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EDITORIAL COMMENT

Combination Cell Therapy for Ischemic Cardiomyopathy

Is the Whole Greater Than Sum of Its Parts?*

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What is the best stem cell type for the treatment of ischemic cardiomyopathy? How and when should stem cells be delivered after myocardial infarction? Are live stem cells even necessary, or can the same therapeutic effects be achieved by administering only their secreted factors? These and other questions have challenged the scientific community for almost 2 decades; the debate is animated, and leaders in the field are trying to come to a consensus (1). Proof-of-concept studies in rodent models yielded very encouraging results (2–4), which were confirmed only in part by preclinical large animal studies (5–10), whereas early phase I and II clinical trials have shown more modest improvements in cardiac structure and function (11–14). Although clinical data indicate that cell therapy is safe in patients with ischemic cardiomyopathy, none of the proposed strategies, to date, is approved as a routine clinical protocol for the treatment of heart diseases. An ideal stem cell candidate is not yet within arm's reach.

As the field has evolved, it has become clearer that the beneficial impact of stem cell therapy is likely the result of poorly defined "paracrine effects," rather than transdifferentiation (1,15). Therefore, the search for a cell that releases factors promoting wound healing or regeneration after injury has become a predominant paradigm shift in the field. C-Kit$^+$ cardiac stem cells (CSCs) and mesenchymal stem cells (MSCs) are certainly 2 of the most intensively studied candidates for cardioregenerative therapy because experimental evidence supports their capacity to enhance revascularization and/or replace lost myocytes (2,5). Early c-Kit$^+$ CSC studies showed the pronounced cardiogenic potential of these cells (2). However, more recent work points to primarily paracrine effects of transplanted CSCs, although this aspect remains controversial (15–18). The proposed explanation of the pro-regenerative effects of MSCs is more balanced, maintaining a combination of paracrine and cardiogenic potential (19,20). MSCs appear to have better retention, likely secondary to a lack of the class II major histocompatibility complex that renders them nonimmunogenic (21), and they also release paracrine factors that are immunomodulatory, promote revascularization, and inhibit pathological remodeling (6,7). MSCs are therefore ideal for allogeneic transplantation, a therapeutic strategy remarkably advantageous when cells can be harvested from healthy and young donors, thus overcoming the disadvantages related to the disease and comorbidities that impair autologous tissue.

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The study by Natsumeda et al. (22) in this issue of the *Journal* was prompted by the hypothesis that the immunomodulatory properties of MSCs can be exploited to favor the engraftment and thus permit the pro-regenerative action of allogeneic CSCs, after combined cardiac delivery of the 2 cell types, without provoking host versus graft reactions. This research group has been a pioneer in the field over the last decade, with more than 60 publications on MSCs and cardiac regeneration in both preclinical large animal models (6,7) and clinical trials (12,13). A phenomenon

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that these investigators have documented is the capacity of MSCs to regulate stem cell niches, specifically niches of CSCs (23). On the basis of previous positive outcomes of MSC- and CSC-based therapy in preclinical models and clinical trials, and on the aforementioned immunological peculiarities of MSCs, Natsumeda et al. (22) speculated that the combination of allogeneic MSCs and CSCs into a single therapeutic intervention could be more effective than the single cell type. In the current labor-intensive study performed with gold standard methodologies, these investigators tested an allogeneic combination cell therapy (ACCT) consisting of a mixture of MSCs and CSCs obtained from male minipigs and transplanted through transendocardial injection into female minipigs at 3 months after acute myocardial infarction (AMI). Minipigs were randomized to receive ACCT, allo-MSCs, allo-CSCs, or placebo (vehicle) and were assessed for structural and functional changes by cardiac magnetic resonance and invasive hemodynamics. Natsumeda et al. (22) found a significant reduction in the percentage of change of scar-to-left ventricular mass ratio with allo-MSCs and ACCT when compared with their 3-month post-AMI time point. End-diastolic and end-systolic volumes within the ACCT group did not change significantly from 3 months post-AMI to 3 months post-ACCT, whereas myocardial perfusion, assessed with a semiquantitative method, increased significantly, thus indicating greater perfusion within the infarct zone. Invasive hemodynamics demonstrated a significant increase in the percentage of change of the end-systolic elastance, a cardiac load-independent index of contractility, in the ACCT group, from 3 months post-AMI to 3 months post-ACCT. Furthermore, histopathological analysis revealed minimal focal lymphocyte aggregates with ACCT and MSCs treatment and almost none observed in CSC-treated animals. Interestingly, these aggregates were composed of subpopulations of T lymphocytes that promote immune tolerance (24), a finding suggesting that the MSCs could be exerting their immunomodulatory effects.

Although these data support the conclusions drawn by Natsumeda et al. (22) that ACCT is safe, reverses remodeling with improved systolic function, and does not elicit immunologic responses, the superior efficacy of the cell combination over MSCs alone was not supported by statistical analysis. In fact, it is true that ACCT treatment led to within-group improvements, but most of the between-group comparisons with MSCs alone did not indicate significant differences. This finding confirms previous work by the same group, in the same model, when using autologous combination cell therapy compared with a single cell type (25). Nonetheless, such quasinegative findings do not detract from the importance of this study. Testing the superiority of ACCT over single cell types alone in clinically relevant animal models was necessary to leave no stone unturned in the context of novel strategies aimed at halting the progression of ischemic cardiomyopathy to heart failure. This testing assures the scientific community that novel therapeutic strategies have been rigorously screened in valuable models before investigators embark on costly clinical trials. Another important aspect of the current study to consider is the negligible efficacy of allogenic CSCs alone, which, in addition, did not elicit a stronger immunogenic response compared with MSCs. This latter phenomenon was perhaps the result of species-specific tolerance to allogeneic tissue and/or to some genetic homogeneity of purpose-bred experimental animals. Therefore, it is possible that the immunomodulatory or adjuvant action of MSCs would be better exalted by their combination with more immunogenic and possibly more therapeutically efficacious allogeneic stem cells.

With novel populations of cells currently being screened (26,27), as well as cell-based products (e.g., exosomes) or pro-regenerative microRNAs being tested (28–31), it is plausible that the combinatory approach will harness the peculiar benefits of each component into a single intervention. We do believe that further exploration along this avenue is fully warranted.

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REFERENCES

1. Eschenhagen T, Bolli R, Braun T, et al. Cardiomyocyte regeneration: a consensus statement. Circulation 2017;136:680–6.

2. Beltrami AP, Barlucchi L, Torella D, et al. Adult cardiac stem cells are multipotent and support myocardial regeneration. Cell 2003;114:763–76.

3. Nagaya N, Kangawa K, Itoh T, Iwase T, et al. Transplantation of mesenchymal stem cells improves cardiac function in a rat model of dilated cardiomyopathy. Circulation 2005;112:1128–35.

4. Ellison GM, Vicinanza C, Smith AJ, et al. Adult c-kit(pos) cardiac stem cells are necessary and sufficient for functional cardiac regeneration and repair. Cell 2013;154:827–42.

5. Amado LC, Saliaris AP, Schuleri KH, et al. Cardiac repair with intramyocardial injection of allogeneic mesenchymal stem cells after myocardial infarction. Proc Natl Acad Sci U S A 2005;102:11474–9.

6. Quevedo HC, Hatzistergos KE, Oskouei BN, et al. Allogeneic mesenchymal stem cells restore cardiac function in chronic ischemic cardiomyopathy via trilineage differentiating capacity. Proc Natl Acad Sci U S A 2009;106:14022–7.

7. Schuleri KH, Feigenbaum GS, Centola M, et al. Autologous mesenchymal stem cells produce reverse remodelling in chronic ischaemic cardiomyopathy. Eur Heart J 2009;30:2722–32.

8. Lee ST, White AJ, Matsushita S, et al. Intramyocardial injection of autologous cardiospheres or cardiosphere-derived cells preserves function and minimizes adverse ventricular remodeling in pigs with heart failure post-myocardial infarction. J Am Coll Cardiol 2011;57:455–65.

9. Simioniuc A, Campan M, Lionetti V, et al. Placental stem cells pre-treated with a hyaluronan mixed ester of butyric and retinoic acid to cure infarcted pig hearts: a multimodal study. Cardiovasc Res 2011;90:546–56.

10. Bolli R, Tang XL, Sanganalmath SK, et al. Intracoronary delivery of autologous cardiac stem cells improves cardiac function in a porcine model of chronic ischemic cardiomyopathy. Circulation 2013;128:122–31.

11. Bolli R, Chugh AR, D'Amario D, et al. Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. Lancet 2011;378:1847–57.

12. Hare JM, DiFede DL, Rieger AC, et al. Randomized comparison of allogeneic versus autologous mesenchymal stem cells for nonischemic dilated cardiomyopathy: POSEIDON-DCM trial. J Am Coll Cardiol 2017;69:526–37.

13. Hare JM, Fishman JE, Gerstenblith G, et al. Comparison of allogeneic vs autologous bone marrow-derived mesenchymal stem cells delivered by transendocardial injection in patients with ischemic cardiomyopathy: the POSEIDON randomized trial. JAMA 2012;308:2369–79.

14. Makkar RR, Smith RR, Cheng K, et al. Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial. Lancet 2012;379:895–904.

15. van Berlo JH, Molkentin JD. An emerging consensus on cardiac regeneration. Nat Med 2014;20:1386–93.

16. Vicinanza C, Aquila I, Scalise M, et al. Adult cardiac stem cells are multipotent and robustly myogenic: c-kit expression is necessary but not sufficient for their identification. Cell Death Differ 2017 Aug 11 [E-pub ahead of print].

17. Molkentin JD, Houser SR. Are resident c-Kit+ cardiac stem cells really all that are needed to mend a broken heart? Circ Res 2013;113:1037–9.

18. Hong KU, Guo Y, Li QH, et al. c-kit+ Cardiac stem cells alleviate post-myocardial infarction left ventricular dysfunction despite poor engraftment and negligible retention in the recipient heart. PLoS ONE 2014;9:e96725.

19. Gnecchi M, He H, Noiseux N, et al. Evidence supporting paracrine hypothesis for Akt-modified mesenchymal stem cell-mediated cardiac protection and functional improvement. FASEB J 2006;20:661–9.

20. Silva GV, Litovsky S, Assad JA, et al. Mesenchymal stem cells differentiate into an endothelial phenotype, enhance vascular density, and improve heart function in a canine chronic ischemia model. Circulation 2005;111:150–6.

21. Le Blanc K, Tammik C, Rosendahl K, Zetterberg E, Ringden O. HLA expression and immunologic properties of differentiated and undifferentiated mesenchymal stem cells. Exp Hematol 2003;31:890–6.

22. Natsumeda M, Florea V, Rieger AC, et al. A combination of allogeneic stem cells promotes cardiac regeneration. J Am Coll Cardiol 2017;70:2504–15.

23. Hatzistergos KE, Saur D, Seidler B, et al. Stimulatory effects of mesenchymal stem cells on cKit+ cardiac stem cells are mediated by SDF1/CXCR4 and SCF/cKit signaling pathways. Circ Res 2016;119:921–30.

24. Hu M, Wang C, Zhang GY, Saito M, et al. Infiltrating Foxp3(+) regulatory T cells from spontaneously tolerant kidney allografts demonstrate donor-specific tolerance. Am J Transplant 2013;13:2819–30.

25. Karantalis V, Suncion-Loescher VY, Bagno L, et al. Synergistic effects of combined cell therapy for chronic ischemic cardiomyopathy. J Am Coll Cardiol 2015;66:1990–9.

26. Duran JM, Makarewich CA, Sharp TE, et al. Bone-derived stem cells repair the heart after myocardial infarction through transdifferentiation and paracrine signaling mechanisms. Circ Res 2013;113:539–52.

27. Mohsin S, Troupes CD, Starosta T, et al. Unique features of cortical bone stem cells associated with repair of the injured heart. Circ Res 2015;117:1024–33.

28. Khan M, Nickoloff E, Abramova T, et al. Embryonic stem cell-derived exosomes promote endogenous repair mechanisms and enhance cardiac function following myocardial infarction. Circ Res 2015;117:52–64.

29. Lang JK, Young RF, Ashraf H, Canty JM Jr. Inhibiting extracellular vesicle release from human cardiosphere derived cells with lentiviral knockdown of nSMase2 differentially effects proliferation and apoptosis in cardiomyocytes, fibroblasts and endothelial cells in vitro. PLoS One 2016;11:e0165926.

30. Gallet R, Dawkins J, Valle J, et al. Exosomes secreted by cardiosphere-derived cells reduce scarring, attenuate adverse remodelling, and improve function in acute and chronic porcine myocardial infarction. Eur Heart J 2017;38:201–11.

31. Lesizza P, Prosdocimo G, Martinelli V, Sinagra G, Zacchigna S, Giacca M. Single-dose intracardiac injection of pro-regenerative microRNAs improves cardiac function after myocardial infarction. Circ Res 2017;120:1298–304.

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