



Sistema inmunitario
de las mucosas

recirculación **respuesta**

respuesta intraepitelial

[illegible]

Grandes ligas

- Burnett y Fenner
 - ✓ Discriminación entre lo propio y lo extraño
- Polly Matzinger
 - ✓ Señales de peligro

Aquí si vamos a
discriminar!!!!



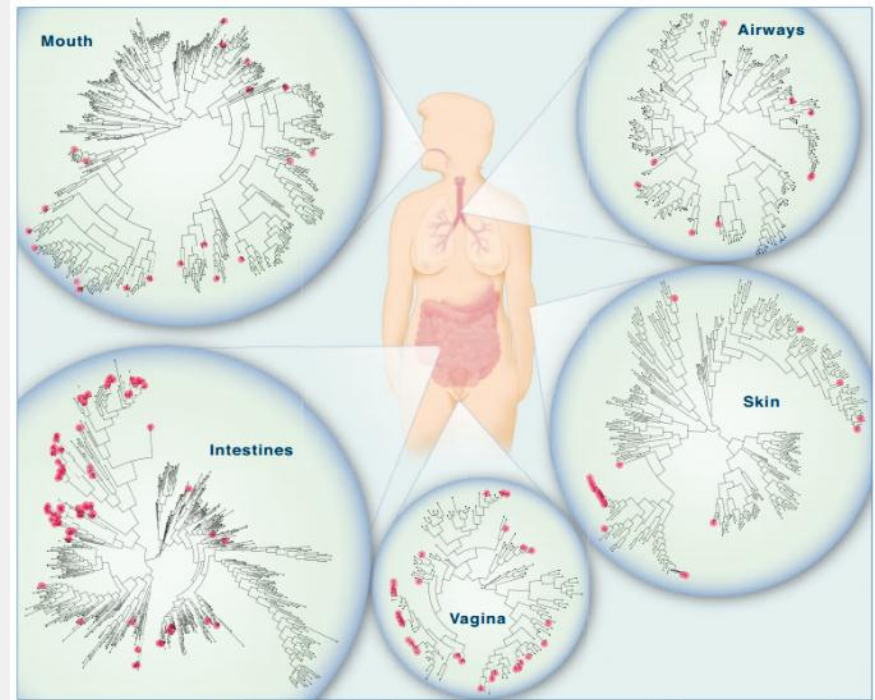
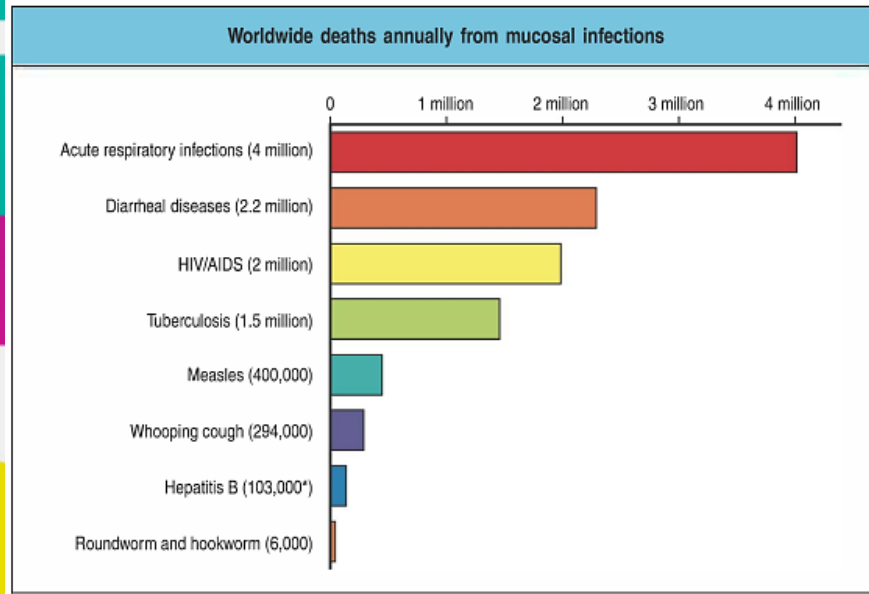
Grandes ligas



© aquí cerquita!!!



Relevancia



- **Funciones en la inmunomodulación**
 - ✓ Prevenir el desarrollo de respuesta inflamatoria frente a los antígenos inocuos
 - ✓ Responsable de mediar la relación simbiótica entre los microorganismos comensales y el hospedador
 - ❖ Superficie de 400m² (intestino humano)
 - ❖ Expuesto constantemente a millones de antígenos: dieta, alimentos y flora bacteriana (10¹⁸ microorganismos residentes, 15000 especies diferentes)
 - ✓ Promover la tolerancia, es su **OBJETIVO PRINCIPAL**

Características

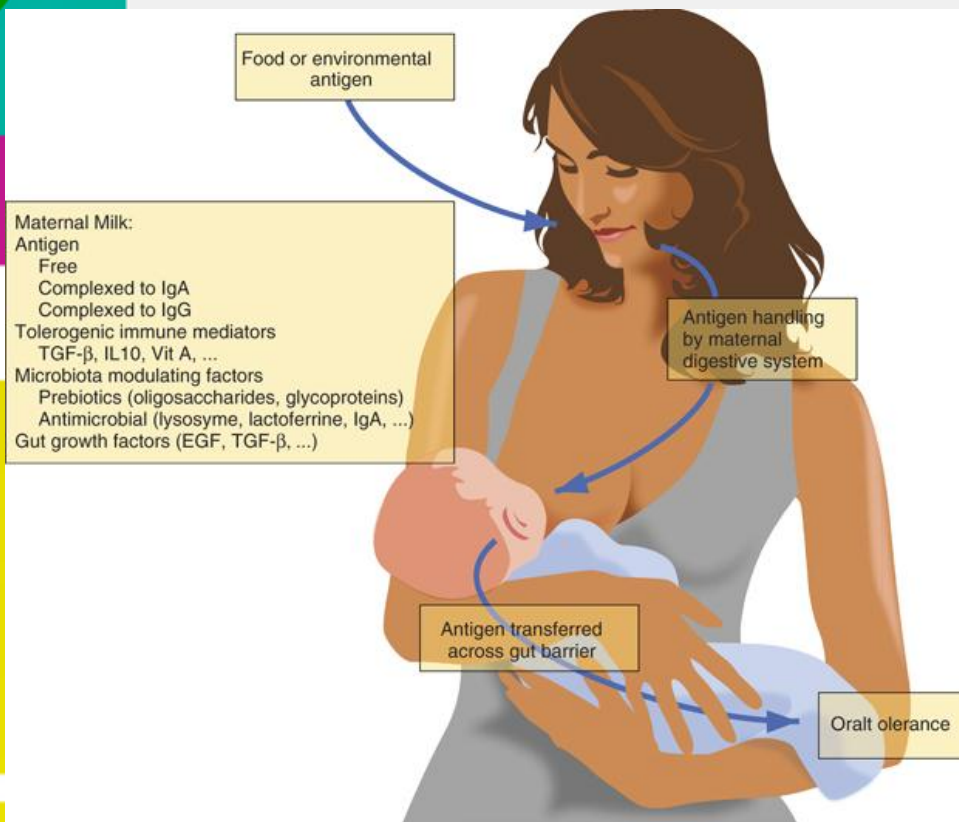
TABLE 14-1 Features of Regional Immunity

Region	Special Challenges	Special Anatomic Structures	Specialized Cells or Molecules: Functions
Gastrointestinal tract	Tolerance of food antigens Tolerance of commensal microbiota but responsive to rare pathogens Enormous surface area	Tonsils Peyer's patches, lamina, propria follicles	Intestinal epithelial cells: mucus secretion M cells: luminal antigen sampling Paneth cells: defensin production Secretory IgA, IgM: neutralization of microbes in the lumen Dendritic cell subsets: luminal antigen sampling; lamina propria antigen sampling; T cell tolerance induction; effector T cell activation; induction of B cell IgA class switching; imprinting gut-homing phenotypes of B and T cells
Respiratory system	Exposure to mix of airborne pathogens and innocuous microbes and particles	Tonsils Adenoids	Ciliated respiratory epithelial cells: mucus and defensin production and movement of mucus with trapped microbes and particles out of airways Secretory IgA, IgM, IgG: neutralization of microbes outside epithelial barrier
Cutaneous immune system	Large surface area	Keratinizing stratified squamous epithelial barrier	Keratinocytes: keratin production, cytokine and defensin secretion Langerhans cells: epidermal antigen sampling Dendritic cell subsets: dermal antigen sampling; T cell tolerance induction; effector T cell activation; imprinting skin-homing phenotype of T cells

Características distintivas

Distinctive features of the mucosal immune system	
Anatomical features	Intimate interactions between mucosal epithelia and lymphoid tissues
	Discrete compartments of diffuse lymphoid tissue and more organized structures such as Peyer's patches, isolated lymphoid follicles, and tonsils
	Specialized antigen-uptake mechanisms, e.g. M cells in Peyer's patches, adenoids, and tonsils
Effector mechanisms	Activated/memory T cells predominate even in the absence of infection
	Multiple activated 'natural' effector/regulatory T cells present
	Secretory IgA antibodies
	Presence of distinctive microbiota
Immunoregulatory environment	Active downregulation of immune responses (e.g. to food and other innocuous antigens) predominates
	Inhibitory macrophages and tolerance-inducing dendritic cells

Origen extendido

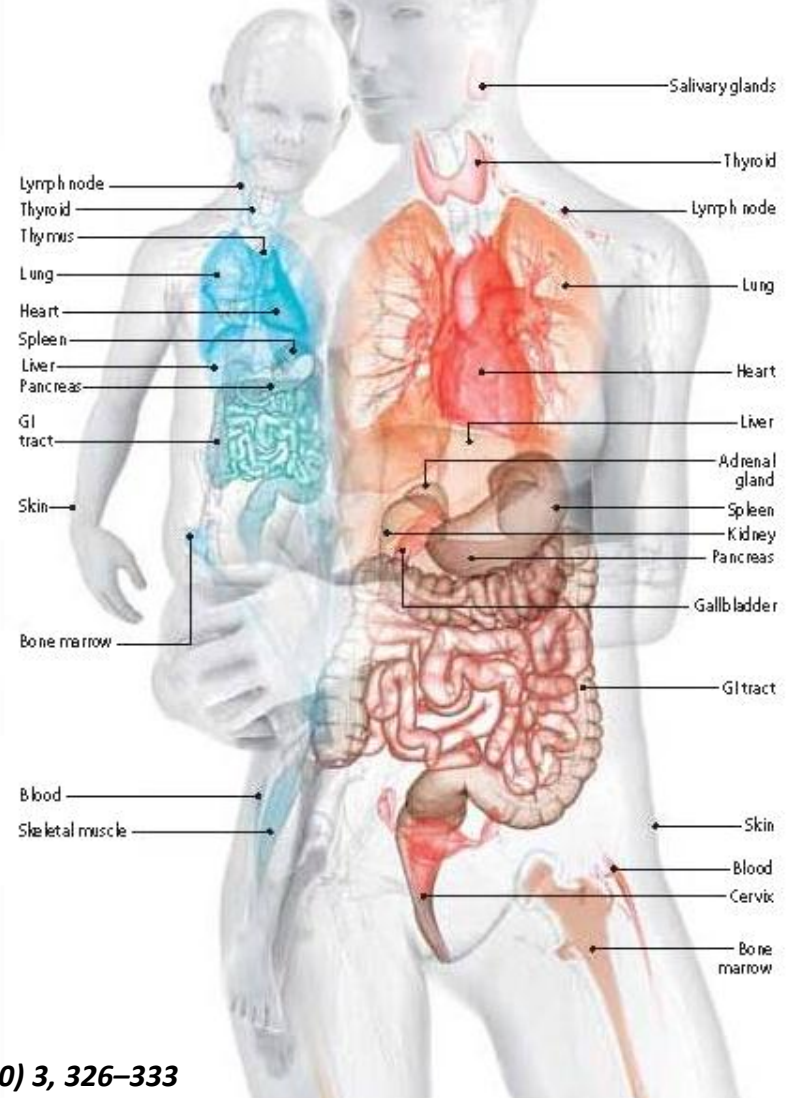


MATERNAL MICROCHIMERISM

(Mother's cells take root in child)

FETAL MICROCHIMERISM

(Fetal cells take root in mother)

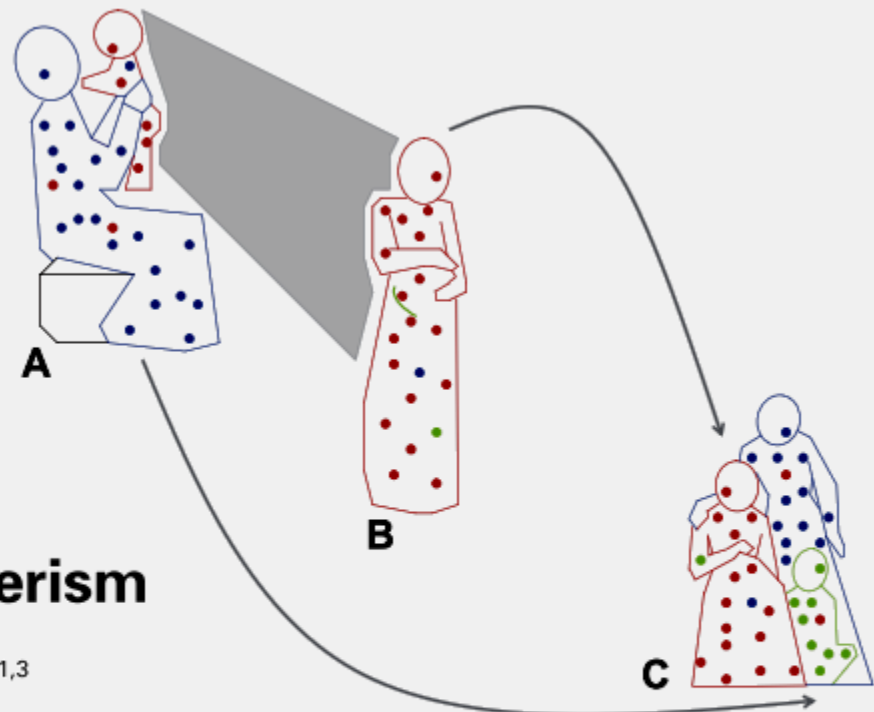
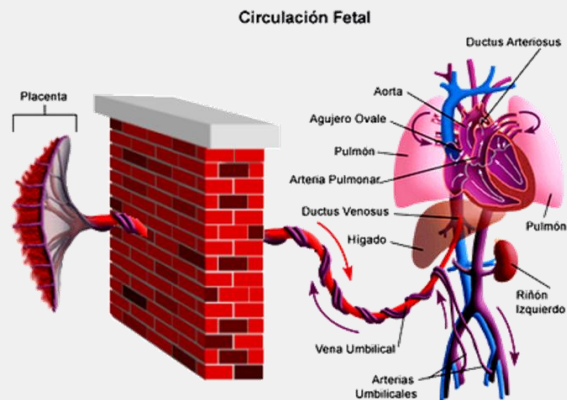


Mucosal Immunology (2010) 3, 326–333

Best Pract Res Clin Obstet Gynaecol. 2015 Sep 10. pii: S1521-6934(15)00148-0

Curr Opin Pediatr. 2014 Jun; 26(3): 377–382.

Microquimerismo



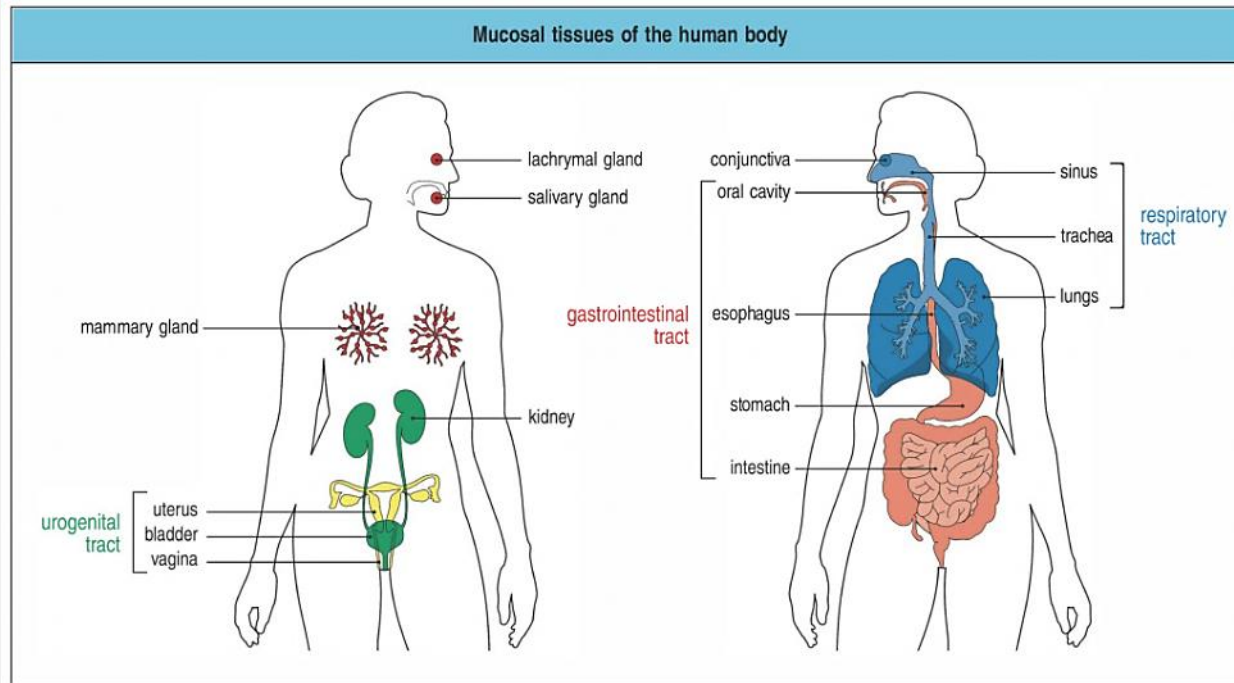
Naturally acquired microchimerism

HILARY S. GAMMILL^{*,1,2} and J. LEE NELSON^{1,3}

Int. J. Dev. Biol. 54: 531-543 (2010)

Fig. 1. Microchimerism (Mc) in three generations. (A) Proband as infant (red) exchanges Mc with her mother (blue), resulting in maternal Mc in the infant and fetal Mc in the mother. (B) As an adult, proband (red), still harboring maternal Mc, experiences pregnancy herself (green) and acquires new source of fetal Mc. (C) Later, proband (red), child (green), and proband's mother (blue), all with persistent Mc from maternal and/or fetal sources.

Ubicación "geográfica"

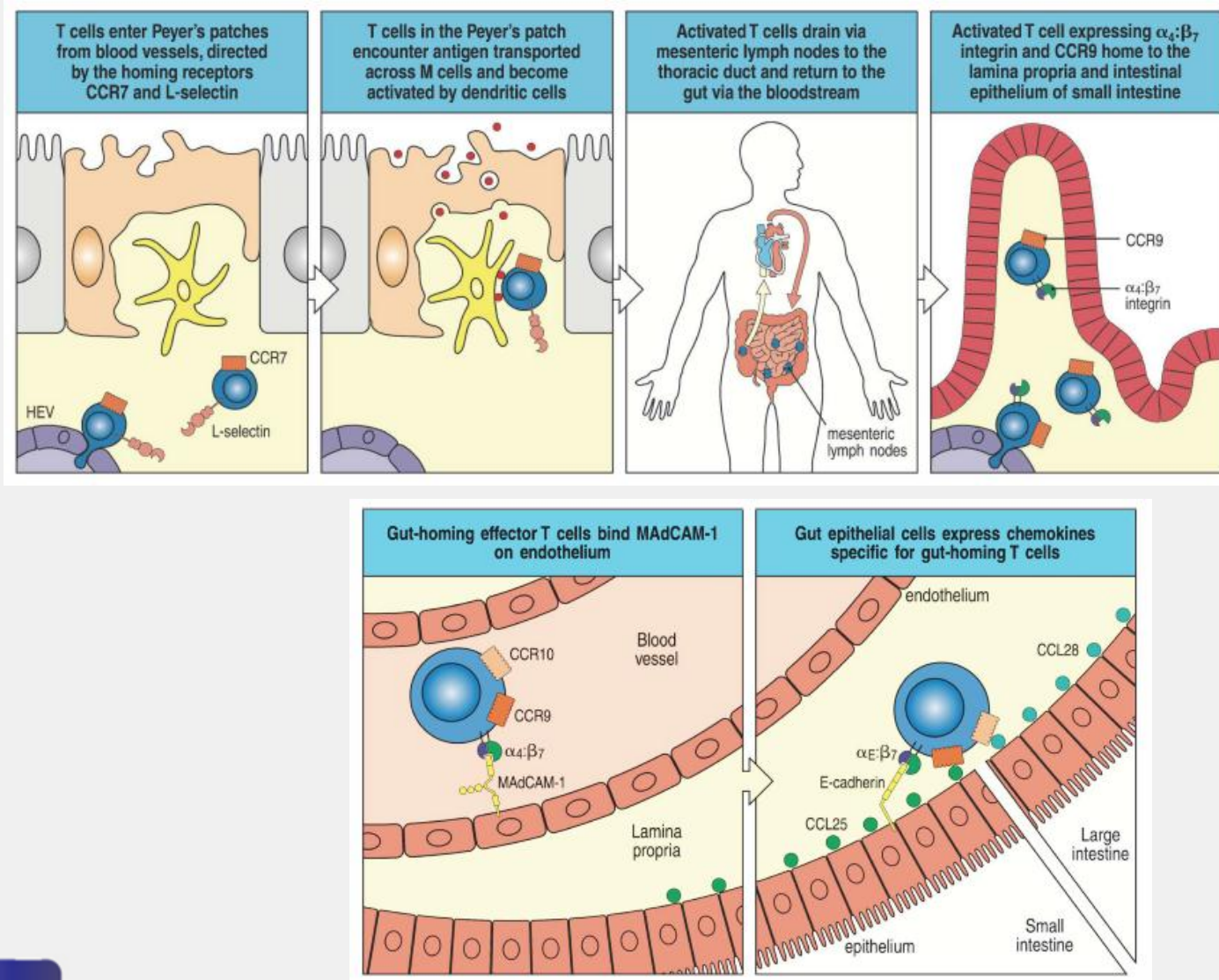


- BALT: asociado al tracto respiratorio
- NALT: asociado al tracto nasofaríngeo
- GALT: asociado al tracto digestivo

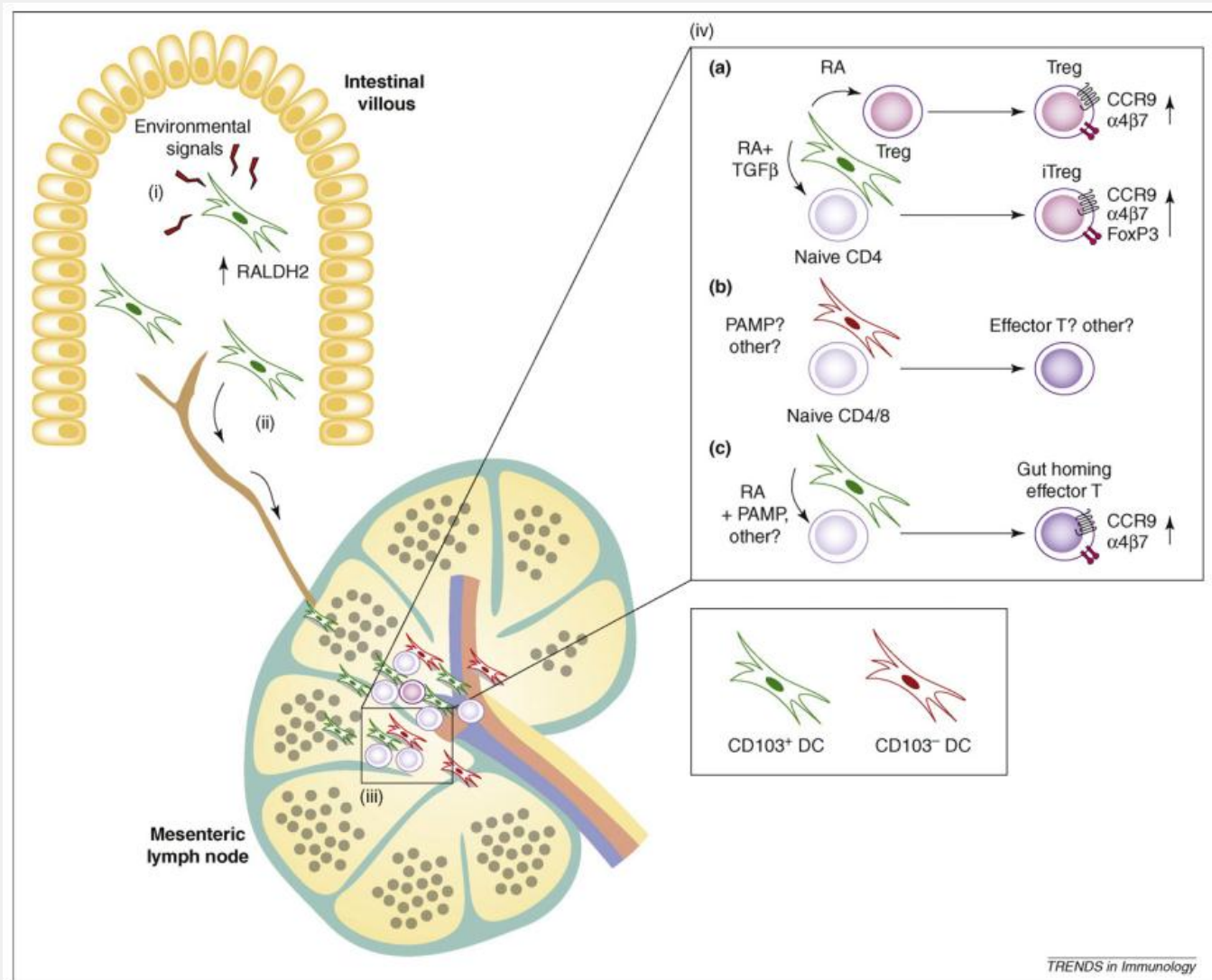
✓ Tiene vasos linfáticos eferentes pero no aferentes, así limita la entrada de antígenos sistémicos

- Flora bacteriana comensal
- Actividad motriz en la mucosa
- Moco
- Sustancias como ácido gástrico y sales biliares
- Glucocálix
- Enzimas (lactoferrina, lactoperoxidasa, lisozimas)

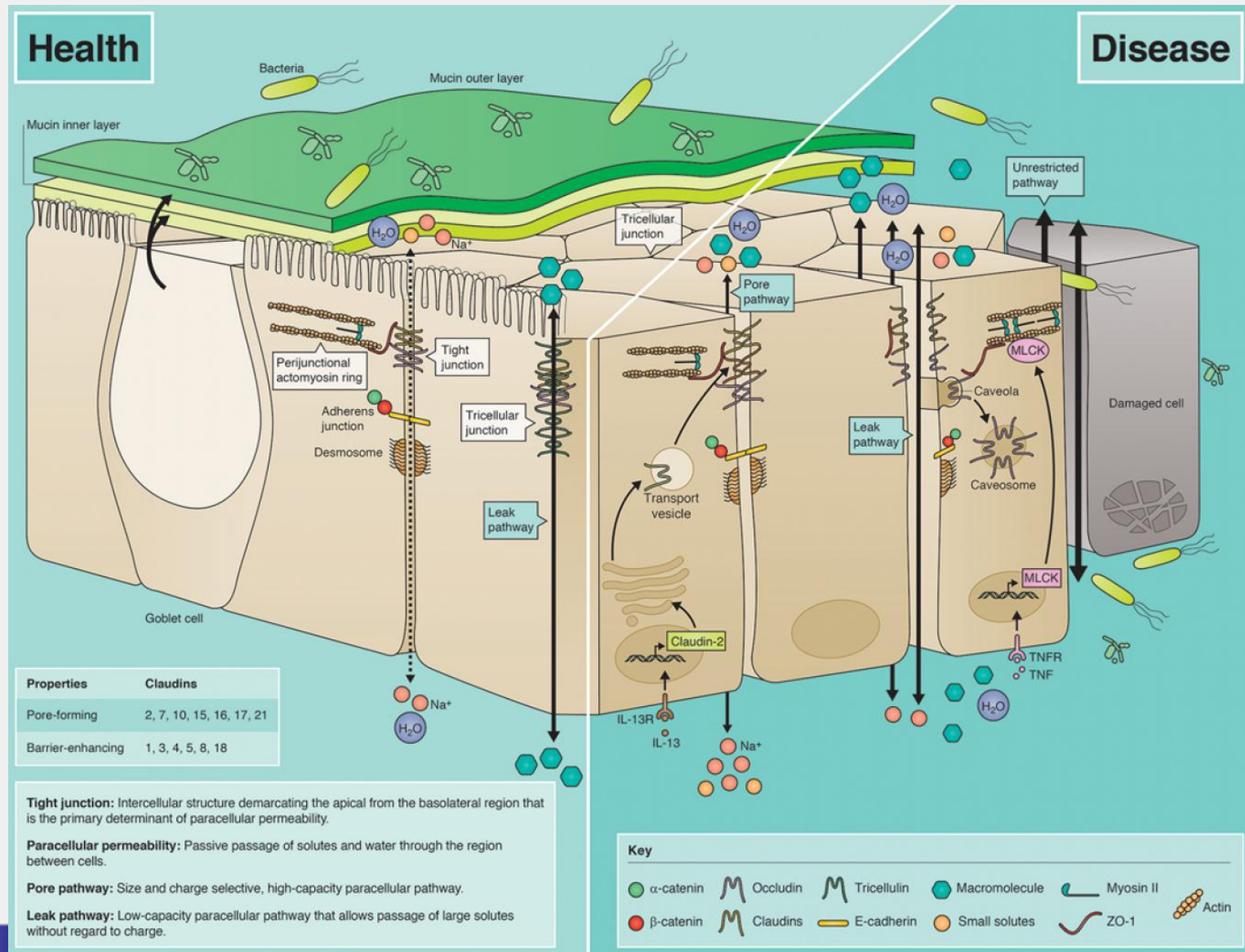
Gut homing



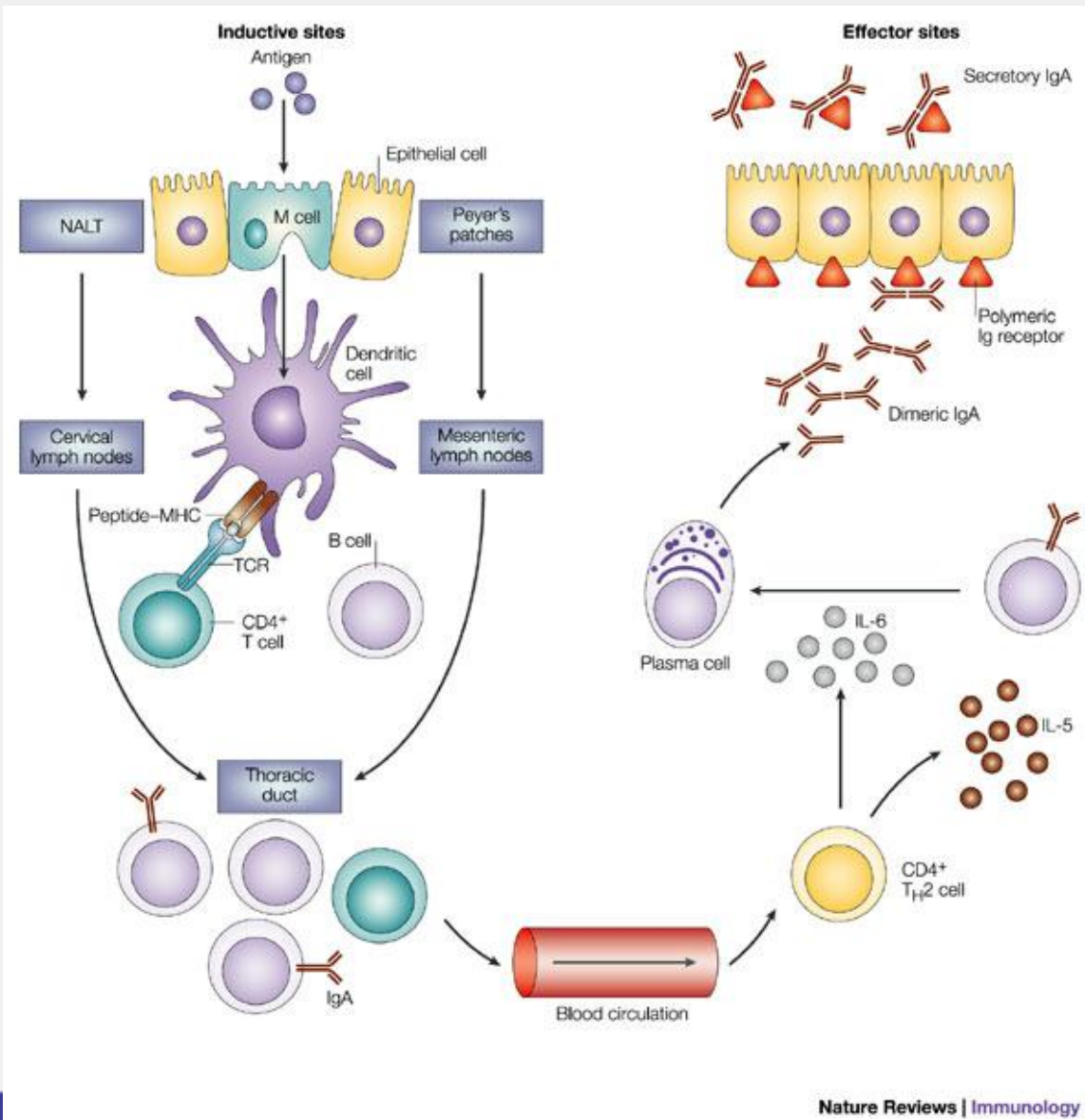
Gut homing



Ante todo una barrera

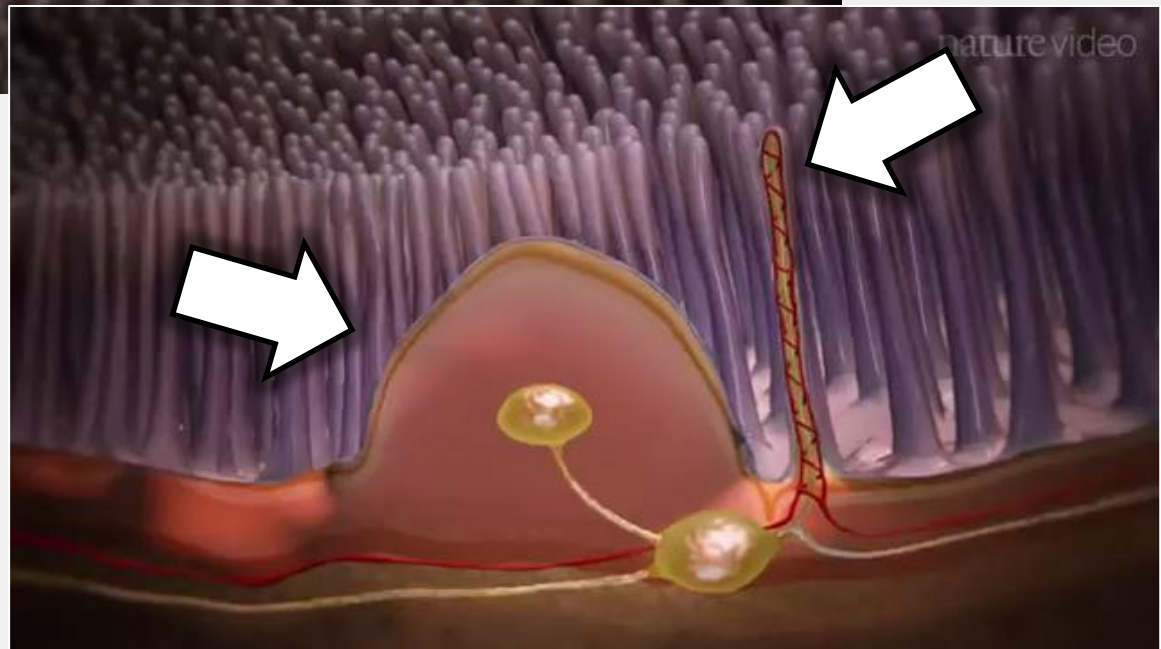
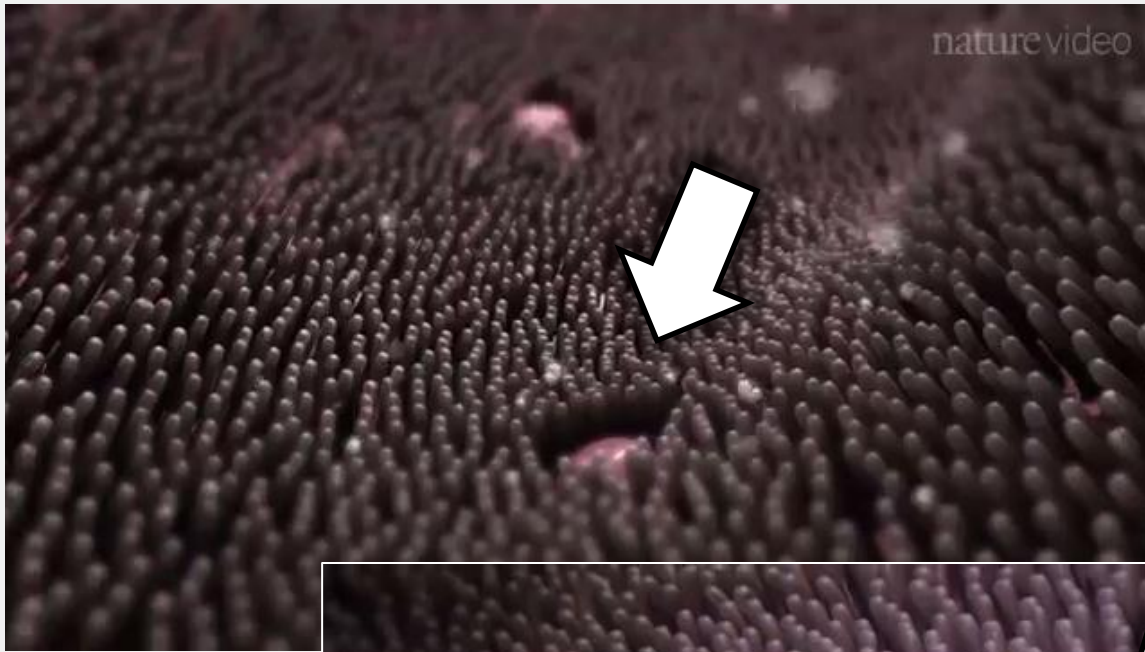


División anatómica y funcional

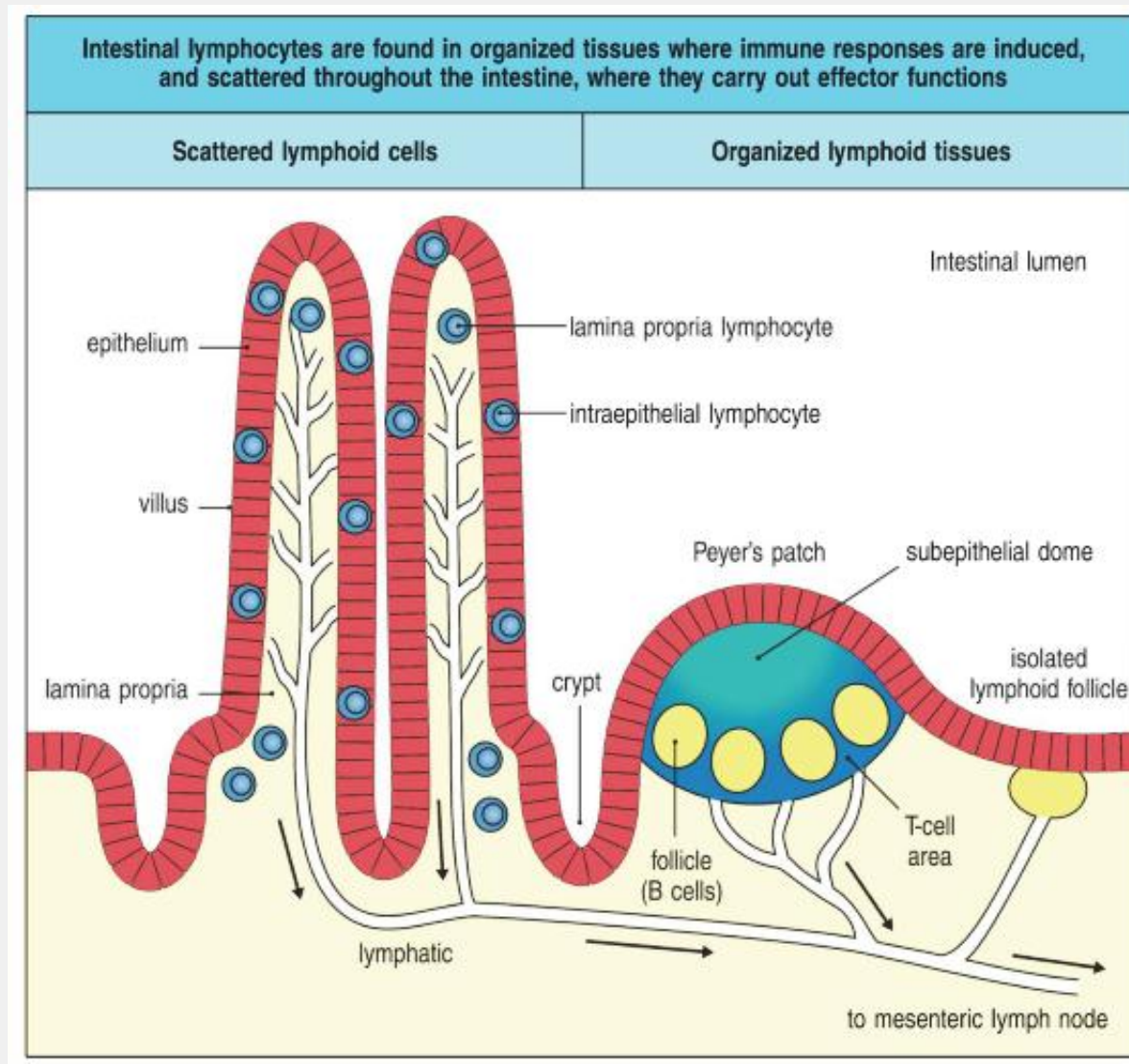


- Sitios inductores
 - ✓ Placas de peyer
 - ✓ Folículos linfoides aislados
- Sitios efectores
 - ✓ Lámina propia
 - ✓ Epitelio intestinal

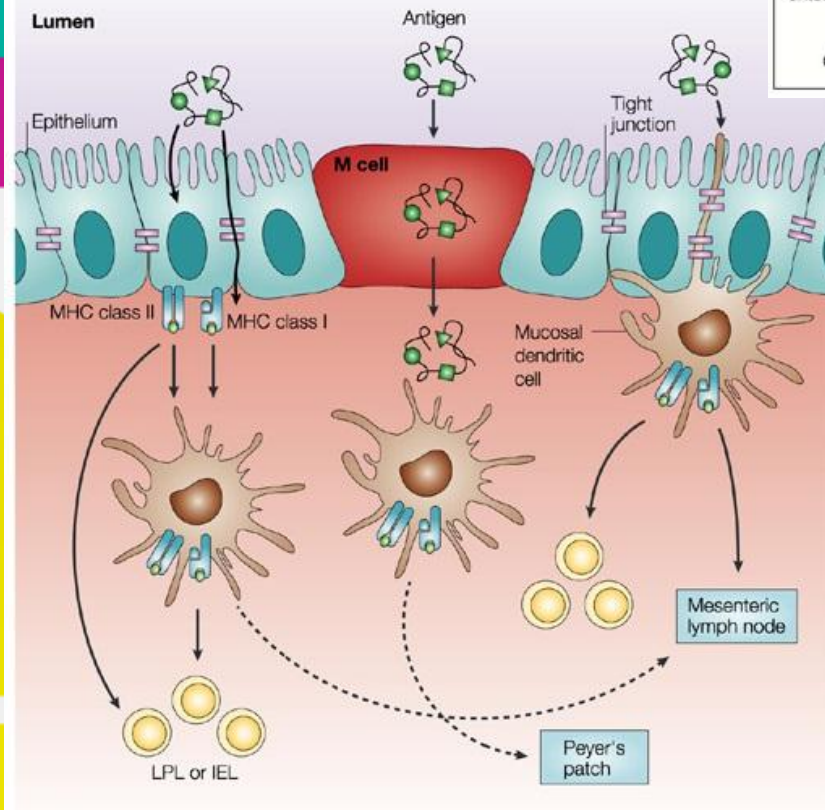
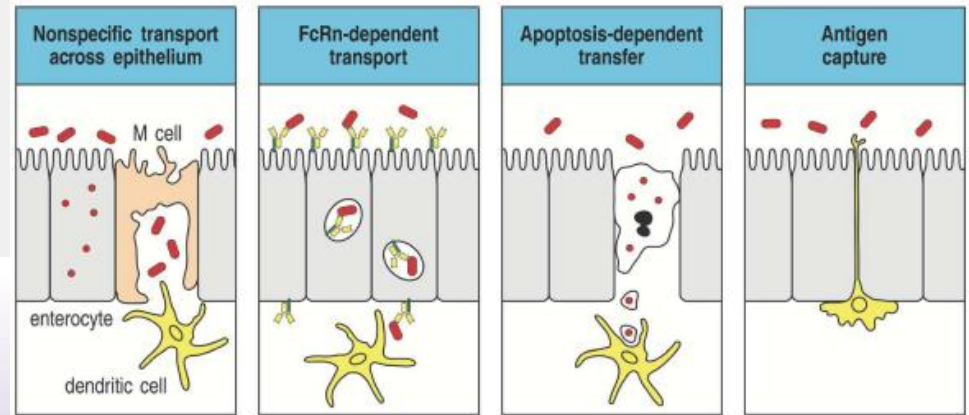
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División anatómica y funcional

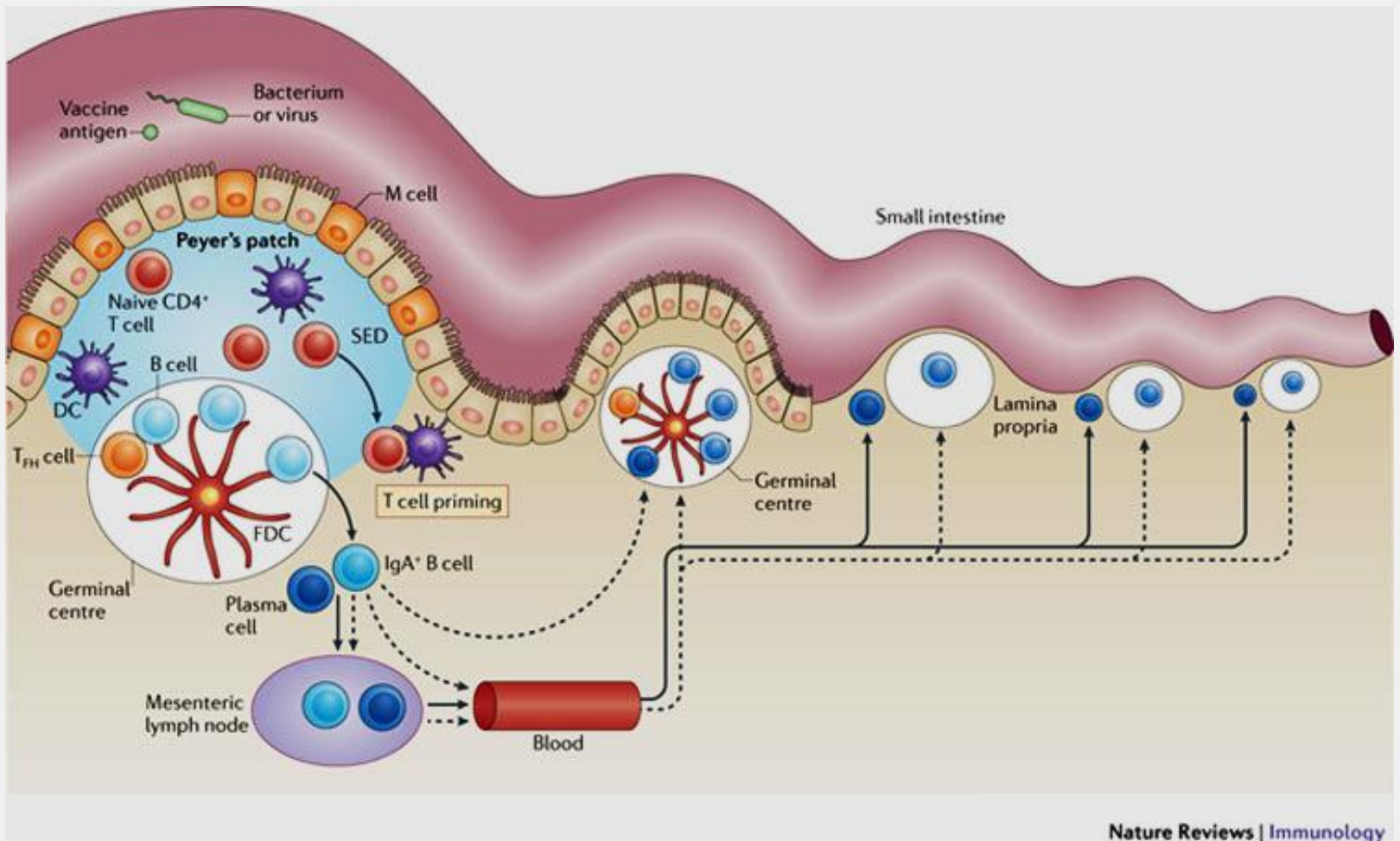


Captura de antígenos



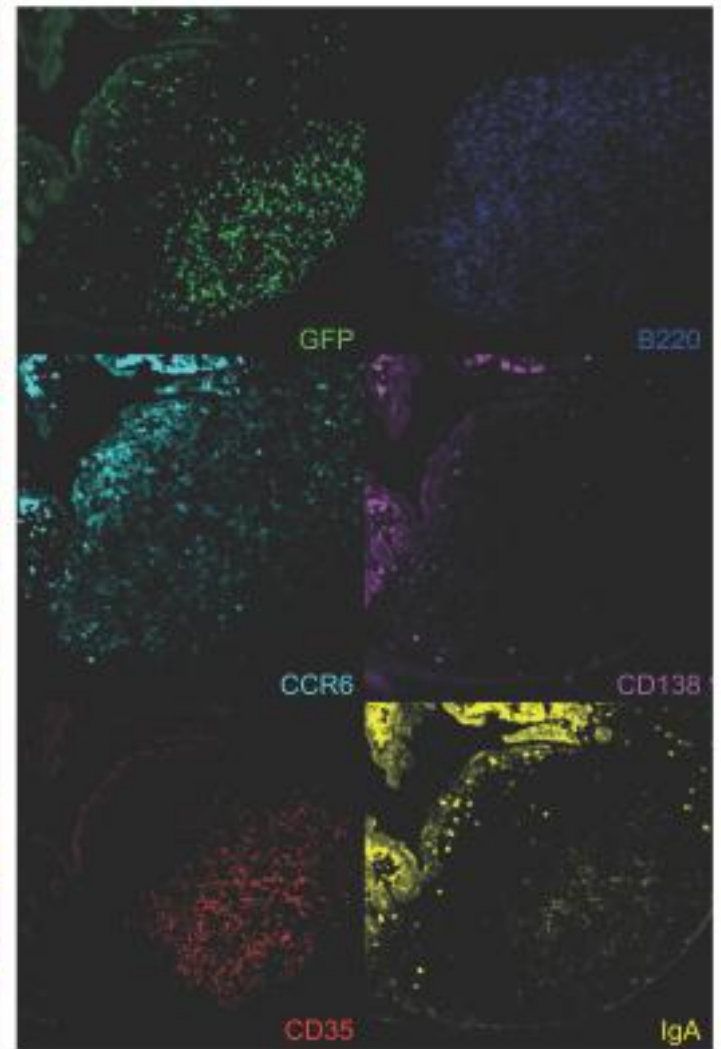
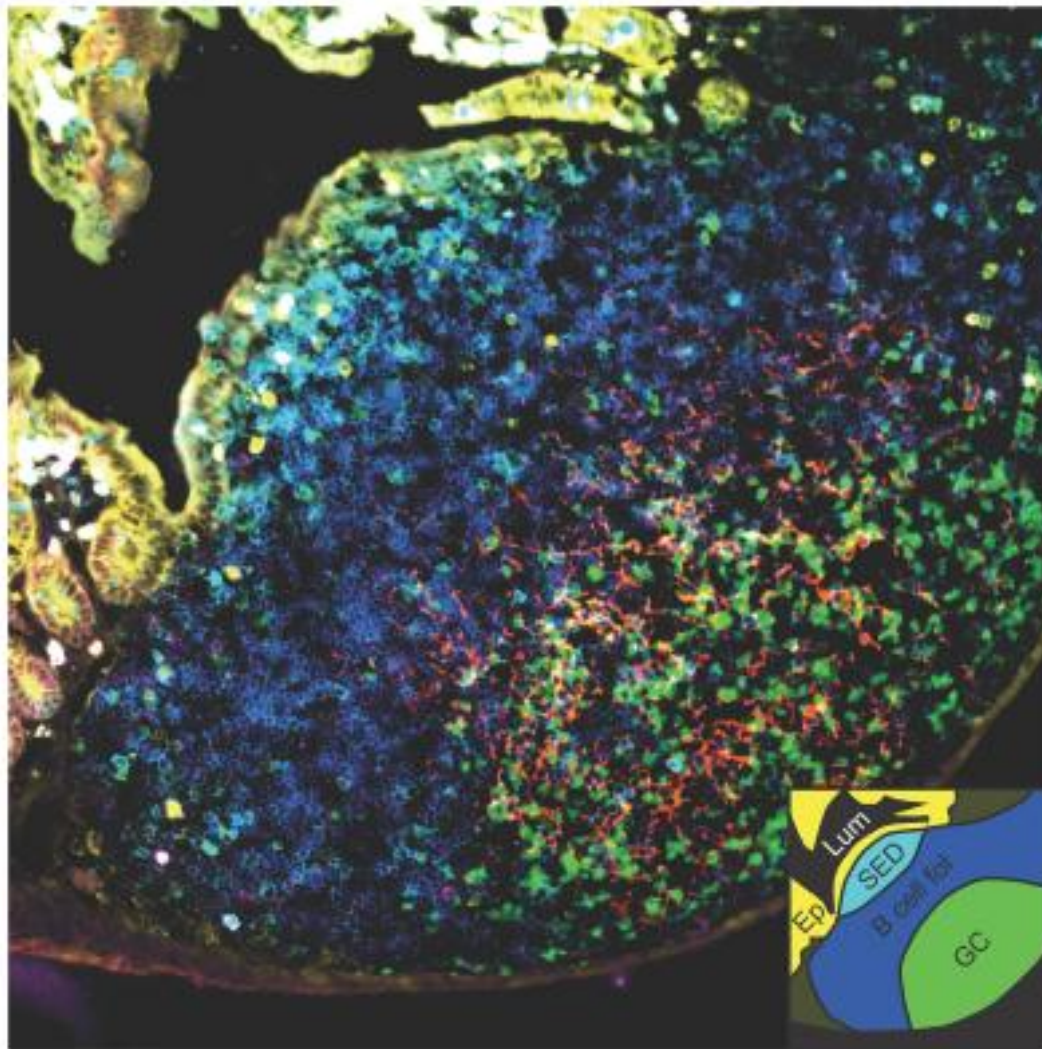
- A través de Células M
 - ✓ Pasan los antígenos intactos a los macrófagos y DC
- Trans-epitelial a través de las células dendríticas
 - ✓ Exponen dendritas a través del epitelio hacia la luz intestinal
- Transferencia a través del epitelio
 - ✓ Pasan los antígenos intactos, mecanismos mediado por receptores
- Transferencia de productos apoptóticos

Placa de Peyer

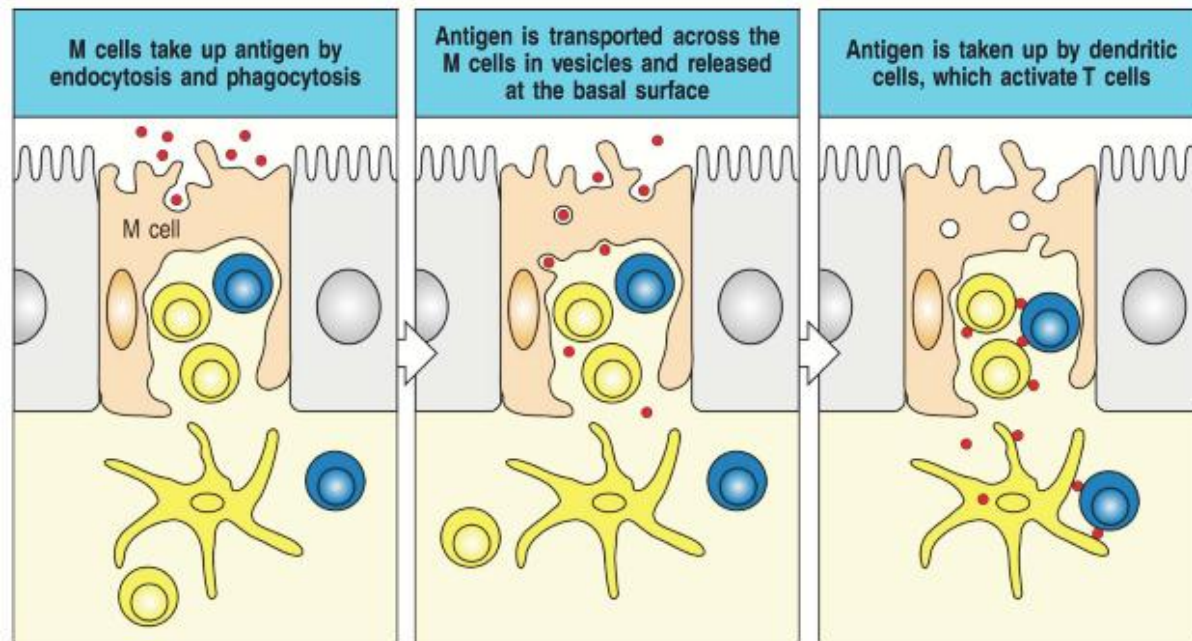


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Placa de Peyer

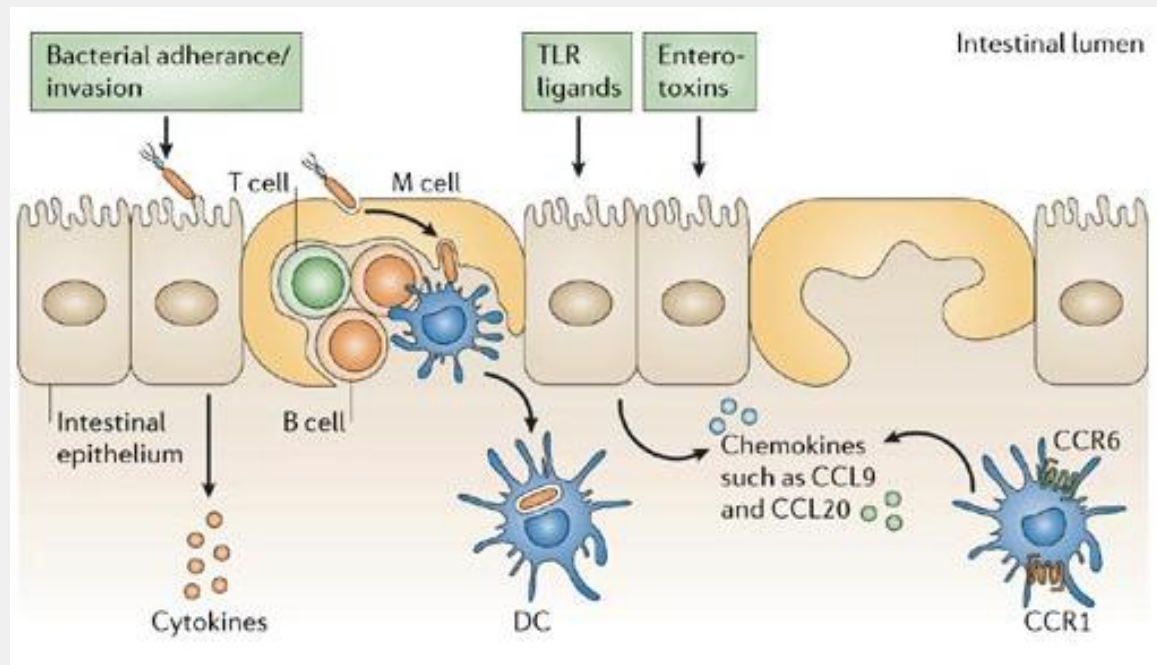


La célula M



- Células epiteliales especializadas en la captura de Ag
- Transportan el Ag sin procesarlo
- Bolsillo: CD y linfocitos
- Superficie apical: clatrina, patrones de glicosilación (sialyl Lewis A)
- No expresan MHC clase II

La célula M



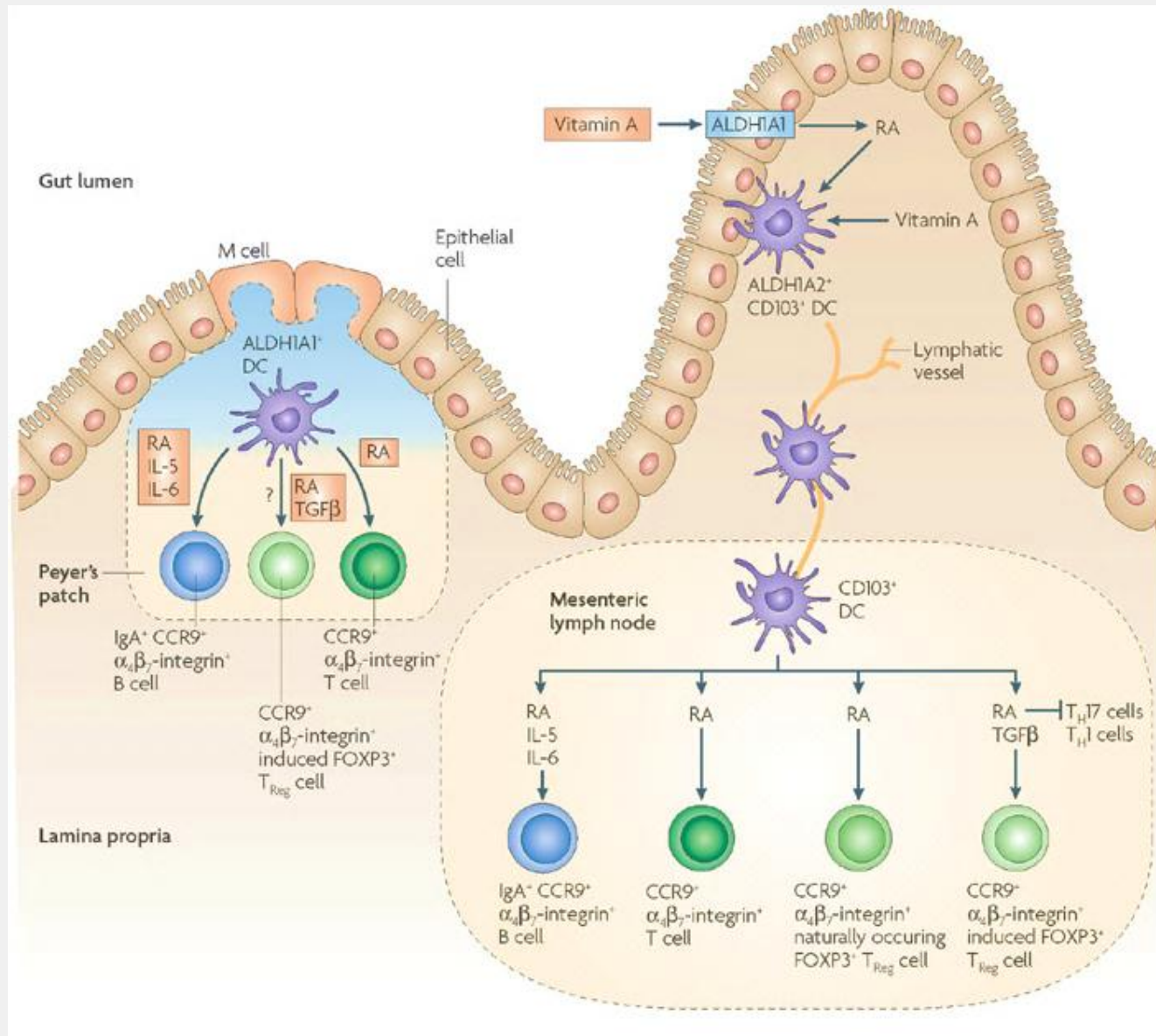
- Ag tomados y liberados directamente a folículos adyacentes
- Transporte vesicular de Ag
- Requiere de 10 a 15 minutos para transportar los antígenos
- Alícuotas pequeñas de Ag dieta = tolerancia (favorecen T CD4 supresoras, productoras de TGF- β , supresión de respuesta Th1 y cambio de isotipo a IgA)
- Interés para el desarrollo de vacunas

Célula M (m de multiplicidad)

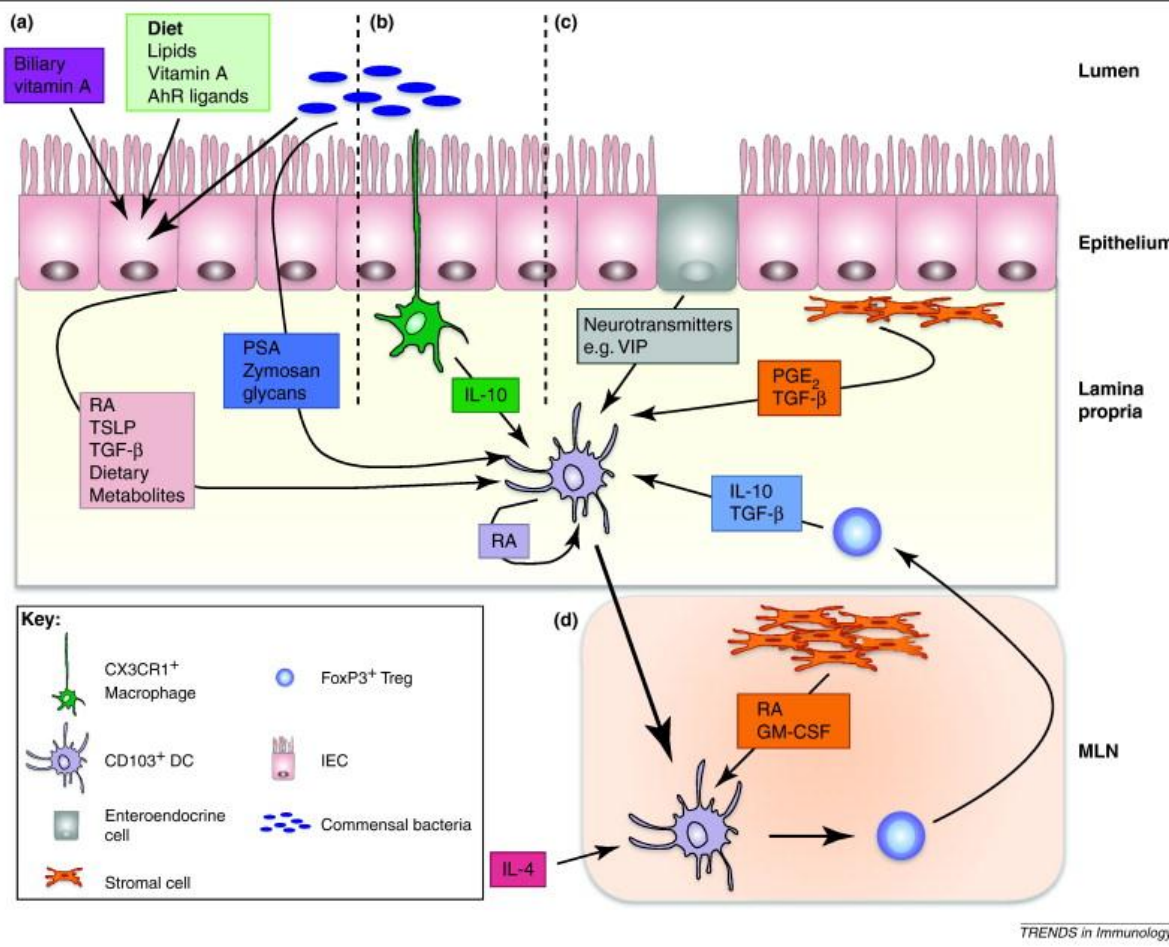
Table 1. Summary of M Cell Types^{a,b}

Type	Constitutive/inducible	Progenitor (lifespan)	Differentiation factors	Morphologic features	Transcytosis function
Intestine					
Peyer's patch	Constitutive	Crypt stem cell (5–7 d)	Lymphotoxin, TNF α , RANKL	Basolateral pocket with lymphocytes, associated DC	Yes
Isolated lymphoid follicle	Constitutive/ Inducible (immune activity)	Crypt stem cell (?5–7 d)	Lymphotoxin, TNF α , RANKL	Basolateral pocket with lymphocytes, associated DC	?Yes
Colonic patch	Constitutive	Crypt stem cell (?5–7 d)	Lymphotoxin, TNF α , RANKL	Basolateral pocket with lymphocytes, associated DC	Yes
Inducible colonic	Inducible (inflammation)	?Crypt stem cell (?5–7 d)	?RANKL, TNF α (TNFR2 dependent)	Basolateral pocket with lymphocytes, associated DC	Yes
Villous	Mainly Inducible (cholera toxin)	<i>Trans</i> -differentiation from enterocytes (<5 d)	?	No basolateral associations; clustered at villous tips	?No
Airway					
NALT	Constitutive	Basal cell (weeks)	Lymphotoxin, TNF α , RANKL	Basolateral pocket with lymphocytes, associated DC	Yes
Inducible NALT	Inducible (cholera toxin)	<i>Trans</i> -differentiation from ciliated airway epithelium (weeks)	Lymphotoxin, TNF α , RANKL, cholera toxin	Basolateral pocket with lymphocytes, associated DC	Yes
?IBALT	?Inducible (chronic inflammation)	?Basal cell (?weeks)	? (lymphotoxin independent)	?	?Yes

Células dendríticas

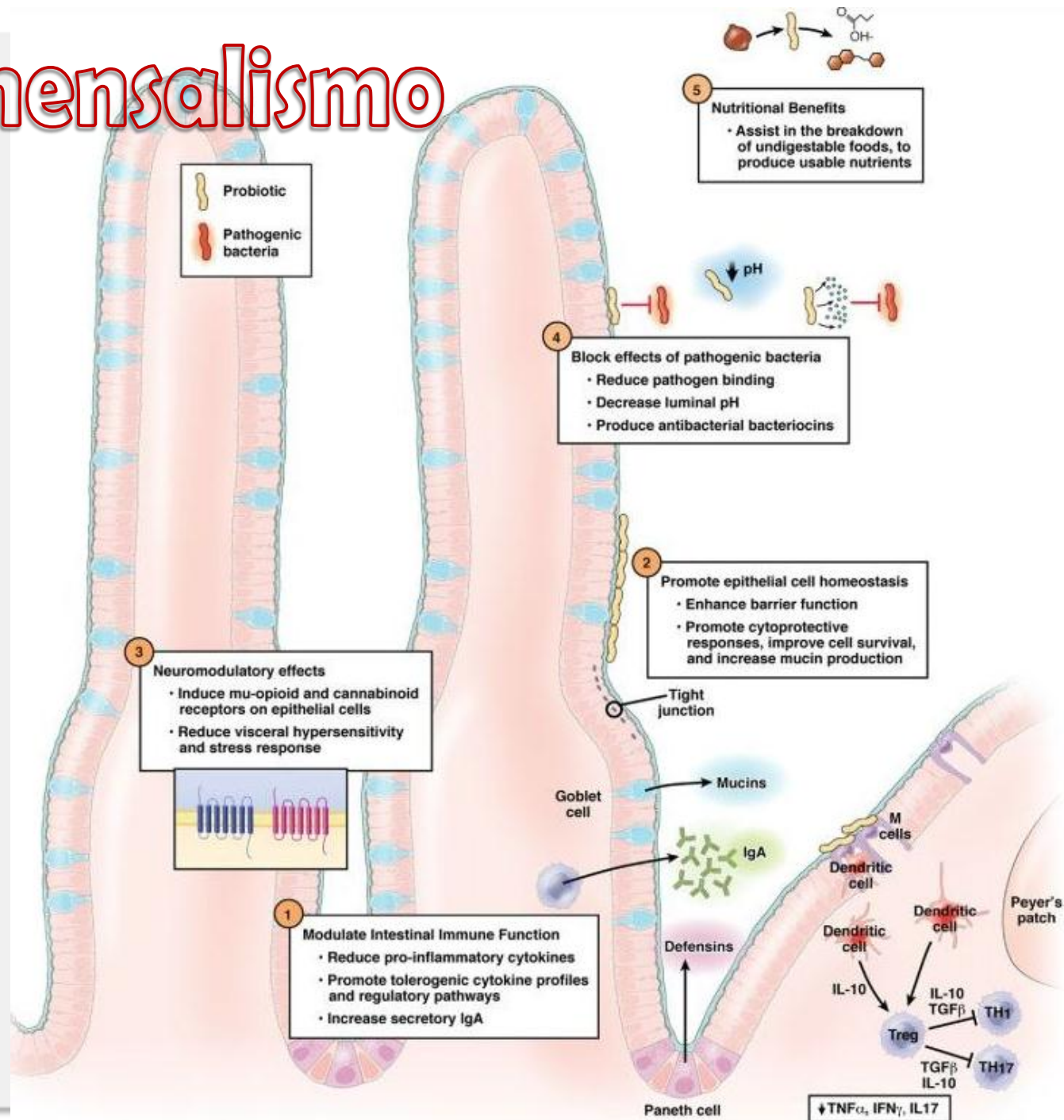


Células dendríticas

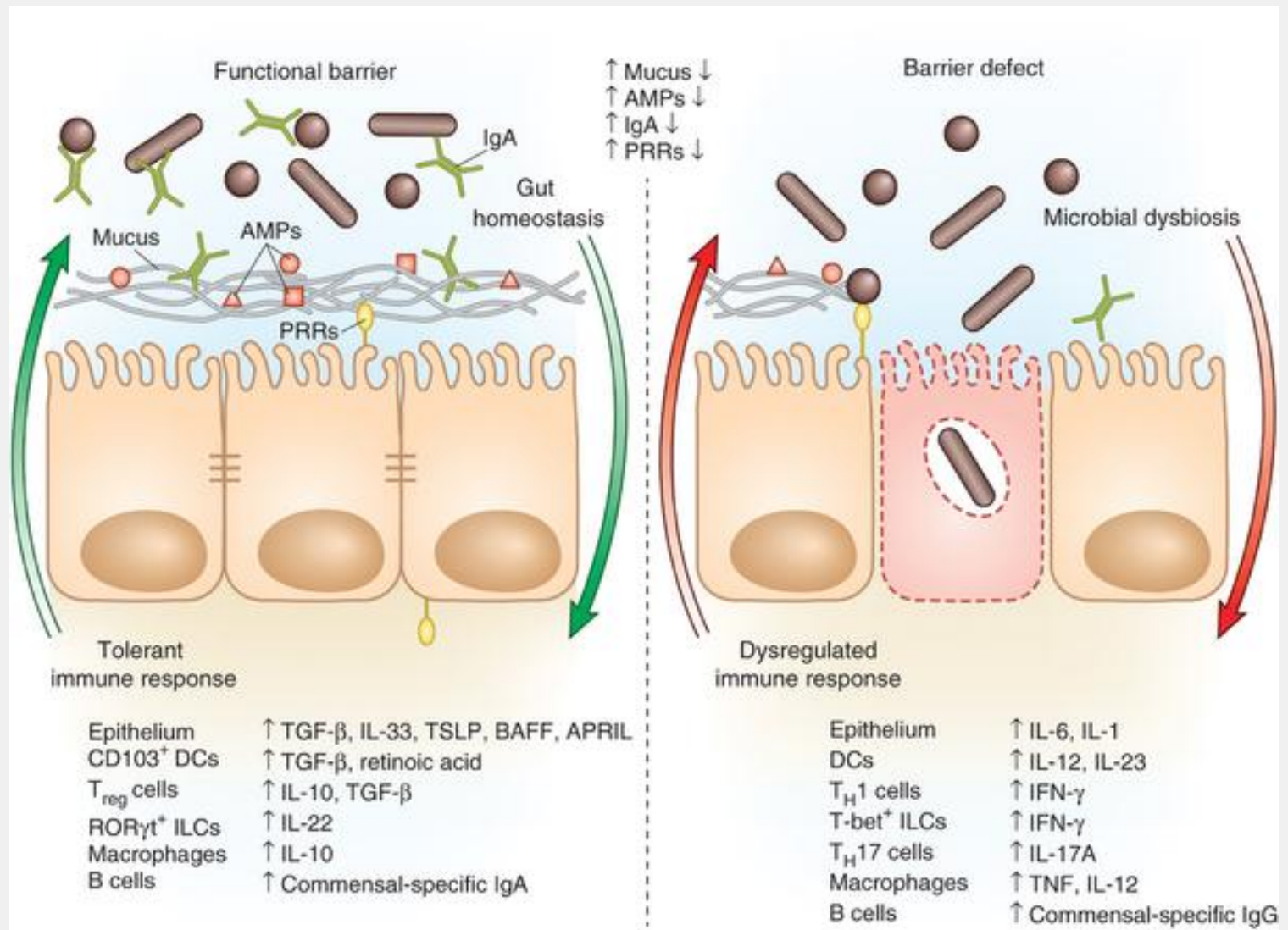


- **Placas de Peyer**
 - ✓ DC CD11b⁺/IDO⁺ (Indoleamina 2,3-dioxygenase), productoras de IL-10 (región sub-epitelial), inductoras de Treg
 - ✓ DC CD8 α ⁺ (región interfolicular) y CD11b⁻/CD8 α ⁻, productoras de IL-12, inductoras de respuesta Th1
- **Lamina propria**
 - ✓ DC CD103⁺, inductoras de TREG, productoras de ácido retinoico
- **Nódulos linfáticos Mesentéricos (NLM)**
 - ✓ DC CD103⁺ migran de la lamina propria

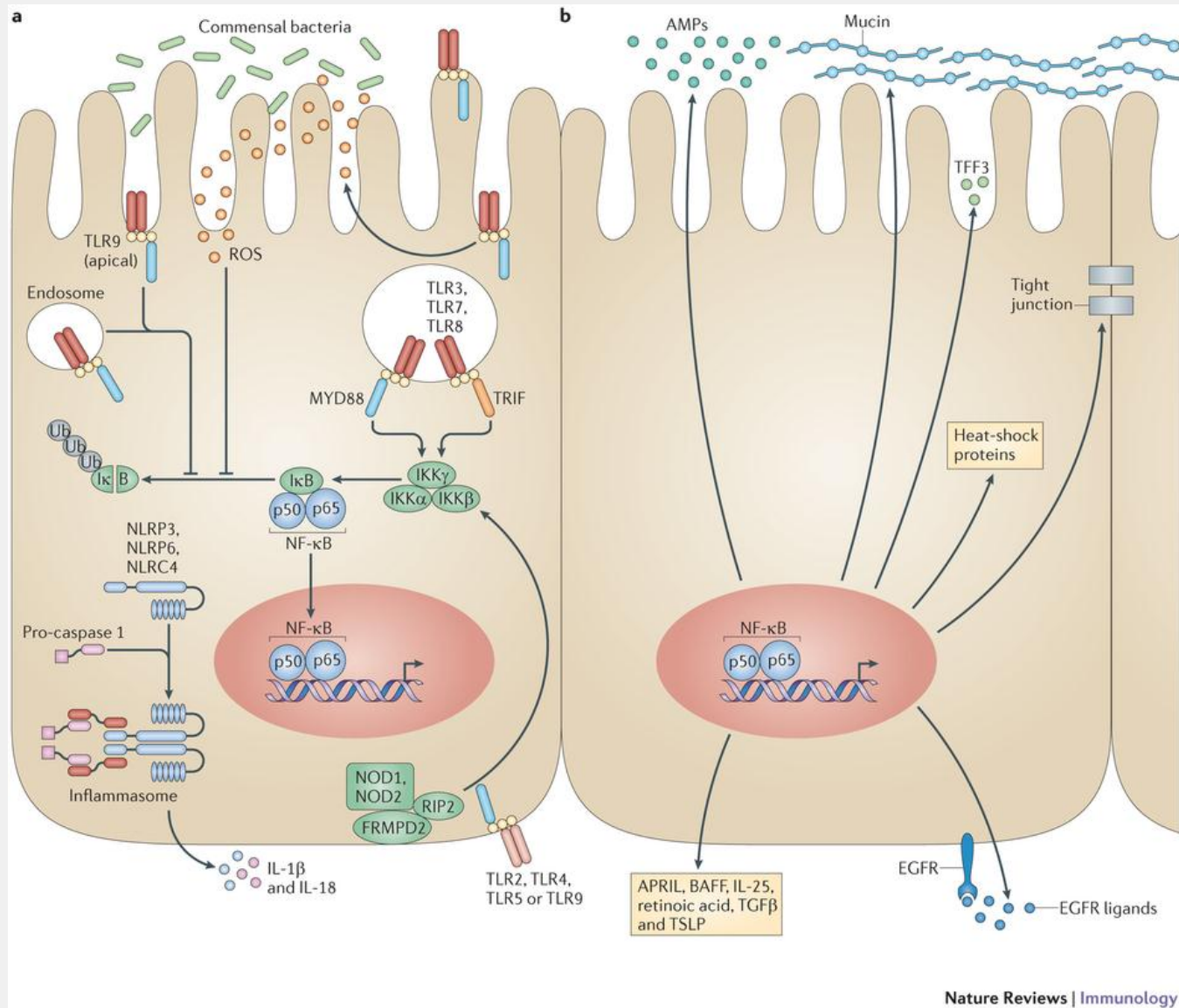
Comensalismo



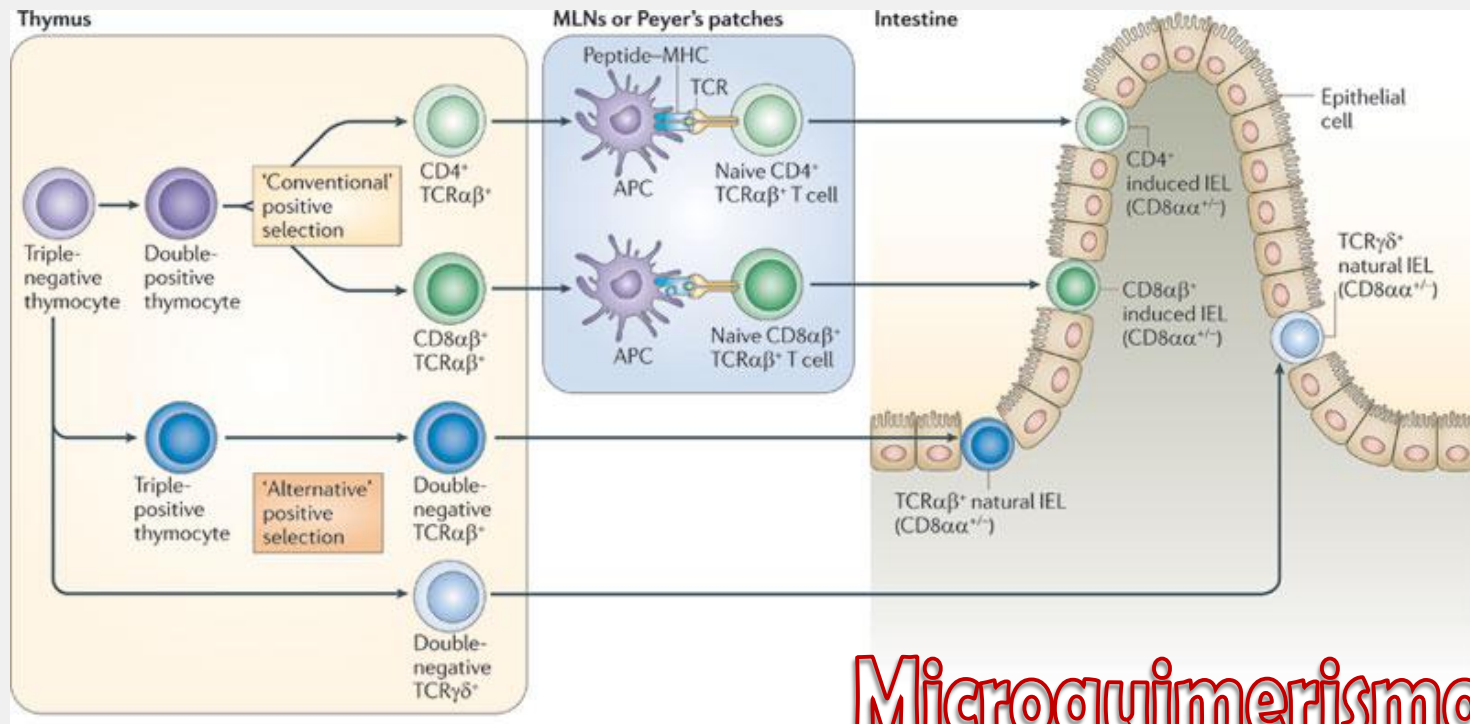
Alteración del comensalismo



Células epiteliales



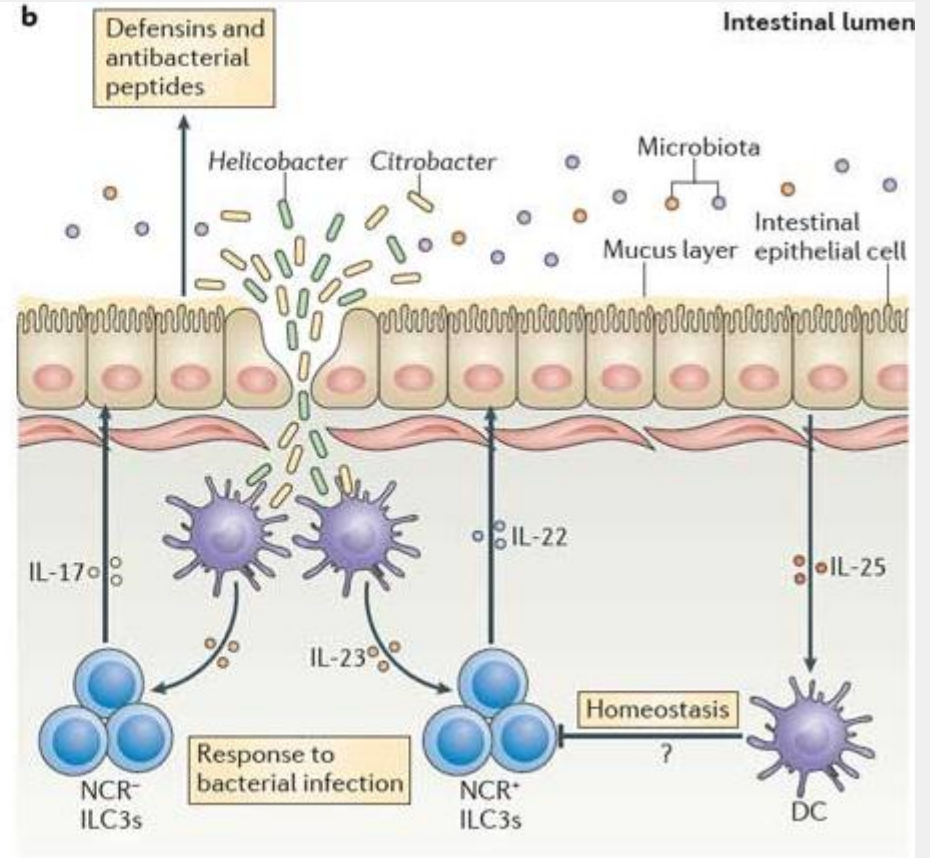
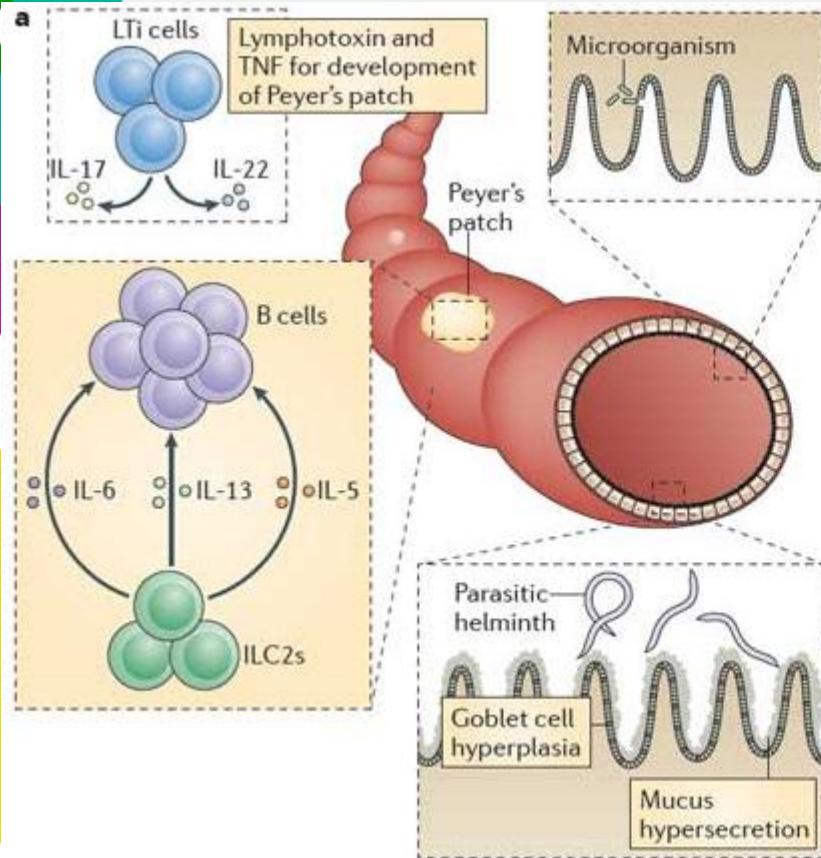
Linfocitos intra epiteliales



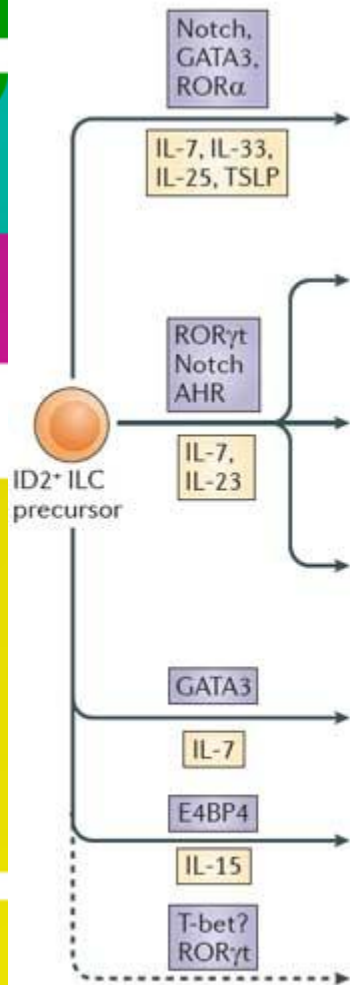
Microquimerismo???

- No se activan con facilidad
- Pocos NK
- Defensa innata y vigilancia tumoral
- Especificidad limitada de TCR (tanto αβ como γδ), oligoclonal
- 40% son TCR γδ, reconocen Ag sin procesamiento previo
- Criptas intestino delgado ontogenia de linfocitos Tγδ
- Linfocitos T CD8αα

Aja, y los "linfocitos" INNATOS????



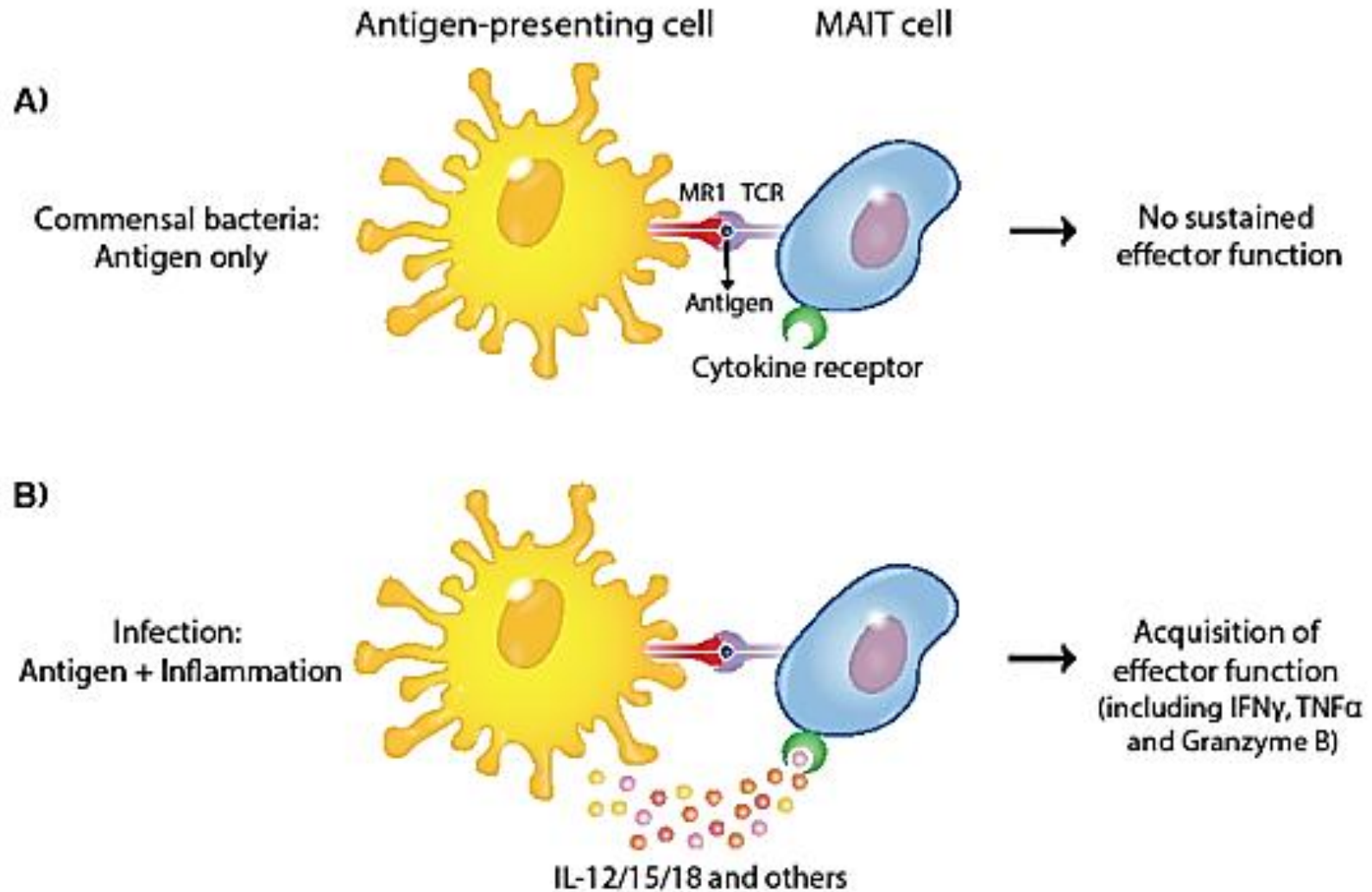
Innate lymphoid cells



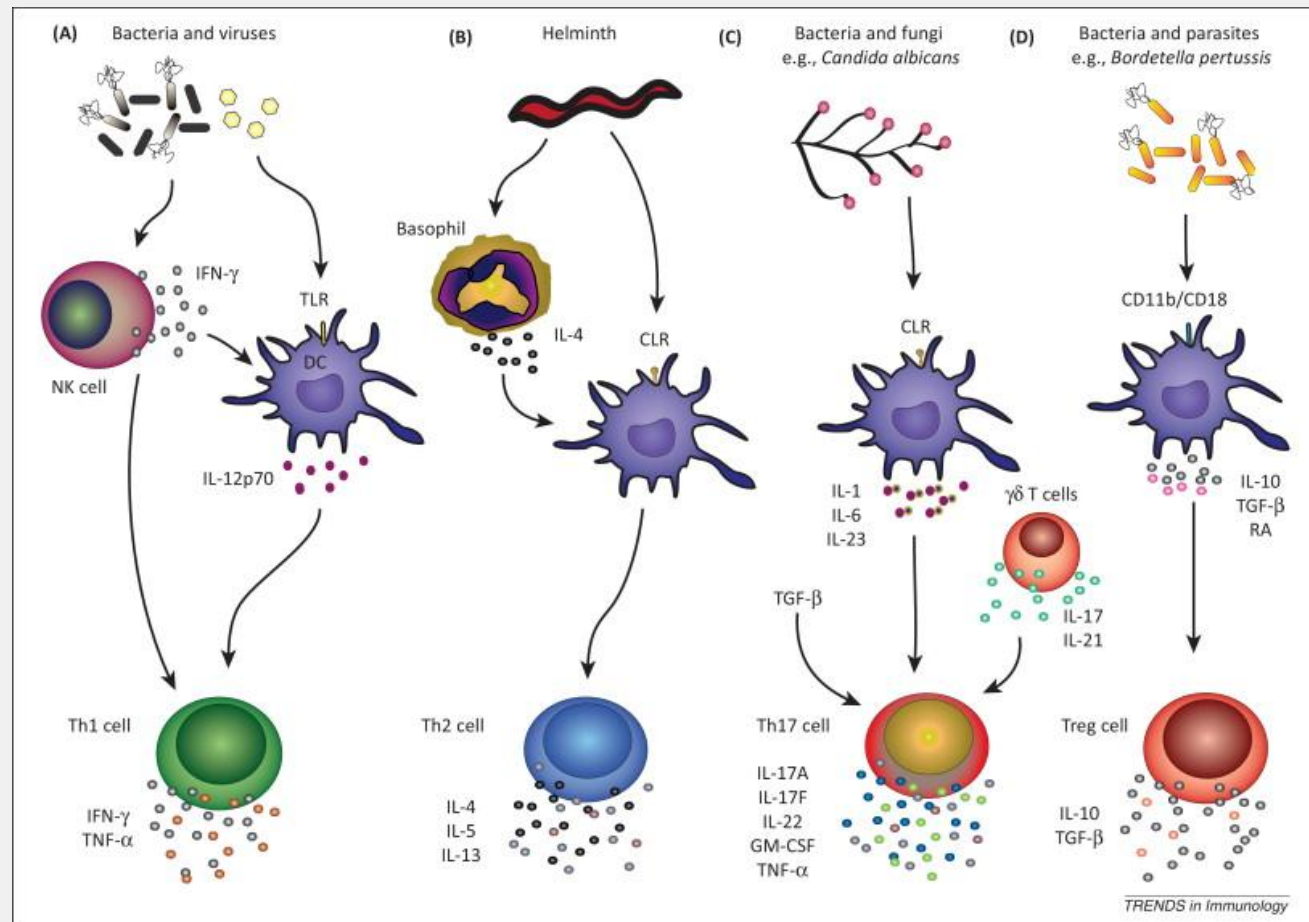
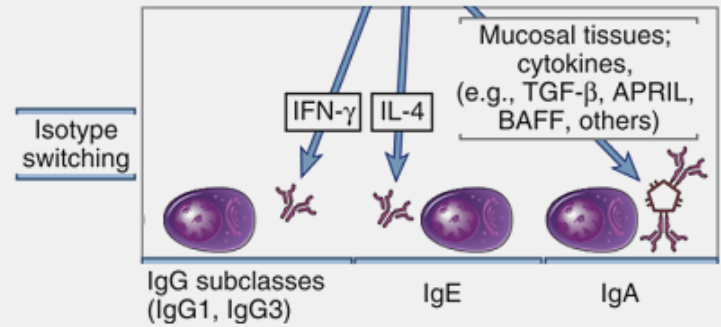
	New nomenclature	New group nomenclature	Mediators produced	Function	Disease association
 Nuocyte, NHC, I _H 2 cell	ILC2	Group 2 ILCs	IL-5, IL-9, IL-13, amphiregulin	• Immunity to helminths • Wound healing	Allergy and asthma
 LTi cell	LTi cell	Group 3 ILCs	Lymphotoxin, IL-17, IL-22	• Lymphoid tissue development • Intestinal homeostasis • Immunity to extracellular bacteria	
 NK22 cell, NCR22 cell, NKR-LTi cell, ILC22	NCR ⁺ ILC3		IL-22	• Homeostasis of epithelia • Immunity to extracellular bacteria	IBD?
 ILC17	NCR ⁻ ILC3		IL-17, IFN γ	• Immunity to extracellular bacteria?	IBD
 Thymic NK cell	NK cell	Group 1 ILCs	IFN γ (high levels)	• Immunity to viruses and intracellular pathogens • Tumour surveillance	Inflammatory conditions, IBD
 Conventional NK cell	NK cell		IFN γ (low levels), perforin, granzymes	• Immunity to viruses and intracellular pathogens • Tumour surveillance	Inflammatory conditions, IBD
 ILC1	ILC1		IFN γ	• Inflammation?	IBD?

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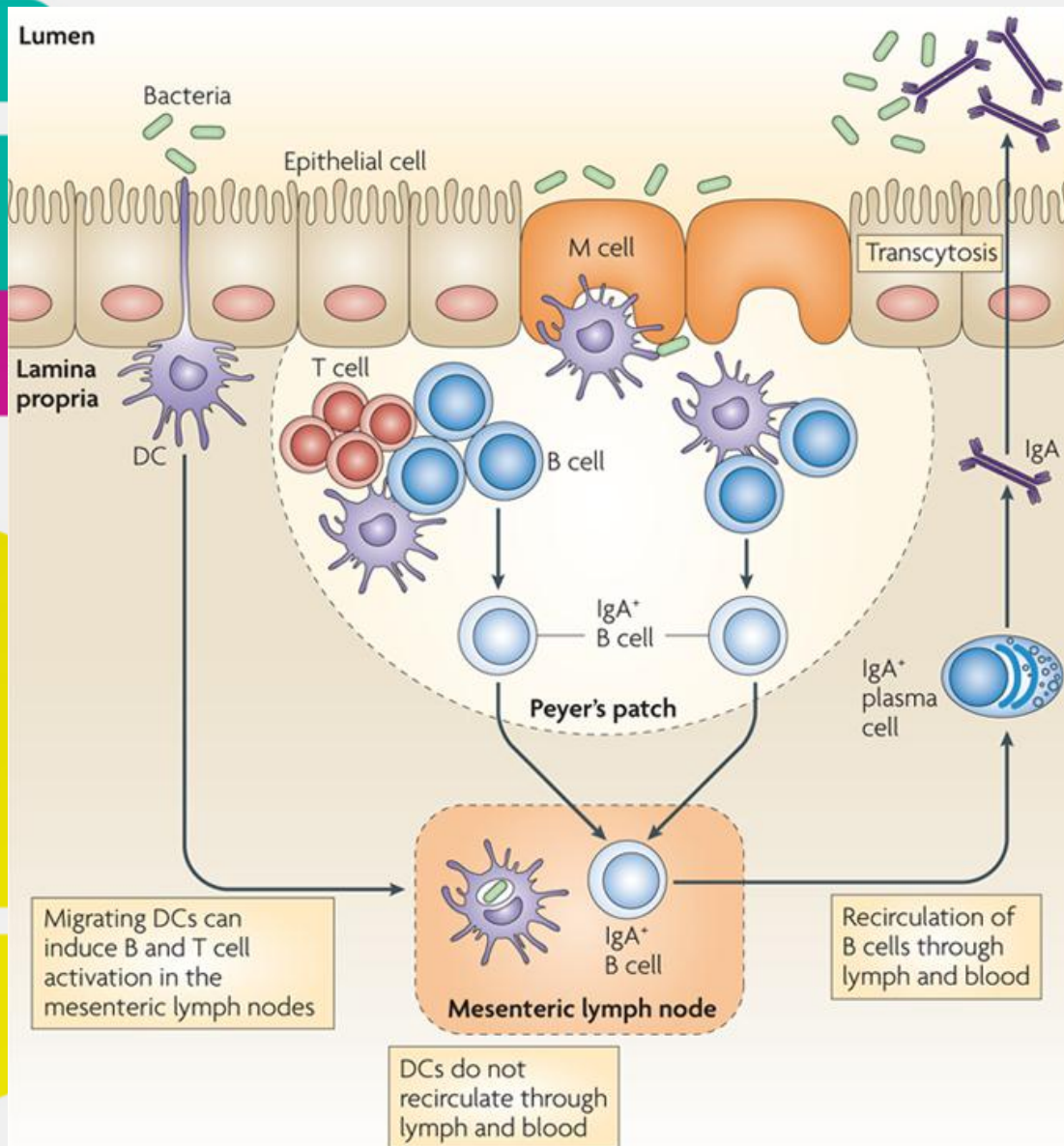
Y Ias MAIT!



Y Ia R. humoral?

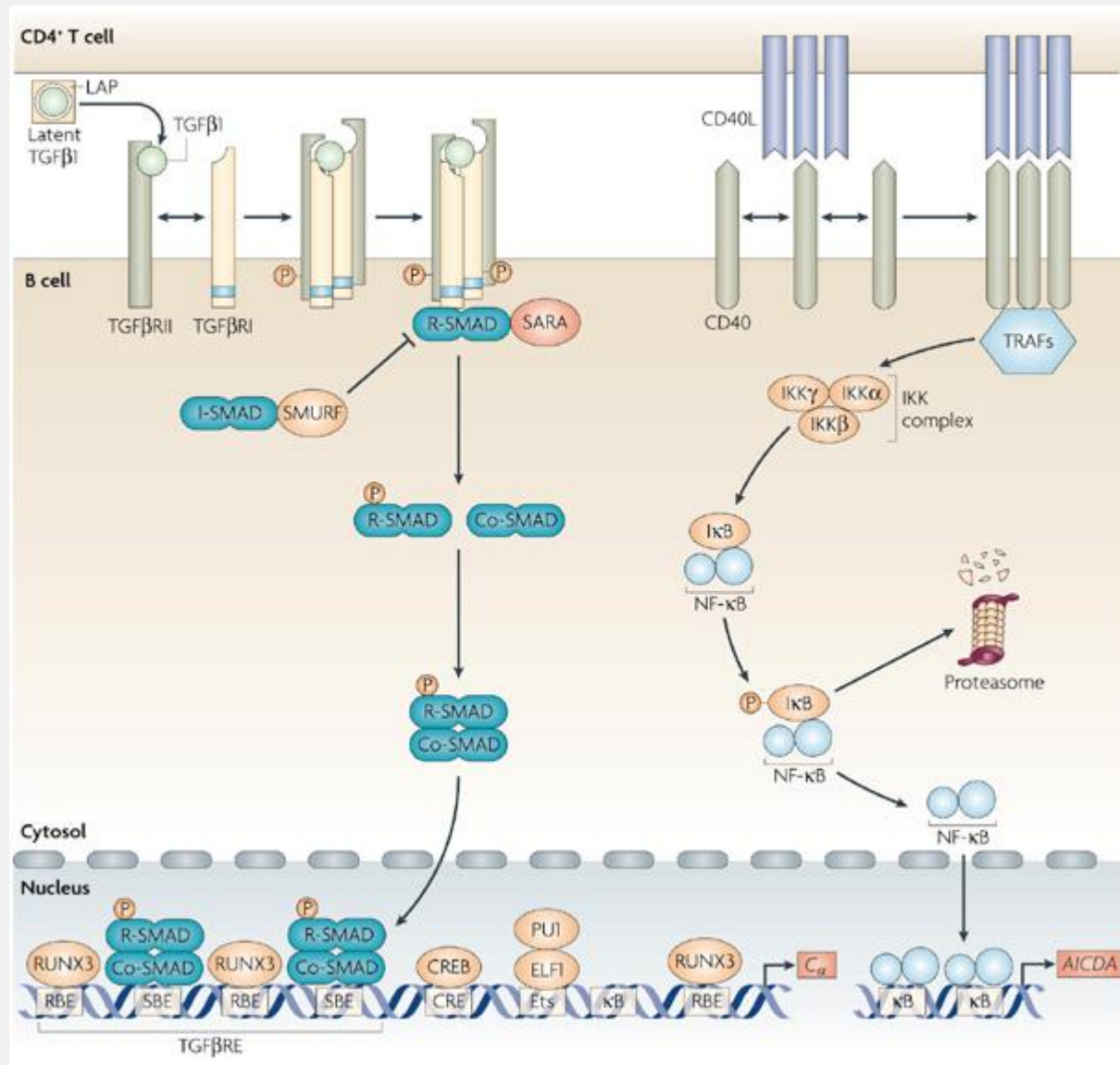


IgA: La Vedette

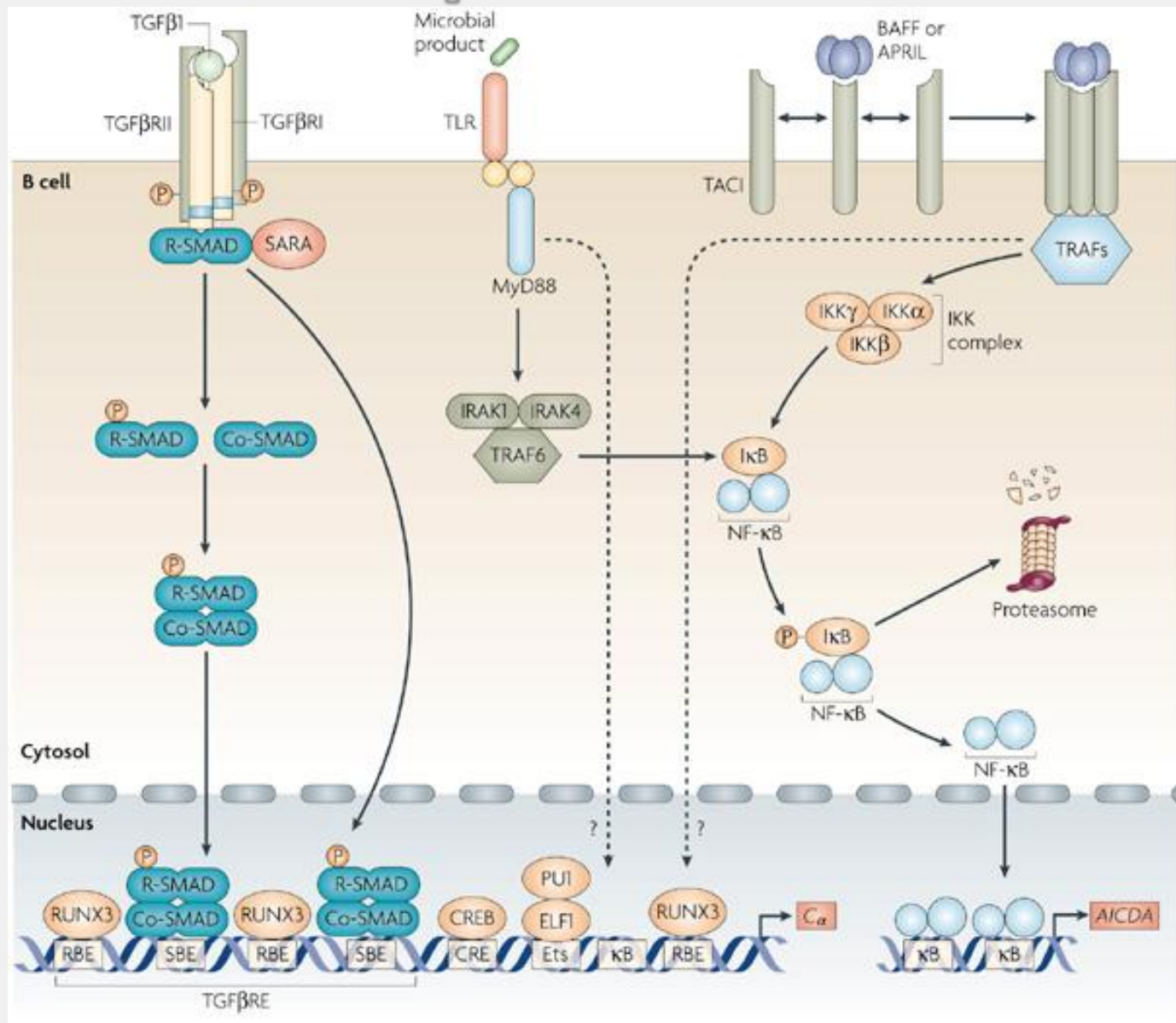


- Inmunoglobulina no inflamatoria, une débilmente el complemento
- Abunda en las secreciones
- En la circulación se encuentra en forma monomérica, mientras que en las secreciones está en forma dimérica
- Componente secretor la protege de las enzimas proteolíticas

Producción T dependiente

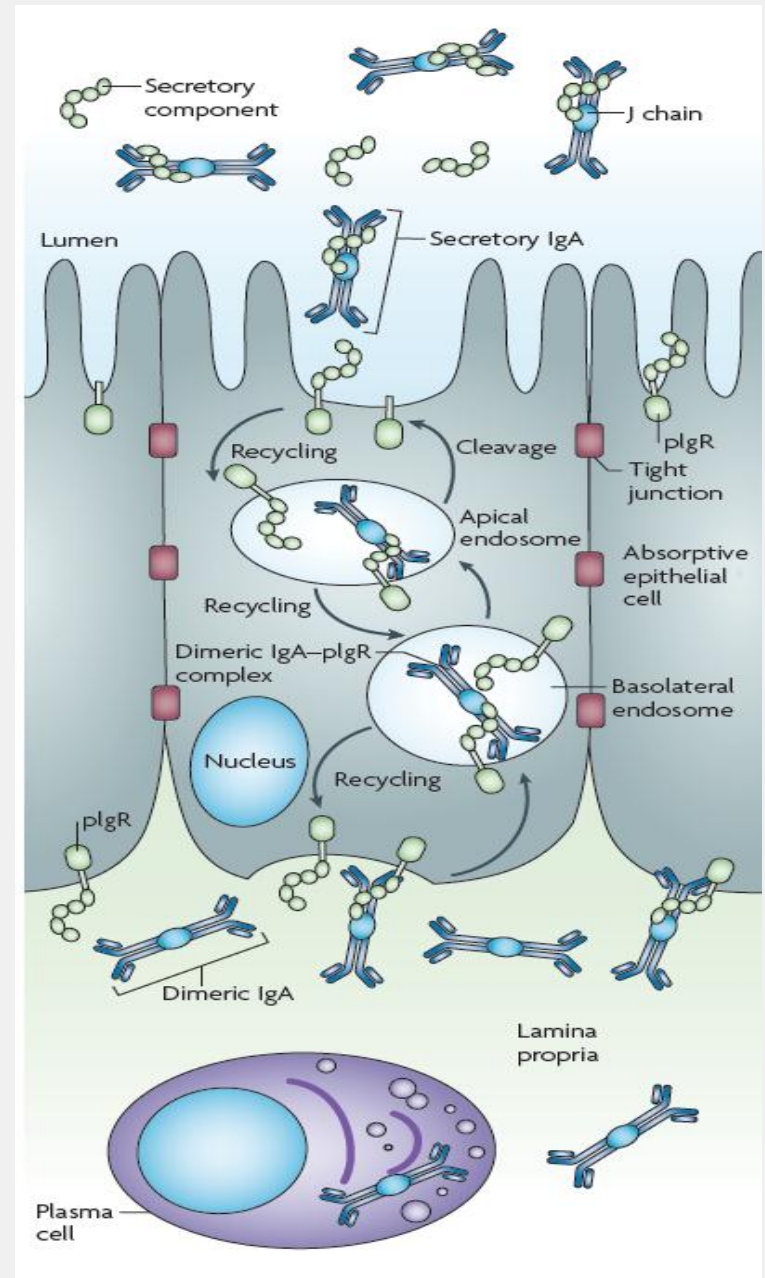


Producción T independiente

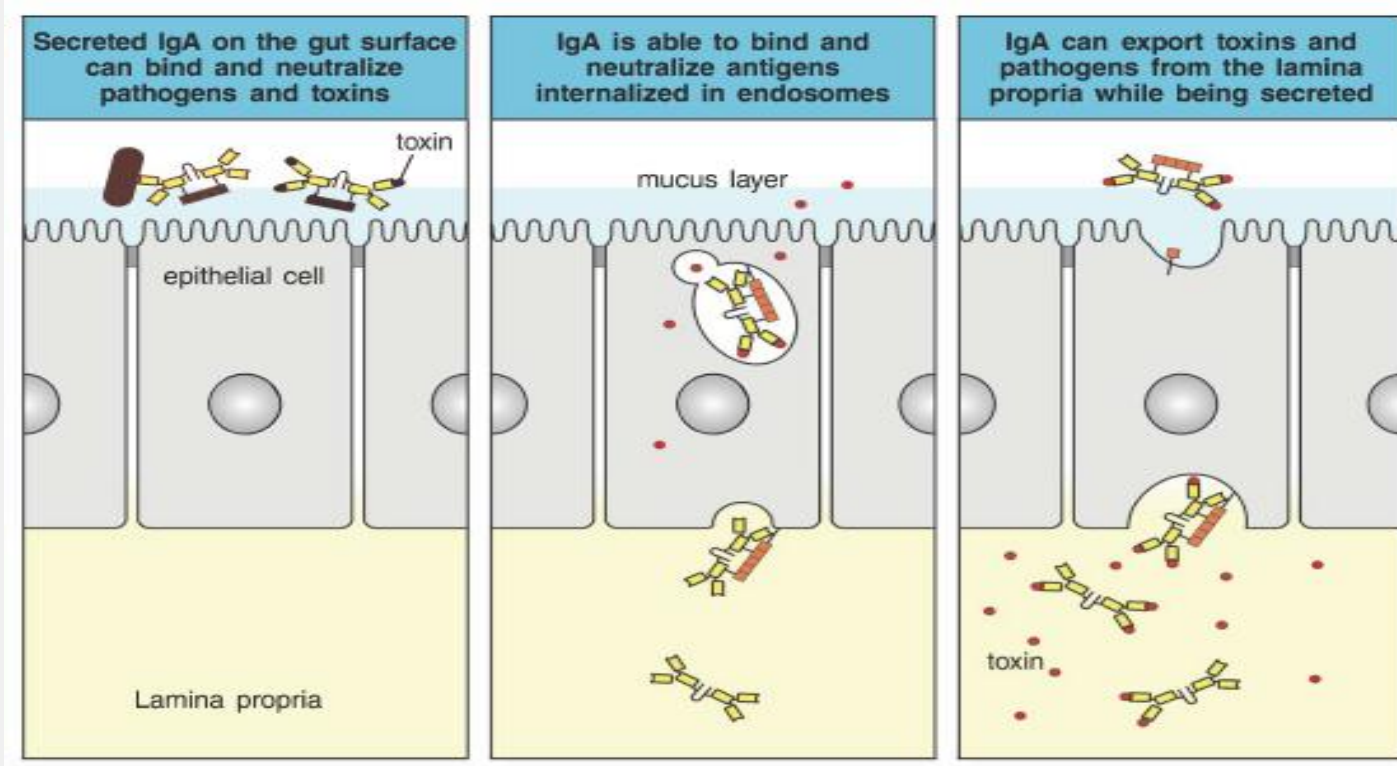


Transporte

- Predominantemente en forma dimerica, por la unión a la cadena J
- Permite su asociación con el receptor de inmunoglobulina polimérica (pIgR)
- Favorece transcitosis de IgA hacia la luz a través de CE
- Componente secretor confiere propiedades mucofilicos



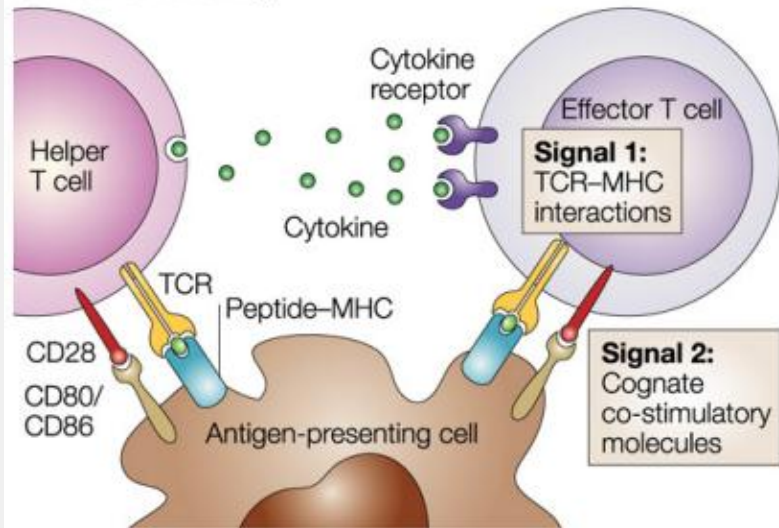
Mecanismos efectores



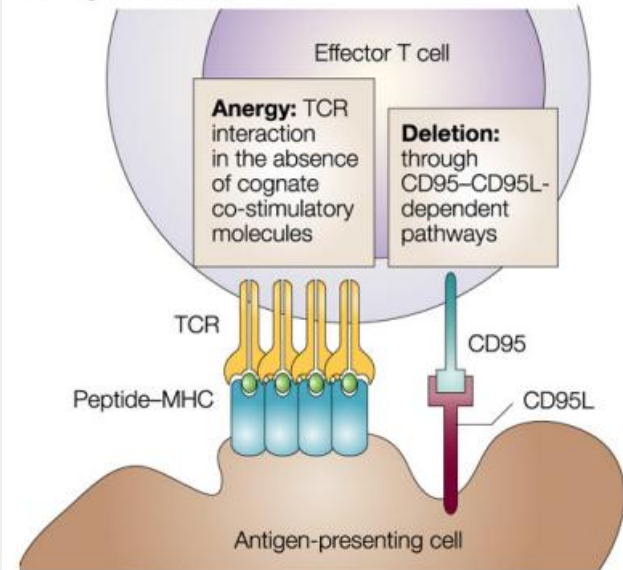
- Exclusión antigénica, impide la entrada de antígenos
- Expulsa antígenos de la lámina propia utilizando en transporte a través del receptor de Ig polimérica
- Neutraliza la replicación de virus y Ag pro-inflamatorios por promover su exporte
- Incapacidad para activar complemento
- Favorece la formación de “biofilm” que permite crecimiento de comensales y atenúa patógenos

Tolerancia oral

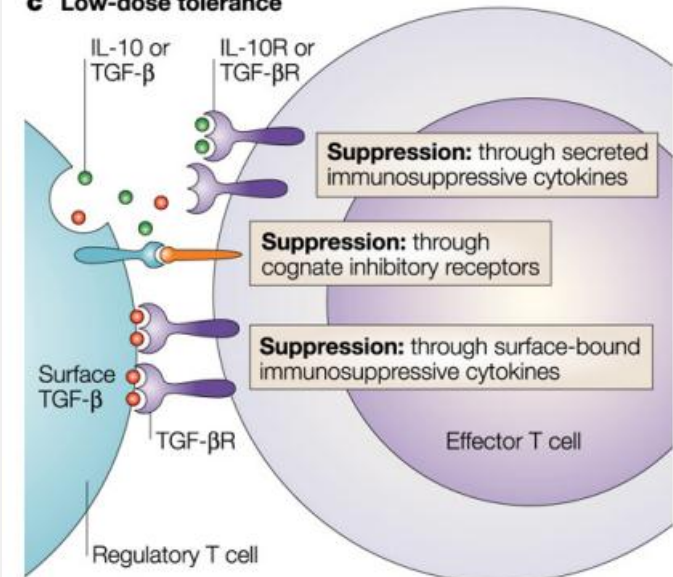
a Active immunity



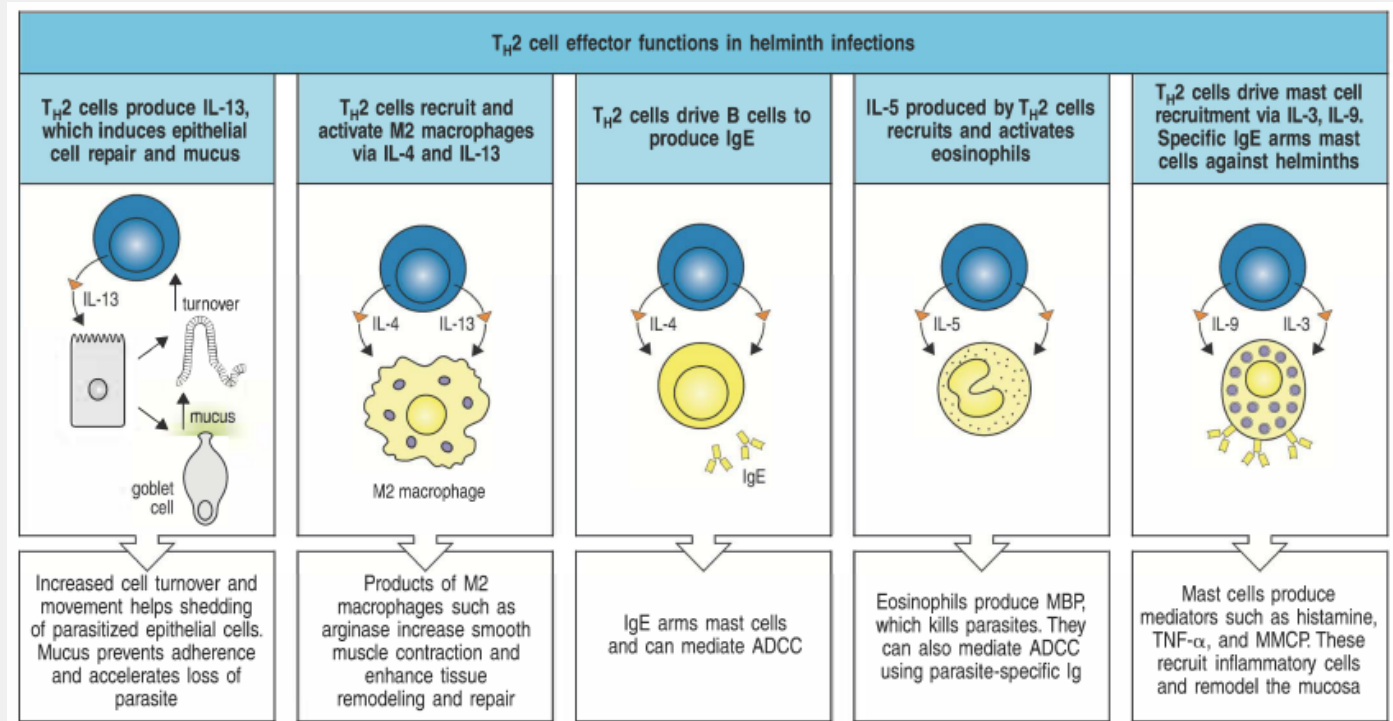
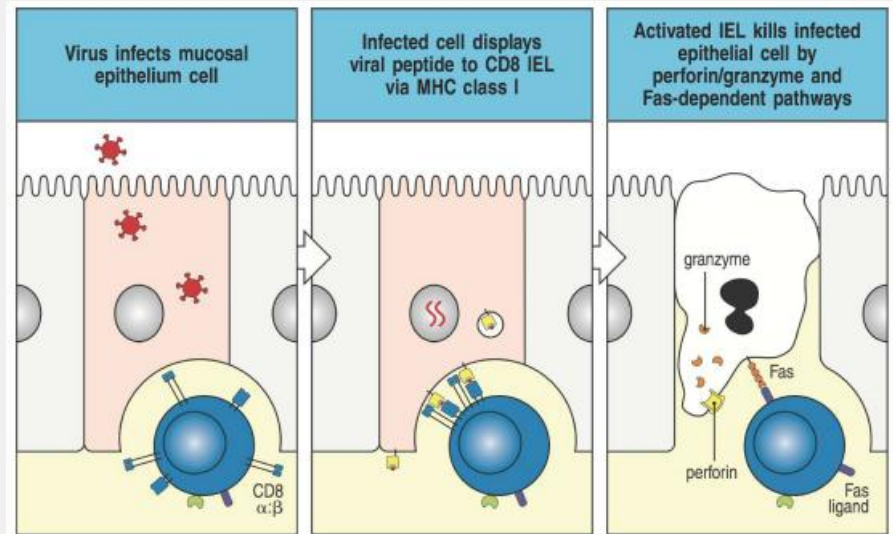
b High-dose tolerance



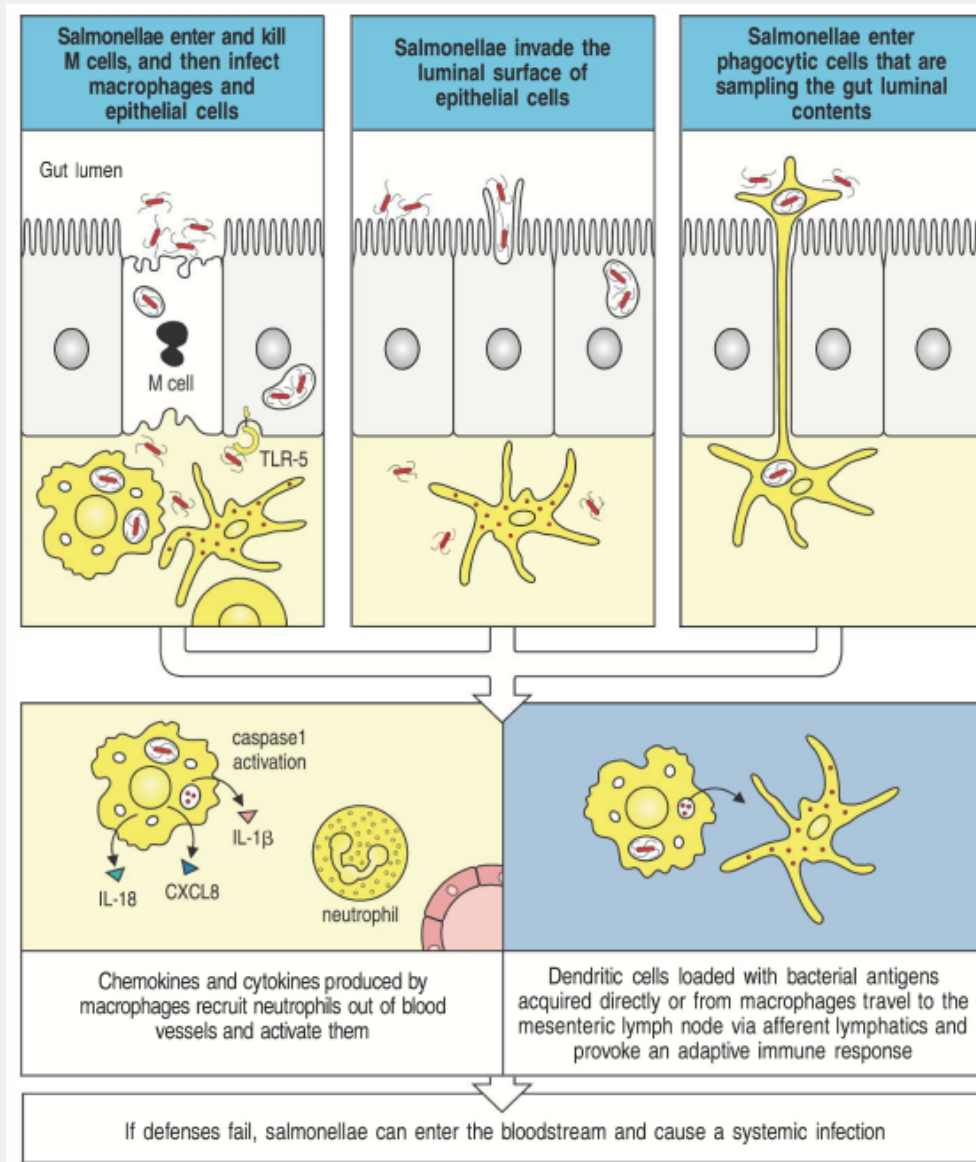
c Low-dose tolerance



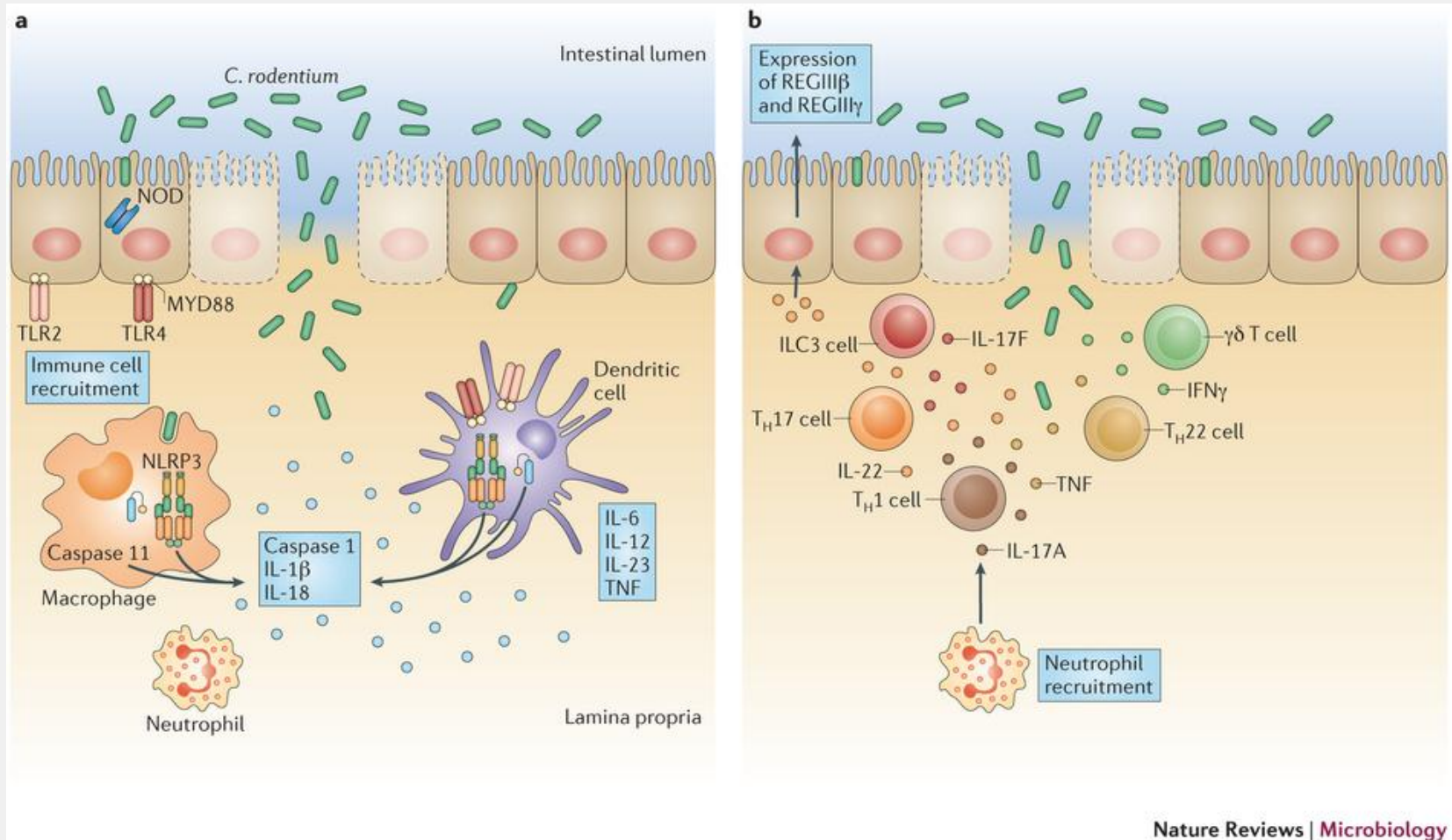
Respuesta frente a virus y helmintos



Respuesta frente a bacterias patógenas

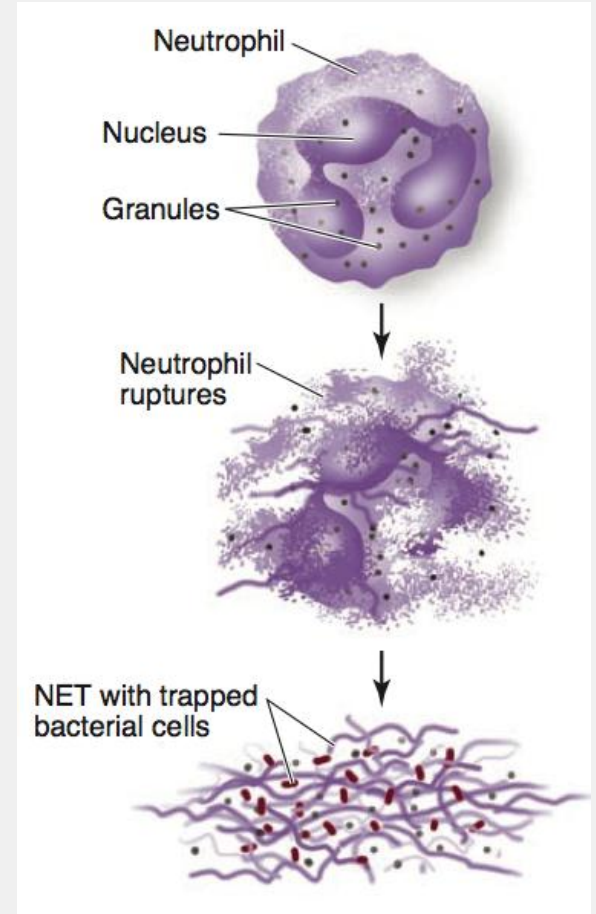
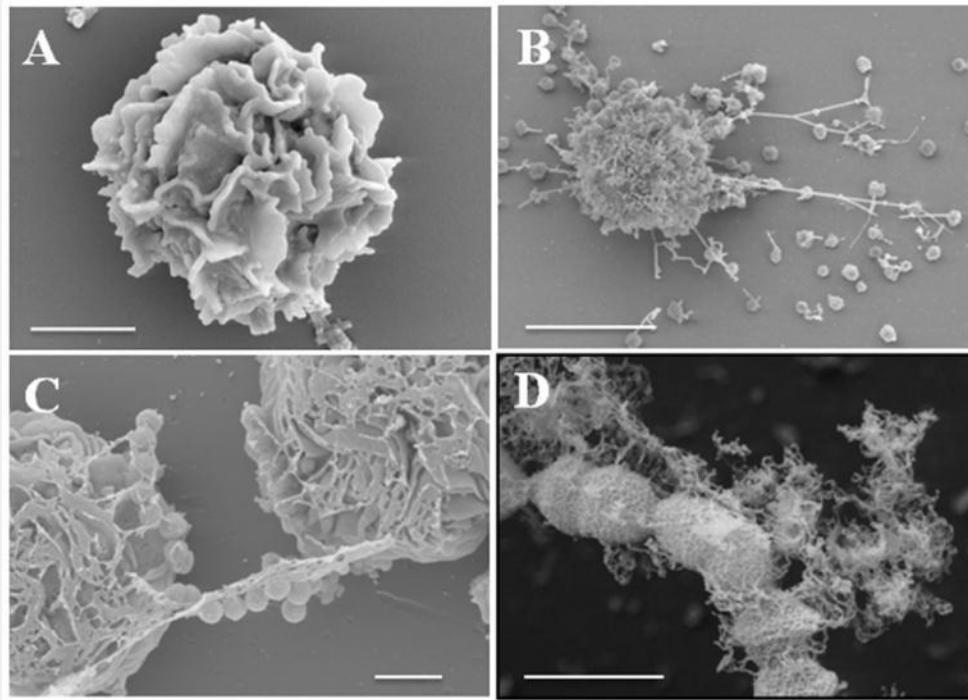


Rol del neutrófilo en la resolución de infecciones



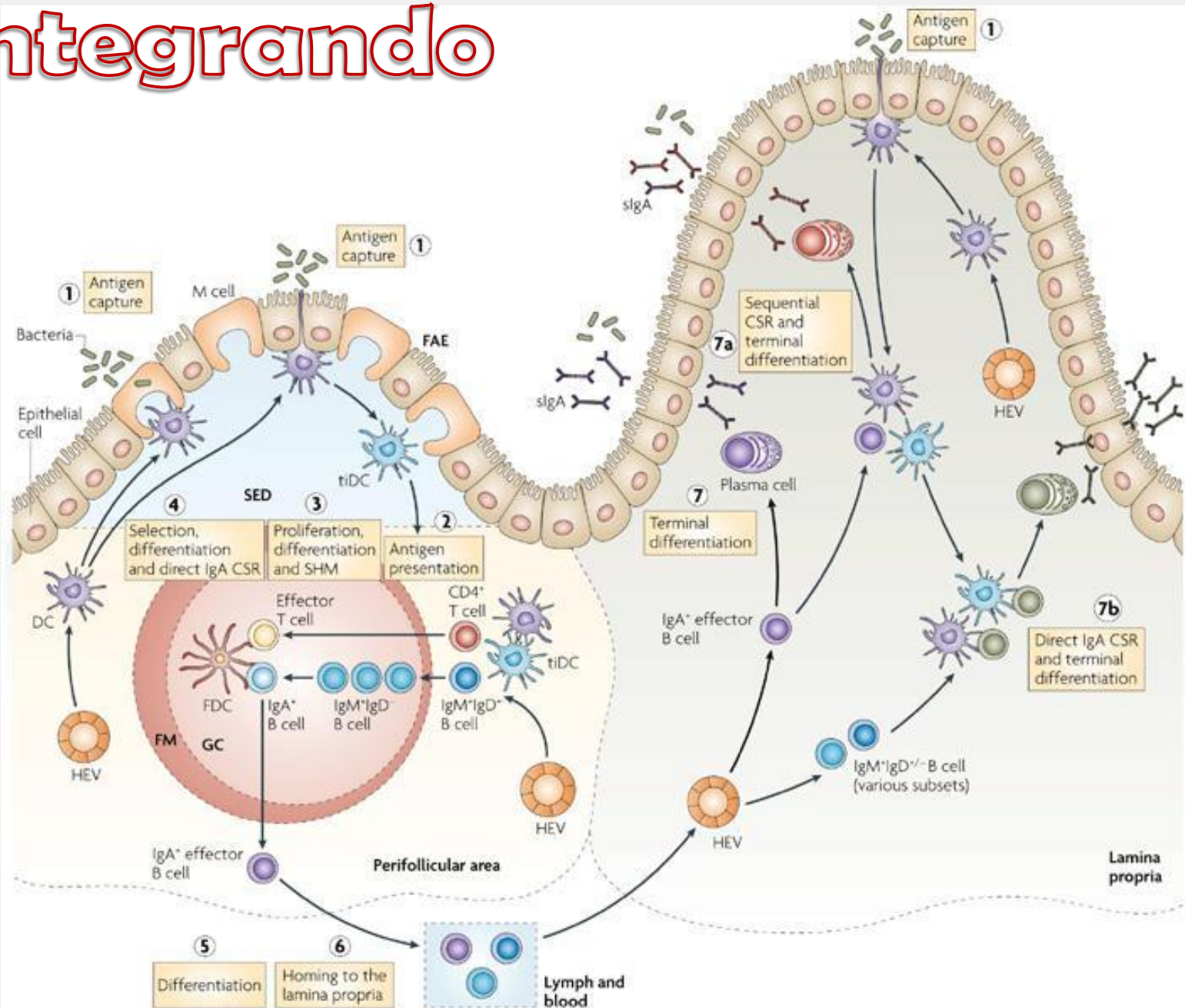
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NET = NOS EXPLOTAMOS TODOSSSSSS

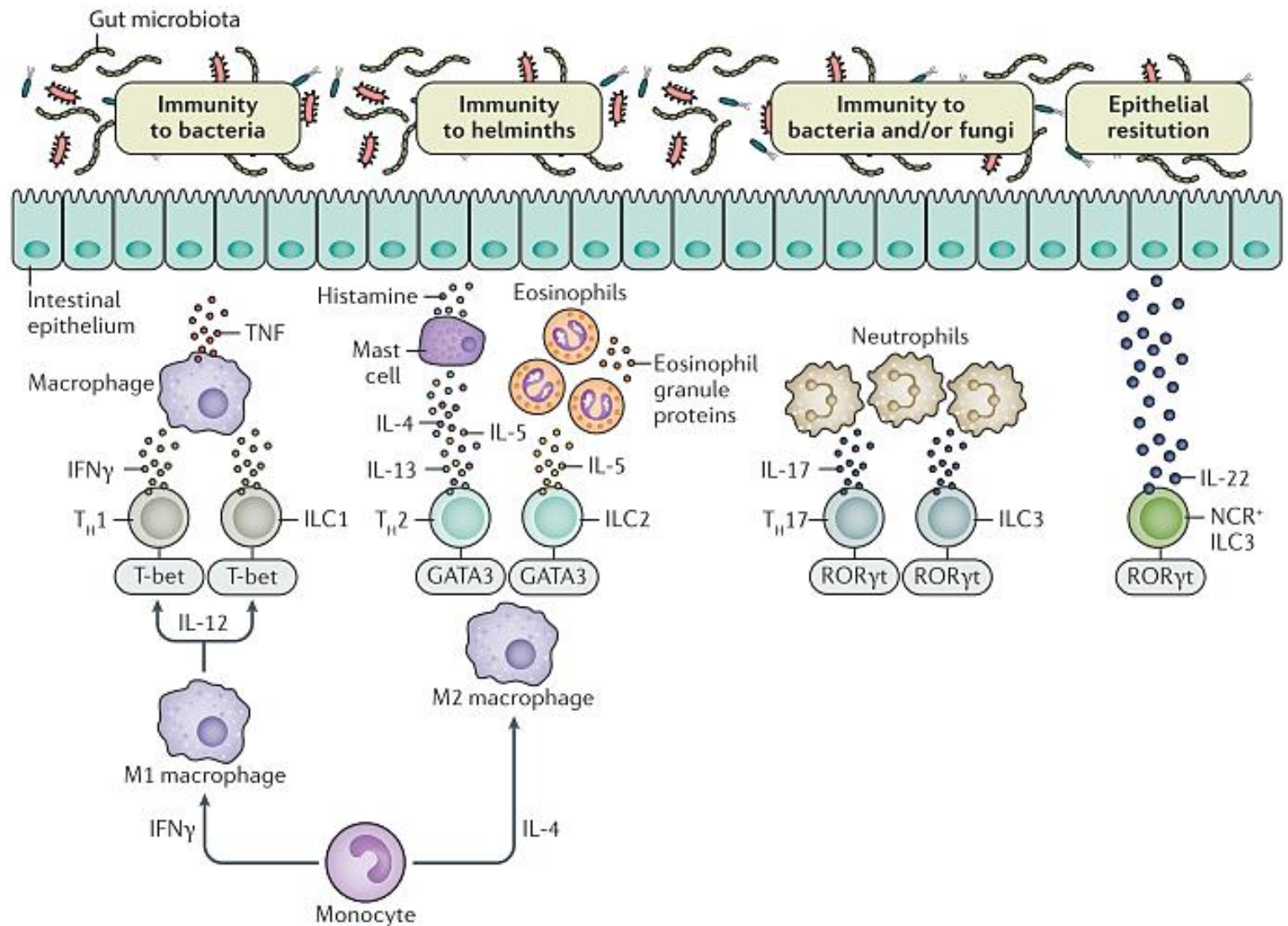


- NET: Neutrophil extracellular traps

Integrando



Integrando



¡Pregunten Ahora o Callen Para Siempre!



Guillermo Teran-Angel
guillermondi@gmail.com
<http://guillermo.vv.si>

Actividad adicional

- Una de las principales puertas de entrada de los agentes infecciosos son las mucosas. Muchos virus y bacterias pueden penetrarlas y posteriormente invadir otros tejidos, siempre y cuando logren vencer las barreras impuestas por el sistema inmune
 - ✓ Describa que elementos de la respuesta inmune están presentes en el sistema inmune de las mucosas
 - ✓ Describa el mecanismo de procesamiento y presentación antigénica llevados a cabo en el tejido linfoide asociados a las mucosas y que elementos participan
 - ✓ ¿Cuál es el papel de la inmunoglobulina A secretora?
 - ✓ ¿Cómo evidenciaría la presencia de IgA secretora en las mucosas?
 - ✓ ¿Cuál es el papel del sistema inmune asociado a las mucosas en la tolerancia inmunológica?
 - ✓ ¿Qué utilidad clínica tiene ésta función?



¡Gracias por la atención!