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: To (a) 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 the context of SLE.

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 (Ips-like monocytes) [2]. To recapitulate the female/male difference in SMC1A expression, ex vivo cultured lupus-like monocytes were transfected with si-SMC1A (to downregulate SMC1A) versus si-control reagent, followed by genome-wide transcriptome analysis by RNA-seq.

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-seq, 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 ILA, 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 in monocytes. Our findings of gender-biased SMC1A levels in SLE monocytes raise the hypothesis that differential SMC1A expression and function might contribute to the disease gender bias and/or sexual dimorphism.

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AB0015

HOMEBOX D13 TRANSCRIPTION FACTOR MODULATES THE FORMATION OF THE PRIMARY CILIA 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-relevant 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.

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 (12.5nM). Transcriptional profiles were determined by RNA-seq (Illumina NovaSeq 6000). Pathway enrichment analysis of RNA-seq data was performed using web-based tools (TopGene, 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 IFIT8 using qPCR. Actinolysis of alpha-tubulin was assessed by immunofluorescence staining. Imaging was performed with the CellSight™ CX platform.

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