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The Microbiome Mediates Environmental Effects on Aging

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Humans' indigenous microbes strongly influence organ functions in an age- and diet-dependent manner, adding an important dimension to aging biology that remains poorly understood. Although age-related differences in the gut microbiota composition correlate with age-related loss of organ function and diseases, including inflammation and frailty, variation exists among the elderly, especially centenarians and people living in areas of extreme longevity. Studies using short-lived as well as nonsenescent model organisms provide surprising functional insights into factors affecting aging and implicate attenuating effects of microbes as well as a crucial role for certain transcription factors like forkhead box O. The unexpected beneficial effects of microbes on aged animals imply an even more complex interplay between the gut microbiome and the host. The microbiome constitutes the major interface between humans and the environment, is influenced by biosocial stressors and behaviors, and mediates effects on health and aging processes, while being moderated by sex and developmental stages.

1. Introduction: What Is Aging?

Aging is an irreversible process of nearly all multicellular organisms, ultimately contributing to the demise of the organism. Age is the largest risk factor for many diseases and in humans the risk of dying doubles every eight years. Many factors contribute to this complex process of aging, which ultimately results in physical degeneration of cells, tissues, and organs. Interestingly, the aging process is characterized by a gradual loss of function and occurs as a consequence of several steps of dysfunction in the body.[1] In a recent review, van Ginneken[2] elegantly described the gradual loss of function with age. For example, by the age of 65 one has an approximate 25% reduction in cardiac output and almost 50% reduction in respiration capacity. This is, of course, subject to individual variation.[2] This illustrates the network of increasing impairment on the functional pathways and reduced interorgan crosstalk that collectively is associated with aging.

Both genetics and environmental factors contribute to aging. It has been estimated that an organism's genetics accounts for 25% of the factors, while the environment contributes to about 75%.[3,4] The major environmental contribution includes lifestyle components such as diet, exercise, and stress. The remarkable environmental contribution suggests that humans should be able to further increase their life span by modulating environmental factors.

2. Is There a Link between the Microbiome and Aging?

Perhaps one of the most interesting findings of environmental contributions to aging is the role of microbes. Complex organisms live in intimate association with multitudes of

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DOI: 10.1002/bies.201800257

bacteria, viruses, and simple eukaryotes, with the eukaryotes colonizing surfaces exposed to the environment.[5,6] It is estimated that trillions of microbes inhabit the human body, large numbers being found in the gastrointestinal tract, oral and nasal passages, the skin, and the urogenital tract. Interactions with our environment are filtered through a layer of microbes—be it on our skin when we touch something or in our gut when we eat or drink. By metabolizing environmentally acquired molecules, bacterial metabolites are produced that affect distant physiological functions. Moreover, multicellular eukaryotes have developed sophisticated methods to keep microbes from overtaking their bodies: the innate and acquired immune responses. If microbes do breach surface barriers, a robust immune response ensues, resulting in inflammation. Although inflammation can control unwanted microbial invaders, it can also lead to tissue and organ damage.[7]

As we age, the reduced organ function, including the vascular structures and heart function, require an increased supply of nutrients to maintain body function.[2] These changes are assumed to be sensed and reciprocated by changes in microbiome species composition and metabolic capabilities. Simply put, our host-associated microbial communities serve as accessory genetic reservoirs that can aid the "holobiont" (i.e., the multipartite entity of a host and its associated microbial communities),[8] as well as the microbes. The microbiome gradually adapts to age-related physiological impairment of respiration, locomotion, circulation, metabolism, and immune functions. The observation that fecal transplantation of microbes from old mice into young increase intestinal length and thus the surface area for absorption support a beneficial role of the microbes.[9,10] However, this adaptation process of the microbiome comes with drastic consequences. A surplus of energy-driven changes in the microbiome by age, as well as increased gut permeability, results in chronic low-grade inflammation that results in accelerated aging through tissue and organ damage, referred to as inflammaging. As a result, more permeable barriers in the gut and oral cavity (releasing bacterial inflammatory molecules such as lipopolysaccharide) further limit the microbes' ability to reduce inflammation. For example, in a similar transplantation experiment (old mice microbes into young mice), the transplantation significantly increases inflammatory cytokines and inflammation (see Thevaranjan et al.[11] for comment). The changes in the microbiome and the resulting penetration of microbes systemically result in an increase in inflammatory cytokines ensuing inflammation. This inflammation then causes further tissue damage, resulting in age-associated effects.

If one examines the mortality tables of developed countries in North America and Europe, of the top ten causes of death, nine of them now have microbial associations (accidents are exceptions) (see e.g., National Center for Health Statistics[12]). Cardiovascular diseases (which cause heart attacks and strokes) have a strong association with microbes related to the metabolism of red meat products. Specific diets (that alter the microbiome) can significantly affect the disease outcome. For example, the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet has been reported to significantly decrease Alzheimer's and dementia risk.[13] Similarly, good oral hygiene (brushing one's teeth three times a day) also reduces the risk of these diseases, presumably by decreasing inflammaging and by decreasing inflammatory bacterial products penetrating through the damaged gums.[14] Realizing that the environment affects the aging processes is not new, diet and exercise are well-established factors. However, through the use of animal models and other experimental methods, we now recognize that the microbiome is at the interface of environmental factors, providing a novel aspect to our understanding of the aging process.

3. Microbiome Composition and Interorgan Crosstalk in the Elderly

Given the intimate and ongoing communication between the microbiome and its host, microbes and their metabolites may participate in and modulate the interorgan crosstalk within the host. How an interorgan crosstalk communicator can be modulated by microbes is illustrated by fibroblast growth factor 21 (FGF21).[15] FGF21 is predominantly a liver-derived hormone that exerts a range of metabolic effects in rodents and humans ranging from normalizing blood glucose in diabetic animals, enhancing fatty acid oxidation, alleviating pancreatic β-cell dysfunction, reducing body weight in diet-induced obese mice, and regulating food intake and energy expenditure. Mechanistically, microbial-derived short-chain fatty acids (SCFAs) like butyrate induce the expression and secretion of FGF21 through derepressing transcriptional activation via peroxisome proliferator-activated receptor α (PPAR-α), to activate FGF21, by displacing histone deacetylase 3 (HDAC3) on the FGF21 promoter. FGF21, in turn, is known to regulate the AMP-activated protein kinase—Sirtuin1–mammalian target of rapamycin (mTOR) pathway, which is associated with longevity. Further, exercise is known to induce the secretion of SCFA and people who exercise have been reported to have elevated levels of FGF21. Hence, microbes, exercise, and FGF21 are interconnected. Notably, old people with a sedentary lifestyle have reduced production of SCFA, thereby suggesting that their microbes may be less able to produce SCFA leading to reduced levels of FGF21. Experiments to test this hypothesis are highly warranted.

Another way to understand aging in a "holobiont" context is to study the gut microbiome associated with longevity, especially microbes among extremely elderly individuals.[16,17] Biagi et al.[17] examined the microbiome of young adults, elderly, and 24 semi-supercentenarians (105–109 years old) and identified a possible core aging-related microbiome that seems to be stable across age but differed in the relative abundance of the species of which it was composed of. Further, a distinct microbial footprint appears to exist for semi-supercentenarians, including the health-associated *Bifidobacterium*, *Christensenellaceae*, and *Akkermansia*. However, it is still not clear and would require a life-time longitudinal study to verify whether these supposedly "beneficial microbiome species" are present throughout life and prolonged life expectancy, or if they are lost during "normal" aging and regained by the people who reach extreme longevity.

4. The Value of a Comparative Approach to Understand the Complex Process of Aging

Aging is a universal phenomenon, which occurs in different degrees in all species. During the past two decades, studies in

model organisms including the yeast *Saccharomyces cerevisiae*, the nematode worm *Caenorhabditis elegans* (*C. elegans*), the fruit fly *Drosophila melanogaster* (*D. melanogaster*), and the mouse *Mus musculus* have all contributed greatly to the development of an integrated and functional understanding of the diverse processes of aging revealing important aging-regulating mechanisms, including insulin signaling, TOR, and telomere maintenance (**Figure 1**).

Beside these "canonical" laboratory models, recent work in extremely short-lived vertebrates and nonsenescent invertebrates has added to our understanding of the mechanisms controlling life span and disease prevention; in particular, it has drawn attention to the role of microbes in the aging process. In the African turquoise killifish *Nothobranchius furzeri*, one of the shortest lived vertebrate species, the gut microbiota plays a key role in modulating life span. Recolonizing the gut of middle-aged individuals with bacteria from young donors results in life span extension and delayed behavioral decline.[18] This intervention prevented a decrease in microbial diversity associated with host aging and maintained a young-like gut bacterial community. These findings demonstrate that the natural microbial gut community of young individuals can causally induce long-lasting beneficial systemic effects that lead to life span extension in older individuals.[18] Similar observations in mice[11] demonstrate a causal link between decreased diversity in intestinal microbiota and increasing inflammation as the rodents age.

The freshwater polyp *Hydra vulgaris* (*H. vulgaris*) is considered nonsenescent[19] due to three everlasting stem cell lineages,[20] which allow the animals to continuously reproduce asexually via budding. Because the transcription factor forkhead box O3 (FoxO3)—which regulates genes involved in growth and

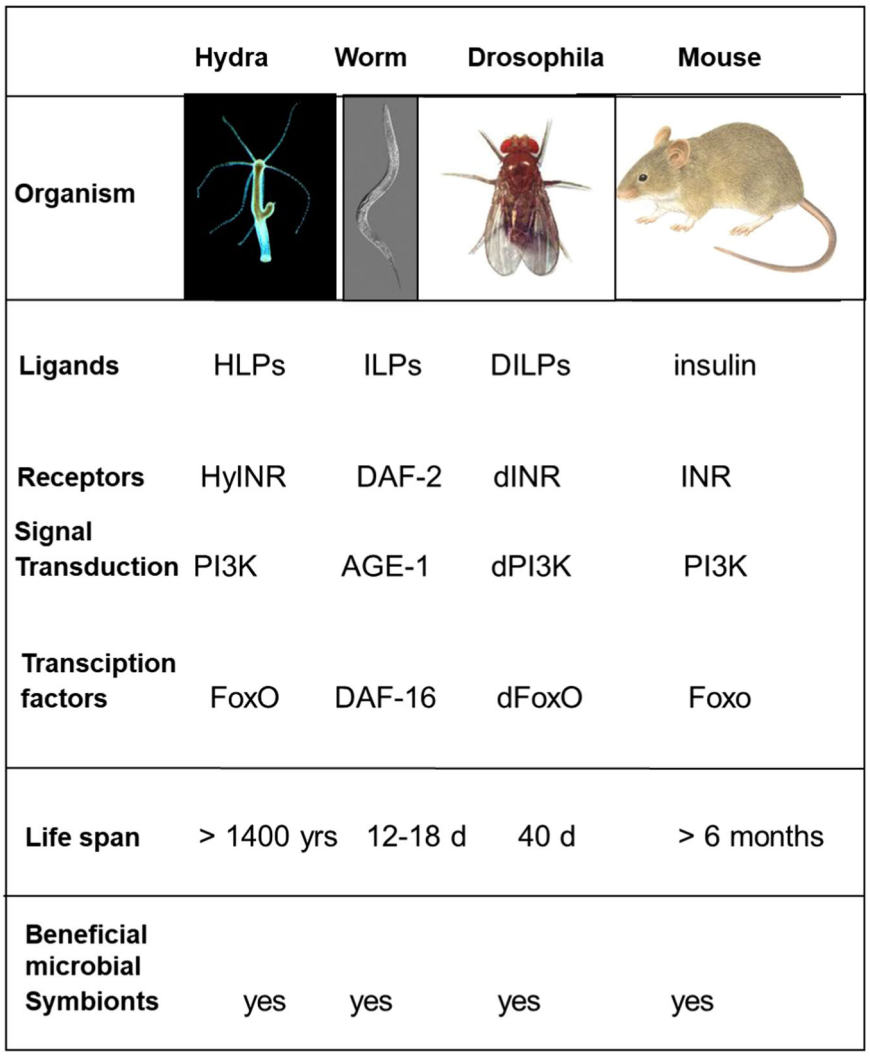

Figure 1. FoxO and key components of the PI3K pathway are well conserved throughout the evolution. The corresponding orthologues for these components in *Hydra*, worm (*C. elegans*), *D. melanogaster*, and mouse are illustrated. AGE-1, encodes the phosphatidylinositol-3 kinase age-1 gene in the worm; DAF-2, encodes the insulin-like growth factor 1 (IGF-1) receptor in the worm; DILPs, *Drosophila* insulin-like peptides; dINR, *Drosophila* insulin receptor; dPI3K, *Drosophila* phosphoinositide-3 kinase; HLPs, *Hydra* insulin-like peptides; HyINR, *Hydra* insulin receptor; ILPs, insulin-like peptides; INR, insulin receptor; PI3K, phosphoinositide-3 kinase.

differentiation, has been consistently associated with human aging and longevity[21,22] and since in *Hydra* the single FoxO gene is strongly expressed in all stem cell lineages,[23] FoxO loss-of-function mutants can provide insights into the evolutionary conserved function of this gene. Epithelial FoxO loss-of-function mutants revealed that a deficiency in FoxO signaling leads not only to malfunctions in the cell-cycle progression but also to dysregulation of multiple families of genes encoding antimicrobial peptides (AMPs).[24] FoxO loss-of-function polyps were more susceptible to colonization by foreign bacteria and impaired in selection for bacteria resembling the native microbiome. FoxO deficiency reduces the expression of AMPs, resulting in decreased selective pressure on colonizing microbial taxa and ultimately in reduced resilience of the microbiome.

Similar to *H. vulgaris*, FoxO modulates the innate immune system in mouse,[25] *Drosophila*,[26] and *C. elegans*.[27] In mice, FoxO transcription factors directly regulate Toll-like receptor 3 (TLR3)-mediated innate immune responses as well as the expression of AMPs.[25] FoxO signaling has been shown to reduce susceptibility to bacterial infections by reducing oxidative stress and induction of inflammatory cytokines.[28] Functional analyses in *C. elegans* and *Drosophila* have verified that the level of FoxO expression is indeed directly linked to life span without detectable costs for the individuals.[29–31]

Supporting the strikingly conserved components of the FoxO signaling pathway (Figure 1) are candidate gene studies of long-lived French population[32] and Japanese/Okinawans in Hawaii,[21] which have uncovered FoxO3 as part of the genetic aging code in humans. These observations together with the functional studies in model organisms suggest a key role for FoxO controlling aging and health in multicellular organisms: FoxO seems to serve as a protective gene responsible for both stem cell regulation, including tissue maintenance and renewal, and also controlling the innate immune system. The capabilities of the FoxO transcription factor to extend life span and control effectors of the immune system demonstrate a strong and unique mechanism of cross-regulation of tissue homeostasis and innate immunity.

5. How Does the Microbiome Mediate Biosocial Factors that Influence Aging?

Biosocial investigations of aging examine not only how sociocultural factors (e.g., diet) become embodied, but also how biological aging is experienced in varying sociocultural contexts. Aging is characterized by increased phenotypic variation and reduced adaptive capacity resulting from complex interactions between genetic, environmental (including sociocultural, biotic, and physical components), and historical factors.[33,34] How these biosocial factors become embodied remain unclear, but the microbiome may play a mediating role. Health behaviors (e.g., diet, exercise, and sleep) have direct effects on the body and the microbiome, but factors such as work–life balance, social status and support, and expectations about aging may also influence longevity and quality of life in later years (**Figure 2**).[35] To what extent is the microbiome simply a biomarker of other correlated pathways,[36] or might it provide the missing link in how biosocial pathways influence aging?

5.1. Biosocial Factors May Impact the Microbiome via the Gut–Brain Axis

The hypothalamic–pituitary–adrenal (HPA) axis plays a role in aging through accumulated "wear and tear" of chronic stress. Variations in resources and stressors result in individuals experiencing varying kinds and amounts of stress and responding with varying resilience. Is it possible that the effect of biosocial stressors might vary not only with dose, timing, and duration but also with the microbiome composition?

Bidirectional signaling between the gut microbiota and nervous system[37] challenges the conventional ideas of how environmental factors influence the body and aging. The vagus nerve links the central nervous system with the abdominal viscera and acts as a bidirectional bridge between the gut microbiome and brain. While the components of the gut–brain axis are anatomically distinct, functional boundaries are

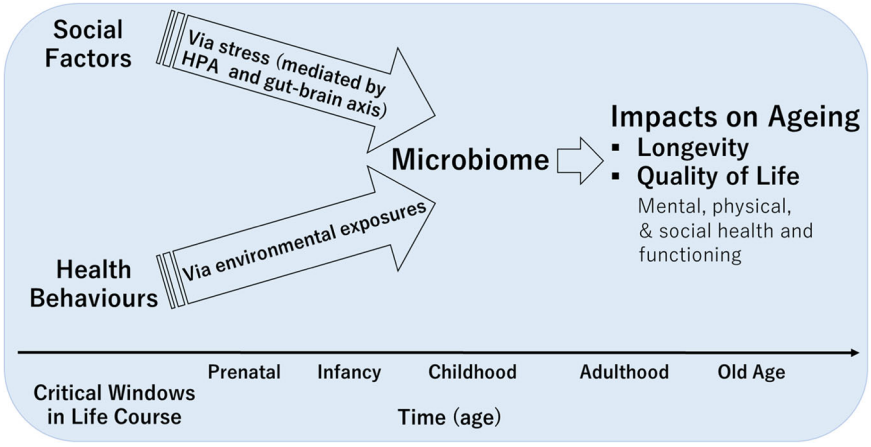

Figure 2. Conceptual model of how social factors (e.g., socioeconomic status, work–life balance, expectations, and beliefs) and health behaviors (e.g., diet, exercise, and sleep) may impact longevity and quality of life via the microbiome. Some effects may be bidirectional, with aging impacting the microbiome and the microbiome impacting the biosocial factors (e.g., eating behavior, sleep, and health status). These effects may differ throughout the life course, at different developmental windows, and may also be moderated by sex hormones.

blurred, with gut microbiota producing neuroactive compounds with epigenetic effects that likely play a critical role in brain homeostasis. Thus, while social factors and health behaviors such as those involving HPA activation and diet influence the microbiome, the microbiome also influences behaviors and social interactions, leading to bidirectional pathways and possible feedback loops that may vary throughout the life course.

5.2. Microbiome Effects of Environmental Stressors Vary with Developmental Window

The stressor of caloric restriction appears to extend the average life span for many animals as well as alter the microbiome composition. The Okinawan cultural idea of "hara hachibu" (eating until 80% full) has partly been credited for their longevity. Yet dietary restriction experienced in utero appears to have opposite effects on a fetus, increasing later life risks of obesity and metabolic conditions such as insulin resistance,[38,39] highlighting critical windows of nutritional restriction for different organs.[40,41] Critical windows for the microbiome may extend until roughly 2–5 years of age, and then stabilize in adult composition and diversity.[42] But critical windows for other organs may depend on the presence of certain microbiota. Although the microbiome of breastfed and formula-fed babies appears similar at 3 years, microbial differences in earlier critical time periods in immune system development may have long-term health effects,[43] highlighting the importance of interactions between the microbiome and biosocial exposures (e.g., feeding practices) across the life course.

Furthermore, evidence exists that prenatal exposure to the chemical milieu that manifests as depression in mothers, as well as prenatal exposure to serotonin reuptake inhibitor antidepressants or changes they induce, affect developmental trajectories in infants.[44] Given the role of gut microbiota in regulating host-serotonin biosynthesis,[45] the microbiome may influence the timing of critical windows of development and mediate host responses to psychosocial stressors via serotonin and other pathways. Serotonin varies with social status,[46] which correlates with health outcomes.[47,48] Thus, the microbiome effects on host serotonin and other physiological pathways may constitute a critical link influencing how biosocial factors such as perceived social status impact health and longevity.

5.3. Sex Differences Moderate the Microbiome Influences on Aging

Sex is a critical factor influencing aging, evidenced by longer life expectancies among women and reflecting sex differences not only in genes but also biosocial environmental exposures, mediated by hormones and epigenetic processes. Clear sex differences exist not only in nutritional and energy demands associated with reproduction but also with growth and development, likely influencing life history trade-offs in organ maintenance and thus aging.[49,50] Sex-specific shifts in the gut microbiome ecosystem to meet such energy demands may be part of the adaptive complex influencing the gut–brain axis and contributing to sex differences in physiology, behavior, and aging across the life span.[51] As many biosocial factors influencing aging and health involve perceptions rather than ingestible substances, the gut–brain axis provides a connecting pathway between microbiota, enteric, and central nervous systems[52] as well as bidirectional influences between psychosocial factors and the microbiome.

5.4. Microbiome Influences Variation in Health and Experience of Aging: Evidence from Japan

Which aspects of the microbiome (species diversity, specific bacteria, and bacterial metabolites) should we investigate to better understand the aging processes and experience, including not only longevity but physical and mental function and quality of life? Among diverse microbiota, there exists considerable metabolic redundancy in functional metabolites that may influence aging. Japan leads the world in life expectancy. Investigations of the Japanese diet, particularly the high soy intake and physiological effects of soy isoflavones, provide evidence for reduced chronic disease risk and thus increased longevity.[53] Yet interpopulation variation in soy's health effects suggests that there may be more to the story. Isoflavone intake is strongly correlated with healthy midlife outcomes among Japanese populations,[54] but less so among western populations taking isoflavone supplements.[55] Biosocial analysis of aging in the perimenopause[56] suggests that this could result from differences in microbial populations, related to endogenous and possibly also exogenous (such as dietary phytoestrogen) estrogen levels, since the gut microbiome regulates circulating estrogen through secretion of the enzyme β-glucuronidase, which deconjugates estrogens into active forms.[57]

Daidzein, a common soy isoflavone, can be converted to the metabolite equol, but only in the presence of certain gut bacteria.[58] Interestingly, estimates of the proportion of equol producers (those harboring appropriate bacteria to produce equol) range from 20–30% among US populations to 50–60% among Japanese middle-aged women.[59] Such population differences in diet and microbiota may partly explain the population differences in symptomatology and experience of aging,[60] and higher quality of life during the menopausal transition for Japanese women compared to their North American counterparts. If bacterial metabolites are the key to the health-promoting effects of dietary factors such as soy isoflavones, then studies that do not separate human subpopulations by microbiome-metabolizing ability risk the missing key factors. Such observations argue for the need for more nuanced studies of the microbiome and aging, focusing on key microbial metabolites that may affect not only longevity but also the experience of aging.

6. Conclusions and Outlook

A deeper understanding of the aging process in humans requires a careful analysis of both model and nonmodel organisms. Observations in different organisms indicate that,

in contrast to the essentially static genome, the microbiome is rather dynamic throughout life history, especially at the bookends of life. These findings have three major implications: i) there is a need to consider the holobiotic nature of an organism when thinking about longevity; ii) the microbial environment matters in the context of senescence and contributes to complex processes such as aging; and iii) the hub regulator FoxO presents a direct link between age-related processes and microbial colonization. Human aging is explicitly biosocial and the microbiome may not only play a critical role influencing how biosocial environmental factors become embodied but also in how ageing is experienced in varying biosocial contexts. Future studies should examine the key microbial metabolites that may affect not only longevity but also the experience of aging, in a framework that considers developmental trajectories and exposures to biosocial factors as well as multiple aspects of aging and quality of life (physical, mental, and social).

Acknowledgements

This work was supported by the Canadian Institute for Advanced Research (CIFAR). T.C.G.B. appreciates the support from the Deutsche Forschungsgemeinschaft (DFG) and Collaborative Research Centre (CRC) 1182 "Origin and Function of Metaorganisms." Work in B.B.F.'s lab was supported by the Canadian Institutes for Health Research (CIHR). T.C.G.B. thanks the Wissenschaftskolleg (Institute of Advanced Studies) in Berlin for a sabbatical leave.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

biosocial factors, FOXO transcription factors, holobiont, inflammaging, longevity, microbiomes, model organisms

Received: December 11, 2018
Revised: February 26, 2019
Published online:

[1] C. López-Otín, M. A. Blasco, L. Partridge, M. Serrano, G. Kroemer, *Cell* **2013**, *153*, 1194.
[2] V. van Ginneken, *Biomed. J. Sci. Tech. Res.* **2017**, *1*, 193.
[3] A. R. Brooks-Wilson, *Hum. Genet.* **2013**, *132*, 1323.
[4] C. Giuliani, P. Garagnani, C. Franceschi, *Circ. Research* **2018**, *123*, 745.
[5] I. Sekirov, S. L. Russell, L. C. M. Antunes, B. B. Finlay, *Physiol. Rev.* **2010**, *90*, 859.
[6] M. McFall-Ngai, M. G. Hadfield, T. C. G. Bosch, H. V. Carey, T. Domazet-Lošo, A. E. Douglas, N. Dubilier, G. Eberl, T. Fukami, S. F. Gilbert, U. Hentschel, N. King, S. Kjelleberg, A. H. Knoll, N. Kremer, S. K. Mazmanian, J. L. Metcalf, K. Nealson, N. E. Pierce, J. F. Rawls, A. Reid, E. G. Ruby, M. Rumpho, J. G. Sanders, D. Tautz, J. J. Wernegreen, *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 3229.
[7] B. Kokkas, *Ann. Gen. Psychiatry* **2010**, *9*, S1.
[8] F. Rohwer, V. Seguritan, F. Azam, N. Knowlton, *Mar. Ecol.: Prog. Ser.* **2002**, *243*, 1.
[9] C. Franceschi, J. Campisi, *J. Gerontol., Ser. A* **2014**, *69*, S4.
[10] C. Franceschi, P. Garagnani, P. Parini, C. Giuliani, A. Santoro, *Nat. Rev. Endocrinol.* **2018**, *14*, 576.
[11] N. Thevaranjan, A. Puchta, C. Schulz, A. Naidoo, J. C. Szamosi, C. P. Verschoor, D. Loukov, L. P. Schenck, J. Jury, K. P. Foley, J. D. Schertzer, M. J. Larché, D. J. Davidson, E. F. Verdú, M. G. Surette, D. Bowdish, *Cell Host Microbe* **2018**, *23*, 570.
[12] National Center for Health Statistics, https://www.cdc.gov/nchs/fastats/deaths.htm (accessed: May 21, 2019).
[13] M. C. Morris, C. C. Tangney, Y. Wang, F. M. Sacks, D. A. Bennett, N. T. Aggarwal, *Alzheimers Dement.* **2015**, *11*, 1007.
[14] A. Harding, U. Gonder, S. J. Robinson, S. Crean, S. K. Singhrao, *Front. Aging Neurosci.* **2017**, *9*, 398.
[15] A. Montagner, A. Korecka, A. Polizzi, Y. Lippi, Y. Blum, C. Canlet, M. Tremblay-Franco, A. Gautier-Stein, R. Burcelin, Y. C. Yen, H. S. Je, M. Al-Asmakh, G. Mithieux, V. Arulampalam, S. Lagarrigue, H. Guillou, S. Pettersson, W. Wahli, *Sci. Rep.* **2016**, *6*, 20127.
[16] E. Biagi, L. Nylund, M. Candela, R. Ostan, L. Bucci, E. Pini, J. Nikkïla, D. Monti, R. Satokari, C. Franceschi, P. Brigidi, W. De Vos, *PLoS One* **2010**, *5*, e10667.
[17] E. Biagi, C. Franceschi, S. Rampelli, M. Severgnini, R. Ostan, S. Turroni, C. Consolandi, S. Quercia, M. Scurti, D. Monti, M. Capri, P. Brigidi, M. Candela, *Curr. Biol.* **2016**, *26*, 1480.
[18] P. Smith, D. Willemsen, M. Popkes, F. Metge, E. Gandiwa, M. Reichard, D. R. Valenzano, *eLife* **2017**, *6*, e27014.
[19] O. R. Jones, A. Scheuerlein, R. Salguero-Gómez, C. G. Camarda, R. Schaible, B. B. Casper, J. P. Dahlgren, J. Ehrlén, M. B. García, E. S. Menges, P. F. Quintana-Ascencio, H. Caswell, A. Baudisch, J. W. Vaupel, *Nature* **2014**, *505*, 169.
[20] T. C. G. Bosch, *BioEssays* **2009**, *31*, 478.
[21] B. J. Willcox, T. A. Donlon, Q. He, R. Chen, J. S. Grove, K. Yano, K. H. Masaki, D. C. Willcox, B. Rodriguez, J. D. Curb, *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 13987.
[22] B. J. Morris, D. C. Willcox, T. A. Donlon, B. J. Willcox, *Gerontology* **2015**, *61*, 515.
[23] A. M. Boehm, K. Khalturin, F. Anton-Erxleben, G. Hemmrich, U. C. Klostermeier, J. A. Lopez-Quintero, H. H. Oberg, M. Puchert, P. Rosenstiel, J. Wittlieb, T. C. G. Bosch, *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 19697.
[24] B. M. Mortzfeld, J. Taubenheim, S. Fraune, A. V. Klimovich, T. C. G. Bosch, *Front. Microbiol.* **2018**, *9*, 629.
[25] F. Seiler, J. Hellberg, P. M. Lepper, A. Kamyschnikow, C. Herr, M. Bischoff, F. Langer, H. J. Schafers, F. Lammert, M. D. Menger, R. Bals, C. Beisswenger, *J. Immunol.* **2013**, *190*, 1603.
[26] T. Becker, G. Loch, M. Beyer, I. Zinke, A. C. Aschenbrenner, P. Carrera, T. Inhester, J. L. Schultze, M. Hoch, *Nature* **2010**, *463*, 369.
[27] N. Libina, J. R. Berman, C. Kenyon, *Cell* **2003**, *115*, 489.
[28] J. Joseph, E. S. Ametepe, N. Haribabu, G. Agbayani, L. Krishnan, A. Blais, S. Sad, *Nat. Commun.* **2016**, *7*, 12748.
[29] C. Kenyon, J. Chang, E. Gensch, A. Rudner, R. Tabtiang, *Nature* **1993**, *366*, 461.
[30] C. J. Kenyon, *Nature* **2010**, *464*, 504.
[31] D. S. Hwangbo, B. Gersham, M. P. Tu, M. Palmer, M. Tatar, *Nature* **2004**, *429*, 562.
[32] F. Schächter, L. Faure-Delanef, F. Guénot, H. Rouger, P. Froguel, L. Lesueur-Ginot, D. Cohen, *Nat. Genet.* **1994**, *6*, 29.
[33] R. J. Angel, *Fam. Community Health* **2009**, *32*, S46.
[34] J. D. Pearson, D. E. Crews, *Am. J. Hum. Biol.* **1989**, *1*, 303.
[35] T. Gruenewald, in *New Directions in the Sociology of Aging* (Eds: L. Waite, T. Plewes), National Academies Press, Washington, DC, US **2013**.
[36] C. M. Worthman, E. J. Costello, *Ann. Hum. Biol.* **2009**, *36*, 281.
[37] K. C. Bauer, T. Rees, B. B. Finlay, *BioEssays* **2019**.

[38] G. J. Howie, D. M. Sloboda, M. H. Vickers, *Br. J. Nutr.* **2012**, *108*, 298.
[39] M. E. Symonds, S. P. Sebert, H. Budge, *Proc. Nutr. Soc.* **2009**, *68*, 416.
[40] S. R. de Rooij, *Int. J. Psychophysiol.* **2013**, *90*, 21.
[41] R. C. Painter, T. J. Roseboom, O. P. Bleker, *Reprod. Toxicol.* **2005**, *20*, 345.
[42] J. M. Rodriguez, K. Murphy, C. Stanton, R. P. Ross, O. I. Kober, N. Juge, E. Avershina, K. Rudi, A. Narbad, M. C. Jenmalm, J. R. Marchesi, M. C. Collado, *Microb. Ecol. Health Dis.* **2015**, *26*, 26050.
[43] M. B. Azad, T. Konya, H. Maughan, D. S. Guttman, C. J. Field, R. S. Chari, M. R. Sears, A. B. Becker, J. A. Scott, A. L. Kozyrskyj, CHILD Study Investigators, *Can. Med. Assoc. J.* **2013**, *185*, 385.
[44] W. M. Weikum, T. F. Oberlander, T. K. Hensch, J. F. Werker, *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 17221.
[45] J. M. Yano, K. Yu, G. P. Donaldson, G. G. Shastri, P. Ann, L. Ma, C. R. Nagler, R. F. Ismagilov, S. K. Mazmanian, E. Y. Hsiao, *Cell* **2015**, *161*, 264.
[46] N. Watanabe, M. Yamamoto, *Front. Neurosci.* **2015**, *9*, 154.
[47] P. Demakakos, J. P. Biddulph, C. de Oliveira, G. Tsakos, M. G. Marmot, *Eur. J. Epidemiol.* **2018**, *33*, 729.
[48] A. Singh-Manoux, N. E. Adler, M. G. Marmot, *Soc. Sci. Med.* **2003**, *56*, 1321.
[49] C. E. Finch, M. R. Rose, *Quart. Rev. Biol.* **1995**, *70*, 1.
[50] C. E. Finch, *The Biology of Human Longevity: Inflammation, Nutrition and Aging in the Evolution of Lifespans*, Academic Press, San Diego, CA **2007**.
[51] E. Jašarević, K. E. Morrison, T. L. Bale, *Philos. Trans. R. Soc. London, Ser. B* **2016**, *371*, 20150122.
[52] M. Carabotti, A. Scirocco, M. A. Maselli, C. Severi, *Ann. Gastroenterol.* **2015**, *28*, 203.
[53] M. Messina, *Nutrients* **2016**, *8*, 754.
[54] C. Nagata, *Am. J. Epidemiol.* **2001**, *153*, 790.
[55] A. E. Lethaby, J. Brown, J. Marjoribanks, F. Kronenberg, H. Roberts, J. Eden, *Cochrane Database Syst. Rev.* **2007**, CD001395.
[56] M. K. Melby, M. Lampl, *Ann. Rev. Anthropol.* **2011**, *40*, 53.
[57] J. M. Baker, L. Al-Nakkash, M. M. Herbst-Kralovetz, *Maturitas* **2017**, *103*, 45.
[58] K. D. R. Setchell, N. M. Brown, E. Lydeking-Olsen, *J. Nutr.* **2002**, *132*, 3577.
[59] K. D. R. Setchell, S. J. Cole, *J. Nutr.* **2006**, *136*, 2188.
[60] M. K. Melby, *Menopause* **2007**, *14*, 752.