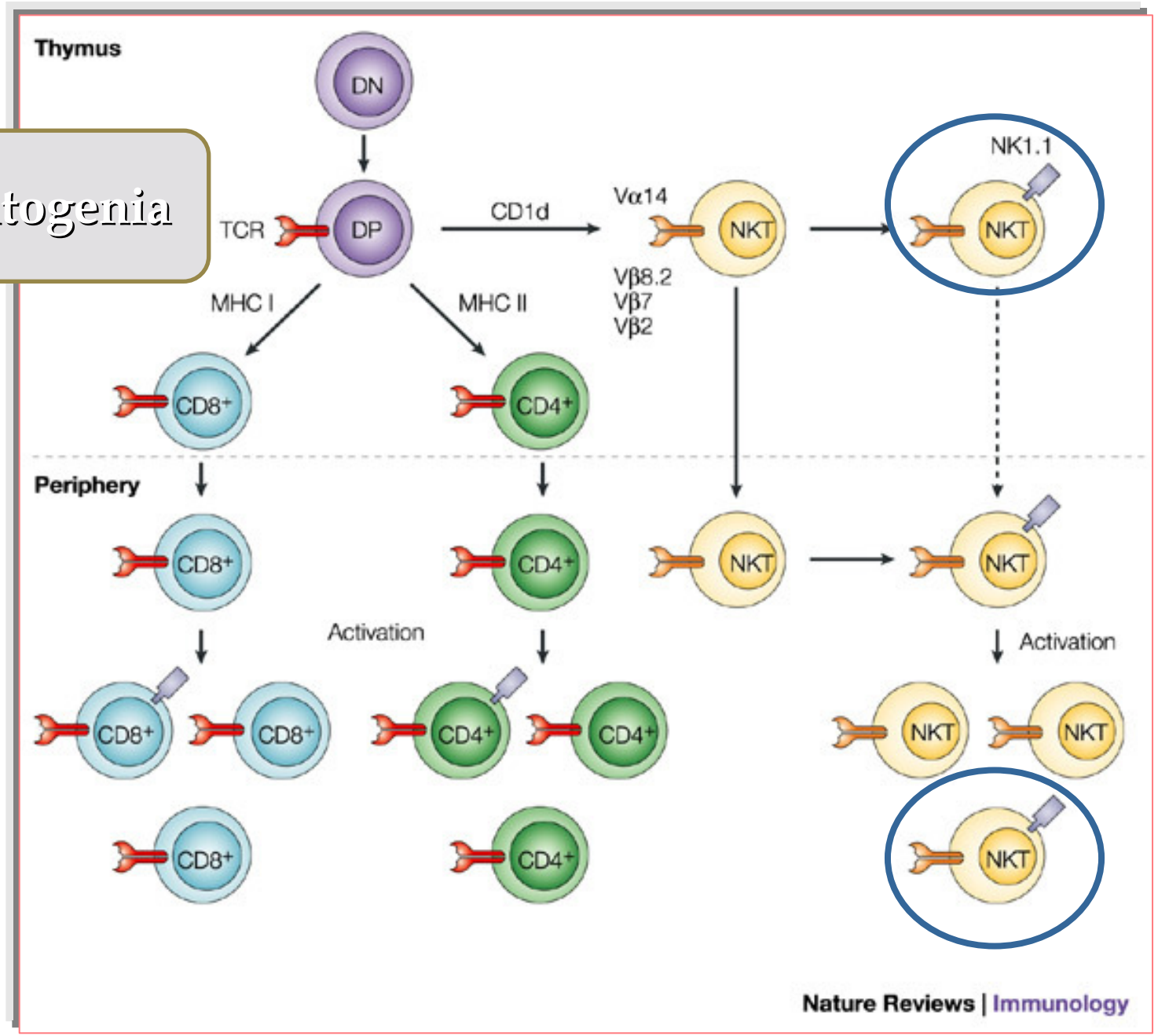

MÁS
CÉLULAS……

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

CÉLULAS NKT


NKT
Rapid/high IL-4 production
CD1d restricted
CD3/αβTCR+
Thymus-dependent
TCR-dependent
NK1.1+
Non-MHC
restricted
Cytotoxic
IFN-γ
production
MHC-I/II restricted
T
Thymus-independent
NK
Immunology Today

Ontogenia


Thymus
DN
TCR
DP
CD1d
Vα14
NKT
NK1.1
NKT
Vβ8.2
Vβ7
Vβ2
MHC I
MHC II
CD8+
CD4+
Periphery
CD8+
CD4+
NKT
NKT
Activation
Activation
CD8+
CD8+
CD4+
CD4+
NKT
NKT
CD8+
CD4+
NKT
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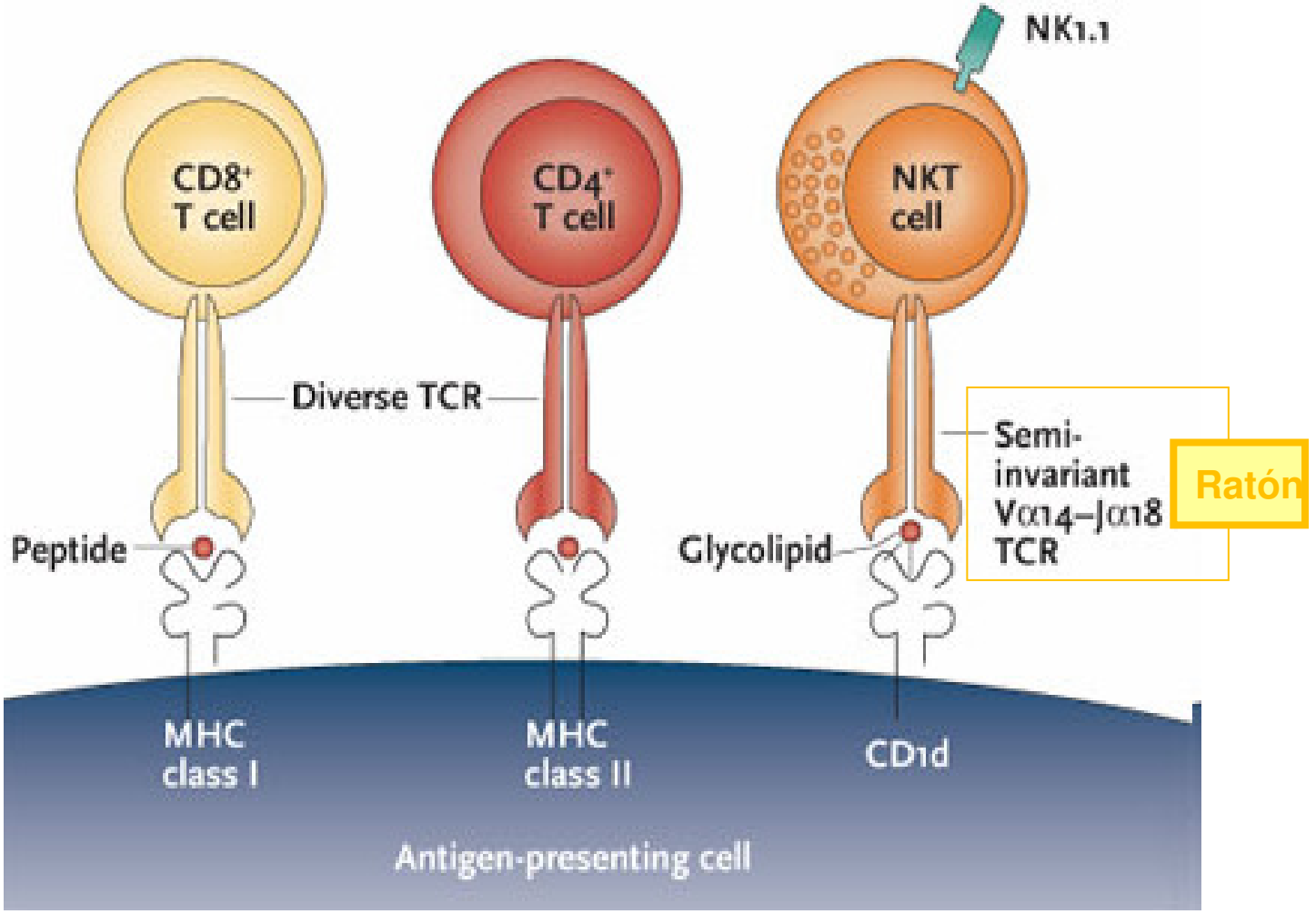

NK1.1
CD8+ T cell
CD4+ T cell
NKT cell
Diverse TCR
Semi-invariant Vα14–Jα18 TCR
Ratón
Peptide
Glycolipid
MHC class I
MHC class II
CD1d
Antigen-presenting cell

Características

- Son un subtipo de linfocitos T con dos posibles fenotipos: $CD4^+$ y $CD4^-$ $CD8^-$ (DN).
- Expresan
  1. receptores de células NK
  2. Un TCR semi-invariante, restricto por la molécula de histocompatibilidad CD1d.
- Se considera que participan en la respuesta inmune innata pues sus TCR son semiinvariantes
- Su capacidad de secretar inmediatamente grandes cantidades de citocinas (IFN-γ, IL-4, TNF) cuando sus TCR son activados les confiere un papel inmunoregulador.
- Falta de memoria inmunológica

Distribución

- ✓ **NKT pueden encontrarse en los mismos lugares que las células T, en el ratón.**
- ✓ **La relación de NKT: T varía según los distintos tejidos.**
- ✓ **NKT son más frecuentes en hígado (30–50%), médula ósea (20–30%) y timo (10–20%) .**

Las células NKTinv proporcionan cooperación a los LB……

- **Los Ag naturales presentados por CD1d a las células NKT inv se desconocen pero si se ha aislado un glicoesfingolípido de esponjas marinas llamado α-GalCer, que fija específicamente CD1d y activa a las células NKT inv**

- **Las NKTinv son tan eficientes como los linfocitos $CD4^+$ TH0 para promover in vitro la proliferación de linfocitos B autólogos y la producción de Igs.**

- Los dos mayores subtipos de células NKT expresan niveles comparables de CD40L y citocinas, e inducen niveles similares de proliferación de células B.

- Las células NKT $CD4^+$ inducen altos niveles de producción de Igs.

Hoy definidas como….

…células que tienen

una cadena invariante Vα 24-Jα 18

y

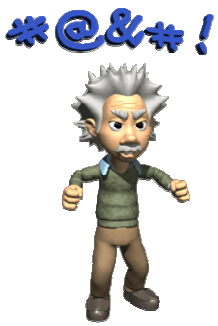
reactividad para α-GalCer.

Annu. Rev. Immunol. 2005. 26:877–900

Clasificación de NKT y NKT-like cells

	Type I cells (Classical NKT cells)	Type II cells (Non-classical NKT cells)	NKT-like cells
CD1d dependent	Yes	Yes	No
α-GalCer reactive	Yes	No	No
TCR alpha chain	Vα14-Jα18 *(mice)* Vα24-Jα18 *(human)*	Diverse	Diverse
IL-4 production	Yes	Yes	No
IFN-γ production	Yes	Yes	Yes

SUS FUNCIONES….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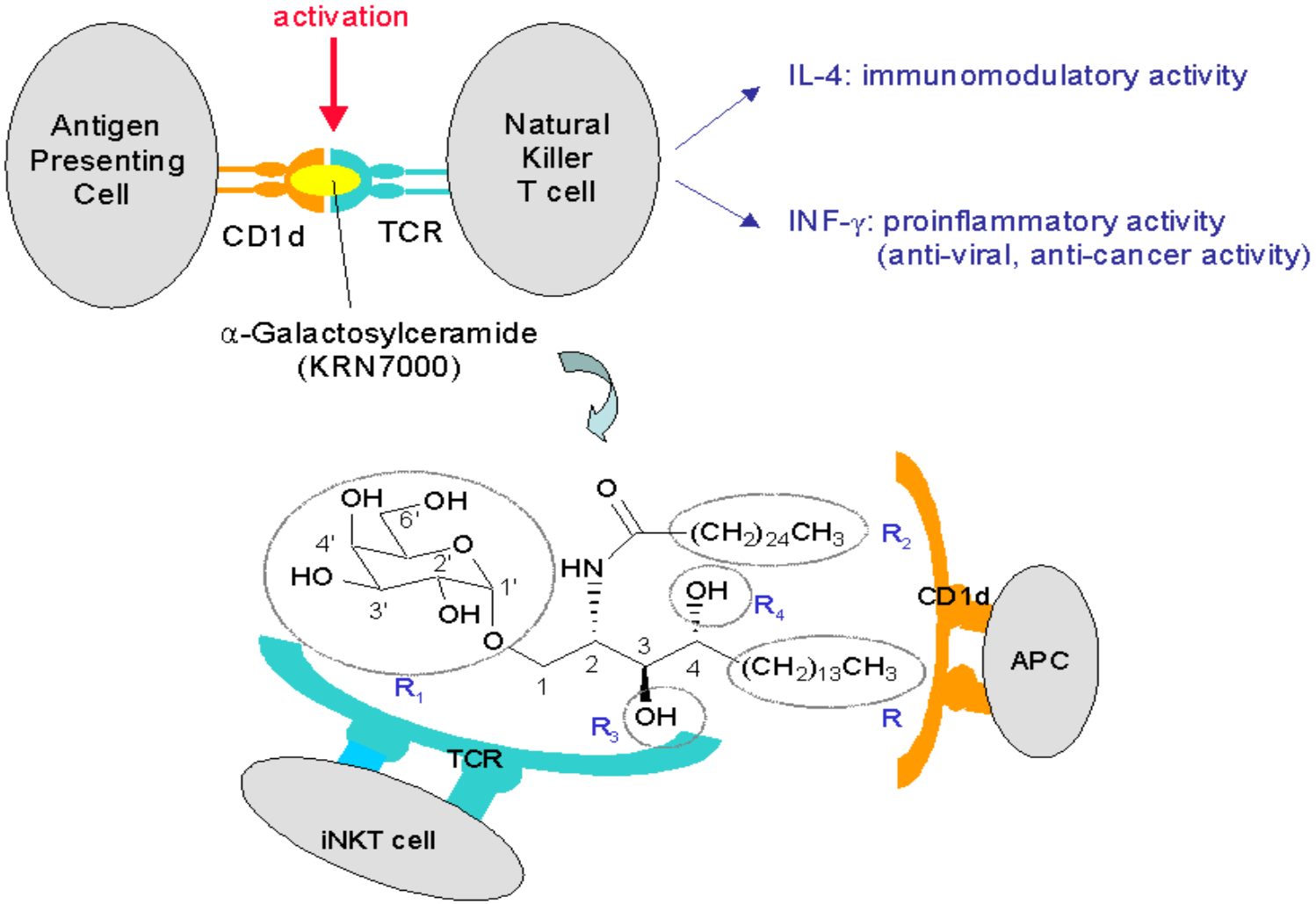
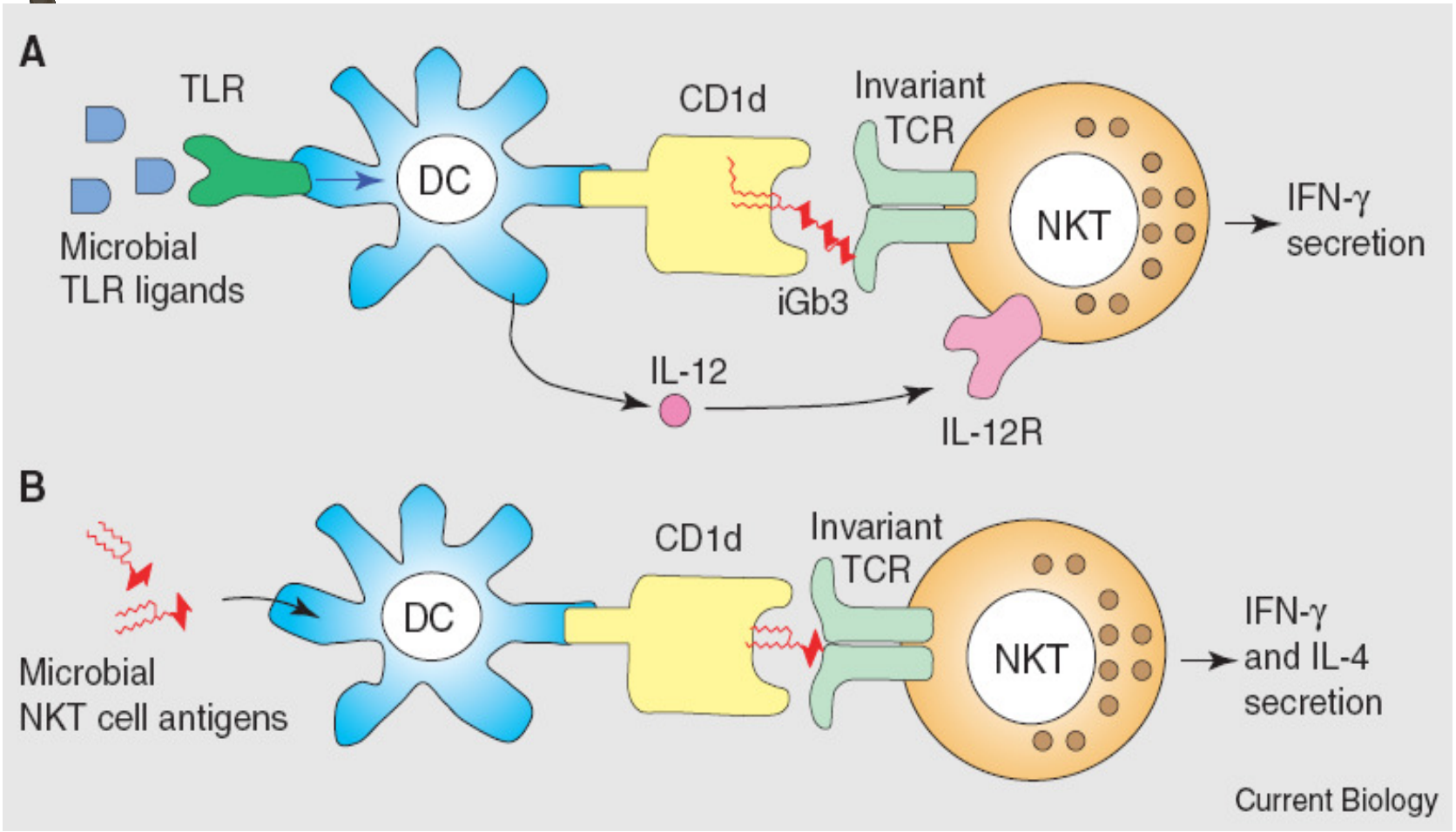
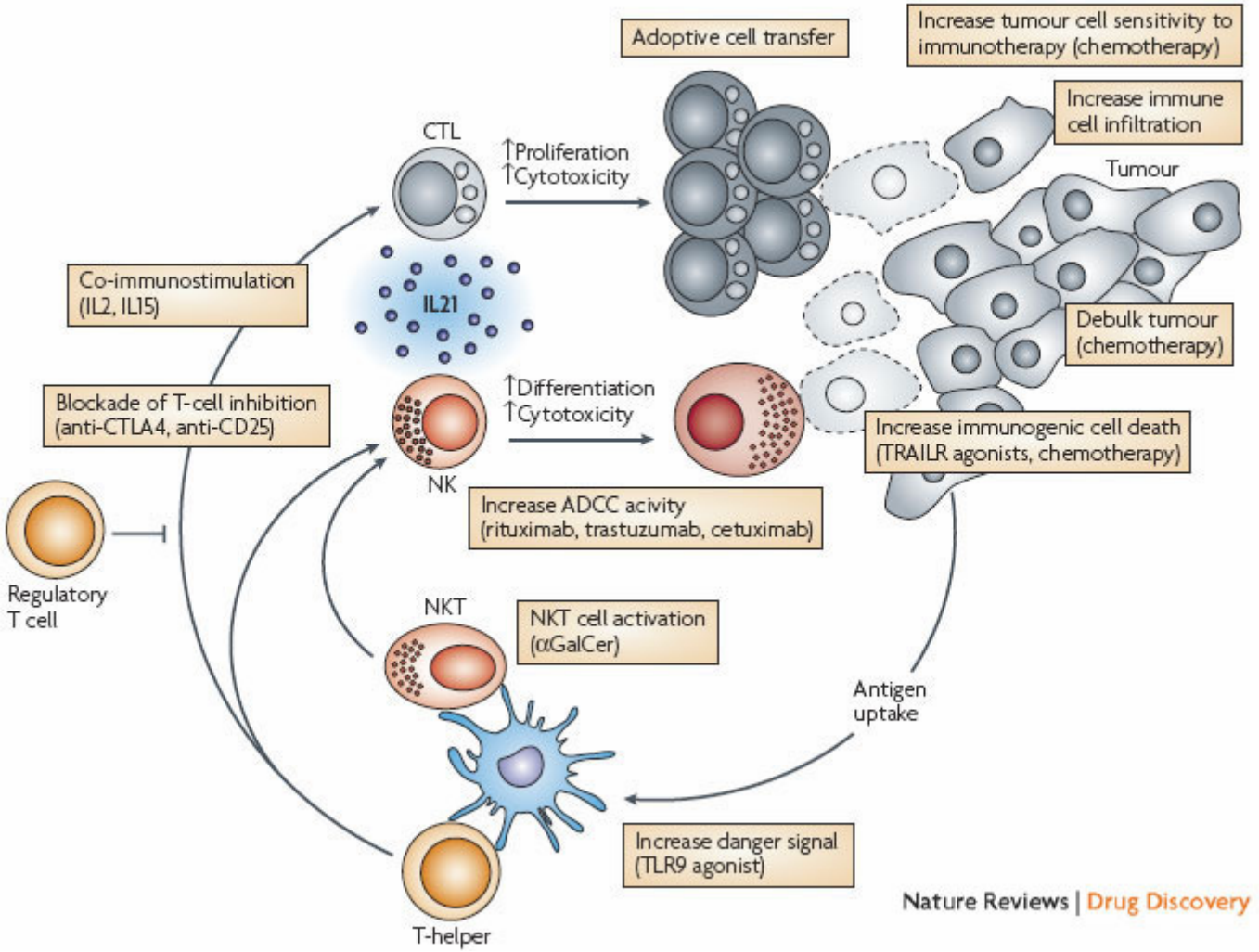

activation
Antigen Presenting Cell
CD1d
TCR
Natural Killer T cell
IL-4: immunomodulatory activity
INF-γ: proinflammatory activity
(anti-viral, anti-cancer activity)
α-Galactosylceramide
(KRN7000)
OH
OH
6'
4'
O
2'
HO
1'
3'
OH
O
HN
O
(CH2)24CH3
R2
OH
R4
CD1d
APC
1
2
3
4
(CH2)13CH3
R1
R3
OH
R
TCR
iNKT cell

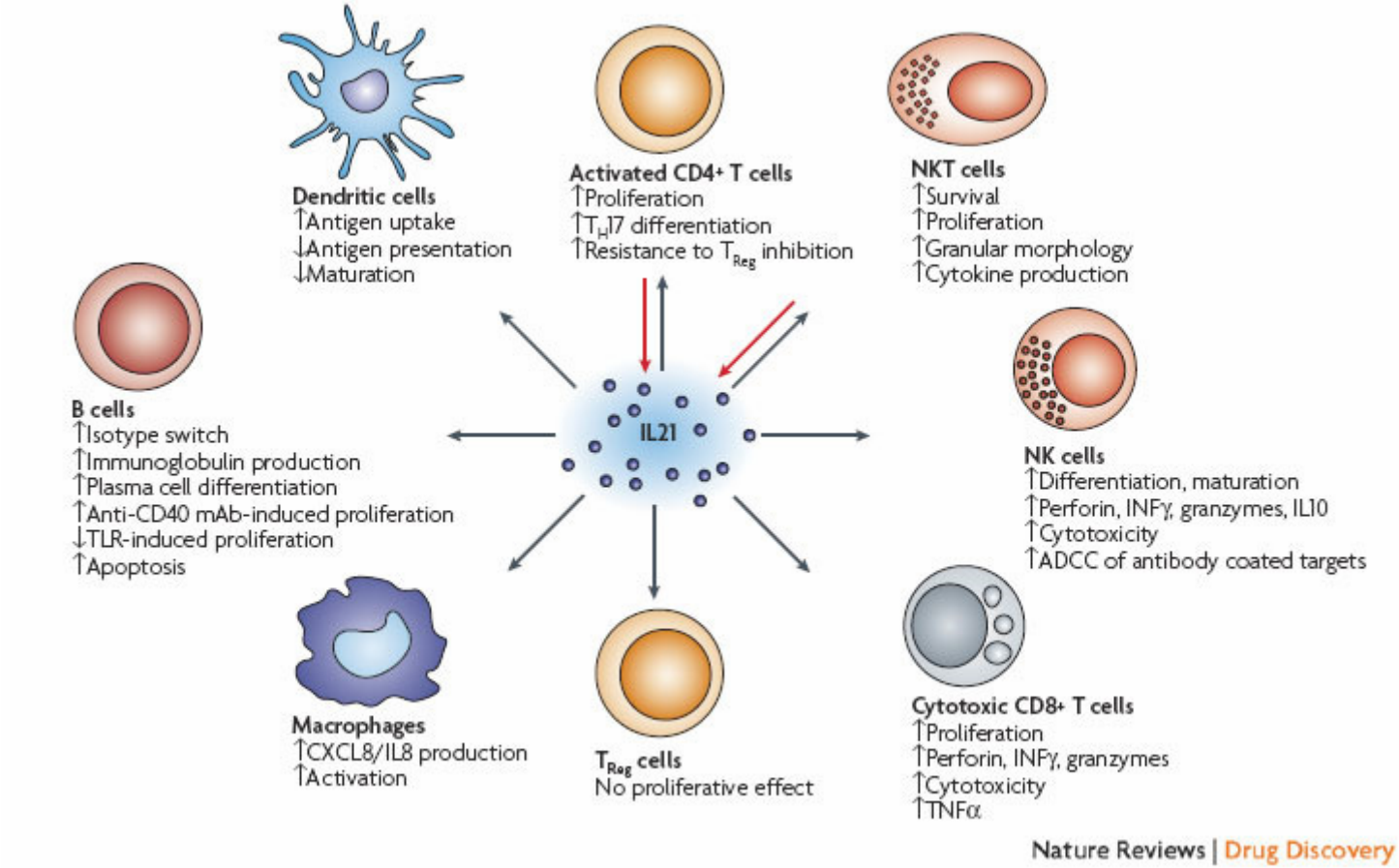
Control de infecciones



Inmunidad antitumoral

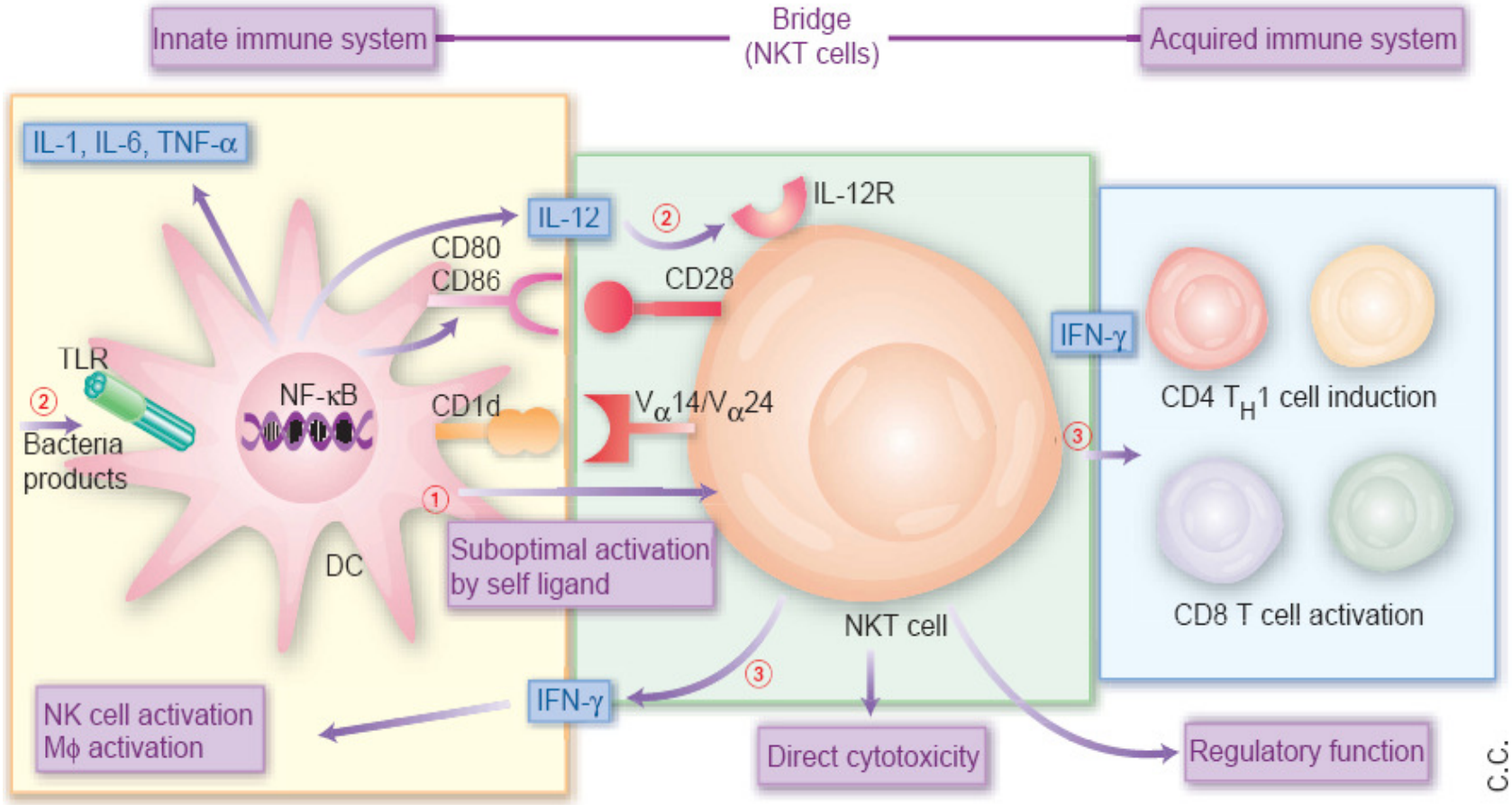


Nature Reviews Drug Discovery 7, 231-240 (March 2008)



Nature Reviews Drug Discovery 7, 231-240 (March 2008)

”Bridging” la inmunidad innata y la adquirida...



Nature Immunology Vol 4 Nº 12 December 2003

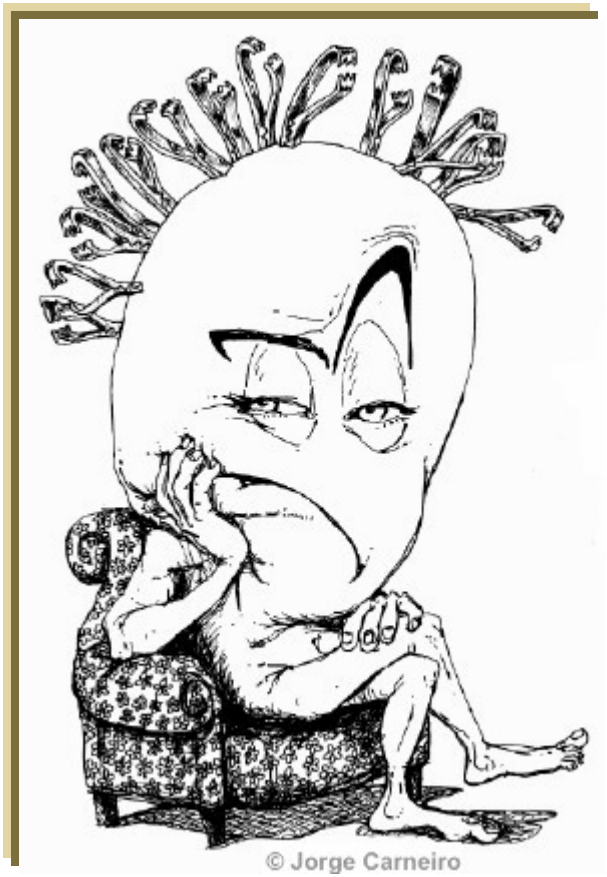
Implicaciones inmunopatogénicas

* Enfermedades autoinmunes: artritis reumatoide, PTA

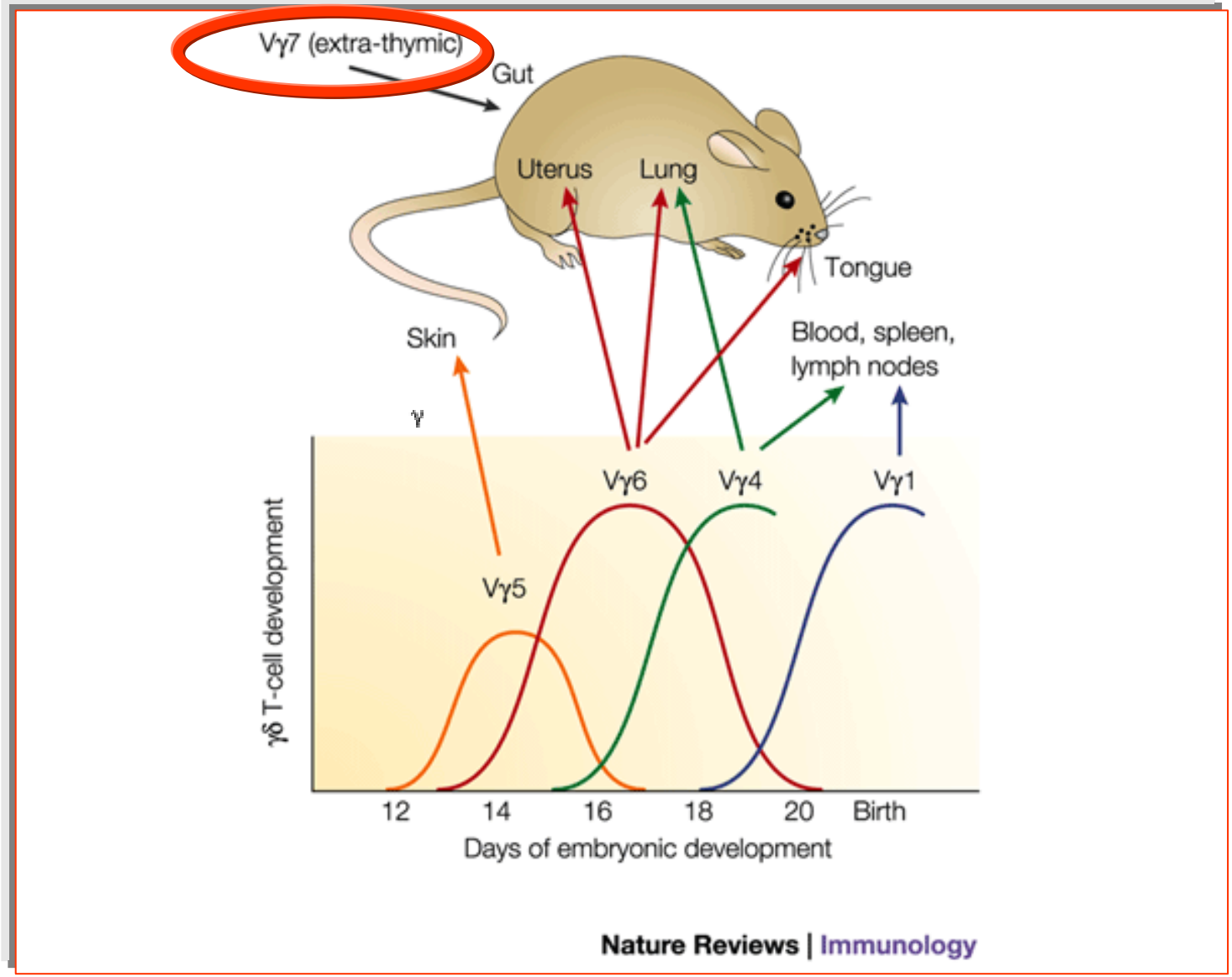
* Fracaso de la tolerancia injerto placentaria

* Rechazo de trasplantes

* Enfermedad de injerto frente a huésped



CÉLULAS Tγδ


Vγ7 (extra-thymic)
Gut
Uterus
Lung
Tongue
Skin
Blood, spleen,
lymph nodes
γ
Vγ6
Vγ4
Vγ1
Vγ5
γδ T-cell development
12
14
16
18
20
Birth
Days of embryonic development
Nature Reviews | Immunology

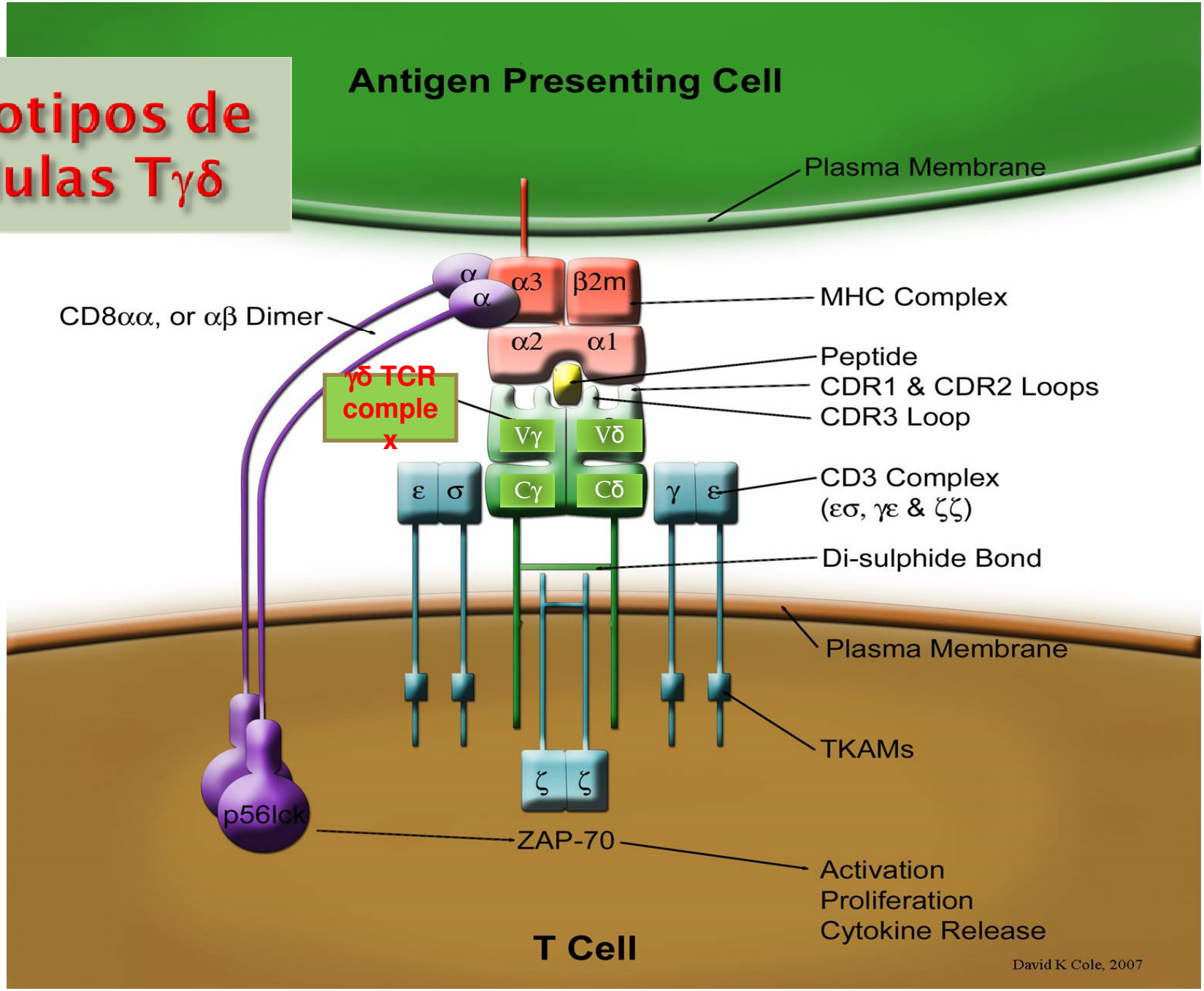
Algunas características.....

Table 1 | **γδ T cells can be distingulshed from other lymphocyte lineages**

Characteristic	αβ T cells	γδ T cells	B cells
Antigen-receptor configuration	CD3 complex + αβ TCR	CD3 complex + γδ TCR	Ig
Theoretical receptor number	~10^{15}	~10^{20}	~10^{11}
Antigen recognition	Peptide + MHC	Protein and non-protein	Protein and non-protein
MHC restriction	Yes	Rare	No
Phenotype	$CD4^+$ or $CD8^+$	Most are $CD4^-CD8^-$; iELs are $CD8(\alpha\alpha)^+$	$CD19^+CD20^+$
Frequency in blood	65–75%	1–5% (25–60% in gut)	5–10%
Distribution	Blood and lymphoid tissues	Blood, epithelial and lymphoid tissues	Blood and lymphoid tissues
Effector capability	CTLs ($CD8^+$) Cytokine release (T_H1/T_H2)	CTLs Cytokine release ($T_H1>T_H2$)	Ig production
Function	Immune protection and pathogen eradication	Immunoregulation and immunosurveillance	Humoural immunity

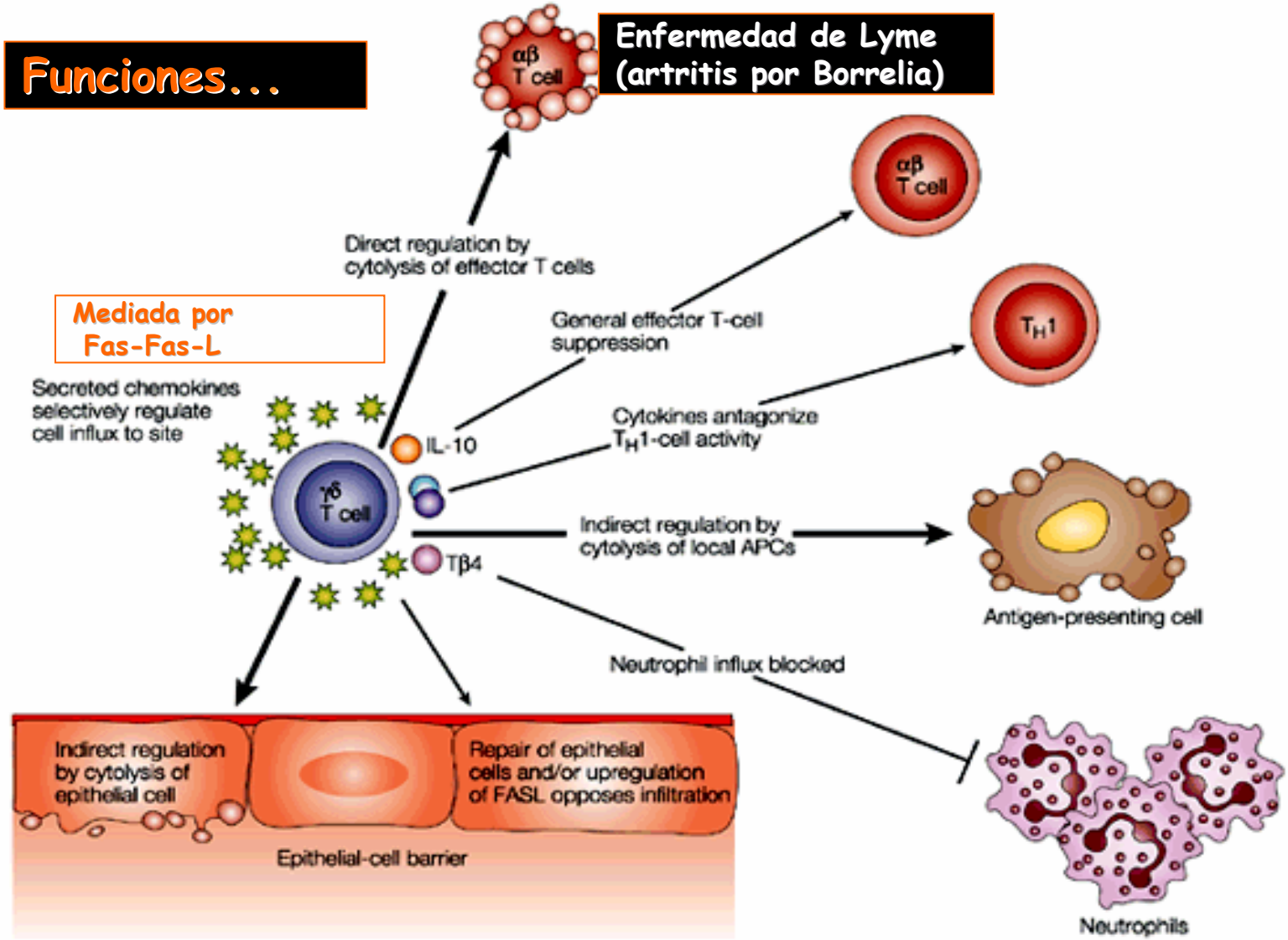
CTLs, cytotoxic T lymphocytes; iELs, intestinal intraepithelial T lymphocytes; Ig, immunoglobulin; T_H cell, T helper cell; TCR, T-cell receptor. Data adapted from REFS 64,65.

Fenotipos de células Tγδ



Funciones...

Enfermedad de Lyme (artritis por Borrelia)



Tβ 4, thymosin- β4;

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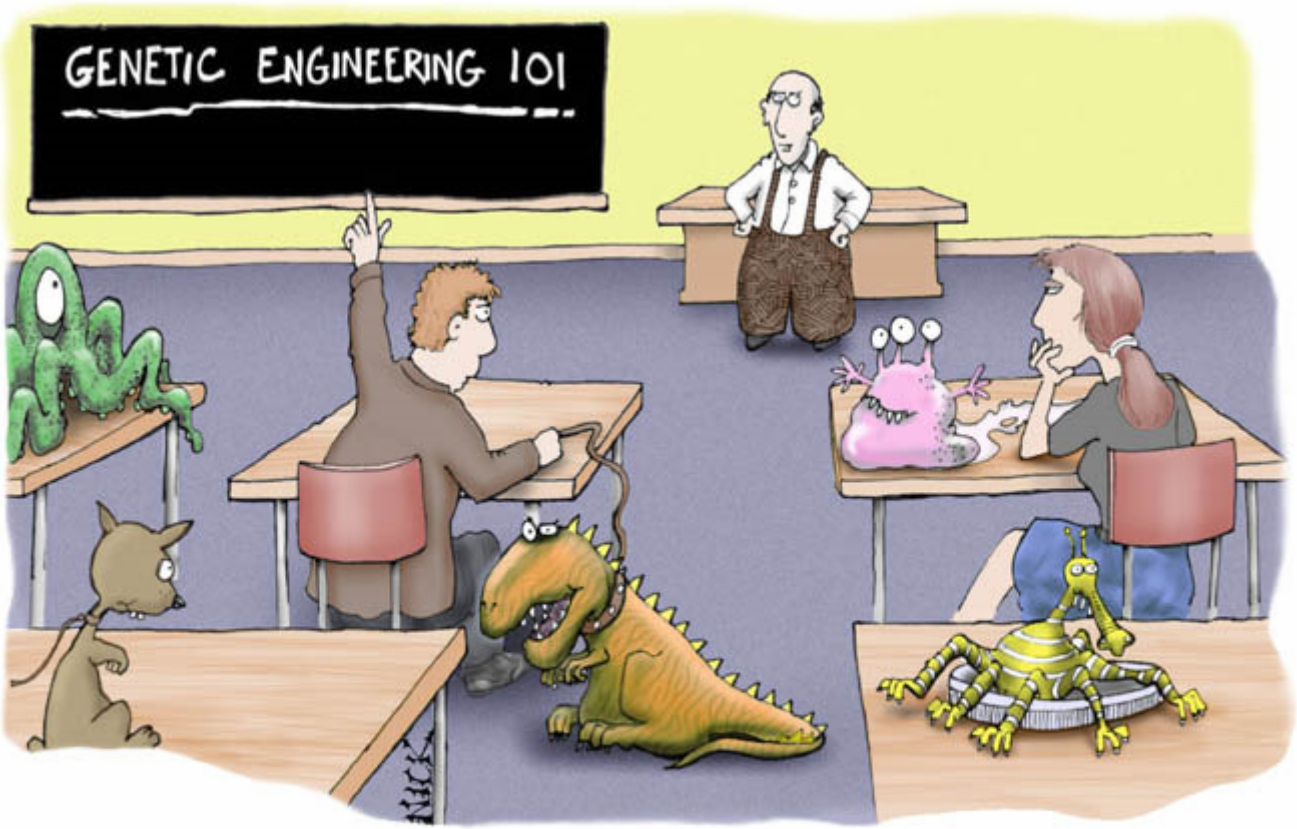
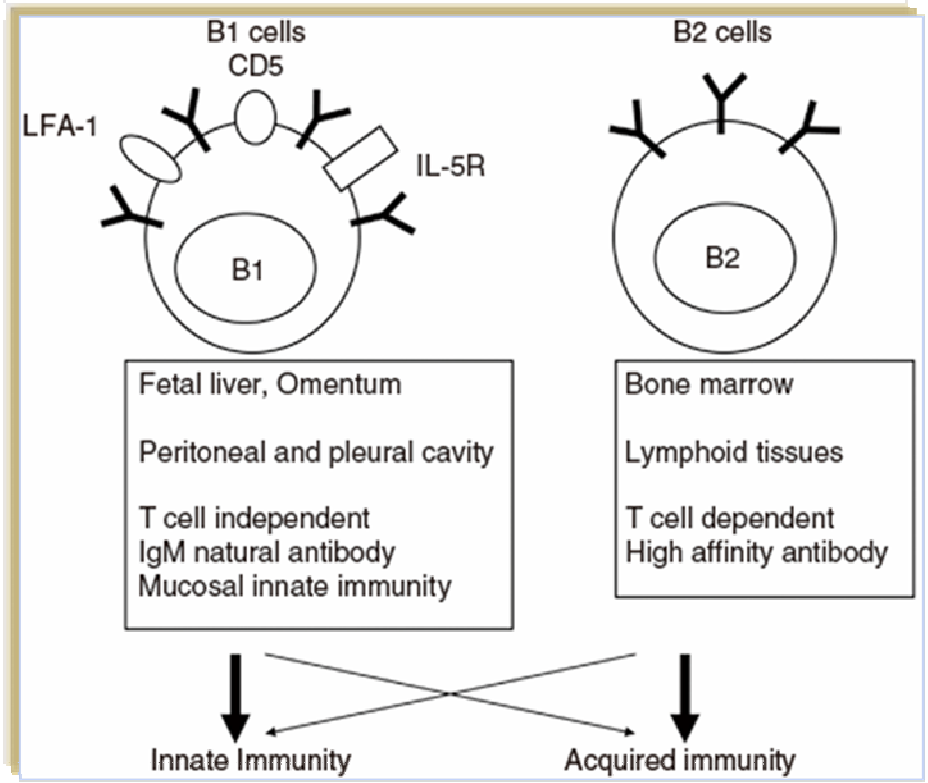


"Okay—is there anybody ELSE whose homework ate their dog?"

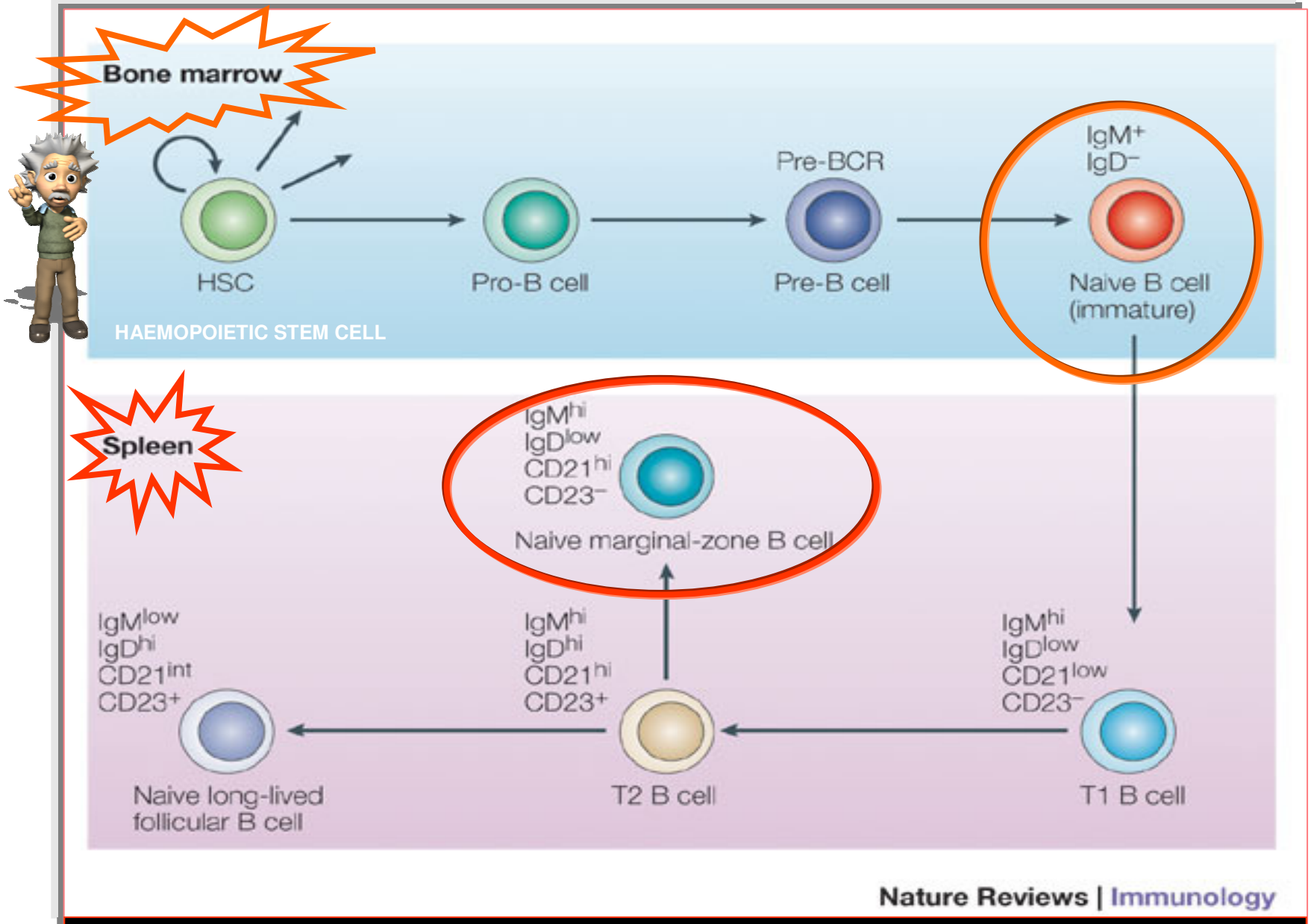
LINFOCITOS B_1

LINFOCITOS B1

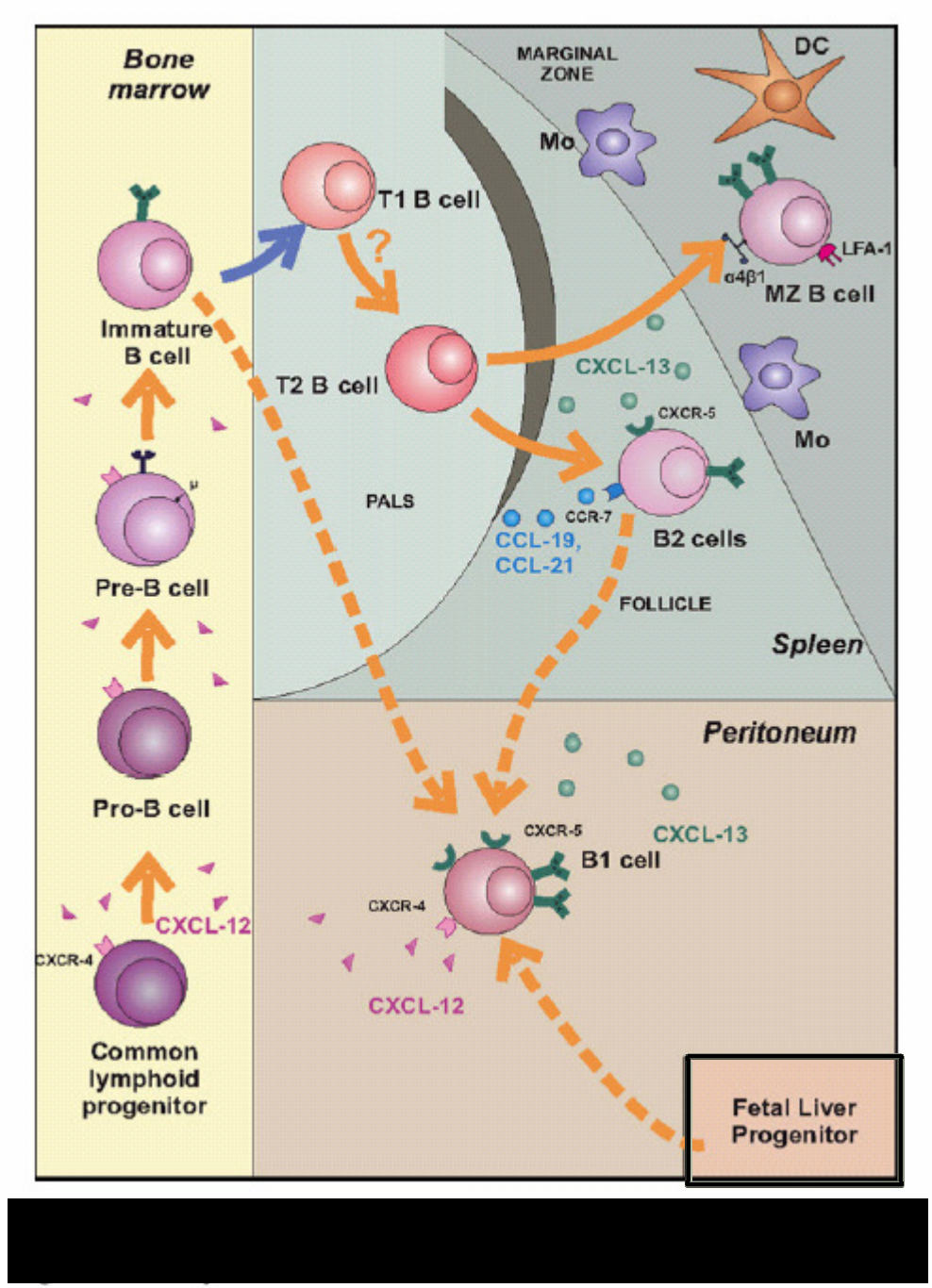


Omento: lámina constituída por una bicapa de células mesoteliales que conecta el bazo, páncreas, estómago y colon.

- **En el humano representan alrededor del 5% de la población total de LB, no así en otras especies (conejos y bovinos).**
- **Expresan CD5 aunque no es un componente indispensable del linaje B-1.**
- **Los anticuerpos producidos por LB-1 exhiben escasa afinidad por sus antígenos y en general son multiespecíficos.**

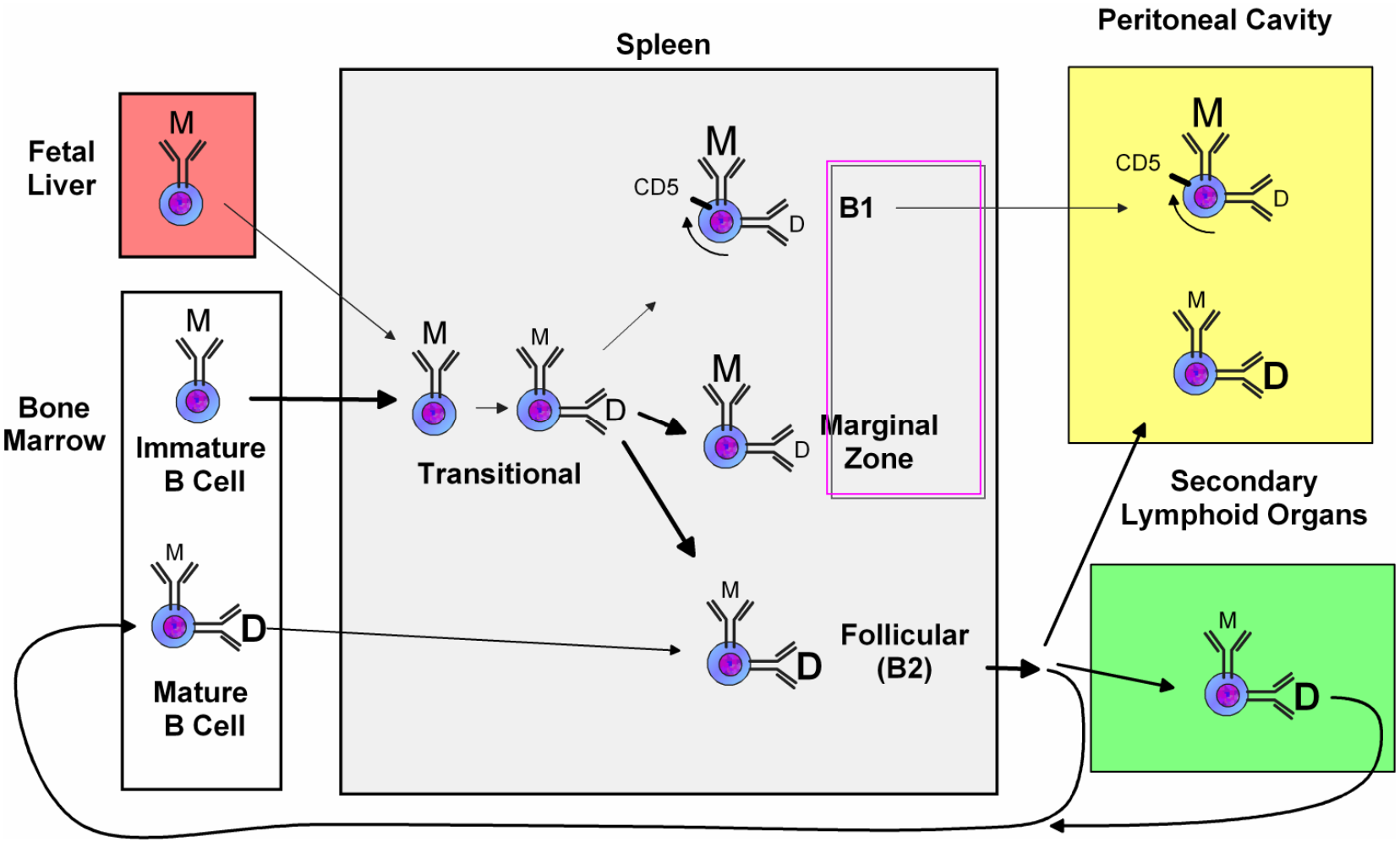


Desarrollo de células B antígeno independiente



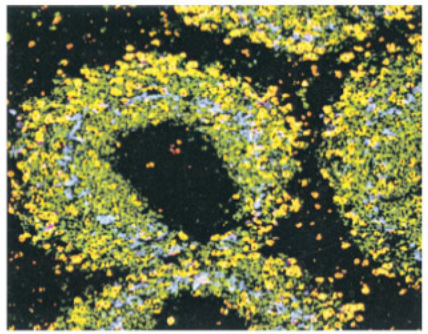
Homing de las células B en órganos y cavidades

Tres tipos de células B maduras



Células B1 constituyen el 30-50% (1 x 10^6 cells) de las células B en cavidades peritoneal y pleural.

Células B1 representan 2% (1 x 10^6 cells) de las células B cells en el bazo, pero raro hallarlas en ganglios linfáticos.



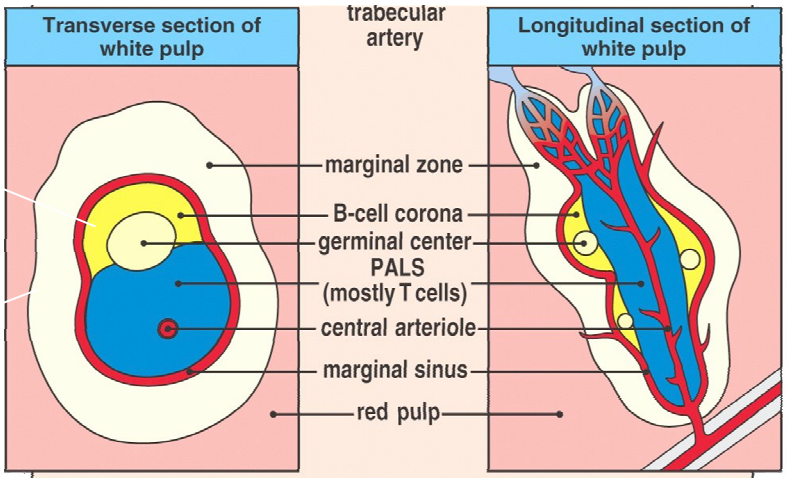


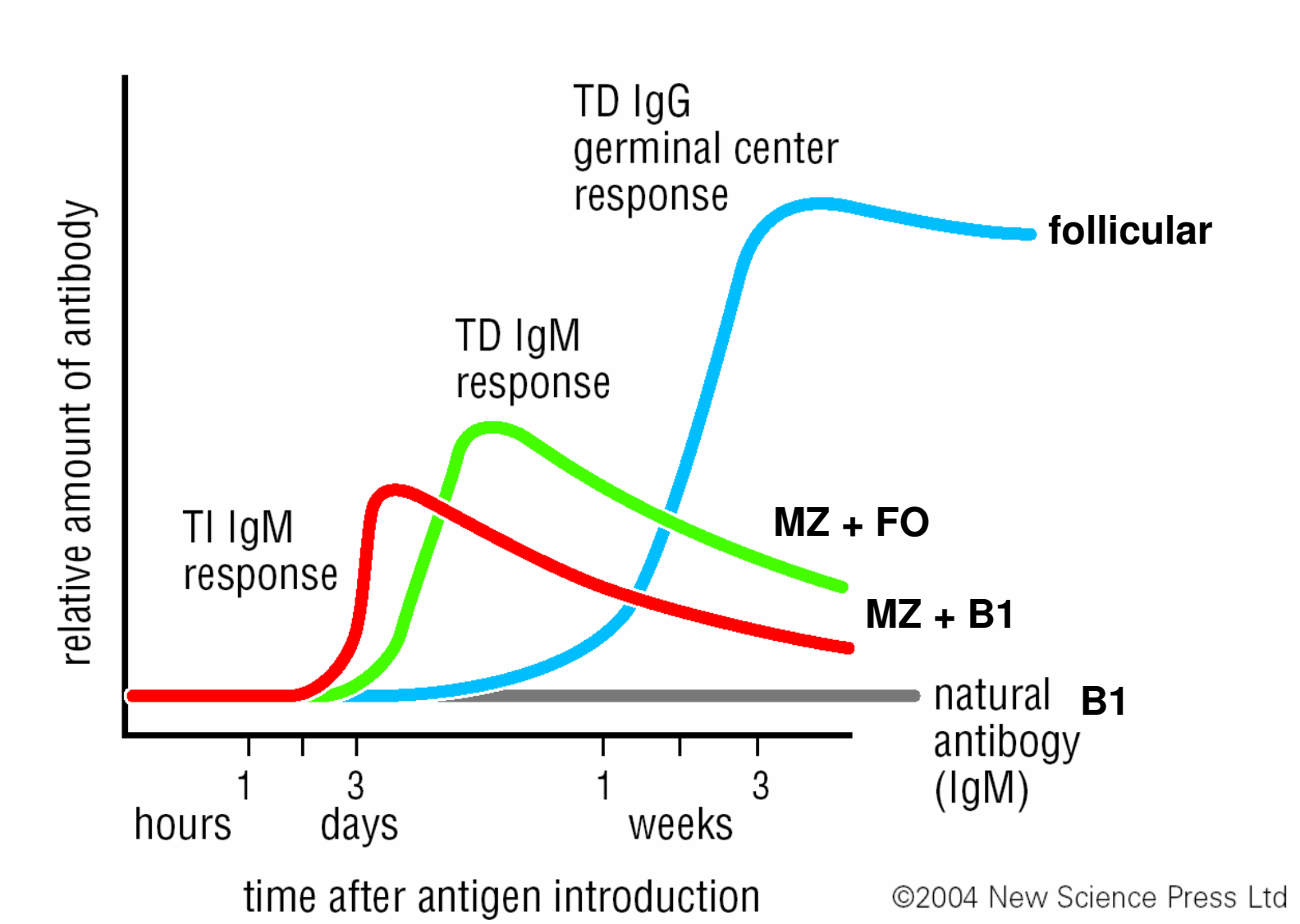
Table 1

Characteristic features of four distinct B-cell subsets.

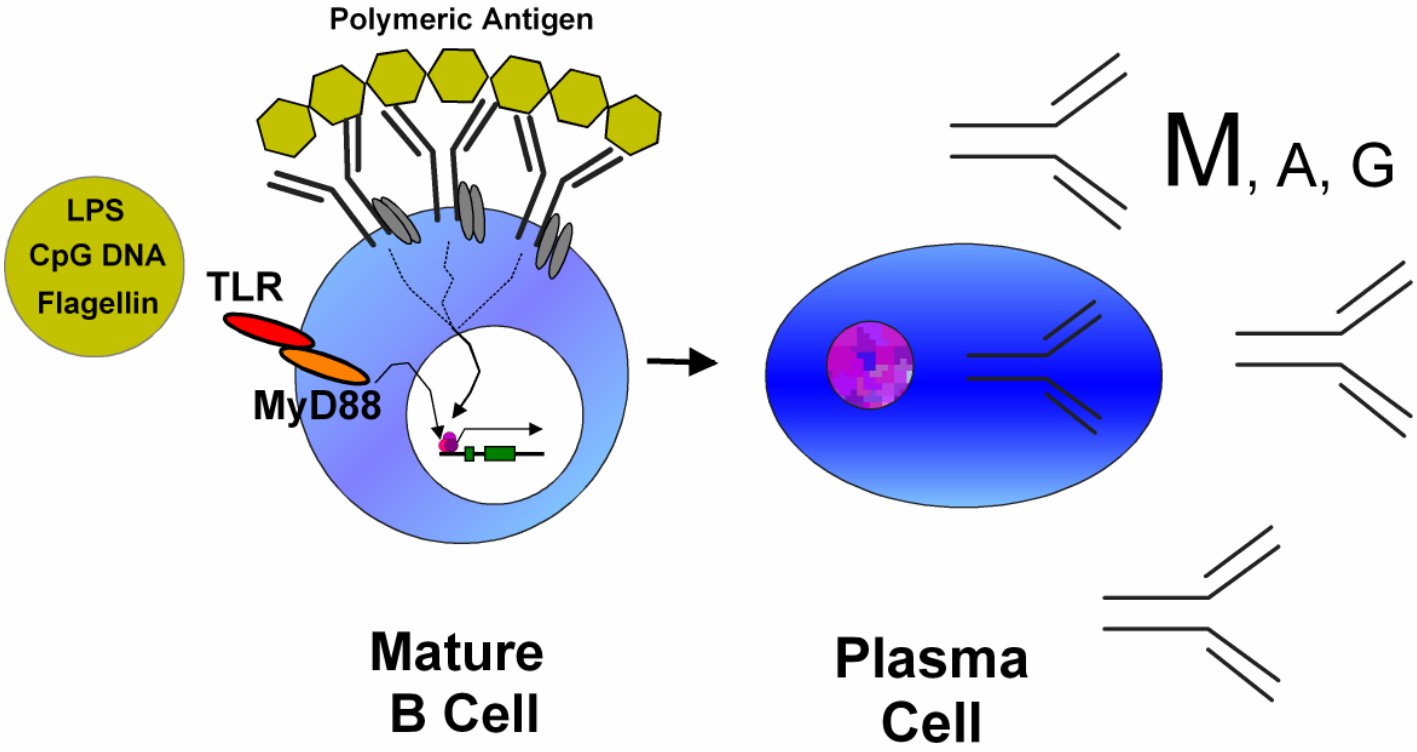
	B-1a	B-1b	MZ	B-2/follicular
CD19	+	+	+	+
CD45R/B220	+	+	++	++
IgM	++	++	+++	+
IgD	+/–	+/–	+/– to ++	++
CD5	+	–	–	–
Mac-1/CD11b	+ (PerC only)	+	–	–
CD43	++	++	–	–
CD21	+	+	+++	++
BCR signaling	+++	++	+	+/–
Notch-2	+?	+?	++	–
BAFF	–	–		+
Location	Spleen, PerC	PerC	Spleen	Spleen, lymph node
Development	Mainly fetal	Fetal and adult	Fetal and adult	Mainly adult
BCR diversity	Restricted	Restricted	Restricted	Diverse
Response	T cell independent; carbohydrate	T cell independent; carbohydrate	Blood-borne particulate	T cell dependent; protein
Natural autoantibody	+	+	+	–

Abbreviation: PerC, peritoneal cavity washout cells.

Roles biológicos de los distintos tipos de células B

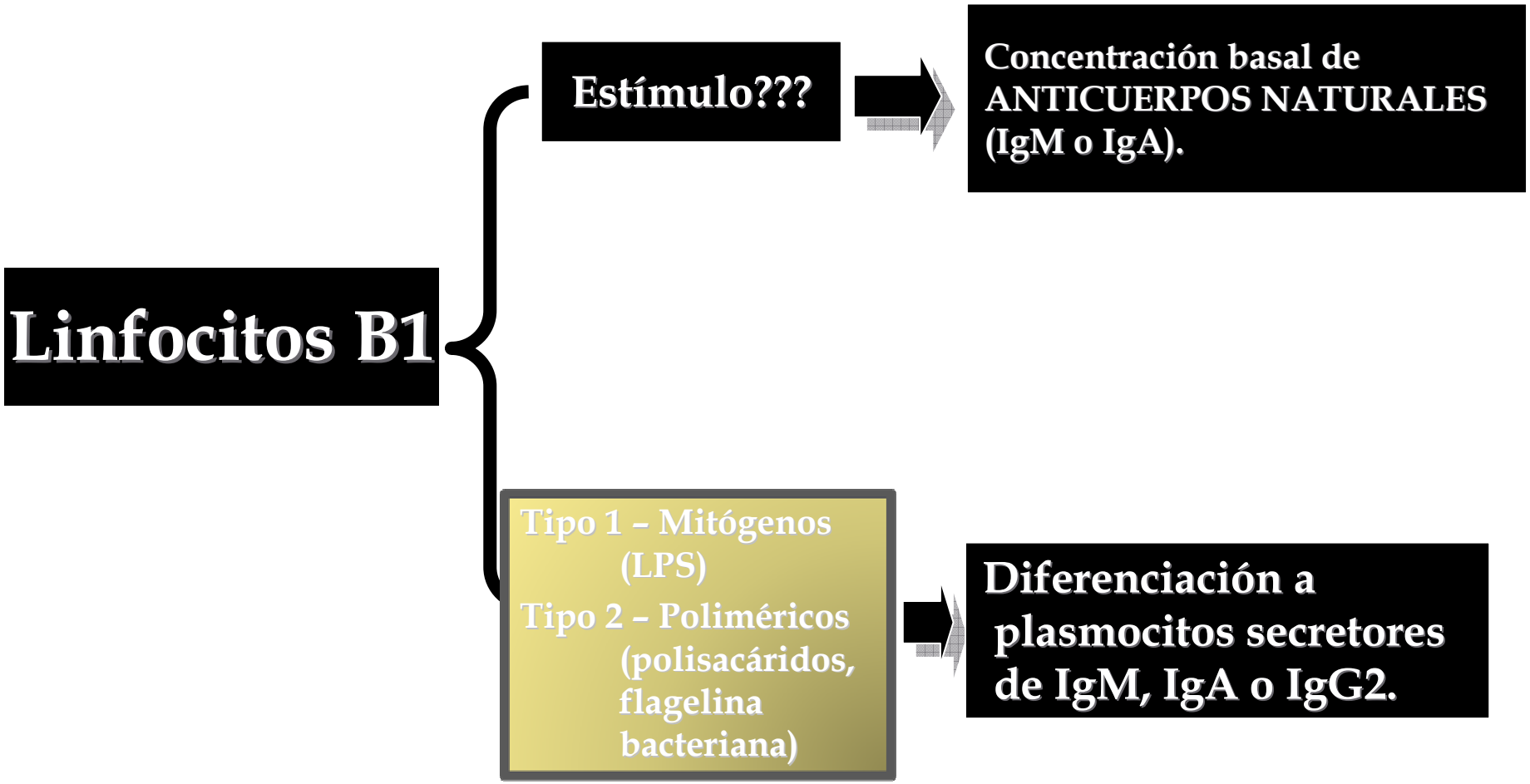


Respuesta T-independiente



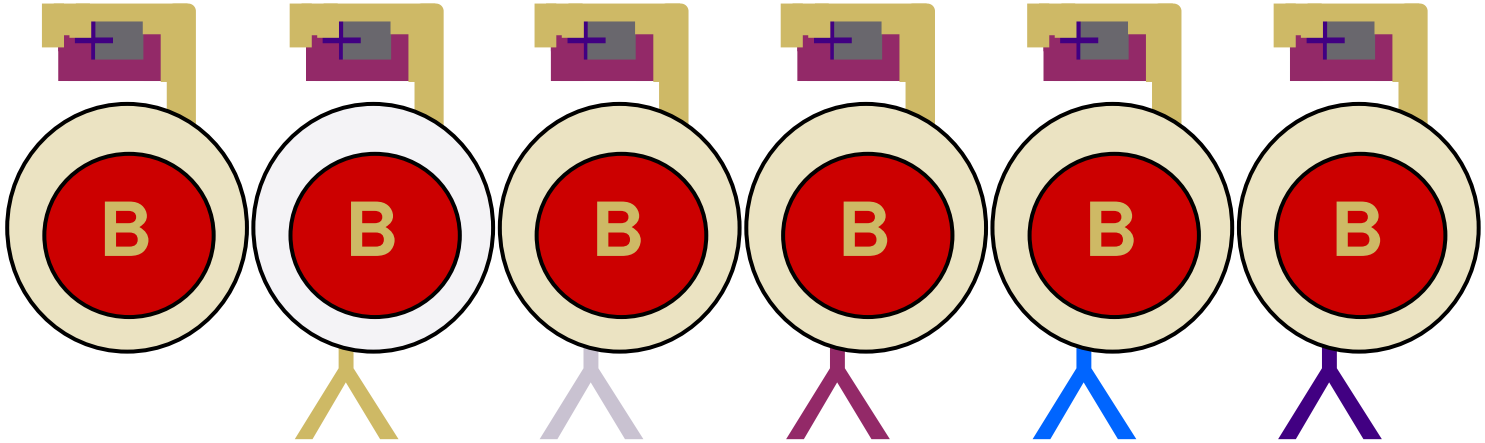
- Tipo 1 – Mitógenos (LPS)
- Tipo 2 – Poliméricos (polisacáridos, flagelina bacteriana)

Recordemos algo importante….



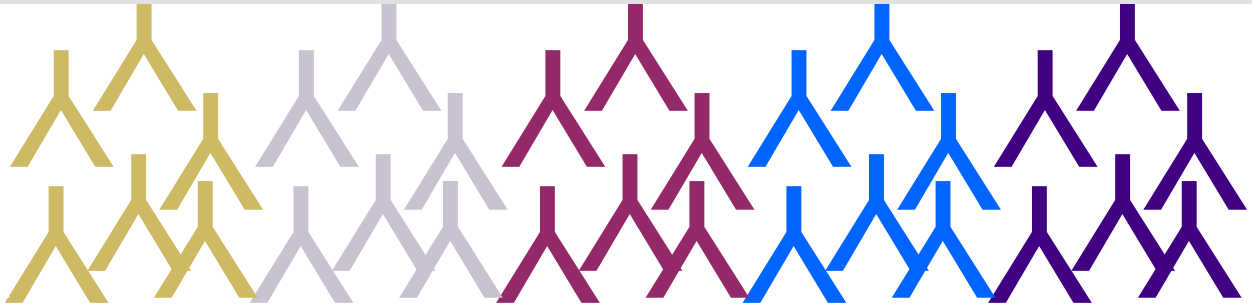
Antígenos T independientes

LPS forma complejos con CD14, LBP y TLR4



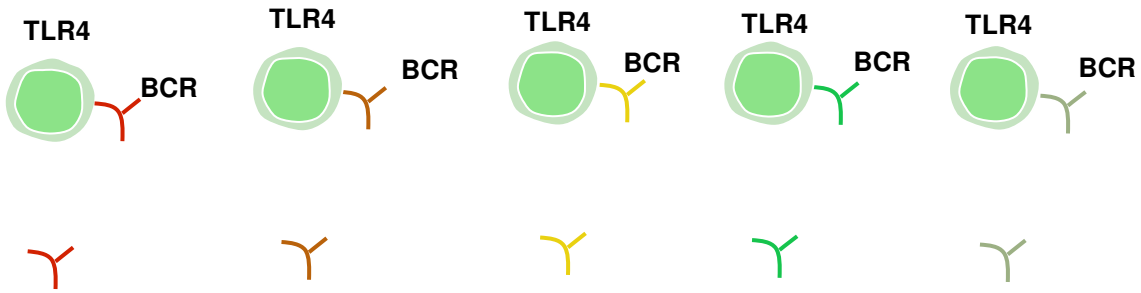
Los linfocitos B requieren antígenos diferentes para activarse....

Antígenos TI-1 (LPS), en **ALTAS CONCENTRACIONES** pueden **ACTIVAR POLICLONALMENTE** a todas las células B, independientemente de su especificidad ➡ **MITÓGENOS.**



Respuesta TI-I

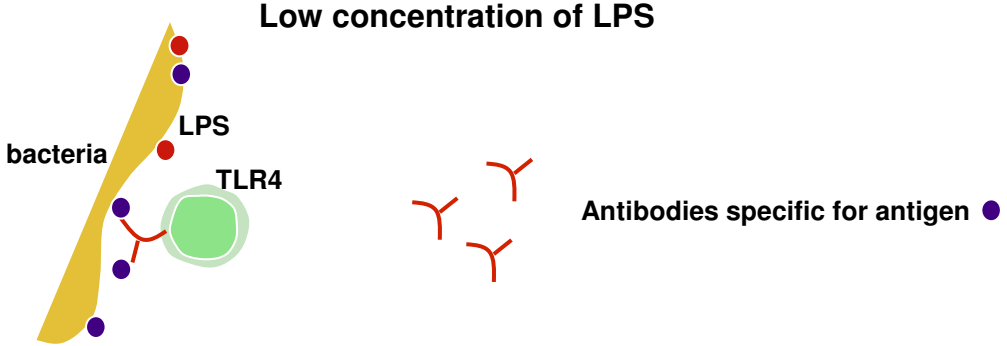
High concentration of LPS (B cell mitogen)



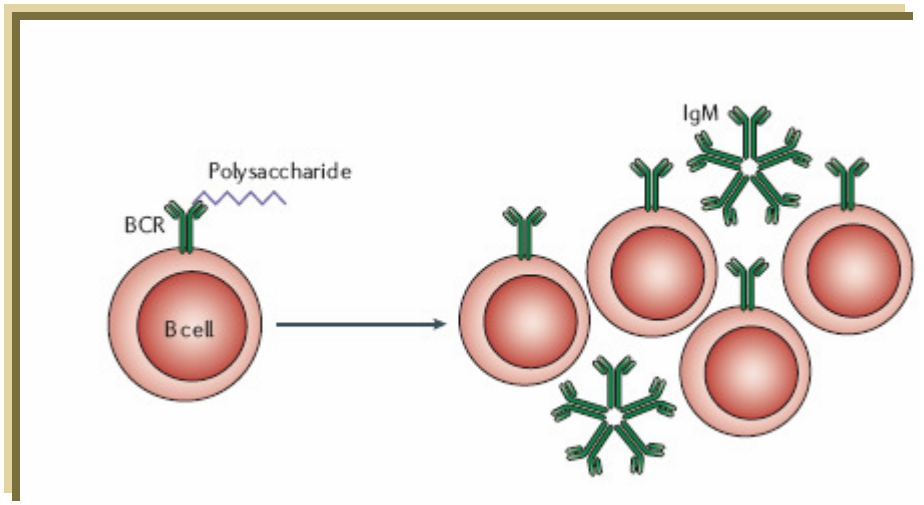
Polyclonal activation of B cells

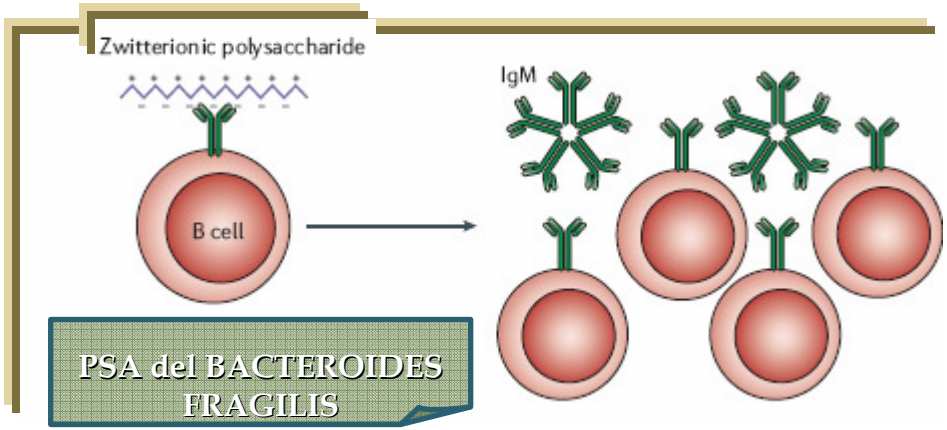
Class switching to IgG3, IgG2b; No affinity maturation or memory.

Low concentration of LPS



Respuesta TI-2





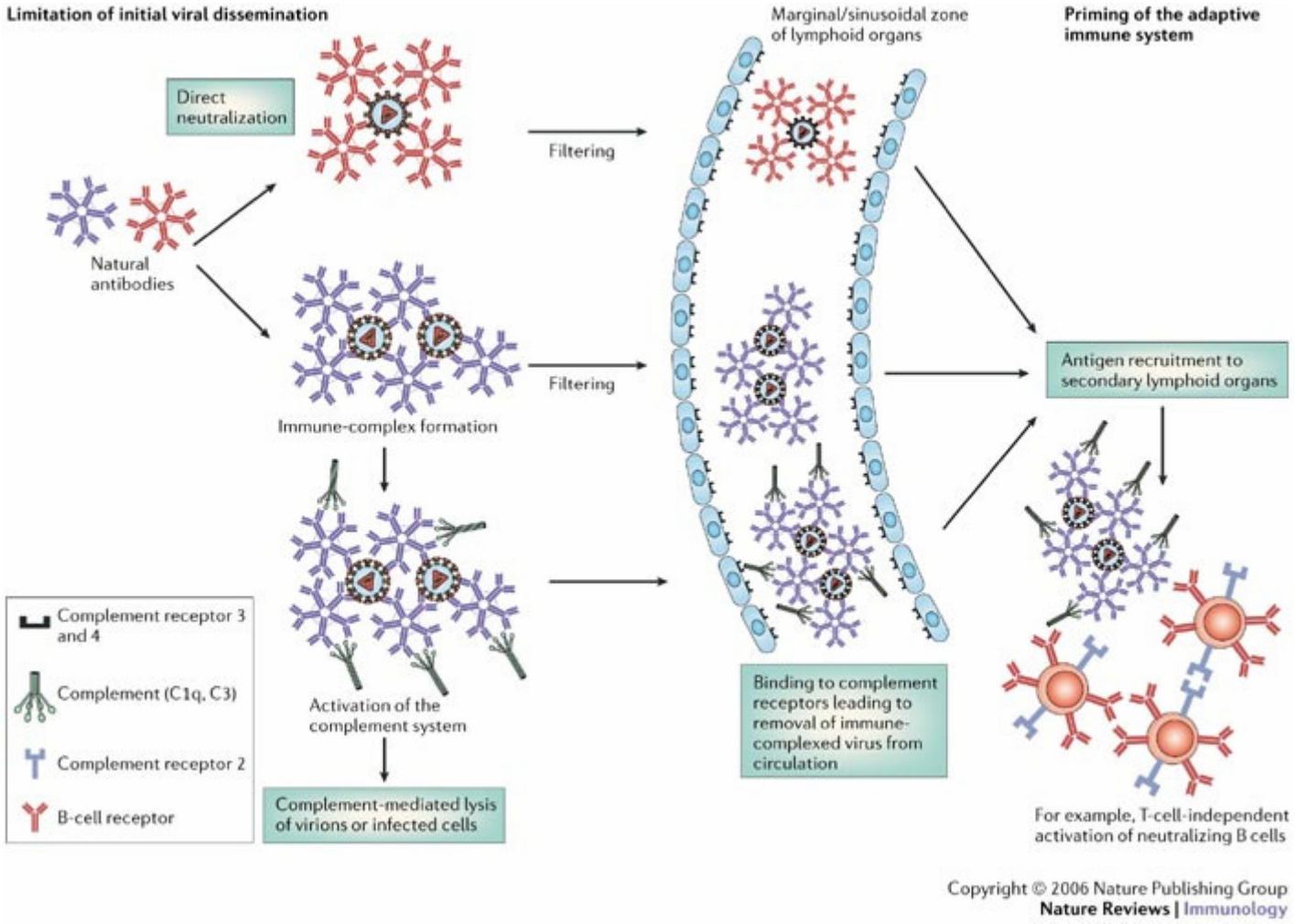
- Anticuerpos frente a antígenos TI-2 son de isotipo IgM, IgG3 .
- Células B1 producen IgA en el intestino.
- NO hay MADURACIÓN DE LA AFINIDAD.
- NO hay MEMORIA INMUNOLÓGICA.

Células MZB y B1 median la respuesta temprana TI contra la infección.

B_1 Y ANTICUERPOS NATURALES

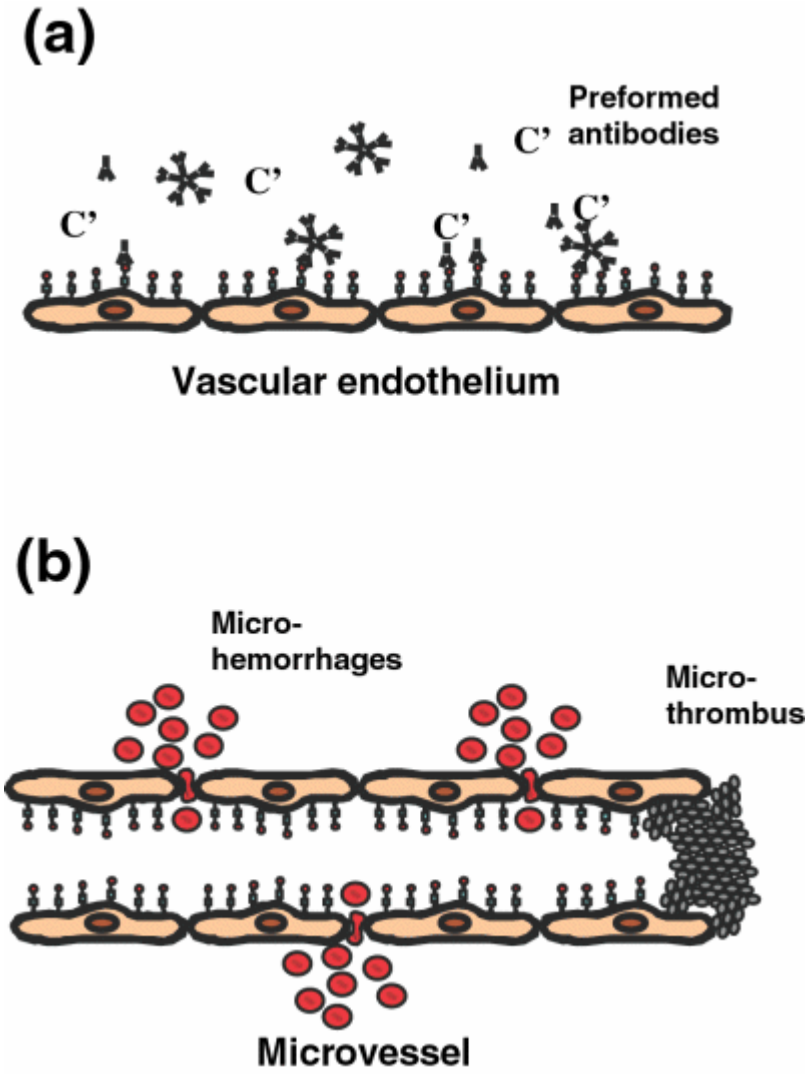
Lo que nos beneficia…….

- **Son anticuerpos presentes en el suero de individuos normales, generados en ausencia de estímulo antigénico exógeno.**
- Son capaces de proteger frente a determinadas infecciones.
- Participan en la depuración de células apoptóticas.
- Desempeñan un papel en la vigilancia inmunitaria contra los tumores.
- A nivel intestinal, la IgAs protege la mucosa intestinal de las posibles acciones nocivas de la flora comensal, como la penetración en los tejidos del huésped.



Natural antibodies provide an important link between the innate and adaptive immune systems. Before the adaptive immune system is activated, they restrict viral dissemination by direct neutralization, complement activation and elimination of virus in the marginal/sinusoidal zone of secondary lymphoid organs. Moreover, natural antibodies favour priming of the adaptive immune system by contributing substantially to antigen recruitment in secondary lymphoid organs.

Pero, hay circunstancias donde son dañinos…..



Hyperacute rejection following ABO-incompatible allotransplantation (e.g. kidney transplantation) or pig-to-human organ xenotransplantation, which occurs within minutes following the binding of preformed natural antibodies (mainly of the IgM class) to target carbohydrate epitopes on blood vessel endothelial cells of the transplanted organ. Antibody binding leads to complement fixation and activation. Subsequent activation, retraction and destruction of endothelial cells lead to the formation of microhaemorrhages and microthrombi, causing a cessation of blood flow and organ damage

Linfocitos B1 asociados a enfermedades

- Enfermedades autoinmunes.

- Enfermedad por transformación maligna (leucemia linfocítica crónica (CD5+).

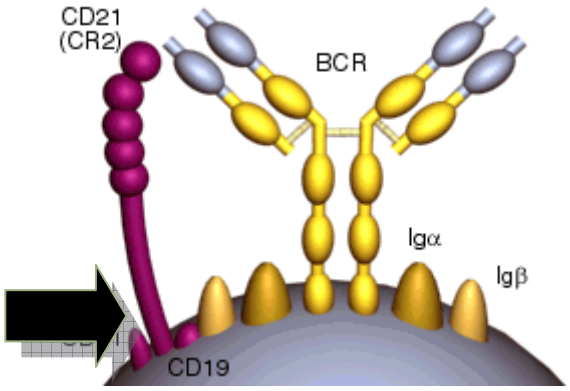
LINFOCITOS MZB

Phenotypes of naïve mature B cell subtypes

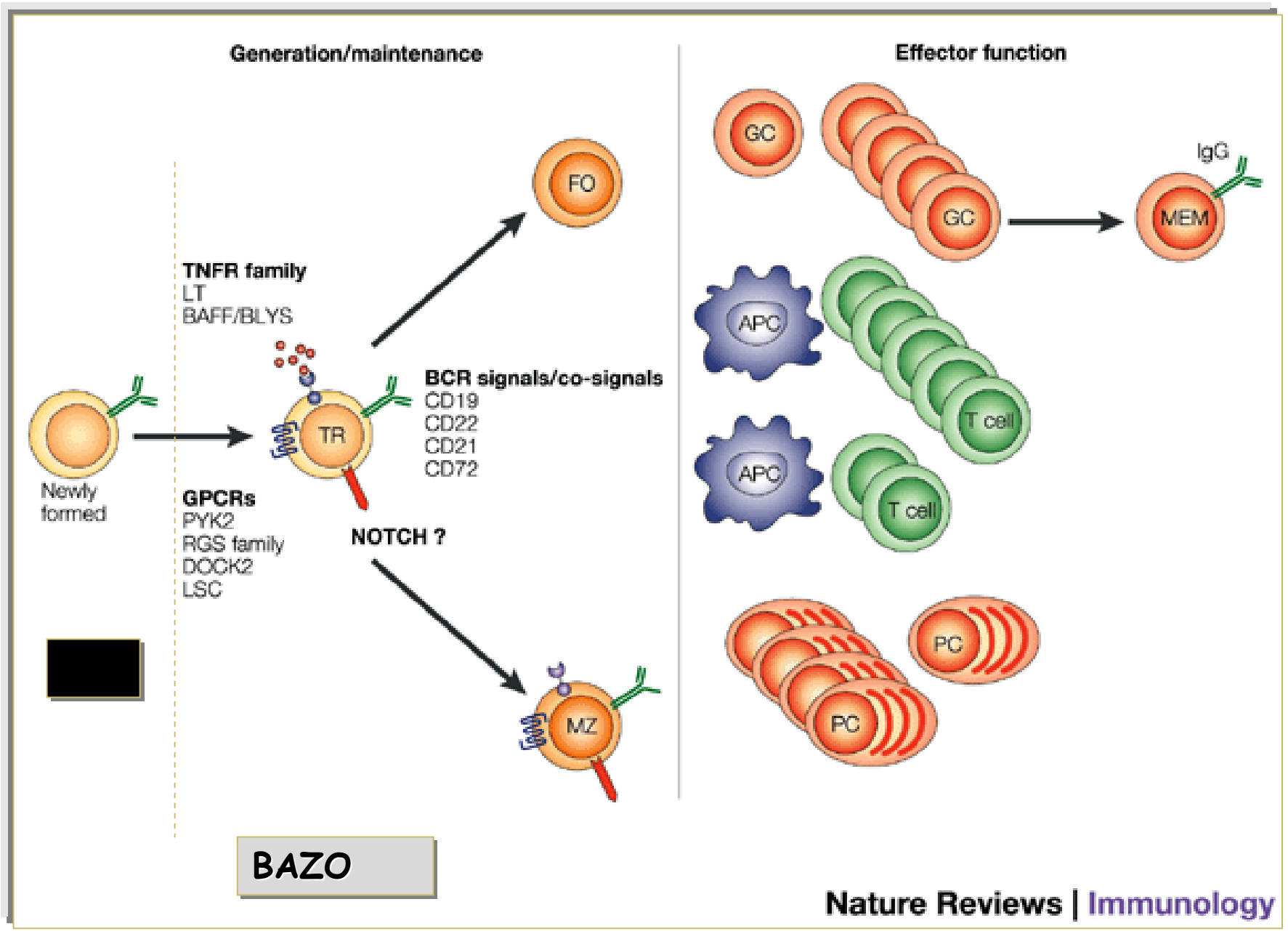
	Type of B cell		
Surface molecule	**B-1**	**MZ**	**Follicular**
IgM	+++	+++	+
IgD	+/-	+/-	+++
CD45R	+/++	++	+++
CD21	+/-	+++	++
CD23	++or -	-	++
CD5	+	-	-
$\alpha_M\beta_2$ integrin	+ or -	-	-
CD9	+	+	-

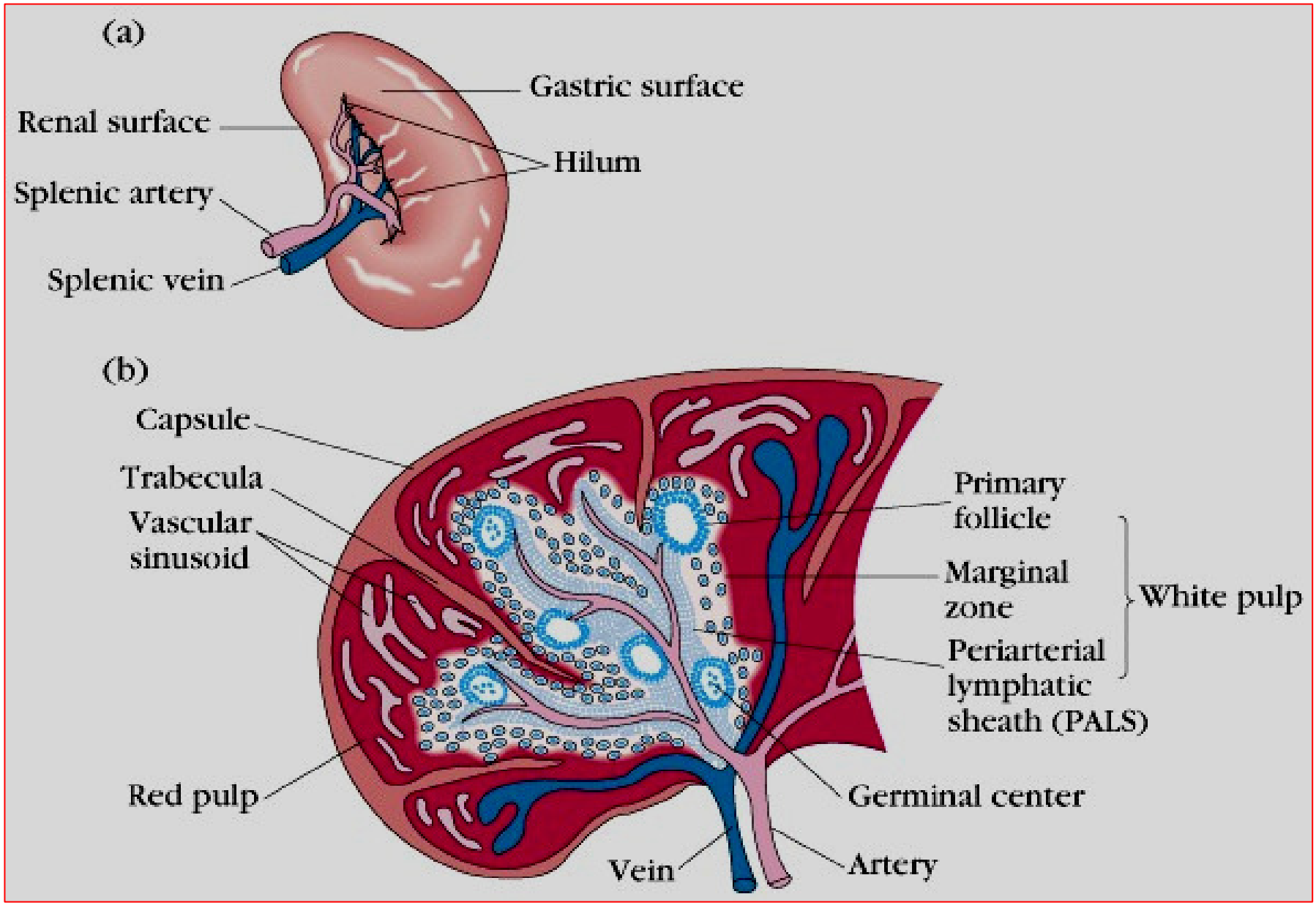
Algunas características

- Representan la primera línea de defensa capaz de detectar la presencia de microorganismos en sangre y producir importantes cantidades de anticuerpos neutralizantes en forma rápida para detener la multiplicación bacteriana.
- Su arquitectura permite un contacto íntimo entre los antígenos y células efectoras. Dentro de los primeros 3 a 4 días de la estimulación antigénica producen grandes cantidades de IgM específica.
- Producen anticuerpos sin necesidad de recibir coestimulación y **responden preferentemente a antígenos PS de bacterias capsulares.**
- **Los linfocitos MZB son particularmente dependientes del complemento para diferenciarse a plasmocitos productores de Ig.**



- **Los niños menos de 2 años tienen una respuesta pobre frente a las infecciones por bacterias encapsuladas como Streptococcus pneumoniae, Neisseria meningitidis o Haemophilus influenzae.**
- **La protección contra este tipo de bacterias está dada por anticuerpos específicos que permiten el reconocimiento y fagocitosis de las mismas por parte de macrófagos y PMNs.**
- **La incapacidad de los infantes para producir anticuerpos anti-PS bacterianos parece radicar en la inmadurez de los linfocitos MZB, que expresan bajos niveles de CD21.**


Generation/maintenance
Effector function
FO
TNFR family
LT
BAFF/BLYS
BCR signals/co-signals
CD19
CD22
CD21
CD72
TR
Newly formed
GPCRs
PYK2
RGS family
DOCK2
LSC
NOTCH ?
MZ
GC
GC
IgG
MEM
APC
T cell
APC
T cell
PC
PC
BAZO
Nature Reviews | Immunology


(a)
Gastric surface
Renal surface
Hilum
Splenic artery
Splenic vein
(b)
Capsule
Trabecula
Vascular sinusoid
Primary follicle
Marginal zone
Periarterial lymphatic sheath (PALS)
White pulp
Red pulp
Germinal center
Vein
Artery

Summary of Immunity to different types of pathogens

class	subclass	key immune mechanisms	memory?	example
Extracellular				
	bacterial			
		complement (alternative pathway)	No	Staph aureus
		phagocytosis via innate receptors	No	Strep pneumoniae (capsule -ve)
		IgM/IgG antibody/ complement (CP)	Yes	Staph aureus
		IgG/IgM iC3bR/FcγR phagocytosis	Yes	Strep pneumoniae (capsule+ve)
	helminths			
		IgG/ADCC (granulocytes+eosinophils)	Yes	Schistosoma mansoni
Intracellular				
	bacteria + protozoa	activated macrophage (by NK cells)	No	Listeria monocytogenes
		activated macrophage (by T_H1 cells)	Yes	Leishmania major
		cytotoxic T cell	Yes	Chlamydia trachomatis
	viruses	interferon α/β	No	Influenza virus
		NK cell killing	No	Cytomegalovirus
		Cytotoxic T cell killing	Yes	Smallpox (Variola major)
		activated macrophage (by T_H1 cells)	Yes	Herpes Simplex virus
		neutralising antibody	Yes	Influenza virus

INMUNIDAD DE MUCOSAS

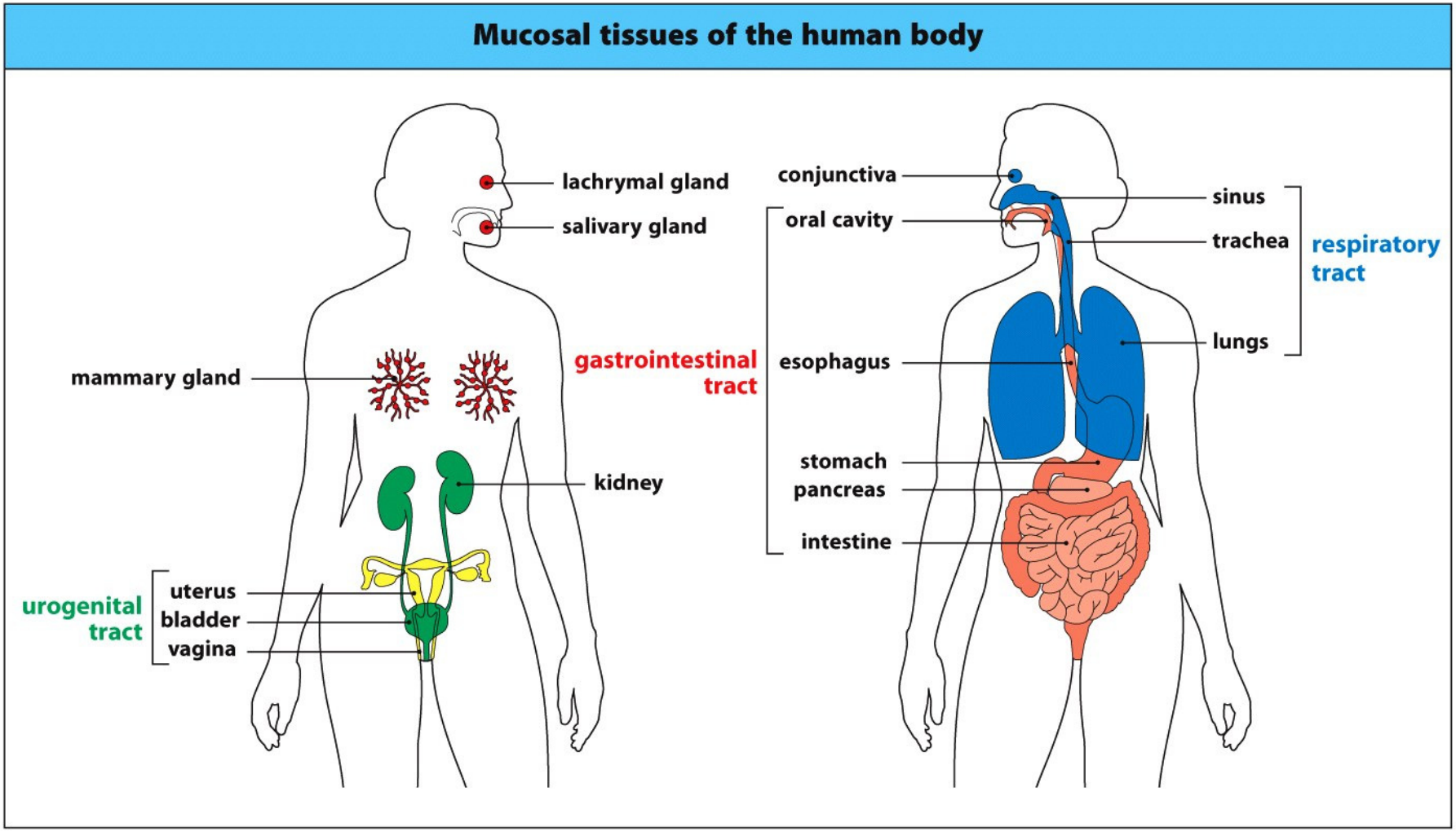


Figure 10.1 The Immune System, 3ed. (© Garland Science 2009)

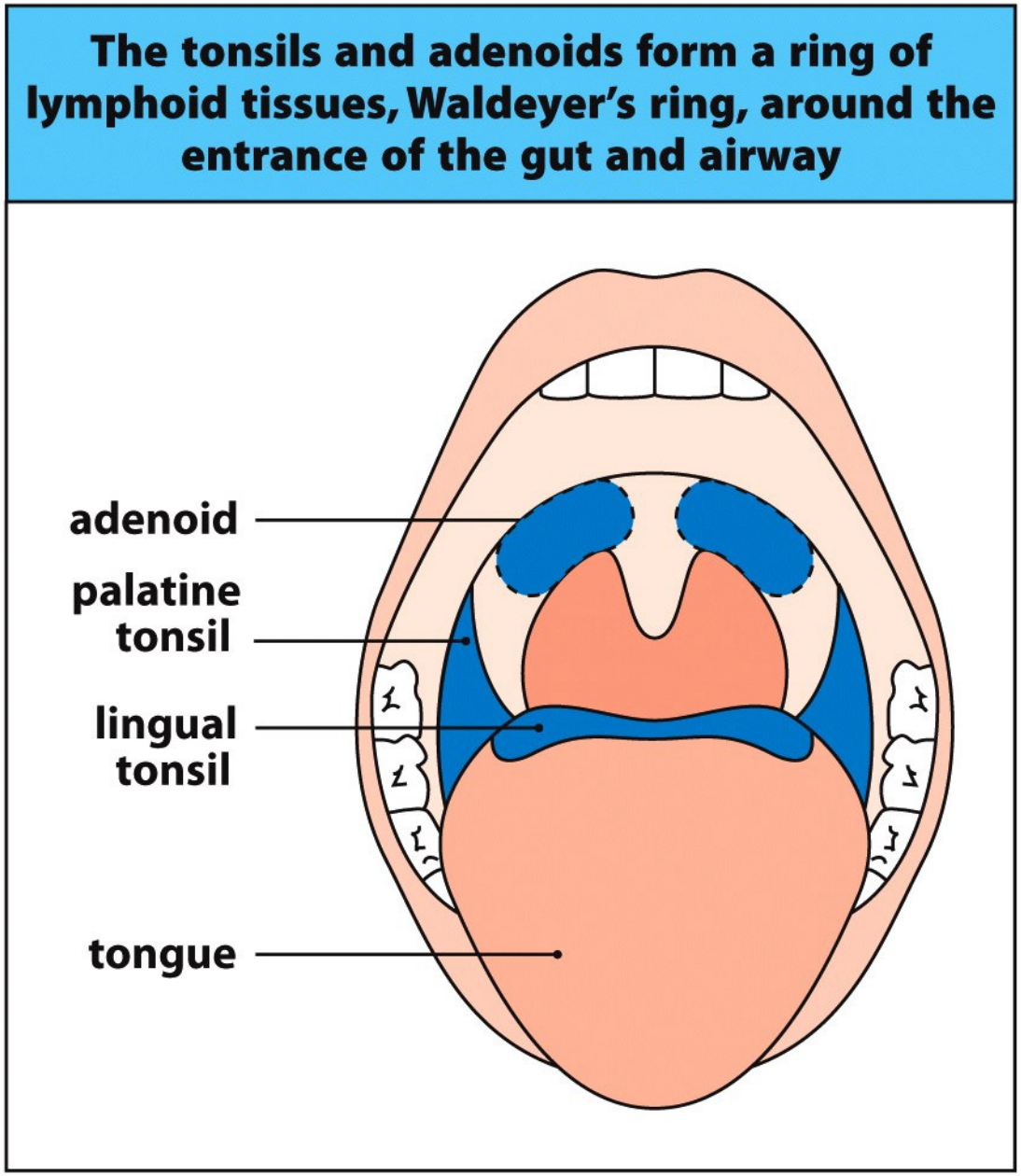
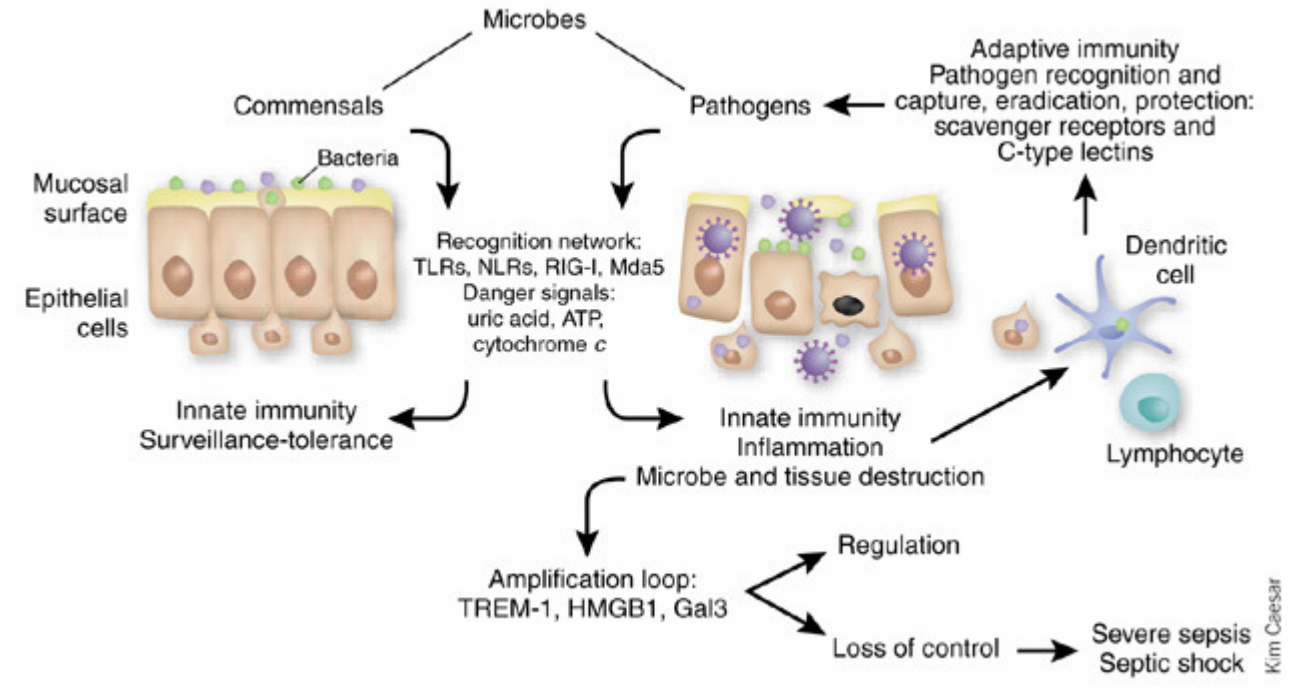


Figure 10.3 The Immune System, 3ed. (© Garland Science 2009)

Nature Immunology - **7**, 1237 - 1242 (2006)



For commensals, bacteria produce a 'tolerance' response and homeostasis is maintained.

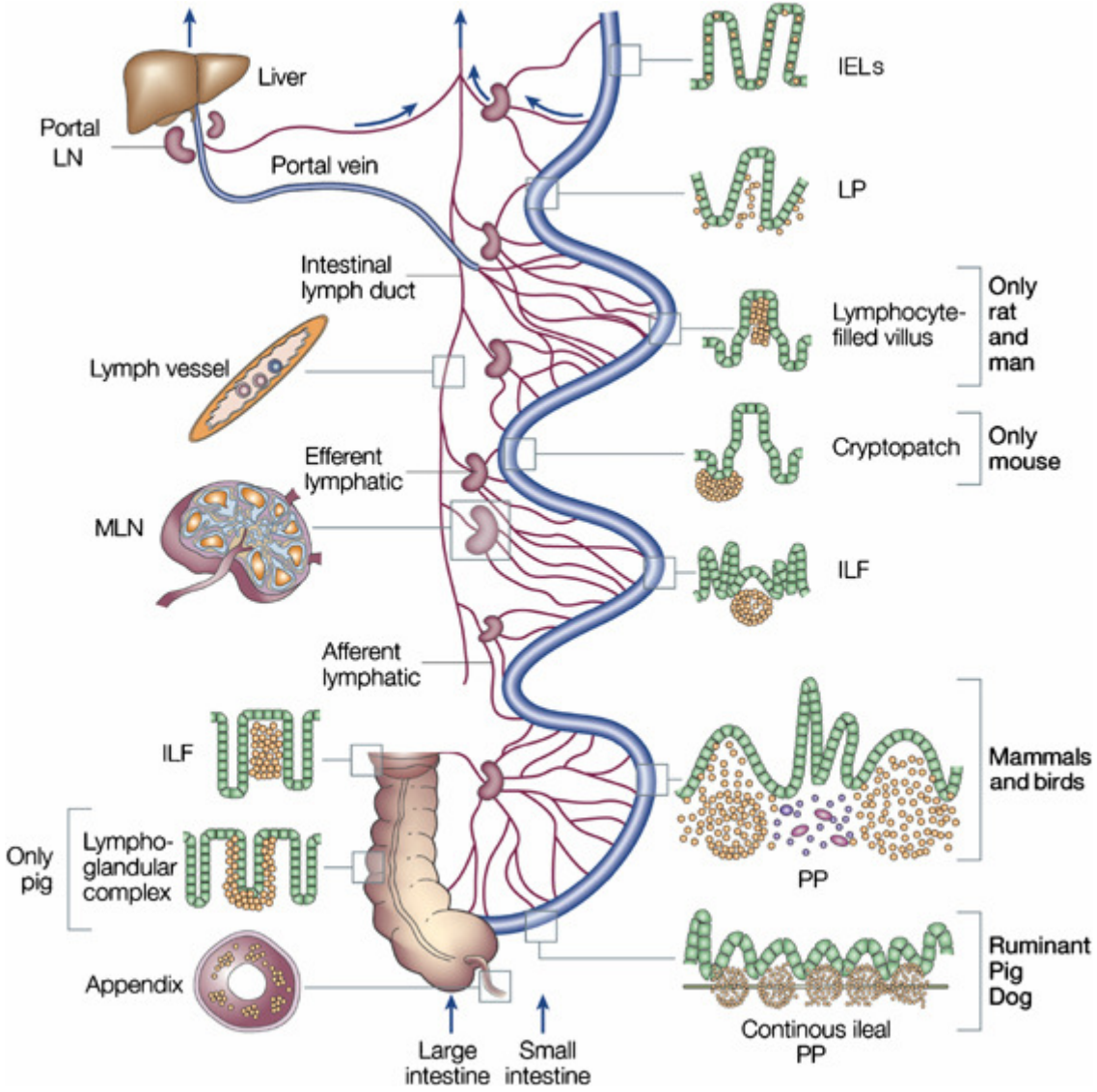
Alternatively, for pathogenic microbes, a different type of signaling occurs that can lead to innate immunity and inflammation. TREM proteins and other proteins amplify such signals and help to bring about either regulation of the inflammatory response or, when amplification goes too far, loss of control, leading to severe shock in some cases. When pathogens activate innate immune responses, beneficial adaptive immune responses ensue that lead to pathogen recognition, capture and eradication, all of which can be mediated by germline-encoded innate molecules such as scavenger receptors and C-type lectins. The 'paradox' of the different outcomes for commensal microflora and pathogenic bacteria is that both types of microbes express many of the same 'molecular patterns', yet the former somehow stimulate the induction of tolerance rather than induction of the proinflammatory process.

Table 2 Recommended nomenclature for mucosa-associated immune-cell compartments

Preferred abbreviations	Explanations
LP	Lamina propria
	Refers usually to the connective tissue of gut mucosa, restricted to the stroma above the muscularis mucosae (thus excluding the submucosa), but can also be used in relation to other mucosae
IEL compartment	Surface epithelium
	Refers usually to the epithelium of the small intestine where most intraepithelial lymphocytes (IELs) occur
FAE	Follicle-associated epithelium
	Covers the domes of MALT structures and contains variable numbers of M cells
MALT	Mucosa-associated lymphoid tissue
	The principal inductive sites for mucosal immune responses, subdivided according to anatomical location as below
GALT	Gut-associated lymphoid tissue
PP	Peyer's patch
ILF	Isolated (solitary) lymphoid follicle
	PPs and ILFs constitute the major part of GALT, but also the appendix is included although functionally less explored
NALT	Nasopharynx-(or nose)-associated lymphoid tissue
	In humans, NALT consists of the lymphoid tissue of Waldeyer's pharyngeal ring, including the adenoids (the unpaired nasopharyngeal tonsil) and the paired palatine tonsils. Rodents lack tonsils, but have paired NALT structures dorsally in the floor of the nasal cavity
BALT	Bronchus-associated lymphoid tissue
	Not generally present in the normal lungs of adult humans
MLN	Mesenteric lymph node
CLN	Cervical lymph node
	Should be specified as deep or superficial

More details can be found in ref. 1

MucosalImmunology


Liver
Portal LN
Portal vein
Intestinal lymph duct
Lymph vessel
Efferent lymphatic
MLN
Afferent lymphatic
ILF
Only pig
Lympho-glandular complex
Appendix
Large intestine
Small intestine
IELs
LP
Lymphocyte-filled villus
Only rat and man
Cryptopatch
Only mouse
ILF
Mammals and birds
PP
Ruminant Pig Dog
Continous ileal PP

GALT: GUT ASSOCIATED LYMPHOID TISSUE

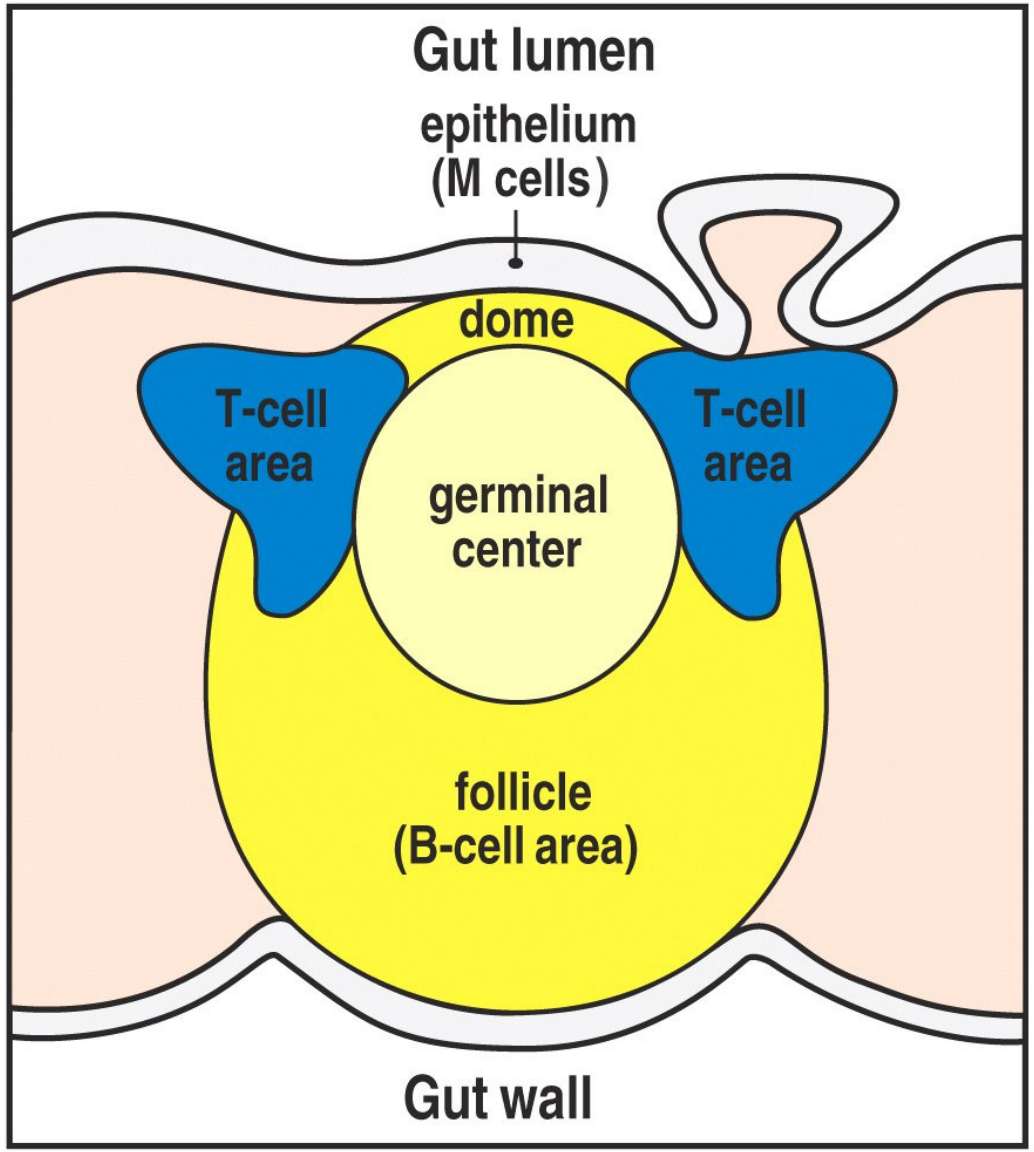


Figure 8-38 part 1 of 2 The Immune System, 2/e (© Garland Science 2005)

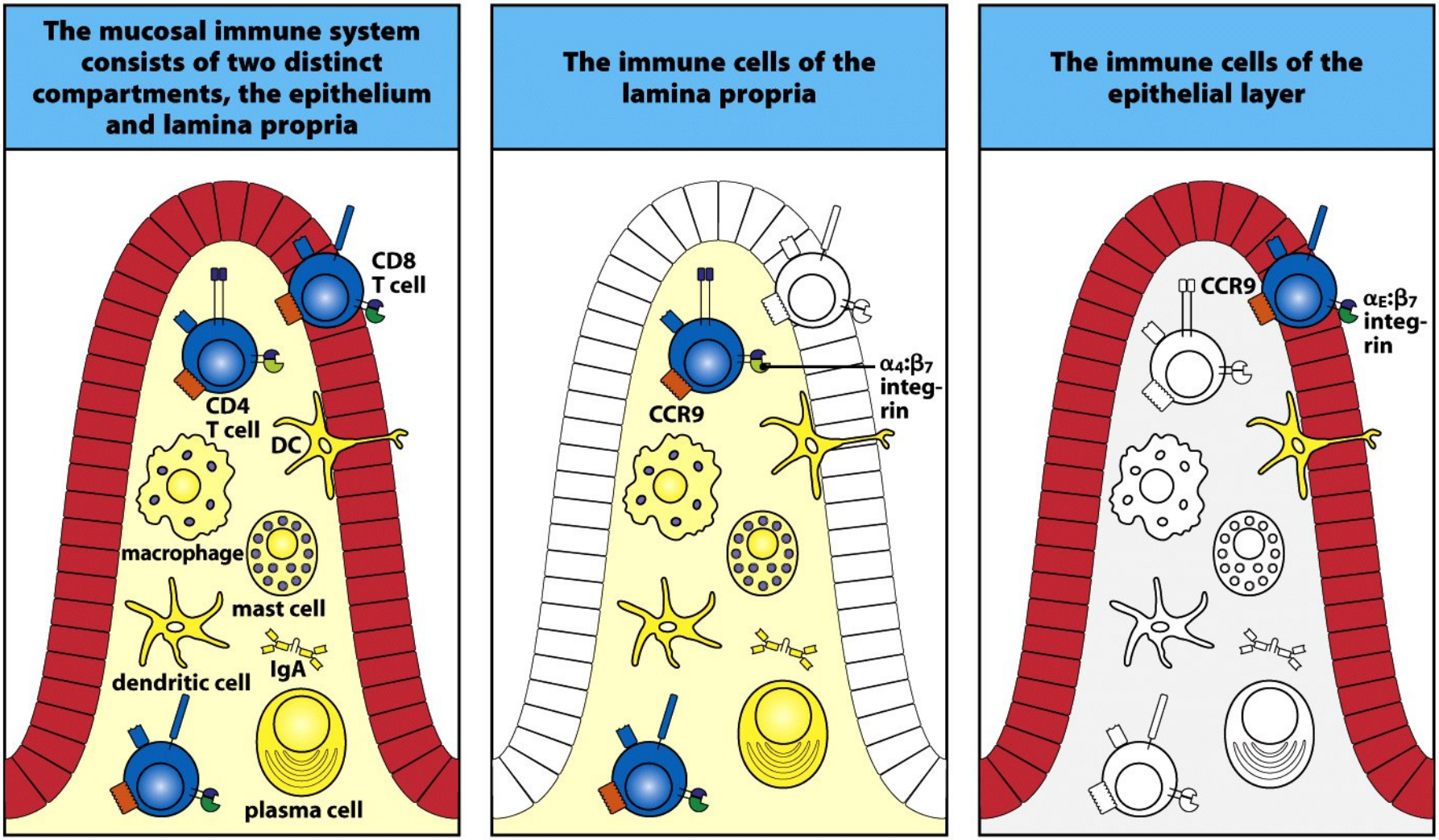


Figure 11-10 Immunobiology, 7ed. (© Garland Science 2008)

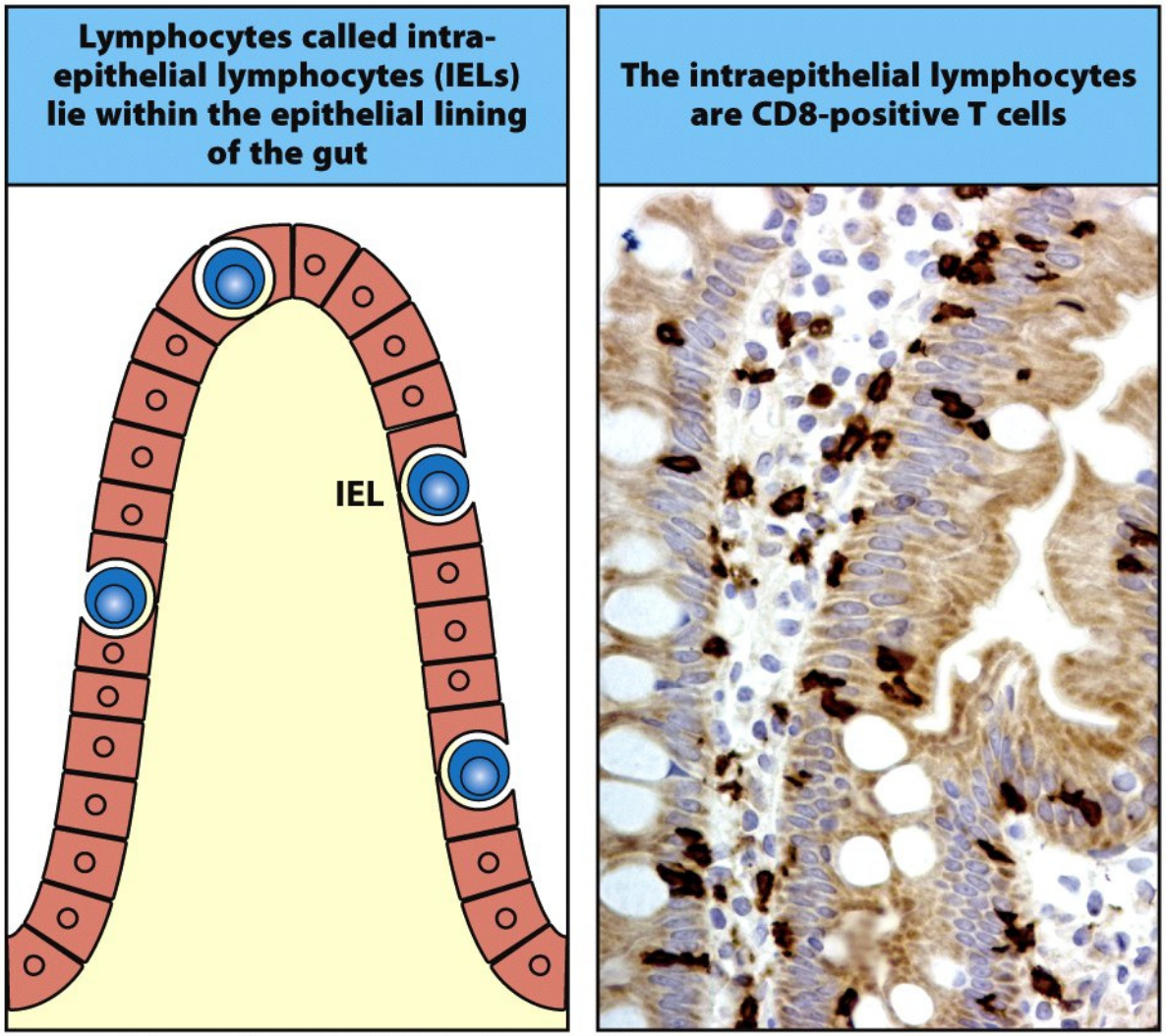


Figure 11-16 Immunobiology, 7ed. (© Garland Science 2008)

-IEL are divided into two groups on the basis of which form of CD8 is expressed :

· type a : CD8$\alpha\beta$ heterodimer, $\alpha\beta$ TCR conventional T cell.

· type b : CD8$\alpha\alpha$ homodimer, $\alpha\beta$ TCR or $\gamma\delta$ TCR T cells.

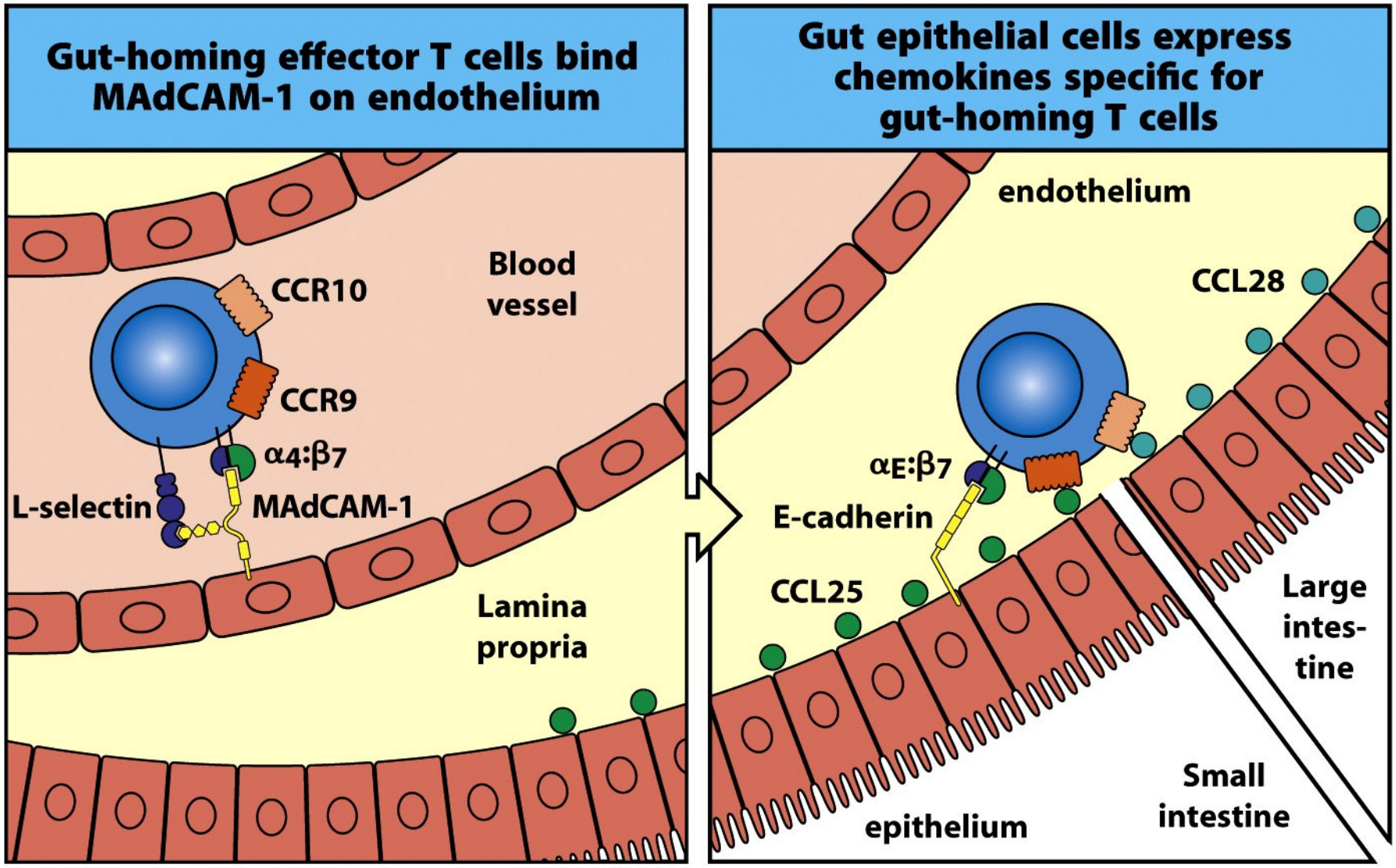


Figure 11-12 Immunobiology, 7ed. (© Garland Science 2008)

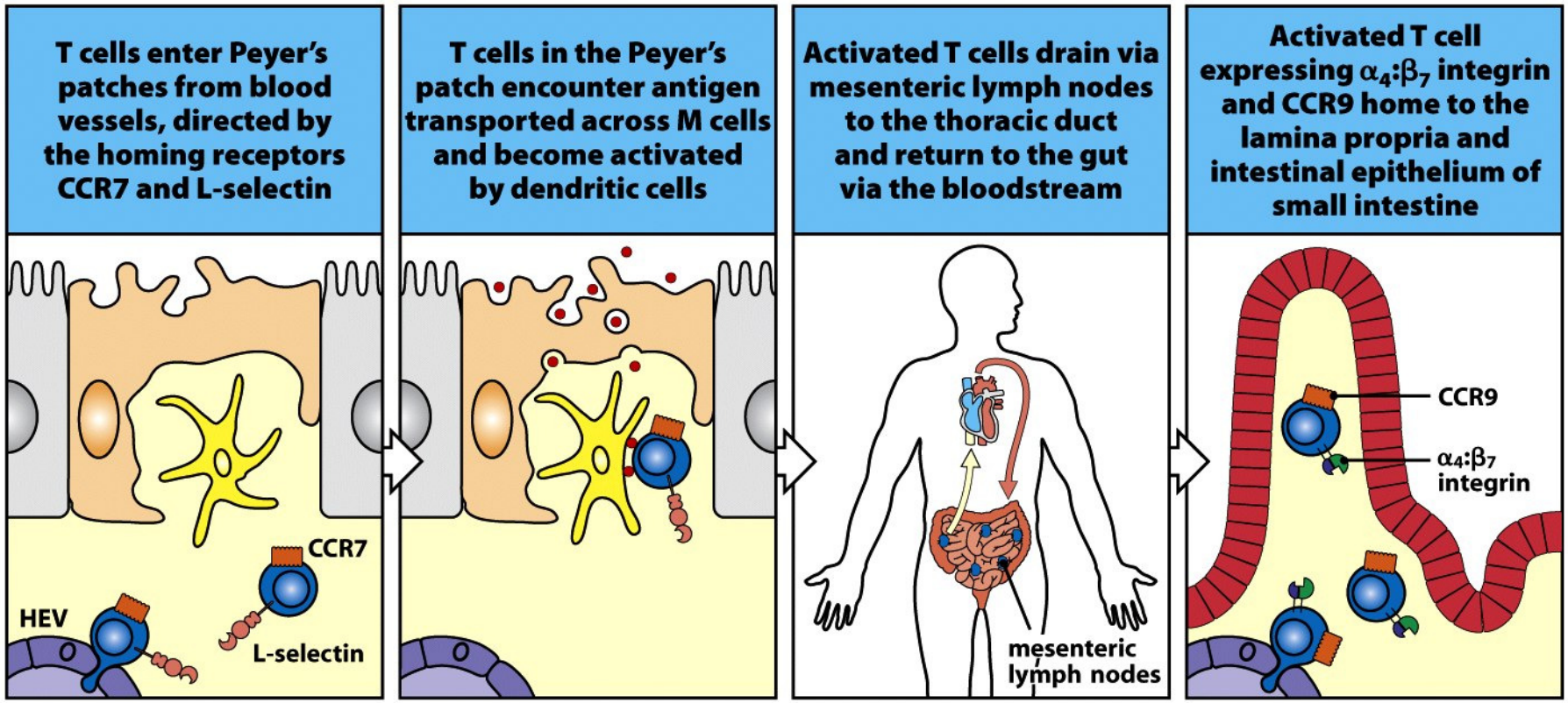
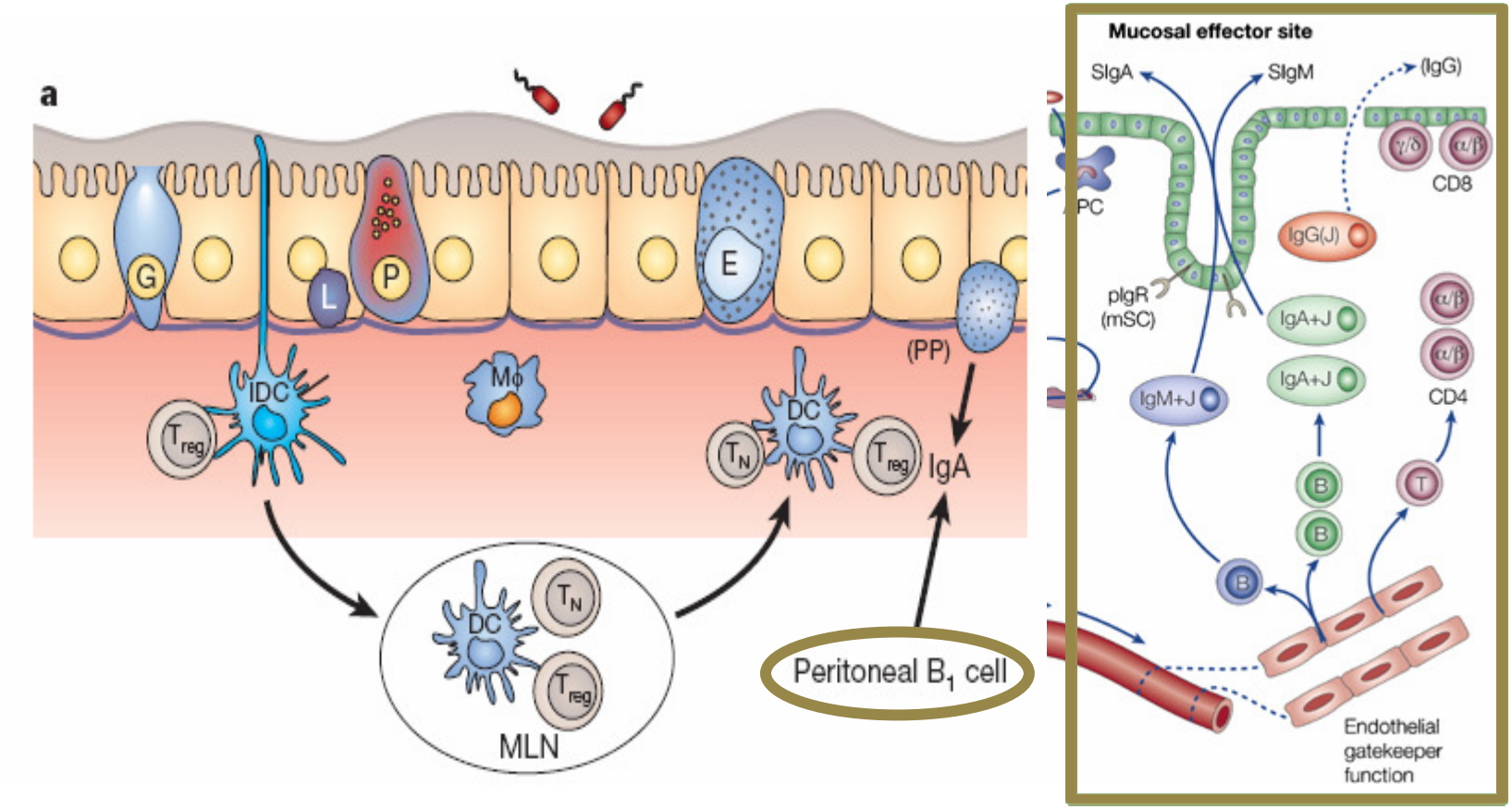


Figure 11-11 Immunobiology, 7ed. (© Garland Science 2008)

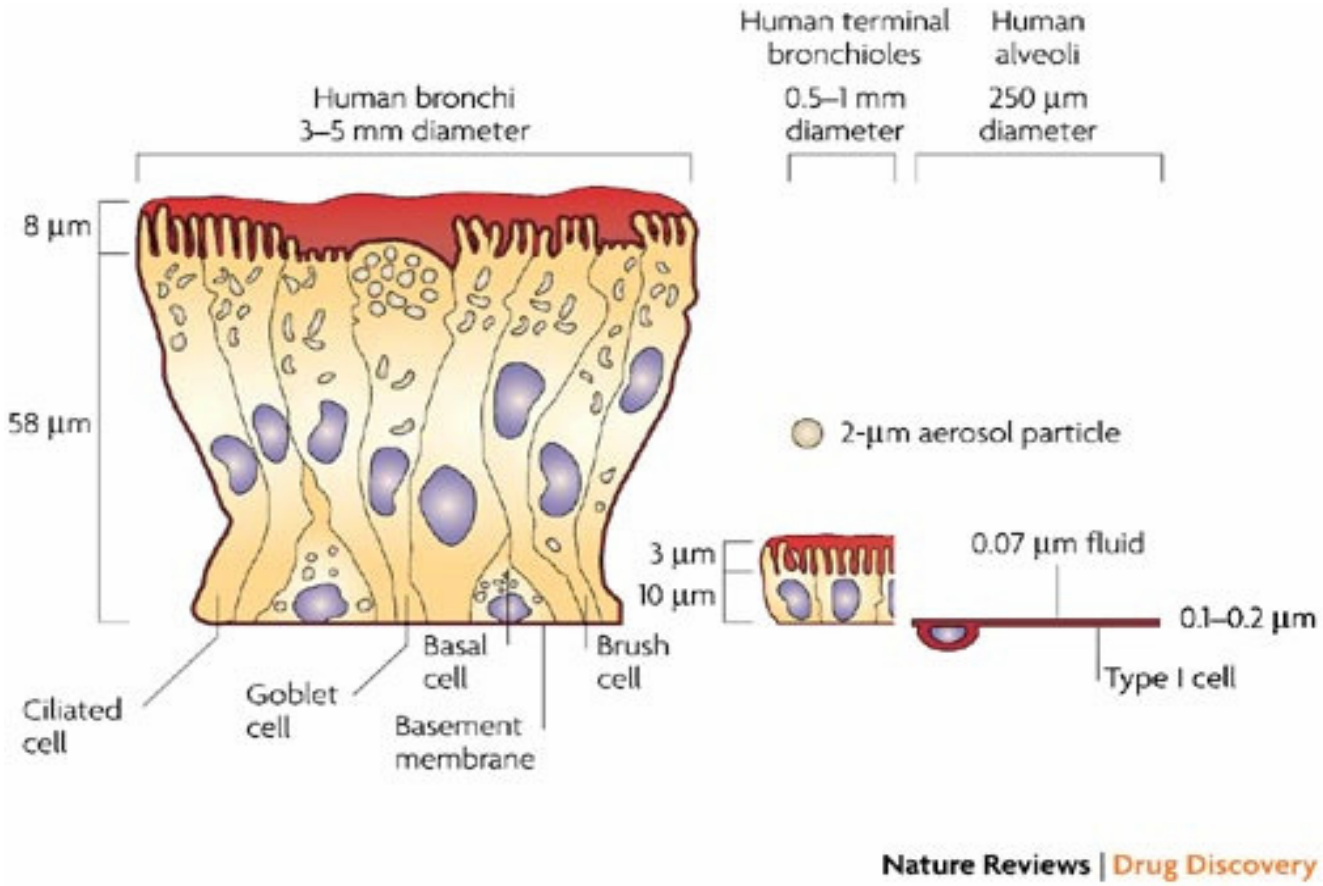


Review *Nature* **448**, 427-434 (26 July 2007)

After being primed to become memory/effector B and T cells, they migrate from MALT and lymph nodes to peripheral blood for subsequent extravasation at mucosal effector sites (exemplified by gut mucosa on the right). This process is directed by the local profile of vascular adhesion molecules and chemokines, the endothelial cells thus exerting a local gatekeeper function for mucosal immunity. The gut lamina propria contains few B lymphocytes but many J-chain-expressing IgA (dimers/polymers) and IgM (pentamers) plasmablasts and plasma cells. Also, there are normally some rare IgG plasma cells with a variable J-chain level (J), and many T cells (mainly $CD4^+$). Additional features are the generation of SIgA and SIgM via pIgR (mSC)-mediated epithelial transport, as well as paracellular leakage of smaller amounts (broken arrow) of both locally produced and plasma-derived IgG antibodies into the lumen. There may also be some active transport of IgG mediated by the neonatal Fc receptor (not indicated). Note that IgG cannot interact with J chain to form a binding site for pIgR. The distribution of intraepithelial lymphocytes (mainly T-cell receptor α/β^+CD8^+ and some γ/δ^+ T cells) is also depicted. The inset (lower left corner) shows details of an M cell and its "pocket" containing various cell types

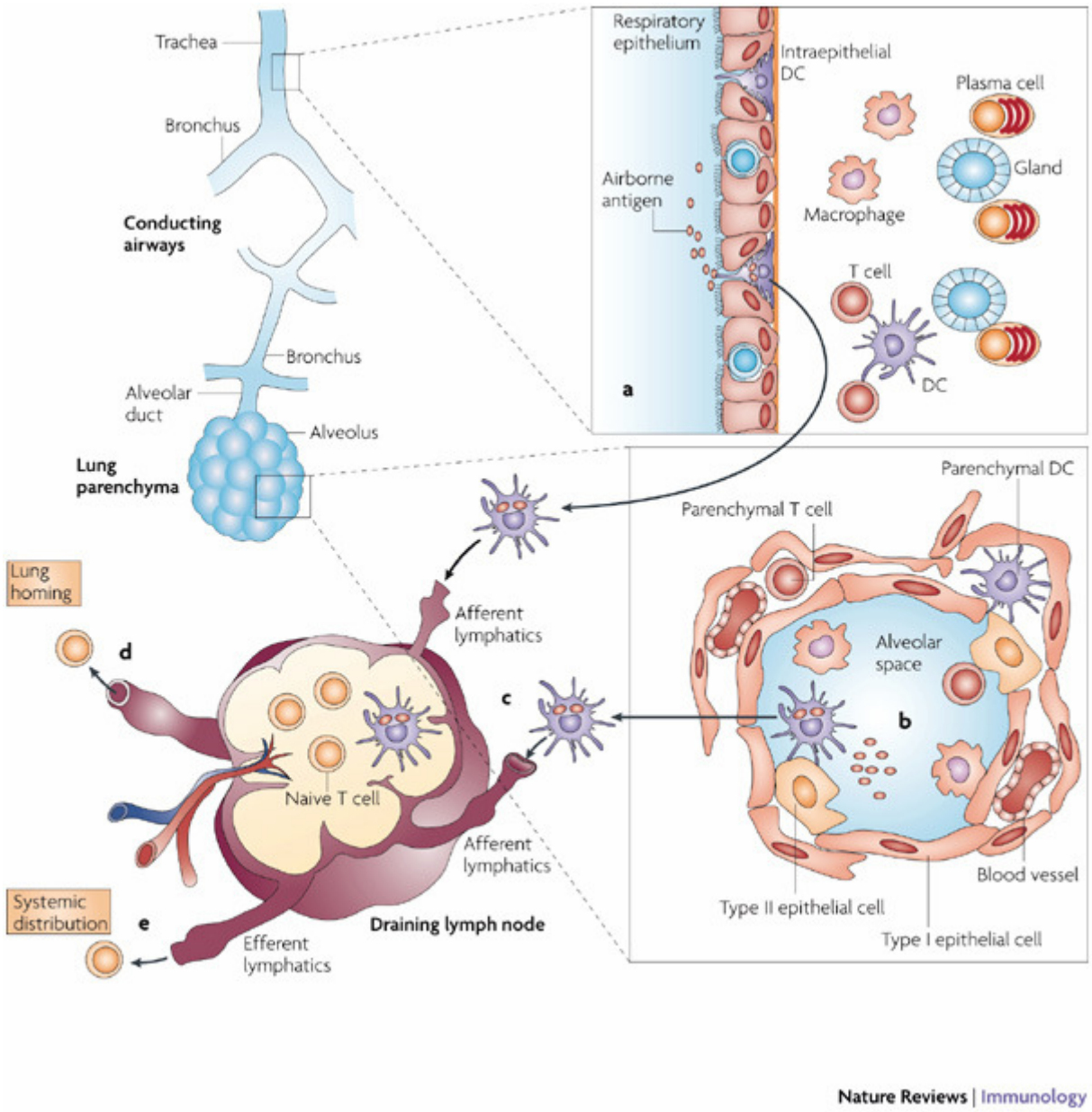
APCs, antigen-presenting cells; DCs, dendritic cells; FDCs, follicular dendritic cells; HEVs, high endothelial venules; MALT, mucosa-associated lymphoid tissue; mSC, membrane secretory component; pIgR, polymeric Ig receptor; SIgA, secretory IgA; SIgM, secretory IgM.

COMPARACIÓN DEL EPITELIO PULMONAR EN DISTINTOS SITIOS DENTRO DEL PULMÓN

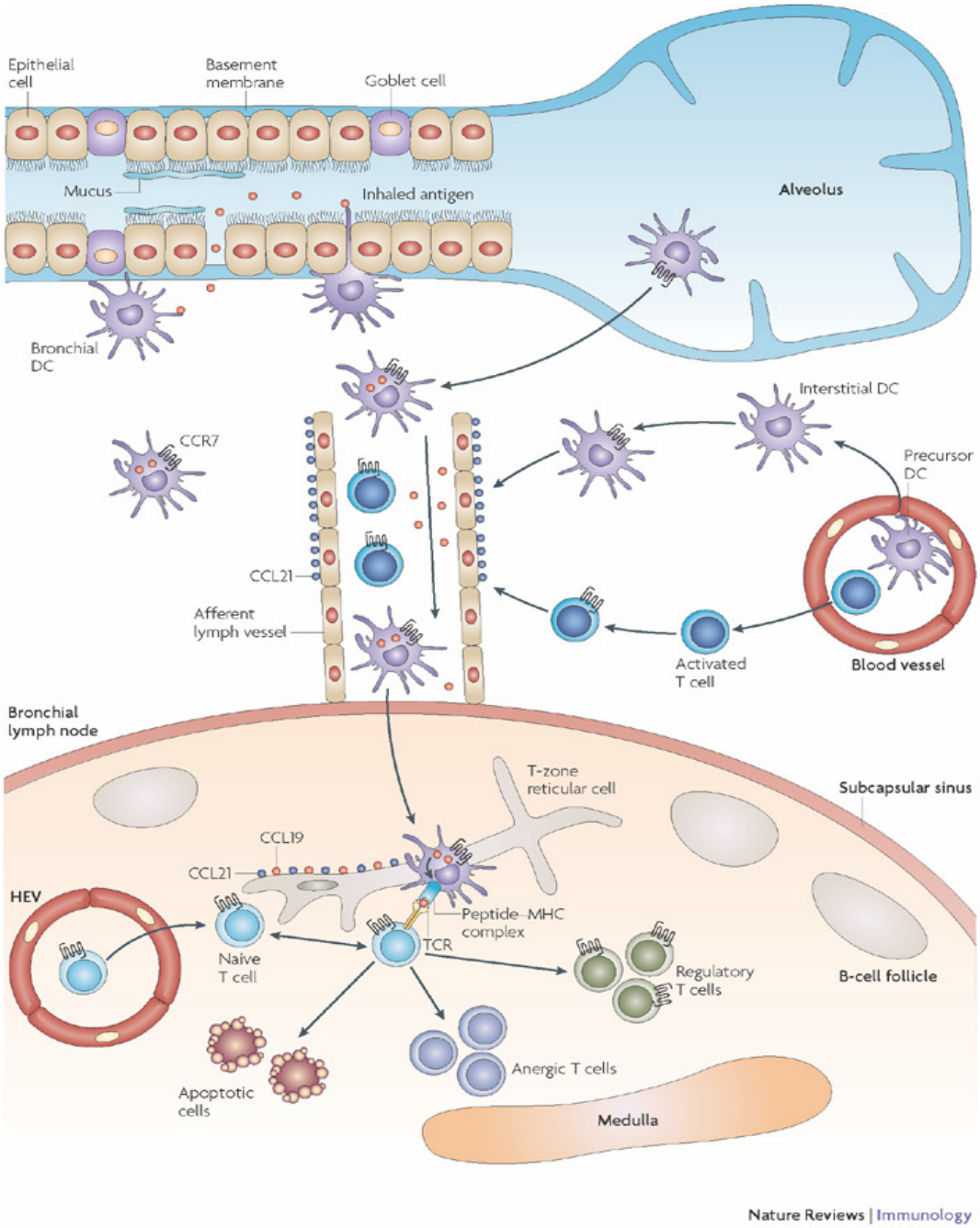


In the bronchi there are a variety of cells that make up the epithelium: the basal cells, which are the stem or progenitor cells for the epithelium and differentiate to form the other cells in the case of injury or apoptosis; the ciliated cells, which provide the mechanism for moving the mucus blanket; the goblet cells, which secrete the mucus; and the brush cells, which are involved in drug metabolism. These same types of cells persist in the smaller airways but are not as tall. The basement membrane is actually not a membrane but an extracellular matrix of different biopolymers to which the epithelial cells attach

Nature Reviews Drug Discovery 6, 67-74 (January 2007)

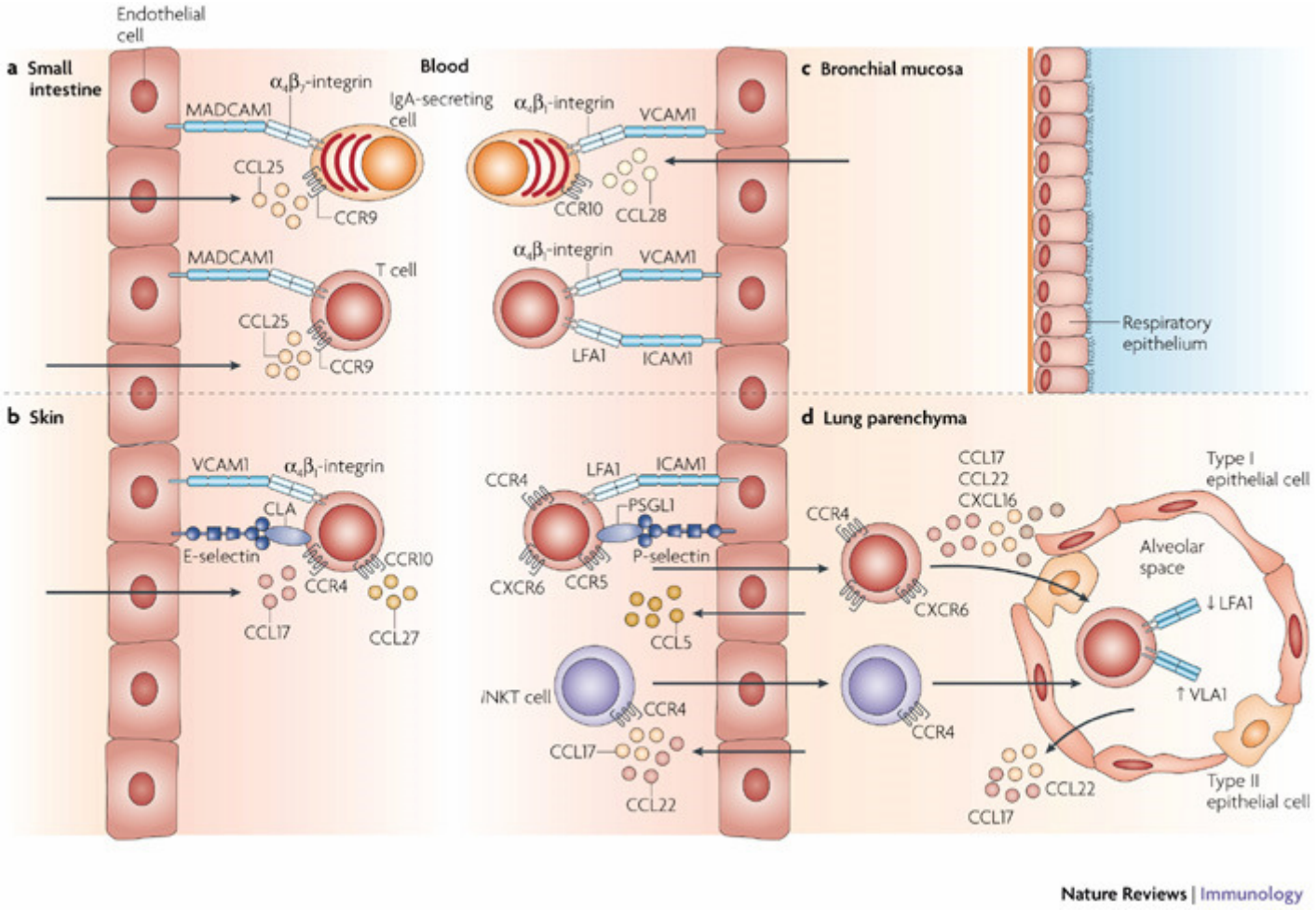


Nature Reviews Immunology 8, 142-152 (February 2008)

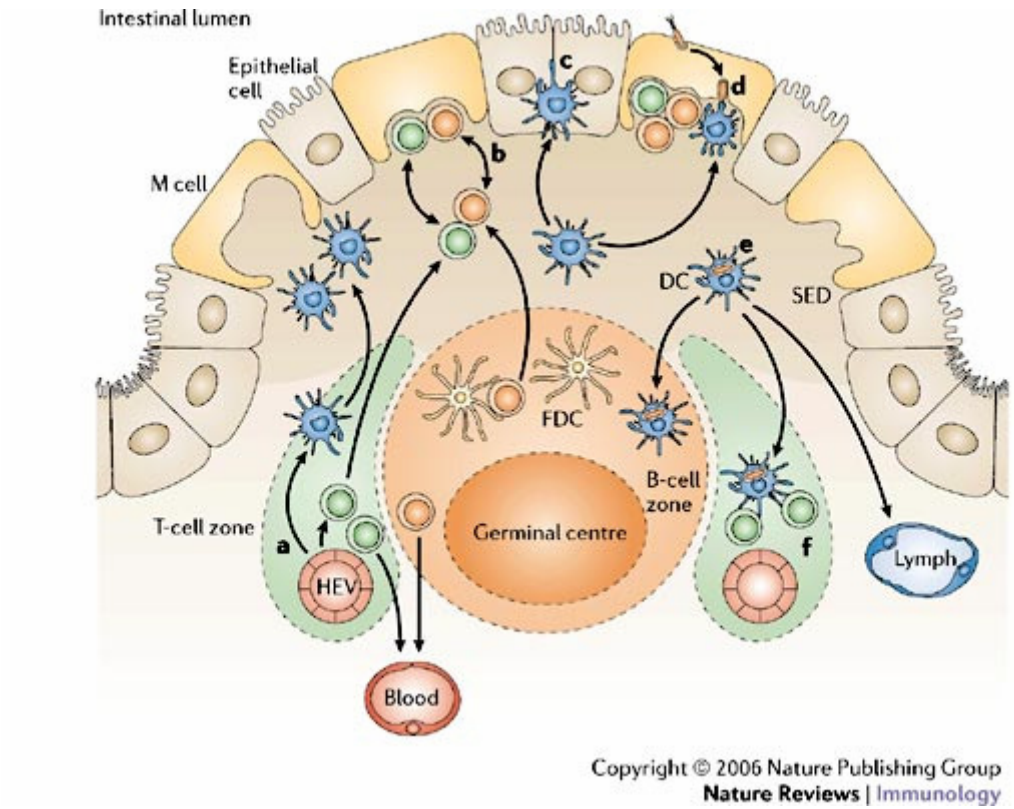


Dendritic cell (DC) precursors enter the lung via blood vessels and give rise to sessile interstitial and bronchial DCs. Inhaled antigens are taken up by bronchial DCs that are located below the basement membrane. Some DCs spontaneously upregulate CC-chemokine receptor 7 (CCR7) and migrate towards the initial segments of lymphatic vessels that express CC-chemokine ligand 21 (CCL21). Following CCR7-mediated entry into the lymphatics, DCs are passively carried with the afferent lymph into the draining lymph node. Under experimental conditions, intratracheally applied DCs migrate from the bronchus and/or alveolus into afferent lymphatics. It is as yet unknown whether the migration of DCs from the subcapsular sinus into the T-cell area of the bronchial lymph nodes depends on CCR7. Within the lymph-node paracortex, DCs present antigens to naive T cells, which enter the lymph node via the high endothelial venules (HEVs). T cells randomly migrate on reticular cells, which express CCL19 and CCL21. These chemokines enhance the velocity of T-cell locomotion within the lymph node and thus increase the likelihood of their encounter with DCs presenting cognate antigen. T cells that recognize inhaled innocuous antigens either undergo apoptosis, become anergic or gain regulatory capacities. Some T cells that are present in the lung parenchyma also rely on CCR7 for their entry into the afferent lymphatics. TCR, T-cell receptor.

Nature Reviews Immunology 8, 362-371 (May 2008)

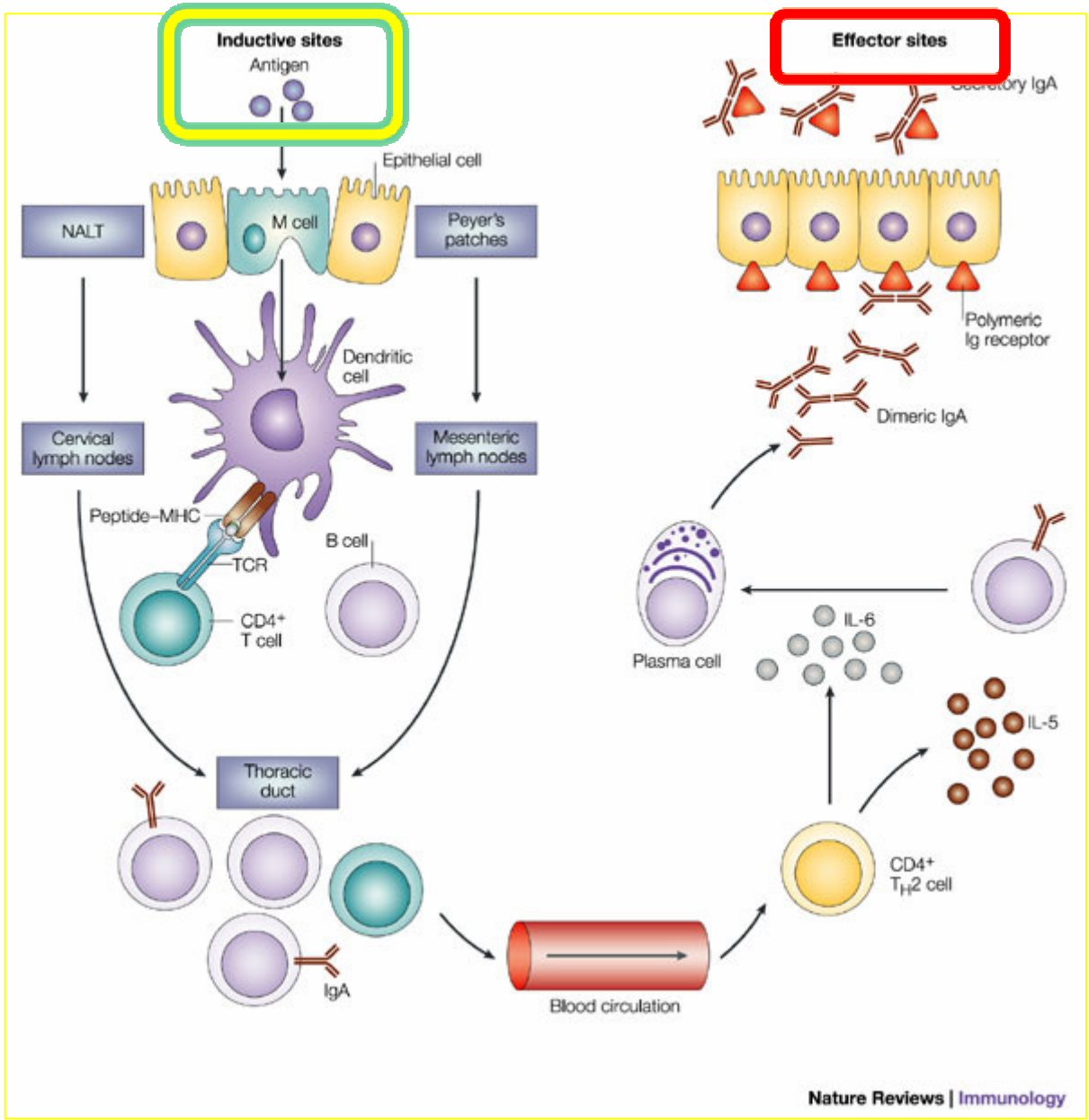


Nature Reviews Immunology 8, 142-152 (February 2008)

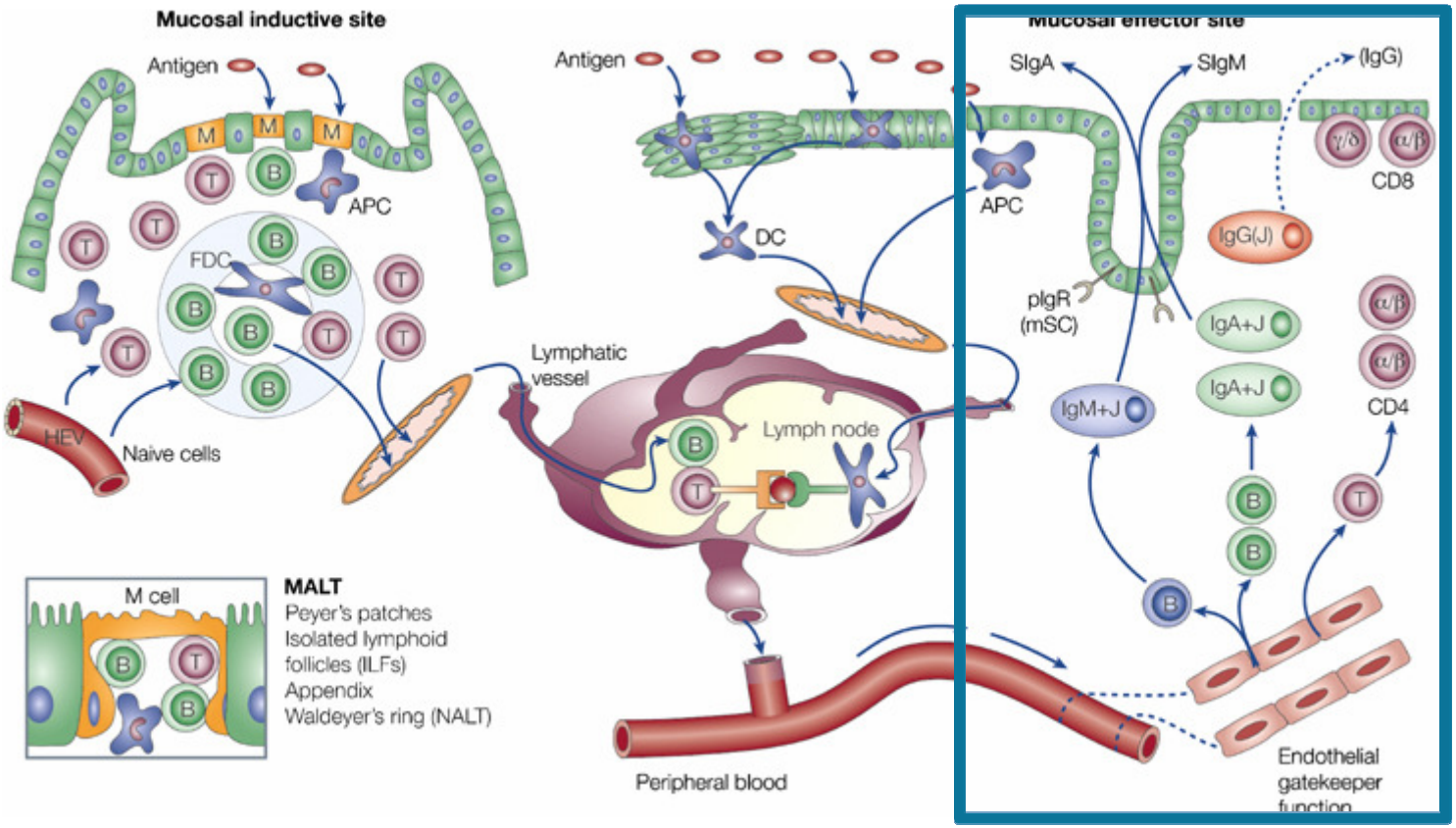


The choreography of cellular movements in organized mucosal lymphoid tissues is complex and only partly understood. A simplified version based on studies of Peyer's patches is shown here. a | Naive and memory lymphocytes as well as immature dendritic cells (DCs) enter the mucosa through high endothelial venules (HEVs). Some of these cells are attracted to the subepithelial dome (SED) region by chemokines released from the follicle-associated epithelium (FAE). b | Some B and T cells migrate into microfold (M)-cell pockets, where they express maturation or memory markers. c | Most immature DCs remain in the SED region but a few migrate into the FAE. d | Antigens and microorganisms transported by M cells are captured by DCs. e | Antigen capture along with other signals induces DC maturation and movement into interfollicular T-cell areas, the B-cell zone, and perhaps into draining lymphatics. f | In interfollicular areas, DCs process and present antigen to naive T cells. FDC, follicular dendritic cell.

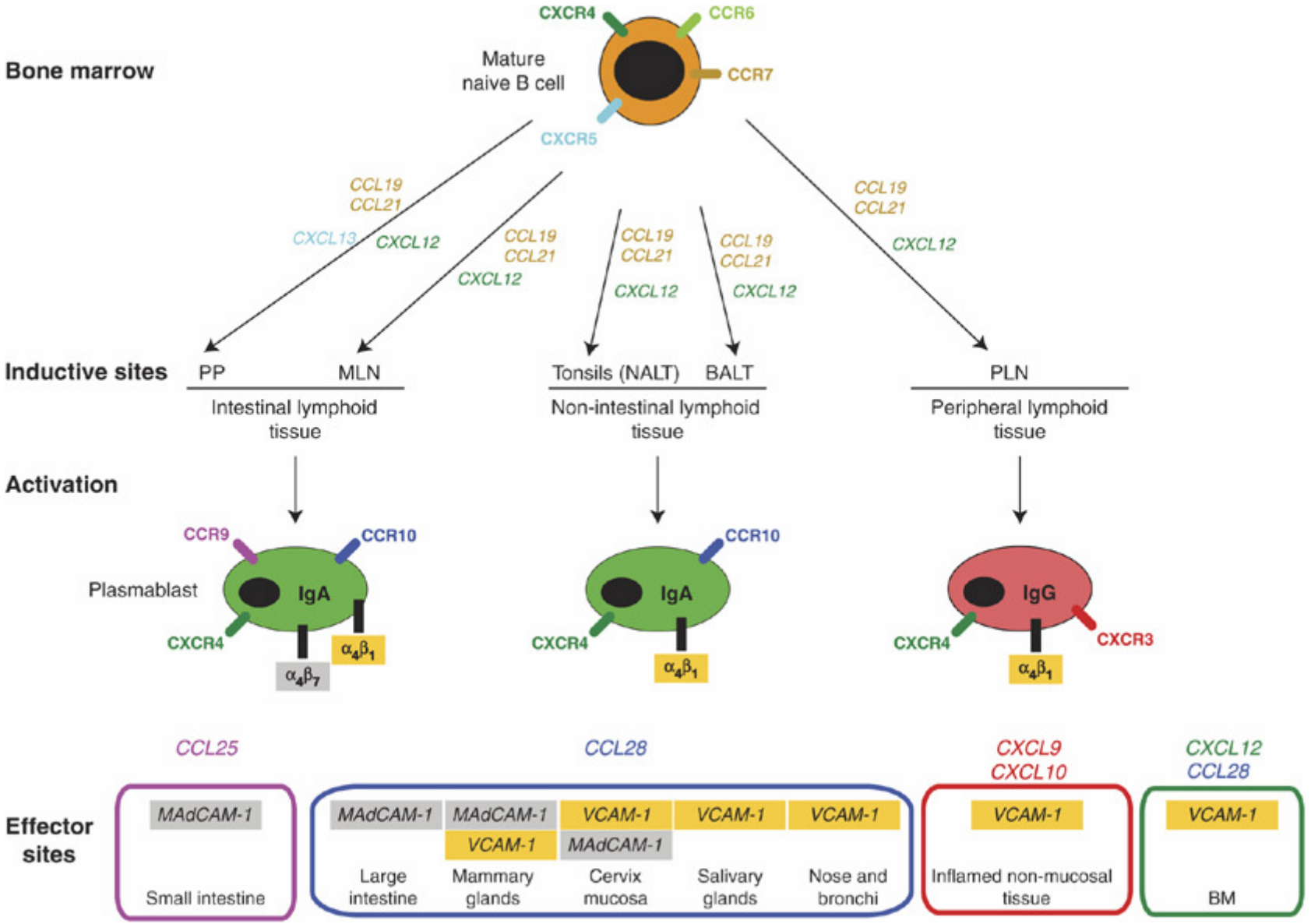
- Las mucosas tienen tejido linfoide que se clasifica en:
- SITIOS INDUCTIVOS:PROCESAN LOS ANTÍGENOS Y SE INICIA LA RESPUESTA INMUNITARIA.
- SITIOS EFECTORES: FORMACIÓN DE ANTICUERPOS Y RESPUESTA MEDIADA POR CÉLULAS.



Nature Reviews Immunology 4, 699-710 (September 2004)


Mucosal inductive site
Antigen
M
M
M
T
B
APC
FDC
HEV
Naive cells
Lymphatic vessel
Antigen
DC
Lymph node
Peripheral blood
M cell
MALT
Peyer's patches
Isolated lymphoid follicles (ILFs)
Appendix
Waldeyer's ring (NALT)
SIgA
SIgM
(IgG)
APC
γ/δ
α/β
CD8
IgG(J)
pIgR (mSC)
IgA+J
IgA+J
IgM+J
α/β
α/β
CD4
Endothelial gatekeeper function

DISTRIBUCIÓN DE CÉLULAS B



Mucosal Immunology (2008) **1,** 11–22.

B-cell homing to mucosal and peripheral tissues is mediated by specific combinations of chemokine receptors and adhesion molecules. Newly developed B cells express specific chemokine receptors that mediate responsiveness to chemokine ligands expressed in secondary lymphoid tissues, bone marrow (BM), and mucosal effector sites. Within secondary lymphoid tissues, B cells encounter specific antigen leading to their activation and differentiation. In general, activation of B cells and differentiation to mucosal IgA antibody-secreting cells (plasmablasts and plasma cells) induce upregulation of CCR10 and expression of $\alpha_4\beta_1$ integrin, which mediate attraction to CCL28 and VCAM-1, respectively. Expression of VCAM-1 in effector sites is indicated, although the expression of vascular adhesion molecules (like VCAM-1) at various effector sites is not yet systematically worked out. Differentiation of IgA plasmablasts within small intestinal lymphoid tissues additionally induces upregulation of CCR9 and $\alpha_4\beta_7$ and directs homing back to the small intestine, which expresses CCL25 and MAdCAM-1. In contrast, differentiation to IgG plasmablasts of systemic type leads to upregulation of CXCR3, allowing responsiveness to CXCL9 and CXCL10 and migration to inflamed mucosal and non-mucosal tissues. Homing to the bone marrow is mediated through CXCR4, which is expressed on all types of plasmablasts, as well as CCR10. Memory B cells (not shown) retain expression of CCR7, CXCR5, and CXCR4 to allow their recirculation through lymphoid tissues. Retained expression of CCR7 and CD62L on effector B cells from tonsils/NALT may explain their joint tropism for organized lymphoid tissue and the upper aerodigestive tract (not shown). Specific chemokine–chemokine receptor pairs are indicated by corresponding colored text; specific integrin–ligand pairs are depicted by gray and yellow boxes. Bold text indicates the molecule is expressed on lymphocytes; text in italics indicates expression on endothelial or stromal cells. BALT, bronchus-associated lymphoid tissue; CCL, CC-chemokine ligand; CCR, CC-chemokine receptor; CXC-chemokine ligand; CXCL, VCAM-1, vascular cell-adhesion molecule-1; CXCR, CXC-chemokine receptor; MAdCAM-1, mucosal addressin cell-adhesion molecule-1; MLN, mesenteric lymph nodes; NALT, nasopharynx-associated lymphoid tissue; PP, Peyer's patches; PLN, peripheral lymph nodes.

Respuesta humoral después del nacimiento

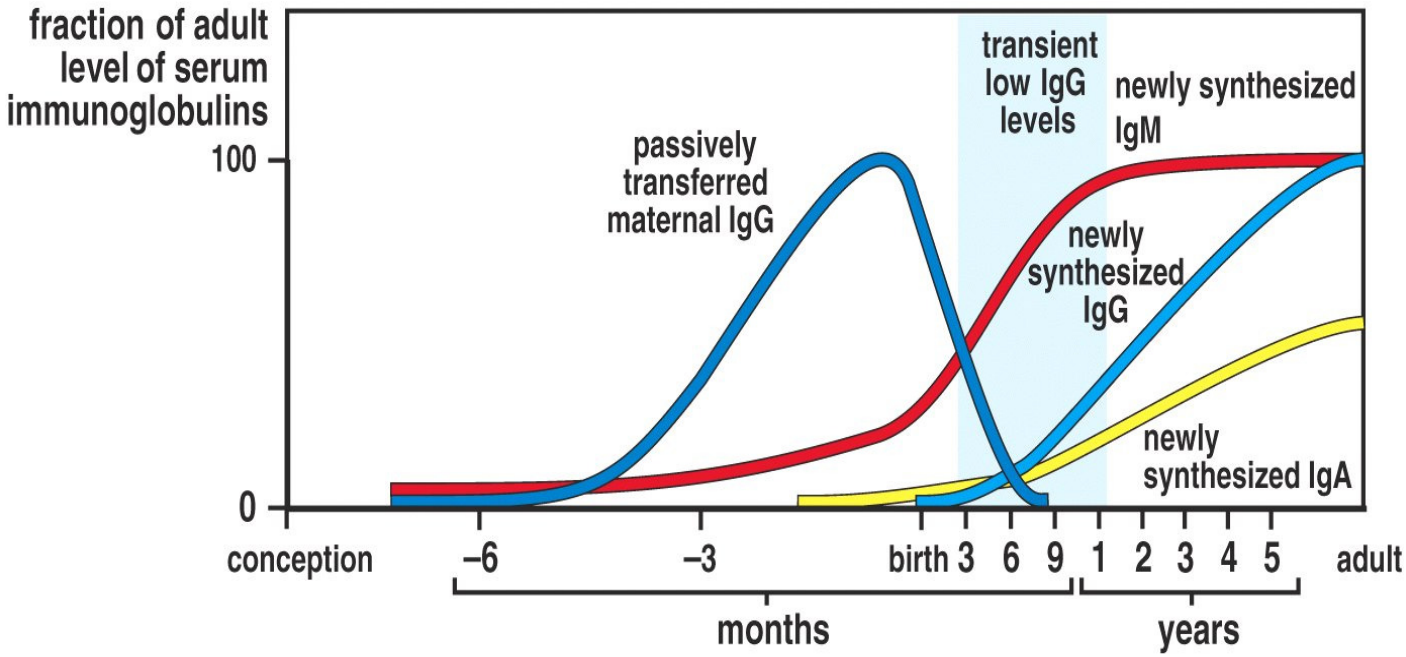
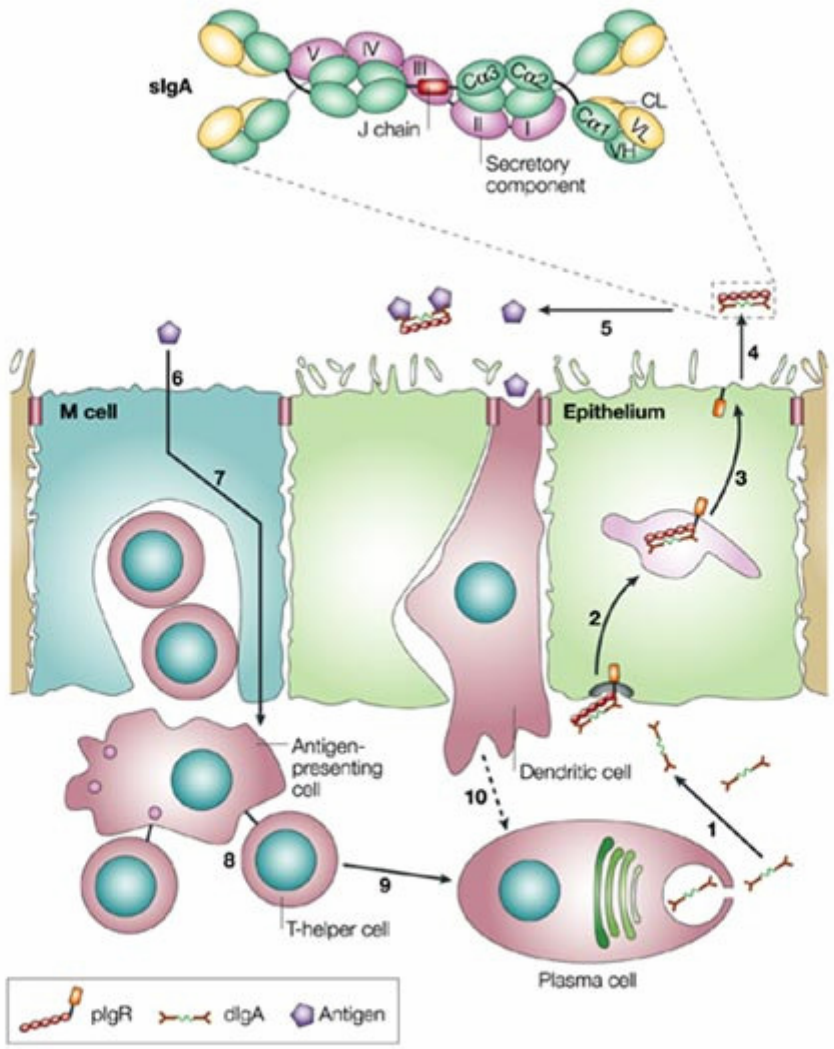


Figure 7-20 The Immune System, 2/e (© Garland Science 2005)

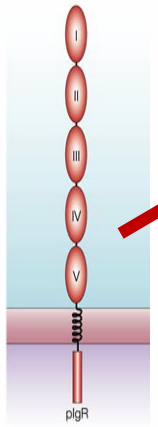


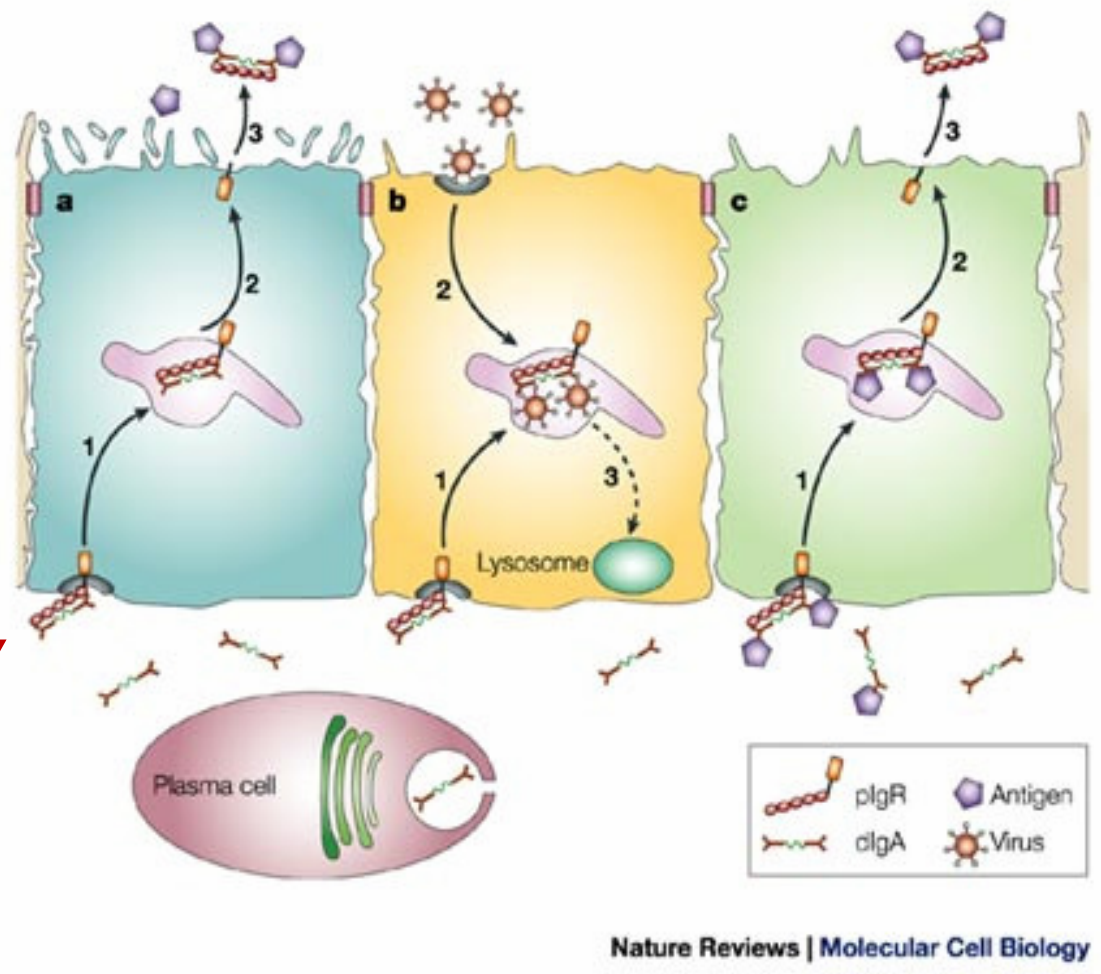
Nature Reviews | Molecular Cell Biology

In human, two isotypic forms IgA1, IgA2

・In blood, IgA1 : IgA2 ⇒ 10:1 : mainly monomer

・In mucosal , IgA1 : IgA2 ⇒ 3:2 : mainly dimer





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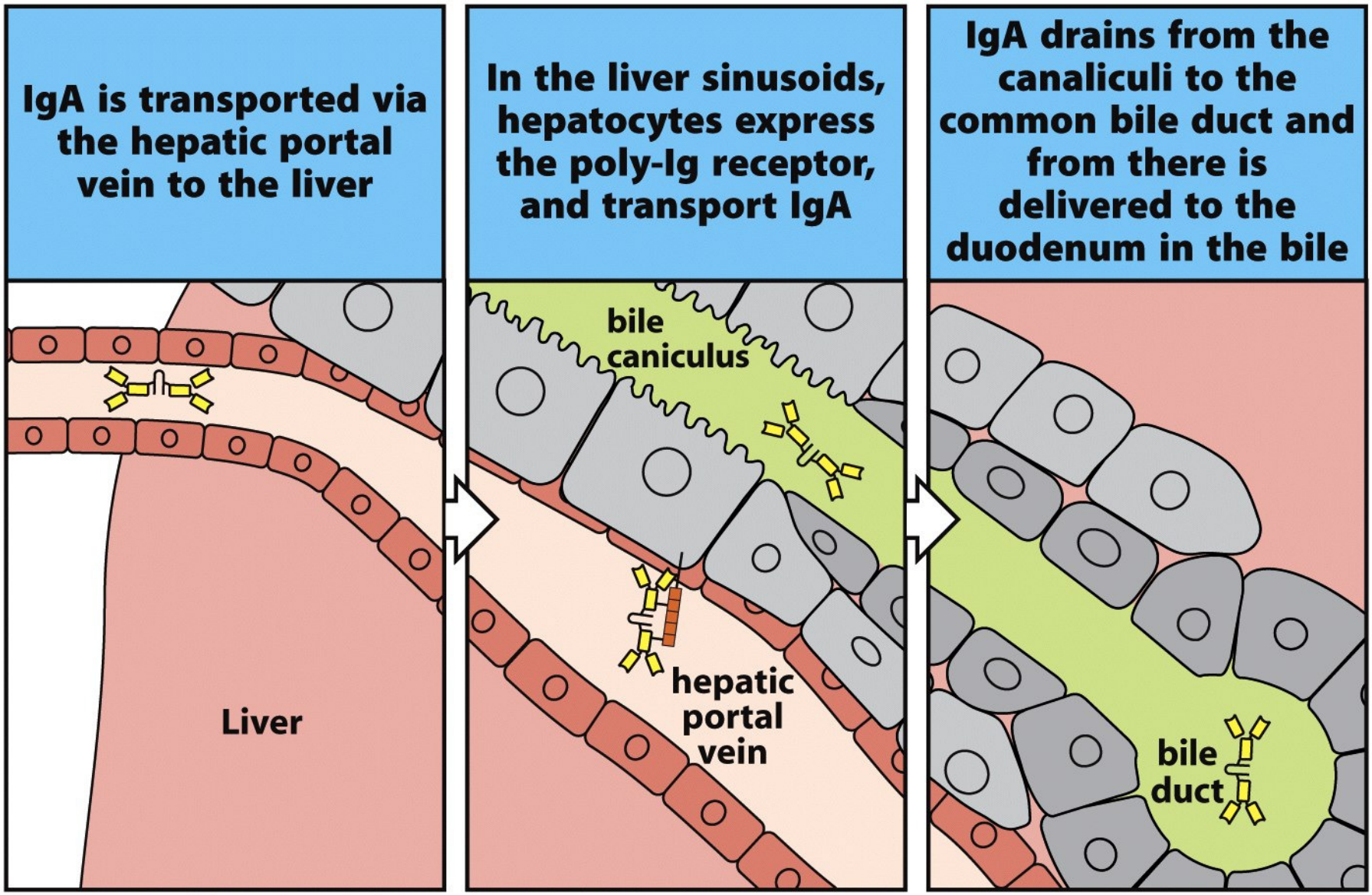
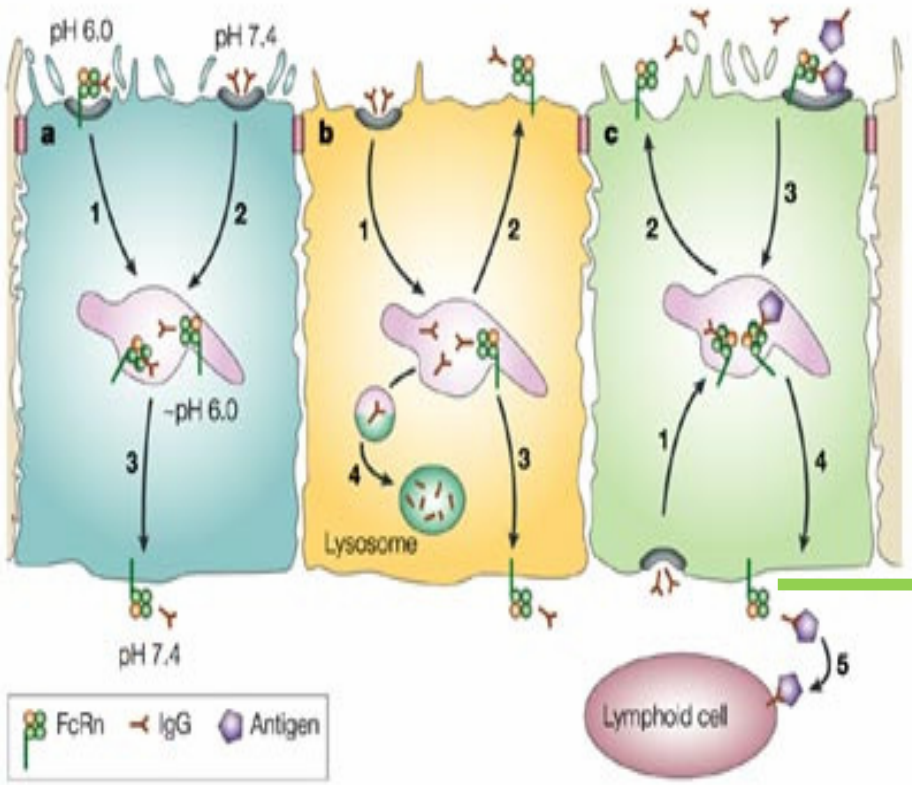
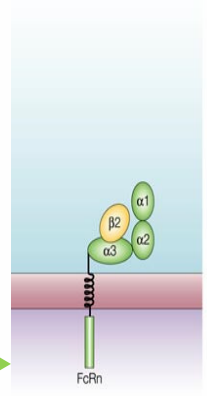


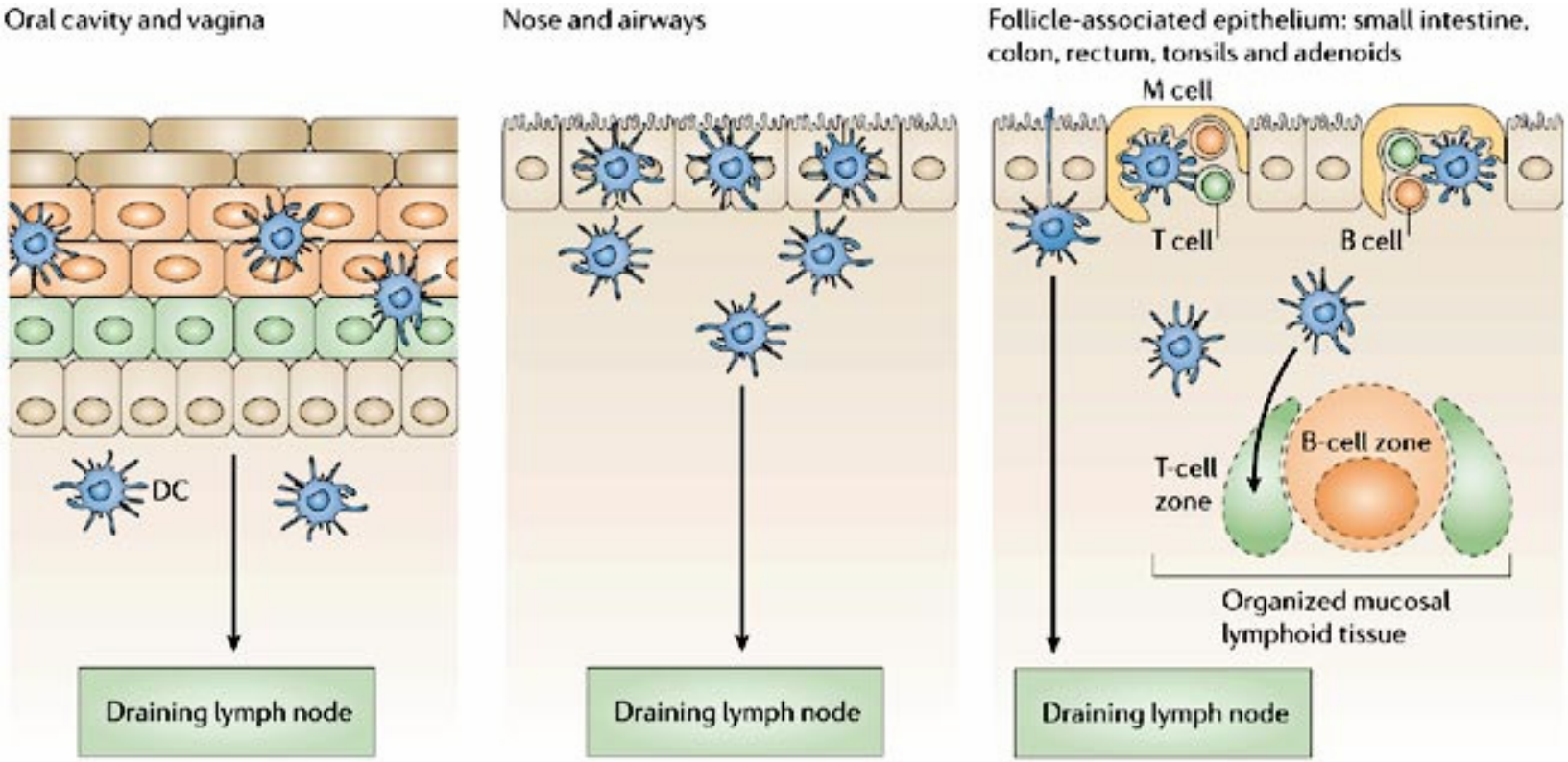
Figure 11-14 Immunobiology, 7ed. (© Garland Science 2008)

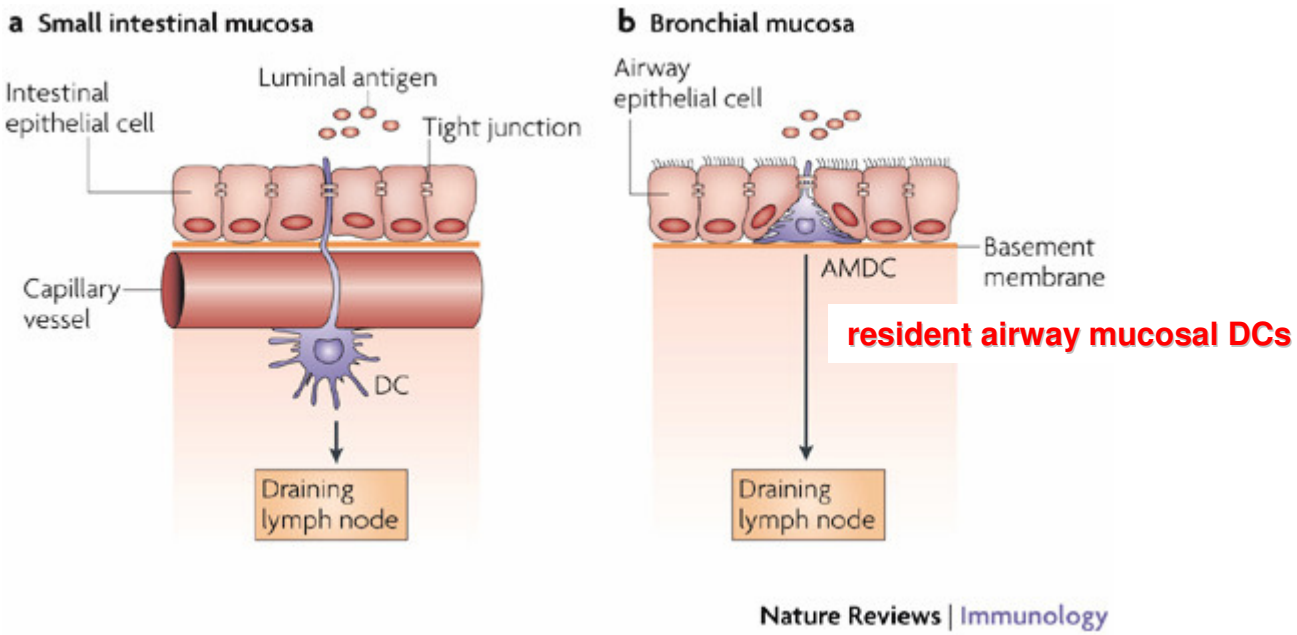

pH 6.0
pH 7.4
a
b
c
1
2
3
4
5
~pH 6.0
pH 7.4
Lysosome
Lymphoid cell
FcRn
IgG
Antigen
Nature Reviews | Molecular Cell Biology


α1
β2
α3
α2
FcRn
ure Reviews | Molecular Cell Biology

a | Formation of sIgA. dIgA is secreted by the plasma cells, where it binds to the pIgR at the basolateral pole of secretory epithelial cells. dIgA is transported through a series of endosomal compartments (step 1) en route to the apical plasma membrane domain (step 2), where a proteinase cleaves the large extracellular domain of the receptor, thereby releasing it, bound to dIgA, into secretions (step 3). dIgA, in association with the cleaved receptor fragment (also known as secretory component, SC) form sIgA. In secretions, sIgA interacts with antigens/pathogens, neutralizing their ability to cause disease. b | Intracellular virus neutralization. pIgR–dIgA complexes are delivered to endocytic compartments (step 1) where they encounter infecting viruses (step 2) or newly synthesized viral membrane proteins. The interaction of pIgR–dIgA with the virus prevents virus assembly/disassembly and the exit from the cell, possibly by targeting pIgR–dIgA–virus complexes to lysosomes (step 3) where they are degraded. c | Antigen secretion. Pathogenic antigens that penetrate the epithelium and enter the lamina propria are bound to pIgR–dIgA, internalized (step 1), transported across the cell (step 2) and released at the apical pole of the cell (step 3) where they are cleared. dIgA, dimeric IgA; pIgR, polymeric immunoglobulin receptor; sIgA, secretory IgA.

CAPTURA DEL ANTÍGENO A NIVEL DE LAS MUCOSAS





Resident dendritic cells (DCs) that are located beneath the microvasculature in the small intestinal villi extend cellular projections around the subepithelial vessels and up between the intestinal epithelial cells[5]. These cellular protrusions enable them to directly sample antigens on the luminal side. The DCs preserve the integrity of the epithelial-cell barrier by expressing tight-junction proteins. After antigen uptake the DCs upregulate CC-chemokine receptor 7 (CCR7), which allows them to migrate to the draining lymph nodes.

b | Analogous to intestinal resident DCs, **resident airway mucosal DCs** (AMDCs) that are situated within the epithelial compartment in the respiratory mucosa (both in rodents and humans) extend cellular projections into the airway lumen. Although direct evidence for the uptake of luminal antigens by AMDCs is still lacking, this model provides a plausible mechanism for continuous immune surveillance of intact respiratory mucosal surfaces.

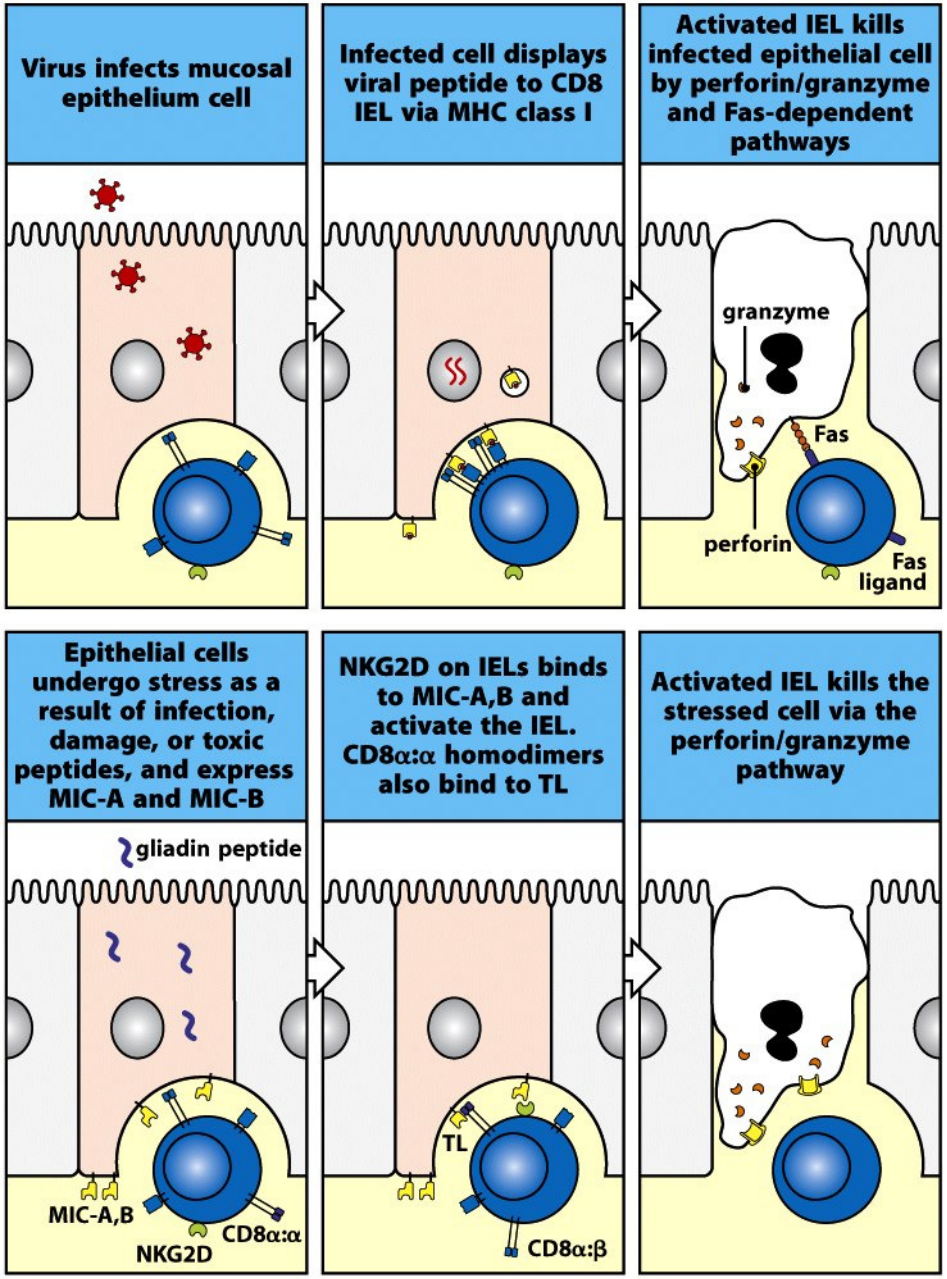
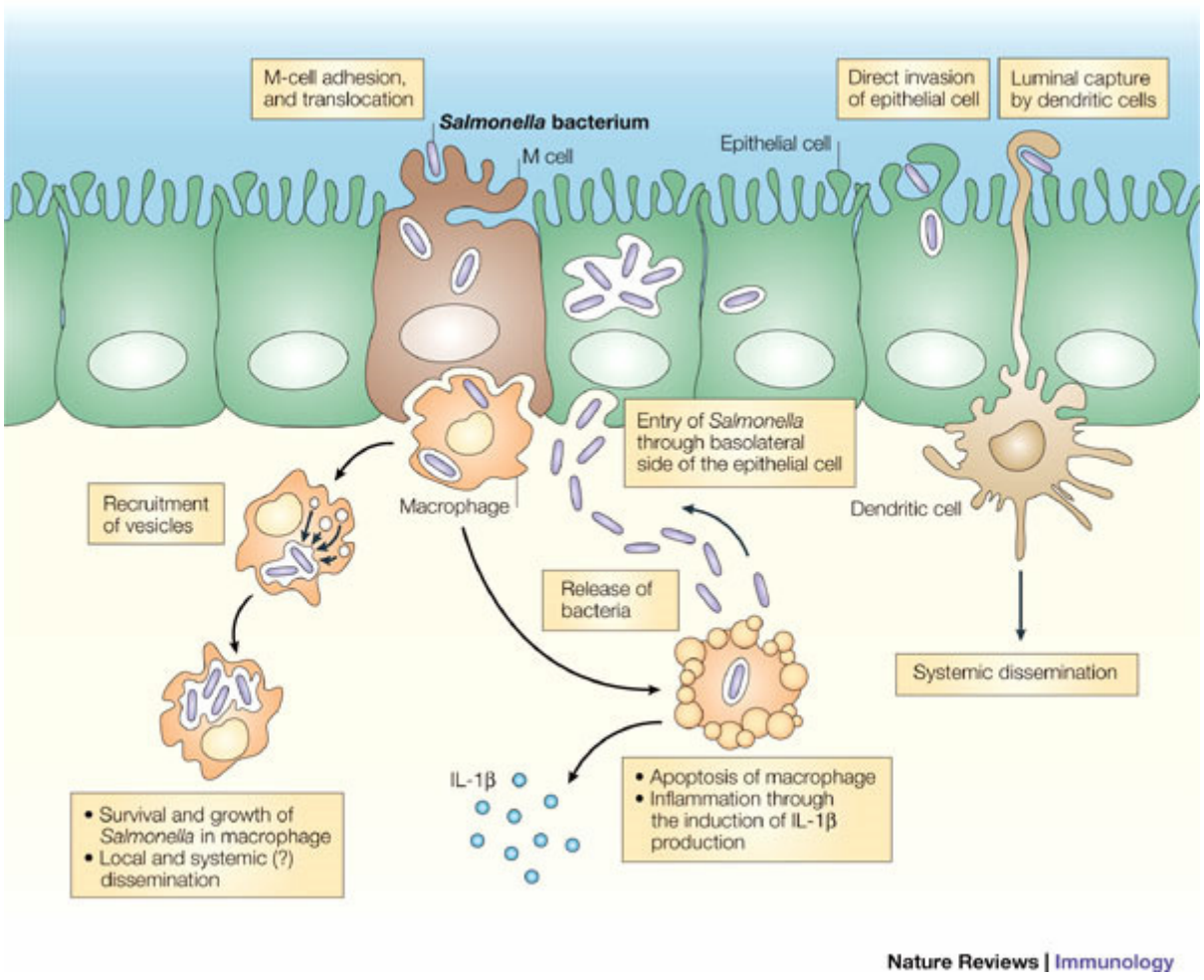


Figure 11-17 Immunobiology, 7ed. (© Garland Science 2008)

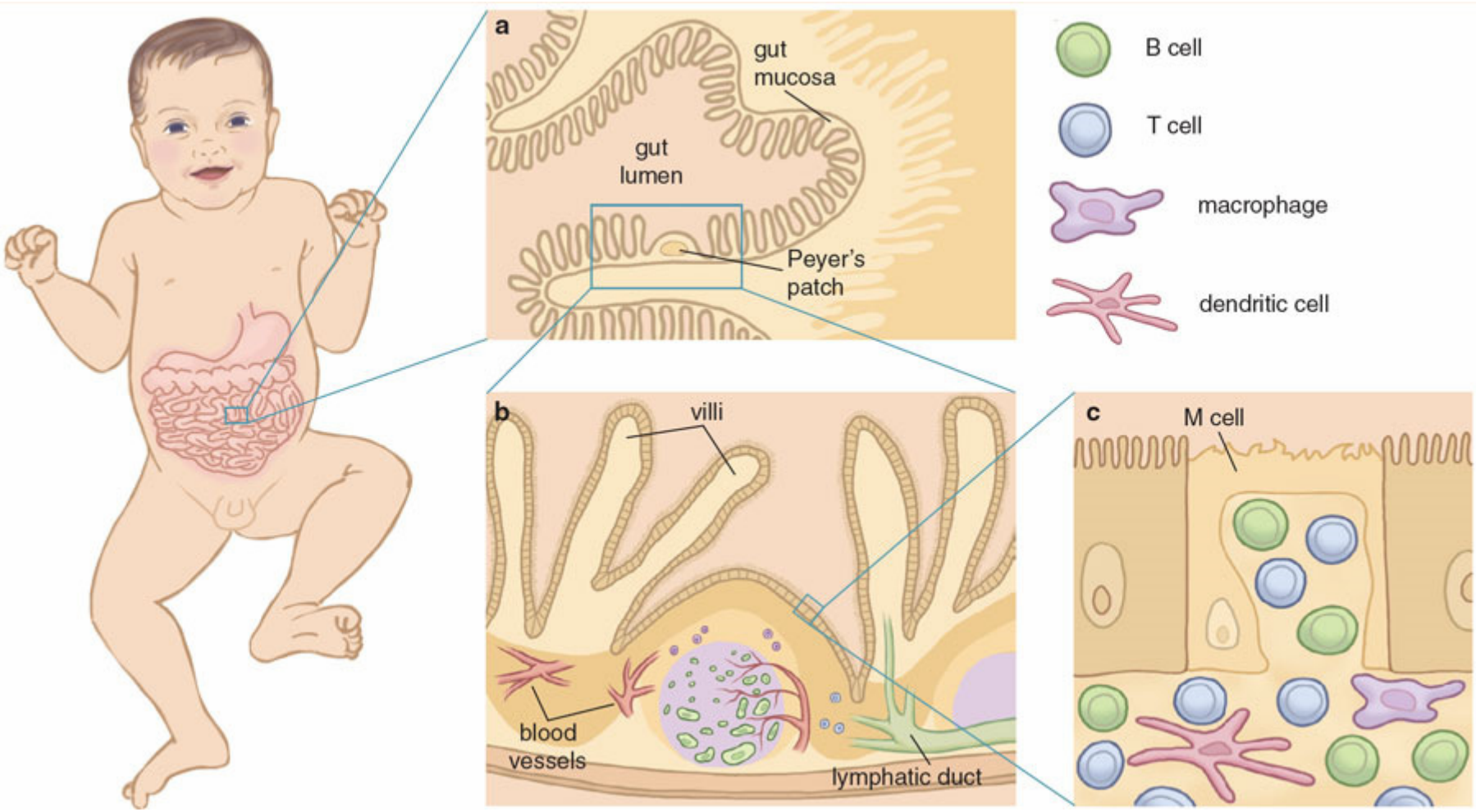


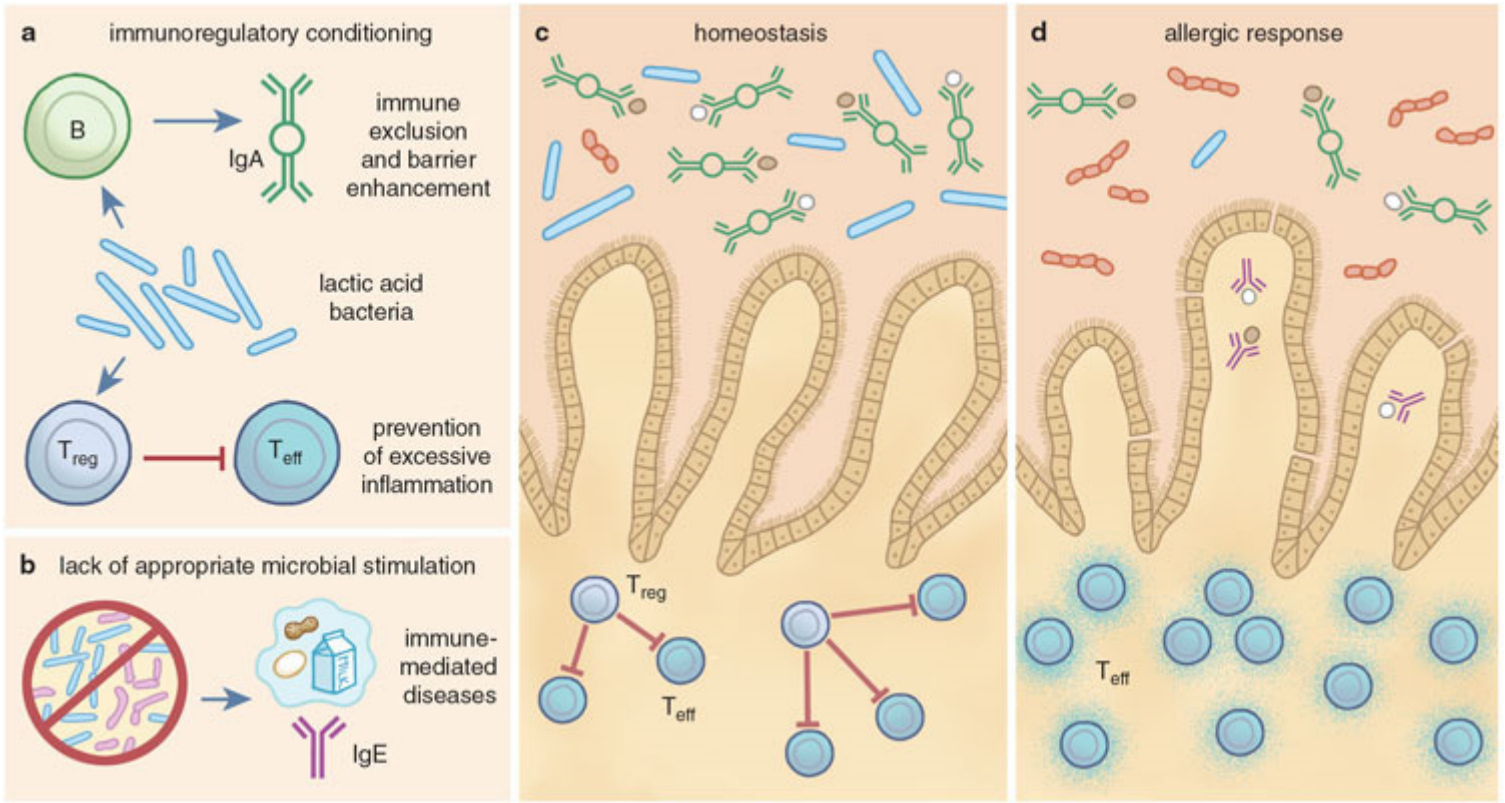
Salmonella spp. cross M (microfold) cells of the follicle-associated epithelium mainly in the Peyer's patches of the ileal portion of the small intestine but possibly also in the colon. In this subepithelial location, Salmonella spp. might cause macrophage apoptosis through effectors injected using a type III secretory system that is encoded by Spi1 (Salmonella pathogenicity island 1), thereby also triggering inflammation. Salmonella spp. also switch to expression of Spi2, which encodes a type III secretory system that allows injection of effector proteins from the endocytic vacuole into the cell cytoplasm, thereby enabling bacteria to modify the vacuole to a Salmonella-containing vacuole, which supports bacterial survival and multiplication. This provides bacteria with the capacity to both invade epithelial cells basolaterally, owing to expression of Spi1 effectors, and to disseminate systemically. Alternatively, Salmonella spp. can also directly enter intestinal cells by the apical pole of the cell or be captured by dendritic cells that emit pseudopods between epithelial cells. The latter process promotes systemic dissemination of Salmonella spp.

IL-1β , interleukin-1 β .

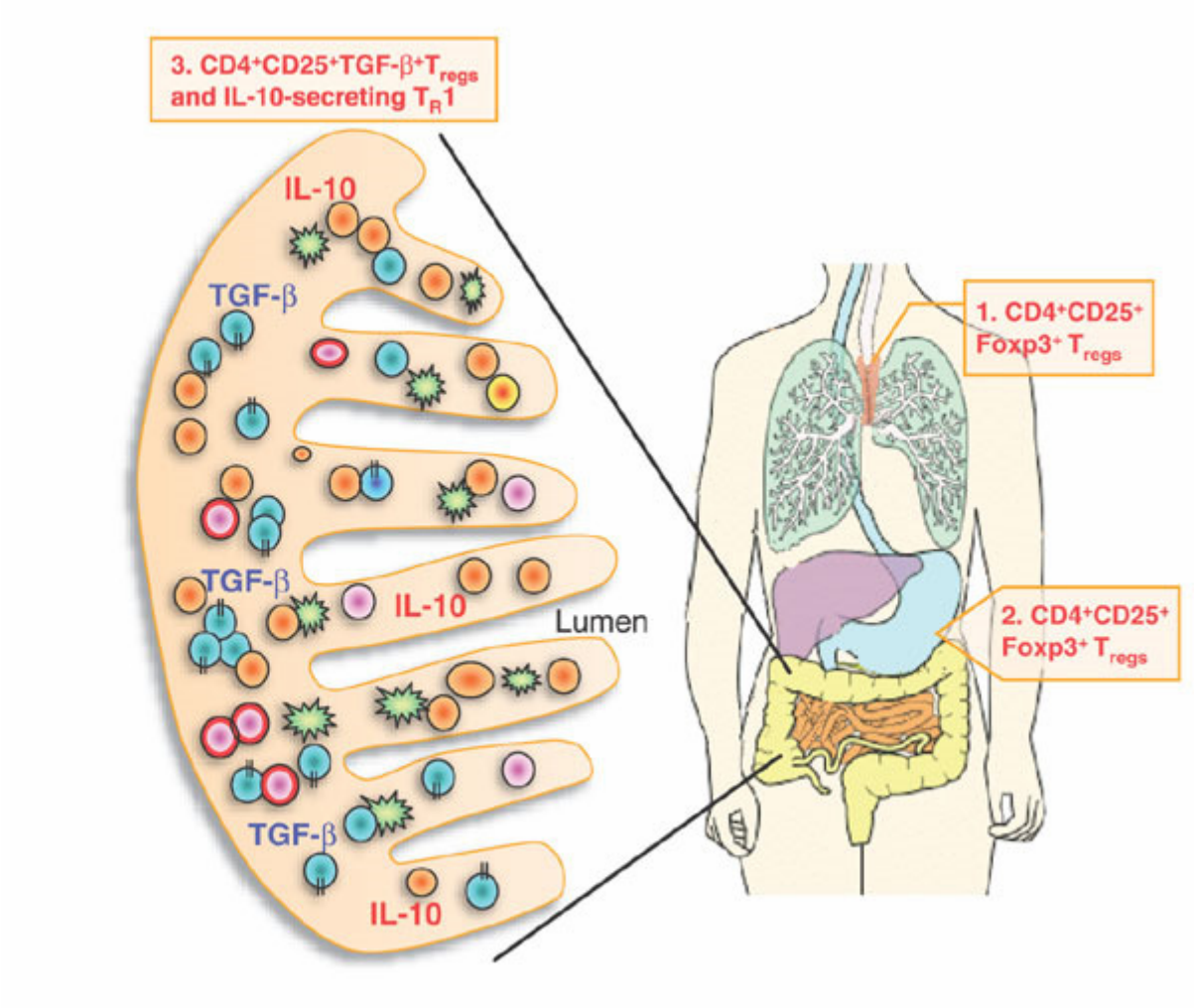
Nature Reviews Immunology 4, 953-964 (December 2004)

Inmunidad de mucosas en el recién nacido


a
gut
mucosa
gut
lumen
Peyer's
patch
b
villi
blood
vessels
lymphatic duct
c
M cell
B cell
T cell
macrophage
dendritic cell

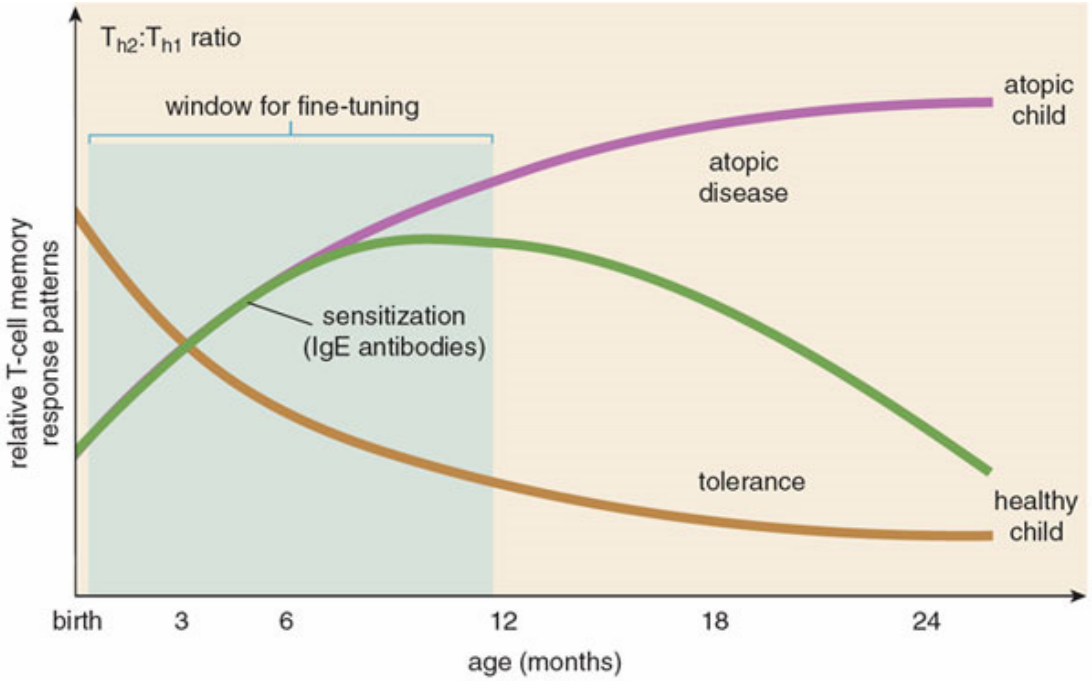

a
immunoregulatory conditioning
B
IgA
immune exclusion and barrier enhancement
lactic acid bacteria
T_{reg}
T_{eff}
prevention of excessive inflammation
b
lack of appropriate microbial stimulation
immune-mediated diseases
IgE
c
homeostasis
T_{reg}
T_{eff}
d
allergic response
T_{eff}

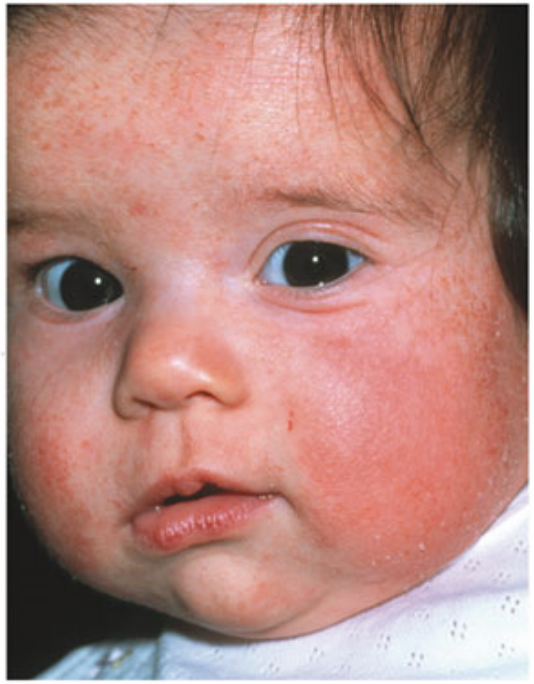
β



Different types of regulatory T cells. (1) $CD4^+CD25^+$ $Foxp3^+$ Tregs are a naturally occurring T_{reg} subset that is mainly thymus derived. (2) $CD4^+CD25^+$ T_{regs} are central in the prevention of autoimmunity; they were originally identified by the development of autoimmune gastritis in neonatally thymectomized mice. (3) In the intestine, dietary antigens and the commensal flora present an enormous antigenic load to the gut-associated lymphoid tissue. $CD4^+CD25^+TGF\text{-}\beta^+$ T_{regs} and IL-10-secreting T_R1 cells are induced by unique subsets of APCs and provide overlapping layers of immunosuppression that prevent chronic intestinal inflammation.

Nature Immunology **5**, 119 - 122 (2004)

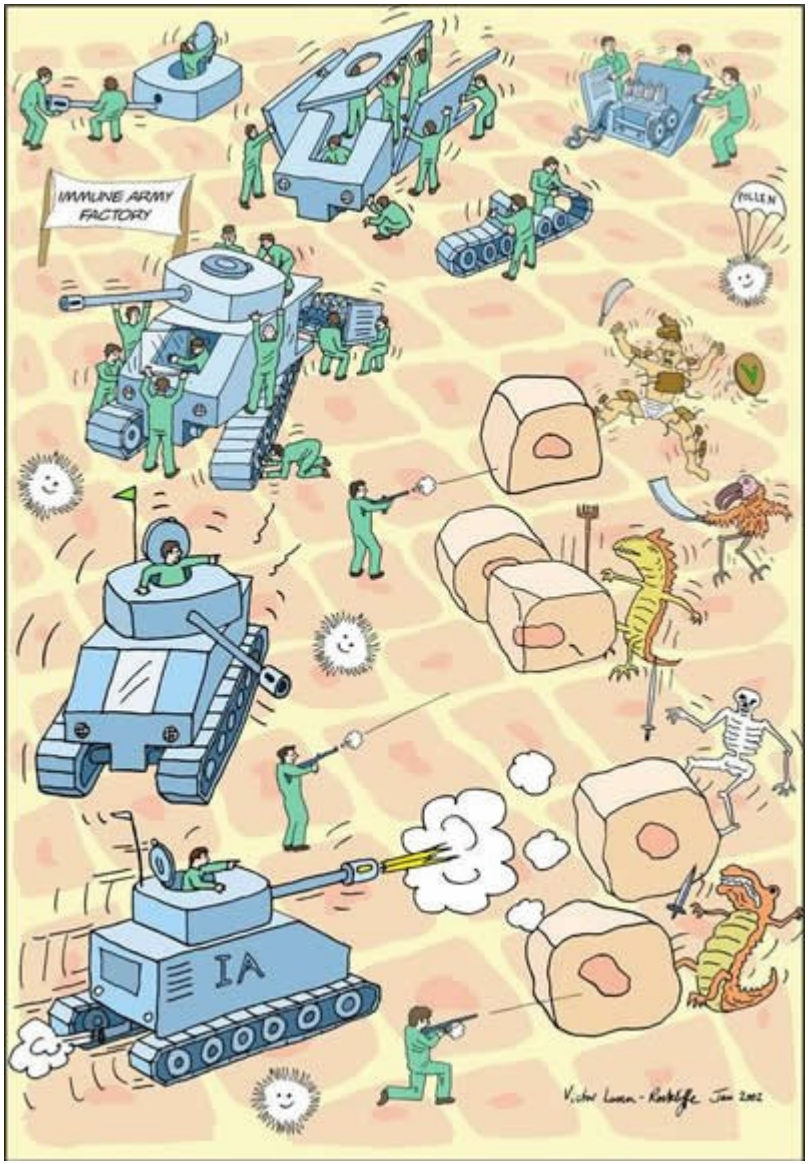




The ratio of two types of T cells—helper 1 (T_{h1}) and helper 2 (T_{h2})—indicates the presence or absence of allergy in young children. A newborn's immune system is skewed toward the T_{h2} response, but the system gradually becomes dominated by T_{h1} signals in a healthy child (*brown line*). In a child who suffers from allergies (*purple line*), the continued dominance of T_{h2} signals may lead to conditions such as eczema (*bottom*). Homeostatic balancing of the T_{h2}:T_{h1} ratio appears subject to microbial modulation, particularly during a narrow postnatal window (*shaded region*).

Even for "sensitized" infants with high levels of IgE antibodies, an increase in beneficial gut bacteria may coax the release of cell signals that balance the T_{h2}:T_{h1} ratio to promote homeostasis (*green line*).

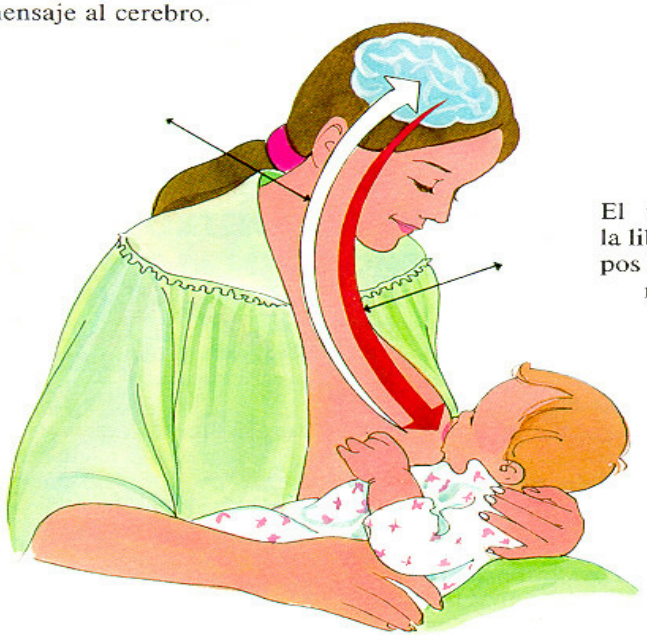
(Modified from Rautava *et al.* 2004.)


IMMUNE ARMY FACTORY
POLLEN
IA

For newborn babies, human milk hastens the development of the gut and immune systems, which are immature at birth. Breast milk reinforces the barrier function of neonatal gut epithelium and provides the principal source of secretory IgA antibodies during the first months of life. These antibodies bind to food antigens to limit the reactivity of the immune system and to microbial antigens to retard infection. Babies who consume only breast milk for at least four months tend to experience less asthma and eczema, particularly if they have a family history of allergy.

MECANISMO DE PRODUCCION DE LA LECHE

Cuando el niño succiona se envía un mensaje al cerebro.



El mensaje estimula la liberación de dos tipos de sustancias químicas (hormonas).

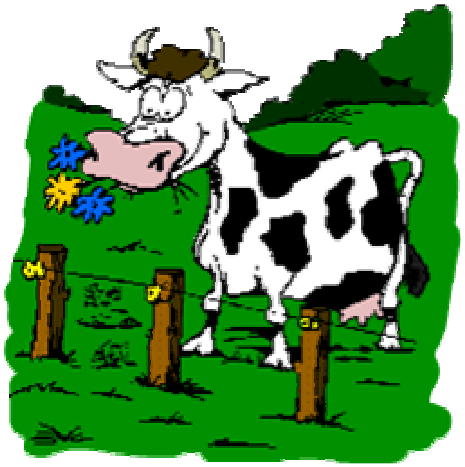
Una de las hormonas estimula la producción de la leche.

La otra, favorece su salida.

La producción de la leche será adecuada siempre que el niño succione con frecuencia.

Nutrimento	Calostro (5 días)	**Leche de Transición (6 -15 días)**	Leche Madura (> 15 días)
Calorías Kcal/L	671	735	680 - 700
Proteínas g/L	22.9	15.9	10
Albúmina/Caseína	90:10		60:40
Lactosa g/L	53	64	72
Grasas g/L	29	35.2	42
Colesterol g/L	270	241	160

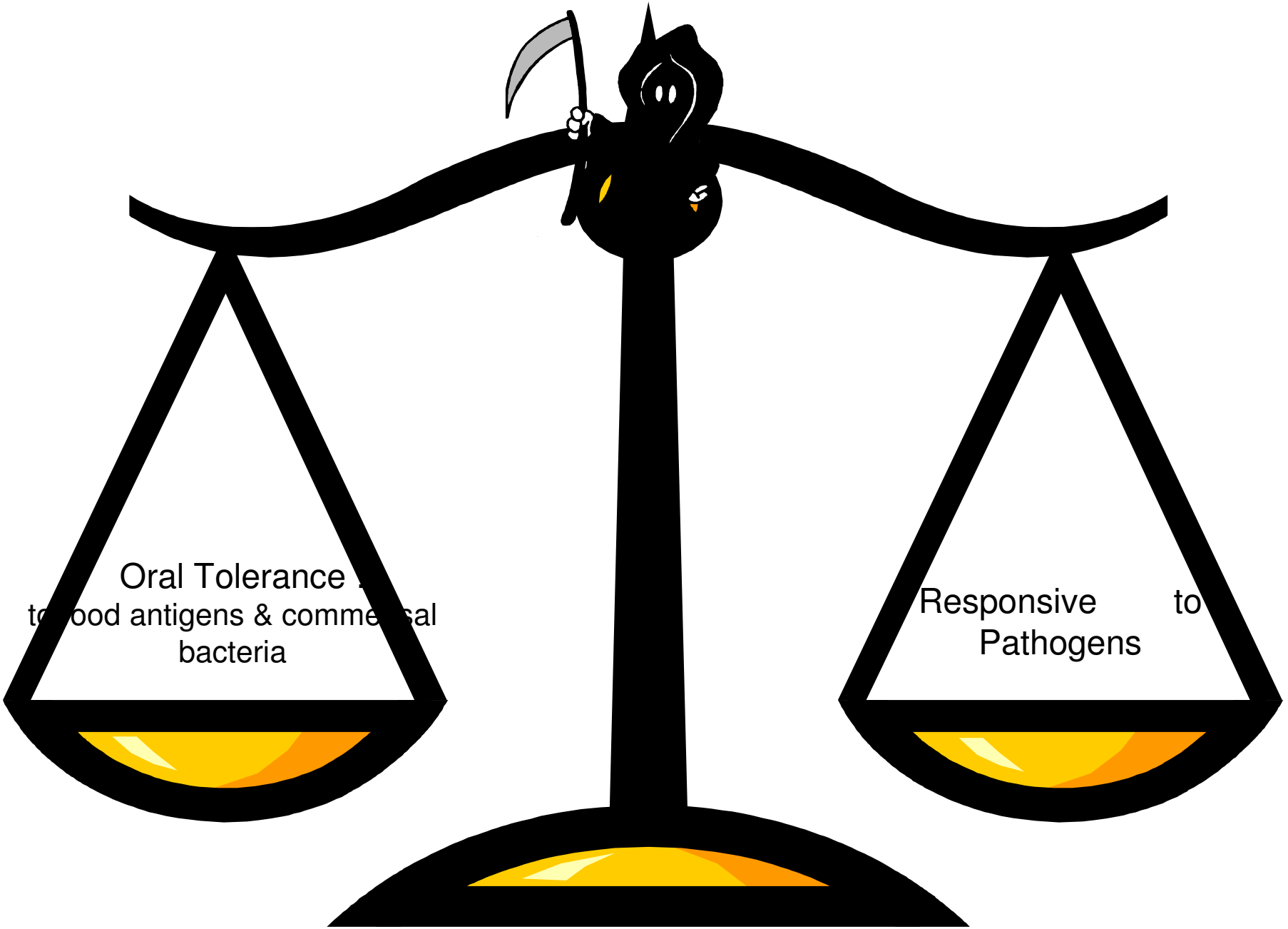

Breastfeeding
is best feeding.




HUMAN milk for
HUMAN babies

TOLERANCIA ORAL

- La producción de anticuerpos contra los alimentos es un fenómeno mundial tanto en adultos como en niños saludables.
- En su mayoría son de isotipo IgG sin embargo no activan al sistema inmune.
- No están involucrados en fenómenos alérgicos……


Oral Tolerance
to food antigens & commensal
bacteria
Responsive to
Pathogens

- La **TOLERANCIA ORAL** es el mecanismo natural que el sistema inmunológico usa para permitir el proceso de la nutrición sin provocar rechazos o reacciones de hipersensibilidad frente a los alimentos.
- En este mecanismo se encuentran involucrados tejido linfoideo intestinal, entre ellos: las placas de Peyer, células epiteliales de las vellosidades, linfocitos intraepileliales y linfocitos diseminados a través de la lámina propia.
- Por cualquiera de los métodos por los cuales se induzca el efecto de tolerancia oral, es un proceso inmunológico natural que puede ser empleado con éxito en el tratamiento de las patologías autoinmunes.

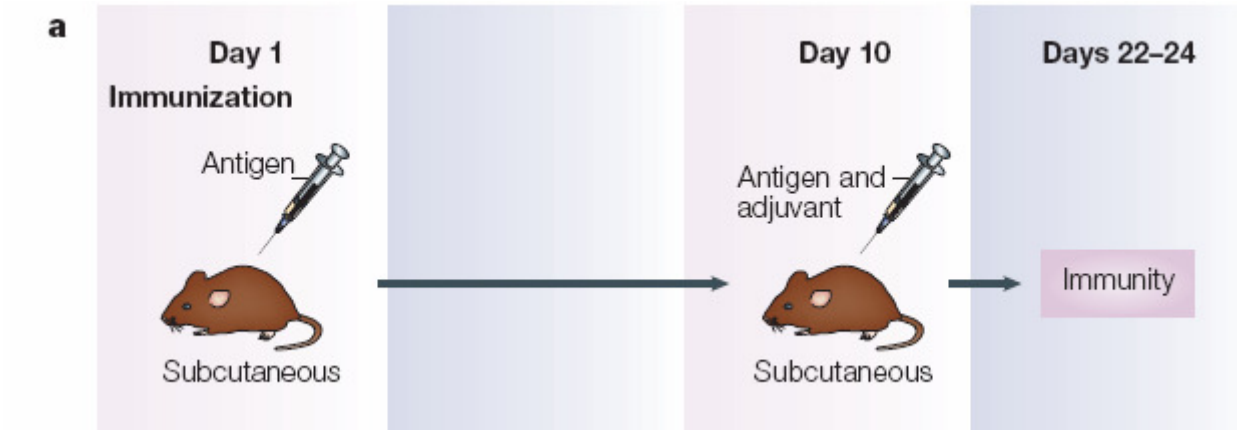
Antígeno vs RESPUESTA

Factors that affect response to Ag	Favor immune response	Favor tolerance
physical form of antigen	large, aggregated, complex molecules;	soluble, aggregate-free, relatively smaller, less complex molecules, Ag not processed by APC or processed by cell without class II MHC
route of Ag administration	sub-cutaneous or intramuscular	oral or sometimes intravenous
dose of antigen	optimal dose	very large (or sometime very small) dose
age of responding animal	older and immunologically mature	Newborn (mice), immunologically immature
differentiation state of cells	fully differentiated cells; memory T and memory B cells	relatively undifferentiated: B cells with only IgM (no IgD), T cells (*e.g.* cells in thymic cortex)

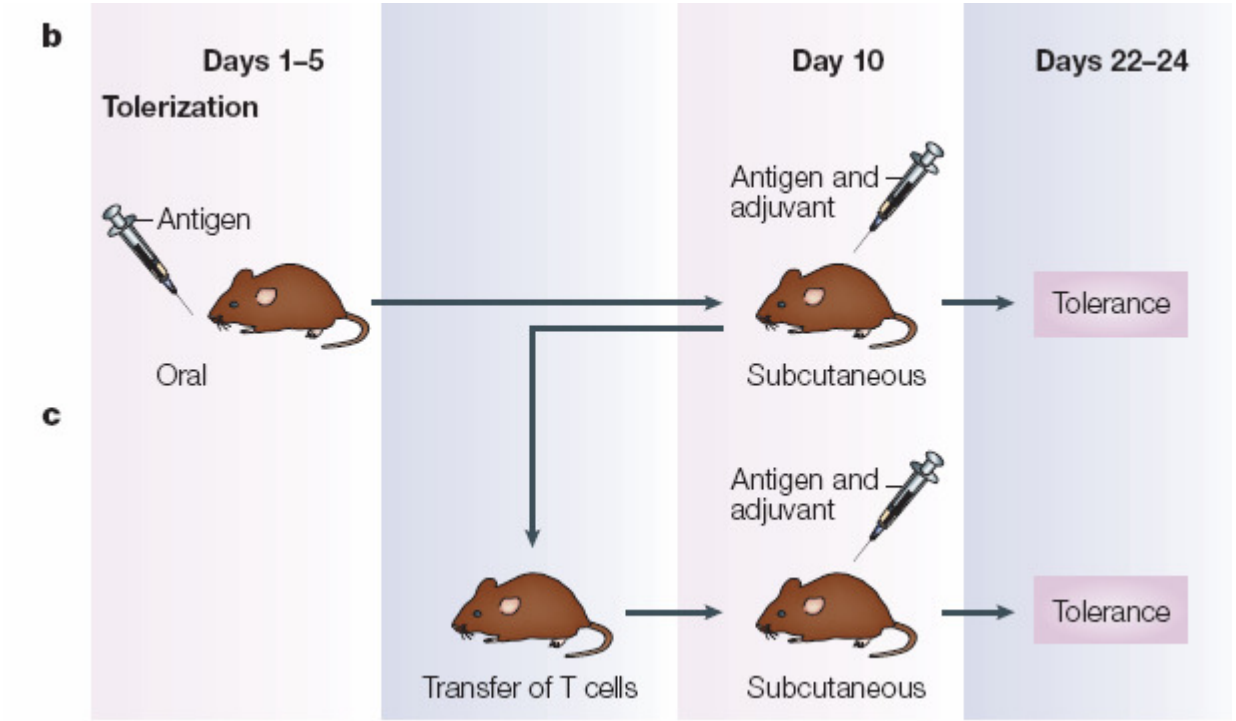
Distintas rutas de administración de antígenos y sus efectos

Route of antigen administration	Usual outcome
Subcutaneous	Immunization
Intramuscular	Immunization
Injury	Immunization
Intravenous	Tolerance
Mucosal (oral, nasal and respiratory)	Tolerance
Portal vein	Tolerance
Anterior chamber of the eye	Tolerance

Introduction of antigen through different routes lead to distinct outcomes. Immunization is characterized by local inflammation and specific antibody production. Tolerance is characterized by inhibition of systemic immunity to the specific antigen being administered.

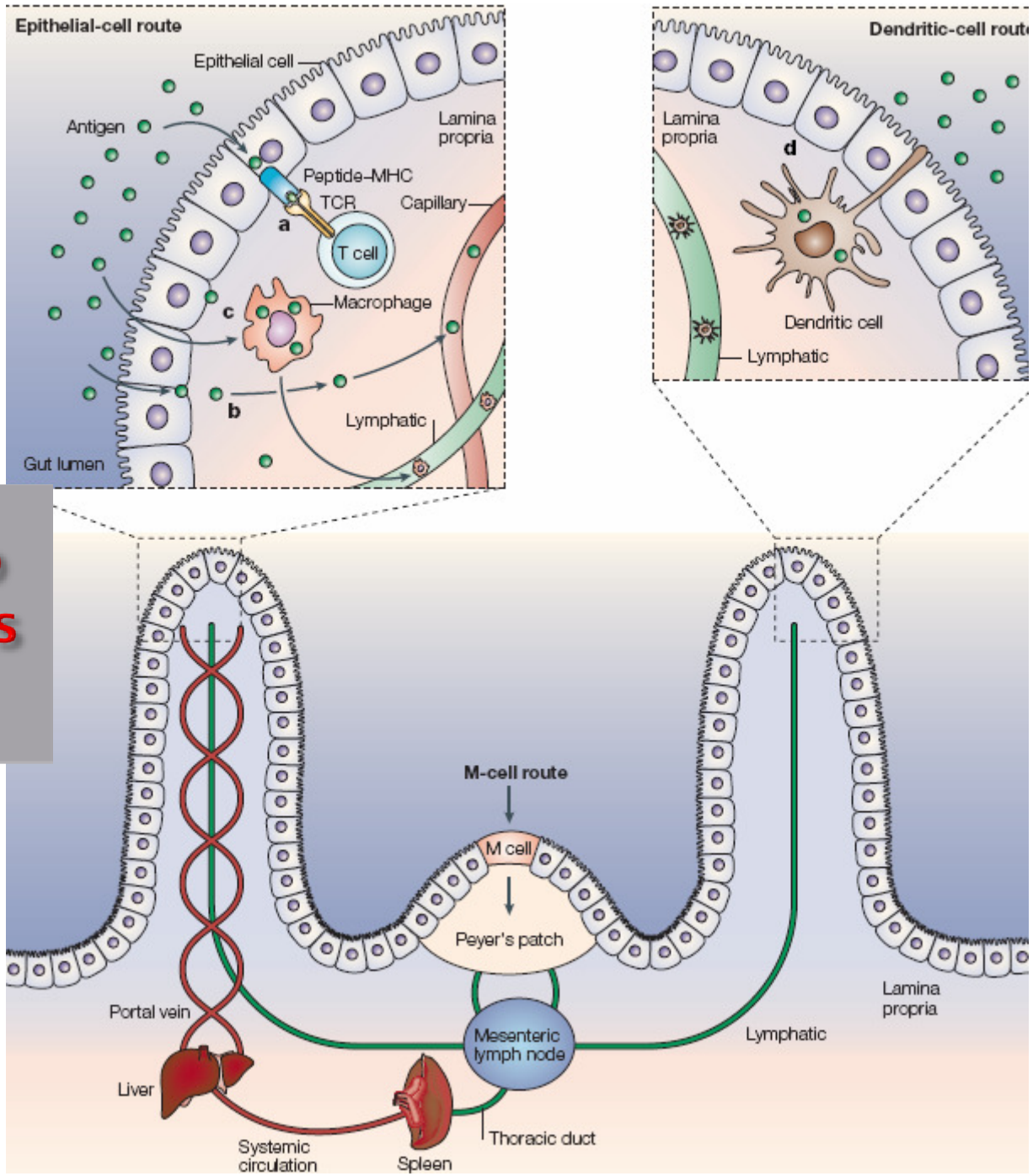


a | Mice that are immunized subcutaneously and then boosted subcutaneously with antigen plus adjuvant, such as Freund's complete adjuvant or alum, show a robust *in vitro cell-mediated and antibody response to the immunizing antigen.*

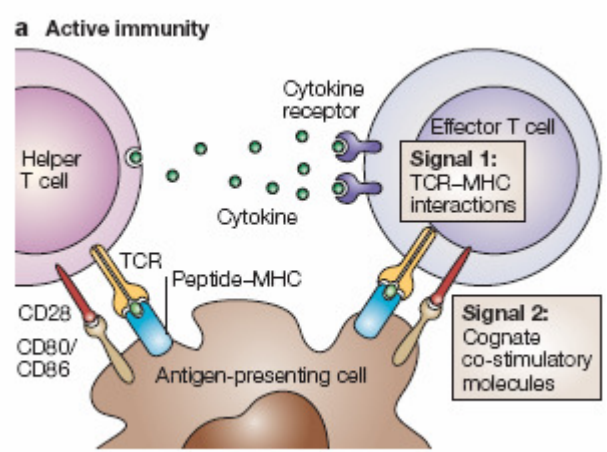


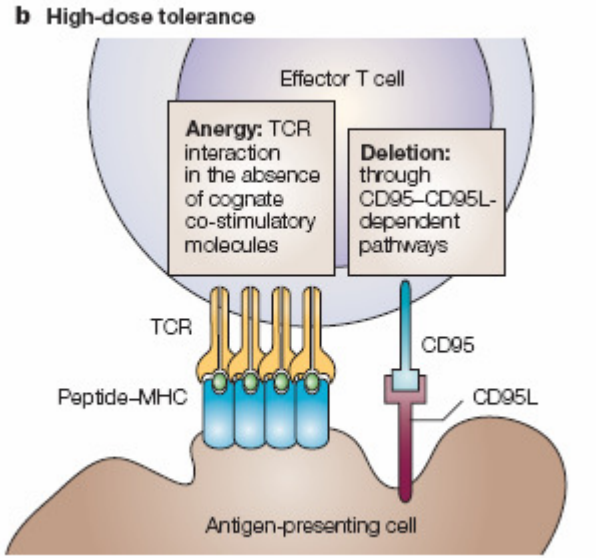
b | Mice that are first orally fed antigen, then immunized subcutaneously with antigen plus an adjuvant have reduced immune responses to that antigen after *in vitro restimulation. c | Finally, T cells from mice* that are fed antigen (low dose) can be transferred to naive mice. Immunization of mice that received the tolerized T cells results in the same reduced response as seen in the mice that were fed antigen orally. This shows that oral feeding of antigen can induce an active (but inhibitory) immune response that is mediated by T cells.

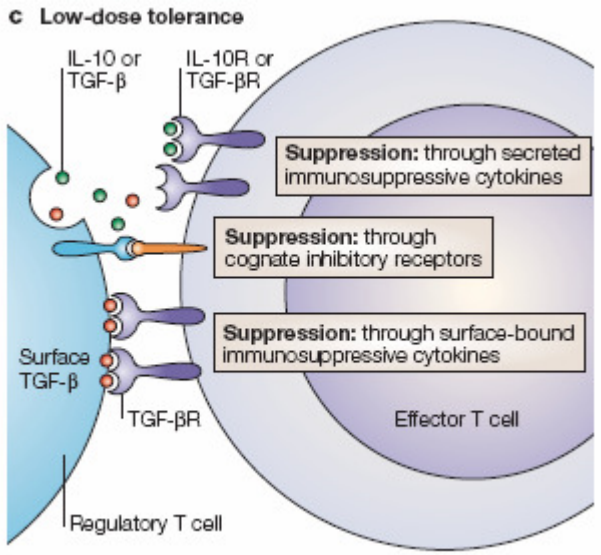
Vías de ingreso de los antígenos alimentarios



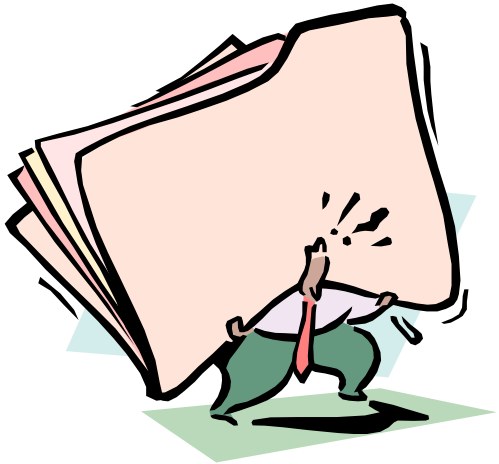
Mecanismos potenciales de inducción de TOLERANCIA ORAL







Nature Reviews Immunology 4, 407-419 (June 2004)



GRACIAS!