Score B was highly correlated with neutrophil (R=0.554, p<0.001), myeloid (R=0.725, p<0.001), plasmablast (R=0.323, p<0.001), inflammation (R=0.599, p<0.001) and erythropoiesis (R=0.0.376, p<0.001) scores. In NEA, IFN Score B correlated with myeloid (R=0.724, p<0.001) and inflammation (R=0.463, p<0.001) but only weakly with erythropoiesis (R=0.316, p=0.003) and no correlation with neutrophils (R=0.192, p=0.078) or plasmablasts (R=0.023, p=0.832).

Since in NEA these weaker correlations presented a more heterogeneous transcriptomic picture, we further analysed this group using hierarchical clustering of individual transcript expression. This revealed 3 clusters; cluster 1 (low IFN, low plasmablast); cluster 2 (globally high); and cluster 3 (low neutrophil and myeloid, high plasmablast). In the rituximab study these clusters differed in clinical response, which was not explained by other clinical features. Cluster 1 were older with higher glucocorticoid dose and low rituximab response rate. Clusters 2 and 3 were similar in clinical features but rituximab response was significantly higher for cluster 2 (table 1). IFN Score B was the strongest predictor of rituximab response (OR=3.021/unit (95% CI 1.4, 6.6, p=0.006).

Conclusions NEA SLE patients have more heterogeneous transcriptomic profiles, which predict clinical response to B cell targeted therapy independent of clinical features.

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1700 – B cells and autoantibodies

1701 CURLI AMYLOID/DNA COMPLEXES FROM BACTERIAL BIOFILMS BREAK TOLERANCE IN MURINE LUPUS USING T CELL-INDEPENDENT AND T CELL-DEPENDENT MODALITIES

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Background Epidemiological studies suggest that bacterial infections promote SLE disease in predisposed individuals, but the underlying mechanisms remain unknown. We have found that a subset of SLE patients has asymptomatic bacteriuria associated with markers of inflammation and flares, suggesting that chronic exposures to microbial products may trigger flares in lupus. Our labs have shown that the bacterial amyloid curli, expressed in multicellular communities (*biofilms)* by many bacteria including *E. coli*, plays a major role in triggering lupus autoimmunity during infection. Curli amyloid/DNA complexes strongly activate dendritic cells and macrophages. When given systemically, curli/DNA complexes and infections with curli-expressing *E. coli* trigger production of anti-dsDNA and anti-chromatin autoantibodies in lupus prone mice and in wild type mice. This stimulation is diminished in TLR2 or TLR9 deficient mice, suggesting a TLR-mediated activation of innate immunity. *We have now focused on the effects of curli/DNA complexes on B cells.*

Methods Young wild type C57BL/6 mice, lupus prone Sle1,2,3 mice, 3H9 mice and CD40L-/- mice were injected with curli/DNA complexes from biofilms or infected with amyloid for short and long-term studies. Splenic B cells were stained by flow cytometry *ex vivo*. For *in vitro* experiments, B cells were sorted by positive selection with CD45R (B220), supplemented with anti-CD43Ab-Biotin. B cell purity (>98%), proliferation, activation markers and signaling molecules were measured by Flow cytometry, Western Blot and qRT-PCR. Autoantibodies were measured by ELISA.

Results *In vitro,* curli/DNA complexes could induce class switch to IgG, in the absence of T cell help, in wildtype B cells, and even more in Sle1,2,3 and 3H9 B cells, which recognize DNA, suggesting an antigen-specific activation of B cells by curli/DNA. Curli/DNA induced non-canonical NFκB activation and transcription of *aicda*, the master regulator of class switch recombination. *In vivo*, exposure to curli/DNA broke tolerance to DNA in 3H9 mice. Moreover, it induced autoantibodies in CD40L-/- mice, though at lower levels than in WT mice.

Conclusions The induction of non-canonical NFκB activation, *aicda*, and class switch recombination, in the absence of T cells help *in vitro*, suggests that the fibrillar structure of curli/DNA complexes can cross-link BCRs, some recognizing DNA, and can also trigger a second pathway which substitutes T cell help to induce isotype switching. The lower levels of autoantibodies elicited by curli/DNA in mice deficient of T cell help suggests that curli/DNA complexes break tolerance to DNA with T cell-independent and T cell-dependent modalities.

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1702 COMPARISON OF THE B CELL RESPONSE TO SELF- VERSUS FOREIGN- ANTIGEN IN MICE REVEALED BY SINGLE CELL TRANSCRIPTOMICS

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Background In an autoimmune environment, rogue self-reactive B cells escape tolerance, differentiate to a variety of self-antigens (epitope spreading) and are selected into germinal centers (GC) in a T cell dependent manner. We investigated this question using a mixed bone marrow chimera model that combines transgenic B cells from lupus-like mice (564 Igi) with those from wild type (WT) B6 mice. In this model, WT B cells, specific for self-antigens distinct from those targeted by the Tg B cells, expand and dominate in GC.

Methods Autoimmune and WT chimeric mice were prepared using the tamoxifen-inducible *Aicda*-CreERT2-EYFP mice to track WT cells. WT chimeras were immunized with NP-CGG. At peak GC stage, EYFP+ splenic B cells from both cohorts, were sorted and processed for gene expression using RNAseq.

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.