Peroxisome Proliferator-Activated Receptors Mediate Pleiotropic Actions of Statins

Réjane Paumelle, Bart Staels

High plasma concentrations of LDL-cholesterol (LDL-c) are a major risk factor for atherosclerosis, a chronic inflammatory disease of the large arteries. Statins are potent inhibitors of cholesterol biosynthesis which efficiently decrease plasma LDL-c concentrations. A large number of clinical trials has shown beneficial effects of statins in the primary and secondary prevention of cardiovascular disease. Although it is generally assumed that these beneficial effects are directly related to the decrease of LDL-c, certain benefits of statin therapy may occur earlier and possibly to a larger extent than what might be expected from changes in plasma LDL-c levels alone. These observations have led to the suggestion of effects beyond LDL-c-lowering, collectively termed “pleiotropic” effects.

Statins are competitive inhibitors of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis. As a result, intracellular cholesterol concentrations decrease after statin treatment leading to proteolytic activation of the transcription factor sterol responsive element-binding protein-2 (SREBP-2), which regulates several genes controlling cholesterol homeostasis, including the LDL-receptor (LDLR). Hence, as a consequence of increased LDL clearance, plasma LDL-c concentrations decrease. The so-called pleiotropic effects of statins are thought to be because of the inhibition of the parallel pathway of biosynthesis of isoprenoids, which constitute lipid attachments allowing membrane anchoring and activation of intracellular signaling molecules, such as the small GTP-binding proteins Rho, Ras, and Rac. These proteins then can activate various downstream signaling pathways including mitogen-activated protein kinases (MAPKs) such as extracellular signal-regulated kinases (ERKs) and p38-MAPKs, c-jun N-terminal kinases (JNKs) and phosphatidylinositol 3-kinase (PI3K). As a consequence, statins also exert antiinflammatory properties by inhibiting transcription factors pathways, such as nuclear factor-kappa B (NF-κB) and activator protein-1 (AP1). By decreasing small G protein activation, statins may interfere with diverse biological pathways thought to be involved in atherogenesis such as cell proliferation, oxidative stress and inflammation.

In this issue of Circulation Research, Yano et al provide further mechanistic insight linking statin action in macrophages, important cellular components of atherogenesis, to specific nuclear effectors, the peroxisome proliferator-activated receptors (PPARs). PPARs are ligand-activated transcription factors belonging to the nuclear receptor superfamily. PPARα and PPARγ regulate metabolic pathways involved in glucose and lipid homeostasis resulting in the clinical application of synthetic PPARα (fibrates) and PPARγ (thiazolidinediones) ligands respectively in the treatment of dyslipidemia and type 2 diabetes. Moreover, PPARs also exert antiinflammatory actions in atherosclerotic lesion cells, such as macrophages. Yano et al now show, using standard activity assays, that, although they are not direct ligands for these receptors, different statins induce PPARγ transcriptional activity, data which are in line with results from previous studies showing that statin-induced expression of the HDL-receptor ABCA1 is dependent on PPARγ activity. The authors go further to identify a novel molecular mechanism of statin-PPAR cross-talk. They provide compelling evidence, by using both pharmacological inhibition and siRNA approaches, that statins induce PPARγ transcription activity in macrophages by inducing the expression of cyclooxygenase-2 (COX-2), which converts arachidonic acid into various bio-active lipids, including prostaglandins. This activation of COX-2 in macrophages results in the production of endogenous PPAR ligands such as 15d-PGJ2, which activate PPARγ and also PPARα. Moreover, by using dominant negative mutants and pharmacological inhibitors, they show that statins induce COX-2 expression via activation of the ERK and p38 MAPK pathways, the latter being dependent on the inhibition of the small G proteins Rho and Cdc42. Finally, the authors demonstrate using siRNA knockdown of PPARα and PPARγ that the antiinflammatory activity of statins, measured by the inhibition of LPS-induced TNFα and MCP1 expression and transcriptional activation of NF-κB and AP1, is dependent on the presence of these receptors. These data confirm that statins exert anti-inflammatory activities via PPARα and show that PPARγ is also involved.

These data reinforce the existence of a cross-talk between the statin and PPAR pathways, first demonstrated in hepatocytes in which statins induce the expression of the HDL-apolipoprotein A-I, as well as the liver fatty acid binding protein (L-FABP), a cytosolic protein involved in intracellular long-chain fatty acid trafficking, via a PPARα-dependent mechanism. In hepatocytes and adipocytes, PPARγ expression is also regulated by statins and SREBP-1 and SREBP-2 induce PPARγ promoter activity. A PPAR-statin cross-talk is thus also observed in macrophages. In these cells, as well as in neutrophils, PPARα contributes to the inflammatory response.
response to statins. In this study, it was shown that acute treatment with statins inhibits LPS-induced inflammatory gene expression not only in vitro but also in vivo via a PPARα-dependent mechanism, involving the inhibition of LPS-induced PPARα phosphorylation by the PKC signaling pathway (Figure). Although Yano et al. do not provide evidence of the in vivo relevance of their findings, their data add a novel pathway of cross-talk between statins and PPARγ, and likely PPARα, via COX-2-mediated generation of PPAR ligands such as 15d-PGJ2. These data further confirm that PPARα and PPARγ might play a role in the pleiotropic effect of statins acting on different, converging pathways (Figure). However, a major question is whether this mechanism of cross-talk contributes to the atheroprotective activity of statins in vivo. It would be interesting to test the antiatherogenic effects of statins in animal models of atherosclerosis in which PPARα and/or PPARγ are selectively deleted in macrophages.

The existence of molecular cross-talk pathways between statins and PPARs offers potentially interesting perspectives for the treatment of cardiovascular complications of type 2 diabetes and dyslipidemia. Combination treatment of statins with PPAR agonists may thus result in a more than additive effect, which may result in more efficient clinical control of cardiovascular risk factors related to atherosclerosis, although the appearance of more pronounced adverse events should be monitored for. Such hypothesis is currently being tested in the ACCORD study (www.accordtrial.org), in which the influence of simvastatin and fenofibrate combination therapy on cardiovascular disease in diabetes patients is being assessed. Recent clinical studies on intermediary end points are in line with this hypothesis showing that combined therapy with statins and fibrates has complementary effect and modulate to a greater extent the lipoprotein profiles and inflammatory parameters in patients with combined hyperlipidemia.

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**Disclosures**

None.

**References**


**Key Words:** HMG-CoA reductase inhibitors, PPARs, atherosclerosis, macrophages, signaling pathways.

**Cross-talk of statins/PPARs in the antiatherogenic properties of statins.**

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Acetyl-CoA

HMG-CoA

Mevalonate

Cholesterol

SREBP2

PPARα

P

LDL-C

HDL-C

TNFα

MCP1

CD36

ABCA1

HMG-CoA Reductase

MAPK

PPARγ

15d-PGJ2

LDL-R

ApoA1

L-FABP

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