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# Pravastatin Inhibits Expression of Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1 (LOX-1) in Watanabe Heritable Hyperlipidemic Rabbits

## A New Pleiotropic Effect of Statins

Oliver Hofnagel, Birgit Luechtenborg, Heike Eschert, Gabriele Weissen-Plenz,  
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**Background**—LOX-1, a receptor for oxidized low-density lipoprotein (OxLDL), seems to play a critical role in foam cell formation of macrophages (M $\phi$ s) and smooth muscle cells (SMC). Inhibition of LOX-1 expression reduces foam cell formation and might influence lipid core formation in atherosclerotic lesions. Because statins are able to downregulate LOX-1 expression in vitro, we examined if pravastatin can be used to reduce LOX-1 expression and lipid core formation in lesions of Watanabe heritable hyperlipidemic (WHHL) rabbits.

**Methods and Results**—Pravastatin downregulated LOX-1 expression in cultured human M $\phi$ s and in cultured human aortic SMCs. Homozygous WHHL rabbits were treated with 50 mg kg<sup>-1</sup> d<sup>-1</sup> pravastatin for 32 weeks. Immunohistochemical studies revealed that LOX-1 was expressed in intimal M $\phi$ s and SMCs of atherosclerotic lesions. The pravastatin-treated rabbits showed, compared with untreated rabbits, a significantly reduced LOX-1 protein and mRNA expression in the aortic arch. Lipid labeling of this aorta region also demonstrated a strong reduction of the ratio of lipid core area/total lesion area in pravastatin-treated rabbits.

**Conclusions**—The in vivo inhibition of LOX-1 expression by pravastatin demonstrated here represents a new pleiotropic effect of pravastatin. This in vivo inhibition of LOX-1 might be one mechanism for the lipid core reducing effect of pravastatin in atherogenesis. (*Arterioscler Thromb Vasc Biol.* 2006;26:604-610.)

**Key Words:** atherosclerosis ■ cardiovascular disease prevention ■ lipoproteins ■ oxidized lipids  
■ smooth muscle cells

Oxidized low-density lipoprotein (OxLDL) is believed to play a key role in accumulation of foam cells in atherogenesis. The cellular uptake of OxLDL is mediated by so-called scavenger receptors, a heterogenous family of membrane bound proteins.<sup>1</sup> Among them, the receptor LOX-1 is expressed in macrophages (M $\phi$ s) and smooth muscle cells (SMCs) in the intima of atherosclerotic lesions.<sup>2</sup> Foam cells derive from M $\phi$ s and SMCs and have been implicated in the formation of the lipid core. Therefore, a role of LOX-1 in foam cell formation has been suggested, and downregulation of LOX-1 could in theory reduce the lipid core development by inhibition of foam cell formation.

Several authors have reported downregulation of LOX-1 expression in cultured cells in response to different stimuli. For example, upregulation of LOX-1 expression by angiotensin II can be inhibited by means of the angiotensin II type 1 receptor blocker losartan in endothelial cells (ECs).<sup>3,4</sup> Upregulation of LOX-1 expression by tumor necrosis factor

(TNF)- $\alpha$  and IL-1 $\beta$  is inhibited by peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ) activators in SMCs and ECs.<sup>5,6</sup> Furthermore, Chen et al (2000) showed that losartan decreased LOX-1 expression in cultured cells and also in the neointima of rabbits.<sup>7</sup>

Lipid-lowering 3-hydroxy-3-methyl glutaryl coenzyme A (CoA) (3-hydroxy-3-methylglutaryl [HMG]-CoA) reductase inhibitors (statins) are also known to downregulate LOX-1. In cultured M $\phi$  lovastatin inhibits LOX-1 expression in cultured M $\phi$ s.<sup>8</sup> Li et al (2001) reported downregulation of LOX-1 expression and reduced uptake of OxLDL in EC after incubation with simvastatin and atorvastatin.<sup>9</sup> It is known that statins are potent agents for lowering total and low-density lipoprotein cholesterol. Clinical trials have demonstrated that these agents are able to reduce the incidence of cardiovascular diseases. The risk of myocardial infarction of individuals treated with statins is significantly lower than that of individuals treated with other cholesterol-lowering agents. These

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