Dexmedetomidine alleviates acute lung injury in humans by modulating the JAK1-STAT3 axis

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Abstract. The clinical efficacy of dexmedetomidine (Dex) in acute lung injury (ALI) and its related molecular mechanisms in human systems are poorly defined. In the present study the modulatory functions of Dex in human ALI were investigated, together with identification of the key molecular pathways involved. Human respiratory epithelial cell lines (A549 and BEAS2b) were cultured *in vitro* and categorized into four experimental groups: Untreated control (Con), Dex-treated, lipopolysaccharide (LPS)-treated, and both LPS + Dex-treated (LPS + Dex) groups. In BEAS-2B cells, inflammatory cytokine levels in the culture supernatant and cell viability were measured in all groups. In A549 cells, proliferative capacity and apoptosis rates were evaluated. The mRNA levels of caspase-3 and BCL-2, BAX within the BEAS-2B cells after LPS exposure were examined using reverse transcription-quantitative PCR. The levels of Janus kinase 1 (JAK1) and signal transduction and transcription activation 3 (STAT3) proteins, along with their phosphorylated forms in A549 cells, were analyzed via western blotting. Dex substantially suppressed LPS-mediated elevation of IL-1β, IL-6 and TNF-α. LPS-associated reductions in cell viability and proliferative activity were markedly attenuated following Dex treatment. It also lowered the LPS-induced increase in apoptotic cell populations. The upregulation of *caspase-3* and *BAX* gene expression after LPS stimulation in BEAS-2B cells was decreased by Dex treatment. The downregulation of BCL-2 gene expression after LPS stimulation in BEAS-2B cells was alleviated by Dex treatment. Moreover, Dex suppressed LPS-induced stimulation of the JAK1/STAT3 signaling cascade, as evidenced by downregulation of phosphorylated (p-)STAT3 and p-JAK1 in the A549 cells. Dex showed a protective effect against human ALI *in vitro* by reducing inflammatory responses, maintaining epithelial cell viability and decreasing apoptosis rate of epithelial cell. Modulation of the JAK1/STAT3 signaling cascade plays a crucial role in mediating these effects.

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Introduction

Acute lung injury (ALI) is a major global health burden with ~75,000 deaths each year (1). The features of ALI include an exaggerated inflammatory response and abnormally increased vessel permeability (2). Exaggerated inflammatory response is a result of neutrophil infiltration and macrophage polarization, which was characterized by excessive release of pro-inflammatory cytokines such as IL-1β, IL-6, or TNF-α. Pathogenesis of increased vessel permeability involves damage to the alveolar epithelial cells, dysfunction of the alveolar capillary barrier, and injury of the vascular endothelial cells (3). Apoptosis, a self-controlled cell death pathway, is vital in the process of ALI (4). Bcl-2 family members and caspase family members are involved in the regulation of apoptosis (5). In the absence of timely and effective intervention, ALI may progress to acute respiratory distress syndrome, a condition associated with markedly increased mortality. The development of ALI has been closely linked to excessive exposure to bacterial endotoxins, chemical injury, and immune system dysregulation (6). Therefore, treatment strategies for ALI primarily focus on suppressing uncontrolled inflammation. Drugs with potent anti-inflammatory effects, such as glucocorticoids, enhance clinical outcomes in ALI patients (7). As well as glucocorticoids, other compounds, such as daphnetin (8), corylin (9) and astaxanthin (10), have shown promise for treating ALI by targeting inflammatory pathways.

Dexmedetomidine (Dex) is a potent and specific agonist of α2-adrenergic receptors and has well-documented systemic anti-inflammatory effects (11). These effects protect multiple organs during septic conditions (12). Emerging evidence suggests that Dex can improve ALI (13); however, the molecular mechanisms behind this protective action are not fully understood and appear to involve multiple signaling pathways. In a study by Li *et al* (14), it was found that Dex reduced the sepsis-induced ALI by regulating macrophage phagocytic activity via the reactive oxygen species-a disintegrin and Metalloproteinase 10/AXL axis. Cui *et al* (15) reported that Dex reduces lipopolysaccharide (LPS)-induced ALI by inhibiting the Phosphoinositide 3-kinase/Akt/phosphorylated forkhead box-O transcription factor 1 axis. Han *et al* (16) also showed that Dex reduces ALI by suppressing TLR4/NF-κB signaling.

The Janus kinase 1 (JAK1) and signal transduction and transcription activation 3 (STAT3) cascade is crucial for modulating inflammatory and immune responses (17) and is critical

in the development of cytokine storms (18). Hyperactivation of the JAK/STAT pathway has been shown to exacerbate ALI by promoting the excessive release of pro-inflammatory mediators (19), whereas suppression of this pathway attenuates lung injury (20). The JAK/STAT signaling cascade comprises membrane-associated JAK tyrosine kinases JAK1, 2, 3 and TYK2) and intracellular STAT transcription factors (STAT1, 4, 5a, 5b and 6) (21). JAK and STAT proteins both become functionally active after phosphorylation, enabling phosphorylated STAT molecules to dimerize and enter the nucleus, where they modulate the transcriptional activity of specific downstream genes. Previous studies suggested that the JAK1/STAT3 axis is involved in modulating ALI in mouse models (22,23). However, its function in actions of Dex in ALI remain unclear. The present investigation aimed to examine the function of the JAK1/STAT3 pathway in Dex-mediated protection against human ALI.

Materials and methods

Chemicals and reagents. A549 and BEAS-2B cell lines were both obtained from HySigen Biosciences. LPS was obtained from Bioseth Biotechnology Co., Ltd. Dex was supplied by THIAI (Shanghai) Chemical Industry Development Co., Ltd. The CCK-8 assay kit was provided by Bebo Biotech. ELISA kits were purchased from Quanzhou Jiubang Biotechnology Co., Ltd. The reverse transcription-quantitative (RT-q)PCR reagent kit was from AidLab Biotechnologies Co Ltd. The BCA kit was from Beijing Solarbio Science & Technology Co., Ltd. A PAGE gel preparation kit was from Epizyme Biotechnology. Rabbit anti-human GAPDH antibody was from Affinity Biosciences. Rabbit anti-human primary antibodies against phosphorylated (p-)JAK1, JAK1, STAT3 and p-STAT3 were from Proteintech Group, Inc. Goat anti-rabbit secondary antibody was from Proteintech Group, Inc. A TUNEL apoptosis detection kit was from Wuhan Elabscience Biotechnology Co., Ltd.

Experimental subjects and grouping. A549 cells were maintained in DMEM enriched with 1% penicillin-streptomycin and 10% newborn calf serum, while BEAS-2B cells were grown in RPMI 1640 with 10% newborn calf serum and 1% antibiotics (all Keygen BIO). Cells were subcultured every alternate day and experiments were conducted using third-passage cells (P3). The two cell lines were randomly assigned to four treatment conditions: Untreated control, Dex, LPS, and combined LPS + Dex. The control group was not treated. The Dex group was exposed to 10 μmol/l Dex (final concentration). The LPS group was exposed to LPS at 10 μg/ml. In the combined treatment group, the culture media contained both LPS (10 μg/ml) and Dex (10 μmol/l).

Detection of inflammatory cytokines. BEAS-2B cells ($1x10^5$/well) were grown in six-well plates at 37˚C with 5% CO_2. Culture supernatants from each treatment group were obtained, and the inflammatory cytokines were detected via ELISA) kits (cat. nos. QZ-10489, QZ10469, QZ10789) as directed. Standard curves were plotted using the provided recommendations, and cytokine levels in each group were calculated from these curves.

CCK-8 assays. BEAS-2B cells ($2x10^3$/well) were grown in 96-well plates, after which 10 μl of CCK-8 reagent was introduced to the wells for a duration equal to 2 h. Absorbance values (450 nm) were obtained using a microplate reader at predetermined time points, and cell viability was determined.

Colony formation assays. The proliferative ability of A549 cells was observed using colony formation assays. Cells from each treatment group were grown ($1x10^3$/well in 2.5 ml of medium) in six-well plates over 2 weeks, after which cells were fixed [4% paraformaldehyde (PFA)] at 4 ˚C for 15 min and stained (crystal violet) at 20˚C for 30 min. Visible colonies (diameter >1 mm) were counted and recorded for each well.

Detection of cell apoptosis. Apoptosis in all cell lines was examined using TUNEL) assay. A549 cells ($5x10^5$/well in 2.5 ml medium) were grown in 6-well plates. Treated cells were fixed (4% PFA, 20 min), permeabilized (0.1% Triton X-100, 30 min room temperature) and cleaned (thrice) using PBS. TUNEL staining was performed as per the kit protocol. Cell nuclei were labelled using DAPI at 20˚C for 5 min, and apoptotic cells were labeled with the TdT enzyme at 37˚C for 30 min. All images (fluorescence field) were captured and analyzed using ImageJ (version 1.6.0, National Institutes of Health).

Gene expression analysis. A549 cells ($5x10^5$/well in 2.5 ml medium) were grown in 6-well plates for 24 h, Then total content of RNA was isolated from A549 cells using TRIpure (Aidlab Biotechnologies Co., Ltd.), followed by RT to synthesize cDNA with TRUEscript RT MasterMix (Aidlab Biotechnologies Co., Ltd.). RT was performed at 42˚C for 15 min, followed by inactivation at 85˚C for 5 sec. Quantitative PCR was conducted on a QuantStudio 5 system (Thermo Fisher) using SYBR Green qPCR Mix (Aidlab Biotechnologies Co., Ltd.), with denaturation for 3 min at 94˚C, 40 cycles at 94˚C for a duration equal to 10 sec each and at 60˚C for a duration equal to 30 sec. Primer sequences were: *β-actin* Forward CGTTGACATCCG TAAAGACC, Reverse GCTAGGAGCCAGGGCAGTA; *Bax* Forward TGTTTTCTGACGGCAACTTCA), Reverse AGC CCATGATGGTTCTGATCA; *Bcl-2* Forward CCTGTGGAT GACTGAGTACCTGAAC, Reverse CAGCCAGGAGAAATC AAACAGA; *caspase-3* Forward TGGATTATCCTGAGA TGGGTTTATG), Reverse GCTGCATCGACATCTGTACCA).

β-actin represented the reference gene. Relative gene levels were noted via the $2^{-\Delta\Delta Cq}$ technique (24). This experiment was repeated three times. Data were visualized in Excel (version 2016, Microsoft Corporation).

Western blotting. BEAS-2B cells were grown until 90% confluence in six-well plates, and were then lysed with 100 μl RIPA lysis buffer (Solarbio Science & Technology Co., R0010) per well. Cell lysates were obtained, and the concentrations of the protein were determined via BCA assays. Proteins were electrophoresed on 10% SDS-PAGE at 150 V for 50 min, and blotted onto PVDF membranes at 250 mA for 90 min. Blots were kept in blocking solution (0.1% TBST with 5% BSA) at room temperature for a duration equal to 1 h, and then treated for 24 h at a temperature equal to 4˚C for 24 h with primary antibodies for GAPDH (Affinity, cat. no. AF7021, 1:3,000), JAK1 (Proteintech, 27284-1-AP, 1:3,000), p-JAK1 (FabGennix, PJAK1-140AP, 1:3,000), STAT3 (Proteintech, 10253-2-AP, 1:3,000) and p-STAT3 (FabGennix, PSTAT3-340AP, 1:3,000).

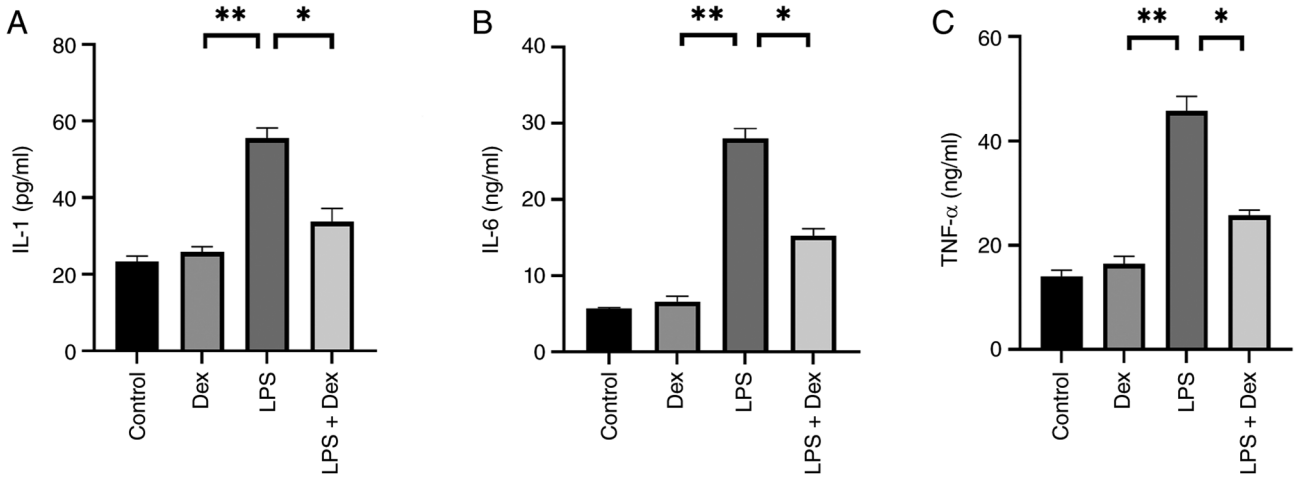

Figure 1. Dex suppresses LPS-induced inflammation in BEAS-2B cells. (A) IL-1β, (B) IL-6, and (C) TNF-α. Data are expressed as mean ± SD (n=3). *P<0.05, **P<0.01. Dex dexmedetomidine; LPS, lipopolysaccharide.

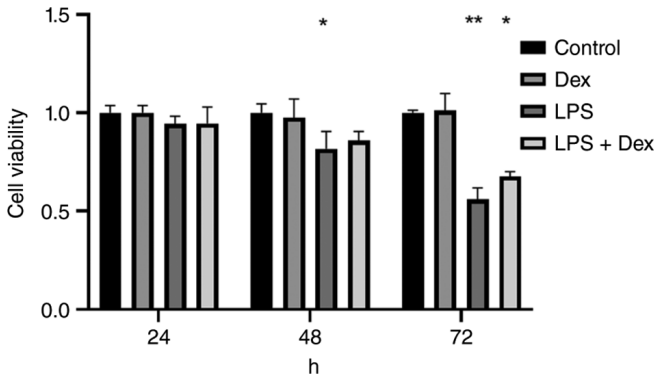

Figure 2. Influence of Dex on cell viability after LPS exposure. Cell viability of BEAS-2B cells was assessed at different time points under different treatment conditions. Data are expressed as mean ± SD (n=4). *P<0.05, **P<0.01. Dex dexmedetomidine; LPS, lipopolysaccharide.

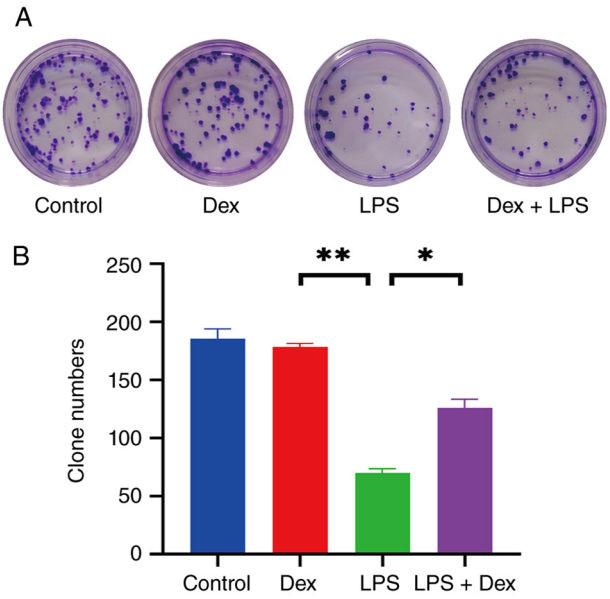

Figure 3. Dex attenuates inhibition of A549 cell propagation induced by LPS. (A) Representative images of colony formation assays under different treatment conditions. (B) Quantification of colony numbers. Data are expressed as mean ± SD (n=3). *P<0.05, **P<0.01. Dex dexmedetomidine; LPS, lipopolysaccharide.

Following cleaning with TBST, the membranes were kept with a goat anti-rabbit HRP-linked secondary antibody (Proteintech Group, Inc.; cat. no. SA00001-2, 1:1,000) at room temperature for a duration equal to 1 h. Bands were detected using an enhanced chemiluminescence reagent (MedChemExpress, HY-K2005) and ImageJ (version 1.6.0, National Institutes of Health) was used to quantify band intensities.

Statistical analysis. Data were statistically analyzed using SAS software (version 9.2, SAS Institute Inc.), while GraphPad Prism (v9.0; Dotmatics) was used to generate graphs. Data that followed a normal distribution were depicted as mean ± standard deviation (SD). Differences among multiple experimental groups were evaluated using one way ANOVA before Bonferroni post hoc tests. P<0.05 was considered to indicate a statistically significant difference.

Results

Dex suppresses LPS-induced inflammation in BEAS-2B cells. Levels of inflammatory mediators in culture supernatants were initially quantified across all experimental groups. Exposure to Dex alone did not markedly alter IL-1β, IL-6, or TNF-α levels relative to the control condition (P>0.05). By comparison, LPS induction remarkably upregulated the levels of these pro-inflammatory factors (P<0.01). Co-treatment with Dex substantially reduced the LPS-induced inflammatory response, as shown by lower cytokine levels (P<0.05; Fig. 1).

Effect of Dex against LPS-induced suppression of BEAS-2B cell viability. Cell viability of BEAS-2B cells was evaluated at different time points after treatment. At 24 h post-treatment, no substantial differences were found in all four groups. At 48 h, a marked reduction in cell viability was found in the LPS-treated cells relative to the controls (P<0.05). This

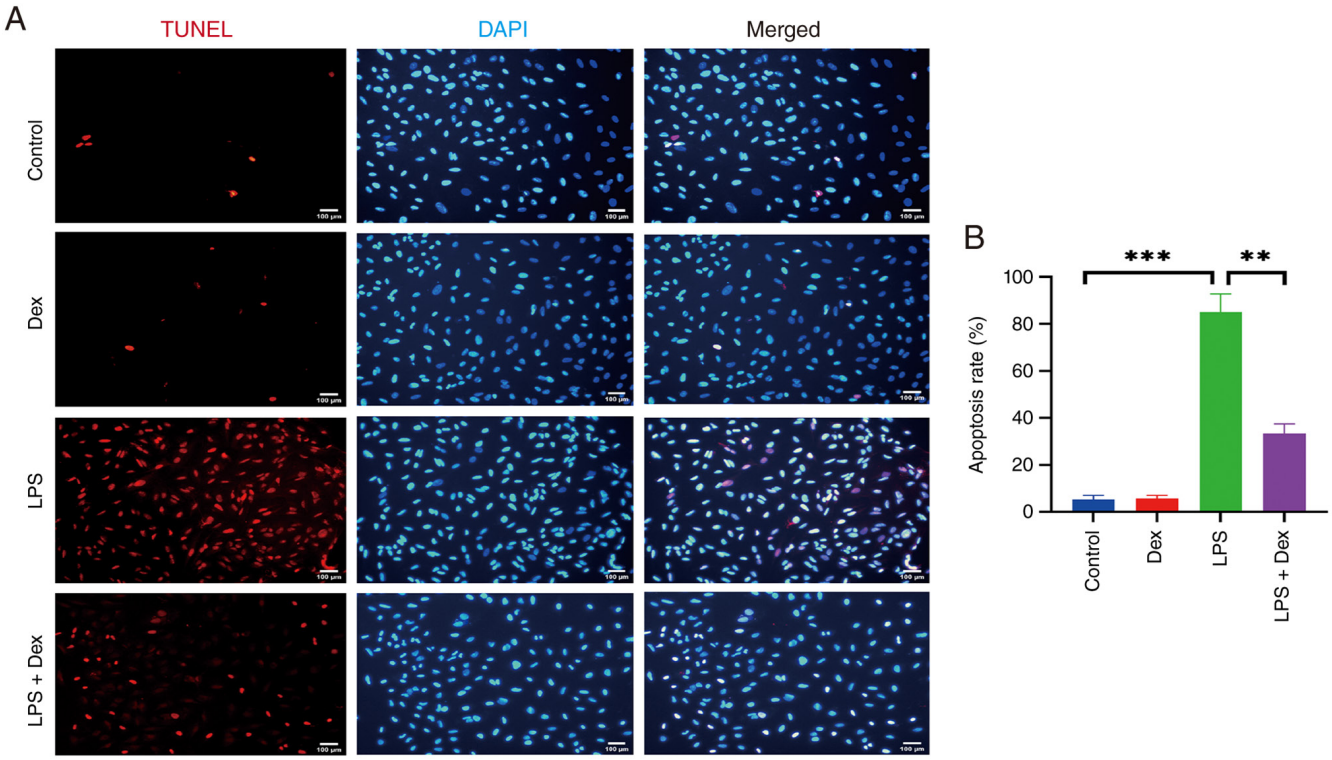

Figure 4. Dex reduces apoptosis induced by LPS in A549 cells. (A) TUNEL staining of A549 cells following different treatments (scale bar, 100 μm). (B) Quantification of apoptotic cell rates in all groups. Data are expressed as mean ± SD (n=3). **P<0.01, ***P<0.001. Dex dexmedetomidine; LPS, lipopolysaccharide.

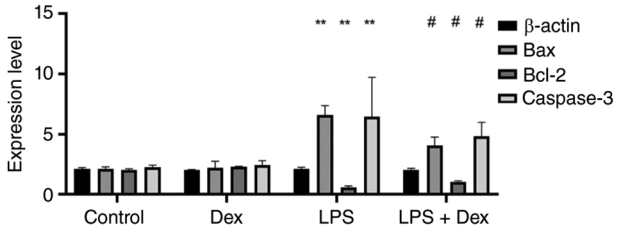

Figure 5. Dex modulates apoptosis-related gene level in LPS-stimulated A549 cells. $^{\#}$P<0.05 vs. LPS group, **P<0.01 vs. Control. Dex dexmedetomidine; LPS, lipopolysaccharide.

reduction was alleviated in the group receiving combined LPS and Dex treatment, with viability levels not considerably different from the control (P>0.05). At 72 h, LPS exposure continued to reduce cell viability substantially relative to the control (P<0.01). Although Dex attenuated this inhibitory effect, cell viability in the combined treatment group remained considerably less than in the controls (P<0.05; Fig. 2).

Dexmedetomidine attenuates LPS-induced inhibition of A549 cell propagation. The proliferative ability of A549 cells was evaluated using a colony formation assay. No substantial variances in colony numbers were detected Dex-exposed and control cells (P>0.05). LPS exposure resulted in a significant decrease in colony formation relative to the control (P<0.05). Co-administration of Dex partly reversed the inhibitory effect of LPS. Colony counts in the Dex + LPS treatment group increased compared with following LPS exposure (P<0.05; Fig. 3).

Dex decreases LPS-induced apoptosis in A549 cells. Apoptosis is crucial to the development of ALI, and modulating apoptotic activity can substantially influence disease severity. The apoptosis rates of A549 cells under different treatment conditions are illustrated in Fig. 4. LPS stimulation substantially accelerated the number of apoptotic cells relative to the control (P<0.05). Dex treatment considerably reduced the LPS-induced rise in apoptosis (P<0.05).

Dexmedetomidine modulates apoptosis-related gene levels in LPS-stimulated A549 cells. The effects of Dex on apoptosis were assessed by measuring *BAX*, *BCL-2*, and *caspase-3* levels. As shown in Fig. 5, Dex exposure did not change the levels of these genes relative to the controls (P>0.05), although LPS significantly upregulated *BAX* and *caspase-3* expression while markedly downregulating *BCL-2* (P<0.01). Co-treatment with Dex considerably attenuated these LPS-induced changes, decreasing the upregulation of *BAX* and *caspase-3* and partially restoring *BCL-2* levels (P<0.05).

Dexmedetomidine inhibits the stimulation of the JAK1/STAT3 signaling in LPS-treated BEAS-2B cells. Stimulation of the JAK1/STAT3 axis is characterized by increased JAK1 and STAT3 phosphorylation (25). The western blotting results of p-JAK1, JAK1, STAT3, and p-STAT3 are shown in Fig. 6. Treatment with Dex alone did not considerably change the expression of these proteins relative to the control. Similarly, total JAK1 and STAT3 levels remained unchanged after LPS stimulation. However, LPS exposure substantially enhanced p-JAK1 and p-STAT3

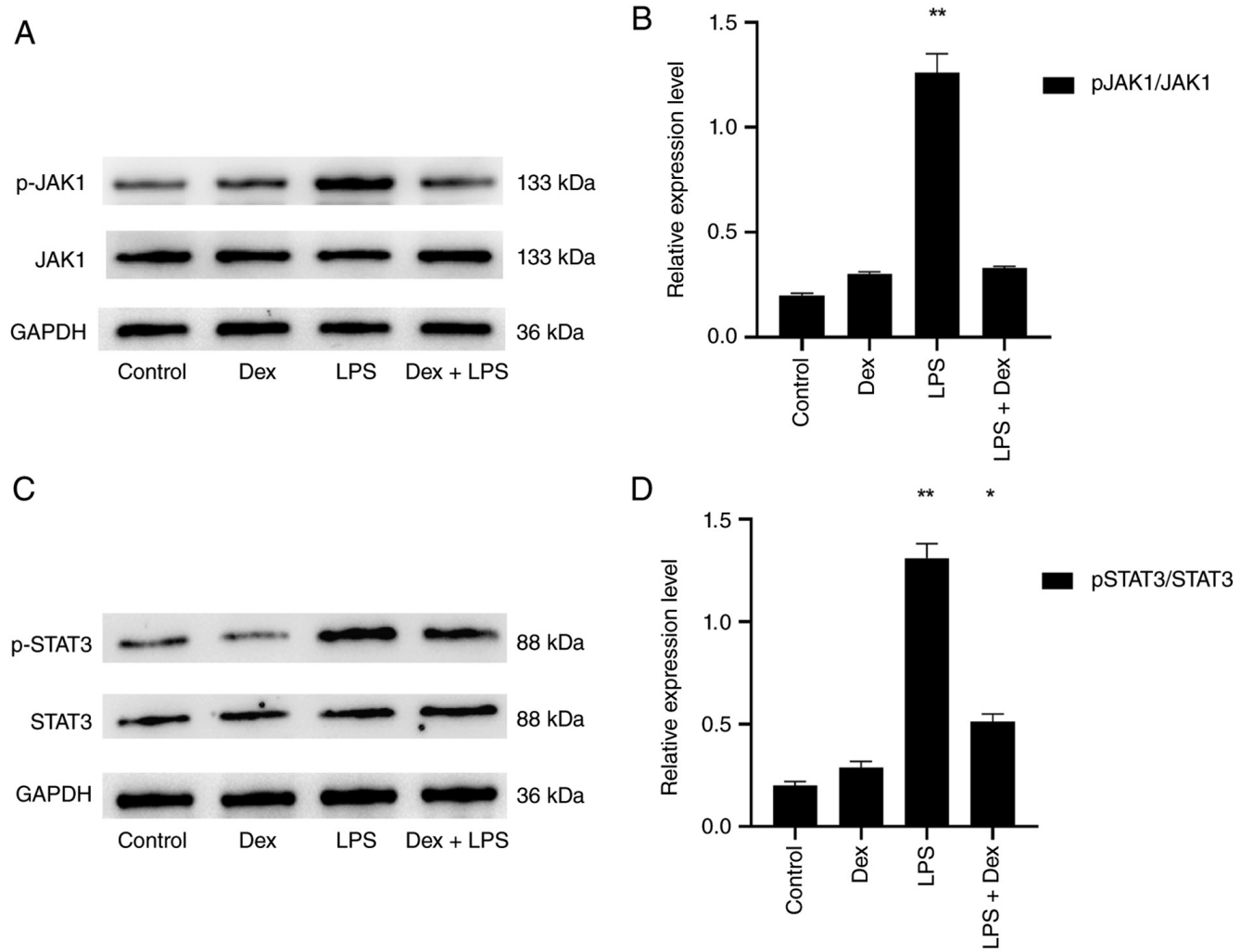

Figure 6. Dex modulates apoptosis-related gene level in LPS-stimulated A549 cells. (A) Western blotting images of JAK1, p-JAK1, and GAPDH. (B) Densitometric analysis of relative protein expression levels. (C) Western blotting images of STAT3, p-STAT3, and GAPDH. (D) Quantification of relative STAT3 and p-STAT3 levels. Data are mean ± SD. *P<0.05, **P<0.01. Dex dexmedetomidine; LPS, lipopolysaccharide; JAK1, Janus kinase 1; p-, phosphorylated; STAT3, signal transduction and transcription activation 3.

expression (P<0.01), indicating pathway activation. In the group treated with both LPS and Dex, the JAK1, p-JAK1, and STAT3 levels did not differ considerably from those in the control, whereas p-STAT3 levels remained elevated (P<0.05). Importantly, the level of p-STAT3 upregulation was substantially less than that of the LPS-only group, suggesting that Dex partially inhibited the stimulation of the JAK1/STAT3 pathway.

Discussion

As aforementioned, ALI is pathologically characterized by an uncontrolled and excessive inflammatory response (26). Therefore, inflammation indicators within the respiratory system are widely accepted as reliable markers for ALI severity. The current *in vitro* study showed that Dex attenuated inflammatory responses and apoptosis in two human respiratory epithelial cell lines, involving the JAK1/STAT3 signaling cascade. Although animal models are often used to study ALI, they do not fully mimic the pathological processes observed in humans. Due to the ethical and practical limitations of *in vivo* human experiments, the present study used human respiratory epithelial cell lines for an improved simulation of human disease conditions.

LPS from the cell walls of Gram-negative bacteria causes acute lung inflammation in humans (27). Exposure of A549 and BEAS-2B cells to LPS was therefore used to simulate the pathological features of human ALI. Pro-inflammatory mediators are key factors that markedly aggravate lung injury (28) and their levels serve as indicators of the severity of the inflammatory response. The elevation of these cytokines following LPS stimulation and their decrease with Dex treatment suggest a potent anti-inflammatory effect of Dex in human ALI. The number of α2-adrenergic receptors may vary between these two kinds of airway epithelial cells, but the protective effects of Dex can be observed in both cells. It was thus hypothesized that a canonical signal pathway, such as the JAK/STAT pathway, may be the underlying mechanism.

Apoptosis is crucially involved in the progression of ALI (29), although apoptotic responses differ among different cell types involved in lung injury (30). Increased

apoptosis of inflammatory cells, such as neutrophils and macrophages, may aid in resolving inflammation and promoting recovery (31). By comparison, excessive apoptosis of respiratory epithelial cells disrupts alveolar and bronchial barrier integrity, resulting in increased alveolar protein-rich fluid leakage and exacerbation of lung injury (32). Suppression of epithelial cell apoptosis has been shown to improve LPS-induced ALI (33). Key mediators of apoptosis, such as Bcl-2, Bax, and caspase-3, are commonly used to evaluate apoptotic activity (34). Among these, Bcl-2 acts as an anti-apoptotic protein, while Bax and caspase-3 promote apoptotic processes (35). The present findings revealed that Dex attenuated LPS-induced elevation of Bax and caspase-3 and counteracted the LPS-associated reduction in Bcl-2. These results indicated that Dex efficiently inhibited LPS-induced apoptosis in epithelial cells. Consistent with these observations, Huang *et al* (36) reported that nerelimomab alleviates ALI by inhibiting apoptosis in A549 cells, and that modulating apoptosis in BEAS-2B cells has also been shown to markedly improve ALI outcomes (37). The inhibitory influence of Dex on apoptosis within both the BEAS-2B and the A549 cells further support its potential therapeutic role in human ALI.

The JAK1/STAT3 axis is known to be linked to ALI onset. Stimulation of JAK1 induces phosphorylation of STAT3, which enhances the transcription of genes involved in inflammation (38). Pharmacological inhibition of JAK1 is commonly used to treat inflammatory and immune-mediated disorders (39) and has also shown efficacy in viral pneumonia (40). In a study by Joshi *et al* (41), it was found that rapalol alleviated ALI by blocking JAK1 activation. Consistent with these findings, the present study revealed that Dex substantially reduced LPS-induced JAK1 phosphorylation, thereby attenuating inflammatory amplification and protecting against lung injury in human cell models. Phosphorylated STAT3 has been shown to exacerbate inflammatory responses by promoting the recruitment of inflammatory cells (17), an effect related to increased neutrophil extracellular trap formation during sepsis (42). By upregulating pro-inflammatory cytokines in lung epithelial cells, p-STAT3 leads to increased alveolar-capillary permeability (43). Kubra and Barabutis (44) reported that activation of STAT3 potentiates ALI by damaging the endothelial cells. Moreover, STAT3 activation supports M1 macrophage polarization, which further boosts inflammation in ALI (45). Therefore, inhibiting STAT3 has been reported to provide substantial protection against ALI (46). In line with these findings, Dex treatment substantially decreased STAT3 phosphorylation following LPS exposure, thus suppressing excessive inflammatory signaling. Unlike p-JAK1, the level of p-STAT3 did not return to normal under the combined treatment of LPS and Dex in the present study. This phenomenon indicated that STAT3 was not only activated by JAK1, but other upstream regulatory proteins, such as IL-6, also play a certain role (47).

Therapeutic agents exert protective effects against ALI through modulation of the JAK1/STAT3 pathway. Li *et al* (48) demonstrated that HHC alleviates ALI by regulating JAK1/STAT3 signaling, while Yin *et al* (49) reported that Zuojin Fang reduces ALI severity by downregulating this pathway. Zhang *et al* (50) showed that Dex alleviates ALI in mice by inhibiting JAK1/STAT3 signaling. The current findings extended these observations by demonstrating that Dex also exerts protective effects against ALI in human-derived cell models by modulating the JAK1/STAT3 signaling axis.

Despite these findings, the present study had several limitations. First, the study focused solely on the JAK1/STAT3 pathway and the potential involvement of other signaling pathways in Dex-mediated protection remains to be examined. Second, the exact mechanistic relationship between JAK1/STAT3 inhibition and the observed regulation of inflammatory and apoptotic responses has not been fully explored, necessitating further in-depth research. Third, the experiment model was an epithelial-only model, while the ALI pathology involves alveolar-capillary failure, neutrophil infiltration, and endothelial injury. More research should be performed to clarify the mechanism of Dex in ALI.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XD contributed to study conception and design. The manuscript was drafted by XD and revised by ZY. Data collection was performed by DS and JW. DS and JW confirm the authenticity of all the raw data. Data analysis were performed by HC. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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