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Stem Cell Therapy for Acute Myocardial Infarction: On the Horizon or Still a Dream?

Kenneth M. Fish^a, Kiyotake Ishikawa^a, and Roger J. Hajjar^a

^aIcahn School of Medicine at Mount Sinai, Cardiovascular Research Center, New York, New York

Background

Heart failure (HF) remains a major cause of mortality and morbidity¹ accounting for one in three deaths. Nearly 800,000 Americans experience an acute myocardial infarction (AMI) annually and about half develop HF within 5 years of their first event. This highlights the urgent need for novel therapeutic approaches to repair the injured heart muscle, improve cardiac function, quality of life and long-term survival. While the current standard of care including beta blockers and ACE inhibitors modestly improve long-term prognosis, major efforts by the biomedical community have been spent on novel therapeutic approaches to further improve clinical outcomes.

Stem cell research: A major biomedical effort

Globally, the biomedical community has made major investments in the development of stem cell therapies for AMI and subsequent HF. Basic scientists continue to focus on understanding cardiac pathophysiology and to develop disruptive technologies including cell therapies as an approach to regenerate injured heart tissue over the past two decades. In that period, there are more than 1,200 scientific reports entered into the NCBI PubMed database that refer to AMI and stem cells, most of which focus on in-vitro and in-vivo pluripotency, differentiation, cardiomyogenesis and paracrine signaling in animal models of HF and in clinical trials. In addition, ~100 clinical trials have been entered into the NIH clinicaltrials.gov database, many of which specifically address myocardial infarction. Early clinical trials have focused on use of skeletal myoblast and over time mesenchymal stem cells (MSCs) have been most commonly delivered. Currently, MSC delivery is the most advanced stem cell clinical trial in the cardiology field.²

Historically, the adult heart has been considered to be a post-mitotic, non-regenerating organ. The first research report of significant cardiac self-renewal in zebrafish³ appeared just three years before first in man delivery of stem cells harvested from the periphery was entered into clinicaltrials.gov.⁴ This highlights the fact that while efforts were underway to understand mechanisms of cardiac regeneration, major efforts were already underway to develop stem cell delivery as a viable option to alter the progression of heart disease for AMI patients.

Clinical trial results have modulated optimism for direct regeneration after stem cell delivery

A recent review by Golpanian et al⁵ summarizing available data from both pre-clinical studies and clinical trials employing stem cell delivery to the failing heart indicates that we have yet to realize the true potential of cell therapies for HF due to “paradoxical results,” with inconsistent findings regarding the relationship between the cell dose and clinical benefit. With early establishment of consensus that cell delivery via the vascular system or direct injection into the heart muscle is safe for humans, clinical trials have advanced at a rapid pace. The reported benefits range broadly from no-significant effect or transient beneficial improvements in quality of life to improved cardiac performance with decreased scar mass. Significant regeneration remains an unattained goal.

What we have learned about stem cell based therapies for AMI

The broad spectrum of success in achieving improved outcomes spans nearly two decades of delivering stem cells to the failing heart, with the best results reporting modest improvements in cardiac performance (~4% EF), even with very high cell doses reaching 3–5% of the total cardiomyocyte mass (Hare 100 million cell dose)⁶. While we have learned that delivery of allogeneic stem cells from younger donors may result in improved outcomes compared to delivery of autologous stem cells, expectations that they will directly replace lost cardiomyocytes from AMI remain guarded. Imaging studies suggest that the most delivered cells cannot be found within days of delivery. Modest functional improvements and the lack of cell retention have led us to consider alternative modes of action including non-regenerative modes of cardiac repair. Consensus that delivered stem cell secretion of paracrine factors is responsible for the documented modest improvements in outcomes continues to grow and optimism for stem cell therapy continues. Perhaps some of key therapeutic components of these secretomes are packaged in extracellular vesicles known as exosomes. As we expand our knowledge in microRNAs and small vesicles, exosomes harvested from stem cell cultures have attracted attentions of basic and translational biologists. Several exosomes sources including those from bone marrow (MSCs) as well as the heart (CPCs) have been shown to be efficacious in AMI models of HF.⁷

Although delivery of ex vivo cultured stem cells have been extensively examined, it remains unclear what the roles of endogenous stem cells in cardiac repair are. Hare et al reported that MSC delivery results in activation of endogenous cardiac stem cells and promotes repair. Consistently, we reported that recruitment of endogenous c-kit⁺ stem cells using gene transfer of stem cell factor, a c-kit ligand, promotes cardiac repair⁸.

The status of stem cell therapies for AMI

The spectrum of results reported thus far are likely due to a number of challenges we face in the development of any approach to repairing the myocardium including the diversity of HF etiologies, patient characteristics, co-morbidities, time to therapy post AMI, as well as cell processing methods, routes of delivery, delivered cell viability and molecular phenotypes diversity within the delivered population. These results, together with only mild efficacy

found in meta-analyses highlight the need to consider subject inclusion/exclusion criteria, stem cell source (autologous, allogeneic, bone marrow derived, hematopoietic, cardiac progenitors, iPSCs), donor age and health status, cell dose, endpoints and follow-up times. These parameters have been addressed in some recent clinical trials, which are likely to progress to stages III/IV.⁶ However, without further investigation into their precise mode of action, it is not clear that these trials will improve our understanding of the true reparative and regenerative potentials of stem cell therapy.

What remains to be studied in stem cell therapy for AMI

Clearly, further studies will be needed to understand existing results from clinical studies, to define mechanisms of action for the modest improvements that have been realized thus far and to guide the best informed next clinical trials. The iterative process of basic, translational and clinical research is needed to improve therapeutic performance and patient outcomes. While some of the more advanced studies have documented improved MSC retention, cardiomyogenesis, and stimulation of endogenous CPCs in models of myocardial infarction⁹, further enhancements are needed. The impacts of stem cell viability, diversity of molecular phenotypes, cell processing and storage as well enhancing their therapeutic capacity prior to delivery still need to be addressed. Approaches to enhance endogenous repair and whether the endogenous CPC biological phenotypes are different compared to cells cultured for delivery need to be examined. Furthermore, efficacy of delivering cells compared to delivering stem cell secreted products such as exosomes also needs further studies.

As the major emphasis in stem cell therapy was on its potential on cardiac regeneration, we should also consider alternative approaches that have regenerative potential. Novel mechanisms including CPC-cardiomyocyte fusion and proliferation, transdifferentiation of cardiac fibroblasts to cardiomyocytes¹⁰ and hypoxia induced cardiomyocyte mitosis¹¹ have been reported. These new discoveries are in the early exploratory phases of discovery. Further investigation is needed to ultimately lead to future adult cell regulatory factors that can be targeted to stimulate regenerative processes in the setting of the post-AMI HF. While in the very early stages of exploration, these results have been also met with optimism and could lead to some of the most promising next generation therapeutics for post AMI patients.

Stem cell therapy remains on the horizon

The potential of stem cells to impart benefit to the failing heart is becoming more generally accepted, while ability to induce production of new cardiomyocytes in the failing heart at clinically meaningful levels remains less promising. Therefore, stem cell therapies will be limited to incremental improvements in cardiac function, quality of life and survival without significant cardiomyogenesis, remaining on the horizon over next ~10 years without changes in the trajectory of clinical trial efforts. Stem cell secretomes for cardiac repair is an attractive complement or alternative to cell delivery. Furthermore cardiac regeneration by stimulating endogenous CPCs, reprogramming endogenous non-cardiomyocytes into cardiomyocytes, or inducing cardiomyocyte re-entry to the cell cycle have emerged from the

evolution of stem cell therapy research efforts. These technologies will need to be developed such that their cardiomyogenesis can be temporarily upregulated to clinically relevant levels without becoming pathophysiological. Therefore, novel mechanisms of in-vivo adult repair and regeneration are just over the horizon and may either complement stem cell delivery, or may offer next-generation therapeutic alternatives to the AMI patient.

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Central Figure.

The current consensus from stem cell clinical trials suggest only incrementally improved outcomes. Continued efforts along this trajectory (A) are unlikely to result in transition to standard of care for AMI patients in the next 10 years. Relatively rare events but inter-related including CM mitotic re-entry, transdifferentiation, stem cell differentiation as well as stem cell secretome driven angiogenesis and endogenous stem cell recruitment in the course of regenerative studies (including stem cells) have been reported (B). Further discovery efforts are needed to understand the detailed mechanisms responsible for these events and identify new therapeutic targets to enhance their frequency. These efforts will likely alter the trajectory of regenerative medicine for AMI patients and could lead to more promising novel therapeutics.