Conclusion: Distinct histological features of LN are paralleled by specific signatures of circulating soluble mediators. Within LN, proliferative LN is associated with higher circulating levels of inflammatory cytokines, notably, type 1 IFNs. Furthermore, a decline in the titers of several immune mediators correlated with LN activity was associated with treatment response, suggesting a possible role in LN pathogenesis. These signatures and trajectories provide insight into LN pathogenesis, heterogeneity, and biomarker development.

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POS0290

NOVEL ANTI-MITOCHONDRIAL ANTIBODIES IDENTIFY PATIENTS WITH PROPENSITY TO THROMBOSGENESIS IN SYSTEMIC LUPUS ERYTHEMATOSUS

Keywords: Autoantibodies, Biomarkers

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Background: Venous and arterial thrombotic events are leading causes of mortality in systemic lupus erythematosus (SLE), amounting to up to a quarter of deaths[1]. Other than traditional risk factors, SLE-specific factors, including chronic inflammation, have also been shown to contribute to thrombosis development. Nonetheless, the four times higher relative risk of thrombosis compared to healthy individuals is not fully accounted to the presence of conventional cardiovascular risk factors and anti-phospholipid antibodies[1]. As such, novel biomarkers of thrombosis are needed in early identification and preventative management of SLE patients.

Objectives: To characterize novel antibodies directed against mitochondrial constituents, and investigate their capacity to stratify patients based on thrombotic events.

Methods: Highly purified mitochondria were isolated from HepG2 cells (ATCC HB-806STM) as previously described[2]. Briefly, cells were harvested and homogenized by a glass Douncer, followed by sequential centrifugation. Upon DNase-mediated removal of extracellular DNA, ultra-pure mitochondria (confirmed by flow cytometry, qPCR, and Western blot), labeled with MitoTracker, were incubated with sera (diluted 1:100) from SLE patients or healthy individuals. Binding of IgG to the mitochondrial outer membrane was detected using a secondary FITC-conjugated anti-human-IgG antibody, and analyzed by FACS. In some experiments, mitochondria were treated with trypsin (0.05%) prior to incubation with sera. Finally, reactivity towards mitochondrial protein lysate was confirmed using WB. Samples and clinical data from SLE patients (n=92) and healthy individuals (n=80) were provided from Division of Rheumatology, Lund University, Sweden. Statistical analyses were performed on SPSS 22.0.


Background: Iberdomide is a high affinity cereblon ligand that promotes ubiquitination and proteasomal degradation of Ikaros (IKZF1) and Aiolos (IKZF3) transcription factors, and thereby altering specific aspects of immune responsiveness. Iberdomide has been shown to be efficacious in a randomized controlled trial in patients with generalized SLE (NCT03161483) and to be specifically effective in patients with high baseline expression of the interferon gene signature (IGS)[1,2].

Objectives: The goal of this study was to identify subsets of SLE patients responsive to iberdomide more effectively by analyzing baseline gene expression profiles.

Methods: Baseline whole blood samples from 276 female SLE patients from the phase 2b iberdomide trial were utilized for this analysis. These patients had >6 month history of SLE and disease activity determined by SLEDAI-2K >/=6. Patients were randomized to placebo, or one of three doses of iberdomide (0.15, 0.3 or 0.45mg per day). Clinical response was determined by the SLE Responder Index 4 (SRI-4) at 24 weeks. RNAseq was performed and analyzed by Gene Set Variation Analysis (GSVA) using 32 informative gene modules and K-means clustering.

Results: Whole blood K-means clustering of the GSVA scores yielded 5 clusters or endotypes (Figure 1). Cluster 0 had the fewest molecular abnormalities whereas Cluster 1 had the most disturbances in immune function, including enrichments in the interferon gene signature (IGS), immunoproteasome, IL-1 inflammasome pathway, and neutrophil/granulocyte genes. Clusters 2-3 had intermediate degrees of abnormal enrichment in specific gene modules. Cluster 4 had high IGS, immunoproteasome, plasma cell/Ig chains, and IL-23 complex genes. No differences were noted between the subsets with regard to steroid or hydroxychloroquine use and differed only slightly in disease activity as measured by SLEDAI-2K. In general, cluster 1 had the most severe clinical laboratory measures with the highest anti-dsDNA antibodies and lowest C3 and C4. Clinical responses to iberdomide were confined to clusters 1 and 4. Effect sizes of responses in these groups approximated 30%. Other clusters had higher placebo responses and no additional response to iberdomide.

Conclusion: K-means clustering of GSVA scores from baseline samples of the iberdomide trial successfully clustered patients into endotypes that exhibited differences in response to iberdomide treatment, with the greatest responses observed in patients with the highest IGS, immunoproteasome, plasma cell, inflammasome, and IL-23 pathways. Gene expression based subsetting (endotyping) may be useful to enrich trials for responsive patients.

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Figure 1. K-means clustering of GSVA scores from baseline gene expression profiles effectively identifies 5 subsets of SLE patients.

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