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Project Summary: NIH estimates that 24 million Americans suffer from autoimmune diseases, a significant percentage of whom develop end organ failure for which organ transplant would be the only curative treatment. Recurrence of primary autoimmune diseases (RPAD) is among the leading causes of graft loss and patient morbidity and mortality following solid organ transplantation (SOT). A major challenge in managing these patients is determining whether immune-mediated graft dysfunction is the result of an autoimmune or alloimmune process or both. Current diagnostics involving a combination of serological, radiological and histological criteria do not clearly distinguish between acute cellular rejection (ACR) and RPAD. A better understanding of the interplay between these two processes may ultimately improve the safety and efficacy of RPAD and ACR treatment, targeting the specific mechanism of graft injury in individual patients. Adaptive T and B cell responses are implicated in both autoimmune disorders and allograft rejection. We propose to use a novel approach to identify the specific roles of alloreactive T cells and autoreactive T and B cells in post-transplant allograft dysfunction in patients with autoimmune disease. Using high-throughput sequencing (HTS) of the T-cell receptor (TCR) beta chain complementarity-determining region 3 (CDR3), we have developed a novel method of identifying and tracking the human alloresponse in transplant recipients. We now propose to use this method in combination with a HTS-based method of identifying and tracking the autoimmune TCR and B-cell receptor (BCR) repertoire to distinguish the roles of allograft rejection and RPAD in graft dysfunction following transplantation due to autoimmune disease. We will use liver transplantation (LT) for autoimmune liver diseases (ALD) as a system in which to test this approach. HTS of the TCR beta CDR3 (hypervariable) region will be used to identify donorreactive
T cell clones in pre-transplant blood and autoreactive T and B cell clones from patient liver explants and biopsies. Following the transplant, we will track these clones in the blood, graft, bile and possibly stool during and following periods of allograft dysfunction in order to discern the roles of donor-specific T cell clones and autoreactive T and B cells in causing graft dysfunction and to assess their responsiveness to therapy. We hypothesize that autoreactive clones will be more abundant in blood or liver tissues when graft dysfunction is caused by recurrent ALD, whereas donor-reactive T cell clones will predominate in ACR. We will also test whether it is possible to identify and track these lymphocytes in stool, which, if positive, could ultimately be evaluated as a non-invasive method that would avoid the need for liver biopsies in the future. If successful, a new tool to distinguish ACR and rALD will become available, allowing a deeper understanding of liver dysfunction following LT and enabling improved therapies. Our novel approach has enormous potential to provide a diagnostic and prognostic biomarker of alloimmune and autoimmune processes following SOT and will be applicable to graft dysfunction in other types of SOT for autoimmune diseases.