

## PERSPECTIVE

## Gut microbiota and aging

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The potential for the gut microbiota to affect health has a particular relevance for older individuals. This is because the microbiota may modulate aging-related changes in innate immunity, sarcopaenia, and cognitive function, all of which are elements of frailty. Both cell culture-dependent and -independent studies show that the gut microbiota of older people differs from that of younger adults. There is no chronological threshold or age at which the composition of the microbiota suddenly alters; rather, changes occur gradually with time. Our detailed analyses have separated the microbiota into groups associated with age, long-term residential care, habitual diet, and degree of retention of a core microbiome. We are beginning to understand how these groups change with aging and how they relate to clinical phenotypes. These data provide a framework for analyzing microbiota-health associations, distinguishing correlation from causation, identifying microbiota interaction with physiological aging processes, and developing microbiota-based health surveillance for older adults.

Prolongation of life span is a triumph of modern medicine, with most citizens of developed countries now looking forward to four-score-years-plus on the planet. The challenge now is to promote health span and to reduce the duration and severity of morbidity that precedes death. Simultaneously, changes in family and societal structures mean that an increasing proportion of older people desire, or are required to be capable of, independent living. The greatest barrier to independent living is frailty. Frailty occurs because of the accumulation of disorders rather than the chronological age of an individual. An "organ" in the human body that might not be expected to follow the general trajectory of physiological decline is that consisting of the microorganisms in the gut. Bacterial cells in the gut do not age per se, but people growing older may begin to experience comorbidities associated with the gut and with gut bacteria. So the question naturally arises as to how the microbiota in the human gut might affect the aging process, or if the gut microbiota simply changes as a function of age.

The gut microbiota composition of the elderly differs considerably between individuals in the ELDERMET cohort that we have studied most extensively (1). We observed a shift in the microbiota toward a *Bacteroidetes*-predominated population in frailer older individuals compared to younger individuals (1). However the variation in the microbiota profiles of these elderly subjects is large, so this trend is minimally informative in terms of prediction of the phenotype. This large variance can be explained by external factors influencing the microbiota, such as diet, exercise and mobility, medication, and cohabitation patterns (2), even after adjusting for the inferior health of residential care subjects. To identify associations with the phenotype and external influencing factors, we need to identify patterns in the other-

wise heterogeneous microbiota populations within aging individuals. We have therefore performed a fine-detail analysis using model microbiota associations generated through the use of a data-mining technique that successfully identified four subpopulations within the microbiota that are associated with biological phenotypes (3).

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These subpopulations, or microbiota profiles, were operationally defined as core, reduced core, diversity-associated, and longstay/age associated. A single individual's microbiota profile can consist of one or more of these subprofiles, as well as a number of rare species and strains. Age-related changes in the microbiota that are least influenced by other environmental factors can be identified in a relatively homogeneous data set of community-dwelling people (Fig. 1A, top), and this gradient is mirrored by length of stay in residential care (Fig. 1B, top).

The mechanism of microbiota change with age is not totally understood because the importance of senescence of the gut and the altered physical environment therein has not yet been systematically investigated. Extreme-age people (centenarians) have a microbiota that differs from those of older adults (4), consistent with general age-related microbiota trends (Fig. 1). Lifestyle, and particularly diet, play a large role, since aging is often accompanied by a reduction in the amount and variety of fiber-containing foods, and there is

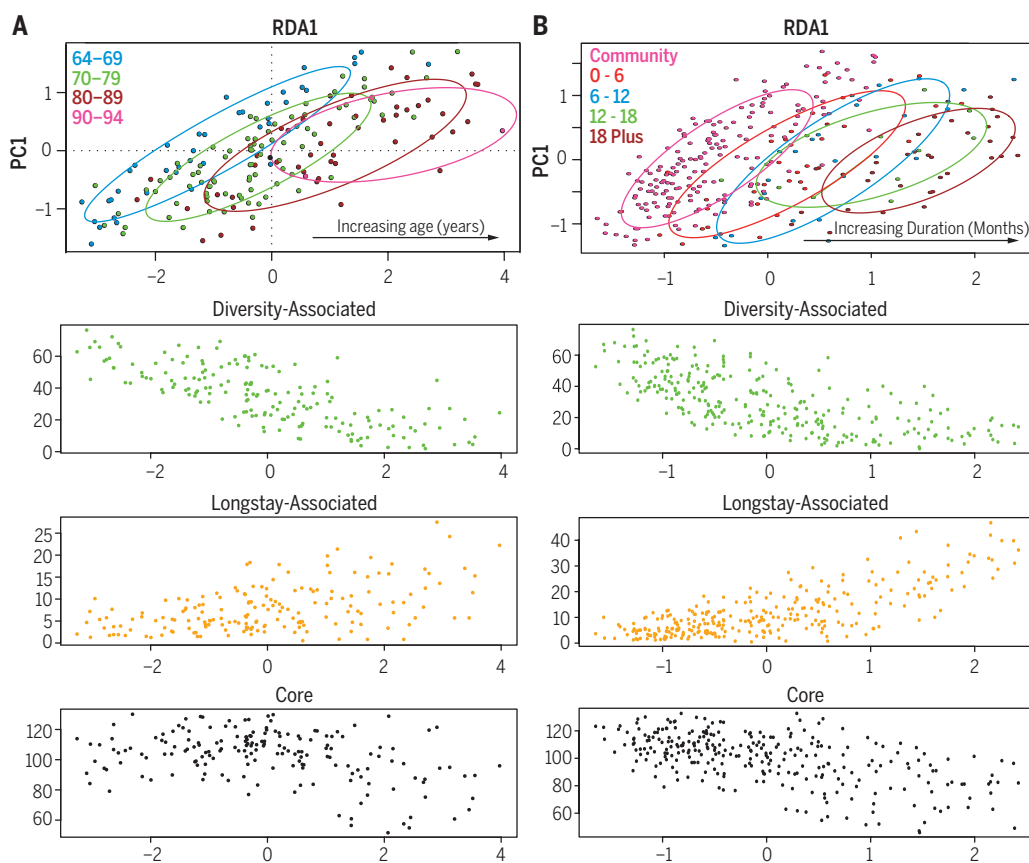
often a risk of malnutrition (2). Lower fiber intake leads to a decrease in microbiota diversity, which may be detrimental to gut health (5). The risk of malnutrition is associated with increased microbiota diversity, particularly with a coabundant *Clostridiales* subpopulation. This is admittedly a counterintuitive idea, because many studies have shown that in adults, higher microbiota diversity correlates with being healthier. However, the composition of the microbiota associated with the risk of malnutrition is also associated with age in the community-dwelling people and their duration of stay in residential care (3). The *Clostridiales* subpopulation is also significantly associated with increased frailty, even after adjusting for age, to a much greater degree than loss of gut microbiota diversity.

There is evidence that loss of gut microbiota diversity can occur and does affect the aging process. Although not significantly associated with chronological aging, loss of diversity in the core microbiota groups is associated with increased frailty and reduced cognitive performance. The microbiota changes associated with duration in long-term care can be treated as a proxy for the changes associated with biological aging (Fig. 1) and the known deterioration in health that occurs when people enter long-term care. The group of organisms that are affected the most by aging are the diversity-associated taxa, comprising *Prevotella* and associated genera (Fig. 1). Their abundance also declines rapidly once individuals enter long-term care (2), but these organisms occur in high proportions in less than half the community-dwelling subjects of the ELDERMET cohort to begin with (3). The core microbiota are those taxa that are present in the vast majority of the subjects in appreciable proportions and, thus in our study, any loss of these taxa defines a microbiota profile as low diversity (3). The core microbiota may decline and be supplanted by highly abundant species, but the full core microbiota is rarely lost. Thus, the microbiota associated with low diversity is a subset of the core microbiota.

The age-related changes in the microbiota that we observed in the ELDERMET data sets can largely be associated with diet and reduced abundance of taxa from the diversity-associated core group. However, several specific coabundant taxa do seem to be associated with old age and risk of malnutrition. In the fruit fly, *Drosophila melanogaster*, the composition and diversity of the microbiota are correlated with food intake and the bacteria associated with the food (6). Diet and the microbiota of *Drosophila* act in concert on the health of the fly (7); for example, the microbiota associated with young flies promotes amino acid harvest during undernutrition. In a *Drosophila* model of aging (6), an age-related taxonomic profile develops that is characterized by bacterial overgrowth, and acquisition of aging-related taxa associates with subsequent mortality (6). Targeting of aging-related taxa in *Drosophila* using antibiotics increased fly life span. Obviously one cannot directly extrapolate these findings to humans, but the fruit fly could still be a useful discovery tool and model for investigating

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**Fig. 1. Microbiota and aging.** Top panels: Redundancy analysis plot of microbiota composition [log-transformed operational taxonomic unit (OTU) data set] of (A) community-dwelling individuals by age (in years),  $n = 176$ ;  $P < 0.002$ . (B) Full data set of community and long-term residential care individuals by duration in care (logarithm of days),  $n = 282$ ;  $P < 0.001$ . Lower panels indicate corresponding values for the OTUs of the indicated microbiota modules (sum of the log-transformed OTU abundances). Analysis was performed on ELDERMET microbiota data (3).

the drivers, consequences, and mechanisms of age-related microbiota change.

Our most detailed analysis of microbiota composition changes over time in the elderly was based on multiple time points and samples per individual (2). Previously we assumed that because the diversity in the long-stay subjects was lower than that of community dwellers, this led to instability of the microbiota, and when combined with the high-frequency use of antibiotics in the elderly population, the composition of the microbiota would be vulnerable to change (2). However, detailed investigation of the microbiota over time did not support a model of unstable low diversity. Over a 3-month period, a similar level of microbiota instability was seen among people living in the community and in those in long-stay residential homes, and antibiotic treatment increased instability in both subject groups. The real difference between community and long-stay microbiota types was detected when the microbiota was monitored for more than 6 months. In the community, these differences were similar to those occurring during the initial 3 months, whereas in the residential care population, this change was significantly

greater, indicating that changes were at least partially cumulative (3). The most unstable microbiota profiles, showing the largest shifts in composition, tended to be low-diversity profiles. After an initial change, diversity tended to recover best among people living in the community and less well in those in long-stay residential care.

### Conclusion

Diet-microbiota-health interactions must be viewed in the broader context of the genetic and lifestyle changes that accompany aging, and the notable and sometimes conflicting effects of diet alone. For example, dietary restriction extends life span in a wide range of animal models from nematodes to Rhesus monkeys [reviewed in (7)], by mechanisms that include modulation of key pathways involved in nutrient sensing, metabolism, and inflammation. Restriction of specific amino acids can also be effective in increasing longevity. The activity of the innate immune system may also be directly influenced by members of the microbiota (8), making it challenging to dissect these mechanisms, especially in humans. As elderly people age and/or spend time in a long-stay res-

idential facility, they gain a long-stay-associated defined population of bacteria that are associated with increased frailty (Fig. 1). Centenarians also experience an overall decline in microbiome function (9), and these changes occur simultaneously with physiological loss of function. Considering the weight of evidence summarized elsewhere in this issue that the gut microbiota modulates or affects cardiometabolic and inflammatory processes, then the microbiota alterations that occur during aging may mean that some subjects are more prone to accelerated aging-related health loss. However, as some frailty-associated alterations may increase the diversity of the age-related microbiome, the assessment of diversity or stability by longitudinal sampling may be a less useful parameter to monitor than the phylogenetic composition of the microbiota. Several ongoing national and international studies, such as the NuAge project (10), will apply multi-omics analysis to determine if microbiota changes are correlative or causative of health loss and how other physiological processes are involved. This will establish if the microbiota could be a target for diagnostics that characterize aging health status, or could be a direct target for interventions that promote healthier aging by modulating the microbiota composition and function.

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