Systemic lupus erythematosus (SLE) is characterized by IgG autoantibodies to ubiquitous intracellular components. Several inbred mouse strains also develop spontaneous lupus, with the same spectrum of autoantibodies. Certain of these specificities are pathogenic, including those directed against chromatin that induce immune-complex glomerulonephritis.

Autoantibodies in lupus arise as a consequence of autoantigen-specific CD4+ T cell help, although autoantibody-independent pathways of tissue injury may also occur. The defect(s) in SLE that lead to activation of autoreactive T cells, and the precise events that then promote B cell help for pathogenic autoantibody production, remain incompletely defined. We have shown that CD4+ T cells from lupus-prone mice appear to have defects that, compared to non-autoimmune T cells, render them hyper-responsive after T cell receptor (TCR)-CD3 complex contact with self-peptides, a defect(s) that contributes to tolerance loss with expansion of autoreactive T cells in secondary lymphoid organs. The TCR signaling abnormalities that contribute to the autoreactive phenotype are contributed to in part by the aberrant cytokine milieu found in active disease. Furthermore, autoreactive T cells that promote autoantibody production, versus those that appear to promote tissue injury directly, can be phenotypically distinguished.