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Research article

Exosomes derived from ITGB1 modified Telocytes alleviates LPS-induced inflammation and oxidative stress through YAP1/ROS axis

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ABSTRACT

Aims: Previous studies have demonstrated a significant upregulation of Integrin Beta 1 (ITGB1) in Telocytes. This study aims to explore the roles and underlying mechanisms of ITGB1 in inflammation and oxidative stress following Lipo-polysaccharide (LPS) administration in Telocytes.
Methods: We observed an increase in reactive oxygen species (ROS) production, accompanied by a reduction in ITGB1 levels post-LPS treatment.
Results: Notably, inhibiting ROS synthesis markedly reduced LPS-induced ITGB1 expression. Additionally, ectopic ITGB1 expression mitigated LPS-induced inflammation and oxidative stress, evident through decreased levels of pro-inflammatory markers such as Tumor Necrosis Factor-alpha (TNF-α), Interleukin (IL)-1β, IL-6, and Monocyte Chemoattractant Protein (MCP)-1. Depletion of endothelial Yes-Associated Protein 1 (YAP1) notably diminished the levels of inflammatory markers and ROS production. Furthermore, exosomes secreted by ITGB1-modified Telocytes promoted Human Umbilical Vein Endothelial Cells (HUVECs) proliferation and inhibited apoptosis. In vivo experiments revealed that exosomes from ITGB1-modified Telocytes modulated functional and structural changes, as well as inflammatory responses in Acute Lung Injury (ALI).
Conclusion: These findings highlight the critical role of the YAP1/ROS axis in LPS-induced Telocyte injuries, underlining the therapeutic potential of targeting ITGB1 for mitigating inflammation and oxidative stress in these cells.

1. Introduction

Acute Lung Injury (ALI), characterized by the exudation of protein-rich inflammatory fluid, infiltration of inflammatory cells, and lung tissue hemorrhage, leads to damage alveolar epithelial and capillary endothelial cells [1–3]. When the alveolar oxygen partial pressure to inhaled oxygen fraction (PaO2/F1O2) ratio falls below 300, ALI progresses to acute respiratory distress syndrome (ARDS), which still has a mortality rate exceeding 50% due to the complex molecular mechanisms and a lack of effective therapies [2,4]. Despite significant advancements, the annual mortality rate of ALI/ARDS remains high [5,6], underscoring the need for new

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therapeutic strategies and the exploration of potential combination therapies.

Telocytes (TCs), a unique type of stromal cell with extensive telopodes (Tps) [7,8], have been identified in various organs, including the lungs, heart, spleen, skin, and reproductive system [9–11]. TCs engage in extensive crosstalk with neighboring tissues and cells, suggesting their involvement in multiple biological functions [12,12,13,13]. Prior studies have highlighted distinct gene expression profiles in pulmonary TCs compared to other local cell types, indicating unique biological properties and behaviors [14,15]. TCs form three-dimensional network structures through Tps to contact with the homocytic or heterocytic cells, transmitting signaling molecules through pre-secretion and/or para-secretion, which enter the vascular, neural and endocrine systems through the growth and shedding of vesicles [16]. Thus, TCs can protect tissue from acute injury via cell–cell communication. Integrin Beta 1 (ITGB1), a subunit of integrins, is a critical factor for extracellular matrix (ECM)-receptor interaction and focal adhesion and involved in the regulation of various signaling pathways including FAK signaling, Wnt/β-catenin, and Hippo pathways, and has been associated with inflammatory responses in renal ischemia/reperfusion injury [17–20]. These findings suggest a potential protective role for ITGB1 in ALI.

This study aims to elucidate the functional role of ITGB1 in TCs and in tissue repair. We assessed ITGB1 expression in TCs treated with LPS or N-Acetylcysteine (NAC) and investigated the anti-inflammatory and antioxidative effects of ITGB1, including the underlying molecular mechanisms in vitro. Additionally, we explored the protective effects of exosomes from ITGB1-modified TCs in HUVECs post-LPS treatment.

2. Materials and methods

2.1. Cell culture and treatment

Murine pulmonary Telocytes (TCs) were isolated and characterized as previously described [9]. The HUVEC cell lines were obtained from Cell Bank of the Chinese Academy of Sciences (Shanghai, China). All cells were cultured in DMEM (GIBCO, USA), supplemented with 10% FBS and 100 U/ml penicillin/100 μg/mL streptomycin (Sigma-Aldrich, St. Louis, MO, USA), in a humidified environment of 37 °C and 5% CO2. For Lipopolysaccharide (LPS) treatment, cells were exposed to LPS concentrations of 1, 2, 4, 8, and 16 μg/ml for 24 h. We observed that the protein expression level of ITGB1 decreased most significantly when the LPS concentration reached 8 μg/ml, so we chose 8 μg/ml LPS for subsequent experiments. 8 μg/ml LPS was used for durations of 6, 12, 24, and 48 h. A sterile saline solution served as the control. Post-incubation, analyses were conducted on cell apoptosis, ROS levels, tube formation assay, and protein expression were analyzed. The levels of IL-6, TNF-α, MCP, IL-1β, and VEGF in the culture medium were measured.

2.2. RNA extraction and quantitative real-time PCR (qPCR)

Total RNA from cultured cells and mouse kidneys was extracted using Trizol reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. 500 ng of total RNA from each sample was reverse-transcribed into cDNA using the PrimeScript RT reagent kit (Takara, China). qPCR to measure gene expression was performed using SYBR Green I Master Mix (Takara) on an Applied Biosystems 7500 Real-time PCR System (Applied Biosystems; Foster City, CA, USA). The primer sequences used were as follows: ITGB1 forward primer: GTCTTGGAACGGATTTGATGA and reverse: TTTGCTGGGGTTGTGCTAAT; GAPDH forward: CGGAGTCAACGGATTTGGTCGTAT and reverse: AGCCTTCTCCATGGTGGTGAAGAC. GAPDH served as the internal control.

2.3. Animal model

All animal studies were conducted in accordance with the national guide for the care and use of laboratory animals, with ethical approval from the Institutional Review Board of the Department of Laboratory Animal, Shanghai ZY (Permit No. SHZY-202105143). The acute lung injury model was performed as previously described [9]. Mice were randomly divided into four groups: PBS-treated (VV), 2 μg/kg LPS-treated (VA), 2 μg/kg LPS plus EXO-Vector (300 μg of total protein in 50 μL), and 2 μg/kg LPS plus EXO-ITGB1 (300 μg of total protein in 50 μL). Exosomes were intraperitoneally injected for 24 h, followed by LPS administration. All mice were euthanized using an overdose of pentobarbital.

2.4. Plasmid construction and cell transfection

The full-length cDNA of the ITGB1 gene was PCR-amplified from TCs and cloned into the pCDH-CMV-MCS-EF1-Puro lentiviral vector (System Biosciences, Mountain View, CA, USA). The plasmids were confirmed by sequencing. Lentiviruses carrying ITGB1 were produced in HEK293T cells co-transfected with pCDH-ITGB1, pMD2. G, and pSPAX.2 plasmids using Lipofectamine 3000 (Invitrogen). Viral supernatant was collected after 48 h and transduced into TCs with 4 μg/ml polybrene (Sigma-Aldrich). TCs were selected using 2 μg/ml puromycin (Sigma-Aldrich) for 48 h.

2.5. Apoptosis analysis

Following the aforementioned treatments, cells were harvested, washed with PBS, and stained with an Annexin V-FITC/PI apoptosis detection kit (Invitrogen). After 15-min incubation in darkness, samples were analyzed using flow cytometry (Becton Dickinson, NJ, USA).

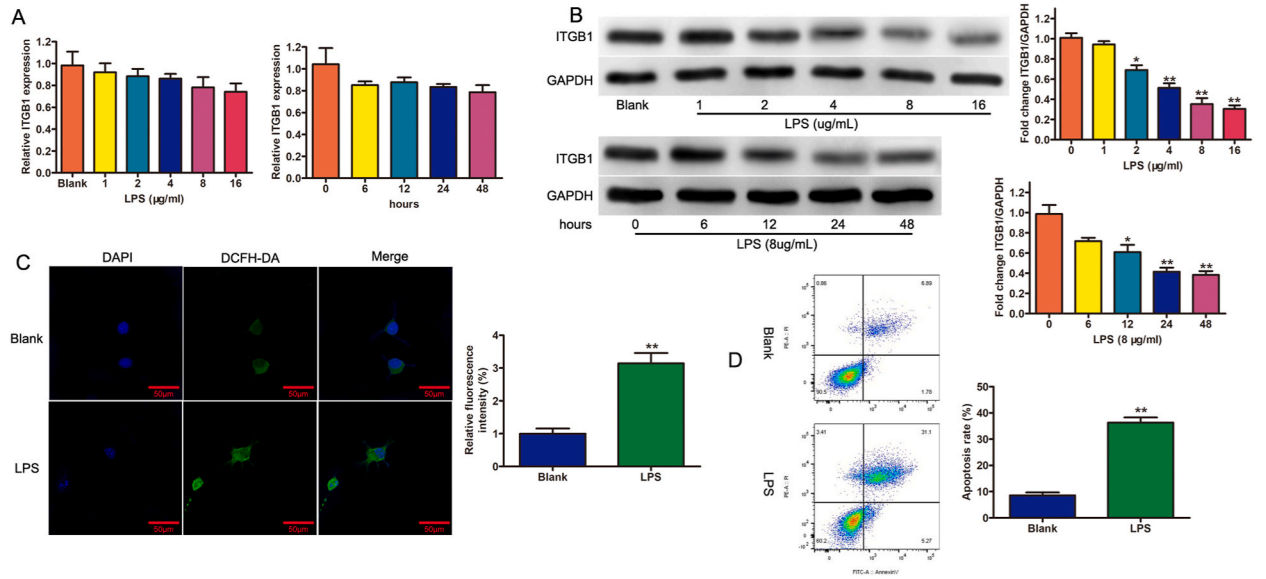

Fig. 1. Downregulation of ITGB1 Expression in TCs Treated with LPS, (A) Real-time qPCR analysis of ITGB1 expression in TCs treated with varying LPS concentrations (left) for 24 h and different time points (right), (B) Protein expression of ITGB1 in TCs under similar conditions, (C) ROS production in TCs with or without 8 μg/ml LPS, (D) Apoptosis levels in TCs post-LPS treatment. $^{**}p < 0.01$ indicates significant differences.

2.6. Tube formation assay

TCs, with or without ITGB1 overexpression, were treated with 8 μg/ml LPS for 24 h. Following a wash with PBS and a subsequent refresh with serum-free culture medium, the supernatant was harvested for tube formation assays. 200 μl of Matrigel (BD Biosciences) was plated in a 6-well plate and incubated at 37 °C for 1 h to pre-solidify. Then, HUVECs (3×10^5) were resuspended in the above medium, and capillary-like structure formation was monitored under a light microscope (100×) 6 h later. The branch points of the tubes were quantified by randomly selecting five fields per well.

2.7. Isolation and characterization of exosomes from TCs

Exosomes isolated from TCs or ITGB1-modified TCs, referred to as EXO-Vector and EXO-ITGB1, respectively, were extracted from cell culture media using Total Exosome Isolation Reagent (ThermoFisher) following the manufacturer's instructions. Exosomes were characterized by TEM and Western blotting, as previously described [21].

2.8. Enzyme-linked immunosorbent assay

Levels of IL-6, IL-1β, MCP-1, TNF-α, and VEGF in the cell supernatant were assessed using respective ELISA Kits (Invitrogen) according to the manufacturer's protocols.

2.9. Reactive oxygen species (ROS) staining

Intracellular ROS levels were measured using 2,7-dichlorofluorescein diacetate (DCFH-DA, Sigma, USA) following a previous method [22]. Briefly, after a 24-h treatment, cells were incubated with serum-free media containing 10 μM DCFH-DA probe at 37 °C in darkness for 30 min. DCFH-DA fluorescence intensity was determined using a fluorescence microscope and quantified by ImageJ software (version 1.48v, NIH, Bethesda, MD).

2.10. Western blot analysis

Cells were lysed in RIPA lysis buffer (Cell Signaling Technology, Danvers, MA, USA) with a Protease/Phosphatase Inhibitor Cocktail (Cell Signaling Technology). Protein concentrations were quantified using a BCA kit (Thermo Scientific). Equal amounts of protein were separated on 10% SDS-PAGE gels and transferred to PVDF membranes. After blocking, membranes were incubated with primary antibodies: anti-ITGB1 (cat: 26918-1-AP, Proteintech Group, Inc, IL, USA), anti-YAP1 (cat: 4912, Cell Signaling Technology), anti-phospho-YAP1 (Ser127) (cat: 4911, Cell Signaling Technology), and anti-GAPDH (cat: CW0100, Cwbiotech, China). Immunoreactive bands were visualized using the Pierce™ ECL Plus Western Blotting Substrate (Thermo Scientific™) and quantified with ImageJ software.

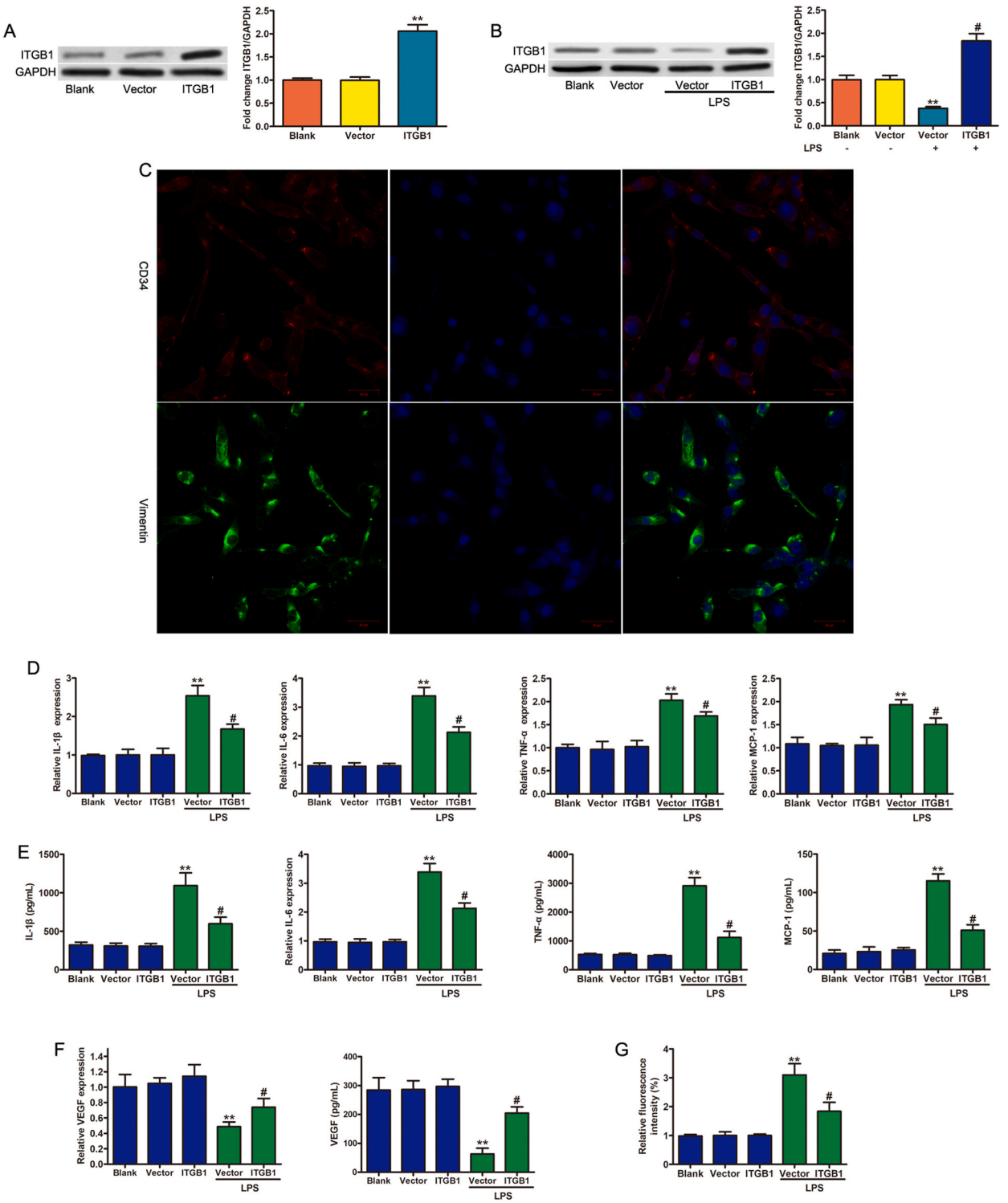

Fig. 2. ITGB1 Modulation of Inflammation, ROS, and VEGF in TCs, (A–B) Western blot analysis of ITGB1 overexpression efficiency in TCs, with or without LPS treatment, (C) Immunofluorescence staining for CD34 (red) and vimentin (green), with DAPI (blue) for nuclear staining. Magnification: 400×, scale bar: 50 μm, (D–E) qRT-PCR and ELISA analysis of IL-1β, IL-6, TNF-α, and MCP-1 expression, (F) qRT-PCR and ELISA for VEGF levels in TCs culture supernatants after ITGB1 overexpression, (G) Intracellular ROS levels in TCs following ITGB1 overexpression with/without LPS treatment. $^{**}p < 0.01$ signifies statistical significance.

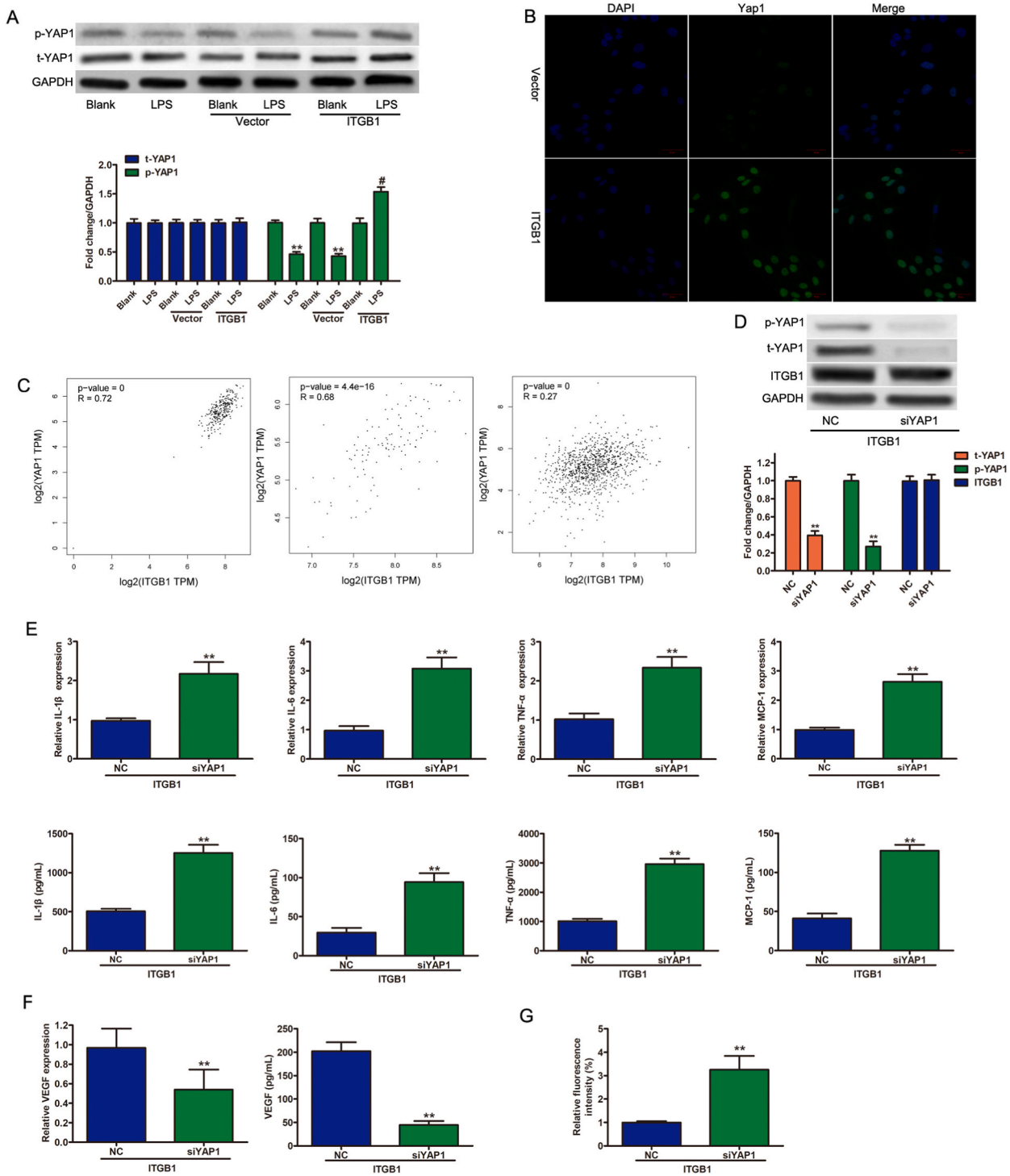

Fig. 3. Essential Role of YAP1 in ITGB1-Regulated Inflammatory and ROS Response to LPS, (A) YAP1 protein expression post-ITGB1 overexpression assessed via real-time PCR and Western blot, (B) Immunostaining of YAP1 in TCs after ITGB1 overexpression. Magnification: 400×, scale bar: 50 μm, (C) Correlation analysis between ITGB1 and YAP1 based on GTEx and TCGA databases, (D) Western blot analysis of ITGB1, total YAP1, and phosphorylated YAP1 in TCs with ITGB1 overexpression and YAP1 knockdown, (E–F) qRT-PCR and ELISA for IL-1β, TNF-α, IL-6, MCP-1, and VEGF levels in TCs with ITGB1 overexpression and siYAP1 transfection, with or without LPS treatment, (G) Intracellular ROS levels in similar experimental conditions. $^{**}p < 0.01$ indicates significant differences.

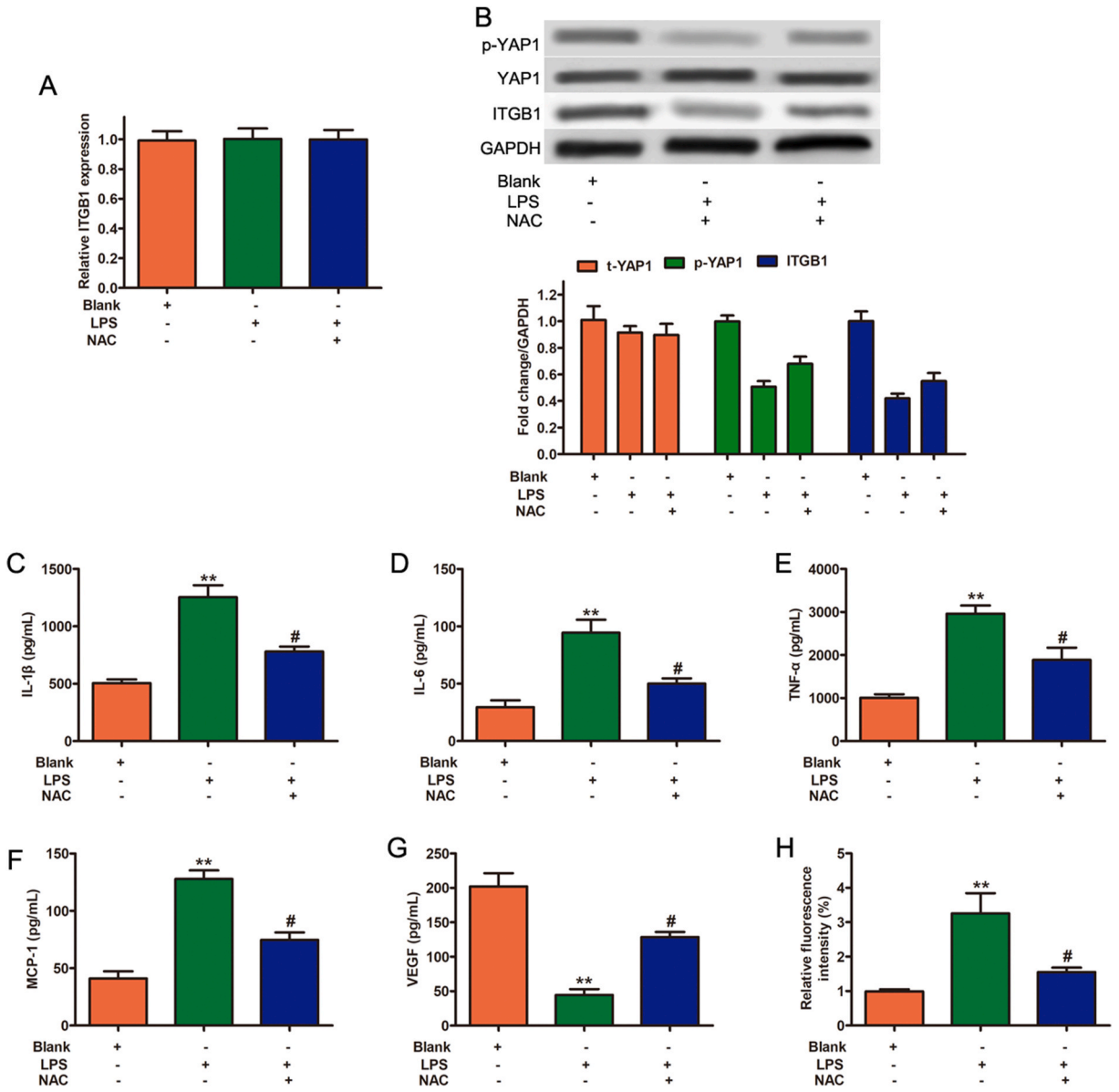

Fig. 4. NAC Reverses LPS-Induced Effects in TCs, TCs were incubated with 5 mM NAC (a ROS scavenger) for 24 h before adding 8 μg/ml LPS, (A) ITGB1 mRNA expression in TCs under specified conditions, (B) ITGB1 and YAP1 protein levels in TCs, (C–G) ELISA for inflammatory factors:IL-1β, TNF-α, IL-6, MCP-1 and VEGF levels in TCs culture supernatants, (H) ROS production in TCs culture supernatants. $^{**}p < 0.01$ compared to the blank group; $\#p < 0.05$ compared to the LPS group.

2.11. Statistical analysis

Data are presented as mean ± SD (standard deviation). Two-group comparisons were performed using paired or unpaired Student's t-test, while multiple group comparisons were analyzed using one-way ANOVA followed by Tukey's post hoc test. Statistical analyses were conducted using GraphPad Prism (version 5.0; GraphPad Software, Inc.). Each experiment was repeated three times. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Expression of ITGB1 in LPS-induced TCs

Our previous research identified high expression levels of ITGB1 in mouse lung TCs, suggesting a role in tissue repair and recovery

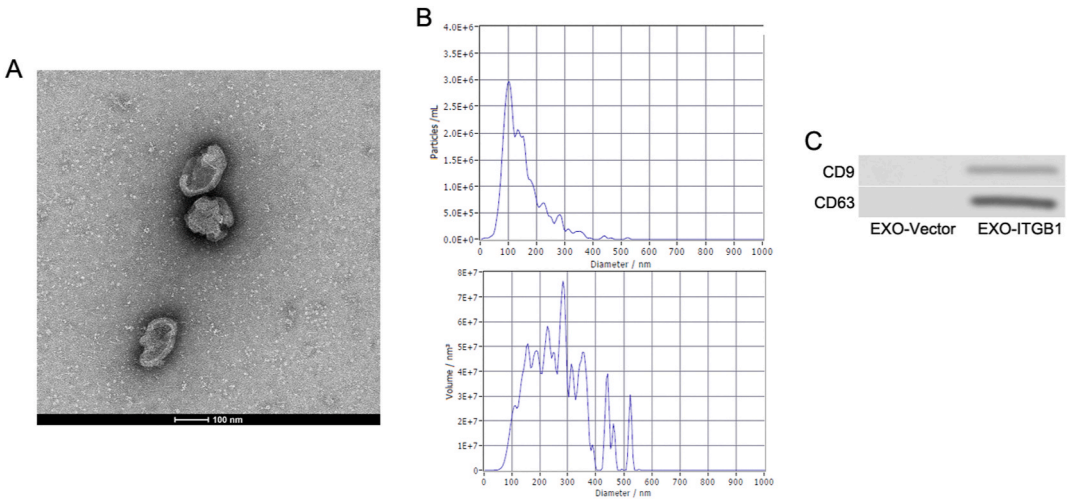

Fig. 5. Characterization of Exosomes Derived from TCs, (A) Transmission electron microscopy images of exosomes. Scale bar: 200 nm, (B) Nanoparticle Tracking Analysis (NTA) for exosome particle size, (C) Western blot analysis for exosomal markers CD9 and CD63.

post-injury [23]. To investigate ITGB1's role in stress-induced injury, we examined its expression in LPS-treated TCs. Fig. 1A shows that LPS treatment did not alter ITGB1 mRNA levels in TCs. However, ITGB1 protein levels decreased at 4 μg/ml LPS and were most reduced at 8 μg/ml LPS (Fig. 1B). Subsequent experiments used 8 μg/ml LPS. Given the known role of ROS in LPS-induced inflammation, we measured ROS production in TCs post-LPS treatment. Fig. 1C reveals significantly upregulated ROS levels following LPS exposure. Flow cytometry indicated a notable increase in TC apoptosis after LPS treatment (Fig. 1D), suggesting that LPS reduces ITGB1 expression and induces cell apoptosis.

3.2. *Overexpression of ITGB1 protects TCs from LPS-induced injury*

Western blot analysis confirmed the efficacy of ITGB1 overexpression in TCs, even post-LPS treatment (Fig. 2A and B). Immunofluorescence cytochemistry verified TC markers, CD34 and vimentin (Fig. 2C). We observed no significant difference in inflammatory factors or VEGF at the mRNA and secretion levels without LPS treatment (Fig. 2D–F). Similarly, ROS production showed no statistically significant change (Fig. 2G). Interestingly, ITGB1 overexpression reversed the LPS-induced increase in inflammatory factors (IL-1β, IL-6, TNF-α, MCP-1) at both mRNA and secretion levels (Fig. 2D and E). LPS inhibited VEGF expression, while ITGB1 overexpression had the opposite effect (Fig. 2F). Additionally, ITGB1 overexpression negated LPS-induced ROS production (Fig. 2G), indicating ITGB1's role in tissue repair under pathological conditions.

3.3. *YAP1 is essential for ITGB1-regulated ROS*

There are mounting pieces of evidence highlighting the eminence of Hippo pathway-YAP/TAZ in organ size control, tissue regeneration, and self-renewal [24]. Considering the significance of the Hippo pathway-YAP/TAZ in tissue regeneration, we examined the modulation of YAP1 expression by ITGB1. Fig. 3A shows no significant change in YAP1 mRNA levels between vector and ITGB1 overexpression, under normal or LPS-treated conditions (data not shown). However, LPS treatment significantly reduced YAP1 protein levels. Confocal microscopy revealed increased YAP1 in TCs following ITGB1 overexpression (Fig. 3B). The GEPIA database analysis demonstrated a positive correlation between ITGB1 and YAP1 expression in normal lung tissues, tissues adjacent to lung cancer, and lung cancer tissues (Fig. 3C). ITGB1 overexpression counteracted LPS-induced YAP1 and phosphorylated YAP1 inhibition (Fig. 3D). Silencing YAP1 partly negated the inhibitory effects of ITGB1 overexpression on inflammatory factors (IL-1β, IL-6, TNF-α, MCP-1) and VEGF expression, both at mRNA and secretion levels (Fig. 3E and F), as well as ROS production (Fig. 3G). These findings suggest that YAP1 activation is necessary for ITGB1-regulated inflammatory response and oxidative stress.

3.4. *NAC mitigates LPS-induced TC injuries*

We investigated whether ROS affects ITGB1 expression and inflammatory factor release. Following LPS treatment, TCs were treated with NAC (a ROS scavenger). No notable change in ITGB1 mRNA levels was observed in TCs, regardless of LPS or NAC treatment (Fig. 4A). NAC effectively mitigated ITGB1 and p-YAP1 inhibition post-LPS treatment (Fig. 4B). NAC treatment significantly decreased IL-1β, IL-6, TNF-α, and MCP-1 following LPS treatment, while remarkably increasing VEGF expression (Fig. 4C–G). ROS release decreased, confirming NAC's efficacy (Fig. 4H). These results suggest that ROS is upstream of ITGB1 and involved in ITGB1-mediated YAP1 activation and inflammatory factor release.

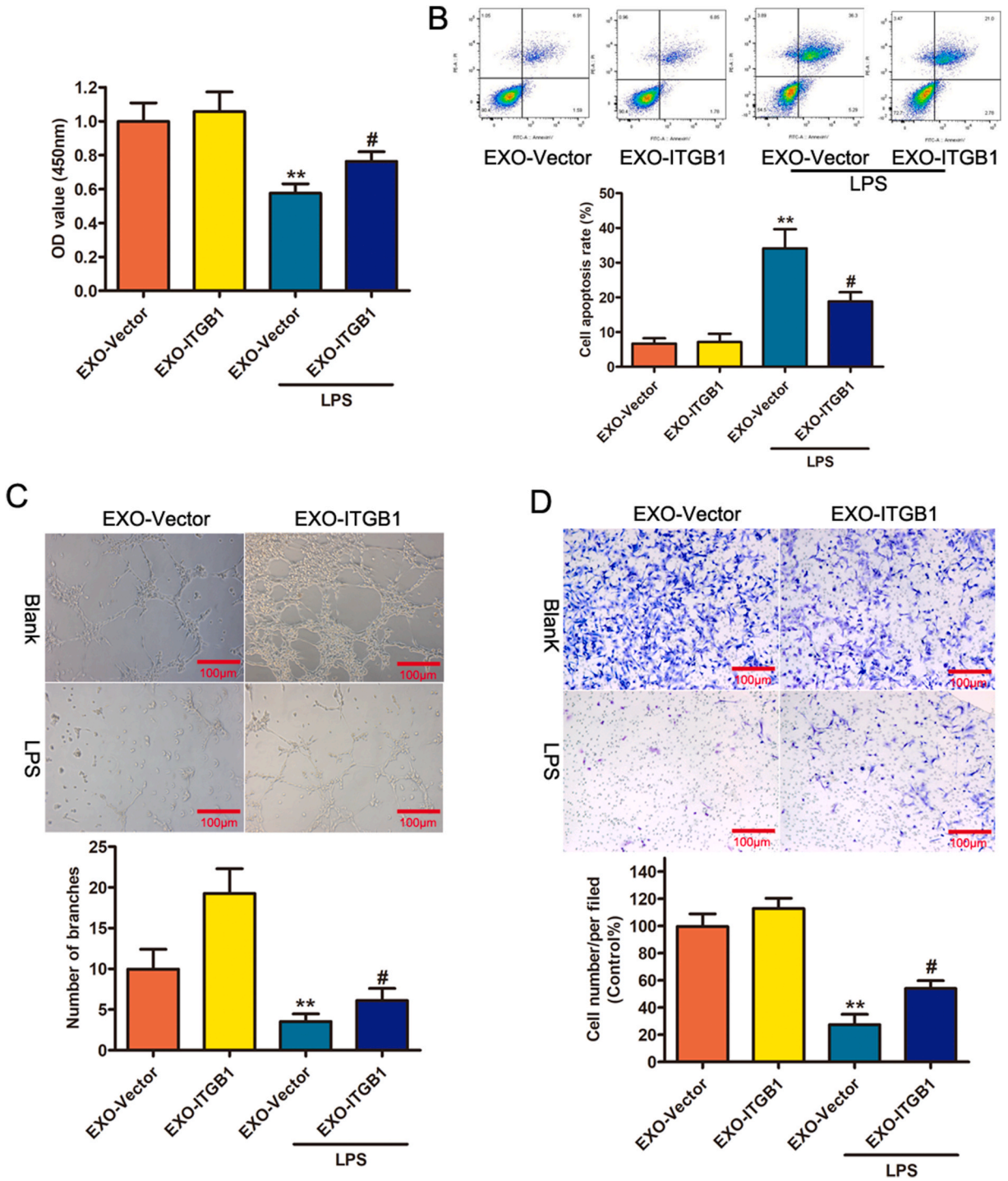

Fig. 6. Protective Effects of EXO-ITGB1 on HUVECs Against LPS-Induced Injury In Vitro, (A) Cell viability of HUVECs post-LPS treatment and incubation with EXO-ITGB1, (B) Flow cytometry analysis of HUVECs post-LPS treatment and incubation with EXO-ITGB1, (C) Tube formation assay in HUVECs post-LPS treatment and incubation with EXO-ITGB1, (D) Transwell cell migration assay in HUVECs post-LPS treatment and incubation with EXO-ITGB1. $^{**}p < 0.01$ compared to the vector group; #p < 0.05 compared to the vector with LPS treatment group.

3.5. Extraction and characterization of exosomes from TCs

Previous reports indicated that TCs possess long extensions and bead-like portions, facilitating cellular connections [25,26]. TEM analysis showed round-shaped exosomes with diameters ranging from 60 to 700 nm (Fig. 5A and B), and Western blotting confirmed

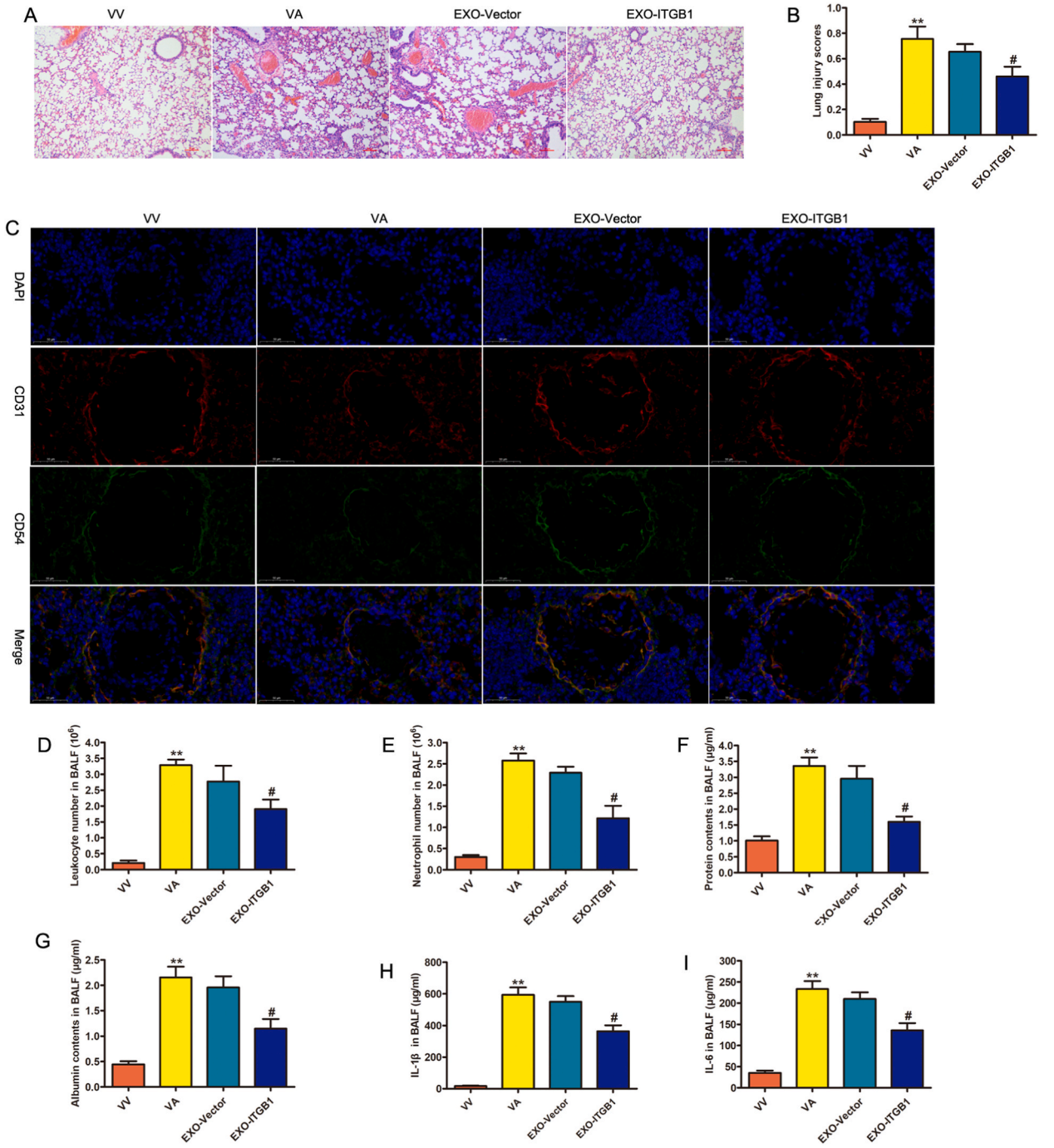

Fig. 7. Therapeutic Effects of EXO-ITGB1 in LPS-Induced Acute Lung Injury, (A) Histological images of lungs from mice intraperitoneally injected with vehicle (VV), LPS-induced ALI with vehicle (VA), EXO-Vector, or EXO-ITGB1, stained with H&E, (B) Histological lung injury scores for each group, (C) Double fluorescence immunohistochemistry for CD31 (red) and CD54 (green) with DAPI (blue) for nuclei. Endothelial cells are identifiable as CD31+/CD54+ cells. Scale bar: 50 μm, (D–I) Measurement of leukocytes, neutrophils, total proteins, albumin, IL-1β, and IL-6 levels in bronchoalveolar lavage fluid at 24 h $^{**}p < 0.01$ compared to vehicle-administered mice; $\#p < 0.05$ compared to ALI mice administered with EXO-ITGB1 (n = 8/group).

exosomal surface markers CD9 and CD63 (Fig. 5C), indicating these particles were authentic exosomes.

3.6. ITGB1 enhances HUVEC survival and angiogenesis post-LPS stimulation

Increasing evidence has shown that exosomes play an important role in material and information exchange between cells [27]. Given the role of exosomes in cell-to-cell communication, we explored the protective effects of ITGB1-modified TC exosomes (EXO-ITGB1) on HUVECs. EXO-ITGB1 alleviated LPS-induced HUVEC survival inhibition (Fig. 6A) and significantly reduced apoptosis (Fig. 6B). Matrigel-based tube formation assays demonstrated that EXO-ITGB1 treatment enhanced HUVEC vessel-like tube formation compared to EXO-Vector treatment (Fig. 6C). Transwell migration assays showed increased HUVEC migration rates in the EXO-ITGB1 group compared to the EXO-Vector group (Fig. 6D), indicating that EXO-ITGB1 offers significant cytoprotective effects and angiogenic potential.

3.7. Local injection of EXO-ITGB1 alleviates inflammation in LPS-induced lung injury

In vivo, EXO-ITGB1 remarkably repaired pathological features and lung interstitial inflammation in LPS-induced mice (Fig. 7A) and reduced lung injury scores (Fig. 7B). EXO-ITGB1 significantly attenuated LPS-induced lung endothelial cell injury (Fig. 7C) and reduced leukocyte recruitment, neutrophil infiltration, protein leakage, and over-production of IL-1β and IL-6 in bronchoalveolar lavage fluid (Fig. 7D–I). These findings highlight EXO-ITGB1's therapeutic potential in ALI.

4. Discussion

Acute Lung Injury (ALI), a common respiratory complication often precipitated by acute and severe hypoxia, can progress into acute respiratory distress syndrome (ARDS) when inflammation becomes uncontrollable [4,6]. Hypoxia-induced excessive Reactive Oxygen Species (ROS) disrupt normal physiological structures and functions, exacerbating this condition [28,29]. Our prior studies have highlighted the role of Telocytes (TCs) in ameliorating LPS-induced inflammation and lung injury, with ITGB1 showing high expression in TCs [23]. This study further elucidates the complex interplay between Telocytes (TCs), Integrin Beta 1 (ITGB1), and the regulatory mechanisms underlying acute lung injury (ALI) and its progression to acute respiratory distress syndrome (ARDS). Our findings highlight the pivotal role of ITGB1 in modulating the inflammatory and oxidative stress responses in TCs following LPS treatment, and importantly, underscore the therapeutic potential of ITGB1-modified TC-derived exosomes in mitigating endothelial dysfunction in ALI [3,11].

Consistent with prior research, our study observed a significant reduction in ITGB1 protein levels post-LPS treatment, despite stable mRNA levels, suggesting post-transcriptional regulation mechanisms might be involved in ITGB1 degradation under oxidative stress conditions induced by LPS [23,28,29]. The increase in ROS production following LPS treatment and the protective effect of NAC in preventing ITGB1 degradation further supports the hypothesis that oxidative stress is a key factor in modulating ITGB1 expression and function in TCs.

The beneficial effect of ITGB1 overexpression in reducing the release of inflammatory markers (IL-1β, IL-6, TNF-α, and MCP-1) and ROS in TCs underlines ITGB1's role in the cellular defense mechanism against LPS-induced injury. These observations are in line with the increasing body of evidence suggesting that ITGB1 plays a crucial role in tissue repair processes, partly by modulating the inflammatory response and oxidative stress [23,25]. Exosomes, as highlighted in our study, serve as critical mediators of intercellular communication, capable of transferring bioactive molecules such as proteins, lipids, RNA, and DNA between cells [27,30]. The formation of these nanoscale vesicles and their role in physiological and pathological processes, including tissue repair and inflammation, provides a novel insight into the mechanisms of disease progression and potential therapeutic strategies [31,32]. The inclusion of exosome-related findings in our discussion emphasizes their emerging significance in the context of ALI/ARDS, particularly as vehicles for delivering therapeutic agents like ITGB1-modified TC-derived exosomes to injured tissues.

Yes-Associated Protein 1 (YAP1), a central effector of the Hippo pathway, is known for its regulatory role in organ development and tissue homeostasis, perceiving and communicating with the tissue environment [33,34]. Previous studies have linked YAP1 overexpression to various malignancies, correlating positively with proto-oncogenes such as KRAS, Wnt/β-catenin, and CTGF [24,35], influencing tumor progression through regulation of the tumor microenvironment. In our study, YAP1 also emerged as a regulatory molecule for ITGB1 under stress conditions, influencing the expression of inflammatory factors and ROS. Silencing YAP1 attenuated the inhibitory effects of ITGB1 on LPS-treated TCs, indicating ITGB1's role in activating YAP1 phosphorylation to inhibit inflammatory factor and ROS production.

The primary pathogenesis of ALI includes loss of alveolar-capillary membrane integrity and increased permeability of pulmonary capillary endothelial cells [4,22]. Endothelial cell apoptosis, triggered by inflammatory factors and hypoxia, jeopardizes vascular and alveolar epithelial cell integrity, impairing lung respiratory function [6]. Hence, pulmonary microvascular barrier dysfunction is a hallmark of ALI. TCs participate in various biological functions through cell-to-cell signaling, extracellular shedding vesicles, and paracrine molecules [12,25]. The investigation into the effects of EXO-ITGB1 on HUVECs presents a novel approach to addressing the endothelial dysfunction characteristic of ALI. By effectively negating LPS-induced inhibition of HUVEC function, EXO-ITGB1 not only demonstrates the therapeutic potential of ITGB1-modified TC-derived exosomes but also reinforces the critical role of the ITGB1/YAP1 signaling axis in the repair and regeneration of lung tissue.

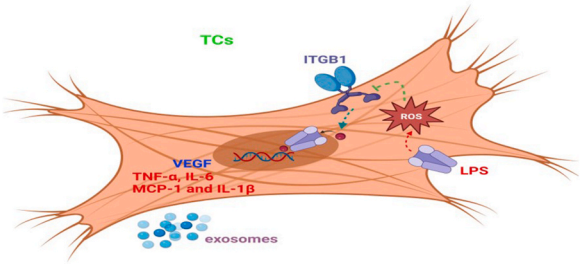

Fig. 8. Proposed Model Illustrating the ITGB1-YAP1/ROS Axis in LPS-Induced Inflammatory Injury and ROS Release. This model shows that LPS-induced ROS decreases ITGB1 expression, affecting YAP1 expression. YAP1 decreases ROS release, creating a negative feedback loop with ROS attenuating ITGB1 expression.

5. Conclusion

In conclusion, our study provides compelling evidence that aberrant ITGB1 expression plays a crucial role in the pathogenesis of ALI, with ITGB1's protective effects being modulated through the YAP1 signaling pathway (Fig. 8). The novel use of ITGB1-modified TC-derived exosomes as a therapeutic strategy offers promising insights into the treatment of ALI/ARDS. Future research should focus on further elucidating the molecular mechanisms underlying ITGB1 and YAP1's effects on lung tissue repair and exploring the therapeutic potential of exosome-based interventions in clinical settings.

Ethics statement

Ethical approval was acquired from the Institutional Review Board of Department of Laboratory Animal, Shanghai ZY (Permit No. SHZY-202105143).

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Ruixue Qi: Writing – original draft, Funding acquisition, Formal analysis, Data curation. **Yuchao Wang:** Validation, Investigation, Formal analysis. **Furong Yan:** Validation, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation. **Jinlong Zhong:** Writing – review & editing, Supervision, 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.

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Abbreviations

ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
EXO	exosomes
PaO2/FIO2	alveolar oxygen partial pressure/inhaled oxygen fraction
TCs	Telocytes
Tps	telopodes
MSCs	mesenchymal stem cells
FBs	fibroblasts
ATII	alveolar type II cells
qPCR	Quantitative Real-Time PCR
BCA	bicinchoninic acid assay

ROS reactive oxygen species
HDMEC human dermal microvascular endothelial cell

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27086.

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