LOX-1 and Atherosclerosis
Proof of Concept in LOX-1–Knockout Mice

Henning Morawietz

An increased plasma level of low-density lipoprotein (LDL) is a well-known risk factor for endothelial dysfunction and atherosclerosis. The proatherosclerotic potential of LDL may even increase after oxidative modification to oxidized LDL (oxLDL), whose uptake by macrophage scavenger receptors is thought to be a key process in the formation of foam cells, the hallmark of atherosclerotic lesions. However, there is less clarity on oxLDL uptake regulation in endothelial cells and its role in early stages of atherosclerosis.

A decade ago, Tatsuya Sawamura and colleagues discovered the lectin-like oxLDL receptor LOX-1 in endothelial cells. LOX-1 is a 50-kDa type II membrane glycoprotein and contains a short N-terminal cytoplasmic domain, a single transmembrane domain, a NECK domain or stalk, and an oxLDL-binding C-terminal extracellular C-type lectin-like domain. LOX-1 assembles on the cell surface in hexamers or larger, comprising 3 homodimeric LOX-1 molecules bound to oxLDL.

Although LOX-1 is expressed at very low levels in healthy endothelium, several lines of evidence support a role of LOX-1 in the pathogenesis of atherosclerosis. LOX-1 may be upregulated by its own ligand oxLDL or by proinflammatory cytokines in endothelial cells. Because proatherosclerotic angiotensin II and endothelin-1 vasoconstrictors increase endothelial LOX-1 expression and oxLDL uptake, LOX-1 has been suggested as a link between hypertension and atherogenesis. In line with these findings, a high-cholesterol diet induced intimal thickening and a marked increase in LOX-1 expression in the endothelium and neointima of rabbits, which was successfully reduced by an angiotensin II receptor (LDLR)–knockout mice and feeding the latter a high-cholesterol diet for 18 weeks, atherosclerotic lesion formation was significantly reduced in the aorta of double knockout mice compared with the LDLR-knockout mice. Furthermore, luminal obstruction and intima thickness were reduced in the double knockout mice. Proatherosclerotic and prooxidative signaling and inflammatory response, measured as vascular NF-κB and CD68 expression and p38 MAPK phosphorylation, was increased in LDLR–knockout mice, but not in double knockout animals. In contrast, antioxidative superoxide dismutase activity and antiinflammatory cytokine IL-10 were expressed at lower levels in LDLR-knockout mice compared with double knockout mice, whereas endothelial nitric oxide synthase expression (eNOS) was also preserved in the double knockout mice. These data suggest a LOX-1–dependent balance of pro- and antiatherosclerotic processes in the vessel wall (Figure), whereby deletion or low expression of LOX-1 is associated with low levels of atherosclerosis, low intimal thickness, NF-κB, CD68 expression, and p38 MAPK activation. Whereas endothelial function, eNOS, IL-10, and SOD activity is preserved in double knockout animals, a high-fat diet with high LOX-1 expression or with LOX-1 overexpression is associated with a proatherosclerotic, prooxidative, and proinflammatory gene expression pattern together with accelerated atherosclerosis. Therefore, this study provides the proof of concept of a proatherosclerotic role of LOX-1.

In this context, it has to be considered that the human situation differs from the murine atherosclerosis model regarding lipoprotein metabolism and atherosclerotic lesion structure, although additional studies will be necessary to provide additional support for these findings. Indeed, genetic LOX-1 deletion led to detectable uptake of oxLDL in the vessel wall and atherosclerotic lesion formation in the current study, but apart from LOX-1, additional endothelial oxLDL receptors such as SR-AI/II, CD36, SR-BI, macrosialin/CD68, and SREC have also been discussed and may be responsible for the oxLDL uptake observed in double knockout animals.

Although endothelial LOX-1 is considered to play a major role in the initial phase of atherosclerosis, LOX-1 expression is not completely restricted to endothelial cells. LOX-1 can also be found on a lower but inducible level in vascular...
Impact of LOX-1 expression on atherosclerosis. The degree of LOX-1 expression is a critical determinant of reactive oxygen species (ROS) formation, inflammation, endothelial dysfunction, atherosclerosis, and corresponding marker genes.

What evidence is there for a role of LOX-1 in human atherosclerosis? Increased expression of LOX-1 has been shown in atherosclerotic plaques from human samples. LOX-1 expression is a critical determinant of reactive oxygen species production, and LOX-1 expression.

Reports on the impact of available pharmacological therapies on LOX-1 expression in patients are still limited, but one report has demonstrated reduced LOX-1 expression in internal mammary arteries in patients receiving ACE inhibitors. In the recent prospective clinical Endothelial Protection, AT1 blockade and Cholesterol-Dependent Oxidative Stress (EPAS) trial, statin and AT1 blocker therapy independently and in combination improved the endothelial expression quotient of anti- and proatherosclerotic genes (including eNOS, NADPH oxidase subunit gp91phox, and LOX-1) and endothelial function in internal mammary arteries of patients with coronary artery disease undergoing elective coronary artery bypass surgery. However, LOX-1 expression itself was not significantly regulated by either medication.

In view of these findings, antihypertensive and lipid-lowering drugs currently available may not be sufficient to reduce LOX-1 expression and atherosclerosis in a clinically relevant manner. Even if LOX-1 blocking antibodies have been shown to preserve endothelial function in response to oxLDL in the current study, their application in clinical settings is limited. Because the recently defined basic spine structure of LOX-1–mediating ligand recognition accelerates the development of specific nonpeptide LOX-1 inhibitors, inhibition of LOX-1 might be an interesting and novel therapeutic strategy in the treatment of atherosclerosis and its clinical implications.

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None.

References

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