Le giornate della salute e del benessere: Innovazione e Ricerca

Milano, 30 Giugno - 1 Luglio

Il Microbiota nelle diverse età della vita

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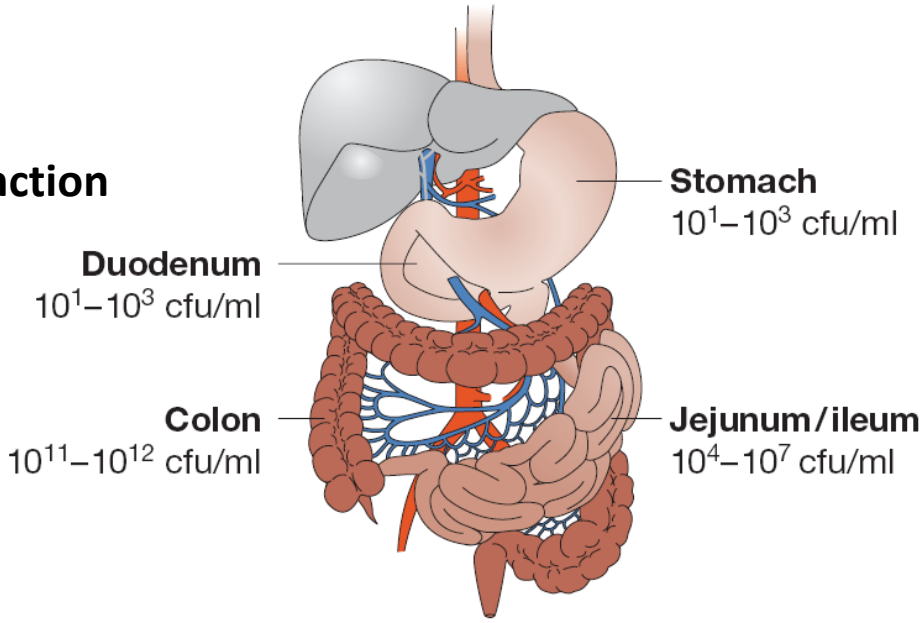
MICROBIOTA

"The human body is colonized by a **vast number of microbes**, collectively referred to as the human microbiota. The link between these **microbes and our health** is the focus of a growing number of research initiatives, and new insights are emerging rapidly, some of which we are proud to present in this special collection"

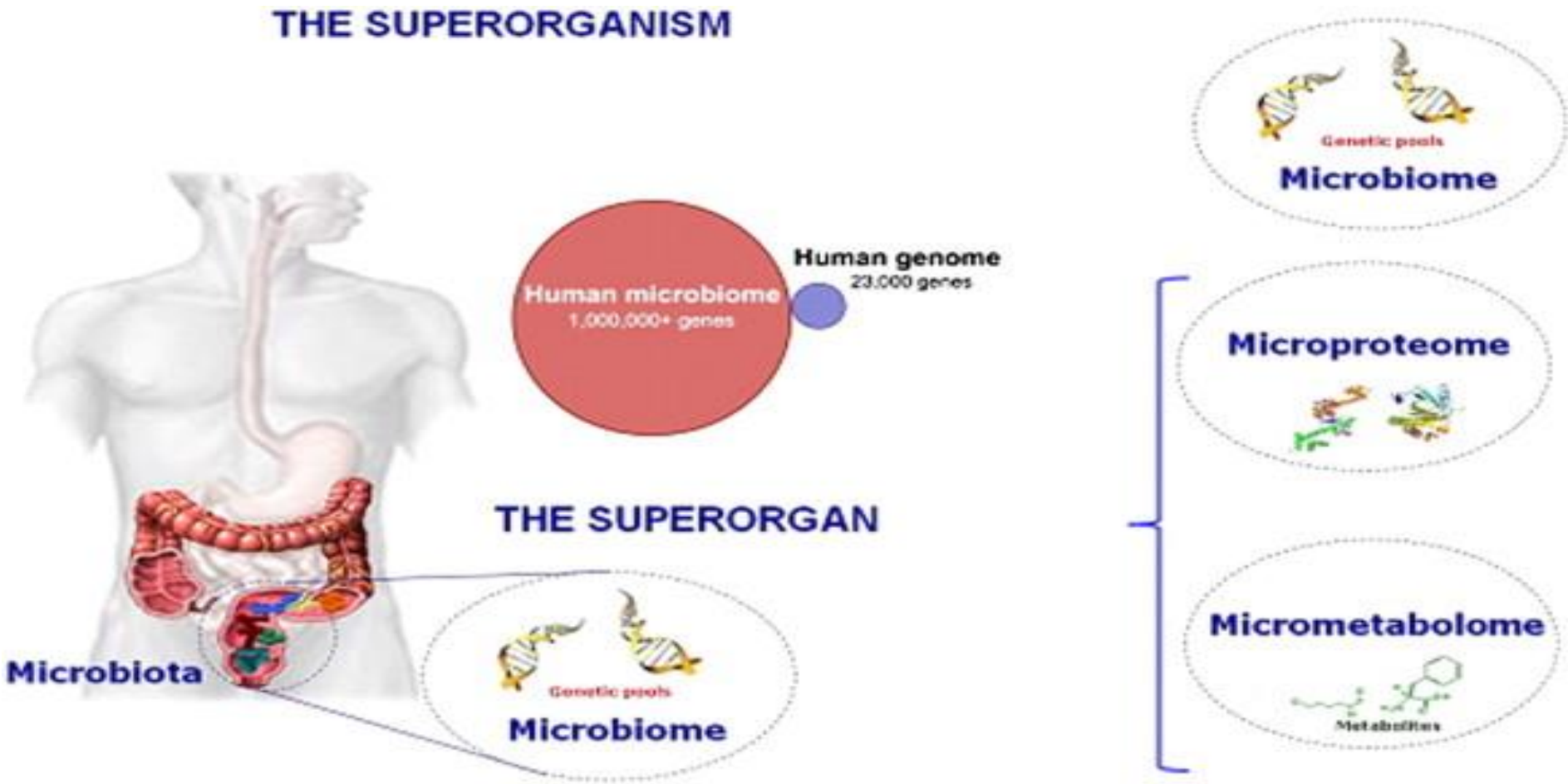
Gut microbiota

- more than 1000 species
- collective weight of about 1kg in human intestine
- colonization begins immediately after birth
- symbiotic bacteria provide benefits to the host:
  - nutrient supply
  - pathogen defense
  - immune system development/ function

Anaerobic genera	Aerobic genera
Bifidobacterium	*Escherichia*
Clostridium	*Enterococcus*
Bacteroides	*Streptococcus*
Eubacterium	*Klebsiella*



O´Hara and Shanahan, EMBO reports, 2006



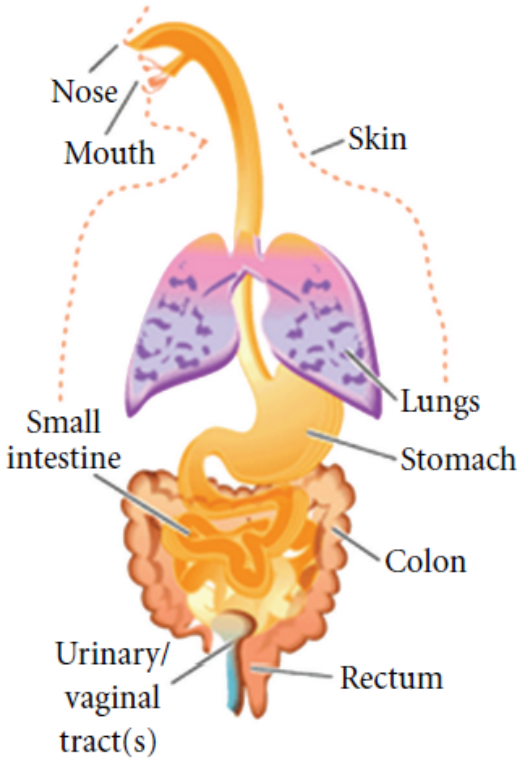
The microbial gut ecosystem. Schematic representation of the gut microbiome. The old definition of the human organism opens the way to the "superorganism", which houses the resident genomes, called microbiome and the related microproteome ...

Federica Del Chierico , Pamela Vernocchi , Luigi Bonizzi , Rita Carsetti , Anna Maria Castellazzi , Bruno Dallapic...

Early-life gut microbiota under physiological and pathological conditions: The central role of combined meta-omics-based approaches

Journal of Proteomics Volume 75, Issue 15 2012 4580 - 4587

Some number to be considered



Human body 10^{13} cells 23,000 genes

Normal flora 10^{14} microbial cells on the human body. 3.3 million genes

Amount of bacteria per gram of cellular component

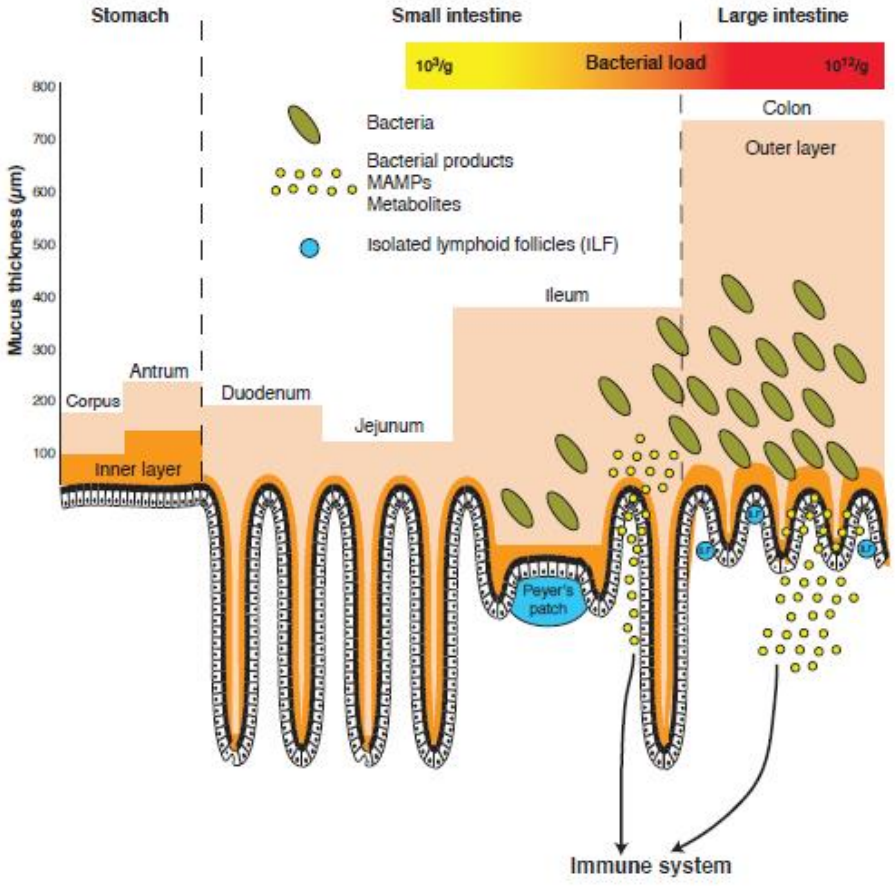
- Stomach– 10^1 to 10^2 cells
- Duodenum– 10^3 cells
- Jejunum– 10^4 cells
- Ileum 10^4 to 10^7 cells
- Proximal colon 10^{10} to 10^{11} cells
- Transverse colon 10^{11} to 10^{12} cells
- Distal colon $>10^{12}$ cells

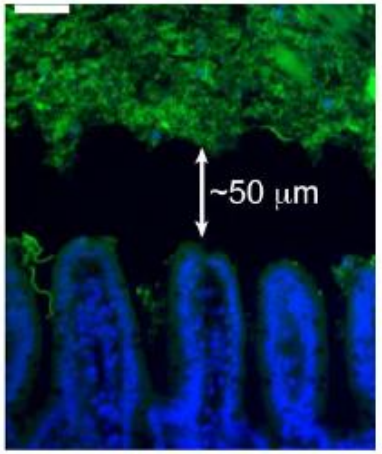
"the microbiota can be viewed as a metabolic organ exquisitely tuned to our physiology that performs function we have not had to evolve on our own"

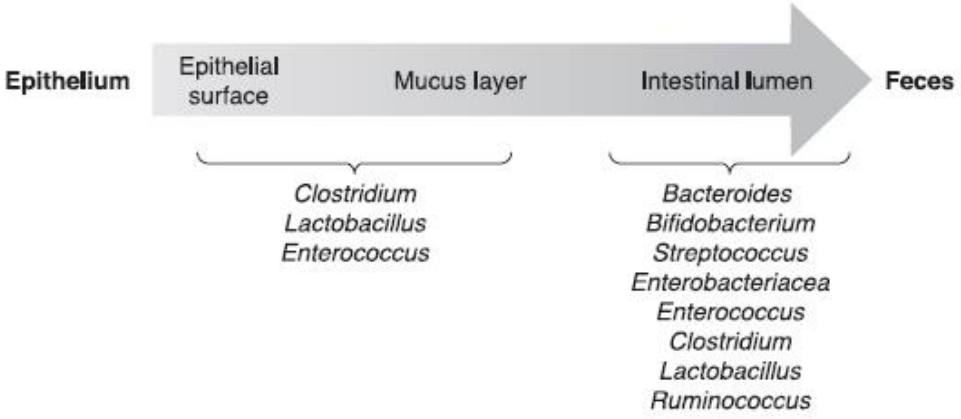
Backhed et al. 2004. PNAS 101:15718-15723

FIGURE 1: The Human Body and number of bacteria present in the total microflora.

Gut microbiota: where



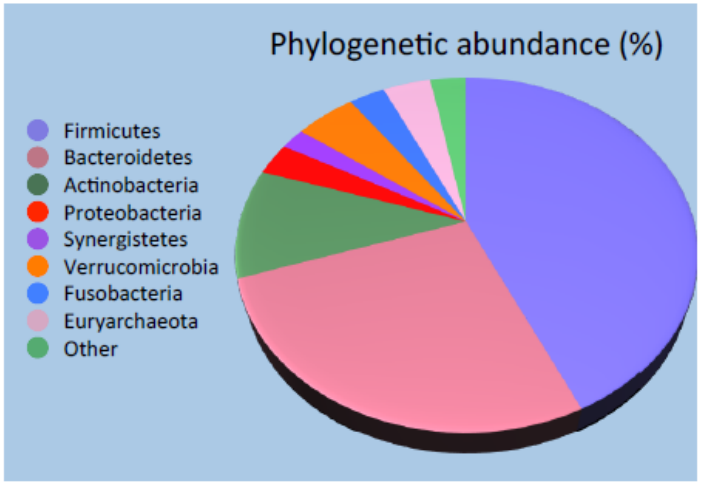


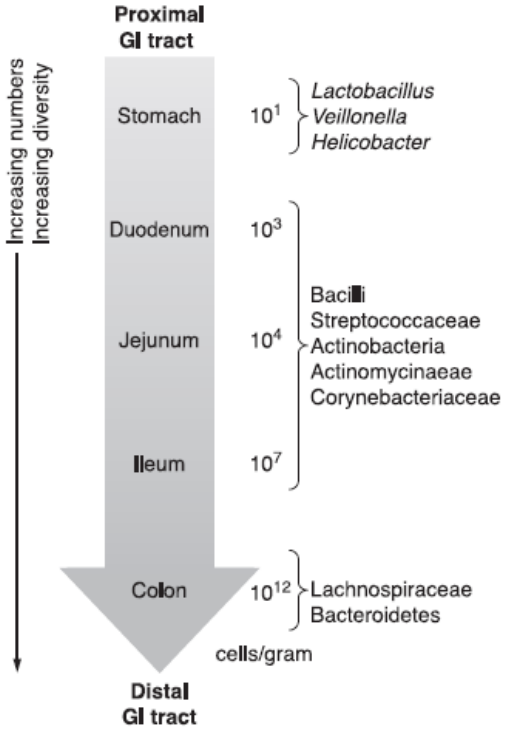


Gut microbiota: composition

- All mucosal surfaces are colonised with bacteria
- The intestine is a preferred site – over 70% of all bacteria are found in the **colon**

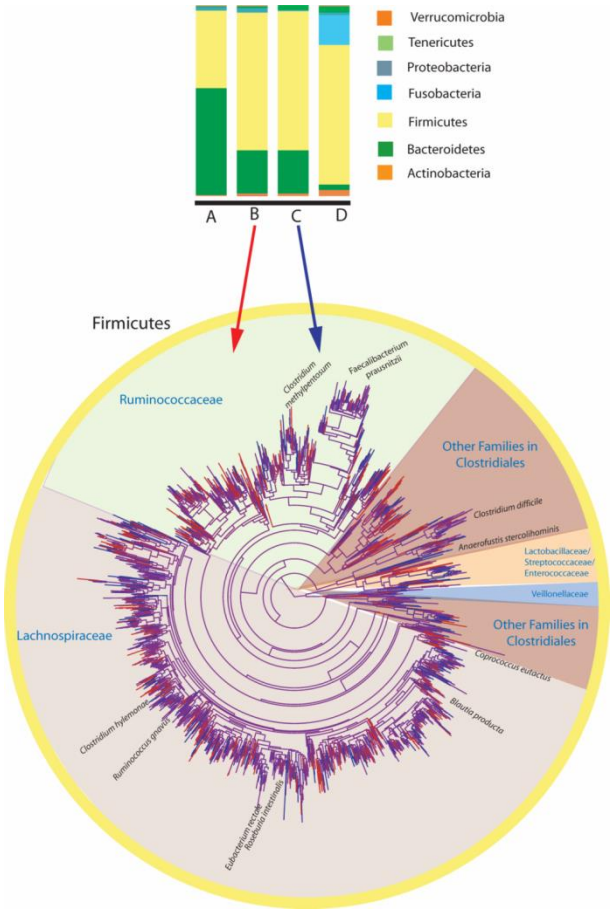
large organ
rich in nutrients

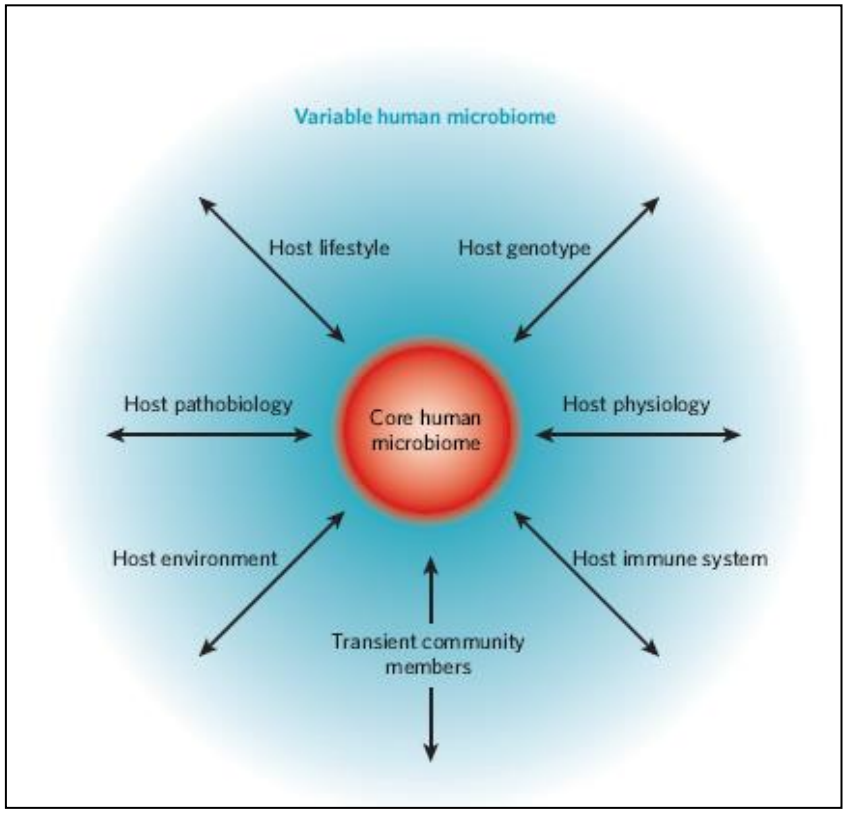




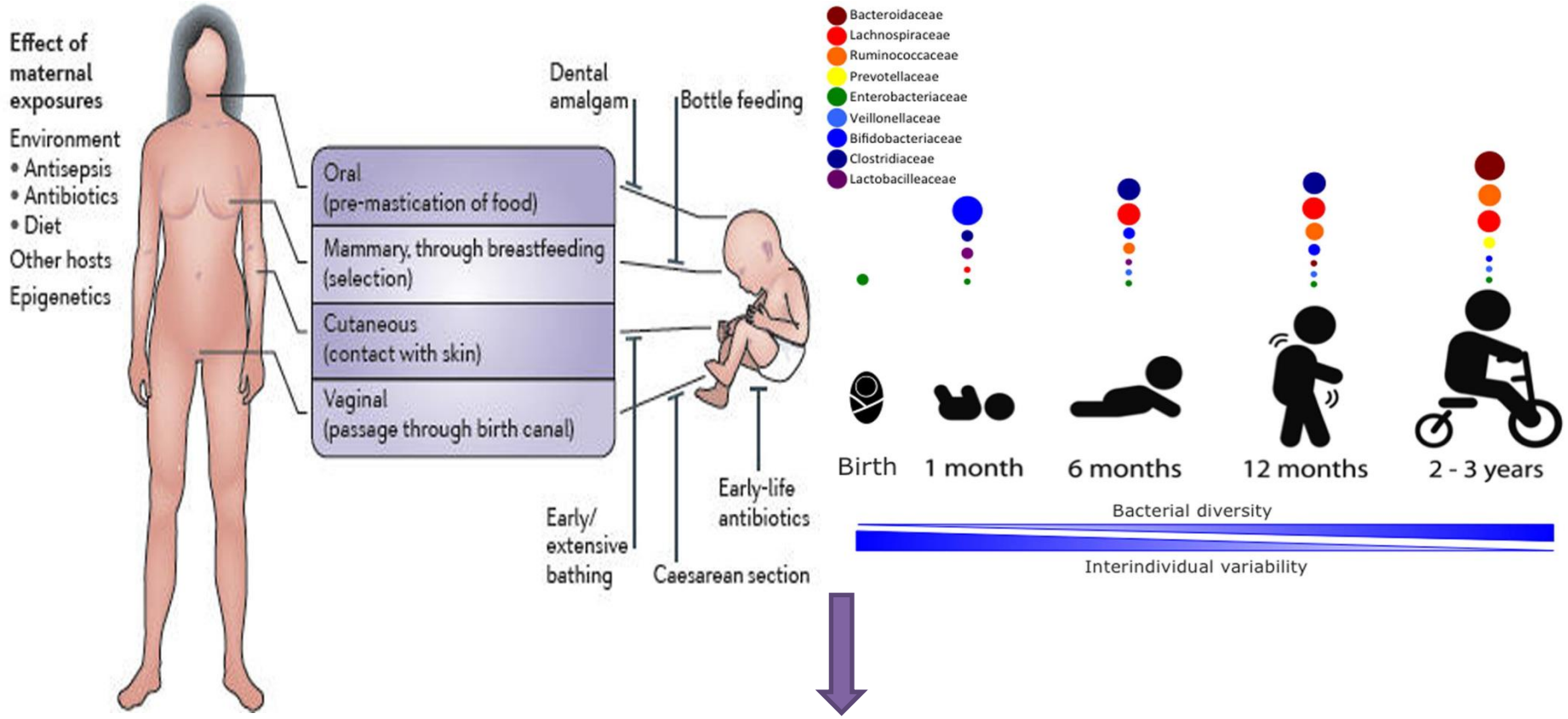
Bacteria increase in number and composition changes from proximal to distal GI tract

The microbiota of each individual has a specific "bacteria fingerprint",a profile of its own species which is different from other individuals; nevertheless, there exists a core of at least 57 bacterial species that can be considered common to all humans.





Gut microbiota – the beginning



Initial exposure occurs during passage through birth canal
During first year of life, heavily influenced by mother and environment

Diet and the development of the human intestinal microbiome

*Noah Voreades, Anne Kozil and Tiffany L. Weir**

Department of Food Science and Human Nutrition, Colorado State University, Fort Collins, CO, USA

frontiers in MICROBIOLOGY

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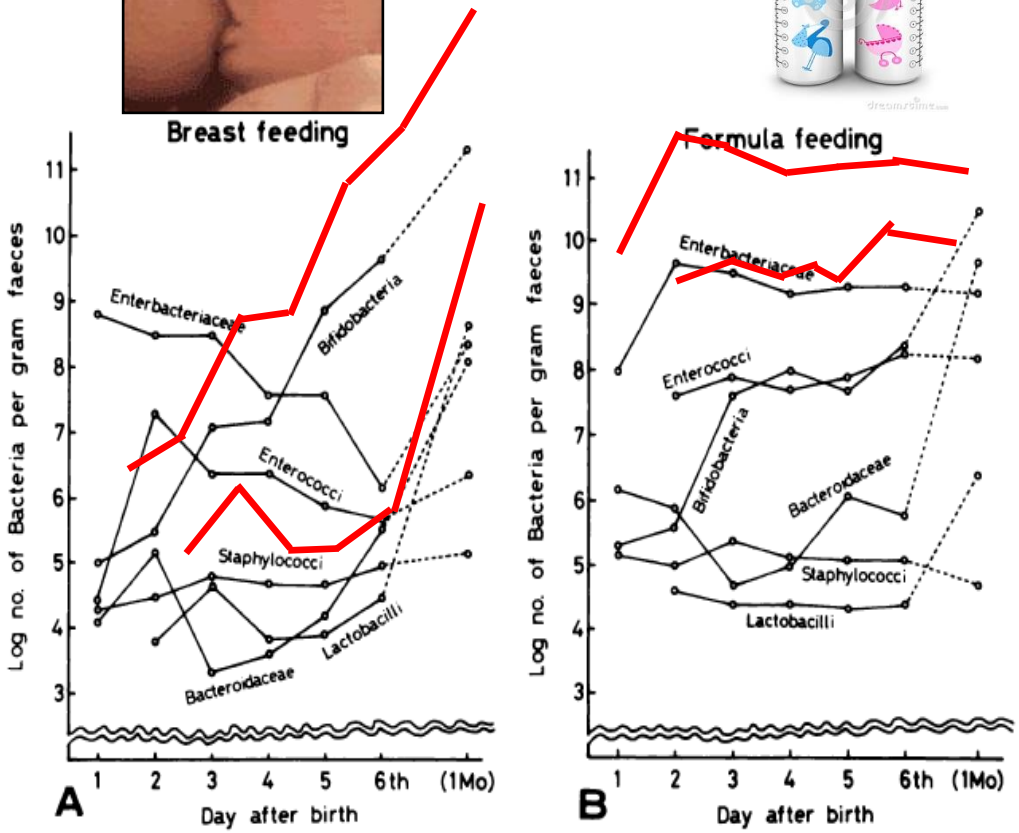
1° shift **2° shift** **3° shift**

0-9 Months (Newborn)		9-18 Months (Infant-Pre-Toddler)	18-36 Months (Toddler)
Breast-Fed Characteristics (BF) • Low Species Diversity • Bacterial Composition Flux • Major Phyla: *Actinobacteria & Firmicutes*	**Formula-Fed Characteristics (FF)** • Low Species Diversity • Bacterial Composition Flux • Major Phyla: *Actinobacteria & Bacteriodetes*	**Introduction of Weaning & Solid Food** • Increased Species Diversity • Bacterial Composition Flux Persists • Increasing Butyrate Producing Bacteria • Major Phyla: *Bacteriodetes & Firmicutes*	**Diet-Influenced Microbiome Profile** • Stable Gut Microbiome Formation • Increased Species Diversity • Breast-Feeding History Ceases To Impact Gut Microbiome Profile • Increasing Butyrate Producing Bacteria Abundance • Dietary Intake Strongly Influences Abundances (*Prevotella* vs *Firmicutes*) • Major Phyla: *Bacteriodetes & Firmicutes*

FIGURE 1 | Representation of the infant gut microbiome development from birth to 3 years of age. By 3 years old, toddler's microbiomes are similar to that in adults and long-term dietary patterns are beginning to establish.

Development and Differences of Intestinal Flora in the Neonatal Period in Breast-Fed and Bottle-Fed Infants



Formula fed newborns

- Bacteroides
- Bifidobacteria
- Clostridium
- Enterobacteria

Breastfed newborns

- Bifidobacteria
- E. Coli
- Streptococcus

PEDIATRICS Vol. 72 No. 3 September 1983

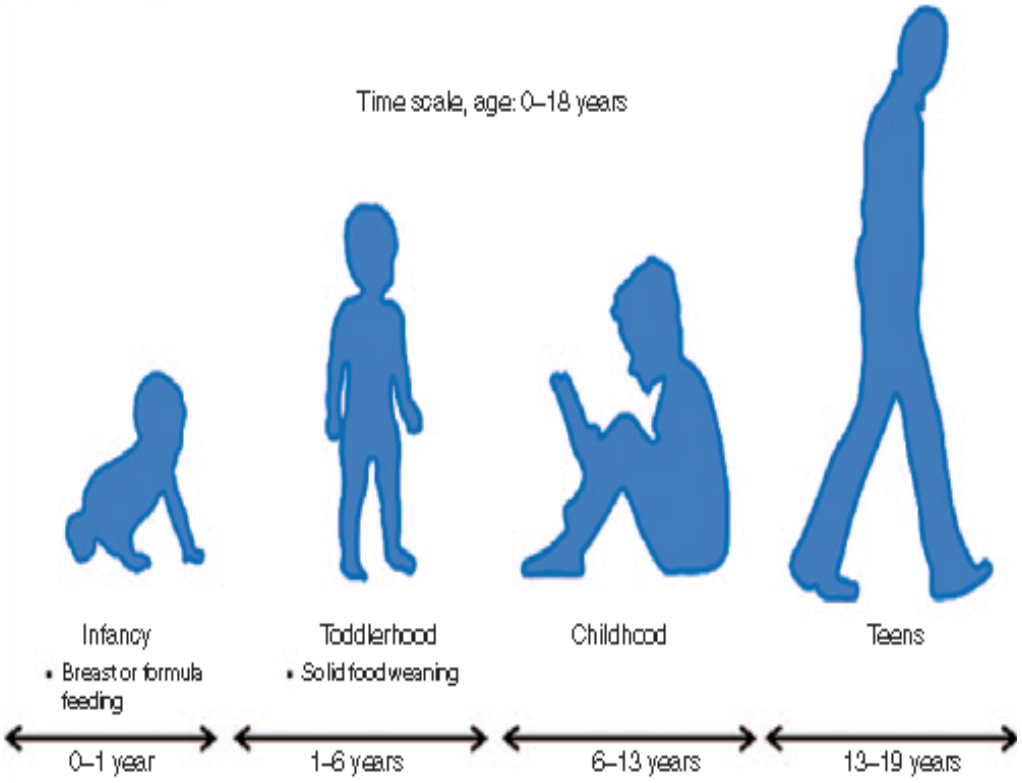
Dinamic development of intestinal microbiota

Microbiota determination at birth

Microbial colonization begins with birth.

Maternal factors: intrapartum antibiotics, mode of delivery (natural or cesarean delivery)

Feeding: Breastfeeding, formula feeding, mixed.



Adulthood

High inter - individual variability

unique and unrepeatable for each individual

Quite stable composition

influenced by several environmental factors such as nutrition, antibiotics, stress and lifestyle

Infancy and adolescence: great variations into microbioma

Determined by nutrition, immune system development, puberal develompent, lifestyle

Intestinal colonization in the development of immune tolerance

• Early intestinal colonization is peculiar for the establishment and mantaing of the so called **IMMUNE TOLERANCE, which is necessary for immune-mediated pathologies prevention.**

• The lack of immune tolerance development in the early months of life and / or the loss of immune tolerance in later periods predisposes to the onset of **ALLERGIC OR AUTOIMMUNE DISEASES.**

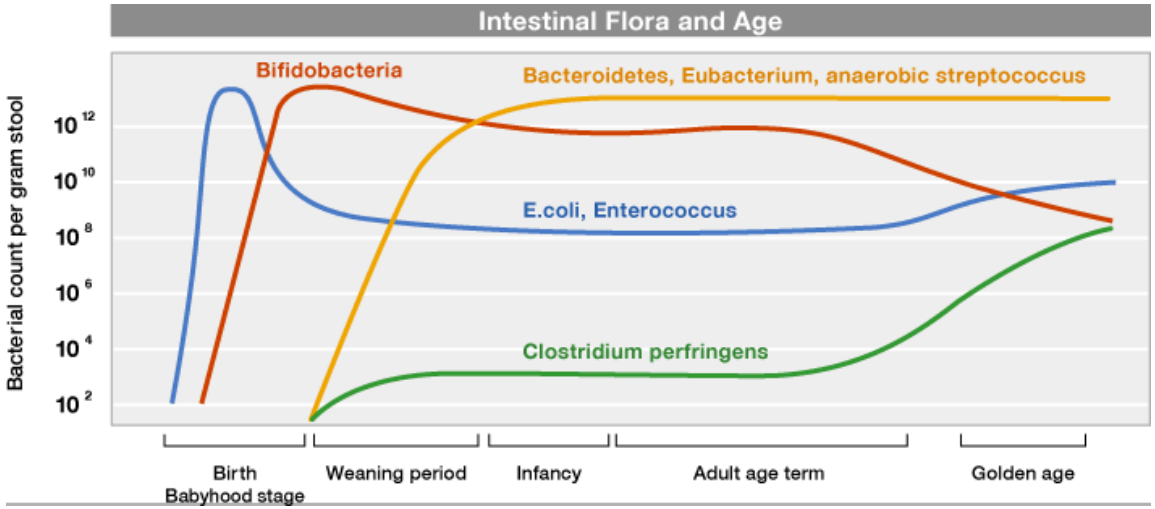
• **SPECIFIC BACTERIA** can contribute to immune tolerance establishment :

-***Bacteroides fragilis*** **e** ***Clostridia*****:** can favor the proliferation of **regulatory T lynphocytes** into intestinal mucosa lamina propria.

Walker et al. Breast milk, microbiota, and intestinal immune homeostasis. Pedaitric RESEARCH. 2015; 77 (1): 220-228.

Gut microbiota changes during life

The “adult” composition of the intestinal microbiota is reached one year of life and tends to remain stable throughout life

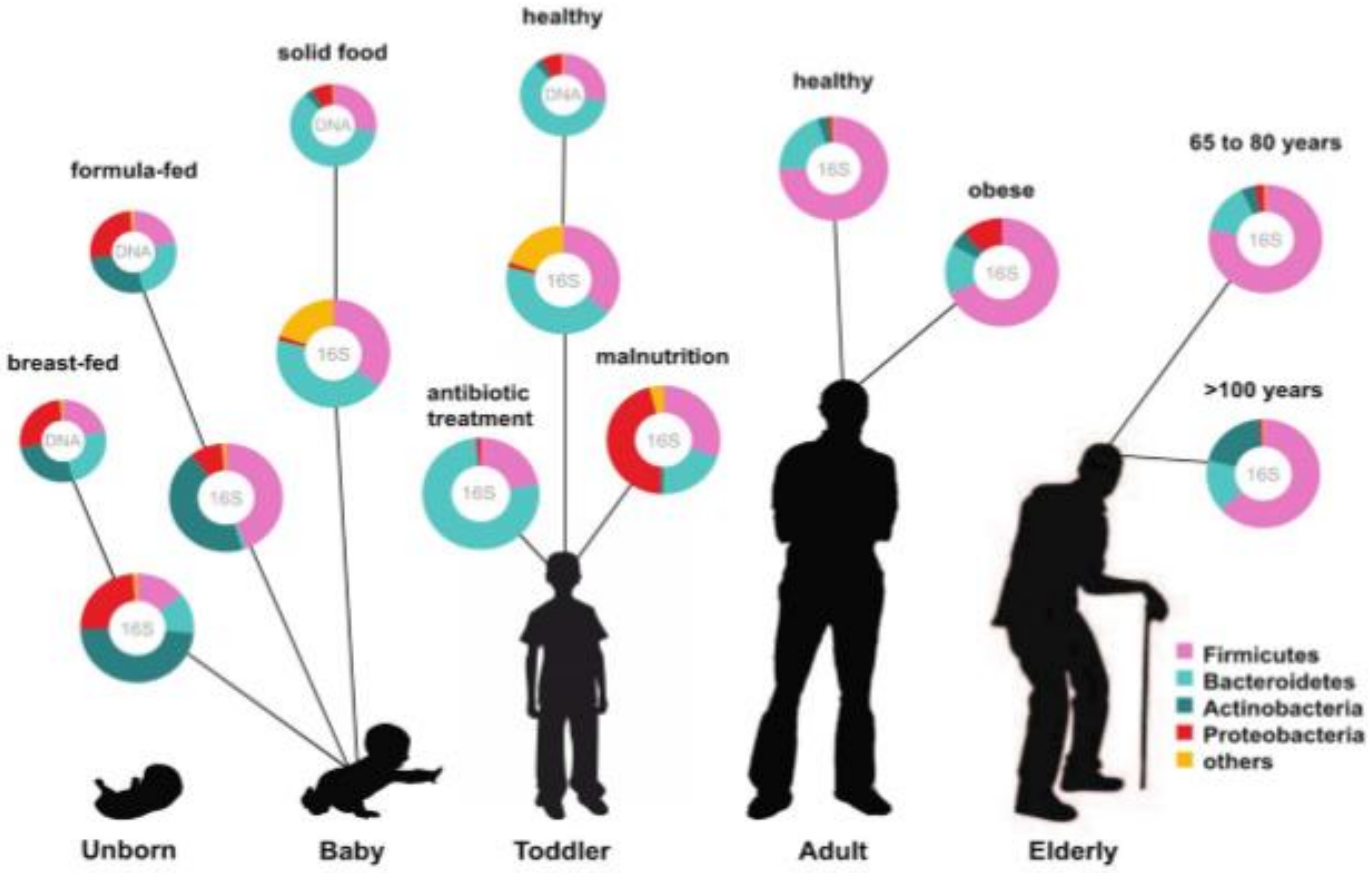


Literature regarding composition of the elderly intestinal microbiota is very varied and makes it difficult to define a " **threshold age**" in which the intestinal environment begins to be really **affected by the aging process**

Bacterial cells in the gut do not age per se, but people growing older may begin to experience comorbidities associated with the gut and with gut bacteria.

So the question naturally arises as to how the microbiota in the human gut might affect the aging process, or if the gut microbiota simply changes as a function of age.

Gut microbiota changes during life



Ottmann N et al. Front Cell Infect Microb 2012

Changes in the composition and structure of the intestinal microbiota may be related to conditions typical of old age:

- Fragility
- Immunosenescence
- Metabolic syndrome
- Diabetes
- Sarcopenia

Bacteroides and ***Firmicutes*** are the dominant phyla and the relationship between these two groups of bacteria could be considered an information parameter of the general state of the intestinal microbiota.

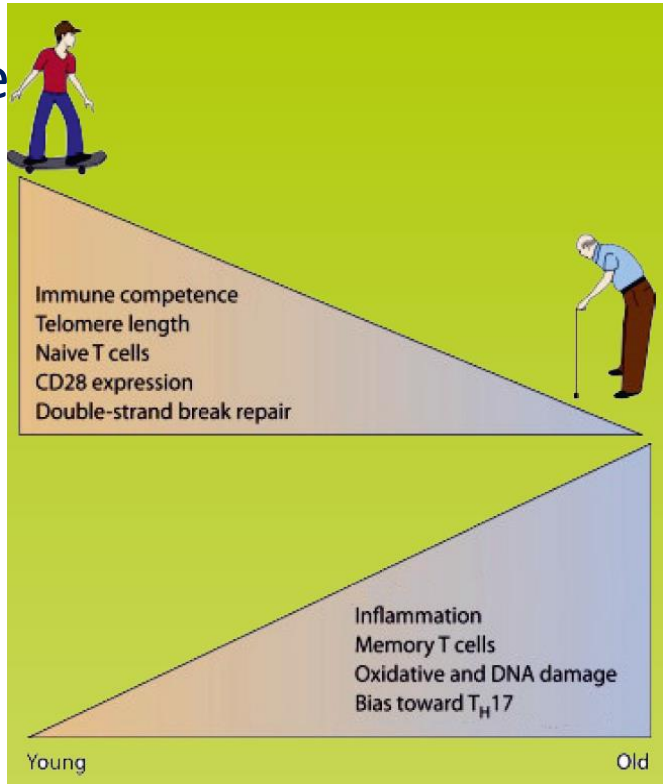
Firmicutes / Bacteroides is lower in the elderly (70-90 years) than in younger adults (Mariat et al, 2009)

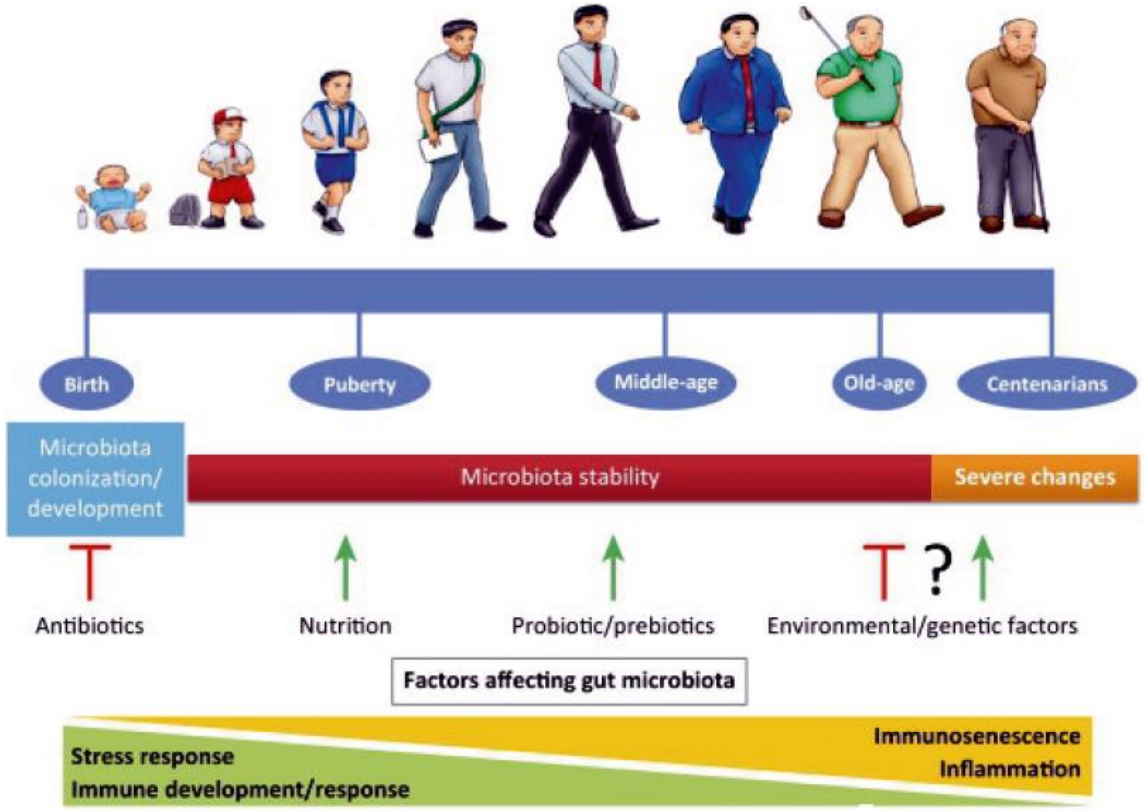
In the elderly, there is an **increase** in facultative anaerobes species:

- *Streptococci*
- *Staphylococci*
- *Enterococci*
- *Enterobacteria*: include potentially pathogenic species that can grow abundantly in case of inflammation and which may cause infections.

The fragility of the elderly microbiota increase significantly in the presence of the following **factors**:

Physiological Changes
Diet
Diseases
Drugs
Lifestyles





In the elderly , the immune system function is reduced due to "**IMMUNOSENESCENCE**" and the body is characterized by **low-grade chronic inflammatory (inflammaging**).
Persistent inflammation in the GI mucosa may help the onset of systemic inflammation correlated with no GI disease.

Elderly gut microbiota: disturbing factors

Physiological changes: In the elderly , increases the threshold of perception of flavors and odors , masticatory function and masticatory muscle strength decrease due to the loss of teeth, leading to **a restricted diet , little varied and nutritionally unbalanced**. The decay of motor functions and digestive GI results in **malabsorption of nutrients and vitamins**

Nutritional defects: toghter with tissues weakness contribute to the onset of inflammation in the presence of symbiotic microflora,
Pathogens: thanks to the weakness of the SI and the chronic inflammatory state , they can grow in number and feed the inflammatory process in a sort of vicious circle.

Elderly gut microbiota

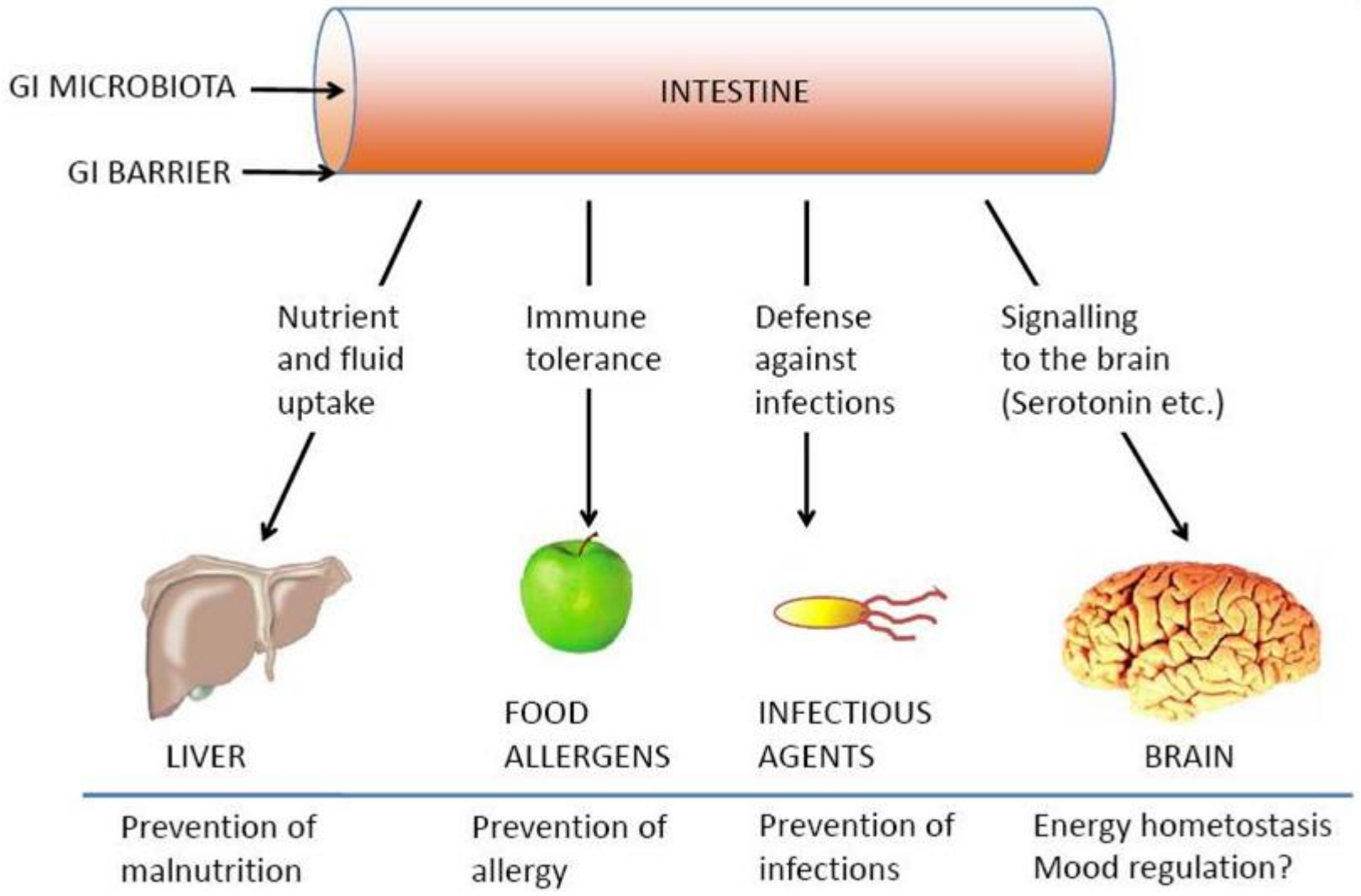
The maintenance of an " **healthy** " intestinal microflora during aging can prevent the inflammatory processes

Some bacterial species such ***as Faecalibacterium, Bifidobacterium, Lactobacillus*** are able to:

- Suppress the pro - inflammatory response,
- Prevent the transcription of pro- inflammatory genes
- Prevent the production of cytokines such as TNF-α, IL - 6 and IL – 8

On the other hand ***Enterobacteriaceae*** and other gram-negative bacteria are responsible for the increase of endotoxins that stimulate an inflammatory response

Gut microbiota contributions to host physiology



How to help host physiology: PROBIOTICS

World Health Organization DEFINITION

"live microorganisms which when administered in adequate amounts confer a health benefit to the host"

A bacterial strain that:

- Survives the stomach acid and bile
- Adheres to intestinal lining
- Grows and establishes temporary residence in the intestines
- Imparts health benefits

R Fuller. Probiotics: The Scientific Basis. London: Chapman and Halls. 1992

PROBIOTICS

- *Lactobacillus* sp.
  - *reuteri*
  - *casei*
  - *ramnosus*
  - *Acidophilus*

- *Streptococcus* sp.

- *Bifidobacterium* sp.
  - *infantis*
  - *lactis*
  - *longum*
  - *breve*
  - *bifidum*

PROBIOTICS: proposed mechanisms

- Adherence and subsequent stimulation of gut immune system
  - Up-regulation of mucin gene
  - Enhance secretory IgA
  - Maintain normal macrophage function
- Competition for essential nutrients
- Production of antimicrobial factors
- Provide favorable environment for growth of other beneficial bacteria
- Production of short-chain fatty acids with anti-inflammatory properties

Diverse Targets for Probiotics

Gut function
- ✓Acute diarrhea
- ✓AAD, travelers diarrhea
- ✓C. difficile
- ✓Lactose digestion
- ✓IBS symptoms
- ✓Colic
- ✓Inflammatory bowel conditions
- ✓Gut pain sensation

Allergy
- ✓Atopic dermatitis
- ✓Asthma

Encompassing effects
- •Growth parameters of undernourished children
- •Reduced absences from work, daycare
- •QOL

Colds, respiratory infections

Skin microbiology, inflammation

Oral microbiology
- ✓Dental caries

Metabolic syndrome
- ✓Obesity, Diabetes

Vaginal infections

Thanks for the attention