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ORIGINAL ARTICLE

Sirt1 inhibits gouty arthritis via activating PPARγ

Juan Wang[1] · Guangliang Chen[2,3] · Liangjing Lu[1] · Hejian Zou[4,5]

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Abstract

Objective To identify the effects of Sirtuin 1 (Sirt1) on gouty arthritis and investigate the underlying mechanisms.

Methods A gouty arthritis model was established by intra-articular injection of monosodium urate (MSU, 1 mg) crystal solution into the left foot pad of C57BL/6 mice. After pretreating the gouty arthritis mice with intra-articular injection of Sirt1 agonist (Resveratrol, RSV, 20 mg/kg) or peroxisome proliferator-activated receptor γ (PPARγ) inhibitor (T0070907, 1 mg/kg), the degree of joint inflammation of the gouty arthritis mice was evaluated by clinical integration of joint inflammation and hematoxylin and eosin (H&E) staining. The mRNA expression of Sirt1 and PPARγ were determined by real-time polymerase chain reaction (PCR). The expression profiling of inflammatory cytokines and chemokines in mouse joint tissues were determined by multi-factor assay kits. Peritoneal macrophages were isolated from mice and tested the effects of RSV and/or PPARγ on pro-inflammatory cytokines secretion by PCR.

Results Sirt1 agonist significantly suppressed the onset of gouty arthritis induced by MSU and reduced the infiltration of inflammatory cells in the joints. Sirt1 agonist significantly promoted the expression of PPARγ, while decreased the expression of interleukin (IL)-1β, IL-1α, IL-6, interferon-γ (IFN-γ), monocyte chemotactic protein 1(MCP-1), tumor necrosis factor a (TNF-α), and chemokines (CXCL-1, CXCL-5, CCL-22) induced by MSU in joint tissues. After blocking PPARγ with T0070907 or by siRNA, the anti-inflammatory effect of Sirt1 agonist on gouty arthritis disappeared and the expression of pro-inflammatory molecules were not significantly reduced.

Conclusions Sirt1 may control the acute onset of gouty arthritis in mice by inhibiting the infiltration of inflammatory cells and the secretion of pro-inflammatory molecules through PPARγ.

Key Points
- *Sirt1 and its activator, RSV, attenuate the severity of gouty arthritis in mice.*
- *Sirt1 inhibits the infiltration of inflammatory cells and the secretion of pro-inflammatory molecules in MSU-induced arthritis.*
- *Sirt1 inhibits inflammation partially dependent on PPARγ.*

Keywords Gouty arthritis · PPARγ · Sirt1

Juan Wang and Guangliang Chen are co-first authors.

✉ Liangjing Lu
lu_liangjing@163.com

✉ Hejian Zou
hjzou@fudan.edu.cn

[1] Department of Rheumatology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

[2] Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

[3] Department of Oncology, Shanghai Medical College, Fudan University, 270 Dong-An Rd, Shanghai 200032, China

[4] Division of Rheumatology, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China

[5] Institute of Rheumatology, Immunology and Allergy, Huashan Hospital, Shanghai Medical College, Fudan University, No. 12, Middle Wulumuqi Road, Shanghai 200040, China

Introduction

Gout is one of the most common forms of inflammatory arthritis and is characterized by deposition of monosodium urate (MSU) crystals within the joints [1]. When recognized as "danger" signals by the immune system, MSU crystals initiated the onset of gouty arthritis, featured with increased levels of pro-inflammatory cytokines such as interleukin (IL)-1 β, IL-6, IL-8, and tumor necrosis factor a (TNF-α) [2–5]. Gouty arthritis is associated with hyperuricemia, which is disordered by purine metabolism, and (or) decreased excretion of uric acid. Therefore, gout is also considered a metabolic-related disease. Our previous data demonstrated that Sirtuin 1 (Sirt1) and its activator, resveratrol (RSV), have clear anti-hyperuricemia functions via the peroxisome proliferator-

activated receptor γ (PPARγ) co-activator 1α (PGC-1a)/PPARγ-ATP-binding cassette subfamily G member 2 (ABCG2) pathway in mouse model [6]. In addition, RSV can also inhibit the onset of gouty arthritis [7] but its possible mechanism needs further study.

RSV has been shown to be a specific activator of Sirt1, which is a NAD+-dependent class III histone deacetylase. In addition to regulating cell proliferation, apoptosis, and autophagy, accumulating evidences indicate that Sirt1 and its specific activator RSV have been found to influence metabolism and inflammation [8] [9]. Sirt1 acts on a wide range of histones and non-histone substrates, including PPARγ [10]. PPARγ belongs to the PPAR family, which also contains PPARα and PPARβ/δ. PPARs sense the increased flux of fatty acids and activate a transcriptional program that regulates lipid metabolism. PPARγ also has anti-inflammatory effects in several tissues [11, 12].

Using in vivo and in vitro experimental system, we try to study the effects of Sirt1 on gouty arthritis and investigate the potential role of PPARγ in this process. This study may provide an insight into how Sirt1 regulates the onset of gouty arthritis.

Methods

Synthesis of MSU crystals

MSU crystals were prepared as described by Denko and Whitehouse [13]. Briefly, 4 g uric acid was dissolved in 800 mL of deionized water, heated to 60 °C, adjusted to pH 8.9 with 0.5 N NaOH, and crystallized overnight at room temperature. MSU crystals were recovered by centrifugation, washed with distilled water, and dried at 40 °C for 24 h. Crystal shape and birefringence were assessed by compensated polarized light microscopy. MSU crystals were milled and then sterilized by heating at 180 °C for 2 h before each experiment. We measured < 0.015 EU/mL endotoxin in MSU crystal preparations using a Limulus amebocyte lysate assay (Sigma-Aldrich, St. Louis, MO, USA).

Animals

Mice were housed at 24 ± 2 °C with 12-h light/12-h dark cycles in a pathogen-free facility at the Central Institute for Experimental Animals of Renji Hospital. Ad libitum access to food and water was provided. All the animal procedures were approved by the ethics committee of the Animal Experiments Committee of Shanghai Jiao Tong University. C57BL/6 mice were anesthetized in by inhalation of 3% isoflurane (Forane; Abbot, Chicago, IL, USA) and then intra-articular injected with 50 μL (1 mg) MSU suspension into the left foot pad [11]. PBS was injected into the right foot pad at the same time as a control. RSV (20 mg/kg) and/or PPAR γ inhibitor (T0070907, 1 mg/kg) was given intra-articularly once 2 h prior to MSU crystal administration. At 6 h after MSU crystal administration, mice were killed after monitoring for joint swelling. Joint tissues were removed and stored for further RNA and protein extraction, or fixed in formalin for histopathologic analysis.

Histological studies

Mouse joint tissue sections were prepared and stained with hematoxylin and eosin (H&E). Images were acquired by using a light microscope (Olympus, Tokyo, Japan) and analyzed with image processing software (Olympus).

RNA isolation and quantitative real-time polymerase chain reaction

Total RNA was isolated from the mouse joint tissues using TRIzol (Invitrogen, Carlsbad, USA). The total RNA quantity was measured using a Nanodrop-1000 (Nanodrop Technologies, Wilmington, USA). Complementary single-stranded DNA was synthesized from the total RNA by reverse transcription (PrimerScript® RT Master Mix, TaKaRa, Japan). Real-time PCR was performed using SYBR Green master mix (SYBR® Premix ExTaq™, TaKaRa, Japan). Quantification of cDNA targets was performed using the ABI Prism7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). All reactions were run in triplicate. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as an internal control. The following specific primers were used for amplification: Sirt1: fwd 5′-GGAGCAGATTAGTAAGCGGCTTG-3′ and rev 5′-GTTACTGCCACAGGAACTAGAGG-3′; PPARγ: fwd5′-GTACTGTCGGTTTCAGAAGTGCC-3′ and rev 5′-ATCTCCGCCAACAGCTTCTCCT-3′; MCP-1: fwd 5′-GCTACAAGAGGATCACCAGCAG-3′ and rev 5′-GTCTGGACCCATTCCTTCTTGG-3′; IL-1α: fwd 5′-ACGGCTGAGTTTCAGTGAGACC-3′ and rev 5′-CACTCTGGTAGGTGTAAGGTGC-3′; IL-1β: fwd 5′-TGGACCTTCCAGGATGAGGACA-3′ and rev 5′-GTTCATCTCGGAGCCTGTAGTG-3′; IL-6: fwd 5′-TACCACTTCACAAGTCGGAGGC-3′ and rev 5′-CTGCAAGTGCATCATCGTTGTTC-3′; TNF-α: fwd 5′-GGTGCCTATGTCTCAGCCTCTT-3′ and rev 5′-GCCATAGAACTGATGAGAGGGAG-3′; IFN-γ: fwd 5′-GAGCCTAGAGACTATCACACCG-3′ and rev 5′-TACCAGAGGGTGTAGTTAGCGG-3′; and GAPDH: fwd 5′-AACTCCCACTCTTCCACCTTCG-3′ and rev 5′-TCCACCACCCTGTTGCTGTAG-3′.

Cell culture

C57BL/6 mice were injected intra-peritoneally with phosphate-buffered saline (PBS) (3 mL). Mice were killed 10 min later, and cells were isolated from peritoneal lavage. Cells were washed and resuspended in DMEM supplemented with 10% FBS. After overnight culture, non-adherent cells were removed, and adherent cells were cultured and seeded in 24-well culture plates (1×10^5 cells/well). Peritoneal macrophages were exposed to 100 μmol/L MSU with or without the additional application of RSV (5 μmol/L) an hour earlier.

The cultured peritoneal macrophages were transfected with 40 nmol/L control siRNA or with 40 nmol/L PPARγ siRNA using a transfection reagent (SiRNA-Mate; GenePharma Co., Ltd., China). Approximately 24 h after transfection, we analyzed the levels of pro-inflammatory cytokines.

Multi-analyte flow assays

The levels of pro-inflammatory cytokines and chemokines in mouse joint tissues were measured separately by LEGENDplex™ Multi-Analyte Flow Assays (Biolegend) Mouse Cytokine Panel and Chemokine Kits. Methods were performed as recommended by the manufacturer.

Statistical analysis

The data are presented as the mean ± SD. Statistical significance was determined by Student's test or one-way ANOVA using GraphPad Prism software (*$p < 0.05$, **$p < 0.01$).

Results

Sirt1 attenuated the severity of gouty arthritis in mice

We have confirmed that Sirt1 and its specific activator RSV prevented hyperuricemia in mice [6]. To investigate the potential effect of Sirt1 on gouty arthritis mice model, RSV was given intra-articularly once 2 h prior to the administration of MSU crystals into the foot pad. Mice were sacrificed 6 h after MSU crystals injection. As shown in Fig. 1A, MSU crystals induced marked foot swelling in gouty arthritis mice at the time point of 6 h after the intra-articular injection. Similarly, an increase in the inflammatory scores in MSU crystal–treated mice was also observed (Fig. 1B). However, the administration of RSV significantly ameliorated the MSU-induced foot swelling as well the inflammation scores in the gouty arthritis mice (Fig. 1A, B). To confirm those findings, sections stained with H&E in the MSU-induced arthritis mice revealed remarkable inflammatory cell infiltration in the subcutaneous soft tissues and joint spaces (Fig. 1C). In contrast, RSV treatment resulted in less inflammatory cell infiltration into the MSU-treated mice (Fig. 1C). These data show that RSV, the Sirt1 agonist, can control the acute onset of gouty arthritis in mice and reduce the inflammatory cell infiltration.

Sirt1 activated the mRNA expression of PPARγ

PPARγ was reported to exert anti-inflammatory effects in several tissues [11, 12]. To investigate the underlying mechanism involved in the inhibitory properties of RSV, total RNA from experimental joints was extracted and the qPCR-array was carried out. Sirt1 was activated after RSV treatment in the joints of gouty arthritis mice (Fig. 2A). Compared with the control group, the mRNA expression of PPARγ was slightly increased in the joints of gout arthritis mice and PPARγ was noticeably increased after RSV treatment (Fig. 2B). These data indicate that Sirt1 may be an upstream regulator of PPARγ.

Sirt1 inhibited the infiltration of inflammatory cells via PPARγ in MSU-induced arthritis

The main feature of gouty arthritis is the infiltration of inflammatory cells to the joints. We have found that Sirt1 markedly reduced the MSU-induced recruitment of inflammatory cells to the joint; in order to investigate if this effect is dependent on PPARγ, we used T0070907, a small-molecule inhibitor of PPARγ, in the next experiments. A dose of T0070907 (1 mg/kg) was injected intra-articularly into mice 2 h prior to the administration of MSU crystals in the presence or absence of RSV treatment. Mice given with RSV showed a nearly free arthritis, while mice treated with T0070907 evidently abolished the effects of RSV on the gouty arthritis mice, presenting an exacerbated foot swelling, enhanced inflammation scores, and aggravated infiltration of inflammatory cells (Fig. 3A–C). These data suggest that PPARγ mediates, at least in part, the protective effects of Sirt1 on gouty arthritis.

Sirt1 reduced the production of pro-inflammatory cytokines and chemokines via PPARγ in MSU-induced arthritis

A number of literatures showed that macrophage initiates and drives inflammation in MSU-induced inflammation [14, 15]. To confirm the contribution of PPARγ to Sirt1-mediated inflammation inhibition, we blocked PPARγ activity with T0070907 in MSU-induced arthritis model or with siRNA in the peritoneal macrophages. As shown in Fig. 4A and B, MSU robustly promoted the section of pro-inflammatory cytokines both in mouse joint tissues and peritoneal macrophages. Indeed, RSV, the Sirt1 agonist, apparently suppressed the secretion of pro-inflammatory cytokines exposed to MSU. However, these effects were diminished after the inhibition of PPARγ

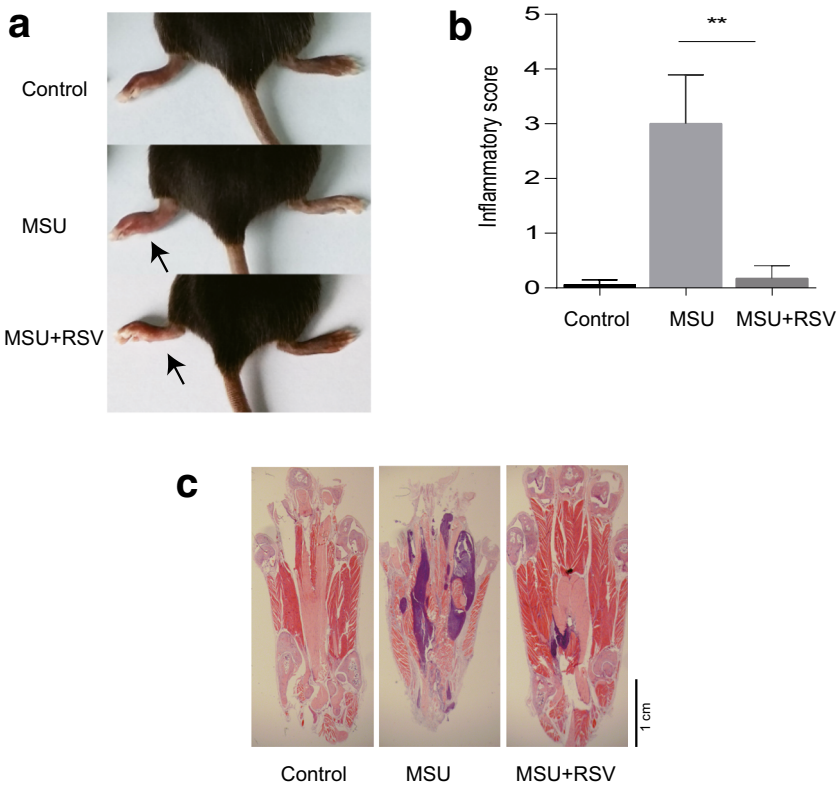

Fig. 1 Sirt1 attenuated the severity of gouty arthritis in mice. Gouty arthritis model was established by intra-articular injection of monosodium urate crystal solution (MSU, 1 mg) into the left foot pad of C57BL/6 mice. Sirt1 agonist (Resveratrol, RSV, 20 mg/kg) was given intra-articularly once 2 h prior to MSU crystal administration. (A) Joint manifestations of control, gouty arthritis, and resveratrol (RSV) (20 mg/kg)–treated mice at 6 h after MSU injected. (B) The inflammatory score of mice joints were evaluated $^{**}p < 0.01$. (C) Histopathological analysis of joints by H&E staining

with T0070907 or SiRNA. Inhibition of PPARγ reduced the Sirt1-mediated inhibition of inflammation, resulting in upregulation of MCP-1, IFN-γ, IL-1α, IL-1β, IL-6, and TNF-α both in mouse joint tissues and peritoneal macrophages.

In addition, chemokines have been linked with inflammatory cell infiltration into the joint during gouty arthritis. We next detected the change pattern of the chemokines expression in the mouse joint tissues. As shown in Fig. 4C, multi-analyte flow assay analysis of the joint tissues showed that Sirt1 also suppressed the expression levels of CXCL-1, CXCL-5, and CCL-22, while increased the levels of CXCL13. Nevertheless, inhibition of PPARγ exert an opposite effect in terms of the expression levels of these chemokines except CXCL13. These findings suggest that Sirt1-mediated inhibition of inflammation is partly dependent on PPARγ.

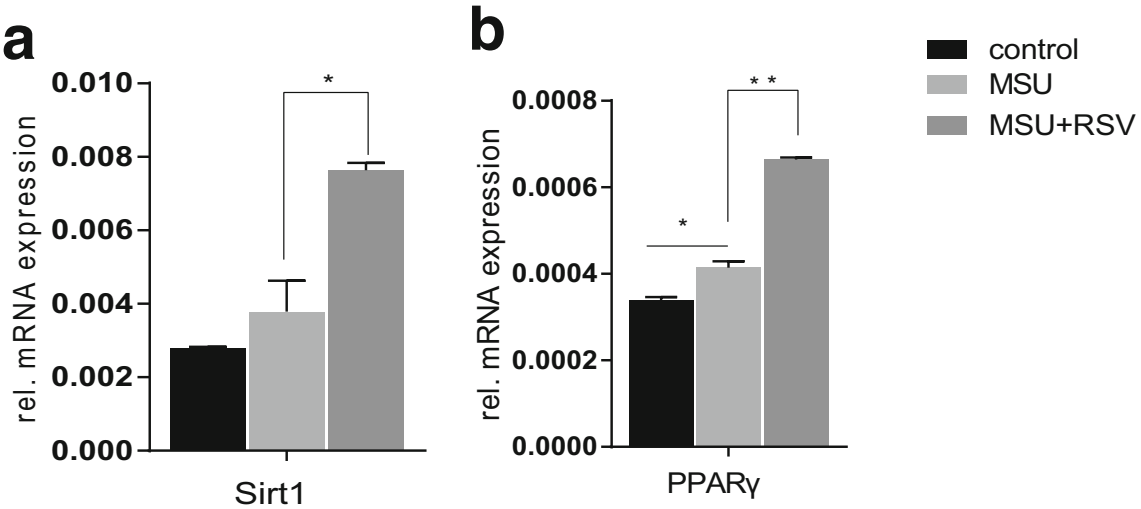

Fig. 2 Sirt1 activated the mRNA expression of PPARγ. Relative mRNA levels of Sirt1 (A) and peroxisome proliferator-activated receptor γ (PPARγ) (B) in the joints of control, gouty arthritis, and resveratrol (RSV) (20 mg/kg)–treated mice were determined by real-time PCR

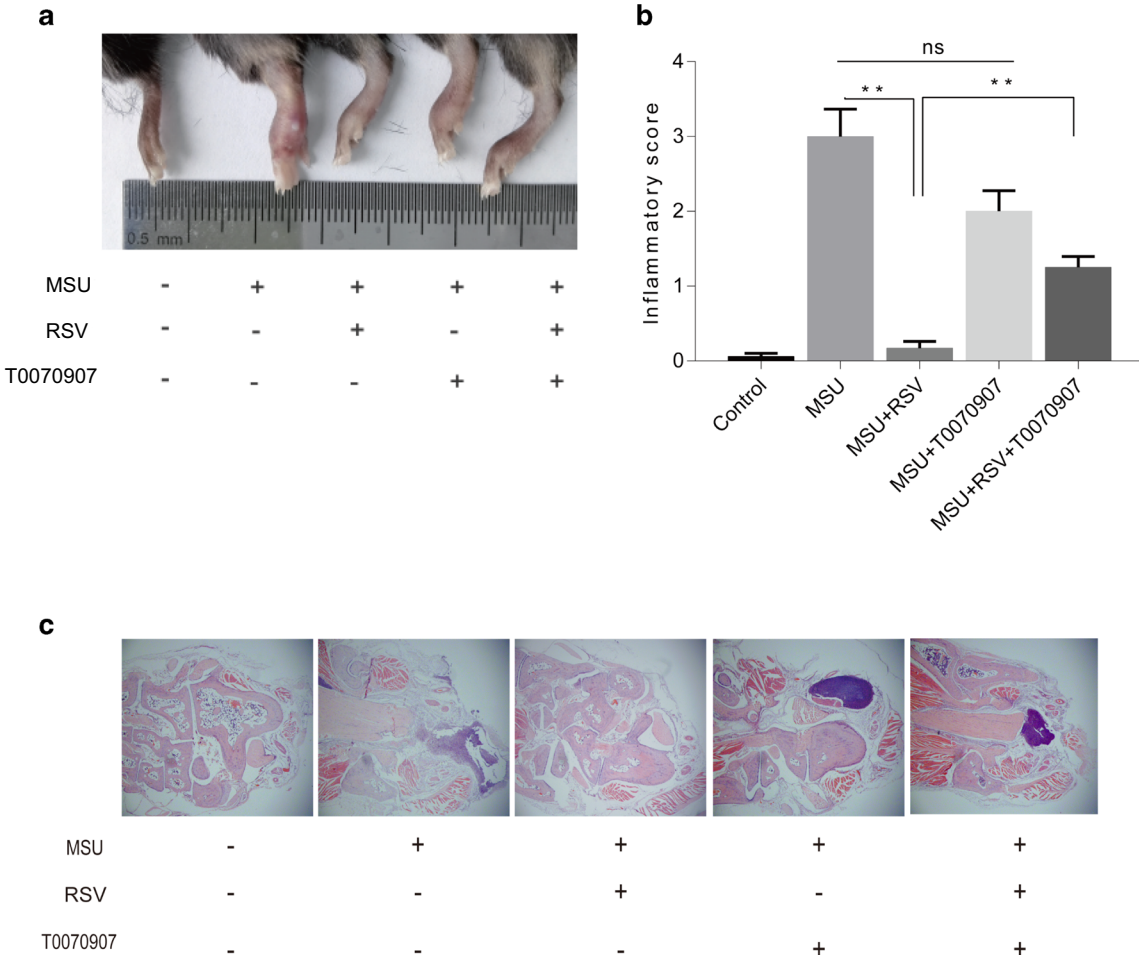

Fig. 3 Sirt1 inhibited the infiltration of inflammatory cells via PPARγ in MSU-induced arthritis. (A) The swelling degree of joints treated with or without peroxisome proliferator-activated receptor γ (PPARγ) antagonist (T0070907) in mice with gouty arthritis were evaluated. (B) The inflammatory score of mice joints were evaluated $^{**}p < 0.01$. (C) Histopathological analysis of joints by H&E staining

Discussion

This study showed that Sirt1 inhibits the onset of gouty arthritis by reducing the infiltration of inflammatory cells and the secretion of inflammatory cytokines and chemokines via activating PPARγ.

Sirt1, the mammalian Sirt2 homolog, is a class III histone deacetylase that acts on a wide range of histones and non-histone substrates, including nuclear factor κB (NF-κB), p53, FOXO1, PGC-1a, and PPARγ [10]. In addition to regulating cell proliferation, apoptosis, and autophagy, Sirt1 has been found to influence inflammation [9]. Notably, Sirt1 exerts the anti-inflammatory effects through several pathways. For example, Sirt1 can suppress transcription activity of NF-κB directly interacting with this factor and deacetylating its p65-subunit [16]. What's more, the inhibitory effect of Sirt1 on NF-κB activity is mediated by activating AMP-dependent protein kinase, PPARα, and PGC-1 [17]. Another powerful regulator of intracellular inflammatory is the PPARγ signaling. PPARγ has recently been suggested to function as a negative regulator of inflammatory responses. PPAR ligands are capable of reducing the expression of genes for cytokines (e.g., TNF, IL-6, and IL-1), iNOS, gelatinaseB, scavenger receptor A, and COX-2 in activated macrophages [18]. We herein propose that Sirt1 regulates the acute episode of gout by anti-inflammatory effects which is dependent on PPARγ.

Two opposite effects of Sirt1 on PPARγ were appreciated. Sirt1 acts as a PPAR antagonist through its direct interaction with PPARγ [19], thus inhibiting adipogenesis and enhancing fat mobilization [20]. However, one study has shown that Sirt1-mediated deacetylation of PPARγ leads to the recruitment of a co-activator, Prdm1, and selective activation of PPARγ to promote "browning" of white fat [21]. Although the negative regulation of PPARγ by Sirt1 has been the most well studied, our study identified that Sirt1 activated PPARγ in the gouty arthritis mouse model. In addition, PPARγ can also be an upstream negative regulator of Sirt1, both by binding and inhibiting its deacetylase activity and by reducing its transcription [22], providing a mechanism by which Sirt1 expression can be reduced in situations of nutrient overload. So

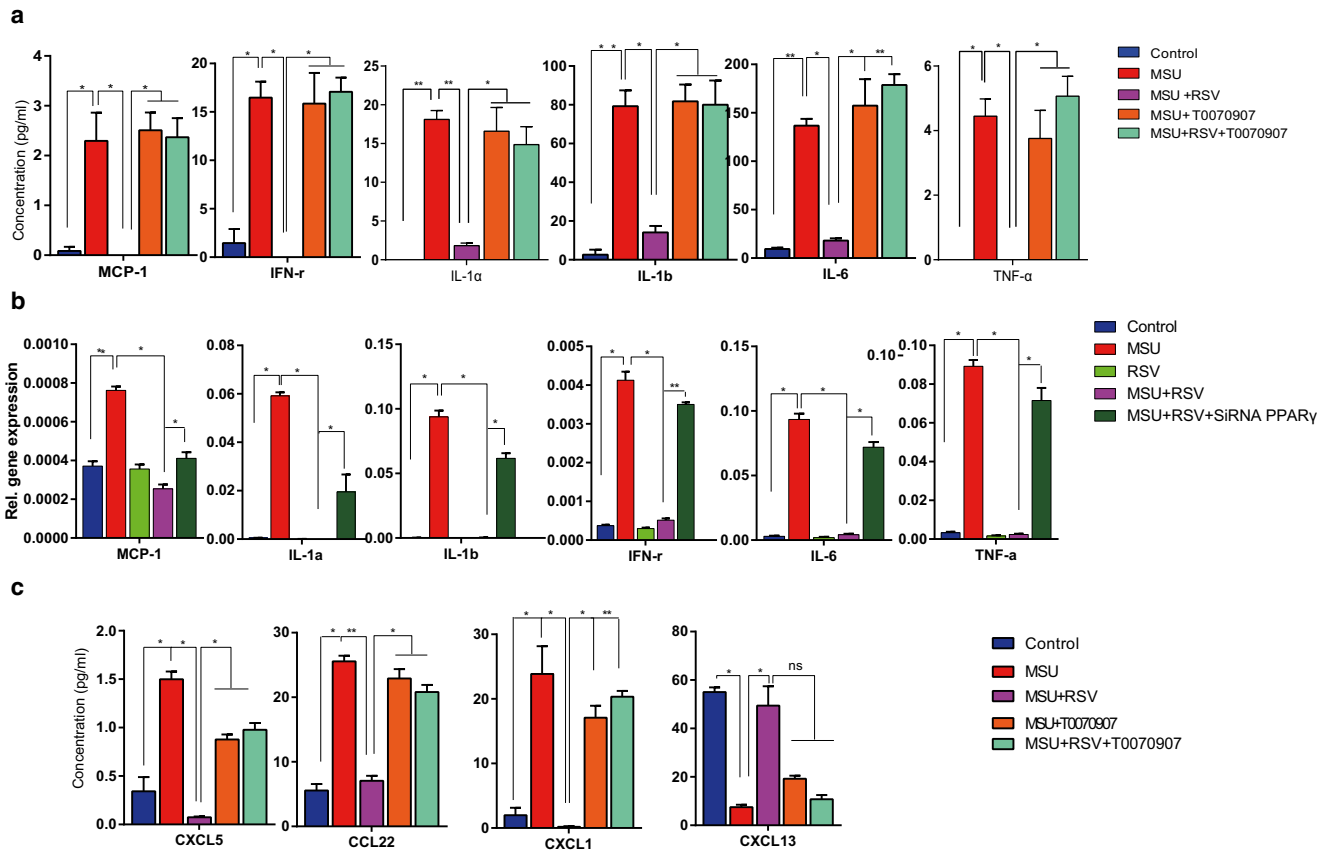

Fig. 4 Sirt1 reduced the production of pro-inflammatory cytokines and chemokines via PPARγ in MSU-induced arthritis. (A) Concentrations of secreted pro-inflammatory cytokines in mouse joint tissues were measured by multi-analyte flow assay mouse cytokine panel. (B) Relative mRNA levels of pro-inflammatory cytokines in peritoneal macrophages stimulated with monosodium urate crystal solution (MSU) in the presence of resveratrol (RSV) and/or blocked peroxisome proliferator-activated receptor γ (PPARγ) by siRNA method. (C) Concentrations of secreted chemokines in mouse joint tissues were measured by multi-analyte flow assay mouse chemokine kits

the relationship between these two proteins is by no means simple [10].

PPARγ is a member of the nuclear hormone receptor superfamily and functions as a key regulator of lipid and glucose metabolism, atherosclerosis, and inflammatory responses [18].

In addition, PPARγ also involved in hyperuricemia, three tag-single nucleotide polymorphisms, rs2292101, rs4684846, and rs1822825, of the PPARγ gene were selected to explore their association with hyperuricemia [23]. The gene expression levels of PPARγ in the peripheral blood mononuclear cells (PBMCs) and synovial fluid cells of patients with gout were higher than the healthy volunteers. PBMCs or monocytes stimulated with MSU crystals caused a rapid increase of PPARγ expression [18]. Consistently, we observed that the mRNA expression of PPARγ was increased in gouty arthritis mice model compared with the control group. 15d-PGJ2, a natural ligand of PPARγ, significantly reduced the crystal-induced production of cytokines by monocytes [24], by direct inhibition of NF-κB kinase activity [25] or by alkylating p50/p65 dimers through PPARγ-dependent pathways [26]. Our study found that Sirt1 suppressed the proinflammatory cytokines (MCP-1, IL-1 β,IL-1α, IL-6, and IFN-γ) and chemokines (CXCL-1, CXCL-5, and CCL-22), while increased CXCL13 expression depended on PPARγ, as inhibition of PPARγ reduced the Sirt1-mediated inhibition of inflammation. Interestingly, a recent study demonstrated that eosinophils control the resolution of inflammation in a mouse model of zymosan-induced peritonitis by upregulating expression of macrophage CXCL13 [27]. This finding makes this chemokine a candidate marker of M2 regulatory or wound-healing macrophages. In our study, whether Sirt1 drives macrophage differentiation toward M2-type cells and then increases the production of CXCL13 needs future investigation.

Conclusions

In conclusion, the present study demonstrated that Sirt1 and its activator, RSV, control the acute onset of gouty arthritis by inhibiting the infiltration of inflammatory cells and the secretion of inflammatory cytokines via activating PPARγ.

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Compliance with ethical standards

All the animal procedures were approved by the ethics committee of the Animal Experiments Committee of Shanghai Jiao Tong University.

Disclosures None.

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