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Review Article

The link between gut microbiota and atherosclerosis

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ABSTRACT

Infections have been linked to development of cardiovascular complaint and atherosclerosis. Cardio vascular conditions like atherosclerosis are the major cause of mortality and morbidity in the ultramodern society. The rupture of atherosclerotic plaque can induce thrombus conformation, which is the main cause of acute cardiovascular events. Lately, numerous studies have demonstrated that there are some connections between microbiota and atherosclerosis. There are three metabolite pathways by which gut microbiota can affect atherosclerosis. Either original or distant- causing inflammation which might lead to atherosclerotic plaque formation and rupture. Second, metabolism of lipids and cholesterol by gut microbiota can affect atheromatous atheromatous plaque conformation. Third, diet and specific factors that are metabolized by gut microbiota can have various effects on atherosclerosis; for illustration, salutary fiber is beneficial, whereas the bacterial metabolite trimethylamine- N- oxide (TMAO) is considered dangerous. We'll conclude by discussing new remedial strategies for targeting gut microbiota to ameliorate atherosclerosis and related cardiovascular issues.

1. Introduction

A major cause of cardiovascular illness and mortality globally is atherosclerosis, a chronic inflammatory disease of the artery wall. Despite significant research on conventional risk factors including smoking, cholesterol, and hypertension, it is possible that the gut microbiota plays a crucial role in the development of atherosclerosis. Study of the part of gut microbes have grown in recent times due to advancement in knowledge and technology. The gut microbiome is the collection of microorganisms that live in the gastrointestinal tract. The mortal body hosts a vast number of micro organisms including bacteria, contagions, protozoa, archaea, and fungi, which constitute the commensal microbiota that substantially resides in the gut.[1] Recent exploration has suggested that the gut microbiome may play a part in the development of atherosclerosis, a condition in which atheromatous plaque builds up in the arterial walls and can lead to heart complaint. Studies have shown that certain types of gut bacteria may contribute to inflammation and the conformation of atheromatous plaque in the highways.

The microbiota can impact host physiology, but external factors similar as genetics, diet, pharmacological composites, life, and hygiene also affect the microbial composition.[1]

Also, changes in the gut microbiome have been observed in individuals with atherosclerosis. Early work in the gut microbiome field demonstrated that differences in fecal microbial community composition are associated with the development of rotundity and insulin resistance and that microbial transplantation could transmit heightened

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obesity in the host. Later, it was discovered that dislocations to the microbiome beforehand in life can promote heightened obesity.[2–5] 16 S RNA sequencing have enabled us to know that bacterial DNA exists in atheromatous plaque.[6] Besides, there are several studies proving that the metabolites from microbiota also can impact the development of atherosclerosis. Short- chain adipose acids have formerly been proven to play defensive places in atherosclerosis, stabilizing atheromatous plaque. Contemporaneously, they also set up that trimethylamine-N- oxide and lipopolysaccharide make the vascular endothelium complain and atheromatous plaque unstable and grease thrombosis.[6]

Still, further exploration is demanded to completely understand the relationship between the gut microbiome and atherosclerosis.[7]

2. Discussion

2.1. Infection and Inflammation

Development of atherosclerosis can be affected via two different mechanisms direct infection of vessel wall cells, which creates a point prone to lesion development, or a circular infection at a point distant from the atherosclerotic atheromatous plaque, which activates the vulnerable system that in turn increases the systemic inflammatory status.[3]

Inflammation plays a crucial part in the development and progression of atherosclerosis. When the inner lining of endothelium is damaged by factors such as high blood pressure, smoking, or high situations of LDL cholesterol, white blood cells called monocytes and macrophages travel to the area and phagocytose the damaged cells.

These vulnerable cells release chemicals such as cytokines and growth factors that initiate inflammation, leading to chain of events that can eventually affect in the formation of atherosclerotic plaque. Over time, the plaque can become unstable and rupture, leading to blood clots that can block blood inflow to the heart or brain, causing a heart attack or stroke.

In addition to these vulnerable cells, other factors such as high levels of C- reactive protein (CRP), a marker of inflammation, have also been linked to an increased threat of atherosclerosis and cardiovascular impact. One way that infection is linked with atherosclerosis is through inflammation. Infection leads to inflammation which begin damage to inner linings of endothelium, which can make it easier for atheromatous plaque to form. Certain bacterial species in the gut microbiome have been linked to increased atherosclerosis risk. For example, infections with periodontal bacteria such as Porphyromonas gingivalis have been associated with systemic inflammation and atherosclerosis. These bacteria may translocate into the bloodstream, triggering an immune response and endothelial dysfunction resulting in atherosclerosis.

In addition to Porphyromonas gingivalis, many other gut bacteria contribute in atherosclerosis. For example, *Escherichia coli* (*E. coli*)- Certain strains of *E. coli* can produce lipopolysaccharides (LPS), which are potent inflammatory molecules. Elevated levels of LPS in the bloodstream have been linked to inflammation, endothelial dysfunction, and atherosclerosis. Enterococcus faecalis: This bacterium has been associated with the production of trimethylamine (TMA), a precursor to trimethylamine-N-oxide (TMAO), which is linked to atherosclerosis. TMAO has been shown to promote the development of atherosclerotic plaques by affecting cholesterol metabolism and promoting inflammation.

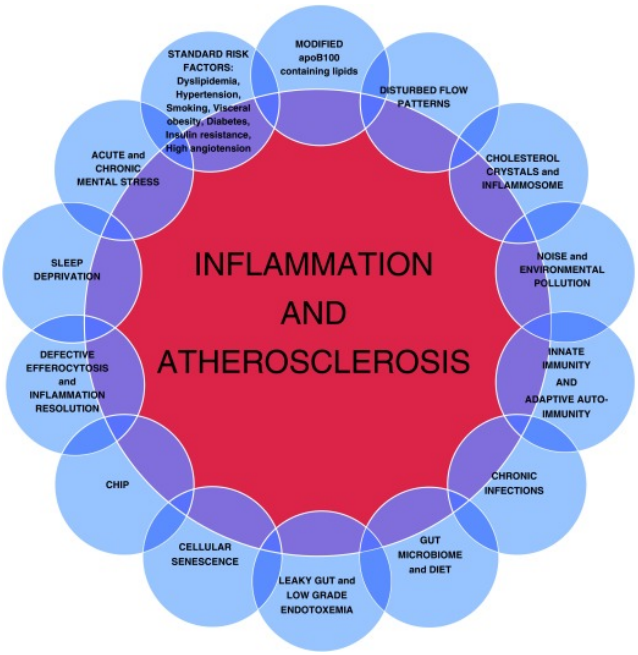

Fig. 1: Different pathways for inflammation in atherosclerosis

2.2. Metabolism of lipid and cholesterol

Cholesterol is a type of lipid molecule that is essential for many important physiological functions in the human body, including the formation of cell membranes, the production of hormones, and the synthesis of bile acids. However, high levels of cholesterol in the blood can contribute to the development of atherosclerosis, a condition in which fatty plaques build up inside the arteries, restricting blood flow and increasing the risk of heart attack and stroke.[8]

The gut microbiome plays an important role in regulating lipid metabolism and cholesterol levels in the body. Certain types of bacteria in the gut are able to produce enzymes that can break down bile acids, which are produced by the liver to help digest fats in the diet. This process leads to the production of secondary bile acids, which have been shown to lower cholesterol levels in animal studies.

In addition, some types of gut bacteria have been shown to produce short-chain fatty acids (SCFAs), which have been linked to lower cholesterol levels and a reduced risk of cardiovascular disease. SCFAs are produced when certain types of bacteria ferment dietary fiber in the colon, and they have been shown to inhibit the synthesis of cholesterol in the liver.

Patient with atherosclerosis have altered lipid metabolism and bacterial flora in gut and oral cavity which correlate with plasma cholesterol levels. bacterial richness (that is, the number of bacterial taxa identified) and specific taxa were associated with BMI and levels of triglycerides and HDL, whereas no such clear association was found with levels of total cholesterol or LDL. Compared with germ-free mice, the levels of cholesterol and triglycerides in the plasma of conventionally raised mice are reduced, whereas they are increased in adipose tissue and liver. These findings support a relationship between the composition of the gut microbiota and plasma levels of cholesterol and lipids.[2]

2.3. TMAO metabolism

Large proportion of humans now consume a diet with cholesterol, fats and sugar. Dietary components are also involved in the atherogenic process. One such example is the proatherogenic metabolite trimethylamine (TMA) generated from microbial metabolism of phosphatidylcholine, which is common in red meat, shellfish, and eggs. TMA is later converted by liver into trimethylamine N-oxide (TMAO).[9]

TMAO may promote inflammation, impair cholesterol metabolism, and alter endothelial cell function.[10,11] Inflammation plays a key role in the development of atherosclerosis, and TMAO has been shown to increase the expression of inflammatory markers such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha). TMAO also upregulates the expression of macrophage CD-36 and SR-A1. It results in increase in formation of macrophage foam cells, which are a key component of atherosclerotic plaques. TMAO also increases the instability of atherosclerotic plaque resulting in plaque rupture. The rupture of plaque might cause diseases like myocardial infarction and stroke.[12] Additionally, TMAO has been shown to alter endothelial cell function, which can lead to endothelial dysfunction and impaired vascular function.[8,11]

As a result, high TMAO levels causes reduction in removal of bad cholesterol from arteries and make blood more likely to clot. If you have high TMAO, one should consider changing the diet to alter the gut bacteria. Eating a Mediterranean style diet rich in green leafy vegetables and reducing the intake of red meat will help reduce TMAO production. This will lower the risk of atherosclerosis and its related diseases.

2.4. Remedial strategy to target gut microbiota and lower the risks of atherosclerosis

Studies that suggest microbiome as a risk factor for atherosclerosis also raise hope for novel therapeutic and remedial strategies for the same. One of such potential remedial strategy to alter the gut microbiota and reduce the risk of atherosclerosis is through dietary modification. Studies have shown that certain plant-based diets like eating green leafy vegetables, fruits and whole grain can promoted a diversified and beneficial gut microbiome thus results in reduction in chances of atherosclerosis.[2,13] Plant based food also contain phytochemicals in them, which have anti-inflammatory effect.[13] Another novel therapeutic strategy might be using prebiotics & probiotics.

A further prospective therapeutic approach for atherosclerosis is fecal microbiota transplantation (FMT). FMT restores microbial diversity and function by transferring the microbiota of a healthy donor to a recipient. FMT has a lot of potential for changing the gut microbiome and reducing inflammation associated with atherosclerosis, despite the fact that its safety and effectiveness in treating cardiovascular disease still need to be thoroughly investigated.[14,15]

3. Limitation

While our work highlights the link between the gut microbiome and atherosclerosis, there are a number of limitations that should be taken into consideration. Most research' cross-sectional designs make it impossible to determine cause and effect, hence longitudinal and interventional studies are required. The complexity of the gut microbiome makes it difficult to define a consistent "atherosclerosis-associated microbiota profile," as inter-individual variation is still quite high.

Clarifying particular microbial taxa and functional pathways that control atherosclerosis-related activities should be the main goal of future study. Metagenomic and metabolomic investigations can give information on possible biomarkers for early atherosclerosis diagnosis and risk stratification as well as insights into microbial-host interactions. Additionally, extensive clinical trials are required to evaluate the security, effectiveness, and long-term consequences of microbiota-based therapies on the development of atherosclerosis and cardiovascular outcomes.

4. Conclusion

In conclusion, the impact of the gut microbiota on atherosclerosis has become an exciting research area. Pathogenesis of atherosclerosis is influenced by immunological activation, inflammation, and metabolic disturbances brought on by dysbiosis. Innovative microbiome-targeted medicines have the potential to

revolutionize the treatment of cardiovascular disease as our understanding of the subject advances. Researchers, medical professionals, and microbiologists must work collaboratively in order to effectively utilize the gut microbiome's potential to battle atherosclerosis and its dire consequences.

5. Source of Funding

None.

6. Conflict of Interest

None

References

1. Jonsson AL, Bäckhed F, 1, . Role of gut microbiota in atherosclerosis. *Nat Rev Cardiol*. 2017;14(2):79–87.
2. Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, et al. The gut microbiota as an environmental factor that regulates Fat storehouse. *Proc Natl Acad Sci USA*. 2004;101(44):15718–23.
3. Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. *Proc Natl Acad Sci U S A*. 2005;102(31):11070–5.
4. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An rotundity- associated gut microbiome with increased capacity for energy crop. *Nature*. 2006;444(7122):1027–31.
5. Cho I, Yamanishi S, Cox L, Methé BA, Zavadil J, Li K, et al. Antibiotics in early life alter the murine colonic microbiome and obesity. *Nature*. 2012;488(7413):621–6.
6. Shen X, Li L, Sun Z, Zang G, Zhang L, Shao C, et al. Gut Microbiota and Atherosclerosis—Focusing on the Plaque Stability. *Front Cardiovasc Med*. 2021;8:668532. doi:10.3389/fcvm.2021.668532.
7. Barrington W, Lusis AJ. Association between the gut microbiome and atherosclerosis. *Nat Rev Cardiol*. 2017;14(12):699–700.
8. Tang WH, Kitai T, Hazen SL. Gut Microbiota in Cardiovascular Health and Disease. *Circ Res*. 2017;120(7):1183–96.
9. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med*. 2013;19(5):576–85.
10. Senthong V, Wang Z, Fan Y, Wu Y, Hazen SL, Tang WHW, et al. Trimethylamine N-Oxide and Mortality Risk in Patients With Peripheral Artery Disease. *J Am Heart Assoc*. 2016;5:e004237. doi:10.1161/JAHA.116.004237.
11. Chen S, Henderson A, Petriello MC, Romano KA, Gearing M, Miao J, et al. Trimethylamine-N-oxide binds and activates PERK to promote metabolic dysfunction. *Cell Metab*. 2019;30(6):1141–51.
12. Cao H, Zhu Y, Hu G, Zhang Q, Zheng L. Gut microbiome and metabolites, the future direction of diagnosis and treatment of atherosclerosis? *Pharmacol Res*. 2023;187:106586. doi:10.1016/j.phrs.2022.106586.
13. Singh RK, Chang HW, Yan D, Lee KM, Ucmak D, Wong K. Influence of diet on the gut microbiome and implications for human health. *J Transl Med*. 2017;15(1):73.
14. Kim ES, Yoon BH, Lee SM, Choi M, Kim EH, Lee BW, et al. Fecal microbiota transplantation ameliorates atherosclerosis in mice with C1q/TNF-related protein 9 genetic deficiency. *Exp Mol Med*. 2022;54(2):103–14.
15. Jie Z, Xia H, Zhong SL, Feng Q, Li S, Liang S, et al. The gut microbiome in atherosclerotic cardiovascular disease. *Nat Commun*. 2017;8(1):845.

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