Activation of toll-like receptor-9 induces progression of renal disease in MRL-Fas(lpr) mice.

How bacterial or viral infections trigger flares of autoimmunity is poorly understood. As toll-like receptor (TLR)-9 activation by exogenous or endogenous CpG-DNA may contribute to disease activity of systemic lupus erythematosus, we examined the effects of CpG-oligodeoxynucleotides (ODN) or DNA derived from Escherichia coli (E. coli) on the course of nephritis in MRL(lpr/lpr) mice. In kidneys of these mice, TLR9 localized to glomerular, tubulointerstitial, and perivascular infiltrates. After intraperitoneal injection labeled CpG-ODN localized to glomerular and interstitial macrophages and dendritic cells in nephritic kidneys of MRL(lpr/lpr) mice but not in healthy MRL controls. Furthermore, murine J774 macrophages and splenocytes from MRL(lpr/lpr) mice, but not tubular epithelial cells, renal fibroblasts, or mesangial cells, expressed TLR9 and up-regulated CCL5/RANTES mRNA upon stimulation with CpG-ODN in vitro. In vivo both E. coli DNA and CpG-ODN increased serum DNA autoantibodies of the IgG2a isotype in MRL(lpr/lpr) mice. This was associated with progression of mild to crescentic glomerulonephritis, interstitial fibrosis, and heavy proteinuria. CpG-ODN increased renal CCL2/MCP-1 and CCL5/RANTES expression associated with increased glomerular and interstitial leukocyte recruitment. In contrast control GpC-ODN had no effect. We conclude
that TLR9 activation triggers disease activity of systemic autoimmunity, for example, lupus nephritis, and that adaptive and innate immune mechanisms contribute to the CpG-DNA-induced progression of lupus nephritis.