

Molecular Crosstalk between T cells and B cells in Pediatric Liver Transplant Rejection

Late rejection of a liver graft (late ACR) is more difficult to treat and more likely to progress to chronic rejection or re-transplantation than rejection that occurs early after liver transplantation. Current therapies for rejection include corticosteroids and increased tacrolimus, which negatively affect recipient growth, metabolism, kidney function, and infection risk. There is currently an unmet need for non-invasive predictors of rejection and response to treatment, as well as for more targeted immunosuppressive therapies to treat rejection and promote long-term allograft and recipient health. Some liver transplant recipients develop antibodies against donor tissue, which are called donor specific antibodies (DSA). DSA are a risk factor for late ACR, however, it is not known whether the immune cells which make DSA are contributing to the rejection episode or whether current treatments for late ACR effectively target these pathologic groups of immune cells.

We will perform gene expression and protein expression studies on liver biopsies obtained from patients with late rejection, comparing patients with DSA to those without DSA, to discover signaling pathways which could lead to new anti-rejection therapies to improve treatment for ACR and prolong allograft survival.

Innovation:

- Antibody-mediated rejection is a newly emerging concept in liver transplantation. This study will investigate the role of B cells and donor-specific antibodies in late ACR.

Approach:

Aim 1: Identify gene sets and regulatory pathways associated with late acute cellular rejection (ACR) in patients with donor specific antibodies (DSA).

Aim 2: Determine the localization of liver-infiltrating immune cell subsets in the transplanted liver during late ACR in DSA-positive patients as compared to DSA-negative patients.

Impact: Late ACR and the nonspecific immunosuppressive medications used to treat it are a significant cause of morbidity and graft loss in the pediatric liver transplant population. The studies we propose will provide novel insight into the cellular and molecular mechanisms of late ACR in pediatric liver transplant recipients, and will form the rationale for either the repurposing of existing biologic therapies or the development of new therapies to more effectively and safely treat ACR, promote long-term allograft health, and avoid re-transplantation. The data generated from this pilot study will be used to calculate a sample size needed for future prospective and multi-center studies and generate preliminary data that will be utilized to garner additional external NIH and industry funding.