Small Molecule-Mediated TGF-beta Type II Receptor Degradation Promotes Cardiomyogenesis in Embryonic Stem Cells.

Journal: Cell Stem Cell

Publication Year: 2012

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PubMed link: 22862949

Funding Grants: Chemical Genetic Approach to Production of hESC-derived Cardiomyocytes, Discovering Potent Molecules with Human ESCs to Treat Heart Disease, Type III CIRM Stem Cell Research Training Program

Public Summary:
The cellular signals controlling the formation of cardiomyocytes, vascular smooth muscle, and endothelial cells from stem cell-derived mesoderm are poorly understood. We didscovered ITD-1 as a highly selective TGF-beta inhibitor that induces cardiomyocyte differentiation from multipotent cardiovascular precursors.

Scientific Abstract:
The cellular signals controlling the formation of cardiomyocytes, vascular smooth muscle, and endothelial cells from stem cell-derived mesoderm are poorly understood. To identify these signals, a mouse embryonic stem cell (ESC)-based differentiation assay was screened against a small molecule library resulting in a 1,4-dihydropyridine inducer of type II TGF-beta receptor (TGFBR2) degradation-1 (ITD-1). ITD analogs enhanced proteasomal degradation of TGFBR2, effectively clearing the receptor from the cell surface and selectively inhibiting intracellular signaling (IC(50) approximately 0.4-0.8 muM). ITD-1 was used to evaluate TGF-beta involvement in mesoderm formation and cardiopoietic differentiation, which occur sequentially during early development, revealing an essential role in both processes in ESC cultures. ITD-1 selectively enhanced the differentiation of uncommitted mesoderm to cardiomyocytes, but not to vascular smooth muscle and endothelial cells. ITD-1 is a highly selective TGF-beta inhibitor and reveals an unexpected role for TGF-beta signaling in controlling cardiomyocyte differentiation from multipotent cardiovascular precursors.