LOX-1, a Possible Clue to the Missing Link Between Hypertension and Atherogenesis

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Our understanding of the molecular mechanism of atherosclerosis has changed during the past 20 years. A large variety of different risk factors such as smoking, shear stress, hypertension, hypercholesterolemia, diabetes mellitus, and obesity lead to endothelial activation and/or dysfunction, which can elicit a series of cellular interactions that culminate in the lesions of atherosclerosis. To date, there have been many studies investigating how hypercholesterolemia, particularly hyperLDL-cholesterol, affects endothelial cells and forms atherosclerotic lesions.1-3 Although hypertension is an established risk factor for the development of atherosclerosis, the underlying molecular mechanisms have not been clearly elucidated. There is a great deal of experimental, epidemiological, and clinical evidence suggesting that the renin-angiotensin system plays an important role in the pathogenesis of atherosclerotic formation. It has been suggested that hypertensive patients with high renin profiles, who are likely to be associated with increased plasma angiotensin II (Ang II) levels, have a higher risk of myocardial infarction than those with low renin profiles.4,5 Several experimental studies on hyperlipidemic animal models have suggested that interaction of the renin-angiotensin system and hyperLDL-cholesterol could play an important role in atherogenesis. In addition, it has been shown that angiotensin-converting enzyme (ACE) inhibitors reduce atherosclerotic formation in several experimental animal models, such as Watanabe heritable hyperlipidemic (WHHL) rabbits.3,13 Furthermore, accumulating evidence suggests that ox-LDL is a key component in the formation of atherosclerosis.3,13,14, and ox-LDL is a chemoattractant for monocytes15 and is cytotoxic for endothelial cells in the culture system.16 Also, ox-LDL is a mitogenic activator for macrophages and smooth muscle cells.17 Ox-LDL is recognized by the scavenger receptors on the surface of macrophage membranes, and the macrophage becomes foam cells. Incorporation of ox-LDL into macrophages is mediated by at least six membrane proteins, including the class A and class B scavenger receptors, such as CD36, SRBI, and so on.18,19 Sakai et al20 demonstrated that lysophosphatidylcholine from endocytosed ox-LDL, through a class A scavenger receptor, plays an essential role in ox-LDL-induced macrophage proliferation. Nagy et al21 and Tontonoz et al22 showed that ox-LDL activates CD36-mediated ox-LDL uptake through a peroxisome proliferator-activated receptor gamma (PPARγ)-dependent transcriptional signaling pathway. They identified two of the major oxidized lipid components of ox-LDL, 9-HODE (9-hydroxyoctadecadienoic acid) and 13-HODE (13-hydroxyoctadecadienoic acid), as endogenous activators and ligands of PPARγ.

With regard to the biological effect on endothelial cells, ox-LDL and its lipid constituents (such as lysophosphatidylcholine) impair endothelial production of nitric oxide (NO)23 and induce the endothelial expression of leukocyte adhesion molecules and smooth muscle growth factors, which may be involved in atherosclerosis.24-26 It has been suggested that oxidation of LDL by monocytes and macrophages,12 it is strongly suggested that the cross talk between Ang II and ox-LDL plays an important role in atherosclerotic formation in the body. Although the Li et al20 study is limited to in vitro findings, these results may provide a long-sought molecular link between hypertension, hyperlipidemia, the principal risk factors for coronary artery disease, and the development of atherosclerosis.

Oxidized LDL and Its Receptor (LOX-1)
The earliest events in atherosclerosis have suggested that monocyte recruitment into lesions might involve the activation and/or dysfunction of vascular endothelial cells or, in other words, endothelial adhesiveness for circulating monocytes and T lymphocytes into the subendothelial spaces. This endothelial activation and/or dysfunction has been implicated in the pathogenesis of atherosclerosis, characterized by intimal thickening and lipid deposition in the arterial wall, ie, "fatty streak."2 Oxidative modification appeared to be a biologically plausible modification of LDL. The importance of ox-LDL in atherosclerosis was first established through the use of the antioxidant protocol, in studies of genetic hyperlipidemic rabbits (WHHL rabbits).3,13 Furthermore, accumulating evidence suggests that ox-LDL is a key component in the formation of atherosclerosis.3,13,14, and ox-LDL is a chemoattractant for monocytes15 and is cytotoxic for endothelial cells in the culture system.16 Also, ox-LDL is a mitogenic activator for macrophages and smooth muscle cells.17 Ox-LDL is recognized by the scavenger receptors on the surface of macrophage membranes, and the macrophage becomes foam cells. Incorporation of ox-LDL into macrophages is mediated by at least six membrane proteins, including the class A and class B scavenger receptors, such as CD36, SRBI, and so on.18,19 Sakai et al20 demonstrated that lysophosphatidylcholine from endocytosed ox-LDL, through a class A scavenger receptor, plays an essential role in ox-LDL-induced macrophage proliferation. Nagy et al21 and Tontonoz et al22 showed that ox-LDL activates CD36-mediated ox-LDL uptake through a peroxisome proliferator-activated receptor gamma (PPARγ)-dependent transcriptional signaling pathway. They identified two of the major oxidized lipid components of ox-LDL, 9-HODE (9-hydroxyoctadecadienoic acid) and 13-HODE (13-hydroxyoctadecadienoic acid), as endogenous activators and ligands of PPARγ.

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vascular endothelial cells in culture and in vivo internalize and degrade ox-LDL through a receptor-mediated pathway that does not involve the macrophage scavenger receptors.27 Sawamura, Kume et al30 first identified LOX-1 as a critical molecule that is responsible for ox-LDL uptake by endothelial cells.28,29 The expression of endothelial LOX-1 is induced by tumor necrosis factor-α (TNF-α) and shear stress.30,31 Moreover, in animal models such as WHHL rabbits and spontaneously hypertensive rats (SHR), LOX-1 is expressed in the endothelial cells.32–35 Because foam cell formation of endothelial cells has not been identified either in vitro or in vivo, ox-LDL uptake by LOX-1 in vascular endothelial cells in vivo may not result in massive lipid accumulation. However, ox-LDL uptake via LOX-1 in vascular endothelium may cause endothelial activation and/or dysfunction, given that a variety of biological effects of ox-LDL and its lipid constituents on endothelial cells have been reported. Physiological levels of laminar fluid flow shear stress transcriptionally induced LOX-1 expression in bovine aortic endothelial cells by a mechanism dependent upon [Ca2+] mobilization.35 Endothelial expression of LOX-1 may also be dynamically modulated, in vivo, in response to changes in blood flow.31

An in vivo study by Nagase et al33 suggested this possibility. Although pathophysiological consequences of ox-LDL uptake by vascular endothelial cells through LOX-1 still need to be fully clarified, modulated expression of this novel ox-LDL receptor by inflammatory stimuli and fluid mechanical stimuli may play an important role in the selective localization of atherosclerotic lesions in vascular tissues. Recently, it was demonstrated that LOX-1 is expressed in human and murine macrophages,36–38 which are induced by TNF-α;38 however, we do not know how the mechanism is regulated. We do know that the macrophages incorporate ox-LDL through the scavenger receptors, such as class A and CD36, and then get converted into foam cells, but the role of LOX-1 in macrophages is not clear.

**Hypertension and Atherosclerosis**

Endothelial cells play numerous physiological roles in the maintenance of vascular tonus. The molecules involved in these events, prostacyclin (PGI2), endothelin (ET), Ang II, and NO, have all attracted an increasing amount of attention from researchers. Vasomotor tone of the artery appears to be controlled by the constant action of NO.2 Inhibition of the formation of NO and PGI2 permits opposing forces of vasodilation, which results from vasoconstrictors such as ET, Ang II, or thromboxane A2, to determine the capacity of the artery to maintain its lumen in the presence of the changing forces caused by the formation and progression of the lesions of atherosclerosis. Several studies have already proved that LDL from hypertensive patients is more susceptible to oxidation than LDL from normotensive controls. In addition, hypertensive patients with elevated plasma Ang II levels show a 5-fold increased incidence of myocardial infarction compared with normal or decreased levels of Ang II.3,59 Treatment of patients with left ventricular dysfunction using ACE inhibitors reduces the incidence of recurrent myocardial infarction and its mortality.40 In addition to its vasoactive role, Ang II directly induces oxidative stress in the vasculature by generating superoxide anions through the activation of NADH/NADPH oxidase in cultured rat aortic smooth muscle cells and in aortas of rats made hypertensive by infusion of Ang II.41,42 Capers et al43 showed a marked inflammatory response characterized by the infiltration of monocytes/macrophages in the aortas made hypertensive by infusion of Ang II. Chen et al44 directly stimulates MCP-1 gene expression in the vasculature via AT1. Keider et al32 demonstrated that Ang II stimulates macrophage-mediated oxidation of LDL, and they also showed that Ang II enhanced the uptake and oxidation of monocytes and macrophages. The study by Li et al10 described the presence of AT1 in HCAECs and showed that Ang II increases the uptake of ox-LDL by HCAECs in a concentration-dependent manner. This increased uptake is due to the upregulation of LOX-1 by Ang II, which causes a concentration-dependent increase in ox-LDL uptake by HCAECs and enhanced ox-LDL-mediated cell injury. This study helps to explain the previous report that LOX-1 expression was found to be upregulated in SHR, which increases Ang II expression.33

We still do not know whether endothelial cells are injured in SHR or other animal models. However, a recent study by Rueckschloss et al45 demonstrated that LOX-1 is downregulated in arteries of patients undergoing therapy with ACE inhibitors. In the near future, we should know the molecular mechanism for which Ang II upregulates LOX-1 and how incorporated ox-LDL injures endothelial cells. Furthermore, in general, we still do not know the physiological or even the pathophysiological implications of how LOX-1 molecules act in the body. We should continue to seek further evidence of how LOX-1 is regulated both in vitro and in vivo and how LOX-1 recognizes ox-LDL particles.

**References**


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