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Intestinal microbiota – a possible contributor to cardiovascular diseases?

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ABSTRACT

The intestinal microbiota represents an interesting and emergent field of research, with already known implications in metabolic and immunological functions. Recently, there is increasing evidence that specific gut microbial populations are associated with cardiovascular diseases. Numerous completed and ongoing studies aim to evaluate the potential of intestinal microbiota assessment to improve the prevention, diagnosis, and therapeutic arsenal of cardiovascular diseases, considering dysbiosis as a cardiovascular risk factor. There is strong evidence for a correlation between intestinal flora imbalance and metabolic changes secondary to bacterial metabolites. In this minireview, we discuss recent data about the connections between intestinal microbiota and cardiovascular disease.

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Introduction

Microbial cells are an important part of the human body, surpassing the number of normal cells [1]. Recent findings have shown that microbiota is responsible for multiple metabolic effects, interfering with body functions and creating the predisposition for specific diseases. Thus, in 2007, the Human Microbiome Project was launched by the United States National Institutes of Health to characterize the microbiota and microbe genomics, its role in human physiology and diseases' pathogenesis, opening the door to developing innovative methods to alter microbial flora [2]. However, identification of certain microbial species in some particular diseases does not necessarily demonstrate an etiological relationship with individual health state or specific diseases. Furthermore, the project focused on microbial genomics, protein and metabolite production, and metabolism shifts, based on three longitudinal studies that had evaluated the role of gut microbiota in viral respiratory infections [2].

Studies have demonstrated that changes in gut microbiota composition over the years can interfere with aging processes such as muscular atrophy or a decrease of innate immunity and cognitive impairment, opening the opportunity to investigate the relationship of microbiota phenotypes and frailty [3]. The presence of a microbial population is vital for the human body physiology. However, it was demonstrated that a scarce exposure of the human body to bacterial organisms or antibiotic treatments is implicated in inflammatory dysregulation, linked to metabolic disorders and even to malignant diseases [4-6]. Thus, the current efforts have focused on research for modalities to repopulate the microbial flora, which proved to be efficient in trials, with emerging indications of probiotic bacteria as therapeutic intervention [4-6].

The normal gut microbiota is mainly formed by anaerobic organisms, such as Firmicutes and Bacterioidetes, the dominant families, and also Fusobacteria, Proteobacteria, Actinobacteria, Verrucomicrobia etc. The symbiotic relationship between

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the host and the gut flora represents an important condition for human evolution. An optimal environment for bacterial growth is necessary for nutrient absorption and intestinal barrier, stimulating also the immune system [4].

Some bacterial organisms, such as Lactobacillus strains, induce the production of reactive oxygen species into the intestinal cells, which enter into the redox cascade signaling pathways modulation, stimulating cytoprotective genes, with cellular proliferation and differentiation, hence maintaining the integrity and function of the epithelium [7].

Intestinal bacteria digest the nutrients that the human body is unable to, such as partially and non-digestible polysaccharides (starch and fibers), releasing short fatty chain acids which are absorbed and involved in signaling pathways, metabolism regulation, and the release of satiety hormones (peptide YY, glucagon-like peptide-1) [8]. One significant metabolite is acetate, which demonstrated in murine experiments a decrease of total body fat as compared to a control group [9]. In human subjects, acetate reduced the circulating levels of free fatty acids by decreasing the lipolysis mechanism and improving insulin sensitivity [10]. Butyrate, another bacteria metabolite, has shown a reduction of insulin resistance and body weight in obese mice [11].

The bacterial metabolites also demonstrated an unexpected effect on the immunological response, by mediating the T-cell differentiation into T-cells that produce interleukin 17, interferon-gamma or interleukin-10 through a direct effect on histone enzyme activity, changing the conformation of the DNA-histone complex and gene expression [12]. The short-chain fatty acids decreased the pro-inflammatory response, measured by serum cytokines levels (tumor necrosis alpha) after four weeks of prebiotic and probiotic supplementation [13]. In experimental studies, butyrate decreased the activity of T helper 1 cells and interleukin 2 production, thus explaining the beneficial effects in patients with inflammatory bowel disease [14]. Mainly, the short-chain fatty acids selectively promote immunological tolerance, with an increase of regulating T lymphocytes and decrease of effector T cells [15], influencing even the immune response to other bacterial antigens such as lipopolysaccharide [16].

The commensal bacterial populations survive in niches, producing antimicrobial factors that prevent an invading pathogen to multiply. They ensure that neither one of the populations out-compete the other, and preserve the balance. Besides reactive oxygen species and short-chain fatty acids that are locally produced, bacteria generate bacteriocins, which are antimicrobial peptides released extracellular [17]. The Bifidobacterium strains, for example, produce bacteriocin against Clostridium difficile and Escherichia coli, to ensure competition [18].

Discussions

Gut microbiota and atherosclerosis

Atherosclerosis represents a cardiovascular risk factor, the result of multiple concurring causes. It is responsible not only for coronary artery disease but also for stroke, peripheral artery disease, etc. Atherosclerosis is responsible for the majority of acute coronary syndromes (over 80% of non-ST-segment elevation myocardial infarction, according to the European Society of Cardiology Guidelines) [19].

The microorganisms have been implicated in atherosclerosis since late 1880. Infection with Chlamydia pneumoniae, an intracellular bacterium, induces the transformation of macrophages into foam cells, with leukocyte recruitment, inflammation, and smooth muscular fiber proliferation, leading to atherosclerotic changes in the vascular wall [20]. Porphyromonas gingivalis, a gram-negative, anaerobic Bacteroidetes species, is implicated in periodontal disease and colonic colonization, but it has also been isolated from atherosclerotic lesions in animal models [20]. Intestinal presence of Veillonellaceae species, as part of Firmicutes phylum, has been associated with elevated circulating vascular cell adhesion molecule 1 (VCAM-1) in obese children [21]. Elevated circulating levels of VCAM-1 are correlated with subclinical atherosclerosis and are implicated in monocyte recruitment, hence demonstrating its role in diagnosis and secondary prevention [22].

In murine experiments with apolipoprotein E-deficient knock-out mice predisposed to atherosclerosis, the germ-free group presented increased atherosclerotic plaques compared to mice with a conventional microbiota, even when fed with low-lipid diet. This study strengthened the previous conclusion that commensal flora has a protective role in atherosclerosis [23].

Gut microbiota and inflammation

Microbial products represent potential activators of the host immune system, especially lipopolysaccharides and peptidoglycans that bind to the toll-like receptors (TLR) and nucleotide-binding oligomerization domain [24]. However, not all subgroups of TLR are implicated in atherosclerosis. The absence of some TLRs, such as TLR 2 and TLR 4, decreased the rate of lipid accumulation and monocyte chemotaxis in animal models [8].

In an experimental murine study, after one month of high-fat meals, an increase in circulating levels of lipopolysaccharides was correlated with an increase in insulin resistance and obesity. The result was similar in normal fed mice but with induced endotoxemia. Thus, chronic inflammation produced by bacterial metabolites represents a cornerstone in the pathophysiology of cardiovascular diseases and can explain why gut microbiota may be a cardiovascular risk factor [25].

However, obesity itself is a cause of chronic inflammation, because of immune cells activated by metabolic stress, thus switching to pro-inflammatory cells, with an increase in lymphocytes and macrophages population [26] and alterations of adipocytes such as hypertrophy, ischemia, and adipocytokine production [27-29].

Gut microbiota and cardiovascular disease

Bacterial metabolites are implicated in immune responses, as shown above, but butyrate and beta-hydroxybutyrate were correlated with atherosclerosis inhibition, thus cardiovascular protection [20]. However, other bacterial metabolites, such as trimethylamine (TMA) and trimethylamine N-oxide (TMAO), have demonstrated a pro-atherogenic effect, with the strongest evidence of positive correlation with cardiovascular risk in a trial on 4007 patients during 3 years of follow-up [30,31].

Recently, a cohort study demonstrated that the consumption of processed and unprocessed red meat is associated with an increased risk of cardiovascular disease and all-cause mortality [32]. The mechanism can be explained by the high levels of L-carnitine, phosphatidylcholine, and choline found in red meat, that increase the serum TMAO, hence inducing atherosclerosis by the accumulation of macrophages, alteration of the reverse cholesterol transport, and increase of thrombocytes activity [30,33]. The incriminated bacteria may belong to the Clostridiaceae and Peptostreptococcaeae families [30,34]. However, some molecules counteract the effects of TMA and TMAO production, even in a high-choline diet, such as dimethyl-butanol found in olive oil, grape-seed oil, and red wine [35].

The imbalance of commensal flora, with a predominance of the phylum Firmicutes over Bacteroidetes, was associated with obesity [35]. An increased count of Lactobacillus strains (belonging to the phylum Firmicutes) was found in diabetic patients [30,36], although the reasons are unclear. Consistently, the phylum Bacteroidetes was present at low levels in diabetic patients [30].

Gut microbiota and heart failure

Heart failure is the final stage of evolution of the majority of cardiovascular diseases, such as coronary artery disease, arterial hypertension, etc. Recent studies have evaluated microbiota involvement in heart failure and demonstrated an increase in species like Campylobacter, Shigella, and Candida [36,37]. Intestinal congestion encountered in heart failure is responsible for the intestinal epithelial alteration, with secondary bacterial translocation and persistent endotoxemia that contribute to chronic inflammation and disease worsening [38,39]. Bacterial translocation has been associated with an inflammatory syndrome and an increase of circulating levels of C-reactive protein and interleukin 6 [40-42].

Gut microbiota and arterial hypertension

Consistent with the findings described above, patients with arterial hypertension have increased phylum Firmicutes to Bacteroidetes ratio. Also, short-chain fatty acids have been associated with an increase of Bacteroidetes population in mice and a decrease in blood pressure values, due mainly to the direct stimulation of receptors in renal arteries [43-45].

Conclusions

Gut microbiota and its involvement in cardiovascular diseases represent an emerging field of research that may offer attractive therapeutic options to a large category of patients. The changes in the gut microbiota population are highly correlated with cardiovascular diseases, obesity, diabetes mellitus, and even malignant diseases. The characterization of the microbiota genome and isolation of their metabolites are important steps forward to create new methods of prevention, diagnosis, and improvement of the therapeutic interventions. Lifestyle changes, higher food quality, avoidance of unnecessary antibiotic treatment, and use of pre- and probiotics are universal preventive measures.

Highlights

- ✓ Recent findings have shown that microbiota is responsible for multiple metabolic effects, interfering with body functions and creating the predisposition for specific diseases.
- ✓ There is increasing evidence that specific gut microbial populations are associated with cardiovascular diseases.
- ✓ The characterization of the microbiota genome and isolation of their metabolites are important steps forward to create new methods of prevention, diagnosis, and improvement of therapeutic interventions.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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