Toll-like receptor 9-independent aggravation of glomerulonephritis in a novel model of SLE.

The generation of anti-DNA auto-antibodies is characteristic for the human autoimmune condition systemic lupus erythematosus (SLE) and its animal models. However, the contribution of the toll-like receptor (TLR) system of innate immunity receptors and, in particular, TLR9 to this B cell-mediated autoimmune process remains controversial. Here we report that in a novel murine model of SLE, based on hyper-reactive B cell activation mediated by mutant phospholipase Cg2, the genetic deficiency of TLR9 does not protect from spontaneous anti-DNA auto-antibody formation and glomerulonephritis. On the contrary, disease induction is aggravated and additional nucleolar antibody specificity develops in autoimmune TLR9-deficient mice. In vitro studies demonstrate that, in autoimmune-prone mice, dual signaling via the B cell receptor and non-CpG DNA results in synergistic B cell activation in a TLR9-independent manner. These results suggest that engagement of a TLR9-independent DNA activation pathway may promote autoimmunity, while TLR9 signaling can ameliorate SLE-like immune pathology in vivo.