Predicting the Future With Stem Cells

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The best way to predict future is to invent it.
—Alan Kay

The efficacy of bypass surgery in patients with ischemic cardiomyopathy remains impossible to forecast accurately. In particular, individual variability in factors such as disease comorbidities, genetic background, aging, disease progression, lifestyle, and medications makes the prediction of the outcome of bypass surgery a herculean task. Identifying readily available patient-specific information to prognosticate the likelihood of benefit with highly invasive procedures such as bypass surgery not only could minimize patient suffering but also could significantly reduce the cost and resource burdens on a healthcare system that is already stretched to the limit.

Over the last several years, the cardiovascular field has embraced (with varying degrees of enthusiasm) regenerative medicine. Indeed, expert opinions in the field have ranged from beliefs that stem cells can do virtually anything (eg, repair and replace damaged myocardium) to the notion that they are essentially useless (eg, whatever observed biological effects are functionally meaningless). Despite the ongoing debate, most available evidence now suggests that the heart is a self-renewing organ to some (yet to be clarified) extent and that such reparative processes involve a resident pool of self-replicating and renewing c-kit–positive cardiac stem cells (CSCs). Indeed, CSCs have been shown to repair damaged heart after myocardial infarction, to contribute to neomyogenesis and angiogenesis, and to augment heart function. If the functional outcome of bypass surgery depends substantially on the functional competency of CSCs, then forecasting the potential benefit of major surgical interventions such as coronary bypass grafting may be accomplished by preemptively assessing the regenerative potential of the CSC pool.

Indeed, an initial step toward this brave new world of patient-specific therapy is provided by D’Amario et al in this issue of Circulation, who showed that the same CSCs used as a cellular therapy in regenerating damaged myocardium can also predict outcomes for bypass surgery. They demonstrated a critical correlation between the biological characteristics of endogenous CSCs and the recovery of patients after bypass surgery. The role of these CSCs in revealing the success of bypass surgery may lead to a new predictive tool for cardiologists to make more accurate and timely recommendations for patient candidates before they undergo a costly and painful surgical intervention. Moreover, these initial correlative findings suggest that phenotyping the functional status of endogenous stem cells, as has been done in animal studies, may be required for identifying the patients who will be most likely to benefit from regenerative therapy versus those “refractory” patients who are unlikely to improve.

In the D’Amario et al study, the reparative capability of CSCs was evaluated by population doubling time, telomere length, telomerase activity, and expression of circulating insulin-like growth factor-1 (IGF-1) receptor. Strong correlations were found between these 4 parameters and left ventricular remodeling in patients suffering from ischemic cardiomyopathy. CSCs with higher replicative potential exhibited enhanced reparative function. These findings using a clinical population of bypass patients echo similar correlations established between telomere length–telomerase axis with enhanced reparative potential of CSCs. Increased expression of the IGF-1 receptor is not coincidental; ample studies in the literature show a correlation between telomerase and IGF-1. In addition, IGF-1 plays an important role in enhancing the function of CSCs after myocardial infarction and aging.

Biologically young CSCs possess increased capacity to augment myocardial regeneration, whereas senescent CSCs exhibit compromised functional capacity. Therefore, CSCs with a youthful phenotype will possess increased neovascularogenesis capacity after surgery, which will have an additive effect to improve the structural and functional recovery of heart after coronary artery bypass graft surgery. The replicative potential of isolated CSCs correlated with ventricular remodeling after revascularization in patients undergoing bypass surgery, as evidenced by anatomic indexes of wall thickening, a reduction in chamber diameter and volume, and an increase in ventricular mass–to–chamber volume ratio. Conversely, diminished replicative potential of CSCs is associated with ventricular wall thinning and a reduction in left ventricular mass–to–chamber volume ratio after surgery. Circulating paracrine factors, including IGF-1, hepatocyte growth factor, stem cell factor, vascular endothelial growth factor, granulocyte colony-stimulating factor, and basic fibroblast growth factor, were assessed at baseline and 1 year through the use of patient blood samples. Levels of IGF-1 and hepatocyte growth factor were higher before surgery in patients with positive left ventricular remodeling; however, only IGF-1 was elevated 1 year after surgery.

One remarkable aspect of this correlative study is the prognostic value of CSCs as a tool to predict favorable outcomes...
and to indicate cases in which benefit is likely to be modest at best. The implicit mechanism from these observations is that regenerative potential is intimately involved in the process of recovery and improvement after bypass surgery to promote revascularization and blunt ischemic damage. CSCs have already proven their regenerative potential in laboratory\(^1\)\(^\text{19}\) and clinical settings,\(^1\)\(^\text{19}\) and now their growth characteristics can be used as an indicator of positive or negative left ventricular remodeling in the heart after surgery. However, these findings must be further confirmed by enrolling more patients with diverse medical conditions, ages, and genetic backgrounds. For now, factors such as diabetes mellitus, age, and sex have not been shown to be correlated within the CSC pool. In contrast, the negative correlation of variables like diabetes mellitus and aging with CSC proliferation is well established.\(^1\)\(^\text{10}\)\(^\text{16}\) Similarly, aging and diabetes mellitus also have been shown to correlate negatively with other stem cell types such as mesenchymal stem cells.\(^1\)\(^\text{17}\)\(^\text{18}\) To assess whether these variables are associated with surgery outcome in patients with heart problems, greater sample cohorts from the CSC pool are needed. Further investigations into specific characteristics of CSCs before and after surgery should improve our understanding of CSCs and their functional capacity. Such studies, however, are hard to implement in humans because patients are exposed to additional risks in the process of obtaining heart tissue samples to isolate CSCs. As a substitute, CSCs could be isolated before and after surgery in animal models to study the roles and characteristics of CSCs after myocardial insult.

The finding presented by D’Amario et al have implications for therapy, in addition to those predicting outcome of bypass surgery. Indeed, the Stem Cell Infusion in Patients with Ischemic Cardiomyopathy (SCIPIO) trial represents just a first step in the development of cell-based therapy using CSCs. The fact that CSCs can be isolated reliably from patients with advanced atherosclerotic heart disease augurs well for future large-scale efforts to perform autologous therapy with these culture-expanded cells. Of course, the variability in the cells may play a role in the outcome of cell-based therapeutic attempts using ex vivo expanded CSCs. A second major implication arising from this work relates to the use of other cell types such as mesenchymal stem cells. It is noteworthy that one of the mechanisms of action of mesenchymal stem cells may be the activation of the endogenous CSCs. Thus, the present findings showing the presence of CSCs in all of the patients may help explain the success of clinical trials using mesenchymal stem cells. Finally, given the variability in CSCs, attempts to enhance them with Pim-1\(^\text{19}\) or other enhancing factors and mixing them with mesenchymal stem cells may have value.\(^\text{20}\)

The exciting results presented by D’Amario et al remind us that the role of new agents such as CSCs is complex and requires intensive investigation into their specific environment and other ambient factors. These findings highlight the profound need to understand mechanisms underlying impaired regenerative capacity and to restore reparative potential for vulnerable patients who, through age, injury, or chronic conditions, have lost most self-healing ability in their heart tissue. With more insight into how a heart with healthy CSCs can better recover from damage, we will also be able to apply that knowledge to tailor therapy to individual patients and to predict their postsurgery outcomes, bringing us one step closer to the age of personalized medicine.

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