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Review

Exploring the Potential Links between Gut Bacteria-Related Metabolites and the Risk of Cardiovascular Diseases

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Abstract: This mini-review examines the complex relationship between the gut microbiota and human health, with a special focus on its role in conditions such as inflammatory bowel disease (IBD) and cardiovascular disease (CVD). It explores how dietary patterns can affect the composition of the gut microbiota, thus contributing to the development of various diseases. The gut microbiota is crucial in the production of metabolites such as trimethylamine N-oxide (TMAO), which play a significant role in the development of both IBD and CVD. High levels of TMAO and other metabolites, such as phenylacetylglutamine, have been linked to an increased risk of CVD. The review highlights the potential of dietary interventions and therapies designed to modulate the gut microbiota in reducing these risks. Following a Mediterranean diet may offer cardiovascular protection, emphasizing the need for further research into the molecular mechanisms of diet-related changes in the microbiota.

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Introduction

The intestinal microbiota, often referred to as the gut microbiome, is composed of various microorganisms, including bacteria, viruses, fungi and other microbes, found in the gastrointestinal tract. These microorganisms interact with the host, playing a significant role in digestion, immune defense, nervous system regulation, and metabolism. It is essential to maintain a delicate balance between the microbiome and the human host for overall health (Jia et al., 2019). Approximately 10 trillion to 100 trillion microbial cells inhabit the human body, most of which are found in the gastrointestinal (GI) tract. The relationship between the gut microbiome and an individual's health is especially beneficial when the host is in good health and properly nourished (Jovanovich et al., 2018). Recent research has highlighted the critical role of gut microbiota in the development of various human diseases, with a particular focus on inflammatory bowel disease (IBD) and cardiovascular diseases (CVD). The etiology of IBD is multifaceted, involving complex interactions between genetic variation, host immune responses, and environmental factors (Tie et al., 2023; Faqerah et al., 2023; Lin et al., 2023). Current scientific consensus suggests that intestinal dysbiosis, defined as an abnormal mucosal immune response in genetically susceptible individuals, plays a key role in IBD pathogenesis and is further influenced by dietary factors. Extensive research has revealed that the consumption of a high-fat diet (HFD) is associated with alterations in the gut microbiome, indicative of dysbiosis, persistent intestinal inflammation, and increased intestinal permeability (Stiegeler et al., 2021) However, progress in understanding how dietary interventions can mitigate IBD has been hindered by the scarcity of appropriate animal models. Epidemiological data has established a link between the consumption of high-calorie, low-fiber, high-monosaccharide, and high-fat diets and the prevalence of several chronic diseases with high morbidity and mortality rates in modern Western

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societies, including type II diabetes, IBD, and colorectal cancer. Notably, there is accumulating evidence suggesting that IBD in canines and humans share analogous clinical and molecular features (Xing et al., 2023). Consequently, preclinical studies involving dogs with naturally occurring IBD present a valuable opportunity to deepen our understanding of disease pathogenesis and pioneer new therapeutic strategies. Mechanistic studies conducted *in vitro* can incrementally explore the impact of dietary interventions on chronic intestinal inflammation and increased intestinal permeability, employing tools such as intestinal organoids (Ambrosini et al., 2020; Kopper et al., 2021; Dotti et al., 2022; Gabriel et al., 2022a, 2022b; Sahoo et al., 2023). The utility of organoids stems from their ability to recapitulate the inherent pathomechanisms of the disease process (Mochel et al., 2017; Chandra et al., 2019; Sahoo et al., 2022).

In addition to the impact of gut dysbiosis on IBD pathogenesis, numerous studies conducted in humans and animals have shown how changes in the composition and activity of intestinal flora can accelerate the onset of CVD (Ding et al., 2020; Wang et al., 2022). Additionally, the intestinal flora can break down dietary components into various metabolites, such as trimethylamine N-oxide, short-chain fatty acids, secondary bile acids, and indoxyl sulfate. These metabolites can affect the host's physiological functions by activating various signaling pathways. This short review aims to elucidate the important role of the gut microbiota in the pathogenesis of CVD.

Trimethylamine N-oxide

Microbial metabolism in the gut plays a pivotal role in the synthesis of trimethylamine (TMA) from dietary choline and l-carnitine, which is then converted into trimethylamine-N-oxide (TMAO) by the liver enzyme flavin monooxygenase 3 (FMO3). The concentration of TMAO in plasma is dependent on genetic factors, dietary habits, and gut microbiota composition. Numerous studies have established a link between elevated TMAO levels in plasma and the risk of atherothrombotic CVD (Canyelles et al., 2018).

TMAO may increase the production of foam cells in the liver by upregulating macrophage scavenger receptors, impairing enterohepatic cholesterol and bile acid metabolism, and hindering macrophage reverse cholesterol transfer (RCT). Additionally, FMO3 may contribute to dyslipidemia by modulating various genes that control hepatic lipogenesis and gluconeogenesis, ultimately affecting cholesterol levels (Canyelles et al., 2018).

Over the past two decades, there has been growing interest in understanding the gut microbiota composition, its intrinsic and extrinsic impact on intestinal health, and its implications as a risk factor for the development of CVDs, including metabolic syndrome. The gut microbiota is essential to human health and disease (Rahman et al., 2022), and current research highlights its potential to influence host's physiology. TMAO, among other metabolites such as short-chain fatty acids and primary and secondary bile acids, has gained attention for its association with several chronic diseases, including insulin resistance, atherosclerotic plaque formation, diabetes, cancer, heart failure, hypertension, chronic kidney disease, liver steatosis, cardiac fibrosis, endothelial injury, neural degeneration, and Alzheimer's disease (Papandreou et al., 2020).

The fermentation of dietary components, such as choline and carnitine, by gut microbiota leads to the generation of trimethylamine (TMA), which is then metabolized to TMAO in the liver by flavin-containing monooxygenases 1 and 3 (FMO1 and FMO3). Given the multifaceted role of TMAO in the development of numerous chronic diseases, therapeutic strategies for maintaining a healthy gut microbiota have been explored. Studies have suggested that dietary nutrients and bioactive compounds may modulate gut microbiota and potentially reduce TMAO production (Simo and Garcia-Canas, 2020; Coutinho-Wolino et al., 2021).

Phenylacetyl glutamine

Phenylacetylglutamine (PAG) is a well-known microbial metabolite that conjugates glutamine and phenylacetate, primarily arising from bacterial metabolism of phenylalanine. Extensive metabolomic investigations have consistently associated circulating PAG levels with specific gut microbial families, including Coriobacteriaceae, Mogibacteriaceae, Bifidobacteriaceae, as well as

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genera within the Lachnospiraceae, Christensenellaceae, and Ruminococcaceae families, and overall gut microbial diversity. In large-scale clinical studies, increased blood concentrations of phenylacetylglutamine, a gut microbiota-dependent metabolite, have been linked to an increased risk of CVD. Numerous mechanistic studies using animal models have demonstrated significant associations between these gut microbial metabolites/pathways and CVD (Witkowski et al., 2020). Recent research has revealed that phenylacetylglutamine can induce adverse cardiovascular effects in the host by interacting with adrenergic receptors (ARs), a critical class of autonomic receptors for cardiovascular homeostasis.

Additionally, the plasma metabolite phenylacetylglutamine (PAGln) has been identified and independently associated with CVD and significant adverse cardiovascular events such as myocardial infarction, stroke, or death (Witkowski et al., 2020). PAGln, derived from the gut microbiota, has been found to enhance platelet activation-related characteristics and increase the risk of thrombosis in systemic circulation, isolated platelets, and animal models of arterial injury. Functional and genetic studies involving human commensals and microbial colonization of germ-free mice have elucidated the microbial-driven nature of this process. A specific porA gene found in some bacterial strains facilitates the conversion of dietary phenylalanine into phenylacetic acid, ultimately leading to the production of PAGln and phenylacetylglycine (PAGly) by the host, consequently increasing platelet activity (Nemet et al., 2020).

Clearance of uremic toxins

Disruptions in the equilibrium of the intestinal microbial community, as a consequence of chronic kidney disease (CKD), are emerging as key factors in the initiation and progression of various comorbidities. Notably, patients with renal insufficiency are at an increased risk for suffering from heart attacks or strokes, and recent research has shed light on the strong correlation between dysbiosis of the microbiome and the increased incidence of cardiovascular events in this patient population.

The relationship between microbial community imbalance and cardiac health has been confirmed through prior association studies and current causative investigations using experimental animal models. These studies emphasize the significant impact of microbiota dysregulation on cardiovascular health, with implications extending beyond individuals with renal impairment (Bryniarski et al., 2019).

In addition, changes in the composition of the gut microbiota, along with a range of host responses, have been closely associated with the progression of CKD. Dysregulation of the gut microbiota has been linked to an increased cardiovascular risk, the emergence of uremic toxicity, and a state of chronic inflammation (Nallu et al., 2016). Of particular importance are the uremic toxins produced by dysbiotic intestinal bacteria, which play a key role in the pathogenesis of CKD. Furthermore, the gut microbiome has garnered attention in the context of kidney transplantation (Nallu et al., 2016), highlighting the pivotal role that commensal microbes play in shaping immune responses to transplantation.

Additionally, elevated plasma levels of PAG have consistently been observed in patients with CKD (Velasquez et al., 2018). This elevation can largely be attributed to reduced tubular secretion (Velasquez et al., 2018). Additionally, a smaller-scale study involving individuals with CKD revealed a significant association between circulating PAG levels and the risk of future CVD. This association between PAG and coronary artery disease (CAD) also appears to be independent of inflammatory processes, emphasizing its potential use as a biomarker for assessing cardiovascular risk (Bryniarski et al., 2019).

Potential therapeutic strategies

Clinical data has established a link between plasma TMAO concentrations and the risk of CVD. However, the exact role of dietary components in influencing plasma TMAO levels and CVD biomarkers is still a subject of ongoing research. Contemporary strategies for reducing CVD risk by altering gut microbiota include dietary interventions, targeting host enzymes involved in the

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production of meta-organismal metabolites, fecal microbial transplantation, pre/probiotics, bacterial enzyme inhibitors, and antimicrobials (Witkowski et al., 2020). Chronic low-grade inflammation is an underlying process that connects metabolic risk factors to an increased risk of CVD. Adopting a Mediterranean diet approach has been shown to reduce inflammatory biomarkers and prevent cardiovascular and cerebrovascular events (Meslier et al., 2020). A study has demonstrated that TMA levels were substantially reduced when exposed to sitosterol and resveratrol. This research provides supporting evidence that sitosterol and resveratrol possess inhibitory effects on the gut microbiota responsible for choline metabolism into TMA (Heng et al., 2021). Evidence suggests that berberine (BBR) could treat obesity, diabetes, and atherosclerosis. The mechanism underlying its effects, attributed to TMA/TMAO synthesis, reduction has been linked to BBR-modulated gut flora. *In vivo* experiments have demonstrated that a single dose of choline inhibits TMA/TMAO synthesis, with BBR acting on TMA-producing bacteria. These findings offer new insights into the mechanisms influencing CVD (Li et al., 2021). Furthermore, numerous Chinese herbal medications have been used to manage CVD. One study aimed to identify choline-degrading bacteria from healthy human feces and establish a platform for screening TMA-lyase inhibitors from Chinese herbal medicine *in silico* and *in vitro*. Flavonoids found in Lu'an GuaPian tea were shown to regulate gut microbiota by reducing TMA-lyase activity, thus preventing acute myocardial infarction (AMI) (Hua et al., 2022). These flavonoids are present in various plant foods, including fruits and vegetables, making them accessible through dietary choices. The following are among the top dietary sources of flavonoids (Tuttolomondo et al., 2019):

1. Berries - especially blackberries, blueberries, cherries, and raspberries.
2. Cabbage.
3. Onion.
4. Kale.
5. Parsley.
6. Green tea.
7. Oolong tea.
8. Black tea.
9. Red wine (in moderation).
10. Dark chocolate and cocoa.
11. Citrus fruits such as oranges, grapefruit, tangerines, lemons, and limes.
12. Soybeans and soy-based products like edamame, tofu, tempeh, and soy sauce.
13. Turmeric contains Curcumin, a potent anti-inflammatory compound. These foods also provide a rich source of flavonoids, which have been studied for potential health benefits, including protection for the cardiovascular system.

Conclusion

Heart failure has been associated with congestion in the splanchnic circulation for many years, leading to edema of the colon wall and compromised function of the intestinal barrier. Bacterial products entering the systemic circulation are believed to exacerbate the overall inflammatory state. Recent research has revealed several metabolites generated by gut microorganisms during nutritional digestion and metabolism, which have been linked to conditions such as atherosclerosis, hypertension, heart failure, chronic kidney disease, obesity, and type 2 diabetes mellitus. These findings suggest that the gut microbiota functions as an endocrine organ, producing bioactive compounds that can directly or indirectly influence host physiology (Witkowski et al., 2020).

One such gut microbiota-dependent metabolite is PAG, which has been linked to atherothrombotic heart disease in humans and has been mechanistically connected to the development of CVD in animal models through the activation of adrenergic receptors.

Studies have shown that individuals adhering to a Mediterranean diet enriched with either extra-virgin olive oil or nuts have a lower risk of major cardiovascular events compared to those on a reduced-fat diet. However, more research is needed to understand the molecular mechanisms through which the Mediterranean diet exerts its effects. Additionally, transitioning individuals to a

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Mediterranean diet while controlling their energy intake has been shown to lower blood cholesterol levels and induce changes in their microbiota and metabolome. These changes are significant for future initiatives aiming to improve metabolic health (Tuttolomondo et al., 2019).

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