Stem Cell in the Rough

Repair Quotient Mined Out of a Bone Marrow Niche

Atta Behfar, Andre Terzic

Regenerative medicine aims to repair, replace, or restore diseased, damaged, or missing tissues. Cardiovascular indications account for over a quarter of all cell-based regenerative medicine products currently in development. Indeed, during the past decade, translation of stem cell technology has been increasingly realized, formulating an emergent body of clinical trial experience that defines the prospect of cardiovascular regenerative medicine.

In the setting of ischemic heart disease, regenerative approaches are deployed as protective and restorative strategies, designed to complement standard-of-care algorithms. Early postinfarction, the aim of cell-based interventions is to limit the extent of damage and prevent organ failure by altering the myocardial response to injury. In advanced heart failure, the goal of regenerative therapy becomes restorative in nature, aimed at re-establishing normative function and structure through direct cell-mediated or indirect paracrine-mediated repair mechanisms. Tested in phase I and phase II trials, within diverse patient populations and across healthcare systems, clinical-grade stem cell platforms demonstrate encouraging feasibility and safety profiles. Experience to date has helped establish scalable standard operating procedures for isolation, expansion, and formulation of cell-based biotherapeutics aimed at re-establishing normative function and structure through direct cell-mediated or indirect paracrine-mediated repair mechanisms. Tested in phase I and phase II trials, within diverse patient populations and across healthcare systems, clinical-grade stem cell platforms demonstrate encouraging feasibility and safety profiles. Experience to date has helped establish scalable standard operating procedures for isolation, expansion, and formulation of cell-based biotherapeutics amenable for broader human use. However, initial indicators of benefit, in either acute or chronic disease, have not been consistently reproduced in follow-up studies dictating careful evaluation of cell therapy practices.

Lack of uniformity in cell procurement and processing has been associated with divergent outcomes across trials. Furthermore, significant patient idiosyncrasy in responsiveness has been documented within trials. To address the observed intertrial and interpatient variability, ongoing efforts are focused on ensuring reliable efficacy of cell-based therapy. Beyond stratifying patients, and determining timing/mode of cellular administration, particular emphasis has been placed on identifying stem cell features that predict best clinical outcomes. In this context, the newest cell therapy initiatives strive to incorporate quality systems that certify, with high-fidelity and reproducibility, the regenerative quotient of stem cells before delivery.

In this issue of Circulation Research, a study by investigators of the Cardiovascular Cell Therapy Research Network (CCTRN) underscores the importance of preselecting cell subsets. A series of larger trials performed under the auspices of the CCTRN had suggested the absence of therapeutic benefit of bone marrow–derived mononuclear cells after myocardial infarction. Human bone marrow is a desirable source because of accessibility for harvest, favorable biological profile, and extensive clinical experience. Yet, stem cells constitute only a limited portion of the unselected bone marrow–derived cell population. Three trials by the CCTRN, namely TIME, Late-TIME and FOCUS, were network-implemented across the United States as randomized, multicenter evaluations of bone marrow–derived mononuclear cell therapy. TIME and Late-TIME assessed regeneration of left ventricular function after acute myocardial infarction. In these trials, MRI at follow-up revealed that intracoronary delivery of autologous bone marrow–derived mononuclear cells had no effect on left ventricular function compared with placebo-treated cohorts. Also, there was no significant difference between an earlier versus a later timing of intervention. The FOCUS trial evaluated the influence of autologous bone marrow–derived mononuclear cells on patients with symptomatic heart failure and reported no clinical benefit derived from intramyocardial delivery. In consideration of more favorable outcomes reported in European trials predating the CCTRN effort, the present analysis was undertaken to evaluate whether the material content of bone marrow mononuclear cells may underpin disparate results.

To this end, flow-cytometry and colony assays mined for regenerative propensity within heterogeneous mixtures of bone marrow cellular compartments. Bone marrows exhibiting increased CD34+ and decreased CD11b+ cell content were found to confer an ejection fraction benefit both in the setting of acute and chronic left ventricular dysfunction. The clinical use of this subpopulation is independently supported by separate trials with CD34+ cells delivered in purified form, as CD34+-based therapy has been shown to yield signals of improvement in refractory angina and in ischemic cardiomyopathy. Collectively these results point to the importance of particular stem cell niches within the bone marrow that are associated with the capability to direct cell repair behavior, serving thereby as putative predictors of myocardial restoration.

Of note, individual patients within CCTRN cohorts that harbored a proreparative niche were exceptionally rare, at an incidence not exceeding 5% in studied populations experiencing myocardial infarction or heart failure (Figure). This finding is in line with previous studies establishing a low
incidence of patients with ischemic heart disease whose bone marrow progenitors exhibit a measurable cardioregenerative aptitude. Characterization of these rare reparative stem cell populations, within the bone marrow niche or in isolation, would inform the selection, or alternatively the induction, of progenitor population empowered to repair the failing heart (Figure). An opportunity to boost stem cell function is through targeting of the cellular microenvironment. In this context, lineage-specific stem cells derived through cardiopoietic induction embody the translation of such principle, achieving improved therapeutic effect beyond that attained with lineage-unspecified cell sources (Figure). Specifically, cardiopoietic stem cell technology uses purified stem cell populations from the patient’s bone marrow and imposes a guiding step to yield a reparative phenotype. This conditioning step, consisting of exposure to cardiotrophic factors mimicking natural cardiogenic cues, introduces a means to incorporate patients benefitting from cell therapy—beyond only rare subsets—to the general heart failure population, an optimizing strategy currently tested in advanced clinical trials (Figure). To this end, scalable standard operating procedures have been developed to generate a cell phenotype consistently that meets release criteria metrics set to ensure repair. Endowed with enhanced healing aptitude, next-generation stem cell products thus harness the growing understanding of critical determinants defining regenerative potency. Translating new knowledge into delivery of science-supported regenerative protocols is ultimately predicated on deployment of cost-effective algorithms to address the unmet needs of patients and populations.

Sources of Funding

A. Behfar is Director, Cardiac Regeneration Program, Center for Regenerative Medicine, Mayo Clinic. Dr Terzic is Michael S. and Mary Sue Shannon Director, Center for Regenerative Medicine, and Marriott Family Endowed Professor in Cardiovascular Diseases Research, Mayo Clinic. Dr Terzic is member of the SHAPEHEART Network funded by the Fondation Leducq.

Disclosures

None.

References


Keywords: clinical trial ■ heart failure ■ myocardial infarction ■ regeneration ■ stem cells
Stem Cell in the Rough: Repair Quotient Mined Out of a Bone Marrow Niche
Atta Behfar and Andre Terzic

Circ Res. 2014;115:814-816
doi: 10.1161/CIRCRESAHA.114.305075
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/115/10/814

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the
Editorial Office. Once the online version of the published article for which permission is being requested is
located, click Request Permissions in the middle column of the Web page under Services. Further information
about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/