Editorial

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 lacking 12/15-LO show a reduction of 12-HETE and 15-HETE levels as well as decreased magnitude of the monocyte adhesion event in response to 12(S)-HETE challenge. These results suggest that 12/15-LO is a key regulatory enzyme in monocyte adhesion and the formation of atherosclerotic lesions.

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, 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.\(^\text{1,4,18,19}\) However, other investigators have shown that the human 15-LO pathway and transgenic 15-LO macrophage overexpressing rabbits may contribute antiinflammatory compounds like lipoxins and lead to a reduction in atherosclerosis.\(^\text{20,21}\)

To further complicate matters there have been a substantial number of studies in the past few years implicating the 5-LO pathway in atherogenesis in humans and mice with a large number of inconsistencies between studies (reviewed in refs. 22, 23). 5-LO–derived leukotriene B\(_4\) appears to influence early atherosclerotic events in mouse studies perhaps also by mediating monocyte adhesion and recruitment via monocyte chemoattractant protein-1 (MCP-1).\(^\text{24–27}\) However, lesion development resulting from complete loss of leukotriene biosynthesis (both LTB\(_4\) and the cysteinyl leukotrienes LTC\(_4\), LTD\(_4\), and LTE\(_4\)) 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.\(^\text{28}\)

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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