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Review Article

Revisit gut microbiota and its impact on human health and disease

Rui-xue Ding [a], *Wei-Rui Goh* [b], *Ri-na Wu* [a], *Xi-qing Yue* [a], *Xue Luo* [a], *Wei Wei Thwe Khine* [b], *Jun-rui Wu* [a,**], *Yuan-Kun Lee* [b,*]

[a] *College of Food Science, Shenyang Agricultural University, Shenyang 110866, PR China*
[b] *Department of Microbiology & Immunology, Yong Loo Lin School of Medicine, National University of Singapore, 5 Science Drive 2, Singapore 117597, Singapore*

ARTICLE INFO

Article history:
Received 23 October 2018
Received in revised form
18 December 2018
Accepted 27 December 2018
Available online 1 February 2019

Keywords:
Gut microbiota
Human health
Disease

ABSTRACT

Trillions of microbes have evolved with and continue to live on human beings. With the rapid advances in tools and technology in recent years, new knowledge and insight in cross-talk between the microbes and their hosts have gained. It is the aim of this work to critically review and summarize recent literature reports on the role of microbiota and mechanisms involved in the progress and development of major human diseases, which include obesity, hypertension, cardiovascular disease, diabetes, cancer, Inflammatory Bowel Disease (IBD), gout, depression and arthritis, as well as infant health and longevity.

1. Introduction

With recent estimates placing the ratio of human to bacteria cells to an approximate 1:1 ratio, we are about as much bacteria as we are human [1]. With the genome of each bacterial strain harbouring thousands of genes, the collective bacterial genome contains about 100 times more genes than the human genome [2]. Yet, the estimates do not account for fungi, viruses and other microorganisms present in the human body, further contributing to the vast genetic diversity. Together, the collection of microorganisms and their respective genomes make up the human microbiome.

The microbiome has been identified and proposed to be a key modulator of human health, to the extent that it has been proposed to be an 'essential organ' of the human body [3,4]. While distinct changes to the microbiome composition – a state known as 'dysbiosis' – has been described in various diseases, defining a characteristic composition of a 'healthy' microbiome has been difficult, attributable to inter-individual variation [5].

Technological improvements have facilitated the growth of microbiome research and the rapid expansion of knowledge over the past few years has helped to reinforce our appreciation of the microbiome and health, paving the way for translational studies including mechanistic studies and

* Corresponding author. Fax: +86 24 88487162.
** Corresponding author. Fax: +65 67766972.
E-mail addresses: junruiwu@126.com (J.-r. Wu), micleeyk@nus.edu.sg (Y.-K. Lee).
https://doi.org/10.1016/j.jfda.2018.12.012

clinical interventions [2]. Therefore, it is the aim of this work to critically review and summarize recent literature reports on the role of the microbiome in the progress, development and possible treatment of major human diseases, as well as longevity and infant health.

2. Obesity

Obesity, a chronic systemic disease characterized by excessive fat accumulation, has increased tremendously over the past 40 years affecting almost 40% of adults and 19% of youths in the United States. It is defined as a body mass index of 30 or greater for adults and above 95th percentile for the respective age group and gender among youths [6,7].

Accumulating evidence from the last few years both in-vivo and human studies suggest that the gut microbiome plays a key role in the development of obesity, with the interactions between the microbiome, diet and host genotype being the key focus of research [8,9].

Our dietary habits influence the composition of our gut microbiome and has been the focus of novel therapeutic treatments by using dietary interventions to modulate our gut microbial composition in order to treat diseases. (−)-epigallocatechin 3-O-(3-O-methyl) gallate (EGCG3″Me), a polyphenol present in oolong tea, has been shown to be effective in increasing the abundance of *Bacteroidetes* genus of bacteria, while decreasing the abundance of *Firmicutes* genus in the intestinal microbiome of human flora-associated mice models, resulting in an overall decrease in the *Firmicutes/Bacteroidetes* ratio [10], reflecting the ability of EGCG3″Me to regulate the composition of the intestinal microbiome. The protective effect conferred by EGCG3″Me against obesity suggests its potential role as a functional food component to prevent dysbiosis observed in obesity. A study using nanocomplexes loaded with EGCG3″Me was found to promote the growth of *Bifidobacterium* and *Lactobacillus-Enterococcus spp*, while inhibiting *Bacteroides–Prevotella and Clostridium-histolyticum* groups in high fat diet-induced obesity mice models [11].

A common caveat in the study of obesity using mice fed with refined high-fat diet is the use of chow as a control diet, which are often not standardized. Differences in dietary composition between chow and refined high-fat diet introduces confounding factors that may play a role in modulating the microbiome composition. This could potentially affect the results obtained and its interpretation in mice model studies employing the use of chow and refined high-fat diets [12].

Bariatric surgery remains to be a popular treatment option for morbid obesity. In obese individuals, abundance of *B. thetaiotaomicron* was markedly decreased and observed to be inversely correlated with serum glutamate levels. In mice models, gavage with *B. thetaiotaomicron* was found to decrease plasma glutamate levels and improved diet-induced obesity in mice. In obese individuals, bariatric surgery was found to reverse the decrease in *B. thetaiotaomicron* abundance and elevated serum glutamate levels commonly associated with obesity, which is also associated with weight loss after bariatric surgery [13]. In a systematic review investigating the effects of different bariatric surgeries on the gut microbiome composition, it was noted that Roux-en-Y gastric bypass (RYGB) lead to an increase in *Proteobacteria* and a decrease in *Firmicutes* whereas laparoscopic sleeve gastrectomy (LSG) had less severe changes to the gut microbiome, with the anti-inflammatory species *Fecalibacterium prausnitzii* increasing after LSG. Therefore, bariatric surgery causes changes to the gut microbiome, but more investigation needs to be done to identify the specific bacteria involved in weight-loss after surgery [14]. LSG has been shown to shift obesity-associated microbiome composition to that of a lean microbiome phenotype, but this shift was not observed with dietary restriction. While the microbial capacity for butyrate fermentation was decreased, no changes in fecal butyrate levels were observed [15].

3. Hypertension

Emerging evidences have further strengthened the claim that gut microbiota is critical in the maintenance of physiological homeostasis. Dysbiosis in the richness, diversity and Firmicutes/Bacteroidetes ratio in gut microbiome has been reported to be associated with hypertension in both animal and human studies [16].

Recent studies have employed the use of fecal transplants to examine the relationship between microbiome and blood pressure regulation. By transplanting dysbiotic cecal contents from hypertensive obstructive sleep apnea (OSA) rats on a high-fat diet to OSA rats on a chow diet, it resulted in the development of hypertension in the recipient rats, demonstrating a causal relationship between gut dysbiosis and hypertension. This also suggests that manipulation of the microbiota could be a viable treatment for OSA-induced hypertension [17]. Similarly, hypertension could be induced in a normotensive strain of rats or attenuated in a hypertensive strain of rats by exchanging the gut microbiota between the 2 strains [18]. In a study of cecal microbiome transplantation between hypertensive Dahl salt-sensitive (S) rats and normal Dahl salt-resistant (R) rats, systolic BP of S rats transplanted with cecal contents from R rats were observed to be significant increased during the rest of their life, and also had a shorter lifespan, demonstrating the ability of microbiome composition in regulating blood pressure [19].

Furthermore, indole and indoxyl sulfate have been shown to affect arterial blood pressure via peripheral and central mechanisms dependent on serotonin signaling. Indole and indoxyl sulfate may be served as mediators in the interaction between gut bacteria and circulatory system [20].

4. Cardiovascular disease

Despite encouraging advances in prevention and treatment of atherothrombosis, cardiovascular disease (CVD) remains a major cause of deaths and disability worldwide and will continue to grow mainly due to the increase in incidence in low and middle income countries (LMIC) [21]. The potential role of the gut microbiome in metabolic diseases, especially cardiovascular diseases, is a focus of recent investigations [22].

It has been shown that the gut microbiome composition is associated with both atherosclerosis and arterial stiffness

markers [23], and this may be potentially due to the bioactive metabolites derived from commensal organisms [24]. In a metabolomic study of specific indole and phenyl-derived metabolites originating solely or partly from gut microbes, it was concluded that specific microbe-derived metabolic signatures are associated with advanced human atherosclerosis and postoperative cardiac complications. In particular, indole and indole-derived metabolites trp, kyn/trp ratio, I3P, and I3A are associated with advanced atherosclerosis, whereas the kyn/trp ratio and the phenyl derivative hippuric acid are associated with post-operative major cardiac events and with major adverse cardiac events. These findings suggest the potential role of these metabolites as new biomarkers for atherosclerotic disease and highlights the imperative need for a better understanding of the mechanisms by which the gut microbiome and its derived metabolites contribute to the development of atherosclerosis [24].

The gut microbiome has also been shown to be associated with atherosclerotic cardiovascular disease (ACVD), characterized by an increase in abundance of *Enterobacteriaceae* and *Streptococcus spp* [25]. In addition, it was also observed that there was an association between the copies of bacterial genes coding for TMA lyase and ACVD [25]. TMA lyase is responsible for the generation of trimethylamine-N-oxide (TMAO), a gut microbiome-derived metabolite that has been shown to play a causal role in the development of ACVD in animal models and is highly associated in human studies, highlighting the key role TMAO may play in the pathogenesis of ACVD [26]. In a double-blind, placebo-controlled study, administration of probiotic *Bifidobacterium animalis subsp. lactis LKM512* was shown to be able to reduce TMA levels and relative abundance of certain TMA-producing groups of bacteria (*Clostridia, Clostridiales*, and *Lachnospiraceae*) in healthy subjects, potentially reducing the risk of developing arteriosclerosis [27].

In inflammatory atherosclerosis, characterized by the accumulation of inflammatory cells and lipids in the vascular tissue, both dietary intervention and *Porphyromonas gingivalis* infection lead to distinct microbiome composition of ApoE−/− mice, opening up possibilities on studying gut microbiome, diet and *P. gingivalis* infection on the development of atherosclerosis [28].

In a study investigating the role of *Akkermansia muciniphila* on the pathogenesis of atherosclerosis, a Western diet significantly reduced the abundance of *A. muciniphila* in ApoE−/− mice. However, replenishment of *A. muciniphila* leads to attenuation of atherosclerotic lesions mediated by reducing metabolic endotoxemia-induced inflammation and restoring gut barrier permeability [29].

In Mongolian adults, increased abundance of *Faecalibacterium prausnitzii* and *Coprococcus* comes were suggested to contribute to gut health through anti-inflammatory properties and butyrate production respectively. The enriched genus *Collinsella*, a biomarker in asymptomatic atherosclerosis patients, might be associated with the high morbidity of cardiovascular and cerebrovascular diseases in Mongolian adults [22].

5. Diabetes

In 2016, the world health organization (WHO) expanded the prevalence of diabetes from current levels to 592 million (12%) in 2035 [30], becoming the third major disease after cancer and cardiovascular disease.

The gut microbiome has also been suggested to play a role in the development of Type 1 diabetes mellitus, possibly through its role in regulating immune response. Since the proliferation and composition of the gut microbiome is dependent on the nutrients available, it is imperative to suggest that the generation of metabolites depend on the food intake. Eα16/NOD mice were found to confer vertical protection to their offspring from diabetes and insulitis that is mediated by the gut microbiome, suggesting that protection of autoimmune disorders conferred by MHC/HLA alleles may be dependent on the gut microbiome and highlights the social implications of treating infants and pregnant women with antibiotics [31]. In pre-diabetic individuals, an altered gut microbiome composition, characterized by a reduced abundance of *Clostridium genus* and *A. muciniphila*. The findings are also similar to microbiome composition changes in diseases characterized by low-grade inflammation [32]. Abundance of *A. muciniphila* was found to be inversely correlated to the risk of developing Type 1 diabetes-related autoantibodies. When *A. muciniphila* was transferred to a high-incidence NOD colony, mucus production was improved and diabetes development was delayed. Therefore, *A. muciniphila* may be a potential probiotic in the treatment of Type 1 diabetes, and the development of Type 1 diabetes is likely to be regulated by interactions between specific individual members of the microbiome rather than the overall balance in the microbiome itself [33].

In patients with Type 2 diabetes (T2D), abundance of *F. prausnitzii* was found to be significantly lower than healthy individuals. There were no significant differences in abundance of *Bacteroides fragilis* and *Bifidobacterium longum*, although abundance of *B. fragilis* was noted to be under-represented compared to healthy individuals [34]. In another study comparing gut microbiome composition and T2D, it was observed that T2D patients had a significantly lower abundance of *Lactobacillus* genus of bacteria and significantly higher abundance of *Bifidobacterium* genus as compared to healthy individuals [35]. The significant alterations in dominant fecal bacterial genera found in T2D patients highlight the link between T2D and compositional variation in intestinal microbiota.

Metabolomic analysis of insulin-resistant individuals showed that serum levels of branched-chain amino acids (BCAA) were elevated, correlating with a gut microbiome composition with an enriched biosynthetic potential of BCAA synthesis and a reduction in genes coding for bacterial amino acid transporters. In particular, *Prevetolla copri* and *Bacteroides vulgatus* were identified to be the main players involved in BCAA synthesis and insulin resistance. *P. copri* was also shown to induce insulin resistance and elevate serum BCAA levels in mice models, highlighting its potential role in pathogenesis of insulin resistance [36].

Metformin has been shown to modulate gut microbiome composition and fecal transplants of metformin-treated patients to germ-free mice improved glucose tolerance in the recipient mice. In addition, metformin was shown to regulate the expression of genes coding for metalloproteins in the gut microbiome, suggesting that metformin's antidiabetic effects may be modulated through metal homeostasis mediated by the gut microbiome [37]. In another study, metformin was also

found to modulate the gut microbiome composition, with a particular increase in abundance of *Escherichia spp*. which also resulted in enrichment of virulence factors and gas metabolism genes [38]. This would suggest that future antidiabetic treatments target specific bacterial strains causing an imbalance in amino acid metabolism [39].

6. Cancer

The human microbiome has been garnering much attention for its complex relationship in the development of cancer and is believed to account for approximately 20% of all cases of cancer worldwide [40]. With a better understanding of the role of the microbiome in the pathogenesis of cancer, the potential of microbiome based therapeutics in the treatment of cancer has become an increasingly researched topic.

A higher abundance of *Bacteroides massiliensis* was observed in patients with prostate cancer, whereas *F. prausnitzii,* and *Eubacterium rectalie* were observed in relatively lower abundance, suggesting the potential role of these bacteria in the development of prostate cancer [41]. *B. fragilis* toxin on the other hand has been shown to activate a pro-carcinogenic inflammatory pathway in colonic epithelial cells [42].

The gut microbiome has also been shown to be involved in the carcinogenesis of colorectal cancer (CRC), with *Bacteroides fragilis, Fusobacterium nucleatum*, and *Peptostreptococcus anaerobius* being highlighted as potential players in its development [43].

While *H. pylori* is a known risk factor in gastric cancer, new evidence suggests that *Clostridium* and *Fusobacterium* bacteria are elevated in gastric cancer patients as well. In particular, *C. colicanis* and *F. nucleatum* have been suggested as diagnostic markers in gastric cancer [44]. Recent research indicates that *F. nucleatum* is able to supress host immune response and upregulates cellular proliferation. Additionally, a diet rich in whole grains and dietary fiber is associated with a lower risk of *F. nucleatum* positive colorectal cancer, suggesting that intestinal microbiome could be an important mediator between the interaction of diet and colorectal cancer [45].

The microbiome has also been shown to be critical in regulating efficacy of checkpoint blockade immunotherapy, suggesting that modulation of microbiome composition could be employed to improve patient response [46]. Oral administration of *Bifidobacterium spp*. exhibits anti-tumour immunity with efficacy similar as that of programmed cell death protein 1 ligand (PD-L1)-specific antibody therapy in mice models of melanoma, and a combination of both therapies was able to nearly eradicate all tumour growth. The effect is mediated by elevated dendritic cell function, resulting in improved CD8+ T cell priming and accumulation in the tumour microenvironment [47]. Higher abundance of *Ruminooccaceae* family and higher alpha diversity of the gut microbiome is also associated with better response to anti-programmed cell death 1 (PD1) immunotherapy. Patients with a 'favourable' gut microbiome who responded towards PD1 treatment display elevated systemic and antitumour immunity that is mediated by increased antigen presentation and T cell effector function [48]. Elevated abundance of *B. longum, Enterococcus faecium and Collinsella aerofaciens* have also been reported to be associated with improved anti-PD1 therapy in patients with metastatic melanoma [49]. Efficacy of CTLA-4 blockage immunotherapy is also regulated by microbiome composition – specifically *B. fragilis, B. thetaiotaomicron* and *Burkholderiales* genus bacteria [50].

7. Inflammatory Bowel Disease (IBD)

IBD is often associated with a state of dysbiosis accompanied by a shift towards an elevated abundance of microbes capable of coping with oxidative stress with a notable increase in facultative anaerobic bacteria of the *Enterobacteriaceae* family. *Ruminococcus gnavus* abundance is also found to be elevated in IBD and certain strains may have evolved to thrive in IBD gut environment through mechanisms of oxidative stress responses [51]. Antibiotic usage during pregnancy, but not during infantile age, is positively correlated with an elevated risk of developing very early onset IBD and may be attributed to changes in gut microbiome [52].

Lactobacillus gasseri SF1138 strain probiotic has been shown to exhibit anti-inflammatory effects in mice models of colitis and is able to maintain gut barrier integrity, suggesting its protective role against the progression of inflammatory intestinal diseases. Interestingly, *L. gasseri SF1138* does not modulate the dysbiotic microbiome composition observed in colitis, and is suspected to secrete molecules that interact with intestinal cells to protect from inflammation [53].

The approach of tungstate-mediated editing of the gut microbiome is able to reduce the severity of intestinal inflammation by inhibiting molybdenum-cofactor-dependent microbial respiratory pathways expressed in specific bacterial populations. They are operational only during episodes of inflammation without major changes to the microbiome composition [54].

8. Gout

Gout is a genetic or acquired metabolic disease with symptoms of joint severe caused by increase of uric acid synthesis resulted from purine metabolic abnormalities [55].

The gut microbiome of gout patients have been shown to be dysregulated as compared to healthy individuals, with an increased abundance of opportunistic pathogens, and similar enrichment were also observed in auto-immune diseases [56]. *Bacteroides caccase* and *Bacteroides xylanisolvens* were also found in higher abundance in gout patients, whereas *F. Prausnitzii* and *Bifidobacterium pseudocatenulatum* were found in lower abundance.

The Microbial Index of Gout, based on the relative abundance of 17 bacterial markers, was proposed as a new method of diagnosis for gout and achieved a higher accuracy of 88.9% compared to conventional blood uric acid tests [57].

9. Depression

The gut microbiome has been increasingly described to be implicated in various neuropsychiatric disorders, with

particularly strong evidence for its role in depression [58]. Researchers have since been invested in exploring the potential and efficacy of using probiotics to provide mental health benefits in patients diagnosed with psychiatric illnesses.

In a double-blinded, placebo-controlled randomized clinical trial, administration of *Lactobacillus reuteri* showed no significant improvements in stress, anxiety or well-being in Swedish elderly group, with dosage of probiotic used and lack of study participants suggested as possible factors contributing to the lack of positive results observed [59]. Similarly, despite promising preclinical study results, *Lactobacillus rhamnosus* did not improve stress or cognitive performances in male volunteers [60]. On the other hand, *B. longum* has been shown to reduce depression and improve quality of life in patients with irritable bowel syndrome [61]. A combination of protiobic species *Lactobacillus helveticus* and *B. longum* was able to reduce depression scores in patients diagnosed with major depressive disorder (MDD) [62].

While reviews have suggested that probiotics may have the potential to reduce the risk of depression [63,64], majority of the studies were conducted on healthy individuals and there remains a lack of significant studies focused on patients with MDD [65]. More recently, a review concluded that probiotics have a negligible effect on overall mood, again emphasising the need for properly designed studies with a greater sample of clinically depressed patients [66].

Although animal models have provided us with insight into relationship between the gut microbiome and cognitive development, there is still a lack of well-designed human studies investigating this relationship and a proper understanding of the complex mechanisms underlying the influence gut microbes have on the brain [67]. While inconsistent, there have been some encouraging results in showcasing the ability of probiotics to modulate depressive symptoms and it is imperative to shift the focus to investigating the effects of these probiotics in patients diagnosed with MDD in order to have a clearer understanding of the mechanistic features behind the ability of probiotics to modulate mental health.

10. Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joints which results in bone and cartilage damage, and even disability [68,69]. However, much of its aetiology remains unknown and the gut microbiome has been suggested to play a role in its pathogenesis [70].

Gut and oral microbiome dysbiosis were observed in RA patients and the alterations in microbiome were able to distinguish RA patients from healthy individuals. *Haemophillus spp* were found in lowered abundance and were negatively correlated with serum autoantibodies level in RA patients. On the other hand, abundance of *Lactobacillus salivarius* was found to be elevated [71,72].

It has been shown that changes to the gut microbiome precedes the development of arthritis, and that it is possible to attenuate arthritis development via total elimination of the gut microbiome using antibiotics. Abundance of intestinal Th17 immune cells is also highly associated with severity of arthritis, but is greatly reduced when the gut microbiome is eliminated, suggesting that the gut microbiome propagate inflammatory signals to promote arthritis development, possibly mediated by Th17 T cell immune response [73–75].

Probiotics have been suggested as an adjuvant therapy for arthritis and aims to target the imbalanced production of cytokines in RA. Probiotics display a potential therapeutic effect in the treatment of RA by significantly reducing the level of pro-inflammatory IL-6 cytokines with no significant differences were observed for other pro-inflammatory cytokines, but the clinical outcome in treating RA is still unknown [76].

11. Infant health

The mode and place of delivery are able to influence gut microbiome composition and subsequently, the risk of atopic manifestations as well, with the effects being mediated by *Clostridium difficile* colonization in infants [77]. The enrichment of *Clostridia* and *Firmicutes* is also associated with milk allergy resolution by 8 years of age, suggesting potential ability as probiotics in treating milk allergies [78]. The gut microbiome composition at 1 year of age, clustered into 3 main groups - those enriched in *Faecalibacterium, Bacteroides* or an unnamed genus in *Ruminococcaceae* - is also associated with cognitive development in infants [79].

Topical corticosteroid, a common treatment for atopic dermatitis (AD), was found to restore cutaneous microbiome on lesional atopic dermatitis to a composition similar to non-lesional atopic dermatitis, but remains distinct from that of healthy control skin levels [80].

Staphylococcus genus of bacteria is a known pathogen in the development of atopic dermatitis – patients with more severe AD harbour more *Staphylococcus aureus* while patients with mild AD are colonized with more *S. epidermidis*. Clonal *S. aureus* strains were identified in severe AD and were able to promote epidermal thickening and immune response via Th2 and Th17 cells [81].

Infants at high-risk of asthma display a unique microbiome profile in the first year of life. Administration of probiotic *L. rhamnosus GG* is able to modulate the microbiome composition in early life, but the effectiveness is diminished after termination of probiotic supplements. This highlights the plasticity of the microbiome and suggests the importance of identifying early postnatal period as an important window for novel intervention methods using probiotics [82].

While reviews have shown that probiotic interventions may be moderately effective in treating eczema, there remains a lack of specific probiotic regimens in clinical usage due to the heterogeneity between studies and low quality evidence from current results [83]. As such, proper clinical trials needs to be designed and conducted in order to critically ascertain the effectiveness of specific probiotic strains to treat eczema and other allergy diseases in a clinical setting.

12. Longevity

The gut microbiome's influence on human metabolism and immunology makes it a possible factor in determining

longevity. The core microbiome in Italian centenarians – consisting mainly of *Ruminococcaceae, Lachnospiraceae*, and *Bacteroidaceae* families decreases in abundance with age and there is a corresponding increase in abundance of subdominant species and health-associated genera such as *Bifidobacterium, Akkermansia* and *Christensenellaceae* [84]. On the other hand, profiling of gut microbiome of Chinese centenarians revealed that the abundance of *Escherichia* and *Roseburia* was significantly elevated whereas that *Lactobacillus, Faecalibacterium, Parabacteroides, Butyricimonas, Coprococcus, Megamonas, Mitsuokella, Sutterella, and Akkermansia* were depleted [85]. While the results may be inconsistent, the differences could be attributed to different factors such as diet and geographical location [86]. Alpha diversity is also highlighted a key indicator in predicting longevity and *Ruminococcaceae*, *Clostridium* cluster XIVa, *Akkermansia* and *Christensenellaceae* are suggested as beneficial bacteria in promoting longevity [86]. Secretion of colanic acid (CA) promotes longevity through regulation of mitochondrial dynamics and unfolded protein response in host [87].

Supplementation of branched-chain amino acid-enriched mixture (BCAAem) could possibly promote healthy ageing. In mice models, BCAAem supplementation increases the abundance of *Akkermansia* and *Bifidobacterium bacteri* while reducing the relative ratio of *Enterobacteriaceae*. 12 metabolites involved in lipid and sugar metabolism were also altered and serum levels of lipopolysaccharide-bind protein was reduced as well [88].

13. Future perspectives

In the past few years, there has been a surge in microbiome research and the focus has begun to shift from correlational studies towards mechanistic and clinical studies in understanding how the microbiome is able to influence human health and disease progression [89]. However, it is not without its limitations and improvements need to be made in order to enhance our understanding of the microbiome and to be able to translate this understanding to help us modulate the microbiome to improve our health.

Given the diversity, variability and complexity of the gut microbiome, interactions between microbial species may be a key player in affecting human health as opposed to the sole influence of a single species or strain [3] and ought to be considered when investigating mechanistic pathways [90]. A 'bottom-up' approach, based on analysing pairwise interactions in a synthetic gut microbiome community using a generalized Lotka-Voltera model, has been suggested to complement the understanding of the gut microbial ecology and how the vast bacterial communities interact with each other. The use of pairwise interactions may be more appropriate in predicting the ability of specific probiotics to persist in the gut, or to determine the effects of removing a particular species, as opposed to higher order interactions [91,92]. Both synbiotics and multi-strain probiotics have also been proposed to confer longer lasting benefits compared to single-species probiotics often employed in current studies and could be an interesting area of research in the future [93].

The 'holy grail' of microbiome research is to be able to safely and effectively manipulate the microbiome to improve health. The ability to tailor therapies according to an individual's personal microbiome, and at the same time accounting for inter-individual variation, is a lofty ideal but makes it an indispensable arm in personalized medicine [3]. While alluring, the promise of microbiome-based therapeutics is still limited by the literature gap exploring causal relationships between the microbiome and disease status [90,94]. Additionally, while the effects of probiotics have been explored in clinical studies, harms reporting are still lacking and is inappropriate to ascertain the safety of probiotic interventions [95].

Funding

This study was funded by the Natural Science Foundation of China (Grant No. 31871831, 31471713, 31470538); Liaoning BaiQianWan Talents Program Project, Shenyang Science and Technology Project (Grant No.17-189-9-00), Shenyang Youth Science and Technology Innovation Talent Project (Grant No. RC170212)

Conflict of interest

The authors declare that they have no conflict of interest.

Research involving human participants and/or animals

Ethical approval: This article does not contain any studies with human participants performed by any of the authors.

Ethical approval: This article does not contain any studies with animals performed by any of the authors.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

Informed consent: Informed consent was obtained from all individual participants included in the study.

If identifying information about participants is available in the article: Informed consent: Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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