Beneficial Effects of Activated Protein C on Amelioration of Hyperglycemia in Streptozotocin-induced Diabetic Mice Receiving Intrahepatic Syngenic Islets From a Single Donor

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Abstract: The inability to achieve successful islet transplantation from one donor to one recipient has been a major obstacle facing clinical islet transplantation. The present study focused on the effects of activated protein C (APC) which plays a key role in crosstalk between coagulation and inflammation and determined whether APC has any beneficial effect on engraftments of islets transplanted into the liver of mice. Streptozotocin (STZ)-induced diabetic mice (n=8) receiving intrahepatic 200 syngeneic islets, the number of islets isolated from a single donor, remained hyperglycemic after transplantation. In marked contrast, all of diabetic mice (n=7) receiving 200 islets and treated with APC (40 μg, i.v. at 0, 2 and 4 hr) became normoglycemic. A histological examination revealed that APC prevented islet graft loss during the early post-transplant period and more of the islets were detected in the liver of the APC treated mice than in the controls. Sixty days after transplantation, the APC treated mice showed better glucose tolerance than the control mice. A flow cytometry analysis disclosed that $Gr\text{-}1^{+}CD11b^{+}$ cells (neutrophils) with a high production of proinflammatory cytokines had accumulated in the liver of control mice at a peak of 6 hr after transplantation. In mice receiving islets and treated with APC, the production of proinflammatory cytokines in these cells was down-regulated without affecting their number. These findings show that APC prevents early loss of transplanted islets by inhibiting the production of proinflammatory cytokines deleterious to islet grafts, enabling successful transplantation from one donor to one recipient in mice. The present study indicates that APC may improve the efficiency of clinical islet transplantation when the effect of APC is also the case in human.

Key words: **Islet transplantation, Engraftment, Activated protein C (APC), Proinflammatory cytokine**