

P067 Toll-like receptor (TLR)-7 inhibition protects against systemic lupus

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Small nuclear RNA and associated lupus autoantigens activate B cells and dendritic cells via Toll-like receptor (TLR)-7. We hypothesized that the inhibition of TLR7 may represent a potential therapeutic target in lupus. We injected MRL^{lpr/lpr} mice with either saline or synthetic oligodeoxynucleotides with immunoregulatory sequences (IRS) that specifically block signaling via TLR7 (IRS 661) or TLR7 plus TLR9 (IRS 954 which uses an active sequence from IRS 661 alongwith a TLR9 inhibitory sequence) from week 11 to 24 of age. IRS 661 and IRS 954 both significantly reduced the weights of spleen and lymph-nodes as well as serum levels of TNF as compared to saline-treated MRL^{lpr/lpr} mice. Only IRS 661 significantly reduced serum levels of IL-12p40, anti-dsDNA IgG2a, IgG2b, and anti-Smith IgG. This was associated with significant reduction of renal glomerular and interstitial macrophage infiltrates and the number of interstitial T cells. Both IRS could also significantly reduce the autoreactive T cells in spleen. Autoimmune lung injury was also attenuated with IRS 661 and IRS 954. These results indicate that the TLR7 antagonism, initiated after the onset of autoimmunity, can attenuate autoimmune kidney and lung injury in MRL^{lpr/lpr} mice. Concomitant blockade of TLR9 with IRS 954 neutralized the effect of TLR7 blockade on dsDNA IgG2a, dsDNA IgG2b, and Smith antigen autoantibodies but had neither additive nor opposing effects on autoimmune lung and kidney injury. We conclude that the TLR7 is a potential novel therapeutic target in SLE.