Vascular Cross-Talk: A Conversation
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The development of atherosclerotic lesions is a complex process that requires monocyte recruitment to the vascular endothelium. In response to oxidized lipid accumulation in the vessel wall, endothelial cells (ECs) express a series of chemokines and adhesion molecules that promote the recruitment and chemotaxis of monocyte/macrophages into the subendothelial space where they phagocytize oxidized lipids, forming foam cells and initiating processes leading to advanced lesions (Figure). Of the chemotactic molecules, monocyte chemotactic protein 1 (MCP1) is key in directing molecular signals essential for this process.1,2 However, little is known regarding the concerted actions of pathways and networks that coordinate this sequence of events. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Huang and colleagues provide in vitro evidence for the involvement of the 5-lipoxygenase (5-LO) metabolite, leukotriene B4 (LTB4), and its receptors, BLT1 and 2, as critical players in monocyte chemotaxis and atherosclerosis.3

A series of recent findings suggest that 5-LO and other members of the leukotriene (LT) pathway play an important role in atherosclerosis. In 1991, Hagihara and colleagues observed that adherence of leukocytes to injured endothelium and intimal thickening of the artery following cuff-sheathing of rabbit carotid arteries was considerably diminished by inhibition of 5-LO.4 Studies from other groups showed that atherosclerotic coronary arteries, but not normal arteries, stained positive for 5-LO, 5-lipoxygenase activating protein (FLAP), and LTA4 hydrolase.5 Recent genetic evidence in mice and humans also supports the hypothesis that the 5-LO pathway contributes to atherosclerosis susceptibility. For example, mice deficient in 5-LO were shown to be resistant to aortic lesion formation, even on a hyperlipidemic background,6 and two major human studies have since emerged associating LT metabolism with cardiovascular disease. Dwyer and colleagues initially found an established indicator of systemic atherosclerosis, among carriers of variant 5-LO promoter alleles compared with individuals with the common allele.7 In a separate study, variations of the FLAP gene were associated with an increased risk of myocardial infarction and stroke in Icelandic and British populations.8 Because both 5-LO and FLAP are required for LT synthesis, these studies suggest that 5-LO metabolites play an important role in atherosclerosis.

From a biochemical perspective, LTs have long been known to be involved in broncho-constriction and leukocyte chemotaxis/aggregation, as is evident from their role in asthma.9 For example, LTB4 (and its metabolites) are considered potent chemoattractants that are thought to act primarily through the G-protein coupled LTB4 receptors to mediate chemotaxis and adhesion of a number of leukocytes, including macrophages, to sites of inflammation.10–14 With respect to atherosclerosis, Aiello and colleagues reported that treatment of LDLR−/− and apoE−/− mice with the BLT1/2 antagonist, CP-105 696, significantly reduced monocyte infiltration and aortic lesion formation.15 Interestingly, there was no effect on lesions when MCP1−/−/apoE−/− double knockout mice were treated with CP-105 696. Thus, MCP1 and BLT1/2 may interact to modulate monocyte chemotaxis, but the underlying mechanisms remain unclear. Subsequently, Subbarao and colleagues showed that LTB4 activation in RBL-2H3 cells expressing human BLT1 upregulated several genes known to be involved in atherosclerosis, including CD36, MCP1, and macrophage colony stimulating factor (CSF1).16 Moreover, this study demonstrated BLT1−/− mice on an apoE-null background had significantly reduced early aortic lesion development compared with controls.

Huang and colleagues now show that primary human monocytes treated with LTB4 exhibit a striking, dose dependent increase in MCP1 expression at both the transcriptional and protein level.3 Again, the same BLT1/2 receptor antagonist CP-105 696 significantly decreased this induction, indicating that LTB4 signaling may play a prominent role in the recruitment of monocytes/macrophages to the vascular endothelium. Interestingly, the cysteinyl LTs, LTC4, LTD4, and LTE4, do not appear to be mediators of MCP1 induction in this system. BLT1/2 are thought to mediate proinflammatory responses through G-protein linked kinases.17 Although it had previously been shown that inhibition of the extracellular signal regulated kinase (ERK) and PKC pathways attenuates shear induced MCP1 expression,18 Huang and colleagues further demonstrate that activation of the ERK1/2 and JNK pathways are necessary for the induction of MCP1 by LTB4 in human monocytes. Additionally, nuclear extracts from LTB4-treated monocytes showed a significant increase in NF-kB DNA binding activity, which was attenuated by CP-105 696. Thus the experiments by Huang et al begin to shed light on the molecular mechanisms by which LTs can exert their proin-
A model for LTB4 initiation of monocyte activation and recruitment. LTB4 regulates vascular monocyte chemotactic activity driven by MCP1, through the BLT1/2 signal transduction pathway. As monocytes tether onto endothelial cells, 5-lipoxygenase is induced, resulting in increased LTB4 production. This activates β1 (Itgb1, VLA4) and β2 (CD11b) integrins on monocytes. The β1 and β2 integrins bind to their cognate receptors, vascular cell adhesion molecule and intracellular adhesion molecule, firmly arresting monocytes on the endothelium. Binding of LTB4 to BLT1/2 on monocytes and endothelial cells induces MCP1 expression, thereby initiating a looping mechanism through which LTB4 and MCP1 can further regulate monocyte adhesion, spreading, and transmigration into the subendothelial space. This mechanism is dependent on the activation of MAPKs, particularly ERK1/2 and JNK, which may influence both the spreading and transmigration of monocyte/macrophages. Furthermore, the LTB4 signaling cascade activates of NF-κB.

References
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4. Hagihara H, Nomoto A, Mutoh S, Yamaguchi I, Ono T. Role of inflammatory effects in the vessel wall. By integrating these new results with what is already known about the role of monocytes/macrophages and atherosclerosis, a model for the future would be to develop those same therapeutic strategies as novel treatments for cardiovascular disease.

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