Exploratory Research and Hypothesis in Medicine **2025** vol. 10(2) | 122–134
DOI: 10.14218/ERHM.2024.00045

Review Article

The Hidden Drivers of Aging: Microbial Influence on Genomic Stability and Telomere Dynamics

Swarup K. Chakrabarti[1*] and Dhrubajyoti Chattopadhyay[1,2]

[1]*H. P. Ghosh Research Center, New Town, Kolkata, West Bengal, India;* [2]*Sister Nivedita University, New Town, West Bengal, India*

Received: December 20, 2024 | **Revised:** February 19, 2025 | **Accepted:** February 25, 2025 | **Published online:** April 17, 2025

Abstract

This review explores the complex interplay between the microbiome and human aging, highlighting how dysbiosis impacts host physiology and health, particularly in relation to genomic stability and telomere attrition. Recent advances in cellular and molecular biology have underscored the role of both intrinsic and extrinsic factors in human aging, with the microbiome emerging as a key determinant of host physiology and health. Dysbiosis—disruptions in microbiome composition—is linked to various age-related diseases and impacts genomic stability and telomere attrition, the progressive shortening of telomeres that limits cell division and contributes to aging. This review examines how microbiome dynamics influence aging by triggering inflammation, oxidative stress, immune dysregulation, and metabolic dysfunction, all of which affect two primary hallmarks of aging: genomic instability and telomere attrition. Understanding these interactions is essential for developing targeted interventions to restore microbiome balance and promote healthy aging, offering potential treatments to extend healthspan and alleviate aging-related diseases. The convergence of microbiome and aging research promises transformative insights and new avenues for improving global population well-being.

Introduction

In recent years, research on human aging has placed greater emphasis on the biological processes that underlie it.[1] This shift has been driven by technological advances and a deeper understanding of the intricate cellular and molecular interactions that regulate aging.[2,3] Central to this exploration is the recognition that aging is not a singular event but a complex interaction of numerous inherent and external factors that together shape the timing and nature of the process.[4,5] Among these factors, the human microbiome has emerged as an important influence on host physiology and health outcomes.[6–8] Consisting of a diverse array of microorganisms that inhabit various areas of the body, the microbiome significantly impacts metabolic functions, immune responses, and even brain health.[9] Dysbiosis, or imbalances in the microbiome, is linked to age-related conditions such as cardiovascular diseases (CVDs), neurodegenerative diseases (NDs), and metabolic syndromes.[10] DNA repair mechanisms and cell cycle checkpoints protect genetic material, ensuring its stability across cell generations.[11] However, internal and external factors—such as reactive oxygen species (ROS), radiation, and environmental toxins—continuously threaten this stability by causing DNA damage.[12] As DNA damage accumulates over time, it can result in mutations, chromosomal abnormalities, and, eventually, cellular dysfunction and aging.[13–15] An important factor in cellular aging is the progressive shortening of telomeres, repetitive DNA sequences found at the ends of chromosomes.[16] Telomeres protect chromosomal ends, preventing them from being mistaken for DNA breaks and maintaining genomic stability.[17] However, with each cell division, telomeres shorten because DNA polymerase cannot fully replicate the lagging strand. As a result, telomeres act as a molecular timer, restricting the ability of cells to proliferate and leading to replicative senescence.[18,19] Understanding how the human microbiome, genomic stability, and telomere shortening are interconnected is crucial to uncovering the mechanisms of aging and developing strategies for healthy aging.[20–25]

Thus, this review aimed to integrate current studies and provide a comprehensive understanding of the complex interactions among various factors that contribute to the aging process. In particular, we emphasize genomic instability and telomere attrition—two crucial primary hallmarks of aging outlined by López-Otín C and colleagues.[26] These hallmarks are essential to the biology of aging and are closely linked to cellular dysfunction and the emergence of age-related diseases. Genomic instability, resulting from the buildup of DNA damage and mutations, accelerates aging at the cellular level, whereas telomere attrition, which limits

Keywords: Microbiome; Aging; Dysbiosis; Genomic instability; Telomere attrition; Inflammation; Oxidative stress; Immune dysregulation; Metabolic dysfunction; Healthspan; Age-related disease.

***Correspondence to:** Swarup K. Chakrabarti, H. P. Ghosh Research Center, HIDCO (II), EK Tower, New Town, Kolkata, West Bengal 700161, India. ORCID: https://orcid.org/0000-0001-5666-7662. Tel: +91-9831643038, E-mail: swarupkchakrabarti@gmail.com

How to cite this article: Chakrabarti SK, Chattopadhyay D. The Hidden Drivers of Aging: Microbial Influence on Genomic Stability and Telomere Dynamics. *Explor Res Hypothesis Med* 2025;10(2):122–134. doi: 10.14218/ERHM.2024.00045.

cellular replication, plays a key role in cellular senescence.[20–25,27] While epigenetic changes and the loss of proteostasis also qualify as primary hallmarks of aging, their inclusion would significantly expand the scope of this review.[27] Considering the complexity of these processes and their evolving connections with the microbiome, we have chosen to focus specifically on genomic instability and telomere attrition. This targeted approach allows for a more detailed and precise investigation of these well-established aging mechanisms, which are directly affected by the microbiome, without delving into the complex interactions with other hallmarks. Through this strategy, we aimed to provide valuable insights into the evolving relationship between aging and the microbiome, a growing area of interest in gerontological studies.

Key hallmarks that shape our journey through life

The phenomenon of biological aging is complex and gradual, marked by a steady decline in both physiological and cellular functions, resulting in reduced resilience to stress, slower healing, and disrupted homeostasis in the organism.[1–5,28] Scientists are actively exploring the molecular and cellular foundations of aging, identifying twelve distinct hallmarks associated with this process.[26,28–31] This growing body of knowledge highlights the intricate nature of aging and drives ongoing efforts to unravel its essential mechanisms and develop strategies that promote healthier aging trajectories. The proposed hallmarks of aging involve various cellular and molecular mechanisms that are crucial in the aging process of diverse organisms. These features include genomic instability, telomere shortening, epigenetic changes, a decline in proteostasis, disrupted nutrient sensing, mitochondrial dysfunction (MD), cellular senescence, stem cell depletion, altered cell communication, dysbiosis, chronic inflammation, and impaired macroautophagy.[28–31] Genomic instability refers to the buildup of DNA damage, whereas telomere attrition involves the progressive shortening of the protective ends of chromosomes.[20–25] In contrast, epigenetic modifications change gene expression without altering the DNA sequence, while loss of proteostasis disrupts the structure and function of proteins.[27,32,33] Disruption of nutrient sensing negatively impacts metabolic pathways, and MD results in diminished energy output and increased production of ROS.[34,35] Cellular senescence halts cell growth permanently, stem cell decline reduces tissue regeneration, and altered intercellular communication disrupts tissue balance.[36–38] Dysbiosis disrupts gut microbe balance, chronic inflammation keeps the immune system overactive, and impaired macroautophagy leads to the accumulation of cellular waste, exacerbating age-related decline.[39–41] These hallmarks reveal the complex interactions of cellular, molecular, and microbial processes in aging, highlighting the potential for targeted interventions to promote healthier aging.[26] It is important to emphasize that each hallmark should be present during normal aging, with their exacerbation potentially speeding up aging and their alleviation possibly extending a healthy lifespan.[28–31]

Microbiome and hallmarks of aging

The human microbiome, especially the gut microbiota, develops in tandem with its host, and changes within it are significantly linked to the aging process. The microbiome consists of a wide range of microorganisms inhabiting various regions of the body, and it undergoes ongoing transformations in harmony with its host— a trend supported by many scientific investigations exploring its complex relationship with aging.[21–25] Research has revealed that alterations in gut microbiota composition can affect how individuals respond to stress and their overall health as they age. Recent empirical studies suggest an innovative method focused on gut microbiota to alleviate symptoms associated with brain aging and improve cognitive health.[42] Experimental data shows that gut microbiota metabolism changes with age, suggesting a possible link to age-related metabolic disorders.[23,43,44] Studies tracking specific groups over time have shown that the composition of gut microbiota evolves gradually as a person ages, and these changes are linked to the onset of age-related diseases.[45,46] These findings highlight the strong impact of the gut microbiota on aging and the need for further study into the mechanisms behind this connection. Research also shows that maintaining a balanced gut microbiota is crucial for encouraging optimal physical and mental development during infancy and childhood.[47,48] Aging causes physiological changes that alter gut microbiota composition and function, highlighting their role in dysbiosis and the aging process.[49,50] Furthermore, dysbiosis-related changes in gut microbiota can impact various aspects of aging through the body's interconnected ecosystem.[51–53]

Thus, this review article takes an important initial step in exploring the complex connection between the microbiome and critical aspects of aging, including genomic instability and telomere shortening. Acknowledging the difficulties inherent in this subject, the following sections aim to clarify the nuanced interaction between these elements. By initiating this journey of exploration, this review paves the way for further research and advancements in this vibrant and rapidly evolving field.

Evolving interaction between the microbiota and genomic instability

In the intricate realm of human biology, the relationship between the human microbiome and the stability of our genes is a fascinating topic that warrants further exploration. Recent pioneering research has illuminated the considerable impact that the microbial populations residing within us have on various health and disease factors. As our understanding grows, an engaging narrative unfolds: the evolving connection between genetic stability and these microorganisms.[21–24,42–44] One common characteristic observed in numerous diseases is genomic instability, which refers to the increased frequency of genetic alterations, including DNA mutations, chromosomal rearrangements, and aberrant recombination events. In biomedical research, understanding the causes and factors contributing to this instability has been essential.[54] However, new findings are revealing a crucial, yet previously overlooked, element affecting genetic stability: the complex microbial communities within both our internal and external environments.[11–15]

Central to this investigation is a pivotal shift in perspective: microbiota are now recognized not merely as passive bystanders but as active contributors to the development of host physiology, including the optimal maintenance of the host genome, a process intricately linked to aging. The dynamic interplay between the microbiota and the genome introduces additional complexity, as environmental factors, diet, antibiotic use, and host genetics combine to shape microbial communities, influencing genomic stability in diverse ways.[55–58] This convergence of genetic and microbiological research represents a transformative shift in our understanding, emphasizing the microbiota's crucial role in human health and disease. Embracing this comprehensive perspective not only enhances our insight into the origins of diseases but also opens avenues for new treatments and personalized medicine aimed at

preserving genomic balance. For instance, studies have demonstrated the profound effects of *Helicobacter pylori* infection on the gastrointestinal (GI) system, unveiling DNA-damaging processes triggered by this pathogenic bacterium.[59,60] These studies revealed the detrimental impacts of *H. pylori* on host cells and provided preliminary evidence linking microbial infections to the activation of DNA damage responses (DDR).[59–61] Moreover, they highlighted the disruption of the host's DNA repair mechanisms in the presence of *H. pylori*, underscoring the potential threat to genomic stability posed by pathogenic bacteria and the urgent need to explore targeted therapeutic strategies to mitigate microbial-induced DNA damage. Similarly, *Fusobacterium nucleatum*, a bacterium frequently found in the human digestive system, causes persistent inflammation, leading to the production of ROS, which damage cellular components, including DNA.[62,63] Over time, this accumulation of DNA damage may hasten the aging process by promoting cellular senescence, weakening DNA repair functions, and contributing to the hallmarks of aging.[64,65] Additionally, *Enterococcus faecalis* produces superoxide anions and hydrogen peroxide during metabolism, both of which can cause oxidative damage to DNA, resulting in base modifications, strand breaks, and cross-linking.[66] Over time, the continuous cycle of DNA damage and repair leads to the accumulation of mutations and chromosomal instability, indicators of aging that reduce cellular functionality and increase the risk of degenerative diseases, including cognitive deterioration.[64,65] Gut microbiota also play a critical role in processing bile acids, which is vital for preserving DNA integrity.[67] Gut microbiota convert primary bile acids into secondary forms, including deoxycholic acid, which can produce ROS and directly interact with DNA, causing strand breaks and genetic mutations.[67–69] This DNA damage is particularly significant as we age, as the accumulation of damage can overwhelm the cells' repair capabilities, impairing function in critical organs like the colon and liver. As a result, chronic exposure to dysbiosis-induced altered bile acid compositions may contribute to inflammation related to aging and tissue degeneration.[70,71] Moreover, the role of *Clostridium difficile* further exemplifies how gut bacteria contribute to DNA damage. This bacterium secretes powerful toxins, such as Toxin A and Toxin B, which enzymatically modify Rho GTPases, impairing the actin cytoskeleton and cellular signaling.[72,73] The resulting disruption of cellular integrity activates DDR pathways, initiating repair or inducing cell death when the damage is irreparable. Prolonged exposure to these toxins induces inflammation, exacerbating cellular stress and accelerating the accumulation of DNA damage. Over time, these chronic assaults can overwhelm DNA repair mechanisms, causing genomic instability and mutations that hinder tissue function.[64,65] The intestinal epithelium, with its rapid turnover rate, is particularly vulnerable to accelerated aging and degeneration as DNA damage disrupts regeneration and organ function.[74,75] Furthermore, the synthesis of genotoxins, such as colibactin and *Bacteroides fragilis* toxin, by commensal bacterial strains like *Escherichia coli* and *Bacteroides fragilis* presents a significant concern for cellular health.[76,77] Interestingly, the healthy GI tract is predominantly inhabited by obligate anaerobic bacteria, including *Bacteroides*, *Bifidobacterium*, *Clostridium*, and *Ruminococcus*,[78–80] which help maintain gut health and support essential metabolic functions. However, dysbiosis—an imbalance in the microbiota—leads to an increase in facultative anaerobes such as *Escherichia*, *Enterobacter*, *Enterococcus*, and *Klebsiella*.[81,82] Unlike obligate anaerobes, facultative anaerobes can thrive in both oxygen-rich and oxygen-poor environments, and their proliferation triggers gut inflammation, resulting in ROS production and DNA damage. This cascade of events accelerates genomic instability, particularly in the GI tract, and increases the risk of age-related disorders.[83–85] Furthermore, older individuals exhibit elevated oxidative stress markers, such as 8-oxoguanine and γ-H2AX, which indicate DNA damage that worsens with dysbiosis, contributing to neurodegeneration and systemic aging.[86,87] Dysbiosis also promotes MD, further exacerbating mtDNA damage and cellular aging. This process is characterized by impaired energy production and immune responses—hallmarks of aging.[88,89]

Recent research has reinforced the connection between gut microbiota, genomic instability, and aging, emphasizing the pivotal role of inflammation in this process. Studies have found that aging impairs DNA double-strand break repair in mouse livers following diethylnitrosamine exposure, with gut microbiota-induced inflammation playing a crucial role.[90,91] Age-related microbiota changes lead to dysregulated innate immunity, heightened inflammatory cytokine levels, and reduced DNA repair efficiency.[92,93] Notably, interventions such as antibiotic treatment, MyD88 gene (myeloid differentiation primary response gene 88) deletion, or germ-free conditions have been shown to reduce inflammation and enhance DNA repair in older mice.[94–96] Conversely, pro-inflammatory factors, such as a high-fat diet, exacerbate DNA repair deficiencies; however, antibiotic treatment mitigates this effect, highlighting the microbiota's significant influence.[97,98] These findings suggest that modifying inflammatory responses, rather than directly targeting DNA repair mechanisms, may help prevent genomic instability during aging.[99,100]

Clinical trials investigating the microbiota-genomic instability link are also exploring potential therapeutic avenues. For example, the Canakinumab trial, which targets interleukin-1β to reduce inflammation, demonstrated benefits in managing age-related diseases like hypertension and diabetes, further confirming inflammation's role in genomic instability.[101–103] Similarly, the Metformin Aging Study suggests that metformin, a diabetes drug, may enhance genomic stability and slow cellular aging, positioning it as a potential anti-aging therapy.[104,105] Additionally, fecal microbiota transplantation trials aim to restore a healthy microbiome, potentially improving genomic stability and mitigating aging-related issues.[106,107] Trials examining rapamycin, a drug believed to delay menopause, further suggest that modulating immune responses and cellular aging mechanisms can help combat genomic instability.[108–110] Collectively, these studies underscore the significant role of microbiota and inflammation in aging, offering insights into novel therapies that could enhance healthspan and reduce the impact of genomic instability. In summary, microbial metabolites and toxins contribute to DNA damage through oxidative stress, genotoxic by-products, and direct interactions with DNA. The accumulation of this damage over time drives genomic instability. While the relationship between the microbiome and aging remains complex, growing evidence suggests that microbial effects on DNA integrity play a pivotal role in the aging process. This underscores the importance of maintaining a balanced microbiome for healthy aging and minimizing the risk of age-related diseases.

Intricate interplay between microbiome dynamics and telomere attrition

At the ends of each chromosome, there is a protective structure called a telomere, which consists of repeating DNA sequences of the motif TTAGGG.[17,18] Telomeres play an essential role in protecting genetic information during cell replication, as the processes responsible for copying DNA encounter challenges in fully repli-

cating the ends of chromosomes.[17–20] Additionally, telomeres are composed of repetitive DNA sequences and are capped by a unique protein complex known as shelterin.[111–114] This shelterin assembly includes six specific proteins: telomeric-repeat binding factor (TRF) 1, TRF2, tripeptidyl peptidase 1, protection of telomerase 1, TRF1-interacting nuclear factor 2, and repressor activator protein 1. The shelterin complex is essential for protecting telomeres and executing several critical functions. First, it acts as a shield, preventing the identification of telomeres as sites of DNA damage. This blockage of DDR pathways helps prevent undesirable biological reactions, such as cell cycle arrest or apoptosis. Second, shelterin plays a vital role in preserving the integrity of telomeres, stopping the cellular machinery responsible for DNA repair from mistakenly identifying them as damaged. This action helps prevent the fusion of telomeres with the ends of other chromosomes, ultimately reducing the risk of genomic instability or rearrangement. Lastly, shelterin modulates the telomerase enzyme, which restores lost telomeric DNA during cellular division by managing its availability and function. This regulation ensures that telomerase is active only when needed, avoiding excessive elongation of telomeres that could result in age-related disorders. Together, the shelterin complex plays a crucial role in maintaining telomere integrity by striking a balance between shielding them from damage and ensuring they function correctly in essential biological activities like replication and repair.[111–117] Although telomerase activation is typically inhibited in mature somatic cells, it peaks during the developmental phases of humans.[118] Throughout embryonic growth, telomerase remains highly functional to promote effective cell division and tissue development.[119] However, as cells specialize and mature, the activity of telomerase is generally reduced in most somatic cells.[120] Nevertheless, specific cell types, such as stem cells and immune cells, retain their telomerase activity throughout an individual's life.[121–123] This persistent activity allows stem cells to continually divide and differentiate into different cell types, repairing damaged or aging cells. Similarly, immune cells rely on telomerase to aid in their rapid growth and effective function when responding to pathogens and ensuring ongoing immune monitoring.[124,125] The persistence of telomerase activity within these essential cell types enables the body to maintain tissue balance, healing, and regeneration over time. This highlights the importance of telomerase not just for enhancing lifespan but also for safeguarding tissue quality and functionality as aging occurs.[126,127]

Research indicates that dysbiosis initiates a cascade of events leading to shortened telomeres in host cells through various pathways.[128–130] Initially, dysbiosis triggers chronic, low-grade inflammation, which produces ROS and other damaging substances that accelerate telomere shortening.[131,132] This inflammation also increases cellular turnover and oxidative stress, further hastening telomere loss. Additionally, dysbiotic microbiota produce metabolites and byproducts that contribute to oxidative stress in host cells.[133] Interestingly, certain beneficial microorganisms, such as those generating short-chain fatty acids (SCFAs), have been identified as potential protectors of telomeres.[133–135] SCFAs influence both oxidative stress and inflammation, which are closely linked to telomere shortening.[136,137] Thus, microbial metabolites like SCFAs may mitigate telomere loss, creating a favorable environment for maintaining telomere length and cellular vitality. Additionally, an imbalanced microbiota disrupts the host immune system, leading to irregular immune responses, including impaired T cell activity and increased production of pro-inflammatory cytokines. These changes amplify inflammation and oxidative stress, which, in turn, accelerate telomere shortening.[138–140] Moreover, dysbiosis impacts host metabolism, leading to complications such as insulin resistance and dyslipidemia.[141,142] These metabolic disturbances exacerbate systemic inflammation and oxidative stress, contributing to accelerated telomere attrition. Furthermore, microbial imbalances could influence the host's epigenetic processes, including changes in DNA methylation and histone modifications.[143–145] These epigenetic alterations can disrupt telomere regulation, accelerating telomere shortening. For instance, modifications in DNA methylation at genes associated with telomeres might impair telomerase function or affect telomere structure, exacerbating telomere loss.[146,147]

Numerous studies reinforce the link between dysbiosis, telomere shortening, and the onset of diseases. Research shows that metabolic diseases, like type 2 diabetes, are associated with accelerated aging due to shortened telomeres, which may result from disrupted gut microbiota.[148,149] Changes in diet or weight-loss surgery can alter gut microbiota composition, reducing inflammation caused by gut-derived Gram-negative bacterial fragments known as endotoxins.[150,151] This shift may similarly influence the gradual shortening of telomeres over time. A distinct study further demonstrated that enhancing telomerase activity, particularly in the GI tract, could counteract aging processes. This intervention extended the lifespan of telomerase-deficient *zebrafish* and alleviated age-related symptoms in wild-type counterparts.[152,153] This finding underscores the potential of strategic interventions to mitigate the impacts of aging and improve health outcomes. Additionally, research into the gut microbiome's role in mental health, particularly depression, reveals a connection between telomere shortening and an imbalance of beneficial gut bacteria.[154,155] These studies contribute to the growing body of evidence suggesting that changes in gut microbiota composition play a crucial role in the acceleration of telomere shortening, especially in mood disorders like depression. Further research highlights the gut microbiome's critical role in regulating telomere length and the development of age-related diseases, primarily through inflammation and oxidative stress. Studies show that a diverse microbiota helps preserve telomere length, while imbalances or dysbiosis accelerate telomere loss and exacerbate aging-related issues.[156,157] For instance, individuals with less diverse microbiota exhibit significantly shorter telomeres, indicating that microbial imbalances increase the risk of age-related conditions. Animal models support these findings, with germ-free mice showing notably shortened telomeres due to abnormal immune responses and increased oxidative stress.[158,159] In humans, an imbalanced microbiome is correlated with higher inflammatory markers, such as C-reactive protein, which contribute to telomere shortening.[160] Conversely, correcting dysbiosis in animal models has been shown to reverse telomere shortening, likely by reducing inflammation and oxidative stress through beneficial SCFAs.[161,162] A balanced microbiome, supported by dietary interventions or probiotics, has also been associated with longer telomeres, suggesting that such strategies could slow telomere loss and delay aging.[163,164] These studies strongly suggest that maintaining a balanced microbiome is essential for preserving telomere length and preventing age-related diseases.

Recent human studies have further established a link between gut microbiome changes and telomere shortening, emphasizing the importance of gut health in aging. Research indicates that individuals with a more diverse microbiome tend to have longer telomeres, suggesting that a balanced microbiota can protect against aging.[165,166] Diet, particularly fiber-rich foods, plays a key role by promoting beneficial bacteria that produce SCFAs, such as butyrate.[163,164] These SCFAs reduce inflammation and oxidative stress—major contributors to telomere shortening—and enhance immune func-

tion. The microbiome also significantly influences immune cells like T-cells, which in turn affect telomere length. Imbalances in microbiota can weaken immune responses and accelerate telomere loss. Overall, these findings demonstrate that the microbiome's regulation of inflammation, oxidative stress, and immune function is vital for preserving telomere length and slowing aging.[167,168]

In summary, imbalances in the microbiota trigger a series of physiological changes, including inflammation, oxidative stress, immune dysfunction, metabolic issues, and genetic modifications. Together, these factors lead to shorter telomeres and genomic instability, accelerating cellular aging and increasing the risk of aging-related diseases. However, a comprehensive analysis of how disruptions in microbial balance influence these interconnected factors goes beyond the scope of this article. Nonetheless, this section aims to shed light on the intricate relationship between microbiota, telomere shortening, and aging, emphasizing the need for continued research in this evolving field.

Microbiome and aging: interplay between genome stability and telomere attrition

In the complex field of human health and aging, an important molecular-level topic emerges: the relationship between genome stability and the gradual deterioration of telomeres. This section explores this connection comprehensively by summarizing findings from key studies in the literature, with a focus on how genome stability and telomere attrition impact human health and aging, particularly in relation to the microbiome. For example, Werner syndrome (WS) is an inherited disorder characterized by the early onset of aging symptoms.[169] At the molecular level, WS results from a mutation in the Werner protein, which is a crucial member of the RecQ helicase family involved in DNA replication, repair, and recombination.[170,171] Consequently, WS is associated with heightened genomic instability, accelerating the development of aging and age-related diseases. Cells obtained from WS patients exhibit limited growth in culture, entering a senescent state after a certain number of cell divisions, indicating telomere dysfunction.[172] Nevertheless, bypassing p53- and retinoblastoma protein-dependent tumor-suppressing mechanisms allows for enhanced cell division and an extended replicative lifespan, further emphasizing the link between telomere dysfunction and the accelerated aging observed in WS.[173,174] Critically short telomeres in humans initiate signaling through the p53 and retinoblastoma protein tumor suppressor pathways, exacerbating genomic instability.[175] This relationship highlights why individuals with WS face a higher risk of age-related diseases, given the close connection between genomic instability and aging, likely stemming from telomere dysfunction. It underscores the increasing recognition of the interconnections among the hallmarks of aging, particularly in the context of accelerated aging in WS. Although direct links between microbial dysbiosis and WS are still emerging, numerous studies suggest that dysbiosis may exacerbate aging-related conditions, potentially impacting WS.[176,177] For instance, research has shown that an imbalance in the microbiome can lead to increased levels of pro-inflammatory cytokines and ROS, both of which can negatively affect cell health and intensify concerns tied to premature aging, such as in WS.[178,179] Impaired DNA repair mechanisms are a hallmark of WS, and factors triggered by dysbiosis, such as oxidative stress and inflammation, might indirectly impede these repair processes, potentially worsening genomic instability in WS patients. Additional studies present intriguing results regarding the efficacy of telomeric DNA repair across different cell types.[180,181] Comparisons indicate that as individuals age, their cells exhibit diminished repair efficiency, particularly in those from older adults.[182] This reduction is notably severe in cells from individuals with WS. While repair efficiency in cells from Alzheimer's patients meets expectations, there is a slight drop in efficiency observed in WS cells.[183,184] These findings prompt inquiries into the possible functional ramifications of compromised telomeric repair mechanisms in relation to the genomic instability linked to aging. Furthermore, the connection between reduced DNA repair capacity and age-associated alterations in the microbiome underscores a complex interplay between cellular aging mechanisms and microbial dynamics, highlighting how these factors may collectively influence the aging process and age-related diseases.[185–189]

The role of the gut microbiome in longevity: insights from centenarians

Centenarians, those who live to be 100 years old or more, demonstrate remarkable longevity and resilience to age-related health challenges.[190,191] Recent research has highlighted how their gut microbiome composition may play a critical role in sustaining their long lives.[192,193] Studies suggest that the microbiomes of centenarians differ significantly from those of younger individuals, exhibiting greater diversity of beneficial microbes.[192,194,195] Notably, centenarians tend to have increased levels of gut bacteria such as *Akkermansia*, *Bifidobacterium*, and *Christensenellaceae*, which are linked to anti-inflammatory effects and improved gut health. These microbial compositions likely play a pivotal role in maintaining immune homeostasis, reducing systemic inflammation, and modulating metabolic pathways, all of which are crucial for promoting healthy aging and extending lifespan. Moreover, centenarians possess a broader variety of microbes that produce beneficial compounds like SCFAs, which support both gut health and overall physiological balance.[196,197] While the evidence remains limited, primarily due to small sample sizes and observational studies, current findings suggest significant correlations between specific gut microbiota profiles in centenarians and factors such as SCFA production and gut health. However, these studies do not yet establish definitive causal relationships, and further research is needed to clarify how the microbiome connects with the hallmarks of aging. Understanding these microbial patterns could offer valuable insights for developing strategies to promote healthy aging and potentially extend lifespan in broader populations. This exploration of the microbiome's influence on aging intersects with broader biological processes like telomere shortening and genetic stability. Telomeres, the protective caps at the ends of chromosomes, naturally shorten as we age, and this genetic instability is a key driver of age-related decline. The relationship between the microbiome, telomere preservation, and genome stability is a fascinating area of study. Researchers are increasingly focused on understanding how the microbiome may help protect telomeres, which could open new avenues for therapies aimed at promoting healthy aging. These studies highlight that the gut microbiome plays a crucial role in protecting overall well-being, offering a pathway to improve longevity and health through its potential interactions with genome stability and telomere length.[198–200]

Studies on centenarians from around the world reinforce these concepts, highlighting specific microbial features linked to longevity. For instance, research on Okinawan centenarians has found that their microbiomes are enriched with *Akkermansia muciniphila*, a bacterium known for enhancing gut barrier function and reducing inflammation.[201,202] This microbe, along with others like

Bifidobacterium, is associated with improved metabolic health, a balanced immune system, and lower levels of inflammation—factors crucial for aging well.[203,204] Similarly, Italian centenarians possess a microbiome with greater diversity, including strains like *Faecalibacterium prausnitzii* and *Bifidobacterium*, which are recognized for their anti-inflammatory properties.[205] These microbes may help reduce chronic inflammation, a key driver of age-related diseases such as CVDs and type 2 diabetes.[206] The microbial diversity in these populations suggests that a varied and balanced gut microbiome may be protective against these diseases and contribute to healthy aging. In Sardinia, a region known for its significant number of centenarians, studies have revealed that these individuals possess microbiomes that generate higher levels of SCFAs, such as butyrate, which are crucial for preserving gut health, immune responses, and metabolic balance.[205,207] The microbiome of Sardinian centenarians strengthens the gut barrier and aids in diminishing inflammation, further supporting the notion that a robust gut microbiome is a vital component of healthy aging.[208] Additional research indicates that centenarians exhibit greater microbial diversity compared to younger people and older individuals who do not live to 100.[209] This diversity, along with a prevalence of bacteria such as *Bifidobacterium* and *Prevotella*, is linked to enhanced metabolic health and reduced inflammation, implying that these microbial characteristics shield centenarians from the typical diseases related to aging, thus bolstering their overall well-being.[210,211] A recent cross-sectional study involving 1,575 participants ranging from 20 to 117 years of age in Guangxi province, China, which included 297 centenarians, further examined the relationship between the gut microbiome and increased longevity.[198] This research found that centenarians have microbiomes commonly found in younger people, dominated by *Bacteroides* species, showing increased species diversity and enrichment with potentially beneficial *Bacteroidetes*. Additionally, the microbiomes of centenarians demonstrated a reduction in potential pathobionts, which are thought to help lower systemic inflammation and improve metabolic health—key elements in preserving genomic stability and reducing telomere shortening.[212,213] Although current findings indicate that the microbiome plays a role in promoting conditions favorable for genomic stability and telomere maintenance, conclusive studies directly comparing telomere length and genomic stability in centenarians with younger or similarly aged non-centenarians are still required. The results show a strong link but do not yet confirm that enhanced genomic stability or longer telomeres are defining traits of centenarians. Across these studies, one clear theme emerges: centenarians tend to have gut microbiomes rich in specific, beneficial microbes that support immune function, reduce inflammation, and regulate metabolic processes. These factors are critical for promoting healthy aging and may help extend lifespan. While much of the evidence remains correlational rather than causal, the research underscores the significant role the microbiome plays in aging. It may hold the key to understanding longevity at a microbial level, offering a promising path forward in efforts to improve health and extend longevity (Fig. 1).

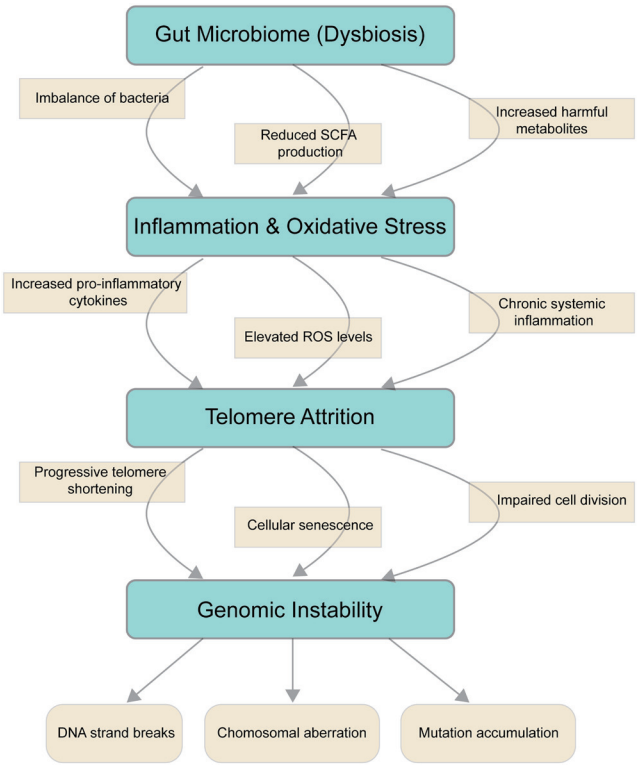

Fig. 1. This figure depicts the pathways linking gut microbiome dysbiosis, telomere attrition, and genomic instability. In dysbiosis, an imbalance between beneficial and harmful gut bacteria reduces protective metabolites like short-chain fatty acids (SCFAs) and increases harmful substances, leading to systemic inflammation and oxidative stress. These conditions accelerate telomere shortening, which contributes to cellular senescence and DNA damage. As telomeres shorten, chromosomal instability increases, elevating the risk of age-related diseases such as neurodegeneration and metabolic disorders. Chronic inflammation further disrupts the microbiome, creating a feedback loop that accelerates telomere attrition and genomic instability.

Future directions

Future investigations into how the microbiome influences aging have the potential to significantly enhance our comprehension of personal health while also delivering substantial benefits to society. By elucidating the molecular mechanisms involved in aging, we can reduce the financial burden that age-related diseases place on healthcare systems. This research could lay the foundation for innovative treatments aimed at prolonging both lifespan and healthspan. Such advancements could transform healthcare systems worldwide, alleviating the pressure of aging-related challenges and promoting a healthier, more active aging population. Furthermore, expanding our understanding of genome stability and telomere health is essential for understanding the complex relationships between these elements, aging, and the microbiome. Exploring these relationships could reveal new avenues for interventions, ultimately improving public health. Importantly, the close anatomical connection between the gut microbiota and immune cells in the intestine underscores the potential effects of telomere shortening and genomic instability in these immune cells on the fragile balance of the gut microbiome. Disruptions to this balance may lead to microbial imbalances, further complicating the ongoing interactions between the microbiome, telomere attrition, and genomic instability. This interconnectedness highlights the critical need for thorough studies to enhance our understanding of how these elements influence overall health. The convergence of microbiome research and aging biology presents an exciting new realm in biomedical science, offering the potential for significant advancements in aging studies. However, the field must also account for the complex interactions between genomic stability,

telomere attrition, and the other hallmarks of aging to better understand the independent role these factors play in the aging process. Grasping the microbiome's impact on each hallmark of aging requires comprehensive research to unravel the intricate network of interactions that drive aging processes. In essence, this review has focused on two primary hallmarks of aging—genomic instability and telomere degradation—and their potential interactions, elucidating their roles within the broader framework of aging biology. While these hallmarks are inherently interrelated, their connections with other aging mechanisms remain inadequately explored, indicating the need for further inquiry. Future studies should strive to unravel the individual contributions of each hallmark to longevity, providing deeper insights into their singular and synergistic impacts on the aging process. Furthermore, the meta-hallmark framework, which examines the interconnections between various aging mechanisms, offers a crucial perspective for enhancing our comprehension of the aging process.[214,215] This approach acknowledges that aging arises not from isolated biological events but from intricate interactions among diverse cellular and systemic systems. By focusing on meta-hallmarks, scientists can gain deeper insights into how distinct hallmarks—such as genomic instability, telomere shortening, epigenetic changes, and loss of proteostasis—interrelate, affecting each other in ways that can either accelerate or decelerate the aging process. This comprehensive framework is crucial for pinpointing potential therapeutic targets capable of addressing multiple dimensions of aging concurrently, rather than isolating a single factor. In addition, the meta-hallmark framework has substantial implications for the research of age-related diseases. Many chronic conditions linked to aging, including NDs and CVDs, arise from complex, multifaceted disturbances in cellular and systemic processes. Gaining insights into the interconnections of these disruptions through the lens of meta-hallmarks could facilitate the development of more comprehensive and effective strategies for disease prevention, intervention, and treatment.[216] By recognizing that aging is a systemic process shaped by the interactions of multiple biological pathways, we can more accurately pinpoint the root causes of age-related diseases and formulate therapies targeting these fundamental mechanisms. Moreover, the meta-hallmark perspective encourages a more integrated approach to understanding aging, healthspan, and lifespan. By reframing these aspects as interconnected rather than isolated phenomena, this perspective creates a cohesive framework in which the interactions among biological processes influence not only the aging trajectory but also the overall quality of life during aging. This approach underscores the importance of a multi-faceted understanding of aging that encompasses not just cellular health but also the systemic balance and resilience required to promote healthy aging and extend lifespan.

This review synthesizes findings from existing literature, forming a foundation for future studies aimed at refining this framework and investigating the interrelationships among aging mechanisms. As the field evolves, this comprehensive approach will be critical for devising targeted strategies that promote human health, enhance healthspan, and ultimately extend longevity. Considering the complex nature of aging and the intricate interplay of biological factors, ongoing research is imperative for deepening our understanding and developing interventions that foster healthier aging and improved quality of life across various populations.

Conclusions

The hallmarks of aging—genome stability and telomere shortening—serve as crucial indicators of the complex aging process, underscoring the intricate relationship between cellular health and the passage of time. Their close connection to a variety of human diseases reveals the significant complexity of aging. Within this complexity, the host microbiome plays a critical role, creating a dynamic and reciprocal relationship that influences the course of aging and longevity. The interdependent relationship between the microbiome and the hallmarks of aging is not merely coincidental; it forms a central axis around which the aging process unfolds. This two-way communication emphasizes the interconnectedness of various physiological functions and presents an exciting opportunity for therapeutic strategies. Understanding and manipulating this interplay could hold significant potential for preventing and managing age-related diseases. By altering the composition and activity of the microbiome through dietary modifications, probiotics, or targeted microbial approaches, it may be possible to mitigate the adverse effects of genome instability and telomere attrition. Additionally, combining these microbiome-focused strategies with methods aimed at directly improving genome stability and preserving telomere length could provide a holistic approach to addressing the fundamental causes of age-associated conditions.

Acknowledgments

This research is supported by Bandhan, Kolkata, India.

Funding

None.

Conflict of interest

The authors affirm that they have no conflicts of interest to disclose in relation to the publication of this research.

Author contributions

Conceptualization (SKC), formal analysis (SKC), original draft preparation (SKC), writing—review and editing (SKC, DC), supervision (SKC), project administration (SKC), and funding acquisition (SKC).

References

[1] Ferrucci L, Gonzalez-Freire M, Fabbri E, Simonsick E, Tanaka T, Moore Z, *et al*. Measuring biological aging in humans: A quest. Aging Cell 2020;19(2):e13080. doi:10.1111/acel.13080, PMID:31833194.

[2] Mc Auley MT, Guimera AM, Hodgson D, Mcdonald N, Mooney KM, Morgan AE, *et al*. Modelling the molecular mechanisms of aging. Biosci Rep 2017;37(1):BSR20160177. doi:10.1042/BSR20160177, PMID:28096317.

[3] Li Z, Zhang W, Duan Y, Niu Y, Chen Y, Liu X, *et al*. Progress in biological age research. Front Public Health 2023;11:1074274. doi:10.3389/fpubh.2023.1074274, PMID:37124811.

[4] Melzer D, Pilling LC, Ferrucci L. The genetics of human ageing. Nat Rev Genet 2020;21(2):88–101. doi:10.1038/s41576-019-0183-6, PMID:31690828.

[5] Fraser HC, Kuan V, Johnen R, Zwierzyna M, Hingorani AD, Beyer A, *et al*. Biological mechanisms of aging predict age-related disease co-occurrence in patients. Aging Cell 2022;21(4):e13524. doi:10.1111/acel.13524, PMID:35259281.

[6] Ogunrinola GA, Oyewale JO, Oshamika OO, Olasehinde GI. The Human Microbiome and Its Impacts on Health. Int J Microbiol

2020;2020:8045646. doi:10.1155/2020/8045646, PMID:32612660.
[7] Aggarwal N, Kitano S, Puah GRY, Kittelmann S, Hwang IY, Chang MW. Microbiome and Human Health: Current Understanding, Engineering, and Enabling Technologies. Chem Rev 2023;123(1):31–72. doi:10.1021/acs.chemrev.2c00431, PMID:36317983.
[8] Martinez FD. The human microbiome. Early life determinant of health outcomes. Ann Am Thorac Soc 2014;11(Suppl 1):S7–12. doi:10.1513/AnnalsATS.201306-186MG, PMID:24437411.
[9] Afzaal M, Saeed F, Shah YA, Hussain M, Rabail R, Socol CT, *et al*. Human gut microbiota in health and disease: Unveiling the relationship. Front Microbiol 2022;13:999001. doi:10.3389/fmicb.2022.999001, PMID:36225386.
[10] Durack J, Lynch SV. The gut microbiome: Relationships with disease and opportunities for therapy. J Exp Med 2019;216(1):20–40. doi:10.1084/jem.20180448, PMID:30322864.
[11] Choi EH, Yoon S, Koh YE, Seo YJ, Kim KP. Maintenance of genome integrity and active homologous recombination in embryonic stem cells. Exp Mol Med 2020;52(8):1220–1229. doi:10.1038/s12276-020-0481-2, PMID:32770082.
[12] Jensen RB, Rothenberg E. Preserving genome integrity in human cells via DNA double-strand break repair. Mol Biol Cell 2020;31(9):859–865. doi:10.1091/mbc.E18-10-0668, PMID:32286930.
[13] Ferrari S, Gentili C. Maintaining Genome Stability in Defiance of Mitotic DNA Damage. Front Genet 2016;7:128. doi:10.3389/fgene.2016.00128, PMID:27493659.
[14] Schumacher B, Pothof J, Vijg J, Hoeijmakers JHJ. The central role of DNA damage in the ageing process. Nature 2021;592(7856):695–703. doi:10.1038/s41586-021-03307-7, PMID:33911272.
[15] Chen JH, Hales CN, Ozanne SE. DNA damage, cellular senescence and organismal ageing: causal or correlative? Nucleic Acids Res 2007;35(22):7417–7428. doi:10.1093/nar/gkm681, PMID:17913751.
[16] Shammas MA. Telomeres, lifestyle, cancer, and aging. Curr Opin Clin Nutr Metab Care 2011;14(1):28–34. doi:10.1097/MCO.0b013e32834121b1, PMID:21102320.
[17] Srinivas N, Rachakonda S, Kumar R. Telomeres and Telomere Length: A General Overview. Cancers (Basel) 2020;12(3):558. doi:10.3390/cancers12030558, PMID:32121056.
[18] Muraki K, Nyhan K, Han L, Murnane JP. Mechanisms of telomere loss and their consequences for chromosome instability. Front Oncol 2012;2:135. doi:10.3389/fonc.2012.00135, PMID:23061048.
[19] Victorelli S, Passos JF. Telomeres and Cell Senescence - Size Matters Not. EBioMedicine 2017;21:14–20. doi:10.1016/j.ebiom.2017.03.027, PMID:28347656.
[20] Razgonova MP, Zakharenko AM, Golokhvast KS, Thanasoula M, Sarandi E, Nikolouzakis K, *et al*. Telomerase and telomeres in aging theory and chronographic aging theory (Review). Mol Med Rep 2020;22(3):1679–1694. doi:10.3892/mmr.2020.11274, PMID:32705188.
[21] Jang DH, Shin JW, Shim E, Ohtani N, Jeon OH. The connection between aging, cellular senescence and gut microbiome alterations: A comprehensive review. Aging Cell 2024;23(10):e14315. doi:10.1111/acel.14315, PMID:39148278.
[22] Assis V, de Sousa Neto IV, Ribeiro FM, de Cassia Marqueti R, Franco OL, da Silva Aguiar S, *et al*. The Emerging Role of the Aging Process and Exercise Training on the Crosstalk between Gut Microbiota and Telomere Length. Int J Environ Res Public Health 2022;19(13):7810. doi:10.3390/ijerph19137810, PMID:35805470.
[23] Al-Daghri NM, Abdi S, Sabico S, Alnaami AM, Wani KA, Ansari MGA, *et al*. Gut-Derived Endotoxin and Telomere Length Attrition in Adults with and without Type 2 Diabetes. Biomolecules 2021;11(11):1693. doi:10.3390/biom11111693, PMID:34827691.
[24] Malik JA, Zafar MA, Lamba T, Nanda S, Khan MA, Agrewala JN. The impact of aging-induced gut microbiome dysbiosis on dendritic cells and lung diseases. Gut Microbes 2023;15(2):2290643. doi:10.1080/19490976.2023.2290643, PMID:38087439.
[25] Salazar J, Durán P, Díaz MP, Chacín M, Santeliz R, Mengual E, *et al*. Exploring the Relationship between the Gut Microbiota and Ageing: A Possible Age Modulator. Int J Environ Res Public Health 2023;20(10):5845. doi:10.3390/ijerph20105845, PMID:37239571.
[26] López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. Cell 2023;186(2):243–278. doi:10.1016/j.cell.2022.11.001, PMID:36599349.
[27] López-Gil L, Pascual-Ahuir A, Proft M. Genomic Instability and Epigenetic Changes during Aging. Int J Mol Sci 2023;24(18):14279. doi:10.3390/ijms241814279, PMID:37762580.
[28] Tenchov R, Sasso JM, Wang X, Zhou QA. Aging Hallmarks and Progression and Age-Related Diseases: A Landscape View of Research Advancement. ACS Chem Neurosci 2024;15(1):1–30. doi:10.1021/acschemneuro.3c00531, PMID:38095562.
[29] Tartiere AG, Freije JMP, López-Otín C. The hallmarks of aging as a conceptual framework for health and longevity research. Front Aging 2024;5:1334261. doi:10.3389/fragi.2024.1334261, PMID:38292053.
[30] Keshavarz M, Xie K, Schaaf K, Bano D, Ehninger D. Targeting the "hallmarks of aging" to slow aging and treat age-related disease: fact or fiction? Mol Psychiatry 2023;28(1):242–255. doi:10.1038/s41380-022-01680-x, PMID:35840801.
[31] Skowronska-Krawczyk D. Hallmarks of Aging: Causes and Consequences. Aging Biol 2023;1(1):20230011. doi:10.59368/agingbio.20230011, PMID:38274125.
[32] Hamilton JP. Epigenetics: principles and practice. Dig Dis 2011;29(2):130–135. doi:10.1159/000323874, PMID:21734376.
[33] Labbadia J, Morimoto RI. The biology of proteostasis in aging and disease. Annu Rev Biochem 2015;84:435–464. doi:10.1146/annurev-biochem-060614-033955, PMID:25784053.
[34] Efeyan A, Comb WC, Sabatini DM. Nutrient-sensing mechanisms and pathways. Nature 2015;517(7534):302–310. doi:10.1038/nature14190, PMID:25592535.
[35] Srivastava S. The Mitochondrial Basis of Aging and Age-Related Disorders. Genes (Basel) 2017;8(12):398. doi:10.3390/genes8120398, PMID:29257072.
[36] Di Micco R, Krizhanovsky V, Baker D, d'Adda di Fagagna F. Cellular senescence in ageing: from mechanisms to therapeutic opportunities. Nat Rev Mol Cell Biol 2021;22(2):75–95. doi:10.1038/s41580-020-00314-w, PMID:33328614.
[37] Mancinelli L, Intini G. Age-associated declining of the regeneration potential of skeletal stem/progenitor cells. Front Physiol 2023;14:1087254. doi:10.3389/fphys.2023.1087254, PMID:36818437.
[38] Larson A, Codden CJ, Huggins GS, Rastegar H, Chen FY, Maron BJ, *et al*. Altered intercellular communication and extracellular matrix signaling as a potential disease mechanism in human hypertrophic cardiomyopathy. Sci Rep 2022;12(1):5211. doi:10.1038/s41598-022-08561-x, PMID:35338173.
[39] Talapko J, Včev A, Meštrović T, Pustijanac E, Jukić M, Škrlec I. Homeostasis and Dysbiosis of the Intestinal Microbiota: Comparing Hallmarks of a Healthy State with Changes in Inflammatory Bowel Disease. Microorganisms 2022;10(12):2405. doi:10.3390/microorganisms10122405, PMID:36557658.
[40] Nieto-Torres JL, Hansen M. Macroautophagy and aging: The impact of cellular recycling on health and longevity. Mol Aspects Med 2021;82:101020. doi:10.1016/j.mam.2021.101020, PMID:34507801.
[41] Cheon SY, Kim H, Rubinsztein DC, Lee JE. Autophagy, Cellular Aging and Age-related Human Diseases. Exp Neurobiol 2019;28(6):643–657. doi:10.5607/en.2019.28.6.643, PMID:31902153.
[42] Boehme M, Guzzetta KE, Wasén C, Cox LM. The gut microbiota is an emerging target for improving brain health during ageing. Gut Microbiome (Camb) 2023;4:E2. doi:10.1017/gmb.2022.11, PMID:37179659.
[43] Juárez-Fernández M, Porras D, García-Mediavilla MV, Román-Sagüillo S, González-Gallego J, Nistal E, *et al*. Aging, Gut Microbiota and Metabolic Diseases: Management through Physical Exercise and Nutritional Interventions. Nutrients 2020;13(1):16. doi:10.3390/nu13010016, PMID:33374578.
[44] Bradley E, Haran J. The human gut microbiome and aging. Gut Microbes 2024;16(1):2359677. doi:10.1080/19490976.2024.2359677, PMID:38831607.
[45] Grieneisen L, Blekhman R, Archie E. How longitudinal data can contribute to our understanding of host genetic effects on the gut microbiome. Gut Microbes 2023;15(1):2178797. doi:10.1080/19490976.2023.2178797, PMID:36794811.
[46] Andreani NA, Sharma A, Dahmen B, Specht HE, Mannig N, Ruan V, *et al*. Longitudinal analysis of the gut microbiome in adolescent patients with anorexia nervosa: microbiome-related factors associated with clinical outcome. Gut Microbes 2024;16(1):2304158. doi:10.10

80/19490976.2024.2304158, PMID:38294867.
[47] Pantazi AC, Balasa AL, Mihai CM, Chisnoiu T, Lupu VV, Kassim MAK, *et al*. Development of Gut Microbiota in the First 1000 Days after Birth and Potential Interventions. Nutrients 2023;15(16):3647. doi:10.3390/nu15163647, PMID:37630837.
[48] Park H, Park NY, Koh A. Scarring the early-life microbiome: its potential life-long effects on human health and diseases. BMB Rep 2023;56(9):469–481. doi:10.5483/BMBRep.2023-0114, PMID:37605613.
[49] Hrncir T. Gut Microbiota Dysbiosis: Triggers, Consequences, Diagnostic and Therapeutic Options. Microorganisms 2022;10(3):578. doi:10.3390/microorganisms10030578, PMID:35336153.
[50] Acevedo-Román A, Pagán-Zayas N, Velázquez-Rivera LI, Torres-Ventura AC, Godoy-Vitorino F. Insights into Gut Dysbiosis: Inflammatory Diseases, Obesity, and Restoration Approaches. Int J Mol Sci 2024;25(17):9715. doi:10.3390/ijms25179715, PMID:39273662.
[51] Kontizas E, Tastsoglou S, Karamitros T, Karayiannis Y, Kollia P, Hatzigeorgiou AG, *et al*. Impact of Helicobacter pylori Infection and Its Major Virulence Factor CagA on DNA Damage Repair. Microorganisms 2020;8(12):2007. doi:10.3390/microorganisms8122007, PMID:33339161.
[52] Haran JP, McCormick BA. Aging, Frailty, and the Microbiome-How Dysbiosis Influences Human Aging and Disease. Gastroenterology 2021;160(2):507–523. doi:10.1053/j.gastro.2020.09.060, PMID:33307030.
[53] Farah A, Paul P, Khan AS, Sarkar A, Laws S, Chaari A. Targeting gut microbiota dysbiosis in inflammatory bowel disease: a systematic review of current evidence. Front Med (Lausanne) 2025;12:1435030. doi:10.3389/fmed.2025.1435030, PMID:40041456.
[54] Veschetti L, Treccani M, De Tomi E, Malerba G. Genomic Instability Evolutionary Footprints on Human Health: Driving Forces or Side Effects? Int J Mol Sci 2023;24(14):11437. doi:10.3390/ijms241411437, PMID:37511197.
[55] Ussar S, Fujisaka S, Kahn CR. Interactions between host genetics and gut microbiome in diabetes and metabolic syndrome. Mol Metab 2016;5(9):795–803. doi:10.1016/j.molmet.2016.07.004, PMID:27617202.
[56] Abdul-Aziz MA, Cooper A, Weyrich LS. Exploring Relationships between Host Genome and Microbiome: New Insights from Genome-Wide Association Studies. Front Microbiol 2016;7:1611. doi:10.3389/fmicb.2016.01611, PMID:27785127.
[57] Ahn J, Hayes RB. Environmental Influences on the Human Microbiome and Implications for Noncommunicable Disease. Annu Rev Public Health 2021;42:277–292. doi:10.1146/annurev-publhealth-012420-105020, PMID:33798404.
[58] Rinninella E, Raoul P, Cintoni M, Franceschi F, Miggiano GAD, Gasbarrini A, *et al*. What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. Microorganisms 2019;7(1):14. doi:10.3390/microorganisms7010014, PMID:30634578.
[59] Kalisperati P, Spanou E, Pateras IS, Korkolopoulou P, Varvarigou A, Karavokyros I, *et al*. Inflammation, DNA Damage, Helicobacter pylori and Gastric Tumorigenesis. Front Genet 2017;8:20. doi:10.3389/fgene.2017.00020, PMID:28289428.
[60] Cai Q, Shi P, Yuan Y, Peng J, Ou X, Zhou W, *et al*. Inflammation-Associated Senescence Promotes Helicobacter pylori-Induced Atrophic Gastritis. Cell Mol Gastroenterol Hepatol 2021;11(3):857–880. doi:10.1016/j.jcmgh.2020.10.015, PMID:33161156.
[61] Murata-Kamiya N, Hatakeyama M. Helicobacter pylori-induced DNA double-stranded break in the development of gastric cancer. Cancer Sci 2022;113(6):1909–1918. doi:10.1111/cas.15357, PMID:35359025.
[62] Fan Z, Tang P, Li C, Yang Q, Xu Y, Su C, *et al*. Fusobacterium nucleatum and its associated systemic diseases: epidemiologic studies and possible mechanisms. J Oral Microbiol 2023;15(1):2145729. doi:10.1080/20002297.2022.2145729, PMID:36407281.
[63] Groeger S, Zhou Y, Ruf S, Meyle J. Pathogenic Mechanisms of Fusobacterium nucleatum on Oral Epithelial Cells. Front Oral Health 2022;3:831607. doi:10.3389/froh.2022.831607, PMID:35478496.
[64] Delint-Ramirez I, Madabhushi R. DNA damage and its links to neuronal aging and degeneration. Neuron 2025;113(1):7–28. doi:10.1016/j.neuron.2024.12.001, PMID:39788088.
[65] Qin Y, Liu H, Wu H. Cellular Senescence in Health, Disease, and Lens Aging. Pharmaceuticals (Basel) 2025;18(2):244. doi:10.3390/ph18020244, PMID:40006057.
[66] Djorić D, Kristich CJ. Oxidative stress enhances cephalosporin resistance of Enterococcus faecalis through activation of a two-component signaling system. Antimicrob Agents Chemother 2015;59(1):159–169. doi:10.1128/AAC.03984-14, PMID:25331701.
[67] Larabi AB, Masson HLP, Bäumler AJ. Bile acids as modulators of gut microbiota composition and function. Gut Microbes 2023;15(1):2172671. doi:10.1080/19490976.2023.2172671, PMID:36740850.
[68] Qu Y, Su C, Zhao Q, Shi A, Zhao F, Tang L, *et al*. Gut Microbiota-Mediated Elevated Production of Secondary Bile Acids in Chronic Unpredictable Mild Stress. Front Pharmacol 2022;13:837543. doi:10.3389/fphar.2022.837543, PMID:35321330.
[69] Matei E, Ionescu AC, Enciu M, Popovici V, Mitroi AF, Aschie M, *et al*. Cell death and DNA damage via ROS mechanisms after applied antibiotics and antioxidants doses in prostate hyperplasia primary cell cultures. Medicine (Baltimore) 2024;103(37):e39450. doi:10.1097/MD.0000000000039450, PMID:39287312.
[70] Jena PK, Sheng L, Di Lucente J, Jin LW, Maezawa I, Wan YY. Dysregulated bile acid synthesis and dysbiosis are implicated in Western diet-induced systemic inflammation, microglial activation, and reduced neuroplasticity. FASEB J 2018;32(5):2866–2877. doi:10.1096/fj.201700984RR, PMID:29401580.
[71] Ma J, Hong Y, Zheng N, Xie G, Lyu Y, Gu Y, *et al*. Gut microbiota remodeling reverses aging-associated inflammation and dysregulation of systemic bile acid homeostasis in mice sex-specifically. Gut Microbes 2020;11(5):1450–1474. doi:10.1080/19490976.2020.1763770, PMID:32515683.
[72] Chandrasekaran R, Lacy DB. The role of toxins in Clostridium difficile infection. FEMS Microbiol Rev 2017;41(6):723–750. doi:10.1093/femsre/fux048, PMID:29048477.
[73] Aktories K, Schwan C, Jank T. Clostridium difficile Toxin Biology. Annu Rev Microbiol 2017;71:281–307. doi:10.1146/annurev-micro-090816-093458, PMID:28657883.
[74] Li X, Liu J, Zhou Y, Wang L, Wen Y, Ding K, *et al*. Jwa participates the maintenance of intestinal epithelial homeostasis via ERK/FBXW7-mediated NOTCH1/PPARγ/STAT5 axis and acts as a novel putative aging related gene. Int J Biol Sci 2022;18(14):5503–5521. doi:10.7150/ijbs.72751, PMID:36147468.
[75] Wang Q, Qi Y, Shen W, Xu J, Wang L, Chen S, *et al*. The Aged Intestine: Performance and Rejuvenation. Aging Dis 2021;12(7):1693–1712. doi:10.14336/AD.2021.0202, PMID:34631215.
[76] Li S, Liu J, Zheng X, Ren L, Yang Y, Li W, *et al*. Tumorigenic bacteria in colorectal cancer: mechanisms and treatments. Cancer Biol Med 2021;19(2):147–162. doi:10.20892/j.issn.2095-3941.2020.0651, PMID:34586760.
[77] Zhang G, Sun D. The synthesis of the novel Escherichia coli toxin-colibactin and its mechanisms of tumorigenesis of colorectal cancer. Front Microbiol 2024;15:1501973. doi:10.3389/fmicb.2024.1501973, PMID:39744397.
[78] Rezazadegan M, Forootani B, Hoveyda Y, Rezazadegan N, Amani R. Major heavy metals and human gut microbiota composition: a systematic review with nutritional approach. J Health Popul Nutr 2025;44(1):21. doi:10.1186/s41043-025-00750-4, PMID:39871318.
[79] Maier E, Anderson RC, Roy NC. Understanding how commensal obligate anaerobic bacteria regulate immune functions in the large intestine. Nutrients 2014;7(1):45–73. doi:10.3390/nu7010045, PMID:25545102.
[80] Browne HP, Neville BA, Forster SC, Lawley TD. Transmission of the gut microbiota: spreading of health. Nat Rev Microbiol 2017;15(9):531–543. doi:10.1038/nrmicro.2017.50, PMID:28603278.
[81] Baldelli V, Scaldaferri F, Putignani L, Del Chierico F. The Role of Enterobacteriaceae in Gut Microbiota Dysbiosis in Inflammatory Bowel Diseases. Microorganisms 2021;9(4):697. doi:10.3390/microorganisms9040697, PMID:33801755.
[82] Carding S, Verbeke K, Vipond DT, Corfe BM, Owen LJ. Dysbiosis of the gut microbiota in disease. Microb Ecol Health Dis 2015;26:26191. doi:10.3402/mehd.v26.26191, PMID:25651997.
[83] Lu Z, Imlay JA. When anaerobes encounter oxygen: mechanisms

of oxygen toxicity, tolerance and defence. Nat Rev Microbiol 2021;19(12):774–785. doi:10.1038/s41579-021-00583-y, PMID:34183820.
[84] Mittal M, Siddiqui MR, Tran K, Reddy SP, Malik AB. Reactive oxygen species in inflammation and tissue injury. Antioxid Redox Signal 2014;20(7):1126–1167. doi:10.1089/ars.2012.5149, PMID:23991888.
[85] Bhattacharyya A, Chattopadhyay R, Mitra S, Crowe SE. Oxidative stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases. Physiol Rev 2014;94(2):329–354. doi:10.1152/physrev.00040.2012, PMID:24692350.
[86] Zhang X, Li L. The Significance of 8-oxoGsn in Aging-Related Diseases. Aging Dis 2020;11(5):1329–1338. doi:10.14336/AD.2019.1021, PMID:33014540.
[87] Radak Z, Bori Z, Koltai E, Fatouros IG, Jamurtas AZ, Douroudos II, *et al*. Age-dependent changes in 8-oxoguanine-DNA glycosylase activity are modulated by adaptive responses to physical exercise in human skeletal muscle. Free Radic Biol Med 2011;51(2):417–423. doi:10.1016/j.freeradbiomed.2011.04.018, PMID:21569841.
[88] Somasundaram I, Jain SM, Blot-Chabaud M, Pathak S, Banerjee A, Rawat S, *et al*. Mitochondrial dysfunction and its association with age-related disorders. Front Physiol 2024;15:1384966. doi:10.3389/fphys.2024.1384966.
[89] Bartman S, Coppotelli G, Ross JM. Mitochondrial Dysfunction: A Key Player in Brain Aging and Diseases. Curr Issues Mol Biol 2024;46(3):1987–2026. doi:10.3390/cimb46030130, PMID:38534746.
[90] Kay J, Thadhani E, Samson L, Engelward B. Inflammation-induced DNA damage, mutations and cancer. DNA Repair (Amst) 2019;83:102673. doi:10.1016/j.dnarep.2019.102673, PMID:31387777.
[91] Gao H, Nepovimova E, Adam V, Heger Z, Valko M, Wu Q, *et al*. Age-associated changes in innate and adaptive immunity: role of the gut microbiota. Front Immunol 2024;15:1421062. doi:10.3389/fimmu.2024.1421062, PMID:39351234.
[92] Guedj A, Volman Y, Geiger-Maor A, Bolik J, Schumacher N, Künzel S, *et al*. Gut microbiota shape 'inflamm-ageing' cytokines and account for age-dependent decline in DNA damage repair. Gut 2020;69(6):1064–1075. doi:10.1136/gutjnl-2019-318491, PMID:31586932.
[93] Obonyo M, Rickman B, Guiney DG. Effects of myeloid differentiation primary response gene 88 (MyD88) activation on Helicobacter infection in vivo and induction of a Th17 response. Helicobacter 2011;16(5):398–404. doi:10.1111/j.1523-5378.2011.00861.x, PMID:21923686.
[94] Liu JC, Wang P, Zeng QX, Yang C, Lyu M, Li Y, *et al*. Myd88 Signaling Is Involved in the Inflammatory Response in LPS-Induced Mouse Epididymitis and Bone-Marrow-Derived Dendritic Cells. Int J Mol Sci 2023;24(9):7838. doi:10.3390/ijms24097838, PMID:37175545.
[95] Everard A, Geurts L, Caesar R, Van Hul M, Matamoros S, Duparc T, *et al*. Intestinal epithelial MyD88 is a sensor switching host metabolism towards obesity according to nutritional status. Nat Commun 2014;5:5648. doi:10.1038/ncomms6648, PMID:25476696.
[96] Lee JY, Cevallos SA, Byndloss MX, Tiffany CR, Olsan EE, Butler BP, *et al*. High-Fat Diet and Antibiotics Cooperatively Impair Mitochondrial Bioenergetics to Trigger Dysbiosis that Exacerbates Pre-inflammatory Bowel Disease. Cell Host Microbe 2020;28(2):273–284.e6. doi:10.1016/j.chom.2020.06.001, PMID:32668218.
[97] Dudek-Wicher RK, Junka A, Bartoszewicz M. The influence of antibiotics and dietary components on gut microbiota. Prz Gastroenterol 2018;13(2):85–92. doi:10.5114/pg.2018.76005, PMID:30002765.
[98] Zhao Y, Simon M, Seluanov A, Gorbunova V. DNA damage and repair in age-related inflammation. Nat Rev Immunol 2023;23(2):75–89. doi:10.1038/s41577-022-00751-y, PMID:35831609.
[99] Andarawi S, Vodickova L, Uttarilli A, Hanak P, Vodicka P. Defective DNA repair: a putative nexus linking immunological diseases, neurodegenerative disorders, and cancer. Mutagenesis 2025;40(1):4–19. doi:10.1093/mutage/geae029, PMID:39937585.
[100] Everett BM, Donath MY, Pradhan AD, Thuren T, Pais P, Nicolau JC, *et al*. Anti-Inflammatory Therapy With Canakinumab for the Prevention and Management of Diabetes. J Am Coll Cardiol 2018;71(21):2392–2401. doi:10.1016/j.jacc.2018.03.002, PMID:29544870.
[101] Rothman AM, MacFadyen J, Thuren T, Webb A, Harrison DG, Guzik TJ, *et al*. Effects of Interleukin-1β Inhibition on Blood Pressure, Incident Hypertension, and Residual Inflammatory Risk: A Secondary Analysis of CANTOS. Hypertension 2020;75(2):477–482. doi:10.1161/HYPERTENSIONAHA.119.13642, PMID:31884854.
[102] Ridker PM, MacFadyen JG, Glynn RJ, Koenig W, Libby P, Everett BM, *et al*. Inhibition of Interleukin-1β by Canakinumab and Cardiovascular Outcomes in Patients With Chronic Kidney Disease. J Am Coll Cardiol 2018;71(21):2405–2414. doi:10.1016/j.jacc.2018.03.490, PMID:29793629.
[103] Soukas AA, Hao H, Wu L. Metformin as Anti-Aging Therapy: Is It for Everyone? Trends Endocrinol Metab 2019;30(10):745–755. doi:10.1016/j.tem.2019.07.015, PMID:31405774.
[104] Chen S, Gan D, Lin S, Zhong Y, Chen M, Zou X, *et al*. Metformin in aging and aging-related diseases: clinical applications and relevant mechanisms. Theranostics 2022;12(6):2722–2740. doi:10.7150/thno.71360, PMID:35401820.
[105] Zikou E, Koliaki C, Makrilakis K. The Role of Fecal Microbiota Transplantation (FMT) in the Management of Metabolic Diseases in Humans: A Narrative Review. Biomedicines 2024;12(8):1871. doi:10.3390/biomedicines12081871, PMID:39200335.
[106] Biazzo M, Deidda G. Fecal Microbiota Transplantation as New Therapeutic Avenue for Human Diseases. J Clin Med 2022;11(14):4119. doi:10.3390/jcm11144119, PMID:35887883.
[107] Selvarani R, Mohammed S, Richardson A. Effect of rapamycin on aging and age-related diseases-past and future. Geroscience 2021;43(3):1135–1158. doi:10.1007/s11357-020-00274-1, PMID:33037985.
[108] Sharp ZD, Strong R. Rapamycin, the only drug that has been consistently demonstrated to increase mammalian longevity. An update. Exp Gerontol 2023;176:112166. doi:10.1016/j.exger.2023.112166, PMID:37011714.
[109] Blagosklonny MV. Rapamycin for longevity: opinion article. Aging (Albany NY) 2019;11(19):8048–8067. doi:10.18632/aging.102355, PMID:31586989.
[110] Lim CJ, Cech TR. Shaping human telomeres: from shelterin and CST complexes to telomeric chromatin organization. Nat Rev Mol Cell Biol 2021;22(4):283–298. doi:10.1038/s41580-021-00328-y, PMID:33564154.
[111] Mir SM, Samavarchi Tehrani S, Goodarzi G, Jamalpoor Z, Asadi J, Khelghati N, *et al*. Shelterin Complex at Telomeres: Implications in Ageing. Clin Interv Aging 2020;15:827–839. doi:10.2147/CIA.S256425, PMID:32581523.
[112] Ghilain C, Gilson E, Giraud-Panis MJ. Multifunctionality of the Telomere-Capping Shelterin Complex Explained by Variations in Its Protein Composition. Cells 2021;10(7):1753. doi:10.3390/cells10071753, PMID:34359923.
[113] Diotti R, Loayza D. Shelterin complex and associated factors at human telomeres. Nucleus 2011;2(2):119–135. doi:10.4161/nucl.2.2.15135, PMID:21738835.
[114] Shiekh S, Feldt D, Jack A, Kodikara SG, Alfehaid J, Pasha S, Yildiz A, Balci H. Protection of the Telomeric Junction by the Shelterin Complex. J Am Chem Soc 2024;146(36):25158–25165. doi:10.1021/jacs.4c08649, PMID:39207958.
[115] Romero-Zamora D, Rogers S, Low RRJ, Page SG, Lane BJE, Kosaka S, *et al*. A CPC-shelterin-BTR axis regulates mitotic telomere deprotection. Nat Commun 2025;16(1):2277. doi:10.1038/s41467-025-57456-8, PMID:40097392.
[116]Amir M, Khan P, Queen A, Dohare R, Alajmi MF, Hussain A, *et al*. Structural Features of Nucleoprotein CST/Shelterin Complex Involved in the Telomere Maintenance and Its Association with Disease Mutations. Cells 2020;9(2):359. doi:10.3390/cells9020359, PMID:32033110.
[117] Kalmykova A. Telomere checkpoint in aging and development. Int J Mol Sci 2023;24(21):15979. doi:10.3390/ijms242115979, PMID:37958962.
[118] Anifandis G, Samara M, Simopoulou M, Messini CI, Chatzimeletiou K, Thodou E, *et al*. Insights into the Role of Telomeres in Human Embryological Parameters. Opinions Regarding IVF. J Dev Biol 2021;9(4):49. doi:10.3390/jdb9040049, PMID:34842724.
[119] Huang X, Huang L, Lu J, Cheng L, Wu D, Li L, *et al*. The Relationship between telomere length and aging-related diseases. Clin Exp Med 2025;25(1):72. doi:10.1007/s10238-025-01608-z, PMID:40044947.
[120] Lupatov AY, Yarygin KN. Telomeres and Telomerase in the Control of

Stem Cells. Biomedicines 2022;10(10):2335. doi:10.3390/biomedicines10102335, PMID:36289597.
[121] Li JSZ, Denchi EL. How stem cells keep telomeres in check. Differentiation 2018;100:21–25. doi:10.1016/j.diff.2018.01.004, PMID:29413749.
[122] Penev A, Markiewicz-Potoczny M, Sfeir A, Lazzerini Denchi E. Stem cells at odds with telomere maintenance and protection. Trends Cell Biol 2022;32(6):527–536. doi:10.1016/j.tcb.2021.12.007, PMID:35063336.
[123] Effros RB. Telomere/telomerase dynamics within the human immune system: effect of chronic infection and stress. Exp Gerontol 2011;46(2-3):135–140. doi:10.1016/j.exger.2010.08.027, PMID:20833238.
[124] Nassour J, Przetocka S, Karlseder J. Telomeres as hotspots for innate immunity and inflammation. DNA Repair (Amst) 2024;133:103591. doi:10.1016/j.dnarep.2023.103591, PMID:37951043.
[125] Schellnegger M, Hofmann E, Carnieletto M, Kamolz LP. Unlocking longevity: the role of telomeres and its targeting interventions. Front Aging 2024;5:1339317. doi:10.3389/fragi.2024.1339317, PMID:38333665.
[126] Bernardes de Jesus B, Blasco MA. Potential of telomerase activation in extending health span and longevity. Curr Opin Cell Biol 2012;24(6):739–743. doi:10.1016/j.ceb.2012.09.004, PMID:23085234.
[127] El Maï M, Bird M, Allouche A, Targen S, Şerifoğlu N, Lopes-Bastos B, *et al*. Gut-specific telomerase expression counteracts systemic aging in telomerase-deficient zebrafish. Nat Aging 2023;3(5):567–584. doi:10.1038/s43587-023-00401-5, PMID:37142828.
[128] Li R, Li J, Zhou X. Lung microbiome: new insights into the pathogenesis of respiratory diseases. Signal Transduct Target Ther 2024;9(1):19. doi:10.1038/s41392-023-01722-y, PMID:38228603.
[129] Hou K, Wu ZX, Chen XY, Wang JQ, Zhang D, Xiao C, Zhu D, Koya JB, Wei L, Li J, Chen ZS. Microbiota in health and diseases. Signal Transduct Target Ther 2022;7(1):135. doi:10.1038/s41392-022-00974-4.
[130] Barnes RP, Fouquerel E, Opresko PL. The impact of oxidative DNA damage and stress on telomere homeostasis. Mech Ageing Dev 2019;177:37–45. doi:10.1016/j.mad.2018.03.013, PMID:29604323.
[131] Ruiz A, Flores-Gonzalez J, Buendia-Roldan I, Chavez-Galan L. Telomere Shortening and Its Association with Cell Dysfunction in Lung Diseases. Int J Mol Sci 2021;23(1):425. doi:10.3390/ijms23010425, PMID:35008850.
[132] Tan J, Taitz J, Nanan R, Grau G, Macia L. Dysbiotic Gut Microbiota-Derived Metabolites and Their Role in Non-Communicable Diseases. Int J Mol Sci 2023;24(20):15256. doi:10.3390/ijms242015256, PMID:37894934.
[133] Fusco W, Lorenzo MB, Cintoni M, Porcari S, Rinninella E, Kaitsas F, *et al*. Short-Chain Fatty-Acid-Producing Bacteria: Key Components of the Human Gut Microbiota. Nutrients 2023;15(9):2211. doi:10.3390/nu15092211, PMID:37432351.
[134] Galiè S, Canudas S, Muralidharan J, García-Gavilán J, Bulló M, Salas-Salvadó J. Impact of Nutrition on Telomere Health: Systematic Review of Observational Cohort Studies and Randomized Clinical Trials. Adv Nutr 2020;11(3):576–601. doi:10.1093/advances/nmz107, PMID:31688893.
[135] Du Y, He C, An Y, Huang Y, Zhang H, Fu W, *et al*. The Role of Short Chain Fatty Acids in Inflammation and Body Health. Int J Mol Sci 2024;25(13):7379. doi:10.3390/ijms25137379, PMID:39000498.
[136] Ogłuszka M, Lipiński P, Starzyński RR. Effect of Omega-3 Fatty Acids on Telomeres-Are They the Elixir of Youth? Nutrients 2022;14(18):3723. doi:10.3390/nu14183723, PMID:36145097.
[137] Shim JA, Ryu JH, Jo Y, Hong C. The role of gut microbiota in T cell immunity and immune mediated disorders. Int J Biol Sci 2023;19(4):1178–1191. doi:10.7150/ijbs.79430, PMID:36923929.
[138] Yoo JY, Groer M, Dutra SVO, Sarkar A, McSkimming DI. Correction: Yoo, J.Y., *et al*. Gut Microbiota and Immune System Interactions. Microorganisms 2020, 8, 1587. Microorganisms 2020;8(12):2046. doi:10.3390/microorganisms8122046, PMID:33371530.
[139] Calder PC, Ortega EF, Meydani SN, Adkins Y, Stephensen CB, Thompson B, *et al*. Nutrition, Immunosenescence, and Infectious Disease: An Overview of the Scientific Evidence on Micronutrients and on Modulation of the Gut Microbiota. Adv Nutr 2022;13(5):S1–S26. doi:10.1093/advances/nmac052, PMID:36183242.
[140] Scheithauer TPM, Rampanelli E, Nieuwdorp M, Vallance BA, Verchere CB, van Raalte DH, *et al*. Gut Microbiota as a Trigger for Metabolic Inflammation in Obesity and Type 2 Diabetes. Front Immunol 2020;11:571731. doi:10.3389/fimmu.2020.571731, PMID:33178196.
[141] Dabke K, Hendrick G, Devkota S. The gut microbiome and metabolic syndrome. J Clin Invest 2019;129(10):4050–4057. doi:10.1172/JCI129194, PMID:31573550.
[142] Reva K, Laranjinha J, Rocha BS. Epigenetic Modifications Induced by the Gut Microbiota May Result from What We Eat: Should We Talk about Precision Diet in Health and Disease? Metabolites 2023;13(3):375. doi:10.3390/metabo13030375, PMID:36984815.
[143] Woo V, Alenghat T. Epigenetic regulation by gut microbiota. Gut Microbes 2022;14(1):2022407. doi:10.1080/19490976.2021.2022407, PMID:35000562.
[144] Wu Y, Wang CZ, Wan JY, Yao H, Yuan CS. Dissecting the Interplay Mechanism between Epigenetics and Gut Microbiota: Health Maintenance and Disease Prevention. Int J Mol Sci 2021;22(13):6933. doi:10.3390/ijms22136933, PMID:34203243.
[145] Carlund O, Norberg A, Osterman P, Landfors M, Degerman S, Hultdin M. DNA methylation variations and epigenetic aging in telomere biology disorders. Sci Rep 2023;13(1):7955. doi:10.1038/s41598-023-34922-1, PMID:37193737.
[146] Kmiołek T, Filipowicz G, Bogucka D, Wajda A, Ejma-Multański A, Stypińska B, *et al*. Aging and the impact of global DNA methylation, telomere shortening, and total oxidative status on sarcopenia and frailty syndrome. Immun Ageing 2023;20(1):61. doi:10.1186/s12979-023-00384-2, PMID:37964387.
[147] Wang J, Dong X, Cao L, Sun Y, Qiu Y, Zhang Y, *et al*. Association between telomere length and diabetes mellitus: A meta-analysis. J Int Med Res 2016;44(6):1156–1173. doi:10.1177/0300060516667132, PMID:28322101.
[148] Khalangot M, Krasnienkov D, Vaiserman A. Telomere length in different metabolic categories: Clinical associations and modification potential. Exp Biol Med (Maywood) 2020;245(13):1115–1121. doi:10.1177/1535370220931509, PMID:32515222.
[149] Davis CD. The Gut Microbiome and Its Role in Obesity. Nutr Today 2016;51(4):167–174. doi:10.1097/NT.0000000000000167, PMID:27795585.
[150] Hamamah S, Hajnal A, Covasa M. Influence of Bariatric Surgery on Gut Microbiota Composition and Its Implication on Brain and Peripheral Targets. Nutrients 2024;16(7):1071. doi:10.3390/nu16071071, PMID:38613104.
[151] Şerifoğlu N, Lopes-Bastos B, Ferreira MG. Lack of telomerase reduces cancer incidence and increases lifespan of zebrafish tp53M214K mutants. Sci Rep 2024;14(1):5382. doi:10.1038/s41598-024-56153-8, PMID:38443436.
[152] Kishi S, Slack BE, Uchiyama J, Zhdanova IV. Zebrafish as a genetic model in biological and behavioral gerontology: where development meets aging in vertebrates—a mini-review. Gerontology 2009;55(4):430–441. doi:10.1159/000228892, PMID:19654474.
[153] Xiong RG, Li J, Cheng J, Zhou DD, Wu SX, Huang SY, *et al*. The Role of Gut Microbiota in Anxiety, Depression, and Other Mental Disorders as Well as the Protective Effects of Dietary Components. Nutrients 2023;15(14):3258. doi:10.3390/nu15143258, PMID:37513676.
[154] Limbana T, Khan F, Eskander N. Gut Microbiome and Depression: How Microbes Affect the Way We Think. Cureus 2020;12(8):e9966. doi:10.7759/cureus.9966.10.7759/cureus.9966.
[155] Donati Zeppa S, Agostini D, Ferrini F, Gervasi M, Barbieri E, Bartolacci A, *et al*. Interventions on Gut Microbiota for Healthy Aging. Cells 2022;12(1):34. doi:10.3390/cells12010034, PMID:36611827.
[156] Yan Z, Guan G, Jia H, Li H, Zhuoga S, Zheng S. The association between gut microbiota and accelerated aging and frailty: a Mendelian randomization study. Aging Clin Exp Res 2025;37(1):82. doi:10.1007/s40520-025-02971-3, PMID:40074999.
[157] Luczynski P, McVey Neufeld KA, Oriach CS, Clarke G, Dinan TG, Cryan JF. Growing up in a Bubble: Using Germ-Free Animals to Assess the Influence of the Gut Microbiota on Brain and Behavior. Int J Neuropsychopharmacol 2016;19(8):pyw020. doi:10.1093/ijnp/pyw020, PMID:26912607.
[158] Aghighi F, Salami M. What we need to know about the germ-free animal models. AIMS Microbiol 2024;10(1):107–147. doi:10.3934/microbiol.2024007, PMID:38525038.
[159] Hu J, Cheng S, Yao J, Lin X, Li Y, Wang W, *et al*. Correlation between al-

tered gut microbiota and elevated inflammation markers in patients with Crohn's disease. Front Immunol 2022;13:947313. doi:10.3389/fimmu.2022.947313, PMID:36045690.
[160] Li L, Peng P, Ding N, Jia W, Huang C, Tang Y. Oxidative Stress, Inflammation, Gut Dysbiosis: What Can Polyphenols Do in Inflammatory Bowel Disease? Antioxidants (Basel) 2023;12(4):967. doi:10.3390/antiox12040967, PMID:37107341.
[161] Mostafavi Abdolmaleky H, Zhou JR. Gut Microbiota Dysbiosis, Oxidative Stress, Inflammation, and Epigenetic Alterations in Metabolic Diseases. Antioxidants (Basel) 2024;13(8):985. doi:10.3390/antiox13080985, PMID:39199231.
[162] Boyajian JL, Ghebretatios M, Schaly S, Islam P, Prakash S. Microbiome and Human Aging: Probiotic and Prebiotic Potentials in Longevity, Skin Health and Cellular Senescence. Nutrients 2021;13(12):4550. doi:10.3390/nu13124550, PMID:34960102.
[163] Landete JM, Gaya P, Rodríguez E, Langa S, Peirotén Á, Medina M, *et al*. Probiotic Bacteria for Healthier Aging: Immunomodulation and Metabolism of Phytoestrogens. Biomed Res Int 2017;2017:5939818. doi:10.1155/2017/5939818, PMID:29109959.
[164] Badal VD, Vaccariello ED, Murray ER, Yu KE, Knight R, Jeste DV, *et al*. The Gut Microbiome, Aging, and Longevity: A Systematic Review. Nutrients 2020;12(12):3759. doi:10.3390/nu12123759, PMID:33297486.
[165] Coman V, Vodnar DC. Gut microbiota and old age: Modulating factors and interventions for healthy longevity. Exp Gerontol 2020;141:111095. doi:10.1016/j.exger.2020.111095, PMID:32979504.
[166] Xu X, Li G, Zhang D, Zhu H, Liu GH, Zhang Z. Gut Microbiota is Associated with Aging-Related Processes of a Small Mammal Species under High-Density Crowding Stress. Adv Sci (Weinh) 2023;10(14):e2205346. doi:10.1002/advs.202205346, PMID:36965140.
[167] Kunst C, Schmid S, Michalski M, Tümen D, Buttenschön J, Müller M, *et al*. The Influence of Gut Microbiota on Oxidative Stress and the Immune System. Biomedicines 2023;11(5):1388. doi:10.3390/biomedicines11051388, PMID:37239059.
[168] Oshima J, Sidorova JM, Monnat RJ Jr. Werner syndrome: Clinical features, pathogenesis and potential therapeutic interventions. Ageing Res Rev 2017;33:105–114. doi:10.1016/j.arr.2016.03.002, PMID:26993153.
[169] Lebel M, Monnat RJ Jr. Werner syndrome (WRN) gene variants and their association with altered function and age-associated diseases. Ageing Res Rev 2018;41:82–97. doi:10.1016/j.arr.2017.11.003, PMID:29146545.
[170] Mukherjee S, Sinha D, Bhattacharya S, Srinivasan K, Abdisalaam S, Asaithamby A. Werner Syndrome Protein and DNA Replication. Int J Mol Sci 2018;19(11):3442. doi:10.3390/ijms19113442, PMID:30400178.
[171] Shamanna RA, Croteau DL, Lee JH, Bohr VA. Recent Advances in Understanding Werner Syndrome. F1000Res 2017;6:1779. doi:10.12688/f1000research.12110.1, PMID:29043077.
[172] Flores M, Goodrich DW. Retinoblastoma Protein Paralogs and Tumor Suppression. Front Genet 2022;13:818719. doi:10.3389/fgene.2022.818719, PMID:35368709.
[173] Zhu L, Lu Z, Zhao H. Antitumor mechanisms when pRb and p53 are genetically inactivated. Oncogene 2015;34(35):4547–4557. doi:10.1038/onc.2014.399, PMID:25486431.
[174] Wang H, Guo M, Wei H, Chen Y. Targeting p53 pathways: mechanisms, structures, and advances in therapy. Signal Transduct Target Ther 2023;8(1):92. doi:10.1038/s41392-023-01347-1, PMID:36859359.
[175] Sharon G, Sampson TR, Geschwind DH, Mazmanian SK. The Central Nervous System and the Gut Microbiome. Cell 2016;167(4):915–932. doi:10.1016/j.cell.2016.10.027, PMID:27814521.
[176] Tsuge K, Shimamoto A. Research on Werner Syndrome: Trends from Past to Present and Future Prospects. Genes (Basel) 2022;13(10):1802. doi:10.3390/genes13101802, PMID:36292687.
[177] Ren J, Li H, Zeng G, Pang B, Wang Q, Wei J. Gut microbiome-mediated mechanisms in aging-related diseases: are probiotics ready for prime time? Front Pharmacol 2023;14:1178596. doi:10.3389/fphar.2023.1178596, PMID:37324466.
[178] Giorgi C, Marchi S, Simoes ICM, Ren Z, Morciano G, Perrone M, *et al*. Mitochondria and Reactive Oxygen Species in Aging and Age-Related Diseases. Int Rev Cell Mol Biol 2018;340:209–344. doi:10.1016/bs.ircmb.2018.05.006, PMID:30072092.
[179] Nelson CB, Alturki TM, Luxton JJ, Taylor LE, Maranon DG, Muraki K, *et al*. Telomeric Double Strand Breaks in G1 Human Cells Facilitate Formation of 5′ C-Rich Overhangs and Recruitment of TERRA. Front Genet 2021;12:644803. doi:10.3389/fgene.2021.644803, PMID:33841503.
[180] Fouquerel E, Parikh D, Opresko P. DNA damage processing at telomeres: The ends justify the means. DNA Repair (Amst) 2016;44:159–168. doi:10.1016/j.dnarep.2016.05.022, PMID:27233113.
[181] Yousefzadeh M, Henpita C, Vyas R, Soto-Palma C, Robbins P, Niedernhofer L. DNA damage-how and why we age? Elife 2021;10:e62852. doi:10.7554/eLife.62852, PMID:33512317.
[182] Golde TE. Disease-Modifying Therapies for Alzheimer's Disease: More Questions than Answers. Neurotherapeutics 2022;19(1):209–227. doi:10.1007/s13311-022-01201-2, PMID:35229269.
[183] Wang H, Lautrup S, Caponio D, Zhang J, Fang EF. DNA Damage-Induced Neurodegeneration in Accelerated Ageing and Alzheimer's Disease. Int J Mol Sci 2021;22(13):6748. doi:10.3390/ijms22136748, PMID:34201700.
[184] Abavisani M, Faraji S, Ebadpour N, Karav S, Sahebkar A. Beyond the Hayflick limit: How microbes influence cellular aging. Ageing Res Rev 2025;104:102657. doi:10.1016/j.arr.2025, PMID:39788433.
[185] Ghosh TS, Shanahan F, O'Toole PW. The gut microbiome as a modulator of healthy ageing. Nat Rev Gastroenterol Hepatol 2022;19(9):565–584. doi:10.1038/s41575-022-00605-x, PMID:35468952.
[186] Rampelli S, Candela M, Turroni S, Biagi E, Collino S, Franceschi C, *et al*. Functional metagenomic profiling of intestinal microbiome in extreme ageing. Aging (Albany NY) 2013;5(12):902–912. doi:10.18632/aging.100623, PMID:24334635.
[187] Claesson MJ, Jeffery IB, Conde S, Power SE, O'Connor EM, Cusack S, *et al*. Gut microbiota composition correlates with diet and health in the elderly. Nature 2012;488(7410):178–184. doi:10.1038/nature11319, PMID:22797518.
[188] Hohman LS, Osborne LC. A gut-centric view of aging: Do intestinal epithelial cells contribute to age-associated microbiota changes, inflammaging, and immunosenescence? Aging Cell 2022;21(9):e13700. doi:10.1111/acel.13700, PMID:36000805.
[189] Andersen SL. Centenarians as Models of Resistance and Resilience to Alzheimer's Disease and Related Dementias. Adv Geriatr Med Res 2020;2(3):e200018. doi:10.20900/agmr20200018.10.20900/agmr20200018.
[190] Holstege H, Beker N, Dijkstra T, Pieterse K, Wemmenhove E, Schouten K, *et al*. The 100-plus Study of cognitively healthy centenarians: rationale, design and cohort description. Eur J Epidemiol 2018;33(12):1229–1249. doi:10.1007/s10654-018-0451-3, PMID:30362018.
[191] Sepp E, Smidt I, Rööp T, Štšepetova J, Kõljalg S, Mikelsaar M, *et al*. Comparative Analysis of Gut Microbiota in Centenarians and Young People: Impact of Eating Habits and Childhood Living Environment. Front Cell Infect Microbiol 2022;12:851404. doi:10.3389/fcimb.2022.851404, PMID:35372105.
[192] Santoro A, Ostan R, Candela M, Biagi E, Brigidi P, Capri M, *et al*. Gut microbiota changes in the extreme decades of human life: a focus on centenarians. Cell Mol Life Sci 2018;75(1):129–148. doi:10.1007/s00018-017-2674-y, PMID:29032502.
[193] Wang J, Qie J, Zhu D, Zhang X, Zhang Q, Xu Y, *et al*. The landscape in the gut microbiome of long-lived families reveals new insights on longevity and aging - relevant neural and immune function. Gut Microbes 2022;14(1):2107288. doi:10.1080/19490976.2022.2107288, PMID:35939616.
[194] Kim BS, Choi CW, Shin H, Jin SP, Bae JS, Han M, *et al*. Comparison of the Gut Microbiota of Centenarians in Longevity Villages of South Korea with Those of Other Age Groups. J Microbiol Biotechnol 2019;29(3):429–440. doi:10.4014/jmb.1811.11023, PMID:30661321.
[195] Wu L, Xie X, Li Y, Liang T, Zhong H, Yang L, *et al*. Gut microbiota as an antioxidant system in centenarians associated with high antioxidant activities of gut-resident Lactobacillus. NPJ Biofilms Microbiomes 2022;8(1):102. doi:10.1038/s41522-022-00366-0, PMID:36564415.
[196] Chulenbayeva L, Issilbayeva A, Sailybayeva A, Bekbossynova M, Kozhakhmetov S, Kushugulova A. Short-Chain Fatty Acids and Their Metabolic Interactions in Heart Failure. Biomedicines 2025;13(2):343. doi:10.3390/biomedicines13020343, PMID:40002756.

[197] Pang S, Chen X, Lu Z, Meng L, Huang Y, Yu X, *et al*. Longevity of centenarians is reflected by the gut microbiome with youth-associated signatures. Nat Aging 2023;3(4):436–449. doi:10.1038/s43587-023-00389-y, PMID:37117794.
[198] Lozada-Martinez ID, Lozada-Martinez LM, Anaya JM. Gut microbiota in centenarians: A potential metabolic and aging regulator in the study of extreme longevity. Aging Med (Milton) 2024;7(3):406–413. doi:10.1002/agm2.12336, PMID:38975304.
[199] Cătoi AF, Corina A, Katsiki N, Vodnar DC, Andreicuț AD, Stoian AP, *et al*. Gut microbiota and aging-A focus on centenarians. Biochim Biophys Acta Mol Basis Dis 2020;1866(7):165765. doi:10.1016/j.bbadis.2020.165765, PMID:32169505.
[200] Morita H, Ichishima M, Tada I, Shiroma H, Miyagi M, Nakamura T, *et al*. Gut microbial composition of elderly women born in the Japanese longevity village Ogimi. Biosci Microbiota Food Health 2021;40(1):75–79. doi:10.12938/bmfh.2019-055, PMID:33520572.
[201] Rodrigues VF, Elias-Oliveira J, Pereira ÍS, Pereira JA, Barbosa SC, Machado MSG, *et al*. Akkermansia muciniphila and Gut Immune System: A Good Friendship That Attenuates Inflammatory Bowel Disease, Obesity, and Diabetes. Front Immunol 2022;13:934695. doi:10.3389/fimmu.2022.934695, PMID:35874661.
[202] Gavzy SJ, Kensiski A, Lee ZL, Mongodin EF, Ma B, Bromberg JS. Bifidobacterium mechanisms of immune modulation and tolerance. Gut Microbes 2023;15(2):2291164. doi:10.1080/19490976.2023.2291164, PMID:38055306.
[203] Ruiz L, Delgado S, Ruas-Madiedo P, Sánchez B, Margolles A. Bifidobacteria and Their Molecular Communication with the Immune System. Front Microbiol 2017;8:2345. doi:10.3389/fmicb.2017.02345, PMID:29255450.
[204] Wu L, Zeng T, Zinellu A, Rubino S, Kelvin DJ, Carru C. A Cross-Sectional Study of Compositional and Functional Profiles of Gut Microbiota in Sardinian Centenarians. mSystems 2019;4(4):e00325–19. doi:10.1128/mSystems.00325-19, PMID:31289141.
[205] Tang J, Wei Y, Pi C, Zheng W, Zuo Y, Shi P, *et al*. The therapeutic value of bifidobacteria in cardiovascular disease. NPJ Biofilms Microbiomes 2023;9(1):82. doi:10.1038/s41522-023-00448-7, PMID:37903770.
[206] Palmas V, Pisanu S, Madau V, Casula E, Deledda A, Cusano R, *et al*. Gut Microbiota Markers and Dietary Habits Associated with Extreme Longevity in Healthy Sardinian Centenarians. Nutrients 2022;14(12):2436. doi:10.3390/nu14122436, PMID:35745166.
[207] Palmas V, Pisanu S, Madau V, Casula E, Deledda A, Cusano R, *et al*. Gut Microbiota Markers and Dietary Habits Associated with Extreme Longevity in Healthy Sardinian Centenarians. Nutrients 2022;14(12):2436. doi:10.3390/nu14122436, PMID:35745166.
[208] Beaver LM, Jamieson PE, Wong CP, Hosseinikia M, Stevens JF, Ho E. Promotion of Healthy Aging Through the Nexus of Gut Microbiota and Dietary Phytochemicals. Adv Nutr 2025;16(3):100376. doi:10.1016/j.advnut.2025.100376, PMID:39832641.
[209] Ku S, Haque MA, Jang MJ, Ahn J, Choe D, Jeon JI, *et al*. The role of Bifidobacterium in longevity and the future of probiotics. Food Sci Biotechnol 2024;33(9):2097–2110. doi:10.1007/s10068-024-01631-y, PMID:39130652.
[210] Brooks CN, Wight ME, Azeez OE, Bleich RM, Zwetsloot KA. Growing old together: What we know about the influence of diet and exercise on the aging host's gut microbiome. Front Sports Act Living 2023;5:1168731. doi:10.3389/fspor.2023.1168731, PMID:37139301.
[211] Piggott DA, Tuddenham S. The gut microbiome and frailty. Transl Res 2020;221:23–43. doi:10.1016/j.trsl.2020.03.012, PMID:32360945.
[212] Galkin F, Mamoshina P, Aliper A, Putin E, Moskalev V, Gladyshev VN, *et al*. Human Gut Microbiome Aging Clock Based on Taxonomic Profiling and Deep Learning. iScience 2020;23(6):101199. doi:10.1016/j.isci.2020.101199, PMID:32534441.
[213] Biga PR, Duan JE, Young TE, Marks JR, Bronikowski A, Decena LP, *et al*. Hallmarks of aging: A user's guide for comparative biologists. Ageing Res Rev 2025;104:102616. doi:10.1016/j.arr.2024.102616, PMID:39643212.
[214] López-Otín C, Pietrocola F, Roiz-Valle D, Galluzzi L, Kroemer G. Meta-hallmarks of aging and cancer. Cell Metab 2023;35(1):12–35. doi:10.1016/j.cmet.2022.11.001, PMID:36599298.
[215] Tenchov R, Sasso JM, Wang X, Zhou QA. Aging Hallmarks and Progression and Age-Related Diseases: A Landscape View of Research Advancement. ACS Chem Neurosci 2024;15(1):1–30. doi:10.1021/acschemneuro.3c00531.10.1021/acschemneuro.3c00531.
[216] Guo J, Huang X, Dou L, Yan M, Shen T, Tang W, Li J. Aging and aging-related diseases: from molecular mechanisms to interventions and treatments. Signal Transduct Target Ther 2022;7(1):391. doi:10.1038/s41392-022-01251-0, PMID:36522308.