Stem Cells

The Chameleon Fountain of Youth
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Senescence requires rejuvenation of organs critical to survival. To date, efforts at “rejuvenation” of the heart have largely used replacement (orthotopic transplantation) and, more recently, mechanical biventricular assist devices. These strategies have been hampered by the limited availability of donor organs and the high levels of immunosuppression required to prevent transplanted organ rejection and consequent infectious/neoplastic complications, as well as the physical, rheologic, and thrombotic issues attendant mechanical devices. Most patients suffering from advanced myocardial dysfunction with clinical congestive heart failure will die waiting for heart “organ replacement.” This reality has prompted recent advances in both electrical resynchronization and adjunctive pharmacotherapy that target myocardial remodeling and the inflammatory pathogenesis of myocardial dysfunction. The conceptual revelation and experimental observations that primitive, pluripotential stem cells may differentiate into functional myocardial or vascular tissue has ignited great interest. Indeed, if stem cell–myocardial regeneration becomes a clinical reality, the potential widespread applicability and impact of this therapy on the modern industrialized world’s leading healthcare problem (congestive heart failure) is profound. Although embryonic stem cells have an exceptional capacity for proliferation and differentiation, potential immunogenicity, arrhythmogenicity, and particularly ethical considerations limit their current use. As eloquently outlined by Perin et al and Strauer and Kornowski in the current issue of Circulation, adult stem cells capable of myocardial regeneration may be derived from bone marrow (endothelial precursor cells, stromal, mesenchymal, and hematopoietic stem cells), skeletal muscle (myofibroblasts), or even adipose tissue.

Bone marrow–derived stem cells appear to have the capacity to home, graft, differentiate, and participate in myocardial contractile function. Further expansion of a selected cell population from bone marrow aspiration or skeletal muscle biopsy requires cell culture but can be accomplished expeditiously (≤2 weeks) with currently available technologies.

Many questions and challenges remain. What stem cell(s) or combination will provide optimal/maximal myocardial regeneration? How will stem cell therapy be administered to ensure maximum therapeutic efficacy? Noninvasive (intravenous), transcatheter (coronary arterial or venous, intra-ventricular) and surgical applications are all currently being explored. Different strategies, ie, global “seeding” versus aliquot “targeted” injections, may be preferable for different clinical scenarios (generalized cardiomyopathy versus regional infarction). Can adjunctive growth factor, chemokine, immune regulatory, or pharmacological therapy augment/enhance grafting, proliferation, and function of stem cell implants? Will stem cell therapy be applied earlier in the course of ischemic cardiomyopathy and thus alter the “natural history” of this disease? For example, regional stem cell therapy in the left anterior coronary artery distribution early after anterior myocardial infarction could favorably influence the myocardial remodeling process and provide late beneficial effects on left ventricular geometry, volume, and wall stress. As such, stem cell therapy might be incorporated into the pharmacological and catheter-based care process for acute myocardial infarction. Importantly, despite providing func-
tional contractile recovery, will stem cell implants become “islands” of temporal dispersion in electrical repolarization and thus, a nidus for re-entrant arrhythmogenesis? Lastly, what is the durability or longevity of stem cell implants? Will their lifespan be similar to or shorter than the myocardial cells they replace? No doubt these regenerative myocardial cells will have similar nutritive requirements and susceptibility to (re)infarction as did the cells they replace. Thus, maintenance of macrovascular and microvascular integrity will be crucial to the long-term success of stem cell myocardial regenerative therapy. The coming years will bring maturation to this exciting, young field.

“In youth we learn, in age we understand.”

Marie von Ebner-Eschenbach

References
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