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Up-Regulated LRRN2 Expression as a Marker for Graft Quality in Living Donor Liver

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Introduction: The quality and size of liver grafts are critical factors that influence living donor liver transplantation (LDLT) function and safety. However, the biomarkers used for predicting graft quality are lacking. Only donor age has been used as a graft quality marker, and the mechanism of increased donor age and decreased graft function is not well understood. In rodents, several functional and genetic changes reportedly occur in the liver with aging. However, there are some problems that short-lived rodents cannot adequately reproduce human aging. Non-human primates are considered one of the best preclinical models due to their genetic, physiological, and anatomical similarity to humans compared to rodents. In this study, we sought to identify unique graft quality markers, aside from donor age, by utilizing the livers of non-human primates.
Methods: Hepatic gene microarray analysis from young (n=7, 5-9 years old) and elderly (n=6, 26-27 years old) cynomolgus macaques was performed to examine the age-related gene change. The candidate age-related gene expression in 350 human LDLT donor liver tissue was examined by rtPCR. The correlation between the gene expression and 6-month graft survival rates was investigated.
Results: We conducted the principal component analysis with microarray analysis data and observed clear segregation of young and elderly groups, suggesting the age-related changes in gene expression were obviously captured. In addition, this analysis revealed a total of 271 genes with significantly increased expression in the elderly. These candidate genes were then narrowed down to six through bioinformatics analyses. The expression patterns of these candidate genes in human donor liver tissues were subsequently examined. Importantly, we found that grafts exhibiting up-regulated expression of these six candidate genes were associated with an increased incidence of liver graft failure. Multivariate analysis further revealed that up-regulated expression of LRRN2 (encoding leucine-rich repeat protein, neuronal 2) in donor liver tissue served as an independent risk factor for graft failure (Odds ratio 4.50, confidence interval 2.08–9.72, p-value = 0.0003). Stratification based on graft expression of LRRN2 and donor age was also significantly associated with 6-month graft survival rates [LRRN2 low/donor age < 50 years; 97.3% LRRN2 low/donor age ≥ 50 years; 100%, LRRN2 high/donor age < 50 years;95.1%and LRRN2 high/donor age ≥ 50 years; 66.6%, p-value < 0.0001].
Conclusions: Upregulated LRRN2 expression of liver graft is significantly correlated with graft failure in LDLT. In addition, the combination of graft LRRN2 expression and donor age may represent a promising marker for predicting LDLT graft quality.

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Modified Approach for Improved Islet Allotransplantation Into Pre-vascularized Cell Pouch Device - Preliminary Results of the Phase I/II Clinical Trial at University of Chicago

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Introduction: After the pilot study demonstrated safety of the Sernova Cell Pouch™ (SCP), we modified islet transplantation (ITx) conditions for improved engraftment in the SCP.
Methods: SCPs were implanted in the abdominal anterior rectus sheath of 7 patients with T1DM and problematic hypoglycemia. Immunosuppression was initiated 1 month after SCP implantation and a marginal dose ITx of highly purified islets 1 month later. A second ITx was scheduled 6 to 12 months later. Sentinel SCPs are explanted for histopathology 3 months after ITx. Graft function is monitored by blood glucose (BG), C-peptide and insulin usage.
Results: Seven patients underwent 29 study-related surgeries with wound infection in 2 (6.8%) patients after SCP implantation. One patient discontinued following device excision and the second patient's infection resolved. SCPs are well tolerated with implant durations exceeding 35 months. Three patients received two ITx into SCPs, resulting in new, measurable islet function documented by detectable levels of stimulated C-peptide. A supplemental, single intraportal ITx was sufficient for the first two patients to achieve ongoing insulin independence and freedom from severe hypoglycemic events for over 24 and 4 months with HbA1c 5.4 and 5.5%, respectively. The third patient discontinued insulin support 2 months after a single supplemental intraportal ITx and presented normal blood glucose control during MMTT on post-transplant day 75 with fasting and peak values of 97 and 142mg/ml, respectively, serum C-peptide of 1.11 and 3.39 ng/ml and HbA1c of 5.8%. Two of the remaining 3 patients developed donor specific antibodies with islet graft failure in the SCP after unintended periods of suboptimal immunosuppression. One patient awaits a second ITx into SCP.
Conclusion: ITx with SCP demonstrates long-term safety in an early subset of trial patients. Ongoing results for transplanted SCPs have led to procedural adjustments to further optimize clinical outcomes.