

Achievement Report: Genetic engineering of stem cells with retroviruses encoding HIF to improve cardiac function.

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Bone marrow stromal cells (BMSCs) contain progenitors capable of participating in postnatal angiogenesis. Hypoxia-inducible factors (HIFs) mediate endothelial activation by driving the expression of multiple angiogenic factors. We explored the potential of HIF-1alpha and HIF-2alpha modification in BMSCs, as a tool to improve cell-based angiogenic therapy. BMSCs were retrovirally transduced to express stable forms of HIF-1alpha and HIF-2alpha. HIF-1alpha and, to a greater extent, HIF-2alpha overexpression promoted differentiation of BMSCs to the endothelial lineage, evident by CD31 and Tie-2 expression and improved adhesive properties. Whereas chemotaxis toward stromal-derived factor 1 was higher in both HIF-alpha-expressing BMSCs, enhanced migration toward vascular endothelial growth factor was found only following overexpression of HIF-2alpha, supported by a robust expression of its receptor, Flk-1. HIF-alpha expression was associated with upregulation of angiogenic proteins and improved tube formation. Cytokine arrays of endothelial cells stimulated by medium collected from HIF-alpha-expressing BMSCs revealed further angiogenic activation and improved adhesive capacity. Eventually, delivery of HIF-2alpha-transduced BMSCs induced a more robust angiogenic response, compared with sham-transduced or HIF-1alpha-transduced BMSCs in the corneal micropocket angiogenesis model. Our results support the use of HIF-alpha genes, particularly HIF-2alpha, to augment the efficacy of future cell-based therapy. Disclosure of potential conflicts of interest is found at the end of this article.