hypothesized that lymphatic dysfunction could contribute to photosensitivity in SLE.

Methods We examined MRL/lpr lupus prone mice for lymphatic function by injecting Evan's Blue into the ear and measuring retention. Ear thickness and flow cytometric analysis were used to assess photosensitivity. Lymphatic drainage was manipulated using two approaches. First, we used manual lymphatic drainage (MLD) in the MRL/lpr mice. MLD improved lymphatic drainage and reduced photosensitivity. Second, we induced a lupus phenotype in a novel mouse model with enhanced lymphatic function (inducible lymphatic endothelial cell specific PTEN KO) using topical imiquimod.

Results MRL/lpr mice had greater Evan's blue retention compared to controls suggesting lupus prone mice have impaired lymphatic drainage. MLD improved lymphatic drainage and reduced photosensitivity. PTEN KO mice had reduced photosensitivity and reduced systemic immune activation.

Conclusions This data suggests that lymphatic dysfunction contributes to photosensitivity in murine lupus and improving lymphatic flow, even with simple MLD, can ameliorate photosensitivity. Future studies will determine the etiology of lymphatic dysfunction in murine lupus and the mechanism of lessened photosensitivity with improved lymphatic drainage. If similar immune circuitry defects are present in patients with SLE, altering lymphatics could be a novel target for new therapeutics.

Acknowledgments Lupus Research Alliance

300 – Transcriptomics

301

DIFFERENTIALLY EXPRESSED TRANSCRIPTS ASSOCIATED WITH LUPUS RISK LOCI IDENTIFY PATHOGENIC DISEASE PATHWAYS

Mikhail Olfieriev*, Dina Greenman, Jeffrey Zhang-Sun, David Fernandez, Kyriakos A Kirou, Mary K Crow. *Hospital for Special Surgery, New York, USA*

10.1136/lupus-2021-lupus21century.10

Background Genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) that tag genomic sites with a high statistical association with a diagnosis of SLE. As most risk SNPs mark regulatory rather than coding regions of the genome, the functional impact of the risk loci on molecular mechanisms and pathways has not been clearly defined. In addition, how disease-associated loci differentially impact pathogenic mechanisms in females and males with SLE has not been explored. We analyzed RNA sequencing data relevant to previously identified risk loci to understand the molecular pathways impacted by genetic variation.

Methods Forty subjects (10 SLE females; 10 SLE males; 10 healthy females; 10 healthy males) were identified for study, with careful matching of SLE and healthy donor subjects for age and ethnicity. Next generation RNA sequencing was performed and unsupervised clustering of transcript expression displayed for genes previously identified in GWAS as near SNPs associated with a diagnosis of SLE. Identified pathways were also investigated using an expanded RNAseq dataset, including 30 patients with lupus nephritis, 29 patients with non-renal SLE and 3 healthy donors.

Results Four major clusters of gene transcripts were identified, along with multiple subclusters. The most striking transcript subcluster preferentially expressed in lupus males identified

mechanisms involved in nucleic acid sensing and type I interferon production (IRF7, IFIH1, IKBKE, TLR7, JAK2, CXorf21/TASL, and SLC15A4). Another subcluster that favored males included T and B cell transcripts associated with generation of autoantibody producing B cells (ITGAX, IRF5, SH2B3, TET3, NOTCH4, ICAM4). The cluster with transcripts showing decreased expression in SLE included DEF6 and PHRF1, potentially contributing to impaired transcriptional regulation of lymphocyte function in patients. Genes located in the MHC (ATF6B, NOTCH4, MICB, TNXB, ITPR3) or an X chromosome risk locus (IRAK1, TMEM187, MECP2, NAA10, HCFC1) were distributed among different transcript subclusters, suggesting the broad impact of risk haplotypes at those loci on regulation of multiple disease-associated pathways. Of interest is the observation that PHRF1 and IRF7, adjacent genes identified by a risk SNP (rs4963128), distributed to distinct clusters, with PHRF1 decreased and IRF7 increased in SLE patients. The expanded SLE dataset was also analyzed to further characterize lupus risk-associated functional transcript clusters.

Conclusion Genes located near lupus risk SNPs are differentially expressed in patients with SLE and cluster based on functional relationships. Transcripts differentially expressed in male patients suggest important involvement of nucleic acid sensing pathways in their disease.

302

TRANSCRIPTOMIC ANALYSIS REVEALS A CRITICAL REGULATORY ROLE FOR CD8 T CELLS IN A MOUSE MODEL OF SYSTEMIC LUPUS ERYTHEMATOSUS

¹Andrea R Daamen*, ²Chih-Hao Chang, ²Derry C Roopenian, ¹Amrie C Grammer, ¹Peter E Lipsky. ¹AMPEL BioSolutions and the RILITE Research Institute, Charlottesville, VA, USA; ²The Jackson Laboratory, Bar Harbor, ME, USA

10.1136/lupus-2021-lupus21century.11

Background Pre-clinical mouse models are invaluable tools to investigate the mechanisms driving systemic lupus erythematosus (SLE) and identify therapeutic targets to treat human disease. The BXSB.Yaa (Yaa) mouse spontaneously develops SLE-like disease, that is accelerated by the loss of CD8 T cells in BXSB.Yaa.CD8a^{-/-}IL15^{-/-} (DKO) mice, suggesting that CD8 T cells have a protective role against autoimmunity in this model. The role of CD8 T cells in human SLE remains unclear as studies have found conflicting associations with increased disease severity or with a loss of regulatory activity. Therefore, we carried out transcriptome analysis of Yaa and DKO mice to clarify the role of CD8 T cells in SLE.

Methods Six week old 'pre-disease' mice were examined to determine the impact of CD8 T cells before the development of inflammatory disease. Gene expression profiles from spleens of 6 week old BXSB.B6 (CTL), Yaa, and DKO mice were obtained by RNA-seq. Log₂ gene expression values were normalized between datasets using housekeeping genes. Differential enrichment of immune cell and pathway gene modules curated for analysis of lupus mouse datasets was determined by Gene Set Variation Analysis (GSVA). Immune cell population GSVA scores were then correlated with functional pathways by linear regression.

Results Spleens from 6 week BXSB.Yaa mice showed evidence of extensive immune activation. GSVA revealed shared enrichment of SLE-associated lymphocyte populations including germinal center (GC) B cells and T follicular helper (Tfh) cells in