Commentary

Hypoxia-preconditioned allogeneic mesenchymal stem cells can be used for myocardial repair in non-human primates

Kuan-Cheng Chang[1,2,3], Shih-Chieh Hung[1,4,5,6,7]

[1]Graduate Institute of Clinical Medical Science, China Medical University, Taichung 40402, Taiwan; [2]Division of Cardiovascular Medicine, Department of Medicine, [3]Cardiovascular Research Laboratory, [4]Integrative Stem Cell Center, Department of Orthopedics, China Medical University Hospital, Taichung 40447, Taiwan; [5]Institute of Clinical Medicine, School of Medicine, National Yang-Ming University, Taipei 112, Taiwan; [6]Stem Cell Laboratory, Department of Medical Research and Education, Taipei Veterans General Hospital, Taipei 112, Taiwan; [7]Institute of Biomedical Sciences, Academia Sinica, Taipei 11529, Taiwan

Correspondence to: Shih-Chieh Hung, MD, PhD. Integrative Stem Cell Center, China Medical University Hospital 7F, No. 6, Xueshi Rd., North Dist., Taichung 404, Taiwan (ROC). Email: hung3340@gmail.com.

Submitted Apr 22, 2016. Accepted for publication May 05, 2016.
doi: 10.21037/jtd.2016.05.46
View this article at: http://dx.doi.org/10.21037/jtd.2016.05.46

Although advances in pharmacotherapy and interventional cardiology have greatly reduced the mortality and morbidity following myocardial infarction (MI), there remains an ongoing need for innovative cell transplantation techniques that can reverse cardiac ventricular remodeling post-MI. Despite the barriers facing the application of cell-based interventions (1,2), a growing number of preclinical studies and clinical trials have demonstrated the safety of a variety of adult stem cell types. Mesenchymal stem cells (MSCs) are one of the most well-studied cell types used in regenerative medicine (3). Human MSCs have the capability for self-renewal and can differentiate into various mesenchymal and non-mesenchymal tissues and are currently under evaluation in clinics for the treatment of cardiovascular diseases, such as MI (2). However, different isolation and expansion techniques result in remarkable differences in their proliferation capacity and differentiation potentials (4). Furthermore, clinical applications of MSCs require a large number of expanded cells; however, many studies have reported that expanded MSCs are heterogeneous and contain a significant portion of senescent cells (4). Thus, the development of novel culture methods for expanding homogenous and non-senescent MSCs without the loss of proliferation, stemness, and multi-differentiation abilities would be of great value for this research field.

Culturing MSCs under hypoxic conditions before transplantation, also known as hypoxic preconditioning, is one strategy for improving the homogeneity and properties of expanded cells. Preclinical animal studies have demonstrated the therapeutic advantages of MSCs cultured under hypoxic conditions (referred to as hypoxic MSCs) over those cultured under ambient conditions (referred to as normoxic MSCs) in diseases, such as bony defects (5), tendon tear (6), stroke (7), and hindlimb ischemia (8). Hypoxic MSCs have also been applied in animal models to treat diseases, such as osteoarthritis (9), fulminant hepatitis (10), and early atherosclerotic lesion (11). Although hypoxic MSCs have previously been evaluated in various disease models with positive outcomes, it remains to be determined how this technique will function in future clinical applications to treat MI. A prior study on the application of hypoxic MSCs to reduce MI complications reported improvements in left ventricular function in pigs that received allogeneic hypoxic MSCs compared with pigs that received allogeneic normoxic MSCs (12). Although this large animal study demonstrated the safety and efficacy of hypoxic MSCs for treating chronic ischemic heart failure, there is a lack of primate studies demonstrating the superiority of hypoxic MSCs over normoxic MSCs. The most recent study by Hu *et al*. was the first study in non-human primates and the first large animal study of acute MI (13). The authors tested whether hypoxic MSCs were more effective than normoxic MSCs in the treatment of myocardial injury in a randomized trial in which cynomolgus monkeys (Macaca fascicularis) were subjected to acute MI. MSCs were isolated from the bone marrow, labeled with green-fluorescent protein

by lentiviral transduction, and cultured under hypoxic conditions (0.5% O_2) or under ambient conditions (21% O_2) for 24 h. Aliquots of cells (1×10^7 cells per heart) were then intramyocardially injected into the infarcted hearts of allogeneic recipients at five different sites in the border zone 30 min after the induction of left anterior MI. Infarct size and left ventricular function 90 days after MI were measured using magnetic resonance imaging and positron emission tomography, and monkeys treated with hypoxic MSCs, but not normoxic MSCs, had significant improvements in infarct size and function compared with monkeys treated with the control vehicle. Hypoxic MSC transplantation was also associated with increases in endogenous cardiomyocyte survival and proliferation, glucose uptake, vascular density, and engraftment of the transplanted cells but did not cause long-term arrhythmogenic complications, which were observed in non-human primate hearts treated with human embryonic-stem-cell-derived cardiomyocytes (14). Because Hu *et al*. did not observe neocardiomyogenesis and the engraftment rates for normoxic and hypoxic MSCs were low, the benefit of hypoxic MSC transplantation was likely due to the upregulation of transcription factors or the secretion of paracrine factors that stimulated endogenous cytoprotective or regenerative mechanisms. These factors include hypoxia-inducible factor-1, angiopoietin-1, and erythropoietin.

Hypoxic culture has been considered to be a solution for the problems facing MSC-based regenerative medicine (15). The reasons for the use of hypoxic culture with MSCs are as follows: in long-term culture, hypoxia can inhibit senescence, increase the proliferation rate, and enhance differentiation potential along the different mesenchymal lineages (16). More importantly, hypoxic culture increases the expression of pluripotency transcription factors in MSCs, which in turn upregulate Dnmt1, thereby inhibiting the expression of p16 and p21, and the developmental markers or lineage genes (17). Hypoxia also modulates the paracrine effects of MSCs, causing the upregulation of various secretable factors, including vascular endothelial growth factor and IL-6 (18). Hypoxia also plays an important role in the mobilization and homing of MSCs, primarily by inducing SDF-1-CXCR4 (19). Furthermore, hypoxic MSCs have immune privilege and are less likely than normoxic MSCs to be rejected by the immune system of allogeneic recipients (8).

Aside from the technology used to expand cells, successful cell transplantation depends on many factors, including CMC data preparation, IND, and an excellent design for preclinical and clinical trials. For example, the timing of cell transplantation is the key to success. The Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) trial using intracoronary bone marrow mononuclear cell delivery to treat MI found that delivery 5 to 7 days after acute MI resulted in a greater improvement in global cardiac function compared to an earlier delivery time (20). The mode of cell delivery is important in determining initial engraftment and retention. In a direct head-to-head comparison among different cell delivery methods, myocardial engraftment or retention was highest when peripheral blood mononuclear cells were delivered intramyocardially (11%±3%) compared to intracoronary (2.6%±0.1%) or intravenous delivery (3.2%±1%) (11). Hu *et al.* used intramyocardial injection as a delivery route, which may have also contributed to the success of their preclinical trial.

In conclusion, Hu *et al*. demonstrated that hypoxia-preconditioned allogeneic MSCs pass the test for use in myocardial repair in non-human primates. MSCs may indeed be an ideal cell source for cardiac repair. Before MSC therapy can be used to treat MI, it will be necessary to identify the critical components that determine successful cellular therapy, as well as the biological mechanisms underlying their effects.

Acknowledgements

Funding: Grants supported by National Science Council (103-2321-B-010-018) and the Academia Sinica Translational Medicine Program (5202401023-2325). Space and administrative support was provided by the Institute of Biomedical Sciences, Academia Sinica.

Footnote

Provenance: This is an invited Commentary commissioned by the Section Editor Lei Zhang (Department of Vascular Surgery, Changhai Hospital, Second Military Medical University, Shanghai, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: Hu X, Xu Y, Zhong Z, *et al*. A Large-Scale Investigation of Hypoxia-Preconditioned Allogeneic Mesenchymal Stem Cells for Myocardial Repair in Non-Human Primates: Paracrine Activity Without Remuscularization. Circ Res 2016;118:970-83.

References

1. Galipeau J. The mesenchymal stromal cells dilemma--does a negative phase III trial of random donor mesenchymal stromal cells in steroid-resistant graft-versus-host disease represent a death knell or a bump in the road? Cytotherapy 2013;15:2-8.
2. Telukuntla KS, Suncion VY, Schulman IH, et al. The advancing field of cell-based therapy: insights and lessons from clinical trials. J Am Heart Assoc 2013;2:e000338.
3. Karantalis V, Hare JM. Use of mesenchymal stem cells for therapy of cardiac disease. Circ Res 2015;116:1413-30.
4. Pittenger MF. Mesenchymal stem cells from adult bone marrow. Methods Mol Biol 2008;449:27-44.
5. Yew TL, Huang TF, Ma HL, et al. Scale-up of MSC under hypoxic conditions for allogeneic transplantation and enhancing bony regeneration in a rabbit calvarial defect model. J Orthop Res 2012;30:1213-20.
6. Huang TF, Yew TL, Chiang ER, et al. Mesenchymal stem cells from a hypoxic culture improve and engraft Achilles tendon repair. Am J Sports Med 2013;41:1117-25.
7. Wei N, Yu SP, Gu X, et al. Delayed intranasal delivery of hypoxic-preconditioned bone marrow mesenchymal stem cells enhanced cell homing and therapeutic benefits after ischemic stroke in mice. Cell Transplant 2013;22:977-91.
8. Huang WH, Chen HL, Huang PH, et al. Hypoxic mesenchymal stem cells engraft and ameliorate limb ischaemia in allogeneic recipients. Cardiovasc Res 2014;101:266-76.
9. Chiang ER, Ma HL, Wang JP, et al. Allogeneic mesenchymal stem cells in combination with hyaluronic acid for the treatment of osteoarthritis in rabbits. PLoS One 2016;11:e0149835.
10. Lee KC, Lin HC, Huang YH, et al. Allo-transplantation of mesenchymal stem cells attenuates hepatic injury through IL1Ra dependent macrophage switch in a mouse model of liver disease. J Hepatol 2015;63:1405-12.
11. Hou D, Youssef EA, Brinton TJ, et al. Radiolabeled cell distribution after intramyocardial, intracoronary, and interstitial retrograde coronary venous delivery: implications for current clinical trials. Circulation 2005;112:I150-6.
12. Jaussaud J, Biais M, Calderon J, et al. Hypoxia-preconditioned mesenchymal stromal cells improve cardiac function in a swine model of chronic myocardial ischaemia. Eur J Cardiothorac Surg 2013;43:1050-7.
13. Hu X, Xu Y, Zhong Z, et al. A large-scale investigation of hypoxia-preconditioned allogeneic mesenchymal stem cells for myocardial repair in nonhuman primates: paracrine activity without remuscularization. Circ Res 2016;118:970-83.
14. Chong JJ, Yang X, Don CW, et al. Human embryonic-stem-cell-derived cardiomyocytes regenerate non-human primate hearts. Nature 2014;510:273-7.
15. Haque N, Rahman MT, Abu Kasim NH, et al. Hypoxic culture conditions as a solution for mesenchymal stem cell based regenerative therapy. ScientificWorldJournal 2013;2013:632972.
16. Tsai CC, Chen YJ, Yew TL, et al. Hypoxia inhibits senescence and maintains mesenchymal stem cell properties through down-regulation of E2A-p21 by HIF-TWIST. Blood 2011;117:459-69.
17. Tsai CC, Su PF, Huang YF, et al. Oct4 and Nanog directly regulate Dnmt1 to maintain self-renewal and undifferentiated state in mesenchymal stem cells. Mol Cell 2012;47:169-82.
18. Hung SC, Pochampally RR, Chen SC, et al. Angiogenic effects of human multipotent stromal cell conditioned medium activate the PI3K-Akt pathway in hypoxic endothelial cells to inhibit apoptosis, increase survival, and stimulate angiogenesis. Stem Cells 2007;25:2363-70.
19. Hung SC, Pochampally RR, Hsu SC, et al. Short-term exposure of multipotent stromal cells to low oxygen increases their expression of CX3CR1 and CXCR4 and their engraftment in vivo. PLoS One 2007;2:e416.
20. Schächinger V, Erbs S, Elsässer A, et al. Improved clinical outcome after intracoronary administration of bone-marrow-derived progenitor cells in acute myocardial infarction: final 1-year results of the REPAIR-AMI trial. Eur Heart J 2006;27:2775-83.

Cite this article as: Chang KC, Hung SC. Hypoxia-preconditioned allogeneic mesenchymal stem cells can be used for myocardial repair in non-human primates. J Thorac Dis 2016;8(7):E593-E595. doi: 10.21037/jtd.2016.05.46