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Mesenchymal stem cell-based FGF2 gene therapy for acute lung injury induced by lipopolysaccharide in mice

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Abstract. – OBJECTIVE: Bone marrow-derived mesenchymal stem cells (MSCs) can serve as a vehicle for gene therapy. FGF2 (basic fibroblast growth factor) is a multifunctional growth factor and exhibits diverse function in different cell types, it also has pleiotropic effects in different tissues and organs, including potent angiogenic effects and an important role in the differentiation and function of the central nervous system. We hypothesized that MSC-based FGF2 gene therapy might be a potential therapeutic approach for lipopolysaccharide (LPS)-induced lung injury.

MATERIALS AND METHODS: MSCs were isolated from 6 week-old inbred male mice and transduced with the FGF2 gene, using a lentivirus vector.

RESULTS: In the *in vivo* mouse model, the LPS-induced lung injury was markedly alleviated in the group treated with MSCs carrying FGF2 (MSCs-FGF2), compared with groups treated with MSCs alone. The histopathological index of LPS-induced lung injury was improved after MSCs-based FGF2 gene treatment. The MSCs-FGF2 administration also reduced the level of inflammatory cytokines.

CONCLUSIONS: These results suggest that MSCs and FGF2 have a synergistic role in the treatment of LPS-induced lung injury.

Key Words:
Bone marrow-derived mesenchymal stem cells, Fibroblast growth factor, LPS-induced lung injury, Gene therapy.

Abbreviations

ALI: Acute Lung Injury; ARDS: Acute respiratory syndrome; MSCs: Mesenchymal stem cells; FGF2: Fibroblast growth factor 2; LPS: Lipopolysaccharide; HE: Hematoxylin-eosin; BALF: Bronchoalveolar lavage fluid; MPO: Myeloperoxidase; PBS: Phosphate-buffered saline.

Introduction

Acute lung injury (ALI) and its more severe form, the acute respiratory distress syndrome (ARDS) are syndromes of acute respiratory failure, which was defined by radiological (bilateral lung field infiltrates) and physiological criteria in which widespread damage to cells and structures of the alveolar capillary membrane occurs within hours to days[1]. The ALI/ARDS may occur as a consequence of critical illness of diverse etiologies, including direct injury to lung, such as pneumonia, aspiration, toxic inhalation, near-drowning, or lung contusion; as well as indirect mechanisms, such as sepsis, burn, pancreatitis, gynecological insults (abruption of placenta, amniotic embolism, eclampsia), or massive blood transfusion[2]. The mortality rate associated with ARDS has declined from 90% about twenty years ago to 30%-40% at present[3]. However, it is still one of the major causes of pulmonary and nonpulmonary morbidity in patients after discharge[4].

Recently, transplantation of various stem or progenitor cells such as bone marrow-derived mesenchymal stem cells (MSCs) or endothelial progenitor cells was reported to reduce mortality and attenuate ALI induced by endotoxins or sepsis in a rodent model[5-7]. This attenuation was associated with moderation of the inflammatory reaction that accompany ALI, with variable antibacterial effects[8,9]. These studies indicate that MSCs treatment could be a new therapeutic

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modality for the treatment of ALI. Mesenchymal stem cells or marrow stromal cells are being studied with increasing intensity as their potential grows for use as a therapeutic tool[10]. These cells, commonly referred to as adult mesencyhymal stem cells (MSCs) or progenitor cells, have been collected from the bone marrow of several species and from human umbilical cord blood[10]. An attractive feature of these cells is their capacity to differentiate into a number of mature cell types, including fibroblasts, myofibroblasts, osteoblasts, chondroblasts, adipocytes, myoblasts, and epithelial cells[11,12].

FGF2, also known as basic fibroblast growth factor, is a member of the fibroblast growth factor family[13]. FGF2 is the prototype member of a large family of structurally related, heparin binding, polypeptide growth factors and it found in virtually all tissues studied, both normal and malignant. Classically it is known as an angiogenic factor, stimulating the proliferation and invasion of the endothelial cells required for capillary formation as well as being a potent mitogen for fibroblast cells[14]. However, FGF2 is now known to be pleiotropic, having a variety of functions depending on its location.

In this study, we hypothesize that the FGF2 gene contained MSCs have a potential therapeutic effect on LPS-induced lung injury. We construct a lentivirus vector containing FGF2 gene, and then transduce the MSCs which isolated from the bone marrow of C57/B6 mice by lentivirus infection. Our data suggested that the treatment of FGF2 gene contained MSCs have a benefical effect on LPS-induced lung injury compared with the control group mice which treated with MSCs alone, such as low lung injury scores, proinflammatory cytokines secretion and neutrophils infiltration. In summary, our data demonstrate a potential new approach to the therapy of the acute lung injury.

Materials and Methods

Mice

Thirty-six C57/B6 mice were purchased from the SLRC Laboratory (Shanghai, China). The mice were randomized into control group (n=10, PBS treated), ALI group (n=10, LPS treated only), MSCs control group (n=10, LPS+MSCs-GFP treated) and MSCs-FGF-2 treated group (n=10). Mice were sacrificed at 24 hours after LPS and MSCs administration.

Establishment of the Acute Lung Injury Model of Mice

Eight-to-ten-week-old female C57/B6 mice were treated with either 20 mg/kg lipopolysacharide (LPS, Sigma-Aldrich, St. Louis, MO, USA) from Escherichia coli (serotype 0111:B4) in 100 ul PBS or an equal volume of PBS, as vehicle control, by intraperitoneal injection.

MSC Isolation and Culture

MSC culture was obtained from C57/B6 mice. Bone marrow was obtained by flushing the tibias and femurs using DMEM medium with 25 mM HEPES and 10% fetal bovine serum (FBS, Invitrogen Life Technologies, Carlsbad, CA, USA). The bone marrow mononuclear cells were isolated by density gradient centrifugation (Ficoll-Paque PLUS, Pharmacia, Walkersville, MD, USA). The cells were washed and resuspended in low-glucose DMEM containing 15% FBS and 1% penicillin/streptomycin (Solarbio, Beijing, China) to a density 5×10^6/ml. The resuspended cells were cultured immediately at a density of 2×10^6/ml in a 5% CO_2 incubator at 37°C. The non-adherent cells were removed by medium changes. The cells were passaged every 3-4 days by trypsinization, and the 4th passage cells were used for *in vivo* experiments.

Lentivirus Preparation and Infection

Vectors for lentivirus packaging including pMDL, pRev pVSVG and lentivirus transfer vector were purchased from Clontech (TaKaRa, Kyoto, Japan). Lentiviral vector were transfected into 293T cells using $CaPO_4$ precipitation. After 24h, the medium was changed to DMEM containing 15% FBS. Forty-eight hours post tranfection, the lentiviral supernatants were harvested, supplemented with 6 ug/ml polybrene, and used to infect MSCs cells.

MSC Administration

One hour after LPS injection, the mice were given either 5×10^6 MSCs in 100 μL phosphate buffered saline (PBS) (in MSCs-treated ALI group) or 100 μL PBS (in PBS-treated ALI group and control group) via tail vein injection. At 24h after the injection, samples were collected from each mouse for assessment of lung injury.

Histopathologic Analysis and Lung Injury Scores

Following sacrifice at each time point, the whole left lower lobe of the lung was fixed in a

4% formaldehyde neutral buffer solution for 24 hours, dehydrated in a graded ethanol series, embedded in paraffin, and sliced at 5 μm. Paraffin sections were stained with hematoxylin-eosin (HE) for histopathological analysis.

In order to assess the severity of the lung injury, we used a semi-quantitative histological index of quantitative assessment (IQA) of lung injury. Eight sections were randomly selected from each group of rats, and 10 fields from each section were examined by microscopy (40×). A pathologist who was blinded to this study evaluated all of the sections. The average values of the lung injury obtained were considered a semi-quantitative histological IQA of lung injury.

qRT-PCR Analysis

Total RNA was extracted from pulmonary tissues using Trizol reagent (Invitrogen; Carlsbad, CA, USA) according to the manufacturer's protocol. RT-PCR kits (TaKaRa, Kyoto, Japan) were used for RT-PCR experiment. Four micrograms of total RNA template were used to make cDNA by using AMV reverse transcriptase and random 9 mers as the first-strand primer. Synthesized cDNA was used in qPCR experiments. Quantitative real-time PCR (qRT-PCR) was performed using a 40-cycle two-step PCR with sepuence-specific primer pairs using the ABI7900 fast real-time detection (ABI, Life Technology, Carlsbad, CA, USA). Primers were designed using the Primer Express 3.0 software. The level of the mRNA expression were evaluated as a ratio based on qRT-PCR results for lung tissue GAPDH mRNA.

Elisa

Detection of TNF-α and IL-6 amount with ELISA according to the manufacturer's protocol (R&D Systems Inc., Minneapolis, MN, USA). The experiment was repeated three times and results were shown with the mean value.

Lung Wet/dry Weight Ratio

The superior lobe of the right lung was cleansed and weighed to obtain the wet weight, and was then placed in an oven at 80 Gray for 48h for measurement of the dry weight. The ratio of the wet weight to dry weight was calculated to assess the tissue edema.

Btonchoalveolar Lanage (BAL) Examination

The trachea was exposed and cannulated with a catheter. The left lung was lavaged for 3 times with sterile PBS in a volume of 0.5 ml/wash. The fluid recovered after lavage was greater than 90% on average. The BAL fluid (BALF) was centrifuged at 2000 rpm for 10 min at 4°C, and the supernatant was stored at –80°C for cytokine and protein analysis, while the cell pellet was resuspended in PBS for counting the neutrophils.

Myeloperoxidase (MPO) Activity Assay

MPO activity in the homogenized lung tissue was measured as described by Gray et al. The MPO concentration was detected using a MPO ELISA kit (Bluegene, Shanghai, China). Briefly, the lung tissue was homogenized and centrifuged at 15000 rpm for 20 min at 4°C. The supernatants and standard sample were added into a microtiter plate (100 μL/well) precoated with a murine anti-MPO mAb. After incubation for 1h at 37°C, the plate was washed for 6 times followed by addition of the substrate and stop solution, and the optical density (OD) at 450 nm was measured using a microplate reader. All the samples were assayed in triplicate.

The Measure of Protein Concentration in Lung BALF

The concentration of protein in the BALF was measured using Bradford reagent (Bio-Rad Protein Assay kit, Hercules, CA, USA). Briefly, 160 ul of each standard and sample solution was pipetted into separate microtiter plate wells, and 40 ul of the dye reagent was added to each well and mixed thoroughly. The mixture was incubated at room temperature for at least 5 min before measurement of the OD at 595 nm. Comparison to a standard curve provided a relative measurement of the protein concentration.

Cell Culture and Treatments

Calu-3 human airway epithelial cells and human pulmonary epithelial cells were cultured as described previously[15]. Lentivirus containing mouse basic fibroblast growth factor (FGF-2) gene (LeFGF-2) and control GFP (LeGFP) were constructed above. Cells were cultured for 24 hours to reach 70% confluence and transduced with LeFGF-2 or LeGFP respectively. And then the transfected cells were collected at indicated time point for the MTT assay.

Cell Proliferation Analysis

The cell proliferation of LeFGF-2-transfected and LeGFP-transfected cells was evaluated by MTT analysis at indicated time points (n=3 for

each group). Briefly, MTT (Amresco, Solon, OH, USA) solution was added and then incubated for 4h. Finally, the medium was replaced with dimethyl sulfoxide (DMSO) and the absorbance was measured at 490 nm by ELX Ultra Microplate Reader (Bio-Tek, Winooski, VT, USA). All experiments were performed in triplicate.

Statistical Analysis

All the data were analyzed using SPSS13.0 software (SPSS Inc., Chicago, IL, USA) and expressed as Means±SD. Significant differences were assessed by one-way analysis of variance (ANOVA) followed by Fisher protected least significant difference test. A probability value of less than 0.05 was considered to indicate a statistical significance.

Results

Decreased Expression of FGF-2 in LPS-induced Acute Lung Injury

Previous studies have demonstrated that, as a member of the fibroblast growth factor family, FGF2 could stimulate the proliferation and invasion of the endothelial cells required for capillary formation as well as being a potent mitogen for fibroblast cells. In order to study the function of FGF2 in the acute lung injury, we induced acute lung injury in mice by intravenous endotoxin injection, and then the lung tissue of ALI group mice and control mice were taken for paraffin section. Representative histologic sections from lungs of mice from each experimental group are presented in Figure 1A. Lungs from mice receiving PBS but no LPS appeared histologically normal. Compared with the control group, the lung from mice receiving LPS induction appeared markedly alteration in lung architecture, with increased cellularity and fibrosis. To further assess the level of FGF2 in the injured lung tissue, we detected the expression of FGF2 in different mice lung tissue by real-time PCR and Western blot. Our results showed that the level of FGF2 mRNA and protein was decreased compared with the control group mice (Figure 1B).

MSC Characterization and Retrovirals Induced FGF-2 Overexpression in MSCs

Previous studies have demonstrated that the MSCs has the therapeutic effect on mice LPS-induced ALI, in addition, the FGF2 have the function of promoting the proliferation of fibroblast cells. So we hypothesis that whether the FGF2 overexpressed MSCs have an optimal effect on ALI. As we know, MSCs have many markers[16-18]. To characterize the phenotype of the MSCs that we isolated, we detected the typical mesenchymal stem cell surface markers such as CD105, CD90, CD73, and CD106, in the addition, we also detected the hematopoietic lineage markers CD45,

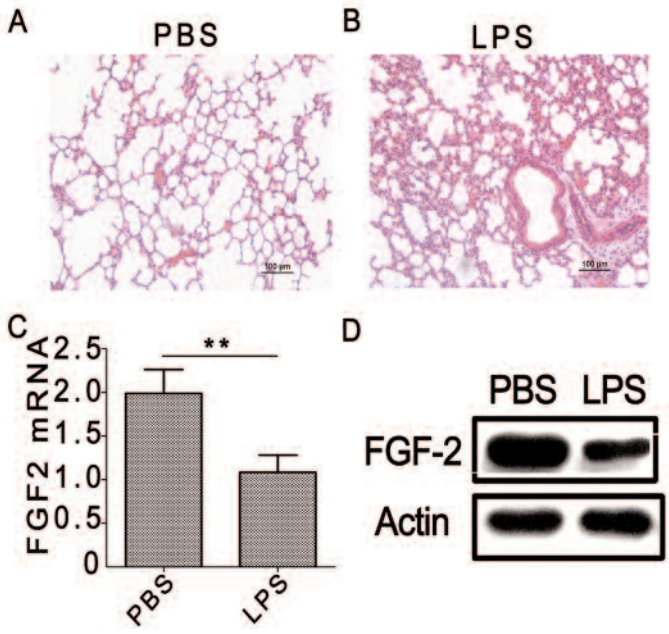

Figure 1. The induction of ALI in mice and expression of FGF-2 in different ALI mice lung tissues. The H&E-stained lung sections following 24h of induction of ALI in the ***(A)*** PBS control mice and ***(B)*** LPS-induced ALI mice. ***(C)*** Level of FGF-2 mRNA in different ALI mice groups (*$p <$ 0.05, compared with PBS control). ***(D)*** Level of FGF-2 protein in different ALI mice groups. Data are expressed as mean ± SD (error bars). ALI, acute lung injury; FGF-2, basic fibroblast growth factor 2; PBS, phosphate-buffered saline; LPS, lipopolysaccharide; H&E, hematoxylin and eosin. (***A-B*** 100 ×).

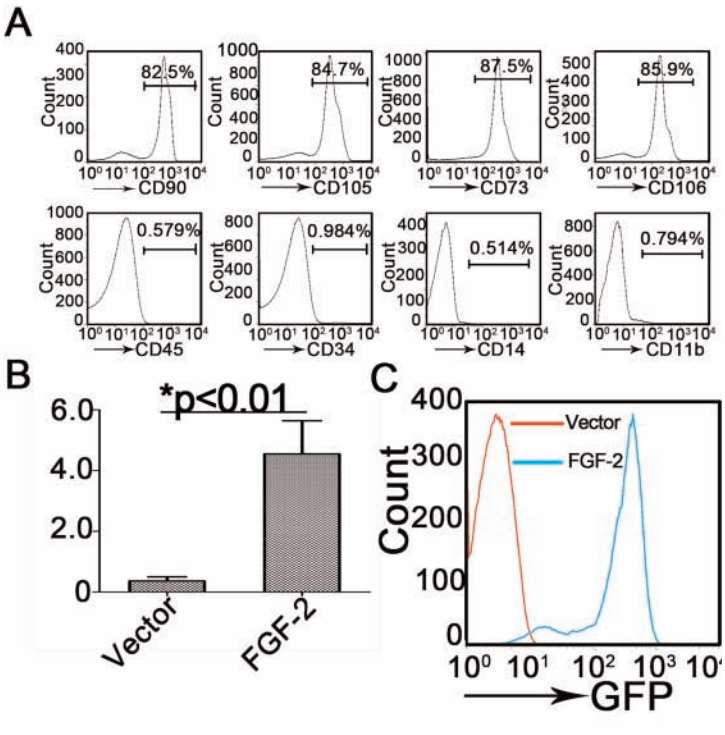

Figure 2. Flow cytometric immunophenotype analysis of the mesenchymal stem cells (MSCs) and the expression of FGF-2 in transducted MSCs using lentivirus vector. ***(A)*** The adherent MSCs expressed CD90, CD105, CD73, and CD106, but not CD45, CD34, CD14, and CD11b; ***(B)*** The level of FGF-2 mRNA and protein in lentivirus infected MSCs. ***(C)*** The transduction of FGF-2 into MSCs using lentivirus vector. MSCs, mesenchymal stem cells; FGF-2, basic fibroblast growth factor 2.

CD34, CD14, and CD11b. We found that the MSCs expressed the typical MSC surface marker CD105, CD90, CD73, and CD106, meanwhile the flow cytometry analysis demonstrated that the cells did not express the cell surface markers CD45, CD34, CD14, and CD11b (Figure 2A).

To investigate the therapeutic effect of FGF2 and MSCs on LPS-induced ALI, we generated a FGF2 carried MSCs using a lentivirus vector which containing FGF2 gene. Then we detected the expression of FGF2 in the lentivirus infected MSCs by Real-Time PCR (Figure 2B) and confirmed the over-expression of FGF2 mediated by lentivirus transduction by FACS sorting (Figure 2C). Collectively, these results indicate that the FGF2 expressing lentivirus vector increased the expressing level of FGF2 in bone marrow derived MSCs.

Effect of Different Treated MSC Transplantation on the Lung Histopathology and Lung Injury Scores

As shown in Figure 3, the administration of MSCs after LPS induction reduced the extent of inflammation within the lung as evidenced by large areas of undamaged tissue with normal alveolar architecture compared with the PBS treated ALI group (Figure 3A and C). Moreover, the transplantation of a FGF2-MSCs had a distinct therapeutic effect on LPS-induced ALI compared with the MSCs treated group (Figure 3D).

To further assess the degree of pulmonary injury, the lung injury was scored according to the degree of alveolar congestion, hemorrhage, neutrophil infiltration, and wall thickening (Figure 3E). As shown in Figure 3E, the administration of MSCs decreased the lung injury index compared with the PBS treated ALI mice. In addition, the index of the FGF2-MSCs treated group was significantly lower than those of the PBS-treated ($p < 0.001$) and MSCs treated group ($p < 0.05$).

In ALI mice, the LPS induction dramatically increase the neutrophil counts and the lung wet/dry ratio (Figure 3F and H). However, as shown in Figure 3F and 3H, these increases were markedly reduced by treatment of MSCs and FGF-2-MSCs compared with those PBS treated group mice. In addition, the administration of the FGF-2-expressed MSCs also reduced the neutrophil counts in BALF and the lung wet/dry ratio, and the difference in cell count and wet/dry ratio between MSCs treated group and FGF-2 treated group was significant.

Additionaly, the mRNA level of FGF-2 in the lung tissue of different MSCs treated group mice was detected by Real-Time PCR, we found the

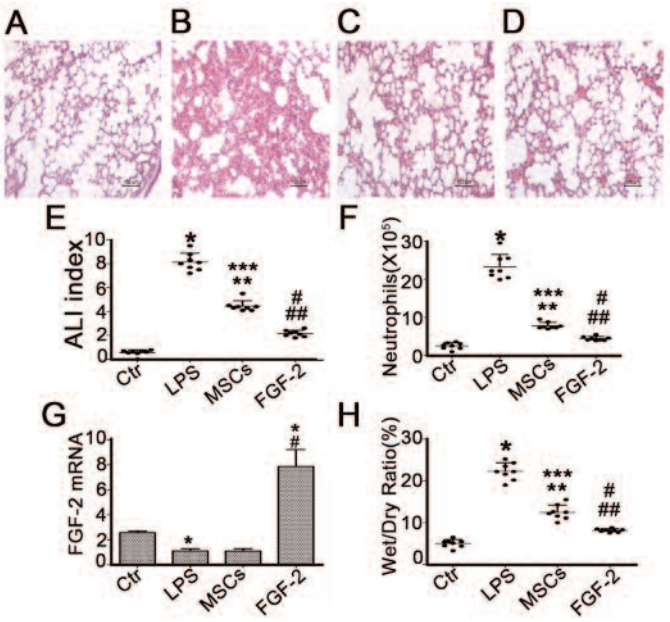

Figure 3. Histopathological index of injured mice lung. The H&E-stained lung sections following the different treatments in ***(A)*** healthy controls; ***(B)*** PBS treated group; ***(C)*** MSCs-treated only group and ***(D)*** FGF-2-MSCs treated group. ***(E)*** The lung injury index of the different treated mice. ***(F)*** The neutrophil count in the BALF of different treated mice. ***(G)*** The level of FGF-2 mRNA in different treated mice. ***(H)*** The wet/dry ratio of different groups of mice. $^{*}p < 0.05$ compared with the Ctr group mice; $^{**}p < 0.05$ compared with LPS group mice; $^{***}p < 0.05$ compared with the Ctr group mice; $^{\#}p < 0.05$ compared with the LPS group mice; $^{\#\#}p < 0.05$ compared with the MSCs group mice. ALI, acute lung injury; FGF-2, basic fibroblast growth factor 2; PBS, phosphate-buffered saline; LPS, lipopolysaccharide; H&E, hematoxylin and eosin; BALF, bronchoalveolar lavage fluid; MSCs, mesencyhmal stem cells; Ctr, control. (***A-D*** 100 ×).

expression of FGF-2 was increased in the FGF2-expressed MSCs treated mice, this result was consistent with the data of the therapeutic effect.

IL-6, TNF-α and protein concentration in BALF and MPO in lung homogenates

To determine effects of MSCs and FGF-2-MSCs transfer on the local inflammatory milieu in the lung, we detected the concentration of pro-inflammatory cytokines in BALF by ELISA, such as TNF-α and IL-6. As shown in Figure 4A and 4B, the level of TNF-α and IL-6 in BALF were significantly increased in PBS-treated ALI group mice compared with those in the health control group. Moreover, the administration of MSCs and FGF-2-MSCs significantly reduced the elevated TNF-α and IL-6 concentration. In addition, the level of TNF-α in BALF was markedly decreased in FGF-2 expressed MSCs treated group compared with those in the MSCs alone treated group. But the secretion of IL-6 was no change between MSCs-treated group and

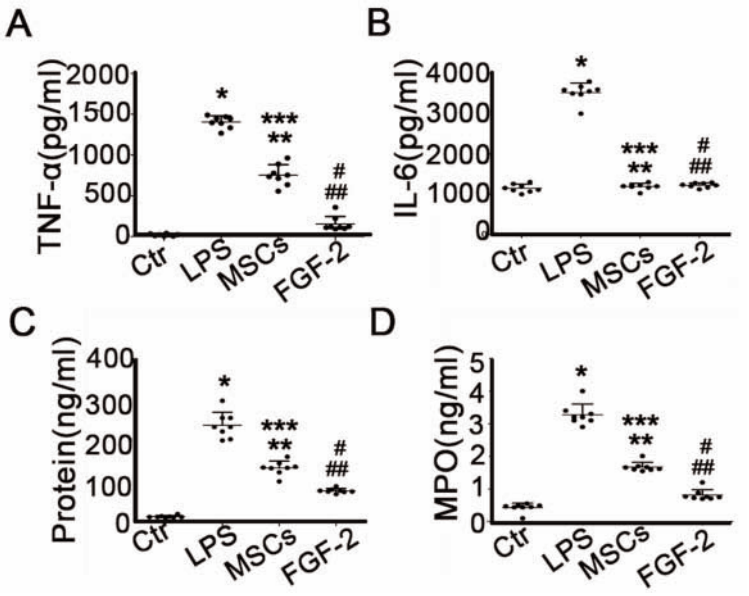

Figure 4. Proinflammatory cytokines, protein and MPO concentration in BALF of ALI mice lung homogenates. ***(A)*** TNF-α; ***(B)*** IL-6; ***(C)*** protein and ***(D)*** MPO concentration in BALF of ALI mice following the different types of treatment. $^{*}p < 0.05$ compared with the Ctr group mice; $^{**}p < 0.05$ compared with LPS group mice; $^{***}p < 0.05$ compared with the Ctr group mice; $^{\#}p < 0.05$ compared with the LPS group mice; $^{\#\#}p < 0.05$ compared with the MSCs group mice. ALI, acute lung injury; FGF-2, basic fibroblast growth factor 2; PBS, phosphate-buffered saline; LPS, lipopolysaccharide; H&E, hematoxylin and eosin; BALF, bronchoalveolar lavage fluid; MSCs, mesencyhmal stem cells; MPO, myeloperoxidase; Ctr, control.

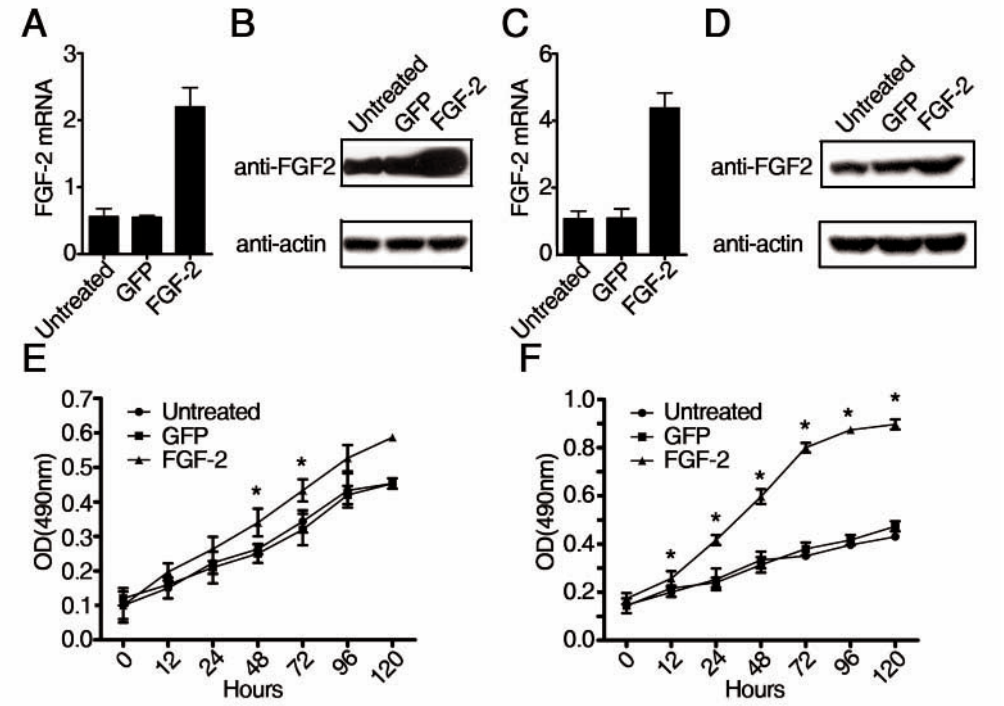

Figure 5. Gene transfection confirmation and cell proliferation. ***(A)*** The expression of FGF-2 mRNA in different transfected or un transfected Calu-3 human airway epithelial cells; ***(B)*** The level of protein of FGF-2 in different transfected or untransfected Calu-3 human airway epithelial cells; ***(C)*** the expression of FGF-2 mRNA in different transfected or untransfected human pulmonary epithelial cells; ***(D)*** the level of protein of FGF-2 in different transfected or untransfected human pulmonary epithelial cells; (E) MTT assay of untransfected, GFP transfected (LeGFP) and FGF-2 transfected (LeFGF-2) Calu-3 human airway epithelial cells at indicated time points; (F) MTT assay of untransfected, GFP transfected (LeGFP) and FGF-2 transfected (LeFGF-2) human pulmonary epithelial cells at indicated time points. $*p < 0.05$ compared with untransfected or GFP transfected control group.

FGF2 expressed MSCs treated group. Meanwhile, we detected the protein concentration in BALF and the level of MPO in the lung homogenates, the data was consistent with the results of the cytokine level in BALF and the lung injury index (Figure 4C and D).

FGF-2 Promote the Proliferation of Lung Epithelial Cell in vitro

The above data showed that the treatment of FGF-2-MSCs could protect mice from LPS-induced lung injury. Previous studies demonstrated that, as a fibroblast growth factor, FGF-2 could stimulate the proliferation and invasion of the endothelial cells. So we hypothesized that whether FGF-2 promote the lung epithelial cells proliferation and subsequent lung tissues repair. To further investigate the mechanism of FGF-2 on the lung injury, we transfected the FGF-2 contained lentivirus into lung airway epithelial cells and lung epithelial cell, and then measured the proliferation with the MTT assay. We found that the transfection of FGF-2 enhanced the expression of FGF-2 in the mRNA and protein levels, whether in lung airway epithelial cells or lung epithelial cells (Figure 5A-5D). Meanwhile, the MTT assay results revealed that, compared with the untransfected or GFP transfected control group, the FGF-2 transfection could remarkably promote the proliferation of lung epithelial cell (Figure 5F), but the effect of FGF-2 on the lung airway epithelial cells was not significant (Figure 5E). These data suggested that FGF-2 might enhance the proliferation of lung tissue epithelial cells to repair the damaged lung tissue.

Discussion

Previous acute lung injury animal model studies demonstrated that, bone marrow derived MSC have an markedly therapeutic effect on LPS-in-

duced acute lung injury, such as restoring lung function, repairing damaged lung tissue and increasing survival rate via its anti-inflammation, anti-apoptosis, and immune regulation properties. This may serve as a potential therapy for ALI induced by endotoxins or sepsis in a rodent model. As we know, fibroblast growth factors (FGFs) are signaling proteins of 150-300 amino acids with diverse functions, mainly in development and metabolism. Recently, it was demonstrated that FGF-2 function as an angiogenic factor[19], neurogenesis and neurodegeneration[20], bone homeostasis and fracture repair[21], heart development[22] and the self-renewal of embryonic fibroblasts[23].

In this report, we demonstrate that FGF-2 gene carried MSCs exerted a beneficial therapeutic effect on the LPS-induced lung injury. But the treatment of MSCs only had limited effect. Moreover, our *in vivo* data suggested that the transplantation of FGF-2 gene modified MSCs could markedly improve the histopathology and decrease the lung injury index of lung injury induced by LPS.

As showed in previous studies over the last few years on the MSCs[24-27] or FGF2[28-30], we generated a FGF2 gene carried MSCs with a FGF2 gene contained lentivirus vector. We found that MSCs and FGF2 gene have a beneficial synergistic effect on the therapy of LPS-induced acute lung injury. Our data suggested that the MSCs have not only been used as therapeutic cells, but also developed as vehicles for gene delivery.

In our experiments, the MSCs was isolated from the bone marrow of C57BL/6 mice, and then we chose several typical cell surface markers for bone marrow, such as CD45, CD34, CD14 and CD11b, and for MSCs, such as CD73, CD90, CD105 and CD106. We characterized the differentiation of MSCs from bone marrow by Flow cytometric immunophenotype, as shown in Figure 2, almost all these cells expressed the MSCs specific surface marker CD105, CD90, CD73 and CD106, but not the hematopoietic lineage typical markers, such as CD45, CD34, CD14 and CD11b (Figure 2).

To further investigate the therapeutic function of MSCs on LPS-induced ALI, we chose lentivirus vectors to modify MSCs with FGF2 gene because of the high efficiency of gene delivery and the integration of the gene into dividing MSCs. In our experiment, we achieved a high gene transduction efficiency at day 5 after exposure to lentivirus vectors (Figure 2).

Previous studies revealed that FGF2 have a function of promoting the self-renew of embryonic fibroblastes[31]. In this study, we found that the inflammatory response and vascular leakage in the lung after LPS induction were attenuated with the administration of the FGF2 modified MSCs. In addition, treatment of FGF2 gene modified MSCs suppressed the expression of pro-inflammatory cytokine gene, such as TNF-a and IL-6 (Figure 4). Meanwhile, the MTT assay suggested that the FGF-2 might enhance the proliferation of lung tissue epithelial cell and promote the reparation of damaged lung tissue (Figure 5).

Conclusions

Our findings demonstrated that the FGF2 gene modified MSCs has a perfectly therapeutic effect on LPS-induced acute lung injury. As a highly efficient gene vehicle for the therapy of lung injury, MSCs and the modification of FGF2 may provide a platform for designing novel therapeutic approaches to attenuate the tissue injury in lung injury disease.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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