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Endothelial Cell Function is Regulated by Circulating Metabolites Caused by Gut Microbiota

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Introduction

Worldwide, cardiovascular diseases (CVDs) account for the majority of deaths. By 2030, it is anticipated that CVD mortality rates will reach 23.3 million per year. In 2019, nine million people died from cardiovascular disease; representing almost a third of all global deaths. The disease is caused by a number of risk factors, including age, gender, family history, hypertension, diabetes, obesity, smoking, and stress. Worldwide, atherosclerosis and myocardial infarction (MI) are on the rise as a result of rapid environmental changes and modern lifestyle factors like eating a lot of meat, eating a diet high in lipids, and not getting enough exercise. However, a meta-analysis of prospective cohort studies found that saturated fat intake did not correlate with cardiovascular disease (CVD), suggesting that other environmental factors are to blame. The blood that continuously flows through our veins and arteries to ensure our survival performs numerous essential functions. Recent studies, particularly cross-sectional studies targeting the SrRNA gene, have revealed a dominant group of blood-borne bacterial phyla (i.e., Proteobacteria, followed by Actinobacteria, Firmicutes, and Bac) and similar blood microbiota compositions, with Proteobacteria dominating (relative abundance values typically ranging from 85 to 90%) and Firmicutes, Actinobacteria, and Bactero This indicates that there is a core blood microbiome profile that is constant regardless of the study environment or analytical technique [1].

In the past two years, numerous studies have been published on the connection between human health and disease and the microbial composition of blood. Amino acid derivatives, hormones, short-chain fatty acids (SCFAs), vitamins, and antioxidants are examples of microbial metabolites that can be absorbed directly into the patient's circulatory system. The current study aimed to summarize the intricate interplay between blood microbiota, circulating metabolites, and their putative roles in the development and progression of cardiovascular disease (CVD). In addition, a number of recent studies demonstrated that the tissue microbiome plays a significant role in the onset of pre-diabetic and type 2 diabetic patients, COVID-19, metabolic diseases, portal hypertension, polycystic ovary syndrome, and myocardial infarction. For instance, a population-based study conducted several decades ago found a connection between endotoxemia (the elevation of endotoxin from gram-negative bacteria in the blood) and atherosclerosis. Trimethyl amine oxide, a bacterial metabolite, has recently been linked to negative effects [2].

Description

Despite the discovery of bacterial S rRNA in healthy human blood two decades ago, the final processes and presence of the bacteria had not been investigated. However, in recent years, a study investigating the composition of the blood microbiome in the various fractions used quantitative polymerase chain reaction to sequence 16 S rRNA gene V3-V4 hypervariable regions in the blood of 30 young healthy volunteers. Bacterial DNA was most abundant in the buffy coat (93.74 percent), followed by RBCs (6.23 percent) and plasma (0.03%). Different microbial communities exist within the digestive tract and on the skin's surface. In healthy individuals, microbial DNA is frequently present in cellular components, and significant changes were observed in the microbial community composition of the healthy gut and blood. Proteobacteria dominated the blood, while Firmicutes and Bacteroidetes phyla predominated in the gut. Because they do not cause problems like sepsis and inflammation, healthy bacteria that are circulating in humans are referred to as being dormant. Despite the fact that the circulating microbiome plays a crucial role in natural physiology and immunology, these findings indicated that the blood microbiota is primarily translocated from the gastrointestinal tract. Also, more research is needed to learn more about how the blood microbiota affects health, immunity, and physiology [3].

Circulating microbial metabolites

The diversity of the microbiota's functional genes indicates that the human microbiota is more metabolically adept than human cells. Dietary compounds and other substances are only partially digested by host systems; The rest is processed by gut bacteria, particularly in the anaerobic environment of the large intestine. When developing toxicological risk assessment methods for environmental toxins and medications, the microbiota in the gut should be considered. Our microbial cells use various mixtures through proteolysis, decrease, hydrolysis, utilitarian gathering evacuation, N-oxide cleavage, denitration, deconjugation, amine development, amide hydrolysis, thiazole ring-opening, acetylation, and isoxazole scission. Among microbial metabolites, trimethylamine N-oxide (TMAO) has received a lot of attention as a major cause of cardiovascular disease (CVD). Esterases, lipases, azoreductases, nitroreductases, -glucuronidases, sulfatases, and –lyases are among the involved enzymes. Plasma TMAO levels have been found to directly correlate with elevated CVD risk in human cohorts and germ-free mice. In mice fed choline- and carnitine-rich diets, which resulted in high plasma TMAO levels and the formation of atherosclerotic plaques, intestinal microbiota suppression or depletion of food supplements can stop TMAO production and lessen atherosclerosis. As a result, people who take broad-spectrum antibiotics deplete their gut microbiota and have significantly lower levels of circulating TMAO.

Since diet is a primary source of TMAO, people are also advised to limit their intake of foods high in carnitine, choline, and lecithin to lower their risk of CVD. The discovery of the TMAO receptor PERK in the endoplasmic reticulum suggests that elevated TMAO levels may also indicate an increased risk of heart failure, peripheral artery disease, stroke, and stable coronary artery disease. It is interesting to note that TMAO has been shown to prevent vascular damage in hemodialysis patients, possibly as a result of its inhibition of AGE. Several choline analogs have been shown to lower TMAO levels in the blood. Animal experiments have demonstrated that contributing pathways of TMAO influence vascular dysfunction, inflammatory responses, and oxidative stress. The natural substance 3,3-dimethyl-1-butanol, which is abundant in red wines, vinegar, and a variety of grape seed oils, inhibits the microbial choline TMA lyase activity. There is evidence that a number of choline analogs, such as chloromethylcholine, bromomethylcholine, iodomethylcholine, fluromethylcholine, and chloromethylcholine, are better TMA lyase inhibitors that can lower TMAO levels in the blood. Without affecting blood cholesterol levels, this substance could prevent atherosclerotic lesions from developing in Apoe/ mice [4].

The human intestine cannot digest the complex carbohydrates found in dietary fiber to support cell functions. Short-chain fatty acids, which are saturated fatty acids with one to six carbon chains, are produced when fibers are utilized by gut bacteria during the fermentation process. Acetate, propionate, and butyrate are the most common forms of SCFAs in the human body. Controlling gluconeogenesis, lipid metabolic pathways, and anti-inflammatory responses all depend on SCFAs. Additionally, it is believed that these substances, particularly

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butyrate, provide energy to intestinal epithelial cells [4].

Microbiota-targeted therapeutics

Changes in the blood microbiota and circulating metabolites are being discovered using cutting-edge techniques like metabolomics and next-generation sequencing. As biosensors and nanosensors for the detection of particular bacteria or their metabolites advance, it will be simpler to incorporate these biomarkers into routine clinical analysis. Restoring the blood's microbiota and circulating metabolites has been used as an alternative treatment option. Prebiotics, probiotics, and antimicrobials have all been used to fix the digestive boundary and reestablish the blood microbiota's equilibrium. Reestablishing the variety of microorganisms in the stomach could have a significant impact on the blood microbiota and its flowing metabolites. Hemodialysis, which is a common treatment for kidney failure, may be a way to help sick people's blood microbiotas get back on track. Through hemodialysis membranes, precise filtering of intestinal microbes and their derivatives is possible. Drugs that, for instance, target the microbiota, their metabolites, and host mediators are being developed using small synthetic chemical compounds. The oral charcoal adsorbent has been used to clinically remove indoxyl sulfate from patients with advanced renal failure; some of these patients are currently undergoing clinical preliminary testing [3].

Good scientific practice is important in all areas of science. In recent years, this has received a growing amount of attention, particularly in light of the issues with scientific reproducibility. The majority of researchers are aware of the issues associated with good scientific practice; however, not all of these issues are necessarily obvious, and the particulars can be extremely complex. Without proper controls, sequencing-based microbiome studies have been published and accepted for a considerable amount of time. Despite the fact that more scientists are now recognizing the necessity of controls, this is challenging due to the field's complexity. Another concern in microbiome research is the inability to correctly interpret control data. In the microbiological field, contamination is one of the main problems with S-based categorization, especially when there are only very few bacteria or compounds made from bacteria. In this circumstance, the presence of environmental pollutants, laboratory reagents, and individuals participating in sample preparation could significantly influence the investigations' findings and lead to incorrect conclusions. It's interesting to note that Turner et al.'s longitudinal study These examples unmistakably demonstrate that microbiological investigations should always include several negative controls in order to account for contaminants and produce reliable results. This is because it is possible for different batches of the same extraction kits to identify different contaminants.

It is now abundantly clear that the microbial communities in the systemic circulation of various populations are extremely diverse, and these quantitative and compositional changes in the circulating microbiota may play a role in the onset and progression of cardiometabolic disease. However, a lot of important questions remain regarding the nature of the circulating microbiota, such as where they originate, how they contribute to pathophysiology, how they can be found in various blood fractions, and how to distinguish them from potential contamination. In the future, more in-depth basic, clinical, and population-based research must provide answers to these questions. The development of novel biomarkers for diagnosis and prognosis, particularly in personalized therapeutic approaches to premature morbidity and mortality in cardiometabolic disease, where patterns are emerging in the ongoing quest to improve the outcomes of patients with cardiometabolic disease, may need to go beyond the "gut feeling" and rigorously incorporate the potential pathophysiological insights gained from the circulating microbiota [5].

Conclusion

We have selected a few of the most recent cross-sectional studies of human cohorts to highlight the changes in the blood microbiome that are linked to cardiovascular disease and other diseases in this review. New insights into ecological differences (dysbiosis), biological entities (new species), gene-based variations (biomarkers) related to illness diagnosis, and the effects of current treatments on the circulating microbiota have been gained through these investigations. Numerous studies have demonstrated that the blood microbiome plays a significant role in the onset of cardiovascular and other diseases. The "omics"-based techniques are providing new insights into disease pathogenesis despite the complexity of the microbiome and the confounding effects of host genetics, nutrition, medical co-morbidities, and other lifestyle factors. Certain may result in the creation of medications that could be utilized to treat and prevent metabolic diseases. It is challenging to accurately comprehend their role in disease development and prevention and to use this information to apply microbiome research to medicine because many of these microbes are still difficult to cultivate. There is an urgent need for a resurgence of importance in microbial science in order to successfully complement and communicate the advancements being made by microbial genomics. Individualized therapeutic and/or preventative interventions, such as "next generation," logically assembled microbial consortia and probiotics, as well as dietary changes for reestablishing a gut microbiota that promotes and sustains health, will be supported by bringing metagenomic data to life in the form of viable microbes.

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