S
ingle cell bone marrow transplantation leaves no doubt as to the ability of bone marrow cells to differentiate and integrate into the endothelium, though the physiological significance of this remains controversial. Reported rates of bone marrow cell integration into the endothelium after injury vary widely, ranging from almost no cells to large percentages. Bone marrow cell maintenance of the quiescent (ie, nongrowing) vasculature has been less well studied, but at least one mouse study suggests it could be significant.1 Whether or not large numbers of circulating cells integrate into the vessel wall, a consensus seems to be emerging that circulating bone marrow–derived cells can promote vascular growth. Exactly how this is accomplished is not clear, though it is presumably due to release of proangiogenic factors.

Mobilization of various circulating endothelial cell progenitor (CEP)–containing populations correlates with increased vascularization in tissues undergoing neovascularization, and vascular trauma including burns, coronary artery bypass graft, and myocardial infarct all mobilize CEPs.2–6 In light of these findings, the loss or dysfunction of CEPs could impact on vascular health. Hence, over the past several years a number of studies have begun to examine whether there is a relationship between CEP function and vascular disease. Of course, to do this, one must define a CEP. Therein lies the rub. No consensus has been reached as to what constitutes a CEP, and each laboratory seems to use a different definition. Generally speaking, CEP-containing populations that have been studied fall into two broad categories: cells related to hematopoietic stem cells and cells (probably) of the myeloid lineage. Hematopoietic stem cell–related populations are thought to yield “late outgrowth colonies” when plated in conditions that promote endothelial cell differentiation. Late outgrowth colonies derive from the nonadherent mononuclear cells and arise only after long-term culture. In contrast, myeloid lineage cells probably are the predominant source of “EPCs,” endothelial-like cells that derive from 4 day cultures of adherent mononuclear cells.

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Arterioscler Thromb Vasc Biol. is available at http://www.atvbaha.org
DOI: 10.1161/01.ATV.0000154484.58485.24
likely to mobilize a different subset of CD133⁺ cells. Further, there is some evidence that G-CSF mobilization may be harmful in certain clinical settings, so it may not represent an ideal mobilizing agent.9 Also, one might speculate that the affected subset(s) of CD133⁺ cells might be disease-specific, as would then be the appropriate mobilizing agent.

The Powell study also examines whether the loss of primitive CEPs is functionally significant, by measuring the ability of nonadherent mononuclear cells to form late outgrowth colonies. Cells derived from CAD patients formed almost no colonies, but the ability to form colonies was restored to levels of healthy controls after treatment of the patients with G-CSF. Unlike an earlier study that assayed EPC formation by cells from CAD patients,10 there was no correlation between the number of risk factors for CAD and the ability to form colonies among CAD patients. However, there did appear to be an association between the number of risk factors and colony formation among healthy patients.

Thus, CD133⁺ cells may prove to be a useful biomarker of vascular disease. Still, though there is an association between the loss of circulating CD133⁺ cells and CAD, that this translates to a loss of CEPs has not been proven. This cannot happen until we know the precise phenotypes of CEPs. Further, decreases in EPCs or late outgrowth colonies could be due to changes in CEPs that render them less able to survive, proliferate, or differentiate in culture. In support of this, simvastatin both induced proliferation and increased survival under stress of EPCs in culture.11 Careful analysis of plating efficiencies, apoptosis, proliferation, and related parameters will be needed before more definitive conclusions can be reached. Nevertheless, it is clear that vascular disease does alter CEP function, and all evidence suggests that this is not for the better.

References

Are Circulating CD133+ Cells Biomarkers of Vascular Disease?
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doi: 10.1161/01.ATV.0000154484.58485.24
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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