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 transport to LXR activity.

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Kappus et al. now add another nail to the coffin of the LXR-cholesterol efflux hypothesis. In this new work, the authors demonstrate that LXR agonist treatment in mice with hematopoietic- or macrophage-specific deletion of ATP-binding cassette transporter A1 and ATP-binding cassette transporter G1 reduces atherosclerosis to a degree comparable with control mice, an effect independent of cholesterol efflux because macrophages lacking ABC transporters are unable to efflux cholesterol in an LXR-dependent manner. If not cholesterol efflux, what then is the mechanism of LXR agonist–dependent antiatherogenic activity? Like many nuclear receptors, LXRs also inhibit inflammation in an agonist-dependent manner by interfering with the activity of nuclear factor-κB. Kappus et al. demonstrate that the anti-inflammatory effects of LXR agonist treatment are preserved in Abca1−/−/Abcg1−/− macrophages in vitro and in vivo. Taken together, the studies tilt the LXR seesaw strongly in the direction of inhibiting inflammation and away from macrophage cholesterol transport.

Along with regulating genes involved in macrophage cholesterol efflux, treatment with LXR agonists promotes triglyceride synthesis by upregulating the gene encoding the sterol regulatory element–binding protein 1c, the master transcriptional regulator of fatty acid synthesis. Consequently, hepatic steatosis has been observed in multiple species treated with LXR agonists, slowing the movement of these compounds to the clinic. The work described by Kappus et al. adds weight to the potential therapeutic use of LXR ligands that retain anti-inflammatory activity in macrophages but that do not positively upregulate target genes such as ATP-binding cassette transporter A1 and sterol regulatory element–binding protein 1c. Based on this new study, such ligands would be predicted to reduce atherosclerosis without promoting lipogenesis. Molecular studies have suggested that inhibition of inflammatory gene expression by LXRs (transrepression) is mechanistically distinct from the transactivation of target genes such as ATP-binding cassette transporter A1 and sterol regulatory element–binding protein 1c, raising the possibility that such dissociated or pathway-selective LXR ligands could be identified. Recent studies, however, suggest that LXR anti-inflammatory activity largely arises from the production of anti-inflammatory fatty acids in macrophages, making it difficult to imagine how anti-inflammatory activity could be easily dissociated from lipogenesis. The potential use of anti-inflammatory LXR ligands is also muddled by the observation that LXR agonists can proinflammatory activity in human macrophages. Finally, LXR agonists can also influence cholesterol metabolism in other tissues. Future studies that 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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