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Linking gut microbiota to aging process: a new target for anti-aging

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ABSTRACT

The human gut microbiota is a huge ecosystem that provides lots of functions for host development, immune system, and metabolism. Gut microbiota is linked to lots of diseases, including human metabolic diseases such as obesity, type 2 diabetes (T2D), irritable bowel syndrome, and cardiovascular disease (CVD). Few studies, however, have noted the relationship between aging and microbiota, the connection between aging and microbiota remain largely to be researched. In this review, recent research findings are summarized on the role of gut microbiota in aging processes with emphasis on therapeutic potential of microbiome-targeted interventions in anti-aging medicine.

1. Introduction

The human gut microbiota is a huge ecosystem that provides lots of functions for host development, immune system, and metabolism. Gut microbiota is linked to lots of diseases, including human metabolic diseases such as obesity, type 2 diabetes (T2D), irritable bowel syndrome, and cardiovascular disease (CVD). Few studies, however, have noted the molecular mechanisms, the connection between host and microbiome remain largely to be researched. Here we have reviewed how aging may affect gut microbiota in the complex interactions of diet, microbiota, and host metabolism and show the new theories about the signaling pathway of modulating gut microbiota.

Human intestinal tract has a large number of bacteria, these bacteria is related to the host immune system development, metabolic regulation, nutrient digestion and absorption [1]. Because of the application of systems biology approaches and new computational tools, there has been increasing interest in exploring the gut microbiota and their combined genomes, the microbiome, as diagnostic and therapeutic targets for prolonging human lifespan and treating aging-related diseases [2]. Through plenty of experiments, the molecular mechanism of gut- host interaction has been elucidated.

Microbiota is defined as the collection of microbial taxa in a given environment. The concept of microbiome is the collection of the genes/genomes encoded by the microbiota. Compositional and functional changes of the human gut microbiome have been linked to lots of chronic metabolic disease, like malnutrition [3] as well as obesity [4] and obesity-associated diseases such as cirrhosis [5]. Then, alterations of the gut microbiome have also been linked to intestine-related diseases, including inflammatory bowel disease (IBD) [6], colorectal cancer [7], neuro-developmental disorders [8]. Changes in lifestyle and diet have been argued to contribute to the shifting gut microbiota ecology.

Obesity, T2D, and IBD are characterized by reduced fecal microbial diversity and studies have shown that uses of dietary emulsifier alters the gut microbiota's composition, which results in intestinal inflammation, devastation of gut barrier and development of the metabolic syndrome. These findings suggest that the modern lifestyle, especially diet, has the potential to affect the gut microbiota, which may contribute to disease development. Therefore, understanding factors which influence the gut microbiota might lead to the finding of new therapies for both metabolic and inflammatory diseases.

There are three major factors which influences the composition of gut microbiota, including host genetic background, diet and microbes. Human genetics might play a role in shaping the composition of the gut microbiota. For instance, people homozygous for loss-of-function alleles of the FUT2 gene have an altered microbiota. FUT2 encodes an enzyme which is required for the fucosylation of surface carbohydrates on intestine mucosal linings. Loss in FUT2 altered both the composition and the function of the gut

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microbiota. FUT2 gene has been linked to Crohn's disease and IBD, suggesting that an altered gut microbiota may explain the association between FUT2 gene background and increased possibilities to Crohn's disease. Besides FUT2 gene, FXR gene and NOD2 gene also plays a vital role in shaping gut microbiota. However, further investigations are needed to determine the extent to which host genotype impacts and shapes the microbiome, as studies in mice show that environmental factors like diets, might have nominating effects [9]. Recently, there have been new reports on the relationship between host genetic background and gut microbiota, caspase recruitment domain family member 9 (CARD9), a susceptibility gene for inflammatory bowel disease (IBD) that functions in the immune response against microorganisms, which promotes recovery from colitis by promoting interleukin (IL)-22 production, and Card9$^{-/-}$ mice are more susceptible to colitis. Card9 can change the composition of gut microbiota, when transplantation its feces to normal mice, which can lead to the occurrence of colitis in mice [10]. This research proves that there is exactly relationship between host genetic background and composition/function of the gut microbiota, demonstrating the mechanism by researching the production of microbial metabolites.

Energy intake and the nutrients composition of the diet affect human health and impact the composition of the human gut microbiota; in particular, recent studies in mouse performed on different genetic background and different living environment shows that diet has a stronger effect than host genotype in determining gut microbial composition [11]. The gut microbiota responds to dietary interventions very quickly and short-term consumption of diets composing of either animal or plant products can alter the overall structure of the gut microbiota [12]. For example, people with proteins and fats as the main food, Bacteroides dominated the gut microbiota, while those with fiber and carbohydrate as the main foods, the gut microbiota dominated by the genus Prevotella [13].

The microbes, including pathogens and prebiotics, are an important key of the way of shaping gut microbiota. Recent research shows that the interaction between microorganisms and microorganisms also affects the gut microbiota. For example, Salmonella and Clostridium difficile, two antibiotic-associated pathogens, improve their numbers and activities after antibiotic treatment by utilizing microbiota-liberated mucosal carbohydrates such as sialic acid [14]. Now, as a beneficial bacteria, probiotics should be mentioned. Probiotics is a living microorganisms that confer a health benefit on the host. Prebiotics is an activator of probiotics. Prebiotics is dietary ingredients that are fermented by specific gut microbes, which results in specific changes in the composition of the gastrointestinal tract microbiota, making benefits on host-health [15].

2. The gut microbiota's changes during aging process

As mentioned above, the body's aging process is accompanied by the occurrence and development of inflammation, meanwhile the function of each organ has declined. Conversely, gut microbiota may have their own unique way of changing [16]. At the same time, it could not be ignored that the elderly usually have a variety of comorbidities, changes in diet and exercise habits, and other changes associated with gut bacteria that affect the gut microbiota. Therefore, the question of how to interact with gut bacteria still deserves further exploration (Figs. 1 and 2).

Compared to evidence related to aging and inflammation, less is known regarding associations between aging and the microbiome. In fact, in contrast to the thousands of peer-reviewed publications on aging and inflammation, a PubMed search for "aging and microbiome" yielded only 466 results and a search for "aging and dysbiosis" yielded a mere 34. Moreover, only a handful of studies to date have investigated the aging microbiome in humans. Still, at least two early studies in this area have documented that advanced age is associated with changes to both the composition and stability of gut microbiota [17]. Biagi et al. reported that a group of centenarian from Northern Italy displayed low species diversity compared to younger adults (~30 years of age). They also noted specific changes within Firmicutes (one of the two dominant phyla commonly found in the gut) subgroups and enrichment of Proteobacteria – a group containing many opportunistic bacteria which can overtake commensal bacteria and induce pathology. These microbiome changes were also characterized by a loss of genes for short-chain fatty acid production and an overall decrease in the saccharolytic potential, while proteolytic functions were more abundant than in the intestinal metagenome of younger adults [18]. Interestingly, these changes in bacterial content were also moderately associated with circulating plasma concentrations of inflammatory cytokines interleukins six (IL-6) and eight (IL-8). Surprisingly, however, despite these interesting findings is happened among the centenarians, we did not find significant differences in microbiota composition between the younger adults and a group of older adults with an average age of 70 years. In contrast, a study of gut microbiora in Ireland found that core populations of people over the age of 65 did indeed change [19]. These changes are mainly manifested in the substantial increase in the proportion of *Bacteroides* spp. and Clostridium compared to younger individuals. Gut microbiota's diversity of the elderly will decline, mainly in the diversity of related species, including Prevotella [20], which may lead to the instability of the composition of the entire microbial community. However, it would not be ignored that the difference in gut microbiota between the elderly is so great that the prediction of the phenotype is more difficult to carry out. A few key factors are the predominant predictors of gut microbiota in community-dwelling and long-term care residents, such as diet and the use of antibiotics. Differences in cohort studies in Italy and Ireland may be explained by diet differences.

Interestingly, the ELDERMET study reveals a possible link between gut microbiota and body vulnerability, a link that can be used to measure the difference between elderly and community-dwelling elderly living in long-term care and/or rehabilitation facilities [20]. These differences are closely related to the degree of inflammation, mainly in the changes of some systemic inflammatory factors, such as IL-6, IL-8, CRP, and TNF-α.The association with frailty in the cohort is recently demonstrated more formally along with concordant findings from 728 female twins enrolled in the Healthy Ageing Twin Study [21]. These findings are similar to those from a prior small cohort of older adults from The Netherlands [20]. Thus, available data suggests that the gut microbiome may play at least some role in the development of physical frailty among the elderly.

The composition of gut microbiota can change significantly with aging and aging-related diseases [22]. Age-related changes in gut physiology, such as gastric motility disorders, achlorhydria, and degenerative changes in the enteric nervous system, have a significant impact on the composition and function of gut microbes [23]. Long-term stimulation of the immune system can lead to decreased immune system function, leading to immunosenescence, which in turn causes the above age-related differences. Subsequent to this are many aging-related diseases, including gastrointestinal related (Clostridium difficile colitis) and other (cachexia, frailty, cancer) [24] diseases. Such inflammatory state might make the host more sensitive to gut bacteria.

The age-related changes in the gut microbiota composition include a decline in microbiota diversity, a decrease in saccharolytic bacteria and an increase in proteolytic bacteria, decreased abundance of core (dominant) species and increased abundance of subdominant species, an increase of certain Proteobacteria, a

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