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Gut microbiota and aging-A focus on centenarians

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ABSTRACT

Gut microbiota (GM) is a dynamic organ throughout the lifespan. Aging is a complex process that comprises a plethora of mechanisms such as senescence, immunosenescence and inflammaging, representing important pathways of age-related diseases. GM structure could both influence and be influenced by aging occurring changes within the host. A unique category of long living individuals exists, namely centenarians that have the outstanding capacity to adapt to various challenges. Longevity seems to be associated with certain GM which, among other factors, might render individuals more resistant to age-related diseases and subsequently to long living. Diet, prebiotics, probiotics and synbiotics may contribute to longevity through GM modulating. Currently, the exact mechanisms of the association between GM and the host in relation with extended lifespan remain unknown and should be further investigated.

1. Introduction

Gut microbiota (GM) has been related to the development of several diseases, as well as aging [1–6]. The healthy microbial population within the human gut lives in perfect symbiosis with the host; it is now recognised as an "organ" involved in several functions such as energy balance, glucose and lipid metabolism, immunity, gut wall trophicity and motility of the gastrointestinal tract, as well as metabolism of harmful compounds from the environment [7]. GM has a dynamic structure that can change along the lifespan, according to diet, drug use and other environmental factors, leading to a specific structure and composition in the elderly [8]. Despite people aging, gut bacteria are constantly renewed [9]. There is a bidirectional interrelationship between aging and the rearrangement of the gut microbial environment. Moreover, given the broad range of functions attributed to GM and its alterations associated with age-related diseases, there is still a need to establish whether these changes are a consequence or a cause of these diseases [10].

Aging is a complex mosaic of processes that have challenged researchers worldwide in an attempt to interpret its underlying mechanisms and, although inevitable, to delay its consequences by identifying possible pathways to modulate it [11]. World population is continuously aging; the percentage of people over 60 years will nearly double from 12% to 22% between 2015 and 2050 [12] Broadly, aging refers to the gradual decline of the physiological functions as a result of the interaction between genetic, epigenetic, environmental and stochastic factors [13,14]. Genes are considered to contribute 25–30% to aging, whereas the other 70–75% are attributed to environmental factors, thus, rendering aging a possible therapeutic target [15]. The progressive decline in biological functions exposes aged people to a high risk of morbidity, being more prone to neurodegenerative, metabolic, cardiovascular, (CV) and immune disorders, as well as cancer. Therefore, it is important to discover potential mechanisms to prevent the installation these diseases in order to achieve a healthy aging [8].

Longevity, on the other hand, allows reaching extreme limits of the lifespan such as 100 years (centenarians) or even more [16]. Centenarians is a category of exceptional aged individuals that succeed in preventing or delaying the onset of age-related disorders such as CV

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disease, type 2 diabetes mellitus (T2DM), Alzheimer's disease or cancer [10,17]. Several studies have investigated the potential mechanisms that lead to longevity with GM gaining much attention lately [18–22]. In this context, centenarians and semi-supercentenarians (> 105 years) have been studied as a model of longevity, displaying certain age-related GM alterations, as well as a specific rearrangement of the microbial populations [2,10]. Overall, revealing the biological mechanisms of extreme longevity, as well as discovering pathways to delay or inhibit the biological changes that lead to human health decline is of paramount importance [18,23].

In the present narrative review we discuss GM focused mainly in the comparison between adult, elderly centenarians and semi-centenarians as well as its associations with the pathophysiology of human aging. Furthermore, we review possible mechanisms to beneficially affect the link between GM and aging.

2. GM structure

The human body consists of host cells and several types of microbes that live in a symbiotic manner [24]. Microbes can modulate their functions according to internal and external signals [10]. Human microbiota includes a large spectrum of microorganisms namely bacteria, archaea, viruses, and some unicellular eukaryotes, displayed in several sites of the body such as skin surface, gastrointestinal, genitourinary and respiratory tracts [7]. Since bacteria significantly outnumber the rest of them, the term “bacteria” is frequently used when referring to the microbial cells in the human body [25]. Most bacteria are located within the gastrointestinal tract, predominantly in the colon, whereas only a few exist in the stomach and the small intestine [7,25,26]. A previous study found that, there is about 0.2 kg of bacteria in the colon and thus in the body overall [25]. Moreover, the authors updated the ratio of bacteria to human cells from 10:1 or 100:1 to closer to1:1 [25].

In healthy adult individuals, GM mainly includes Firmicutes and Bacteroidetes (90%), whereas Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia are present at a percentage of 1–8% [7,27,28]. More precisely, within the colon, most of the bacteria is anaerobic such as the *Bacteroides*, *Porphyromonas*, *Bifidobacterium*, *Lactobacillus* and *Clostridium* (genera belonging to phyla: Bacteroidetes, Actinobacteria, and Firmicutes), due to the low oxygen concentration [7]. The term “microbiome”, has been often used to define just the collective genome of a microbial community [29]. However, it has also been suggested that the microbiome could refer to the microorganisms, their genomes (i.e., genes), and the surrounding environmental conditions altogether [30].

Human microbiota was reported to include > 35,000 species of bacteria [31]. The MetaHIT consortium [32] discussed the concept of intestinal enterotypes referring to three different types of microbial dominance i.e. *Bacteroides*, *Prevotella*, *or Ruminococcus*. However, emerging data supported the notion that GM is an organ with an ability to alter and adapt to the needs of the host, rather than a stable structure [10]. Hence, the “enterotypes” concept was debated [33,34], highlighting the presence of a continuous variation of the microbial structure. Furthermore, Biagi et al. [19] reported the presence of a core microbiota of symbiotic bacterial groups (mostly belonging to the dominant *Lachnospiraceae*, *Ruminococcaceae and Bacteroidaceae* families), which remains almost constant during aging. However, the abundance of subdominant species is increased with aging, accompanied by their rearrangement [19].

Although a considerable inter-individual variance of GM diversity and abundance has been reported, the metabolic pathways seem to be stable among individuals, suggesting that different microbial species can perform the same functions [27,35]. Therefore, the concept of an ideal collection of genes and pathways rather than specific populations, namely a “core” healthy microbiome that remains stable during the lifespan and is responsible for a stable host-associated ecology, has been discussed [36].

GM is a highly dynamic organ throughout the lifespan [37] as it is influenced by a plethora of factors including age, gender, genetic background, ethnicity, type of delivery, use of antibiotics, immunological stimuli and nutrition [17]. In infancy, GM is defined by gestational age, delivery type, maternal microbiota, feeding, genetics, and environmental factors [37]. While the initial infant GM has a simple structure, mainly dominated by *Bifidobacterium*, the adult pattern becomes more complex [20]. Indeed, the number and diversity of human GM increases from birth until around 12 years, becomes relatively stable during adulthood and then declines with aging [37,38]. Overall, GM undergoes substantial changes from the infancy to the older age [20].

Zhernakova et al. [39] used metagenomic shotgun sequencing to analyse the gut microbiome of 1135 participants from a Dutch population-based cohort within the LifeLines-DEEP study. They found that the gut microbiome was associated with 126 exogenous and intrinsic host factors, including 60 dietary factors, 31 intrinsic factors, 19 drug groups, 12 diseases and 4 smoking categories [39]. Altogether, these factors collectively explained 18.7% of the variation seen in the inter-individual difference of microbial composition, with diet being the main contributor [39].

3. GM and human metabolism

From a physiological point of view, GM is considered as the “forgotten organ” [40,41] being involved in several functions of the human body such as energy extraction of ingested food, metabolism and immunity, while also exerting trophic and endocrine properties [7,26,28,39,41] by which it can interact with the host's organs [42]. GM is also recognised as a complex environment with a high variability and heterogeneity, being able to adjust to the host's changing conditions in order to cover the needs of the human body [17].

As a metabolically active organ, GM is involved in energy production from the undigested (non-digestible) food substrates such as polysaccharides and proteins that escape intestinal digestion due to humans' lack of the specific metabolic pathways [26]. Upon GM degradation, the resulting oligosaccharides and monosaccharides undergo bacterial fermentation by which they are subsequently transformed into short-chain fatty acids (SCFA) i.e. acetate, propionate and butyrate [7,26,43]. Once produced, about 90–95% of the SCFA are absorbed in the colon, where they are either used as energy for the colonocytes or transported to various peripheral tissues, thus affecting the human metabolism [43]. SCFA exert also anti-inflammatory and antineoplastic effects [44]. Indeed, SCFA promote the formation as well as the protection of the intestinal barrier from the disruption of lipopolysaccharide (LPS) through its anti-inflammatory role [45]. In detail, butyrate, is the preferred nutrient as well as the main energy source for the colonic epithelial cells as within the mitochondria it generates an important amount of ATP [46]. Also, butyrate has an anti-inflammatory role, protects the epithelial cells against LPS-induced impairment and maintains the barrier integrity through the increase of the tight junction proteins synthesis [47,48]. Moreover, butyrate is involved in the reduction of glucose intolerance and of insulin resistance and reduces appetite and energy intake via gut-brain neural circuit [49,50]. Finally, it exerts a protective role against colorectal cancer [8,43,50,51]. Propionate exerts beneficial effects on β-cell function as it maintains β-cell mass through inhibition of apoptosis and potentiates glucose-stimulated insulin release [52]. Also, propionate can reduce gluconeogenesis through activation of AMP-activated protein kinase (AMPK), which is a major regulator of the hepatic glucose metabolism [53]. On the other hand, propionate is involved in the regulation of cholesterol synthesis within the liver [8,43]. Furthermore, propionate may protect against the development of neoplasia that usually determines hepatic metastasis [54].

Another important involvement of both propionate and butyrate consists in the activation of intestinal gluconeogenesis (IGN). It has

been demonstrated that glucose released by IGN can be detected by a hepatoportal glucose sensor that induces signals to the brain through vagal and spinal nerves which in turn results in decreased food intake as well as enhanced insulin secretion and glucose utilization [55]. Propionate and butyrate activate IGN through different processes. Briefly, butyrate directly activates IGN gene expression through a cAMP-dependent mechanism. On the other hand, propionate is itself a substrate of IGN and by acting as an agonist of G-protein-coupled receptors (GPR41 or free fatty acid receptor 3 FFAR3) in the periportal afferent neural system activates IGN gene expression via gut-brain neural axis. This is an important finding as the aforementioned metabolic benefits seem to be absent in mice deficient for IGN as compared to normal mice, despite similar changes in GM composition [56].

Finally, acetate, the principal SCFA in the circulation, is used by the liver for lipogenesis and cholesterol synthesis, and also acts as a hepatic carcinogenesis preventive factor [8,43,57].

GM is also involved in lipid metabolism and fat deposition, via alterations in the levels of adenosine monophosphate-activated protein kinase (AMPK), which under normal conditions stimulates fatty acid oxidation in peripheral tissues [41] Furthermore, GM can suppress the expression of the fasting-induced adipose factor (FIAF) (i.e., a lipoprotein lipase-LPL inhibitor), thus increasing LPL activity and subsequently fatty acid absorption and accumulation of triglycerides in adipocytes [41]. Altogether these activities of GM explain its role in regulating energy stores and promoting weight gain. In this context, Bäckhed et al. [58] showed that germ free (GF) mice displayed 40% less total body fat compared with normal mice and that GM transplantation from normal to GF mice induced a 60% increase in body fat. Moreover, a reduced intestinal SCFA level and an increase of urinary secretion of calories were observed in the GF mice [59].

A GM-brain axis has also been suggested, highlighting the presence of an important interplay between the microbial metabolites and the brain, thus potentially explaining the involvement in brain health and disease [60]. Briefly, by acting as signaling molecules that bind to G protein-coupled receptors such as GPR41 and GPR43 which are expressed by gut enteroendocrine cells, SCFA trigger the production of anorectic hormones peptide YY (PYY) and glucagon-like peptide 1 (GLP-1) involved in weight control [61–63]. Moreover, the vagal afferent pathway has been recently identified as a circuit through which SCFA control of feeding behaviour [64]. On the other hand, SCFA exert beneficial effects on blood-tissue barrier integrity and brain function and behaviour [65–67]. They are also involved in the modulation of some neurotransmitters synthesis and of their receptors expression [68].

Finally, GM has an important role in the xenobiotic metabolism, namely in degrading harmful environmental compounds and modulating the efficacy and toxicity of drugs, thus potentially representing a therapeutic tool of the 21st century [69] (Fig. 1). More precisely, GM acts through direct mechanisms that metabolize xenobiotics into active, inactive, or toxic metabolites or through indirect mechanisms that involve complex host-microbial interactions which modulate pathways for xenobiotic metabolism or transport. Two biochemical pathways used by the GM gene repertoire have been identified for drug metabolism i.e. reduction and hydrolysis [69]. Overall, based on the diversities and abundances of the enzymes, the bacterial has been classified into least versatile, intermediately versatile and highly versatile xenobiotic metabolizers [70].

4. Inflammaging, immunosenescence and GM

Aging is associated with a pro-inflammatory milieu named “inflammaging” [71]. This pro-inflammatory status in the older people is expressed by high circulating levels of pro-inflammatory markers, including interleukin (IL)-1, IL-1 receptor antagonist protein (IL-1RN), IL-6, IL-8, IL-13, IL-18, C-reactive protein (CRP), transforming growth factor-β (TGFβ), tumour necrosis factor α (TNF) and its soluble receptors (TNF receptor superfamily members 1A and 1B) [72]. The exact reason for the onset of the pro-inflammatory milieu during aging remains unknown, yet some possible explanations have been proposed. Firstly, lifelong accumulated damage and contact with antigens may promote such changes [73]. Secondly, one of the complex hallmarks of human aging, i.e. cellular senescence [74], represents a response to the deleterious age-related processes such as genomic instability and telomere attrition, serving therefore as a proliferation halter for the aged or damaged cells [75]. The two main characteristics of senescence are stable growth arrest and production of several factors including pro-inflammatory cytokines, chemokines, growth factors and proteases, altogether termed as the senescence-associated secretory phenotype (SASP) [73]. The SASP phenotype elicits an autocrine role on the senescent cells but it is also involved in the recruitment of immune cells, such as macrophages, neutrophils, and natural killer (NK) cells in order to eliminate the senescent cells [76]. Upon accumulation of senescent cells, the production of cytokines is enhanced, along with the recruitment of immune cells, jointly paving the way towards the installation of the inflammaging status [73]. However, in the elderly, senescence also contributes to a decline in the immune system, referred to as immunosenescence, which compromises the elimination of senescent cells and in turn worsens chronic inflammation [73]. Therefore, apart from the positive roles of senescence via SASP, emerging data has shown that senescence can itself be also a contributor to aging [73]. Moreover, senescent cells show decreased mitophagy, therefore resulting in an impaired mitochondrial network that may promote age-related metabolic dysfunction [77]. To sum up, progressive cellular deterioration processes, including senescence, that promote aging, as well as inflammaging and immunosenescence, render the elderly more susceptible to age-related disorders (e.g. neurodegenerative, metabolic, CV diseases and cancer) [73] (Fig. 2).

Thirdly, GM has also been reported to contribute to the chronic inflammatory status. Under normal conditions GM (through SCFA) plays an important role in maintaining the gut wall trophicity, by modulating the proliferation, differentiation, maturation and repair after injury of the epithelial cells [7]. Moreover, via SCFA, GM increases the expression of tight junctional proteins in enterocytes, therefore contributing to their protection against pathogens colonization [78]. Accumulating evidence has shown that GM is involved in modulating the innate and adaptive immune system, resulting in maintaining the balance between pro and anti-inflammatory responses [79,80]. Enterocytes can sense the microbes and act as a first line factor in the crosstalk between the GM and the immune cells [80–82]. Within the intestinal tract, the immune cells (e.g. mononuclear, dendritic cells and macrophages) display Toll-like receptors (TLR) [7,83]. These receptors recognize specific microbial ligands and activate certain molecular pathways, inducing a status of “low-grade physiological inflammation” [24,84], which is a valid defence mechanism against pathogens [24]. Importantly, under normal conditions, the gut mucosa immune system exerts tolerance and controls GM, thus maintaining a mutual balanced association [8]. However, during aging, the intestinal epithelial cells in the colon, the enterocytes and the gut-related lymphoid tissue, which form a specific barrier against invading pathogens, are impaired [80]. Therefore, upon stimulation by the rise of pathogens, the enterocytes activate specific cytokines and chemokines that induce dendritic cells to initiate a pro-inflammatory response by differentiation of the T helper cells [80,85].

In elderly, GM is characterized by reduced saccharolytic genes and increased proteolytic genes, thus promoting the overgrowth of pathobionts that, in turn, intensify inflammaging [86]. Inflammaging leads to a status of aerobiosis accompanied by a high production of reactive oxygen species that inactivate the strictly anaerobic bacteria (i.e. Firmicutes) and promote the facultative aerobes. Within this specific environment, GM pathobionts rise and prevail over symbionts as they are relatively oxygen tolerant, thus subsequently maintaining the inflammatory status [78]. Eventually, the elevated levels of inflammatory

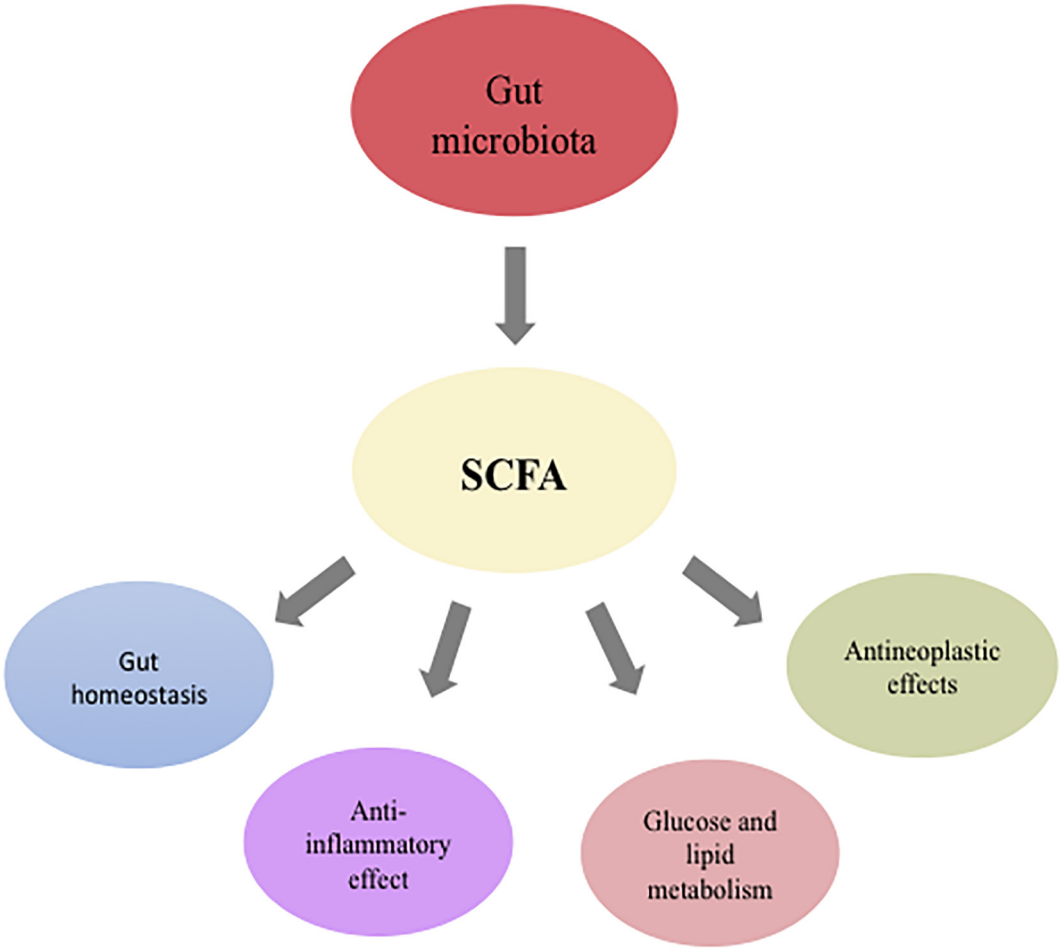

Fig. 1. Gut microbiota effects via short-chain fatty acids.
SCFA; short-chain fatty acids.

mediators induce the dysregulation of the tight junction barrier, leading to increased gut permeability ("leaky gut") [82]. One of the age-related changes consists of the rise in the abundance of Gram-negative bacteria, that can secrete LPS, termed also as endotoxin, a carbohydrate-fat complex, that may cause inflammation in the gut [87]. Subsequently, due to the enhanced permeability, circulating LPS levels are increased, thus further supporting the pro-inflammatory status [83]. Overall, inflammaging links aging to a wide range of diseases such as T2DM [88], obesity [89], atherosclerosis, heart disease [72], Alzheimer's disease, Parkinson's disease [90] and cancer [91] through the dysregulation of the three main pathways that regulate inflammation i.e. mitogen-activated protein kinase (MAPK), nuclear factor kappa-B (NF-κB), mitogen-activated protein kinase (MAPK) and Janus kinase (JAK)-signal transducer and activator of transcription (STAT) [92]. Such alterations in the host immunity are highly related to modifications in the GM, breaking the balanced mutual association, thus resulting in the occurrence of the aforementioned pathologies [93,94].

5. Factors affecting GM changes with aging

There is considerable evidence linking aging with GM alterations, namely a decreased diversity along with increased colonization by pathobionts [19,21,95]. This raises the question whether GM composition could influence or be influenced by the aging process [10]. Interestingly, some long-living individuals manage to "avoid" or delay the onset of age-related morbidity. This might be partly due to the high plasticity of GM that is permanently renewed and preserving its ability to adjust to the host's needs, thus promoting human health [10,19]. In this context, Biagi et al. [10] describe GM in long-living people as a dynamic organ maintaining its functional interplay with the host, rather than as a dysbiotic damaged environment.

An important challenge would be to identify the factors that can preserve health during the lifespan, since aging is linked to several diseases. In this respect, the questions to what extent GM changes might be involved in these processes and whether age-related GM alteration is a contributor or a consequence of geriatric diseases remain to be answered [10]. Infectious diseases, antibiotics and various drug use in the elderly can induce harmful GM rearrangements, i.e. dysbiosis, often resulting in age-related diseases [93]. On the other hand, as GM is highly influenced by diet, individuals who ingest high amounts of fats, mainly saturated have increased circulating levels of bacterial endotoxins, leading to endotoxemia and chronic low-grade inflammation that subsequently promotes age-related disorders (such as muscle mass decline and sarcopenia) [96]. However, despite its high plasticity, the GM stands out also as resilient to change as shown by late alteration of the bacterial environment, i.e. one year after the initiation of diet change [97].

As mentioned above, aging is accompanied by GM rearrangements [98]. From a clinical point of view, aging is reflected at the gastrointestinal level by the impairment of intestinal motility and its protective role due to mucosa barrier disturbances, as well as by alterations of the intestinal nervous system, accompanied by changes in GM [20,24,99]. Furthermore, teeth loss, leading to impaired mastication, disorders in saliva secretion, taste and smell, dysphagia, dyspepsia, gastroesophageal reflux, delayed intestinal transit time, diverticulosis, reduction of appetite and constipation, as well as physical exercise

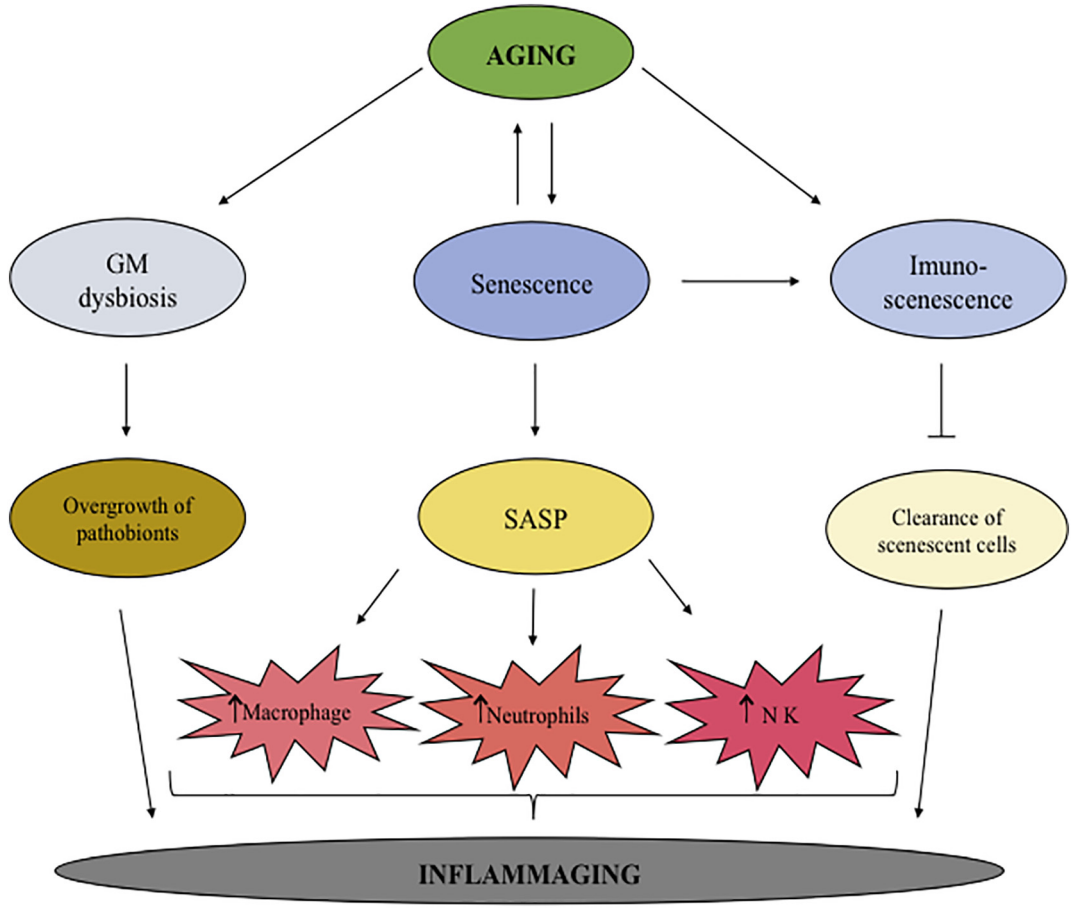

Fig. 2. Potential pathways linking aging with inflammaging.
GM, gut microbiota; NK, natural killer; SASP, senescence-associated secretory phenotype.

reduction can affect diet, thus resulting in GM changes [10,78,93,98]. Furthermore, unhealthy eating, such as inadequate ingestion of fruits and vegetables, leads to the disruption of the GM as highlighted by Wang et al. [100]. The authors also reported that a high-fibre diet could establish a structurally balanced microbial population that may preserve health in centenarians [100].

The influence of both diet and residence location on GM in elderly people was investigated by Claesson et al. [97] in a study resulting from the complex ELDERMET project that evaluated 178 individuals aged between 64 and 102 years from different settings such as community, day-hospital, rehabilitation or long-term residential care. The authors reported differences between the GM of people in long-stay care compared with the community dwellers; the former displayed a significantly less diverse GM, highlighting the role of diet [97]. In detail, those living in the residential care settings had a higher proportion of phylum Bacteroidetes, compared with the community dwellers that showed a greater proportion of Firmicutes. Furthermore, it was shown that, despite the rapid changes in diet, which occur when moving into a long-stay facility, the GM needs one year to alter [97]. In terms of diet, the analysis revealed four dietary groups (DGs) i.e. DG1 'low fat/high fibre', DG2 'moderate fat/high fibre', DG3 'moderate fat/low fibre' and DG4 'high fat/low fibre'. The first two groups included 98% of the community dwellers and outpatients, while the last two groups included 83% of the long-stay subjects [97]. Both GM and diet were most diverse in DG1, and least diverse in DG3 and DG4. Interestingly, the decrease of the GM diversity was associated with increased frailty, markers of inflammation and other diseases [97]. Further data form the ELDERMET project showed that individuals with the "long-stay-associated" GM ingested increased amounts of sugars and fats and were more likely to be frail [101]. Such GM pattern is mostly found in the elderly living in the long-term care facilities but was also detectable in the community dwellers. On the other hand, the "diversity-associated" microbiota group was related to a healthy diet and was found usually among the community-dwellers [101]. Furthermore, the "community-associated" GM pattern was more influenced by antibiotic use than the GM of individuals in the long-term care settings; the former GM exhibits more significant loss, but also greater recovery, after antibiotic treatment [101].

Overall, age-related complex changes can occur in GM structure and function, potentially predisposing to the development of several diseases. Therefore, GM could be regarded as a potential target to prevent or delay the onset of disorders associated with the aging process [8].

6. GM changes in long living people

Aging is characterized by a reduced diversity of GM and an increase in the colonization by opportunistic species and pathobionts, such as streptococci, staphylococci, enterobacteria and enterococci [10]. Furthermore, rearrangements of Firmicutes and Bacteroidetes with a decrease in SCFA production, mostly butyrate, have been reported [10]. Rampelli et al. [86] showed an age-related altered profile of the gut microbiome with a loss of genes for SCFA production (i.e. decreased saccharolytic and increased proteolytic bacteria), highlighting the presence of pathobionts, which are pro-inflammatory bacteria. When analysing the fecal microbiota in 161 older individuals (aged ≥65 years) and 9 younger controls, Claesson et al. [20] noted that in 68% of the cases, GM was dominated by phylum Bacteroidetes, with an average proportion of 57%, while phylum Firmicutes had an average

proportion of 40%. However, the interpretation might be hampered by the differences in the definition of the older age (i.e. generally over 60 years, but sometimes over 65 or 70 years) [93,102–104]. Nevertheless, Biagi et al. [21] found that the aging process starts to affect GM later than the age of 65 years, and thus it seems that the threshold for an "aged" GM population should be considered as the 75–80 years.

Over the last decade, studies evaluated centenarians that are regarded as the best model of human longevity [10]. Centenarians are, however, considered not the most robust ones, but those who better adapt and adjust to the biological and non-biological challenges during aging [16]. In this context, Biagi et al. [21] reported in 2010 that this special age category display a different and unique GM composition compared with the young adults (aged 30 years in average) and the elderly (70 years old) who both seem to share a similar GM structure, with Bacteroidetes and Firmicutes as dominators and Actinobacteria and Proteobacteria as minor populations. Moreover, these two latter groups had a similar diversity [21]. Interestingly, neither GM composition nor diversity followed a linear association with age [21]. In addition, the authors reported that in centenarians although Bacteroidetes and Firmicutes are still the dominating GM, there is a shift of the Firmicutes population to a low diversity in terms of species composition, namely a decrease in the contributing *Clostridium* cluster XIVa, an increase in *Bacilli*, and a rearrangement of the *Clostridium* cluster IV composition [21]. In detail, the butyrate-producing bacteria belonging to Firmicutes i.e. *Ruminococcus obeum et rel*, *Roseburia intestinalis et rel*, *Eubacterium ventriosum et rel*, *Eubacterium rectale et rel*, *Eubacterium hallii* et rel (all belonging to the *Clostridium* cluster XIVa), as well as *Papillibacter cinnamovorans* et rel and *Faecalibacterium prausnitzii* et rel (*Clostridium* cluster IV) were fewer in this specific age category [21]. This is an important finding considering that butyrate is a major energy source for the enterocytes and holds a significant anti-inflammatory role. On the other hand, the butyrate producers *Anaerotruncus colihominis et rel* (*Clostridium* cluster IV) and *Eubacterium limosum et rel* (*Clostridium* cluster XV), were reported to be increased in centenarians [21]. Furthermore, elevated levels of the mucin degrading *Akkermansia muciniphila* were found in aged people compared with the young adults [21]. Along with this disturbed GM, a high inflammation score was reported in centenarians, thus confirming the inflammaging hypothesis [21]. Indeed, the GM of centenarians is enriched in facultative anaerobes belonging to the Proteobacteria phylum, a group containing several pathobionts bacteria, supporting the hypothesis that these changes may either affect inflammaging or be affected by the systemic inflammation. Finally, the Biagi et al. [21] study also analysed a group of centenarians' offsprings and found that, when co-housed, there is a trend of an increased occurrence of opportunistic or potentially pathogenic bacterial groups in these offsprings, compared with those who did not share a living place with the centenarians [21]. This finding highlights that co-housing may influence GM composition.

Later, in 2016, Biagi et al. [19] investigated the microbial ecosystem in semi-supercentenarians, i.e., those aged 105–109, in comparison to adults, elderly, and centenarians. They found a decrease in core GM abundance of symbiotic bacteria, belonging mainly to the dominant *Ruminococcaceae*, *Lachnospiraceae*, and *Bacteroidaceae* families as well as an increase in opportunistic bacteria along with age. However, interestingly, a peculiar feature emerged mostly in semi-supercentenarians i.e. an enrichment in health-associated *Akkermansia* and *Bifidobacterium* (well known in promoting immunomodulation and healthy metabolic homeostasis) as well as in *Christensenellaceae* [19]. Based on these findings, a question arises i.e. whether gut bacteria are lost during aging and then become reacquired by those individuals who live longer or if they are maintained only by long-living individuals. The authors speculated that it might well be that these particular bacterial taxa could be involved in a new homeostasis within the aging host, favouring survival to extreme ages [19].

Apart from studies in Europe, Wang et al. [100] analysed the GM of centenarians (aged 100–108 years) and younger elderly (aged 85–99 years) living in Bama County, Guangxi, China, as well as the elderly (aged 80–92 years) living in Nanning City, Guangxi, China. They reported that the abundance of *Roseburia* and *Escherichia* was significantly greater, whereas that of *Lactobacillus*, *Faecalibacterium* and *Akkermansia* was significantly less in centenarians at the genus level [100]. Overall, the authors observed that the GM of centenarians was more diverse as compared to that of the younger elderly. Indeed, a significant structural change in butyrate-producing bacteria in the phylum Firmicutes was observed whereas a more commonly presence of Bacteroidetes in centenarians than in young elderly form the same area was identified [100]. However, it should be noted that Chinese people have a specific diet based mostly on rice and plant foods, i.e. a diet that may favour a more balanced GM structure, leading to health maintenance in centenarians. Finally, the authors argued that both age and a high-fibre diet can set out a new structurally balanced GM that may underpin health in centenarians [100]. In another study, in Korea, Kim et al. [22] compared the GM of centenarians in longevity villages with the GM of elderly and adults in the same region, as well as in urban areas. Overall, they found a higher abundance of Firmicutes and a lower population of Bacteroidetes in people from rural areas compared with those from towns. Furthermore, greater proportions of Bacteroidetes and lower proportions of Firmicutes were observed in centenarians compared with the elderly [22]. Noteworthy, the centenarians displayed reduced proportions of *Faecalibacterium* and *Prevotella*, as well as a higher abundance of *Escherichia*, *Akkermansia*, *Christensenellaceae*, and *Lactobacillus*, which are beneficial from an immunological and metabolic point of view [22]. Finally, three metabolic pathways of GM, i.e. the phosphatidylinositol signaling system, glycosphingolipid biosynthesis, and various types of N-glycan biosynthesis, were predicted to be higher in centenarians, a feature that might support health maintenance and longevity.

In an attempt to identify the possible common features of "healthy aging", regardless of nationality, some studies performed comparisons of GM between different countries. In this context, Kong et al. [105] compared the GM of Chinese healthy centenarians and nonagenarians with the GM of Italian centenarians/semi-supercentenarians. There were both differences, potentially due to the genetic background, geography nutritional culture and DNA-extraction methods and, similarities in the GM, leading to the conclusion that certain "longevity" features of GM do exist [105]. Briefly, long-living individuals in both populations had a high proportion of the *Clostridium* cluster XIVa, *Ruminococcaceae*, *Akkermansia* and *Christensenellaceae*, which are regarded as beneficial bacteria.

Tuikhar et al. [106] analysed the GM and fecal metabolites composition of a centenarian group (aged 100 years) in comparison to young people (aged 25–45 years) from a region with a high prevalence of centenarians as well as to young people from the nearby region of low prevalence of centenarians in India. They also compared the results with those of similar groups, including 125 centenarians from three countries Italy, Japan and China. Overall, the authors observed an extremely high variation in bacterial richness and diversity among the centenarians across the four countries. In detail, regardless of the nationality of the individuals, higher diversity of species within the family *Ruminococcaceae* (well-known gut symbionts from the Firmicutes phylum) was observed in centenarians with respect to younger adults [106]. Among the *Ruminococcaceae* family, there was an enrichment of the unclassified species such as *Ruminococcaceae* D16, which is an important butyrate source involved in preventing inflammation and immunosenescence [106]. Moreover, the authors reported a decline in the abundance of the putative butyrate producer namely *Faecalibacterium* (phylum Firmicutes), linked to inflammation as well. Within the Bacteroidetes phylum, *Rikenellaceae* (*Alistipes*) and *Porphyromonaceae* (*Parabacteroides*, *Odoribacter*, *Porphyromonas*), also butyrate producers, were increased in all centenarians [106]. Moreover, the authors observed a decrease in *Prevotella* (phylum Bacteroidetes) richness in Indian centenarians. This genus seems to be associated with chronic

inflammation and therefore the reduced *Prevotella* richness might be a significant factor sustaining longevity. Further, *Akkermansia*, *Alistipes*, *and Ruminococcoaceae* D16 emerged as a common longevity signature. Also, some disparities between different study populations were identified. In detail, enrichment with *Enterobacteriaceae* and lactic acid bacteria (*Lactobacillaceae and Leuconostocaceae*) was observed in the GM of the Indian population in comparison to the Italian, Japanese and Chinese samples [106]. However, members of the phylum Bacteroidetes, i.e., *Bacteroidaceae and Rikenellaceae*, were relatively lower in the Indian population. Furthermore, the Indian and Italian populations displayed higher species richness than the Chinese and Japanese populations. In terms of bacterial diversity, an exceptional high variety was observed in the Italian population [106]. Finally, the authors found that both centenarians and young adults coming from the longevity area showed a significantly higher total bacterial load as compared to the young group from the non-longevity area [83].

In order to study longevity from the metabolic point of view, Tuikhar N et al. [83] analysed the metabolites present in the fecal extract obtained from the Indian population. They found a higher level of compounds with neuro-pharmacological properties such as gamma-Aminobutyric acid (GABA) and Imidazole 4-acetic acid, as well as azole compounds with antifungal and amebicidal activity. Also, lower levels of cyclohexanecarboxylic acid have been revealed in the fecal extract of centenarians, implying that GM of these individuals might degrade this environmental contaminant. [83]. Collino et al. [107] used a combined metabonomic approach to investigate the longevity phenotype in a cohort comprising mostly female centenarians, elderly, and young individuals. The authors showed the presence of metabolic signatures of extreme longevity (centenarians) in terms of a complex remodeling of lipids, amino acids, and gut microbiota metabolism. First, a unique alteration of specific glycerophospholipids and sphingolipids was observed in the longevity phenotype. Second, with increasing age, tryptophan serum concentrations have been demonstrated to be markedly decreased which seems to be linked to the chronic inflammatory phenotype [107]. However, recent research has shown that the activation of tryptophan metabolism has anti-inflammatory and immunosuppressive effects. In detail, it seems that tryptophan depletion activates dendritic cells and macrophages causing them to produce anti-inflammatory cytokines such as interleukin-10 (IL-10) [108]. Third, centenarians show an increased concentration of hydroxybenzoate (2-HB) as compared to elderly, which is a compound that can be found in most fruits and vegetables with anti-inflammatory roles [84]. Fourth, centenarians displayed increased levels of phenylacetylglutamine (PAG) and p-cresol sulfate (PCS) in the urine which is a result of GM catabolism of protein and aromatic amino acids such as phenylalanine and tyrosine. Hence, late aging process seems to induce an increased p-cresol production via age-related changes of GM [84]. Finally, the authors found that PAG, which is a marker of longevity, correlated positively with Proteobacteria species, namely *Campylobacter*, *E. coli*, *Haemophilus*, *Pseudomonas*, *Serratia*, *Yersinia et rel*, while both PCS and PAG correlated with *Vibrio*. Taken together, these findings support the concept of the presence of a changed GM in longevity holding anti-inflammatory activity [84].

7. Interventions in the GM to promote longevity

Due to improvements in socio-economic conditions, the world elderly population is continuously rising with an estimate of around 2 billion of people > 60 years by 2050 [109]. In Europe, the demographic old-age dependency ratio (i.e. people aged ≥65 years relative to those aged 15–64 years) was about 25% in 2010 and it increased to 29.6% in 2016, being estimated to reach 51.2% in 2070 [110]. As previously mentioned, aging is often associated with a wide range of diseases, leading to a reduced quality of life. Therefore, there is a paramount need to identify the specific pathways that may contribute to avoiding the onset of such diseases. Several strategies were reported to be effective in increasing lifespan, including reduced temperature, food intake, insulin/IGF-1 signaling and mitochondrial respiration [14,111,112]. In this context, modulating GM has been identified as a potential strategy to achieve longevity [78].

Diet is a major factor that alters GM and given the age-related issues with regard to malnutrition, dietary intervention is undoubtedly a useful strategy to affect GM composition [113]. As mentioned above, GM rearrangements in the elderly lead to a consecutive decline in SCFA production [114]. Therefore, a high-fibre diet is highly recommended, aiming to increase SCFA (and especially butyrate) levels, reinforce intestinal barrier, reduce the colonization of pathogenic bacteria and mitigate the pro-inflammatory state.

Another modulator of GM involved in sustaining the interplay between the host and the intestinal microbial environment, as well as in promoting healthy longevity are prebiotics. According to The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement, the definition of prebiotics has been updated to “a substrate that is selectively utilized by host microorganisms conferring a health benefit” [115]. In brief, prebiotics are complex non-digestible carbohydrates within the small intestine that upon reaching the colon are submitted to fermentation, thus modulating the composition and metabolic activity of GM [114]. They can be found in grains, fruits and vegetables or they can be produced industrially [114]. The most common prebiotics are manno-oligosaccharides, galacto-oligosaccharides, inulin, lactulose, fructo-oligosaccharides, pectic-oligosaccharides, xylo-oligosaccharides, and trans galactosylated-oligosaccharides [87]. Their mechanisms of action involve modulation of the host's immune system and inhibition of the pathogenic bacteria [116]. In the elderly, prebiotics can increase *Lactobacillus and Bifidobacterium* spp., which are otherwise reduced, and play an important role in improving the immune system activity [98,117].

Probiotics are defined as “live microorganisms which when administered in adequate amounts confer a health benefit on the host” [115]. They are known to exert beneficial effects on the immune, nervous and gastrointestinal systems, as well as on CV and metabolic disorders [118]. Given the role of oxidative stress and inflammation in aging, as well as the antioxidant and immunomodulatory properties of probiotics, it follows that probiotics may promote longevity [87]. In this context, in aging rats and mice, *Lactobacillus* administration improved GM and metabolite profiles [119,120]. Briefly, *Lactobacillus acidophilus* DDS-1 increased the populations of beneficial bacteria, such as *Akkermansia muciniphila and Lactobacillus* spp., and reduced the levels of opportunistic bacteria such as *Proteobacteria* spp. [120]. Furthermore, administration of *Lactobacillus paracasei* PS23 delayed the age-related cognitive decline in senescence-accelerated mouse prone 8 (SAMP8) mice, which are characterized by an early onset of age-related alterations [121]. These results could be attributed, at least partly, to the enhanced antioxidant capacity (indicated by the higher levels of the anti-oxidative enzymes superoxide dismutase and glutathione peroxidase), as well as to the reduced inflammation state (depicted by the lower levels of TNF-α and monocyte chemotactic protein-1 (MCP1), and the increased IL-10 concentrations), thus modulating the gut-brain axis [121,122]. Donato et al. [111] used the nematode *Caenorhabditis elegans*, which seems to be a very appropriate model organism for research on aging, and showed that the formation of *Bacillus subtilis* biofilms increased *Caenorhabditis elegans* lifespan [111]..

There are data supporting the beneficial effects of probiotics supplementation. In human studies, a randomized double-blind placebo-controlled trial evaluated the impact of a biscuit, containing the probiotics *Bifidobacterium longum* Bar33 and *Lactobacillus helveticus* Bar13, on the intestinal microbiota of elderly people (aged between 71 and 88 years) [123]. Probiotic intake reduced the age-related increase of the opportunistic pathogens *Clostridium* cluster XI, *Clostridium difficile*, *Clostridium perfringens*, *Enterococcus faecium* and the enteropathogenic genus *Campylobacter* [124]. In addition, with regard to the duration of probiotic supplementation, in a recent systematic review and meta-

analysis of controlled trials, Miller et al. [123] reported that even a short-term probiotic supplementation (i.e. from 3 to 12 weeks) enhanced the cellular immune function in healthy elderly adults. A longer duration (in average 6 months) of probiotic intake triggered significant changes in the GM structure by inducing an increase in the composition of beneficial microorganisms, thus maintaining the host's health [125]. An important observation was reported by Elie Metchnikoff back in 1907, i.e. that people with a high consumption of a yogurt containing *Lactobacillus bulgaricus* lived longer [126]. Nevertheless, there are still questions to be answered regarding the exact mechanisms by which probiotics may promote healthy longevity [126].

Finally, synbiotics (i.e. prebiotics combined with probiotics) have been tested to modulate GM composition and thus improve the immune system activity and promote longevity [114]. In this context, Costabile et al. [127] showed, in a randomized, double-blind, study that the synbiotic combination of *Lactobacillus rhamnosus* GG and pilus-deficient *Lactobacillus rhamnosus* GG-PB12 combined with Promitor™ Soluble Corn Fibre (a candidate prebiotic) promoted innate immunity by increasing NK cell activity, and decreased the levels of total cholesterol, low density lipoprotein (LDL) cholesterol and inflammatory cytokine IL-6. Therefore, the authors argued that synbiotics, and more precisely this combination, might be an attractive option to control the immune system and maintain health in the elderly [127]

8. Conclusions

GM has been lately regarded as the “forgotten organ” of the human body as it holds several important functions. As a dynamic and plastic organ, GM is continuously altering, mainly by diet and lifestyle intervention, as well as drug use, but still succeeds in maintaining a perfect mutualistic interplay with the host under normal conditions. However, GM undergoes significant changes during aging.

Aging is a complex process that is genetically determined and also modulated by environmental factors; it comprises several mechanisms including senescence, immunosenescence and inflammaging, that are involved in the onset of age-related diseases. GM rearrangements could be a consequence or a cause of aging. Similarly, GM derangements during aging could be a result or a contributor to the age-related disorders. Centenarians represent the specific age category that has the ability to resist, adapt and adjust to the biological and non-biological challenges, and therefore to survive age-related diseases which constitute such challenges. Longevity seems to be associated with a unique shift of GM characterized by enrichment in *Akkermansia*, *Bifidobacterium and Christensenellaceae*. Several strategies can be used to maintain a balanced GM population such as diet, prebiotics, probiotics and synbiotics, which altogether might play their part in achieving longevity. Nevertheless, further studies are warranted for a better understanding of the involvement of GM in aging as well as of its modulation to promote longevity.

Declaration of competing interest

This review was written independently. The authors did not receive financial or professional help with the preparation of the manuscript. The authors have given talks, attended conferences and participated in advisory boards and trials sponsored by various pharmaceutical companies. MR is now “Director, Clinical Medical & Regulatory Affairs, Novo Nordisk Europe East and South”.

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