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miR-132-3p downregulates *FOXO1* in CD4$^+$ T cells and is associated with disease manifestations in patients with lupus

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Abstract

Objective: This study aimed to evaluate the expression status of miR-132-3p in CD4$^+$ T cells in patients with systemic lupus erythematosus (SLE) and explore its potential role in SLE development.
Methods: The study included 60 patients with SLE and 30 healthy controls. miR-132-3p expression in CD4$^+$ T cells was detected by real-time quantitative reverse transcription polymerase chain. Bioinformatics analyses were employed to predict target genes and explore the potential role of miR-132-3p. The associations between miR-132-3p levels and SLE Disease Activity Index (SLEDAI) score, as well as laboratory characteristics, were analyzed.
Results: miR-132-3p levels in CD4$^+$ T cells were significantly higher in patients with SLE compared with healthy controls. Bioinformatics analysis identified *FOXO1* as a potential target gene of miR-132-3p, with a particular emphasis on the FOXO signaling pathway. miR-132-3p up-regulation in CD4$^+$ T cells was associated with high SLEDAI score, high anti-double-stranded DNA levels, low C3 and C4 levels, positive anti-ribosomal P, and high 24-hour urinary protein levels in patients with SLE.
Conclusions: miR-132-3p may contribute to CD4$^+$ T cell dysregulation during SLE by targeting *FOXO1* and could potentially be used to assess disease severity.

Keywords

Systemic lupus erythematosus, CD4$^+$ T cell, miR-132-3p, FOXO1, biomarker, disease severity

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease associated with severe organ injury, including nephritis and encephalopathy.[1] SLE is mediated by the production of diverse auto-antibodies against a wide range of self-antigens and immune complexes. Although the pathogenic mechanism of SLE remains unclear, increasing evidence suggests that $CD4^+$ T cell dysfunction plays a pivotal role in promoting the production of auto-antibodies via activating B cells.[2] $CD4^+$ T cells exhibit numerous functional abnormalities in patients with SLE, including an imbalance of T-helper cells and regulatory T (Treg) cells, impaired signaling, and increased spontaneous activation.[3,4] It is therefore crucial to investigate the dysfunctional mechanisms of $CD4^+$ T cells in patients to further our understanding of the pathogenesis and therapeutic strategies for this autoimmune disease.

MicroRNAs (miRNAs) comprise a substantial family of endogenous small non-coding single-stranded RNAs, approximately 18 to 25 nucleotides in length, that play a crucial role in negatively regulating gene expression by initiating the degradation or inhibiting the translation of target mRNAs.[5] miRNAs play various roles in the immune system, especially with regard to $CD4^+$ T cells, including regulating immune responses and the proliferation and differentiation of immune cells.[6,7] Although a previous study linked the specific miRNA, miR-132-3p, with disease activity and some manifestations of SLE,[8] the specific mechanism underlying this association remains unclear.

In this study, we aimed to explore the expression and underlying mechanism of miR-132-3p in $CD4^+$ T cells in patients with SLE. We initially assessed miR-132-3p expression in $CD4^+$ T cells from patients with SLE and healthy controls using real-time quantitative reverse transcription polymerase chain (RT-qPCR). We then conducted bioinformatics analyses to identify potential target genes regulated by miR-132-3p and explored the associated pathways in $CD4^+$ T cells. Finally, we evaluated the associations of this miRNA with the SLE Disease Activity Index (SLEDAI) score and various laboratory characteristics in patients with SLE.

Materials and methods

Study design and subjects

This translational study included inpatients with SLE recruited from the Department of Dermatology, Huashan Hospital, affiliated with Fudan University, between July 2017 and June 2019. Healthy age- and sex-matched control individuals also participated voluntarily in the study. The study protocol was approved by the Independent Ethics Committee of Huashan Hospital (ethical code number 2014-025), and all participants provided written informed consent.

Inclusion and exclusion criteria

All patients fulfilled the 1997 American College of Rheumatology revised criteria for the classification of SLE.[9] We excluded any patients with drug-induced SLE, acute or chronic infection, pregnancy, malignant tumors, and other rheumatologic or connective tissue diseases.

Clinical evaluation

Relevant demographic information was collected, including sex, age, and current medication use. Disease activity was assessed using the SLEDAI,[10] with a SLEDAI score >6 defined as active disease and a score ≤ 6 defined as stable disease. Lupus nephritis (LN) was diagnosed according to the Systemic Lupus International

Collaborating Clinics criteria, and patients with proteinuria >0.5 g/24 hours were defined as having LN at the time of enrollment.[11]

Laboratory investigations

Anti-double-stranded DNA (dsDNA) antibodies were detected using an anti-dsDNA enzyme-linked immunosorbent assay (IgG) kit (Euroimmun, Germany) and anti-SSA, anti-SSB, and anti-ribosomal P antibodies were detected using a EUROLINE ANA Profile (IgG) kit (Euroimmun), according to the manufacturer's instructions. Complement C3 and C4 levels were detected by immunoturbidimetric assay (Siemens Healthineers, Germany). Urinary 24-hour protein levels were measured using the pyrogallol red colorimetric method (Purebio, China).

$CD4^+$ T cell isolation

Peripheral blood mononuclear cells (PBMCs) were isolated by Ficoll-Hypaque (Sigma, MO, USA) density-gradient centrifugation (Eppendorf, Germany). $CD4^+$ T cells were isolated by incubation of freshly isolated PBMCs with anti-CD4 magnetic beads (Miltenyi Biotec, Germany) for 15 minutes at 4°C in the dark. The cells conjugated with magnetic beads were then sorted using MACS separators (Miltenyi Biotec) and the purity was assessed by flow cytometry (purity: 94.5% to 96%; Becton Dickinson, NJ, USA).

mRNA extraction and RT-qPCR

Total RNA containing miRNA was isolated using a spin or vacuum purification total RNA isolation system (Promega, WI, USA). The miRNA was then reverse transcribed into cDNA using an All-in-One™ miRNA First-strand cDNA Synthesis Kit (GeneCopoeia, MD, USA) and qPCR was performed using an All-in-One™ miRNA qPCR Kit (GeneCopoeia) with a Rotor-Gene Q (Qiagen, Germany). U6 served as an internal control. The relative expression levels were calculated using the $2^{-\triangle\triangle Ct}$ method. All primers were obtained from GeneCopoeia (Guangzhou, China; catalog nos.: HmiRQP0161 for miR-132-3p and HmiRQP0161 for U6).

Target gene prediction and bioinformatics analysis of miRNAs

Potential target genes of miR-132-3p were predicted using TargetScan 8.0 (http://www.targetscan.org/) and the miRBase database (http://www.mirbase.org). Differentially expressed target genes of miR-132-3p were then selected by comparing potential target genes with previous data for long non-coding RNA and mRNA arrays from patients with SLE (n = 6) and healthy controls (n = 6).[12] The functions of the down-regulated target genes of miR-132-3p in SLE were then investigated using Gene Ontology (GO) annotations (http://www.geneontology.org) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis (https://www.genome.jp/kegg/). Detailed pathway analysis was performed using the Database for Annotation, Visualization and Integrated Discovery (DAVID) database (https://david.ncifcrf. gov).

Statistical analysis

Statistical analysis was conducted using SPSS 29.0 software. Data were presented as mean ± standard deviation. Student's *t*-test was used to compare data between two independent groups. A *P*-value <0.05 was considered statistically significant. Graphs were analyzed using GraphPad Prism 9.0.

Results

Characteristics of the study groups

Sixty patients with SLE and 30 age- and sex-matched controls were included in the

study. The sex, age, SLEDAI score, and demographic and laboratory data of the patients are summarized in Table 1. Patient medications at time of the study included glucocorticoids 47/60 (78%), hydroxychloroquine 22/60 (37%), azathioprine 1/60 (1.7%), cyclophosphamide 4/60 (6.7%), and no treatment 11/60 (18%). Among the patients with LN, 10 patients were previously confirmed by renal biopsy.

Expression of miR-132-3p in normal and lupus CD4$^+$ T cells

The expression status of miR-132-3p in CD4$^+$ T cells from patients with SLE and healthy controls was assessed by RT-qPCR. miR-132-3p levels were significantly higher in patients with SLE compared with the healthy controls ($P < 0.0001$; Figure 1).

miR-132-3p could downregulate FOXO1 *expression in lupus CD4$^+$ T cells*

We explored the potential function of miR-132-3p in CD4$^+$ T cells in patients with SLE by predicting its target genes using TagerScan8.0 and the miRBase database. We then compared these potential target genes with previous data for differentially expressed mRNAs in patients with SLE.[12] Forty-eight differentially expressed target genes were identified in patients with SLE compared with healthy controls, comprising 18 up-regulated and 30 down-regulated mRNAs ($P < 0.05$; Figure 2(a)). Considering the up-regulation of miR-132-

Table 1. Clinical and laboratory characteristics of subjects.

Characteristic	SLE (n = 60)	Controls (n = 30)
Male/female	8/52	4/26
Age (years)	32.68 ± 11.46	31.93 ± 8.12
Disease duration (years)	6.07 ± 4.93	NA
Skin lesion (P/N (n))[a]	16/44	NA
Alopecia (P/N (n))	12/48	NA
Arthritis (P/N (n))	19/41	NA
SLEDAI score (P/N (n))[b]	17/43	NA
Anti-dsDNA (P/N (n))[c]	30/30	NA
C3 (P/N (n))[d]	47/13	NA
C4 (P/N (n))[e]	31/29	NA
Anti-SSA (P/N (n))	36/24	NA
Anti-SSB (P/N (n))	12/48	NA
Anti-ribosomal P (P/N (n))	22/38	NA
Proteinuria (P/N (n))[f]	19/41	NA
Red cell count ($\times 10^{12}$/L)	3.98 ± 0.39	NA
Lymphocyte count ($\times 10^9$/L)	4.89 ± 1.76	NA
Platelet count ($\times 10^9$/L)	183.43 ± 41.62	NA
ESR (mm/hour)	24.23 ± 12.90	NA

Values presented as mean ± standard deviation, unless indicated otherwise.

SLE, systemic lupus erythematosus; P/N (n), positive/negative (number of patients); SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; ESR, erythrocyte sedimentation rate.

[a]P, with butterfly erythema or discoid erythema, N, no butterfly erythema or discoid erythema; [b]P, SLEDAI >6, N, SLEDAI ≤6; [c]P, serum level >100 IU/mL, N, serum level ≤100 IU/mL; [d]P, serum level <0.9 g/L, N, serum level ≥0.9 g/L; [e]P, serum level <0.1 g/L, N, serum level ≥0.1 g/L; [f]P, >0.5 g/24 hours, N, ≤0.5 g/24 hours.

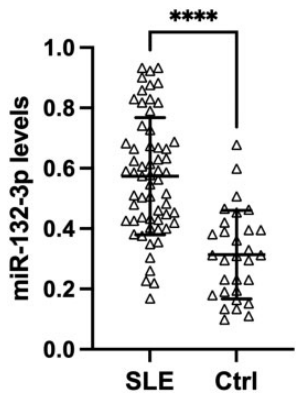

Figure 1. Elevated expression of miR-132-3p in $CD4^+$ T cells in patients with systemic lupus erythematosus (SLE). Relative expression levels of miR-132-3p in $CD4^+$ T cells in patients with SLE ($n = 60$) and healthy controls (Ctrl, $n = 30$). ****$P < 0.0001$.

3p in lupus $CD4^+$ T cells and the inhibitory role of miRNAs on target gene expression, we further investigated the 30 down-regulated mRNAs using GO and KEGG pathway analyses. GO analysis revealed that the down-regulated target genes of miR-132-3p in lupus $CD4^+$ T cells were involved in response to transforming growth factor beta, regulation of binding, and positive regulation of cell cycle in the biological processes category, cytoplasm, nucleoplasm, cytosol, and nucleus in the cellular components category, and beta-catenin binding, pre-mRNA binding, and nuclear receptor binding in the molecular function category (Figure 2(b)). KEGG pathway analysis indicated that the down-regulated target genes of miR-132-3p were involved in the FOXO signaling pathway, which is a critical pathway in immune regulation (Figure 2(c)). Visual representation of the FOXO signaling pathway using the DAVID database highlighted *FOXO1*, a target gene of miR-132-3p, as a key gene in this signaling pathway (Figure 2(d)). These findings suggested that up-regulation of miR-132-3p expression might target *FOXO1* in patients with SLE, potentially contributing to immune dysregulation.

Association of miR-132-3p expression with clinical and laboratory characteristics

We also investigated the correlation between miR-132-3p expression and clinical and laboratory characteristics in patients with SLE. miR-132-3p expression levels in $CD4^+$ T cells were significantly up-regulated in patients with high SLEDAI scores (>6, $P < 0.0001$; Figure 3(a)), high anti-dsDNA levels (>100 IU/mL, $P < 0.05$; Figure 3(b)), low C3 levels (<0.9 g/L, $P < 0.05$; Figure 3(c)), low C4 levels (<0.1 g/L, $P < 0.0001$; Figure 3(d)), and high 24-hour urinary protein (>0.5 g/24 hours, $P < 0.001$; Figure 3(e)). There were no significant differences in miR-132-3p expression levels in relation to anti-SSA and anti-SSB (Figure 3(f, g)); however, high miR-132-3p levels were significantly associated with positive anti-ribosomal P antibody ($P < 0.05$; Figure 3(h)), but not with the erythrocyte sedimentation rate (Figure 3(i)).

Discussion

miR-132 (also designated miR-132-3p) is derived from the miR132/212 cluster and has primarily been characterized in the pathogenesis of nervous system disorders, such as Alzheimer's disease and tumor progression, where it regulates target transcription factors and signaling pathways.[13,14] miR-132 has also recently emerged as a crucial player in immune regulation, including T cell activation and function. Studies have reported a critical role of miR-132-3p in antigen-dependent T cell activation, via suppression of pik3r1,[15] and miR-132 was shown to enhance protective immunity against pathogenic infections in innate

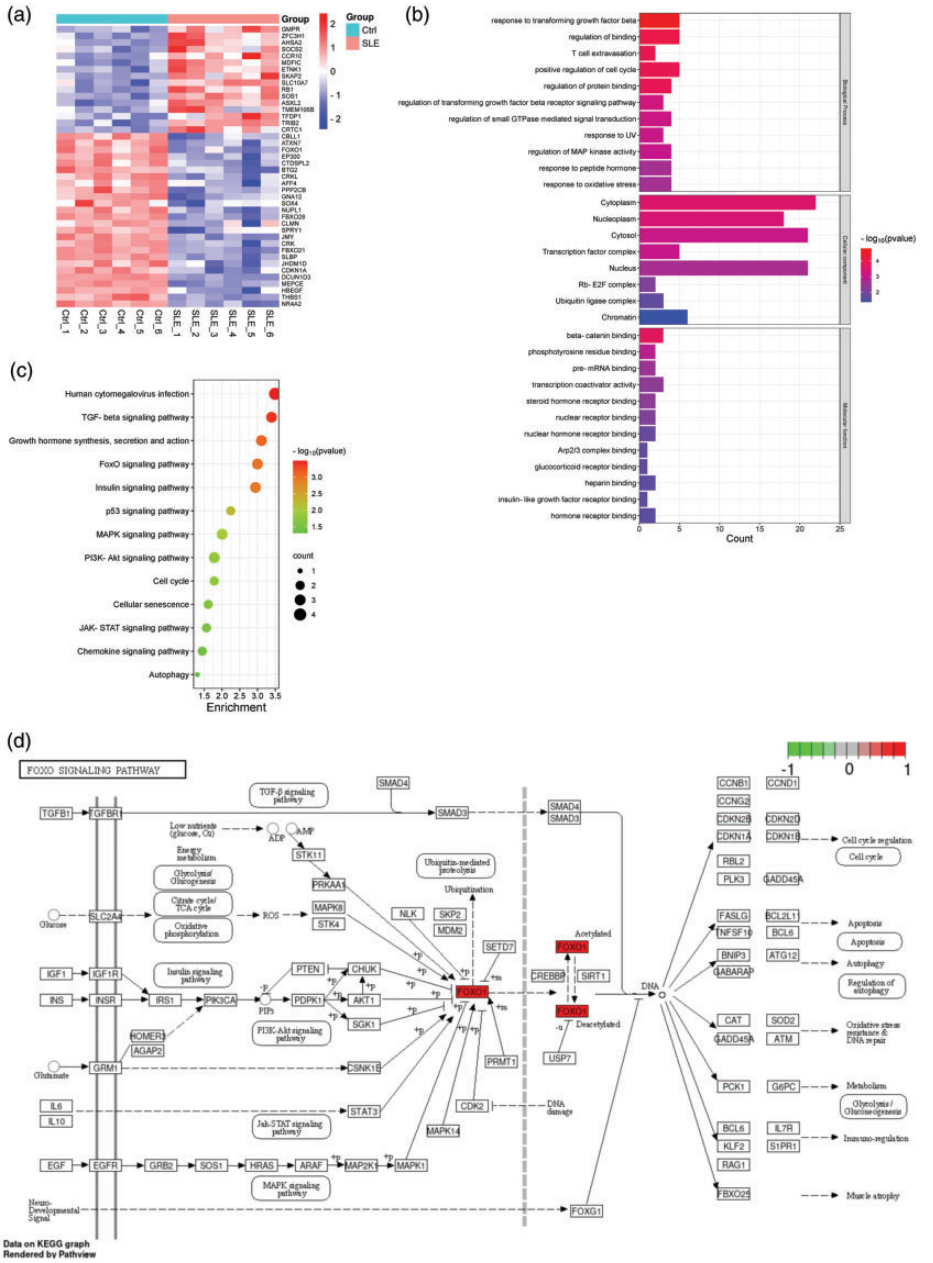

Figure 2. Pathway analysis of target genes of miR-132-3p differentially expressed in $CD4^+$ T cells in patients with systemic lupus erythematosus (SLE). (a) Heatmap of differentially expressed target genes of miR-132-3p in $CD4^+$ T cells in patients with SLE (n = 6) and healthy controls (Ctrl, n = 6). Red indicates up-regulated and blue indicates down-regulated target mRNAs. (b) Gene Ontology analysis of down-regulated target mRNAs of miR-132-3p in $CD4^+$ T cells in patients with SLE, comprising biological process, cellular component, and molecular function. (c) Kyoto Encyclopedia of Genes and Genomes pathway analysis of down-regulated target mRNAs of miR-132-3p in $CD4^+$ T cells in patients with SLE. Spot size indicates number of down-regulated target genes; spot color represents *P* value and (d) FOXO signaling pathway analysis using the Database for Annotation, Visualization, and Integrated Discovery (DAVID) tool.

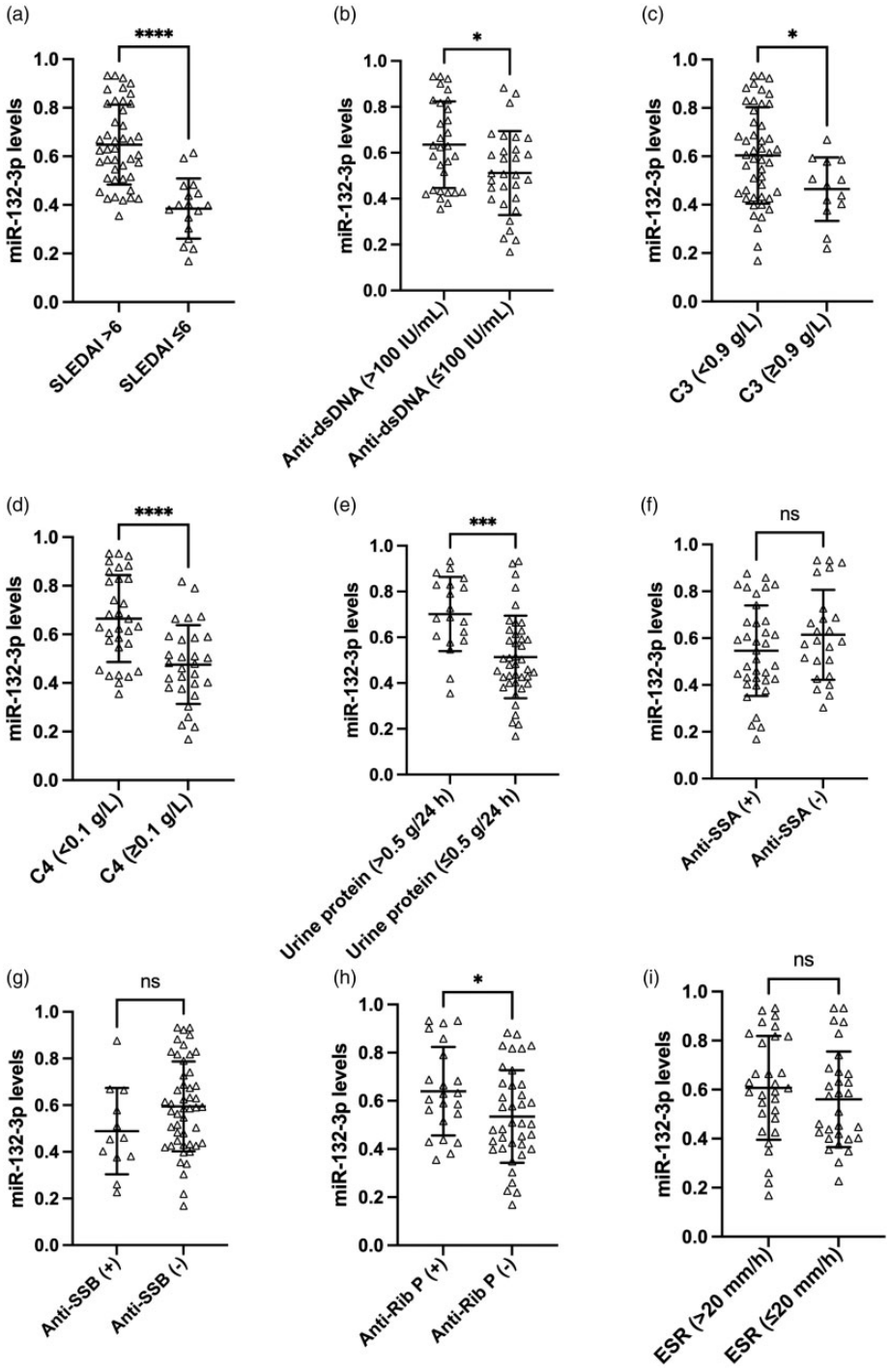

Figure 3. Relative expression levels of miR-132-3p in $CD4^+$ T cells in patients with systemic lupus erythematosus (SLE) with different clinical and laboratory indices. Expression levels of miR-132-3p in $CD4^+$ T cells in patients with SLE in relation to (a) Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) Continued.

immune cells and $CD4^+$ T cells.[16,17] Up-regulated miR-132 has also been implicated in Th17 differentiation, enhancing the function of Th17 cells with potential tumor-promoting effects.[18] The current study demonstrated up-regulation of miR-132-3p levels in peripheral blood $CD4^+$ T cells in patients with SLE, suggesting its potential involvement in $CD4^+$ T cell dysfunction during SLE development.

We investigated the molecular mechanisms influenced by miR-132-3p in relation to $CD4^+$ T cell dysfunction in lupus by bioinformatics analyses to predict its target genes and associated pathways. The FOXO signaling pathway was identified as a potential target pathway for miR-132-3p. FOXO transcription factors, including FOXO1, are critical regulators of immune homeostasis and play pivotal roles in T cell development and function.[19,20] Several studies have implicated FOXO1 in autoimmune diseases, including SLE. Kraus et al. demonstrated an important role of FOXO1 signaling in regulating auto-reactive $CD4^+$ T cells in central nervous system autoimmunity through suppressing encephalitogenic effector T (Teff) cells and shifting the Teff/Treg balance.[21] Another study found that long non-coding RNA-GM directly targeted FOXO1 and promoted its phosphorylation, thus relieving the interleukin-23 receptor from FOXO1-mediated transcriptional inhibition and facilitating the development of Th17 cells.[22] A recent study also showed that FOXO1 inhibited the Th17 program *in vitro* by introducing a specific FOXO1 inhibitor or phosphoinositide 3-kinase/Akt pathway inhibitors acting upstream of FOXO1 in naive $CD4^+$ T cells.[23] FOXO1 was also significantly decreased in PBMCs in patients with SLE.[24] Overall, these studies indicate that dysregulation of FOXO1 was associated with aberrant T cell activation and function, particularly involving Th17/Treg cells, which are crucial in the development of SLE, but the regulatory mechanism of FOXO1 expression remains unclear. The current findings suggest that miR-132-3p may target *FOXO1*, potentially contributing to immune dysregulation in SLE; however, further studies are needed to verify the interactions between miR-132-3p and *FOXO1*, especially regarding their impact on the Th17/Treg imbalance in SLE development.

In light of the efforts to identify miRNA biomarkers for SLE,[25–27] we further analyzed the associations between miR-132-3p expression and clinical and laboratory indices to explore its feasibility as a potential biomarker. Notably, we observed significant associations between miR-132-3p expression and SLEDAI score, anti-dsDNA levels, C3 and C4 levels, and anti-ribosomal P. These results suggest that miR-132-3p may serve as a potential biomarker for disease severity, although the results need to be validated in larger sample sizes and using additional disease activity assessment tools. Elevated miR-132-3p levels might indicate increased renal damage and neuropsychiatric symptoms, reflected by the correlations with anti-dsDNA antibodies, serum complement

Figure 3. Continued.
(>6 and ≤ 6), (b) anti-dsDNA levels (>100 IU/mL and ≤ 100 IU/mL), (c) C3 levels (<0.9 g/L and ≥ 0.9 g/L), (d) C4 levels (<0.1 g/L and ≥ 0.1 g/L), and (e) urine protein (>0.5 g/24 hours and ≤ 0.5 g/24 hours). Expression levels of miR-132-3p in $CD4^+$ T cells in patients with SLE in relation to (f) positive and negative anti-SSA, (g) positive and negative anti-SSB, and (h) positive and negative anti-ribosomal P (Rib P). (i) Expression levels of miR-132-3p in $CD4^+$ T cells in patients with SLE in relation to erythrocyte sedimentation rate (ESR) (>20 mm/hour and ≤ 20 mm/hour). *$P < 0.05$; ***$P < 0.001$; ****$P < 0.0001$; ns, not significant.

C3 and C4 levels,[28] and the presence of anti-ribosomal P antibody, which may indicate a higher risk of neuropsychiatric involvement in patients with SLE.[29] Nevertheless, further studies, including mediation analysis with larger sample sizes, are needed to verify if miR-132-3p is associated with renal damage and neuropsychiatric symptoms independently or via anti-dsDNA antibodies, C3 and C4 levels, and anti-ribosomal P. We also identified an association between miR-132-3p expression and high 24-hour urinary protein, further indicating its potential role in renal involvement in SLE. Notably however, only 10 LN cases in this study were confirmed by renal biopsy, and the remaining cases were defined solely by proteinuria (>0.5 g/24 hours), and we could therefore not compare patients with SLE with and without biopsy-confirmed LN. Nevertheless, our findings aligned with a previous study that reported increased serum miR-132 levels in patients with biopsy-confirmed LN,[8] further supporting our results. Overall, these findings suggest that miR-132-3p levels could serve as an indicator of disease severity and may potentially play a role in organ damage; however, further validation in larger samples is necessary to confirm these findings.

The present study had several limitations. The relatively small sample size may restrict the generalizability of the results and the statistical power needed to establish the efficacy of miR-132-3p as a biomarker. Additionally, this was a preliminary study, and additional functional verification is needed regarding the role of *FOXO1* as a direct target of miR-132-3p in lupus $CD4^+$ T cells and the mechanism by which it regulates lupus $CD4^+$ T cells, particularly regarding Th17/Treg imbalance.

Conclusions

miR-132-3p may contribute to $CD4^+$ T cell dysfunction in SLE by targeting *FOXO1* and could potentially be used to assess disease severity. Further studies in a larger sample of patients are planned to confirm the feasibility of miR-132-3p as a potential biomarker and to verify the interactions between miR-132-3p and *FOXO1* in $CD4^+$ T cell dysregulation, particularly concerning their impact on Th17/Treg imbalance in SLE development.

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Author contributions

XZ designed the study. HQ and SC participated in data collection and drafted the manuscript. XL performed statistical analyses. JL and HW critically revised the manuscript. All authors read and approved the final manuscript.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

Declaration of conflicting interests

The authors declared no potential conflicts of interest.

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