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The transcription factor Foxp1 regulates the differentiation and function of dendritic cells☆

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ABSTRACT

Dendritic cells (DCs) are the sentinels of the immune system and play a critical role in initiating adaptive immune responses against pathogens. As the most powerful antigen presenting cells, DCs are also important in maintaining immune homeostasis and participating in the development of autoimmune diseases. How the maturation and function of DCs is regulated in these conditions and what is the function of various transcription factors is still unclear. In this study, we found that the expression of the transcription factor Foxp1 gradually increased during the maturation of DCs. Then, we constructed a recombinant adenovirus carrying Foxp1-interfering RNA (Ad-simFoxp1) and transfected murine bone marrow-derived DCs *in vitro*. DCs transfected with Ad-simFoxp1 exhibited markedly lower costimulatory molecules, and decreased cytokines. And Ad-simFoxp1 greatly inhibited mature DC-induced T cell responses. Moreover, *in vivo* infusion with Ad-simFoxp1-modified DCs significantly delayed the onset of experimental autoimmune encephalomyelitis (EAE). Therefore, adoptive transfection of Ad-simFoxp1 in DCs may be a potential treatment strategy against autoimmune diseases.

1. Introduction

As the most powerful antigen presenting cells, DCs play a critical role in both stimulating the immune response and maintaining immune tolerance (Audiger et al., 2017; Iberg et al., 2017). Immature DCs reside in peripheral tissues and specialize in antigen capture, whereas mature DCs reside mostly in the secondary lymphoid organs where they act as antigen-presenting cells (Iwasaki and Medzhitov, 2015; Qian and Cao, 2018). During the processing of antigens, DCs differentiate into mature DCs, which can promote T cell activation and proliferation (Gao et al., 2013; Permanyer et al., 2018). It has been confirmed that aberrant activation of DCs has been linked to the development of some diseases, such as autoimmune diseases and tumors (Ganguly et al., 2013; Mackern-Oberti et al., 2015; Tran Janco et al., 2015). Therefore, the functional characteristics and immune effects of DCs are closely related to their maturation status.

Gene regulation of cell development occurs at multiple levels, including modulation of transcriptional activity, mRNA processing, and posttranslational modification of proteins. Many transcription factors (TF), such as the Fox transcription factors, are involved in development of cells. The Fox transcription factors containing winged helix DNA binding domains are highly conserved across species. In addition to participating in various organ development, they also have significant effects on many biological processes, such as cell cycle, carbohydrate and lipid metabolism, body aging, and immune regulation (Benayoun et al., 2011; Golson and Kaestner, 2016). Currently, subclasses FOXA to FOXS are defined based on a phylogenetic analysis of the forkhead domain. In the previous study, we analyzed various transcriptional regulators expressed by DCs by RNA sequencing. Foxp1, a member of the Forkhead box gene family, caught our attention. It has been reported that Foxp1 regulates the differentiation and function of B cells, macrophages and T cells (Feng et al., 2011; Konopacki et al., 2019;

☆ Summary statement: Foxp1 is highly upregulated during dendritic cells maturation. Downregulation of Foxp1 suppresses DC activation, cytokine production, and T cell priming ability. Disrupt Foxp1 expression in DCs would ameliorate autoimmune EAE induction, which suggest DC Foxp1 expression may serve as potential targets in autoimmune diseases.

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Patzelt et al., 2018; Shi et al., 2008; van Keimpema et al., 2014; Wang et al., 2014). Specifically, in macrophages, Foxp1 is involved in macrophage function, including cytokine production, phagocytosis and respiratory burst (Shi et al., 2008). Whether Foxp1 also functions in DCs remains undetermined. Our results showed that Foxp1 expression was increased during the maturation of DCs which share a common precursor with macrophages (Goudot et al., 2017; Menezes et al., 2016; Tang-Huau et al., 2018). Therefore, we hypothesized that Foxp1 may also contribute to the differentiation and development of DCs.

Here, we investigated the role of Foxp1 in the maturation and function of DCs and the underlying mechanisms. Our results showed that Foxp1 regulated the functions of DCs by the regulation of costimulatory molecules (CD80, CD86) and cytokines. Antigen-specific immune tolerance was induced by DCs with Foxp1 silencing *in vivo*. Our study demonstrated the clinical potential of Foxp1 in the treatment of some immune-related diseases.

2. Results

2.1. Foxp1 expression increases with the maturation of dendritic cells, and Ad-simFoxp1 can significantly inhibit Foxp1 expression without inducing apoptosis

To investigate the differential expression of Foxp1 in DC differentiation and activation, we first detected the expression of Foxp1 protein in DCs by Western blotting. The expression of Foxp1 protein in immature DCs cultured *in vitro* for three day 3 was extremely low but gradually increased with the maturation of DCs (Fig. 1A, B). And Foxp1 expression was increased in LPS-induced DC maturation with prolonged stimulation time. These results indicate that the expression level of Foxp1 is related to the maturation status of DCs, suggesting that Foxp1 may contribute to regulate the development and function of DCs.

To explore the effect of Foxp1 on the function of DCs, we first infected DCs with interfering adenoviruses targeting Foxp1 (Ad-simFoxp1). And Ad-simFoxp1 significantly inhibited the expression of Foxp1 in DCs with increased MOI of adenoviruses (Fig. 1C). To determine whether interfering adenoviruses may induce DC apoptosis, we observed the morphological changes and apoptosis of cells infected with Ad-simFoxp1. However, morphological changes in Adenovirus infected DCs showed more dendrites (Supplementary Fig. 1). This indicated the maturation of DCs post adenovirus infection, which was consistent with previous reports (Miller et al., 2002; Morelli et al., 2000). And interfering adenoviruses did not promote apoptosis of DCs (Fig. 1D), indicating that the regulation of DC function by Ad-simFoxp1 in subsequent studies was not caused by the apoptosis induced by the adenovirus.

2.2. Silencing Foxp1 inhibits the expression of costimulatory molecules and the secretion of cytokines by dendritic cells and enhances the phagocytic ability of dendritic cells

With the differentiation and maturation of DCs, their antigen capture function is gradually reduced, while the MHC class II molecule on the cell membrane is upregulated, and the expression of costimulatory molecules is increased. Since Foxp1 expression is lower in immature DCs and is gradually increased after maturation after LPS activation we speculated that Foxp1 may be involved in the regulation of the functions during DC maturation. The expression of the costimulatory molecules CD80, CD86 and CD40 in DCs with Foxp1 silencing was significantly decreased, but MHC class II molecules had no significant changes (Fig. 2A).

During DC maturation, the ability of uptaking and processing antigens is diminished, while the ability of presenting antigens is enhanced in response to exogenous antigen (Hammer and Ma, 2013). To investigate the phagocytosis of exogenous antigen by DCs, FITC-labeled OVA was used as a foreign antigen. We infected immature DCs with interfering adenovirus on the 5th day and took the uninfected DCs as well as the LPS-stimulated DCs as controls. Each group of DCs was incubated with OVA-FITC for and the mean fluorescence intensity detected by flow cytometry was used to assess the ability of DCs to phagocytose foreign antigens. We found that the phagocytic function was significantly decreased after LPS stimulation, while the phagocytosis of DCs after Foxp1 silencing was enhanced (Fig. 2B). These data indicated that Foxp1 regulated the phagocytic function of DCs.

Cytokine secretion by DCs is also important for their function (Hedl et al., 2014). Thus, we detected the secretion of major cytokines, including IL-12p70, IL-6, IL-1β and TNF-α, in DCs after Foxp1 silencing. As shown in Fig. 2C–F, the cytokines of DCs after Foxp1 silencing were significantly reduced, suggesting that Ad-simFoxp1 may inhibit the function of DCs by the inhibition of cytokine secretion. Another Ad-siFoxp1 sequence also showed the same effect of Foxp1 knockdown, including reduced expression of costimulatory molecules (Supplementary Fig. 2A) and inflammatory cytokines production (Supplementary Fig. 2B-D). Further avoiding the off target of siRNA, we overexpressed Foxp1 in DCs and tested their function post LPS stimulation. As shown in Supplementary Fig. 3, Foxp1 promoted co-stimulatory molecules expression and cytokine production. All these data suggested that Foxp1 may be necessary for the optimal activation of DCs.

2.3. Foxp1 silencing suppresses DC-induced T cell proliferation

We further investigate the role of DCs pretreated with Ad-simFoxp1 to the proliferation of allogeneic T lymphocytes by a mixed lymphocyte reaction. The ability to stimulate T cell proliferation of DCs was decreased after silencing Foxp1 expression, indicating that Foxp1 regulated the function of DCs (Fig. 3A).

Since silencing Foxp1 in DCs showed a decrease in the secretion of various cytokines, we speculated that the antigen presentation function of DCs will also be affected. We cocultured of DCs with OVA-specific T lymphocytes at a ratio of 1:10 for 5 days and detected T cell proliferation of DCs after silencing Foxp1. This partial result showed that the ability of DCs that interfere with Foxp1 expression to stimulate antigen-specific T lymphocyte proliferation was significantly reduced, indicating that DCs that block Foxp1 expression negatively regulated immune responses (Fig. 3B).

2.4. In vivo administration of DCs pretreated with Ad-simFoxp1 can delay the onset and attenuate EAE progression

Experimental autoimmune encephalomyelitis (EAE) is an inflammatory and demyelinating autoimmune disease that occurs in the central nervous system and is often used as an animal model of human multiple sclerosis (MS) (Blankenhorn et al., 2011). $CD4^+$ T cells and their specific cytokines play an important role in the onset and progression of EAE. According to the methods reported in the literature, the EAE model of C57BL/6 mice was successfully established by using the $MOG_{35–55}$ polypeptide as an antigen supplemented with peritoneal injection of the pertussis toxin.

We found that the adoptive transfer of Ad-ctrl-DCs/MOG group showed weakness in the tail, and some mice developed hind limb paralysis on the 9th day after EAE induction. In contrast, the progress of Ad-simFoxp1-DCs/MOG group developed much later on the 12th day after EAE induction, compared with the control group. And the clinical neurological score of Ad-simFoxp1-DCs/MOG group was significantly improved. On day 30, the mean clinical score for the Ad-ctrl-DCs/MOG group was up to 4 points, while the Ad-simFoxp1-DCs/MOG group was < 3 points (Fig. 4). This result indicates that *in vivo* administration of DCs interfering with Foxp1 expression can significantly delay the subsequent onset of EAE and markedly improve the clinical symptoms. Thus, targeting Foxp1 in DCs may represent a therapeutic strategy to treat autoimmune encephalomyelitis by suppressing neuroinflammation.

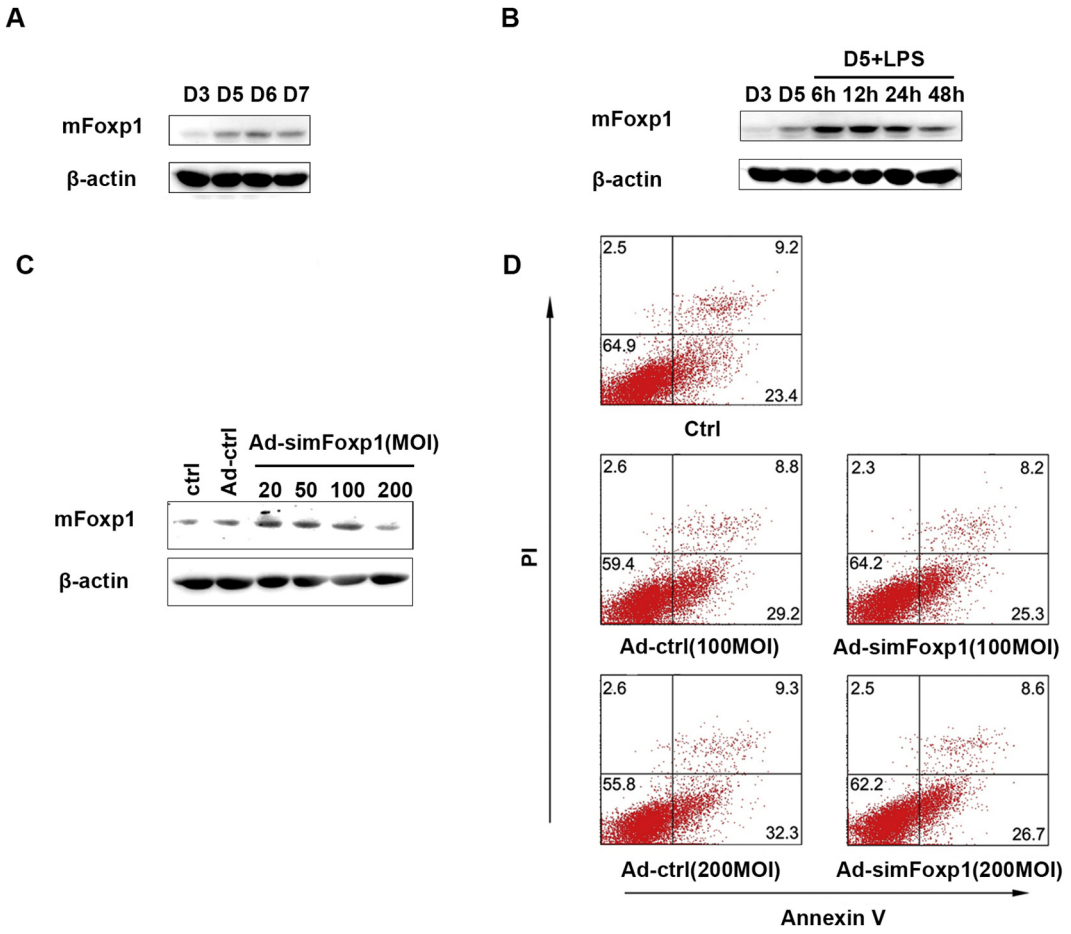

Fig. 1. The expression of mFoxp1 in BMDCs and the apoptosis of BMDCs treated with Ad-simFoxp1.
A: BMDCs (3×10^5/ml) from WT mice were induced by GM-CSF plus IL-4 for indicated time. The expression of mFoxp1 protein was determined by Western blot. B: BMDCs on day 5 (3×10^5/ml) were stimulated with 100 ng/ml LPS for different time. The expression of mFoxp1 protein was determined by Western blot. C: BMDCs on day 5 (1×10^6/ml) were pretreated with different MOIs of Ad-simFoxp1 or Ad-ctrl (MOI 200) for 24 h. The expression of mFoxp1 protein was determined by Western blot. D: BMDCs (1×10^6/ml) transfected with Ad-mFoxp1, Ad-ctrl or not were cultured for 24 h, stained with Annexin-V Alexa Fluro 647 and PI, and then analyzed by FACS LSR II. One representative result of three independent experiments was shown.

3. Discussion

Due to the important role in the initiation and regulation of immune responses, scientists have deeply investigated the function of DCs using various methods, including the application of RNA silencing (Wang et al., 2011; Yang et al., 2015; Zheng et al., 2010). The transcription factors, such as c-rel, NF-κBp65, NF-κBp50 and rel−B, play an important role in the differentiation and development of DCs. However, key transcription factors during the differentiation and development of DCs have not been fully identified yet. As the forkhead family is important in the development of immune cells, we suspect that the members of the family may participate in DC differentiation and development.

The forkhead family is characterized as a class of transcription factors with a wing-like helical structure in the DNA-binding domain. They can not only regulate gene transcription by recruiting coactivators but also directly participate in their remodeling by combining condensed chromatin and cooperating with other transcription factors to participate in transcriptional regulation (Cabrera-Ortega et al., 2017; Chokas et al., 2010; Geissmann et al., 2010). In recent years, several new Fox genes have been identified, but the function of a considerable number of members is still unclear. Since DCs share common precursors with macrophages (Geissmann et al., 2010), we speculated that the transcription factor Foxp1 may also have effects on DCs.

To explore this issue, we initially examined the expression of Foxp1 protein during the differentiation and maturation of murine bone marrow-derived DCs and found that the expression of the Foxp1 protein was gradually increased in DCs. How does the transcription factor regulate the function of DCs? We next silenced the expression of Foxp1 in DCs by recombinant interfering adenovirus and detected the functional changes of DCs. The results show that interfering with Foxp1 expression can inhibit the function of DCs independent of promoting apoptosis. Thus, can Foxp1 affect the phenotype, phagocytosis, and the cytokine secretion of DCs? We found that after blocking Foxp1, DCs had significantly decreased expression of CD80, CD86, and CD40 but not the MHC class II molecule. This indicated that Foxp1 silencing inhibited the expression of costimulatory molecules of DCs. An important feature of DCs after foreign antigen stimulation is to uptake and process antigens, with the increased ability to present antigens. The results showed that blocking Foxp1 enhanced the phagocytosis of DCs, so the phagocytosis of immature DCs is likely to be related to the low expression of Foxp1; however, the mechanism by which Foxp1 inhibits the phagocytosis of DCs remains to be further explored. In view of decreased costimulatory molecules and enhanced phagocytosis of DCs after Foxp1 silencing, we speculated that the secretion of cytokines by DCs treated with adenovirus also showed some changes. The results showed that the secretion of cytokines by DCs, such as IL-10, IL-6, IL-1β, TNF-α and IL-12p70, was widely inhibited after blocking Foxp1 expression. It is well known that IL-10 is an important immunosuppressive factor and that TNF-α is an important pro-inflammatory cytokine. Therefore, the

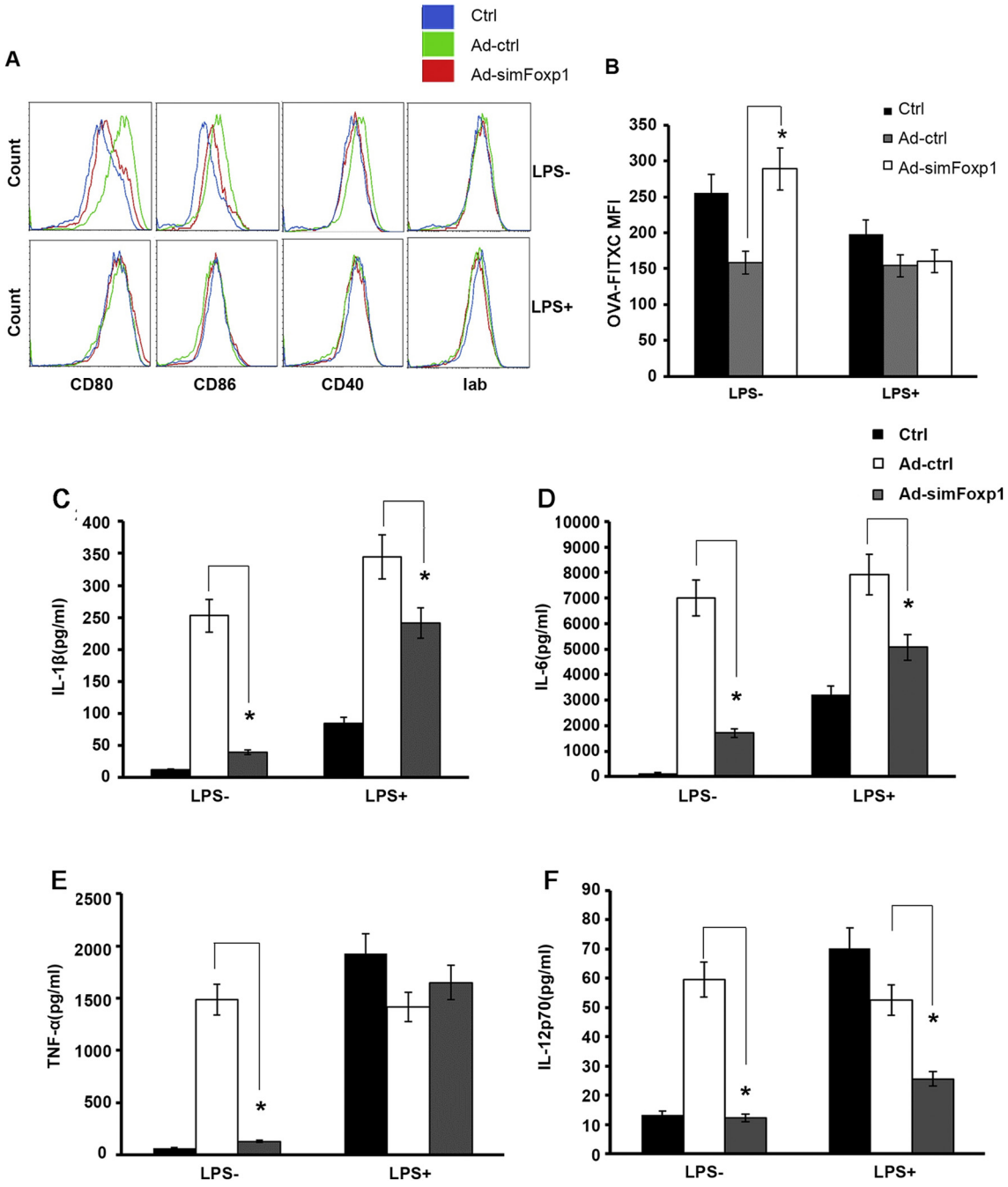

Fig. 2. The expression of co-stimulatory molecules, cytokines and the phagocytic ability of BMDCs treated with Ad-simFoxp1.
A: BMDCs transfected with Ad-mFoxp1or Ad-ctrl or not for 24 h were stimulated with or without LPS for another 24 h, then the cells were stained with FITC-conjugated Iab mAb, PE-conjugated CD40 mAb, PE-conjugated CD80 mAb, FITC-conjugated CD86 mAb, and analyzed by FACS LSR II. B: BMDCs pretreated with Ad-simFoxp1, Ad-ctrl or not were stimulated with or without LPS (100 ng/ml) for 24 h, incubated with OVA-FITC, and then measured by flow cytometry. One representative result of three independent experiments was shown. C-F:BMDCs were pretreated with Ad-simFoxp1, Ad-ctrl or not for 24 h, and then stimulated with or without LPS (100 ng/ml) for an additional 24 h. IL-1β, IL-6, TNF-α and IL-12p70 in the supernatants were detected using ELISA. Data shown as mean ± s.d. of three determinants. Representative results were shown from three independent experiments. $^{*}p < 0.05$.

mechanism of the decrease of DC cytokine secretion after blocking Foxp1 expression may be through extensive inhibition of cytokine secretion, including inhibitory factors and activating factors. Since DCs exhibit the characteristics of certain immature DCs after blocking Foxp1 expression, we hypothesized that the ability of DCs that interfere with Foxp1 expression to stimulate T cell proliferation may be reduced. This assumption was verified by the mixed lymphocyte reaction and antigen-specific T cell proliferation response.

Experimental autoimmune encephalomyelitis (EAE) is the most commonly used experimental model for human inflammatory demyelinating disease, multiple sclerosis (MS). Innate immunity and acquired immunity play an important role in the process of the disease (Kirschbaum et al., 2016; Nylander and Hafler, 2012). We used the EAE model to explore the effect of DCs with Foxp1 silencing on the pathogenesis of EAE mice. We utilized an adoptive transfer of DCs with Foxp1 silencing to the peritoneal cavity of mice before EAE induction. The results showed that DCs with Foxp1 silencing greatly delayed the subsequent onset of EAE induction and significantly improved clinical

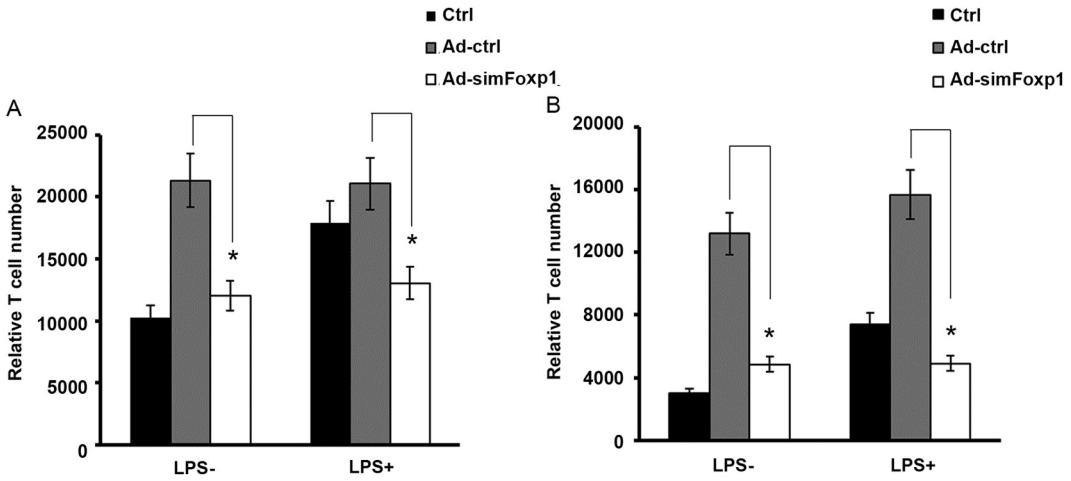

Fig. 3. The T cell responses by BMDCs treated with Ad-simFoxp1 in response to LPS.
A, B: BMDCs transfected with Ad-simFoxp1, Ad-ctrl or not were stimulated with or without LPS for 24 h, then incubated with allogenous splenic $CD4^+$ T cells(A) or $OVA_{323–339}$-specific $CD4^+$ T cells(B) at a ratio of 1:10 for 5 days, and the total number of live $CD4^+$ T cells was measured by flow cytometry. Data shown as mean ± s.d. of three determinants. Representative results were shown from three independent experiments. *$p < 0.05$.

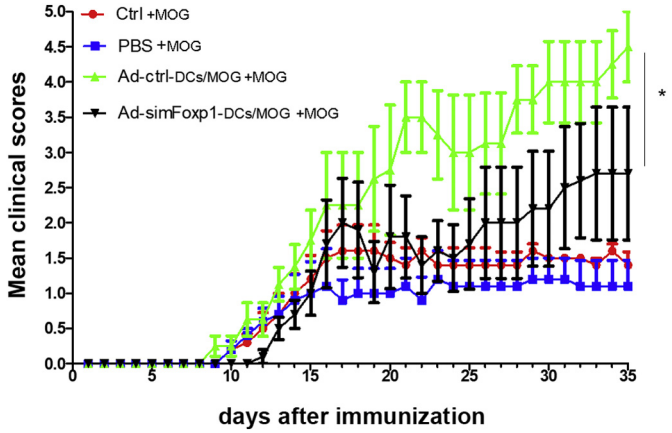

Fig. 4. The effects of Ad-simFoxp1 treated BMDCs on the development of EAE. BMDCs pretreated with Ad-simFoxp1 for 24 h were pulsed with $MOG_{35–55}$ peptide (45 μg/ml) for additional 6 h. The resulting cells (2×10^6/mice) were injected peritoneally into mice. 24 h later, mice were challenged to EAE induction and the disease development was observed and the clinical scores were recorded in each group of mice daily. One representative result of three independent experiments was shown.*$p < 0.05$.

symptoms. Therefore, adoptive transfection of Ad-simFoxp1 in DCs may be a potential treatment strategy against autoimmune diseases.

4. Materials and methods

4.1. Mice, cell lines and reagents

C57BL/6J (H-2b), BALB/C (H-2d) mice at 6–8 week of age were purchased from Joint Ventures Sipper BK Experimental Animal (Shanghai, China) and maintained in a pathogen-free environment. OT-2 mice were obtained from Jackson Laboratory (Bar Harbor, ME). All animal experiments were undertaken in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, with the approval of the Scientific Investigation Board of Second Military Medical University (Shanghai, China). Unless stated otherwise, cell lines were obtained from the American Type Culture Collection (Manassas, VA) and maintained in RPMI 1640 medium or DMEM (PAA Lab) supplemented with 2 mM glutamine, penicillin (100 U/mL), streptomycin (100 μg/mL), and 10% (vol/vol) heat-inactivated fetal calf serum (FCS; Hyclone, Logan, UT) in a 37 °C 5% CO_2 atmosphere. MOG35-55 peptides were synthesized and purified by the Chinese Peptide Biotechnology; peptide purity was over 95%. Pertussis toxin from Bordetella pertussis (PTX) was purchased from Sigma.

4.2. Culture of BMDCs

BMDCs from mice were generated as described previously (Carrera Silva et al., 2013; Lobo et al., 2015). Briefly, bone marrow progenitors were cultured in 10 ng/ml GM-CSF and 1 ng/ml IL-4 (PeproTech, London, U.K). Non-adherent cells were gently washed out on the second day of culture; the remaining loosely adherent clusters were cultured for additional 3–4 days and immature DCs were positively selected using CD11c magnetic microbeads (Miltenyi Biotec). In some experiments, immature DCs were stimulated with 100 ng/ml LPS.

4.3. Preparation of recombinant interfering adenovirus and transfection of DCs with recombinant adenovirus

Recombinant adenoviral vectors carrying Foxp1-siRNA, GFP or LacZ were constructed using pAdeasy1 system according to the manufactures' instruction (Stratagene Biotechnologies). The base sequences of siRNA were GGCCCTCTGTCCTTAGTGA, and GAGCTTACCTCATAC TCCA for Ad-siFoxp1 and Ad-siFoxp1 #2. These recombinant adenoviruses were amplified in HEK 293 cells, purified by CsC1 gradient centrifugation, dialyzed and stored at −80 °C until use. The titers of Ad-simFoxp1, Ad-GFP and Ad-LacZ (Ad-Ctrl) were 200MOI.

Immature DCs at 8×10^5/ml were transfected with recombinant Ads at indicated MOIs for 24 h. After extensively washing with PBS, cells were cultured for another 24 h with 5% FBP in RPMI1640. Using Ad-ctrl as a control adenovirus, Ad-GFP was used to determine the infection efficiency, and the number of GFP-positive cells was observed under a fluorescence microscope, thereby determining the optimal MOI value.

4.4. Western blot assay

The cells were lysed in cell lysis buffer (Cell Signaling Technology) supplemented with protease inhibitor mixture (Calbiochem, San Diego, CA) for 20 min on ice. Equal amounts of extracts were loaded on each lane of 10% SDS-PAGE, electrophoresed, and transferred to nitrocellulose membrane (Schleicher & Schuell BioScience). Membrane was blocked in 1× TBST with 5% nonfat milk for 2 h and hybridized

with primary antibodies at 1/1000 overnight at 4 °C. The membrane was incubated with HRP-conjugated secondary antibodies for 1 h at room temperature. SuperSignal West Femto Maximum Sensitivity substrate (Pierce) was used for the chemiluminescent detection. Anti-mouse Foxp1 antibody was purchased from Cell Signaling Technology. Antibodies specific to mouse Foxp1, and their respective horseradish peroxidase–coupled secondary antibodies were purchased from Cell Signaling Technology.

4.5. Detection of DC apoptosis

DCs collected from each group were added in Alexa Fluro 647-labeled Annexin V, and incubated at room temperature protected from light for 15 min. After incubation, DCs were added in 400 μl of buffer containing calcium ions and 10 μl of PI (20 μg/ml) immediately for flow detection. PI^{+}-Annexin-V^{+} cells were regarded as dead cells or late apoptotic cells, and Annexin-V^{+} in PI^{-}cells was early apoptotic cells, and the proportion of each cell was calculated.

4.6. Flow cytometry

DCs were stained with fluorescence-conjugated anti-I-A^{b}, -CD80, -CD86, -CD40 (all from eBioscience) respectively after blocking with 30% rat serum. The stained cells were analyzed with FlowJo software.

4.7. ELISA assays

IL-1β, IL-6, IL-12p70 and TNF-α (R&D Systems) were detected according to the manufacturers' instructions.

4.8. Detection of phagocytic for DCs

DCs were incubated with OVA-FITC (100 μl/ml) at 37 °C for 4 h. The cells were incubated with OVA-FITC for 4 h at 4 °C as a negative control. After washing with PBS, OVA-FITC pulsed DCs were detected by Flow cytometer and the average intensity of FITC fluorescence is used to indicate the amount of DCs phagocytizing OVA, thereby reflecting the ability of DCs to phagocytose exogenous antigens.

4.9. Allogeneic mixed lymphocyte reaction

DCs were incubated with CD4 + cells from Balb/c mice's spleen at a ratio of 1:10 in round–bottomed 96-well plates for 4–5 days. Anti-CD4-FITC and PI were added in each sample at 4 °C for 15 min and then acquired (BD Bioscience). The number of CD4 + PI-cells were calculated to reflect the degree of proliferation of T cells.

4.10. Assay for DC-triggered antigen-specific T-cell response

DCs were incubated with $OVA_{323–339}$-specific splenic CD4 + T cells from DO11.10 × C57BL/6J F1 mice at a ratio of 1:10 in round-bottomed 96-well plates for 5 days. All cultures were performed in triplicate. Anti-CD4-FITC and PI were added in each sample at 4 °C for 15 min and then acquired (BD Bioscience). The number of CD4 + PI-cells were calculated to reflect the ability of DCs to stimulate antigen-specific T cell proliferation.

4.11. Construction and evaluation of EAE model

The $MOG_{35–55}$ polypeptide was dissolved in PBS to a final concentration of 3 mg/ml, and thoroughly mixed with an equal amount of complete Freund's adjuvant (CFA) containing 10 mg/ml BCG, completely emulsified to a water-in-oil state. An antigen emulsion that induces EAE is prepared. The normal control group was only injected with physiological saline. Each group of mice was injected subcutaneously with the corresponding antigen emulsion in the back and tail roots, and each mouse was injected at a dose of 200 μl (about 300 μg $MOG_{35–55}$ polypeptide). The day of immunization was recorded as day 0, and each mouse of each group were intraperitoneally injected with pertussis toxin (PTX) 400 ng on day 0 and day 2.

4.12. Neurological function clinical score

On the day of immunization, the mice were observed daily for food intake and body changes, and neurological function scores were performed. We use the internationally accepted clinical 5-point scale: 0 points: asymptomatic; 1 point: tail weakness; 2 points: one side of lower limb paralysis; 3 points: both sides of lower limb paralysis; 4 points: both sides of lower limb paralysis with forelimb paralysis; 5 points: sudden death or death after onset.

4.13. Statistical analysis

Statistical analysis was performed using unpaired Student's *t*-test, and $p < 0.05$ was considered of statistical significance.

Declaration of Competing Interest

The authors declare no financial or commercial conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mod.2019.05.001.

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