From Genes to Regenerative Medicine
Approaches in Development
Marc Ruel, Alexandre F.R. Stewart, Erik J. Suuronen

Coronary artery disease (CAD) persists as a leading cause of morbidity and mortality in the industrialized world. Patients with myocardial damage who have not adequately responded to medical therapy and revascularization may, if eligible, be treated by surgical ventricular restoration, ventricular assist devices, and, ultimately, by transplantation. Although these treatments can extend the lives of some patients, they can only be offered to a minority of affected patients and remain “mechanical” in that they do not biologically address the functional deficit of the heart. This has led to great interest in cell replacement strategies, with the goal of safely and effectively restoring perfusion and/or contractility to ischemic, stunned, hibernating, or scarred myocardium. A number of clinical trials in cell therapy have been performed, most of them using simpler approaches such as the transplantation of unslected bone marrow mononuclear cells. Recent systematic reviews reveal a significant, although modest, benefit of these clinical trials to myocardial function.1,2 Moreover, growing evidence suggests that neovascularization of the dysfunctional myocardium from paracrine/humoral factors and secondary recruitment of host stem/progenitor cells are the likely mechanisms leading to functional improvement rather than cardiomyocyte replacement.3–5 Nevertheless, the development of therapies to actually regenerate contractile myocardium will likely be required for the treatment of larger areas of damage or dysfunction in the heart, which will also necessitate adequate blood supply for the transport of oxygen and nutrients to ensure survival of the regenerated tissue. Considering this, a cell-based therapeutic “angiogenesis” (or “vasculogenesis,” a distinction in nomenclature not continued in this editorial) approach in ischemic, as well as in infarcted, myocardium may be a promising primary or adjuvant strategy to improve the results of cell therapy in the presence of either myocardial ischemia or scar.

Circulating progenitor cells (CPCs) are an autologous source of cells that could 1 day lead to clinically significant therapeutic neovascularization in humans. There is evidence that marrow-derived circulating progenitor cells are augmented in response to cardiac events and that they home to sites of injured heart tissue.6–7 Notably, increased numbers of CPCs are associated with improved vascular function and recovery following a cardiac event,8,9 and a reduced number predicts future cardiovascular events.10 It is also relevant to consider that autologous stem/progenitor cells derived from patients with cardiovascular disease may have defects in their regenerative activities,10,11 In this regard, it was recently demonstrated that the number of CPCs may be genetically regulated, suggesting a role for CPCs in the inheritance of CAD.12 These revelations have implications on the development of cell therapies, which would benefit from greater elucidation of the genes responsible for stem/progenitor cell differentiation and for their neovascularization potential.

In this issue of Circulation Research, Liu and Patient provide further insight into the role of ETS domain genes, which encode transcription factors, in the regulation of hemangioblast differentiation and angiogenesis (Figure).13 The authors analyzed the ETS family from the zebrafish genome and identified 12 genes that were expressed in blood and endothelial precursors during embryonic development.13 It had previously been demonstrated that the ETS family contains transcription factors linked to angiogenesis (with ets-1 upregulating the expression of angiogenic growth factors, for instance14) and to the regulation of vascular differentiation of flk1-positive endothelial progenitors derived from embryonic cells.15 By gene expression profiling, the authors identified that etsrp is strongly expressed in the putative hemangioblast population during early embryonic development and that its expression is later restricted to endothelial cells. Using loss-of-function analysis, it was demonstrated that etsrp was required for the differentiation of anterior hemangioblasts and of their flk1-positive endothelial progeny.13 A role for etsrp in regulating hemangioblast differentiation was previously unknown, and the finding of Liu and Patient in this regard is relevant to CPC biology, because the hemangioblast is a primitive precursor to both blood and endothelial lineages.

The authors also investigated the function during development of 2 other ETS family members, namely erg and fli1. It was shown, through loss-of-function analysis, that erg and fli1 are required for angiogenesis.13 Vessel patterning was similarly disrupted in the erg and fli1 morphants, and both resulted in a comparable hemorrhage phenotype in the head at the same developmental stage. When a double knockdown of erg and fli1 was performed, the patterning and hemorrhagic phenotypes were even more severe, suggesting that erg and fli1 act cooperatively and additively in regulating vessel integrity and angiogenic modeling.13 Furthermore, expression of VE-cadherin was reduced in erg morphants just before the

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occurrence of the hemorrhage, suggesting that the angiogenic function of erg may act through direct regulation of this endothelial junction molecule. However, this association was not investigated in the *fli1* morphants, and therefore it is unknown whether erg and *fli1* act additively on angiogenesis through the same mechanism.

These findings improve our understanding of the function and mechanisms that link ETS domain genes to hematopoiesis and vessel development and provide insight into the identification of targets for improving stem/progenitor cell function and their use in angiogenic therapies. For example, the expansion of stem cells in culture can lead to alterations in their genome and function, and these changes may negatively impact on their clinical safety and efficacy.\(^\text{16}\) The development of techniques to control the changes of stem/progenitor cells in culture will benefit from greater knowledge of the genes responsible for the regulation of their differentiation and function.

Depressed CPC number/function may represent a cardiovascular risk factor with a significant genetic contribution,\(^\text{12}\) making it plausible that CPC dysfunction is a multigene disorder with a complex relationship to the other traditional cardiovascular risk factors.\(^\text{17}\) In this scenario, the identification and study of single candidate genes based on function would be less likely to provide targets for improving the efficacy of autologous progenitor cells in therapy. This is because with multiple contributing genetic factors, the effect of each gene is only a fraction of the resultant phenotype in CAD.\(^\text{17}\) Support for this concept comes from the observation in the study by Liu and Patient that 2 ETS domain genes under investigation acted cooperatively in regulating angiogenesis.\(^\text{13}\) Whereas these studies are essential to elucidate the function of the known suspects, unbiased genome-wide association studies, such as those being performed to identify genetic contributors to coronary disease,\(^\text{18,19}\) may uncover genetic loci containing genes with previously unsuspected links to CPC function. Such information could define mechanisms of importance for individual patients, toward the development of strategies to enhance autologous progenitor cell function and ultimately enable personalized cell-based regenerative therapy.

Regardless of the approach, namely candidate gene versus genome-wide association studies, it is probable that major improvements in the success of regenerative strategies can be translated from understanding the regulators of stem/progenitor cell differentiation and function. The success of therapy using solely autologous cells in CAD patients may come from the study of genes and development.

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None.

**References**


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