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Healthy aging and the human gut microbiome: why we cannot just turn back the clock

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Abstract

The aging research field has largely focused on reversing aging-related changes in the body. However, emerging evidence about the gut microbiome indicates that it may not be optimal to just turn back the clock. Here, we advocate for a more tailored and function-focused approach promoting health across the lifespan.

Recent advances in gut microbiome research have revealed its broad impacts on host physiology and health[1]. As such, understanding the relationship between the gut microbiome and the aging process is likely key to designing holistic interventions to promote healthy aging. Although much remains to be discovered along the aging–microbiome axis, key nonhuman animal and human cohort studies provide a preliminary roadmap to population-scale variation in gut microbiome composition across aging-related comorbidities throughout the lifespan.

Though the gut microbiome is relatively stable during much of adulthood, compositional changes in the gut microbiota in the latest decades of human life have been tied to both age-associated health decline and healthy aging[2,3]. Importantly, microbiome characteristics of extremely long-lived, healthy individuals do not resemble those of healthy younger or less-than-healthy older adults, but instead have their own unique features[4], some of which are highly consistent across culturally and geographically distinct centenarian populations[5]. The distinctness of the centenarian microbiome signature from signatures of youth in the gut, coupled with fairly inconsistent aging–microbiome patterns that have been reported in mouse studies, indicates that it may not be enough to reverse age-associated changes and optimize for a ‘younger’ microbiome. We need to think beyond this simple paradigm when evaluating and targeting the gut microbiome to promote healthier aging in the latest decades of life.

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Competing interests

N.D.P. is CSO of Thorne HealthTech, which sells a microbiome test with personalized health recommendations. The test is not discussed in this article.

Gut microbiome interventions can promote or reverse host aging processes in animal models

A number of exciting findings in recent years from fecal microbiota transplants (FMTs) in mouse models have provided strong causal evidence for the direct involvement of the gut microbiota in host aging processes. Transgenic *Lmna*^{G609G} and *Zmpste*$^{-/-}$ mice, two mouse models of Hutchinson–Gilford progeria syndrome (HGPS), in which individuals exhibit accelerated aging, demonstrated drastic microbiome shifts reflective of aging: higher levels of *Bacteroides* and *Prevotella*, accompanied by a depletion in the anti-inflammatory commensal *Akkermansia muciniphila*[6]. Importantly, transplanting fecal microbiota from wild-type mice into progeroid mice, or providing the latter with an *A. muciniphila* probiotic treatment, were sufficient to extend their survival and reverse some age-associated pathologies[6]. Similarly, in a separate study, FMT from a young donor mouse into an older host reverted some, but not all, immunological, hippocampal and behavioral deficits accompanying aging[7]. However, in this same study, the anti-inflammatory cytokine IL-10 was significantly increased in older mice receiving FMTs from age-matched donors but not in older mice that received an FMT from a younger donor pool[7].

Indeed, complex and even opposing effects have been reported across studies using different mouse models. For example, young, germ-free mice transplanted with a microbiota from an older mouse showed greater hippocampal neurogenesis and intestinal growth, as well as higher short-chain fatty acid production, compared to control young, germ-free mice transplanted with a microbiota from a younger mouse[8]. This lends some credence to the idea that gut microbiome compositional changes during the aging process are not necessarily detrimental to host health, and that it may not always be a good idea to try to ‘turn back the clock’ in the gut by introducing microbes from a younger animal.

These results run somewhat counter to prior work that showed how blood from younger mice can rejuvenate older mice[9]. In these groundbreaking studies, exposing aged mice to the blood of young mice via injection or surgical parabiosis improved cognitive function and synaptic plasticity in the hippocampus. However, unlike aging signatures in the blood, aging-related developmental trajectories in the gut, alongside physiological and immunological changes on the host side, may be cooperative and help to dampen aging-related morbidities. Although some effects of the gut microbiome on aging might be targeted through reversal of aging signatures, others may require harnessing the natural progression of gut microbiome development observed in healthily aging individuals.

Microbiome changes converge with age-associated decline, but diverge with healthy aging

The relatively recent emergence of next-generation sequencing for microbiome analysis has limited the availability of long-term longitudinal human studies of gut microbiome dynamics over the course of the lifespan. To date, the majority of aging–microbiome studies have therefore used cross-sectional cohorts, either comparing individuals across the decades of human life, or focusing on older individuals (65+) exhibiting heterogeneous health states.

One of the most studied populations in the context of the gut microbiome and aging is the ELDERMET cohort[10], which has revealed a marked stability and an increasing dominance of core gut bacterial genera, up until the very late stages of aging-associated declines in health[11], when a drop in diversity and a rise in pathobionts has been observed[12]. However, the ELDERMET cohort is in part composed of individuals within long-term care facilities[3,11], rather than more independent, and likely healthier, community-dwelling individuals. In contrast, studies of community-dwelling centenarian populations across the globe have shown a steady loss of prevalent (i.e., core) gut commensal taxa and a rise in subdominant taxa and alpha diversity with increasing age[4,5,13].

Recent work by our group and others has attempted to reconcile these divergent signatures, by showing how older individuals stratified by health status show distinct gut–aging trajectories, with less healthy, community-dwelling individuals showing relatively stable gut microbiome profiles and healthier individuals showing signatures akin to what has been observed in centenarians[2,14]. Thus, there appear to be (at least) two distinct gut aging signatures in humans associated with unhealthy and healthy aging, respectively, with those aging healthily showing a steady decline in the dominance of core taxa, an overall rise in compositional uniqueness and a lower risk of mortality[2].

In our study, the most dominant core genus to decline in healthily aging individuals was *Bacteroides*, which tends to dominate the guts of younger individuals, particularly in highly developed countries[2,4,5]. A major physiological difference between younger and older individuals is that mucus production in the gut epithelium declines with age, due to a steady loss of gut epithelial goblet cells[15]. Many species within the *Bacteroides* can facultatively degrade host mucus, which may be well tolerated in a younger host with surplus mucus production capacity, but may lead to thinning of the mucus layer, increasing inflammation and reducing intestinal barrier integrity in an older host. Although it is uncertain why core taxa decline and are replaced with rarer taxa during the course of healthy aging, the timing of this process overlaps with the earliest stages of immune system aging, which appear to begin in the 40s for both men and women[16]. Thus, aging-associated changes in the gut may help to accommodate changes in host physiology, whereas a more static microbiome may exacerbate the effects of these changes on host health (Fig. 1).

Microbial metabolites as potential biological mediators and targets for healthy aging

Although the ecological composition of the gut microbiome appears to become increasingly *divergent* with healthy aging, there is evidence for a concomitant *convergence* in the metabolic output produced by the gut microbiota[2,13,17]. This metabolic signature in the blood may serve as an alternative window into understanding the gut microbiome's impact on aging[18]. Gut-derived metabolites exert their effects both locally, in the gastrointestinal tract, and on distal organs through their absorption into the bloodstream[1]. Importantly, many of these metabolites are modified and excreted via the liver–kidney axis, while many others mediate signaling across the gut–brain axis or show strong immunomodulatory effects. Furthermore, the gut microbiota is known to degrade and transform pharmaceuticals,

potentially influencing inter-individual heterogeneity in responses to various drugs, such as statins[19]. Many of these microbially derived metabolic products appear to be critical to the health and well-being of an aging host.

In the context of aging, several preclinical proof-of-concept studies have demonstrated that certain microbial metabolites may mitigate the effects of host aging. For example, microbial degradation products of tryptophan (i.e., indoles) were shown to extend healthspan and prolong survival in *Caenorhabditis elegans*, *Drosophila melanogaster* and mouse models of aging[20]. Additionally, indoles have also been shown to improve intestinal barrier function during aging in humans[21]. Consistent with these results, plasma levels of several indole metabolites were positively associated with increasing gut microbiome community uniqueness, a compositional pattern of increased dissimilarity in microbiome composition that we found to be correlated with better health and decreased risk of mortality in the latest decades of human life[2].

Several additional metabolites are emerging as key mediators of biological processes that play increasingly important roles in age-associated diseases. The microbiota-derived metabolite δ-valerobetaine was recently reported to be positively associated with age in humans and was shown to impair neuronal function and promote memory deficits in mice, indicating that microbiota-targeted interventions aimed at lowering this metabolite's production could delay neurocognitive decline[22]. Carnitine and phosphatidylcholine can be microbially metabolized in some people's guts into trimethylamine, which is then converted in the liver to trimethylamine *N*-oxide (TMAO). TMAO has been implicated in cardiovascular disease, neurodegeneration and kidney disease progression. Similarly, the histidine microbial metabolite imidazole propionate was shown to promote insulin resistance, a key hallmark of age-associated metabolic dysregulation[23].

For many microbiota-derived metabolites in blood, their beneficial versus detrimental effects appear highly context dependent[2,18,24]. For example, certain microbial metabolites, such as phenylacetyl-glutamine and *p*-cresol sulfate, are known to cause kidney or cardiovascular damage at higher concentrations in vulnerable individuals, but they are also found to be enriched in the blood of centenarians[17]. Furthermore, although dietary phosphatidylcholine in the presence of certain bacteria can be converted into the precursor for potentially harmful TMAO production in the liver (as discussed above), evidence suggests phosphatidylcholine itself has a positive effect on delaying dementia[25]. Thus, personalized insights into the microbiome can make a big difference in whether something is healthy or not for each individual. Systems-scale studies of human–microbial metabolic interactions are needed in which longitudinal, multi-omic data are collected from blood and stool and paired with clinical measures of health and disease, the better to inform how these metabolites can be tested in nonhuman animal models and potentially leveraged to promote healthy aging in human populations.

Concluding remarks

Our understanding of the biological effects of aging in humans has grown exponentially in the last several years[16]. To date, much of the aging research field has focused on reversing

the progression of aging-related changes in the body. When it comes to the development of the human gut microbiome across the lifespan, however, it may not always be optimal to turn back the clock. Indeed, certain core gut microbes, such as mucus-degrading *Bacteroides* species, may have a neutral impact on younger hosts, when mucus is plentiful, but be detrimental in older age as the mucus layer thins. Furthermore, aging-associated changes in the gut microbiome are correlated with a rise in anti-inflammatory microbial metabolites, such as indoles, and immunosuppressive bacterial proteins in healthily aging individuals, which may serve to counteract rising systemic inflammation associated with aging (i.e., inflammaging)[2,16]. For these and other reasons, we may want to rethink whether or not reverting microbiomes of older hosts to a 'younger' state is the optimal approach to advancing microbiome-mediated healthy aging in humans.

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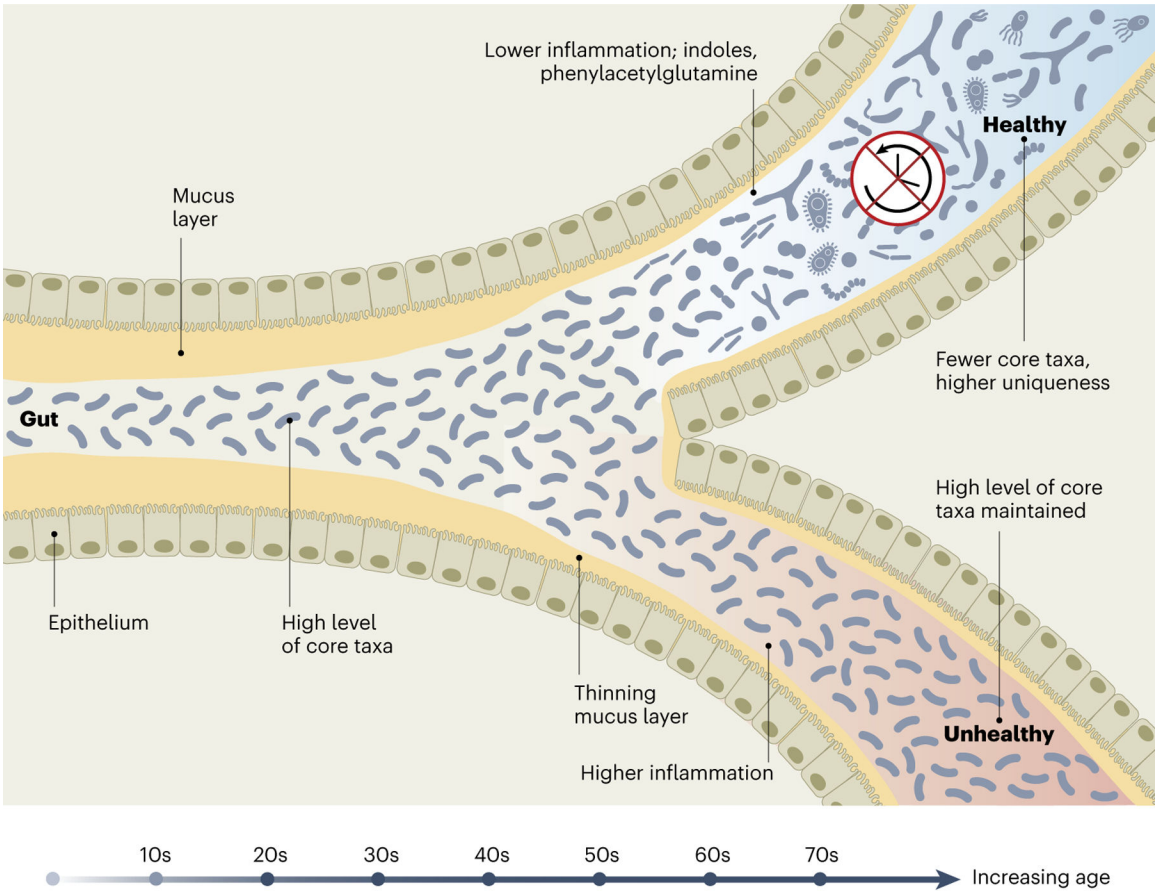

Fig. 1 |. Why reverting gut microbiomes of older hosts to a 'younger' state may not be the optimal approach.

Healthy aging (upper right) in humans appears to be associated with a decline in core taxa that normally dominate the gut microbiomes of younger individuals and unhealthy older adults (lower right). Additionally, there is a rise in the levels of several potentially favorable microbial metabolites with healthy aging that may be less readily synthesized by the microbiomes of younger hosts. Therefore, it does not appear to be favorable to 'turn back the clock' via fecal microbiota transplants and revert older microbiomes to a younger state, as a healthy microbiome may be one that develops alongside its aging host throughout the course of the human lifespan.