adiponectin on RA in both European (OR 0.97; 95% CI 0.78 – 1.22; p=0.81) and East Asian (OR 0.97; 95% CI 0.72 – 1.31; p=0.85) populations after adding BMI as a confounder in the multivariable MR model (Figure 1).

Figure 1. Forest plot of the causal effects of adiponectin-associated genetic variants on rheumatoid arthritis after adjustment for body mass index in a multivariable mendelian randomization (MR) analysis. Shown are European (EUR) and East Asian (EAS) populations. An Odds Ratio (OR) of 1 indicates no causal effect.

Conclusion: This MR study does not support a causal effect of genetically determined adiponectin levels on the risk of developing RA in both European and East Asian populations. By using multivariable MR to account for possible shared genetic predictors between circulating adiponectin levels and BMI we have shown that circulating adiponectin is not causally linked to RA risk after adjustment for BMI.

REFERENCES:

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POS0038 GENOMICS OF JAK-STAT SIGNALING IN VENOUS THROMBOEMBOLISM
S. Hayzen1, A. L. L. Nielsen1, P. Ovist1, T. W. Krastrup1, 1Aarhus University, Department of Biomedicine, Aarhus, Denmark

Background: Janus kinase inhibitors (JAKi) have been associated with an increased risk of venous thromboembolism (VTE) [1]. VTE comprises deep vein thrombosis and pulmonary embolism and is associated with complications such as recurrent VTE, post thrombotic syndrome, pulmonary hypertension, and death. These concerns limit the use of JAKi-based therapy. To improve risk stratification and drug development, it is crucial to understand the possible implication of dysregulated JAK-signal transducers and activators of transcription (STAT) signaling in the pathogenesis of VTE.

Objectives: The objective of this study is to clarify the putative genomic vulnerabilities to dysregulated JAK-STAT signaling in VTE.

Methods: We are systematically mine and analyze large-scale genomic datasets generated from studies comparing VTE patients with healthy controls. Using VTE genome-wide associated (GWA) summary statistics, we evaluate the representation of genes encoding the JAK-STAT pathway (KEGG hsa040630) in associated loci and assess their association to VTE. Further, we examine the genetic VTE risk burden in the chromatin interactome of STAT family transcription factors (TFs). We extract available STAT family (STAT-1) TF binding site (TFBS) consensus DNA motifs (JASPAR database) and assess the association of genes containing STAT family TFBSs within their promoter sequence (TSS – 2000bp) to VTE. Through mining of deposited OMICs data from VTE patients, we examine molecular characteristics related to JAK-STAT signaling, including potential enrichment of STAT family TFBSs among query promoter sequences of differentially expressed genes (DEGs).

Results: We do not observe a significant overrepresentation of JAK-STAT genes (n_overlap=162) among genes annotated to VTE significant GWA loci (n_total=147, p=0.48). Similarly, the JAK-STAT gene set show no cumulative association to VTE (p=0.98). Applying the same gene set association approach to the STAT target gene sets (n_overlap=4570) does not reveal significant association between VTE and STAT1 (n_overlap=10, p=0.47), STAT1:STAT2 heterodimer (n_overlap=18, p=0.17) and STAT3 (n_overlap=46, p=0.20) target gene sets. At the functional molecular level, we do not see any significant overlap between molecules acting in the JAK-STAT pathway and DEGs (n_overlap=507, p=0.06) or differentially abundant proteins (DAPs; n_overlap=35, p=0.57). However, we observe a significant overlap between downregulated DEGs (n_overlap=362) and the STAT1:STAT2 heterodimer target gene set (n_overlap=2155, p=0.0001) including downregulation of IL-27RA and CCND3 (Figure 1). Supporting the biological relevance of this finding, we find a weak but statistically significant enrichment of STAT1 TFBS motifs in the promoter sequence of downregulated DEGs compared to non-DEGs (p=0.02).

Figure 1. Overlap between STAT1:STAT2 heterodimer gene set and differently expressed genes (DEGs) in venous thromboembolism (VTE).

Conclusion: Here, we provide a coherent approach to assess the genomic basis for the reported association between JAKi treatment and VTE. Our preliminary data suggest that genes under transcriptional control of STAT family TFs may be dysregulated in VTE patients. It is conceivable, that the genomic actions of JAKi is overlapping with the molecular risk profile of VTE. CCND3 is especially interesting because VTE occurs in up to 10% of patients treated with cyclin-dependent kinase inhibitors such as Palbociclib [2]. Obviously, genomic data mining alone cannot guide medical decision making concerning the use of JAKi. However, our results provide a basis for further investigation of adverse events seen with JAKi.

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POS0039 MONOCYTE TRANSCRIPTOMICS AND TARGETED PROTEOMICS DEFINE HETEROGENEOUS SUBGROUPS IN WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) AND SUBCLINICAL ATHEROSCLEROSIS
L. Woodridge1,2,3, E. Chocano1,2, P. Ashford3, G. Robinson4, K. Waddington1,2, A. Rahman1, C. Oreno2, E. jury2, I. Pineda Torra1, 1Centre for Cardiometabolic Science, Division of Medicine, UCL, London, United Kingdom; 2Centre for Rheumatology Division of Medicine, UCL, London, United Kingdom; 3Institute of Structural and Molecular Biology, Biociences, UCL, London, United Kingdom

Background: Patients with systemic lupus erythematosus (SLE) and subclinical atherosclerosis represent a high-risk subgroup for cardiovascular events with a strong association between SLE and atherosclerosis. The pathophysiological basis of SLE-related atherosclerosis remains unclear. Here, we aimed to investigate heterogeneity in monocytes of SLE patients with and without subclinical atherosclerosis and examine for differences in gene expression and protein abundance.

Methods: SLE patients and controls were recruited from the Lupus Cohort Study. Monocytes were isolated and subjected to transcriptomic and targeted proteomic analysis. Hierarchical clustering and unsupervised analysis were performed to identify clusters of patients.

Results: We identified three distinct clusters of SLE patients: cluster 1 (n=15) had a high expression of genes associated with inflammation and immune response, cluster 2 (n=12) had a high expression of genes associated with cell cycle and proliferation, and cluster 3 (n=3) had a high expression of genes associated with metabolism and lipid transport.

Conclusion: Our findings suggest that SLE patients with subclinical atherosclerosis are heterogeneous and may represent distinct subgroups with varying pathophysiological mechanisms.
Background: Systemic lupus erythematosus (SLE), a chronic, inflammatory autoimmune disease, predominantly affects women with a 9:1 female:male incidence. Cardiovascular disease (CVD) is a leading cause of mortality in SLE via accelerated atherosclerosis: the build-up of cells and lipids in the vascular wall and the main pathology underlying CVD.

Objectives: To define molecular profiles of SLE with subclinical atherosclerosis using multi-omics data analysis and clinical data in a well-characterised cohort of CVD-free SLE women.

Methods: Multi-omics analyses were conducted to explore the molecular signatures of SLE patients with (SLE-P) and without (SLE-NP) subclinical atherosclerosis defined by non-invasive ultrasound scanning of the carotid and femoral arteries. SLE blood CD14+ monocyte transcriptomes were investigated by bulk RNA-sequencing (SLE-P N=13, SLE-NP N=8), and targeted serum cardiometabolic and cardiovascular proteomics (OLINK) were used to explore matched protein expression (SLE-P N=17, SLE-NP N=20) (no difference in disease activity between groups). Bioinformatics approaches, including pathway and disease module enrichment analyses and extended protein-protein interaction networks, further defined molecular profiles of SLE patients with atherosclerosis from patients that remained plaque free. Gene signature-derived interferon (IFN) scores were applied to investigate heterogeneous subgroups within the cohort as a measure of inflammation.

Results: Distinct monocyte gene and protein expression profiles were identified in SLE and enriched in biological pathways relating to extracellular mechanisms, including purinergic and cytokine signalling. Lipid regulatory mechanisms were enriched in SLE-P whereas SLE-NP patient’s transcriptome and proteome profiles were defined by pathways relating to inflammation. Specifically, the type-I IFN pathway was exclusively reduced in SLE-P compared to SLE-NP. IFN scores derived from published responsive gene expression signatures stratified patients into significantly distinct subgroups (high versus low IFN response, p=0.0001) with 66% (N=14) of patients showing high IFN expression across multiple signatures not associated with age, ethnicity, or disease activity. However, IFN scores did not predict the presence of sub-clinical atherosclerosis and further heterogeneity was revealed with 46% of SLE-P patients showing a low IFN response (N=8). Further, a measure of plaque lipid content (echogenicity) was inversely correlated with IFN score (grey scale median, p=0.03, r=−0.8) which may reflect distinct plaque phenotypes between these subgroups relating to clinical presentation and risk of cardiovascular events.

Conclusion: Lipid dysregulation is a key mechanism that drives atherosclerosis pathology and genes and proteins relating to lipid metabolism distinguished SLE patients with and without subclinical atherosclerosis. Differences in levels of interferons and other inflammatory molecules may contribute to unique patterns of gene expression between SLE patients. A distinct subset of SLE-P patients showed low interferon expression, which may be suggestive of a dampened immune response in early subclinical CVD. Further elucidating the complexity of lipid dysregulation, inflammation and immune function in atherosclerosis in SLE will help improve patient stratification towards investigating the efficacy of anti-atherosclerotic therapies.


HPR Poster Tour: Moving together towards person-centred care

Figure 1. Steroid PRO Initial Themes

A long-list of 134 initial candidate questionnaire items was developed from the individual themes. These items were reviewed by a qualitative working group of patient research partners, researchers and clinicians to reduce duplication and ambiguity of items. The resulting 62 items were tested and refined by piloting with patient research partners, iterative rounds of cognitive interviews with patients with a range of rheumatic conditions from the UK, USA and Australia, and a linguistic translatability assessment, to define a draft questionnaire of 40 items. Purposive sampling of participants provided a broad range of demographic features, GC dosages and inflammatory rheumatic conditions, with 27% having connective tissue disease, 25% inflammatory arthritis, 30% systemic vasculitis and 16% other rheumatic conditions. Initial domains were developed to identify key themes relating to treatment using GCs and their impact on HRQoL; see Figure 1.