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Review

New Aspects on the Metabolic role of Intestinal Microbiota in the Development of Atherosclerosis

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ABSTRACT

Gut microbiota remains a very interesting, yet largely unexplored ecosystem inside the human organism. The importance of this ecosystem for the physiology and the pathophysiology of the organism is being slowly unraveled. Recent studies reveal a connection between intestinal microbiota and atherosclerosis development. It seems that alterations in the function and composition of this bacterial population lead through complex mechanisms to a high risk for atherosclerosis. Although these mechanisms remain largely unknown, published studies show that microbiota can lead to atherosclerosis either by augmenting known risk factors or via other, more "direct" mechanisms. This review article summarizes the available literature regarding this matter.

1. Introduction

Intestinal microbiota is one of the richest bacterial environments inside the human organism. The complexity of this ecosystem is still far from being completely understood and analyzed, although important steps have been made in this direction. It is estimated that the cumulative genome of all these microorganisms contains more than 100 times as many genes as the whole human genome [1]. This microbial population has developed commensal relationships with the human organism, thus providing various physiological benefits in exchange for the tolerance of the immune system. Gut microbiota take part in the fermentation of otherwise non-digestible dietary substances and the control of intestinal epithelial cell proliferation. Moreover, they hold a significant role in the protection of the host against pathogens, and the host immunity in general [2]. It can be speculated that this relationship of mutual benefit between gut microbiota and the host organism strongly depends on a physiological equilibrium, the perturbation of which leads to disease. Indeed, there is evidence that an impaired balance of gut microbiota is associated, for example, with inflammatory bowel disease [3]. On the other hand, the use of probiotics or synbiotics has been reported to significantly reduce complications in the critically ill patients [4].

Atherosclerosis is a major burden of modern society and ischemic heart disease is the leading cause of death worldwide, according to the 2011 report by the World Health Organisation [5]. In the past, there have been several studies suggesting that microbes may play a role in the development of atherosclerosis. Chronic Chlamydia pneumoniae infection and periodontitis have been found to be associated with coronary atherosclerosis [6–8]. Additionally, bacterial translocation from the gut may lead to transient endotoxemia and cell-free DNA circulating in the blood, both conditions being associated with cardiovascular disease [9–11].

Abbreviations: CAD, coronary artery disease; TLR5, toll-like receptor 5; TMAO, trimethylamine-N-oxide; TMA, trimethylamine; FMO3, flavin-containing monooxygenase form 3; DMA, dimethylamine.

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As we will discuss in this review, there is recent evidence on the association of intestinal microbiota with atherosclerotic cardiovascular disease. Although the exact mechanisms are not yet clear, we divide the available literature in two categories according to the mechanism that gut microbes lead to an increased risk of atherogenesis. The first category of studies associates microbiota with atherosclerosis "indirectly" by increasing the risk for obesity and diabetes, which are important risk factors for atherosclerosis. The second category contains studies that have shown a "direct" effect of the microbiota on the risk for the development of atheromatous lesions. Fig. 1 provides a schematic overview of this classification.

2. "Indirect" association of intestinal microbiota with atherosclerosis

Obesity, hyperlipidemia, and diabetes are three important modifiable risk factors for coronary artery disease (CAD) [12]. There has been a lot of scientific evidence that links the intestinal microbiota with these risk factors. Here we present only some important studies that have been conducted in the field; more research on this subject and mechanisms that govern these associations (short chain fatty acids fermentation by the microbiota, low-grade inflammation due to circulating endotoxin etc.) are reviewed elsewhere [13–17]. Gordon et al. have published four important studies concerning the association of intestinal microbiota with obesity, which will be presented, among others, in this section [18–21].

The first of these studies reported that in obese leptin-deficient mice (*ob/ob* mice), the relative abundance of Bacteroidetes in the intestine was 50% less in comparison to lean mice. Moreover, the abundance of Firmicutes was significantly higher in obese mice than in lean ones [21]. Firmicutes and Bacteroidetes represent the most abundant bacterial phyla in the intestine of both humans and mice [21,22]. This shift of the microbiota balance towards Firmicutes in obesity was also observed in humans [18], and the numbers

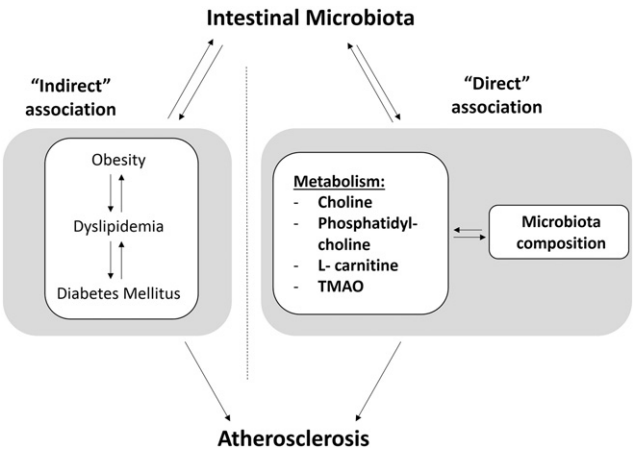

Fig. 1 – A schematic overview of the observed correlations between features of the intestinal microbiota and the development of atherosclerosis, as presented in the text.

of Bacteroides (a genus of the phylum Bacteroidetes) have been found to inversely correlate with body weight in individuals with increased risk for metabolic syndrome [23]. Additionally, low-calorie diets in humans can restore this balance, increasing the proportion of Bacteroidetes and decreasing the proportion of Firmicutes [18]. In a recent study, Kumar et al. analyzed the epigenetic profiles of pregnant women and reported that there is an important association of these profiles with gut microbiota composition [24]. More specifically, this study showed that there is a distinct methylation status of genes implicated in obesity and lipid metabolism in women in which Firmicutes were the dominant microbiota. However, there are studies that do not support the view that there is a relationship between obesity and the proportion of these two major groups of intestinal bacteria [25]. The total number of gut bacteria and/or the relative number of different species of bacteria have been found to be affected by different types of dietary interventions. These interventions also affect total and LDL cholesterol levels, fasting glucose, and insulin levels [26]. This fact also implies a possible complex role for gut microbiota in the pathogenesis of obesity and type 2 diabetes.

Type 2 diabetes has also been linked with altered intestinal microbiota composition [17]. A comparison of intestinal microbiota between humans with type 2 diabetes and non-diabetics showed significant differences in the composition of gut microbiota, and these differences exhibited a correlation with plasma glucose levels. In this case, the ratio of Bacteroidetes to Firmicutes correlated with reduced glucose tolerance and, in contrast to the case of obesity, Bacteroidetes were higher in diabetic persons [27].

Interestingly, transplantation of gut microbiota from normal into germ-free mice (raised in the absence of microorganisms) increased the recipient mice total fat content by 57%, without increasing food consumption. In addition to the increase in fat, there was also an increase in the levels of fasting glucose and insulin. Finally, microbiota was found to promote the storage of energy in the form of triglycerides in adipocytes [20]. These results indicated that, for some reason, the intestinal microbiota may affect the way energy is extracted from food. Indeed, in a subsequent study, it was shown that the microbiota in obese mice is more effective at extracting energy from food in comparison to lean mice [19]. Another similar study was conducted using Toll-like receptor 5 (TLR5) deficient mice. These mice develop features of metabolic syndrome (dyslipidemia, hypertension, insulin resistance, increased total fat) and exhibit changes in intestinal microbiota. After transferring the microbiota from TLR5 deficient mice to wild type germ-free mice, the latter exhibited some features of metabolic syndrome [26].

Most of the studies mentioned in this section show a correlation between gut microbiota composition and risk factors for CAD. In a recently published study, the richness of bacteria in the intestinal microbiota was also found to correlate with markers of cardiovascular disease. In particular, individuals with a low bacterial richness in their gut microbiota were characterized by higher levels of insulin resistance and dyslipidemia in comparison to individuals having a high bacterial richness [28]. Conclusively, it seems that there are various elaborate connections that could lead from obesity, diabetes, and hyperlipidemia to an altered