**Gut microbiota and aging**

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**Abstract.** – The hypothesis of an important role of gut microbiota in maintaining physiological state into the gastrointestinal (GI) system is supported by qualitative and quantitative alteration of the intestinal flora in a number of physiological and pathological condition as shown in several studies. The evidence of the inflammatory state alteration, highlighted in neurodegenerative diseases such as Parkinson’s and Alzheimer’s strongly recalls the microbiota disturbance, highly suggesting a link between the gastrointestinal system and cognitive functions. Given this perspective, looking at the mutual influence between microbiota products, inflammation mediators and immune system, the modulation of gut microbiota may help to facilitate a physiological and non-pathological aging process and, perhaps, to contrast the progression of degenerating mechanisms. Some studies have already characterized gut microbiota in elderly, with promising results. Future studies should be designed to better understand the correlation between the gut microbiota, the ageing process and degenerative diseases typical of the elderly.

**Key Words:**

**Introduction**

Human beings are superorganism, consisting in host cells and microbes. The intestine houses most of these microorganisms that are called “gut microbiota” and include more than 15000 kinds of bacteria, for a weight equal to 1 kg.

Two bacterial phyla, *Firmicutes* and *Bacteroidetes*, are the most represented microorganisms within the human gut microbiota, but it is also possible to recognize Archaea, Eukaryotes, Fungi, and many viruses and bacteriophages.

At present, our knowledge mainly concerns the sphere of bacteria, which will then be mostly considered in our discussion.

The microbiota is also composed by fungi and viruses. The composition of this microbial populations has not yet well characterized as the bacterial population, even if numerous studies have been conducted in *in vivo* and *in vitro* models. Furthermore, it has been demonstrated a predominance of the taxa of the genus *Candida* with about 160 species, with particular abundance of *C. albicans*, *C. glabrata* and *C. parapsilosis*.

The gut microbiota changes markedly from the duodenum to the ileum, and the microbial load increases further up to $10^{12}$ germs within the colon. This is due to the increase in pH, gastrointestinal transit, availability of nutrients, mucin secretion, immune function, host’s age and health.

The functions exerted by the gut microbiota are varied. It promotes the constitution of intestinal barrier and its maintenance through the production of short chain fatty acids (SCFAs); these molecules exert a trophic action on enterocytes and stimulate mucus production. The gut microbiota is also involved in the immune system priming, as it triggers innate immune response in early life leading to maturation of gut-associated lymphoid tissue (GALT) and shaping adaptive local and systemic immunity.

In adult life, the immune system is continuously kept under stimulation by gut microbiota, leading to a state of “low-grade physiological inflammation”, which is a rapid and effective mechanism of defense against pathogens. Also, the gut flora exerts its protective role competitively metabolizing those nutrients necessary for survival of pathogens, and producing molecules that inhibit the growth of these microbes.

The confirmation of the key role of the gut microbiota in the maintenance of host health is supported by several studies that correlate its qualitative and quantitative alterations with various gastrointestinal and systemic disorders. Nevertheless, it is not surprising that changes in the gut microbiota have been asso-
Associated with physiological conditions, such as aging, characterized by a reduced performance of the human organism.

**Aging as an Inflammatory Condition**

Aging is defined as a genetically-determined and environmental-modulated process that leads to a generalized decline of physiological functions. The gastrointestinal tract is involved in this process, undergoing degeneration of the enteric nervous system (ENS), alteration of intestinal motility and of the mucosal barrier with relative reduction of the defense function, favoring the development of gastrointestinal pathologies. The alteration of these functions is associated with the change of the gut microbiota with consequences on the gut-brain axis.

Immunosenescence, defined as a deterioration of the immune system, plays a key role in the aging process. Through this mechanism, the establishment of a state of basal inflammatory activity seems to be correlated with both morbidity and mortality in the elderly people, being a major risk factor for most of the age-associated pathologies. The term “inflammaging” has been first coined by Franceschi et al. to describe a low-grade pro-inflammatory state characteristic of the aging process. Macrophages, cellular stress and genetic factors are the mainly involved mediators (Figure 1).

This pro-inflammatory state is characterized by the increased expression of cytokines such as IL-6 and TNF-α, and the activation of transcription factors such as NF-kB. This condition has been hypothesized to predispose the organism to the development of various diseases related to age, such as Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, multiple sclerosis, atherosclerosis, heart disease, age-related macular degeneration, insulin resistance and type 2 diabetes, osteoporosis, cancer and other diseases. Conversely, centenarians show high levels of both pro- and anti-inflammatory mediators that may delay disease onset.

This low-grade inflammation also induces an anti-inflammatory response sustained by cortisol, which elicits insulin resistance and

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*Figure 1.* The inflammaging process in the elderly is associated with decline in physical and cognitive functions. The gut microbiota is involved in this process through the modulation of the immune system and brain function.
hepatic production of hormone-binding proteins, including cortisol binding globulin. This process results in cortisol inactivation and in the vanishing of the anti-inflammatory process due to the paradoxical coexistence of immunodeficiency and inflammation. Over time, the anti-inflammatory response causes a marked reduction of immunological functions; this condition and the concomitant increase of circulating pro-inflammatory cytokines have a negative impact on metabolism, bone density, strength, exercise tolerance, vascular system, cognitive function, and mood, resulting in the inflamming process.

**Gut Microbiota and Aging**

Microbial colonization of the human body begins before birth, and increases after delivery when the baby comes in contact with several microbial communities, including mother fecal, vaginal and skin microbiota. Then, the composition of the gut microbiota is influenced by age, sex, development of the immune system and environmental factors, becoming more stable between 6 and 36 months of age. Thereafter, it is possible to distinguish a constant endogenous flora, which is considered the “core microbiota”, and bacteria that are still provisional, highly sensitive to external perturbations.

The age-related changes of the intestinal flora begin after a genetically and environmental determined age, depending on individual characteristics related to race and ethnicity, drugs, life style and diet habits. Most of the members of the genus *Firmicutes* and *Bacteroidetes* remain dominant, although *Firmicutes* microorganisms are predominant in adults, and *Bacteroidetes* in the elderly. What mostly characterizes the gut microbiota composition in the elderly is a decreased diversity, a reduced abundance of species producing butyrate, and the presence of potential pathogens in the centenarian.

The production of SCFAs has been regarded as a central point in the relationship between the host and the gut microbiota, explaining the correlation between alteration of the flora and frailty in the elderly. Moreover, SCFAs have systemic actions, such as the modulation of intestinal transit time and insulin response, which is closely related to the metabolic syndrome.

Such characteristics of these compounds are permitted by the ability to influence cell proliferation and differentiation and hormone production. This has been demonstrated also in colon cancer cell lines, where they have been shown to induce cell death by inhibiting histone deacetylase. This feature of SCFA explains their role in modulating the immune response by inhibiting the production of inflammatory mediators such as TNF-α, IL-6, and NO or by promoting IL-10 production.

Biagi et al. reported the gut microbiota of the elderly has a peculiar composition. This study has been conducted in a restricted area of Italy, comparing four groups: 21 subjects aged 99 to 104 years, 22 aged 63 to 76, 20 aged 25 to 40 years and finally 21 offsprings of centenarians aged 59 to 78.

Results showed that bacterial diversity is low: in particular, *Bacteroidetes* and *Firmicutes* still dominate the gut microbiota of extremely old people, but the relative proportion of *Firmicutes* subgroups changes: *Clostridium cluster XIVa* is decreased, whereas an increase in *Bacilli* and a rearrangement of the *Clostridium cluster IV* have been observed. Moreover, the gut microbiota of centenarians is enriched in *Proteobacteria*, a phylum including many pathobionts, or potentially pathogenic bacteria, while several butyrate producers can be found in lower amounts (*Ruminococcus obeum, Roseburia intestinalis, Eubacterium ventriosum, Eubacterium rectale, Eubacterium hallii*), all belonging *Clostridium cluster XIVa*, *Papillibacter cinnamovorans* and *Faecalibacterium prausnitzii* of the *Clostridium cluster IV*). Interestingly, *Faecalibacterium prausnitzii* is a species protective against gut inflammation. Conversely, the butyrate producers *Anaerotruncus colihominis* (*Clostridium cluster IV*), and *Eubacterium limosum* (*Clostridium cluster XV*) increase. This probably suggests that specific components of the gut microbiota are characteristic of the long life. A decrease in Bifidobacteria and increased levels of the mucin degrading *Akkermansia muciniphila* have also been detected in aged people compared to the young adults. As already discussed, the study also included a group of offsprings of the centenarian patients. Although the overall structure of the gut microbiota was similar to that of other subjects...
of matching age (70 years-old in average), those offsprings who lived in the same house with their centenarian parent showed an increased occurrence of opportunistic or potentially pathogenic bacterial groups, with respect to those who did not share the living environment with their old parent. Therefore, co-housing can influence the composition of the gut microbiota in these subjects.

Factors Affecting the Gut Microbiota in the Elderly

Diet is one of the most well-known factors potentially able to change the composition of the intestinal microbiota and this has been confirmed in old subjects\(^69,60-67\). With aging, the diet undergoes drastic changes that can be attributed to the loss of taste and smell and difficulty in chewing. These conditions often lead to prefer foods rich in sugars and fats, reducing the intake of foods of plant origin\(^68\). Recently, the Healthy Food Diversity (HFD)\(^69\), which values healthy foods within diet, has been created. The ELDERMET consortium study confirmed the association between microbial components and a diet with low HFD score\(^70\). Claesson et al\(^70\) observed an association between microbial diversity, the functional independence measure (FIM) and the performance in daily routine activities evaluated according to the Barthel index in elderly people in relation to their condition of stay in community, in day-hospital, in rehabilitation or in long-term residential care. In particular, changes in the dietary habits of the institutionalized elderly with respect to the community dwelling ones were found to affect the gut microbiota composition: a less diverse diet was linked to reduced gut microbiota diversity.

In another work\(^71\), age-related differences in the gut microbiota composition between healthy subjects form different European Countries show a characteristic colonization pattern. This may be associated with country specific dietary habits and lifestyle, thus emphasizing the importance of not generalizing about the gut microbiota structure of subjects from different countries. However, the diet is not the only factor involved in the variation in the composition of the microbiota in the elderly\(^72\). In the research by Claesson et al\(^70\), the decrease in microbial diversity correlated not only with diet but also with increased frailty, inflammatory markers and impaired health parameters. Residence location and antibiotic treatment also had a role in the modulation of gut microbiota. Indeed, among patients on antibiotic treatment, the highest abundance of *Bifidobacteria* was found in the community-dwelling group and the lowest in those in long-term residential care. In the antibiotic-untreated group, *Lactobacilli* were higher in rehabilitation (hospital stay < 6 weeks) as compared to long-stay or community-dwellers. In a study conducted in Ireland on 161 healthy people aged 65 years or more\(^73\), in most subjects the intestinal microbiota was distinct from that of the younger adults, with a composition that appeared dominated by the phylum *Bacteroidetes* followed by the *Firmicutes*, with inverse percentages compared to those found in younger adults. *Faecalibacterium* represented the most abundant genus with a prevalence of 6%, followed by *Ruminococcus, Roseburia* and *Bifidobacterium* (the latter around 0.4%).

These investigations have demonstrated that variability of microbial communities composition in elderly subjects may be due to several factors, such as the increased morbidity associated with age, the use of medications, and lifestyle changes (Figure 2).

Finally, it should be noted that some changes in the bacterial composition are less susceptible to external factors and may probably represent the core features of the gut microbial community in the elderly. Indeed, the decrease of *Ruminococcus* and *Blautia spp.* and of other butyrate-producing microorganisms (*Clostridium cluster XIVa* and *Clostridium cluster IV*) reported across studies in the elderly compared to young subjects seem to be less affected from diet\(^59,70,74\). Another frequent observation is the increasing prevalence of facultative anaerobes such as *Escherichia coli* with aging and inflammation\(^71\). Probably, modifications of the immune system function associated with immunosenescence overcome the variability related to dietary habits in determining these changes\(^50,75,76\).

Gut Microbiota and Inflammaging

Recent evidence\(^77\) suggests a role of the gut microbiota in the induction and maintenance of the inflamming process (Figure 1).

Fransen et al\(^78\) analyzed the effects of transferring the gut microbiota of elderly mice to young germ-free mice on the main lymphopoietic organs such as spleen, lymph nodes and small intestines. An important connection was found between the structure of the gut microbiota and inflamming; in particular the lack of *Akkermansia* and the increased abundance of *TM7* bacteria and Proteobacteria was associated with the
activation of the local and systemic inflammatory response. This gut microbiota structure promoted small intestinal inflammation and the activation of T cells in the systemic compartment.

Inflammaging is correlated with the inflammatory response induced by lipopolysaccharide (LPS), a component of the Gram-negative bacteria wall.

In the colon of elderly mice, the expression of p16, a senescence marker, and of the sterile α-motif domain- and HD domain-containing protein 1 (SAMHD1), a regulator of cells cycle, was increased, as well as the *Firmicutes* to *Bacteroidetes* ratio and levels of circulating LPS; in addition, the nuclear factor kappa B (NF-kB) was activated. The lipopolysaccharide fraction of fecal lysates (LFL) was able to induce the expression of NF-kB and SAMHD1 in Toll-Like Receptor 4 (TLR-4) wild-type mice, but not in TLR-4 deficient mice. Similarly, p16 was induced more potently in TLR-4 wild-type mice than in knock-out mice.

The alteration of inflammatory cytokines associated with changes in the gut microbiota can also module the function of the central nervous system, in particular of microglia. Germ-free mice show altered maturation and global defect of the microglial system; nevertheless, temporary complete or partial gut decontamination can affect microglial function. SCFAs are key regulators of the microglia integrity. This is extremely relevant in the elderly, and contributes to the cognitive decline.

Furthermore, there are some evidences that compounds derived from the gut microbiota, either constituents of bacterial structure or metabolism, entering the bloodstream can activate macrophages to a pro-inflammatory state responsible for atherosclerosis. This process could cause the development of cardiovascular disease as well as vascular dementia.

Hence a modification of the gut microbiome in neurodegenerative disorders has been suggested. Indeed, there is evidence that the modulation
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Gut microbiota plays a key role in biological functions concurring in maintenance of host health. Age-related physiological and non-physiological changes, associated with dietary habits and lifestyle, affect microbial diversity and composition.

Chronic inflammation and changes in gut microbiota profile related to age follow a similar trajectory.

Many works have shown a correlation between the composition of the gut microbiota and cognitive performance, frailty and comorbidity of the elderly.

Given this perspective, the modulation of gut microbiota may help to facilitate a physiological and non-pathological aging process and, perhaps, to contrast the progression of degenerating mechanisms. Currently, available studies on the characterization and modulation of the gut microbiota in other diseases, such as IBS and diabetes, show promising results. It is possible to hypothesize that these interventions may be beneficial in the elderly (Figure 2). In particular, as direct and indirect effects on the immune response can be expected, this could modify the risk of infectious diseases that are frequently observed in the elderly, indirectly reducing hospitalization and long-term care.

However, whether a stable modification of the gut microbiota could be obtained and what its long-term effects on parameters such as frailty and cognitive tests could be still need to be clarified.

Considering the paramount interest of this topic, future researches should be designed to better understand the correlation between the gut microbiota, the ageing process and degenerative diseases typical of the elderly. This should be accompanied by a practical approach in the modulation of the gut microbiota easily applicable in the clinical context.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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