Effect of Hypoxic Preconditioning on Cortical Bone Stem Cells (CBSCs)

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Rationale: Cortical Bone Stem Cells (CBSCs) improve cardiac performance when delivered in an infarcted heart, in part, through secretion of paracrine factors. However transplanted cells can die due to hypoxia or other hostile fators within the infarcted heart. Hypoxia is known to also influence several biological process including migration, proliferation and secretory activity.

Objective: the aim of this study is to define the effects of hypoxia on biological properties of CBSCs.

Methods and Results: CBSCs were isolated from C57Bl/6 mouse, expanded in vitro and characterized. CBSCs were subjected to hypoxia (1% O_2) or normoxia (21% O_2) condition and then several biological properties were analysed. Hypoxia resulted in upregulation of CAIX and GLUT1 expression, two HIF1α downstream targets (3.2 and 5.1 fold increase of GLUT1; 6.7 and 65 fold increase of CAIX after 6 and 24 hours respectively). This indicates an effective hypoxic response activation in our experimental conditions. Cell proliferation was assessed by CyQuant assay: no significant difference between normoxic and hypoxic cells were found after 1 and 2 days. Growth curves were determined to evaluate hypoxia effects at longer time points. Hypoxic cells had the same growing rate as cells in normoxia in the first days, but their number increased at longer time points, indicating different kinetics with respect to normoxic when cells were grown in a challenging condition like an exhausted media. CBSCs migration and chemotaxis decreased when cells were cultured at 1%O_2. Hypoxia preconditioning increased the paracrine activity of CBSCs. VEGF expression was increased after 6 hours (3 fold), and this effect remain stable after 24 hours and 3 days of 1% O_2. Hypoxia resulted in 2.2 and 1.9 fold increase of SDF1 after 24 hours and 3 days respectively and a 1.8 fold increase of IGF1 after 1 day. The expression of bFGF, Angiopoietin and SCF was not affected.

Conclusion: CBSCs can survive hypoxia and their paracrine activity increases without adversely affecting their proliferative capacity. In vivo experiments are needed to investigate if hypoxic preconditioning will enhance the ability of CBSCs to improve the structure and function of the injured heart.

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