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Biphasic Effects of Statins on Angiogenesis

To the Editor:

I read with interest the recent article by Weis et al¹ that investigated the effects of HMG-CoA reductase inhibitors, or statins, on angiogenesis in vitro and in vivo. The report, along with recent publications,²⁻⁴ raised clinical interest in the potential use of statins for therapeutic angiogenesis to treat patients with ischemic diseases. On the other hand, there is a growing concern that statins may promote tumor growth, diabetic retinopathy, and atherosclerosis, by stimulating angiogenesis. If this were the case, we should reconsider the clinical use of statins, although recent evidence suggests that statins exert a number of beneficial effects, even in normocholesterolemic patients.

Statins have been widely used to lower cholesterol levels for >10 years without serious adverse effects. There is no clinical evidence that statins increase the morbidity of cancer, diabetic complications, or myocardial infarction. Conversely, it has been suggested that statins suppress pathological angiogenesis such as neovascularization in atherosclerotic plaques or tumors at clinically relevant doses. A randomized controlled trial revealed that pravastatin prolongs survival of patients with advanced hepatocellular carcinoma.⁵

To explain the puzzling effects of statins on angiogenesis, Weis et al propose a biphasic dose-dependent effect of statins on angiogenesis, ie, proangiogenic at low therapeutic doses (0.5 mg/kg/d of cerivastatin), but angiostatic at high doses (2.5 mg/kg/d), based on their observations in mouse models of inflammation and tumor-induced angiogenesis.¹ On the contrary, my colleagues and I have previously reported that cerivastatin-augmented collateral vessel growth in response to acute ischemia even at a higher dose (6 mg/kg/d).⁴ We also found that the same dose of cerivastatin suppressed the development of tumors and atherosclerosis in the same animal in which hindlimb ischemia had been induced (Sata et al, unpublished observation, 2002). Thus, it is likely that proangiogenic or antiangiogenic effects of statins depend on the distinct mechanisms of angiogenesis associated with cancer, tissue ischemia, or inflammation. We should be cautious when extrapolating the findings reported by Weis et al to patients.

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Response

We thank Dr Sata for his comments on our article concerning the biphasic effects of statins on angiogenesis. Dr Sata states that the angiogenic effects of statins depend on the model and the milieu. In his paper, which investigated the effect of statins on arteriogenesis, high-dose cerivastatin promoted collateral growth.¹ However, angiogenesis and arteriogenesis are activated and mediated by different molecular pathways. It is not surprising that statins may have different effects on these 2 very different processes. However, we do agree that the effects of statins on angiogenesis may vary with the model, eg, tumor angiogenesis, inflammation-triggered angiogenesis, wound healing, or plaque neovascularization in the setting of hypercholesterolemia.

However, our observations about the antiangiogenic potential of statins are consistent with those of other investigators.²⁻⁴ Very recently, Urbich et al validated our finding that statins exert a biphasic effect on angiogenesis signaling.⁴ They demonstrated that statins promote the migration of mature endothelial cells and endothelial progenitor cells at low concentrations, whereas antiangiogenic effects were achieved at high concentrations (>0.1 $\mu\text{mol/L}$ atorvastatin).⁴

One crucial question remains: Are human statin concentrations proangiogenic or antiangiogenic? Serum levels of statins in humans range between 0.002 and 0.1 $\mu\text{mol/L}$. In our in vitro studies, proangiogenic effects were observed at statin concentrations between 0.005 and 0.05 $\mu\text{mol/L}$ (low-to-midrange concentrations in humans), whereas angiostatic effects were observed at 0.05 $\mu\text{mol/L}$ (high-dose concentrations in humans).² Therefore, one might speculate that chronic exposure to high-dose statins would have angiostatic effects in our patients. This property of the statins might explain in part their beneficial effect on atherosclerotic plaque, the growth of which is dependent on neovascularization.⁵

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