

Our Gut Microbiome: The Evolving Inner Self

Parag Kundu,^{1,2,5,*} Eran Blacher,^{3,5} Eran Elinav,^{3,*} and Sven Pettersson^{1,2,4,6,*}

¹Singapore Centre for Environmental Life Sciences Engineering, 60 Nanyang Drive, Singapore 637551, Singapore

²Lee Kong Chian School of Medicine, Nanyang Technological University, 60 Nanyang Drive, Singapore 637551, Singapore

³Department of Immunology, Weizmann Institute of Science, 7610001 Rehovot, Israel

⁴Department of Microbiology, Tumor and Cell Biology, Karolinska Institute, SE-171 77 Stockholm, Sweden

⁵These authors contributed equally

⁶Lead Contact

*Correspondence: pkundu@ntu.edu.sg (P.K.), eran.elinav@weizmann.ac.il (E.E.), sven.pettersson@ki.se (S.P.)

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SUMMARY

The “holobiont” concept, defined as the collective contribution of the eukaryotic and prokaryotic counterparts to the multicellular organism, introduces a complex definition of individuality enabling a new comprehensive view of human evolution and personalized characteristics. Here, we provide snapshots of the evolving microbial-host associations and relations during distinct milestones across the lifespan of a human being. We discuss the current knowledge of biological symbiosis between the microbiome and its host and portray the challenges in understanding these interactions and their potential effects on human physiology, including microbiome-nervous system inter-relationship and its relevance to human variation and individuality.

Introduction

Without symbiosis, life on earth as we see it today would not exist. Symbiosis between microbes and simple one-cell organisms have been assumed to be essential for the subsequent expansion of multicellular eukaryotes, as well as for the diversification of species. Moreover, any given human cell carries remnants of prokaryotes in the form of mitochondria and organelles, without which we cannot sustain life. The last decades of research in understanding the symbiosis between the microbiome and its host has revealed new insights into mechanisms driving complex “multi-factorial” physiological and pathophysiological processes. The microbiome, a diverse ecosystem of mostly commensals and mutualists that occupies different niches in the human body, is assumed to interact with most, if not all, organs of the host. Although the microbiome can substantially vary between subjects and is influenced by nutrition, lifestyle, gender, diurnal changes, and physiology, it is hallmarked by distinctive compositional and functional features across different life periods. It is still debatable whether microbial shifts during an organism’s lifetime—for instance, during the shift from breastfeeding to solid nutrition during infancy, hormonal changes during puberty, maturation of the gastrointestinal tract in adulthood, and low-grade chronic inflammation associated with aging—merely reflect secondary biological changes occurring at different periods of life or whether they contribute to some of these age-related physiological transitions. Irrespective, the gut microbiome, which changes along the life cycle of the host, is increasingly considered to be a potent physiological contributor to development and homeostasis.

Given the microbiome’s potential person-specific physiological roles, recent studies suggest that it may serve as a good predictor for disease risk (Griffin et al., 2015), post-prandial glycemic

responses (Korem et al., 2017; Suez et al., 2014; Zeevi et al., 2015), the risk of re-gaining weight after weight loss (Thaiss et al., 2016), and more. With better understanding of the nature and mechanisms by which a microbiome in homeostasis changes during life and the means by which those changes affect biological pathways, one may envision that age-specific characterization of a disrupted (“dysbiotic”) microbiome may enable the prediction and stratification of disease risk in a number of complex lifestyle- and age-related human disorders, including inflammatory, metabolic, neoplastic, and neurodegenerative diseases. In this review, we focus on major hallmarks of the gut microbiome, the most diverse and well-studied commensal ecosystem in the human body, along the normal lifespan of healthy individuals. Other non-gastrointestinal and non-bacterial microbiomes may play equally important roles in human development but are less studied and discussed elsewhere (Ferretti et al., 2017; Shoemark and Allen, 2015).

The Neonatal Period

Until recently, it was generally assumed that newborns are sterile and that the initial microbial contact occurs during birth—a dogma first proposed by Tissier (Stinson et al., 2017; Tissier, 1900). The human placenta is thought to act as a barrier that selectively prevents maternal antibodies, toxic molecules, and microorganisms from translocating into the fetal bloodstream, thus maintaining the “sterility” of the growing offspring. Recent findings, however, challenge this sterility dogma by suggesting that diverse microbial communities may exist in human semen and in the womb (Hou et al., 2013; Mändar et al., 2015; Verstraelen et al., 2016). Moreover, a host of other studies suggest that parental microbial species may colonize different niches, even during normal embryonic development, including



the placenta (Aagaard et al., 2014; Pettker et al., 2007; Satokari et al., 2009; Stout et al., 2013; Zheng et al., 2015), the amniotic fluid (Bearfield et al., 2002; Markenson et al., 2003; Rautava et al., 2012) and the umbilical cord blood (Jiménez et al., 2005), indicating a maternal-to-offspring *in utero* initial colonization of selected microbes in the developing fetus. The presence of a transient microbial community in the meconium, the first stool of an infant, further supports a possible *in utero* route of colonization (Chang et al., 2011; Gosalbes et al., 2013; Jiménez et al., 2008a). Comparing multiple microbiome samples from mother-offspring pairs revealed shared microbial signatures between placenta, amniotic fluid, and meconium, which suggest that early gut colonization may be initiated prenatally by a distinct trajectory of maternal microbes (Collado et al., 2016). The placenta and the amniotic fluid, for example, showed similar signatures with relatively low diversity and Proteobacteria dominance (Figure 1). A majority of these studies are supportive of the notion that maternal gut microbiota is a key source that seeds the fetal gut. To test this hypothesis, Jiménez et al. colonized pregnant mice with genetically labeled *Enterococcus faecium* isolated from human breast milk and could successfully culture the labeled strain from the amniotic fluid of these mice 2 days before full term (Jiménez et al., 2005). Although these findings might endorse the vertical transfer of a less complex microbiome in the fetus prior to birth, this field is highly controversial due to the increased probability of contamination during the process of microbiome assessment in low-biomass specimens (Perez-Muñoz et al., 2017). Hence, further studies addressing this issue are warranted before a full consensus can be reached on these controversial findings.

Another major phase of vertical microbiome transmission occurs during birth. At the time of delivery, newborns are commonly exposed to vaginal microbes dominated by *Lactobacillus* and *Prevotella* spp. (Dominguez-Bello et al., 2010). In contrast, the microbiome of babies born via C-section is dominated by *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* spp. that differ from those of vaginal delivery and resemble microbial communities of skin (Dominguez-Bello et al., 2010). This maternal-to-offspring transfer of microbial species is an important early-life checkpoint because the newborn faces a massive metabolic switch as it leaves the uterine environment supported by the umbilical cord and initiates its own respiration and actively starts to seek for food.

Other potential sources of postnatal transmission are colostrum and breast milk. Some evidence indicates that colostrum and breast milk may constitute low biomass communities of symbiotic and potentially probiotic bacteria for the infant gut (Beasley and Saris, 2004; Heikkilä and Saris, 2003; Jiménez et al., 2008b; Martín et al., 2003, 2005, 2009), possibly supplying up to 8×10^4 to 8×10^6 bacteria daily (Heikkilä and Saris, 2003). This source of microbial inoculum, together with the unique and massive lipid burst in breast milk, increases the diversity and functionality of the infant's perinatal gut microbiome as reflected by the shift from meconium to a much more complex fecal microbiome during the first week of life (Moles et al., 2013). Intriguingly, each mother appears to harbor a unique microbial pattern in her breast milk (Martín et al., 2007), suggesting a possible individualized microbial mother-to-infant imprinting. Several reports

also indicate a commonality in bacterial strains in this initial mother-to-infant vertical transfer of microbiomes, with most occupants belonging to genera *Lactobacillus*, *Staphylococcus*, *Enterococcus*, and *Bifidobacterium* (Albesharat et al., 2011; Fernández et al., 2013; Jiménez et al., 2008c; Makino et al., 2011; Martín et al., 2003, 2009; Matsumiya et al., 2002) (Figure 1). In contrast, formula feeding may considerably alter our gut microbiota during this initial stage of microbial priming in early life by changing the composition of microbial communities (Bezirtzoglou et al., 2011; Le Huërou-Luron et al., 2010). The relative contribution of these milk-associated low-biomass microbial communities—and their impact on physiology and disease later in life—merits further studies.

Early Stage Maturation

The relatively simple maternally acquired microbiome gradually matures and acquires greater complexity upon introduction of dietary supplements, solid food, and withdrawal from breast milk to increasingly resemble that of a typical omnivore (Favie et al., 2002; Palmer et al., 2007). In particular, the dominance of *Bifidobacteria* in the microbiome, best suited to process milk oligosaccharides (Sela et al., 2008), diminishes with the introduction of solid food (Palmer et al., 2007). This gradual microbiome transition from an infant to a functionally more mature gut microbiome coincides with rapid development of the immune system, as well as a significant alteration in dietary intake. This transition is believed to take up to three years with maximal shifts in the relative abundances of taxonomic groups. Antibiotic treatment during this critical period may alter this transition phase and the composition of this childhood microbiome (Koenig et al., 2011). During this period, the infant microbiome is characterized by the presence of microbial genes facilitating the breakdown of polysaccharides from plants in exclusively breast milk-fed infants (Koenig et al., 2011; Kurokawa et al., 2007; Vaishampayan et al., 2010), exemplifying how the microbiome may acquire properties “priming” its host for its anticipated shift toward a plant-derived diet. A broad cross-cultural study identified differences in bacterial pathways between babies and adults irrespective of geographic location. For instance, babies' microbiomes were enriched in *de novo* folate biosynthesis genes, whereas adults featured an enrichment in genes involved in metabolism of dietary plant-derived folate (Yatsuneneko et al., 2012). Intriguingly, a greater inter-personal functional gene variability among infant gut microbiomes compared to adults (Kurokawa et al., 2007) reflects maternally acquired microbial signatures being gradually overridden with increase in gut microbial biodiversity and complexity of the growing infant. A longitudinal comparative study on Malawian twin pairs below 3 years of age who became discordant for kwashiorkor showed abnormal microbiome signatures in the malnourished ones when compared to their healthy co-twins (Smith et al., 2013). Interestingly, transplantation of fecal microbiota from the kwashiorkor co-twins into germ-free mice fed with nutrient-deficient Malawian diet led to marked weight loss in the recipients compared to mice harboring the healthy sibling's microbiota (Smith et al., 2013), suggesting the causal relevance of early-life gut microbiomes in malnutrition-associated diseases, a key global health problem of this century.

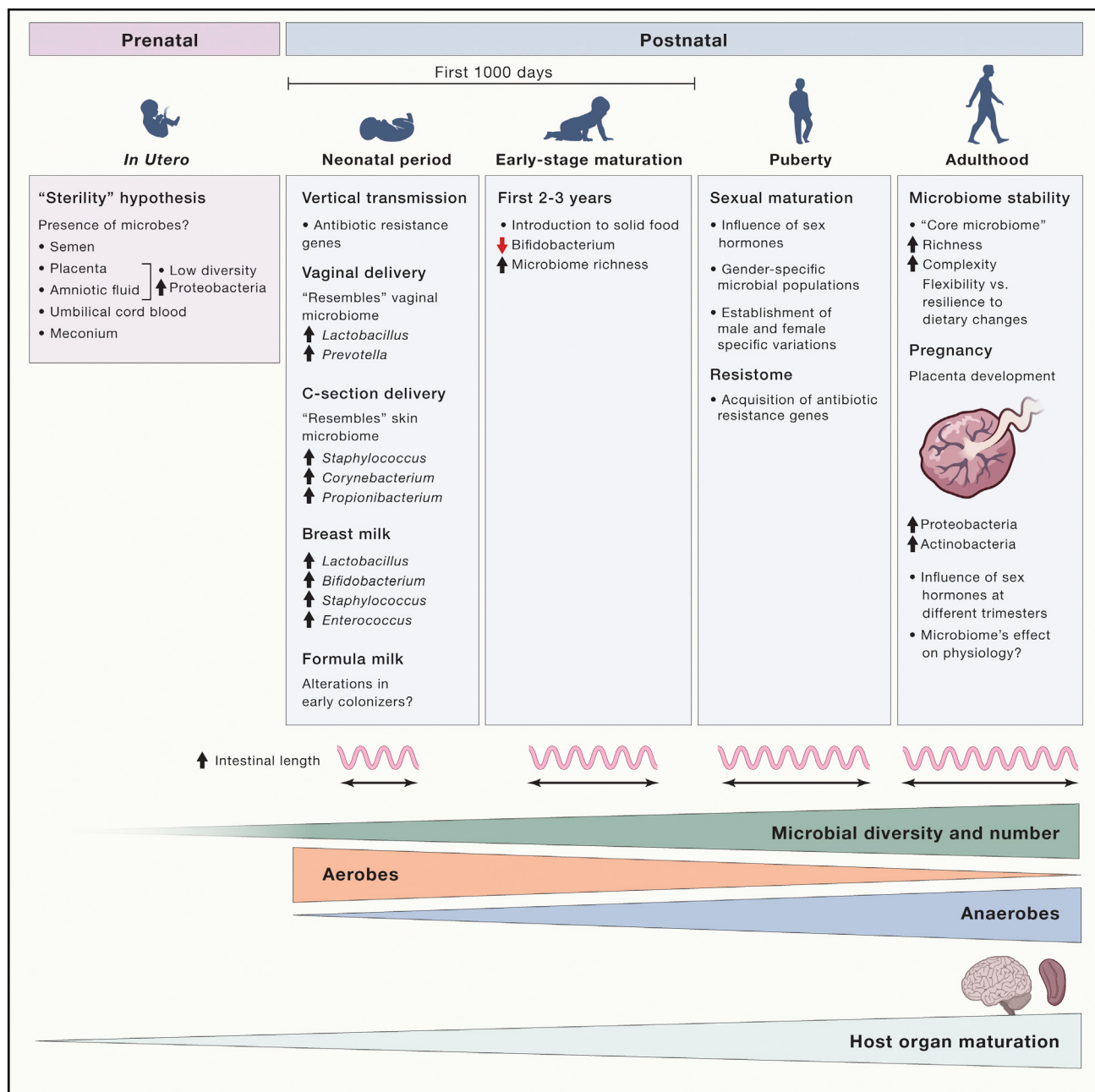


Figure 1. Gut Microbiome Changes from Infancy to Adulthood

The composition of the gut microbiome changes with host's age. According to the existing notion, our embryo is sterile; however, presence of microbes in semen, placenta, amniotic fluid, umbilical cord blood, and meconium contests this hypothesis and suggests colonization of the fetus *in utero*. The mode of delivery and the choice of diet (breast milk or formula milk) after birth influence the colonization process in the newborn. With age, introduction to solid food brings in additional complexity to the immature, less complex microbiome. Puberty-associated influx of sex hormones introduces features related to gender specificity of the existing microbiome. Finally, in adults, the richness and complexity of the gut microbiome peaks with the formation of a robust “core microbiome” that adds flexibility and reduces vulnerability to external and internal challenges. This process of microbiome maturation takes place in parallel with development of host organs, including the intestine, which elongates with age, providing additional niches for the microbiome to expand in number and diversity.

Already at this developmental stage, the infant gut microbiome may influence many different organs and systems. The “microbiome-gut-brain axis” (Braniste et al., 2014; Collins et al., 2012; Diaz Heijtz et al., 2011; O'Mahony et al., 2011; Rhee et al., 2009) represents the complex crosstalk between the gut,

its microbiome, and the brain. An essential component of this axis that may also be influenced by the gut microbiota is the enteric nervous system (ENS). Apart from directly controlling the physiology and functioning of the intestine, such as peristalsis, intestinal blood flow, and epithelial secretion (Kabouridis

et al., 2015; Obata and Pachnis, 2016), the ENS also communicates bi-directionally with the central nervous system (CNS) by neuronal transmission via vagal parasympathetic and sympathetic tracts. A direct effect of the gut microbiota on ENS has been demonstrated by decreased enteric neural networks and associated deficits in gut functioning in germ-free animals (Kabouridis et al., 2015; Obata and Pachnis, 2016). Even though the infant gut microbiota is less diverse, it has a significant impact on ENS development, as recently shown by the reduction of myenteric neurons in germ-free mice at postnatal day 3 compared to conventionally raised mice (Collins et al., 2014; Kabouridis et al., 2015). The downstream effects of these developmental alterations in microbiome on host's CNS development and function merits further studies, given some suggested correlations between early life compositional changes in the microbiome to neurological diseases occurring later in life. Altogether, it is evident that the first 2 to 3 years of human life are crucial for what may be considered as "the basic maturation" of the microbiome, which is shaped by major dietary shifts and the developing immune system and possibly influences CNS and ENS development and its functions.

Puberty

Adolescence and puberty constitute a phase of life associated with major physiological changes related to sexual maturation and a transition toward adulthood. This period of major developmental changes is predominantly driven by hormones and an intense inter-organ crosstalk including organs like the brain, skin, and genitalia. Therefore, this period represents a captivating age to survey potential hormonal impacts on the gut microbiome. Indeed, diversification of gender-specific gut microbiomes appears to outset during this age (Markle et al., 2013). In parallel, with increasing age, there is a gradual reduction in the population of aerobes and facultative anaerobes, with a simultaneous upsurge in the number of anaerobes (Hopkins et al., 2002). In mice, the nearly identical gut microbiomes of male and female at weaning diverges into distinct gender-specific populations during puberty (Markle et al., 2013). Surprisingly, transfer of gut microbiota from adult males to immature females altered the recipient's microbiota, leading to elevated levels of testosterone release similar to males and conferred protection against diabetes (Markle et al., 2013). It remains to be explored if a similar phenomenon exists in humans and whether hormonal changes occurring at puberty initiate gut microbiome shifts or, alternatively, changes in the microbiome influence some of the hallmarks of sexual maturation, behavior, or hormonal secretion patterns.

In contrast to previous reports (Koenig et al., 2011; Palmer et al., 2007), recent studies suggest that adolescents feature a less complex and considerably different microbiome from that of adults, even though they apparently share a core microbiome configuration (Agans et al., 2011; Ringel-Kulka et al., 2013). In particular, it was observed that while adolescents have significantly higher levels of *Clostridia* and *Bifidobacteria* genera compared to adults, the number of species between the two groups remained similar (Agans et al., 2011; Hollister et al., 2015). Moreover, the adolescent microbiome was found to functionally differ from that of adults, expressing genes related to

development and growth, while the adult microbiome was more associated with inflammation and obesity (Agans et al., 2011; Hollister et al., 2015). It is increasingly recognized that during the maturation from infancy to adolescence, the microbiome acquires a repertoire of antibiotic-resistance genes termed the "resistome" (Moore et al., 2013). Whether the presence of these antibiotic-resistance genes in early-life microbiome influences host-microbiome co-existence is an outstanding question. Adolescence marks the onset of several mood disorders, like anxiety, depression, psychosis, schizophrenia, and eating disorders (Kessler et al., 2005; Paus et al., 2008). In parallel, key developmental processes—like synaptic pruning (a progressive fine-tuning of the brain achieved by erasing synapses [Holtmaat and Svoboda, 2009]) and increased myelination (especially in the frontal cortex [Benes, 1989; Fair et al., 2008])—are achieved during adolescence. Whether microbiome variations impact these processes in this age group merits further investigation.

Adulthood

The adult microbiota is relatively more stable compared to that of early life (Borre et al., 2014; Palmer et al., 2007), probably due to the development of what looks like a core community of permanent colonizers that buffer exogenous insults like stress and exposure to antibiotics and help restore the original microbial configuration upon these challenges (Rajilić-Stojanović et al., 2012). Thus, it seems like a core gut microbiome exists at the functional level (what they do) among healthy adults, despite the high level of individual variation (who they are) (Turnbaugh and Gordon, 2009). Increased microbial richness and complexity, a hallmark of the adult microbiome, is supported by age-associated gradual expansion in gut surface area that peaks in adults (Saffrey, 2014; Weaver et al., 1991), creating additional distinct niches for the recruitment of new symbionts (Figure 1). Although the adult microbiome is personified as mature and fairly stable, it may still be amenable to changes by environmental perturbations. A recent study shows that even a short-term exposure to either plant-based or animal-based diet can dramatically change the adult gut microbial community structure (David et al., 2014), indicating the tremendous flexibility of the communities to functionally evolve. Other studies involving short-term human nutritional interventions challenge that notion and offer a more nutritionally resilient view on the microbiome (Korem et al., 2017). Moreover, environmental shifts, like seasonal variations or temperature fluctuations, have also been suggested to influence gut microbiota in animals by changing their composition and function (Chevalier et al., 2015; Maurice et al., 2015). Thus, differences observed in the gut microbiota of adults living in distant countries (Yatsunenko et al., 2012) are plausibly the outcome of multiple region-specific environmental factors that collectively shape the composition and function of the gut microbiome (Bonder et al., 2016; Goodrich et al., 2016; Wang et al., 2016). High altitude has also been implicated as a factor in modulating microbiome configuration. A recent report suggests that the microbiomes of high-altitude ruminants have evolved to support energy harvest in these extreme environments (Zhang et al., 2016). It is possible that reduced oxygen availability in high altitudes could be another contributor in regulating gut microbiome dynamics in the host.

During pregnancy, a major alteration in the composition of gut microbiome occurs particularly in the third trimester with increased abundance in Proteobacteria and Actinobacteria species (Collado et al., 2008; Koren et al., 2012). Transplantation of microbiome from third-trimester mothers into germ-free mice induced metabolic changes like increased body-weight gain and inflammatory responses compared to recipients transplanted with microbiota from first-trimester mothers (Koren et al., 2012). Of note, a follow-up study by DiGiulio et al. was unable to detect major shifts in gut microbiomes of mothers between trimesters (DiGiulio et al., 2015). It is tempting to speculate that alterations in gut microbiome composition, together with dramatic changes in hormonal dynamics during pregnancy and early postpartum periods, may affect the psychiatric balance and well-being of mothers and, in some cases, predispose them to develop psychiatric problems like anxiety and depression. Whether these hormonal and microbial fluctuations during pregnancy impact the psychiatric homeostasis of mothers later in life remain to be scrutinized (Borre et al., 2014).

Aging

As humans age, they universally develop a gradual loss of function in multiple organ systems related to growth, metabolism, energy homeostasis, and immunity. Several studies have attempted to examine the aging-related changes in the dynamics of the gut microbiome by comparing the microbiome composition of infants and adults to those of elderly people and centenarians (Biagi et al., 2010, 2016; Claesson et al., 2011, 2012; Mariat et al., 2009; Ottaviani et al., 2011). One of the pioneering studies in this field that characterized the microbiome profiles of 161 elderly Caucasian individuals using 16S rDNA sequencing revealed a dramatic shift from Firmicutes that dominate the gut microbiome of young adults toward Bacteroidetes in the elderly aged over 65 years (Claesson et al., 2011). In fact, the proposed core microbiome—defined as the unique microbiome species present in at least 50% of the participants—was significantly different between old and young humans. The genera *Bacteroides*, *Alistipes*, and *Parabacteroides*, which comprised more than half of the core microbiomes of elderly, represented merely 8%–27% of the microbiome core in the younger cohort (Claesson et al., 2011). Interestingly, a strong inter-individual variability was noted in the elderly gut microbiome, with maximal fluctuations featuring *Faecalibacterium* and *Ruminococcus*. Some *Clostridium* clusters, especially IV and XIVa, were also highly variable in their proportions. Furthermore, time-dependent sampling of microbiome from the same individuals revealed that inter-individual variability was way greater than intra-individual variations with time (Claesson et al., 2011). However, the 3-month study period chosen to monitor intra-individual variations may not have been sufficient to capture major community shifts. Hence, the dynamics that occur as the microbiome evolves across decades, comprising the lifespan of an individual, may have been under-represented in this experimental scheme. Longitudinal human population studies are warranted in studying microbiome changes, potentially contributing to a healthy aging process.

The links between the microbiome and age-related health decline (Claesson et al., 2012) are influenced by residential

status, lifestyle, and diet, since the microbiomes of elderly living in long-term residential care bear a distinct signature from community-dwelling elderly individuals and young participants (Figure 2). Bacteroidetes were enriched in the long-stay group, while Firmicutes dominated the community-dwelling microbiome. *Coprococcus* and *Roseburia* were the most abundant genera in community-living subjects, whereas *Coprobacillus*, *Anaerotruncus*, *Parabacteroides*, *Lactonifactor*, and *Eubacterium* characterized the microbiome of individuals residing in long-stay communities (Figure 2). Correspondence analysis describing microbiome variance based on food consumption between community-dwelling and long-stay elderly groups had clustered individuals into four groups according to their fiber/fat consumption ratio. In general, community-dwelling subjects were found to consume a more fiber-enriched diet, which correlated with a more diverse microbiome and reduced inflammatory state (serum TNF- α , IL-6, IL-8, and C-reactive protein). While this study was performed on a relatively small number of individuals and did not confirm microbiome components to feature causative impacts on “healthy aging,” metagenomic shotgun sequencing revealed an enrichment in bacterial genes associated with the metabolism of short-chain fatty acids (SCFAs)—specifically acetate and butyrate—in the community-dwelling microbiome compared to long-stay individuals, thus suggesting an association between microbiome features of the long-stay group and health parameters—such as functional independence (FIM), Barthel index and nutrition (MNA), and blood pressure and calf circumference—indicating overall frailty (Claesson et al., 2012) (Figure 2). These interesting associations merit future mechanistic follow-up studies.

Aging research in small animal models have identified distinct microbiome changes, particularly in aged mice, that bear partial resemblance to microbiome changes observed in humans with a similar condition. Although the significant expansion of *Alistipes* genus noted in middle-aged and old mice was also documented in humans, a negative correlation between the abundances of *Faecalibacterium* and *Lactobacillus* and frailty was observed in humans but not in mice. As opposed to some of the human studies, the microbiomes of old mice did not feature any representation of the *Eubacteriaceae* family members, and no differences in the Firmicutes:Bacteroidetes ratios were observed (Langille et al., 2014). However, some similarities between the aged human and mouse microbiomes—for instance, low levels of microbiome-associated metabolites cobalamin (vitamin B12) and biotin (vitamin B7) and their respective microbial metabolic pathways—do exist. In contrast, creatine and creatinine degradation were elevated with age, correlating with muscle atrophy and frailty, as in humans (Langille et al., 2014) (Figure 2). In mice, some studies have reported a decrease in *Lactobacillus* spp. with aging (Zhang et al., 2013), which was not recapitulated by others (Langille et al., 2014). Interestingly, the genus *Akkermansia*, which is associated with beneficial effects in certain diseases in mice and humans, significantly decreased in middle-aged mice and almost completely disappeared in old mice (Langille et al., 2014). Since *Akkermansia* is involved in intestinal remodeling and autophagy and controls intestinal absorptive capacity via maintenance of the Bacteroidetes/Firmicutes dynamics (Chevalier et al., 2015),

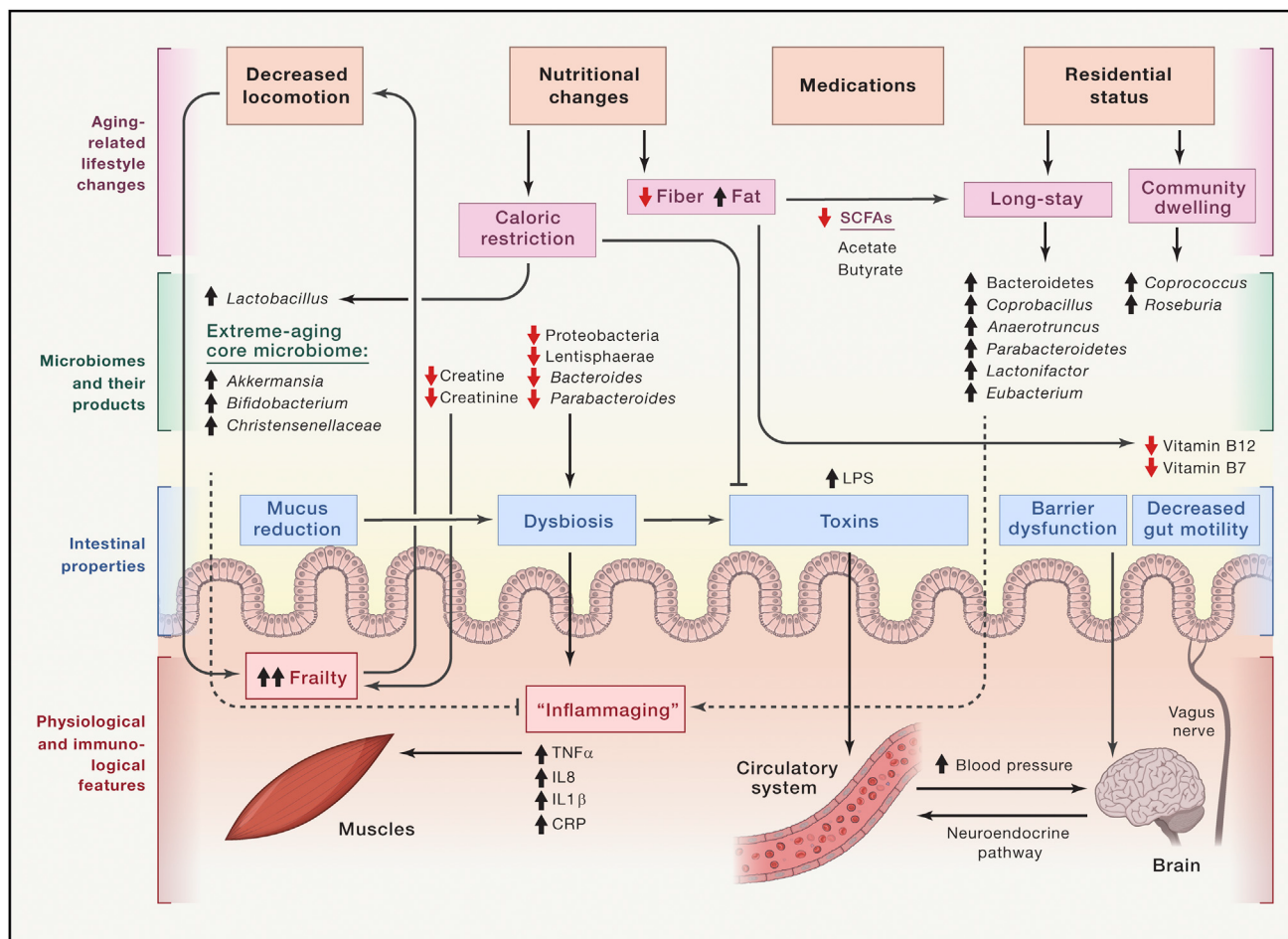


Figure 2. The Gut Microbiome in Aging

Aging is accompanied by significant changes in lifestyle, such as decreased locomotion, nutritional changes, chronic consumption of medications, and in some cases, change in residential status. It is yet to be fully determined whether these factors lead to microbiome shifts that further support aging-related deterioration or the personalized microbiome itself dictates some of the physiological responses to the changing environment with aging. The general expansion of Bacteroidetes at the expense of Firmicutes phyla was observed in individuals over 65 years, in particular the reduced richness of the phyla Proteobacteria and Lentisphaerae and the genera *Bacteroides* and *Parabacteroides*. Microbiome-associated metabolites, such as vitamins B7 and B12, creatine and creatinine, and their biosynthetic pathways, are reduced in aging, contributing to muscle atrophy and frailty. The microbiomes of individuals living in long-term residential care are significantly different than those of community-dwelling elderly people, most likely due to nutritional regimes richer in fiber in the community-living group, which is further supported by enriched short-chain fatty acid (SCFA) synthesis genes in this group. In contrast, a low-fiber diet correlates with increased inflammatory state and frailty. In mice, caloric restriction correlates negatively with blood LPS levels and frailty and positively with *Lactobacillus* levels. In semi-supercentenarians, a core microbiome with enriched health-associated *Bifidobacteria*, *Christensenellaceae*, and *Akkermansia* was identified. The substantial microbiome change in aging may affect changes in gut physiology such as reduced bowel contractility, decreased mucus secretion, gut-barrier dysfunction, and consequential dysbiosis. These changes can further mediate the translocation of bacterial toxins and metabolites into the bloodstream and affect brain function through circulatory, immune-mediated, hormonal pathways or by a direct neural transmission via the vagus afferents.

its disappearance with age merits further retrospection. The age-related changes in mouse microbiome might arise from differences in environment, mostly dietary factors. For example, long-term caloric restriction (CR; e.g., 30% restriction of diet) in mice fed with a low-fat diet enriched *Lactobacillus* communities with aging and was associated with prolonged lifespan and reduced serum lipopolysaccharide (LPS) levels (Zhang et al., 2013). On the contrary, most of the microbiome species responding to CR in mice fed with a high-fat diet were distinctly different and belonged to *Porphyromonadaceae* family (Zhang et al., 2013). In contrast to the effects of dietary habits or residential status on microbiome composition in the elderly, the role of

host intrinsic factors in this process remain less studied. Langille and coworkers monitored the fecal microbiome of young (~174 days), middle-aged (~589 days), and old (~857 days) C57BL/6J mice and noticed significant age-dependent differences in the microbiomes of these genetically similar cohorts (Langille et al., 2014). This suggests that intrinsic cues from the aging host may modulate microbiome composition, function, and richness. However, husbandry-related confounders need to be ruled out in that regard.

Other age-related host functions that could impact microbiome configuration may include menopause in women impacting estrogen levels, which in turn have “spillover” effects on

muscle and bone growth and functions (Chen et al., 2017; Maltais et al., 2009). Recent findings from the Pettersson lab (P.K. and S.P., unpublished data), involving microbiome transplants from conventionally raised young or old mice into germ-free young mice suggested enhanced growth-promoting potential of the old donor microbiota compared to that of the young in metabolically active organs like the intestine and hippocampus. These growth-supporting signals, generated by the old donor microbiome (old microbiome), suggest an interesting microbiome-mediated link to the observed increased incidence of cancers with age. Whether some of these changes contribute to histological, behavioral, or clinical manifestations of aging merits further studies.

Our brain is also subject to age-related unwanted changes, like impaired development in early life or accelerated neurodegeneration later in life. Intriguingly, clinical associations between some neurodegenerative disorders and gastrointestinal disorders, including autism spectrum disorders (Hsiao et al., 2013), Parkinson's disease (PD; Fasano et al., 2015; Hardoff et al., 2001; Jost, 1997; Kelly et al., 2014), and Alzheimer's disease (AD; Chen et al., 2016), have prompted interest in exploring possible links between microbiome disturbances and manifestations of these disorders. Indeed, microbiome-CNS associations in animal models have been highlighted in autism (Hsiao et al., 2013), PD (Kelly et al., 2014; Sampson et al., 2016), and AD (Harach et al., 2017). Preliminary studies in humans suggest that PD is associated with alterations in gut microbiome composition, particularly in the genus *Prevotella* and enterobacteria (Scheperjans et al., 2015), the impact of which on intestinal or other manifestations of PD remains to be studied. Multiple cell types and pathways can mediate this "gut microbiome-central nervous system" axis (Figure 3). Collectively, these interesting associations (discussed extensively in Sharon et al. [2016] and Lee et al. [2017]) stress the importance and necessity of further investigation of the mechanisms orchestrating gut microbiome-nervous-system axis in order to broaden the knowledge needed in deciphering the environmental component of neuropathologies and in establishing potential microbiome-based therapies addressing this environmental factor.

Extreme Aging: The Centenarians

An interesting approach aimed at understanding potential roles of the gut microbiome in aging and longevity involves the exploration of the microbiome of extremely elderly individuals (Biagi et al., 2010, 2016). Studies exploring the microbiome at the extremes of human lifespan have pointed out that the differences in the gut microbiome composition between young adults and elderly subjects (separated by ~40 years) are smaller than the differences observed between the elderly people and centenarians, separated by <30 years of life. Biagi et al. examined the microbiome of young adults, elderly adults, and 24 semi-supercentenarians (105–109 years old) (Biagi et al., 2016) to identify a possible core aging-related microbiome that seems to be stable across age but differ in the relative abundance of species that contribute to this microbiome core (Biagi et al., 2016). One of the most striking findings was the emergence of a unique microbial footprint in semi-supercentenarians characterized by increased abundance of "health-associated" taxa

like *Bifidobacterium*, *Christensenellaceae*, and *Akkermansia* (Figure 2) (Biagi et al., 2016). While demonstration of causation of such "beneficial" microbiomes has yet to be performed, it provides the fascinating glimpse of a possible biological print that could be used to explore sets of "aging-supportive" microbial communities and functions.

Impact of the Microbiome on Lifespan

The contribution of the gut microbiome to human lifespan has not been studied to date. However, several studies in simpler life forms and recently in animal models represent the beginning of the exploration into how genomes within metaorganisms may interact to influence host longevity. Invertebrate model systems such as the fruit fly *Drosophila melanogaster* and the nematode *Caenorhabditis elegans* were used as attractive and proof-of-concept models for studying the possible microbiome-aging axis, as they harbor a microbiota both in nature and in the laboratory (Ren et al., 2007; Zhang and Hou, 2013). Such studies produced interesting observations related to age-dependent interactions between *C. elegans* and specific worm commensal bacteria and how they may significantly impact worm lifespan. For example, *E. coli* "OP50" bacteria (Watson et al., 2013; Zhang et al., 2012) and *Comamonas* "DA1877" were shown to induce differential metabolic responses in the worm, modulating development and aging (MacNeil et al., 2013; Watson et al., 2013). A recent study highlighted the role of nitric oxide (NO), produced exclusively by NO-producing commensal bacteria, in regulating worm longevity (Gusarov et al., 2013). Lately, two other studies demonstrated that the anti-diabetic medication metformin, previously shown to be a potent *C. elegans* longevity factor, acts on the folate metabolism pathways of *C. elegans*' commensal bacteria, resulting in reduced worm microbiota methionine content that, in turn, enhances worm longevity (Cabreiro et al., 2013; Virk et al., 2012). Interestingly, Han et al. recently found a set of 29 *E. coli* genes that, when deleted, increased the lives of their *C. elegans* hosts significantly, suggesting a robust microbial link to longevity in more complex organisms (Han et al., 2017). The study highlights a unique mechanism where colanic acid, a bacterial polysaccharide, promotes lifespan increase in worms by modulating mitochondrial dynamics and unfolded protein response in the host (Han et al., 2017).

As in *C. elegans*, several recent studies highlighted possible regulatory effects of the microbiota on aging of *D. melanogaster* flies. A newly discovered aging-relevant signaling pathway in the fly gut epithelial layer was recognized to be regulated by the transcription factor Foxo, which reduces a downstream innate immune sensor named SC2 (Guo et al., 2014). Impaired signaling through this pathway was shown to drive compositional and functional alterations in the fly microbiota, disruption in epithelial integrity, and a reduction in the lifespan of flies. Restoring this pathway enhanced longevity, suggesting that the microbiota and its effects on host transcriptional programs may act as longevity factors (Guo et al., 2014). In the *Drosophila* larvae, growth on a nutrient-poor diet drove growth retardation that was secondary to the activity of the fly microbiota—in particular the *Lactobacillus plantarum* strain, which induces upregulation of the host TOR pathway. Since TOR suppression is linked to

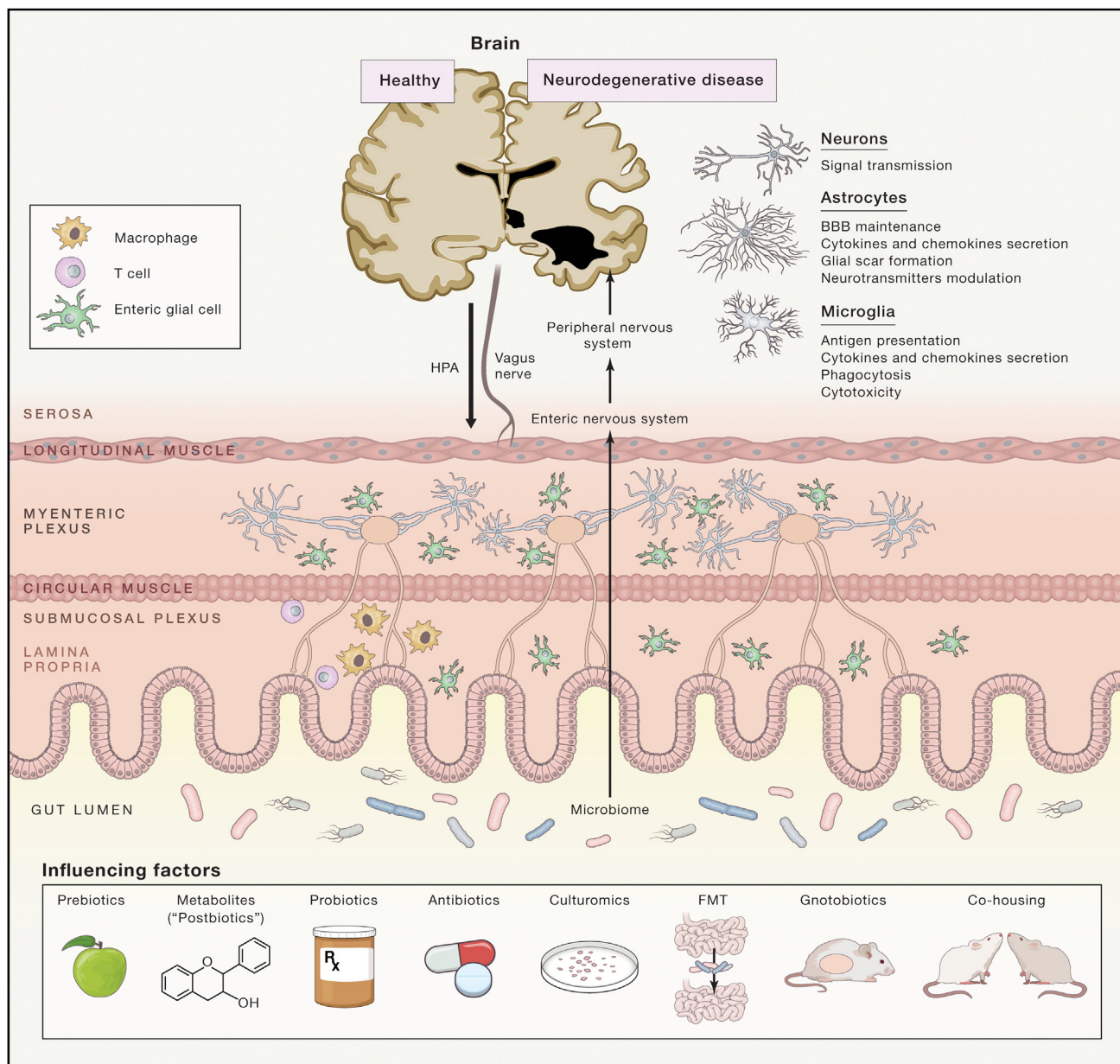


Figure 3. The Bi-directional Microbiome-Gut-Nervous System Crosstalk and Possible Means of Manipulating It

The crosstalk between the gut microbiome and the central nervous system (CNS) is a complex network of interaction only starting to be understood. Microbial-associated molecules are constantly sensed by immune cells (e.g., macrophages and dendritic cells) and enteric glial cells (EGCs) in the lamina propria that can further secrete neuro-modulatory signaling molecules, affecting enteric nerves in the submucosal and myenteric plexi. The brain and the spinal cord can be affected from the enteric nerves' response or from these microbial-associated signals directly from vagal transmission or by systemic circulation through the choroid plexus in the brains' ventricles. In the CNS, different cell types, such as neurons, microglia, and astrocytes, might respond to these signals by changing their transcriptional program in a way that supports or inhibits pathological conditions. Phagocytosis of pathogenic amyloid beta ($A\beta$) plaques, elevation of $A\beta$ degrading enzymes, and secretion of nitric oxide (NO) and inflammatory cytokines and chemokines in Alzheimer's disease are possible examples of such cellular responses. An increased arsenal of research paradigms is evolving to assist in dissecting the mechanisms underlying microbiome-gut-brain axis in neuropathologies. These paradigms include the usage of chronic antibiotics treatment and germ-free animal models for neurological diseases; fecal microbiome transplantation from human patients or animal models into antibiotic-treated- or germ-free animals; co-housing of animal models with naive or specifically colonized controls; treatment with pre-, pro-, or postbiotics to colonize the gut with selected microbiome of choice; and application of culturomics methodologies to isolate potential disease-relevant bacterial strains.

enhanced longevity across species, it will be interesting to determine if microbiota members such as *L. plantarum* may regulate aging, in addition to its noted effects on growth (Storelli et al.,

2011). Whether such interesting microbiome roles also impact more complex life forms—including humans—and if such putative longevity mechanisms could be manipulated remains

elusive and merits further studies. Notably, a recent interesting association between the microbiome and age-related inflammation was described in a mammalian model (Thevaranjan et al., 2017). Germ-free mice were shown to live longer than conventionalized mice and feature reduced levels of circulatory pro-inflammatory cytokines. Co-housing of germ-free mice with old conventional animals, but not with young conventional animals, resulted in an increased inflammatory state. The aging-dependent microbiome's effect on inflammation was suggested to be mediated by TNF- α , as co-housing of germ-free mice with *tnf α ^{-/-}* mice or anti-TNF- α treatment abolished the age-associated inflammation (Thevaranjan et al., 2017). The short-lived African turquoise killifish (*Nothobranchius furzeri*) is being increasingly used and seems to be an attractive model to study aging. Interestingly, microbiome transplantation from young to middle-aged killifish resulted in increased lifespan, delayed aging-related behavioral features, and higher microbial diversity in the young microbiome transplanted fish (Smith et al., 2017).

Conclusions and Prospects

The Dynamics of the Microbiome

In multiple association studies, the gut microbiome seems to feature hallmark characteristics in different life phases. Starting with a relatively simple microbial composition, which appears to be impacted by the mode of delivery at birth, the offspring matures with an increased microbiome complexity associated with environmental and physiological influences, such as nutrition, lifestyle, hormonal changes, immunity, and possibly microbiome-gut-brain axis crosstalk. Although considered flexible and influenced by environmental cues, the microbiome's composition and function is probably dominated by a slowly changing, vertically transmitted core microbiome coupled with a more "flexible" microbial component that responds more quickly to environmental dynamics. Humans seem to substantially vary in their microbial societies and their functions in part due to geographic location and dietary intake. These variabilities may be utilized as part of personalized medicine, in which patient- or disease-specific microbes and/or their metabolites would be clinically exploited as potential diagnostics or as therapies. Although much progress has been made in characterizing microbial signatures associated with different stages of life, more research needs to determine whether and which components of the microbiome confer causal effects on the holobiont. Reasonably, there is an imminent need to include functional studies in microbiome research involving transcriptomics to better understand the intricate crosstalk between the microbes and their host. Due to the field's young age, it is currently lacking prospective studies following microbial changes within the same individual across life. At present, most age-related studies remain at a descriptive level, reporting microbial compositional changes between different age groups, while to the best of our knowledge, there are no studies presenting a causal relation between age-dependent phenotypes and specific microbiome and/or their products. For example, it would be imperative to examine the aging process of germ-free mice colonized with microbiomes of individuals of different ages. Further limitations stem from the frequent use of 16S rDNA sequencing as a means of microbiome characteriza-

tion, which allows identifying most bacteria only down to the genus level. Utilizing shotgun metagenomic sequencing could enable the identification of specific aging-driving or affected bacterial strains, which could then be cultured (if possible) and studied in depth using germ-free animals and transgenic animal models of age-dependent diseases. Metatranscriptomic approaches could further help pinpoint specific microbial pathways involved in the process of aging and age-related disorders. This integrative approach would potentially lead to deciphering the mechanisms by which the microbiome is being affected and/or is actively affecting maturation and aging. Likewise, better awareness should be paid to experimental conditions, enabling better reproducibility between studies (Stappenbeck and Virgin, 2016).

The interesting recent observations highlighting the possible colonization of low-biomass microbial communities within tissues and organs—like fat, urinary bladder, gallbladder, and the placenta (Aagaard et al., 2014; Brubaker and Wolfe, 2017; Pettker et al., 2007; Satokari et al., 2009; Schieber et al., 2015; Stout et al., 2013; Verdier et al., 2015; Zheng et al., 2015)—raise the possibility of functional roles they may play in organ homeostasis or perturbation. In this regard, an elegant example recently demonstrated how simply altering the experimental conditions may impact conclusions reached on the effects of microbiome on host physiology. Methane gas is required to allow microbes to enter eukaryotic cells of deep-sea clams (Assié et al., 2016). However, harboring the deep-sea clams under laboratory conditions in the absence of methane results in evasion of the microbes from the clams, leading to an impaired physiological function of the clam. This suggests that low-biomass microbial colonization of seemingly sterile tissues may impact their functions, but their study may necessitate distinct environmental conditions that may be missed in the "regular" laboratory setting.

Finally, it is becoming clear that microorganisms, like humans, live in communities that, in some cases, form distinct biofilm structures. The *in vivo* communication networks underlying these highly structured microbial societies and their impacts on the host are poorly studied in the *in vivo* microbiome setting and merit further exploration.

Emerging Human Microbiome Intervention Strategies

Treatments targeting the microbiome are considered as potentially attractive future modalities, as gut microbes are relatively accessible to interventions through oral routes and since the microbiome—in contrast to the human genome—may be potentially amenable to change by such interventions. However, reliable and reproducible interventions specifically targeting microbes of interest are currently limited. Fecal microbiota transplant (FMT) from tested donors seems particularly promising for patients with *Clostridium difficile* enterocolitis, but its efficacy in age-related disorders is yet to be tested. Probiotics are another such intervention, but their colonization efficiency and downstream host effects remain controversial. An example of a provocative and currently speculative probiotic modality aimed at utilizing specific bacteria toward induction of healthy mind-altering effects is collectively termed "psychobiotics" (Kao et al., 2016). According to recent reports, administration of specific microbial species may impact brain function either by

modulating the levels and availability of neurotransmitters, such as serotonin, glutamate, and γ -aminobutyric acid (GABA), or by affecting immunological functions or hormonal signals (e.g., glucocorticoids-mediated responses) of the hypothalamic-pituitary-adrenal (HPA) axis (Maqsood and Stone, 2016; Sarkar et al., 2016). Notwithstanding these observations, mechanistic research is required to determine colonization efficacies and stability, molecular mechanisms of action, and combinatorial interactions and crosstalks between the administered bacteria, the endogenous commensals, and their effects on the host. In that aspect, colonizing germ-free animals with microbiomes from human patients/donors results in a partial long-term stability of donor microbial configuration yet still may prove beneficial in mechanistically exploring physiological and pathological conditions and should be emphasized together with improved sequencing tools. Other currently explored microbiome-modulating modalities include integration of individually tailored bacterial products ("postbiotics") (Suez and Elinav, 2017), rational person-specific modulation of the microbiome by prebiotics or by personalized nutrition (Zeevi et al., 2015) (Figure 3), and targeted microbial disruption by phage therapy. Collectively, these modalities might serve as future ways of modulating the microbiome in a controlled manner, thereby potentially impacting microbiome-associated disorders. The realization that gut microbiota influences human physiology represents a paradigm shift in modern medicine and marks a phenomenal conceptual advancement in our understanding of modern biology and human evolution. Detailed understanding of our elusive and evolving gut microbiome that possesses the ability to respond and adapt continually to intrinsic and environmental fluctuations—like age, diet, and stress—will provide a fantastic opportunity to support the 21st century medicine in its attempt to develop intervention regimes to promote human health across ages.

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