



Avances en Diabetología



O-030. - THE IMPACT OF PTP1B ON THE SURVIVAL AND REVASCULARIZATION OF TRANSPLANTED ISLET GRAFTS

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Resumen

Introduction and objectives: Transplantation of pancreatic islet as an acknowledged curative treatment for type 1 diabetes still remains limited by post-transplantation massive islet loss and graft failure. Protein tyrosine phosphatases are essential for intracellular signal transduction modulating cell growth, apoptosis or gene transcription by maintaining critical phospho-tyrosine levels of several key proteins. Protein tyrosine phosphatase 1B (PTP1B) is a negative regulator of insulin, growth-factor signalling and recently angiogenic, migration and survival signaling pathways in endothelial cell. In the view of these data, we hypothesized that PTP1B inhibition might play a crucial role in graft survival and revascularization and therefore constitute a potential therapeutic target for islet transplantation protocols.

Material and methods: Before being submitted to transplant BALB/c mice were made diabetic through a single injection of streptozotocin (160 mg/Kg). The transplantation procedure consist in transfer into the anterior chamber of the eye Islets isolated from PTP1B^{+/+} and PTP1B^{-/-} (150-200 islets/animal). Three groups of animals were constituted (n = 9 animals per group): CTRL - non-transplanted; T - transplanted with PTP1B^{+/+} isolated islets; and T - KO - transplanted with PTP1B^{-/-} isolated islets. Weight, glycemic levels were evaluated during 25 days, and then cell viability and islet graft revascularization were accessed *in vivo* by two-photon microscopy. Post-mortem morphometric analysis and functional studies were conducted on graft-containing eyes.

Results: By the end of the 25 day, and regarding glycemic levels T group exhibited a decrease when compared to the CTRL group (T: 418 ± 48 mg/dL, CTRL: 528 ± 20 mg/dL, p < 0.05). Outstandingly, the T-KO group showed a greater decrease in glycaemia (211 ± 26 mg/dL) both when compared to the T group (49% decrease, p < 0.01) or to the CTRL group (60% decrease, p < 0.01). *In vivo* cell death was access bypropidium iodide injection revealing a 73% decrease in the T-KO when compared to the T group (0.25% and 0.95%, respectively; p < 0.001). Islet revascularization namely functional vasculature, was accessed by *in vivo* dextran injection, It was found an increase of 58% in vascular density (T-KO: 0.0297 ± 0.0035% vs T: 0.0187 ± 0.0053%; p < 0.05) and a 2-fold increase in vascularization area (T-KO: 23.180 ± 1.9% versus T: 10.027 ± 2.6%; p < 0,001) of T-KO group relatively to T group. Morphometric analyses of the graft-containing eyes support *in vivo* findings, it was found a 3-fold increase in the percentage of endothelial cells within grafts (T-KO: 0.121 ± 0.0096% and T: 0.0351 ± 0.005%; p < 0,001) as well as a 62% decreased in total graft apoptotic cells of T-KO group relatively to T group (T-KO: 0.114 ± 0.037% and T: 0.0422 ± 0.0078; p < 0.05).

Conclusions: Our results support the hypothesis that PTP1B plays a negative role on the survival and revascularization of islet grafts suggesting that PTP1B may be a potential target for a post-transplantation therapy. Future work will focus on further unravelling the molecular mechanism involved in these findings.

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