Liver X Receptors and Atherosclerosis
It Is Not All Cholesterol
Irena D. Ignatova, Ira G. Schulman

A critical event in the development of atherosclerosis is the recruitment of macrophages to the underlying epithelial layer of blood vessel walls and the uncontrolled uptake of oxidized/modified cholesterol. Continued accumulation of oxidized/modified cholesterol by macrophages and an associated inflammatory response leads to foam cell formation and the initiation of atherosclerosis. Reversing the process of macrophage cholesterol accumulation and inhibiting inflammation in the blood vessel wall have been held out as potential novel treatments for atherosclerosis; however, other than injectable forms of apolipoprotein A1, no drugs that either enhance macrophage cholesterol efflux or inhibit inflammation have been validated in the clinic for the treatment of cardiovascular disease. The liver X receptors (LXRα and LXRβ), members of the nuclear hormone receptor superfamily of ligand-activated transcription factors, are promising drug targets for treating atherosclerosis because they regulate cholesterol efflux from macrophages at the transcriptional level and exert anti-inflammatory activity.

The efflux of cholesterol from macrophages to lipid-poor apolipoprotein A1 and high-density lipoprotein is mediated by the ATP-binding cassette transporters A1 and G1. Both genes are directly regulated by LXRs, and it is widely assumed that the atheroprotective effects of synthetic LXR agonists are caused by increased macrophage cholesterol efflux via the upregulation of these 2 genes. Indeed, bone marrow transplantation experiments indicate that LXR activity in macrophages is required for the atheroprotective action of LXR agonists. A recent study by Zhang et al., however, indicated that LXR agonists could be antiatherogenic without stimulating macrophage cholesterol efflux, calling into question the contribution of cholesterol metabolism in other tissues. Future studies are needed to further define the tissue-specific activities of the LXRs and the genetic networks they control should help to better clarify the role of LXRs in atherosclerosis.

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References


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