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Commentary: Mending a broken heart: The ongoing quest for mesenchymal stem cell therapy for ischemic cardiomyopathy

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CENTRAL MESSAGE

Future success of MSC therapy for ischemic cardiomyopathy may depend on an integrated approach, boosting regenerative cell function while tailoring therapy to the receiving patient's background.

Effective strategies to restore cardiac function following myocardial infarction and prevent development of heart failure are much needed. Translational research in this area is very active, yet unsatisfactory.[1] Regenerative medicine via cell therapy promised huge benefits in preclinical studies; however, although mesenchymal stem cell (MSC) therapy trials have shown promising results to improve limb ischemia,[2] whether or not this approach can be effective for ischemic cardiomyopathy (ICM) remains elusive. In patients with ICM, intramyocardial injection of MSCs led to modest improvement of left ventricular function and clinical outcomes.[3] Among the limitations were quality of study design (eg, sample size and statistics), heterogeneity of MSCs from different sources, route of delivery, dose, and culture methods. Therefore, one wonders if there is still hope for MSC therapy or if, 20 years after the initial proposal of progenitor cells capable of mending the broken heart,[4] we should explore different approaches.[5]

Mazine and colleagues[6] review evidence that the field might still be alive. Although the original hypothesis that MSCs can replace injured cardiomyocytes or support differentiation of cardiac-resident stem/progenitor cells has remained unproven, a paracrine action of MSCs seems an undisputed salutary effect of cell therapy. The authors review the latest MSC clinical trials, and propose the following strategies to improve efficacy.

Priming consists of gene modification or treatment with cytokines/growth factors able to rejuvenate MSCs. This might be important because injected MSCs may become dysfunctional due to aging and/or comorbidities of receiving patients.[7] Recently, some noncoding RNA, either small or long chain, have been associated with MSC function; this might represent a target for priming or for selecting optimal cell therapy recipients.[8] MSCs can be injected along with other cells capable to support their survival and differentiation. Examples are immune cells and induced pluripotent stem cell-derived cardiomyocytes. Indeed, the immunomodulatory action of MSCs has prompted their testing as a therapy for coronavirus disease 2019.[9] Induced pluripotent stem cells represent promising candidates, overcoming limitations of embryonic stem cell-derived cardiomyocytes,[10] showing regenerative capabilities in nonhuman primates.[11] However, being newly differentiated, plastic cells, they demand further studies before clinical translation to exclude risk of tumorigenesis. Pericytes; that is, adult somatic cells guiding endothelial cells to support angiogenesis, have proven successful in preclinical studies.[12] Extracellular vesicles that can deliver a cargo of reparative molecules to injured myocardium, such as proteins and noncoding RNAs,[13,14] or nanoparticles,[15] represent another interesting approach. Lastly, scaffolds and hydrogels are promising means to deliver cells and cell products, but their use is still confined to preclinical settings.

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These suggested actions might prove successful, but much research is needed before going translational, also considering that the ischemic nature of a recipient's heart is a hostile microenvironment that could jeopardize survival and function of injected cells. Well-designed trials are necessary to establish the efficacy of MSC therapy for ICM. To circumvent the problem of recruiting large cohorts to document hard end points, we should refine the target population in terms of the age, comorbidities, and molecular landscape of recipients. Artificial intelligence techniques, especially Deep Learning, integrating functional, imaging, and biomolecular and omic data,[16] might help identifying specific patterns to deliver personalized regenerative medicine.

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