Results B cells grouped into 4 clusters: GCs (DZ and LZ), plasma cells and memory B cells. DZ, LZ and PC clusters were represented in similar proportions in both conditions; whereas, MemB cells were more expanded in the immunized chimeras. Using the paired single cell BCR sequences and repertoire analysis, we observed clones with clear expansion both in the autoimmune and immunized chimeras. We observed levels of mutation in a similar range though DZ, LZ and MemB from autoimmune mice had a significantly higher number of nucleotide replacement mutations, and the reverse was observed in PCs. Nevertheless, PCs in both conditions reached similar maximum levels of mutation. Interestingly, autoimmune cells showed more isotype diversification in all compartments. Notably, we observed distinct gene expression for the autoreactive B cells such as CXCL10 by GC B cells and SLPI expression by autoreactive plasma cells. Strikingly, we identified DN2- and DN4-like memory B cells in both conditions.

Conclusions We find WT B cells break tolerance, expand in GC and develop into MemB and PCs in a seemingly unrestricted manner, similar to immune mice. Results should open the way to new approaches to control pathogenicity of rogue B cells in autoimmune disease.

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1703 ACTIVATED PI3Kδ SIGNALS COMPROMISE PLASMA CELL SURVIVAL VIA LIMITING AUTOPHAGY AND INCREASING ENDOPLASMIC RETICULUM STRESS

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Background Understanding key signals that control the differentiation, function, and survival of plasma cells (PCs) is critical for development of improved therapeutic approaches to attenuate pathogenic antibody responses in SLE. While phosphatidylinositide 3-kinase delta (PI3Kδ) plays an essential role in humoral immune responses, its role(s) in PC function remains poorly understood.

Methods We utilized a conditional mouse model of Activated PI3Kδ Syndrome (APDS), to interrogate the role of this key signaling program.

Results Mice expressing a gain-of-function mutation in *PIK3CD* in B cells, referred to as activated (a) PIK3CD, generated increased numbers of memory B cells, mounted enhanced secondary response, yet exhibited a rapid decay of antibody levels over time. Consistent with these findings, aPIK3CD expression markedly impaired plasma cell generation. Remarkably, PC specific aPIK3CD expression was sufficient to diminish humoral responses in vivo. Mechanistically, aPIK3CD disrupted endoplasmic reticulum proteostasis and autophagy, leading to increased PC death. Notably, this defect was driven primarily by elevated mTORC1 signaling and modulated by treatment with PI3Kδ-specific inhibitors.

Conclusions Taken together, these data demonstrate an unexpected requirement to down-regulate PI3Kδ activity to balance autophagy and the unfolded protein response, events essential to modulate ER stress and ensure PC survival. Thus, enhancing PI3Kδ activity may provide a novel means to trigger early PC death and dampen autoantibody responses.

1704 IDENTIFYING CLUSTERS OF LONGITUDINAL AUTOANTIBODY PROFILES ASSOCIATED WITH SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE OUTCOMES

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Background Prior studies of SLE clusters based on autoantibodies have utilized cross-sectional data from single centers. We applied clustering techniques to longitudinal and comprehensive autoantibody data from a large multinational, multiethnic inception cohort of well characterized SLE patients to identify clusters associated with disease outcomes.