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Abstract
The goal of this study is to advance understanding of the role of T cells in the development and progression of chronic lupus nephritis (LN). It addresses the clinical problem of why in nearly half of cases, LN does not respond to therapy and progress to chronic glomerulonephritis.
Preliminary data show LN kidney biopsies have a variable infiltrate of clonally expanded CD4 and/or CD8 T cells with features suggesting these cells drive the inflammatory process. Certain kidney biopsies xhibit clonally expanded CD8 T cells with a CD28null memory effector phenotype that adhere to Bowman[1]s capsule or to tubular epithelium in a manner resembling a cytotoxic cell synapse. On repeat biopsies of patients with diminishing renal function, these same clonotypes persisted for many years, became widely distributed in periglomerular and intratubular sites, and were found in the peripheral blood. CD4 T cells exist in two different patterns: large diffuse periglomerular and intertubular aggregates, some of which appear either polyclonal or as a memory effector phenotype T cell adhering to Bowman[1]s capsule or tubules, similar to the CD8 T cells. The finding of clonally expanded memory-effector CD8 T cells with features of an adaptive immune response does not fit the current paradigms of LN, and we advance the hypothesis that while acute glomerulitis is driven by immune complexes, chronic LN is driven by the development of CD4 and especially CD8 T cell clonal recognition of self-peptides, resulting in glomerular and tubular cell injury. In the first aim we will delineate the extent and detailed characteristics of the infiltrating intrarenal CD4 or CD8 T cells in new onset nephritis and define their role in renal injury. We will discriminate between clonally expanded CD4 or CD8 T cells that potentially drive renal injury and polyclonal T cells secondarily recruited by inflammation. We will correlate these findings with outcomes to identify features in the T cell infiltrate that predict poor response to therapy and progressive renal disease. In the second aim we will similarly determine the T cell characteristics of cases of chronic LN with worsening renal involvement requiring repeat biopsy, comparing current and prior biopsies for the features of intrarenal T cells that might predict progression.