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論 文 要 旨

THESIS SUMMARY

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要旨（英文 800 語程度）
Thesis Summary（approx.800 English Words ）

Introduction

Diabetes mellitus, defined by high blood glucose levels, with 8.4 million individuals worldwide diagnosed with type 1 diabetes mellitus (T1DM), which mainly results from the autoimmune destruction of pancreatic islet β cells. Islet transplantation is successfully performed by intraportal transplantation. However, this method might not be desirable for future cell therapy transplanting pluripotent stem cell-derived beta cells. Facing issues such as hard-to-retrieve cells and graft loss due to instant blood- mediated inflammatory reaction (IBMIR)[1]. Finding an alternative site for islet transplantation has become a hot topic recently, including the gastric submucosa, spleen, eyes, submandibular gland, and intramuscular have been explored for their physiological and immunological compatibility[2][3][4][5]. The subcutaneous space offers a potential site due to its safety, accessibility, and low risk of IBMIR. However, the lack of vascular beds limits its application. My research addresses this issue by carrying out angiogenesis stimulation via basic fibroblast growth factor (bFGF). I am also employing an atelocollagen sponge as a cell-carried scaffold for islet transplantation into a pre-vascularized subcutaneous site, aiming to establish a stable subcutaneous transplantation platform and broaden its utilization to stem-cell-based cell therapy.

Experimental methods

Single high dose of Streptozotocin (STZ) treatment induced diabetes model BALB/c and *Rag-2/Jak3* double-deficient (BRJ) mice have received (Angio-treated mice) or not received (Non_angio-treated mice) the angiogenesis stimulation via 10 μg bFGF (Fiblast) contained gelatin sponge (Spongel, Astellas) subcutaneous transplantation. The gelatin sponge was carefully removed after 1 week, followed by 800 freshly isolated donor mouse islets carrying atelocollagen sponge scaffold (Mighty, Koken) that was transferred to the pocket-like subcutaneous cavity left after the removal of the gelatin sponge. Non- fasting blood glucose levels and body weights of recipients were measured every week. An intraperitoneal glucose tolerance test (IPGTT) was also conducted to examine the performance of the implanted islets. The graft was removed

since 20 weeks post transplantation and removed grafts were characterized by Hematoxylin and Eosin (H&E) staining and immunohistochemistry analysis.

Results and Discussion

1. Reversal of hyperglycemia by subcutaneous islet transplantation in BALB/c mice

Immediately after 800 donor islets subcutaneously transplanted, Angio-treated mice's conditions improved, as evidenced by a gradual decrease in blood glucose levels and a steady increase in body weight until the graft removal. At the same time, Non_angio-treated mice exhibited featured higher glucose levels and lower body weights. 8- and 16-weeks post transplantation, IPGTT results also show different outcomes, Angio-treated mice responded to glucose challenge similar to healthy control mice, while Non_angio-treated mice exhibited typical diabetes response. Additionally, areas under the curve (AUC) of IPGTT clearly showed that mice in the angio-treated and healthy groups had significantly lower AUCs than those in the non-angio-treated group, with no significant difference between the AUCs of the angio-treated group and healthy mice. Furthermore, much more vascularized islets were found in harvested angio-treated mice's graft. The results jointly demonstrated we have successfully established a subcutaneous transplantation platform in BALB/c mice.

2. Reversal of hyperglycemia by islet transplantation in Rag-2/Jak3 Double-Deficient BALB/c (BRJ) mice

STZ-induced diabetes BRJ mice were also cured by 800 ICR donor mouse islets subcutaneous transplantation. Non-fasting blood glucose levels returned to healthy levels 5 weeks post transplantation and maintained normoglycemia until the removal of the graft. Which was accompanied by an increase in body weight. Immediately after graft removal, their non-fasting blood glucose levels backed to the diabetic levels, suggesting that the insulin required to maintain normal blood glucose levels is originally from our subcutaneously transplanted donor islets. Furthermore, high vasculature and preserved morphologies were observed in the removed islet grafts, indicating that I extended the application of the developed platform to immunodeficient mice, thus thus demonstrating its potential for use in stem-cell based cell therapy.

References

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