Co-Transplantation of VEGF-Expressing Human Embryonic Stem Cell Derived Mesenchymal Stem Cells to Enhance Islet Revascularization in Diabetic Nude Mice

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Background:
Pancreatic islet transplantation has emerged as a promising treatment for type I diabetes. However, its efficacy is severely hampered due to poor islet engraftment and revascularization, which have been resulted to partially loss of transplanted islets. It has been shown that local delivery of vascular endothelial growth factor (VEGF) could accelerate transplanted islet revascularization, although permanent high level of VEGF may lead to undesirable side effects. In this study we investigated the effects of conditional cell-based delivery of VEGF through collagen-fibrin hydrogel on transplanted islet function and revascularization.

Material and Methods:
RH6 human embryonic stem cell derived mesenchymal stem cells (ES-MSCs) have been generated, characterized and transduced by two lentiviruses containing rtTA and VEGF-A. Tet-on expression of VEGF from these cells was shown by tube formation assay and was confirmed through VEGF ELISA. After co-transplantation of these cells and mouse isolated islets through collagen-fibrin hydrogel in the omental pouch of diabetic nude mice, the blood glucose, body weight, glucose tolerance and serum C-peptide was measured after 28 days. As control groups, islets were transplanted alone and with non-transgenic ES-MSCs. For measurement of revascularization, immunohistoflourscence examination was done and micro vessel density (MVD) and vessel size have been measured.

Results:
Receiving the same number of islets (300 IEQ) in all transplanted groups, the average blood glucose concentrations of mice transplanted with islets/hESC-MSC:VEGF were significantly lower than mice transplanted with islets or islet/hESC-MSC at different time points. This notable difference in blood sugar of transplant groups, was also reflected in their weight gain. Serum C-peptide level was higher in islet/hESC-MSC:VEGF (349.8±51.2 pM) compared with islet/hESC-MSC group and islet group but it was not markedly different from C-peptide levels in normal mice. In intraperitoneal glucose tolerance test (IP-GTT) to examine glucose responsiveness of the islet graft, mice in islet/hESC-MSC:VEGF group returned to normoglycemic state at the same rate as normal mice, while mice in islet/hESC-MSC and islet groups responded more slowly and did not return to the normoglycemic state. The results showed improved islet functionality and micro-vessel density in the group of mice received islets with VEGF expressing hESC-MSC, compared with control groups.

Conclusion:
We conclude that conditional expression of VEGF from hESC-MSCs during islet transplantation could enhance islet functionality and revascularization. This result can be used to improve the outcome of clinical islet transplantation.

Keywords: Co-transplantation, Embryonic stem, Mesenchymal stem cells.

Poster Presentation

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