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Transcription factor directed differentiation of human embryonic stem cells into the pancreatic endocrine lineage

Qing Le Liang[1], Xiao Xun Wang[1], Xiao Fei Yan[1], Li Jun Yang[1], Dong Qi Tang[1], Dong Sheng Li[1]

[1]*Hubei Provincial Key Laboratory of Embryonic Stem Cell Research, Taihe Hospital, Yunyang Medical College, 32S. Renmin Road, Shiyan 442000, China. Stem Cell Center of Qingdao University. University of Florida*

Human embryonic stem (hES) cells represent a potentially unlimited source of transplantable beta-cells for the treatment of diabetes. It has been reported that hES cells can be directly induced through cytokines or gene manipulations to insulin-producing cells ((IPCs). Here we describe a novel differentiation strategy that robustly directs H1, an National Institutes of Health (NIH)-registered hES cell line, into IPCs. Pdx1, a crucial regulator for pancreatic development, has been shown to convert hES into IPCs by viral vector mediated gene manipulation. Here we report that the TAT-Pdx1 protein can efficiently permeate H1 cell line due to the TAT protein transduction domain sequence fused to its structure. The TAT-Pdx1 protein was transduced in a dose-dependent manner. The transuded Pdx1 functions similarly to endogenous Pdx1: it binds to the insulin promoter and activates its expression. It also activated the expression of transcription factors that are critical to the differentiation of the pancreas such as endogenous Pdx1, NeroD, Ngn3. Functional secretion of insulin into the medium after glucose challenge was observed by ELESA. We also investigated the mechanism of TAT-Pdx1 protein transduction. The Tat-Pdx1 protein penetrated cells by macropinocytosis and was released from endosomes homogeneously in cytoplasm and nuclei. These data suggest that TAT-Pdx1 protein transduction could be a safe and valuable strategy for enhancing insulin gene transcription without requiring gene transfer.

***Keywords*:** human embryonic stem cells, PDX1, protein transduction domain

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Correspondence: Dong Sheng Li[a], Dong Qi Tang[b]
[a]E-mail: dsli@yymc.edu.cn
[b]E-mail: tangdq@pathology.ufl.edu

Qingle Liang was born in 1980. After graduation from HuBei Normal University as a major in Biology in 2002, he entered the graduate school of Peking Union Medical College at the department of Pharmacognosy. In 2005, he got his master's degree and since then he have been doing research on Human Embryonic Stem Cells, especially in the differentiation of insulinproducing cells. Right now he is working as a research assistant in Hubei Provincial Key Laboratory of Embryonic Stem Cell Research, Taihe Hospital, Yunyang Medical College.