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LXRs and Atherosclerosis: It's Not All Cholesterol

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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[1]. 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[2] 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 (LXR□ and LXRβ), members of the nuclear hormone receptor superfamily of ligand-activated transcription factors, are promising drug targets for treating atherosclerosis since they regulate cholesterol efflux from macrophages at the transcriptional level and exert anti-inflammatory activity[3].

The efflux of cholesterol from macrophages to lipid poor ApoA1 and HDL is mediated by the ATP binding cassette transporters A1 and G1 (ABCA1 and ABCG1)[4]. Both genes are directly regulated by LXRs[3] and it is widely assumed that the athero-protective effects of synthetic LXR agonists are due to the increased macrophage cholesterol efflux via the up-regulation of these 2 genes. Indeed, bone marrow transplantation experiments indicate that LXR activity in macrophages is required for the athero-protective action of LXR agonists[5]. A recent study by Zhang et al.[6], however, indicated that LXR agonists could be anti-atherogenic without stimulating macrophage cholesterol efflux calling into question the contribution of cholesterol transport to LXR activity.

In this issue of ATVB Kappus et al.[7] 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 ABCA1 and ABCG1 reduces atherosclerosis to a degree comparable to control mice; an effect independent of cholesterol efflux since macrophages lacking ABC transporters are unable to efflux cholesterol in a LXR-dependent manner. If not cholesterol efflux, what then is the mechanism of LXR agonist-dependent anti-atherogenic activity? Like many nuclear receptors, LXRs also inhibit inflammation in an agonist-dependent fashion by interfering with the activity of NFκβ[3]. Kappus et al.[7] demonstrate that the anti-inflammatory effects of LXR agonist treatment are preserved in *Abca1*$^{-/-}$/*Abcg1*$^{-/-}$ macrophages *in vitro* and *in*

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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 promote triglyceride synthesis by up-regulating the gene encoding the sterol regulatory element binding protein 1c (SREBP1c), 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[8]. The work described by Kappus et al.[7] adds weight to the potential therapeutic utility of LXR ligands that retain anti-inflammatory activity in macrophages but that do not positively up-regulate target genes such as ABCA1 and SREBP1c. 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 ABCA1 and SREBP1c raising the possibility that such “dissociated” or “pathway-selective” LXR ligands could be identified[9]. Recent studies, however, suggest that LXR anti-inflammatory actively 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[10, 11]. The potential utility of anti-inflammatory LXR ligands is also muddied by the observation that LXR agonists can have pro-inflammatory activity in human macrophages[12]. Finally, LXR agonists can also influence cholesterol metabolism in other tissues[8]. 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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