Statins induce anti-atherosclerotic action in VSMCs through the activation of PPARγ.

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Recent studies suggest that some of the beneficial effects of 3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitors (statins) are independent of their cholesterol-lowering effects on the blood vessels. The peroxisome proliferator-activated receptor-γ (PPARγ) is an important regulator in lipid and glucose metabolism, and its activator is reported to suppress the development of atherosclerosis. We have reported that statins activate PPARγ in macrophages (Circ Res. 100:1442-1451, 2007). In the present study, we investigated the involvement of PPARγ on statin-mediated anti-atherosclerotic effects in several vascular cells, including human vascular smooth muscle cells (VSMCs) and human umbilical vein endothelial cells (HUVECs). Fluvastatin and pitavastatin activated PPARγ in VSMCs, as well as in macrophage cell-line, RAW264.7 cells. However, statins did not activate PPARγ in HUVECs. Statins induced cyclooxygenase-2 (COX-2) expression, and subsequently increased intracellular 15d-PGJ2 in SMCs but not in HUVECs. Moreover, treatment of COX-2-siRNA abrogated the statin-mediated PPARγ activation in SMCs. Statins suppressed cell migration, cell proliferation and LPS-induced MCP-1 expression in SMCs, and knockdown of PPARγ by PPARγ-siRNA restored the statin-mediated suppression of cell migration, cell proliferation and MCP-1 expression. Treatment of statins suppressed atherosclerotic lesion formation in apoE deficient (apoE-/-) mice. Moreover, MCP-1 expression and the number of VSMCs and PCNA-positive SMCs were decreased, and transcriptional activity of PPARγ was increased in the atherosclerotic lesions of the statin-treated apoE-/- mice. These effects of statins on SMCs may explain in part of the anti-atherogenic effects by statins.