

Statins' benefits begin to sprout

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Commentary

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Just flip through your favorite news magazine, and almost invariably you'll find the good news in the advertisement pages. If you can't exercise every day, if you stop a bit too often for a burger and fries, or if you still horrify your family with cigarette cravings, statins are broadly advertised to bail you out from vascular diseases and atherosclerosis. The statins — potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, an enzyme that plays a critical role in cholesterol metabolism — block substrate accessibility to HMG-CoA reductase (1), effectively subverting cholesterol metabolism. These drugs result in lower total and LDL cholesterol levels, while increasing the levels of HDL. After five major placebo-controlled clinical trials with a total of 31,000 patients, there is little doubt that statins epitomize the "good-for-you" drug, in that they safely reduce the incidence of acute coronary events, are effective in both sexes, and can protect even individuals with serious risk factors, like diabetes or history of ischemic heart disease (2). The atheroprotective effects of statins appear to be proportional to the reduction in LDL cholesterol, and the odds get even better with more prolonged therapy.

functions of statins, a good place to start is certainly the endothelium (4). Vascular endothelial cells play a pivotal role in modulation of leukocyte and platelet adherence, thrombogenicity, anticoagulation, and vessel wall contraction and relaxation, so that endothelial dysfunction has become almost a synonym for vascular disease (5). Indeed, there is now evidence that statins improve endothelial function in a number of ways, increasing production of nitric oxide, promoting blood flow, dampening inflammation, antagonizing thrombogenicity, and reducing endothelial vasoconstrictions (4).

Now, in two papers that appear back to back in this issue of the *JCI*, Llevadot et al. (6) and Dimmeler et al. (7) add a new twist to the statin story and demonstrate that inhibitors of HMG-CoA reductase also promote vasculogenesis. This process, the sprouting of new blood vessels from differentiated endothelial cell progenitors, may not be limited to the developing embryo but may also occur in the adult organism. Endothelial cell progenitors have been shown to leave the bone marrow in response to cytokines or ischemic injury, and they are recruited to the periphery to promote compensatory new blood vessel formation. One of the

genitors, Llevadot et al. (6) show that these cells do everything they are supposed to do to make new blood vessels: They proliferate, migrate, and acquire resistance to apoptotic cell death.

These activities are, furthermore, not a mere curiosity of in vitro culture. Both groups showed that statins mobilized endothelial cell progenitors from the bone marrow, in vivo, and Llevadot et al. (6) took this one elegant step further by transplanting mice with the bone marrow of a transgenic animal carrying the *LacZ* reporter gene under control of the *Tie2* promoter, which is active in endothelial cells. This reporter allowed them to show that statin-treated animals accumulate marrow-derived endothelial cells at the site of corneal neovascularization (6, 7). Both groups also identified activation of Akt as a critical signaling requisite of the statin response, and Dimmeler et al. linked this effect to the block of mevalonate formation mediated by HMG-CoA inhibitors (7).

The papers by Llevadot et al. (6) and Dimmeler et al. (7) raise several interesting points. First, a good drug has obviously gotten even better. The ability of statins to mobilize and differentiate endothelial cell precursors may be exploited for therapeutic strategies of peripheral revascularization after ischemic injury. Applications to improve collateral blood flow in patients with myocardial infarction or stroke come quickly to mind, and administering statins is probably safer than giving VEGF to promote angiogenesis or vasculogenesis. Secondly, Akt activation has emerged as an indispensable signaling gateway at the crossroads between angiogenesis and endothelial stem cell recruitment and differentiation.

Still several tantalizing questions remain to be answered. Can statins really do all this alone or do these pleiotropic responses depend on as-yet unidentified mediators? If there is an intermediate second messenger, Dim-

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On the other hand, vascular diseases are by definition multifactorial, and the beneficial effects of statins occur earlier than what would be expected from simple plaque regression. This has prompted the question of whether statins work so well because they do more than just lower LDL cholesterol (3). To look for additional beneficial

critical mediators of this process is VEGF itself, bringing together both vasculogenesis and angiogenesis to restore blood flow to tissues suffering from ischemia. Now, statins appear to do the same job, and just as well as VEGF. Whereas Dimmeler et al. (7) show that statins increase the number of differentiated endothelial cell pro-

meler et al. argue that it is not VEGF that is being somehow upregulated by statins (7). On the other hand, other “vasculogenic factors” clearly exist, and one of the most intriguing may be placental growth factor, which seems preferentially involved in facilitating post-natal blood vessel formation, very much like what the statins appear to do (8). Second, what is the role of nitric oxide in statin-dependent vasculogenesis? Increase in endothelial nitric oxide synthase expression and activity is clearly stimulated by statins, which results in Akt activation (9) and could conceivably mediate some aspects of mobilization or differentiation of endothelial cell precursors. Finally, what are the genes downstream of Akt that are required for the vasculogenic

program induced by statins? A few candidate molecules for the antiapoptotic effect of Akt are just beginning to emerge. However, it is likely that many more exist to account for what is clearly a multifaceted developmental pathway of stem cell mobilization and differentiation exploited by statins. Given the fast pace of research on this exciting topic, the answer to some of these questions may not be too far behind.

Acknowledgments

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