Heliyon 10 (2024) e35949

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

B cell function in patients with systemic lupus erythematosus is regulated by the upregulation of JunD

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ARTICLE INFO

Keywords:
Systemic lupus erythematosus (SLE)
B cells
JunD
Immunity
Autophagy

ABSTRACT

Purpose: Systemic lupus erythematosus (SLE) is largely caused by B cell dysfunction. JunD is an activator protein 1 family protein that has been linked to the regulation of apoptotic and proliferative activities. However, the precise mechanism(s) by which JunD functions remains to be fully elucidated. Accordingly, this study aimed to clarify the functional importance of JUND gene expression in SLE, with further analyses of the functional role that JunD plays as a regulator of B cell proliferation and immune function.

Methods: Reverse transcriptase quantitative polymerase chain reaction techniques were used to analyze JunD expression in B cells of patients with SLE and healthy subjects. Cell Counting Kit-8 (CCK-8) assays and flow cytometry methods were used to characterise proliferative activity, cell cycle progression, and apoptosis of B cells in which JunD was either knocked down or overexpressed. The immune status and autophagic activity of these cells were assessed using Western immunoblotting and enzyme-linked immunosorbent assay (ELISA). Additionally, a JunD knockdown mouse model was established, and the functional role of B cell JunD expression in the pathogenesis of SLE was assessed using Western immunoblotting, ELISA, and haematoxylin and eosin staining.

Results: B cells from patients with SLE exhibited upregulation of JunD, with overexpression facilitating *in vitro* cellular proliferation and modulation of the immune and autophagic status of these B cells. JunD knockdown was also sufficient to modulate *in vivo* immune function and the autophagic status of B cells.

Conclusion: JunD was upregulated in the B cells of patients with SLE, where it regulates proliferation, autophagy, and immunity.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic and debilitating autoimmune condition characterised by highly autoreactive B cells, high autoantibody levels, and the consequent development of pronounced organ damage. The estimated global prevalence of SLE

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https://doi.org/10.1016/j.heliyon.2024.e35949
Received 18 November 2023; Received in revised form 6 August 2024; Accepted 6 August 2024
Available online 8 August 2024

in the affected population is approximately 43.7 per 100,000 individuals (range, 15.87 to 108.92 per 100,000 individuals), with approximately 3.41 million affected individuals [1]. The disease most commonly develops between 20 and 30 years of age and exhibits a strong sex bias, affecting only one male for every nine to 10 affected females [2–4]. The pathogenesis of SLE remains unclear but appears to be associated with genetic, environmental, and immunological factors. Patients are commonly treated with nonspecific regimens that include immunosuppressive drugs and glucocorticoids. However, these drugs can cause a wide range of adverse events, including metabolic dysfunction and impaired immune function, which render those affected more susceptible to opportunistic infections [5]. As such, there is a pressing need to design new targeted therapies that can more effectively treat SLE with fewer side effects.

Autoimmune diseases are often diagnosed based on autoantibody profiles exhibited by affected patients, underscoring the key role of autoreactive B cells in these conditions [6]. Under physiological conditions, B cells facilitate durable immune responses against a diverse array of pathogens, serving as both antigen-presenting cells and sources of secreted neutralising antibodies. Compared with healthy subjects, patients with SLE exhibit abnormal peripheral B cell profiles [7] and changes in various signalling pathways within these cells, including higher levels of interleukin (IL)-6 and other inflammatory mediators, together with reductions in the levels of FCgRIIb and other inhibitory receptors [8–11]. As such, B-cells have emerged as promising targets for treating SLE.

The activator protein-1 (AP-1) family of transcription factors, also known as the JunD proto-oncogene subunit (JUND), is an essential regulator of angiogenic and proliferative activity [12]. Immortalised fibroblasts overexpressing JUND exhibit impaired proliferative activity [13], whereas those lacking JUND exhibit higher cyclin D1 levels and, consequently, enhanced proliferation [14]. A previous study reported that, upon stimulation with inflammatory cytokines, such as IL-16 or tumour necrosis factor-alpha (TNF-α), AP-1 binding activity in rheumatoid synovial cells is further increased. Additionally, increased AP-1 protein was composed of heterodimers of Fos and JunD, which were previously not considered to be the major components of AP-1 in rheumatoid synovial cells [15]. Whether JunD participates in SLE is unclear and whether JUND loss is associated with intrinsic changes in B cell function or their responses to stressful conditions remains to be determined. In the present study, JUND was identified as a novel transcription factor upregulated in the B cells of patients with SLE. Analyses of B cell apoptotic activity, proliferation, and autophagy demonstrated that JUND promoted aberrant B cell responses in the pathogenesis of SLE.

2. Materials and methods

2.1. Ethics oversight

The protocol for sample collection was consistent with all requisite regulations and guidelines, and was approved by the Ethics Committee of the Second Affiliated Hospital of Kunming Medical University (Kunming, China; Approval number: FEY-BG-39-2.0), with participants providing informed written consent.

2.2. Sample collection

In total, six patients with SLE fulfilling $\geq$4 of the revised SLE criteria, established by the American College of Rheumatology (1997) [16], and six healthy age- and sex-matched individuals were recruited. Peripheral blood (8 mL) was collected from each patient and density gradient centrifugation (Ficoll-Hypaque) was used to isolate mononuclear cells, which were then rinsed with cold phosphate-buffered saline (PBS), counted, and stored on ice for subsequent use.

2.3. Peripheral B cell characterization

B cells were detected by staining for CD19 and CD27 using the appropriate antibodies (BioLegend, Beijing, China), followed by analysis using a flow cytometer (FACSCalibur, BD Biosciences, Franklin Lakes, NJ, USA), assessing 10,000 events for each sample. Sample analyses were conducted in triplicate.

2.4. B cell culture

The normal human BALL-1 cell line was obtained from Pricella (Wuhan, China). After thawing, these cells were suspended in 10 mL of culture media, centrifuged (1000 rpm, 5 min, room temperature), resuspended in RPMI-1640, and transferred to a culture flask for routine culture in a 37 °C, 5 % CO_2 incubator.

2.5. Reverse transcriptase quantitative polymerase chain reaction

After extracting total RNA and reverse transcribing it to produce complementary DNA, quantitative polymerase chain reaction (qPCR) analyses were performed using 2 × Universal Blue SYBR Green qPCR Master Mix kit (Servicebio, Wuhan, China), and the following reaction conditions: 95 °C for 1 min; 40 cycles of 95 °C for 20 s, 55 °C for 20 s, and 72 °C for 30 s. The PCR primers used for these analyses are listed in Table 1.

2.6. JUND knockdown and overexpression

JUND cDNA and short hairpin (sh)RNA were subcloned into the lentiviral vector PWPI-GFP (Honorgene) to obtain lentiviral JUND overexpression (JUND) and shRNA (shJUND) constructs, and the empty lentiviral vector PWPI-GFP was used as negative control in further analysis. The JUND interference and lentivirus packaging overexpression vectors interfering and overexpressing plasmids were transfected into 293T cells using Lipofectamine 2000 (Invitrogen/ThermoFisher Scientific, Waltham, MA, USA). Eight hours after transfection, the medium was replaced. After 48 h of culture, the supernatant, rich in lentiviral particles, was collected and stored at −80 °C.

2.7. CCK-8 assay

Cells from individual groups were added to 96-well plates, washed two times with PBS, and 100 μL of media was added per well. At 0, 24, 48, or 96 h, media was exchanged for 95 μL of media containing 5 μL of CCK-8 reagent (DOJINDO, Japan), followed by further incubation for 2 h at 37 °C. The optical absorbance of each well was assessed at 450 nm using a microplate reader (Bio-Rad, Hercules, CA, USA).

2.8. Apoptosis analyses

After rinsing the cells with cold PBS, apoptotic death was analysed using Annexin V-PE/7-AAD (Meilunbio, Dalian, China) and flow cytometry. Briefly, cells were suspended in 1 × binding buffer, after which 100 μL cell volumes were stained with 5 μL of Annexin V-PE and 5 μL of 7-AAD for 15 min while protected from light. Apoptosis was assessed using flow cytometry.

2.9. Cell cycle analyses

The cells were harvested, resuspended at 1×10^6/mL, and stained using a cell cycle kit (Millipore, Shanghai, China) per provided directions. Briefly, cells were centrifuged, fixed for 30 min in cold 75 % ethanol at 4 °C, centrifuged (1000×*g*, 3–5 min), resuspended in PBS, then stained with a mixture of 480 μL staining buffer, 10 μL propidium iodide (50 μg/mL), 10 μL RNase A (50 μg/mL) for 30–60 min at 37 °C while protected from light, followed by flow cytometry analysis.

2.10. ELISA

Levels of supernatant IL-6, IL-10, IL-12, TNF-α, immunoglobulin (Ig)M, IgA, and IgG, as well as serum creatinine (Scr), blood urea nitrogen (BUN), TNF-α, IL-6, and IL-18 levels were measured using appropriate, commercially available, ELISA kits (Mlbio, Shanghai, China) in accordance with manufacturer's instructions.

2.11. Western immunoblotting

Cells were lysed for 10 min on ice, followed by centrifugation (15 min, 14,000×*g*, 4 °C). A commercially available BCA kit was used to measure protein levels, and 80 μL protein samples were combined with 20 μL of 5 × protein loading buffer, followed by boiling for 5 min in a water bath and separation via sodium-dodecyl polyacrylamide gel electrophoresis (i.e., "SDS-PAGE") before transfer onto polyvinylidene difluoride (i.e., "PVDF") membranes. Blots were blocked for 40 min at room temperature using 5 % non-fat milk before overnight incubation with rabbit anti-β-actin (1:5000; Proteintech, Wuhan, China), mouse anti-JUND (1:2000; Santa Cruz Biotechnology, Dallas, TX, USA), rabbit anti-LC-3 II (1:2000; Affinity Biosciences, Cincinnati, OH, USA), or rabbit anti-Beclin-1 (1:2000; Bioss, Beijing, China). After probing with secondary antibodies for 40 min, the blots were developed and imaged.

2.12. SLE model animal establishment

Thirty-six female MRL/lpr lupus mice were used to establish an SLE model, with JUND viruses injected into these animals (1×10^8 plaque forming units/mL) every other day for eight weeks. This study was approved by the Ethics Committee of Kunming Medical University (approval number: Kmmu20230173). The National Institutes of Health guidelines for the Care and Use of Laboratory Animals were followed in all animal experiments.

Table 1
The sequences of the Primers.

Gene	Forward(5′–3′)	Reverse(5′–3′)
GAPDH	CCCATCACCATCTTCCAGG	CATCACGCCACAGTTTCCC
JUND	AAACACCCTTCTACGGC	AACTCCTGCTCCTCGCT

2.13. Immunohistochemistry

After overnight fixation using 4 % paraformaldehyde (PFA), tissues were dehydrated using an ethanol gradient, paraffin-embedded, and sliced into 5 μm sections, and stained with rat anti-JUND antibody.

2.14. Immunofluorescence

Samples were fixed for 30 min at room temperature using 4 % PFA, then blocked for 1 h using PBS containing 2 % Triton X-100 (PBST) and 5 % goat serum. Samples were then probed overnight with anti-C3 or anti-IgG antibodies at 4 °C, followed by incubation for 1 h with appropriate secondary antibodies at 37 °C. The cells were then imaged using a fluorescence microscope.

2.15. Tissue histology

After fixation overnight with 4 % PFA, tissues were dehydrated using an ethanol gradient, paraffin-embedded, sliced to yield 5 μm sections, stained with haematoxylin and eosin (H&E). Randomly selected fields were imaged using a light microscope.

2.16. Statistical analysis

The data were analysed using Prism version 9.0 (GraphPad Software Inc., San Diego, CA, USA), and expressed as mean ± standard error of the mean (SEM). Group comparisons were performed using one-way analysis of variance (i.e., "ANOVA") followed by the Tukey post-hoc test. Differences with $P < 0.05$ were considered to be statistically significant.

3. Results

3.1. JUND was upregulated in peripheral blood cells from patients with SLE

Initially, B cells were collected from the peripheral blood of healthy individuals and patients with SLE for culture (Fig. 1A) and identification (Fig. 1B). qPCR analysis revealed significantly higher levels of JUND messenger RNA (mRNA) in the peripheral blood B cells of patients with SLE compared with healthy individuals ($P < 0.05$) (Fig. 1C).

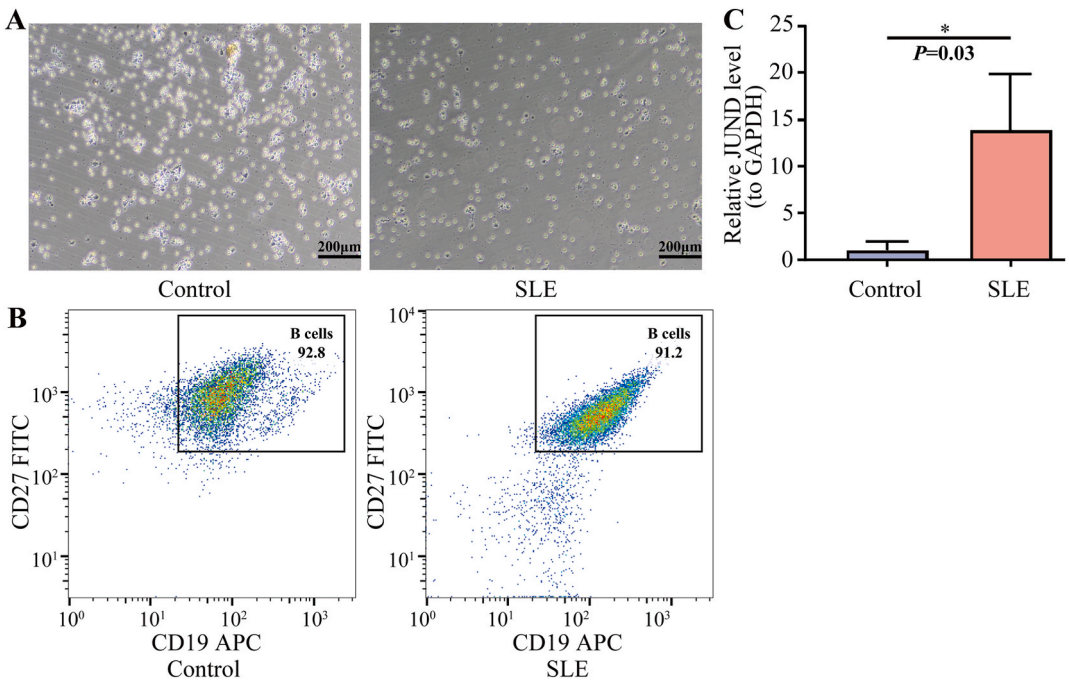

Fig. 1. Peripheral blood B cells of patients with systemic lupus erythematosus (SLE) exhibit JUND upregulation. (A) Analyses of B cells from the peripheral blood of patients with SLE. (B) Surface markers, including CD19 and CD27, were assessed via flow cytometry. (C) Reverse transcriptase-quantitative polymerase chain reaction was used to analyze JUND protein levels in samples from patients with SLE and healthy subjects (n = 6). Data are presented as mean ± standard deviation. *$P < 0.05$.

3.2. JUND gene functional validation

To better explore the functional role of JUND in SLE, JUND was stably silenced or overexpressed in the human BALL-1 B cell line or primary B cells. Western blotting was used to confirm successful knockdown or overexpression ($P < 0.05$, or $P < 0.001$) (Fig. 2A–A1). JUND knockdown suppressed BALL-1 cell growth ($P < 0.0001$) (Fig. 2B) and promoting apoptosis ($P < 0.0001$) (Fig. 2C) and cell cycle arrest (Fig. 2D), whereas the opposite was evident when JUND was overexpressed similar results were also detected in primary B cells (Fig. 2B1, C1, and D1).

3.3. JUND influences B cell inflammatory cytokine and immunoglobulin production

JUND knockdown was found to suppress the production of IL-6 and TNF-α in BALL-1 cells while enhancing IL-10 and IL-12 secretion, whereas its overexpression yielded the opposite outcomes (P < 0.0001) (Fig. 3A). Similar findings were also evident for overexpression in B cells (P < 0.01) (Fig. 3A1). Moreover, JUND knockdown suppressed IgM, IgA, and IgG secretion from B cells, whereas JUND overexpression enhanced their secretion (Fig. 3B and B1).

3.4. In vivo validation of the functional role of JUND

To confirm the ability of JUND to affect B cell functionality and to assess its impact on autophagic activity, a mouse model of SLE was established. SLE model mice exhibited high levels of JUND expression, which were significantly reduced in response to sh-JUND-AAV treatment (Fig. 4A). Scr and BUN levels were also increased in the plasma of SLE mice relative to controls; however, silencing of JUND reversed these disease-related changes (Fig. 4D). H&E staining of renal tissue samples also revealed extensive SLE-related injury to the glomeruli and interstitial tissue, which was alleviated in mice treated with sh-JUND-AAV (Fig. 4C). Immunofluorescence staining revealed high C3 and IgG levels in the tubulointerstitium of SLE model animals, whereas JUND knockdown reversed these damaging changes (Fig. 4B). ELISA additionally demonstrated the sh-JUND-AAV administration was sufficient to normalise elevated TNF-α, IL-6, and IL-18 concentrations present in this murine model of SLE (Fig. 4E). Autophagy-associated proteins were also examined to clarify the association between JUND and autophagy, revealing higher Beclin-1 and LC3B protein (Fig. 4F) and mRNA (Fig. 4G) levels in SLE model mice relative to controls, whereas silencing JUND reversed this change.

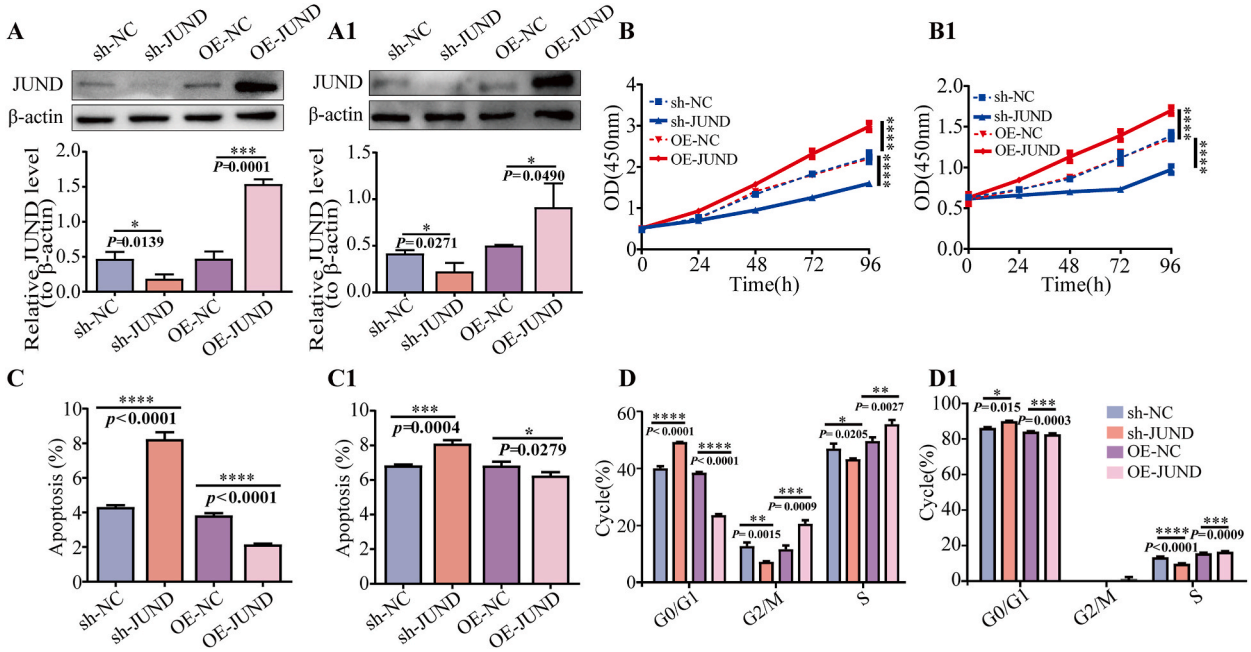

Fig. 2. JUND gene functional validation in B cells. (A, A1) Western immunoblotting was used to confirm changes in JUND expression in BALL-1 cells (A) and B cells (A1). (B, B1) CCK-8 assays were used to evaluate the impact of JUND on BALL-1 (B) and B cell (B1) proliferation. (C, C1) Flow cytometry was used to detect the impact of JUND on BALL-1 (C) and B cell (C1) apoptosis. (D, D1) Flow cytometry was used to assess the impact of JUND on BALL-1 (D) and B cell (D1) cell cycle arrest. Data presented as mean ± standard deviation (n = 3/group). NC, negative control; OE, overexpression; G0/G1 phase, pre-DNA synthesis stage; S phase, DNA synthesis stage; G2/M phase, post-DNA synthesis stage. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$.

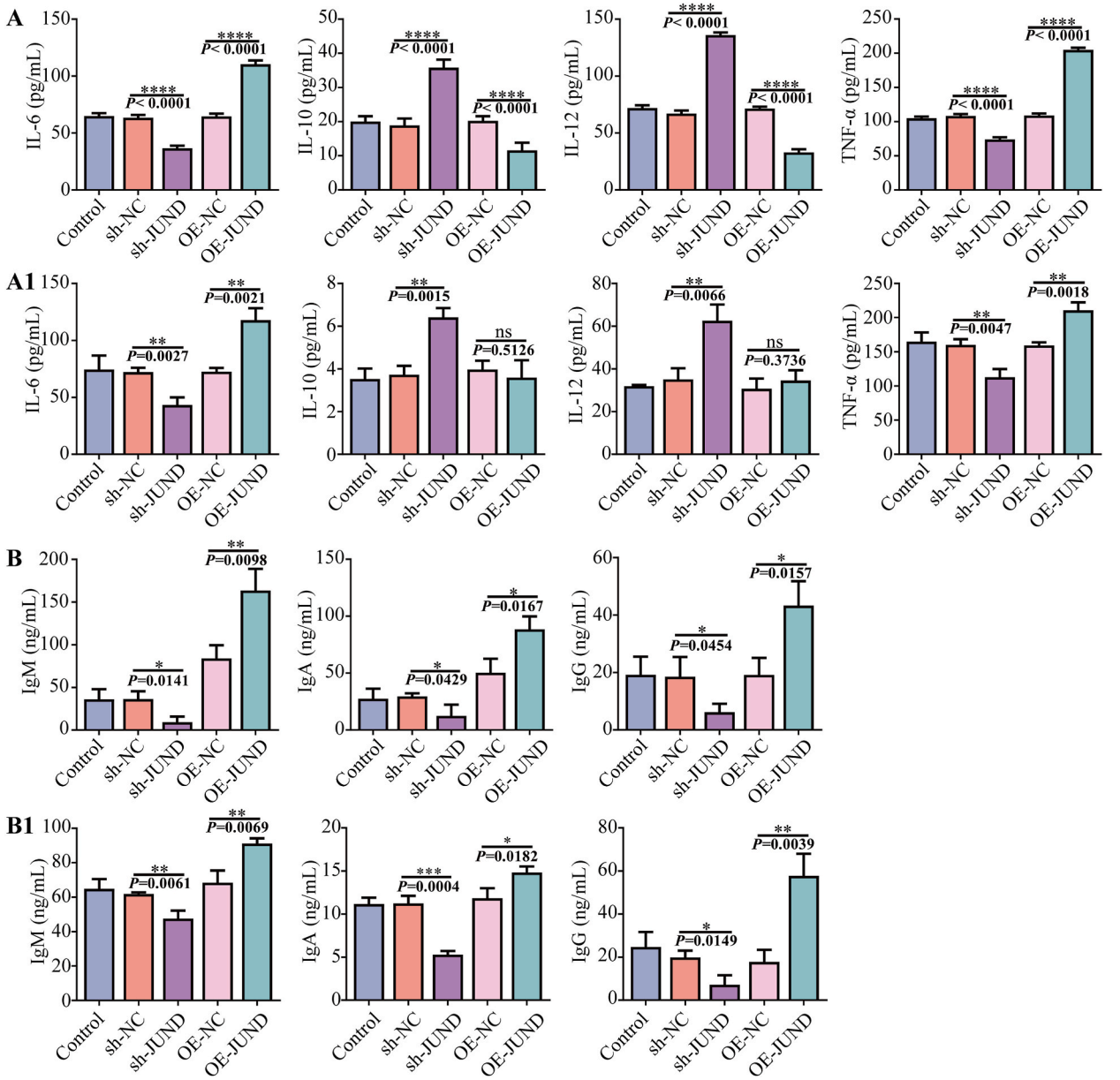

Fig. 3. JUND influences B cell inflammatory cytokine and immunoglobulin production.
(A, A1) Inflammatory cytokine levels in the supernatants of BALL-1 cells (A) and B cells (A1) were measured using ELISA. (B, B1). The concentrations of immunoglobulin (Ig)M, IgA, and IgG secreted by BALL-1 cells (B) and B cells (B1) were measured using ELISA. Data presented as mean ± standard deviation (n = 3/group). NC, negative control; OE, overexpression. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$; ns, no significant.

3.5. JUND modulated autophagic activity in the B cells of SLE model mice

To better clarify the impact of JUND on autophagic activity in B cells of SLE model mice, these cells were isolated from murine peripheral blood, cultured, and characterised (Fig. 5A). Relative to the control group, the B cells of SLE model mice exhibited significantly elevated JUND mRNA and protein levels, which were successfully reversed by adenovirus-mediated JUND knockdown (Fig. 5B). These SLE model mice also exhibited B cells with significantly higher beclin-1 and LC3B expression, which was significantly reduced by sh-JUND-AAV treatment.

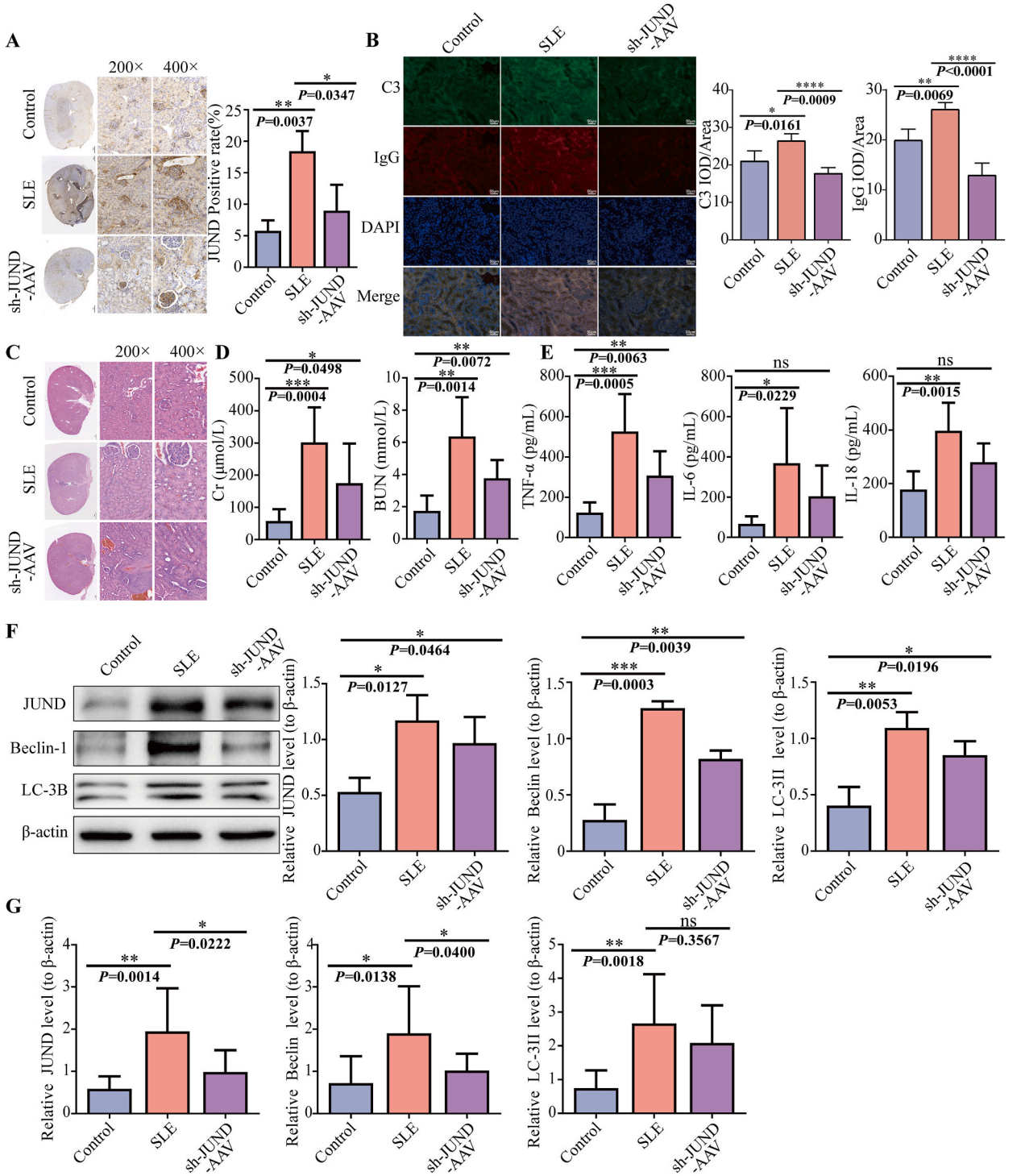

Fig. 4. *In vivo* validation of the function of JUND in systemic lupus erythematosus (SLE). (A) Immunohistochemical staining for JUND in renal tissue samples. (B) Immunofluorescent staining for immunoglobulin (Ig) G and C3 in renal tissue samples. (C) Haematoxylin and eosin (H&E) staining of damaged renal tubular and glomerular endothelial cells. (D) ELISA was used to assess serum creatinine (Scr) and blood urea nitrogen (BUN) levels in plasma samples. (E) ELISAs were used to detect plasma levels of tumour necrosis factor-alpha (TNF-α), interleukin (IL)-6, and IL-18. (F, G) JUND, Beclin-1, and LC3B expression in renal samples was assessed via Western immunoblotting (F) and quantitative polymerase chain reaction (G). Data presented as mean ± standard deviation (n = 4/group). *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ns, no significant.

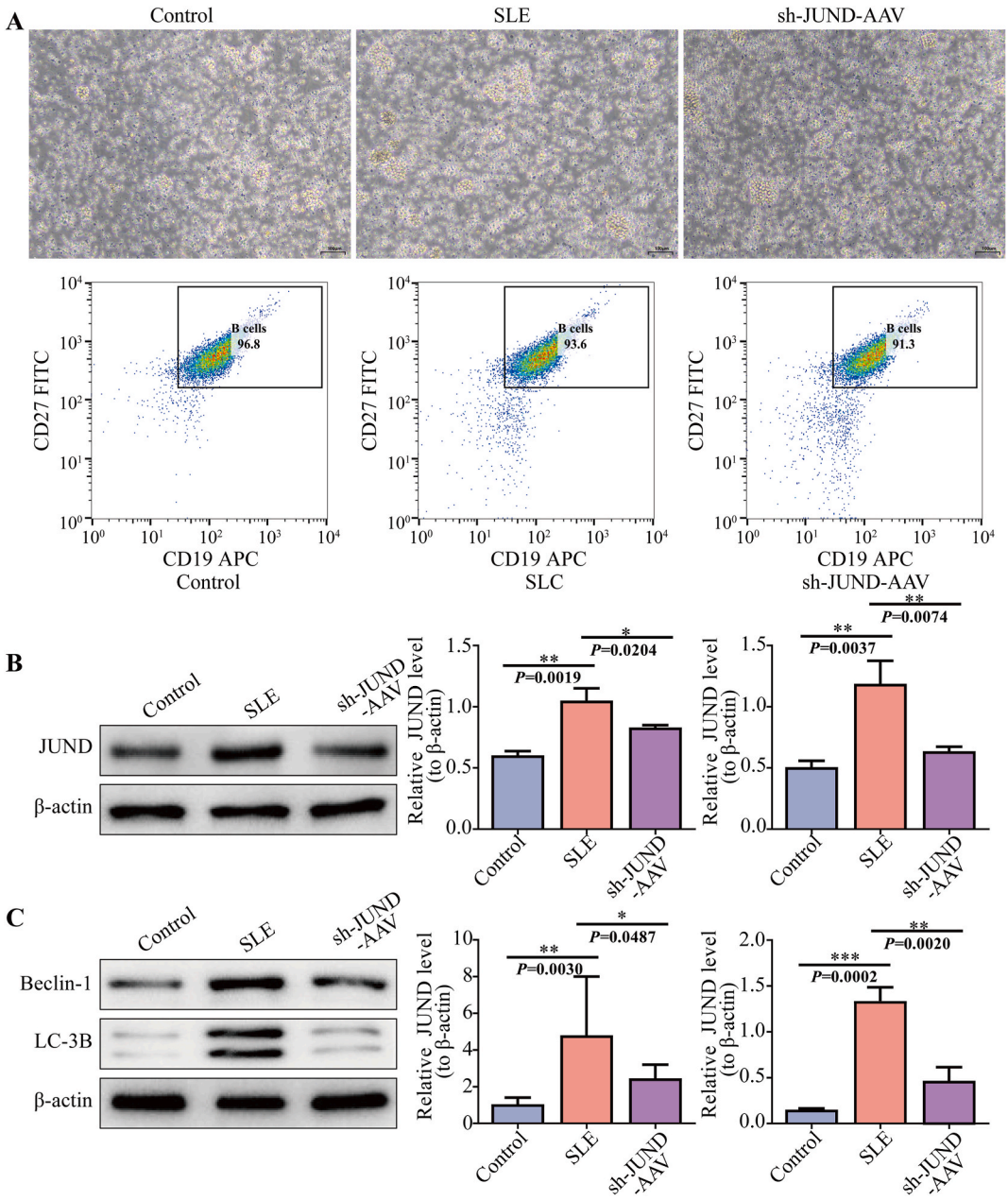

Fig. 5. JUND knockdown normalizes autophagic activity in systemic lupus erythematosus (SLE) model mice. (A) Murine B cells were analysed via flow cytometry. (B) Western immunoblotting and quantitative polymerase chain reaction were used to detect JUND in B cells. (C) Western immunoblotting was used to detect autophagy-related LC3B and Beclin-1 levels in B cells. Data presented as mean ± standard deviation (n = 5/group). $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

4. Discussion

SLE is a systemic autoimmune disease driven by adaptive and immune cell populations, culminating in multisystem organ damage [17]. Recent reviews have highlighted the differences in peripheral B cell subsets between patients with SLE and healthy controls, emphasising the importance of B cells as viable therapeutic targets for this disease [7]. Although clinical efforts to apply B-cell-targeting agents, such as rituximab and belimumab, have been implemented, further research focusing on the safety and efficacy of these regimens is needed [18]. Given the lack of complete clarity regarding the mechanistic roles by which B cells shape the progression of SLE, the development of drugs specific to particular pathogenic subsets of B cells and autoantibodies remains a key area of ongoing research interest.

JunD is the most widely expressed member of the Jun family of proteins, and has been suggested to regulate proliferative activity

while shielding cells against apoptotic death in response to stress [19]. In this study, SLE patient-derived B cells were found to express JunD at higher levels than those in healthy subjects. Proliferation occurs early during B cell activation, providing a means of rapidly scaling-up the size of the pool of antigen-responsive B cells to establish an effective anti-pathogen response [20]. Herein, marked changes in the characteristics of BALL-1 cells and primary B cells were observed following JunD knockdown or overexpression. Specifically, the proliferation of these cells was impaired following silencing of JunD, whereas its overexpression had the opposite effect. The high levels of JunD expression evident in most patients with diffuse large B-cell lymphoma (60/101 cases, cutoff score 50 %) may be indicative of its ability to enhance proliferative activity, particularly given that silencing this gene using small interfering RNA (i.e., "siRNA") constructs resulted in the suppression of cutaneous T-cell lymphoma cell line growth [21]. JunD can also protect against apoptotic induction, with fibroblasts deficient in JunD exhibiting enhanced sensitivity to treatment with TNF-α or ultraviolet irradiation [14]. Myocardial tissues lacking JunD expression also exhibit greater hypertrophy and apoptotic death, which can be enhanced by pressure overload [14]. JunD-overexpressing cell lines exhibited more rapid proliferation, as confirmed by a greater number of cells in the S phase of the cell cycle. Millena et al. reported that JunD silencing contributes to the downregulation of many proteins associated with the cell cycle, thus causing cell cycle arrest [22].

B cells are central to the induction of adaptive immunity against diverse pathogens; however, they can also aberrantly direct immune responses against host cells by secreting cytokines, producing autoantibodies, and serving as antigen-presenting cells, culminating in autoimmunity [23]. In this study, B cells overexpressing JunD exhibited enhanced IL-12, TNF-α, IgM, IgA, and IgG secretion together with weakened IL-6 and IL-10 expression. JunD dynamics have been previously suggested to play a role in oxidative stress-related inflammatory activity and cardiac function [12], with further evidence that JunD can regulate the activation of macrophages and the synthesis of IL-1β [24,25]. Collectively, these results indicate that JunD may be a viable target for therapeutic intervention in SLE, providing a means of alleviating disease-related immune dysregulation and inflammation.

In the present study, we established a murine model of JunD knockdown. While SLE model mice exhibited low C3 levels and robust IgG production, JUND silencing reversed this effect. H&E staining of renal tissues from these mice revealed kidney damage, while JUND knockdown was found to reverse disease-related increases in the levels of the inflammatory mediators TNF-α, IL-1β, and IL-6. Additional analysis of autophagy-related proteins in the kidney tissues of the SLE model mice revealed that JUND silencing reduced both Beclin-1 and LC3B levels in these tissues, both of which exhibited SLE-related upregulation. JUND knockdown was found to modulate immune function and autophagic activity in SLE, suggesting that this transcription factor influences the development of this devastating autoimmune disease by regulating immune and autophagic functions in B cells.

The present study had some limitations. The amount of data analysed from the blood samples of patients with SLE was small; as such, the sample size needs to be further increased for validation.

In summary, our results highlight the key roles of JUND as a regulator of B cell proliferation, cell cycle progression, survival, autophagy, and immune function in the context of pathogenesis. This suggests that blocking JUND pathway signalling in B cells may represent a novel approach to effectively treat SLE and other forms of B-cell-mediated autoimmunity.

Ethical approval

The protocol for sample collection was consistent with all requisite regulations and guidelines, and was approved by the Ethics Committee of the Second Affiliated Hospital of Kunming Medical University (Kunming, China; Approval number: FEY-BG-39-2.0), with participants providing informed written consent. For animal experiments, this study was approved by the Ethics Committee of Kunming Medical University (approval number: Kmmu20230173). The National Institutes of Health guidelines for the Care and Use of Laboratory Animals were followed in all animal experiments.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability statement

Data included in article/supp. material/referenced in article.

Funding

This study was supported by the National Natural Science Foundation of China (grant no. 82160595, 82373474), Applied Basic Research Programs of Yunnan Province (grant no. 202301AY070001-014).

CRediT authorship contribution statement

Yongzhuo Wu: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Yali Zhou:** Methodology. **Qinghuan Zhu:** Methodology. **Yingying Liu:** Methodology. **Danqi Deng:** Writing – review & editing, Funding acquisition. **Jianzhong Zhang:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35949.

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