

# Role of Gut Microbiota-Bile Acid Pathway in the Pathogenesis of Cardiovascular Diseases?

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## ABSTRACT

The importance of gut microbial metabolites has been implicated in the development of Cardiovascular Diseases (CVDs). One key aspect in which the gut microbiota gets involved is bile acid metabolism. This mini-review was to summarize how the gut microbiota-bile acid pathway contributes to CVDs and how modulating gut microbiota can serve as a potential therapeutic target.

**Keywords:** Bile acids; Gut microbiota; Cardiovascular diseases

## INTRODUCTION

It has been well established in recent years that gut microbiota plays a vital role in the pathogenesis and prognosis of a range of Cardiovascular Diseases (CVDs). A key contribution of these microorganisms is the production of myriads of metabolites and small molecules, which can act as signaling molecules and metabolism modulators in the context of both health and disease [1]. Among them, Bile Acids (BAs) are synthesized from cholesterol in the liver and have been reported as a biomarker for the severity of CVDs in diverse studies [2]. Apart from the association between BA and CVDs, there remains a need for further mechanistic insight taking advantage of methods like Fecal Microbiota Transplantation (FMT) in Germ-Free (GF) mice. In this perspective, we summarized studies focusing on the interaction between microbiota-mediated BA metabolism and the development of CVDs.

## IMPACT OF GUT MICROBIOTA ON BILE ACID METABOLISM

Primary BAs, including Chenodeoxycholic Acid (CDCA) and Cholic Acid (CA), are synthesized from cholesterol in the liver requiring at least 17 different enzymes via the classic (or neutral) pathway initiated by Cholesterol-7 $\alpha$ -Hydroxylase (CYP7A1) accounting for at least 75% BA production, or the alternative (or acidic) pathway initiated by the sterol-27 $\alpha$ -Hydroxylase (CYP27A1) [3]. Before being secreted from hepatocytes into bile canaliculi, BAs are conjugated to taurine or glycine and then passed into the gall bladder to form bile. After ingestion of a meal, bile is secreted

into the duodenum, where bile salts emulsify dietary lipids and fat-soluble vitamins to improve their absorption [1]. Approximately 95% of the primary BAs are reabsorbed in the terminal ileum by the Apical Sodium-Dependent Bile Acid Transporter (ASBT) and returned to the liver through the enterohepatic circulation about six times per day [3,4]. Expression of several enzymes involved in the process of BAs synthesis and uptake are under microbial regulation [5].

The BAs reaching the colon are subject to extensive metabolism by the gut microbiota and/or are excreted. In the distal small intestine and colon, primary BAs are deconjugated (removal of glycine and taurine) with the participation of Bile Salt Hydrolase Enzymes (BSHs) [1]. The presence of BSHs was found within several bacterial genera, including Clostridium, Bifidobacterium, Lactobacillus, and others. Deconjugated primary BAs avoiding reabsorption are further metabolized by the gut microbiota through dehydroxylation, epimerization and oxidation of hydroxyl groups to produce secondary BAs, such as Lithocholic Acid (LCA), Hyodeoxycholic Acid (HDCA) and Ursodeoxycholic Acid (UDCA) [3]. In addition to direct participation in BAs metabolisms, the gut microbiota also regulates BAs synthesis by negative feed-back inhibition through the nuclear Farnesoid X Receptor (FXR) which is highly expressed in the ileum and liver. Some secondary BAs may act as potent ligands for FXR activation, while some conjugated primary BAs have been identified as naturally occurring FXR antagonists [5]. Previous studies have shown that FXR activation induces the expression of Small Heterodimer Partner (SHP) in

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the liver and FXR-Fibroblast Growth Factor 15 (in mice) /19 (in humans) (FGF15/FGF19) in the ileum, thereby inhibiting the expression of CYP7A1 as the rate-limiting enzyme and ultimately suppressing BAs synthesis [3].

## MECHANISMS UNDERLYING THE GUT MICROBIOTA-BILE ACID PATHWAY AND CVDS

Metabolic disorders such as dyslipidemia, hyperglycemia and obesity are crucial risk factors of the development of CVDs. BAs exert their influences on host tissues mainly through binding to two receptors: FXR and G-protein-coupled bile acid receptor 1 (known as TGF5), both of which participate in the regulation of lipid, glucose and energy metabolism [4]. Notably, BAs are also capable of activating other receptors, including the human Steroid And Xenobiotic Receptor (SXR), Rodent Pregnane X Receptor (PXR), Vitamin D Receptor (VDR), and Constitutive Androstane Receptor (CAR), while the activation of these receptors requires nonphysiological BAs concentrations [5,6].

Studies using mice deficient for FXR have generated contradictory results, potentially caused by different microbiota composition and diets [3]. FXR deficiency in apoE<sup>-/-</sup> mice on a high-fat diet developed more severe atherosclerosis [7]. On the other hand, it has been demonstrated in different studies that FXR-deficient mice on a LDLR<sup>-/-</sup> genetic background had improved lipid profile and decreased plaque burden [8]. FXR activation by CDCA leads to elevated LDLR expression and activity through inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) [8]. In addition, the absence of FXR in genetically obese mice model exerts a protective effect against obesity and glucose homeostasis [9]. In contrast, TGR5 activation can decrease serum glucose level and augments glucose tolerance in mice on a high-fat diet [10].

The mechanistic connections between gut microbiota-bile acid pathway and CVDs were explored in our previous work via FMT into GF mice on a high-fat diet [11]. Transplantation of gut microbiota from CAD patients resulted in dramatic changes of the composition of BAs pool. In both feces and serum of the recipient mice, conjugated BAs like TCA, T $\alpha$ MAC and T $\beta$ MCA were decreased while secondary BAs, including LCA, HDCA, TDCA and keto-LCA, were increased, leading to suppressed BAs synthesis and serum cholesterol accumulation. Further analysis into the taxonomic proportions of gut microbiota revealed an increased abundance of *Clostridium symbiosum* and *Eggertheella*, which have been proved to be more competent at the generation of secondary BAs. Gut microbiotas associated with the catalysis of LCA were also more common in CAD mice, such as *Bacteroides intestinalis*, *Butyricimonas virosa* and *Pseudoflavonifractor capillosus*. Functional analysis exploring the enzymes involved in secondary BAs metabolism also suggests transitions in accordance with the alterations in BAs pool.

Besides, the colonization of gut microbiota collected from CAD patients promoted a systemic inflammation phenotype in mice marked by activated immune response patterns in transcriptome analysis and elevated IL-1 $\beta$ , TNF- $\alpha$ , and LPS levels in the serum [12]. Further investigation of the immune cell distribution in the CAD mice intestine exhibited a greater amount of T helper cells 17 (Th17) cells along with the decreased presence of regulatory T cells (Tregs), implicating a skewed Th17 response. Even though such alteration in the immune response could be caused by a mix

of factors, a connection between bile acid pathway and adaptive immune response was reported in recent work [13]. Two of the metabolites derived from LCA, 3-oxoLCA and isoalloLCA, were able to modulate Th17 cell and Treg differentiation, respectively. 3-oxoLCA was found to directly interact with ROR $\gamma$ t and suppress its transcription, thus inhibiting Th17 cell differentiation. On the other hand, isoalloLCA was capable of augmenting Treg differentiation through the generation of Mitochondrial Reactive Oxygen Species (mitoROS). Immune cells other than T cells are also affected by bile acids. TGR5-induced cAMP signaling in macrophages results in inhibition of nuclear factor  $\kappa$  light-chain enhancer of activated B cells (NF- $\kappa$ B) pathway and consequent generation of pro-inflammatory cytokines, which augments the atheroprotective effect of TGR5 agonist in LDLR-deficient mice [14].

## THERAPEUTICS IN MICROBIOTA-BILE ACID PATHWAY

The gut microbiota-bile acid pathway may become one of the major targets for translational and interventional studies of CVDs. New therapeutic approaches that target the pathway, including but not limited to probiotics, prebiotics and FMT for the treatment and prevention of CVDs represent exciting areas of investigation.

### PROBIOTICS

Mounting evidence has supported that probiotics can be used in the treatment of metabolic disorders that increase the risk of CVD, including obesity, type 2 diabetes, hypercholesterolemia and nonalcoholic fatty liver disease [15]. The potential mechanisms associated with the hypocholesterolemic effect of probiotics may involve deconjugation of bile salts by BSHs and co-precipitation of intestinal cholesterol with the deconjugated bile salts [16,17]. Deconjugation of bile salts increases the excretion of free BAs into the feces, leading to a decrease in reabsorption and compensatory increase in the synthesis of BAs by the host, which may cause a reduction in the serum cholesterol. Moreover, some probiotics may decrease the absorption of intestinal cholesterol by increasing co-precipitated with deconjugated bile salts. Probiotics for BSH activity should continue to be explored as treatment options to lower cholesterol.

### PREBIOTICS

Prebiotics are non-digestible food ingredients that beneficially affect the host's health by selectively stimulating the growth and/or activity of some genera of gut microorganisms. Resveratrol (RSV) is a natural polyphenol that mainly exists in grapes, berries, and other dietary constituents with the effect of anti-atherosclerosis. One of the potential mechanisms related to gut microbiota was that RSV increased levels of the genera *Lactobacillus* and *Bifidobacterium*, which increased the activity of BSHs, thereby increasing BAs deconjugation and fecal excretion in ApoE<sup>-/-</sup> mice. This was associated with a reduction in the content of ileal BAs, repression of the FXR-FGF15 axis, and elevated CYP7A1 expression and hepatic BAs synthesis [18]. That theabrownin in Pu-erh tea suppressed microbes associated with BSH activity and increased the levels of ileal conjugated BAs. The conjugated BAs also played a role in inhibiting the FXR-FGF15 signaling pathway, leading to increased hepatic production of BAs and decreased lipogenesis [19]. It is suggested that prebiotics could act as therapeutics of BAs dysmetabolism, indicating that the gut microbiota may become an effective target in preventing and treating CVDs.

## FECAL MICROBIOTA TRANSPLANTATION

FMT is a relatively straightforward method to influence the gut microbiota. However, most studies associated with FMT are conducted in animal models instead of humans. Our previous work suggested that the transplanted microbiota from patients played a role in regulating BAs and cholesterol homeostasis, as well as in facilitating systemic and intestinal immune responses in germ-free mice [20]. Our findings raised the possibility of FMT in treating CVDs, which needed to be further explored in humans. FMT also has disadvantages, like introducing other substances in the host's intestine such as donor colonocytes, viruses, fungi, and metabolites. Therefore, the reliable and smooth application of FMT in clinical use is still on its way [21].

## FURTHER DIRECTIONS AND PERSPECTIVES

There is increasing attention towards the gut microbiota-bile acid pathway as a new target for the treatment and prevention of CVDs. However, we are just at the beginning to understand how the pathway affects our cardio metabolic health and various new therapeutic options are in the developing phase. Whether specific bacterial and metabolites are the cause or consequence of the disease remains a big doubt, as many mechanisms still need to be identified. Most of the current studies are based on animal models, and human data are scarce. The differences in BAs profiles between mice and humans warrant caution when translating findings to humans. Due to the absence of well documented clinical evidence, more large prospective (cohort and intervention) trials are needed to provide a solid base for the role of gut microbiota involved in CVDs. Likewise, therapeutic tools available to modulate the microbiota-driven pathogenesis of CVDs remain to be validated. Further advances in this area have enormous potential in the development of novel therapeutic tools targeting microbiota-bile acid pathway for CVDs.

## CONCLUSION

Evidence from the available studies highlights the important contribution of the gut microbiota-bile acid pathway in the pathogenesis of CVDs. The complex interactions between gut microbiota, BAs and CVDs involve diverse aspects of biology, including metabolic homeostasis, immune regulation, and inflammatory response, etc, which provide potential targets for the future development of drugs and therapies. Further researches into the specific mechanisms are needed, which then share the potential of being applied to clinical practice.

## AUTHOR CONTRIBUTION

YC and YW drafted and prepared the manuscript. HN was responsible for the overall manuscript preparation. All authors read and approved the final manuscript.

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## DECLARATION OF CONFLICTING INTERESTS

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this review.

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