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The dynamic interplay between the human microbiome and aging – implications for health and disease

Dynamiczna interakcja pomiędzy mikrobiomem ludzkim a starzeniem się – implikacje dla zdrowia i choroby

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Abstrakt

Mikrobiota ludzka, czyli złożony ekosystem mikroorganizmów zamieszkujących wewnątrz i na powierzchni ludzkiego ciała, wywiera istotny wpływ na fizjologię, metabolizm oraz funkcjonowanie układu odpornościowego gospodarza. W niniejszej pracy poddano analizie wieloaspektowy związek między mikrobiotą a procesem starzenia się w kontekście terapii rewitalizujących. Poruszamy zmiany w składzie i funkcjonalności mikroorganizmów towarzyszące starzeniu, oraz ich wpływ na homeostazę układu odpornościowego, metabolizm składników odżywczych i funkcje poznawcze. Ponadto analizujemy rolę dysbiozy mikrobioty w chorobach związanych z wiekiem, w tym w chorobach neurodegeneracyjnych, zespole metabolicznym oraz immunosenesencji. Pełne zrozumienie tych interakcji kryje potencjał innowacyjnych strategii wspierających zdrowe starzenie się oraz łagodzenia patologii związanych z wiekiem.

Słowa kluczowe: mikrobiota, starzenie się, odnowa

Abstract

The human microbiome, an intricate ecosystem of microorganisms residing within and on the human body, exerts profound influence on host physiology, metabolism, and immune function. This review explores the multifaceted relationship between the host microbiome and the aging process in the context of rejuvenating therapies. We delve into the shifts in microbial composition and functionality that accompany aging, and their impact on immune homeostasis, nutrient metabolism, and cognitive function. Furthermore, we examine the role of microbiome dysbiosis in age-rela-

ted diseases, including neurodegenerative disorders, metabolic syndrome, and immunosenescence. A comprehensive understanding of these interactions holds potential for innovative strategies to promote healthy aging and mitigate age-related pathologies.

Keywords: microbiome, aging, rejuvenation

INTRODUCTION

Age-related disorders affect an ever-growing number of people around the world. By 2050, the estimated number of elders (60-years-old and older) will double to peak at 2 billion worldwide (WHO, 2022). In Poland, this population is estimated to reach 14 million people accounting for 40% of the Polish population (Wyszkowska et al. 2022). In 2018, only a quarter of the elderly population perceived their health as good and two-third of them reported long-lasting health-related issues or chronic diseases. A nationwide, multicenter study (Klich-Rączka et al. 2014) conducted from 2007 to 2011 in the Polish elderly population revealed that between 12.1% to 20.4% of the respondents aged 65-years-old and older were suspected of cognitive impairments associated with onset of dementia (Karczewska et al., 2019). Correspondingly, the leading cause for more than half the deaths occurring in elders concern age-related conditions. This constitutes a significant burden for the healthcare system and socio-economic challenges for the individuals suffering from such conditions (Olesen et al., 2012). Since multiple comorbidities often occur at an advanced age, therapeutic intervention aiming at managing one condition fails to target the root of the problem that is aging.

DEFINITION OF AGING AND ITS MULTIFACETED NATURE

Aging is a universal biological process, encompassing a myriad of complex and interrelated changes that occur over time at various organizational levels, from molecular to systemic. Aging is a dynamic and multifaceted process characterized by a progressive decline in physiological function and an increased vulnerability to age-related diseases. The definition of aging has evolved over time, reflecting advances in our understanding of the underlying mechanisms. Aging is intricately linked to a repertoire of molecular changes that occur at the cellular level. Key hallmarks, including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication, collectively contribute to the aging process (López-Otín et al., 2013). Recently, these hallmarks of aging have been updated to include disable macro-autophagy, chronic inflammation and dysbiosis (López-Otín et al., 2023). This review aims to provide a comprehensive framework on the current knowledge in regard to the relationship between aging, microbiome composition and rejuvenating therapies. We will discuss the implications of these interactions for overall healthy aging and aging-related pathologies.

SIGNIFICANCE OF MICROBIOME IN HUMAN HEALTH

The human microbiome comprising trillions of microbial organisms (bacteria, viruses, fungi, archaea, protist and parasites) (Dai et al., 2023), has emerged as a critical determinant of human health and disease. Advancing age is associated with notable shifts in the composition of the gut, skin, oral microbiota (Larson et al., 2022). These alterations, collectively termed "age-related dysbiosis," entail a decrease in microbial diversity, with a concomitant increase in the prevalence of certain taxa. The gut microbiome exerts a profound influence on host metabolism, influencing nutrient absorption, energy regulation, and glucose homeostasis.

Disruption of the communication between the microbiota and the host leads to dysbiosis, contributing to conditions like obesity, type 2 diabetes, ulcerative colitis, cardiovascular diseases, and cancer. Emerging evidence suggests a crucial link between the gut microbiome and neurodegenerative disorders such as Alzheimer's and Parkinson's diseases (Chandra et al., 2023; Salim et al., 2023). Nevertheless, the gut microbiota is highly variable among individuals due to genetic, dietary, lifestyle, and environmental factors. To add another layer of complexity, the gut is not the only localization where the microbiome can exert a profound effect on the body. The oral microbiota and oral health are closely linked to systemic health such as cardiovascular diseases, obesity, and diabetes (Illuzzi et al., 2014). These variables complicate the understanding of the relationship between microbiota and age-related diseases.

EMERGING PARADIGM: MICROBIOME AS A PLAYER IN AGING

As individuals age, their gut microbiomes become increasingly unique. This uniqueness is associated with specific microbial metabolites related to immune regulation, inflammation, and aging (Dugan et al., 2023). While bacterial diversity remains relatively stable during adulthood, the composition and activity of the microbiota change gradually with age. These changes often lead to a decrease in ecological diversity, alongside an increased expansion of opportunistic pathobionts (Ghosh et al., 2022). This imbalance can occur in various parts of the body, but it is most commonly studied in the gut. Furthermore, the integrity and function of the intestinal epithelial barrier decline with age across various animals, from nematodes to humans. This "leaky gut" contributes to conditions like inflammatory bowel disease, colitis, cancer, and inflammaging (Di et al., 2021).

Aging is accompanied by a decline in immune function, a phenomenon known as immunosenescence. In turn, immunosenescence may lead to a low-grade, sterile chronic inflammation called "inflammaging" (Santoro et al., 2022) which translates in the progressive reduction of the ability to trigger effective immune responses. The gut microbiome plays a pivotal role in modulating the immune responses, influencing the development, maturation, and function of immune cells (Aurora et al., 2022).

Addressing the recent COVID-19 pandemic, Alan Landay and colleagues reviewed the complex interplay between inflammaging, the microbiome and SARS-CoV-2 infection (Landay et al., 2021). The SARS-CoV-2 virus can infect the intestinal epithelial cells indicating a potential role of the microbiome in the COVID-19 pathogenesis (Hussain et al., 2021). Moreover, markers of fungal and bacterial metabolism translocating from the gut have been shown to correlate with COVID-19 severity (Giron et al., 2021). Therefore, age-related gut dysbiosis in the elderly population may account for the COVID-19 morbidity and mortality. Concomitantly, in the nasal and oral cavities, the airway microbiome plays a vital role in the respiratory tissue-specific immunity and resistance to pathogens and has been shown to change with aging (Santoro et al., 2020). Consequently, the airway microbiome may influence SARS-CoV-2 susceptibility and offers a therapeutic venue for prevention.

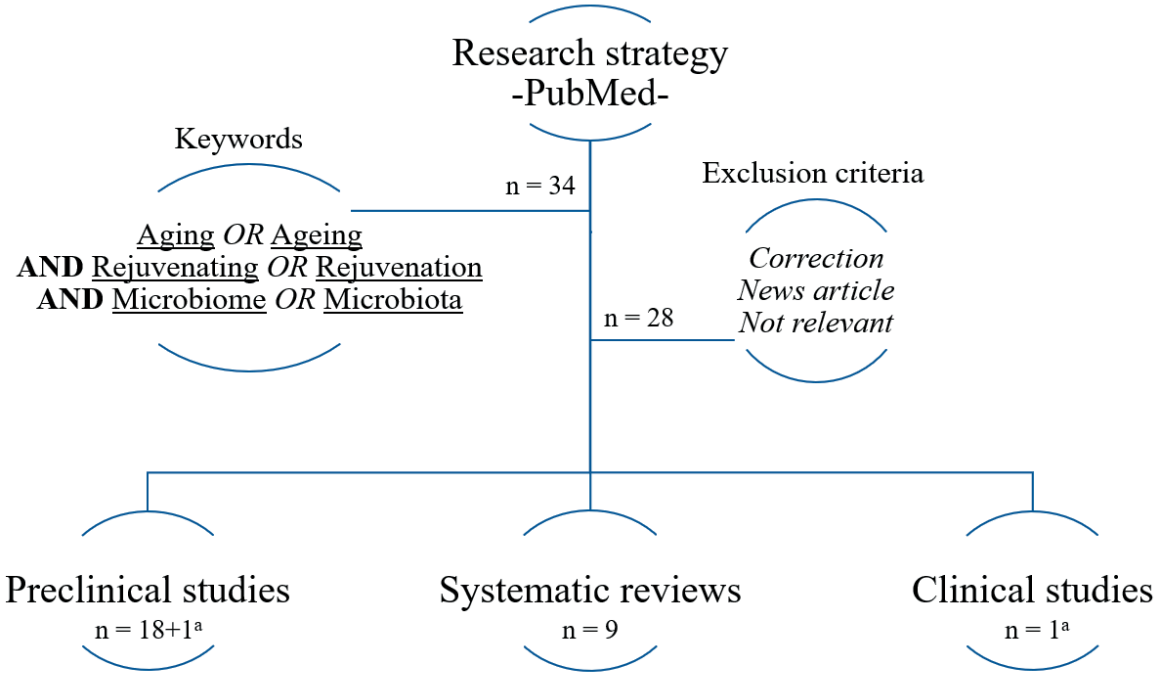

Fig. 1. Research strategy for narrowing the literature review. Keywords included Aging (or Ageing), Rejuvenating (or Rejuvenation) and Microbiome (or Microbiota). Exclusion criteria included correction from previously published work, news articles and opinions, publications that were not dimmed relevant to the present search (ex: only mentioning the terms of the search in the authors affiliation). One study (1a) presented results from both precliniclal and clinical work. Time interval: from the first published article fitting the criteria (September 3rd 2008) to September 15th 2023.

Understanding the intricate interplay between the human microbiome and aging offers promising opportunities for interventions to promote healthy aging and ameliorate age-related pathologies. We will discuss the recent potential strategies, including dietary interventions, prebiotics, probiotics, and fecal microbiota transplantation, and highlight the need for further research in this field. The following review was performed with the research strategy depicted in Figure 1: briefly, there were considered for review the research articles on preclinical and clinical studies that intersected with the following keywords: microbiome, aging and rejuvenation.

MICROBIOME AND AGING

Gut microbiota composition shifts with age

As humans age, there is a noticeable shift in the composition and diversity of the microbiome. This shift is influenced by a combination of intrinsic and extrinsic factors, including genetics, diet, lifestyle, and environmental exposures.

One of the most consistent observations in aging microbiomes is a reduction in microbial diversity. This means that there are fewer types of microorganisms present in older individuals compared to younger ones. This reduction in diversity can have negative implications for health, as a diverse microbiome is generally associated with better overall well-being.

Certain species of bacteria become more prominent in older individuals. For example, studies have shown an increase in potentially harmful species like Proteobacteria and a decrease in beneficial species like Bifidobacteria (Bosco et al., 2021). This shift can lead to a less balanced and potentially less resilient microbiome.

Firmicutes and Bacteroidetes are the most abundant phyla in the human gut. In general, a healthy gut microbiome maintains a balance between Firmicutes and Bacteroidetes. However, studies have shown inconsistent findings regarding the changes in the Firmicutes/Bacteroidetes ratio with aging. The ratio of Firmicutes over Bacteroidetes (F/B) is a widely used biomarker in microbiota studies, reflecting the proportional composition of Firmicutes and Bacteroidetes. High F/B ratios were previously associated with dysbiosis and were linked to age, with an increase from birth to adulthood (Mariat et al., 2009), although some research reported no significant change (Nagarajan et al., 2023).

At lower taxonomic levels, shifts have been observed in the relative abundance of various genera and species (Xu et al., 2019). Bifidobacteria and Lactobacilli are generally considered beneficial bacteria (Hiippala et al., 2018). They are known for their roles in maintaining gut health, promoting nutrient absorption, and supporting the immune system. Studies have reported that decrease in *Bifidobacterium* abundance with age is associated with age-related conditions. *Akkermansia muciniphila* or *Roseburia* are beneficial commensal bacteria promoting intestinal integrity, supporting the mucus layer, associated with a healthy gut lining and metabolic health (Hiippala et al., 2018). *A. muciniphila* scarcity seen in aged individuals, is linked to inflammatory bowel disease and colorectal cancer precursor.

It is important to note that individual variations are significant, and not all older individuals will experience the same changes in their microbiome. Despite these significant interindividual and lifestyle differences, the composition of the gut microbiota of elderly humans markedly differs from that of young and middle-aged adults (Ragonnaud et al., 2021).

Dysbiosis and its impact on health

Dysbiosis refers to an imbalance or disruption in the composition and function of the microbiota that normally reside in and on the human body. Such phenomena can have a profound impact on human health, influencing a wide range of conditions and diseases. To note, the use of antibiotics, which can disrupt the balance of the microbiome, can lead to the overgrowth of potentially harmful bacteria as well as the development of antibiotic-resistant strains.

Age-related dysbiosis has been implicated in various gastrointestinal disorders like irritable bowel syndrome, inflammatory bowel disease, gastroesophageal reflux disease and can interfere with the normal process of nutrient absorption. These microbial disturbances induce changes in the intestinal structures such as loss of intestinal epithelial cells, "cell shedding", impaired self-repair, neurodegeneration of the enteric nervous system, loss of microvilli and altered cell composition (Larrick et al., 2019), which translate to degenerative digestion and malabsorption potentially due to reduced enzyme activity or production (Wang et al., 2021).

As the gut microbiota plays a crucial role in training and modulating the immune system, dysbiosis can lead to a dysfunctional immune response, potentially contributing to autoimmune disorders, allergies, and chronic inflammatory conditions. Dysbiosis, particularly in the gut, has been associated with an increased risk of colorectal cancer (Biragyn et al., 2018). Certain harmful bacteria can produce substances that promote inflammation and damage the lining of the colon, potentially leading to cancerous growths. Imbalances in gut bacteria

can influence energy metabolism, inflammation, and potentially contribute to weight gain and metabolic dysfunction leading to the development and progression of type 2 diabetes and cardiovascular disease (Mendelsohn et al., 2013).

Emerging research indicates a strong connection between the gut microbiota and mental health. Dysbiosis has been linked to conditions like depression, anxiety, and even neurodevelopmental disorders like autism spectrum disorder. It may also contribute to neurodegenerative diseases (Homolak 2023) like Alzheimer's and Parkinson's. The gut--brain axis, a bidirectional communication system between the gut and the brain, is thought to play a significant role in these conditions.

Gut-brain axis: implications for cognitive aging

The gut-brain axis is a bi-directional communication network connecting the central nervous system with the enteric nervous system of the gut. This communication occurs through various pathways, including the autonomic nervous system, immune system, and the production of neurotransmitters and hormones. The gut-brain axis has profound implications for cognitive aging, influencing both normal cognitive function and age-related cognitive decline (Carabotti et al., 2015).

The gut microbiota plays a crucial role in the production of neurotransmitters, including serotonin, dopamine, and GABA. These neurotransmitters are vital for mood regulation, cognitive function and memory. Dysbiosis (microbial imbalance) can disrupt the production and availability of these neurotransmitters, potentially impacting cognitive aging (Chen et al., 2021).

The gut microbiome can influence the integrity of the blood-brain barrier, a protective barrier that regulates the passage of substances between the blood and the brain. Dysbiosis-induced inflammation can compromise this barrier, potentially allowing harmful substances to enter the brain, resulting in neuroinflammation which has been associated with cognitive decline and neurodegenerative diseases (Tang et al., 2020).

Gut bacteria produce a range of neuroactive compounds, including short-chain fatty acids and other metabolites. These compounds can influence neural function, synaptic plasticity, neurogenesis and cognition. Changes in the gut microbiome composition can alter the levels of these neuroactive compounds, potentially impacting cognitive aging (Ahmed et al., 2022).

The gut microbiota can influence the hypothalamic-pituitary-adrenal axis, which regulates the body's stress response. Dysbiosis-induced alterations in hypothalamic-pituitary-adrenal axis function can lead to increased stress levels, potentially exacerbating cognitive aging (Alsegiani et al., 2022).

Emerging research suggests that dysbiosis may be linked to neurodegenerative disorders such as Alzheimer's and Parkinson's disease. Imbalances in the gut microbiome may contribute to the accumulation of pathological proteins (e.g., amyloid-beta and alpha--synuclein) in the brain, which are characteristic of these conditions. Carolina Osorio and her colleagues (Osorio et al. 2019), suggested a paradigm shift regarding the cause of Alzheimer's disease, advocating for the inclusion of the gut microbiota. The authors summarized how microbial translocation from the gut to the central nervous system can contribute to age-related disease like Alzheimer's disease through disruption of biological barriers, induction of cellular senescence and impaired immunity by targeting pathways like mTOR. The authors advocate for the use of senotherapeutic interventions which aim to target the aging process itself by reducing the organismal senescence burden. It is their expectation that such treatment will influence both the central nervous system and the body periphery to reduce the risk of Alzheimer's disease and mitigate its symptoms.

Rejuvenating therapies

Modulating the human microbiome for rejuvenation is an area of active research that holds significant promise for promoting healthy aging. Preclinical studies have shown that age-related dysbiosis is characterized by specific changes in the microbial community which can precede or predict age-related intestinal barrier dysfunction, immune activation and organismal aging. Pharmaceutical intervention (anti-inflammatory, senolytics or senomorphics) and dietary supplementation (prebiotics, probiotics, synbiotics or postbiotics) are emerging anti-aging therapies with the potential to rejuvenate the immune system, the cognitive system, and the overall health in aging individuals.Such interventions, aimed at restoring a more youthful microbiome, have the potential to extend healthspan and lifespan but need careful evaluation of the possible side effects (Bosco et al., 2021). Besides dietary supplementation, one of the most promising interventions to slow aging in recent years has been dietary restriction which has been shown to induce broad--spectrum health improvement across various organisms. In preclinical studies, dietary restricted microbiome in mice has shown the ability to reduce weight gain, improved glucose tolerance and insulin sensitivity (Partridge et al., 2020).

Proof-of-concept from recent preclinical trials

A recent study provided proof-of-concept that changes in microbial composition through several models of gut microbiota modulation induced beneficial effects in regard to age-related biological functions. Jongoh Shin and colleagues (Shin et al., 2021; Shin et al., 2022) reported the changes in the function and key microbial communities during aging and rejuvenating therapies. The authors performed co-housing, young serum injection and parabiosis experiments in rodents to investigate the dynamic interactions of the microbiome during aging. Their observations suggest that microbial diversity changes with age are associated with specific taxa changes (decrease *Akkermansia* and *Parabacteroides*, increase *Turicibacter* and *Helicobacter*). These changes implied significant shifts in the microbiome functions, especially related to butyrate and GABA biosynthesis, which are normally involved with improved intestinal barrier function and reduced systemic inflammation. Rejuvenating therapies impacted the microbiome composition with increased *Oscillospira* and *Akkermansia*; and reduction of *Paraprevotella*, *Prevotella*, *Odoribacter, cc_115, AF12, Turicibacter* and *Helicobacter*. Finally, the authors showed that administration of *Akkermansia muciniphila* reduced lipopolysaccharide levels, improved intestinal tight junction proteins and secretory mucin protein expression. Moreover, supplementation with *Akkermansia muciniphila* improved frailty index, cognitive function and muscle strength of aged individuals.

However, another study by Taha Ceylani and colleagues (Ceylani et al., 2022) provided contradictory results in terms of microbiota composition in young plasma administration models of middle-aged rats. In particular, the authors showed a reduced Firmicutes/Bacteroidetes (F/B) ratioassociated with changes in the abundance of specific bacterial families, genera and species such as a decrease in *Oscillopiraceae* family and increase in *Turicibacter*. These discrepancies highlight the tremendous difficulty that hinders the field in providing consistent reports that may result from between bacterial species, study design and technology use for analysis of samples.

Senolytics and senomorphics interacting with the microbiome against senescence

Utilizing xenobiotics, senolytics, and senomorphics to modulate the human microbiome for anti-aging purposes is an innovative and promising approach. Senolytics, such as dasatinib and quercetin, curcumin or fisetin, are compounds that selectively target and induce the death of senescent cells. Senomorphics, such as rapamycin, on the other hand, are a relatively new class of compounds designed to modulate cellular senescence, but instead of eliminating senescent cells, they aim to alter their behavior and secretory profile (Kirkland et al., 2020).

Beside their direct effect on senescent cells, these senolytics and senomorphics drugs may directly influence the host microbiome. Several studies have shown microbial composition change following treatment with these xenobiotics (Maher 2020). For instance, Jonathan Y. An and colleagues (An et al., 2020) demonstrated that the use of short-term treatment with rapamycin can rejuvenate the oral cavity of aged rodents which may prevent and reverse the occurrence of periodontal disease that they previously observed during aging (An et al., 2017). The authors showed that the treatment was able to induce periodontal bone regeneration, attenuate gingival and periodontal bone inflammation as well as reverse the oral microbiome toward a younger composition. Rapamycin induced a reduction in *Bacteroidetes* phylum with a significant difference in beta-diversity between treated and untreated animals.

Emerging research suggests that senolytics may indirectly influence the microbiome by reducing inflammation. Senescent cells secrete inflammatory molecules, and by clearing these cells, senolytics could create a more favorable environment for a healthy microbiome. In that regard, Tatiana Dandolini Saccon and colleagues (Saccon et al., 2021) describe for the first time the effects of senolytic treatment with dasatinib and quercetin on the gut inflammation, senescence and microbiome composition in aged and young mice. The senolytic treatment reduced intestinal cellular senescence and inflammation in aged mice, with significant effects on the gut microbiota composition (increased abundance of Verrucomicrobia especially *Akkermansia* and reduced abundance of Firmicutes especially *Lactobacillus*). The microbiome signatures were associated with senescence and inflammation markers vary across different sections of the gastrointestinal tract, indicating complex interactions between the microbiota and host health. Recently, Alistaire D. Ruggiero and colleagues (Ruggiero et al., 2023) provided valuable insights into the potential benefits of senolytic therapy in a non-human primate model, with a focus on multiple health aspects, including senescence biomarkers (reduction of p16 and p21), immune response (decrease immune markers and M1 polarization), intestinal barrier function (decrease lipopolysaccharide-bin-

ding protein LBP-1, liver fatty acid-binding protein FABP-1, IgA), metabolism (decrease HbA1c) and Alzheimer's disease-related markers (decrease CSF aβ40 and aβ42). The authors reported no significant changes in the microbiome composition which may not indicate an absence of changes in the metabolic pathways of the residing microbes.

Beyond the direct and indirect effects of the xenobiotics on either the microbiome or the host cellular function, the gut microbiome may affect the bioavailability of the compounds passing through the gastrointestinal tract. Anna Bielak-Zmijewska and colleagues (Bielak-Zmijewska et al., 2019) reviewed the many roles of curcumin in the modulation of aging. The authors summarized the pivotal role of the microbiome for addressing the bioavailability of senolytic compounds through the metabolism of the beta-glucuronidase that can elevate the concentration of unconjugated curcumin. Moreover, the authors summarize that curcumin in itself may influence the microbiota which can positively influence certain organismal functions.

The use of xenobiotics (senolytics, senomorphics or any -biotics) to modulate the human microbiome in the fight against aging represents an exciting frontier in anti-aging research. While these approaches hold great promise, continued research and clinical trials will be crucial to understanding their full potential and ensuring their safety and efficacy for use in aging interventions.

Caloric restriction for diet modulating anti-aging strategy

Caloric restriction is a dietary intervention that involves reducing calorie intake without causing malnutrition. It has been extensively studied for its potential to extend lifespan and improve healthspan in various organisms, from rodents to primates. In recent years, research has also begun to explore how caloric restriction affects the microbiota and whether this modulation could be a key factor in its anti-aging effects.

Two studies in recent years have assessed how caloric restriction impacts aging function in relation to the host microbiome. First, Ting Zeng and colleagues (Zeng et al., 2019) provided the first evidence that short-term dietary restriction in old mice was able to rejuvenate dysfunctional aged microbiota which may provide beneficial holistic effects. Their findings demonstrate that aging leads to alterations in intestinal flora composition (increase F/B ratio and specific taxa enrichment) which correlates with lipid accumulation and inflammation. Short-term dietary restriction can reverse these changes, promoting a microbiota composition resembling that of younger and healthier mice.

Shanlin Ke and colleagues (Ke et al., 2021) demonstrated the potential of caloric restriction in the complex association between the gut microbiota, aging and frailty. They confirmed the increased frailty index score with chronological age in rodents and the beneficial effect of calorie restriction diet on frailty. Frailty being defined as a medical and physiological term that refers to a state of increased vulnerability and decreased resilience typically associated with aging. Frailty often involves a combination of physical weakness, decreased mobility and reduced muscle mass. At the gut microbiome level, they observe increased Firmicutes/Bacteroidetes, decrease in Verrucomicrobia ratio and alpha diversity with aging (*C. sensu stricto* and *Enterorhabus* for example). Their analysis revealed that frailty index was either positively or negatively correlated with specific microbial taxa. Furthermore, the authors applied an Elastic-net logistic regression model to their data that accurately predicted healthy aging using microbial signatures. Their results suggest that caloric restriction may further drive the changes observed in aging.

Understanding the interactions between the microbiome and any type of dietary pattern that aim at slowing down aging (caloric restriction, intermittent fasting, specialized diet) can provide insights into novel interventions and dietary strategies for promoting healthy aging and preventing age-related diseases (Duan et al., 2022). However, more research is needed to elucidate the specific mechanisms and to develop practical, sustainable approaches for implementation in humans.

Targeting the gut with prebiotics, probiotics and postbiotics

The intestinal microbiota composition can be readily adjusted through the addition of prebiotics, probiotics, synbiotics or postbiotics, and this modification can potentially amplify or acquire enhanced effects on the improved microbiome. The ultimate goal of modulating the microbiome this way is to provide a rapid and effective effect on various age-related diseases (Song et al., 2022).

Prebiotics are dietary compounds that serve as a food source for beneficial bacteria, promoting their growth and activity. Common examples include inulin and galacto-oligosaccharides. Another type of prebiotic can be derived from the intestinal lining metabolism such as the intestinal alkaline phosphatase which supplementation can reverse age-induced gut barrier dysfunction by maintaining tight

junction proteins, and to reduce systemic inflammation by dephosphorylate gut-derived metabolites such as lipopolysaccharide (Larrick et al., 2020). Prebiotics can stimulate the growth of commensal gut bacteria and can reduce inflammation, as observed in older individuals. One of such compounds has been studied by Si-Young Cho and colleagues (Cho et al., 2016). The authors investigated whether syringaresinol, a polyphenolic lignan, modulates immune aging and the gut microbiota associated with this effect in middle-aged mice. They showed that syringaresinol restores age-dependent immune system dysregulation by enhancing the proliferation of splenic T cells and the numbers of CD3+ T cells, naive T cells and decreasing the number of B cells, as well as by rebalancing the levels of IFNy and IL-2 production. They showed also that the compound modulates Treg cells and apoptosis-related factors by inducing the expression of Bim and activation of FOXO3 in a decreased population of CD4+ Foxp3+ Treg cells. Moreover, syringaresinol can influence the gut microbiota composition and diversity by increasing the Firmicutes/Bacteroidetes ratio, increasing the abundance of *Lactobacillus* and *Bifidobacterium* and decreasing opportunistic pathogenic bacteria abundance from the *Staphylococcaceae* family, which all together potentially contributes to improved gut integrity through reduce serum LPS-binding protein. Lastly, they observed that syringaresinol enhances cellular and humoral immune responses to influenza vaccination assessed by higher HA-specific IgG titers and HI antibody titers. Their findings suggest that syringaresinol treatment could potentially offer a comprehensive strategy to mitigate age-related immune decline, enhance vaccine responses, and maintain gut microbiota homeostasis in middle-aged individuals. Another polyphenolic compound, genistein, was evaluated by Qihang Hou and colleagues (Hou et al., 2023,). The authors reported that genistein supplementation extends lifespan, improves healthspan and alleviates age-associated health issues in aging mice. These effects are associated with modifications in gut microbiota composition (increase Firmicutes/Bacteroidetes ratio), increased short-chain fatty acid production associated with *Lachnospiraceae* NK4A136 abundance, and the enhancement of anti-inflammatory processes in the gut. The authors concluded that genistein beneficial effects on gut health and inflammation are partly mediated by microbiota-induced short-chain fatty acids and enhanced Treg cell function.

Probiotics are live microorganisms, often bacteria or yeasts, that, when consumed in adequate amounts, provide health benefits. These beneficial microorganisms can be found in fermented foods like yogurt, kefir, and kimchi, as well as in dietary supplements. Probiotics can also be engineered to achieve therapeutic outcome (Ochoa-Sanchez et al., 2021). Probiotics improve gut barrier function by increasing the secretion of antimicrobial peptides (such as defensins, lysozyme), thereby reducing persistent immune activation and inflammation. They restore gut microbiome homeostasis, increase short-chain fatty acid levels, promote IL-10-secreting regulatory T cells, reduce Th17 responses, and decrease pro-inflammatory cytokine production (IL-6, TNFα). Such intervention was demonstrated as early as in 2008 by Karine Vidal and colleagues (Vidal et al., 2008) who showed that oral intake of *Lactobacillus paracasei* NCC2461 to aged mice enhanced the specific Th1 cell-dependent adaptive immune response to an antigenic challenge without altering other cellular or humoral immune responses. Following immunochallenge with keyhole limpet hemocyanin, they observed in the animal supplemented with the probiotic an increase in antigen-specific IgG2a immunoglobulin and delayed type hypersensitivity. They conclude that the poor responsiveness to antigenic challenge, frequently observed in elderly people, may be improved by supplementation with *L. paracasei* NCC2461. Later on, Domonica N. Powell and colleagues (Powell et al., 2020), demonstrated that colonization with commensal bacteria producing indole-derived metabolites increased goblet cell proportion which is closely associated with gut health during aging. The authors showed that indole-derived metabolites can sustain colonic stem cell turnover which led to increase numbers of Goblet cells in a process mediated by IL-10 and aryl hydrocarbon receptor. Recently, Hongwon Kim and colleagues (Kim et al., 2022), demonstrated that probiotics supplementation with *B. bifidum BGN4* and *B. longum BORI* improved hippocampal function in aged mice and showed that the overall attenuated age-related phenotypes were associated with changes in the gut microbiome composition. The authors reported that the probiotics restored locomotor activity and spatial recognition memory in aged mice. These improvements were supported by an increased number of BDNF, PSD-95 and Homer1 expressing neurons and decreased the expression of H3K-9me3, caspase-3 and H2yA.X expressing neurons in the hippocampus of aged mice. Moreover, the treatment decreases the number of Iba1 microglia cells as well as the expression of COX2, IL-6 mRNA and serum TNF-a level. The probiotics also induced changes in the overall microbial composition of the gut bacterial genera including higher

relative abundance of *Lachnoclostridium* and higher proportion of genes related to valine, leucine and isoleucine metabolism. Interestingly, these findings showed that introducing a new strain is able to profoundly alter the existing micro-environment.

Synbiotics combine prebiotics and probiotics in a synergistic manner. By providing both beneficial live microorganisms (probiotics) and their preferred food sources (prebiotics), synbiotics aim to create an environment that supports the growth and activity of these beneficial microbes. In this perspective Denise Mafra and colleagues (Mafra et al., 2021), advocate for the concept of food-as-medicine on the clinical outcomes in kidney disease, which could also be extended to other age-related diseases.

Postbiotics are bioactive compounds or metabolites produced by probiotic bacteria during their fermentation process. These include substances like short-chain fatty acids (SCFAs), antimicrobial peptides, and certain vitamins. Postbiotics exert their effects through various mechanisms, including regulating the immune system, supporting gut barrier function, and influencing metabolic processes. Interestingly, these postbiotics can come from various sources including components of fungus such as the heteropolysaccharide L2 isolated from the fruit body of *L. edodes* as described by Xiaofei Xu and colleagues (Xu et al., 2015). Their study demonstrates that L2 treatment in old mice enhances immune responses by reversing the immunocompromised status of the aged individuals indicated by increased levels of IL-2 and IL-6 cytokines. Moreover, the L2 treatment altered the gut microbiota composition by increasing the number of Firmicutes and decreasing the number of Bacteroidetes, reversing the decrease Firmicutes/Bacteroidetes ratio; restoring the level of *Bacteroidaceae*, *Lactobacillaceae*, and *Alcaligenaceae* and specifically down-regulate or up-regulate*Bacteroides acidifaciens* and *Lactobacillus* taxonomic units respectively. They highlight the potential of L2 as an intervention to modulate immune responses and gut microbiota in aging. Similarly, P. Chen and colleagues (Chen et al., 2018) assess the cytoprotective effect of *S. fusiforme* polysaccharides (SFPS) in the small intestine of mice embarking on the aging process. They observed that dietary intake of SFPS could ameliorate the declined cytoprotective capacity of the small intestine by upregulating the Nrf2/ARE signaling pathway and rejuvenate the small intestine microbiota.

Understanding and utilizing these concepts can lead to personalized approaches for promoting gut health and overall well-being. However, it is important to note that while these interventions hold promise, further research is needed to fully understand their mechanisms and optimize their applications in clinical settings.

Fecal microbiota transplantation

Fecal Microbiota Transplantation (FMT), is a medical procedure that involves the transfer of fecal material from a healthy donor to a recipient with the aim of restoring a balanced and diverse gut microbiome. This therapy gained prominence primarily for its remarkable success in treating recurrent *Clostridium difficile* infections, where it demonstrated high cure rates. Extending FMT potential to anti-aging therapy is an area of growing interest (Fischer et al., 2018). FMT experiments in mice, humans and other organisms have shown that transferring microbiota from young to old individuals can enhance healthspan and lifespan (Boehme et al., 2021; Heijtz et al., 2021). Conversely, FMT from old donors to young recipients can induce detrimental effects.

This has been shown by Nana Zhang and colleagues (Zhang et al., 2022) who reported the positive impact from fecal microbiota transplantation from young donors on the locomotor exploration abilities of aging mice and influence on the gut microbiome composition. This was particularly the case regarding the abundance of *Akkermansia* which appears to increase with chronological age but this trend was delayed by the transplantation of young microbiota. The authors found a correlation between the abundance of *Akkermansia* and locomotor and exploration abilities. Similarly, Kwang H. Kim and colleagues (Kim et al., 2022) demonstrated the significant influence of fecal microbiota transplantation from young mice to aged mice which showed to improve various aspects of aging including muscle strength and skin health. The authors identified specific microbial clusters (*Muribaculaceae*, *Prevotellaceae*, *Bacteroidaceae* in the phylum Bacteroidetes) associated with improved grip strength, skin moisture and other beneficial phenotypes following fecal microbiota transplantation. Their study highlights potential microbial targets for interventions to counteract age-related declines in physical function and skin properties. Finally, Xiangjun Zeng and colleagues (Zeng et al., 2023), highlight the crucial role of the gut microbiota and its impact on hematopoiesis and hematopoietic stem cell function in aging. They demonstrated that fecal microbiota transplantation from young mice has the potential to rejuvenate aged hematopoietic stem cells, improve intestinal barrier function, reduce inflammation and alter the microbiome composition, in particular they observed an

enrichment of *Lachnospiraceae* and tryptophan-associated metabolites. These results offer promising insights into strategies for combating age-related hematopoietic decline. FMT holds significant potential not only in treating gastrointestinal disorders but also in influencing a range of age-related conditions. As research continues to advance, personalized FMT approaches may become a valuable tool in anti-aging therapies, offering the potential to modulate the gut microbiota in order to slow-down accelerated aging.

CLINICAL APPLICATIONS

Current rejuvenation trials and studies

In the framework of this review, we identified one clinical study from Marie Meunier and colleagues (Meunier et al., 2018) who investigated the impact of *Orabanche rapum* extract on the skin aspect of a cohort of middle-aged women who suffer from dry skin condition. The compound, applied on the forearm, increased water, lipid, and protein content which translated to better skin organization and reduced total wrinkled area and number. Moreover, the extract has proven to be able to stabilize phylum levels, particularly in the Firmicutes and to inhibit an opportunistic pathogen of the genus *Finegoldia*. Their study identified a natural compound able to rejuvenate the skin and modulate the skin microbiota balance, leading to better protection.

Challenges and promising results

In this review, we aim to highlight the considerable potential of microbiome research in the context of aging as a significant target for anti-aging therapies. However, our field of research faces significant challenges that hinder the realization of its therapeutic potential.

Firstly, the complexity of interactions between microbial composition and host biological processes poses a formidable obstacle. The composition of the microbiome represents just one facet, as subtle changes in the overall composition can lead to profound alterations in the metabolic activities of different species. Moreover, due to the bidirectional relationship between the microbiome and the host, accurately assessing their respective impacts on each other is exceedingly challenging. The same holds true for the xenobiotics used for targeting aging and their bidirectional effects with the microbiome (Salekeen et al., 2023).

Secondly, in recent decades, research has overwhelmingly concentrated on the role of bacteria, largely overlooking the presence and functions of other microorganisms, such as viruses, fungi, archaea, protists, and parasites.

Thirdly, the majority of studies provide observational data on the microbiome and establish correlations with biological or behavioral parameters, which does not necessarily imply causation between the two.

Fourthly, conflicting results from preclinical trials regarding specific microbial families, taxa, or species following various interventions are a common issue. For example, *Akkermansia* has been linked both negatively (Zhang et al., 2022) and positively (Saccon et al., 2021; Shin et al., 2021) to healthy aging, possibly due to differences in experimental models, study designs, treatment interventions, or individual variability.

Lastly, there are currently no definitive guidelines for therapeutic approaches concerning the microbiome in the care of elderly patients in regard to their microbiome and their age-related comorbidities. This aspect is also overlooked for their younger caregivers and family members. While older individuals may benefit from sharing and diversifying their microbiome through interactions with younger individuals, the younger counterparts may experience accelerated aging of their microbiome.

Addressing these challenges and advancing our understanding of the microbiome's role in aging will be crucial for the development of effective anti-aging strategies. Several groups already took advantage of the fast-growing bioinformatic field and advanced neuronal network to uncover new therapeutic agents and their probable targets (Wong et al., 2023). Fortunately, new models are being continuously developed and used to elucidate the complex interactions between the microbial composition of the host and its biological functions. For example, Christian H. Bucher and colleagues (Bucher et al., 2022), utilized an immunoaged mouse model to investigate immunological diversity and immunoaging in the context of bone regeneration. Among their fundings, the authors analyzed the microbiome in the caecum at different phases during fracture healing and observed a shift in the microbiome composition following an initial absence due to the treatment. The immunoaged group (experienced immune system) had a slower reconstitution process of their microbiome and specific taxa enrichment difference were found between immunoaged and the aged groups (less-experienced immune system) such as less effective repopulation of *Porphyromonadaceae* and more effective repopulation of *Verrucomicrobiaceae* in the immunoaged group. The significant delay for the microbiome to

return to baseline state may suggest that the microbiome is not a contributing factor to the delayed healing driven by the immune system.

Another area of great interest has been discussed by Iwona Gierlicka and colleagues (Gierlicka et al., 2022) who provided an interesting review discussing the therapeutic potential of using bacteriophages in biogerontological research and its therapeutic applications. Bacteriophages have the potential to be major therapeutic agents since they cannot use mammalian cells for replication and exhibit minimal toxicity, moreover they can easily penetrate the body and overcome anatomical and physiological barriers that are difficult for other vectors to pass. Bacteriophage can be specifically constructed offering genetic flexibility and ability to introduce various chemical groups for specific functions such as therapeutic or active targeting effects. Phages can be used to maintain a healthy gut microbiome and potentially improve overall healthspan and lifespan of elderly population by reducing the proportion of inflammation-inducing bacteria.

CONCLUSION

This review highlights the significant role of dysbiosis in various age-related conditions, from gastrointestinal disorders to neurodegenerative diseases. The modulation of the microbiome through interventions like senolytics, senomorphics, and dietary strategies like caloric restriction offers promising avenues for anti-aging interventions. These approaches have shown potential not only in influencing the composition of the microbiome but also in impacting broader aspects of health, including immune function, cognitive aging, and metabolic health.

Moreover, the use of prebiotics, probiotics, synbiotics, and postbiotics provides an additional layer of potential interventions. These strategies can promote the growth of beneficial microorganisms, improve gut barrier function, reduce inflammation, and impact various physiological processes.

Cited studies, spanning across various interventions and methodologies, collectively emphasize the complexity and potential of targeting the microbiome in the pursuit of healthy aging.

However, there are significant challenges in this field. The complexity of microbiome-host interactions, the presence of various microorganisms beyond bacteria, and the need for causative evidence rather than just correlations are all critical considerations. Additionally, the variability in results across studies may stem from various factors, underscoring the need for standardized protocols and further research.

Therefore, it is crucial to acknowledge that the field is still evolving, and continued research and clinical trials are essential to fully understand the nuanced interactions and to ensure the safety and efficacy of these interventions.

In conclusion, the presented research underscores the pivotal role of the microbiome in the aging process and provides a valuable foundation for future studies and interventions aimed at promoting healthy aging and preventing age-related diseases. As the field continues to advance, these findings hold the potential to revolutionize approaches to aging and geriatric care, ultimately enhancing the quality of life for aging individuals around the world.

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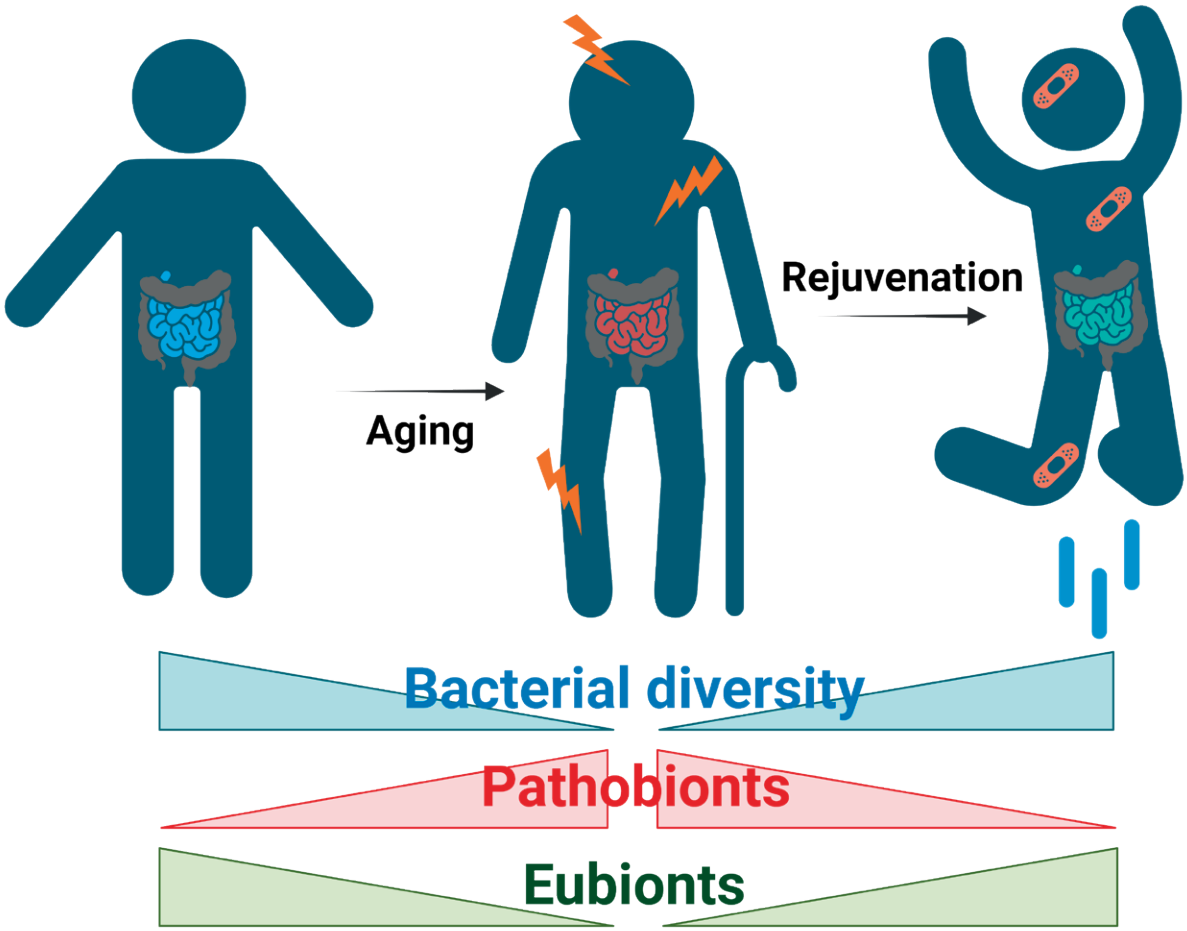

Graphical abstract: Aging induces a variety of disturbance in the whole body. The body microbiome plays an instrumental role in keeping our overall body homeostasis. Chronological aging induces changes in the microbiome composition, including decreased diversity of the microorganism population and appearance of opportunistic pathobionts (pathological, microorganisms). Rejuvenating therapies that aim to decrease age related morbidities also affect the microbiome and are able to restore its diversity, protect from pathobionts appearance and favors the growth of eubionts (beneficial microorganisms) which supports beneficial holistic effects. Created with BioRender.com.