Abstract

Islet Cytoprotection

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Given the limited supply of donor pancreatic islets, considerable efforts have been made to prevent the loss of islet mass in the post-TPL period. Islets may be manipulated in vitro prior to TPL, providing opportunities for therapeutic strategies aiming at conferring cytoprotection to maximize their engraftment and survival. Since the substantial early post-TPL graft loss is mainly due to apoptosis from hypoxic and inflammatory insults, intervention of these cell death pathways may substantially enhance preservation of islet mass following TPL.

Utilization of additives in the culture media (antioxidants, growth factors, etc.) may result in reduced islet cell death and better function, representing a simple strategy toward the optimization of islet engraftment. In our study, an antioxidant alpha-lipoic acid alleviated hydrogen peroxide-induced islet cell apoptosis, reactive oxygen species production, mitochondrial membrane depolarization and c-JNK activation. Thus, alpha-lipoic acid, which showed cytoprotective effects on beta-cells under oxidative stress by its antioxidant properties, may be a useful antiapoptic agent during peri-TPL period.

The possibility to modify islets by gene therapy utilizing viral and non-viral vectors represents an appealing approach for the cytoprotection of islet cells. There are two areas to be studied: (1) which vectors will efficiently deliver cytoprotective genes? (2) Which specific target genes will be best to enhance islet survival in the harsh post-TPL period? In our study, among non-viral carriers, Effectene showed relatively high transfection efficiency in islet cells. The delivery of hypoxia-inducible VEGF to islets using Effectene induced VEGF expression specifically under hypoxia in vitro. In syngeneic mouse islet TPL under the kidney capsule, hypoxia-inducible VEGF overexpression in islet grafts leads to improvements in blood glucose regulation in the recipient mice. This may be one of useful ex vivo strategies that could confer cytoprotection to beta-cells in order to achieve a better outcome of islet TPL.