Response by Fotakis et al to Letter Regarding Article, “Anti-Inflammatory Effects of HDL (High-Density Lipoprotein) in Macrophages Predominate Over Proinflammatory Effects in Atherosclerotic Plaques”

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In Response:

It is now clear that HDL (high-density lipoprotein) can induce both anti-inflammatory and proinflammatory effects in activated macrophages. The letter by Biessen et al addresses the important issue of whether HDL’s proinflammatory or anti-inflammatory effects predominate in macrophages in lesions of atherosclerosis. Our recent study confirmed that HDL can exert proinflammatory effects in lipopolysaccharide-stimulated macrophages, consistent with a previous study by van der Vorst et al. The proinflammatory effects of HDL in macrophages occur late (after 2 hours) and are dependent on the cellular cholesterol content and cholesterol efflux. However, our studies clearly demonstrate that HDL also exerts anti-inflammatory effects in the same macrophages, responses that are likewise dependent on cholesterol efflux, and that the proinflammatory and anti-inflammatory effects of HDL are mediated through distinct signaling pathways. Biessen et al suggest that mechanisms of proinflammatory effects could be complementary in the two studies; however, we were not able to show a specific role of PKC (protein kinase C) signaling in inflammatory responses to HDL as they suggested. We used rHDL (reconstituted HDL; CSL-111; provided by CSL Behring), which consists of human APOA1 and phosphatidylcholine at a 1:150 ratio, as well as nHDL (native HDL) isolated from human APOA1-transgenic mice. Both HDL preparations had similar effects, mediated through the same mechanism (cholesterol efflux), and lipopolysaccharide-stimulated resident peritoneal macrophages from human APOA1-transgenic mice exhibited an increased inflammatory response similar to that of macrophages incubated with rHDL followed by lipopolysaccharide in vitro. Thioglycollate-elicited sorted peritoneal macrophages from these mice also exhibited both proinflammatory and anti-inflammatory responses after lipopolysaccharide stimulation, similar to the in vitro findings (V. Kothari and K. E. Bornfeldt, unpublished data, 2019). Moreover, our study is consistent with the notion that the anti-inflammatory effects of rHDL predominate over proinflammatory effects in CD11b-positive cells in lesions of atherosclerosis (primarily lesional macrophages). Biessen et al suggest that different properties or concentrations of rHDL versus nHDL could have explained the lack of proinflammatory effects of rHDL in lesional CD11 b+ cells. Although this cannot be completely ruled out, ample data from human APOA1-transgenic mice and mice with liver-directed gene transfer of human APOA1 show that these mice are protected from atherosclerosis, as compared with wild-type controls, and that lesional macrophages are fewer and appear to exhibit a reduced inflammatory phenotype, at least under diabetic conditions. Native HDL, therefore, has atheroprotective and anti-inflammatory effects in lesional macrophages in mice. A more likely explanation for the lack of proinflammatory effects of rHDL in lesional macrophages might be (1) that the highly activated inflammatory state of toll-like receptor-stimulated macrophages needed to bring out the proinflammatory effects of HDL does not mimic the environment in the atherosclerotic lesion and (2) that the levels of cholesterol efflux required to induce proinflammatory effects cannot be obtained in the cholesterol-rich environment of the atherosclerotic plaque. We fully agree that further studies are needed to clarify the actions and properties of different HDL populations in various inflammatory conditions and cell types in vivo in animal models and humans.

ARTICLE INFORMATION

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Disclosures
A.R. Tall reports being a consultant to Amgen, CSL, Staten Biotechnology, Fortico Biotech, and Janssen Pharmaceuticals. K.E. Bornfeldt reports receiving research support from Novo Nordisk A/S on an unrelated project. The other authors report no conflicts.

REFERENCES