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THE EFFECT OF HYPOXIA ON GLOBAL GENE EXPRESSION AND ALTERNATIVE SPLICING OF HUMAN MESENCHYMAL STEM CELLS

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Objectives Hypoxia preconditioning has become a novel strategy to improve the in vivo therapeutic potential of bone marrow-derived mesenchymal stem cells (MSCs). However, the underlying molecular mechanisms responsible for the hypoxia-induced survival and migration of MSCs are not fully characterised, and a better understanding of such process may lead to a novel strategy for stem cell-based therapies.

Methods To elucidate the molecular mechanisms underlying the beneficial effect of hypoxia preconditioning on MSCs, we used standard expression microarray and exon microarray to investigate the global profiling of gene expression and alternative splicing (AS) in hypoxia preconditioned-MSC (H-MSC) and normoxia treated-MSC (N-MSC) respectively.

Results A total of 414 differentially expressed genes were identified in H-MSC compared with N-MSC, including 138 unregulated genes and 276 down regulated genes. A large number of genes are responsible for enhanced therapeutic effect of H-MSC, especially associated with promoting cell survival, proliferation, migration, angiogenesis and glucose metabolism. Based on the genes that regulate cell survival and migration, most of them are respectively involved in mitochondrial apoptosis pathway and cell cytoskeleton organisation. These results were further confirmed by mitochondrial membrane potential assay and F-actin staining, indicating the effect of hypoxia on MSC survival and migration may relate with mitochondrial apoptosis pathway and cytoskeleton organisation. Furthermore, the high expression of glucose metabolism-associated genes such as leptin in H-MSC may indicate a novel mechanism of hypoxia-driven anti-apoptosis, migration and angiogenesis of MSCs. Besides the gene expression difference, hypoxia also resulted in 93 AS events that were associated with anti-apoptosis, proliferation, migration and angiogenesis.

Conclusions Our work provides a general framework for the systematic study of stem cell biology under clinically relevant pathophysiological conditions.