

The effect of mesenchymal stem cells on dynamic changes of T cell subsets in experimental autoimmune uveoretinitis

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Introduction

Autoimmune uveitis is one of the major causes of visual loss worldwide. A wide range of systemic and ocular complications associated with long-term usage of corticosteroids and immunosuppressive medications has pushed the development of new therapies to decrease the burden of these traditional immunosuppressive agents on patients with refractive uveitis. Biologics, also known as cytokine inhibitors, targeting specific mediators of the immune-inflammatory system potentially offer a safer profile and faster response than traditional immunosuppressive agents [1]. However, as human uveitis is highly heterogeneous, with a wide spectrum of disorders, targeting one specific mediator [such as tumour necrosis factor (TNF) or interleukin (IL)-1] does not necessarily apply to all cases. In addition, it is still difficult to make an evidence-based decision for which agent is best for a given clinical entity. Hence, the development of specific and effective therapeutic approaches is important and urgent.

Summary

Mesenchymal stem cells (MSCs) are being explored extensively as a promising treatment for autoimmune diseases. We have recently reported that MSCs could ameliorate experimental autoimmune uveoretinitis (EAU) in rats. In this study, we examined further the effects of MSCs on the dynamics of T cell subsets in both eye and spleen and their cytokine production during the course of EAU. We focused on when and where the MSCs had inhibitory effects on T helper type 1 (Th1) and Th17 cells and how long the inhibitory effect lasted, in order to provide more mechanistic evidence for MSCs on the treatment of uveitis. Compared to the control group, administration of MSCs decreased the production of Th1 and Th17 cytokines significantly, while the production of Th2 and regulatory T cell (T_{reg}) cytokines [interleukin (IL)-10 and transforming growth factor (TGF)- β] was elevated during the entire course of EAU. Correspondingly, the dynamic levels of IL-17 in the aqueous humour (AqH) were reduced in MSC-treated rats. Moreover, the ratio of Th17/T_{reg} cells in both spleen and eye was decreased. These results provide powerful evidence that MSCs can regulate negatively both Th1 and Th17 responses and restore the balance of Th17/T_{reg} in the whole course of EAU, which is important for the regression of the disease.

Keywords: experimental autoimmune uveoretinitis, mesenchymal stem cells, Th1, Th17, T_{reg}

Mesenchymal stem cells (MSCs) are the current focus of research for their potential therapeutic usage in the clinic. As well as features such as the capacities of multilineage differentiation and prompting tissue repair, anti-inflammatory and neurotrophic effect, ease of isolation and expansion and poor immunogenicity [2], MSCs can exert profound immunosuppression by inhibiting proliferation and functions of a number of cell types including T lymphocytes, natural killer (NK) cells and dendritic cells (DCs), and up-regulating regulatory T cells (T_{reg}) cells [3,4]. The mechanisms underlying these effects are largely unknown, but are likely to be mediated by soluble factors [4,5]. These immunosuppressive properties have been exploited extensively in a number of experimental autoimmune diseases and translated recently to the clinical setting in several diseases, such as systemic lupus erythematosus (SLE) [6], Crohn's disease [7], multiple sclerosis (MS) [8], rheumatoid arthritis [9] and Sjögren's syndrome [10]. In autoimmune diseases, MSCs can inhibit both T helper type 1 (Th1) and Th17 responses and modulate the Th17/T_{reg} balance

[11,12]. Contrary to corticosteroid and immunosuppressive agents, no tissue toxicity of MSCs has been found so far, and MSCs could even enhance the ability of the host immune cells on bacterial clearance [13]. Together with their neurotrophic effect in nervous system [14], MSCs could therefore be an ideal approach for treating uveitis.

We reported recently that MSCs could ameliorate experimental autoimmune uveoretinitis (EAU) in rats [15]. The therapeutic role of MSCs on EAU might be due to the inhibition of both Th1 and Th17 responses and an up-regulation of Th2 response and T_{reg}s. Similar results have also been demonstrated in the mouse model of uveitis, in which MSCs inhibited EAU by inducing antigen-specific T_{reg} [16]. In this study, we examined further the effects of MSCs on the dynamics of T cell subsets in both eye and spleen and their cytokine production during the course of EAU, focusing on when and where the inhibitory effects of MSCs develop on Th1 and Th17 cells and how long the effects last, in order to provide more mechanistic evidence for MSCs on the treatment of uveitis.

Materials and methods

Animals

Male Lewis and Wistar rats (6–8 weeks old), purchased from Vital River (Beijing, China), were housed under pathogen-free conditions. All procedures involving rats were approved by the Laboratory Animal Care and Use Committee of the Tianjin Medical University and adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Reagents

Interphotoreceptor retinoid-binding protein (IRBP) peptide 1169-1191(R16) was synthesized by Sangon (Shanghai, China). Complete Freund's adjuvant (CFA) was purchased from Sigma (St Louis, MO, USA). *Mycobacterium tuberculosis* strain H37RA was obtained from Difco (Detroit, MI, USA). Enzyme-linked immunosorbent assay (ELISA) kits of IL-2, IL-4, IL-6, IL-10, IL-17A, interferon (IFN)- γ and TGF- β were obtained from Xinbo Sheng (Shenzhen, China) and antibodies used for flow cytometry from eBioscience (San Diego, CA, USA).

Isolation and characterization of MSCs

Bone marrow MSCs were isolated from Wistar rats, as described previously [15]. Briefly, the tibiae and femurs were removed aseptically from Wistar rats, and the bone marrow (BM) was flushed and suspended in phosphate-buffered saline (PBS). MSCs were isolated using a Percoll gradient ($d = 1.073$ g/ml; Sigma) and incubated in low-glucose Dulbecco's modified Eagle's medium (L-DMEM)

(HyClone, Logan UT, USA) containing 10% fetal bovine serum (FBS) (HyClone), 100 U/ml penicillin and 100 μ g/ml streptomycin at 37°C in 5% CO₂ for at least 24 h. Non-adherent cells were discarded and the remaining adherent cells were then incubated for 10–14 days in L-DMEM with 10% FBS until they reached approximately 80% confluence. MSCs from passages three to five were used in the subsequent experiments.

Mature MSCs were defined by their capacity, when cultured under appropriate *in-vitro* conditions, to differentiate into adipocytes, endothelial cells and osteocytes. Further characterization was based on the expression of CD90 and CD73 and the lack of haematopoietic markers CD45 and CD34 on their surfaces, as described previously [17].

Induction of EAU and treatment protocols

Lewis rats were immunized subcutaneously in one rear footpad with 200 μ l emulsion containing 30 μ g R16 and 500 μ g *M. tuberculosis* H37Ra in CFA. To investigate both preventive and therapeutic effects of MSCs on EAU, the immunized rats were treated intravenously with 5×10^6 MSCs for 3 consecutive days starting either on day 0 (preventive group) or day 12 (therapeutic group) post-R16 immunization. Control groups received an equal volume of PBS. Each group comprised 10 rats.

Clinical and histological assessment of EAU

The immunized rats were examined daily for clinical signs of uveitis by slit-lamp biomicroscope starting on day 4 post-immunization. The incidence and severity of EAU were scored in a masked fashion on a scale of 0–4, according to the criteria reported by Caspi's group [18]. For histology, animals were killed on days 6, 9, 12, 15 and 20 in the preventive group and on days 15 and 20 in the therapeutic group. Eyes were collected and immersed for 1 h in 4% glutaraldehyde/PBS and transferred into 10% glutaraldehyde/PBS for 24 h until further processing. Fixed and dehydrated tissues were embedded in paraffin wax and 4 μ m sections were stained with standard haematoxylin and eosin. The presence of disease was evaluated in a double-blinded fashion by examining four sections at different levels in each eye. Severity of EAU was scored on a scale of 0–4, according to Caspi's criteria [18].

Cytokine production

Mononuclear cells (MNCs) enriched from the spleens and lymph nodes of either healthy or EAU-induced rats by Ficoll gradient (Roche, Mannheim, Germany) were cultured at a density of 2×10^5 cells/well with 30 μ g/ml of R16 peptide in a final volume of 200 μ l RPMI-1640 medium containing 2 mM glutamine, 100 U/ml penicillin, 100 μ g/ml streptomycin and 10% FBS (GIBCO, Carlsbad,

CA, USA). After 72 h incubation at 37°C in 5% CO₂, supernatants were collected for cytokine detection. Cytokine levels of IL-2, IL-4, IL-6, IL-10, IL-17, TGF-β and IFN-γ were detected by ELISA kits according to the manufacturer's instructions.

Flow cytometry analysis

MNCs from spleens and lymph nodes were prepared and stimulated as described above, and then incubated with 50 ng/ml phorbol myristate acetate (PMA) (Sigma), 1 μg/ml ionomycin (Sigma) and 10 μg/ml monensin (Sigma) for an additional 5 h. Aliquots of 1 × 10⁶ cells were two-colour-stained with combinations of phycoerythrin cyanin 5 (PECy5)-conjugated anti-CD4 monoclonal antibody (mAb) and PE-conjugated anti-IL-17 mAb and three-colour-stained with combinations of PECy5-, PE- or fluorescein isothiocyanate (FITC)-conjugated mAbs against rat CD4, CD25 and forkhead box protein 3 (FoxP3). The cells were first incubated for 30 min at room temperature (RT) with anti-CD4, anti-CD25 or isotype control antibodies, fixed overnight at 4°C with 1 ml FoxP3 staining buffer set (Fix and Perm Cell Permeabilization Kit; eBioscience, San Diego, CA, USA). The cells were then incubated for 30 min at RT with anti-rat IL-17 or FoxP3, fixed with 2% paraformaldehyde and analysed by flow cytometer (FACS-Calibur; BD Biosciences). The ratios of CD4⁺IL-17⁺ (Th17) cells/CD4⁺T cells and CD4⁺CD25⁺FoxP3⁺ (T_{reg}) cells/CD4⁺T cells were calculated in each group.

Aqueous humour collection

Aqueous humour (AqH) was collected from both eyes by an anterior chamber puncture using a 30-gauge needle under a surgical microscope on the days indicated above and stored immediately in a -80°C freezer until use. The concentrations of IL-17 and IFN-γ in the AqH were measured by ELISA.

Isolation of eye-infiltrating cells

Uveitic eyes were collected from five rats per group after PBS perfusion [19]. External tissues were trimmed, and the eyes were dissected carefully along the limbus for lens removal. The remaining tissue was transferred into six-well plates containing 3 ml RPMI-1640, 10% FCS, collagenase D (1 mg/ml) and DNase (100 μg/ml), minced with scissors and incubated for 10 min in 37°C. Cell suspension was passed through the cotton column, dispersed by pipetting several times, resuspended in staining buffer (PBS containing 3% FCS and 0.1% sodium azide) and stained with fluorescent mAb to identify inflammatory cells by flow cytometry.

Statistical analysis

Data were expressed as mean ± standard deviation (s.d.). SAS version 9.2 software was used for statistical analysis. EAU clinical scores and histopathological scores were assessed by repeated-measures analysis of variance (ANOVA) using mixed models. Data were tested using the Kolmogorov–Smirnov test for normal distribution and the Levene test for homogeneity of variance. Concentrations of cytokines released from T cells in the mice with or without MSC treatment were evaluated by a two-factorial design analysis of quantitative variance. The correlation analysis of cytokine expression and histopathological scores were analysed by Spearman's rank correlation test. A value of $P < 0.05$ was considered significant.

Result

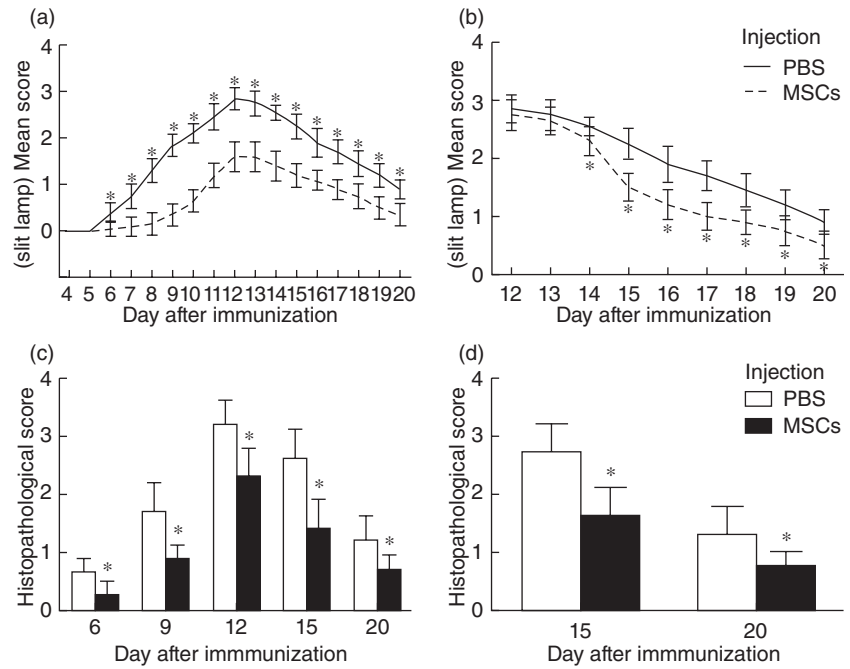
MSCs ameliorate EAU

MSCs have been proven effective in treatment of autoimmune diseases. To determine whether MSCs had an effect on R16-induced uveitis, R16-immunized Lewis rats received three consecutive i.v. injections of MSC (5 × 10⁶/injection) starting on the same day (Fig. 1a) of R16 immunization (day 0), while control rats received PBS. The results showed that, although all control animals developed full disease, MSC-treated rats developed mild disease with a delayed onset, and the differences between MSC-treated and vehicle-treated conditions were statistically significant from day 6 (Fig. 1a). It was then determined whether or not delayed injection of MSCs had a similar protective effect. As shown in Fig. 1b, three i.v. injections starting on day 12 (i.e. at disease peak) also had a significant effect on EAU development, indicating that MSC treatment not only prevents EAU, but also suppresses EAU when given at the peak of the disease. Histological results confirmed further the efficacy of MSC on EAU. Eyes collected at the indicated days after R16 immunization revealed that MSC-treated eyes displayed less inflammation and tissue damage than those of PBS-treated eyes (Fig. 1c,d).

Dynamic effects of MSCs on cytokine expression of Th1/Th17/Th2/T_{reg} cells

To identify the role of MSCs on R16-specific T cell subsets, we collected kinetically the splenic cells from both MSC- and PBS-treated rats, stimulated them with immunized R16 peptides and measured the cytokines in their culture supernatants. In the control group, the expression levels of Th1 and Th17 cytokines such as IL-2, IFN-γ, IL-6 and IL-17 began to increase on day 6, reached a peak on day 12 and decreased gradually on days 15 and 20. The dynamic change of these cytokines presented the same trend as the EAU

Fig. 1. Effects of mesenchymal stem cells (MSCs) on the clinical development and histological changes of autoimmune uveoretinitis (EAU). In the group treated simultaneously with immunization the rats developed mild disease with a delayed onset, and the differences between MSC-treated and vehicle-treated conditions were statistically significant from day 6 (a). The group treated on day 12 after immunization also showed significant improvement, which started from day 14 (b). Histological examinations revealed that MSC-treated eyes displayed less inflammation and tissue damage than those of phosphate-buffered saline (PBS)-treated (control) eyes at all time-points (Fig. 1c,d).



course. Histopathological scores of EAU had a strong positive correlation with Th1 and Th17 cytokine levels, especially with levels of IL-2 ($r=0.837$, $P<0.05$), IFN- γ ($r=0.839$, $P<0.05$), IL-6 ($r=0.736$, $P<0.05$) and IL-17 ($r=0.906$, $P<0.05$) (Fig. 2). Moreover, the expression levels of Th2 and T_{reg} cytokines (IL-4, IL-10 and TGF- β) were at a higher level on day 6, decreased at the peak of disease and then increased again when inflammation started to resolve on days 15 and 20. The dynamic change of these cytokines presented the opposite trend with EAU course. Histopathological scores of EAU had a strong negative correlation with Th2 and T_{reg} cytokine levels, especially with levels of IL-4 ($r=-0.965$, $P<0.05$), IL-10 ($r=-0.878$, $P<0.05$) and TGF- β ($r=-0.893$, $P<0.05$) (Fig. 2).

In contrast, MSCs treatment showed immunosuppressive potential with regard to Th1 and Th17 cytokine secretion. In the group treated simultaneously with R16-immunization, MSCs reduced significantly the production of IL-2, IFN- γ , IL-6 and IL-17 compared to the control group at all time-points ($P<0.05$) (Fig. 2). In the group treated on day 12 post-immunization, MSCs reduced significantly the cytokine production released by R16-specific Th1 and Th17 cells when the cells were collected on days 15 and 20 post-immunization ($P<0.05$) (Fig. 3). Conversely, MSC treatment increased Th2 and T_{reg} cytokines. In the group treated simultaneously with R16 immunization, MSCs elevated significantly the production of IL-4, IL-10 and TGF- β at all time-points ($P<0.05$) (Fig. 2). In the group treated on day 12 (disease peak), MSCs elevated significantly the production of IL-4, IL-10 and TGF- β on days 15 and 20 post-immunization ($P<0.05$) (Fig. 3).

Reduced IL-17 and IFN- γ and elevated IL-10 levels were detected in the AqH of MSC-treated EAU

To determine whether MSC's effects on R16-specific T cell subsets in the periphery were reflected in the inflamed eye, we measured kinetically the cytokine released by Th1/Th17/T_{reg} in the AqH. As seen in Fig. 4, in the control group the production of IFN- γ and IL-17 in AqH increased from day 6 and reached a peak on day 12, then decreased gradually on days 15 and 20 post-immunization. The levels of IFN- γ and IL-17 were correlated with histopathological scores ($r=0.872$, $r=0.903$; $P<0.05$) (Fig. 4a,b). In contrast, the levels of IFN- γ and IL-17 in the AqH of the MSC-treated group either on the same day or 12 days after R16 immunization were significantly lower than those in the AqH collected from the non-treated (control) group (Fig. 4a,b,d,e). Conversely, IL-10 in AqH was high at the early stage of EAU, but decreased when EAU reached a peak and then increased again when the disease started to resolve. Thus, the level of IL-10 in the AqH was correlated negatively with histopathological scores ($r=-0.765$, $P<0.05$) (Fig. 4c). However, in the groups when MSCs were given at either days 0 or 12 post-immunization, the level of IL-10 in AqH was high in comparison to the control group at all time-points ($P<0.05$) (Fig. 4c,f). Hence, the data suggest that the cytokine profile in the eye is similar to that observed in splenic R16-specific T cells.

MSCs inhibited Th17, but up-regulated T_{reg} cells in EAU

Further, we examined the ratio of Th17/T_{reg} in the groups with and without MSC treatment, because the cytokines in

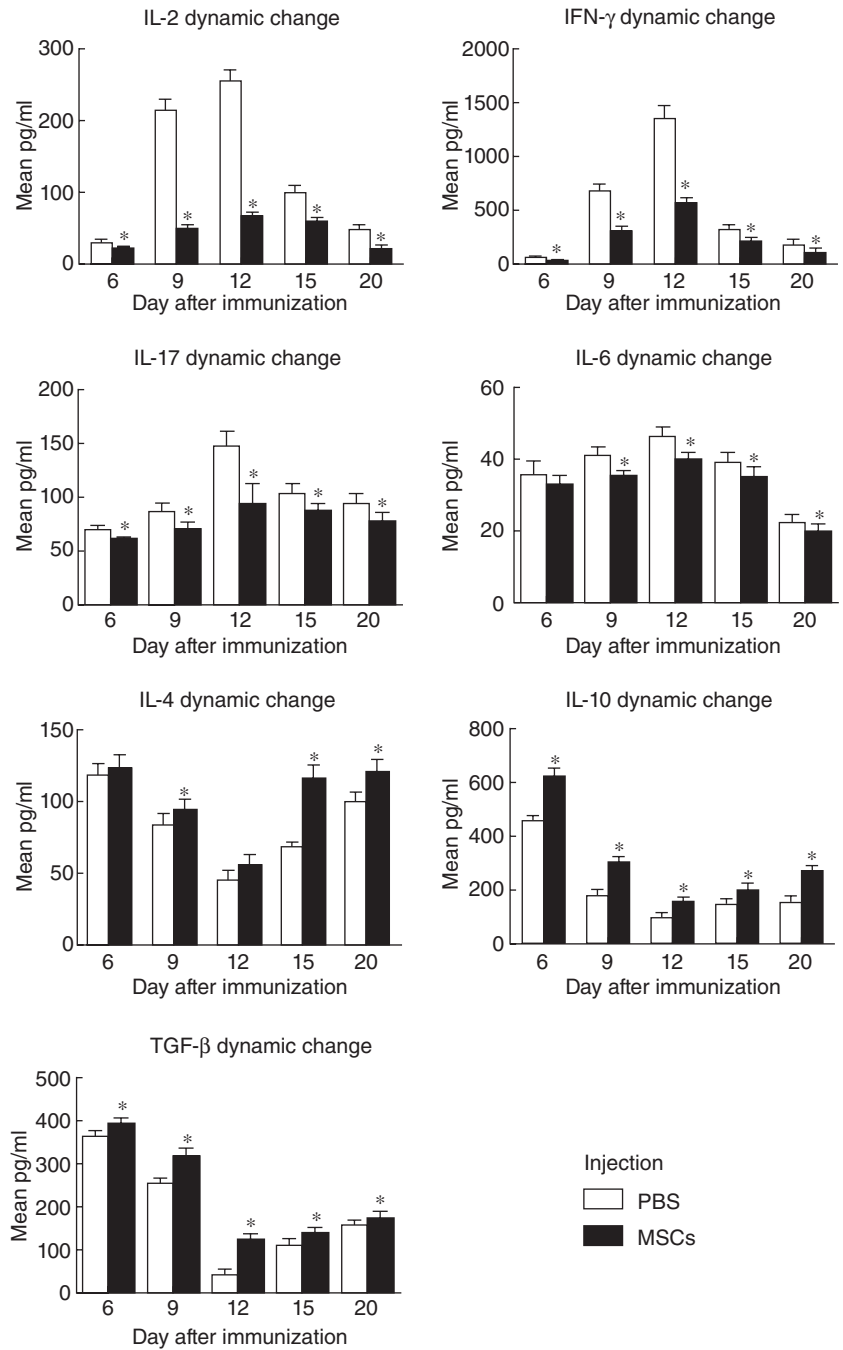


Fig. 2. Dynamic effects of mesenchymal stem cells (MSCs) on cytokine expression in the group treated simultaneously with immunization. In the control group, the expression levels of T helper type 1 (Th1) and Th17 cytokines [interleukin (IL)-2, interferon (IFN)- γ , IL-6 and IL-17] began to increase on day 6, reached a peak on day 12 and decreased gradually on days 15 and 20; the expression levels of Th2 and regulatory T cell (T_{reg}) cytokines [IL-4, IL-10 and transforming growth factor (TGF)- β] were at a higher level on day 6, decreased at the peak of disease and then increased again when inflammation started to resolve on days 15 and 20. MSCs reduced significantly the productions of IL-2, IFN- γ , IL-6 and IL-17 compared to the control group at all time-points ($P < 0.05$).

the environment may direct the conversion of T cell subsets. As shown in Fig 4, the trends of Th17 and T_{reg} cell numbers from the spleen and eye in both groups are parallel with those of Th17 and T_{reg} cytokines. In the control group, Th17 cells from spleen ($r = 0.897$, $P < 0.05$, Fig. 5a) and eye ($r = 0.933$, $P < 0.05$, Fig. 5c) presented the same trend as the EAU course and were correlated positively with the histopathological scores of EAU. By contrast, MSCs, when given at either days 0 or 12 post-immunization, decreased significantly the number of Th17

cells in both spleen and eye compared with the control group at all time-points ($P < 0.05$) (Fig. 5a–d). Conversely, T_{reg} numbers in the spleen ($r = -0.449$, $P < 0.05$, Fig. 5e) and the eye ($r = -0.449$, $P < 0.05$, Fig. 5g) showed the opposite trend to the EAU course and were correlated negatively with the histopathological scores of EAU. MSC treatment either at days 0 or 12 after immunization increased significantly the number of T_{regs} in both spleen and eye when compared to the control group at all time-points ($P < 0.05$) (Fig. 5e–h).

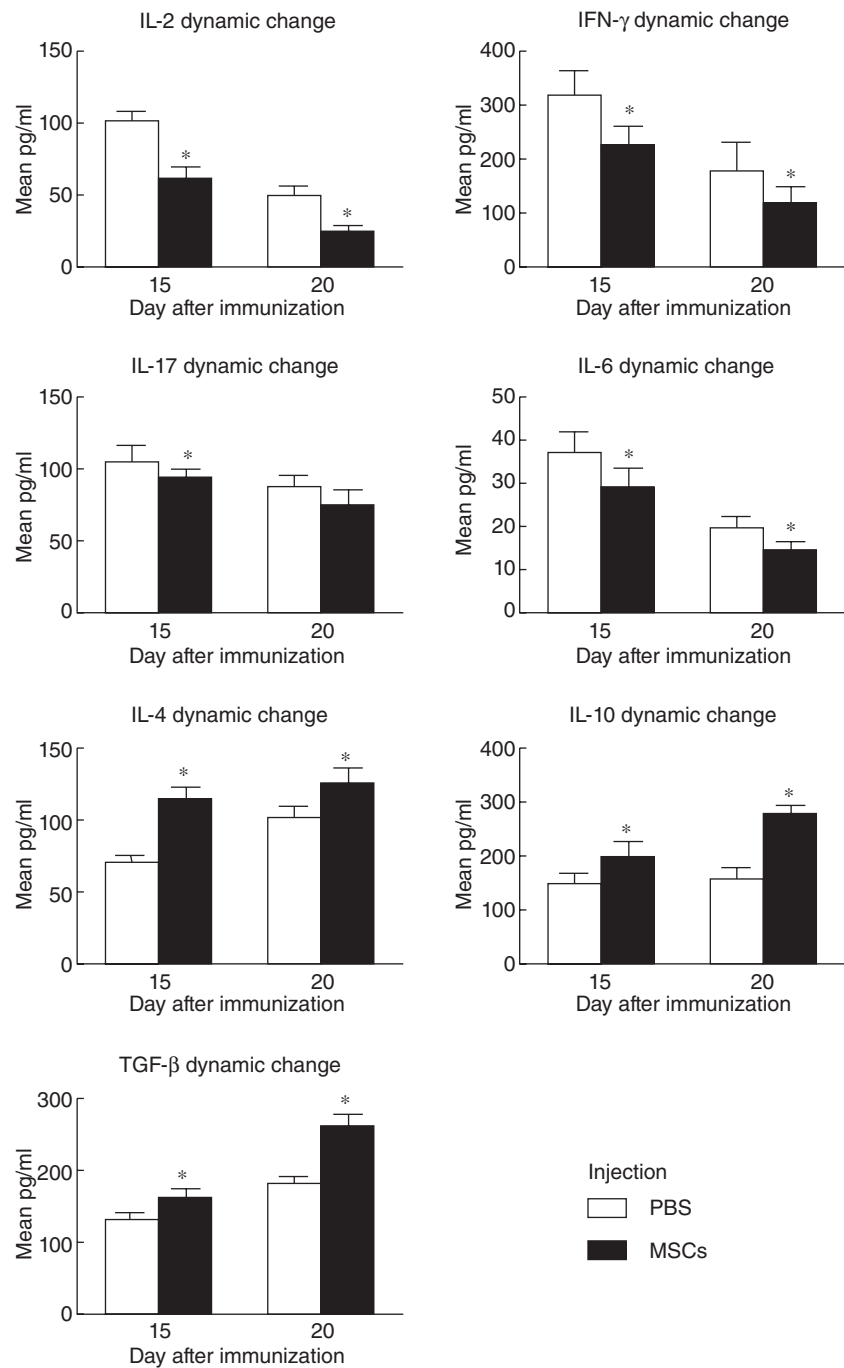


Fig. 3. Dynamic effects of mesenchymal stem cells (MSCs) on cytokine expression in the delay-treated group. Therapeutic administration of MSCs at the peak of the disease also reduced significantly the cytokine production released by R16-specific T helper type 1 (Th1) and Th17 cells ($P < 0.05$), while the production of Th2 and regulatory T cell (T_{reg}) cytokines was elevated on days 15 and 20 post-immunization ($P < 0.05$).

Discussion

Early studies have implicated Th1 cells as the aetiological agent of EAU; however, subsequent studies on human uveitis and its animal models have revealed that the Th17 cell lineage (IL-17-producing $CD4^+$ effector lineage) is another main contributor to autoimmune diseases [20–22]. Th1 and Th17 subsets have the capacity to cause autoimmune disease independent of each other. However, cytokines produced by these two subsets can be paradoxical and counter-regulated, as well as co-operated, depending on

when and where the cytokines are produced [23–25]. Therefore, therapies targeting one subset specifically may prove potentially therapeutic for patients suffering from autoimmune uveitis, but might cause simultaneously an exacerbation of the other, leaving disease progression unaffected or even worsened.

In our study, the dynamic changes of R16-specific Th1 cytokines, such as IL-2 and IFN- γ , and Th17 cytokines, including IL-17A and IL-6, from EAU-inducing rats presented the same trend as the EAU course, and had a strong positive correlation with histopathological scores. Both

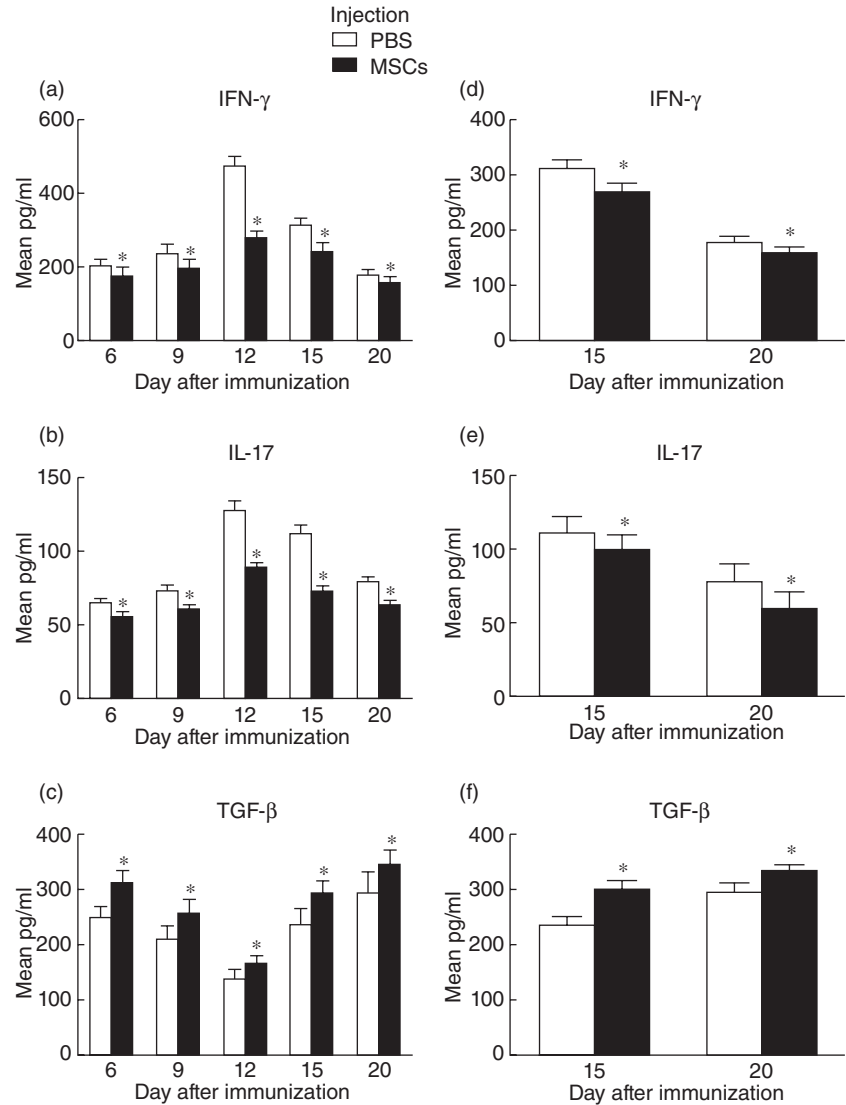


Fig. 4. Cytokine release in the aqueous humour (AqH). In the control group, the production of interferon (IFN)- γ and interleukin (IL)-17 in AqH increased from day 6 and reached a peak on day 12, then decreased gradually on days 15 and 20 post-immunization, and both preventive and therapeutic administration of mesenchymal stem cells (MSCs) decreased the levels of IFN- γ and IL-17 in the AqH at all time-points (a,b,d,e). IL-10 in AqH was high at the early stage of autoimmune uveoretinitis (EAU), but decreased when EAU reached a peak and then increased again when the disease started to resolve, and both preventive and therapeutic administration of MSCs elevated the level of IL-10 in AqH at all time-points ($P < 0.05$) (c,f).

preventive and therapeutic administration of MSCs decreased significantly the production of these Th1 and Th17 cytokines compared to the control group at all time-points. The levels of IFN- γ and IL-17 in the AqH were also lowered significantly by MSC therapy. These results suggest that MSCs regulate negatively both Th1 and Th17 responses simultaneously in the whole course of EAU, avoiding the potentially adverse effect of targeting one subset specifically.

CD4⁺CD25⁺ T_{regs} are powerful inhibitors that contribute to recovery from autoimmune uveitis [26,27], and decreased frequency and diminished function of T_{regs} are associated with active uveitis [28]. In addition, it is believed that Th2 cells, as counter-regulatory to Th1, would be protective although they also have the ability to induce uveitis under special conditions [25]. T_{regs} can produce abundant anti-inflammatory cytokines (IL-10 and TGF- β), while IL-4 and IL-10 are the main cytokines produced by Th2 cells. We found that the dynamic change of the production of IL-4, IL-10 and TGF- β from T cells isolated from EAU-inducing

rats presented the opposite trend to EAU course, and had a strong negative correlation with histopathological scores. Both preventive and therapeutic administration of MSCs elevated significantly the production of these Th2 and T_{reg} cytokines compared to the control group at all time-points. The kinetic levels of IL-10 in the AqH were also significantly higher in the group treated with MSCs. These results suggested that MSC treatment could up-regulate the levels of cytokines released by Th2 cells and T_{regs} during the whole course of EAU, thereby decreasing the severity of EAU in rats.

Th17 cells and T_{regs} have a common induced pathway [29–31] and a disturbed Th17/T_{reg} balance has been found in several autoimmune diseases [32–34]. TGF- β and IL-6 are the most important cytokines that can orchestrate the differentiation of T_{regs} and Th17 cells in a concentration-dependent manner. High concentrations of TGF- β favour the development of FoxP3⁺ T_{regs}, while in low TGF- β concentrations IL-6 suppresses FoxP3 expression, and the

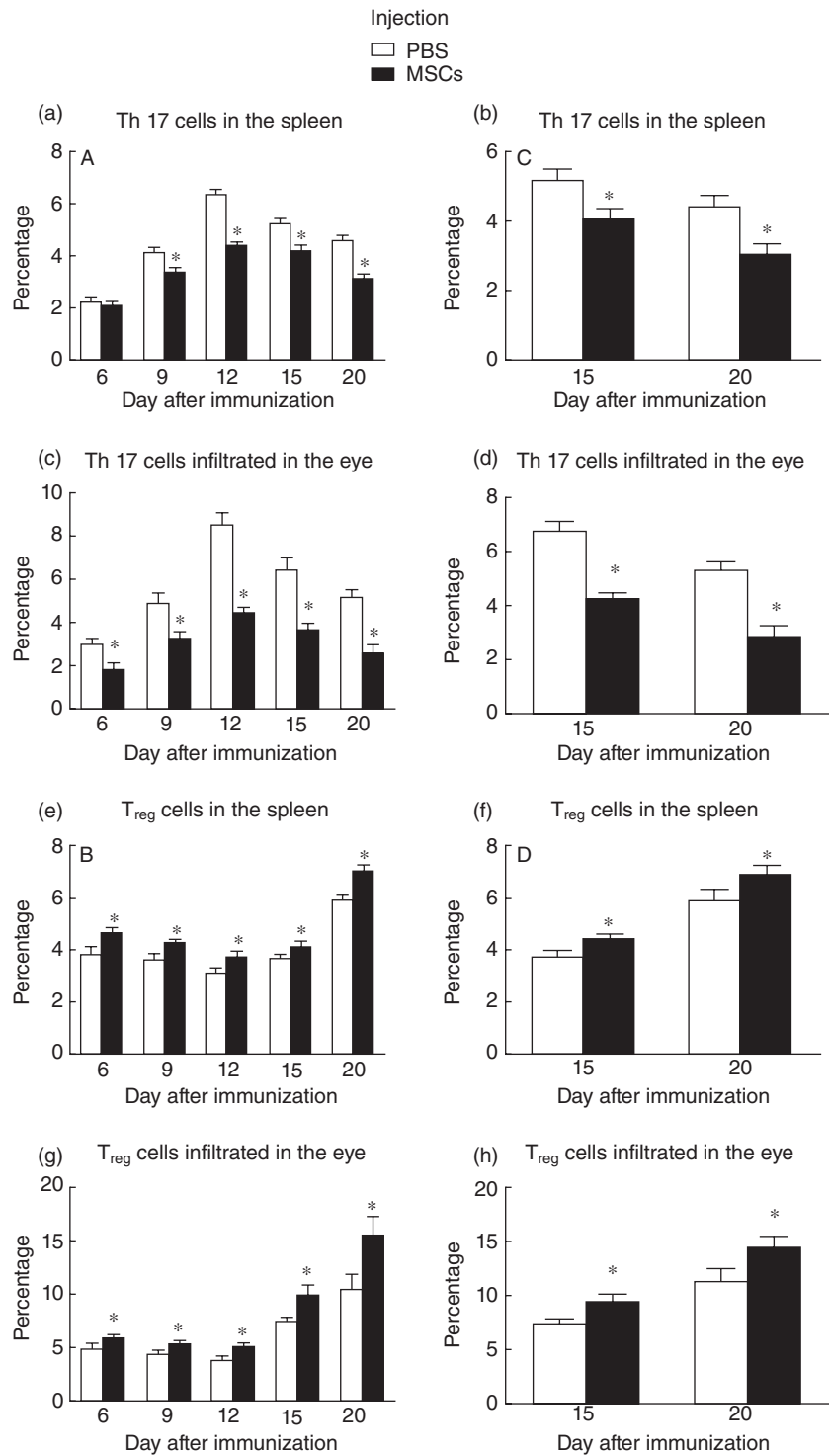


Fig. 5. Dynamic effects of mesenchymal stem cells (MSCs) on T helper type 17 (Th17) and regulatory T cell (T_{reg}) cells from spleen and eye. In the control group, Th17 cells from spleen and eye presented the same trend as the autoimmune uveoretinitis (EAU) course ($P < 0.05$, a–d), while T_{regs} in the spleen and the eye presented the opposite trend to the EAU course ($P < 0.05$, e–h). By contrast, MSCs, when given at either days 0 or 12 post-immunization, decreased significantly the number of Th17 cells and increased the number of T_{regs} in both spleen and eye compared with the control group at all time-points ($P < 0.05$).

development of Th17 cells prevails [29–31]. Restoring the balance of Th17 and T_{regs} may represent a new therapy to autoimmune diseases such as uveitis.

In this study, we found that Th17 cells from both the spleen and the eye presented the same trend as the EAU course, and was correlated positively with the histopathological scores of EAU, while T_{regs} presented an opposite

trend. As described above, MSC therapy reduced the production of IL-6, whereas it elevated TGF- β secretion from T cells isolated from EAU-inducing rats. Correspondingly, dynamic levels of IL-17 in both AqH and produced from T cells *in vitro* were decreased by MSC infusion, while IL-10 secretion was prompted. Parallel with the trends of Th17 and T_{reg} cytokines, the number of Th17 cells in both the

spleen and the eye was decreased, while the number of T_{regs} was increased by preventive as well as therapeutic administration of MSCs in comparison to the control group at all time-points. These results provide powerful evidence that MSCs can restore the balance of Th17/T_{regs} in EAU, which is important for the disease regression.

In this study, MSCs were isolated from the BM of the rats. Nevertheless, in the clinical setting, invasiveness of the BM aspiration procedure and the age-dependent degradation in quantity and quality of the BM–MSCs limit their clinical potential. Alternative sources such as MSCs obtained from Wharton's jelly of the umbilical cords have gained much attention during recent years, as they can be isolated easily and without ethical concerns [35]. Wharton's jelly-derived MSCs also represent a more primitive population than their adult counterparts, with an equal or higher degree of self-renewal capacity, multi-differentiation potential and immunomodulatory effect, increasing the feasibility for cell-based therapies.

In conclusion, we have demonstrated that a systemic infusion of MSCs ameliorated autoimmune uveoretinitis effectively by inhibiting Th1 and Th17 responses, up-regulating T_{regs} and modulating the balance of T_{reg}/Th17 cells during the whole course of the disease. These regulatory effects of MSCs occur not only in the systemic lymphoid organs but also in the local target site, suggesting that MSCs is a strong autoimmune inhibitor in both autoreactive T cell priming and effector phases. In addition, retinal damage is the major cause of vision defect in uveitis and MSCs could repair and restore damaged central nervous system tissues and cells [13]. Thus, MSC therapy has the potential to target multiple levels of uveitis pathology, including immunomodulation and photoreceptor cell repair and regeneration, which make it more applicable in the treatment of uveitis.

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Disclosure

The authors have no competing interests.

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