Statins Inhibit Leukocyte Recruitment
New Evidence for Their Anti-Inflammatory Properties

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Atherosclerosis and its devastating clinical complications, such as arterial thrombosis; ischemia and infarction of the heart, brain, and other vital organs; ruptured aortic aneurysms; and peripheral vascular insufficiency, continue to account for the majority of morbidity and mortality in the adult population of industrialized nations. The process of atherosclerosis is not simply an inevitable degenerative consequence of aging in the large arteries but a progressive disease characterized by chronic inflammation. Increasing evidence suggests that atherosclerosis is a multifactorial process involving the interplay of lipid metabolism, mononuclear leukocytes, coagulation proteins, cytokines, extracellular matrix, and hemodynamic forces. Since their introduction in the late 1980s, statins have revolutionized the treatment of dyslipidemia and demonstrated their ability to reduce and prevent coronary morbidity and mortality in both primary and secondary intervention trials. Statins competitively inhibit 3-hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase, an enzyme crucial to cholesterol biosynthesis. The resulting decrease in hepatic cholesterol concentration leads to a compensatory increase in expression of hepatic LDL receptors, which clear cholesterol-rich LDL and LDL precursors from the circulation. However, mevalonate, the product of HMG-CoA reductase, is the precursor not only for cholesterol but also for many nonsterol isoprenoid compounds. The isoprenoids farnesyl pyrophosphate and geranylgeranyl pyrophosphate are known to play an important role in signal transduction pathways by their attachment to signaling proteins, such as Ras and Rho.

The effectiveness and rapidity with which statins decrease coronary events already led a few years ago to the speculation that statins might influence vascular biology through mechanisms other than lowered plasma cholesterol. Indeed, numerous pleiotropic effects of statins on vascular cells have been identified during the past several years that could modulate atherogenesis, plaque rupture, or thrombosis. For example, statins upregulate nitric oxide (NO) expression in endothelial cells by inducing transcriptional activation of the endothelial NO synthase (eNOS) gene and inhibit induced ischemic cerebral stroke in normal but not in eNOS-deficient mice. Statins inhibit smooth muscle cell proliferation in vitro and in vivo and stimulate apoptosis. Statins affect fibrinolysis by enhancing the expression of tissue plasminogen activator and platelet activator inhibitor-1 and by decreasing the expression of matrix metalloproteinases. Finally, statins inhibit leukocyte adhesion and the expression of monocyte chemoattractant protein-1 (MCP-1), thereby possibly affecting the recruitment of inflammatory cells into the vascular intima of the atherosclerotic lesion. Recently, our group has demonstrated that statins also regulate some crucial molecules of the immune system and thus could be seen as immunomodulators.

In this issue and in the July issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, 2 articles describe exciting findings involving cholesterol-independent effects of statins on leukocyte recruitment. The study by Diomede and colleagues compared the effects of sterol and nonsterol derivatives arising from mevalonate biosynthesis on a well-defined in vivo model of local, acute inflammation: the air-pouch model. In 1 condition, mice received within 24 hours 3 repetitive doses of lovastatin, which did not affect levels of circulating cholesterol but reduced hepatic HMG-CoA reductase activity. In contrast, in the second condition, the animals received squalestatin, a selective inhibitor of the synthesis of sterol derivatives only, which reduced circulating cholesterol levels and increased hepatic HMG-CoA reductase activity through a negative-feedback mechanism. Subsequent pouch leukocyte recruitment induced by lipopolysaccharide or carrageenan was inhibited only in the group that received lovastatin and could be reversed by mevalonate administration to these mice. The authors then tested for the production of proinflammatory mediators in the air-pouch exudate. Inhibition of interleukin-6, MCP-1, and RANTES (Regulated upon Activation, Normally T-cell Expressed and Secreted) production could be detected in the exudates of lovastatin-treated mice only and not in those of squalestatin-treated mice. By excluding the anti-inflammatory effects of the inhibition of sterol synthesis through the use of squalestatin, the authors elegantly showed in this study that the biosynthesis of nonsterol derivatives arising from mevalonate is important for the anti-inflammatory effects of statins in vivo.

In a recent study, effects of simvastatin were tested in mice deficient for apoE, a model for atherogenesis. Without affecting plasma cholesterol levels, daily doses of simvastatin for 6 weeks significantly reduced the development of atherosclerotic plaques. It would be worth testing squalestatin, and thus involvement of sterol derivatives arising from mevalonate, in this model of chronic inflammation. The study by Yoshida and colleagues sheds light on the mechanism responsible for the inhibitory effects of statins on leukocyte recruitment. In an in vitro model mimicking low physiolog-
ical flow conditions, they observed that pretreatment of monocytic U937 cells with cerivastatin reduced adhesion of these cells to an activated endothelial monolayer. This effect, which could be reversed by mevalonate, coincided with decreased expression of cell surface integrins, such as CD11a, CD18, and VLA-4 and a disruption of F-actin organization. It has been recently reported that protein geranylgeranylation, and more specifically, RhoA geranylgeranylation, is required for integrin-dependent adhesion of leukocytes. In their study in this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Yoshida and colleagues also show that cerivastatin prevented the translocation of RhoA to the membrane fraction of the cell and that C3 transferase, an inhibitor of RhoA, inhibited adhesion of monocytic U937 cells to an endothelial monolayer. It is thus tempting to speculate that statins modulate integrin affinity by inhibition of geranylgeranylation of Rho protein. Alternatively, statins may act through altered actin polymerization or through Rho-regulated altered clustering of adhesion molecules, as reported by Wojciak-Stothard et al. More recently, confirming the results of the 2 articles in this issue, it has been reported that the new statin rosuvastatin inhibits leukocyte rolling, adherence, and transmigration in a rat mesenteric microvasculature model in vivo. Furthermore, as seen for protection from ischemic stroke, the influence of statins on leukocyte recruitment was mediated via NO, because the statins had no effect in eNOS-null mice.

In concert, the 2 studies published in this issue demonstrate that during acute inflammation, treatment with statins inhibits leukocyte recruitment, independent of their cholesterol-lowering properties. These findings provide further mechanistic insights that could explain, in part, the great beneficial effects of statins described within a relatively short period of treatment, even in patients without hypercholesterolemia in secondary as well as primary prevention clinical trials to reduce morbidity and mortality. Because of the relatively high doses of statins required to achieve their anti-inflammatory effects, the development of novel inhibitors of nonsterol mevalonate-derived compounds that dissociate cholesterol-lowering effects from anti-inflammatory activities would be highly desirable. As we learn more about statins as anti-inflammatory agents in vitro and in a growing number of in vivo animal models, we await information that will establish their relevance in acute inflammation in humans. One can speculate that using animal models in in vivo animal models, we await information that will establish their relevance in acute inflammation in humans. One can speculate that using animal models in in vivo animal models, we await information that will establish their relevance in acute inflammation in humans.

**References**


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