EDITORIAL

Cell Therapy for Heart Failure

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The pandemic of ischemic heart disease is increasingly recognized as a leading cause of global morbidity. While modern treatment modalities for acute myocardial infarction have reduced early mortality, they have concurrently precipitated a higher incidence of chronic heart failure among survivors. Recurrent hospitalizations and premature death, prevalent in this growing patient population, have imposed a major unmet need associated with the inability of current, largely palliative, therapies to address massive tissue destruction post-infarction. The myocyte-deficit in infarction-induced heart failure is in the order of 1 billion cells with a 25% loss of the left ventricle mass.[1] The hallmark of this malignant pathology is the progressive maladaptive remodeling of the myocardium that precipitates contractile dysfunction, and ultimately leads to the overt syndrome of congestive organ failure. Repair of failing infarcted hearts is a formidable challenge confronted by cardiovascular medicine, considering not only the magnitude of cardiomyocyte loss but also the requirements to reestablish optimal supply in support of functional and structural demands.[2] A compelling clinical need thus exists for the establishment of innovative cardiovascular therapies that will extend the reach of the medicine of today. In this context, the emergence of regenerative medicine—a vanguard in healthcare paradigms—has begun to transform the perspectives of clinical practice.[3] Applied in the management of cardiovascular diseases, regenerative medicine tools aim at enabling the functional restoration of damaged heart tissues, not a mere abatement or mitigation of symptoms. Accordingly, the ongoing global efforts of the scientific and healthcare community are essential steps in ensuring safe and effective translation of fundamental knowledge underlying cardiac cell repair therapy into algorithms for broader clinical use.[4] Indeed, based on rapid advances in stem cell biology, successful application of regenerative medicine principles promises significant human health benefit with tangible outcomes for increased quality of life and improved future patient care.

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Rationale for Cell-Based Therapy

The revolution in stem cell technology, coupled with the increased understanding of the endogenous processes underlying organ repair, has provided the scientific foundation for the development of regenerative approaches. A number of natural or bioengineered stem cell platforms have been successfully tested in various experimental models of cardiovascular disease.[1-6] Stem cell-based regeneration applied to the treatment of heart disease is based on the realization that natural self-renewing processes are innate to the myocardium, but may not be sufficient to salvage the infarcted heart muscle. The unexpected recognition that the heart is not a terminally differentiated organ as conventionally believed, but rather harbors self-repair mechanisms as natural processes for tissue homeostasis has been recently documented. Quantitative monitoring of innate cardiomyogenesis has established a significant growth reserve of the adult human heart capable of replacing both its myocyte and nonmyocyte compartment during lifespan.[7] Furthermore, within failing hearts, increase in stem cell load can contribute to the regenerative response, and involves the derivation of cardiomyocytes from circulating or resident progenitors. Yet, in the context of large-scale destruction associated with massive ischemic injury, the regenerative potential is typically insufficient to rescue a deteriorating myocardium. In fact, the overall efficacy of self-repair is further compromised by patient age, disease status, co-morbidities or drug therapy, and defined by significant individual genetic/environmental variance. Beyond heart muscle self-renewal, or rejuvenation, whole organ transplantation or replacement has offered a lifesaving procedure, but donor shortage limits the number of potential recipients. Therefore, biogenesis

of new tissue parts for de novo tissue restoration, or regeneration, is increasingly considered as a therapeutic strategy to enhance repair post-injury in refractory heart failure.[8] Extrapolating from the paradigms of natural heart rejuvenation and transplant-based organ replacement, activation of endogenous and/or introduction of exogenous progenitor cells into the injured heart offers a legitimate strategy to ameliorate the burden of disease.[8]

Targets for Therapy

Stem cell therapy is targeted on halting or reversing progression of myocardial injury. It should be noted that while early after myocardial injury, the primary therapeutic goal is the salvage of the jeopardized myocardium to prevent further myocardial expansion and negative remodeling, at later stages of developed ischemic left ventricular dysfunction, the aim is to reverse maladaptive remodeling and ensure improved contractility.[9] In particular, excessive inflammatory response, oxidative stress and apoptosis are the primary targets in the initial stages, whereas fibrosis, loss of fibre organization, and impaired excitation-contraction coupling are key features of florid ischemic cardiomyopathy. In addition, multidimensional interactions between cardiomyocytes, extracellular matrix and blood vessels determine the outcome of global remodeling and ventricular dynamics. Thus, differences in the molecular and cellular substrate during the course of disease pathogenesis are likely to require distinct regenerative strategies to prevent progression or treat overt heart failure.[9]

Responders Versus Non-Responders

Most clinical studies to date have been performed with total bone marrow mononuclear cells, which comprise hematopoietic progenitor cells, mesenchymal stem cells, and monocytes.[10] Analysis of clinical trial outcomes underscores feasibility and safety of bone marrow cell therapy, and point to modest albeit variable improvement in functional parameters of recovery, including myocardial perfusion and contractile performance, in patients with acute myocardial infarction, heart failure or chronic myocardial ischemia.[1,4,9,11] Indeed, trial results are not uniform owing to the current lack of standardization and optimization of cell isolation and delivery protocols.[4,12] Beyond inter-trial variability, inter-patient variability has been increasingly recognized triggering an ongoing quest for optimization and identification of the most appropriate cell source and cell type, stratification and selection of patient populations most amenable to cell-based therapy, targeting ideal timing of intervention and most favorable routes of administration.[1,3] It should be noted that in contrast to traditional medications, regenerative cytotherapy products contain viable cells as the active ingredient.[13] Cell therapy is currently limited by low rates of cell engraftment and poor cell survival.[12] Advanced patient age, cardiovascular risk factors, and underlying heart disease appear to also have a negative impact on the functional activity of progenitor cells.[4] Mechanism of improved benefit have implicated, among other variables, a defining role for the extent of cardiovascular lineage commitment.[10,14] Establishing the individual efficacy profiles is thus paramount to maximize benefit of cell-based therapy in the management of cardiovascular disease.

In this issue of Revista Española de Cardiología, Suárez de Lezo et al report significant individual variability in the response to intracoronary infusion of autologous bone marrow-derived mononuclear cells in a small cohort of patients with chronic anterior myocardial infarction and severely depressed ventricular function.[15] Indeed, within a rather homogenous group of high-risk patients, a variable proportion of eligible patients failed to benefit from this treatment, and were recognized as "non-responders." Age, time from infarction, and number of cells infused were among factors excluded influencing outcome, although hypertension was more common in the non-responders subgroup.[15] Characteristically, the "responders" were revascularized close to the time of cell therapy. An inverse relationship between functional recovery and biological parameters that reflect a state conducive to cell migration was also noted.[15] This study exemplifies the critical need in directing the selection of patient cohorts and matching the most valuable stem cell types, guiding thereby the rational design of cell enhancement strategies to realize the full potential of cell therapy in next generation clinical trials.

To date, despite intensive investigations aimed at identifying reliable diagnostic tools for the selection of responders, partly due to the complexity and multi-factorial nature of the mechanism underlying cell-based repair, no conclusive evidence is available regarding which of the many variables assessed predict most accurately individual response and should thus be included among selection criteria. This gap in knowledge underscores the necessity for continuous advancements in discovery science to increase the understanding of stem cell biology in the context of the recipient diseased environment and the mechanisms of myocardial repair. Critical variables, raised by this study,[15] need consideration for a more efficient translation from proof-of-concept studies

to targeted application. In fact, it is anticipated that an increasing number of comparative studies will be the focus topic of imminent basic and clinical studies in cardiovascular regenerative medicine.[3] Ultimately, the rigor of comparative effectiveness outcome analysis with the potential to inform practice, improve care, and influence costs applied across regenerative platforms, as well as between stem cell-based therapies and current medical/surgical state-of-the-art management options, will provide the cornerstone of future evidence-based standard of care.[3]

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