INVESTIGATION ON THE UTILITY OF KRP-203 IN REGULATING IMMUNE REJECTION OF ALLOGENEIC ISLET TRANSPLANTATION

（書式１８）

学　位　論　文　要　約
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博士論文題目 Title of dissertation

INVESTIGATION ON THE UTILITY OF KRP-203 IN REGULATING IMMUNE REJECTION OF ALLOGENEIC ISLET TRANSPLANTATION

（同種膵島移植の免疫拒絶反応制御における KRP-203 の有用性に関する検証）

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Background. The current standard immunosuppressive regimens, calcineurin inhibitors, have diabetogenic and anti-vascularization effects on islet grafts. KRP-203, a sphingosine-1-phosphate functional antagonist, exerts its immunomodulatory function through lymphocyte sequestration. However, the effect of this antagonist on islets is unclear. We examined the effect of KRP-203 on the islet function and vascularization and sought a calcineurin-free regimen for islet allotransplantation.

Methods. KRP-203 was administered for 14 days to mice, then diabetogenic effect was evaluated by blood glucose levels and a glucose tolerance test. Static glucose stimulation, the breathing index, and insulin/DNA were examined using isolated islets. Islet neovascularization was evaluated using a multi-photon laser scanning microscope (MPLSM). After islet allotransplantation with either KRP-203 alone, sirolimus alone, or both in combination, the graft survival was evaluated by blood glucose levels and immunohistochemical analyses. A mixed lymphocyte reaction was also performed to investigate the immunological characteristics of KRP-203 and Sirolimus.

Results. No significant differences in the blood glucose levels or glucose tolerance were observed between the control and KRP-203 groups. Functional assays after islet isolation were also comparable. The MPLSM showed no inhibitory effect of KRP-203 on islet neovascularization. Although allogeneic rejection was effectively inhibited by KRP-203 monotherapy (44%), combination therapy prevented rejection in most transplanted mice (83%).

Conclusions. KRP-203 is a desirable immunomodulator for islet transplantation due to the preservation of the endocrine function and lack of interference with islet neovascularization. The combination of KRP-203 with low-dose Sirolimus may be promising as a calcineurin-free regimen for islet allotransplantation.