Transcriptomics

2103 MOLECULAR CHARACTERIZATION OF LUPUS NEPHRITIS KIDNEYS AND BLOOD

[1]Kathryn M Kingsmore*, [1]Sneha Shrotri, [1]Prathyusha Bachali, Nan Shen, [1]Amrie Grammer, [1]Peter Lipsky. [1]*AMPEL BioSolutions, LLC and RILITE Research Institute, Charlottesville, VA, USA*; [2]*Shanghai JiaoTong University School of Medicine, Shanghai, China (People's Republic)*

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Background/Purpose Molecular kidney or blood-based biomarkers of lupus nephritis (LN) would provide an advance over standard renal biopsy analysis. Therefore, we analyzed bulk RNA from renal biopsies and paired blood to determine molecular biomarkers of LN, associated with gene expression-determined lupus nephritis endotypes.

Methods Using Gene Set Variation Analysis (GSVA), we analyzed the enrichment of informative modules of co-expressed genes in the biopsies of 76 kidneys derived from patients with LN and matched blood for 71 patients. Gene modules identifying immune/inflammatory cells, resident kidney cells, and metabolic and inflammatory processes were employed where appropriate.

Results GSVA analysis of LN gene expression elucidated four endotypes of LN (figure 1**)**, which were characterized by minimal disease abnormalities (coral); inflammatory disease with minimal kidney cell damage and minimal metabolic dysfunction (yellow); inflammatory disease with marked kidney cell and marked metabolic dysfunction (purple), and little inflammation with markedly decreased kidney cell and markedly decreased metabolic function (black). GSVA analysis of the same LN-derived clusters in the blood of paired patients revealed the two clusters with marked kidney damage (purple and black) had significant enrichment of the LDG signature (figure 2a). The purple cluster was consistently characterized by decreased blood expression of T cell and T cell receptor chain signatures (figure 2b-f), whereas the black cluster exhibited decreased blood expression of the dendritic cell signature (figure 2g). Although production of erythropoietin is known to decrease with chronic kidney disease,[1] expression of *EPO* was unchanged in the blood across subsets (figure 2h).

Conclusions Transcriptomic analyses support the existence of LN endotypes that progress from acute inflammatory to chronic kidney disease with little inflammation and marked kidney damage. Analysis of the blood of this small cohort of patients with LN suggest that the two most severe molecular endotypes of LN have different profiles than patients with minimal disease. Although the LDG signature can relate to glucocorticoid treatment[2] and T cell lymphopenia is a marker of severe lupus in general,[3] the combination suggests greater suspicion of progression to LN.

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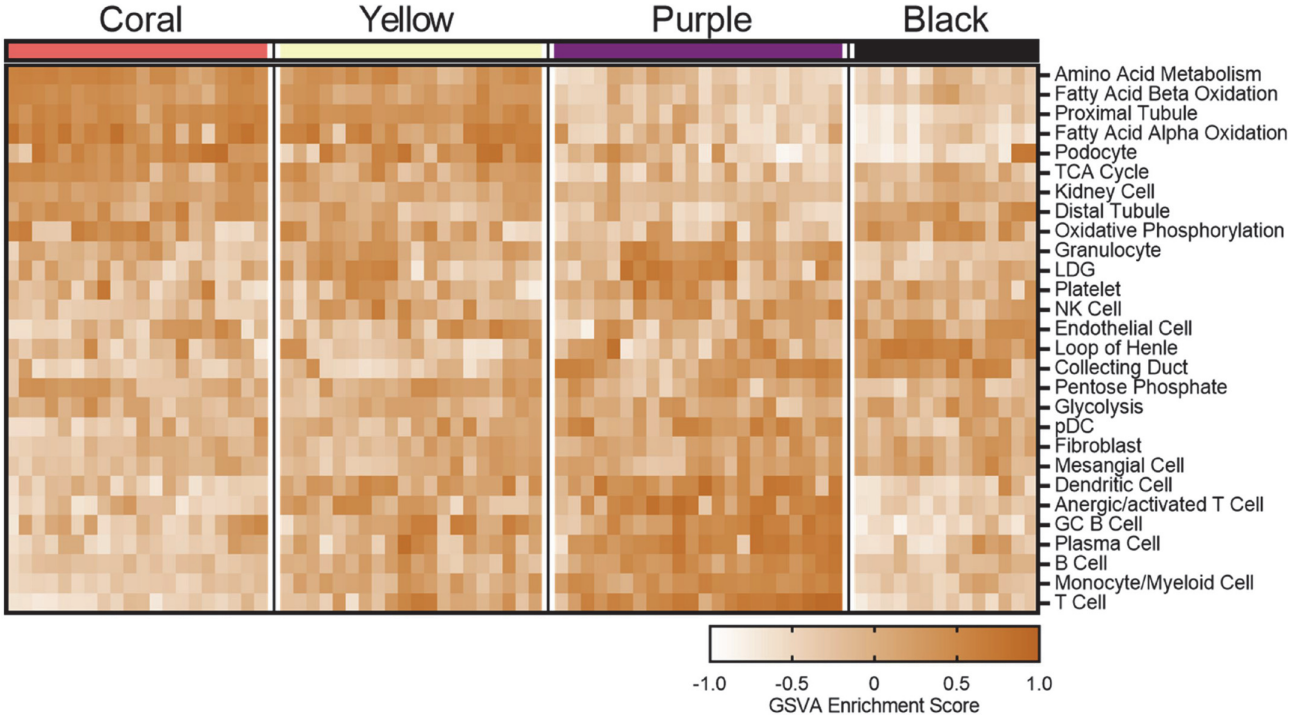
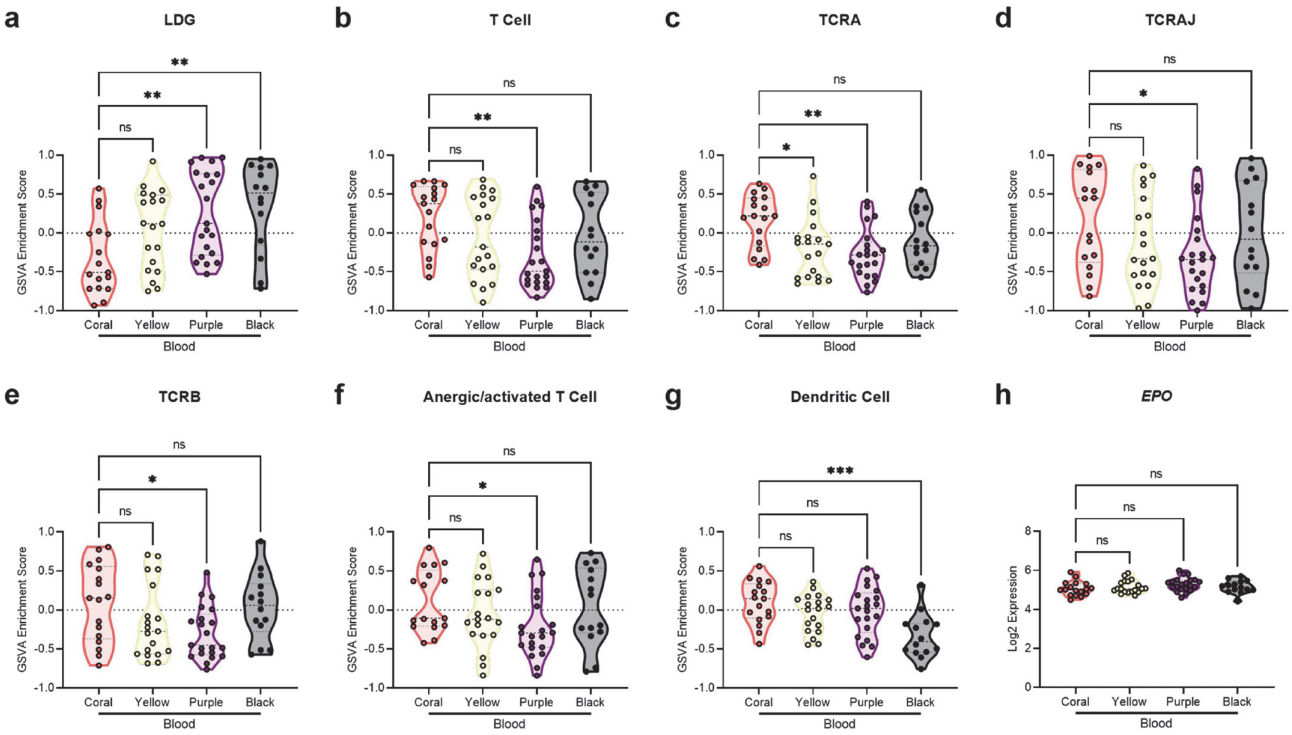


Abstract 2103 Figure 1 Clustering of GSVA enrichment scores in lupus kidneys reveals four distinct endotypes of patients with LN. (a) Row and column hierarchical clustering of 76 patients with LN into four groups based upon gene expression of cellular and pathway gene modules. (b) Reordered clustering of LN patients in order of molecular disease severity from least to greatest. The columns represent individual patients that are grouped into four clusters (black, coral, yellow, and purple). The rows represent gene modules indicative of immune/inflammatory cells, non-hematopoietic cells, and cellular metabolism.



Abstract 2103 Figure 2 Analysis of paired blood of patients with LN demonstrates cluster-specific enrichment of inflammatory signatures. GSVA of (a) LDG, (b) T cell, (c) TCRA, (d) TCRAJ, (e) TCRB, (f) anergic/activated T cell, and (g) dendritic cell signatures in the blood of patients with LN. (h) Log2 expression of *EPO* in the blood of patients with LN. X-axis clusters denote the cluster to which the sample belongs based upon analysis of paired kidney gene expression. Significant differences in enrichment of gene signatures or log2 expression between each cluster and Coral was assessed by Brown-Forsythe and Welch ANOVA with Dunnett's T3 multiple comparisons. *, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.001$.

Transcriptomics

2104 LUPUS AUTOANTIBODIES ASSOCIATED WITH CELL CYCLE GENE EXPRESSION IN PERIPHERAL BLOOD OF SLE PATIENTS

[1,2]Mikhail Olferiev, [1]Dina Greenman, [1]Jeffrey Zhang-Sun, [1]David Fernandez, [1]Kyriakos A Kirou, [1]Mary K Crow. *[1]Mary Kirkland Center for Lupus Research, Hospital for Special Surgery; [2]Weill Cornell Medical College, NY, NY, 10021, USA*

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Background Gene-expression studies of SLE peripheral blood indicate the expression of relevant categories of functionally related transcripts. The most pronounced changes have been reported among interferon-inducible genes, genes specific to neutrophil granules and genes involved in cell cycle. Although autoantibodies are considered to be the main pathogenic mediators in SLE, there is little knowledge regarding how their titer is associated with peripheral blood gene expression. To gain insight into mechanisms of autoimmunity, we simultaneously investigated the presence of classical SLE autoantibodies (ANA, dsDNA, Sm/RNP, Ro, La) and gene expression in a cohort of 80 SLE patients followed from 1 to 14 visits over a period of 3(0- 12) years.

Methods All blood samples were collected at HSS and processed within 1 hour using the same protocol. Gene expression was studied either by RNA-seq (62 samples) or DNA microarray (189 samples) and then merged into a single matrix using the MatchMixeR software. The obtained matrix was used to generate functionally annotated groups of co-expressed genes, also known as gene-modules, using the WGCNA algorithm. The comparison of autoantibody titer with gene expression was analyzed by linear mixed model, using either a per module or per gene approach. Several clustering techniques were used to aggregate common genes and investigate the association with clinical and laboratory parameters.

Results All studied patients fulfilled ACR criteria for SLE and received standard care at HSS. We excluded samples obtained after treatment with biologics (rituximab, belimumab).

Autoantibodies expressed above the normal range were detected in the following frequencies: 90% ANA, 85% dsDNA, 84% Histone, 54% Sm/RNP, 32% Sm, 65% Ro52 (SSA), and 23% La

(SSB) A significant negative correlation between the described autoantibodies and level of complement C3 was observed. Based on gene expression, the only significant association was obtained for genes involved in cell division. Among those, the strongest association was demonstrated with anti-dsDNA titer. Among cell cycle related genes, the most significant correlations ($p < 10^{-5}$) were seen for TK1, AURKB, KIFC1, KIF15, FOXM1, GINS2, NGAPG, CDC45, CDCA5, CCNA1, CCNB1.

Conclusions Autoantibodies directed against nucleic acid-containing immune complexes are a characteristic trait in SLE. The aberrant expression of TK1 has been previously shown in bone marrow of SLE patients. Cell-cycle related genes were identified earlier in microarray studies of SLE PBMC. However, association of those transcripts with autoantibodies has not been previously described. Abnormal expression of genes related to cell cycle might cause cell cycle arrest, a DNA