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EDITORIAL

Induction of Autophagy: A Novel Anti-inflammatory Function of High-Density Lipoprotein

The inverse relationship between plasma high-density lipoprotein (HDL) cholesterol levels and the risk for development of atherosclerotic cardiovascular disease has led to extensive studies of HDL and its major apoprotein apolipoprotein A-I (apoA-I) with respect to their antiatherogenic role. The ability of HDL and apoA-I to promote the efflux of cholesterol from cells in peripheral tissues, including macrophages in atherosclerotic plaques, and to transport the cholesterol to the liver for excretion via biliary secretion is considered their major atheroprotective role. However, HDL and apoA-I also have other functions that impact cardiovascular disease and other disorders, including diabetes, autoimmune dysfunction, and neurodegeneration. The activities of HDL are derived from its antioxidant, anti-inflammatory, and antiapoptotic properties.

Much of the anti-inflammatory effect of apoA-I and HDL is thought to be mediated by modulation of the cholesterol content of membrane lipid rafts due to their promotion of cholesterol efflux via ATP-binding cassette subfamily A member 1 (ABCA1), ATP-binding cassette subfamily G member 1 (ABCG1), and scavenger receptor class B type I (SR-BI). The article in this issue of *Cellular and Molecular Gastroenterology and Hepatology* by Gerster et al[1] has demonstrated that HDL also protects the colon from inflammation, providing insight into a novel mechanism by which HDL exerts its anti-inflammatory effect.

Using apoA-I knockout and transgenic mouse models, the investigators have demonstrated a protective effect by HDL/apoA-I on colitis induced by dextran sodium sulfate or 2,4,6-trinitrobenzenesulfonic acid. In vitro studies using pharmacologic manipulations or genetic knock down in a colonic epithelial cell line indicate that HDL and apoA-I induce autophagy via inhibition of the mammalian target of rapamycin (mTOR), a negative regulator of autophagy, that leads to the trafficking of phosphorylated IκB kinase (p-IKK) to the autophagosome for degradation and the consequent attenuation of nuclear factor κB (NF-κB)-mediated expression of proinflammatory genes. The anti-inflammatory role of the induction of autophagy by HDL was further confirmed using mucosal fibroblasts from patients with a Crohn's disease polymorphism of the autophagy-related gene *ATG16L1*.

Although HDL has been shown to interfere with NF-κB-mediated transcription of proinflammatory genes, the molecular mechanisms are not well understood. This study identifies the induction of autophagy by HDL and the recruitment of p-IKK, which is necessary for the activation of NF-κB, to autophagosomes as a novel mechanism mediating the anti-inflammatory function of HDL. The induction of autophagy by HDL is somewhat surprising. Several studies have implicated HDL/apoA-I in the activation of the phosphoinositide 3-kinase/protein kinase B (PI3K-Akt) pathway via SR-BI or sphingosine-1-phosphate (S1P) receptors. Because PI3K-Akt is a positive regulatory of mTOR, it might have been anticipated that HDL would inhibit autophagy.

What mechanism(s) may be involved in the induction of autophagy by HDL, and why should HDL induce autophagy? The study by Gerster et al suggests that the HDL induction of autophagy is independent of the promotion of cellular cholesterol efflux. HDL attenuation of tumor necrosis factor-mediated inflammation in T84 colonic epithelia was not affected by small interfering RNA (siRNA)-mediated down-regulation of SR-BI and ABCG1 expression, the two major proteins mediating efflux to HDL. Although apoA-I is the major apoprotein on HDL, recent proteomic and lipidomic analyses have revealed that HDL contains a diverse protein content and contains a number of minor bioactive lipids, including sphingosine-1-phosphate, that function in signaling pathways. One or more of these proteins or lipid cargo may interact with cell surface or intracellular receptors.

An intracellular function cannot be ruled out, as HDL was shown to be localized in autophagosomes. Thus, the induction of autophagy may function to bring important protein components of HDL, such as enzymes capable of degrading oxidized lipids, or bioactive lipids into the cells, which in turn may contribute to the decrease in cellular inflammation.

Interestingly, lipid-free apoA-I also attenuated the tumor necrosis factor-mediated inflammation. This might argue that all of the signaling mediated by HDL may be via apoA-I and not by its lipid or other protein cargo. However, lipid-free apoA-I mediates cholesterol efflux via interaction with ABCA1 not ABCG1 or SR-BI. Because the small interfering RNA (siRNA)-mediated ABCA1 knock down in T84 cells was not efficient, cholesterol efflux cannot be completely excluded as a mechanism of apoA-I anti-inflammatory activity.

Finally, the investigators demonstrate that increases induced by dextran sodium sulfate or 2,4,6-trinitrobenzenesulfonic acid in mucosal myeloperoxidase (MPO) activity are attenuated in apoA-I transgenic mice. Given that MPO can act on apoA-I and impairs apoA-I and HDL function, it is intriguing to speculate that MPO-mediated modifications may trigger HDL trafficking to the autophagosome and autophagy, resulting in clearance of these functionally impaired HDL particles and making way for intact HDL to reduce inflammation.

The study by Gerster et al[1] demonstrates a novel mechanism mediating the anti-inflammatory effect of HDL, namely, via the induction of autophagy and the trafficking of

p-IKK to the autophagosomes. Their work also demonstrates that HDL has a role in modulating inflammation in the colon. Although further mechanistic studies are needed, this study has added to the complexity of HDL functions.

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Reference

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