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Genetics and molecular biology: HDL plasticity and diversity of functions

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It has become clear in recent years that one should not consider HDLs as a homogenous entity when studying their functions. It is now indeed recognized and well documented that the HDL pool in the blood is made of a variety of HDL particles that differ in terms of structure, composition and signaling molecules they carry. More than 80 proteins and peptides and more than 200 lipid species have been detected on HDLs [1]. However, a single HDL particle only carry a distinct subset of these molecules. For example, less than 10% of HDL particles carry the bio-active sphingosine-1-phosphate (S1P) lipid [1]. The diversity in the composition of HDLs can potentially explain the variety of their functions ranging from reverse cholesterol transport to antioxidative, anti-inflammatory and cytoprotective activities (reviewed recently in [2]) and [3]).

HDL particles are more plastic and dynamic than initially thought as recently highlighted by O'Neill and colleagues [4] in their study on patients with periodontitis. This human model is of interest because it involves a low-grade inflammation systemic status developing from a local inflammation site (the teeth). The etiology of the inflammation is therefore somehow simpler than what is seen in more complex diseases such as diabetes or the metabolic syndrome. Moreover, this model allows researchers to study the impact of low-grade inflammation in individuals that serve as their own controls after periodontitis is treated. In this study, periodontitis led to disturbed HDL vascular functions such as diminished paraoxonase activity and reduced ability to induce NO production by endothelial cells. Intriguingly, the cholesterol extraction capacity of HDLs was not affected by periodontitis, suggesting that only a subset of HDL functions and activities are affected by low-grade inflammation. While this study is in line with others (see [5-7] for recent publications) that showed disease-induced alterations in HDL functions, its salient point is that low-grade inflammation-associated perturbations in HDL functions and composition could be fully normalized with the resolution of the disease. Hence, HDLs are very plastic particles whose functions are dynamically regulated by transition between healthy and disease states.

Two recent studies by the group of Timothy Hla [8;9] demonstrated the importance of the structure and molecules that carry S1P in the responses elicited by this lipid in cells and

tissues. In the blood, about two third of the S1P molecules are bound to ApoM, an apolipoprotein present in about 10% of HDL particles [1], while the remaining molecules are associated with albumin. HDL-S1P was shown to bind to the S1P₁ receptor on endothelial cells and to activate a protective anti-inflammatory and anti-atherosclerotic signals in the vasculature [8]. Surprisingly, S1P bound to albumin did not generate these protective responses, despite being able to activate S1P₁. The resolution of this conundrum came through detailed investigation of the signaling pathway activated by albumin-S1P and HDL-S1P: at similar S1P concentrations (1-2 μ M), both albumin-S1P and HDL-S1P stimulated the MAPK pathway efficiently but albumin-S1P triggered greater G_i activation and receptor endocytosis, whereas only HDL-S1P induced the formation of a S1P₁- β -arrestin-2 complex that attenuated pro-inflammatory cytokine signaling. In a different experimental system, the same group reported that HDL-S1P, but not albumin-S1P, kept in check lymphopoiesis and, in a mouse model of autoimmune encephalitis, restrained the development of self-reacting lymphocytes [9]. These two studies open the possibility that ApoM-containing HDL particles “present” S1P to S1P receptors in a manner different than when S1P is carried by other carriers. As suggested by the authors, HDL-S1P may in fact act as a biased agonist for S1P receptors. How this is structurally and mechanistically brought about will now need to be characterized.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

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8. •Galvani S, Sanson M, Blaho VA, Swendeman SL, Conger H, Dahlback B, Kono M, Proia RL, Smith JD, Hla T: **HDL-bound sphingosine 1-phosphate acts as a biased agonist for the endothelial cell receptor S1P1 to limit vascular inflammation.** *Sci.Signal.* 2015, **8**:ra79.

In this article, the role of the S1P receptor 1 in vascular pathology was investigated. The expression of sphingosine-1-phosphate (S1P) receptor 1 on the plasma membrane of aortic endothelial cells was found to be inversely correlated with inflammatory adhesion molecule abundance. This is an indication that S1P signaling in the vasculature dampens inflammation. Interestingly, the vasculature protective function of S1P occurred when this ligand was bound to ApoM-positive HDL particles but not when it was bound to albumin. Hence, an intriguing finding of this paper was that S1P signaling is modulated by its carrier.

9. ••Blaho VA, Galvani S, Engelbrecht E, Liu C, Swendeman SL, Kono M, Proia RL, Steinman L, Han MH, Hla T: **HDL-bound sphingosine-1-phosphate restrains lymphopoiesis and neuroinflammation.** *Nature* 2015, **523**:342-346.

This study extends some of the notions highlighted in ref. 8 and, importantly, characterizes a new function for HDLs. The authors discovered that S1P, when bound to ApoM-positive HDLs, but not when bound to albumin, acts as a negative regulator of lymphocytes differentiation

and proliferation. In the absence of S1P signaling in bone marrow progenitors, lymphopoiesis was augmented and this worsened neuroinflammation in a model of experimental autoimmune encephalomyelitis. Apparently therefore, S1P₁ receptor activation by HDL-S1P in lymphocyte progenitors participates in the maintenance of an adequately sized lymphocyte compartment.

FURTHER RECOMMENDED READING

Schwendeman A, Sviridov DO, Yuan W, Guo Y, Morin EE, Yuan Y, Stonik J, Freeman L, Ossoli A, Thacker S, Killion S, Pryor M, Chen YE, Turner S, Remaley AT: **The effect of phospholipid composition of reconstituted HDL on its cholesterol efflux and antiinflammatory properties.** *J.Lipid Res.* 2015, in press.

Apolipoprotein A1, one of the major protein present in HDL particles, has long been recognized as having anti-inflammatory and anti-apoptotic properties. This study shows for the first time that the type of phospholipid used to reconstitute HDL particles from ApoA1 has significant influence on the reconstituted HDL (rHDL)-mediated protective effects. Hence, the phospholipids present in the “membrane” of HDLs particles are not just fulfilling a structural role in HDLs but also actively participate in the biological functions of the particles.