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ORIGINAL RESEARCH

The Role of miR-30d-5p in Neutrophil-Derived Exosomes in Promoting Systemic Lupus Erythematosus

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Background: In this study, we investigated the role of neutrophil-derived exosomal miR-30d-5p in systemic lupus erythematosus (SLE).

Methods: We extracted exosomes from the neutrophils collected from SLE patients and healthy donors and analyzed the relative level of miR-30d-5p. The exosomes were characterized by transmission electron microscopy (TEM) and nanoparticle tracking analysis (NTA). We mimicked SLE using MRL/lpr mice and treated the mice with exosomes and miR-30d-5p inhibitors. The RNA level of miR-30d-5p in serum of mice was analyzed by qPCR. The images of spleen were captured to evaluate splenomegaly. The serum levels of anti-nuclear antibodies (ANAs), total IgG, total IgM, and anti-dsDNA IgG were measured by ELISA. The kidney injury was analyzed by albumin level, haematoxylin and eosin (HE) staining, active index, and chronic index. The T cell differentiation and B cell activation were detected by flow cytometry. For T follicular helper (TfH) cell analysis, cells were stained with anti-CXCR5 and anti-PD-1 antibodies. Levels of inflammatory cytokines in serum were measured by ELISA.

Results: The exosomes from SLE patients showed significant higher level of miR-30d-5p. Treatment with neutrophil-exosomes enhanced the degree of splenomegaly in MRL/lpr mice and production of anti-nuclear antibodies (ANAs), total IgG, total IgM, and anti-dsDNA IgG, which was repressed by miR-30d-5p inhibitor. Compared with MRL/lpr mice, mice treated with neutrophil-derive exosomes exhibited a notable increase of proteinuria and infiltration of lymphocytes in kidney, whereas inhibition of miR-30d-5p reduced this elevation. Exosome treatment elevated the number of IL17+ Th17 cells, CXCR5+PD-1+ TfH cells, reduced the portion of Foxp3+ Treg cells, and elevated B cells, and inhibition of miR-30d-5p reversed these effects.

Conclusion: The neutrophils from SLE exhibited higher level of miR-30d-5p, and inhibition of miR-30d-5p could suppress the T cell and B cell activation, reduce inflammatory cytokine and antibodies production, and alleviate the lupus nephritis during SLE.

Keywords: systemic lupus erythematosus, neutrophil, exosomes, miR-30d-5p, T cell, B cell

Introduction

Systemic lupus erythematosus (SLE) is a complex, chronic autoimmune disorder characterized by its ability to affect multiple organs within the body. The spectrum of clinical presentations in SLE is broad, ranging from relatively benign skin rashes to severe, potentially life-threatening kidney inflammation.[1] Despite this variability, individuals with SLE exhibit shared pathological hallmarks, including the expansion of pathogenic T cells and heightened autoimmune reactions. Hyperactive B cells are central to the pathogenesis of SLE, as they contribute to the disease through the production of a plethora of autoantibodies, aberrant antigen presentation, and the secretion of diverse cytokines.[2] A subset of T cells known as T follicular helper (TfH) cells plays a crucial role in supporting B cell development, germinal center (GC) formation, and the production of antibodies. Notably, an overexpansion of Tfh cells is recognized as a significant contributor to the dysregulated autoimmune responses observed in SLE.[3,4] Studies have consistently reported abnormalities in the frequency and function of Tfh cells in both lupus patients and relevant mouse models,[5–7] highlighting the importance of these cells in the pathogenesis of the disease.

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Neutrophil-derived exosomes play a significant role in the pathogenesis of systemic lupus erythematosus (SLE). They contribute to the disease progression through several mechanisms. These exosomes act as a source of autoantigens, leading to the activation of lymphocytes and the release of proinflammatory cytokines, which in turn form immune complexes.[8] They also impact the activation, differentiation, and apoptosis of cells, thereby regulating the inflammatory process.[8] Recent studies in both SLE patients and experimental murine models (eg, MRL/lpr mice) have demonstrated that neutrophil-derived exosomes exacerbate autoimmune responses by enhancing Tfh cell differentiation and promoting autoantibody production.[9,10] Exosomes can deliver signaling molecules such as proteins, RNA, and DNA recipient cells.[11] In comparison to stem cell therapy, exosomes can reduce immune-mediated rejection reactions and malignant transformation.[12,13] Noteworthy, microRNA (miRNA) in exosomes can regulate the expression of target genes in recipient cells and affect the pathogenesis of SLE.[14,15] For example, miR-146a is highly expressed in urine exosomes of SLE patients, which may regulate inflammation by inhibiting TRAF6 and IRAK1 negatively.[16] Among these miRNAs, miR-30d-5p has been implicated in immune regulation and inflammatory diseases, though its role in neutrophil-derived exosomes during SLE remains unexplored.

In this study, we focused on miR-30d-5p as a key mediator in neutrophil-derived exosomes and evaluated its specific contribution to SLE pathogenesis using both clinical samples and the MRL/lpr murine model. We aimed to determine how exosomal miR-30d-5p modulates T cell differentiation, B cell activation, and lupus nephritis progression.

Materials and Methods

Ethical Statement

This study was approved by the ethics committee of Ningbo Medical Center Lihuili Hospital (Approval No. Nb-2023-09465, China). Informed consent was obtained from all study participants. All the methods were carried out in accordance with the Declaration of Helsinki.

The animal experiments in this study were approved prior to commencement by the Ningbo Medical Center Lihuili Hospital (Approval No. ACUC-2023-0847, China). All procedures was carried out in accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the Chinese Academy of Sciences.

Patient Sample Collection and Neutrophil Isolation

A cohort of 10 patients with systemic lupus erythematosus (SLE), diagnosed according to the 2012 SLICC criteria, and 10 age- and sex-matched healthy controls without autoimmune disease history or prior immunomodulatory treatment were enrolled in this study. The mean age of participants was approximately 30 years (range: 25–45 years), and females accounted for 90% (9/10) of both groups, consistent with the known epidemiology of SLE. SLE disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Among the patients, 3 had mild disease activity (SLEDAI 5–9), 3 had moderate activity (SLEDAI 10–14), and 4 had severe activity (SLEDAI ≥15). Regarding treatment regimens, 80% of patients were receiving hydroxychloroquine (HCQ) as baseline therapy. Glucocorticoids (prednisone 10–30 mg/day) were administered to patients with moderate to severe disease. Immunosuppressive agents including azathioprine, mycophenolate mofetil (MMF), and cyclophosphamide were used based on clinical indications. One patient with refractory disease received the B-cell-targeting biologic belimumab. Detailed demographic and clinical characteristics are summarized in Supplementary Table S1.

Peripheral blood (10 mL per donor) was collected into EDTA tubes. Neutrophils were isolated using a modified Ficoll-based density gradient protocol. Briefly, erythrocytes were lysed with erythrocyte lysis buffer (Beyotime, China) for 10 minutes at 4°C, followed by layering the remaining cells over Ficoll-Paque PLUS (Cytiva) and centrifugation at 400×g for 30 minutes. Neutrophils were harvested from the granulocyte layer, washed twice with PBS, and their purity (>98%) was confirmed by flow cytometry using CD16 and CD11b antibodies (BioLegend), well-established markers for mature neutrophils.[17]

Isolation and Identification of Exosomes

The isolated neutrophils were cultured in RPMI 1640 supplemented with 100 U/mL penicillin, 100 μg/mL streptomycin, and 20% autologous serum (from SLE patients or healthy controls) to mimic the inflammatory microenvironment, as serum components enhance neutrophil activation and exosome release.[18] Exosomes were characterized by: TEM showed cup-shaped morphology; NTA revealed a mean size of 98.5 ± 12.3 nm; Western blot demonstrated positivity for CD9, CD63, CD81, TSG101 and negativity for Calnexin; flow cytometry indicated that CD63+ particles accounted for 82.3 ± 5.6% of total vesicles. Exosome dosage (50 μg/kg) corresponded to approximately 2.5×10^9 particles per injection, quantified by NTA.

Mouse SLE Model

Seven-week-old female MRL/lpr mice were procured from the Shanghai Laboratory Animal Center of the Chinese Academy of Sciences and maintained under specific pathogen-free conditions. Intraperitoneal (i.p.) injection was chosen for exosome delivery due to its proven efficacy in systemic distribution to lymphoid organs in lupus models.[19] In the treatment phase, these mice received intraperitoneal injections of exosomes derived from neutrophils every two days over a 10-week period. At the onset of the treatment, the mice were randomly assigned to one of three groups (n = 6/group): Control group: 50 μL PBS; Exosome-treated group: 50 μg/kg exosomes in PBS; Exosome + miR - 30d - 5p inhibitor group: Exosomes (50 μg/kg) + 15 nmol/20g miR - 30d - 5p inhibitor. Proteinuria levels were monitored biweekly. At 22 weeks of age, mice were euthanized via CO2 asphyxiation followed by cervical dislocation to preserve RNA/protein integrity; tissues were harvested immediately for analysis.

Histological Analyses

Thin sections were meticulously cut from kidney tissue that had been embedded in paraffin and then stained using the classic haematoxylin and eosin (HE) protocol. The active and chronic indices were independently scored by two blinded renal pathologists using validated criteria for lupus nephritis. Active Index (0–24) assessed acute inflammatory lesions: glomerular hypercellularity, neutrophil infiltration, fibrinoid necrosis, cellular crescents, hyaline thrombi, interstitial inflammation, tubulitis, and vascular inflammation.

Chronic Index (0–12) evaluated chronic damage: glomerulosclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis. Each parameter was graded 0–3 (0: absent; 1: <25% involvement; 2: 25–50%; 3: >50%).

RNA Isolation and RT–qPCR

Total RNA was meticulously extracted from both exosomes and blood samples using a NanoDrop spectrophotometer (model ND-2000, Thermo, USA) to ensure accurate quantification. Complementary DNA (cDNA) was synthesized through reverse transcription with the aid of the PrimeScript RT reagent Kit, which includes gDNA Eraser, from Takara (Japan), strictly following the manufacturer's guidelines. This process effectively removed any genomic DNA contamination. MicroRNAs (miRs) were selectively reverse-transcribed using specific miRNA primers, along with U6 as a reference. The relative gene expression levels were then determined by employing the SYBR Green Premix, also from Takara (Japan), which provided a sensitive and reliable measurement of the target genes' expression.

Western Blotting Assay

Total protein extracts were obtained from neutrophils and exosomes by employing RIPA lysis buffer. These proteins were then separated via electrophoresis and transferred onto PVDF membranes from Millipore. The membranes were subsequently incubated with primary antibodies targeting CD66, CD81, TSG101, and Calnexin, which was carried out overnight at 4°C. Afterward, the membranes were treated with HRP-conjugated secondary antibodies, and the protein bands were made visible by applying the ECL plus reagent from ThermoF (USA). β-actin served as an internal control to ensure the accuracy and consistency of the protein loading.

Enzyme-Linked Immunosorbent Assay

Mouse serum samples were gathered for the detection of autoantibodies. The presence of anti-double-stranded DNA (anti-dsDNA) antibodies in the serum was identified employing established methodologies. In essence, 96-well high-binding microplates were layered with calf thymus dsDNA sourced from Sigma (St. Louis, MO, USA) and left to incubate at 4°C for an entire night. Subsequently, diluted serum samples were introduced and incubated. Following this, HRP-conjugated goat anti-mouse IgG antibodies from Invitrogen (San Diego, CA, USA) were added and allowed to incubate. Serum from 5-month-old female MRL/lpr mice served as a reference standard. For quantifying total IgG and IgM levels, we adhered to the manufacturer's protocols using the mouse IgG ELISA Kit and anti-IgM ELISA Kit, both procured from Sigma (St. Louis, MO, USA). The presence of antinuclear antibodies (ANA) was assessed with the mouse anti-ANA Ig ELISA Kit, also from Sigma (St. Louis, MO, USA). Cytokine levels in the serum were determined using a suite of ELISA kits designed to detect mouse TNF-α, IFN-γ, IL-10, IL-12, IL-17a, and MCP-1, all of which were sourced from Thermo and used in accordance with the provided user instructions.

Flow Cytometry

From blood samples, single-cell suspensions were extracted for flow cytometry analysis, utilizing the FACSCanto II system from BD Biosciences. The subsequent data analysis was conducted with FlowJo software, version 10.7. The process involved incubating cells with fluorochrome-tagged antibodies at a cool 4°C for 30 minutes, ensuring they were shielded from light to prevent any interference with the staining. For the detection of intracellular cytokines, cells were exposed to a cocktail of PMA and ionomycin, supplemented with GolgiPlug (BD Pharmingen, catalog number 550583), and incubated at a physiological 37°C with 5% CO2 for a duration of 6 hours. The antibodies employed in this study included a range of specific markers for distinct immune cell populations: FITC-labeled anti-mouse CD4 (Biolegend), PerCP-Cy5.5-labeled anti-mouse IL-17 (Biolegend), PE-Cy7-labeled anti-mouse CXCR5 (Biolegend), APC-labeled anti-mouse PO-1 (Biolegend), PerCP-Cy5.5-labeled anti-mouse Foxp3 (Biolegend), APC-labeled anti-mouse B220 (Biolegend), and PE-labeled anti-mouse CD19 (Biolegend). These antibodies were crucial for the precise identification and characterization of various immune cell subsets.

Statistical Analysis

The graphical data is depicted as average values, accompanied by their respective standard errors. For multi-group comparisons (eg, cytokine levels across treatment groups), one-way ANOVA with Tukey's post-hoc test was applied. Comparisons between SLE patients and healthy controls were analyzed using unpaired Student's t-tests. Data normality was verified by Shapiro–Wilk test prior to analysis. All statistical analyses were performed using GraphPad Prism software (version 5.0), with statistical significance defined as $p < 0.05$.

Results

The SLE-Derived Exosomes Exhibit Higher Level of miR-30d-5p

We collected peripheral blood from SLE patients and healthy donors to isolate neutrophil-derived exosomes. NTA quantification revealed a 1.8-fold increase in exosome yield from SLE neutrophils compared to Normal controls ($p < 0.01$; Supplementary Figure S1A), likely due to enhanced neutrophil activation in SLE. As shown in Figure 1A, SLE-derived neutrophil exosomes exhibited higher CD66b protein levels. Both groups showed similar bilayer spherical structures (Figure 1B), with a mean particle size of 150 nm (Figure 1C). Western blot confirmed exosomal markers (TSG101, CD81, CD9, and CD63) and absence of Calnexin (Figure 1D). qPCR confirmed that miR-30d-5p was predominantly enriched in neutrophil-derived exosomes (vs whole neutrophil lysates; Supplementary Figure S1B). SLE exosomes showed significantly higher miR-30d-5p levels (***$P < 0.001$; Figure 1E).

Neutrophil-Derived Exosomes and miR-30d-5p Regulate SLE

To determine the effects of neutrophil-derived exosomal miR-30d-5p on SLE, we established a MRL/lpr mouse model and performed exosome treatment with or without miR-30d-5p inhibitor. The results from qPCR indicated that treatment

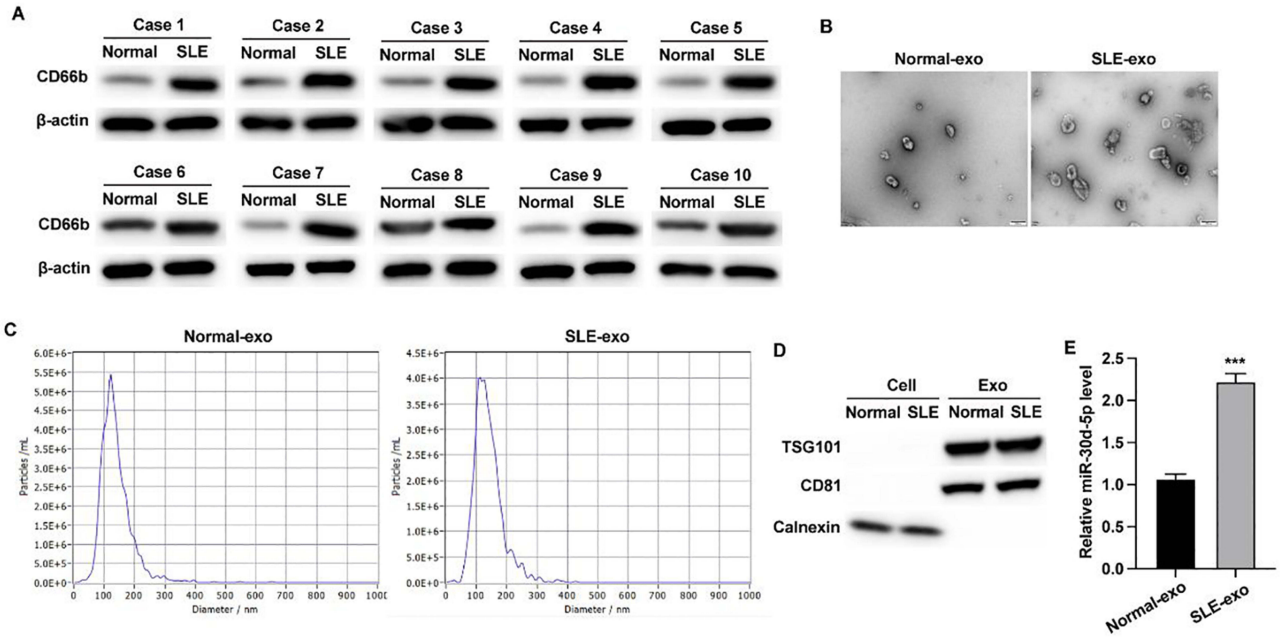

Figure 1 The SLE-derived exosomes exhibit higher level of miR-30d-5p. (**A**) The level of miR30d-5p in neutrophil-derived exosomes from SLE patients (n=10) and healthy donors (n=10). (**B**) TEM images of exosomes from neutrophil-derived exosomes from SLE patients (SLE-exo) and healthy donors (normal-exo). Scale detail: 200nm. (**C**) The diameter of exosomes measured by NTA. (**D**) The protein expression of exosome biomarkers in exosomes was measured by Western blot. (**E**) RNA level of miR-30d-5p in exosomes was detected by qPCR. ***P < 0.001 vs Normal-exo group.

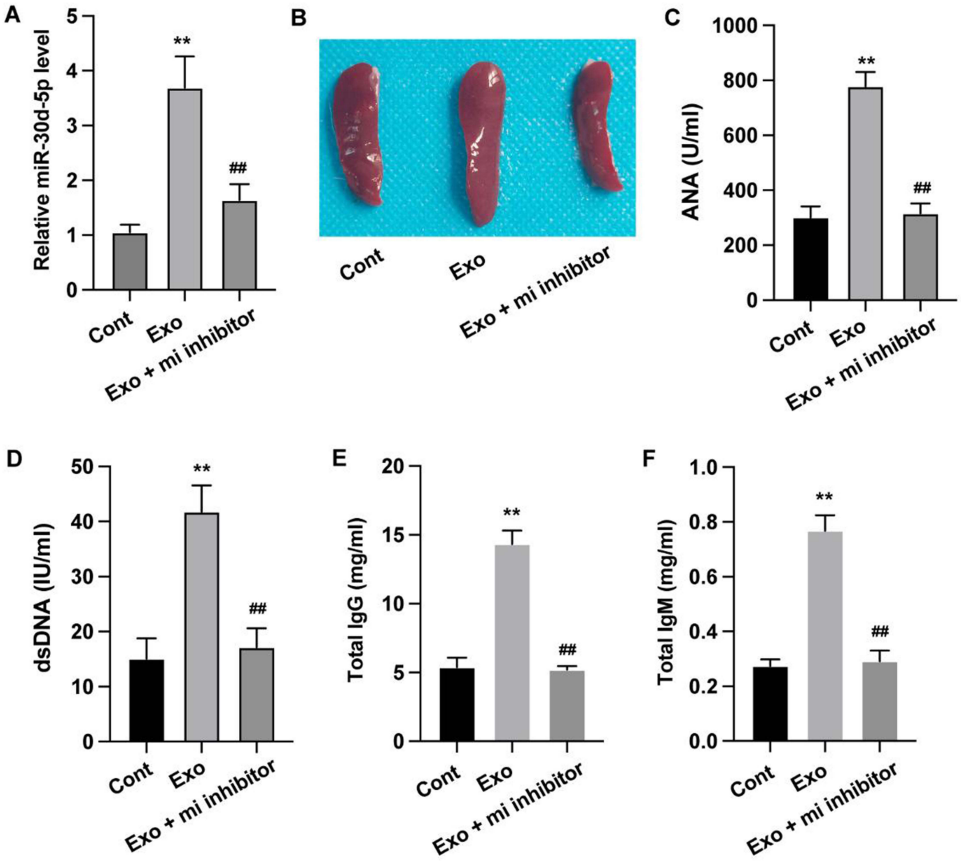

Figure 2 Neutrophil-derived exosomes and miR-30d-5p regulate SLE. (**A**) The level of miR-30d-5p in serum of MRL/lpr mice after indicated treatment. (**B**) The representative images of spleen. (**C**) Serum levels of ANA (**D**) anti-dsDNA. (**E**) Total IgG. (**F**) Total IgM. (n = 8). **P < 0.01 vs Control group; ##P < 0.01 vs Exo group.

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with miR-30d-5p inhibitor notably suppressed the elevated level of miR-30d-5p that caused by treatment with neutrophil-derived exosomes from SLE (Figure 2A). Moreover, treatment with neutrophil-exosomes enhanced the degree of splenomegaly in MRL/lpr mice, whereas inhibition of miR-30d-5p alleviated this phenomenon (Figure 2B). The production of anti-nuclear antibodies (ANAs), total IgG, total IgM, and anti-dsDNA IgG were significantly enhanced by SLE neutrophil-exosomes, which was repressed by miR-30d-5p inhibitor (Figure 2C-F).

Neutrophil-Derived Exosomal miR-30d-5p Regulates Lupus Nephritis

Compared with MRL/lpr mice, mice treated with neutrophil-derive exosomes exhibited a notable increase of proteinuria (Figure 3A), whereas inhibition of miR-30d-5p reduced this elevation. The results from HE staining showed a significant elevation in the infiltration of lymphocytes in the kidneys of MRL/lpr mice that treated with neutrophil-derived exosomes (Figure 3B), as well as increased active index (Figure 3C) and chronic index (Figure 3D). Treatment with miR-30d-5p inhibitor alleviated the pathological changes in kidney.

Neutrophil-Derived Exosomal miR-30d-5p Modulates Immune Response During SLE

Subsequently, we analyzed the T cell and B cell activation during SLE. The results from flow cytometry demonstrated that exosome treatment elevated the number of IL17+ Th17 cells (Figure 4A), CXCR5+PD-1+ TfH cells (Figure 4B), reduced the portion of Foxp3+ Treg cells (Figure 4C), indicating the activated adaptive immune response. Moreover, neutrophil-derived exosomes also elevated B cell portion in MRL/lpr mice (Figure 4D). Nevertheless, the inhibition of miR-30d-5p repressed the activation of Th17, TfH and B cells, as well as promoted Treg activation. Moreover, the serum levels of inflammatory cytokines and chemokines, including TNF-α, IFN-γ, MCP-1, IL-10, IL-2, and IL-17A were significantly elevated in exosome-treated MRL/lpr mice compared with the untreated group (Figure 5), and inhibition of miR-30d-5p reversed this elevation.

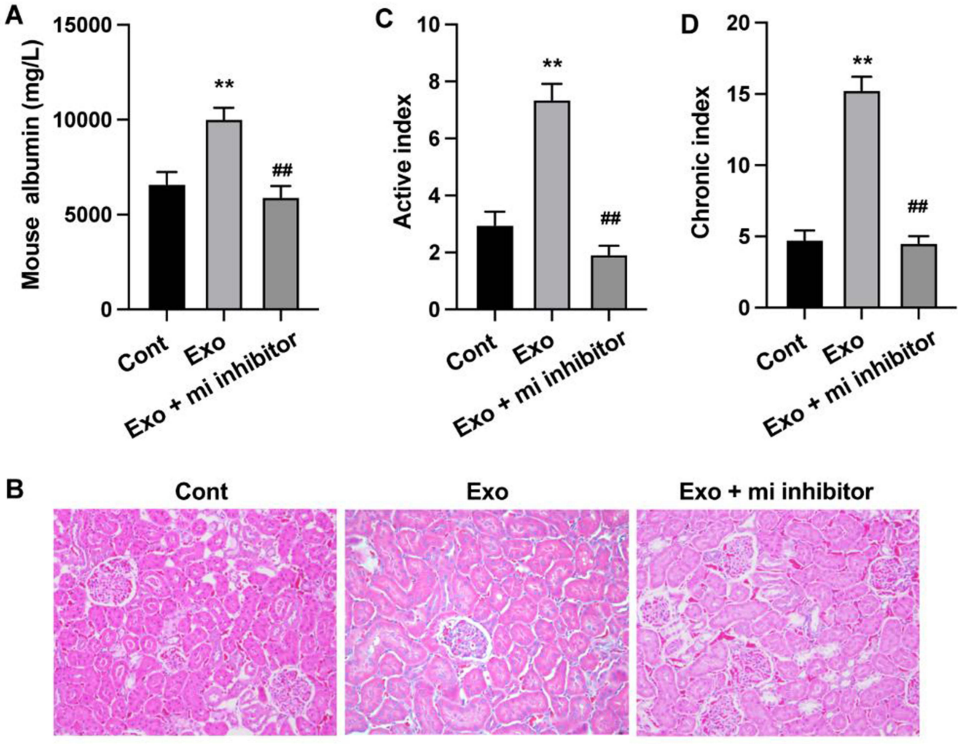

Figure 3 Neutrophil-derived exosomal miR-30d-5p regulates lupus nephritis. (**A**) Proteinuria was determined by ELISA. (**B**) HE staining of kidney tissues. (**C** and **D**) The active index (**C**) and chronic index (**D**) was analyzed from the HE images. **P < 0.01 vs Control group; ##P < 0.01 vs Exo group.

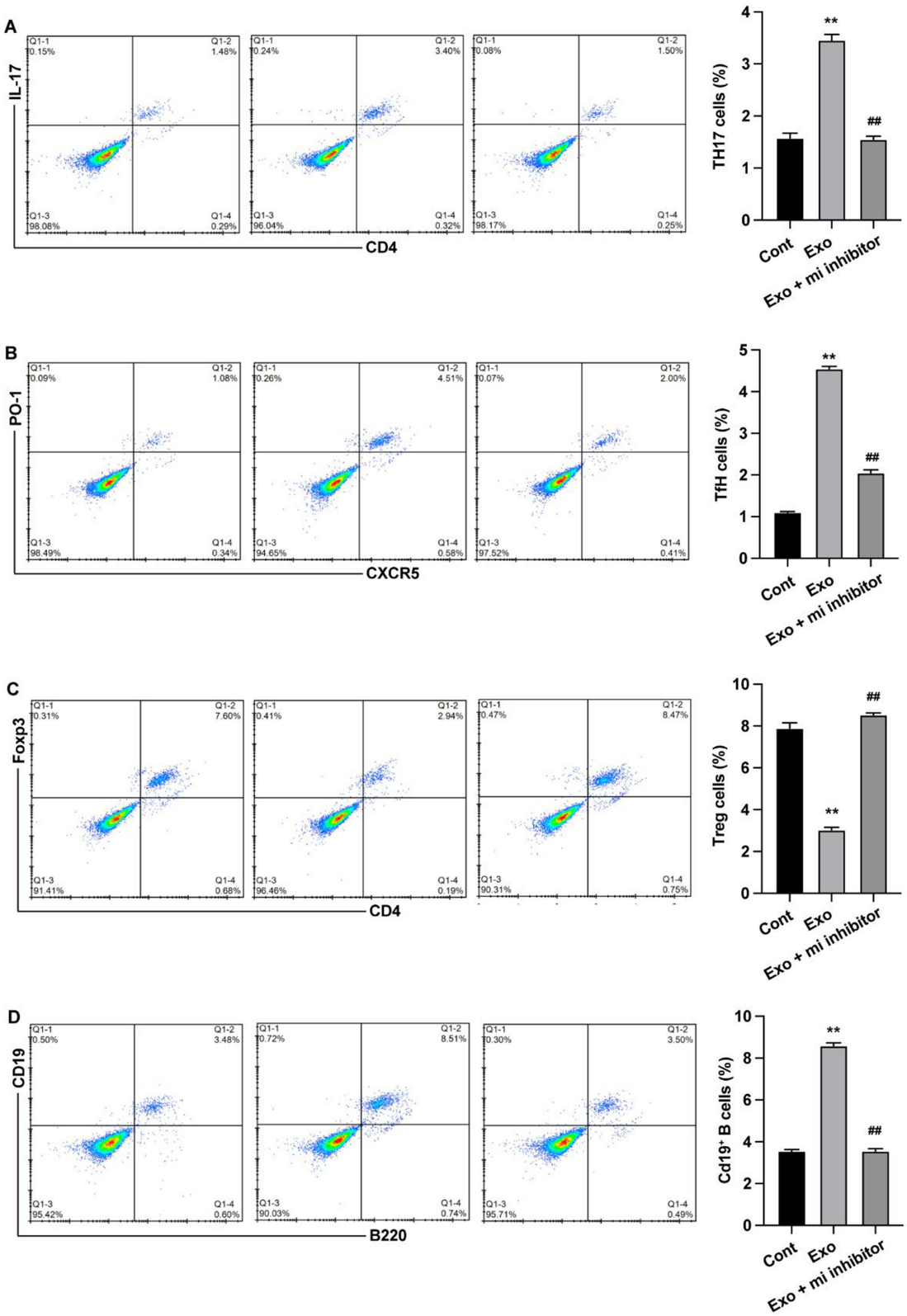

Figure 4 Neutrophil-derived exosomal miR-30d-5p modulates T cell and B cell activation during SLE. The portion of IL17+ Th17 cells (**A**), CXCR5+PD-1+ TfH cells (**B**), Foxp3+ Treg cells (**C**) and B220+CD19+ B cells were detected by flow cytometry (**D**). **P < 0.01 vs Control group; ##P < 0.01 vs Exo group.

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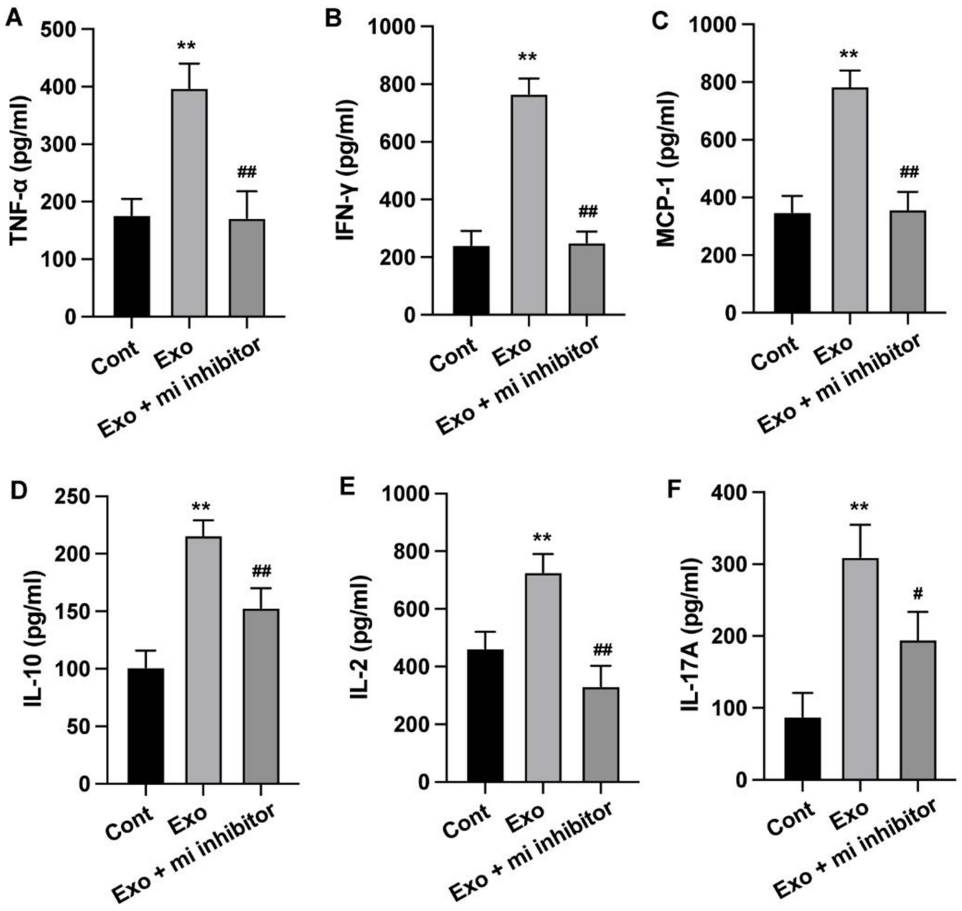

Figure 5 Neutrophil-derived exosomal miR-30d-5p modulates Inflammatory cytokines production during SLE. The serum levels of TNF-α (**A**), IFN-γ (**B**), MCP-1 (**C**), IL-10 (**D**), IL-2 (**E**), and IL-17A (**F**) were measured by ELISA. **P < 0.01 vs Control group; ##P < 0.01, #P < 0.05 vs Control group.

Discussion

Exosomes from SLE patients have been shown to have a higher number and express more surface proteins than those from healthy individuals, which can activate immune cells such as lymphocytes, monocytes, and neutrophils, increasing their expression of IFNR1 and BLyS, and keeping these cells in a heightened activation state. This can create a vicious cycle that accelerates disease progression. Additionally, the presence of exosomes in the plasma of SLE patients may lead to thrombosis and increase cardiovascular risk. The composition of exosomes in SLE also shows abnormal expression of proteins, which can significantly influence the disease's pathogenesis. Furthermore, exosomes have been considered as potential biomarkers and therapeutic targets in SLE, given their ability to transport various molecules and their potential use in drug delivery.[20] In current study, we revealed that neutrophils-derived exosomes extracted from patients with SLE exhibited notable higher level of miR-30d-5p compared with that from healthy donors.

Previous studies have indicated the involvement of miR-30d-5p in multiples diseases and pathological processes, such as cancers, diabetes, acute myocardial infarction, and lung injury.[21–23] For instance, in cholangiocarcinoma, miR-30d-5p is often overexpressed and has been suggested as a potential biomarker due to its higher specificity and sensitivity in distinguishing malignant from benign biliary tract diseases. In gallbladder carcinoma, miR-30d-5p is typically under-expressed, and its decreased expression correlates with reduced patient survival rates. It targets lactate dehydrogenase A (LDHA) to suppress glycolysis in malignant tumors, thereby inhibiting cancer development.[24] Besides, it has been reported that exosomal miR-30d-5p from polymorphonuclear neutrophils contributed to sepsis-related acute kidney injury by inducing M1 macrophage polarization and priming macrophage pyroptosis through activating NF-κB signaling.[25,26] In the context of SLE, we propose that exosomal miR-30d-5p may similarly target immunoregulatory

genes in recipient T and B cells. For instance, miR-30d-5p is predicted to bind the 3'UTR of SOCS1 (a JAK-STAT inhibitor) and Tsc1 (an mTORC1 suppressor), potentially amplifying Th17/Tfh differentiation while impairing Treg function—a mechanism consistent with our observed Th17/Tfh expansion and Treg reduction in exosome-treated mice.

Our therapeutic intervention with miR-30d-5p inhibitors highlights its translational relevance. The attenuation of splenomegaly, autoantibody production, and renal pathology aligns with the clinical efficacy of BAFF inhibitors (eg, belimumab), suggesting miR-30d-5p blockade could complement existing biologics. Notably, neutrophil exosomes' natural tropism for lymphoid organs[27] positions them as both pathogenic drivers and potential drug delivery vehicles —antagomirs loaded into exosomes may achieve targeted immunosuppression.

Study limitations must be acknowledged: Mechanistic Specificity: While we demonstrate miR-30d-5p's functional impact, direct mRNA targets in lupus-relevant cells remain unvalidated. Model Constraints: MRL/lpr mice recapitulate lupus nephritis but may not fully mirror human neutrophil exosome biology. Sample Size: Our patient cohort (n=10) warrants expansion to assess miR-30d-5p's biomarker potential across SLE subtypes. Future studies should prioritize: Target Validation: CLIP-seq or CRISPR editing to identify miR-30d-5p's direct targets in T/B cells. Clinical Correlation: Correlating circulating exosomal miR-30d-5p levels with SLEDAI scores and renal pathology in larger cohorts.

Conclusion

To summarize, our current study focused on the participation of neutrophil-derived exosomes in the progression of SLE. We determined that inhibition of miR-30d-5p could suppress the T cell and B cell activation, reduce inflammatory cytokine and antibodies production, and alleviate the lupus nephritis. Our findings provided a novel target for treatment of SLE.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Dubois EL, Tuffanelli DL. Clinical manifestations of systemic lupus erythematosus. computer analysis of 520 cases. *JAMA*. 1964;190:104–111. doi:10.1001/jama.1964.03070150014003
2. Almaani S, Rovin BH. B-cell therapy in lupus nephritis: an overview. *Nephrol Dial Transplant*. 2019;34(1):22–29. doi:10.1093/ndt/gfy267
3. Chen PM, Tsokos GC. T cell abnormalities in the pathogenesis of systemic lupus erythematosus: an update. *Curr Rheumatol Rep*. 2021;23(2):12. doi:10.1007/s11926-020-00978-5
4. Mountz JD, Hsu HC, Ballesteros-Tato A. Dysregulation of T follicular helper cells in lupus. *J Immunol*. 2019;202(6):1649–1658. doi:10.4049/jimmunol.1801150
5. Dang WZ, Li H, Jiang B, et al. Therapeutic effects of artesunate on lupus-prone MRL/lpr mice are dependent on T follicular helper cell differentiation and activation of JAK2-STAT3 signaling pathway. *Phytomedicine*. 2019;62:152965. doi:10.1016/j.phymed.2019.152965
6. Huang X, Wu H, Qiu H, et al. The expression of Bcl-6 in circulating follicular helper-like T cells positively correlates with the disease activity in systemic lupus erythematosus. *Clin Immunol*. 2016;173:161–170. doi:10.1016/j.clim.2016.10.017
7. Wang L, Zhao P, Ma L, et al. Increased interleukin 21 and follicular helper T-like cells and reduced interleukin 10+ B cells in patients with new-onset systemic lupus erythematosus. *J Rheumatol*. 2014;41(9):1781–1792. doi:10.3899/jrheum.131025
8. Shen J, Zhang M, Peng M. Progress of exosome research in systemic lupus erythematosus. *Cytokine X*. 2022;4(2–3):100066. doi:10.1016/j.cytox.2022.100066
9. Frese-Schaper M, Voll RE, Frese S. Increased binding of anti-dsDNA antibodies to short oligonucleotides modified with topoisomerase I reveals a potential new enzyme function independent from DNA relaxation. *BMC Res Notes*. 2023;16(1):298. doi:10.1186/s13104-023-06592-9
10. Lindblom J, Toro-Domínguez D, Carnero-Montoro E, et al. Distinct gene dysregulation patterns herald precision medicine potentiality in systemic lupus erythematosus. *J Autoimmun*. 2023;136:103025. doi:10.1016/j.jaut.2023.103025
11. Jin J, Shi Y, Gong J, et al. Exosome secreted from adipose-derived stem cells attenuates diabetic nephropathy by promoting autophagy flux and inhibiting apoptosis in podocyte. *Stem Cell Res Ther*. 2019;10(1):95. doi:10.1186/s13287-019-1177-1
12. Bacakova L, Zarubova J, Travnickova M, et al. Stem cells: their source, potency and use in regenerative therapies with focus on adipose-derived stem cells - a review. *Biotechnol Adv*. 2018;36(4):1111–1126. doi:10.1016/j.biotechadv.2018.03.011
13. An Y, Lin S, Tan X, et al. Exosomes from adipose-derived stem cells and application to skin wound healing. *Cell Prolif*. 2021;54(3):e12993. doi:10.1111/cpr.12993
14. Chen F, Shi B, Liu W, et al. Circulating exosomal microRNAs as biomarkers of lupus nephritis. *Front Immunol*. 2023;14:1326836. doi:10.3389/fimmu.2023.1326836

15. Zhang M, Johnson-Stephenson TK, Wang W, et al. Mesenchymal stem cell-derived exosome-educated macrophages alleviate systemic lupus erythematosus by promoting efferocytosis and recruitment of IL-17(+) regulatory T cell. *Stem Cell Res Ther*. 2022;13(1):484. doi:10.1186/s13287-022-03174-7
16. Perez-Hernandez J, Martinez-Arroyo O, Ortega A, et al. Urinary exosomal miR-146a as a marker of albuminuria, activity changes and disease flares in lupus nephritis. *J Nephrol*. 2021;34(4):1157–1167. doi:10.1007/s40620-020-00832-y
17. Martinez-Sanz P, Laurent ARG, Slot E, et al. Humanized MISTRG as a preclinical in vivo model to study human neutrophil-mediated immune processes. *Front Immunol*. 2023;14:1105103. doi:10.3389/fimmu.2023.1105103
18. Tsai CY, Hsieh S-C, Liu C-W, et al. Cross-talk among polymorphonuclear neutrophils, immune, and non-immune cells via released cytokines, granule proteins, microvesicles, and neutrophil extracellular trap formation: a novel concept of biology and pathobiology for neutrophils. *Int J Mol Sci*. 2021;22(6):3119. doi:10.3390/ijms22063119
19. Ando-Matsuoka R, Ando H, Abu Lila AS, et al. I.p.-injected cationic liposomes are retained and accumulate in peritoneally disseminated tumors. *J Control Release*. 2022;341:524–532. doi:10.1016/j.jconrel.2021.12.004
20. Samavati SF, Yarani R, Kiani S, et al. Therapeutic potential of exosomes derived from mesenchymal stem cells for treatment of systemic lupus erythematosus. *J Inflam*. 2024;21(1):20. doi:10.1186/s12950-024-00381-2
21. Zhao Q, Yuan X, Zheng L, et al. miR-30d-5p: a non-coding RNA with potential diagnostic, prognostic and therapeutic applications. *Front Cell Dev Biol*. 2022;10:829435. doi:10.3389/fcell.2022.829435
22. Jia K, Shi P, Han X, et al. Diagnostic value of miR-30d-5p and miR-125b-5p in acute myocardial infarction. *Mol Med Rep*. 2016;14(1):184–194. doi:10.3892/mmr.2016.5246
23. Huang JP, Chang CC, Kuo CY, et al. Exosomal microRNAs miR-30d-5p and miR-126a-5p are associated with heart failure with preserved ejection fraction in STZ-induced type 1 diabetic rats. *Int J Mol Sci*. 2022;23(14):7514.
24. Zhao Q, Yuan X, Zheng L, Xue M. miR-30d-5p: a non-coding RNA with potential diagnostic, prognostic and therapeutic applications. *Front Cell Develop Biol*. 2022;10:829435.
25. Jiao Y, Zhang T, Zhang C, et al. Exosomal miR-30d-5p of neutrophils induces M1 macrophage polarization and primes macrophage pyroptosis in sepsis-related acute lung injury. *Crit Care*. 2021;25(1):356. doi:10.1186/s13054-021-03775-3
26. Xia W, Wu L, Lei S. Integrative analysis identified rs907091 at the miRNA binding region of the IKZF3 gene as a potential functional variant for rheumatoid arthritis. *Clin Mol Epidemiol*. 2024;1:7. doi:10.53964/cme.2024007
27. Zhang W, Han Y, Huang H, et al. CD22 blockade exacerbates neuroinflammation in Neuromyelitis optica spectrum disorder. *J Neuroinflammation*. 2024;21(1):313. doi:10.1186/s12974-024-03305-2