KSN 2020
FULLY VIRTUAL MEETING

Abstract Type : Oral
Abstract Submission No. : OR-1364

New approaches for predicting tacrolimus-induced diabetes after transplantation using patient-specific progenitor pancreatic cells from iPSC

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Objectives: New-onset diabetes after transplantation (NODAT) is a serious and common complication that reduces recipient survival. Tacrolimus is necessary but is related with development of NODAT by causing beta cell failure. In this study, we aim to predict the tacrolimus-induced beta cell failure before KT using patient-derived induced pluripotent stem cells (iPSC).

Methods: A total non-diabetic 20 pre-KT recipients blood was obtained, of which 20% were noted as NODAT one year after transplantation. 4 NODAT and 4 Non-NODAT patients were selected for further study, and each iPSC were established successfully. iPSCs were differentiated into progenitor pancreatic cells (PP) using defined STEMdiff™ Pancreatic Progenitor Kit that supports efficient and reproducible generation of PP. Real-time qPCR (RT-qPCR) and flow cytometric analysis were performed to confirm that the differentiated PP. Tacrolimus toxicity was evaluated via monitoring of cell viability.

Results: Each patient-specific iPSC lines expressed pluripotency marker. Flow cytometry revealed that about 80% in iPSCs were positive for OCT3/4. Each PPs generated from the iPSC expressed the PP's specific markers. We found that % of insulin positives in PP was significantly lower in NODAT group than the Non-NODAT group (43 ± 7% vs. 66 ± 1%, $P < 0.05$) using flow cytometric analysis. Using cytotoxicity assay using tacrolimus, area under the curve derived from drug concentration and time revealed that 40 and 50 μg/mL of tacrolimus were significantly difference between the NODAT and Non-NODAT group (40 μg/mL, 168 ± 8 vs. 272 ± 7, $P < 0.05$; 50 μg/mL, 127 ± 4 vs. 215 ± 5, $P < 0.05$).

Conclusions: These results suggest that PPs derived from NODAT patients were more sensitive to tacrolimus-induced toxicity than those of Non-NODAT patients. Our finding provides the evidence that patients-derived iPSCs platform could recapitulate tacrolimus-induced beta cell disorder before KT.