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Wharton's jelly-mesenchymal stem cells alleviate atopic dermatitis by regulating TXNIP/NLRP3 and HDAC3/TGF-β1 signaling pathway in mice

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ABSTRACT

Background: Atopic dermatitis (AD) is a chronic immune and inflammatory dermatologic disease. Preclinical and clinical studies have indicated that stem cell transplantation is considered an alternative treatment option for ameliorating the symptoms of AD. However, the molecular mechanisms by which stem cells treat AD remain unclear. This study aimed to evaluate the therapeutic effects of Wharton's jelly mesenchymal stem cells in a 2,4-dinitrofluorobenzene (DNFB)-induced mouse model of AD.

Methods: Human Wharton's jelly-mesenchymal stem cells (hWJ-MSCs) were subcutaneously injected into mice receiving DNFB on day 7 (DNFB-MSC 7 group) and days 7 and 16 (DNFB-MSC 7, 16 group).

Results: hWJ-MSCs improved the symptoms of AD and lowered the clinical skin score. After treatment with hWJ-MSCs, the skin thickness of the epidermis was reduced in AD mice. hWJ-MSCs decreased the serum concentration of IgE. Mechanically, hWJ-MSCs inhibited the expression of proteins associated with the NLRP3 inflammasome, such as NLRP3, ASC/TMS1, TXNIP, and caspase-1. Furthermore, hWJ-MSCs regulated the expression of TGF-β1 and histone deacetylase 3 (HDAC3) proteins.

Conclusions: Taking these results together, treatment with hWJ-MSCs improved the clinical symptoms by regulating TXNIP/NLRP3 and HDAC3/TGF-β1 signaling cascade.

Keywords: atopic dermatitis, HDAC3, mesenchymal stem cells, NLRP3, TGF-β

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INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by intense itching and eczematous lesions. AD can cause persistent itching of the skin, undermine the quality of life, and result in financial burden. Several factors are involved in the development and progression of AD, such as genetic defect, epidermal barrier, epigenetic changes and immunological aberrations [1-4]. The cytokines regulate the immune response in the initial event in the development of AD, leading to weakening of the epidermal barrier. The imbalance between T-helper 2 (Th2) cells and T-helper 1 (Th1) cells has been observed in AD [1]. The immune response of acute and chronic-phase mast cells plays a pivotal role in the progression of AD. Th2 cell activation induces IL-4- and IL-13-mediated secretion of IgE [5]. 2,4-dinitrofluorobenzene (DNFB) is a skin sensitizer which causes delayed hypersensitivity responses. Thus, DNFB-induced dermatitis animal model has been widely employed in many studies and can mimic AD [6, 7]. Topical corticosteroids and topical calcineurin inhibitors are used as a first line for the treatment of AD. Long-term administration of corticosteroids is the most commonly used treatment for AD [8]; however, corticosteroids often lead to serious side effects such as skin atrophy. Unlike topical corticosteroids, topical calcineurin inhibitors do not cause skin thinning [9]. Narrow band ultraviolet B phototherapy is used as the second-line treatment for AD, but the side effect of phototherapy is a sunburn-like reaction [10]. It is urgent to explore safety and inexpensive medications or treatments for AD.

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The inflammasome can respond to stimulation by triggering the inflammatory cascade. When the cells are stimulated, nucleotide-binding domain, leucine-rich–containing family, pyrin domain-containing-3 (NLRP3) binds to apoptosis-associated speck-like protein containing a CARD (ASC) and recruits procaspase-1, leading to the release of the inflammatory cytokine IL-1β [11]. NLRP3 is involved in the progression of AD. Inhibition of inflammasome can relieve the symptoms. Histone deacetylases remove acetyl groups from histones, leading to gene silencing and transcriptional repression. Histone deacetylase 3 (HDAC3) is a class I HDAC, which can mediate immune and inflammatory responses in many diseases [12, 13]. HDAC3 inhibitor (BRD3308) decreased inflammation through PPARγ/NLRP3/GSDMD signaling pathway in intraventricular hemorrhage mice [14]. HDAC3 expression was increased in lesional atopic dermatitis, but HDAC3 inhibition can activate the Nrf2/HO-1 signaling pathway in AD [15]. Studies also demonstrated that phytochemicals can attenuate inflammation by downregulating NLRP3 expression in AD [16, 17]. HDAC3 and NLRP3 are associated with the development of AD.

Mesenchymal stem cells (MSCs) can be isolated from different tissues. They possess differentiation ability, suppress inflammation, and promote angiogenesis. MSCs can modulate the immune response and treat many inflammatory diseases, including type 1 diabetes, asthma, allergic rhinitis, and dermatitis. Additionally, MSCs can interact with effector T cells to downregulate pro-inflammatory cytokines. Treatment with MSCs attenuated airway hyperresponsiveness by downregulating Th2-associated cytokines. Bone marrow-derived MSCs have some limitations, and the number of stem cells decreases with age [18]. Human Wharton's jelly-mesenchymal stem cells (hWJ-MSCs) are a class of stem cells with low immunogenicity and high differentiation capacity [19].

hWJ-MSCs can modulate the immune system and inhibit inflammation. This study aimed to investigate the therapeutic effects of hWJ-MSCs in the DNFB-induced mouse model of AD. We measured whether hWJ-MSCs can alleviate the immune response and improve the function of the skin barrier. The potential mechanism of action of hWJ-MSCs in DNFB-induced mice was also explored.

METHODS

Isolation, characterization, and quality of hWJ-MSCs

The study was approved by the Ethics Review Board of Yichun University (Approval No.2023038) before any tissue collection. Human umbilical cord tissues were obtained from voluntarily donated samples by healthy post-natal females. The volunteers signed an informed consent form and received a maternal health check. The isolation and expansion were conducted based on the in-house standard operating procedure (SOP) in Jiangxi Baiming Medical Health Technology Co., Ltd (Yichun, Jiangxi, China). Briefly, the umbilical cord tissue was cut and opened under sterile conditions. The umbilical cord was washed with saline, and the umbilical vein and artery were removed. Wharton's jelly was minced into a small size and resuspended in a serum-free medium (Yocon MSC serum-free medium, YOCON Biotech Company) specially formulated for the growth and expansion in a 5% CO_2 incubator at 37 °C. hWJ-MSCs were detected based on their cell surface markers at passage 3. The cell-surface markers of hWJ-MSCs cells are expressed as positive markers (CD73, CD90, and CD105) and negative markers (HLA-DR, CD34, and CD45). The primary antibodies CD73, CD90, CD105, CD45, CD34, and HLA-DR were purchased from BD Biosciences. These markers were detected using a flow cytometer (Beckman Coulter). Briefly, when the cells reached 60-80% confluence, the cells were trypsinized. 100 µL cell suspension (2 x 10^5) cells were incubated in the dark for 15 min at room temperature with CD73 antibody-conjugated to FITC, CD34 antibody-conjugated to FITC, PE-conjugated anti-CD90, PE-conjugated anti-CD45, APC-conjugated anti-CD105, and APC-conjugated anti-HLA-DR antibodies. Cells were identified by light scatter for 10000 gated events, and the markers were analyzed. The data were evaluated using a Cytomics FC500 flow cytometer (Beckman Coulter) and Kaluza Software (version 1.3; Beckman Coulter).

Induction of AD in ICR mice and treatment with hWJ-MSCs

Seven-week-old male Institute of Cancer Research (ICR) mice were purchased from Changsha Tianqin Biotechnology Co., Ltd (Changsha, Hunan, China). All procedures adhered to the guidelines of the Animal Care and Ethics Committee of Yichun University (Approval No.2024038). This study accepted standards for animal research, following the 3Rs principle and was conducted according to the guidelines of the Animal Care. DNFB was purchased from Aladdin Biochemical Technology Co., Ltd (Shanghai, China). DNFB was dissolved in acetone/olive at a 3:1 ratio. 0.15% of DNFB sensitization was applied to the outer and the inner surfaces of the right ears on days 1, 4, and 7. The same solution was applied to the shared dorsal skin on the same day. The mice were treated with hWJ-MSCs at passage 3 for the study. The sensitization mice were challenged by 0.2% DNFB, which was rubbed on the dorsal skin and ears on

days 10 and 13. The mice were randomly divided into four groups: (1) control (n = 12); (2) DNFB (n = 12) (3) DNFB-MSC 7 (n = 6) (4) DNFB-MSC 7,16 (n = 6). 1 x 10^6 cells were injected into the subcutaneous tissue around the dorsal skin in the DNFB-MSC 7 and DNFB-MSC 7,16 groups on days 7 and 16. Mice in the DNFB-MSC 7 group were sacrificed on the 10th day, and mice in the DNFB-MSC 7,16 group were sacrificed on the 19th day. Mice were euthanized via cervical dislocation. The spleen, inguinal, and dorsal skin were harvested. During the experiment, the mouse skin parameters and ear thickness were recorded.

Skin score

The skin score was determined based on the scoring system once a week according to the previous method [20]. Briefly, the symptoms such as lichenification, Itching/ dryness, erosion, edema, and erythema/hemorrhage were scored 0 (none), 1 (mild), 2 (moderate), and 3 (severe). The severity of AD was determined based on the sum of individuals' scores (maximum score: 15).

Measurement of serum IgE

After sacrificing the mice, their serum samples were obtained by centrifugation at 1000 x g for 15 minutes. The serum level of IgE was determined using an ELISA kit (Ruixin Biotech). Briefly, serial dilutions of standard IgE and diluted serum samples were added to the wells following the protocol. Finally, the absorbance was measured by a microplate reader at a wavelength of 405 nm. The levels of serum IgE were determined by the standard curve.

Histopathological analysis

The skin and ear were harvested, fixed in formalin, and embedded in paraffin. The section was 4-μm-thick slices. The sections were stained with hematoxylin and eosin (H&E) staining. The images were captured using a 10 (eyepiece lens) x 20 (objective lens) inverted microscope (Nikon TIDH) and analyzed with NIS Elements software (version 4.30, Nikon).

Western blotting

Skin samples were extracted by using T-PER (Thermo Fisher Scientific, Inc.) containing protease inhibitors. The skin samples were boiled with sample buffer (100 mM Triss, pH6.8,20% glycerol,4% SDS,) at a ratio of 4:1 for 5 minutes. Equal amounts (20 μg) of protein per lane were electrophoresed using 10% or 12% SDS-PAGE at 100V for 90 minutes. After running, the gels were transferred to PVDF membrane at 100V for 90 minutes. The PVDF membranes were blocked with TBST (Tris-Buffered Saline with Tween-20), 5% skimmed milk at room temperature for 1 hour. The membranes were incubated overnight at 4°C with primary antibodies (1:1000). Then, the membranes were washed three times with TBST. After adding secondary antibodies (1:1000) at room temperature for 1 hour, the membranes were washed three times with TBST. Primary antibodies against HDAC3, NLRP3, thioredoxin-interacting protein (TXNIP), caspase-1, apoptosis-associated speck-like protein containing a CARD (ASC)/ target of methylation-mediated silencing (TMS1), glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and secondary antibodies, anti-rabbit IgG HRP-linked antibody and anti-mouse IgG HRP-linked antibody were purchased from Beyotime Biotechnology (China). Primary antibody against TGF-β1 was purchased from Abways Technology (China). Finally, chemiluminescence was detected using an ultra-sensitive ECL kit (Biosharp). The bands were detected using a ChemiScope 3300 Mini (Clinx Science Instruments Co., Ltd.). GAPDH was used as a housekeeping protein for Western blotting. Densitometry analysis was conducted using ImageJ 1.52a software (National Institutes of Health, USA).

Statistical analysis

All data are expressed as mean ± standard error (SE). Differences among groups were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. Statistical significance was set at $p<0.05$.

RESULTS

hWJ-MSCs alleviated AD

In this study, we detected a high expression level (> 95%) of CD90, CD105 and CD73 and a low expression level (< 2%) of CD45, CD34, and HLA-DR in hWJ-MSCs. The results showed the characteristics of MSCs (Figure 1). To determine whether hWJ-MSCs mitigated DNFB-induced AD skin lesions, the mice received hWJ-MSCs subcutaneously on days 7 and 16. The symptoms of AD and treatments are presented in Figure 2A, 2B. Treatments with hWJ-MSCs alleviated the symptoms, including erythema, dryness, and scarring. The clinical score and ear thickness were increased in the DNFB-induced groups, but decreased in the DNFB-MSC 7 and DNFB-MSC 7,16 treatment groups (Figure 3A, 3B).

hWJ-MSCs reduced the serum levels of IgE

Elevated serum level of IgE is an important hallmark of AD. The results showed that the serum levels of IgE in the DNFB group were higher than those in the control group on days 10 and 19 (Figure 3C). The serum levels of IgE in the DNFB-MSC 7,16 were significantly reduced after 19 days.

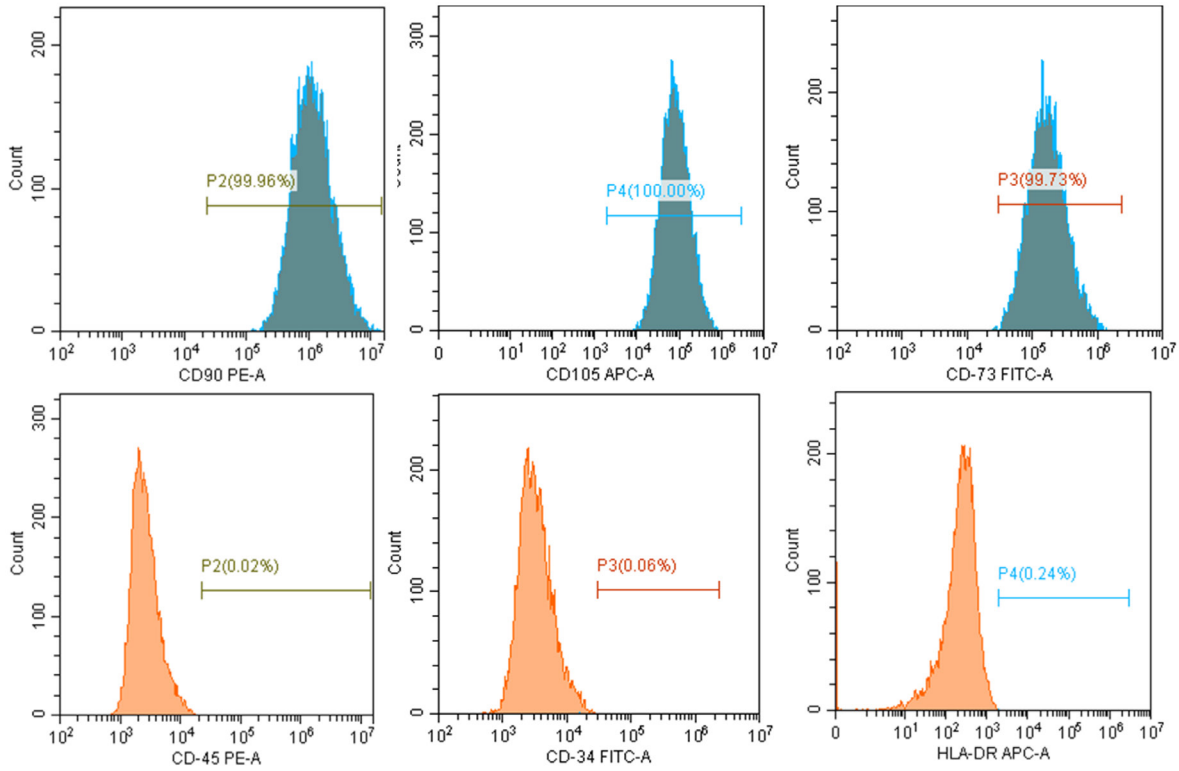

Figure 1. Identification and characteristics of hWJ-MSCs

The flow cytometry histogram analysis of CD90, CD105, CD73, CD45, CD34, and HLA-DR in hWJ-MSCs.

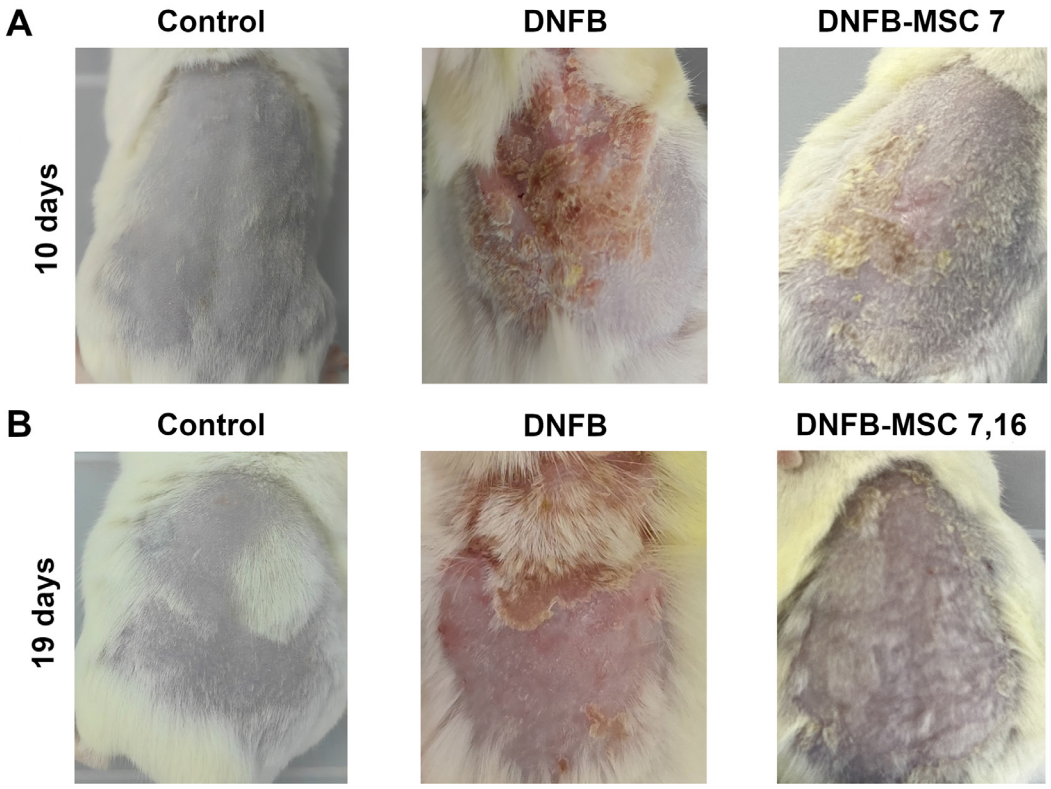

Figure 2. Effects of hWJ-MSCs on AD-like lesions induced by DNFB in mice

The mice were sensitized with 0.15% DNFB on day 1, 4 and 7. The mice were challenged with 0.2% DNFB on day 10 and 13. (A) DNFB-induced mice were treated with hWJ-MSCs on day 7 (DNFB-MSC 7 group) and sacrificed on day10. (B) DNFB-induced mice were treated with MSC on day 7, 16 (DNFB-MSC 7, 16 group) and sacrificed on day19. Representative images of mice were captured.

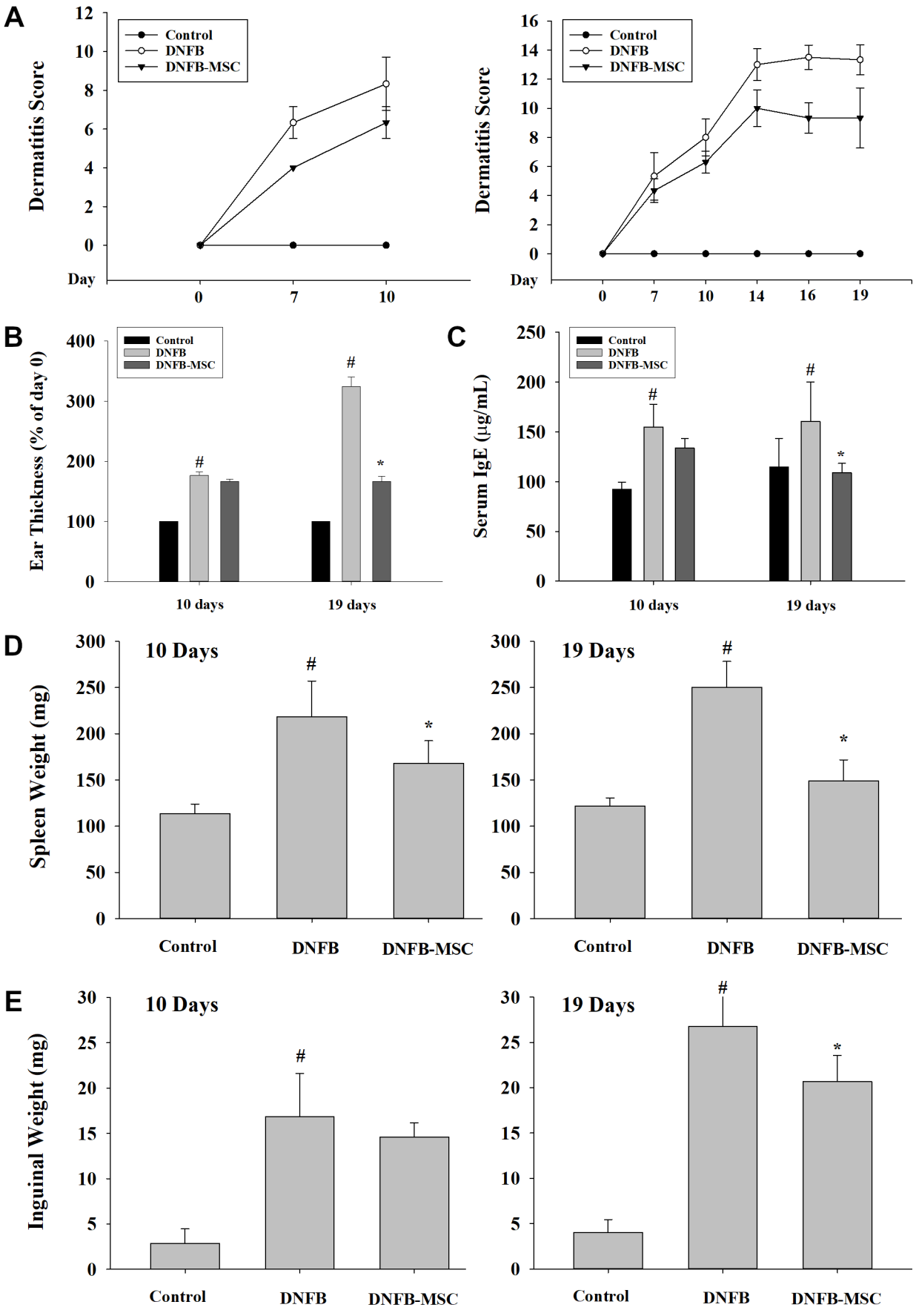

Figure 3. Effects of hWJ-MSCs on AD-like lesions induced by DNFB in mice

(A) The severity of dermatitis score; (B) Ear thickness; (C) IgE levels; (D-E) Spleen and lymph nodes weight. Data are presented as mean ± SE. (#p<0.05 compared with the control, *p<0.05 compared with the DNFB group).

hWJ-MSCs ameliorated histological changes, spleen, and lymph nodes weight

The spleen and lymph nodes are secondary lymphoid organs that play key roles in the body's immune defense by filtering fluids and facilitating interactions between antigens and immune cells.

The results from this study showed that the weight of the spleen and lymph nodes was increased in DNFB-induced AD mice but decreased after treatment with hWJ-MSCs (Figure 3D, 3E). Compared to the DNFB-induced mice groups, the weight of lymph nodes was also reduced after treatment with hWJ-MSCs (Figure 3E). H&E staining showed that the skin thickness of the epidermis was enhanced in DNFB-induced AD mice compared to the control group, but the effect was reversed in the DNFB-MSC 7 and DNFB-MSC 7,16 groups (Figure 4A, 4B). Similar histological results were observed in the ear. Compared to the normal group, the thickness of the ear epidermis was increased in the DNFB-induced group. Treatments with hWJ-MSCs relieved the symptoms on days 10 and 19.

hWJ-MSCs regulated the expression of TGF-β1, TXNIP/NLRP3, and HDAC3

The expressions of NLRP3 inflammasome, TGF-β and HDAC3 were determined in the dorsal skin tissue of mice in order to explore the molecular effects of hWJ-MSCs on atopic dermatitis.

The relative expressions of proteins were measured for NLRP3, ASC/TMS1, TXNIP, and caspase-1 (Figure 5A, 5B). It was found that the expression levels of these proteins were increased in the DNFB group, while decreased in the DNFB-MSC 7 and DNFB-MSC 7,16 groups (Figure 5A, 5B). Furthermore, we found that TGF-β1 and HDAC3 proteins were upregulated in the DNFB group (Figure 5A, 5B).

On day 10, the protein expression of TGF-β1 was higher in the DNFB-MSC 7 group than in the DNFB group (Figure 5A, 5B). On the contrary, on day 19, the protein expression of TGF-β1 was lower in the DNFB-MSC 7,16 group than in the DNFB group (Figure 5A, 5B). The protein expression of HDAC3 showed a similar pattern to that of TGF-β1.

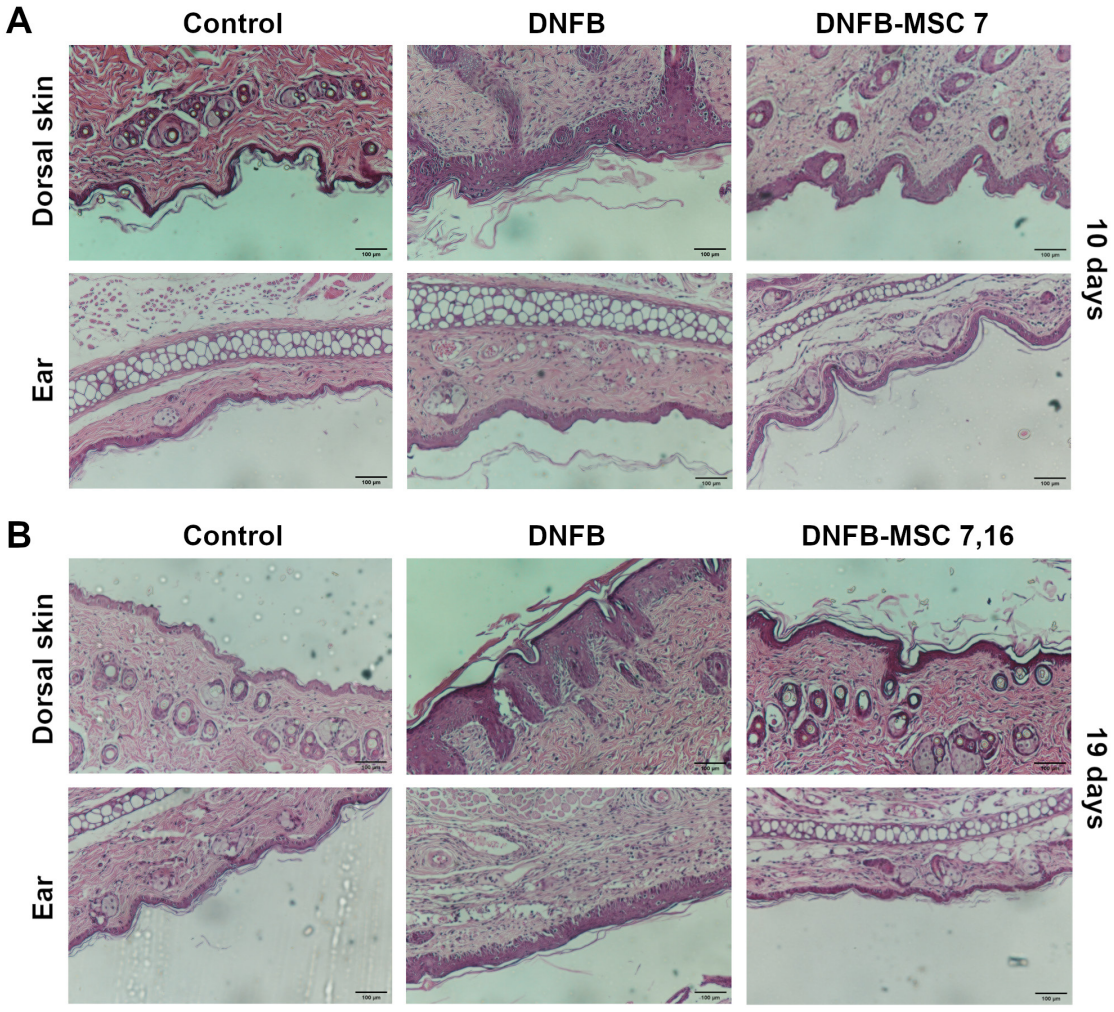

Figure 4. Histological analysis of DNFB-induced dorsal skin and ear after treatment with hWJ-MSCs in mice
Results were visualized by H&E staining (magnification, x200; scale bar = 100 μm).

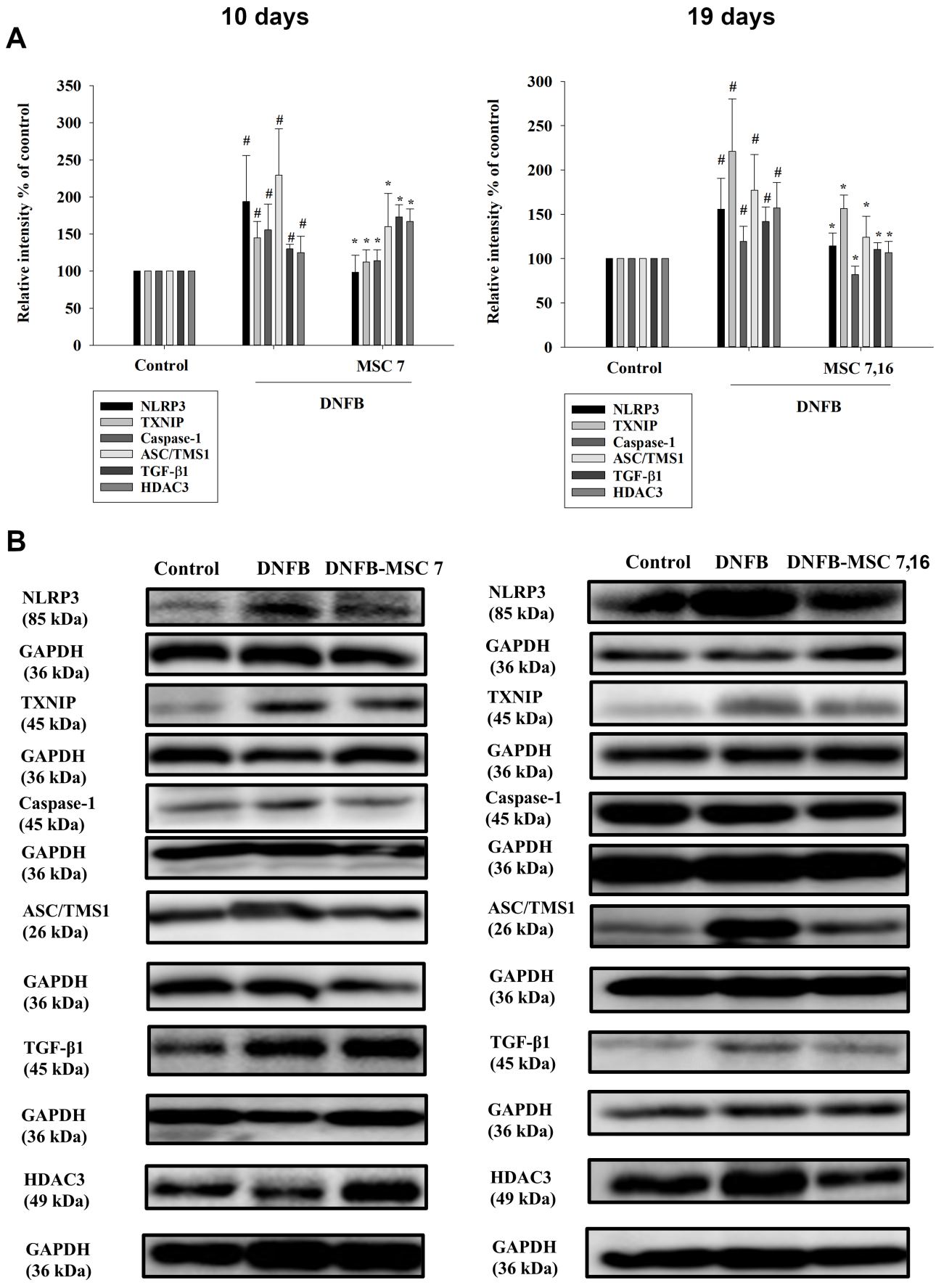

Figure 5. hWJ-MSCs inhibited NLRP3 formation and HDAC3/ TGF-β1 signaling pathway

(A) The relative protein expression of NLRP3, TXNIP, ASC/TMS1, caspase-1, HDAC3 and TGF-β1 were determined via Western blotting; (B) Western blotting of protein expression. Data are presented as mean ± SE. (#p<0.05 compared with the control, *p<0.05 compared with the DNFB group).

DISCUSSION

Atopic dermatitis is a chronic immune response of the skin accompanied by impaired function of the skin barrier. In the current study, we used DNFB to induce AD following previous studies [6, 7, 21]. Studies have shown that human umbilical cord blood-, tonsil-, and adipose tissue-derived MSCs can alleviate AD. Treatment intervals were different in these studies [21-23]. The molecular mechanisms by which hWJ-MSCs treat AD remain unclear.

The clinical symptoms of AD, such as erythema, dryness, and scarring, were observed in DNFB-treated dorsal mouse skin in this study. Increased thickness of the epidermis was also observed on the dorsal skin of DNFB-treated mice. Mast cells can secrete histamine, cytokines, and chemokines. Mast cells regulate the differentiation of T cells and the synthesis of IgE by B cells. IgE plays a critical role in immediate hypersensitivity reactions [24]. High levels of IgE regulate acute and chronic phase skin symptoms of AD. Our study demonstrated that IgE levels increased in the DNFB group on the 10th and 19th days. High IgE levels are associated with the severity of AD. IgE levels were decreased after repeated injections. hWJ-MSCs regulated the immune response in lesional atopic dermatitis skin by decreasing IgE levels. In the current study, hWJ-MSCs alleviated the symptoms of AD via their immunomodulatory activities. Therefore, repeat doses of hWJ-MSCs may be beneficial for the treatment of AD.

TGF-β is a cytokine involved in tissue fibrosis, immune response, and tissue scarring. TGF-β1 can regulate T cell differentiation and B cell function. Studies have shown that TGF-β1 induces the inflammatory response in different diseases, such as allergic diseases, including AD [25, 26]. The mRNA and protein expression levels of TGF-β1 in the skin were higher in patients with AD than in normal controls [25]. TGF-β is a vital immunomodulatory factor secreted by hWJ-MSCs. Several studies have reported that TGF-β release by MSCs can alleviate AD [21, 27]. Subcutaneous injection of recombinant TGF-β1 significantly inhibited inflammation in the skin lesions of AD in NC/Nga mice [28]. These findings suggest that TGF-β production can alleviate the severity of AD. However, a study reported that TGF-β type 1 receptor inhibitor attenuated symptoms by downregulating the TGF-β1 signaling pathway in DNCB-induced AD mice [29]. In our study, the protein expression of TGF-β1 was upregulated on the 10th day but downregulated on the 19th day after treatments. The different number of stem cells, injection route, treatment interval or the source of stem cells might affect the TGF-β1 expression in the treatment of AD. We believe that TGF-β1 is an important immunomodulatory downstream effector of hWJ-MSCs in the treatment of atopic dermatitis.

Studies have reported that TXNIP induced NLRP3 inflammasome activation in diabetic nephropathy and high glucose–treated human lens epithelial cells [30, 31]. NLRP3 inflammasome includes the adapter molecular ASC, which regulates the recruitment of procaspase-1. Activation of the NLRP3 inflammasome can induce the secretion of mature IL-1β, upregulating TGF-β expression [32, 33]. In this study, activation of the TXNIP/NLRP3 inflammasome was accompanied by TGF-β induction. hWJ-MSCs treatment modulated TGF-β induction and then decreased TXNIP/NLRP3 inflammasome production in the treatment of AD mice.

HDACs are involved in many diseases, including fibrosis, cancer development, and inflammatory conditions. HDAC3 inhibitor has a promising effect by inhibiting NLRP3 expression in lipopolysaccharide-induced and high-fat diet-induced inflammation [34]. A previous study demonstrated that HDAC3 is upregulated in AD [15]. Consistently, an HDAC3 inhibitor, RGFP966, prevented DNCB-induced AD [15]. Astragaloside I is a bioactive compound extracted from Astragalus. It can attenuate diabetic kidney fibrosis by regulating the HDAC3/Klotho/TGF-β1/Smad2/3 pathway [35]. Based on the previous findings, we think that HDAC3 and TGF-β1 can upregulate NLRP3 expression in inflammatory diseases. In this study, the protein expression of HDAC3 and NLRP3 was increased in DNFB-treated mice. The treatment with hWJ-MSCs inhibited HDAC3 expression on day 19, but the HDAC3 expression was increased on day 10. hWJ-MSCs can decrease NLRP3 expression by regulating the HDAC3/ TGF-β1 signaling pathway in the treatment of AD.

CONCLUSIONS

AD is a chronic disease, and current treatments reduce inflammation, itching, and improve the skin barrier. The inflammation, immunological aberrations, and skin barrier disorder were observed in the DNFB-induced mice model of AD. The subcutaneous injection of hWJ-MSCs alleviated the inflammation and repaired the skin barrier. hWJ-MSCs displayed regenerative and immunomodulatory capacities. Moreover, treatment with hWJ-MSCs can attenuate the inflammation and immune response in lesional atopic dermatitis skin by regulating TXNIP/NLRP3 and HDAC3/TGF-β1 signaling pathways. In the future, more clinical studies are needed to evaluate the safety and efficiency of hWJ-MSCs in the treatment of AD.

ABBREVIATIONS

AD – atopic dermatitis
ANOVA – analysis of variance
ASC – apoptosis-associated speck-like protein containing a CARD
DNFB – 2,4-dinitrofluorobenzene
ELISA – enzyme-linked immunosorbent assay
H&E – hematoxylin and eosin
HDAC3 – histone deacetylase 3
hWJ-MSCs – human Wharton's jelly mesenchymal stem cells
ICR – Institute of Cancer Research
IgE – immunoglobulin E
IL-1β – interleukin-1 Beta
IL-4 – interleukin-4
IL-13 – interleukin-13
MSCs – mesenchymal stem cells
NLRP3 – NOD-like receptor family pyrin domain containing 3
Nrf2 – nuclear factor erythroid 2-related factor 2
PVDF – polyvinylidene fluoride
SE – standard error
TBST – Tris buffered saline with Tween
TGF-β1 – transforming growth factor beta 1
Th1 – T-helper 1
Th2 – T-helper 2
TMS1 – target of methylation-induced silencing
TXNIP – thioredoxin-interacting protein

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AUTHORS' CONTRIBUTION

ZPW: conceptualization, investigation, writing (original draft preparation)
JYC: validation, visualization, investigation
NL: conceptualization, methodology, resources
DH: investigation
HL: validation, visualization
XWM: investigation, validation
SYC: formal analysis, data curation
MYL: investigation, validation
PZ: investigation, data curation
C-ML: conceptualization, writing (review and editing), project administration, funding acquisition, supervision.

CONFLICT OF INTEREST

Author Ning Li was employed by Jiangxi Baiming Medical Health Technology Co., Ltd (Jiangxi Province, China), which also provided funding for this research. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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