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Discovering the mechanism of tacrolimus induced pancreatic beta cell injury by using single-cell RNAseq analysis

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Objectives : Tacrolimus is an important immunosuppression agent following kidney transplantation which frequently causes the development of diabetes mellitus. In this study, we investigated the transcriptomic changes of pancreatic β cells exposed under tacrolimus in a single cell resolution.
Methods : Sprague-Dawley rats (n=3 per each group) were randomly assigned to normal control group and tacrolimus treatment group. Tacrolimus was administered subcutaneously at doses of 1.5mg/kg/day. After 2 weeks of tacrolimus treatment, pancreatic islets were isolated from both groups. These isolated islets were dissociated into a single cell level, and libraries were prepared using the 10X Chromium library v3.1 kit, targeting approximately 8,000 cells from each group. The prepared libraries were sequenced by using Hiseq X Ten.
Results : The relative proportion of β cells was decreased while α cells was increased in tacrolimus treated islets. However, we did not observe any changes in the expression of β cell de-differentiation markers, including mature β cell genes (Ins1, Ins2, Ucn3, MafA, and Slc2a2) or progenitor genes (Ngn3 and Sox9). Notably, endoplasmic reticulum (ER) stress genes (Fkbp11, Ddit3, Atf3, and Atf5), along with senescence genes (Igf1r and Bambi), were upregulated in the tacrolimus-treated β cells. Furthermore, genes involved in de novo cholesterol biosynthesis (Hmgcs1 and Hmgcr) were also upregulated in tacrolimus-treated β cells, suggesting a potential novel mechanism behind tacrolimus-induced β cell injury.
Conclusions : In conclusion, tacrolimus administration results in a decrease in the number of β cells, accompanied by an increase in ER stress and cellular senescence. The present study suggests the involvement of the cholesterol biosynthesis pathway in the adaptation of β cell islets to tacrolimus, highlighting a potential novel mechanism of tacrolimus-induced β cell injury.