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Review Article

Gut Microbiota and Cardiovascular Disease

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Abstract

Microbiota within the intestines and the host interact with each other and there by affect the host's health status, which in turn affects the structure of gut microbiota. With advances in metagenomics, metabolomics and bioinformatics, as well as traditional culturing, the causality and association between gut microbiota and cardiovascular diseases have been well studied. Some underlying mechanisms, especially metabolic pathways, include the role of trimethylamine N-oxide in the pathogenesis of atherosclerotic heart disease and heart failure and that of short chain fatty acids and their receptors in blood pressure regulation. This review covers advances inresearch of gut microbiota and cardiovascular diseases, including coronary artery disease, hypertension and heart failure.

Keywords: Gut microbiota; Cardiovascular disease; Metagenomics; Metabolomics; TMAO; Fecal transplantation

Abbreviations

TMAO: Trimethylamine N-oxide; SCFAs: Short Chain Fatty Acids; TMA: Trimethylamine; FMO: Flavin Mono-Oxygenase; BSH: Bile Salt Hydrolase; PCA: Protocatechuic Acid; F/B: *Firmicutes*/*Bacteroidetes*; S: Salt-sensitive; R: Salt-resistant; Olfr78: Olfactory receptor 78; Gpr41: G protein couple receptor 41; OSA: Obstructive Sleep Apnea; HF: Heart Failure; CHF: Chronic Heart Failure

Introduction

More than 100 trillion microbes in habit the human body [1], so in some sense, humans could be considered super organisms containing human cells and microbes, with the human and microbial genome together affecting human metabolic and inflammatory features [2,3]. Among the numerous species of microbes within our intestine, very few can be cultured. Metagenomic sequencing and metabolomic profiling have been of great help for investigating the composition and function of gut microbiota, the host-gut microbiota interaction and possible pathways associated with the development of particular diseases [4]. Numerous studies of animals and humans have revealed the connection between gut microbiota and diverse diseases, such as inflammatory bowel disease, autism spectrum disorders and metabolic disorders [5-8]. In this review, we cover the latest studies of the relationship between gut microbiota and cardiovascular diseases.

Gut microbiome and coronary artery disease

Chronic infection and inflammation: Inflammation plays an important role in the initiation and progression of atherosclerotic diseases [9]. Not unsurprisingly, the possible association between infectious agents and atherosclerosis has long attracted attention [10,11]. However, consensus is lacking. Some studies suggested that infectious agents such as *Helicobacter pylori* [12], *Chlamydia pneumonia* [13], cytomegalovirus [14], and herpesvirus [15] could accelerate atherosclerosis and some others gave opposite answers [12,16]. Clinical trials of whether antibiotics could have positive effects on patients with coronary artery disease also presented controversial results [17-20].

16S rRNA gene sequencing and metagenomics: 454 pyrosequencing of 16S rRNA genes of atherosclerotic plaque, the oral cavity, and gut microbial communities of 15 patients with clinical atherosclerosis and 15 age- and sex-matched healthy controls identified *Chryeomonas* in all atherosclerotic plaque samples and *Veillonella* and *Streptococcus* in most samples. However, the relative abundance of the phyla was similar between patients and controls, and nearest shrunken centroids analysis did not reveal any operational taxonomic units with different abundance that could differentiate patients and controls [21]. Another study of shotgun sequencing of the gut microbial metagenome demonstrated that the genus *Collinsella* was enriched in patients with stenotic atherosclerotic plaques in the carotid artery, leading to cerebrovascular events, where as *Roseburia* and *Eubacterium* were enriched in healthy controls [22].

Metabolomics analysis

Trimethylamine N-oxide (TMAO): Recent studies have revealed a pathway from dietary phosphatidylcholine, choline, and *L*-carnitine to cardiovascular disease risk, with gut microbiota-dependent synthesis of Trimethylamine (TMA) and subsequent oxidation of TMA to TMAO playing a core role. Through metabolomics approach, three metabolites of the dietary lipid phosphatidylcholine (choline, TMAO and betaine) were identified and shown dose-dependent associations with cardiovascular disease risk in an independent large clinical cohort. Dietary supplementation of choline, TMAO or betaine to atherosclerosis-prone mice (C57BL/6J ApoE$^{-/-}$) upregulated macrophage scavenger receptor simplicated in the endogenous formation of cholesterol-laden macrophage foam cells and atherosclerosis. By contrary, suppression of intestinal microbiota with broad-spectrum antibiotics inhibited atherosclerosis [23]. Also, diet-induced TMAO production and atherosclerosis susceptibility could be induced by cecal microbial transplantation [24]. A 3-year follow-up of 4007 patients undergoing elective coronary angiography furtherly revealed TMAO levels associated with increased risk of incident Major Adverse Cardiovascular Events (MACEs) in humans [25]. These associations were then validated in ethnically diverse populations [26]. Gut microbiota is also indispensable in TMAO

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production from dietary *L*-carnitine, which is abundant in red meat, and plasma *L*-carnitine levels predicted increased risk of both prevalent cardiovascular disease and incident MACEs only among patients with concurrently high TMAO levels [25]. Further study in mice revealed that γ-butyrobetaine was the intermediary and major gut microbial metabolite formed after *L*-carnitine ingestion and then converted into TMA [27]. Conversion of TMA to TMAO needs the Flavin Mono-Oxygenase (FMO) family, especially FMO_3 [23,25,28]. Plasma TMAO levels were significantly increased in mice with FMO_3 over expression and decreased with silenced FMO_3 [29]. In cholesterol-fed mice, knockdown of FMO_3 altered biliary lipid secretion, reduced both the intestinal cholesterol absorption and hepatic oxysterol and cholesterylester production, and accelerated basal and liver X receptor-stimulated macrophage reverse-cholesterol transport, thereby improving cholesterol balance [30]. In insulin-resistant mice, knockdown of FMO_3 suppressed $FoxO_1$, a central node for metabolic control, and completely prevented the development of hyperglycaemia, hyperlipidemia and atherosclerosis [31]. Choline TMA lyase, a C-N bond-cleaving glycyl radical enzyme, was revealed as the enzyme required in the microbial conversion of choline to TMA [32], and its activity required the presence of both CutC and CutD [33]. Use of a structural analog of choline, 3,3-dimethyl-1-butanol,could non-lethally inhibit distinct microbial TMA lyases, which reduced TMA production from physiologic polymicrobial cultures and TMAO levels in mice fed a high-choline or *L*-carnitine diet [33].

Bile acid metabolism: Gut microbiota also affects atherosclerosis by influencing bile acid metabolism. Bile acids are amphiphilic molecules synthesized from cholesterol exclusively in the liver that interact with the farnesoid X nuclear receptor and so play a role in controlling plasma lipid level and affecting the pathology of atherosclerosis [34,35]. Microbial Bile Salt Hydrolase (BSH) activity is distributed across the major bacterial divisions and archaeal species in the gastrointestinal tract, and different BSH alleles may differ in their impact on *in vivo* bile metabolism and downstream responses [36]. Expression of cloned bacterial BSH enzymes in the gastrointestinal tract significantly modified plasma bile acid profiles ingnotobiotic mice and both local and systemic gene expression profiles in pathways governing lipid metabolism (*Ppary, Angptl4*), cholesterol metabolism (*Abcg5/8*), gastrointestinal homeostasis (*RegIIIγ*), and circadian rhythm (*Dbp, Per1/2*). Elevating BSH activity in conventionally raised mice harboring normal gut microbiota significantly reduced atherosclerosis risk factors, including weight gain and serum cholesterol and liver triglycerides levels [37].

Other metabolites

Protocatechuic Acid (PCA) and GlcNAc-6-P: Anthocyanins, abundant in various colorful fruits and vegetables, have long drawn attention for their health-promoting properties, especially the antiatherogenic effect [38,39]. However, only about 0.1% of the intact anthocyanins can be typically absorbed in human beings, with the plasma concentration about 0.0014 to 0.0120 μmol/L, far less than the effective levels of 10 to 200 μmol/L [40]. Actually, their microbial catabolites may be the virtual contributor [41]. PCA, which accounts for about 73% ingested cyanidin-glucosides [42], has an athero protective function by inhibiting c-Jun N-terminal kinase and p38 activation and subsequent interruption of CD40-induced endothelial cell activation and apoptosis, the miRNA-10b-ABCA1/ABCG1-cholesterol efflux signaling cascade. It also affects the expression of genes related to atherosclerosis, including those coding for AOX1, CYP2E1 or TXNIP implicated in the regulation of oxidative stress; JAM-A coding for adhesion molecules; and vascular endothelial growth factor receptor 2 implicated in regulation of angiogenesis [43-45]. Recently, some other metabolites, including GlcNAc-6-P and mannitol, were identified by integrated metabolomics and metagenomics analysis of plasma and urine samples from 59 patients with coronary heart disease patients and 43 healthy controls. Moreover, a close correlation between *Clostridium sp. HGF2* and GlcNAc-6-P, *Clostridium sp. HGF2, Streptococcus sp. M143, Streptococcus sp. M334* and mannitol was revealed by association analysis of species and function levels between intestinal microbes and metabolites [46].

Gut microbiome and hypertension

16S rRNA gene sequencing: A study involving 16S rRNA gene sequencing and bioinformatics analysis revealed gut microbial dysbiosis in fecal samples from two rat models of hypertension, spontaneously hypertensive and chronic angiotensin II infusion rat models, and a small cohort of patients with normal (119±2 mm Hg; n=10) and high (144±9 mm Hg; n=7) systolic blood pressure. The dysbiosis was characterized by increased *Firmicutes/Bacteroidetes* (F/B) ratio and significantly decreased population of acetate-, butyrate-, and lactate-producing microbes. Furthermore, minocycline was able to reduce the F/B ratio so as to rebalance the dysbiotic hypertension gut microbiota and attenuated high blood pressure [47]. Another study of the Dahl rat model suggested that interactions between the host and its gut microbiota were linked to the development of salt-sensitive hypertension. 16S rRNA gene sequencing of cecal samples from Dahl salt-sensitive (S) and -resistant (R) rats showed greater accumulation of bacteria of the phylum *Bacteroidetes* in S than R rats. Furthermore, the frequency was higher for the family S24-7 in the phylum *Bacteroidetes* and family *Veillonellaceaein* the phylum *Firmicutes* in S than R rats. However, cecal transplantation from R to S rats failed to attenuated the hypertension of S rats, which was inconsistent with the assumption that cecal content from the S rats would promote hypertension and that from the R rats would contribute to normotension [48].

Short Chain Fatty Acids (SCFAs): SCFAs, the most abundant of which are acetate, propionate and butyrate, are produced by microbial fermentation of complex polysaccharides in the colon [49]. Two sensory receptors for SCFAs, olfactory receptor 78 (Olfr78) and G protein couple receptor 41 (Gpr41), have a mutually antagonistic effect in blood pressure regulation: stimulation with Olfr78 increased blood pressure and stimulation with Gpr41 lowered it [50,51]. Gpr41 is expressed in various tissues and cell types including the colon, kidneys, sympathetic nervous system, and blood vessels, where it affects blood pressure and weight gain in response to SCFAs [49]. Olfr78 is expressed in the renal juxtaglomerular apparatus, where it mediates renin secretion [52]. Olfr78 also localizes to a subset of smooth muscle cells and autonomic nerves, which also play a role in blood pressure regulation. Suppressing gut microbiota biomass with antibiotics increased blood pressure in *Olfr78*$^{-/-}$ mice, with no significant effect in wild-type mice [52].

Obstructive Sleep Apnea (OSA): Recently, a study of a rat model of OSA found increased blood pressure at 24 and 29 mmHg after 7 and 14 days, respectively, in rats fed a high-fat diet, with no significant change in rats fed a normal chow diet. The authors also found a significant decrease in bacterial taxa known to produce the SCFA butyrate in hypertensive high-fat fed OSA rats. Importantly, transplantation of cecal contents from hypertensive high-fat fed OSA rats to normotensive OSA rats fed a normal chow diet resulted in hypertension similar to that of the donor, which strongly suggested the role of gut microbiota in OSA-induced hypertension [53].

Interventions: Previous human clinical trials have tested whether probiotic consumption may improve blood pressure control. A meta-analysis of randomized controlled trials showed that probiotic consumption significantly changed systolic blood pressure by -3.56 mm Hg (95% confidence interval, -6.46 to -0.66) and diastolic blood pressure by -2.38 mm Hg (95% confidence interval, -2.38 to -0.93) as compared with controls. The effectiveness of probiotics on blood pressure to some extent indirectly supported the causal relationship of gut microbiota content and hypertension [54]. As well, a case report showed that the blood pressure-lowering effects of antibiotic treatment lasted for several months, so antibiotics may initiate underlying mechanisms for blood pressure regulation [55]. Studies of patients undergoing gastrointestinal surgery, including Roux-en-Y gastric bypass and colectomy, showed blood-pressure-attenuating effects and reduced risk of hypertensive disorder, for which the mechanisms are still unclear but suggest a role of gut microbiotain the process [56-58].

Gut microbiome and heart failure

Gut microbial translocation: Intestinal blood flow is reduced in patients with Heart Failure (HF), which may contribute to destroyed intestinal mucosa and subsequent translocation of microbial components and metabolites into the circulation; the process may induce systemic inflammation and contribute to malnutrition and cachexia in patients with Chronic HF (CHF) [59,60]. A recent study analyzed 60 well-nourished patients with mild, stable CHF, moderate to severe CHF and matched healthy controls. Through traditional culturing rather than genomic sequencing methodologies, a significant increase in pathogenic bacteria and fungi such as *Campylobacter, Shigella*, *Salmonella*, *Yersinia enterocolitica*, and *Candida* species was found in the feces of all CHF patients as compared with controls. In addition, intestinal permeability, determined by cellobiose sugar test, was significantly increased in CHF patients. These data were associated with increased right atrial pressure and C-reactive protein level, representing venous blood congestion and inflammation, respectively, which implied that gut microbial translocation into the systemic circulation might contribute to progression of disease severity of CHF [61].

TMAO: High plasma TMAO levels were observed in patients with HF. Moreover, elevated TMAO level predicted risk of long-term mortality independent of traditional risk factors and cardio renal indexes. In a study of 720 patients with stable HF, the median TMAO level was 5.0 μM, which was higher than in participants without HF (3.5 μM; $p < 0.001$), and high plasma TMAO level were associated with a 3.4-fold increased mortality risk. After adjusting for traditional risk factors and brain natriuretic protein level, elevated TMAO level remained predictive of 5-year mortality [62]. Another recent study of patients admitted to hospital for acute heart failure analyzed 972 plasma samples for TMAO concentration and examined the association with in-hospital mortality (72 events), all-cause mortality (death, 268 events) and a composite of death or rehospitalization due to HF (death/HF, 384 events) at 1 year. TMAO contributed additional information to patient stratification for in-hospital mortality with available clinical scores on admission of these patients, and elevated TMAO levels were associated with poor prognosis [63].

Conclusion

Abundant evidence supports that gut microbiota participate in and even play a central role in the development of coronary artery disease, hypertension and heart failure, and these cardiovascular diseases in turn affect the composition and characteristics of microbiota. Besides traditional culturing, advanced technology and strategies such as metagenomics and metabolomics contribute immensely to studies of gut microbiota. Multiple studies have shown the phenomenon and also suggested various potential mechanisms, especially metabolic pathways. With better understanding of gut microbiota and the host-microbiota crosstalk, potential interventional strategies, including but not limited to adjustment of diet, appropriate use of probiotics and antibiotics, and even fecal transplantation may provide new solutions beyond the optimal traditional medication for patients with cardiovascular disease.

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