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Review Article

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Role of Intestinal Bacteria and their Mechanisms on Host Health and Aging at the Genetic Level

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Abstract

Researcher have paid more and more attention to the mechanisms by which intestinal flora affect the health and wellbeing of the host, and to what extent intestinal flora contribute to illness in the general population. Researchers also intend to determine the changes of intestinal flora over time, and the consequences of those changes for aging. This review will focus on the role that intestinal bacteria play in health and aging by providing a landscape of the intestinal flora with age, as well as the clinical signs/symptoms and mechanisms by which intestinal flora may affect aging. We anticipate that by exploring the relationship between intestinal flora and the host, it may ultimately be possible to identify particular classes of intestinal flora that affect aging.

Keywords: Gut bacteria; Aging; Probiotics

Introduction

There are a great variety of microbial groups that coexist within the human body. The colon has about 10^{14} bacteria, far greater than the number present on the skin 10^{12} [1]. Every individual has a distinct gut bacteria composition, which is subject to change with age, with the highest differences occurring as we get older [2,3]. Gut microbials play a very important role in human health; for example, some of their more important activities include helping to break down hard-to-digest proteins and fibers, and producing short-chain fatty acids such as acetic acid, propionic acid and butyric acid [4,5]. These short-chain fatty acids can have a significant effect on the T cells of the host, alter the regulation of inflammation in the intestine, and can even have an impact on the host's metabolism [6-9]. All of these suggest that our daily diet and/or pharmaceutical usage will affect the flora in the gut, which will in turn affect our health [10]. The gut microbiome plays an important part in the gut environment and influences the host's physiology and pathology [11]. The gut microbiome also affects our endocrine performance directly or indirectly through their metabolites [12]. The gut microbiome can also influence our neurological functions via the so-called "gut-brain axis" or "liver-gut axis" [13,14]. The gut flora have a core microbiome "enterotype" that is different for each individual [15]. Researchers have identified three enterotypes based on a variation of *Bacteroides* (enterotype 1), *Prevotella* (enterotype 2) and *Ruminococcus* (enterotype 3) [16]. When we age, the abundance of core microbes has a tendency to occur [17]. This change can be contributed by many factors, such changes in the composition of food [18,19]. The nature of the broader society can also have a significant effect, as the composition of gut microbes are different in industrial and non-industrial countries due to environment and diet [20,21].

Literature Review

The study of intestinal flora began with the study of the rDNAs of intestinal bacteria; Subsequently, 16S rDNA that was PCR amplified from human feces was used as a reference [22-24]. Since many microbiomes have distinctive functions, understanding the precise composition of the intestinal microbiome may yield valuable insights as to the health status of an individual patient [25]. Thus, improvements in bioinformatics technology and high-throughput sequencing technology may allow us to process large quantities of data, helping to advance the field in a rapid and meaningful way (Figure 1) [26,27].

Alterations in the intestinal flora with age

Recently, some groups have analyzed the relationship between intestinal bacteria and aging, even to the point of being able to predict age from microbiome composition [28]. The diversity of the gut flora appears to be negatively correlated with age, raising the possibility that the maintenance or improvement of gut flora diversity maybe help counteract or slow the aging process [29]. It is also important to note that microbiota diversity appears to be associated only with the biological age of an individual, and not with their chronological age [30].

Newborns

Previous studies have shown that the unique microbes present in the placenta suspected to be the first microbes to colonize the intestinal flora during fetal development, and at least partially associated with the adverse reactions of pregnancy or premature birth [31,32]. However, it has also been shown that the microbial population in the placenta is very small, and that even more of the adverse reactions of pregnancy could result from vaginal microorganisms [33,34]. This putative effect of vaginal microbes on the reactions of pregnancy and preterm birth has been verified in multiple publications [35,36]. The delivery mode in particular appears to have a significant effect on the gut flora; vaginally-delivered children are more likely to have the mother's vaginal microbiota, while infants born by C-section are more likely to be colonized by *Lactobacillus*, *Bifidobacterium*, and *Bacteroides* [37]. This can have impacts on the incidence of childhood obesity, inflammatory bowel disease, food allergies, asthma, and diabetes mellitus [38-40]. The gut flora can also be affected by many other factors such as breastfeeding. Breastfeeding can compensate for the colonization of *B. bifidum* and *L. gasseri* in C-section infants, resulting in flora more

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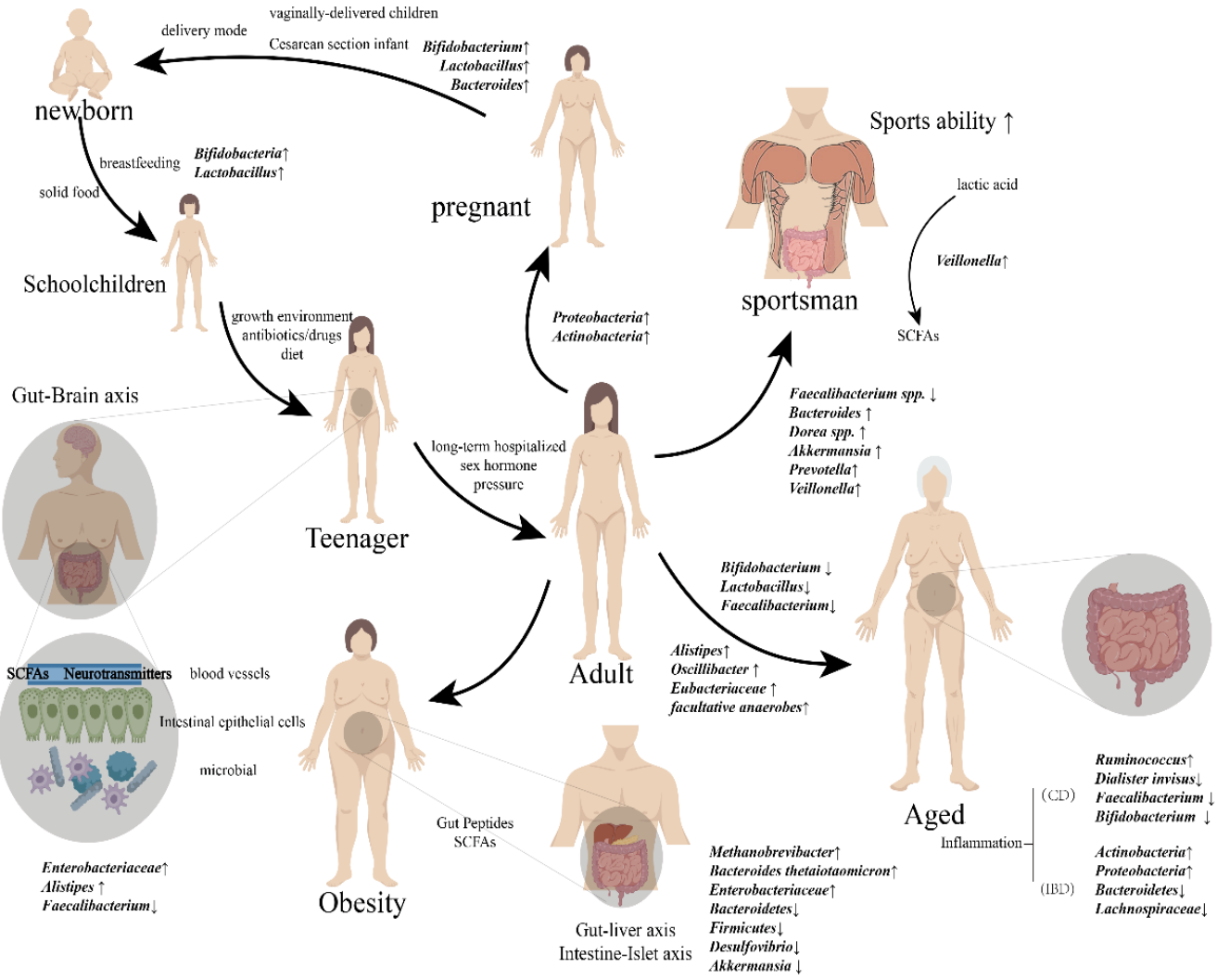

Note: The intestinal flora has been affected by external factors such as diet, antibiotics, environment, and stress, from the beginning of the newborn to the end of the elderly. The mode of delivery has a huge impact on neonatal flora, then breast milk plays a vital role in young children. In adults, our lifestyles and eating habits affect our health through our gut flora, such as obesity and inflammation, and exercise improves this condition very well. The gut flora affects the host primarily through metabolic pathways such as SCFAs affect our body and brain through the "Gut-Brain Axis" and "Gut-Liver Axis".

Figure 1: Gut microbiome changes from newborn to aged.

similar to those observed in infants who underwent vaginal delivery [41,42]. Breast milk can increase *Bifidobacterium* and help promote the health of the baby. As children grow, the consumption of breast milk in the diet decreases, and the abundance of *Bifidobacterium* decreases [43-46]. Through careful monitoring of the growth environment, food, and use of antibiotics, parents can also have a significant impact on their babies' intestinal flora [47].

School children

The bacteria that initially colonize a newborn are determined by the delivery mode. Subsequently, the environment dramatically alters that newborn's intestinal flora. For example, it has been demonstrated that a baby's intestinal bacteria moves closer to those observed in its cohabiting family members [48]. Treatment with antibiotics can also significantly reduce the abundance of intestinal flora [49]. Breast-feeding is perhaps the biggest factor affecting the intestinal flora of a newborn [50,51]. However, introducing solid food produces a dramatic switch of the microflora. One of the most critical changes involves *Bifidobacteria* and *Lactobacillus*, as these two genera of bacteria are known to be lower in adults compared to younger individuals [52]. *Bifidobacteria* are the most abundant gut flora in a breast milk-fed infant, and formula milk and dairy milk can change the abundance of the *Bifidobacteria* in the first 3 months after birth [53,54]. The introduction of solid foods migrates the baby's gut flora to a more adult composition [55,56]. The flora obtained from the mother gradually shifts to the acquired flora as the child gets older. Dietary structure is one of the most important factors. Malnourished children tend to have abnormal microbial composition, which may lead to increased risk of various diseases or even death [57].

Teenagers

Puberty represents a period of transition to independence, during

which major lifestyle changes take place; it is a critical period for future adult behavior. The differences in life span between males and females is well-studied [58,59]. The male sex hormone testosterone has been shown to correlate with increased pro-inflammatory cytokine release, while estrogens can reduce mitochondrial free-radical production [60]. In mice, the gut microbiota begins diverging between males and females in puberty [61]. Sex hormones potentially impact on the gut microbiome and its diversification in a gender-specific manner [61-64]. Recent research has shown that the timing of androgen exposure can affect a mouse's gut microbiome [65]. Since microbial exposures, sex hormones or both could have an influence on the age of human beings, the question is whether hormonal changes in puberty initiate gut microbiome shifts, or if changes in the microbiome influence sexual maturation and growth.

Adolescence is a pivotal period for brain maturation [66]. The lifestyle and physiological changes that occur during this period can be stressful, and may cause long-lasting detrimental changes [67-70]. Intestinal microbes susceptible to environmental influence may affect the development of the nervous system through the Microbiota-Gut-Brain Axis [71]. The details of the Microbiota-Gut-Brain Axis and mental illness will be further discussed below.

Adults

As human intestinal flora continues to be exposed to diet, antibiotics and other environmental factors, the composition of flora continues to evolve and become more and more complex, until it reaches its peak in adulthood [72-74]. In general, children have a higher number of enterobacteria than adults [52]. On the other hand, the intestinal flora of adults is very stable, but can be affected by many factors, including diet, antibiotics, geographical location, and seasonal/temperature conditions [75-83]. Even oxygen availability in high altitudes can affect the adult intestinal flora [84].

Interestingly, pregnancy can reset gut flora in adulthood [61,73]. In the early stages of pregnancy, some unique microbes can be detected in women who subsequently have preterm delivery [85]. *Proteobacteria* and *Actinobacteria* have also been shown to be increased in the third trimester of pregnancy relative to the first [86]. This shift is very similar to what is observed in obese populations [87]. *Bacteroides-Prevotella* group bacteria are also higher in overweight mothers [88]. The dietary consumption of pregnant women, particularly as it relates to probiotics, can have a significant impact on their blood glucose regulation [89]. Sex hormones can also affect pregnant women's emotional state through the brain-gut axis [90].

Aged people

The intestinal flora of the elderly has been widely studied in an attempt to identify any correlations between aging and intestinal flora [91-94]. Thus far, there has been no clear conclusion on this topic [95]. It appears that there is little difference in the gut flora between young adults and the elderly, while there is a much greater difference in the gut flora of the elderly when compared with centenarians [96]. With advancing age, the elderly suffer a variety of increasingly serious and complex diseases, and the gut microbiota in the elderly is a reflection of this reality, showing an extreme variability in composition not usually observed in younger individuals [3]. Long-term hospitalized patients have a higher *Bacteroidetes* and *Firmicutes* composition (and thus, less microbial complexity) than other individuals, and higher microbial complexity is associated with resistance to vulnerability in the elderly [97,98]. *Bifidobacterium* and *Lactobacillus* in core microbiota was found to be quite different in the elderly as compared with younger adults [99,100]. The loss of *Lactobacillus* and *Faecalibacterium* and the increased abundance of the *Oscillibacter* and *Alistipes* genera and *Eubacteriaceae* family were found in older populations, while the ratio of *Firmicutes*/*Bacteroidetes* first rises and then falls with age [101]. The genus *Alistipes* is also overrepresented in aged mice [102]. The proportion of the families *Ruminococcaceae*, *Lachnospiraceae*, and *Bacteroidaceae* decreases with age, and the aged population also has a decreased presence of the beneficial bacteria of *A. muciniphila*, *F. prausnitzii*, *lactobacilli*, and *bifidobacterial,* along with increased presences of *Clostridia*, enterobacteria, *Streptococci*, *Staphylococci*, yeast and facultative anaerobes in gut microbiota [103,104]. This changed composition of flora may be largely associated with diet [105].

It is possible that gut microbiota interventions may extend lifespan and improve age-related diseases [106]. In traditional Chinese medicine (TCM), fecal microbiota transplantation was used some Chinese medicine to treat diseases, including Gegen Qinlian Decoction (GQD), Rhizoma Coptis, and yellow soup [107-110]. It has also been reported that fecal microbiota transplantation can extend the lifespan of mice and fish [111,112]. Have study showed that fecal microbiota transplantation can affects expression of host genes associated with the TOR-pathway (DEPTOR) and with cell adhesion and extracellular matrix composition (DSCAM) [113]. Other studies find that fecal microbiota transplantation prolongs life is considered to be associated with the suppression of chronic low-grade inflammation resulting from the intestinal luminal environment and tissue or produce short-chain fatty acids (SCFAs) [114-116]. In addition, dietary management to control the composition of intestinal flora could be beneficial for counteracting the aging process [117,118].

The variation of microbiota in different age groups

Bifidobacterium, *Eubacterium*, *Bacteroides* and *Lactobacillus* are higher in younger individuals than in older individuals. In contrast, *Ruminococcus* is more common in older individuals. *Bacteroides*, *enterococci*, *enterobacteria* and *clostridia* do not change at all during aging [119,120].

The others factors influencing flora

The intestinal flora can change for a variety of reasons [15]. Long-term changes in diet and the use of drugs can affect the flora [10,99,121-126]. On the dietary side, fructo-oligosaccharides (FOS), vitamins, creatine, bile acids, NO and colanic acid (CA) are among some of these factors [102,127-131]. On the pharmaceutical side, more than 75% of people age 65 or older take at least one prescription medication, which may affect the intestinal flora and even lifespan [119,122,132]. Several medicines showed attenuating or reversal effects on the aging process in animal models, and may also extend lifespan in humans [133]. Rapamycin, metformin, acarbose and NAD precursors have been particularly well-studied [134-138]. Rapamycin has long been known as a modulator of extended aging in yeast, and affected the life of the animal model such as *Drosophila* and mice with a way that is not fully understood [139-145]. Rapamycin plays a mechanistic role in longevity in mammals by targeting mTOR and regulating important cellular processes [146]. Short-term rapamycin treatment can improve health in mice, and down-regulation of the TOR pathway with RNAi supports the roles of nutrients and the mTOR pathway in lifespan [147,148]. Interestingly, the mTOR pathway has greater impact on females than males [149-151]. In animals, short-term rapamycin treatment can improve learning and memory as observed in the case of a low-calorie diet or caloric restriction (CR) [152-154]. T. *Lactobacillus plantarum*

can affect lifespan in *Drosophila* through a mechanism whereby lactic acid triggers ROS via the intestinal NADPH oxidase Nox [155]. SKN-1/Nrf and DAF-16/FoxO-mediated transcription regulates protective genes when TORC1 is inhibited with rapamycin [143]. There is also a feedback loop in the TOR regulatory pathway, as SKN-1 increases the transcription of TORC1 pathway genes when TORC1 is inhibited, and the IIS and TOR pathways each influence aging by regulating SKN-1 and DAF-16 [143]. In addition, the most common used medicine in elder include acetylcholinesterase inhibitors (AchEIs), multivitamins, HMG-CoA reductase inhibitors (statins), analgesics (NSAIDs, weak and strong opioids), antihypertensives, antiplatelet agents (aspirin) and metformin [156-163]. In the above drugs, metformin can indirectly regulate the lifespan of the host by affecting the bacteria [164]. Metformin also extends lifespan through mTOR signaling, and it has been shown that the mucin-degrading species *Akkermansia muciniphila* is more abundant in mice which have been metformin treated [165]. The mechanism by which metformin inhibits mTORC1 is by activating AMP-activated protein kinase (AMPK) or the Ragulator complex (Rag GTPase), or by REDD1 upregulation [166,167]. Previous studies have speculated that metformin affects host longevity by changing the production of secondary metabolites, and by affecting level of folate metabolism in the host intestinal flora. However, there is no evidence to support that the lifespan of the host is affected when the level of folate in the host is changed [15,144,168]. In a recent study, metformin was found to extend the host lifespan by affecting host lipid metabolism with metformin-bacterial interactions, and there is another research finding that Bacterial colanic acid (CA) is also known to promote longevity in *C. elegans* [169,170].

Intestinal bacteria and aging

Bifidobacteria has been recognized as a probiotic that plays an important role in human development [99]. Similarly, changes in gut flora composition can also affect human aging. For example, age-related changes in the gut microbiome have implicated in decreases in immunity, gastrointestinal dysfunction, increased risk of infectious diseases, increased risk of cardiovascular diseases, liver diseases, alopecia, decreased ability to exercise and even Alzheimer's disease [94,171-178].

Obesity and gut flora

Obesity is a common and increasingly severe problem across the world [179]. Inappropriate diet may adversely impact our health by effecting microbial composition, with reverberating effects throughout the gut-liver-adipose tissue axis and intestine-islet axis [180,181]. Obese individuals are known to have specific microbial populations within their faeces, and even gastric bypass surgery (Roux-en-Y gastric bypass, or RYGB) can affect the composition of the gut microbiota [182,183]. RYGB is a treatment option for morbid obesity, and after surgical treatment with RYGB, obese individuals will undergo unique changes in their intestinal microbial community lead to further improvements in long-term weight loss, improved metabolic status and extended lifespan [184-186]. Fecal transplantation could also be a promising approach for treating the morbidly obese [187,188]. The species present in the gut microbiota can be affected by many factors, such as energy balance, delivery mode, antibiotics, diet, neural signals, genetics, health status, environment, lifestyle and endocrine factors [189-195]. Gut microbiota can influence adipose tissue metabolism through gut peptides (e.g. glucagon-like peptide-1 and -2) in the ECB system or by changing the short-chain fatty acids to affect metabolic diseases [196]. In mice, there is a well-studied interrelation between diet and the species composition of the gut microbial community [188]. For instance, *Methanobrevibacter* and *Bacteroides thetaiotaomicron* have been shown to lead to weight gain in gnotobiotic mice, and levels of *Bacteroidetes* and *Firmicutes* are significantly different between lean and obese mice [197-199]. Most intriguingly, *Akkermansia muciniphila*-induced obesity in mice can be cured by treatment with the prebiotic oligofructose, raising the possibility that similar dietary interventions may help reverse obesity in humans as well [200].

In humans, a number of studies have compared the gut flora of obese and normal-weight people, resulting in a number of insights and correlations [189]. For instance, *Lactobacillus* and *Bifidobacterium* are known to affect obesity or lean status in the gut [201]. Additionally, *B. eggerthii* is observed at higher levels in obese schoolchildren, and the abundance of *Enterobacteriaceae* is also higher in overweight children [202,203]. The *Firmicutes/Bacteroidetes* ratio may also be associated with degree of the obesity in schoolchildren [204]. In contrast, *Akkermansia muciniphila*-like *bacteria* and *Desulfovibrio* are more abundant in normally-weighted children [205].

Athletic ability and gut flora

As we age, loss of skeletal muscle mass and the probability of sarcopenia increase [177,206,207]. Exercise also plays a beneficial role in neurocognition by protecting the damage of hippocampal nerves through microbial flora [66,208]. Many studies have analyzed the gut flora of athletes. These efforts have shown that Low Carbohydrate High Fat (LCHF) diet can decrease the relative abundance of *Faecalibacterium spp.* and increase *Bacteroides and Dorea spp.* in the stool microbiota of race walkers [209]. A greater abundance of *Akkermansia* and *Prevotella* was also found in the gut microbiomes of sportsmen; the latter genus is particularly interesting, being mucin-degrading bacteria that can affect the biosynthesis of branched-chain amino acid (BCAA) [210,211]. On the other hand, the genus *Veillonella* utilizes exercise-induced lactate as its sole carbon source to make propionate, and fecal metabolites such as short-chain fatty acids (SCFAs), acetate, propionate, and butyrate are known to be increased in athletes as compared to sedentary individuals [212,213]. *Veillonella* metabolizes lactic acid through Methylmalonyl-CoA-related gene expression during exercise [212,214]. The short-chain fatty acids (SCFAs) converted from metabolic lactic acid by *Veillonella* can increase athletic ability by optimizing lipid oxidation, heart rate and maximum oxygen consumption [215-217].

Inflammation and intestinal flora

Gut dysbiosis is closely related to inflammation in the intestinal tract [172]. The immune dysfunctions seen in senescence-associated phenotype are associated with increased ROS [218,219]. The microbial changes associated with aging have a broad correlation with the occurrence of intestinal inflammatory disorders; in particular, the proportions of *Proteobacteria* and *Firmicutes* appear to be positively correlated with such disorders [220]. The number of anaerobic bacteria is also increased in the gut of the elderly [221]. *Ruminococcus gnavus* is increased in patients with Crohn's disease (CD), while the levels of *Dialister invisus*, *Faecalibacterium prausnitzii* and *Bifidobacterium adolescentis* are decreased [222,223]. Increased *Actinobacteria* and *Proteobacteria* and decreased *Bacteroidetes* and *Lachnospiraceae* are associated with inflammatory bowel disease (IBD) [224,225]. *Akkermansia*, *TM7 bacteria*, and *Proteobacteria* cause inflammation, as shown in the case of microbiota transferred from aged mice into young GF mice [226]. In particular, *Akkermansia muciniphila* has been found to have many roles in human health and disease [201,227-229]. Diet is very important for patients with inflammatory bowel

disease, particularly as it relates to probiotic intake [230]. Probiotics in the gut flora protect the host through the immune response system in the intestinal epithelial cells and help develop biofilms in the gut (such as *Bacillus subtilis*) [175,231-233]. All of these factors may also be affected by sex hormones [234].

The influence of gut flora on the brain

The gut flora is associated with the mental health of the host [71]. Therefore, the influence of the intestinal flora on the host nervous system has been widely studied, with some intriguing insights. For instance, it has been demonstrated that the microbes in the human gut can affect the nerves system by production neurochemicals [235,236]. Probiotics have also been shown to affect neurotransmitter levels and chronic inflammation that are associated neurodegenerative disease [237]. The change in gut motility, acidity and neurochemicals can also alter the microbial composition of the gut flora [182]. Together, this reciprocal interaction between the gut flora and the brain is referred to as the "Gut Microbiota-brain Axis", and it is clear that disruptions of the microbial composition in the human gut can result in neurological disease by this axis [238-242]. For instance, the microbial composition of patients with depression has been shown to have a higher abundance of *Enterobacteriaceae* and *Alistipes* and a lower abundance of *Faecalibacterium* than observed in individuals not diagnosed with depression, and *Faecalibacterium* has been shown to protect against depression via microbiota transplantation [243]. Gut microbes have also been implicated in PD progression by producing SCFA to act on the enteroendocrine cells (EECs) [244]. Parkinson's disease in the elderly is often affected by the gut microbiota-brain axis, and intestinal infection can also trigger the occurrence of Parkinson's disease [245,246]. Together, these results would seem to suggest that fecal microbiota transplantation may provide treatment (or at least some level of preventative power) for many forms of neurological diseases.

Conclusion

Here, we provide a brief overview of the effects of gut microbiota on host health and aging. It seems clear that intestinal flora play an important role in human aging and age-related diseases. Of course, the intestinal flora is affected by the host's diet, antibiotic use, exercise, the external environment and the effects of the host's immune system. There are many ways to improve the health and healthy aging of the host by manipulating gut flora. The development of such treatments may provide a major opportunity for improving human health.

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