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FGF5 alleviated acute lung injury via AKT signal pathway in endothelial cells

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ABSTRACT

Acute lung injury (ALI), with high morbidity and mortality, is mainly resulted by infectious or non-infectious inflammatory stimulators, and it will further evolve into acute respiratory distress syndrome if not controlled. Fibroblast growth factors (FGFs) consist of more than 23 kinds of members, which are involved in various pathophysiological processes of body. However, the effect of FGF5, one member of FGFs, is still not certain in lipopolysaccharide (LPS)-induced ALI. In this study, we explored the possible impacts of FGF5 in LPS-induced ALI and primarily focused on endothelial cell, which was one of the most vulnerable cells in septic ALI. In the mouse group of FGF5 overexpression, LPS-induced lung injuries were mitigated, as well as the pyroptosis levels of pulmonary vascular endothelial cells. Additionally, in vitro human umbilical vein endothelial cells (HUVECs), our results showed that the level of cell pyroptosis was ameliorated with FGF5 overexpression, and AKT signal was activated with the overexpression of FGF5, whereas after administration of MK2206, an inhibitor of AKT signal, the protection of FGF5 was inhibited. Therefore, these results suggested that FGF5 exerted protective effects in endothelial cells exposed to LPS, and this protection of FGF5 could be attributed to activated AKT signal.

1. Introduction

Acute lung injury (ALI), manifested as the diffuse edema of interstitial and alveolar, is resulted by various factors including those inside and outside the lungs [1,2]. Damages to alveolar epithelial cells and capillary endothelial cells result in restricted alveolar gas exchange, ultimately leading to the dyspnea, hypoxemia, and even acute respiratory distress [3]. It's common that ALI is triggered by sepsis, which is one of the common complications and causes of death after severe infection, trauma, and shock et al. At present, the treatments for sepsis are limited, and mainly through controlling the source of infection, applying antibiotics, and supporting organ functions [4]. Anti-inflammation treatment is widely believed to be critical in sepsis-induced ALI, however, the underlying molecular biological mechanism is poorly understood. Therefore, based on above descriptions, our current study was mainly conducted in endothelial cells, and focused on the interventions for sepsis-induced-lung injury in a level of molecular biology, thus providing a possible direction for future treatment.

FGF5 belongs to the FGF4 subfamily of FGFs, and is widely expressed in multiple tissues [5]. Similar to other FGFs family members, FGF5 conducts cell signal transduction by binding to FGF receptor (FGFR), of which FGFR1 and FGFR2 are high-affinity receptors for FGF5 [6]. The effect of FGF5 on the regulation of hair growth has been considered prominent [7–9], and previous studies have also validated various biological functions of FGF5 [10–13]. Besides, recent studies have shown null of FGF5 results in more severe hepatic injuries induced by high-fat diet [14], which indicates a possible regulatory effect of FGF5 on inflammation-related disease. Nevertheless, there is no other studies about the effect of FGF5 on inflammatory disease, and the mechanism by which FGF5 play a part in regulation of inflammation is not clear. Thence, in our current studies, we mostly paid close attention to the effects of FGF5 on endothelial cells which were subjected to inflammatory injuries induced by LPS, and explored the possible mechanism by which FGF5 exerted its impacts.

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Pyroptosis, highly programmed by the body, is a new form of cell death and is closely related to inflammation [15]. The occurrence of pyroptosis is an initiation of cell lysis and death in which the cell membrane is perforated under the induction of inflammasomes. In the classic pyroptosis pathway, inflammasome activated by exogenous or endogenous injuries promotes the hydrolysis of caspase-1 precursor to release active caspase1, which further cleaves IL-1β and IL-18 precursors into activated IL-1β and IL-18, and facilitates the formation of cell membrane pores [16]. In the process of inflammation responses caused by sepsis, the elevated level of pyroptosis in endothelial cells undoubtedly leads to impaired alveolar gas exchange, thus ALI induced by sepsis can be improved by suppressing the level of endothelial cell pyroptosis.

Therefore, based on the above theory, our studies paid attention to the impacts of FGF5 on LPS-induced endothelial cell injuries, and the possibly protective effects of FGF5 on pyroptosis.

2. Methods

2.1. Experimental animals and treatments

We purchased 8-week-old male C57 mice from Animal Experimental Center of Three Gorges University. The mice, free to food and water, were raised under specific pathogen-free conditions. All animal experiments were approved by Animal Experimental Center of Wuhan third Hospital (Animal Ethical Number: SY2022-010), and were performed in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health.

The mice were randomly divided into four groups: Normal group: treated with an injection of saline; LPS group: received an intraperitoneal injection of LPS (L2880, Sigma-Aldrich, USA); LPS + FGF5 group: injected intravenously with FGF5 overexpressed adenovirus one week before LPS injection; LPS + NC (negative control) group: injected with NC adenovirus one week prior to LPS injection. The LPS at a dose of 10 mg/kg was applied for ALI, and mice were killed after 12 h of LPS stimulation.

2.2. Cell culture and treatments

Human umbilical vein endothelial cells (HUVECs) were obtained from YRGene (NC006) and cultured at 37 °C in 5% (v/v) CO2 in RPMI 1640 medium (GIBCO, USA) supplemented with 10% FBS (GIBCO, USA). 1ug/ml LPS (Sigma-Aldrich, USA) was administrated to HUVECs for inducing the endothelial injury. There were five groups at the cellular level: CTL group: normal cells without any treatment; LPS group: cells with the stimulation of 1ug/ml LPS for 24 h; LPS + FGF5-plasmid group: cells were transfected with the plasmid carrying human FGF5 gene (GeneChem Co. Ltd., Shanghai) for 48 h before the stimulation of LPS; LPS + control-plasmid group: cells were transfected with the negative control plasmid (GeneChem Co. Ltd., Shanghai) for 48 h before the stimulation of LPS. LPS + FGF5-plasmid + MK2206 (MedChemExpress, United States) group: MK2206, a selective AKT inhibitor, was added (100 nM), and the other treatments were the same as LPS + FGF5-plasmid group. Lipo8000™ transfection reagent (Beyotime Biotechnology, China) was used for transfection. Endothelial cell passages between 3 and 8 were used in our study.

2.3. Immunofluorescence

The distribution of FGF5 in the lung were analyzed using immunofluorescence assay. The specific experimental steps are as previously described [17]. The primary antibodies of FGF5 (1:200, Proteintech, China), CD31 (1:2000, Abcam, UK) and F4/80 (1:200, Proteintech, China), a secondary antibody, and DAPI solution were used for staining. The images were acquired using an immunofluorescence microscope system (NIKON, Japan).

2.4. Immunohistochemistry

The lung tissue from each group was made into paraffin slices, which were successively treated with dewaxing, Citrate Antigen Retrieval Solution (PH 6.0) to retrieve the antigen in microwave, the solution of 3% hydrogen peroxide to block endogenous peroxidase, 3% bovine serum albumin for 30min, and anti-FGF5 antibody (1:200, Proteintech, China) overnight. Finally, the slices were incubated with horseradish peroxidase (HRP)-conjugated secondary antibody for 60min at room temperature, and with diaminobenzidine for about 2 min at room temperature till a brown color developed.

2.5. TUNEL staining

Pyroptosis rate of cells was evaluated by TUNEL staining. We performed TUNEL staining using a commercial kit (Vazyme Biotech Co., Ltd, China) according to the manufacturer's instructions. Cells which were red fluorescence under a fluorescence microscope are TUNEL-positive cells. The percentage of positive cells in one field of view was considered as the rate of pyroptosis.

2.6. Flow cytometry

The HUVECs after intervention were harvested by trypsin and washed with PBS. Next, 1X annexin binding buffer was applied to resuspend the cells. Afterwards, the cells were stained with 5 μl Annexin V-PE (BD Biosciences) and 5 μl 7-amino-actinomycin D (7AAD; BD Biosciences) for 15min, and finally analyzed by the flow cytometer (NovoCyte, USA).

2.7. Hematoxylin-eosin (HE) staining

The mice were sacrificed, and the fresh lung tissue from each group were removed and fixed in 4% paraformaldehyde for more than 24 h. Then, the tissue was trimmed at the target site with a scalpel in a fume hood, and placed in a dehydration box with the corresponding labels. Next, the tissue was sequentially dehydrated, embedded, sectioned, deparaffinized, stained for nuclei with hematoxylin and cytoplasm with eosin, and finally examined under a microscope (Leica Microsystems, Germany). The severity of lung injury was evaluated as the sum of the scores as previously described [18].

2.8. Wet/dry ratio of lung

The lung wet/dry (W/D) weight ratio was analyzed to assess the degree of pulmonary edema in each treated group. Specifically, mice were killed, and the lungs were removed and weighed (wet weight). The dry weight was obtained after the lung was heated at 80 °C for 24 h, and the W/D ratio was calculated.

2.9. Real time-quantitative PCR (RT-qPCR)

Total RNA was extracted by RNAiso Plus regent (TaKaRa, Japan). Then Servicebio RT First Strand cDNA Synthesis Kit (Servicebio, China) was applied to synthesize complementary DNA (cDNA). Subsequently, RT-qPCR was performed using Servicebio 2*SYBR Green qPCR Master Mix kit (Low ROX) (Servicebio, China) and ABI ViiA7 Real-Time PCR system (Applied Biosystems, USA).

2.10. Western blot

Western blot assays were performed to evaluate the expressions of related proteins. Protein extracts from the lung tissues were obtained 12 h after LPS administration, and protein from cells was acquired 24 h after LPS stimulation. The specific experimental steps are as previously described [17]. In general, the proteins, extracted from lungs and cells, were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and then transferred to PVDF membranes. With the blocking in the 5% skim milk buffer for 2 h, the membranes were then incubated at 4 °C overnight with primary antibodies for FGF5 (1:500, Affinity Biosciences, China), NLRP3 (1:500, Proteintech, China), Caspase1 (1:1000, ABclonal, China), IL-1β (1:1000, Abcam, UK), IL-18 (1:500, ABclonal, China), phosphorylated (p)-AKT (1:1000, CST, USA), AKT (1:1000, CST, USA), VEGF (1:1000, Abcam, UK), VE-cadherin (1:1000, ABclonal, China) and GAPDH (1:1000, CST, USA). The next day, after three washes with TBST buffer, the membranes were incubated with HRP-conjugated secondary antibody for 1 h at room temperature. Finally, the enhanced chemiluminescence reagent was used for visualization of membranes through a ChemiDoc XRS + system (BIO-RAD, USA). Image J software was used to quantity protein expressions.

2.11. Statistical analysis

The data in our study were analyzed by SPSS22.0 software. One way analysis of variance (ANOVA) followed by Tukey post-hoc test was performed when comparing multiple groups, while unpaired Student's t-test was performed to distinguish differences in two groups. $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. FGF5 was downregulated in pulmonary endothelial cells in ALI

First of all, in order to understand the expression distribution of FGF5 in the lung tissue, we performed the immunofluorescence staining of normal and septic lungs. As shown in Fig. 1A, the expressions of FGF5 and CD31 in normal lung were co-located, which indicated FGF5 was expressed in the endothelial cells of lung. Besides, interestingly, in ALI induced by the administration of LPS, a significant decrease in FGF5 expression was seen in the cells expressing CD31, which implicated a possible regulatory effect of FGF5 in sepsis-induced endothelial cell injury. Furthermore, the results of immunohistochemistry also confirmed the phenomenon that FGF5 was downregulated in the lung suffering from LPS (Fig. 1B), and our RT-qPCR (Fig. 1C) and Western blot results (Fig. 1D and E) further demonstrated that the level of FGF5 was significantly reduced in HUVECs with the stimulation of LPS. Therefore, above results suggested that FGF5 was expressed in the endothelial cells of lung, and the levels of FGF5 were obviously decreased in ALI-induced endothelial cell injury.

3.2. FGF5 exerted protection effects against pyroptosis in endothelial cells

Afterwards, given the apparent alterations in FGF5 expression, we were aimed to figure out whether FGF5 could regulate the injury of endothelial cells exposed to LPS. The plasmid carrying FGF5 gene was constructed and transfected into HUVECs to investigate whether FGF5 had protective effect on endothelial cells. As pyroptosis, a newly discovered form of death, played an important role in endothelial injury [19–21], we thus subsequently detected related proteins reflecting the pyroptosis process. As expected, the process of pyroptosis was significantly mitigated with the overexpression of FGF5. As depicted in Fig. 2C, the expressions of NLRP3, Caspase1, IL-1β, IL-18 were elevated in LPS-treated group compared to CTL group, while these indicators were all moderated in LPS + FGF5-plasmid group compared to LPS + control-plasmid group. Similarly, our flow cytometry (Fig. 2D and E) and TUNEL results (Fig. 2F and G) also showed an improved pyroptosis rate in LPS + FGF5-plasmid group. Taken together, these data indicated that FGF5 ameliorated endothelial cell injury followed LPS stimulation by reducing pyroptosis levels.

3.3. Overexpression of FGF5 attenuated LPS-induced ALI

Next, we explored the possible impact of FGF5 on LPS-induced ALI in vivo. The adenovirus carrying FGF5 or negative control gene was constructed and was injected into mice through tail vein one week before exposure to LPS. There were no obvious pathological changes in Normal group, whereas the mice exposed to LPS showed increased edema, alveolar wall thickness, bleeding, and infiltration of inflammatory cells at 12 h after LPS administration (Fig. 3A), which represented the occurrence of ALI. Interestingly and in line with expectations, mice with FGF5 overexpression exhibited improved pathological injuries shown as significantly less distortion of pulmonary architecture (Fig. 3A, C), infiltration of macrophages (Fig. 3B, D) and W/D ratio (Fig. 3E) after LPS administration compared to LPS + NC group.

3.4. FGF5 overexpression activated AKT signal in LPS-treated HUVECs

AKT signal plays an important role in cell survival [22], death, proliferation [23], etc., and has been reported to be a considerable regulator in cell pyroptosis [24]. Additionally, our above results confirmed the occurrence of LPS-induced endothelial pyroptosis, which was alleviated in FGF5 overexpression group. Therefore, the protein expressions of p-AKT and AKT was evaluated, and our data shown in Fig. 4A and B manifested that p-AKT/AKT was significantly declined in vitro HUVECs with the stimulation of LPS, whereas with the overexpression of FGF5, the levels of p-AKT/AKT was restored compared to LPS + control-plasmid group. Moreover, Intriguingly, there were also significant changes in other indicators reflecting endothelial integrity. The protein of VEGF, a notable vascular permeability factor [25], and the expression of VE-cadherin, an important protein participating in maintaining endothelial barrier integrity [26], were all tested in each group. As indicated in Fig. 4A and D, overexpression of FGF5 in HUVECs obviously improved the LPS-triggered increase of VEGF compared to LPS + control-plasmid group. Furthermore, VE-cadherin was down-regulated under the stimulation of LPS, while increased in HUVECs following FGF5 overexpression when compared to their respective control group (Fig. 4A, E). These above results clarified FGF5 overexpression could ameliorate LPS-induced endothelial injuries and these beneficial effects might be attributed to the activation of AKT signal.

3.5. The protection of FGF5 was abrogated with the inhibition of AKT signal

In order to further demonstrate that FGF5 exerted effects through AKT signal, we used MK2206, the inhibitor of AKT signal, in HUVECs. As expected, the results shown in Fig. 5 further revealed that the pyroptosis proteins of endothelial cell including NLRP3, Caspase1, IL-1β, IL-18 were forced to be highly expressed again with the administration of MK2206. In other words, the inhibition of AKT signal impaired the anti-pyroptosis protection of FGF5 in

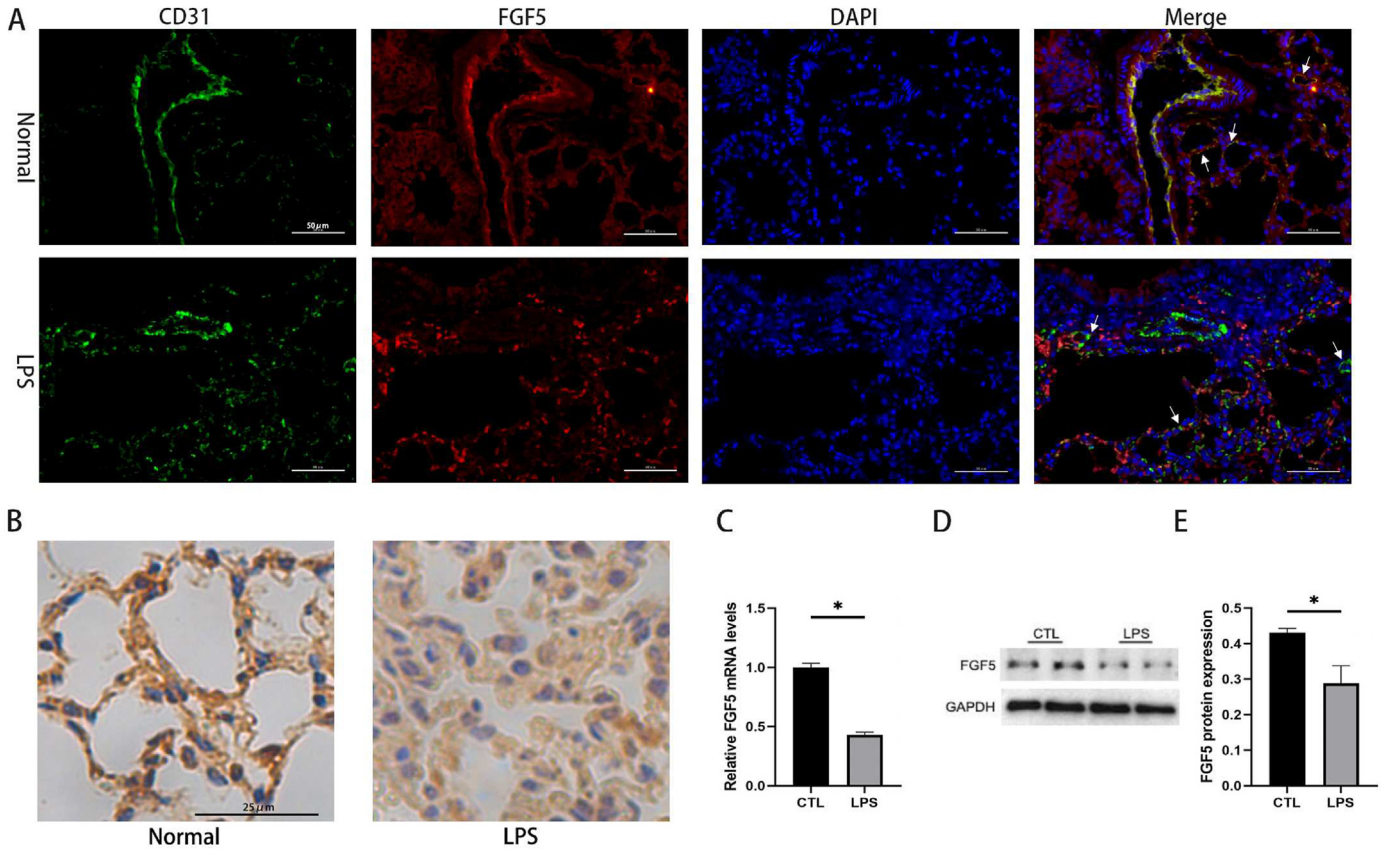

Fig. 1. FGF5 was downregulated in endothelial cells under the stimulation of LPS. A: Double immunofluorescence staining of lungs for CD31 and FGF5 (Representative endothelial cells were indicated by white arrows). B: Immunohistochemical staining for FGF5 in the lungs. C: The relative mRNA level of FGF5 in HUVECs was shown as a bar chart (n = 4). D–E: The representative bands and the bar graph were shown to reflect the expression level of FGF5 in HUVECs (n = 3). (*: $p < 0.05$).

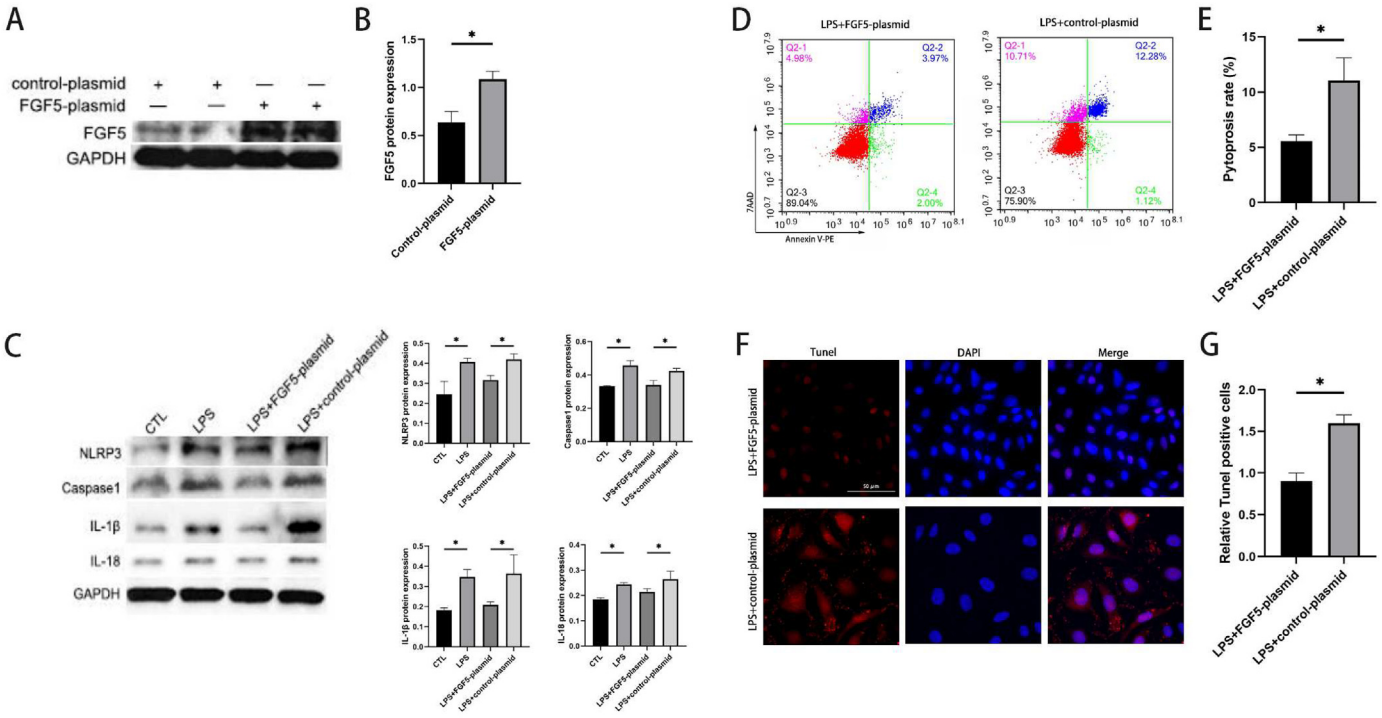

Fig. 2. Overexpression of FGF5 ameliorated the pyroptosis level of HUVECs induced by LPS. A–B: Representative protein bands and statistical bar graph were shown to reflect FGF5 expression level in HUVECs with the FGF5 overexpression plasmid (n = 3). C: Representative protein bands and statistical bar graph were applied to show the level of proteins which were related to pyroptosis (n = 3). D: Representative images of flow cytometry and its statistical analysis bar graph (n = 3). F–G: Representative images of TUNEL staining in HUVECs and its statistical analysis bar graph (n = 3). (*: $p < 0.05$).

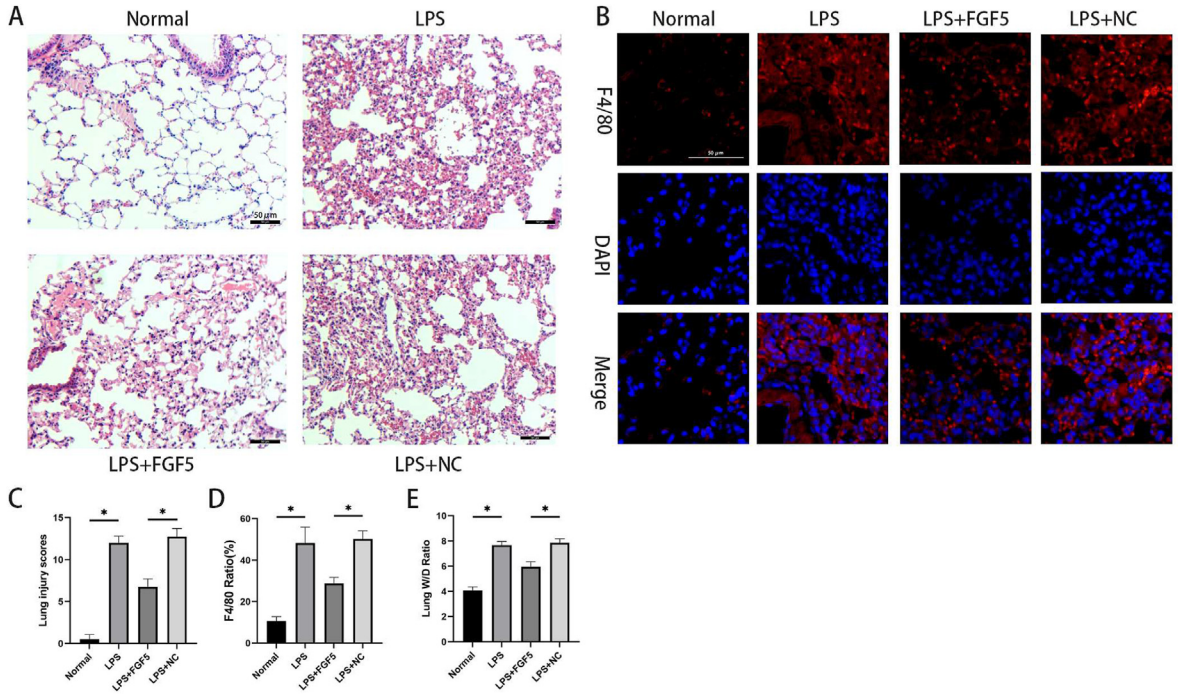

Fig. 3. Overexpression of FGF5 alleviated the pathological changes of lung stimulated by LPS. A, C: Representative images of HE staining and the corresponding evaluation of lung injuries. B, D: Immunofluorescence staining of lungs for F4/80 and its statistical analysis bar graph (n = 4). E: Statistical analysis of lung wet/dry ratio in different groups (n = 4). (*: $p < 0.05$).

endothelial cells. Altogether, our data could prove the protection of FGF5 on LPS-induced endothelial cell injury, and demonstrate the essential intermediate factor of AKT signal for the action of FGF5.

4. Discussion

In LPS-induced ALI models, our current results suggested a protective role of FGF5, which exerted beneficial effects on endothelial cells through regulating the pyroptosis level. FGF5 was downregulated in HUVEC exposed to LPS, accompanied by significantly increased levels of pyroptosis. In order to figure out whether FGF5 had a relationship with cell pyroptosis, we then constructed the overexpression plasmid and adenovirus carrying FGF5 gene vectors, and found that overexpression of FGF5 could indeed reduce the pyroptosis levels of endothelial cell. In addition, AKT signal pathway might explain for this beneficial effect of FGF5.

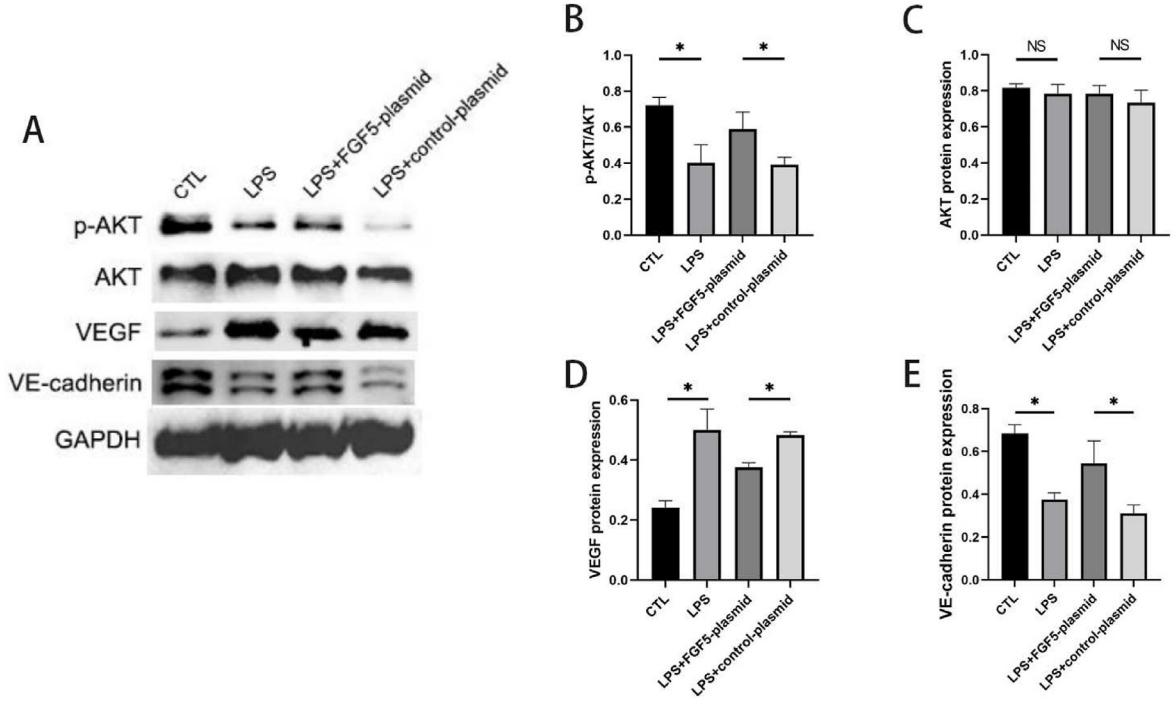

Fig. 4. FGF5 overexpression in HUVECs activated AKT signal pathway. A–E: Representative images of protein bands and its statistical analysis (n = 3–4). (*: $p < 0.05$).

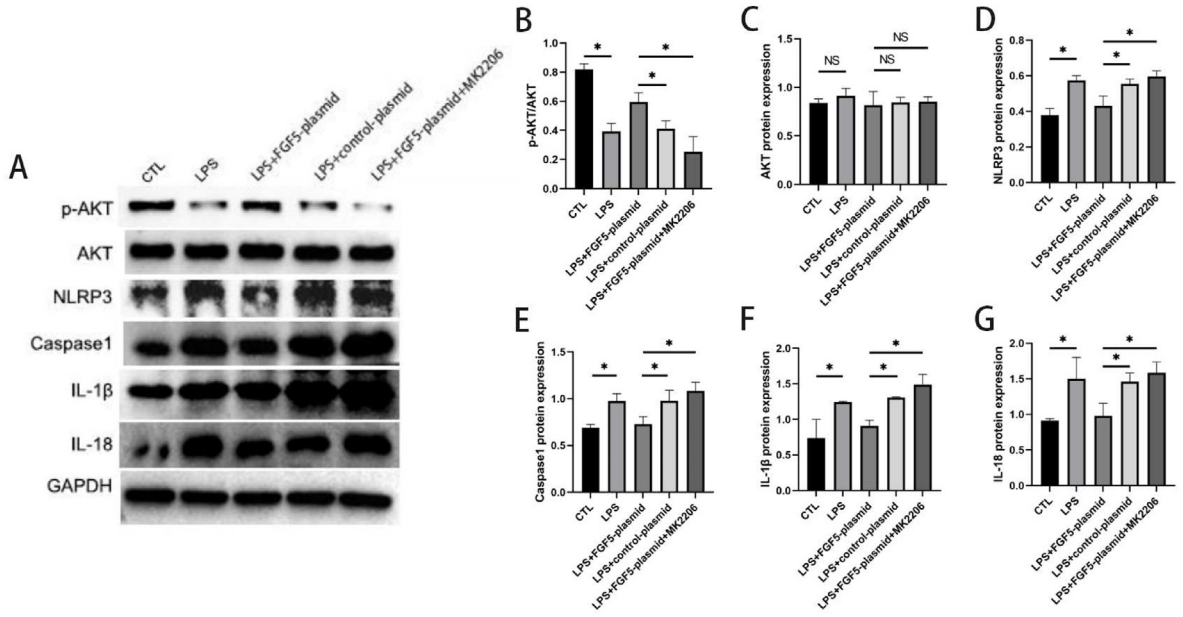

Fig. 5. The protection of FGF5 against pyroptosis was compromised with the inhibition of AKT signal. A–G: Representative images of protein bands and its statistical analysis (n = 3–4). (*: $p < 0.05$).

There is currently no research on FGF5 in lung injuries, and no studies about the anti-pyroptosis effect of FGF5. However, given that pyroptosis is a pathological process highly associated with inflammation [27], we can speculate from other inflammation-related diseases regulated by FGF5, that the possible regulatory effects of FGF on inflammation response, and its possible impact on pyroptosis. Li J. et al. [28] found that the variance of FGF5 was associated with hypertension in humans, and Nakashima, H. et al. [14] demonstrated that null of FGF5 brought more severe hyperlipidemia and liver injuries resulted from a high-fat diet. Considering high blood pressure and fatty liver are both relevant to high levels of chronic inflammatory responses in the body, we boldly speculate that FGF5 may be involved in the regulation of inflammation-related pathological processes. Interestingly, our present results indeed confirm our guesses. Overexpression of FGF5 ameliorated the pyroptosis level of endothelial cells, and improved lung injuries resulted from sepsis.

AKT signal pathway is always confirmed to be one of the most important pro-proliferation [23,29] and anti-death signal pathways [30–32]. In endothelial cells, AKT signal has also been widely demonstrated to be protective: Lin, F., et al. [33] proved that exogenous H2S protects endothelial cells against HG-induced injuries by activating AKT-related pathway. Besides, Duan, M. X., et al. [34] also confirmed the protective role of AKT signal in high glucose-induced injury of vascular endotheliocytes. Not only that, but AKT signal has also been shown to have a protective effect in pyroptosis of endothelial cell: A recent study from Liu, Y., et al. [35] illustrated that activated AKT signal could account for the mechanism of Apolipoprotein-M and Sphingosine-1-Phosphate's protective effect on TNF-α induced injury and inflammatory response in HUVECs. Therefore, from the previous studies above, we can see that activated AKT signal might participate in the protection of endothelial cells suffering from injuries. Looking back at our findings, FGF5 restored the activation of AKT signal, thus promoting the survival and inhibiting the pyroptosis level of endothelial cells. Furthermore, with the inhibitor of AKT signal—MK2206, the improvement effects of FGF5 were eliminated, which further confirmed the AKT pathway was an indispensable part of the function of FGF5.

5. Conclusion

Our present results firstly showed the functions of FGF5 in LPS-induced lung injuries, and indicated that overexpression of FGF5 protected endothelial cells against LPS-induced pyroptosis. Additionally, based on our findings above, we demonstrated that AKT signal might account for the effects of FGF5. Moreover, our findings also highlight the pathological process of pyroptosis in septic lung injuries, and suggest new insights into the mechanism of lung injury induced by sepsis.

Ethics approval and consent to participate

All animal experiments were approved by Animal Experimental Center of Wuhan third Hospital (Animal Ethical Number: SY2022-010), and were performed in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health.

Consent for publication

All authors provided consent for publication.

Availability of data and materials

The data in the current study are not publicly available because that it also forms a part of another ongoing study, but are available on reasonable request from corresponding authors.

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Authors' contributions

Hao Xia, Furong Zhang, and Yuhua Li designed the experiments. Yuhua Li and Shengyu Cui wrote the paper. Yuhua Li, Shengyu Cui, Bing Wu, Jixian Gao, Ming Li, worked together to

complete the experiment. All authors read and approved the final article.

Declaration of competing interest

The authors declared there was no conflict of interest.

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