Primed for lethal battle: A step forward to enhance the efficacy and efficiency of stem cell transplantation therapy

Molly E. Ogle, BS, Shan Ping Yu, MD, PhD, and Ling Wei, MD

As an emerging strategy of regenerative medicine, stem cell transplantation therapy has provided an exciting possibility for the treatments of many devastating diseases, including ischemic heart and brain disorders. For the clinical efficacy and efficiency to be fulfilled, however, a number of issues are still to be resolved in the potential cell-based therapy. The poor survival of transplanted cells (often 70%–90% death in a few days after transplantation) is one of the most critical dilemmas that have been seriously and specifically addressed in our recent investigations.^{1,2} Our article recently published in this *Journal*, titled “Transplantation of Hypoxia-Preconditioned Mesenchymal Stem Cells Improves Infarcted Heart Function via Enhanced Survival of Implanted Cells and Angiogenesis,” demonstrated a markedly enhanced cell survival in the ischemic heart and functional benefits achieved by the “hypoxic preconditioning” of stem cells before transplantation.² The letter from Haider and associates advocates the idea of preconditioning transplanted cells and has provided new experimental evidence for this novel approach.

Hypoxic or ischemic preconditioning is the principle by which a brief, sublethal exposure of cells, tissues, or animals to hypoxia or ischemia induces a cytoprotective phenotype on subsequent potentially lethal challenges. The preconditioning stimulus may be accomplished by many means. For example, we have successfully preconditioned mesenchymal stem cells with 24-hour 0.5% oxygen before transplantation into the ischemic heart and embryonic stem cells before transplantation into the ischemic brain. Haider and associates discuss the use of an alternate preconditioning protocol, using short bursts of ischemia and reperfusion, which they similarly find effective for enhancing cell survival. These and other studies illustrate that there could be different means to activate the cytoprotective pathways in the different cells or even in the same type of cells for transplantation therapy.

Following our published work mentioned above, we have been exploring the use of small molecule inhibitors of the oxygen-dependent hydroxylase enzymes as another means to activate preconditioning pathways. Proline and asparagine

hydroxylases are oxygen-dependent enzymes that hydroxylate target proteins to effect signaling changes. In this way, environmental oxygen concentration controls the signaling pattern of the oxygen-dependent enzymes. Our very recent data show that pharmacologic inhibition of prolyl hydroxylase enzymes mimics the effect of hypoxic or ischemic preconditioning. We³ demonstrate that the prolyl hydroxylase competitive inhibitor dimethyl-oxylglycine activates protective pathways in mesenchymal stem cells, reducing cell death by the serum deprivation insult. This protection is concurrent with hypoxia-inducible factor 1 α activation and is blocked by inhibition of phosphoinositide 3-kinase and downstream Akt activation. Oxygen-dependent hydroxylase inhibitor preconditioning may therefore be another strategy to enhance the survival of cells before transplantation.

An important ongoing challenge in this field is the identification of downstream mediators of hypoxic preconditioning protection. Hypoxia inducible factor is the most studied transcription factor activated by hypoxia; however, it does not account for all the changes in gene expression that occur under preconditioning. Using a microarray technique, Frank Sharp's group (Xu and associates⁴) has identified thousands of genes that are upregulated or downregulated by hypoxic preconditioning in the brain. Haider and associates discuss the potential for participation of hypoxia-regulated microRNAs in the mechanism of preconditioning-enhanced cell survival. MicroRNAs are an important posttranscriptional/pretranslational level of control of gene expression and can mediate the degradation of messenger RNA or suppression of protein translation. Inasmuch as a number of gene transcripts are downregulated by hypoxia, understanding the role of microRNAs in this process will be an interesting contribution to the field. Ultimately, understanding the cellular and molecular mechanisms that mediate the increased capacity for cell survival by preconditioning will help to identify new, more directed therapeutic targets for facilitating cell transplantation-based regenerative medicine.

References

1. Theus MH, Wei L, Cui L, Francis K, Hu X, Keogh C, et al. In vitro hypoxic preconditioning of embryonic stem cells as a strategy of promoting cell survival and functional benefits after transplantation into the ischemic rat brain. *Exp Neurol*. 2008;210:656-70.
2. Hu X, Yu SP, Fraser JL, Lu Z, Ogle ME, Wang JA, et al. Transplantation of hypoxia-preconditioned mesenchymal stem cells improves infarcted heart function via enhanced survival of implanted cells and angiogenesis. *J Thorac Cardiovasc Surg*. 2008;135:799-808.
3. Liu XB, Wang JA, Ogle ME, Wei L. Prolyl hydroxylase inhibitor dimethyl-oxylglycine enhances mesenchymal stem cell survival. *J Cell Biochem*. 2009;106:903-11.
4. Xu H, Ran R, Lu A, Sharp F. Genomic response to hypoxia preconditioning in the adult mouse brain. *Abstr Neurosci*. 2008;413:6.

From the Department of Anesthesiology, Emory University School of Medicine, Atlanta, Ga.

Received for publication May 3, 2009; accepted for publication June 8, 2009.

Address for reprints: Ling Wei, MD, Professor, Department of Anesthesiology, 101 Woodruff Circle, Emory University School of Medicine, Atlanta, GA 30322 (E-mail: lwei7@emory.edu).

J Thorac Cardiovasc Surg 2009;138:527
0022-5223/\$36.00

Copyright © 2009 by The American Association for Thoracic Surgery
doi:10.1016/j.jtcvs.2009.06.003