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REVIEW
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The Role of Gut Microbiota in Atherosclerosis and Hypertension

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In recent years, accumulating evidence has indicated the importance of gut microbiota in maintaining human health. Gut dysbiosis is associated with the pathogenesis of a number of metabolic diseases including obesity, type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), and cardiovascular diseases (CVDs). Indeed, CVD has become the leading cause of death worldwide, especially in developed countries. In this review, we mainly discuss the gut microbiota-involved mechanisms of CVD focusing on atherosclerosis and hypertension, two major risk factors for serious CVD. Then, we briefly discuss the prospects of gut microbiota-targeted therapeutic strategies for the treatment of CVD in the future.

Keywords: gut microbiota, cardiovascular disease, atherosclerosis, TMAO, bile acids, hypertension, SCFAs

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INTRODUCTION

Gut microbiota is the collection of bacteria that inhabit in the gastrointestinal tract producing a diverse ecosystem about 10^{14} microorganisms (Kamada et al., 2013). The majority of the gut microbiota is composed of five *phyla*, namely *Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria*, and *Cerrucomicrobia*, in which the relative abundance of *Bacteroidetes* and *Firmicutes phyla* is >90% (Qin et al., 2010). The homeostasis of gut microbiota is critical for maintaining human health (Hansen et al., 2015; Kamo et al., 2017; Tang et al., 2017), with gut dysbiosis contributing to the development of various diseases including cardiovascular disease (CVD; Wang et al., 2011; Emoto et al., 2017), obesity (Ley et al., 2006; Henao-Mejia et al., 2012), type 2 diabetes mellitus (T2DM; Cani et al., 2008; Khan et al., 2014; Pedersen et al., 2016), non-alcoholic fatty liver disease (NAFLD; Mouzaki et al., 2013; Zhu et al., 2013), and even some types of cancer (Gopalakrishnan et al., 2018; Tilg et al., 2018).

Cardiovascular disease is the leading cause of death worldwide, especially in developed countries, and encompasses multiple disorders including atherosclerosis, hypertension, stroke, and heart failure (Mozaffarian et al., 2016). Although genetic contributions are intimately involved, other factors such as nutrition and gut microbiota have also been implicated as the main risk factors for developing CVD. Wang et al. (2011) reported the gut microbiota-dependent mechanism of CVD, highlighting the intricate relationship between gut microbiota and CVD. Recently, gut dysbiosis has been recognized as an important factor contributing to the development of atherosclerosis and hypertension, two major risk factors for CVD (Lau et al., 2017). Consequently, gut microbiota-targeted therapy is a promising strategy to treat CVD (Koopen et al., 2016; Anbazhagan et al., 2017; Santisteban et al., 2017).

In this review, we extensively retrieved the publications on the topics of gut microbiota and CVD mainly published within the past 10 years through PubMed. We discuss the roles of gut microbiota implicated in the development of CVD, especially focusing on atherosclerosis and hypertension, and briefly summarize the recent advances of gut microbiota-targeted therapies for CVD.

GUT MICROBIOTA AND ATHEROSCLEROSIS

Atherosclerosis is the major risk factor for CVD, which is characterized by accumulation of cholesterol and recruitment of macrophages into artery walls, contributing to the formation of atherosclerotic plaques (Gui et al., 2012). Interestingly, recent studies have suggested that gut dysbiosis can also contribute to the development of atherosclerosis (Drosos et al., 2015; Gregory et al., 2015; Jie et al., 2017). Using shotgun sequencing of the gut metagenome in patients with or without symptomatic atherosclerosis, scientists found that the relative abundance of *Roseburia* and *Eubacterium* was lower, while *Collinsella* was higher in atherosclerosis patients compared to healthy controls (Karlsson et al., 2012). In addition, *Akkermansia muciniphila* was found to improve gut barrier functions and exert protective effects against atherosclerosis (Li et al., 2016). Although meta-analysis showed no significant benefit in coronary artery disease patients treated with antibiotics (Andraws et al., 2005), nevertheless, evidence is accumulating which indicates that gut microbiota play a causative role in atherosclerotic by modulating inflammation and the production of microbial metabolites (Kasahara et al., 2017).

Gut Dysbiosis and Inflammation in Atherosclerosis

Inflammation is commonly involved in a number of diseases (Xu et al., 2003; Ding et al., 2010), including atherosclerosis, which is a classical chronic inflammatory disease (Gui et al., 2012). Gut epithelium is the first barrier of the host, which protects against the invasion of pathogens (Desai et al., 2016). Given its critical role in preventing the translocation of intestinal content, mainly bacterial components, the integrity of the gut barrier is essential for maintaining the health of the host. Intestinal permeability is associated with reduced expression of tight junction proteins, including zonula occludens-1 (ZO-1), claudin-1, and occludin, and an imbalance between intestinal epithelial cell death and regeneration (Wang H. et al., 2014; Chen W.Y. et al., 2017). If the intestinal epithelial barrier is impaired, the invasion of pathogen associated molecular patterns (PAMPs) drives an immune response and results in systemic and tissue-specific inflammation. Accordingly, impairments to the gut barrier integrity induced by gut dysbiosis have been suggested as risk factor for chronic inflammation in various diseases. It is noteworthy that lipopolysaccharide (LPS) and peptidoglycan are microbial components that are recognized as risk factors for CVD.

Lipopolysaccharide is a cell wall component of Gram-negative [G(–)] bacteria, which has been extensively studied as it is one of the PAMPs involved in CVD risk. The association between LPS and CVD was first proposed in 1999 by measuring plasma endotoxin levels in the clinic (Wiedermann et al., 1999). Subsequently, the relationship was gradually confirmed by multiple experiments by different research groups (Niebauer et al., 1999; Stoll et al., 2004; Miller et al., 2009; Mitra et al., 2015). For example, in one study, it was concluded that the level of circulating endotoxemia was most notable in patients with the highest CVD burden (McIntyre et al., 2011). Cani et al. (2007) found that gut dysbiosis suppressed the expression of tight junction proteins, leading to an increase in intestinal permeability and subsequently the translocation of LPS into the blood (Harris et al., 2012). Gut dysbiosis-derived LPS may play important roles by modulation of Toll-like receptors (TLRs) and their downstream targets (Libby, 2002; Chacon et al., 2017). As part of the pattern-recognition receptors family, TLRs can recognize bacterial products and modulate the host immune system (Akira and Takeda, 2004; Akira et al., 2006). Circulating LPS can bind to cell-surface-receptor complexes composed of TLR4 and its co-receptors cluster of differentiation 14 (CD14; Neves et al., 2013). Using TLR4 and LDL receptors double knockout mice, Ding et al. (2012) found that a TLR4 deficiency reduced atherosclerosis without effect on inflammation (Ding et al., 2012). Consistently, clinical investigations have revealed that upregulation of TLRs was associated with inflammatory activation in human atherosclerosis, and promoted the development of atherosclerosis (Xu et al., 2001; Edfeldt et al., 2002). However, a meta-analysis in 2012 indicated that Asp299Gly, a TLR4 polymorphism, did not play an obvious role in the development of atherosclerosis (Zhang et al., 2012). Moreover, the binding of LPS to TLR4 activated its downstream pathways including MYD88 and nuclear factor kappa B (NF-κB), contributing to the increased production of pro-inflammatory cytokines such as IL-6, IL-1, IL-27, and tumor necrosis factor-alpha (TNF-α), leading to an increased risk of developing CVD (Barton and Kagan, 2009; Guzzo et al., 2012). Bjorkbacka et al. (2004) showed that a deficiency of MyD88 reduced atherosclerosis by decreasing macrophage recruitment (Bjorkbacka et al., 2004). The main interactions between gut microbiota and inflammation are shown schematically in **Figure 1**.

In addition, another bacterial PAMP, peptidoglycan (PG), was also found to be associated with CVD risk by impairing the intestinal epithelial barrier. PG is a minor cell wall component of [G(–)] bacteria; however, it is also a major component of Gram-positive [G(+)] bacteria. Using metagenomic sequencing, scientists found that patients with atherosclerosis had enrichment of genes that encoded PG synthesis (Karlsson et al., 2012). Indeed, pro-inflammatory bacterial PG was observed in atherosclerotic arteries and associated with vulnerable plaques (Laman et al., 2002). Through PG recognition, the nucleotide-binding oligomerization domain (NOD) proteins NOD1 and NOD2 promote intracellular bacteria clearance through a program involving NF-κB and mitogen-activated protein kinase (MAPK) signaling pathways (Philpott et al., 2014). Studies in Nod2-deficient mice revealed that NOD2 was a critical regulator of intestinal bacterial immunity and helps to maintain the integrity of the gut barrier (Kobayashi et al., 2005). In recent years, scientists have investigated the potential role of NOD1 in atherosclerosis using Nod1 knockout mice. Data showed that knockout of apolipoprotein E and Nod1 in mice significantly reduced the development of atherosclerotic lesions (Kanno et al., 2015). Additionally, there are other PAMPs that can promote inflammatory processes through the engagement of host pattern recognition receptors (PRRs), such as CpG

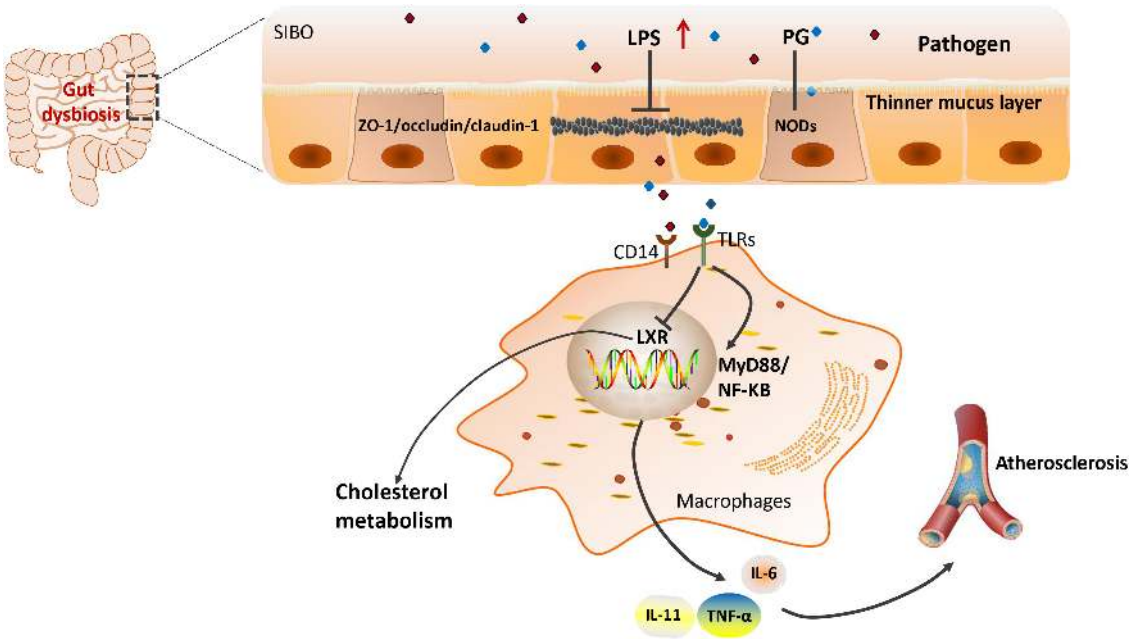

FIGURE 1 | Gut microbiota and LPS-induced inflammation in atherosclerosis. LPS, lipopolysaccharides; ZO-1/occludin, two tight junction proteins; CD14, the monocyte differentiation antigen; TLR4, Toll-like receptor 4; LXR, liver X receptor; MyD88, myeloid differentiation primary response gene 88; NF-κB, nuclear factor kappa B; IL, interleukin; TNF-α, tumor necrosis factor-alpha; PG, peptidoglycan; NODs, nucleotide-binding oligomerization domain proteins.

oligodeoxynucleotides flagellin, lipopeptides, and so on (Kholy et al., 2015). Collectively, all of the evidence suggests that functional changes in the gut microbiota might be involved in the atherosclerosis risk. Although the vast majority of studies revealed that pathogenic bacteria contributed to atherosclerosis pathogenesis, two antibiotic trials reported controversial benefits of antibiotic therapy in CVD (Caligiuri et al., 2001; Munford, 2016).

Gut Microbial Metabolites in Atherosclerosis

In addition to gut dysbiosis-related inflammation, increasing evidence has revealed that gut microbiota-derived metabolites play essential roles in the development of CVD (Brown and Hazen, 2015; Bergeron et al., 2016). A variety of metabolites are derived from the gut microbiota, as well as co-metabolism of gut microbiota such as amines methylamines, polyamines, short-chain fatty acids (SCFAs), trimethylamine N-oxide (TMAO), and secondary bile acids (BAs). SCFAs are a group of well-established gut microbial metabolites that are critically involved in metabolic diseases (Li et al., 2017). Recent advances detailing their involvement in atherosclerosis in both human and animal models have been extensively reviewed (Brown and Hazen, 2018). Therefore, in the current review, we mainly focused on the roles of TMAO and secondary BAs in atherosclerosis.

TMAO and Atherosclerosis

Dietary phosphatidylcholine or L-carnitine is metabolized by gut microbiota into trimethylamine (TMA) in the intestine (Brown and Hazen, 2015). It is a precursor of TMAO, which is transported to liver and oxidized by flavin monooxygenase 3 (FMO3), one member of the hepatic FMO enzymes family, leading to the production of TMAO (Wang Z. et al., 2014). Hepatic knockdown of FMO3 in mice using an antisense oligonucleotide decreased circulating TMAO levels and attenuated atherosclerosis through stimulating basal metabolism and activating macrophage reverse cholesterol transport (RCT; Miao et al., 2015; Shih et al., 2015; Warrier et al., 2015). It was also found that plasma levels of gut microbial dietary phosphatidylcholine metabolites and TMAO that produced related molecules (L-carnitine and γ-butyrobetaine) were associated with the risk of CVD (Koeth et al., 2014; Chen K. et al., 2017; Guasch-Ferre et al., 2017). The higher level of plasma TMAO was correlated with atherosclerosis formation and the extent of the atherosclerotic plaque area (Wang et al., 2011). Consistently, a prospective and observational clinical study on patients with or without chronic heart failure has shown that plasma levels of TMAO were positively correlated with the risk of chronic heart failure (Troseid et al., 2015). These findings suggest that circulating levels of TMAO are important risk factors for the pathogenesis of CVD.

Given the roles of TMAO in the pathogenesis of CVD, the underlying mechanisms have been extensively investigated. To explore potential mechanisms by which TMAO might promote atherosclerosis, a dietary choline supplement was administered to ApoE$^{-/-}$ mice, in which the expression of CD36 and steroid receptor RNA activator 1 (SR-A1), two macrophage scavenger receptors implicated in atherosclerosis, was measured. The results revealed elevated levels of CD36 and

SR-A1 in the macrophages of TMAO-treated mice compared to normal controls, and antibiotic intervention reduced the formation of foam cells by decreasing TMA production (Wang et al., 2011). However, no significant impact of TMAO on foam cell formation was observed in mouse macrophages. In contrast, TMAO can lead to atherosclerosis by suppressing RCT and modulating the activity of cholesterol transporters in macrophages (Koeth et al., 2013). In addition, TMAO administration could suppress levels of liver BA synthetase (Cyp7a1 and Cyp27a1) and BA transporters (Oatp1, Oatp4, Mrp2, and Ntcp), leading to a disorder of BA-related pathways and atherosclerosis (Koeth et al., 2013), suggesting that the atherosclerotic promoting effect of TMAO is also associated with the variation in BA metabolism. Farnesoid X receptor (FXR) is an important nuclear receptor that controls BA metabolism, which can also regulate the expression of hepatic FMO3, resulting in an alteration in TMAO production (Bennett et al., 2013). An FXR agonist inhibited the expression of CYP7A1 and CYP8B1 in ApoE$^{-/-}$ mice and protected mice against atherosclerosis (Mencarelli et al., 2009; Bennett et al., 2013; Miyazaki-Anzai et al., 2014; Miao et al., 2015). Recently, Ma et al. (2017) found that TMAO upregulated the expression of vascular cell adhesion molecule-1 (VCAM-1) and activated protein kinase C (PKC) and NF-κB, highlighting that TMAO may speed up the development of atherosclerosis by inducing endothelial cell dysfunction and by increasing monocyte adhesion. Additionally, the direct exposure of platelets to TMAO increased stimulus-dependent platelet activation by elevating Ca^{2+} release from intracellular stores, contributing to the increased risks of thrombosis and plaque instability (Zhu et al., 2016). Generally, TMAO accelerates the development of atherosclerosis by promoting cholesterol influx, inhibiting cholesterol efflux, blocking the BA pathway, and/or causing excessive activation of platelets. All of these findings confirmed TMAO as a biomarker for CVD risk and a promoter of atherosclerotic diseases (Senthong et al., 2016a,b; Zheng et al., 2016). TMAO is regarded as one of the most promising metabolites that may not only be an independent risk factor for CVD, but also a potential therapeutic target for CVD on the basis of a large amount of experimental and clinical data. However, inconsistent results were also observed, especially in large population observations (Dalmeijer et al., 2008; Nagata et al., 2015; Meyer et al., 2016). Choline is generally regarded as a dietary source of TMAO; however, in a cohort study, there was no clear evidence of significant associations between choline intake and the risk of developing CVD (Nagata et al., 2015). Likewise, in ApoE(−/−)mice, L-carnitine administration resulted in a significant increase in circulating TMAO levels, which surprisingly was inversely correlated with aortic lesion size(Collins et al., 2016). Unfortunately, several large population studies conducted by different countries have demonstrated that dietary choline and betaine intake was not associated with the pathogenesis of CVD (Bidulescu et al., 2007; Dalmeijer et al., 2008). Consequently, more studies are needed to confirm the exact roles of TMAO in atherosclerosis, as well as the validation of its therapeutic potential by targeting TMAO-producing bacteria or enzymes.

Bile Acids and Atherosclerosis

Bile acids are another group of gut microbiota-derived metabolites involved in various metabolic diseases (Kuipers et al., 2014; Parseus et al., 2017), which are stored in the gallbladder and released into the intestine to facilitate the absorption of dietary lipids and fat-soluble vitamins. Primary BAs are synthesized from cholesterol in the liver and mainly include cholic acid (CA) and chenodeoxycholic acid (CDCA). Primary BAs are usually metabolized into secondary BAs including deoxycholic acid (DCA) and lithocholic acid (LCA), hyodeoxycholic acid, and ursodeoxycholic acid through gut microbiota-derived enzymes (Midtvedt, 1974; Russell, 2003). Previous studies reported that germ-free mice had higher levels of primary BAs, but non-detectable secondary BAs in the enterohepatic system (Sayin et al., 2013). It was found that suppression of hepatic BA biosynthesis could inhibit the HFD-induced gut microbiome alterations, which highlights the liver–BA–gut microbiome metabolic axis (Zheng et al., 2017). Thus, there is a bidirectional relationship between gut microbiota and BA metabolism (Jones et al., 2014).

Bile acids are also important signaling molecules that modulate host metabolism and energy expenditure processes (Dawson and Karpen, 2015; Joyce and Gahan, 2017). Bile salts can be diversified into biologically active species by gut microbiota that can survive in the bile salt-rich microenvironment. Gut microbiota-mediated BA metabolism in CVD has been well reviewed recently (Brown and Hazen, 2018). Nevertheless, to date, the role of BAs in CVD development is still poorly understood so far. It is well recognized that BAs can promote the development of atherosclerosis mainly through bile-salt hydrolase (BSH) and BA receptors (Lefebvre et al., 2009; Ridlon et al., 2016). The C24 N-acyl bond of glycine-conjugated or taurine-conjugated bile salts can be hydrolyzed into free BAs by BSH (Klaassen and Cui, 2015). In addition to deconjugation, the BA pool can also be chemically diversified by bacteria-derived 7α-dehydroxylase and 7β-dehydroxylase. The produced secondary BAs enter the portal circulation to function as signaling molecules with profound effects on host physiology and pathology (Lepercq et al., 2004). Bacteria-mediated BSH activity can affect the processes underlying the pathogenesis of atherosclerosis by increasing cholesterol accumulation, foam cell formation, and the size of the atherosclerotic plaque (Hansson et al., 2006). BSH is present in a wide range of bacteria such as *Methanobrevibacter smithii*, *Clostridium*, *Enterococcus*, and so on (Jones et al., 2012a; Tremaroli and Backhed, 2012).

In addition to BA itself, BA receptors are indispensable in mediating their biological functions. Farnesoid X-activated receptor (FXR) is one of the most important and well-studied BA receptors that regulates glucose and lipid metabolism by affecting transcription of genes that are involved in primary BA synthesis (Makishima et al., 1999; Wahlstrom et al., 2016). The critical role of FXR in mediating cholesterol metabolism was elucidated by using FXR$^{-/-}$ mice which have increased plasma high density lipoprotein (HDL) cholesterol, non-HDL cholesterol and triglyceride levels compared to wild-type mice (Lambert et al., 2003). In a previous study, loss of functional FXR in apolipoprotein E-deficient (ApoE−/−) mice, a mouse model

of atherosclerosis, resulted in more severe lipid metabolism defects and enhanced aortic plaque formation (Hanniman et al., 2005). Furthermore, FXR deficiency can result in a decrease of plasma low-density lipoprotein cholesterol and CD36 expression in macrophages, leading to a reduced risk of atherosclerosis in LDLR knockout ($LDLR^{-/-}$) mice (Zhang et al., 2006). On the other hand, research indicates that activation of FXR with an agonist can protect against atherosclerosis in $LDLR^{-/-}$ and $ApoE^{-/-}$ mice, which may be associated with suppression of genes involved in BAs synthesis (Hartman et al., 2009). The G protein-coupled BA receptor, also known as TGR5, is another important host BA receptor that is responsive to BAs (Li and Chiang, 2015). Recent investigations have indicated that activation of TGR5 can inhibit atherosclerosis formation, an effect associated with a reduction of macrophage inflammation and lipid loading (Pols et al., 2011). Moreover, activation of TGR5 also contributes to enhanced energy expenditure and improved glycemic control (Watanabe et al., 2006). Pregnane X receptor (PXR) is another type of nuclear hormone receptor that regulates the expression of genes involved in the biosynthesis, transport, and metabolism of BAs, and can also be activated by secondary BAs such as LCA (Staudinger et al., 2001). Deletion of PXR attenuates the development of atherosclerosis in PXR and apoE double knockout ($PXR^{-/-}$ and $ApoE^{-/-}$) mice, which may be associated with the reduction of CD36 expression and lipid uptake in macrophages (Sui et al., 2011). It has been reported that activation of PXR by a PXR agonist increases the levels of atherogenic lipoproteins VLDL and LDL, and that PXR activation accelerates atherosclerosis in $ApoE^{-/-}$ mice (Zhou et al., 2009). In addition, the vitamin D3 receptor (VDR) is a sensor for bacteria-induced BA that is much more sensitive to LCA and its metabolite (3-oxo-LCA) than other nuclear receptors (Makishima et al., 2002). It has been found that macrophage VDR signaling attenuates atherosclerosis in mice in part by inhibiting the local renin-angiotensin system (Szeto et al., 2012). Finally, sphingosine-1-phosphate receptor 2 (S1PR2) can be activated by various conjugated BAs and then promotes atherosclerosis by regulating macrophage retention and inflammatory cytokine secretion (Studer et al., 2012), whereas S1PR2 knockdown attenuates atherosclerosis in $ApoE^{-/-}$ mice (Skoura et al., 2011).

In summary, gut microbiota-derived secondary BAs play important roles in the development of atherosclerosis through the modulation of various BA receptors such as FXR, PXR, TGR5, VDR, and S1PR2. This finding highlights the great potential for novel atherosclerosis therapy by targeting gut microbiota (Levi, 2016). The main mechanisms associated with gut microbiota-derived metabolites and atherosclerosis is shown schematically in **Figure 2**.

GUT MICROBIOTA AND HYPERTENSION

Hypertension is another important risk for CVD that is induced by both genetic susceptibility and environmental factors (Townsend et al., 2016). Given the increasing recognition of the role of gut microbiota in metabolic diseases (Karlsson et al., 2012; Tremaroli and Backhed, 2012; Jonsson and Backhed, 2017; Yamashiro et al., 2017), the relationship between gut microbiota and hypertension has also been evaluated in recent years. In 1982, it was demonstrated that antibiotic treatment could produce a higher blood pressure, which implicated the probable involvement of gut microbiota in regulating blood pressure (Honour, 1982). In spontaneously hypertensive rats, Yang et al. (2015) observed a significant decrease in microbial richness and diversity, and an increase in the ratio of *Firmicutes*/*Bacteroidetes*. In another study, compared with conventionally raised (CONV-R) mice, GF mice infused with AngII showed attenuation of the blood pressure increase in response to AngII, indicating that gut microbiota promotes AngII-induced vascular dysfunction and hypertension (Karbach et al., 2016). Accordingly, the gut microbiota is probably involved in the development of hypertension. Although the relationship and mechanism underlying gut microbiota and hypertension have not yet been fully elucidated, the existing evidence has highlighted the critical roles of SCFAs and oxidized low-density lipoprotein (ox-LDL) in hypertension.

SCFAs and Hypertension

Short-chain fatty acids (such as acetate, proprionate, and butyrate), which are derived from dietary fiber (mainly polysaccharides), play crucial roles in maintaining the homeostasis of the gut microbiome and host immunity (El Kaoutari et al., 2013; Canfora et al., 2015; Koh et al., 2016; Miyamoto et al., 2016). Interestingly, bacteria that metabolize polysaccharides into different types of SCFAs are specific (Rey et al., 2010). For instance, the major acetate-producing bacteria are *Streptococcus* spp., *Prevotella* spp., *Bifidobacterium* spp., *Clostridiums* pp., *A. muciniphila*, and so on (Rey et al., 2010). Propionate is generated from carbohydrate fermentation by *Bacteroides* spp., *Salmonella* spp., *Dialister* spp., *Veillonella* spp., *Roseburia inulinivorans*, *Coprococcus catus*, *Blautia obeum*, etc. (Louis and Flint, 2017), while butyrate is derived from *Lachnospiraceae*, *Ruminococcaceae*, and *Acidaminococcaceae* families (Duncan et al., 2002). Clinical evidence has shown that the abundance of butyrate-producing bacteria is associated with a lower blood pressure in obese pregnant women (Gomez-Arango et al., 2016). A recent study found that fiber and acetate supplementation improved gut dysbiosis, associated with an increase in *Bacteroides acidifaciens*, which may play a protective role in hypertension and heart failure in hypertensive mice (Marques et al., 2017).

The role of host G-protein-coupled receptors (GPCRs) in the development of hypertension has been well reviewed (Pluznick et al., 2013). To date, there are at least three GPCRs that are regulated by SCFAs including GPR41, GPR43, and GPR109A (Tan et al., 2017). SCFAs can stimulate host GPCRs-regulated pathways to affect renin secretion and therefore blood pressure (Furusawa et al., 2013; Pluznick et al., 2013). One study has reported that GPR41 knockout mice exhibited systolic hypertension compared with wild-type mice, and that SCFAs lowered blood pressure by regulating endothelial GPR41 (Natarajan et al., 2016). Olfactory receptor 78 (Olfr78) is another type of GPCR expressed in the kidney, which can

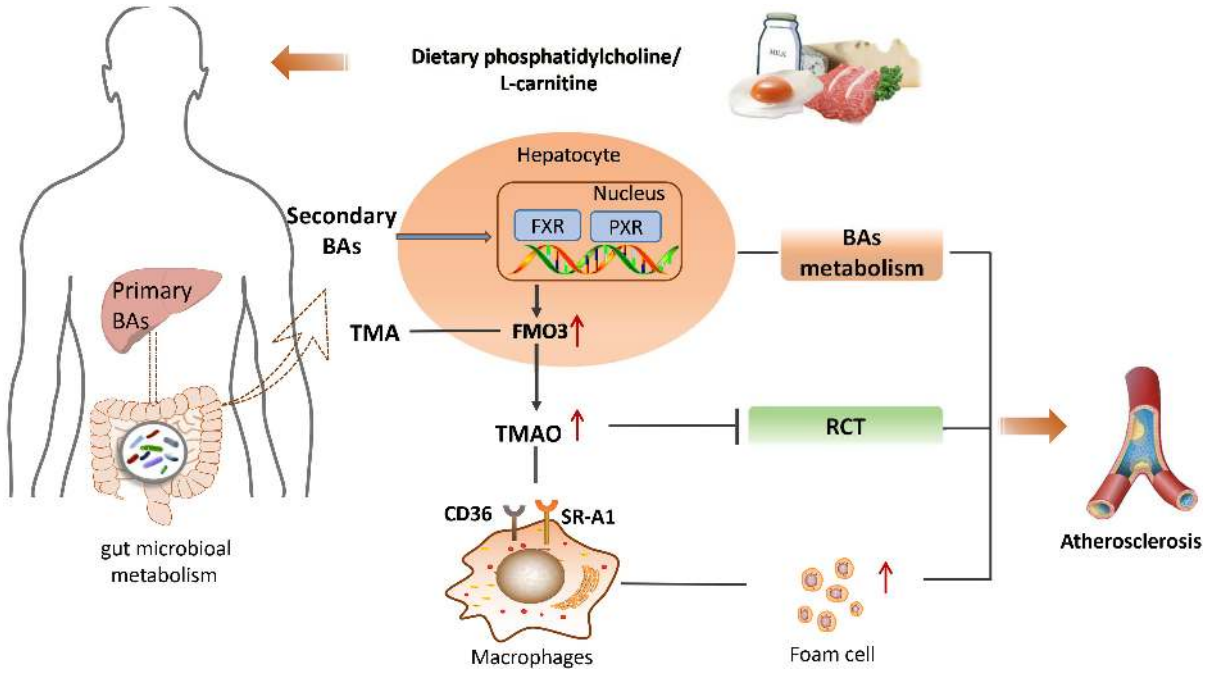

FIGURE 2 | The main mechanisms between gut microbiota-derived metabolites and atherosclerosis. BA, bile acids; TMA, trimethylamine; FXR, farnesoid X receptor; PXR, pregnane X receptor; FMO3, flavin monooxygenase 3; TMAO, trimethylamine N-oxide; CD36, the monocyte differentiation antigen; RCT, reverse cholesterol transport; SR-A1, steroid receptor RNA activator 1.

also be modulated by SCFAs such as acetate and propionate (Tan et al., 2017). In addition, both Olfr78 and GPR41 are expressed in smooth muscle cells of small resistance blood vessels (Pluznick et al., 2013). Propionate can induce vasodilation and produce an acute hypotensive response in mice through modulation of Olfr78 and GPR41 activity (Miyamoto et al., 2016). On the other hand, it was found that stimulation of GPR41 resulted in a reduction of the hypotensive response, and this effect could be opposed by stimulating Olfr78 (Pluznick, 2013). Interestingly, antibiotic treatment not only altered the composition of gut microbiota, but also increased blood pressure in Olfr78 knockout mice (Pluznick et al., 2013). In recent years, Reijnders et al. (2016) conducted a randomized double-blind placebo-controlled trial, in which SCFAs and a number of metabolic parameters were measured. The inconsistent outcome was reported that the levels of SCFAs had no significant effects on energy or glucose homeostasis in humans (Reijnders et al., 2016). Overall, although all these findings revealed that gut microbiota may play important roles in modulating the host blood pressure through production of microbial SCFAs, the potential for SCFAs to be a therapeutic target for CVD needs to be confirmed by additional investigations in the future.

Oxidized Low Density Lipoprotein (ox-LDL) and Hypertension

Generally, the regulation of blood pressure depends on the magnitude of blood vessel vasoconstriction and vasodilation (Luscher and Barton, 1997). In addition to the regulation of various receptors, gut dysbiosis also contributes to hypertension through vasoconstriction mediated by oxidation of LDL (Packer et al., 2014).

Dysbiosis can promote the expression of pro-inflammatory cytokines and induce oxidative stress, which can stimulate Ox-LDL (Chawla et al., 2011; Peluso et al., 2012). Previous studies have shown that higher levels of oxLDL contribute to hypertension by inhibiting the production of nitric oxide (NO) and endothelin-1 (Subah Packer, 2007). NO is a well-established vasodilator that is produced through oxidation of L-arginine by NO synthase. Ox-LDL decreases the production of NO and reduces the degree of vasodilation (Ma et al., 2006). Moreover, endothelin-1 plays crucial roles in maintaining basic vascular tension and cardiovascular system homeostasis. Interestingly, the activity of endothelin-1 on blood vessels is concentration-dependent, that is, endothelin-1 produces vasodilatory effects at low concentrations by activating the endothelial receptor B (ETB) and promoting NO production, but produces vasoconstriction at high concentrations by increasing ox-LDL production in plaques and activating the endothelial receptor A (ETA; Boulanger and Luscher, 1990).

Although a causative relationship between gut dysbiosis and hypertension has been acquired (Kamo et al., 2017; Santisteban et al., 2017), the exact role of gut microbiota in mediating hypertension still requires further extensive investigation. The main mechanisms associated with gut microbiota and hypertension are shown schematically in **Figure 3**, together with a summary of microbial-derived metabolites and CVD development in **Table 1**.

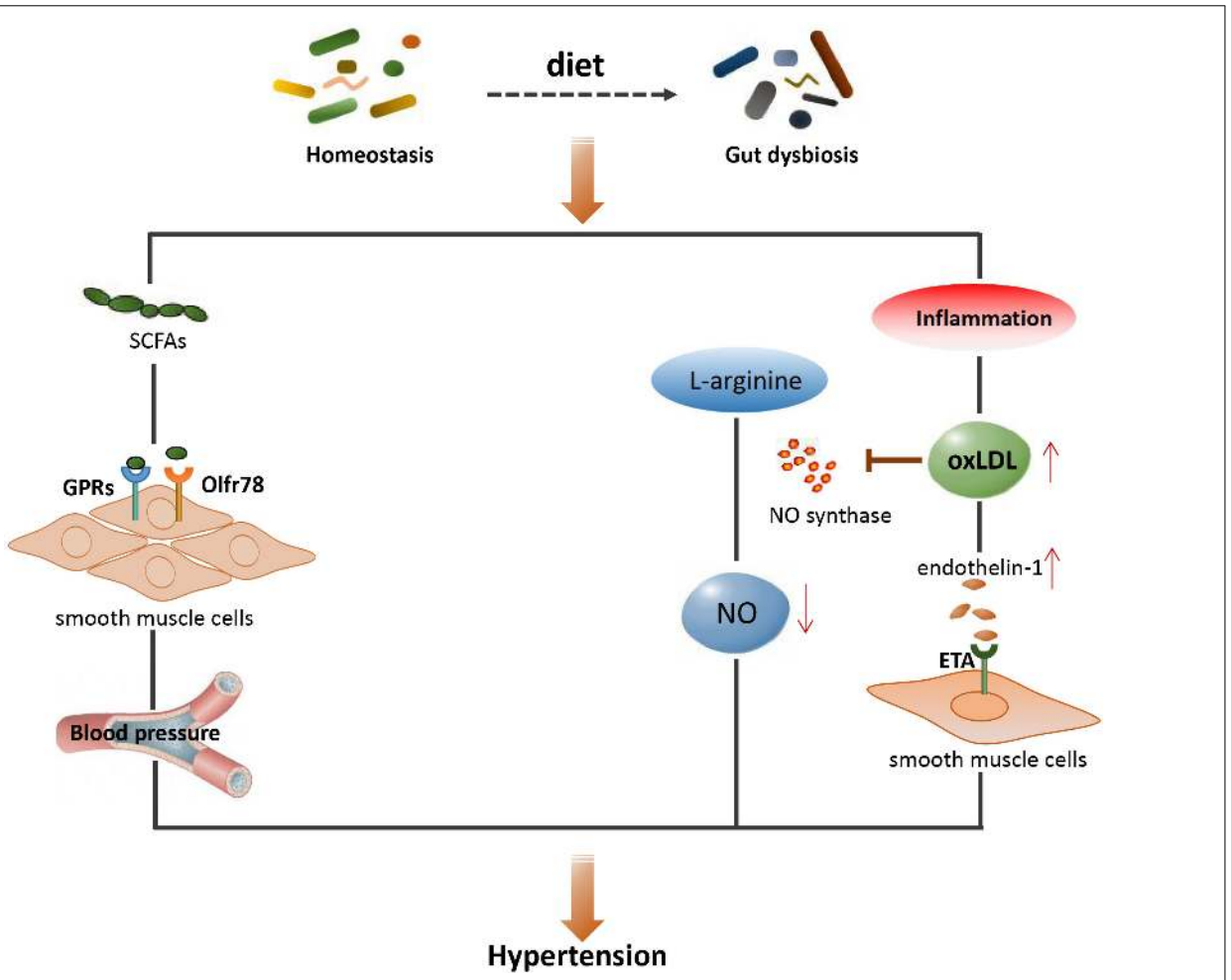

FIGURE 3 | The main mechanisms between gut microbiota and hypertension. SCFAs, short-chain fatty acids; GPRs, G-protein-coupled receptors; Olfr78, olfactory receptor 78; NO, nitric oxide; OxLDL, oxidized low density lipoprotein; ETA, endothelin receptor A.

GUT MICROBIOTA-TARGETED THERAPY OF CVD

Given the contributions of gut microbiota to the development of CVD, they have emerged as a potentially important target for CVD therapy (Daliri et al., 2017; He and Shi, 2017). The most frequently used approaches to manipulate the gut microbiota include probiotic, prebiotic, natural components, fecal transplantation, and so on.

Probiotic is a collection of bacteria with a wide range of beneficial effects on host metabolism (Sanders, 2008; Ettinger et al., 2014; Yoo and Kim, 2016). The widely used probiotics are *Lactobacillus*, *Bifidobacterium*, and *Satreptococcus* (Kailasapathy and Chin, 2000; Miura and Ohnishi, 2014). In a randomized double-blind clinical trial, Fuentes et al. (2013) found that a probiotic of *Lactobacillus plantarum* CECT 7527, 7528, and 7529 reduced circulating cholesterol levels and inhibited the formation of atherosclerotic plaques in hyper-cholesterol patients. In another randomized control study, subjects taking *Lactobacillus reuteri NCIMB* 30242 showed more significant reductions of LDL-C and total cholesterol levels compared to subjects given placebo capsules (Jones et al., 2012b). In addition, the benefits of probiotics of different *Lactobacillus* bacteria (*Lactobacillus fermentum* CECT5716 (LC40), *Lactobacillus coryniformis* CECT5711 (K8) and *Lactobacillus gasseri* CECT5714 (LC9) in the regulation of blood pressure have been investigated in spontaneously hypertensive rats, and it was found that long-term administration of these probiotics could reduce systolic blood pressure (Gomez-Guzman et al., 2015). A recent study has reported that the probiotic *L. plantarum* ECGC13110402 was well tolerated and can be used as an alternative or supplement to reduce cardiovascular risk (Costabile et al., 2017).

Prebiotic is a class of indigestible food ingredients with benefits via selectively stimulating the growth of "good" and suppressing the growth of "bad" bacteria in the intestinal tract (Gibson and Roberfroid, 1995). Prebiotic can usually cause specific changes in the composition of gut microbiota and exert beneficial effects on host metabolism. Recent investigations have

TABLE 1 | Gut microbial-derived metabolites and CVD.

Metabolite	Experimental models	Main observations	References
TMAO	FMO3 knockdown mice	The TMAO-generating enzyme FMO3 is a central regulator of cholesterol balance	Warrier et al., 2015
	Western diet (WD)-induced obese mice	Consumption of a WD increases circulating TMAO levels, which contributes to cardiac dysfunction	Chen K. et al., 2017
	C57BL/6 mice	TMAO promotes pathological process of atherosclerosis by impairing endothelial self-repair capacity and enhancing monocyte adhesion	Ma et al., 2017
	Apoe−/− female mice	Gut microbial metabolite γ-butyrobetaine is converted into TMA and TMAO, and accelerates atherosclerosis	Koeth et al., 2014
	Apoe−/− mice	Dietary choline or TMAO supplementation enhances atherosclerotic lesion development	Wang et al., 2011
	Apoe−/− mice	Dietary L-carnitine supplementation alters gut microbial composition, enhances production of TMA/TMAO, and increases atherosclerosis	Koeth et al., 2013
	Germ-free mice	Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk	Zhu et al., 2016
	ApoE(−/−) mice	L-carnitine intake and high plasma TMAO levels correlate with low aortic lesions	Collins et al., 2016
	155 patients with chronic heart failure	TMAO is associated with survival of patients with chronic heart failure	Troseid et al., 2015
	817 participants (young adults)	TMAO may not significantly contribute to early atherosclerotic disease risk	Meyer et al., 2016
	7447 participants (aged 55–80 years)	Plasma metabolites from choline pathway are associated with an increased risk of CVD	Guasch-Ferre et al., 2017
	4007 participants	Increased TMAO levels are associated with an increased risk of cardiovascular	Tang et al., 2013
	13,355 male and 15,724 female subjects	Choline and betaine intakes are not associated with CVD mortality risk	Nagata et al., 2015
	14,430 middle-aged subjects	No association exists between dietary choline intake and incident coronary heart disease	Bidulescu et al., 2007
	18 healthy participants	Gut microbe-generated TMAO from dietary choline is prothrombotic in subjects	Zhu et al., 2017
Bile acids	ApoE−/− and LDLR−/− mice	Dual activation of the bile acid nuclear receptor FXR and G-protein-coupled receptor TGR5 protects mice against atherosclerosis	Miyazaki-Anzai et al., 2014
	Germ-free (GF) mice	Gut microbiota inhibits bile acid synthesis in the liver by alleviating FXR inhibition	Sayin et al., 2013
	FXR-deficient (−/−) mouse	The function of FXR is associated with the potential to be pro-atherogenic	(Lambert et al., 2003)
	FXR−/− ApoE−/− mice	Loss of FXR function is associated with more extensive aortic plaque formation in atherosclerotic disease	Hanniman et al., 2005
	LDLR−/− mice	FXR deficiency causes reduced atherosclerosis	Zhang et al., 2006
	Fxr−/− Ldlr−/− (DKO) mice	Activation of FXR protects against atherosclerosis in mice	Hartman et al., 2009
	Ldlr(−/−)Tgr5(−/−) and Ldlr(−/−)Tgr5(+/+) mice	TGR5 activation inhibits atherosclerosis by reducing macrophage inflammation and lipid loading	Pols et al., 2011
	PXR(−/−) apoE(−/−) mice	Deficiency of PXR attenuates atherosclerosis development	Sui et al., 2011
	ApoE(−/−) mice	Activation of PXR accelerates atherosclerosis development	Zhou et al., 2009
	LDLR−/− VDR−/− mice	Macrophage VDR signaling inhibits atherosclerosis in part by suppressing the local renin-angiotensin system	Szeto et al., 2012
SCFAs	205 women	Blood pressure is associated with alterations in gut microbiota and production of butyrate	Gomez-Arango et al., 2016
	Hypertensive mice	Acetate supplementation changes the development of hypertension and heart failure	Marques et al., 2017
	Olfr78−/− mice	SCFAs produced by the gut microbiota modulate blood pressure via Olfr78 and Gpr41	Pluznick et al., 2013
	Gpr41 knockout mice	Microbial SCFAs lower blood pressure via endothelial GPR41	Natarajan et al., 2016

SCFAs, short-chain fatty acids; TMAO, trimethylamine N-oxide; BAs, bile acids; Gpr41, G-protein-coupled receptor 41; Olfr78, olfactory receptor 78; FMO3, flavin monooxygenase 3; CD36, the monocyte differentiation antigen; FXR, farnesoid X receptor; ABCA1, ATP-binding membrane cassette transporter A1; LDL-R, lipoprotein receptor; TGR5, G-protein-coupled bile acid receptor; S1PR2, sphingosine-1-phosphate receptor-2; ApoE−/−, apolipoprotein E-deficient.

shown that an inulin-type fructans (ITFs) supplement improved endothelial function in ApoE$^{-/-}$ mice, while administration of ITFs promoted the production of butyrate and resulted in atheroprotective effects(Watzl et al., 2005; Catry et al., 2018). A previous investigation reported that long-chain inulin could inhibit the formation of atherosclerotic plaque in ApoE$^{-/-}$ mice, an effect that may be associated with alterations in lipid metabolism (Rault-Nania et al., 2006). In a randomized, single-blind, controlled crossover clinical trial, consumption of β-glucan altered the composition of gut microbiota, an effect associated with a reduction of CVD risk markers. Additionally, mannan oligosaccharide (MOS) is another type of prebiotic. In a recent study, a MOS supplement modulated the composition of gut microbiota, lowered plasma cholesterol levels, and improved atherosclerotic plaques in high cholesterol diet-fed mice (Hoving et al., 2018).

In addition to probiotic and prebiotic, some natural active ingredients from herbs also have protective or therapeutic actions on CVD by modulating the gut microbiota. For example, berberine is a well-studied herbal-derived chemical with effective activity against atherosclerosis. It was found that the anti-atherosclerotic effect of berberine was associated with the stimulation of *Akkermansia* in ApoE$^{-/-}$ mice (Zhu et al., 2018). Another example is resveratrol that may have protective effect against several cardiovascular risk factors such as hyper-cholesterol and TMAO by modulating the gut microbiota and expression of genes involved in maintaining the integrity of the gut barrier (Bird et al., 2017). Moreover, resveratrol was found to attenuate TMAO-induced atherosclerosis by decreasing gut microbiota-mediated TMAO synthesis and increasing BA metabolism (Chen et al., 2016).

Fecal microbiota transplantation (FMT) is a promising method of introducing "healthy" bacteria from healthy subjects into the gastrointestinal tract of patients with dysfunctional guts, which has received much attention in recent years (Colman and Rubin, 2014). In one study, the insulin sensitivity of recipients was significantly enhanced after 6 weeks transfer of microbiota from lean normal donors to male recipients with metabolic syndrome. FMT increased the abundance of butyrate-producing bacteria suggesting that FMT is a potential strategy for CVD therapy (Vrieze et al., 2012). Nevertheless, the use of FMT is also limited in the clinic due to the possible risk of transferring endotoxins or infectious diseases to recipients (De Leon et al., 2013).

Although gut microbiota-targeted therapy to treat CVD is promising in the context of increasing positive experimental and clinical evidence, discrepant results have also been reported in both experimental and clinical studies. For instance, recently, scientists evaluated the effects of probiotic intervention on plasma TMAO levels in CKD patients, but there no significant change was observed after 3 months supplementation (Borges et al., 2018). Similarly, FMT from vegans resulted in a slight alteration in the composition of the gut microbiota, but no improvement in TMAO production or vascular inflammation (Smits et al., 2018).

CONCLUSION

Although many types of medicines are available in the clinic to treat CVD, currently, it is still the leading cause of death worldwide. In recent years, increasing evidence has suggested an important role for gut microbiota in the development of both metabolic diseases and CVD. The findings have shed light on the great potential of targeting the gut microbiota to aid the elucidation of the fundamental mechanisms underlying disease and/or to uncover novel preventative or therapeutic regimes. Currently, most of the research efforts have focused on paid on establishing the relationship between gut dysbiosis and the development of CVD. Although much progress has been made, there is some way to go before the unequivocal establishment of gut microbiota-targeted therapy for CVD in the clinic.

Given the experimental and clinical advances with regard to the mechanisms of gut microbiota in the pathogenesis of CVD, there is great promise of finding new approaches to treat CVD by using gut microbial metabolites such as SCFAs and some types of BAs, or blocking the production of detrimental microbial metabolites such as TMAO with inhibitors. In addition, methods to alter the gut microbial composition with probiotic, prebiotic, natural components, and FMT should be further explored. In the future well-designed large-scale clinical studies will be needed to validate experimental and other small-scale preliminary clinical data. The integration of omics approaches (metabolomics, metagenomics, and metatranscriptomics) may be of critical significance to explore the exact roles of identified gut bacteria in the pathogenesis of many diseases.

AUTHOR CONTRIBUTIONS

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