1709 A THRESHOLD OF B CELL COSTIMULATORY SIGNALS IS REQUIRED FOR SPONTANEOUS GERMINAL CENTER FORMATION IN AUTOIMMUNITY

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Background Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by polyclonal B cell activation. Rather than being downstream targets of $CD4^+$ T cell activation, B cells can initiate breaks in T cell tolerance by orchestrating the formation of spontaneous germinal centers (GC). Engagement of CD28 on $CD4^+$ T cells with CD80/CD86 (B7.1/B7.2) on antigen presenting cells (APCs) is required for GC formation, but recent data suggest a limited role for B cell-intrinsic CD80/CD86 in this process (Watanabe, *J Exp Med*, 2017). However, whether B cell costimulatory signals are similarly redundant in immunization models vs. humoral autoimmunity is unclear, given differences in (auto) antigen abundance, affinity and adjuvant load.

Methods To determine whether B cell costimulatory signals modulate autoimmune GCs, we used a chimeric model of B cell-driven autoimmunity to contrast the impact of global CD28 and B cell-intrinsic CD80/CD86 deletion in humoral autoimmunity.

Results Whereas myeloid signals were critical for initial $CD4^+$ T cell priming and CXCR5 upregulation, complete T follicular helper (Tfh) cell maturation required B cell-intrinsic CD80/CD86 expression. Surprisingly, loss of CD28 and B cell-intrinsic CD80/CD86 similarly abrogated the formation of spontaneous autoimmune GCs. Interestingly, absent GCs differentially impacted serum autoantibody (autoAb) titers. In keeping with distinct extra-follicular (EF) and GC activation pathways driving lupus autoAb, lack of GCs correlated with loss of RNA-associated autoAb but preserved anti-dsDNA and connective tissue antigen reactivity. These data suggest a prominent role for GC-independent B cell activation via an EF pathway in the genesis of diverse pathogenic autoAb in SLE. Finally, based on CTLA-4 haploinsufficiency promoting spontaneous humoral autoimmunity in humans, we tested whether modulating B cell CD80/CD86 levels impacts spontaneous GCs. Strikingly, heterozygous B cell CD80/CD86 deletion recapitulated the phenotype of complete deletion, resulting in lack of Tfh expansion, GC formation and generation of RNA-associated autoAb.

Conclusion Our data show that during initial interactions between antigen-primed, autoreactive T and B cells, a threshold of B cell costimulatory signals is required for T cell activation and spontaneous GC formation. In addition, our findings support a model in which both EF and GC activation pathways provide distinct contributions to the lupus autoAb repertoire. Loss of B cell costimulatory signals uniquely dissociates these events, by abrogating the formation of autoimmune GCs without preventing T cell-dependent EF B cell activation.