Exploring the molecular basis of gender bias in systemic lupus erythematosus (SLE)

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Background/objectives SLE features a substantially greater frequency in females than in males (ratio ranging 7:1–15:1). By contrast, males tend to suffer from more severe disease. Understanding the molecular basis of SLE variability and sex-dimorphism may advance our understanding of disease mechanisms. We performed full transcriptome analysis (RNA-seq) to monitor for differentially expressed genes (DEGs) between male and female SLE patients that are not differentially expressed between male and female healthy subjects, thus identifying a gender-biased molecular signature specific for the disease.

Materials and methods Whole blood RNA was extracted from SLE patients and healthy individuals. Paired-end mRNA sequencing was performed using the Illumina HiSeq2000 platform. A list of DEGs in SLE males versus females were generated using 5% false discovery rate (FDR). To increase the specificity of our results, we generated a similar list of DEGs in healthy males versus females using a 50% and 90% FDR cut-off, and the two lists were intersected.

Results We studied 142 SLE patients with diverse levels of disease activity/severity (120 SLE females, 22 SLE males) compared to 58 matched healthy volunteers (48 healthy females, 10 healthy males). We identified 39 genes which were significantly differentially expressed in SLE males versus females. Notably, 6 of these genes were not differentially expressed in healthy males versus females at either 50 or 90% FDR, highlighting a potential role in disease sexual dimorphism. The proteins encoded by these genes are implicated in various biological processes such as transcriptional regulation and DNA damage repair (SMC1A), lipoprotein particles catabolism (APOE), glutathione biosynthesis and metabolism (OPLAH), correct composition of bone and cartilage matrix (ARSD), whereas 2 of these genes do not code for proteins (MTCO2 and FRG1B). Further validation of these genes is in progress.

Conclusions A gender-biased molecular signature specifically associated with SLE was unraveled. Further investigation of the molecular pathways which are associated with these genes will give us insights for the molecular basis of gender bias in SLE and lead to novel, more effective treatments tailored for male and female patients.

REFERENCES