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DUSP1/MKP-1 regulates proliferation and apoptosis in keratinocytes through the ERK/Elk-1/Egr-1 signaling pathway

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ABSTRACT

Psoriasis is an inflammatory skin disease with preference for the skin and joints that occurs due to hyper-proliferation and abnormal apoptosis of keratinocytes. DUSP1 expression in dermal mesenchymal stem cells (MSCs) is obviously lower in psoriasis patients than that in healthy individuals. The present study aimed to explore the roles of DUSP1 in the proliferation and apoptosis of HaCaT cells treated with a cocktail of M5. We showed that DUSP1 was markedly reduced in psoriasis patients and M5-treated HaCaT cells compared with the control subjects. MTT and BrdU assays revealed that overexpression of DUSP1 significantly suppressed the proliferation of HaCaT cells. Furthermore, DUSP1 decreased M5-induced the upregulation of cyclin D1 and Rb. In addition, we demonstrated that forced overexpression of DUSP1 caused an augment of cell apoptosis rate, c-caspase 3 protein level and the Bax/Bcl-2 ratio. Finally, we determined that enhancing DUSP1 expression resulted in the reduction of p-ERK, p-Elk-1 and Egr-1 protein levels using western blot, and the Chromatin immunoprecipitation (ChIP) assay displayed that p-Elk-1 binds to the promoter of Egr-1 in HaCaT cells. The roles of DUSP1 in cell proliferation and apoptosis were abolished by overexpression of Egr-1. In summary, gain function of DUSP1 regulates proliferation and apoptosis of HaCaT cells through the ERK/Elk-1/Egr-1 signaling pathway.

1. Introduction

Psoriasis is an inflammatory skin disease with characteristic skin lesions that usually located on the umbilicus, elbows, scalp and knees [9,22]. It is common in American, Canadian, and European, and threats to the health of 125 million people globally [12]. At present, the treatments of psoriasis mainly includes drug treatment, physical therapy, biological therapy, which is aimed at alleviating symptoms and skin lesions, avoiding repetition, and improving the quality of life of patients [29]. The pathogenesis of psoriasis is related to multiple factors such as heredity, immunity and metabolism after a large number of studies, HLA genetic susceptibility, T cell abnormal activation and differentiation, streptococcal infection, abnormal cell proliferation and lack of apoptosis in keratinocytes are central events in the pathophysiology of psoriasis [23,27].

Psoriasis usually shows erythematous plaques with adherent silvery scales, which is resulted from hyper-proliferation of keratinocytes and infiltration of inflammatory cells [34]. Presently, it is generally believed that keratinocytes plays a key role in the pathogenesis of psoriasis. It is imbalance between apoptosis and proliferation of keratinocytes because lesions of keratinocytes have stronger anti-apoptotic ability [26]. Thus, it is a pathogenic driver of aberrant keratinocyte biology. Keratinocytes apoptosis contributes to elimination of plaque and psoriasis during routine treatment [35].

Dual-specificity phosphatase-1 (DUSP1) belongs to the dual-specificity phosphatase family [5], which are implicated in inactivating different MAPK family isoforms [32]. DUSP1 plays integral roles in various physiological processes, including cell proliferation, cell cycle arrest, and cell apoptosis in normal and tumor cells [3]. It contributes to carcinogenesis of prostate and lung cancer, yet it suppressed the development of HCC and prevents carcinogenesis of head and neck SCC [30]. Recently, DUSP1 was significantly reduced in psoriatic skin lesions compared with paired samples of non-lesional psoriatic skin [16]. In addition, DUSP1 in dermal MSCs was significantly lower in psoriasis

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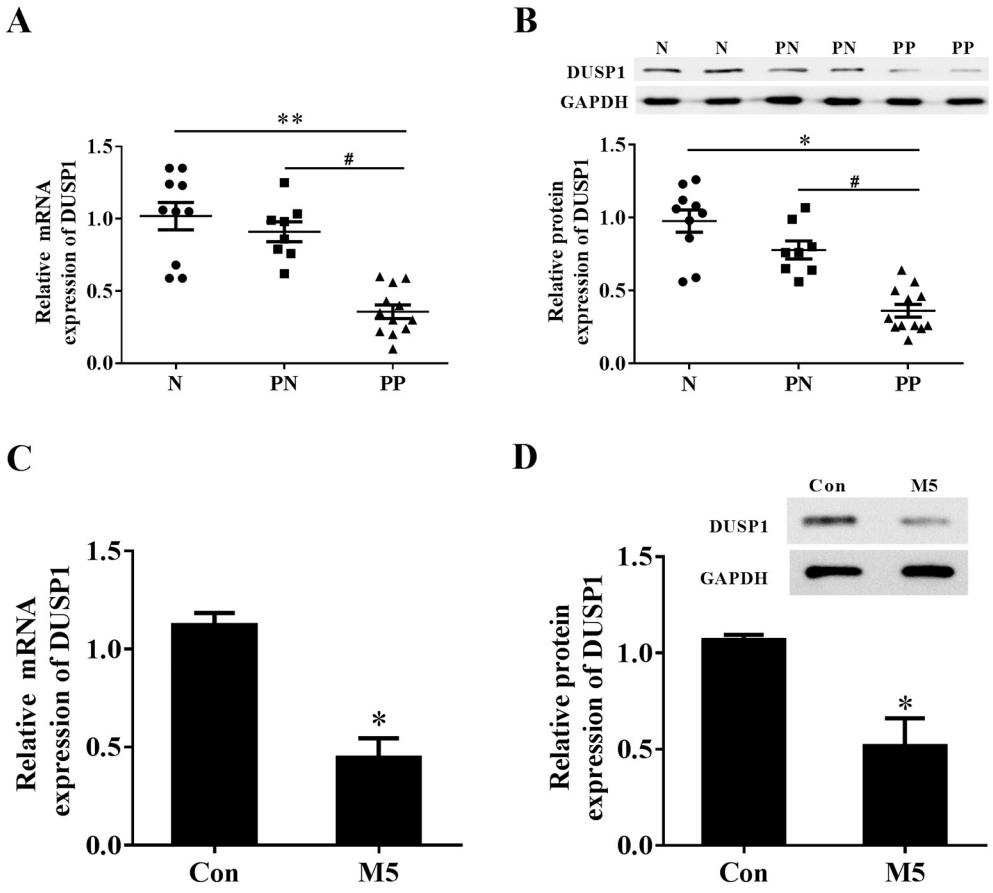

Fig. 1. DUSP1 expression in psoriasis patients and HaCaT cells treated with M5. (A, B) The mRNA (A) and protein (B) expression of DUSP1 were determined using real-time PCR and western blot, respectively in healthy individuals (N group), patients with non-lesional psoriasis (PN group) and patients with lesional psoriasis (PP group). (C, D) HaCaT cells were treated with M5 for 48 h. The mRNA (C) and protein (D) levels were assessed. Con: control; $^{*}P < 0.05$, $^{**}P < 0.01$ vs. the N group or Con group; $^{\#}P < 0.05$ vs the PN group.

patients than that in healthy individuals [6], which indicates a relationship between psoriasis and DUSP1.

Therefore, we assessed the expression of DUSP1 in healthy individuals, patients with non-lesional and lesional psoriasis. Besides, we explored the roles and potential mechanisms of DUSP1 in the proliferation and apoptosis of keratinocytes exposed to M5.

2. Materials and methods

2.1. Skin specimens

10 healthy individuals, 8 psoriasis non-lesional (PN) and 12 psoriasis lesional (PP) were recruited for this study, and they signed the informed consent before the study. Skin biopsies (4–6 mm punch biopsies) were collected from these subjects. Patients did not receive any systemic medication and use any topical medication in the biopsy area for several weeks.

2.2. Cell culture

HaCaT cells were used because it has been shown to be suitable for studies relevant to psoriasis [2,37]. HaCaT cells were obtained from ATCC (Manassas, VA, USA) and grown in RPMI 1640 medium (Logan, UT, USA) supplemented with 10% fetal bovine serum (FBS, Hyclone, Logan, Utah, USA). HaCaT cells were cultured in a humidified atmosphere (95% air/5% CO_2) at 37 °C. Adenovirus control (Ad-βgal), Ad-DUSP1 and Ad-Egr-1 were constructed by Shanghai GeneChem Co., Ltd. (Shanghai, China). Ad-DUSP1 and Ad-Egr-1 was infected into cells to drive the overexpression of DUSP1 and Egr-1 respectively. The M5 cocktail (interleukin (IL)-1 α, IL-17A, IL-22, oncostatin M and TNF-α, each at 10 ng/ml) was added to the medium for 48 h to induce proliferation and reduce apoptosis in keratinocytes [1].

2.3. Real-time PCR analysis

An RNeasy Mini Kit (QIAGEN, Valencia, CA, USA) was employed to collect total RNA from skin biopsies and HaCaT cells. 5 μg RNA was reverse-transcribed into cDNA using the Applied Biosystems cDNA kit (Carlsbad, CA, USA). RT-PCR was performed using SYBR Green (Invitrogen) for DUSP1. The following primers were used: human DUSP1 sense: 5′-GCTGTGCAGCAAACAGTCGA-3′, anti-sense: 5′-CGAT TAGTCCTCATAAGGTA-3′; human β-actin sense: 5′-TCCTGTGGCATCC ACGAAACT-3′; 5′-GAAGCATTTGCGGTGGACGAT-3′. Relative quantification was calculated using the $2^{-\Delta\Delta Ct}$ method and the DUSP1 mRNA level was normalized to the human β-actin endogenous control.

2.4. Western blot analysis

Cells and specimens were harvested and lysed by RIPA lysis buffer (Beyotime, Shanghai). Total protein of 50 μg was loaded in SDS-PAGE gel electrophoresis and transferred to an NC membrane. After blocking, the membrane incubated with antibodies recognizing DUSP1 (1:200; Abcam, Cambridge, MA, USA), cyclin D1 (1:100; Abcam), Rb (1:1500; Abcam), E2F1, p-Elk-1 (1:500; Abcam), t-Elk-1 (1:500; Abcam), Egr-1 (1:200; Abcam), β-actin (1:5000; Abcam), GAPDH (1:4000; Abcam), p-ERK (1:1000; CST, Danvers, MA, USA), t-ERK (1:1000; CST), c-caspase 3 (1:500; CST), Bcl-2 (1:1000; CST) and Bax (1:1000; CST) overnight. After washing, secondary antibodies (1:5000; ZSGB-BIO, Beijing, China) were incubated for 1 h at room temperature. The bands were visualized with an enhanced chemiluminescence system (Amersham Life Sciences, Arlington Heights, IL, USA).

2.5. Cell proliferation assessment

Cell proliferation was determined using MTT assay in accordance

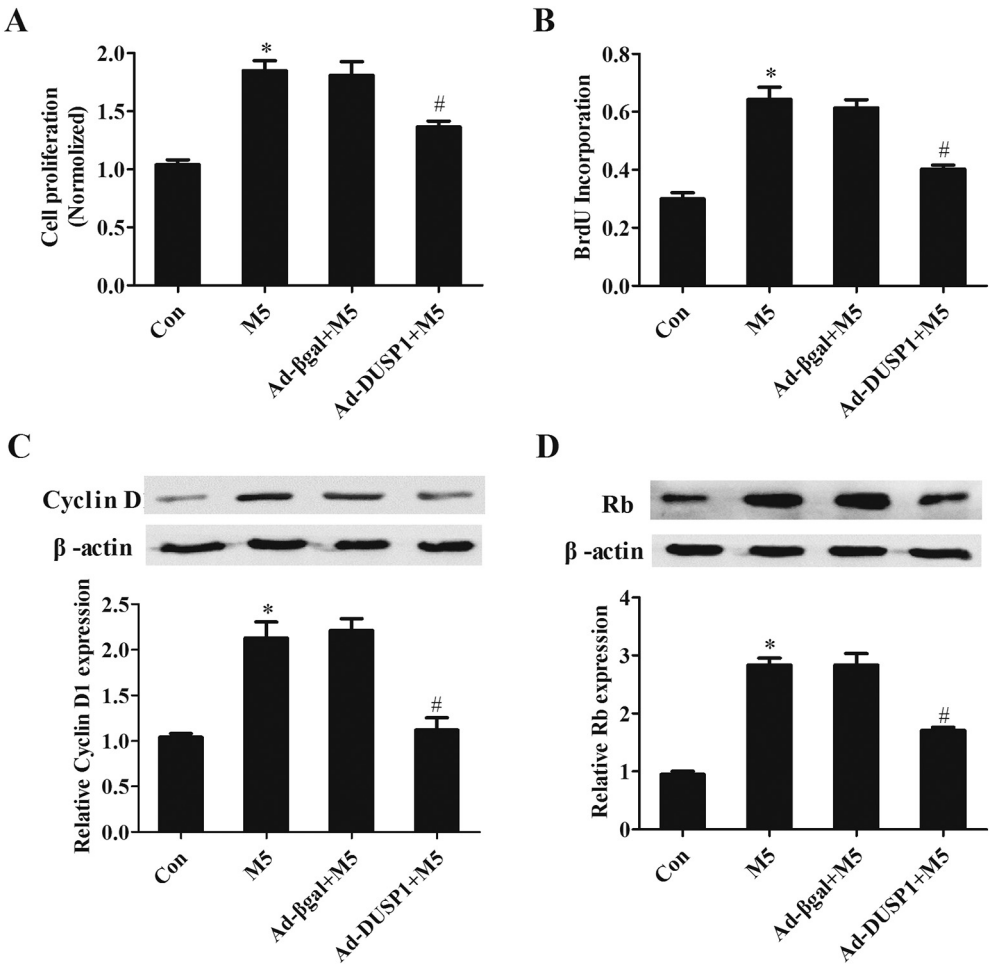

Fig. 2. DUSP1 inhibits the proliferation of HaCaT cells and reduces cyclin D1 and Rb levels. HaCaT cells were infected with Ad-DUSP1 for 48 h followed by treatment with M5 for 48 h. (A) The MTT assay was used to detect cell proliferation. (B) The BrdU assay was used to evaluate BrdU incorporation. (C, D) Western blot was used to determine the protein levels of cyclin D1 (C) and Rb (D). Con: control; $^{*}P < 0.05$ vs the Con group; $^{\#}P < 0.05$ vs the Ad-βgal + M5 group.

with the standard protocol. Subsequently, HaCaT cells were cultured in 96-well plates and treated with Ad-DUSP1 for 48 h at a concentration of 2×10^4 cells/well, followed by exposed to M5 cocktail for 48 h. These cells were treated with 0.5 mg/ml of MTT solution for additional 3 h and the precipitates were dissolved in DMSO to dissolve the MTT-formazan complex. Absorbance was measured at 540 nm.

2.6. BrdU assay

A BrdU Cell Proliferation ELISA kit (Roche, Indianapolis, IN, USA) was performed in line with the manufacturer's instructions to detect proliferation in HaCaT cells. Briefly, HaCaT cells were seeded in 96-well plates. After treatment with Ad-DUSP1 and M5, cells were incubated with BrdU labeling solution (1 μM) for 4 h. Absorbance was measured at 450 nm.

2.7. Apoptosis assay

Apoptosis was assessed by the Cell Death Detection ELISA Plus kit (Roche Applied Science, Mannheim, Germany) following the manufacturer's instructions. Briefly, HaCaT cells were seeded in a 96-well plate and treated with Ad-DUSP1 and M5. Cells from each condition were used to detect fragmented DNA, which was measured on a BioRad microplate reader at 405 nm. All experiments were conducted in triplicate.

2.8. Chromatin immunoprecipitation (ChIP) assay

ChIP was performed using a ChIP assay kit (Millipore, Upstate, NY, USA). In brief, HaCaT cells were exposed to M5 for 48 h after infection with Ad-DUSP1 for 48 h. Cells were administrated with 1% formaldehyde at room temperature for 10 min and harvested in ice-cold PBS containing protease/phosphatase inhibitors. After incubation for 15 min on ice with vortexing every 5 min, cells were sonicated for 10 min. Immunoprecipitation was performed overnight with a purified anti-Egr-1 antibody (Santa Cruz, CA, USA) or IgG as a negative control overnight at 4 °C with rotation. The immune complexes then were washed and eluted with the ChIP elution buffer. 5 M NaCl was utilized to reverse the DNA-protein crosslinks at 65 °C for 6 h, and DNA was purified. PCR was carried out using 2 μl of DNA with the primers: Egr-1: forward primer: 5′-GTGCCCACCACTCTTGGAT-3′, reverse primer: 5′-CGAATCGGCCTCTATTTCAA-3′.

2.9. Statistical analysis

Statistical differences were analyzed with SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) using a *t*-test or one-way ANOVA. $P < 0.05$ was considered statistically significant.

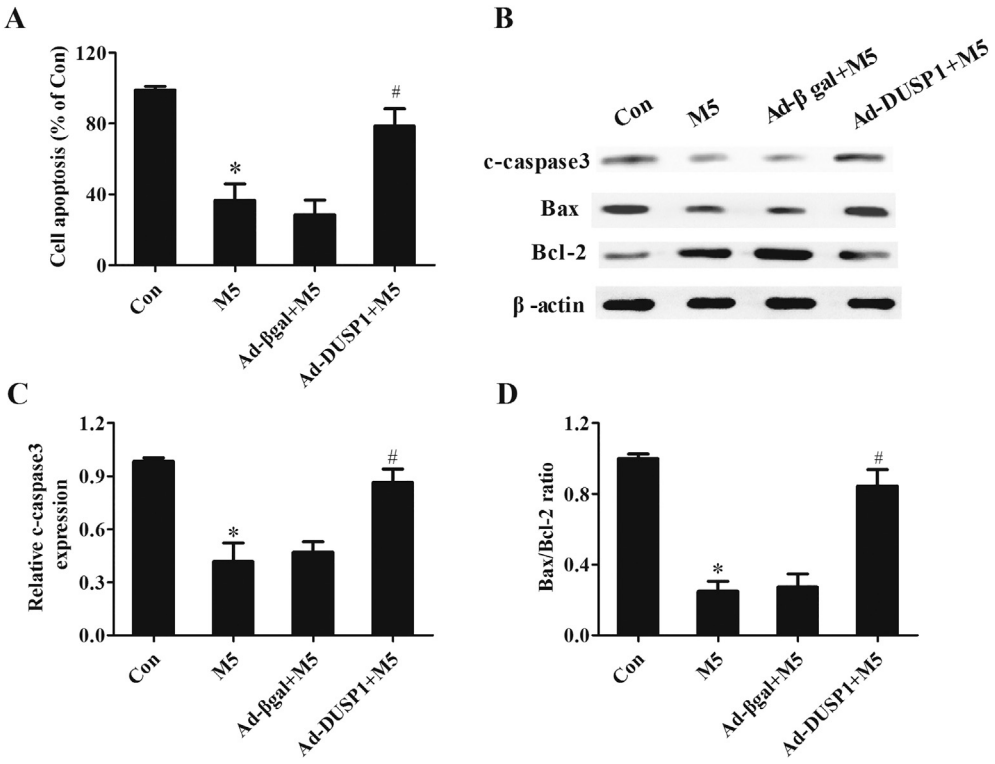

Fig. 3. DUSP1 promotes apoptosis in HaCaT cells. Cells were incubated with Ad-DUSP1 and then exposed to M5 for 48 h. (A) Apoptosis was assesses using the Cell Death Detection ELISA Plus kit. (B, C) The expression of c-caspase 3 was detected using western blot. (B, D) The expression of Bax and Bcl-2 were evaluated using western blot. Con: control; $^{*}P < 0.05$ vs the Con group; $^{\#}P < 0.05$ vs the Ad-βgal + M5 group.

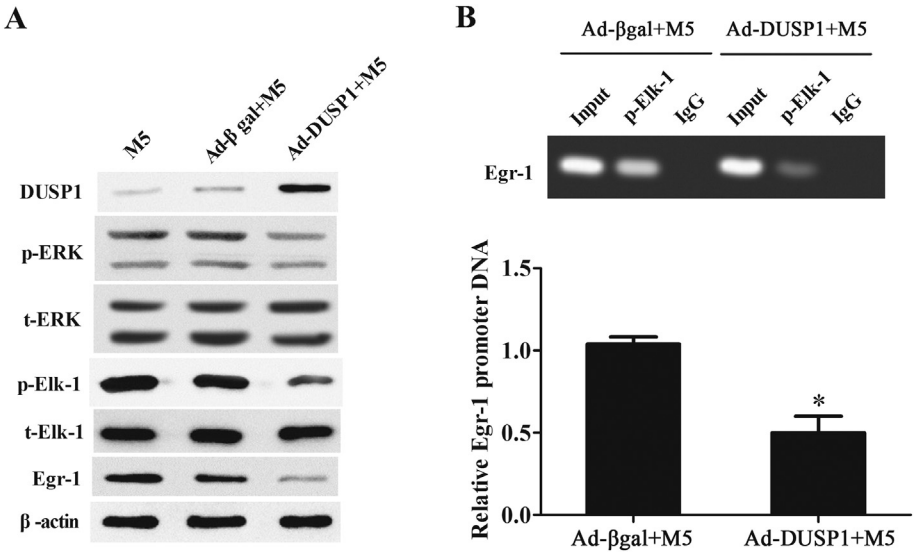

Fig. 4. DUSP1 negatively regulates the ERK/Elk-1/Egr-1 pathway. HaCaT cells were infected with Ad-DUSP1 for 48 h and then exposed to M5 for 48 h. (A) The protein expression of DUSP1, p-ERK, t-ERK, p-Elk-1, t-Elk-1 and Egr-1 were determined using western blot. (B) ChIP was performed on M5-treated or untreated HaCaT cells. Chromatin extracts were immunoprecipitated with specific antibodies recognizing p-Elk-1 or IgG. The detection of the Egr-1 promoter was performed by PCR. $^{*}P < 0.05$ vs the Ad-βgal + M5 group.

3. Results

3.1. DUSP1 expression in psoriasis patients and HaCaT cells exposed to M5

It has been reported that DUSP1 levels in dermal MSCs are clearly lower in psoriasis patients than that in healthy individuals [6]. Therefore, we assessed the expression of DUSP1 in psoriasis patients. Real-time PCR and western blot were performed to measure DUSP1 expression. Both protein (Fig. 1A) and mRNA (Fig. 1B) levels of DUSP1 were decreased in non-lesional psoriasis (PN group; $n = 8$), and a significant reduction was observed in lesional psoriasis (PP group; $n = 12$) compared with healthy individuals. In addition, the expression of DUSP1 was also evaluated when HaCaT cells were treated with M5 for 48 h. As shown in Fig. 1C and D, M5 reduced the expression of DUSP1 at both the mRNA and protein levels. These results indicate that DUSP1 is implicated in the development of psoriasis.

3.2. DUSP1 suppresses the proliferation of HaCaT cells induced by M5

HaCaT cells were incubated with Ad-DUSP1, and then subjected to M5. The MTT and BrdU assays were carried out to explore the effects of DUSP1 on cell proliferation induced by M5. In Fig. 2A, we observed that M5 significantly increased the proliferation of HaCaT cells, overexpression of DUSP1 obviously inhibited M5-induced cell proliferation. The BrdU assay revealed that M5 markedly augmented BrdU incorporation in HaCaT cells, and enhanced DUSP1 expression reduced M5 mediated BrdU incorporation (Fig. 2B). Moreover, the expression of the cell cycle related proteins cyclin D1 and Rb was assessed; the results revealed that M5 upregulated cyclin D1 (Fig. 2C) and Rb (Fig. 2D) protein levels. Infection with Ad-DUSP1 notably suppressed the M5-

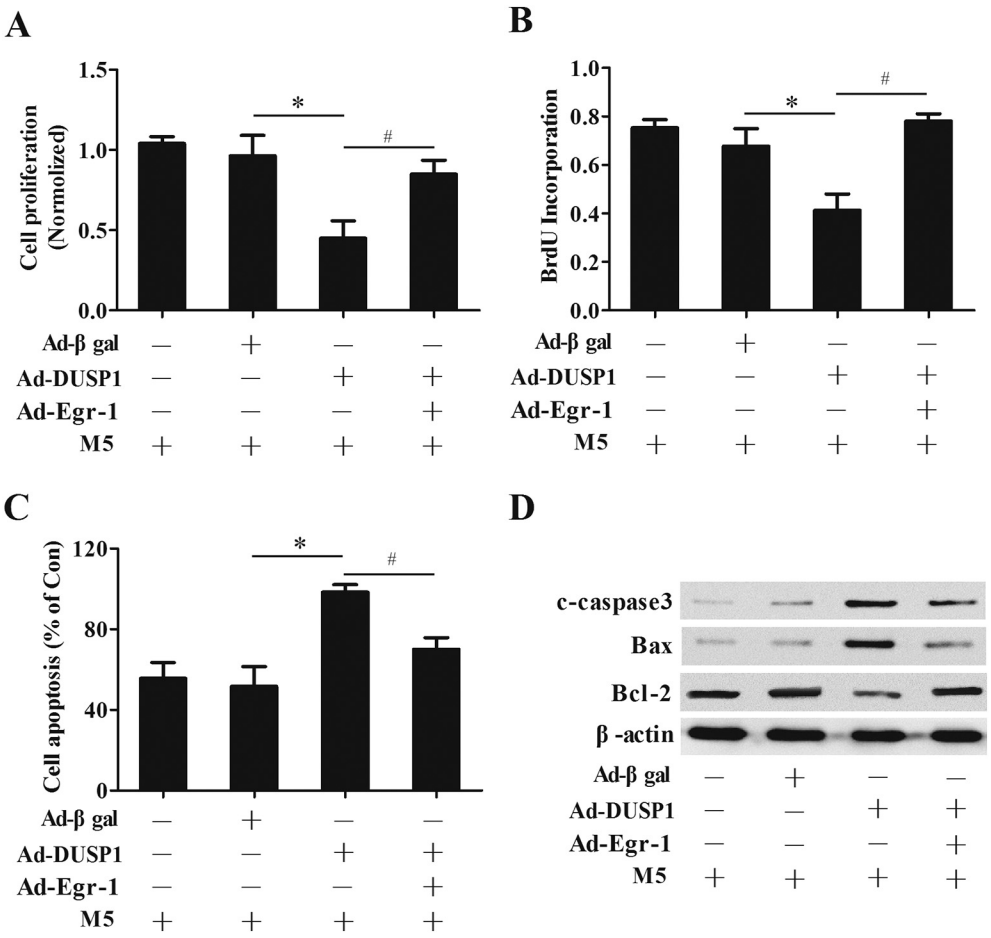

Fig. 5. DUSP1 inhibits proliferation and promotes apoptosis through the ERK/Elk-1/Egr-1 pathway. Cells were treated with Ad-DUSP1 and Ad-Egr-1 for 48 h and then exposed to M5 for 48 h. (A, B) Cell proliferation was detected using the MTT (A) and BrdU (A) assays. (C) Apoptosis was tested using the Cell Death Detection ELISA Plus kit. (D) The protein levels of c-caspase 3, Bax and Bcl-2 were detected using western blot.

induced augment in cyclin D1 and Rb. These data support that DUSP1 overexpression reduces M5 caused cell proliferation, cyclin D1 and Rb expression in HaCaT cells.

3.3. DUSP1 promotes apoptosis in HaCaT cells

We investigated the functions of DUSP1 on the M5-induced suppression of apoptosis in HaCaT cells. Cell apoptosis was obviously reduced by M5 stimulation, whereas restoration expression of DUSP1 reversed this (Fig. 3A). Moreover, the protein expression of c-caspase 3, Bax and Bcl-2 was determined. As illustrated in Fig. 3B and C, DUSP1 overexpression abolished the suppression of M5 in c-caspase 3 expression. The ratio of Bax/Bcl-2 was clearly decreased by M5 administration, while gain function of DUSP1 elevated Bax/Bcl-2 ratio in the presence of M5 (Fig. 3B and D). These results suggest that DUSP1 promotes cell apoptosis after M5 treatment.

3.4. DUSP1 negatively regulates the ERK/Elk-1/Egr-1 pathway

Recent report has found that DUSP1 dephosphorylated and inactivated ERK [19], blocked the activation of ERK/Elk-1 signaling pathway. Mayer SI et al. demonstrated that the phosphorylated form of Ekl-1 could binds to the 5′-upstream region of the Egr-1 gene [21]. Additionally, it has been reported that knockdown of Egr-1 reduces proliferation in KG-1a leukemia cells [36]. To investigate the mechanisms of DUSP1 in proliferation and apoptosis, we tested the protein expression of p-ERK, p-Elk-1 and Egr-1. Reinforced expression of DUSP1 suppressed p-ERK, p-Elk-1 and Egr-1 in HaCaT cells in the presence of M5 (Fig. 4A). To further determine whether p-Elk-1 protein directly binds to the Egr-1 promoter, we carried out a ChIP experiment on HaCaT cells. As shown in Fig. 4B, the binding of p-Elk-1 to the Egr-1 promoter was reduced by DUSP1 overexpression in the presence of M5. These data indicate that DUSP1 negatively regulates the ERK/Elk-1/Egr-1 pathway, and p-Elk-1 binds to the promoter of Egr-1 in HaCaT cells.

3.5. DUSP1 inhibits proliferation and promotes apoptosis through the ERK/Elk-1/Egr-1 pathway

In order to further study the potential mechanisms of DUSP1 in proliferation and apoptosis, HaCaT cells were infected with both Ad-DUSP1 and Ad-Egr-1 before M5 treatment. As shown in Fig. 5A, MTT assay showed that Ad-DUSP1 treatment decreased the proliferation of HaCaT cells, and overexpression of Egr-1 abolished the inhibitory function of DUSP1 on proliferation. Similar results were observed using BrdU assay (Fig. 5B). In addition, we evaluated apoptosis and the expression of c-caspase 3, Bax and Bcl-2. Overexpression of DUSP1 promoted apoptosis in HaCaT cells, and enhanced Egr-1 expression abrogated the role of DUSP1 in apoptosis (Fig. 5C). Gain function of DUSP1 resulted in augment of c-caspase 3 protein level and the Bax/Bcl-2 ratio, but forced expression of Egr-1 abrogated the function of DUSP1 in driving apoptosis (Fig. 5D). These data reveal that DUSP1 promotes proliferation inhibition and apoptosis through the ERK/Elk-1/Egr-1 signaling pathway in HaCaT cells.

4. Discussion

In the present study, we confirmed that DUSP1 expression was decreased in psoriasis patients and M5-treated HaCaT cells. Furthermore, the present results showed that overexpression of DUSP1 facilitated

proliferation inhibition and apoptosis in HaCaT cells. Importantly, we found that DUSP1 negatively regulated the ERK/Elk-1/Egr-1 pathway, and DUSP1 promoted proliferation inhibition and apoptosis through the ERK/Elk-1/Egr-1 signaling pathway.

DUSP1 is a member of the subfamily of the Dusl specific phosphatases (DUSPs). High levels of DUSP1 observed in lung, liver and placenta, and low levels have been found in the brain and kidney. DUSP1 has been shown to be elevated in various diseases [18]. DUSP1 was increased in the late stages of breast cancer, gastric adenocarcinoma and the liver in patients with chronic hepatitis C virus [8]. However, a reduction DUSP1 expression was reported in lentiviral models of Huntington's disease [31]. In this study, our data revealed that DUSP1 was clearly reduced in psoriasis patients, which is accordance with the results of Palagummi et al. [25]. Additionally, DUSP1 was also decreased in HaCaT cells exposure to M5. Thus, there may be a role for DUSP1 in the development of psoriasis.

Keratinocyte proliferation has been occur in various benign and malignant skin conditions, including psoriasis, actinic keratosis and seborrheic keratosis [4]. It has been reported that overexpression of DUSP1 blocks the proliferation of osteoblasts [13]. In our study, cells were treated with M5 to mimic the proliferation and apoptosis observed in psoriasis; we found that enhancing DUSP1 expression suppressed proliferation in HaCaT cells. Moreover, overexpression of DUSP1 inhibited the protein expression of cyclin D1 and Rb, implying an anti-proliferation role of DUSP1 in HaCaT cells. Additionally, suppression of DUSP1 expression resulted in a reduction in oxidative stress-induced cell death [15]. In this study, we showed that enhancing DUSP1 expression resulted in an augment of cell apoptosis rate, c-caspase 3 expression and the Bax/Bcl-2 ratio in HaCaT cells in the presence of M5.

DUSP1, as a phosphatase can inactivate MAP kinase, ERKs, p38 MAPKs and JNKs [24]. Elk-1 is a downstream transcriptional target of MAPK/ERK, and inhibition of the MAPK/ERK cascade prevents Elk-1 phosphorylation [10]. The Egr-1 promoter contains five serum response elements (SREs). A ternary complex factor Elk-1 is essential for SRE-mediated activity [33]. Activation of the ERK signaling induced the biosynthesis of Egr-1 [28]. In this study, we demonstrated that enhancing DUSP1 expression reduced the protein expression of p-ERK, p-Elk-1 and Egr-1. Report revealed that Egr-1 is significantly increased in the skin lesions of patients with psoriasis [11,20]. Furthermore, the ChIP assay revealed that p-Elk-1 can bind to the promoter of Egr-1 in HaCaT cells, and DUSP1 reduced this binding effect. These data indicate that DUSP1 negatively regulates the ERK/Elk-1/Egr-1 signaling pathway in HaCaT cells. Egr-1 overexpression stimulated keratinocyte proliferation [14,17]. Furthermore, Egr-1 knockdown increases the PA-induced cleavage of caspase 3 and poly(ADP-ribose) polymerase (PARP) [7]. It would therefore be of interest to determine whether the ERK/Elk-1/Egr-1 pathway is involved in the regulation of DUSP1-mediated proliferation and apoptosis in HaCaT cells. Our data confirmed that enhancing Egr-1 abrogated the roles of DUSP1 in the proliferation and apoptosis of HaCaT cells, suggesting that DUSP1 regulates proliferation and apoptosis in HaCaT cells through the ERK/Elk-1/Egr-1 pathway.

In summary, our data demonstrated that DUSP1 is downregulated in psoriasis patients and M5-treated HaCaT cells. Forced expression of DUSP1 promoted proliferation inhibition and apoptosis in HaCaT cells through ERK/Elk-1/Egr-1 signaling pathway. These results supported that DUSP1 may serve as a potential therapeutic target for the treatment of psoriasis.

Conflict of interest

There is no conflict of interests.

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