Conclusions Transcriptomic analysis of Yaa mice before onset of SLE like clinical disease and DKO mice that develop accelerated disease uncovered differences in immune profiles, which point to a role for CD8 T cells in protection from autoimmunity in this model. In the absence of CD8 T cells, DKO mice exhibited an increase in gene signatures of M2-like Mϕs representing a unique functional subset correlated with pathologic pathway signatures. This analysis provides evidence for a protective, regulatory function of CD8 T cells against autoimmune pathology with implications for understanding their role in human SLE.

303 A STEPWISE TRANSCRIPTOMIC ANALYSIS USING GENE MODULES AND IMMUNE CELL SIGNATURES TO STRATIFY SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS AND IDENTIFY POTENTIAL TREATMENT TARGETS

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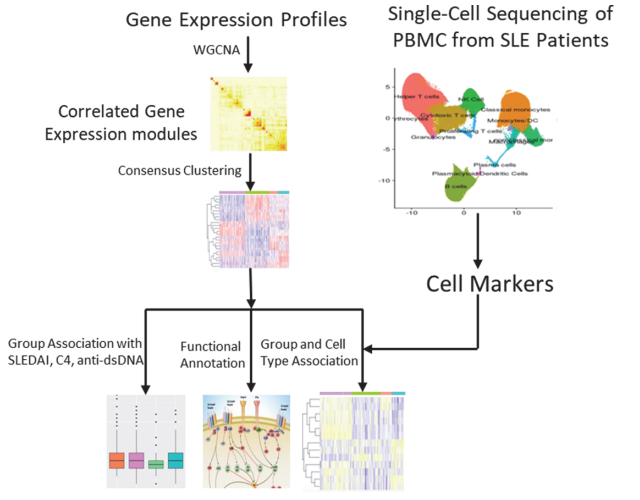
Background A major challenge in drug development for systemic lupus erythematosus (SLE) is the heterogeneous clinical presentation of SLE patients, which necessitates personalized treatment strategies. We aimed to identify clusters of SLE patients based on molecular transcriptomic signatures associated with clinical phenotypes to help address this challenge.

Methods To address this question, we developed an integrated pipeline that defines subsets of patients based on cell type-specific gene expression in blood. Gene expression profiles from two large independent SLE trials, ILLUMINATE-1 and ILLUMINATE-2, were analyzed to identify SLE patient clusters. We first performed a gene expression correlation network analysis to identify co-expressed gene modules. Then, unsupervised consensus clustering was performed on the modules to identify molecular clusters. We correlated cluster membership with clinical phenotypes and immune cell signatures from high resolution scRNA-seq data. We also determined whether immune cell signatures were stable over time.

Results We identified four molecular clusters of SLE patients. Cluster 1 exhibited high signature scores for T cells, B cells, plasma cells, macrophages, and monocytes. Conversely, Cluster 2 exhibited low signature scores for the aforementioned cells.



Abstract 303 Figure 1 Overview of analysis

Cluster 3 had high T and B cell signature scores. Cluster 4 had a high signature score for neutrophils. Clinically, Cluster 3 subjects exhibited the lowest disease severity compared to other clusters. We validated these four molecular clusters in three additional independent SLE cohorts. We identified four molecular clusters of SLE patients that were consistent across five independent genomics datasets totaling 2,100 patients. For individual patients, cluster membership was not necessarily stable over time.

Conclusions We have established methods to address SLE heterogeneity in a data-driven, unbiased manner using transcriptomic data. We have uncovered reproducible patterns in stratifying SLE patients using this method and connected SLE patient subsets to cellular alterations in the blood. Our findings have important implications for personalized treatment of SLE and provide guidance for clinical trials in this highly heterogeneous disease.

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304 METABOLIC DYSREGULATION CHARACTERIZES THE TISSUE RESPONSE TO IMMUNE INJURY IN SYSTEMIC LUPUS ERYTHEMATOSUS AND INFLAMMATORY SKIN DISEASES

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Background Autoimmune and inflammatory diseases such as systemic lupus erythematous (SLE) affect tissues throughout the body. Alterations to inflammatory cell metabolism are often cited as a contributing factor in diseases such as lupus[1], however, changes to metabolism in diseased tissues are poorly understood. Therefore, we investigated changes to cellular metabolic processes in the tissues affected by SLE as well as samples from other inflammatory skin diseases.

Methods Gene expression data collected from patients with lupus nephritis (LN) glomerulus (GL), LN tubulointerstitium (TI), discoid lupus erythematosus (DLE), psoriasis (PSO), atopic dermatitis (AD), and systemic sclerosis (SSc), or murine LN was obtained from Gene Expression Omnibus. Enrichment of metabolic and cellular signature in individual samples was analyzed using Gene Set Variation Analysis (GSVA). Stepwise regression and classification and regression tree (CART) analyses were performed to determine correlations between each metabolic signature and all cellular signatures in each diseased tissue.

Results Comprehensive gene expression analysis of samples derived from glomerular and tubulointerstitial LN kidneys, and DLE, PSO, AD, and SSc skin revealed concurrent changes to genes reflective of cellular metabolic processes and cellular transcripts. In lupus-affected tissues there were shared decreases to metabolic gene signatures[2], whereas in other inflammatory skin diseases some metabolic transcripts were increased. In glomerular LN, decreased glycolysis gene expression was correlated with increased endothelial cell transcripts[2].

Conversely, regression analyses demonstrated that decreased tricarboxylic acid (TCA) cycle and lipid metabolism signatures reflected decreased kidney cell transcripts, which was confirmed by the negative relationship between the TCA cycle signature and expression of the tubule damage marker, *HAVCR1*.[1] Indeed, similar alterations to metabolism were observed in some less severe LN patients, in which inflammatory cell transcripts were not yet increased.[2] Although interferon can induce metabolic changes at the transcriptional level,[3] examination of metabolic gene expression in the murine interferon alpha-accelerated LN model revealed that metabolic changes were not driven by acute exposure to type I interferon.[2] Moreover, evaluation of metabolic changes in murine LN following various treatments demonstrated that metabolic gene expression could be restored with immunosuppressive therapy.[2] Regression analyses in DLE and PSO demonstrated that there was a positive correlation between the glycolysis signature and the keratinocyte signature, whereas in PSO, AD, and SSc the glycolysis signature was positively correlated with the monocyte/myeloid cell signature.

Conclusion These results indicate that altered metabolic dysfunction is a common change in lupus- and inflammatory disease-affected tissues and appears to reflect immunologic damage.

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401 TRIM21 AS A REGULATOR OF UVB-DRIVEN IFN RESPONSES IN LUPUS

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Background Patients with systemic lupus erythematosus (SLE) experience photosensitivity, with exposure to ultraviolet light (UV) driving lupus flares, triggering symptoms like joint pain and fatigue, in addition to causing cutaneous lesions. Our previous work has shown that TRIM21, an autoantigen in SLE, functions as a negative regulator on the pathways driving IFN expression. *Trim21*$^{-/-}$ mice develop systemic autoimmunity due to an inability to regulate type I IFNs. These mice also spontaneously develop skin lesions, leading us to hypothesize that *Trim21*$^{-/-}$ mice may have enhanced sensitivity to UV-induced skin inflammation.

Methods Wild type (WT, C57BL/6) and TRIM21 KO mice were irradiated with UVB (100 mJ/cm^2) consecutively for 1 and 3 weeks, and blood, spleen and kidney analyzed by qPCR, histology, and flow cytometry. Bone marrow derived macrophages (BMDMs) and mouse skin fibroblasts (MDF) were analyzed by qPCR and western blotting. Peripheral blood samples from SLE patients were analyzed by qPCR for interferon stimulated genes (ISG) RSAD2, IFI44, IFI44L, IFI27 and used to calculate IFN scores.

Results Macroscopically, both WT and *Trim21*$^{-/-}$ mice developed similar levels of erythema, edema and induction of inflammatory cytokines in response to UVB exposure. However, compared to WT mice, expression of IFNβ and ISGs were elevated in the skin of *Trim21*$^{-/-}$ mice following UVB. Most notably after UVB exposure, we observed splenomegaly and enhanced expression of ISGs in the blood and spleen of *Trim21*$^{-/-}$ mice. *Trim21*$^{-/-}$ mice also demonstrated enhanced total IgG levels in serum, significantly increased deposition of IgG in the skin and increased ISG expression in the kidneys, all suggesting that loss of TRIM21 in mice results in enhanced IFN-driven responses systemically. Enhanced basal, UVB- and cGAMP-dependent IFNβ expression was observed in *Trim21*$^{-/-}$ BMDMs and MDFs which was restored in BMDMs from *Trim21*$^{-/-}$/Sting$^{-/-}$, suggesting the cGAS-STING pathway was inappropriately regulated in these absence of TRIM21. As TRIM21 is an E3 ligase and known to regulate protein stability, we assessed levels of cGAS, DDX41 (a DNA sensor and regulator of STING signaling) and STING itself. Mechanistically, we found only DDX41 protein levels were stabilized in *Trim21*$^{-/-}$ MDFs or BMDMs, respectively, suggesting it to be a target on this pathway.

Conclusions Taken together our results indicate that TRIM21 protects against IFN induction both at a local and systemic level in response to DNA sensing. Understanding the role of TRIM21 in preventing systemic disease will have important understandings of its role in driving increased disease activity and flare in SLE.

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402 GENETIC DISSECTION OF TLR9 REVEALS COMPLEX REGULATORY AND CRYPTIC PRO-INFLAMMATORY ROLES

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Background Toll like receptors (TLR) 7 and 9, endosomal sensors for ssRNA and dsDNA, are key mediators of lupus autoreactivity. Although considered homologous, they have opposing effects on lupus severity: TLR7 exacerbates disease while TLR9 protects. One theory is that TLR9 induces protection by competing with TLR7 for endosomal trafficking, thus restraining TLR7 expression and signaling. However, since both TLR9 and TLR7 ligands are available in lupus, and both TLRs are supposed to signal via MyD88, this theory doesn't explain the differential effects of the two TLRs on disease. To reconcile this, we hypothesized that TLR9 could induce counter-regulatory signaling and/or regulate TLR7 via a ligand- or signaling-independent mechanism.

Methods and Results To differentiate between these hypotheses, we created mutants of TLR9 that prevent ligand binding (TLR9^{K51E}) or MyD88 signaling (TLR9^{P915H}) in the TLR9 locus of MRL/lpr mice. Mutant mice were assessed by for dermatitis, nephritis, immune dysregulation, and auto-antibodies.

TLR9$^{K51E/K51E}$ mice had increased survival and decreased kidney pathology compared to TLR9$^{-/-}$ mice, indicating that