Background: Lupus nephritis (LN) is one of the most severe organ manifestations of systemic lupus erythematosus (SLE) and constitutes an important cause of morbidity and death among patients with SLE [1]. The associated renal injury, and ultimately mortality, is the result of an immune-mediated process which involves leukocytes, immune complexes, complement, and cytokines [2].

Objectives: Lupus nephritis (LN) is one of the most severe organ manifestations of systemic lupus erythematosus (SLE) and constitutes an important cause of morbidity and death among patients with SLE [1]. The associated renal injury, and ultimately mortality, is the result of an immune-mediated process which involves leukocytes, immune complexes, complement, and cytokines [2].

Methods: We analysed differentially expressed genes (DEGs), pathways and their drug- networking via the Drug Gene Interaction database (DGIdb) in active LN (n=41) versus healthy controls (HC; n=497), and eQTLs in active or past LN (n=87), based on validated (identified in two independent SLE populations) DEGs in SLE (n=350) vs HC (n=497), in whole blood collected within the frame of the European PRECISESADS consortium [4]. Genome-wide RNA-sequencing and genotyping was previously performed by Illumina assays, and serum levels of 17 cytokines and 18 autoantibodies were analysed using a Luminex assay, ELISA, IDS-YSY and SPAPLUS analyser [4].

Results: A total of 6869 significant and validated DEGs were identified in active LN patients compared with HC. Of these, 1010 validated DEGs were tagged to 202 different drugs, 18 cis-eQTLs and 3 trans-eQTLs, and 2 genes from 8 trans-eQTLs, and 2 genes from 17 cytokines that differed significantly between active LN and HC. Moreover, 2446 validated DEGs were tagged to 216 Reactome pathways included 85 DEGs with a |fold change (FC)| > 1.5, 6 genes from 14 cis-eQTLs and 5 trans-eQTLs, and 1 gene from cytokines that differed significantly between active LN and HC. These genes could be targeted by 203 different drugs, with the proteasome inhibitor bortezomib interfering with cathepsin B (CTS B) regulation and cyclophosphamide interfering with the regulation of tumour factor receptor superfamily member 1A (TNFRSF1A) being of particular interest.

Conclusion: Integrated multilevel omics analysis in LN revealed a set of enriched pathways of potential interest for future drug investigation. A prospect for proteasome inhibition was implicated.

References:


REFERENCES: