Imunologia de Mucosa

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Instituto de Ciências Biomédicas – Universidade de São Paulo

BMI0103 -2019

Como está organizado o sistema imunológico pelo corpo ?

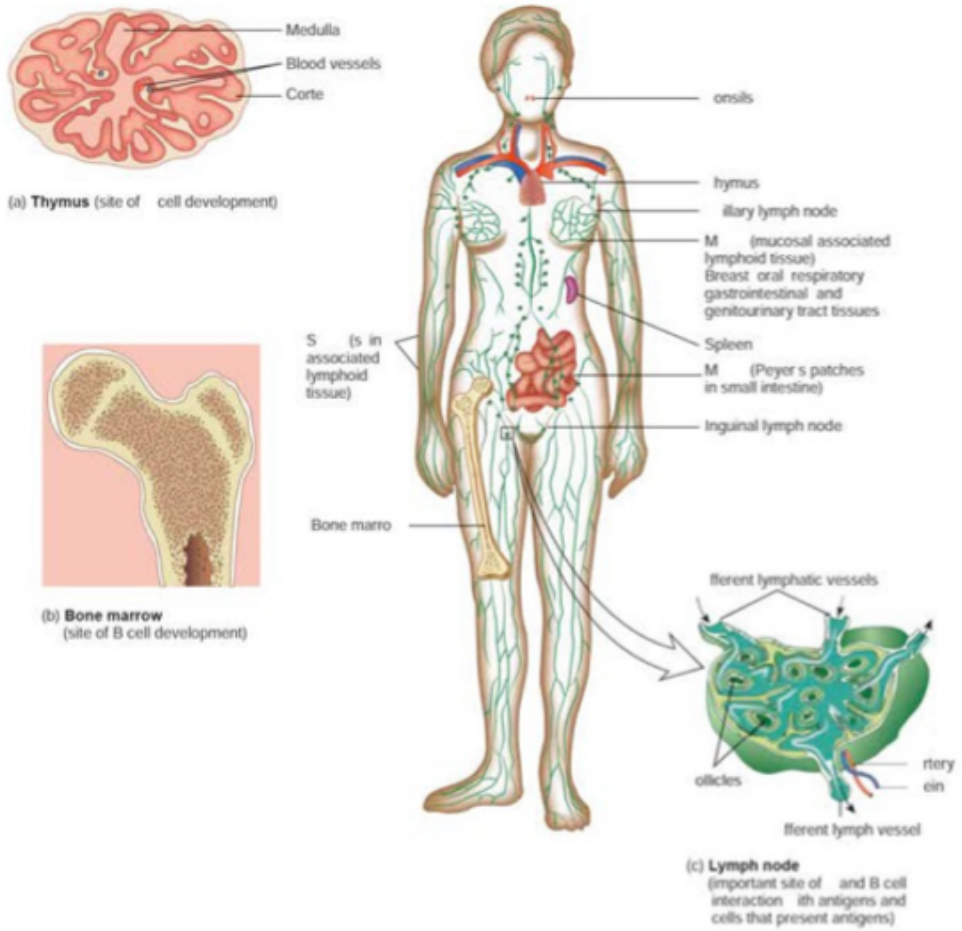
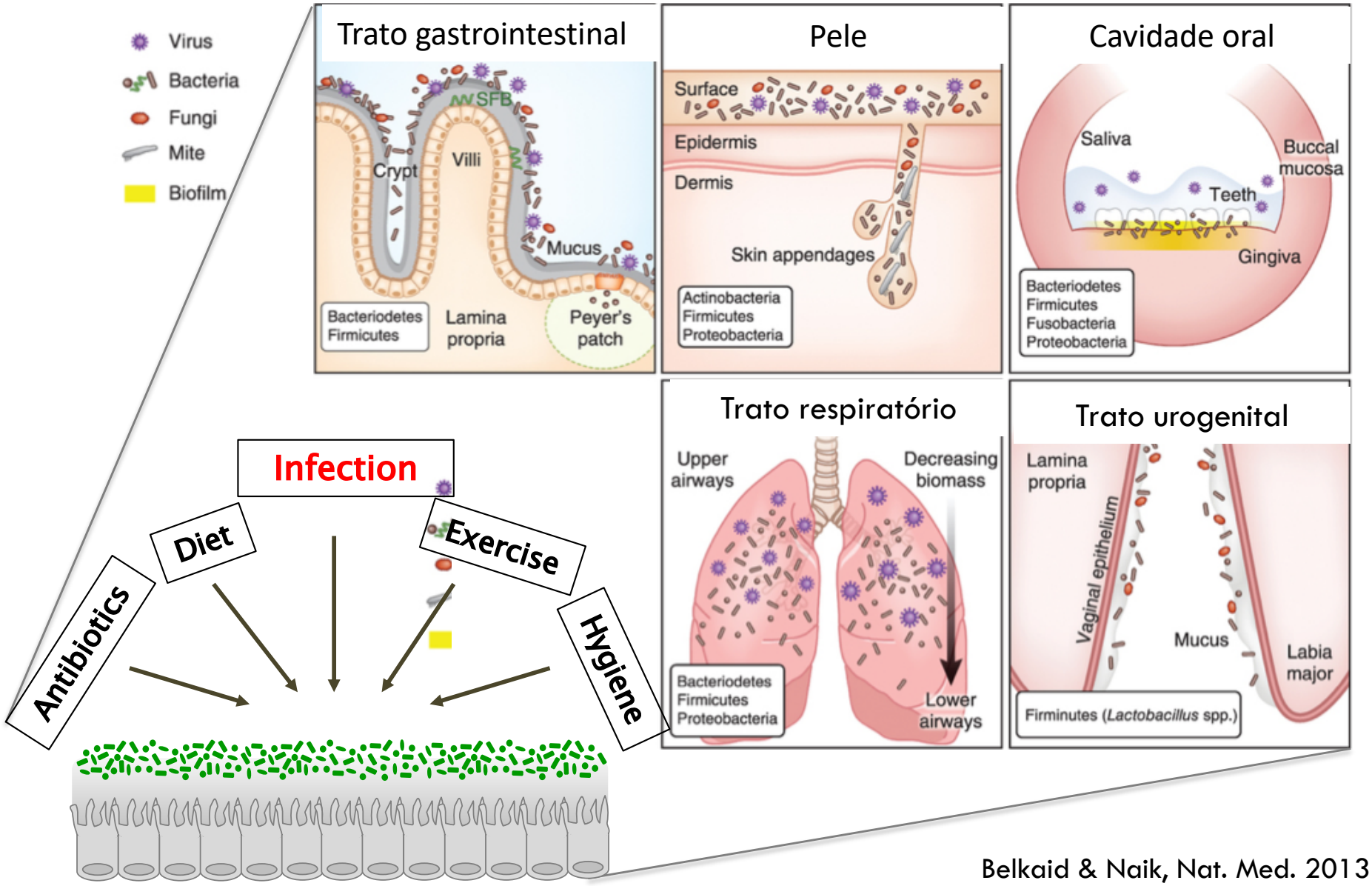


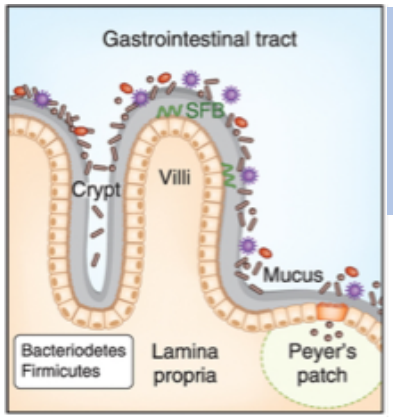
Figure 13.2: The distribution of Lymphoid tissues in the body

Tecidos de barreira

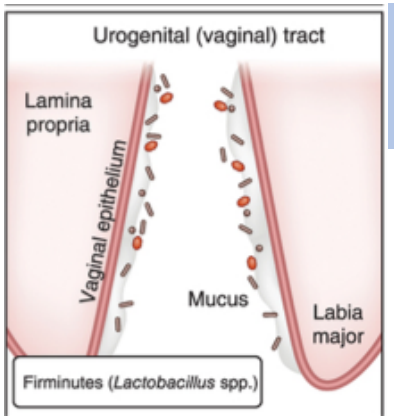


Belkaid & Naik, Nat. Med. 2013

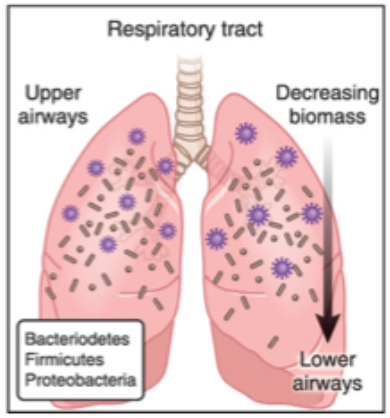
Porque estudar o Sistema Imune de mucosa?



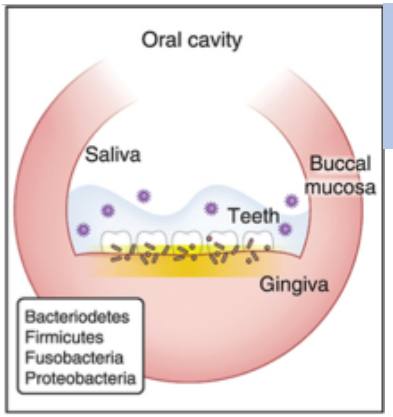
- Absorção de nutrientes
- Tolerância
- Superfície (200m^2)



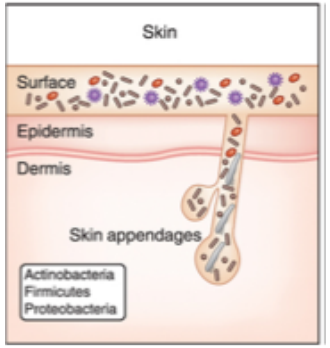
- Reprodução
- Exposição ambiental



- Respiração
- Exposição a antígenos ambientais

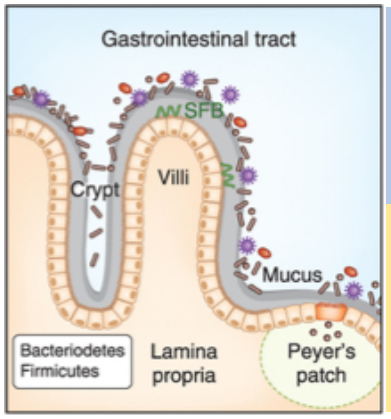


- Digestão
- Exposição ambiental



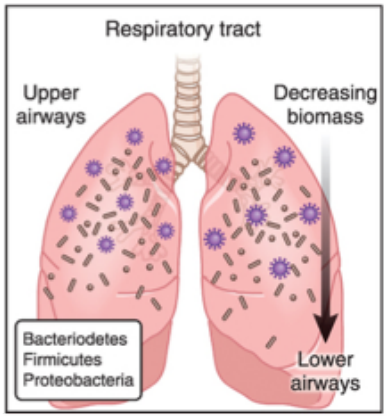
- Superfície
- Exposição ambiental

Porque estudar o Sistema Imune de mucosa?



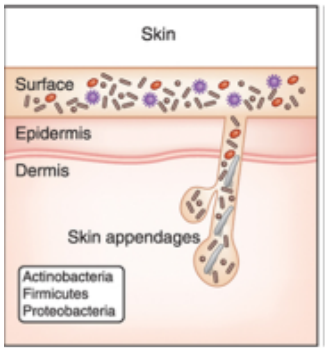
- Absorção de nutrientes
- Tolerância
- Superfície (200m^2)

- Tonsilas, linfonodos dren.
- Placas de Peyer
- Lâmina própria, GALT



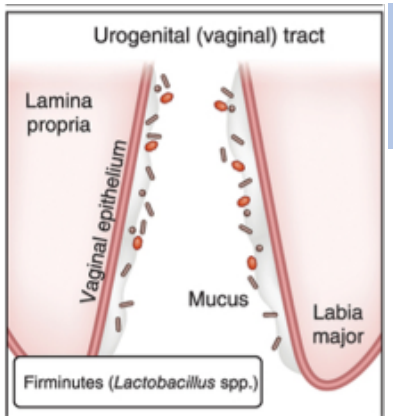
- Respiração
- Exposição a antígenos ambientais

- Tonsilas
- Adenóides
- Folículos linfóides associados

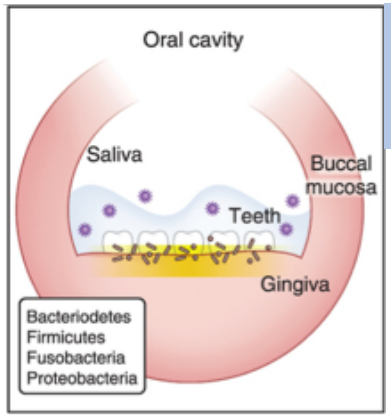


- Superfície
- Exposição ambiental

- Epitélio estratificado queratinizado
- Aglomerados celulares



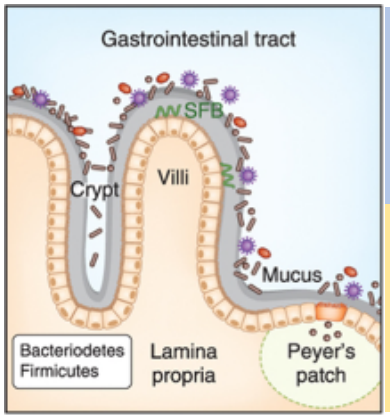
- Reprodução
- Exposição ambiental



- Digestão
- Exposição ambiental

GALT: Gut-associated lymphoid tissue
BALT: Bronchial-associated lymphoid tissue
NALT:-Nasal-associated lymphoid tissue

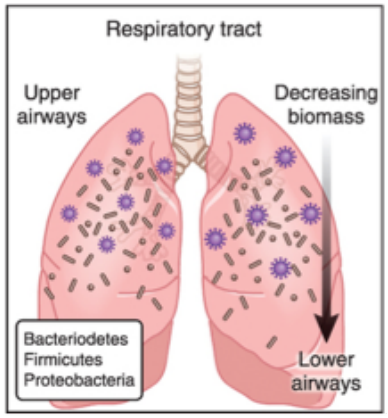
Porque estudar o Sistema Imune de mucosa?



- Absorção de nutrientes
- Tolerância
- Superfície (200m^2)

- Tonsilas
- Placas de Peyer
- Lâmina própria, GALT

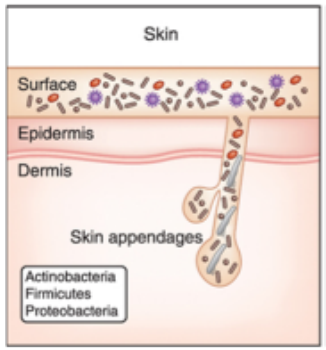
- Epitélio
- Muco e peptídeos antimicrobianos
- Células M
- Células de Paneth
- Células B (IgA e IgM)
- Células Dendríticas especializadas



- Respiração
- Exposição a antígenos ambientais

- Tonsilas
- Adenóides
- Folículos linfóides associados

- Epitélio ciliado
- Muco e defensinas
- Células M
- Células B (IgA, IgM e IgG)



- Superfície
- Exposição ambiental

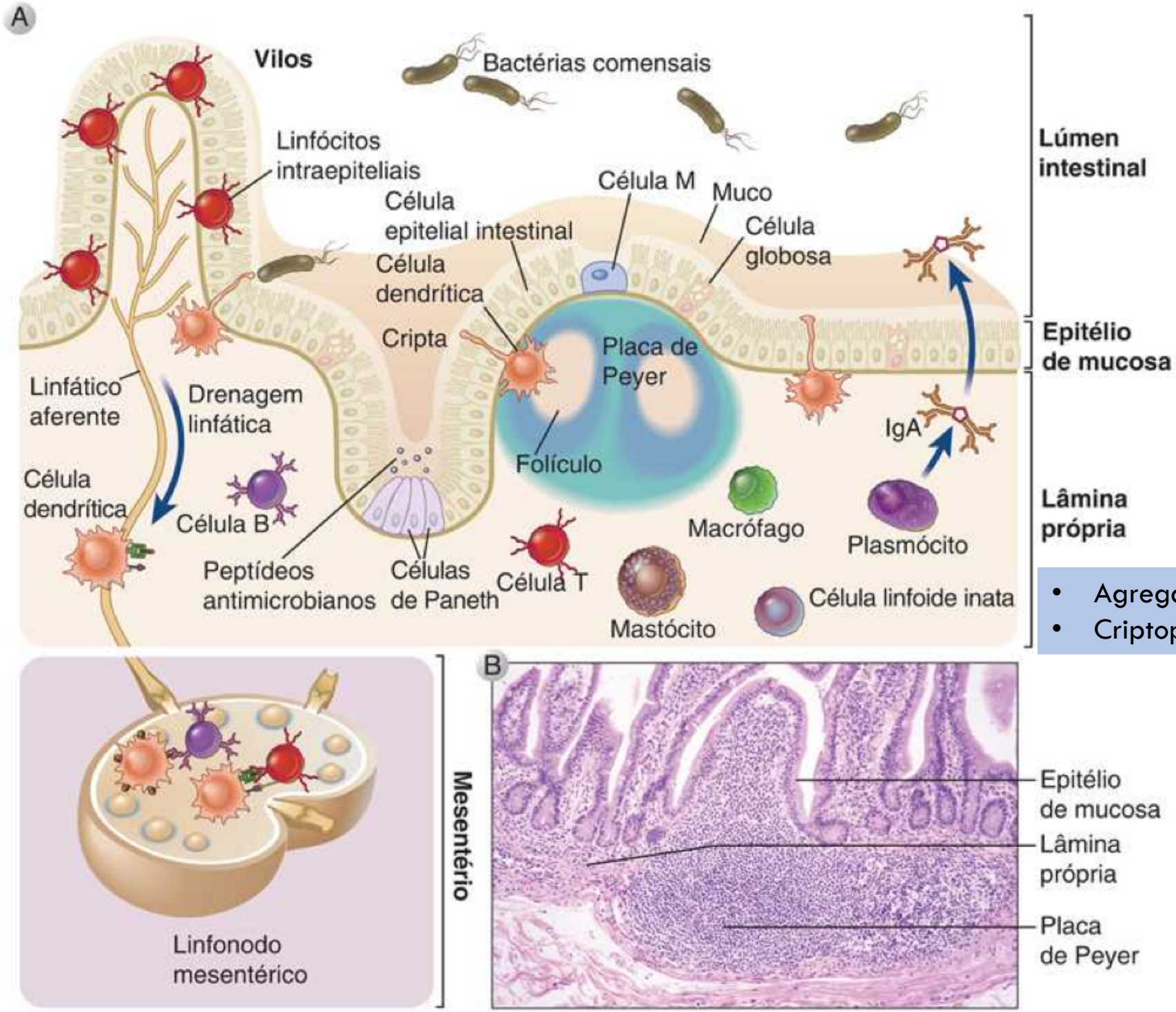
- Epitélio estratificado queratinizado
- Aglomerados celulares

- Queratinócitos
- Células de Langerhans
- Células Dendríticas especializadas

Porque estudar o Sistema Imune de mucosa?

Números de Linfócitos em Diferentes Tecidos

Baço	70×10^9
Linfonodos	190×10^9
Medula óssea	50×10^9
Sangue	10×10^9
Pele	20×10^9
Intestinos	50×10^9
Fígado	10×10^9
Pulmões	30×10^9



- Agregados linfóides
- Criptoplacas

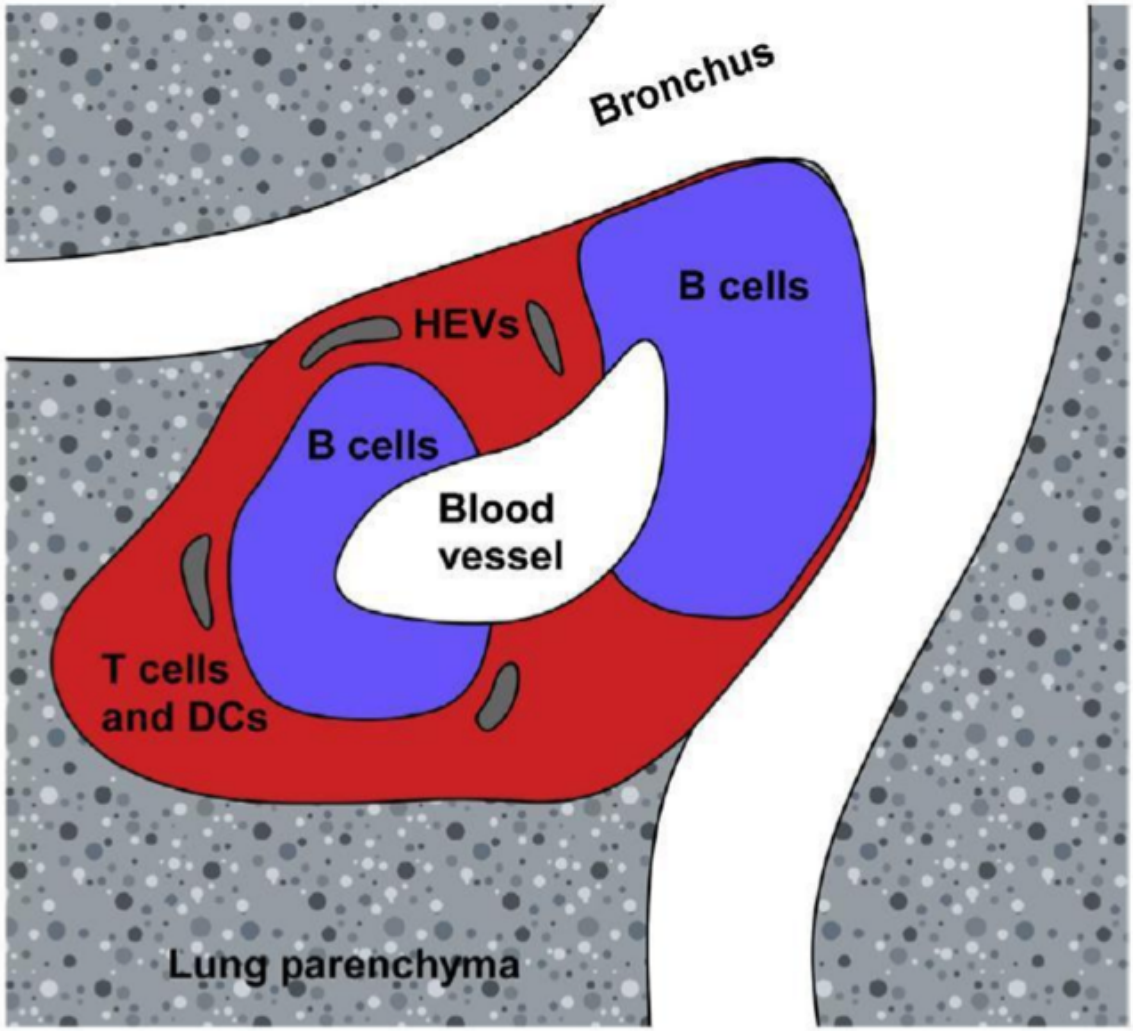
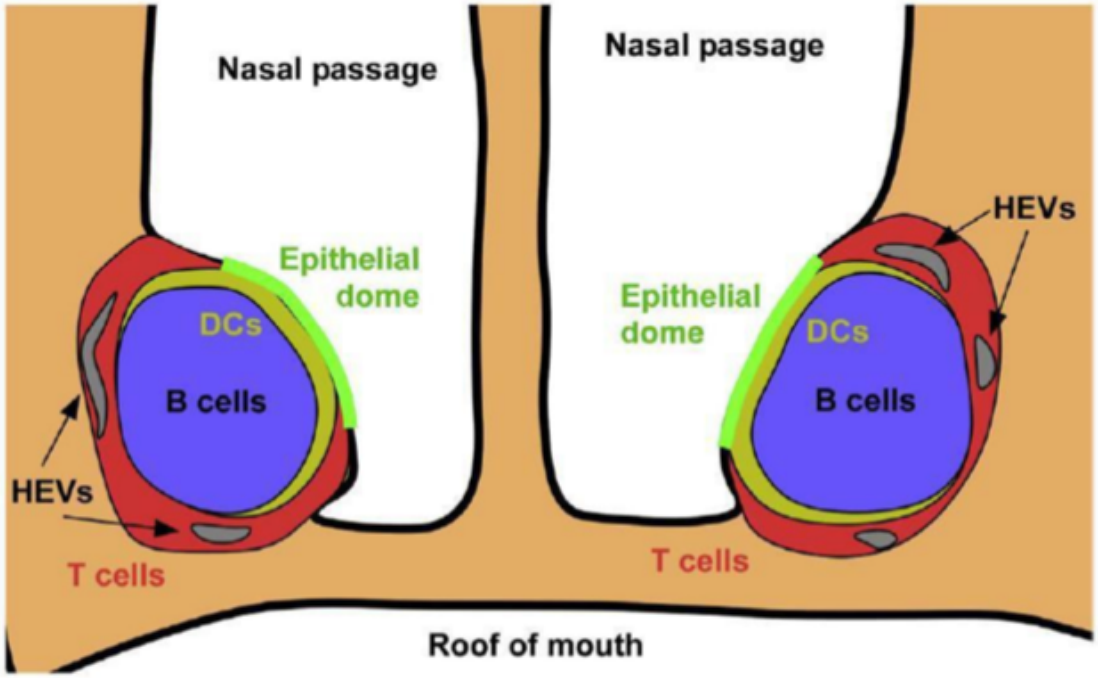


FIGURE 2 Structure of BALT. Although the structure of BALT varies widely, it is often observed along the major airways in the lung and typically fills the perivascular space surrounding small pulmonary arteries. B cell follicles (blue) are observed underneath the bronchial epithelium, but also away from the epithelium as well. T cell areas (red) surround the B cell follicles and may fill in the space between follicles in larger areas of BALT. HEVs (gray) are observed surrounding the B cell follicles in the T cell zone. (See color plate section.)

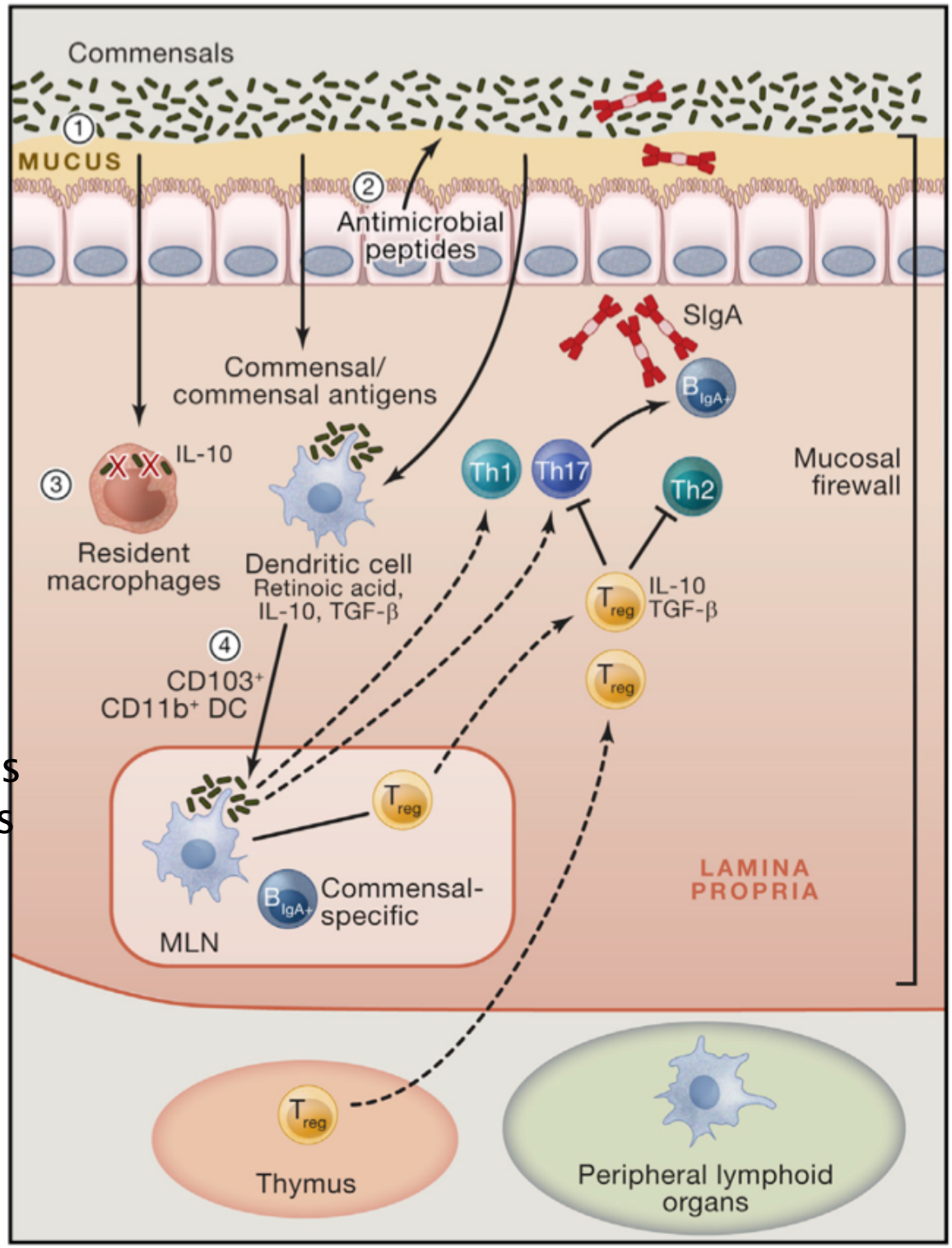
FIGURE 1 Cross-section of murine NALT. NALT is seen in cross-section as a single B cell follicle, but consists of a series of B cell follicles that run lengthwise along the nasal passages. The B cell follicle (blue) is situated underneath a dome epithelium (green) that is underlined with a thin layer of DCs (yellow) that are poised to receive antigens transported across the epithelium. The T cell area (red) surrounds the B cell follicle and may also be between B cell follicles. HEVs (gray) are found in the T cell zone and at the border of the T and B cell areas. (See color plate section.)



Componentes

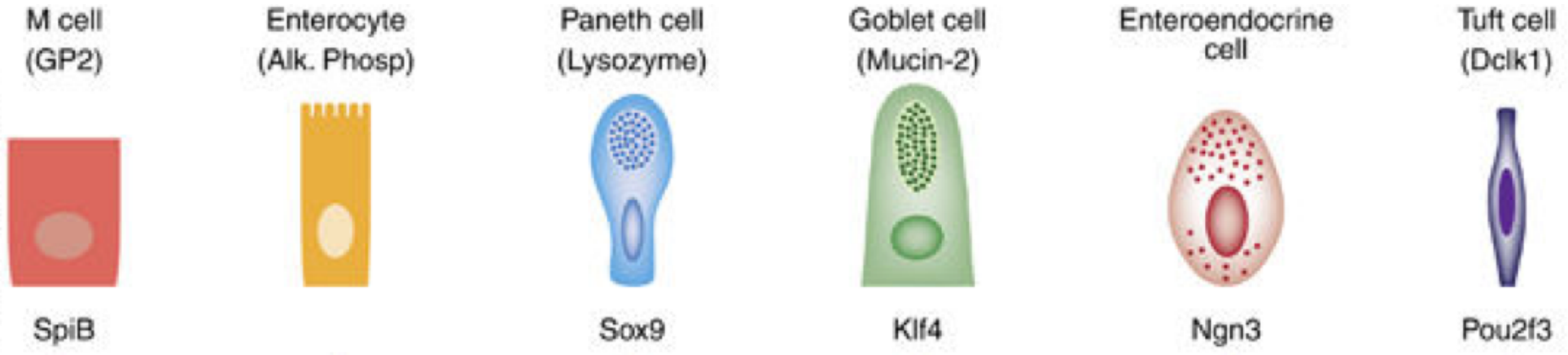
Barreira Física
- Epitélio/ Junções celulares
- Muco
- Peptídeos antimicrobianos
- *Epitélio Ciliado
- *pH

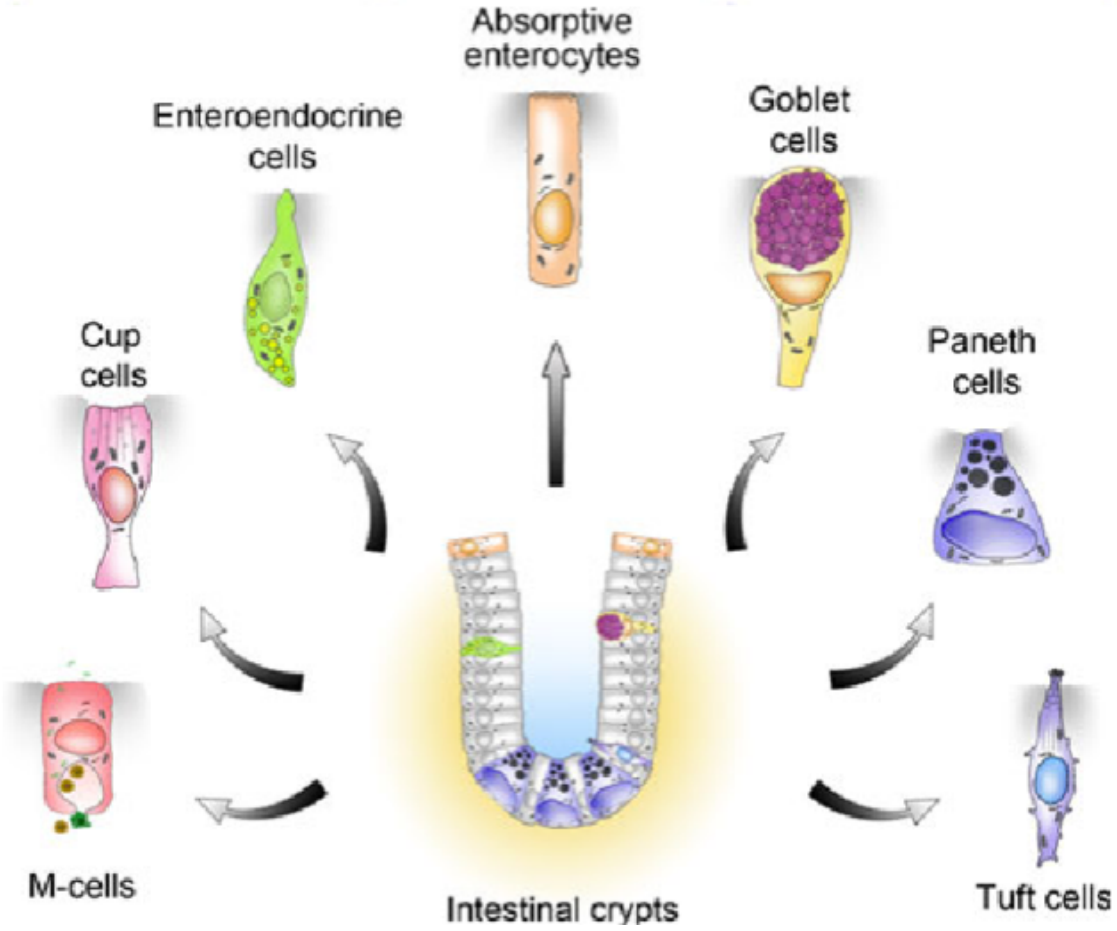
Barreira ativa
- Células dendríticas especializadas
- Células T efetoras especializadas (Th17 e Treg)
- IgA
- Células Inatas (macrófagos e ILCs)
- Microbiota



Cell 157, March 27, 2014

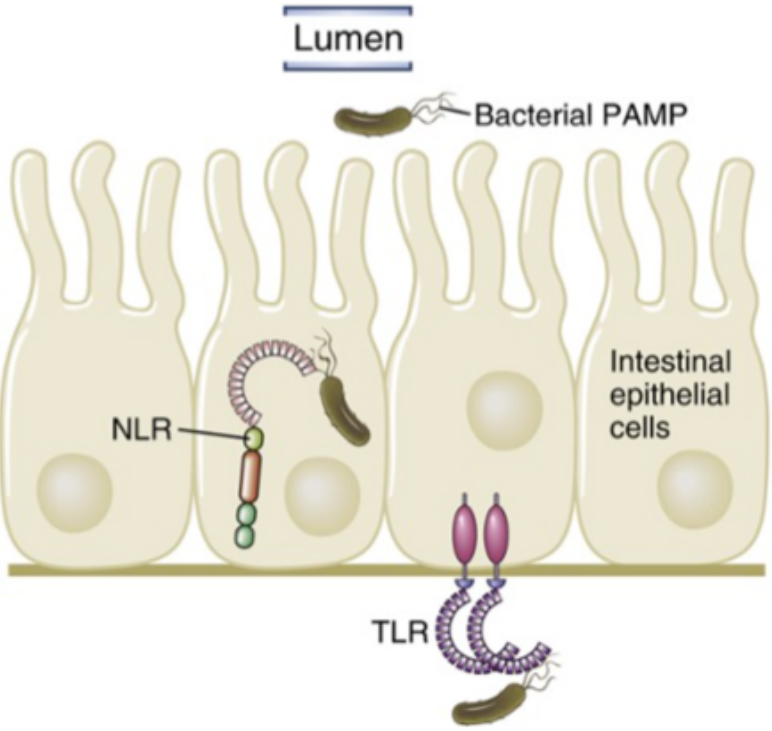
Epitélio


M cell
(GP2)
Enterocyte
(Alk. Phosp)
Paneth cell
(Lysozyme)
Goblet cell
(Mucin-2)
Enteroendocrine
cell
Tuft cell
(Dclk1)
SpiB
Sox9
Klf4
Ngn3
Pou2f3

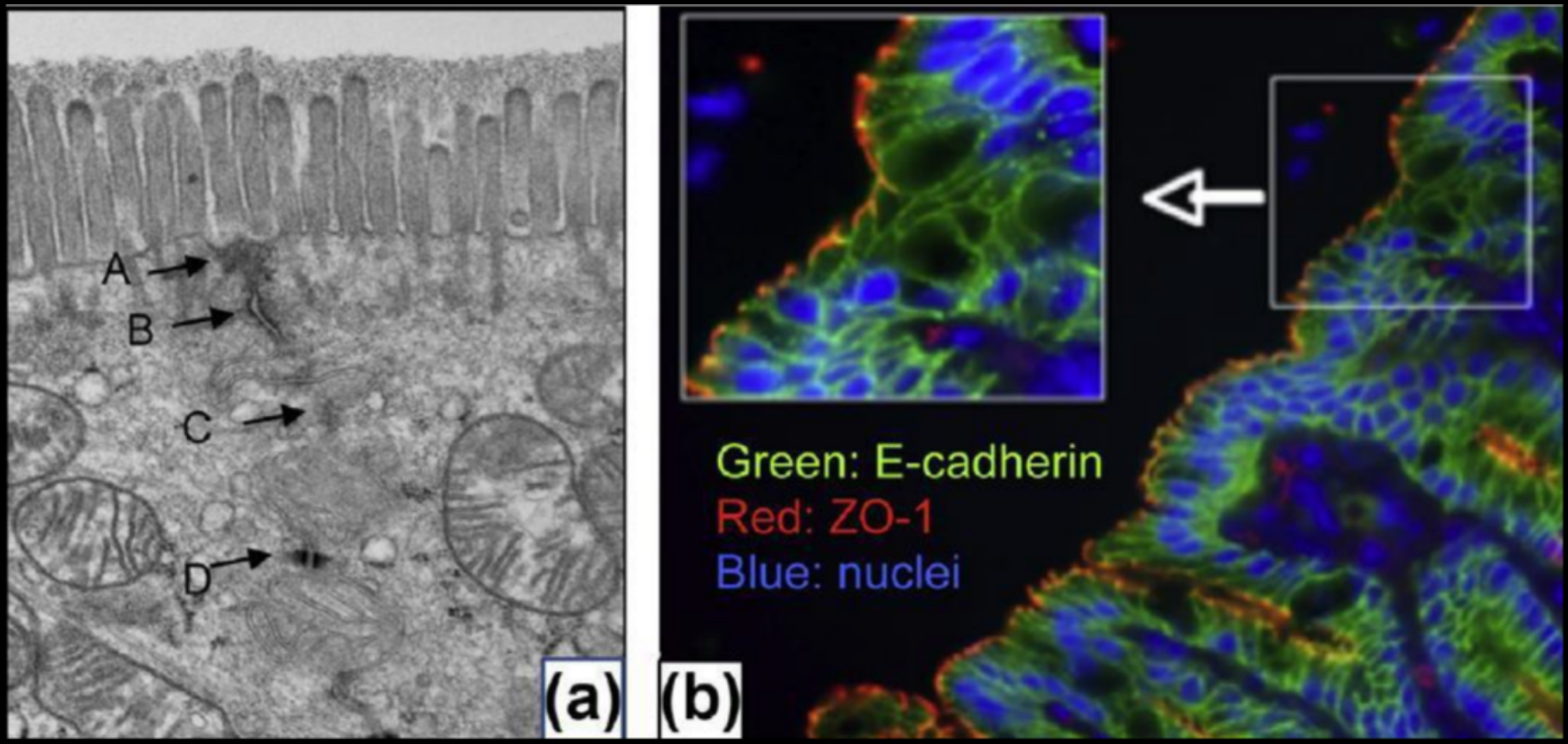

Absorptive
enterocytes
Enteroendocrine
cells
Goblet
cells
Cup
cells
Paneth
cells
M-cells
Intestinal crypts
Tuft cells

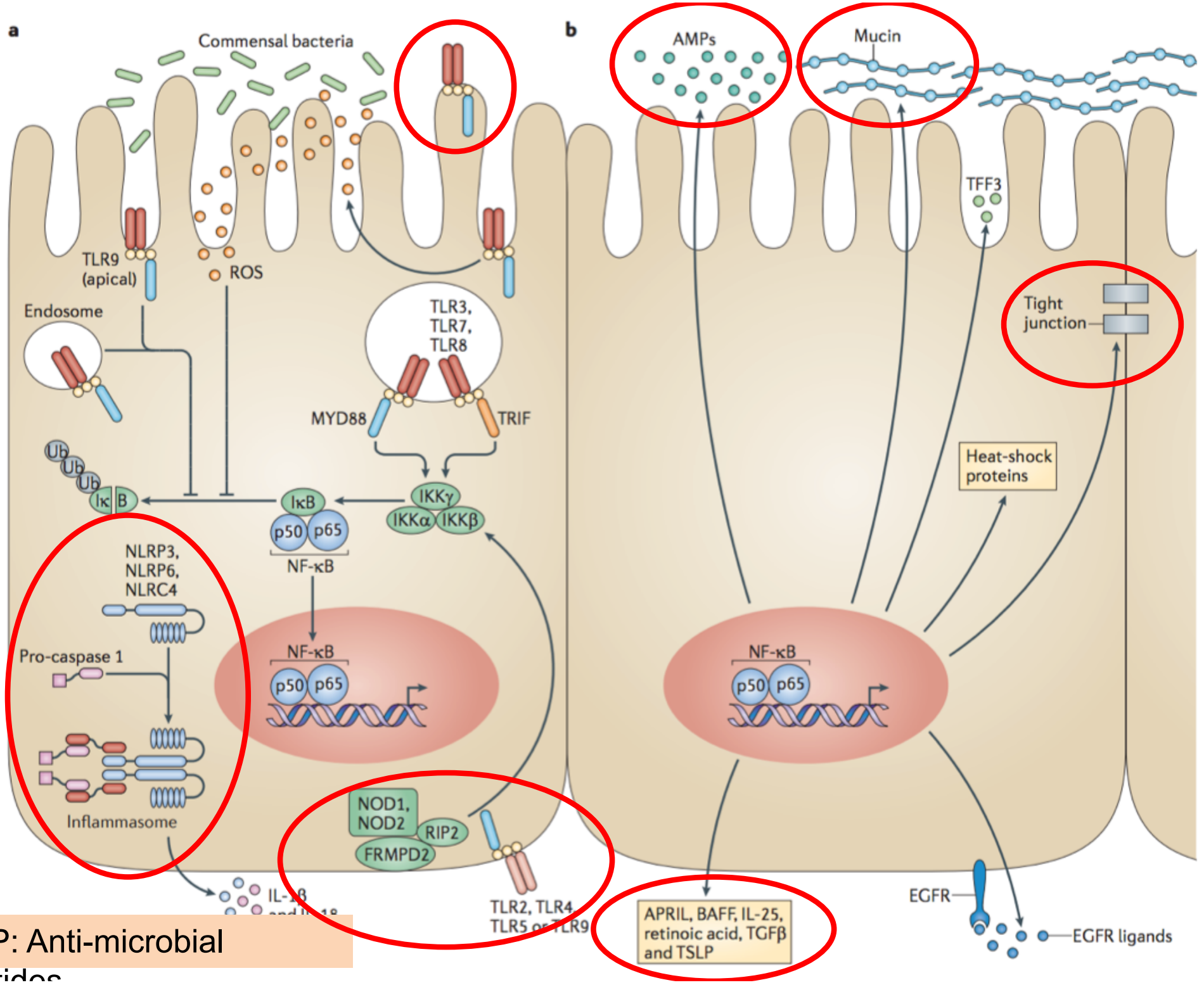
Epitélios

- Junções
- Microvilosidades
- Cílios
- Produção de peptídeos antimicrobianos: defensinas, catalecidinas e lectinas do tipo C
- Surfactantes (pulmão)
- Expressão de Receptores de reconhecimento de padrões moleculares

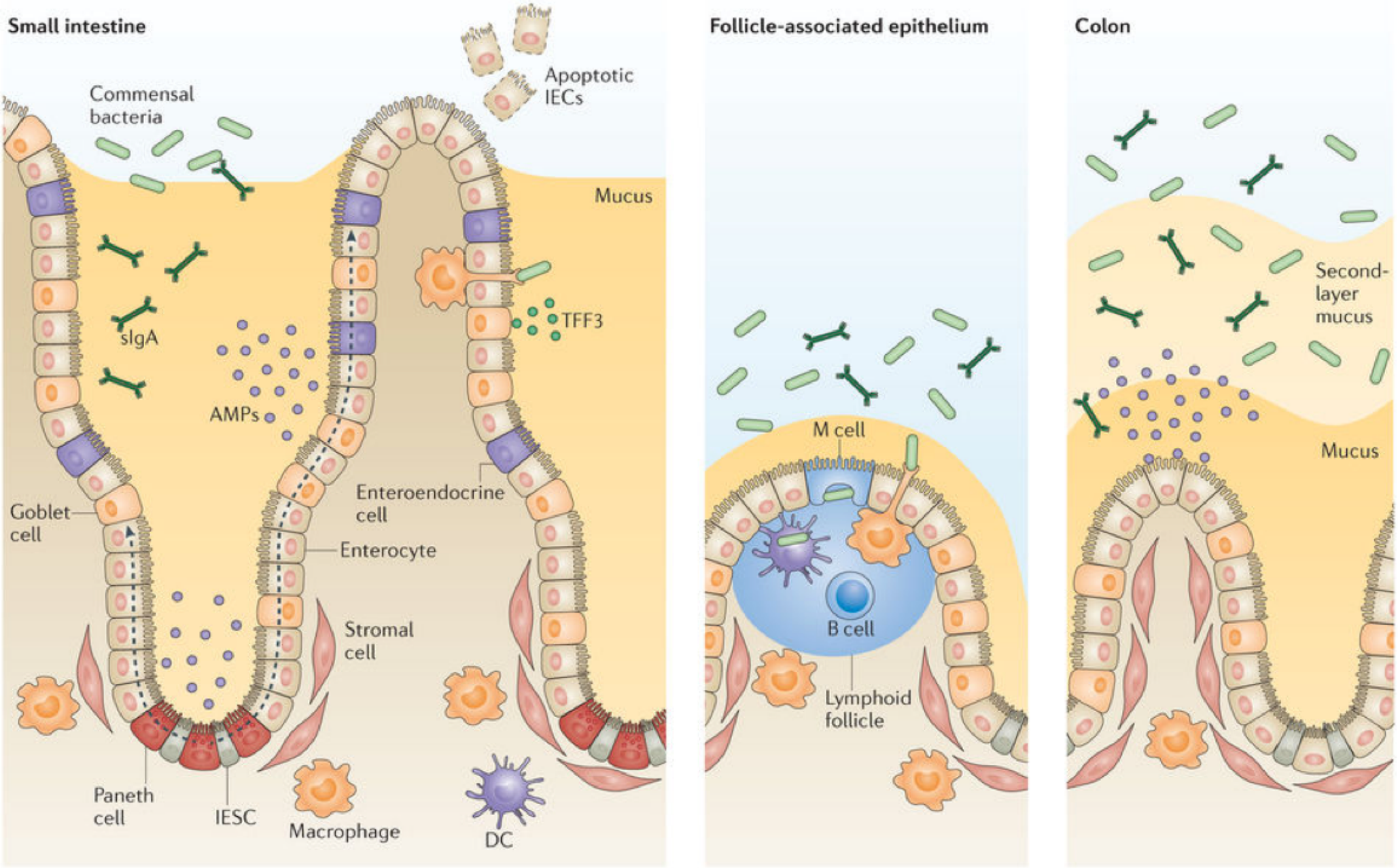


✓ IBD / Crohn


A
B
C
D
(a)
(b)
Green: E-cadherin
Red: ZO-1
Blue: nuclei

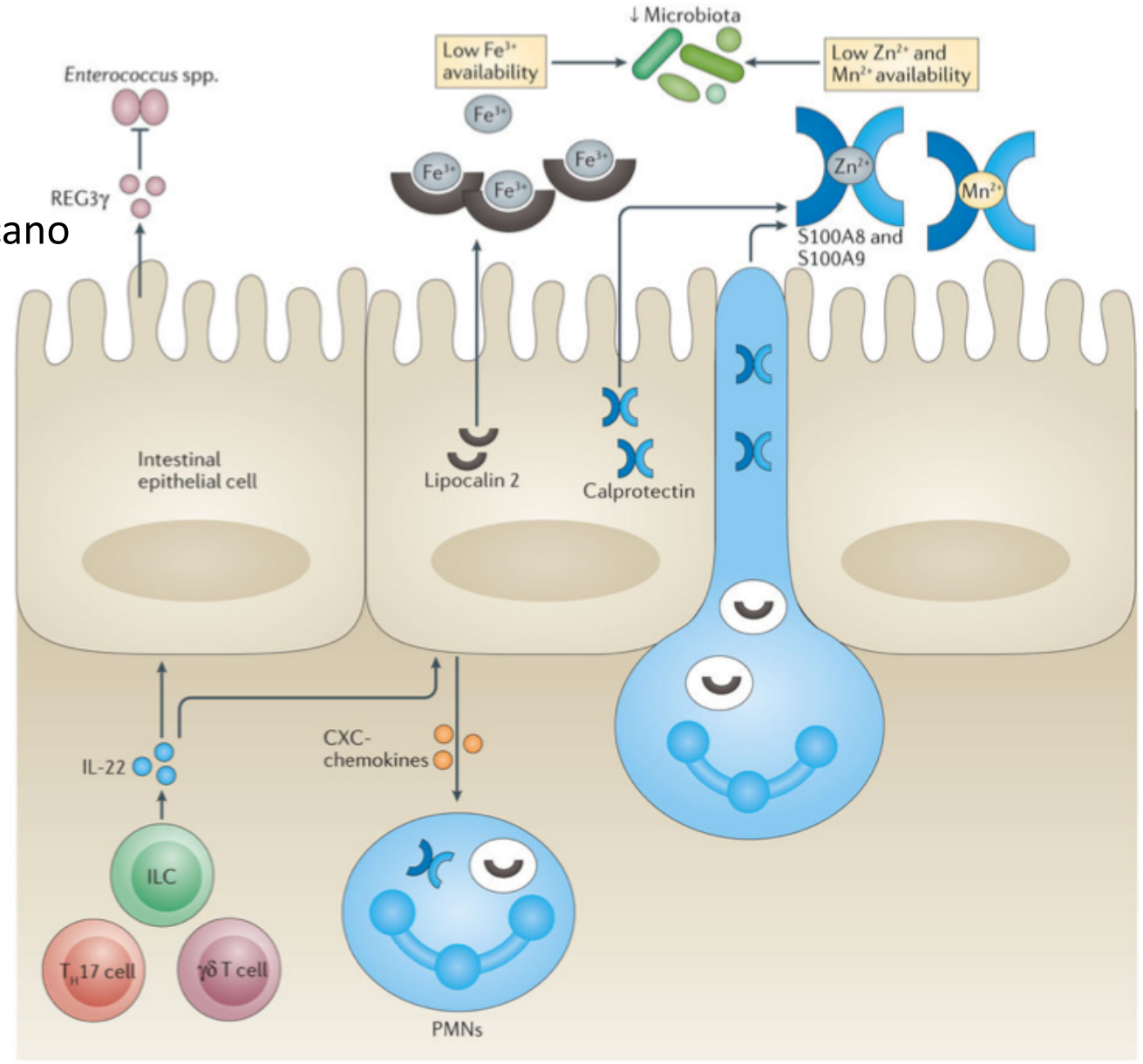


AMP: Anti-microbial peptides


Small intestine
Apoptotic IECs
Commensal bacteria
Mucus
sIgA
TFF3
AMPs
Enteroendocrine cell
Goblet cell
Enterocyte
Stromal cell
Paneth cell
IESC
Macrophage
DC
Follicle-associated epithelium
M cell
B cell
Lymphoid follicle
Colon
Second-layer mucus
Mucus

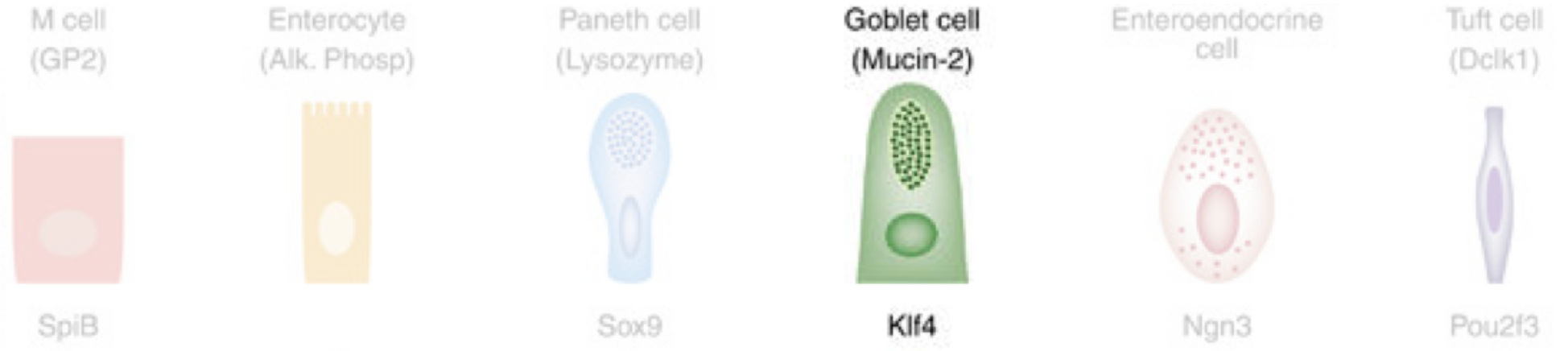
Peptídeos antimicrobianos

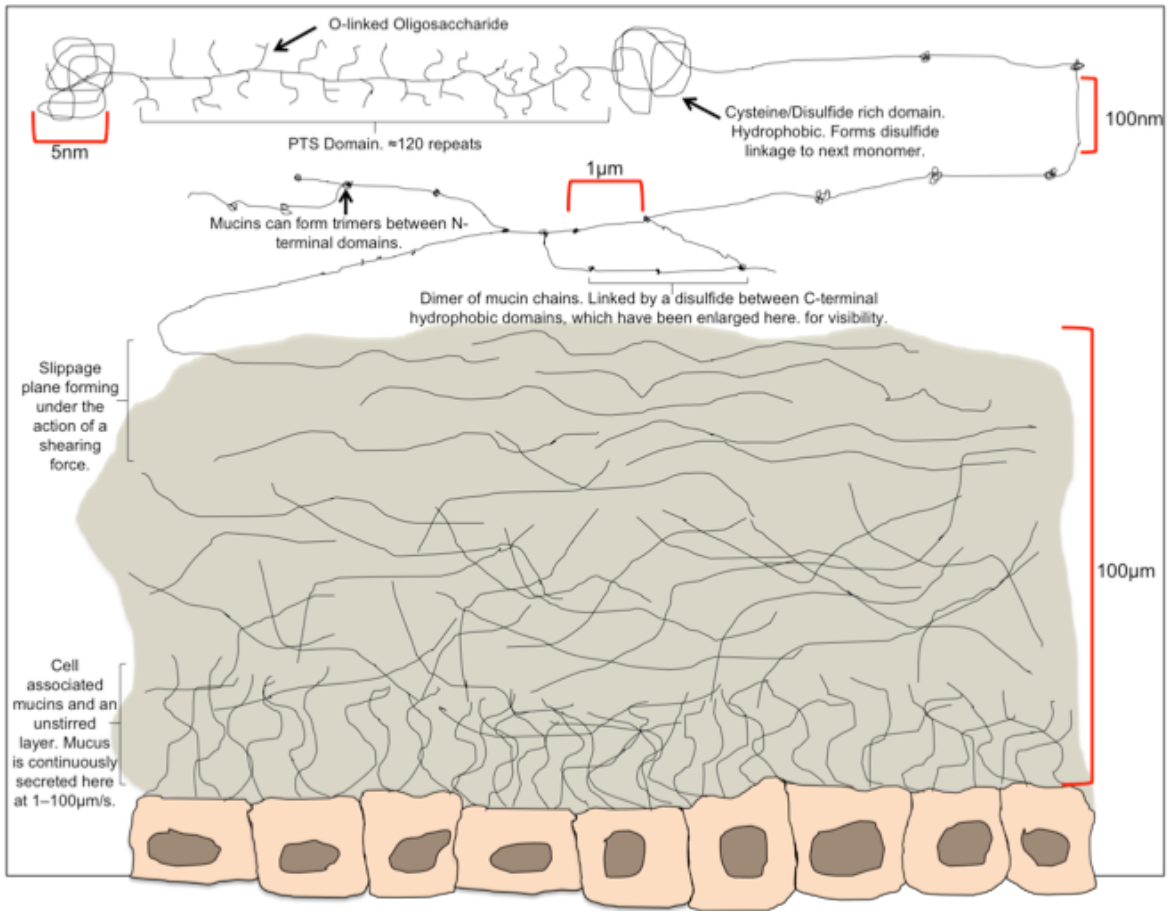
Liga peptideoglicano



Nature Reviews | Immunology

Epitélio: Muco





Mucins

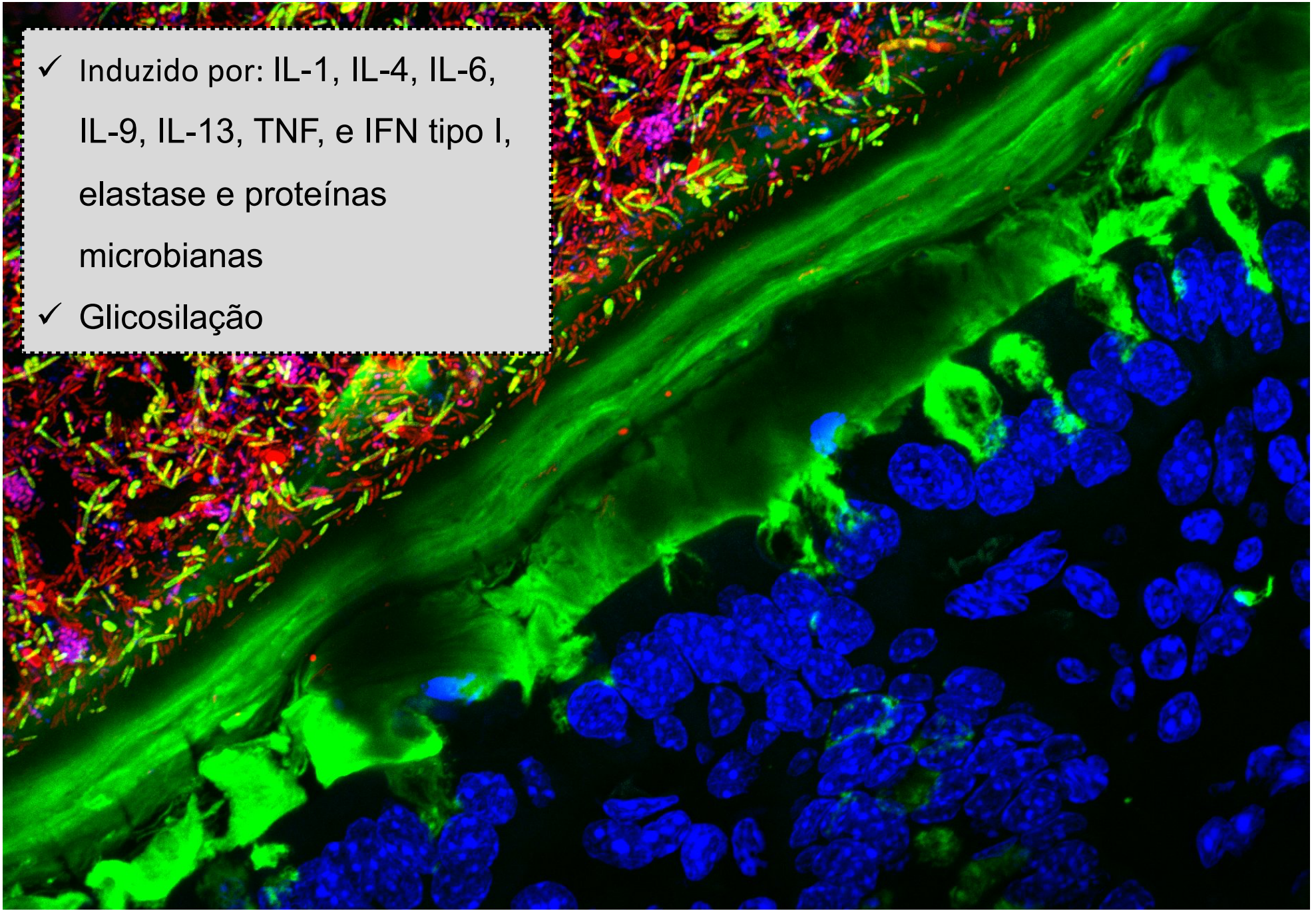
17 MUC

7 Muc = mucin

(Muc2, Muc5A,Muc5B, Muc6, Muc7, Muc8 Mucc19)

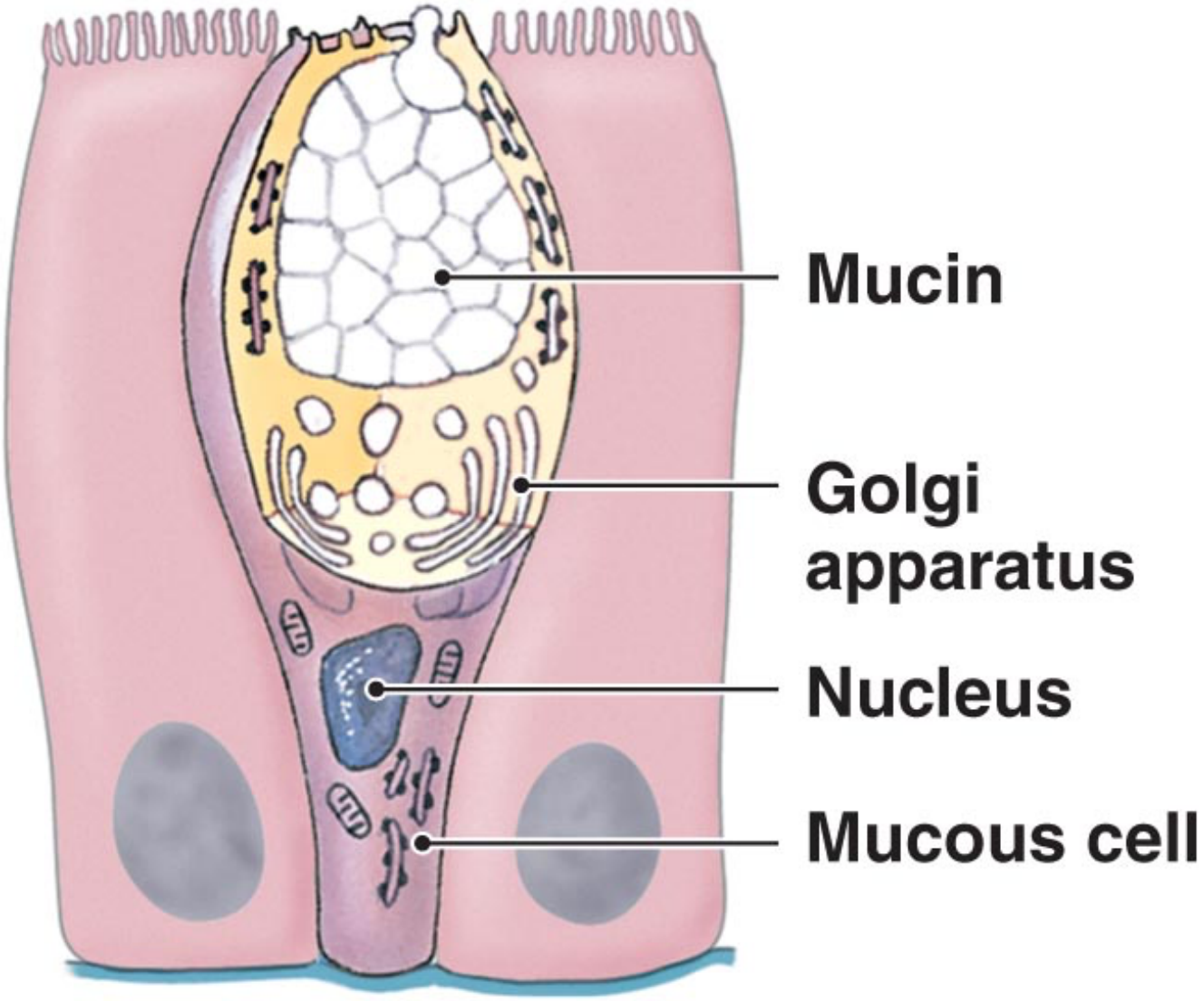
100-700um

Epitélio: Muco



Células Globulares / Caliciformes

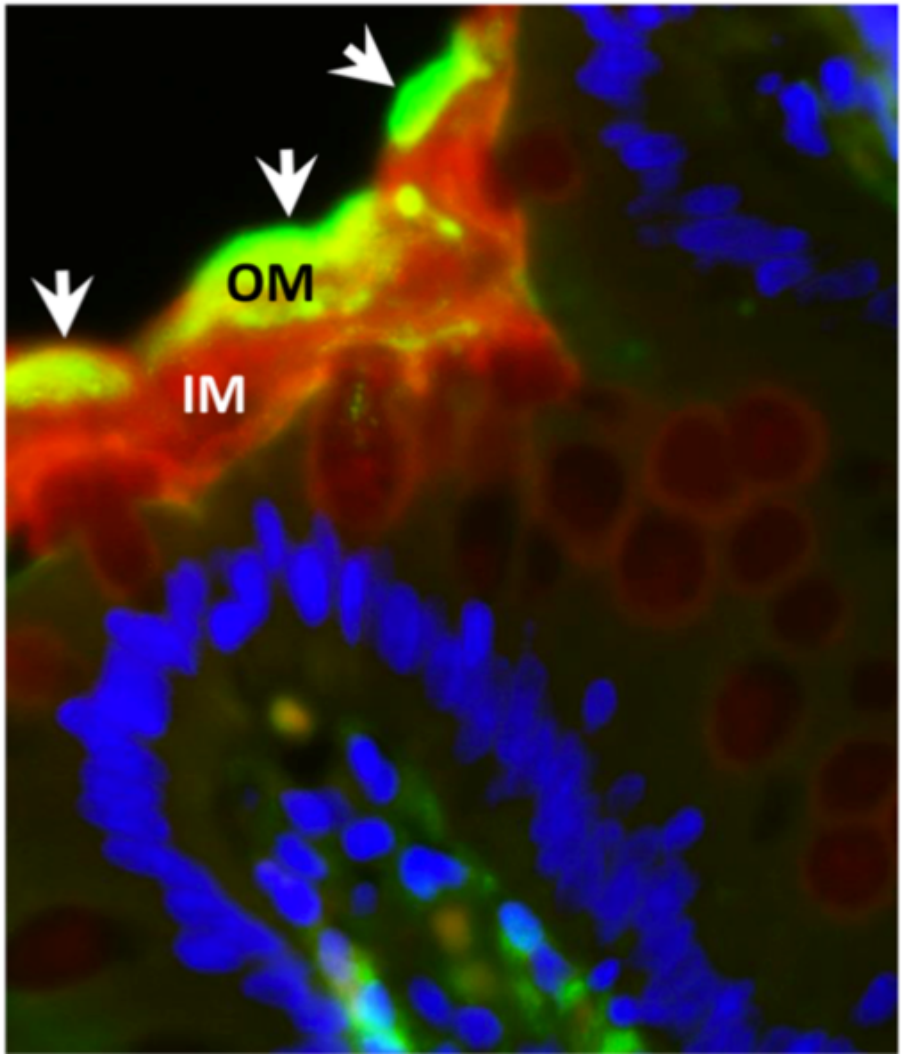
çç



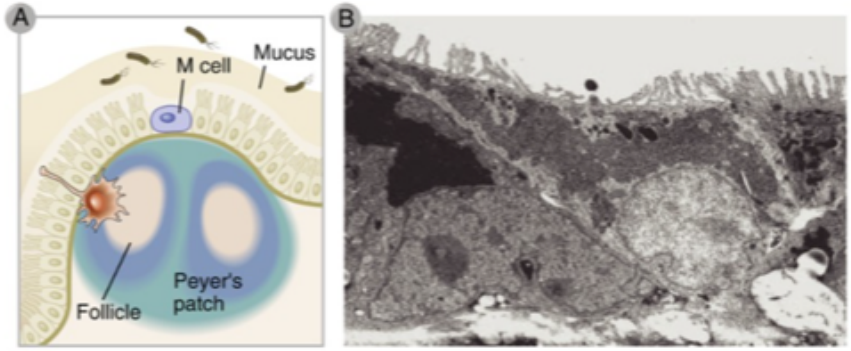
Muco

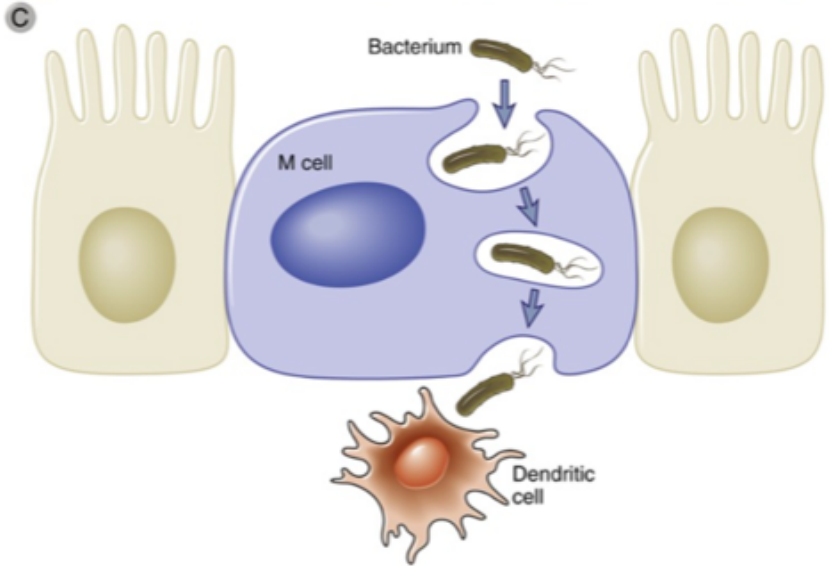
çç

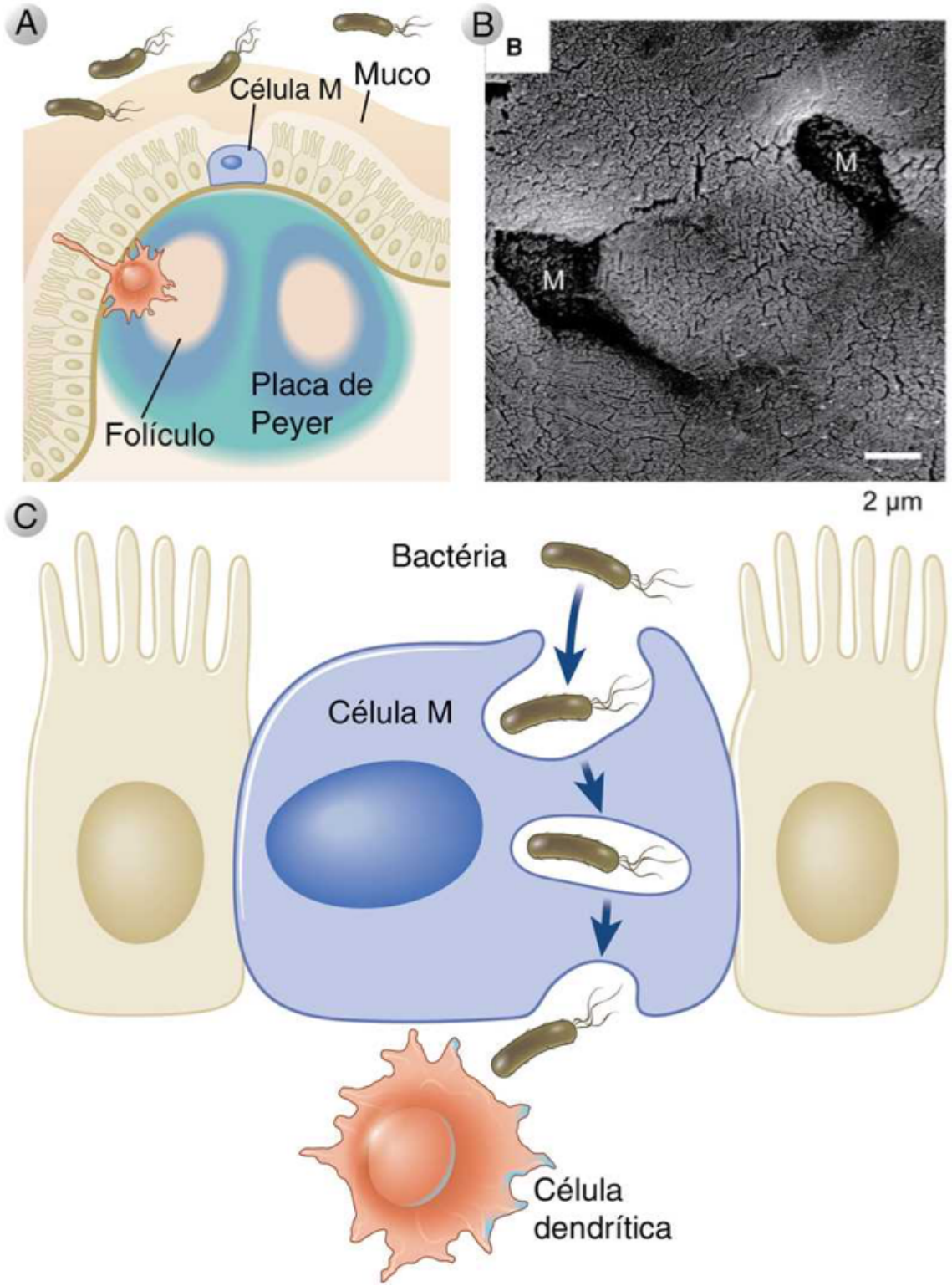
Muc2 IgA DNA



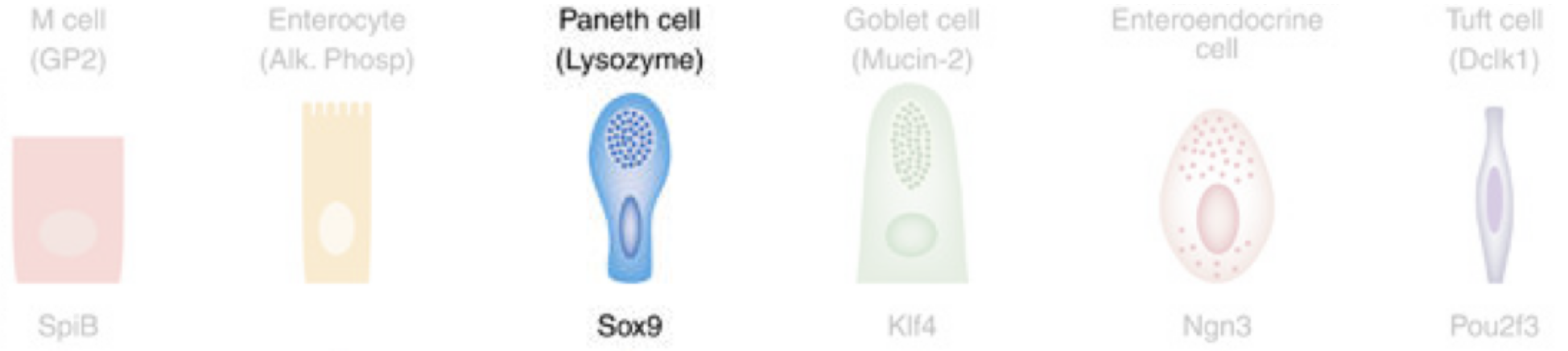
Epitélio: Células M (Microfenestradas)

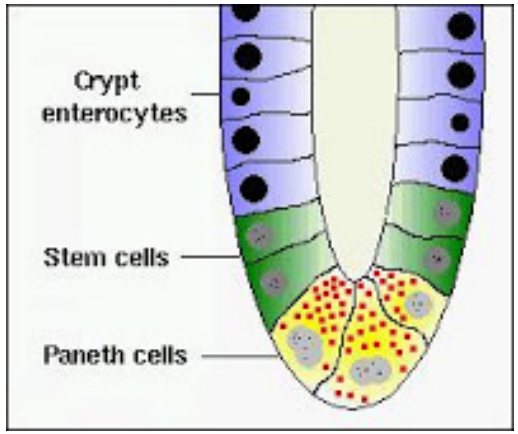


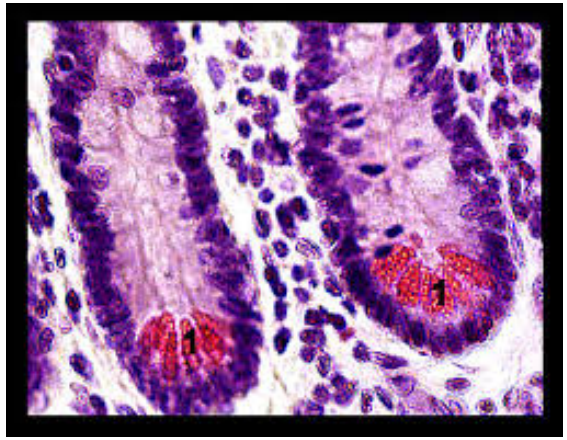


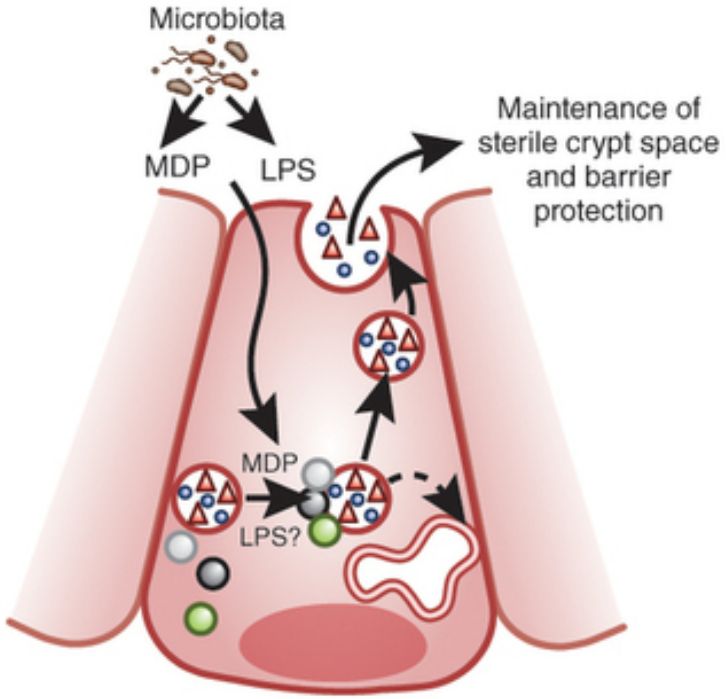

A
Célula M
Muco
Placa de
Peyer
Folículo
B
B
M
M
2 µm
C
Bactéria
Célula M
Célula
dendrítica

Epitélio: células de Paneth



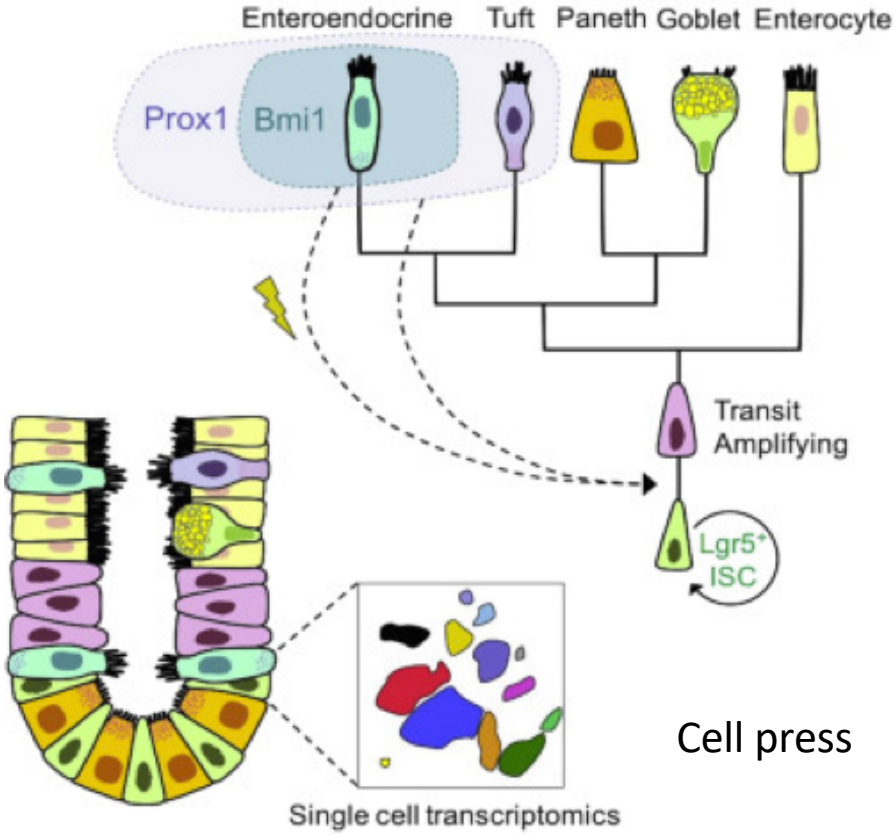




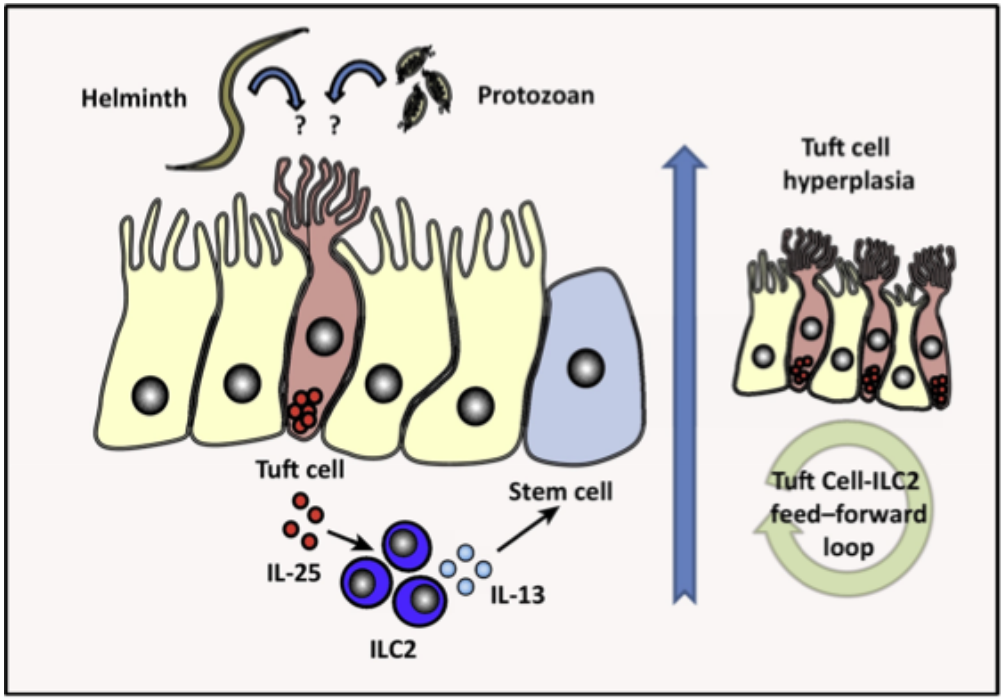


- Antimicrobial peptides: defensins, catalecidins, C-type lectin

Epitélio: células de Tuft



Cell press



Trends in Parasitology

Componentes

Barreira Física
- Epitélio/ Junções celulares
- Muco
- Peptídeos antimicrobianos
- *Epitélio Ciliado
- *pH

Barreira ativa
- Células dendríticas especializadas
- Células T efetoras especializadas (Th17 e Treg)
- IgA
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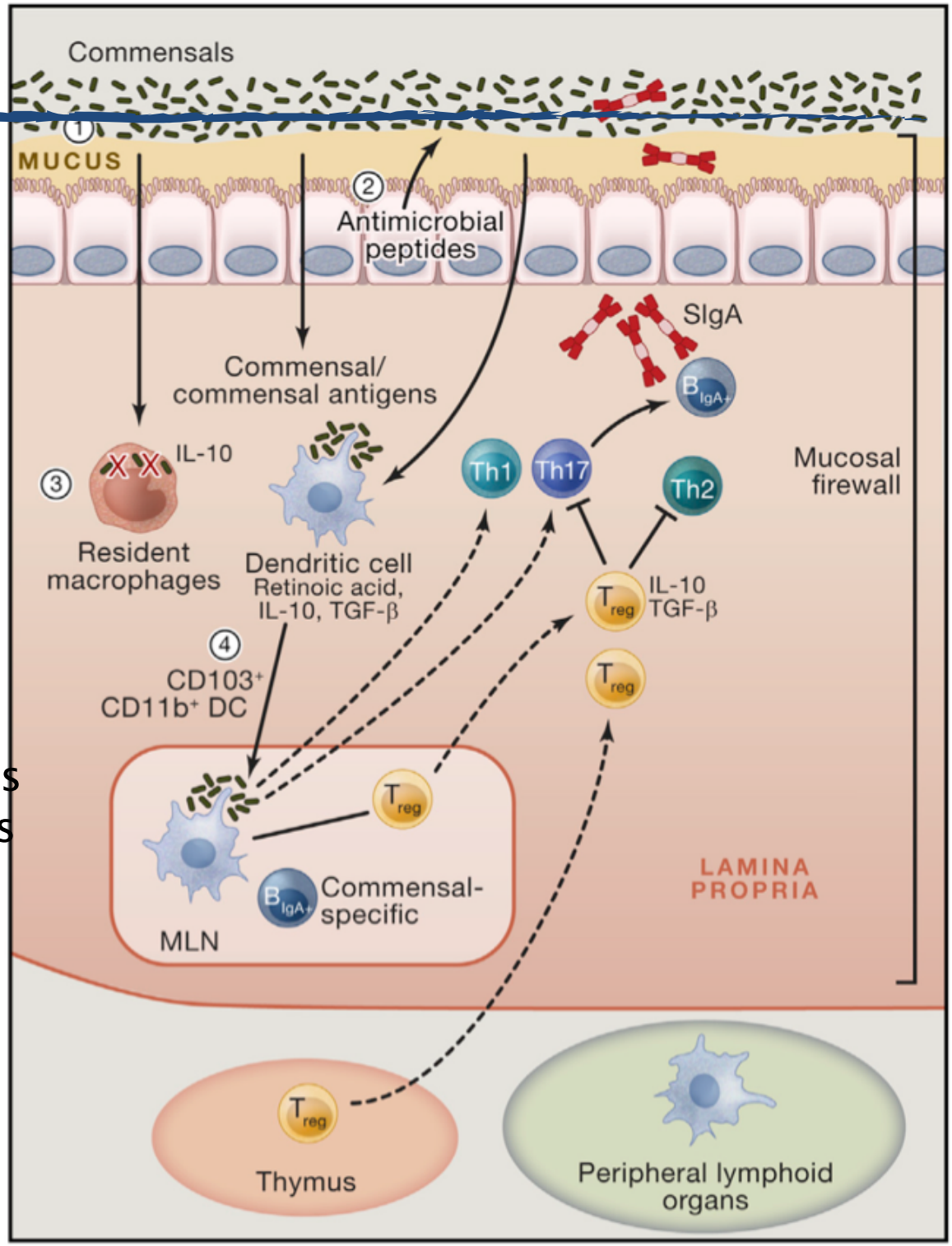
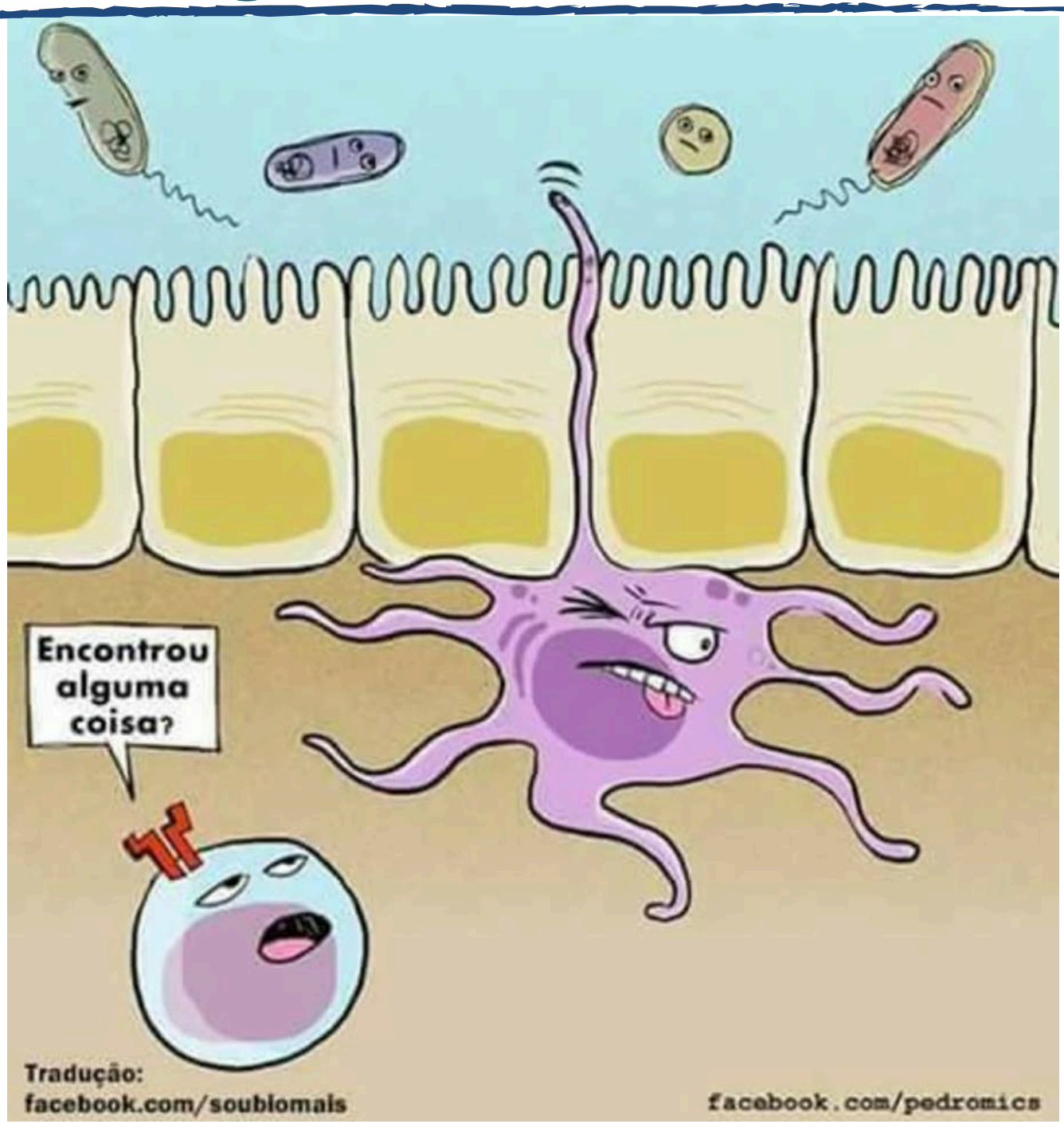
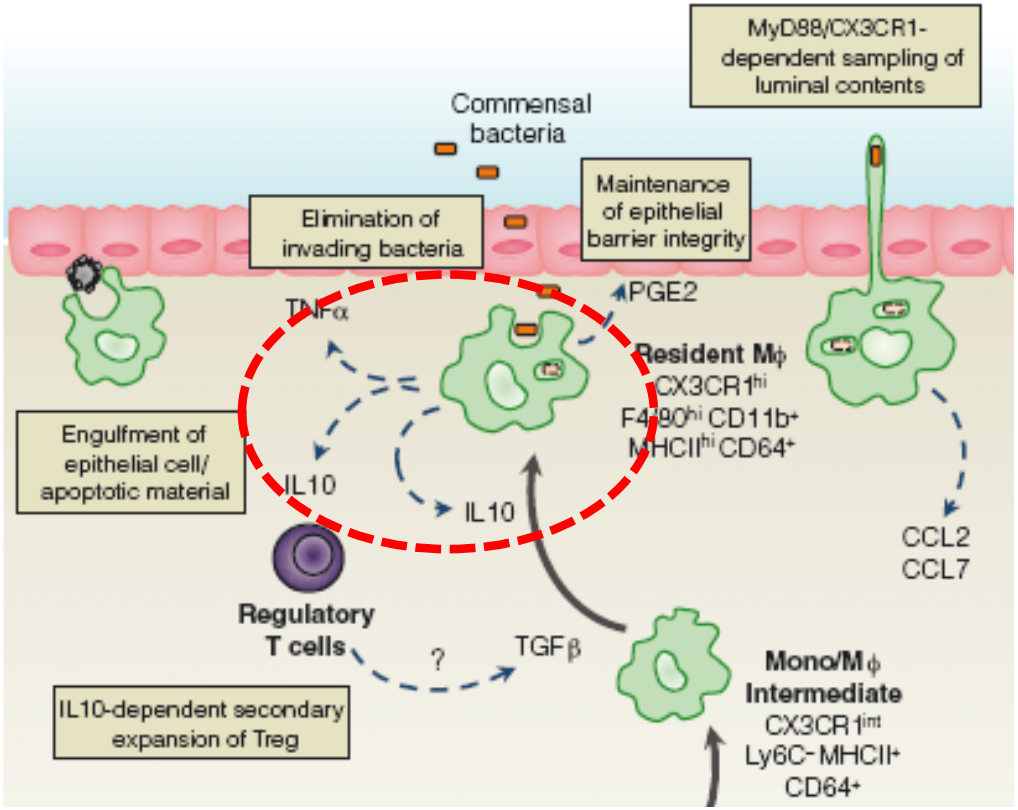


Cell 157, March 27, 2014

Sistema Fagocítico Mononuclear

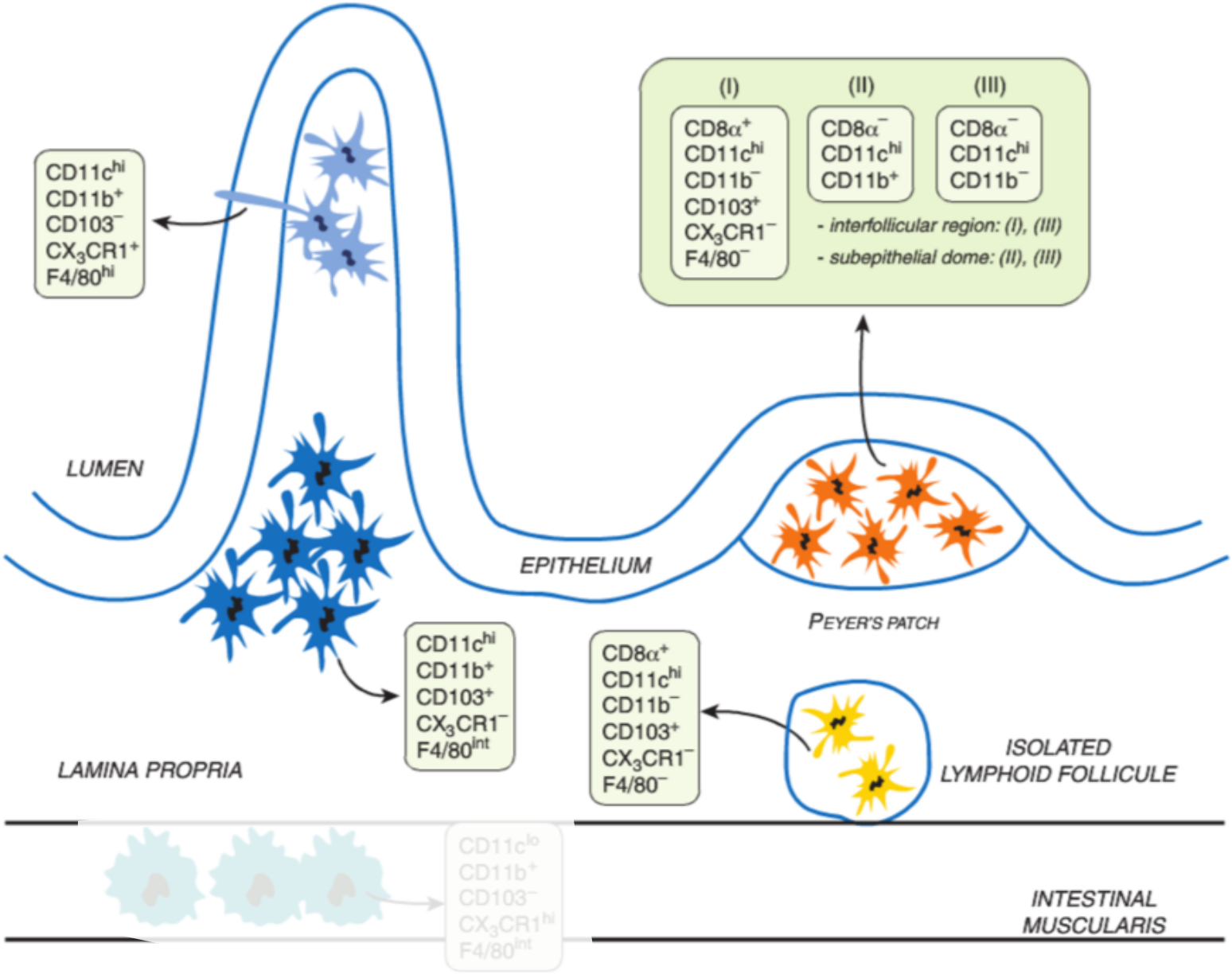


Sistema Fagocítico Mononuclear

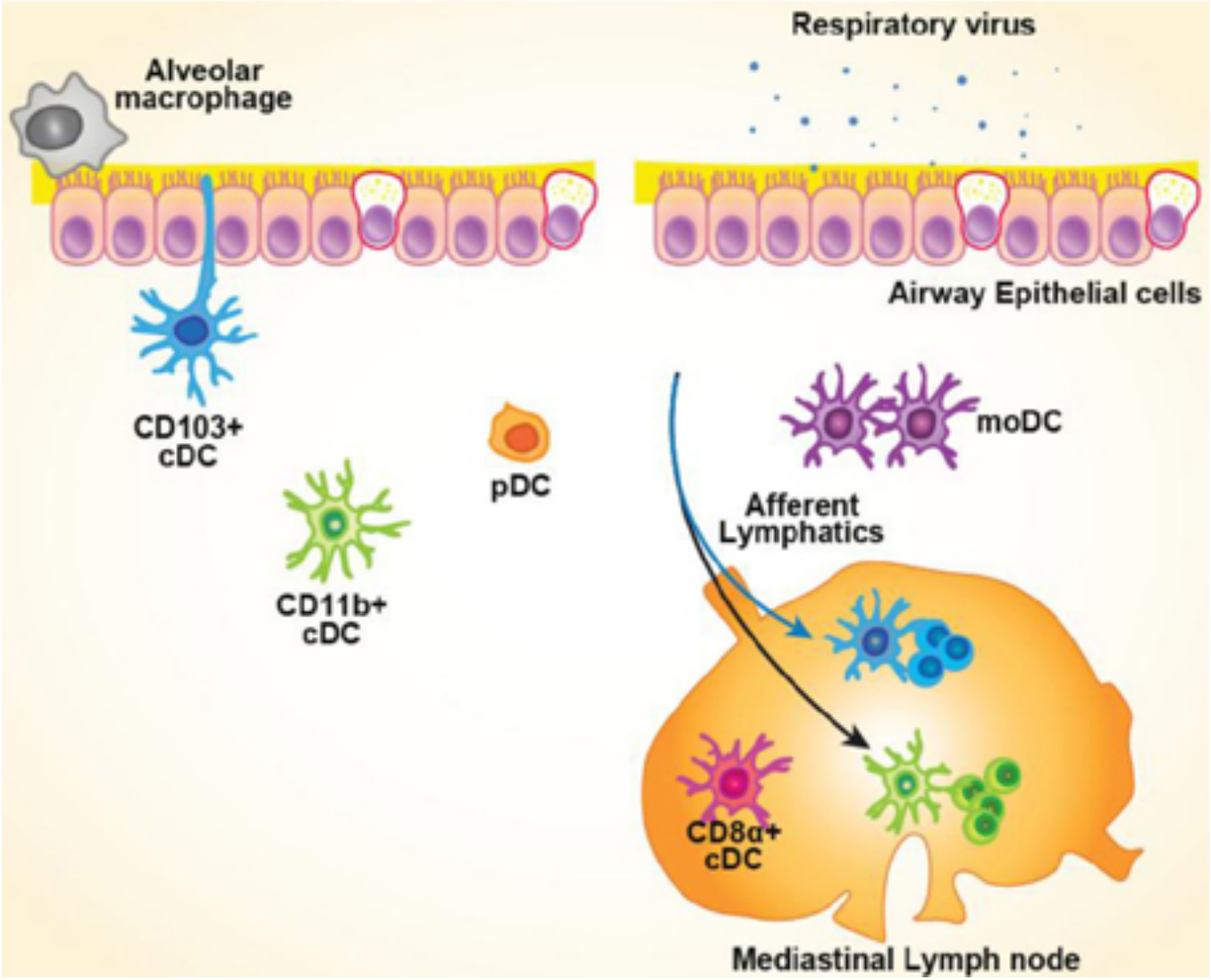


doi: 10.1111/imr.12192

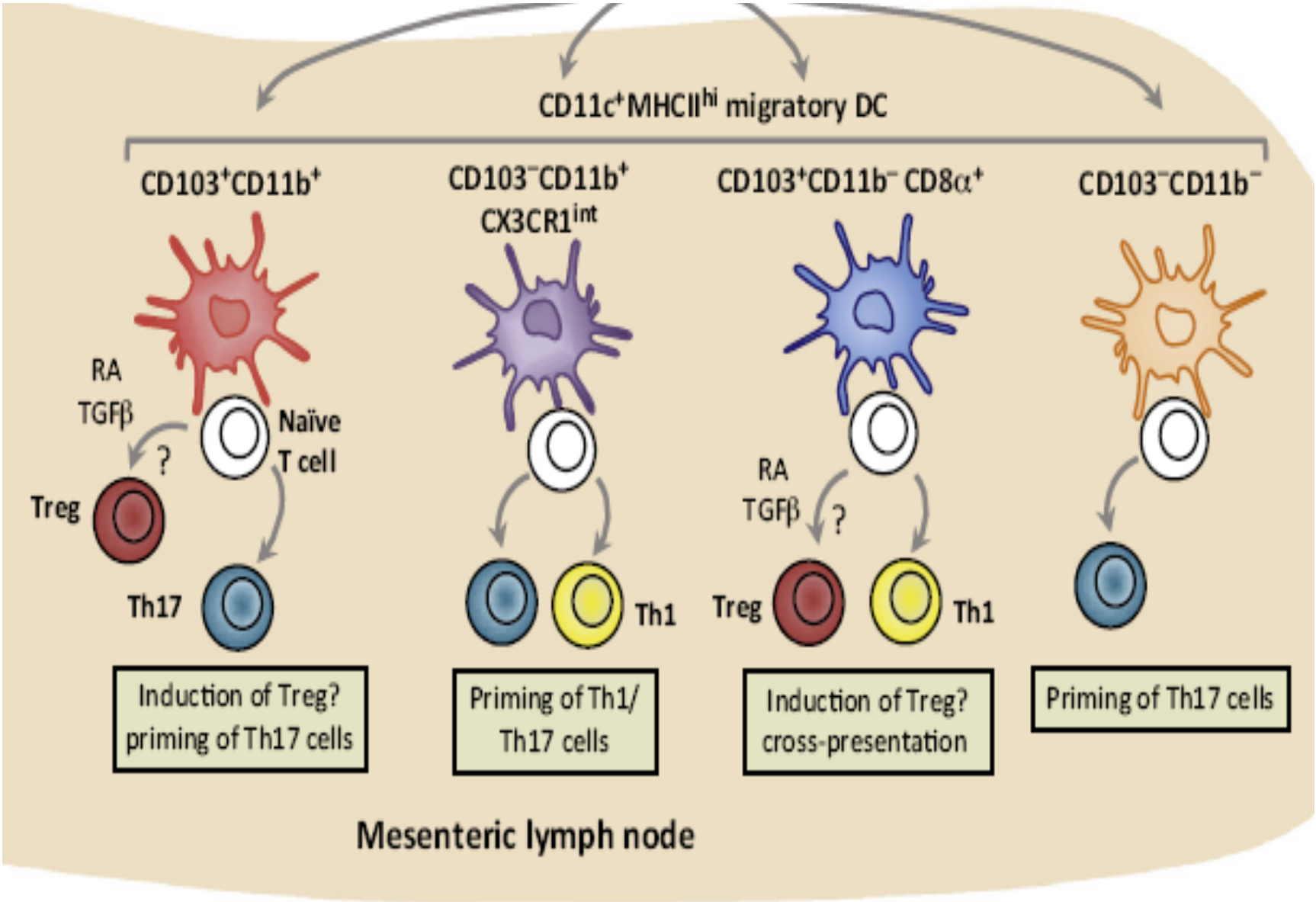
Sistema Fagocítico Mononuclear



Fagócitos mononuclerares no pulmão

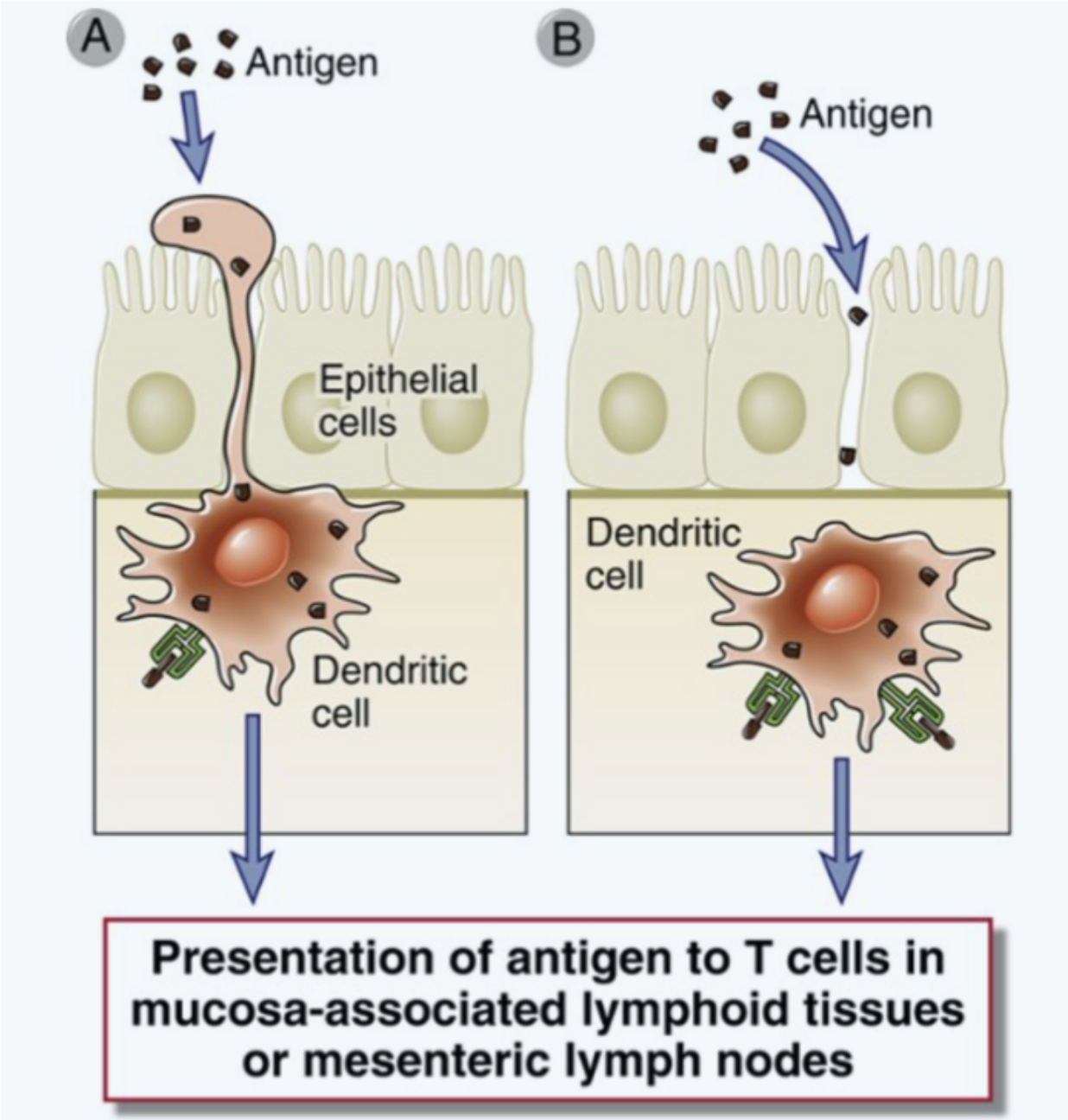


Subtipos de Células Dendríticas

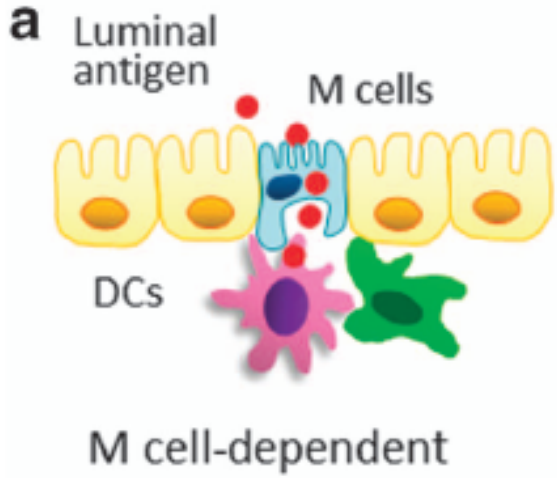


http://dx.doi.org/10.1016/j.it.2014.04.003

Captura de Antígeno

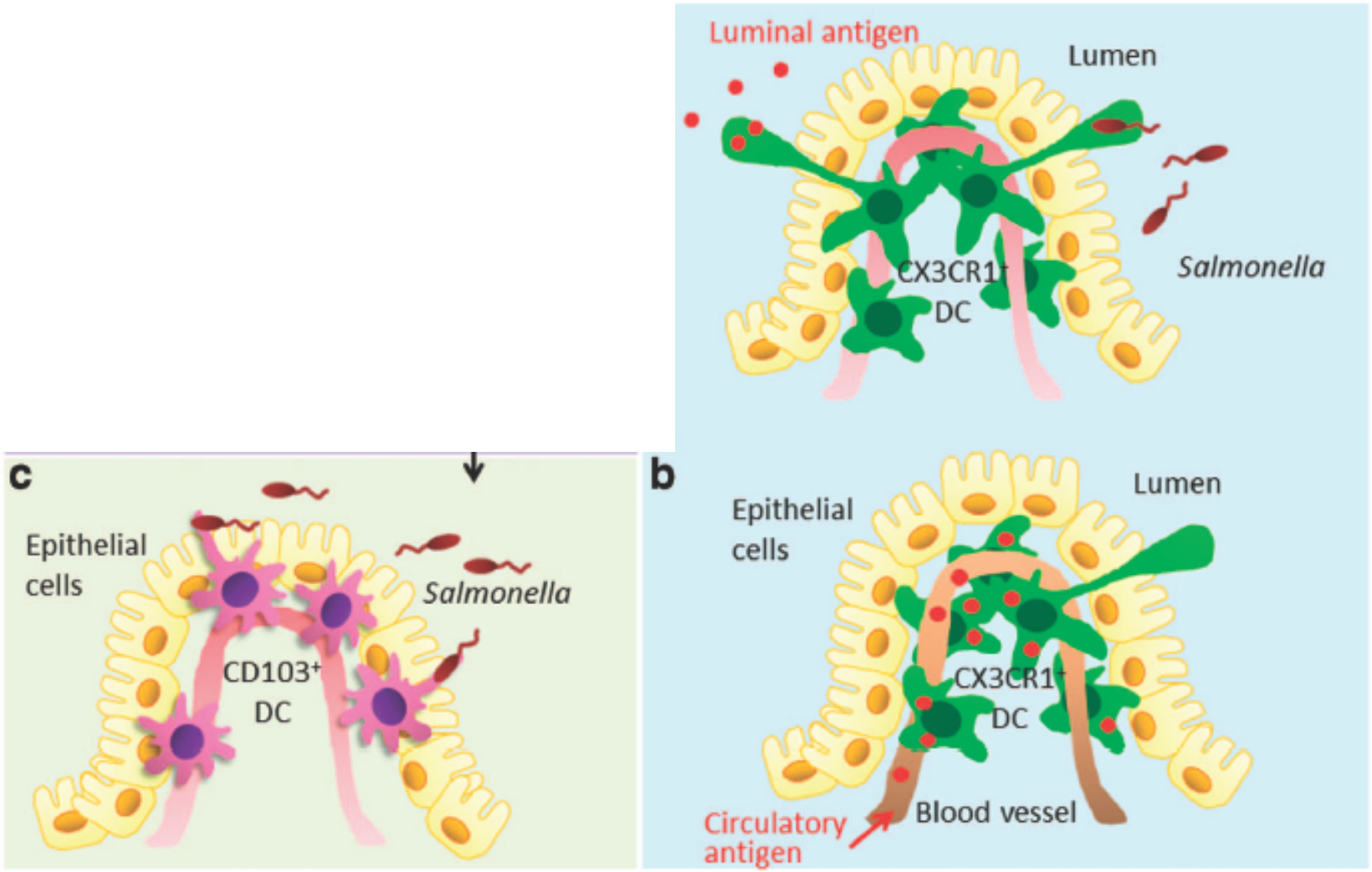


Via indireta de captação de antígenos por DCs



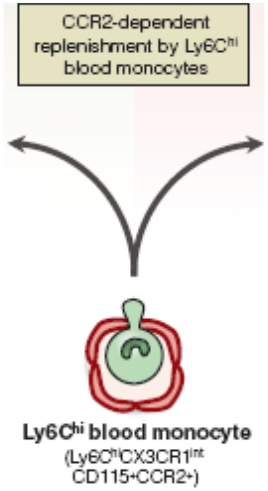
doi:10.1038/emm.2014.16

Captura de Antígeno



doi:10.1038/emm.2014.16

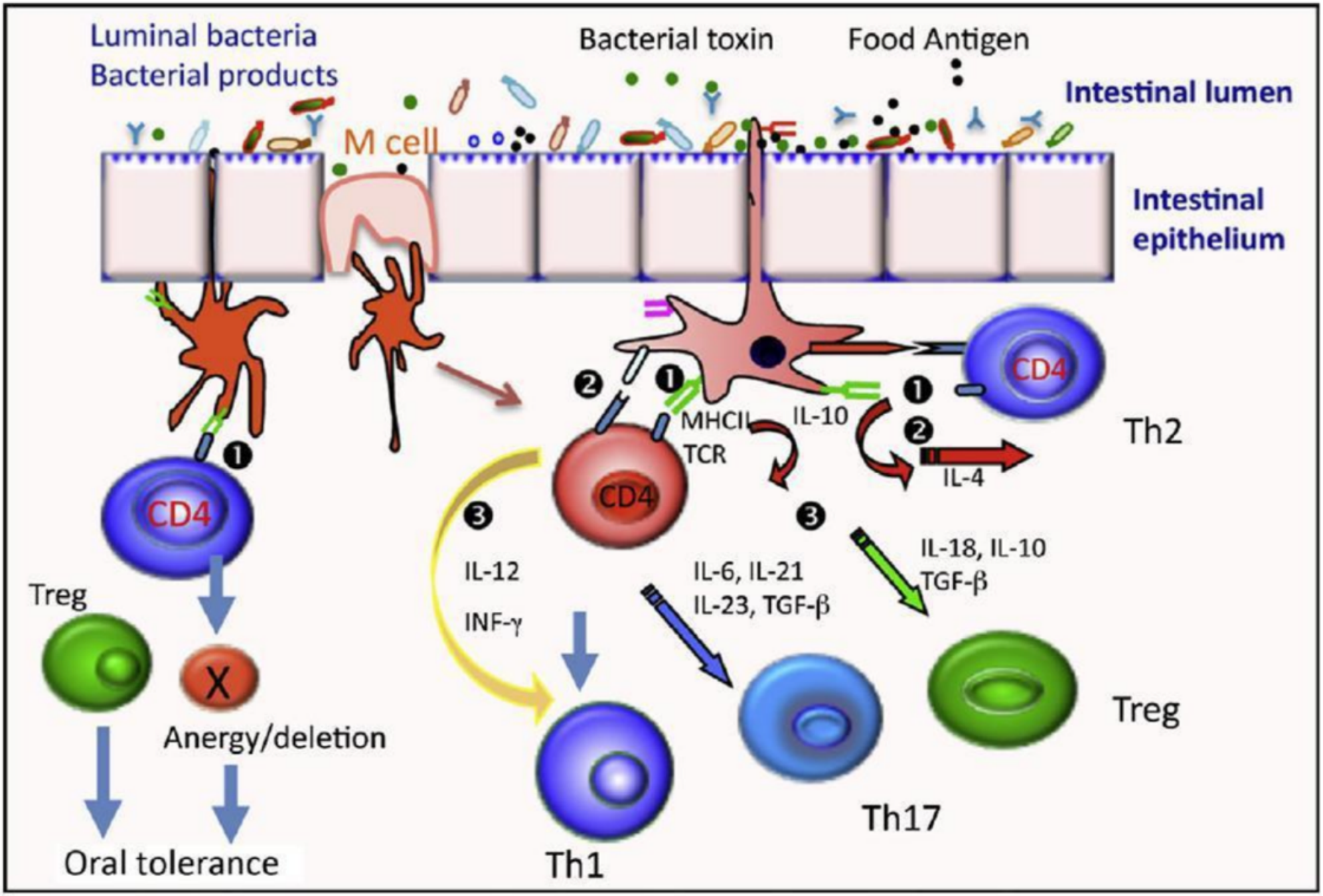
Ontogenia, fenótipo e função de MØ intestinais



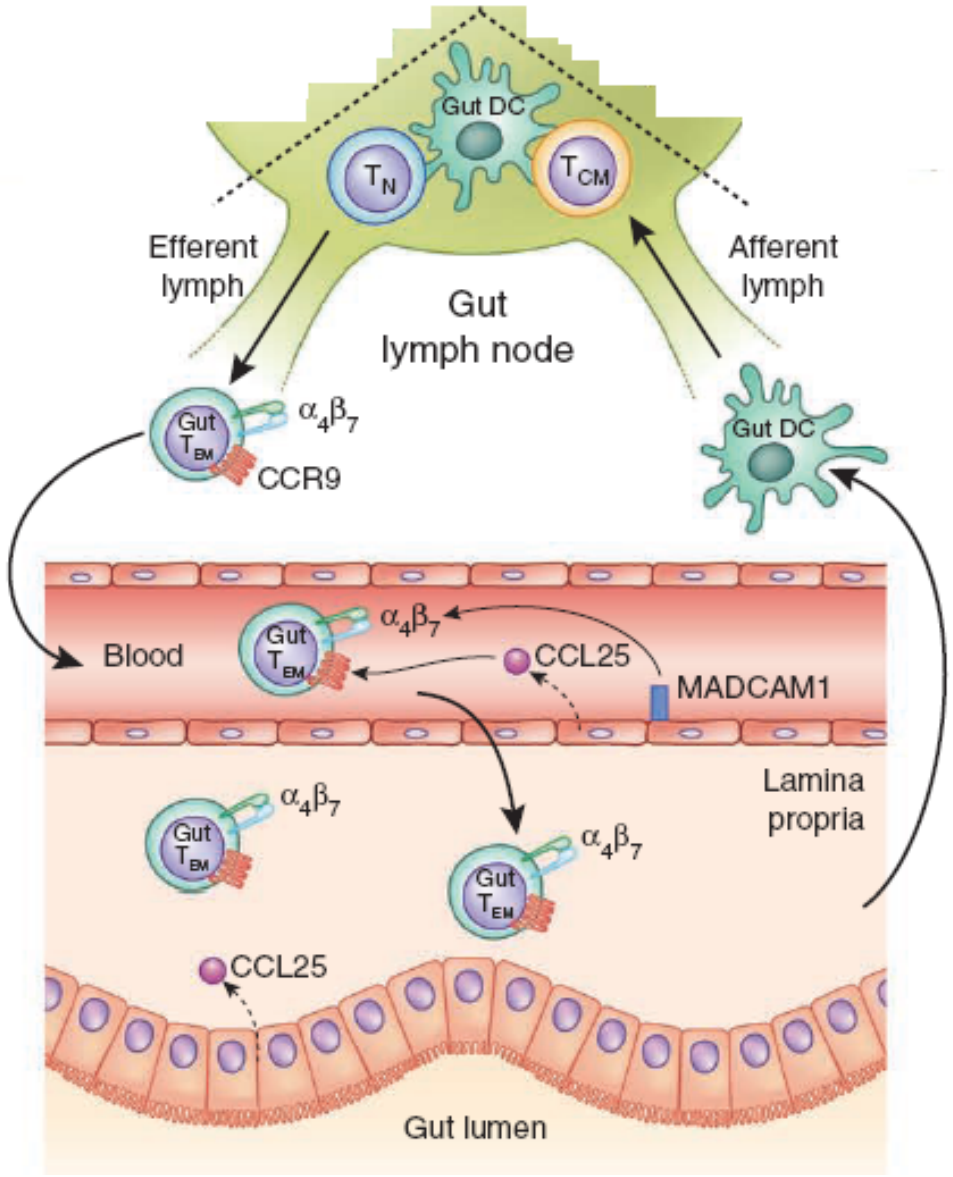
doi: 10.1111/imr.12192

Função das células do sistema mononuclear fagocítico da mucosa

- Reparo tecidual
- Vigilância do tecido de barreira
- Ativação de linfócitos especializados com capacidade de migração para a mucosa


Luminal bacteria
Bacterial products
Bacterial toxin
Food Antigen
Intestinal lumen
M cell
Intestinal epithelium
CD4
MHCII
TCR
IL-10
IL-4
Th2
IL-12
INF-γ
IL-6, IL-21
IL-23, TGF-β
IL-18, IL-10
TGF-β
Treg
X
Anergy/deletion
Oral tolerance
Th1
Th17
Treg

Formação de células T com tropismo para o intestino



DCs → ácido retinóico

↓

CCR9 e α4β7
em linfócitos T

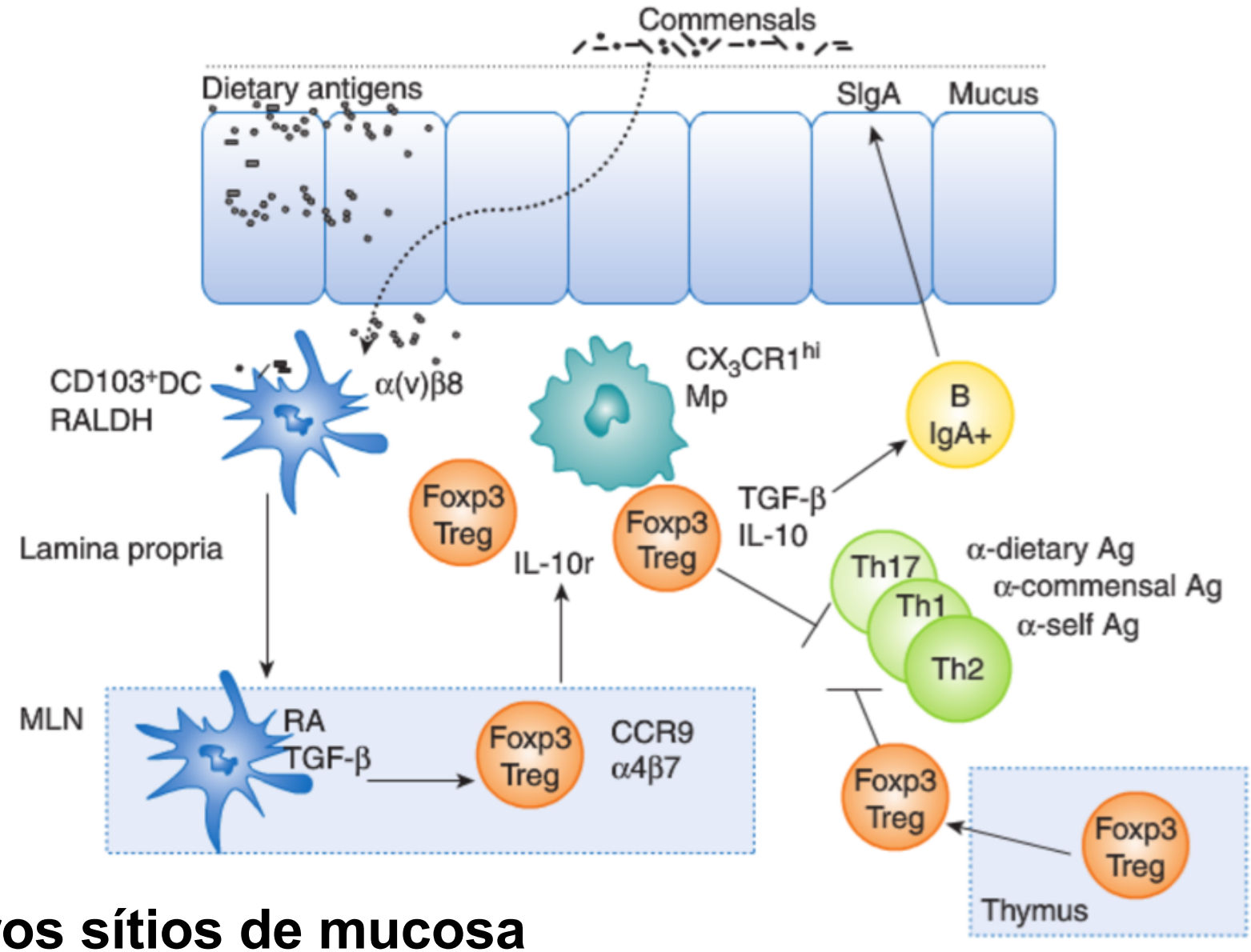
✓ Falta de evidências *in vivo*

✓Camundongos deficientes para DCs 103+ possuem Linf. T CCR9+ α4β7+

✓Papel de células do estroma?

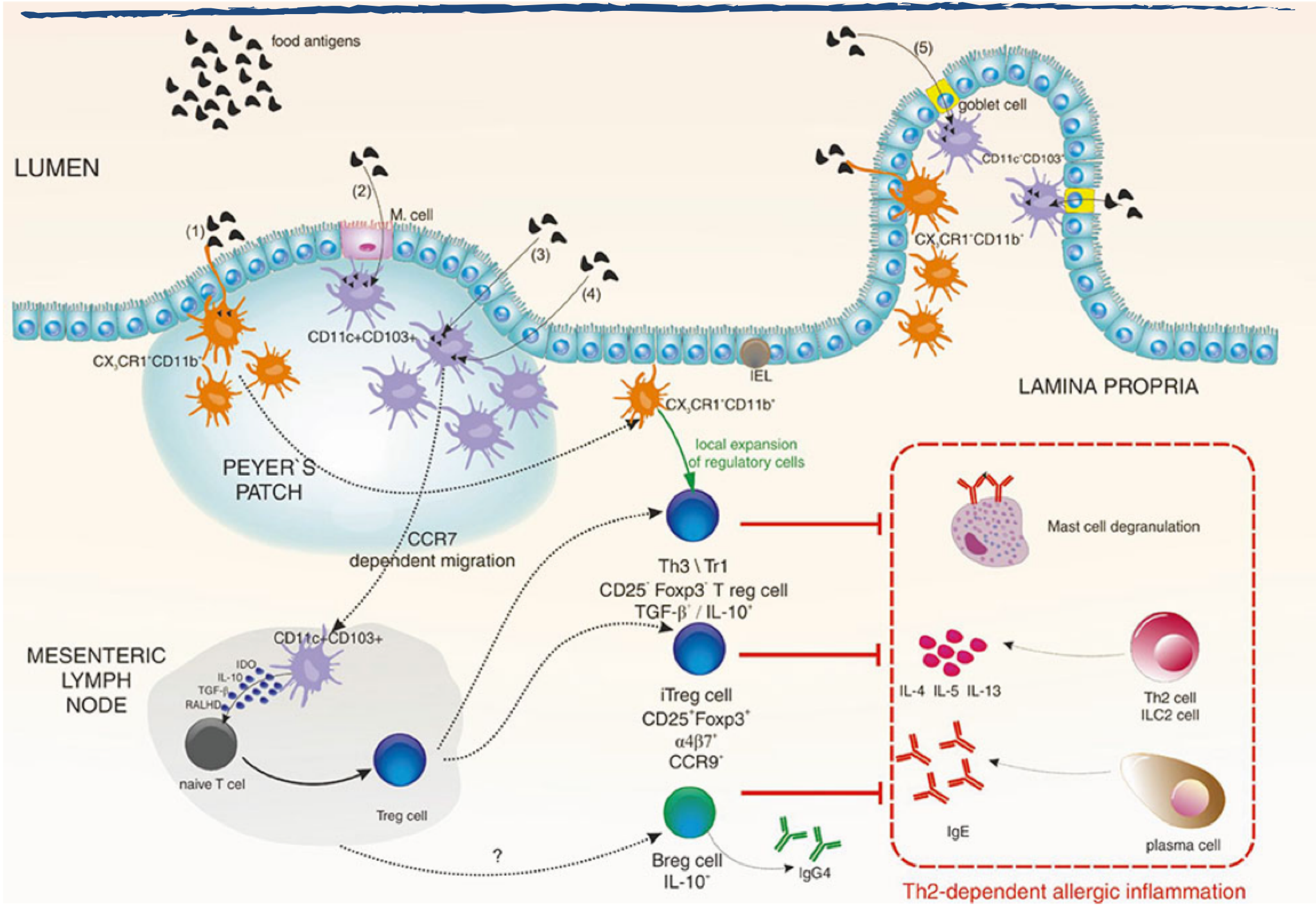
✓**Outros tecidos de barreira**

Ativação de linfócitos especializados

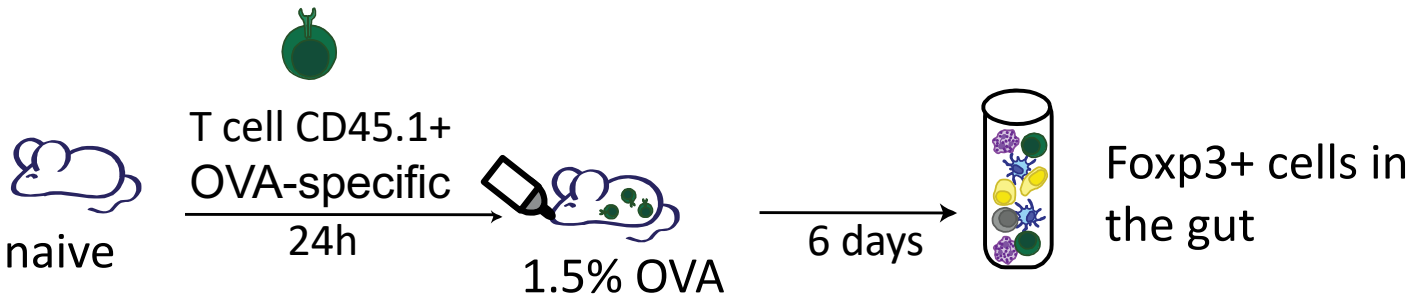


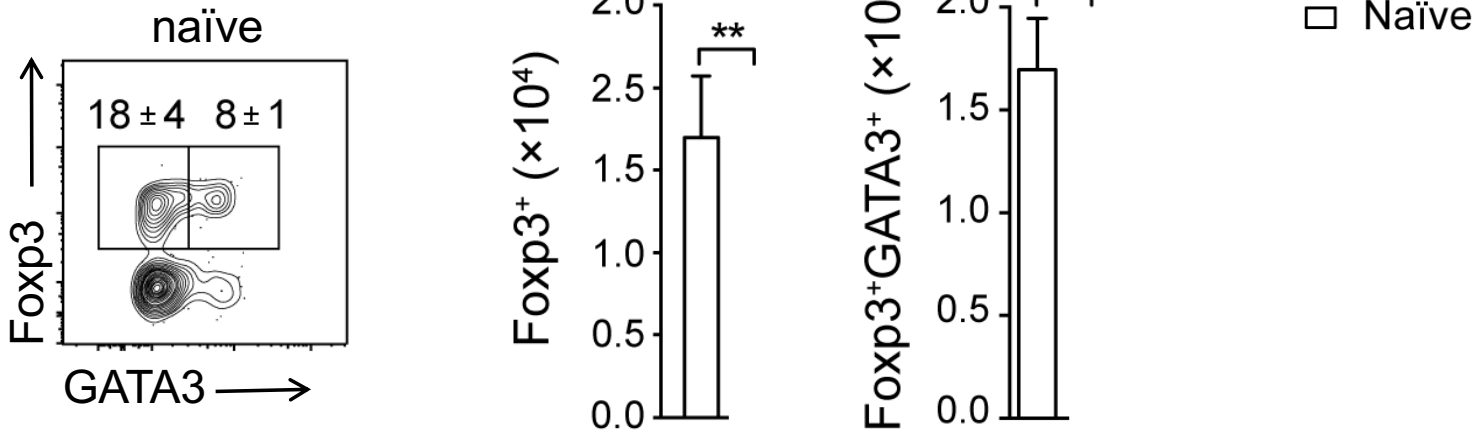
Outros sítios de mucosa

Tolerância Oral



Tolerância Oral

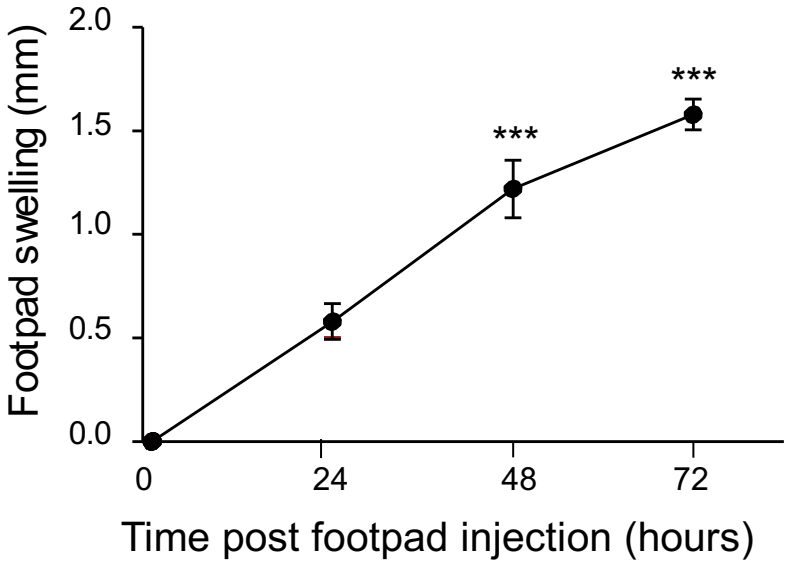




Tolerância Oral

1.5% OVA → 6 days → Foxp3+ cells → Sensitization OVA + Adjuvant → Challenge: DTH response

Oral tolerance induction



Tolerância Oral

1.5% OVA

6 days

Foxp3+ cells

Sensitization
OVA + Adjuvant

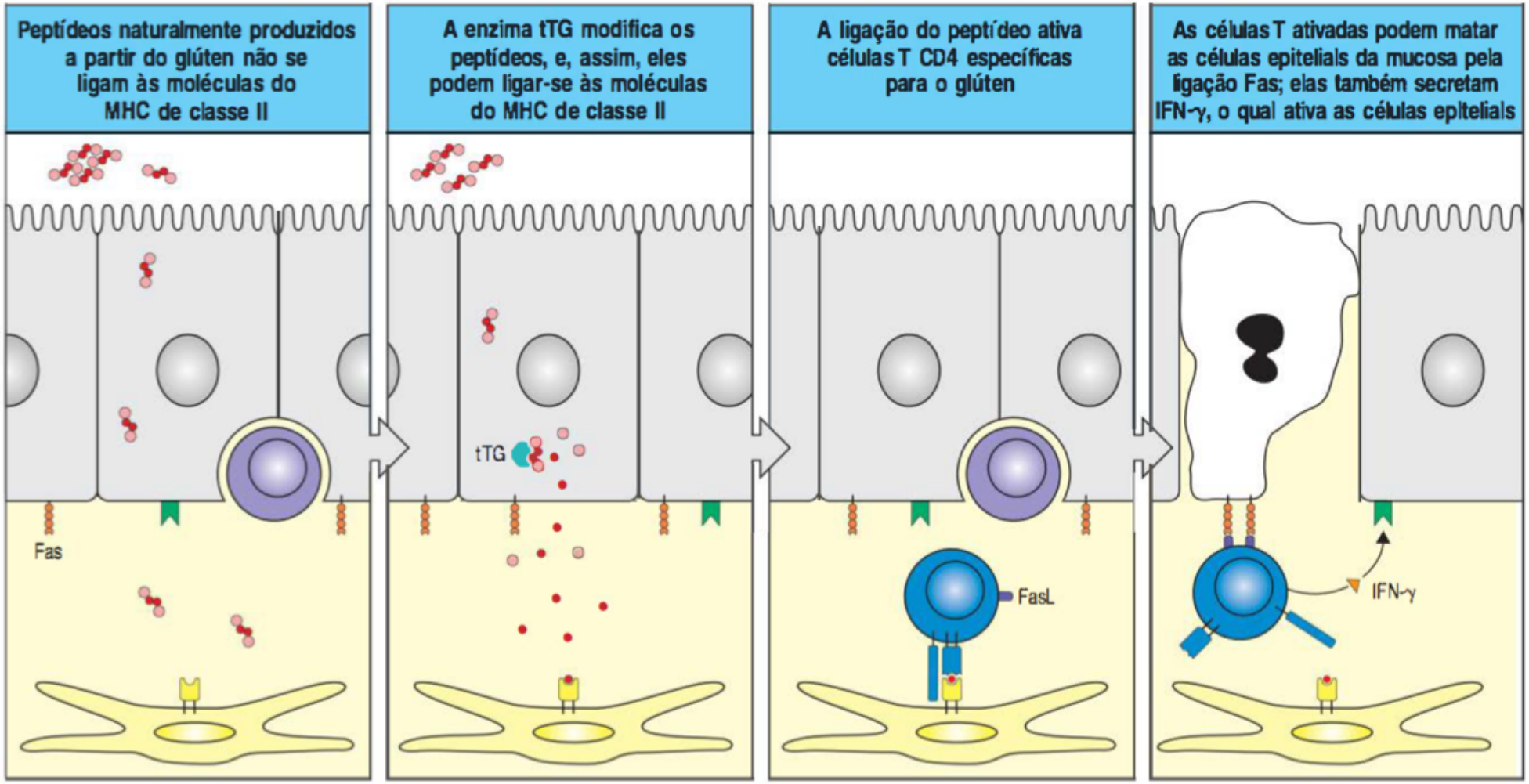
Challenge:
DTH response

Oral tolerance induction

-tolerized

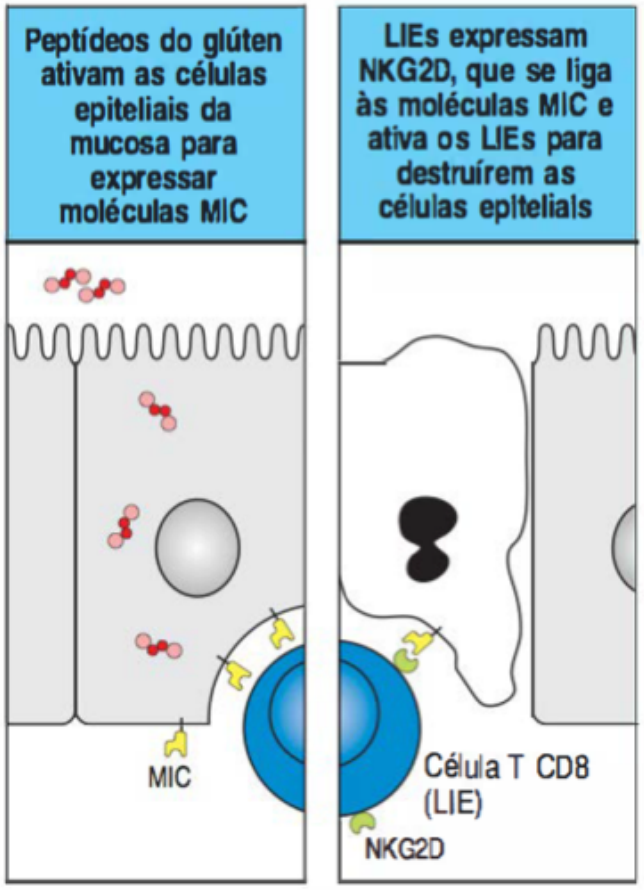
erized

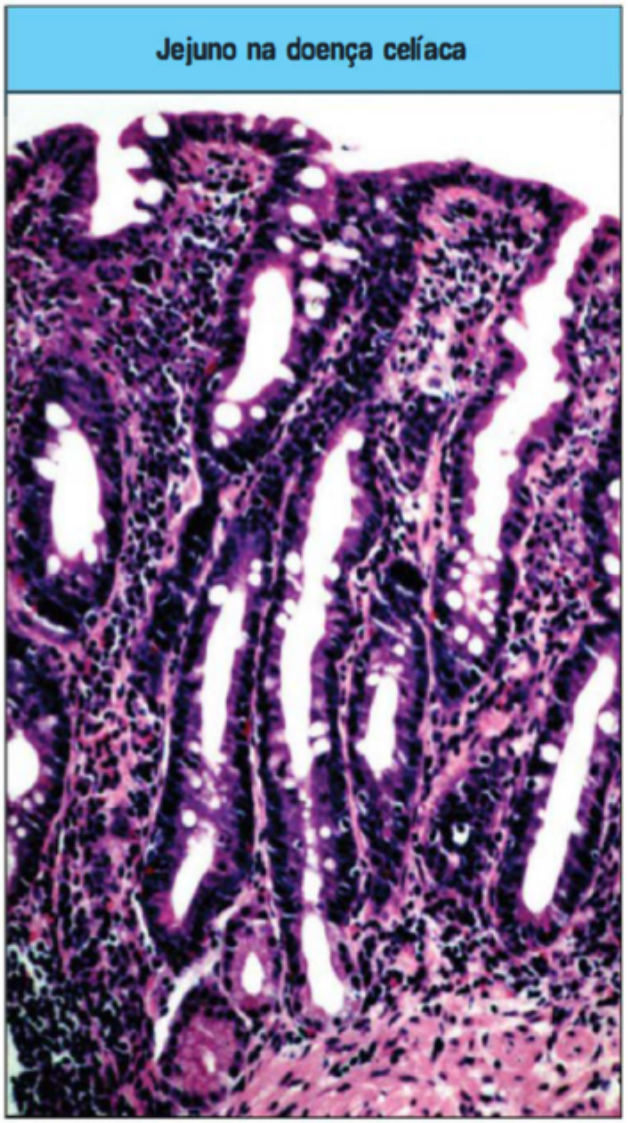
Doença celíaca, alergia alimentar intolerância à lactose



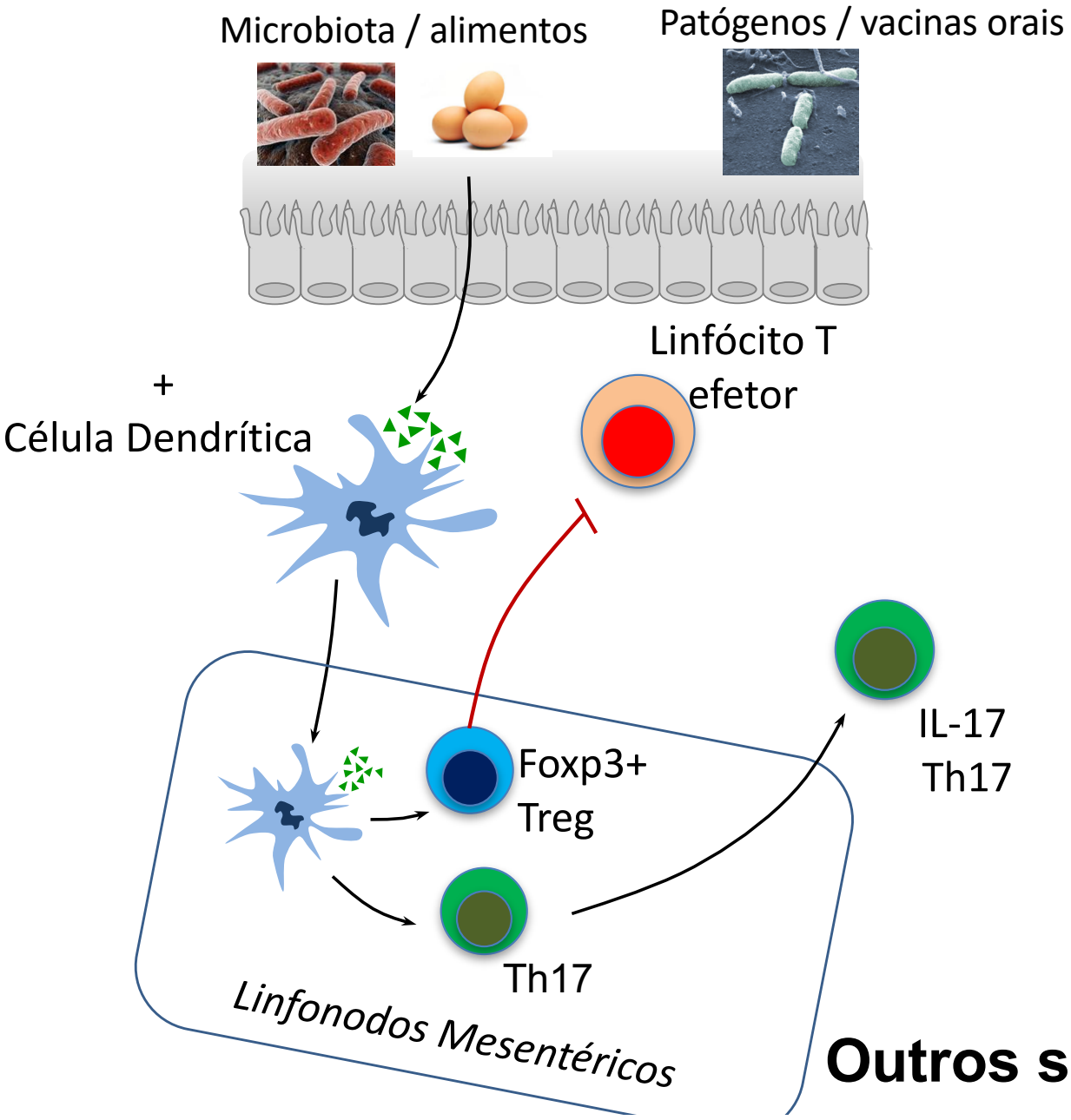
A doença celíaca demonstra uma predisposição genética extremamente forte, e mais de 95% dos pacientes expressam o alelo do MHC de classe II HLA-DQ2, e

Doença celíaca, alergia alimentar intolerância à lactose





Ativação de linfócitos especializados



Vacinas Orais/nasais

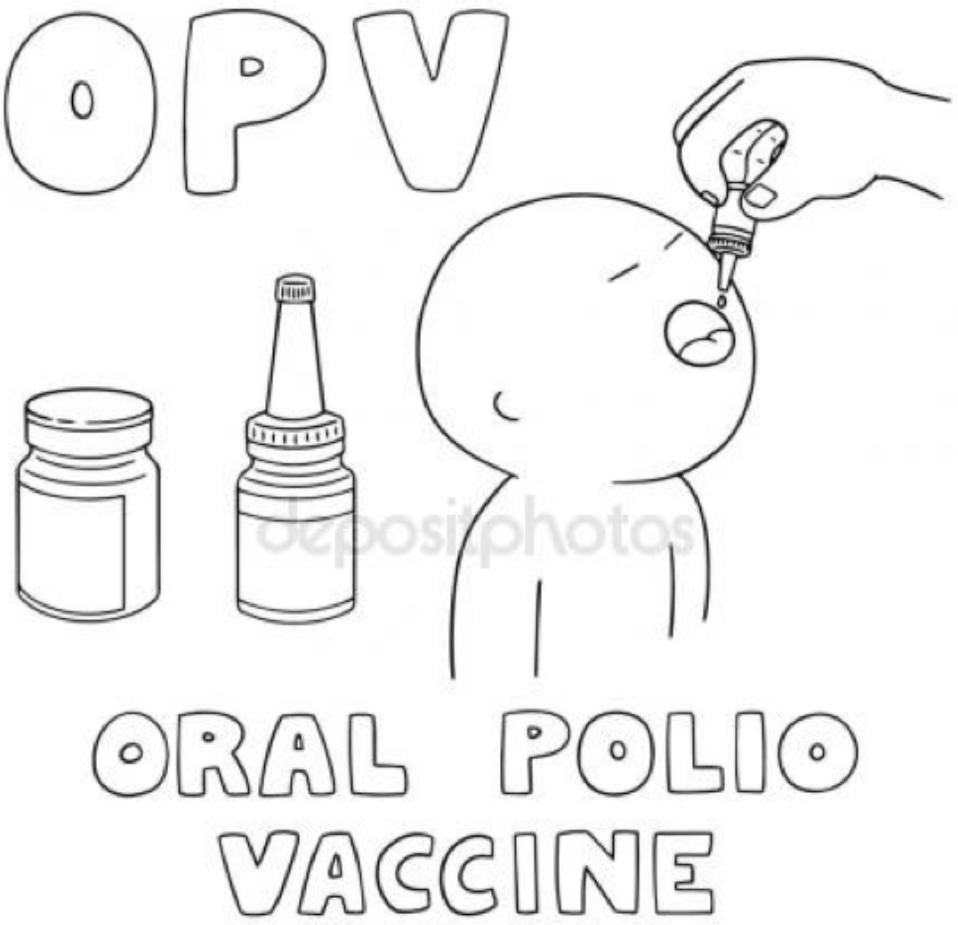


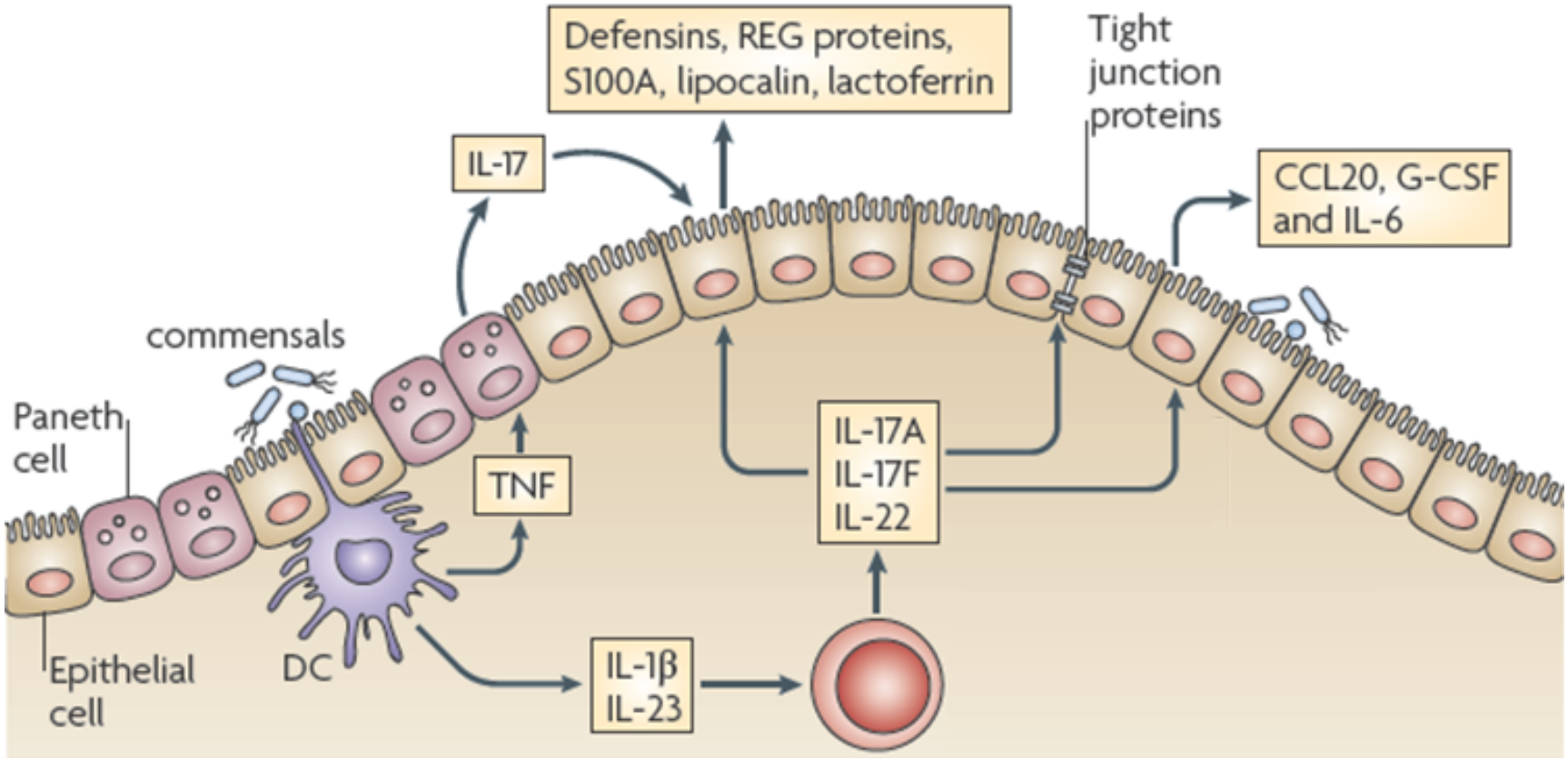
Table 1 Selected List of Bacterial and Food Antigens Used in Mucosal Immunization Studies in Humans and Animals

Antigen	Results and Comments	Author
Yersinia multocida (chicken cholera)	Oral immunization; protection induced	Pasteur (1880)
Vibrio cholerae	Oral immunization, moderate protection	Klemperer (1892) and Metchnikoff (1903)[a]
Mycobacterium tuberculosis	Serum antibodies induced by oral immunization	Calmette and Guérin (1906–1923)[a]
Yersinia pestis		
Corynebacterium diphtheria		Dserzgowdky (1910) and Enlows (1925)
Shigella dysenteriae	Limited protection	Besredka (1919, 1927)
Salmonella typhi	Oral immunization preferable to systemic	Vaillant (1922)[a], Besredka (1919, 1927) and Combiesco et al., (1923)
Streptococcus pneumoniae	Protection achieved by nasal immunization	Bull and McKee, 1929
Staphylococcus pyogenes	Protection achieved by oral immunization	Ross (1930)
Abrin, ricin, robin	Partial protection Oral immunization results in systemic and mucosal protection	Combiesco and Calab (1924) and Ehrlich (1891a, 1891b)
Cow's milk and whey	Prevention of anaphylaxis by feeding	Besredka (1909)
Cow's milk, ox blood, egg white, zein, oats	Decrease in systemic reactivity after prolonged but not short ingestion of these antigens	Wells and Osborne (1911)
Dinitrochlorobenzene	Inhibition of systemic (skin) reactivity after hapten feeding; inability to suppress skin sensitivity by oral immunization in previously sensitized animals[b]	Chase (1946)
Poison ivy	Oral ingestion results in decreased skin reactivity in a few studies; discouraged for lack of efficacy	Stevens (1945)
Horse serum and meat	Sensitization for anaphylaxis	Rosenau and Anderson (1907)[a]
Proteins from rice, corn, and oat flour	Precipitins in serum	Magnus, 1906[a]

[a]*Data from Bull and McKee (1929), Chase (1946), Gay (1924), Stevens (1945), Klingman (1958), Wells and Osborne (1911), and Calmette (1923).*
[b]*See Table 3.*

Intranasal immunization is particularly beneficial in eliciting immunity in the female genital tract (Czerkinsky and Holmgren, 2012; Mestecky and Fultz, 1999). For example, intranasal immunization against a variety of sexually transmitted diseases, including human immunodeficiency virus-1 (HIV-1) (Peacock et al., 2004), herpes simplex virus-2 (HSV-2) (Milligan et al., 2004), human papillomavirus (HPV) (Dupuy et al., 1999; Kawana et al., 2001), and *Chlamydia pneumoniae* (Manam et al., 2013), elicits both B and T cell responses that protect the vaginal tract. Interestingly, although both nasal and vaginal

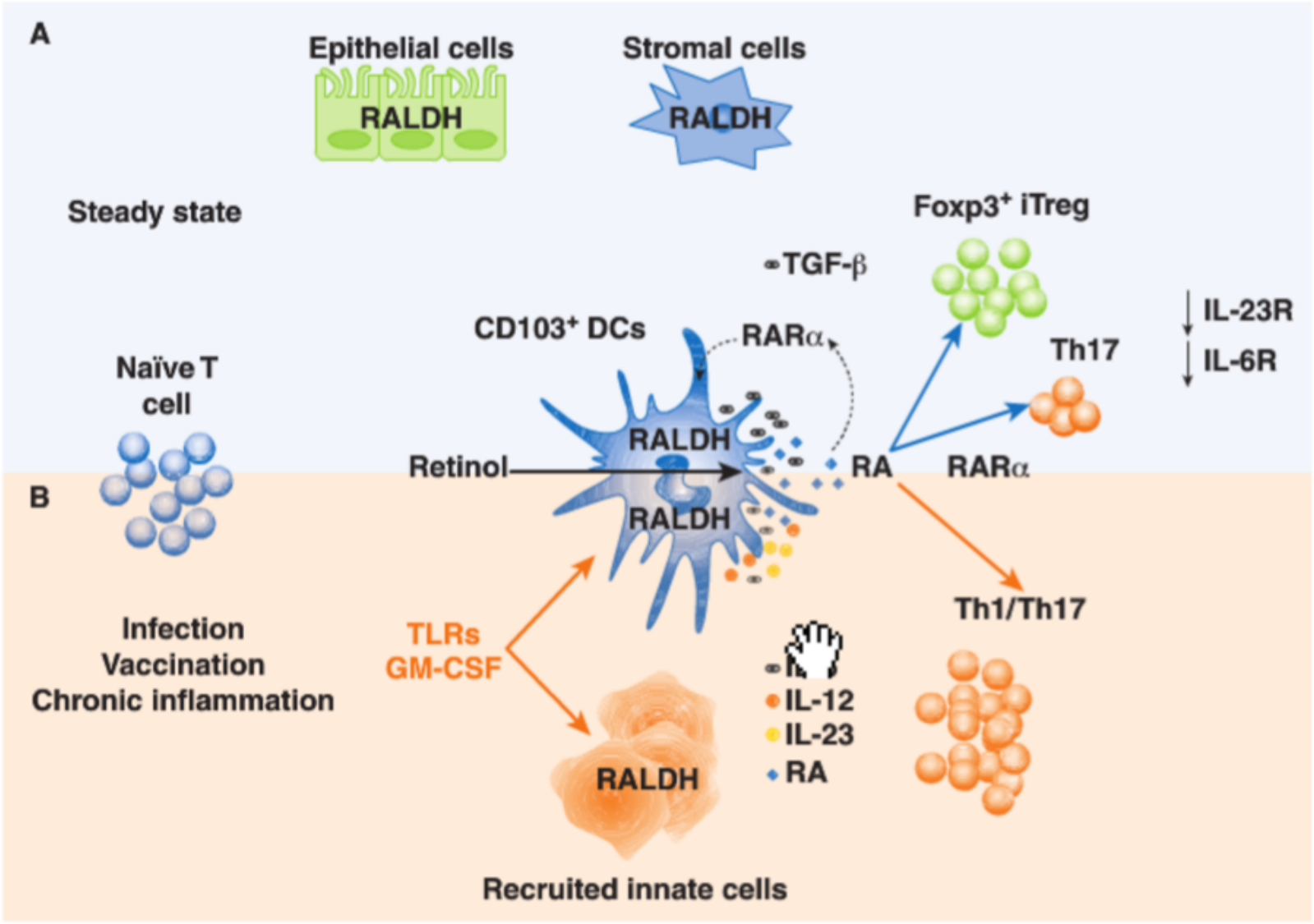
Th17/22



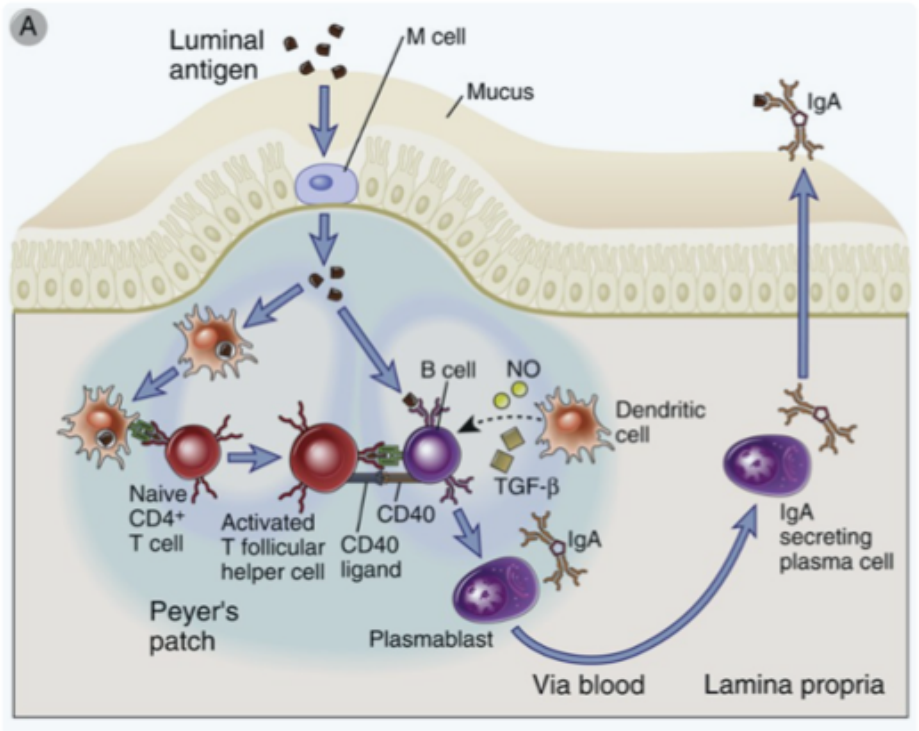
Patógenos extracelulares
Vacinas

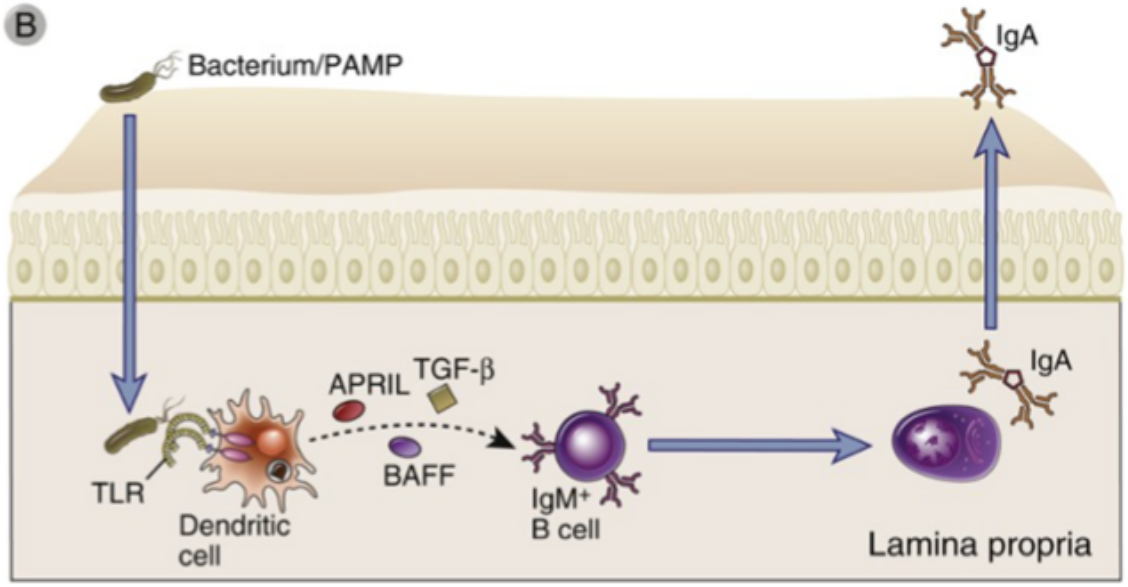
doi:10.1038/nri2800

Ácido retinóico na imunidade da mucosa intestinal



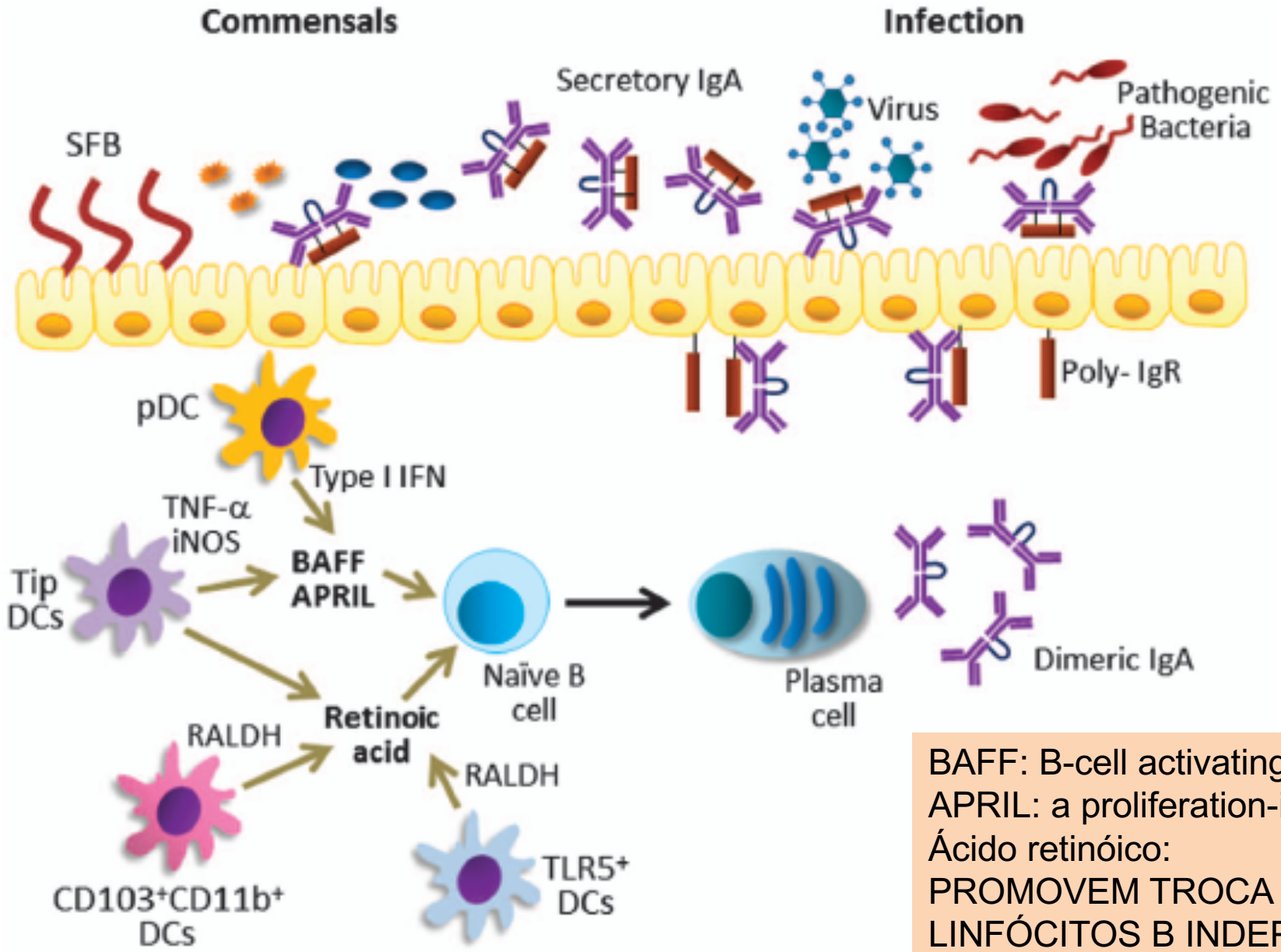
Produção de IgA





- Pulmão, troca de classe acontece nas tonsilas
- Trato urogenital: IgG

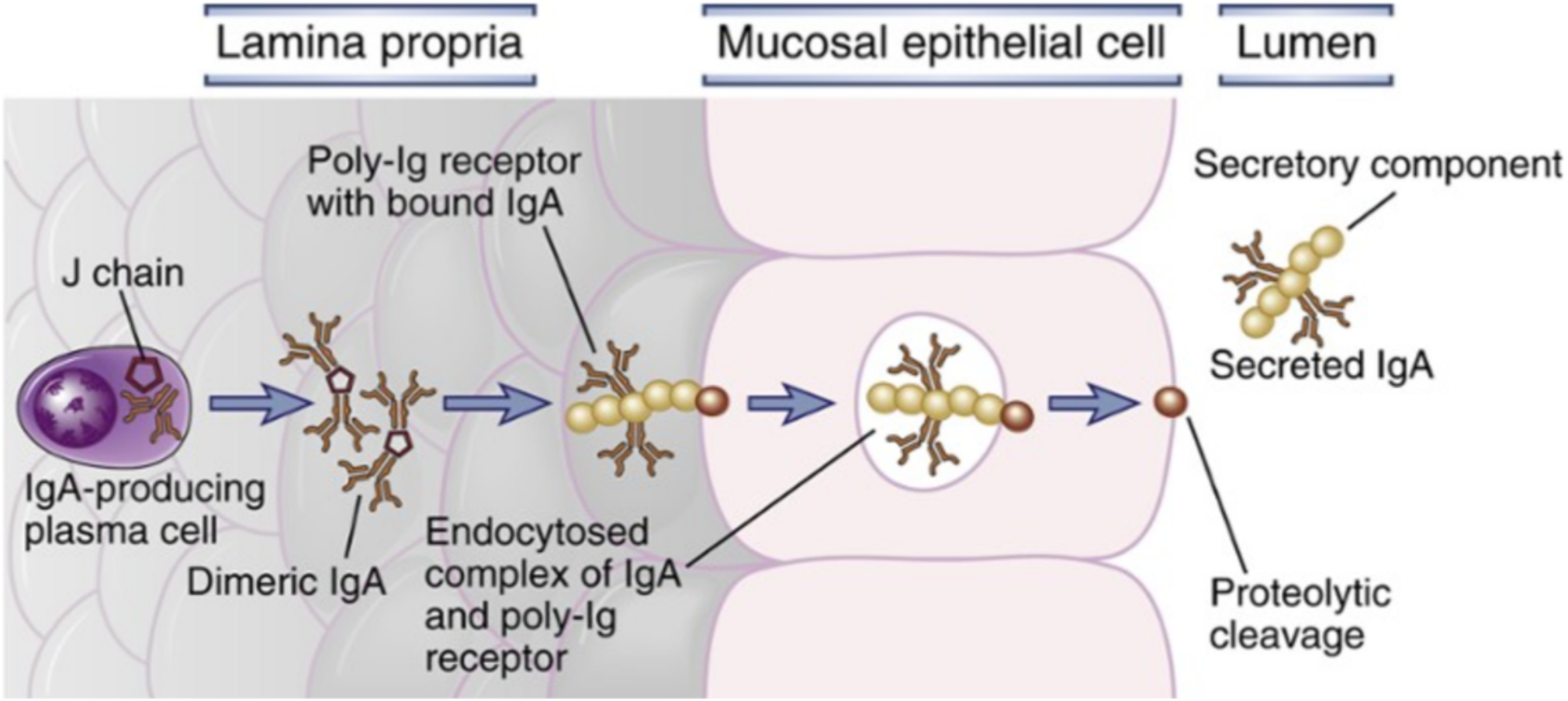
Indução da produção de IgA por células dendríticas



doi:10.1038/emm.2014.16

BAFF: B-cell activating factor
APRIL: a proliferation-inducing ligand
Ácido retinóico:
PROMOVEM TROCA DE ISOTIPO POR LINFÓCITOS B INDEPENDENTE DE T

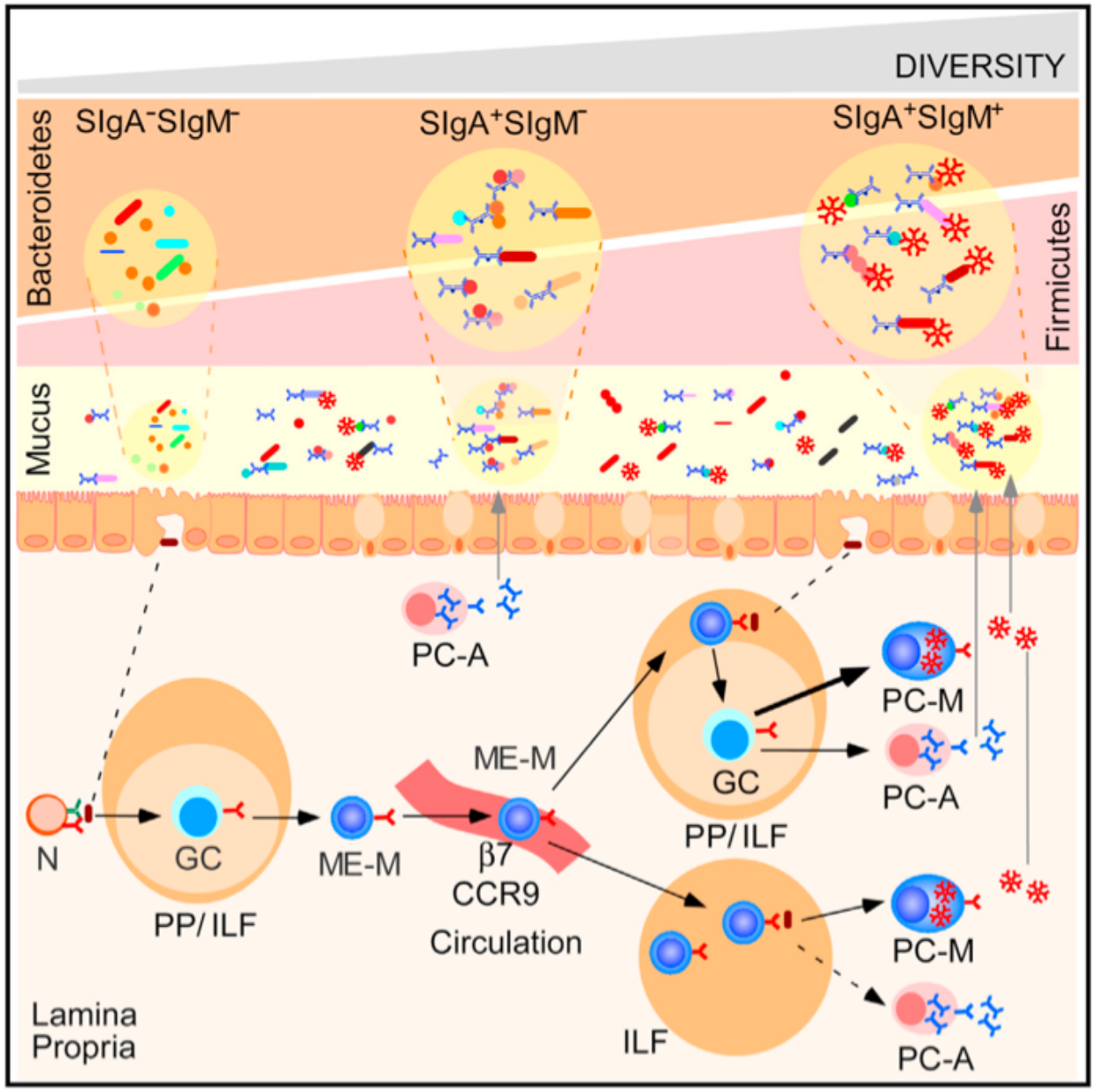
Secreção de IgA



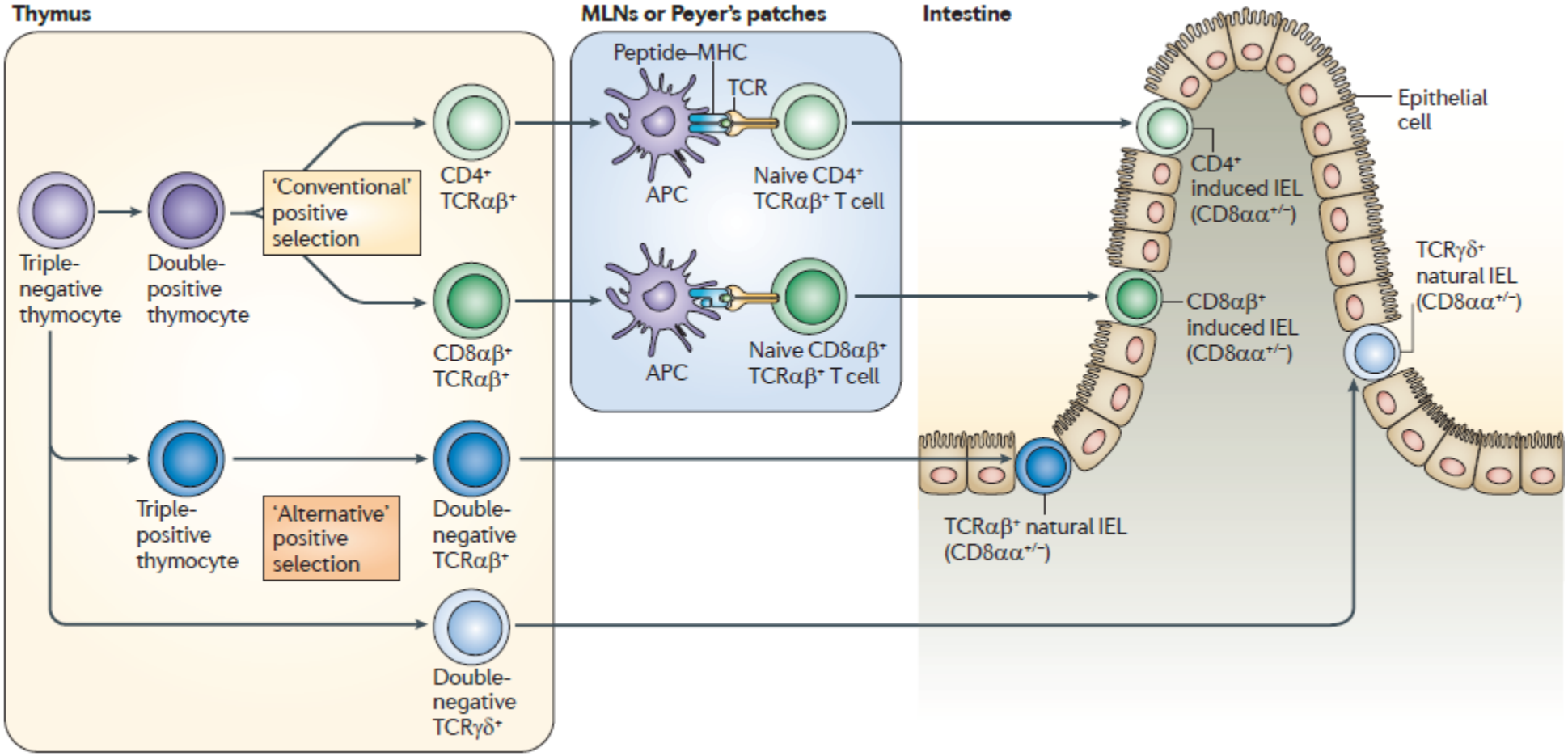
*Leite Materno

* Pele???

Células produtoras de IgM

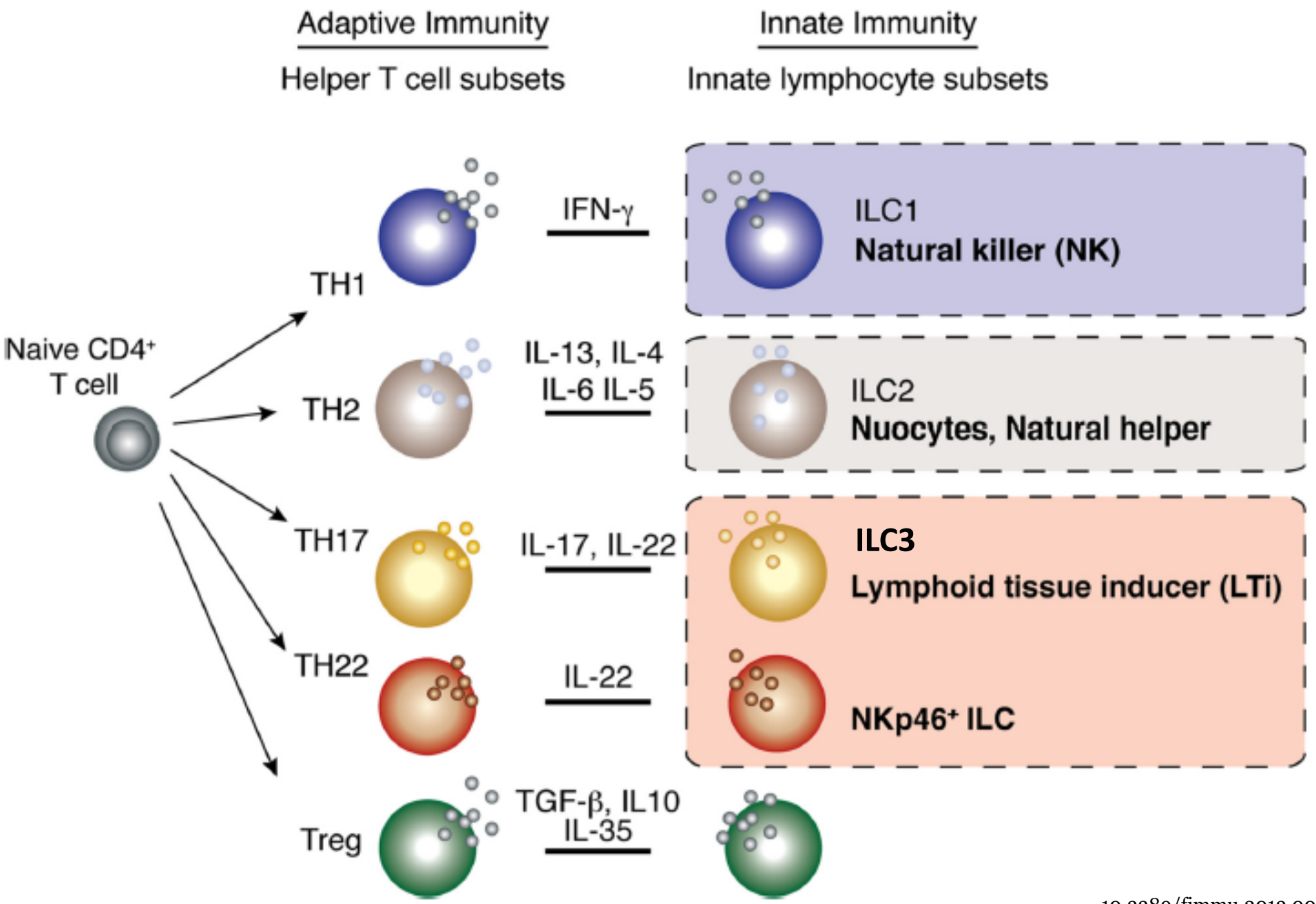


Linfócitos intraepiteliais



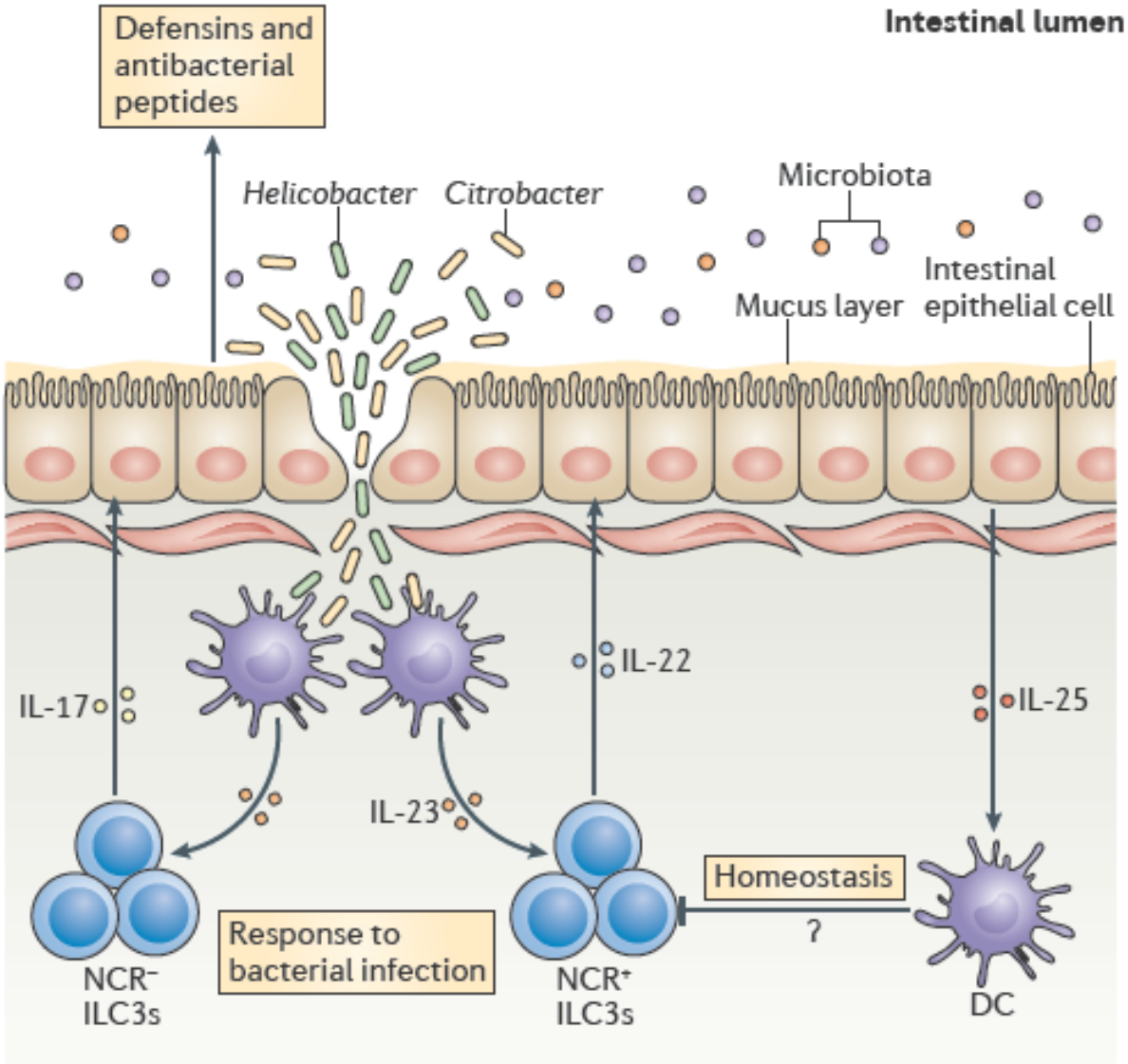
doi:10.1038/nri3007

Innate Lymphoid Cells (ILCs)



10.3389/fimmu.2013.00022

ILCs – Função no intestino e pulmão



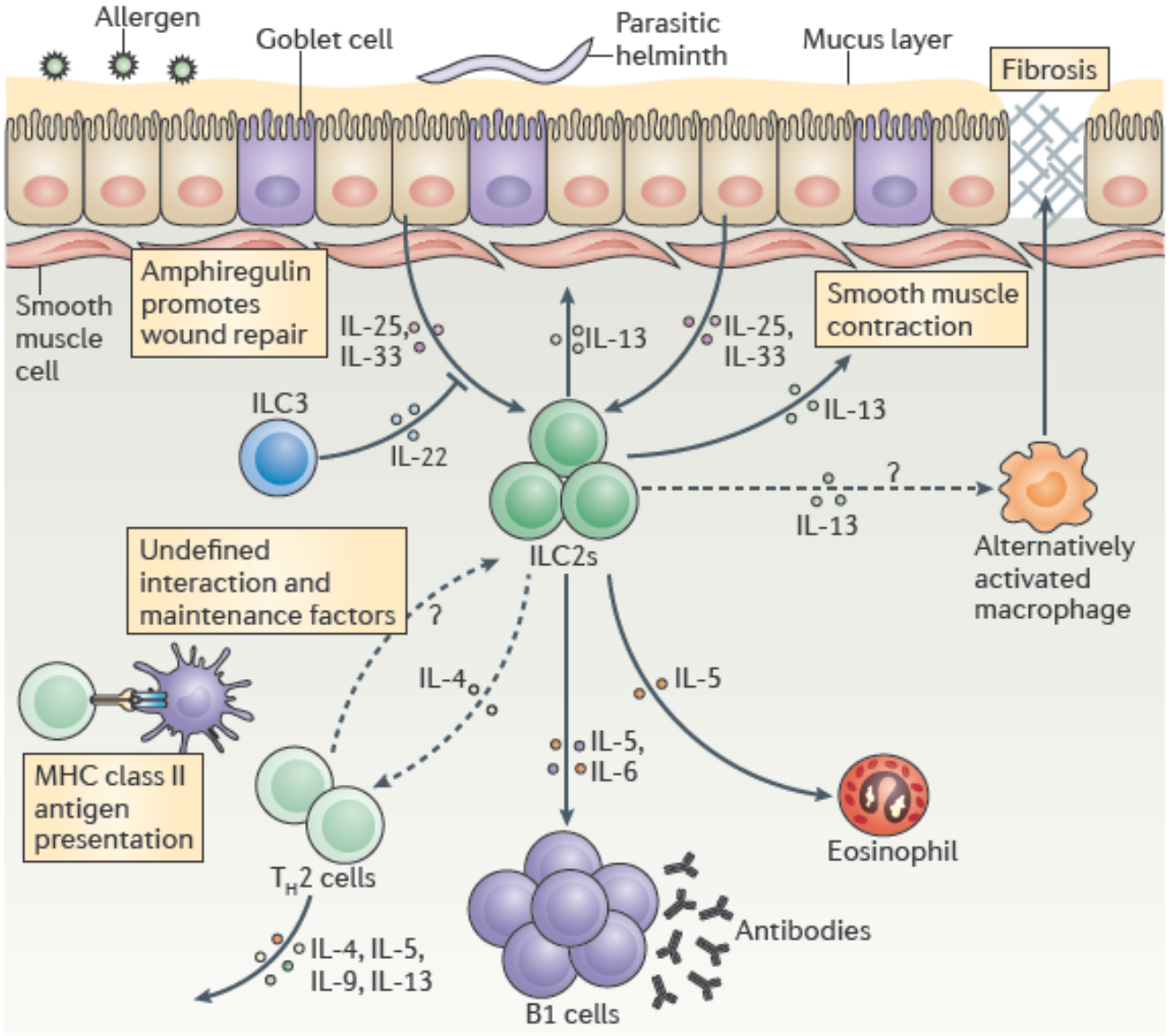
ILC1: imunidade contra bactérias intracelulares

ILC2: indução da produção de muco, recrutamento de eosinófilos

ILC3: Produção de peptídeos antimicrobianos, Reforço da barreira

doi:10.1038/nri3349

ILCs – Função no intestino e pulmão



ILC1: imunidade contra bactérias intracelulares

ILC2: indução da produção de muco, recrutamento de eosinófilos

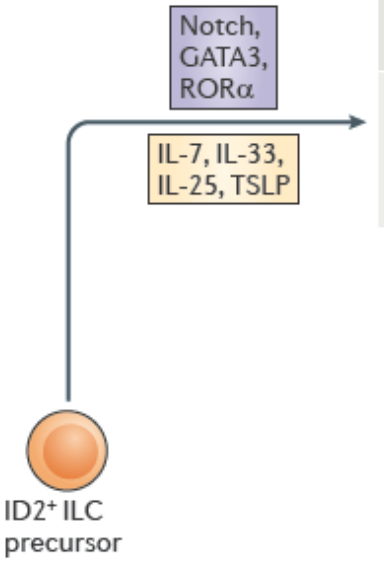
ILC3: Produção de peptídeos antimicrobianos, Reforço da barreira

doi:10.1038/nri3349

Diferentes subtipos de ILC colonizam diferentes tecidos de barreira:

Pulmão
Pele
Intestino
Trato urogenital

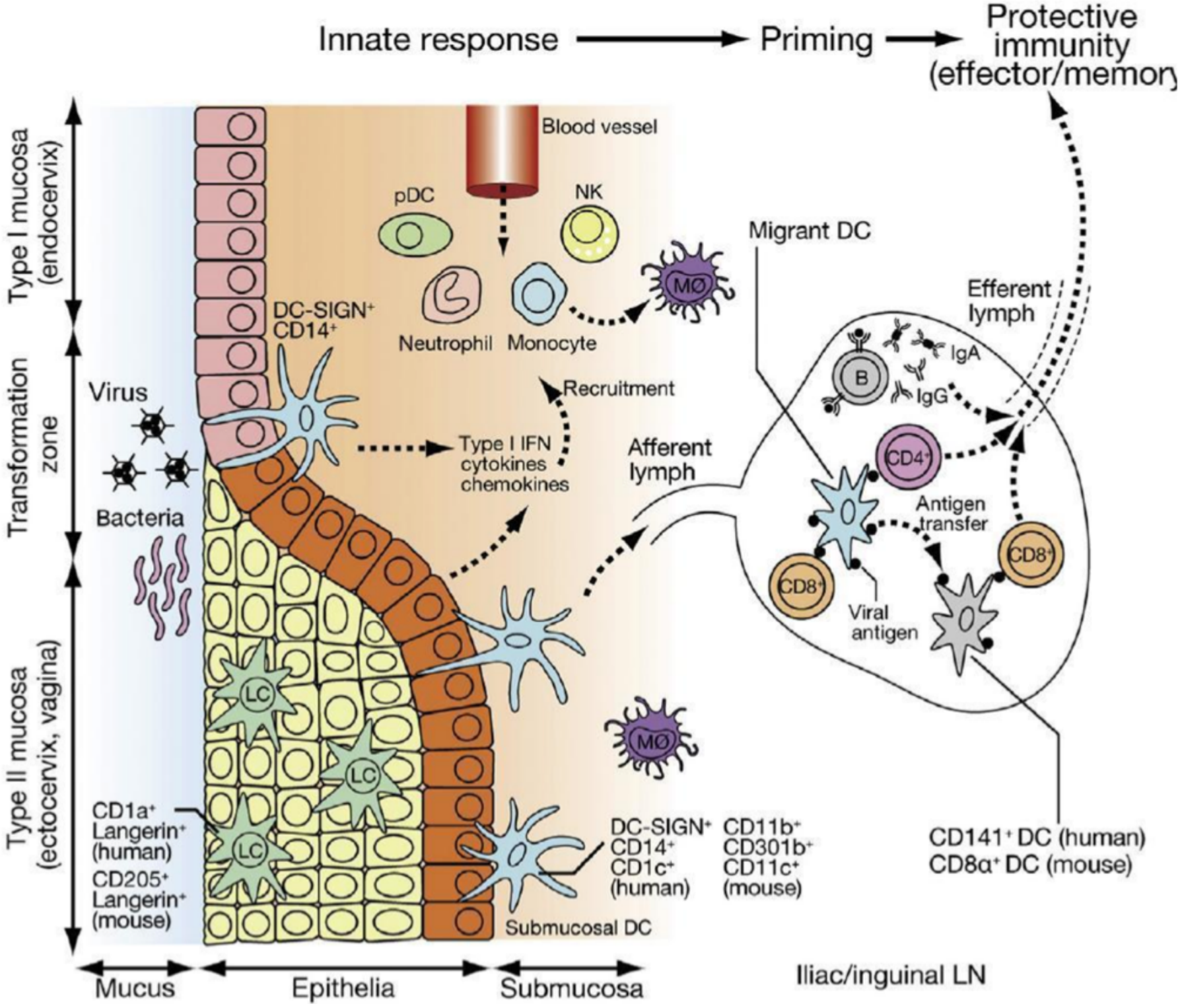
Função de linfócitos inatos e adaptativos e associação com doença



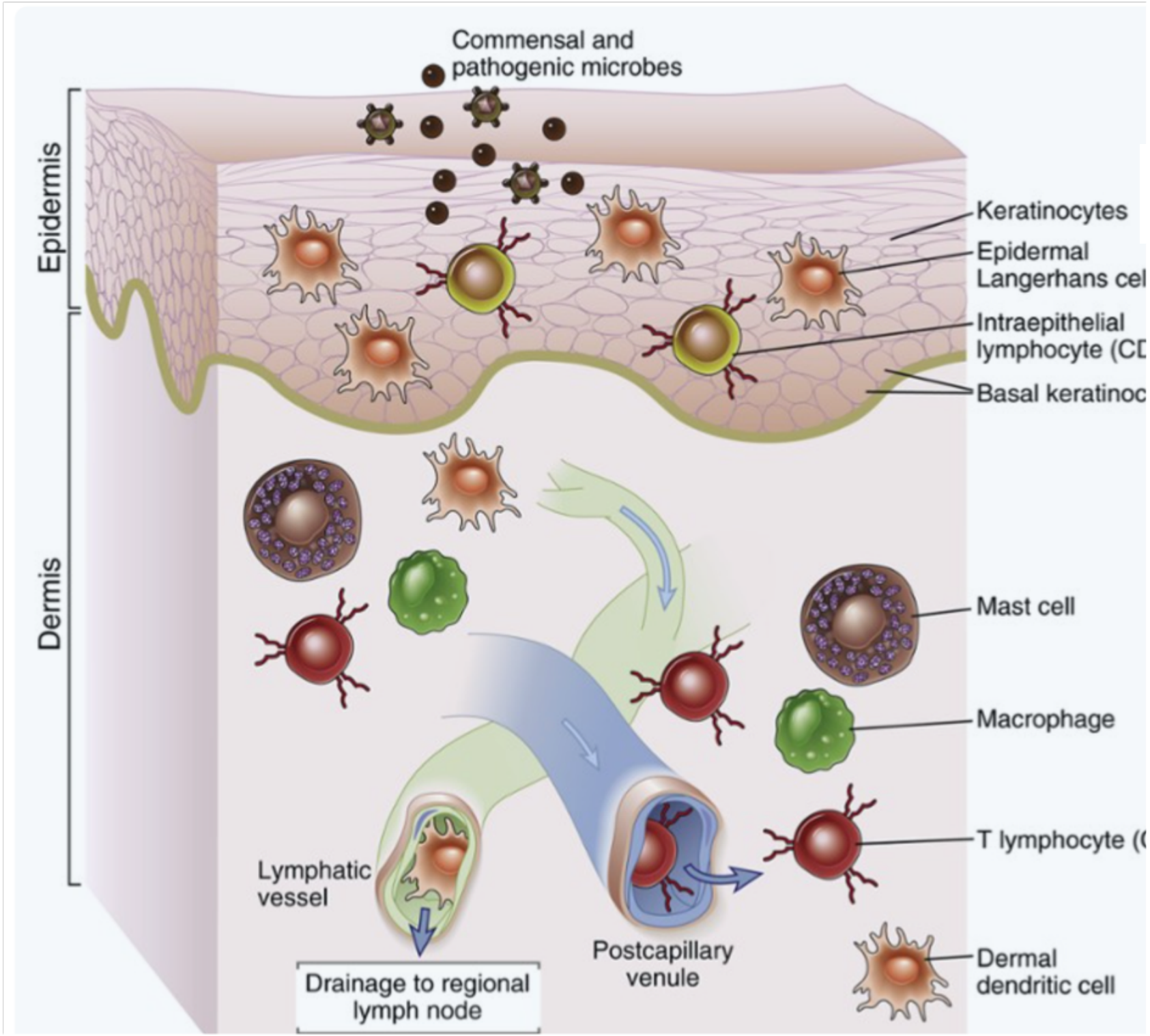
	New nomenclature	New group nomenclature	Mediators produced	Function	Disease association
Nuocyte, NHC, I_H2 cell	ILC2	Group 2 ILCs	IL-5, IL-9, IL-13, amphiregulin	• Immunity to helminths • Wound healing	Allergy and asthma

doi:10.1038/nri3349

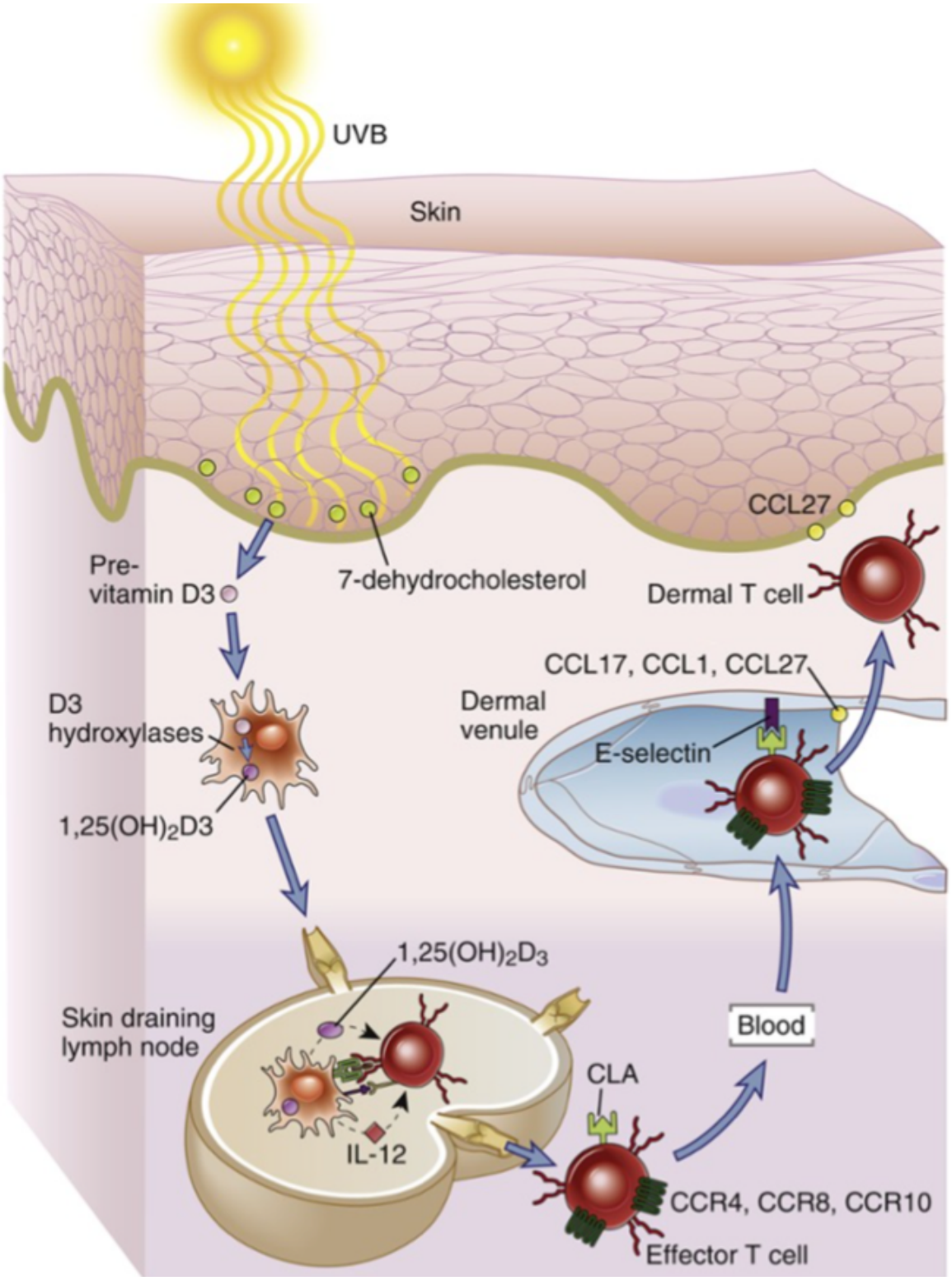
SISTEMA IMUNE DO TRATO GENITO-URINÁRIO


Innate response
Priming
Protective immunity (effector/memory)
Type I mucosa (endocervix)
Transformation zone
Type II mucosa (ectocervix, vagina)
Blood vessel
pDC
NK
Neutrophil
Monocyte
MØ
Migrant DC
Efferent lymph
DC-SIGN+ CD14+
Virus
Bacteria
Recruitment
Type I IFN cytokines chemokines
Afferent lymph
IgA
IgG
B
CD4+
CD8+
Antigen transfer
Viral antigen
LC
CD1a+ Langerin+ (human)
CD205+ Langerin+ (mouse)
DC-SIGN+ CD14+ CD1c+ (human)
CD11b+ CD301b+ CD11c+ (mouse)
Submucosal DC
CD141+ DC (human)
CD8α+ DC (mouse)
Mucus
Epithelia
Submucosa
Iliac/inguinal LN

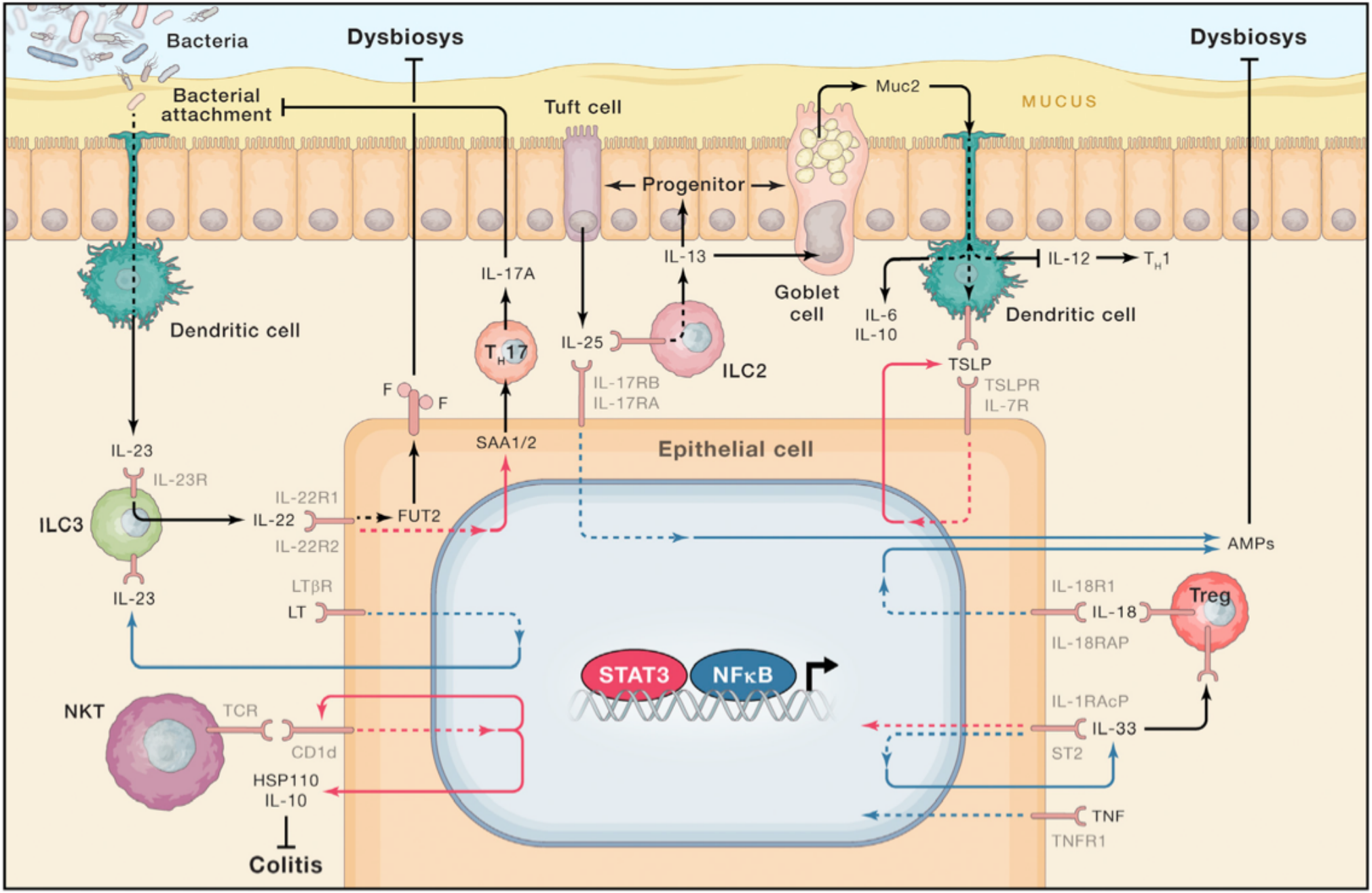
SISTEMA IMUNE CUTÂNEO



Defensinas
Calatecidinas

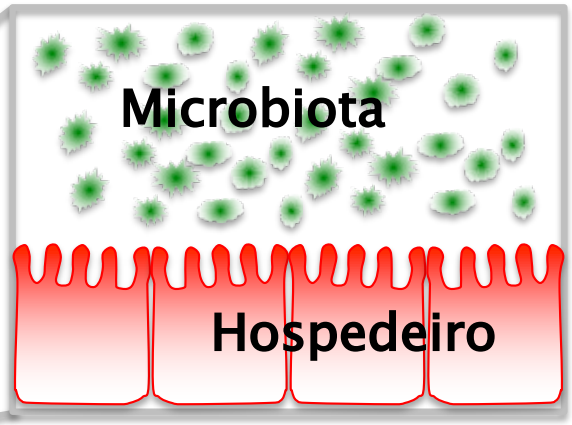

UVB
Skin
CCL27
Pre-
vitamin D3
7-dehydrocholesterol
Dermal T cell
CCL17, CCL1, CCL27
D3
hydroxylases
Dermal
venule
E-selectin
1,25(OH)2D3
1,25(OH)2D3
Skin draining
lymph node
Blood
CLA
IL-12
CCR4, CCR8, CCR10
Effector T cell

Integrando os componentes

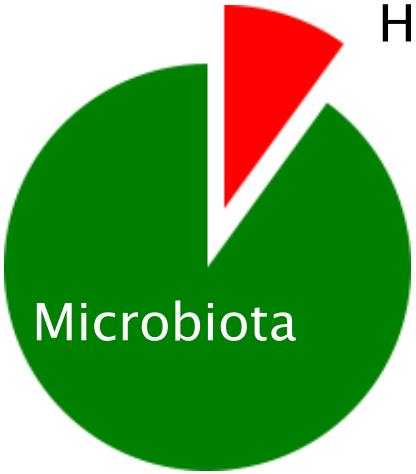


Microbiota e imunidade de mucosa

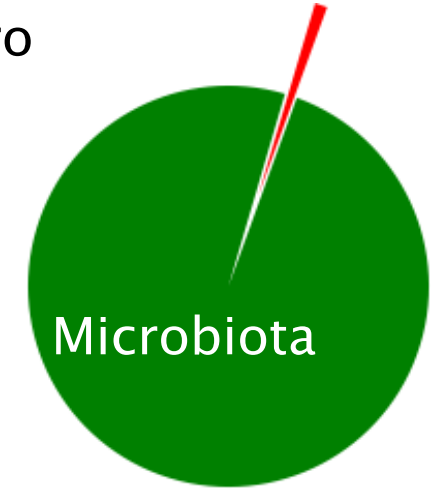
‘Meta’organismo humano



Células no seu corpo

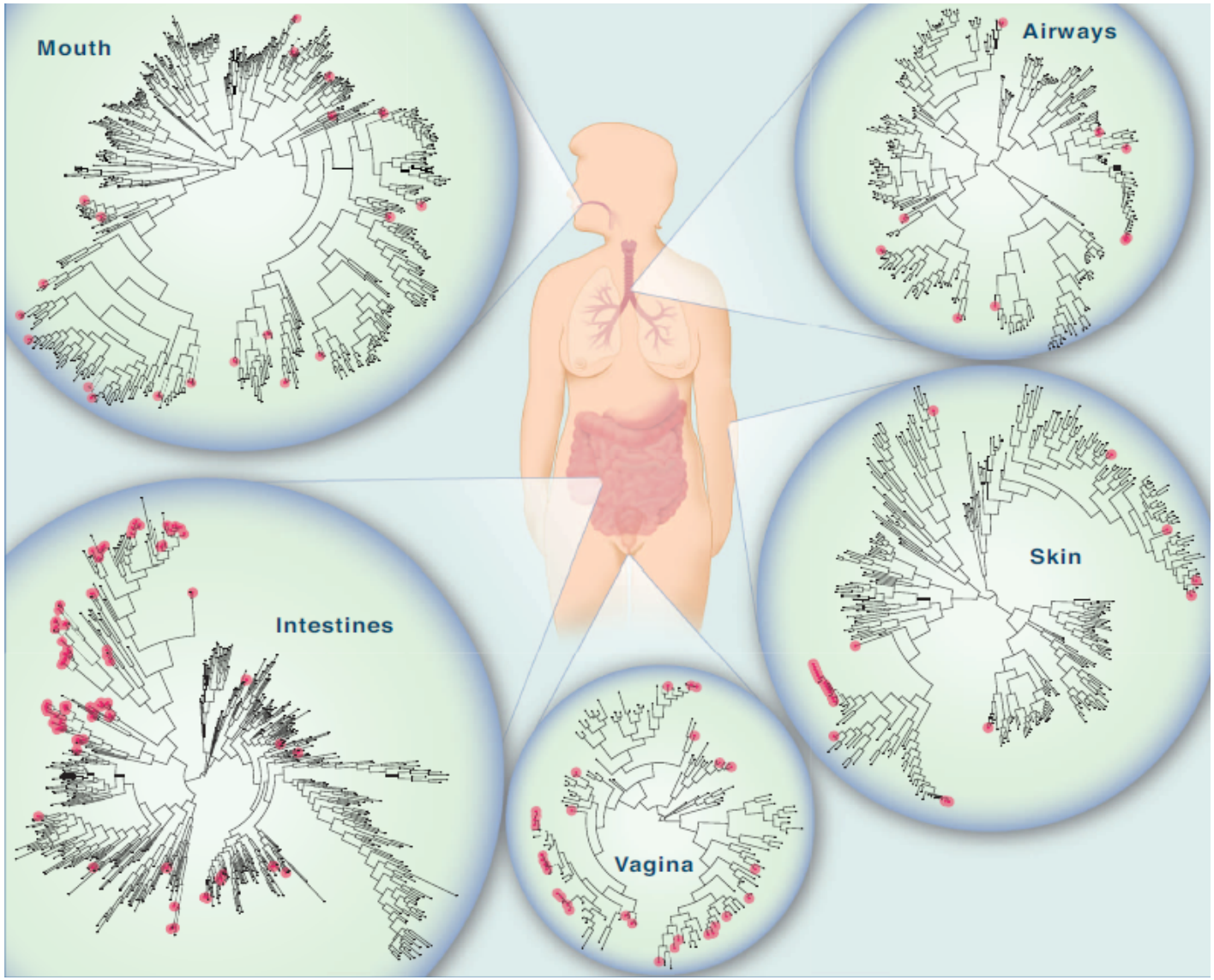


Genes no seu corpo



Gordon, Knight, Relman, Wang

‘Meta’organismo humano



Fisiologia

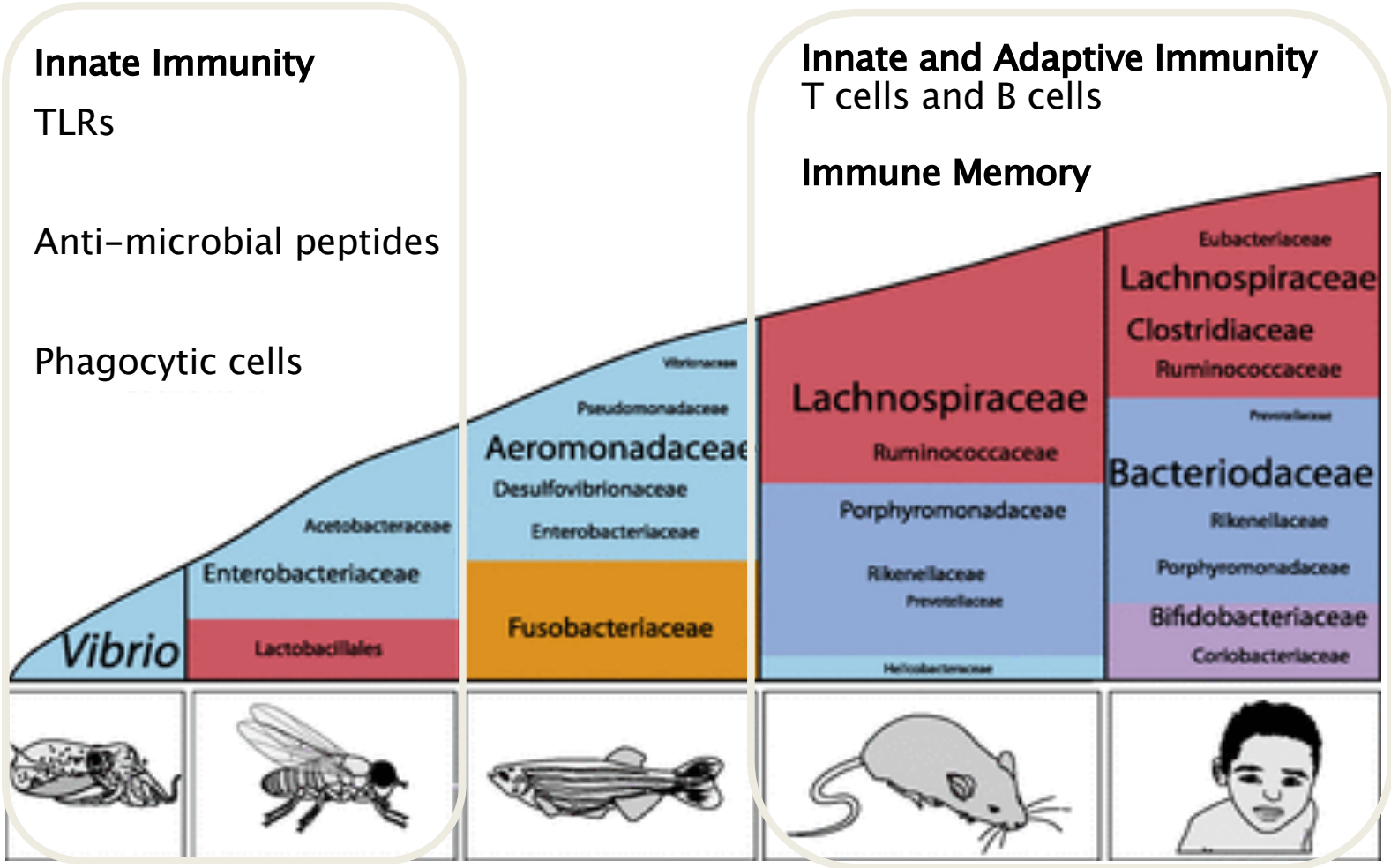
- Absorção de Nutrientes
- Síntese de Vitaminas
- Metabolismo de bile e hormônios
- Fermentação de caboidratos

- Comportamento e Cognição

- **Sistema Imunológico**

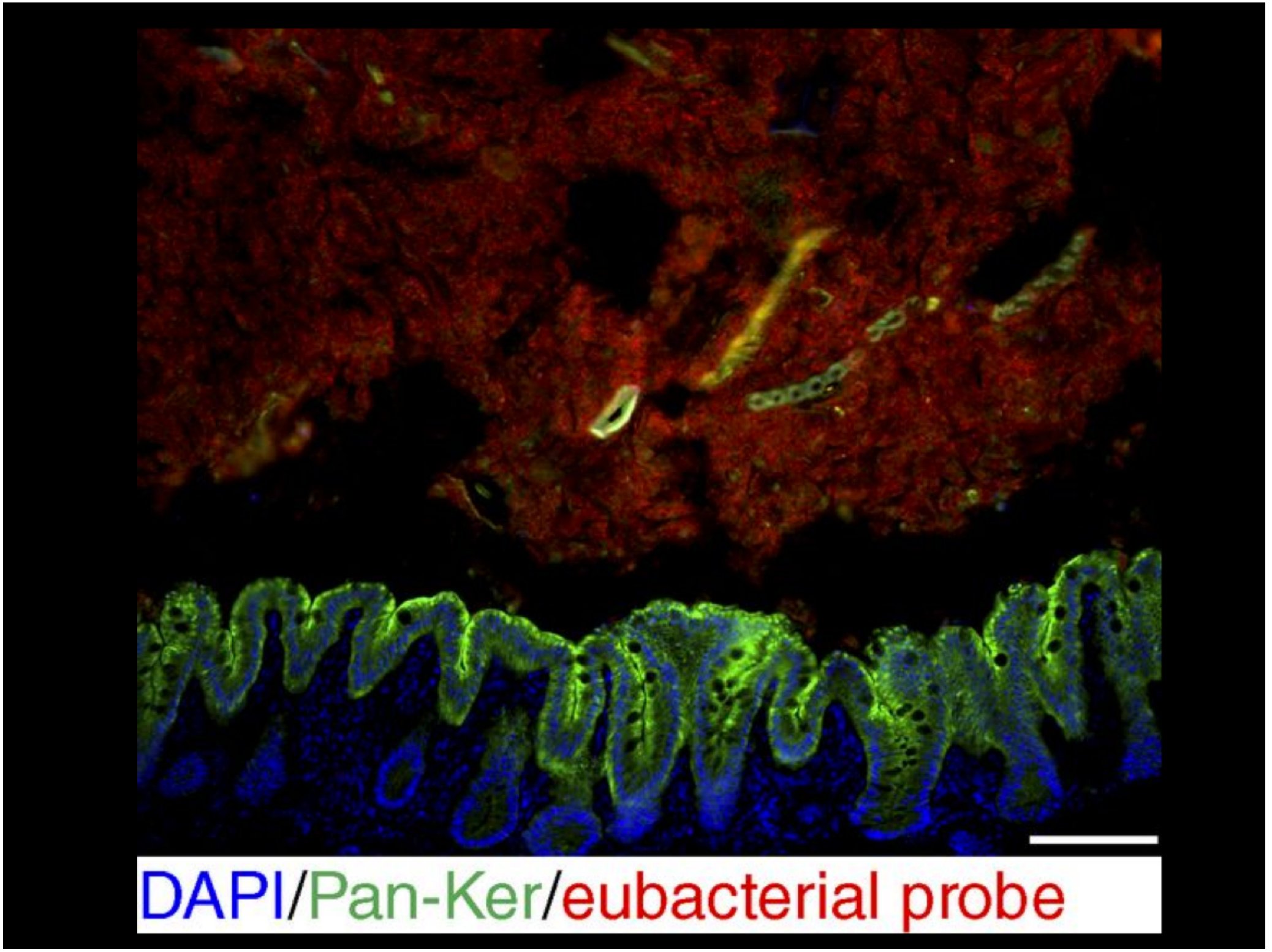
doi: 10.1126/science.1195568

Complexidade da microbiota aumentou à medida em que o sistema imune evoluiu

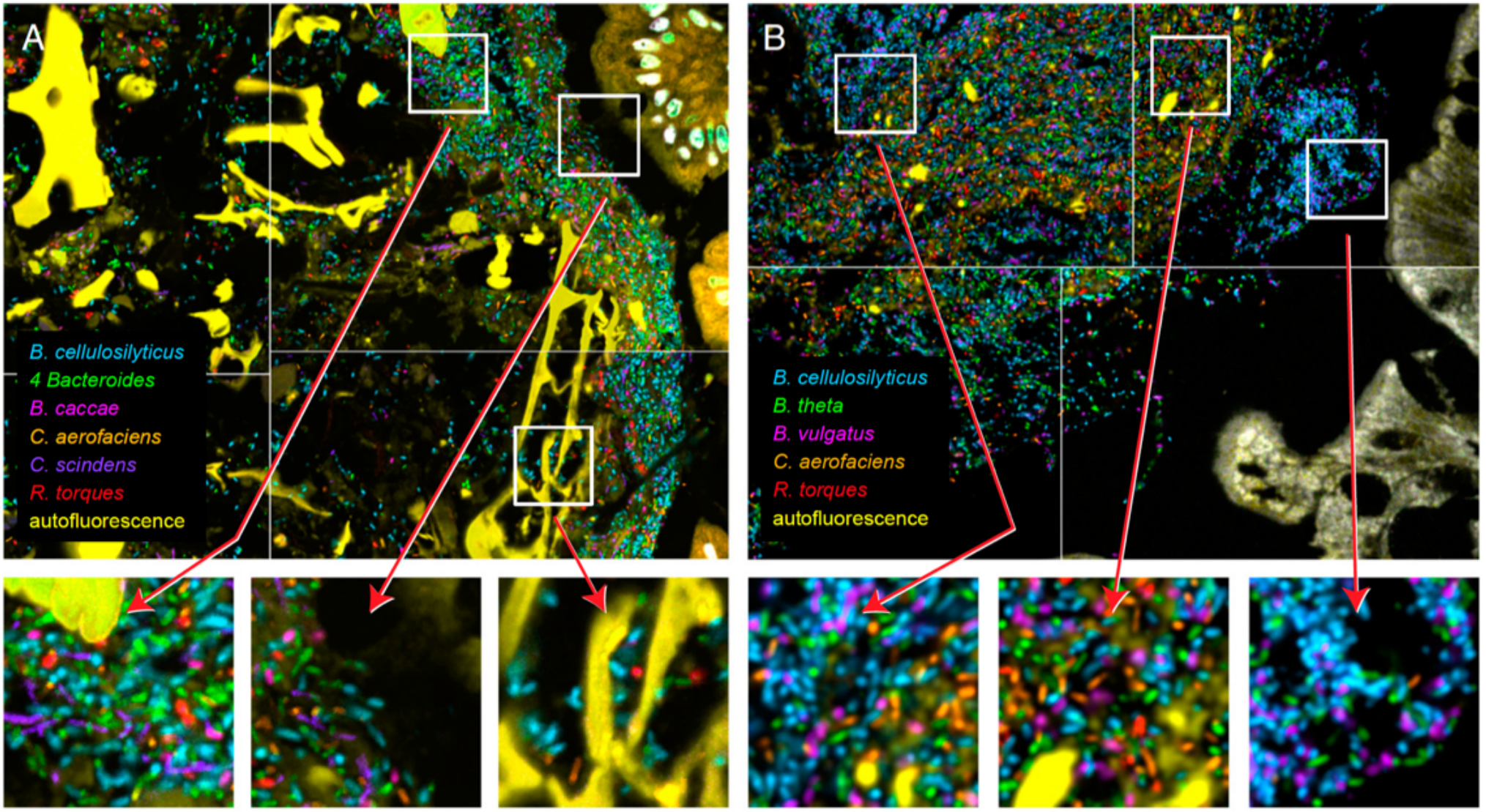


~6 OTUs ~1000 OTUs

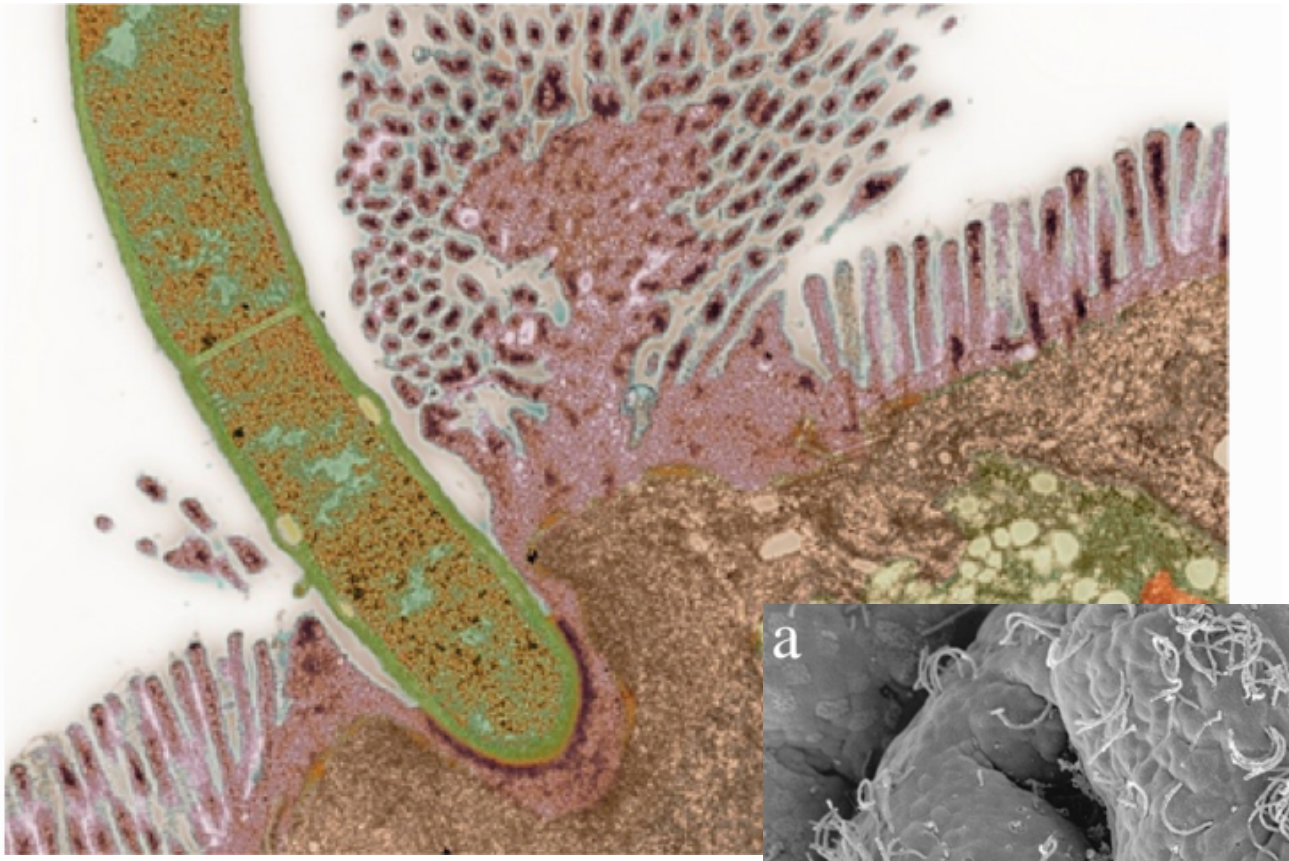
Modified from Kostic, Howitt and Garrett *Genes Dev.* 2012 and McFall-Ngai *Nature* 2007


DAPI/Pan-Ker/eubacterial probe

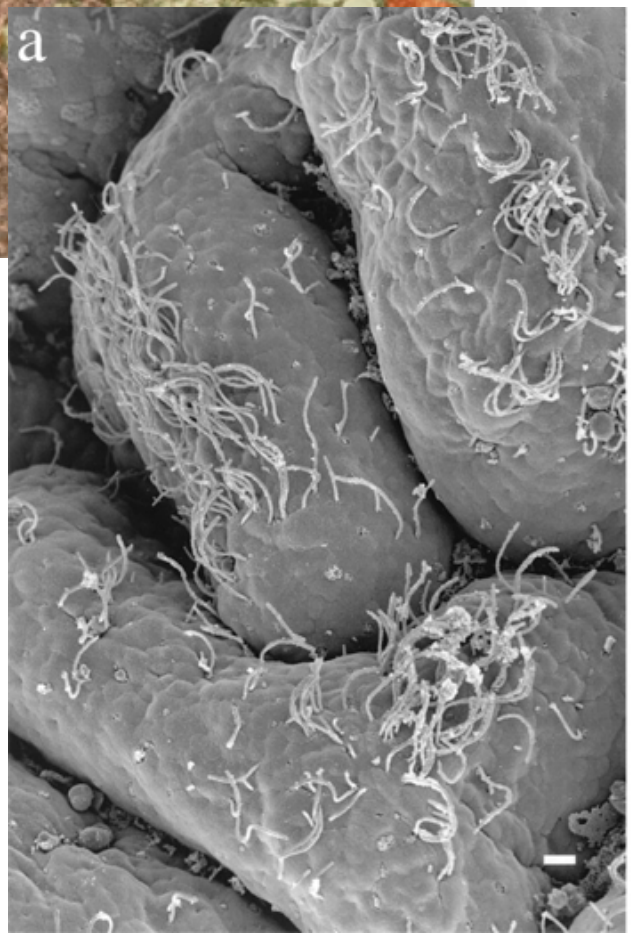
Mapa 3D da Microbiota Intestinal

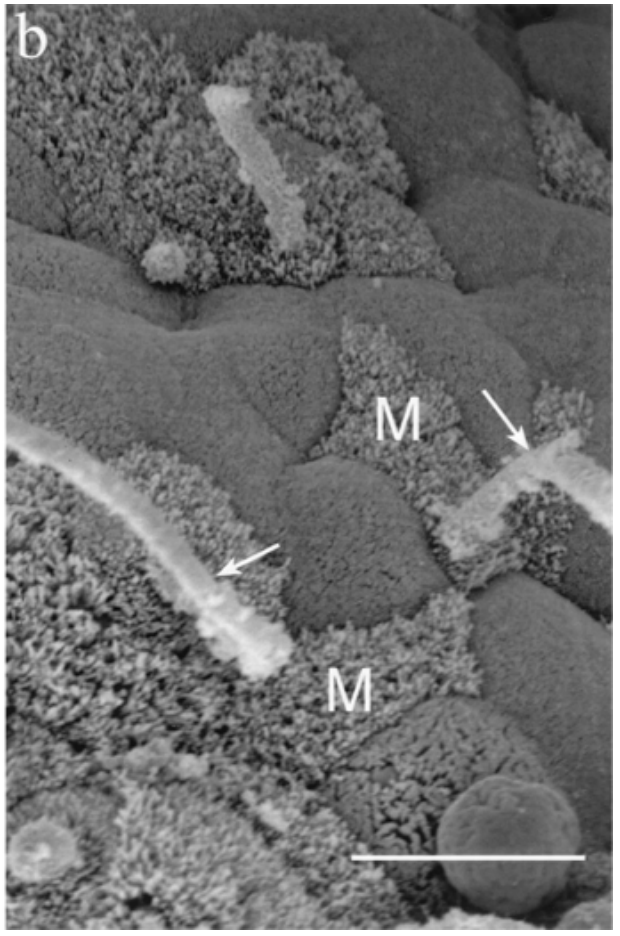


Welch et al, PNAS 2017.

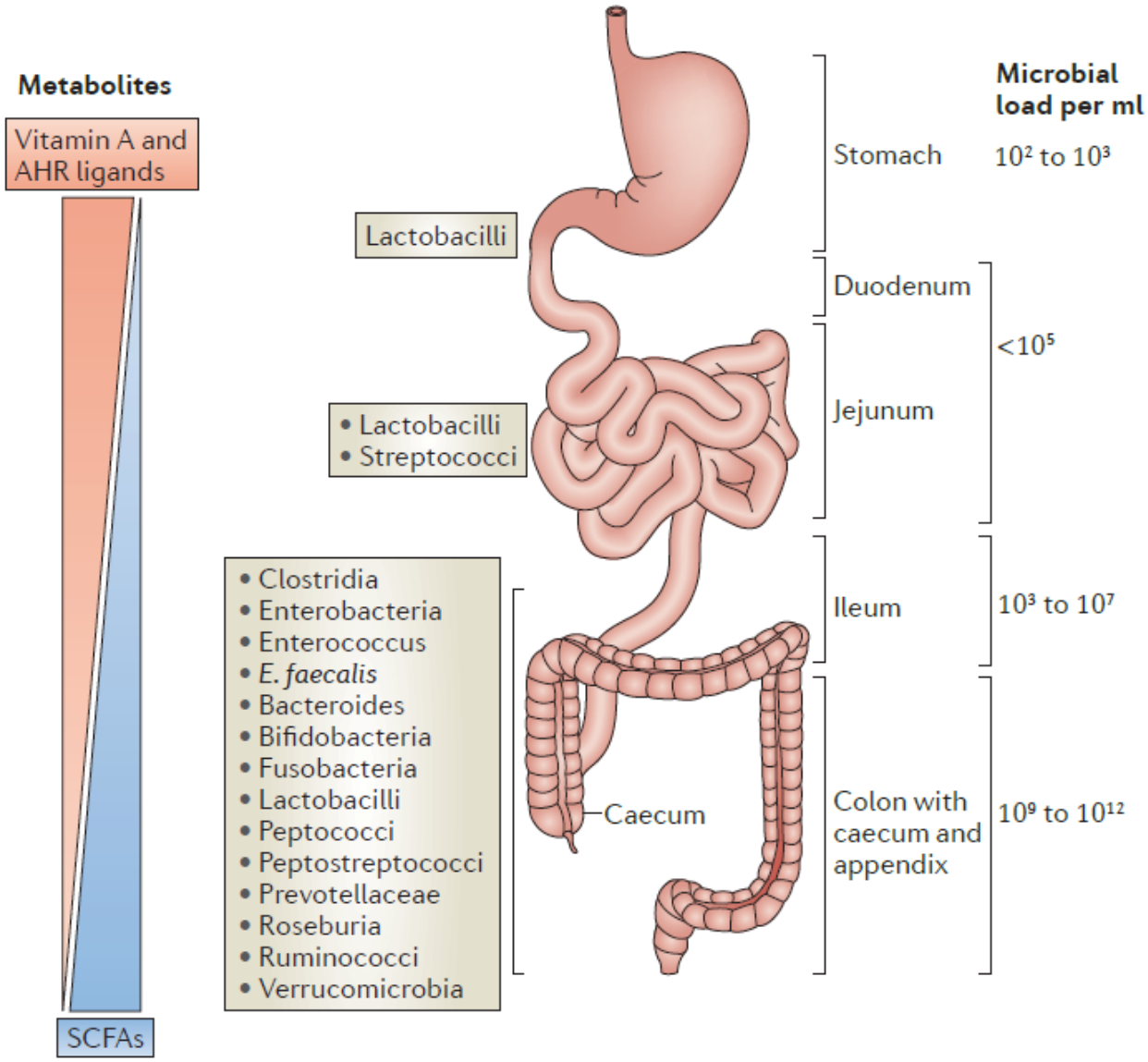



Cell
Volume 10
Number 3
September 15, 2011
www.cellpress.com
Host & Microbe
Genome of Segmented
Filamentous Bacteria


a

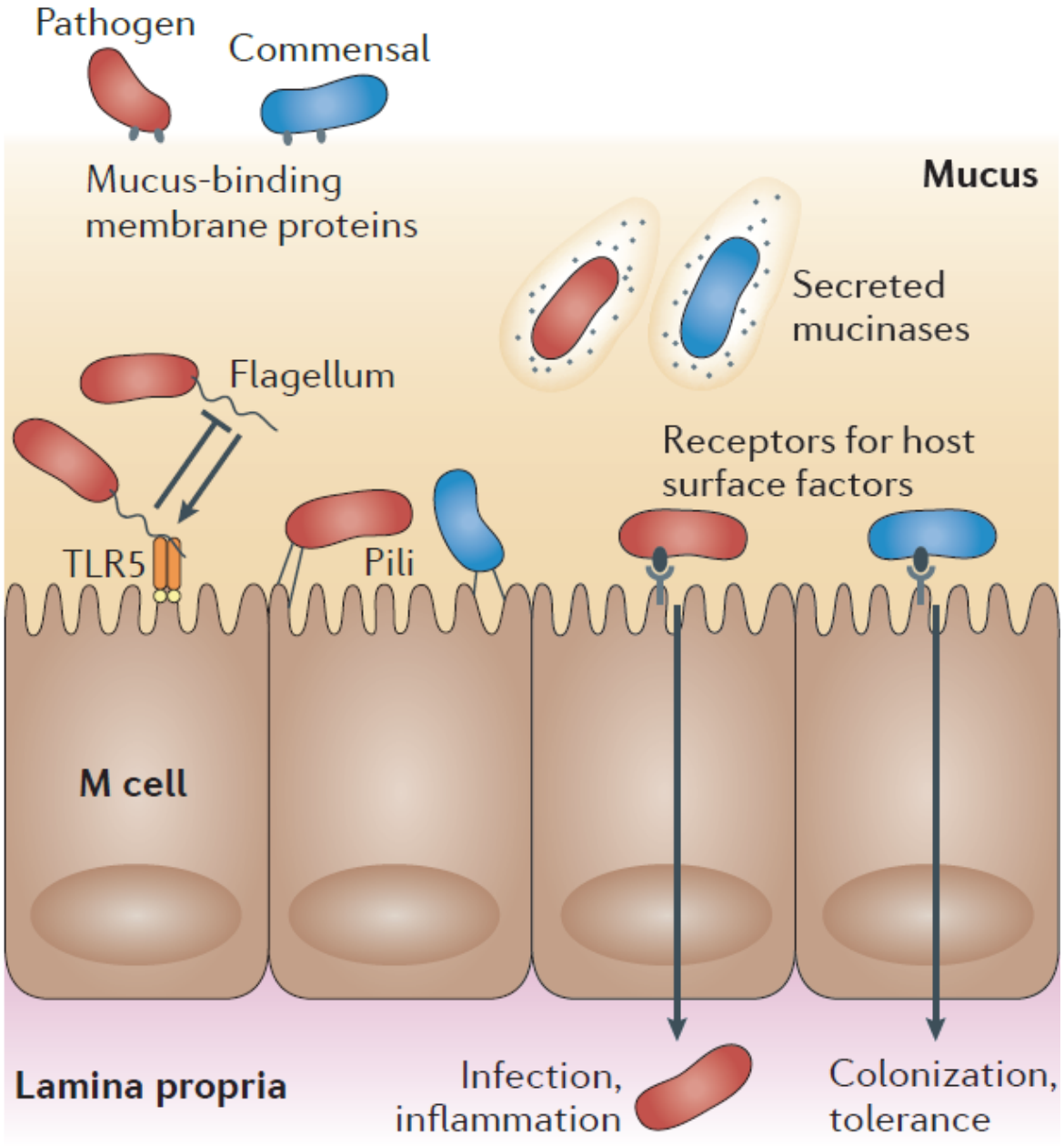

b
M
M

Distribuição das comunidades microbianas ao longo do intestino



doi:10.1038/nri3738

Microbiota



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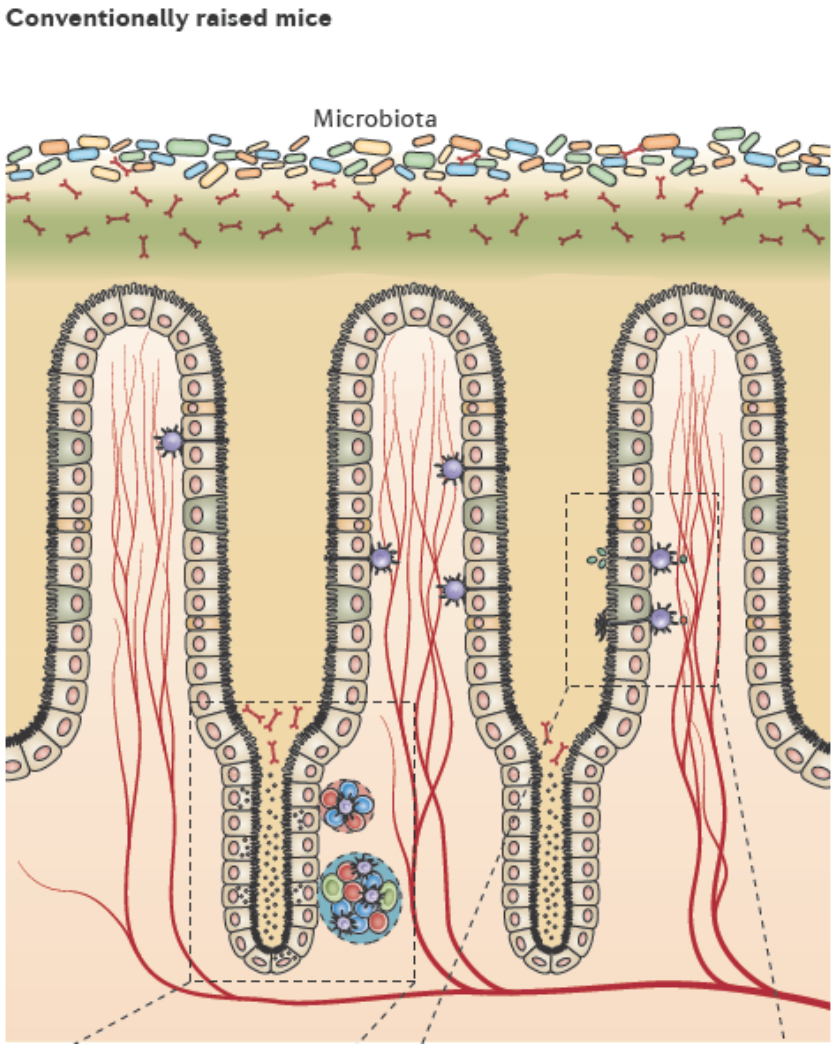
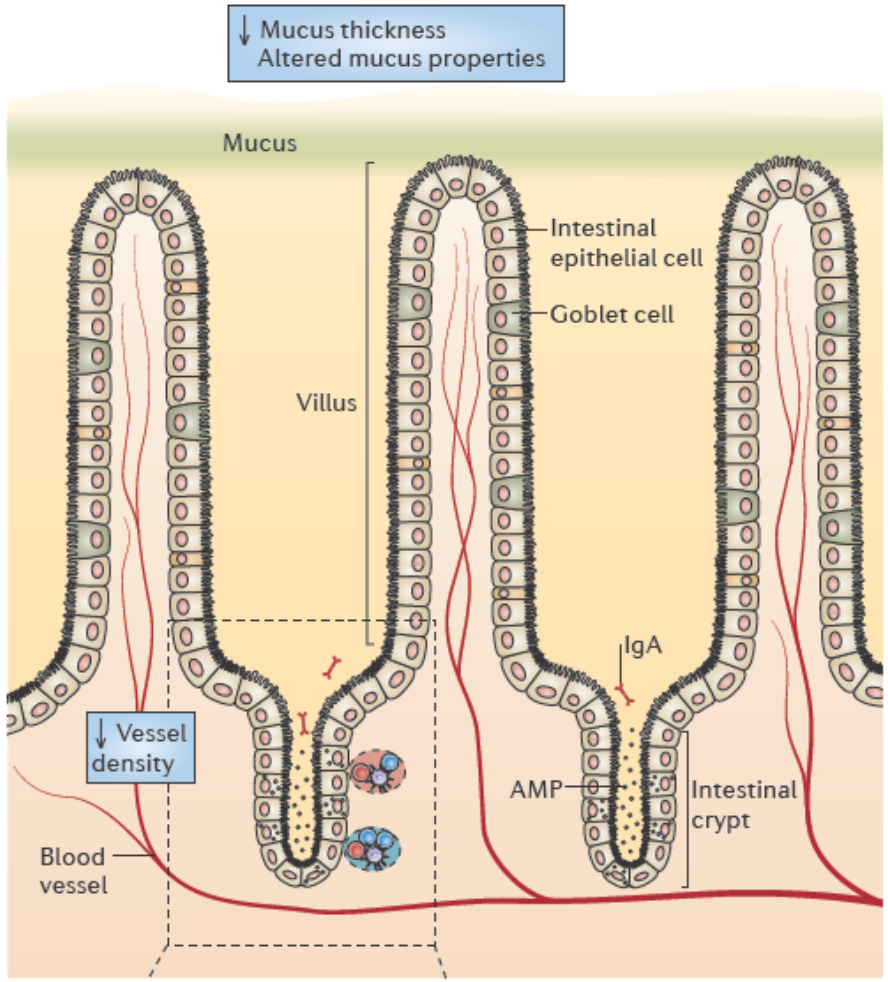
doi:10.1038/nrmicro3552

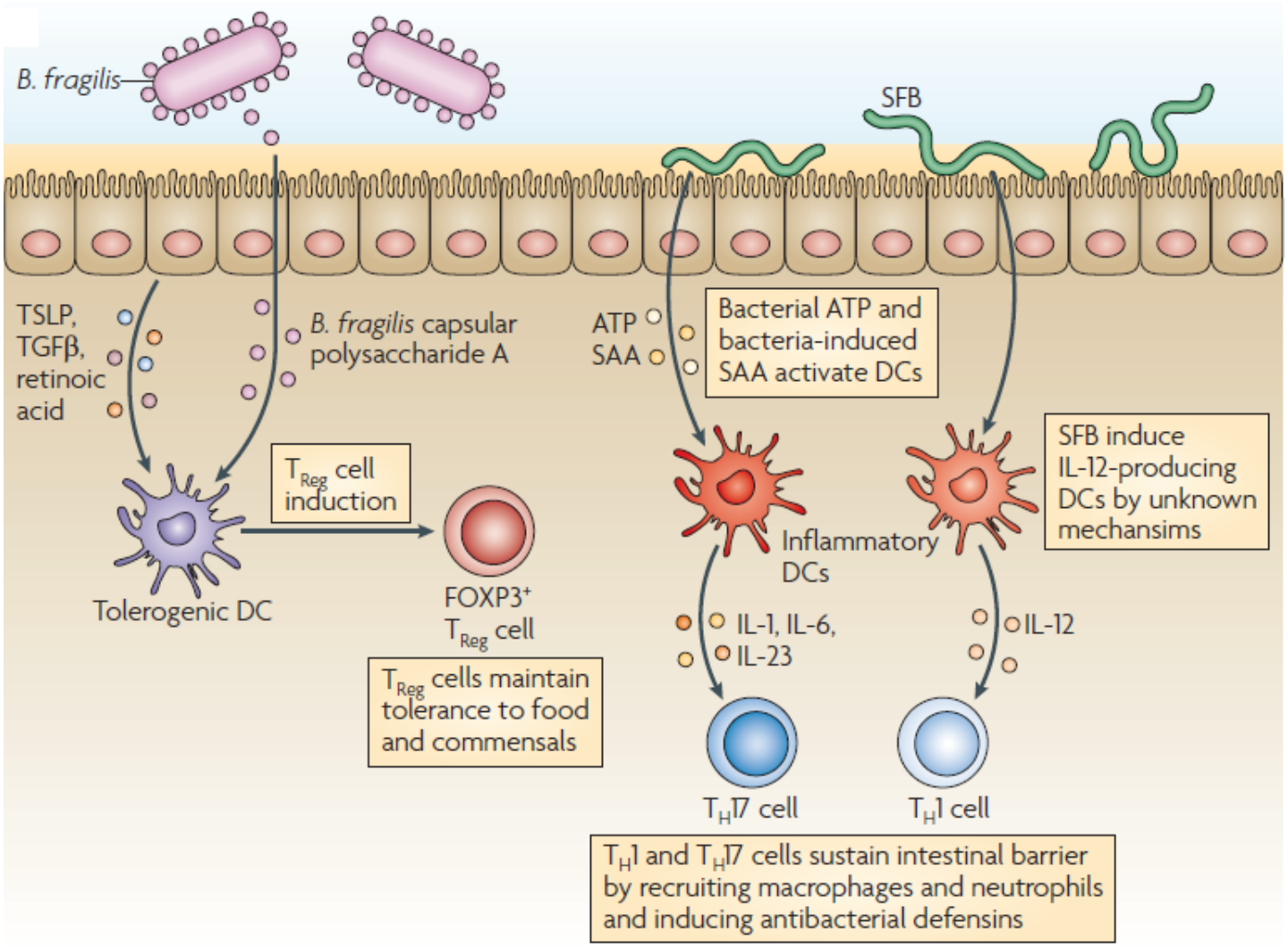
Microbiota





doi:10.1038/nrmicro2974

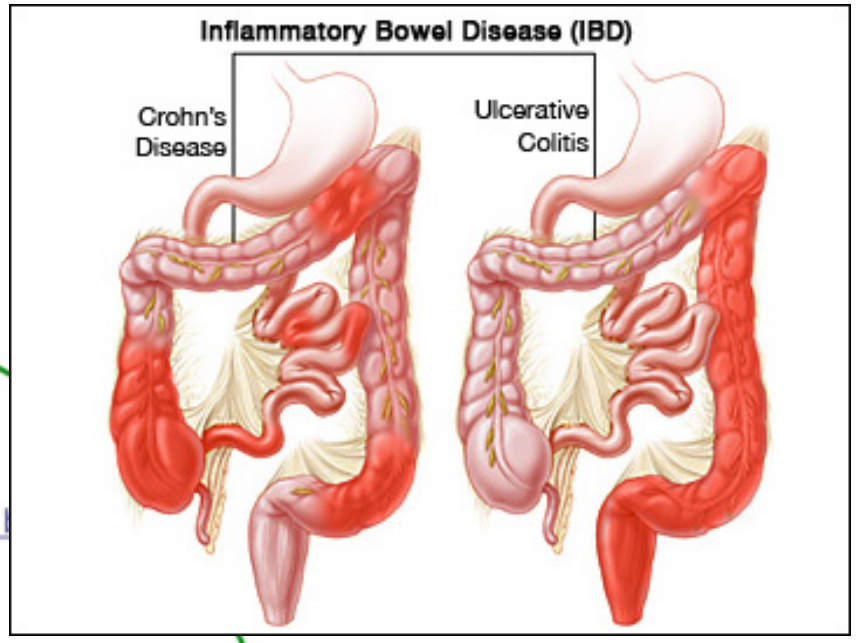
Microbiota



- **Indução de Treg**
- **Vacina oral**
- **Th17**
- **Troca de isotipo IgA**

doi: 10.1038/nri2850

IBDs



Crohn's

Cellular innate immunity
NOD2
ATG16
IRGM
LRRK2

Immune-mediated
PTPN22
CCR6
IL2RA
IL18RAP
IL27
ERAP2
ITLN1
CCL2/CCL7
TNFSF11
BACH2
TAGAP
VAMP3

Other
DENNDIB
DNMT3A
GCKR
THADA
SP140
PRDX5
ZPF36L1
ZMIZ1
MUC1/SCAMP3
CPEB4
FADS1
5q31 (IBD5)

IBD

Th17
*IL23R**
*IL12B**
*STAT3*J*
*AK2**
TYK2

HLA
*DRB*103*

Immune-mediated
*MST1**
*IL10**
*CARD9**
*REL**
*PRDM1**
*TNFSF15**
*ICOSLG**
*IL1R2**
YDJC
SMAD3
PTPN2

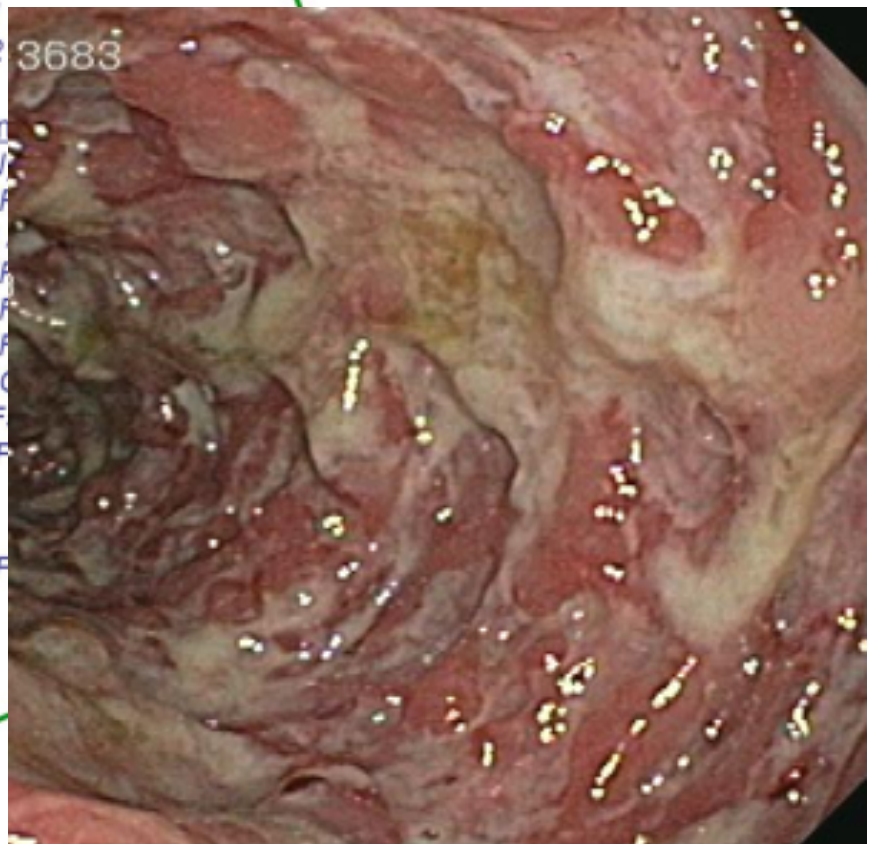
Other
*NKX2-3**
*CREM**
*C11Orf30**
*ORMDL3**
*RTEL1**
*PTGER4**
*KIF21B**
CDKAL1
ZNF365

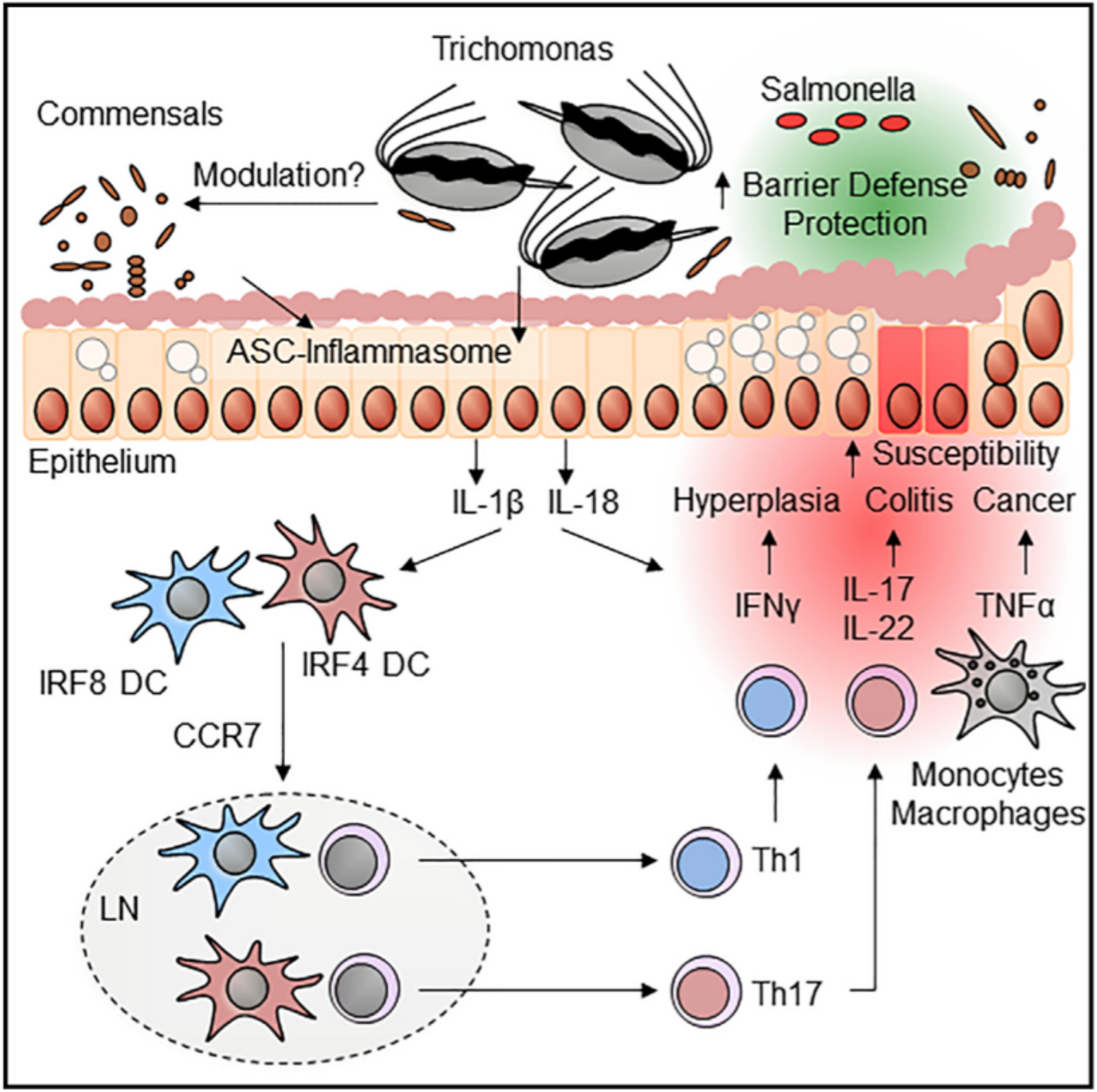
UC

Epithelial
ECM1
HNF4A
CDH1
LAMB1
GNA12

Imm
IFN
IL8
IL2
IL7
TNF
TNF
FC
IRF
LSF

Other
OTUD3 / F
DAP
PIM3
CAPN10





Intestino:

- *Crohn's Disease*
- *Colite Ulcerativa*
- *Câncer*

Estômago

- *Úlcera, câncer colorretal*

Trato Urogenital

- *Câncer*

Pulmão

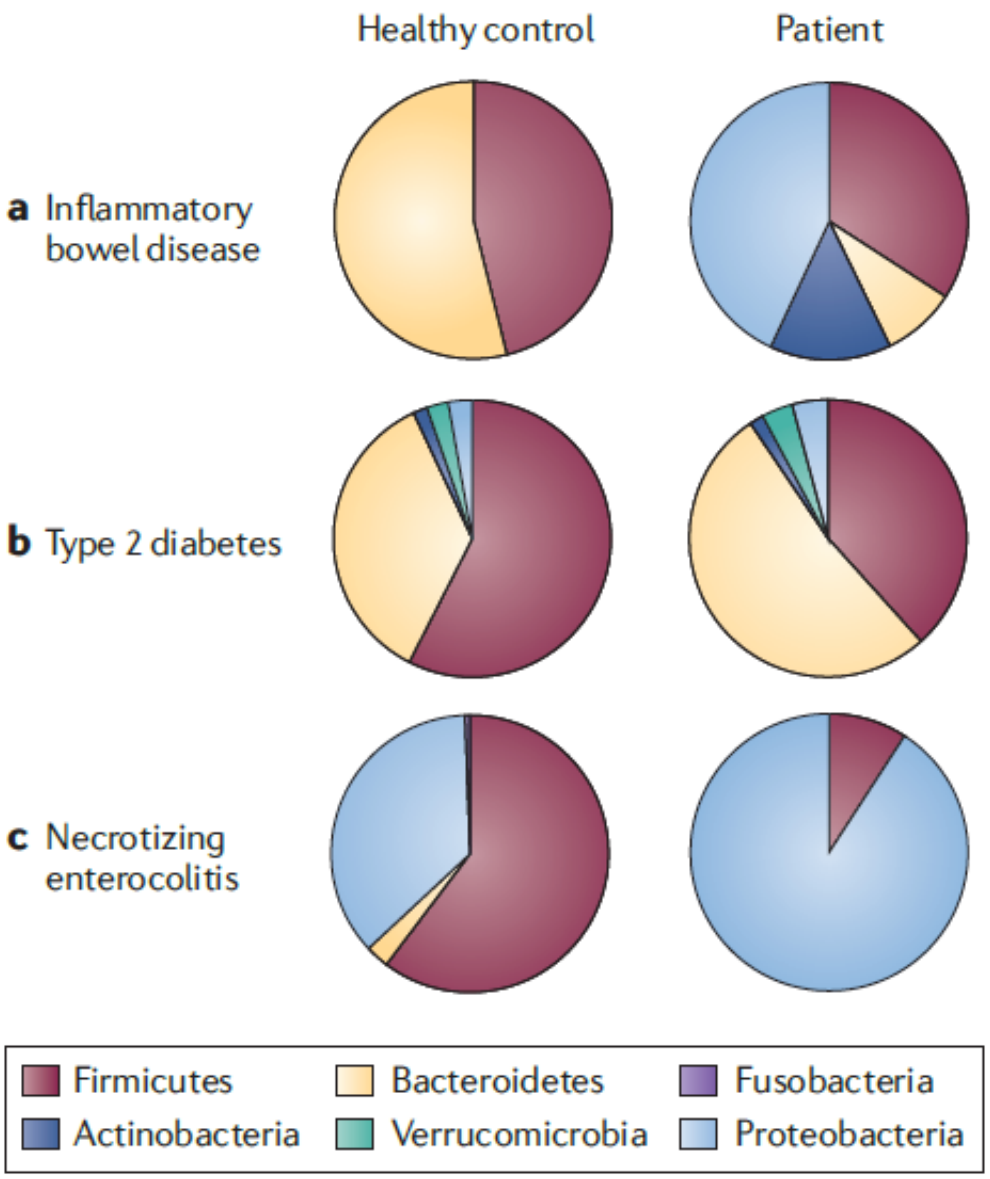
- *Fibrose cística*

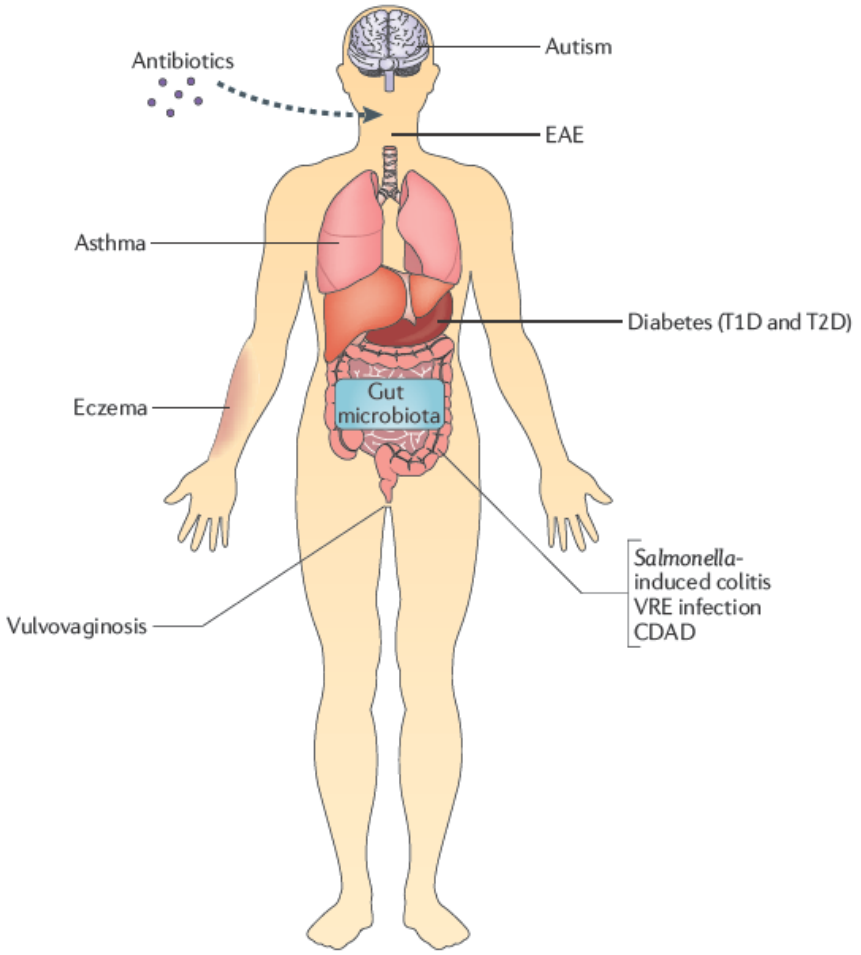
Pele:

- *Psoríase*

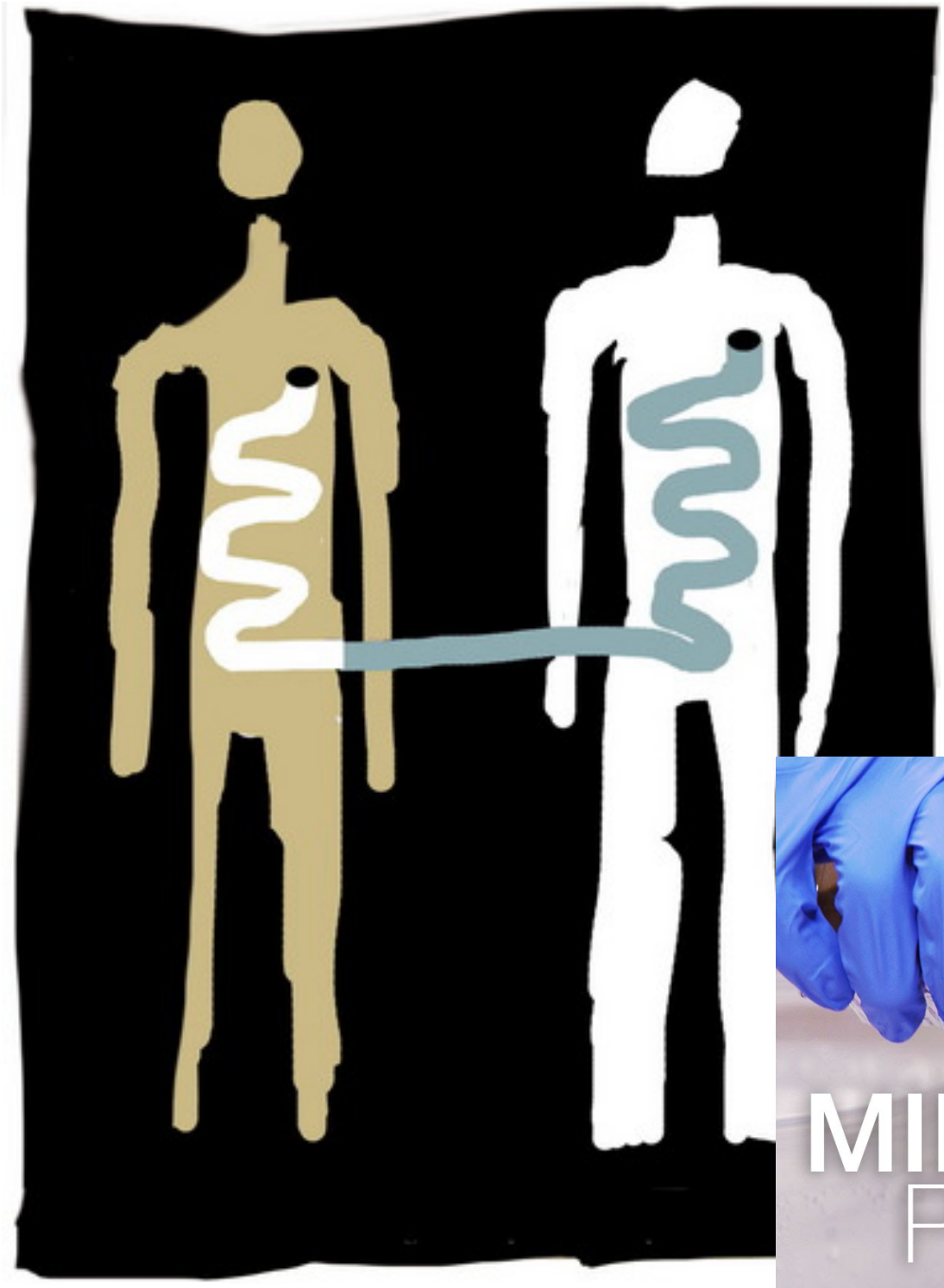
Chudnovskiy et al., 2016,
Cell 167, 444–456

Disbiose x Doença



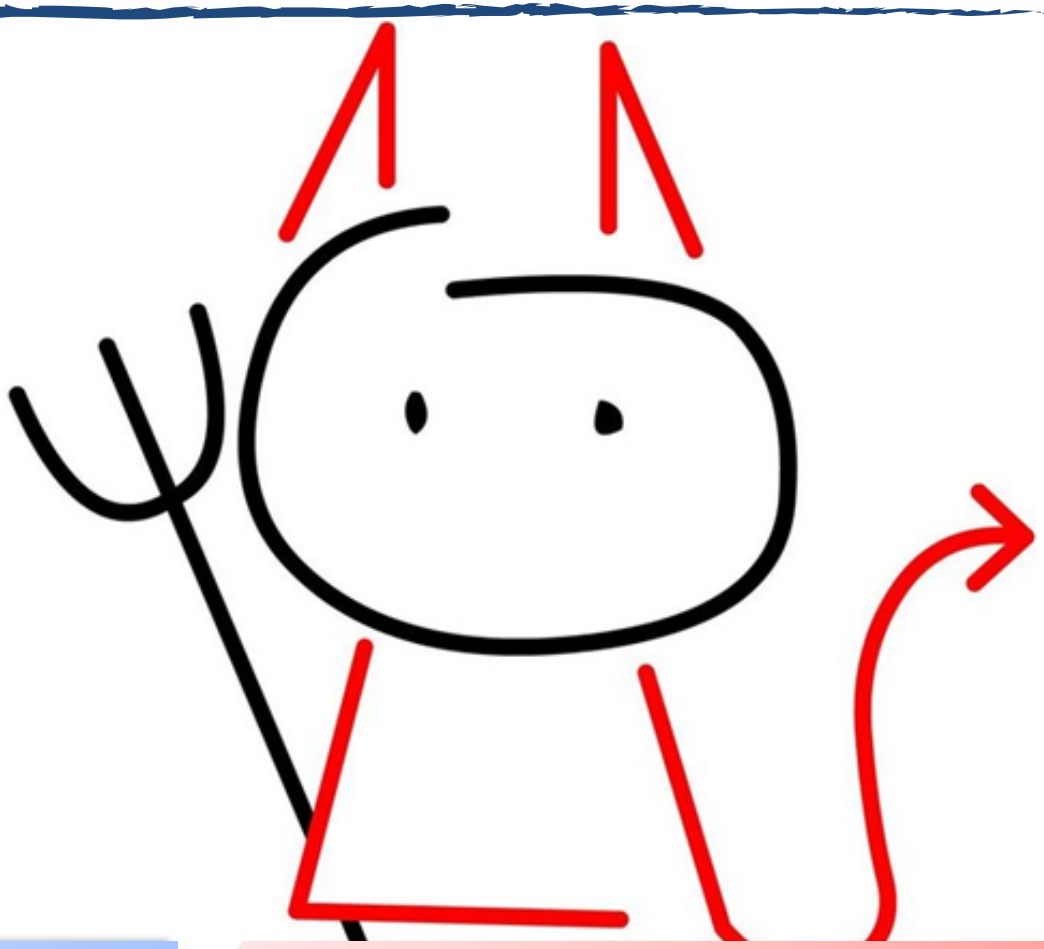


doi:10.1038/nrmicro2540




MIRACLE
POOP

Microbiota



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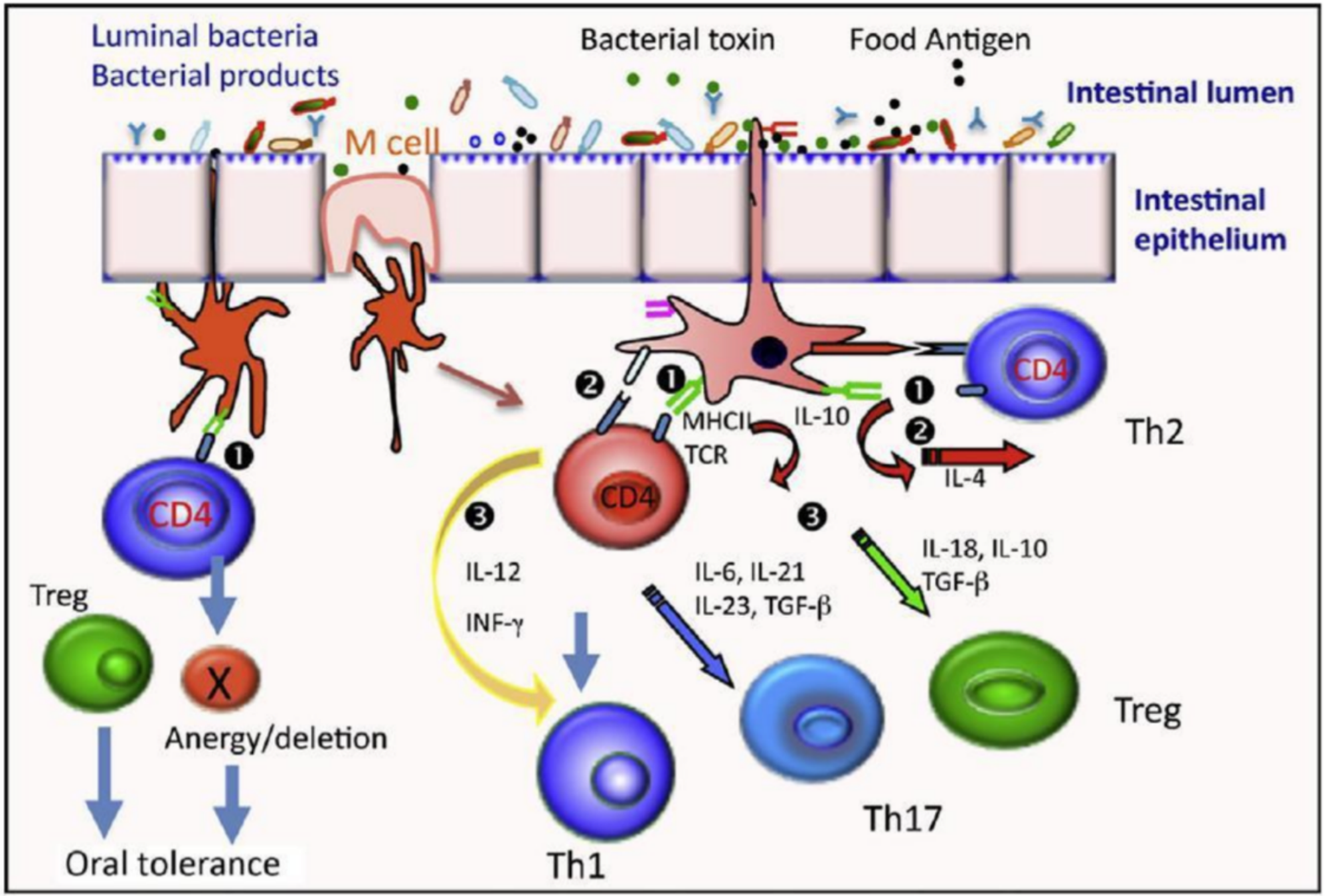
- ✓ Doença inflamatórias crônicas
- ✓ Doenças cardiovasculares
- ✓ Câncer
- ✓ Obesidade
- ✓ Doenças neurológicas

Resumindo...


Luminal bacteria
Bacterial products
Bacterial toxin
Food Antigen
Intestinal lumen
M cell
Intestinal epithelium
CD4
MHCII
TCR
IL-10
IL-4
Th2
IL-12
INF-γ
IL-6, IL-21
IL-23, TGF-β
IL-18, IL-10
TGF-β
Treg
X
Anergy/deletion
Oral tolerance
Th1
Th17
Treg