Lipoxygenase Pathways as Mediators of Early Inflammatory Events in Atherosclerosis

Colin D. Funk

Oxidative modification of low density lipoproteins has been a leading hypothesis in atherogenesis, and throughout the 1990’s there was intense interest in the discovery of pathways leading to this modification.1-2 In a commentary to an article dealing with 12/15-lipoxygenase gene disruption in the atherosclerotic apolipoprotein E (apoE)-deficient mouse model in 1999, Daniel Steinberg declared “at last direct evidence that lipoxygenases play a role in atherosclerosis.”3-4 Since this article seven years ago, the lipoxygenase pathway involvement in atherogenesis has become rather more complicated.

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Lipoxygenases are non-heme iron-containing enzymes that catalyze the stereospecific incorporation of molecular oxygen into polyunsaturated fatty acids with a 1,4-cis, cis-pentadiene motif.5 With respect to atherosclerosis 2 of the 6 (human)/7 (mice) lipoxygenase family members have received the most attention because of their expression patterns in inflammatory cells and in some settings within endothelial cells; these are the 12/15-lipoxygenase (12/15-LO; also known as the leukocyte-type 12-lipoxygenase and 15-lipoxygenase-1) and 5-lipoxygenase.6,7 12/15-LO catalyzes the transformation of free arachidonic acid to 12-hydroperoxyeicosatetraenoic acid (12-HPETE) and 15-HPETE. These products are reduced to the corresponding hydroxy derivatives 12-HETE and 15-HETE by cellular peroxidases. Mice make predominantly 12-HETE whereas humans produce mainly 15-HETE. Both human and mouse 12/15-LO enzymes metabolize linoleic acid to 13-hydroperoxy-octadecadienoic acid (13-HPODE; the reduced product is 13-HODE) as well as metabolizing more complex lipids including cholesteryl linoleate and sn2 polysaturated fatty acids within phospholipids. Thus, 12/15-LO has been shown to oxidatively modify the key lipid components of LDL. 5-Lipoxygenase, on the other hand, only metabolizes free arachidonic acid leading to the formation of proinflammatory leukotrienes and cannot participate in the direct oxidative modification of LDL.6,7

The ability to generate oxidatively-modified LDL by 12/15-LO is only one potential mechanism for its atherogenic promoting role. 12/15-LO can also modulate the expression of a key proinflammatory proatherosclerotic Th1 cytokine, interleukin (IL)-12.8 Hedrick and colleagues9-11 have been following a line of studies over the past 7 years indicating that 12/15-LO can also enhance the adhesion of monocytes to endothelial cells, an early event in atherogenesis. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, these researchers further our understanding of the intracellular pathways involved in the 12/15-LO-mediated monocyte adhesion events.12 Using 12/15-LO knockout mice cross-bred to apoE-deficient mice, they demonstrate a dramatic reduction of monocyte binding to endothelial cells derived from these mice. A lipoxygenase inhibitor, CDC (cinnamyl-3,4-dihydroxy-α -cyanocinnamate), mimics the effect observed by gene disruption. The monocyte adhesion appears to be mediated primarily by intercellular adhesion molecule-1 (ICAM-1), and previous work by this group9 also demonstrated the importance of the fibronectin isoform containing connecting segment-1 in monocyte adhesion. Here, and in another recent publication,10 they show that the 12/15-LO product, 12(S)-HETE, but not the stereoisomer 12(R)-HETE, mediates the ICAM-1 induction through a G protein (G12/13). RhoA, protein kinase Ca, NF-κB activation pathway (see the Figure). The authors postulate that the 12/15-LO product can activate a G protein–coupled receptor (GPCR) to initiate these events. The isolation of this receptor has proven elusive. With the full complement of human GPCRs cloned and expressed it is surprising that no research group has “adopted” one of the orphan members as a 12-HETE receptor. Others have demonstrated the capacity of 12-HETE to bind an intracellular receptor that complexes with other proteins, which is more reminiscent of nuclear hormone signaling.13,14 In any case, knowing the pathway of activation from 12-HETE synthesis to ICAM-1 induction and monocyte adhesion is a significant step forward in determining molecular eicosanoid signaling translated to vascular biological activities. The authors’ work with both 12/15-LO overexpressing endothelial cells from transgenic mice10,11 and experiments with 12/15-LO deficient mouse-derived endothelial cells12 provide a compelling argument for this mode of signaling.

The next important step will be to establish the connection between the enhanced ICAM-1 induction by 12(S)-HETE and atherogenesis. The case for ICAM-1 involvement in mediating early atherogenic events is unclear with some groups reporting that ICAM-1 deficiency reduces lesion development in apoE-deficient mice,15-16 whereas another team of investigators contends evidence that vascular cell adhesion molecule (VCAM)-1, but not ICAM-1, is important in early atherogenesis.17 Returning to the complicated area of lipoxygenases in atherosclerosis mentioned in the first paragraph, the role for 12/15-LO in atherogenesis has been
Proposed signaling pathway in endothelial cells from 12/15-LO mediated conversion of arachidonic acid (20:4) to activation of monocyte adhesion. In mice, a mixture of two hydroperoxides results from this conversion (12-HPETE and 15-HPETE). Cellular peroxidases reduce these to the corresponding HETE molecules. Generation of the stereoisomer 12(S)-HETE predominates in a 4:1 ratio and is the likely ligand for activation of a putative HETE receptor and signaling through the G protein G12/13 to a pathway consisting of RhoA, protein kinase C, and nuclear factor xB transcription factor activation that leads to enhanced intracellular adhesion molecule-1 surface endothelial expression that can promote monocyte binding to the endothelial cell layer. This is a potential pathway that can explain some of the proinflammatory events of the 12/15-LO pathway in atherosclerosis.

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