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*Original Research*

# hAD-MSCs Ameliorated Psoriasis-Like Skin Inflammation by Inhibiting the Neutrophil Migration

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**Abstract**

**Background**: Psoriasis is a chronic inflammatory skin disease driven by an abnormal immune response. Mesenchymal stem cells have strong immunomodulatory properties. Therefore, we investigated the therapeutic effects and underlying mechanisms of human adipose-derived mesenchymal stem cells (hAD-MSCs) in a psoriasis-like mouse model. **Methods**: A psoriasis-like mouse model was established and hAD-MSCs were administered via subcutaneous injection. Skin thickness was evaluated using hematoxylin and eosin (H&E) staining, and disease severity was assessed using the Psoriasis Area Severity Index (PASI). Neutrophil counts and Signal Transducer and Activator of Transcription 3 (STAT3) positive keratinocytes in the skin were evaluated by immunohistochemistry (IHC). Additionally, we evaluated the cytokine expression by quantitative PCR (q-PCR). **Results**: hAD-MSCs significantly attenuated psoriasis-like skin inflammation. Neutrophil infiltration was markedly reduced in psoriatic lesions following hAD-MSC treatment. We found that hAD-MSCs inhibit neutrophil recruitment by lowering CXCL1 levels in the skin, which may be linked to reduced phosphorylation of STAT3. **Conclusions**: Our findings highlight the potential of hAD-MSCs as a potent therapeutic strategy for inhibiting neutrophil recruitment and ameliorating psoriasis-like inflammation.

**Keywords:** psoriasis; MSCs; neutrophil; CXCL1; STAT3

## 1. Introduction

Psoriasis is a chronic inflammatory disease involving the immune system, and is often associated with comorbidities such as psoriatic arthritis, metabolic syndrome, non-alcoholic fatty liver disease, cardiovascular disease, and Crohn's disease [1,2]. While the exact mechanisms underlying psoriasis are not fully understood, extensive research suggests that activated Th1, Th17, and Th22 cells contribute to disease development by producing elevated levels of cytokines, including TNF-$\alpha$, IFN-$\gamma$, IL-6, IL-17, and IL-22 in the skin [3]. Recently, there has been increasing interest in the role of neutrophils in this context.

Traditionally, neutrophils were recognized as a crucial component of innate immunity [4]. However, recent studies have highlighted their involvement in the pathogenesis of a variety of diseases, including infections, cancer, inflammation, and autoimmune disorders [4,5]. One study even noted that the symptoms of psoriasis improved during agranulocytosis but relapsed once neutrophil levels were restored [6,7]. This finding suggests that neutrophils might actively contribute to the progression of psoriasis, making them a potential target for treatment.

Mesenchymal stem cells (MSCs), which are multipotent progenitor cells, possess potent immunosuppressive and anti-inflammatory effects. They exert these effects either through cell-cell contacts or by secreting soluble factors [8]. MSCs can be isolated from various tissues, including bone marrow, umbilical cord blood, adipose tissue, the placenta, and synovia.

Human adipose-derived MSCs (hAD-MSCs) are particularly abundant in adipose tissue and relatively easy to obtain [9]. Moreover, hAD-MSCs exhibit regenerative and immunosuppressive propertie [10]. As a result, they are considered favorable candidates for clinical applications. Our findings demonstrated that infusion of hAD-MSCs reduced both the development and severity of psoriasis in psoriatic mice [11]. Neutrophils are important innate immune cells that promote the progression of inflammation by releasing inflammatory mediators [12]. CXCL1 is a primary neutrophil chemokine, mainly secreted by keratinocytes [13]. It is highly expressed in psoriatic skin and is regulated by the Signal Transducer and Activator of Transcription 3 (STAT3) signaling pathway [13,14]. However, the regulatory effects and underlying mechanisms of MSCs on

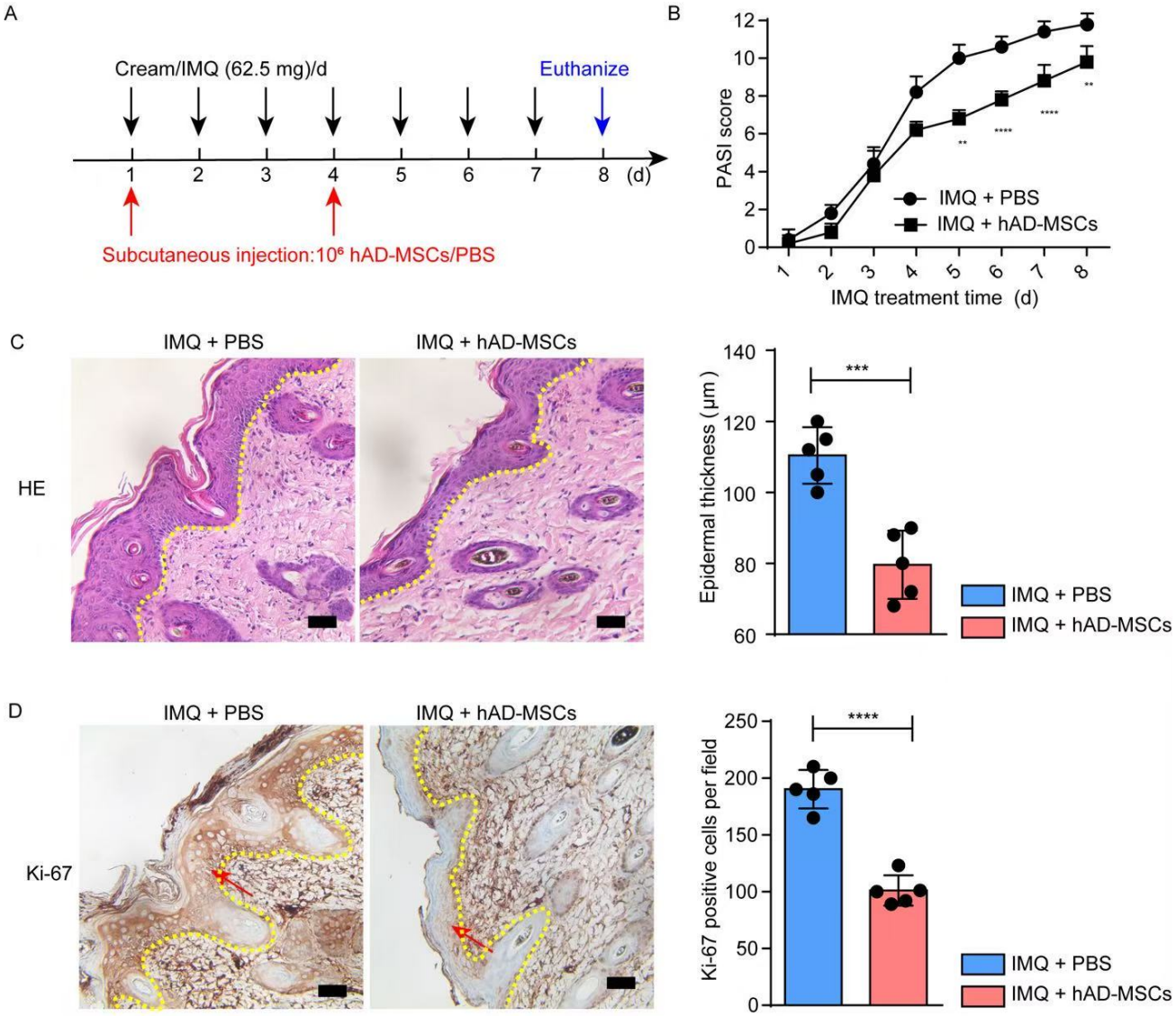


**Fig. 1. hAD-MSCs alleviated the inflammation of psoriatic mice.** (A) The setting of the experiment, Time axis represents experimental days. (B) The PASI scores in the hAD-MSC treated and PBS treated groups. (C,D) H&E staining and IHC of Ki-67 in the hAD-MSC treated and PBS treated groups. The red arrow points to the Ki-67 positive cells. The Data was collected on day eight. Scale bars: 50 μm. Data were shown as means ± SEM. The statistical significance was assessed by two-way ANOVA for (B), and they were assessed by Student's *t* test for the two-group comparison in (C,D). $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$. hAD-MSCs, human adipose-derived mesenchymal stem cells; PASI, Psoriasis Area Severity Index; H&E, hematoxylin and eosin; IHC, immunohistochemistry; PBS, phosphate-buffered saline.

neutrophils in psoriasis remain unclear. In this study, we observed that hAD-MSCs improved psoriasis by decreasing the expression of CXCL1 and inhibiting neutrophil infiltration, which may be linked to reduced levels of STAT3 phosphorylation.

## 2. Materials and Methods

### *2.1 Patients and Specimens*

All specimens were collected from The First Affiliated Hospital of Soochow University. The study included six men and ten women, with ages ranging from 30 to 66 years, with a mean age of 48 years. These participants had no other systemic diseases or prior treatment and sought care at the Department of Dermatology. All participants provided informed consent, and tissue procurement was in accordance with institutional guidelines. The study was carried out in accordance with the guidelines of the Declaration of Helsinki.

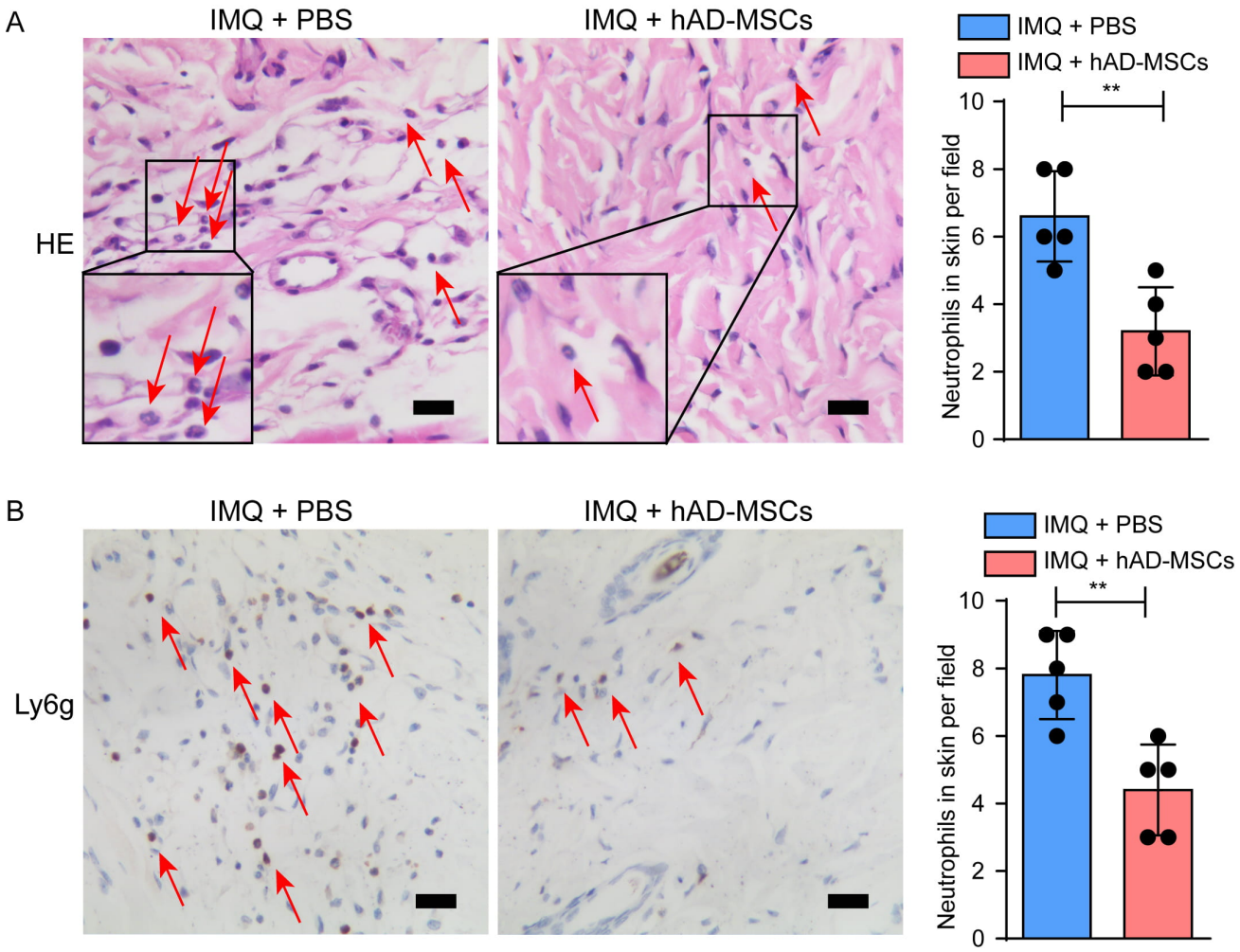


**Fig. 2. Neutrophils were decreased with the hAD-MSC treatment.** (A) H&E staining of the skin in the hAD-MSC and PBS treatment groups. The red arrow points to the neutrophils. (B) IHC staining of Ly6g in the skin in the hAD-MSC and PBS treatment groups. The red arrow points to Ly6g positive cells. The statistical significance was assessed by Student's *t*-test for the two-group comparison in (A,B). Scale bars: 50 µm. Data were shown as means ± SEM, $^{**}p < 0.01$.

*2.2 hAD-MSCs Isolation*

All procedures in this study were conducted in accordance with the ethical standards of the Ethics Committee of the First Affiliated Hospital of Soochow University (20220238). Human adipose tissue was collected from healthy volunteers undergoing liposuction. The lipoaspirates were stored in sterile phosphate-buffered saline (PBS). Samples were treated with 1 mg/mL collagenase-I for about 120 minutes at 37 °C. After digestion, adipocytes were separated by centrifugation at 1000 rpm for 5 minutes. The cells were then resuspended in DMEM supplemented with 10% FBS, 10 ng/mL bFGF, and 100 U/mL penicillin/streptomycin, and cultured in a humidified incubator at 37 °C with 5% $CO_2$. The cells were validated for their identity by surface marker analysis using flow cytometry and tested negative for mycoplasma.

*2.3 Animals and the Psoriasis Mouse Model*

C57BL/6 mice were purchased from Shanghai SLAC Laboratory Animal Co., Ltd. (Shanghai, China). The mice were kept in a specific pathogen-free environment. Animals were cared for in accordance with the Guide for the Care and Use of Laboratory Animals. The experimental procedures were approved by the ethical clearance by Suzhou Municipal Hospital (K-2024-026-K01). To induce psoriasis-like symptoms, the mice were administered 62.5 mg of IMQ cream (Aldara, 3M Pharmaceuticals, MN, USA) daily for a consecutive period of 7 days (n = 5 mice for each group). The severity of symptoms, including scaling, erythema, and thickness, was assessed and scored on a scale ranging from 0 to 4 (none 0; slight 1; moderate 2; marked 3; very marked 4), using the Psoriasis Area Severity Index (PASI) scoring system. The mice were euthanized by intraperitoneal injection of 200 µL of 0.1% pentobarbital sodium, followed by cervical dislocation.

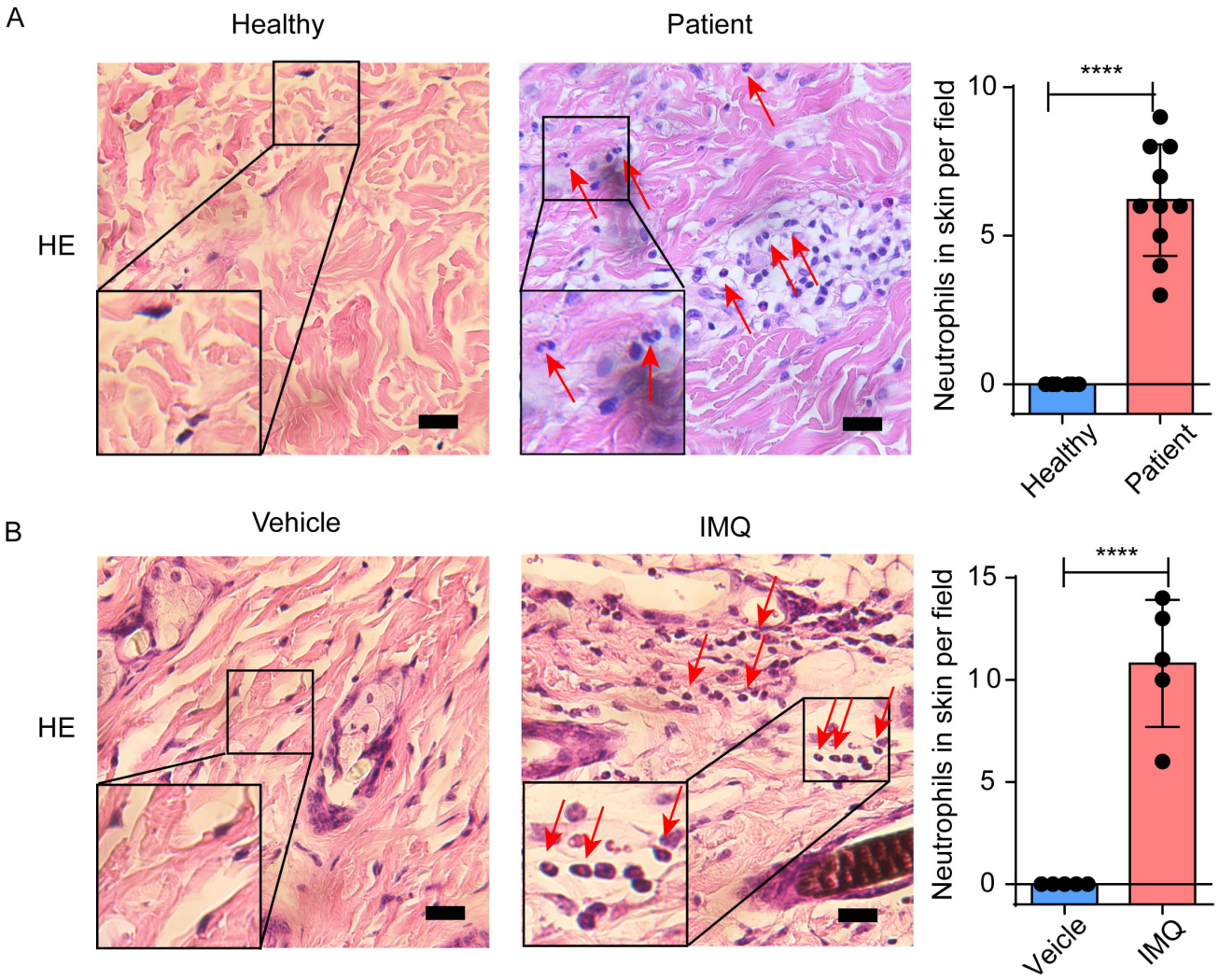


**Fig. 3. The neutrophils are infiltrated in the psoriatic lesions.** (A,B) H&E staining in the skin of the patients and the psoriatic mice. The red arrow points to the neutrophils. The statistical significance was assessed by Student's *t*-test for the two-group comparison in the Figures. Scale bars: 50 µm. Data were shown as means ± SEM, ****$p < 0.0001$.

*2.4 H&E and IHC*

For H&E staining, 3 µm-thick sections were prepared from paraffin-embedded skin tissues of psoriatic mice. These sections were subsequently stained with hematoxylin for eight minutes, followed by a 20-second eosin stain after hydration.

For IHC staining, skin sections underwent rehydration and antigen retrieval before being stained with CXCL1, Ly6g, Ki-67, and P-STAT3 antibodies (Abcam, Cambridge, United Kingdom; Cat. Nos. [ab322200], [ab238132], [ab16667], [ab76315] at a dilution 1:300). Samples were then incubated with secondary antibody (Abcam, ab150077, at a dilution 1:1000) and subsequently stained with hematoxylin.

*2.5 qPCR*

We extracted total RNA from skin tissue, followed by DNase I treatment to remove contaminating genomic DNA. The purified RNA was reverse-transcribed into complementary DNA (cDNA) using a reverse transcriptase. Quantitative PCR (qPCR) was performed on the cDNA. All reactions were run in triplicate, and no-template controls were included to assess contamination.

*2.6 Statistical Analysis*

All data are expressed as mean ± SEM. Statistical analysis was performed with GraphPad Prism 6 software (GraphPad Software, San Diego, CA, USA; Version 6). A two-tailed unpaired *t*-test for two-group comparisons. For Multiple groups, one- or two-way ANOVA with post hoc tests (Tukey's multiple comparison test) was performed. Data were normally distributed and exhibited homogeneous variances. Each experiment was repeated at least twice. $p < 0.05$ was considered statistically significant.

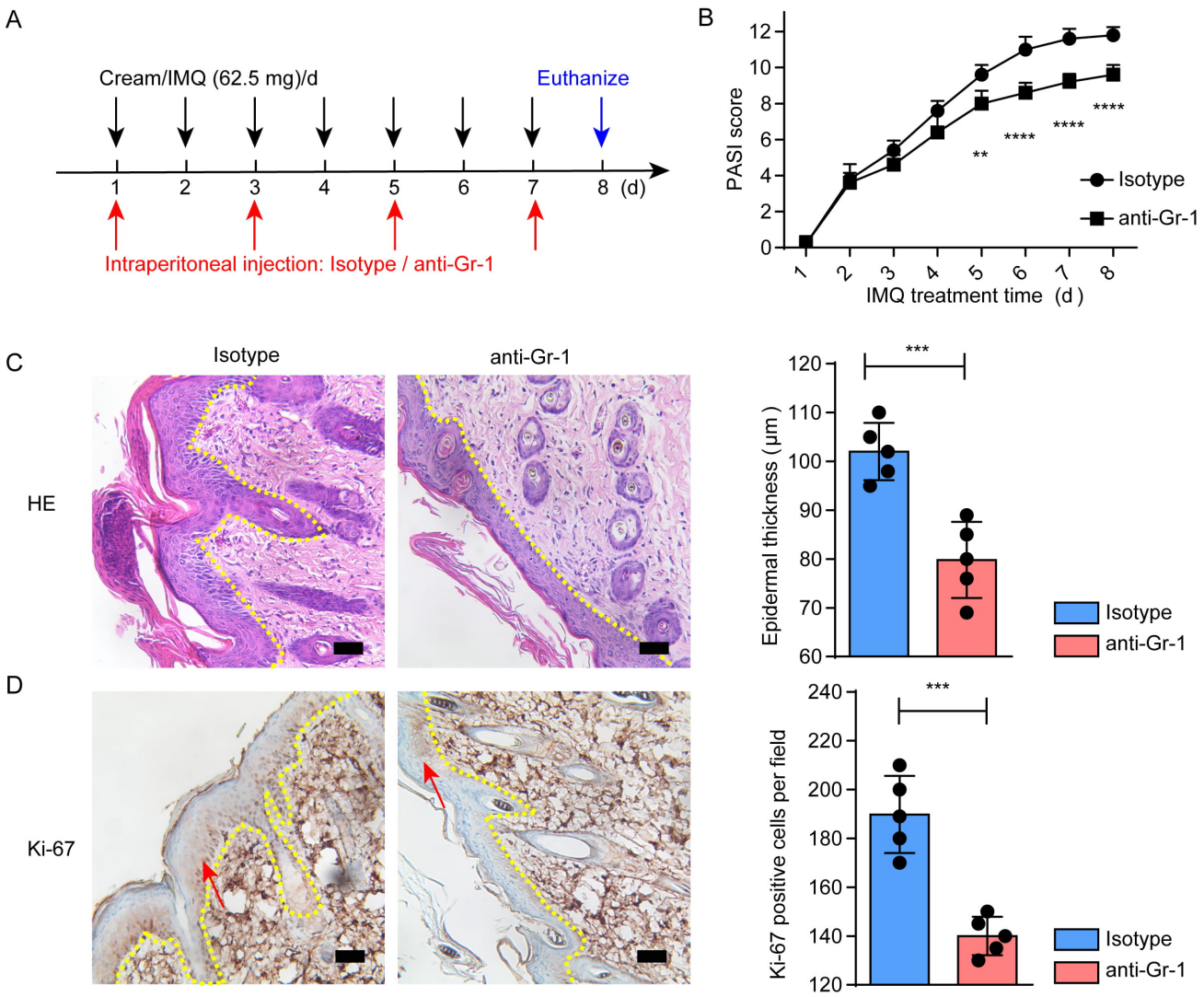


**Fig. 4. Gr-1 antibody alleviated the inflammation of psoriatic mice.** (A) The setting of the experiment. (B) The PASI scores in the anti-Gr-1 treatment group and isotype group. (C,D) H&E staining and IHC of Ki-67 in the anti-Gr-1 treatment group and isotype group. The red arrow points to the Ki-67 positive cells. The data was collected on day eight. Data were shown as means ± SEM. The statistical significance was assessed by two-way ANOVA for (B), and they were assessed by Student's *t*-test for the two-group comparison in (C,D). Scale bars: 50 μm. Data were shown as means ± SEM, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$.

## 3. Result

### *3.1 hAD-MSCs Alleviated the Psoriasis-Like Inflammation of Mice*

To examine the therapeutic efficiency of hAD-MSCs in mouse models of psoriasis, we induced psoriasis in the mouse by applying imiquimod (IMQ) for seven days. The psoriatic mice were euthanized on day eight (Fig. 1A). Treatment involved administering hAD-MSCs subcutaneously on the first and fourth days. The severity of inflammation was assessed using the Psoriasis Area and Severity Index (PASI) score. Compared to the PBS treatment group, the PASI score showed a significant decrease starting from day five (Fig. 1B). Furthermore, hematoxylin and eosin (H&E) staining revealed a reduction in epidermal thickness compared to the PBS group (see Fig. 1C). The proliferation of keratinocytes was also found to be decreased (Fig. 1D). These results indicate that the inflammation in the psoriatic mice are alleviated following treatment with hAD-MSCs.

### *3.2 hAD-MSCs Reduced the Neutrophil Accumulation in the Psoriatic Lesions*

Research indicates that hAD-MSCs have significant immune regulatory effects that could be beneficial for treating various inflammatory diseases [15,16]. We hypothesized that hAD-MSCs might alleviate the inflammation of psoriatic mice by regulating the immune cells. In our study, we observed a significant reduction in neutrophil levels, as evidenced by H&E staining, which allowed us to identify distinct lobed nucleus, pale pink cytoplasm, with their size and distribution (Fig. 2A). We confirmed this observation through IHC, which revealed that neutrophil lev-

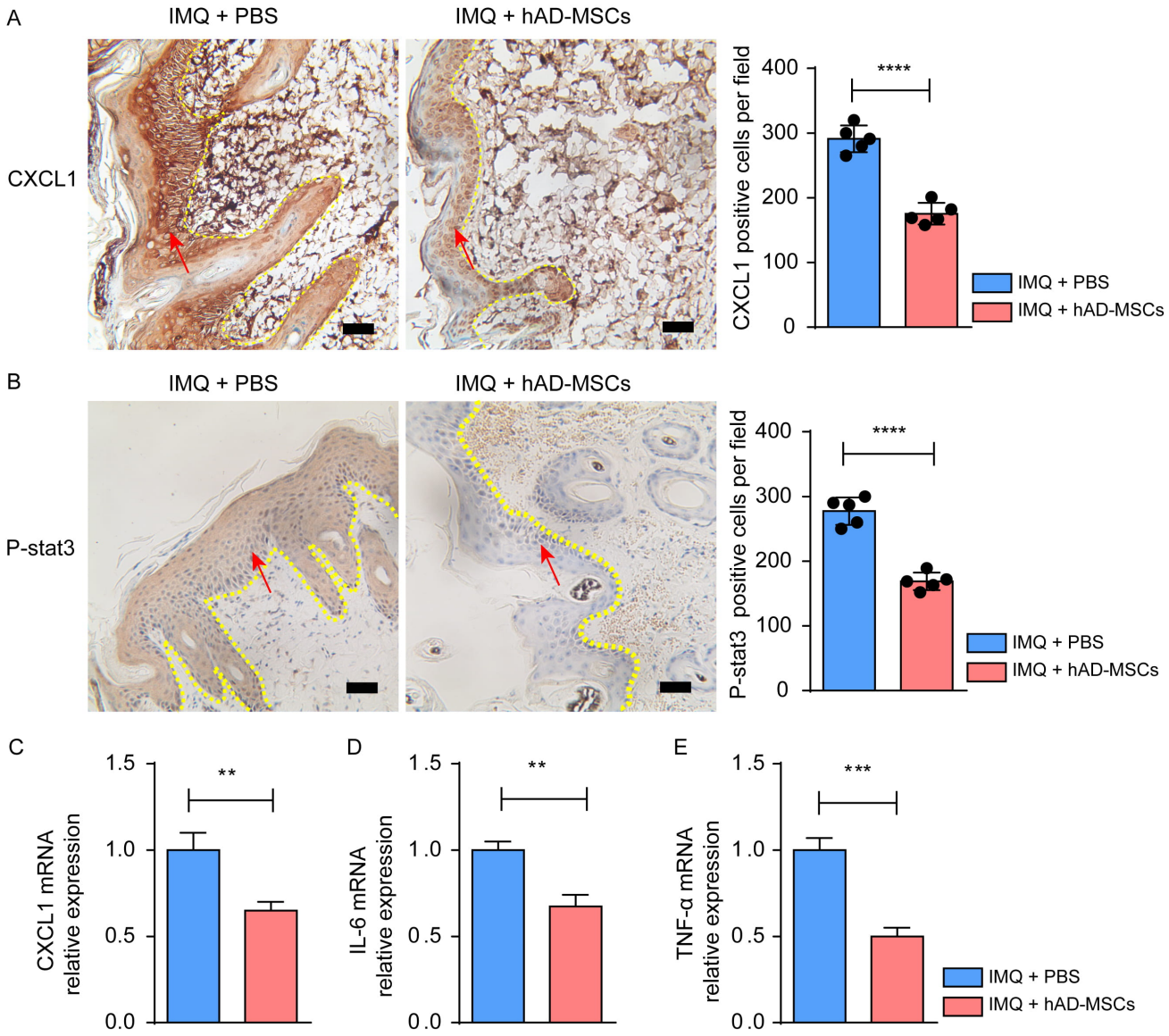


**Fig. 5. hAD-MSCs inhibited CXCL1 expression, potentially by decreasing the phosphorylation of STAT3.** (A,B) IHC staining of CXCL1 and P-STAT3 in the hAD-MSC and PBS treatment group. The red arrow points to the CXCL1 and Ki-67 positive cells. Statistical significance was assessed using Student's *t*-test for the two-group comparisons in (A,B). Scale bars: 50 µm. (C–E) mRNA of *CXCL1*, *IL-6* and *TNF-α* in the hAD-MSC and PBS treatment group. Data are presented as means ± SEM, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$.

els were dramatically decreased following hAD-MSC treatment (Fig. 2B). Together, these findings suggest that hAD-MSCs reduce inflammation by inhibiting neutrophil infiltration.

### *3.3 Neutrophils Were the Hallmark of Psoriasis*

To further investigate neutrophil levels in psoriasis patients, we obtained skin samples from affected individuals. Pathological staining showed a marked increase in neutrophils in the skin of psoriasis patients compared to healthy individuals (Fig. 3A). Additionally, we noted a significant accumulation of neutrophils in a mouse model of psoriasis (Fig. 3B). This indicates that neutrophils can infiltrate psoriatic lesions, potentially contributing to the progression of the disease.

### *3.4 Neutrophils Depletion Alleviated the Inflammation of the Psoriasis Model*

To investigate the role of neutrophils in human psoriasis, we sought to deplete the neutrophils by intraperitoneal injection with the anti-Gr-1 and construct the psoriatic mouse models (Fig. 4A). The PASI scores were decreased compared with the control group injected with the isotype antibody (Fig. 4B). The thickness was also decreased dramatically (Fig. 4C). Moreover, IHC results for Ki-67 showed that the proliferative capacity of keratinocytes had

declined after neutrophil depletion (Fig. 4D). Thus, neutrophils are the critical contributors to the psoriasis-like inflammation.

### *3.5 hAD-MSCs Inhibited the Neutrophil Infiltration by Decreasing the Expression of CXCL1*

Neutrophils in the skin primarily migrate from the blood vessels, driven mainly by the chemokine CXCL1. CXCL1 is the most important chemokine for neutrophils in the mouse model and is predominantly produced by the keratinocytes in the psoriasis mouse model. To investigate whether hAD-MSCs inhibit the neutrophil infiltration by reducing the CXCL1 expression, we used IHC to examine the expression of CXCL1. Our findings revealed that CXCL1 was reduced (Fig. 5A). Thus, hAD-MSCs inhibit the neutrophil infiltration by lowering CXCL1 levels. Previous reports indicated that CXCL1 expression is regulated by the P-STAT3 [14]. We assessed the P-STAT3 expression by IHC, and the results showed a reduction in STAT3 phosphorylation following the hAD-MSCs treatment (Fig. 5B). Additionally, *CXCL1*, *IL-6* and *TNF-*$\alpha$ in the skin were also decreased after hAD-MSC treatment, which indicated that the inflammation of the skin was alleviated after treatment (Fig. 5C–E). Therefore, hAD-MSCs is a potent therapeutic strategy for inhibiting neutrophil recruitment and ameliorating psoriasis-like inflammation, with that hAD-MSCs may inhibit the CXCL1 expression by decreasing the phosphorylation of STAT3.

## 4. Discussion

Psoriasis is an immune-mediated, recurrent, and refractory skin disease that requires lifelong treatment [17]. Currently, the primary treatment for psoriasis targets T cells, while effective methods for regulating neutrophil infiltration are limited. Our study demonstrated that hAD-MSCs have a strong potential to inhibit neutrophil infiltration and its associated chemokines, possibly mediated by the low expression of CXCL1, which may be regulated by P-STAT3. Future experiments should confirm the relationship between CXCL1 and STAT3 in psoriasis by using STAT3 inhibitors. These results suggest that hAD-MSCs could be a promising treatment option for psoriasis by inhibiting neutrophil infiltration and regulating inflammation.

Several studies have demonstrated the significant anti-inflammatory potential of hAD-MSCs [18,19]. In addition to adipose-derived mesenchymal stem cells, umbilical cord– and bone marrow–derived mesenchymal stem cells also possess strong immunomodulatory capabilities [20]. We found that hAD-MSCs effectively inhibited neutrophil infiltration in the psoriasis mouse models by decreasing CXCL1 expression. Beyond inhibiting neutrophil recruitment, hAD-MSCs can also promote neutrophil homing to the bone marrow, thus reducing their accumulation into lesion sites [21]. Therefore, hAD-MSCs offer promise as a treatment option for immune diseases primarily mediated by neutrophils. In addition to psoriasis, MSCs exert immunomodulatory effects that treat atopic dermatitis and enhance wound healing [22,23]. Moreover, mesenchymal stem cells (MSCs) exhibit enhanced immunomodulatory capacity after stimulation with inflammatory factors [24]. However, whether adipose-derived MSCs achieve stronger immunomodulatory effects to treat psoriasis following inflammatory factor stimulation requires additional experimental designs to demonstrate.

Neutrophils are the most abundant innate immune cells and can influence adaptive immune responses while participating in various autoimmune diseases [25,26]. Consistent with the previous study, we found that the neutrophil infiltration is a hallmark of psoriasis, potentially promoting disease progression through the formation of NETs, respiratory burst, and the release of granule [12]. These inflammatory mediators drive substantial keratinocyte proliferation, recruit more neutrophils, and continuously accelerate skin inflammation [12]. Moreover, in mice, the recruitment of neutrophils is primarily driven by CXCL1, which is expressed in keratinocytes and regulated by P-STAT3. Our study revealed that hAD-MSCs significantly inhibited P-STAT3 expression, suggesting a potential mechanism by which hAD-MSCs suppress CXCL1 production. However, the exact mechanism through which hAD-MSCs inhibit STAT3 phosphorylation remains to be elucidated.

## 5. Conclusion

In conclusion, our study has shown that hAD-MSCs can significantly reduce psoriasis-like inflammation by inhibiting neutrophil infiltration, which is mediated by CXCL1. Additionally, we have identified a potential link between CXCL1 and reduced STAT3 phosphorylation. These findings may have broader implications for understanding and addressing inflammation involving neutrophils in various contexts.

## Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

## Author Contributions

FS and LZ: conception and design, data analysis. PC and LC: collection and assembly of the data, data analysis and interpretation. QM: data analysis and interpretation, and manuscript writing. JJ: conception and design and final approval of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Ethical approval for all procedures involved in this study was obtained prior to initiation. Specifically, the human research segment received ethical review and approval from The First Affiliated Hospital of Soochow University, with the assigned ethics approval number 20220238. All participants provided informed consent, and tissue procurement was in accordance with institutional guidelines. The study was carried out in accordance with the guidelines of the Declaration of Helsinki. Meanwhile, the animal experimental component was granted ethical clearance by Suzhou Municipal Hospital, corresponding to the ethics approval number K-2024-026-K01. Animals were cared for in accordance with the Guide for the Care and Use of Laboratory Animals.


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## Conflict of Interest

The authors declare no conflict of interest.

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