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Review Article

Understanding Aging through the Lense of Gut Microbiome

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Abstract

Aging is an intricate process driven by various factors, including the dynamic interplay between the host microbiome and aging. The gut microbiome undergoes several changes throughout the entire lifespan of a healthy human. Numerous factors, ranging from the mode of childbirth and sex differences to lifestyle, are known to impact the gut microbiome in healthy individuals. As a result, the gut microbiome varies widely among individuals and exhibits robustness after early childhood. However, as one ages, the human body undergoes several important changes, and so does the gut microbiome. This review addresses the relationship between aging and the dynamics of the host microbiome from *in utero* to over 100 years of age. Additionally, we attempted to untangle this intricate relationship between the gut microbiome and aging by presenting various microbiota-dependent mechanisms involving intrinsic and extrinsic factors such as metabolic, neurological, immunological, dietary, and lifestyle factors that potentially regulate aging. Furthermore, we aimed to highlight microbiome-based aging intervention studies focused on modulating or rejuvenating the microbiota for healthy aging and longevity.

Introduction

All organisms undergo the natural process of aging, which vastly regulates their body shape, health, and functioning. An aging phenotype is characterized by nine genetic hallmarks: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication.[1] As one ages, the body experiences numerous physical and biochemical changes. On average, people >30 years old experience cell loss in various organs such as muscles, liver, and kidneys. Aging is also accompanied by the demineralization of bones, which reduces their density, and changes in the body's water content, which influence overall health.[2] Another key process during aging is the accumulation of body fat in middle age. This results in the accumulation of around one-third of extra fat in this age group as compared to youngsters, leading to an increased risk of insulin resistance.[3] Eventually, aging may result in the development of numerous diseases and disorders.[2] However, this physical decline varies due to several factors, including the organism itself, gender, geographical location, lifestyle, etc.[2]

Keywords: Aging; Gut microbiota; Immunity; Gut metabolites; Neurological disorders; Stem-cell aging.

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The collection of genomes from all microbes (including bacteria and fungi) and viruses, as well as microbial structural elements that inhabit the host, is termed the "microbiome". However, the terms "microbiome" and "microbiota" are often used interchangeably, though there are important differences between the two. Microbiota refers to the living microorganisms present in a defined environment, such as the gut, oral, skin, etc. The human gut microbiota (GM) comprises a rich and diverse microbial community consisting of more than a trillion microorganisms that live in harmony with each other.[4] Several studies have highlighted the significant role of GM in human health and disease.[5] Many studies have focused on the relationship between changes in GM and aging, considering various physiological aspects of this process, such as alterations in beneficial metabolite producers and increased susceptibility to disease due to a weakened immunological response.[5] Indeed, significant associations between the gut microbiome and both gastrointestinal and extra-intestinal diseases have been reported.[6] In this review, the importance of both intrinsic and extrinsic factors associated with the gut microbiome and aging is comprehensively discussed. Additionally, the interactions of gut microbes with various host-associated processes, such as sex differences, neurology, and immune responses, are highlighted in detail. Finally, intervention studies on modulating or rejuvenating the microbiome for healthy aging and longevity are reviewed to understand the associations between the gut microbiome and the aging process.

Dynamics of gut microbiome during humans' lifespan

The gut microbiome and aging processes are influenced by vari-

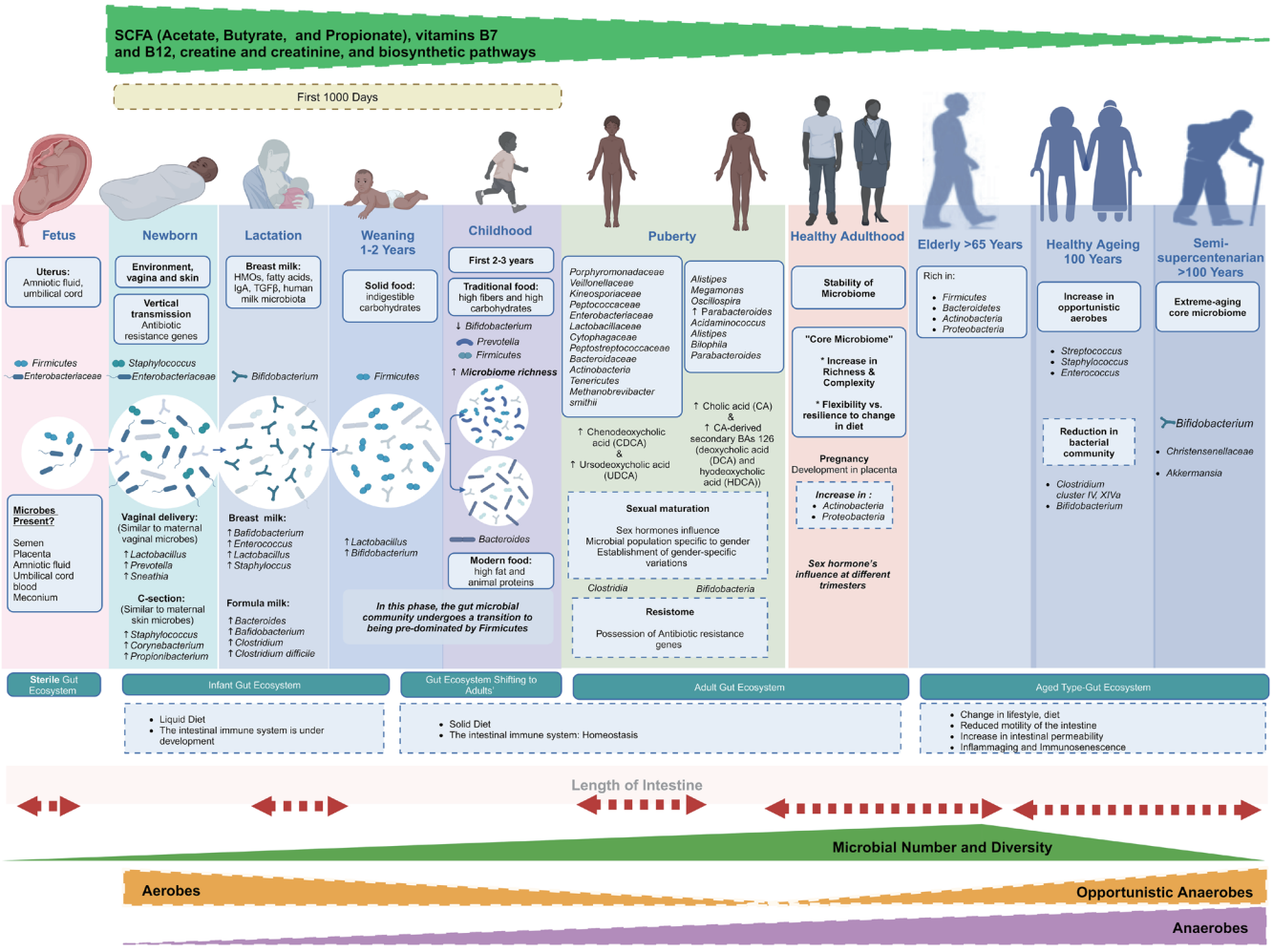

Fig. 1. Gut microbiome alterations from infancy to old age in humans. The composition of the gut microbiome exhibits genus-level variations across different age groups. The early-age gut microbiome is shaped by the embryonic environment, type of delivery, and exposure to microbes through breast/formula feeding. During weaning, the microbiome undergoes changes from a simple (less diverse) to a complex (more diverse) microbial mixture and attains stability until adulthood. During puberty, the microbiota differentiates based on the sex of the host due to associated hormonal changes. In elderly individuals, the microbiota is affected by lifestyle, dietary habits, and immunosenescence of the intestinal immune system. In this age group, the microbiome is mainly dominated by pathogenic and opportunistic microbes. The major changes in the metabolites associated with human GM and the length of the intestine concerning the aging process are also shown. Created by biorander.com. GM, gut microbiota; HMOs, human milk oligosaccharides; IgA, immunoglobulin A; SCFA, short-chain fatty acids; TGF-β, transforming growth factor-β.

ous intrinsic (gender, genetics, and ethnicity) and extrinsic factors (geographical location, demographic factors, physical activity, diet, medications, smoking, reduced social contact, and others).[7] The aging process involves specific changes in GM and metabolic composition (Fig. 1). The gut microbiome transduces environmental signals, modulates disease risk factors in all age groups, and varies with host age. Overall richness of the gut microbiome declines while a particular frailty-linked bacterial group increases when measures of biological age are applied with adjustments for chronological age.[8]

Gut microbiome alterations in infancy and early childhood

At birth, a sterile environment is transformed into a rich and active microbial ecology.[9] Although the embryo is considered sterile, the presence of germs in semen, placenta, amniotic fluid, umbilical cord blood, and meconium indicates that the fetus is colonized by microbes *in utero*.[10] This suggests that the transmission of the maternal microbiome to the offspring might occur vertically. The gestational age at birth, delivery method, feeding strategy, and maternal variables are known to impact the infant's GM colonization process.[10]

The GM of infants (<1 year old) is known to be less diverse,[11] while that of adults is relatively stable.[12] The core GM of infants can be categorized into six groups based on the prevalent population and makeup.[13] Group 1 includes *Bifidobacteriales, Lactobacillales, Anaerostipes, Clostridiales, and Faecalibacterium*; Group 2 includes *Verrucomicrobiales and Bacteroidales*; Group 3 includes *Clostridiales*; Group 4 includes *Enterobacteriales*; Group 5 includes *Pasteurellales*; and Group 6 primarily includes *Selenomonadales*. More recently, the GM of infants has been found to involve core species from the genera *Bifidobacterium, Bacteroides, Clostridium, Lactobacillus, Streptococcus, Veillonella, Akkerman-*

sia, and *Collinsella.*[14]

Newborns are exposed to vaginal microorganisms during birth, which are mainly dominated by *Prevotella* and *Lactobacillus*.[14] Contrarily, infants delivered by cesarean section (c-section) have a prevalence of *Corynebacterium*, *Staphylococcus*, and *Propionibacterium* spp. (Fig. 1), resembling the microbial composition found on the skin.[14] Immediately after birth, species of the genus *Lactobacillus* (*L. gasseri* and *L. rhamnosus)* are predominantly found in the GM of infants.[15,16] Since meconium contains several species of the genus *Lactobacillus*, such as *L. reuteri*, *L. plantarum*, *L. sakei*, *L. brevis*, and *L. casei*, the relative abundance of these taxa is substantially greater in infants delivered vaginally than by c-section.[17] This maternal-to-offspring transmission of the microbial community is a crucial early-life checkpoint because when a baby exits the umbilical cord-supported uterine environment, commences respiration, and actively seeks a meal, the baby faces a significant metabolic shift. The early-life microbiome is crucial for the development of the brain and immune system of offspring which have an impact on the infant as well as the long-term health.[14]

In breastfed infants, the GM is predominated by *Bifidobacterium*, whereas *Bacteroides* and *Bifidobacterium* predominate in the gut microbiome of formula-fed infants.[18] However, in the feces of vaginally delivered and formula-fed infants, the abundance of *Bacteroides* is relatively higher compared to c-section-delivered ($p < 0.01$) and breastfed babies.[19] Furthermore, the c-section delivery causes a delayed colonization of *Bacteroides*, which may be linked to the Th1 response.[20] Nursing exposes the baby to the mother's microorganisms, antibacterial agents, and nutrients crucial to the baby's well-being. Human milk oligosaccharides (HMOs), natural prebiotics present in breast milk, specifically influence the development of beneficial bacteria in an infant.[18] HMOs do not directly provide nutrients for infants; instead, they influence the development of the infant's gut microbiome and promote long-term health.[21] Bifidobacteria play a crucial role in the ability of an infant's intestinal tract to absorb HMOs.[22] However, there is also evidence of a negative correlation between the amount of bifidobacteria and the concentration of HMOs in newborn feces.[21] Importantly, the stool samples of infants show a higher relative abundance of *Bifidobacterium*, which is associated with the risk of later acquiring non-communicable diseases like asthma and obesity. Additionally, the development of innate and acquired immunity in early infancy can be promoted by *Bifidobacterium* and *Lactobacillus.*[23]

In the first year of life, up to weaning, opportunistic microbes frequently colonize the gut ecosystem based on the surroundings the baby is exposed to.[24] Such early colonization shows the primary predominance of aerobes like *Staphylococcus*, *Streptococcus*, and enterobacteria, followed by anaerobic colonizers such as clostridia and eubacteria. It is commonly believed that *Bifidobacterium* dominates the microbiota of breastfed newborns after these earliest stages.[9] After weaning or ablactation, the intestinal immune system and gut mucosa undergo developmental changes. These changes, along with the introduction of solid food, cause the transformation of the human GM into an adult-like composition that is resilient and characterized by increased microbial diversity,[9] which remains largely constant throughout healthy adulthood.[25] These observations suggest that the composition of the GM alters as the host ages.

Gut microbiome alterations during puberty and adulthood

The adult microbiome acquires characteristics related to gender due to the influence of sex hormones associated with puberty (Fig. 1). Numerous studies on animal models and humans have shown different microbiome compositions in males and females. A study on pre-obese diabetic mice reported similar microbiota compositions in both sexes before puberty. However, after puberty, the male mice's GM showed shifts in composition, with increased abundance in the families *Porphyromonadaceae*, *Veillonellaceae*, *Kineosporiaceae*, *Peptococcaceae*, *Enterobacteriaceae*, *Lactobacillaceae*, *Cytophagaceae*, *Peptostreptococcaceae*, and *Bacteroidaceae*.[26] Org *et al.*[27] conducted a study on the GM of 89 inbred mice, showing distinct composition and diversity between sexes of each strain, with a high abundance of *Actinobacteria* and *Tenericutes* in males. However, the biological definition of aging differs between humans and mice and remains debatable.

Sex-based microbiome differences have also been observed in humans. Sex hormones, including estrogen and testosterone, play significant roles in influencing the GM during adolescence or puberty (age group of 13–17 years). For instance, *Adlercreutzia, Clostridium, Dorea, Parabacteroides*, and *Ruminococcus* have all been associated with testosterone levels.[28] An investigation of the fecal microbiota of opposite-sex twins aged 13 to 17 years showed the highest variations between them compared to same-sex twins (Fig. 1).[29] A large-scale investigation of more than 2,500 Chinese individuals discovered sex-specific markers, which become less pronounced with age.[30] Similar observations were made in two other studies based on large cohorts from Israel, the Netherlands, and the American Gut Project.[30–32] Sex-dependent changes in microbiome composition (β-diversity) were more pronounced in younger individuals compared to older ones, with females having higher GM α-diversity than males.[31] Apart from distinct microbial communities, differences in the abundance of bacterial genes and metabolic pathways have also been reported between males and females. For example, metabolic pathways associated with carbohydrates, lipids, and proteins were prominent in the gut microbiomes of females,[33] showing the possibility that metabolites such as fatty acids may be involved in adipose tissue remodeling during puberty.[34]

In adulthood, the gut microbiome reaches its highest level of complexity and richness, with the development of a strong "core microbiome" that increases adaptability and decreases sensitivity to both internal and external stresses.[35] The maturity of the microbiome occurs concurrently with the growth of the host organs, particularly the gut, which lengthens with age and creates new habitats for the microbiome to diversify and multiply.[14] A gut ecosystem of a healthy adult is estimated to include around 1,000–1,200 phylotypes up to the species level, of which 75–82% are considered unculturable.[9,36] However, this notion was challenged by a recent study using a broad-range yeast casitone fatty acid agar-based culturing approach for massive bacterial identification and discovery.[37] A substantial percentage of this diversity (90–99%) is restricted to the bacterial phyla *Firmicutes* (including major genera *Clostridium, Faecalibacterium, Lactobacilli, Ruminococcus*) and *Bacteroidetes* (*Bacteroides, Prevotella*), where the dominating *Firmicutes* (50–80%) are predominantly composed of bacteria from *Clostridium* clusters XIVa and IV.[38] The human gut also contains other bacteria belonging to the phyla *Actinobacteria* (3–15%), mainly genus *Bifidobacterium*; *Proteobacteria* (1–20%), mainly *Escherichia, Helicobacter, Shigella*; *Verrucomicrobia* (0.1%), mainly *Akkermansia*, *Cyanobacteria*, *Fusobacteria*, *Lentisphaerae*, and *Spirochaetes*.[9,38,39] Although the changes from youth to adulthood may not be considered aging, the changes in the body and microbiome during these stages can influence later life

stages. For example, Valeri and Endres summarized differences in the sex-associated GM throughout the human lifespan, from infancy to elderly age (>75 years).[28]

Gut microbiome alterations in the elderly age group

The elderly microbiota is generally characterized by a decline in microbial diversity, the emergence of *Bacteroidetes* phyla at the expense of *Firmicutes*, a rise in the abundance of opportunistic enteropathogens, and a decrease in species that produce short-chain fatty acids (SCFAs), particularly butyrate.[9,40] A recent study found that an increase in fecal *Christensenellaceae*, *Porphyromonadaceae*, and *Rikenellaceae* was specifically linked to more favorable body composition in old age, namely decreased abdominal obesity.[41] Additionally, the microbiome has been linked to alterations in bone density with age. *Lactobacillus reuteri* has shown promising results in maintaining and increasing bone mineral density in murine models and an increase in tibial bone density in elderly women.[42,43] These studies provide valuable insights that *L. reuteri* may be an effective treatment for osteoporosis.[42] The aged-type microbiota exhibits a less diverse microbial community, similar to what occurs during the initial stages of our lives. It is characterized by a rise in environmental facultative aerobes, such as *Staphylococcus*, *Streptococcus*, and *Enterobacteriaceae*, along with a decrease in anaerobes like *Bacteroidetes* and *Clostridium* clusters IV and XIVa. In contrast to the microbiota of newborns, the old type of microbiota is marked by a lower abundance of *Bifidobacterium*.[9] Additionally, longevity and slower aging may also be influenced by the gut microbiome. *Christensenella*, *Akkermansia*, and bifidobacteria were reported in greater abundance in the gut of exceedingly older people (above 99 years old; known as centenarians Fig. 1), suggesting potential life-extension effects.[44] These gut microbiome members may be crucial in defending against pathogenic infection and various other environmental stresses.

Interesting associations have been observed between aging and microbiome diversity in terms of the number of distinct species and their relative abundance (richness and evenness) in a given microbial ecosystem or between ecosystems (known as α-diversity and β-diversity, respectively). For example, an increase in the frailty index, which is regarded as a quantitative indicator of biological age, was found to be associated with a decrease in the diversity of the core microbiome.[45] In contrast, a higher taxonomic α-diversity of the gut is linked with longer lifespans and better aging,[46] while a decrease in gut microbial diversity has been linked to hospitalization.[47] Notably, numerous studies have demonstrated that α-diversity, or more specifically microbial richness, is not negatively associated with chronological age but is adversely correlated with the frailty index (biological age).[7]

Factors affecting the aging-related alterations in hosts and their gut microbiomes

The gut microbiome plays an essential role in host health by educating the immune system and producing health-promoting microbial metabolites like SCFAs, which are signature metabolites of healthy aging as found in studies on centenarians.[40] Perturbations in gut homeostasis are common with aging, causing a condition termed "leaky gut", defined as increased permeability of the gut and unregulated tight junction blockade.[48] Elderly people suffer from GM dysbiosis, with increased expression of proteolytic rather than saccharolytic genes, which intensifies inflammation due to an increase in pathobionts.[49] The enhanced gut permeability allows foreign substances to enter the bloodstream and then circulate throughout the body, leading to systemic inflammation. This causes "inflammaging", which supports the growth of aerobic and facultative aerobic pathobionts and restricts strict anaerobes (such as the *Firmicutes* phylum), sustaining inflammatory conditions and increasing inflammation mediators. For instance, enteric pathogens such as *Clostridium difficile* and *Helicobacter pylori* disintegrate the intestinal barrier through different mechanisms and trigger chronic inflammation, which further aggravates microbial dysbiosis and gastrointestinal infections, including diarrhea, gastritis, stomach cancer, pseudo-membranous colitis, and periodontitis.[38] Inflammaging is linked to various age-related pathologies (Fig. 2), such as Alzheimer's disease (AD), Parkinson's disease (PD), obesity, heart disease, Type 2 diabetes, and cancer.[31]

According to a recent study, immunity, metabolism, and survival were all strongly impacted by variations in the gut microbiome of mice after exposure to antibiotics in their early lives.[50] Similarly, in humans, associations have been observed between the usage of antibiotics in early life and increased risk factors for shorter life expectancies, such as susceptibility to infections and obesity.[31] In addition, excessive antibiotic use by residents of aged care facilities is shown to lower colonization resistance and increase the prevalence of antibiotic-resistant bacteria, which may put the elderly at risk for fatal infections.[51]

Muscle mass, power, and functionality decrease by 3–8% per decade in individuals aged 30–60, with the decline rate being higher for those over 60 years.[52] With aging, several changes at the cellular level contribute to sarcopenia pathology.[53] These changes include a reduction in cell number and metabolism, twitch force and time, basal muscle protein synthesis (regulates muscle mass), disorganized sarcomere spacing, lower calcium transport capacity, mitochondrial dysfunction, and the accumulation of fats within and around muscle cells. The gut microbiome contributes to the determination of skeletal muscle mass, function, and architecture as part of the aging process. *Butyricicoccus* and *Clostridium XIVa* are SCFA producers positively correlated with muscle mass.[54] These bacteria also produce host metabolites, including vitamin B_{12}, lipids, folate, and microbial metabolites essential for muscle development. Gut dysbiosis and leaky gut are known to have a negative association with muscle protein synthesis due to inflammation and declined defense action upon infection.[54] Dysbiosis might also contribute to sarcopenia pathology, as changes in microbial diversity have led to reduced metabolites for muscle development in sarcopenic rats.[55]

The skin, the largest body organ, is part of innate immunity, being the first line of defense. With age, skin becomes dry, stiff, and inflexible, losing some of its fatty tissues, making it thin with impaired sweat glands. The gut microbiome influences the skin microbiome via the gut-skin axis and gut-skin-brain axis. Skin resembles the gut in the presence of epithelial cells, which are in contact with microbes, and a low adherence of microbes occurs due to a higher rate of cellular turnover, thereby reducing infection. Several studies have shown that gut microbial dysbiosis is related to various skin diseases such as psoriasis, rosacea, and acne vulgaris, indicating a combined action of gut and skin microbiomes.[56]

Interplay between immunity and gut microbiome in aging

The immune system is the major host defense mechanism that protects against harmful stimuli, including microbes. The *in utero* environment is relatively sterile, and the immune system of the fetus exhibits tolerance to maternal alloantigens. The immune system gradually matures as the infant grows, attaining full maturity by

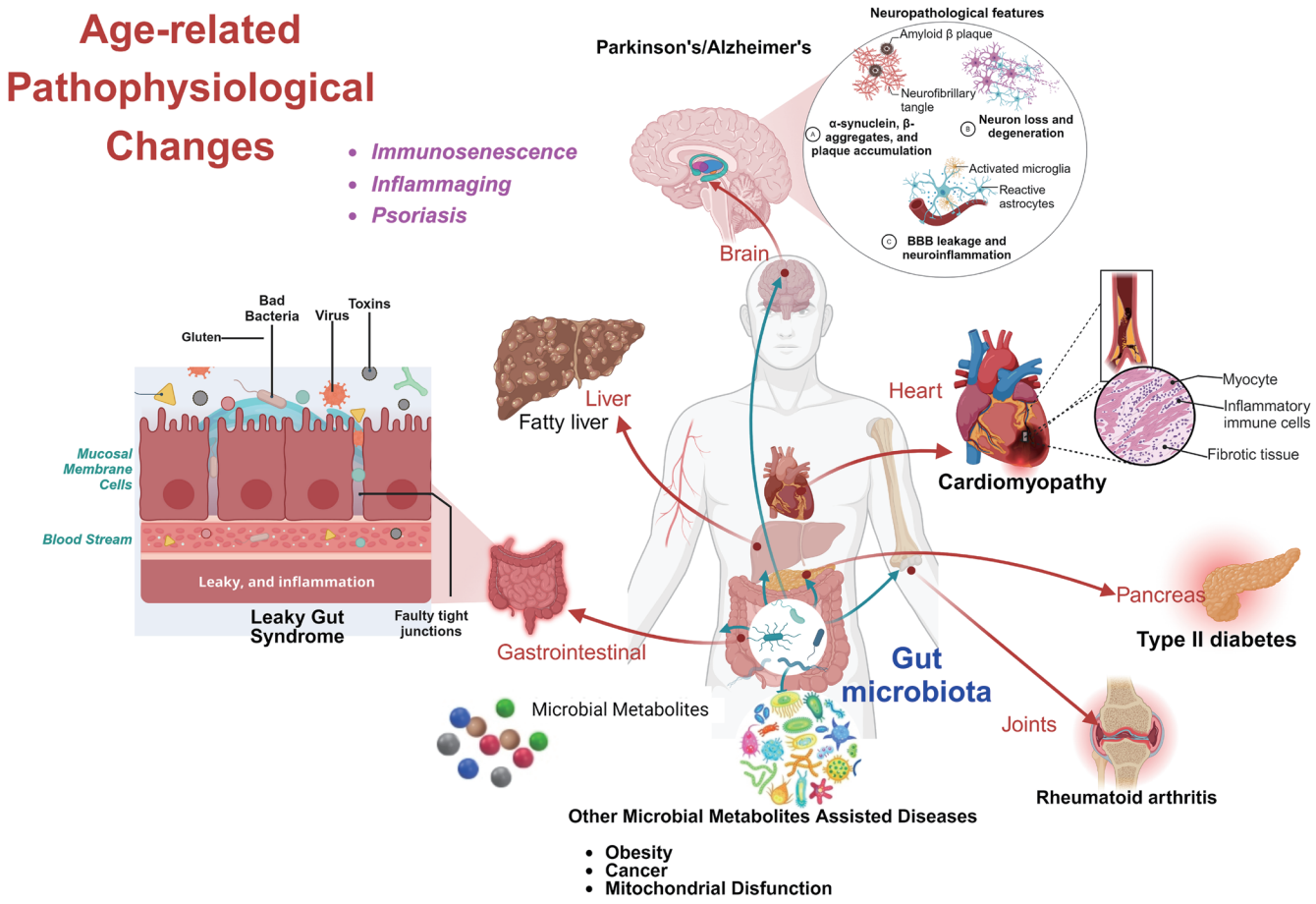

Fig. 2. Summary of age-related pathophysiological changes in host associated with gut microbiome. BBB: blood-brain barrier. Created by biorander.com.

late childhood. As one reaches old age, their immune system declines, leading to a variety of diseases. This strongly suggests that aging impacts the recognition of stimuli and may trigger several pathogenic processes linked with aging.[31,48] Immunosenescence and inflammaging are two important hallmarks of the immune system in the elderly.[57] Immunosenescence represents a decline in immune response in aging cells and is a complex biological process. It predisposes the elderly population to infections and comorbidities, and the elderly exhibit weaker vaccination responses than young and middle-aged adults.[58] Functional and phenotypic modifications in aging immune cells result in decreased immunosurveillance and cytotoxic effector functions.[59] Inflammaging refers to the rise in inflammation commonly observed with the development of some chronic inflammatory conditions as aging occurs. It also includes chronic low-grade inflammation that increases the risk of common non-communicable diseases.[60] With advancing age, the microbiome affects immunity and predisposes elderly people to oxidative and inflammatory disorders. Thus, an intricate link exists between immunity and the microbiome in aging, especially the gut microbiome.[61]

From infancy to old age, gut microbiome composition and development are essential for the functioning, maturation, and regulation of the host immune system. Many of the bacteria that colonize the gut and other mucosal sites, besides being essential for a healthy life, also impact the development of the immune system.[62] Loss of gut microbial diversity or modifications in the composition of the gut microbiome (often referred to as dysbiosis) may potentiate aging and disease.[63] The mechanisms of the involvement of gut microbiome members in the development of immunity are well documented and reviewed.[57,60,64,65]

During aging, the host microbiome influences the local immune system in addition to epigenetics and host metabolism alterations.[61] Recent studies confirmed that immune cells are responsible for the bidirectional regulation of changes in the diversity of the gut microbiome. For instance, changes in the gut microbiome's composition, including a decrease in *Faecalibacterium prausnitzii* and an increase in *Proteobacteria*, are both linked to inflammatory disorders brought on by aging.[66] One notion is that maintaining a "healthy" gut microbiome composition as one ages can aid in slowing down or ceasing the inflammatory aging process. It is known that several gut bacterial species, which belong to the genera *Bifidobacterium*, *Faecalibacterium*, and *Lactobacillus*, have the potential to suppress the pro-inflammatory response at the gut epithelium level or indirectly block the transcription of pro-inflammatory genes, for example, by *Bacteroides thetaiotaomicron*.[9,67,68] Similarly, *Akkermansia muciniphila*, one of the few known species of the phylum *Verrucomicrobia*, is known for its potential to degrade mucin and promote intestinal integrity by reducing toxicity levels associated with high-fat diets. An increase in the abundance of *Verrucomicrobia* is also associated with better-quality sleep.[69] Badal *et al*.[69] highlighted in their study that *Christensenellaceae*, *Verrucomicrobia*, and *Akkermansia* may support healthy aging and

gut homeostasis by decreasing adiposity, inflammation, and the future risk of developing metabolic disorders.

Associations of host metabolic alterations, gut microbiome, and aging

Microorganisms produce a wide range of organic and inorganic molecules that can interfere with the host's metabolism and affect aging (Table 1).[1,39,70–83] Flint *et al*.[84] have reviewed variations in metabolism due to gut microbial metabolites such as SCFAs, cholesterol, lipids, vitamins, gasses, and atherogenic compounds, which may alter host sensitivity towards metabolic syndromes, obesity, cardiovascular disease, and irritable bowel syndrome.

The associations of these microbial metabolites with host aging have been explored extensively. Colon bacteria produce SCFAs, which are a subset of fatty acids, by fermenting dietary fibers and resistant starch.[85] Butyrate, propionate, acetate, and valerate are common SCFAs derived from the gut microbiome. Butyrate plays a significant role in preventing physiological decline during aging. It prevents inflammation by downregulating adipogenesis, enhancing the intestinal barrier, preventing insulin resistance, regulating B1 cell activity to prevent cancer, inhibiting histone deacetylase, and facilitating apoptosis by counteracting amyloidosis and neuroinflammation while also preventing cellular senescence.[70,86]

Microbes like *Akkermansia muciniphila* produce acetate and facilitate the growth of butyrate-producing microorganisms.[31] Biagi *et al*.[87] observed that the presence of *Faecalibacterium prausnitzii*, a gut inflammation-protectant species, along with *Anaerotruncus colihominis* and *Eubacterium limosum*, which are butyrate producers, is characteristic of long-lived people. Additionally, the gut microbiome profiles of the offspring of elderly parents were found to be more similar when they cohabited with their parents compared to those who lived separately. This has escalated the incidence of pathobionts and opportunistic species in the gut microbiome of cohabiting family members, indicating an environmental influence.

Epigenetic modifications such as DNA methylation, histone modifications, noncoding RNA action, and chromatin remodeling affect living organisms throughout their lives.[1] Commensals alter histone-changing enzymes by modifying their activity or substrates, affecting cell fate and development. High concentrations of SCFAs like propionate inhibit histone deacetylase activity and protect against colorectal cancer. Butyrate also induces hyperacetylation of histones and stimulates cell differentiation.[70]

Polyamines are small organic molecules involved in various physiological processes, including cell growth, differentiation, and apoptosis.[88] These gut microbiome-derived metabolites are essential for normal cellular function and play an important role in aging (Table 1). Several studies have suggested that polyamines not only increase longevity but promote healthy aging by improving age-related markers and protecting against age-induced memory impairment.[88] Levels of polyamines decline with age in various tissues, including the liver, kidney, and brain. Additionally, studies in animal models have found that increasing levels of polyamines can extend lifespan and improve healthspan.[70]

Reactive oxygen species (ROS) are metabolites containing partially reduced oxygen, primarily produced by the mitochondria inside a cell.[89] These molecules can cause oxidative stress and damage cellular components such as proteins, lipids, and DNA, leading to various age-related diseases and the overall aging process.[1] *Lactobacillus rhamnosus* causes rapid ROS generation in the epithelial lining and induces oxidative stress. ROS also act as signaling molecules in inflammatory response generation, the ubiquitin-proteasome pathway, and regulate post-translational modifications such as SUMOylation and neddylation. When commensal bacteria contact gut epithelial cells, they produce ROS.[70] As we age, the body's ability to regulate ROS production decreases, leading to an increase in oxidative damage. This can result in the accumulation of mutations and errors in cellular function, causing the gradual deterioration of tissue and organ function, ultimately resulting in age-related diseases.

Extracellular amyloid is produced by gut microbes and can alter proteostasis, forming insoluble aggregates that speed up the development of cerebral amyloidosis. The bacterial amyloid load increases due to the gastrointestinal system and immune modification with age, which affects immune homeostasis. As we age, the body's ability to clear amyloid decreases, leading to its accumulation and aggregation in the brain. These amyloid plaques can interfere with the normal functioning of brain cells, causing inflammation, oxidative stress, and ultimately, cell death.[90] The accumulation of amyloid in the brain is strongly associated with the development of AD. Studies have shown that SCFAs can inhibit the formation and aggregation of amyloid protein in the brain, potentially helping to prevent or slow the progression of AD. Additionally, SCFAs have been shown to promote the clearance of amyloid protein from the brain by enhancing the activity of immune cells that remove these toxic proteins.[70]

Age-related neuro-pathologies and GM variations

The brain is separated from the rest of the organs by the blood-brain barrier. The central and enteric neuronal systems communicate bidirectionally through the gut-brain axis (also known as the microbiome-gut-brain axis), which connects the brain's cognitive and emotional regions with the peripheral functions of the intestine.[91] The vagus nerve directly connects the gut to the brain, sensing changes in the gut microbiome and influencing brain activity based on metabolites released by normal gut flora (Table 1).[92] Recent reports suggest that aging, host-microbiome diversity, and aging-associated diseases may have a close relationship.[59] The human gut microbiome has been associated with the origin and treatment of multiple neurological disorders such as multiple sclerosis, AD, and PD. Interestingly, the incidence and severity of these diseases also increase with age.

Behavior is regulated by gastrointestinal hormones released locally or by bacterial fragments and metabolites that interact with the central nervous system, directly impacting the hypothalamus. Additionally, it has been demonstrated that the blood-brain barrier's permeability and serotonin release are controlled by gut bacteria.[91] Despite the anatomical separation between the gut and the brain, numerous studies indicate that intestinal health substantially impacts neurodegeneration.[93] There may be gastrointestinal roots to neurodegenerative conditions, including amyotrophic lateral sclerosis and AD.[93] Notably, primary symptoms in a mouse model with amyotrophic lateral sclerosis included disease-specific disruption to intestinal restrictive junctions, higher gut permeability, and decreased levels of butyrate-producing bacteria (*Butyrivibrio fibrisolvens*).[94]

Age-related alteration in the morphology of microglia is termed dystrophic microglia and has been intimately linked to neurodegenerative disease.[95] Several studies conducted on animal models to explore the relationship between AD and gut microbiome changes have indicated a strong connection between altered gut microbes and the progression of the illness.[96] A study exploring the association of gut microbiome alterations with preclinical AD

Table 1. Microbial-produced metabolites associated with the aging process

Metabolites	Effect	Microbes associated	Reference
Nicotinic acid	Positively affects stem cell proliferation in the colon helping in intestinal epithelium renewal. Advantageous for healthy aging.	*Bacillus subtilis* 29784	70,71
Lipopolysaccharide (LPS)	Insulin resistance due to immune dysregulation causes inflammation and disturbed metabolic and biochemical pathways leading to metabolic diseases. Disadvantageous for healthy aging.	*Bacteroidetes* and *Proteobacteria* (produce LPS). *Firmicutes* and *Actinobacteria* (increases LPS absorption)	72,73
Colibactin & Bacteroides fragilis toxin	DNA damage by these toxins increases the chances of colon tumorigenesis which may lead to mortality observed in colorectal cancer-associated murine models also inflammation pathway role is recorded. Disadvantageous for healthy aging.	*E. coli* and *Bacteroides fragilis*	70
Short-chain fatty acids (SCFA)	SCFAs act as follows: (I) Neurodegeneration, (II) Energy homeostasis, (III) Immunomodulatory effect, (IV) Gut function and immunity regulation, (V) Anti-cancerous, (VI) Anti-inflammatory, and (VII) Gut dysbiosis prevention. Advantageous for healthy aging.	Butyrate producers (*Fusobacterium*, *Clostridium*, *Eubacterium*, and *Faecalibacterium*)	74
Nitric oxide	Shown to increase organismal lifespan (*C. elegans* model study) in a gene DAF-16 a solo FoxO (forkhead box transcription factor class O), i.e. $FoxO^{DAF\text{-}16}$-dependent signaling pathway. Advantageous for healthy aging.	Lactobacilli, bifidobacteria, *and E.coli*	70,75
Reactive oxygen species (ROS)	Induced oxidative stress and important signaling pathways modulation which produced diversified results on different model organisms related to aging. The role remains unclear.	*Lactobacillus rhamnosus* caused the rapid generation of epithelial ROS	1,70
Hydrogen sulfide	Smaller concentrations are used by colonocytes and are observed to be associated positively with longevity in model organisms. Advantageous for healthy aging in a concentration-dependent manner.	Sulfate-reducing bacteria residing in the human intestine	70
Bacterial polysaccharide colonic acid	Mitochondrial homeostasis improvement in *C. elegans* and *D. melanogaster* studies helping in longevity. Advantageous for healthy aging.	*E. coli K-12* and other mutants *of E. coli*	39,76
Polyamines	Polyamines help in the following: (I) Age-related markers improvement, (II) Age-induced memory impairment protection, (III) Longevity increment, (IV) Intestinal barrier integrity and function enhancement, (V) Intestinal and systemic adaptive immune system maturation, (VI) Cancer development due to dysregulated polyamine metabolism, and (VII) Pro-inflammatory M1 macrophage activation inhibition by spermine. Advantageous for healthy aging.	*Bifidobacterium lactis LKM512*	76,77
Indole derivatives	Indole-3-Propionic Acid acts as (I) A powerful antioxidant; (II) Amyloid-beta fibril formation inhibitor (III) Neuroprotective and cytoprotective agent against a variety of oxidotoxins (IV) Intestinal barrier function, intestinal permeability, and mucosal integrity regulator. Advantageous for healthy aging.	*E. coli, Bacteroides* spp., lactobacilli, *Clostridium sporogenes,* Fifty-one species of *Bifidobacterium*, probiotic *Lactobacillus* spp., *Lechevalieria aerocolonigenes.* Various *Peptostreptococcus* spp. and *Clostridium* spp. play's role in promoting the synthesis of indoleacrylic acid (IA) and indole propionic acid (IPA)	78–81
Phenolic derivatives	Help in (I) oxidative stress protection, (II) Urolithin exhibits anti-inflammatory and cancer prevention, (III) Chemo-preventive effects. Advantageous for healthy aging.	*Proteus* sp., *Streptococcus faecalis, Bacteroides fragilis, Fusobacterium* sp., and *Clostridium* sp.	82,83

in patients with and without cerebral Aβ deposition in cognitively normal individuals.[97] It was found that certain genera categorized as opportunistic pathogens, including *Megamonas*, *Serratia*, *Leptotrichia*, and *Clostridium* (family *Clostridiaceae*), were increased in Aβ+ cases. However, commensal genera with the ability to synthesize lactic acid and probiotic potential, including *Victivallis*, *Enterococcus*, *Mitsuokella*, and *Clostridium* (family *Erysipelotrichaceae*), were decreased in Aβ+ cases.[97] An altered gut microbiome was observed in AD patients compared to controls, with a lower abundance of *Firmicutes* and *Actinobacteria* and a higher relative abundance of *Bacteroidetes*.[98] In AD patients, families of *Firmicutes* namely *Ruminococcaceae*, *Turicibacteraceae*, *Peptostreptococcaceae*, *Clostridiaceae*, and *Mogibacteriaceae*, along with the genera *SMB*53 (family *Clostridiaceae*), *Dialister*, *Clostridium*, *Turicibacter*, and *cc*115 (family *Erysipelotrichaceae*), were less prevalent. However, the families *Gemella, Bacteroidaceae*, and *Rikenellaceae*, along with genera *Bacteroides* and *Alistipes*, were more prevalent in the patient cohort. A decline in *Actinobacteria* resulted in a decline of *Bifidobacteriaceae* at the family level and *Adlercreutzia* and *Bifidobacterium* at the genus level. Additionally, those with AD had a higher abundance of the genera *Proteobacteria* and *Bilophila.*[98]

PD is a peculiar neurodegenerative condition marked by the loss of substantia nigra cells and has recently been linked to gut microbial dysbiosis. In PD patients with motor complications, the relative abundance of the genus *Blautia* of the *Lachnospiraceae* family was decreased, while an increase in the genus *Lactobacillus* was observed.[99] Similarly, *Lachnospiraceae incertaes edis* and *Faecalibacterium prausnitzii* were less abundant in PD patients, while most taxa of the phylum *Proteobacteria*, especially *Enterobacteriaceae*, were more abundant.[99] A study comparing the alpha and beta diversity of PD patients and healthy controls after 14 months of clinical observation showed that the alpha and beta diversity was stable in PD patients and healthy controls, with no significant change in diversity with respect to disease pathology. However, the richness parameter of alpha diversity was reduced in both healthy individuals and PD patients.[100] It was previously reported that *Desulfovibrio* bacteria were more prevalent in the gut of PD patients compared to healthy controls.[99] Furthermore, the severity of PD was associated with the quantity of *Desulfovibrio* species. These bacteria produce H_2S, lipopolysaccharide, and various types of magnetite, which likely cause the oligomerization and aggregation of the α-synuclein protein, leading to PD.[100]

Stem cell aging and gut microbiome

Intestinal stem cells play an important role in maintaining intestinal homeostasis and repairing damaged epithelial tissue. These cells function in a regenerative manner to generate new tissue throughout the growth phase and repair damaged tissue during the aging process.[101] The interactions between the gut microbiome and intestinal stem cells are crucial because, if this interaction is comprehended, it may be possible to address various disorders that require stem cell therapy, heal wounds, and improve the durability of organ transplants.[101] A recent study showed a connection between hematopoietic stem cells and the microbiome through altering metabolic stress.[66] Therefore, the microbiota is crucial for maintaining microbial homeostasis, regulating metabolism, and the innate and adaptive immune systems.[101] Furthermore, the study reveals that compositional alterations in the gut microbiome driven by dysbiosis are related to stem cell aging, metabolic dysregulations, stem cells' epigenetic instability, and abnormal immune system activation.[66]

In the field of anti-aging, stem cells are regarded to have great potential. In numerous organs, it has been demonstrated that as we age, stem cells lose their capacity for self-renewal and differentiation and run out of resources.[89] The emergence of anti-aging medications should address the dysregulation caused by aging that affects stem cells' capacity for differentiation and self-renewal by re-regulating intrinsic and extrinsic variables. The host microbiome, hormones, local immune system, systemic inflammation, and niche structure are just a few examples of microenvironmental and systemic factors that influence stem cell aging.[66]

Endogenous ethanol is a class of microbiological metabolites. *Proteobacteria*, including *E. coli* and other *Enterobacteriaceae*, produce ethanol with bacterial origins. High endogenous ethanol levels in the human hippocampus inhibit proliferating stem cells and reduce progenitor and stem cells.[102] Additionally, when more ethanol accumulates in the gut, it enhances the permeability of the gut by disrupting epithelial tight junctions, particularly zonula occludens. This enables the movement of pathogenic microbes, their endotoxins, and ethanol across the epithelial layer, causing more immediate and adverse effects on tissues. As a result, the stem cell reserve depletes, hastening the aging process and compensating for damaged tissues.[103]

The host microbiome regulates the generation of aging-associated stem cells via various pathways, namely Wnt, transforming growth factor beta, Notch, JUN N-terminal kinase, and mitogen-activated protein kinases (p38) signaling pathways. However, it is still unclear how the host microbiome influences stem cell functioning in terms of aging.[66]

Modulation of microbiome for a healthy aging

Over a century ago, Russian microbiologist and Nobel Laureate E. Metchnikoff observed that having the wrong kind of intestinal microflora could adversely affect health over time.[104] He proposed that gastrointestinal metabolisms cause putrefactive effects on the body, gradually contributing to illness and aging, which can be mitigated by regularly consuming fermented dairy products.[105] Although his concept initially gained popularity among the masses, it only caught mainstream medical attention in the mid-1990s.

Currently, several studies report that aging is associated with increased dysbiosis in the gut, where proinflammatory microbes are enriched at the expense of beneficial gut commensals.[106] The gut microbial composition of elderly individuals and centenarians is characterized by a reduction in bacterial diversity and depletion of health-promoting genera such as *Bifidobacterium* and *Lactobacillus*.[107] As a result, aging populations may be more prone to inflammation and morbidity. The administration of pre- and probiotic supplements is recommended as an approach to correct such dysbiotic changes in the aging intestinal microbiota.[108]

Most probiotics used today are bifidobacteria and subpopulations of lactobacilli, widely considered the health-promoting constituents of the human microbiome. Several strains of these organisms have exhibited anti-aging properties in nematode models. Strains such as *Bifidobacterium longum* BB68,[109] *Lactobacillus gasseri* SBT2055,[110] *L. fermentum* MBC2,[111] and *B. infantis* ATCC15697 have been shown to enhance the lifespan of *C. elegans* by modulating DAF-16,[112] a transcription factor that controls multiple signaling pathways associated with aging and longevity. Other strains of lactobacilli, such as *L. rhamnosus* CNCM I-3690,[113] *L. salivarius* FDB89,[114] and *L. fermentum* LA12, have been shown to improve the life expectancy of *C. elegans* by exhib-

iting antioxidative properties.[115]

In rodent models, the administration of the *L. brevis* OW38 strain resulted in reduced expression of senescence markers p16, p53, and SAMHD1, which contributed to anti-inflammatory effects in aged mice.[116] In another study, the *L. paracasei* PS23 strain showed promising effects in delaying sarcopenia progression during aging by preserving mitochondrial function.[117] Additionally, *Lactobacillus* strains such as *L. fermentum* DR9, *L. plantarum* DR7, and *L. reuteri* 8513d significantly reduced telomere shortening, while strains *L. plantarum* AR501 and *L. helveticus* KLDS1.8701 reduced hepatic oxidative stress by elevating the gene expression of Nrf2 and other antioxidant genes.[118,119] The outcomes of these studies directly impact the central hallmarks of aging.

Probiotics are generally recognized as safe for human consumption and can impart substantial health benefits to the elderly. These benefits include modulation of the microbiome, prevention of inflammatory intestinal disorders, enhanced intestinal barrier function, stimulation of the innate immune system, and improvements in cognitive function and quality of life.[120] Human dietary intervention studies involving probiotic supplements have been documented to increase beneficial microbes such as bifidobacteria, lactobacilli, and enterococci species in the elderly population.[121] Daily consumption of the probiotic strain *Bacillus coagulans* GBI-30, 6086 among aged adults has been shown to improve immune and gut-related functions by increasing levels of butyrate-producing species such as *Fecalibacterium prausnitzii*. Administration of certain probiotics can induce favorable responses from the residents of the elderly human gut, such as *Lactobacillus rhamnosus* GG, which was found to mediate interactions between key members of the gut microbiome and the host epithelium by promoting anti-inflammatory pathways in the resident microbes.[122]

The administration of probiotics has been observed to manage many age-related pathophysiological conditions affecting the immune system. Studies on elderly human subjects show that probiotic intake can boost immunity and improve several immune-related markers.[123] Dietary supplementation with a mixture of *B. longum* Bar33 and *L. helveticus* Bar13 strains in elderly humans improved their immune response by increasing regulatory T cells, B cells, and natural killer cells while decreasing memory T cells.[123] In another study, consumption of *L. gasseri* KS-13, *B. bifidum* G9-1, and *B. longum* MM-2 produced a less inflammatory cytokine profile by maintaining $CD4^+$ lymphocyte levels in elderly hosts.[124] Other studies examining immune-related markers found a decrease in levels of the proinflammatory cytokine IL (interleukin)-8 and C-reactive protein among the elderly with probiotic intake.[125] Furthermore, these studies observed that probiotic supplementation could counteract reduced naïve T cell production and increase less-differentiated T cell populations in aging populations.[123]

Aside from enhancing immune function and longevity, probiotic interventions have been used to improve the quality of life in the elderly. Probiotic therapy has been shown to reduce abdominal pain,[126] improve bowel movements,[127] enhance oral health,[128] and increase vitamin levels in the blood.[129] Studies have also demonstrated that probiotics can positively impact the general well-being of the elderly by decreasing anxiety and depression, improving cognitive functions,[130] and alleviating stress.[131]

Bifidobacterium is one of the potential candidates for boosting longevity by producing polyamine biosynthesis observed in animal models.[132] When *Lactobacillus rhamnosus* GG and soluble corn fiber were fed to healthier elderly participants, there was a reduction in chronic inflammation and an improvement in the microbial profile.[125] In addition to probiotic interventions, physical activity plays a pivotal role in modulating the gut microbiome. Regular exercise has been linked to a diverse and balanced gut microbiome, which is crucial for maintaining overall health and preventing age-related diseases. Studies indicate that regular exercise can modify the gut microbiome composition of older individuals towards a more favorable state by increasing the populations of beneficial bacteria, such as SCFA producers, and by reducing the prevalence of potential pathogens.[107] This interplay between exercise and the gut microbiome can be effectively harnessed to enhance overall health and well-being among the elderly. The microbial outline and host health have a shared functional relationship; therefore, it is recommended to adopt a healthy lifestyle, exercise regularly, and maintain a proper diet to balance the beneficial microbiome. This balance contributes to longevity and reduces morbidities associated with aging. For instance, the deteriorating physiology of the alimentary canal inevitably impacts the gut microbiome. These alterations include elevated inflammation linked to aging, cellular malfunction (including mitochondrial dysfunction), genomic instability, epigenetic dysregulation, and diminished proteostasis, which further contribute to the onset of metabolic disorders, chronic illnesses, and altered gut-brain communication.[7]

Future directions

With the introduction of novel molecular biological techniques and advances in next-generation sequencing technologies, we finally have a snapshot of the gut microbiome and its taxonomical and functional constituents. Understanding factors that bridge the gut microbiome and long healthy life is a significant challenge. Initially, animal models have been used to understand the molecular mechanism of aging. Such studies have identified several genes associated with both the microbiome and aging. Knock-out studies involving these genes can further explore the effects of microbes on healthy aging. Various studies have been conducted on healthy elderly individuals to characterize their gut microbiome composition and identify alterations that help delay the onset of age-associated disorders.[133] Many age-related pathophysiological conditions are known to influence older adults' dietary habits, causing compositional changes in the gut microbiome that ultimately lead to senescence. At the DNA level, microbial function can only be predicted or assessed based on genetic components that can potentially produce or degrade specific compounds, such as metabolites or engage in other enzymatic activities. Evaluating mRNA (metatranscriptomics), small molecule (metabolomics), and protein levels (metaproteomics) is necessary for a more comprehensive evaluation of microbial functions. Considering that metabolic alterations are associated with aging, presumably reflecting changes in the biological roles of the host and microbiome, metabolic profiling may serve as a promising method for determining the biological age of a person.[134] By analyzing the circulating microbial metabolites, a biological aging clock can be established, although this research field is still in its beginnings.[135] For example, Johnson *et al*.[136] used the plasma metabolite profiles of individuals aged 18 to 80 and reported 21 metabolites connected to biological aging, many of which had previously been recognized as "microbe-associated metabolites".[137] Elevated levels of indole-3-acetate and putrescine are linked to biologically younger ages, while a high concentration of phaseolic acid is associated with elderly age groups.[136] Similarly, metabolites secreted in urine and feces have been investigated in relation to aging clocks, such as phenylacetylglutamine (PAG),[138] trimethylamine-N-oxide,[139] 4-cresyl sulfate,[138] and

p-cresol sulfate (PCS),[140] etc. In addition to innovations in metabolomics, proteomic studies are increasingly helpful in comprehending the composition and functioning of microbial proteins in various health aspects. More comprehensive studies are required to evaluate the relationship between the proposed metabolic-proteomic aging clock and the resident microbiome.

Advancements in the different "omics" fields have provided us with a clear understanding of various host-microbe interactions and their influences on aging. Enrichment of certain taxa, such as *Bifidobacterium*, *Christensenellaceae*, and *Akkermansia*, has been shown to promote longevity and improve quality of life during senescence. To improve the gut microbiome and encourage healthy aging, techniques such as fecal microbiome transplantation (FMT) and oral probiotic treatment have been used. Administration of pre- and probiotics may mitigate age-related alterations linked to sarcopenia and longevity.[31] Further studies in this area can potentially enhance such taxonomic profiles, imparting positive health benefits to the host. More focused studies on metagenomic exploration of the aged population would help identify species-level microbial information positively associated with the healthy aging process. However, these methods suffer from the major limitations of predicting metagenomic diversity till the genus level, missing out on species and strain-level differences.[141] Therefore, whole metagenome-based shotgun sequencing methods can be used to address these issues and explore the strain/species-level diversity of the gut microbiome.

Microbes generally do not exist in isolation and exhibit a bidirectional relationship with several other microbial members in an environment. Most current studies focus on identifying individual microbial members associated with the aging process. However, it may be useful to explore the social behavior of gut microbiome members by adopting tools and pipelines to identify co-occurring taxa or those taxa that do not occur together. To explore the activity of such beneficial taxa and how they are co-associated with each other, culturomics or culture-based methods are an alternative approach. Recent methods such as yeast casitone fatty acid agar can be employed to cultivate more than 90% of members of the gut microbiome under lab conditions.[37]

Since age-related disorders are known to increase intestinal permeability, regaining intestinal permeability by FMT may be a regenerative and successful medicinal technique in producing stem cells for the elderly. Nevertheless, more research is needed to determine whether FMT to old recipients from young donors restores the ability of stem cells to self-renew, regenerate, and differentiate, thereby improving lifespan. To pave the way for discovering therapeutic medications for extending lifespan and treating disorders linked to aging, more research into the interactions between intestinal stem cells and the microbiome is necessary.

Constructing a reliable aging model based on microbiomes can only be possible by integrating different types of approaches and data sources. Additionally, novel and advanced computational methods are needed considering the heterogeneity and complexity of aging and the microbiome. Machine learning models trained on metagenomic, transcriptomic, proteomic, and metabolomics data can predict microbial behaviors associated with aging. These models can also account for external factors such as geographical features and lifestyle, further refining our understanding of biological and chronological aging.[142] Furthermore, such advancements can assist in modulating the gut microbiome and developing personalized longevity therapies in a clinical context. Therefore, adopting a healthy lifestyle with proper nutrition and exercise, along with positive modulation of GM through probiotics, can bring us closer to prolonged healthy lives.

Conclusions

Hippocrates' emphasis on the importance of gut health resonates through the centuries to our modern understanding of the pivotal role of the gut microbiome in human health and aging. Although aging is a complex biological process that has yet to be fully understood, we have an increasing volume of evidence supporting the existence of a dialogue between the gut microbiome of a host and its aging process. Aging brings about changes in the gut microbiome, disrupting its balance and functionality, which can accelerate senescence through inflammatory processes and reduced production of beneficial metabolites. Advancements in the various "omics" fields have provided us with a clear understanding of various host-microbe interactions, their influences on aging, and the enrichment of certain longevity-associated taxa, such as *Bifidobacterium, Christensenellaceae*, and *Akkermansia*, offering promising avenues for interventions such as FMT and probiotic treatments. Although we are still far from solving the "curious case of aging" or finding "the path to longevity", it is possible that a healthy aging process with less morbidity and frailty can be achieved through a healthy diet and proper modulation of the gut microbiome.

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Conflict of interest

The authors declare no conflict of interests.

Author contributions

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