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Human pluripotent stem cell-derived mesenchymal stem cells prevent chronic allergic airway inflammation via TGF-β1-Smad2/Smad3 signaling pathway in mice

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ABSTRACT

Background: Asthma is a chronic disease involving inflamed airways, which were previously demonstrated, can be modulated by the mesenchymal stem cells derived from induced pluripotent stem cells (iPSC-MSCs). However, the long-term effects of iPSC-MSCs in inflamed airways are still unidentified. This study investigated the long-term effects and potential mechanisms involved in the immunomodulatory effects of iPSC-MSCs in the chronic mouse asthma model.
Methods: Both human iPSC-MSCs and bone marrow (BM)-MSCs were transplanted into the long-term ovalbumin-induced mice before sensitization phase or during the challenge phase. Airway hyper-respnsiveness measurement, immunohistochemistry and ELISA were employed to assess the effects of MSCs. In addition, Smad2/3 levels were assessed by western blot analysis to investigate the possible mechanism involved.
Results: The systemic administration of human iPSC-MSCs before the challenge protected the mice from the characters of the chronic allergic airway inflammation, in particular improving the airway remodeling and preventing fibrosis. In addition, the TGF-β1/Smad pathway was identified involved in the immunomodulatory effects of iPSC-MSCs on chronic allergic airway inflammation.
Conclusions: The study demonstrated that iPSC-MSCs are capable of preventing chronic allergic airway inflammation over a prolonged period, which further proved the iPSC-MSC therapeutic potential for allergic airway inflammation in a clinical scenario.

1. Introduction

Asthma is a chronic lung disease involving inflamed and narrowed airways, which could cause symptoms including coughing, wheezing, shortness of breath and/or chest tightness. Nearly 60% of asthmatics have limited physical activities because of the symptoms. Nevertheless, the disease not only affects specific individuals but also brings large burden to the society (Braido, 2013; Nunes et al., 2017). Bronchial asthma has been characterized by chronic and acute allergic airway inflammation, which induces both cytological and histological changes in the airway structure over time (Bonfield et al., 2010b). Long-term remodeling of the lung is observed in chronic allergic airway inflammation, which results in thickening of the basement membranes in the lung/airways, smooth muscle proliferation, increased fibrosis and decreased lung capacity (Walsh et al., 2010). There are several effective medicines to treat asthma, however, current therapeutics do not have the capacity to reverse the ongoing remodeling process (Ogulur et al., 2014; Szymczak et al., 2016). New treatment options are more desirable to focus on the pathophysiological characters that cause development and persistence of asthma for the chronic asthma patients.

Abbreviations: α-SMA, α-smooth muscle actin; AHR, airway hyper-responsiveness; ANOVA, one-way analysis of variance; BALF, bronchoalveolar lavage fluid; BM-MSCs, bone marrow-derived mesenchymal stem cells; ELISA, enzyme-linked immunosorbent assay; FITC, fluorescein isothiocyanate; H&E, hematoxylin and eosin; IL, interleukin; iPSC-MSCs, mesenchymal stem cells derived from induced pluripotent stem cells; OVA, ovalbumin; PAS, periodic acid–Schiff; PBS, phosphate-buffered saline; PE, phycoerythrin; Th2, type 2 T helper

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We have previously reported that mesenchymal stem cells derived from induced pluripotent stem cells (iPSC-MSCs) are able to inhibit Th2-dominant allergic airway inflammation in the mouse asthma model (Sun et al., 2012). And iPSC-MSCs were also capable of improving peripheral blood T lymphocyte subsets in allergic rhinitis patients with immune imbalances (Fu et al., 2012). However, the long-term effects of iPSC-MSCs in chronic allergic diseases are still out of understanding. It would be preferable if stem cell therapy were able to focus on the pathophysiological characters that cause the persistence of asthma.

Since it has been shown that the intravenously administrated bone marrow-derived mesenchymal stem cells (BM-MSCs) could localize to the lung and thereby provide a local source of trophic factors in the pulmonary environment (Bonfield et al., 2010a; Loebinger et al., 2008). This study investigated the long-term effects and potential mechanisms involved in the immunomodulatory effects of iPSC-MSCs in chronic asthma in mice. We identified that iPSC-MSCs prevented mouse chronic allergic airway inflammation and remodeling via the production of bioactive factors. The results of this study further demonstrate the potential application of iPSC-MSCs in the treatment of chronic allergic airway inflammation in a clinical scenario.

2. Material and methods

2.1. Preparation of human iPSC-MSCs and BM-MSCs

iPSC-MSCs were generated according to the protocol described in our previous study (Gao et al., 2017). The generated iPSC-MSCs were maintained in knockout Dulbecco's modified Eagle's medium (Gibco, Invitrogen Corporation, Carlsbad, CA) supplemented with 10% serum replacement medium (Gibco), basic fibroblast growth factor (10 ng/ml, Gibco) and Penicillin-Streptomycin (100 U/ml, Gibco). MSC identity was verified by using phycoerythrin (PE)- or fluorescein isothiocyanate (FITC)-conjugated antibodies against CD24, CD31, CD44, CD73, CD90, CD105, and CD166 on the cell surface (BD Biosciences, San Jose, NJ). Human BM-MSCs were commercially purchased from Cyagen Bioscience Inc. (Jiangsu, China), they were applied as positive control. iPSC-MSCs with passage number 12 to 20 and BM-MSCs with passage number 4 to 6 were utilized for transplantation during the study.

2.2. Mouse model of chronic allergic airway inflammation

Female BALB/c mice (4 weeks of age) were purchased from Medical Experimental Animal Center of Guangdong Province, China. The procedures performed in this study were carried out according to protocols approved by the Institutional Animal Care and Use Committee, Sun Yat-sen University (No. IACUC 20110228002).

A mouse model of chronic allergic airways inflammation was induced as previously reported with minor modification (McMillan et al., 2005). Briefly, mice were sensitized with 40 μg ovalbumin (OVA, Sigma-Aldrich, Shanghai, China) and 2 mg aluminium hydroxide (Sigma-Aldrich) on day 1, 7, and 14 by intraperitoneal injection. From day 21 to 53, mice were first challenged with 5% aerosolized OVA for 30 min, and then intranasally infused with 20 μl OVA (40 mg/ml) every other day. The mice were tested for airway hyper-responsiveness (AHR) on day 54 and sacrificed via cervical dislocation on day 55.

2.3. AHR measurement

AHR was measured 24 h after the last aerosol OVA exposure. Briefly, increasing doses aerosolized methacholine (0, 6.25, 12.5, 25, 50 and 100 mg/ml) were administered to the mice, which were placed in a whole-body plethysmography chamber connected to the measured machine via a small polyethene catheter. The Penh was measured with a 2 min period for each methacholine dose using a Transducer Medlab to evaluate the airway resistance and dynamic compliance.

2.4. Human iPSC-MSC/BM-MSC transplantation

In our previous research (Sun et al., 2012), we have found that different clones of iPSC-MSCs exhibited similar effects in preventing allergic airway inflammation in mice model, so we chose one clone to use in this study. The BM-MSCs were bought from the Cyagen Biosciences Inc., which were donated from one volunteer, so the consistency of each batch could be ensured. On day 20, 22 and 24, 0.2 ml cell suspension with 5×10^6 cells/ml human MSCs or sterile phosphate-buffered saline (PBS) was injected into the model mice via the tail vein. Mice were divided into six groups: (A) PBS/PBS/PBS, mice that sensitized and challenged with PBS were then injected with PBS (n = 6); (B) naive/naive/iPSC-MSCs, mice that were naive mice only treated with iPSC-MSCs (n = 6); (C) OVA/OVA/PBS, mice that sensitized and challenged with OVA were then injected with PBS (n = 6); (D) OVA/OVA/iPSC-MSC, mice that sensitized and challenged with OVA were then injected with iPSC-MSCs (n = 6); (E) OVA/OVA/BM-MSC, mice that sensitized and challenged with OVA were then injected with BM-MSCs (n = 6); (F) iPSC-MSC/OVA/OVA, mice that injected with iPSC-MSCs on day 0 were then sensitized and challenged with OVA (n = 6).

2.5. Bronchoalveolar lavage fluid (BALF) analysis

On day 55, BALF was obtained by lavaging 1 ml of cold PBS through the upper part of the trachea. Then the BALF was centrifuged (2500 rpm, 10 min), and the supernatants were collected for cytokine analyses. Cell pellets were resuspended in PBS and then cytospun onto glass slides for Diff-Quick staining (Baso Diagnostics Inc., Wuhan, China), by which to evaluate the eosinophils in each group.

2.6. Evaluation of the inflammatory cytokines in BALF

The IL-4 and IL-13 levels in the BALF were measured using sandwich enzyme-linked immunosorbent assay (ELISA) analysis following the manufacturer's instructions (R&D Systems, Minneapolis, MN). In addition, the measurement of TGF-β1 was assayed using commercial ELISA analysis (Abnova, Taiwan, China) following the manufacturer's instructions.

2.7. Immunohistochemistry of lung sections

After the lavage, the lung tissues were removed and fixed with 10% neutral formalin for 36h and then embedded in paraffin fixation. A 4 μm thick lung section was stained with both hematoxylin and eosin (H&E) and periodic acid–Schiff (PAS) to evaluate the lung inflammatory level. Goblet cell (PAS positive cell) counts and inflammation score in the lungs were performed in a blind-way using a reproducible scoring system (Wang et al., 2017). Masson trichrome staining and a-smooth muscle actin (α-SMA) immunostaining were employed to assess peribronchial collagen deposition and the thickness of the airway smooth muscle layer, respectively. The staining area was outlined and quantified using a bright microscope (Olympus DP20) and the attached image analysis system (Image-Pro Plus 5.1). Results were expressed by the basement membrane perimeter in two to four preparations of one mouse (Chen et al., 2011).

2.8. Western blot analysis

Lung homogenates were prepared for the immunoblotting. After transferred, thePVDF membranes were incubated with Smad2/3 (D7G7) XP® Rabbit mAb and Phospho-Smad2 (Ser465/467)/Smad3 (Ser423/425) (D27F4) Rabbit mAb (Cell Signaling Technology, Danvers, MA), respectively. HRP-conjugated secondary antibody (Santa Cruz Biotechnology, Dallas, TX) was then used to detect the bands. GAPDH was used as a loading control for protein normalization. All immunoblot experiments were conducted in triplicate.

2.9. Statistical analysis

All experimental data were presented as the mean ± SEM. Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Student-Newman-Keuls test for multiple comparisons of the data with the Gaussian distribution. Kruskal–Wallis rank sum test followed by Mann–Whitney U test was performed for the data with abnormal distribution. *P* values < 0.05 were considered statistically significant.

3. Results

3.1. Administration of human iPSC-MSCs attenuated OVA-induced chronic airway inflammation in mice

Mouse model of chronic allergic airway inflammation was successfully established through repetitive OVA challenge in this study as previous study including high mouse airway hyperresponsiveness, and high levels of inflammation, goblet cell hyperplasia, airway remodeling and collagen deposition due to the OVA sensitization and chronic challenge (Lee et al., 2017). In this study, mice were subjected to extended OVA challenge every other day from day 21 to 53 (Fig. 1A), significant airway inflammation and remodeling similar to that of human chronic asthma were established.

The degree of airway responsiveness to methacholine was measured 24 h after the last challenge. Compared with control mice, mice sensitized and challenged with OVA exerted significant elevated *Penh* value in response to the methacholine (Fig. 1B). As shown in Fig. 1B, the AHR to methacholine was reduced in the human iPSC-MSCs or BM-MSCs treated mice during OVA challenge. In addition, administration of iPSC-MSCs before sensitization was also able to reduce the AHR in mice.

H&E and PAS staining showed that OVA/OVA/PBS mice exhibit obvious inflammatory cell infiltration and goblet cell hyperplasia in the peribronchial tissue. Treatment with human iPSC-MSCs/BM-MSCs significantly decreased the lower airway inflammation and reduced goblet cell hyperplasia in the lungs (Fig. 1C–E). What's more, the transplanted human iPSC-MSCs before sensitization also significantly inhibited inflammatory cell infiltration in the lungs but did not considerably reduced the goblet cell hyperplasia reduced compared to that in OVA/OVA/PBS group (Fig. 1C–E). There was no significant difference found between PBS/PBS/PBS and naive/naive/iPSC-MSC group, with no allergen-driven airway inflammation in the mice. These data suggested

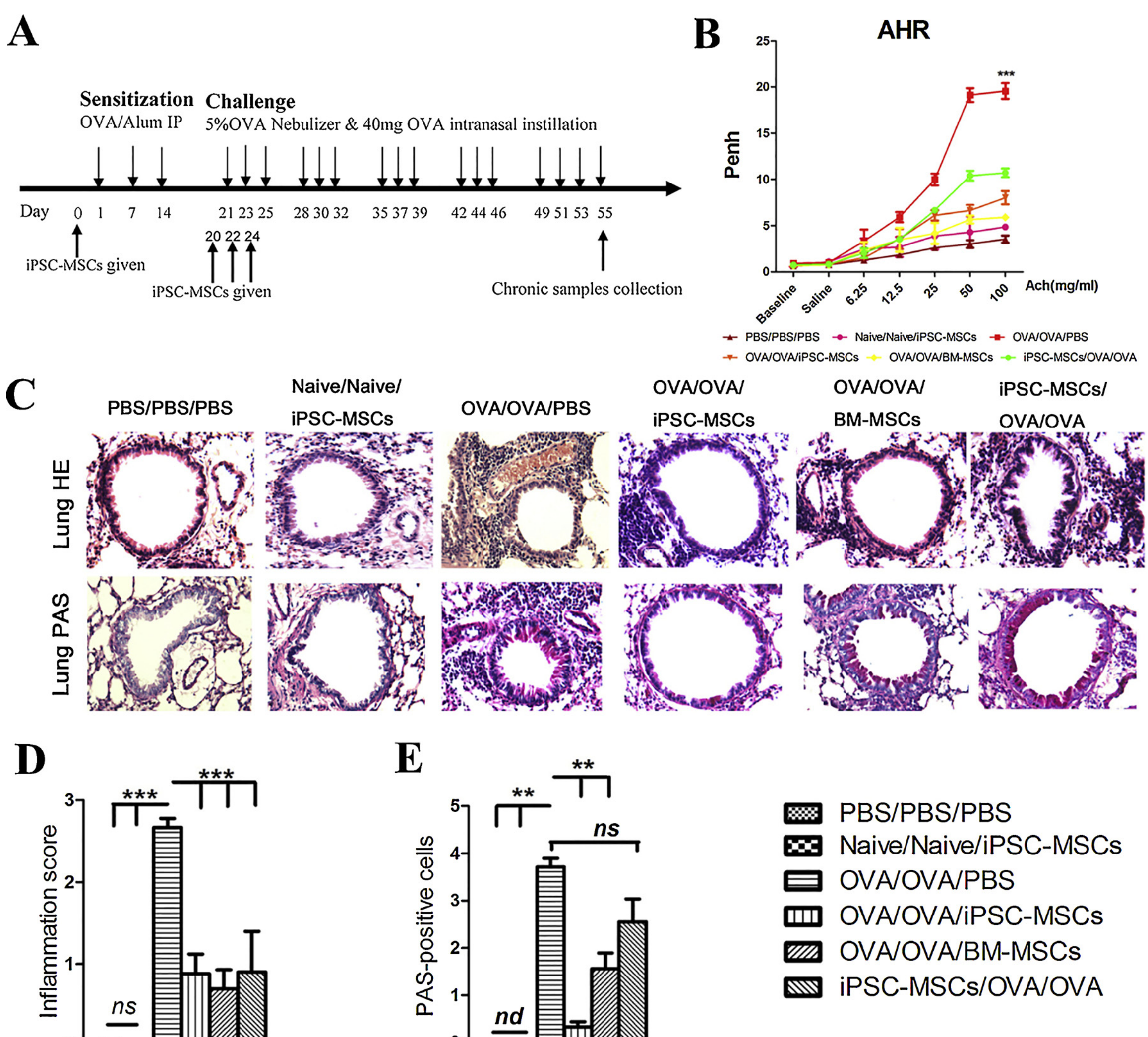

Fig. 1. Administration of human iPSC-MSCs attenuated OVA-induced chronic airway inflammation in mice. A. Schematic illustration of the establishment of mouse chronic allergic airway inflammation model; B. Systemic administration of human MSCs during challenge inhibits airway hyper-reactivity (n = 6); C. Representative photographs of H&E and PAS stained lung sections from each group (Original magnification X200); D&E. The inflammatory infiltration and goblet cell hyperplasia were quantified by H&E and PAS scores (n = 6). ** for *p* value < 0.01, *** for *p* value < 0.001. Abbreviations: BM-MSCs, bone marrow-derived mesenchymal stem cells; H&E, hematoxylin and eosin; iPSC-MSCs, induced pluripotent stem cell-derived mesenchymal stem cells; *nd*, not detectable; *ns*, not significant; OVA, ovalbumin; PAS, periodic acid–Schiff; PBS, phosphate-buffered saline.

that both human iPSC-MSCs and BM-MSCs are able to focus on the pathophysiological characters and attenuate chronic airway inflammation in a long-term manner. The human iPSC-MSCs applied during challenge phase showed better ability to inhibit the development of chronic allergic inflammation than that before the sensitization phases of the disease.

3.2. MSC administration reduced inflammatory cell infiltration and inflammatory cytokine levels in the BALF

The effects of human iPSC-MSCs on the OVA-induced chronic allergic airway inflammatory cells and cytokine profiles in the BALF were further examined. The numbers of total inflammatory cells and eosinophils were dramatically increased in the BALF from OVA/OVA/PBS mice. However, treatment with iPSC-MSCs decreased both total inflammatory cells and eosinophil numbers of in the BALF. Treatment with BM-MSCs demonstrated the same effects on the total inflammatory cells and eosinophils in the BALF. The decreased eosinophils were also found in the BALF of mice that were pretreated with iPSC-MSCs before sensitization. The cellular profiles in the BALF from the naive mice treated with human iPSC-MSCs alone were similar to that from the PBS/PBS/PBS mice (Fig. 2A).

The levels of the type 2 T helper (Th2) cell-derived cytokines in the BALF after administration of human iPSC-MSCs and BM-MSCs were also examined using ELISA assay. OVA-challenged mice showed increased levels of IL-4 and IL-13 in the BALF. In contrast, treatment with both human iPSC-MSCs and BM-MSCs were able to significantly decrease the levels of IL-4 and IL-13 in the BALF. iPSC-MSCs pretreatment before sensitization also dramatically reduced the levels of IL-4 and IL-13 in the BALF (Fig. 2B). These findings demonstrated that iPSC-MSCs are able to consistently attenuate the inflammatory cell and Th2-type cytokine infiltration in a long-term manner in the OVA-induced mouse lung.

3.3. iPSC-MSC administration prevented airway remodeling in chronic airway inflammation

We next measured the effect of iPSC-MSC treatment on the airway remodeling, which is the major character symptom of chronic asthma. OVA/OVA/PBS group mice exhibited obvious collagen formation in the peribronchial tissue as shown by Masson trichrome staining. While iPSC-MSC treatment resulted in a significant decrease of collagen formation; similar improving effects were detected in the BM-MSC-treated mice (Fig. 3A&B). In addition, more α-SMA was detected in the lung of OVA-induced mice compared to that in the lungs of MSC treated mice (Fig. 3A&C). However, the pretreated iPSC-MSCs before sensitization did not prevent collagen deposition or inhibit α-SMA expression as effective as the other MSC treated groups. These data suggested that iPSC-MSC treatment is effective in preventing the airway remodeling in the chronic airway inflammation, such action may constantly focus on the pathophysiological characters of chronic asthma.

3.4. iPSC-MSC administration prevented chronic allergic airway inflammation via TGF-β1-Smad2/Smad3 signaling pathway

In order to further demonstrate the mechanisms of iPSC-MSC treatment on chronic allergic airway inflammation, we measured TGF-β1 levels in the BALF as such cytokine is able to induce epithelial hyperplasia (Chen et al., 2011). The level of TGF-β1 was significantly increased in the OVA-induced group compared to that in the control group. iPSC-MSC and BM-MSC treatment significantly reduced the TGF-β1 levels. iPSC-MSC pretreatment also significantly reduced the TGF-β1 level in the BALF, but not as efficient as that in the iPSC-MSC treatment group (Fig. 4A). Furthermore, western blot analysis demonstrated a significant increase of Smad2, Smad3 and pSmad2/3 in the OVA-induced mice. Whereas, both iPSC-MSC and BM-MSC treatment significantly decreased pSmad2/3 expression, the levels of Smad2 and

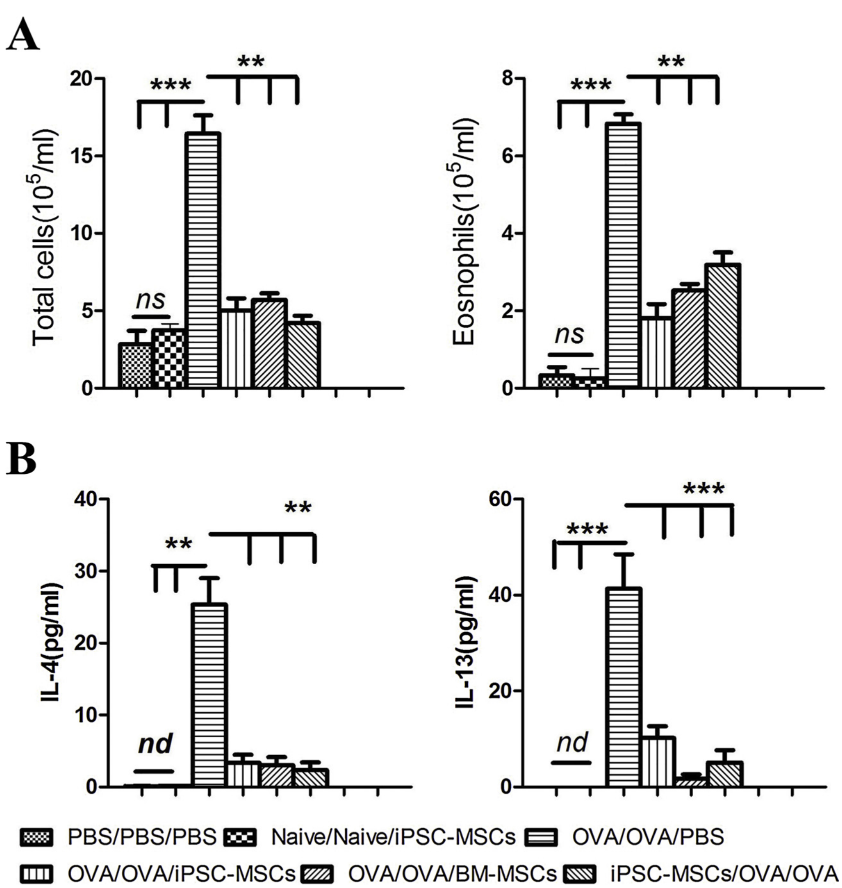

Fig. 2. MSC administration reduced inflammatory cell infiltration and inflammatory cytokines in the BALF. A. Statistical analysis of the total inflammatory cells and eosinophils in the BALF (n = 6); B. Statistical analysis of IL-4 and IL-13 levels in the BALF as measured by ELISA (n = 6). ** for *p* value < 0.01, *** for *p* value < 0.001. Abbreviations: BALF, bronchoalveolar lavage fluid; BM-MSCs, bone marrow-derived mesenchymal stem cells; IL: interleukin; iPSC-MSCs, induced pluripotent stem cell-derived mesenchymal stem cells; *nd*, not detectable; *ns*, not significant; OVA, ovalbumin; PBS, phosphate-buffered saline.

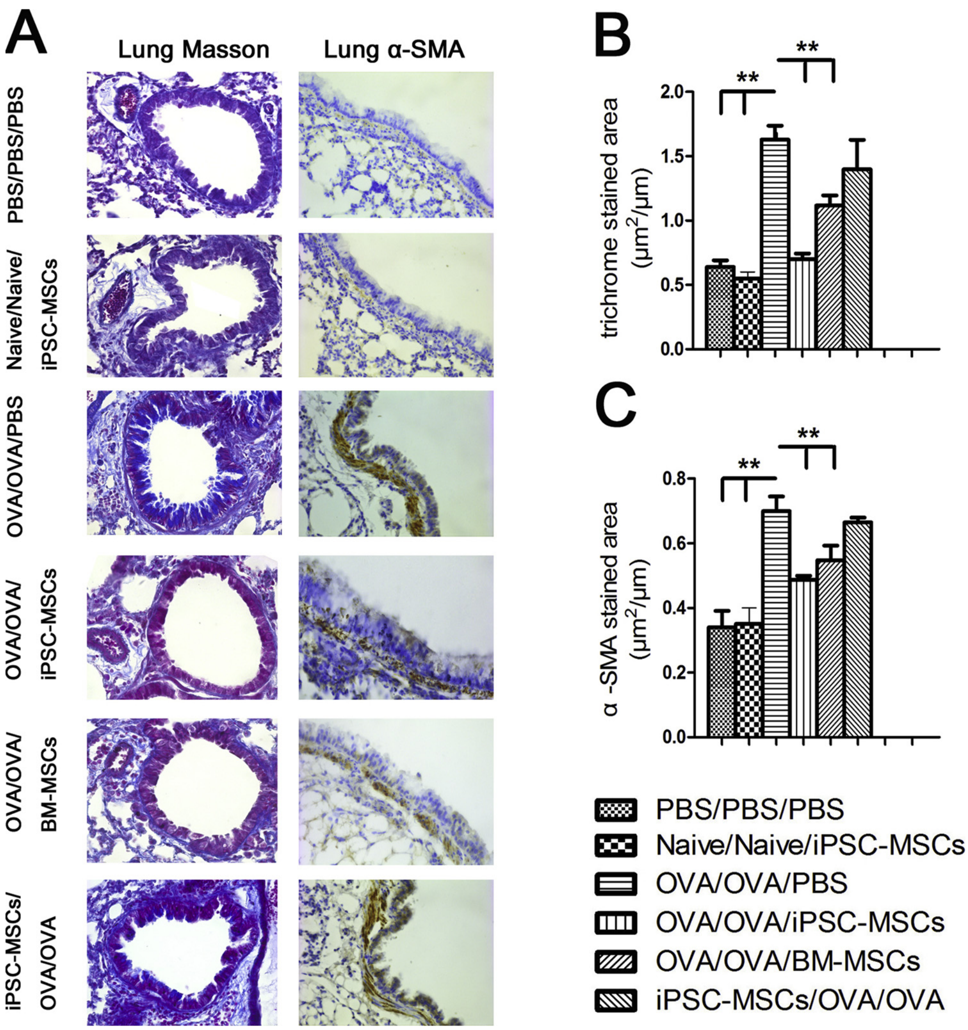

Fig. 3. Administration of human iPSC-MSCs prevented the airway remodeling and fibrosis in chronic airway inflammation. A. Representative photographs of Masson trichrome staining and α-SMA immunostaining stained lung sections from each group (Original magnification X200); B. Statistical analysis of trichrome stained area in the lungs (n = 6); C. Statistical analysis of α-SMA stained area in the lungs (n = 6). ** for *p* value < 0.01. Abbreviations: α-SMA, α-smooth muscle actin; BM-MSCs, bone marrow-derived mesenchymal stem cells; Masson, Masson trichrome staining; iPSC-MSCs, induced pluripotent stem cell-derived mesenchymal stem cells; OVA, ovalbumin; PBS, phosphate-buffered saline.

Smad3 were also decreased. In contrast, the levels of Smad2, Smad3 and pSmad2/3 in iPSC-MSC pretreatment group still maintained high after prolonged allergen challenge (Fig. 4B&C). Therefore, the iPSC-MSC administration is able to prevent chronic allergic airway inflammation via inhibiting the TGF-β1-Smad2/Smad3 signaling pathway in the lung. In addition, the iPSC-MSC administration during challenge phase showed much better therapeutic effects than that before allergen sensitization.

4. Discussion

In this study, we examined the long-term effects of MSC treatment on OVA-induced chronic allergic airway inflammation in the mice. MSC administration is able to focus on the pathophysiological characters and attenuate chronic airway inflammation in a long-term manner by reducing inflammatory cell and inflammatory cytokine infiltration. Both iPSC-MSCs and BM-MSCs were able to inhibit the progress of airway remodeling in mice exposed to repetitive allergen challenge. In addition, we have demonstrated that human MSCs may modulate airway remodeling via regulating the expression of signaling molecules of the TGF-β1/Smad pathway.

Airway tissues with chronic asthma have been characterized with goblet cell hyperplasia, mucous gland hypertrophy, subepithelial fibrosis and smooth muscle cell hyperplasia or hypertrophy, which are in part irreversible (Hassan et al., 2010; Trifilieff et al., 2000). The consistent infiltration of inflammatory cells in chronic asthma will induce airway remodeling, which differs from normal wound healing (Chen et al., 2011). It is observed that remodeling can be elevated by as much

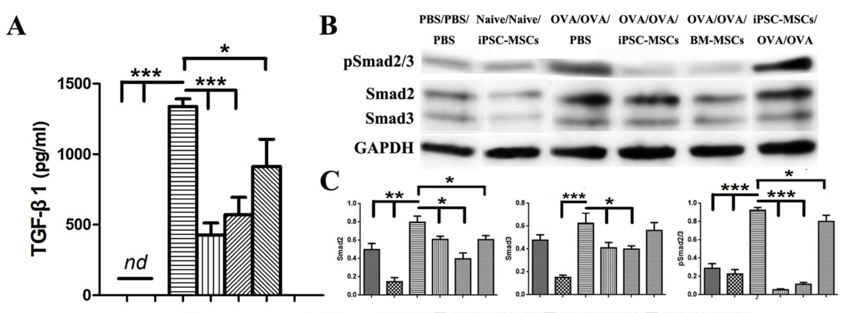

Fig. 4. Administration of human iPSC-MSCs decreased the levels of TGF-β1-Smad2/Smad3 in chronic allergic airway inflammation. A. Statistical analysis of TGF-β1 levels in the BALF from each group as measured by ELISA; B. Western blot analysis of Smad2, Smad3 and pSmad2/3 expression in the lungs from each group; C. Quantification of Smad2, Smad3 and pSmad2/3 expression in the lungs from each group (n = 3). * for *p* value < 0.05, ** for *p* value < 0.01, *** for *p* value < 0.001. Abbreviations: BM-MSCs, bone marrow-derived mesenchymal stem cells; iPSC-MSCs, induced pluripotent stem cell-derived mesenchymal stem cells; *nd*, not detectable; OVA, ovalbumin; PBS, phosphate-buffered saline.

as 50–300% in asthma patients who have died (Niimi et al., 2003). Human bone marrow-derived MSCs have the unique capacity to support tissue regeneration and secrete soluble mediators that can modulate inflammation (Zhang et al., 2009); therefore, MSCs may offer a much desirable therapeutic strategy for chronic asthma prevention.

Our results have demonstrated the therapeutic effect of iPSC-MSCs on airway remodeling in chronic allergic airway inflammation. In this study, iPSC-MSCs effectively decreased Th2 cytokines and inhibited inflammatory cells in the chronic mouse asthma model induced by OVA. We also observed that the iPSC-MSCs reduced collagen deposition and airway thickening, which demonstrated the long-term immunomodulatory effects of iPSC-MSCs on chronic allergic airway inflammation. These findings have further extended current knowledge of iPSC-MSC immunomodulatory effects in chronic allergic airway inflammation. However, pretreatment of iPSC-MSCs before sensitization didn't exhibit significant immunomodulatory effects compared to that administrated during challenge phase in the chronic mouse model. This is probably due to the lack of stimulus signals, which could recruit the iPSC-MSCs to the site of injury (Hocking, 2015).

The administration of iPSC-MSCs after OVA sensitization significantly reduced the expression of TGF-β1, and as demonstrated by a decrease in pSmad2/3 expression. TGF-β1 is a potent fibrotic factor responsible for the synthesis of extracellular matrix, and it is also related to the airway remodeling (Bartram and Speer, 2004; Chen et al., 2011). TGF-β1 binds to the TGF-β type II receptor leading to the recruitment of the TGF-β type I receptor, which induces the phosphorylation of the downstream targets Smad2 and Smad3 (Roach et al., 2015). The phosphorylated Smad2 and Smad3 will then mediate the biological effects of TGF-β1 to stimulate fibroblast to myofibroblast differentiation, especially increase α-SMA expression (Gu et al., 2007; Hu et al., 2003). Therefore, iPSC-MSCs are able to inhibit direct airway cell proliferation via anti-proliferative activity, which could prevent allergic airway inflammation in long-term.

Human iPSC-MSCs acting as the new cell type have been investigated in immunoregulation and showed encouraging results (Fu et al., 2012; Gao et al., 2016). The iPSC-MSCs represent the effective source of multipotent cells, which incorporates the advantages of both induced pluripotent cells and traditional MSCs (Lian et al., 2010; Zomer et al., 2015). iPSC-MSCs not only have a greater proliferation capacity in vitro without senescence, but also are non-tumorigenic and safe for transplantation (Zomer et al., 2015; Gao et al., 2017). In this study, we observed the presence of green fluorescent protein (GFP)-transfected iPSC-MSCs in the lungs at day 1, day 7 but not at day 10 after transplantation before the challenge (data not shown). We recently reported the survival and distribution of GFP-iPSC-MSCs in the lung at 1 h, 4 h, 1 days and even 4 days after intratracheal transplantation in the OVA-treated mice (Yao et al., 2018). Our findings were consistent with previous studies. The intravenous route in almost all cases let to a distribution of MSCs mostly in lungs, but also in spleen, liver, bone marrow, thymus, kidney, skin, and to tumors (Kurtz, 2008). It was found that there was no significant difference of MSC distribution between healthy animals and disease models in most studies. Tracking of the cells *in vivo* revealed that only a small proportion of the cells home and persist in the target sites, and that most of the cells are not detectable after 7 ~ 14 days post transplantation. It seems that MSCs can deliver a profound clinical effect without differentiation, without homing to target organs in significant numbers and despite the cell's disappearance within short periods of time (Kurtz, 2008). Of course, the detailed mechanism for the long-term effects of MSCs on chronic allergic airway inflammation even under short-time survive should be carefully addressed in the future. Interestingly, some studies suggest that the protective effects mediated by MSCs administration may be associated with education of macrophages through phagocytosis of apoptotic MSCs (Galipeau and Sensebe, 2018).

Our findings also provide a potential therapeutic method to reverse chronic airway hyperplasia that contributes to airway hyperresponsiveness and airflow limitation. However, further studies need to be done to confirm the effects of iPSC-MSC administration. In addition, there might be more than one possible mechanism by which iPSC-MSCs inhibit airway remodeling in chronic allergic airway inflammation, which also needs to be focused on in the future.

5. Conclusions

In conclusion, this study demonstrated that iPSC-MSC administration could effectively inhibit chronic allergic airway inflammation through decreasing TGF-β1 production in the lung. The cells might provide a potential therapeutic candidate for the treatment of long-term asthma airway remodeling. However, further studies need to be done to fully reveal the mechanisms of iPSC-MSC immunomodulatory effects, by which to support iPSC-MSC clinical application in chronic allergic airway inflammation.

Author contributions

H.Z.: acquisition of data and analysis; X.L.F.: analysis and interpretation of data, drafting the article; S.B.F., Y.D.L.: collection of data; W.W.: design; Q.L.F.: conception and design, drafting the article, and final approval of the article.

Disclosure

The author reports no conflicts of interest in this work.

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