Regeneration of Insulin-Producing Cells from Stem Cells

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Current therapies for type 1 diabetes, such as daily insulin injections, cannot prevent the progression of secondary complications of the disease. Promising approaches to overcoming this problem include the expansion of existing beta-cells, the differentiation of ES cells into beta-cells, and the conversion of either pancreatic or nonpancreatic adult stem/progenitor cells into beta-cells. Although various attempts have been made to obtain insulin-positive cells from ES cells, these *in vitro* attempts have not been successful. We are attempting to differentiate ES cells into endodermal cells, which will be further differentiated into pancreatic beta-cells by controlled expression of Pdx-1, a master transcriptional regulator of pancreatic development. On the other hand, attention has turned to the possibility of islet neogenesis *in vivo*. We previously reported that the expression of Pdx-1 in the pancreas induced the neogenesis of insulin-producing cells in the ductal complex, although too few cells were generated for therapeutic purposes. To induce insulin-producing cells more efficiently, we produced a transgenic mouse line, RTF-Pdx-1-EGFP, in which Pdx-1 are expressed throughout the body under the control of tetracycline. However, Pdx-1 expression alone did not induce beta-cell neogenesis in the pancreas or any other organs. We next examined the effect of simultaneously expressing genes for other transcription or growth factors in the RTF-Pdx-1-EGFP mice, using adenovirus-mediated gene transfer. Simultaneously expressed Isl-1 and Pdx-1 clearly enhanced the neogenesis of insulin-producing cells and cell clusters in the ductal complex area. In this symposium, I will talk about the present status of the research on the beta-cell neogenesis *in vitro* and *in vivo*.