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Aging, Frailty, and the Microbiome—How Dysbiosis Influences Human Aging and Disease


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The human gut microbiome is a collection of bacteria, protozoa, fungi, and viruses that coexist in our bodies and are essential in protective, metabolic, and physiologic functions of human health. Gut dysbiosis has traditionally been linked to increased risk of infection, but imbalances within the intestinal microbial community structure that correlate with untoward inflammatory responses are increasingly recognized as being involved in disease processes that affect many organ systems in the body. Furthermore, it is becoming more apparent that the connection between gut dysbiosis and age-related diseases may lie in how the gut microbiome communicates with both the intestinal mucosa and the systemic immune system, given that these networks have a common interconnection to frailty. We therefore discuss recent advances in our understanding of the important role the microbiome plays in aging and how this knowledge opens the door for potential novel therapeutics aimed at shaping a less dysbiotic microbiome to prevent or treat age-related diseases.

Keywords: Microbiome; Elderly; Age-related Diseases; Frailty; Inflammation.

Microbiome Changes Occurring With Aging

Health care systems in the United States are experiencing increased and unsustainable burdens due to their aging populations. Improving elder health is essential, as the proportion of people older than 65 years is increasing in many countries. In fact, at the current rate of increase, it is projected that by 2030 more 1 in 5 Americans will be older than 65.[1] Gut microbes occupy the interface between the external environment and the host, and interactions between the gut microbiota and humans occur at each stage of life; largely beginning soon after birth and continuing through old age (Figure 1). This sophisticated intestinal microbial ecosystem plays a pivotal role in an array of physiologic activities that are critical to human development and support health.[2] This ecosystem is also finely tuned because when the cooperation between our own cells and the gut microbes falter, the microbial community within the gut can become a source of infection, and at times can lead to life-threating diseases.

Healthy individuals have many different types of microbes, whereas individuals with poor health, or older people (elders), will often have a less diverse and a higher proportion of disease-causing microbes. Therefore, as we age, our "aging microbiome" can undergo a number of compositional changes that can adversely affect digestive health and absorption,[3,4] as well as immune function.[5] Dysbiosis is a term describing a microbial imbalance or maladaptation on or inside the body and can be defined as either the loss or gain of bacteria that promote health or disease.[6,7] A healthy non-dysbiotic microbiome works in a symbiotic fashion with its host to facilitate health by imparting critical protective functions (ie, pathogen displacement, nutrient competition, production of antimicrobials), structural functions (ie, barrier fortification, induction of immunoglobulin A, immune system development), and metabolic functions (ie, synthesis of biotin and folate, fermentation of nondigestible dietary products, energy salvation, ion adsorption, and control of intestinal epithelial cell differentiation and proliferation). Conversely, a dysbiotic, or maladaptive, microbiome has been associated with disease not only within the intestine[8–10] but also several other organ systems with a few examples including but not limited to the cardiovascular,[11,12] immune,[13,14] neurological,[15,16] and respiratory systems.[17,18]

Given the potential for the microbiome to influence a variety of dynamic disease processes, there is great interest

Abbreviations used in this paper: **AD, Alzheimer disease; APP, Aβ precursor protein; ARD, age-related disease; IL, interleukin; MDRO, multidrug-resistant organism; NH, nursing home; PD, Parkinson disease; P-gp, P-glycoprotein; αSyn, alpha-synuclein.**

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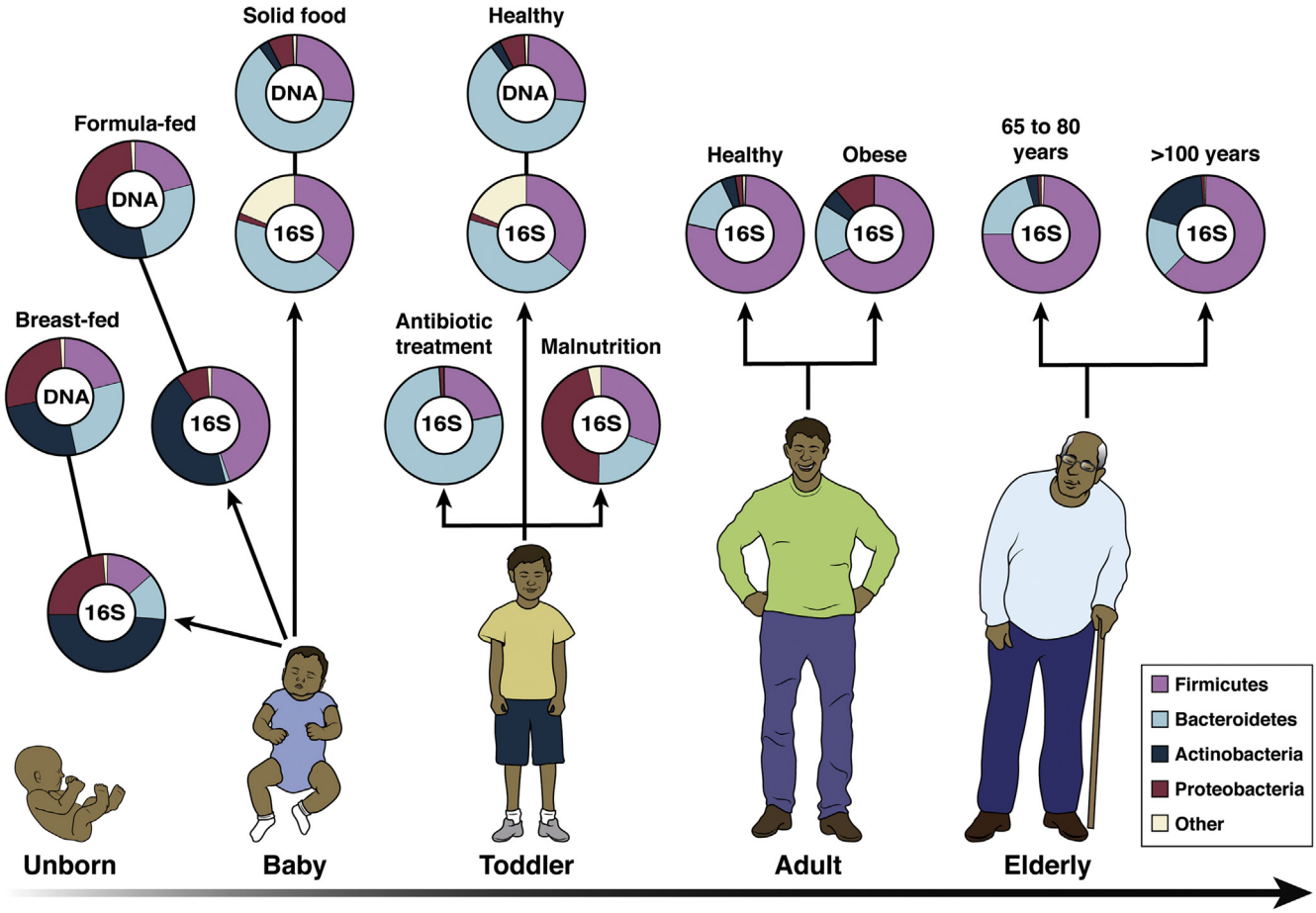

Figure 1. Human microbiota: onset and shaping through life stages. The graph provides a global overview of the relative abundance of key phyla of the human microbiota composition in different stages of life. Measured by either 16S RNA or metagenomic approaches (DNA). Data arriving from infants breast- and formula-fed (Schwartz et al,[163]), infant solid food (Koenig et al,[164]), toddler antibiotic treatment (Koenig et al,[164]), toddler healthy or malnourished (Monira et al,[165]), adult, elderly, and centenarian healthy (Biagi et al,[32]), and adult obese (Zhang et al,[166]).

to determine the composition of the gut microbiota of elders and to also characterize its variation as possible determinants of health.[19–23] This is particularly germane to the elderly and aging individuals because increasing age is aligned with age-related morbidities that affect the quality and quantity of life (eg, heart disease, stroke, hypertension, cognitive impairment, and cancer). However, the changes that occur within the intestinal microbiome as we age are not completely understood.

Animal model systems have clearly demonstrated that the presence of certain gut-associated microbes have an influence over cellular aging; an excellent model being the fruit fly *Drosophila melanogaster*.[24] Alterations in fruit fly microbiota composition have been linked to age-related intestinal barrier dysfunction, which also was found to lead to systemic immune activation, and eventually death.[25] In addition, elimination of certain microbes, without causing detrimental side effects, has been shown to increase the fly's life span.[26] More recently, Smith et al[27] used the short-lived African turquoise kill fish as another model to manipulate gut microbes in the study of longevity. Quite strikingly, this group found that when middle-aged fish were colonized with microbes transferred from younger fish, they lived longer and were significantly more active later in life than their control counterparts. It was also observed that middle-aged fish engrafted with the younger fish microbes retained a more diverse microbial community throughout their adulthood and shared key microbes with young fish; an observation inferred to also be associated with the improved health. Results from this study therefore suggest that the ability to control the composition of gut microbes can improve health and increase life span. Moreover, this model could be an important resource in providing new insights into how microbes can affect aging and to also delay the onset of age-related diseases (ARDs). Consistent with these findings, aging studies performed in other animal models and model organisms, such as in *Caenorhabditis elegans*[28] and mice[29,30] lend further support to the idea that microbiome modulation can lead to changes in the aging timeline with increasing evidence that such alterations can augment longevity. Collectively, these studies all point to the gut microbiome as playing a central role in the aging of the host.

Evidence of age-related changes in the gut microbiome are beginning to be described in different human aging

populations. Such studies, however, have been limited by the paucity of elders as a research group on top of challenges that involve elders with dementia as a research group or elders who live in nursing home (NH) settings. Nevertheless, age-related microbiome changes are being uncovered that show a decline in bacterial diversity, shifts in dominant species, and changes in beneficial microorganisms and metabolic pathways.[31–33] These changes are better resolved from a higher taxonomy approach where the major phyla of *Bacteroidetes* and *Firmicutes* switch in predominance with older adults having higher abundances of *Bacteroidetes* as compared with higher *Firmicutes* abundances observed in younger counterparts.[34] However, these observed shifts in composition do not stop at the phylum level; the species whose abundances are most prominently reduced in elders are the anaerobes,[31,35] specifically with lower levels of *Clostridium* cluster XIVa, *Faecalibacterium prausnitzii*, and Actinobacteria (mainly among the bifidobacterial genus).[32,34–39] Other key metabolic species shown to decrease with increasing age include *Akkermansia muciniphila*,[40] a mucin-degrading bacterium, *Ruminococcus bromii*,[41] a keystone species in degradation of starch, as well as a prevalent gut commensal, *Ruminococcus gnavus*.[32,33] Although these changes speak to an age-related dysbiotic microbiome, the variability in species abundance reported with age is likely due to external factors related to nationality, such as diet, environment, and life style.[42]

Apart from differences in nationality-based influences, elders living under different conditions also have been observed to differ in their microbiome structure. For instance, clear separations in microbiome signatures are noted between elders living in the community from those living in the NH setting.[43,44] In fact, there is a distinct time-dependent manner in which the microbiome changes after an elder moves into a new NH environment with community structural changes taking approximately 1 year to occur.[34] Although NHs in the United States provide services for elders that can be for custodial or skilled nursing in nature, these care settings also present an environment with frequent medication exposures, including antimicrobials, poorer diets, and increased pathogen prevalence, all which adversely affect the microbiome.[36,45–48] Microbiota differences between NH and community-dwelling elders, in general, include higher proportions of *Bacteroidetes* and lower proportions of various other bacteria at the family and genus levels.[36] Such changes in the bacterial populations among NH elders also represent loss of species that are associated with either a healthy or "youthful" microbiome.[20] Curiously, and contrary to initial impressions, the elder gut microbiome exhibits temporal stability, outside of changes in medications, antimicrobial exposures, or major changes in health status.[34,41] Each individual NH environment (such as floor/wing of residence) also plays a substantial role in shaping the microbiome,[49] which may help to inform decisions and impart important consideration when grouping frail elders together to live.

In step with taxonomy differences, the metabolic potential of the microbiome also changes with age. Among elders (after accounting for nutrition and frailty) the metabolic dysbiosis associated with increasing age includes decreases in mucin and starch degradation, essential amino acid synthesis, and decreases in nitrogenous base and vitamin synthesis.[41] Similarly, aging has been associated with a progressive loss of muscle mass (sarcopenia), which is linked to lower availability of essential amino acids.[50,51] Moreover, among elder groups it has further been observed that intestinal microbiome alterations not only reveal a loss of genes for short-chain fatty acid production but also show an overall decrease in the saccharolytic potential, which correlates with the presence of opportunistic pathogens.[52]

Medications Influence Microbiome Composition

A key influencer of the aging microbiome structure is medications. Many medications commonly prescribed in elders (comprehensive of both NH and community settings) are well known to have specific effects on microbiota composition. The best example of this is with antibiotic exposures where there is a profound loss in diversity and shifts in microbial taxonomy abundances.[48,53] Antibiotic exposures also lead to development of multidrug-resistant organisms (MDROs). This is a growing and significant health care problem among the elderly, especially those living in the NH environment. To date, there are an estimated 1.6 to 3.8 million infections per year in NHs [54,55] with as many as 400,000 resulting in death.[56] Unfortunately, infections with MDROs continue to rise in NHs,[56,57] and the mortality rate can be as high as 40% when an elder is hospitalized with an MDRO infection.[58]

Moreover, NHs in the United States have become the major reservoir for introduction of MDROs into other health care settings due to their uniquely high colonization prevalence.[59–61] Because the microbiome plays a pivotal role that is central to human health,[62] a healthy microbiome will, in turn, engage with the host immune system and contribute to pathogen resistance.[63] Antibiotic therapies markedly decrease the intestinal microbiota diversity and richness. This creates a vulnerable immunodeficient environment that can be exploited by both antibiotic-resistant pathogenic and opportunistic bacteria that are frequently encountered nosocomially in the hospital as well as in the NH setting. The most clinically significant antibiotic-resistant intestinal pathogens include gram-positive *C difficile* and vancomycin-resistant *Enterococcus faecium*, along with gram-negative bacilli belonging to the Enterobacteriaceae family.[64,65] Thus, the profound contributions made by commensal microbes toward resisting colonization and infection by pathogens are fundamental to host health and have long been observed. In spite of this, we are only now beginning to shed light on the molecular details underlying microbiome dysbiosis that occurs among elders and how this may be linked to pathogenic disease.[9,41] Therefore, how we feed, treat, and group frail NH elders may offer new approaches to prevent MDRO spread.

Nonantibiotic medications have also been associated with changes in microbiome composition, and approximately 24% of marked drugs approved by the Food and Drug Administration have been shown to inhibit at least one

Table 1. List of Microbiota Members by Genus or Species and the Published Disease Conditions With Which Each Has Been Shown to Have an Association

Genus/Species	Related disease conditions	Abundances in disease	References
Butyrate producers			
Anaerostipes	Alzheimer disease/ Cancer/ Colitis	Decreased	1–3
Butyricicoccus	Food allergy/ IBD	Decreased	4,5
Butyrivibrio	Age/ Alzheimer's disease/ Amyotrophic lateral sclerosis	Decreased	6–8
Blautia hansenii	Alzheimer's disease/ Autism/ Obesity	Decreased	9–11
Clostridial clusters IV and XIVa	Cystic Fibrosis/ IBD/ Multiple Sclerosis/ Parkinson's	Decreased	12–15
Clostridium saccharolyticum	Alzheimer's disease/ Parkinson's disease	Decreased	16,17
Eubacterium species	Alzheimer's disease/ Crohn's disease/ Kidney stones	Decreased	18 19–21
Faecalibacterium prausnitzii	Alzheimer's disease/ IBD/ Parkinson's/ Psoriasis	Decreased	20,10,15,27,28,22–24
Roseburia hominis	Allergies/ Autoimmune diseases/ Diabetes Type 2/ Ulcerative Colitis	Decreased	12,24,25
Ruminococcus obeum	Age/ Liver Disease Obesity	Decreased Increased	26,27 28
Ruminococcus bromii	Age/ Crohn's disease/ Parkinson's disease	Decreased	29–31
Lachnospiraceae bacterium	Diabetes / HIV/ Obesity/	Increased	32,33
Frailty associated			
Eggerthella lenta	Autoimmune/ Intestinal Infections	Increased	34,35
Eubacterium dolichum	Obesity	Increased	36,37
Methanobrevibacter	IBD	Decreased	38,39
Ruminococcus gnavus	Age/ Allergies/ Crohn's disease/ Lupus	Increased	31,40–42
Malnutrition associated			
Bifidobacterium	Antibiotic-associated diarrhea/ Cancer/ Eczema/ Ulcerative colitis	Decreased	43–47
Citrobacter freundii	Opportunistic pathogen	Increased	31,48
Enterococcus faecalis	Hospital-associated infections	Increased	31,49
Roseburia intestinalis	Anti-inflammatory/ Arthrosclerosis	Decreased	50,51
Inflammation /Autoimmune			
Adlercreutzia equolifaciens	Multiple Sclerosis/ Primary sclerosing cholangitis	Decreased	52,53
Akkermansia muciniphila	Age/ Obesity/ Psoriasis/ Type 1 diabetes	Increased Decreased	54–56 31,57
Bacteroides dorei	Autoimmune Diseases/ Type 1 diabetes	Increased	58,59
Bacteroides vulgatus	Autism/ Autoimmune diabetes	Increased	54,58,60,61
Collinsella	Alzheimer's disease/ Rheumatoid arthritis	Increased	8,62
Desulfovibrio fairfieldensis	IBD/ Obesity	Increased	63,64
Firmicutes bacterium	Obesity/ Type 2 diabetes	Decreased	65,66
Odoribacter splanchnicus	Hypertension/ IBD/ Lupus	Decreased	67–69
Parabacteroides distasonis	Multiple sclerosis/ Obesity/ Rheumatoid arthritis	Decreased	70–72
Pathogens			
Bacteroides fragilis	Alzheimer's disease/ Cancer/ Diarrhea/ Infections Multiple Sites	Increased	73–76
Campylobacter jejuni	Autoimmune/ Gastroenteritis/ Neurodegeneration	Increased	77–79
Cloacibacillus porcorum	Alzheimer's disease/ Bacteremia	Decreased	80–82

Table 1. Continued

Genus/Species	Related disease conditions	Abundances in disease	References
Desulfovibrio fairfieldensis	Bacteremia/ IBD	Increased	83,84
Klebsiella pneumonia	Alzheimer's disease/ Autoimmune/ Infections multiple sites	Increased	85–89
Peptostreptococcus anaerobius	Colorectal Cancer/ Multiple infections/ Septicemia	Increased	90,91

NOTE. This list is based off of literature review of these microbiome members and organized into general categories that influence elder health. It is not intended to capture all of the published literature on each member but provide references to some of the relevant literature available.
HIV, human immunodeficiency virus; IBD, inflammatory bowel disease.

common intestinal microbiome bacterial strain.[66] The relative abundances of many microbiome members and changes noted during disease processes is extensive (Table 1). Furthermore, the effects of some nonantibiotic medications such as proton pump inhibitors,[47,67,68] statins,[69–71] nonsteroidal anti-inflammatory drugs,[72] and atypical antipsychotics[73–76] on the intestinal microbiome have been described only in healthy younger adults. Common among the elderly are the use of medications belonging to these classes as well as the mixture of these drugs in an individual. The combination of medications especially in excess, known as polypharmacy, is widespread in elders and has its own adverse effect on the microbiome and elder health.[77,78] Indeed, polypharmacy is especially prevalent in the NH where more than half of the residents are on 5 or more daily medications.[79]

Role of Modulating the Microbiome to Improve Longevity

Taxonomy does inform and influence metabolic potential of the gut microbiome. Therefore, given that microbiome components change with age, it may offer an opportunity to intervene and slow or even reverse such age-related changes. In humans, centenarians have been used as a model for healthy aging studies because of their ability to delay, or even avoid, chronic diseases,[80,81] and in addition their genetics have been extensively studied.[82] However, to date only a few studies have interrogated the gut microbiome of this coveted population. To gain insight into which gut microbiome signatures are associated with longevity, Kong et al[83] recently characterized the microbiota of a group of long-living (90 years of age or older) from the Dujiangyan region of China; 1 of 5 "longevous counties" in China. Comparing the gut microbiota in this long-living cohort with that of a younger adult group, Kong and colleagues[83] found that the long-living group had a greater gut microbiome diversity than the younger adult group.

These results were not only validated using data from an independent Italian cohort that also included a group of long-living individuals[32,84] but was also supported by 2 additional recent studies.[37,85] Deeper characterization of the microbiota in the long-living cohort by Kong et al[86] showed enrichment of several potentially beneficial bacterial taxa that are known to be short-chain fatty acid producers. Curiously, this result was coupled with a decrease of certain operational taxonomic units commonly associated with beneficial bacteria, such as *Faecalibacterium*, and an increase of some operational taxonomic units related to potential bacterial pathogens (eg, *Escherichia* and *Shigella*). Although it is too premature to draw any causal relationships between gut microbiota and healthy aging, this observational study does provide an important clue to suggest that maintaining a diverse and balanced gut microbiome may be a key contributor to healthy aging. All the same, whether one can modulate the intestinal microbiome to specifically target and promote healthy aging is an important question that needs to be carefully addressed. More specifically, because increasing age also engenders age-related morbidities that affect the quality and quantity of life (eg, heart disease, stroke, hypertension, cognitive impairment, and cancer), understanding how the aging microbiome affects these disease processes is critical to improving human health via the gut microbiome beyond just prevention of opportunistic pathogens.

The first association between microbes and healthy aging was made by Elie Metchnikoff, one of the founding fathers of modern microbiology and immunology. In 1908, he not only shared the Nobel Prize for Medicine with Paul Ehrlich but also published one of the most impactful books of that era entitled *The Prolongation of Life* (Metchnikoff, 1908). In this book Metchnikoff develops the concept that higher animals need an increasingly complex intestine to struggle for existence, and distinguished 2 types of metabolism for gut bacteria: (1) putrefaction that resulted in noxious metabolites as waste products, and (2) fermentation that resulted in beneficial metabolic end-products like lactic acid. To combat the process of putrefaction in the gut, he recommended improvements in diet and championed the notion that the fermentative metabolism of lactic acid bacteria would counterbalance putrefaction by the noxious gut bacteria and their toxic effect on our tissues. He backed these concepts by the observation that populations showing traditionally high yogurt consumption also showed increased longevity. More than 100 years later, modulation of the microbiome by either diet or probiotic interventions is evidenced in animal models supporting the tantalizing hypothesis that host longevity can be lengthened by shifting

microbiome communities.[87] Although this potential among humans is still relatively unexplored, and can be complicated by individual heterogeneity, it does tender a unique and potentially promising strategy to influence the aging process.

Inflammation and Age-related Diseases

One of the basic mechanisms shared in ARDs and geriatric syndromes is chronic low-grade inflammation called inflamm-aging.[5,88] ARDs are diseases that increase in incidence exponentially with age and include disorders such as atherosclerosis, diabetes, hypertension, cancer, and Alzheimer disease (AD).[89,90] Chronic upregulation of proinflammatory mediators (eg, tumor necrosis factor-α, interleukin (IL)-6) have been shown to be induced during the aging process. These proinflammatory mediators activate many signaling pathways[91] that have a dramatic impact on immune function, which leads to a gradual deterioration of the immune system, called immunosenescence.[14,92] Currently, both inflamm-aging and immunosenescence are thought to be responsible for most ARDs (and not just by the increased risk of bacterial infections) and are fertile ground for novel interventions to promote healthy aging.[93] Dysbiosis of the gut microbiome can serve as a catalyst for fueling inflamm-aging (Figure 2).[14] However, the contribution of dysbiosis in the context of the human microbiome interaction particularly regarding its impact on systemic immune functioning or deterioration of this function among the elderly as it relates to ARDs has not been rigorously studied.[13]

Nevertheless, there is a growing body of literature that implicates age-related dysbiosis of the gut microbiome as contributing to a global inflammatory state in the elderly.[94,95] For example, neuroinflammation, one result of immunosenescence, has long been thought to promote progression of several neurological disorders, including AD and Parkinson disease (PD).[96,97] Both acute and chronic systemic inflammation are associated with declining cognitive function in AD.[98] To put this in perspective, more than 46 million people worldwide live with dementia, and this number is predicted to double in the next 20 years[99] with an alarming projection of 3.3% of the US population being affected by AD.[100] Both inflamm-aging and immunosenescence have been well described in patients with AD.[101–104] The inflammatory response that accompanies AD pathology is hallmarked by higher peripheral concentrations of cytokines IL-6, tumor necrosis factor-α, IL-1β, transforming growth factor-β, IL-12, and IL-18.[101] Moreover, both the innate and acquired immune systems have been shown to be altered in AD.[105–107] For instance, patients with AD exhibit decreased levels of naïve T cells, along with elevated memory T-cell populations,[108] and higher percentages of activated CD4+ CD25+ T cells.[103] Such variances in T-cell populations, which are common in patients with AD, denote a heightened differentiated T-cell state. This is consistent with an adaptive immune system undergoing persistent antigen exposure and dysregulation of the naïve/memory T-cell balance.[108]

One area coming into focus as a potential driver of this proinflammatory state is the intestinal microbiome. The dysbiotic intestinal microbiome has been shown to induce systemic inflammation that triggers neuroinflammation leading to cognitive impairment.[109] Glial cell phenotypes are known to be profoundly modulated by peripheral inflammatory stimuli, including those due to dysbiosis of the gut microbiota.[110,111] Increased abundance of proinflammatory, with reduced abundance of anti-inflammatory, bacteria in the intestine also has been shown to be associated with systemic inflammatory states in patients with cognitive impairment and brain amyloidosis.[112] With respect to the AD-intestinal microbiome interaction, AD pathogenesis has long been thought to be linked to chronic bacterial infections as a possible etiology.[113] More recent 16S-based studies have found significant changes in the abundance of certain taxa in patients with AD compared with healthy controls,[114,115] and one of these studies also linked microbiota composition back to AD cerebrospinal fluid biomarker levels.[114] Thus, one prevailing theory is that AD pathogenesis is closely related to the imbalance of the gut microbiome and, in fact, may originate in the gut.

Although the role of microbes in promoting the inflammatory causal pathway of AD is becoming increasingly recognized,[113,116,117] it is yet to be established. In taking a step toward addressing this goal, studies performed by Harach et al[118] were among the first to report that gut microbes play a role in the development of cerebral Aβ amyloidosis in patients with AD. A key finding in this study was the dramatic shift in the gut microbiota of Aβ precursor protein (APP) transgenic mice as compared with non-transgenic wild-type mice. In addition, they also observed a profound reduction in cerebral Aβ amyloid pathology when APP transgenic mice were raised in a germ-free environment as compared with control mice, which harbored an intestinal microbiome. This observation was further supported by demonstrating that colonization of germ-free APP transgenic mice with microbiota from conventionally raised APP transgenic mice increased cerebral Aβ pathology, whereas colonization with microbiota from wild-type mice was much less effective. In summary, these findings reveal the potential of microbial involvement in the development of Aβ amyloid pathology, and more generally suggest that microbiota may contribute to the development of neurodegenerative diseases.

More recently, our group has reported findings among a cohort of NH elders that demonstrates a dysbiotic pattern is seen when comparing AD elders with those with no dementia.[16] Such dysbiosis is characterized by a reduction in the proportion and prevalence of bacteria with the potential to synthesize butyrate, an essential metabolite in the human colon with anti-inflammatory properties, as well as an acquisition of taxa that are known to cause proinflammatory states. Consistent with these changes, we also demonstrated how the "AD microbiome" can adversely affect intestinal epithelial homeostasis via dysregulation of P-glycoprotein (P-gp). P-gp is a critical mediator of intestinal homeostasis,[119] and when downregulated, can lead to a proinflammatory state (Figure 3). The bacterial species that

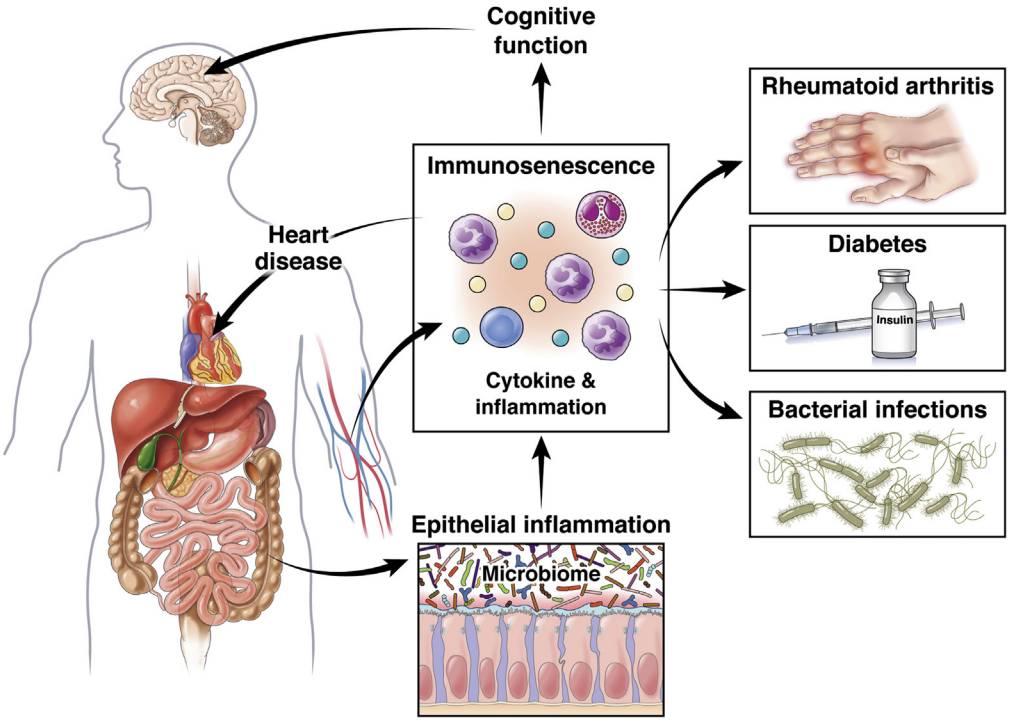

Figure 2. Inflamm-aging and related ARDs. The intestinal microbiome has been linked to disorders of the brain, heart, endocrine, musculoskeletal, and immune systems. This is an overview of the sections along the inflamm-aging to age-related disease pathways.

differentiates the microbiome of AD from elders without dementia was also found to be predictive of lower P-gp expression levels among patients with AD. These species are key butyrate producers and include members of the *Eubacterium*, *Clostridium*, and *Butyrivibrio* genera,[120] as well as bacteria known to associate with proinflammatory states in the intestines, such as *Bacteroides dorei* and *Akkermansia glycaniphila*.[121] Therefore, the microbial members found to best predict the observed lower P-gp expression in patients with AD are all known to influence colonic inflammation in other pathological states. We are just beginning to disentangle the complex interplay involved in the gut-brain axis. Hence, a deeper understanding of the taxa and the role these microbial communities play in contributing to the progression of AD (as well as other neurodegenerative diseases) is needed to help advance our knowledge of causal relationship between dysbiosis and cognitive decline with the ultimate goal of preventing or halting disease.

The gut microbiota also has been found to regulate motor deficits in neuroinflammation in a murine model of PD.[122] Motor dysfunction in patients with PD is often characterized by aggregation of the protein alpha-synuclein (αSyn). Sampson et al[122] used a mouse model that overexpresses αSyn to demonstrate that gut microbiota is required for motor deficits, microglia activation, and αSyn pathology. In this same study, colonization of αSyn-overexpressing mice with microbiota from PD-affected patients was also found to enhance physical deterioration as compared with microbiota engrafted from healthy human donors. Although the mechanism by which gut microbes affect the progression of PD is not well understood, the recent finding that αSyn is found in gut endocrine cells before appearing in the brain supports the contention that PD pathology originates first in the gut and then may spread to the central nervous system in a manner analogous to cell-to-cell prion-like propagation.[123]

Other ARDs share a similar inflamm-aging/immunosenescence profile that may have origins in the inflammatory type dysbiosis of the gut. For example, Fransen et al,[29] when transferring aged microbiota to young germ-free mice, identified certain bacterial species within the aged microbiota that promote inflamm-aging. This effect was primarily associated with lower levels of *Akkermansia* and higher levels of TM7 bacteria and *Proteobacteria* in the aged microbiota after transfer. Such changes in the microbiota composition correlated with intestinal inflammation predominantly in the small intestine, leakage of inflammatory bacterial components into the circulation, and increased T-cell activation in the systemic compartment.[29] In other examples, inoculation of mice with fecal samples from patients with rheumatoid arthritis promoted development of rheumatoid arthritis in the arthritis-prone mice via a Th17-dependent manner.[124] Likewise, gut dysbiosis has been shown to contribute to systemic homeostasis disruption and subsequent proinflammatory pathways leading to obesity, B-cell decline, and type 2 diabetes.[125] Lipopolysaccharides and other microbial factors promote inflammatory signaling and skeletal muscle changes that are also the hallmarks of the aging muscle phenotype.[126] Finally, there is even an emerging, yet unproven, contributing role for the human microbiome in the cause and development of multiple different cancer types.[127] Therefore, different forms of dysbiotic-induced inflammation, commencing locally and then exerting effects systemically, just might serve as the initiation and/or driver of many ARDs that pose significant burden to healthy human aging.

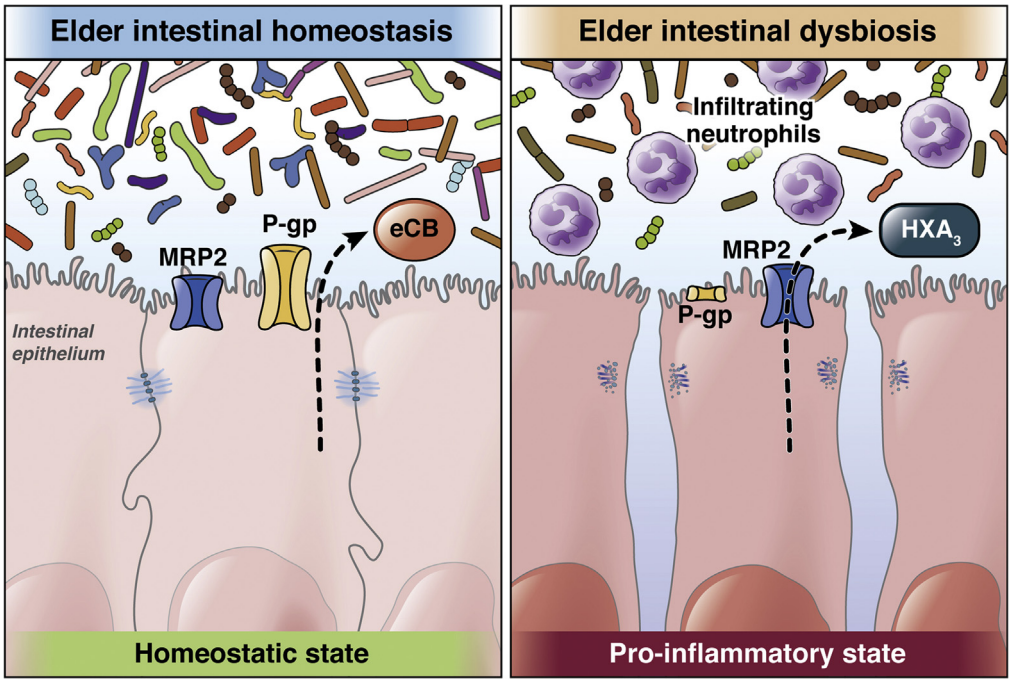

Figure 3. The MRP2/HXA_3 (hepoxilin A3) axis forms the proinflammatory arm of a dynamically regulated system in which inflammatory pathways that activate responses to pathogens or aberrant signals are balanced against the anti-inflammatory P-glycoprotein (P-gp)/endocannabinoid (eCB) pathway that suppresses neutrophil responses in the context of normal commensal colonization. The 2 sets of lipid-based signaling molecules (eCB and HXA_3) are released from the apical surface during periods of either tolerance or inflammation, which control the recruitment of neutrophils to the intestinal lumen. Dysregulation of this critical balance may contribute directly to inflammatory disorders of the intestine.

Is the Microbiome Frailty Connection a Linchpin to Other ARDs?

Frailty is a state of increased vulnerability and poor resolution of homeostasis following a stressful event to the elder.[128,129] Frailty is highly prevalent in community-dwelling elders[130] but is especially high in NH populations, with as many as 50% of elders being frail and an additional 40% meeting a prefrail definition.[131] Fried et al[128] provided one of the first operational definitions of frailty as meeting 3 of 5 phenotypic criteria indicating compromised energetics: low grip strength, low energy, slowed waking speed, low physical activity, and/or unintentional weight loss. Since then many other scoring systems have emerged that are easier to apply clinically.[132,133] But even with all of these established parameters there remains a lack of a gold standard in defining an older adult as frail.[134–136] Nevertheless, regardless of the instrument tool used to measure frailty, elders defined as frail have a clear increased risk of mortality among elders in the emergency department,[137] admitted to the hospital,[138] or living in either the community[139,140] or NH[141,142] settings.

This complex process, which is linked closely with aging, involves a decline in a constellation of physiological systems that leads to increased vulnerability and disproportionate changes in health status following even a minor stressor event.[143] Outside of the relatively few medical causes (eg, medications, nutrition, or lack of exercise) the cause of frailty remains poorly understood.[136,143,144] An emerging theory of a cause of frailty, however, ties back to inflammaging and the development of immunosenescence. As with other ARDs, frailty also has associations with immune dysfunction and inflammation, with a complex altered production of inflammatory cytokines.[145,146] Nestled within this theory is an association to the gut microbiome; however, studies linking dysbiosis to frailty have been relatively unexplored.[147] What is known is that frailty is hallmarked by a loss of microbiota diversity and specific taxonomic associations, such as increased abundances of *Eubacterium dolichum* and *Eggerthella lenta* and decreases in *Faecalibacterium prausnitzii*.[21] In NH elders, this is associated with losses of community-dwelling associated microbiota[36] that specifically involves a dysbiotic pattern where there is a loss of butyrate-producing organisms coupled with an increase in abundances of inflammation-associated organisms, as well as an increase in lipopolysaccharide biosynthesis and peptidoglycan biosynthesis metabolic pathways.[41] Given the important connection to clinical outcomes and health-related quality of life in elders, combined with emerging theories and lack of any mechanism to treat frailty, the gut microbiome may hold a vital key to improving healthy aging.

Challenges and Opportunities to Improve the Elder Microbiome

The identification of gut microbiome associations with diseases in the elderly opens up the door for interventions to improve or prevent diseases. These microbiome-based

interventions have lagged behind studies of younger-aged populations, but offer a great opportunity to improve human health given the increasing aging population and the burden of disease among elderly individuals. Microbiome-based interventions have traditionally focused on probiotics, typically lactobacilli and bifidobacterial, or prebiotics with nondigestible oligosaccharides.[148] Clinical trials among elder participants have demonstrated not only the ability to manipulate the gut microbiome but also the safety among this population in doing so.[149] However, clinical efficacy in this regard is yet to be well substantiated.

Advancing clinical trial work focused on manipulating the microbiome would avail new opportunities with the potential to address a wide range of disease processes. Lactobacilli, historically, have been one of the most chronicled probiotics studied. Since its first isolation from the feces of a normal healthy individual in 1987, *Lactobacillis* has been used for a wide variety of clinical indications. In healthy individuals it temporarily colonizes the distal gastrointestinal track and positively affects the resident microflora.[150,151] In addition, *Lactobacillis* has been used in clinical trials addressing diarrhea from use of antibiotics[152,153] to travelers' diarrhea[154] and diarrhea from autoimmune causes.[155] Outside of gastrointestinal disorders, *Lactobacillis* has been used to prevent urinary tract infections,[156] to treat rheumatoid arthritis,[157] as an immune modulator for vaccine administration,[158] and as preventive treatment in intensive care unit patients.[159] Beyond *Lactobacillis,* other probiotic bacteria and bacterial combinations have been tested as a therapy to treat a multitude of human disease, many of which are age-related. Clearly, probiotics have a track record and potential to treat multiple disease processes that needs to be soundly tested in elder populations.

However, most probiotics are manufactured as food, which makes it challenging to ensure the quality and safety of these products as novel therapeutic agents. The basic issues of dosing, safety, and mechanism of action of these agents still need to be worked out because it is still unclear which bacterial strains hold benefit under different disease conditions. With the emergence of multistrain probiotics onto the market and the premise of engineered microorganisms for designer probiotics, it is even more crucial to move forward our understanding of how food and probiotics can influence exact mechanistic action on the microbiome and also necessitates a better understanding of the elder microbiome in health and disease.

Among elderly individuals, dietary interventions have shown promise in addressing some of the most devastating ARDs, such as AD. Large epidemiological studies have shown that healthy eating is protective against dementia and cognitive decline, which has been proven with diet interventions such as the MIND diet in AD.[160] Large-scale interventions, such as the Finnish FINGER trial are under way and show promising results in preventing AD.[161] Although the exact mechanism of these dietary interventions is not well known, there is mounting evidence that the gut microbiome alterations that occur during a dietary intervention may be the driving force behind the improved outcomes in AD.[95,162] In this regard, it is important for us to have a better understanding of how dietary interventions change the microbiome and if these changes are the primary drivers that improve AD symptomology. Whether the microbiome acts as a mediator or the primary agent in the causal pathway during a dietary intervention is still unclear; however, unraveling this mystery would greatly help us to understand the pathophysiology and treatment of cognition decline via the gut-brain axis.

The future of microbiome research is full of exciting possibilities. There is a wealth of evidence that links the gut microbiome to healthy human development and how dysbiosis of the microbiome leads to disease. It is now being increasingly recognized that it may not be the abundance of individual bacterial populations that drives a disease process, but the collective microbiome (ie, microbial consortia of functional genes and pathways) and its metabolites termed the "functional core microbiome" that may hold the key to understanding increased susceptibility to diseased states. Clinically, how we can alter the "functional core microbiome" in disease prevention or treatment still has a long way to go before it is put into practice.

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