THE ROLE OF VEZF1 IN CARDIOMYOCYTE DEVELOPMENT

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Epigenetic regulation in conjunction with signaling pathways govern cellular differentiation and mammalian development. Vascular endothelial zinc finger 1 (VEZF1) is a transcription factor expressed predominantly in the mesoderm of a developing mouse embryo. The mesoderm generates progenitor cells that form the cardiovascular system (heart and blood vessels) postgastrulation. Previous studies have established the role of Vezf1 as an insulator binding protein, with a potential to regulate chromatin conformation genome-wide. Based on its expression profile, we hypothesize that Vezf1 has a critical role in development of the cardiovascular system. Using murine embryonic stem cells (mESCs), we sought to investigate the early role(s) of VEZF1 in cardiomyocyte differentiation. We show that genetic ablation or conditional knockdown of Vezf1 in mESCs impairs cardiomyocyte differentiation, as determined by the absence of contractile activity in these mutants. The absence of cardiomyocytes from Vezf1 mutant cell lines was confirmed using gene expression analysis and immunofluorescence. We observed a strong reduction in mesodermal cells in the Vezf1 mutants despite small molecule stimulation of Wnt signaling, suggesting a potential role of VEZF1 regulation of Wnt signaling pathway. Indeed, our gene expression analysis and ChIP-qPCR indicate that VEZF1 associates with the promoters of Wnt signaling genes to activate their expression. Mechanistically, we identified that in absence of VEZF1, the insulator binding protein, CTCF, binds opportunistically to repress the expression of Wnt signaling genes. These studies point towards a model where VEZF1 regulates the formation of cardiac progenitor cells by activating the Wnt signaling pathway. Our observations suggest that a central role of VEZF1 in determining the fate of mesodermal cells into cardiovascular progenitors, the absence of which impairs cardiomyocyte differentiation. This study is the first to delineate the functional role of VEZF1 in the early development of cardiomyocytes and may form the foundation for future cardiac regenerative medicine.