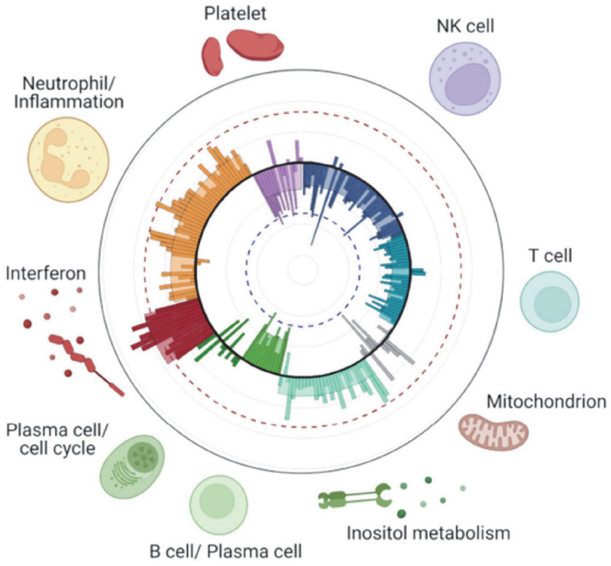

Abstract PO.1.5 Figure 1

Results My PROSLE allows to molecularly summarize patients in 206 gene-modules, clustered into 9 main lupus signatures (Example in figure 1, the combination of which revealed highly differentiated pathological mechanisms. We show that dysregulation of certain gene-modules is strongly associated with specific clinical manifestations, the occurrence of relapses or the potential presence of long-term remission and drug response. Therefore, My PROSLE could be used to accurately predict these clinical outcomes.

Conclusions My PROSLE (https://myprosle.genyo.es) allows molecular characterization of individual Lupus patients and it extracts key molecular information to support more precise therapeutic decisions.

PO.1.6 INVESTIGATING MONOCYTE TRANSCRIPTOMICS AND TARGETED PROTEOMICS SIGNATURES IN SLE WITH ATHEROSCLEROSIS UNCOVERS HETEROGENEITY IN INFLAMMATORY PROFILES

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10.1136/lupus-2022-elm2022.40

Purpose Accelerated atherosclerosis and the build-up of fatty lipids in the arteries leading to an inflammatory cascade and cardiovascular disease (CVD) are a leading cause of mortality in women with systemic lupus erythematosus (SLE). Despite this, lipid-lowering drugs have shown mixed efficacy in SLE and a female-focused mechanistic understanding of atherosclerosis in the context of SLE is lacking.

Methods A well-characterised cohort of CVD-free women with SLE were non-invasively scanned for the presence of subclinical atherosclerotic plaques and monocyte bulk-RNAsequencing (n=18) and targeted proteomics (n=29) were performed. To explore molecular gene and protein signatures of atherosclerosis in SLE, it is important to acknowledge how they interact within the interactome whereby clusters of connected genes and proteins can offer insight into shared function or disease association. Disease module identification using a modularity optimization method (MONET) was applied to multiple networks (ConsensusPathDB and STRINGdb) and modules were ranked by number of seed genes (n seeds=372) or proteins (n seeds=10) differentially expressed between SLE patients with and without subclinical atherosclerotic plaques that were represented in the module. Pathway enrichment analysis was applied to key modules to elucidate potential mechanisms underpinning subclinical atherosclerosis pathology in SLE.

Results Highly enriched modules were defined by inflammatory mechanisms. The highest ranked module (n seed genes=3, proteins=2 across both networks) implicated genes and proteins involved in the complement pathway as associated with atherosclerosis in SLE, supporting prior knowledge that complement is dysregulated in SLE pathology and emerging evidence suggesting a role for complement in atherosclerotic plaque development. Other key modules suggested dysregulation of genes and proteins associated with mitochondrial function and inflammatory interferon signalling. Interferon-regulated genes, known to be elevated in SLE, were downregulated in SLE patients with subclinical plaque. Notably, unsupervised hierarchical clustering applied to interferon-gene signature-derived scores stratified patients into three distinct subgroups based on interferon response ($p<0.0001$) that could not be explained by differences in routine disease measures or known clinical predictors. Interferon response did not predict the presence of plaques and 55% of plaque patients showed a low interferon-response, potentially indicative of an anti-inflammatory profile.

Conclusions SLE and atherosclerosis are both characterised by chronic inflammation. Complement and interferon production are critical regulators of the inflammatory response and contribute to immune dysfunction in SLE. Nevertheless, we have established a complex signature of genes and proteins associated with inflammatory functions as both up and downregulated in SLE patients with subclinical atherosclerosis, suggesting a potential dysregulation or dampening of inflammatory processes. This presents an exciting opportunity for improved patient stratification to identify SLE patients at greatest risk for CVD.

PO.1.7 URINARY METABOLOMIC PROFILE OF SYSTEMIC LUPUS ERYTHEMATOSUS AND LUPUS NEPHRITIS BASED ON LIQUID AND GAS CHROMATOGRAPHY/MASS SPECTROMETRY (LC-QTOF-MS AND GC-QTOF-MS)

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10.1136/lupus-2022-elm2022.41

Purpose Systemic lupus erythematosus (SLE or lupus) is a chronic autoimmune disease, and kidney involvement with SLE, lupus nephritis (LN), is a frequent and severe complication of SLE that increases patient morbidity and mortalityis. The current gold standard for classifying LN progression is a renal biopsy, an invasive procedure with potential risks. Undergoing a series of biopsies for monitoring disease progression and treatments is unlikely suitable for patients with LN. Thus,

there is an urgent need for non-invasive alternative biomarkers that can facilitate LN class diagnosis. Such biomarkers will be very useful in guiding intervention strategies to mitigate or treat patients with LN. The current study aims to explore new biomarker candidates for non-invasive diagnosis of LN and explore the pathogenic mechanisms that contribute to renal injury.

Materials and Methods A metabolomics approach using LC-QTOF-MS in both positive and negative electrospray ionization (ESI) modes and GC-QTOF-MS was developed for comparison of urine metabolic profile of 23 LN patients, 16 SLE patients, and 10 healthy controls (HCs). Differential metabolites were evaluated with univariate (UVA) and multivariate (MVA) analysis using a nonparametric t test, principal component analysis (PCA) and orthogonal partial least squares regression (OPLS-DA).

Results Both UVA and MVA showed a clear discrimination in the urinary metabolome between LN, SLE and HCs. The significant altered metabolites between LN and SLE correspond mainly to fatty acyls, amino acids, bile acids in particular methylglutamic acid, monopalmitin methyl-L-proline, 3-oxo-4-pentenoic acid, glutaric acid, 3-hydroxyglutaric acid, citraconic acid, glutamine, glycocholic acid and ureidoisobutyric acid. Analysis of metabolic pathways shows disturbances in biosynthesis of alanine, aspartate and glutamate metabolism, citrate cycle (TCA cycle) and glutamine and glutamate metabolism.

Conclusions The urinary metabolome of SLE and LN patients made it possible to determine metabolic alterations and discriminate LN patients from SLE patients. If confirmed in larger studies, these urine metabolites may serve as biomarkers to help discriminate between SLE with and without renal involvement.

PO.1.8 DISTINCT TRANSCRIPTOMIC SIGNATURE OF PERIPHERAL BLOOD IN NEUROPSYCHIATRIC LUPUS

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10.1136/lupus-2022-elm2022.42

Purpose We sought to identify distinct blood transcriptomic signatures of NPSLE patients that could serve as potential biomarkers and therapeutic targets.

Methods NPSLE was defined as patients with primary neuropsychiatric events (attributed to SLE) using a combination of multidisciplinary physician judgment with attribution models. Patients without neuropsychiatric events or secondary NPSLE (neuropsychiatric manifestations not attributed to SLE) were classified as non-NPSLE. Diagnosis of SLE was established by the Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) 2012 criteria. RNA-sequencing was performed in peripheral blood from 172 individuals (54 NPSLE, 94 non-NPSLE and 24 healthy controls). Relative expression levels of transcripts and differentially expressed genes (DEGs) (FC >1.5, FDR <0.2) were calculated. Gene set enrichment analysis (GSEA; Preranked) and Gene ontology (GO; gprofiler) analyses were performed in RNA datasets.

Results Comparison of NPSLE with healthy controls revealed 103 DEGs mainly involved in inflammatory pathways (leukocyte cell-cell adhesion, regulation of leukocyte proliferation, neutrophil aggregation, complement and coagulation cascades, Toll-like receptor binding, NF-kappa B signaling pathway) suggesting that systemic inflammation is a key component in NPSLE pathogenesis. Comparison of NPSLE with non-NPSLE patients by GSEA analysis (FDR<0.25) revealed angiogenesis (FGFR1, LPL, PGLYRP1), complement (C3, ITGAM, CASP7), coagulation (VWF, ADAM9, CAPN2) G2M checkpoint (CHEK1, MKI67, CDKN3), MYC targets (XRCC6, PCNA, ILF2), E2F targets (CDK1, CKS1B, SMC3), estrogen response (MYB, CKB, SLC1A4), neutrophil degranulation (TNFAIP6, MMP8, LCN2) and PPAR signaling pathway (DBI, LPL, FABP5) being significantly enriched in NPSLE.

Conclusions NPSLE patients exhibit distinct transcriptomic signature compared to SLE patients without NP events. These data could facilitate the development of novel biomarkers and therapeutic targets.

Acknowledgments The European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement no.742390); and the SYSCID (A Systems Medicine Approach to Chronic Inflammatory Diseases) under the European Union's Horizon 2020 research and innovation programme (grant agreement no.733100).

PO.1.9 SERUM SPHINGOLIPIDS AS A POTENTIAL BIOMARKER IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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10.1136/lupus-2022-elm2022.43

Purpose Sphingolipids, an essential signaling molecules for the biological and structural functions of cells, are increasingly recognized as playing an important signaling role in the pathophysiology of chronic inflammatory diseases. We hypothesized that the pathogenesis of systemic lupus erythematosus (SLE), a chronic autoimmune disease, is related to altered composition and dysregulation of sphingolipids.

Methods We performed liquid chromatography tandem mass spectrometry to evaluate the levels of sphingolipids in plasma from 38 women with SLE, including 11 lupus nephritis, and 30 controls. The receiver operating characteristic curve (ROC) was analyzed to calculate the area under the curves (AUC) to determine whether sphingolipids can be efficiently used to diagnose SLE. Further, Pearson's correlation coefficient was used to analyze the correlation between sphingolipids and the disease activity markers.

Results The mean age of SLE patients was 44.5 years and the mean disease duration was 110.7 months. The levels of serum ceramide (Cer) and Cer to sphingosine-1-phosphate (S1P) ratio subspecies were increased in patients with SLE, while the levels of sphingomyelins were decreased compared to the controls. The ratio of Cer16:0 to S1P showed especially strong increments in patients with lupus nephritis, and the AUC value for discriminating lupus nephritis from controls was 0.739 (95% confidence interval, 0.581–0.898). In addition, their levels were associated with disease duration, anti-double stranded DNA antibody, SLE disease activity index 2000, and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.