Article

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Lysine-Specific Histone Demethylase 1A Contributes to Cutaneous Psoriatic Lesions by Regulating Ferroptosis

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Background: Psoriasis is a prevalent immune-mediated chronic inflammatory skin disorder, and the persistent challenge associated with its high recurrence rates remains. This study aimed to investigate the involvement of lysine-specific histone demethylase 1A (KDM1A) in psoriasis pathogenesis.
Methods: An imiquimod-induced psoriasis-like dermatitis mouse model was generated and KDM1A knockdown was conducted using lentivirus. Skin appearance was scored and pathological changes were observed. Oxidative stress, lipid peroxidation, inflammatory response, iron accumulation, and ferroptosis-related proteins in the skin were assessed. Afterward, human HaCaT keratinocytes were treated with proinflammatory cytokines to mimic psoriatic conditions and ferroptosis-related proteins were determined. The ferroptosis inducer erastin was used to treat HaCaT keratinocytes, and its influences on oxidative stress and inflammation were assessed.
Results: Imiquimod increased the levels of KDM1A, and KDM1A knockdown ameliorated skin psoriatic lesions in mice and reduced inflammatory infiltration. Oxidative stress, lipid peroxidation, iron accumulation, and iron transport-related proteins in skin were also reduced. In HaCaT keratinocytes, KDM1A knockdown similarly mitigated lipid peroxidation and reduced iron transport-related proteins. Importantly, erastin disrupted the inhibition of oxidative stress and inflammation in keratinocytes induced by KDM1A knockdown.
Conclusion: This study highlights the significance of KDM1A in psoriasis pathogenesis and suggests that its regulation of ferroptosis may play a critical role in disease development.

Keywords: psoriasis; keratinocyte; ferroptosis; oxidative stress; imiquimod

Introduction

Psoriasis, which is a prevalent immune-mediated chronic inflammatory skin disorder, is characterized by erythema, scales, and local skin infiltration and is often accompanied by systemic symptoms such as itching [1]. Epidemiological surveys have demonstrated a global incidence rate of psoriasis ranging from 3% to 4% [2]. While significant progress has been made in the development of immunosuppressants and targeted biological agents, the persistent challenge of high recurrence rates remains [3,4]. Thus, the exploration of novel intervention targets and the development of effective therapeutic agents is critical for addressing this condition.

Many studies have shown elevated levels of oxidative stress markers in the circulatory system and the affected skin of psoriasis patients [5]. These changes are accompanied by alterations in the antioxidant defense system, which collectively lead to a state of oxidative stress. For instance, markers of lipid peroxidation, such as malondialdehyde (MDA), are increased in the plasma, red blood cells, and skin lesions of psoriasis patients [6]. Additionally, inducible nitric oxide synthase (iNOS) expression is upregulated in keratinocytes within skin lesions, resulting in increased nitric oxide (NO) release [7,8]. These observations underscore the clear impact of oxidative stress on psoriasis pathogenesis, emphasizing the therapeutic potential of targeting oxidative stress for disease management and treatment.

Within the realm of skin biology, lysine-specific histone demethylase 1A (KDM1A, also known as LSD1) has been identified as a pivotal regulator of differentiation [9]. Recent research has suggested that inhibiting KDM1A within the epidermis could mitigate the development of cutaneous squamous cell carcinoma [10]. Notably, KDM1A has also been implicated in the progression of Merkel cell carcinoma, a highly aggressive cutaneous neuroendocrine cancer [11]. Inhibition of KDM1A has been shown to induce cancer cell cycle arrest and apoptosis. Additionally, in the context of rheumatoid arthritis, which is another immune-mediated inflammatory condition affecting the joints, KDM1A knockdown has been associated with reduced disease severity and elevated levels of anti-type II collagen antibodies [12]. These findings illustrate the

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broader role of KDM1A in regulating excessive cell proliferation in skin cancer and inflammatory diseases. However, the specific involvement of KDM1A in psoriasiform dermatitis has yet to be elucidated. Recent investigations of psoriatic lesions have revealed decreased expression of glutathione peroxidase 4 (GPX4), a crucial regulator of ferroptosis, compared to that in unaffected skin and samples from healthy individuals [13]. This observation was consistent with an increase in cellular import of iron, indicating the potential activation of ferroptosis in psoriatic lesions.

Hence, we hypothesize that KDM1A may play a pivotal role in the pathogenesis of psoriasis by regulating ferroptosis. In this study, we used an imiquimod (IMQ)-induced mouse model of psoriasis to investigate the impact of KDM1A on skin lesions. Additionally, human HaCaT keratinocytes were exposed to a mixture of cytokines to elucidate the underlying regulatory mechanisms of KDM1A. The findings of this study provide a compelling theoretical foundation for targeting KDM1A for the treatment of psoriasis.

Methods and Materials

Animal Modeling

Female BALB/c mice (7–8 weeks, Lilai, Chengdu, China) were kept under standard laboratory conditions with a controlled 12-hour light-dark cycle and had ad libitum access to water and a standard diet. All procedures involving animals were conducted in accordance with ethical guidelines and received approval from the Institutional Animal Care and Use Committee of Shaanxi Provincial People's Hospital (No. IACUC-20230004). In the experimental groups, 5% IMQ cream (62.5 mg, H20100157, Aldara, INOVA, Singapore) was applied topically on the shaved back skin of each mouse for 5 consecutive days (n = 6). The control group received a similar application of Vaseline (n = 6). To assess the effects of KDM1A inhibition, a specific *KDM1A* short hairpin RNA (sh-*KDM1A*) lentivirus (Tsingke, Beijing, China) was administered intradermally 3 days before IMQ application. Meanwhile, the non-targeted shRNA lentivirus was injected and this group was served as the negative control (sh-NC). Target sequences (5′-3′) were as follows: for sh-*KDM1A*, CGGCATCTACAAGAGGATAAA; for sh-NC, GCAAGCTGACCCTGAAGTTCAT. Upon completion of the treatment regimen, the mice were euthanized with excess CO_2, and skin samples were collected for histopathological analysis.

Psoriasis Area and Severity Index (PASI)

The skin lesions of mice were scored according to erythema, desquamation and epidermal thickening (0–4 points, respectively) [14]. 0 was classified as no injury, 1 as mild, 2 as moderate, 3 as severe, and 4 as extremely severe. The overall scores of mouse skin lesions ranged from 0 to 12.

Histopathological Examination

Skin tissues were fixed in 4% paraformaldehyde (BL539A, Biosharp, Anhui, China) overnight, dehydrated with gradient alcohol, and subsequently embedded in paraffin. Sections (4 μm thick) were cut, stained with hematoxylin and eosin (H&E, C105S, Beyotime, Shanghai, China), dehydrated with gradient alcohol and examined under a light microscope. The area of infiltrated cells was quantified using ImageJ software (version 1.8.0; National Institutes of Health, Bethesda, MD, USA) to reflect the degree of inflammation.

Immunohistochemistry (IHC)

Paraffin-embedded skin sections were subjected to deparaffinization and antigen retrieval by microwave treatment in a 10 mM sodium citrate solution. Endogenous peroxidase activity was quenched using 3% hydrogen peroxide, and the sections were incubated in 5% goat serum for 30 min. Then, primary antibodies targeting F4/80 (70076, 1:200), CD8 (98941; 1:500), and LY-6G (87048, 1:200, all from CST, Shanghai, China) were added and incubated overnight at 4 °C. Subsequently, a biotinylated secondary antibody (ab207995, 1:2000, Abcam, Shanghai, China) was used. Hematoxylin (C105S, Beyotime, Shanghai, China) was used for counterstaining, and positive immunostaining was examined under a microscope.

Prussian Blue Staining

Deparaffinized skin tissue sections were stained with Prussian blue solution (60533ES, Yeasen, Shanghai, China) for 20 min. This was followed by staining with Nuclear Fast Red solution for 2 min at room temperature. The sections were dehydrated with gradient alcohol and then cleared with xylene. The specimens were subsequently observed under a microscope.

Cell Culture and Treatment

Human HaCaT keratinocytes (4201HUM-CCTCC00106, China Center for Type Culture Collection, Wuhan, China) were cultured in DMEM (11965092, Gibco, Thermo Fisher, Shanghai, China) supplemented with 10% fetal bovine serum (12484028, Gibco, Thermo Fisher, Shanghai, China) and 1% penicillin–streptomycin (ST488S, Beyotime, Shanghai, China) in a 5% CO_2 incubator at 37 °C. This cell line was validated by short tandem repeat (STR) DNA profiling and tested negative for mycoplasma. HaCaT cells were treated with an M5 mixture of cytokines including interleukin (IL)-17A (CYT-250), IL-22 (CYT-328), oncostatin M (CYT-231), IL-1α (CYT-253), and TNF-α (CYT-223, Prospec, East Brunswick, NJ, USA), each at a concentration of 2.5 ng/mL, for 24 h to simulate psoriatic conditions. Erastin (30 mM, SC0224, Beyotime, Shanghai, China), which is a ferroptosis inducer, was used to pretreat keratinocytes for 24 h for mechanistic experiments.

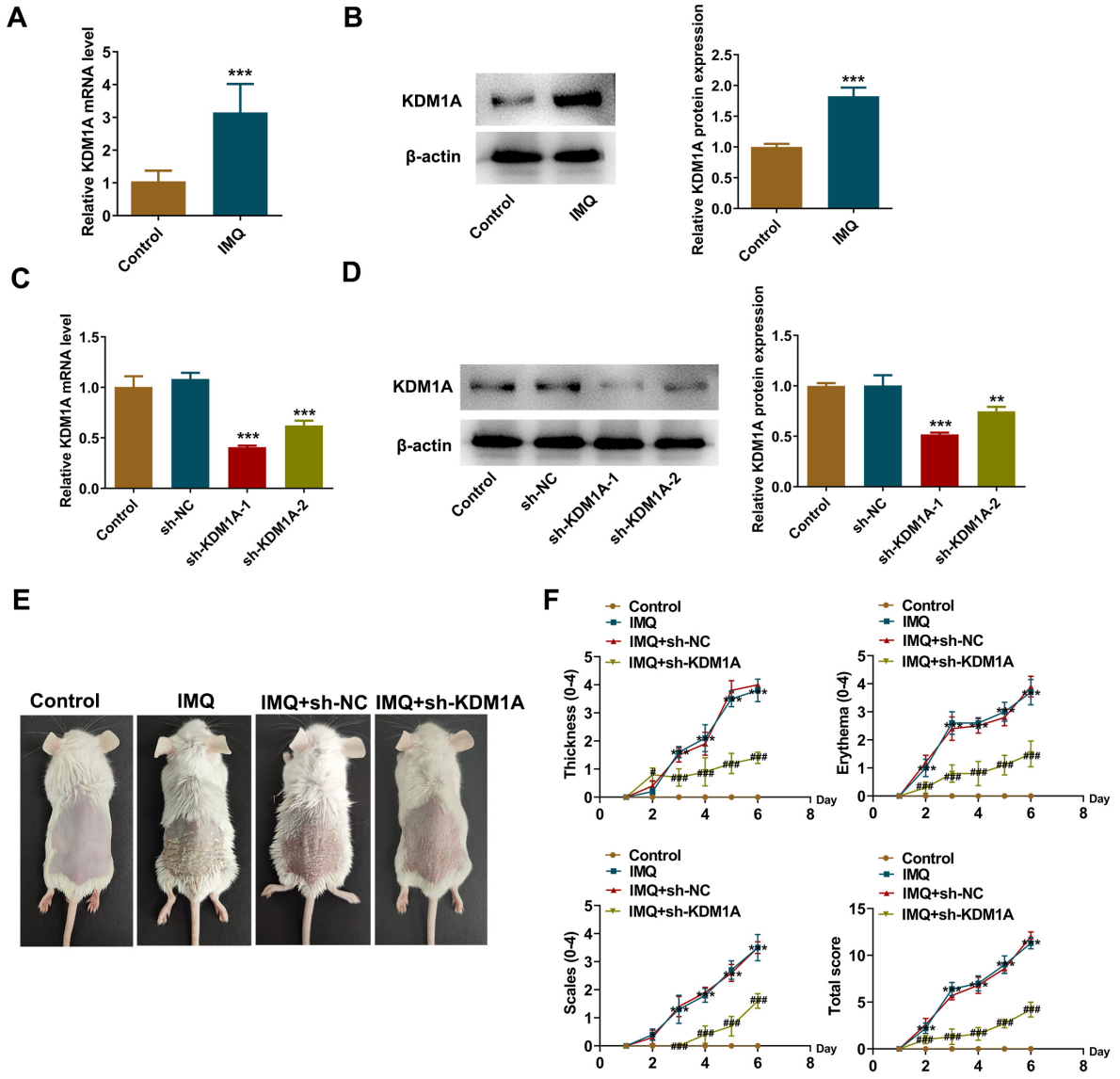

Fig. 1. Lysine-specific histone demethylase 1A (KDM1A) inhibition ameliorates skin psoriatic lesions in mice. (A) KDM1A protein and mRNA levels in imiquimod -treated tissues were determined using western blotting and (B) real-time quantitative PCR (RT–qPCR). (C) KDM1A expression in mice was knocked down, and the efficacy was determined using western blot and (D) RT–qPCR. (E) Photos of the back skin of mice. (F) The skin lesions of mice were scored according to erythema, desquamation and epidermal thickening. N = 6, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ vs. control or sh-NC; $^{\#}p < 0.05$, $^{\#\#\#}p < 0.001$ vs. IMQ + sh-NC. sh, short hairpin; NC, negative control; IMQ, imiquimod.

Plasmid Transfection

KDM1A knockdown was induced by transfection using Lipofectamine™ 3000 (L3000008, Thermo Fisher, Shanghai, China) mixed with shRNA targeting *KDM1A* (sh-*KDM1A*) and scrambled shRNA was used as the sh-NC (PackGene Biotech, Guangzhou, China). Target sequences (5′-3′) were as follows: for sh-*KDM1A*, CCACGAGTCAAACCTTTATTT; for sh-NC, GCACTACCAGAGCTAACTCAG. These agents were added to the culture medium, HaCaT cells were cultured for 48 h, and then the culture medium was replaced with fresh medium.

Real-Time Quantitative PCR (RT–qPCR)

Total RNA was extracted from skin tissue or HaCaT cells using TRIzol reagent. The obtained total RNA was reverse transcribed into cDNA using the iScript cDNA Synthesis Kit (1708891, Bio-Rad, Hercules, CA, USA) according to the manufacturer's instructions. SYBR Green assay kits (10039761, Bio-Rad, Hercules, CA, USA) were used to quantitatively assess target mRNA expression on an ABI Prism™ 7900 real-time quantitative PCR system (Applied Biosystems, Carlsbad, CA, USA), and *β-actin* served as an internal reference. Relative expression of the target mRNA was calculated using the

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$2^{-\Delta\Delta Ct}$ method. Primer sequence (5′-3′) were as follows: *KDM1A* (mus), forward, ATCTTGGCGCCATGGTTGTA, reverse, GTCAGCTTGTCCATTGGCTTC; *β-actin* (mus), forward, GCAGGAGTACGATGAGTCCG, reverse, ACGCAGCTCAGTAACAGTCC; *KDM1A* (homo), forward, AAACTTCAGGAGTTGGAAGCGA, reverse, TGGCTGCCAGTGAACTCAAA; *β-actin* (homo), forward, CTTCGCGGGCGACGAT, reverse, CCACATAGGAATCCTTCTGACC.

Western Blot Analysis

Protein concentration was determined by a Nanodrop 2000 (ND-2000C, Thermo Fisher Scientific, Waltham, MA, USA). Total protein samples underwent SDS-PAGE and were subsequently transferred onto PVDF membranes. The protein strips were blocked with 5% milk at room temperature for 1 h, and primary antibodies against KDM1A (ab194286, 1:5000, Abcam, Shanghai, China), solute carrier family 7 member 11 (SLC7A11, 26864-1-AP, 1:1000, Proteintech, Wuhan, China), acyl-CoA synthetase long chain family member 4 (ACSL4, 22401-1-AP, 1:5000, Proteintech, Wuhan, China), GPX4 (30388-1-AP, 1:1000, Proteintech, Wuhan, China), transferrin receptor (TFR1, 10084-2-AP, 1:50000, Proteintech, Wuhan, China), cytochrome c oxidase subunit II (Cox2, 27308-1-AP, 1:1000, Proteintech, Wuhan, China), iNOS (22226-1-AP, 1:1000, Proteintech, Wuhan, China), β-actin (ab8227, 1:4000, Abcam, Shanghai, China) were added and incubated overnight at 4 °C. Then, an appropriate secondary antibody (31460, 1:100000, Thermo Fisher, Shanghai, China) was added and incubated at room temperature for 1 h. Protein bands were visualized using enhanced chemiluminescence (ECL, E423-01, Vazyme, Nanjing, China) reagent. The grayscale values of protein bands were analyzed by Quantity One software (version 4.6.7, Bio-Rad, Hercules, CA, USA), and β-actin was used as an internal reference.

Assessment of Oxidative Stress

Oxidative stress in tissue and cells was assessed using reactive oxygen species (ROS, S0033S), superoxide dismutase (SOD, S0101), and catalase (CAT, S0051) assay kits (Beyotime, Shanghai, China). Tissue homogenate or cell lysate was centrifuged at 10,000 ×g for 10 min before the supernatant was obtained for analysis. The values were computed using a standard curve.

Assessment of Inflammatory Factor Levels

Inflammation, including IL-23 (PI655 and PI660), IL-17A (PI545 and PI550), and IL-6 (PI326 and PI325, all from Beyotime, Shanghai, China) levels, in tissue and cells was assessed using commercial enzyme linked immunosorbent assay (ELISA) kits according to the manufacturer's protocol. The supernatant of the tissue homogenate and cell lysate were collected as described above. The absorbance was measured, and the levels were computed using a standard curve.

Iron and Lipid Peroxidation Analysis

Iron and lipid peroxidation levels in tissue or cells were determined using iron colorimetric assay kits (E-BC-K139-M) and thiobarbituric acid reactants (TBARS) colorimetric assay kits (E-BC-K298-M, Elabscience, Wuhan, China) according to the manufacturer's instructions.

Statistical Analysis

All data are expressed as the mean ± standard deviation (SD). Statistical analysis was performed using GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA, USA), unpaired Student's *t* tests (two groups) and one-way or two-way analysis of variance (ANOVA), followed by Tukey's test (multiple groups). A p value < 0.05 was considered significant.

Results

KDM1A Inhibition Ameliorates Skin Psoriatic Lesions in Mice

According to the RT–qPCR and western blot results, KDM1A mRNA and protein levels were increased significantly in IMQ-treated tissues (Fig. 1A,B). To further explore the role of KDM1A, KDM1A expression in mice was knocked down, and the efficacy in the sh-KDM1A-1 group was superior (Fig. 1C,D). sh-KDM1A-1 was selected for subsequent knockdown. As observed by the naked eye, the skin on the backs of mice in the IMQ group was thickened with red rashes and scales, while the features of psoriasis in the KDM1A knockdown group were significantly reduced (Fig. 1E). The Psoriasis Area and Severity Index (PASI) scores based on clinical improvements showed a significant difference between the two groups (Fig. 1F).

KDM1A Inhibition Reduces Oxidative Stress and Inflammatory Infiltration in Mice

H&E staining demonstrated clubbing hyperplasia of the epidermis and inflammatory infiltration of the dermis in the IMQ group, and the thickening was significantly mild in the KDM1A knockdown group (Fig. 2A,B). IMQ induced a significant increase in ROS and a decrease in SOD and CAT activities in tissues, and KDM1A knockdown slowed these alterations (Fig. 2C). IHC was used to assess the levels of the markers F4/80, CD8, and LY-6G to identify macrophages, T cells, and neutrophils in mice. The results showed that compared with that in the control, the positive rate of these proteins in the skin tissue of mice in the IMQ group was significantly increased. KDM1A knockdown reduced the increase in these inflammatory cells (Fig. 2D–F). The ELISA results revealed that IMQ induced a significant increase in IL-23, IL-17A and IL-6 levels, and the increase in the levels of these cytokines was inhibited to a certain extent in the KDM1A knockdown group (Fig. 2G).

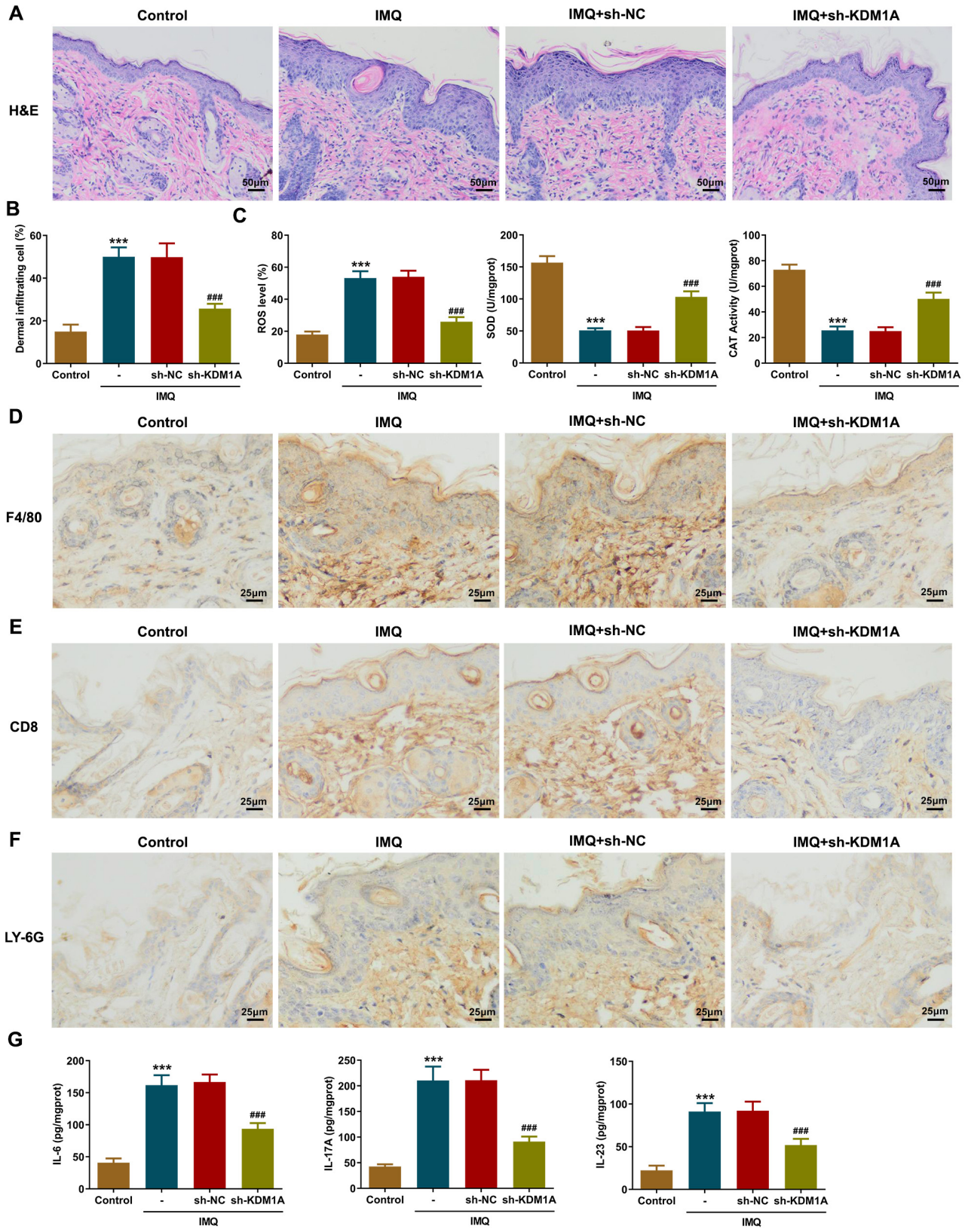

Fig. 2. KDM1A inhibition reduces oxidative stress and inflammatory infiltration in mice. (A) Hematoxylin and eosin (H&E) staining showing pathological skin damage, and (B) dermal infiltrating cells were quantified. (C) Oxidative stress levels in skin tissue were assessed. (D) Immunohistochemistry analysis of macrophage, (E) T-cell and (F) neutrophil infiltration in skin tissue. (G) Enzyme linked immunosorbent assay (ELISA) analysis of inflammatory factor levels in tissues. N = 3, $^{***}p < 0.001$ vs. control; $^{###}p < 0.001$ vs. IMQ + sh-NC.

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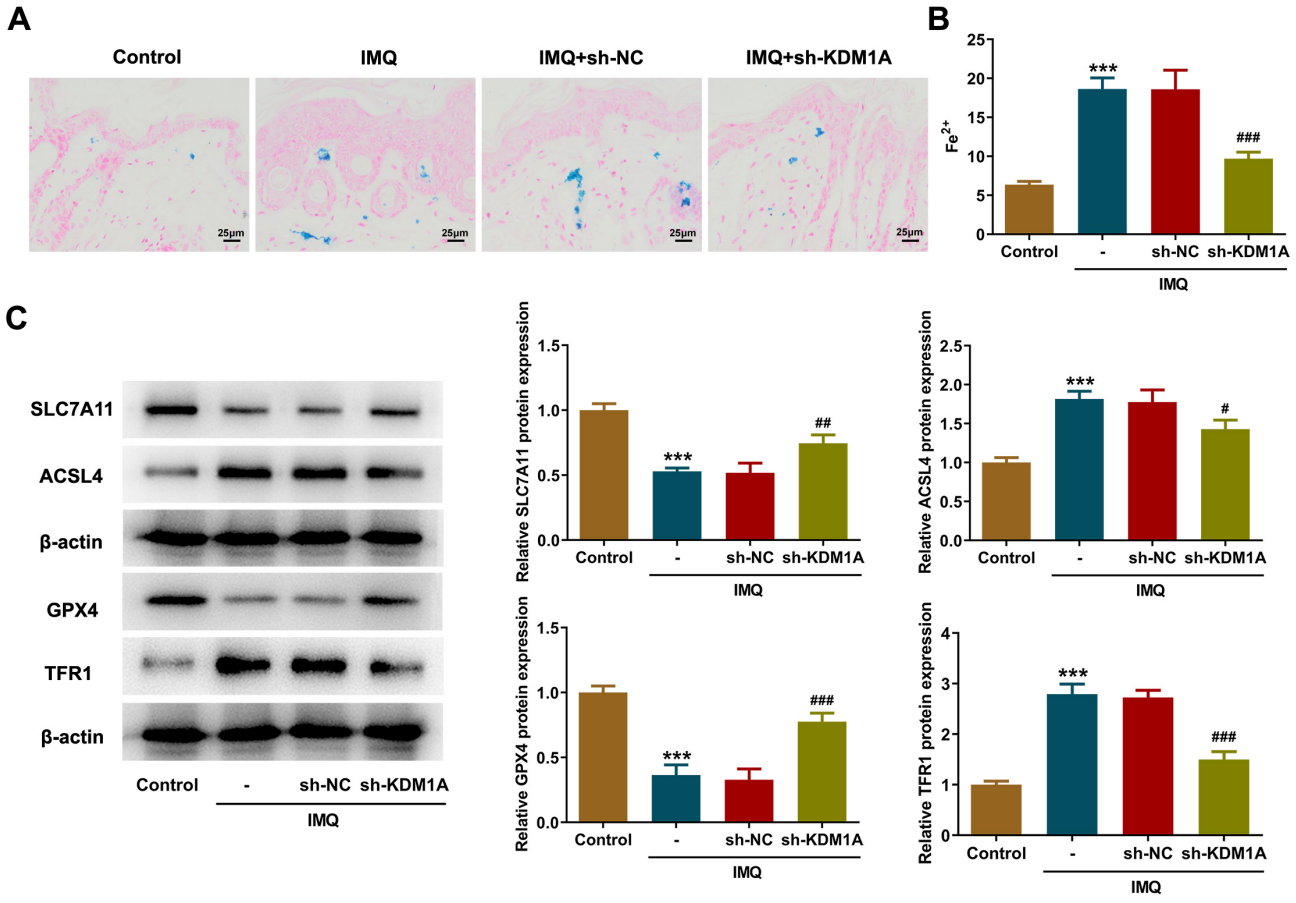

Fig. 3. KDM1A inhibition reduces ferroptosis in mice. (A) Prussian blue staining showing iron deposition in skin tissue. (B) Iron ion levels in tissues were detected by kits. (C) Ferroptosis-related protein expression levels in tissues were determined by western blot analysis. N = 3, ***$p < 0.001$ vs. control; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ vs. IMQ + sh-NC. SLC7A11, solute carrier family 7 member 11; ACSL4, acyl-CoA synthetase long chain family member 4; GPX4, glutathione peroxidase 4; TFR1, transferrin receptor.

KDM1A Inhibition Reduces Ferroptosis in Mice

To assess the presence of ferroptosis in tissues, tissues were subjected to Prussian blue staining. Compared with that in the control group, there was obvious iron deposition in the tissues of the IMQ group, and the KDM1A knockdown group had less iron deposition than the IMQ group (Fig. 3A). Likewise, iron ion levels were increased by IMQ, and KDM1A knockdown reduced iron ion production (Fig. 3B). The levels of ferroptosis-related proteins was assessed by immunoblotting. SLC7A11 and GPX4 were decreased significantly by IMQ, while ACSL4 and TFR1 were increased. Compared with that in the IMQ + sh-NC group, KDM1A knockdown increased SLC7A11 and GPX4 protein expression and decreased ACSL4 and TFR1 protein expression (Fig. 3C).

KDM1A Inhibition Reduces Lipid Peroxidation and Ferroptosis in Keratinocytes

The level of KDM1A was upregulated in M5-induced HaCaT keratinocytes, and even in response to M5 treatment, keratinocytes with KDM1A knockdown showed reduced levels compared with those in the M5 + sh-NC group (Fig. 4A,B). The thiobarbituric acid reactants (TBARS) production rate showed that lipid peroxidation in keratinocytes was increased by M5, and KDM1A knockdown significantly reduced lipid peroxidation (Fig. 4C). Lipid peroxidation is closely related to ferroptosis, and the levels of iron ions and ferroptosis-related proteins in keratinocytes were also detected. *In vitro*, M5 increased intracellular iron ion levels, and KDM1A knockdown inhibited iron ion accumulation (Fig. 4D). SLC7A11 and GPX4 were decreased by M5, ACSL4 and TFR1 were increased significantly, and KDM1A knockdown partially reversed these protein levels (Fig. 4E).

The ferroptosis-inducing agent erastin was used to treat keratinocytes. Compared with that in the M5 + sh-KDM1A group, erastin treatment caused an increase in ROS and reduced SOD and CAT activities (Fig. 5A). The levels of IL-23, IL-1β, and IL-6 increased in response to erastin treatment (Fig. 5B), which was accompanied by an increase in the levels of the inflammation-related proteins Cox2 and iNOS (Fig. 5C).

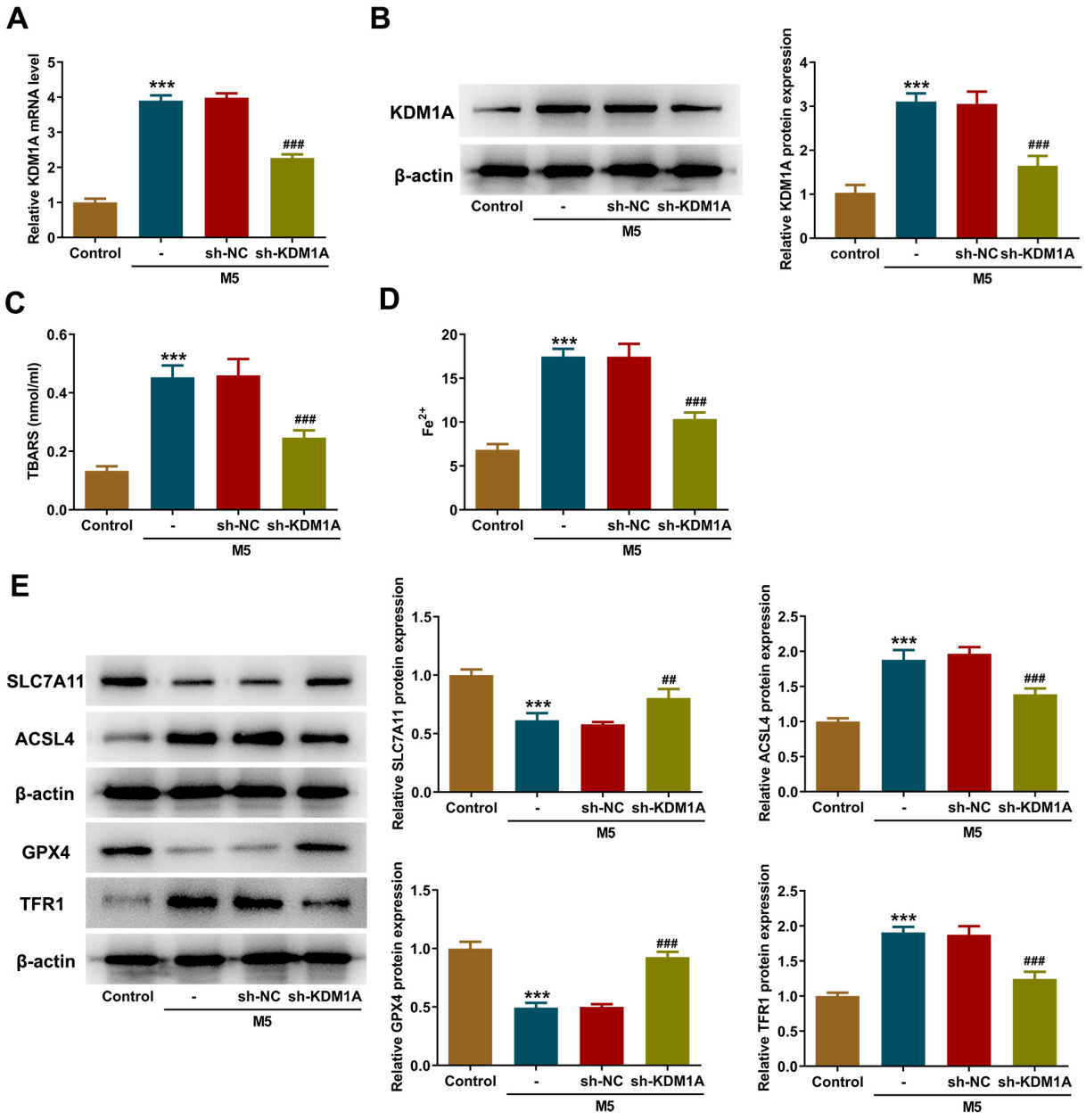

Fig. 4. KDM1A inhibition reduces lipid peroxidation and ferroptosis in keratinocytes. (A) M5-treated HaCaT keratinocytes and transfected keratinocytes; the levels of KDM1A were detected using western blotting and (B) RT–qPCR. (C) The thiobarbituric acid reactants (TBARS) production rate indicates cellular lipid peroxidation. (D) Iron ion levels in keratinocytes were detected by kits. (E) Ferroptosis-related protein expression levels in keratinocytes were determined by western blot analysis. N = 3, ***$p < 0.001$ vs. control; $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ vs. M5 + sh-NC.

Discussion

Given the intricate etiology of psoriasis, the precise causes of this disease remain unclear [15]. The principal histopathological features of psoriatic lesions include epidermal hyperproliferation, the infiltration of inflammatory cells in the epidermis and dermis, and abnormal neovascularization [16]. Our investigation revealed that KDM1A plays a pivotal role in orchestrating immune cell recruitment and instigating inflammatory responses within the skin lesions of our mouse model. Additionally, we observed an increase in the levels of inflammatory mediators in M5-treated keratinocytes.

Keratinocytes, which are the predominant cellular constituents of the epidermis, occupy a vital position within the innate immune system [17]. These cells play a crucial role in initiating, sustaining, and regulating cutaneous immune responses while also contributing to the pathogenesis of psoriasis [18]. Although keratinocytes may traditionally be considered downstream effector cells that are

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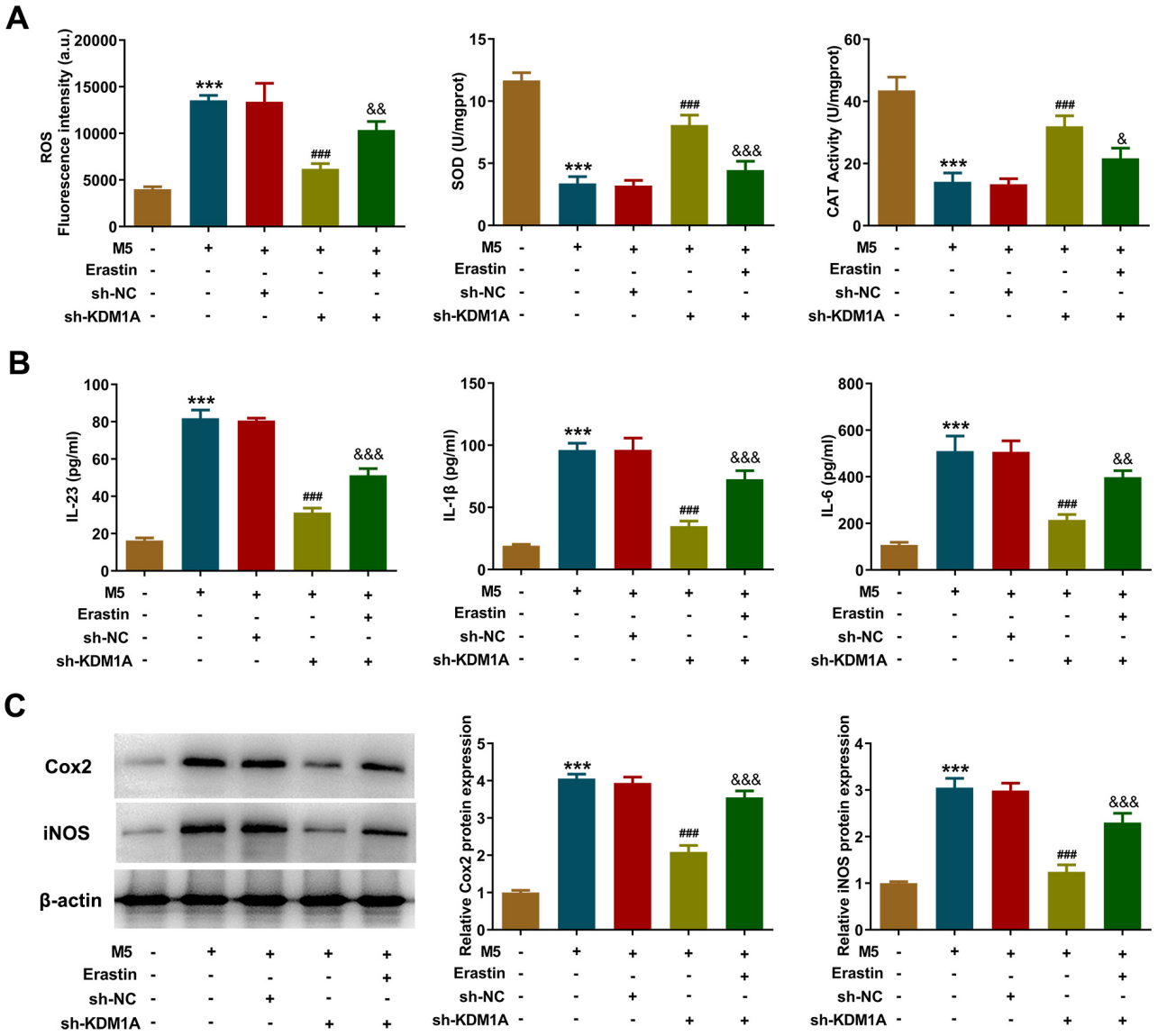

Fig. 5. Ferroptosis inducers disrupt the regulation of KDM1A. (A) The ferroptosis inducer erastin was used to treat keratinocytes, and its effects on oxidative stress levels in keratinocytes were assessed. (B) ELISA analysis of inflammatory factor levels in keratinocytes. (C) Inflammation-related protein expression levels in keratinocytes were determined by western blot analysis. N = 3, $^{***}p < 0.001$ vs. control; $^{\#\#\#}p < 0.001$ vs. M5 + sh-NC; $^{\&}p < 0.05$, $^{\&\&}p < 0.01$, $^{\&\&\&}p < 0.001$ vs. M5 + sh-KDM1A.

subject to aberrant immune activation and respond to cytokines such as IL-17 and IL-22, recent investigations have unveiled a close association between abnormal keratinocyte differentiation and the epigenetic state of basal layer keratinocytes [19–21]. This indicates that certain signaling aberrations in keratinocytes hold a central position in the pathogenesis of psoriasis. Our findings underscore the critical role of KDM1A within cells in the development of IMQ-induced psoriasis-like dermatitis in mice, suggesting that endogenously elevated KDM1A signaling and subsequent regulation may be one of the contributing factors to psoriasis susceptibility. Previous studies have also implicated keratinocyte-derived IL-23 in the pathogenesis of psoriasis through epigenetic regulation [22].

Furthermore, a wealth of evidence suggests that oxidative stress exacerbates the onset of psoriasis. Impairment of the antioxidant defense system affects lipid peroxidation, DNA modification, and the release of inflammatory molecules [23]. Our research demonstrates that inhibiting KDM1A can effectively reduce ROS production while enhancing the activities of SOD and CAT *in vivo* and *in vitro*. Additionally, our study used TBARS to assess the levels of lipid oxidation products, including the prominent product MDA and related compounds, and revealed significant inhibition of lipid peroxidation products. As previously mentioned, the concept of ferroptosis is intrinsically linked to lipid peroxidative buildup and iron overload [15]. Our research indicates a marked decrease in Fe^{2+} lev-

els in KDM1A knockdown cells, which is accompanied by an increase in GPX4 (responsible for inhibiting ferroptosis through lipid hydroperoxide scavenging) and a decrease in ACSL4 (which contributes to lipid peroxidation and subsequent ferroptosis) [24,25]. Previously, limited studies have also shown the association of KDM1A with ferroptosis. For example, KDM1A knockdown was found to reduce ferroptosis and oxidative stress caused by renal ischemia-reperfusion injury, urging it a potential target for the treatment of acute kidney injury [26]. Research on the regulation of ferroptosis by KDM1A is still in its initial stages and deserves more attention. Herein, given the substantial activation of ferroptosis during the progression of psoriasis, targeting KDM1A to mitigate ferroptosis holds promise as a therapeutic approach. However, the role of KDM1A in clinical settings requires more cohort studies.

Conclusion

To summarize, our study demonstrates that inhibiting KDM1A ameliorates IMQ-induced skin psoriatic lesions in mice and attenuates oxidative stress and inflammatory responses in HaCaT keratinocytes by regulating ferroptosis. Nevertheless, psoriasis is a complex immune disease, and whether other pathways mediate the regulatory mechanism of KDM1A remains unclear. We still emphasize that these findings unveil a novel and potential therapeutic target for the treatment of psoriasis, thereby facilitating the development of clinical therapeutic agents and interventions.

Availability of Data and Materials

The data are available from the corresponding author upon reasonable request.

Author Contributions

JT and LZ contributed to the conceptualization and investigation. XZ and LY contributed to the investigation, methods, and formal analysis. LY contributed to the draft. 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

All animal experiments were carried out in accordance with the National Institutes of Health guide for the care and use of Laboratory animals. This study was approved by Shaanxi Provincial People's Hospital (No. IACUC-20230004).

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest.

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