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Trans-differentiated Human Hepatic Progenitors into Insulin producing β-Cells: A Step closer towards the Diabetes Cell Therapy

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Over the past few years, islet transplantation has emerged as one of innovative strategy for the treatment of diabetes mellitus, but the limited yield of quality donor pancreata makes this strategy inadequate. Therefore, patients affected with diabetes mellitus are in great need for the alternative source of β-cells. Liver is the most promising source of cells, as it has the same embryonic origin as the pancreas. Liver and pancreas develops from the same endoderm and share the similarity in most of their developmental regulatory pathways. Various studies from past have differentiated liver cells into pancreatic β-cells by transfecting with specific transcription factors like Pdx-1, Ngn-3, Isl-1, Pax-4, and Pax-6 [1-5].

But, such genetically modified cells have limitation of using in therapeutic purposes. In our earlier study we have demonstrated the presence of pancreatic transcription factors involved in the development of pancreas in induced hepatic progenitors [6]. Later we studied the responses of pancreatic transcription factors in hepatic progenitors following induction with various glucose concentrations (5–30 mmol/L) in vitro for 0–32 h [7]. Relative gene expression was quantified and compared with un-induced and pancreatic cells to identify the activated transcription factors (Pdx-1, Ngn-3, Isl-1, Pax-4, Pax-6 and Nkx-6.1) involved in β-cell production. The study showed high in vitro trans-differentiation potential of human hepatic progenitors towards the β-cell phenotype with 23 mmol/L glucose induction after 24 h. The transcription factors showed eminent expression in induced cells and was found significantly high in 23 mmol/L than un-induced cells. Interestingly, a significant increase in expression level of Nkx-6.1 almost similar to Pdx-1 showed a more committed β-cells phenotype for insulin production.

The study strongly suggests that human hepatic progenitors possess the capacity to trans-differentiate into functional insulin producing β-cells after 24 h of 23 mmol/L glucose induction. This holds a continual promise of exciting new insight for clinical implications for trans-differentiated insulin secreting functional β-cells without any genetic manipulation.

These finding are further supported by a recent study by Pagliuca et al. [8] where they have demonstrated production of insulin producing glucose responsive β-cells from human pluripotent stem cells. The study has also demonstrated the preclinical evaluation for functionality of these β-cells into hyperglycemic diabetic mice model. These β-cells were found to secrete insulin into the serum of mice shortly after transplantation in a glucose-regulated manner which later ameliorates hyperglycemia in diabetic mice.

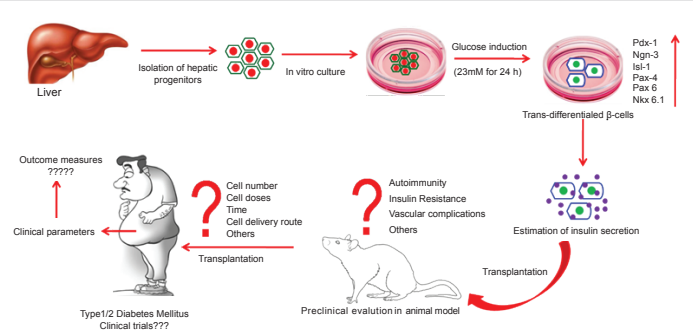

Figure 1: Therapeutic strategy for the treatment of diabetes using in vitro trans-differentiated functional β-cells from hepatic cells.

These studies might lead the way to new therapeutic path for their clinical implications in the treatment of both type 1 and type 2 diabetes mellitus. However, before reaching to the clinics, the problems of autoimmunity, insulin resistance and the vascular complications of diabetes need to be addressed in preclinical models.

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