Journal of Inflammation Research

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ORIGINAL RESEARCH

ALDH2 Ameliorates Acute Gouty Arthritis Through Inhibiting NLRP3 Inflammasome and Pyroptosis by Nrf2/ROS Pathway

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Background: Gouty arthritis is a common disease characterized by the deposition of monosodium urate (MSU) crystals in joint and non-joint structures. Nonetheless, the role of aldehyde dehydrogenase 2 (ALDH2) in the pathophysiology of acute gout remains unclear. This study aimed to evaluate the role of ALDH2 in MSU crystal-induced acute gout attacks and related mechanisms and to identify potential therapeutic strategies for gout management.

Methods: Peripheral blood mononuclear cells (PBMCs) from gout patients and healthy controls were isolated via Ficoll-Paque Plus density gradient centrifugation. A mouse model of gouty arthritis was established by injecting MSU crystal suspension into the foot pad. In vitro, PMA-differentiated THP-1 cells were stimulated with MSU crystals. We then investigated the effect of the ALDH2 agonist Alda-1 on MSU crystal-induced acute inflammation. Furthermore, the Nrf2 inhibitor ML385 was used to define the Nrf2 pathway's role in mediating ALDH2 activation effects during acute gout attacks.

Results: We found that compared to healthy controls, ALDH2 expression was significantly decreased in the PBMCs of patients with acute gout and negatively correlated with C-reactive protein levels. In mice models with acute gout, treatment with Alda-1 effectively mitigated MSU-induced footpad edema, along with reductions in inflammatory cell infiltration and pro-inflammatory cytokine production in the local tissue of the footpad. In vitro studies demonstrated that Alda-1 significantly reduced oxidative stress induced by MSU crystal stimulation and suppressed the activation and assembly of the NLRP3 inflammasome, as well as the resulting pyroptosis. Further experiments revealed that Alda-1 treatment promoted Nrf2 nuclear translocation, alleviating oxidative stress and cellular inflammation.

Conclusion: Our findings suggest that Alda-1-mediated activation of ALDH2 can alleviate MSU-induced oxidative stress and inflammation by regulating the Nrf2/ROS pathway and may represent a promising therapeutic strategy for managing acute gouty arthritis.

Keywords: ALDH2, Nrf2, acute gouty arthritis, pyroptosis, reactive oxygen species (ROS)

Introduction

Gout is a common disease resulting from the deposition of monosodium urate (MSU) crystals in both joint and non-joint structures,[1] with an overall prevalence ranging from 1% to 4% in the general population. In certain countries or regions, this prevalence can increase to as much as 10%. Acute gout attacks arise when deposited MSU crystals interact with resident macrophages and activate the NLRP3 inflammasome, resulting in the release of interleukin-1β (IL-1β),[2] which is characterized by pain, swelling, fever, and restricted mobility in the affected joints.[3]

The activation of the NLRP3 inflammasome is vital for acute gout attacks. This process begins in macrophages and occurs in two steps: First, exposure to MSU crystals, and second, activation of the NF-κB transcription factor pathway. Once activated, NLRP3 and the adaptor protein ASC move from the endoplasmic reticulum and mitochondria to form a complex near the nucleus. This complex then recruits pro-caspase-1, leading to caspase-1 activation

Received: 9 May 2025
Accepted: 8 August 2025
Published: 14 August 2025

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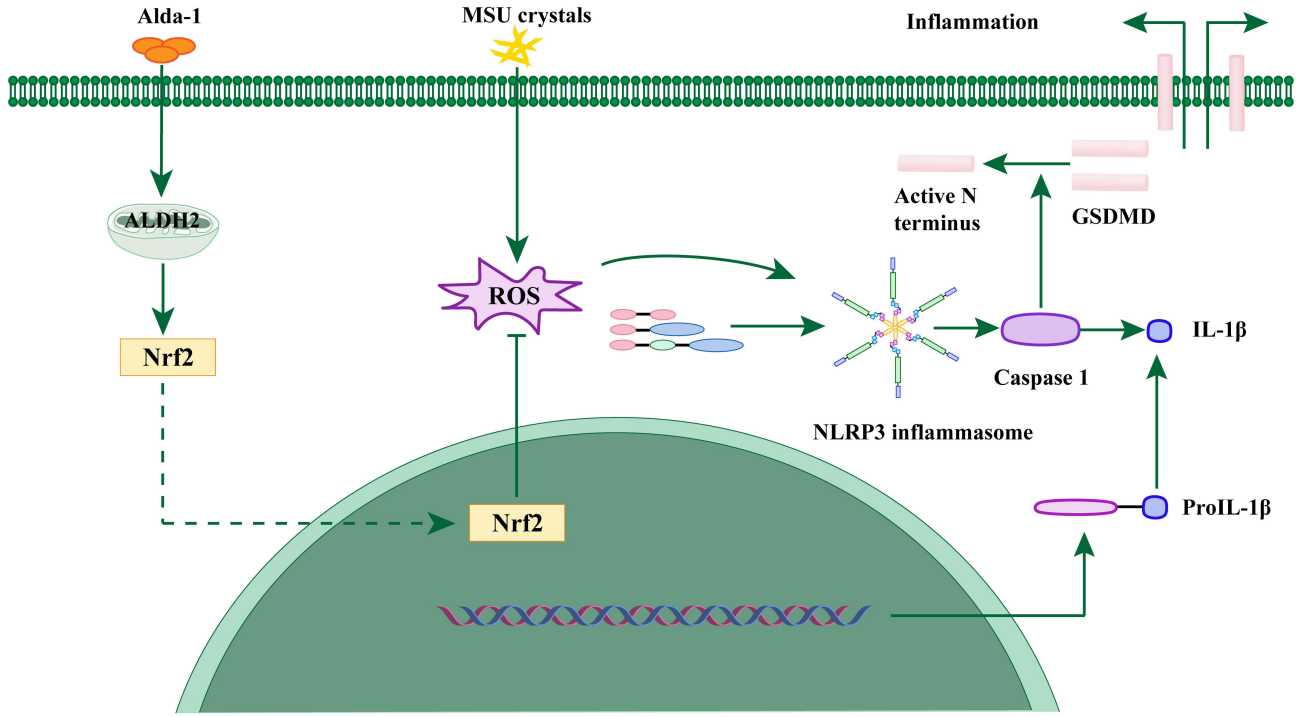
Graphical Abstract



and conversion of the inactive precursor of IL-1β into its active form.[4–6] Activated caspase-1 can also trigger pyroptosis by cleaving gasdermin D (GSDMD), which creates pores in the cell membrane and releases IL-1β, further promoting gout attacks.[7] Additionally, MSU crystals stimulate the production of reactive oxygen species (ROS) within cells, activating inflammatory responses and oxidative stress, which can ultimately lead to cell death.[8] Oxidative stress can further exacerbate inflammatory responses by facilitating the assembly and activation of the NLRP3 inflammasome.[9]

Aldehyde dehydrogenase 2 (ALDH2) is an enzyme that is critical for mitigating oxidative stress damage within the human body and is primarily responsible for oxidizing acetaldehyde, a by-product of alcohol metabolism, into acetic acid and metabolizing reactive aldehydes generated by oxidative stress-induced lipid peroxidation.[10] ALDH2 deficiency induces excessive acetaldehyde accumulation and oxidative stress, leading to mitochondrial DNA (mtDNA) damage and consequent mitochondrial dysfunction.[11] Oxidized mtDNA (Ox-mtDNA), released into the cytosol, binds to NLRP3, thereby triggering inflammasome activation. Furthermore, Ox-mtDNA fragments activate the cGAS-STING signaling pathway, generating pro-inflammatory extracellular DNA.[12,13] A critical cellular antioxidant system is the nuclear factor-erythroid 2 related factor 2 (Nrf2) pathway. Nrf2, a transcription factor, induces the expression of genes containing the antioxidant response element (ARE)/electrophile response element, thereby protecting cells from exogenous substances and electrophilic stress while restoring redox homeostasis.[14–16] Recently, Zeng et al demonstrated that pharmacological activation of Nrf2 counteracts gouty arthritis in a mouse model via Nrf2-mediated antioxidant signaling.[17] Small molecule agonists of ALDH2, such as Alda-1, can activate ALDH2, reduce oxidative stress damage, and inhibit NLRP3 inflammasome activation, which has been exhibited to improve various diseases, including cardiovascular disorders, neurodegenerative diseases, diabetes, and liver diseases.[18–21] Nevertheless, the precise role of ALDH2 in acute gout remains unclear.

In summary, we hypothesized that ALDH2 may possess the capacity to inhibit MSU crystal-induced activation of the NLRP3 inflammasome and pyroptosis, as well as reduce ROS, thereby suggesting that ALDH2 can interact with the ROS/Nrf2 axis to regulate acute gout attacks.

Methods and Reagents

Antibodies and Reagents

Antibody against ALDH2 (ab133306), IL-1 beta (ab254360), cleaved N-terminal GSDMD (ab215203), NLRP3 (ab263899), Goat Anti-Rabbit IgG H&L (Alexa Fluor® 488) (ab150077), and Goat Anti-Rabbit IgG H&L (Alexa Fluor® 594) (ab150080) was acquired from Abcam. Antibodies against GSDMD (20770-1-AP), F4/80 (28463-1-AP), ASC (10500-1-AP), Caspase 1/P20 Polyclonal antibody (22915-1-AP) and β-actin (66009-1-Ig) were bought from Proteintech. Antibody against NRF2 (12721), Cleaved Caspase-1 (4199), Horseradish peroxidase (HRP)-conjugated goat anti-rabbit IgG (7074S), and HRP-conjugated goat anti-mouse IgG (7076S) were procured from Cell Signaling Technology. Alda-1 (HY-18936). The DSS Crosslinker (HY-W019543), Mito-TEMPO (HY-112879), N-Acetylcysteine (HY-B0215), and ML385 (HY-100523) were obtained from MedChemExpress.

Participants

Male patients diagnosed with primary gout at the Department of Rheumatology, the Second Affiliated Hospital of Zhejiang University School of Medicine from November 2023 to July 2024, aged 18 to 60, were selected, and age-matched healthy males with serum uric acid levels < 420 μmol/L were used as the control group. Patients were diagnosed with primary gout according to the 2015 American College of Rheumatology/European League Against Rheumatism classification criteria for gout.[22] Specifically, patients who experienced gout attacks within three days were classified as having acute gout, while those who had not experienced gout attacks for at least 14 days were identified as intermittent patients. Blood samples were collected from patients during their visits and from healthy controls during physical examinations. Peripheral blood mononuclear cells (PBMCs) were isolated from patients with gout and healthy controls using Ficoll gradient centrifugation, and RNA was extracted. This study was approved by The Second Affiliated Hospital of Zhejiang University School of Medicine Ethics Committee (2021–0027).

MSU Crystal-Induced Acute Gouty Arthritis Model Establishment

Male C57BL/6J mice (6–8 weeks old) were obtained from the Experimental Animal Center of the Second Affiliated Hospital of Zhejiang University School of Medicine and housed under a 12-h light/12-h dark cycle. Mice were acclimated to the housing conditions for one week before the experiment. All animal experimental protocols followed the Guidelines for the Care and Use of Laboratory Animals and were approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine (2024–268). Alda-1 (10% DMSO + 90% corn oil, 200 μL, intraperitoneal injection) was administered 48, 24, and 1 h before MSU injection (40 μL of 25 mg/mL MSU crystal suspension was injected into the right footpad). Mice in the control and model groups were administered vehicle (10% DMSO + 90% corn oil, 200 μL, intraperitoneal injection). The thickness of the footpads was measured using a vernier caliper at 0, 2, 4, 6, 8, 12, and 24 h post-injection of MSU crystals, and the mice were sacrificed 24 h after the injection.

Cell Culture

The THP-1 cell line was obtained from Procell Biotech (Wuhan, China), cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum, 50 μM β-mercaptoethanol, 100 U/mL penicillin, and 100 μg/mL streptomycin, and incubated at 37 °C in a humidified 5% CO_2 incubator. THP-1 cells were differentiated into macrophages through treatment with 100 ng/mL phorbol 12-myristate 13-acetate (Sigma-Aldrich) for 48 h.

Preparation of MSU Crystals

Briefly, 1 g of uric acid (Sigma-Aldrich) was dissolved in 200 mL of double-distilled water and heated to 80 °C until completely dissolved; 0.5 N NaOH was titrated to adjust the pH to 8.9. After overnight incubation at 4 °C, crystal

precipitation was observed. The crystals were washed with double-distilled water, dried at 40 °C, then milled, suspended in phosphate-buffered saline (PBS) at a concentration of 20 mg/mL, and sterilized at 180 °C for 2 h for subsequent experiments. Needle-shaped or rod-shaped crystals were observed under a polarizing microscope.

ALDH2 Activity Assay

A mitochondrial ALDH2 activity assay kit (ab115348, Abcam) was used to detect ALDH2 enzyme activity in the cells. Briefly, adherent cells were scraped off, lysed on ice with extraction buffer for 20 min, and then centrifuged at 4 °C for 20 min at 16,000 × *g*. The conversion of oxidized nicotinamide adenine dinucleotide to reduced nicotinamide adenine dinucleotide (NADH) was monitored using a multifunctional microplate reader (Spark Multimode Microplate Reader, TECAN), which measured absorbance changes at 450 nm every 5 min for 120 min. The NADH production level was determined by spectrophotometry. The reaction rate of ALDH2 was expressed as μmol of NADH per minute per mg of protein.

ASC Oligomerization Assay

Crosslinking ASC oligomer crosslinking was performed as previously described.[23] Briefly, THP1 cells were lysed in NP-40 buffer (20 mM HEPES-KOH pH 7.5, 150 mM KCL, 1% NP-40, and protease inhibitors). The lysates were centrifuged at 330 × *g* for 10 min at 4 °C. The pellets were washed, resuspended in PBS and 2 mM disuccinimidyl suberate, and incubated at RT for 30 min with rotation. The samples were centrifuged at 330 × *g* for 10 min at 4 °C. The supernatant was removed, and the crosslinked pellets were resuspended in a sample buffer, boiled, and analyzed by immunoblotting.

Cell Counting Kit-8 (CCK-8) Assay

All procedures were strictly performed following the manufacturer's instructions. The CCK-8 (CK04, Tongren Chemical) was used to assess cell viability after Alda-1 treatment. Briefly, THP-1 cells were seeded in a 96-well plate and treated with varying concentrations of Alda-1 (10, 20, and 40 μM) or with MSU crystal suspension (250 μg/mL) for 12 h. Then, 10 μL of the CCK-8 reagent was added to each well and incubated for 4 h. Finally, the absorbance was measured at 450 nm using a microplate reader.

LDH Assay

Cells were plated in 96-well plates and treated with the appropriate reagents. Subsequently, cell cytotoxicity was evaluated based on the release of LDH (C0017, Beyotime, China), following the manufacturer's guidelines. The optical density was measured using a microplate readerSpark.

ROS and MitoSOX Detection

A 10 μM fluorescence probe, 2′,7′-dichlorodihydrofluorescein diacetate (Beyotime, China), was used to detect the ROS produced by THP-1 cells. Briefly, cells were seeded in a 6-well plate and treated with DCFH-DA at 37 °C for 30 min, followed by three washes with 1 mL PBS. Fluorescence images were captured using a Leica DMi8 inverted biological microscope with an excitation wavelength of 485 nm and an emission wavelength of 525 nm. Mitochondrial ROS (mtROS) levels were measured based on the fluorescence intensity derived from MitoSOX (MCE, HY-D1055) in live-cell imaging, conducted using a 5 μM solution for 15 min at 37 °C. The red fluorescence emitted by MitoSOX in THP-1 cells was detected using a Leica DMi8 inverted biological microscope.

JC-1 Assay

The mitochondrial membrane potential was determined using a JC-1 Assay Kit (C2006, Beyotime, China). The specific steps were performed following the manufacturer's instructions.

Immunofluorescence

After stimulation, THP-1 cells were fixed with 4% paraformaldehyde for 30 min. The cells were permeabilized with 0.1% Triton X-100 for 30 min and blocked with 1% BSA. After dewaxing and antigen retrieval, paraffin sections of the

mouse footpad were blocked with 3% BSA. THP-1 cells and mouse footpad tissue sections were incubated overnight with primary antibodies (anti-F4/80, Proteintech, 28463-1-AP, 1:4000; anti-ASC, Proteintech, 10500-1-AP, 1:100) at 4 °C. The next day, the cells were incubated with Alexa Fluor dye-conjugated secondary antibodies at 1:200 dilution for 1 h. After DAPI staining, fluorescence images were observed using a Leica STELLARIS 5 Confocal Microscope.

Nuclear and Cytoplasmic Protein Separation

After treatment, cells were washed and harvested in cold PBS. Cytoplasmic and nuclear fractions were separated using a cell nucleus and cytoplasm protein extraction kit (P0028, Beyotime, China) following the manufacturer's instructions.

Enzyme-Linked Immunosorbent Assay (ELISA)

The cell supernatant or mouse footpad tissue was added to PBS buffer and homogenized using a tissue grinder, and the supernatant was collected and added to the wells. The secretion levels of IL-1β in the cell supernatant and mouse footpad tissue were detected using an ELISA kit (EK0394, Boster, China).

Histological Studies

After cardiac blood collection from the mice, the footpad tissue was quickly isolated and placed in a tissue fixation solution for hematoxylin-eosin (H&E) staining, allowing visualization of inflammatory infiltration in these tissues.

Quantitative Real-Time Polymerase chain reaction (qRT-PCR) assay

Total RNA was extracted using TRIzol reagent (Ambion, Thermo Scientific), and reverse transcription was performed to convert RNA into complementary DNA using a kit (RR047A, TaKaRa). Next, the PCR reaction mixture was prepared using a SYBR® Premix Ex Taq™ Kit (RR820A, TaKaRa), and qPCR was conducted on a 7500 Fast Real-Time PCR system (Applied Biosystems, Thermo Scientific) with 40 cycles of denaturation, annealing, and extension. The sequences of primers (Biolegend) for the genes are listed in Supplementary Table 1.

Western Blotting

Proteins were extracted from tissues and live cells using RIPA lysis buffer (P0013B, Beyotime) containing a protease inhibitor cocktail. Proteins were separated using 4–20% gradient SDS-PAGE gels and then transferred onto PVDF membranes (Merck Millipore). The membrane was blocked with quick blocking buffer (P0252, Beyotime) at room temperature for 10 min, followed by incubation with primary antibodies at 4 °C overnight. The membrane was then incubated with HRP-conjugated secondary antibodies at a 1:5000 dilution for 1 h. After washing with TBST, the blots were visualized using an enhanced chemiluminescence detection kit (Merck Millipore) and imaged using a chemiluminescent imaging system (Amersham ImageQuant 800). The density values of the bands were calculated using the ImageJ software (National Institutes of Health).

Statistical Analysis

Statistical analysis was performed using the GraphPad Prism software (version 9). Data are expressed as mean ± standard error of the mean (SEM). Comparisons between groups were performed using independent sample t-tests or one-way analysis of variance (ANOVA). Pearson correlation analysis and Spearman correlation analysis were used to explore the correlation between ALDH2 mRNA expression and the laboratory features. The *p*-values less than 0.05 were considered statistically significant.

Results

ALDH2 Expression Was Significantly Decreased in Patients with Acute Gout

Peripheral blood samples were collected from age-matched patients with gout (24 patients with acute gout and 24 gout patients in intermittent phase) and 24 healthy controls. Blood uric acid levels were significantly elevated in patients with acute gout attacks and in intermittent phase compared to healthy controls (Table 1). First, ALDH2 mRNA levels were quantified in PBMCs, and our results indicated that ALDH2 mRNA expression in patients with acute gout were much lower than those from healthy controls and gout patients in intermittent phase (Figure 1A). Furthermore, we found that in

Table 1 Clinical and Laboratory Features in Healthy Controls, Gout Patients in Intermittent Phase, and Patients with Acute Gout

Characteristic	HC group (n=24)	IG group (n=24)	AG group (n=24)	*p* value
Age (years)	38.63±2.305	38.71±2.120	38.13±2.470	ns
BMI	22.54±0.390	24.26±0.729	24.61±0.822	<0.01
UA (μmol/L)	377.6±6.41	493.2±27.56	511.5±26.63	<0.001
CRP (mg/l)	/	4.25 (0.5–13.9)	19.85 (8.1–160.6)	
ESR (mm/h)	/	7.0 (2.0–25.0)	20.5 (5.0–79.0)	
Treatment				
ULT,n (%)	/	21 (87.5%)	13 (54.2%)	
NSAIDs, n (%)	/	2 (8.3%)	19 (79.2%)	
Colchicine, n (%)	/	3 (12.5%)	21 (87.5%)	
Glucocorticoid, n (%)	/	/	4 (16.7%)	

Note: Data are means ± SEM or median (range). "/" means not deteted.
Abbreviations: HC, healthy controls; IG, gout patients in intermittent phase; AG, patients with acute gout; BIM, body mass index; UA, uric acid; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ULT, urate-lowering therapy; NSAIDs, Nonsteroidal Anti-inflammatory Drugs.

patients with acute gout, ALDH2 expression was significantly negatively correlated with CRP (Figure 1B) but not with ESR, blood uric acid levels, or BMI (Figures 1C–E).

In THP-1 Cell Lines, After MSU Crystal Stimulation, ALDH2 Expression Decreased

PMA-induced THP-1 cells served as an in vitro model for acute gout attacks. We evaluated alterations in ALDH2 expression and enzyme activity using an in vitro model. Following MSU crystal stimulation, the mRNA and protein levels of ALDH2 in THP-1 cells were significantly decreased compared to the control group (Figures 2A and B). Furthermore, we employed a kit to measure ALDH2 enzyme activity, which revealed that ALDH2 enzyme activity was

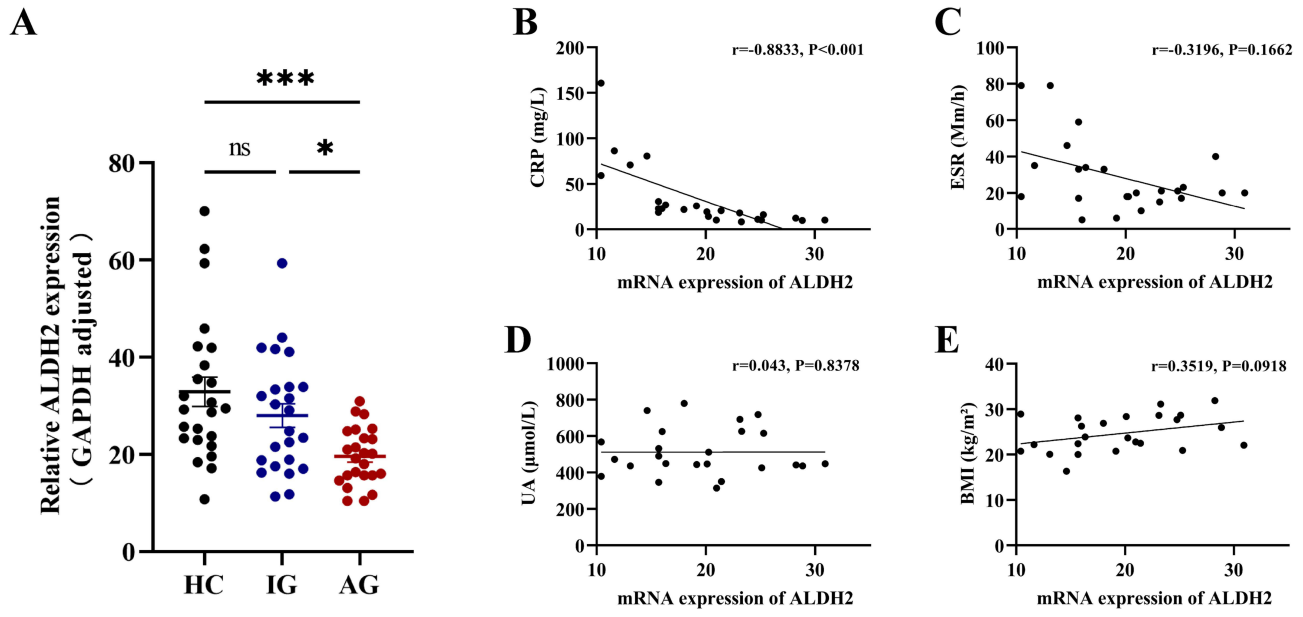


Figure 1 ALDH2 expression is decreased in patients with acute gout attacks. Changes in ALDH2 mRNA expression in PBMCs from healthy controls (HC, n=24), gout patients in intermittent phase (IG, n=24), and patients with acute gout (AG, n=24) was detected by RT-qPCR (**A**). Data are expressed as mean ± SEM, with *$p < 0.05$, ***$p < 0.01$, ns (not significant). Statistical analysis was conducted using one-way ANOVA. Spearman's analysis depicted the correlation between ALDH2 mRNA expression and CRP (r = –0.8833, $p < 0.001$), ESR (r = –0.3196 $p = 0.1662$) (**B** and **C**). Pearson's analysis illustrated the correlation between ALDH2 mRNA expression and UA (r = 0.043, $p = 0.8378$), BMI (r = 0.3519, $p = 0.0918$) (**D** and **E**).

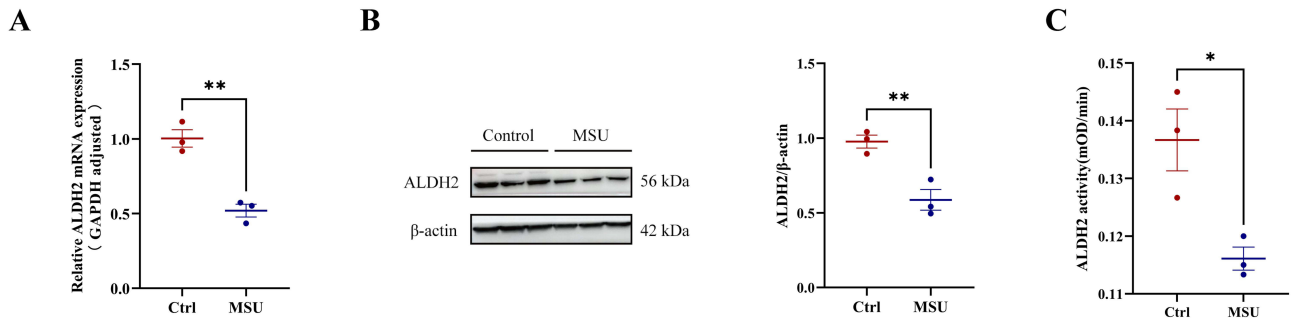


Figure 2 ALDH2 expression is decreased in in vitro models of acute gout attacks. In the THP-1 cell line, changes in ALDH2 mRNA and protein expression in control (n = 3) and MSU crystal-stimulated groups (n = 3) were detected by qRT-PCR and Western blotting (**A** and **B**), and changes in ALDH2 enzymatic activity were assessed using an ALDH2 activity assay kit (**C**). Data are expressed as mean ± SEM, with* $p < 0.05$, ** $p < 0.01$. Statistical analysis was conducted using Student's *t*-test.

significantly reduced in the MSU crystal stimulation group (Figure 2C). Our findings suggest that MSU crystal stimulation markedly reduces the expression and enzyme activity of ALDH2.

In THP-1 Cell Lines, ALDH2 Activation Protected THP-1 Cells From MSU Crystal Induced NLRP3 Inflammasome Activation and Assembly and Pyroptosis

To further verify the role of ALDH2 in MSU crystal-stimulated THP-1 cells, we assessed the activation and assembly of NLRP3 inflammasome and pyroptosis. First, we determined the optimal concentration of Alda-1 in THP-1 cells (Supplementary Figure 1A and B). We chose to treat THP1 cells with 40μM Alda-1 as the treatment group and 0.1% DMSO as the control group. Our findings indicate that MSU crystal stimulation significantly increased the expression of NLRP3, pro-IL-1β, cleaved-caspase-1 (Figure 3A and B), ASC oligomer (Figure 3C), and speck formation (Figure 3D), and pretreatment with Alda-1 reversed these changes. Furthermore, MSU crystal treatment significantly reduced cell

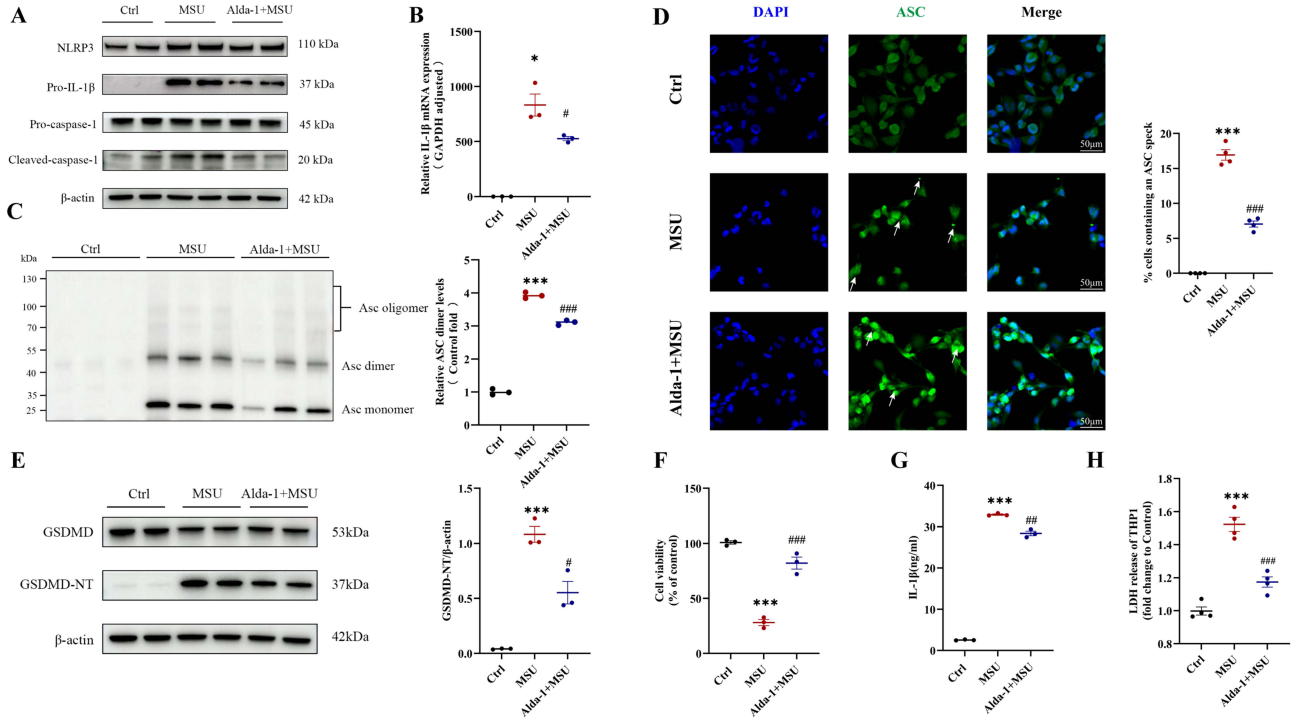


Figure 3 ALDH2 activation in THP-1 cells alleviates MSU crystal-induced NLRP3 inflammasome activation and pyroptosis. THP-1 cells were pretreated with 40 μM Alda-1 for 2 h, followed by stimulation with 250 μg/mL MSU crystal suspension, resulting in significantly reduced expression of NLRP3, pro-IL-1β, pro-caspase-1 and caspase-1 P20 (**A**), and IL-1β mRNA (**B**); inhibited ASC oligomerization (**C**) and reduced the formation of ASC specks (**D**). In THP-1 cells, pretreatment with Alda-1 significantly inhibited pyroptosis, resulting in decreased GSDMD-NT protein expression (**E**), rescued cell viability (**F**), reduced IL-1β secretion (**G**), and LDH release (**H**) in the supernatants. Data are expressed as mean ± SEM, n = 3 or 4, * indicating significant difference compared to the control group, *$p < 0.05$, ***$p < 0.0001$, ns (not significant), and # indicating significant difference compared to the MSU group, #$p < 0.05$, ##$p < 0.01$, ###$p < 0.001$. Statistical analysis was conducted using one-way ANOVA.

https://doi.org/10.2147/JIR.S536042

viability (Figure 3F) and the inflammatory factor IL-1β (Figure 3G) and increased the release of LDH (Figure 3H) as well as the expression of pyroptosis proteins GSDMD-NT/GSDMD-FL (Figure 3E), all of which were reversed by Alda-1 treatment. These data indicate that ALDH2 exerts a significant protective effect against MSU crystal-induced activation and assembly of NLRP3 inflammasome and pyroptosis.

ALDH2 Inhibited ROS Production in MSU-Stimulated THP1 Cell Lines

Oxidative stress has been confirmed to enhance NLRP3 inflammasome activation, leading us to speculate that ALDH2 could regulate oxidative stress induced by MSU crystal stimulation. In MSU crystal-stimulated THP-1 cells, ROS production in THP-1 cells and mitochondria was assessed using DCFH-DA and MitoSOX Red probes. The results indicated that MSU crystal stimulation significantly increased ROS production in THP-1 cells and the mitochondria. However, pretreatment with the ALDH2 agonist Alda-1 inhibited ROS production (Figures 4A). Additionally, the mitochondrial membrane potential was assessed using the JC-1 assay kit, revealing that MSU crystal stimulation impaired the mitochondrial function of THP-1 cells, whereas Alda-1 treatment ameliorated this change (Figure 4B). Subsequently, we treated THP1 cells stimulated by MSU crystals with ROS inhibitor NAC and the mtROS inhibitor Mito-TEMPO, respectively. The results indicated that the treatment with NAC (5 mM) and Mito-TEMPO (10 μM) significantly decreased the ROS and mtROS generation (Supplementary Figure 2) and significantly suppressed the activation of the NLRP inflammasome (Figures 4C) and pyroptosis (Figure 4D and E) induced by MSU crystal stimulation. The above data indicates that Alda-1 treatment can alleviate MSU crystal-induced mitochondrial dysfunction and reduce ROS production in vitro.

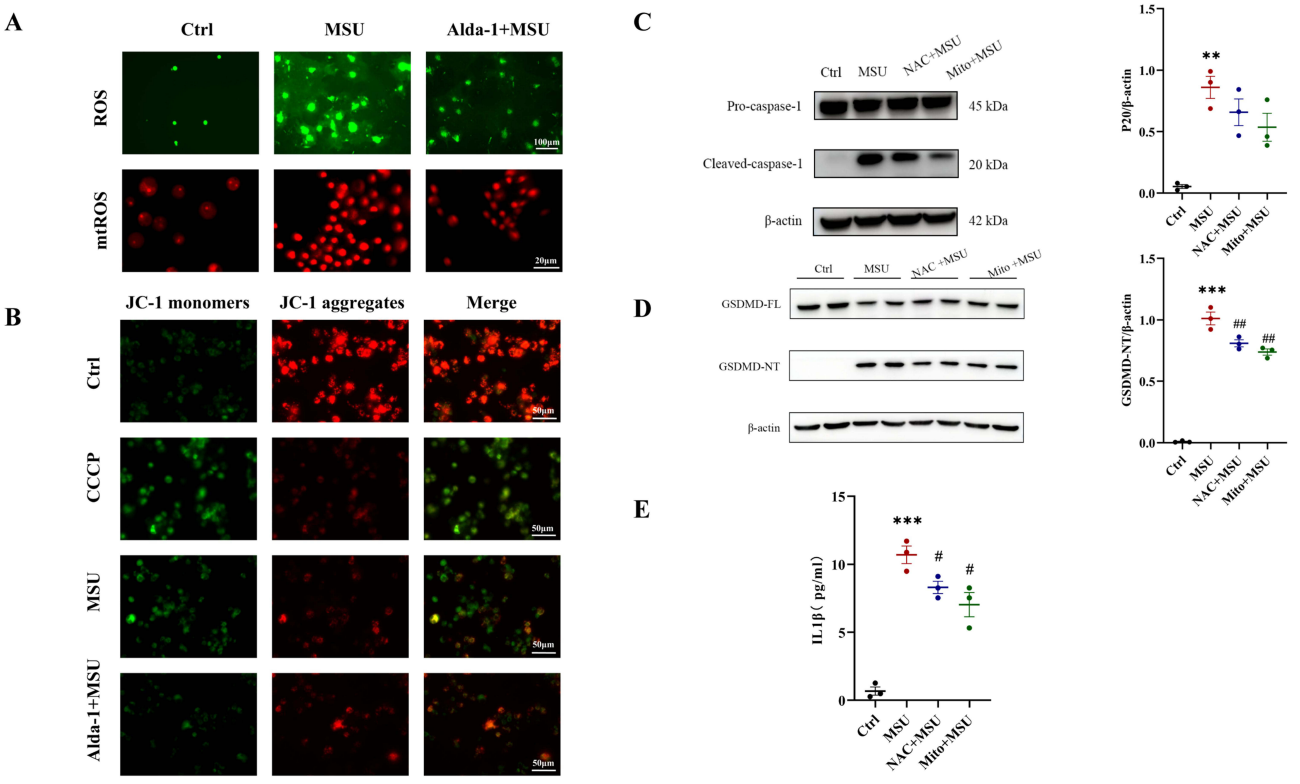


Figure 4 Alda-1 treatment reduces ROS production and mitigates mitochondrial dysfunction in THP-1 cells. In THP-1 cells, intracellular and mitochondrial ROS production was detected using DCFH-DA and MitoSOX Red probes (**A**). After pretreatment with or without Alda-1 (40 μM) followed by stimulation with 250 μg/mL MSU crystal suspension. Mitochondrial membrane potential changes were detected using the JC-1 assay in THP-1 cells (**B**). After pretreatment of THP-1 cells with the NAC (5 mM) or Mito-TEMPO (10 μM), the expression of caspase-1 P20 (**C**) and GSDMD-NT (**D**) and the secretion of IL-1β in the supernatants (**E**) significantly decreased. Data are expressed as mean ± SEM, n = 3, * indicating significant difference compared to the control group, **$p < 0.01$, ***$p < 0.0001$, and # indicating significant difference compared to the MSU group, #$p < 0.05$, ##$p < 0.01$. Statistical analysis was conducted using one-way ANOVA.

In the THP-1 Cell Line, ALDH2 Mitigated Inflammation and Pyroptosis Through the Nrf2 Pathway

Studies have demonstrated that the Nrf2 pathway is crucial for regulating oxidative stress. To clarify whether ALDH2 regulates inflammation induced by MSU crystal stimulation through the Nrf2 pathway, we first assessed the protein level of Nrf2 following Alda-1 treatment. The results indicated that compared with the control group, MSU crystal stimulation significantly reduced Nrf2 protein expression, while Alda-1 treatment reversed this change (Figures 5A). Furthermore, we isolated the nuclear and cytoplasmic proteins of the cells, and the results demonstrated that Alda-1 significantly promoted the nuclear translocation of Nrf2 (Figure 5B). Subsequently, we treated THP-1 cells with the Nrf2-specific inhibitor ML385 (5 μM). The results indicated that the effects of Alda-1 were reversed by ML385, including inhibition of the assembly and activation of the NLRP3 inflammasome (Figures 5C–F), pyroptosis (Figures 5D and E), and oxidative stress (Figure 5G). This data indicates that ALDH2 mitigates oxidative stress, NLRP3 inflammasome activation, and pyroptosis induced by MSU crystal stimulation through the Nrf2 pathway.

ALDH2 Reduced the Severity of MSU-Induced Arthritis in Mice

The MSU crystal suspension was injected into the footpad of mice to simulate the etiology of human gouty arthritis. Compared with the control group, mice in the model group exhibited significant footpad swelling following MSU crystal injection (Figures 6A and B). H&E staining results demonstrated increased infiltration of inflammatory cells in the footpad tissue sections (Figure 6C), while immunofluorescence revealed elevated macrophage expression in the footpad tissue sections (Figure 6D). Besides, IL-1β expression in the supernatant of footpad tissue was increased (Figure 6E), and

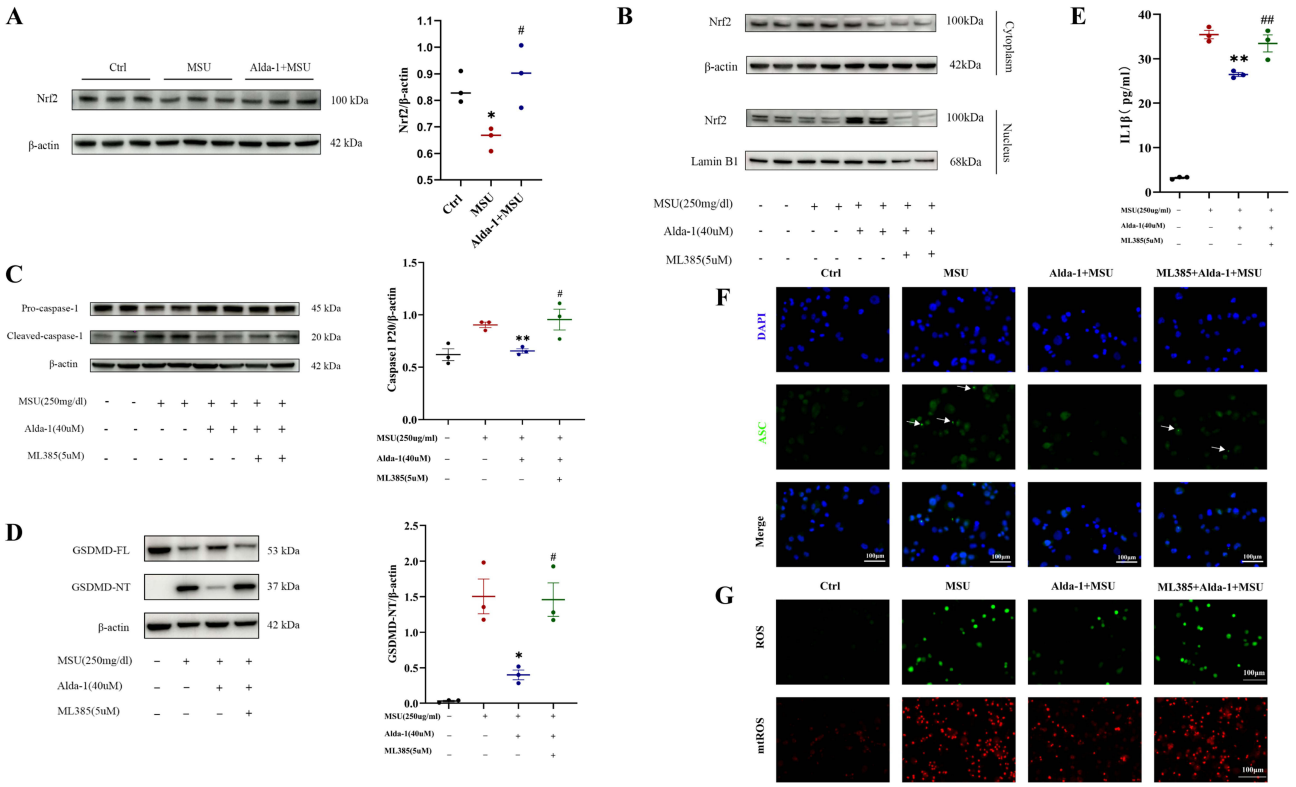


Figure 5 ALDH2 modulates cellular inflammation through the Nrf2 pathway in THP-1 cells. Western blotting results exhibited that Alda-1 treatment significantly increased Nrf2 expression (**A**). Alda-1 promoted Nrf2 nuclear translocation in THP-1 cells (**B**). Nuclear and cytoplasmic proteins were isolated from THP-1 cells to detect changes in Nrf2 protein expression. After pretreatment of THP-1 cells with the Nrf2 inhibitor ML385 (5 μM), the effects of Alda-1 on reducing the expression of caspase-1 P20 (**C**) and GSDMD-NT (**D**), the secretion of IL-1β in the supernatants (**E**), the formation of ASC specks (**F**). ROS and mtROS production were inhibited (**G**). Data are expressed as mean ± SEM, n = 3, * indicating significant difference compared to the control group, *$p < 0.05$, **$p < 0.01$, ns (not significant), and # indicating significant difference compared to the MSU group, #$p < 0.05$, ##$p < 0.01$. Statistical analysis was conducted using one-way ANOVA.

https://doi.org/10.2147/JIR.S536042

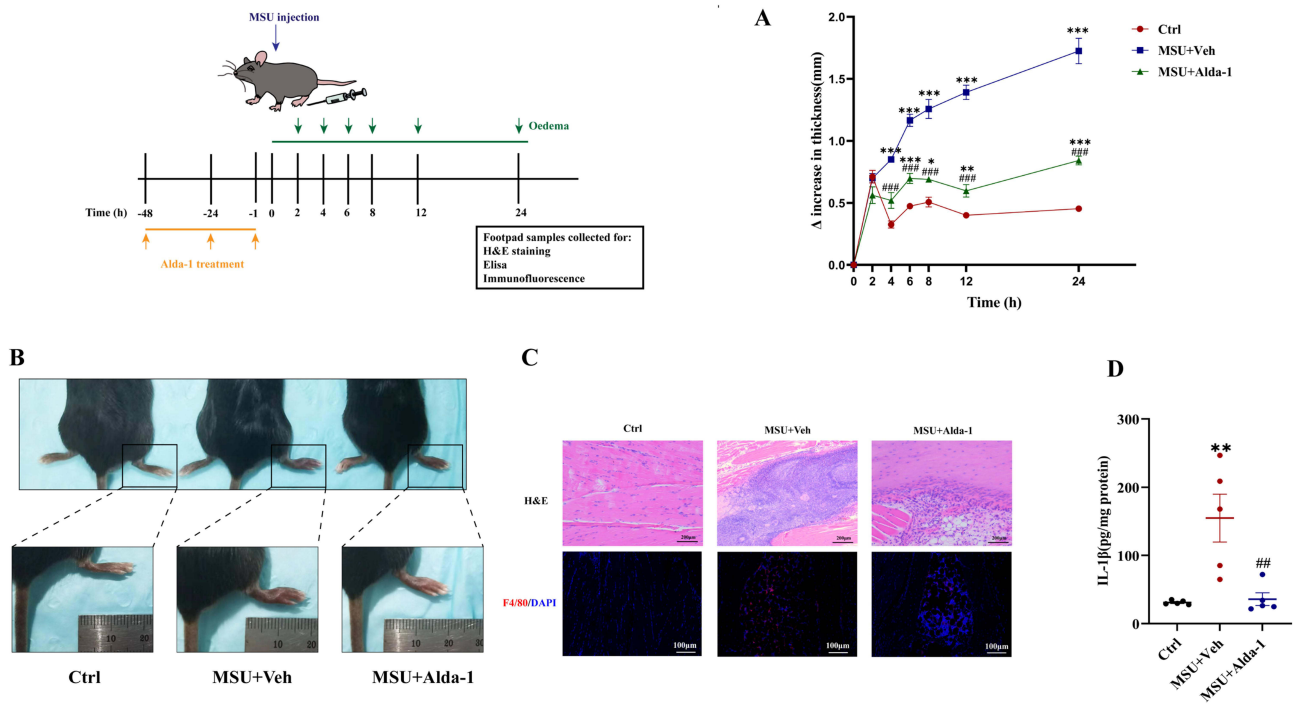


Figure 6 In vivo, Alda-1 treatment significantly alleviates inflammation induced by MSU crystal stimulation. Paw swelling index at 0, 2, 4, 6, 8, 12, and 24 h after MSU crystal and Alda-1 injection (n = 10 mice per group) (**A**), Photographs of mouse footpads 24 h after MSU crystal suspension injection (**B**). H&E staining and F4/80 macrophage expression in the mouse footpad tissues (**C**). ELISA was used to detect changes in IL-1β expression in the homogenates of mouse footpad tissues (**D**). Data are expressed as mean ± SEM, n = 5, with * indicating a significant difference compared to the control group, *$p < 0.05$, **$p < 0.01$, ***$p < 0.0001$, and # indicating a significant difference compared to the MSU group, ##$p < 0.01$, ###$p < 0.001$. Statistical analysis was conducted using one-way ANOVA.

Alda-1 treatment alleviated these changes. The results above indicate that in the acute gout attack mouse footpad model, Alda-1 administration can effectively alleviate the acute symptoms induced by MSU crystal injection.

Discussion

Several recent genome-wide association studies have investigated the association between ALDH2 polymorphisms and gout prevalence. Notably, rs671 in ALDH2 has been identified as a gout locus.[24] Nakayama A. et al demonstrated that ALDH2 was significantly enriched in Japanese patients across all subtypes of gout.[25] However, the role of ALDH2 in alleviating acute gouty arthritis remains unknown. Our initial findings revealed that ALDH2 expression was significantly diminished in PBMCs from patients experiencing acute gout attacks and was negatively correlated with CRP, a marker of inflammation. Consequently, we hypothesized that ALDH2 could potentially alleviate acute gout attacks.

Next, we stimulated cells with MSU crystals to mimic the process of acute gout and investigate the underlying pathological mechanisms. After stimulating THP-1 cells with MSU crystals, we observed an enhanced assembly and activation of the NLRP3 inflammasome. It is well established that MSU crystal-induced inflammation is mediated by NLRP3 inflammasome activation, which plays a central role in gout pathophysiology.[26] The inflammasome is a multi-protein complex that activates caspase-1, promoting the release of the pro-inflammatory cytokines IL-1β and IL-18.[27] The activation of the NLRP3 inflammasome occurs in two distinct phases: The initiation phase and the activation phase. During the initiation phase, toll-like receptors and cytokine receptors are activated, leading to the upregulation of inflammasome components, including NLRP3, caspase-1, and pro-IL-1β, through recognition of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). Subsequently, PAMPs and DAMPs trigger the assembly of the NLRP3 inflammasome complex, leading to caspase-1 activation and maturation and release of inflammatory cytokines.[28,29]

Furthermore, NLRP3 inflammasome activation induces pyroptosis, as confirmed by our in vitro experiments. Following MSU crystal stimulation, we observed increased expression of GSDMD-NT, elevated LDH release, enhanced

IL-1β secretion, and reduced viability of THP-1 cells. Pyroptosis is a form of programmed inflammatory cell death primarily mediated by GSDMD. GSDMD acts as a central mediator of pyroptosis. Caspase-1 cleaves GSDMD and releases its amino-terminal domain (GSDMD-NT). GSDMD-NT binds to phosphatidylinositol phosphates and phosphatidylserine on the inner membrane leaflet, oligomerizes, and forms a 10–14 nm pore of 16 symmetric protomers. This pore formation results in cellular lysis[7,26,27] and the subsequent release of bioactive IL-1β, a cytokine crucial to gout pathogenesis.[28]

ALDH2 is well established to play a protective role in various diseases, including cardiovascular disease and diabetes,[7,29,30] and has been reported to inhibit NLRP3 inflammasome activation in several studies.[18,29,31,32] Alda-1, a specific small molecule activator of ALDH2, enhances the catalytic activity of ALDH2 by two-fold and improves its enzymatic activity by eleven-fold.[33] It is also the most widely studied ALDH2 activator in animal models. Consequently, we used Alda-1 as an ALDH2 agonist in our study. In vitro, preconditioning with Alda-1 partially reversed the activation and assembly of NLRP3 inflammasome and pyroptosis induced by MSU crystal stimulation. We observed consistent results in vivo. Alda-1 treatment reduced MSU crystal-induced paw swelling in mice, decreased inflammatory cell infiltration in paw tissues, and lowered IL-1β release.

ALDH2 is a mitochondrial enzyme that effectively eliminates oxidative stress products and aldehyde metabolites, thereby mitigating oxidative stress, reducing mitochondrial oxidative damage, and protecting cells from stress-induced injury.[34–36] Ballur AFH et al demonstrated that melatonin alleviates inflammation and oxidative stress in an experimental gouty arthritis model. Their study exhibited that MSU crystal stimulation significantly increased oxidative stress parameters, including malondialdehyde levels and total oxidant status.[37] To further investigate this, we used DCFH-DA and MitoSOX Red probes to measure ROS levels. Our results demonstrated that MSU crystal stimulation significantly elevated intracellular ROS and mtROS production in THP-1 cells. Pretreatment with Alda-1 effectively reduced ROS and mtROS production induced by MSU crystals. Oxidative stress is an imbalance between antioxidant defenses and ROS production within biological systems. This state of excessive ROS accumulation can result in cellular damage, dysfunction, and even cell death.[38]

Furthermore, ROS production has been identified as a critical mechanism driving NLRP3 inflammasome activation.[39] To confirm this, we stimulated THP-1 cells with the ROS inhibitor NAC and mtROS inhibitor Mito-TEMPO and observed that MSU crystal-induced NLRP3 inflammasome activation and pyroptosis were partially inhibited. These findings align with previous studies, which have demonstrated that dysregulation of oxidative stress homeostasis, mediated through NLRP3 inflammasome activation and pyroptosis, plays a pivotal role in MSU-induced acute gouty arthritis.[10,40]

Nuclear factor (erythroid-derived 2)-like 2, commonly known as Nrf2, has been widely recognized for its protective role against oxidative stress.[41] Upon oxidative stress stimulation, Nrf2 translocates from the cytoplasm to the nucleus, where it binds to ARE, triggering the expression of genes that encode antioxidant enzymes.[42,43] Through this mechanism, the Nrf2 signaling pathway is pivotal for mitigating oxidative stress and enhancing cell survival. Zeng et al's study confirmed that pharmacological activation of Nrf2 alleviates gout pain, gait abnormalities, and inflammation through Nrf2-dependent endogenous antioxidant mechanisms.[44] Furthermore, studies have indicated that Nrf2 regulates the NLRP3 inflammasome activation by limiting ROS levels. Nrf2 also attenuates NLRP3 inflammasome activity by reducing NF-κB activation and downregulating the expression of inflammasome components.[45,46] Our study further confirms that Alda-1 treatment can reverse the MSU crystal-induced nuclear translocation of Nrf2. Additionally, the results of applying the Nrf2-specific antagonist ML385 highlight that the inhibition of Nrf2 nuclear translocation partially reverses the antioxidant function of ALDH2 in THP-1 cell lines, as well as its role in reducing NLRP3 inflammasome activation.

The treatment of gout remains an active area of research. Inhibitors targeting any step in the gout pathogenesis cascade, such as interleukin-1 (IL-1) inhibitors, caspase inhibitors, and inflammasome inhibitors, serve as effective anti-inflammatory agents for gout.[47] However, although IL-1β inhibitors help reduce inflammation, they do not directly block NLRP3 activation, allowing for persistent IL-1β production. To date, no FDA-approved NLRP3-targeting inhibitors are available. For instance, the development of MCC950 and related compounds was discontinued due to hepatotoxicity, while other small-molecule inhibitors targeting the NLRP3 nucleotide-binding and oligomerization (NACHT) domain

are currently under investigation.[48] Furthermore, Lackner et al identified significant structural homology between the NLRP3 pyrin domain and human 8-oxoguanine DNA glycosylase 1 (hOGG1), a key enzyme that recognizes and excises oxidized DNA bases. Importantly, they demonstrated that the small-molecule hOGG1 inhibitor TH5487 not only binds to NLRP3 but also prevents the NLRP3 pyrin domain from recognizing oxidized mitochondrial DNA (Ox-mtDNA). This reduces the interaction between NLRP3 and Ox-mtDNA, thereby inhibiting NLRP3 inflammasome activation.[49]

ALDH2 activators mitigate oxidative damage by directly enhancing ALDH2 enzymatic activity. For example, Alda-1, a selective ALDH2 activator employed in our study, has been validated in numerous cellular and animal models. Furthermore, AD-9308, a prodrug of the potent selective ALDH2 activator AD-5591, offers favorable water solubility and oral bioavailability, making it an ideal candidate for in vivo applications. Following administration, AD-9308 is rapidly converted to its active form, AD-5591, thereby enhancing ALDH2 activity. AD-9308 represents a promising candidate for evaluation in future clinical trials.[50] Notably, certain antioxidants—such as α-lipoic acid, N-acetylcysteine, and melatonin—provide indirect protection by scavenging ROS and restoring ALDH2 activity.[51–53] Future research should evaluate the efficacy of these agents in both in vitro and in vivo models of acute gout attacks. Subsequent clinical translation could offer novel therapeutic avenues.

This study also raises several additional questions. First, although our research confirms that Alda-1 effectively alleviates inflammatory responses and oxidative stress in THP-1 cells and mouse models of gouty arthritis, the role of the ALDH2 rs671 variant as a risk factor for gout in the context of hyperuricemia requires further investigation. Furthermore, although our findings demonstrate that Alda-1 can promote the nuclear translocation of Nrf2, the underlying mechanism by which ALDH2 mediates this process warrants further exploration.

In summary, our findings demonstrate that ALDH2 alleviates oxidative stress and inflammation in acute gouty arthritis by promoting Nrf2 nuclear translocation, diminishing MSU crystal-induced ROS production, reducing NLRP3 inflammasome formation, and inhibiting the release of pro-inflammatory factors such as IL-1β. Consequently, our study provides a new therapeutic strategy for treating acute gouty arthritis by targeting ALDH2 activation.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Second Affiliated Hospital of Zhejiang University School of Medicine Ethics Committee (2021-0027). Written informed consent was obtained from all participants.

Funding

This work was supported by the Key Research and Development Program of Zhejiang Province (No. 2020C03044) and the National Natural Science Foundation of China (No. 82071810, 82470929, 82200995).

Disclosure

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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