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Interleukin 17 (IL-17)-Induced Mesenchymal Stem Cells Prolong the Survival of Allogeneic Skin Grafts

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Background: Mesenchymal stem cells (MSCs) have the potential of self-renewal and multi-differentiation and have a wide application prospect in organ transplantation for the effect of inducing immune tolerance. It has found that interleukin 17 (IL-17) could enhance the inhibition effect of MSCs on T cell proliferation and increase the immunosuppressive effect of MSCs. In this study, we aimed to investigate the effect of IL-17-induced MSCs on allograft survival time after transplantation.

Material/Methods: BMSCs were characterized by differential staining. The allogenic skin transplantations were performed and the BMSCs pre-treated by IL-17 were injected. To assess the immunosuppressive function of IL-17-induced BMSCs, the morphology of the grafts, the homing ability of the BMSCs, and the survival time of the grafts were analyzed.

Results: BMSCs from BALB/c have multidirectional differentiation potential to differentiate into osteogenic, chondrogenic, and adipogenic lineage cells. IL-17-induced BMSCs prolonged the survival time of allogeneic skin grafts dramatically. We found that there were more labeled MSCs in the skin grafts, and the Treg subpopulations percentage, IL-10, and TGF-β were significantly increased, while the IFN-γ level was decreased compared to the control group and MSCs group. In conclusion, IL-17 can enhance the homing ability of MSCs and regulate the immunosuppressive function of MSC.

Conclusions: Our data demonstrate that IL-17 plays the crucial role in MSC homing behaviors and promotes immunosuppression of MSCs during transplantation procedures, suggesting that IL-17-pre-treated MSCs have potential to prolong graft survival and reduce transplant rejection.

MeSH Keywords: **Interleukin-17 • Mesenchymal Stromal Cells • Skin Transplantation**

Abbreviations: **BMSCs** – bone marrow-derived MSCs; **H&E** – hematoxylin and eosin; **IFN** – interferon; **IL-17** – Interleukin 17; **MSCs** – mesenchymal stem cells; **Treg cells** – regulatory T cells

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Background

Many local and systemic problems after burns are caused by loss of the skin barrier. Reconstruction and restoration of the skin barrier is the final goal in the treatment of burns. Although xenografts or allografts regain skin barrier function temporarily, the strong immune rejection of xenogeneic or allograft skin grafts greatly shortens their survival time [1,2]. Consequently, prolonging graft survival time is a very difficult problem for researchers. To a certain extent, using immunosuppressive drugs could prolong graft survival time, but these drugs bring a series of problems, such as infection and cancer [3]. Moreover, patients with large-area burns often have severe infections, which limits the application of immunosuppressants in suppressing xenograft rejection.

MSCs are a type of pluripotent stem cell [4-6] present in many different tissues such as teeth, bone marrow, skin, muscle, and fat. MSCs not only have the potential of self-renewal and multiple differentiation, but also have strong immunomodulating properties [6,7]. Many animal experiments and preclinical trials showed that MSCs play a very important role in autoimmune diseases and induction of immune tolerance in organ transplantation [8–10]. The MSCs from patients with serious graft-versus-host disease (GVHD) and healthy donors had similar immunophenotype and mesodermal differentiation capacity [11]. Moreover, MSCs can home to the ischemic tissues, tumors, and damaged tissues, and the regulating effect of MSCs is largely dependent on their homing ability and the quantity of homing cells in a specific location [12–14].

Although MSCs can regulate the immune status and decrease immunogenicity, their transplantation rejection effect is limited. Therefore, improving the homing capacity and efficiency of MSCs is the key to achieving excellent effects of transplantation. Many studies have shown that pre-treatment of MSCs with cytokines such as insulin-like growth factor 1 (IGF-1),IL-1β, IL-6, and HGF can improve their migration and homing ability, as well as increase immunosuppressive capacities [15,16].

Interleukin 17 (IL-17) is a key proinflammatory cytokine and is mainly secreted by Th17 cells. IL-17 plays important roles in many physiological processes, such as inducing cell differentiation, promoting secretion of various kinds of cytokines and chemokines, recruiting neutrophils, and immune regulation [17–19]. In inflammation and autoimmune diseases, IL-17 can speed their developmental process, and the IL-17 content in serum and tissues increased significantly. It was previously reported that IL-17 increased the immunosuppressive function of MSCs induced by IFNγ and IFNα [20]. On this basis, to find a potential way to prolong the survival time of allogeneic skin grafts, focus on the therapeutic efficacy of IL-17, and confirm the enhanced immunosuppressive effects of IL-17 pre-treated MSCs, we hypothesized that MSCs pre-treated with IL-17 could prolong allograft survival time, aiming to develop a potent therapeutic method in tissue transplantation.

Material and Methods

Mice and reagents

We purchased 4–8-week-old C57BL/6J and BALB/c mice from the Laboratory Animal Center of Shandong University (Jinan, Shandong) and maintained them under specific pathogen-free (SPF) conditions. Recombinant mouse IL-17, IL-10, and TGF-β were obtained from R&D (Minneapolis, MN) and Cell Tracker™ CM-Dil C7000 was obtained from Life Technologies (Oregon, USA). Mouse IFN-γ secretion was determined by use of an ELISA kit from eBioScience (CA, USA). All animal procedures were approved by the Ethics Review Committee of the Second Hospital of Shandong University.

Cell isolation, culture and identification

Bone marrow (BM) cells were isolated from 4-week-old BALB/c mice by femur, tibia, and humerus flushing. Briefly, the mice were sacrificed by cervical dislocation and the femur, tibia, and humerus were obtained in a sterile manner and washed twice by PBS before exposing the marrow cavity by cutting the ends of the backbone. The bone marrow was washed carefully using a 1-ml syringe with pre-cooled PBS 3–5 times, then the cell suspension was collected. After filtering the cell suspension, the cells were seeded in culture dishes and cultured in DMEM low-glucose medium supplemented with 10% fetal bovine serum (FBS; Gibco) and 1: 100 penicillin and streptomycin in a humidified atmosphere with 5% CO_2 at 37°C.

In vitro differentiation

The differentiation potential of BMSCs was assessed at passages 3–6. Osteogenic, chondrogenic, and adipogenic differentiation were performed using BALB/c Mouse BMSCs Osteogenic, Chondrogenic, and Adipogenic Differentiation Basal Medium, separately (Cyagen, CA, USA) following the instructions. Cells were stained with Alizarin Red S, Alcian Blue, and Oil-Red O, respectively, to confirm cell differentiation potential.

The pre-treatment, labeling, and injection of BMSCs

BMSCs were treated with 50 ng/ml IL-17 for 5 days and then labeled with 5 μg/mL CM-Dil. After labeling, BMSCs were injected into tail veins of C57BL/6J mice. To track the cells, the frozen-section analysis of the grafts was performed at day 7.

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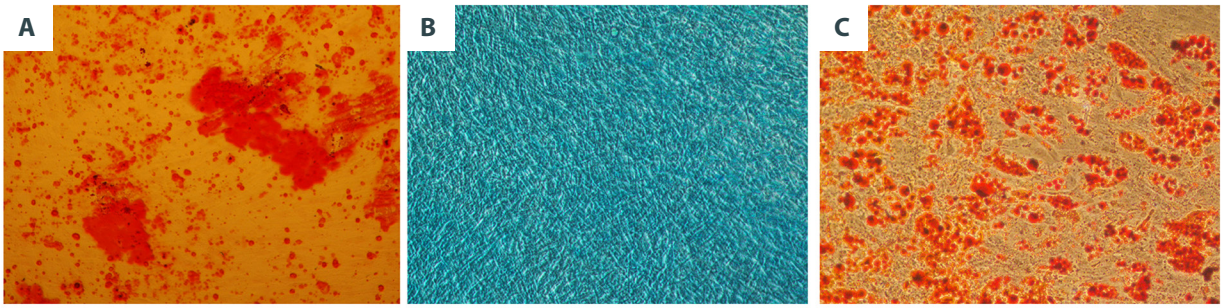

Figure 1. Multipotential differentiation of MSCs. When cultured in the differentiation medium, the bone marrow-derived MSCs differentiated into osteogenic, chondrogenic, and adipogenic lineage cells. (**A**) Cells dyed with Alizarin Red. (**B**) Cells dyed with Alcian Blue. (**C**) Cells dyed with Oil-Red O.

Allogeneic skin graft

The mice were anesthetized using 4% chloral hydrate and cleansed with betadine. Then, a 1.5×1.5 m^2 dorsal full-thickness skin graft was acquired from the donor BALB/c mice while the full-thickness dorsal dermal wounds were created in the recipient C57BL/6J mice. Then, the skin transplant surgery was performed.

Histology

On day 7, the skin graft samples were obtained for histologic analysis. Formaldehyde-fixed samples were sectioned at 4 μm and stained with hematoxylin and eosin (H&E).

Isolation of spleen Treg cells and flow cytometric analysis

The recipient mice were euthanized with an overdose of sodium pentobarbital and the spleens were isolated, washed twice, and ground in a sterile manner to obtain the splenocyte monoplast suspension for further regulatory T cells (Treg cells) population flow cytometry analysis using the Mouse Regulatory T Cell Staining Kit (eBioscience, USA) containing CD4-FITC, CD25-APC, and Foxp3-PE antibodies. Cells were stained with these antibodies and analyzed by flow cytometry on a BD LSR Fortessa flow cytometer, while the untreated splenocytes group was considered as a control group.

ELISA

The venous blood of mice in each group as well as control groups were collected at day 7 after surgery and cytokine measurements were done for TGF-β, IFN-γ, and IL-10 using an ELISA) kit according to the manufacturer's protocol.

Statistical analysis

GraphPad software and SPSS were used for graphs and statistical analysis. Graft survival time results were analyzed using Kaplan-Meier curves. Numerical results are presented as means ±SD and different groups were compared using the one-way ANOVA test.

Results

The bone marrow-derived mesenchymal stem cells have multidirectional differentiation potential

Stem cells are undifferentiated cells or original progenitor cells with slow-cycling and self-renewal capacity. Bone marrow-derived mesenchymal stem cells (BMSCs) are an important type of stem cell [21,22]. BMSCs grow in a whirling manner with spindle shape and have strong self-proliferative and transdifferentiation potential. Under particular external induction conditions, BMSCs can differentiate into adipocytes, osteocytes, chondrocytes, and hepatocytes. BMSCs were cultured in osteogenic differentiation medium, and stained with Alizarin Red. As shown in Figure 1A, the extracellular matrix had a high content of calcium, confirming osteogenic lineage cells formation. When cultured in chondrogenic differentiation medium, BMSCs were dyed with Alcian Blue, as shown in Figure 1B, confirming chondrogenic lineage cells formation. We cultured BMSCs in adipogenic differentiation medium and stained them with Oil-Red O as shown in Figure 1C, confirming adipogenic lineage cells formation.

IL-17-induced MSCs dramatically prolonged the survival time of allogeneic skin grafts

To examine the effect of IL-17-induced MSCs on transplantation, we transplanted them with full-thickness skin graft of BALB/c on C57BL/6J.

As shown in Kaplan-Meier curves (Figure 2A), the survival time of the control group was almost 11.8 days, the survival time of the MSCs group was almost 15.8 days, and the survival time of the IL-17/MSCs group was significantly prolonged to

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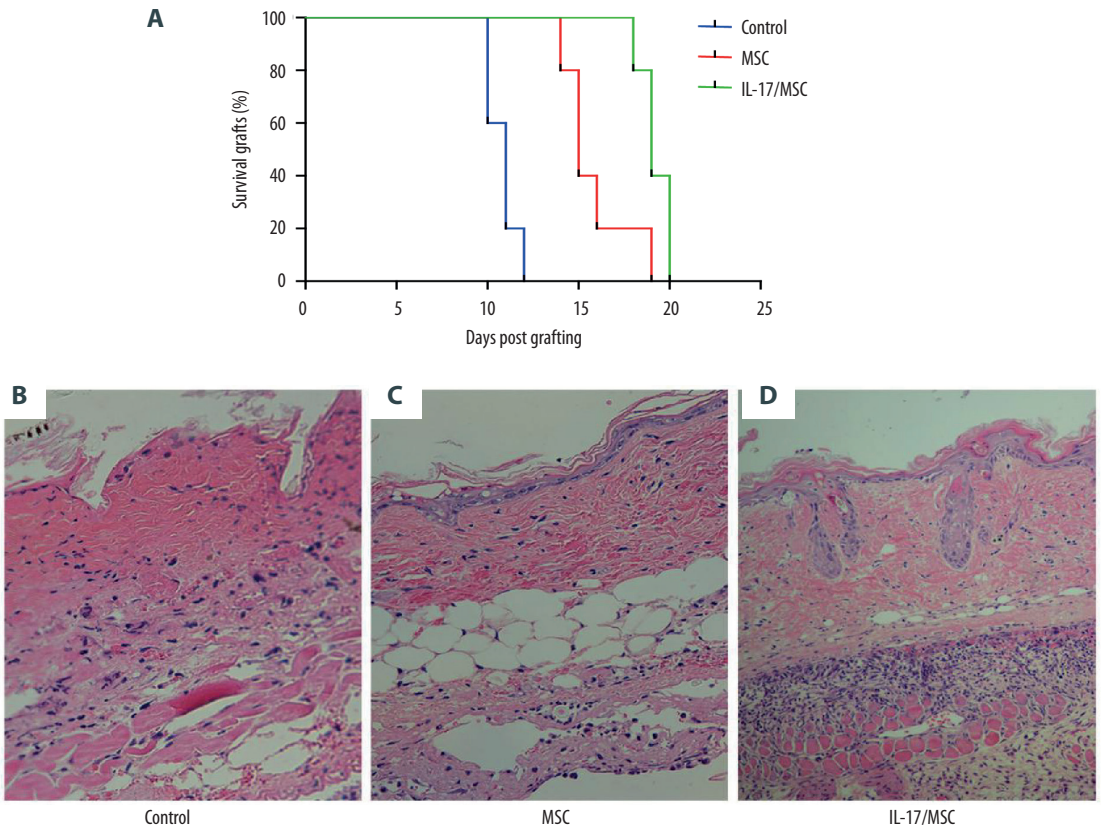

Figure 2. The survival time of allogeneic skin grafts was prolonged by IL-17 induced MSCs. (**A**) Kaplan-Meier survival curves of skin grafts from the different groups. The allografts survival time of control group is much shorter than MSCs group and IL-17/MSCs group (P<0.001). In addition, the allografts survival time is significantly prolonged in IL-17/MSCs group (P<0.01, IL-17/MSCs *vs.* MSCs group). '***' indicated significant difference of P<0.001 *vs.* control group. '##' indicated significant difference of P<0.01 *vs.* MSCs group. (**B–D**) 7 days after transplantation, the morphology of skin grafts by H&E staining, magnification ×40. (**B**) In control group, there is massive inflammatory cellular infiltration, exfoliation and no vascularization. (**C**) In MSCs group, there is some inflammatory cellular infiltration and some vascularization. (**D**) In IL-17/MSCs group, there is little inflammatory cellular infiltration and more vascularization.

19.2 days. The survival time of IL-17/MSCs was much longer than in the control group (P<0.001) and MSCs group (P<0.01). In summary, IL-17-induced MSCs dramatically prolonged the allograft survival times. At 7 days after skin grafting, the grafts in the control group turned black, hard, and necrotizing, but the grafts in the MSCs group and IL-17/MSCs survived in good condition. H&E staining showed that the control group had a large quantity of inflammatory cell infiltrates and exfoliation and no angiopoiesis, as shown in Figure 2B; the MSCs group had little inflammatory cell infiltrate and angiopoiesis, as shown in Figure 2C; the IL-17/MSCs group had little inflammatory cell infiltrate and much more angiopoiesis, as shown in Figure 2D. At 12 days after skin transplantation, almost all the grafts in the control group became hard and necrotic and grafts in the MSCs group became necrotic, but grafts in the IL-17/MSCs group survived in good condition (data no shown).

IL-17 enhanced the homing ability of MSCs

BMSCs are labeled by CM-Dil with almost 100% labeling rate. As the MSCs passed, although the intensity of the fluorescence decreased, the CM-Dil labeling rate kept at 100%. After skin transplantation, mice were injected MSCs or IL-17/MSCs via the tail vein. We took some grafts for frozen-section analysis7 days later. The field of vision was randomly chosen. As shown in Figure 3, after being induced by IL-17, many more MSCs homed to the grafts. In conclusion, the number of BMSCs homing to the implant was increased after IL-17 treatment.

The immunosuppressive function of MSCs was enhanced by IL-17

IL-17 treatment of MSCs prolonged the graft survival times, suggesting that IL-17 enhances the immune suppression of

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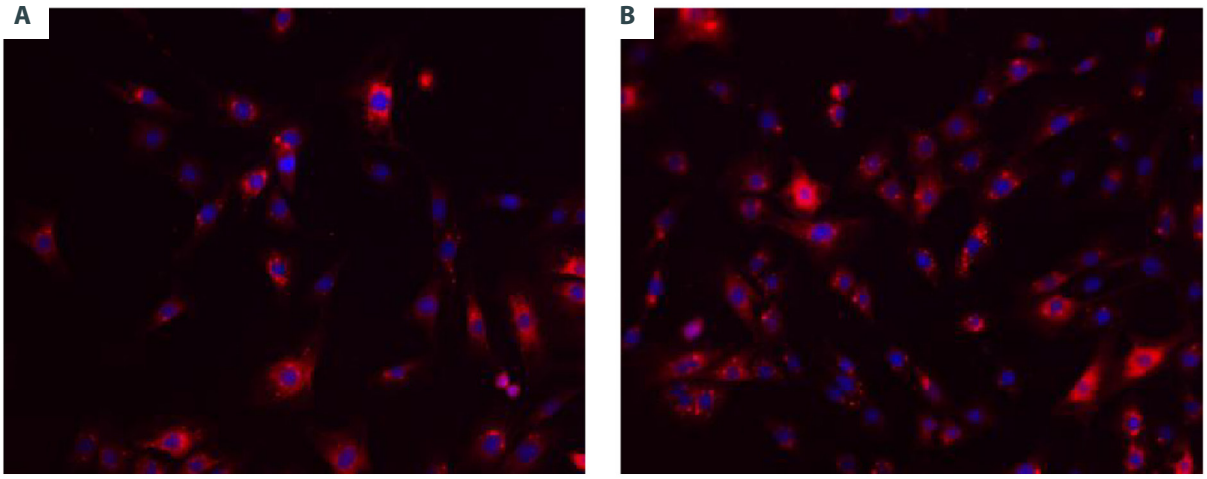

Figure 3. IL-17 treatment can enhance the homing ability of MSCs to skin grafts. The grafts were assessed by frozen-section analysis and the homing CM-Dil-labeled BMSCs are shown. (**A**) MSCs group, (**B**) IL-17/MSCs group. Many more BMSCs were found in the grafts. The homing ability of MSCs was enhanced by IL-17.

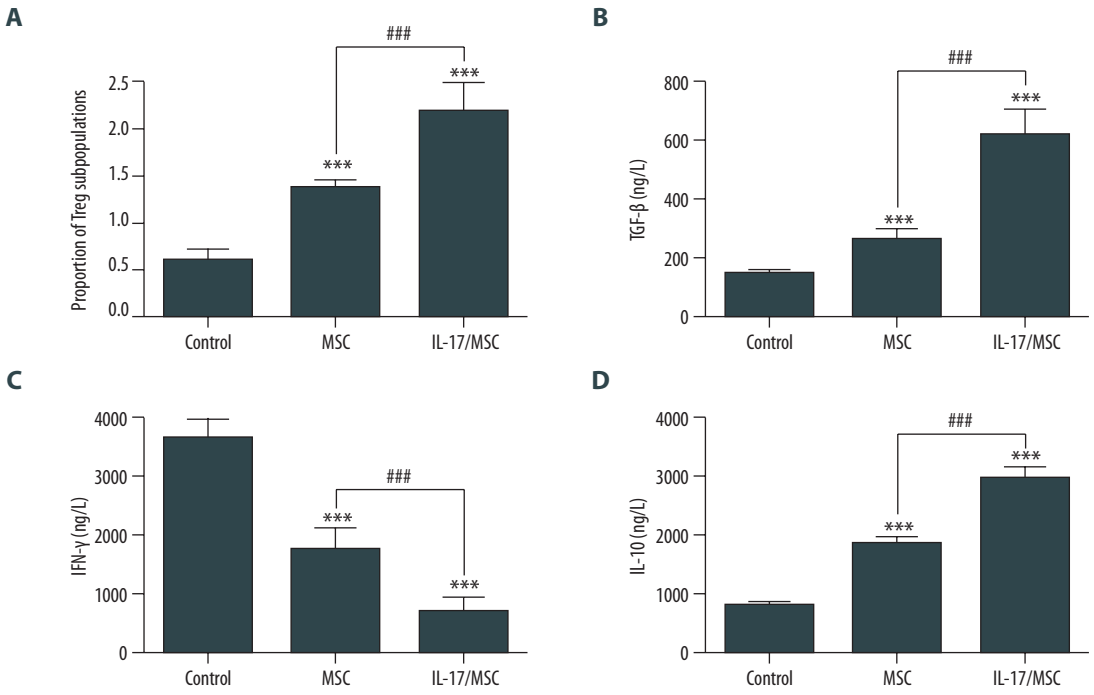

Figure 4. IL-17-induced MSCs exert stronger immunosuppression. (**A**) The proportion of Treg subpopulations were analyzed among different groups. (**B**) The content of TGF-β was measured. (**C**) The content of IFN-γ was analyzed. (**D**) The content of IL-10 was analyzed. '***' indicated significant difference of P<0.001 *vs.* control group. '###' indicated significant difference of P<0.001 *vs.* MSCs group.

MSCs. To verify this hypothesis, we analyzed the percentage of spleen Treg subpopulations among the 3 groups at 7 days after transplantation. The Treg subpopulations percentage in the control group was much lower than in the other 2 groups (P<0.001). Injection of IL-17-induced MSCs increases the Treg subpopulations more than injection of MSCs (P<0.001) (Figure 4A). Furthermore, we examined the anti-inflammatory and proinflammatory cytokines in the serum. TGF-β and IL-10 levels in the control group were much lower than in the other 2 groups (P<0.001). TGF-β and IL-10 levels in the

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IL-17/MSCs group were significantly higher than in the MSCs group (P<0.001) (Figure 4B, 4D). However, IFN-γ levels in the control group were much higher than in the MSCs group and IL-17/MSCs group (P<0.001). IFN-γ levels in the IL-17/MSCs group were much lower than in the MSCs group (P<0.001) (Figure 4C). In summary, our results demonstrated that IL-17 enhances the immune suppression of MSCs.

Discussion

MSCs have the property of multiple differentiations, and in our research, we confirmed that BMSCs could differentiate into osteocytes, chondrocytes, and adipocytes. Although the immunosuppressive effect of MSCs has been widely confirmed, its immunomodulatory mechanism is still not clear. The interactions between MSCs and immunocytes have been thoroughly investigated, and it is thought that the immune inhibition of MSCs typically relies on cellular contact and dissoluble cytokines [23–25]. Many researchers have shown that MSCs make contact with T lymphocytes, B lymphocytes, natural killer (NK) cells, or dendritic cells to exert immunosuppressive effects [26–30]. Remarkably, regulatory T cells (Treg cells) are a kind of T lymphocyte subset with negative immunomodulatory effect. Treg cells play important roles in autoimmune disease, tumor immunity, inflammation response, and transplant rejection [31–33]. Accordingly, Treg cells are one of the most important target cells for immunotherapy. It is reported that MSCs downregulate the interferon (IFN)-γ secretion of Th1 cells and upregulate the IL-4 expression of Th2 cells to alleviate the condition of GVHD [34]. In addition, MSCs can provoke dendritic cells secreting IL-10 to induce immune tolerance [35–38]. TGF-β is regarded as one of the most important soluble immune response suppressors. TGF-β regulates the maturation and activity of dendritic cells [39,40] and TGF-β together with IL-10 inhibit Th1 cells releasing IFN-γ to induce the formation of Th2 cells [41,42]. MSCs inhibit B lymphocyte proliferation only in the presence of IFN-γ [27,43].

IL-17 is one of the most important proinflammatory cytokines and plays important roles in many physiological processes. Despite of their functions in physiological processes such as immune regulation, previous studies have identified that IL-17 is involved in the pathogenesis of pulmonary fibrosis, cancer, and liver injury [44–46]. IL-17 is also a potential therapeutic target of inflammation and autoimmune diseases [47,48]. Moreover, the immunoregulatory effects of IL-17 in tissue transplantation are also worthy of research attention. Examining the modulating effect of IL-17 on the immunosuppressive properties of MSCs is a novel and useful research focus in developing techniques for use of MSCs in graft transplantation. The present study shows that IL-17-induced MSCs significantly prolonged the survival time of transplants in 2 ways: (1) IL-17 increased MSCs homing ability and (2) IL-17 enhanced MSCs immune suppression.

Conclusions

We demonstrated that MSCs pre-treated with IL-17 had prolonged skin graft survival times. However, the detailed molecular mechanism needs to be further explored. Until the mechanism is illuminated, there must be important breakthroughs in use of MSCs in organ transplantation.

Conflicts of interest.

None.

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