
Inhibitors of Src and focal adhesion kinase promote endocrine specification: impact on the derivation of beta-cells from human pluripotent stem cells.

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Public Summary:

hESC-derived beta cells can become a renewable source of beta cells to treat type 1 diabetes. However, the differentiation of hESCs into beta cells is not efficient. In this report, we describe a novel approach to improve the differentiation efficiency. This advance could be helpful for clinical development of hESC-based cell therapy of type 1 diabetes.

Scientific Abstract:

Stepwise approaches for the derivation of beta-cells from human embryonic stem cells have been described. However, low levels of endocrine specification limit the final yield of insulin-producing beta-cells. In this study, we show that the pyrrolo-pyrimidine Src family kinase (SFK) inhibitor PP2 effectively promotes the endocrine specification of human embryonic stem cell derivatives based on its capacity to induce the expression of proendocrine transcription factors (NGN3, NEUROD1, NKX2.2, and PAX4) and to significantly increase the final yield of insulin-positive cells. We further demonstrate that PP2 inhibits the activation of focal adhesion kinase (FAK), and selective inhibition of this kinase is also sufficient to induce early endocrine commitment based on increased expression of NGN3, NEUROD1, and NKX2.2. Additional studies using dominant negative constructs and isolated human fetal pancreata suggest that c-Src is at least partially responsible for inhibiting early endocrine specification. Mechanistically, we propose that inhibition of SFK/FAK signaling can promote endocrine specification by limiting activation of the TGFbetaR/Smad2/3 pathway. Moreover, we show that inhibition of SFK/FAK signaling suppresses cell growth, increases the expression of the beta-cell-associated cyclin-dependent kinase inhibitor p57kip2, and simultaneously suppresses the expression of Id1 and Id2. This study has important implications for the derivation of beta-cells for the cell-based therapy of diabetes and sheds new light on the signaling events that regulate early endocrine specification.

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