Hypoxic Preconditioning Enhances Survival and Proangiogenic Capacity of Human First Trimester Chorionic Villus-Derived Mesenchymal Stem Cells for Fetal Tissue Engineering.

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Public Summary:
Prenatal stem cell-based regenerative therapies have progressed substantially and have been demonstrated as effective treatment options for fetal diseases that were previously deemed untreatable. Due to immunoregulatory properties, self-renewal capacity, and multilineage potential, autologous human placental chorionic villus-derived mesenchymal stromal cells (CV-MSCs) are an attractive cell source for fetal regenerative therapies. However, as a general issue for MSC transplantation, the poor survival and engraftment is a major challenge of the application of MSCs. Particularly for the fetal transplantation of CV-MSCs in the naturally hypoxic fetal environment, improving the survival and engraftment of CV-MSCs is critically important. Hypoxic preconditioning (HP) is an effective priming approach to protect stem cells from ischemic damage. In this study, we developed an optimal HP protocol to enhance the survival and proangiogenic capacity of CV-MSCs for improving clinical outcomes in fetal applications. Total cell number, DNA quantification, nuclear area test, and cell viability test showed HP significantly protected CV-MSCs from ischemic damage. Flow cytometry analysis confirmed HP did not alter the immunophenotype of CV-MSCs. Caspase-3, MTS, and Western blot analysis showed HP significantly reduced the apoptosis of CV-MSCs under ischemic stimulus via the activation of the AKT signaling pathway that was related to cell survival. ELISA results showed HP significantly enhanced the secretion of vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) by CV-MSCs under an ischemic stimulus. We also found that the environmental nutrition level was critical for the release of brain-derived neurotrophic factor (BDNF). The angiogenesis assay results showed HP-primed CV-MSCs could significantly enhance endothelial cell (EC) proliferation, migration, and tube formation. Consequently, HP is a promising strategy to increase the tolerance of CV-MSCs to ischemia and improve their therapeutic efficacy in fetal clinical applications.

Scientific Abstract:
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