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Commentary: Evidence-based human stem cell therapy for myocardial healing: Miles to go

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CENTRAL MESSAGE

Despite many challenges, MSC-based therapies are promising for the management of ischemic cardiomyopathies.

Stem cell-based therapy has successfully emerged as a promising platform for myocardial regeneration in the management of ischemic cardiomyopathies (ICM). Versatile stem cell candidates have been tested in preclinical models and in clinical trials that revealed appreciable experimental and/or clinical outcomes.[1] Adult human tissues, including bone marrow, adipose tissue, and myocardium are home to stem cells with tremendous potential to differentiate into cardiomyocytes and regenerate failing myocardium. Unfortunately, potential challenges exist due to gaps in the scientific knowledge regarding the differentiation signals, cellular microniche, complexity of myocardial regenerative machinery, and regulatory events that are hurdles in the translation to clinical arenas.[2] Considering human applications, mesenchymal stem cells (MSCs) have been hailed as promising candidates owing to their immense regenerative potential accelerated through paracrine signaling by upregulating the pool of growth/repair signals, including vascular endothelial growth factor, fibroblast growth factor 2, and hepatocyte growth factor facilitating angiogenesis, neovascularization, and cell survival. In addition, MSCs are the repertoire of antifibrotic factors, including matrix metalloproteinases (MMPs) especially MMP-2, MMP-9, and MMP-14, which facilitate extracellular matrix remodeling and cardiac healing.[3] Hence, it is vivid that regenerative functions of MSCs largely depend on the paracrine signaling elicited by their secretome. Despite the growing advancements in stem cell biology and regenerative cardiology, human cardiac regenerative therapy using stem cells awaits further milestones and success stories.

The past few decades witnessed increased demand/trend toward stem-cell–based cardiac management strategies where the application of MSCs have been extensively explored. The global market for stem cells and/or stem-cell–based products have significantly increased and several seminal discoveries have been reported at preclinical and clinical levels. For instance, the myocardium being associated with abundant vasculature, the stem-cell–based approaches warrant focus on vascular regeneration as well.[3] We attempted to address this issue by deciphering the critical role of angiotensin type 2 receptors on the differentiation of porcine bone-marrow–derived MSCs to endothelial cells improving the translational relevance.[4] Such findings are crucial while considering clinical applications. In this context, Mazine and colleagues[5] critically reviewed the available literature regarding the successful Phase I and Phase II clinical trials on stem cell therapy for myocardial healing in the management of ICM.[5] Expository analysis of Prevention of Contrast Renal Injury with Different Hydration Strategies (POSEIDON) trial, Transendocardial Autologous Cells in Ischemic Heart Failure (TAC-HFT) trial, Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization (PRECISE trial), Bone-marrow-derived mesenchymal stromal cell in Ischemic Heart Failure (MSC-HF) trial, Randomized Clinical trial of Intravenous Infusion Umbilical Cord Mesenchymal Stem Cells on

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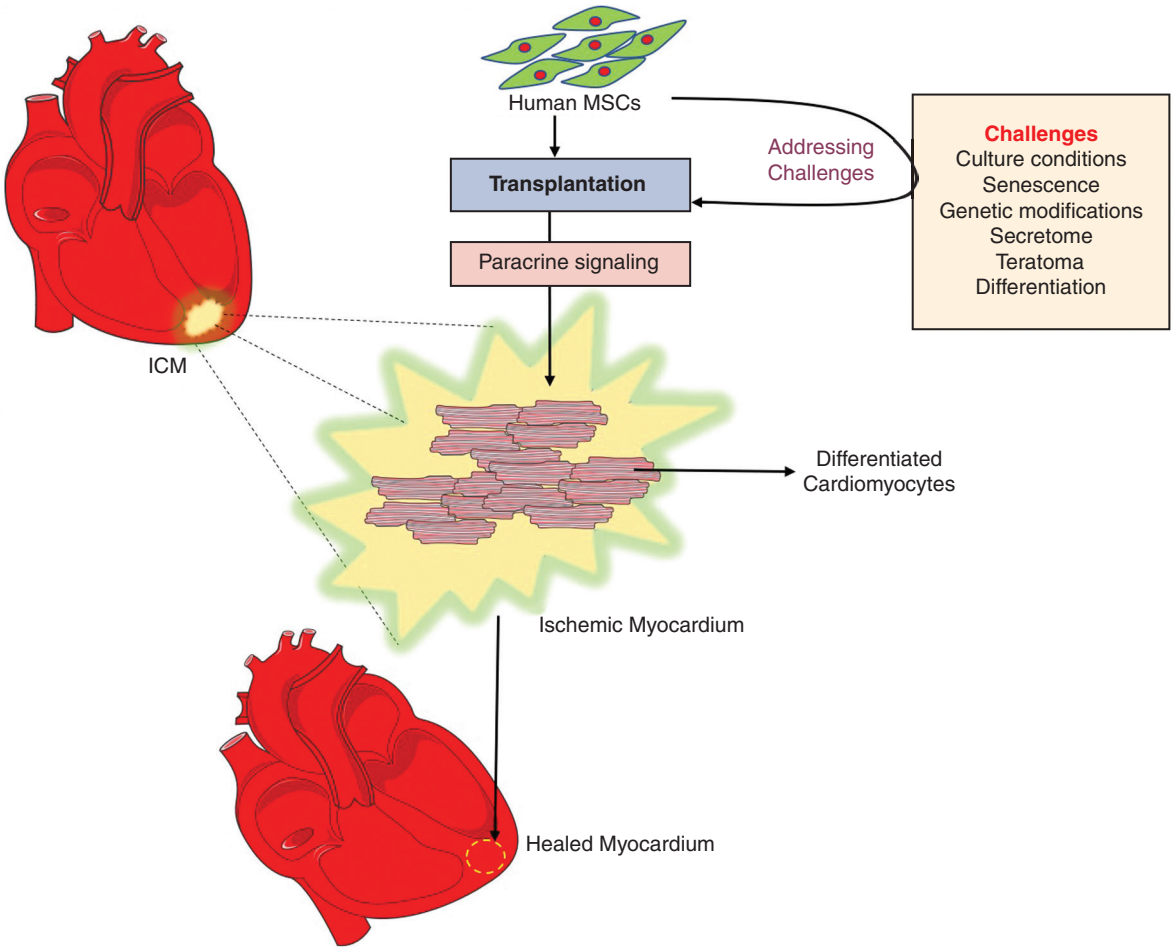

FIGURE 1. Illustration demonstrating the central message and potential challenges associated with human mesenchymal stem cell (*MSC*) therapy for the management of ischemic cardiomyopathy (*ICM*).

Cardiopathy (RIMECARD trial), and left ventricular assist device Mitochondrial Pyruvate Carrier 2 (MPC2) trial have been detailed by the authors. Unfortunately, their comprehensive analysis revealed an absence of Phase III clinical trials that warrants further advancements in stem cell research. Hence, it is worth exploring the potential hurdles to translational applications of MSCs. The major potential challenges in stem cell therapy for cardiac regeneration and the interpretation of published findings include inconsistency of available data due to the heterogeneity of culture conditions, spontaneous senescence of transplanted cells, unsuccessful stem cell priming due to genetic modifications, lack of understanding of immunology/immunomodulatory effects, conflict between exosome therapy and stem cell therapy with MSCs and induced pluripotent stem cells, discrepancy regarding the site and mode of injection, dysregulated differentiation profile and teratoma formation, unavailability of unique differentiation strategies toward multiple cells of cardiac lineage, and the list continues. Certainly, the review by Mazine and colleagues[5] provides insights into these potential scientific questions based on the lessons from the available clinical trials on stem-cell–based myocardial regeneration. The central message of their review is illustrated in Figure 1. It is noteworthy that the emerging advancements in cellular reprogramming,[6] synthetic stem cells,[7] and tissue engineering[8] offer significant promises for stem-cell–based therapies for improved cardiac healing.

Mazine and colleagues[5] have narrated the present clinical scenario of MSC therapies for the management of ICM and ignite multiple concepts and research ideas to address the potential challenges to successful human outcomes. Although the findings are optimistic, the survey of confounding comorbidities, including hypertension and hyperlipidemia, warrant further attention. In conclusion, investigations are required to potentiate the paracrine effects of MSCs on patient outcomes to upgrade MSC-based therapeutics in clinical practice.

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