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Does HDL play a causal role in host defenses against infection?

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Over most of human evolution, two key factors—adequate nutrition and surviving infection—have been critical for passing genes from one generation to the next. Although lipoproteins are known largely for their ability to deliver nutrients, HDL also interacts with macrophages—a key player in both the innate and adaptive immune systems (1,2). HDL can also regulate immune signaling in dendritic cells, megakaryocytes, T-cells, and B-cells, likely by pathways involving receptors in cholesterol-rich plasma membrane.

These observations raise the possibility that HDL is an important regulator of the immune system and host defense mechanisms against invading pathogens (3). Indeed, HDL strongly binds and inactivates lipopolysaccharide, a membrane component of Gram-negative bacteria. It also carries a family of acute-phase proteins linked to inflammation and regulation of the complement system. Moreover, inflammation itself is a potent regulator of HDL's protein composition and function.

Recent clinical studies support the proposal that HDL, quantified as HDL-cholesterol, might be linked to host defense mechanisms. For example, two large, prospective studies of apparently healthy subjects, the Copenhagen City Heart and Copenhagen General Population Study, found that increased risk of infection associated with both low and high HDL-C levels (4).

In this issue of ATVB, Trinder and colleagues determined whether low HDL-C levels could be a causal risk factor for infection (5). They used lipid values from more than 400,000 subjects in the UK Biobank study who had been followed prospectively for 6 to 10 years. Associations of hospitalization rates for infection, antibiotic use, and 28-day survival during sepsis were quantified for HDL-C, LDL-C, and triglyceride levels on entry into the study, using standard statistical methods. Importantly, the authors also constructed polygenic risk scores, using 223 SNVs linked to variations in HDL-C, LDL-C, and triglycerides, and they adjusted for many potential covariates. This approach potentially avoids limitations of epidemiological studies such as confounding covariates and reverse causation.

HDL-C, LDL-C, and triglyceride levels all associated with risk of hospitalization for infectious disease. As others have previously reported, low levels of HDL-C or LDL-C associated with increased risk, as did high levels of triglycerides. Because of the well-established link between high triglyceride levels and low HDL-C levels, the authors repeated the analyses after adjusting for levels of each lipid. The positive association of triglyceride levels with risk disappeared when the analysis was adjusted for HDL-C, but low levels of

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HDL-C remained a risk factor for infection after adjustment for triglyceride levels, strongly implicating HDL-C as the primary risk factor.

To avoid the potential confounding of environmental factors on lipids, the authors next used polygenic risk scores to explore the role of HDL-C, LDL-C, and triglycerides in the risk of hospitalization for infection. The HDL-C polygenic score, but not the LDL-C or triglyceride polygenic score, associated inversely with the risk of hospitalization for infection. However, a low HDL-C polygenic score in the cohort also associated with diabetes, a known risk factor for infection. Importantly, the low HDL-C polygenic score remained significant after the analysis excluded diabetic subjects.

The authors used a 2-step Mendelian randomization procedure to investigate whether the association of the HDL polygenic risk score with infection was potentially causal. This approach demonstrated that a low HDL-C polygenic score associated with increased risk of infection, which was confirmed by a multivariable Mendelian randomization analysis that included adjustment for HDL-C, LDL-C, and triglyceride levels.

As a further test of the relationship between HDL-C and infection, the authors examined the relationship between the polygenic risk scores for HDL-C, LDL-C, and triglycerides and the 28- day survival rate for septic patients. Subjects with a high HDL-C polygenic risk score were significantly more likely to survive their infection, but LDL-C and triglyceride polygenic scores failed to associate with differences in mortality.

These observations provide strong evidence that HDL, quantified as HDL-C, is causally linked to host defense mechanisms against infection. Subgroup analyses suggested that the HDL-C polygenic score associated with protection against bacterial and viral infection, but not with fungal infection.

The links between HDL-C, the HDL-C polygenic risk score and infection raise the exciting possibility that HDL plays an important role in host defense mechanisms against infection. In future clinical studies, it will be important to confirm and extend these observations in other large cohorts with diverse genetic backgrounds. One key question is whether HDL-C itself or some component such as APOA1, the major protein in HDL, is the prime mediator of resistance to infection. Indeed, HDL carries over 80 proteins implicated in acute inflammation, proteolysis, and regulation of the complement system. It will also be critical to uncover potential mechanisms that enable HDL to protect humans against a diverse array of pathogens (6,7), such as suppression of deleterious changes in inflamed tissue and regulation of anti-microbial defense mechanisms.

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