increased levels of antinuclear antibodies versus wild-type controls. Our data also suggest that the MSH6 GV identified in lupus-prone individuals results in the accumulation of mutations at A in the WA hotspot (W is A or T; adenine or thymine, respectively; A is adenine) motif. Therefore, these mutations are likely to be the result of processing of the activation induced cytidine deaminase (AID)-generated U:G mispair by the MSH2/6 complex followed by error-prone DNA synthesis by DNA polymerase eta.

Conclusions Importantly, these types of mutations likely result in an overall increase in positively charged amino acids in the autoantibodies that are produced, a trait that is commonly found in anti-DNA antibodies. In summary, our results suggest that the MSH6 GV has strong potential to be associated with the development of lupus.

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The MSH6GV mice develop antinuclear antibodies at 6 months of age. +/+are WT; Mut/+are heterozygotes and Mut/Mut are homozygotes.

204 THE IMMUNE CELL LANDSCAPE IN KIDNEYS OF LUPUS NEPHRITIS PATIENTS

[1]Celine C Berthier*, [2]Arnon Arazi, [3]Deepak Rao, [4]Anne Davidson, [5]Edward Browne, [2]Thomas Eisenhaure, [6]Nir Hacohen, [7]David J Lieb, [4]Betty Diamond, [8]Matthias Kretzler. *[1]University of Michigan; [2]Broad Institute; [3]Brigham and Women's Hospital/Harvard Medical School; [4]Feinstein Institute for Medical Research; [5]UNC-Chapel Hill; [6]Harvard Medical School; [7]Broad Institute of MIT and Harvard; [8]University of Michigan Medical School*

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Background Lupus nephritis is a potentially fatal autoimmune disease, whose current treatment is ineffective and often toxic. In 2014, the National Institute of Health (NIH), industry and non-profit organizations joined their efforts with the AMP project, whose goal is to identify new diagnostic and therapeutic targets through a better understanding of the mechanisms by which individual cell types contribute to autoimmune tissue damage.

Methods To gain insights into disease mechanisms, we analyzed kidney samples from lupus nephritis patients and healthy controls using single-cell RNA-seq. Renal biopsies from 24 LN patients and 10 pre-transplant living donors (LD) were acquired across a distributed research network using a single, uniform pipeline developed by the AMP network. In brief, biopsies were cryopreserved and shipped to a centralized processing site for tissue dissociation. A total of 3541 leukocytes and 1621 epithelial cells were sorted from LN kidney samples. 438 leukocytes and 572 epithelial cells were sorted from LD biopsies. The transcriptome of those LN single tissue-infiltrating cells were assessed using single cell RNA-seq.

Results Our analysis revealed 21 subsets of leukocytes active in disease, including multiple populations of myeloid, T, NK and B cells, demonstrating both pro-inflammatory and resolving responses. We found evidence of local activation of B cells correlated with an age-associated B cell signature, and of progressive stages of monocyte differentiation within the kidney. A clear interferon response was observed in most cells. Two chemokine receptors, C×CR4 and C×3CR1, were broadly expressed, pointing to potential therapeutic targets. Gene expression of immune cells in urine and kidney was highly correlated, suggesting urine may be a surrogate for kidney biopsies.

Conclusions Our results provide a first comprehensive view of the complex network of leukocytes active in lupus nephritis kidneys. Results from this Phase 1 study identified LN active cells and pathways that can be used to guide the development of novel therapies. Analyses at a bigger scale (n=200 LN) in Phase 2 will allow to correlate patterns and signatures of infiltrating cells with those of intrinsic renal cells, particularly the epithelial cells that make up 90% of renal cells and that are prone to hypoxic damage and cellular stress. It will accelerate the discovery of new therapeutic targets and identification of biomarkers to guide therapeutic decisions in LN and integrate the treatment effect.

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205 SINGLE CELL RNA EXPRESSION IN LUPUS NEPHRITIS COMPARING AFRICAN-AMERICAN AND CAUCASIAN PATIENTS IDENTIFIES DIFFERENTIAL EXPRESSION OF TYPE I INTERFERON PATHWAY

[1]Andrea Fava*, [2]Yuji Zhang, [3]Nir Hacohen, [4]Arnon Arazi, [5]Celine C Berthier, [6]Deepak Rao, [7]Michael Brenner [8]David Wofsy, [9]Anne Davidson, [10]Matthias Kretzler, [11]David Hildeman, [12]E Steve Woodle, [9]Betty Diamond, [13]Michelle Petri. *[1]Johns Hopkins University; [2]University of Maryland; [3]Harvard Medical School; [4]Broad Institute; [5]University of Michigan; [6]Brigham and Women's Hospital/Harvard Medical School; [7]Brigham And Women's Hospital; [8]Russell/Engleman Rheumatology Research Center, University of California, San Francisco, CA, USA; [9]Feinstein Institute for Medical Research; [10]University of Michigan Medical School; [11]University of Cincinnati Department of Pediatrics; [12]University of Cincinnati; [13]Johns Hopkins University School of Medicine*

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Background African-American ethnicity is associated with a 3-fold higher risk of developing systemic lupus erythematosus (SLE). In addition, there is an increased risk of lupus nephritis (2-fold), high-risk histological features, and resistance to treatment. This may account for the increased mortality rate compared to Caucasian patients, especially in women. In Phase One of the Accelerating Medicines Partnership (AMP) study, we used single-cell RNA sequencing on kidney biopsies from patients with active lupus nephritis to identify pathways that were differentially expressed in African-American patients.

Methods Single cell RNA sequencing was performed on renal biopsies obtained for clinical purpose for active nephritis using CEL-Seq2. Cell clusters with similar expression profile were identified using t-distributed stochastic neighbor embedding (t-SNE). First, the relative abundance of a cluster in AAs compared to Caucasian was determined using a logistic mixed model. Second, the differential expression profile was determined for each cell cluster and we applied Ingenuity Pathway Analysis (IPA) (QIAGEN Bioinformatics) to identify pathways of interest.

Results Samples from 13 AA and 7 Caucasian patients were obtained. Of the 3097 sequenced cell libraries, we used 2354 which passed our quality filter for a total of 30 155 unique molecular identifiers. We identified 16 cell clusters including CD4, CD8, B and plasma cells, NK, myeloid cells, and tubular cells. We identified 2 cell clusters unique to African-American patients, a T and a B cell population with high expression of interferon inducible genes. We also identified that same cell populations may have differential gene expression profiles