Recent observations suggest that circulating stem cells contribute to neointimal formation. For example, DNA in situ hybridization for the human Y chromosome in sex-mismatched heart transplants has detected up to 2.6% to 16% of human coronary artery smooth muscle cells of host origin. This process likely contributes not only to transplant vasculopathy but also to neointimal thickening in atherosclerosis and restenosis. Yet, the factors that modulate this process are unknown.

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In this issue of Circulation, Inoue and coworkers provide tantalizing translational evidence that local arterial inflammation signals the release of bone marrow–derived stem cells. These investigators placed a coronary sinus catheter to sample blood traversing the coronary circulation before and up to 48 hours after elective percutaneous coronary intervention with bare-metal or sirolimus-eluting stents. Peripheral blood (equivalent to aorta sampling) also was sampled to determine the presence of a transcardiac gradient. Bare-metal stent deployment was accompanied by a burst of neutrophil activation across the coronary artery bed. Neutrophil activation was highest in bare-metal stent patients who subsequently developed restenosis, intermediate in bare-metal stent patients without restenosis, and lowest in patients receiving sirolimus-eluting stents. Accumulation of CD34 cells in the peripheral blood peaked at 7 days and correlated with the extent of transcardiac inflammation at 48 hours and, importantly, with late lumen loss within the stent at follow-up angiography. CD34 cell number was lowest in patients with sirolimus-eluting stents. Most interestingly, endothelial precursor cells in peripheral blood were increased after deployment of bare-metal stents but markedly reduced after deployment of sirolimus-eluting stents.

These observations indicate that stent deployment itself sets off a cascade of biological events that act not only locally but also likely at a distance. Stent-induced inflammation promotes the release of stem cells into the peripheral blood that participate in the healing response of the injured blood vessel, possibly contributing smooth muscle cells to the developing neointima and endothelial cells to the denuded surface. Although the precise mediators responsible for stem cell recruitment remain to be defined, the coronary sinus catheter technique described by Inoue and coworkers provides a particularly attractive opportunity to screen for candidate molecules with proteomic and/or transcriptional profiling approaches. Indeed, evidence is presented for one such mediator, granulocyte-colony stimulating factor, the level of which is increased in coronary sinus blood after stent deployment and correlates with the accumulation of peripheral blood CD34 cells.

The findings of the present study also have important implications for our understanding of vessel wall healing after drug-eluting stenting. Suppression of neointimal growth by sirolimus is a consequence of potent antiinflammatory and antiproliferative actions. Angioscopic and pathological evidence suggests, however, that delayed healing may go hand-in-hand with neointimal suppression. Reendothelialization of stent struts may be impaired significantly after drug-eluting compared with bare-metal stenting. From the observations of Inoue and colleagues, it is intriguing to speculate that the favorable antiinflammatory effects of sirolimus may also silence endothelial cell repair signals emanating from the vessel wall.

Their findings also implicate bone marrow–derived and bone marrow–mobilized CD34 stem cells in the development of in-stent restenosis. In fact, others have reported that both mobilization of circulating stem cells with granulocyte-colony stimulating factor and direct infusion of marrow-derived CD133 progenitor cells are associated with a higher incidence of restenosis after deployment of bare-metal stents. The mechanism of enhanced late lumen loss secondary to stem cell mobilization is incompletely defined. Although transdifferentiation of the progenitor cell to a smooth muscle cell lineage is theoretically possible, local paracrine effects of accumulating progenitor cells on vascular smooth muscle proliferation and migration are more likely to be operative. Indeed, our group has reported the significant paracrine effect of CD133 progenitor cells on vasculogenesis in response to ischemia that involves the modulation of local inflammatory cytokine production.

Taken together, it is interesting to speculate that there is likely a balance between favorable healing promoted by bone marrow–derived progenitor cells in the form of an antithrombotic and antiadhesive endothelium on the one hand and adverse healing in the form of enhanced neointimal thickening on the other hand. The findings of Inoue and coworkers have potentially important implications. Identification of factor(s) that recruit bone marrow–derived stem cells, especially endothelial precursor cells, might allow one to restore or to accelerate the healing response by administering the soluble recruiting factor(s) after drug-eluting stent deployment. Alternatively, endothelial progenitor cells could be

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isolated, expanded, and infused locally or systemically in the post–percutaneous coronary intervention setting.

Finally, interventional cardiologists would do well to heed the prescient words of the famous 19th-century British surgeon John Hilton: “It would be well, I think, if the surgeon would fix on his memory, as the first professional thought which should accompany him in the course of his daily occupation, this physiological truth—that Nature has a constant tendency to repair the injuries to which her structures may have been subjected, whether those injuries be the result of fatigue or exhaustion, of inflammation or accident.” On Rest and Pain, Lecture 3 John Hilton, MD, 1804 to 1878

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References

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