Pathogenesis of anti-Sm/RNP autoantibodies in SLE patients

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Autoantibodies against the U1 snRNP (anti-Sm/RNP) are strongly associated with SLE. Interestingly, levels of anti-Sm/RNP are extraordinarily high and remain relatively constant over time. Our research is aimed at understanding how these autoantibodies are induced and why their levels remain elevated. Studies in pristane-induced lupus indicated that these autoantibodies were absent in mice lacking TLR7 or intermediates in the TLR7 signaling pathway (MyD88, IRF5, IRF7) and also in mice lacking the interferon α/β receptor. Ectopic lymphoid tissue (ELT) from mice with pristane-lupus was transplanted to naïve mice to examine development of anti-U1A (RNP) B cells. Plasma cells and/or plasmablasts (PC/PB) capable of transferring autoantibody production to the recipient mice were enriched in ELT whereas U1A-specific memory B cells were present in the spleen and bone marrow. A sensitive luciferase immunoprecipitation system (LIPS) assay was developed to show that U1A-specific memory cells and PC/PB circulate in peripheral blood of SLE patients. By treating with a TLR7 ligand, autoantibody secretion could be induced in memory B cells and enhanced in PB, but not PC or naive B cells. In SLE patients, U1A-specific cells were mainly PB, whereas total circulating IgG secreting cells were mainly memory B cells, suggesting that there is a chronic and specific activation, possibly TLR7 mediated, of U1A-specific B cells. Consistent with that interpretation, a similar picture was seen in pristane-lupus and total PB numbers were significantly reduced in spleens of TLR7 deficient vs. wild type mice. Together, the data suggest that anti-Sm/RNP antibody levels may be maintained by chronic TLR7-mediated activation of memory B cells.