



LITAF, HHEX, and DUSP1 expression in mesenchymal stem cells from patients with psoriasis

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ABSTRACT. Psoriasis is a common chronic relapsing inflammatory skin disease, in which mesenchymal stem cells (MSCs) have been hypothesized to play an important role in abnormal localized inflammation and vascular proliferation observed in skin lesions. Previous studies have revealed abnormal gene expression patterns, DNA methylation status, and cytokine secretion of MSCs in psoriatic skin lesions, as well as some gene expression abnormalities related to inflammation and angiogenesis. We further verified the gene and protein expressions of inflammation-related lipopolysaccharide-induced tumor necrosis factor- α transcription factor (LITAF), dual-specificity protein phosphatase 1 (DUSP1), and angiogenesis-related hematopoietically expressed homeobox (HHEX) in MSCs derived from the skin lesions of psoriasis patients. The gene expression of *LITAF*, *DUSP1*, and *HHEX* in dermal MSCs was measured at the mRNA level using reverse transcription-polymerase chain reaction and the corresponding protein expression levels were analyzed by western

blotting analysis. The gene and protein expression levels of LITAF, HHEX, and DUSP1 in dermal MSCs were significantly lower in psoriasis patients compared to controls. Amplification and western blotting results were consistent with our previously reported gene chip data. Our results suggest that dermal MSCs in psoriatic skin lesions may be involved in the development, progression, and regulation of localized inflammatory abnormalities by reducing the expression of LITAF, HHEX, and DUSP1, which are related to inflammation and angiogenesis.

Key words: Dual-specificity protein phosphatase 1; Mesenchymal stem cell; Hematopoietically expressed homeobox; Lipopolysaccharide-induced tumor necrosis factor-alpha transcription factor; Psoriasis

INTRODUCTION

Psoriasis is an immune-mediated chronic inflammatory skin disease mainly characterized by excessive proliferation of keratinocytes, infiltration of T cells, dendritic cells, monocytes and neutrophilic myelocytes, and proliferative expansion of superficial dermal capillaries. Although the underlying mechanism is presently unclear, substantial evidence suggests that T cell-based immune disorders play a key role in the pathogenesis of psoriasis (Cai et al., 2012). Such immune disorders mainly manifest as overactivation of CD4⁺ T lymphocytes, joint participation of a variety of immune cells such as monocytes, dendritic cells, and B lymphocytes, and high expression of Th1 and Th17 cytokines such as interleukin (IL)-2, IL-6, IL-8, IL-22, IL-23, tumor necrosis factor- α (TNF- α), and interferon- γ (Loffredo et al., 2009).

Mesenchymal stem cells (MSCs) are a class of mesoderm-derived adult stem cells with high proliferation, self-renewal, and pluripotency. In addition to bone marrow, MSCs can be derived from other tissues such as fat, umbilical cord blood, and the dermis (Chunmeng and Tianmin, 2004; Rebelatto et al., 2008). MSCs play regulatory and inhibitory roles in immune responses, and thus have been increasingly used in research on immune-related diseases such as autoimmune diseases, inflammatory diseases, and graft-versus-host disease (Le et al., 2004; Nemeth et al., 2010; Gu et al., 2010).

We previously investigated the biological characteristics and related gene expression patterns of bone marrow-derived MSCs in patients with psoriasis (Zhang et al., 2010; Hou et al., 2014). In addition to reduced proliferation activity and increased spontaneous apoptosis, bone marrow-derived MSCs in psoriasis were found to be associated with high expression of stem cell factor and granulocyte-colony stimulating factor, as well as low expression of inflammatory cytokines such as IL-1, IL-3, IL-18, and TNF- α . Moreover, differential gene expression analysis showed that the expression of genes related to immune responses, inflammation, and lymphocyte adhesion and chemotaxis in MSCs were down-regulated in psoriatic skin lesions (Zhang et al., 2010; Hou et al., 2014). Based on previous studies, we applied gene chip technology to conduct a comparative analysis of gene expression patterns in dermal MSCs (DMSCs) in skin lesions of psoriasis patients and normal skin of healthy individuals (Hou et al., 2013, 2014). Abnormalities were detected in the methylation status and expression level of a number of genes related to inflammation, immune responses, angiogenesis, and cell proliferation (Hou et al., 2013, 2014). Our previous findings suggested that MSCs in skin lesions may be involved in localized immune responses and proliferative expansion of blood vessels in psoriasis. Based on these previous findings, in

the present study, we further analyzed the expression of inflammation-related lipopolysaccharide-induced TNF-alpha transcription factor (LITAF), hematopoietically expressed homeobox (HHEX), and angiogenesis-related dual-specificity protein phosphatase 1 (DUSP1/DSP1) at the gene and protein levels in DMSCs derived from psoriasis patients.

MATERIAL AND METHODS

Patients and sample collection

Twelve patients with psoriasis vulgaris (7 males and 5 females; mean \pm SD age, 37 \pm 13 years) were enrolled in this study (Table 1). The mean Psoriasis Area and Severity Index (PASI) at the time of sample collection was 18.6 \pm 7.5. Detailed information on the patient characteristics is shown in Table 1. Control samples were obtained from 14 healthy volunteers who agreed to undergo plastic surgery. Written informed consent was obtained from all participants, and the study protocol was approved by the Medical Ethics Committee of Taiyuan Central Hospital.

None of the 26 participants had received systemically or topical corticosteroids, biological agents, immunosuppressive agents, or ultraviolet phototherapy within 1 month before enrolment.

Skin tissues were removed from the participants and immediately used for MSC isolation.

Table 1. Patient information.

Sample	Age (years)	Gender	Illness duration	PASI	Biopsy site
Y5	23	male	3 years	15.8	abdomen/center of plaque
Y8	45	female	10 years	27.7	buttock/center of plaque
Y46	52	female	8 years	31.4	waist/edge of plaque
Y50	19	male	1 year	10.4	thigh/edge of plaque
Y54	36	male	6 months	16.8	waist/edge of plaque
Y62	42	male	6 years	11.4	thigh/edge of plaque
Y64	34	female	9 years	9.6	waist/center of plaque
Y65	21	male	5 months	14.5	dorsum/center of plaque
Y66	58	female	23 years	23.4	dorsum/center of plaque
Y68	54	female	30 years	28.8	arm/edge of plaque
Y69	28	male	5 years	14.2	dorsum/edge of plaque
Y73	33	male	7 years	19.6	abdomen/center of plaque

PASI = Psoriasis Area and Severity Index.

Isolation and expansion of DMSCs

DMSCs were isolated and expanded as previously described (Hou et al., 2013). Briefly, the dermis was separated from the epidermis using 0.25% dispase (Sigma-Aldrich, St. Louis, MO, USA) and subsequently digested into a monoplast suspension. After being filtered and washed with Dulbecco's modified Eagle's medium/nutrient mixture F-12 (DMEM/F12), the cells were resuspended at a concentration of 1.0×10^5 cells/mL in DMEM/F12 containing 5% fetal bovine serum, 10 ng/mL basic fibroblast growth factor (Sigma-Aldrich), 10 μ L/mL B27, and 1% antibiotic mixture (100 U/mL penicillin and 100 μ g/mL streptomycin sulfate) and incubated at 37°C in a humidified atmosphere supplemented with 5% CO₂. Non-adherent cells were removed after 72 h, and half of the medium was changed every 3-4 days. The adherent MSCs were passaged at 80% confluence. Cell surface markers such as cluster of differentiation CD105, CD29, CD44, CD73, CD90, CD45, CD34, and human leukocyte antigen-DR (BD Biosciences, Franklin Lakes, NJ, USA) were detected using flow cytometry (Beckman Coulter, Inc., Brea, CA, USA).

Differentiation of MSCs

Osteoblast and adipocyte differentiation

At passage 3, the cultured cells were induced to differentiate into osteoblasts and adipocytes according to published protocols (Cheng et al., 2011). DMEM without the induction factors containing only 10% fetal bovine serum was used as a negative control in the differentiation experiments.

Reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR)

RNA from all 26 samples was extracted using TRIzol (Invitrogen, Carlsbad, CA, USA) and cDNA was synthesized using 4 μ L total RNA, 4 μ L 5X PrimeScript buffer, and 12 μ L RNase-free dH₂O in a total volume of 20 μ L (TaKaRa, Shiga, Japan). PCR amplification was performed in a 20- μ L system containing 2 μ L cDNA, 10 μ L 2X SYBR Premix EX Taq II buffer (TaKaRa), 0.4 μ L Rox Reference Dye, 6 μ L RNase-free dH₂O, and 0.8 μ L of each 10 μ M primer. The thermal cycling conditions included pre-denaturation at 95°C for 30 s, 40 cycles of denaturation at 95°C for 10 s, and annealing at 60°C for 30 s. β -actin was used as an internal control as previously reported. PCR products were identified using 2% agarose gel electrophoresis. Primer sequences and amplification product sizes are shown in Table 2.

Table 2. Primer information.

Gene	Primer sequence	Annealing temperature (°C)	Product size (bp)
β -actin	F: 5'-CTACAATGAGCTGCGTGTGGC-3' R: 5'-CAGGTCCAGACGCAGGATGGC-3'	60°	271°
LITAF	F: 5'-AACATCACGCGGGCTTCTAAC-3' R: 5'-GCATACTCGTAAAGCTGCATGTC-3'	58°	182°
HHEX	F: 5'-GGGCCAATCCTGTCGCTTAAT-3' R: 5'-GTTATGCGCTTGCGAACCT-3'	57°	81°
DUSP1	F: 5'-TGTCCGATTCATAGTCTGTCC-3' R: 5'-CTCACAGCGATAAGTGCCCTC-3'	58°	93°

Western blot analysis

DMSCs were rinsed with ice-cold phosphate-buffered saline, and total cell protein extracts were prepared using a cell lysis buffer (Beyotime Technology, Shanghai, China) containing protease inhibitors. Next, 10 μ g total protein from the MSCs was boiled with sample loading buffer for 5 min and then separated by 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis, followed by electro-transfer to a polyvinylidene difluoride membrane (Millipore, Billerica, MA, USA). The membranes were blocked in 5% skim milk at 4°C overnight and then sequentially incubated with different diluted primary antibodies the next morning [(LITAF): mouse anti-human, 1:2000; (HHEX): rabbit anti-human, 1:2000; (DUSP1): rabbit anti-human, 1:1000; glyceraldehyde 3-phosphate dehydrogenase (GAPDH):mouse anti-human, 1:5000; Abcam, Cambridge, UK] at 4°C overnight followed by horseradish peroxidase-conjugated secondary antibodies (goat anti-mouse IgG and goat anti-rabbit IgG; Bioss, Beijing, China) at 37°C for 2 h. Enhanced chemiluminescence was performed for color development and exposure. The ratio in gray scale of the objective band under test to GAPDH was calculated to semi-quantitatively analyze protein levels.

Statistical analysis

The SPSS 13.0 software (SPSS Inc., Chicago, IL, USA) was used to perform all statistical analyses. All data are reported as means \pm SD. The independent sample *t*-test was used to compare the mean values of the 2 groups, and the level of significance was set at $P < 0.05$.

RESULTS

Identification of cultured DMSCs

Consistent with our previously published data (Hou et al., 2014), the cultured cells were positive for CD105, CD29, CD44, CD73, and CD90, negative for CD45, CD34, and human leukocyte antigen-DR, showed typical fibroblast morphological characteristics, and could be induced to differentiate into both osteoblasts and adipocytes.

LITAF, HHEX, and DUSP1 expression levels in DMSCs

We previously used gene chip technology to compare gene expression patterns in MSCs between skin lesions of psoriasis patients and the normal skin of healthy individuals. In a previous study, a total of 1927 differentially expressed genes were detected, including 1090 up-regulated genes and 837 down-regulated genes. Furthermore, the expression of a number of inflammation- and angiogenesis-related genes showed obvious abnormalities in the DMSCs of psoriasis skin lesions (Hou et al., 2014). Based on these preliminary results, we further analyzed the expression of 3 genes (*LITAF*, *HHEX*, and *DUSP1*) on the mRNA and protein levels in DMSCs of psoriasis patients.

The results of the RT-qPCR assay showed that compared with the control group, psoriasis patients had significantly down-regulated expression of *LITAF* (0.52 ± 0.15 vs 0.79 ± 0.27 , 0.66-fold, $P < 0.01$), *HHEX* (0.67 ± 0.17 vs 0.99 ± 0.38 , 0.67-fold, $P < 0.05$), and *DUSP1* (0.70 ± 0.19 vs 0.89 ± 0.21 , 0.78-fold, $P < 0.05$) in the DMSCs, supporting the previously reported gene chip data (Figure 1 and Table 3).

Using GAPDH as an internal reference, western blotting analysis demonstrated that compared with the control group, psoriasis patients had significantly reduced protein expression levels of *LITAF* (0.31 ± 0.11 vs 0.45 ± 0.17 , $P < 0.05$), *HHEX* (0.25 ± 0.09 vs 0.45 ± 0.19 , $P < 0.01$), and *DUSP1* (0.19 ± 0.10 vs 0.36 ± 0.15 , $P < 0.01$) in the DMSCs, which was consistent with the results of the RT-qPCR assay (Figure 2 and Table 4).

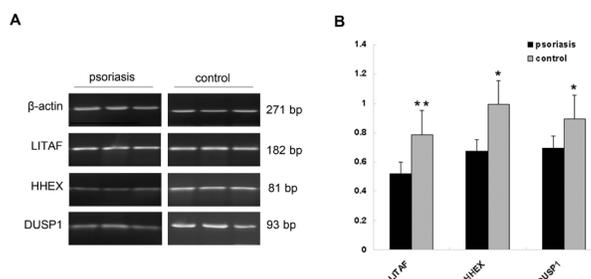


Figure 1. RT-qPCR detection of the expression of *LITAF*, *DUSP1*, and *HHEX*. **A.** mRNA expression of inflammation-related *LITAF*, *DUSP1*, and angiogenesis-related *HHEX* were detected by RT-qPCR and normalized against β -actin. Comparison with healthy controls. **B.** Graph displays the relative mRNA expression of the different genes in the psoriasis and control groups. * $P < 0.05$, ** $P < 0.01$.

Table 3. Expression level of LITAF, HHEX, and DUSP1 genes in psoriatic and normal DMSCs detected by RT-PCR.

Gene	Psoriasis	Control	Fold-change	P value
LITAF	0.52 ± 0.15	0.79 ± 0.27	0.66	0.005332
HHEX	0.67 ± 0.17	0.99 ± 0.38	0.67	0.012004
DUSP1	0.70 ± 0.19	0.89 ± 0.21	0.78	0.019803

Data are reported as means ± SD.

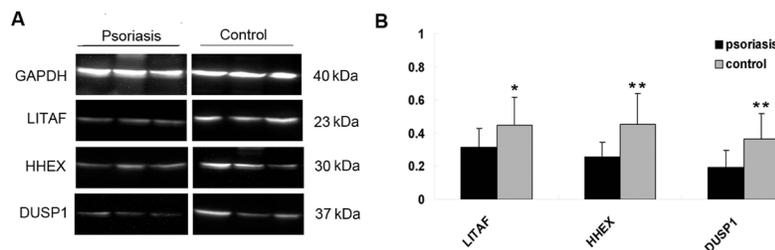


Figure 2. Western blot verification of the protein expression of LITAF, DUSP1, and HHEX. **A.** Protein expressions of inflammation-related LITAF, DUSP1, and angiogenesis-related HHEX were determined using western blotting and normalized against GAPDH. Comparison with healthy controls. **B.** Graph displays the relative protein expression of LITAF, HHEX, and DUSP1 in the psoriasis and control groups. *P < 0.05, **P < 0.01.

Table 4. Expression level of LITAF, HHEX, and DUSP1 proteins in psoriasis compared to control by western blotting.

Protein	Psoriasis	Control	P value
LITAF	0.31 ± 0.11	0.45 ± 0.17	0.034792
HHEX	0.25 ± 0.09	0.45 ± 0.19	0.003009
DUSP1	0.19 ± 0.10	0.36 ± 0.15	0.004119

Data are reported as means ± SD.

DISCUSSION

Previous studies have shown that MSCs can inhibit the activation of T cells, proliferation of natural killer cells, and maturation of dendritic cells *in vitro*, thereby playing a negative regulatory role in the immune response (Di Nicola et al., 2002; Spaggiari et al., 2006; Nauta et al., 2006). Additionally, MSCs have been demonstrated to express vascular endothelial growth factor (VEGF), which facilitates the process of angiogenesis (Liu et al., 2011). Taking into account the functions of MSCs and the pathological features of psoriasis, we hypothesized that MSCs play an important role in the pathogenesis of this disorder.

HHEX is a transcription factor involved in the development of multiple organs, particularly of the cardiovascular system. It is encoded by the homeobox gene *Hhex* and is also known as proline-rich homeodomain protein (PRH), as it contains an N-terminal domain rich in proline residues (Noy et al., 2010). In *Hhex*^{-/-} mice, HHEX/PRH was found to bind to the promoter regions of key members of the VEGF signaling pathway, such as VEGF, VEGF receptor (VEGFR)1, VEGFR2, and neuropilin-1, inhibiting their transcription, preventing cell proliferation, and playing a negative regulatory role in angiogenesis (Noy et al., 2010). The negative regulatory effect of HHEX/PRH on angiogenesis can be blocked by casein kinase 2 (Noy et al., 2012). We previously reported that VEGF was highly expressed in DMSCs derived from psoriatic skin lesions (Hou et al., 2014) and that for the treatment of psoriasis, TNF- α inhibition resulted in localized inhibition of

angiogenesis and improved skin lesion status by inhibiting VEGF, inducible nitric oxide synthase, and nitric oxide expression in DMSCs (Campanati et al., 2012). These previous findings suggest that MSCs can influence the localized proliferative expansion of blood vessels in psoriasis through the VEGF signaling pathway. In the present study, we found that reduced expression of HHEX/PRH in MSCs from psoriatic skin lesions may represent another cause of localized proliferative expansion of blood vessels.

Mitogen-activated protein kinase (MAPK) phosphatase 1, also known as DUSP1, is a protein phosphatase with dual substrate specificity that catalyzes the dephosphorylation of phosphorylated threonine/tyrosine residues. DUSP1 is widely present in different tissues and is known to regulate various cellular activities, including gene expression, cell proliferation, division, differentiation, and apoptosis (Pearson et al., 2001). Moreover, DUSP1 also specifically inhibits the activity of various MAPK family members, such as p38, c-Jun N-terminal kinase, and extracellular signal-regulated kinase. It is an important regulatory factor that mediates the self-limitation and promotes the resolution of inflammation in cells. Activation of the MAPK signaling pathway is considered to be a key step in the maturation and function of immune cells. DUSP, as a specific inhibitor of the MAPK signaling pathway, can specifically degrade and inactivate MAPK (Zheng and Guan, 1993), and thus plays a key role in both autoimmunity and acquired immunity (Liu et al., 2007). In the cell, DUSP1 preferentially inhibits the p38 and c-Jun N-terminal kinase pathways rather than the extracellular signal-regulated kinase pathway (Franklin and Kraft, 1997). The extracellular signal-regulated kinase 1/2 signaling pathway regulates cell growth and differentiation, whereas the c-Jun N-terminal kinase and p38 MAPK signal transduction pathways play roles in stress responses such as inflammation and apoptosis. A variety of stimuli (e.g., mitogens, hypoxia, hormones, oxidative stress, ultraviolet radiation, and Ca^{2+}) that can activate the MAPK signaling pathway can also induce the gene expression of *Dusp1* (Ryser et al., 2001). In turn, DUSP1 can degrade the MAPK molecule for negative feedback inhibition of the MAPK signaling pathway, thereby inhibiting the expression of a variety of inflammatory cytokines, including IL-6, IL-8, chemokine (C-C motif) ligand 2, chemokine (C-X-C motif) ligand (CXCL)3, CXCL1, and CXCL2 (Kondoh and Nishida, 2007; Shah et al., 2014), and reducing the stimulatory effects on the body. Decreased DUSP1 expression in the DMSCs of psoriasis patients may reduce its inhibitory effects on the MAPK signaling pathway, and localized enhancement of MAPK signaling activity in skin lesions is thought to be an important factor contributing to the development of psoriasis, particularly in the early stage. Thus, DUSP1 may provide a new target for the clinical treatment of inflammation-related diseases.

TNF- α is a key inflammatory factor involved in the pathogenesis of psoriasis, and its expression is influenced by various factors. LITAF is a novel transcription factor that has been demonstrated to be overexpressed upon stimulation of bacterial lipopolysaccharide and phosphorylated by p38 α kinase. Phosphorylated LITAF can form a complex with STAT6(B), which is subsequently transferred from the cytoplasm into the nucleus, where it binds to the promoter region of lipopolysaccharide-induced genes such as TNF- α , resulting in increased transcription of certain inflammatory cytokines such as CXCL1 (GRO), IL-1 α , CCL5 (RANTES), TNF- α , interferon- γ , CCL8 (MCP-2), and IL-10 (Tang et al., 2003, 2005, 2006). Accordingly, this complex plays a crucial role in the innate immune response. Furthermore, LITAF is expressed to varying degrees in different lymphoid tissues such as the peripheral blood cells, lymph nodes, and the spleen, as well as in non-lymphoid organs. However, this is the first study to report that LITAF is also expressed in the DMSCs of psoriasis patients, although at a low level. This reduced expression of LITAF in MSCs derived from psoriatic skin lesions may be caused by localized negative feedback inhibition of inflammatory factors. Alternatively, MSCs may inhibit LITAF expression during the chronic phase of the disease, thereby regulating localized expression of inflammatory factors in the skin lesions

and further influencing the outcome of psoriasis. However, the underlying mechanisms behind this down-regulation must be verified in future studies.

In conclusion, this study revealed abnormal expression of several inflammation- and angiogenesis-related genes in DMSCs in skin lesions from patients with psoriasis. Combined with our previous findings and those of other researchers, we speculate that DMSCs play an important role in the development, progression, and outcome of psoriasis. In the early stage of the disease, MSCs may promote disease progression by promoting angiogenesis and releasing pro-inflammatory cytokines, as well as by inhibiting the reduction of inflammatory cytokines; conversely, in the late stage of the disease, MSCs may inhibit angiogenesis and release inflammatory factors, thereby improving the skin lesion status. Further experimental data are needed to support this hypothesis, and this will be the focus of our future research efforts.

Conflicts of interest

The authors declare no conflict of interest.

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