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Editorial for 309907, Oxidized lipid uptake by scavenger receptor CD36 modulates endothelial surface properties and may contribute to atherogenesis

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For many years vascular biologists and pathologists have known that atherosclerosis is a spatially discontinuous disease; plaque tends to form in specific locations, especially branch points in large arteries where blood flow is discontinuous and disordered. Furthermore, plaque formation progresses temporally from the proximal arterial tree to more distal vessels. It is also well known that vascular endothelial cells are sensitive to shear stress patterns and blood flow[1] and, in fact, express a robust mechano-sensory system made up of intracellular signaling pathways that are triggered by integrins, selectins and cilia[2]. Unidirectional flow in straight vessels, such as the distal aorta, is atheroprotective, while disordered flow at curvatures and branch points, such as the aortic arch, promotes inflammatory signaling, endothelial dysfunction, leukocyte recruitment, and plaque formation[3]. A manuscript by Le Master et al. published in this issue of *Atheroslerosis, Thrombosis and Vascular Biology*[4] presents elegant new data that helps integrate these observations into a pathogenic model that relates disordered blood flow to upregulated endothelial cell expression of the scavenger receptor CD36, increased uptake of oxidized lipids, and increased endothelial cell stiffness.

The team utilized atomic force microscopy (AFM), a powerful microscopy based technique that uses a cantilevered probe to scan surfaces. With AFM they were able to measure endothelial monolayer “stiffness” in fresh aortae that were removed from mice and opened *en face* to expose the luminal surface. By measuring micro-indentation depth at multiple sites a mean elastic modulus was calculated to estimate the degree of deformability or stiffness of the cell surface. Under basal conditions they found that endothelial stiffness was ~2-fold greater in the atherosclerosis-prone aortic arch, compared to the distal aorta. Then, using a well-accepted model of moderate hyperlipidemia induced by feeding mice a high fat diet for one month, they found a further 4-fold increased stiffness in the aortic arch from the hyperlipidemic mice. This was associated with a significant increase in lipid and oxy-lipid accumulation in the aortic arch, suggesting possible mechanistic connections between disordered flow, lipid accumulation, EC stiffness, and susceptibility to atherosclerosis[4]. To probe mechanisms, they also studied human aortic EC (HAEC) in culture using two well-characterized in vitro model systems of disordered flow (DF) and showed that HAEC

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exposed to DF compared to laminar flow had increased uptake of oxidized lipids when incubated with oxLDL, and that this was associated with increased EC stiffness measured by AFM.

While oxidized LDL (oxLDL) uptake and signaling through CD36 is well described in macrophages and clearly play critically important roles in foam cell formation, reactive oxygen species generation, inflammatory signaling, dysregulated cell migration, and plaque formation[5], a role for this system in arterial EC is not well understood. CD36 is expressed prominently in microvascular EC where it mediates anti-angiogenic, pro-apoptotic signaling[6], but expression of CD36 in large vessel EC has been controversial, and other scavenger receptors, such as LOX1 and SRB1[7], have been proposed to be more important in endothelial atherogenesis. Le Master et al now show quite convincingly, using functional knockdown, mRNA expression assays, immunoblots, and immunofluorescence imaging that human aortic EC in culture and mouse aortae in vivo express CD36. Although baseline expression is low (approximately 25% of that seen in capillary EC), it was increased by exposure to disturbed flow or oxLDL in vitro and by high fat diet in vivo. Interestingly, CD36 expression was higher in the aortic arch compared to the distal aorta, consistent with a potential role in mediating the spatial differences in lipid uptake and endothelial stiffness seen in these two sites.

To probe these mechanistic connections, the authors used siRNA to knock down CD36 expression in cultured HAEC and studied aortae isolated from *cd36* null mice. They found that loss of CD36 abrogated the in vitro effects of DF plus oxLDL on both oxLDL uptake and increased stiffness. Importantly the *cd36* null mice on high fat diet had less lipid deposition in their aortic arches and did not show the increase in endothelial stiffness seen in wild type animals. Transplant of *cd36* null bone marrows into irradiated wild type mice did not rescue the phenotype, and transplant of wild type bone marrows into *cd36* null mice did not recapitulate the phenotype, strongly suggesting that the observed effects of high fat diet on aorta lipid uptake and monolayer stiffness were mediated by CD36 in the vasculature, not in monocytes or macrophages. While the evidence points to a role for EC CD36 in promoting endothelial stiffness, they cannot rule out roles for smooth muscle cells[8] or other CD36 expressing vascular cells in the process.

Left unanswered by this sophisticated work is just what is the biological and pathological relevance of endothelial stiffness? Does it contribute to vascular stiffness, which is generally thought to be mediated by changes in the extracellular matrix, but which is known to increase with aging[9] and with atherosclerosis progression, and to associate with endothelial dysfunction? Does it influence atherogenic processes, such as leukocyte transmigration, endothelial barrier function, or pro-inflammatory signaling? Is it related to plasma membrane cholesterol or oxysterol content and could it therefore influence membrane microdomain formation, membrane protein localization, and signal transduction? These are interesting questions for further study, but enthusiasm for the work must be tempered by published results [10] showing that transplant of *apoe;cd36* double null bone marrow into *apoe* null mice led to >80% reduction in aortae atherosclerosis area compared to *apoe* null mice transplanted with *apoe* null;*cd36* wild type marrows. These data suggest strongly that it is CD36 expression on hematopoietic cells, rather than vascular cells that accounts for

atheroprotection seen by deleting CD36 in mouse models, and may imply that CD36-mediated changes in aorta endothelial stiffness and lipid uptake may not directly impact atherogenesis.

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