RNA sequencing (scRNAseq) analysis may accurately differentiate types of renal involvement at the transcriptomic level, and better inform treatment decisions and prognosis.

Methods scRNAseq was performed on kidney and non-lesional skin tissue collected from 20 SLE patients undergoing a clinically indicated renal biopsy. Cell types were determined using principal component analysis and t-distributed stochastic neighbor embedding (tSNE) plotting, resulting in the definitive identification of keratinocytes, tubular cells, mesangial cells, fibroblasts, endothelial cells, and leukocytes.

Results LN patients expressed upregulated IFN response genes in both their tubular cells and keratinocytes. This IFN response signature in tubular cells predicted poor response to therapy 6 months post-biopsy. Tubular cells of non-responder patients also expressed upregulated extracellular matrix proteins and fibrotic markers (figure 1A and 1B). Using logistic regression analysis, a 4-gene tubular fibrosis score was created and able to predict response to treatment with an area under curve of 0.9 (figure 1C). Keratinocytes of non-responders also upregulated certain extracellular matrix genes and this response was not observed in peripheral blood mononuclear cells. Differential expression analysis between histology classes indicated an upregulation of IFN and TNF signaling in the tubular cells of patients with proliferative LN compared with membranous.

Conclusions scRNAseq from 2–10 mm of renal biopsy tissue in SLE can differentiate between the different classes of LN, and provide important insights into potential pathogenic mechanisms. Further, changes in the skin of LN patients can provide a useful source of biomarkers and may reflect important information concerning concurrent kidney pathological events.

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301 NOVELMIRNA-25 INHIBITS AMPD2 IN PERIPHERAL BLOOD MONONUCLEAR CELLS OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND REPRESENTS A PROMISING NOVEL BIOMARKER

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Background Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease with various clinical manifestations. MicroRNAs (miRNAs) and immunometabolism are recognized as key elements in SLE pathogenesis; however, the relationship between miRNAs in peripheral blood mononuclear cells (PBMCs) and metabolism in SLE remains unclear.

Methods We detected PBMC miRNA and mRNA profiles from 3 pooled SLE patients and 3 healthy controls (HCs) using next-generation sequencing, predicted miRNA targets in dysregulated mRNAs, predicted functions and interactions of differentially expressed genes using bioinformatics analysis, validated candidate miRNAs using qRT-PCR, and investigated the association between the expression of candidate miRNAs and SLE clinical characteristics. Moreover, we validated the direct and transcriptional regulatory effect of NovelmiRNA-25 on adenosine monophosphate deaminase 2 (AMPD2) using a dual-luciferase reporter assay and western blot and confirmed AMPD2 mRNA and protein expression in PBMCs using qRT-PCR and western blot, respectively.

Results Multilayer integrative analysis of microRNA and mRNA regulation showed that 10 miRNAs were down-regulated and 19 miRNAs were up-regulated in SLE patient PBMCs compared with HCs. Bioinformatics analysis of regulatory networks between miRNAs and mRNAs showed that 19 miRNAs were related to metabolic processes. Two candidate miRNAs, NovelmiRNA-25 and miR-1273h-5p, which were significantly increased in the PBMCs of SLE patients ($p<0.05$), represented diagnostic biomarkers with sensitivities of 94.74% and 89.47%, respectively (area under the curve=0.574 and 0.788, respectively). NovelmiRNA-25 expression in PBMCs was associated with disease activity in SLE patients, in both active and stable groups ($p<0.05$). NovelmiRNA-25 overexpression downregulated AMPD2 expression in HEK293T cells through direct targeting of the AMPD2 3'UTR ($p<0.01$), while inhibition of NovelmiRNA-25 activity led to increased AMPD2 expression ($p<0.01$). NovelmiRNA-25 overexpression also downregulated AMPD2 protein expression in HEK293T cells; AMPD2 protein expression in SLE patient PBMCs was decreased. Our results show that differentially expressed miRNAs play an important role in SLE.

Conclusions Our data demonstrate a novel mechanism in SLE development that involves the targeting of AMPD2 expression by NovelmiRNA-25. miRNAs may serve as novel biomarkers for the diagnosis and evaluation of disease activity of SLE and represent potential therapeutic targets for this disease.

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