Statins’ benefits begin to sprout

Dario C. Altieri

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 horrified 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 epimerize the “good-for-you” drug, in that they safely reduce “bad” cholesterol metabolism. These drugs may not be limited to the developing embryo. Indeed, there is now evidence 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 thrombogenesis, and reducing endothelial vasoresponses (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 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-

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 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, thrombogenesis, 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 thrombogenesis, and reducing endothelial vasoresponses (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 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-

The Journal of Clinical Investigation | August 2001 | Volume 108 | Number 3
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 postnatal 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 antipoptotic 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
This work was supported by NIH grant HL-54131.