

CARDIAC REPAIR WITH HUMAN STEM CELLS AND NEW MOLECULES HARBORING DIFFERENTIATING AND PARACRINE LOGICS

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Stem cells may hold promise for cardiovascular repair in patients with heart failure resulting from acute myocardial infarction or hereditary cardiomyopathies. So far, the use of human adult stem cells for cardiac cell therapy is hampered by an extremely low yield of spontaneous cardiovascular commitment *in vitro* and *in vivo*. Developing synthetic molecules that coax human stem cells into cardiovascular lineages and enhance their potential for cardiac repair is an emerging field in cardiac cell therapy.

We have developed a mixed ester of hyaluronan with butyric and retinoic acid (HBR) and provide evidence that it acted as a novel cardiogenic/vasculogenic agent in human mesenchymal stem cells isolated from bone marrow (BMhMSCs), and alternative sources, including dental pulp (DPhMSCs), and fetal membranes of term placenta (FMhMSCs). HBR remarkably enhanced the gene expression of vascular endothelial growth factor (VEGF), KDR (a major VEGF receptor), and hepatocyte growth factor (HGF). Notably, HBR increased the secretion of the angiogenic, mitogenic, and antiapoptotic factors VEGF, and HGF, priming stem cell differentiation into endothelial cells. In each cell population, HBR also increased the transcription of the cardiac lineage-promoting genes GATA-4 and Nkx-2.5, and the yield of cardiac marker-expressing cells. These responses were significantly more pronounced in FMhMSCs than in DPhMSCs or BMhMSCs. To assess whether HBR-pretreated hMSCs may enhance their potential as cardiac therapeutics, FMhMSCs were transplanted *in vivo* into the heart of rats subjected to acute myocardial infarction after ligation of the left anterior descending coronary artery. Transplantation of untreated FMhMSCs was associated with increased capillary density at the infarct border zone, normalization of left ventricular function, and significant decrease in scar tissue. Transplantation of HBR-preconditioned FMhMSCs further enhanced capillary density and the yield of human von Willebrand factor (hVWF)-expressing cells, additionally decreasing the infarct size. Some engrafted, HBR-pretreated FMhMSCs, were also positive for connexin 43, and cardiac troponin I. Thus, the beneficial effects of FMhMSCs and the enhanced cardiac rescue by HBR-exposed FMhMSCs may be mediated by a large supply of angiogenic and antiapoptotic factors and may also involve increased FMhMSC differentiation into vascular cells. These findings may contribute to further development in cell therapy of heart failure. Within this context, FMhMSCs may hold promise for allogenic, “off the shelf” strategies of cardiovascular rescue.