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Microbiota and Aging. A Review and Commentary

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Although there is a consensus that the dominant species that make up the adult microbiota remains unchanged in elderly people, it has been reported that there are significant alterations in the proportion and composition of the different taxa, leading to reduced microbiota diversity, as well as an increase of enteropathogens that may lead to chronic inflammation. The ageing of mucosal immune and motor systems also contributes to these changes. As the individual ages, there is a loss in the number of Peyer's patches, an altered local capacity of T and B cell functions as well as chronic macrophage activation. Also, environment, diet, place of residence and biogeography are regulatory factors of the microbiota. Communication in the gut-brain-axis is regulated by many intermediaries including diverse metabolites of the microbiota. Microbial changes have been observed in several geriatric diseases, like Parkinson's and Alzheimer's. In addition, evidence has shown that individuals with high frailty scores had a significant reduction on *lactobacilli* species when compared to non-frail individuals. Oral microbiota may be also especially important because of the opportunities for access to the brain through the olfactory nerve at the roof of the nose or through the abundant innervations of the oral cavity by the trigeminal and other cranial nerves. Also, there are an increasing number of reports that have suggested potential mechanisms by which the microbiota promote human health span and aging. The study of the microbiota represents an important advance in the understanding of the aging process.

Key Words: Microbiota, Aging, Inmunoinflamatory system, Frailty, Neurodegeneration.

Introduction

The human microbiota can be defined as a highly variable and compartmentalized ecosystem of commensal, symbiotic and pathogenic microorganisms that lives in our body. These populations consist of bacteria, fungi, parasites and archaea, which coevolved with our ancestors over millions of years. Numerous reports show an immense diversity in the human microbiota, depending on body localization, health and disease status, as well as age. In contrast with the genomic variation between humans, which reaches minimal differences, microbiome achieves 80–90% variation between regions of the same person (1,2). Specialized populations are a product of their coevolutionary interactions, which contributes significantly to our physiology, facilitating the provision of nutrients and protection against pathogens (3). In this context, researchers have demonstrated that changes in the composition of the microbiota contribute to the development of diseases and the aging process (4,5).

Despite the high inter-individual variability, determined by height, sex, age, or place of residence, it has been determined that three specific microbial enterotypes (Bacteroides, Prevotella or Ruminococcus) are constants (6). These enterotypes are linked with dietetic pattern (7). In the case of gut microbiota it has been reported that there are around 1500 bacterial species, 10% of which could be present per person (8). In healthy adults approximately 80% of the total gut microbiota is integrated by the phyla Firmicutes and Bacteroidetes (9).

Taking into account the potential of the gut microbiota to affect the health status of individuals, particularly of elderly

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people, the understanding of this field has fundamental relevance and must likely will become one of the most significant current research areas because of its relation with healthy aging, longevity, chronic diseases, and neurodegeneration, among others. Therefore, the aim of this review is to present and analyze the relevant literature regarding the topic, to discuss gaps in knowledge and consider the future of microbiota research in aging.

Microbiota During Life Course

The gut microbiota evolution is determined by the individual's aging process. Despite extensive interpersonal variation as well as its fluctuations over time, several studies have found similar patterns of microbiome's modification associated with both host and environmental factors. Host factors such as genetics, gut senescence and immunesenescence have been involved in the composition of the microbiome (10–12). Gut microbiota may also be influenced by genetic factors through diverse mechanisms, such as biliary secretion, dietary patterns, digestive enzymes, mucosal barrier composition, intestinal immunity and intestinal motility, among others (13). Changes in gut microbiota have also been associated with age related conditions such as chronic inflammation present in frailty and other neurological conditions like Parkinson's and Alzheimer's (14,15).

The gut microbiota development starts at the birth, showing instability and reduced diversity. Environmental factors include the mother's intrauterine microbiota (16) and birth type. In this sense, the infant's microbiota will be more or less diverse depending on the birth method, inducing quick changes. This finding are supported by many studies comparing gut microbiota of babies born by caesarean section or vaginal delivery, showing that the first have less diversity of bacteria, specifically, less *Bifidobacteria* (17,18). As soon as the baby starts feeding, the food source (formula or breast) will also determine the gut microbiota (19). Some argue that microbiota from formula fed babies is characterized by having more pro-inflammatory taxa as well as higher bacterial loads (20). Gut microbiota will remain unstable until the infant is 2–3 years old, and will highly depend on environmental factors such as introduction of solid food, place of residence, antibiotic exposure and genetic host factors (10,21,22). The child's microbiota matures at around three years old when it reaches a more stable composition, as reported in adulthood (9,23) (Figure 1).

The microbiota remains relatively stable throughout adulthood (under healthy conditions). However the ageing process deeply affects the composition of the microbiota, losing diversity, reducing the proportion of beneficial bacteria and changing the dominant species (23). In this sense a direct correlation between bacterial diversity and healthy status of microbiota has been recognized (24,25). Therefore, age-related changes in microbiota induce physiological alterations able to modify immune system homeostasis and inflammatory state that contribute to increased risk of disease and frailty (26–28).

Aged-related Changes in Microbiota

As previously discussed, several studies have focused on the determination of the standard composition of the microbiota in adulthood, however the findings in elderly people has been inconsistent. These results could be explained

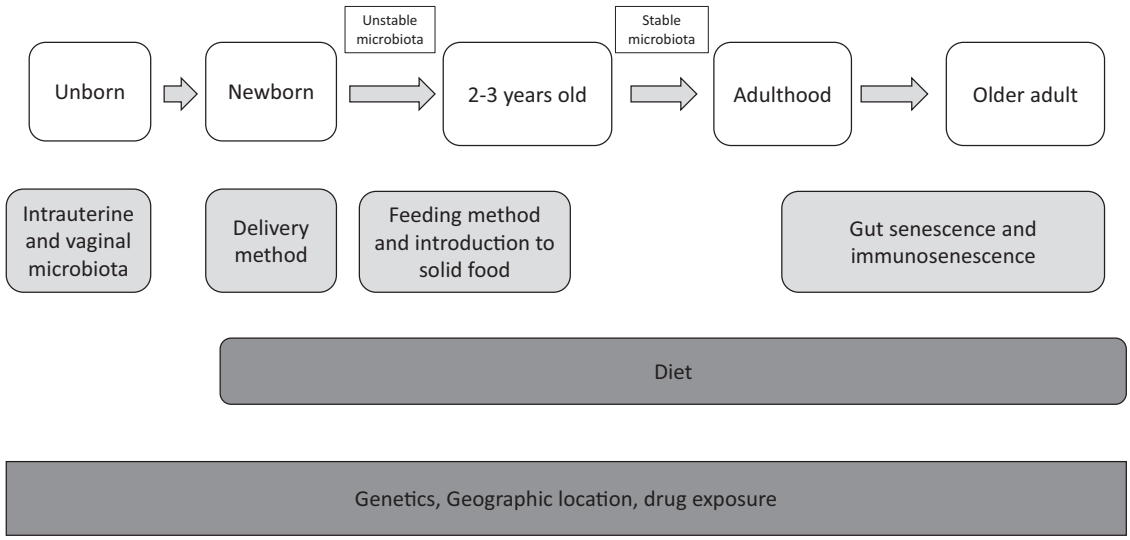

Figure 1. Gut microbiota development.

partially by geographic variation, individual conditions and even by variations in methodological and analysis procedures. Table 1 shows the main differences between the young and elderly gut microbiota composition found by various studies.

Although there is a consensus that dominant species that conform microbiota in elderly people remains unchanged, it has been reported that there are significant alterations in the proportion and composition of the different taxa, leading to a reduce microbiota diversity, as well as an increase on some enteropathogens that may lead to chronic inflammation. There are many comparative studies, which address the age-related differences in gut microbiota along the lifespan. Of these it is worth noting studies which include centenarians. In 2010, Biagi E, et al. reported the microbiota composition at three stages: young adults, elderly and centenarians (33). They found no essential differences between the young and elderly groups, and confirmed Firmicutes and Bacteroidetes as dominant phyla as it had been reported previously (35,36). In contrast, centenarians showed low microbiota diversity, with significantly different composition and enriched presence of Proteobacteria, known as pathobionts bacteria (37). Authors suggest that at approximately 75−80 years old is the group of age at which microbiota changes with aging (33).

In the elderly population associations between the gut microbiota and inflammatory status has been demonstrated (4). However metabolic characterization of centenarians suggests that a complex remodeling of lipid and amino acid metabolism and gut microbiota functionality are determinant processes for longer longevity. This study found that changes in the microbiota of centenarians increases the presence of secondary products of protein and aromatic amino acid catabolism such as phenylacetylglutamine and *p*-cresol sulfate (38), as well as increased levels of 2-Hydroxybenzoate, a compound with anti-inflammatory properties (39). Probably these changes can explain the successful aging process observed in centenarians, and understanding the underlying biological mechanisms may help to promote a healthy aging phenotype.

Ageing of the Mucosal Immune System

The gastrointestinal tract is the body's largest immunologic organ (40). In young individuals Peyer's patches, cryptopatches, and isolated lymphoid follicles work together promoting immune tolerance to commensal microorganisms and food proteins as well as protection against pathogenic agents, leading to intestinal homeostasis (41). In the same way that exposures to certain kind of food and environments help to shapes the elderly's gut microbiota, the ageing of mucosal immune and motor systems also contributes to these changes. As the individual ages, there is a loss on the number of Peyer's patches, an apparently altered local capacity of T and B cell functions as well as chronic macrophage activation (40,42−44). The resulting compromise in innate and adaptive immunity results in lower antigen specific antibody titers and less tolerance to harmless antigens (12,40). It has been suggested that these immune and motility alterations reported at older ages are related

Table 1. Studies comparing microbiota between different age groups

Author	Population	Findings
Hopkins MJ, 2001 (29)	four groups from UK: 10 children, seven adults, five healthy older adults, four older adults with *C. difficile* diarrhea	Older adults with *C. difficile* showed a significant decrease number of *Bifidobacteria* when compared to the other three groups. Older adults showed lower proportion of hybridised bacteria on the *Bacteroides/Prevotella, Enterobacteria* and *bifidobacteria.*
Mueller S, 2006 (30)	France, Italy, Germany and Sweden two groups: young adults (mean age 35), and older adults (mean age 75)	There are age related differences in the composition of an individual's microbiota, but they differ country to country.
Mariat D, 2009 (31)	Infants, adults and older adults	Infants showed inferior bacterial counts. Older adults had higher counts of *E. Coli* and *Bacteroidetes*. The ratio *firmicutes/bacteroidetes* peaks in adulthood and decreases as the individual ages.
Zwielehner J, 2009 (32)	Institutionalized elderly and younger adults	High individual variations, with a decrease in the diversity of institutionalized elderly
Biagi E, 2010 (33)	Young adults (20−40 years), elderly (60−80 years), and centenarians.	Young and elderly showed similar composition with dominant *Bacteroidetes* and *firmicutes* and similar diversity values. Centenarians seem to have a remodeled microbiota, with higher counts of *pathobionts* and rearrangement in the *firmicutes* group. This group also showed a decrease in the proportion of *faecalibacterium prauznitzii* and higher *eubacterium limosum*
Claesson MJ, 2012 (34)	Older adults (64−102 years)	Individuals microbiota of people in long-stay care was significantly less diverse that community dwellers. Data indicate a role for diet-driven microbiota alterations

to an increased bacterial growth. Both pathological bacterial growth and chronic activation of macrophages are secondary events related to the levels of advanced glycation end products and reactive oxygen species that increase during cellular senescence, leading to a chronic inflammation state (45). Chronic inflammation plays a critical role in age related chronic conditions, such as cardiovascular disease, diabetes, cancer, frailty, as well as Alzheimer or Parkinson (40,42,46–48). Recent evidence shows that changes in gut microbiota through probiotics treatment may in fact reduce chronic inflammation (49–51). Some reports suggest that probiotics may increase bacterial growth and restore the microecology, normalizing mucosal permeability (52). It has also been suggest that probiotics may act as immunomodulators (53), however the anti-inflammatory effect depends on the specific bacterial taxa (54,55). In this sense, further studies are needed for the development of diets and nutritional supplements with preventive and therapeutic capacities.

Regulatory Factors of the Microbiota in the Elderly

Diet. It has been well documented that diet is a critical modulator of microbiota composition. The gut microbiota of vegetarians differs from population whose dietary habits are characterized by high consumption of animal proteins (56). Also, caloric restriction diets which lengthens lifespan in various animal models, significantly changes the overall structure of the gut microbiota. This kind of diet significantly increase the population of beneficial phylotypes which are positively correlated with raising lifespan, and in contrast shows a reduction in harmful bacteria such as opportunistic pathogens, which affect negatively the lifespan (57). The caloric restriction-induced microbiota causes also reduced serum levels of lipopolysaccharide and antigen load from the gut, promoting an anti-inflammatory state.

Other studies have addressed the effect of diet changes on microbiota composition and its relation with aging. Young and middle-aged rats were subjected to a protein-enriched diet, and significant differences between normal and enriched diet group at both ages were observed. Interestingly, protein-enriched diet induced in the young group an increase in the phyla Firmicutes and a reduction in the Bacteroides, while middle-aged group had the opposite effect. Reduction of *Lactobacillus* (which may reduce the antigen load and inflammatory response) in middle-aged group may affect host health (58). The difference between age groups can be explained by changes in the capacities of protein digestion and absorption (59).

Place of Residence. Additional to the differences at the microbiota along the aging process, a cross-sectional study performed in four different European populations conclude that the geographical affiliation act as a driving force able to generate differences in microbiota composition (30). Furthermore, significant differences in microbiota have been detected in rural elderly compared to urban elderly people (60). Geographical differences in microbiota composition have also been noted in research studies of wild type mice (61).

Body Localization (Biogeography). In 2009, Costello EEK, et al. performed a detailed study to obtain an integrated view of the spatial and temporal distribution of the human microbiota (62). The authors propose that the description of the ‘‘biogeography’’ of bacterial communities on the human body help to establish healthy baselines and detect associative differences within diseases. They found a large inter-individual variation across all body niches (stool, oral cavity, nostrils, external auditory canal, hair on head, and a variety of skin sites). Most bacteria belonged to four phyla: Firmicutes, Actinobacteria, Proteobacteria, and Bacteroidetes. Within each niche there were specific compositions of microbiota determinated by local environment necessities (1,62,63).

Microbiota and Geriatric Syndromes

Neurodegeneration and mental disorders. Interest in the relationship between gut microbiota and brain is a relatively recent field. The term ‘‘gut-brain-axis’’ has been used to describe its bidirectional interactions, which is involved in maintaining homeostasis (64). The role of microbiota on the regulation of this axis is a critical aspect for physiological processes like neurodevelopment or age-related neurodegenerative disorders (65). Modification on microbiota composition as a result of environmental influences, antibiotic exposure, infection or stress, can induce long-term effects on physiology and behavior of the individual. An altered microbiota has been implicated in a variety of disorders, including depression, autism, schizophrenia, Alzheimer’s disease or Parkinson’s disease.

Communication in the gut-brain-axis is regulated by many intermediaries such as the immune system, the vagus nerve, gut hormonal signaling, amino acid metabolism and the microbiota’s metabolites (66,67). The microbiota can also alter the levels of neurotransmitter precursors and regulates the synthesis and release of serotonin, dopamine, acetylcholine, norepinephrine and GABA (68–70). Events like psychological or physical stress can significantly dysregulate the gut-brain-axis through the action of the hypothalamic-pituitary-adrenal axis, which regulates the stress response (71,72); an example of this pathological condition is irritable bowel syndrome (73,74).

The contribution of the microbiota to brain development has been addressed in germ free (GF) mice models. Changes in multiple neurotransmitter systems and their receptors in a variety of brain regions and up regulation of genes associated with plasticity and metabolic pathways

(75–77) have been found in GF mice. The hippocampus was found as one of the regions with important alterations in these animals.

Parkinson's Disease. Parkinson's disease (PD) is a neurodegenerative disorder that involves dopaminergic pathways, characterized by damage to the nigro-striatal systems. The diagnosis of PD is based on clinical observations, including resting tremor, bradykinesia, rigidity, and postural instability. Some authors suggest that the enteric nervous system (ENS) is implicated due to the effects of α-synuclein. Aggregated forms of this protein have been detected early in ENS, these inclusions could then appear in peripheral nervous system and extend towards the central nervous system following the neuronal innervations, tracing an space-temporal pattern (78). It has been observed that constipation often precedes the onset of typical motor symptoms of PD, and that the vagus nerve is involved in this process (79). A microbiota analysis of PD patients shows association between the levels of Enterobacteriaceae and the severity of postural instability (80). Keshavarzian et al. showed that PD patients present an altered microbiota composition in the colon together with α-synuclein aggregation. The observed dysbiosis could trigger inflammation-induced misfolding of α-Synuclein and favor the PD pathology (81). However, at this moment there is not enough evidence to understand the role of microbiota in PD (82).

Alzheimer's Disease. Alzheimer's disease (AD) is the most common neurodegenerative disease. Although AD has a complex pathogenesis and its etiology is not well understood, substantial evidence has established that the generation of amyloid β-protein (Aβ) is a key event for the development of AD (83,84) and may be responsible for the synaptic dysfunction and neuronal death. To date there is not an extensive analysis of the microbiota composition in AD patients. The inflammatory reaction around amyloid plaques is a characteristic event present in AD brains. Considering that fact, recent work investigated the possible role of a specific subset of gut microbiota that may promotes brain inflammation. They found an increased abundance of pro-inflammatory *Escherichia/Shigella*, as well as a reduction in anti-inflammatory *Eubacterium rectale*, which may be associated with a peripheral inflammatory state in patients with cognitive impairment and brain amyloidosis (85). An in vitro study provided the first evidence that exposure of human primary brain cells to *Bacteroides fragilis*-Lipopolysaccharide is a potent inducer of the pro-inflammatory transcription factor NF-kB (p50/p65) complex, a known trigger in the expression of pathogenic pathways involved in inflammatory neurodegeneration (86). It is of interest that the microbiota of aged animals treated with a mix of gram-positive bacterial strains showed significant increases in Actinobacteria and Bacteroidetes, compared to vehicle-treated animals (87). At the same time, the bacterial mix was able to reduce the age-related deficit in long-term potentiation (LTP). Together, these data offer hope for novel microbiota-based approach to ameliorate symptoms of AD.

It has been suggested that the production of amyloid proteins by bacteria or fungi in the microbiota may influence neurodegeneration (88). Bacteria are able to produce functional amyloid proteins which contribute to population stabilization. Cross-seeding in which one amyloid protein may cause the amyloid misfolding of another protein has been reported, including interactions of the neurodegenerative disease proteins α-synuclein, Aβ, Tau and TDP 43. Exposure to bacterial amyloid proteins in the gut, mouth and nose, may thereby trigger misfolding of such proteins in the enteric and central nervous systems. Furthermore, the innate immune system recognizes bacterial amyloid as a pathogen associated molecular pattern. The priming of immune defenses caused by exposure to bacterial amyloid may cause enhanced immune responses to the production of amyloid aggregates in the brain. Minter et al. have shown that alterations in the gut microbial composition caused by exposure to broad-spectrum antibiotics decreases the deposition of Aβ plaques in transgenic Alzheimer model mice (89). Aged rats exposed to *E. coli* expressing the bacterial amyloid protein curli displayed increased α-synuclein aggregates in the brain and gut, in addition to evidence of neuroinflammation and up-regulation of toll-like receptor 2 (90). Enhanced α-synuclein aggregation was also seen in *C. elegans* exposed to bacteria producing the curli protein. It has been recently reported that germ-free Parkinson's model mice (α-synuclein overexpressing) have reduced phenotypic and structural changes compared to conventionally raise animals. Furthermore, the disease phenotype can be reproduced by the addition of bacterial populations from Parkinson patients but not from healthy controls. These studies strongly suggest that microbiota is involved in neurodegenerative processes (91), although the biochemical mechanisms related with these processes requires further investigation.

Frailty

Frailty as well as Alzheimer and Parkinson has been associated with alterations of the microbiota (92). This state is characterized by increased vulnerability to poor outcomes due to a reduction in physiological reserve, frequently accompanied by muscular weakness and loss of muscular mass and exercise tolerance (93). As a result of the unfavorable consequences of frailty, recent studies have focused on analyzing differences between microbiota from healthy and frail elderly adults. In 2005, Tongeren et al. analyzed fecal samples from 23 volunteers aged 70–100. Their findings showed that individuals with high frailty scores had a significant reduction on *lactobacilli* species when compared to non-frail individuals. This group also showed

a decrease of bacteria within the *Bacteroides/Prevotella* and *Faecalibacterium prausnitzii* groups (94). Interestingly, elderly adults with a low frailty score had a similar composition of gut microbiota when compared to young healthy adults aged 20–55. In 2012, another study by Claesson MJ, et al. compared the microbiota of 178 individuals by place of residence (living in the community, attending to a day hospital or in long term residential care) and diet (according to fiber and fat content). A shift to a less diverse community microbiota was observed in long-term care individuals. This change took place over a year and was related to diets with higher fat and reduced fiber contents. Thereby, the long-term residence diet was significantly associated with higher frailty rates and higher pro-inflammatory markers (34). In a subsequent study by Jackson et al. comparing fecal microbiota from 728 female twins, the results replicated the associations in the Eldermet cohort, using the Rockwood frailty index (95), showing that frail individuals have a less diverse microbiota. They also reported that species such as *Eubacterium dolichum* and *Eggerthella lenta* were more abundant among frail individuals, while *Faecalibacterium prausnitzii* was less abundant. Thus, in all previous studies frailty and high levels of pro-inflammatory molecules were associated with a lower diversity microbiota, which results are consistent with those obtained in animal models (96).

Oral Health

Although the locations of our microbiota includes all surfaces (skin, eyes, etc) and mucosas (respiratory, reproductive or digestive tract), the immense majority of microbiota studies have been focused on gut organisms. The oral cavity houses more than 800 species of bacteria and other organisms, including both gram-negative and gram-positive and aerobic and anaerobic bacteria. *Streptococcus mutans*, which is partially responsible for dental caries, is an important colonizer of the teeth. It has been reported that these gram-positive bacteria are able to produce an amyloid protein that participate in biofilm formation, and enhances the stability of the colonies (97). The role of this bacterial amyloid on oral and general health has not been investigated. Similarly, the influence of aging on the composition of the oral microbiota has not been as well studied as that of gut organisms. In this sense, the oral microbiota may be especially important because of the opportunities for access to the brain through the olfactory nerve at the roof of the nose or through the abundant innervations of the oral cavity by the trigeminal and other cranial nerves. Oral bacteria have also been shown to be involved in stroke (98).

Future Directions

It is very important to consider the role of our microbiota in human evolution. All of our ancestors had microbial partners, and it is clear that they play an important role in maintenance of health. Just as our evolution was influenced by the ability to maintain these internal populations, the evolution of the microbial communities we harbor was influenced by their need to support the health of their hosts. An important issue here is immune tolerance; microbial communities have evolved the ability to prevent their hosts from adopting an aggressive immune response against their presence. This is due in part to the ability of the bacterial communities in the gut to increase the production of regulatory lymphocytes (Treg cells) with anti-inflammatory activity. When considering evolutionary aspects, it has been reported that the microbiota of hunter-gatherer communities present a greater diversity than those with modern and sedentary lifestyles. It seems like a diverse diet may be directly linked to increased microbial diversity and better health outcomes.

The importance of the microbiota on health and aging can be illustrated with the concept of gene therapy. The ability to perform gene therapy and change human genes is a valuable but difficult goal. However, changing our bacterial populations is relatively easy, as it has been shown that two weeks of dietary intervention can significantly change the nature of microbiota composition in humans, with implications for immunity and cancer (99). There are many ways in which the microbiota can be altered in humans, including diet, probiotics, prebiotics, antibiotics, fecal transplantation, yogurt and other fermented foods, and other means. In this regard, it is worth noting the visionary work by Élie Metchnikoff (1845–1916), who observed in a nursing home that long-lived residents consumed larger quantities of yogurt. He proposed that "senility" could be caused by toxins produced by colon bacteria, so he recommended the daily intake of sour milk or yogurt, prepared with lactic acid bacteria. We need to learn more about the composition and interactions of the microbiota and his microbiome during aging in order to develop strategies capable of preserving and improving the condition of the microbiota and consequently the health of the individual.

Longevity, Health Aging

The link between healthy aging, microbiota and longevity must be addressed considering the genetic background and lifestyle of the people. There are numerous reports that have suggested some potential pathways able to promote human health span and aging. Among the most important reports it might be highlighted the caloric restriction diets, probiotics intake (100), reduction of the proinflammatory status (101), enhancement of antioxidant activity, prevention of insulin resistance (102), lipid dishomeostasis (103), microbiota transplantation, physical activity and maintenance of immune homeostasis.

In this sense, caloric restriction or reduced digestion of particular amino acids are able to extend the useful life in a great variety of animal models. This could be explained by the modulation of microbiota trough cellular pathways

involved in nutrient management, inflammation or innate immunity. Behavioral and psychiatric disorders like depression and anxiety are common during aging, and alteration of gut microbiota has a causative role it their development. Marin I, et al. (104) reported reduced *Lactobacillus* in stressed mice, and the administration of *L. reuteri* improved metabolic homeostasis and corrected stress-induced behaviors. A recent strategy with potential anti-aging properties suggested the use of genetically modified native microbiota microorganisms to avoid metabolic dysfunction, such as insulin resistance, fatty liver or dyslipidemia (105) through the improvement of existing bacterial properties, the addition of new ones or even the introduction of enzymes and regulatory elements of human origin (106).

Conclusions

The study of the microbiota represents an important advance in the understanding of the aging process and how it affects the immunological and neurological development of the individual. Among the host factors involved in the formation of gut microbiota during the aging process are genes, immunosenescence and intestinal senescence. In addition to environmental factors such as diet, place of residence and exposure to antibiotics. Decreased clearance of intestinal pathogens or pathologic responses to normal commensals may lead to an aberrant bacterial growth related to chronic inflammatory processes ''inflammaging'' or to increased production of amyloid proteins. Several aging related conditions such as Alzheimer, Parkinson and frailty have been associated to changes of the normal microbiota and ''inflammaging''. Parkinson's disease studies have shown correlations between enterobacterial growth and postural instability as well as an increased inflammatory response possibly inducing miss-folding of α-synuclein. Many studies have related Alzheimer's disease to higher brain inflammation status in individuals with elevated gut concentration of *Escherichia/Shigella* or *Bacteroides fragilis* and an increased production of amyloid proteins by bacteria or fungi. In the case of frailty, several studies have shown that there is an association between individuals with high frailty scores and a lower diversity in microbiota composition.

Advances in this field allow us to affirm that maintaining a beneficial microbial community can help to prevent or delay aged-associated diseases. From this premise, several studies have shown that simple dietary interventions can significantly change the gut microbioma composition. This is a promising area for future researches, considering that reports of the role of prebiotics and probiotics in aged-associated diseases are limited.

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