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The Gut Microbiome and Frailty

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Abstract

The human microbiome is constituted by an extensive network of organisms that lie at the host/environment interface and transduce signals that play vital roles in human health and disease across the lifespan. Frailty is a critical aging-related syndrome marked by diminished physiologic reserve and heightened vulnerability to stress, predictive of major adverse clinical outcomes including death. While recent studies suggest the microbiome may impact key pathways critical to frailty pathophysiology, direct evaluation of the microbiome-frailty relationship remains limited. In this article, we review the complex interplay of biological, behavioral and environmental factors that may influence shifts in gut microbiome composition and function in aging populations and the putative implications of such shifts for progression to frailty. We discuss HIV infection as a key prototype for elucidating the complex pathways via which the microbiome may precipitate frailty. Finally, we review considerations for future research efforts.

Introduction

There have been notable gains in life expectancy across the globe over the last century, with projections for future gains across many countries in the coming decade.¹ With aging populations has come an increasing burden of aging-associated conditions and aging-related syndromes. Frailty is a critical aging related syndrome of major public health importance that precipitates substantive disparities in health outcomes across aging populations worldwide.^{2,3} Frailty is characterized by dysregulation across multiple core physiologic systems. Understanding upstream determinants of such dysregulation is critical to developing novel and effective frailty-targeted interventions.

With recent advances in molecular techniques, there has been notable expansion in the investigation of the role that the human microbiome may play in health and disease. While these studies suggest that the microbiome may significantly influence several core frailty

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pathophysiologic systems, direct studies of the role of the microbiome in frailty have been limited.

Here, we first will introduce key microbiome concepts and factors identified as having influence on microbiome constitution. We will discuss how microbiome biology and frailty pathophysiological pathways may intersect. We will examine HIV as a prototype for investigation of the microbiome-frailty relationship. Finally, we will discuss opportunities for microbiome modulation as a putative intervention for frailty and future research needs. For this review, our primary focus will be on factors related to the gut microbiome.

Microbiome in health and disease

Microbiome composition

The human host is inhabited by an extensive network of microbial organisms (microbiome) considered essential to maintaining vital functions of a healthy host. This network consists of trillions of organisms at the host/environment interface, including the skin, urogenital tract, respiratory tract and gastrointestinal system.⁴

The human microbiome consists of communities of bacteria, viruses, fungi, protozoa and archaea.⁵ Microbiome composition varies between different host compartments and even along the course of a single host compartment.^{6,7} The gastrointestinal compartment has been one of the most extensively studied and hosts the largest proportion of human microbes, containing 5 primary bacterial phyla - *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria* and *Verrucomicrobia*.⁸ While phyla composition across healthy adults is similar, significant interindividual variation occurs at the genus and species levels.^{9,10} Viral microbiome components including bacteriophages, chromosomal elements and those that infect human cells, as well as fungal, protozoan and archaeal elements have been less well studied.¹¹

Microbiome function

The human microbiome is critical for a range of key host physiologic functions, including host energy metabolism, drug metabolism, and body defense.^{6,12,13} The human microbiome exerts its effect through an integrated gene pool encoding critical metabolic pathways that mediate host-microbe interactions and signaling to human physiologic systems.^{7,8,14} The microbiome signals through microbial components or microbially derived metabolites that engage with neural, endocrine, immune and metabolic systems.⁸

Analyzing microbiome composition and function

Culture independent 16S rRNA sequencing techniques are among the most commonly used methodologies for evaluation of the bacterial microbiome composition. Through imputed methodology of 16S rRNA sequencing output, some aspects of microbiome function may be inferred. However, there is not always full correlation between the imputed and actual microbiome metagenome. More direct evaluation of microbiome function can be achieved through high throughput DNA sequencing methods, evaluation of RNA transcripts via metatranscriptomics, protein content and activity via metaproteomics, and

metabolite content and processes via metabolomics.¹⁵ Evaluation of the virome (viruses) and mycobiome (fungi) may require more targeted techniques, such as directed viral PCR and pan fungal internal transcribed spacer sequences.¹¹

Through these modalities, one can identify the number of taxa present in the microbiome ecological community (richness); relative abundance of taxa (evenness); and diversity, a combined measure of richness and evenness. Diversity within 1 sample type or community (alpha diversity) and differentiation in microbiome constitution between sample types or ecologic niches (beta diversity) are key outputs.

Additional data reduction techniques exist to facilitate methodological evaluation of microbiome relationships in health and disease.¹⁶ The altered state of the microbiome associated with disease has been termed dysbiosis, though what constitutes “dysbiosis” is debated and may differ depending on the disease state and the microbiota described.¹⁷

Several animal models facilitate extension beyond associative studies in evaluation of the microbiome compartment. Among the most commonly applied are germ free mice. Germ free or gnotobiotic mice are mice that are sterile or free of all microbial life including bacteria, viruses, fungi, archaea and protozoa. They provide an effective platform for the direct functional investigation of defined microbial communities, and serve as a key translational model for causal evaluation of the role of the gut microbiome in health and disease.¹⁸

Factors that impact microbiome composition and function

Employing the aforementioned modalities, both intrinsic and extrinsic factors impacting microbiome composition and function have been identified. These factors may be heterogeneous across individuals and may evolve over the human lifespan. Here, we will describe factors that influence the microbiome with particular focus on the gastrointestinal microbiota, for which the most robust data on the microbiome relationship to aging-related conditions exist to date.

Early development of the microbiome

Early microbiome development is influenced by maternal factors, including mode of delivery, maternal antimicrobial exposure, mode of feeding (breast vs. formula), and gestational age at birth.^{8,19} Low alpha diversity and high interindividual variability exist in early infancy.¹⁹ With the shift from breast feeding, increased diversity and a shift to a more adult-like core microbiota occurs.^{8,19}

Intrinsic/genetic factors

Host genetics significantly influence the microbiome, with substantial heritable elements observed.^{20,21} Microbiome constituents between family members are more similar than between unrelated individuals, and are more similar between monozygotic than dizygotic twins.²⁰ Genes suggested to play a role in gut microbiome constitution include those involved in innate and adaptive immune pathways.²²

Diet

Substantial shifts in gut microbiome composition occur with differential dietary intake.^{23–27} Characteristic gut microbial enterotypes have been defined in association with long term dietary patterns.²⁸ Transient changes in the gut microbiome occur with transient changes in diet but such changes revert to baseline soon after diet reversion.²⁹ In general, intake of high levels of saturated fat, high sugar, and low fiber diets have been associated with a less diverse and a more pro-inflammatory microbiome.^{30,31} Conversely, the microbiome and its metabolites may influence dietary intake through signaling to appetite-controlling hypothalamic centers.³²

Geography

Distinct microbiome clustering has been observed by residence, including country of origin, urban vs. rural setting, and even floor residence location.^{24,33–36} From these studies, a role for residence environment and culture on microbiome composition has been inferred.

Disease states and medication treatment

Disease states and the associated medications used for their treatment also can influence microbiome constitution. Antimicrobial agents exert particular influence.³⁷ Antibiotic-mediated shifts in the gut microbiome can be relatively rapid with decreases in microbiome diversity within 3–4 days. The consequent shifts can last weeks to months and possibly even longer.^{38,39} Other therapeutic agents can influence microbiome constitution by altering luminal pH or mucosal structures leading to selection of specific taxa.^{40,41} Some medications may exert a bacteriostatic or bactericidal effect despite their not falling under classification as antimicrobial therapeutics.^{42,43}

Polypharmacy, the use of multiple drugs in a single person at the same time, also has been associated with decreased microbiome diversity and dysbiosis. Multimorbidity, the co-occurrence of multiple comorbid conditions, is a primary determinant of polypharmacy, and can significantly influence microbiome constitution as well.^{44–46}

Environmental, lifestyle and behavioral factors and brain-gut axis

The microbiome demonstrates plasticity in response to a range of environmental and lifestyle or behavioral factors and may play a key role in transducing such signals for the host.^{22,47} Data suggest socioenvironmental factors and health behaviors may positively or negatively impact the host through microbiome-related pathways. Gut microbiome composition has been found to shift across different socioeconomic strata.^{48–50}

Stress-inducing social factors also may impact the microbiome via the brain-gut axis. In this construct, activation of physiologic stress response systems, such as the hypothalamic-pituitary-adrenal (HPA) axis, may influence microbiome composition. Further, a feedback loop in which gut microbiota produce neuroactive metabolites that may modulate gut-brain signaling via neural and endocrine pathways has been postulated, with potential impact on mood and leading to other neuropsychiatric consequences.^{4,8,51,52}

Other lifestyle factors, including alcohol and tobacco use may influence microbiome composition.^{53–56} Opiate use has the potential to alter gut motility, the latter associated with gut dysbiosis.^{57–59} Gut dysbiosis also may adversely influence behavioral responses to drug use by augmenting a negative feedback cycle to sustain active drug use and further promote deleterious microbiota changes.⁶⁰

Reduced exercise and low physical activity have been associated with unfavorable changes in microbiome composition.^{46,61} Conversely, exercise or increased physical activity has been associated with increased microbiome diversity, as well as increased abundance of several organisms and microbial metabolites with putative beneficial health impact.^{62–66} These positive microbiota-related changes have been reported to dissipate with an individual's transition back to a sedentary lifestyle.⁶⁷

Microbiome in disease

Numerous studies have noted reduced gut microbiome diversity to be associated with disease or ill health.^{68–72} Alterations in microbiome composition and function have been reported in many conditions including obesity, insulin resistance, non-alcoholic fatty liver disease/non-alcoholic steatohepatitis, type 2 diabetes, atherosclerosis/thrombosis and stroke, allergic asthma, autism spectrum disorder, anxiety, depression, colorectal cancer, inflammatory bowel disease, systemic lupus and other autoimmune disorders.^{8,17,19,23,73,74}

The potential causal role of the microbiome in disease pathogenesis across these states has been supported in multiple cases by germ free mice adoptive transfer models.^{9,75,76} Ultimately, microbiome-related pathways have been associated with many of the leading disease-related causes of death, many of these aging and inflammatory-related conditions.⁴

Frailty and Heterogeneity of Aging

Frailty is a critical aging-related syndrome, marked by a cumulative loss in physiologic reserve with diminished homeostasis, decreased resilience and heightened vulnerability to stress, precipitating major adverse clinical outcomes including increased hospitalization, institutionalization and death.^{2,77–79} While aging-related, frailty is not equivalent to chronologic age, reflecting the heterogeneity of the aging process between individuals.

Multiple instruments have been developed over the last several decades for frailty assessment.⁸⁰ While there has been no definitive gold standard measure, the physical frailty phenotype (PFP) first operationalized by Fried and colleagues has been most commonly applied in the research literature to date. This phenotype is composed of 5 primary domains – weight loss, exhaustion, muscle weakness, low physical activity, and slow gait. Meeting 3 or more of these criteria classifies an individual as frail.^{2,81}

Of other frailty instruments, the deficit accumulation index (DAI) construct also has been commonly applied.^{82–86} While differing somewhat in operationalization and conceptual basis, both the Fried PFP and the DAI are strongly predictive of significant adverse health outcomes in older adults.^{81–85,87} Given this association, frailty remains a key target for reducing the marked disparities in health outcomes that exist across populations.

Frailty biology

Understanding the biological pathways to frailty is critical to developing effective interventions to reduce frailty-related disparities in health outcomes. Studies of frailty biology have found associations with a range of aberrant, dynamic, multisystem physiologic stress responses among older adults, affecting neuroendocrine, metabolic, and musculoskeletal systems.^{77,88–91} Dysregulated immunity and inflammation have emerged as particularly prominent components of aberrant responses in frailty biology.^{91–97}

Role of inflammation and immune dysregulation in frailty pathogenesis

Markers of inflammation increase with age. Heightened inflammation has been significantly associated with a range of prevalent and incident age-associated disease conditions.^{98–104} Heightened inflammation also has been strongly associated with premature mortality in aging populations.^{98,102,103} Multiple studies in older adults have demonstrated a significant association of dysregulated inflammation with frailty.^{105,106} There have been multiple proposed drivers of heightened inflammation in aging populations. Dysregulated systemic immunity and disruption of immune homeostasis at the host/environment interface can play a key putative role in this regard.^{91,107}

There has been significant recent interest in the putative linkage between the microbiome and frailty. Such interest stems in part from the linkage of dysregulated inflammation and immunity to frailty, along with substantive data linking the microbiome to inflammation, immune dysregulation and immune homeostasis, as well as other frailty pathophysiologic pathways. We will summarize several of these potential linkages below.

The microbiome and its metabolites may influence inflammation, immune dysregulation and immune homeostasis

Multiple studies suggest that the human microbiome plays a critical role in the human host's attempt for a fine continuous balance between tolerance to self and innocuous non-pathogen, non-self and protection against pathogen non-self, through key roles in modulating immune development, immune homeostasis and immune dysregulation alike.^{108–110}

Role of microbiome in immune system development

Several studies support the microbiome's role in the early development, maturation and consequently the effective functioning of mucosal and systemic immune systems.^{18,108,111,112} Host-microbiota communication has been found critical to development of both innate immunity and cellular and humoral adaptive immune compartments.^{18,113,114} This developmental relationship is bidirectional, appreciating that the host immune system itself can significantly shape microbiome composition and function.¹⁰⁸

Role of microbiome in host defense at the mucosal host/environment interface

Beyond its role in early immune system development, the microbiome has been considered to play a critical role in immunity throughout the lifespan. The role of the microbiome in immune function and immune homeostasis has been most well defined in the gut.^{6,8,115,116}

Gut mucosa as a prototype of host mucosal defense

The gut is lined by a single layer of mucosal epithelial cells that form a tight physical barrier mediated by junctional proteins. Mucus, antimicrobial peptides and IgA production by the mucosal immune epithelial cell network constitute an additional barrier to pathogens. Innate immune responses mediated further by neutrophils and intestinal lymphoid cells play a role in containing commensal bacteria. Mucosal antigen presenting cells (APCs) mediate innate induction of adaptive immunity. These APCs could be pro-inflammatory and bactericidal or immunoregulatory (tolerogenic).^{19,117}

Gut regulatory T cells, epithelial and stromal cells all produce TGF beta and IL-10 which induce tolerogenic APCs and immunosuppressive pathways, and in a positive feedback loop further induce regulatory T cell production. Activation of pattern recognition receptors such as Toll like receptors on dendritic cells leads to IL-23 production which in turn induces IL-17 production and differentiation of CD4 T cells into Th17 cells. Th17 cells themselves have a pro-inflammatory role and are critical for the adaptive immune defense against microbial pathogens at mucosal surfaces.^{19,30}

Role of the microbiome in host mucosal defense

In healthy individuals, the gut microbiome plays multiple roles in maintaining a robust mucosal defense system, while ensuring immune homeostasis is sustained. Commensal microbes help maintain the mucus barrier by stimulating pattern recognition receptors on cells of the mucosal immune epithelial network. Commensal bacteria can promote tolerogenic APCs and help control mucus production and antimicrobial peptide expression. IgA secretion is also modulated by microbiota.^{30,118,119}

Gut microbiota directly or via metabolites further play a role in epithelial cell proliferation and the expression of tight junction proteins, necessary for mucosal repair and maintenance of gut mucosal barrier integrity. Commensal bacteria also are necessary for the production of metabolites with key anti-inflammatory properties.^{30,120,121} The microbiota-derived metabolite butyrate also stimulates regulatory T cell production through induction of IL-10 and TGF beta.^{122,123} Butyrate also promotes mucin production and reduces production of pro-inflammatory cytokines.^{108,124} Commensal gut microbiota additionally may directly promote resistance to pathogen colonization in the gut via several modalities, including pH modification, production of antimicrobial products, competition for microbial adhesion sites, and nutrient competition.¹¹⁷

Role of dysbiosis in promoting aberrant mucosal and systemic inflammatory responses

Several studies suggest an association of pro-inflammatory alterations in diversity, composition, and function of the microbiome with adverse inflammatory conditions.^{8,23,30,70,125–128} These include changes such as reductions in butyrate producing

gut microbiota.^{23,129,130} Multiple studies suggest that a putative contributor to the pathogenesis of such conditions is an inflammatory-microbiome signature (Figure 1).^{19,23,110,113,114,131,132} Such a signature has been postulated to be characterized by adverse alterations in microbiome composition and function that may lead to impaired mucosal epithelial integrity, precipitating translocation of commensal and pathogenic microbes and their products across the mucosal barrier. Such translocation further has been postulated to promote both local mucosal and systemic immune activation, and ultimately sustained systemic inflammation that may trigger onset of inflammatory-related disease states.^{5,133–140}

The putative causative role for the microbiome in local and systemic inflammatory pathways and disease is supported by animal models. Whereas the focus of these studies primarily has been on the bacterial microbiome, incipient data support a role for the virome in precipitating mucosal and systemic inflammation as well.¹¹

Association of the microbiome with aging pathophysiology

Microbiome shift to a pro-inflammatory phenotype with increased age

Whereas rapid changes in microbiome composition occur in the first 3 years of life, the gut microbiome subsequently takes on a relatively stable composition over multiple decades in a healthy host.^{35,141,142} Several shifts in microbiome structure have been reported to occur with late age, including reductions in microbiome diversity and increased interindividual variation.^{9,46,110,129,143} Also observed among elderly adults is a reduction in commensal microbiota with putative beneficial functions to the host, such as maintenance of mucus production and mucosal barrier integrity.^{23,35,133,144–147}

Concurrently, emergence of pathobionts has been observed.^{131,146} These pathobionts are symbiotic bacteria with the capacity to become pathogenic and precipitate chronic systemic inflammation. Overall, these findings all reflect a potential shift towards a pro-inflammatory microbiome phenotype with increased age. Among centenarians, models of longevity and healthy aging, enrichment of microbiota known to promote anti-inflammatory activity, metabolic homeostasis, and positive immune function have been observed.^{22,133,135,148}

Changes in host physiology with aging can impact microbiome composition and function

While the microbiome may impact host aging phenotypes, several changes in host behavior and physiology with increased age simultaneously may influence microbiome composition and function through impacts on dietary patterns and gut nutrient delivery. These include reduced appetite, reduced salivary production, changes in dentition and masticatory function, changes in gut enzyme production, and increased orocecal and colonic transit times.^{40,149,150}

Immunosenescence, cellular senescence and the microbiome

Cellular senescence and immunosenescence are central hallmarks of aging and also have been raised as cellular and physiological processes with potential influence on the host microbiome relationship. Cellular senescence is characterized by arrest of cellular

proliferation that may occur in response to cellular damage or stress. This process plays a key role in body repair, including in targeting damaged cells for removal. Senescent cells have been found to accumulate with age across body compartments. Accumulation of senescent cells or decrease in their clearance with age has been associated with a senescence-associated secretory phenotype characterized in part by chronic pro-inflammatory cytokine production.^{91,151,152}

Nascent data suggests a putative relationship of gut microbiota and cellular senescence. Associations of gut microbiota with cellular senescence have been particularly observed in the gut epithelial cellular compartment.^{153–155} A few studies additionally have found associations of gut microbiota metabolites with cellular senescence at distal organ sites.¹⁵⁶ However, data on the relationship of the gut microbiome to cellular senescence remains limited and warrants further study.

Related yet distinct to the concept of cellular senescence is immunosenescence. The term immunosenescence has been used to refer collectively to the multiple changes observed across immune system compartments with increased age.^{157–159} Such changes have been characterized as pro-inflammatory and considered possibly deleterious to the host, with significant associations observed with aging-related syndromes, morbidity and mortality.^{157,159}

These shifts involve both innate and adaptive immune compartments. Decreased phagocytic function, reduced antigen uptake, and impaired innate immune cell activation with decreased chemotaxis, diminished costimulatory molecule expression and dysregulated cytokine production resulting in impaired innate signaling to the adaptive immune system are among the multiple changes observed in the innate immune compartment with increased age.^{159–161} Depletion of naïve lymphocytes, a relative shift to a memory lymphocyte population, impaired B cell function with reduced levels of antibody production and avidity, and shifts in the representative distribution of T cell subpopulations are among the multiple changes in the adaptive immune compartment that have been observed with increased age.^{151,157,159–161} These aging-related immunological shifts may reduce the ability for the aging host to effectively respond to microbial pathogens or pathobionts and alter the host response to commensal organisms, consequently altering the composition and function of the microbiome compartment.

Whereas changes in the innate and adaptive immune compartments with age may precipitate changes in microbiome composition and function, it also has been postulated that the microbiome compartment may bidirectionally promote immunosenescent shifts as well. The human virome has been postulated to play a particular role in the induction of immunosenescence.

The human virome consists of viruses that perpetually reside in host cells, endogenous viral elements integrated into cellular components, and viruses that infect other microbiota elements, particularly bacteriophages which inhabit bacteria.^{162,163} The herpesviridae family member cytomegalovirus (CMV) has been particularly prominently identified as having a significant association with the immunosenescent phenotype. CMV is highly ubiquitous

in the general population, mostly latent in immunocompetent hosts and persistent in its presence in aging populations.^{162,164} Clonal expansion of memory T cells specific for CMV antigens has been observed with age and also associated with heightened pro-inflammatory cytokine production. Marked CMV clonal expansion in older adults has been postulated to restrict the T cell repertoire, with the potential to impair responses to other microbial antigens.¹⁵⁹ While CMV has traditionally been identified as inducing a deleterious, pro-inflammatory effect via the immunosenescent pathway, more recent data has raised the question as to whether CMV might also find a putative beneficial role in the immunocompetent host with potential for enhancing immune responses in some scenarios such as vaccination.^{157,159,165} The role of CMV in immune aging requires further investigation.

The composition of the human virome also varies by host compartment. The gut virome constitutes the largest human virome compartment with an estimated 10^9 viral particles per gram of intestinal content.^{159,162,163} This compartment consists predominantly of bacteriophages that infect prokaryotic cells, primarily inhabiting the gut bacterial microbiome.¹⁵⁸ Studies suggest that bacteriophages can modify the function of the bacterial microbiome. In particular, bacteriophages have been found to induce the production of inflammatory cytokines in vitro.^{158,166} Through this and other pathways, the bacteriophage component of the human microbiome may play a putative role in adverse aging-related conditions. However, very little data currently exist on aging-related changes associated with bacteriophages. The role of these organisms, other viral elements and other microbiota components on immunosenescence as a putative pathway to frailty and other aging-related syndromes merits further study.

Aging, impaired gut mucosal integrity and inflammatory-microbiome signature

With age, impairments in intestinal mucosal integrity also have been observed. This increased intestinal mucosal permeability has been observed in both mice and nonhuman primate models alike.^{134,138,167,168} Age-associated dysfunction of the gut mucosal barrier may lead to translocation of microbes and their products into systemic circulation and contribute to a systemic inflammatory signature.^{135,169,170}

Several animal models support the role for the gut microbiome in precipitating an inflammatory-microbiome signature. In studies of *Drosophila*, microbiome alterations precede and predict the onset of intestinal barrier dysfunction in aged flies. Intestinal dysbiosis in these studies was characterized by expansion of *Gammaproteobacteria* and associated with systemic immune activation and heightened mortality.¹⁷¹ In other experimental models, age-associated changes in the gut microbiota promoted mucosal permeability, increased systemic bacterial products, and increased levels of central inflammatory cytokines such as IL-6 and TNF α .¹³⁹ In murine models, transfer of microbiota from old mice to young germ free mice triggers inflammatory responses. These responses included increased intestinal inflammation, upregulation of inflammatory cytokine genes, and increased circulating systemic inflammatory markers.¹⁴⁰ In humans, increased enterocyte apoptosis has been observed in biopsies of elderly adults.¹⁷² However, definitive evidence for increased gut permeability with translocation of pro-inflammatory microbial

products in healthy older adults in the absence of overt inflammatory disease has been limited.⁴⁵

Microbiome and chronologic vs. biologic age

Changes in diversity, microbiome composition and function with increased age have been reported across multiple studies, yet not universally observed. In several studies, reduced gut microbiome diversity and the putative pathological shifts in microbiome composition and function that have been observed correlate less closely with chronologic age than with aging-related shifts in health status and measures of “biological age”, namely markers considered to capture the underlying dysregulated multisystem physiology that account for the heterogeneity of aging-related outcomes, such as conceptualized in the frailty construct.^{34,40,110,173} Understanding the role of the microbiome in frailty pathophysiology ultimately may help determine its potential use as a key target to improve health outcomes for frail adults.

Association of the microbiome with frailty

Studies on the relationship of the human microbiome to the frailty construct

Despite the significant relationship of gut dysbiosis to inflammation and dysregulated immunity, and the aforementioned microbiome relationships with neuroendocrine dysfunction, and altered energy metabolism, all identified as core pathways in frailty pathophysiology, studies directly evaluating the relationship of the human microbiome to the frailty phenotype have been limited. The limited studies that exist vary in instrument used and population studied. We describe several of these early studies here.

Physical frailty phenotype and microbiome

Applying the Fried physical frailty phenotype in a cross-sectional analysis of 1551 community dwelling older adults, Verdi et al. found the frailty phenotype to be significantly associated with a reduction in microbiome diversity, a feature of the microbiome evidenced in multiple other adverse disease states.¹⁷⁴

Also utilizing the Fried PFP, Buigues et al. performed a randomized double-blind clinical trial of daily administration of an inulin/fructooligosaccharide prebiotic versus placebo among 60 nursing home resident ambulatory adults. No significant change in frailty score was observed with this intervention, though significant improvements in 2 frailty domain criteria exhaustion and grip strength were observed.¹⁷⁵

Ghosh TS et al. applied the Fried PFP in a very recent study of the microbiome relationship to frailty. This study was a single-blind randomized controlled trial of 612 adults across 5 European countries investigating a 1 year Mediterranean diet intervention in relationship to inflammation and frailty. Gut microbiota taxa enriched by adherence to the Mediterranean diet were significantly associated with reduced frailty and reductions in inflammatory markers including CRP and IL-17.¹⁷⁶

Frailty indices and microbiome

Most other studies seeking to examine the relationship of the human microbiome to frailty have applied an index approach to frailty assessment. One of the earliest studies to explore the relationship of the microbiome with frailty, used the Groningen frailty indicator, a 15 item questionnaire based on mobility, physical fitness, comorbidity, weight loss, vision, hearing, cognition and psychosocial resources. Adverse scores on this instrument were associated with reductions in putative health promoting, anti-inflammatory organisms such as *Faecalibacterium prausnitzii* and increased *Enterobacteriaceae* abundance, the latter considered to be pro-inflammatory.¹⁷⁷

Jackson et al. applied a 39 item index comprised of measures of comorbidity, physical function, mental health, self-reported general health, disability, social functioning, polypharmacy and pain. This index was applied in a cross-sectional analysis of community dwelling cohort of 728 female twins. In this study, higher index score was significantly associated with a reduction in alpha diversity, even after adjustments for age, diet, alcohol intake, tobacco use and BMI. Higher index score was associated with significant reductions in microbiome butyrate producers, a characteristic with known anti-inflammatory effects.⁶⁹

Maffei et al. applied a 34 item index of health history and functional variables to a cohort of 85 community dwelling adults. In cross-sectional analysis, this index significantly correlated with decreased gut microbiome richness, with no association of microbiota richness with chronologic age. These findings persisted after adjustment for chronologic age, sex, BMI and antibiotic usage.³⁴

Using the 9 item Rockwood clinical frailty scale (RCFS) in a cross-sectional study of 76 patients hospitalized for acute illness, Ticinesi et al. found no difference in alpha diversity between top and bottom tertiles of the CFS score. Several compositional associations were observed with the CFS including differential abundance of *Prevotella*, *Oscillospira*, *Porphyromonas*, *Peptococcus*, and *Fonticella*.⁴⁴

Also using the RCFS, Haran et al. performed a prospective observational study of 23 nursing home residents with stool collection at regular intervals over a 4 month period. Higher scores indicative of poorer health status were associated with reductions in butyrate producing bacteria and an increase in LPS and peptidoglycan synthesis pathways, agents known to have the capacity to induce systemic inflammation.¹⁷⁸

In a posthoc analysis of a randomized controlled trial designed to examine the impact of an inulin/fructooligosaccharide prebiotic mixture versus placebo among 50 nursing home residents, prebiotic administration was associated with a small reduction in a 62 item frailty index.¹⁷⁹

Microbiome and other measures of heterogeneous aging

Beyond application of the most commonly employed measures of frailty, one of the seminal studies of the relationship of the microbiome to syndromes known to capture differential health status among older adults was performed by Claesson et al. In this cross-sectional

study of 178 elderly adults, the microbiota of community dwelling adults was compared to that of adults in long term residential care.

Long term stay was considered as a proxy for frail status in this study, with these subjects having poor scores on key geriatric markers, including comorbidity, functional impairment, disability, and cognitive impairment. Adults in long term residential care demonstrated a significantly different microbiome signature than community dwelling adults. The long term stay signature was characterized by decreased microbiome diversity, increases in *Bacteroidetes* phyla and decreases in *Firmicutes* phyla. This signature strongly correlated with markers of heightened inflammation (TNF α , IL-6, IL-8, CRP) and reductions in fecal microbial metabolites such as butyrate known to have anti-inflammatory and health promoting effects.²³

Ogawa et al. similarly compared the salivary microbiome of nursing home residents to community dwelling controls. For this study, nursing home residence required certification of an inability to live at home based on frail status, as per the opinion of a medical physician. The study focus was on the salivary microbiota, which was found to differ significantly between the community dwelling and nursing home groups. Study of the oral microbiome is emerging as an important entity, with some studies suggesting a linkage of this compartment with systemic physiology and adverse aging phenotypes.^{180,181} Additionally, while notable regional differences have been reported, there is emerging data in support of a putative linkage between the upper and lower GI tracts relative to microbiome composition.^{182,183} In this study, the salivary microbiome taxa that correlated with inferred frailty status included several taxa known to colonize the lower GI tract as well.¹⁸⁴

In sum, frail status as defined across these different measures was associated with reduced microbiome diversity, reduction in putative beneficial health promoting anti-inflammatory microbes, reduction in health promoting microbiome metabolites (including those with a role in energy metabolism and a positive brain-gut axis), and microbiome compositional changes associated with heightened inflammation.

The primary limitation across these studies is the wide variability in the methodology applied in the attempt to capture frailty. In addition to limiting comparisons across studies, the application of distinct instruments raises the question as to whether the same underlying biological latent construct is being captured across studies. Additional limitations for several of these studies include use of fecal samples, which may not fully capture the full microbiome compartment; the limitations of 16S rRNA sequencing relative to microbiome functional assessment, absence of data on key putative confounders that may significantly additionally influence the microbiome such as antibiotics, diet and substance use, and the cross-sectional nature of most studies which limits causal inference.

Relationship of the microbiome to frailty components and sub-manifestations of frailty

The relationship of the microbiome to additional pathophysiologic mechanisms considered key components of frailty pathophysiology including changes in musculoskeletal physiology such as sarcopenia and endocrine physiology such as insulin resistance, as well as the

microbiome relationship to key frailty phenotypic subdomains such as reduced muscle strength and gait speed has been preliminarily explored.

Sarcopenia

Sarcopenia, characterized by an aging-related decline in muscle mass and quality, has been considered significantly associated with frailty pathophysiology. Studies suggest the microbiome may influence multiple pathways with potential impact on muscle mass and quality. First, the gut microbiome can influence host appetite through endocrine pathways with potential impact on dietary protein intake necessary for muscle formation.⁴⁶ Gut microbiota composition influences protein metabolism and bioavailability, with adverse impact on the bioavailability of amino acids specific to muscle protein synthesis.^{129,185} Synthesis of several vitamins, including B12, folate, and riboflavin necessary for skeletal muscle anabolism also is influenced by the microbiome.^{129,186}

Conversely gut dysbiosis has been associated with impaired mitochondrial quality in myocytes with impaired antioxidant capacity. Accumulation of dysfunctional mitochondria can contribute to muscle atrophy. Further, induction of intramuscular fat infiltration can occur with gut dysbiosis, with potential adverse impact for muscle function and strength.^{129,187,188}

Several key microbiome metabolites can play a key role in these pathways. Short chain fatty acids (SCFAs) play a role in skeletal muscle glucose uptake and protein deposition, modulating the balance between muscle anabolism and muscle breakdown.^{189,190} Microbiota-derived SCFAs may promote mitochondrial activity with positive impact on skeletal muscle cell function. Decrease in SCFA production with aging is considered to precipitate decreased mitochondrial fatty acid oxidation and increased intramuscular fatty acid deposition, resulting in reduced muscle strength and quality as a key putative precipitant to frailty.⁴⁶

Several animal model studies support the putative causal influence of the gut microbiome on muscle mass and quality. Distinct gut microbiome signatures have been observed between rats with sarcopenia relative to those with normal muscle mass.¹⁹¹ Muscle atrophy in mice is associated with a pro-inflammatory gut microbiome with depletion of butyrate producing bacteria.¹⁹² Further, administration of the SCFA butyrate to aged mice has been shown to improve lean muscle mass.¹⁹⁰

Grip strength

Little direct data exist in humans associating gut microbiota with skeletal muscle mass. However, low grip strength – a key functional readout of muscle strength and a primary frailty domain – has been associated with an increased abundance of pro-inflammatory microbiota, decreased abundance of anti-inflammatory microbiota, and reduction in fecal SCFA levels.^{175,193}

Insulin resistance

Insulin resistance also has been identified as an important pathophysiologic pathway in frailty. Healthy gut microbiota can play a role in reducing insulin resistance.¹²⁹ Microbiota-derived SCFAs promote insulin sensitivity, promoting glucose tolerance through increased energy expenditure.¹⁹⁴ SCFAs promote release of systemic IGF-1.¹⁹⁵ IGF-1 release can positively influence insulin sensitivity and inflammation, and is strongly associated with reduced frailty burden.^{129,196,197} Secondary bile acids are additional microbiota metabolites which can activate pathways that protect against insulin resistance.^{198,199} Conversely, gut dysbiosis can result in increased circulating lipopolysaccharide (LPS) which itself can induce insulin resistance and inflammation. Insulin resistance can result in accelerated loss of muscle mass and strength.¹²²

Microbiome and gait speed

Gait speed has been an important predictor of adverse aging outcomes among older adults and is a key domain in the frailty phenotypic construct. In animal models, germ free mice demonstrate hyperactive locomotor behavior compared to animals with gut microbial colonization. *Lactobacillus* administration was shown to correct this hyperactive locomotor behavior.²⁰⁰

In the very few human studies examining the relationship of the gut microbiome to gait speed to date, some changes in gut microbiota composition have been observed. These included increased abundance of *Enterobacteriaceae* and decreased *Lachnospiraceae* with impaired gait in patients with Parkinson's disease compared to controls; reduced *Bacteroides* with reduced gait speed in an exercise intervention study of sedentary women; and increased gait speed with probiotic supplementation in a probiotic randomized controlled trial targeting cirrhotic patients. Though, for the latter no changes in the fecal microbiome were observed.^{201–204} Overall, data on the relationship of the microbiome to frailty and its components in humans remains limited.

Frailty, HIV Infection and the Inflammatory Microbiome

HIV infection may serve as a key prototype for elucidating the complex intersection of biology, behavior and environment for the inflammatory microbiome-frailty relationship in disease states in aging populations.

Antiretroviral therapy (ART) has dramatically increased the lifespan of HIV-infected patients. Consequently, the proportion of people living with HIV worldwide who are over 50 years of age has significantly increased, and the number of older HIV-infected adults is anticipated to rise markedly over the next several decades.^{205–207} Despite these survival gains, disparities in morbidity and mortality remain for Persons Living with HIV (PLWH) even on effective ART.^{208–210} Such disparities are due in part to the rising burden of aging-related conditions in the HIV-infected population, for which PLWH have been found to be disproportionately at risk. This heightened risk has been attributed to both aberrant HIV pathophysiologic pathways that persist even with ART-mediated virologic suppression,

as well as behavioral and environmental factors that may disproportionately impact HIV-infected populations.^{2,211}

Multiple recent studies have demonstrated a heightened frailty burden for PLWH relative to their HIV-uninfected counterparts.² As for older HIV-uninfected adults, this heightened frailty burden in HIV has been shown to be predictive of major adverse clinical outcomes, including hospitalization, falls, fractures, disability, low quality of life and increased mortality.^{212–218} In a study by Piggott et al., being both frail and HIV-infected conferred an over 7-fold increased risk of death, independent of comorbidity or HIV disease stage.²¹⁹ Thus, as for HIV-uninfected older adults, understanding pathways to frailty in HIV remains critical to reducing the marked disparities in morbidity and mortality persistent in this population.

Role of inflammation in aging-related phenotypes and frailty in HIV

As detailed above, heightened inflammation has been identified as central to frailty pathophysiology among HIV-uninfected older adults. Dysregulated inflammation is central to HIV pathophysiology, and a key driver of aging-related morbidity and premature death among PLWH as well.^{220–225} Even amongst PLWH who are virally suppressed on effective ART, inflammation persists.²²⁰ What drives this persistent inflammation remains an area of active study. Putative mechanisms suggested include persistent low-level residual viremia, co-infections (such as CMV), persistent activation of pattern recognition receptors, telomere shortening, as well as inflammatory-promoting behavioral and environmental factors.¹⁰⁵

The findings of several recent cross-sectional studies support a significant role for inflammation in frailty pathogenesis in HIV.^{105,226} In more recent longitudinal evaluation using a nuclear factor kappa B (NFkB)-derived aggregate inflammatory index, reduced inflammation was associated with both reduced frailty progression and greater frailty recovery.²²⁷

Elucidating drivers of frailty-associated inflammation in HIV thus may be critical to reducing frailty-related disparities in this population. Significant interest has surrounded the possibility that an inflammatory microbiome signature may occur in HIV as well, constituted by microbiome changes that may lead to a dysregulated gut epithelial border, associated increases in microbial translocation and immune activation, chronic systemic inflammation and consequently frailty in HIV.

HIV as a putative precipitant of a pro-inflammatory microbiome signature

The intersection of key aspects of HIV biology, microbiome biology, and inflammatory pathways has raised the possibility that the microbiome may play an important role in driving inflammation and frailty in HIV.

HIV infection causes massive depletion of CD4 T cells in the gut, as well as dysregulation of the immune-epithelial network, which may not be fully restored even with effective ART. Depletion of gut mucosal CD4 T cells occurs very early in acute HIV infection, with particular adverse impact on the Th17 compartment. Gut CD4 T cell depletion is accompanied by impairment in gut mucosal barrier function secondary to inflammatory

cytokine-mediated disruption of tight junctional proteins.^{10,228} CD4 T cell loss and particularly loss of IL-17 and IL-22 producing cells further impairs capacity for epithelial cell regeneration, together with mucus and antimicrobial peptide production that serve key mucosal defense functions as well.¹¹⁷

Enterocyte apoptosis and epithelial cell degeneration which occur with HIV infection further precipitate impairment in gut integrity.¹⁰ Markers associated with epithelial injury and increased gut permeability including I-FABP and Zonulin remain elevated and are predictive of increased mortality, even in ART-treated patients.²²² Impaired gut integrity in HIV also has been significantly associated with translocation of microbial products from the gut lumen to peripheral blood.^{10,229,230} These microbial products retain capacity for immune activation and consequently systemic inflammation.¹⁰

There is interest in whether HIV-mediated shifts in gut immunity and gut barrier integrity may substantially shift host-microbe interactions and consequently alter microbiome composition and function in a manner that may promote an inflammatory-microbiome signature in HIV.^{5,17} It is possible that the loss of IL-17 production and antimicrobial peptides could significantly shift microbiome composition as well. In murine models, loss of IL-17 production has been associated with an inflammatory microbiome signature characterized by microbiota changes significantly associated with heightened inflammation.^{231,232}

HIV may additionally adversely impact gut physiology in ways that may further alter microbiome composition and function. Such effects include reducing gastric acidity which may facilitate an increased presence of opportunistic pathogens and decreasing gastric emptying which may further impact colonization of the GI tract.¹¹⁷ HIV-mediated impairment of macrophage phagocytic activity also may alter microbiome composition and precipitate local and systemic inflammation.^{233,234}

Epidemiologic observational shifts in microbiome composition and function in HIV

Many studies have compared the gut microbiota in HIV-infected and HIV-uninfected individuals.^{235–267} Despite the putative intersection of HIV biology and host microbiome biology as described above, a consistent HIV-associated microbiota signature has been slow to emerge, potentially reflective of the complexity of the host-microbiome relationship.

Several studies have reported a significant association of HIV infection with alterations in the gut microbiota. In acute SIV models, increased abundance of bacterial taxa with pathogenic potential has been observed with a corresponding decrease of putatively beneficial microbes such as *Lactobacillus*. These microbiome changes have been associated with impaired pattern recognition receptor expression and gut mucosal Th17 loss in these studies.^{268–270} In chronic SIV infection, gut microbiota changes have not been universally observed.¹⁷

Multiple human studies have been performed seeking to identify a distinct HIV-microbiome relationship. These studies have employed mostly 16S rRNA gene sequencing methodologies and results remain mixed. In human studies in which HIV-associated

microbiome compositional changes have been observed, HIV-associated gut dysbiosis often manifests as reduced gut microbial diversity.^{240,244,246,271} As detailed above, reduced gut microbiome diversity has been associated with aging-related conditions and frail status in older HIV-uninfected populations as well.

While many studies report significant differences in alpha diversity between PLWH and their HIV-uninfected counterparts, such findings have not been universal.^{271–280} For example, in a recent study of HIV-infected women with longstanding HIV infection compared to HIV-uninfected women from the same geography, no difference in alpha diversity was observed.²⁸¹ In a large individual level meta-analysis, Tuddenham et al. found decreases in alpha-diversity in HIV-infected patients as compared to HIV-uninfected patients. However, this reduction was observed only amongst women and men who have sex with women (MSW), but not in the men who have sex with men (MSM) population.²⁸²

Many (though not all) studies have reported differences in individual taxa between HIV-infected and HIV-uninfected individuals.^{271,272,274–280} Where changes in taxa have been observed, unique compositional and functional profiles in HIV distinct from other inflammatory conditions have been suggested. In one study of the gut microbiome from individuals with *Clostridium difficile* infection, lupus, HIV infection and healthy controls – 139 metabolic biomarkers were suggested to differentiate HIV infection from other conditions.²⁸³

Several studies suggest HIV-associated microbiota changes may skew towards pro-inflammatory organisms, though the specific changes observed across studies have differed.^{5,72,236,238,249,261,264,284} Early studies reported increases in *Prevotella* abundance with HIV infection. However, more recent studies suggest the increase in *Prevotella* in HIV possibly to be consequent to the confounding influence of MSM status as detailed further below.

Though significantly less studied, changes in the gut virome have also been reported with HIV infection. Contrary to the relationship observed with the bacterial microbiome, both HIV and SIV infection have been associated with an increased diversity and expansion of the enteric virome. SIV infection also has been associated with changes in the plasma virome.^{11,285} Increased abundance specifically of pathogenesis-associated viruses *Adenoviridae* and *Anelloviridae* have been observed with HIV infection.²⁸⁶

HIV-associated dysbiosis and mucosal and systemic inflammation

Several studies have found correlations of HIV-associated changes in both the bacterial microbiome and virome with immune activation and heightened systemic inflammation. Conversely, several microbiota observed in several studies to be in lower abundance with HIV infection positively correlate with markers of protective immunity.^{236,239,243,244,262,264,273,275,286}

Some microbiota communities reported to be increased in abundance with HIV infection in several studies demonstrate an increased capacity to catabolize tryptophan to kynurenine. An increased kynurenine to tryptophan ratio has been shown to correlate

with loss of mucosal Th17 cells, as well as heightened inflammation in HIV.^{257,264,287} Various microbiome composition changes across different taxa have been reported otherwise in association with microbial translocation, immune activation and systemic inflammation.^{236,239,243,244,246,248,273,288}

More broadly, limitations of studies to date exploring the relationship of HIV infection to the microbiome include small sample sizes, a need for appropriate controls, and potential confounding effects of key putative microbiome modulating factors (including MSM status). Given the heterogeneity of findings to date, the exact role of HIV infection in modulating the microbiome remains to be determined.

Role of ART

ART itself has been considered a putative intervention to reduce inflammation through positive microbiome modulation. Yet, studies of ART in microbiome restoration have yielded discordant findings. A few studies suggest ART may promote gut dysbiosis,^{246,289,290} while others show only partial recovery even with virologic suppression.^{240,242,252,261,264} Functional gene profile analyses of gut microbiota in ART treated subjects may still demonstrate persistent alterations in genes involved in bacterial translocation, systemic immune dysfunction and inflammatory pathways.^{248,291}

In one recent study examining alpha diversity changes prospectively with ART treatment, changes in alpha diversity were observed with ART treatment at CD4 cell counts less than 300 but not with higher counts.²⁹² The challenge of several studies of the relationship of ART to the microbiome include the heterogeneity of ART regimens used and as for studies exploring the role of HIV infection itself, the ability to differentiate ART specific effects from the influence of multiple potential microbiota-modulating confounders.

Putative drivers of inflammatory-microbiome signature in HIV beyond HIV-driven biological pathways

Many prior studies examining the role that HIV infection may play in aging-related phenotypes have sought to tease out the intersecting roles of HIV biology itself with comorbidity, medication effects, and behavior or lifestyle factors on adverse aging phenotypes. In order to elucidate the role that HIV biology, namely HIV-specific pathophysiologic pathways, may have on the gut microbiome in treated and untreated states, it is important to consider additional extrinsic factors that could strongly influence microbiome composition and function in the HIV-infected population.

Several factors known to influence the microbiome as detailed above, are known to disproportionately burden HIV-infected populations. These include maternal antibiotic use and mode of feeding; dietary factors consequent to malnutrition; bacterial infections requiring antibiotic use; multimorbidity and polypharmacy; tobacco use, alcohol use, opiate use, and other substance use; and mood disorders with potential impact for the bidirectional brain-gut axis.^{207,293–300}

MSM/Sexual behavior

Of particular relevance to the HIV-infected population, MSM status has been recently identified as being significantly associated with shifts in gut microbiome composition. Emerging data suggest that the gut microbiota of at least a subset of MSM is characterized by increased *Prevotella* and decreased *Bacteroides*.^{277,279,301} In one study, when the microbiota of MSM was transplanted into mouse models, elevated levels of gut-associated activated T cells were observed, independent of HIV status.³⁰¹ These findings, along with other data suggest that the microbiota of MSM is distinct and may have potentially pro-inflammatory immunologic effects.³⁰² However, what specific factor (e.g. receptive anal intercourse) associated with MSM status may drive such changes is still under investigation.^{277,303–305}

With the recognition of MSM status as a key putative confounder, new studies have attempted to control for this factor, either statistically or by balancing HIV-infected cases and HIV uninfected controls with respect to MSM status. Results remained mixed, and larger, carefully controlled studies accounting for MSM and other key putative microbiome-related factors that differentially burden HIV-infected populations will be needed to fully elucidate relationships between the microbiome, HIV, inflammation and frailty.

Microbiome modulation as putative target for frailty intervention

Increasing data suggest targeted modulation of an unfavorable, pathogenic gut microbiome via probiotics, prebiotics or fecal microbial transplantation (FMT) may restore health across a range of deleterious inflammatory conditions.^{117,306–308} Probiotics are live microorganisms that confer a health benefit to the human host. Probiotics may promote health by positively impacting the immune system, increasing production of mucus, antimicrobial peptides and IgA secretion; limiting pathogen colonization through competitive adherence; controlling gut inflammation, and improving mucosal barrier functions and restoring gut integrity.^{110,309–311}

Prebiotics are non-digestible substances considered to positively impact the host through selective growth of probiotic species.^{49,312} In both HIV-infected and uninfected populations, probiotics and prebiotics have been associated with reduced inflammation, immune activation, and microbial translocation, as well as recovery of gut mucosal integrity.^{310,313–322}

FMT robustly alters microbial communities and is emerging as a safe, effective, durable and innovative tool for microbiome modulation of inflammatory-related disease. In very limited HIV studies to date, FMT was found to be safe, well tolerated and to enhance immunity.^{323–325} Importantly, the ability of probiotics and FMT to reduce inflammation and restore health has been strain, donor, disease and host dependent.^{117,283,326–330} What probiotic strains, and prebiotic or FMT formulations will find optimal efficacy in preventing or reversing aberrant physiologic events in specific target populations or in specific pathogenic states, particularly frailty requires focused evaluation.

Future directions

While there have been significant separate advances in the elucidation of the biology of frailty and that of the human microbiome respectively, limited direct evaluation of the relationship of the human microbiome to the frailty construct exists in the literature to date. Detailed characterization of key microbiota targets, metabolites and other gene products that distinguish a frail microbiome from a non-frail microbiota could significantly inform interventions to rationally modulate the microbiome to combat frailty and promote healthy aging outcomes in HIV-infected and uninfected populations alike.

The few studies of the microbiome-frailty relationship to date have been primarily cross-sectional and correlative in nature. Longitudinal evaluation, use of translational animal models, and ultimately clinical intervention studies will be needed to determine causative pathways and application to combating frailty and promoting health. Beyond conventional 16S rRNA sequencing and metagenomics, future targeted metatranscriptomic, metaproteomic, and metabolomic studies will help elucidate additional novel targets for frailty prevention or recovery. Further, methodological considerations around instruments used for frailty assessment for future microbiome studies will be important for elucidation of common biology.

While most microbiome research has focused on bacterial communities, future studies are needed of the role of the virome, mycobiome, and other microbiome components, as well as the role of non-luminal and extra-intestinal microbiome compartments on frailty and other key aging phenotypes.

Disentangling the impact of HIV infection itself from lifestyle and behavioral factors, comorbidities, ART and other population-relevant microbiota-related factors on the microbiome will require sustained focused attention, appreciating both the promise and the complexity of linking the microbiome to complex and heterogeneous biological pathways such as inflammation across populations in which these multiple influences may be significantly integrated contributors to the microbiome signature.

Ultimately, evaluation of the role of the microbiome in frailty pathophysiology may require a systems approach in which the microbiome is appreciated as a highly complex ecosystem with multiple dynamic inputs, operating as an integrated biological network for host effect. Such an approach may provide optimized targeted opportunities for potential precision interventions to combat frailty and promote healthy aging across populations.

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Figure 1. Inflammatory Microbiome Signature and Frailty

Putative integrative pathway via which the human microbiome may mediate frailty onset and progression. This proposed pathway is based on existing data derived from animal models and human studies to date. In this model, host genetic factors, pro-inflammatory clinical parameters, and environmental, lifestyle and behavioral factors promote an inflammatory-microbiome signature characterized by pro-inflammatory alterations in the microbiome (particularly the gut) and functional metagenome that precipitate decreased epithelial barrier function with consequent increased mucosal permeability, translocation of microbial products, dysregulated innate and adaptive immunity, and a heightened systemic inflammatory state. This inflammatory-microbiome signature may intersect further with microbiome-mediated dysregulation of other key human physiologic systems, including neuroendocrine and energy metabolic pathways to precipitate frailty.