Heart regeneration: The endothelial cell comes first

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Although great therapeutic progress in treating cardiovascular disease has been achieved in recent years, heart failure after ischemic heart disease remains the leading cause of death of people older than 65 years in the United States.¹ The fundamental challenge to treating postinfarct heart failure is that neither the noncontractile, fibrotic scar tissue that replaces ischemic or necrotic cardiomyocytes after myocardial ischemic or infarction events nor the residual native myocardial tissue readily naturally serves as a substrate for myocardial regeneration.² Several strategies have consequently been pursued by cardiac researchers to overcome the limited regenerative capability of the human heart: (1) increasing the regenerative capability of the cardiomyocytes by inducing cell division or recruiting endogenous stem cells or progenitor cells³⁻⁵; (2) implantation of cardiomyocytes or progenitor cells that may differentiate into cardiomyocytes⁶⁻⁸; and (3) in situ reprogramming of cardiac fibroblasts into cardiomyocytes.⁹

Each of these myocardial regeneration strategies has advantages and disadvantages, and further investigation is warranted before the use of any of them can be supported as a viable clinical therapy. One principle that appears to unify all these regenerative strategies is addressing the challenge that any newly generated cardiomyocytes will be located in the ischemic postinfarct environment and will therefore need an augmented source of oxygenated blood to survive. Given this dilemma, we previously demonstrated that angiogenic pretreatment of myocardial scar (with vascular endothelial growth factor) increased scar vascularization and the subsequent cardiac functional improvements rendered by the subsequent administration of cardiac reprogramming factors that have been shown to transdifferentiate scar fibroblasts into induced cardiomyocytes.¹⁰ This work recapitulates similar examples of the benefits of angiogenic pretreatment or cotreatment of scarred myocardium accompanying the use of stem cell administration.¹¹⁻¹³

Ingason and colleagues¹⁴ report in this issue of *The Journal of Thoracic and Cardiovascular Surgery* their

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Central Message

Endothelial cells play an essential role in cardiomyocyte regeneration, not only supplying perfusion but also guiding cardiomyocytes for migration and organization.

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findings that angiogenesis preceded cardiomyocyte migration in a neonatal mouse apical resection model. They concluded that preestablishment of the vasculature is paramount to supporting cardiomyocyte ingrowth and survival, similar to the previous observations of Porrello and associates.^{15,16} These findings are reminiscent of the therapeutic principles noted with angiogenic pretreatment of myocardial scar.

The concept that cardiomyocyte ingrowth more specifically follows the “guidance” of endothelial cells has been suggested by Narmoneva and coworkers,¹⁷ who demonstrated that cardiomyocyte reorganization occurs along endothelial cell and capillarylike networks. In addition, cardiomyocytes started synchronized, spontaneous contraction when cultured in the preformed endothelial cell network, in contrast to cardiomyocyte-only culture, in which such contraction was much less.

The findings of Ingason and colleagues¹⁴ suggest the important principle that endothelial cells play an essential role in cardiomyocyte regeneration in the postinfarct heart, not only by supplying perfusion to the infarcted myocardium but also in the way that endothelial cells guide cardiomyocyte organization. The role of the endothelial cell must therefore be taken into account no matter what approach is taken to regenerate cardiomyocytes in the infarcted heart. The addition of endothelial cells or endothelial development strategies to myocardial regenerative strategies must be seriously considered if we are to improve the efficiency of heart regeneration.

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