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Research article

IOX1 impedes host inflammation in imiquimod-triggered psoriasis

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ABSTRACT

Psoriasis is a chronic autoimmune disease with an unknown etiology and highly limited treatment strategies. The drugs currently used in the treatment of psoriasis are rarely recommended for long-term use owing to the serious side effects. Although different targets have been identified for controlling psoriasis, the role of epigenetic modifications as therapeutic targets is yet to be elucidated. Here, we investigated the therapeutic potential of 8-hydroxyquinoline-5-carboxylic acid (IOX1), a novel drug with a genetic target, in psoriasis. The daily topical administration of IOX1 in a mouse model of imiquimod (IMQ)-induced psoriatic inflammation reduced inflammatory reactions in the skin and lowered the PASI score. Furthermore, intraperitoneally injected IOX1 repressed the inflammatory status induced by IMQ in psoriatic mice by reducing the mRNA levels of pro-inflammatory cytokines, restoring splenocyte populations, and regulating macrophage polarization. Our findings indicate the remedial effects of IOX1 on dermatitis psoriasis and the potential of IOX1 as a therapeutic compound in psoriasis.

1. Introduction

Psoriasis is a chronic inflammatory autoimmune disease with a global incidence rate of 1%–3% [1, 2]. The disease is characterized by the formation of itchy plaques covered with a silvery scale, mostly spanning large areas of the skin, extensor surfaces of the limbs, and the scalp [3, 4], accompanied by histological features such as epidermal keratosis, dermal capillary acanthosis, and keratinization [5, 6]. Although the disease itself is not highly prevalent and its temporary symptoms can be alleviated, the long-term outcomes of the disease are irreversible and might prompt clinical complications such as arthritis, type 2 diabetes mellitus, cardiovascular disease, inflammatory bowel disease, and depression [7, 8]. Furthermore, the options for the treatment of psoriasis are limited to a few classes of drugs, such as retinoids, glucocorticoids, and vitamin D derivatives. However, prolonged treatment with these drugs has led to serious side effects, including immunosuppressive and drug withdrawal symptoms [9].

While the exact etiology of psoriasis has not been identified [9], studies have shown that factors such as immune system dysregulation and genetic alterations trigger a cascade of inflammatory reactions, eventually leading to psoriasis [10]. Activated and inactivated immune cells produce a wide variety of cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-6, IL-17A, IL-17F, and IL-22, triggering psoriasis pathogenesis and hyperproliferation [11, 12, 13]. In particular, the upregulation of IL-17A and the associated genes in patients with psoriasis with lesions or no lesions and the production of IL-17A by

Table 1. Primers for real-time quantitative PCR.

Gene name		5′–3′ primer Sequence
GADPH	Forward	TGTGTCCGTCGTGGATCTGA
	Reverse	TTGCTGTTGAAGTCGCAGGAG
TNF-α	Forward	ACTCCAGGCGGTGCCTATGT
	Reverse	GTGAGGGTCTGGGCCATAGAA
IL-6	Forward	CCACTTCACAAGTCGGAGGCTTA
	Reverse	TGCAAGTGCATCATCGTTGTTC
IL-17A	Forward	GAAGGCCCTCAGACTACCTCAA
	Reverse	TCATGTGGTGGTCCAGCTTTC
IL-17F	Forward	TGTCCCACGTGAATTCCAGA
	Reverse	CATTGATGCAGCCTGAGTGTC
IL-22	Forward	TCCAGCAGCCATACATCGTC
	Reverse	CTTCCAGGGTGAAGTTGAGCA

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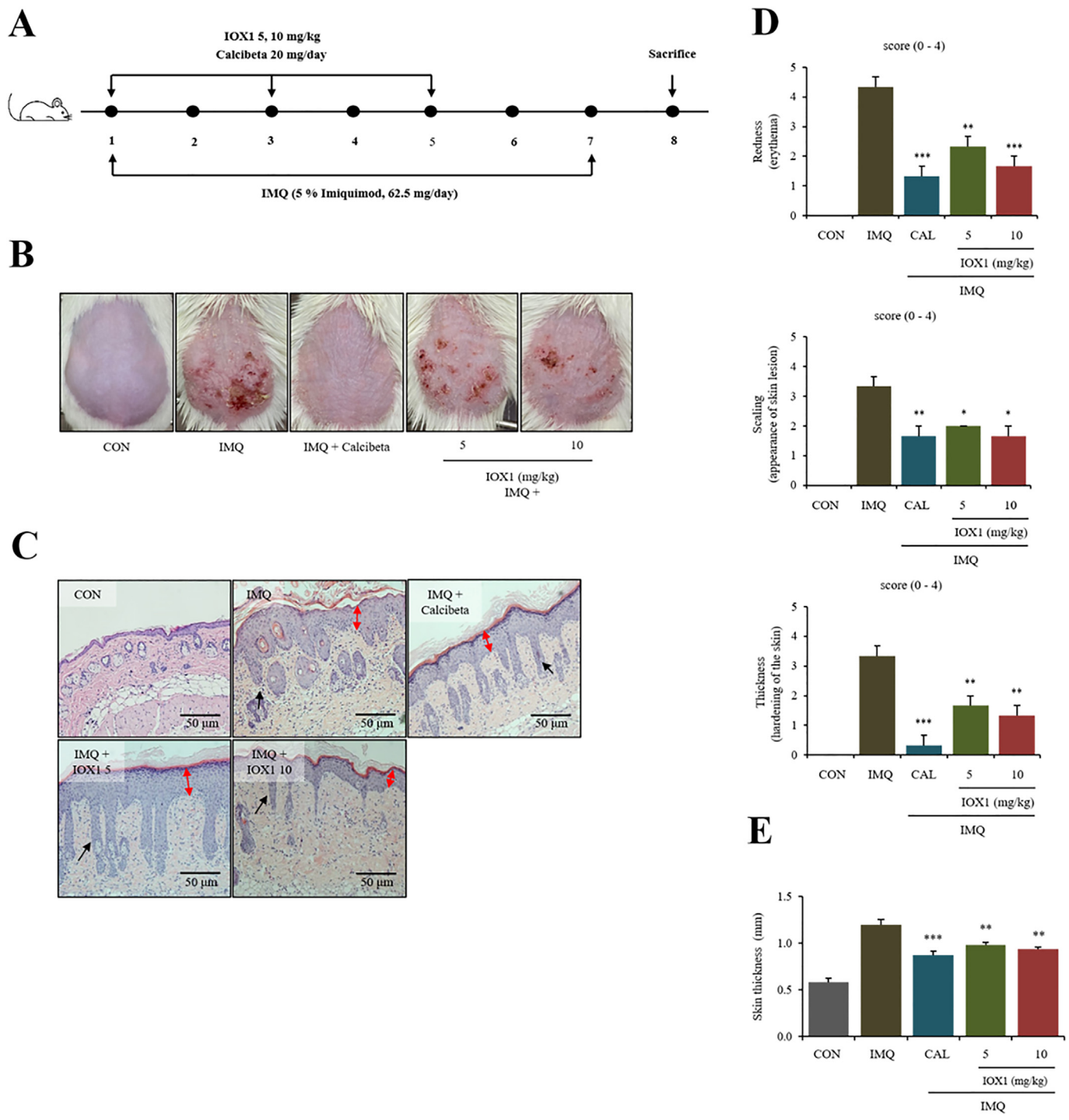


Figure 1. Effects of IOX1 in an IMQ-induced psoriatic mouse model. A) Experimental schedule. Calcibeta (20 mg/cm^2) was topically applied on the shaved back of mice on days 1, 3, and 5. IOX1 (5 and 10 mg/kg) was administered via intraperitoneal injection on days 1, 3, and 5. B) Psoriatic changes on the dorsal skin of mice after 7 days. C) Skin tissues were collected from mice from different groups, fixed in 10% formalin, and cut into sections of 5 μm. Staining was performed using hematoxylin and eosin. Images were acquired using a bright field microscope at 20× magnification. The results of one of three representative experiments are shown. D) Cumulative Psoriasis Area Severity Index (PASI) scoring of mice based on redness, scaling, and thickness was performed with the scores ranging from 0 to 4 (0-none, 1-mild, 2-moderate, 3-severe, and 4-very severe) on the last day of the experiment. IOX1 treatment (10 mg/kg) reduced redness (erythema) ($P < 0.001$), scaling (desquamation) ($P < 0.05$), and thickness (induration) ($P < 0.01$). E) IOX1 reduced skin thickness ($P < 0.05$). Skin thickness was measured using skin calipers. Data are presented as mean ± SEM. *, $P < 0.05$; **, $P < 0.01$; and ***, $P < 0.001$. $p < 0.05$ was considered statistically significant.

psoriatic lesion-related cells plays a key role in the abnormal proliferation and differentiation of keratinocytes, abnormal proliferation of blood vessels, stimulation of immune cells, and mediation of cell–cell interactions [14]. The coordination between the programming of T cell differentiation and epigenetic regulation of histone modification is integrated with transcription factors via control of the chromatin structure and DNA [15]. However, the role of epigenetic modifications in psoriasis is yet to be elucidated.

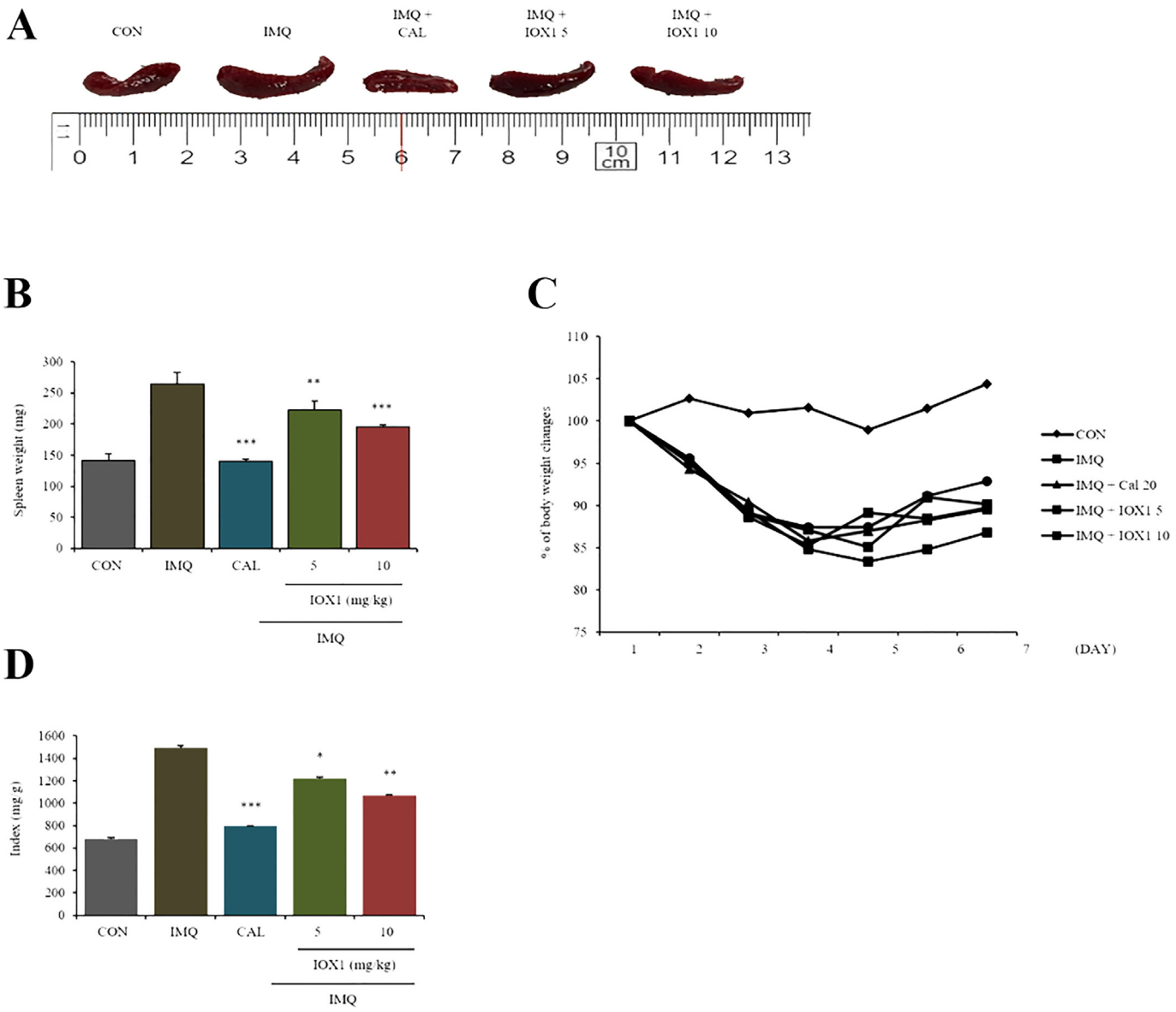


Figure 2. Effects of IOX1 on the spleen and the body weight of psoriatic mice. Mice were treated with IMQ, calcibeta, and IOX1 (schedule Figure 1A), following which A) the spleen sizes were measured, and B) the spleen weights reduction were recorded ($P < 0.01$ for IOX1 (5 mg/kg), and $P < 0.001$ for IOX1 (10 mg/kg)). C) The weight changes in mice were recorded daily. D) The decreased spleen and bodyweight ratio ($P < 0.05$ for IOX1 (5 mg/kg), and $P < 0.01$ for IOX1 (10 mg/kg)) were calculated. The results of one of three representative experiments are shown. Data are presented as mean ± SEM. *, $P < 0.05$; **, $P < 0.01$; and ***, $P < 0.001$. $p < 0.05$ was considered statistically significant.

8-hydroxyquinoline-5-carboxylic acid (IOX1) is a promising and effective cell-permeable chemical known for the broad-spectrum inhibition of most proteins of the 2-oxoglutarate (2OG) oxygenase subfamily [16]. IOX1 mimics the interaction of chelated metals and carboxylate involved in 2OG binding, making it the most potent agent against a representative panel of non-JmjC 2OG oxygenase [17]. Some studies have shown that 2OG oxygenases act as therapeutic targets for diseases such as cancer, anemia, and ischemia-related disorders [18, 19]. Moreover, the interference of IOX1 with gene expression levels has been shown to lead to various therapeutic indications in a wide range of diseases, such as blood disorders, diabetes, fibrosis, neurological disease, and viral infection [20, 21, 22, 23, 24]. Most recently, the effects of IOX1 on acute inflammatory disease and sepsis have been demonstrated [25]. However, the effect of IOX1 on chronic inflammatory diseases, such as psoriasis, remains unknown. To this end, we investigated the potential therapeutic effects of IOX1 against psoriasis in a mouse model of imiquimod (IMQ)-triggered psoriatic inflammation. In this study, IOX1 attenuated the clinical and histological symptoms of psoriasis, suppressed inflammatory reactions, and reduced endotoxin levels in psoriatic mice. Collectively, our results indicate the potential therapeutic effects of IOX1 in dermatitis psoriasis.

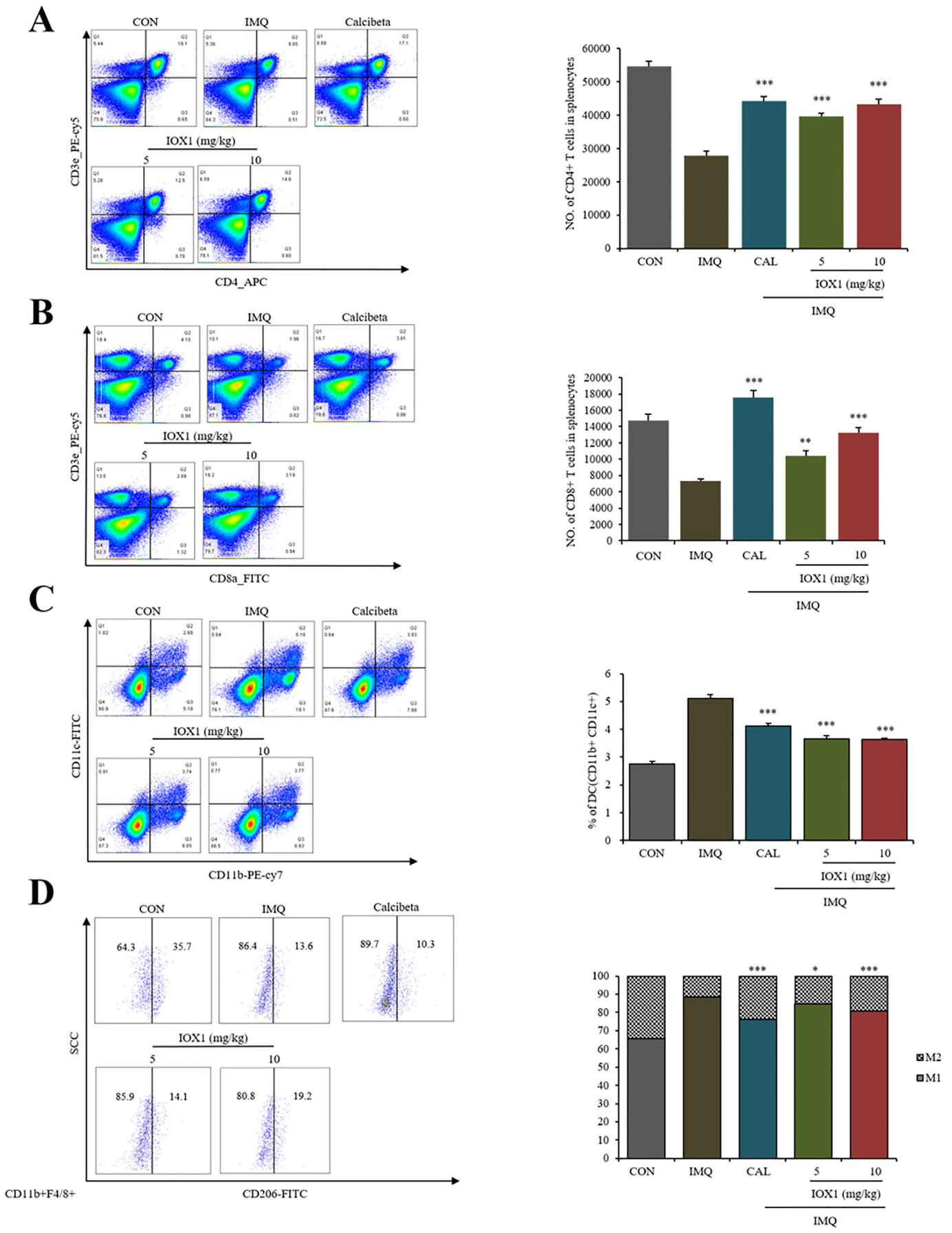
2. Materials and methods

2.1. Mice

Six-week-old male BALB/c mice were purchased from Orient Bio (Daejeon, South Korea). The procedures used in the study were approved and monitored by the Institutional Animal Care and Use Committee of Konkuk University (IACUC number: KU20080).

2.2. Reactives and reagents

IOX1 was purchased from Selleckchem (Houston, TX, USA). IMQ (Aldara cream) was purchased from Dong-a ST (Seoul, Korea). Calcibeta ointment was purchased from Kolmar (Seoul, Korea).



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2.3. Animal treatment and sample collection

Eighteen mice were randomly divided into six groups (n = 3). A 5% IMQ cream (62.5 mg/day) was administered topically on the shaved back of each mouse for 7 consecutive days, and calcibeta ointment (20 mg/cm^2) was topically applied to the shaved back of each mouse on days 1, 3, and 5. IOX1 (5 and 10 mg/kg) was administered intraperitoneally on days 1, 3, and 5. The body weight of each mouse was recorded daily.

2.4. Evaluation of skin inflammation severity

An objective scoring system used in patients with clinical psoriasis was used to evaluate the severity of dorsal skin inflammation. The Psoriasis Area Severity Index (PASI) scores erythema, scaling, and skin thickness of mice on a scale of 0–4 (0-none, 1-slight, 2-suitable, 3-severe, and 4-very severe); scoring was performed on day 8 [20].

2.5. Hematoxylin and eosin (H&E) staining

The skin samples of the dorsal lesions were collected from all groups, fixed in 10% formalin solution, and embedded in paraffin. The tissues were processed as described previously [25, 26].

For histopathological examination, five thick skin sections were cut, stained with H&E, and observed under a microscope [25, 26].

2.6. Spleen weight

After the completion of the study, the spleens were collected from mice from all groups, washed, and cleaned. The weight, shape, and size of each spleen were observed and recorded.

2.7. Isolation of splenocytes

After the completion of the study, the spleens were collected and washed with cold PBS. A single-cell suspension prepared by squeezing the spleen was placed in a culture plate. Red blood cells were lysed with red blood cell lysis buffer purchased from Sigma-Aldrich (St. Louis, MO, USA). Cell suspensions were prepared at a concentration of 4×10^6 cells/mL.

2.8. Population of splenocytes

The splenocytes were treated with fluorescein (FITC) anti-CD11c antibody (clone: N418), PE-cy7 anti-CD11b antibody (clone: M1/70), PE-cy5 anti-CD3e antibody (clone: 145-2C11), FITC anti-CD8a antibody (clone: 5H10-1), antigen-presenting cell (APC) anti-F4/80 antibody (clone: BM8), FITC anti-CD206 antibody (clone: C068C2), and APC anti-CD4 antibody (clone: GK1.5) (BioLegend, Seoul, Korea). The expression of CD3e, CD11b, CD11c, CD8a, and CD4 in splenocytes was analyzed using flow cytometry (FACSCalibur, BD Bioscience, Korea).

2.9. Reverse transcription polymerase chain reaction (RT-PCR)

Skin samples were collected from the sacrificed mice and homogenized in TRIzol reagent using a homogenizer, digested in the presence of DNase I, and reverse transcribed using a high-capacity cDNA reverse transcription kit (Applied Biosystems, Foster City, CA, USA). cDNA amplification was performed using LightCycler 480 II (Roche, Basel, Switzerland) and LightCycler 480 SYBR Green I Master Mix (Roche, Basel, Switzerland) according to the manufacturer's recommendations [25]. The cytokine mRNA levels were corrected relative to the glyceraldehyde-3-phosphate dehydrogenase mRNA levels to normalize the RNA input. The relative mRNA levels of cytokines in the normal group were set to 1. The primer sequences are listed in Table 1.

2.10. Statistical analysis

All experiments were repeated at least three times to obtain consistent results. Unless otherwise stated, data are expressed as mean ± standard error of the mean (SEM). A Student's *t*-test was performed to compare the experimental groups and controls, and Tukey's multiple comparisons test was performed using Prism v3.0 (GraphPad Software, La Jolla, CA, USA) to compare multiple groups. Kaplan–Meier curves for survival rates were analyzed using the log-rank test. The threshold of statistical significance was set at $P < 0.05$.

3. Results

3.1. IOX1 alleviates IMQ-induced psoriatic inflammation

To investigate the potential therapeutic effect of IOX1 in psoriasis, we used a mouse model of IMQ-induced psoriasiform dermatitis-like inflammation. Betamethasone and calcipotriol solutions are often the first line drugs recommended for the treatment of various psoriasis conditions [3]. Therefore, mice treated with calcibeta, a betamethasone/calcipotriol based ointment, were used as the positive control (Figure 1A). As shown in Figure 1B, the patches of psoriasis triggered by IMQ treatment on the shaved dorsal skin of the mice reduced upon IOX1 application. Histological observation using H&E staining of psoriatic lesions in the IMQ group showed the presence of elongated rete ridges, a defined criteria found in psoriasis mouse models, often associated with papillomatosis seen in chronic inflammatory dermatoses [20], and might further suggest hyperkeratosis, parakeratosis, and acanthosis. Remarkably, IOX1 treatment reduced the psoriasiform lesions compared to that in calcibeta-treated mice (Figure 1C). Additionally, redness, scaling, and thickness of skin lesions reduced significantly ($P < 0.001$, $P < 0.05$, $P < 0.01$, and $P < 0.01$ respectively) in the IOX1-treated group (10 mg/kg), as indicated by the decreased PASI score (Figure 1D and E). These data demonstrate the efficacy of IOX1 in alleviating the clinical symptoms of psoriasis.

3.2. IOX1 regulates the high splenocyte count

Chronic inflammation is associated with an increased number of splenocytes; likewise, the diameter of the spleen was observed to increase in patients with psoriasis [27, 28]. We investigated the effects of IOX1 on splenocytes. The spleens of IMQ-treated mice were enlarged with a greater weight compared to those of control mice (Figure 2A and Figure 2B). Treatment with IOX1 (10 mg/kg) inhibited the proliferation of the splenocytes ($P < 0.001$) (Figure 2A and B) despite the absence of any significant effects on reversing the body weight loss observed in the IMQ group (Figure 2C), besides reducing the spleen and body weight ratio calculation index ($P < 0.01$) (Figure 2D).

Next, we examined the splenocyte populations. As shown in Figure 3A–C, IOX1 treatment (10 mg/kg) increased the population of CD3+CD4+ T cells ($P < 0.001$), CD3+CD8+ T cells ($P < 0.001$), and reduced the population of dendritic cells ($P < 0.001$), which was affected by IMQ application. Likewise, the IMQ-induced upregulation of M1

Figure 3. Effects of IOX1 on the splenocytes of psoriatic mice. Flow cytometry was performed to analyze the populations of splenocytes. In contrast to IMQ group, IOX1 (10 mg/kg) A) increased significantly the population of CD4+ T cells ($P < 0.001$), B) the population of CD8, T cells ($P < 0.001$). C) lowered the population of dendritic cells ($P < 0.001$), and D) attenuated the upregulation of M1 macrophages ($P < 0.001$). Representative gating FACs plots are shown on the left-hand side. On the right-hand side. Bar charts are shown. The results of one of three representative experiments are shown. Data are presented as mean ± SEM. *, $P < 0.05$; **, $P < 0.01$; and ***, $P < 0.001$. $p < 0.05$ was considered statistically significant.

macrophage polarization was attenuated in a dose-dependent manner in response to IOX1 treatment ($P < 0.001$, and $P < 0.05$ for 5 mg/kg, and 10 mg/kg respectively) (Figure 3D). These data suggest the importance of IOX1 in the systemic attenuation of inflammatory states in psoriatic mice.

3.3. IOX1 altered pro-inflammatory cytokine production in the spleen

Next, we examined the transcriptional level of pro-inflammatory and Th17-associated cytokines in the spleen. The cells mediate the persistent inflammation in psoriasis. Particularly, the populations of TNF-α-, IFN-γ-, and IL-2-producing Th1 cells and IL-17A-, IL-17F-, IL-22-, and TNF-α-producing Th17 cells were shown to increase in the serum and skin of patients with psoriasis [14]. IOX1 treatment restored the mRNA levels of the key inflammatory cytokines TNF-α ($P < 0.01$), IL-6 ($P < 0.05$), IL-17A ($P < 0.05$), IL-17F ($P < 0.001$), and IL-22 ($P < 0.001$) to normal levels (Figure 4A–E). These data demonstrate the transcription-regulatory effect of IOX1 in attenuating the inflammatory status of psoriatic mice.

4. Discussion

Psoriasis is a serious skin disease triggered by inflammatory agents that can affect the quality of life in patients with long-term disease [29]. Therefore, it is crucial to investigate novel treatments to suppress severe symptoms of psoriasis, especially in the absence of an efficient drug that exhibits lower cytotoxicity for long-term usage. Herein, we demonstrated that IOX1, as a therapeutic candidate that attenuates acute inflammation and a wide range of diseases such as blood disorders and microbial infection [20, 21, 22, 23, 24], exerts a therapeutic effect in chronic inflammation-based diseases such as psoriasis. Our data showed that psoriatic clinical symptoms induced by IMQ and measured using the PASI score were markedly attenuated by IOX1 (Figure 1D). These findings support the therapeutic potential of IOX1 in treating irreversible psoriatic inflammation. It is worth to note that Calcibeta appears to have almost the same effectiveness in comparison to the effectiveness of IOX1 at the least bearing dose due to potential toxicity. However, Calcibeta is only effective in mild-to-moderate psoriasis as a fixed combination, Calcipotriol/betamethasone dipropionate, as described in the manufacturer brochure. Our findings demonstrated the ability of IOX1 to exert the same effects against the inflammatory state in psoriasis with no combination which suggest the potential broad range of anti-inflammatory activities that IOX1 might possess, and that can be further exploited to address other inflammatory based diseases.

Additionally, as observed from the H&E data, the histological and pathological consequences of psoriasis, such as hyperkeratosis, parakeratosis, acanthosis, and elongated rete ridge that suggests papillomatosis, observed in the IMQ-induced psoriasis group, were reverse by IOX1 treatment (Figure 1C) [20]. Correspondingly, the spleen is an important organ in the immune system. The chronic inflammatory state triggers spleen enlargement and later redirects the splenocyte population to the inflammatory site [28]. This was further confirmed by IMQ administration in the mouse model. In particular, the interactions between dendritic cells and T cells and the associated downstream responses play essential roles during plaque formation in chronic psoriasis [30, 31].

Macrophages are a type of immune cells that are active during inflammation; macrophages mature and polarize into different subsets, including pro-inflammatory M1 and anti-inflammatory M2 subtypes [32]. The involvement of inflammatory responses, chemokine ligands, and pro-inflammatory cytokines in immune stimulation and defense against microbial infections drives M1 polarization. In contrast, M2 macrophages participate in tissue repair via anti-inflammatory reactions and anti-inflammatory cytokine production [14, 32]. IOX1 significantly attenuated splenomegaly (Figure 2A). In addition, IOX1 restored the population of CD4+ T cells, CD8+ T cells, and dendritic cells and significantly restored the ratio of M1/M2 polarization (Figure 3). This highlights the effective role of IOX1 in balancing the dynamics of

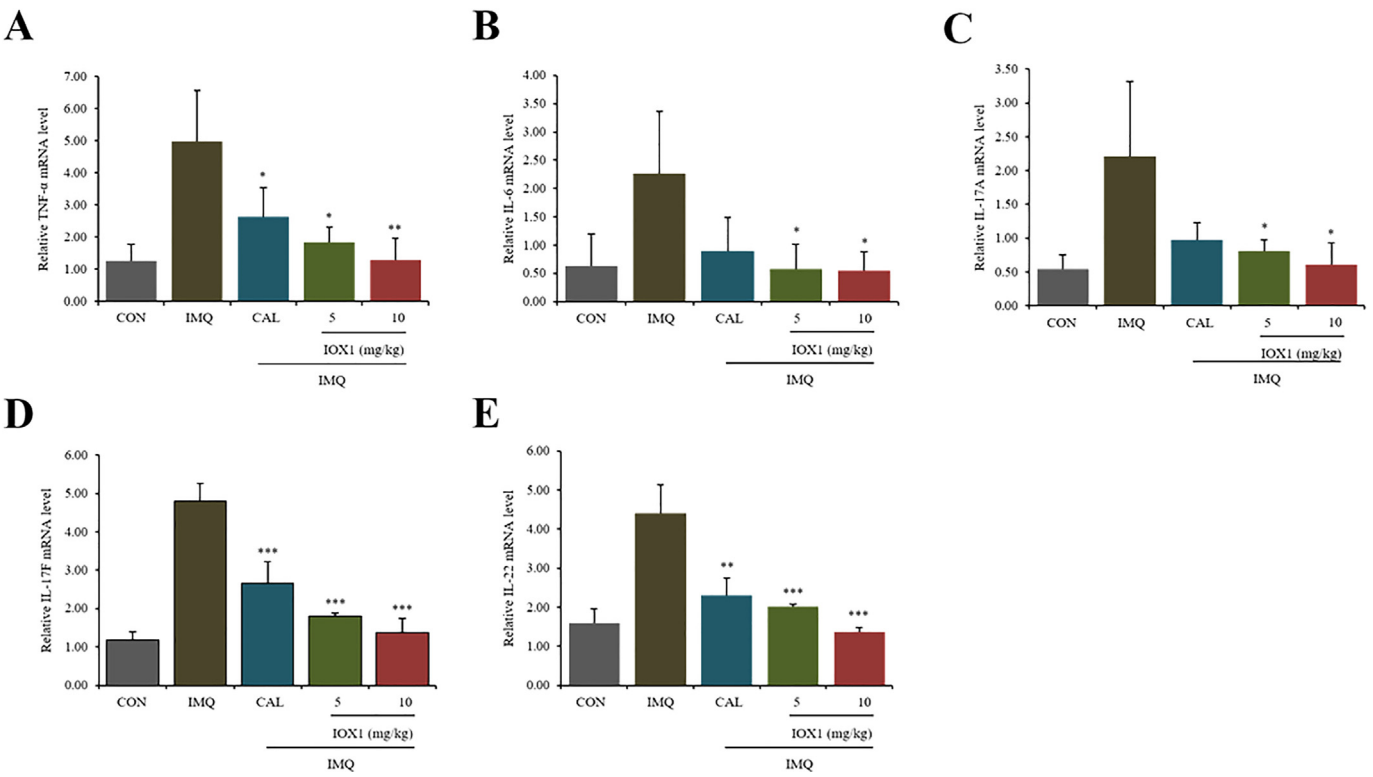

Figure 4. Effects of IOX1 on pro-inflammatory cytokines in the spleen. IOX1 (10 mg/kg) reduced the mRNA levels of the cytokines (A) TNF-α ($P < 0.01$), (B) IL-6 ($P < 0.05$), (C) IL-17A ($P < 0.05$), (D) IL-17F ($P < 0.001$), and (E) IL-22 ($P < 0.001$) in the spleen. Data are presented as mean ± SEM. *, $P < 0.05$; **, $P < 0.01$; and ***, $P < 0.001$. $p < 0.05$ was considered statistically significant.

immune cell trafficking during chronic inflammation-based diseases such as psoriasis.

A wide variety of cells, including endothelial cells, macrophages, and keratinocytes, produce central cytokines associated with the exacerbation of psoriasis [10, 14]. Our data showed that the transcripts of pro-inflammatory cytokines such as TNF-α, IL-6, IL-22, IL-17A, and IL-17F were expressed in the spleen lesions of IMQ-treated mice. The high rate of transcription of pro-inflammatory genes exerts a significant influence on the abnormal proliferation and differentiation of keratinocytes, abnormal proliferation of blood vessels, stimulation of immune cells, and mediation of cell–cell interactions [14]. Notably, IOX1 attenuated the mRNA levels of these cytokines, indicating its potential role in disrupting the pathophysiological state in psoriatic mice at the transcriptional level. Collectively, our findings elucidate the role of IOX1 in regulating immune reactions in a chronic inflammatory environment, particularly in psoriasis, and advocates IOX1 as a promising therapeutic compound that can attenuate long-term damage caused by psoriasis.

Declarations

Author contribution statement

Joo Eun Shin, Su Jin Lee: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Amal Gharbi, In Duk Jung, Yeong Min Park: Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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