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Invited Mini Review

Aging and the microbiome: implications for health and disease

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The gut microbiota plays a fundamental role in maintaining host homeostasis, and the aging process profoundly influences its composition and function. Accumulating evidence suggests that alterations in the gut microbiota are not just a consequence of aging, but also an active driver of age-related physiological decline. In particular, age-dependent gut microbiota dysbiosis has emerged as a critical factor contributing to host aging and aging-related diseases. This review systematically summarizes alterations in the gut microbiota (e.g., reduced alpha diversity, depletion of beneficial commensals, and enrichment of pathobionts) during the aging process, and discusses the spatiotemporal dynamics and causal relationships between microbial aging and host aging. The regulatory mechanisms by which the gut microbiota influences aging-related diseases, such as metabolic disorders (e.g., obesity, type 2 diabetes, and cardiovascular disease), immunosenescence, and neurodegenerative diseases (e.g., Alzheimer's disease and Parkinson's disease), are also elucidated. Finally, microbiota-targeted intervention strategies (e.g., probiotics, prebiotics, and postbiotics) are explored, together with advanced research strategies. [BMB Reports 2026; 59(1): 40-50]

INTRODUCTION

With the escalation in the global aging population, elucidating the biological mechanisms of aging has emerged as a critical challenge in biomedical research. While traditional aging theories have focused on cell-autonomous mechanisms, such as genomic damage, telomere attrition, and epigenetic alterations, recent findings implicate the gut microbiome as a significant factor influencing the aging process (1, 2). The gut microbiome contributes to host health through the production of microbial metabolites, such as short-chain fatty acids (SCFAs) and second bile acids (SBAs), which are known to positively regulate insulin sensitivity, immune homeostasis, and neuroendocrine networks (3). However, age-dependent alterations in the gut microbiome have been observed, and are characterized by decreased alpha diversity, reduced abundance of beneficial bacteria, and enrichment of pro-inflammatory pathobionts. These alterations lead to metabolic dysregulation of SCFAs and bile acid balance, thereby accelerating the progression of metabolic disorders, immunosenescence, and neurodegenerative diseases, including Alzheimer's and Parkinson's diseases (4, 5). Notably, the gut microbiome has co-evolved with the host, and throughout life remains highly responsive to external influences (e.g., dietary patterns, environmental exposures, and pharmacological interventions). Among these, diet is considered the primary factor in modulating microbiome composition and function, shaping microbial composition through its effects on nutrient availability, microbial metabolic substrates, and inter-microbial competition (6). Despite the growing number of reviews on the gut microbiome and aging, few have integrated recent mechanistic and translational discoveries. Recent findings—such as centenarian-associated microbial signatures, fecal microbiota transplantation (FMT)-based evidence for causality, and clinical progress on next-generation probiotic/postbiotic strategies—have yet to be comprehensively discussed. Moreover, as the field advances toward personalized microbiome interventions, there is a pressing need for a synthesis that bridges basic microbiome-aging biology with emerging therapeutic applications.

In this review, we systematically summarize the dynamic alterations of the gut microbiome during the aging process, elucidate the mechanisms by which microbial dysbiosis contributes to age-associated disorders, and explore the promising prospects of microbiome-targeted strategies for mitigating aging and the onset of aging-associated disorders. By highlighting recent discoveries, clinical translation efforts, and the potential of individualized biotic-based interventions, this review aims to provide an updated and integrative perspective that distinguishes it from prior work.

AGING AND ALTERATIONS IN THE GUT MICROBIOME

As a vast endogenous ecosystem, the gut microbiome co-evolves with the host from birth, establishing a mutually beneficial symbiotic relationship (1). In adults, the human gut microbiome typically comprises bacteria, fungi, viruses, and

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bacteriophages. The dominant bacterial phyla include *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, and *Verrucomicrobia*, with *Firmicutes* and *Bacteroidetes* being the majority of the microbial population (7). These gut commensals contribute critically to host metabolism, energy homeostasis, and immune stability by synthesizing key microbial metabolites, such as SCFAs, SBAs, essential vitamins (e.g., B vitamins, vitamin K2), and other key nutrients (8). However, numerous studies have shown that the composition and diversity of the gut microbiota gradually change with age (Fig. 1). For example, *Actinobacteria* and *Proteobacteria* are the dominant phyla in infancy, with *Bifidobacterium* a key genus. In contrast, the adult microbiota is characterized by the dominance of *Firmicutes* and *Bacteroidetes*, and genera such as *Faecalibacterium* and *Blautia*, which during early life are absent or scarce (9). As infants grow to approximately 3 years of age, the diversity of the gut microbiota gradually increases, approaching that of the adult gut microbiota (7). While throughout adulthood, the gut microbiome generally stabilizes, with advancing age, its composition undergoes a significant shifts, most notably a marked decline in diversity (1). Specifically, meta-analysis of global metagenomic sequencing data consistently demonstrates that elderly individuals harbor increased levels of pro-inflammatory pathobionts—including *Enterococcus*, *Streptococcus*, *Actinomyces*, and *Ruminococcus*—and decreased levels of beneficial SCFA-producing bacteria, such as *Faecalibacterium*, *Roseburia*, and *Coprococcus* (1, 10). These microbial signatures may characterize unhealthy aging phenotypes. Interestingly, studies of gut microbiome profiling of centenarians in China and Italy have revealed higher alpha diversity compared to younger individuals, contradicting the general trend of decreasing alpha diversity with age (11). Across various populations—including those in China, Korea, Japan, and Italy—centenarians consistently exhibit enrichment of *Akkermansia* and *Christensenellaceae*, suggesting that these bacterial taxa may serve as potential microbial markers of healthy aging and longevity (1, 12). Consistent with findings in humans, an increase in pathogenic bacteria, such as *Enterococcus* and *Streptococcus*, is observed in aging mice; meanwhile, beneficial bacteria, including *Bifidobacterium* and *Akkermansia*, are reduced (13). In addition, older mice also show significantly lower Operational Taxonomic Unit (OTU) richness and alpha diversity indices (e.g., Chao1, Simpson, ACE) compared to younger mice, and a shift in phylum-level composition, with *Proteobacteria* being more abundant in

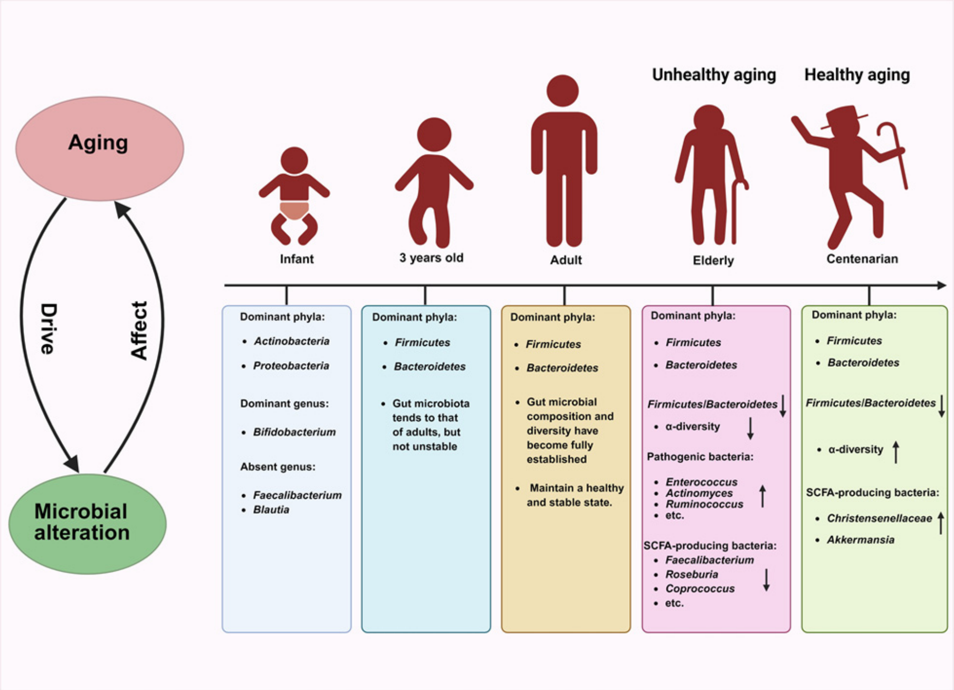

Fig. 1. Aging and alterations in the gut microbiota. With age, the gut microbiota undergoes progressive changes. In infancy, the dominant phyla are *Actinobacteria* and *Proteobacteria*, and the microbiota does not resemble the adult profile until about age three, remaining relatively unstable. In adults, *Firmicutes* and *Bacteroidetes* are predominant, and the microbial community tends to be stable throughout adulthood. However, in the elderly, dysbiosis becomes apparent, characterized by reduced diversity, a decline in beneficial bacteria, and an increase in pathogenic species—hallmarks of unhealthy aging. Intriguingly, centenarians exhibit a more stable gut microbiota, with increased diversity and an enrichment of beneficial *Akkermansia* species. Notably, aging drives changes in the gut microbiota, while alterations in the microbiota may affect the aging process, although the precise temporal sequence and causality remain to be elucidated.

young mice, while *Actinobacteria* and *Fusobacteria* dominate in older mice (14). In *Drosophila melanogaster*, similar shifts occur, so that in young flies, *Acetobacter persici* and *Lactobacillus brevis* are dominant, while in older flies, *Acetobacter malorum* and *Lactobacillus plantarum* become dominant (15). Interestingly, the number of observed OTUs increases with age in fruit flies, which is in contrast to the trend observed in aging mice (14, 15). This discrepancy may be attributed to the shorter lifespan of fruit flies and their lack of an adaptive immune system, where dysregulated immune responses during aging could lead to the overgrowth of certain symbionts (16).

The spatiotemporal sequence and causal relationship between gut microbiome aging and host aging remain contentious and challenging to delineate (Fig. 1). Some studies suggest that host aging serves as the primary driver of gut microbial dysbiosis. With aging, reduced gastrointestinal motility and lower gastric acid secretion create a permissive environment for pathogenic bacteria (e.g., *Escherichia coli*), which suppress beneficial taxa, such as *Lactobacillus* (17). In addition, immunosenescence—characterized by reduced immune cell function and elevated pro-inflammatory cytokines—emerges as a critical factor in gut microbial dysregulation (18, 19). For example, senescent B cells in aged mice exhibit decreased IgA secretion, promoting the expansion of pathobionts and disrupting microbial homeostasis (18). T-cell senescence in both humans and mice is also associated with reduced microbial diversity, likely due to a failure to sustain normal microbial communities in an inflammatory milieu (19). As well, elevated TNF-alpha levels in aged mice trigger microbial dysbiosis, potentially through the induction of antimicrobial peptides (20). However, increasing evidence suggests that gut microbial dysbiosis may precede and actively contribute to host aging acceleration. In *Drosophila*, age-related microbial imbalance appears before intestinal barrier dysfunction, and is a key factor in age-associated mortality (16). FMT has shown that transferring the gut microbiota from aged flies to germ-free recipients accelerates their death, indicating a causative role for aged microbiota (15). Similar findings have been reported in rodents, whereby transplantation of aged microbiota into young germ-free mice subsequently results in systemic inflammation (21). In humans, clinical studies have also shown that patients in the early stages of Alzheimer's disease (AD) and Parkinson's disease (PD) exhibit significant differences in their gut microbial signatures even before the onset of cognitive symptoms, suggesting that changes in the gut microbiota may serve as early biomarkers of neurodegeneration (22, 23).

Taken together, while the causality between host aging and gut microbial dysbiosis is not yet fully elucidated, current evidence supports bidirectional interaction. Future research should leverage longitudinal studies, FMT experiments, and integrated multi-omics analyses (e.g., metabolomics, transcriptomics, and proteomics) to clarify the temporal relationship of gut microbiome changes during host aging. Regardless of the directionality, it is evident that the gut microbiome plays a crucial role in modulating host aging, and represents a potentially significant target for therapeutic intervention.

AGE-RELATED METABOLIC DISORDERS AND GUT MICROBIOME

As aging progresses, the functionality of the metabolic system gradually diminishes, leading to the onset of metabolic disorders, such as obesity, type 2 diabetes mellitus (T2DM), and cardiovascular disease (24). Recent studies have demonstrated that the gut microbiome plays a crucial role in regulating metabolic diseases through the production of microbial metabolites—including SCFAs (e.g., acetate, propionate, and butyrate), SBAs, trimethylamine N-oxide (TMAO), and gut-derived neuroendocrine and immunological factors (25) (Fig. 2). In rodent studies, an elevated *Firmicutes*/*Bacteroidetes* ratio has been consistently associated with obesity. Moreover, transplantation of gut microbiota from young donors via FMT reduced body weight and prevented fat accumulation in aged recipient mice (26). A clinical study conducted in the United Arab Emirates has also revealed significant differences in the gut microbiota between obese and lean adults, although geographical location and dietary culture may have influenced these results (27).

The mechanisms by which gut microbiome influence obesity are diverse. SCFAs can activate the gut-derived G protein-coupled receptors (GPR41 or GPR43), triggering the release of satiety-promoting hormones, such as peptide YY (PYY) and glucagon-like peptide 1 (GLP1), thereby reducing appetite (28). Moreover, certain microbes and metabolites—such as *Akkermansia muciniphila* and SCFAs—promote fatty acid oxidation in adipose tissue, providing a protective mechanism against obesity (29). Regarding SBAs, deoxycholic acid (DCA) has been demonstrated to reduce adipose tissue mass and prevent high-fat diet (HFD)-induced obesity by promoting lipolysis via activation of the TGR5 receptor and subsequent cAMP production (30, 31). Furthermore, both DCA and lithocholic acid (LCA) inhibit hepatic lipogenesis by suppressing the expression of sterol regulatory element-binding protein-1C (SREBP－1C, a key transcriptional regulator of lipid synthesis) through activation of the farnesoid X receptor (FXR), albeit with lower potency compared to primary bile acid, such as cholic acid (32).

T2DM, a hallmark age-associated metabolic disorder, is characterized by insulin resistance and progressive dysfunction of pancreatic β-cells, manifesting as persistent hyperglycemia, and frequently accompanied by dyslipidemia (33). Accumulating evidence indicates that compared to healthy individuals, the gut microbiome of T2DM patients exhibits alterations in both diversity and composition, while specific microbial changes may vary across studies; a consensus is emerging regarding general trends. Although taxonomic details vary, common features include decreased alpha and beta diversity, a reduction in *Firmicutes*, and increased *Bacteroidetes*. At the

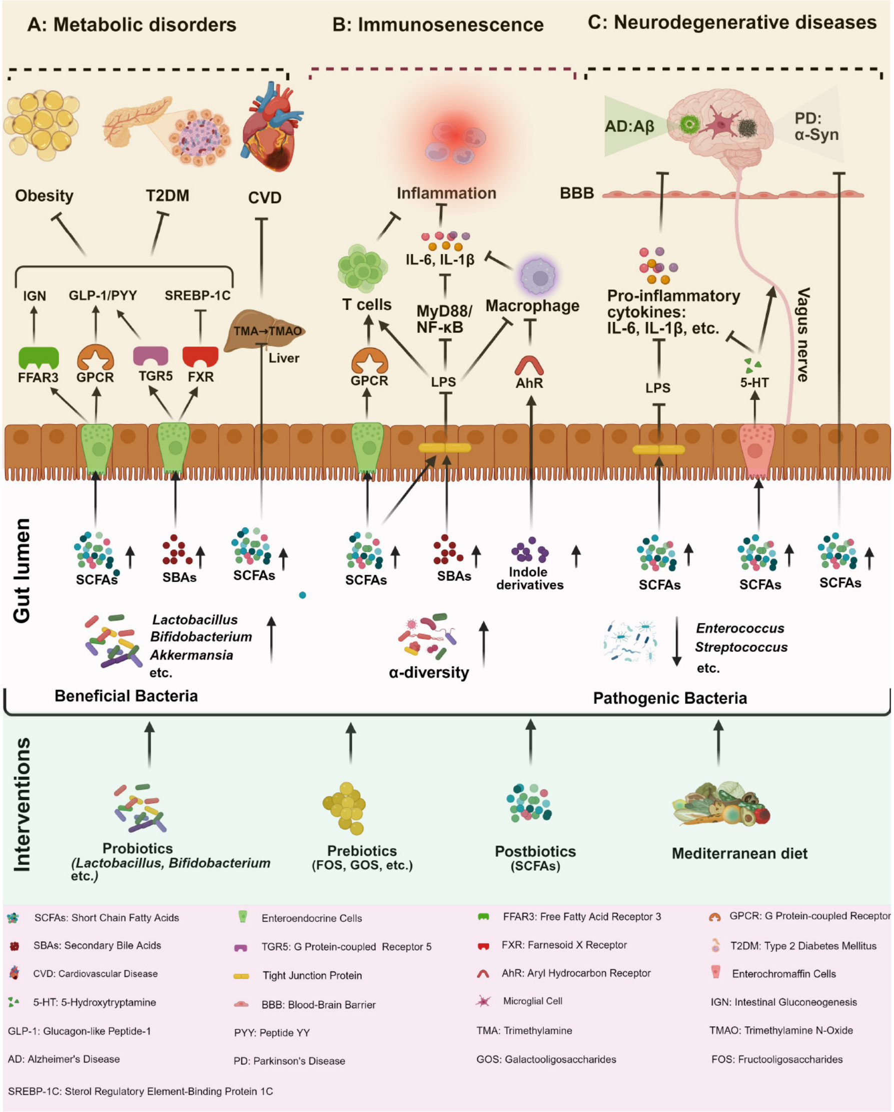

Fig. 2. Mechanisms of interventions targeting the gut microbiota to alleviate aging-related diseases. The gut microbiome plays a pivotal role in the onset and progression of aging-associated diseases, including metabolic disorders, immunosenescence, and neurodegenerative diseases. Interventions (e.g., probiotics, prebiotics, postbiotics, and the Mediterranean diet) can mitigate these diseases by remodeling the gut microbiota and promoting the production of microbial metabolites, such as short-chain fatty acids (SCFAs), secondary bile acids (SBAs), and indole derivatives. (A) (1) SCFAs enhance intestinal gluconeogenesis (IGN) by activating gut-derived fatty acid receptors FFAR3, thereby improving insulin resistance and alleviating obesity and type 2 diabetes mellitus (T2DM). (2) SCFAs stimulate the release of GLP—1 and PYY through the activation of gut-derived G protein-coupled receptors GPCRs, which suppress appetite or enhance insulin secretion, counteracting obesity and T2DM. (3) In addition to promoting GLP—1/PYY release via the activation of gut-derived receptor TGR5, SBAs activate gut-derived FXR receptors to inhibit the expression of the lipogenic factor SREBP—1C, exerting anti-obesity and anti-T2DM effects. (4) SCFAs reduce TMA levels, thereby inhibiting hepatic TMAO synthesis and lowering cardiovascular disease risk. (B) (1) SCFAs promote T-cell development by activating gut-derived GPCRs, reducing the risk of aging-related inflammation. (2) Both SCFAs and SBAs strengthen the intestinal barrier, suppressing LPS translocation into the circulation and attenuating inflammatory responses (e.g., T-cell activation, macrophage inhibition, and the suppression of MyD88/NF-κB-mediated inflammatory cytokine production). (3) Indole derivatives activate AhR receptors on macrophages, thereby modulating macrophage activity and inflammatory cytokine production, reducing cumulative inflammation. (C) (1) SCFAs enhance the expression of tight junction proteins, reinforcing intestinal barrier integrity, which inhibits LPS leakage and the activation of microglia by pro-inflammatory factors, thereby counteracting Aβ and α-Syn accumulation, and alleviating the pathology of Alzheimer's disease (AD) and Parkinson's disease (PD). (2) SCFAs promote 5—HT secretion by activating enterochromaffin cells, which stimulates the vagus nerve to suppress central nervous system inflammation, mitigating AD and PD. (3) SCFAs can directly cross the blood-brain barrier (BBB), inhibit microglial activation, reduce inflammatory accumulation, and ameliorate AD and PD.

genus level, pathogenic bacteria (e.g., *Coprococcus*, *Escherichia*, *Streptococcus*) are enriched, while beneficial genera (e.g., *Bifidobacterium*, *Akkermansia*, *Ruminococcus*, *Lactobacillus*, *Prevotella*) are depleted (33, 34). Intestinal barrier dysfunctions (commonly termed 'leaky gut') are a hallmark of T2DM. This condition facilitates the translocation of lipopolysaccharides (LPS) into systemic circulation, which activates the NF-κB inflammatory pathway, while subsequently inducing insulin resistance (33). Beneficial microbes, such as *A. muciniphila* and butyrate-producing bacteria, help maintain intestinal barrier function by modulating tight junction proteins, thereby reducing the risk of T2DM (35, 36). Another metabolic modulator, hepatic flavin-containing monooxygenase 3 (FMO3), promotes insulin resistance and hyperglycemia. Notably, probiotic interventions using *L. plantarum* and *A. muciniphila* effectively suppressed FMO3 expression, and improved insulin sensitivity in mice (29). Impaired intestinal gluconeogenesis (IGN), a key contributor to metabolic dysfunction in T2DM, can be ameliorated to reduce glycemic level by SCFAs (37). Butyrate and propionate activate IGN via cAMP-mediated pathway and the gut-brain neural circuit associated with the fatty acid receptor3 (FFAR3), respectively, exerting metabolic benefits, such as improving insulin sensitivity, and promoting glucose metabolism (37, 38). Furthermore, SCFAs can enhance peripheral glucose uptake by promoting the expression of glucose transporter 4 (GLUT4) (39). The metabolic benefits of SBAs in T2DM are primarily mediated through TGR5 receptor activation, which stimulates intestinal L-cells to secrete GLP−1, thereby enhancing insulin secretion and reducing glycemic levels (33, 39). Also, the tryptophan-derived microbial metabolite indole has been implicated in GLP−1 modulation through distinct mechanisms (25).

Beyond obesity and diabetes, gut microbial dysbiosis contributes to the pathogenesis of cardiometabolic diseases, notably through the gut microbial metabolite TMAO, which has been linked to hypertension, atherosclerosis, and heart failure (40). TMAO is produced when gut microbes metabolize dietary choline into trimethylamine (TMA), which is subsequently oxidized into TMAO in the liver (41). As well, in these individuals with cardiovascular diseases, TMAO levels are elevated, while TMAO-producing gut microbiota, such as *Enterococcus* and *Escherichia*, are also significantly enriched, indicating that gut microbiota dysbiosis is a critical contributor to the pathogenesis of cardiovascular diseases (25, 40). Importantly, interventions such as probiotics and SCFAs have emerged as promising candidates that are capable of mitigating cardiometabolic disorders by remodeling the gut microbiome to reduce circulating TMAO levels (41).

IMMUNOSENESCENCE AND MICROBIOME

Aging leads to a progressive decline in immune system function, a phenomenon termed immunosenescence. This process is characterized by reduced adaptive immune responses (e.g., fewer naïve T-cells and weaker antibody production), increased susceptibility to infections, and impaired vaccine efficacy (42). For example, elderly individuals have higher risk of severe influenza, and often show reduced antibody responses to flu vaccination (43). Immunosenescence also involves the onset of chronic pro-inflammation, often referred to as "inflammaging", in which circulating inflammatory cytokines are elevated, even without acute infection (42). This chronic low-grade inflammation is thought to stem partly from accumulated immune cell dysfunction and lifelong antigenic stress, contributing to tissue aging and disease susceptibility. The gut microbiome plays a pivotal role in shaping and regulating immune functions throughout life, and its age-associated alterations significantly contribute to immunosenescence (43). As individuals age, the composition and diversity of the gut microbiome undergo significant changes that can exacerbate immunosenescence (18). In elderly populations, studies have reported a loss of beneficial commensal bacteria (such as *Bifidobacterium* and butyrate-producing *Firmicutes*) and a concomitant increase in opportunistic pathogens or pro-inflammatory microbes (44, 45). Microbial diversity tends to decline with age, and beneficial anaerobes that predominate in a healthy adult gut (e.g. *Faecalibacterium prausnitzii* in Clostridial cluster XIVa) become less abundant (46). Meanwhile, potentially pathogenic or pro-inflammatory taxa (including certain *Proteobacteria* like *Enterobacteriaceae*) in the aging gut are often increased (46). These dysbiotic changes have been linked to impaired mucosal immunity, systemic inflammation, and heightened vulnerability to infections (47). As mentioned above, the aged gut microbiota produces fewer SCFAs, such as acetate, propionate, and butyrate, due to the loss of key fiber-fermenting bacteria (48). These metabolites play a critical role in maintaining gut epithelial integrity, regulating inflammatory responses, and supporting T-regulatory (T_{reg}) cell activity (49). Aging-associated depletion of SCFA-producing bacteria has been shown to exacerbate inflammatory states, thereby contributing to the inflammaging process. For example, butyrate and other SCFAs normally support mucosal immunity and have anti-inflammatory effects, so their decline lifts a critical regulatory constraint on inflammation (50). SCFAs also serve as a ligand for G-protein coupled receptors (e.g., GPR41, GPR43) on immune and epithelial cells, thereby promoting regulatory T-cell development and enhancing intestinal barrier function (49, 50). In dysbiosis where butyrate-producing bacteria (like *Faecalibacterium* and *Roseburia*) are reduced (51, 52), macrophages may receive fewer of these positive signals. Aging is naturally accompanied by a decline in naïve T-cell production due to thymic involution, leading to a reliance on memory T-cells. Dysbiosis may further exacerbate this process by promoting the translocation of microbial metabolites, like endotoxin LPS, into systemic circulation when the gut barrier is impaired, continuously activating innate immunity (53). This chronic activation depletes immune reserves, and accelerates the senescence of T cells. Consequently, aged macrophages in a low-SCFA environment may remain in a more inflammatory, but less effective, state (Fig. 2).

Immunosenescence affects both adaptive immunity and the innate immune system. The innate immune system, in particular, macrophages and neutrophils, also undergoes functional decline with age. For example in mice, macrophages from older individuals show impaired inflammatory and microbicidal responses in several ways (54). Aged macrophages produce lower levels of pro-IL−1β upon stimulation, reflecting a blunted inflammatory activation. Dysbiosis reduces the production of microbiota-derived molecules that modulate innate immune responses, leading to impaired pathogen clearance and increased inflammation (55). Dysbiosis-associated leaks of LPS and peptidoglycan into circulation may keep macrophages always in a primed state. Sustained exposure to these inflammatory stimuli leads to elevated baseline levels of IL−1β, contributing to inflammaging and tissue damage (IL−1β being implicated in bone loss, insulin resistance, etc., with age). This environment harms tissues (contributing to frailty and organ decline), while also potentially causing a form of "innate immune exhaustion", where following overstimulation, macrophages and neutrophils may become less responsive (56). Interestingly in mice, experimental studies have shown that transferring the gut microbiota from young to aged hosts can rejuvenate immune function and reduce systemic inflammation (57), highlighting the crucial role of the gut microbiome in modulating host immune responses. In essence, microbial tryptophan metabolites can act as a brake on overactive innate responses, helping to prevent chronic inflammation. Certain gut bacteria metabolize dietary tryptophan into indole derivatives (e.g., indole-3-aldehyde, indole propionic acid) that can bind the aryl hydrocarbon receptor (AhR) on immune cells. Activation of AhR in innate immune cells tends to have immunoregulatory effects. For example, AhR stimulation in macrophages has been shown to dampen the production of IL−6 and other pro-inflammatory cytokines in response to LPS (58). Consequently, aging-associated gut dysbiosis can chronically stimulate the immune system, contributing to inflammaging (59) (Fig. 2).

AGE-RELATED NEURODEGENERATIVE DISEASE AND MICROBIOME

Gut microbes produce a variety of signaling molecules (SCFAs, acetylcholine, 5−HT, etc.) as the neuroactive chemicals that can affect neural function, while the brain can modulate gut physiology and microbial composition through stress hormones and autonomic nerves (60). This bidirectional communication, known as the gut-brain axis (GBA), involves interactions among the gut microbiome, the immune system, and the central nervous system (CNS), and plays a crucial role in maintaining normal brain function and behavior. Increasing evidence suggests that dysregulation of the GBA contributes to the pathogenesis of neurodegenerative diseases, such as AD, PD, and other age-related cognitive impairments, highlighting the importance of gut microbiota in brain health and disease (61, 62). Dysbiosis may trigger or exacerbate neuroinflammation and neuropathology via microbial molecules that reach the brain or peripheral immune system. Thus, investigators are now examining how age-related changes in the microbiome might contribute to the development and progression of neurodegenerative disorders. Aging with dysbiosis can lead to increased gut permeability, also known as 'leaky gut', allowing bacterial components, such as endotoxin LPS, to enter systemic circulation. LPS can cross the blood-brain barrier (BBB), initiating neuroinflammation, a hallmark of neurodegenerative diseases (63). For example, AD, the most common form of dementia in the elderly, is characterized by chronic neuroinflammation and amyloid-beta (Aβ) misfolding pathology. Elevated levels of pro-inflammatory cytokines (e.g., IL−1β, IL−6) and LPS have been shown to promote Aβ aggregation and tau pathology (64). Notably, individuals with AD often exhibit a depletion of anti-inflammatory or neuro-supportive microbes (e.g., *Lactobacillus*, *Bifidobacterium*, *Prevotella*), and an increased abundance of pro-inflammatory genera, such as *Ruminococcus*, particular *Proteobacteria*, and *Enterobacteriaceae* (65, 66). Certain gut bacteria produce amyloid-like proteins that can mimic host amyloids, potentially accelerating the misfolding and aggregation of Aβ in the brain (63). In addition, AD patients have also shown reduced abundance of SCFA-producing bacteria, such as *F. prausnitzii* (67). This microbial shift can affect the host's neurochemistry and immune milieu. For example, the loss of beneficial microbes may lead to decreased production of butyrate, a SCFA that has neuroprotective and anti-inflammatory properties in the brain. Concurrently, an overgrowth of gram-negative bacteria elevates levels of endotoxin LPS in circulation, which can induce systemic inflammation and disrupt the BBB. Such chronic inflammation is believed to promote AD pathogenesis by activating microglia (the brain's immune cells) and facilitating Aβ aggregation in the brain. Supporting this, in AD mouse models, disrupting the gut microbiota with antibiotics was shown to alter neuroinflammation and amyloid deposition, underscoring a causal link (68) (Fig. 2).

Another age-related neurodegenerative disease is PD, which primarily affects motor control due to the degeneration of dopaminergic neurons in the *substantia nigra* of the brain. A hallmark of PD is the misfolding and aggregation of alpha-synuclein (α-Syn) protein into Lewy bodies. Intriguingly, research suggests that PD may, in part, originate in the gut. Braak's hypothesis proposes that misfolded α-Syn may first appear in the enteric nervous system, and then travel to the brain via the vagus nerve (69). Gut microbiome abnormalities have been closely linked to PD. Case-control studies show that PD patients have significant dysbiosis: an increase in certain bacteria (e.g., *Lactobacillaceae*, *Enterococcaceae*, and genera like *Barnesiella*) and a decrease in anti-inflammatory bacteria (notably SCFA-producing *Clostridia*, such as *Clostridium* *coccoides*, as well as *Prevotellaceae* and *Bacteroides fragilis*), compared to healthy controls (70). The overrepresentation of pro-inflammatory microbes in PD can lead to greater exposure to microbial products like LPS and Curli (a bacterial amyloid protein). LPS from gut bacteria has been shown to activate microglia in the brain, and promote dopaminergic neuron death (71). A study utilizing α-Syn-overexpressing (ASO) mice demonstrated the significant influence of gut microbiota on the PD manifestation. ASO mice that received fecal transplants from PD patients exhibited worsened motor symptoms, compared to those that received transplants from healthy donors (70). As well, a case report described a PD patient who received FMT from a healthy donor, and experienced temporary improvement in leg tremors and other PD-related symptoms (72). In addition, a recent epidemiological study revealed that patients with PD exhibit a persistent deficiency of SCFA-producing bacteria, while SCFAs are known to exert beneficial effects on inflammatory responses in the central nervous system, such as preventing the overactivation of microglia (2) (Fig. 2).

PROBIOTICS, PREBIOTICS, AND POSTBIOTICS AS ANTI-AGING INTERVENTIONS

Modulating the gut microbiome through probiotics, prebiotics, and postbiotics has emerged as a promising strategy to promote healthy aging. These interventions operate via distinct mechanisms: probiotics introduce beneficial microbes, prebiotics nourish them, and postbiotics deliver their bioactive metabolites. Collectively, they help restore microbial balance, enhance metabolic disorders and the immune function, and reduce systemic inflammation—contributing to improved health span and longevity (Fig. 2).

Probiotics, such as *Lactobacillus* and *Bifidobacterium*, are live microorganisms that can survive gastrointestinal transit and positively influence microbial balance. In addition to maintaining gut health, probiotic supplementation has been reported to ameliorate metabolic disorders, such as type 2 diabetes and cardiovascular disease, by modulating the gut microbiota, thereby enhancing insulin signaling and reducing circulating cholesterol levels (73). In older adults, strains like *L. rhamnosus* and *B. longum* have been shown to improve immune responses, enhance vaccine efficacy, and reduce infection risk (74, 75). Probiotic supplementation (e.g., *L. rhamnosus* GG, *B. breve*, or *L. casei*) also increases the production of the anti-inflammatory cytokine through several signaling pathways that include STING/TBK1/NF-κB, IL−10R2/STAT3/SOCS3, and TLR2/MyD88 (76-78). Probiotics (e.g., *L. plantarum*, *L. rhamnosus*) help reinforce the gut barrier by upregulating tight junction proteins, and help prevent pathogen overgrowth, lowering the risk of infections like *Clostridioides difficile* colitis (79, 80).

Prebiotics, such as inulin, fructo-oligosaccharides (FOS), and galacto-oligosaccharides (GOS), are non-digestible dietary fibers that selectively promote the growth of SCFA-producing bacteria, notably *Bifidobacterium* and *F. prausnitzii* (49, 80, 81). Elevated SCFA levels, especially butyrate, improve intestinal barrier integrity, reduce systemic inflammation, and enhance macrophage activity (61, 82). Prebiotic intake also supports glucose tolerance, lipid metabolism, insulin sensitivity, and immune function in humans (81, 83). Natural fiber-rich diets—based on fruits, vegetables, and whole grains—are associated with reduced inflammation and healthier aging trajectories.

Postbiotics refer to non-viable microbial cells or their metabolites, including SCFAs, peptides, enzymes, polysaccharides, and cell wall components (84, 85). Unlike probiotics, postbiotics pose no risk of infection, making them suitable for frail or immunocompromised older adults (84). Postbiotics have shown significant promise in alleviating metabolic disorders by modulating host metabolism and inflammation. Specifically, they can increase energy expenditure, inhibit adipogenesis, and improve glucose handling, while also acting on lipid absorption and inflammatory pathways, thereby ameliorating obesity and insulin resistance (86). In addition to SCFAs, SBAs—such as DCA and LCA—modulate immune responses via FXR and TGR5 receptors, promoting anti-inflammatory cytokine IL−10 production while dampening NF-κB-mediated inflammation (87). Aging-related dysbiosis may impair SBA production, contributing to immunosenescence and inflammaging.

Beyond immunity, these interventions show promise in neurodegenerative conditions via the GBA. Probiotic strains (e.g., *Bifidobacterium*, *Lactobacillus*, and *Akkermansia*) and probiotic cocktails have shown promise in reducing neuroinflammation and improving cognitive function in models of AD, PD, and amyotrophic lateral sclerosis (88). Small clinical and preclinical studies have shown cognitive benefits in cognitive impairment (MCI) and mild AD after *Bifidobacterium* and *L. plantarum* supplementation (89, 90), while meta-analysis of 9 randomized controlled trials (663 patients) shows significant improvements in motor symptoms, including better Unified Parkinson's Disease Rating Scale (UPDRS) motor scores, and reduced constipation, anxiety, and depression (91). In addition, the Mediterranean diet, which is rich in dietary fiber, polyphenols, fermented foods, and unsaturated fatty acids, exerts neuroprotective effects by modulating the gut microbiota and increasing beneficial metabolites such as SCFAs, thereby alleviating neuroinflammation and neurodegenerative pathology (92). SBAs also influence neuroinflammation and microglial activity, and altered SBA profiles have been observed in AD (93) (Fig. 2).

Synbiotic interventions, combining probiotics with prebiotics, may yield synergistic benefits. In animal studies, synbiotic regimens extended lifespan more effectively than either component alone (94). Although direct evidence in human longevity is limited, these strategies improve inflammation markers, metabolic health, and immune function—all contributing to a longer health span. Notably, centenarians have identified gut microbiome profiles enriched in SCFA-producing and lactic acid bacteria, alongside reduced inflammation (95). Clinically, biotic-based therapies are being evaluated to manage age-related disorders (96). Fiber-rich, diverse diets remain a low-cost, effective approach to support beneficial microbiota, and to improve age-related outcomes (97). Fermented foods, like kimchi, yogurt, kefir, and sauerkraut, serve as convenient food-based sources of probiotics and postbiotics (98). Looking ahead, personalized synbiotic regimens may be developed based on individual microbiome profiles. Strategically integrating these microbiome-based strategies into individualized nutritional or therapeutic regimens may offer a systems-level approach to mitigate metabolic disorders, delay immunosenescence, preserve cognitive function, and promote healthy longevity.

DISCUSSION AND CONCLUSION

The intricate interplay between the gut microbiome and age-related diseases is rapidly emerging as a pivotal area in aging research. This review systematically elucidates the core alterations in the gut microbiome during aging, including reduced diversity, a decline in SCFA-producing bacteria, and the overgrowth of pathobionts. These changes disrupt host homeostasis through metabolic, immunological, and neuroendocrine pathways, contributing to the onset and progression of various age-associated disorders.

Microbiota-targeted interventions, such as probiotics, prebiotics, and postbiotics, have in preclinical studies demonstrated the potential to modulate the aging process (1). These strategies offer potential benefits, including the enhancement of immune surveillance, reinforcement of the intestinal barrier, attenuation of systemic inflammations, and support for neurocognitive function. Moreover, emerging translational studies in humans, such as FMT, have provided preliminary causal evidence linking microbiota composition to metabolic and cognitive outcomes in older adults. Studies of centenarians consistently reveal a unique gut microbial signature enriched in SCFA-producing bacteria and anti-inflammatory metabolites, offering insights into potential microbiome-based longevity mechanisms. However, the clinical translation of such interventions remains limited by several challenges. First, the inter-individual variability in gut microbial composition, influenced by environment, genetics background, diet, lifestyle, and baseline microbial profiles, suggests that a ‘one-size-fits-all’ approach using single strains or metabolites may have limited efficacy. Recent studies also emphasize that dietary patterns, polypharmacy, and comorbidities act as major confounders in microbiome-aging research, complicating the interpretation of causal relationships (2, 92, 99). Second, although FMT from young to aged donors in animal models has reversed age-associated inflammation and diseases (26), and early-phase clinical studies in older adults report promising effects on age-related sarcopenia (100), most existing human data remain correlative and mechanistic causality is not yet established. Addressing these gaps will require controlled feeding trials, integration of gnotobiotic models, genetically engineered microbes, controlled feeding trials, and longitudinal human cohorts to disentangle microbial effects from lifestyle or treatment-related variables. Safety and regulatory issues, especially concerning engineered probiotic or novel postbiotic delivery systems, must also be addressed.

Despite these challenges, the therapeutic potential of gut microbiome modulation is substantial. As the field moves toward precision microbiome medicine, future research should prioritize: (1) integrating multi-omics technologies (metagenomics, metabolomics, single–cell sequencing, and host transcriptomics) to identify predictive aging-associated microbial biomarkers and their dynamic regulatory networks; (2) developing precision intervention strategies, such as AI-based gut microbiome profiling to guide the design of personalized probiotic combinations; (3) exploring novel delivery systems (e.g., nanoparticle encapsulation of SCFAs or next-generation engineered probiotics) to enhance efficacy; and (4) conducting large-scale longitudinal cohort studies to determine the long-term impact of gut microbiome interventions on health span and resilience in aging populations.

In conclusion, the gut microbiome functions as both a biosensor of aging physiology and a modifiable therapeutic axis. By incorporating insights from centenarian biology, FMT trials, and translational omics, the field is poised to move beyond correlation toward causation and clinical applications. Strategically integrating microbiome-based interventions into personalized geriatric care offers a promising systems-level approach to delay aging, mitigate disease burden, and promote healthy aging.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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