A New Frontier for Reverse Cholesterol Transport
The Impact of Intestinal Microbiota on Reverse Cholesterol Transport

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Numerous epidemiological studies have demonstrated that high-density lipoprotein cholesterol (HDL-C) levels are inversely associated with cardiovascular risk. However, despite intense efforts to develop new pharmacological strategies to increase HDL-C levels, such as with niacin and cholesteryl ester transfer protein inhibitors, few robust associations with improved clinical outcomes have been observed. This failure of HDL-raising interventions has been accompanied by a shift toward gaining a more rigorous, basic understanding of HDL as a molecule with multiple functions that can be differentiated from simple measures of HDL-C mass. Reverse cholesterol transport (RCT) is a pivotal pathway involved in the return of excess cholesterol from peripheral tissues to the liver for excretion in the bile and eventually the feces. RCT involves the efflux of cholesterol and HDL, the first step of a highly important component of the mechanism of RCT from macrophages in atherosclerotic plaques, are crucial to the antiatherogenicity of HDL. In human studies, it has been shown that the capacity of HDL to promote cholesterol efflux from macrophages ex vivo is inversely related to the risk of cardiovascular disease even after adjusting for HDL-C levels. Furthermore, although niacin treatment raises HDL levels in statin-treated patients, it does not augment cholesterol efflux, which could explain the lack of efficacy of niacin. In view of this, an increasing number of studies have investigated the hypothesis that specific therapies, such as those using recombinant HDL and various drugs, could increase cholesterol efflux and RCT and thereby improve cardiovascular outcomes.

See accompanying article on page 419.

Our microbiota has been linked to intestinal health, immune function, bioactivation of nutrients and vitamins, and recently, complex disease phenotypes, such as obesity and insulin resistance. Interestingly, recent studies in this regard by Wang et al and Tang et al showed that intestinal microbiota to HDL metabolism and development of atherosclerosis. In a mouse model carrying a humanized microbiota, may directly infect the arterial wall have not shown any test the hypothesis that certain microorganisms, such as chlamydia, may directly infect the arterial wall have not shown any cardiovascular benefit. However, if bacterial species responsible for decreasing RCT could be identified and eliminated with selective antibiotics, this would be ideal, therapeutically sufficient, and less disruptive to the intestinal microbiota than broad-spectrum antibiotics.

Another approach is to use probiotics, live microorganisms that either inhibit or promote various species in the intestinal microbiota. In a mouse model carrying a humanized microbiota, administration of a certain probiotic reduced trimethylamine production, whereas another probiotic increased it. Also, previous clinical studies have shown that probiotics improved the low-density lipoprotein/HDL ratio, as well as blood pressure, inflammatory mediators, blood glucose levels and body mass index. It would, therefore, be interesting to investigate the effect of probiotics on HDL metabolism and RCT in humans in future studies.

Although the above findings are extremely provocative, cholesterol profiles in the absence of intestinal bacteria observed in the study by Mistry et al and other previous studies have varied. The authors suggest that the phenotypes observed might depend on diet, genetic background, and the composition of the microbiota. In addition, there are large differences between rodents and humans regarding bile acid and cholesterol metabolism. Furthermore, they do not address a possible effect of intestinal microbiota on atherosclerosis. Therefore, further studies are needed to investigate whether the present findings translate into the clinical setting.
In summary, the study of Mistry et al. focuses on the observation that the absence of intestinal microbiota increases RCT, suggesting that the intestinal microbiota might be a new therapeutic target for enhancing RCT, leading to the prevention of atherosclerosis and cardiovascular disease. However, as mentioned earlier, further studies are needed to see whether their findings in mice translate into the clinical setting in humans. In the light of their study, it would be of substantial interest to determine the impact of intestinal microbiota on RCT in patients with atherosclerotic risk. If such an impact were found, it should then be considered whether specific targeting of intestinal microbiota would improve HDL functionality and cardiovascular outcomes in patients with atherosclerotic risk.

Disclosures

None.

References


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