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High Density Lipoproteins Put Out the Fire

Kathryn J. Moore[1] and **Edward A. Fisher**[1,*]

[1]Marc and Ruti Bell Vascular Biology and Disease Program, Leon H. Charney Division of Cardiology, Department of Medicine, New York University School of Medicine, New York, NY 10016, USA

Abstract

Macrophages in atherosclerotic plaques are activated, inflammatory cells that directly contribute to the disease process. De Nardo et al. (2013), now report that high density lipoproteins (HDL) can re-program macrophages to be less inflammatory through an ATF-3-dependent pathway, providing another mechanistic basis for the athero-protective properties of HDL.

Atherosclerosis is commonly referred to as an inflammatory disease. The key player in the early phase of inflammation in plaques is the foot soldier of the innate immune system, the macrophage. These cells become activated in the arterial wall in response to uptake of lipoproteins containing apolipoprotein B, such as low and very low density lipoproteins (LDL, VLDL) (Tabas et al., 2007). The cholesterol carried by these lipoproteins causes the macrophages to become engorged “foam cells”, which become trapped in the arterial intima, establishing the inflammatory milieu of the plaque. The failure to resolve this inflammation is thought to culminate in “vulnerable” atherosclerotic plaques, which are prone to rupture, leading to heart attacks and strokes. Inflammatory mediators (IL-1β, TNFα, and MCP-1, etc.) secreted by macrophage foam cells following the stimulation of innate immune receptors such as Toll-like receptors (TLR), or via inflammasome pathways, have adverse effects on the other two major cell types in the plaques, endothelial and vascular smooth muscle cells. Furthermore, dying macrophage foam cells contribute to the formation of the necrotic core, which is enriched in cholesterol, inflammatory substances and tissue factors, and is a hallmark of vulnerable plaques. Thus, factors that either impede the escalating inflammation process or reverse it may make it possible to derail the march to a clinical event. It is in this context that the studies by Latz and colleagues fall, by showing how HDL may be a fire prevention or extinguishing agent through stimulating an anti-inflammatory pathway in macrophages that is dependent on the transcription factor ATF3 (De Nardo et al., 2013).

De Nardo et al. began by investigating the effects of HDL on the activation of macrophages by TLRs *in vitro*. First, they confirmed previous studies (e.g., Yvan-Charvet et al., 2008), showing that HDL treatment reduced the inflammatory responsiveness of the macrophages to TLR stimulation. For this purpose, they focused on TLR1, 2 and 9 (chosen because they had been implicated in previous studies in atherosclerotic mice), using accepted ligands for each. They found that the anti-inflammatory effects of HDL were independent of HDL binding of TLR ligands and did not involve the classical early signaling downstream of the

*Correspondence:edward.fisher@nyumc.org.

TLRs. They also found that in contrast to Yvan-Charvet et al., there was no evidence that the impaired TLR responsiveness resulted from HDL-mediated depletion of cholesterol from plasma and endosomal membranes. Although different TLRs were investigated in the two studies, each used ligands to activate TLR signaling at both the cell surface (TLR2 and TLR4) and intracellularly (TLR3 and TLR9), so this cannot explain the divergent outcomes. One possibility for this discrepancy could be the lack of the cholesterol efflux factors ABCA1 and ABCG1 in the experimental system of the previous study, resulting in altered membrane lipid composition and microenvironments.

Still searching for an explanation for the effects of HDL on TLR responsiveness, De Nardo et al. turned their attention to the decreases they noted in the mRNAs for numerous cytokine genes including *Il6*, *Il12p40* and *Tnfa*, suggesting a transcriptional mechanism induced by HDL. In a key experiment, the authors performed microarray profiling of HDL-treated macrophages and, through bioinformatics analyses, identified an enrichment in genes regulated by the transcription factor ATF3. ATF3 has been proposed to act as a negative regulator of transcription through its ability to recruit co-repressors, such as histone deacetylase 1, which are thought to promote a closed chromatin conformation at target gene promoters. The authors confirmed that HDL treatment of bone marrow-derived macrophages increased expression of *Atf3* mRNA and protein, and showed ATF3 binding at promoters of cytokine genes down-regulated by HDL. Finally, they used ATF3-deficient mice to show that the HDL-mediated suppression of inflammatory mediator production was dependent on ATF3 *in vitro* and *in vivo*. Overall, the data support a mechanism for anti-inflammatory effects of HDL on macrophages exposed to stimuli resembling those they are likely to encounter in normal and disease states.

HDL is thought to dampen inflammation in the atherosclerotic plaque via multiple mechanisms: e.g., it reduces cellular cholesterol levels, has anti-oxidant effects, inhibits platelet aggregation, and suppresses the proliferation of hematopoietic progenitor cells. In mouse models of atherosclerosis, an increase in functional HDL particles has been reported to reduce the expression in plaque macrophages of inflammatory mediators, an effect similar to that in De Nardo et al., but also to increase the expression of markers of the anti-inflammatory M2 state (Feig et al., 2011; Rayner et al., 2011). Consistent with this latter effect is the recent report that *in vitro*,HDL induces markers of the M2 state in macrophages (Sanson et al., 2013). Although the current study did not examine the effect of ATF3 on plaque macrophages or M2 polarization, the authors did show beneficial effects of HDL on carotid artery re-endothelialization in hypercholesteromic$Apoe^{-/-}$ mice. These protective effects of HDL on carotid injury were driven by ATF3-mediated reduction of macrophage inflammation. Despite these benefits, the resemblances between atherosclerosis and the arterial injury model, which has been likened to a form of accelerated atherosclerosis, are superficial, with many aspects varying from the authentic disease. Thus, a more physiological test of the impact of ATF3 and its regulation by HDL on gene expression in macrophage foam cells of the atherosclerotic plaque awaits. In summary, the current study represents an important advance in the conceptual understanding of the anti-inflammatory effects of HDL. While the authors note how these findings may aid in predicting the clinical benefits of HDL-based therapies by detailing the mechanisms for the effects of HDL on ATF3, it may also be possible for small molecules or other convenient agents to accomplish the same anti-inflammatory effects without having to administer or raise the number of functional HDL particles. Thus, there ultimately may be a number of ways to harness the fire-fighting properties of HDL, with the potential application to inflammatory diseases beyond atherosclerosis.

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