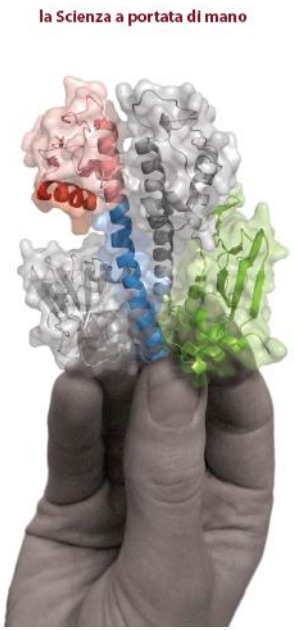
SAPIENZA
UNIVERSITÀ DI ROMA



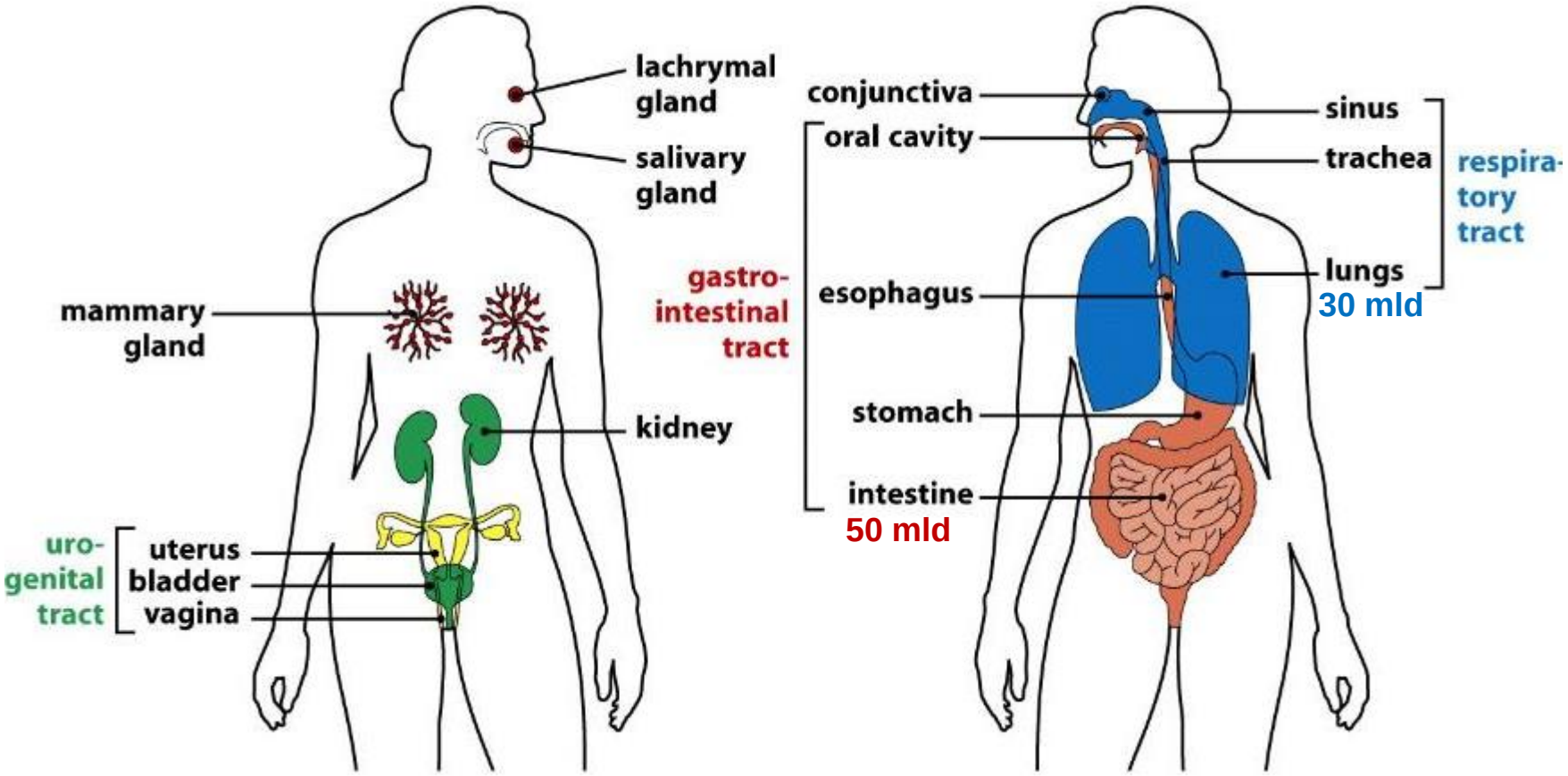
Comunicazione delle Scienze Biomediche

Prof.ssa Cristina Cerboni

Anno Accademico 2023-2024
"Immunità mucosale"

5 dicembre

Mucosal tissues of human body
(and lymphocyte numbers)



Milza: 70 mld
Linfonodi: 190 mld
Midollo osseo: 50 mld
Sangue: 10 mld
Cute: 20 mld
Fegato: 10 mld

- The mucosal immune system forms the largest part of the body's immune tissues:

- ***3/4 of all lymphocytes***
- ***producing the majority of immunoglobulins!***

Immunobiology, Janeway

The organization of the mucosal immune system

- The mucosal immune system (MALT):
  - GI tract (GALT)
  - Respiratory tract (BALT, …)
  - Urogenital tract
  - Exocrine glands associated with these organs

The mucosal immune system protects the internal surfaces of the body

MALT: mucosal-associated lymphoid tissue

Epiteli mucosali

- Funzione di scambio → sottili e permeabili

↓

Vulnerabili all'attacco da parte di microorganismi

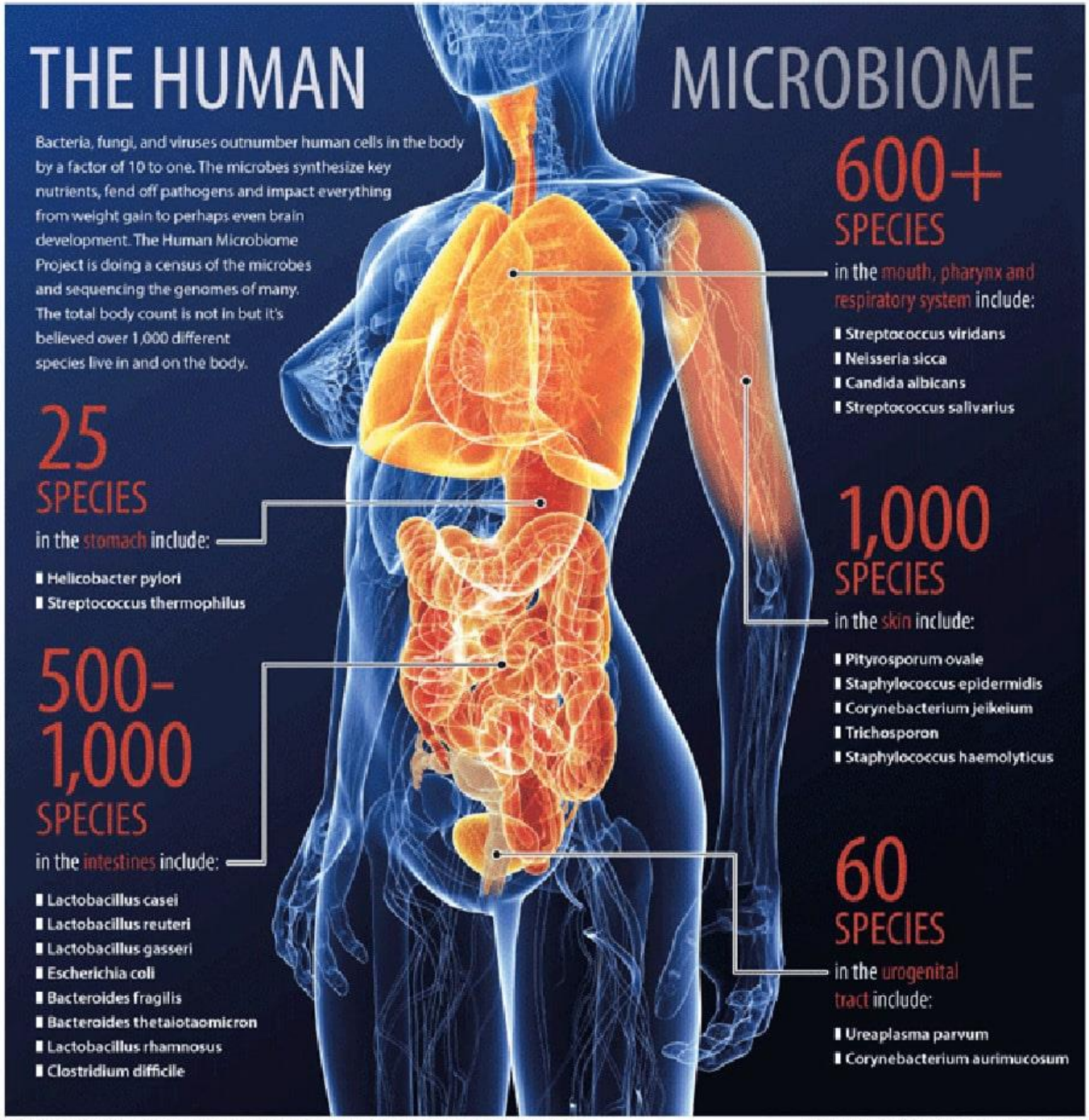
- Colonizzati da microorganismi commensali

↓

Esposti a antigeni estranei non patogeni
(microorganismi commensali, cibo)

Sistema di difesa efficiente

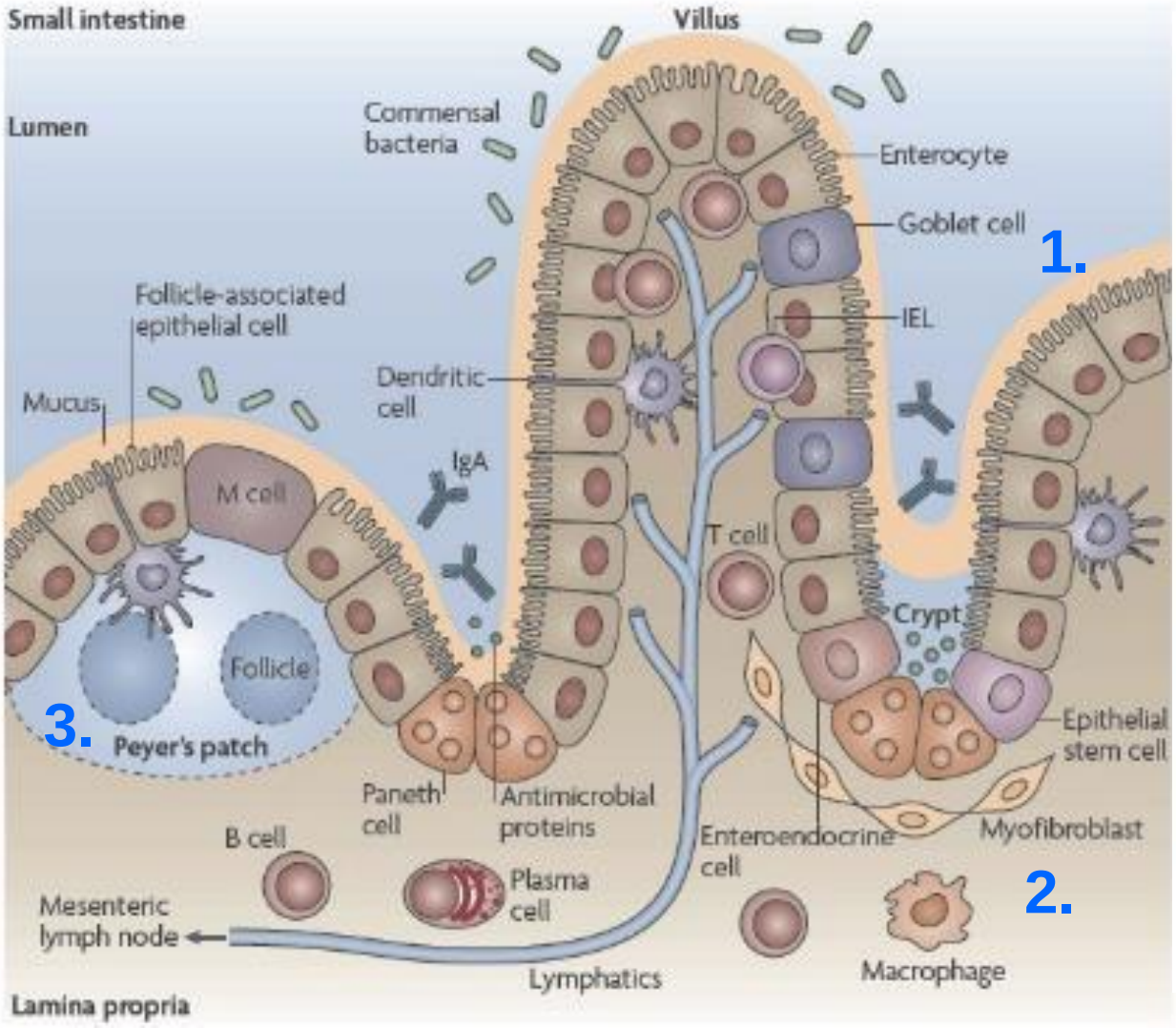
- eliminare selettivamente i microorganismi patogeni
- limitare la diffusione dei microorganismi commensali
- non interferire con l'assimilazione di cibo



SOURCES: NATIONAL INSTITUTES OF HEALTH, SCIENTIFIC AMERICAN; HUMAN MICROBIOME PROJECT

Dean Tweed • POSTMEDIA NEWS / IMAGE: Fotolia

Organizzazione delle barriere epiteliali (3 strati)



Epithelium:
- enterocytes
- Goblet cells
- Paneth cells
- Intra-Epithelial Lymphocytes

1.

Lamina propria: *o derma, ecc*
- CD4 + T / T CD8 +
- Plasma IgA +
- DC
- macrophages
- Innate Lymphoid cells

2.

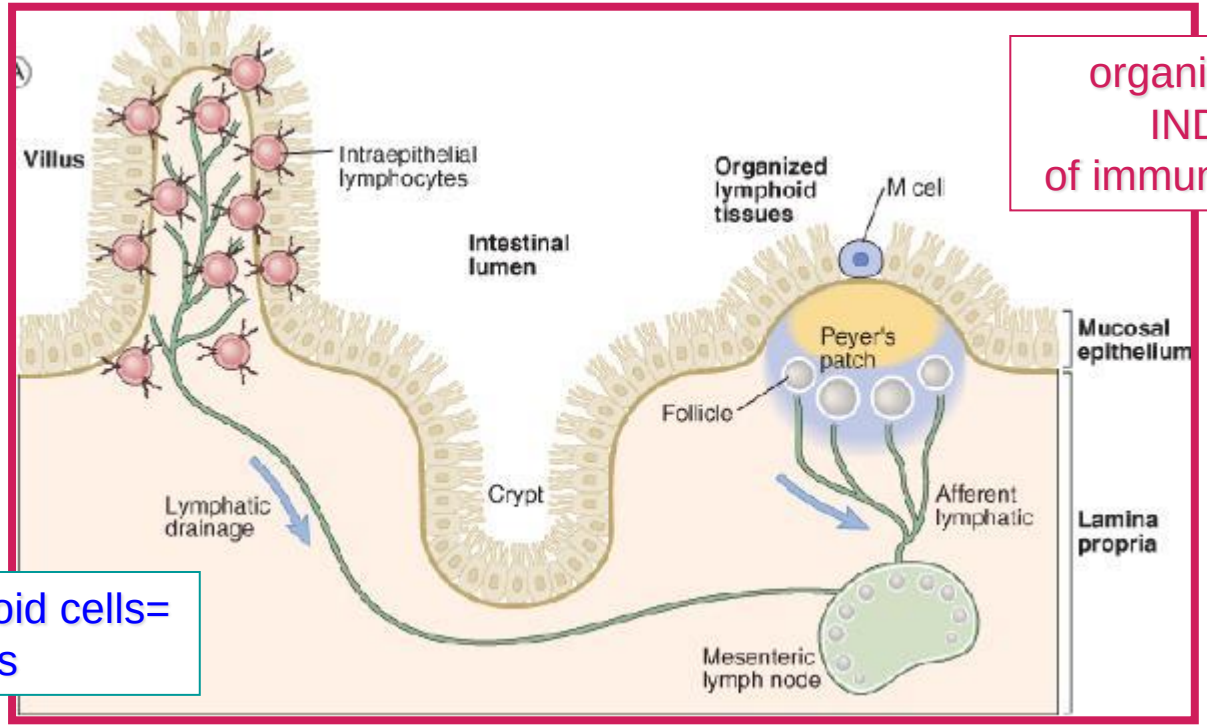
Peyer's patches: *(MALT)*
DC
CD4 + T / T CD8 +
B lymphocytes

3.

MALT: mucosal associated lymphoid tissue

- Soluble components: IgA, antimicrobial peptides, mucous layer, etc…
- Intraepithelial lymphocytes
- Isolated lymphoid follicles
- Lymphoid organs (such as tonsils, adenoids, Peyer's patches, appendix)
- Regional lymph nodes (mesenteric, cervical, bronchial/mediastinal, iliac,…)

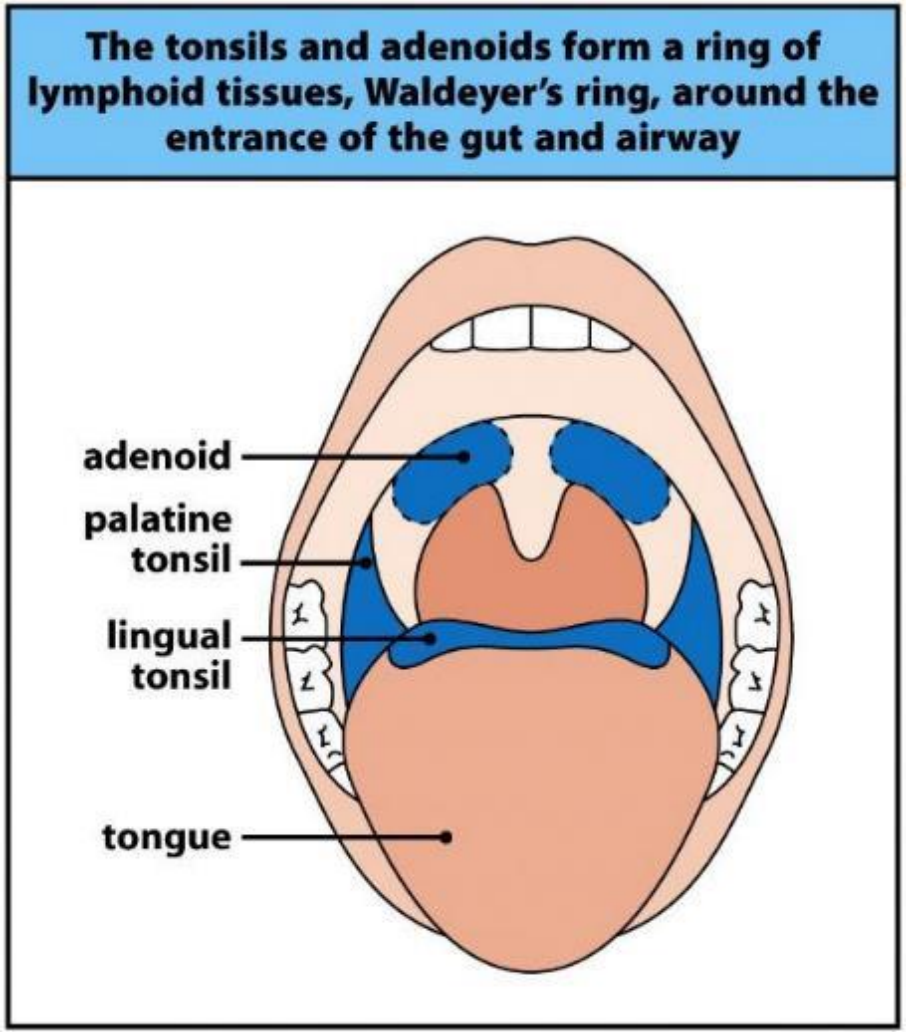
BALT (bronchus), **GALT** (gut), and others



organized tissues=
INDUCTION
of immunity & tolerance

scattered lymphoid cells=
EFFECTOR sites

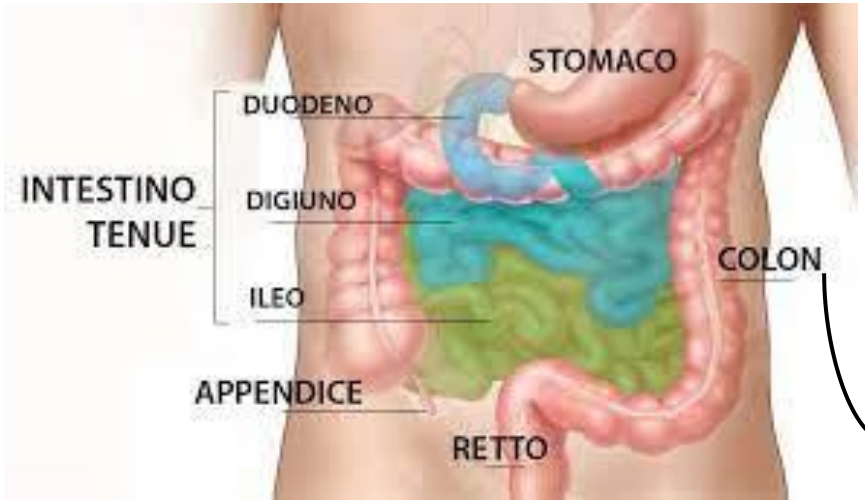
Un esempio di tessuto linfoide organizzato



Anatomia dell'intestino

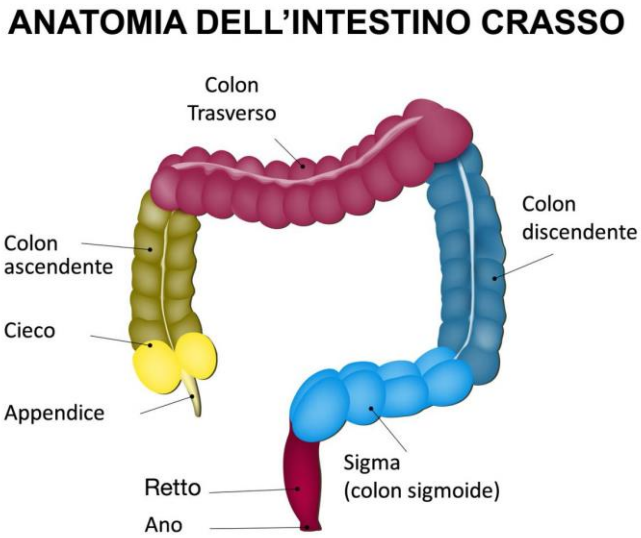
&
Gut-Associated Lymphoid Tissue Anatomy (GALT)

Anatomia dell'intestino



Alcuni numeri:

- ✓ *Tenue: ca. 6 m*
- ✓ *Crasso: ca. 2 m*
- ✓ *Mucosa crasso+tenue: ~ 400 mq (villi e microvilli)*
- ✓ *Da 500 a 1000 specie diverse di batteri (~10^14 cellule) (10x il n. di cellule nucleate dell'organismo)*
- ✓ *>600.000 geni nel microbioma intestinale umano (30x geni umani)*

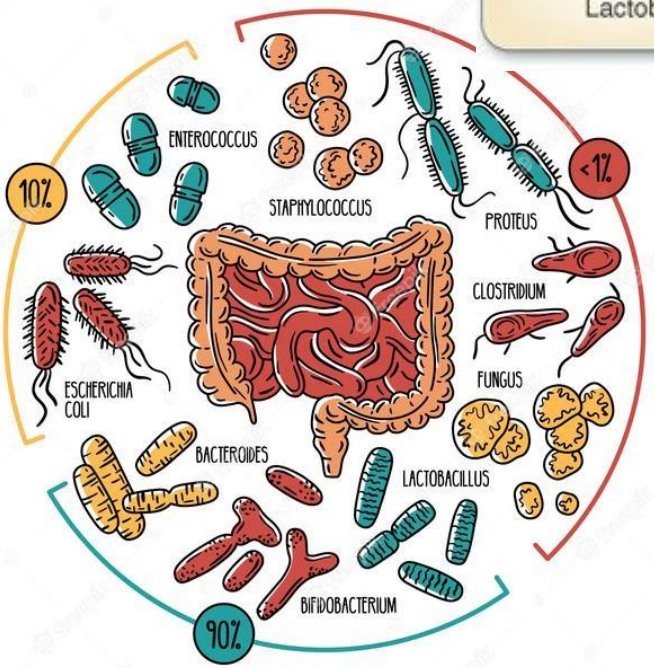


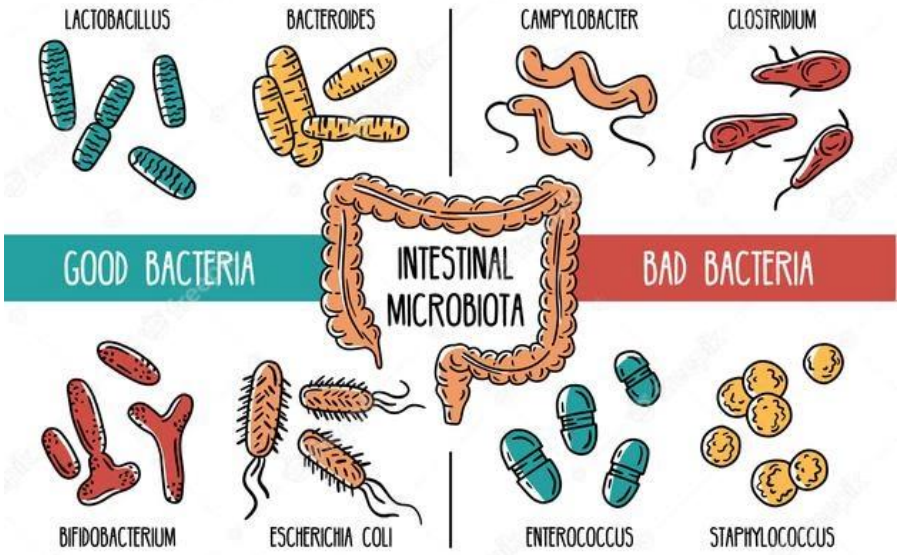
INTESTINAL MICROFLORA

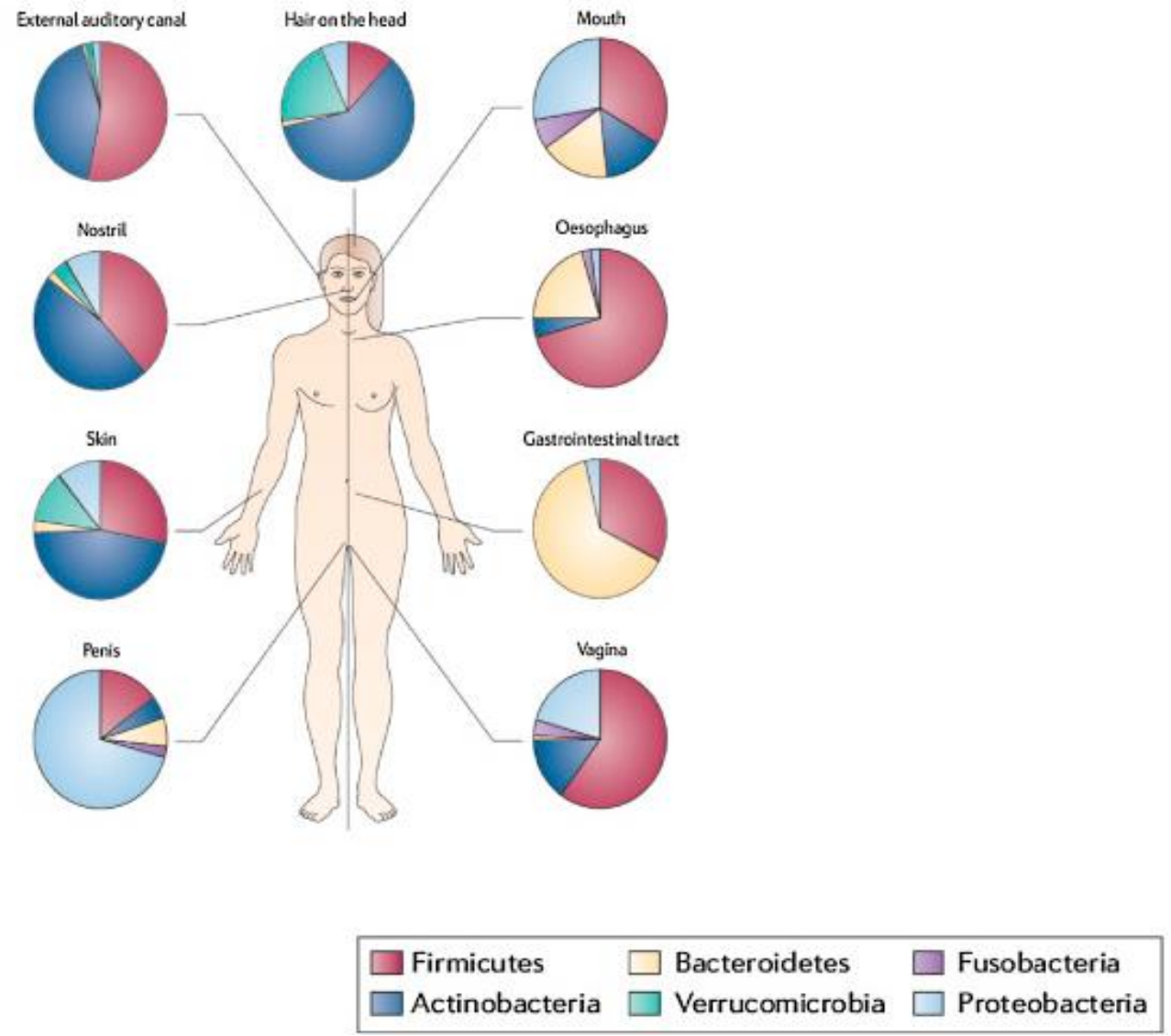
10^{14} micro-organisms, >500 differentes species

Lactobacilli	Stomach	10^2 to 10^3
	Duodenum	$<10^{4-5}$
Streptococci Lactobacilli	Jejunum	
Enterobacteria Enterococcus Faecalis Bacteroides Bifidobacteria Peptococcus Peptostreptococc Ruminococcus Clostridia Lactobacilli	Ileum	10^3 to 10^7
	Colon with appendix	10^9 to 10^{12}

and....

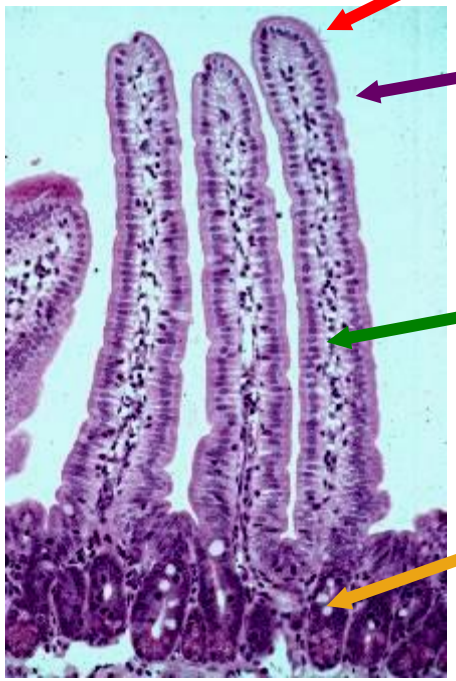






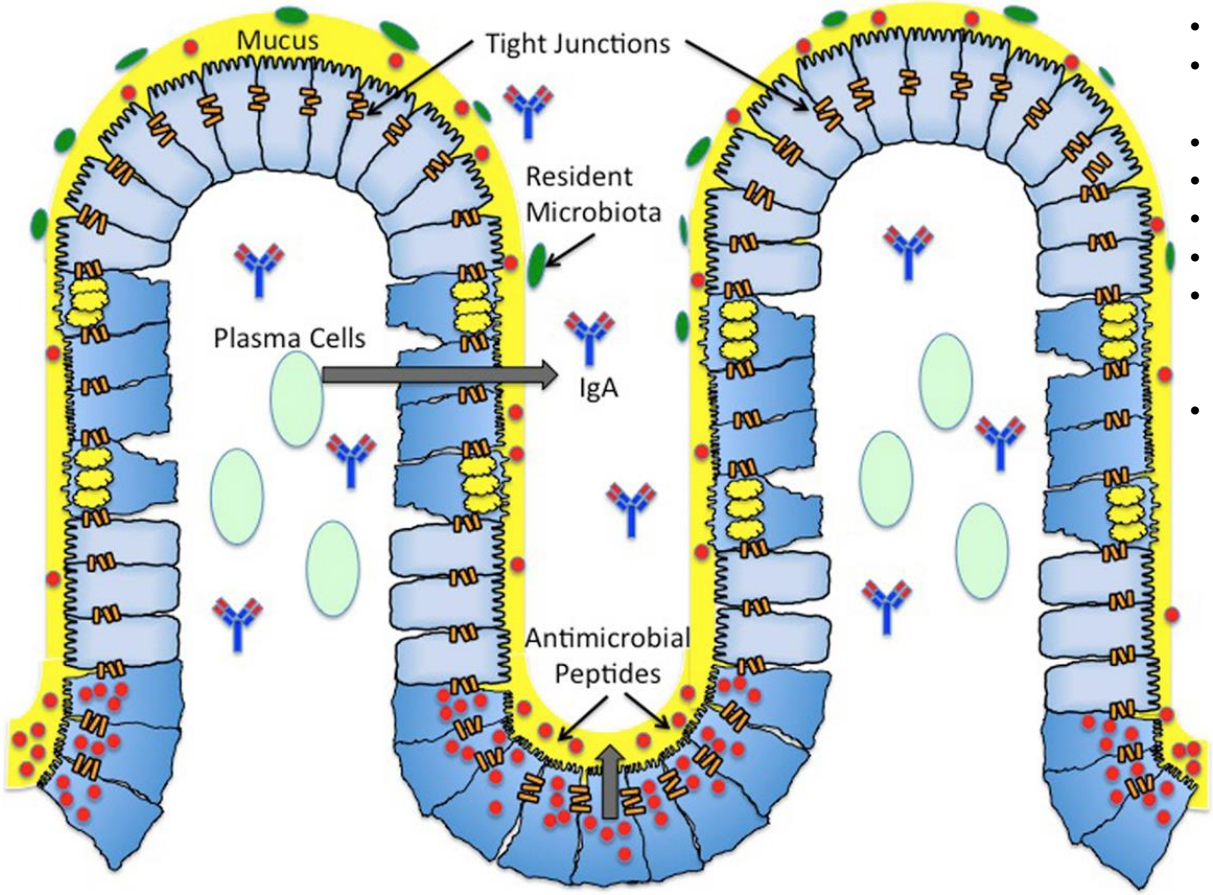
Blum HE, The human microbiome, Advances in Medical Sciences, 2017

La mucosa intestinale



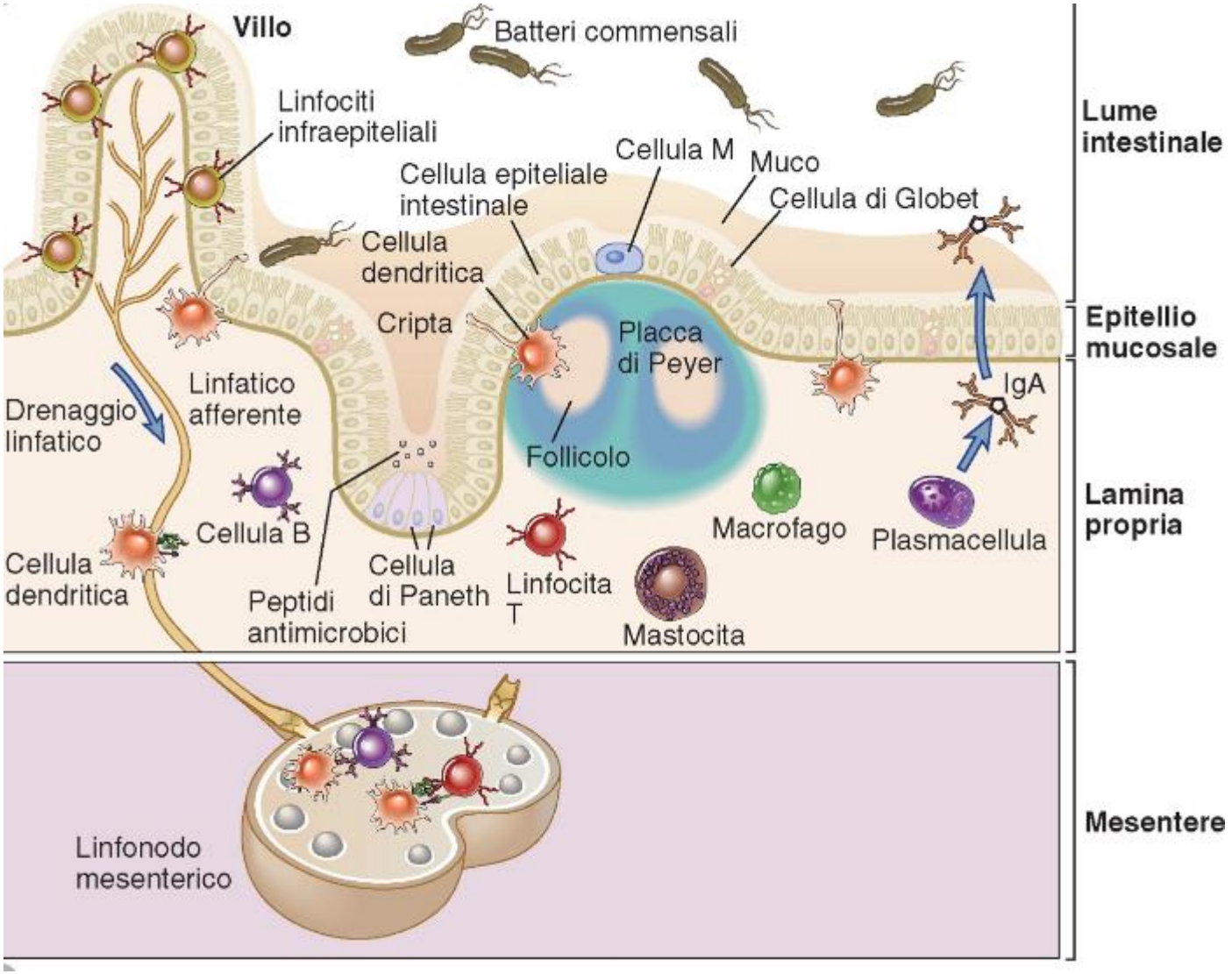
- **Vasta superficie ~ 400m^2**

Architecture of the mucosal surface of the intestine



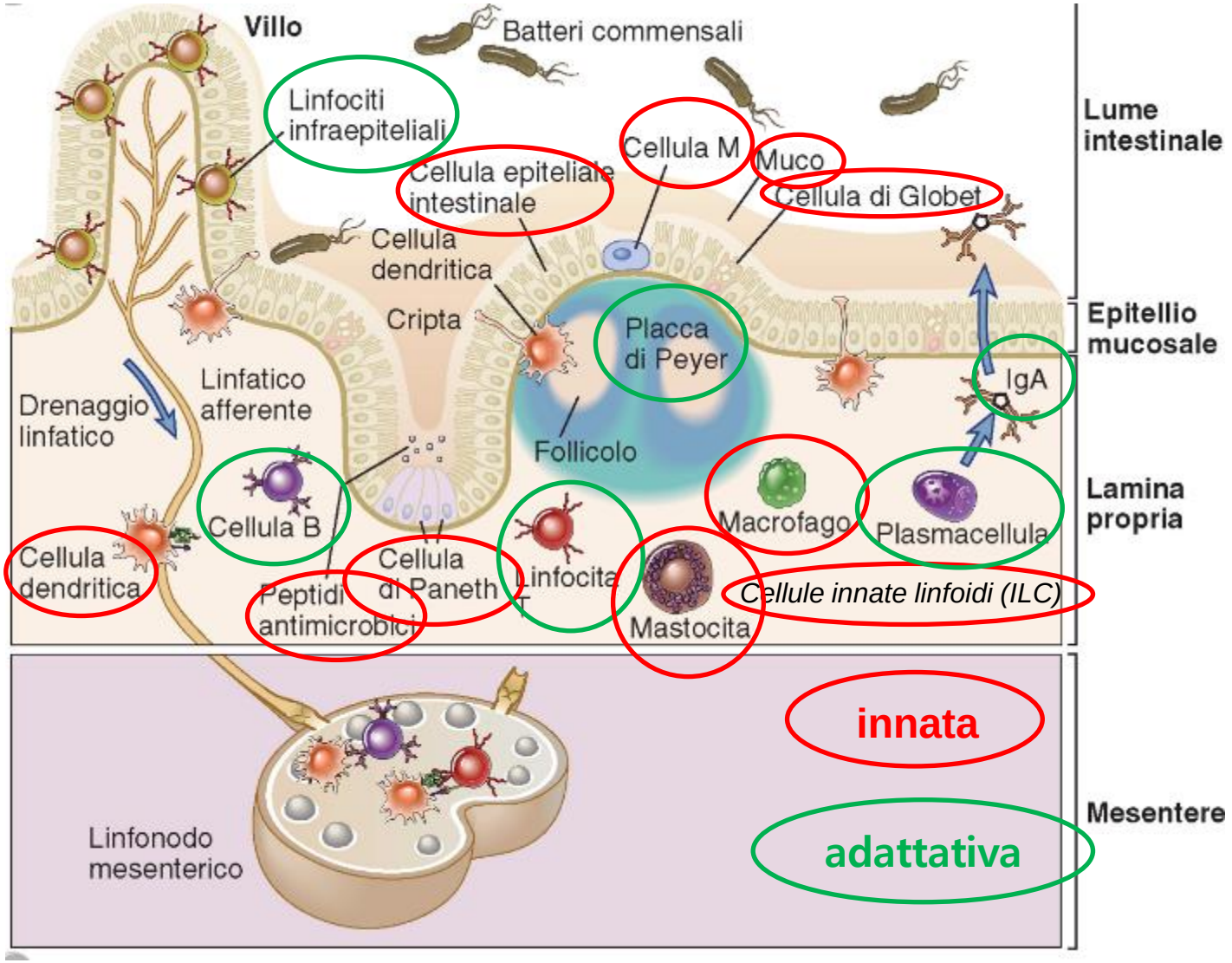
- Mucus (yellow)
- Goblet cells (blue cells with yellow granules)
- Antimicrobial peptides (red)
- Paneth cells (blue cells with red granules)
- B cells (light green)
- Secretory IgA (blue and red antibody).
- Resident microbiota (green) (two major phyla – Firmicutes and Cytophaga–Flavobacterium– Bacteroidetes).
- Tight junctions (orange bars).

Gut-Associated Lymphoid Tissue Anatomy (GALT)



Abbas A.K.

Gut-Associated Lymphoid Tissue Anatomy (GALT)



Abbas A.K

FUNZIONE DI BARRIERA

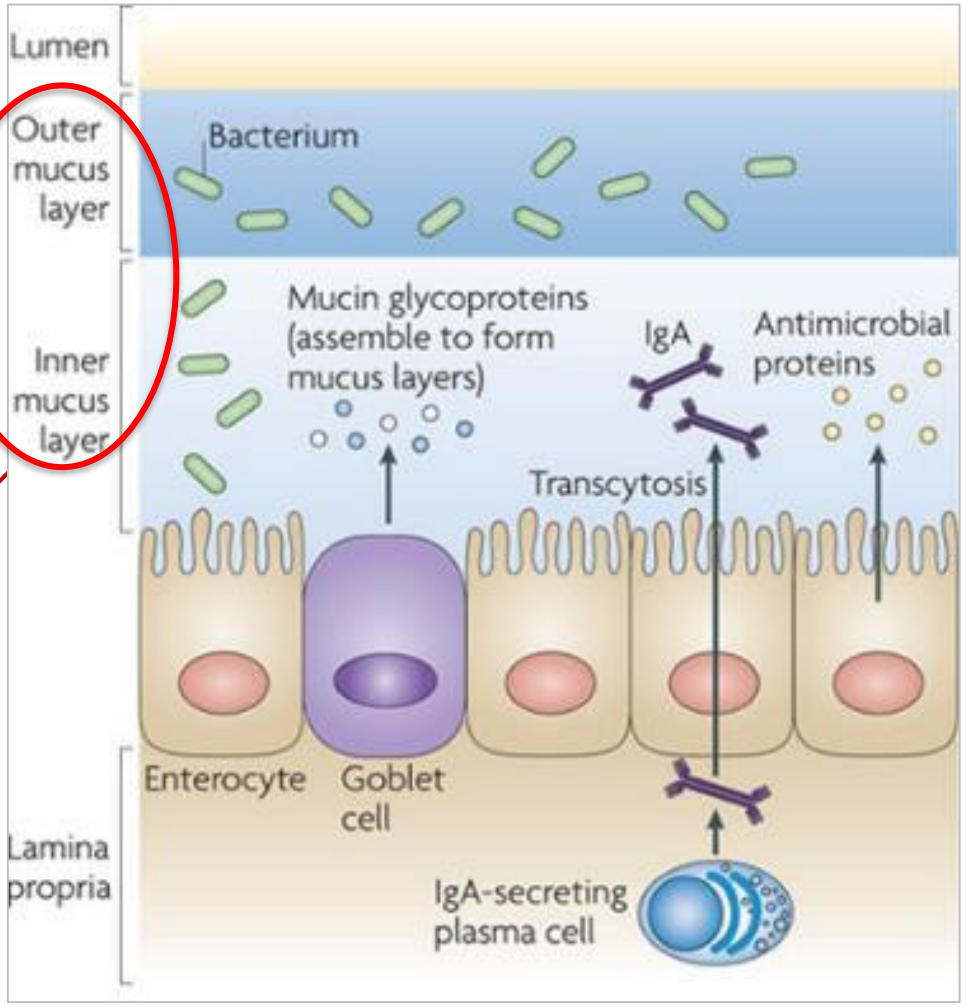
spesso strato di muco secreto dalle GOBLET CELLS

Costituito da mucine

Impedisce fisicamente il movimento dei microrganismi

Contiene defensine e IgA

Viene continuamente espulso



La produzione può aumentatare con stimoli infiammatori: IL1, IL6, TNFalfa, IL13

The mucosal immune system contains large numbers of effector lymphocytes (even in the absence of disease!)

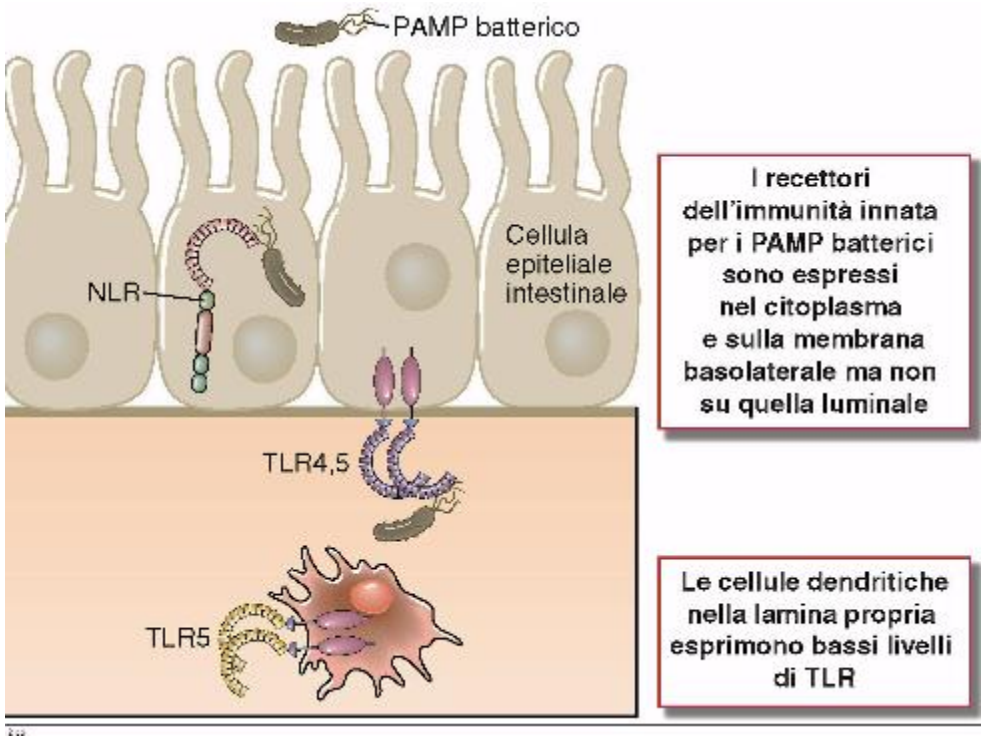
- In the intestine, effector cells are found in two main compartments:
  the epithelium and the *lamina propria*
- The epithelium contains mainly lymphocytes, the vast majority of which are CD8+ T cells
- The *lamina propria:* CD4+ and CD8+ T cells, plasma cells, macrophages, DC, eosinophils, mast cells
- The total number of lymphocytes in the epithelium and *lamina propria* probably exceeds that of most other parts of the body

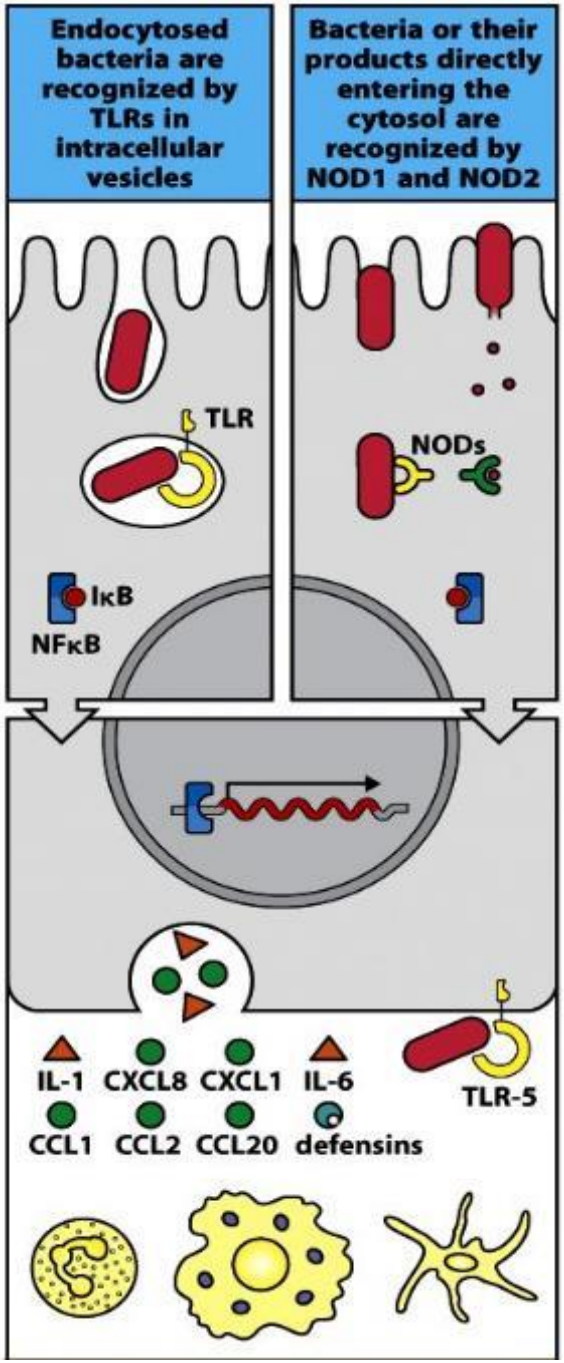
- The healthy intestinal mucosa displays many characteristics of chronic inflammatory response:
  ⇒ Local responses to the myriad of innocuous Ags
  ⇒ Overt disease is rare due to regulatory mechanisms

EPITHELIAL CELLS HAVE A CRUCIAL ROLE IN THE INNATE DEFENSE AGAINST PATHOGENS

Espressione polarizzata del TLR5:

Risposta infiammatoria ridotta nei confronti dei batteri commensali





EPITHELIAL CELLS HAVE A CRUCIAL ROLE IN THE INNATE DEFENSE AGAINST PATHOGENS

- **They express TLR5 on their basal surface ⇔ flagellin on the basal surface**

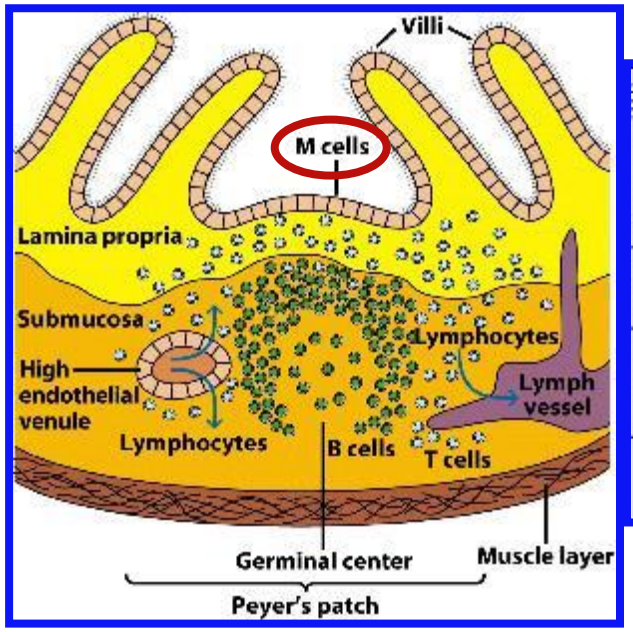
- **They carry TLRs in intracellular vacuoles that can detect pathogens and their products that have been internalized by endocytosis**

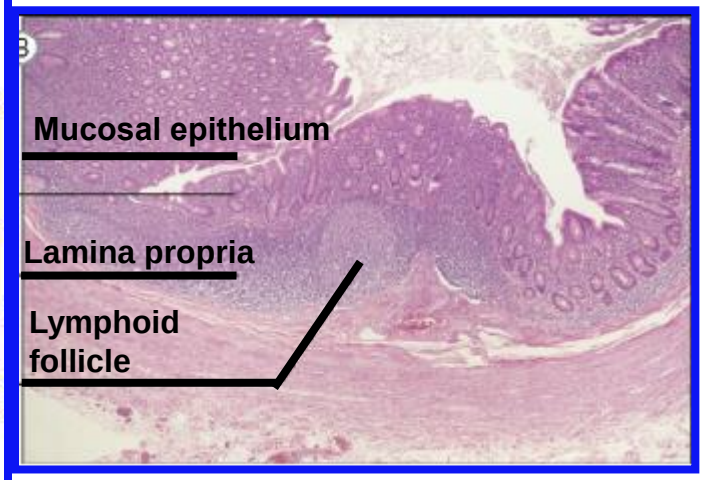
- **They also have intracellular sensors**
  ⇒ interact with microorganism or their products in the cytoplasm
  e.g. NOD1 → muramyl tripeptide in Gram(-) bacteria
  NOD2 → muramyl dipeptide in most bacteria

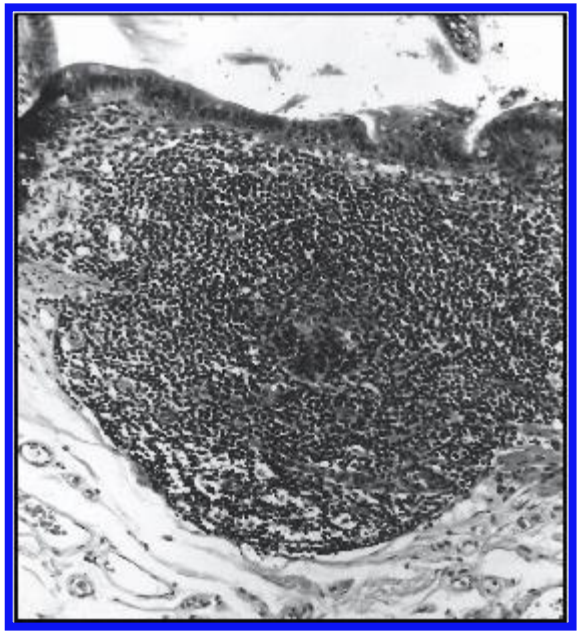
- **They express NLRP3 (a PRR)**
- **Injury and stress to the enterocytes stimulated the expression of MICA and MICB proteins.**

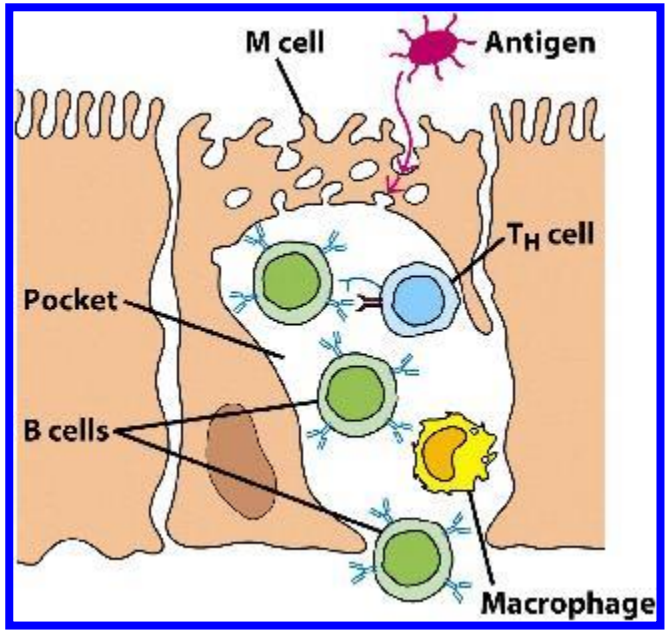
TLR, NOD1 e NOD2 attivano la via di NF-kB, inducendo le cellule epiteliali ad esprimere numerose citochine infiammatorie, chemochine ed altri mediatori che attivano neutrofili, macrofagi e DC

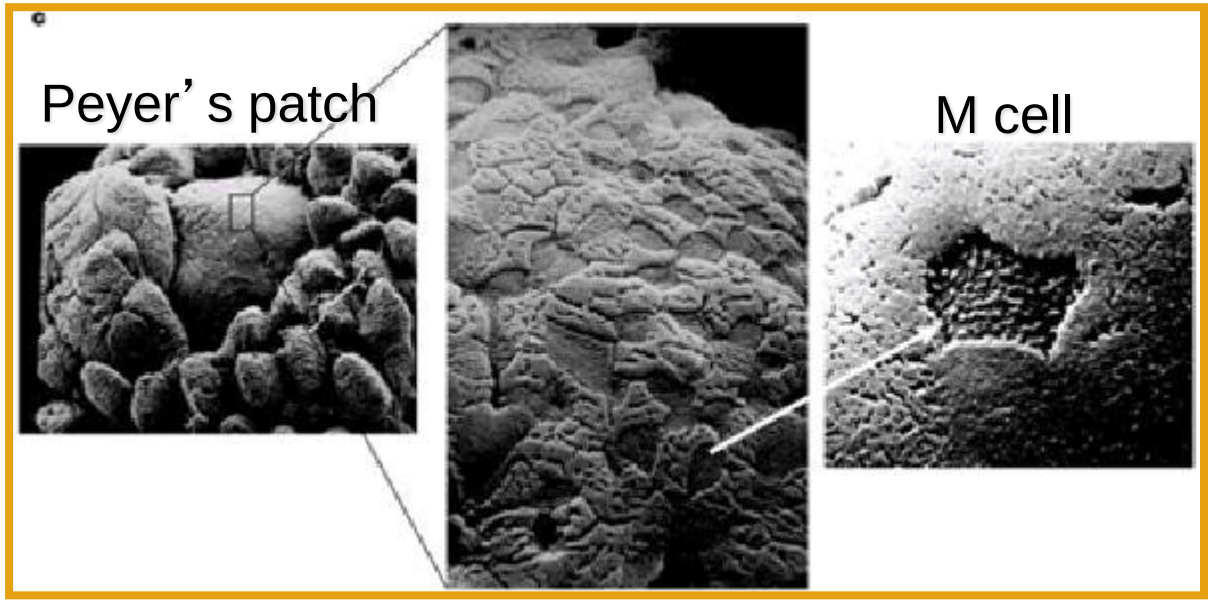
Peyer's patches (Gut-Associated Lymphoid Tissue)











- **Peyer's patches have a distinctive appearance, forming dome-like aggregates of lymphoid cells**

- **Microfold cells (M cells):**

  the route by which Ag enters the Peyer's patch from lumen

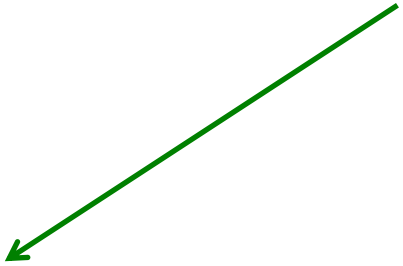
- **isolated lymphoid follicles in the small and large intestine**

  ⇒ contain mainly B cells

- **Similar isolated follicles are found in other sites**
  - **bronchus-associated lymphoid issues (BALT)**
  - **nasal-associated lymphoid tissues (NALT)**

The intestine has distinctive routes and mechanisms of antigen uptake

- M cells in the follicle-associated epithelium are continually taking up molecules and particles from the gut lumen by endocytosis or phagocytosis

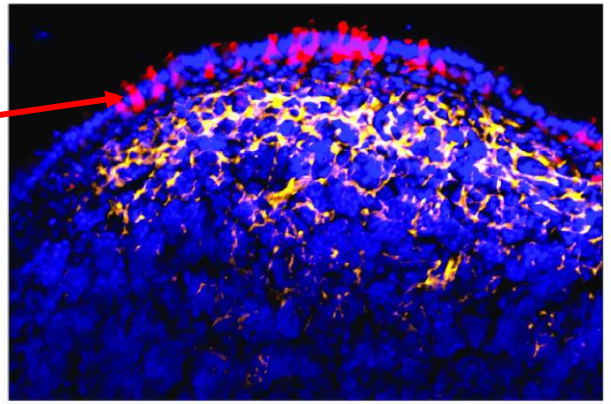


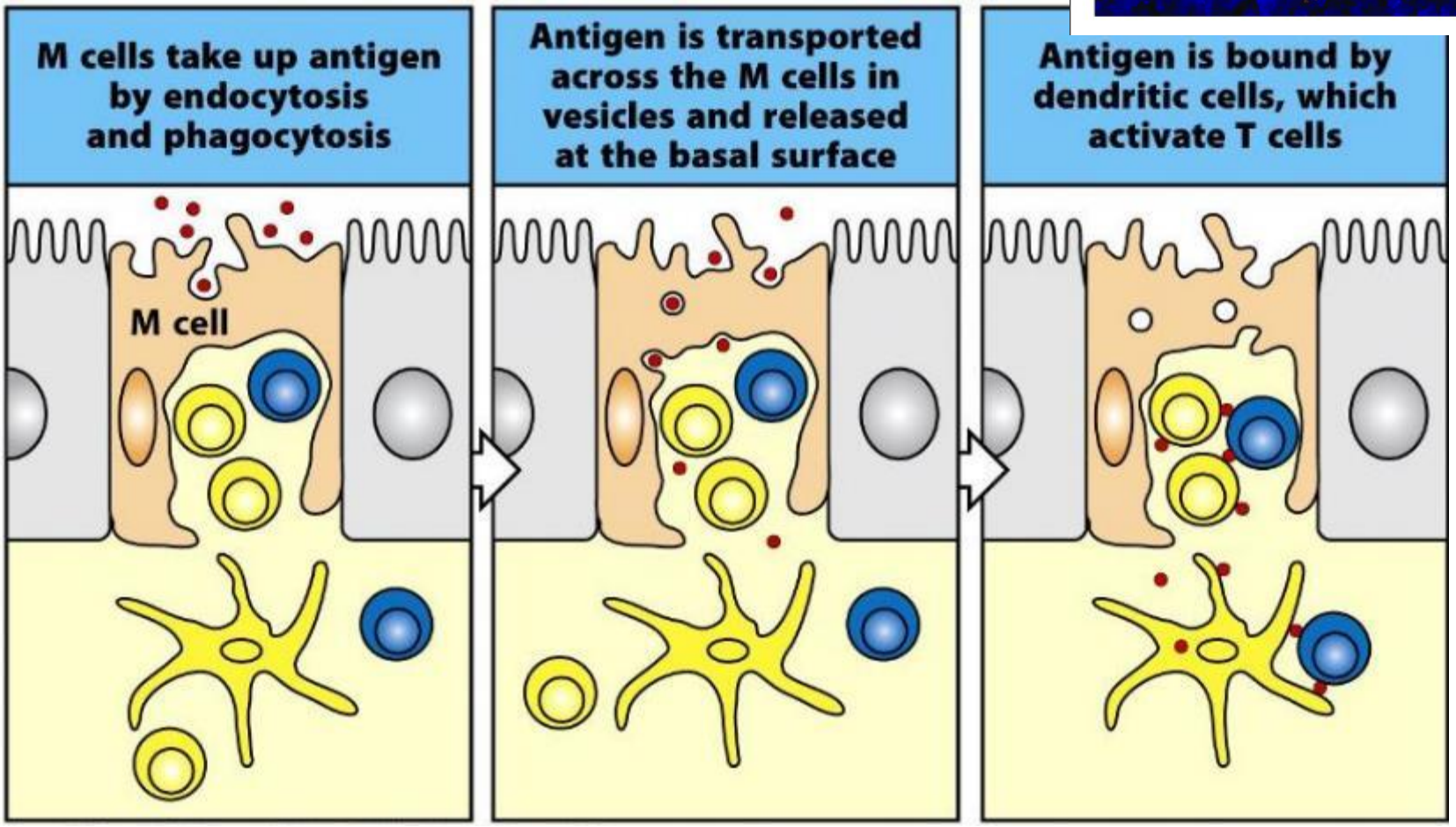
⇒ released into the lamina propria extracellular space by *"transcytosis"*

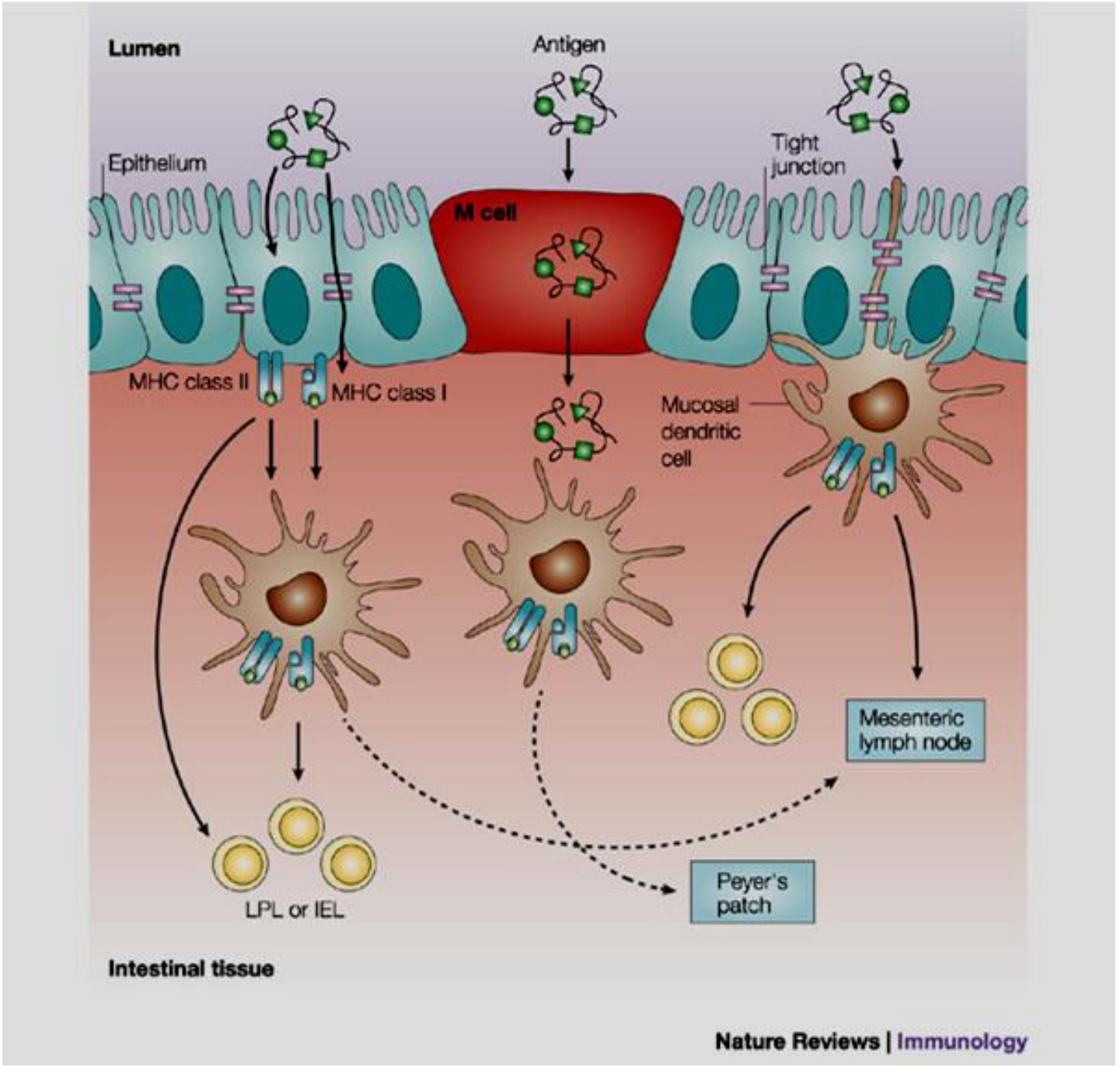
⇒ DC take-up the transported material

⇒ Presentation to T lymphocytes

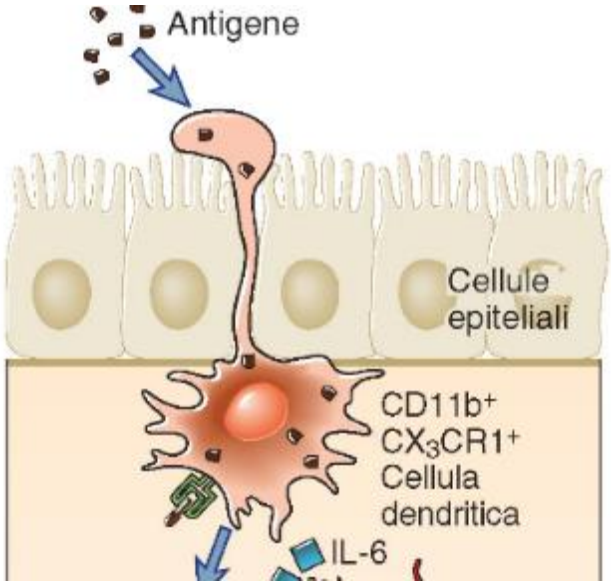
La transcitosi

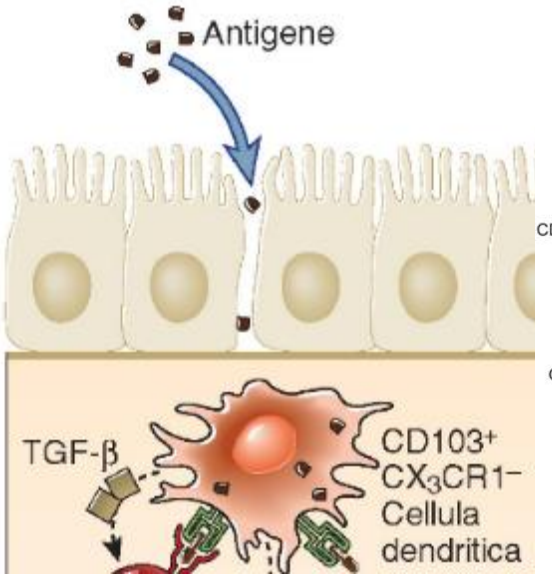


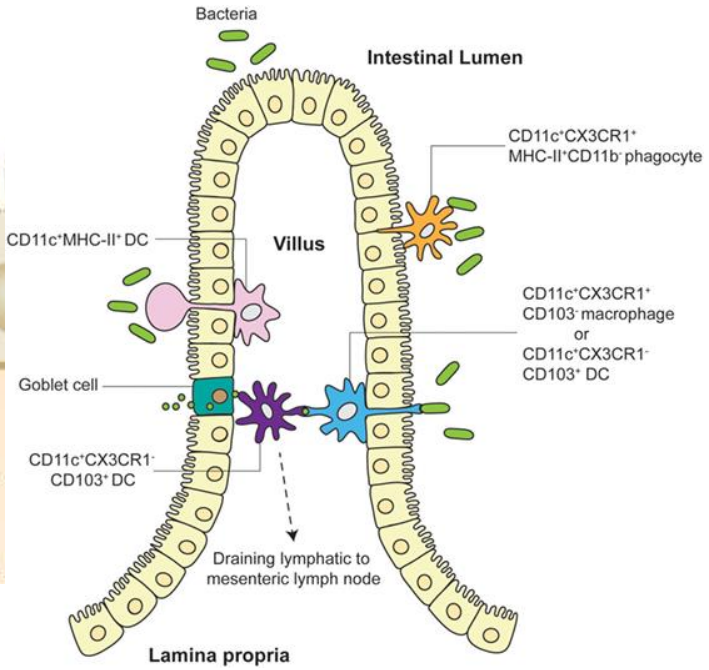



Lumen
Antigen
Epithelium
Tight junction
M cell
MHC class II
MHC class I
Mucosal dendritic cell
Mesenteric lymph node
Peyer's patch
LPL or IEL
Intestinal tissue
Nature Reviews | Immunology

“Campionamento” dell’antigene da parte delle DC intestinali



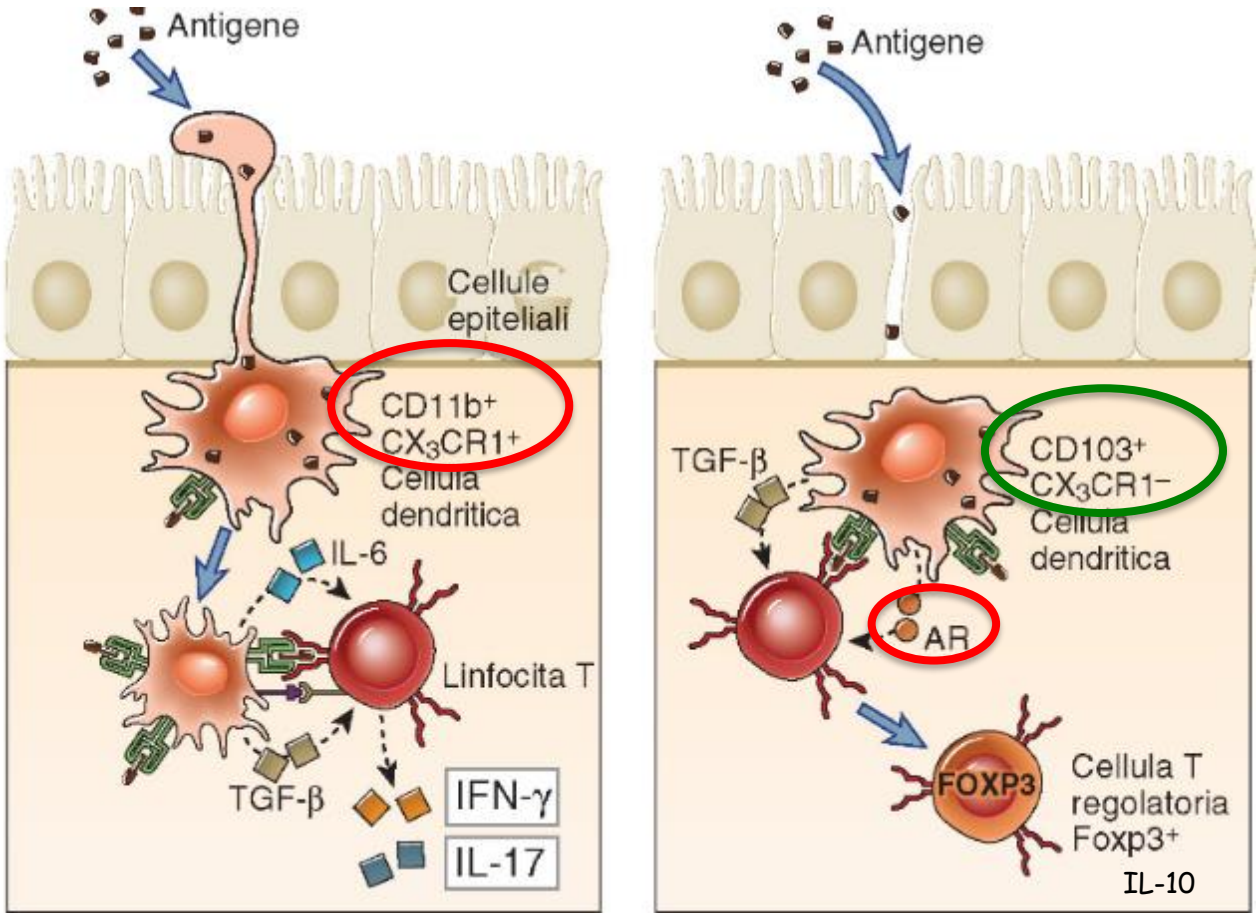




Presentazione dell’antigene ai linfociti T nel MALT o nei linfonodi mesenterci

DC effettrici

DC regolatorie



Chemokines released by the epithelial cells

(CCL20 and CCL9)

recruitment of DC

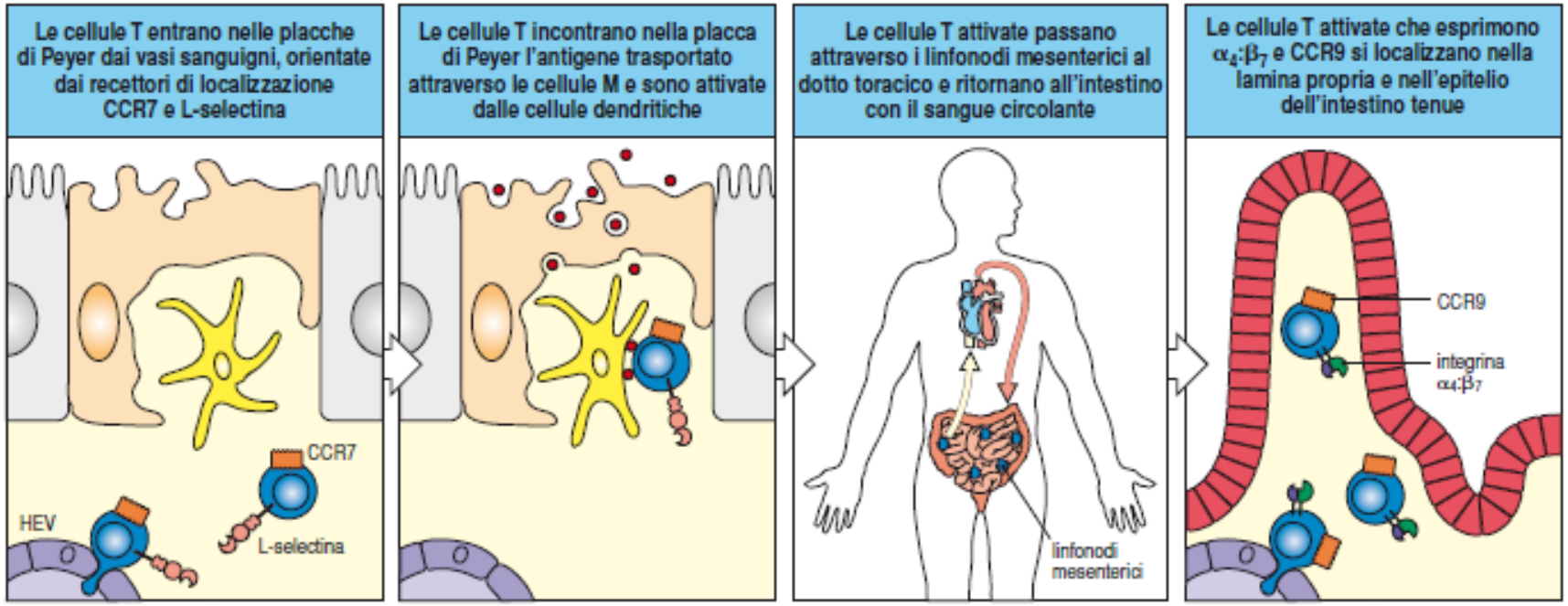
(expressing CCR6/CCR1)

- **DCs are abundant in the wall of the intestine mainly in the *lamina propria*:**

⇒ acquire antigens across an intact epithelial barrier (with or without the need for M cells)

⇒ transport antigen to the T cell areas of mesenteric lymph nodes

I segnali che guidano la migrazione dei linfociti nelle mucose



CCR7: **CCL19**
CCL21

CD62L **MadCAM-1**
(L-selectin

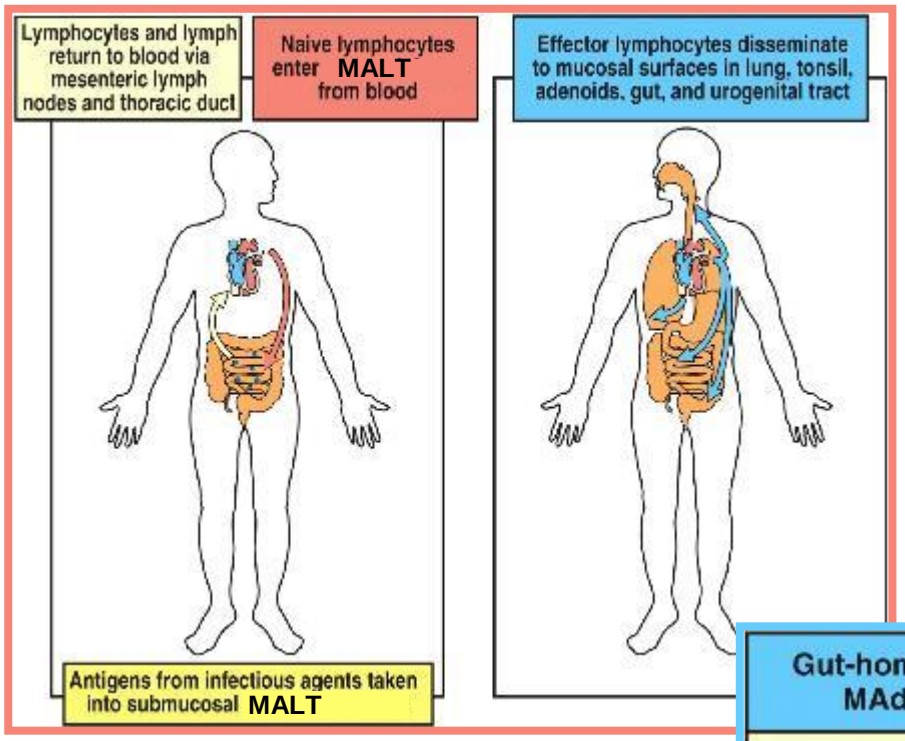
Se il linfocita incontra l'antigene perde l'espressione di CCR7 e CD62L, cioè perde il tropismo per gli organi linfoidi periferici

CCR9: **CCL25 (tenue)**

CCR10 **CCL28 (colon, ghiandole mammarie, salivari)**

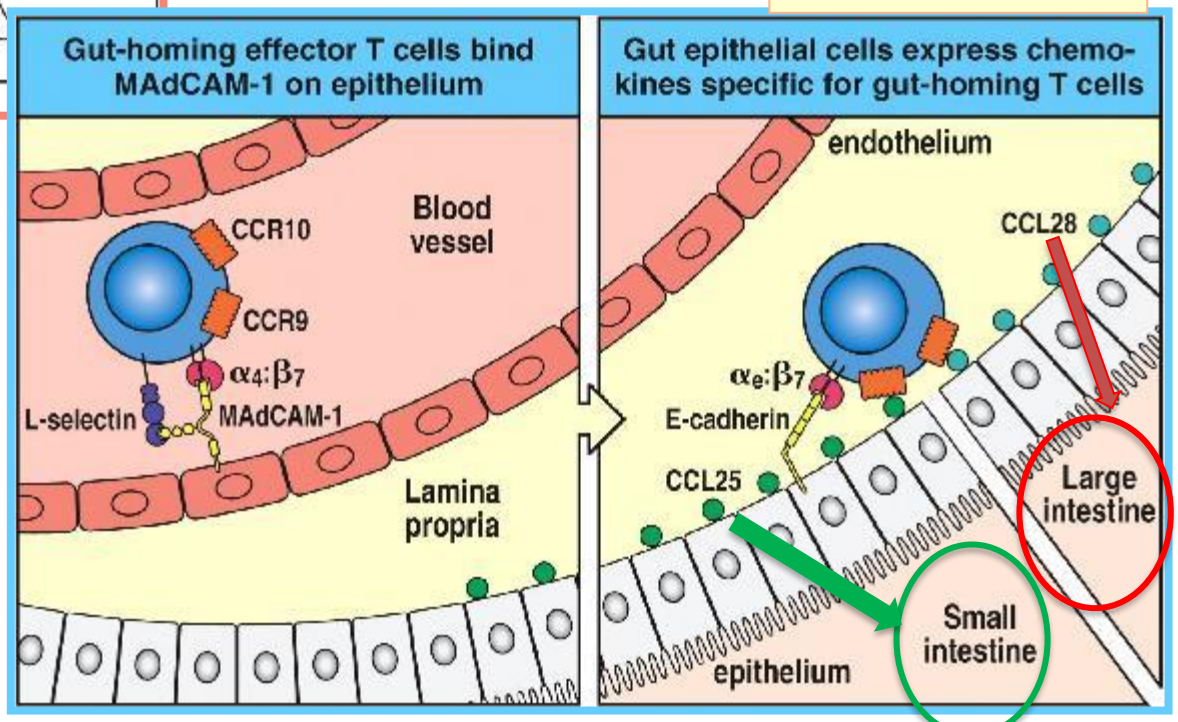
(CCR10/CCL28:HOMING anche dei LINFOCITI B che producono IgA)

I segnali che guidano la migrazione dei linfociti nelle mucose



αEβ7-E-cadherin
CCR9-CCL25
CCR10-CCL28

α4β7-MAdCAM
CCR9-CCL25



- **Priming of lymphocytes in one mucosal tissue can induce protective immunity at other mucosal surface!**

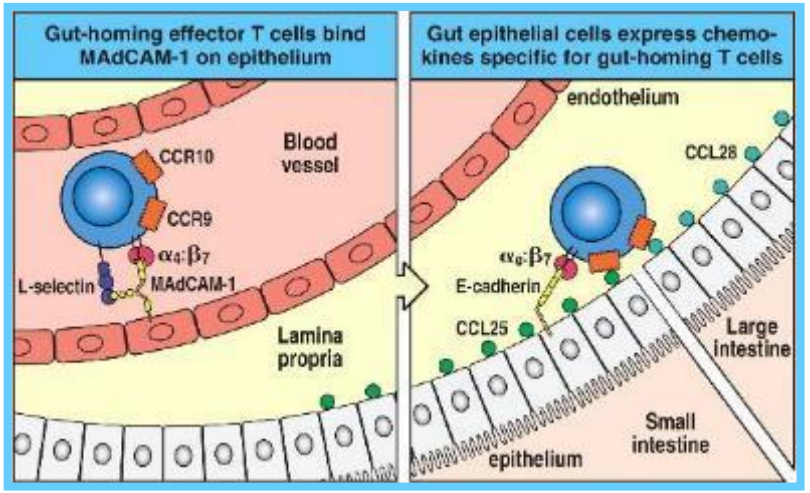
- MAdCAM-1 is not restricted entirely to the blood vessels of the intestine

⇒ also found on the vasculature in the other mucosal surfaces!!

⇒ lymphocytes primed in GALT,

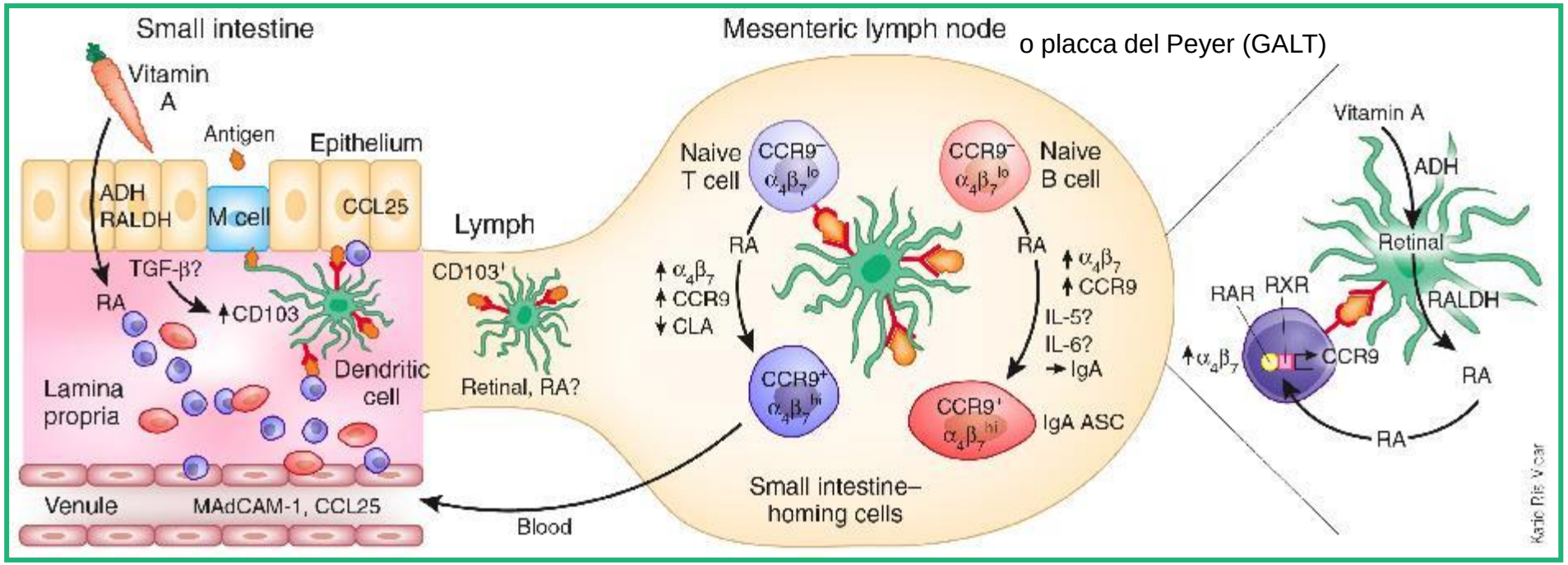
⇒ migrate to other common mucosal immune system

Oral vaccination



Diet and vitamin A affect the imprinting of small intestine trafficking

(and the importance of DCs)



alcohol dehydrogenases (ADH)	retinal dehydrogenases (RALDH)

(Epithelium, intestinal DC)

Vitamin A (retinol) ⇒ **Retinal** ⇒ **Retinoic acid (RA) (active metabolite)**

RAR, retinoic acid receptor; RXR, retinoid X receptor

TOP 10 smart FONTI DI VITAMINA A (RETINOLO EQUIVALENTI)

1. 
   3-4 CAROTE
   2296 µg

2. 
   2 PICCOLE PATATE DOLCI
   1310 µg

3. 
   MEZZO PIATTO DI ZUCCA
   1198 µg

4. 
   MEZZO PIATTO DI CRESCIONE
   840 µg

5. 
   3-4 ALBICOCCHE
   540 µg

6. 
   MEZZO PIATTO DI CICORIA CATALOGNA
   438 µg

7. 
   3-4 GAMBI DI SEDANO
   414 µg

8. 
   UN CACHI
   356 µg

9. 
   UNA RICOTTINA DI VACCA
   200 µg

10. 
    UN UOVO
    113 µg

ASSUNZIONE GIORNALIERA RACCOMANDATA
DI VITAMINA A
(retinolo equivalenti)
PER LA POPOLAZIONE ADULTA

700 µg **600 µg**

I valori sono riferiti all'alimento crudo e derivano dalle seguenti banche dati: BDA - Banca Dati di composizione degli Alimenti. Istituto Europe di Oncologia
CREA - Centro di Ricerca Alimenti e Nutrizione. Tabelle di composizione degli alimenti USDA - National Nutrient Database for Standard Reference

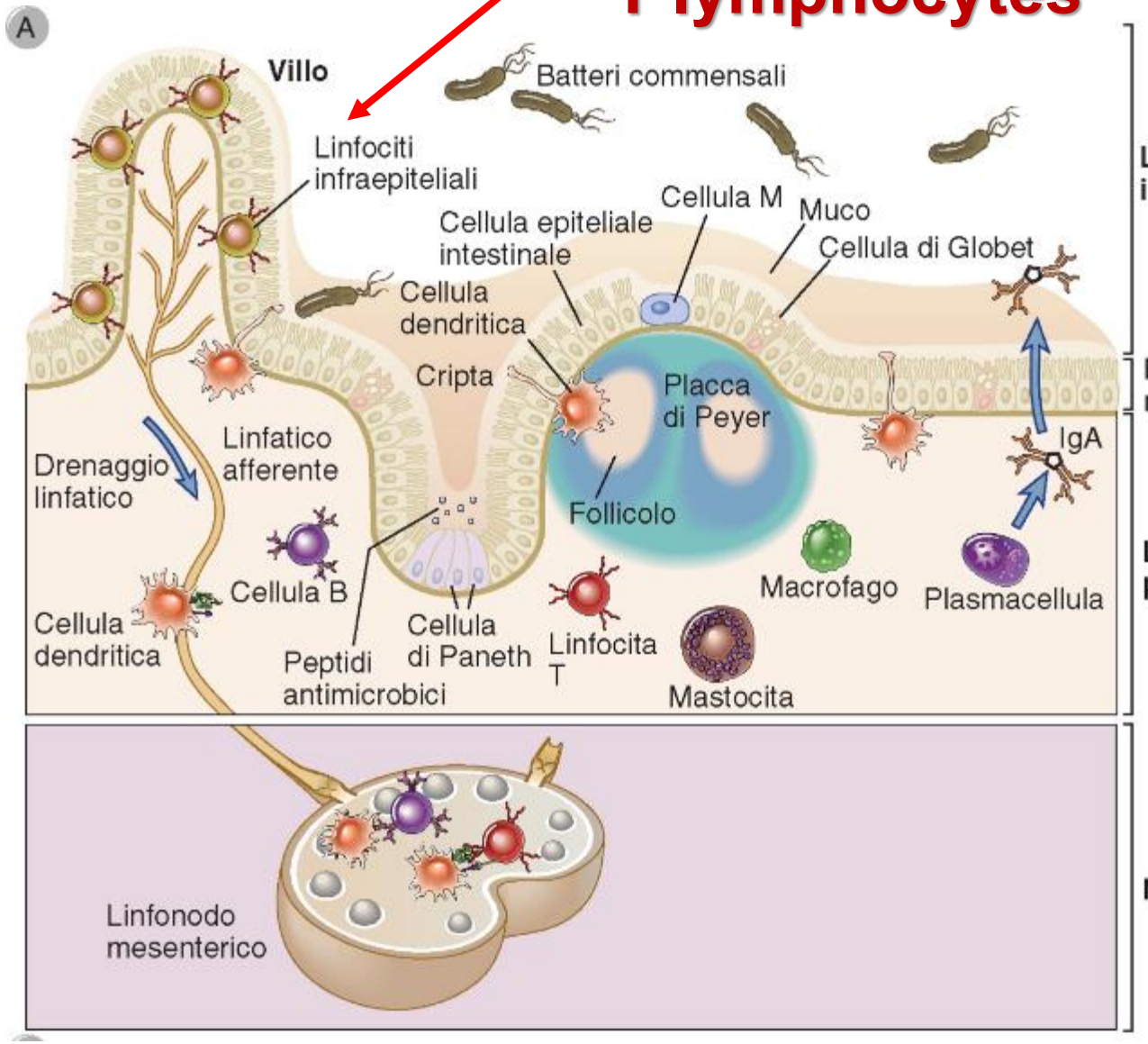
The mucosal immune system contains "T lymphocytes"

In the intestine, scattered T cells are found in two distinct locations:

- *lamina propria*

- epithelium

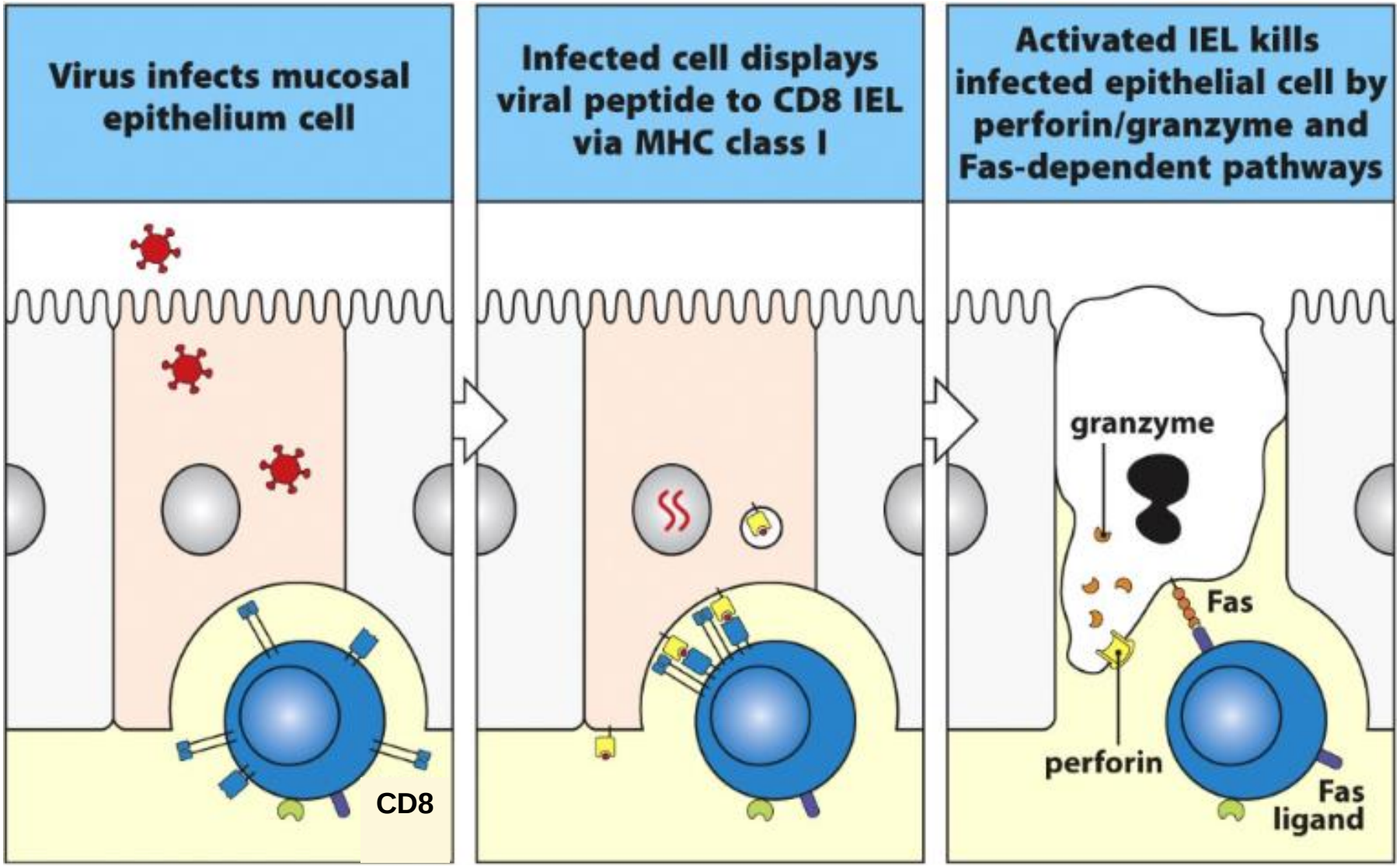
The mucosal immune system contains "T lymphocytes"



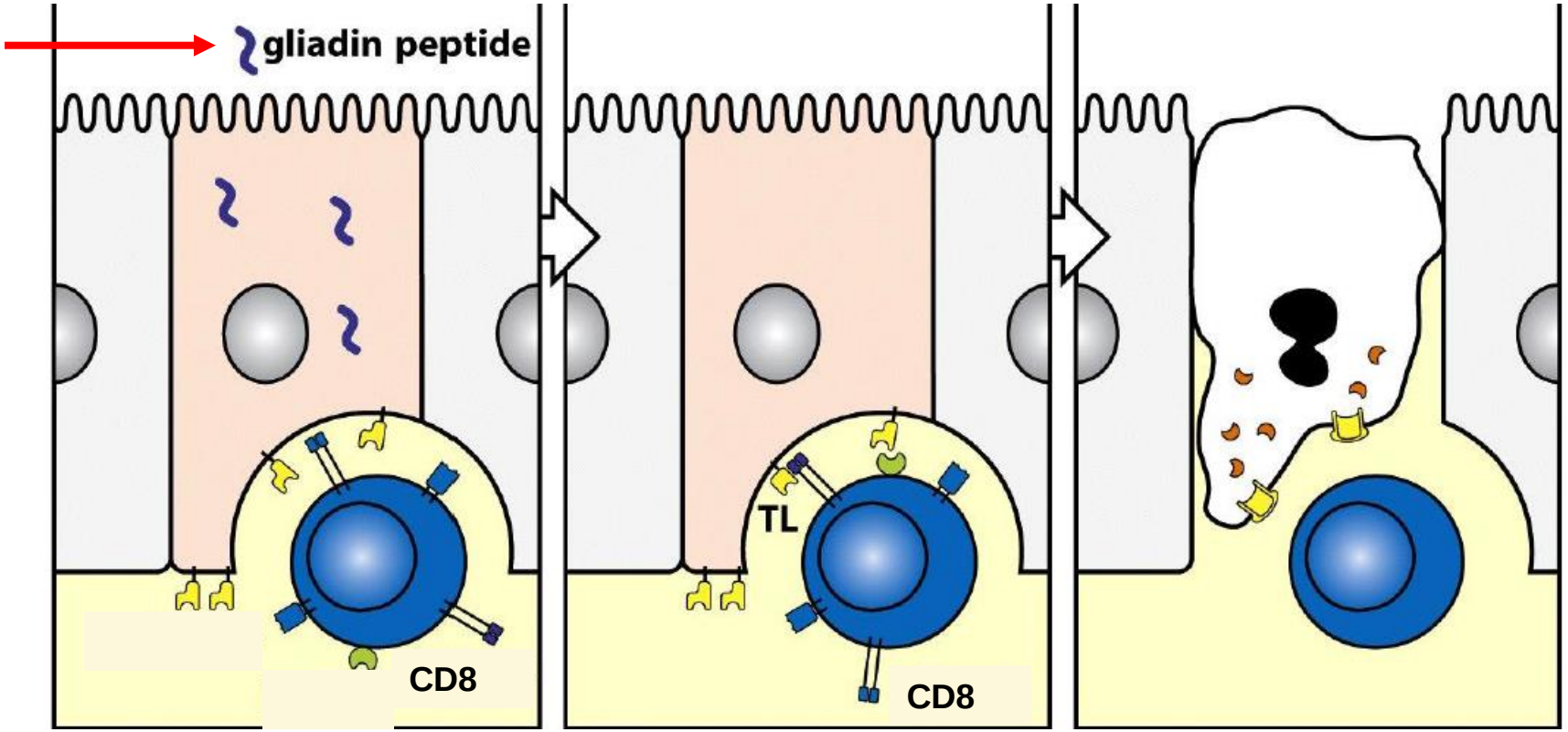
IEL 80% CD8
Granzyme, perforin
CCR9, a_4b_7

CD4:CD8 3:1
CD45RO
CCR9, a_4b_7, CCL5
IFNgamma, IL-5, IL-10

ROLE OF IEL CD8+ T CELLS IN VIRAL INFECTIONS



ROLE OF IEL CD8+ T CELLS IN CELIAC DISEASE



I linfociti B

Immunità umorale nel tratto gastrointestinale

- IgA costituiscono l'isotipo anticorpale più rappresentato nel tratto gastrointestinale: **IgA** (40): IgM (3): IgG (1)

(circa il 60-70% della produzione totale di anticorpi)

- IgA secretorie sono prodotte nel GALT e trasportate attraverso l'epitelio mucosale nel lume intestinale

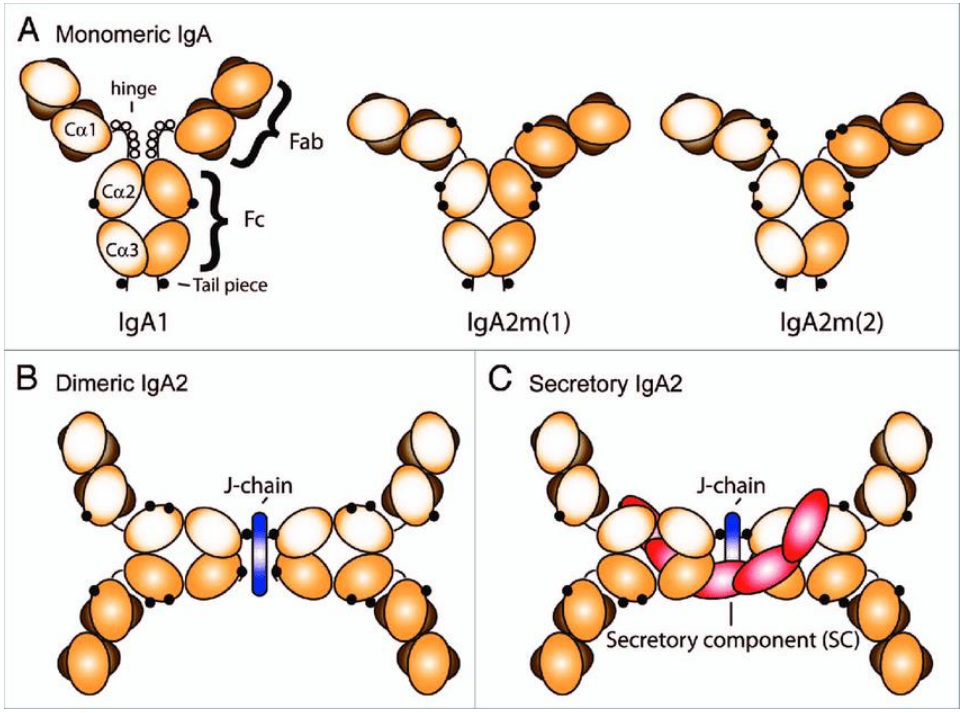
- La prevalenza di plasmacellule producenti IgA (circa l'80% di tutte le plasmacellule dell'organismo) è dovuta a:
  - Scambio isotipico verso IgA che avviene nel GALT e nei linfonodi mesenterici
  - *Homing* preferenziale all'intestino di cellule producenti IgA **(via CCR10-CCL28)**

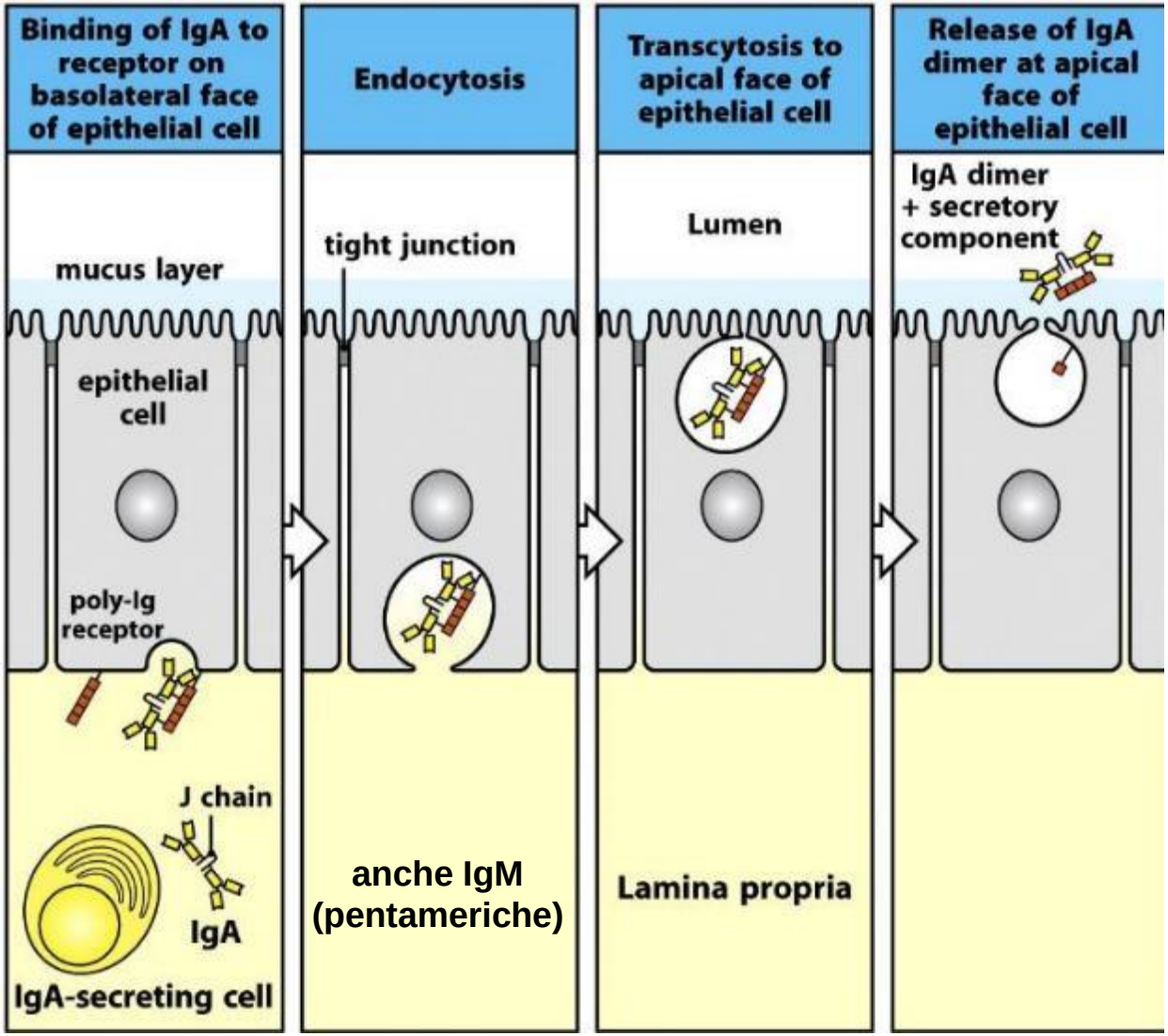
Le IgA

- In human, two isotypic forms: IgA1, IgA2
  - In blood, IgA1:IgA2 ⇒ 10:1 (mainly monomer)
  - In mucosal, IgA1: IgA2 ⇒ 3:2 (mainly dimer)

- naïve B cell $\xrightarrow{\text{TGF-beta}}$ IgA secreting plasma cells

- B lymphoblasts express the mucosal homing integrin a_4b_7





In the lamina propria, plasma cell: ⇒ J chain linked IgA dimers

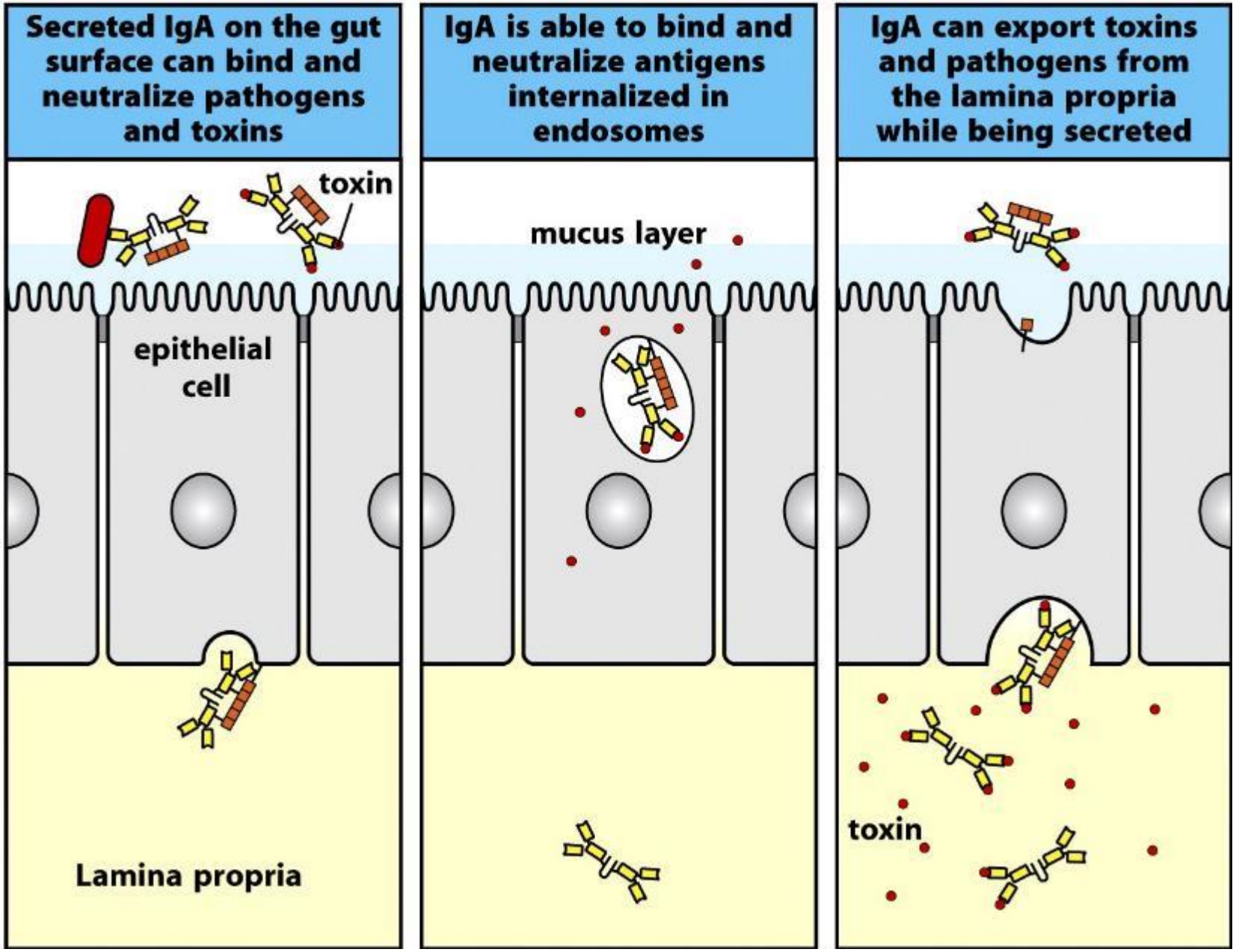
⇒ polymeric Ig receptors

⇒ transcytosis to the lumen

⇒ proteolytic cleavage of the extracellular domain of poly-Ig receptor

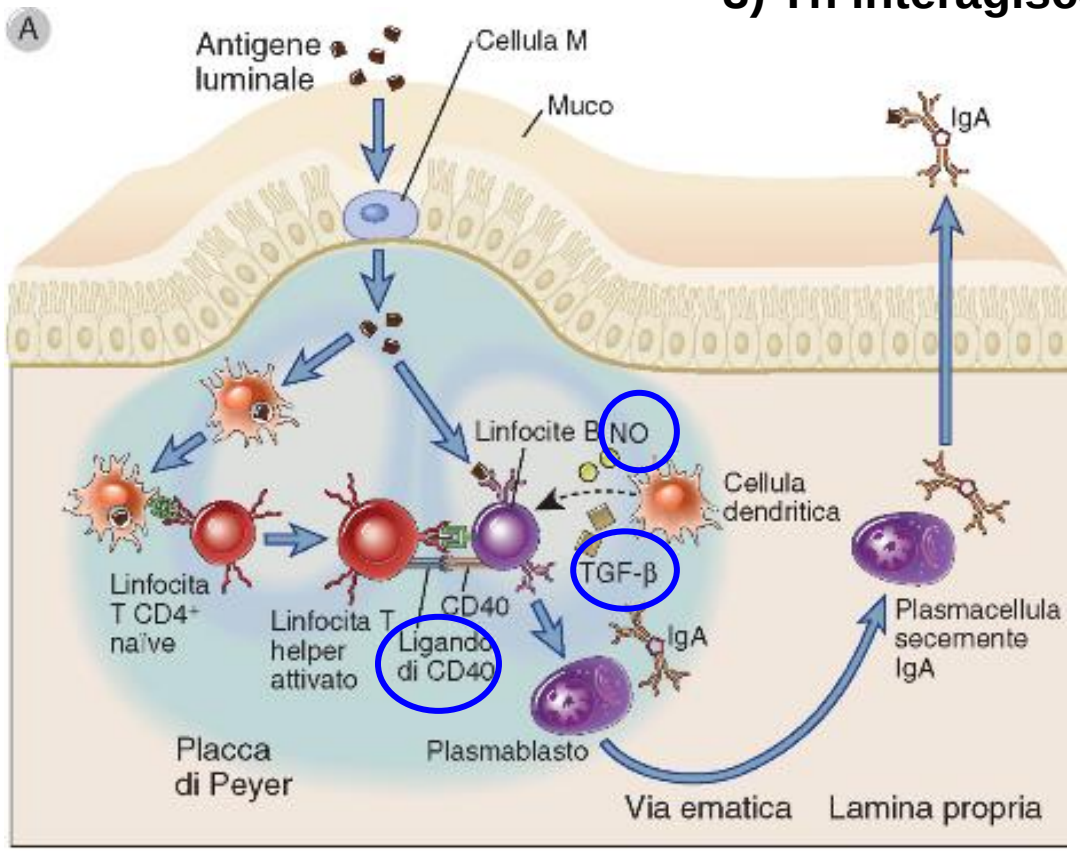
⇒ IgA dimer + secretory component (Secretory IgA)

Le funzioni delle IgA



La generazione delle IgA

Scambio isotipico T-dipendente



1) DC catturano Ag batterici e migrano verso la zona interfollicolare
2) Presentazione Ag a Th *naive*
3) Th interagiscono con cellule B IgM^+IgD^+

↓

-CD40L
-TGF-beta
- Ossido nitrico (**NO**)

↓

SCAMBIO ISOTIPICO

↓

IgA alta affinità vs patogeni e tossine

Abbas A.K

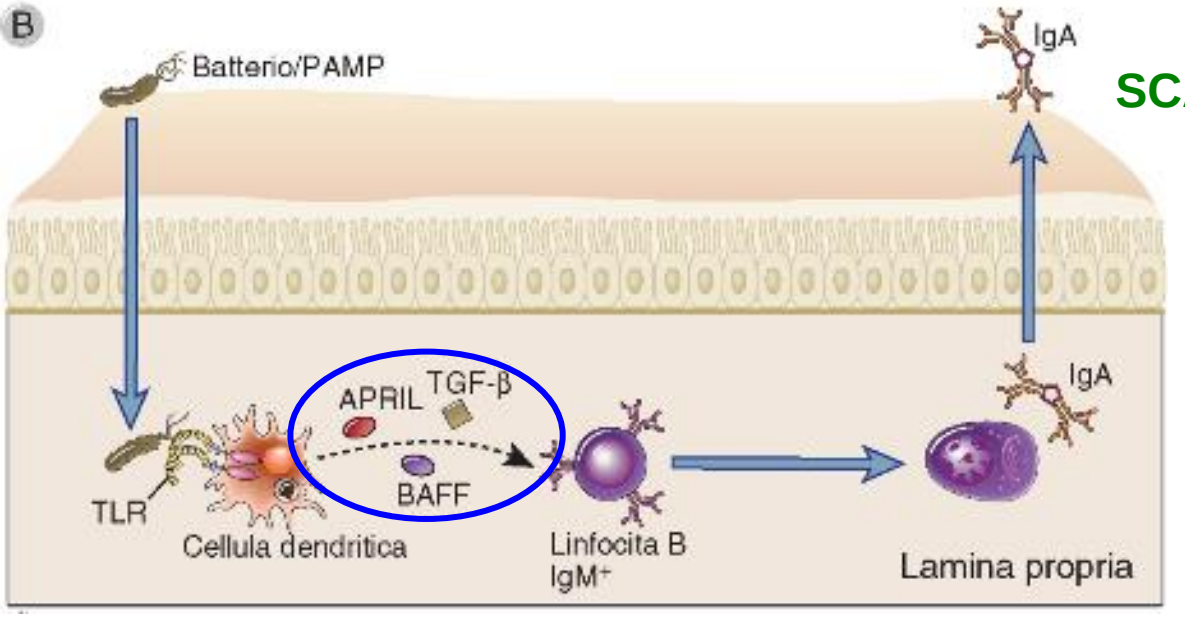
La generazione delle IgA

Scambio isotipico T-indipendente

DC attivate dai ligandi TLR:

-APRIL
-TGF-beta
- IL-6
- Acido retinoico

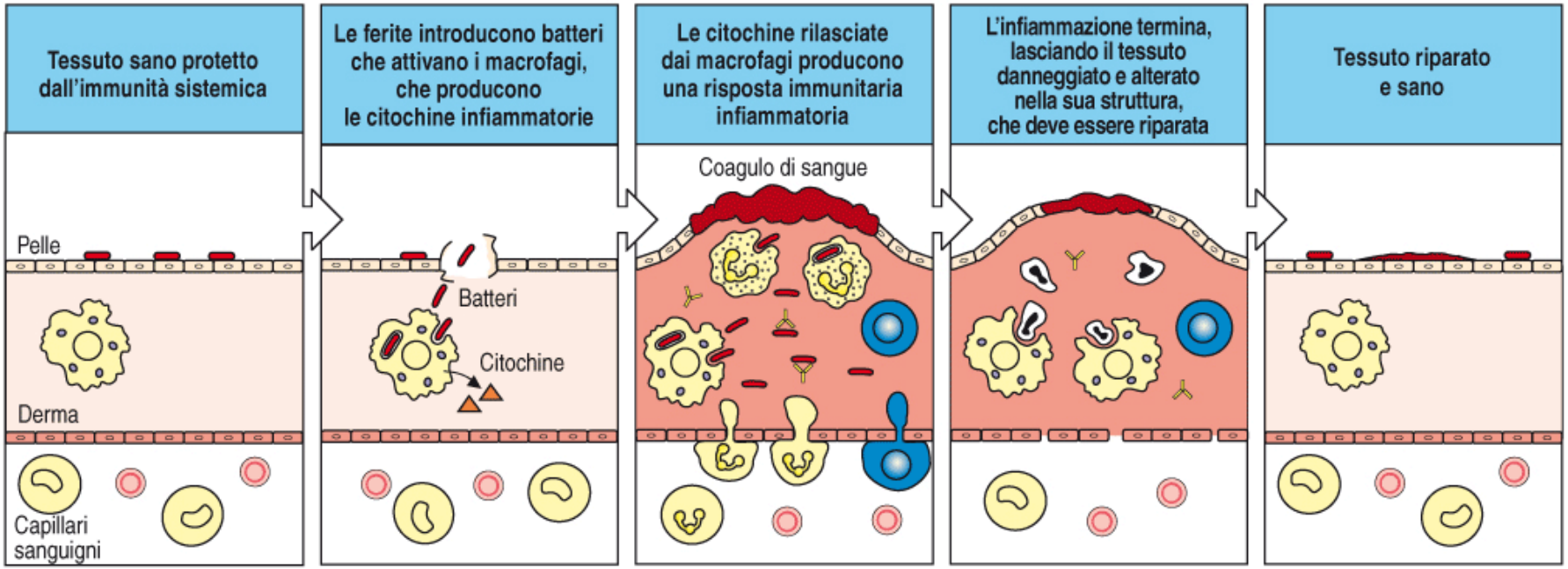
SCAMBIO ISOTIPICO



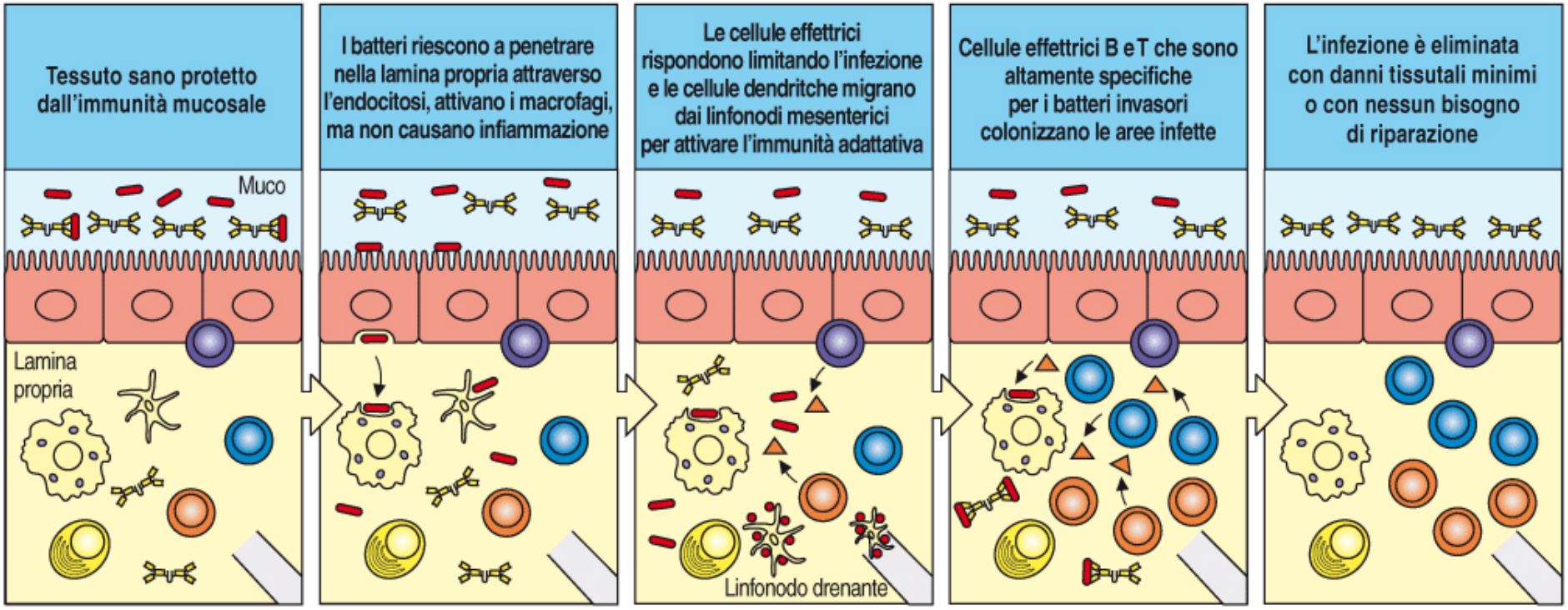
IgA bassa affinità batteri intestinali

Riassumendo…

Mentre la risposta immunitaria sistemica è di tipo reattivo……..



...la risposta immunitaria mucosale è di tipo proattivo



Vantaggi

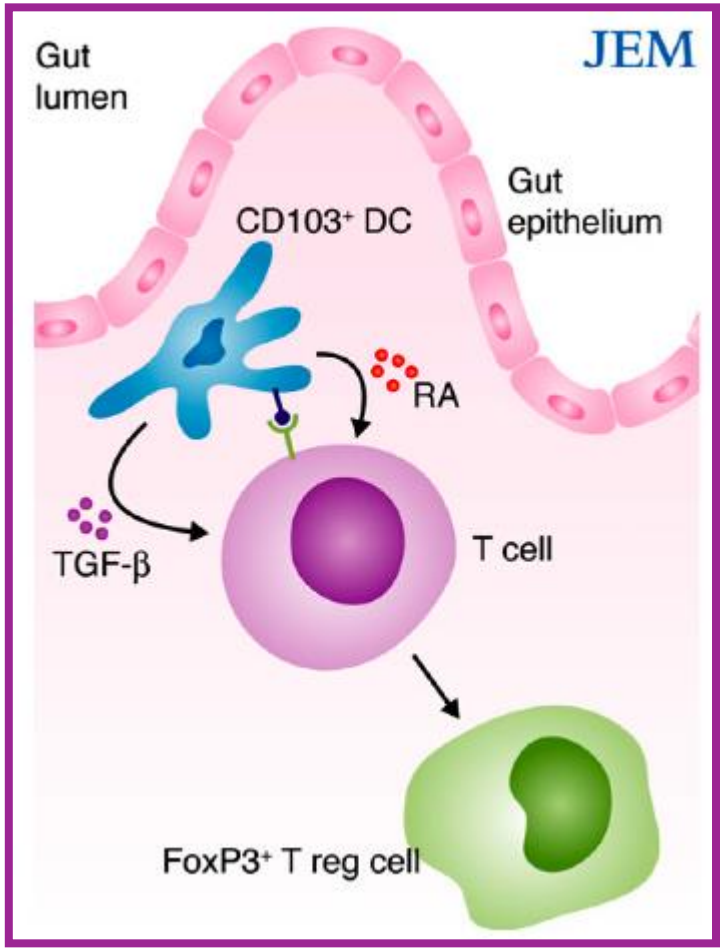
- Bloccare precocemente l'infezione
- Maggiore efficacia
- Prevenire l'infiammazione

- Enteric pathogens cause a local inflammatory response and the development of protective immunity

- The gut is the most frequent site of infection by pathogenic microorganisms

- Innate mechanisms eliminate most intestinal infections rapidly and without significant spread beyond the intestine

Many factors contribute to the tolerance of commensal flora



commensal bacteria:

- deficient escape mechanisms against mucus trapping
- deficient traits for epithelial adherence and invasion
- low endotoxicity (non-stimulatory LPS)
- anti-inflammatory products

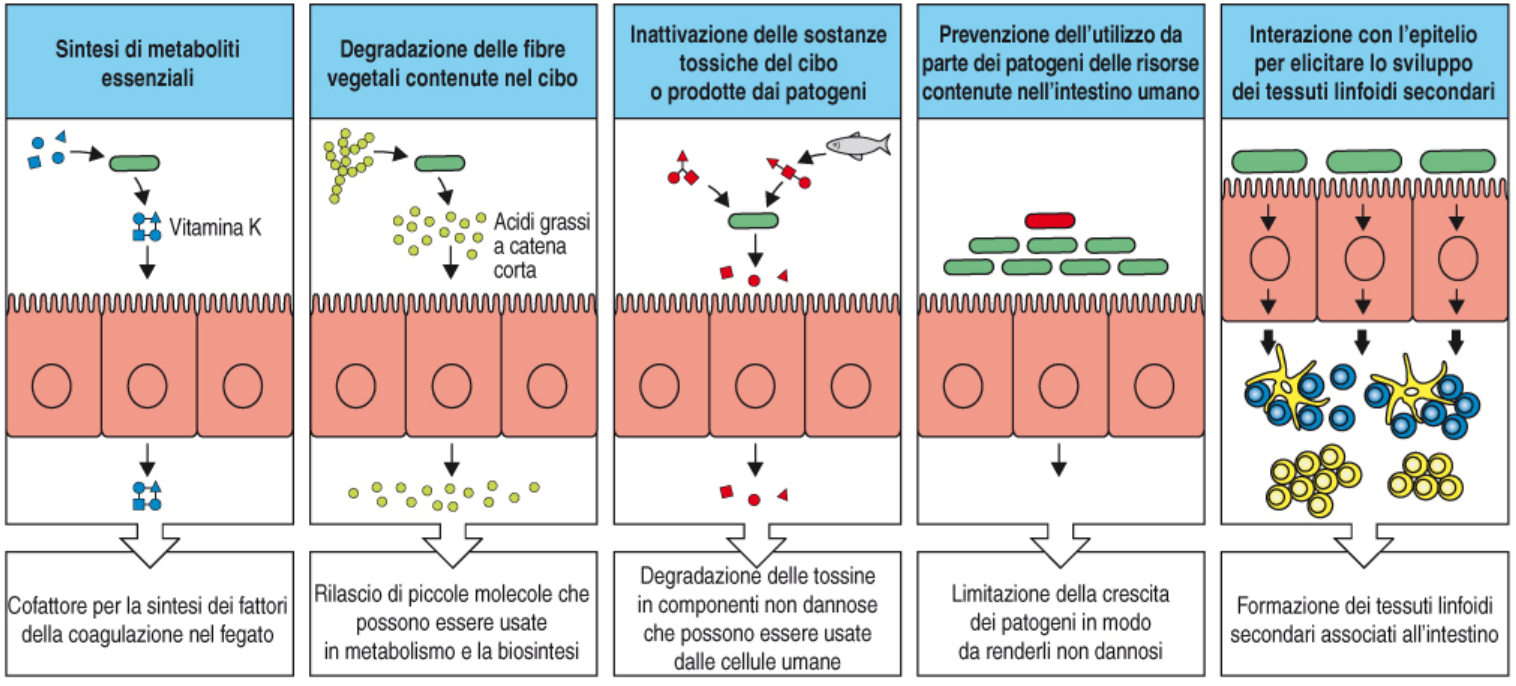
mucosal epithelium:

- tight junctions (regulated transfer of commensal antigens)
- defective sensing of PAMPs
- rapid sensing for invasive microorganisms
- strong antimicrobial crypt functions (defensins)

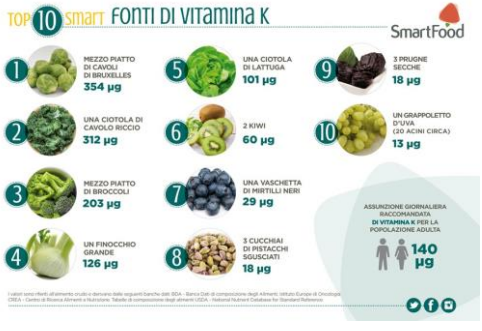
immune system:

- Lamina propria contains tolerogenic DC, macrophages, and regulatory T cells producing anti-inflammatory cytokines (IL-10 and TGF β) in response to commensal bacteria
- DC-derived retinoic acid (RA) and TGF β promote the differentiation and the activation of T reg cells in the gut

Funzioni dei batteri commensali…



La vitamina K viene scarsamente immagazzinata e ha una emivita breve (ca. 18 ore). Necessario un apporto continuo (dieta+batteri)



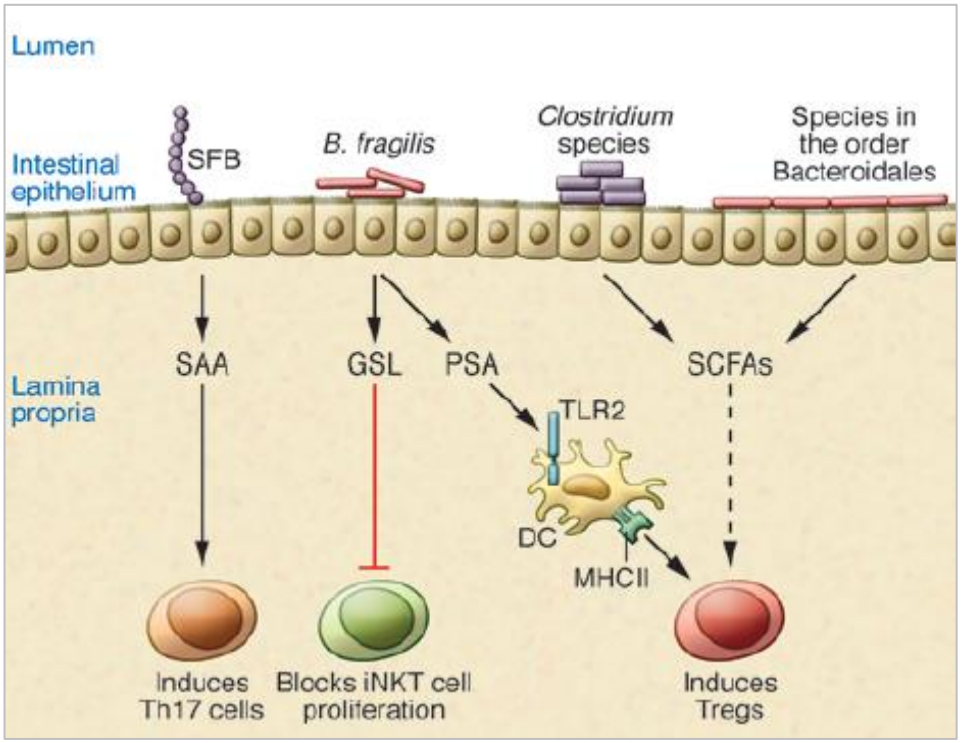
interviene nella sintesi della protrombina
=> vitamina antiemorragica (K= Koagulation vitamin)

Competizione per i nutrienti e produzione di AMPs e metaboliti che influenzano la sopravvivenza e la virulenza dei patogeni

Modulazione delle funzioni delle DC e di altre cellule dell'immunità innata (sia a livello locale che sistemico) che promuovono lo sviluppo di linfociti T e B effettori

… e loro effetto sul sistema immunitario intestinale innato e adattativo (I)

+muco, AMPs



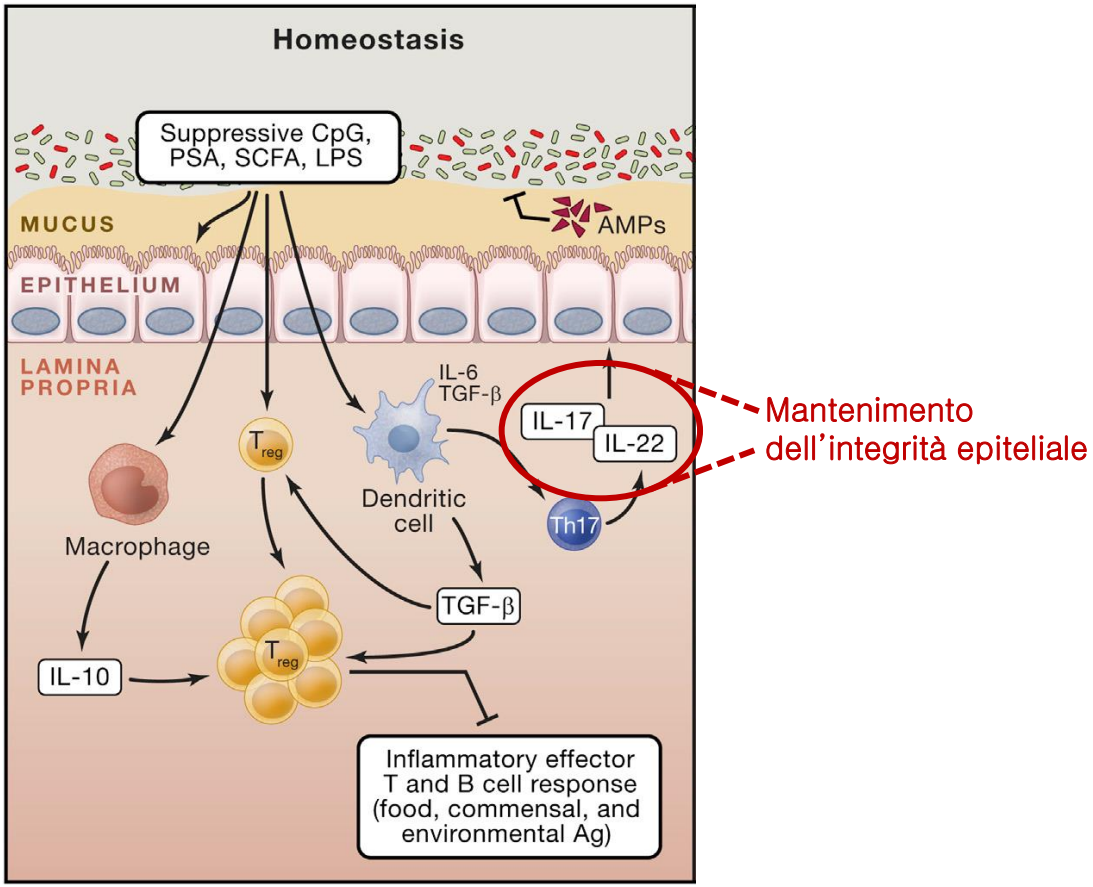
Bacteroides caccae,
Bacteroides massiliensis,
Bacteroides thetaiotaomicron,
Bacteroides vulgatus,
and Parabacteroides distasonis

Segmented filamentous bacteria (SFB)
Serum amyloid A (SAA)
Glycosphingolipid (GSL)
Polysaccharide A (PSA)
Short-chain fatty acids (SCFA)

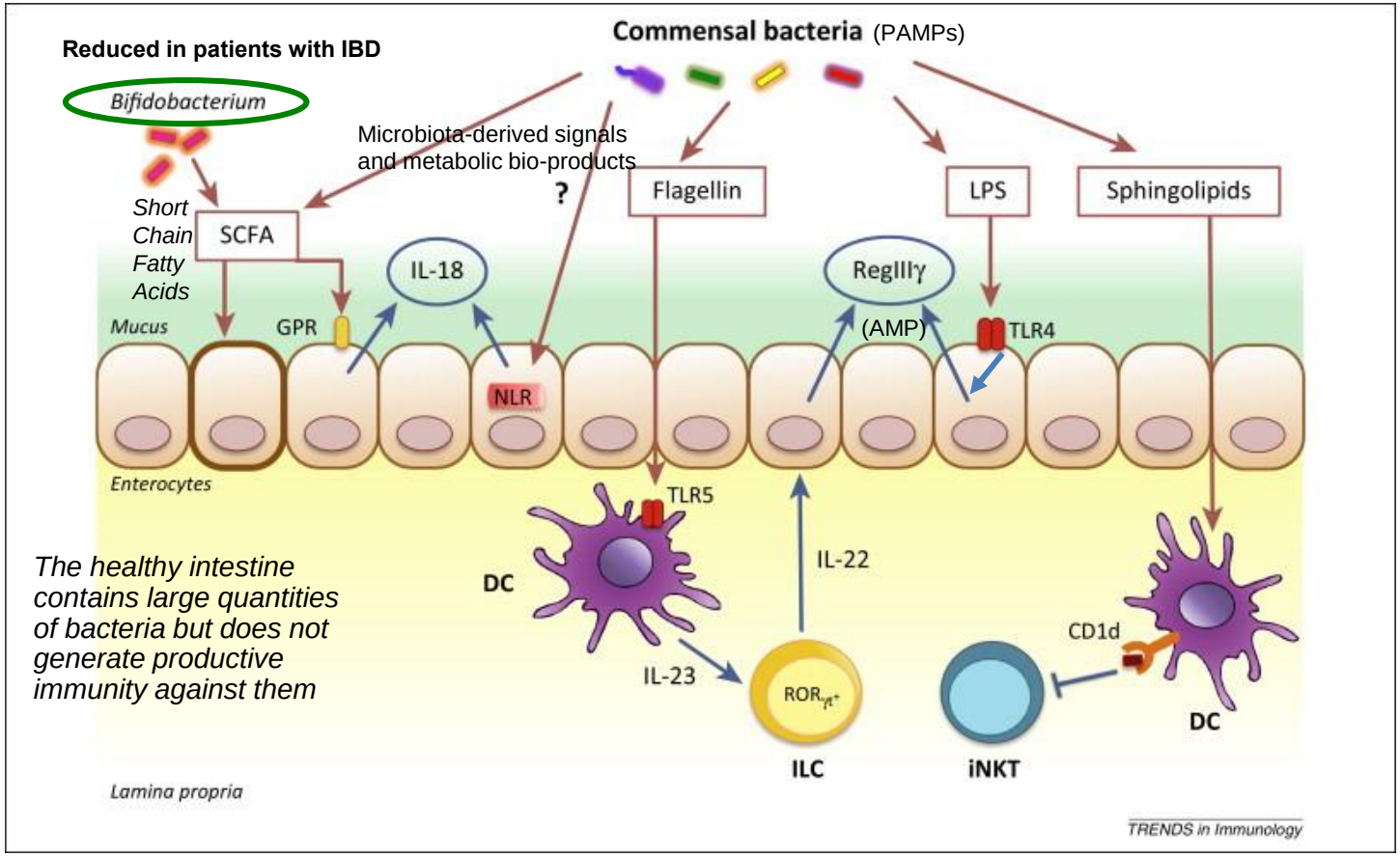
Surana NK and Kasper DL, J Clin Inv 2014

… e loro effetto sul sistema immunitario intestinale innato e adattativo (II)

Serum amyloid A (SAA)
Glycosphingolipid (GSL)
Polysaccharide A (PSA)
Short chain fatty acids (SCFA)

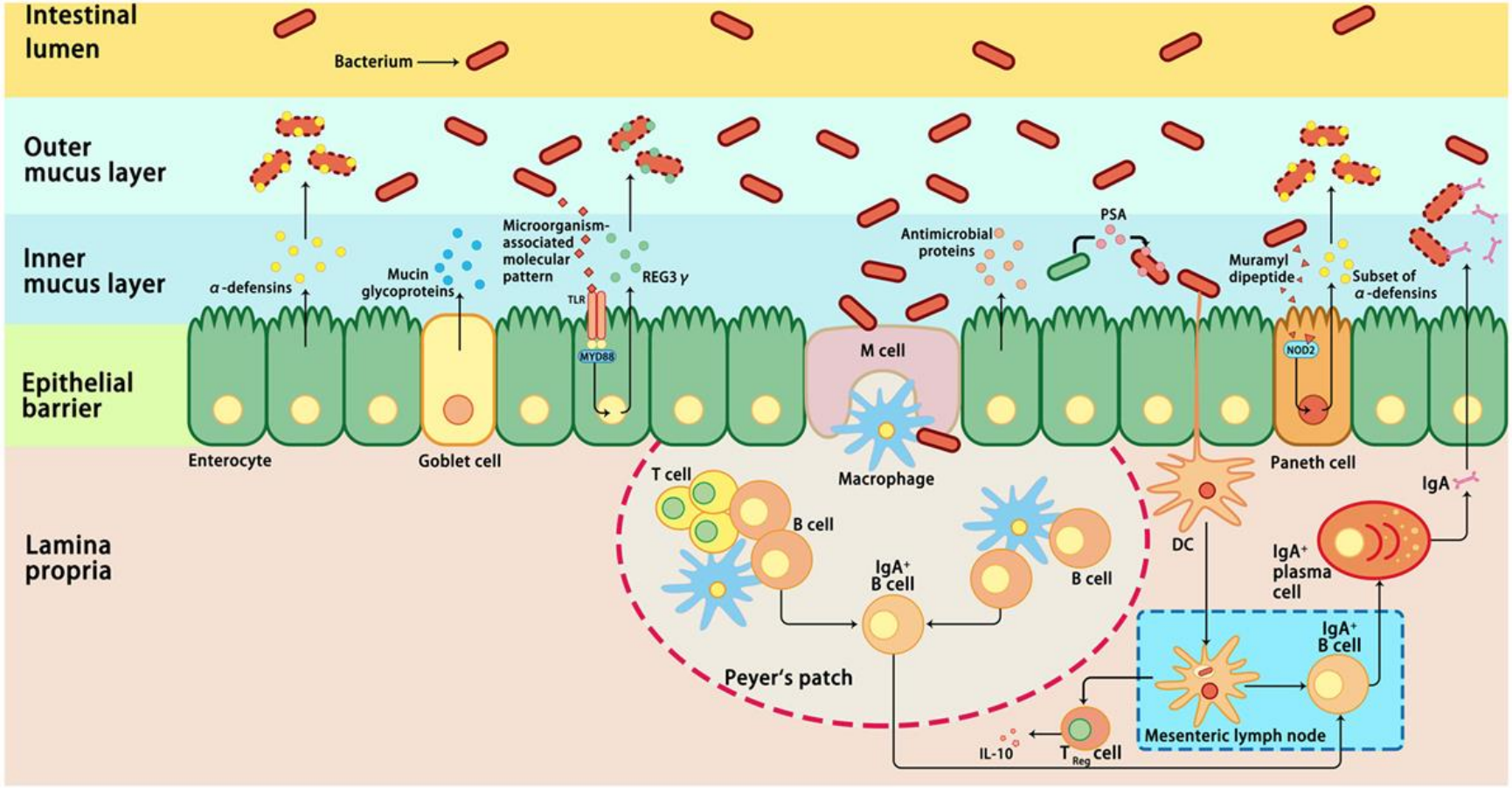


Il microbiota influenza la risposta immunitaria innata

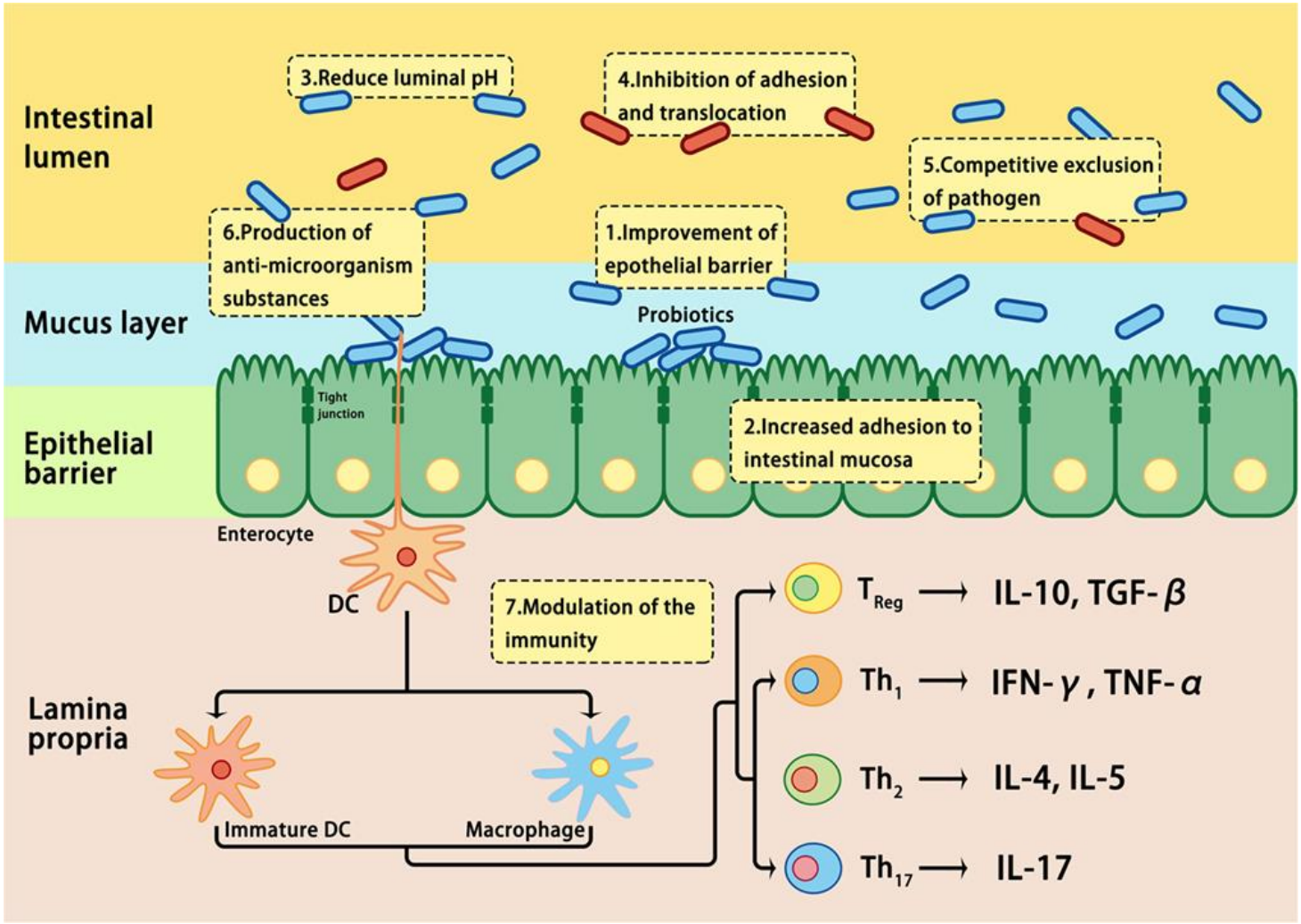


The healthy intestine contains large quantities of bacteria but does not generate productive immunity against them

La funzione principale di mediatori e cellule indotti dalle risposte immunitarie innate: ⇒ iniziare le risposte immunitarie adattative

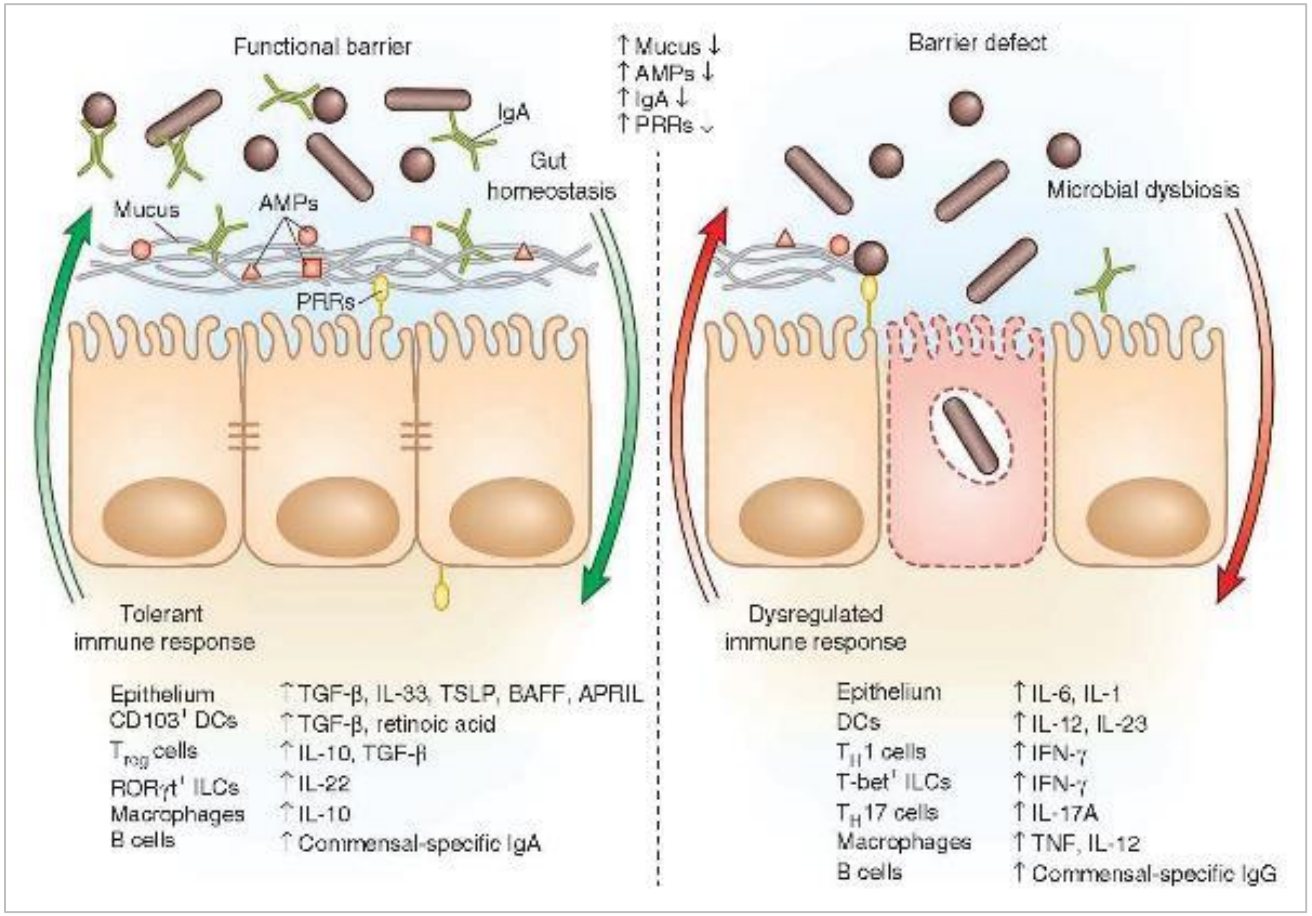


Meccanismi coinvolti nella protezione indotta dai probiotici contro le disbiosi intestinali



L’equilibrio dell’immunità mucosale e del microbiota nell’intestino

+Goblet cells,
Paneth cells, ecc.

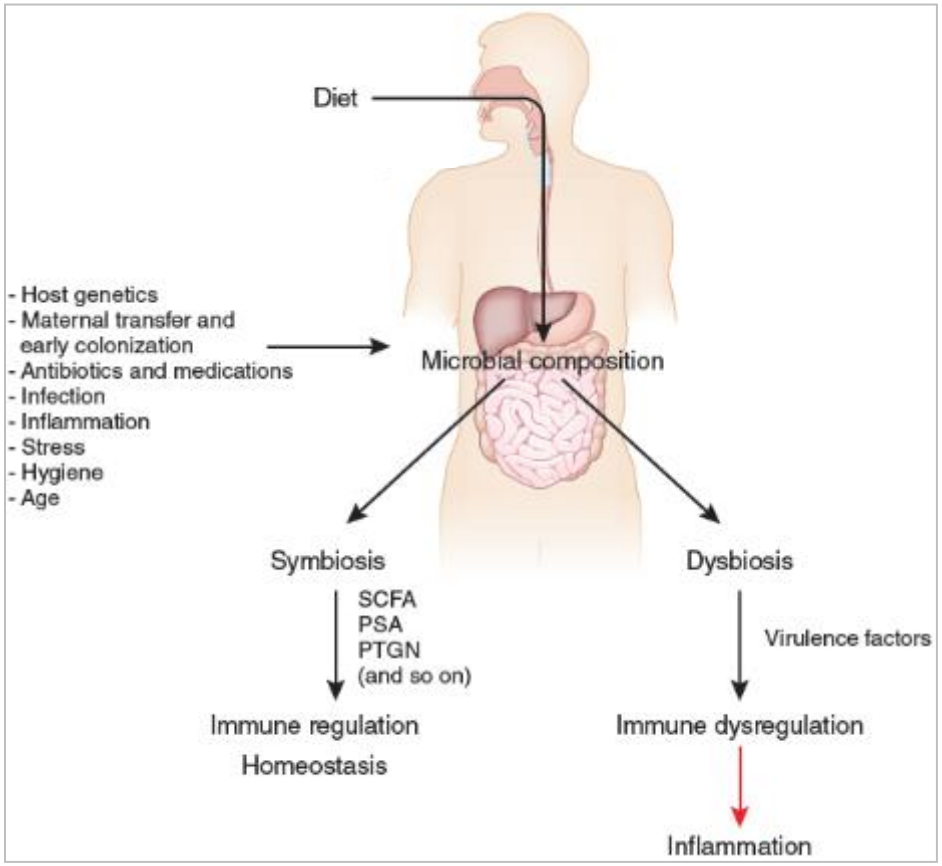


risposta anti-infiammatoria/immunosoppressiva

risposta pro-infiammatoria

Brown E, Nature Immunology 2013

Dieta, microbiota e regolazione del sistema immunitario



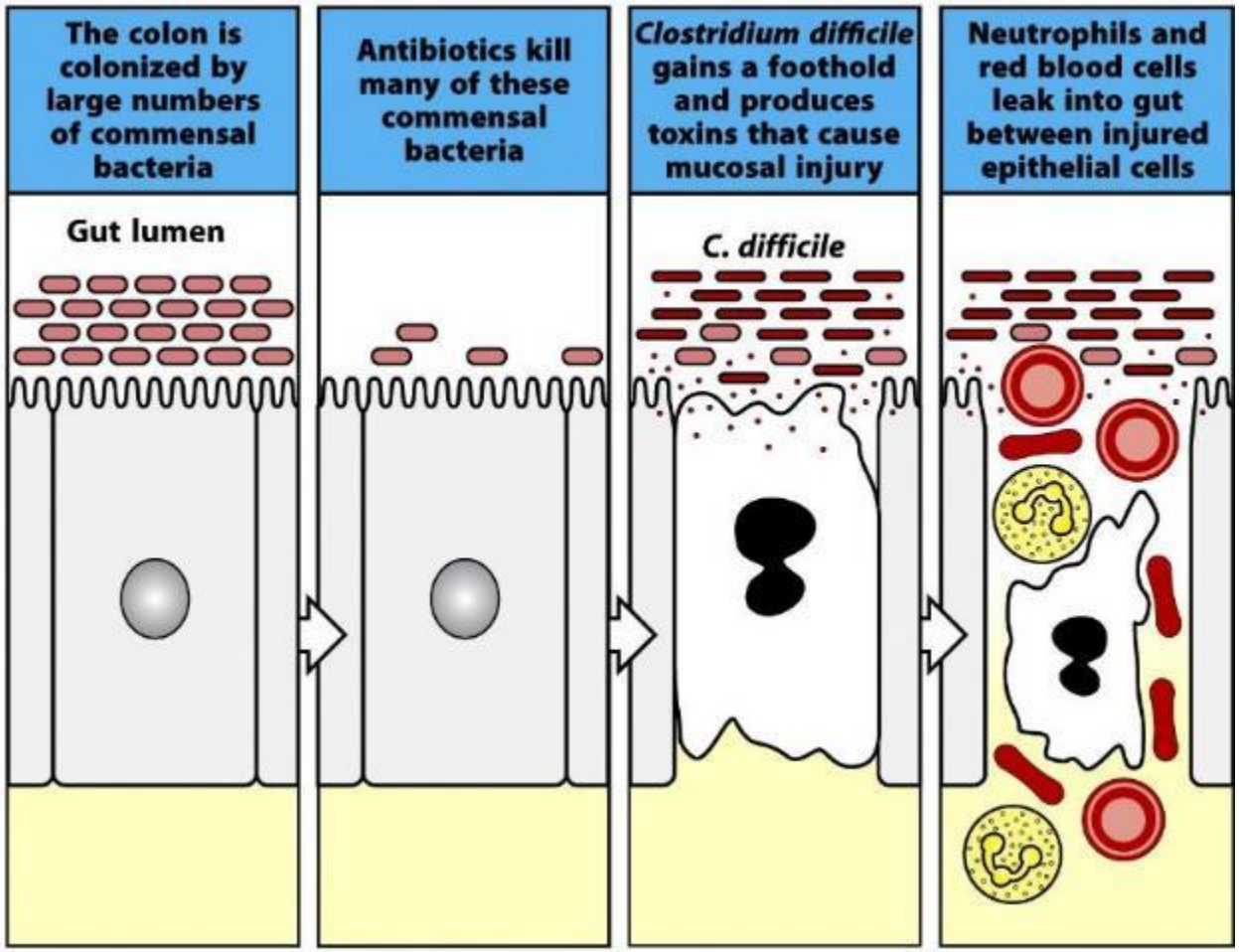
some microbes can shift from mutualist to commensal to parasite according to the state of activation of the host, co-infection or localization

SCFA: short-chain fatty acid
PSA: polysaccharide A
PTGN: peptidoglycan

Maslowski KM & Mackay CR Nature Immunol 2011

The symbiosis between the microbiota and its mammalian host encompasses multiple relationships:

- **Mutualistic**
- **Parasitic**
- **Commensal**


The colon is colonized by large numbers of commensal bacteria
Antibiotics kill many of these commensal bacteria
Clostridium difficile gains a foothold and produces toxins that cause mucosal injury
Neutrophils and red blood cells leak into gut between injured epithelial cells
Gut lumen
C. difficile

Il sistema immunitario delle mucose: un equilibrio complesso

Immunità protettiva

Omeostasi verso un vasto numero di antigeni estranei

La maggior parte degli antigeni che il sistema immunitario dell'intestino incontra non derivano da patogeni ma dal cibo e da batteri commensali

- Il sistema immunitario delle mucose ha sviluppato meccanismi molto sofisticati per discriminare i patogeni dagli antigeni innocui

L’ intestino sano contiene grandi quantità di batteri, ma non sviluppa una risposta immunitaria contro di essi

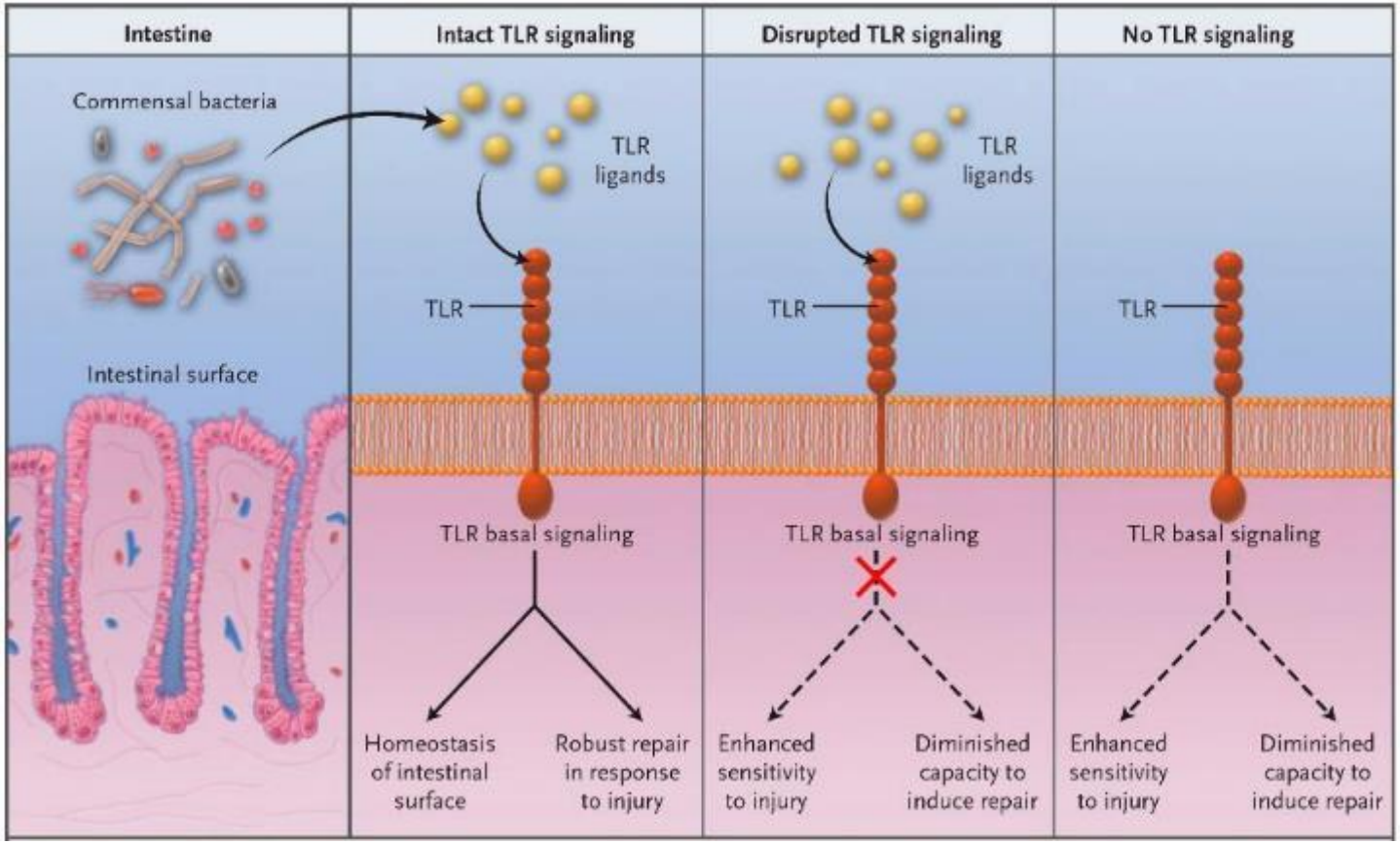
- **Il microbiota è richiesto per la normale funzione di barriera dell’epitelio.**

- **Il ruolo protettivo della flora intestinale è drammaticamente illustrato dagli effetti avversi degli antibiotici.**

- **Il ruolo protettivo dei TLR sembra coinvolgere le cellule epiteliali, che sono più resistenti al dànno indotto dall’infiammazione.**

- **I TLR sono coinvolti nella proliferazione epiteliale, nel mantenimento delle giunzioni strette, nella produzione di peptidi antimicrobici.**

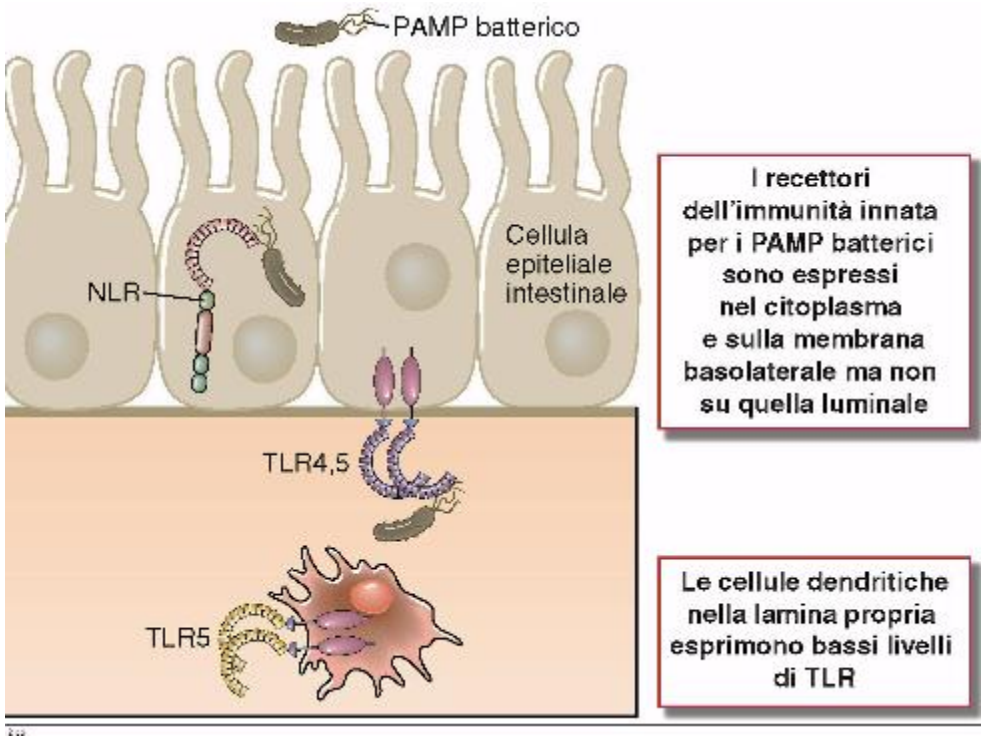
Una stimolazione «basale» dei TLR da parte di batteri commensali aumenta la capacità delle cellule epiteliali di riparare un dànno



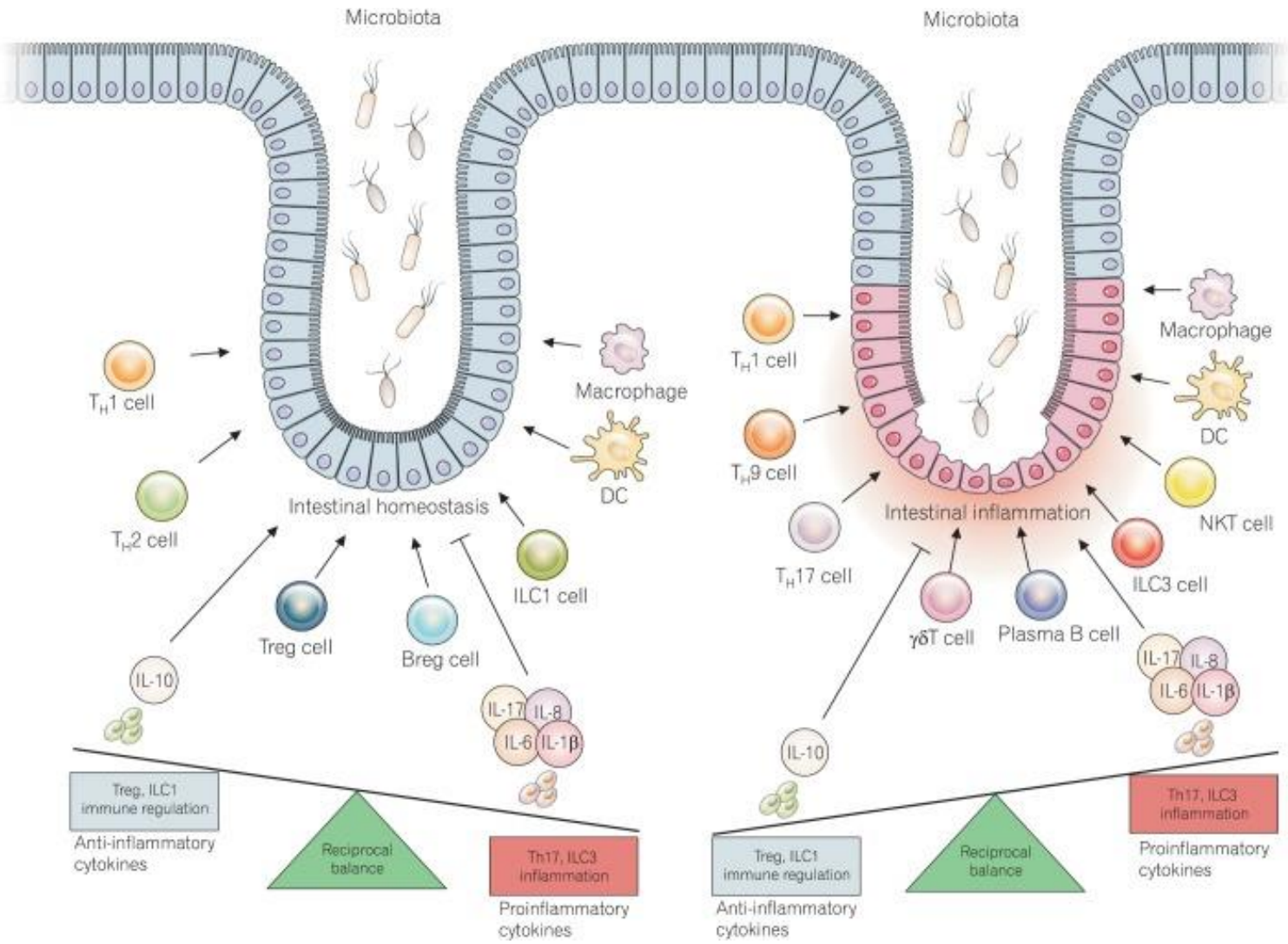
EPITHELIAL CELLS HAVE A CRUCIAL ROLE IN THE INNATE DEFENSE AGAINST PATHOGENS

Espressione polarizzata del TLR5:

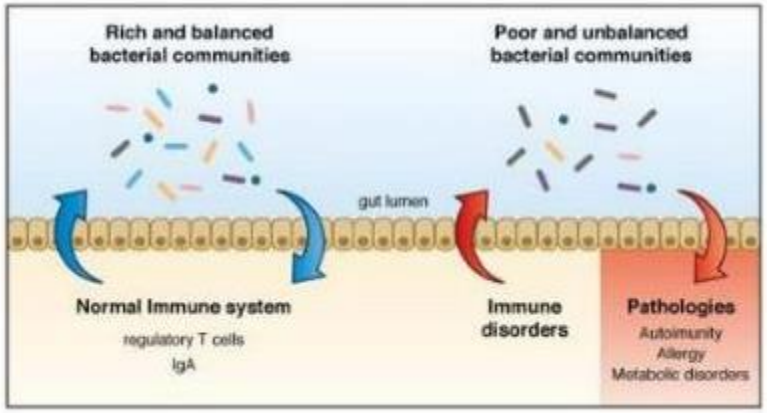
Risposta infiammatoria ridotta nei confronti dei batteri commensali



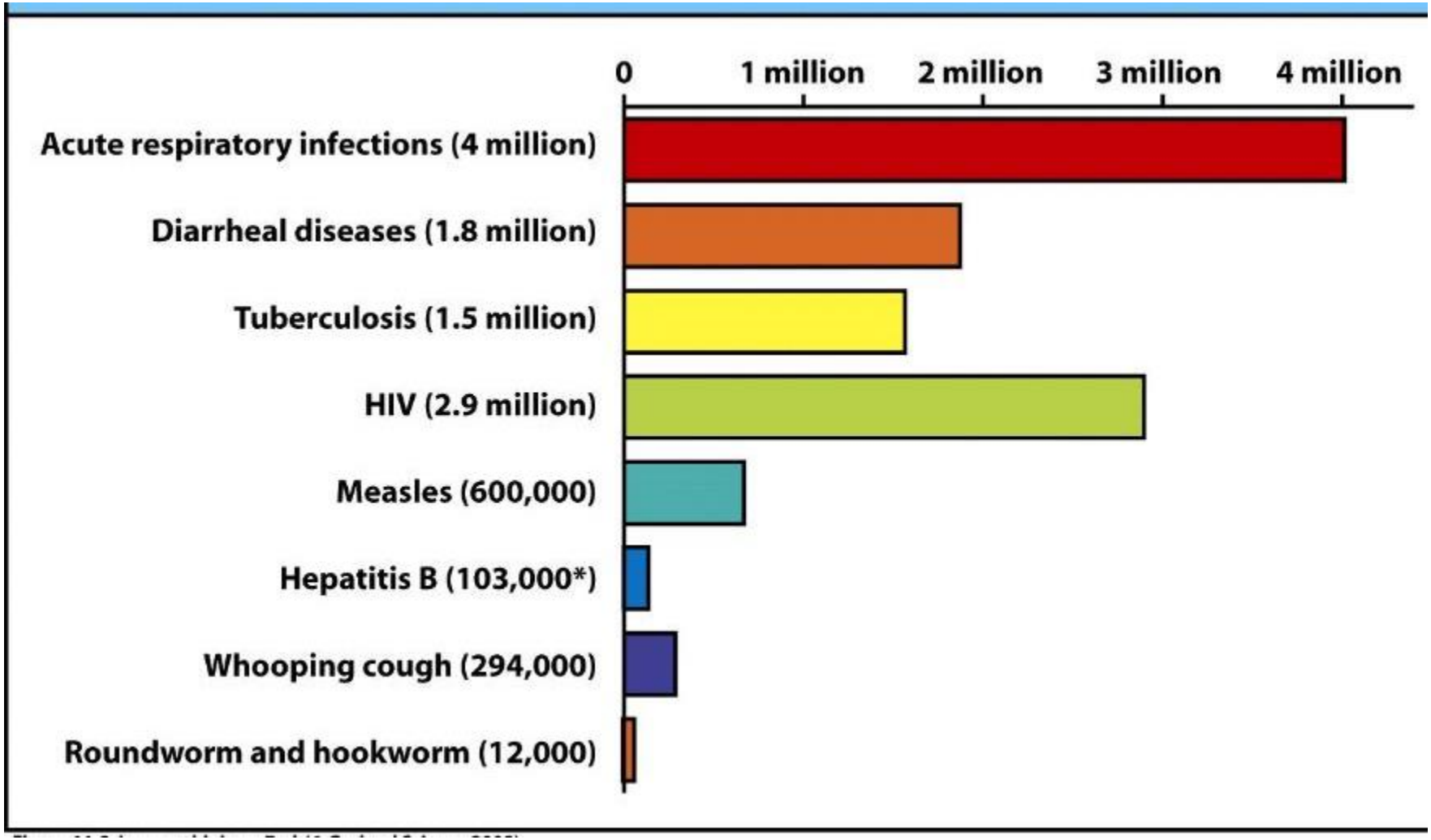
Il sistema immunitario delle mucose: un equilibrio complesso



Malattie correlate alle infezioni e alle risposte immunitarie nell'intestino



Worldwide deaths annually from mucosal infections



Intestinal pathogens and human disease	
Bacteria	
Salmonella typhi	Typhoid fever
Salmonella paratyphi	Enteric fever (paratyphoid)
Salmonella enteritidis	Food poisoning
Vibrio cholera	Cholera
Shigella dysenteriae, flexneri, sonnei	Dysentery
Enteropathogenic *E. coli* (EPEC)	Gastroenteritis, systemic infection
Enterohemolytic *E. coli* (EHEC)	Gastroenteritis, systemic infection
Enterotoxigenic *E. coli* (ETEC)	Gastroenteritis, 'travelers diarrhea'
Enteroaggregative *E. coli* (EAEC)	Gastroenteritis, systemic infection
Yersinia enterocolitica	Gastroenteritis, systemic infection
Clostridium difficile	Necrotizing enterocolitis
Campylobacter jejuni	Gastroenteritis
Staphylococcus aureus	Gastroenteritis
Bacillus cereus	Gastroenteritis
Clostridium perfringens	Gastroenteritis
Helicobacter pylori	Gastritis, peptic ulcer, gastric cancer
Mycobacterium tuberculosis	Intestinal TB
Listeria monocytogenes	Foodborne infection
Viruses	
Rotaviruses	Gastroenteritis
Norwalk-like viruses	'Winter vomiting' disease
Astroviruses	'Winter vomiting' disease
Adenoviruses	'Winter vomiting' disease

Intestinal pathogens and human disease	
Parasites	
Protozoa	
Giardia lamblia	Gastroenteritis
Blastocystis hominis	Gastroenteritis (esp. in immunocompromised hosts)
Toxoplasma gondii	Gastroenteritis, systemic disease (esp. in immunocompromised hosts)
Cryptosporidium parvum	Gastroenteritis (esp. in immunocompromised hosts)
Entamoeba histolytica	Amebic dysentery + liver abscesses
Microsporidium species	Diarrheal disease
Helminths	
Ascaris lumbricoides	Roundworm infection of small intestine
Necator americanus	Hookworm infection of small intestine
Strongyloides species	Roundworm infection of small intestine
Enterobius species	Pinworm infection of large intestine
Trichinella spiralis	Trichinosis
Trichuris trichiura	Whipworm infection of large intestine
Taenia species	Tapeworm infections
Schistosoma species	Schistosomiasis: enteritis, mesenteric vein infection

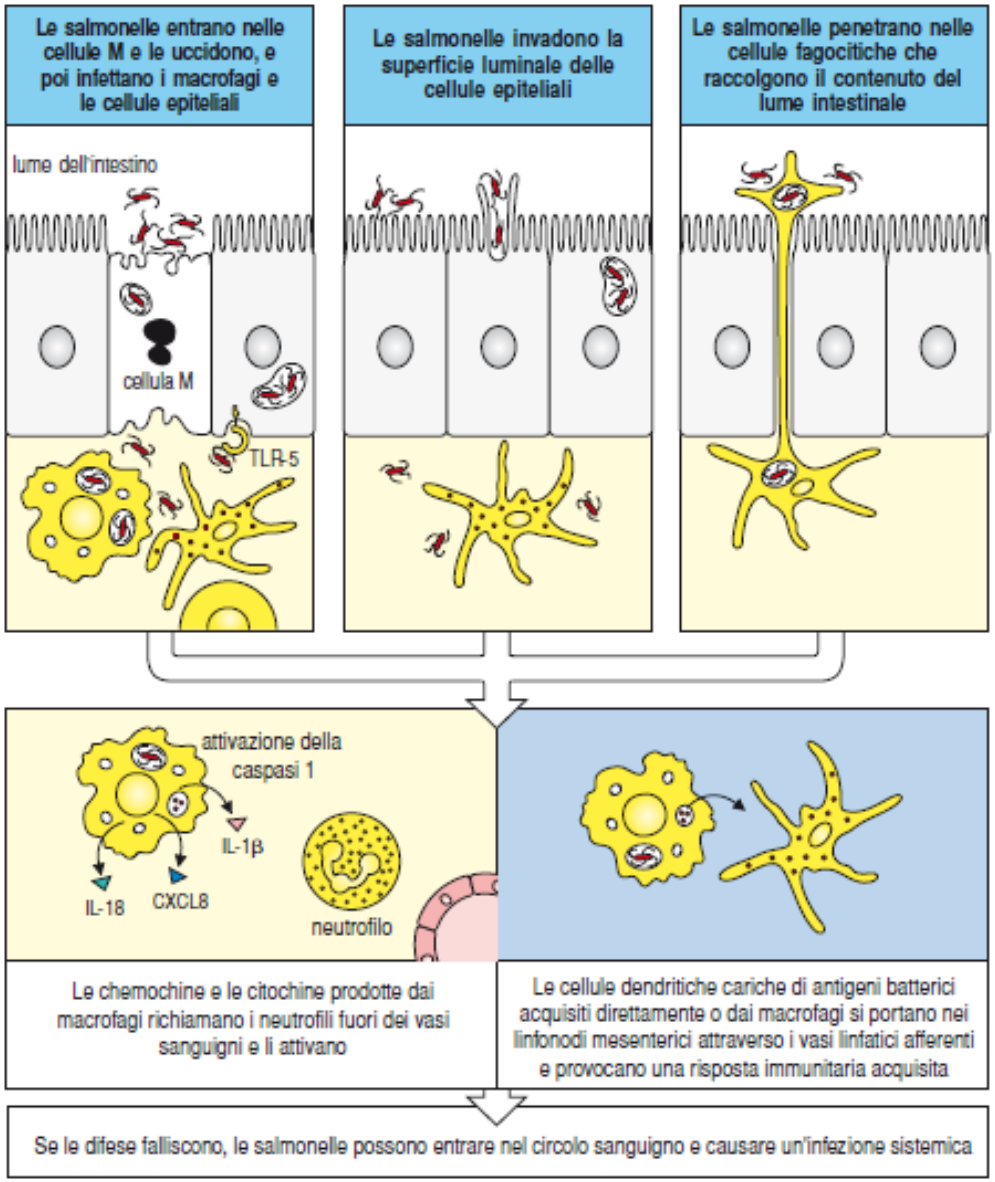
- **Il risultato finale di una infezione da parte di un patogeno intestinale è determinato da interazioni reciproche tra il microrganismo e la risposta immunitaria dell'ospite**

- **Inoltre, molti patogeni enterici sfruttano i meccanismi che l'ospite usa per la cattura dell'antigene attraverso le cellule M e l'infiammazione come parte della loro strategia di infezione**

  (e.g., *Salmonella typhimurium, Shigella flexneri)*

…Le salmonelle sfruttano i meccanismi che l'ospite usa per la cattura dell'antigene attraverso le cellule M e l'infiammazione come parte della loro strategia di infezione

Salmonella Typhimurim



- **La risposta infiammatoria dell'ospite è una parte a volte essenziale nel processo di invasione dei batteri**

- **I batteri che hanno attraversato le cellule M per transcitosi sono liberi di interagire con i TLR espressi dalle cellule infiammatorie ed epiteliali.**

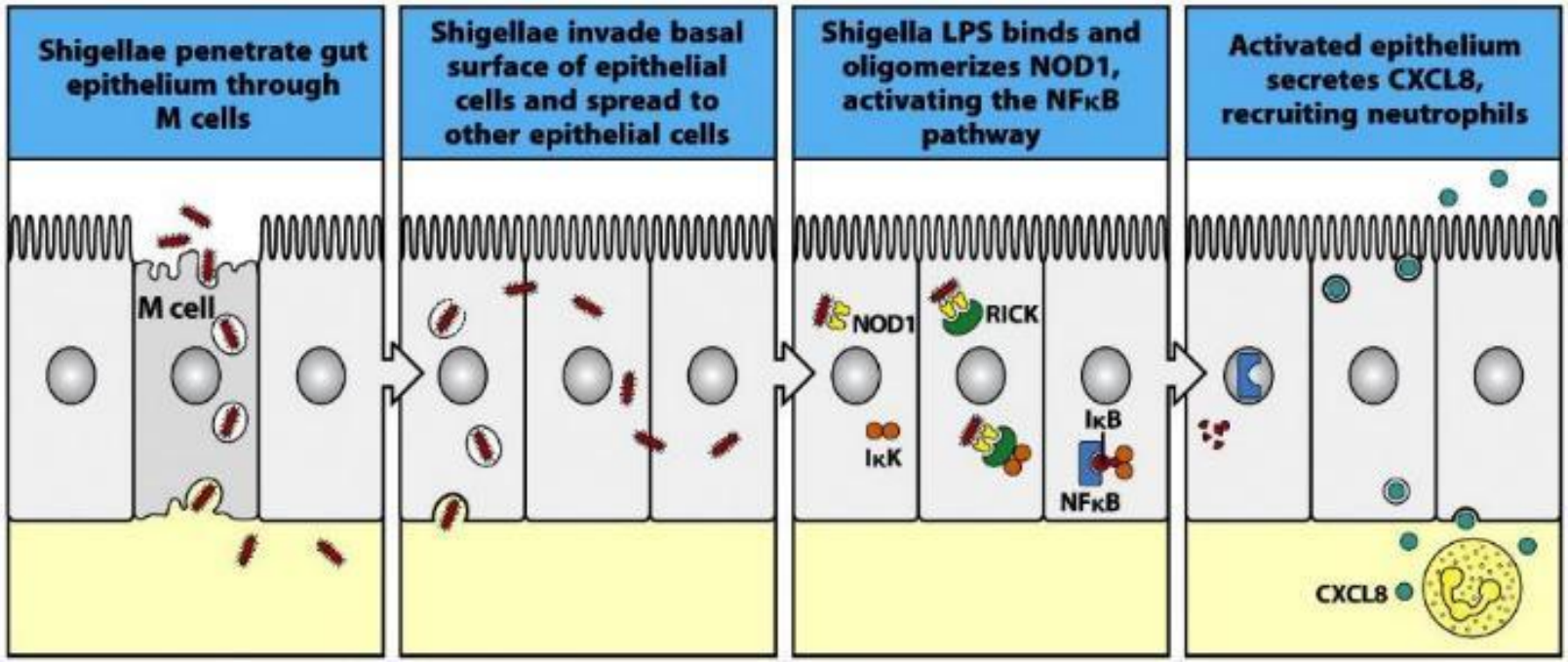
- **Dopo essere stati ingeriti dai fagociti, molti di questi microrganismi inducono la morte per apotosi del fagocita.**

- **Induzione di una cascata di citochine e mediatori dell'infiammazione (es., IL-1-beta, TNF-alfa)**

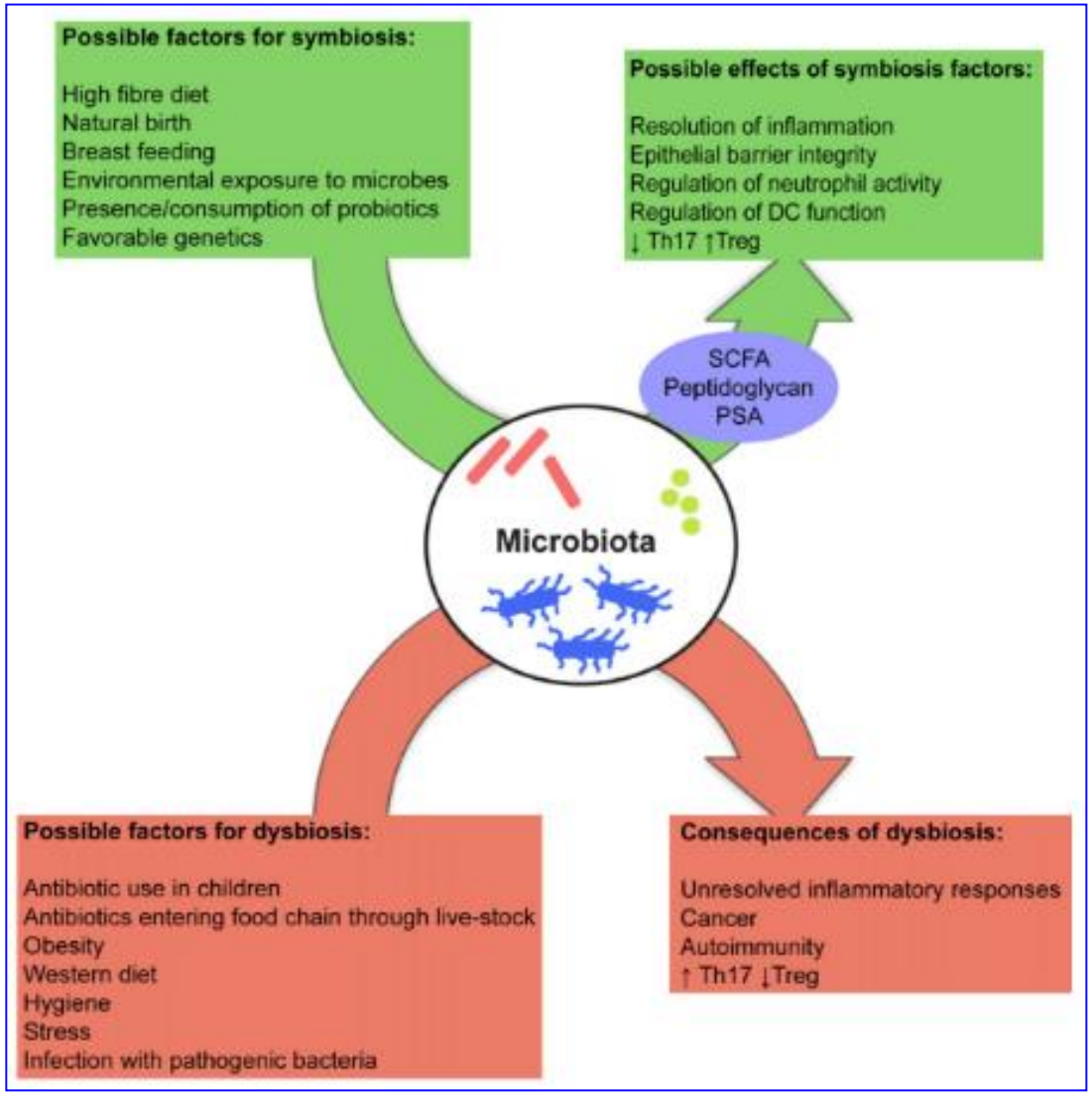
⇒ allentamento delle giunzioni strette tra le cellule epiteliali

⇒ passaggio dei microorganismi nel tessuto sottostante

Shigella flexneri



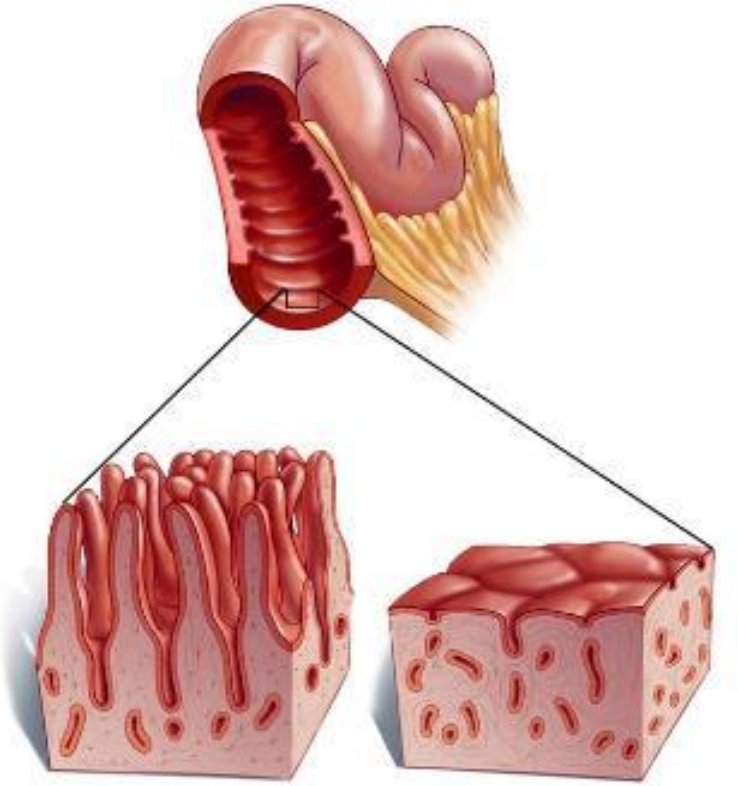
Possible factors controlling gut microbiota



(e.g., *Salmonella typhimurium, Shigella flexneri)*

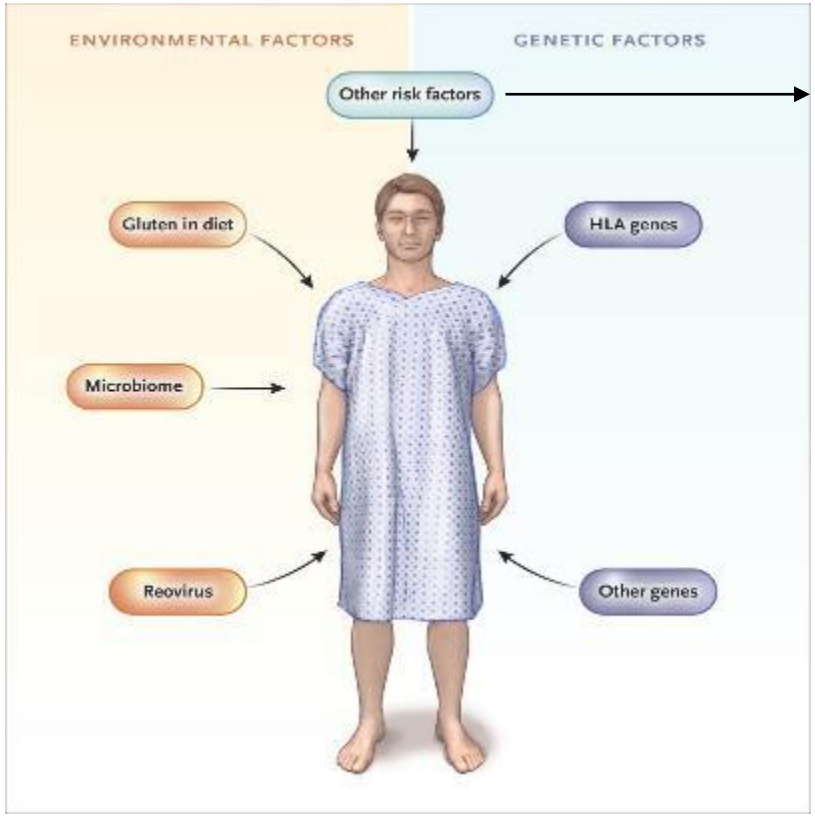
Environmental factors have a great influence on gut microbiota

La celiachia

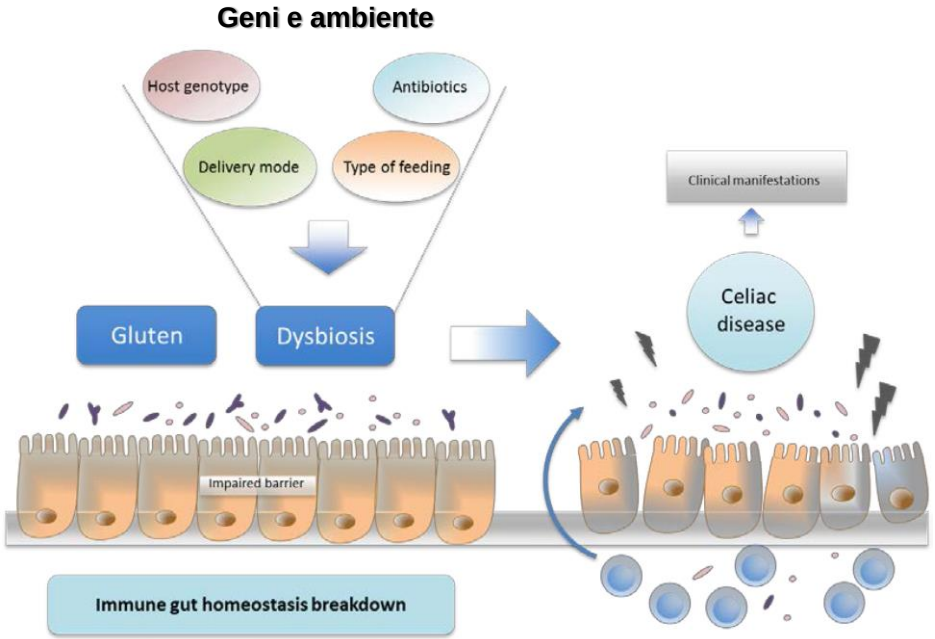


Normale Celiaco

Celiac disease (gluten-sensitive enteropathy)



At least in the mouse model, a combination of HLA-II genetic makeup, gluten in the diet, and reovirus infection was insufficient to cause the characteristic change of villous atrophy in the small intestine.



Rosenbaum JT. N Engl J Med 2017;377:1489-1490.

Glutine

gliadina + glutenina

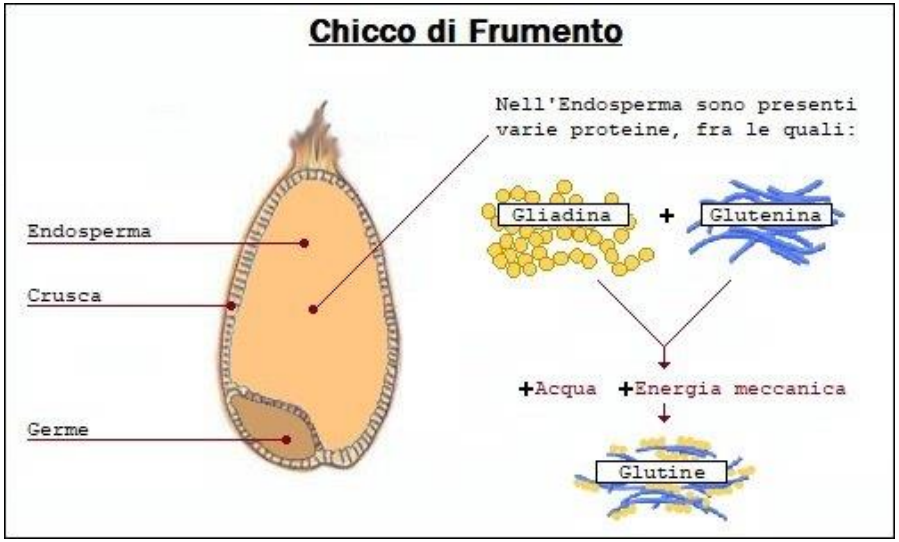
Frumento

Orzo

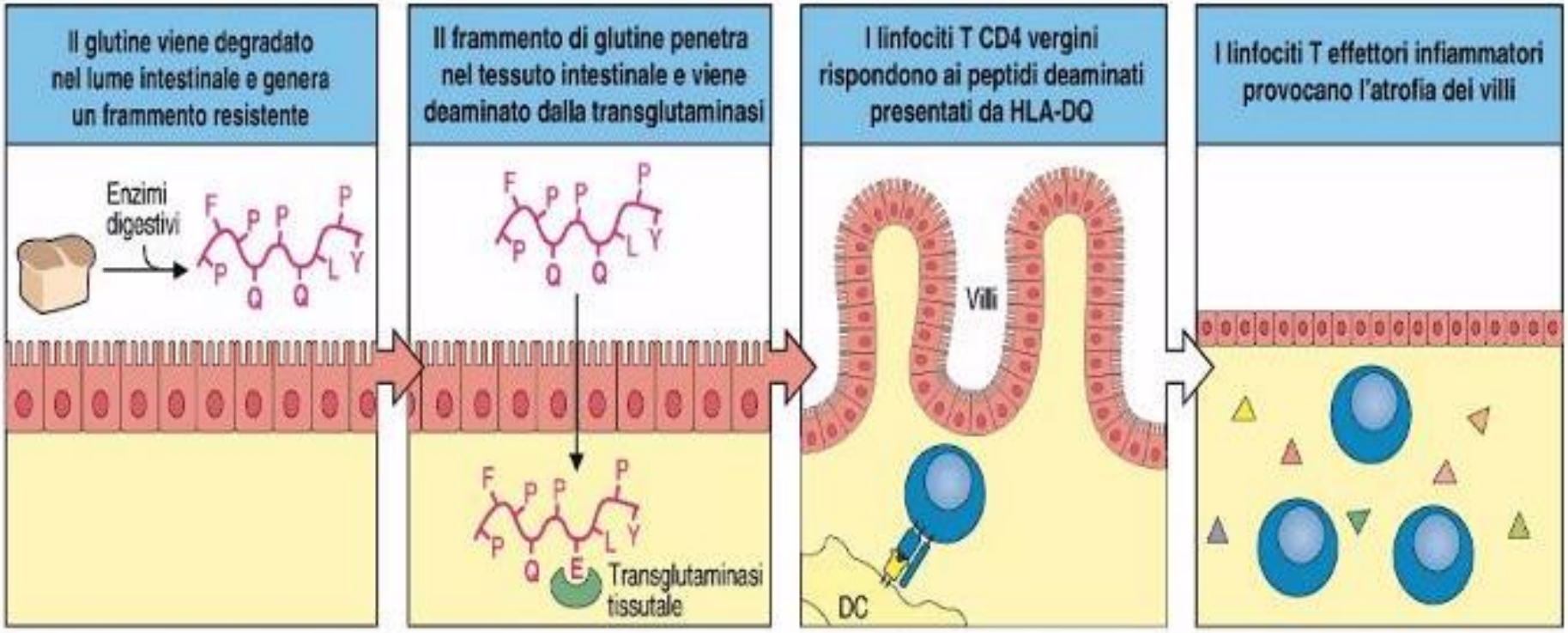
Segale

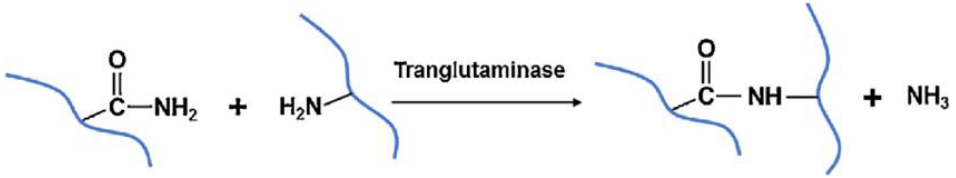
Farro

Nel frumento le proteine ricche in prolina sono le *gliadine,* nell'orzo le *ordeine*, nella segale le *secaline*

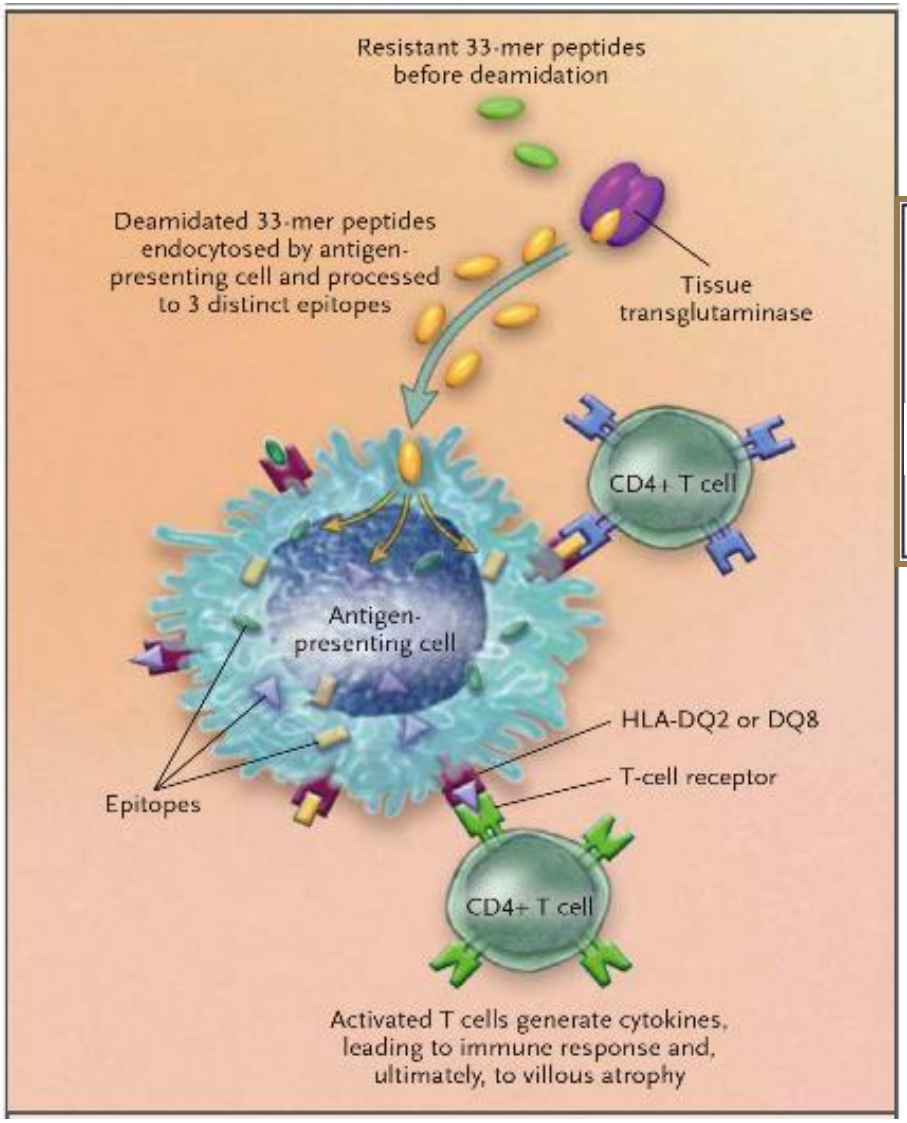


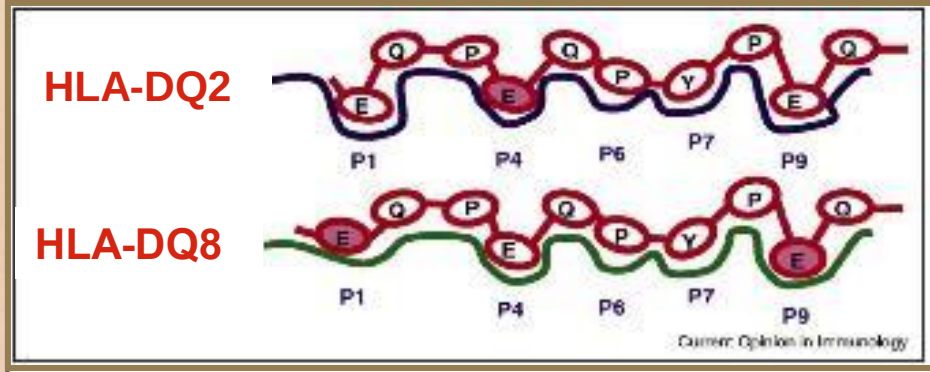
PATOGENESI della malattia celiaca





Fattori genetici nella celiachia: i peptidi deamidati del glutine si legano preferenzialmente alla tasca del peptide delle molecole HLA-DQ2 e HLA-DQ8





I geni HLA contribuiscono alla predisposizione genetica per la celiachia:
le molecole HLA-DQ2 sono presenti nel 95 % dei celiaci e HLA-DQ8 nel 5%

E: acido glutammico

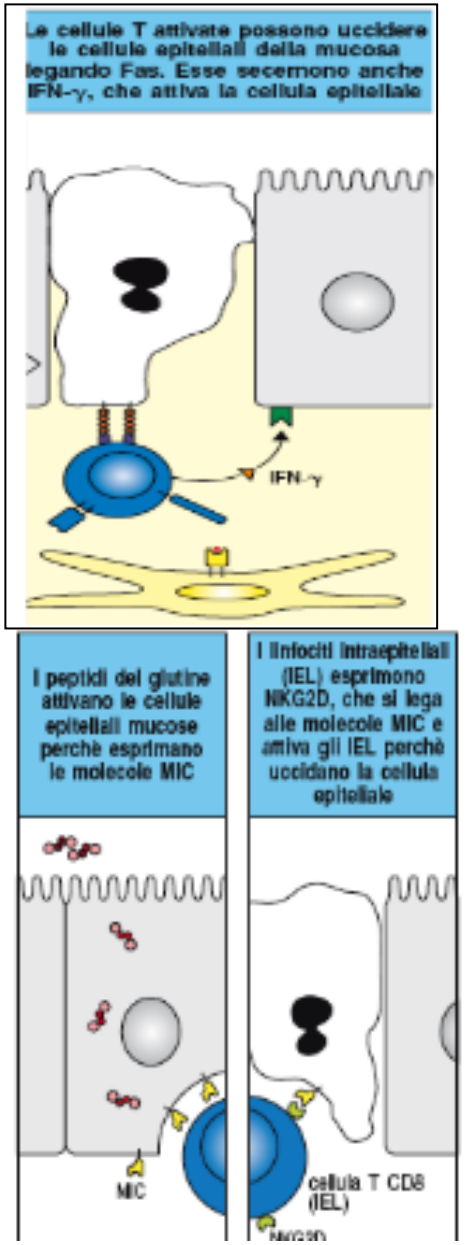
Il meccanismo immunopatogenetico della malattia celiaca

- In condizioni di aumentata permeabilità intestinale, la **gliadina** ingerita passa attraverso le giunzioni strette e giunge nella sottomucosa dove agisce **l'enzima transglutaminasi (tTG)** che deamida la gliadina.

- In soggetti geneticamente predisposti, le **APC** espongono i peptidi della gliadina con molecole **HLA-DQ2 e DQ8** e attivano linfociti CD4 specifici.

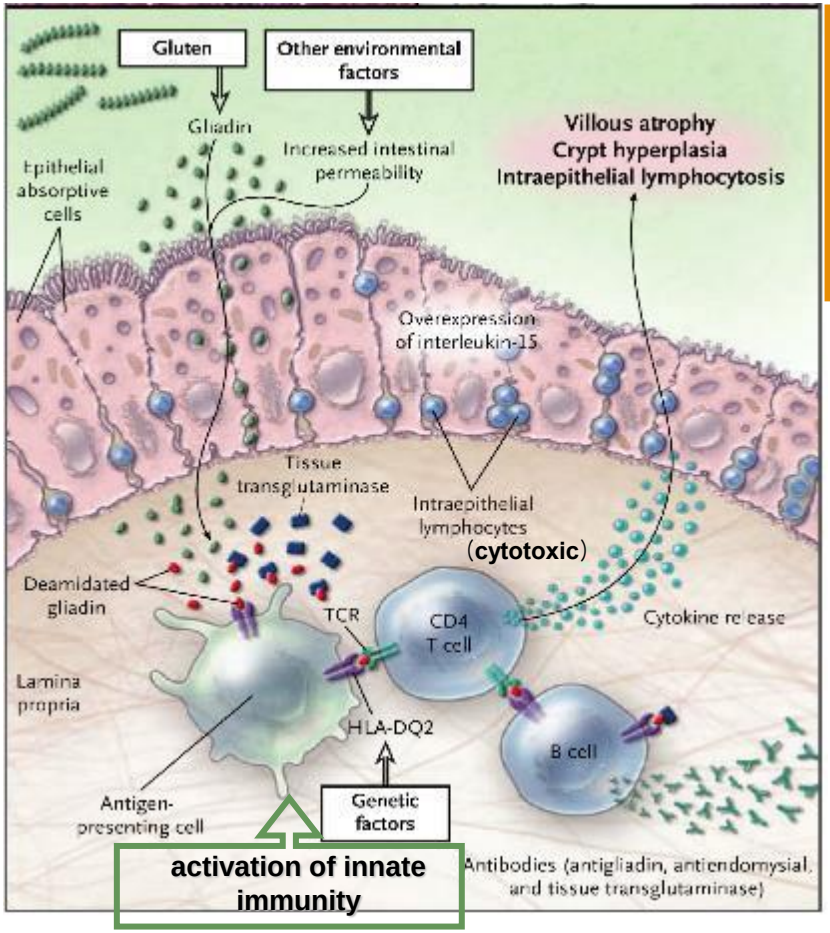
- I **linfociti CD4** si attivano ed esprimono **Fas ligando (FasL)** e sono in grado di uccidere le cellule epiteliali intestinali che esprimono il Fas.

- **IFN-gamma e il peptide del glutine** attivano le **cellule epiteliali** che esprimono molecole **MIC**. Le molecole MIC sono riconosciute dal recettore **NKG2D**, espresso da **linfociti T citotossici intraepiteliali (IELs) CD8+**, che uccidono le cellule epiteliali.



To summarize…

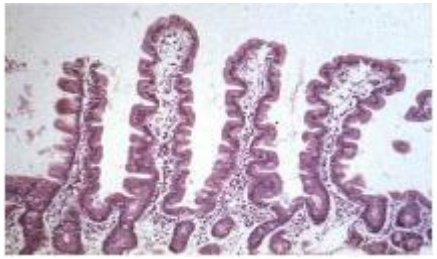
Interaction of gluten with environmental, immune, and genetic factors in Celiac Disease



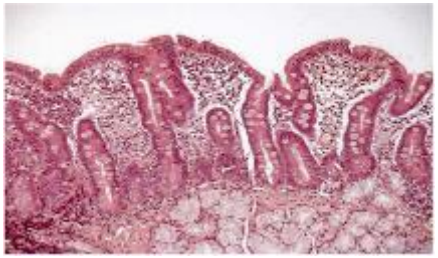
The celiac mucosa is characterized by:

- **villus atrophy,**
- **enlarged hyperplastic cripts,**
- **increased infiltration of CD4+ and CD8+ T cells in the lamina propria and epithelium**

Damage of epithelial cells is mainly attributable to proinflammatory cytokines (IFN γ) and CTL



healthy



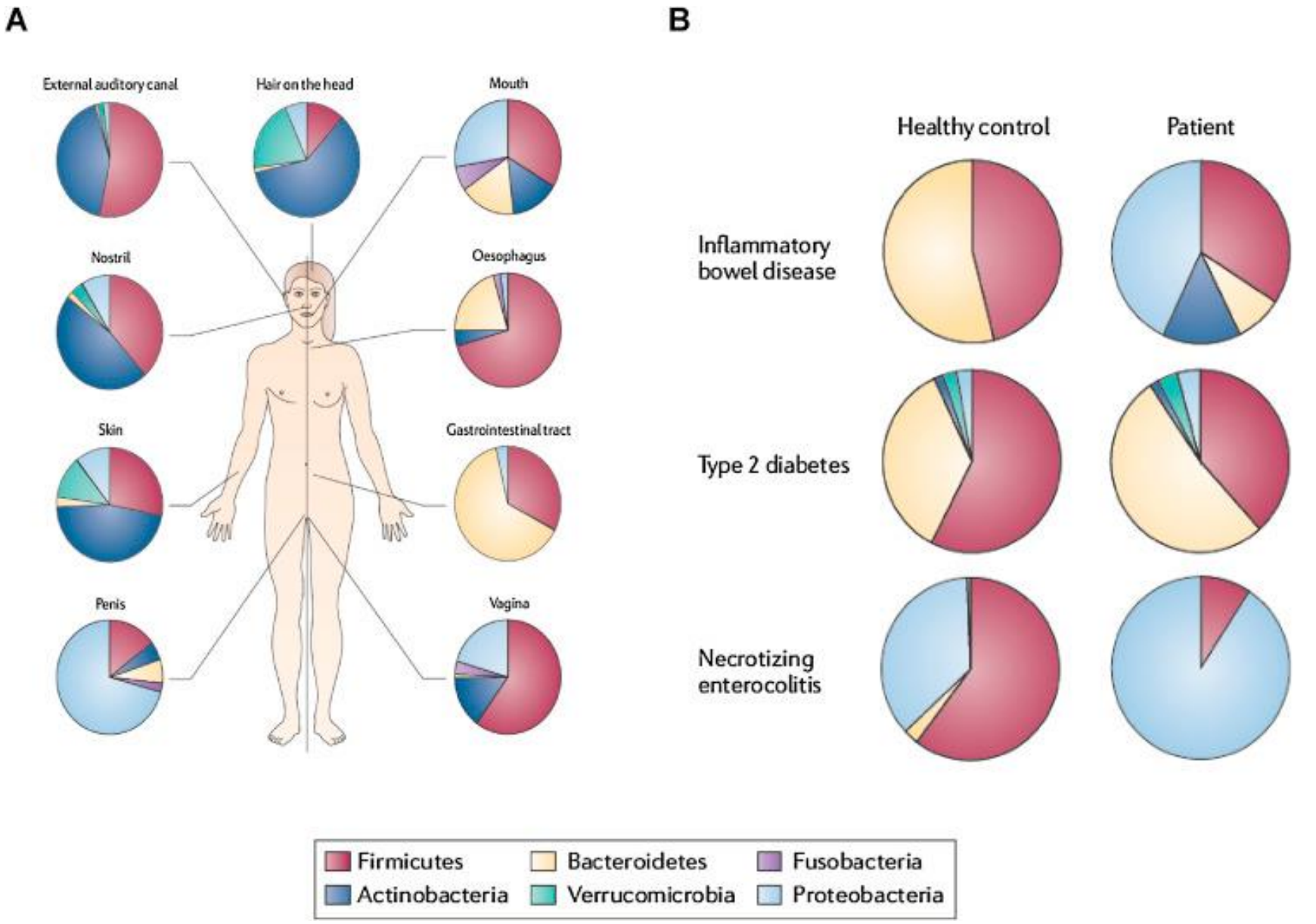
celiac

Le malattie infiammatorie croniche intestinali

(IBD, Inflammatory Bowel Diseases)

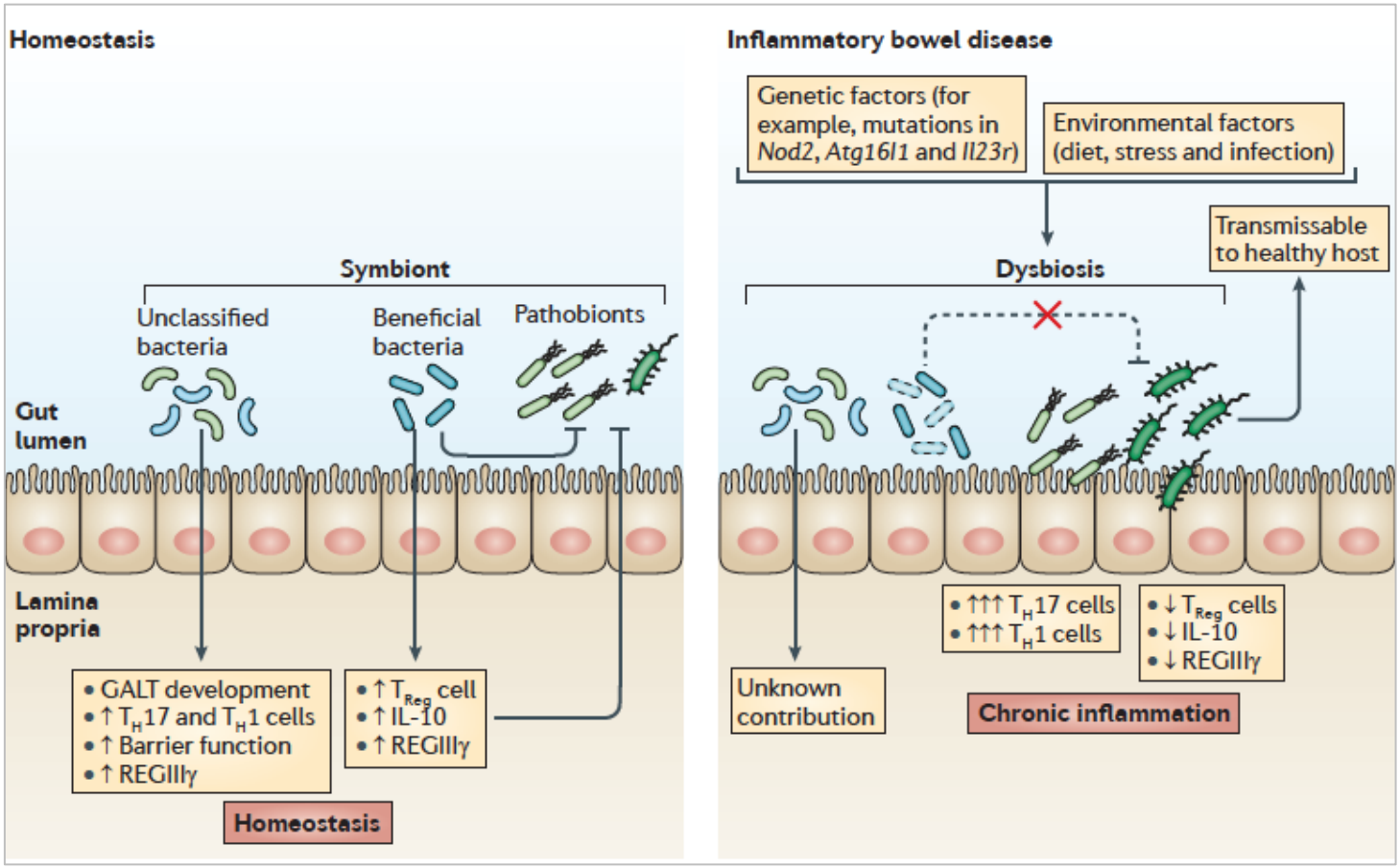
Malattia di Crohn

Rettocolite ulcerosa



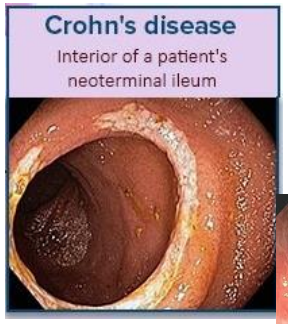
Blum HE, The human microbiome, Advances in Medical Sciences, 2017

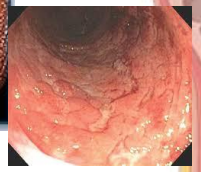
Protective and pathogenic role of the gut microbiota in inflammatory bowel diseases

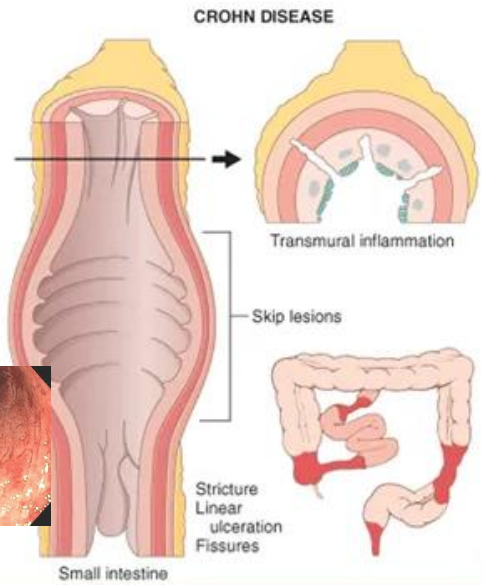


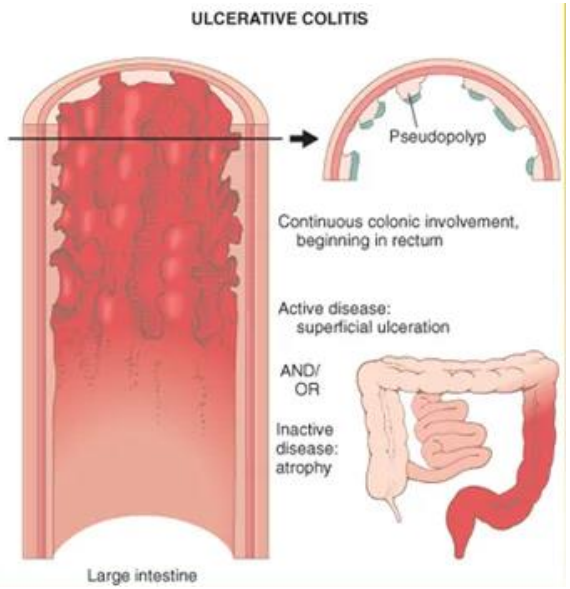
Kamada N et al Nature Rev Immunol 2013

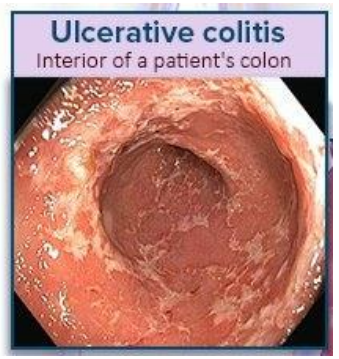
Inflammatory Bowel Diseases (IBD):

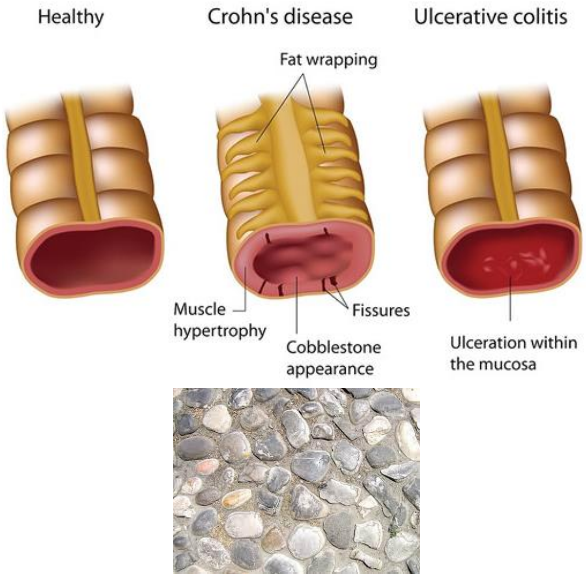


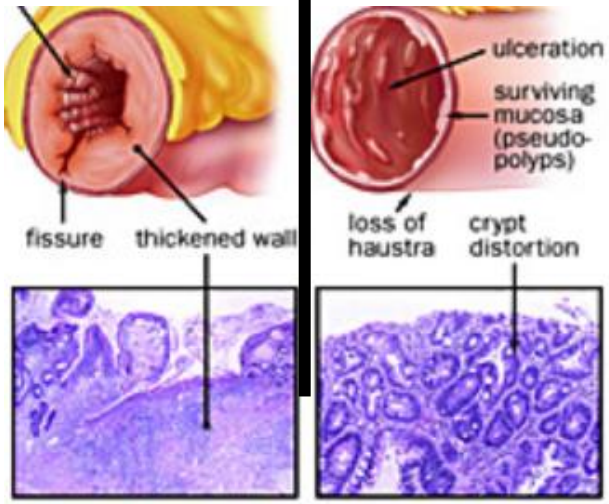




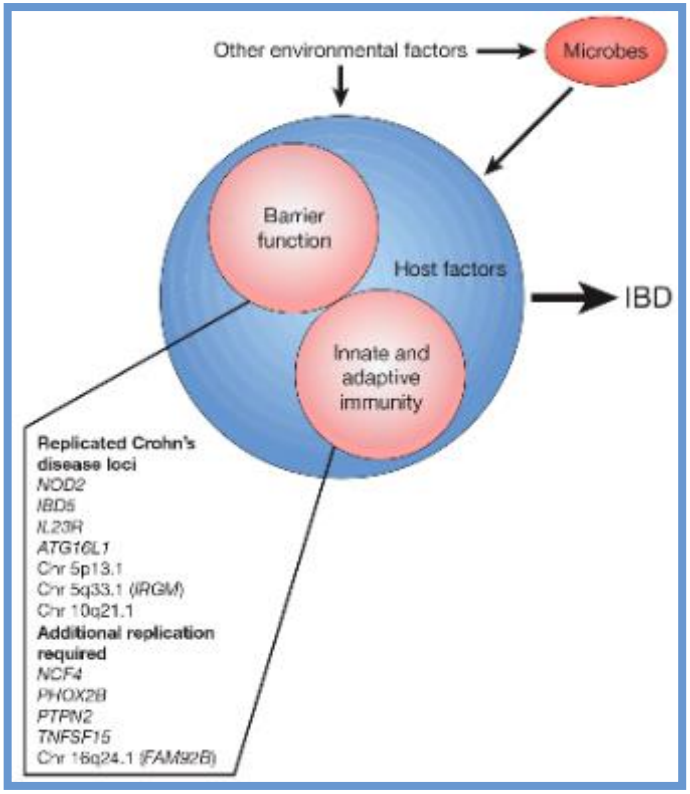








Inflammatory Bowel Diseases (IBD): a dysregulated immune response against commensal bacteria, in genetically predisposed individuals



Possible etiologies for IBD:

- Impairment of mucosal barrier function
- Defective innate immune control of mucosal microorganisms
- Mucosal dysbiosis or specific microbial pathogens
- Defective mucosal immunoregulation

Microbiota-dependent regulation of cancer development, progression and treatment