Review Article

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The influence of gut microbiota in cardiovascular diseases—a brief review

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Abstract

Lately, the gut microbiota has emerged as an important mediator of the development and the outcomes of certain diseases. It's well known that the gut microbiota plays an important role in maintaining human health. Still far from being completely understood and analyzed is the complexity of this ecosystem, although a close relationship between the gut microbiota and cardiovascular diseases (CVD) has been established. A loss of diversity in the microbiota will lead to physiological changes, which can improve inflammatory or infection states like atherosclerosis and hypertension, the basic pathological process of CVD. Targeting the gut microbiota and its metabolites are new and promising strategies for the treatment and prognosis of CVD.

Keywords: atherosclerosis, cardiovascular diseases, gut microbiota, hypertension, SCFAs, TMAO

Introduction

The human intestinal microbiota consists of more than 10 trillion resident microorganisms, including bacteria, archae, viruses, protozoa, and fungi.[1,2] A healthy microbiota is composed mainly of bacteria from four phyla actinobacteria, firmicutes, proteobacetria, and bacteroidetes, and these constantly adapt to lifestyle modifications.[3] The set of microorganisms that inhabit our organism we call it microbiota, and these microorganisms together with their genetic information are called the human microbiome.[2,4]

We now know the trillions of bacteria living within our gut perform a wealth of vital functions, like host metabolism, modulation of immune system, energy homeostasis, vitamin synthesis, toxin removal, and digestion of carbohydrates as well as production of signaling molecules including short-chain fatty acids (SCFAs), bile acids (BAs), and so on.[4,5] The balance between microbial species present in the human organism is essential to maintain the organism's homeostasis, being extremely important for human health. Changes in the composition of the gut microbiota, called dysbiosis, will lead to systemic inflammation, chronic inflammatory diseases, modifications of the immune system, and also increase the risk of developing several diseases such as metabolic syndrome, autoimmune, cardiovascular, and central nervous system diseases, or even cancer.[6–8]

In the last decade, cardiovascular disease has emerged as the leading cause of death worldwide, causing almost two times as many deaths as cancer and covering several disorders such as atherosclerosis.[9,10] In addition to genetic factors, other environmental factors, such as nutrition and intestinal microbiota, were also recognized as the main factor for the development of CVD. Moreover, intestinal dysbiosis has been associated as a risk factor for the development of obesity and diabetes, two main risk factors for cardiovascular disorders.[1,11]

In this review, we debated the roles of gut microbiota concerned in the development of CVD, mainly focusing on atherosclerosis and hypertension.

Methods

A review examining the role of the gut microbiota on cardiovascular diseases was carried out. The literature search was conducted to achieve the goal using several electronic databases including PubMed and Embase, without any year restrictions but privileging the most recent publications. The search issues were based in the keywords "microbiota," "cardiovascular diseases," "atherosclerosis," "hypertension," "SCFAs," and "TMAO."

Further, we will discuss the results of the studies examining the concept of dysbiosis in relation to cardiovascular diseases.

Results and discussion

Gut microbiota and atherosclerosis

In recent years, there has been a growing awareness that the intestinal microbiome could be involved in the occurrence and development of atherosclerosis. Studies suggest that the gut microbiome is capable of producing numerous metabolites, some of which are absorbed by the systemic circulation, being than metabolically activated or metabolized by host enzymes serving as mediators of the influence of the microbiome on the host.[12]

Atherosclerosis is a chronic inflammatory disease and the main pathological basis for CVD, characterized by the formation of plaques in the arteries, with accumulation of lipids and cells, such

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as leukocytes, endothelial and foam cells in membranes, and calcified regions.[13] Almost all cardiovascular diseases are caused by atherosclerosis, which will stop blood circulation. When this happens in the coronary arteries it can lead to episodes of angina or myocardial infarctions, when it develops in the cerebral arteries it can cause memory changes, dizziness or even strokes.[14] Both innate and acquired immunity are involved and inflammation in artery walls is an important feature of atherosclerosis, contributing to the instability of plaques and thrombotic occlusion of the arteries, resulting in cardiovascular events, such as strokes and acute coronary syndromes. This is supported by evidence that found bacterial DNA in atherosclerotic plaques.

Dysbiosis has been implicated in the development of atherosclerosis through metabolism-independent and metabolite-dependent pathways.[15] In the metabolism-independent pathway some bacterial components such as lipopolysaccharides, found on the outer membrane of Gram negative bacteria, can promote the formation of foam cells induced by a metabolic endotoxemia. Foam cells are macrophages that phagocytize large amounts of low density lipoprotein (LDL) cholesterol in an attempt to remove them from the bloodstream. This cells when deposited in the artery plaque, contribute even more to atherosclerosis since they are a major component of atherosclerotic plaque.[16] When dysbiosis is induced by a high fat diet, there will be a reduction in the number of *Bifidobacterium*, which function as an intestinal barrier preventing bacterial translocation.[13] Dysbiosis can also reduce the expression of the intestinal tight junctions proteins, further increasing intestinal permeability and allowing LPS to enter circulation, which will promote inflammation.[17]

Beyond the metabolism-independent pathway, dysbiosis can exert pro-atherosclerotic effects by altering a variety of metabolites, such as trimethylamine-N-Oxide (TMAO), bile acids, and some SCFAs.[18]

Trimethylamine-N-oxide

TMAO is a colorless organic compound that belongs to the group of amines oxidases. This is produced in the intestine and depends on the initial formation of the trimethylamine (TMA) compound by the microbiome present, especially in the first portion of the large intestine.[19] Microbial metabolism of dietary choline and carnitine has been shown to increase risk of cardiovascular disease,[20] and the metabolism of these compounds in the gastrointestinal tract produce trimethylamine, which goes to the liver to be oxidized into TMAO by the hepatic enzyme flavin-containing monooxygenase 3 (FMO3).[12,19] TMAO can be release by the liver and be absorbed by extra-hepatic tissues or be excreted by urine or sweat. It can also be absorbed by macrophages in the atherosclerotic plaque formation process, resulting in high levels of TMAO being associated with an increased risk of CVD, with or without the influence of risk factors.[21]

In addition to what has already been mentioned, TMAO will promote the release of calcium ions due to the stimulation of platelet activity, which in turn will activate the prothrombotic pathways.[22] This molecule will also regulate the differentiation of monocytes into macrophages and foam cells, and will influence pro-fibrotic processes in the heart and kidneys, through growth factors.[23] Therefore, it seems the mechanism by which TMAO can contribute to the progression of these diseases involves increasing the accumulation of cholesterol in machrophages.[18]

Recent studies suggest that the gut microbiota leads to the development of atherosclerosis and the pre-atherogenic power of TMAO has already been demonstrated in studies that have come to prove that this compound is able to modify the metabolism of cholesterol and sterol, suppressing the reverse transport of cholesterol.[24] This leads to an accumulation of cholesterol in the macrophages, promoting the activation of the endothelial cells and the migration of foam cells to the walls of the arteries, triggering the platelet activation.[9,25]

Modulation of microbial metabolism through dietary intervention or direct supplementation might provide an effective strategy for preventing CVD.[7]

Short-chain fatty acids

Short-chain fatty acids or SCFAs are carboxylic acids with less than six carbons, produced by fermentation of dietary fibers, proteins, and peptides which escape digestion by host enzymes in the upper gut, and are metabolized by the microbiota in the cecum and colon. The composition of the diet directly influences the production of SCFAs, with acetate, propionate, and butyrate being the most important metabolites.[25]

They can play an essential role in the regulation of inflammation and result in protective or causative effects, stimulating or attenuating the production of inflammatory cytokines that in excess will attract more immune cells, forming a vicious circle that leads to the formation of foam cells and development of atherosclerosis.[26]

SCFAs are believed to have anti-inflammatory effects, however it is known that changes in concentration of these fatty acids can cause immunological and metabolic imbalances in the body and several studies have already demonstrated the link between SCFAs and risk factors for CVD like atherosclerosis, hypertension, diabetes, and obesity, among others.[27] Moreover, several studies have shown that SCFAs take part in all stages of atherosclerosis development.

Gut microbiota and hypertension

Hypertension is one of the most serious public health problems, contributing to pathological situations such as strokes, coronary heart diseases, kidney failure, and premature death, among others. Environmental factors like dietary salt consumption, alcohol, and lack of physical exercise are also related to the increase in blood pressure.[26]

In addition to atherosclerosis, dysbiosis can contribute to the progression of hypertension, which can be defined as a small decrease in the arterial lumen that consequently can increase peripheral vascular resistance, resulting in high blood pressure.[18] Blood pressure regulation has generally been linked to the renin-angiotensin system, which involves the angiotensin-converting enzyme (ECA), and although the direct link between hypertension and TMAO has not been fully established, it is known that it prolongs the hypertensive effect of angiotensin II.[28]

Inhibition of TMAO production through modulation of the gut microbiota can serve as a good therapeutic approach for the treatment and prevention of CVD.[29]

Recently, several studies have shown a huge decrease in microbial variety and diversity in hypertensive states, where *Bacteroidetes* are quite reduced and *Firmicutes* have increased considerably.[30] It has also been revealed that germ-free mice, where gut bacteria are completely absent, have a relatively lower

blood pressure compared to conventionally raised mice.[31] Another study found that high-fiber diet and acetate supplementation significantly decreased diastolic blood pressure, cardiac fibrosis and ventricular hypertrophy when compared to a control standard diet,[32] which demonstrated that the gut microbiota-producing SCFAs in circulation played an important role in hypertension. SCFAs can also function to stimulate host G-protein coupled receptor (GPR) pathways, impacting renin secretion and blood pressure regulation.[33] Therefore, gut microbiota is potentially interconnected to control blood pressure and dysbiosis could be associated with hypertension.

Therapeutic interventions

Host's microbiota manipulation has demonstrated promising applications in various fields of science. In addition to the therapeutic strategies already used, the modulation of the microbiota through the use of probiotics and prebiotics or a healthy diet have been considered a good option instead antibiotics to enhance the treatment of dysbiosis and to formulate individual susceptibility to atherosclerosis.

Probiotics are live beneficial microorganisms that when administered in adequate amounts improve health by re-establishing an appropriate intestinal balance, and may act through pH modulation, antibacterial compound production and competition with pathogens. The most common probiotics are *Lactobacillus* and *Bifidobacterium*, natural residents of the human gut an in which there is a great activity of the bile salt hydrolase (BSH) enzyme. This enzyme, in addition to alter the composition of the gut microbiota, will also act on bile metabolism, in detoxification and reducing cholesterol levels. The disconnection of bile salts causes them to not be reabsorbed as well as the conjugates, which lead to a greater excretion of free bile acids, decreasing its solubilization and lipids absorption, reducing serum cholesterol levels in circulation.[18,34] High levels of cholesterol is one of the most concerning risk factors for CVD, and the use of probiotics has been shown to significantly reduce its levels, without half the size effects of conventional therapy.[34] Therefore, probiotics present themselves as a new therapy for the treatment and prevention of cardiovascular diseases, interfering in the formation, progression, and eventual rupture of atherosclerotic stages.

Another strategy to regulate intestinal microbiota is the use of prebiotics, which are nondigestible carbohydrates that beneficially affect host health by selectively stimulating the growth and/or activity of the health promoting gut microbiota. In fact, prebiotics can stimulate atheroprotective effects and reduce the risk of cardiovascular disease, promoting the growth of beneficial gut microbiota.[35] The growth of bifidobacteria can help maintain the integrity of the intestinal barrier, as they do not degrade the glycoproteins in the intestinal mucus. However, in dysbiosis there may be an increase in bacterial translocation and metabolic endotoxemia through increased intestinal permeability.[18,36]

A dietary approach to nutritional interventions had proved to be an effective strategy in reducing cardiovascular risk.[20] Fiber-rich diets promote the growth of beneficial commensal bacteria, like acetate-producing microbiota which can lower blood pressure and decrease cardiac hypertrophy, and limit the growth of known opportunistic pathogens.[32] Also, the adequate use of polyphenols, monounsaturated fatty acids and vitamins reduce the risk of developing CVD, due to its antioxidant effect that reduces the levels of LDL, triglycerides, and blood pressure.[33] Modulation of gut microbiota composition through diet intervention represents a promising therapeutic approach, given that an alteration in intestinal microbiota composition has been linked to different diseases.

Conclusion

Studying the microorganisms that live and inhabit out organism is one of the fields of science that promises more innovation in future, particularly with regard to personalized medicine. Recently it was discovered that the microbiota has an enormous relevance in health, starting to be considered a very important therapeutic target and its characterization in places like the gastrointestinal tract is essential to establish a connection with certain pathological states like the CVD.

The pathophysiology of CVD is complex, multifactorial, and poorly understood. However, new information has suggested that the intestinal microbiota may be one of the biggest revolutions in the diagnosis and treatment of these disorders. Dysbiosis caused by TMAO, a potentially pro-atherosclerotic component formed by the metabolism of choline and carnitine is one of the main factors associated with CVD. Thus, some harmful metabolites like TMA/TMAO can worsen the clinical prognosis of CVD, while other beneficial metabolites like SFCAs can slow the progression of the diseases. Dysbiosis also plays a significant role in the development of CVD contributing to risk factors such as atherosclerosis and hypertension through inflammation and dyslipidemia.

Given the tight interplay between gut microbiota and host immunity, efforts have focused on discovering different strategies targeting this complex ecosystem. Thus, new hope arises in finding new approaches to treat CVD using microbial metabolites, such as probiotics or prebiotics that can block or promote the production of harmful or beneficial metabolites, respectively. Further investigations are needed.

Acknowledgments

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Conflicts of interest

None.

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