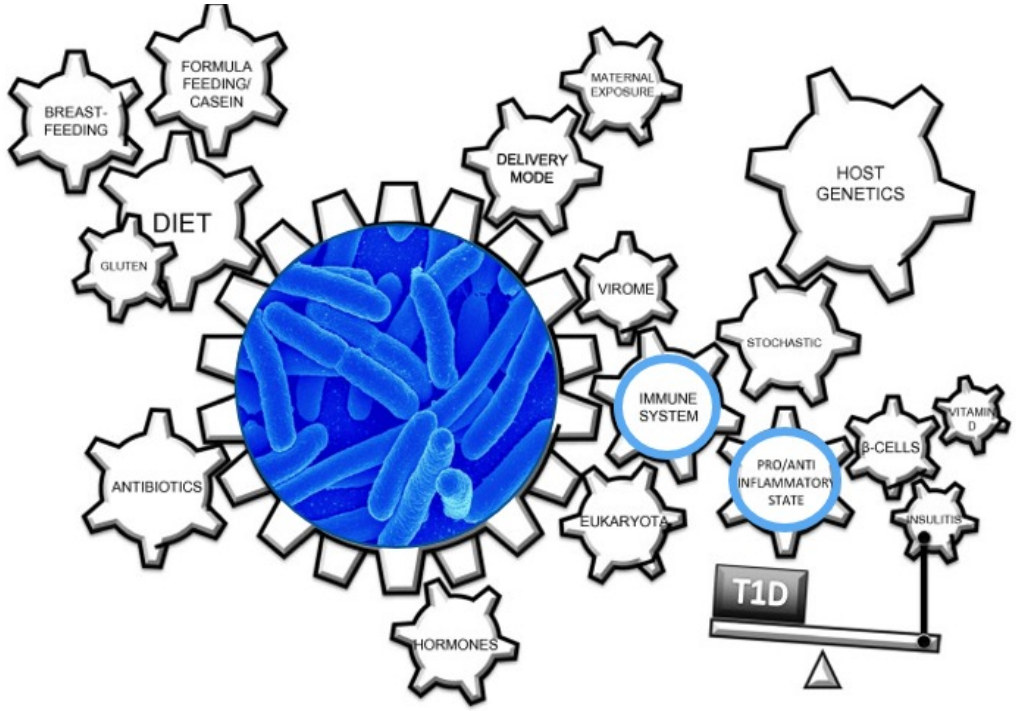
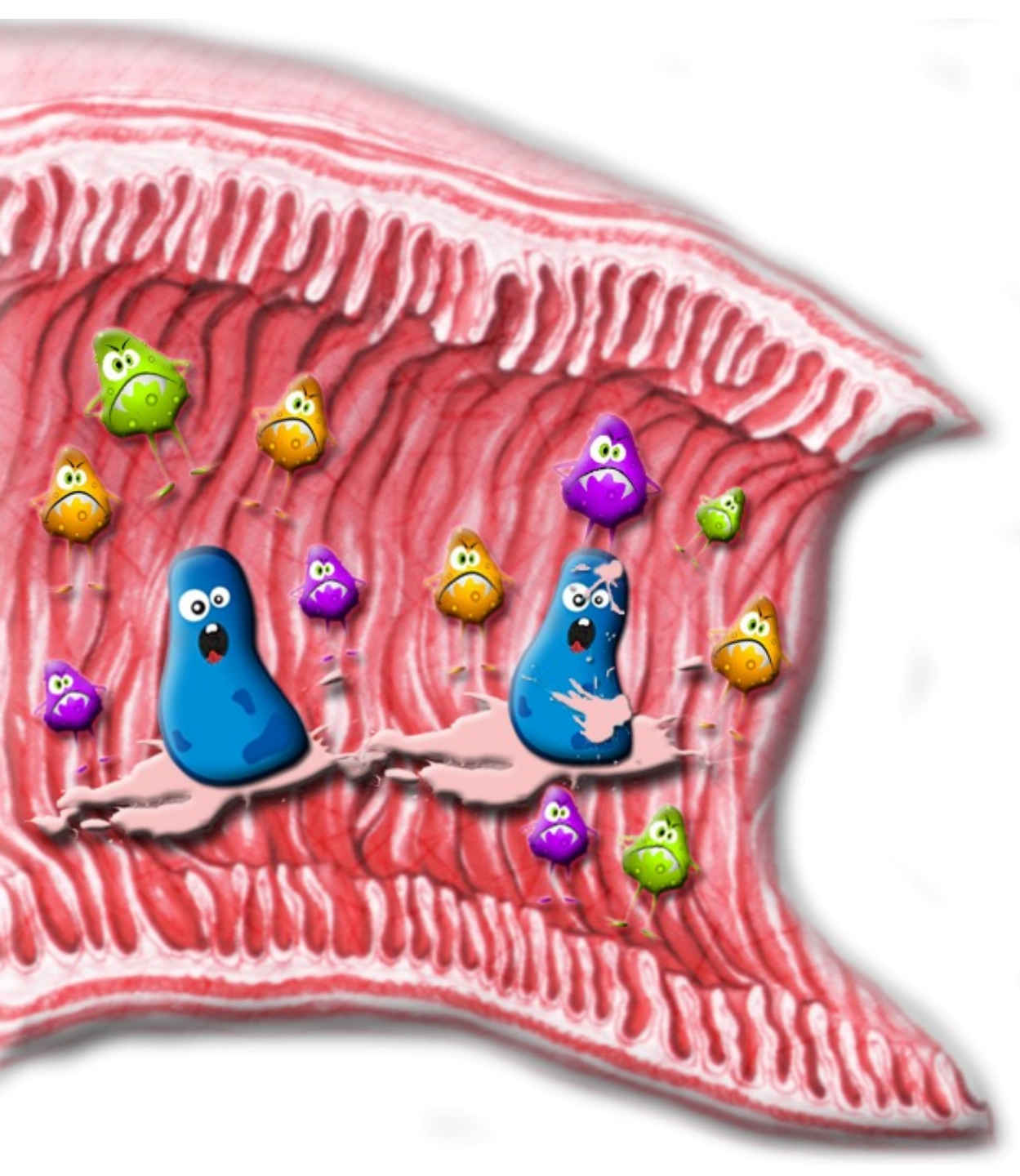
Microbiota and intestinal immune homeostasis



Doctoradelapuerta



INTESTINAL HOMEOSTASIS

gut microbiota

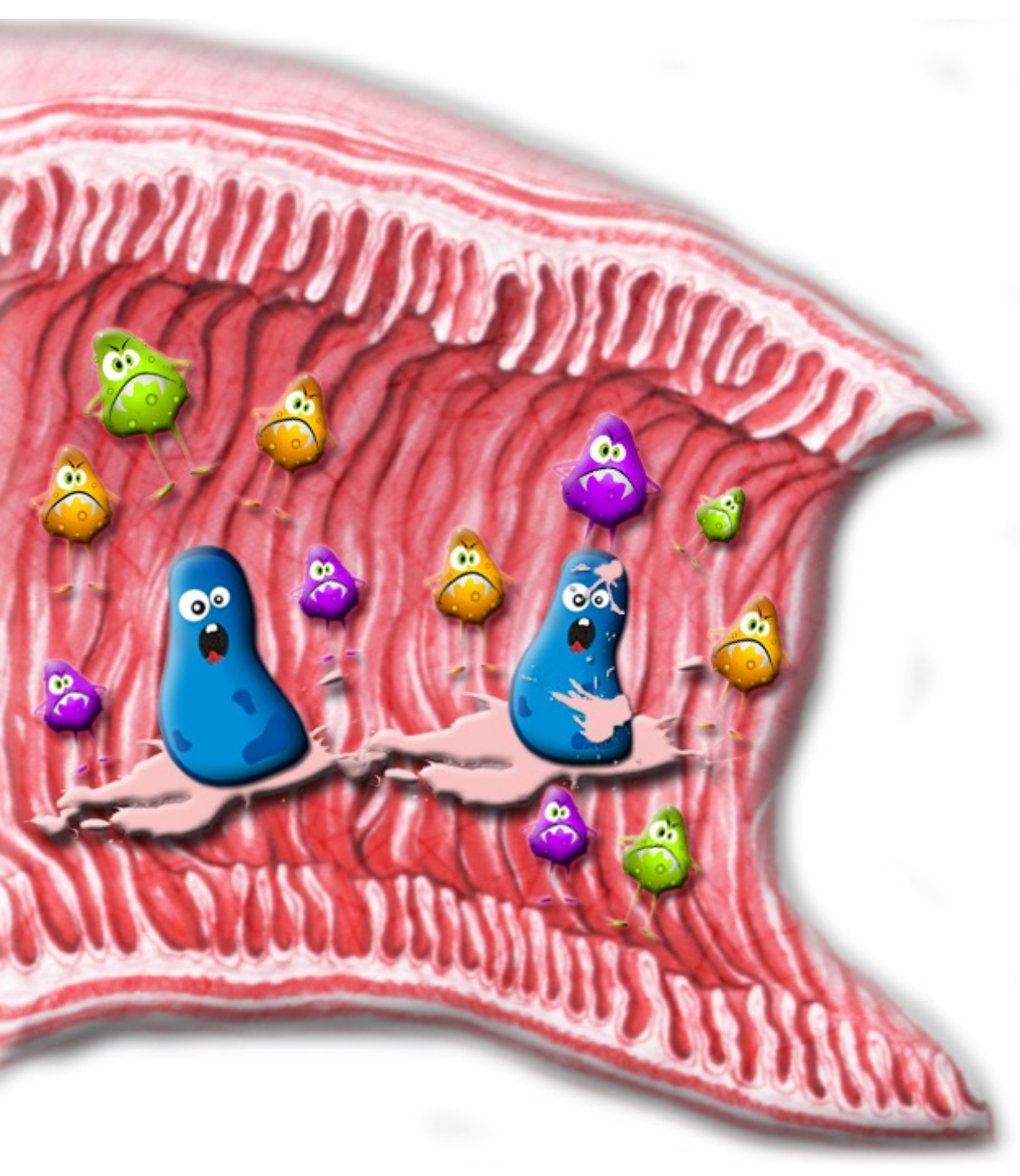
mucus layer stability

barrier - permeability

acid-base balance

enteric nervous system

immune system: GALT



INTESTINAL HOMEOSTASIS

gut microbiota

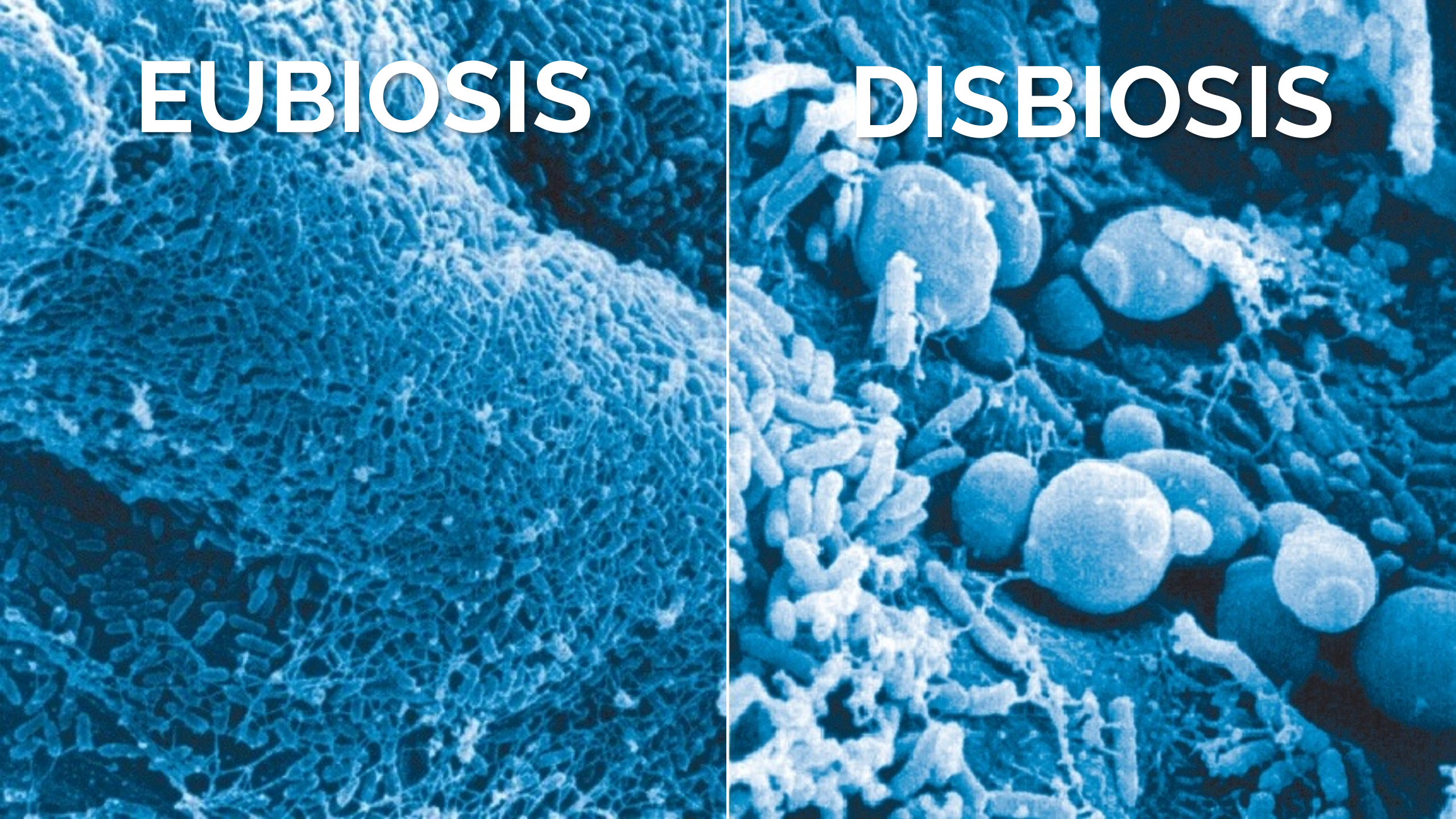
mucus layer stability

barrier - permeability

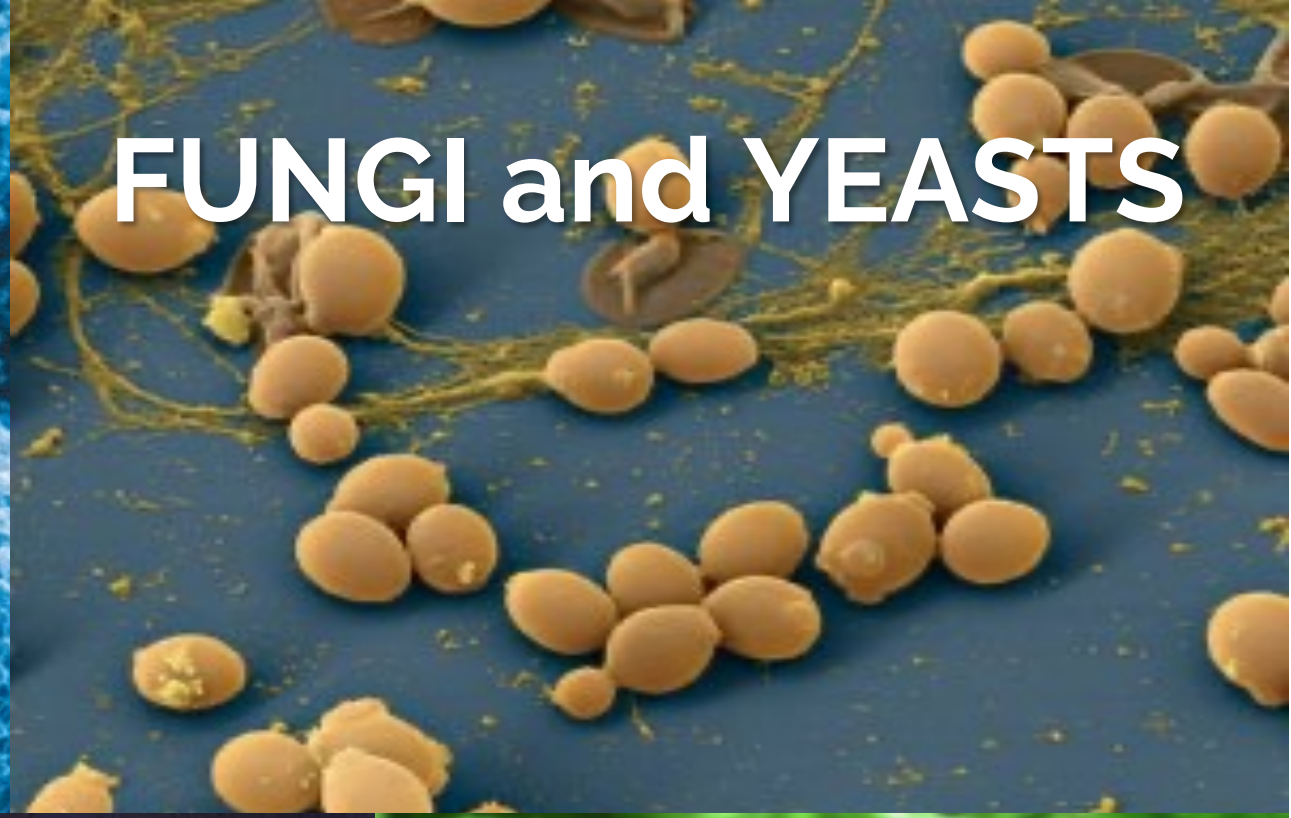
acid-base balance

enteric nervous system

immune system: GALT


EUBIOSIS
DISBIOSIS


BACTERIA


FUNGI and YEASTS


ARCHEAS


PROTOZOA


VIRUS

STABILIZATION MICROBIOTA

immunomodulatory
protective
muconutritive
fiber fermenting
neuroactive

FACULTATIVE PATHOGENS

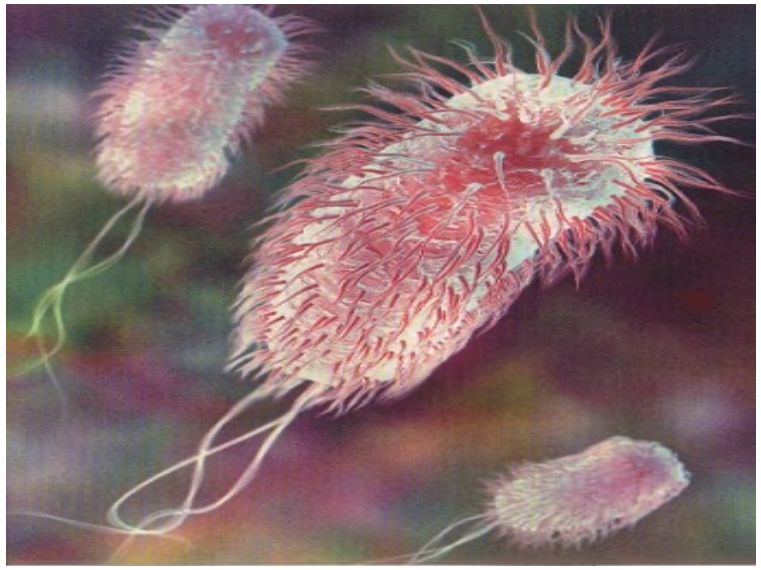
proteolytic bacteria
fungi and yeasts
methanogenic archaea
hydrogen sulfide reducers
lipopolysaccharides

STABILIZATION MICROBIOTA

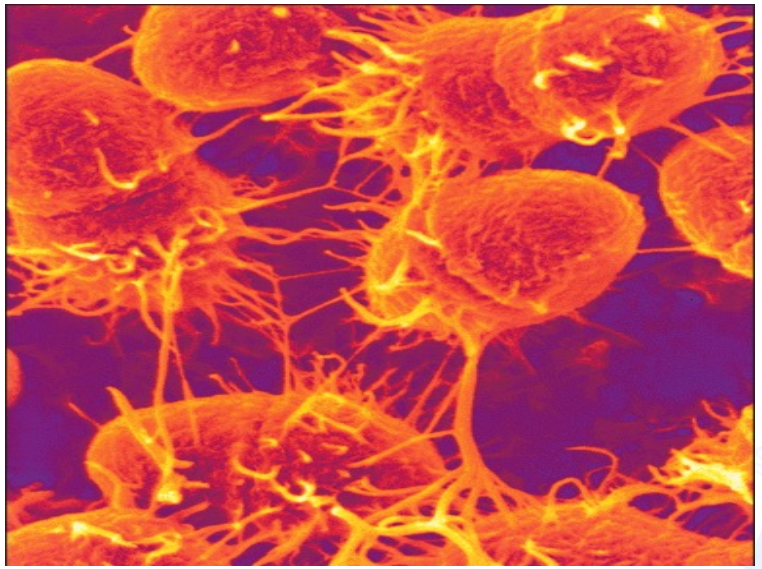
Immunomodulatory bacteria

are trainers of the immune system and induce non-specific local immune responses and are also crucial for maintaining the general order of the microbiota

E. coli



Enterococcus faecalis

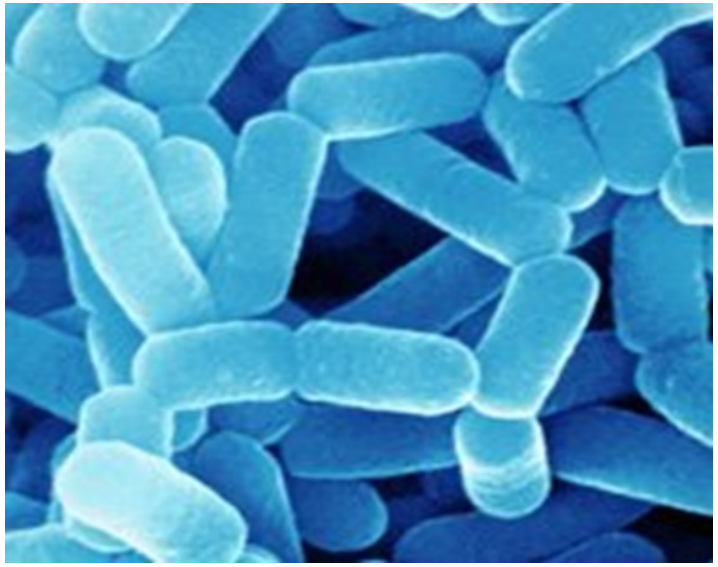


STABILIZATION MICROBIOTA

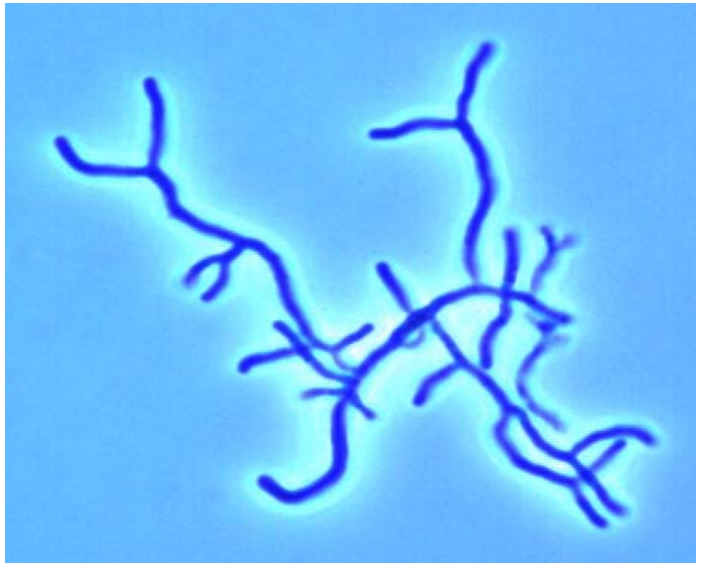
Protective bacteria

contribute to strengthening resistance against colonization by pathogenic microorganisms and the overgrowth of facultative pathogens

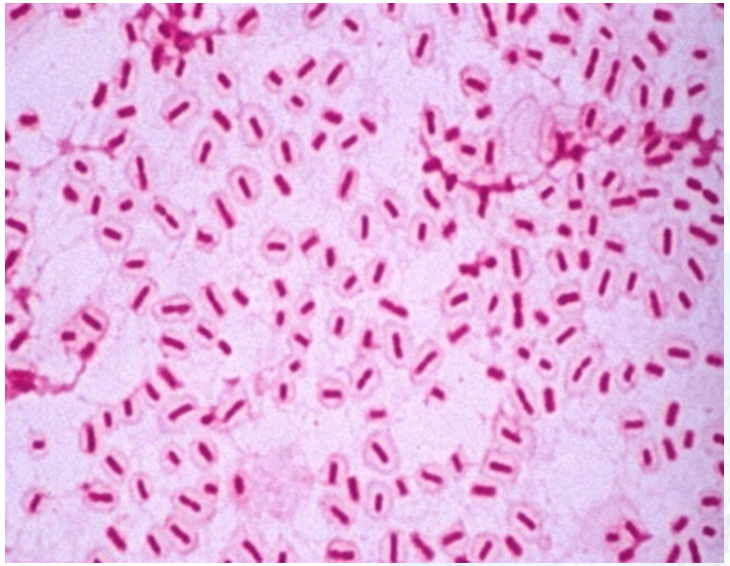
Lactobacillus



Bifidobacterium



Bacteroides

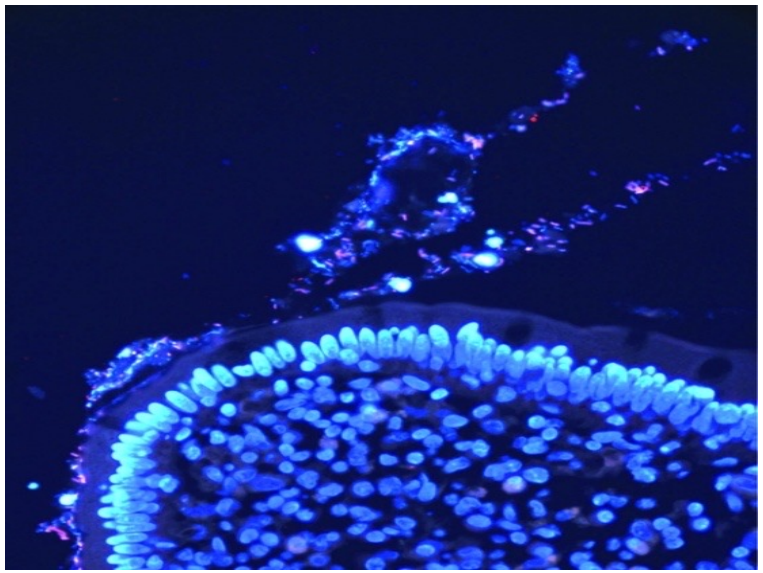


STABILIZATION MICROBIOTA

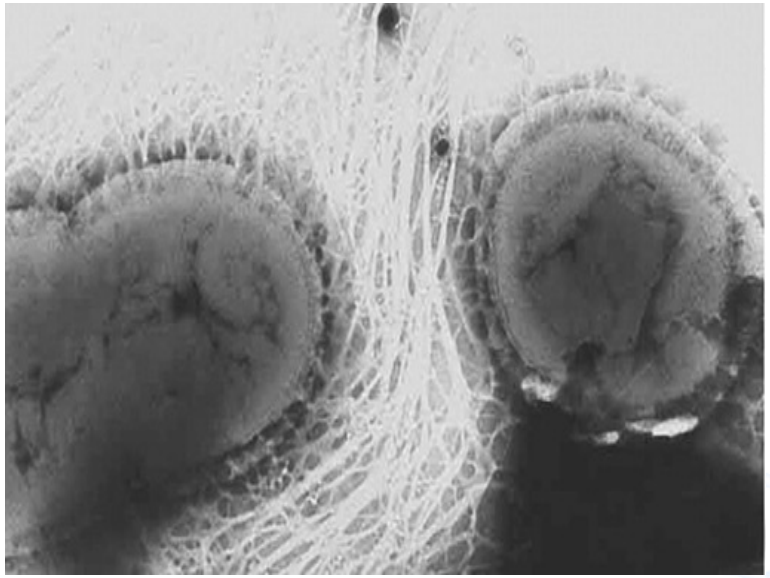
Muconutritive bacteria

ensure the nutrition of the intestinal epithelium and the normal trophism of the mucus layer, inducing the synthesis of glycoproteins and modulating their degradation

Faecalibacterium prausnitzii



Akkermansia muciniphila

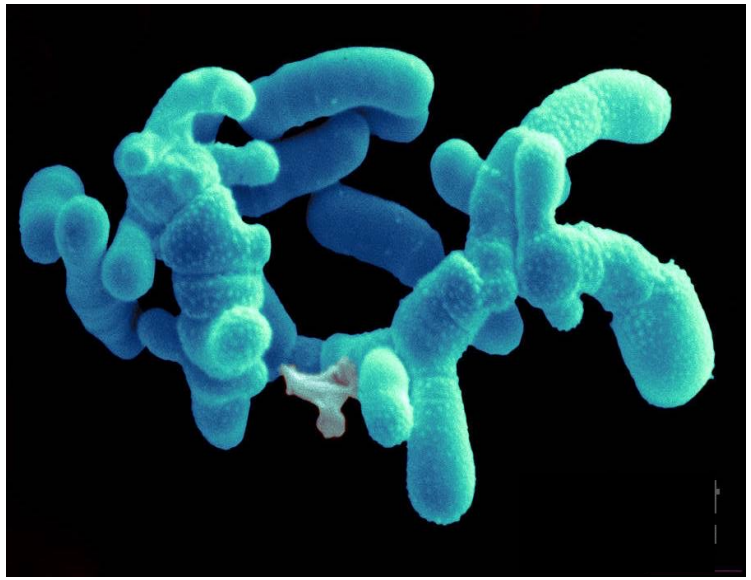


STABILIZATION MICROBIOTA

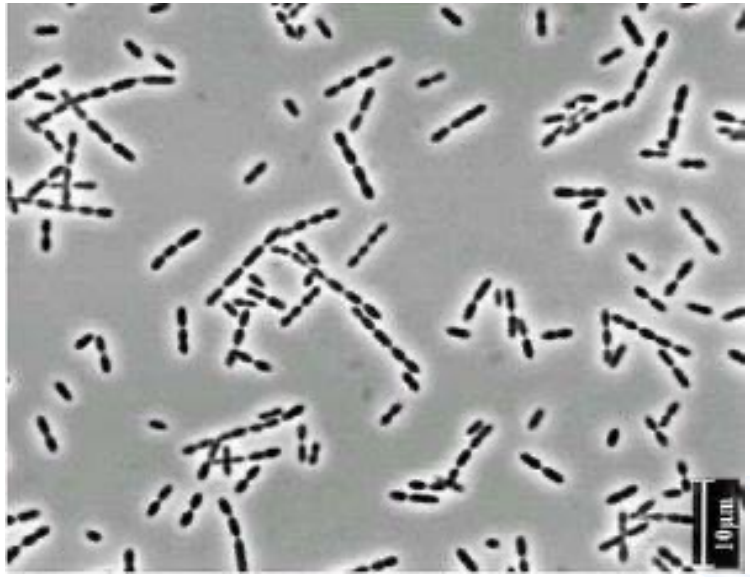
Fiber fermenting bacteria

support the muconutritive microbiota to digest complex carbohydrate structures and stimulates other bacterial species to break down fiber

Bifidobacterium adolescentis



Ruminococcus bromii

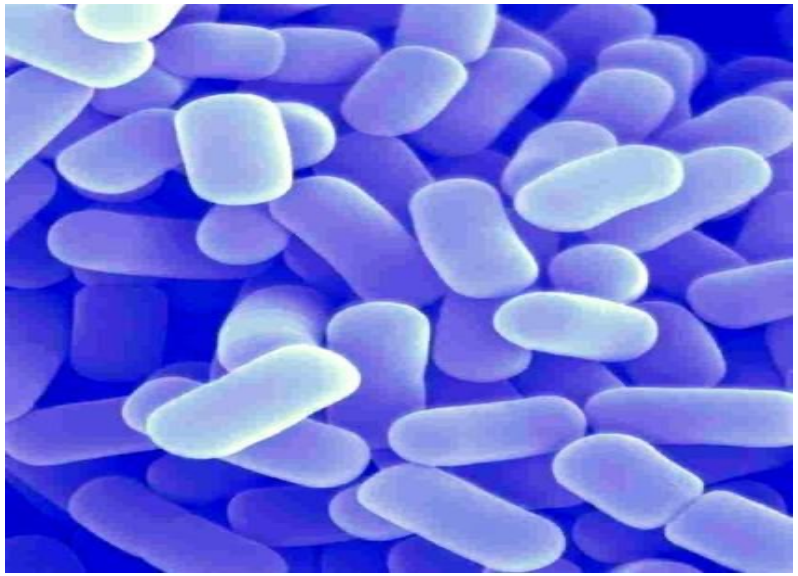


STABILIZATION MICROBIOTA

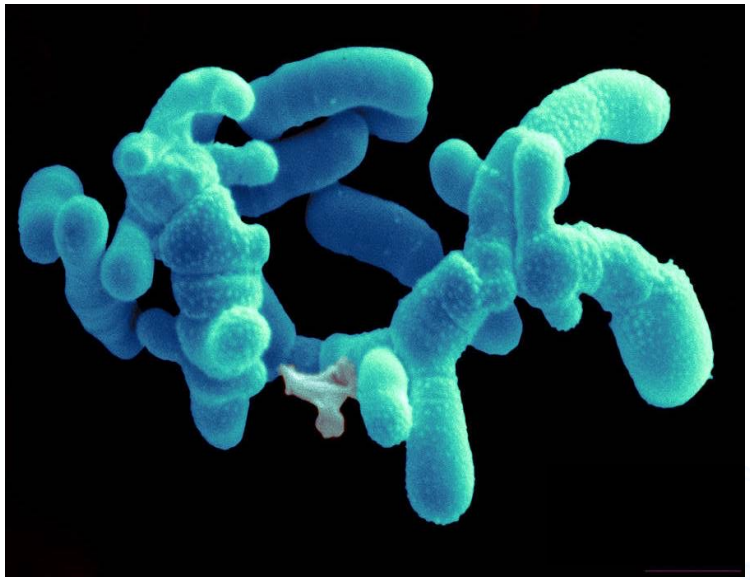
Neuroactive bacteria

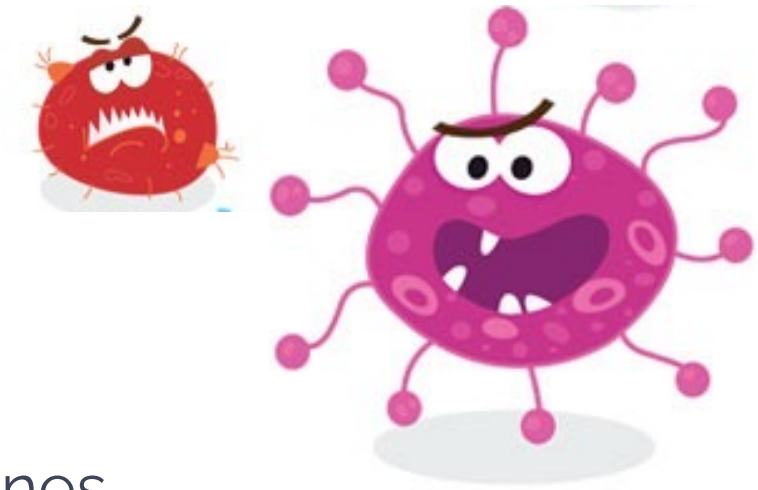
produce γ-aminobutyric acid and modulate serotonin synthesis w also modulating central neurotransmitter receptors to functionally stabilize the gut-brain axis, the immune system and visceral pain

Lactobacillus plantarum



Bifidobacterium adolescentis

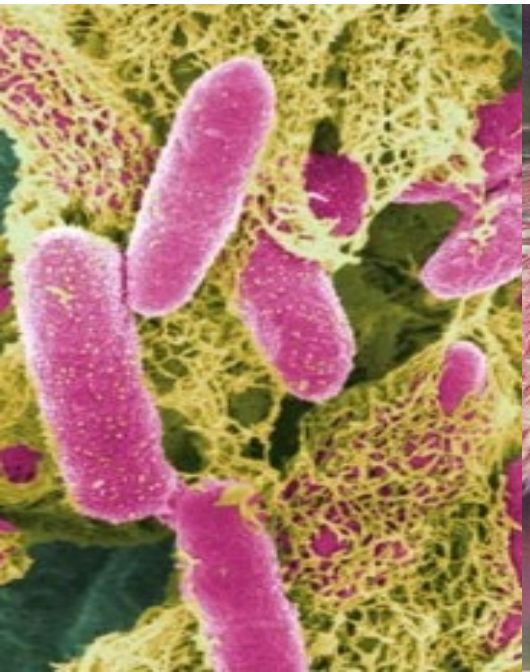


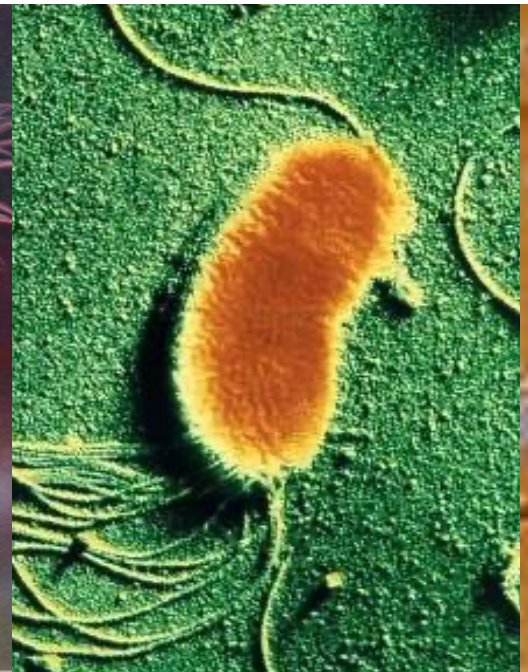


FACULTATIVE PATHOGENS

Proteolytic Bacteria

metabolize proteins releasing amino acids, biogenic amines, ammonia, CO_2, branched-chain fatty acids, indole, skatole, etc. that inflame, change the pH, and functionally overload the liver

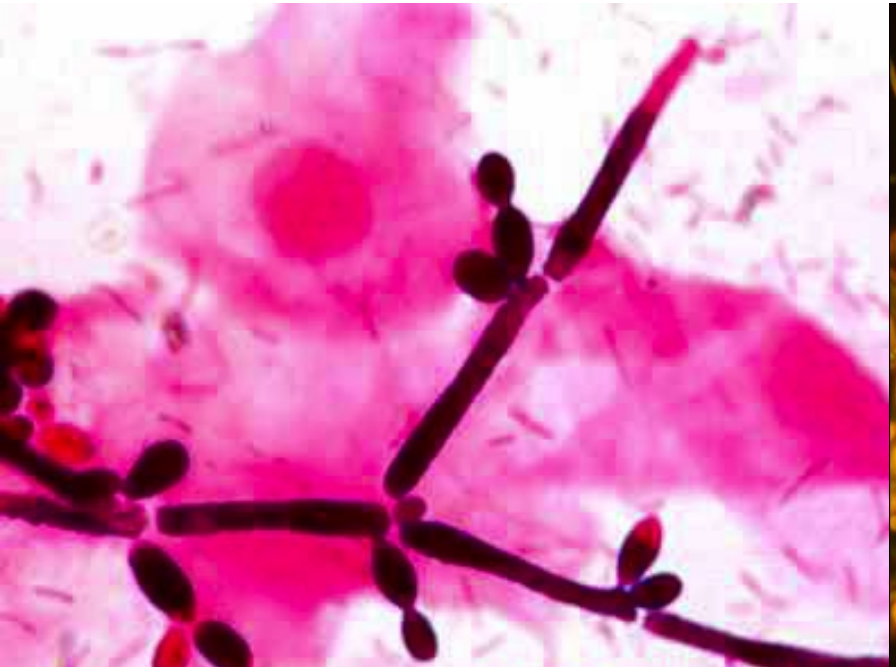


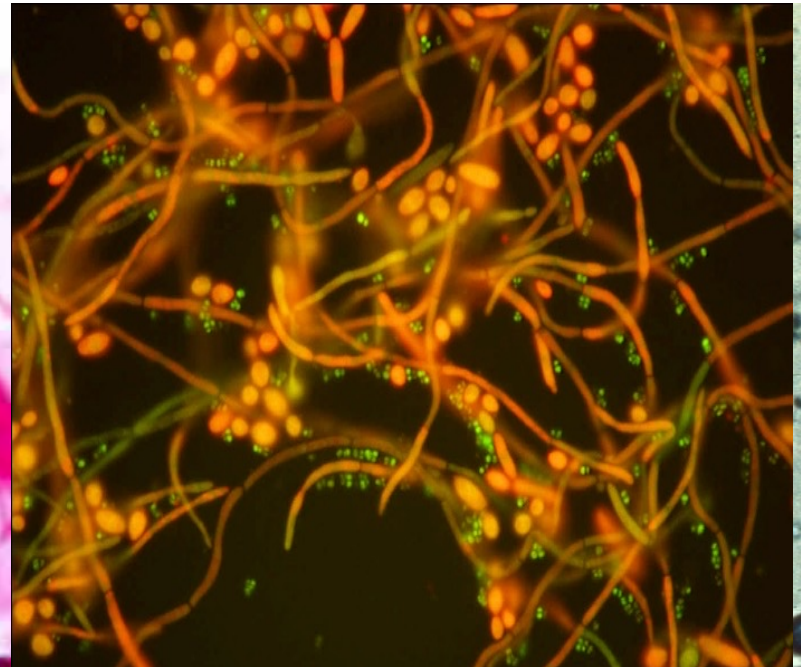


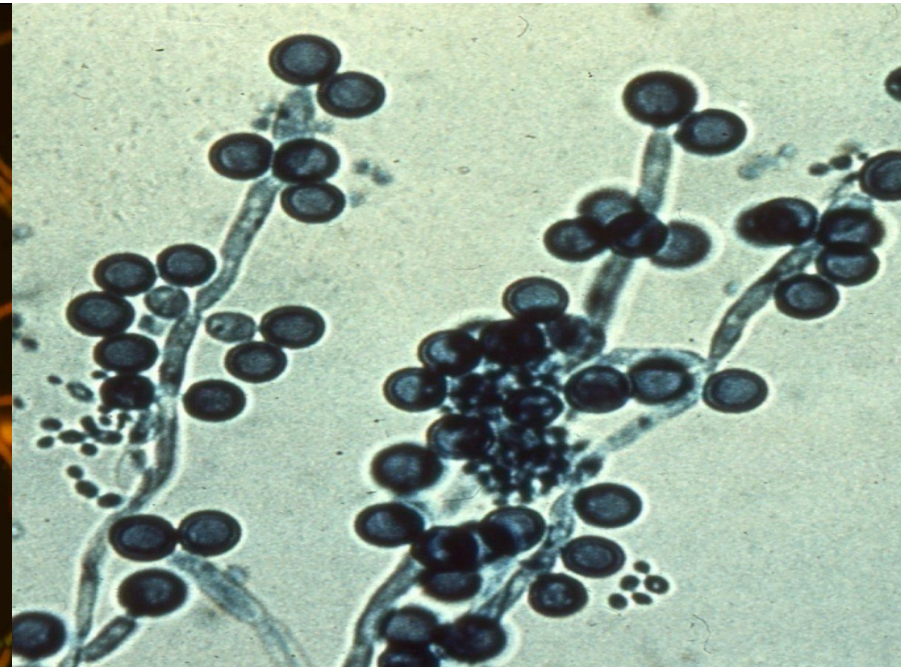
FACULTATIVE PATHOGENS

Fungi and yeasts

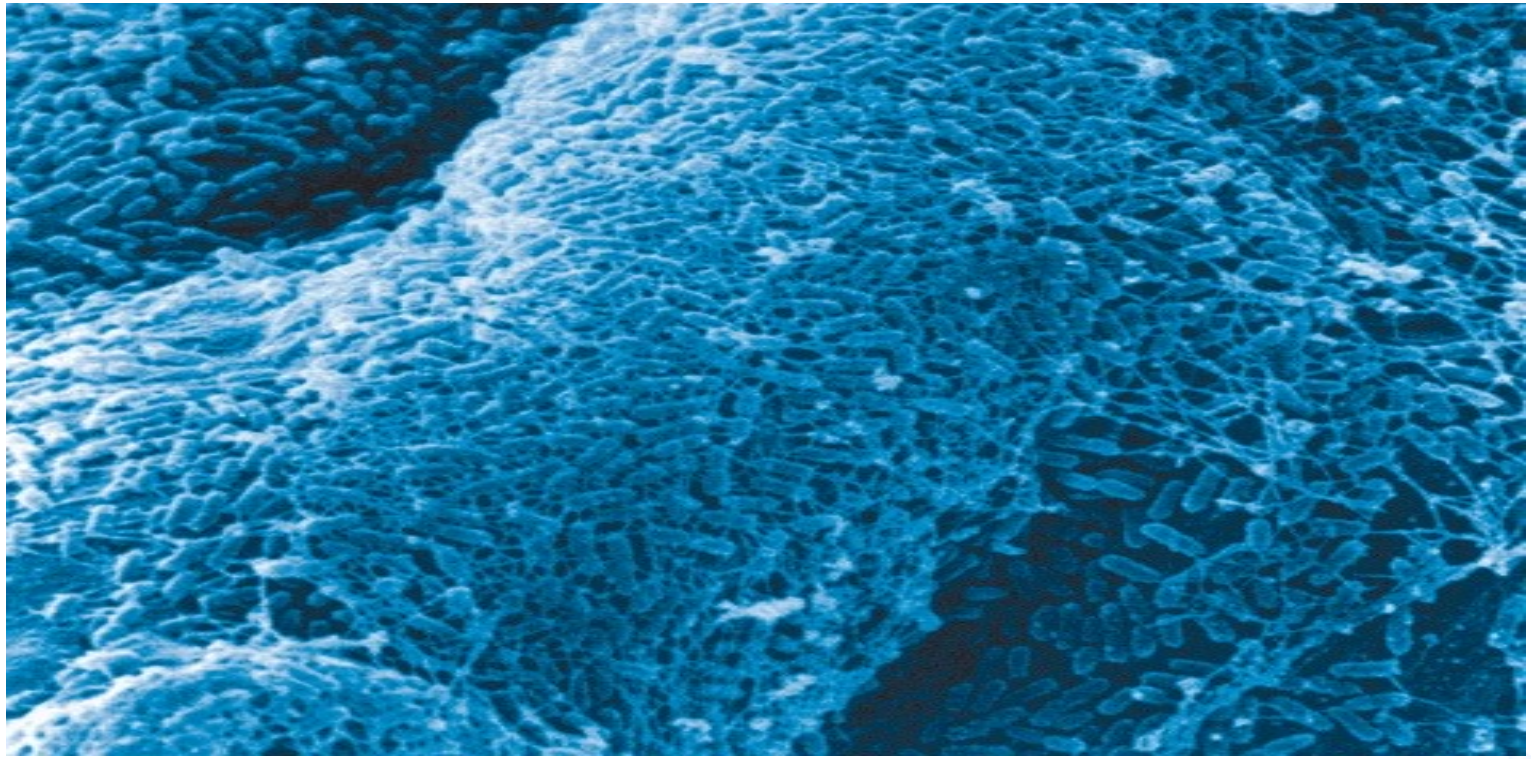
digest and metabolize carbohydrates. If they grow above normal ranges, could inflame the epithelium and disrupt, physical and metabolically, the intestinal environment

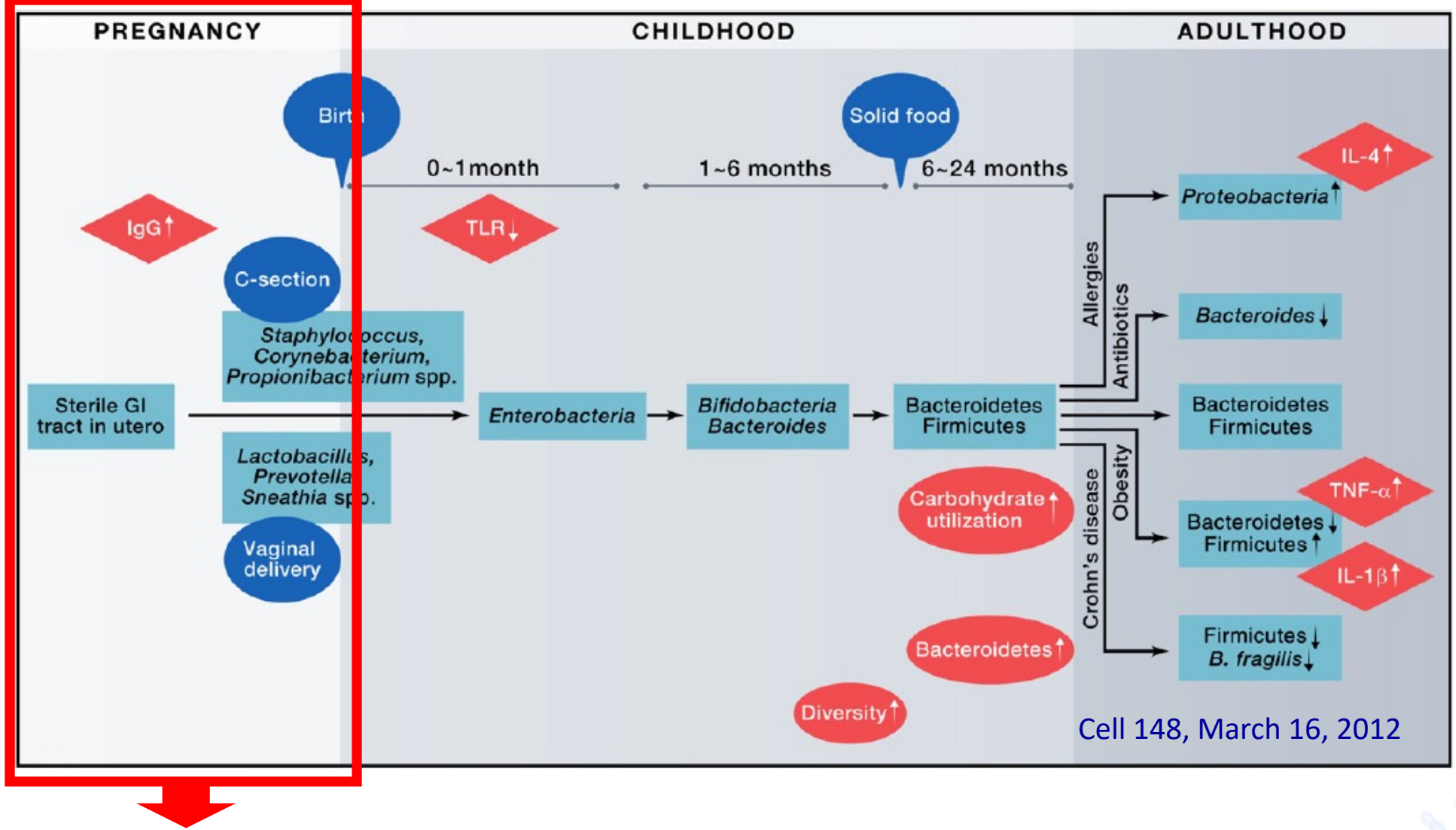




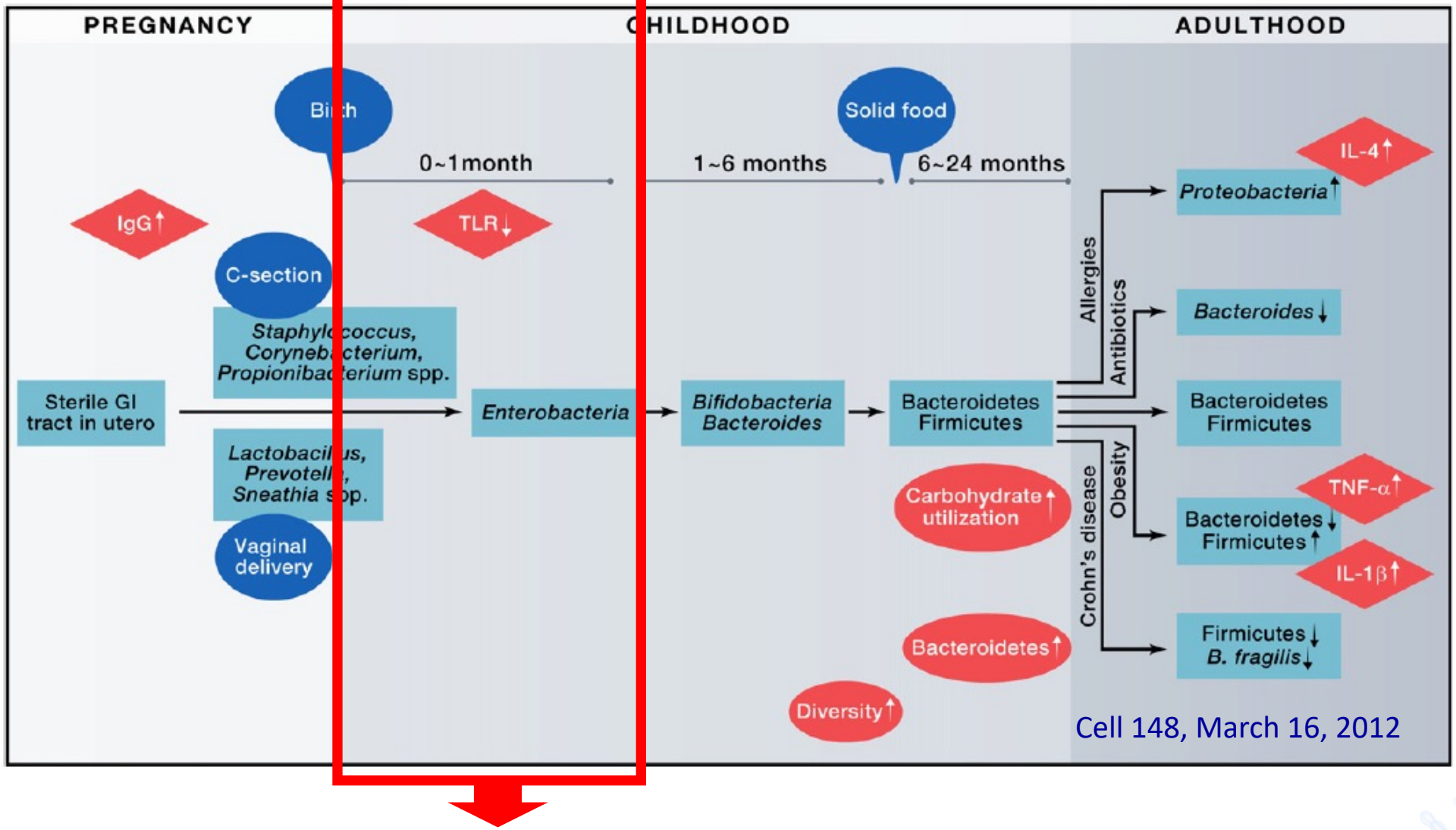


MICROBIOTA COLONIZATION PHASES

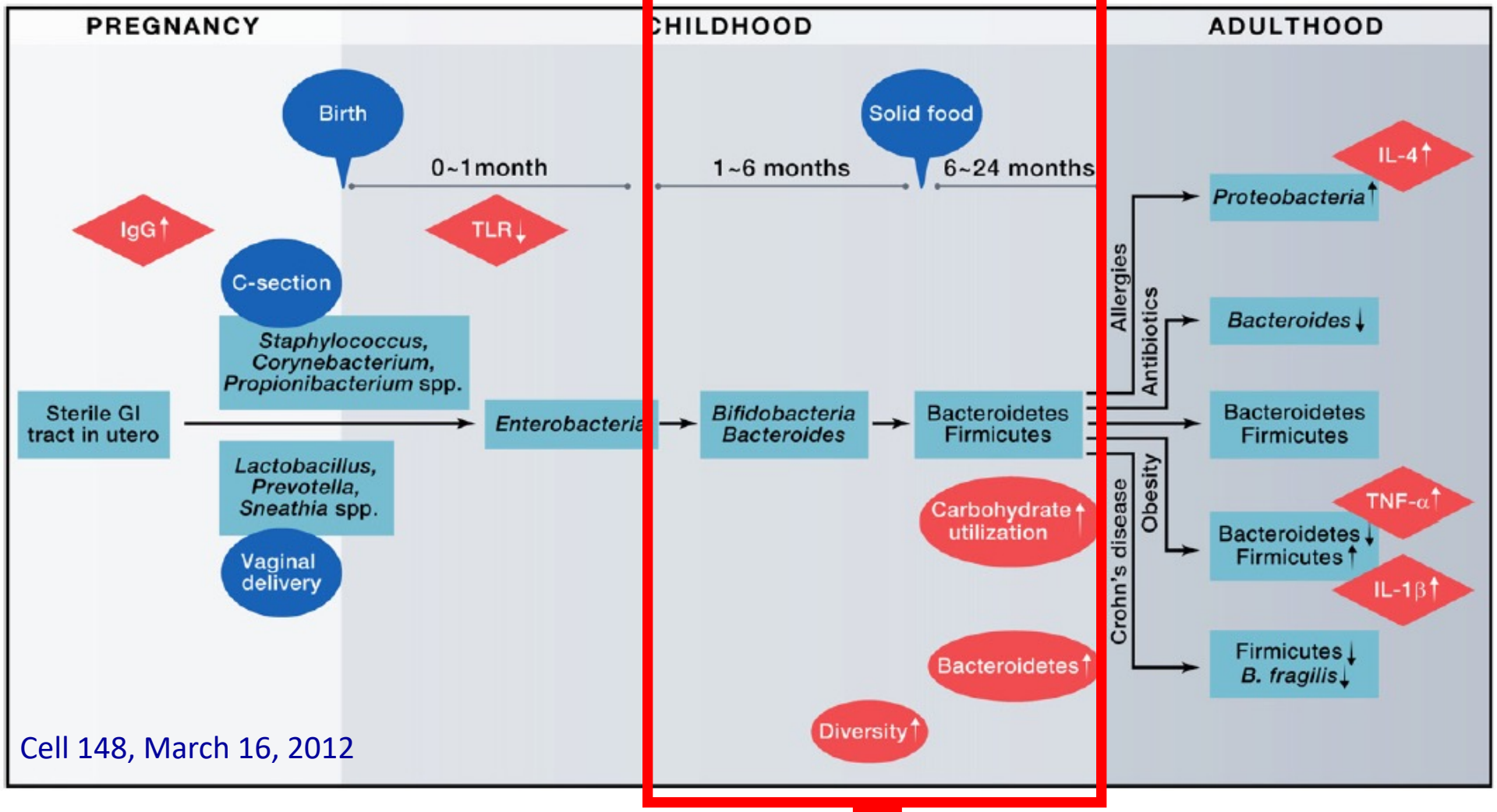




The gastrointestinal tract of the fetus **INTRAUTERINE** is almost sterile.
Colonization begins in **BIRTH**: vaginal: predominance vaginal microbiota
cesarean section: microbiota similar to the skin

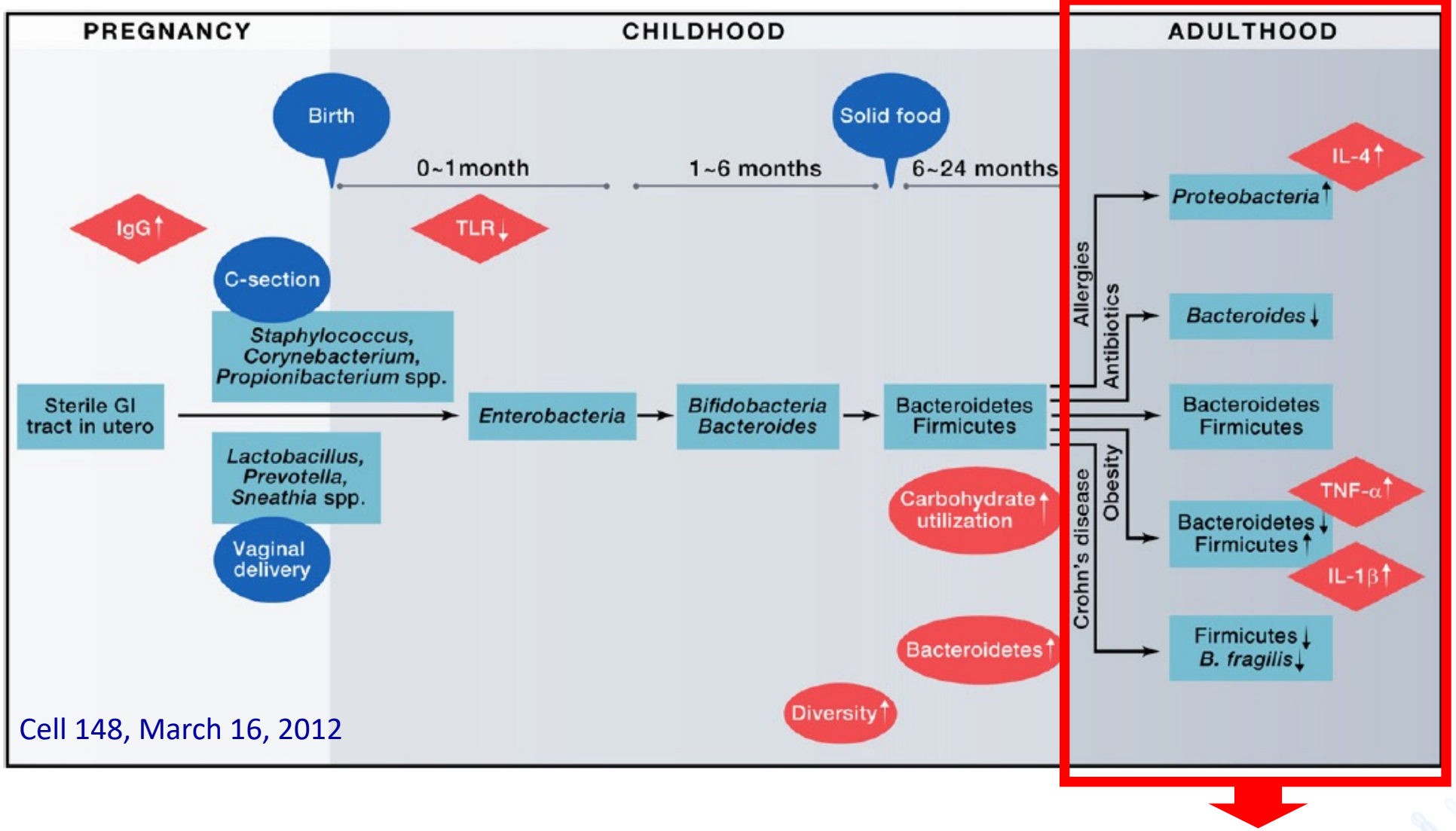


In the **FIRST WEEKS OF LIFE**, the activity of the TLRs is reduced, to allow the stable colonization of bacteria



When the **CHILD** grows, with the incorporation of solid foods, bacterial diversity increases and the microbiota acquires a pattern similar the adults.

At the same time the immune system "learns" to differentiate commensal bacteria from pathogens



In **ADULTS** the microbiota is stable, dominated by *Bacteroidetes* and *Firmicutes*. Different diseases are characterized by significant changes in the microbiota and associated changes in the production of cytokines

FUNCTIONS OF THE MICROBIOTA

INTESTINAL MICROBIOTA

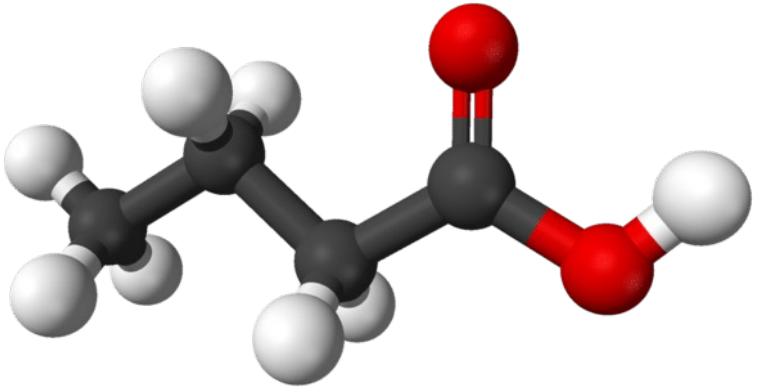
- **Metabolic**
  - fermentation nondigestible substrates to obtain SCFA
  - synthesize vitamins and essential amino acids
- **Nutritive and trophic**
  - functional wall homeostasis (tight junctions)
  - stability of mucus layer
- **Barrier**

  microbial antagonism against external pathogens and autochthonous facultative pathogens

INTESTINAL MICROBIOTA

- **Gut-brain axis**
  - secretion of neurotransmitters with action on CNS
- **Inflammation control**
  - *Faecalibacterium prausnitzii*: butyrate (SCFA)
  - *E. coli*: modulates mast cell degranulation
- **Immunomodulation**
  - modulation of the GALT
  - phenomena of antigenic tolerance

MICROBIOTA - SCFA

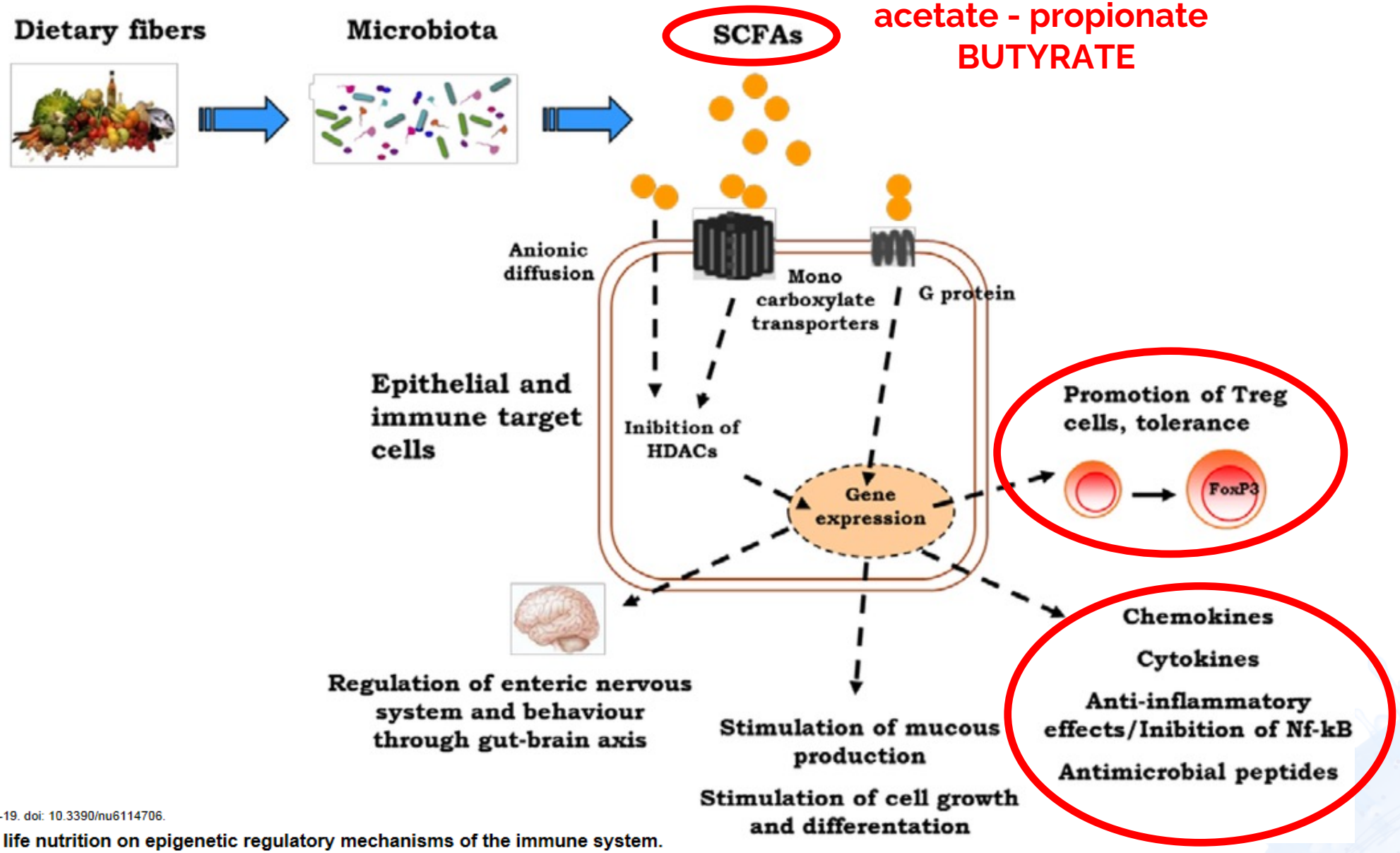


Not only bacteria modulate the immune system

The metabolic products synthesized by bacteria have important anti-inflammatory properties

The main **short chain fatty acids** are:

BUTYRATE – ACETATE - PROPIONATE



Nutrients. 2014 Oct 28;6(11):4706-19. doi: 10.3390/nu6114706.

The influence of early life nutrition on epigenetic regulatory mechanisms of the immune system.

Paparo L[1], di Costanzo M[2], di Scala C[3], Cosenza L[4], Leone L[5], Nocerino R[6], Canani RB[7].

Table 1. Effect of SCFAs in the production of inflammatory mediators by isolated cells.

Cell type	Effect observed	Effective fatty acid	Reference
Raw 264.7 cells	↓ TNF-α, IL-6, NO, ↑ IL-10	Bt	[23,48]
Mononuclear cells of the blood	↓ TNF-α, ↑ PGE_2	Bt	[49]
Monocytes and macrophages	↓ TNF-α	Bt	[50]
Monocytes	↓ TNF-α, IL-12, IFN-γ, ↑ IL-10	Bt	[51]
	↓ MCP-1, IL-10, ↑ PGE_2	Ac, Pr and Bt	[34]
Microglial cells -N9 cells	↑ IL-6, NO	Pr and Bt	[52]
-Rat primary microglia	↓ TNF-α, IL-6, NO	Bt	[52]
-Murine BV2 cell	↓ NO	Bt	[53]
Mesencephalic neuron-glia cultures	↓ TNF-α, NO	Bt	[54]
Kupffer cells	↓ TNF-α, ↑ PGE_2	Bt	[55]

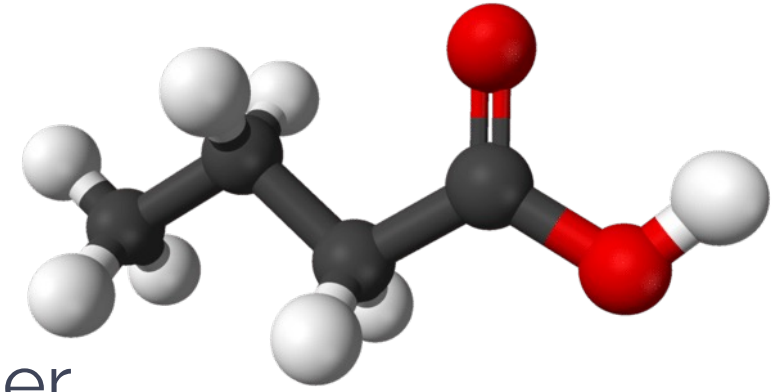
Nutrients. 2011 Oct;3(10):858-76. doi: 10.3390/nu3100858. Epub 2011 Oct 14.

Regulation of inflammation by short chain fatty acids.

Vinolo MA[1], Rodrigues HG, Nachbar RT, Curi R.

butyrate

MICROBIOTA - SCFA



saccharolytic microbiota
cecum - ascending colon

dietary fiber
resistant starch

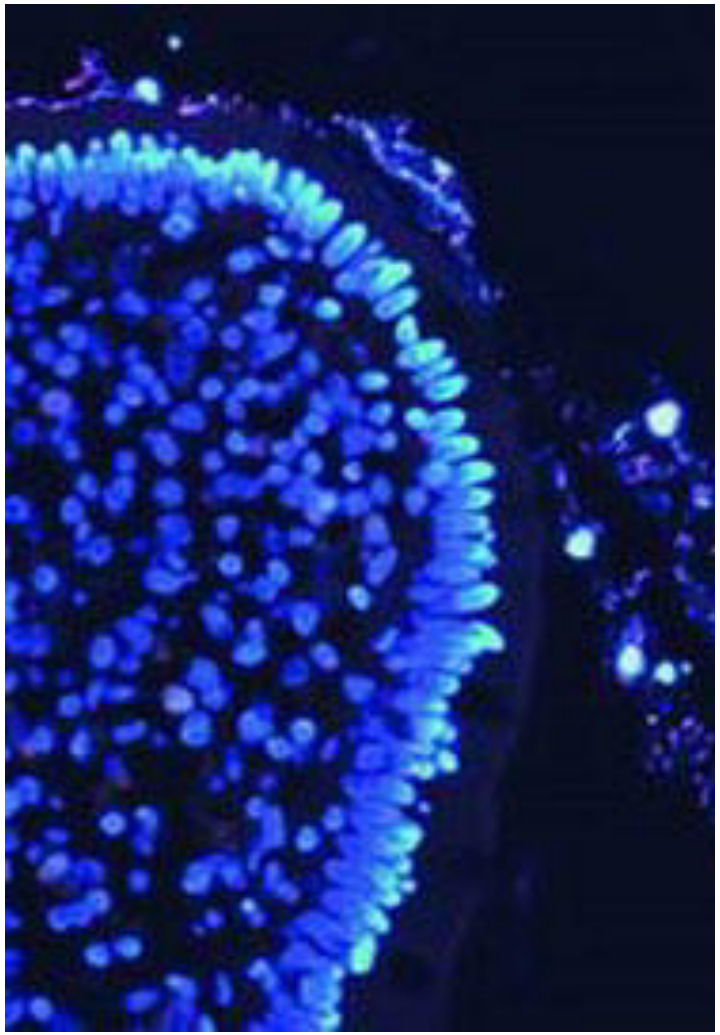
bacterial fermentation

BUTYRATE

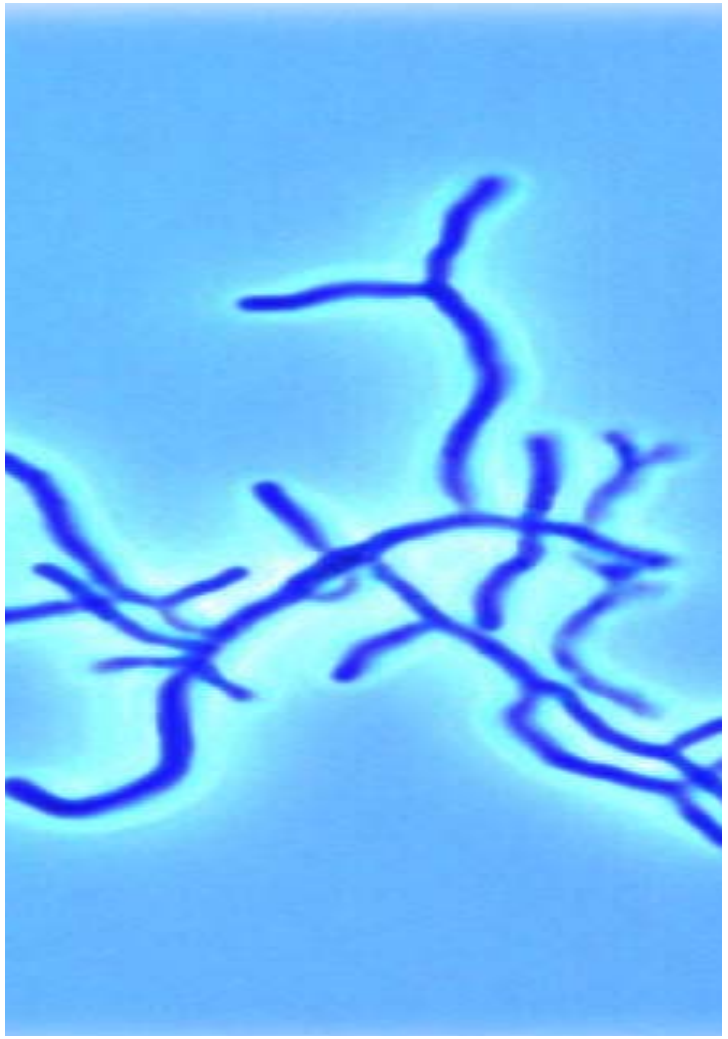
gives nutrients to the epithelium
modulates inflammation
modulates TJ proteins expression

BUTYRATE PRODUCING BACTERIA

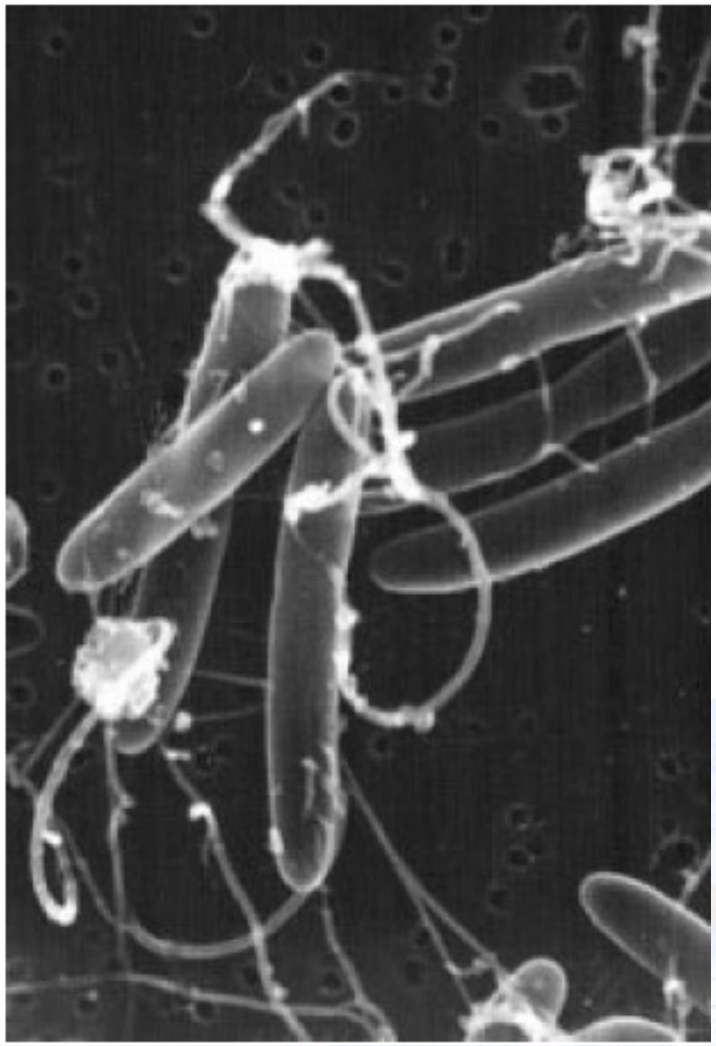
Faecalibacterium



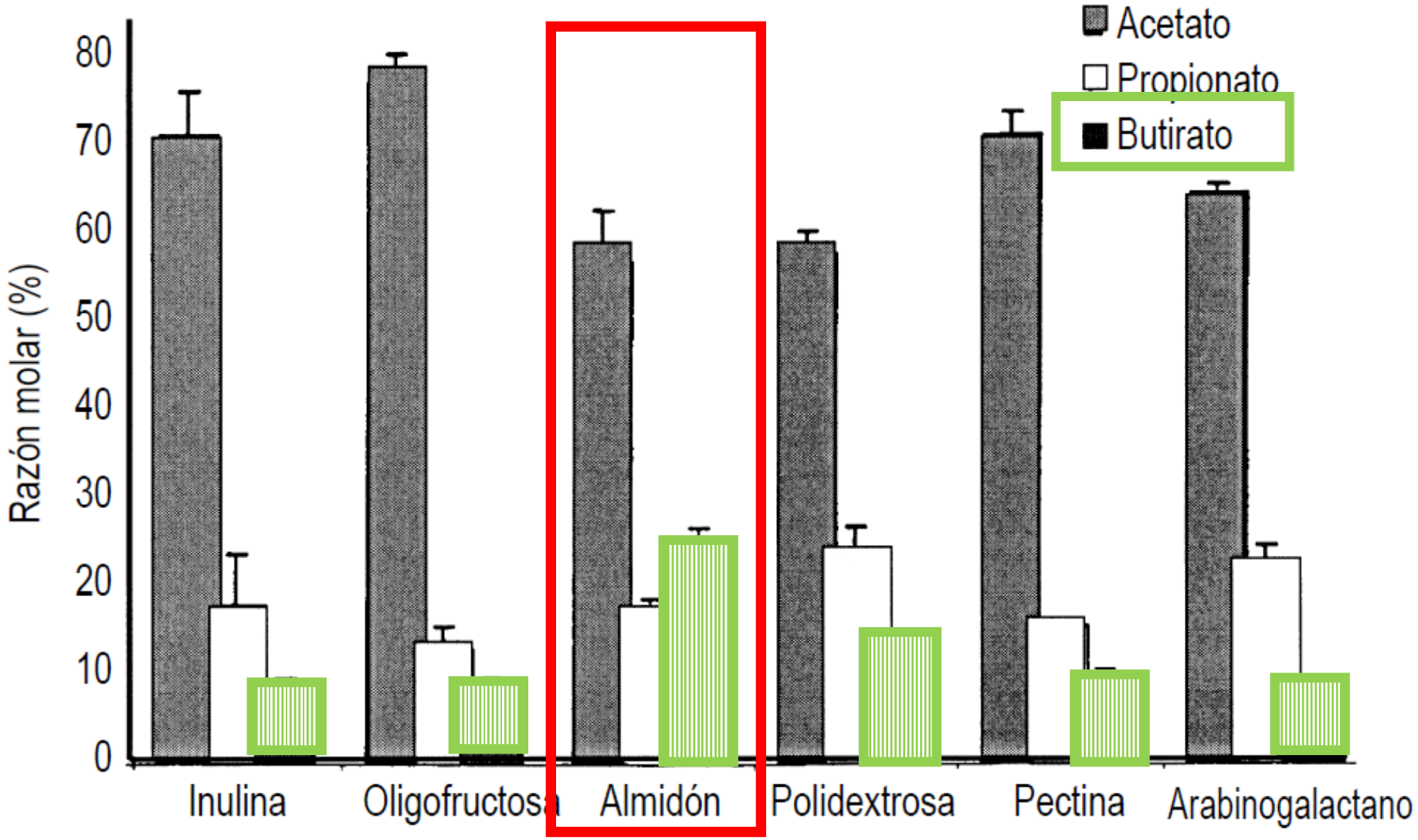
Bifidobacterium



Roseburia



PREBIOTICS - SCFA



J Appl Bacteriol. 1993 Oct;75(4):373-8

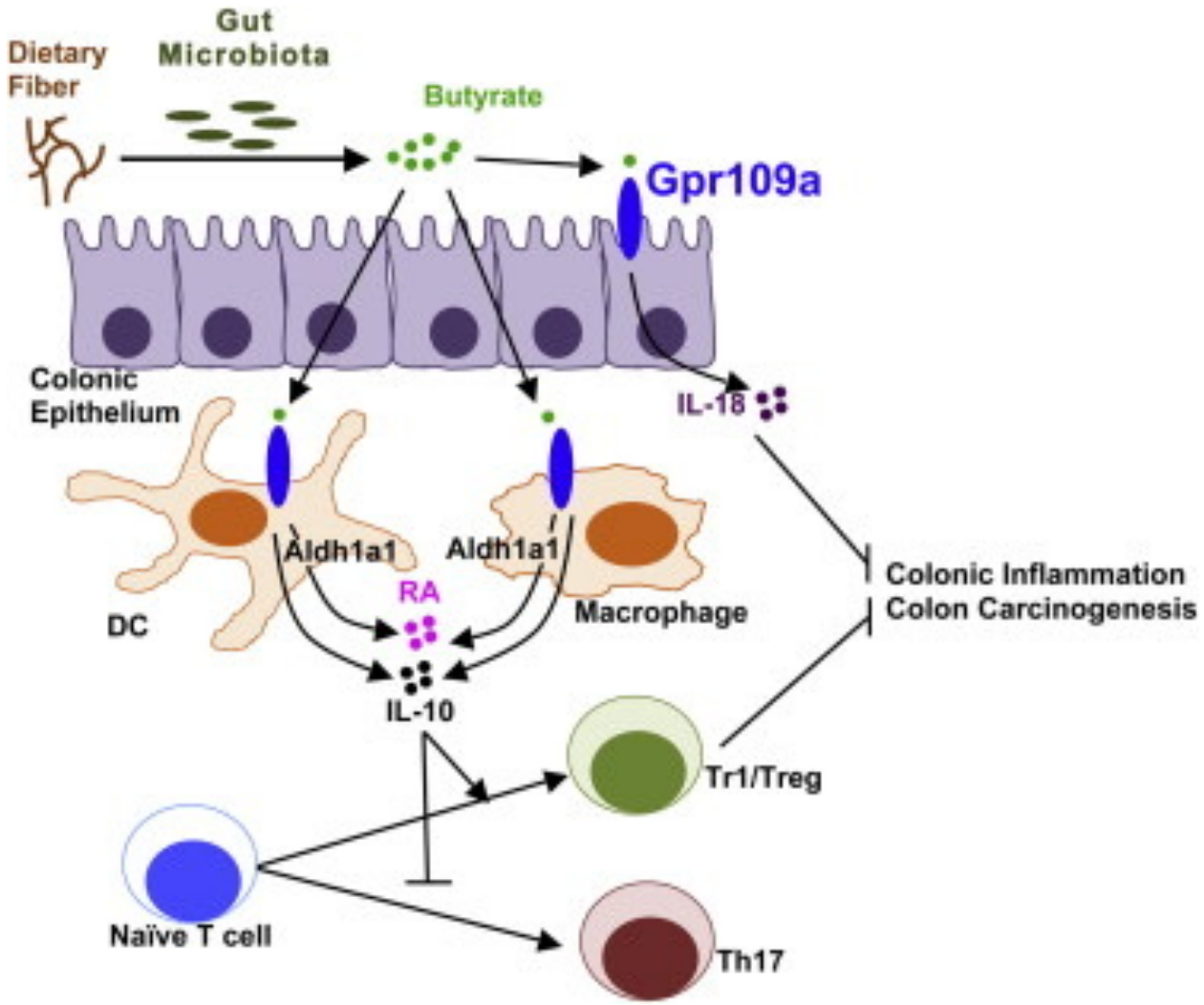
Effects of the in vitro fermentation of oligofructose and inulin by bacteria growing in the human large intestine.

Wang X[1], Gibson GR.

Immunity. 2014 Jan 16;40(1):128-39. doi: 10.1016/j.immuni.2013.12.007. Epub 2014 Jan 9.

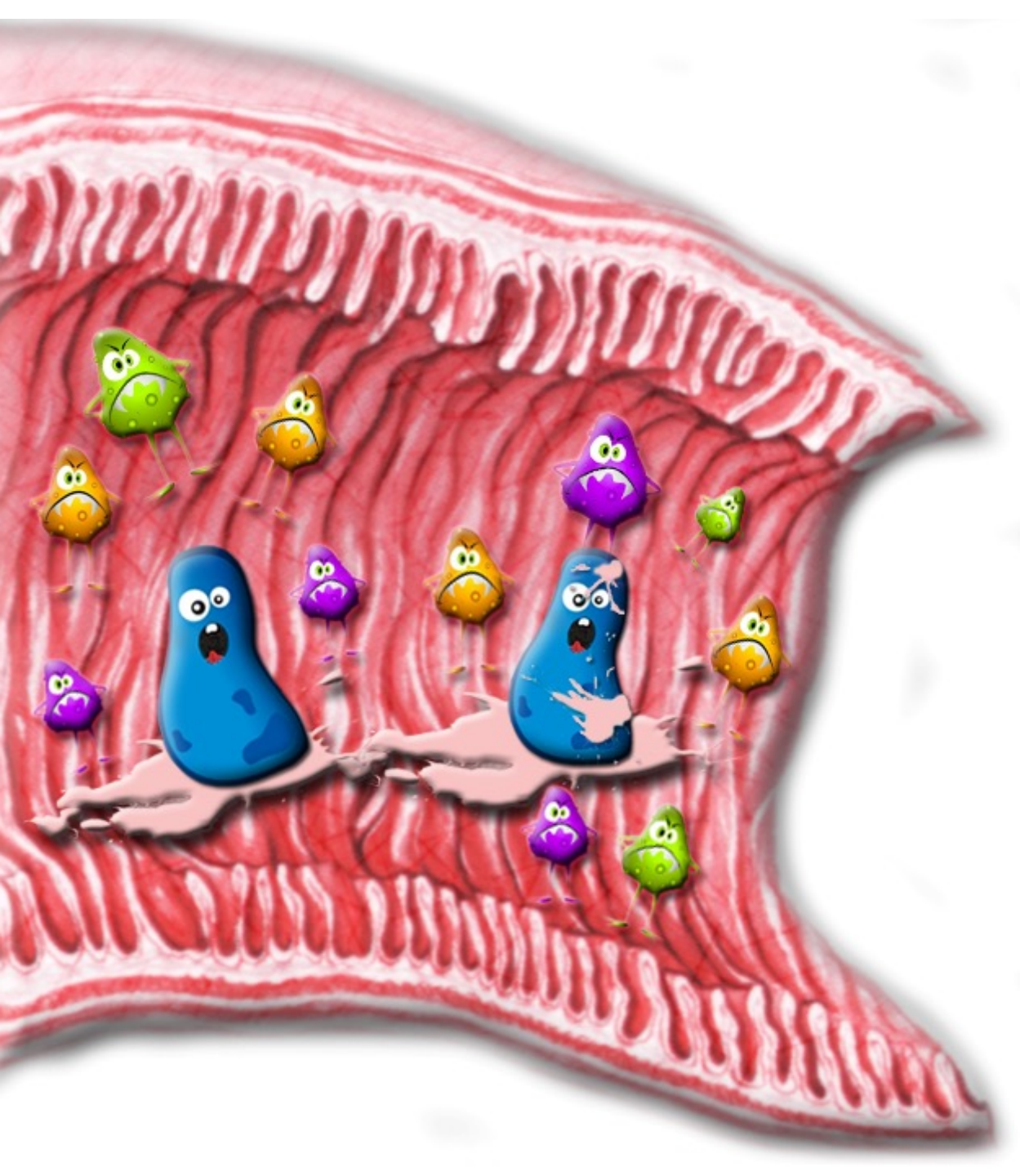
Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis.

Singh N[1], Gurav A[2], Sivaprakasam S[2], Brady E[2], Padia R[2], Shi H[3], Thangaraju M[3], Prasad PD[3], Manicassamy S[4], Munn DH[5], Lee JR[6], Offermanns S[7], Ganapathy V[6].



GPR109A: main receptor for **butyrate**

its activation promotes anti-inflammatory properties



INTESTINAL HOMEOSTASIS

gut microbiota

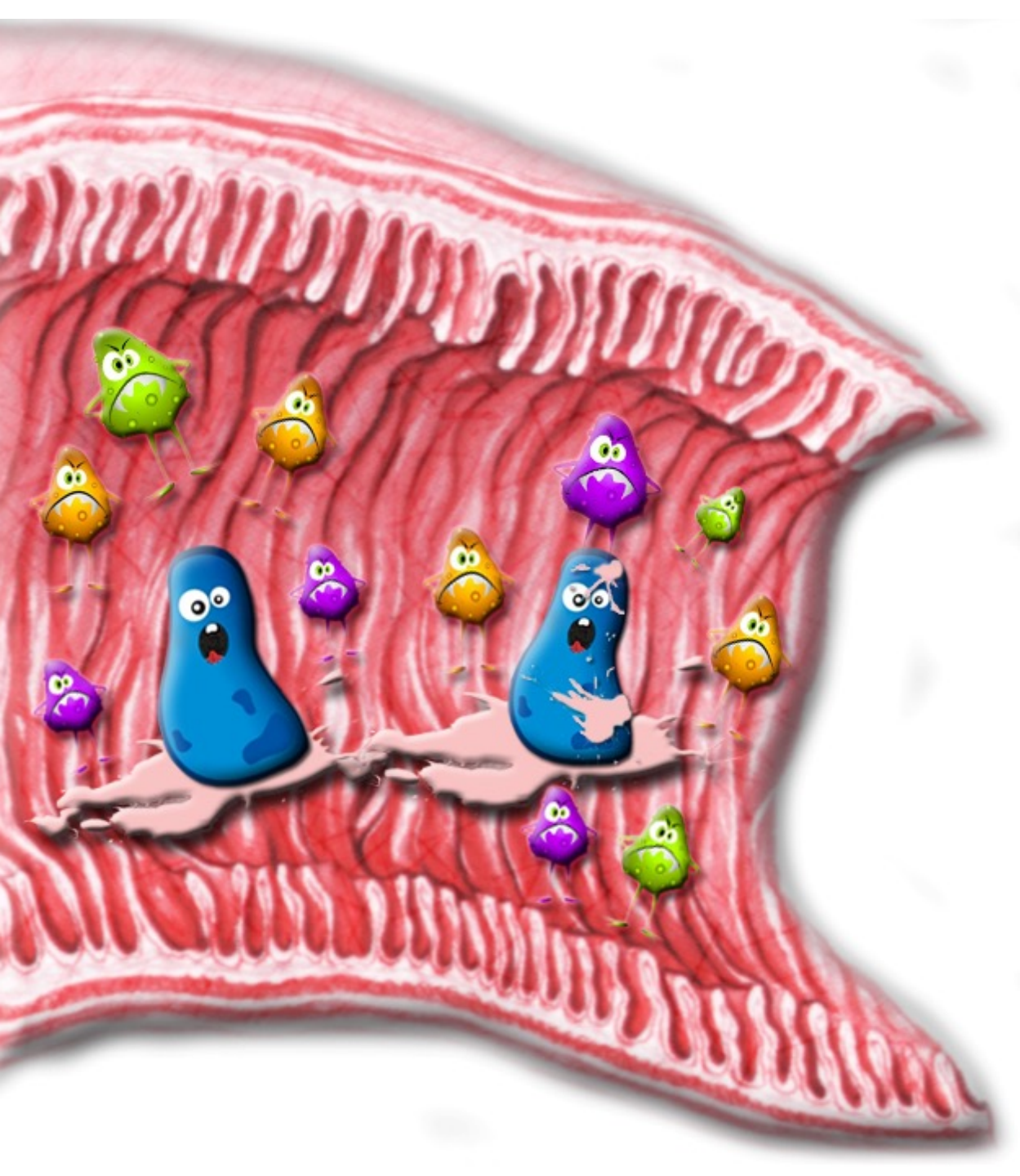
mucus layer stability

barrier - permeability

acid-base balance

enteric nervous system

immune system: GALT



INTESTINAL HOMEOSTASIS

gut microbiota

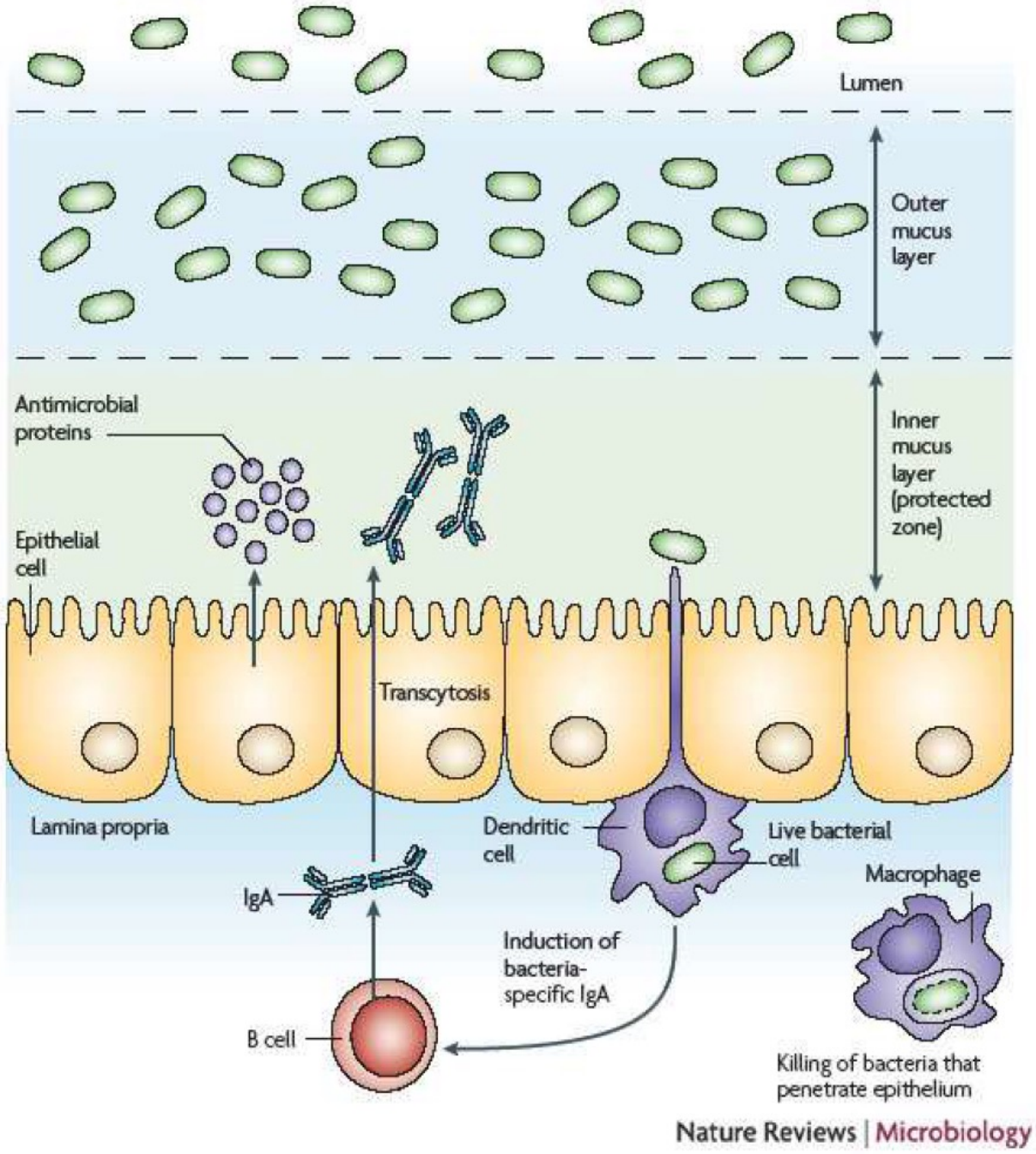
mucus layer stability

barrier - permeability

acid-base balance

enteric nervous system

immune system: GALT



INTESTINAL BARRIER

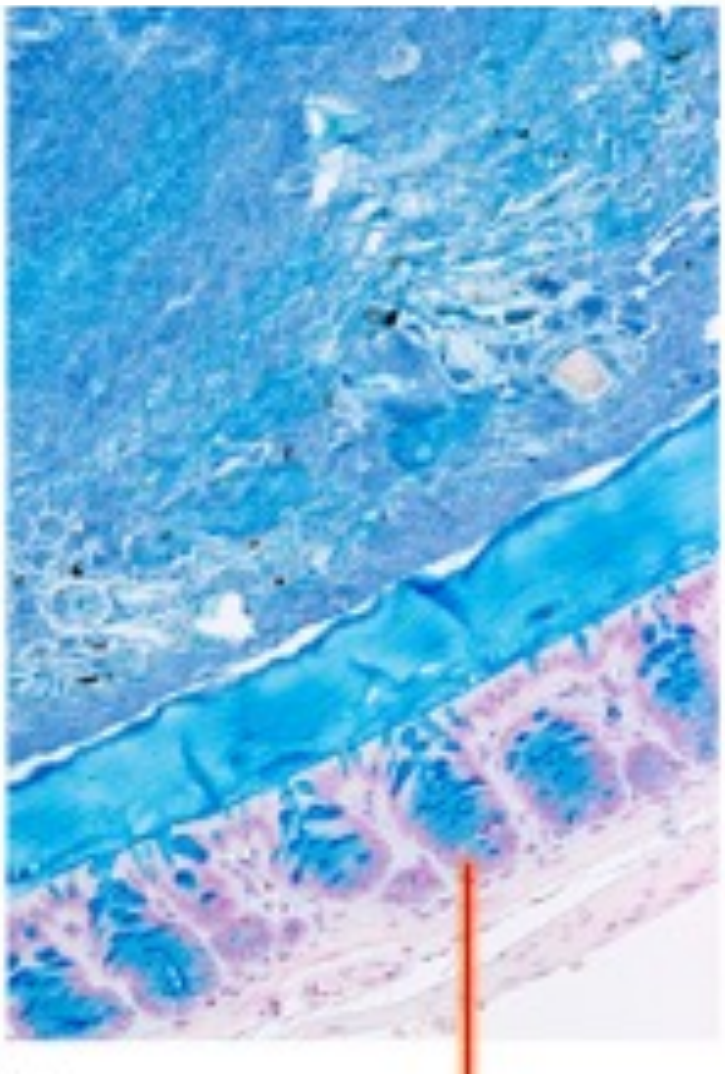
Mucus layer

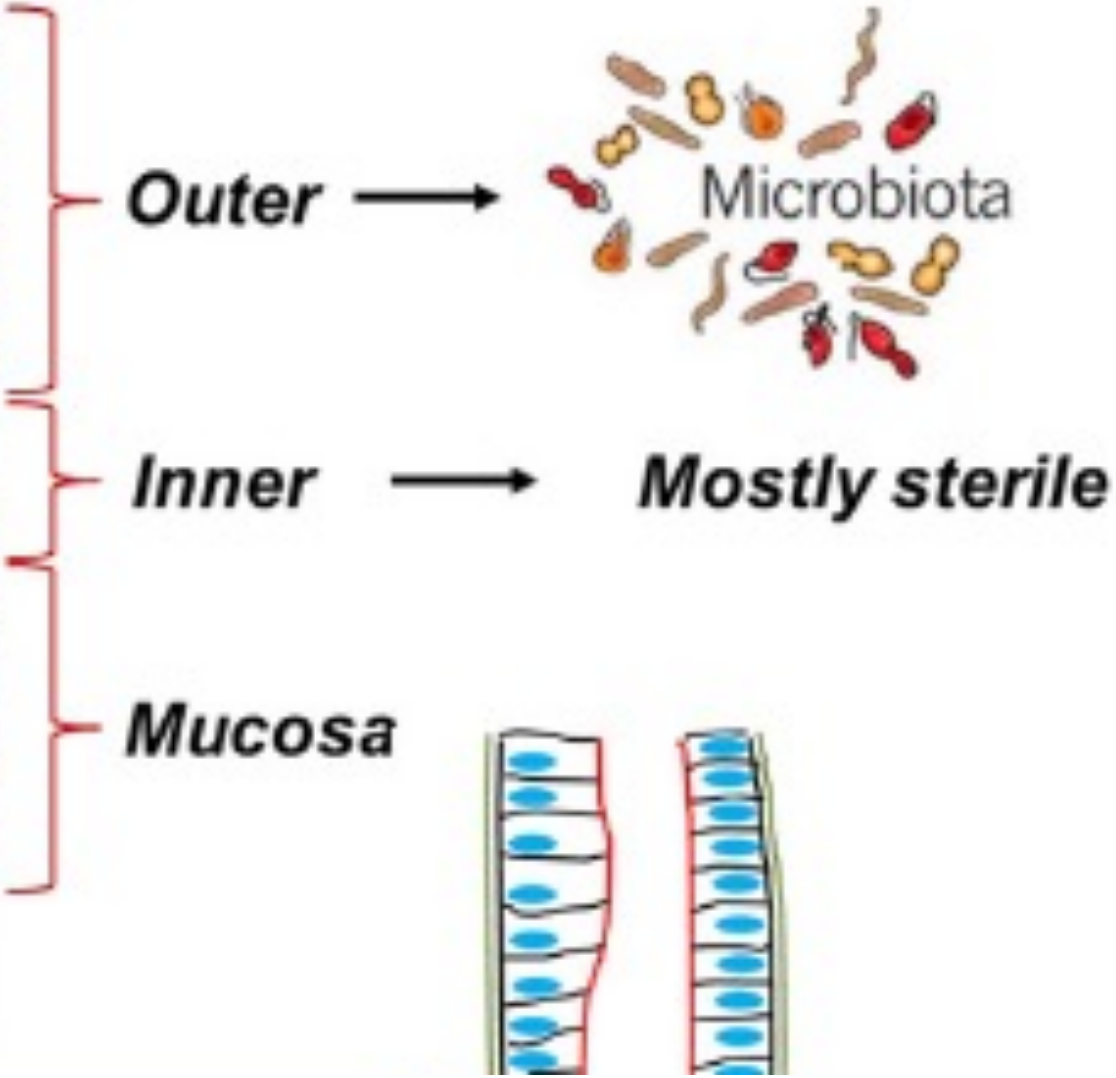
Eubiotic microbiota

Enterocytes & tight junctions
permeability

Ag presenting cells:
cell M Peyer's Patch
dendritic cells
intraepithelial lymphocytes
(10^9 lymphocytes)

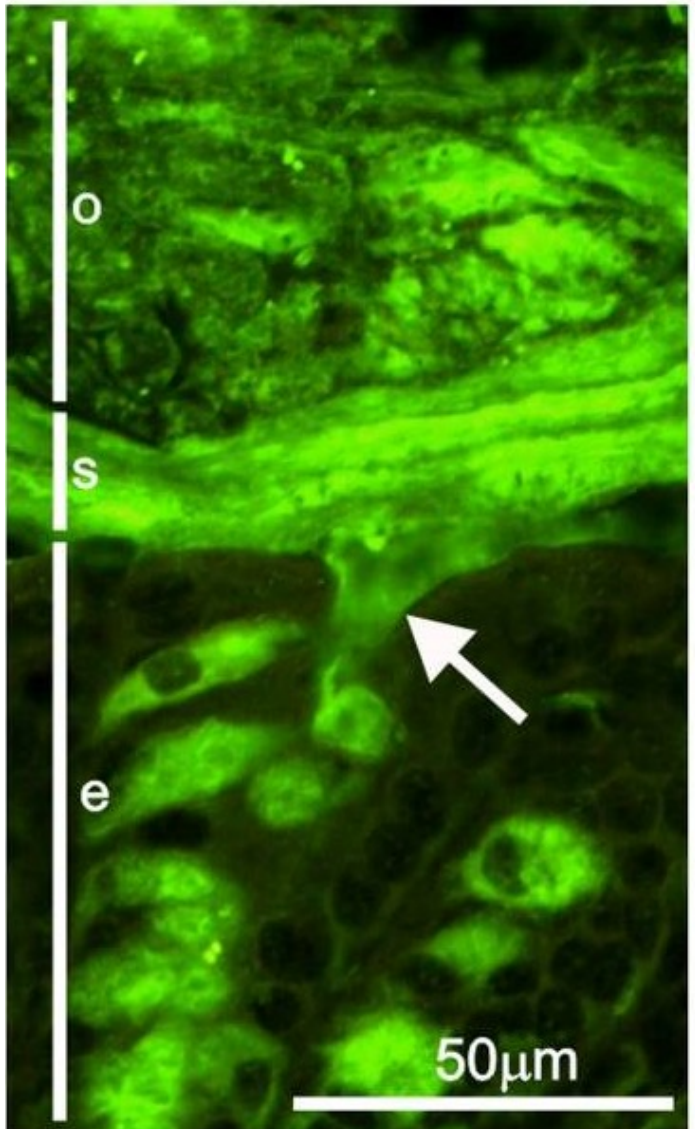
MUCUS LAYER

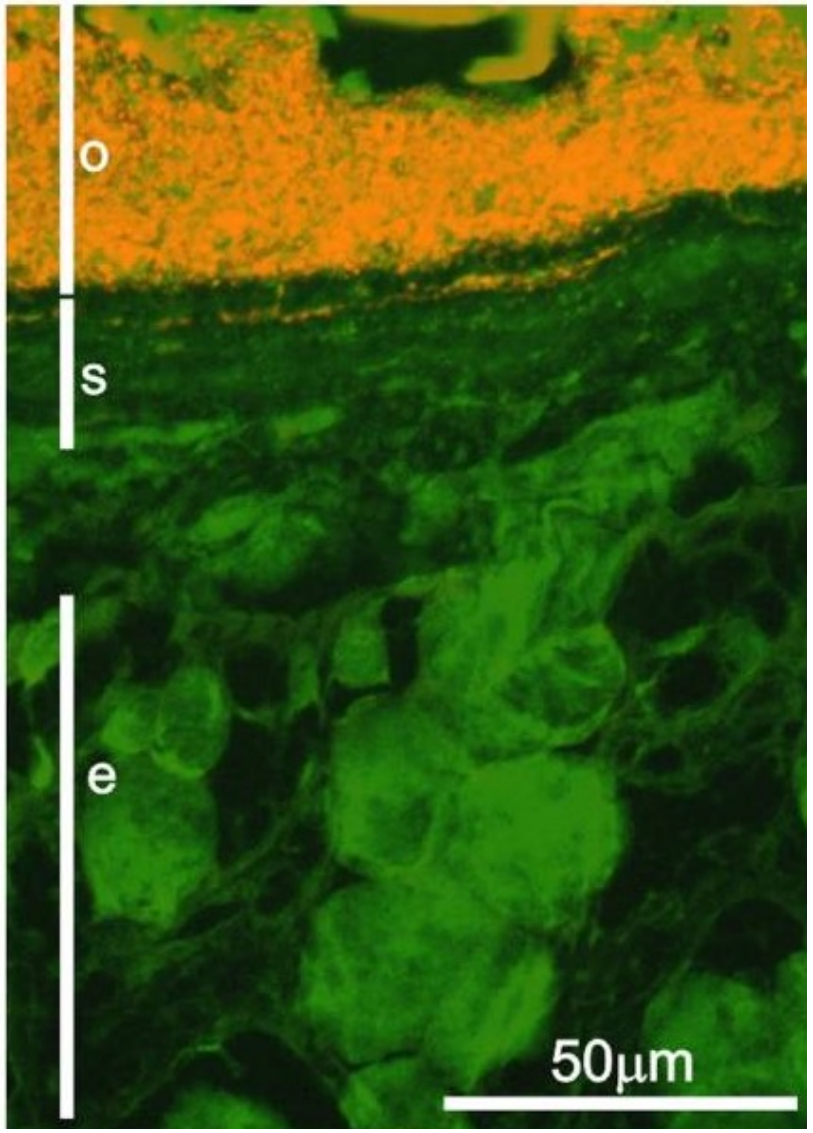




MUCUS LAYER, functions

- **LUBRICATION**
- **BARRIER**: IgA, bacteriocins, acidic pH, antimicrobial peptides (defensins), enzymes
- Degradation brings **NUTRIENTS** to the epithelium and the microbiota
- **ANTI-INFLAMMATORY**:
  - MUC2 provides anti-inflammatory signals to dendritic cells (antigen-presenting cell)
  - regulates the production of ß-defensins
  - interferes with the action of proinflammatory cytokines (IL1ß)





(o).- outer mucus layer

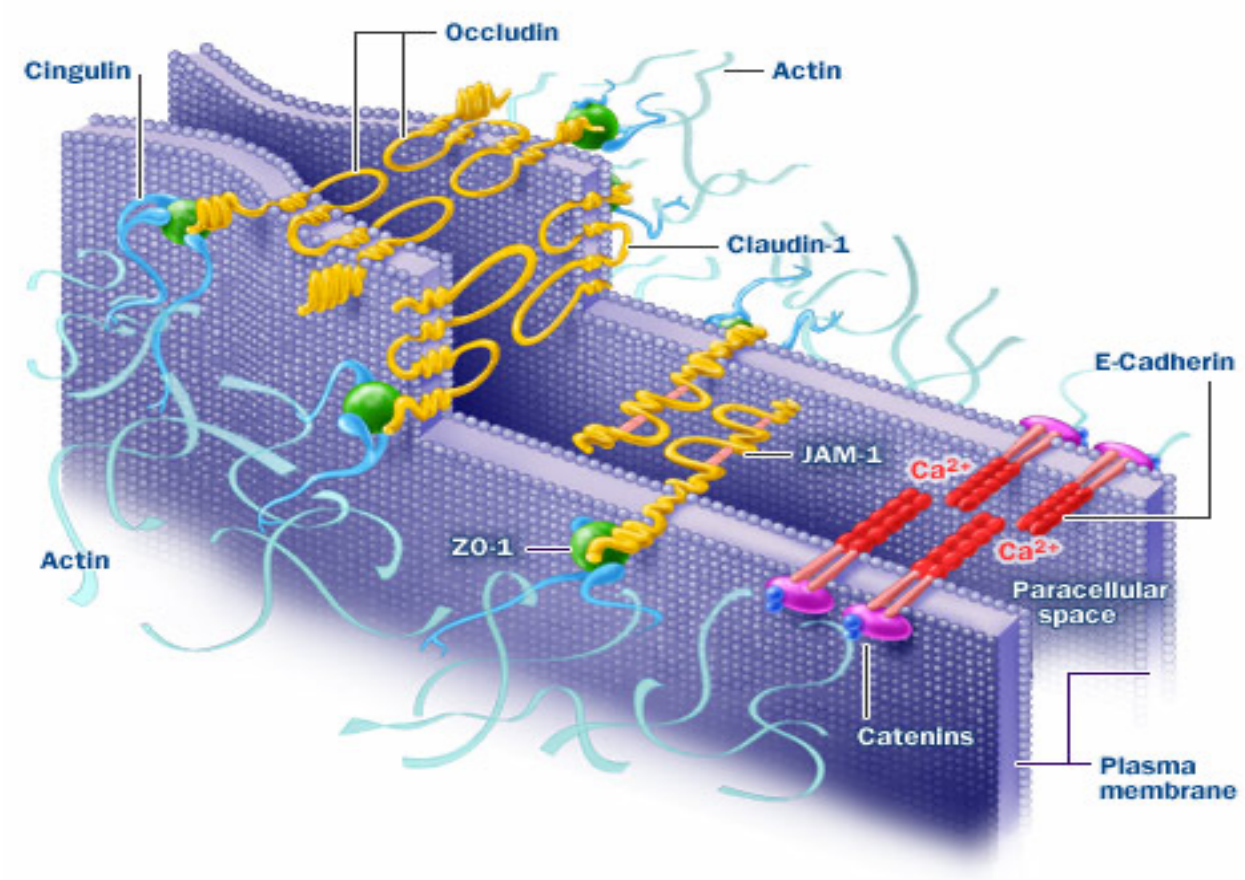
(s).- inner mucus layer

(e).- goblet cells secreting mucins

(o).- microbiota

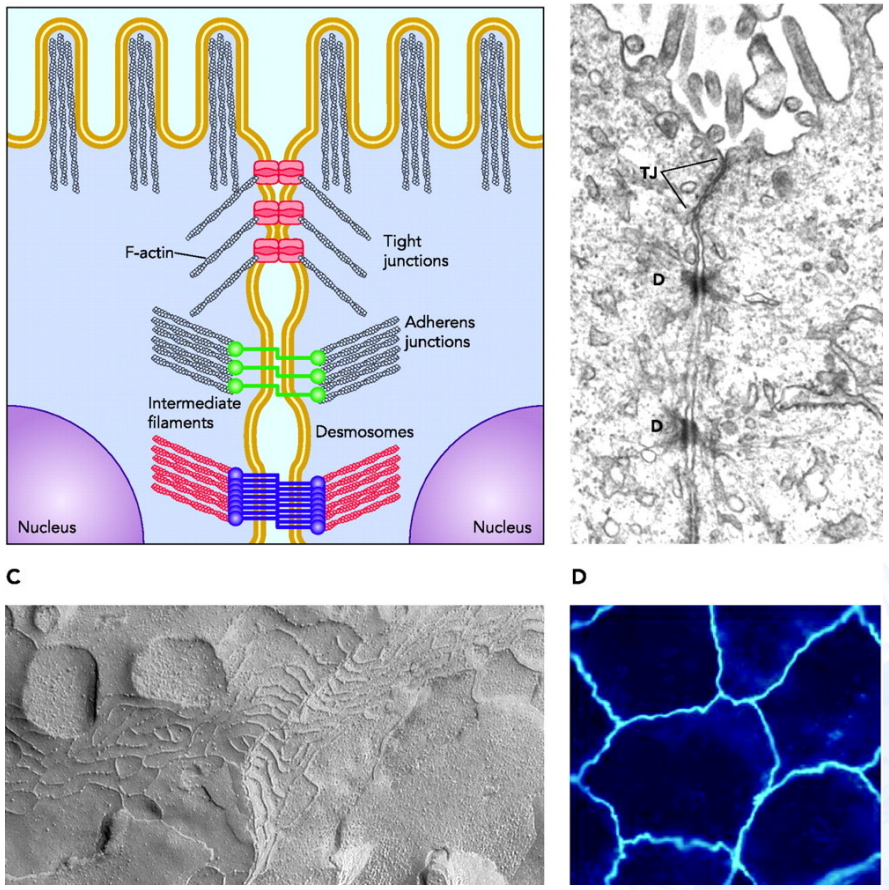
(s).- there is scarcely colonization of microbiota

TIGHT JUNCTIONS
protective chains of intercellular union



TIGHT JUNCTIONS
protective chains of intercellular union

- **PERMEABLE** barrier:
  prevents uncontrolled absorption
  prevents a "spill" of the body
- "**WALL**":
  apical and baso-lateral proteins
  guarantee polarity epithelial cells
- **COMMUNICATION** between cells



if all this doesn't work properly...

LEAKY GUT SYNDROME

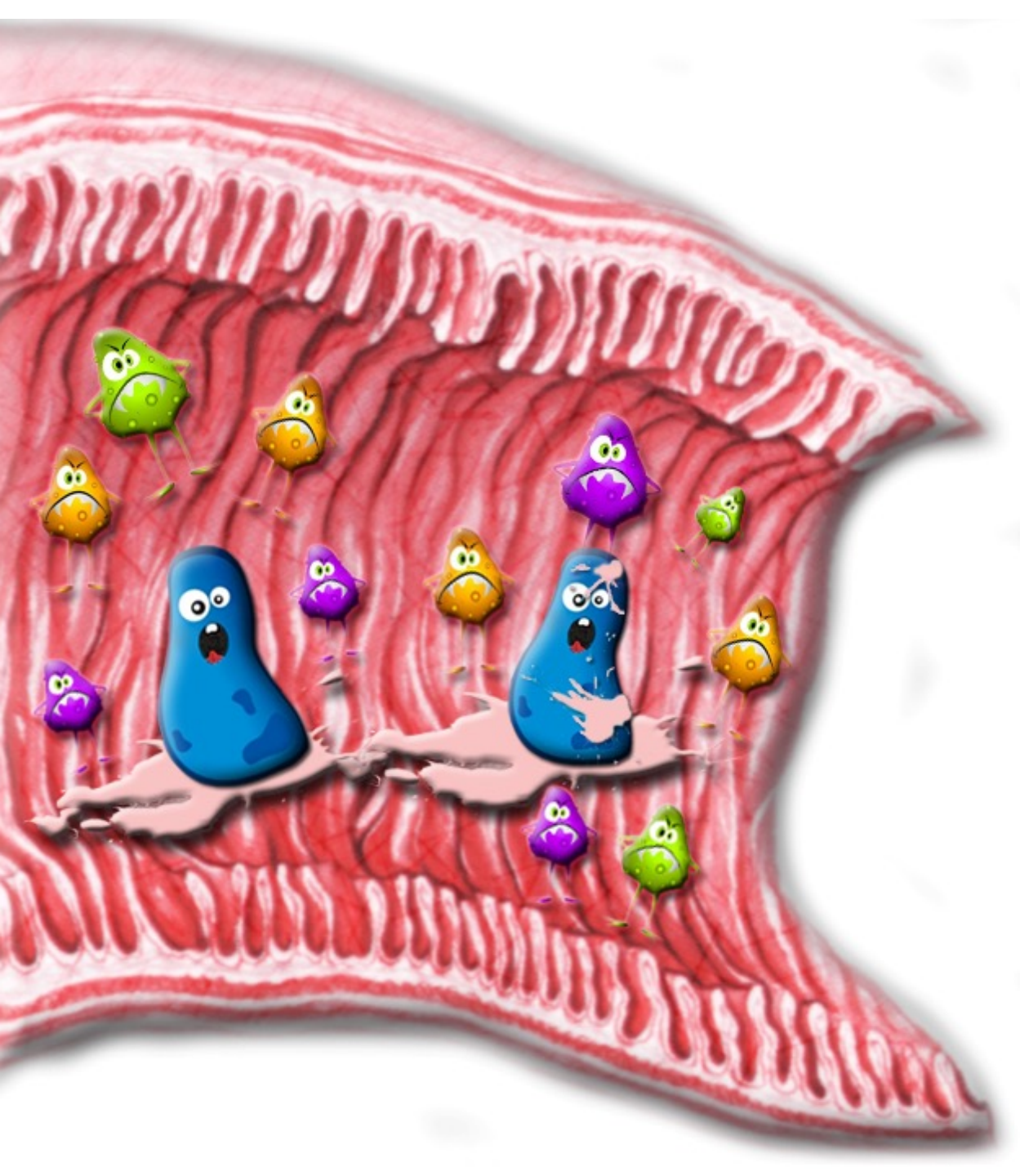
TIGHT JUNCTIONS
Intestinal permeability is selective

Phenomena of antigenic or **IMMUNOLOGICAL TOLERANCE**

The GALT is able to identify and differentiate:

- nutrient = tolerance and absorption
- toxic / antigen = no absorption + activation immune system

If all this doesn't work properly…
the immune system doesn't work properly



INTESTINAL HOMEOSTASIS

gut microbiota

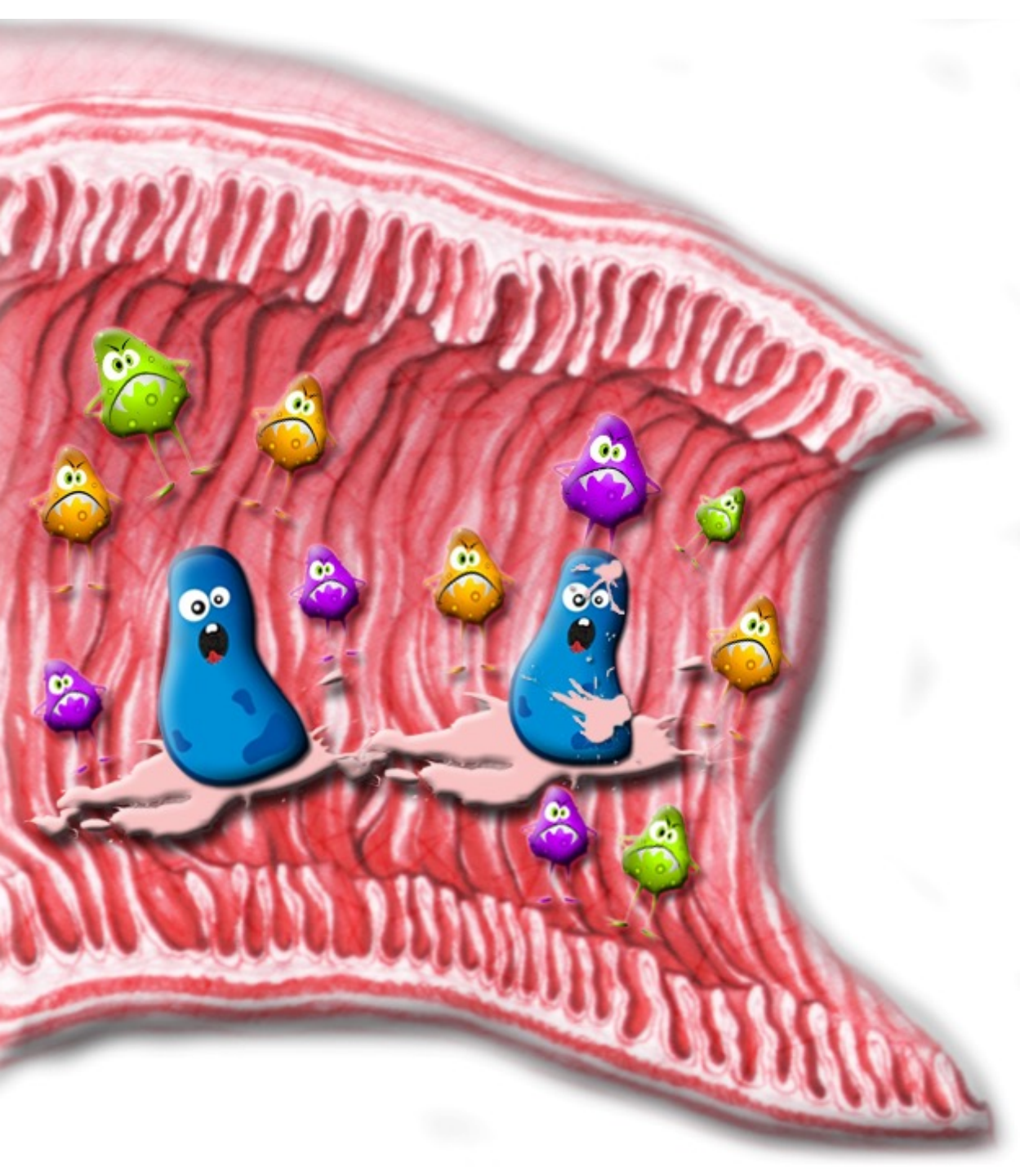
mucus layer stability

barrier - permeability

acid-base balance

enteric nervous system

immune system: GALT



INTESTINAL HOMEOSTASIS

gut microbiota

mucus layer stability

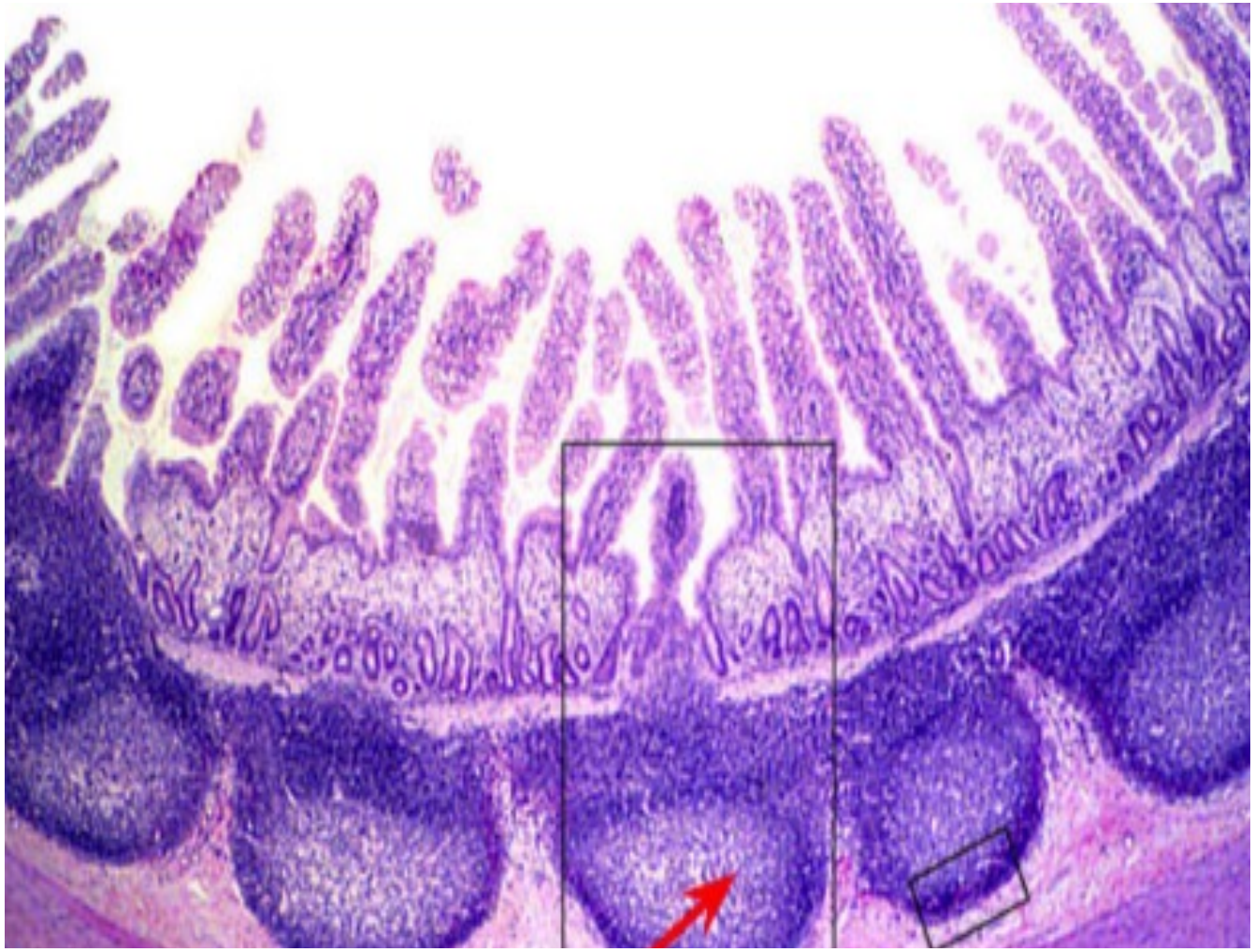
barrier - permeability

acid-base balance

enteric nervous system

immune system: GALT

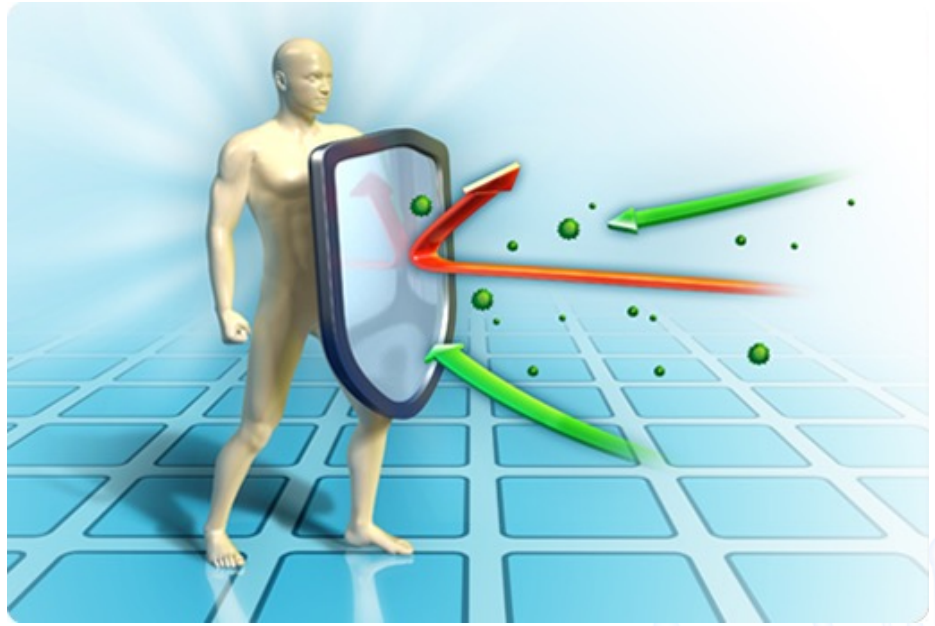
MUCOSAL IMMUNE SYSTEM, GALT



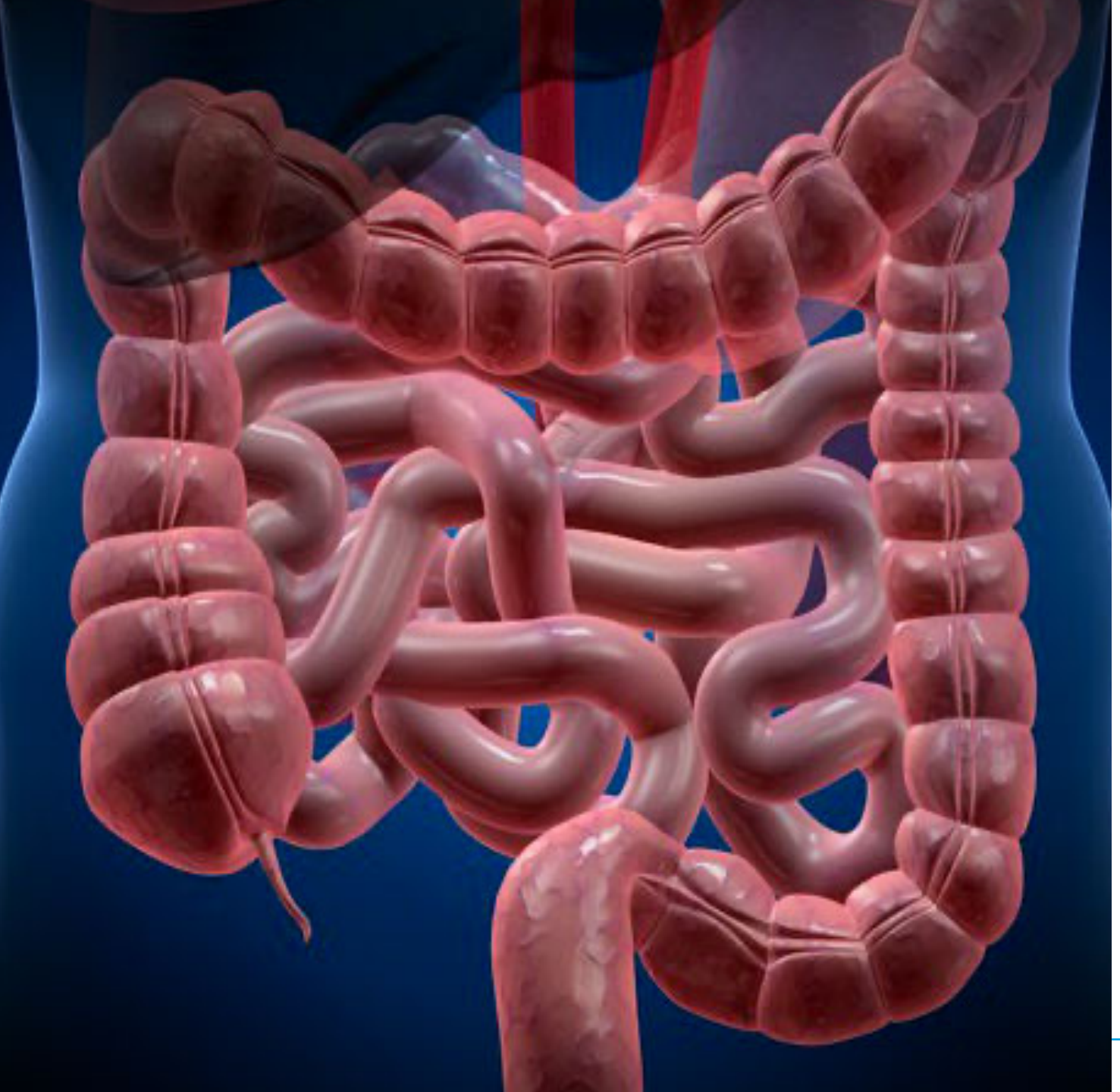
MUCOSAL IMMUNE SYSTEM

The mucosal immune system mainly includes:

- GALT, 400 - 600 m2 gastrointestinal mucosa
- NALT, oro-nasal-pharynx mucosa
- BALT, respiratory tract mucosa
- eye and ear mucosa
- genitourinary mucosa
- vulvovaginal mucosa
- mammary gland



THEY ARE ALL IN COMMUNICATION WITH EACH OTHER

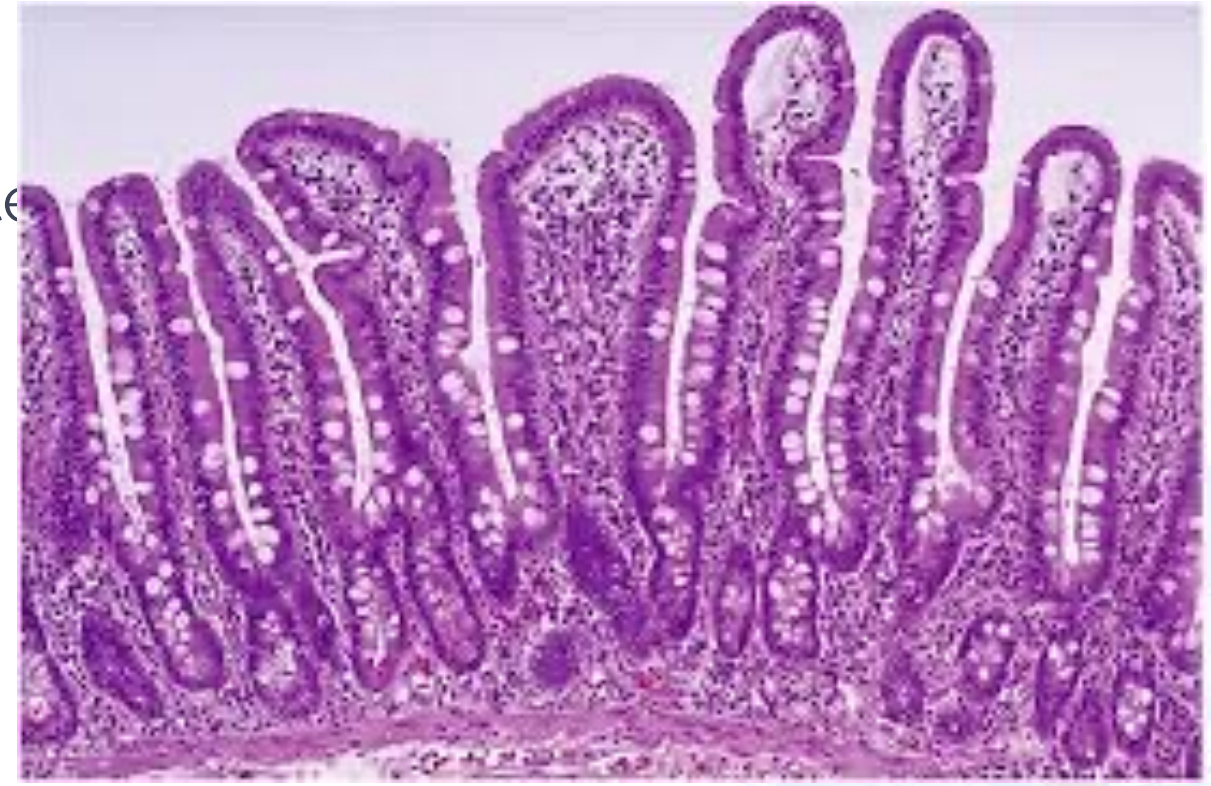


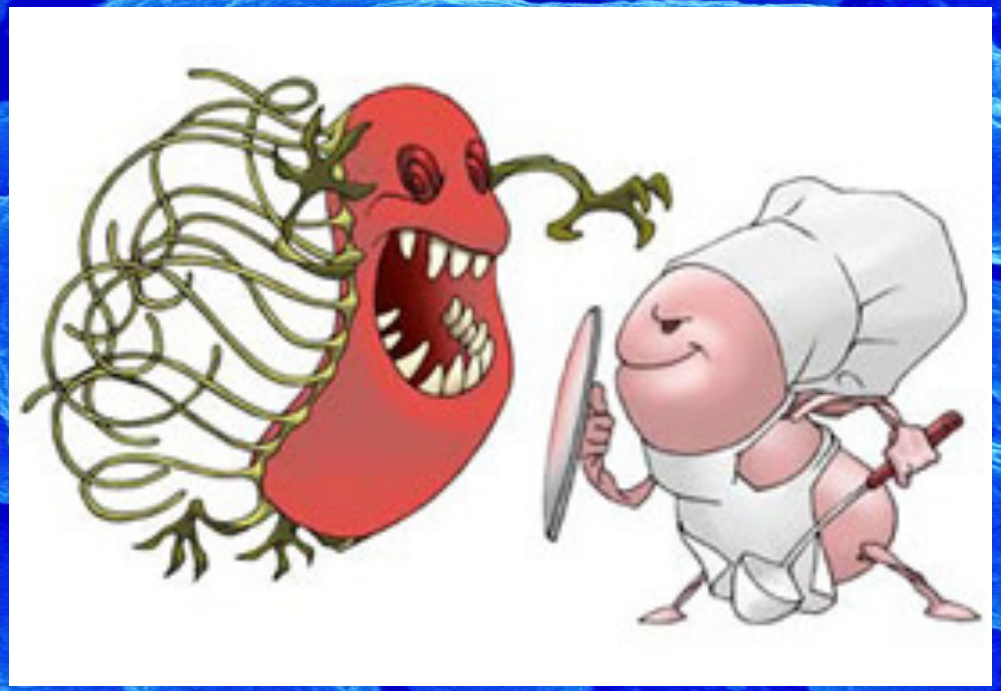
GUT MUCOSA

the largest surface area in contact with the environment

MUCOSAL IMMUNE SYSTEM, GALT
Immune reaction, inmunotolerance

In the **INTESTINAL EPITHELIUM,** there is a predominant environment of **IMMUNOTOLERANCE** which is mediate by regulatory T-cells, allowing continuous exposure to antigens (diet, saprophytic microbiota...), without the development of an inflammatory immune reaction



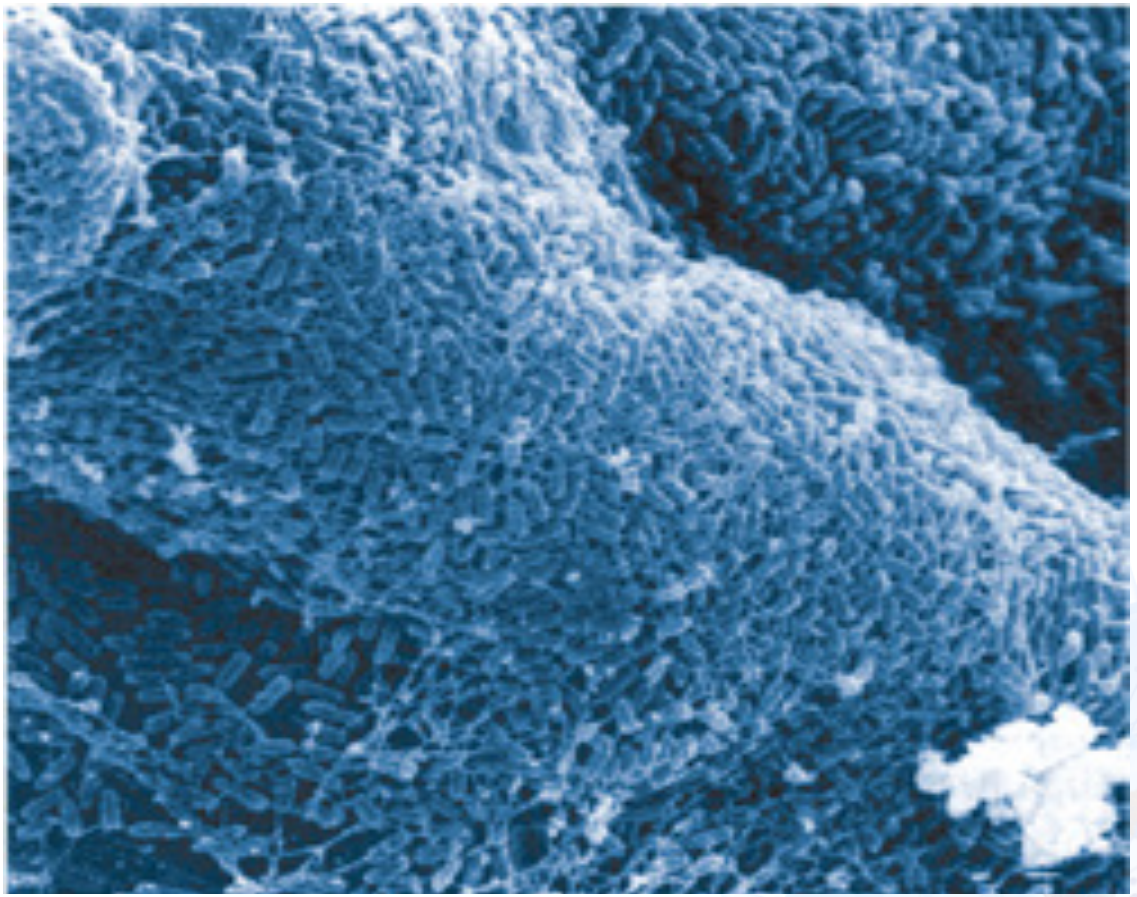


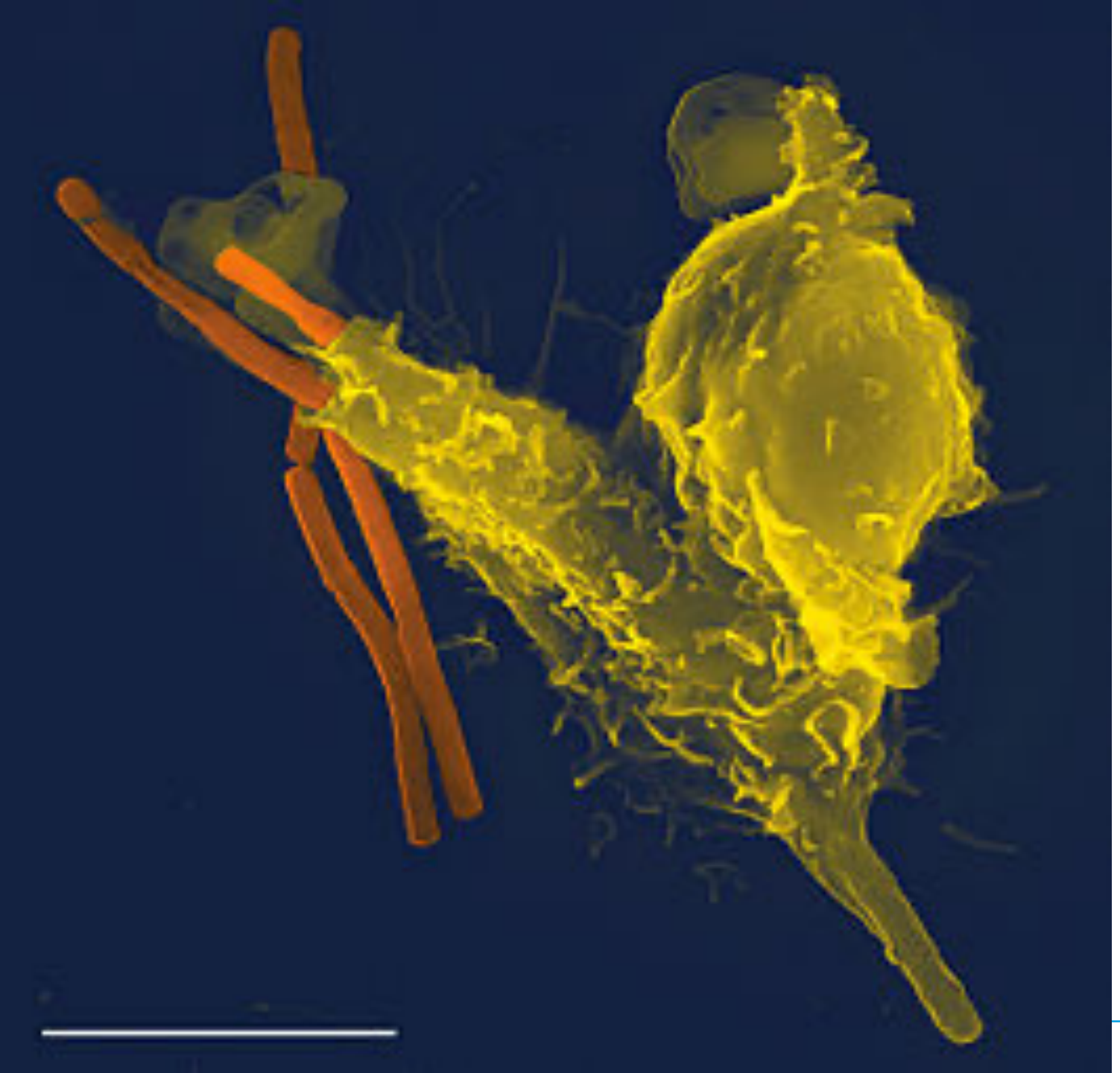
no microbes

no defence

MUCOSAL IMMUNE SYSTEM, GALT
Immune reaction, microbiota

The continuous **INTERACTION** of the host with intestinal bacteria is key to the development and activity of a **COMPETENT IMMUNE SYSTEM**





One of the most important functions of the **microbiota** is the development and maturation of the **immune system**

Other "actors" are involved

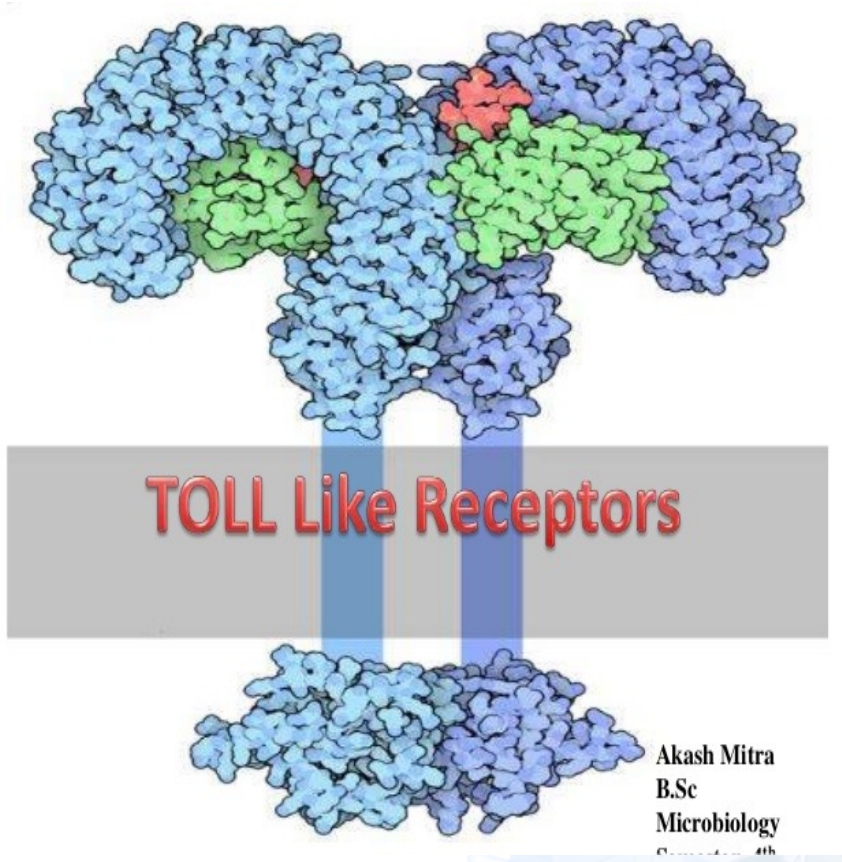
MUCOSAL IMMUNE SYSTEM, GALT Immune reaction, TLR

The Toll Like Receptor (TLR) is the **STARTING POINT** of immunity

TLRs are recognition receptors on cells of the innate immune system.

TLRs are **ACTIVATED** in response to:

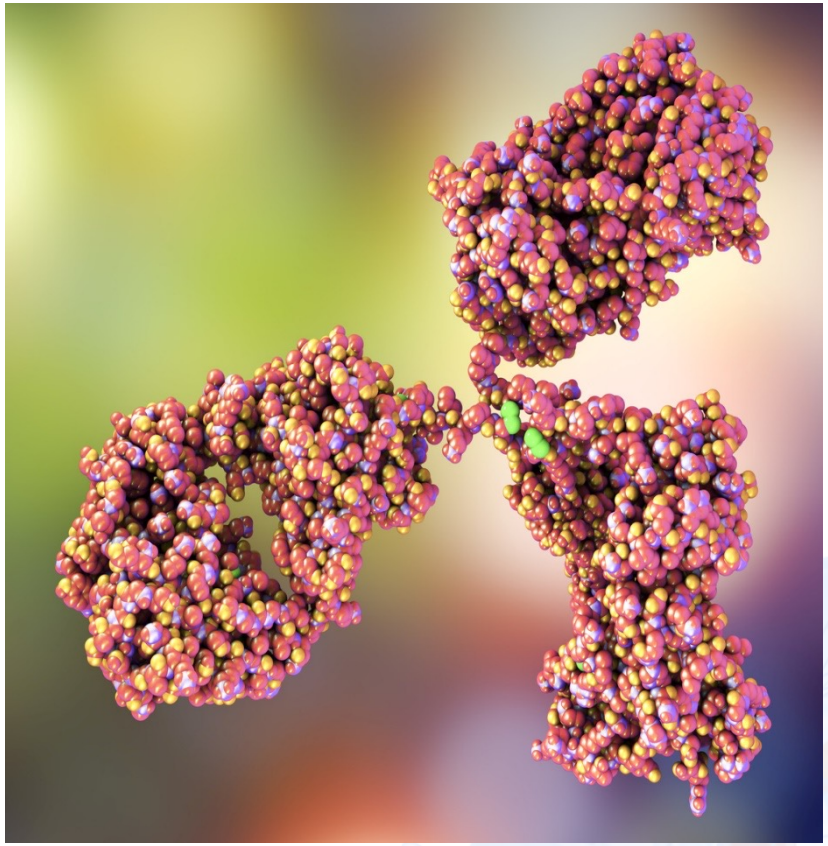
- microbial stimuli
- dietary derivatives (proteins or lipids)



MUCOSAL IMMUNE SYSTEM, GALT
Immune reaction, IgA

Secreted by plasmatic cells of the lamina propria of the mucosa, contributes to mucosal immunity and defence against local infections:

- bind, immobilize and neutralize **ANTIGENS**, blocking their entry into the body
- neutralises **PATHOGENS**, blocking their binding to the mucosa
- contributes to oral **IMMUNOTOLERANCE**

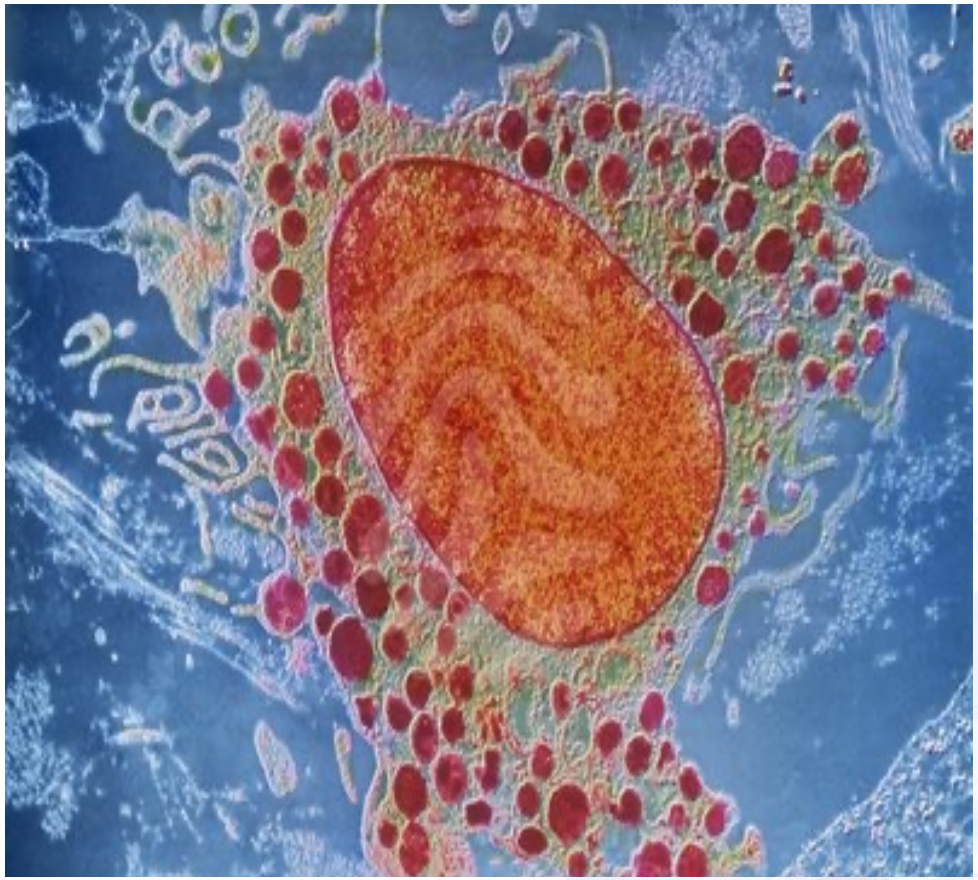


MUCOSAL IMMUNE SYSTEM, GALT
Immune reaction, Mast cells

Promotes **HOMEOSTASIS**:

- immunomodulatory activity
- immunoreactions eliminate pathogens through complement activation

In **DYSBIOSIS**, increased exposure to bacterial antigens activates the mast cells and initiates the inflammatory reaction



INFLAMMATION OF THE INTESTINAL EPITHELIUM

Jejunal biopsy reveals inflammation and enteric neuropathy in IBS-associated dysbiosis

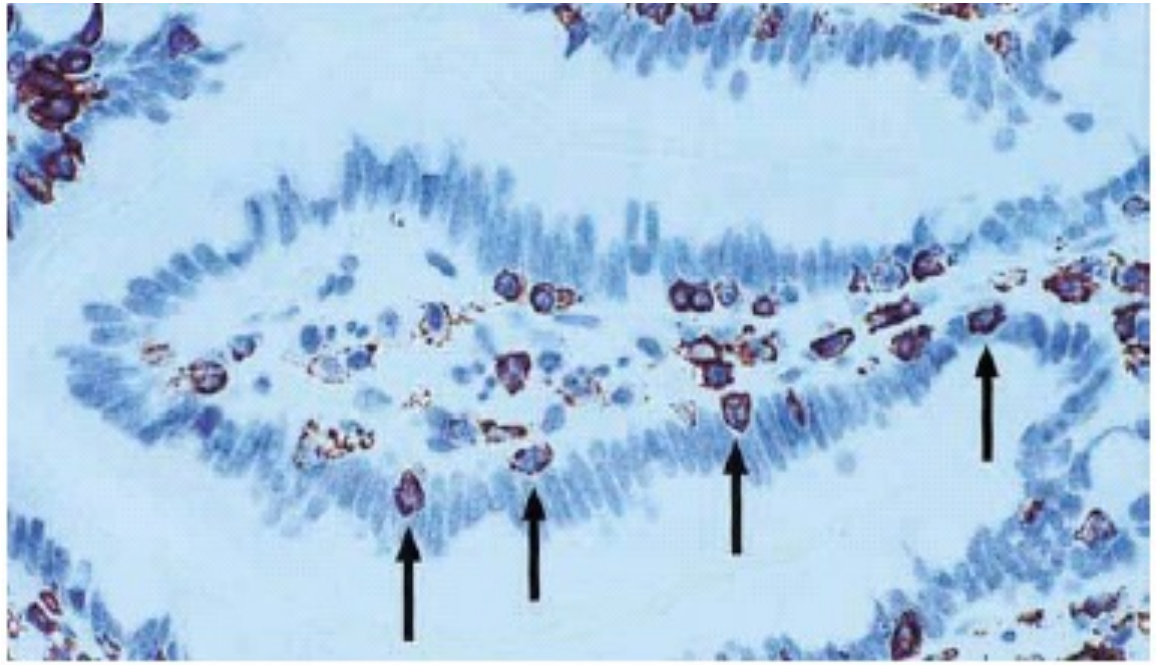


Figure 1. Control ileum with normal number of intraepithelial lymphocytes (*arrows*). (CD3 immunoperoxidase; original magnification ×380.)

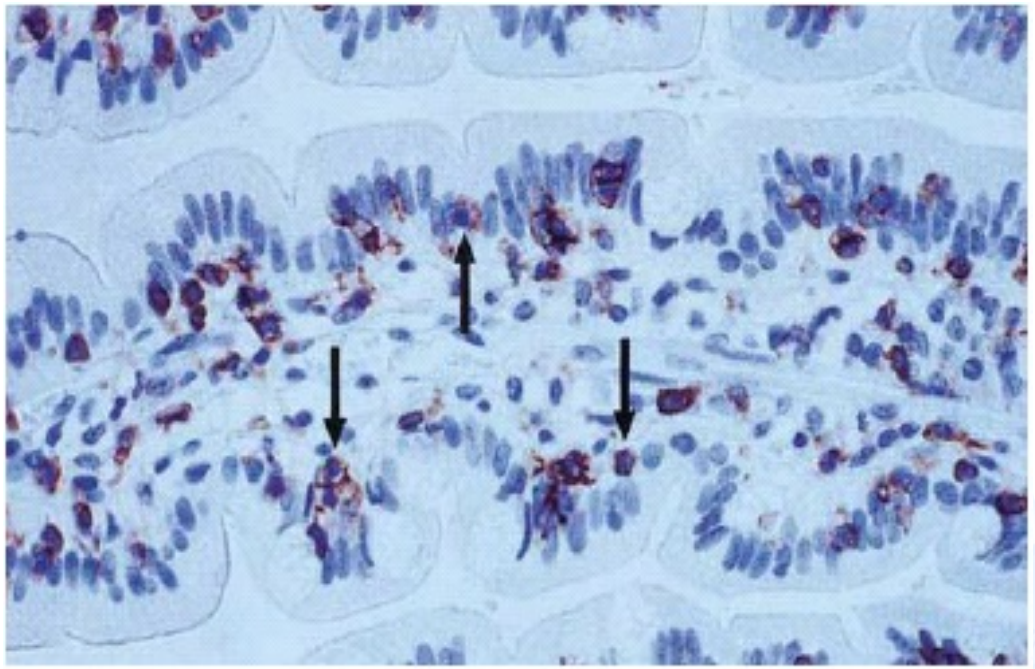


Figure 2. Proximal jejunum with increased number of intraepithelial lymphocytes (*arrows*) (41 IELs/100 epithelial cells). (CD3 immunoperoxidase; original magnification ×380.)

Törnblom et al., *Gastroenterology* 123;2002:1972-9


Eubiotic bacterial
colonisation is essential
for proper induction of
the immune response


Thank you
Doctoradelapuerta