論文の内容の要旨

論文題目

Development of a method for large scale production of pancreatic islet progenitors derived from human iPS cells

（　iPS 細胞由来膵前駆細胞の大量培養に向けた膵前駆細胞増幅法の開発　）

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Transplantation of pancreatic islets is an effective therapy for severe type 1 diabetes. As donor shortage is a major problem for this therapy, attempts have been made to produce a large number of pancreatic islets from human pluripotent stem cells (hPSCs). However, as the differentiation of hPSCs to pancreatic islets requires multiple and lengthy processes using various expensive cytokines, the process is variable and low efficiency and costly. Therefore, it would be beneficial if islet progenitors could be expanded while maintaining their differentiation potential, and the aim of this study was to test this possibility in an in vitro differentiation protocol for pancreatic islets from human induced pluripotent stem cells (hiPSCs). Taking advantage of a modified hiPSC line with a genetically encoded fluorescent marker, Neurogenin3 (NGN3)-expressing pancreatic endocrine progenitor (EP) cells

derived from hiPSCs were isolated. While they exhibited the ability to differentiate into pancreatic islets, their cell cycle was arrested. By using a lentivirus vector, I introduced several growth promoting genes into the NGN3-expressing EP cells. I found that Simian virus-40 large T-antigen (SV40LT) expression induced proliferation of the cells but reduced the expression of endocrine-lineage commitment factors, *NGN3*, *NEUROD1*, and *NKX2.2*, resulting in the suppression of islet differentiation. Removing SV40LT by using the Cre-loxP system after the expansion led to the re-expression of endocrine-lineage commitment genes and restored the cells' ability to differentiate into functional islets. Thus, the present study will lead to a way to generate a large quantity of functional pancreatic islets through the expansion of EP cells from hPSCs.