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Narrative Review of Microbiome and Aging

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ABSTRACT

The human microbiome, composed of trillions of bacteria, archaea, fungi, and viruses, is essential for maintaining metabolic, immune, and neurological homeostasis. With aging, the composition and function of microbial communities undergo profound changes, contributing to systemic inflammation, immune dysfunction, metabolic derangements, and neurodegeneration. Hallmarks of aging, including genomic instability, cellular senescence, and mitochondrial dysfunction, intersect with age-associated dysbiosis, exacerbating the onset and progression of chronic conditions such as cardiovascular disease, diabetes, and Alzheimer's disease. Altered microbiota composition reduces resilience, impairs immune regulation, and disrupts gut–brain communication, fostering frailty and cognitive decline. Conversely, microbiome-targeted strategies, including probiotics, prebiotics, dietary interventions, and fecal microbiota transplantation (FMT), demonstrate potential for restoring balance and promoting healthy aging. Advances in multi-omics and machine learning are improving mechanistic understanding and enabling personalized interventions, though challenges remain in standardization, reproducibility, and long-term efficacy. This review summarizes current insights into the bidirectional relationship between microbiome dynamics and aging, highlighting therapeutic opportunities and future research directions.
Keywords: Microbiome**,** Aging**,** Immunosenescence**,** Gut–brain axis, and Fecal microbiota transplantation.

INTRODUCTION

Various microbial communities colonizing the body in a site-dependent manner are collectively called the microbiome, and include bacteria, archaea, viruses, fungi, and protists [1]. The human microbiome comprises a total of 10–100 trillion symbiotic microbial cells, with the largest concentrations found in the human gut. Notably, gut microbes can play critical roles in human physiology and serve as modulators of several mammalian metabolic and immune functions [2]. The maintenance of homeostasis is necessary for proper functioning, and there is accumulating evidence that alterations in the homeostatic profile accelerate or increase susceptibility to the aging process. Aging is a major risk factor for many human diseases and pathological conditions. Aging-related metabolic changes have been discussed in the context of microbiome alteration, which may have serious implications for health and disease. For example, the gut microbiota also plays a major role in the regulation of immunity, and the age-related change in its composition is strongly associated with immune dysfunction 3. It is estimated that the incidence of contracting infections increases drastically in the elderly population due to the severe decline in immune function [1]. Thus, an examination of the homeostasis of the body and the microbiome has taken on increasing importance. Moreover, the microbiome has been shown to prime the development and function of the central nervous system, and aging-associated changes in its composition induce neurological disorders that include Alzheimer's disease, Parkinson's disease, and depression. This review provides an overview of recent studies on the microbiome and aging, with a particular focus on related diseases and therapeutic interventions [2].

Understanding the Microbiome

The human body harbors a vast number of microbes that substantially exceeds our own cells in quantity. These microbes, collectively known as the microbiota, along with the anatomical sites they colonize, such as skin, gut, and lungs, constitute the microbiome [1]. In healthy adults, microbial communities are relatively stable and resilient over time, supporting essential functions and maintaining homeostasis. Overall, the microbiome acts as a comprehensive metabolic organ that complements and expands the human genome, a function that is particularly important at the extremes of life [2]. The gut microbiota alone encodes more than 3 million genes, forming an extensive metabolic system in mutualistic association with the host. It has been estimated that approximately 20% of the blood metabolites circulating in humans originate from microbial activity [3]. These metabolites can modulate nearly all human metabolic pathways and physiological functions, thereby affecting human health and inflammatory status. The composition of the human microbiome is influenced by various factors, including age, diet, lifestyle, residence and living conditions, drug intake, and the host's physiological state from pre- to post-mortem [3].

Definition and Composition

"Microbiome" encompasses the genetic material of all microbes inhabiting an environment; in this context, those associated with the human body. The human microbiome consists of trillions of microbes, including bacteria, archaea, fungi, and viruses [4]. Hence, the microbiome serves as a reservoir for metabolizing various compounds, including xenobiotics, probiotics, as well as host- and diet-derived nutrients. Essential arrows point right. The human body is a meta-organism comprising both host cells and the microbiome[4]. Following the initial establishment of a proto-microbiome during infancy, it proceeds through assembly, development, and maturation, arriving at a relatively stable state during adulthood, eventually changing with host physiology across the lifespan [5]. Microbiome composition is shaped by the interplay of host-extrinsic factors, such as diet and geographical location, and host-intrinsic factors, such as immunological control and genetic inheritance. Shifts in the microbial composition of aging hosts, coupled with a systemic decline in immune functions and tissue homeostasis, contribute significantly to aging-associated health deterioration [1].

Functions of the Microbiome

The human microbiota can be envisaged as a real organ with multiple metabolic functions indispensable for the maintenance of health. It carries out the digestion of complex carbohydrates to release beneficial short-chain fatty acids, and it carries out this task more efficiently than the human host cells; the intestine housing the microbiota possesses a much greater total surface area in comparison with the host's gut [1]. The microbiota strongly influences the immune and nervous systems, modulates the synthesis and turnover of lipids, amino acids, and vitamins, and intestinal absorption of minerals; it also plays active roles in the regulation of gut motility, modulation of the host's intestinal endocrine system, and synthesis of neurotransmitters and neurological modulators. The microbial ecology of the human intestine is characterized by four dominant bacterial phyla, Bacteroidetes and Firmicutes being the most abundant. Within the dominant microbes, only a relatively small set of species is commonly detected in most of the subjects [1]. Further to host genetic and environmental factors, particular influence is exercised by host lifestyle and diet; thus, microbial diversity and load rise from birth to adolescence, to attain an adult gut microbiota at the age of three years. Once established, the set-up of the microbiota remains rather constant throughout adult life and then declines in old age. Especially in the elderly, it is fitting to consider the host and its microbial communities as a "superorganism" resulting from a tight mutualistic interaction and cross-communication among different genomes [1].

Factors Influencing the Microbiome

The microbiome comprises a myriad of microorganisms distributed across distinct body habitats, including the gastrointestinal tract, lungs, nose, skin, oral cavity, vagina, uterus, and bladder [2]. Commensal microorganisms within the microbiomes provide essential healthy functions, such as nutrient decomposition, immune system development, strengthening of the gut barrier, out-competition against pathogens, colonization resistance, xenobiotic/toxin/vitamin metabolism, and gut-brain axis regulation [2]. The diversity and dynamic evolution of the microbiome vary greatly, depending on the specific body system and clinical status. Internal and external factors contribute to shaping and reshaping the microbiome [6]. External factors include the birth delivery mode (vaginal delivery versus caesarean section), geographical location, cultural habits, dietary patterns, smoking and alcohol consumption, drug use (antibiotics and non-antibiotics), and antibiotic resistance genes. Internal factors encompass age, gender, host gene variations, mucus composition, and host immune system [2, 6].

Aging and Its Impact on Health

Aging is an inevitable biochemical process resulting from the body's limited capacity to regenerate, leading to the gradual decline of physiological functions and is associated with an increased risk of chronic illnesses, including

cancer, cardiovascular diseases, and neurodegenerative disorders. Common hallmarks of aging include genomic instability, reduced telomere length, epigenetic alterations, defective nutrient sensing, loss of proteostasis, cellular senescence, stem cell exhaustion, and altered intercellular communication [3]. Cellular senescence, characterized by irreversible cell-cycle arrest and epigenetic dysregulation, contributes to tissue degeneration and the exacerbation of the aging phenotype. Exposure to factors such as radiation, tobacco smoke, reactive oxygen species (ROS), and chemotherapy can induce premature senescence via mechanisms including DNA damage and telomere attrition. Age-related systemic changes in the epigenome may further amplify these processes and diminish the efficacy of DNA repair mechanisms [3]. The progressive accumulation of senescent cells leads to the development of a pro-inflammatory microenvironment known as the senescence-associated secretory phenotype (SASP), comprising cytokines, proteases, growth factors, and chemokines. This milieu contributes to healthy aging and fosters the onset and progression of age-related diseases [3]. Aging also affects brain structure and function, with evident morphological, biochemical, and metabolic alterations in key regions like the hippocampus and prefrontal cortex. Neuroimaging studies in healthy elderly individuals reveal cortical shrinkage, neuritic dystrophy, mossy fiber sprouting, axonal fragmentation, and impaired transport mechanisms [2]. Decreased plasticity in the aged brain may underlie neurodegenerative changes and associated cognitive deficits. The functionality of the hypothalamic–pituitary–adrenal axis also declines with age, increasing vulnerability to psychological disorders such as depression, anxiety, schizophrenia, and dementia. These shifts in brain structure and function mirror the interplay between physiological and psychological aspects of aging [2].

Biological Mechanisms of Aging

Aging is a progressive decline of physiological function, generally accompanied by an increased risk of death 3. A body of evidence demonstrates that aging is a major risk factor for major chronic diseases. Despite an enormous effort in the last decades, the aging biological network has been only partially elucidated [2]. Notwithstanding the characterization of aging remains elusive, it is possible to observe several biological aging hallmarks at cellular and molecular levels, including genomic instability, loss of proteostasis, epigenetic alterations, mitochondrial dysfunction, telomere attrition, deregulated nutrient sensing, cellular senescence, stem cell exhaustion, and altered intercellular communication [2]. It is well established that aging is associated with major neurological disorders, which significantly impact the quality of life of the elderly population. Alzheimer's disease (AD), mild cognitive impairment (MCI), dementia, and Parkinson's disease are the most common neurological disorders linked to aging [2]. The decline in mental health of the elderly is a frequent and underdiagnosed phenomenon [7]. Depression, anxiety, dementia, and medical comorbidities commonly co-occur, yet they are often not adequately managed with appropriate mental health services. Psychological disorders exert important negative effects on health and are often associated with active distal inflammatory processes [7].

Aging-Related Diseases

Cardiovascular diseases are accompanied by unbalanced gut microbiomes [1]. Chronic heart failure correlates with increased pathogenic species, decreased health-supporting species, and reduced microbial gene richness. Type-2 diabetes mellitus patients display lower Firmicutes-to-Bacteroidetes ratios, Bifidobacterium, Faecalibacterium, Akkermansia, and Roseburia abundances, alongside increased Clostridiales, Lactobacillus gasseri, and Streptococcus mutans 8. Individuals with atherosclerosis have lower Roseburia and Eubacterium and higher Collinsella levels. Gut-derived toxins and metabolites promote inflammatory responses, triggering cardiovascular immune pathogenesis and contributing to disease progression [2]. Microglia undergo functional, morphological, and ultrastructural changes with age, prefacing declining neurological capacity. In aged neurodegenerative diseases such as Parkinson's, Alzheimer's, or multiple sclerosis, microglia are hyperactivated, exacerbating neuroinflammatory responses. Accumulating evidence links the microbiota with neurodegenerative conditions; elevated α-synuclein pathology and motor impairment in Parkinson's disease and amyloid-β deposition in Alzheimer's disease are tied to microbiome alterations [2]. The gut-brain axis, also associated with cognitively healthy aging, critically contributes to microglial maturation and function. Microbe-microglia connections represent a promising therapeutic target to retard age-associated cognitive decline [2]. Aging is a major risk factor for diabetes, characterized by a distinct gut microbiome signature. Taxonomically, induced diabetes manifests as gut dysbiosis. Individuals at risk of diabetes show high levels of Prevotella and low abundances of Akkermansia. Non-obese diabetic subjects exhibit enrichment of Bacteroides, segmented filamentous bacteria, and the anti-inflammatory microorganism Faecalibacterium, suggesting potential for microbial-based strategies in diabetes management. Certain microbial components prompt systemic low-grade inflammation and/or disrupt mucosal integrity; thus, bidirectional interactions between the host immune system and the gut microbiota likely maintain or disrupt health during aging [1, 2]. Expression of specific human miRNAs also regulates composition and homeostasis of the intestinal microbiota[2]. Inflammation fosters a shift in microbial composition towards

opportunistic Proteobacteria, a hallmark of intestinal microbial imbalance and risk factor for disease. Interactions between age-associated microbiota alterations and chronic inflammation represent an important process in aging. Some gut microbial components modulate extraintestinal sites via their products, suggesting multiple pathways connect aging, longevity, and the gut microbiota [1, 2].

Psychological Aspects of Aging

In humans, progressive loss of physiological integrity during aging results in impaired function and increased vulnerability to death. Aging is characterized by genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, and cellular senescence [2]. Hallmark biological effects affecting the nervous system include impaired stress response signaling, genomic instability, loss of proteostasis, dysregulated nutrient sensing, mitochondrial dysfunction, senescence, stem cell exhaustion, and altered intercellular communication. Common age-related psychological changes include increased incidence of depression and anxiety, impaired memory, sleep disturbance, and cognitive decline [2]. Both the onset and progression of atherosclerosis are age-dependent. The risk of developing cardiovascular disease in people of all age groups increases with high blood pressure, high cholesterol, and obesity [9]. Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal lobar degeneration (FTLD), progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), and Creutzfeldt–Jakob disease/dementia with Lewy bodies (CJD/DLB) are the most common age-related neurodegenerative diseases. "Mood/cognitive" and sleep symptoms, depression, dysautonomia, and mild cognitive impairment (MCI)/mild dementia are the most frequent non-motor disturbances in aged individuals [2, 9].

The Relationship between Microbiome and Aging

The microbiome and aging are intrinsically intertwined 2. Physiological aging influences the structure, function, and diversity of intestinal microbiota, contributing to increased susceptibility in the elderly [3]. Disruption of gut flora homeostasis can affect immune system function, gastric mucosa, host metabolism, and cognitive processes through the brain–gut axis. Conversely, the microbiome modulates the rate and quality of aging, further underscoring their intimate relationship. Following the understanding of microbiome composition and the multifactorial overview of aging and its health effects, detailing how aging alters microbial communities and the resulting systemic consequences provides a coherent and logical framework [3]. Aging significantly impacts the microbiota, leading to changes that foster inflammation-related illnesses. The elderly display a unique gut microbiome exhibiting marked inter-individual variability yet shared taxonomic and functional characteristics. Aging induces a shift in biodiversity by degrading and depleting certain species. Compared to younger adults, the elderly show differences in several hundred bacterial phylotypes. Altered and reduced biodiversity destabilizes the microbiome and triggers inflammatory responses. Older individuals exhibit reduced abundance of beneficial bacterial genera such as Bifidobacteria. Consequently, a state of geriatric inflammation arises throughout the host.
The aging microbiome increases vulnerability to opportunistic infections and disease development, which then aggravates alterations to the flora, creating a pernicious cycle. Otherwise, the aging microbiome impairs metastatic efficiency by affecting energy extraction from nutrients. It modifies host digestive and feeding behaviors and disrupts glucose homeostasis, thereby promoting weight loss in late life. Increasing evidence supports the microbiome's critical role in the host aging process and the onset and progression of diseases. This intricate linkage unites microbiology and delves deeper into the multifaceted biological mechanisms active in the aging process [3].

Microbiome Changes with Age

The progression of aging is inevitably accompanied by a steady decline in physiological functions and a heightened susceptibility to numerous chronic diseases. Age-associated modifications encompass changes in diet, diminished gastrointestinal motility, waning immune responsiveness, and a reduction in the regenerative capacity of intestinal stem cells. These factors collectively have the potential to influence the composition and diversity of the microbiome [4]. The human microbiome, which includes the microorganisms residing in the oral cavity and the gut, exhibits extensive variability and plays a crucial role in maintaining health. Dysbiosis, manifesting as a microbiome imbalance, has been implicated in conditions such as periodontitis, chronic respiratory infections, Alzheimer's disease, inflammatory bowel disease, frailty, and opportunistic infections related to aging. Restoring a healthy bacterial community via fecal microbiota transplantation has demonstrated rejuvenating effects and provides insights into the mechanisms underlying these diseases [4]. Although the majority of investigations have concentrated on young adult cohorts, fewer have examined microbiome alterations in disease-free older adults. Existing studies of the gut microbiome in healthy elderly individuals report increased instability, with elevated levels of bacterial taxa such as Clostridiales and Alistipes. Nevertheless, confounding factors, including residential environment and diet, complicate interpretations, contributing to inconsistent findings [4]. The genus

Bacteroides, for instance, displays variable abundances across different aging populations. To circumvent these confounders, comparative analyses of oral and fecal microbiomes were performed on healthy, community-dwelling older and younger adults. This approach aimed to exclude the influences of frailty and illness, thereby enabling a clearer characterization of microbiome changes associated with the aging process [4].

Impact on Immune Function

Preserving immune homeostasis is central to healthy aging. Age-related degeneration of immune function, known as immunosenescence, is associated with chronic systemic inflammation and contributes to the onset of aging-related diseases. Older individuals have increased levels of inflammatory markers such as C-reactive protein, interleukin [6], and tumor necrosis factor α. The aged immune system also demonstrates marked changes in population frequencies and fitness of immune cells. At the same time, the aged microbiota loses diversity and the capacity to induce Th1 and Th17 differentiation. Immune cells express a variety of pattern recognition receptors, including TLRs and C-type lectin receptors, capable of sensing both the microbiota and pathogens. Shifts in microbiota composition resulting from dysbiosis or ageing can therefore manifest as immune dysfunction [10].

The microbiota develops commensurate with the immune system in infancy, exerting a strong influence on T cell differentiation and maturation [2]. Even in adults, immune development is impaired in germ-free mice. Autoimmune and autoinflammatory diseases are enriched compared to conventional mice, and some can be reversed upon microbiota reconstitution. Non-lymphoid immune populations similarly rely on microbial stimuli to differentiate, populate tissues, and initiate antimicrobial defence, and their depletion also predisposes to disease. Accumulation of pathobionts is associated with infiltration of pro-inflammatory macrophages and intestinal inflammation, while reduced abundance of butyrate-producing microbes leads to decreased Foxp3+ regulatory T cells and intestinal inflammation. Microbial-mammalian shared metabolites and pathogen-sensing pathways are thought to further modulate immunological fate [11].

Effects on Metabolism

The ageing microbiome has been implicated in the pathogenesis of a plethora of distinct ageing-related diseases. Some of these diseases have a direct link to ageing-related metabolic alterations. For instance, the association between the microbiome and metabolic syndrome is among the strongest. Metabolic syndrome represents a set of metabolic disorders linked to an increased risk of cardiovascular disease and type 2 diabetes, and further increases the likelihood of developing a neurodegenerative disease such as Alzheimer's disease, in which microbiome dysbiosis has also been described [1]. Elevated levels of pro-inflammatory cytokines and elevated blood pressure have been linked with microbiome alteration in patients with metabolic syndrome, while overall microbial diversity was greatly decreased. It appears that microbial diversity decreases with ageing, and dysbiosis of the microbiome leads to a leaky gut, which more easily allows bacterial products to enter the bloodstream and trigger a systemic inflammatory response [1]. Even as changes in the microbiome in metabolic syndrome manifest in an increased abundance of species belonging to the Bacteroidetes phylum, other metabolic diseases like obesity are associated with an increase in Firmicutes to Bacteroidetes ratios [1]. Type 2 diabetes, present in the majority of subjects with metabolic syndrome, has been associated with a loss of butyrate-producing bacteria and overall higher abundance of pathogenic bacteria, which can enhance systemic inflammation. The interplay of diabetes and the microbiome is so tight that manipulation of the microbiome has been proposed as a new treatment opportunity [1].

Microbiome and Age-Related Diseases

Alterations of the microbiome contribute to the pathogenesis of several diseases. Dysfunctions of the cardiovascular, neurodegenerative, and metabolic systems are common among the elderly [12], and an abnormal microbiome has been associated with each of these impaired processes. Variability of both the composition and function of the intestinal microbiota in cardiovascular diseases is evident. The magnitude of the intestinal microbiota alterations experienced is closely linked to the severity of the disease state. Cardiomyopathy results in a 90% reduction of microbial metabolites, combined with a loss of circadian rhythmicity, whereas heart failure results in 10 to 30% decreases, with a complementary 25 to 50% increase in bacteria linked to human pathologies. Hallmarks of both cardiovascular disease and microbial dysbiosis, such as increased inflammation and permeability of the intestinal barrier, coincide in such multimorbidity. Dysregulated peripheral molecular clocks are partially responsible for age-imposed microbiota alterations; therefore, disruption of circadian rhythms may underlie age-associated cardiovascular disease. The intestinal microbiome is closely linked with the central nervous system and brain activity at both genetic and functional levels [2]. The gut-brain axis provides vital communication and regulation across several body systems; hence, disruptions of microbial stability have the potential to influence brain health, disease onset, and the pace of neurodegeneration. The brains of elderly individuals affected by Alzheimer's disease or status epilepticus contain decreased concentrations of primary bile acids, while deoxycholic

acid and lithocholic acid, secondary bile acids toxic to neurons and glial cells, increase [2]. Acute seizures induce microbiome alterations prior to changes in the central nervous system, indicating that microbial dysbiosis may influence neurological injury. A causal link has also been shown between microbiome perturbations and cognitive decline in mice exhibiting Alzheimer's disease. The serum of such mice contains more hippocampal metabolites implicated in cognitive outcomes, further implicating microbial-metabolomic interactions in neurodegeneration. Perturbations of the fecal microbiome and microbiome-derived metabolites extend into the metabolic system, with both type 1 and type 2 diabetes exhibiting marked gut dysbiosis [2]. Such disorders are prevalent throughout the elderly, and an abnormal microbiome impairs glucose tolerance, lipid metabolism, and insulin sensitivity, thus fostering the model of microbiome-driven metabolic dysfunction. Collectively, these analyses demonstrate that microbiome alterations are a fundamental contributor to the onset and progression of aging-related diseases [2].

Microbiome in Cardiovascular Diseases

Aging is closely associated with adverse cardiovascular health. Microbiome-host interaction plays a critical role in cardiovascular diseases (CVDs). The microbiota-maturation process is nearly completed by two years of age and plays a vital role in the development of the immune system. The early-life accumulation of specific microbes can increase the risk of inflammatory diseases, including hypertension in later life. Gut microbiota regulates immune response, energy metabolism, and intestinal permeability, representing an important factor in the development of the vascular system and the host physiology [13]. The deterioration of renal function with aging, with impaired clearance of proinflammatory metabolites, in combination with an altered microbiome, increases the risk of CVD. These observations point to the potential of chemical therapeutics and microbiota-targeting approaches for age-related CVDs [14]. Gut microbiota can promote the progression of atherosclerosis via diverse mechanisms, including microbial translocation, inflammation, and microbial metabolites. Microbial translocation leads to local immune responses, molecular modification, and endothelial barrier disruption, whereas inflammation is modulated by platelet activation, monocyte recruitment/activation, and cytokine secretion. Microbial metabolites induce metabolic alteration, including aerobic glycolysis and metabolic reprogramming in multiple cell types. The accumulation of atherosclerotic plaques results in the narrowing of blood vessels and a reduction of blood flow. Treatment with trimethylamine N-oxide (TMAO) induces endothelial dysfunction, oxidative stress, and vascular inflammation similar to aging in young mice [13]. Gut microbiota alterations exaggerated TAC-induced cardiac inflammation and fibrosis. A proinflammatory-related old microbiota influences the activity of several immune-response–related pathways in the aorta of animals that underwent fecal microbiota transplantation. Microbiota composition and diversity change markedly with physiological aging [14]. The increased relative abundance of inflammatory pathobionts and decrease in beneficial microbes promote inflamm-aging and extensive cardio-metabolic disorders. Geroscience, a field of research that deciphers the links between age-related chronic diseases and biological mechanisms of aging, could lead to the development of novel microbiota-targeting strategies [13, 14].

Microbiome in Neurodegenerative Disorders

A healthy and diverse gut microbiota is essential for maintaining normal cognitive functions. Aging-related alterations in the gut microbiota can promote systemic inflammation and play a causal role in cognitive decline and the development of cerebrovascular diseases. Recently published studies have linked dysbiosis of the gut microbiota with an increased risk of stroke, particularly ischemic, hemorrhagic, and cerebral cavernous malformation (CCM) strokes, especially in elderly people [9]. The underlying mechanisms remain unclear, but recent research highlights connections between the gut and brain that are important for microglial maturation and function. Microglial cells, which constitute approximately 15% of brain cells, serve as the primary immune defense in the brain [8]. During aging, microglia change from a resting to an active state, contributing to neurodegenerative diseases by producing pro-inflammatory cytokines, blocking amyloid clearance, regulating blood–brain barrier integrity, and affecting synaptic plasticity. Influencing microbiota–microglia cooperation could therefore slow or reverse cognitive aging [8, 9].

Microbiome in Metabolic Disorders

Metabolic disorders refer to conditions characterized by the disruption of normal metabolic processes that can impair the body's ability to maintain homeostasis and increase the risk of chronic disease [3]. An imbalanced microbiome may participate in the development of diabetes, obesity, and other metabolic disorders [1]. In contrast, the normal microbiome supports digestion, absorption, and metabolism of nutrients, and synthesizes various bioactive components such as short-chain fatty acids (SCFAs) that regulate host metabolic homeostasis [2]. The microbiome can affect energy balance by influencing energy extraction from diet and regulating feeding behavior, thermogenesis, physical activity, and adipose tissue. Gut microbes can also impact insulin resistance, promote the development of fatty liver and metabolic diseases, and predispose the host to cardiovascular and

inflammatory disorders. The capacity to maintain a healthy metabolic balance changes with age and often declines in the elderly. Maintaining a stable, balanced, and diverse microbial community resists colonization by exogenous microbial species and is critically important to healthy aging in terms of metabolism and age-related disorders.

The microbial community composition differs substantially between healthy individuals and patients with metabolic diseases [1]. Type 2 diabetes and obesity are associated with alterations of the gut microbiota. A cross-cohort analysis carried out on patients with type 2 diabetes together with non-diabetic control individuals confirms gut microbial dysbiosis in patients and identifies a robust disease signature that includes the depletion of butyrate-producing genera such as Clostridiales, Ruminococcus, and Eubacterium. Dysbiotic microbial communities are incapable of properly supporting host metabolism and physiology, and have also lost colonization resistance properties [2].

Interventions Targeting the Microbiome

Alterations in the microbiome, along with declining immunocompetence and unhealthy lifestyle factors, contribute to age-related conditions and various age-associated metabolic, autoimmune, and inflammatory diseases. Targeting the microbiome through probiotics, dietary interventions, or fecal microbiota transplantation offers a means to rebalance microbial-community imbalances during aging [3]. Despite interindividual differences, the microbiota of elderly persons differs markedly from that of younger individuals [1]. Accumulating evidence supports microbiota-based therapies; however, clinical applications aimed at slowing aging are still lacking, and detailed strain-level studies remain necessary. Future research should focus on microbiota signatures associated with longevity and consider baseline microbiome features to personalize therapies. Predictive models employing machine learning may forecast individual responses to microbiome interventions and evaluate treatment effectiveness across populations. Maintaining a healthy microbiota through a balanced diet rich in unrefined foods and sustained physical activity promotes healthy aging. Prevention of microbiota decline is therefore preferable, yet an improved mechanistic understanding could enable the development of targeted supplements such as probiotics, prebiotics, and nutraceuticals tailored to individual needs [15]. Translating microbiome insights into clinical practice remains challenging, hindered by factors including diet, environment, stress, and medication, but nonetheless represents a valuable opportunity to enhance healthy aging.

Probiotics and Prebiotics

Probiotics and prebiotics represent well-established microbiome modulators capable of maintaining or restoring microbial homeostasis in aged organisms. Probiotics, defined as live microorganisms that confer a health benefit when administered in adequate amounts, have demonstrated efficacy in managing gastrointestinal diseases, irritable bowel syndrome, blood pressure regulation, and depressive symptoms [1]. Several strains isolated from elderly individuals, such as Lactobacillus fermentum, exhibit strong adhesion to intestinal cells, immune-enhancement, anti-inflammatory properties, and survival under gastric conditions. A probiotic combination derived from centenarians, comprising Lactobacillus and Bifidobacterium species, improves motor function, exploratory behavior, and spatial memory in aged mice. Given the decline in immune function with age, probiotics hold potential for supporting healthy aging [3]. The C. elegans model provides a valuable platform for screening and investigating the geroprotective potential and mechanisms of probiotics and postbiotics. Although many probes enhance lifespan and reduce age-associated diseases in worms, knowledge of their geroprotective properties remains limited. Notably, microbiome modulators exhibit strain-specific geroprotective effects, underscoring the need for high-throughput screening studies to fully elucidate the underlying mechanisms. Expanding the scope to include multi-strain probiotics, prebiotics, synbiotics, and fermented foods will further clarify their efficacy as geroprotectors and their capacity to modulate the gut microbiome during aging [16].

Dietary Interventions

The gut microbiota influences host health, is affected by the aging process, and is associated with age-related pathophysiology, suggesting potential therapeutic targets. Probiotics are live microorganisms that, when administered in adequate amounts, confer a beneficial health effect on the host. Probiotic strains mainly belong to the genera Lactobacillus and Bifidobacterium. Other species belonging to the genera Enterococcus, Streptococcus, Pediococcus, Leuconostoc, and Bacillus may also be considered probiotics. Probiotics can modulate the altered composition of gut microbiota in aged people, thereby protecting the host against age-related diseases such as cancer or immunosenescence [2]. Prebiotics are substrates selectively utilized by the host, conferring a beneficial health effect on the host. Most prebiotics are carbohydrates that resist or partially resist cleavage by human digestive enzymes. Prebiotics such as inulin, fructo-oligosaccharides, galacto-oligosaccharides, and resistant starch are utilized by saccharolytic bacteria. The beneficial effects obtained by prebiotic administration mainly include the modulation of the gut microbiota composition. Indeed, oral prebiotic administration significantly stimulates the growth of Bifidobacterium and Lactobacillus, which, in turn, restores the ratio between beneficial and potentially

pathogenic bacteria. These beneficial bacteria ferment prebiotics and produce compounds of pivotal relevance for the host, such as SCFAs and vitamins, particularly vitamin K and several vitamins of the B group [3]. In addition to probiotics and prebiotics, microbiota-derived metabolites may exert several synergistic effects in the regulation of homeostasis. Butyrate and SCFAs have been suggested as a legitimate strategy to improve neurological degenerative disorders such as Parkinson's disease and Alzheimer's disease [17]. Plant polyphenols, alkaloids, terpenoids, phytosterols, amino acids, and plant metabolites can be fermented by the gut microbiota to generate bioactive compounds to modulate the gut microbiota–brain axis, which may be exploited as therapeutics or nutraceuticals for brain aging and cognitive impairment. Only prebiotics and dietary interventions and their effects on the gut microbiota of the elderly have been discussed; however, numerous other strategies can be further assessed to counteract the aging process and age-related diseases by targeting the gut microbiota [3, 17].

Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) from young to aged, and vice versa, modulates microbiota structure and metabolic capability [18]. Transfer of aged microbiota to young mice drives inflammation and loss of intestinal-barrier integrity, with increased systemic and tissue markers of inflammaging, together with inflammation in the retina and brain [18]. The aged microbiota is enriched in Prevotella, Lacnospiraceae, and Faecalibaculum species, and shows depletion of long-chain fatty-acid synthesis following transfer. By contrast, transplanting young microbiota into aged recipient mice reverses these inflammatory changes, and is characterised by enrichment of Bifidobacteria, Eubacteria, and Akkermansia species, accompanied by B-vitamin biosynthesis and lipid-synthesis pathways. These findings are consistent with a role for altered gut microbiota in promoting inflammation and age-related pathologies, and suggest that modulating the gut–brain axis through microbiota alteration may be a potential therapeutic approach to age-associated decline [18].

Future Directions in Research

The demand for novel approaches to healthy aging will grow for the foreseeable future because the population continues to age, life expectancies continue to increase, and the burden of age-related health issues continues to grow [19]. New methods are required for both postponing the occurrence of age-related symptoms and healing or reversing various conditions at least partly induced by age. The gut microbiome is the ecosystem of microorganisms living in the digestive tract. Besides digesting and extracting energy from food, maintaining the integrity of the intestinal barrier, synthesizing a multitude of vitamins and hormones, and contributing to the development and control of immune and neurological responses, it has recently emerged as a pivotal player in the regulation of the aging process [3]. Consequently, interventions on this ecosystem are a promising opportunity for the design of preventive and therapeutic anti-aging strategies, able to positively impact the whole body's health. Advances in sequencing and computation technologies enable advanced characterization of microbial communities, fueling a rapid expansion of gut microbiome research [3]. The emerging complex, bidirectional, and multifaceted relationship between aging and microbiome is attracting growing attention and represents a crucial milestone for the improvement of preventive and therapeutic strategies for safe and healthy aging [2].

Emerging Technologies

Experimental methodologies have been developed to investigate the structure and physiological activities of the microbiome and to identify its compositional components. It is expected that combined methodologies will contribute to a new research paradigm related to microbiome dynamics, health-related applications, and the production of bio-based industrial goods for human well-being [2]. Metagenomics is a promising tool for identifying novel biocatalysts and taxonomic and metabolic diversity, especially when culturing methods are improved for easy and quick cultivation. Although Sanger sequencing has been the leading technology in metagenomic studies, recent attention has shifted toward next-generation sequencing (NGS), with complementary activity between the two technologies [19]. Longitudinal studies are essential to capture the evolution and interplay between the gut microbiome and its host during a continuous interval of time, particularly during the transition from health to frailty that manifests in elderly adults. High-throughput multi-omics laboratories designed for a personalized medicine approach, incorporating genome, metabolome, proteome, transcriptome, and epigenome analysis, are equipped with computational and modeling tools to quantify and collect biological information on systems biology [3]. The integration of multiple datasets with environmental and clinical variables builds the basis for the robust multi-omics of the gut microbiota and personalized medicine of the elderly.

Longitudinal Studies

Longitudinal studies are critical for discriminating host-centric from microbiome-centric aging-primary changes, and host-compensatory secondary changes, thereby more firmly distinguishing causes from consequences. Yet longitudinal cohort studies are relatively rare because of the logistical and cost burden and the typical community-based design of these studies [2]. Numerous longitudinal human microbiome studies have been conducted in

infants, adults, and athletes, whereas obtaining healthy-aged longitudinal cohorts is challenging because of increased medical needs. Zhou et al. compared oral and fecal microbiomes in 20 community-dwelling young adults (median age 30) and 20 older adults (median age 64 years) who were considered healthy based on extensive criteria. Both older adults and the small subgroup of exceptionally long-lived 80+ years adults showed a trend for increasing gut microbiota alpha-diversity, on average, but the older adults also showed reduced population-level compositional variation. Few microbial taxa exhibited consistent shifts between age groups across two different geographic study locations, but the genus Bacteroides was notably depleted in the 80+ year-old group at both locations [4]. Murine gut Microbiome meta-analyses further showed altered carbohydrate metabolism in response to aging. After controlling for confounding factors (diet, study design, location) across 16S rRNA data for 1,320 mouse fecal samples from six independent studies, aging was associated with increased alpha diversity and altered composition, although the beta diversity phylogenetic effect size was low. Random forest models for classification and regression identified 9 genera and 5 predicted carbohydrate metabolism pathways related to aging; Carbohydrate metabolism in the aged gut microbiome was decreased from 3 to 12 months, then increased from 12 to 28 months [5].

Personalized Medicine Approaches

Large individual differences exist, yet the elderly microbiota differs from that of younger people. Microbiota-based therapies show efficacy, although clinical applications for slowing aging are lacking [3]. Future research should identify longevity-related microbiota signatures and consider baseline microbiome features to customize therapies. Machine learning predictive models forecast individual responses and assess applicability across populations. Healthy aging is promoted by a balanced diet rich in unrefined foods and regular physical exercise. Prevention of microbiota decline to delay age-related pathologies is preferable; understanding gut microorganisms' actions will support the development of targeted supplements such as probiotics and prebiotics. Interventions require personalization and appropriate strategies to sustain microbiota health. Translation of microbiome knowledge into clinical applications remains challenging due to diet, environment, stress, and medication, yet offers potential for enabling healthy, long life [3]. Novel approaches to healthy aging are required as the population ages, life expectancies increase, and the burden of age-related health issues grows. The gut microbiome influences aging and neurological processes and represents a potential target for anti-aging interventions. Recent preclinical studies demonstrate the efficacy of microbiota-based approaches, but more advanced human studies with larger samples are needed. Understanding the interaction among aging, the gut microbiome, neurodegenerative diseases, and targeted interventions could lead to methods for delaying aging and combating neurodegenerative diseases [19]. The average human lifespan has increased; aging is associated with cancer, neurodegenerative disorders, and metabolic syndrome, which affect quality of life. Gut microbiota encompasses 500–1,000 bacterial species and plays a crucial health role by aiding digestion, synthesizing vitamins, metabolizing fibers, maintaining the intestinal barrier, regulating immunity, and protecting against pathogens. Gut dysbiosis can lead to physiological deterioration and age-related diseases. Advances in sequencing technology and metagenomics facilitate gut microecology studies, while machine learning analyzes vast data and identifies microbial signatures linked to aging. Research highlights gut microbiota's influence on aging and cognitive decline, whereas diet and probiotics promote a healthy microbiome conducive to healthy aging [2].

Ethical Considerations

Ethical issues are increasingly recognized in microbiome research, particularly regarding the regulation of therapeutic and diagnostic products [3]. Research participants identified safety as the major ethical concern. The complex interplay among age, lifestyle, nutrition, and microbiota must be considered for personalized interventions to promote healthy aging [1]. Despite promising preliminary findings, additional clinical studies on the microbiome and neurodegenerative diseases are needed to identify the most suitable approaches for healthy aging [19].

Ethics of Microbiome Research

Despite its numerous potential applications in improving the quality of life for older adults, microbiome research gives rise to several ethical and regulatory challenges that should be addressed before widespread implementation. Given the high prevalence of age-related illnesses characterized by cognitive decline, such as neurodegenerative, vascular, and metabolic diseases, the use of microbiome-based therapies requires careful consideration not only of social and economic barriers but also of personal respect, dignity, and self-determination [3]. Furthermore, therapeutic strategies should be developed with a specific awareness of age-associated alterations in the microbiome, acknowledging its important physiological contribution to health in older adults [2].

Regulatory Challenges

Regulatory considerations specific to microbiome research are gaining prominence. Establishing guidelines, particularly for vulnerable populations such as elderly individuals, constitutes an integral component of research protocols 2. Given the potential sensitivity of this demographic, targeted regulatory frameworks may be necessary to ensure ethical compliance and safeguard participant welfare [1]. Early-stage research targeting the aging microbiome is rapidly advancing across multiple domains, including sample acquisition, standardized analytical approaches, and the compilation of comprehensive longitudinal datasets. The field is poised for rigorous quantitative analyses aimed at translating biological insights into practical clinical applications 3. These developments highlight the evolving regulatory landscape and underscore the need for adaptable governance structures that can accommodate emerging methodologies and therapeutic strategies [1]. Recent technological advances have generated extensive datasets facilitating a deeper understanding of the aging process. Such data, when applied in clinical settings, demonstrates considerable potential to elongate life expectancy and enhance health conditions in elderly populations [1]. Concurrently, the increasing number of experimental studies focusing on the microbiota and aging accentuates numerous points requiring ethical and governmental attention. Addressing these facets will be essential for the responsible progression of microbiome science and its integration into comprehensive aging paradigms [19].

CONCLUSION

The interplay between the microbiome and aging represents a critical frontier in biomedical science. Aging drives compositional and functional shifts in the microbiome that promote systemic inflammation, immune dysfunction, metabolic disease, and neurodegeneration. In turn, microbiota-derived metabolites and host–microbe interactions modulate the pace and quality of aging, positioning the microbiome as both a marker and mediator of age-related decline. Accumulating evidence suggests that interventions such as probiotics, prebiotics, dietary strategies, and fecal microbiota transplantation may mitigate age-associated pathologies and enhance healthspan, though strain-specific effects and individual variability demand further study. Integrative approaches leveraging metagenomics, metabolomics, and computational modeling are beginning to identify microbial signatures of healthy aging and to inform precision therapeutics. Future work should focus on longitudinal, large-scale human studies, the standardization of microbiome-based interventions, and the ethical integration of microbiome data into personalized care. Harnessing the microbiome's potential offers a transformative opportunity to not only delay age-related disease but also extend healthy lifespan.

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