The interplay between serum amyloid A and HDLs

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Accumulating evidence [1▪] indicate that serum amyloid A (SAA) is not merely a biomarker for atherosclerosis and related diseases but also plays a causal role in the development of these diseases, mainly due to its pro-inflammation function. HDLs have well known antiatherosclerosis effects. A recent article [2▪] further characterized the protective role of HDLs on SAA-induced atherogenesis in ApoE-deficient mouse, a widely established model of atherosclerosis. The authors of this study demonstrated earlier [3] that ApoE$^{-/-}$ mice treated with recombinant human SAA exhibited pro-inflammatory and pro-thrombotic phenotypes. In their new article [2▪], these authors tested ApoE$^{-/-}$ mice that were preincubated with human HDLs prior to the administration of SAA to further investigate the beneficial effects of HDLs. The results showed that HDLs pretreatment in both acute and chronic tissue inflammation response models inhibited the ability of SAA to stimulate pro-atherogenic changes, including deposition of vascular cell adhesion molecule 1 (VCAM-1) on the endothelium (a relevant marker for early atherogenesis), increased oxidative damage, elevated inflammatory cytokines and chemokines expression in aortic vessels and heart tissue. HDLs alleviated SAA-triggered renal injury and inflammation as well. The HDL protective function might be attributable to SAA–HDL interaction. Due to SAA's lipophilicity, SAA can be trapped by lipoproteins. Moreover, lipidated-SAA in plasma is mainly associated with HDLs, consistent with the notion that HDLs sequester circulating SAA to suppress its activities.

In vitro studies have shown that SAA could stimulate inflammation in its lipid-free state but not when bound to HDLs [1▪], which provides strong indication that SAA lipidation is modulating its biological function. But the formation process of SAA-containing HDLs is still incompletely understood. Another recent article [4▪] investigated the lipidation of SAA by using hepatocytes and how this lipidation relates to the formation of nascent HDL particles, as well as the clearance of SAA. SAA was induced by LPS or by an SAA-expressing adenovirus in mice. Primary hepatocytes were then isolated and used to evaluate the extent of lipidation of circulating SAA. As for the ApoA-I apolipoportein, lipidation of SAA is mediated by the ABCA1 transporter, but not by the SR-BI HDL receptor. One of the first steps in HDL biogenesis is the lipidation of ApoA-I, which leads to the formation of nascent HDLs. However, both endogenous and exogenous SAA did not alter the amount and the size distribution of lipidated ApoA-I. Lipidated SAA and ApoA-I are not present on the same nascent particles, which suggests that SAA is not incorporated into newly synthesized HDLs. Consequently, SAA-containing HDLs might be formed through modification of preexisting/mature HDLs. SAA might replace ApoA-I to become the major HDL-associated apolipoprotein during an acute-phase response, possibly through its ability to move from non-HDL lipoproteins to HDL particles [5▪]. In addition, SAA association could promote HDLs degradation. The enrichment of SAA on HDLs has been shown to impair its anti-inflammatory properties as well [6].

HDLs, as SAA carriers, can hamper the latter from exerting its pro-inflammatory activities; in return, SAA, as an apolipoprotein, can change the characteristics of HDL particles. Understanding the dual/mutual relationship between the respective functions of SAA and HDLs will help define their physiologic roles as well as their contribution to the pathophysiology of atherosclerosis. Understanding the relationships between HDLs and its binding proteins will be essential for the development of novel HDL-targeted therapies to treat atherosclerosis and cardiovascular diseases.

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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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A comprehensive review on SAA's potential roles in atherosclerosis.

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4. Ji A, Wang X, Noffsinger VP, *et al.* Serum amyloid A is not incorpo- ■ rated into HDL during HDL biogenesis. J Lipid Res 2020; 61: 328–337.

This work established that the lipidation of SAA is not related to nascent HDL biogenesis *in vitro* and confirmed, in hepatocytes, that the ABCA1 transporter, but not the scavenger receptor SR-BI, mediates SAA lipidation.

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