Are Circulating CD133+ Cells Biomarkers of Vascular Disease?

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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. 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 mobilized 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.

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Among hematopoietic stem cell–related populations, CD133+, CD34+, and VEGFR+ cells have received a great deal of attention. In early experiments, expression of CD34 or mouse VEGFR2 was used to identify CEPs,7 but both of these antigens are expressed on endothelial cells. To exclude differentiated circulating endothelial cells from a study population, CD133+ has been adopted as a marker for primitive CEP, because CD133 is not known to be expressed by endothelial cells. In some circumstances this is a critical distinction, because some disease and injury states can increase the number of circulating endothelial cells. Thus, although the rare CD133+ cells or subsets thereof by no means represent all CEPs, they may be useful for examining how disease affects the most primitive CEP populations. Further, because presumably all other CEPs ultimately derive from CD133+ cells, this may be an important population to follow.

In an article in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Powell et al report that coronary artery disease (CAD) correlates with a 5-fold reduction in the fraction of three different subsets of circulating CD133+ cells: CD133+CD34+, CD133+CXCR4+, and CD133+VEGFR2+ cells. Because of a possible sustained inflammatory state in CAD patients, the reduction in the absolute number of circulating CD133+ cells might be somewhat less than the percentages suggest, but mobilization of total mononuclear cells is unlikely to account for the bulk of it. Thus, it appears that CAD reduces both the fraction and total number of primitive CEPs regardless of which subset one chooses to assay. More importantly, loss of each of these populations may be indicative of the loss of different functional activities of CEPs. CD133+CD34+ are probably the most primitive of the circulating progenitors, so the loss of other CEP populations may be a direct consequence of the reduction in CD133+CD34+ cells. Because SDF-1 is thought to be essential for CEP homing, loss of CD133+CXCR4+ cells could significantly impact on the recruitment of CEPs to sites of injury. Finally, CD133+VEGFR2+ cells may represent CEPs that are committed to differentiate down the endothelial cell pathway, and their loss may compromise the ability of CEPs to differentiate into endothelial cells.

The authors also show that all three CD133+ mononuclear cell populations are effectively mobilized by granulocyte-colony stimulating factor (G-CSF). Yet, although the fold-reduction in CD133+ cells is similar for the three CD133+ subsets, the fold mobilization differs among the populations and relative to mobilization of the same populations in healthy controls. Thus, although therapeutic mobilization of CEPs may be possible in CAD and other patient groups, the choice of mobilizing agent may be critical, because each is...
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

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