#12: Interferon-γ receptor (IFNγR) signaling is essential for the development of Toll like Receptor-7 mediated systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by the production of antibodies against self-antigens (autoantibodies). Spontaneously developed germinal center (Spt-GC) B cells and follicular helper T cells (Tfh) are involved in the generation of these autoantibodies. TLR7 plays a pivotal role in Spt-GC B cell and Tfh development. Autoimmune-prone B6.Sle1b mice carrying an extra copy of TLR7 in the Y-linked autoimmune accelerating (Yaa) locus (B6.Sle1b.Yaa mice) have significantly higher Spt-GC B cells and Tfh cells that strongly correlate with exacerbation of lupus disease. Here we report that IFNγR deficiency in B6.Sle1b mice that carry Yaa locus (B6.Sle1b.Yaa.IFNγR-/-) leads to significantly reduced Spt-GC and Tfh responses, resulting in decreased anti-nuclear antibody (ANA)-specific IgG antibody forming cells, serum autoantibody titers and renal pathology compared to control mice (B6.Sle1b.Yaa). These results are consistent with the data obtained from mice treated with TLR7 ligand. Further, in vitro results demonstrate that STAT1 dependent B cell-intrinsic IFNγR signaling is crucial for TLR7-induced IFNγ production by B cells. Together, these data describe the absolute requirement of IFNγR signaling in TLR7-induced autoimmunity. Future studies will involve deciphering the molecules that associate with TLR7:IFNγR signaling pathways and targeting them for therapeutic interventions to treat SLE.