Conclusions Our report adds evidence concerning the sensitive issue of COVID-19 vaccine AEs and flares in SLE patients during the antenatal and lactation period. Based on the present data, the risk/benefit ratio of COVID-19 vaccination appears favourable, with vaccines both providing passive immunisation to the fetus and active immunisation to the mother with no signals of exacerbation of the mother's autoimmune disease.

Concurrent session 8: omics and breakthrough technology

LO-028 FUNCTIONAL DISSECTION OF DYSREGULATED ENHANCERS INFLUENCING SLE CRITICAL GENE EXPRESSION

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Background The dysregulation of enhancers has been observed in many autoimmune diseases, but it is still a big challenge to identify the function, the target genes, and the pathogenic roles of the dysregulated enhancers. Here, we intend to dissect the enhancer regulatory landscape of a SLE critical microRNA in different cell lineages and identify the SLE-associated enhancers, which would be intervened by CRISPR as possible therapeutic targets.

Methods Epigenomic analysis and 4C-seq study were carried out to identify candidate enhancers of miR-146a. CRISPR-dCas9-VP64 mediated activation was adopted to map the functional enhancers. The chromatin accessibility of different immune cell subpopulations from the healthy control and SLE patients was analyzed to identify SLE-dysregulated enhancer. The transcription factor binding was analyzed to dissect the mechanism that mediates enhancer dysfunction. The SLE-associated enhancer was targeted to intervene in the disease phenotype in SLE patients' PBMCs through CRISPR activation approach.

Results The cell-type-specific and shared enhancers of miR-146a were identified in different cell lineages. An enhancer, 32.5 kb away from the downstream of miR-146a, is dysregulated in SLE, with lower chromatin accessibility than the healthy control. The chromatin openness of this enhancers was positively correlated with the miR-146a expression and negatively correlated with SLEDAI scores of SLE patients. Moreover, the decreased expression of CEBPA mediated the dysregulation of this enhancer. Furthermore, CRISPR-based activation targeting this enhancer attenuated ISGs expression in SLE patients' PBMCs.

Conclusions We developed an integrative approach to establish the enhancer landscape of the SLE critical gene, and dissect the mechanism that mediates the enhancer dysfunction in SLE. Our work reveals a possible therapeutical target for SLE treatment.

LO-029 LONGITUDINAL SINGLE-CELL TRANSCRIPTOMIC ANALYSIS OF PERIPHERAL BLOOD IN LUPUS NEPHRITIS REVEALS DIFFERENT IMMUNE CELL GENE SIGNATURES DEPENDING ON TREATMENT RESPONSE

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Background Cellular immune responses are phenotypically and functionally perturbed in patients with lupus nephritis (LN), leading to severe renal tissue inflammation. Although multiple gene expression landscapes have been identified for LN development, longitudinal cell type-specific immune responses and prognostic signatures during treatment of LN remain largely unknown.

Methods To uncover transcriptome changes during treatment and identify immune markers to predict treatment response, we performed sequential single-cell RNA sequencing using peripheral blood mononuclear cells (PBMCs) obtained from patients with biopsy-proven LN who received mycophenolate mofetil in combination with glucocorticoids. Single-cell libraries were generated using a commercially available droplet method, the Chromium System from 10× Genomics, Inc. (Pleasanton, CA, USA).

Results We profiled ~239,000 PBMCs from 10 female patients with LN. After receiving standard therapy for 1 year, number of individuals with complete response (CR) and non-response (NR) according to ACR response criteria was 5 each. Peripheral blood B cells in patients with NR showed a significant expansion of double-negative switched memory cells (DN2), a distinct subset expressing T-box transcription factor T-bet, at renal flare and the increased proportion was maintained after immunomodulatory treatment. Next, we directly compared myeloid cells between CR and NR groups. Analysis of differentially expressed genes revealed that NR was characterized by up-regulation of various interferon-stimulated genes (ISGs), including IFITM1, IFI44, and ISG15. Both IFN-α and IFN-γ responsive genes were enriched. Patients with CR were accompanied by repression of inflammatory pathways across all types of myeloid cells, with noticeable down-regulation of unphosphorylated IFN-stimulated gene factor 3 (U-ISGF3)-inducible signatures.

Conclusions We provide the first evidence of comparative transcriptional signatures depending on the treatment response in patients with LN. Our results highlight that detailed analysis on immune cells and a dissection of type I IFN-driven inflammatory features enhance the understanding of treatment response dynamics, which might guide the selection of optimal therapeutics for LN.

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