Hypoxic preconditioning of mesenchymal stromal cells induces metabolic changes, enhances survival, and promotes cell retention in vivo.

Journal: Stem Cells
Publication Year: 2015
Authors: Julie Beegle, Kinga Lakatos, Stefanos Kalomoiris, Heather Stewart, R Rivkah Isseroff, Jan A Nolta, Fernando A Fierro
PubMed link: 25702874
Funding Grants: Bone Marrow Mesenchymal Stem Cells to Heal Chronic Diabetic Wounds, Phase I study of IM Injection of VEGF-Producing MSC for the Treatment of Critical Limb Ischemia

Public Summary:
Mesenchymal stem cells/multipotent stromal cells (MSCs) are promising therapeutics for a variety of conditions. However, after transplantation, cell retention remains extremely challenging. Given that many hypoxic signals are transitory and that the therapeutic administration of MSCs is typically into tissues that are normally hypoxic, we studied the effect of hypoxic preconditioning (HP) prior to new exposure to hypoxia. We show that preincubation for 2 days or more in 1% oxygen reduces serum deprivation-mediated cell death, as observed by higher cell numbers and lower incorporation of EthD-III and Annexin V. Consistently, HP-MSCs expressed significantly lower levels of cytochrome c and heme oxygenase 1 as compared to controls. Most importantly, HP-MSCs showed enhanced survival in vivo after intramuscular injection into immune deficient NOD/SCID-IL2Rgamma(-/-) mice. Interestingly, HP-MSCs consume glucose and secrete lactate at a slower rate than controls, possibly promoting cell survival, as glucose remains available to the cells for longer periods of time. In addition, we compared the metabolome of HP-MSCs to controls, before and after hypoxia and serum deprivation, and identified several possible mediators for HP-mediated cell survival. Overall, our findings suggest that preincubation of MSCs for 2 days or more in hypoxia induces metabolic changes that yield higher retention after transplantation.

Scientific Abstract:
Mesenchymal stem cells/multipotent stromal cells (MSCs) are promising therapeutics for a variety of conditions. However, after transplantation, cell retention remains extremely challenging. Given that many hypoxic signals are transitory and that the therapeutic administration of MSCs is typically into tissues that are normally hypoxic, we studied the effect of hypoxic preconditioning (HP) prior to new exposure to hypoxia. We show that preincubation for 2 days or more in 1% oxygen reduces serum deprivation-mediated cell death, as observed by higher cell numbers and lower incorporation of EthD-III and Annexin V. Consistently, HP-MSCs expressed significantly lower levels of cytochrome c and heme oxygenase 1 as compared to controls. Most importantly, HP-MSCs showed enhanced survival in vivo after intramuscular injection into immune deficient NOD/SCID-IL2Rgamma(-/-) mice. Interestingly, HP-MSCs consume glucose and secrete lactate at a slower rate than controls, possibly promoting cell survival, as glucose remains available to the cells for longer periods of time. In addition, we compared the metabolome of HP-MSCs to controls, before and after hypoxia and serum deprivation, and identified several possible mediators for HP-mediated cell survival. Overall, our findings suggest that preincubation of MSCs for 2 days or more in hypoxia induces metabolic changes that yield higher retention after transplantation.

Source URL: https://www.cirm.ca.gov/about-cirm/publications/hypoxic-preconditioning-mesenchymal-stromal-cells-induces-metabolic-changes