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Gut Microbiota in Cardiovascular Health and Disease

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Abstract

Significant interest in recent years has focused on gut microbiota-host interaction because accumulating evidence has revealed that intestinal microbiota play an important role in human health and disease, including cardiovascular diseases. Changes in the composition of gut microbiota associated with disease, referred to as dysbiosis, have been linked to pathologies such as atherosclerosis, hypertension, heart failure, chronic kidney disease, obesity and type 2 diabetes mellitus. In addition to alterations in gut microbiota composition, the metabolic potential of gut microbiota has been identified as a contributing factor in the development of diseases. Recent studies revealed that gut microbiota can elicit a variety of effects on the host. Indeed, the gut microbiome functions like an endocrine organ, generating bioactive metabolites, that can impact host physiology. Microbiota interact with the host through a number of pathways, including the trimethylamine (TMA)/ trimethylamine *N*-oxide (TMAO) pathway, short-chain fatty acids pathway, and primary and secondary bile acids pathways. In addition to these "metabolism dependent" pathways, metabolism independent processes are suggested to also potentially contribute to CVD pathogenesis. For example, heart failure associated splanchnic circulation congestion, bowel wall edema and impaired intestinal barrier function are thought to result in bacterial translocation, the presence of bacterial products in the systemic circulation and heightened inflammatory state. These are believed to also contribute to further progression of heart failure and atherosclerosis. The purpose of the current review is to highlight the complex interplay between microbiota, their metabolites and the development and progression of cardiovascular diseases. We will also discuss the roles of gut microbiota in normal physiology and the potential of modulating intestinal microbial inhabitants as novel therapeutic targets.

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DISCLOSURES

Dr. Hazen is named as inventor on pending patents held by the Cleveland Clinic relating to cardiovascular diagnostics and therapeutics. Dr. Hazen is a paid consultant for Esperion Therapeutics and Procter & Gamble. Dr. Hazen has received royalty payments for inventions or discoveries related to cardiovascular diagnostics or therapeutics from Cleveland HeartLab, Siemens Healthcare, Esperion Therapeutics, and Frantz Biomarkers LLC. Drs. Tang and Kitai have no relationships relevant to the contents of this paper to disclose.

Keywords

Gut microbiota; Cardiovascular disease; Trimethylamine *N*-oxide

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death and disability in developed countries. CVD is responsible for approximately one of every three deaths in the United States and one of every four deaths in Europe.[1] Further, the steady increase of common risk factors for CVD, such as obesity, type 2 diabetes (T2DM) and the metabolic syndrome, compels the search for more effective strategies to prevent and modify the course of these cardiometabolic disorders.[2]

Significant interest has recently focused on the role of human gut microbiota in CVD and metabolic disorders. Microbial sequencing analysis has provided a wealth of information about the presence of characteristic gut microbiota associated with CVD.[3–5] Also, a growing body of evidence shows that manipulation of the composition of gut microbiota affects host metabolism.[6, 7] Furthermore, recent studies suggest that gut microbiota produce numerous metabolites, some of which are absorbed into the systemic circulation and are biologically active, whereas others are further metabolized by host enzymes, and then serve as a mediator of microbial influence on the host.[8–13] Thus, the gut microbiome, functioning as a virtual endocrine system, communicates with distal organs through metabolism-dependent pathways.[8–11, 14–22] This review will discuss the roles of gut microbiota in normal physiology, their associations with disease settings, and the potential of modulating gut microbiota as novel therapeutic targets with particular emphasis on the complex interplay between microbiota, their metabolites and CVD.

THE ROLE OF GUT MICROBIOTA IN HOST PHYSIOLOGY

The human body is inhabited by a huge number of bacteria, archaea, viruses, and unicellular eukaryotes.[23] The collection of microorganisms that live in coexistence with their hosts has been referred to as the microbiota. The microbiota colonize mainly in the gastrointestinal tract, especially in the colon, that is primarily anaerobic, and has a rich nutrient environment serving as a preferred site for intestinal microbial colonization.

Gut microbiota participate in food digestion through two main catabolic pathways categorized as saccharolytic or proteolytic.[24] In the saccharolytic pathway, gut microbiota break down sugars and are responsible for the majority of short-chain fatty acid (SCFA) production. The second catabolic pathway is represented by protein fermentation, which also induces SCFA formation, but leads to other co-metabolites such as ammonia, various amines, thiols, phenols, and indoles. Some of these metabolites are potentially toxic, and because they are predominantly renally cleared, their accumulation are often considered microbial uremic toxins.[25]

Gut microbiota perform multiple functions and interact with the host beyond its role in supporting physiological functions in food digestion. Gut microbiota constitute and regulate

the intestinal mucosal barriers, control nutrient uptake and metabolism, assist with maturation of immunological tissues, and prevent propagation of pathogenic microorganisms.[26–30] Under physiological conditions, gut microbiota continue to stimulate the immune system, which is a rapid and effective mechanism for defending against pathogens.[31] Collectively, the microbiota exert a fundamental influence on systemic immunity and metabolism, and healthy gut microbiota are largely responsible for the overall health of the host.[23]

PATHOGENIC MECHANISM OF GUT MICROBIOTA AND METABOLITES IN CARDIOMETABOLIC DISEASES

Altered composition of gut microbiota

The majority of the gut microbial community is composed of only five phyla (*Bacteroidetes, Firmicutes, Actinobacteria*, *Proteobacteria* and *Cerrucomicrobia*).[32] However, there is considerable diversity on the species level and their relative abundance. In the healthy gut, anaerobic *Bacteroidetes* and *Firmicutes* contribute more than 90 % of the total bacterial species.[32] However, the ratio of the *Firmicutes* to *Bacteroidetes* is not the same in all individuals. Inter-individual variation in bacterial diversity is caused by differences in host genomes and also by environmental factors, such as antibiotic use, lifestyle, hygiene, and diet. [33, 34] Recently, as developments in genome sequencing technologies and bioinformatics have enabled us to identify and characterize in detail these microorganisms, the composition and potential roles of the bacteria in the pathogenesis of cardiometabolic disorders have been intensely studied.[35–38]

Gut microbiota-derived signaling molecules

Gut microbiota can elicit effects on the host through a variety of processes. To communicate with distant organs, gut microbial signals first need to be transmitted across the intestinal epithelium. In some cases, these signalling molecules are a structural component of microbiota such as lipopolysaccharide (LPS) and peptidoglycans that interact with host mucosal surface cells, often through so called pattern recognition receptors (PRR).[39] PRR recognize pathogen-associated molecular patterns (PAMPs), which stimulate and instruct host immune response.[40] Thus, LPS and peptidoglycans can trigger numerous downstream signalling processes with host receptors both at the epithelial cell border, as well as within vasculature, particularly under conditions when gut wall barrier function is impaired.[41, 42] Gut microbiota can also impact host processes via bioactive metabolites that can affect distal organs directly or indirectly.[43] Gut microbiota interact with the host through a number of pathways, including the trimethylamine (TMA)/ trimethylamine *N*-oxide (TMAO) pathway, SCFAs pathway, and primary and secondary bile acid (BAs) pathways.[8–11, 14–22] Some of these molecules have been shown to functionally interact with other endocrine hormones, including ghrelin, leptin, glucagon-like peptide 1 (GLP-1), and peptide YY (PYY).[44, 45] Others have been reported to stimulate the parasympathetic nervous system, thereby impacting glucose homeostasis and other metabolic processes linked to development of metabolic syndrome.[46]

Atherosclerosis, Coronary Artery Disease and Myocardial Infarction

Atherosclerotic plaques contain bacterial DNA, and the bacterial taxa observed in atherosclerotic plaques were also present in the gut of the same individuals.[3, 38] These observations suggest the possibility that the microbial communities at these sites may be a source of bacteria in the plaque, which may impact plaque stability and development of CVD. In addition to gut microbiota, taxa characteristics of oral microbiota have also been detected in atherosclerotic plaque in humans.[3] Given the many epidemiological links between periodontal disease and CVD,[47–49] a role for oral microbiota in the pathophysiology of CVD has also been studied.[3, 49, 50] Metagenomic sequencing of stool microbiota revealed that the microbial composition is altered in patients with unstable versus stable plaques, with unstable plaque associated with reduced fecal levels of the genus Roseburiam and both increased theoretical capacity of the microbiome to produce pro-inflammatory peptidoglycans and reduced production of anti-inflammatory carotenes.[4] The gut microbiome of patients with CVD may thus be fostering inflammation by producing more pro-inflammatory molecules.

Recently, a mechanistic link between the gut microbiota and the severity of myocardial infarction has been reported in rats.[51, 52] Use of broad-spectrum antibiotics was shown to affect levels of leptin and analytes produced during aromatic amino acid catabolism, with associated reduced myocardial infarct size.[51, 52] In addition, in rodent model studies, administration of *Lactobacillus plantarum* was associated with significant reduction in infarct size and improved left ventricular function after myocardial infarction.[51] Another animal model study showed that administration of the *Lactobacillus rhamnosus* GR-1 attenuated left ventricular hypertrophy and heart failure after experimental myocardial infarction.[53] These observations may suggest that probiotics use, in combination with standard medication, could offer additional benefits in heat failure patients, such as reducing the severity of heart failure after myocardial infarction.

In addition to the alterations in gut microbiota composition, the metabolic potential of gut microbiota has been identified as a contributing factor in CVD development. In particular, TMAO, the hepatic oxidation product of the microbial metabolite TMA, has gained considerable attention as a potential promoter of atherosclerosis and cardiometabolic diseases.[40, 54] TMA is an organic compound that is generated by the gut microbiota. Specifically, microbial metabolism of dietary nutrients that possess a TMA moiety (such as choline, phosphatidylcholine, and L-carnitine) is focused primarily on obtaining carbon duel source for the microbe. TMA is then produced as a waste product by a variety of microbial enzymes (TMA lyases).[55–57] TMA is rapidly oxidized into TMAO by flavin monooxygenase enzymes in the liver and then released into the circulation.[58] TMAO is mainly cleared from circulation by the kidneys, and thus, renal function is also important to consider when looking at levels of TMAO in the systemic circulation.[59]

We recently showed the proatherogenic contribution of microbial-host TMA/TMAO generation from metabolism of dietary nutrients by using germ-free mice or short-term antibiotics for eliminating intestinal microbiota.[8] ApoE−/− C57BL/6J mice, only when fed with a choline-rich diet and intact gut microbiota, led to an increase in plasma TMAO levels, macrophage foam cell formation, and enhanced aortic atherosclerotic plaque. In contrast,

germ-free mice and short-term antibiotic suppression of gut microbiota eliminated TMAO generating capacity, and the latter reduced atherosclerotic burden.[8] These effects were not unique to choline or phosphatidylcholine, but have similarly been observed with other dietary nutrients that can generate TMAO downstream, including L-carnitine and gamma butyrobetaine.[9, 55] Comparison of both intestinal microbiota composition and function between omnivores and vegans/vegetarians revealed stark differences in gut microbial capacity to produce TMA and TMAO from dietary L-carnitine, with vegetarians and vegans having minimal capacity to form TMA from carnitine.[9] Further, studies using poorly orally absorbed antibiotics coupled with the use of dietary intake of isotope-labelled phosphatidylcholine have showed a direct demonstration of an obligatory role for gut microbes in TMAO generation in humans.[22]

The association of TMAO levels and adverse clinical consequences has been shown in numerous independent cohorts.[8, 22, 54, 59–62] The original human studies of more than 1,800 stable cardiac patients undergoing elective coronary angiography demonstrated that all TMAO-associated metabolites—choline, betaine, and L-carnitine—had a positive association with prevalent CVDs and incident cardiovascular events.[8] Of these 3 compounds, circulating TMAO levels exhibited a positive correlation with atherosclerotic plaque size, whereas triglyceride, lipoproteins, fasting glucose, and hepatic triglycerides did not.[8] In a subsequent study of over 4,000 subjects undergoing elective coronary angiography, elevated TMAO levels were associated with increased risk of incident major adverse cardiovascular events (MACE), including death, myocardial infarction and stroke over a 3-year follow-up period.[22] Specifically, patients in the highest quartile of circulating TMAO levels had a 2.5-fold increased risk of having a MACE compared to those in the lowest quartile.[22] Such prognostic value was independent of traditional cardiac risk factors, lipid parameters, C-reactive protein, and even renal function, and the hazard ratio for TMAO was much higher than for traditional risk factors such as LDL cholesterol. [22] Since these initial studies, numerous additional reports have shown associations between TMAO levels and incident CVD risks.[22, 59–62] Circulating TMAO was associated with the presence of vulnerable coronary plaque, plaque rupture, and long-term risks of incident cardiovascular events in patients with acute coronary syndrome.[63, 64] Mechanistic studies in animal model studies also reveal TMAO alters platelet calcium signalling, and elicits a pro-thrombotic effect in vivo.[10] These observations suggest that TMAO could be a marker for coronary plaque vulnerability and progression, and a direct participant in enhanced risk for myocardial infarction. Recently, we observed that higher fasting plasma TMAO levels were associated with higher all-cause mortality over five years among 821 consecutive patients with adjudicated peripheral artery disease.[62] However, although these observations highlight that plasma levels of TMAO correlate with CVD risk, there are still some questions regarding the causative effects of TMAO and the underlying mechanistic link that explains how TMAO might directly or indirectly promote CVD. In recent studies use of a small molecule inhibitor of microbial choline TMA lyase activity was shown to suppress microbial TMA and TMAO formation, macrophage foam cell formation, and atherosclerosis in vivo.[65] Whether targeting this pathway elicits parallel reductions in CVD risks in humans remains unknown, but is an important area of future research.

Hypertension

Hypertension is the most prevalent modifiable risk factor for CVD. Though few studies have linked gut microbial signatures to hypertension in humans, recently, early studies showed germ-free rats have an elevated blood pressure, implicating a role for gut microbiota in blood pressure regulation.[66] More recently, a limited number of studies indicate a direct association between gut microbiota and blood pressure control in animal models.[67–70] Yang et al. compared alterations in the fecal microbiota in the spontaneously hypertensive rat and chronic angiotensin II infusion rat models of hypertension.[67] They observed a significant dysbiosis as a result of decreases in microbial richness, diversity, evenness, and increased Firmicutes/Bacteroidetes ratio in hypertensive animals.[67] Mell et al. demonstrated significant differences in cecal microbiota comparing salt-sensitive and salt-resistant strains by using Dahl rats.[68] Studies employing angiotensin II-infused germ-free mice showed that gut microbiota participate in angiotensin II-induced vascular dysfunction and hypertension.[71] Recent study showed a blood pressure-lowering effect in a patient with treatment-resistant hypertension when treated with a combination of antibiotics. [69] Higher abundance of the butyrate-producing genus *Odoribacter* was associated with lower blood pressure in overweight and obese pregnant women.[72] These data suggest a strong association between gut microbial dysbiosis and hypertension pathology.

SCFAs, which are other important signals generated by the gut microbiota, have been recently shown to modulate blood pressure.[11] SCFAs are a major product from the microbial fermentative activity in the gut, and are likely to have broad impacts on various aspects of host physiology, as well as to impact disease susceptibility.[73] SCFAs can function to stimulate host G-protein coupled receptor (GPR) pathways that impact renin secretion and blood pressure regulation.[11] A series of studies using the renal and vascular olfactory receptor (Olfr) 78 and GPR41 knockout mice further supports involvement of these receptors in blood pressure control. For example, stimulation of Olfr78 was observed to elevate blood pressure, whereas stimulation of GPR41 lowered blood pressure.[74] Communication between the gut enteric nervous system and the central nervous system has similarly emerged as a potential link to blood pressure. [75, 76] Gut microbial products have been implicated in sympathetic activation, and maintenance of an influx of lymphocytes to intestinal tissue. [77, 7879]

Thus, gut microbiota are potentially intertwined functionally to control blood pressure, and their dysfunctions could be associated with hypertension. In fact, a beneficial role for *Lactobacillus* probiotics in blood pressure regulation has been reported. [80–82] Furthermore, a meta-analysis demonstrated a significant decrease in blood pressure in patients treated with probiotics. [83]

Heart failure

There is a growing literature to support a role of the gut in the pathogenesis of heart failure - the so-called “gut hypothesis of heart failure.” The gut hypothesis implies that decreased cardiac output and elevated systemic congestion can lead to intestinal muscosal ischemia and/or edema, leading to increased bacterial translocation and increased circulating endotoxins that can contribute to the underlying inflammation seen in patients with heart

failure.[84, 85] Niebauer et al. found that heart failure patients with peripheral edema had higher plasma concentrations of endotoxin and inflammatory cytokines compared to those without edema.[86] After short-term diuretic treatment, serum concentrations of endotoxin, but not cytokines decreased.[86] In another study, heart failure patients with lower intestinal blood flow were shown to have higher serum concentrations of immunoglobulin A–antilipopolysaccharide, which in turn was correlated with increased growth of bacteria obtained from biopsies of colonic mucosa but not stool bacteria.[87] The nature of the bacterial flora in these subjects also appeared to be different from that in the control subjects.[87] Recently, Pacini et al. reported a corresponding increase in the amount of fecal intestinal bacteria and fungi with increased intestinal permeability in patients with chronic heart failure when compared to healthy controls.[88] These data imply that an assessment of intestinal barrier function may lead to greater mechanistic understanding of the impact of gut-directed heart failure therapy.

In addition to the clear link between TMAO and atherosclerotic CVD risk, TMAO levels have also more recently been linked to heart failure development and poor prognosis in heart failure patients.[8, 22, 60, 89] We recently observed that circulating TMAO levels are higher in patients with heart failure compared with age- and gender-matched subjects without heart failure.[60] Moreover, we observed a remarkably strong adverse prognostic value associated with elevated plasma TMAO levels among a cohort of stable patients with heart failure that was incremental to traditional risk factors, cardio-renal indices and markers of systemic inflammation.[60] However, the mechanism explaining why patients with heart failure have increased levels of TMAO remains to be determined.

Recent animal model studies suggest beyond association studies and adverse prognosis data in humans, the TMAO pathway may directly contribute to the development of adverse ventricular remodeling and heart failure phenotype.[90] For example, using a trans-aortic constriction model of heart failure, mice fed a high choline diet had both higher TMAO levels and accelerated adverse ventricular remodeling compared to mice on a chemically defined low but sufficient choline diet.[90] In addition to enhanced chamber dilation, wall thinning and reduced shortening fraction, marked increase in fibrosis was observed in mice on the high choline diet. Moreover, the pro-fibrotic TGF-B phosphor-SMAD3 pathway was shown to be enhanced in the choline diet-fed mice.[59] Whether manipulation of the gut microbial TMAO pathway such as through inhibition of microbial TMA production can attenuate heart failure like phenotype from developing, or reduction in TMAO levels in subjects with heart failure improves long term outcomes, remain to be determined.

Obesity and type 2 diabetes mellitus (T2DM)

Obesity has increased worldwide and is attributed to increased energy intake and reduced energy expenditure. Obesity increases the risk of multifactorial diseases such as T2DM. Initial animal and human studies supported associations between obesity and the higher ratio of *Firmicutes* to *Bacteroidetes*.[36, 91] In an intervention of calorie-restricted diets, weight loss was associated with decreases in *Firmicutes* to *Bacteroidetes* ratio both in low fat and low carbohydrate diets.[36] Metagenomic analysis has revealed increased harvest of energy from

indigestible carbohydrates in the microbiome of obese mice, further supporting an association of altered microbiota composition in obesity and T2DM.[6, 37, 92, 93]

T2DM was associated with a reduced abundance of butyrate-producing bacteria and an increased abundance of *Lactobacillus* spp.[37, 93, 94] SCFAs, in particular butyrate, serve as energy substrates for epithelial cells of the gut. [95, 96] Microbial pathways that generate SCFAs were found to be enriched in metagenomic studies of feces recovered from obese subjects, and levels of SCFAs were elevated in overweight or obese people and animal models, consistent with these products of microbial fermentation providing extra calories to the host.[6, 97, 98] Moreover, computational models based on the gut metagenome were able to predict T2DM-associated phenotype in patients with impaired glucose tolerance.[93] Furthermore, vancomycin treatment in patients with metabolic syndrome reduced the abundance of butyrate-producing bacteria, leading to reduced insulin sensitivity. [99] Moreover, a study using fecal microbiota transplantation from lean donors to insulin resistant patients with metabolic syndrome demonstrated that feces from lean subjects, but not autologous transplantation, improved insulin sensitivity and was associated with enhanced numbers of butyrate-producing bacteria.[100]

SCFA can directly activate G-protein-coupled receptors such as GPR41 and GPR43, which affect several important processes that include inflammation and enteroendocrine regulation.[101, 102] Binding of SCFAs to GPR41 induces expression of the enteroendocrine hormone PYY in gut epithelial L-cells via GPR41, leading to increase in energy harvest from the diet.[102] By contrast, SCFAs can suppress insulin-mediated fat accumulation and stimulate energy expenditure in liver and muscle through the GPR43 in mouse white adipose tissue.[14] SCFAs can also trigger secretion of GLP-1 by intestinal L-cells via both GPR41 and GPR43, which has a substantial impact on pancreatic function and insulin release, as well as central effects regulating appetite.[103, 104] In fact, in a recent study propionate significantly increased postprandial GLP-1 and PYY while reducing calorie intake at a buffet meal, resulting in a significant reduction in weight gain after a long-term supplementation.[105] Furthermore, rectal and intravenous administration of acetate was associated with increased plasma concentration of PYY and GLP-1 in humans.[106] The role of SCFAs, their receptors, and their targets requires further investigation.

Bile acids (BAs) are another group of metabolites with a profound effect on human health. Secondary BAs are metabolized by the microbiota in the lower part of the small intestine and the colon.[107, 108] BAs facilitate the absorption of dietary fat and fat-soluble molecules. There is an astonishing chemical diversity to the BA pool, and while the heterogeneity and function of numerous BAs are just beginning to become dissected, several species are now recognized as regulators of energy metabolism through activation of nuclear receptors such as G-protein-coupled bile acid receptor 1 (TGR5) and farnesoid X receptor (FXR).[109–111]

For example, gut microbiota can regulate TGR5 signalling by producing agonists and FXR signalling by metabolizing antagonists, such as tauro-β-muricholic acid (TβMCA), which is an abundant primary BA. [112, 113] Microbial metabolism of this BA relieves FXR inhibition and increases signaling.[112] FXR activation in the intestine induces fibroblast growth factor 15 expression, which suppresses the expression of cholesterol 7 α-hydroxylase in the liver,

an important hepatic enzyme impacting BA pool size and composition. Thus, the capacity to metabolize TβMCA has been associated with microbiota links to obesity and insulin resistance.[113, 114] BAs have also been described to affect the cecal microbiota composition of rats, and a direct antimicrobial effect of BAs has been described in vitro.[115, 116] Thus, a reciprocal and complex interrelationship exists between gut microbial metabolism of BAs, and BAs impact on microbial composition and function. It will be essential to identify the microbial enzymatic participants, specific BAs, and the host receptors and signaling molecules involved in the complex metaorganismal signaling pathways coordinating gut microbiota participation in human physiological processes and disease susceptibilities.

One intervention that has significant impact on microbial community structure and function is bariatric surgery. Bariatric surgery is associated with an altered microbiota and increased circulating levels of primary and secondary BAs have been observed after bariatric surgery.[117–119] Increased GLP-1 and reduced glucose and triglyceride levels have also been linked to bariatric surgery.[120–122] Although the underlying mechanisms have not been fully elucidated, release of satiety-promoting gut hormones such as GLP-1 and PYY, and a shift in BA metabolism together with an increased signaling through FXR have been suggested to play a role. [44, 45, 123, 124] Similarly, TGR5 is required for improved metabolism of glucose that is observed following bariatric surgery. Germ-free mice that received a fecal transplant from people who had undergone bariatric surgery 10 years earlier gained less fat than did mice that were colonized by microbiota from obese people.[45] Some of the beneficial effects of bariatric surgery might therefore be mediated by the altered microbial metabolism of BAs, which affects their capacity for signalling. Although a direct antimicrobial effect of BAs has been described in vitro,[116] it is still unclear whether BA–mediated microbiota alterations are a direct effect of BAs on the bacteria or whether cross-talk with the intestinal mucosa is involved.

Dyslipidemia

Recent studies suggest that the gut microbiota can mechanistically impact host lipid levels.[8, 9, 125–127] Independent of body mass index and other metabolic disturbances, associations between levels of circulating triglycerides and high density lipoprotein cholesterol with gut microbiota have been reported.[125] Although the underlying biological mechanisms through which gut microbiota or their metabolites can impact host lipid metabolism has not been enumerated, secondary bile acids, which are produced by gut microbiota, have been suggested to modulate both hepatic and/or systemic lipid metabolism, as well as glucose metabolism, through FXR and GPR131.[17, 18, 44] In addition, some of the proatherogenic effects of TMAO are linked to reduction in reverse cholesterol transport, alteration in tissue cholesterol and sterol metabolism, and changes in bile acid composition, pool size and transport in both the liver and intestines.[9] Furthermore, genetic manipulation of the expression of host hepatic FMO3 has been shown to elicit alterations in plasma lipid levels and hepatic lipid metabolism,[126, 127] suggesting a major role for FMO3 in modulating lipid homeostasis.

Chronic kidney disease (CKD)

Cardiovascular and kidney diseases are closely interrelated, and the so-called cardiorenal syndrome is associated with poor clinical outcomes.[128] People with chronic kidney disease (CKD) have a greater risk of CVD-related mortality.[129] The increased CVD risk is only partially explained by traditional cardiovascular risk factors, and there is increasing evidence that non-traditional risk factors such as inflammation, oxidative stress, and endothelial dysfunction play a key role. [130]

It is well known that the composition of gut microbiota is markedly altered in CKD patients, leading to an influx of circulating urea and other uremic toxins into the gut lumen.[131, 132] Within the intestinal tract, urea is hydrolyzed by microbial urease to form large quantities of ammonia, which is then converted to ammonium hydroxide. Ammonia and ammonium hydroxide disrupt the intestinal epithelial tight junctions.[131] This is thought to be a major cause of intestinal epithelial barrier dysfunction in CKD that allows the translocation of gut bacterial DNA and uremic toxins into systemic circulation, resulting in systemic inflammation.[133] Recently, the DNA of gut microbiota has been detected in the plasma of CKD patients on chronic hemodialysis sing bacterial 16S rDNA amplification and DNA pyrosequencing.[134] Moreover, levels of the bacterial DNA correlated with increased plasma inflammatory marker levels. Poorly dialyzable protein-bound uremic toxins such as indoxyl sulfate and p-cresyl sulfate are associated with poor cardiovascular outcomes in patients with uremia, and p-cresyl sulfate is also associated with insulin resistance.[135–137] Both of these sulfates are derived from gut microbiotic metabolism of dietary amino acids and are ineffectively cleared from the circulation in cases of renal dysfunction. In a recent study, a widely distributed family of tryptophanases in the gut commensal *Bacteroides* was identified as a primary and rate limiting source of indoxyl sulfate in human gut bacteria; moreover, modulating the content of the gut microbes harboring the tryptophanases was shown to substantially impact indoxyl sulfate levels in vivo.[138] In clinical studies, levels of this and other uremic toxins have been shown to be associated with angiographic coronary atherosclerosis severity.[139] Collectively, there is significant evidence suggesting the gut could be a target of treatment of CKD in conjunction with efforts to improve dialysis techniques to better remove microbially generated uremic toxins.

TMAO has been known to accumulate in the plasma of patients with CKD, and higher TMAO levels were associated with higher mortality and progressive loss of kidney function.[59–61] Data from the Framingham Heart Study indicated that TMAO was one of the few metabolites in the plasma of healthy subjects whose levels predicted incident development of CKD.[140] In addition, we observed enhanced renal fibrosis and decreased renal function with choline rich diet supplementation.[59] It is clear that further studies exploring the physiology of TMAO generation and metabolism are warranted to more thoroughly define the etiology of TMAO elevations in CKD.

THERAPEUTIC INTERVENTION

The many links between the altered gut microbial community, metabolites, and susceptibility for CVD and metabolic diseases has placed a spotlight on the gut microbiome as a potential novel target for therapeutics. Currently diet modulation is the major

therapeutic tool utilized in clinical practice to impact chronic metabolic diseases, and while this lifestyle interaction can clearly impact gut microbial community structure and function, there are few studies that explore the impact of dietary interventions on the gut microbiome in humans. Additional approaches to manipulate the gut microbiome that hold promise, though have yet to be realized for metabolic disorders, include prebiotics, probiotics and small molecule inhibitors of defined microbial enzyme pathways.

Fecal microbiota transplantation

Gut microbial modulation by fecal microbiota transplantation (FMT) is a possible therapeutic intervention designed to displace intestinal pathogens by introducing fecal contents from healthy subjects into the gastrointestinal tract of patients. This therapeutic approach has been growing and has caught much attention specifically in its utility to treat intestinal diseases.[141] FMT is demonstrated to be effective in the treatment of antibiotic resistant *Clostridium difficile* infection in humans, where fecal transplantation induces an 80% remission rate. [142, 143]

Recently, FMT has also been tested as an emerging therapy to manage cardiometabolic disorders.[144, 145] Overweight patients with metabolic syndrome were transferred microbiota from either their own feces (autologous transfer) or from lean healthy controls (allogeneic transfer). After 6 weeks of follow-up, the allogeneic fecal transfer had improved hepatic and peripheral insulin sensitivity by 119% and 176%, respectively, as shown by a euglycemic–hyperinsulinemic clamp technique.[144] This metabolic improvement was independent of any weight variations. The allogeneic fecal transfer induced an increase in overall gut microbial richness, and more specifically, increased the abundance of butyrate-producing bacteria, such as *Roseburia*, confirming previous results that showed an association between *Roseburia* and glucose homeostasis.[37, 93]

However, the use of FMT is currently limited due its associated risks including possible transfer of endotoxins or infectious agents that could cause new GI complications.[146, 147] Further studies are needed to test if FMT could be extended to other facets of cardiometabolic disorders. Instead of fecal contents, the transplantation of only a defined group of bacteria may be a rational alternative to FMT.[148]

Diet intervention

A dietary approach to nutritional interventions in CVD had proved to be an effective strategy in reducing cardiovascular risk.[149, 150] In a comprehensive study involving more than 900 participants, diet-dependent postprandial blood glucose levels were correlated with individual gut microbiota composition.[151] Although the composition of the microbiota is quite resilient over an individual's life span,[152, 153] dietary interventions that induce rapid changes in certain nutrients can modify the microbiota composition.[154, 155] Changes in *Roseburia* and *E. rectale* have been observed with changes in the proportion of carbohydrate content in the diet.[156, 157] Fiber-rich diets promote the growth of beneficial commensal bacteria and limit the growth of known opportunistic pathogens.[158] A high fiber diet was reported to increase acetate-producing microbiota, lower blood pressure and decrease cardiac hypertrophy and fibrosis.[159] A recent study has shown that dietary intervention with

whole grains, traditional Chinese medicinal foods and prebiotics, resulted in improvement in insulin sensitivity and lipid profile with concomitant reduction of opportunistic pathogen of the *Enterobacteriaceae* family and increase in the family Bifidobacteriaceae, a taxa generally regarded as gut barrier-protecting.[160] In addition, bacterial fermentation of prebiotic soluble fiber generates SCFA, which is thought to exert several beneficial effects including potential amelioration of CVD risk factors.[12, 161, 162]

Given that an alteration in gut microbiota composition has been linked to different diseases, modulation of gut microbiota composition through dietary intervention represents a promising therapeutic target. However, little is known about the mechanistic interplay between the diet intervention and the relevant gut microbial metabolism. By using metagenomic sequence analysis, representative species from the dominant phyla can be extracted and an algorithm (known as CASINO53) was reported to be able to predict metabolite production that reflects the interaction between the gut microbiota composition and the consumed diet of the individual. In one study, this algorithm was validated with a diet intervention study coupled with metabolomic analyses of fecal and blood samples. [163]

Probiotic, Prebiotic and Antibiotic intervention

Probiotics are live “beneficial” bacteria administered to re-establish an appropriate intestinal balance. Probiotics may potentially act through different mechanisms including pH modulation, antibacterial compound production, and competition with pathogens. [164]

Administration of *Christensenella minuta* was reported to alter the microbial ecology and protect mice from obesity.[165] In a recent study, administration of *Lactobacillus reuteri* was reported to increase insulin secretion by promoting incretin release in obese glucose-tolerant subjects.[166] Similarly, administration of *Lactobacillus sp.* was associated with significant reduction of toxins produced by the small intestine, such as dimethylamine and nitrosodimethylamine, in patients with CKD,[167] and changes in colon levels of certain SCFAs in patients with carotid atherosclerosis.[168] In some studies, engineered probiotic bacteria are genetically modified to enhance their potential beneficial effects. For example, Davies and colleagues formed N-acylphosphatidylethanolamines-expressing *Escherichia coli* Nissle 1917 to alleviate high fat diet-induced obesity, insulin resistance and hepatosteatosis in mice.[169] Among other therapeutic targets of interest, the intestinal alkaline phosphatase is well-known to detoxify bacterial LPS by de-phosphorylating its lipid A moiety.[170] In a study using genetically engineered NAPE-expressing *E. Coli* Nissele 1917, a reduction in adiposity, insulin resistance and liver lipid accumulation in mice was reported.[171] However, the mechanism of action and how these microbes affect cardiometabolic risks in humans are yet to be determined.

Another strategy for modulating intestinal microbiota is the use of prebiotics, which are non-microbial entities provided to elicit a favorable impact on microbial community composition and function. Typical prebiotcis are food indigestible molecules such as oligosaccharides or complex saccharides. In some studies, prebiotics administration is associated with both improved glycemic control and plasma lipid profiles. [172, 173] Three months of oligofructose supplementation in obese patients was associated with weight loss and improved glucose tolerance.[174] In a preclinical study employing an insulin resistance mouse model, use of

antibiotics or prebiotics was reported to reverse microbial community features associated with diabetes, improve gut permeability, reduced metabolic endotoxemia, lower inflammation, and improve glucose intolerance.[175] However, in a subsequent follow-up clinical study, the prebiotic treatment in obese women did not show similar strong effects, raising questions as to the translatability of studies performed in mice compared with humans.[176] It has also been found that not all humans respond to dietary changes in a similar manner, and non-responsiveness to either a fiber-rich or weight loss diet was shown to correlate with pre-intervention increased bacterial diversity.[177]

Therapeutic intervention focusing on the elimination of disease-causing microbiota by antibiotics is an obvious concept, but the general consensus is such non-specific anti-microbial approaches may do more harm than good. The use of antibiotics in humans during the first six months of life is associated with childhood obesity.[178] Similar results were observed in mice whereby a subtherapeutic dose of antibiotics increased adiposity in young mice.[179] Surprisingly, ApoE-KO mice fed a standard low cholesterol diet and maintained in germ-free conditions develop severe atherosclerosis compared to their conventionally-housed counterparts.[180] These results suggest that therapeutic alteration in gut microbial composition should also focus on the preservation of the beneficial microbiota that are central in maintaining well-being because those microbiota or their metabolites may mediate cardiovascular protective effects. Taken together, these findings suggest that individualized treatment programs based on the microbiota may provide novel treatment strategies for cardiometabolic disorders.

Small molecule antimicrobial enzyme therapeutics

The recent discovery of the TMAO pathway, its numerous clinical links to adverse CVD outcomes, and its adverse effects on host cardiometabolic phenotypes, has raised the exciting possibility of selectively targeting microbial synthetic enzymes responsible for TMA generation from nutrient precursors as a potential therapeutic strategy. Proof of concept for this strategy was recently shown through development of a small molecule tool drug for the inhibition of microbial choline TMA lyase activity.[65] Use of a choline structural analogue, 1,3 dimethylbutanol (DMB), that inhibited microbial generation of TMA from a variety of nutrients (eg. choline, glycerphosphocholine, phosphorylcholine, phosphatidylcholine, as well as several carnitine related nutrients), was shown to both suppress plasma levels of TMA and TMAO in mice on a high choline or carnitine containing diet, as well as inhibit both diet induced macrophage foam cell formation and aortic root atherosclerosis development.[65] In a rich nutrient broth, use of DMB with multiple human commensals was shown to inhibit TMA production from choline without impacting microbial growth. Thus, with the markedly reduced selective pressures for development of resistance that exist with a targeted non-lethal microbial inhibitor strategy, there is considerable excitement about the potential for future development of microbial enzyme inhibitors for the potential treatment of cardiometabolic phenotypes in subjects.

GAPS IN KNOWLEDGE

Multiple human clinical studies reveal striking associations between either gut microbiota composition, or their derived metabolites, and both the presence and incident development of CVD. Despite these exciting and intriguing findings, by comparison, few studies have provided mechanistic or causal evidence of a direct participatory role of gut microbiota to the development of atherosclerosis or its adverse complications. Study designs using antibiotics or FMT, while compelling in terms of demonstrating mechanistic participation of gut microbiota to the monitored phenotypes, do not typically examine how specific microbiota or their products contribute to development and/or progression of diseases. A combination of both mechanistic investigations, and further prospective studies with large cohorts, are needed to understand whether (or which) gut microbiota is causally linked to host metabolism in humans. Moreover, simpy revealing a specific microbe strain can facilitate accelerated atherosclerosis in animal models and is reproducibly associated with CVD risks does not reveal how or why this association exists, nor the underlying molecular participants involved. Moreover, a better understanding of microbe-microbe interactions, and microbe-host interaction and how these are linked to the underlying molecular participants involved in disease susceptibility represent additional knowledge gaps. Studies aimed at revealing these sorts of details are needed to be able to leverage knowledge gained to develop therapeutic interventions.

CONCLUSION AND FUTURE PERSPECTIVE

Mounting evidence from animal and human studies supports that gut microbiota can influence host health and disease. The recent development of culture-independent techniques for microbiological analysis has uncovered the previously unappreciated complexity of the bacterial microbiome at various anatomic sites. In addition, the identification of bacterial metabolites which can modulate host physiological processes has opened the possibility for numerous microbial pathways as both mediators and potential pharmacological targets for the treatment of cardiometabolic diseases. Major advances are needed in our mechanistic understanding of how gut microbiota convert dietary and endogenous molecules into metabolites that communicate with peripheral organs and tissues in the host. While the advent of next-generation high-throughput sequencing technology and bioinformatics will no doubt help to further discover candidate microbial enzyme machinery involved, the business end of the pathway – the metabolite – and the host receptors that recognize them, represent the true exciting and attractive pieces of the puzzle needed for the next stage of this growing field.

Modulation of gut microbiota composition and function through diet, pre- and probiotics, and targeted non-lethal antimicrobial enzyme inhibitors may enable, in the long term, the capacity to alter host metabolic profile in a desired favorable direction. Coupled with monitoring of the gut microbial metabolite mediator level, much in the same way one can titrate diabetes regimens my monitoring glucose or glycated hemoglobin, or cholesterol levels with lipid lowering strategies, the future may hold promise for targeting a microbial pathway and titrating the intervention by monitoring blood levels of the biologically active microbial derived metabolite. Such a future would envision a more personalized and tailored

therapeutic intervention to occur, with the net readout of the system, the systemic level of the microbial metabolite, serving as an integrated sensor of the myriad processes that impact community gut microbiota organization and function, host genome and environmental (eg. diet) factors that collectively can impact the host.

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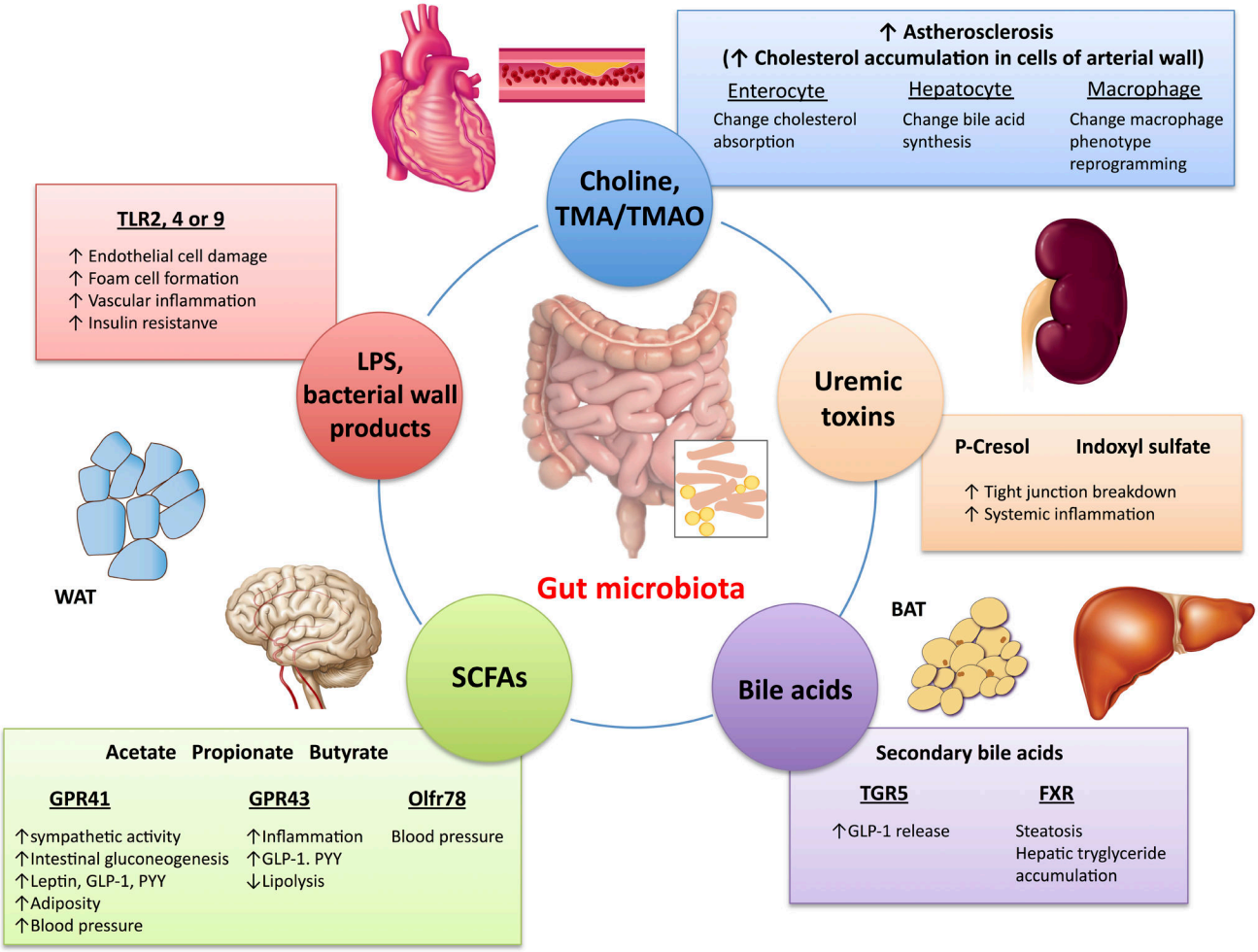

Figure 1.

Gut microbiota and possible molecular pathways linked to cardiovascular and cardiometabolic diseases.

Table 1

	Atherosclerosis	Hypertension	Heart failure	Obesity, T2DM	Chronic kidney disease
Alterations in gut microbiota composition	↑Lactobacillus[5] ↓Roseburiam[4]	↑Firmicutes / Bacteroides ratio[67]	↑Escherichia coli, Klebsiella pneumonia, Streptococcus viridans	↑Firmicutes[36,37,91,93,94] ↓Bacteroides[36, 37, 91]	↑Firmicutes, Proteobacteria and Actinobacteria[131]
Alterations in gut microbiota metabolites	↑TMAO[8, 9]	↑SCFA[180]	↑TMAO[60, 61, 90]	↑BAs, SCFA, LPS and TMAO[98, 172, 182–184]	↑Indoxyl sulfate, [185,186] p-cresol sulfate, [186,187] ammonia and urea, [188] and TMAO[59]
Proof of concept	Dietary choline/ carnitine ↑TMAO[8] DMB suppress TMA/TMAO.[65] ↑TMAO associated with unstable plaque and MACE. [22,63,189] Cecal microbial transplantation transmits disease susceptibility.[145]	Infusion of AngII/ TMAO associated with ↑blood pressure [190]	↑gut permeability[88] ↑TMAO was associated with LV remodelling and poor prognosis[60,61,90]	↑insulin sensitivity related to vancomycin treatment[99] ↑Leptin, GLP1,[103–106] PYY[102, 105, 106] ↑TMAO was associated with glycemic control. [191]	Ammonia disrupt the gut epithelial tight junction[131] Elevated TMAO was associated with decreased renal function, renal fibrosis and mortality.[59–61,192]
Interventions	Diet intervention: ↑Bacteroides and Proteobacteria, ↓Firmicutes [193] Probiotics: ↑LV hypertrophy[53] Probiotics: ↑SCFA [168]	Diet intervention: high fiber diet is associated with ↓blood pressure.[159]	Diet: High fiber diet is associated with ↓cardiac hypertrophy and fibrosis.[159] Probiotics: attenuate heart failure after myocardial infarction.[53]	FMT: improve insulin resistance[99, 100] and Roseburia.[37, 93] Bariatric surgery is associated with ↑BAs and GLP-1[120–122] Probiotics: ↑insulin secretion[166] ↓body weight and adipose tissue mass[172–175]	Probiotics: ↓dimethylamine and nitrosodimithylamine.[167]

T2DM = type 2 diabetes mellitus, TMAO = trymethylamine *N*-oxide, SCFA = short chain fatty acid, BA = bile acid, LPS = lipopolysaccharide, DMB = 1,3 dimethylbutanol, MACE = major adverse cardiac event, AngII = angiotensin II, LV = left ventricular, GLP-1 = glucagon-like peptide 1, PYY = peptide YY, FMT = fecal microbiota transplantation.