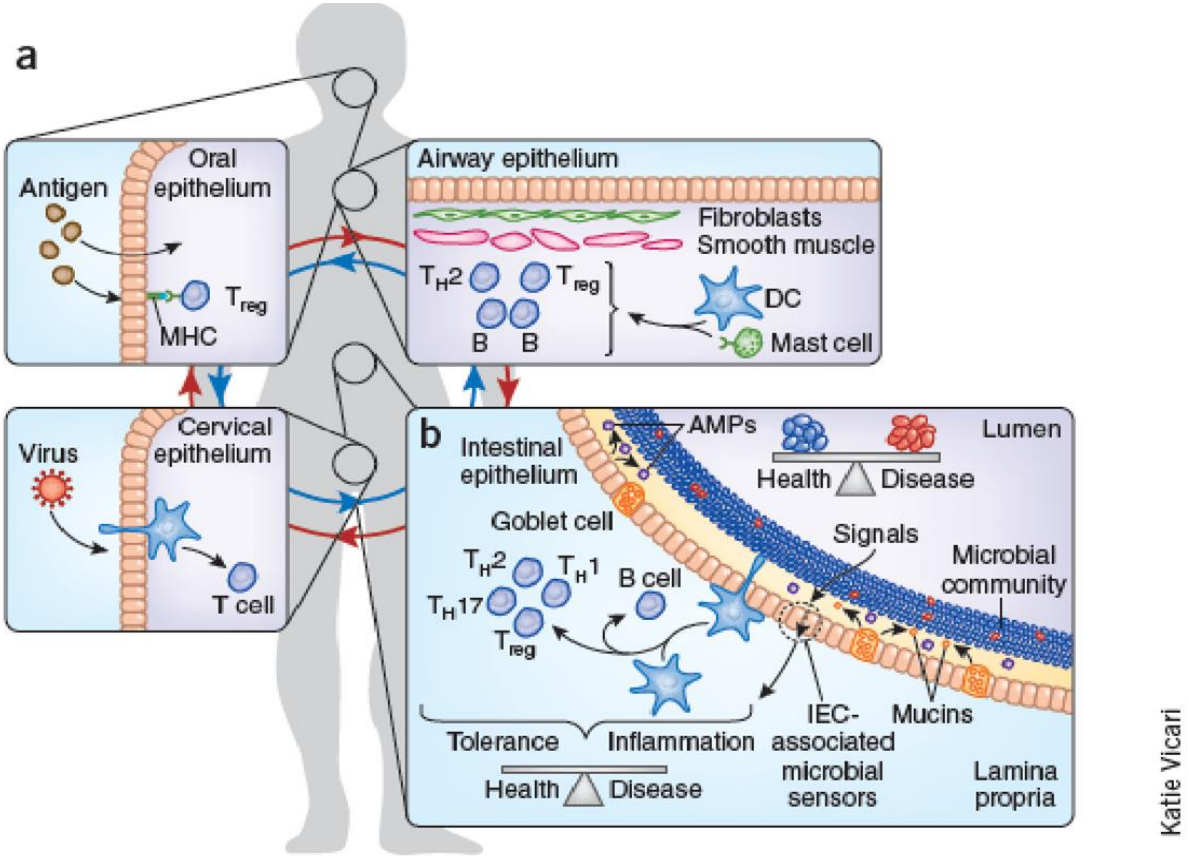
SISTEMA INMUNITARIO DE LA MUCOSA INTESTINAL

CARACTERÍSTICAS DEL SISTEMA INMUNITARIO DE LA MUCOSA INTESTINAL

- Exposición permanente antígenos
- Sólo una capa de células epiteliales separa las células del S.I. del exterior
- Contacto de las células del S.I. con el antígeno es diferente del que ocurre en otros órganos linfoides
- Presencia de estructuras linfoepiteliales especiales (placas de Peyer, amígdalas)
- Producción y secreción de sIgA
- Tolerancia oral (antígenos y flora)

LAS BARRERAS DEL SISTEMA INMUNITARIO



FACTORES NO INMUNITARIOS DE DEFENSA FRENTE A PATÓGENOS

- Microflora comensal
- Actividad motriz (peristaltismo, movimiento ciliar)
- Sustancia químicas: ácidos gástricos, sales biliares, mucinas.
- Sustancias antibióticas: lisozima, defensinas

Funciones del epitelio la en la respuesta inmunitaria

Intestinal function	Importance in mature gut	Importance in infant gut
Peristaltic movements	Expulsion of bacteria in the stool.	Generalized reduced peristalsis in preterm infant gut.
Mucous secretion	Mucous secreted acts as a physical barrier against pathogens by preventing bacterial adherence. It also contains immunologically active immunoglobulin A (IgA).	Preterm infants may be mucin deficient as the mucin gene is only fully expressed between 23 and 27 weeks gestation
Peptide secretion	Lysozymes and defensins are secreted by Paneth cells in response to microbes. They affect the number and composition of the colonizing microbiota	The preterm gut has fewer Paneth cells and reduced expression of alpha-defensin .In mice, cathelin-related antimicrobial peptide (CRAMP) is observed to protect against Listeria monocytogenes in the first 2 weeks of life. CRAMP expression may contribute to normal bacterial colonization and protect against infection in the post-natal period .
Microbial recognition	Epithelial and dendritic cells 'sample' the gut microbiota by detecting pathogen-associated molecular patterns (PAMPs), for example, lipopolysaccharide (LPS) and lipoteichoic acid (LTA). Epithelial cells express NOD-like receptors (NLR) and Toll-like receptors 2 and 4 (TLR-2 and TLR-4) that detect LPS and LTA Ligation of TLRs and NLRs in the gut can produce a localized response (whereas elsewhere in the body this usually activates the innate immune response).	TLR-2 and TLR-4 are active in foetal gut at 18–21 weeks gestation and are thought to be important in infants. TLR-4 expression may play a role in necrotizing enterocolitis (NEC)
Transepithelial antigen transport	Antigen presentation to lymphocytes is undertaken by specialized microfold cells (M cells) and dendritic cells. Enterocytes express MHC class II and may also act as antigen-presenting cells (APCs)	In newborns, the neonatal Fc receptor (FcRn) mediates bidirectional transport of IgG across the epithelium.
Prevention of bacterial translocation	Tight junctions The permeability of the intestine to microbes is dependent on the integrity of 'tight junctions' between enterocytes. Tight junctions are composed of a ZO-1 protein within each enterocyte, which are linked together by claudins TLR signalling MyD88 and TRIF are two adaptors that jointly transduce all TLR signalling. Knock-out mice lacking these two adaptors harbour large numbers of commensal bacteria in the spleen NF-kB pathway Reduced activation of this pathway increases bacterial translocation across the gut wall in mice.	Presence of LPS in the bloodstream of infants with NEC is high at onset of the illness implicating intestinal barrier failure as an early factor in the pathogenesis. A leaky intestinal barrier allows bacterial products and proinflammatory cytokines into the bloodstream to exert effects at organ sites, which can result in multi-organ failure.
Interface to the systemic immune system	Efficacy of mucosal vaccines given orally such as the polio vaccine, which induces systemic immunity).	Needle-free mucosal vaccines are an attractive option for infants; however, infant IFNg responses to oral polio vaccine appear attenuated. Defective IFNg production may predispose infants to infection by intracellular pathogen

Battersby et al Pediatr Allergy Immunol. 2013

SISTEMA INMUNITARIO DE LAS MUCOSAS

- Tejido organizado (inducción)
  - MALT (Mucosa-associated lymphoid tissue)
  - Nódulos linfáticos

- Tejido difuso (fase efectora)
  - Células epiteliales
  - Linfocitos intraepiteliales
  - Células de lámina propia

TIPOS DE MALT Y SUS COMPONENTES

Region	Components
GALT (Gut-associated lymphoid tissue)	Peyer's patches (PPs) and isolated lymphoid follicles constitute the major part of GALT, but also the appendix is included
NALT (Nasopharynx-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. Scattered isolated lymphoid follicles may also occur in nasal mucosa. Rodents lack tonsils, but do have paired NALT structures dorsally in the floor of the nasal cavity
BALT (Bronchus-associated lymphoid tissue)	Not generally detectable in normal lungs of adult humans

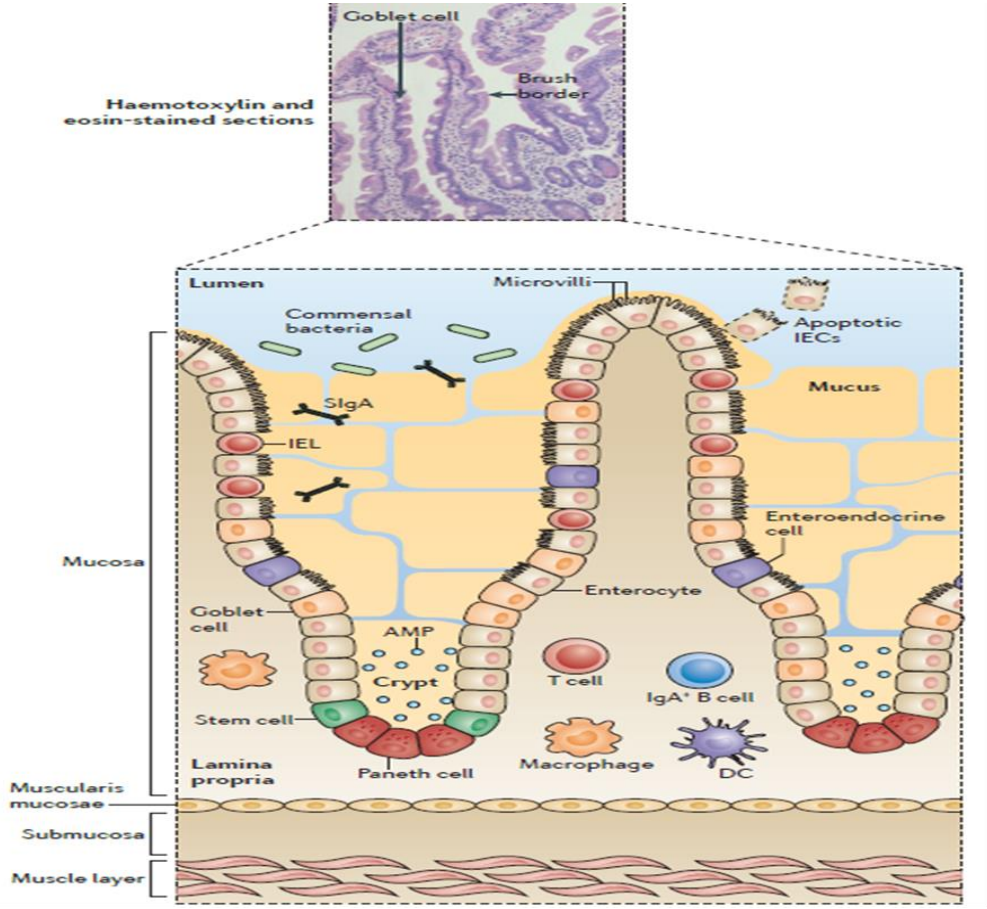
Table 1.1 Principles of Mucosal Immunology (© Garland Science 2013)

SISTEMA INMUNITRIO DE LA MUCOSA INTESTINAL

- TEJIDO LINFOIDE ORGANIZADO (fase de inducción de la respuesta inmunitaria)
  - GALT: PLACA DE PEYER, APÉNDICE, SILT (Solitary Isolated Lymphoid Tissues: Cryptopatches y ILF)
  - NLM

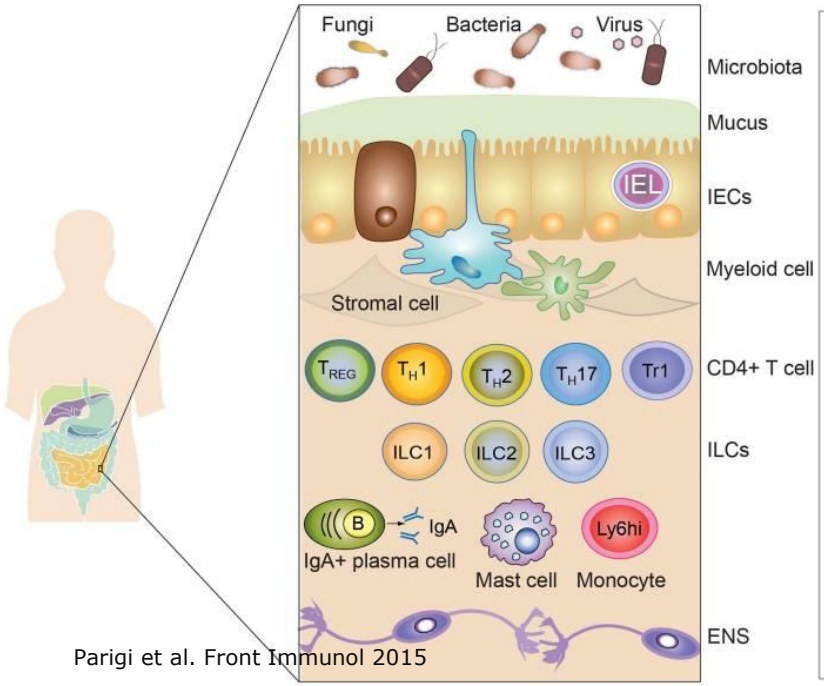
- TEJIDO LINFOIDE DIFUSO (fase efectora de la respuesta inmunitaria)
  - LINFOCITOS INTRAEPITELIALES
  - CÉLULAS DE LÁMINA PROPIA

ESTRUCTURA DE LA MUCOSA INTESTINAL Y SISTEMA INMUNITARIO

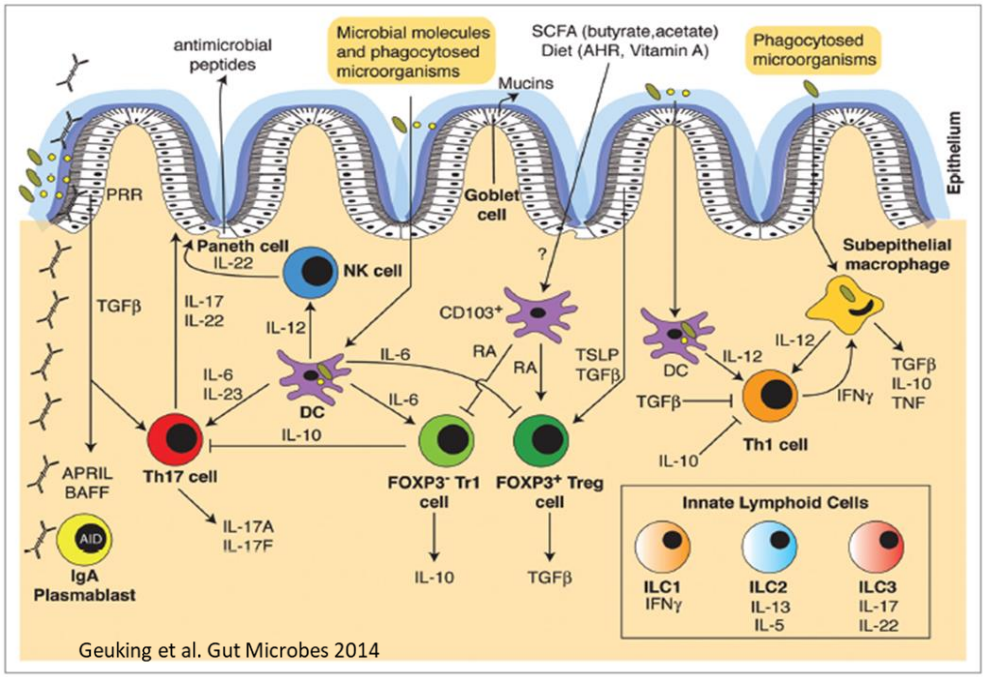


Mowat & Agace Nat Rev Immunol 2014

SISTEMA INMUNITARIO DEL INTESTINO

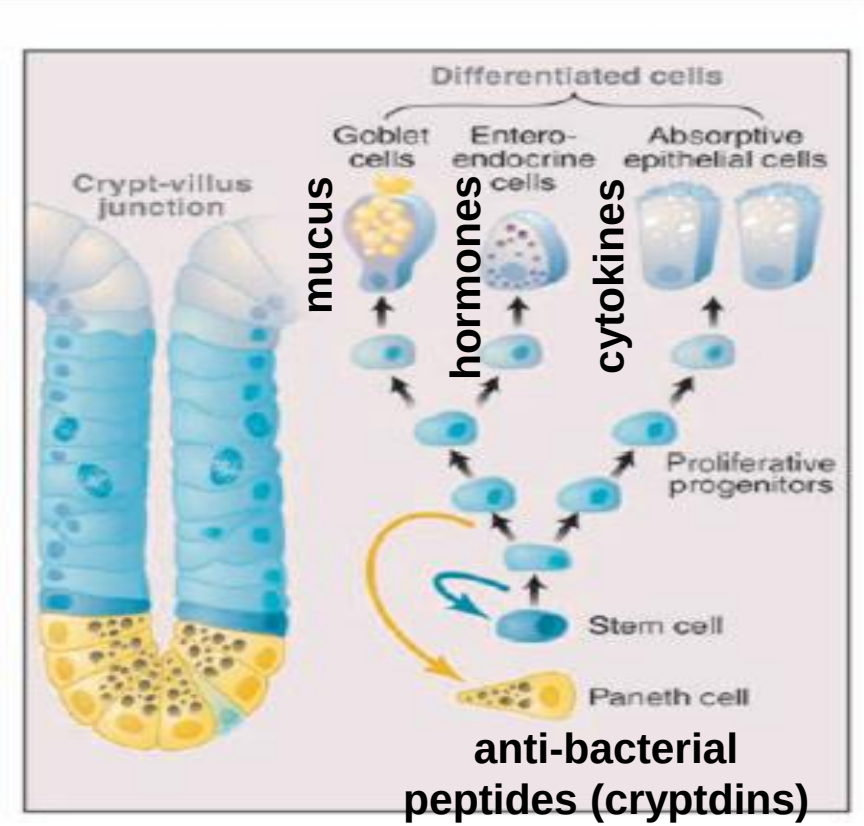


Parigi et al. Front Immunol 2015

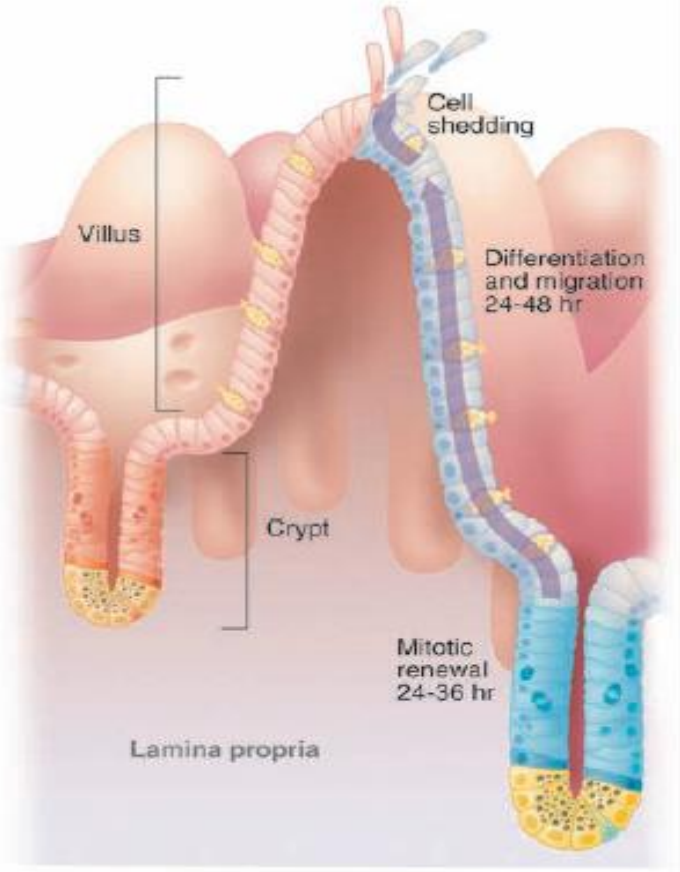


Geuking et al. Gut Microbes 2014

EPITELIO INTESTINAL

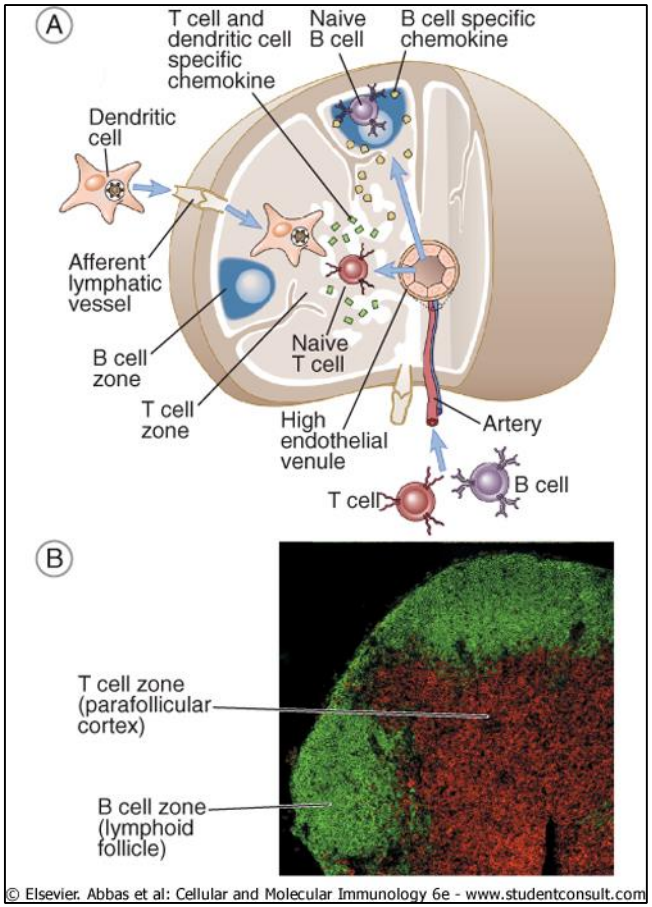


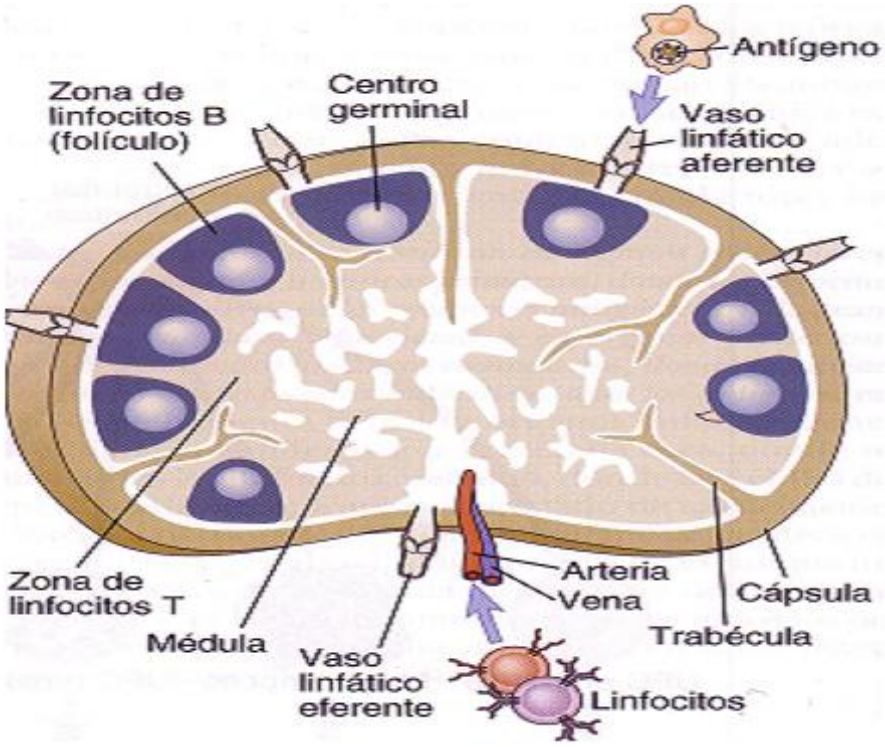
anti-bacterial peptides (cryptdins) (only small intestine & inflammed colon)



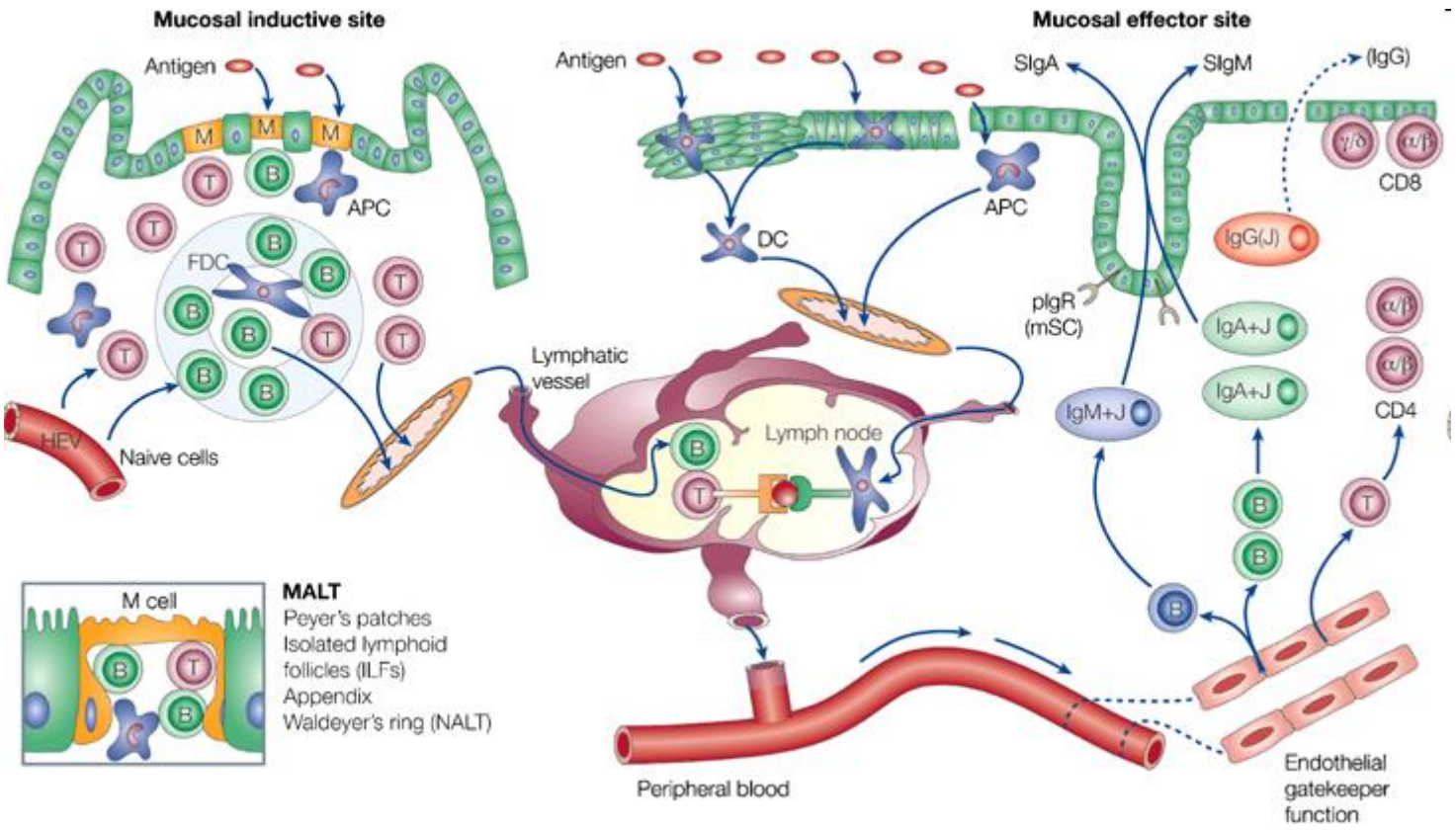
Radtke & Clevers, Science 2005

ESQUEMA GANGLIO LINFÁTICO





LUGARES INDUCTORES Y EFECTORES DE LA RESPUESTA INMUNITARIA EN LA MUCOSA INTESTINAL



RECIRCULACION Y MIGRACION DE CELULAS INMUNITARIAS EN LAS MUCOSAS

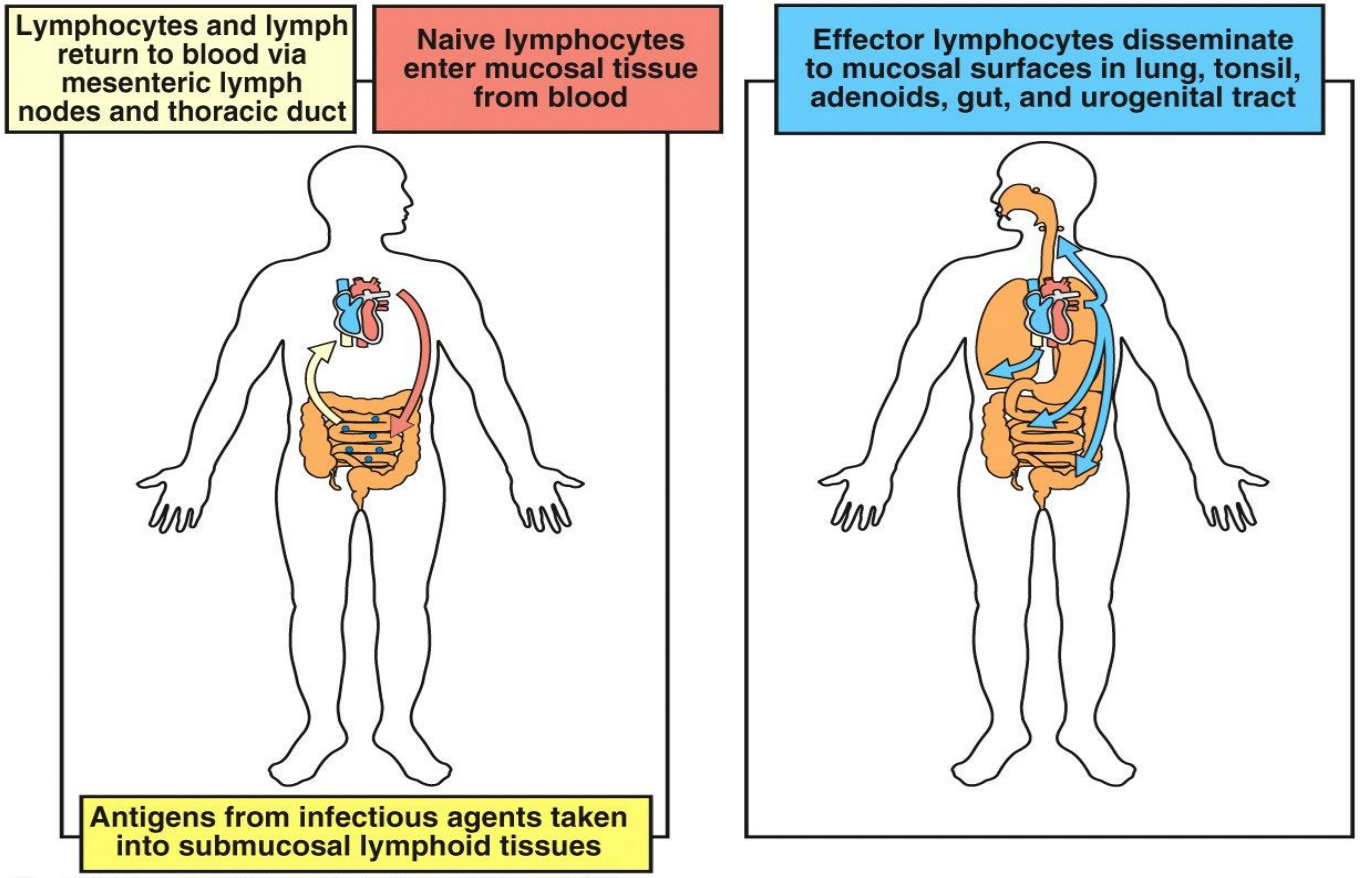


Figure 10-20 Immunobiology, 6/e. (© Garland Science 2005)

MECANISMOS DE "HOMING" DE LINFOCITOS T y B

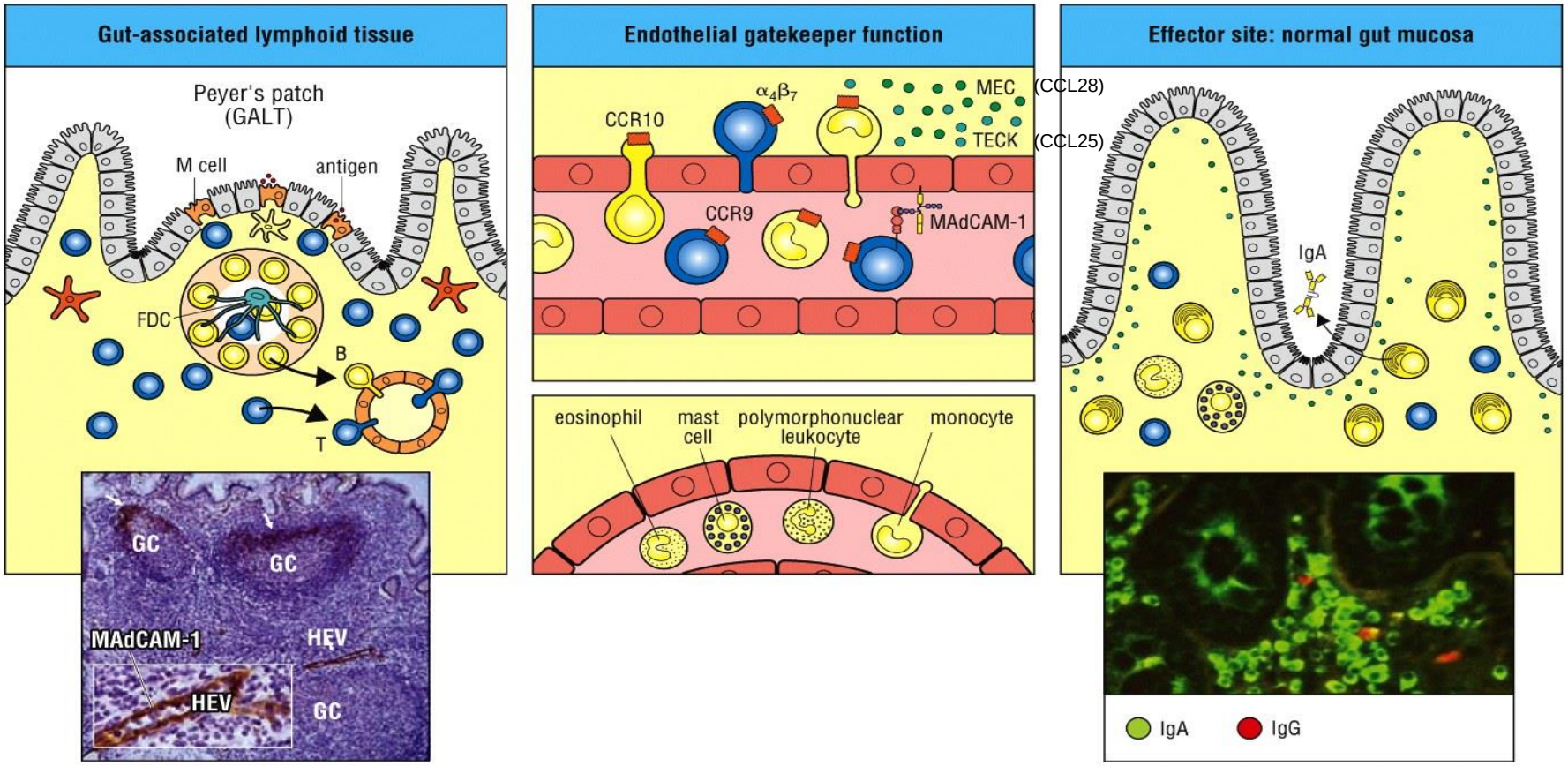
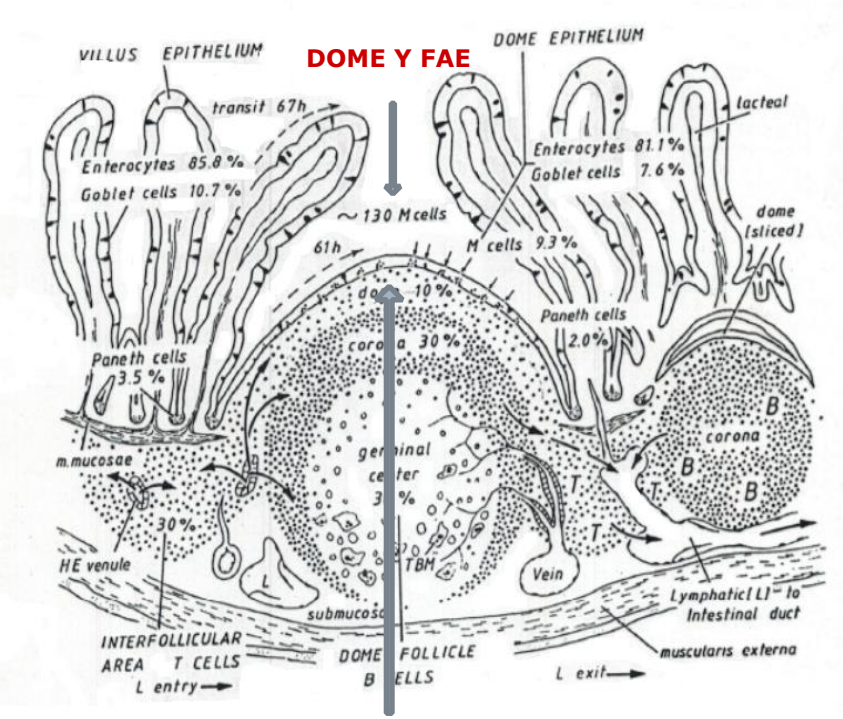
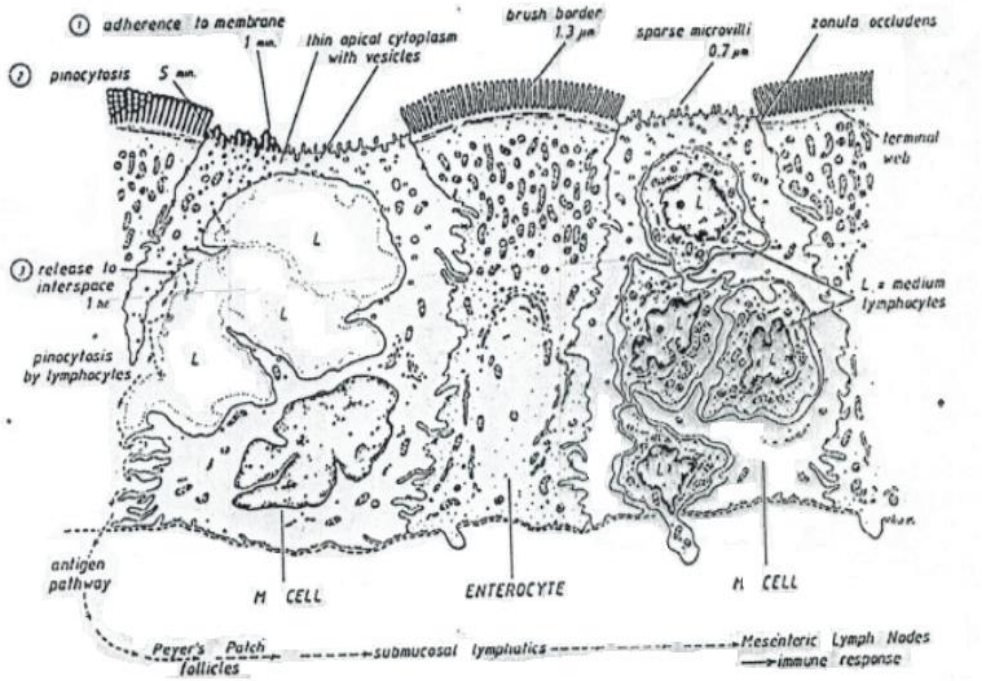


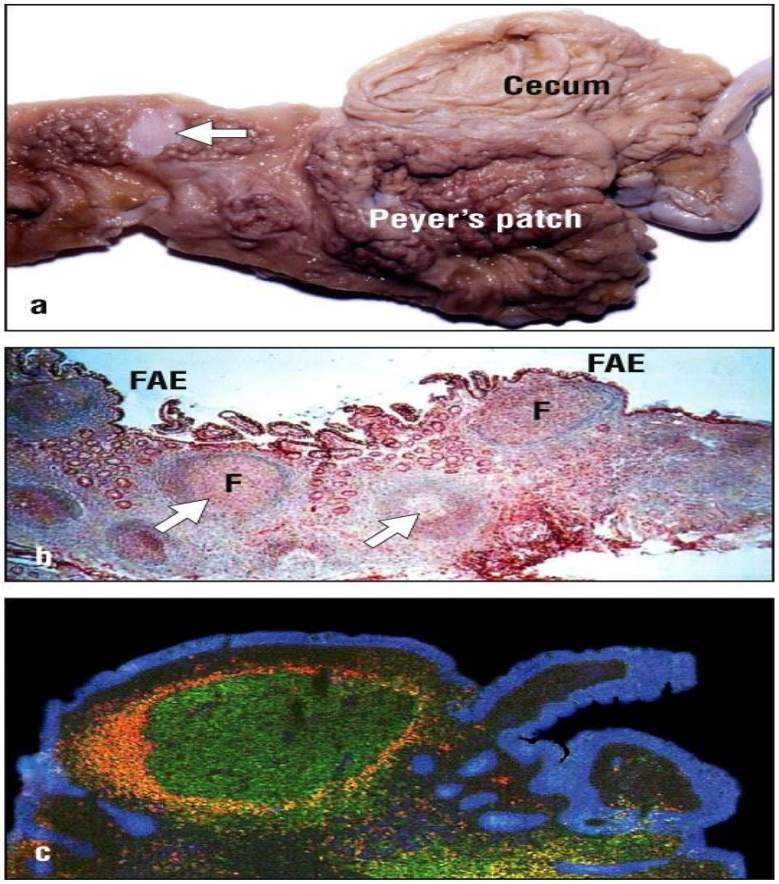
Figure 1.8 Principles of Mucosal Immunology (© Garland Science 2013)

ESQUEMA PLACAS DE PEYER





PLACA DE PEYER



FAE Epitelio asociado al folículo

Azul Citoqueratina
Verde CD20
Naranja IgD

Figure 1.3 Principles of Mucosal Immunology (© Garland Science 2013)

FOLÍCULO SECUNDARIO Y CÉLULAS M

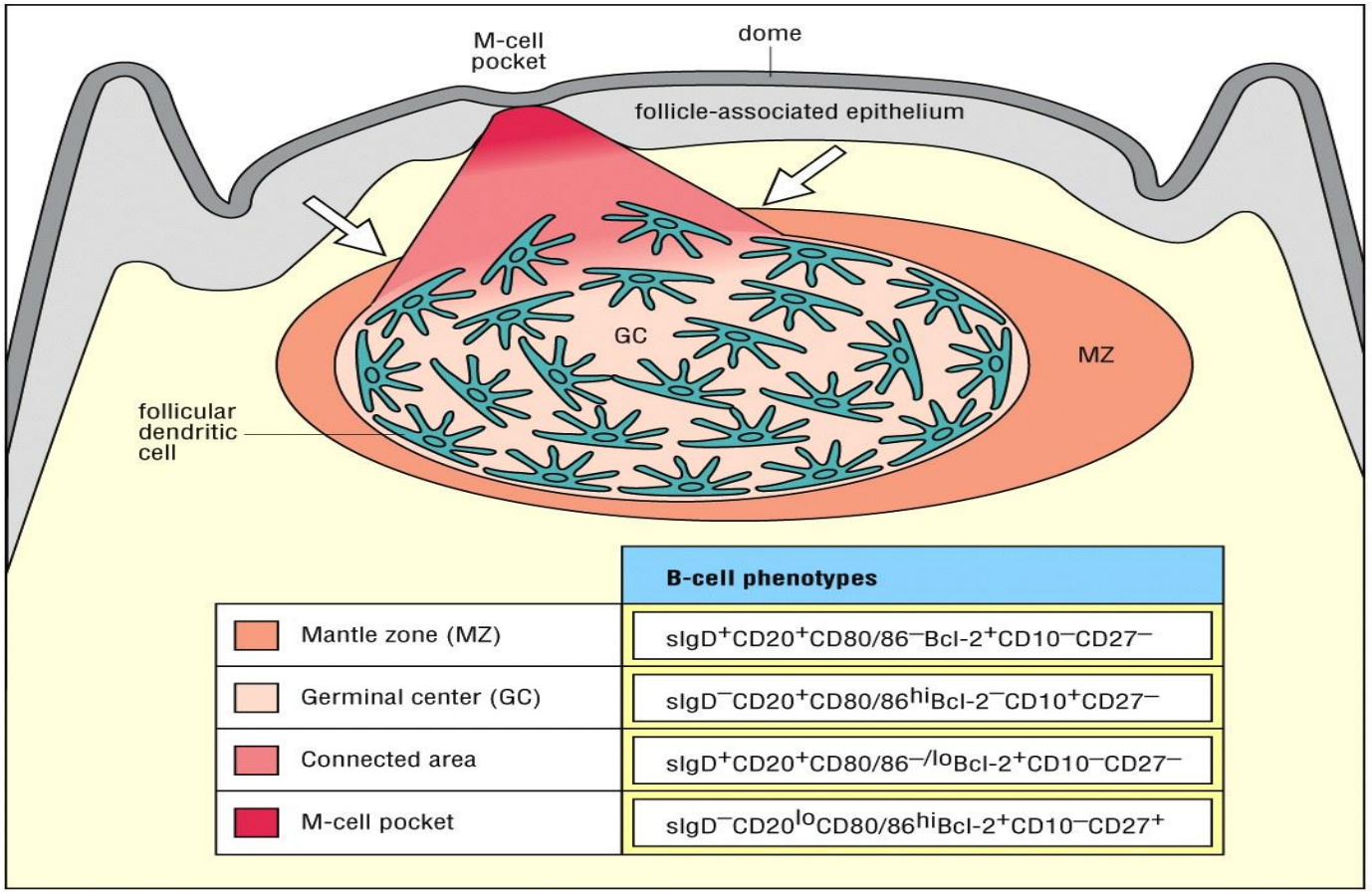
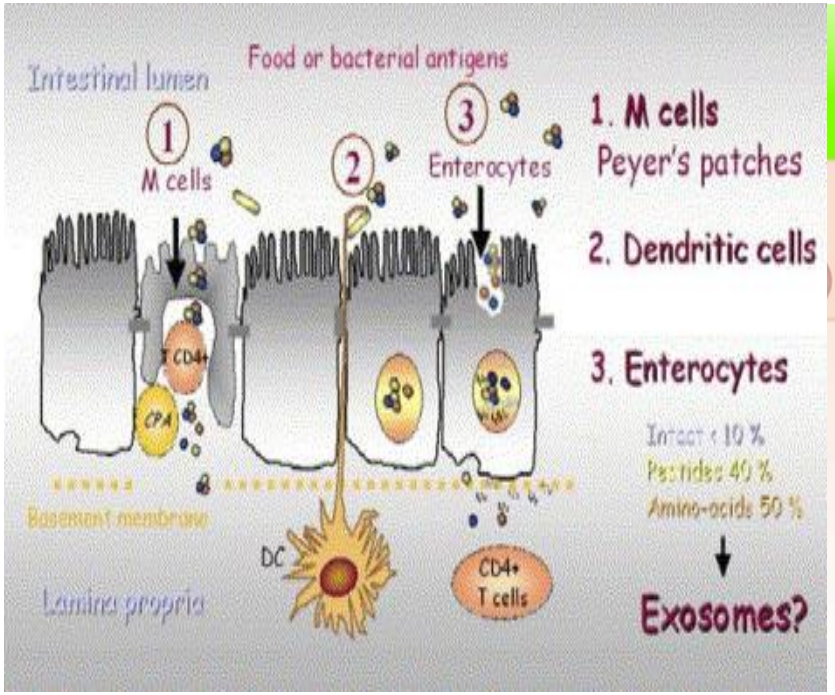
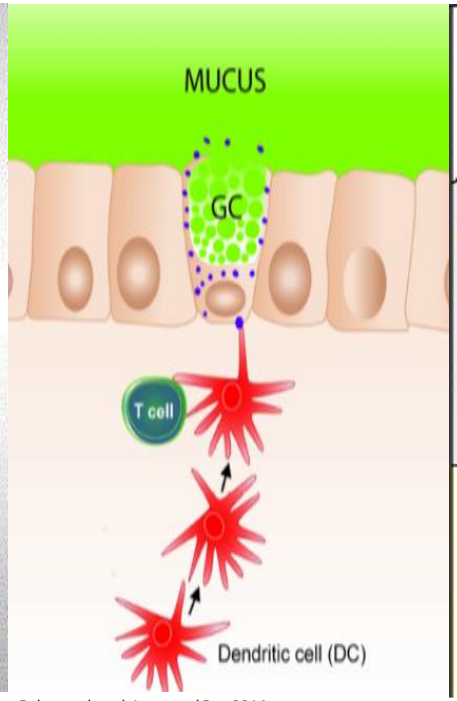


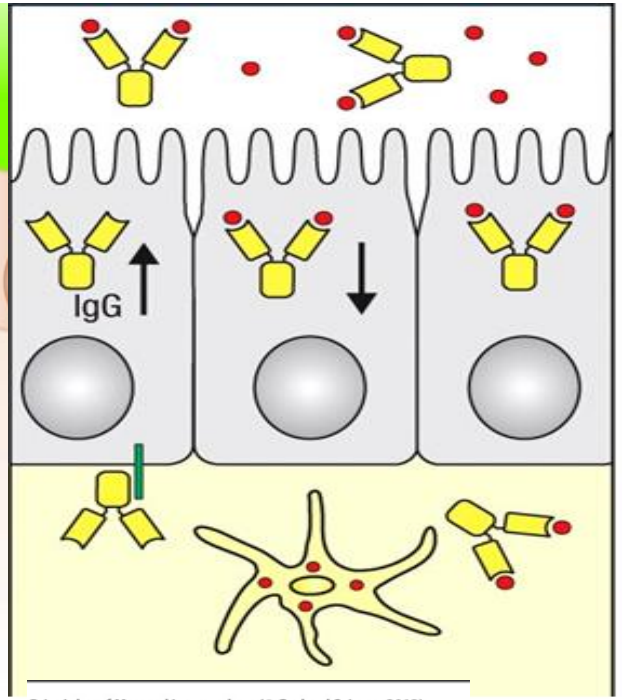
Figure 1.5 Principles of Mucosal Immunology (© Garland Science 2013)

CAPTACIÓN DE ANTÍGENOS EN EL INTESTINO



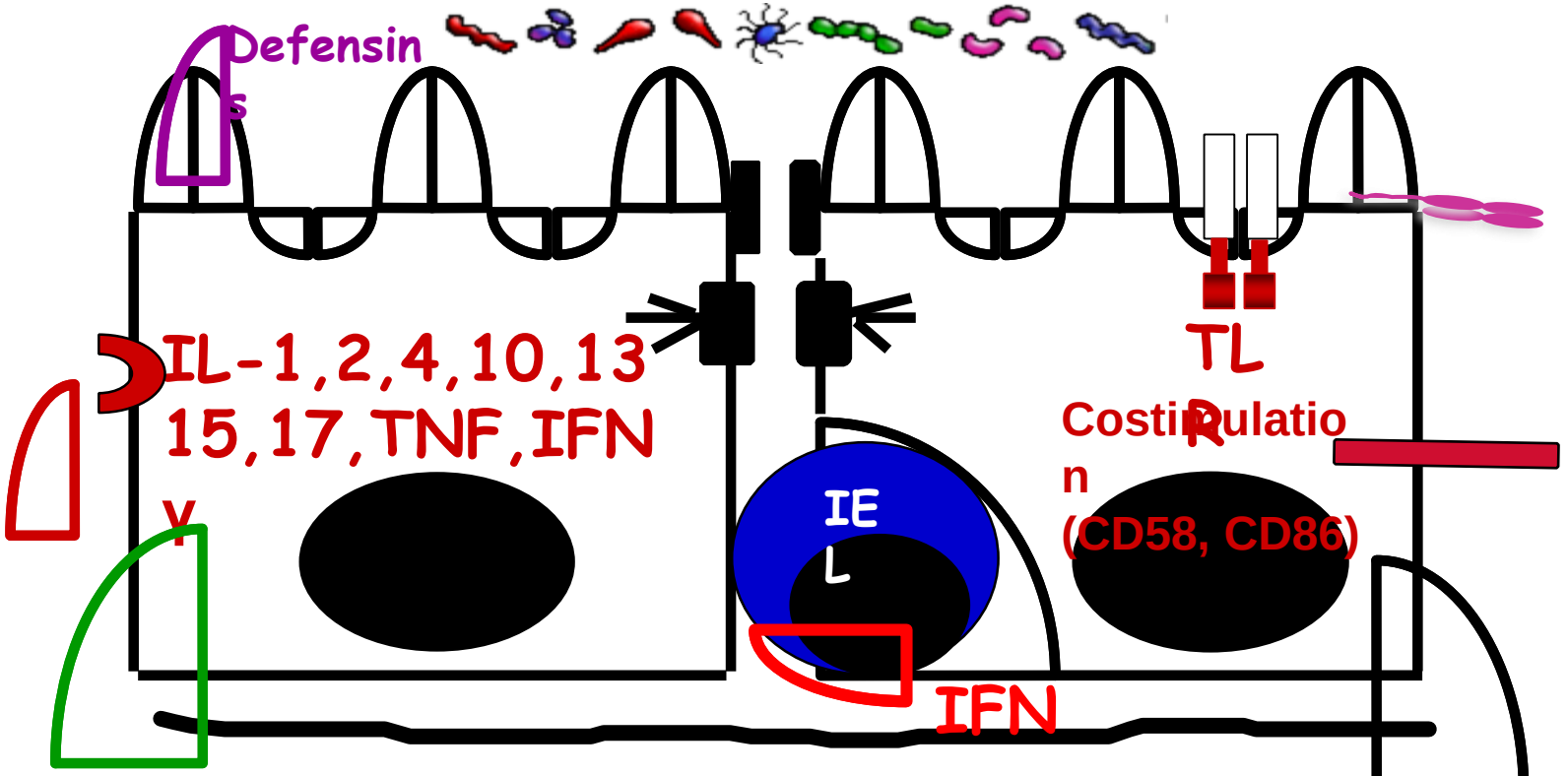


Pelaseyed et al. Immunol Rev 2014

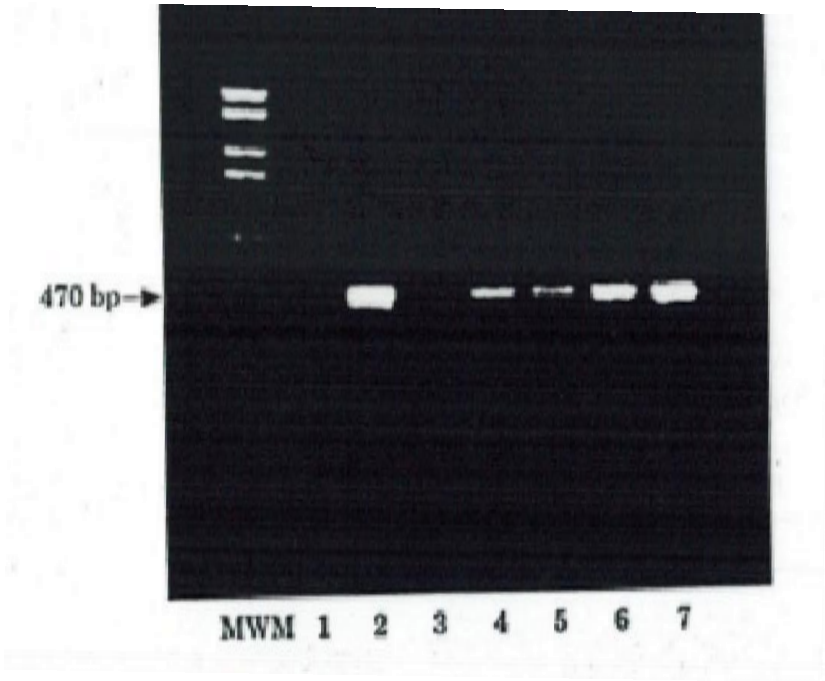


Principles of Mucosal Immunology (© Garland Science 2013)

LAS CÉLULAS EPITELIALES INTESTINALES SON IMPORTANTES EN LA RESPUESTA INMUNITARIA DE LA MUCOSA

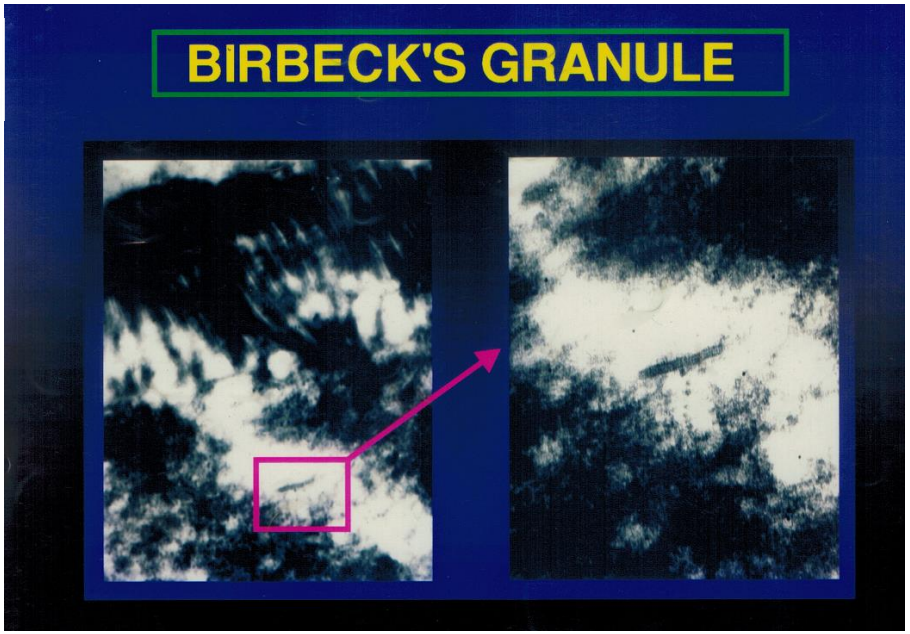


LAS CÉLULAS EPITELIALES INTESTINALES SON IMPORTANTES EN LA RESPUESTA INMUNITARIA DE LA MUCOSA (II)



PRODUCCIÓN DE IL-8

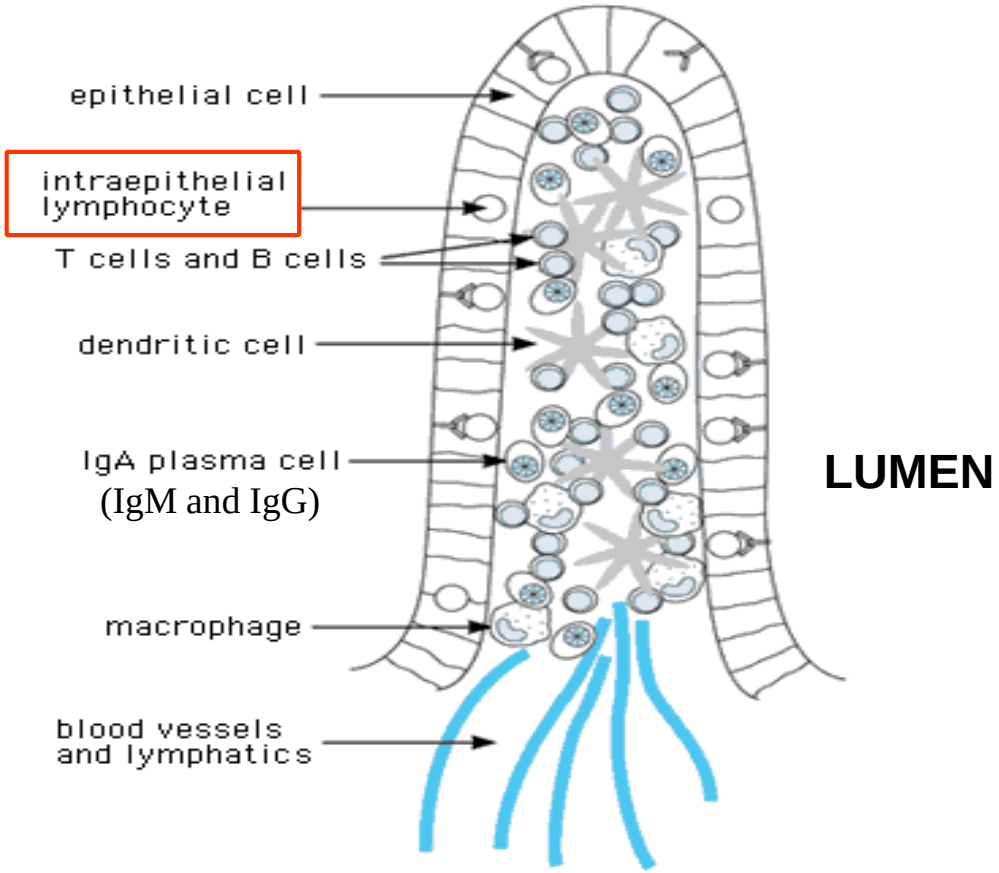
Rodríguez-Juan et al. Cytokine 2008



GRÁNULO DE BIRBECK

Martin-Villa et al. Tissue Antigens 1997

DISTRIBUCIÓN DE CÉLULAS INMUNOCOMPETENTES EN EL TEJIDO LINFOIDE DIFUSO



SISTEMA INMUNITRIO DE LA MUCOSA INTESTINAL

- TEJIDO LINFOIDE ORGANIZADO (fase de inducción de la respuesta inmunitaria)
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  - NLM

- TEJIDO LINFOIDE DIFUSO (fase efectora de la respuesta inmunitaria)
  - LINFOCITOS INTRAEPITELIALES
  - CÉLULAS DE LÁMINA PROPIA

LINFOCITOS INTRAEPITELIALES (LIE)

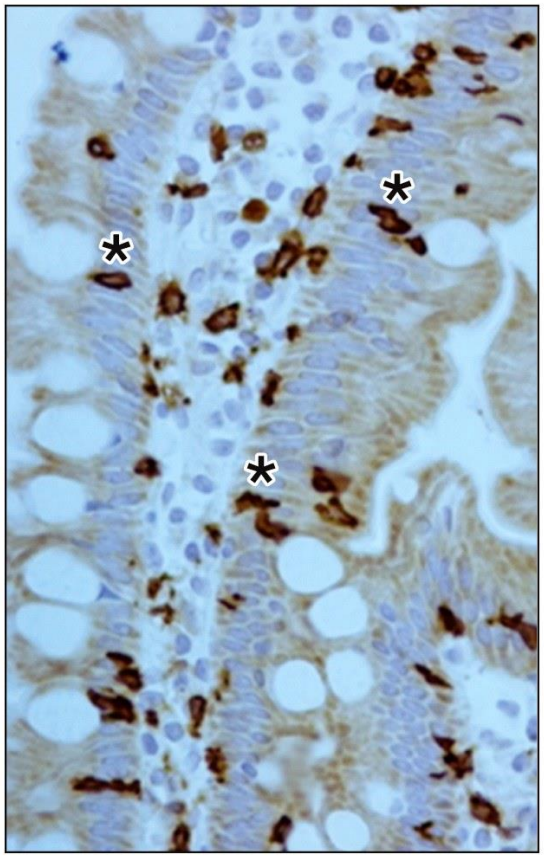
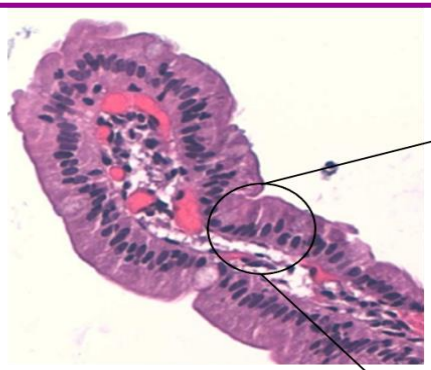


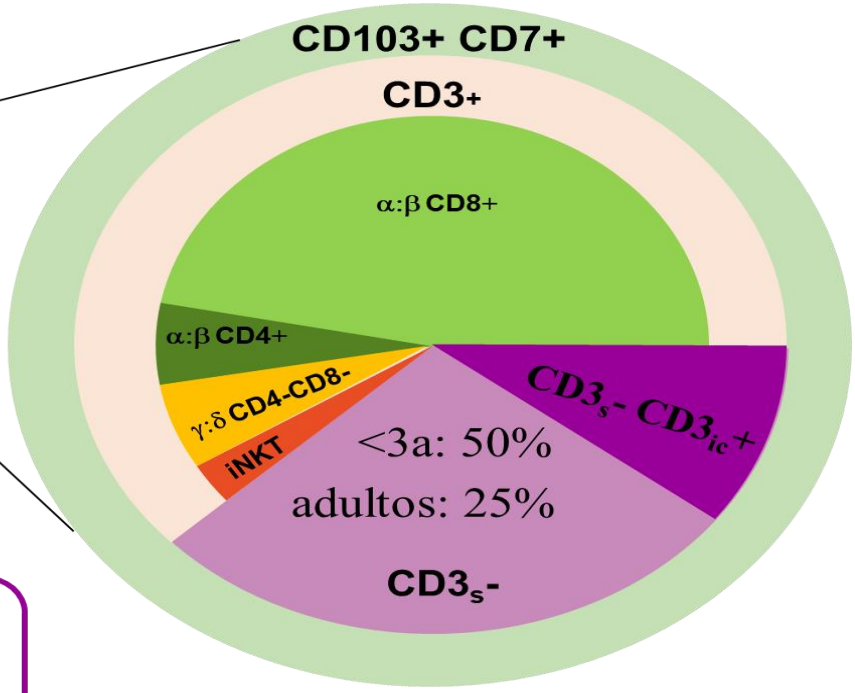
Figure 6.1 Principles of Mucosal Immunology (© Garland Science 2013)

- Linfocitos T
- Tipo a (αβTCR CD8αβ o CD4) y tipo b (CD8αα αβTCR o γδTCR $CD4^-$ $CD8^-$)
- $CD103^+$
- Activados, pero $CD25^-$
- Receptores tipo NK
- Baja síntesis de citoquinas
- Función: Defensa frente infecciones y homoeostasis epitelio

HETEROGENEIDAD LIE

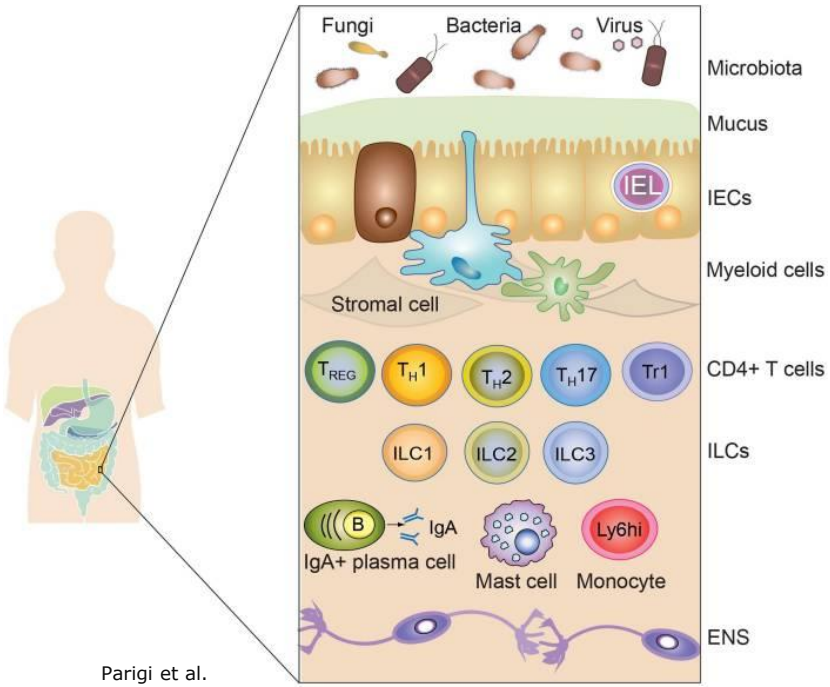
1- IELs HETEROGENEIDAD





3- Receptores NKRs:
NKG2D
NKG2/CD94
NKR-P1A

CÉLULAS LÁMINA PROPIA



Parigi et al.
Front Immunol 2015

- Linfocitos lámina propia $CD8^+$ o $CD4^+$
- $CD45RO^+$, $CD62^{low}$, $CD69^{high}$, $CD25^+$, $Fas/FasL^+$, $\alpha_4\beta_7^+$, $CCR9^+$
- Th1/Th17/(Th2) (Inflamación. Integridad tejidos)
- Treg: nTreg (FoxP3/ IPEX)/iTreg (IL-10)
- Linfocitos B (IgA)
- MAIT/iNKT
- ILC (Innate Lymphoid Cells):

ILC1 (IFNγ; Tbet)/ ILC2 (IL-5; GATA3)/ ILC3 (IL-17; RORγt)

- Macrófagos, células dendríticas, eosinófilos, mastocitos, neutrófilos

RESPUESTA INMUNITARIA T ADQUIRIDA E INNATA EN EL EPITELIO INTESTINAL

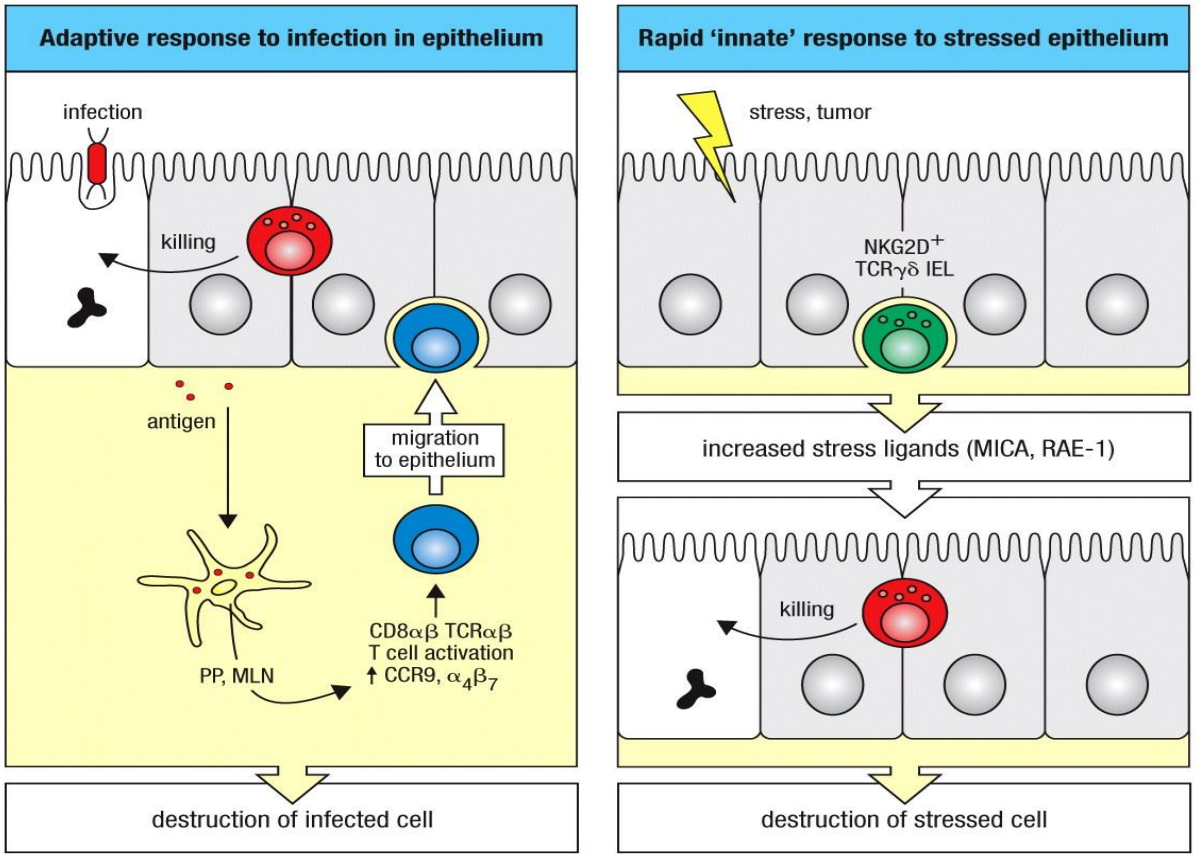


Figure 6.5 Principles of Mucosal Immunology (© Garland Science 2013)

LOS LINFOCITOS T DE LA MUCOSA UTILIZAN SISTEMAS DE RECONOCIMIENTO ESPECIALES

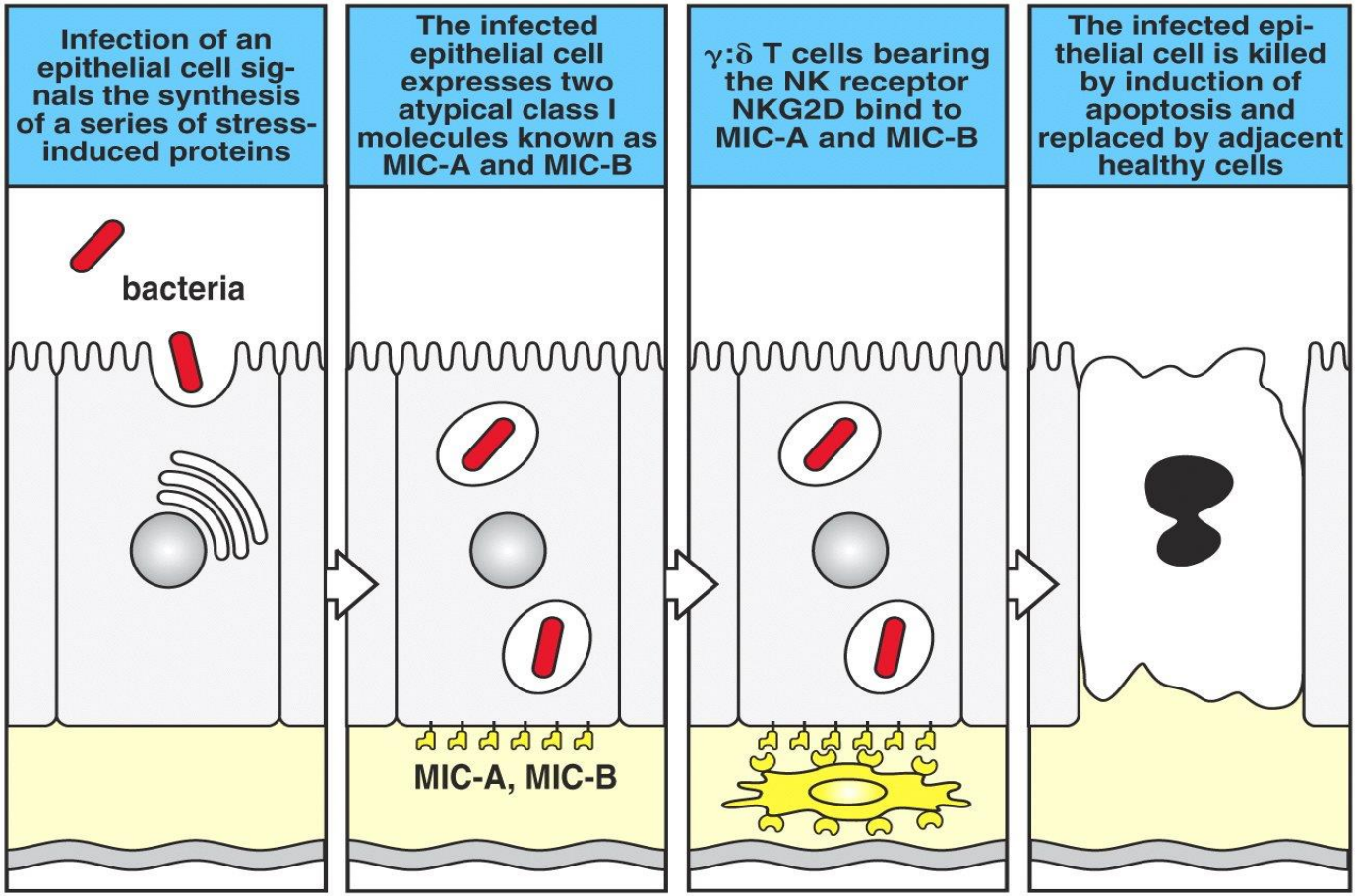


Figure 10-23 Immunobiology, 6/e. (© Garland Science 2005)

LINFOCITOS T EN LA MUCOSA INTESTNAL

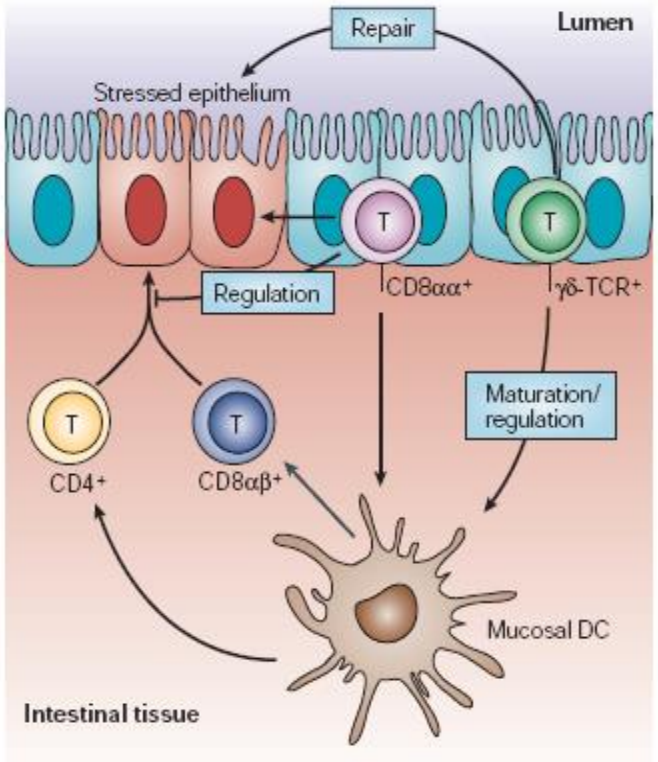


Table 1 | **Mucosal T-cell subsets**

IEL subset	Characteristics	Function
Acquired effector/memory αβ-TCR+ T cells		
CD8αβ+ and CD8αβ+CD8αα+	Acquire gut tropism and a memory phenotype after non-self antigen stimulation by Peyer's patch and MLN DCs	Effector/CTL
CD4+ and CD4+CD8αα+	Acquire gut tropism and a memory phenotype after non-self antigen stimulation by Peyer's patch and MLN DCs	Effector/help
Natural memory αβ-TCR+ T cells		
DN and CD8αα+	Acquire gut tropism and a memory phenotype after self-antigen selection in the thymus	Effector and/or regulatory
γδ-TCR+ T cells		
DN and CD8αα+	Acquire gut tropism and differentiation during ontogeny	Tissue repair and regulatory

CTL, cytotoxic T lymphocyte; DC, dendritic cell; DN, double-negative; IEL, intraepithelial lymphocyte; MLN, mesenteric lymph node; TCR, T-cell receptor.

DIVERSIDAD FUNCIONAL DE LINFOCITOS T EN EL INTESTINO

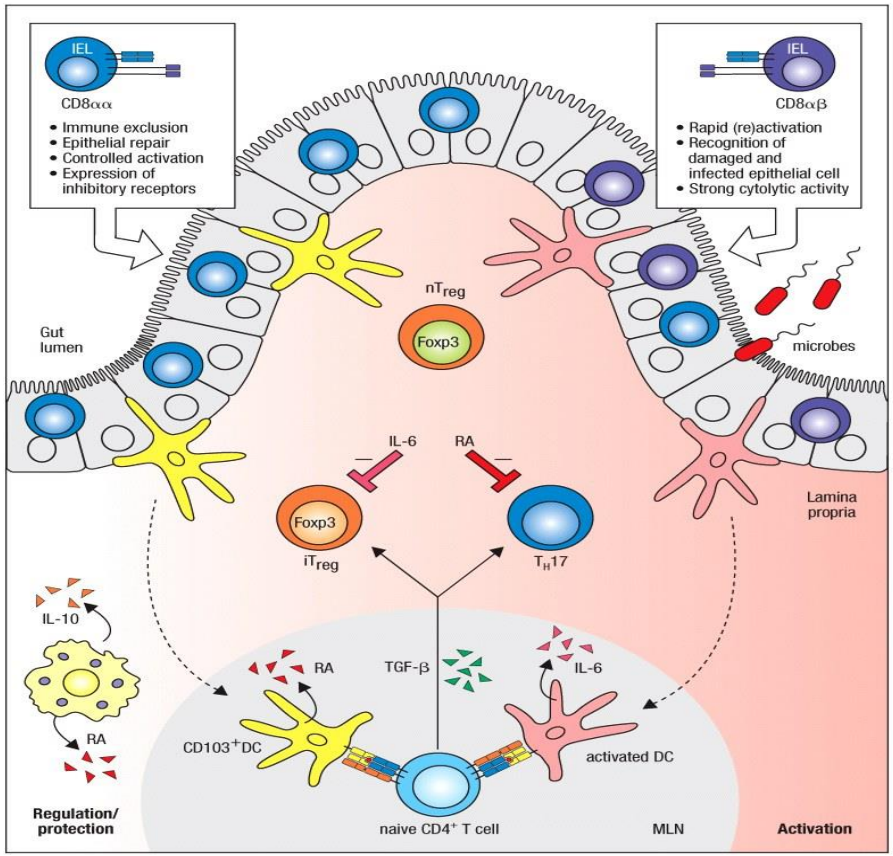
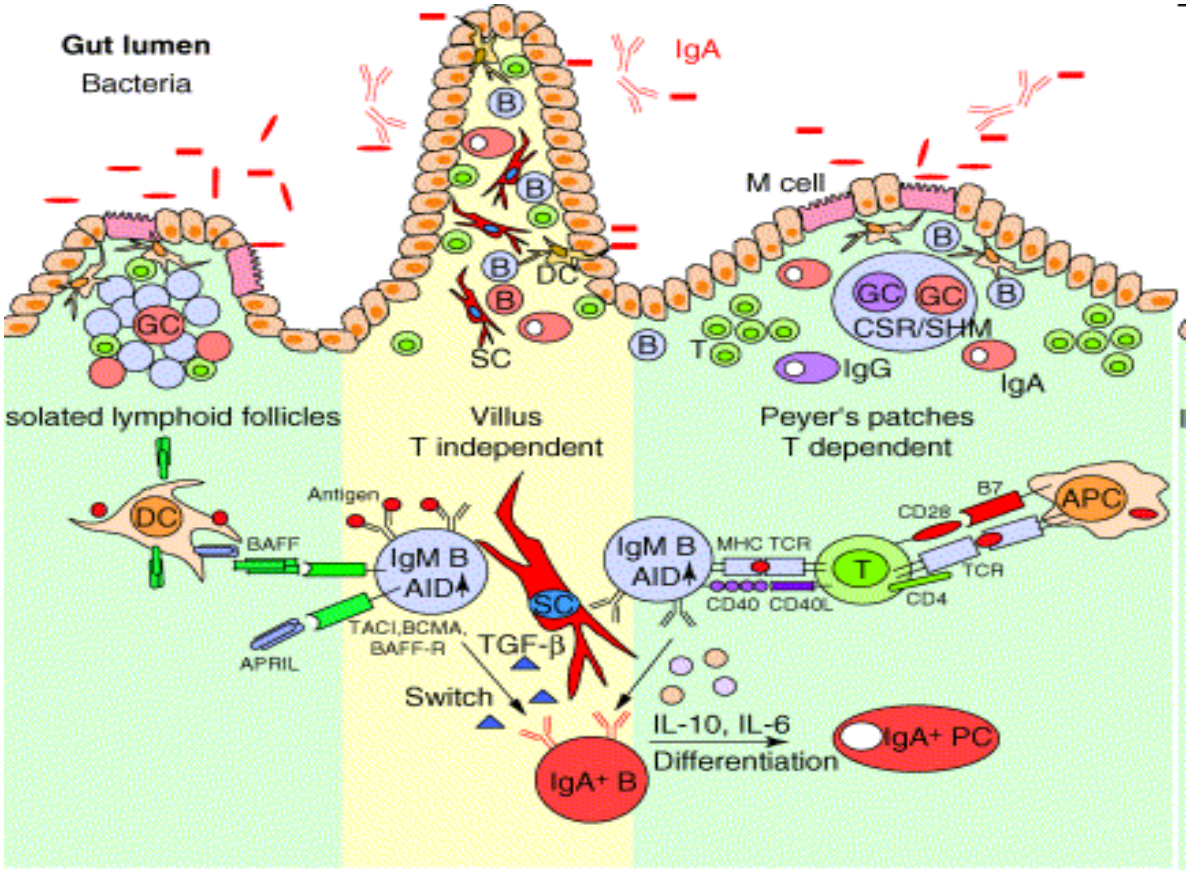


Figure 6.7 Principles of Mucosal Immunology (© Garland Science 2013)

SÍNTESIS DE IgA EN LA MUCOSA INTESTINAL



Current Opinion in Immunology

BIOSÍNTESIS sIgA

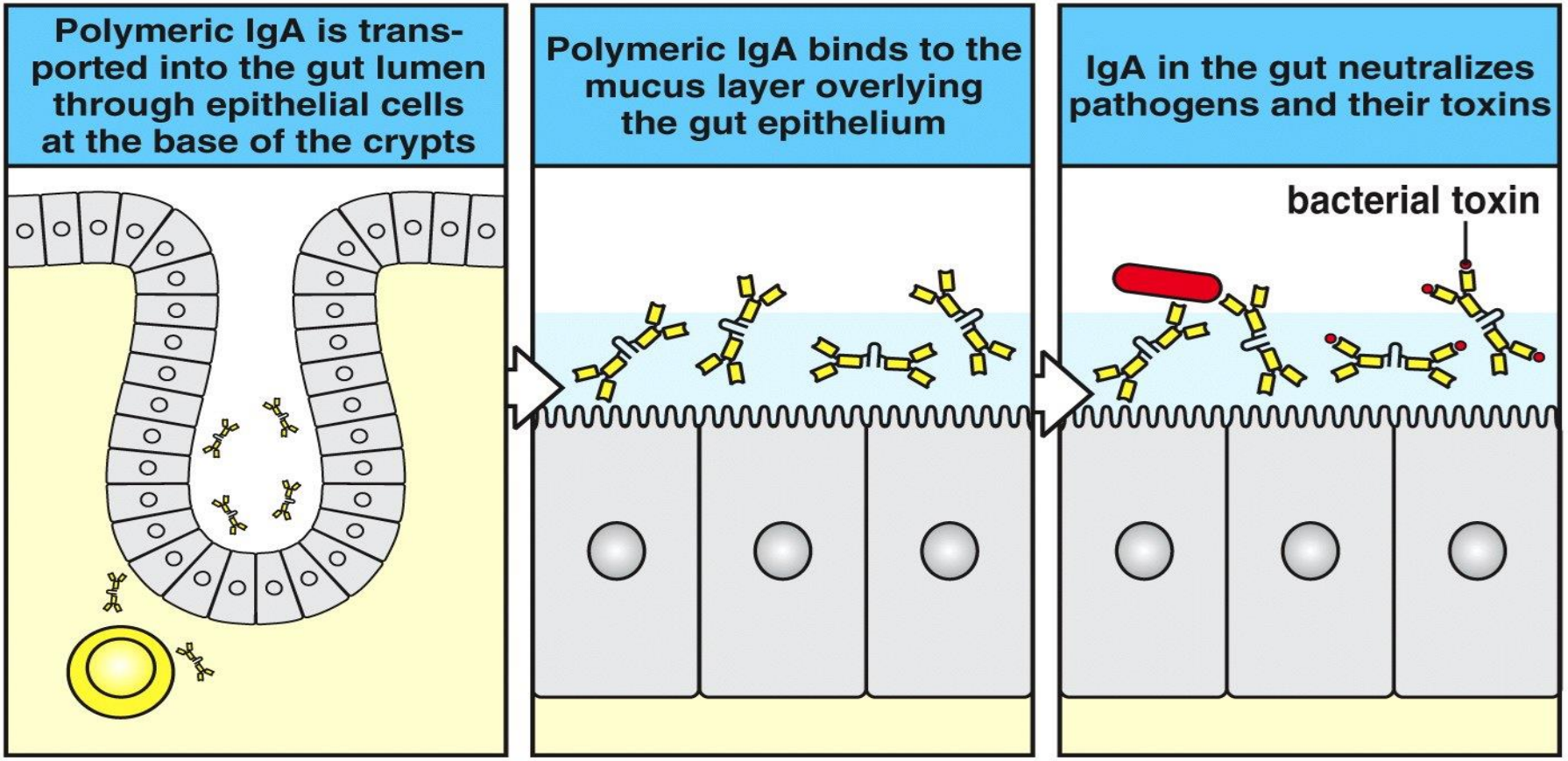
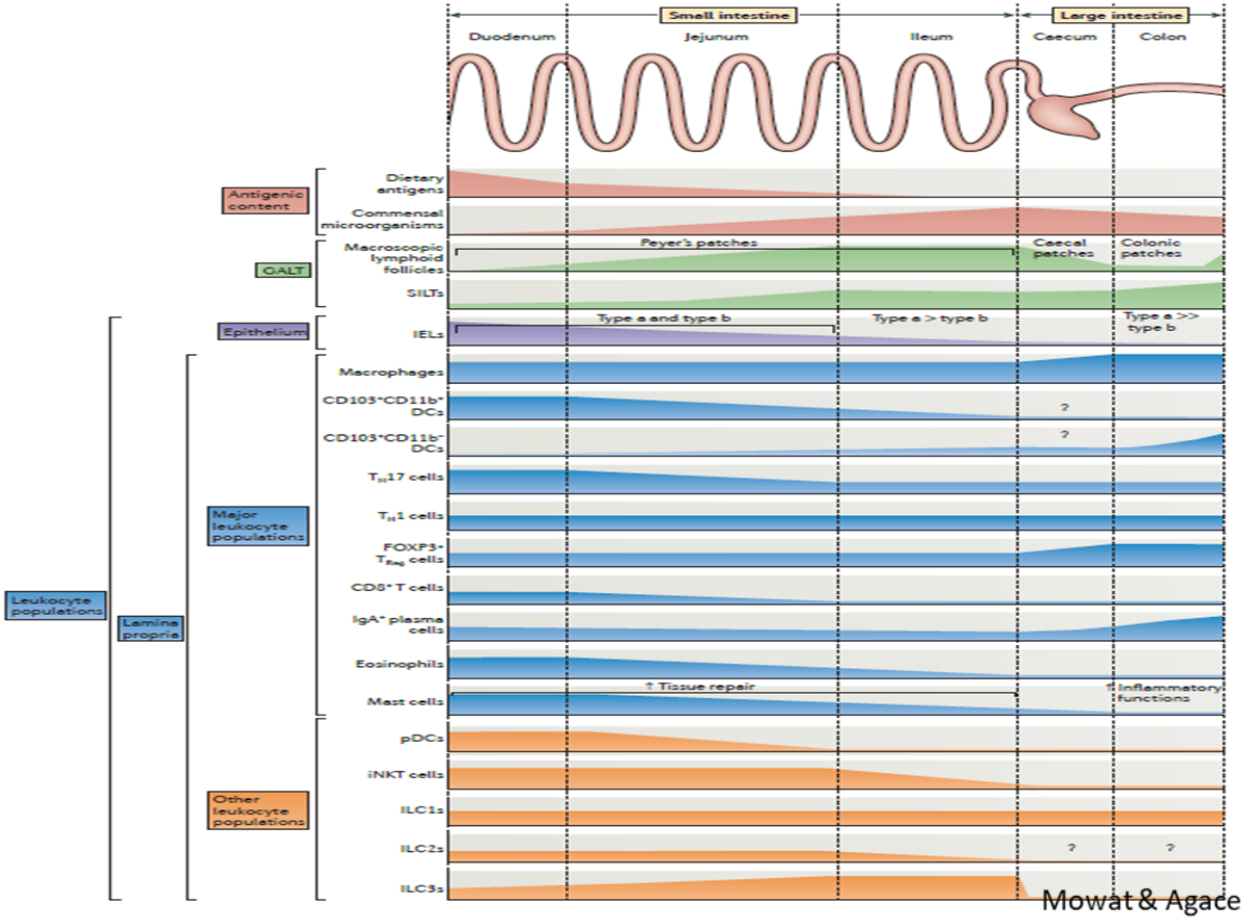


Figure 10-24 Immunobiology, 6/e. (© Garland Science 2005)

EL SISTEMA INMUNITARIO VARÍA A LO LARGO DEL TRACTO INTESTINAL



Mowat & Agace Nat Rev Immunol 2014

TOLERANCIA ORAL

- DEFINICIÓN: Reducción de la respuesta a un antígeno tras suministro por mucosas.
- MECANISMOS:
- Eliminación células T reactivas
- Anergia
- Generación Tregs (FoxP3): TGFβ, IL-10, IL-35
- DOSIS:

  Grandes dosis ⟶ Eliminación/ Anergia

  Pequeñas dosis ⟶ Tregs

TOLERANCIA ORAL

- ¿Dónde?:

  PP (CD4Tregs) Epiteliales (CD8Tregs)

  NLM (Células dendríticas) Sistémico
- ¿QUIÉN SE INHIBE?:

  T> B
- Se puede modular: CTB (Cholera Toxin subunit)
- Usado en autoinmunidad/ enf. nflamatorias/ alergias.

ENCUENTRO ANTIGÉNICO EN LA MUCOSA PUEDE TENER RESULTADOS DIFERENTES

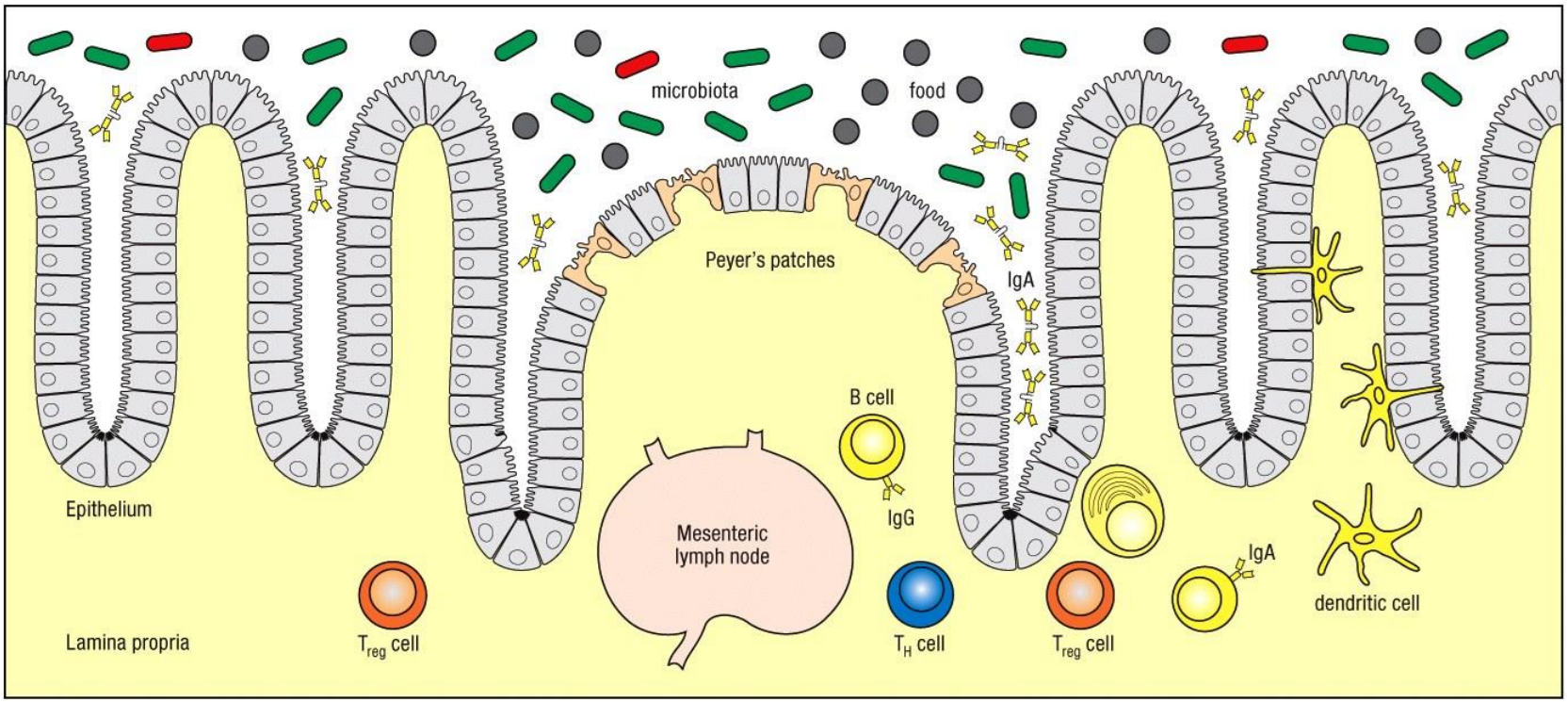


Figure 15.1 Principles of Mucosal Immunology (© Garland Science 2013)

EXPERIMENTO DE TOLERANCIA ORAL

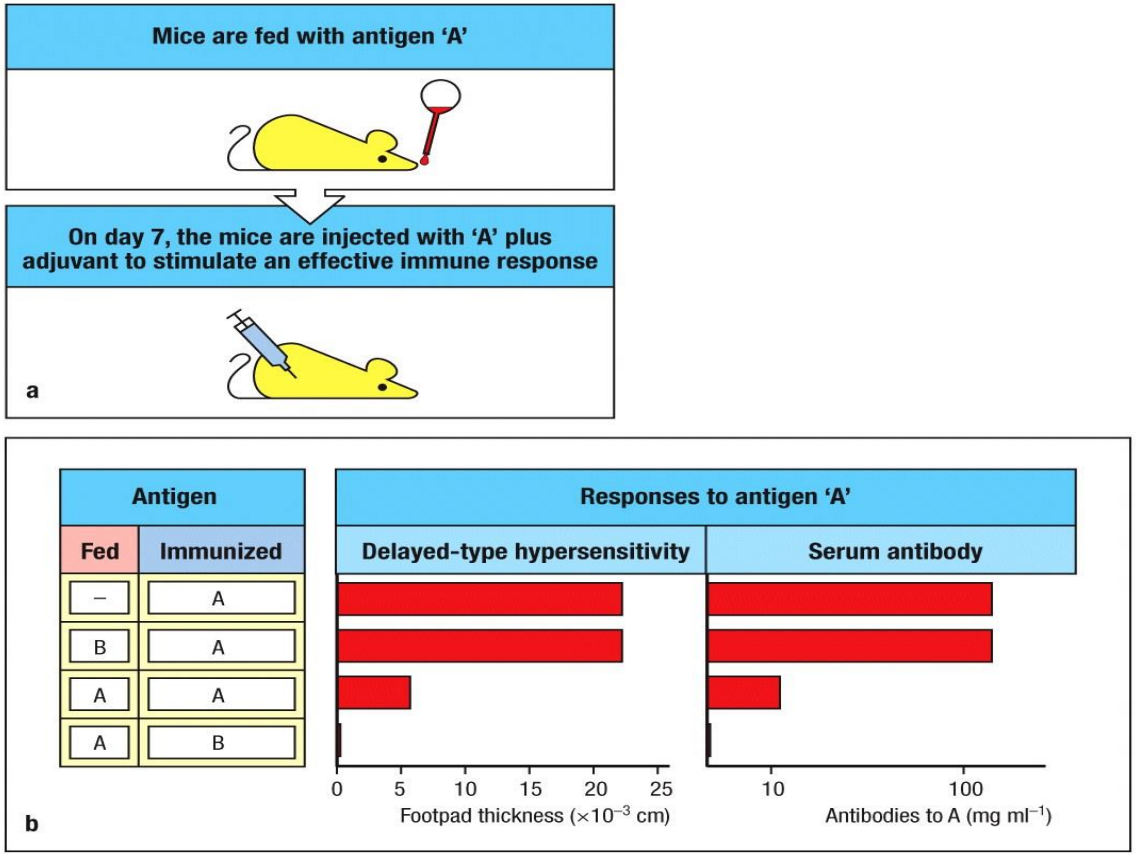


Figure 15.2 Principles of Mucosal Immunology (© Garland Science 2013)