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The interplay between microbial metabolites and macrophages in cardiovascular diseases: A comprehensive review

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Highlights

- Microbial metabolites can modulate macrophage activation and polarization, leading to the development and progression of cardiovascular diseases.
- Short-chain fatty acids produced by the gut microbiome can promote anti-inflammatory macrophage phenotypes and reduce atherosclerosis development.
- Trimethylamine N-oxide (TMAO) produced by the gut microbiome can promote pro-inflammatory macrophage phenotypes and contribute to atherosclerosis development.
- Microbial metabolites can modulate the expression of genes involved in macrophage function, such as cholesterol metabolism and inflammation.
- Targeting microbial metabolites through dietary interventions, probiotics, or pharmacological approaches may be a potential therapeutic strategy for

treating and preventing cardiovascular diseases.

Abstract

The gut microbiome has emerged as a crucial player in developing and progressing cardiovascular diseases (CVDs). Recent studies have highlighted the role of microbial metabolites in modulating immune cell function and their impact on CVD. Macrophages, which have a significant function in the pathogenesis of CVD, are very vulnerable to the effects of microbial metabolites. Microbial metabolites, such as short-chain fatty acids (SCFAs) and trimethylamine-N-oxide (TMAO), have been linked to atherosclerosis and the regulation of immune functions. Butyrate has been demonstrated to reduce monocyte migration and inhibit monocyte attachment to injured endothelial cells, potentially contributing to the attenuation of the inflammatory response and the progression of atherosclerosis. On the other hand, TMAO, another compound generated by gut bacteria, has been linked to atherosclerosis due to its impact on lipid metabolism and the accumulation of cholesterol in macrophages. Indole-3-propionic acid, a tryptophan metabolite produced solely by microbes, has been found to promote the development of atherosclerosis by stimulating macrophage reverse cholesterol transport (RCT) and raising the expression of ABCA1. This review comprehensively discusses how various microbiota-produced metabolites affect macrophage polarization, inflammation, and foam cell formation in CVD. We also highlight the mechanisms underlying these effects and the potential therapeutic applications of targeting microbial metabolites in treating CVD.

Introduction

The most common cause of mortality worldwide, as determined by the World Health Organization (WHO), is cardiovascular disease (CVD), which is mainly caused by a complex chain of events within the arterial wall, including rheology, lipid metabolism, and inflammation, known as atherosclerosis[1], [2]. In CVDs, the increase of macrophages within the artery wall is a critical pathogenic feature shared by atherosclerosis and aortic aneurysm [3], [4]. In a broader sense, macrophages play a role in maintaining local inflammatory reactions via releasing chemokines and cytokines, in addition to substances contributing to oxidative stress [5], [6]. Additionally, macrophages interact with vascular cells and are responsible for the phenotypic modifications of smooth muscle cells in the vascular system [7], [8]. As a significant source of the enzymes that break down matrix proteins, macrophages have an important role in the rupturing of atherosclerotic plaques and the loss of elastin structure in the aneurysmal aorta [9]. The inflammatory process in the heart caused by cardiomyocytes and the regulation of electrical conduction might be influenced by cardiac macrophages [10], [11] (Table 1).

Prior studies have shown the importance of gut bacteria and their metabolites for maintaining homeostasis and maintaining host physiological functions [13], [14]. Gut microbiota and their metabolites can also control blood sugar, cholesterol levels, and other biological parameters [14]. Short-chain fatty acids (SCFAs), such as butyrate, acetate, and propionate, are the byproducts of intestinal microbial metabolism created by the breakdown of dietary fibers and resistant starch in food [15]. Butyrate inhibits monocyte attachment to injured endothelial cells by decreasing the synthesis of adhesion molecules, such as vascular cell adhesion molecule 1 (VCAM-1) and endothelial-leukocyte adhesion molecule 1 (E-selectin) [19]. It has been demonstrated that histone deacetylase (HDAC) is the enzyme mediating butyrate's repression of monocyte adhesion and VCAM-1 expression [20].

Another compound generated by gut bacteria, trimethylamine-N-oxide (TMAO), is thought to be linked to atherosclerosis due to its impact on lipid metabolism [21]. By activating the farnesoid X receptor (FXR) and small heterodimer partners, TMAO restricts bile acid production and facilitates the development of aortic lesions in Atherosclerosis-prone apolipoprotein E-deficient (*Apoe*$^{-/-}$) mice [22]. The capacity of TMAO to enhance the expression of CD36, class A1 scavenger receptor, and the cholesterol migration-associated gene ATP-Binding Cassette Transporter A1 (ABCA1) results in the accumulation of cholesterol in macrophages [23]. The progression of atherosclerosis was inhibited in wild-type-fed *ApoE-/-* mice, according to *in vivo* research by Xue and colleagues, who showed macrophage reverse cholesterol transport (RCT) to the liver and feces and ABCA1 expression in the liver [148]. They discovered that indole-3-propionic acid promotes the development of atherosclerosis by stimulating macrophage RCT and raising ABCA1 expression. It has been demonstrated that stimulating macrophage RCT is an effective method to inhibit the production of macrophage-derived foam cells, a critical stage in the atherogenesis process [141], [142]. Of note, modifying the gut microbiota to enhance the synthesis of indole-3-propionic acid by ingestion is a novel and potentially reliable treatment method for preventing or slowing the atherosclerotic process. This article discusses the effects of gut microbiota metabolites on macrophage polarization, inflammatory processes, and foam cell production. We also highlight the mechanisms underlying these effects as well as the prospective therapeutic benefits of targeting microbial metabolites in the treatment of CVD.

Section snippets

Microbiota and microbiota-derived metabolites in health and disease

The entire microbial community of the gut, which includes at least 1,000 distinct bacterial species and trillions of microbes, is called the gut microbiota [24]. Under normal conditions, intestinal homeostasis is maintained by a delicate balance of commensal and pathogenic microbes [25]. Each location has a unique microbiota that differs in composition. The bacteria in the gut are responsible for several vital functions, including vitamin production, food fermentation, infection protection, and

Gut microbiota, macrophage, and cardiovascular diseases

Several studies have shown that the gut microbiota plays a crucial role in the development of CVD [42], [23]. In this regard, the occurrence of “dysbiosis,” which refers to the dysfunction or maladaptation of microbial communities, has been associated with an increased risk of CVD and has the potential to influence the disease progression [42]. Notably, individuals with atherosclerosis exhibit significant dysbiosis in the composition of their gut microbiota and interactions between different

Macrophage polarization and its importance in cardiovascular defense

Macrophages are key players in the process of tissue regeneration and wound healing [66]. During the healing process, macrophages undergo a process called polarization, which is a critical stage in the restoration of tissue homeostasis [67]. Of note, macrophages in the heart that originate from monocytes play key roles in the development of inflammatory responses (inflammation and resolution) in patients with myocardial problems [68]. Research has revealed that the exosomes and microRNAs

Microbiota metabolites and inflammation in cardiovascular diseases

Inflammation is associated with the development of cardiovascular disease [2]. Systemic inflammation is strictly connected with accelerated atherosclerosis [89]. The gut microbiota may also influence cardiovascular risk through a pro-inflammatory effect, exerted not only by its metabolites but also by bacteria themselves, especially under conditions of dysbiosis [90].

Recent research has shown that microbiota metabolites have a significant impact on the immune system and inflammation, both of

Microbial metabolites and macrophage function in cardiovascular diseases

Microbiota SCFAs have been shown to modulate macrophage polarization, promoting an anti-inflammatory M2 phenotype over a pro-inflammatory M1 phenotype [116]. This shift in macrophage polarization has been linked to a reduction in atherosclerotic lesion size and improved vascular function. TMAO has been shown to promote the accumulation of cholesterol in macrophages, leading to the development of foam cells and the progression of atherosclerosis [117]. These metabolites can have both

Microbial metabolites and risk factors of cardiovascular diseases

Patients and mice models of hypertension exhibit an increased abundance of *Clostridiales* and *Bacterodiales* in their gut microbiota, as well as reduced diversity, according to research [186]. The abundance of *Robinsoniella* in the gut microbiota was found to have a negative correlation with systolic blood pressure in the Coronary Artery Risk Development in Young Adults (CARDIA) study [187]. In comparison to healthy controls or chronic angiotensin-II infusion mice models, spontaneous hypertensive

Microbiota metabolites and macrophage-based therapy against cardiovascular diseases

Given the presence of robust associations between the overall composition of the gut microbiota and a host of health outcomes, its metabolites, and its vulnerability to CVD, the gut microbiota has received greater attention as a potential novel element in the genesis and progression of CVD [216]. Recent studies have explored the potential of macrophage-based therapies for the treatment of CVDs. These therapies aim to modulate macrophage activation and function in order to reduce inflammation

Conclusion

Although traditional risk factors like hypertension, hypercholesterolemia, and smoking have been widely researched, novel evidence indicates that the gut microbiota and its metabolites may also have a crucial role to play in the development of CVDs. There is a complicated link between the gut microbiome, its metabolites, and CVD, as shown by a number of human and animal research. The interpretation of the gut microbiome's genetic information represents a crucial milestone in the advancement of

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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