Prevention of Early Islet Graft Loss in Association with Engraftment in the Liver of Mice by Targeting IL-6/IL-6 Receptor Signaling

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Abstract：Currently, the low success rate in achieving insulin independence in patients with IDDM after islet transplantation from a single donor has been a major obstacle facing clinical islet transplantation. We herein determined whether this could be overcome by targeting IL-6/IL-6R signaling, facilitating to prevent early loss of transplanted islets in association with engraftment in the liver of mice.

Hyperglycemia of streptozotocin-induced diabetic mice was not ameliorated after transplantation of 200 syngenic islets, the number of islets from a single mouse pancreas, into the liver due to early loss of islet grafts. The serum IL-6 concentration was elevated in recipient mice with the peak at 6 hours after islet transplantation with accumulation of IFN-γ- and TNF-α-producing Gr-1$^+$CD11b$^+$ cells in the liver. The treatment with anti-IL-6 antibody or gp130-Fc targeting IL-6/IL-6R signaling produced normoglycemia in diabetic mice receiving 200 islets. FACS analysis revealed that each treatment not only reduced Gr-1$^+$CD11b$^+$ cells（neutrophils）in number but also prevented their IFN-γ and TNF-α production in the liver receiving islets. These findings indicate that IL-6/IL-6R signaling plays a crucial role in early loss of islet grafts, suggesting that it could be a target for intervention to improve the efficiency of islet transplantation.

Key words：**Islet transplantation, IL-6/IL-6R signaling, Early loss of transplanted islets**