Background: A strong female predisposition is characteristic of Systemic Lupus Erythematosus (SLE), with female-to-male ratio ranging from 7:1 to 15:1. The molecular basis of this gender bias remains incompletely understood. In a previous whole-blood RNA profiling study, we identified genes with differential expression in SLE males versus females but not in their healthy counterparts. Among these genes, the cohesin complex protein SMC1A (Structural Maintenance of Chromosomes 1A) displayed the highest statistical significance [1].

Objectives: (a) to determine the immune cell type that displays the strongest gender-biased SMC1A expression in SLE versus healthy individuals, and (b) elucidate the role of SMC1A in regulating immune/inflammatory responses in both genders.

Methods: Multiple immune cell types (CD19+ B cells, CD4+ T cells, CD14+ monocytes, neutrophils) were purified from peripheral blood specimens of SLE and healthy individuals, followed by Taqman PCR and Western blot to measure SMC1A mRNA and protein levels, respectively. The genome-binding properties of SMC1A were assayed by chromatin immunoprecipitation (ChIP)-sequencing in monocytes cultured under lupus-inducing conditions (lupus-like monocytes). Among these genes, the cohesin complex protein SMC1A (Structural Maintenance of Chromosomes 1A) displayed the highest statistical significance [1].

Results: Among the various tested immune cell types, CD14+ monocytes best recapitulated the initial whole blood RNA-seq findings, demonstrating significantly decreased SMC1A mRNA and protein expression in male versus female SLE patients but not in their healthy counterparts. In blood monocytes cultured under lupus-inducing conditions and tested by ChIP-Sequencing, SMC1A binding was increased on enhancers and promoters of genes associated with inflammation (including type I/II interferon and other inflammatory cytokines) and cell migration. In accordance, lupus-like monocytes with lowered SMC1A expression (i.e., male-like) displayed significantly reduced expression of inflammatory genes like IL6, GBP5, ADA and IL1A, as compared to monocytes with unaffected SMC1A (i.e., female-like). Furthermore, IL6 mRNA synthesis was significantly enhanced in female versus male monocytes cultured under lupus-inducing conditions.

Conclusion: SMC1A may transcriptionally regulate genes associated with the inflammatory response of monocytes. Our findings of gender-biased SMC1A expression in SLE monocytes raise the hypothesis that differential SMC1A expression may contribute to the disease gender bias and/or sexual dimorphism.

REFERENCES:

Disclosure of Interests: None declared

AB0014

THE ROLE OF NLRP3 INFLAMMASOME POLYMORPHISMS IN THE GOUT SUSCEPTIBILITY

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Background: Recent reports have demonstrated that polymorphisms within NLRP3 inflammasome signaling pathway are key factors in the risk to develop some joint inflammatory diseases (1). To date, there is still uncertain information about the presence of these genetic variants and their association with risk of gout.

Objectives: To determine the association between the single nucleotide polymorphisms (SNPs) within NLRP3 inflammasome genes and the risk of developing gout.

Methods: We included 220 gout patients and 243 healthy subjects as control group. Clinical examination was performed and laboratory including glucose concentration, total cholesterol and triglycerides were obtained. The frequency and the allelic distribution of eight SNPs from seven different genes within the NLRP3 inflammasome signaling pathway were analyzed using the Step One Plus Real-Time PCR Systems. SNPs were selected by the criterion of minor allele frequency (MAF) (above 1 %), using the 1000 Genomes Project. Genetic association analysis was performed using the Trends and Hardy-Weinberg Equilibrium (HWE) model. The association studies were performed using the Statistic Package for the Social Sciences (SPSS) and Genotype Information dbSNP database (http://www.ncbi.nlm.nih.gov/snp). The SNP results should not to be in linkage disequilibrium. Ancestry was analyzed using ancestry informative markers differentiating mainly American, African, and European ancestries.

Results: The missense SNP rs45520937 in PPARGC1B, showed enhanced association with the risk of developing gout when it was analyzed using the dominant model, evidencing that gout patients carried the A/G-A/A genotype have an elevated risk compared to the control group [OR (95% CI) = 2.30 (1.09-4.86), p=0.030]. While, the adaptor molecule CD14 rs2569190 SNP could be associated with lower risk of gout under an additive model [OR (95% CI) = 0.41 (0.16-1.05), p= 0.064]. No significant association were identified for the remaining SNPs.

Conclusion: Our findings suggest that genetic variant rs45520937 of PPARGC1B is associated with the susceptibility to gout.

REFERENCES:

Disclosure of Interests: None declared

AB0015

HOMEOBOX D13 TRANSCRIPTION FACTOR MODULATES THE FORMATION OF THE PRIMARY CILIUM IN RHEUMATOID ARTHRITIS SYNOVIAL FIBROBLASTS

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Background: Differences in gene expression and functions of synovial fibroblasts between distinct joints might lead to site-specific activation of arthritis-relat-
evant pathways. We previously showed that the transcription factors HOX-D10, -D11 and -D13 are higher expressed in synovial fibroblasts from hands and feet compared to shoulder and knee, and that this expression pattern is epigenetically imprinted (1).

Objectives: To investigate the functional role of HOXD13 in synovial fibroblasts.

Methods: Synovial fibroblasts from patients with rheumatoid arthritis (n=2) were cultured and transfected with HOXD13 antisense LNA GapmeRs (12.5mM). Transcriptional data was determined by RNA-seq (Illumina Novaseq 6000). Pathway enrichment analysis of RNA-seq data was performed using web-based tools (ToppGene, EnrichR and Cytoscape) (a fold change > 1.5, FDR < 0.05). The expression of histone deacetylases (HDACs) and sirtuins was measured by quantitative real-time PCR and immunofluorescence staining. Cilogenesis of synovial fibroblasts was assessed by measuring the expression of PKD2, ARL13B, KIF3A, and JPT8 using qPCR. Acetylation of alpha-tubulin was assessed by immunofluorescence staining. Imaging was performed with the CellInsight™ SX platform.

Disclosure of Interests: None declared

AB0013

THE COHESIN COMPLEX PROTEIN SMC1A IS A PUTATIVE REGULATOR OF SEX-BASED INFLAMMATORY RESPONSES IN SYSTEMIC LUPUS ERYTHEMATOSUS

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