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. 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.” 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. 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. 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 polyunsaturated 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.

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. Hedrick and colleagues 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. 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 group demonstrated the importance of the fibronectin isoform containing connecting segment-1 in monocyte adhesion. Here, and in another recent publication, 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 Cα, 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. 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 mice and experiments with 12/15-LO deficient mouse-derived endothelial cells 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, whereas another team of investigators contends evidence that vascular cell adhesion molecule (VCAM)-1, but not ICAM-1, is important in early atherogenesis. Returning to the complicated area of lipoxygenases in atherosclerosis mentioned in the first paragraph, the role for 12/15-LO in atherogenesis has been
verified in three different mouse models (apoE, LDL-R, and apobec-1/LDL-R deficiency) by at least three research groups and studies suggest a role for 12/15-LO expressing bone marrow–derived cells (eg, macrophages) in preference to endothelial cells in the proatherogenic role.4,8,18,19 However, other investigators have shown that the human 15-LO pathway and transgenic 15-LO macrophage overexpressing rabbits may contribute anti-inflammatory compounds like lipoxins and lead to a reduction in atherosclerosis.20,21 To further complicate matters there have been a substantial number of studies in the past few years implicating the 5-LO pathway in athrogenesis in humans and mice with a large number of inconsistencies between studies (reviewed in refs. 22, 23). 5-LO–derived leukotriene B4 appears to influence early atherosclerotic events in mouse studies perhaps also by mediating monocyte adhesion and recruitment via monocyte chemoattractant protein-1 (MCP-1).24–27 However, lesion development resulting from complete loss of leukotriene biosynthesis (both LTB4 and the cysteinyl leukotrienes LTC4, LTD4, and LTE4) does not appear to substantially impact atherosclerosis in a variety of fat feeding and mid-to-long–term experiments in both apoE- and LDL-R–deficient states.28

Integrating the biological activities of the 5-LO and 12/15-LO pathways into a unified paradigm for early athero- genic events should be the goal for researchers in this area over the next few years. Hedrick and colleagues’ experiments verified in three different mouse models (apoE, LDL-R, and apobec-1/LDL-R deficiency) by at least three research groups and studies suggest a role for 12/15-LO expressing bone marrow–derived cells (eg, macrophages) in preference to endothelial cells in the proatherogenic role.4,8,18,19 However, other investigators have shown that the human 15-LO pathway and transgenic 15-LO macrophage overexpressing rabbits may contribute anti-inflammatory compounds like lipoxins and lead to a reduction in atherosclerosis.20,21 To further complicate matters there have been a substantial number of studies in the past few years implicating the 5-LO pathway in athrogenesis in humans and mice with a large number of inconsistencies between studies (reviewed in refs. 22, 23). 5-LO–derived leukotriene B4 appears to influence early atherosclerotic events in mouse studies perhaps also by mediating monocyte adhesion and recruitment via monocyte chemoattractant protein-1 (MCP-1).24–27 However, lesion development resulting from complete loss of leukotriene biosynthesis (both LTB4 and the cysteinyl leukotrienes LTC4, LTD4, and LTE4) does not appear to substantially impact atherosclerosis in a variety of fat feeding and mid-to-long–term experiments in both apoE- and LDL-R–deficient states.28

Integrating the biological activities of the 5-LO and 12/15-LO pathways into a unified paradigm for early atherogenic events should be the goal for researchers in this area over the next few years. Hedrick and colleagues’ experiments to elucidate the intracellular signaling events in the 12/15-LO pathway are important steps forward toward this goal.

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