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Primed for Lethal Battle: a Step Forward to Enhance the Efficacy and Efficiency of Stem Cell Transplantation Therapy

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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. To fulfill the clinical efficacy and efficiency, however, there are still a number of issues to be resolved in the potential cell-based therapy. The poor survival rate 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 paper recently published in this journal entitled "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 *et al.* 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, sub-lethal exposure of cells, tissues, or animals to hypoxia or ischemia induces a cytoprotective phenotype upon subsequent potentially lethal challenges. The preconditioning stimulus may be accomplished by many means. For example, we have successfully preconditioned mesenchymal stem cells with 24-hr 0.5% oxygen before transplantation into the ischemic heart, and embryonic stem cells before transplantation into the ischemic brain. Haider *et al* 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 there could be different means to activate the cytoprotective pathways in the different cell 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 pharmacological inhibition of prolyl hydroxylase enzymes mimics the effect of hypoxic or ischemic preconditioning. We demonstrate that the prolyl hydroxylase competitive inhibitor dimethyl-oxylglycine (DMOG) activates protective

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pathways in mesenchymal stem cells, reducing cell death by the serum deprivation insult (3). This protection is concurrent with HIF-1 α activation, and blocked by inhibition of PI3K and downstream Akt activation. Oxygen-dependent hydroxylase inhibitor preconditioning may therefore be another strategy to enhance the survival of cells prior to transplantation.

An important on-going challenge in this field is the identification of downstream mediators of hypoxic preconditioning protection. Hypoxia Inducible Factor (HIF) 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 has identified thousands of genes that are up or down regulated by hypoxic preconditioning in the brain (4). Haider *et al* discuss the potential for participation of hypoxia regulated miRNAs in the mechanism of preconditioning enhanced cell survival. MiRNAs are an important post-transcriptional/pre-translational level of control of gene expression, and can mediate the degradation of mRNA or suppression of protein translation. Since a number of gene transcripts are down-regulated by hypoxia, understanding the role of miRNAs 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.

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