

Plasma Exosomal lncRNA XIST Impairs CD4⁺ T Cell Autophagy and Promotes Activation via the miR-98/RICTOR/Akt-mTOR Axis in Systemic Lupus Erythematosus

Li Wang^{1,*}, Fan Lyu^{1,*}, Jun Liang¹, Xi Chen¹, Chenghui Zheng¹, Mingyu Chu¹, Jinhua Xu^{1,2}, Lin Xie¹ 

¹Department of Dermatology, Huashan Hospital, Fudan University, Shanghai, People's Republic of China; ²Shanghai Institute of Dermatology, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Lin Xie; Jinhua Xu, Department of Dermatology, Huashan Hospital, Fudan University, Shanghai, 200040, People's Republic of China, Email xielin@fudan.edu.cn; jinhuaxu@fudan.edu.cn

Background: Systemic lupus erythematosus (SLE) is characterized by immune dysregulation driven in part by aberrant CD4⁺ T cell activation and defective autophagy. Although exosomes are increasingly recognized as mediators of immune communication, the contribution of exosomal long non-coding RNAs (lncRNAs) to T cell dysfunction in SLE remains poorly defined. This study investigated the pathogenic role and mechanism of plasma exosomal lncRNA XIST in regulating CD4⁺ T cell autophagy and activation.

Methods: Quantitative reverse transcription PCR (qRT-PCR) was used to quantify lncRNA XIST levels in plasma exosomes, while Western blotting, flow cytometry, and enzyme-linked immunosorbent assay (ELISA) were employed to assess the effects of exosomes on CD4⁺ T cell function. Gain- and loss-of-function approaches were applied to elucidate the underlying molecular mechanisms.

Results: lncRNA XIST was significantly overexpressed in SLE plasma exosomes and positively correlated with disease activity. These exosomes enhanced lncRNA XIST expression in CD4⁺ T cells from healthy controls (HCs), leading to suppressed autophagy and increased activation. Similar effects were observed with engineered HC plasma exosomes overexpressing lncRNA XIST. Conversely, silencing lncRNA XIST in SLE CD4⁺ T cells promoted autophagy and reduced activation, although these changes were reversed upon treatment with autologous plasma exosomes. Mechanistically, exosomal XIST functioned as a molecular sponge for miR-98, upregulating RICTOR and activating the Akt/mTOR signaling pathway, thereby modulating CD4⁺ T cell function.

Conclusion: Plasma exosomal lncRNA XIST impairs CD4⁺ T cell autophagy and promotes activation through the miR-98/RICTOR/Akt-mTOR axis, representing a mechanistically defined candidate biomarker and potential therapeutic target in SLE.

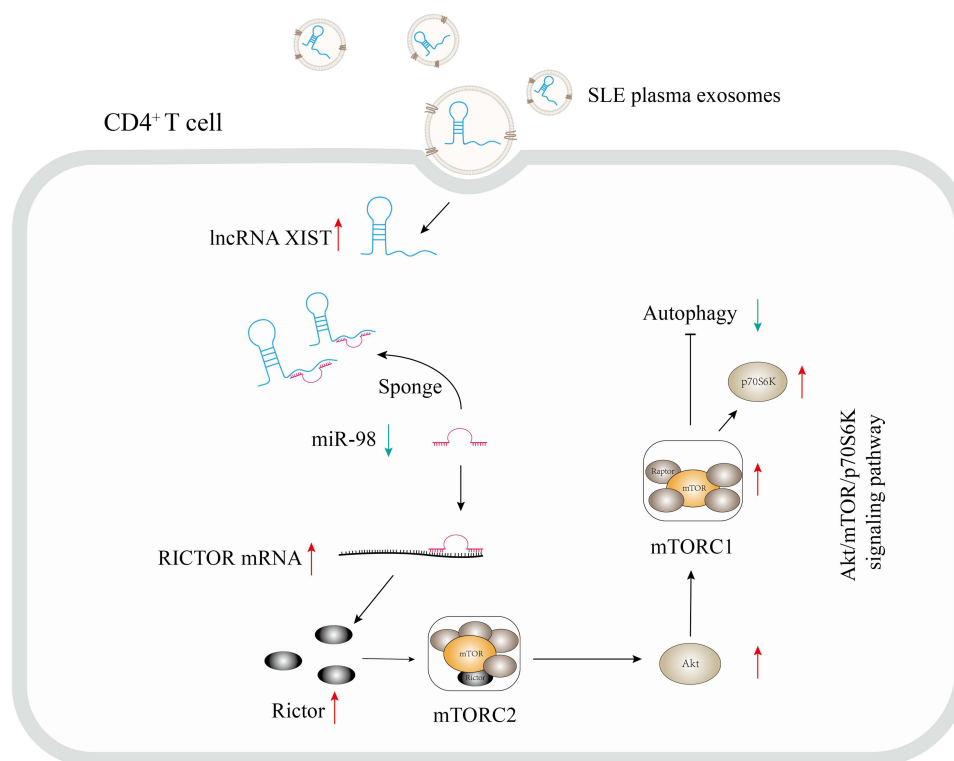
Keywords: systemic lupus erythematosus, exosome, lncRNA XIST, CD4⁺ T cells, autophagy

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by immune dysregulation and the generation of autoantibodies.¹ Although the precise cause of SLE remains unknown, accumulating evidence indicates that aberrant CD4⁺ T cell activation plays a central role in disease pathogenesis by providing excessive costimulatory signals and proinflammatory cytokines that promote B cell differentiation, autoantibody production, and tissue damage.² Importantly, dysregulated T cell activation in SLE is closely linked to altered metabolic programming and defective intracellular quality-control mechanisms, particularly autophagy.^{3,4}

Autophagy is an evolutionarily conserved process that maintains cellular homeostasis by degrading and recycling cytoplasmic components via the lysosomal pathway.⁵ In CD4⁺ T cells, autophagy influences numerous functions including metabolism, survival, development, proliferation, differentiation, and senescence.⁶ It is particularly important during T cell

Graphical Abstract



receptor activation, where it facilitates cell proliferation and cytokine production.⁷ Aberrant regulation of T cell autophagy has been linked to the pathogenesis of SLE, with several studies reporting impaired autophagic flux in immune cells from patients with SLE.^{4,8–10} However, the upstream regulatory mechanisms that couple excessive CD4⁺ T cell activation to defective autophagy in SLE remain incompletely defined.

Given its well-established role in coordinating cellular metabolism and autophagy, the mechanistic target of rapamycin (mTOR) is a serine/threonine kinase that serves as a central integrator of environmental and metabolic cues to coordinate cell growth, activation, metabolism, and autophagy.¹¹ mTOR functions as the catalytic component of two distinct complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2).^{12,13} A key function of mTORC2 is the phosphorylation and activation of Akt, a crucial step in promoting cell survival, proliferation, and growth. Akt exerts its effects by phosphorylating and inhibiting multiple downstream targets, including TSC2, an inhibitor of mTORC1.¹² mTORC1 regulates cellular biosynthesis by enhancing the production of proteins, lipids, and nucleotides, while suppressing catabolic processes such as autophagy.¹² The activation of mTORC1 drives protein synthesis primarily through phosphorylation of two key effectors: 70 kDa ribosomal protein S6 kinase (p70S6K) and eIF4E Binding Protein (4EBP).¹³ Thus, mTORC2 can indirectly stimulate p70S6K and suppress autophagy via mTORC1 activation. Through coordinated regulation of these pathways, mTOR signaling critically shapes T cell metabolic programming, activating status, and autophagic capacity, processes that are increasingly recognized as dysregulated in SLE.^{3,11}

Exosomes are nanoscale, membrane-bound extracellular vesicles that carry a wide variety of bioactive substances, including proteins, nucleic acids, lipids, and metabolites.^{14–16} By delivering nucleic acid cargo to recipient cells, exosomes can modulate gene expression and influence cellular functions. For instance, exosomes derived from human umbilical cord mesenchymal stem cells (HUCMSCs) have been shown to promote M2 macrophage polarization by transferring miR-146a-5p, which down-regulates NOTCH1 expression.¹⁷ These findings highlight the capacity of exosomes to function as potent immunoregulatory

vehicles. Nevertheless, the contribution of plasma-derived exosomes to CD4⁺ T cell dysfunction in SLE, particularly through non-coding RNA cargo, remains insufficiently explored.

Long non-coding RNAs (lncRNAs) are a class of non-coding RNAs longer than 200 nucleotides that lack protein-coding capacity.¹⁸ lncRNAs can function as competing endogenous RNAs (ceRNAs), sequestering shared microRNAs (miRNAs) and thereby regulating the expression of miRNA target genes.¹⁹ In SLE, lncRNAs have been implicated in immune dysregulation. For example, Liu et al demonstrated that upregulated lncRNA GAS5 suppressed autoreactivity in SLE CD4⁺ T cells and inhibited activation of normal CD4⁺ T cells via the miR-92a-3p/E4BP4 axis.²⁰ In lupus nephritis, lncRNA NEAT1 contributed to renal mesangial cell injury by targeting miR-146b, leading to increased TRAF6 expression and activation of the NF- κ B signaling pathway.²¹ Despite these findings, whether lncRNAs delivered by plasma exosomes participate in regulating CD4⁺ T cell activation and autophagy in SLE remains largely unknown.

In our previous study, we found that miR-98 is downregulated in CD4⁺ T cells from SLE patients.²² Based on the ceRNA hypothesis, we used the StarBase (<https://rnasysu.com/encori/>) and TargetScan (<https://www.targetscan.org/>) databases to predict that miR-98 may bind to both lncRNA XIST and RICTOR. These predicted interactions were experimentally confirmed using dual-luciferase reporter assays, which verified the direct binding of miR-98 to both lncRNA XIST and RICTOR.²³ RICTOR encodes a core component of mTORC2, an upstream regulator of the Akt/mTORC1/autophagy signaling pathway.^{24,25} Notably, lncRNA XIST has been shown to inhibit autophagy and promote apoptosis in BV2 cells by sponging miR-374a-5p, thereby negating the protective effects of zinc under LPS-induced stress.²⁶ These findings led us to hypothesize that plasma exosomal lncRNA XIST may act as a ceRNA by sequestering miR-98, thereby modulating RICTOR expression and influencing CD4⁺ T cell autophagy and activation in SLE. Accordingly, the present study was designed to investigate the role of plasma exosomal lncRNA XIST in regulating CD4⁺ T cell autophagy and activation through the miR-98/RICTOR/Akt-mTOR axis, and to elucidate its potential contribution to immune dysregulation in SLE.

Materials and Methods

Subjects

Eighteen patients diagnosed with SLE at Huashan Hospital, Fudan University, were enrolled in this study based on the 1997 classification criteria of the American College of Rheumatology (ACR). Disease activity was evaluated using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Fifty-four healthy individuals, matched by age and gender, were voluntarily recruited as healthy controls (HCs). Detailed clinical and laboratory data are presented in Table 1. The study was approved by the Independent Ethics Committee of Huashan Hospital, Fudan University.

Table 1 Clinical and Laboratory Characteristics of SLE Patients

Characteristics	SLE Patients (n = 18)
Age (years), mean $\pm$ SEM	36.22 $\pm$ 2.67
Sex (male/female)	3/15
Red blood cell count ($\times 10^{12}/L$), median (range)	3.56 (2.42–5.12)
Lymphocyte count ($\times 10^9/L$), median (range)	0.98 (0.49–2.71)
Platelet count ($\times 10^9/L$), median (range)	186.5 (122–391)
Serum C3 (g/L), median (range)	0.7 (0.30–1.39)
Serum C4 (g/L), median (range)	0.12 (0.06–0.26)
SLEDAI score, median (range)	9 (2–25)
Anti-dsDNA (IU/mL), median (range)	180.2 (8–800)
ESR (mm/h), median (range)	18 (2–120)
Renal involvement (yes/no)	14/4
Use of steroids or immunosuppressants (yes/no)	15/3
Use of hydroxychloroquine (yes/no)	12/6

Exosome Isolation and Characterization

Plasma exosomes were isolated from individual donors using the exoEasy Maxi Kit (Qiagen), following the manufacturer's instructions, and analyzed as independent biological samples without pooling. Transmission electron microscopy (TEM) was used to observe exosome morphology, and nanoparticle tracking analysis (NTA) with ZetaView (Particle Metrix) was conducted to determine particle size. The total protein content of exosomes was quantified using a BCA protein assay Kit (Beyotime). Western blotting was performed to detect the expression of established exosomal markers, CD63 and Alix.

Isolation and Co-Culture of Primary CD4⁺ T Cells

Peripheral blood mononuclear cells (PBMCs) were obtained from whole blood using density gradient centrifugation. CD4⁺ T cells were then isolated using CD4 magnetic beads (Miltenyi Biotec), achieving a purity greater than 90%. The purified CD4⁺ T cells (1×10^6 cells/mL) were co-cultured with plasma-derived exosomes at a final concentration of 25 µg/mL total exosomal protein, as determined by the BCA protein assay (Beyotime), in OpTmizer CTS T-Cell Expansion medium (Gibco) supplemented with 1% penicillin/streptomycin. Functional co-culture experiments were performed across independent experimental runs under standardized conditions. After 48 h of incubation, cells and culture supernatants were collected for downstream analysis.

Exosome Uptake Assay

Exosomes were labeled with the membrane dye DiI (Beyotime) according to the manufacturer's protocol. The labeled exosomes were incubated with CD4⁺ T cells from HCs for 24 hours. Fluorescence microscopy (Zeiss) was used to visualize exosome uptake.

Lentivirus Transduction and Exosome Cargo Loading

Lentiviral constructs encoding lncRNA XIST (lv-lncRNA XIST) or short hairpin RNA targeting XIST (shXIST) were generated by GeneChem. For XIST knockdown, purified CD4⁺ T cells isolated from SLE patients were transduced with shXIST lentivirus at a multiplicity of infection (MOI) of 50 in the presence of 5 µg/mL polybrene (Sigma-Aldrich) using OpTmizer CTS T-Cell Expansion medium (Gibco) at 37°C with 5% CO₂ for 12–24 h following standard protocols described previously.²⁷ After replacement with fresh medium, cells were cultured for an additional 48 h. Knockdown efficacy was evaluated by quantitative reverse transcription PCR (qRT-PCR). Lentiviral transduction in primary CD4⁺ T cells resulted in donor-dependent silencing of XIST, with an average knockdown efficiency of 65.9% across independent biological samples (range: 13.5%–93.3%), consistent with the known variability of primary human T cells. All transduced samples were included in downstream functional analyses.

Plasma-derived exosomes from HCs were incubated with lv-lncRNA XIST for 24–48 h. Following incubation, exosomes were re-isolated using the exoEasy Maxi Kit with multiple washing steps to remove unincorporated lentiviral particles. Loading efficiency was assessed by qRT-PCR. Compared with empty vector-treated control exosomes, lv-lncRNA XIST-treated exosomes exhibited an average ~5.6-fold increase in XIST expression (range 4.3–6.8-fold). Engineered exosomes were used in subsequent functional assays.

RNA Extraction and Quantitative Reverse Transcription PCR (qRT-PCR)

Total RNA was extracted from CD4⁺ T cells and exosomes using standard protocols. PrimeScript RT Master Mix (Takara) and SYBR Premix Ex Taq II (Takara) were used for reverse transcription and quantitative PCR analysis of mRNA targets. For miRNA analysis, a First-strand cDNA synthesis kit (GeneCopoeia) and the All-in-one miRNA qRT-PCR Detection kit (GeneCopoeia) were used according to the manufacturer's instructions, as described in previous studies.^{28,29} qRT-PCR reactions were performed in a final volume of 20 µL or 10 µL containing SYBR Premix Ex Taq II, gene-specific primers, and cDNA template, using either an ABI 7500 Real-Time PCR System (Applied Biosystems) or a QuantStudio 6 Flex Real-Time PCR System (Thermo Fisher Scientific). For the amplification of XIST and RICTOR, thermocycling conditions consisted of an initial denaturation at 95°C for 30s, followed by 40 cycles of denaturation at 95°C for 5s and annealing/extension at 60°C for 34s. For miR-98 detection, cycling conditions were 95°C for 10 min, followed by 40 cycles of 95°C for 10s, 60°C for 20s, and 72°C for 32s.

GAPDH and U48 served as internal reference genes for normalization of mRNA and miRNA expression, respectively. Relative gene expression was calculated using the $2^{-\Delta\Delta C_t}$ method. Primer specificity was confirmed by melt curve analysis, and amplification efficiencies of all primer pairs were within an acceptable range for quantitative analysis. The primer sequences used were as follows: RICTOR, Forward: 5'-CTCACGGTTGTAGGTTGCC-3', Reverse: 5'-AGAAA GTGTTCCAATAAATAAAAAG-3'; lncRNA XIST, Forward: 5'-TTTCGTGTGTGCCTTTGCCT-3', Reverse: 5'-GAA ATAAAGCGTGAAAGAAGAGCC-3'; GAPDH, Forward: 5'-AACGGATTGGTTCGTATTGGG-3', Reverse: 5'-TCGCT CCTGGAAGATGGTGAT-3'. Primers for miR-98 and U48 were purchased from GeneCopoeia.

Western Blotting

Total protein was extracted from cells and exosomes using RIPA lysis buffer supplemented with protease and phosphatase inhibitors (Beyotime). Protein concentrations were determined using the BCA protein assay kit (Beyotime). Equal amounts of total protein were loaded for each sample; depending on target protein abundance, 10–25 μ g of protein was loaded per lane. Proteins were separated by SDS-PAGE and transferred to PVDF membranes (Millipore). Membranes were blocked with 5% skim milk and incubated overnight at 4°C with primary antibodies, followed by incubation with HRP-conjugated secondary antibodies (Beyotime) at room temperature for 1 hour, as previously described.³⁰ Protein bands were visualized using ECL reagent (Millipore). The following primary antibodies were used: CD63 (ab193349, Abcam), Alix (ab186429, Abcam), LC3B (#2775, CST), SQSTM1/p62 (#5114, CST), Rictor (#2140, CST), p-AKT (#4058, CST), AKT (#4691, CST), p-p70S6K (#9234, CST), p70S6K (#2708, CST), p-mTOR (#5536, CST), mTOR (#2983, CST), and GAPDH (#5174, CST).

Flow Cytometry

CD4⁺ T cells harvested after co-culture were stained with PE-conjugated antibodies against human CD40L, CD69, and CD70 (BioLegend) in staining buffer for 30 minutes at room temperature in the dark. Autophagy levels in CD4⁺ T cells were assessed using the Cyto-ID™ Green Detection Reagent kit (Enzo), according to the manufacturer's protocol. Flow cytometry data were acquired on a LSRFortessa flow cytometer (BD Biosciences) and analyzed using FlowJo software (Tree Star, Inc). Briefly, lymphocytes were initially gated based on forward scatter (FSC-A) versus side scatter (SSC-A) to exclude debris. Doublets were excluded using FSC-A versus FSC-H gating. A total of 10,000 events was collected per sample. Fluorescence gates were set based on unstained control samples. The percentages of PE-positive cells (CD40L, CD69, and CD70) and Cyto-ID™ Green-staining cells were quantified accordingly. A detailed graphical representation of the gating strategy is provided in [Supplementary Figure 1](#).

Enzyme-Linked Immunosorbent Assay (ELISA)

The concentrations of inflammatory cytokines IL-6, IL-10, and TNF- α in culture supernatants were measured using commercial ELISA kits (Zhili BioTECH) according to the manufacturer's instructions. Each supernatant sample was assayed in technical duplicate or triplicate, depending on sample availability. Independent biological replicates were obtained from supernatants derived from different donors, as indicated by the corresponding n values in the figure legends. No samples were excluded from the analysis unless a predefined technical failure occurred, defined as absorbance values falling outside the linear range of the standard curve.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism 9.3 (GraphPad Software). Data were obtained from at least three independent experiments and are expressed as mean $\pm$ standard error of the mean (SEM). Data normality was assessed using the Shapiro–Wilk test. For normally distributed data, comparisons between two groups were performed using the Student's *t*-test. For non-normally distributed data, either the Mann–Whitney *U*-test or the Wilcoxon signed-rank test was applied. Similarly, for comparisons among multiple groups, one-way analysis of variance (ANOVA) was used for normally distributed data, whereas the Friedman test was employed for non-normally distributed data. Pearson's correlation coefficient was applied for correlation analysis. The number of biological replicates (n), corresponding to independent donors, is specified in the respective figure legends. A p-value < 0.05 was considered statistically significant.

Results

LncRNA XIST Is Upregulated in Plasma Exosomes of SLE Patients

Plasma-derived exosomes from SLE patients were successfully isolated and characterized. TEM revealed that the exosomes exhibited a typical intact oval morphology (Figure 1A), while NTA indicated a mean diameter of 138.5 nm (Figure 1B). Western blot analysis confirmed the presence of exosomal markers CD63 and Alix (Figure 1C). Western blot analysis confirmed the presence of exosomal markers CD63 and Alix (Figure 1C).

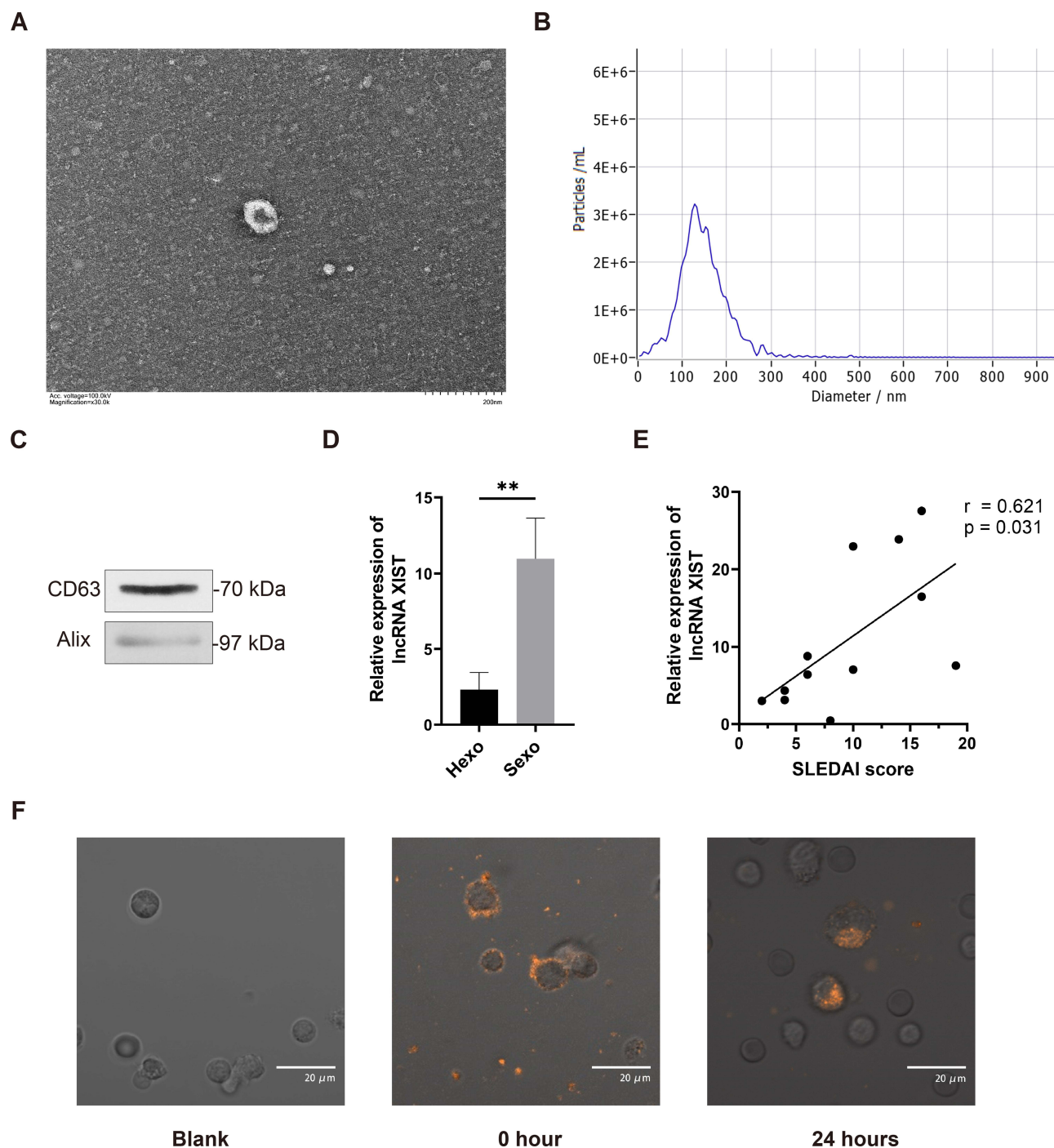


Figure 1 LncRNA XIST is upregulated in plasma exosomes from SLE patients. **(A)** Transmission electron microscopy (TEM) image showing the morphology of plasma-derived exosomes. Scale bar: 200 nm. **(B)** Size distribution of exosomes analyzed using nanoparticle tracking analysis (NTA). **(C)** Expression of exosomal markers CD63 and Alix detected via Western blot. **(D)** qRT-PCR analysis of lncRNA XIST levels in plasma exosomes from SLE patients (n = 12) and healthy controls (HCs) (n = 10). **(E)** Correlation between lncRNA XIST expression in SLE plasma exosomes and disease activity as measured by SLEDAI score (n = 12). **(F)** Uptake of Dil-labeled SLE plasma exosomes (Orange fluorescence) by CD4⁺ T cells from HCs, visualized using confocal microscopy. Scale bar: 20 μ m. ** $p < 0.01$.

qRT-PCR analysis demonstrated that lncRNA XIST expression was significantly elevated in the plasma exosomes of SLE patients compared to HCs (Figure 1D). Furthermore, lncRNA XIST levels positively correlated with SLEDAI scores ($r = 0.621$, $p < 0.05$) (Figure 1E), but showed no significant correlation with red blood cell count, lymphocyte count, platelet count, serum C3/C4 levels, anti-dsDNA titers, or erythrocyte sedimentation rate (ESR) (Table 2).

To assess whether exosomes could be internalized by recipient cells, DiI-labeled exosomes were co-cultured with CD4⁺ T cells. After 24 hours, fluorescence microscopy revealed that exosomes were predominantly localized in the cytoplasm, confirming successful uptake (Figure 1F).

SLE Plasma Exosomes Increase lncRNA XIST Levels, Inhibit Autophagy, and Promote Activation of CD4⁺ T Cells From Healthy Controls

To investigate the functional impact of SLE plasma exosomes, they were co-cultured with CD4⁺ T cells isolated from HCs. Western blot analysis showed a marked reduction in LC3B-II and an increase in SQSTM1/p62, indicating suppressed autophagy (Figure 2A). Flow cytometry further confirmed a decrease in autophagic cell populations (Figure 2B). Additionally, SLE plasma exosomes upregulated the expression of cell surface activation markers CD69, CD70, and CD40L on CD4⁺ T cells and enhanced the secretion of inflammatory cytokines IL-6, IL-10, and TNF- α , as shown by flow cytometry and ELISA, respectively (Figure 2C and D). These findings suggest that SLE plasma exosomes inhibit autophagy while promoting activation of HC CD4⁺ T cells.

We then explored the underlying mechanism. Our previous dual-luciferase assay suggested that lncRNA XIST may function as a ceRNA, sequestering miR-98 and regulating RICTOR expression.²³ Indeed, SLE plasma exosomes significantly increased lncRNA XIST and RICTOR mRNA expression while reducing miR-98 levels in HC CD4⁺ T cells (Figure 2E). Correspondingly, Rictor protein expression was also elevated (Figure 2F).

Given the known role of the Akt/mTOR/p70S6K signaling pathway in regulating autophagy,³¹ we assessed its activation status. Western blot analysis revealed increased phosphorylation of Akt, mTOR, and p70S6K in HC CD4⁺ T cells following treatment with SLE plasma exosomes (Figure 2F).

Collectively, these results indicate that SLE plasma exosomes may impair autophagy and enhance activation in HC CD4⁺ T cells via the lncRNA XIST-miR-98-RICTOR axis and the Akt/mTOR/p70S6K pathway.

SLE Plasma Exosomes Reverse the Effects of lncRNA XIST Knockdown in Autologous CD4⁺ T Cells

To validate the regulatory role of exosomal lncRNA XIST, we knocked down XIST in CD4⁺ T cells from SLE patients using shRNA. qRT-PCR confirmed efficient knockdown (Figure 3A). This led to increased LC3B-II and decreased SQSTM1/p62 protein levels (Figure 3B), along with an elevated proportion of autophagic cells (Figure 3C), suggesting enhanced autophagy. Knockdown of XIST also reduced expression of activation markers CD69 and CD40L (Figure 3D) and decreased secretion of IL-6, IL-10, and TNF- α (Figure 3E).

However, these effects were reversed when the XIST-knockdown CD4⁺ T cells were co-cultured with autologous plasma exosomes, indicating that exosomal lncRNA XIST can restore autophagy suppression and T cell activation

Table 2 Correlation Between lncRNA XIST Expression and Laboratory Parameters in SLE Patients

Parameters	r	p value
Red blood cell count ($\times 10^{12}/L$)	0.035	0.915
Lymphocyte count ($\times 10^9/L$)	-0.14	0.665
Platelet count ($\times 10^9/L$)	0.236	0.461
Serum C3 (g/L)	0.03	0.926
Serum C4 (g/L)	0.151	0.639
Anti-dsDNA (IU/mL)	-0.322	0.307
ESR (mm/h)	-0.191	0.574

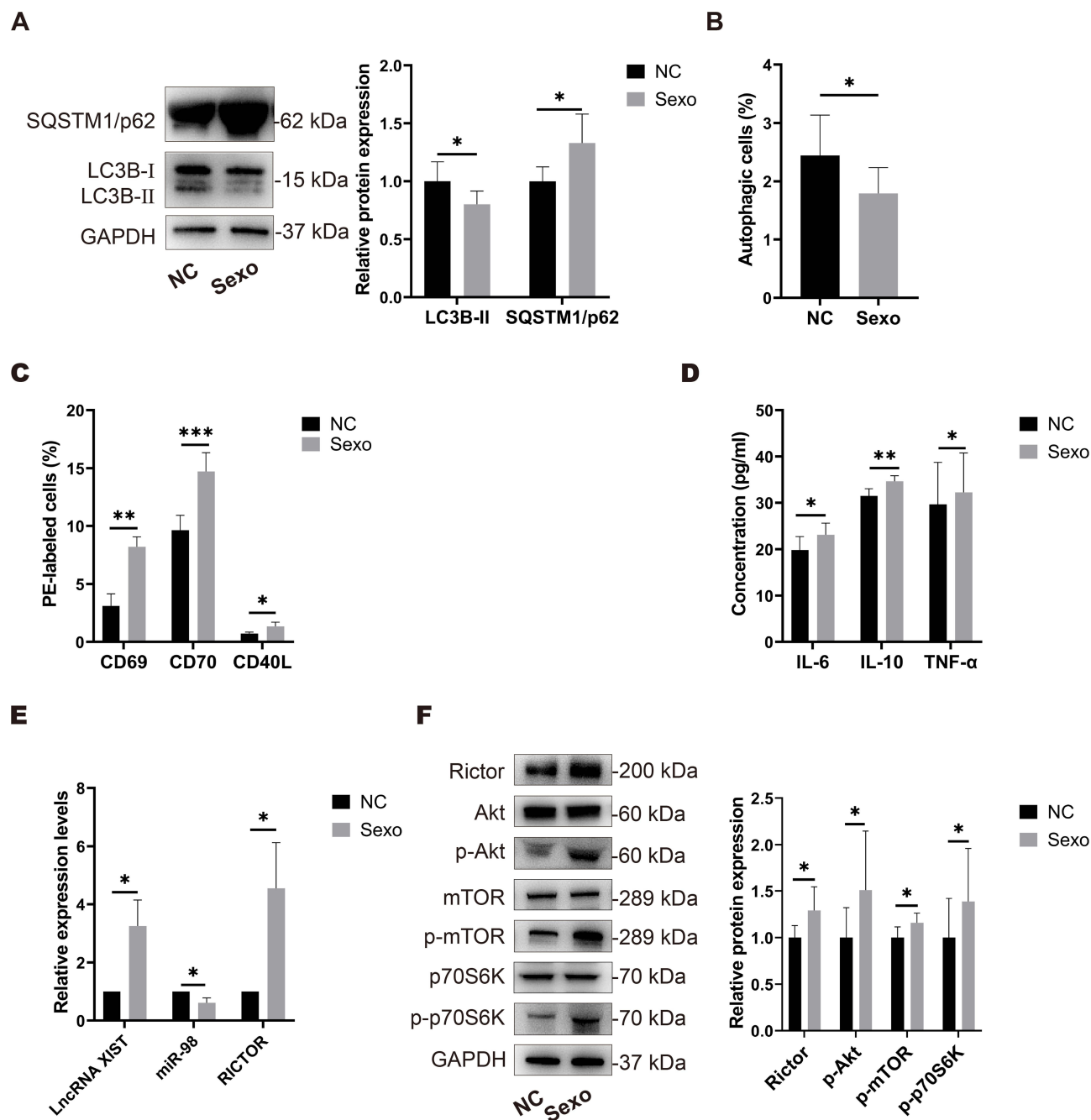


Figure 2 SLE plasma exosomes (Sexo) inhibit autophagy and promote activation of CD4⁺ T cells from healthy controls (HCs). **(A)** Western blot analysis of autophagy markers LC3B-II and SQSTM1/p62 in HC CD4⁺ T cells following co-culture with Sexo (n = 16). Representative immunoblots are shown, with densitometric quantification normalized to the corresponding loading controls presented as bar graphs. **(B)** Flow cytometric assessment of autophagy in HC CD4⁺ T cells (n = 6). **(C)** Surface activation markers CD69, CD70, and CD40L detected by flow cytometry (n = 14). **(D)** ELISA measurement of cytokines IL-6, IL-10, and TNF- α in cell culture supernatants (n = 17). **(E)** qRT-PCR quantification of lncRNA XIST, miR-98, and RICTOR expression in HC CD4⁺ T cells (n = 54). **(F)** Western blot analysis of Rictor, Akt, p-Akt, mTOR, p-mTOR, p70S6K, and p-p70S6K (n = 21). Representative immunoblots are shown, with densitometric quantification normalized to the corresponding loading controls. The co-cultured Sexo were derived from six independent SLE donors, where n represents the number of independent HC CD4⁺ T cell donors. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

(Figure 3A–E). Furthermore, lncRNA XIST knockdown increased miR-98 levels and reduced RICTOR mRNA expression (Figure 3F), which was accompanied by decreased protein levels of Rictor, p-Akt, p-mTOR, and p-p70S6K (Figure 3G). These changes were again reversed by the addition of autologous exosomes (Figure 3F and G), supporting a regulatory role of exosomal lncRNA XIST via the miR-98/RICTOR axis.

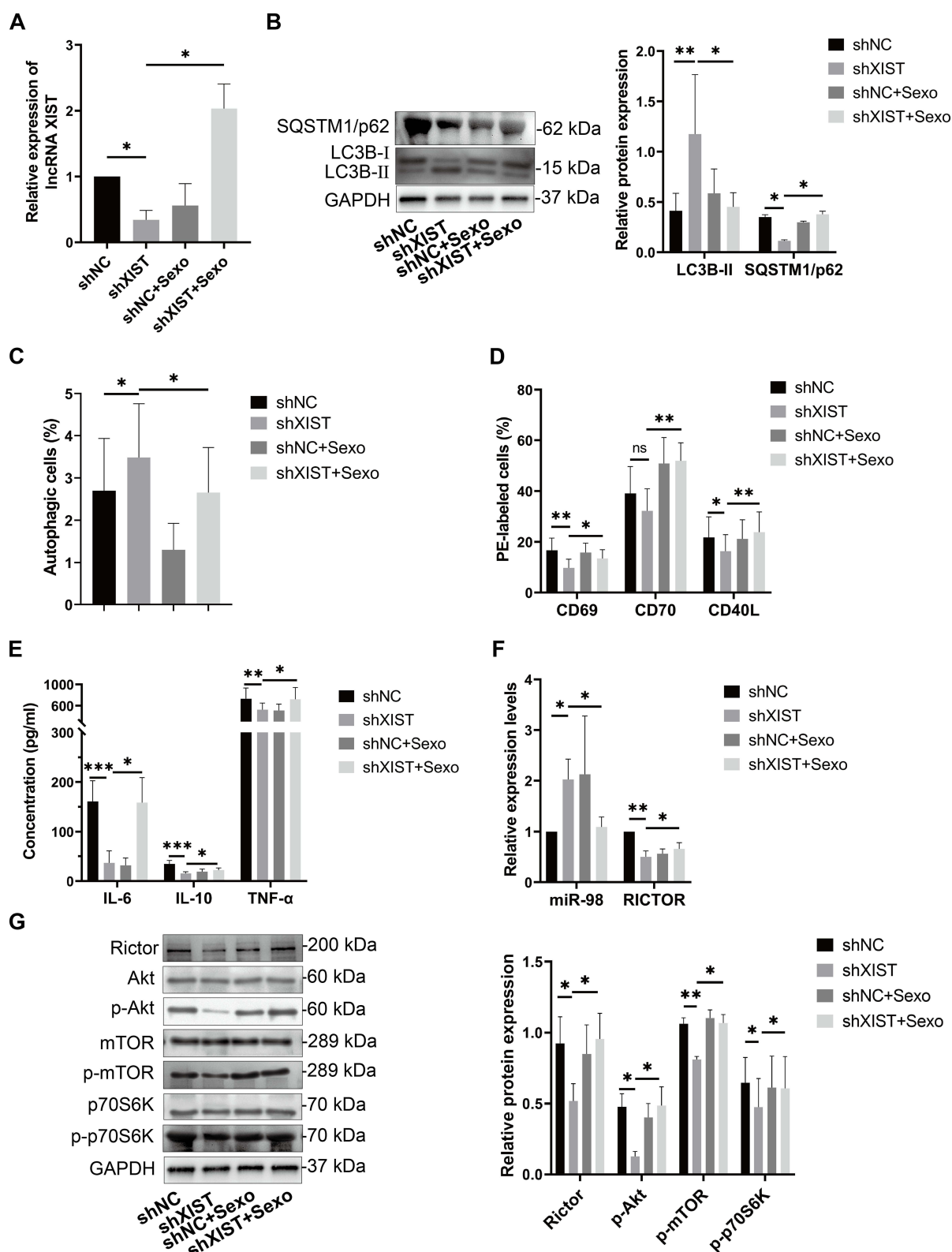


Figure 3 SLE plasma exosomes restore autophagy inhibition and activation in SLE CD4⁺ T cells after lncRNA XIST knockdown. **(A)** qRT-PCR analysis of lncRNA XIST levels in SLE CD4⁺ T cells transduced with sh-lncRNA XIST (shXIST) or control (shNC), followed by co-culture with autologous SLE plasma exosomes (Sexo) (n = 5). **(B)** Western blot detection of autophagy markers LC3B-II and SQSTM1/p62 (n = 5). Representative immunoblots are shown, with densitometric quantification normalized to the corresponding loading controls. **(C)** Flow cytometric analysis of autophagic CD4⁺ T cells (n = 8). **(D)** Flow cytometry for activation markers CD69, CD70, and CD40L (n = 10). **(E)** ELISA quantification of IL-6, IL-10, and TNF- α in the culture supernatant (n = 9). **(F)** qRT-PCR analysis of miR-98 and RICTOR expression (n = 8). **(G)** Western blot analysis of proteins involved in the Rictor/Akt/mTOR/p70S6K pathway (n = 4). Representative immunoblots are shown, with densitometric quantification normalized to the corresponding loading controls. n represents the number of independent SLE CD4⁺ T cell donors and their corresponding autologous exosomes. *p < 0.05, **p < 0.01, ***p < 0.001; ns, not significant.

Exosomal lncRNA XIST Regulates Autophagy and Activation of CD4⁺ T Cells

To further confirm the role of exosomal lncRNA XIST, we engineered exosomes to overexpress lncRNA XIST (Figure 4A) and co-cultured them with CD4⁺ T cells from HCs. qRT-PCR showed significant upregulation of lncRNA XIST in recipient

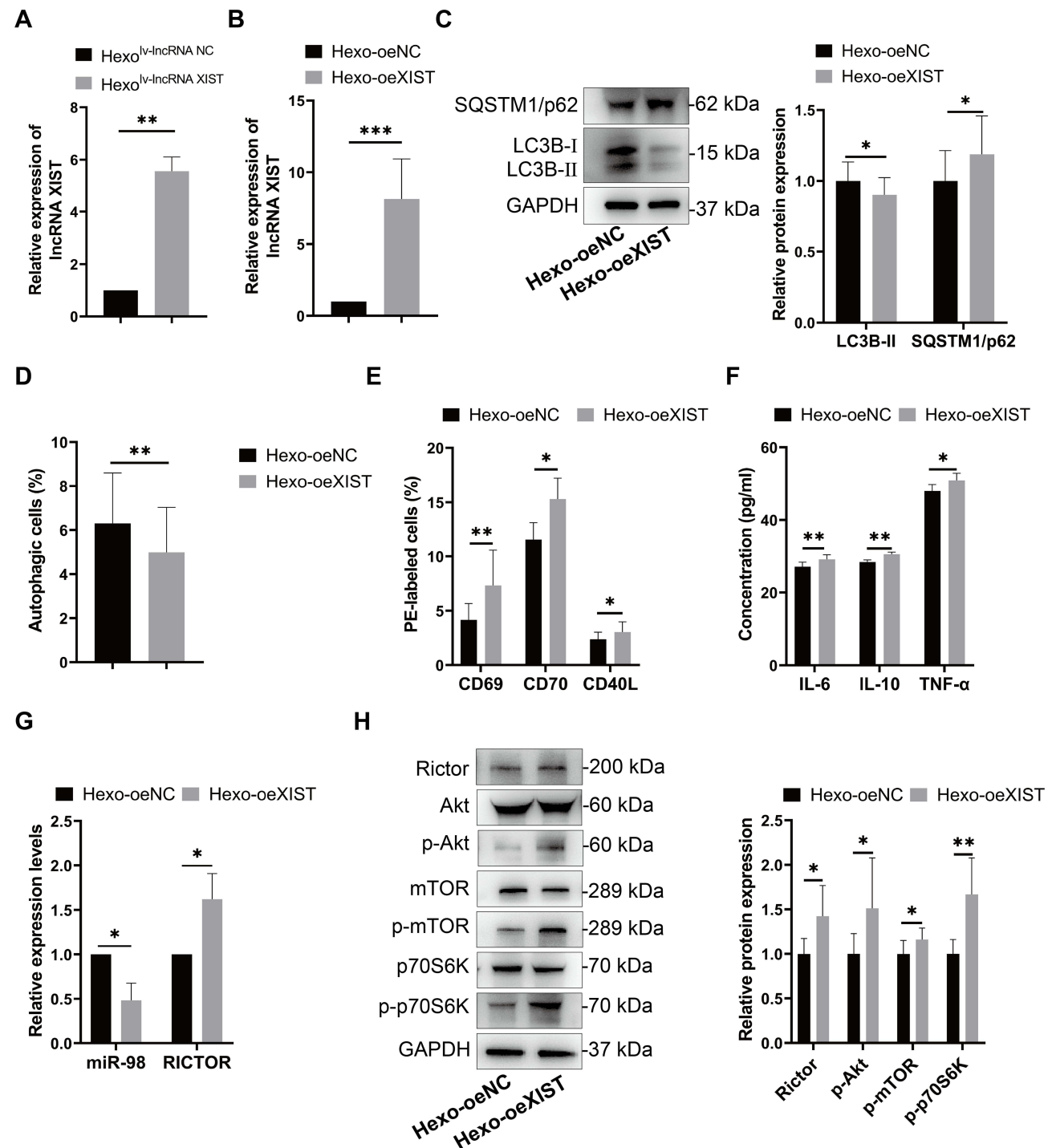


Figure 4 Exosomal lncRNA XIST inhibits autophagy and promotes activation in HC CD4⁺ T cells. **(A)** qRT-PCR validation of lncRNA XIST overexpression in HC plasma exosomes (Hexo) loaded with lncRNA XIST compared to negative control (lncRNA NC) (N = 4). **(B)** qRT-PCR analysis of lncRNA XIST in HC CD4⁺ T cells after co-culture with Hexo loaded with lncRNA XIST (Hexo-oeXIST) or negative control (Hexo-oeNC) (n = 20). **(C)** Western blot detection of autophagy markers LC3B-II and SQSTM1/p62 (n = 8). Representative immunoblots are shown, with densitometric quantification normalized to the corresponding loading controls. **(D)** Flow cytometry analysis of autophagic CD4⁺ T cells (n = 8). **(E)** Flow cytometry for surface activation markers CD69, CD70, and CD40L (n = 9). **(F)** ELISA quantification of IL-6, IL-10, and TNF- α (n = 9). **(G)** qRT-PCR detection of miR-98 and RICTOR expression (n = 21). **(H)** Western blot analysis of Rictor and key signaling proteins in the Akt/mTOR/p70S6K pathway (n = 10). Representative immunoblots are shown, with densitometric quantification normalized to the corresponding loading controls. N indicates the number of independently engineered exosome preparations; n indicates the number of independent HC CD4⁺ T cell donors. * p < 0.05, ** p < 0.01, *** p < 0.001.

T cells (Figure 4B). Western blot analysis revealed downregulation of LC3B-II and upregulation of SQSTM1/p62, consistent with suppressed autophagy (Figure 4C). Autophagy was further shown to be reduced by flow cytometry (Figure 4D).

Engineered exosomes also enhanced the activation of CD4⁺ T cells, as evidenced by elevated surface expression of CD69, CD70, and CD40L and increased secretion of IL-6, IL-10, and TNF- α (Figure 4E and F), mimicking the effect of natural SLE plasma exosomes. Additionally, they suppressed miR-98 expression and increased both RICTOR mRNA levels (Figure 4G) and protein expression of Rictor, p-Akt, p-mTOR, and p-p70S6K (Figure 4H).

These results suggest that exosomal lncRNA XIST modulates CD4⁺ T cell autophagy and activation through the miR-98/RICTOR axis by activating the Akt/mTOR/p70S6K signaling pathway.

Discussion

Recent studies have increasingly highlighted the role of lncRNAs in modulating autophagy in SLE.^{32,33} However, the specific contribution of exosomal lncRNAs to this process remains poorly understood. In this study, we demonstrate that lncRNA XIST is significantly elevated in plasma exosomes from SLE patients. Our findings suggest that these exosomes can suppress autophagy and enhance activation in CD4⁺ T cells by delivering lncRNA XIST. Mechanistically, lncRNA XIST appears to function as a ceRNA, binding to miR-98 and thereby regulating the expression of RICTOR, which modulates the Akt/mTOR/p70S6K signaling pathway and impacts T cell function. This reveals a novel mechanism through which exosomal lncRNA XIST contributes to autophagy regulation in SLE.

Exosomes are critical mediators of intercellular communication and molecular transport in SLE pathogenesis.^{34,35} They carry a diverse array of bioactive molecules, including non-coding RNAs, which can be internalized by recipient cells and alter their biological behavior. Most studies on exosomal non-coding RNAs in SLE have focused on miRNAs. For instance, Tan et al reported that reduced levels of serum exosomal miR-451a were associated with disease activity and renal involvement in SLE.³⁶ Dong et al found that SLE serum exosomal miR-146a regulated mesenchymal stem cell senescence via the TRAF6/NF- κ B pathway.³⁷ Only recently has attention shifted toward exosomal lncRNAs. High-throughput sequencing analyses have identified distinct plasma exosomal lncRNA signatures in SLE, including the differential expression of over 8,000 lncRNAs.³⁸ Among these, LINC00667 and DANCER emerged as potential biomarkers.³⁸ In lupus nephritis, additional lncRNAs such as LINC01015, LINC01986, AC087257.1, and AC022596.1 were implicated in key processes including inflammation, fibrosis, epithelial-mesenchymal transition, and actin cytoskeleton.³⁹ Despite these advances, the functional roles and mechanisms of exosomal lncRNAs in SLE remain poorly defined. Our study addresses this gap by showing that plasma-derived exosomal lncRNA XIST regulates CD4⁺ T cell autophagy and activation via the miR-98/RICTOR axis in SLE.

lncRNA XIST is best known for its role in X-chromosome inactivation in female mammals,⁴⁰ but emerging evidence suggests it also participates in regulating autophagy through interactions with miRNAs. For example, Zhao et al reported that lncRNA XIST suppressed autophagy and promoted apoptosis in BV2 cells by sponging miR-374a-5p.²⁶ Our findings are in line with these results, showing that lncRNA XIST can similarly inhibit autophagy and promote activation in CD4⁺ T cells from SLE patients. However, the role of lncRNA XIST in autophagy appears to be context-dependent. Other studies have shown that lncRNA XIST can promote autophagy in different disease models. For example, in ligamentum flavum hypertrophy, lncRNA XIST enhanced autophagy via the miR-302b-3p/VEGFA axis,⁴¹ and in diabetic peripheral neuropathy, lncRNA XIST induced autophagy through the miR-30d-5p/SIRT1 pathway.⁴² These discrepancies likely stem from variations in disease context, cell type, and pathophysiological conditions.

The mTOR signaling pathway plays a crucial role in regulating autophagy.⁴³ RICTOR, a core component of mTORC2, is critical for the phosphorylation and activation of Akt.^{24,25} Activated Akt in turn stimulates mTORC1, which drives anabolic processes such as proteins, lipids, and nucleotides synthesis while inhibiting autophagy.¹² Thus, RICTOR indirectly suppresses autophagy by enhancing mTORC1 activity. Previous studies have shown that miRNAs can modulate this pathway by targeting RICTOR. For instance, miR-let-7a decreases RICTOR expression in gastric cancer cells, thereby promoting autophagy through regulation of the Akt/mTOR signaling pathway,²⁴ whereas miR-15a/16 reduce RICTOR expression in HeLa cells, downregulate the mTORC1/p70S6K signaling pathway, and enhance autophagy.⁴⁴ Consistent with and extending these findings, our study demonstrates that lncRNA XIST upregulates RICTOR expression in CD4⁺ T cells by sponging miR-98, leading to activation of the Akt/mTOR signaling pathway and suppression of autophagy in SLE.

Despite these important insights, our study has several limitations. First, the experiments were conducted exclusively *in vitro*, which may not fully replicate the complexity of *in vivo* immune regulation. Future studies using lupus-prone mouse models are necessary to validate the functional relevance of the lncRNA XIST/miR-98/RICTOR axis under physiological conditions. Second, although impaired autophagy was inferred based on established molecular markers, autophagic flux assays were not performed. Therefore, we could not distinguish whether the observed changes reflect reduced autophagy induction or blocked flux. Third, while standard isolation and washing procedures were applied, comprehensive exosome purity validation beyond established markers was limited, which should be further strengthened in future studies. In addition, the relatively modest sample size may limit the generalizability of our findings and warrants validation in larger, independent cohorts. Finally, although we focused on a defined ceRNA regulatory pathway, other lncRNAs, miRNAs, and target genes may also contribute to CD4⁺ T cell dysfunction in SLE and merit further investigation. Moreover, the precise cellular source of plasma exosomes enriched in lncRNA XIST remains unclear and should be identified in future studies.

Conclusion

Our study provides evidence that exosomal lncRNA XIST modulates autophagy and activation in CD4⁺ T cells through the miR-98/RICTOR/Akt/mTOR signaling pathway in SLE, supported by consistent molecular and functional readouts. These findings establish a causal regulatory framework linking exosomal XIST to CD4⁺ T cell dysfunction and highlight the role of extracellular vesicle-mediated RNA signaling in lupus pathogenesis. While limitations remain, including incomplete assessment of autophagy flux, exosome purity, cellular origin, and potential involvement of additional XIST-regulated pathways, the present work provides a foundation for further mechanistic investigation and validation in larger cohorts.

Abbreviations

4EBP, eIF4E Binding Protein; ACR, American College of Rheumatology; ANOVA, one-way analysis of variance; ceRNA, competing endogenous RNA; ELISA, enzyme-linked immunosorbent assay; ESR, erythrocyte sedimentation rate; FSC, forward scatter; HC, healthy control; HUCMSC, human umbilical cord mesenchymal stem cell; lncRNA, long non-coding RNA; miRNA, microRNA; MOI, multiplicity of infection; mTOR, mechanistic target of rapamycin; mTORC1, mTOR complex 1; mTORC2, mTOR complex 2; NTA, nanoparticle tracking analysis; p70S6K, 70 kDa ribosomal protein S6 kinase; PBMC, peripheral blood mononuclear cell; qRT-PCR, quantitative reverse transcription PCR; SEM, standard error of the mean; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SSC, side scatter; TEM, transmission electron microscopy.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

Ethical approval was obtained from the Independent Ethics Committee of Huashan Hospital (No. KY2020-056). The study complied with the Declaration of Helsinki, and written informed consent was obtained from all participants.

Author Contributions

Li Wang: Investigation, Validation, Formal Analysis, Data curation, Writing – original draft. Fan Lyu: Investigation, Validation, Formal Analysis, Data curation. Jun Liang: Investigation, Validation, Formal Analysis. Xi Chen: Investigation, Validation, Formal Analysis. Chenghui Zheng: Investigation, Validation, Formal Analysis. Mingyu Chu: Investigation, Validation, Formal Analysis. Jinhua Xu: Funding acquisition, Project administration, Resources, Supervision. Lin Xie: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Tsai YG, Liao PF, Hsiao KH, Wu HM, Lin CY, Yang KD. Pathogenesis and novel therapeutics of regulatory T cell subsets and interleukin-2 therapy in systemic lupus erythematosus. *Front Immunol.* **2023**;14:1230264. doi:10.3389/fimmu.2023.1230264
2. Li H, Boulougoura A, Endo Y, Tsokos GC. Abnormalities of T cells in systemic lupus erythematosus: new insights in pathogenesis and therapeutic strategies. *J Autoimmun.* **2022**;132:102870. doi:10.1016/j.jaut.2022.102870
3. Yang Z, Matteson EL, Goronzy JJ, Weyand CM. T-cell metabolism in autoimmune disease. *Arthritis Res Ther.* **2015**;17(1):29. doi:10.1186/s13075-015-0542-4
4. Gros F, Arnold J, Page N, et al. Macroautophagy is deregulated in murine and human lupus T lymphocytes. *Autophagy.* **2012**;8(7):1113–1123. doi:10.4161/auto.20275
5. Liu S, Yao S, Yang H, Liu S, Wang Y. Autophagy: regulator of cell death. *Cell Death Dis.* **2023**;14(10):648. doi:10.1038/s41419-023-06154-8
6. Jeong J, Choi YJ, Lee HK. The role of autophagy in the function of cd4(+) t cells and the development of chronic inflammatory diseases. *Front Pharmacol.* **2022**;13:860146. doi:10.3389/fphar.2022.860146
7. Jacquin E, Apetoh L. Cell-intrinsic roles for autophagy in modulating CD4 T cell functions. *Front Immunol.* **2018**;9:1023. doi:10.3389/fimmu.2018.01023
8. An N, Chen Y, Wang C, et al. Chloroquine autophagic inhibition rebalances th17/treg-mediated immunity and ameliorates systemic lupus erythematosus. *Cell Physiol Biochem.* **2017**;44(1):412–422. doi:10.1159/000484955
9. Alessandri C, Barbati C, Vacirca D, et al. T lymphocytes from patients with systemic lupus erythematosus are resistant to induction of autophagy. *FASEB J.* **2012**;26(11):4722–4732. doi:10.1096/fj.12-206060
10. Lee WS, Sung MS, Lee EG, et al. A pathogenic role for ER stress-induced autophagy and ER chaperone GRP78/BiP in T lymphocyte systemic lupus erythematosus. *J Leukoc Biol.* **2015**;97(2):425–433. doi:10.1189/jlb.6A0214-097R
11. Liu GY, Sabatini DM. mTOR at the nexus of nutrition, growth, ageing and disease. *Nat Rev Mol Cell Biol.* **2020**;21(4):183–203. doi:10.1038/s41580-019-0199-y
12. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. *Cell.* **2017**;168(6):960–976. doi:10.1016/j.cell.2017.02.004
13. Zoncu R, Efeyan A, Sabatini DM. mTOR: from growth signal integration to cancer, diabetes and ageing. *Nat Rev Mol Cell Biol.* **2011**;12(1):21–35. doi:10.1038/nrm3025
14. Ortega A, Martinez-Arroyo O, Forner MJ, Cortes R. Exosomes as drug delivery systems: endogenous nanovehicles for treatment of systemic lupus erythematosus. *Pharmaceutics.* **2020**;13(1):3. doi:10.3390/pharmaceutics13010003
15. Wei H, Chen Q, Lin L, et al. Regulation of exosome production and cargo sorting. *Int J Biol Sci.* **2021**;17(1):163–177. doi:10.7150/ijbs.53671
16. Peng H, Ji W, Zhao R, et al. Exosome: a significant nano-scale drug delivery carrier. *J Mater Chem B.* **2020**;8(34):7591–7608. doi:10.1039/d0tb01499k
17. Chen X, Su C, Wei Q, Sun H, Xie J, Nong G. exosomes derived from human umbilical cord mesenchymal stem cells alleviate diffuse alveolar hemorrhage associated with systemic lupus erythematosus in mice by promoting m2 macrophage polarization via the microrna-146a-5p/notch1 axis. *Immunol Invest.* **2022**;51(7):1975–1993. doi:10.1080/08820139.2022.2090261
18. Mercer TR, Dinger ME, Mattick JS. Long non-coding RNAs: insights into functions. *Nat Rev Genet.* **2009**;10(3):155–159. doi:10.1038/nrg2521
19. Tay Y, Rinn J, Pandolfi PP. The multilayered complexity of ceRNA crosstalk and competition. *Nature.* **2014**;505(7483):344–352. doi:10.1038/nature12986
20. Liu Q, Deng Y, Li C, et al. LncRNA GAS5 suppresses CD4(+) T cell activation by upregulating E4BP4 via inhibiting miR-92a-3p in systemic lupus erythematosus. *Immunol Lett.* **2020**;227:41–47. doi:10.1016/j.imlet.2020.08.001
21. Zhang LH, Xiao B, Zhong M, et al. LncRNA NEAT1 accelerates renal mesangial cell injury via modulating the miR-146b/TRAF6/NF-kappaB axis in lupus nephritis. *Cell Tissue Res.* **2020**;382(3):627–638. doi:10.1007/s00441-020-03248-z
22. Xie L, Xu J. Role of mir-98 and its underlying mechanisms in systemic lupus erythematosus. *J Rheumatol.* **2018**;45(10):1397–1405. doi:10.3899/jrheum.171290
23. Chen X. *Role of lncRNA XIST and Its Underlying Mechanisms in the Pathogenesis of Systemic Lupus Erythematosus*. Fudan University; **2023**. Master's degree.
24. Fan H, Jiang M, Li B, et al. MicroRNA-let-7a regulates cell autophagy by targeting Rictor in gastric cancer cell lines MGC-803 and SGC-7901. *Oncol Rep.* **2018**;39(3):1207–1214. doi:10.3892/or.2018.6194
25. Sarbassov DD, Guertin DA, Ali SM, Sabatini DM. Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. *Science.* **2005**;307(5712):1098–1101. doi:10.1126/science.1106148
26. Zhao X, Sun J, Yuan Y, Lin S, Lin J, Mei X. Zinc promotes microglial autophagy through NLRP3 inflammasome Inactivation via XIST/miR-374a-5p axis in spinal cord injury. *Neurochem Res.* **2022**;47(2):372–381. doi:10.1007/s11064-021-03441-8

27. Liu X, Lin J, Wu H, et al. A novel long noncoding rna lincrna00892 activates cd4(+) t cells in systemic lupus erythematosus by regulating CD40L. *Front Pharmacol.* **2021**;12:733902. doi:10.3389/fphar.2021.733902
28. Chen S, Wang Y, Qin H, et al. Downregulation of miR-633 activated AKT/mTOR pathway by targeting AKT1 in lupus CD4(+) T cells. *Lupus.* **2019**;28(4):510–519. doi:10.1177/0961203319829853
29. Wang J, Xie L, Wang S, Lin J, Liang J, Xu J. Azithromycin promotes alternatively activated macrophage phenotype in systematic lupus erythematosus via PI3K/Akt signaling pathway. *Cell Death Dis.* **2018**;9(11):1080. doi:10.1038/s41419-018-1097-5
30. Xie L, Yang R, Liu S, et al. TR3 is preferentially expressed by bulge epithelial stem cells in human hair follicles. *Lab Invest.* **2016**;96(1):81–88. doi:10.1038/labinvest.2015.125
31. Zhang HW, Hu JJ, Fu RQ, et al. Flavonoids inhibit cell proliferation and induce apoptosis and autophagy through downregulation of PI3Kgamma mediated PI3K/AKT/mTOR/p70S6K/ULK signaling pathway in human breast cancer cells. *Sci Rep.* **2018**;8(1):11255. doi:10.1038/s41598-018-29308-7
32. Hsieh YT, Chen YC, Chou YC, et al. Long noncoding RNA SNHG16 regulates TLR4-mediated autophagy and NETosis formation in alveolar hemorrhage associated with systemic lupus erythematosus. *J Biomed Sci.* **2023**;30(1):78. doi:10.1186/s12929-023-00969-5
33. Pan X, Chen S, Shen R, Liu S, You Y. HOXA11-OS participates in lupus nephritis by targeting miR-124-3p mediating Cyr61 to regulate podocyte autophagy. *Mol Med.* **2022**;28(1):138. doi:10.1186/s10020-022-00570-w
34. Wu Y, Dong HR, Liu LT, Peng ML, Su XL. Advances in the study of exosome-derived miRNAs in the pathogenesis, diagnosis, and treatment of systemic lupus erythematosus. *Lupus.* **2023**;32(13):1475–1485. doi:10.1177/09612033231212280
35. Zheng C, Xie L, Qin H, et al. The role of extracellular vesicles in systemic lupus erythematosus. *Front Cell Dev Biol.* **2022**;10:835566. doi:10.3389/fcell.2022.835566
36. Tan L, Zhao M, Wu H, et al. downregulated serum exosomal miR-451a expression correlates with renal damage and its intercellular communication role in systemic lupus erythematosus. *Front Immunol.* **2021**;12:630112. doi:10.3389/fimmu.2021.630112
37. Dong C, Zhou Q, Fu T, et al. Circulating exosomes derived-mir-146a from systemic lupus erythematosus patients regulates senescence of mesenchymal stem cells. *Biomed Res Int.* **2019**;2019:6071308. doi:10.1155/2019/6071308
38. Peng XC, Ma LL, Miao JY, Xu SQ, Shuai ZW. Differential lncRNA profiles of blood plasma-derived exosomes from systemic lupus erythematosus. *Gene.* **2024**;927:148713. doi:10.1016/j.gene.2024.148713
39. Flores-Chova A, Martinez-Arroyo O, Riffo-Campos AL, Ortega A, Forner MJ, Cortes R. Plasma exosomal non-coding RNA profile associated with renal damage reveals potential therapeutic targets in lupus nephritis. *Int J Mol Sci.* **2023**;24(8). doi:10.3390/ijms24087088
40. Li J, Ming Z, Yang L, Wang T, Liu G, Ma Q. Long noncoding RNA XIST: mechanisms for X chromosome inactivation, roles in sex-biased diseases, and therapeutic opportunities. *Genes Dis.* **2022**;9(6):1478–1492. doi:10.1016/j.gendis.2022.04.007
41. Cao Y, Li J, Qiu S, Ni S, Duan Y. LncRNA XIST facilitates hypertrophy of ligamentum flavum by activating VEGFA-mediated autophagy through sponging miR-302b-3p. *Biol Direct.* **2023**;18(1):25. doi:10.1186/s13062-023-00383-9
42. Liu BY, Li L, Bai LW, Xu CS. Long non-coding RNA XIST attenuates diabetic peripheral neuropathy by inducing autophagy through MicroRNA-30d-5p/sirtuin1 axis. *Front Mol Biosci.* **2021**;8:655157. doi:10.3389/fmolb.2021.655157
43. Kim YC, Guan KL. mTOR: a pharmacologic target for autophagy regulation. *J Clin Invest.* **2015**;125(1):25–32. doi:10.1172/JCI173939
44. Huang N, Wu J, Qiu W, et al. MiR-15a and miR-16 induce autophagy and enhance chemosensitivity of Camptothecin. *Cancer Biol Ther.* **2015**;16(6):941–948. doi:10.1080/15384047.2015.1040963

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