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Gut Microbiome as a Novel Cardiovascular Therapeutic Target

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Abstract

Over the last two decades, our understanding of gut microbiotal composition and its association with intra- and extra-intestinal diseases including risk factors of cardiovascular disease (CVD) namely metabolic syndrome and atherosclerosis, have been increased exponentially. A pertinent question which often arises in researchers' community is on how to manipulate the gut microbial ecology to 'cure' the cardiovascular risk factors. Accordingly, in this review we summarized the potential strategies, based on our current knowledge on gut microbiota in modulating CVD, how gut microbiota can be therapeutically exploited by targeting their metabolic activity to alleviate the risk factors of CVD.

Keywords

Microbiota; Atherosclerosis; Metabolic Syndrome; Probiotics; Nutraceuticals; Fecal Bacteriotherapy

Introduction

Centuries ago, Hippocrates recognized the key role of gut in human health and proclaimed that "All Diseases Begin in the Gut". Current research advancement accumulated more evidence to support his assertion specifically, the link between the gut microbiota (GM) and 'New Age' disorders: obesity [1], insulin resistance [2], cancer [3] and neurological complications [4]. The influence of GM on human health are extensive as they modulate the therapeutic response of drugs by altering its metabolism [5] and also dictate host responses to anti-cancer therapeutics [6–8].

Out of 52 known bacteria phyla on earth, only five to seven phyla (predominantly *Firmicutes* and *Bacteroidetes*) colonize the mammalian gut [9]. Microbes colonize the human gut immediately after birth and proliferate to number in the trillions, which vastly outnumbers host cells. The composition of the human GM changes with age; *Proteobacteria*

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predominates in the gut of neonates, but is then substantially reduced from childhood (~16% in neonates) to adulthood (~4.6%) [9]. As a ‘virtual endocrine organ’, the GM performs various metabolic activities that influence host physiology, including stimulating the release of gut hormones such as incretin and peptide YY [10]. The GM can rapidly alter its composition to adapt to changing dietary components [11,12]. These alterations can be adverse as for example, New Age foods rich in calorie with reduced fiber facilitate the aberrant expansion of *Proteobacteria* observed in both inflammatory bowel disease (IBD) and metabolic disorders [9,13]. Notably, augmented *Firmicutes/Bacteroidetes* ratio has been found to be associated with many potential risk factors of CVD [1,9,14].

Although the role of GM on intestinal health has been investigated *ad nauseam*, there is limited information regarding their extra-intestinal effects, especially in CVD. IBD patients appear to have a higher risk for coronary heart disease despite a lower prevalence of 'classical' risk factors, indicating a link between the gut and the heart [15]. It is postulated that such gut-cardiovascular axis could be linked by translocation of bacterial products across ‘leaky’ intestinal barrier into systemic circulation which causes metabolic endotoxemia, resulting in low-grade chronic inflammation [16]. Indeed, microbiota and their metabolites are reported to profoundly modulate atherosclerosis, the most common cause of heart attacks, stroke and peripheral vascular disease [17]. Despite so, the mechanism by which the GM drives atherosclerosis and CVD remains elusive and is currently under active investigation.

Compelling evidences from recent findings on microbiota-obesity-metabolic syndrome axis further unravel the profound influence of GM on the initiation and progression of CVD and its risk factors. In this review, we focus on the current advancements made on delineating the role of GM in CVD and conceptualize the GM-targeted strategies that are actively being explored.

The triad of gut microbiota, metabolic syndrome and cardiovascular diseases

Obesity, insulin resistance, hyperglycemia, hyperlipidemia and hypertension collectively termed as metabolic syndrome, are major risk factors for CVD. Our group have demonstrated that gut dysbiosis induces hyperphagia that culminates in the development of metabolic syndrome in mice lacking the toll-like receptor 5 (TLR5-KO) [18]. The increased mucosal translocation of bacterial LPS in mice supports the hypothesis that metabolic endotoxemia eventuate metabolic syndrome [19]. However, bacterial metabolites are not necessarily 'bad' as for instance, bacteria-derived short chain fatty acids (SCFA: acetate, butyrate and propionate) benefit the host as a source of carbon and energy. Indeed, beneficial effects of SCFA on modulating obesity, appetite and colonic inflammation are well-documented in numerous studies [20••, 21•, 22]. Despite all that, elevated fecal SCFA is positively associated with metabolic syndrome in humans [23,24]. Similarly, we demonstrated that uncontrolled prolonged generation of SCFA by dysbiotic microbiota promotes metabolic syndrome in TLR5-KO mice [18]. These observations are further supported by a recent study which demonstrates the positive correlation between obesity and

the augmented abundance of propionate/acetate producers *Phascolarctobacterium, Proteus mirabilis* and *Veillonellaceae* in high fat diet-fed rats [25].

Atherosclerosis is perhaps the most common cause of cardiovascular complications. Koren *et. al* observed that the amount of bacterial DNA in human atherosclerotic plaques correlates with the extent of leukocytes present in the plaque [26]. Furthermore, elevated plasma cholesterol was found to correlate with alterations in several bacterial taxa from oral cavity and the gut [26]. The identification of dental plague-forming Veillonella and Streptococcus bacterial DNA in atherosclerotic plagues [26] implicated a possible causal role of bacteria in atherosclerosis.

Recent findings from Stanley Hazen and colleagues elegantly describe the role of GM in producing the pro-atherogenic molecule trimethylamine N-oxide (TMAO) [17,27,28••]. Specifically, dietary choline and L-carnitine are metabolized by the GM into trimethylamine (TMA), which is further converted into TMAO by hepatic flavin monooxygenase 3 (FMO3) in the liver [17,27]. Intriguingly, dietary supplementation of choline or TMAO blunts reverse cholesterol transport and augments the formation of foam cells that precede atherosclerosis in mice [17]. The transfer of high TMAO-producing cecal microbiota is sufficient to accentuate atherogenesis in atherosclerosis-prone apolipoprotein E deficient mice [29•]. Further, elevated plasma TMAO levels are also associated with increased risk of major adverse cardiovascular events in humans [28••].

Our current understanding on the interplay between the GM and the risk factors for CVD may be just only the tip of the iceberg. Recent advancements in this exciting area of research have certainly fuel the concept that pharmacological interventions of microbiotal metabolic processes can alleviate CVD risk factors. Accordingly, there have been increasing interests to employ the following GM-targeted strategies to reduce the incidence of CVD:

1. Gut microbiotal metabolism: A potential therapeutic target for CVD

It is not the 'census' but the metabolic activity of the GM that is key in dictating host metabolism. Based on this notion, researchers begin to explore the efficacy of pharmacological intervention that targets specific metabolic activity in the gut. For instance, the aza-analogue of carnitine can be utilized to suppress production of proatherogenic TMAO by shifting microbiotal degradation pattern of dietary quaternary amines [30]. Archaebiotic intervention can be employed by administering *Methanomassiliicoccus luminyensis* B10, an Archea strain that reduces TMA formation in the gut by converting it into an inert molecule [31].

2. Fecal transplantation: resetting your gut microbiota

Fecal microbiota transplantation (FMT) is an intervention designed to displace intestinal pathogens by introducing fecal contents from healthy subjects into the gastrointestinal (GI) tract of patients. Despite being a relatively old concept from the late 1960s [32], FMT has caught much attention specifically in its utility to treat intestinal diseases in the last 5–8 years [33]. Indeed, FMT is demonstrated to be effective in treating recurrent spore-forming *Clostridium difficile* infection in humans [34]. Now, researchers view FMT as an emerging

therapy to manage microbiota-driven extra-intestinal diseases, including obesity and CVD. Remarkably, fecal transplantation from lean to obese humans has been shown to improve insulin sensitivity and plasma triglycerides in the recipients [35]. However, the use of FMT is currently limited due its associated risks including possible transfer of endotoxins or infectious agents [36] that could cause deterioration of existing IBD or appearance of new GI complications [37]. Instead of fecal contents, the transplantation of only a defined group of bacteria (e.g. Altered Schaedler Flora) [38] would be a rational alternative to FMT.

3. Genetically engineered probiotics

The human gut houses an extensive collection of bacteria, many of which exhibit probiotic effects that can be exploited to mitigate the risk factors of CVD. For example, the probiotic bile salt hydrolase-active *Lactobacillus reuteri* strain is clinically-tested to be effective in reducing cholesterol levels via modulating the composition of the bile acid pool [39]. In some studies, probiotic bacteria are genetically modified to further enhance their beneficial effects. N-acylphosphatidylethanolamines (NAPEs)-expressing *E. coli* Nissle 1917 is one such genetically engineered probiotic that can alleviate high fat diet-induced obesity, insulin resistance and hepatosteatosis in mice [40••]. Among other therapeutic target of interest, the intestinal alkaline phosphatase (IAP) is well-known to detoxify bacterial LPS by de-phosphorylating its lipid A moiety [41]. Hence, the use genetically engineered, next generation, probiotics that express IAP could be a feasible strategy to reduce luminal LPS and thus metabolic endotoxemia.

4- Dietary modulation: Nutraceuticals

Among environmental factors, diet robustly alters the composition of GM. Fiber-rich diets (e.g. agrarian diet) promote the growth of beneficial commensal bacteria and consequently limit the growth of opportunistic pathogen [42]. Recognizing the interplay between diets and the GM [12], researchers have initiated the formulation of therapeutic functional foods that can improve gut health. Recently, a study has shown that dietary intervention [whole grains, traditional Chinese medicinal foods, and prebiotics (WTP diet)] resulted in the reduction of opportunistic pathogen *Enterobacteriaceae* and increase in gut barrier-protecting *Bifidobacteriaceae*, with concomitant improvement in insulin sensitivity and lipid profile [43•].

In addition, nutritional compounds such as the inulin-type prebiotics are advocated for their beneficial effects, including promoting the growth of the probiotic Bifidobacteria species in the gut [44,45]. Moreover, co-administration of prebiotic polydextrose and probiotic Bifidobacteria B420 further enhances the efficacy of anti-diabetic drugs in improving glycemic control and insulin resistance in mice [46••].

Bacterial fermentation of prebiotic soluble fiber generates SCFA, which exerts several beneficial effects including amelioration of CVD risk factors [20••, 21•, 22]. SCFA can be exploited therapeutically for cardiovascular benefits but, a long-term study needs to be carried out to evaluate the desirable and undesirable effects of SCFA specifically in diabetics [47] before its recommendation for therapeutic use.

Altogether, such observations raise an intriguing possibility that dietary schemes which either modulate the gut microbial composition or its metabolic activities (e.g. modulating fermentation, targeting iron-chelating siderophore expression) can be a valuable approach to reduce CVD risk [48].

5- Keeping your intestinal flora unaltered: A preventive approach to reduce cardiovascular risk factors

Although therapeutic alterations in gut microbiotal composition can improve host well-being, major abrupt changes within the gut milieu (e.g. intake of antibiotics) can counter-intuitively do more harm than good. Notably, the use of antibiotics in humans during the first six month of life is associated with childhood obesity [49]. Similar results were observed in mice whereby subtherapeutic dose of antibiotics increased adiposity in young mice [50]. Quite surprisingly, ApoE-KO mice fed standard low cholesterol diet and maintained in germ-free conditions develop severe atherosclerosis compared to their conventionally-housed counterparts [51], suggesting that microbiota or their metabolites also mediate protective effects against CVD in a manner akin to a double-edged sword.

Altogether, these observations implicate that therapeutic intervention should not only focused on eliminating disease-causing bacteria, but they also have to preserve the beneficial ones that are central in maintaining well-being. A summary of therapeutic approaches that can be employed to alleviate CVD is shown in the schematic diagram (Fig. 1).

Conclusion

Humans may share more than 99.9% homology in their genes, yet their GM/metagenome can be substantially distinct from one person to another. As the adage goes "we are what we eat", it is not a superfluity to assert that CVD prevention can begin from the gut via manipulating the microbiota. However, most of the studies come from North American and European countries where environmental and health regulations are much stringent than Asian countries like India, Bangladesh and Pakistan. Indeed, a study reported that South Asian migrants appear to have higher risk of CVD than their Europeans counterparts, which provide a great opportunity to explore the possible role of microbiota in cardiovascular health [52]. Yet, the discrepancies between the GM among dissimilar human populations means that a generalized therapeutic approach may not work for all humans. In this regard, personalized medicine that take into account individual GM disposition may set the paradigm by which future therapeutics are designed. The advent of next-generation high-throughput sequencing technology, in addition to inclusion of multiple platforms of meta-‘omics’ analysis (metagenomics, metatranscriptomics, metaproteomics, metabolomics) will further aid such endeavors.

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•Special interest

••Outstanding interest

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Highlights

1. The gut microbiota (GM) plays a key role in host macromolecule metabolism
2. GM generates both pro- and anti-inflammatory metabolites
3. GM metabolism modulation can alleviate risk factors of cardiovascular disease (CVD)
4. Probiotics and fecal microbiota transplantation have potential to reduce CVD

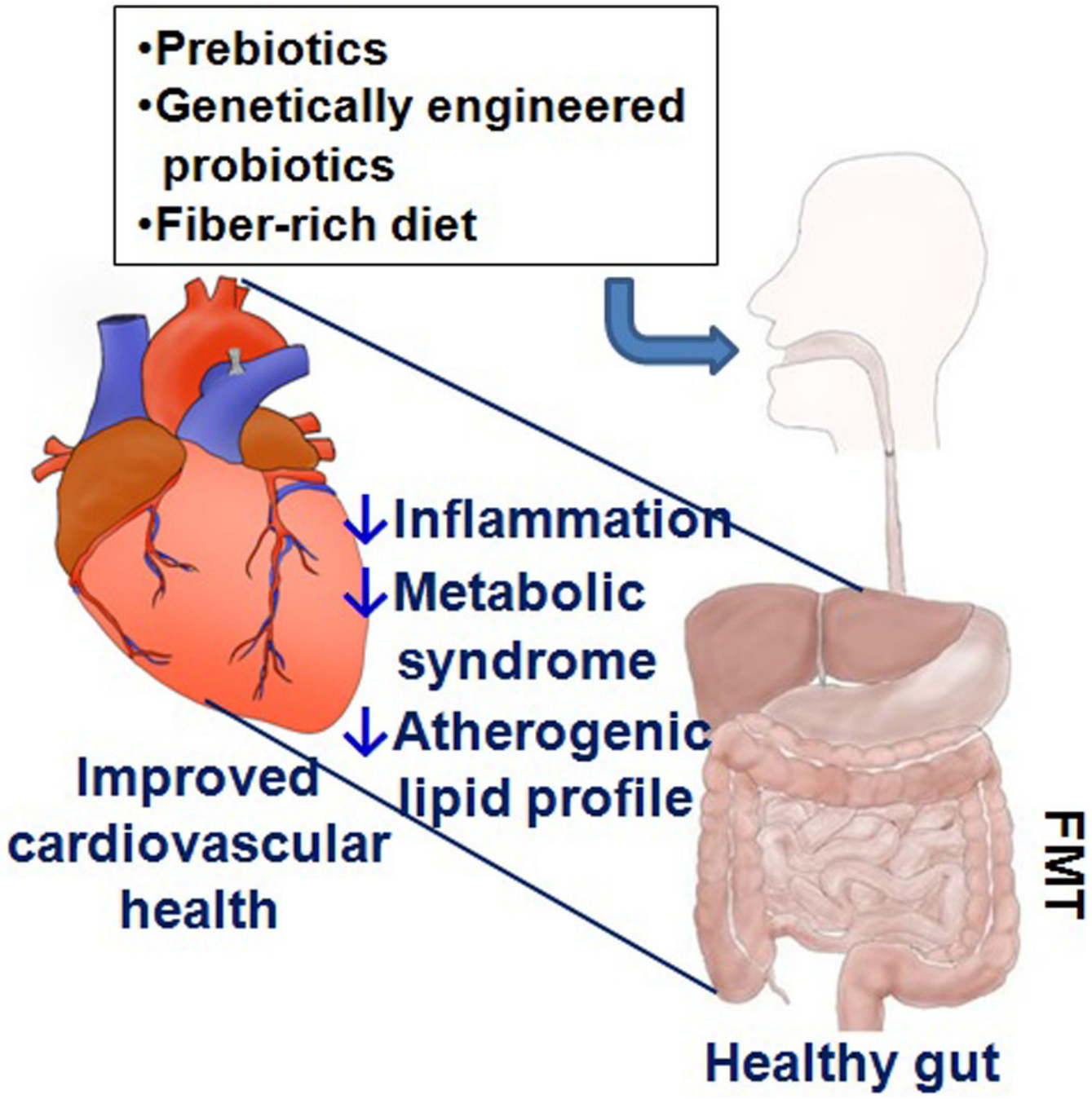

Figure 1. Shaping the gut microbiota for cardiovascular benefits

Selective enrichment, using pre- and probiotics, of beneficial bacteria alleviates major risk factors of cardiovascular disease. FMT: Fecal microbiota transplantation.