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SDF-1 alleviates osteoarthritis by resolving mitochondrial dysfunction through the activation of the Sirt3/PGC-1α signalling pathway

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Abstract

Objective Osteoarthritis (OA) is the most common form of joint disease. Currently, OA treatment is limited to controlling symptoms. Our previous study showed that stromal cell-derived factor 1 (SDF-1) delayed the progression of OA to a certain extent. The aim of this study was to explore the specific mechanism of SDF-1 in OA.

Materials and methods OA chondrocytes and a collagen-induced osteoarthritis (CIOA) mouse model were used as in vitro and in vivo models, respectively. SDF-1 was used to treat OA in vitro and in vivo. To explore the mechanism of SDF-1 in OA treatment, we pretreated chondrocytes with a Sirt 3 inhibitor and assessed mitochondrial function and then analysed related indicators of cartilage anabolic and cartilage metabolism.

Results SOD2 and PGC-1α levels were significantly lower in OA chondrocytes and the cartilage of CIOA model mice than in normal chondrocytes, and mitochondrial dysfunction occurred in OA. After treating OA chondrocytes and CIOA model mice with exogenous SDF-1, mitochondrial dysfunction and abnormal biomarkers of OA normalized. The pretreatment of OA chondrocytes with a Sirt 3 inhibitor or mitochondrial function inhibitor before SDF-1 exposure reversed these changes.

Conclusions SDF-1 can alleviate OA by resolving mitochondrial dysfunction through the activation of the Sirt3/PGC-1α signalling pathway, and therefore, SDF-1 may be a good candidate as a new treatment for OA.

Keywords Osteoarthritis, Stromal cell-derived factor 1, Mitochondrial dysfunction, Chondrocyte, Sirt3

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Introduction

Osteoarthritis (OA) is the most common chronic degenerative joint disease and causes progressive pain and loss of function. OA is the leading cause of disability and places a high socioeconomic burden on health-care systems [1]. The multifactorial pathogenesis of OA includes articular cartilage degradation, subchondral bone osteophyte formation, synovial angiogenesis and hyperplasia [2]. Currently, different guidelines for the treatment of OA are controversial, and clinical therapeutics for OA treatment only relieve pain and symptoms. The fundamental reason for this situation is that OA has strong heterogeneity and a complex pathogenesis. Researchers have shown that many factors, including inflammatory cytokines, mechanical stress, ageing, metabolic factors and other pathological changes, can cause OA [3]. A variety of degenerative diseases have been linked to deregulated mitochondrial function and variations in mitochondrial DNA (mtDNA) sequences. Mitochondrial oxidative stress causes mtDNA damage, further resulting in mitochondrial damage and shortening the life span of chondrocytes [4]. Chondrocytes are the only cells present in articular cartilage, and they can respond to extracellular mechanical signals. Mitochondrial dysfunction related to aging, along with a decline in the activity of mitochondrial superoxide dismutase (SOD2), is linked to a rise in mitochondrial - generated ROS. This, to some extent, accounts for the age-related increase in ROS within chondrocytes [5]. In OA, mitochondrial dysfunction is an important feature of disrupted chondrocyte homeostasis and plays a pivotal role in enhancing inflammation, increasing cell death, decreasing anabolic activity [6].

Stromal cell-derived factor 1 (SDF-1) is an 8-kDa chemokine that was originally isolated from marrow stromal cells [7]. In the joint, SDF-1 is synthesized by synovial fibroblasts [8]. Although some studies have demonstrated that SDF-1 can accelerate the pathological process of OA [9, 10], other research has shown that in OA synoviocytes, the expression of SDF-1 is lower than that in healthy synoviocytes and that exogenous SDF-1 ameliorates the NLRP3 inflammasome and pyroptosis in OA synoviocytes through the activation of the AMPK signalling pathway, subsequently alleviating OA [11]. Based on accumulating evidence, increased mitochondrial ROS and mtDNA release into the extracellular matrix can activate abnormal innate immune responses, such as NLRP3 inflammatory activation, and NLRP3 inflammasome activation is inseparable from mitochondrial dysfunction [12]. Therefore, we hypothesized that SDF-1 may play a crucial role in improving mitochondrial dysfunction in OA chondrocytes. The confirmation of this hypothesis will provide a new theoretical basis for the use of SDF-1 in the treatment of OA.

Materials and methods

Materials

SDF-1 was purchased from R&D Systems (catalogue no. 350-NS-050), and 3-TYP and IL-1β were purchased from MedChemExpress (catalogue no. HY-108331 and HY-P70586G). Rotenone (catalogue no. T2970) was purchased from Topscience. Anti-SOD2, anti-ADAMTS-5 and anti-Sirt3 antibodies were purchased from Abcam (catalogue no. ab68155, ab41037 and ab217319). Anti-aggrecan (catalogue no. ABP54013) and anti-GAPDH (catalogue no. ABL1021) antibodies were purchased from Abbkine. An anti-MMP13 antibody (catalogue no. 69926) was purchased from Cell Signalling Technology. An anti-PGC1α antibody (catalogue no. bs7535R) was purchased from Bioss. Collagenase type VII (catalogue no. C0773) was purchased from Sigma−Aldrich. An enhanced mitochondrial membrane potential assay kit with JC-1 and a reactive oxygen species assay kit were purchased from Beyotime (catalogue no. C2003S and S0033S).

Chondrocyte culture and SDF-1 stimulation of OA chondrocytes

Normal human primary chondrocytes were purchased from Procell (Wuhan, China). We obtained OA chondrocytes from patients with knee OA undergoing total knee replacement (TKR)($n = 16$). OA cartilage tissues were washed with phosphate-buffered saline (PBS) three times, cut into small pieces, and digested in 2 mg/ml collagenase type II (Sigma, St. Louis, MO, USA) at 37 °C overnight. The digested cells were filtered through a cell strainer. OA chondrocytes were used for 2–3 passages. OA chondrocytes were treated with SDF-1 (20 ng/ml, 50 ng/ml or 100 ng/ml) for 24 h or with SDF-1 (100 ng/ml) for 1 h, 3 h, 6 h, 12–24 h. To explore the signalling pathway involved, OA chondrocytes were pretreated with 3-TYP (5 μM) or rotenone (1 μmol/L) for 4–12 h before the application of SDF-1 (100 ng/ml) [11]. For each experiment the experiments were repeated with chondrocytes from different individuals.

In vitro proliferation assay

To explore cell viability after treatment with different concentrations of SDF-1, a cell counting kit-8 (CCK-8) assay (Dojindo Laboratories, Kumamoto, Japan) was carried out. Chondrocytes were seeded into 96-well plates and treated with SDF-1 (20 ng/ml, 50 ng/ml or 100 ng/ml). After SDF-1 treatment for 24 h, CCK-8 solution was added to the culture medium of each well. After 2 h of incubation at 37 °C, the absorbance of each well was measured at 450 nm.

Western blotting

Proteins extracted from chondrocytes subjected to different treatments were separated by 12.5% sodium dodecyl

sulfate–polyacrylamide gel electrophoresis (SDS–PAGE) and transferred to 0.45- or 0.22-μm polyvinylidene fluoride (PVDF) membranes. The proteins were probed with different primary antibodies overnight and then incubated with a fluorescent secondary antibody.

JC-1 staining

Cells were incubated in culture medium with or without different treatments in 6-well plates. After 24 h of treatment, the cells were incubated with 0.5 μg/ml JC-1 at 37 °C for 30 min. The cells were washed with PBS twice and imaged by confocal laser-scanning microscopy.

Reactive oxygen species (ROS) detection

Cells were incubated in 6-well plates. After different treatments, the cells were incubated with 10 μmol/L DCFH-DA and cultured at 37 °C for 20 min. After the cells were washed with serum-free medium 3 times, they were imaged by confocal laser-scanning microscopy. The amount of ROS was quantified as the relative fluorescence intensity of DCF per cell in the scan area. The results of each experimental group were calculated relative to the control group, with the data of the control group set as 1.0, and the values of other groups were expressed as multiples relative to the control group.

Establishment of a collagen-induced osteoarthritis (CIOA) mouse model and treatment with SDF-1

For our in vivo experiments, we adhered to the ARRIVE guidelines and have included the ARRIVE checklist. This study was approved by an ethics review committee (No. 2023JS57). Twenty-four twelve-week-old male C57BL/6 mice (weighing 21.9 ± 1.6 g; purchased from Liaoning Changsheng Biotechnology Co., Ltd.) were randomized into three groups: control group, CIOA group and SDF-1 treatment group. Mice were housed with free access to water and food. The animal experiments were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Sixteen twelve-week-old male C57BL/6 mice were intra-articularly injected with collagenase to establish a CIOA model as previously described [11]. Briefly, CIOA was induced by two intra-articular injections of 5 U of collagenase type VII (Sigma–Aldrich) in the right knee on day 0 and day 2. Then, 8 of the CIOA mice were injected with 120 ng/kg SDF-1 twice a week in the knee joint beginning on day 7. The end point of disease model establishment was day 42. The other 8 CIOA mice were in the CIOA group. We injected saline into the knee joints twice a week starting at day 7 of the mice in the control group ($n = 8$) and in CIOA group ($n = 8$).

Microcomputed tomography (micro-CT) imaging

Mice were anesthetized with isoflurane to alleviate pain and then killed on day 42 following the first injection of collagenase VII. A Quantum GX microcomputed tomography (micro-CT) imaging system was used to investigate the effect of SDF-1 on CIOA model mice as previously described [11].

Haematoxylin and eosin (H&E) staining and immunohistochemistry (IHC)

Whole knee joints were collected and fixed with 4% formalin, decalcified in 10% ethylenediaminetetraacetic acid and then embedded in paraffin. Five-micron-thick coronal sections were stained with H&E or incubated with different primary antibodies. Analyses were performed in a blinded manner by two independent observers. Image-Pro Plus software was used to analyse the acquired images.

Statistical analysis

All data are presented in the form of mean ± standard error of the mean (SEM). For result analysis, we employed GraphPad Prism software. When examining differences among three or more groups, a one-way analysis of variance (ANOVA) was first performed, followed by Tukey's post hoc test. For comparing differences between two groups, the Student's t test was utilized. In all statistical analyses, a p-value less than 0.05 was considered to indicate a statistically significant difference.

Results

SDF-1 improved mitochondrial dysfunction and the imbalance between anabolic and catabolic metabolism in OA chondrocytes

SOD2 is the first line of defence against the generation of superoxide in the mitochondrial electron transport chain, and a lack of SOD2 leads to mitochondrial dysfunction and increased mitochondrial DNA damage. Western blotting was used to assess the protein expression of SOD2 in normal and OA chondrocytes. SOD2 was more lowly expressed in OA chondrocytes than in normal chondrocytes (Fig. 1A). After treatment with different concentrations of SDF-1 (20 ng/ml, 50 ng/ml and 100 ng/ml), SDF-1 (100 ng/ml) increased the expression of aggrecan and suppressed the expression of MMP-13 and Adamts5 ($p < 0.05$, Fig. 1.B).

To explore the ability of SDF-1 to improve OA chondrocyte mitochondrial dysfunction, several experiments were conducted. SDF-1, especially 100 ng/ml, increased the protein level of SOD2 in chondrocytes (Fig. 1. C). To visually evaluate mitochondrial dysfunction and oxidative stress in chondrocytes, we used a fluorescent probe to detect JC-1 in cells to evaluate the mitochondrial membrane potential and analyse intracellular ROS levels.

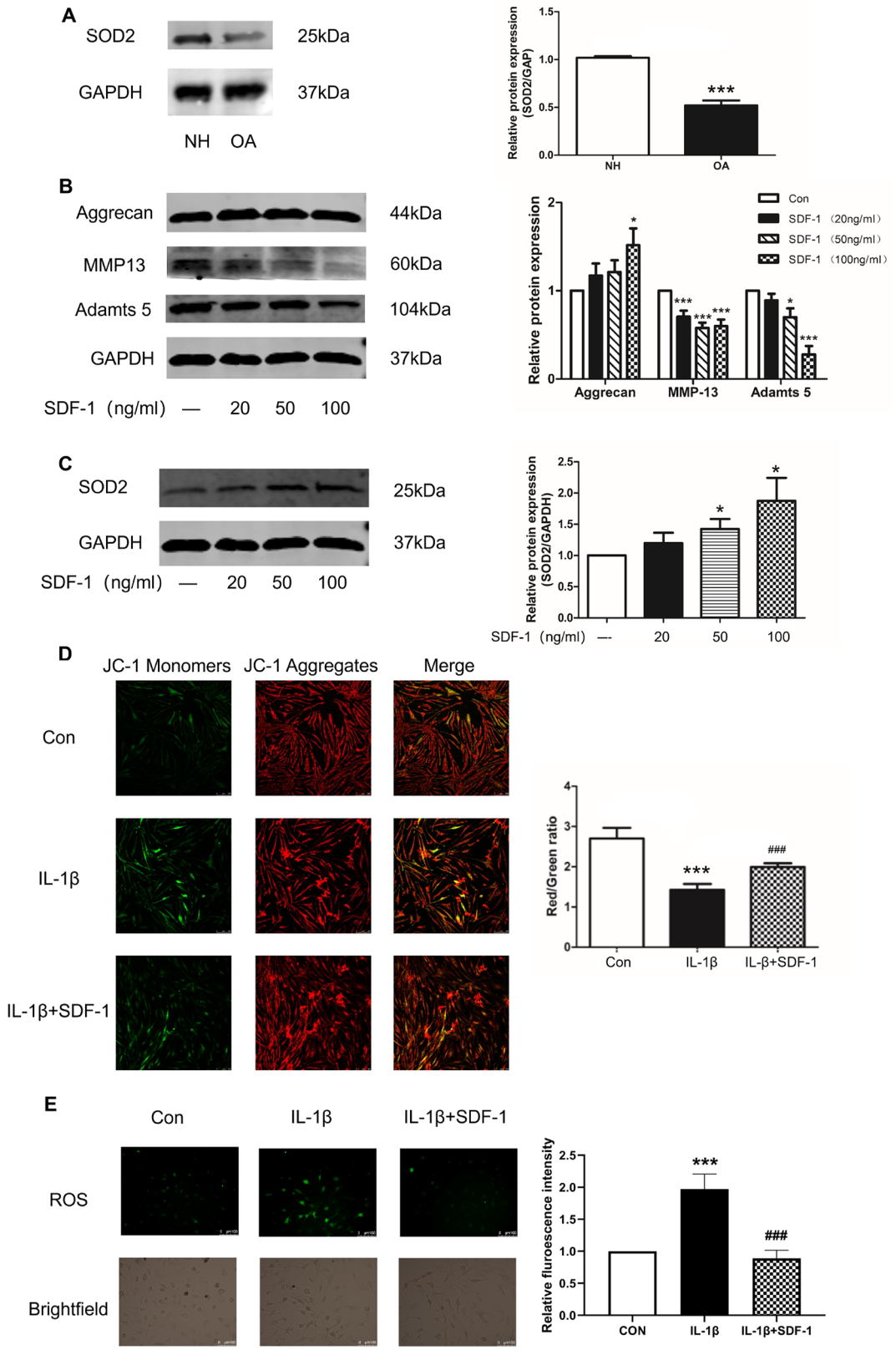

Fig. 1 Function of SDF-1 on mitochondrial dysfunction and imbalance between synthetic and catabolic metabolism in OA chondrocyte. Mitochondrial dysfunction was existed in OA chondrocyte(**A**)($n=6$). SDF-1 could impair the imbalance between synthetic and catabolic metabolism(**B**)($n=5\sim16$) and mitochondrial dysfunction(**C**)($n=9$) in OA chondrocyte. SDF-1 could alleviate IL-1β induced mitochondrial dysfunction in normal chondrocyte(**D**-**E**) ($n=6\sim8$). Compare to Con group $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$; Compare to IL-1β group $\#p<0.05$, $\#\#p<0.01$, $\#\#\#p<0.001$

When the mitochondrial membrane potential is high, JC-1 forms J-aggregates, producing red fluorescence; when the mitochondrial membrane potential is low, JC-1 exists as a monomer and produces green fluorescence. The results showed that the mitochondrial membrane potential of OA chondrocytes decreased after IL-1β(10 ng/ml) treatment and that exogenous SDF-1 (100 ng/ml) partially restored the mitochondrial membrane potential of OA chondrocytes (Fig. 1. D). ROS are oxygen-containing chemically reactive substances, and an increase in ROS levels is indicative of oxidative stress, which may cause serious damage to cellular structure. The experimental results showed that IL-1β significantly increased the level of ROS in a cell model of osteoarthritis and that SDF-1 (100 ng/ml) significantly decreased this effect (Fig. 1. E).

SDF-1 ameliorated OA and mitochondrial dysfunction in vivo

To explore the function of SDF-1 in vivo, we used SDF-1 to treat a CIOA mouse model. Micro-CT and HE staining revealed that CIOA model mice had a narrowing joint space and significant osteophyte formation. When CIOA model mice were treated with SDF-1, OA was ameliorated (Fig. 2A). CIOA model mice had lower expression of a biomarker of cartilage anabolism (Aggrecan) and greater expression of biomarkers of cartilage catabolism (MMP-13 and Adamts 5) ($p < 0.05$, Fig. 2B). IHC staining revealed that the cartilage of CIOA mice had significantly lower expression of PGC-1α and SOD2, revealing that mitochondrial dysfunction is exacerbated in CIOA cartilage. However, the expression of PGC-1α and SOD2 in the SDF-1 treatment group was greater than that in the CIOA group (Fig. 2C). These results showed that SDF-1 could resolve mitochondrial dysfunction in vivo.

SDF-1 ameliorated OA through the Sirt 3/PGC 1α signalling pathway

To explore the underlying mechanism of SDF-1 in OA, we studied the Sirt 3/PGC 1α signalling pathway. Our results showed that SDF-1 increased Sirt 3 and PGC 1α expression ($p < 0.05$, Fig. 3A). These results showed that SDF-1 could activate the Sirt 3 signalling pathway and increase the expression of PGC 1α, which peaked at 3 h. After chondrocytes were pretreated with a Sirt 3 inhibitor (3-TYP) (Fig. 3. B) or a mitochondrial function inhibitor (rotenone) (Fig. 3C), the ability of SDF-1 to protect chondrocytes was reversed ($p < 0.05$). The results above revealed that SDF-1 alleviated OA through the Sirt 3/PGC 1α signalling pathway.

Discussion

Mitochondrial biogenesis is an important process that maintains mitochondrial homeostasis and therefore plays essential roles in energy production, metabolism, intracellular signalling and apoptosis [13]. Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) and SOD2 are two major factors involved in mitochondrial biogenesis; SOD2 is the first line of defence against the generation of superoxide in mitochondrial electron transport chains, and PGC-1α acts as the master regulator of mitochondrial biogenesis [13, 14]. OA is a complex disease, and an increasing number of studies have shown that several pathogenic mechanisms exist in OA. In recent years, mitochondrial dysfunction has been studied in OA [15].

Our results showed that compared with normal chondrocytes, OA chondrocytes have significantly lower level of SOD2. Cartilage from CIOA model mice have significantly lower levels of SOD2 and PGC-1α than normal mice. We also analysed this phenomenon through JC-1 staining and ROS production. The results illustrated that in OA, mitochondrial dysfunction was exacerbated. Notably, our results are consistent with those of previous studies [16, 17].

SDF-1, also known as CXC motif chemokine ligand 12 (CXCL12), is a member of the CXC chemokine family. SDF-1 is involved in regulating various physiological processes in cells and tissues and is a steady-state cytokine. However, due to its high expression in infection or inflammatory environments, it is believed to be a homeostatic/inflammatory dual-purpose chemokine [18]. Currently, SDF-1 is known to be involved in the regulation of cell differentiation and distribution, cell proliferation and adhesion, neovascularization, and embryonic development [19]. However, interestingly, the effects of SDF-1 on various cells and tissues are not the same. The downstream signalling pathways activated by SDF-1 vary depending on cell type. For example, experimental results indicate that the binding of SDF-1 to CXCR4 on chondrocytes does not activate the Erk1/2 and JNK signalling pathways. In contrast, the binding of SDF-1 to CXCR4 on haematopoietic progenitor cells activates the Erk1/2 pathway. SDF-1 participates in the regulation of cartilage tissue homeostasis and can also regulate the proliferation, survival, and differentiation of chondrocytes, playing an important role in the physiological and pathological processes of cartilage. There is still some controversy over the role of SDF-1 in the occurrence of OA. On the one hand, SDF-1 promotes the chemotaxis of endogenous stem cells and is therefore used to achieve better cartilage repair. Studies have shown that SDF-1 can induce mesenchymal stem cells to differentiate into chondrocytes, which then migrate to damaged cartilage, leading to chondrocyte proliferation and further maturation,

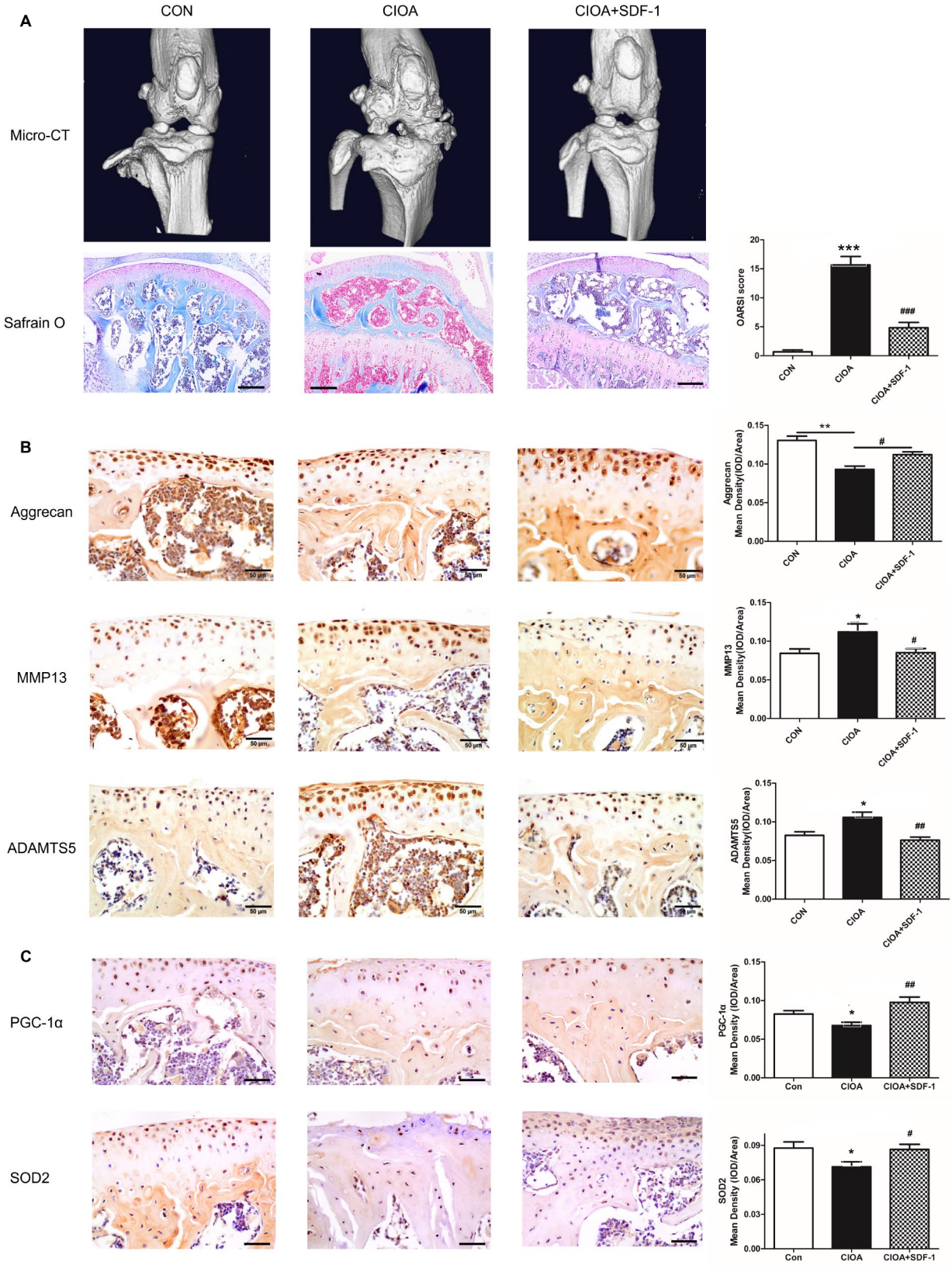

Fig. 2 SDF-1 relieved CIOA in Micro-CT and HE staining(**A**)($n=3$). SDF-1 could improve the imbalance between synthetic and catabolic metabolism(**B**) ($n=4\sim7$), and mitochondrial dysfunction in CIOA cartilage(**C**)($n=5\sim6$). Compare to Con group *$p<0.05$, **$p<0.01$, ***$p<0.001$; Compare to CIOA group #$p<0.05$, ##$p<0.01$, ###$p<0.001$

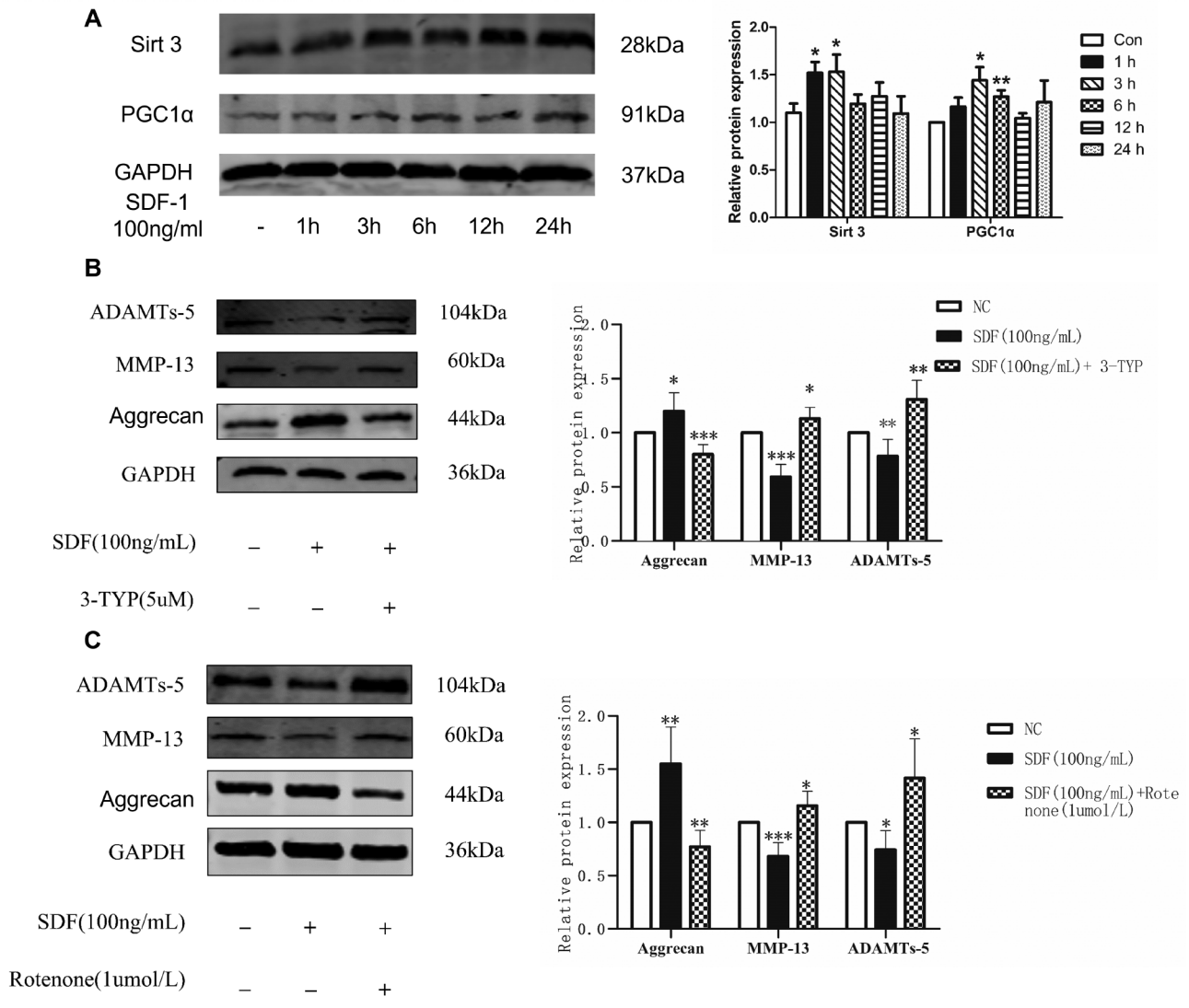

Fig. 3 SDF-1 could ameliorate OA through Sirt 3/PGC 1α signalling pathway. SDF-1 could activate Sirt 3/PGC 1α signalling pathway(**A**)($n = 3 \sim 4$). Inhibitor of Sirt 3 and mitochondrial function could impair the function of SDF-1 on OA chondrocyte(**B**-**C**)($n = 6 \sim 7$). Compare to NC group, *$p < 0.05$, **$p < 0,01$, ***$p < 0.001$; Compare to SDF-1 treatment group, #$p < 0.05$, ##$p < 0.01$, ###$p < 0.001$

thereby promoting the repair of cartilage damage and delaying the pathological process of OA [20–22]. On the other hand, studies have shown that SDF-1 can induce chondrocyte apoptosis and upregulate the expression of matrix metalloproteinases that promote cartilage matrix degradation [23]. After binding to its receptor CXCR4, SDF-1 may participate in the pathogenesis of OA by affecting the interaction between articular cartilage and subchondral bone [24]. These seemingly contradictory results necessitate further investigation of the role of SDF-1 in the complex pathological process of OA. Preliminary results obtained by our research group showed that the expression level of SDF-1 was significantly greater in normal synovial cells than in OA synovial cells. The application of exogenous SDF-1 to OA synovial cells can significantly activate the AMPK signalling pathway and inhibit synovial cell apoptosis and thus plays a therapeutic role in OA [11]. We applied immunohistochemical staining to detect the expression levels of the joint cartilage anabolism marker aggrecan and joint cartilage catabolism markers MMP13 and ADAMTS5. Exogenous SDF-1 has been shown to inhibit cartilage collagen catabolism and promote synthetic metabolism in CIOA model mice. In this study, we conducted a series of experiments using exogenous SDF-1 to treat OA chondrocytes. The discovery that exogenous SDF-1 can increase the protein expression level of aggrecan and decrease the protein expression levels of MMP13 and ADAMTS5 in OA chondrocytes further confirms the protective effect of SDF-1 against OA and that SDF-1 can significantly alleviate

pathological changes in OA model mice, confirming the therapeutic effect of SDF-1 on OA in vivo and in vitro. To visually evaluate mitochondrial dysfunction and oxidative stress in chondrocytes, we used a fluorescent probe to detect JC-1 to evaluate the mitochondrial membrane potential while also assessing the level of intracellular ROS. Exogenous SDF-1 can significantly ameliorate IL-1β-induced mitochondrial dysfunction and oxidative stress in OA chondrocytes.

To investigate the specific mechanism of the above process in depth, we applied the Sirt3 inhibitor 3-TYPE and the mitochondrial electron transfer chain complex I inhibitor rotenone to analyse the role of the Sirt3/PGC 1α signalling pathway. The results showed that SDF-1 can target the Sirt3 signalling pathway to normalize mitochondrial dysfunction, inhibit catabolism, and promote anabolism in OA chondrocytes, thus alleviating OA. Sirt3 has recently become a focus of research on OA progression due to its role in metabolic control, reduced oxidative stress, ageing, and the inhibition of cell apoptosis. A study showed that Sirt3 levels were reduced in mouse OA cartilage and that Sirt3 knockdown induced mitochondrial dysfunction in chondrocytes [25]. Recent studies have suggested that Sirt3 can antagonize mitochondrial dysfunction in the early stages of OA [26–28]. This finding coincides with our research findings. Exogenous SDF-1 can significantly activate the Sirt3 signalling pathway in OA chondrocytes, thereby resolving mitochondrial dysfunction in chondrocytes. Sirt3 plays a crucial role in the ability of SDF-1 to alleviate mitochondrial dysfunction in OA chondrocytes and subsequently inhibit the OA process.

Conclusion

In conclusion, the present study demonstrated that exogenous SDF-1 alleviated OA by resolving mitochondrial dysfunction through the activation of the Sirt3/PGC-1α signalling pathway. These findings may provide a new theoretical basis for the treatment of OA.

Abbreviations

ANOVA	One-way analysis of variance
CCK-8	Cell counting kit-8
CIOA	Collagen-induced osteoarthritis
CXCL12	CXC motif chemokine ligand 12
H&E	Haematoxylin and eosin
micro-CT	Microcomputed tomography
mtDNA	Mitochondrial DNA
OA	Osteoarthritis
PBS	Phosphate-buffered saline
PGC-1α	Peroxisome proliferator-activated receptor-γ coactivator-1α
PVDF	Polyvinylidene fluoride
ROS	Reactive oxygen species
SDF-1	Stromal cell-derived factor 1
SDS–PAGE	Sodium dodecyl sulfate–polyacrylamide gel electrophoresis
SEM	Standard error of the mean

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Acknowledgements

Not applicable.

Author contributions

Yanping Zhao, Shuya Wang contribute to the conception and design of the study. Xiaoying Zhu, Jingyao Yan and Yan liang contributed to the acquisition. Yanli Wang and Tianqi Dai contribute to the analysis or interpretation of data. Yanping Zhao, Dan Lin, Shuya Wang and Zhiyi Zhang contributed to drafting the manuscript and revising it critically for important intellectual content. All authors approved the final version to be published.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of First Affiliated Hospital of Harbin Medical University (No. 2023JS57).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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