

Epigenetic Modifiers and Stem Cell-based Cardiac Regeneration: Role of Wnt Signaling

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ABSTRACT

Cardiac development or cardiogenesis, is a complex process that begins around the third week of gestation and is largely complete by the ninth week. Wnt signaling, a highly conserved signaling pathway, controls specification, proliferation and differentiation of cardiac cells during heart development. We aimed to investigate the role of Wnt/ β -catenin signaling in cardiac lineage commitment of human umbilical cord mesenchymal stem cells (hUC-MSCs) using epigenetic modifiers. hUC-MSCs were treated with zebularine or 2-deoxycytidine and analyzed for Wnt pathway and cardiac lineage commitment at gene and protein levels. Significant upregulation of early and late cardiac markers, GATA4, Nkx2.5, cardiac myosin heavy chain (cMHC), α -actinin, cardiac troponin T (cTnT) and cardiac troponin I (cTnI) was observed in treated MSCs as compared to the untreated control. We also analyzed gene expression of key Wnt/ β -catenin signaling molecules in cultures of treated and untreated hUCMSCs at different time points. The pattern of mRNA gene expression showed that Wnt/ β -catenin signaling is regulated during cardiac lineage commitment of hUC-MSCs in a time-dependent manner, with the pathway being activated early but inhibited later in cardiac development. The in-vivo study confirmed the induction of myocardial infarction, and showed improvement in cardiac functional parameters and homing of cells, demonstrating the regenerative potential of the transplanted cells. In conclusion, this study demonstrated that treatment of hUC-MSCs with Wnt pathway modulators can be chemically induced to differentiate toward the cardiac lineage in vitro and in vivo. The cardiac differentiation potential of these modified stem cells can be clinically tested in future. However, further optimization is necessary to enhance the functionality of the fully differentiated cardiac tissue.