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ORIGINAL ARTICLE

Human Embryonic Stem Cells-Derived Mesenchymal Stem Cells Reduce the Symptom of Psoriasis in Imiquimod-Induced Skin Model

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Abstract

BACKGROUND: Mesenchymal stem cells (MSCs) can be used for a wide range of therapeutic applications because of not only their differentiation potential but also their ability to secrete bioactive factors. Recently, several studies have suggested the use of human embryonic stem cell-derived MSCs (hE-MSCs) as an alternative for regenerative cellular therapy due to mass production of MSCs from a single donor.

METHODS: We generated hE-MSCs from embryonic stem cell lines, SNUhES3, and analyzed immune properties of these cells. Also, we evaluated the *in-vivo* therapeutic potential of hE-MSCs in immune-mediated inflammatory skin disease.

RESULTS: The cell showed the suppression of immunity associated with allogenic peripheral blood mononuclear cells in mixed lymphocyte response assay. We also detected that cytokines and growth factor related to the immune response were secreted from these cells. To assessed the *in-vivo* therapeutic potential of hE-MSCs in immune-mediated inflammatory skin disease, we used imiquimod (IMQ)-induced skin psoriasis mouse model. The score of clinical skin was significantly reduced in the hE-MSCs treated group compared with control IMQ group. In histological analysis, the IMQ-induced epidermal thickness was significantly decreased by hE-MSCs treatment. It was correlated with splenomegaly induced by IMQ which was also improved in the hE-MSCs. Moreover, IMQ-induced inflammatory cytokines; Th1 cytokines (TNF-α, IFN-α, IFN-γ,and IL-27) and Th17 cytokines (IL-17A and IL-23), in the serum and skin showed marked inhibition by hE-MSCs.

CONCLUSION: These results suggested that hE-MSCs have a potency of immune modulation in psoriasis, which might be the key factor for the improved psoriasis.

Keywords hE-MSCs · Skin psoriasis · Immune modulation · Psoriasis

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1 Introduction

Human embryonic stem cells-derived mesenchymal stem cells (hE-MSCs) with self-replenishing that are a better alternative than mesenchymal stem cells (MSCs) derived from diverse adult tissue. hE-MSCs are unlimited source of MSC that can overcome the problems of standard MSC preparation and have immunomodulatory and anti-inflammatory properties similar to MSCs of another source. In a previous study, we successfully derived hE-MSCs from human embryonic stem cells (hESCs) using novel method, and demonstrated that our hE-MSCs can be consistently produced, maintained, and expanded [1]. Furthermore, we observed that therapeutic effects of hE-MSCs in infarcted heart, resected sciatic nerves and fibrotic liver [1, 2].

Psoriasis is a hereditary disease of the skin, which affects approximately 2–3% of the world population [3]. Although the pathogenesis of psoriasis is not well understood, recent studies have reported that this disease is induced by dysregulation of epidermal keratinocytes and infiltrating immune cells [4]. This dysregulation results in the induction of pro-inflammatory cytokines that facilitate the development of skin inflammation in psoriasis. T helper 1 (Th1) cytokines, including tumor necrosis factor (TNF)-α and interferon (IFN)-γ, are abundantly found in psoriasis plaques [5]. Moreover, interleukin (IL)-17, IL-23, and IL-27 producing T helper 17 (Th17) cells are detected in the serum, psoriatic skin lesions, and peripheral blood of psoriasis patients and are correlated with the pathogenesis of psoriasis [3, 6]. Thus, Th1 and Th17 immune cells and their pro-inflammatory cytokines are thought to take part in the development of the pathology [7].

In this study, to assessed the *in-vivo* therapeutic potential of hE-MSCs in immune-mediated inflammatory skin disease, we used imiquimod (IMQ)-induced skin psoriasis mouse model. In mice, IMQ-induced inflammation is a dermatitis that closely resembles human psoriasis, critically dependent on the IL23/IL17 axis [7].

Therefore, we sought whether hE-MSCs have the capability to rescue psoriasis using an IMQ mouse model.

2 Materials and methods

2.1 Animals

Eight-week-old, female C57BL/6 mice were purchased from Orient Bio (Seongnam, Korea). The mice were adapted for 1 week before the start of experiments. During the experiment, animals were maintained under specific pathogen-free conditions in the animal facilities at the Dongguk University School of Medicine. The animal care and use committee of the research institute at the Dongguk University Hospital approved all of the studies used in this investigation (IACUC approval No. 201606150).

2.2 Derivation of hE-MSCs

This study was approved by the institutional review board (IRB) of the Seoul National University Hospital (IRB No. H-1410-093-619). hE-MSCs were obtained as previously described [1]. In brief, SNUhES3 cells (Institute of Reproductive Medicine and Population, Medical Research Center, Seoul National University Hospital, Seoul, Korea) were cultured in culture dishes without fibroblast growth factor-2 to establish embryonic bodies (EBs) at 37 °C with 5% CO_2 for 14 days. The EBs were attached to gelatin-coated dishes for 16 days in low-glucose Dulbecco's modified Eagle's medium (DMEM; Invitrogen, Carlsbad, CA, USA) with 10% fetal bovine serum (FBS; Invitrogen, Carlsbad, CA, USA), and the derived cells were expanded in EGM-2MV medium (Lonza, Walkersville, MD, USA). After characterization, the hE-MSCs were used.

2.3 Flow cytometric analysis

For flow cytometric analysis, the cells were first dissociated by incubation at 37 °C for 1 min in 0.25% trypsin/ethylenediaminetetraacetic acid (Invitrogen, Carlsbad, CA, USA), washed with PBS containing 2.5% FBS, and incubated for 30 min with various combinations of saturating amounts of antibodies, conjugated to fluorescein isothiocyanate (FITC) or phycoerythrin (PE): CD45-FITC, CD34-FITC, CD44-PE, CD73-PE, SSEA4-PE, TRA-1-60-PE (BD PharMingen San Diego, CA, USA), isotype-matched control (BD PharMingen San Diego, CA, USA), and CD105-PE (Serotec, Kidlington, Oxford, UK). Flow cytometric analysis was performed. At least 10^4 events were analyzed using the FACSCalibur system (Becton Dickinson, San Jose, CA, USA) with CellQuest Pro software.

2.4 Mixed lymphocyte response assay

To assess T-cell reactivity against allogeneic cell populations, human responder PBMCs (1×10^5/well) were co-cultured with positive stimulator PHA or hE-MSCs (1×10^4/well) in 96-well tissue culture plates. The PBMCs were purchased from AllCells, LLC. The hE-MSCs were inactivated by treatment with 10 μg/mL mitomycin-C (Sigma-Aldrich, St. Louis, MO, USA) for 1 h at 37 °C. T-cell proliferation in response to alloantigens was determined by adding 20 μL acronym of bromodeoxyuridine (BrdU; Roche Applied Science, Basel, Switzerland) after 6 days of mixed lymphocyte response (MLR) culture. The absorbance of the samples was

measured in a UV max kinetic microplate reader (Molecular Devices, Sunnyvale, CA, USA) at 370 nm (reference wavelength, 492 nm). The data of 3 replicates are shown as the mean and standard deviation [5].

2.5 Human secreted protein antibody assay

To analyze secreted proteins from hE-MSC, cells were seeded in 100 mm dish with EGM-2mv media. When cell confluency was reached 70%, new culture media was replaced and incubated for 2 days. At the same time, EGM-2mv media was incubated in 100 mm dish without cell as a control. After incubating, each supernatants were collected and filtered. Proteins in the supernatant were analyzed using the Human Cytokine Array C1000 (RayBiotech, Norcross, GA, USA), according to the protocol provided in the manual. Arrays images were processed with Chemi Doc XRS (BioRad Laboratories, Hercules, CA, USA) and photographed to identify secreted proteins from hE-MSC.

2.6 Animal experiments

IMQ cream (5%) (Aldara^{TM}; 3M Health Care, Loughborough, UK) was used to induce psoriasis-like skin symptoms in mice, as previously described [8]. Briefly, hair on the backs of the C57BL/6 mice was shaved using an electric shaver, after which they were treated with a skin-hair-remover (Niclean, Ildong, Korea). On day 1, all mice, except for the IMQ-untreated control mice, received a consecutive daily topical dose of 62.5 mg IMQ cream on the shaved back skin for 6 days. The control group was treated only with a vehicle cream (Vaseline; Unilever, Rotterdam, Zuid-Holland, Nederland). The mice were then divided into three groups (n = 5/group): control group, IMQ-treated group, and IMQ/hE-MSCs-treated group (2.5×10^6 cells/mouse in 200 µl of PBS). hE-MSCs were administered to mice subcutaneously (s.c.) on days 2 and 4 after initiating the topical application of IMQ. The dorsal skin, spleen and blood serum were collected for analysis on 7 days.

2.7 Scoring the severity of dermatitis

The extent of erythema, scaling, and thickening was scored. Each scores were indicated that 0 is no increase and 1 is slight increase, 2 is moderate increase, and 3 is marked increase. The cumulative dermatitis score (erythema plus scaling plus thickening) was used to indicate the severity of dermatitis on the back of the skin.

2.8 Assay of cytokine production

To measure the cytokine levels, mouse serum was collected 24 h after the final IMQ administration and stored at − 70 °C until analysis. To measure the cytokine levels in the skin tissue, the dorsal skin of the mice was removed and stored at − 80 °C. For analysis, skin was homogenized using a Bullet Blender^{TM} Blue (Next Advance, Averill Park, NY, USA) at 4 °C, after which the supernatants were stored at − 30 °C. The concentrations of TNF-α, IFN-α, IFN-γ, IL-17A, IL-23, and IL-27 in the mouse serum and skin tissue were measured using the Quantikine mouse IL-17A (R&D system, Minneapolis, MN, USA), TNF-α, IFN-α, IFN-γ, IL23, and IL-27 (eBioscience, San Diego, CA, USA) kits. ELISA was performed in accordance with the manufacturer's instructions.

2.9 Histological analysis

Paraformaldehyde-fixed and paraffin-embedded back skin samples from the mice were sliced and then stained with hematoxylin and eosin (H&E). Epidermal thickening and stratum corneum were observed in association with vascular dilatation and inflammatory cell infiltration in the epidermis or dermis under a light microscope (Olympus optical, Tokyo, Japan). To measure the thickness of the epidermis, cellSense standard 1.7.1 (Olympus Corporation, Tokyo, Japan) software was used.

2.10 Spleen weight and size

The spleen of each mouse was removed, weighed, and sized at the time of sacrifice.

2.11 Statistical analysis

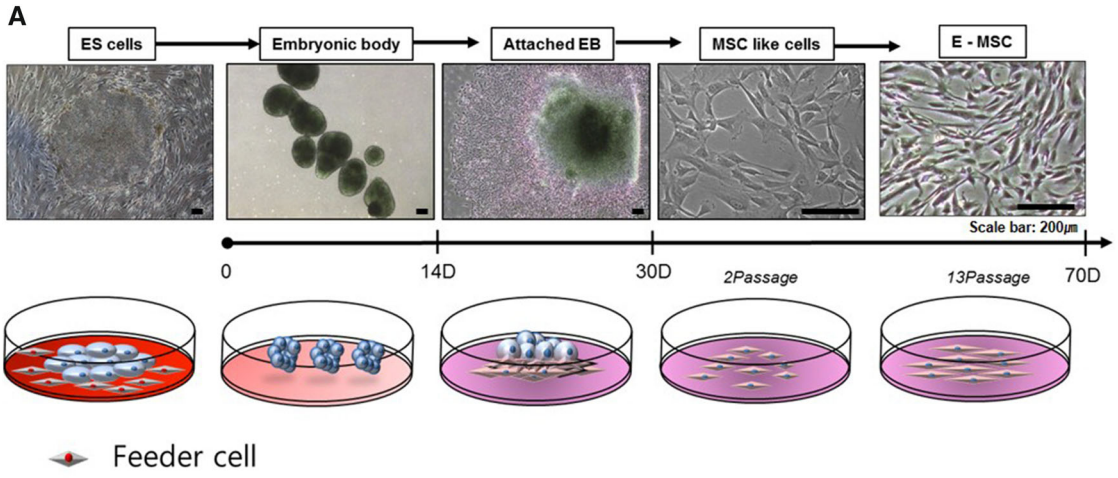
All the groups were compared by a one-way analysis of variance (ANOVA), followed by the Duncan test. The results were expressed as the mean ± SD $p < 0.05$ was considered significant.

3 Results

3.1 Characterized hE-MSCs have potency in application for psoriasis

We generated mesenchymal stem cell from human embryonic stem cell lines, SNUhES3, by an EB-based derivation methods (Fig. 1A). These cells displayed spindle-shaped morphologies and flow cytometry showed that cells were positive for hMSCs positive markers; CD44, 73, 90, 105, and negative for hMSCs negative markers; CD34, 45, and for hESCs positive marker; SSEA-4, TRA-1-60 (Fig. 1B).

To analyze the immunosuppressive ability of hE-MSCs, we performed a mixed lymphocyte response test. hE-MSCs


A
ES cells
Embryonic body
Attached EB
MSC like cells
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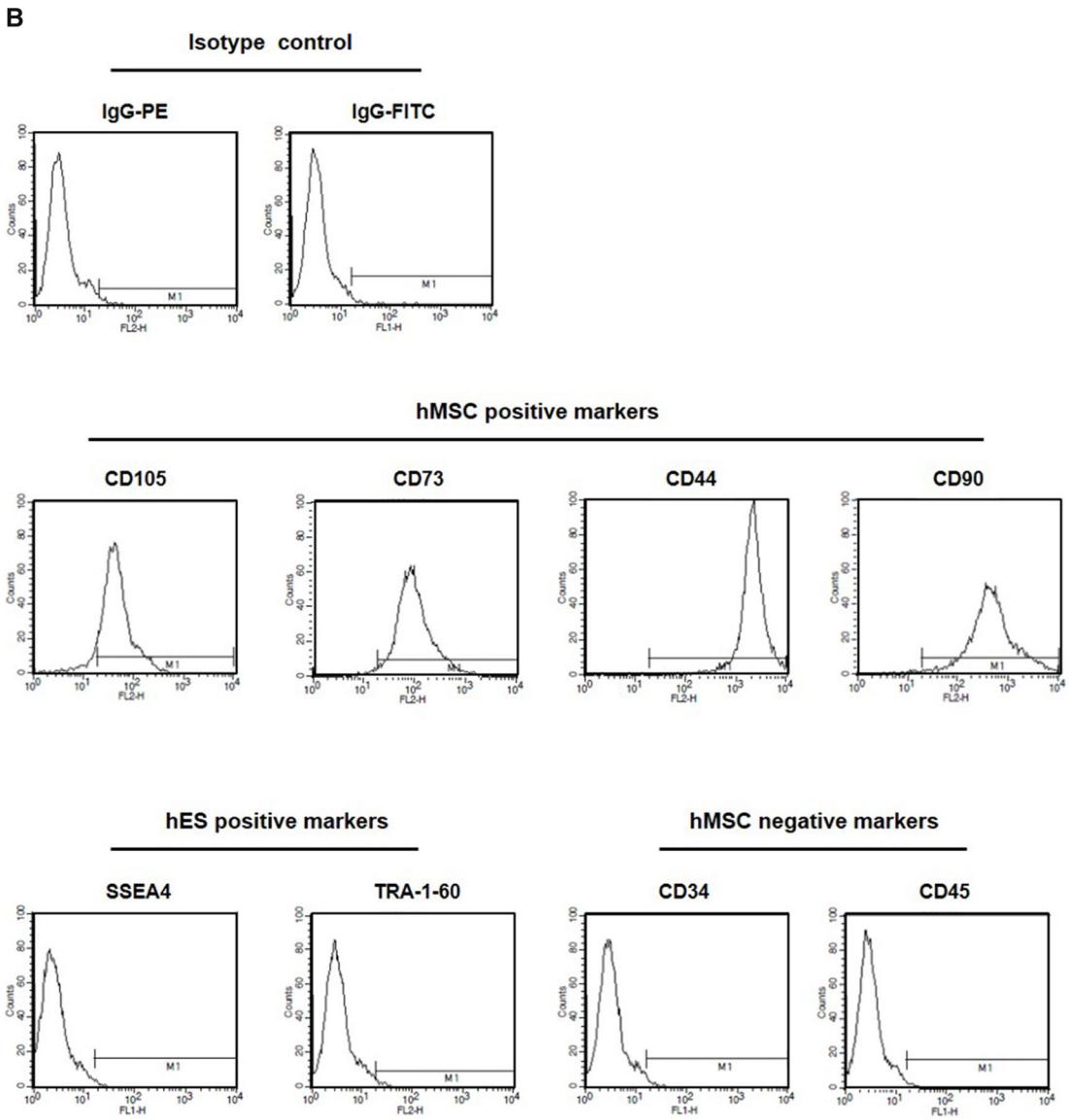
Scale bar: 200μm
0
14D
30D
2Passage
13Passage
70D
Feeder cell


B
Isotype control
IgG-PE
IgG-FITC
hMSC positive markers
CD105
CD73
CD44
CD90
hES positive markers
SSEA4
TRA-1-60
hMSC negative markers
CD34
CD45

◀**Fig. 1** Establishment and characterization of human embryonic stem cell derived mesenchymal stem cells (hE-MSCs). **A** Experimental strategy to establish hE-MSCs via EB-based derivation. Once, hESCs were enzymatically detached and then cultured to form EBs in suspension condition. After 14 days incubating, EBs were seeded on culture dish and then attached EBs were cultured during 16 days. After that, cells, which looked like MSCs, outgrew from the attached EBs. These type of the cells were expanded and subcultured. (Scale bar: 200 μm) **B** Immunophenotyping of hE-MSCs. Passages 7 were evaluated by flow cytometry. hE-MSC stained with negative marker (CD34 and CD45) and positive marker (CD105, CD73, CD44, and CD90) for human mesenchymal stem cell and for human embryonic stem cell specific marker (SSEA4 and TRA-1-60). An isotype mAB was used as a control

have the ability to act as an immunosuppressant to stimulation, such as allogeneic factor PBMCs. Two PBMCs from different individuals were tested and repressed the immunity by hE-MSCs, compared with those treated with stimulator, PHA (Fig. 2).

3.2 Profiling of secreted factors from hE-MSCs

To determine which secretory proteins had trophic and immunomodulatory effects, we profiled cytokines and growth factors in supernatant of hE-MSCs using an antibody array. We detected that various cytokines had dominant signal compared to media only group (Fig. 3A), and these cytokines were identified by datasheet. Among the 120 cytokines tested, hE-MSC secreted mainly 12 cytokines, such as IL-6, brain-derived neurotrophic factor (BDNF), IL-5, bone morphogenetic protein 4 (BMP4), growth-related oncogene alpha/beta/gamma (GRO a/b/g), GRO alpha, hepatocyte growth factor (HGF), insulin-like growth factor binding protein-6 (IGBP-6), osteoprotegerin (OPG), tissue inhibitor of metalloproteinases 1 (TIMP-1), TIMP-2, urokinase receptor (uPAR) (Fig. 3B, Table 1). By using Image J, pixel intensity of each cytokine signal was measured (Fig. 3B) and signals in antibody array membrane were quantified based on positive control (Table 1). We found that hE-MSC secreted several cytokines related immune modulation which needed to relieve psoriasis-related symptoms.

3.3 hE-MSCs improved the dermatitis of mice with IMQ-induced psoriasis

To examine the protective effects of hE-MSCs in the development of IMQ-induced psoriasis in mice, mice were subcutaneously (s.c.) administered hE-MSCs (2.5×10^6 cells/mouse in 200 μl of PBS) 2 and 4 days after IMQ application (Fig. 4A). The clinical skin score was calculated from the sum of the individual scores, based on the symptoms of erythema, scarring, and thickening. These symptoms were ameliorated or resolved in the groups treated with hE-MSCs (Fig. 4B). As expected, the scores were significantly reduced in the IMQ/hE-MSCs group, whereas the clinical scores increased in the control IMQ group (Fig. 4C).

3.4 Histology of skin lesions in mice with IMQ-induced psoriasis treated with hE-MSCs

To confirm the suppressive effects of the hE-MSCs, histopathological analysis of dorsal skin samples was conducted by H&E staining. The control IMQ group, which developed psoriasis-like skin lesions, showed the characteristic changes associated with psoriasis skin lesions, such as inflammatory infiltration, parakeratosis, and hyperkeratosis, compared with the normal group (Fig. 5A, B). However, the IMQ/hE-MSCs group exhibited

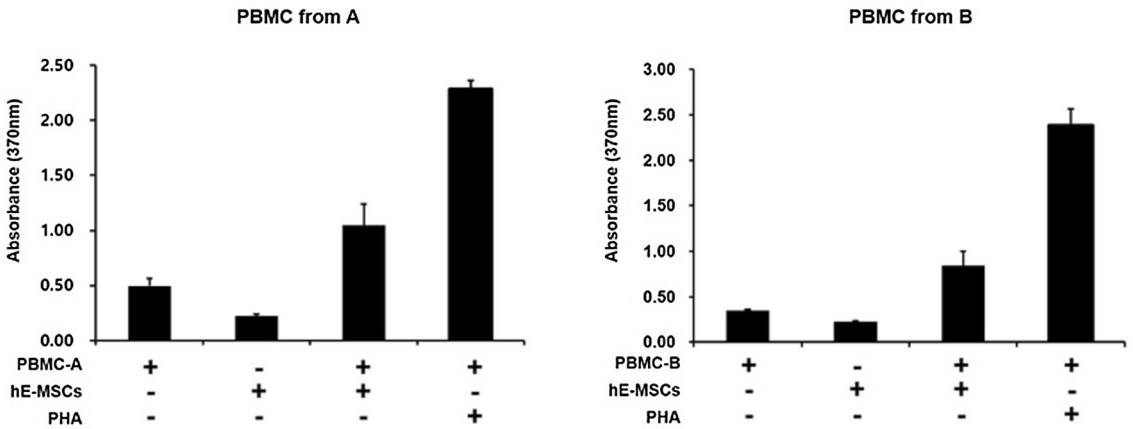


Fig. 2 The immune-modulatory properties of hE-MSCs. The immunosuppressive ability of hE-MSCs was tested using T-cell reactivity against allogeneic cell populations. Two peripheral blood mononuclear cells (PBMCs) from different individuals were co-cultured with hE-MSCs. PHA was used as a positive stimulator

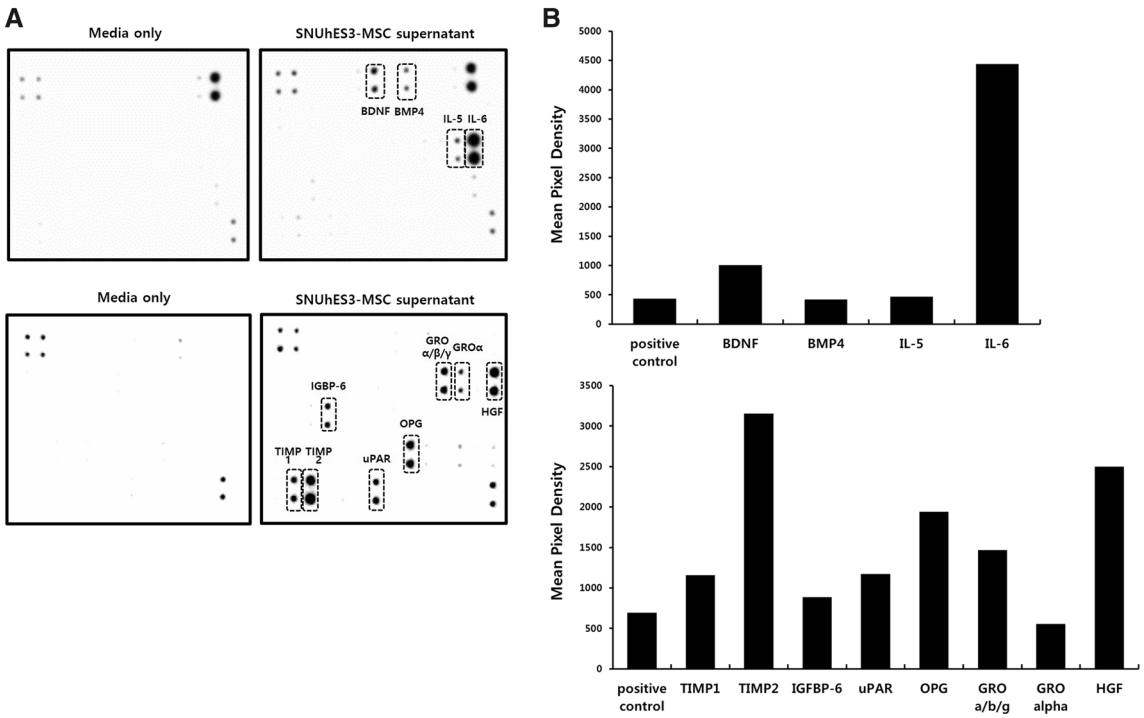


Fig. 3 Screening of immunomodulatory cytokines. A 120 cytokine and growth factor antibody array (C1000; RayBiotech) was probed with control medium without cells or hE-MSCs conditioned medium. **A** Representative images from two independent experiments. A total of 12 cytokines or growth factors were detected positive. **B** Quantification of secreted factor. Protein signals were quantified by NIH ImageJ software and normalized to the signal intensity average of positive controls for each array

Table 1 List of secreted protein from hE-MSCs

Detected protein	Relative fold value
Positive control (array kit supported)	1.00
IL-6 (interleukin-6)	10.23
BDNF (brain-derived neurotrophic factor)	2.31
IL-5 (interleukin-5)	1.08
BMP4 (bone morphogenetic protein 4)	0.97
TIMP-2 (tissue inhibitor of metalloproteinases 2)	4.53
HGF (hepatocyte growth factor)	3.59
OPG (osteoprotegerin)	2.78
GRO a/b/g (growth-related oncogene alpha/beta/gamma)	2.11
uPAR (urokinase receptor)	1.68
TIMP-1 (tissue inhibitor of metalloproteinases 1)	1.66
sIGBP-6 (insulin-like growth factor binding protein-6)	1.28
GRO alpha (growth-related oncogene alpha)	0.80

Positive signals on the same membrane of antibody array were used as control. The data was represented that twelve proteins were mainly secreted in the membrane compared to positive control. Relative fold values were quantified by image J

a significantly decrease in the characteristic changes associated with psoriatic skin lesion development in the control IMQ group. Moreover, the IMQ-induced epidermal thickness was significantly decreased in the IMQ/ hE-MSCs group (Fig. 5A, B).

3.5 Effect of hE-MSCs on splenomegaly in mice with IMQ-induced psoriasis

Previous reports showed that mice with IMQ-induced psoriasis of the skin showed spleen hypertrophy [9]. Accordingly, we investigated whether these hE-MSCs

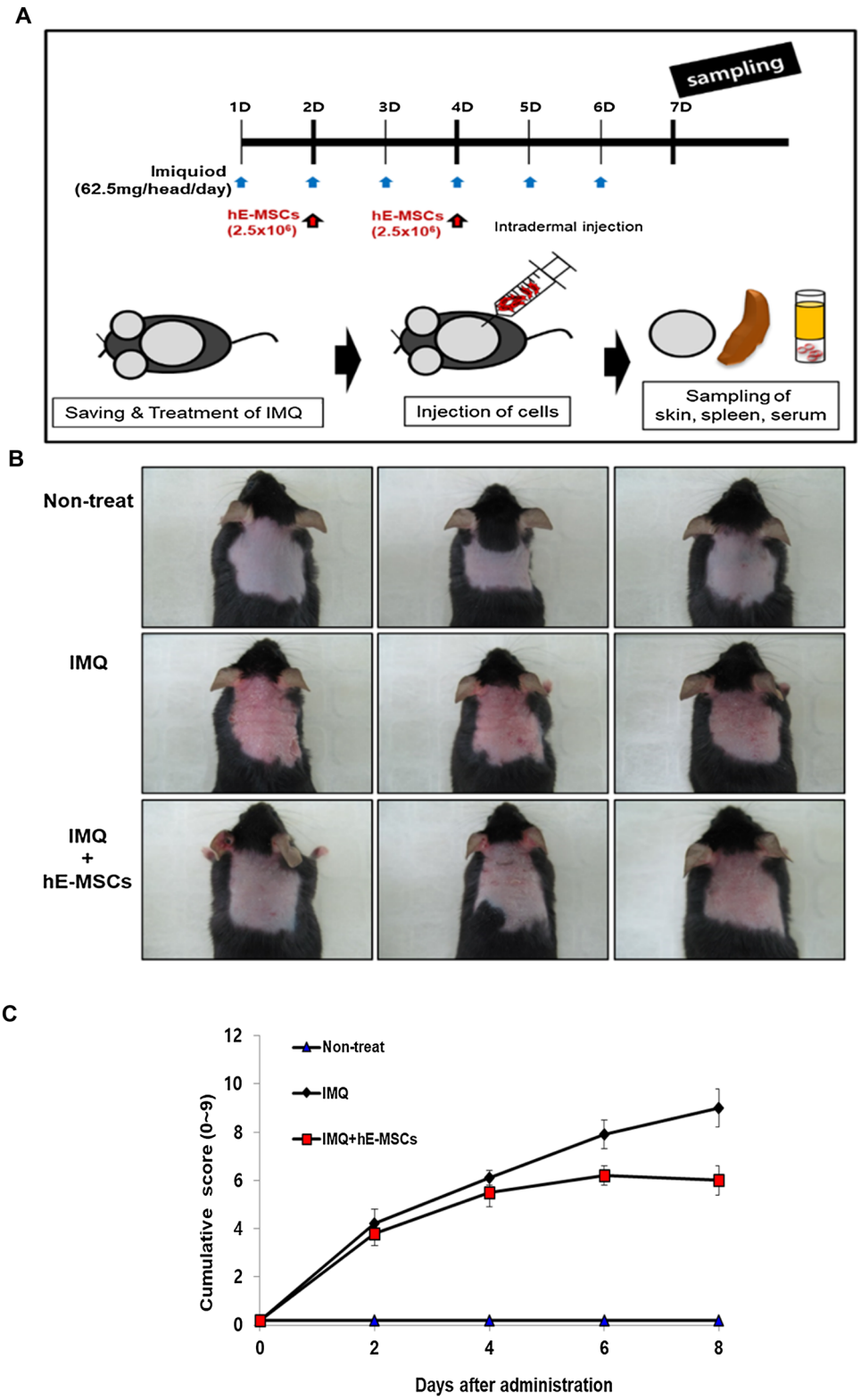


Fig. 4 Effects of hE-MSCs on imiquimod (IMQ)-induced psoriasis-like skin inflammation in mice. **A** Mice were subcutaneously (s.c.) injected with hE-MSCs (2.5×10^6 cells) 2 and 4 days after initiation of the topical application of IMQ. Mice were sacrificed 24 h after the final administration, and several samples were taken. **B** Photographs are representative of five mice. **C** Several representative symptoms were measured by a cumulative score (erythema plus scaling plus thickening). The data represent the average values ± SD from three separate experiments. $*p < 0.05$ indicates a statistically significant difference from the control IMQ group

were partly associated with an improved splenomegaly in mice with IMQ-induced psoriasis. We observed that the size and weight of the spleens in the IMQ/hE-MSCs group were less than that of the control IMQ group, indicating that hE-MSCs alter the splenomegaly in mice with IMQ-induced psoriasis (Fig. 6A, B).

Table 2 Effect of hE-MSCs on the serum and skin cytokine profile

Groups	TNF-α	IFN-α	IFN-γ	IL-27	IL-17A	IL-23
A. In serum (pg/ml)						
Non-treat	116.3 ± 22.2	112.4 ± 33.1	79.2 ± 10.4	64.7 ± 16.8	42.7 ± 9.7	60.2 ± 19.4
IMQ	301.6 ± 18.1	268.4 ± 22.4	214.1 ± 31.3	321.4 ± 3.09	150.4 ± 36.1	122.5 ± 22.7
IMQ + hE-MSCs	179.6 ± 23.5	193.5 ± 32.4	150.8 ± 19.8	191.5 ± 19.1	96.6 ± 19.1	88.9 ± 14.9
B. In skin (pg/ml)						
Non-treat	48.5 ± 8.9	62.8 ± 10.5	65.4 ± 13.7	68.4 ± 12.1	44.7 ± 7.1	66.4 ± 8.1
IMQ	125.8 ± 28.7	205.4 ± 13.1	221.9 ± 33.4	165.4 ± 16.8	98.5 ± 22.4	181.4 ± 24.2
IMQ + hE-MSCs	85.8 ± 19.8	127.8 ± 14.1	149.9 ± 23.7	117.4 ± 22.4	57.1 ± 3.8	128.4 ± 20.8

The concentrations of IL-17A, IL-23, TNF-α, and IFN-γ in the serum **A** and skin **B** were measured using ELISA, 24 h after the final administration. The data represent the average values ± SD from three separate experiments. *$p < 0.05$ indicates a statistically significant difference from the control IMQ group

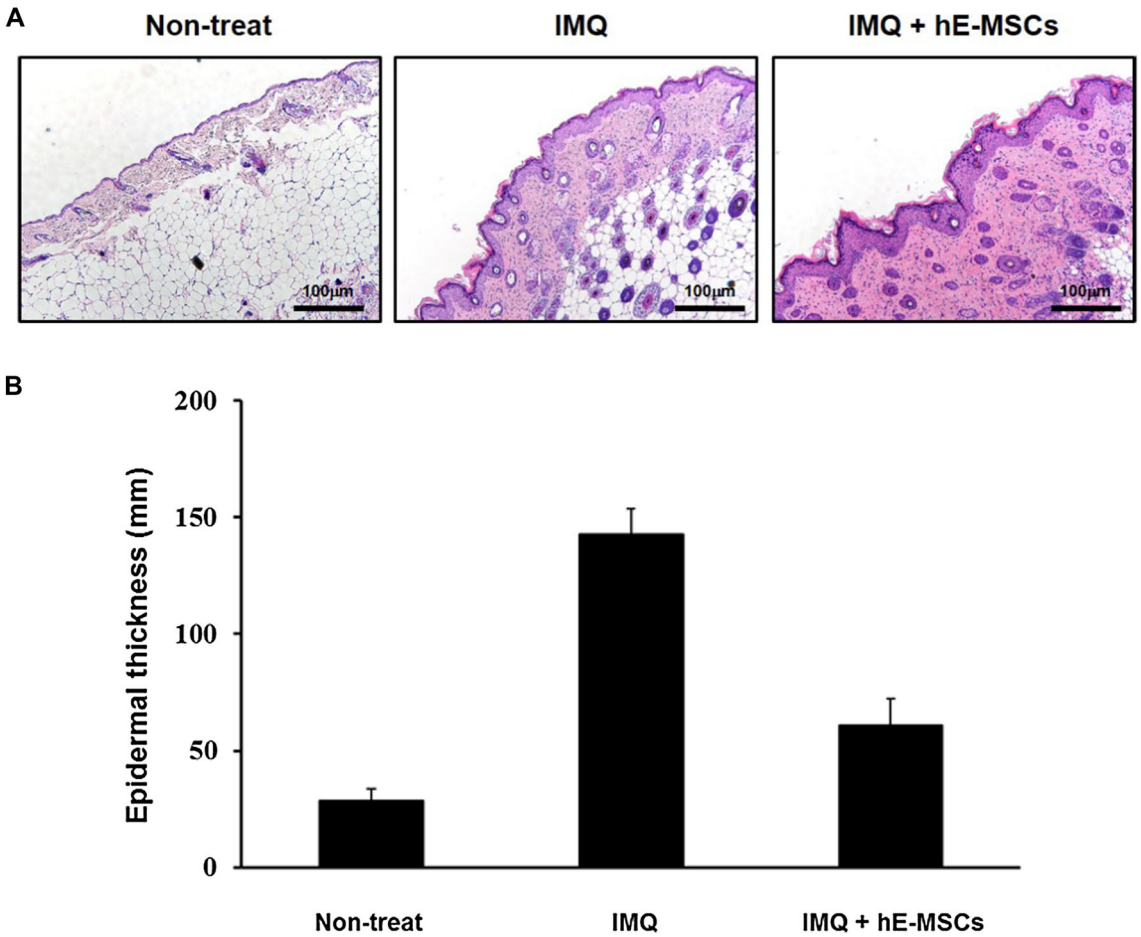


Fig. 5 Histological analysis of skin lesions. Skin samples from the back of the mice were studied 24 h after the final administration. The sections were then stained with hematoxylin and eosin (H&E). **A** Representative histological features of the IMQ-induced mice, treated with hE-MSCs (2.5×10^6 cells). **B** The epidermal thickness was measured. The data represent the average values ± SD from three separate experiments. *$p < 0.05$ indicates a statistically significant difference from the control IMQ group

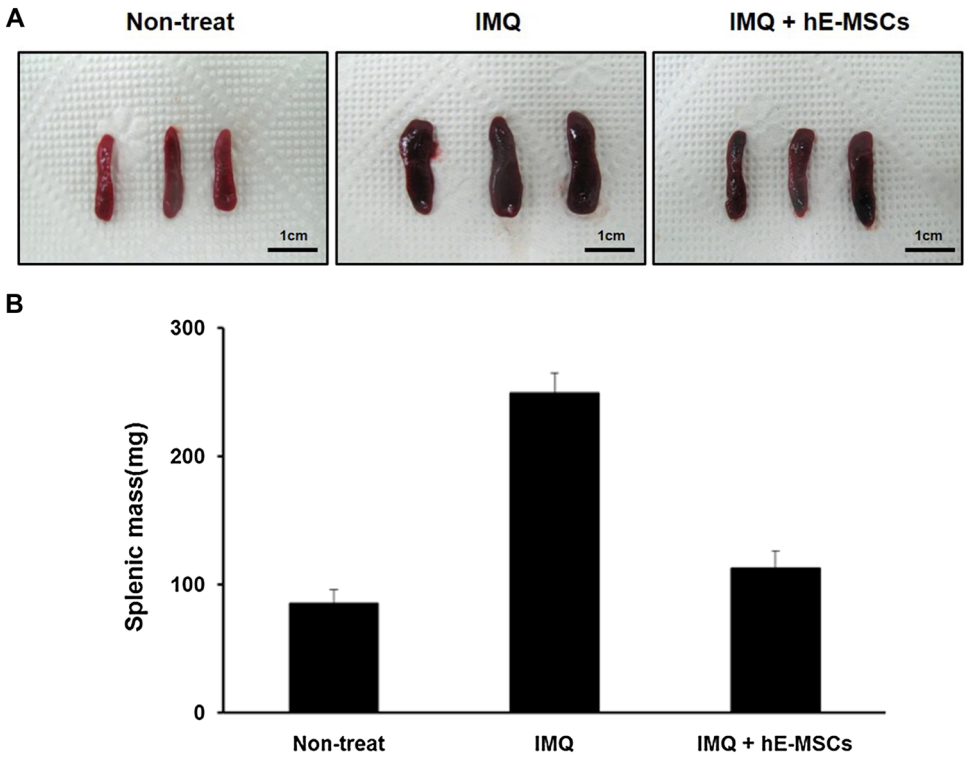


Fig. 6 Effect of hE-MSCs on IMQ-induced splenomegaly. **A** Representative photograph of the spleen size in the IMQ-induced mice, treated with hE-MSCs (2.5×10^6 cells). **B** The spleen mass was determined when the mice were sacrificed. The data represent the average values ± SD from three separate experiments. $*p < 0.05$ indicates a statistically significant difference from the control IMQ group

3.6 Inhibition of IMQ-induced inflammatory cytokine levels by hE-MSCs

To investigate the effect of hE-MSCs on various psoriasis-related inflammatory cytokines, including Th1 and Th17, we analyzed the production of these cytokines in the serum and skin samples of mice with IMQ-induced dermatitis using ELISA. As shown in Table 2, the expression levels of the Th1 cytokines (TNF-α, IFN-α, IFN-γ, and IL-27) and Th17 cytokines (IL-17A and IL-23) in the serum and skin showed marked inhibition in the IMQ/hE-MSCs group, compared to the control IMQ group.

4 Discussion

Psoriasis is a chronic immune-mediated inflammatory disorder, which affects two to three percent of the world's population, with a significant impact on the quality of life [10, 11]. Although the mechanism underlying psoriasis is not yet fully understood, it has been suggested that it is associated with genetic and epigenetic factors, where the immune system has a central role. Therefore, the immune system is the main target of various treatments for psoriasis [10]. There are conventional systemic treatments for psoriasis, such as methotrexate, cyclosporin A, and acitretin, and biologic therapies, like tumor necrosis factor (TNF)-α inhibitors and the interleukin-12/23p40 inhibitor [3, 11]. However, these treatments often show adverse effects and organ specific toxicity, or there is not enough safety data, because of the short period since their emergence [12, 13]. Therefore, alternative treatment with more efficacy and safety is important in psoriasis.

4.1 Benefit of hE-MSCs as an alternative therapeutics

Stem cell therapy could be an alternative option, in addition to the present measures, to achieve the efficacy needed to rescue psoriasis. One possible candidate cell source is adult stem cells such as MSCs. MSCs exert anti-inflammatory functions by cell to cell contact or by secretion of immune regulatory molecules [14]. However, they have several inherent limitations, including the individual variability in their biological characteristics for functionality, which requires validation from each donor [15]. We have developed a method to derive hMSCs from hESCs to overcome these hurdles and proved that this method may provide a more effective cell source for regenerative medicine [1, 2]. However, safety is the main concern for the application of stem cells from hESCs. Previous reports evaluated the tumorigenesis of hE-MSCs *in vivo* and did not show a considerable comparison with hESCs [1]. Additionally, in this study, we found that subcutaneous injection of hE-MSCs in IMQ-treated mice resulted in regression of psoriasis-related symptoms.

4.2 hE-MSCs modulate psoriasis-related symptoms in IMQ mice

There are several reports that MSCs may induce a cytokine profile shift in the Th1/Th2 balance toward the anti-inflammatory phenotype Th2. MSCs can suppress antigen-specific T-cell proliferation and cytotoxicity as well as inducing anti-inflammatory [16].

In this study, hE-MSCs showed systemic effects in IMQ-treated mice. The serum level of the Th1 cytokines (TNF-α, IFN-α, IFN-γ, and IL-27) and Th17 cytokines (IL-17A and IL-23) were dramatically reduced by hE-MSCs, which means that subcutaneous-injected hE-MSCs inhibit systemic IMQ-induced inflammation. Moreover, there was correlation of the data from the skin lesions with the serum data. These results suggested that hE-MSCs suppress the Th1- and Th17-associated cytokines and the psoriatic skin changes induced by IMQ. However, further investigation is required to determine the exact molecular mechanism underlying the anti-inflammatory effects of MSCs.

In summary, we shows that transplantation of hE-MSCs have therapeutic potential for the treatment of an inflammatory dermatitis condition. These cells could have potential applications for the treatment of psoriasis.

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Compliance with ethical standards

Conflict of interest The authors have no financial conflicts of interest.

Ethical statement The study protocol was approved by the institutional review board of Seoul National University Hospital (IRB No. H-1410-093-619). The animal studies were performed after receiving approval of the Institutional Animal Care and Use Committee (IACUC) in Dongguk University Hospital (IACUC approval No. 201606150).

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