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Original Research Article

MiR-493-5p alleviates lipopolysaccharide-induced inflammation in ATDC5 chondrogenic cells by targeting TAB2

Xuan Chen[1], De Li[1], Mangmang Chen[2]*
[1]Department of Hand and Foot Microsurgery, the Sixth Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang Uygur Autonomous Region 830092, [2]Department of Orthopedics Surgery, The Dingli Clinical Institute of Wenzhou Medical University, Wenzhou Central Hospital, Wenzhou, Zhejiang Province 325000, China

For correspondence:* ***Email:* *mangm_c1635@163.com;* ***Tel:*** *+86-057788053090*

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Abstract

Purpose: *To investigate the effect of miR-493-5p in lipopolysaccharide (LPS) -induced ATDC5 chondrogenic cells.*
Methods: *The MTT assay was used to determine the viability of LPS-induced ATDC5 cells. ENCORI (starbase.sysu.edu.cn/) was used to predict the target of miR-493-5p. Quantitative reverse-transcription-polymerase chain reaction (qRT-PCR) was used to determine miR-493-5p expression in ATDC5 controlled cells and cells treated with various combinations of LPS, negative control miRNA (NC), miR-493-5p mimic, TAB2 overexpression vector, and miR-493-5p inhibitor. qRT-PCR, while western blot was used to assess TAB2 mRNA and protein expression levels in control, LPS, LPS + NC, LPS + miR-493-5p mimic, and LPS + miR-493-5p inhibitor groups. The qRT-PCR and ELISA were used to evaluate TNF-α, IL-18, and IL-1β expressions in control, NC, LPS, LPS + NC, miR-493-5p mimic, and LPS + miR-493-5p mimic. Furthermore, the two techniques were also used determine LPS + miR-493-5p inhibitor, LPS + TAB2 overexpression, and LPS + TAB2 overexpression + miR-493-5p mimic groups.*
Results: *MiR-493-5p expression was downregulated in LPS-induced ATDC5 cells ($p < 0.001$). Overexpression of miR-493-5p increased LPS-induced ATDC5 cell viability but decreased expression of inflammatory factors ($p < 0.001$). MiR-493-5p targeted and inhibited TAB2 expression in LPS-induced ATDC5 cells ($p < 0.001$). TAB2 overexpression reversed the suppression of TAB2 by miR-493-5p in LPS-induced ATDC5 cell injury ($p < 0.001$).*
Conclusion: *MiR-493-5p alleviates LPS-induced inflammation of ATDC5 chondrogenic cells by targeting TAB2. Thus, miR-493-5p and TAB2 have potentials for use as clinical therapeutic targets for OA.*

Keywords: *MicroRNA-493-5p, TAK1 binding protein 2, Lipopolysaccharide, Inflammation, ATDC5*

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INTRODUCTION

Osteoarthritis (OA) is a normal chronic degenerative joint disease. The incidence of OA increases with age and thus mainly affects the elderly. It is characterized by progressive degeneration of articular cartilage leading to loss of joint mobility and function and chronic pain [1].

Transforming growth factor-β activated kinase 1 (TAK1 or MAP3K7) belongs to the mitogen-activated protein kinase family. Tab2/3 (TAK1 binding protein 2/3) acts as a bridge to bind TAK1 which binds with TRAF and IKK to form a complex [2]. This complex induces MAPK and activates the transcription factor NF-κB in response to stimulation of the pro-inflammatory cytokines TNF-α or IL-1 [3]. Thus, TAK1 plays a role in autoimmune inflammatory disease development. It has been demonstrated that TAB2 is involved in the development of liver injury, pneumonia, arthritis, cancer, and other diseases [4,5]. Therefore, this study focused on TAB2 and its mechanism in OA.

MicroRNAs (miRNAs/miRs) are non-coding RNAs that regulate gene expression by binding to 3' untranslated regions (3' UTRs) of specific target gene mRNAs [6,7]. miRNAs affect inflammatory diseases, such as cartilage disease and chondrogenesis [8]. It has been reported that miR-493-5p expression was lower in many tumors and that it could target oncogenic genes to inhibit tumor proliferation and migration [9]. The role of miR-493-5p in OA remains unclear.

In this study, the effect of miR-493-5p in lipopolysaccharide (LPS)-induced ATDC5 chondrogenic cells and the binding of miR-493-5p with TAB2 was evaluated.

EXPERIMENTAL

Cell culture

The ATDC5 chondrogenic cells were purchased from the National Collection of Authenticated Cell Cultures (https://www.cellbank.org.cn/, Shanghai, China). The cells were cultured in DMEM (Gibco, CA, USA) containing 10 % fetal bovine serum (Gibco) and 1 % penicillin/streptomycin (Gibco) in a humidified 5 % CO_2 incubator at 37 °C.

Western blot assay

The RIPA buffer (Beyotime, Shanghai, China) was used to extract whole protein from cells. Proteins were separated by SDS-PAGE and transferred to membranes. Membranes were probed with primary antibodies to TAB2 (ab264309, 1:5500; Abcam, Cambridge, USA) and β-actin (ab8227, 1:4000; Abcam, Cambridge, USA).

The membranes were then incubated with HRP-conjugated goat anti-rabbit immunoglobulin G secondary antibody (ab205718, 1:3000; Abcam).

Quantitative reverse transcription-polymerase chain reaction (qRT-PCR)

Cells were collected and lysed with TRIzol (Beyotime, Shanghai, China) to extract total RNA. Gene expression was calculated using the $2^{-\triangle\triangle Ct}$ method [10,11]. The primer sequences are shown in Table 1.

Table 1: Primers for miR-493-5p, TNF-α, IL-1β, IL-18, U6, and GAPDH

Gene	Primer	Sequence (5'→3')
MiR-493-5p	Forward	TCCTACGGAGAGGCTCAG
	Reverse	TCCTCGTAGTCCAACACG
TNF-α	Forward	ACATGGGAGCT GTGTTCCTC
	Reverse	GCAAACACACCGAAAAAGGT
IL-1β	Forward	GAGGCTGACAGACCCCAAAA
	Reverse	GCTCCACGGGCAAGACAT
IL-18	Forward	GGAAGCTTATGGCTGCCATGTCA GAAG
	Reverse	ATAGGGCCCAGGCGCATGTGTG CTAATCATC
U6	Forward	TCCTCCACGACAACCAAAACC
	Reverse	TCTTTTCCCAAAATCCCAGACTC
GAPDH	Forward	CTGGGCTACACTGAGCACC
	Reverse	AAGTGGTCGTTGAGGGCAATG

ELISA

ELISA kits were used to detect TNF-α (Sigma-Aldrich, RAB0477, Shanghai, China), IL-1β (Abcam, ab197742, CA, USA), and IL-18 (Abcam, ab216165, CA, USA) expression in ATDC5 cells.

MTT assay

Cells (3×10^3 cells/mL) were placed into 96-well plates and treated with LPS, LPS + negative control miRNA (NC), LPS + miR-493-5p mimic, or LPS + miR-493-5p inhibitor. The MTT solution (Beyotime) was added to each well at a final concentration of 0.5 mg/mL and the plates were cultured for 4 h at 37 °C. Then, the culture medium was discarded, and 100 μL of dimethyl sulfoxide (DMSO) was added to each well. Finally, the optical densities at 490 nm were measured by a microplate reader (BioTek, Winooski, VT, USA).

Cell transfection

The miR-493-5p mimic, NC, miR-493-5p inhibitor, and pc-TAB2 were purchased from General Biology (Anhui, China). Cells were seeded into 6-well plates and cultured for one day. The next day, cells were transfected with

the miR-493-5p mimic, NC, miR-493-5p inhibitor, or pc-TAB2 using LipoJet™ (SignaGen, Jinan, Shandong).

Dual-luciferase reporter assay

The TAB2 and miR-493-5p binding sites were cloned individually into the pmirGLO luciferase reporter vector (YINGBIOTECH, Shanghai, China). The miR-493-5p mimic and NC were individually co-transfected with the individual reporter plasmids using Lipofectamine 3000. Two days after transfection, luciferase activity was measured using a dual-luciferase kit (Promega).

Statistical analysis

All data are presented as the mean ± standard deviation (SD) of three independent tests. Student's t-test was used to compare two groups. $P < 0.05$ was considered statistically significant.

RESULTS

MiR-493-5p expression decreased in LPS-induced ATDC5 chondrogenic cells

The ATDC5 chondrogenic cells were divided into four groups treated with four different concentrations of LPS (0, 2, 5, or 10 μg/mL). Upon treatment, the MTT assay was used to evaluate cell viability, and the results showed that cell viability decreased as the LPS concentration increased (Figure 1 A). Then, miR-493-5p expression in the four LPS treatment groups was examined by qRT-PCR, and the results showed that miR-493-5p expression decreased as the LPS dose increased (Figure 1 B). However, western blot analysis showed that TAB2 expression increased as the LPS concentration increased (Figure 1 C). These results demonstrated a negative correlation between miR-493-5p and TAB2 expression in LPS-induced ATDC5 cells.

MiR-493-5p overexpression increased LPS-induced ATDC5 chondrogenic cell viability but decreased expression of inflammatory factors

The ATDC5 cells were transfected with NC, the miR-493-5p mimic, or the miR-493-5p inhibitor, and miR-493-5p expression was validated by qRT-PCR. miR-493-5p expression was upregulated in the miR-493-5p mimic group and downregulated in the miR-493-5p inhibitor group when compared with the control and NC groups (Figure 2 A). The MTT assay showed that ATDC5 cell viability decreased upon treatment with LPS and that miR-493-5p overexpression increased ATDC5 cell viability when compared with the LPS + NC group (Figure 2 B).

qRT-PCR and ELISA assays showed expression of inflammatory factors. The TNF-α, IL-18, and IL-1β expression were upregulated in the LPS group when compared with the control group. TNF-α, IL-18, and IL-1β expression was downregulated in the LPS + miR-493-5p mimic group and slightly upregulated in the LPS + miR-493-5p inhibitor group when compared with the LPS + NC group (Figures 2 C and D). These data demonstrated that miR-493-5p overexpression increases the viability of LPS-induced ATDC5 chondrogenic cells and downregulates expression of inflammatory factors.

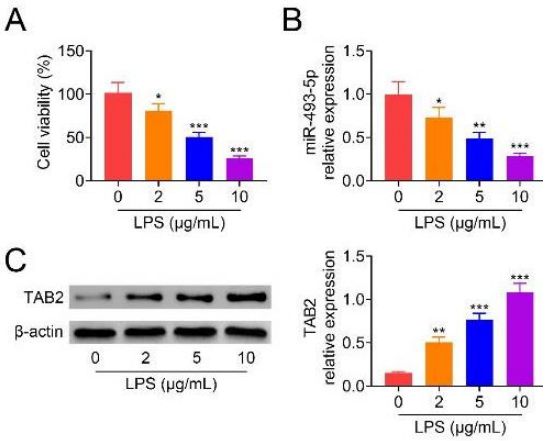

Figure 1: MiR-493-5p expression decreased in LPS-treated ATDC5 chondrogenic cells. (A) The MTT assay result showing ATDC5 cell viability upon treatment with 0, 2, 5, or 10 μg/mL LPS. *$P < 0.05$, ***$p < 0.001$ vs. the 0 μg/mL group. (B) qRT-PCR result showing miR-493-5p expression in ATDC5 cells treated with 0, 2, 5, or 10 μg/mL LPS. **$P < 0.01$, ***$p < 0.001$ vs. the 0 μg/mL group. (C) Western blot analysis showing TAB2 expression in ATDC5 cells treated with 0, 2, 5, or 10 μg/mL LPS. **$P < 0.01$, ***$p < 0.001$ vs. the 0 μg/mL group. β-actin was used as the internal control for normalization

MiR-493-5p targets and inhibits TAB2 expression in LPS-induced ATDC5 chondrogenic cells

The Encyclopedia of RNA Interactomes (ENCORI, starbase.sysu.edu.cn/) predicted that miR-493-5p binds to TAB2 RNA (Figure 3 A). Western blot and qRT-PCR analysis suggested that LPS upregulated TAB2 mRNA and protein expression in ATDC5 cells. However, TAB2 expression decreased in the LPS + miR-493-5p mimic group and increased in the LPS + miR-493-5p inhibitor group when compared with the LPS + NC group (Figures 3 B and C). The

ATDC5 cells were co-transfected with NC + TAB2-3' UTR WT, miR-493-5p mimic + TAB2-3' UTR WT, NC + TAB2-3' UTR MUT, or miR-493-5p mimic + TAB2-3' UTR MUT for the luciferase reporting assay. Relative luciferase activity was lower in the miR-493-5p mimic + TAB2-3' UTR WT group than in the NC + TAB2-3' UTR WT group, but there was no difference between the NC + TAB2-3' UTR MUT and miR-493-5p mimic + Tab2-3' UTR MUT groups (Figure 3 D). These data suggested that miR-493-5p targets and suppresses TAB2 expression in LPS-induced ATDC5 chondrogenic cells. The ATDC5 cells were co-transfected with miR-NC + TAB2-3' UTR WT, miR-493-5p mimic + TAB2-3' UTR WT, miR-NC + TAB2-3' UTR MUT, or miR-493-5p mimic + Tab2-3' UTR MUT.

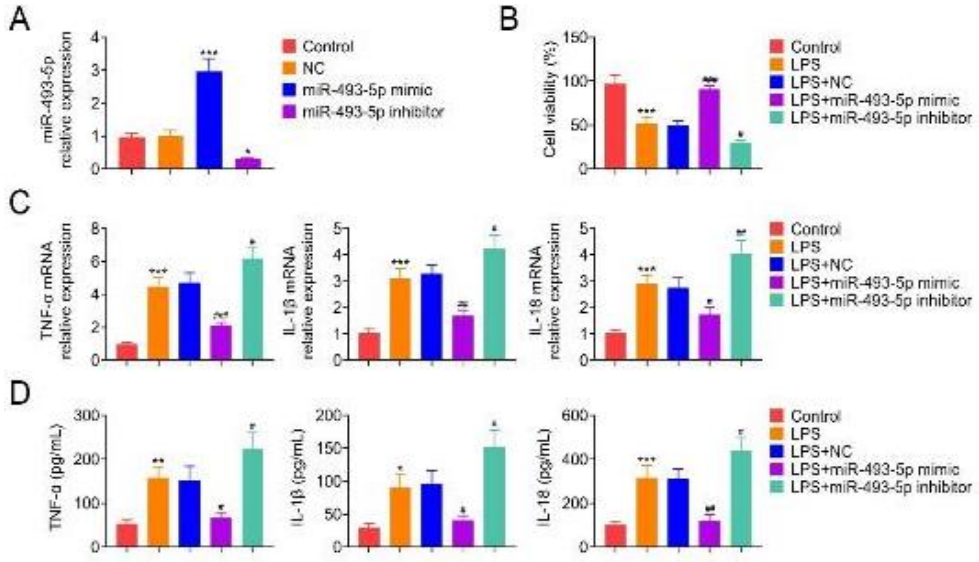

Figure 2: MiR-493-5p overexpression increased the viability of LPS-induced ATDC5 chondrogenic cells and decreased expression of inflammatory factors. (A) miR-493-5p expression in the control, NC, miR-493-5p mimic, and miR-493-5p inhibitor groups. *P < 0.05, ***p < 0.001 vs. the NC group. (B) ATDC5 cell viability in the control, LPS, LPS + NC, LPS + miR-493-5p mimic, and LPS + miR-493-5p inhibitor group. *** P < 0.001 vs. the control group, $^{\#}p$ < 0.05, $^{\#\#\#}p$ < 0.001 vs. the LPS + NC group. (C–D) TNF-α, IL-1β, and IL-18 expression in the control, LPS, LPS + NC, LPS + miR-493-5p mimic, and LPS + miR-493-5p inhibitor groups and ELISA. $^{*}P$ < 0.05, $^{**}p$ < 0.01, $^{***}p$ < 0.001 vs. the control group. $^{\#}p$ < 0.05, $^{\#\#}p$ < 0.01, $^{\#\#\#}p$ < 0.001 vs. the LPS + NC group

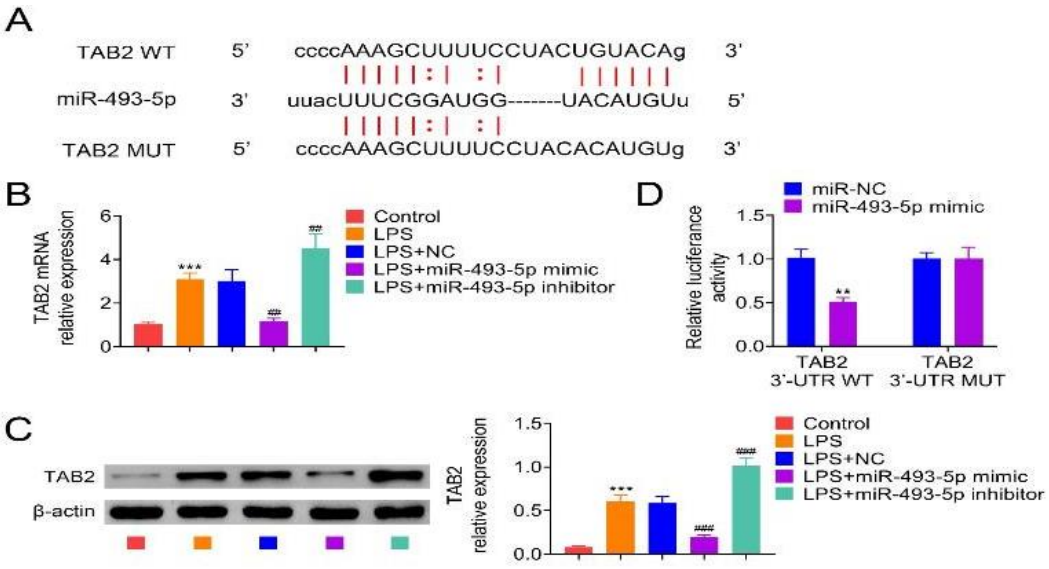

Figure 3: miR-493-5p targets and inhibits TAB2 expression in LPS-treated ATDC5 chondrogenic cells. (A) ENCORI predicted binding between TAB2 RNA and miR-493-5p. (B-C) qRT-PCR and western blot analysis showing TAB2 mRNA and protein expression levels in control, LPS, LPS + miR-493-5p mimic, and LPS + miR-493-5p inhibitor groups. ***P < 0.001 vs. the control group, $^{\#\#}p$ < 0.05 and $^{\#\#\#}p$ < 0.001 vs the LPS + NC group. β-actin was used as the internal control for normalization. (D) The luciferase reporter assay result showing binding between TAB2 and miR-493-5p. **P < 0.05

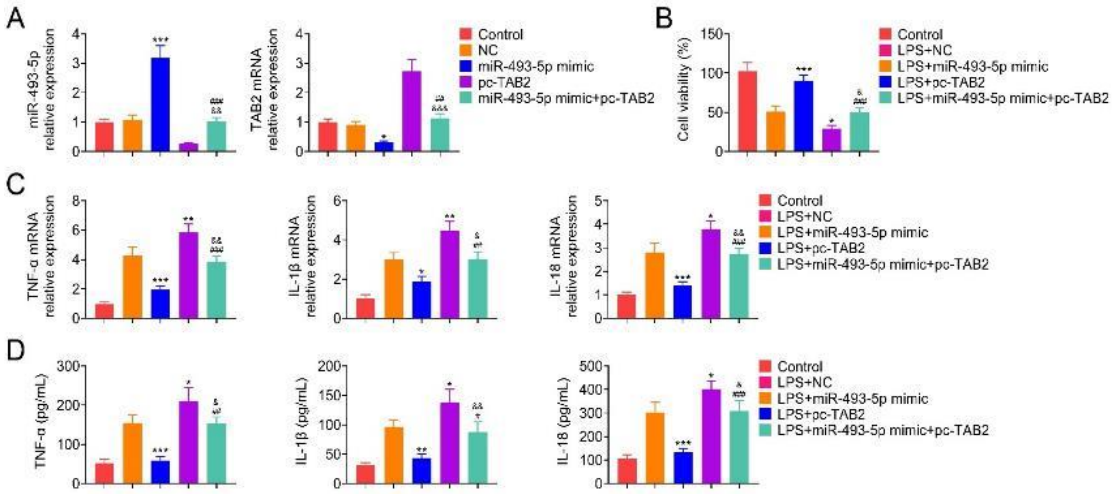

Figure 4: TAB2 overexpression reversed TAB2 inhibition by miR-493-5p upon LPS-induced injury in ATDC5 chondrogenic cells. (A) miR-493-5p expression in the control, NC, miR-493-5p mimic, PC-TAB2, and miR-493-5p mimic + PC-TAB2 groups. $^{*}P < 0.05$ and $^{***}p < 0.001$ vs. the control group, $^{\#\#}p < 0.01$ and $^{\#\#\#}p < 0.001$ vs. the miR-493-5p mimic group, $^{\&\&}p < 0.01$ and $^{\&\&\&}p < 0.001$ vs. the PC-TAB2 group. (B) Cells viability in the control, LPS + NC, LPS + miR-493-5p mimic, LPS + pc-TAB2, and LPS + miR-493-5p mimic + pc-TAB2 groups. $^{*}P < 0.05$ and $^{***}p < 0.001$ vs. the LPS + NC group, $^{\#\#\#}p < 0.001$ vs. the LPS + miR-493-5p mimic group, $^{\&}p < 0.05$ vs. LPS + the PC-TAB2 group. (C–D) TNF-α, IL-1β, and IL-18 expression in the control, LPS + NC, LPS + miR-493-5p mimic, LPS + PC-TAB2, and LPS + miR-493-5p mimic + PC-TAB2 groups was measured by qRT-PCR and ELISA. $^{*}P < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$ vs. the LPS + NC group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, and $^{\#\#\#}p < 0.001$ vs. the LPS + miR-493-5p mimic group; $^{\&}p < 0.05$ and $^{\&\&}p < 0.01$ vs. the LPS + PC-TAB2 group

TAB2 overexpression reversed TAB2 suppression by miR-493-5p upon LPS-induced injury in ATDC5 chondrogenic cells

The NC, miR-493-5p mimic, PC-TAB2, or miR-493-5p mimic + PC-TAB2 were transfected into ATDC5 cells, and miR-493-5p and TAB2 expression levels were measured. qRT-PCR results showed no difference between the control and NC groups. miR-493-5p was upregulated in the miR-493-5p mimic group when compared with the NC group, as expected. Although miR-493-5p expression decreased in the TAB2 overexpression group, it recovered to control and NC levels in the miR-493-5p mimic + PC-TAB2 group. TAB2 expression was downregulated in the miR-493-5p mimic group when compared with the NC group. However, it increased in the TAB2 overexpression group and recovered to control and NC levels in the miR-493-5p mimic + PC-TAB2 group (Figure 4 A). The MTT assay showed that LPS treatment reduced cell viability, miR-493-5p overexpression increased cell viability, and TAB2 overexpression reduced cell viability when compared with the LPS + NC group. Cell viability was recovered in LPS + miR-493-5p mimic + PC-TAB2 group (Figure 4 B).

The ELISA and qRT-PCR assays showed that expression of TNF-α, IL-18, and IL-1β was upregulated in the LPS group. TNF-α, IL-18, and IL-1β expression was downregulated in the LPS + miR-493-5p mimic group and upregulated in the LPS + PC-TAB2 group when compared with the LPS + NC group. TNF-α, IL-18, and IL-1β expression recovered to LPS + NC levels in the LPS + miR-493-5p mimic + PC-TAB2 group (Figure 4C and D). These results showed that TAB2 overexpression reverses the miR-493-5p-induced inhibition of TAB2 in LPS-treated ATDC5 chondrogenic cells.

DISCUSSION

Although there has been progress in the medical science of OA, the molecular mechanism remains unclear. Recently, it has been shown that miR-493-5p regulates the progression of several diseases, especially cancer. It was shown that miR-493-5p/ROCK1 affects malignant progression and cisplatin resistance of non-small cell lung cancer cells via circ_PIP5K1A in a xenograft murine model [12]. However, there has only been one study on the role of miR-493-5p in OA. In addition, core regulatory RNA molecules, such as miR-493-5p, are present in articular cartilage stem/progenitor cells that progress to OA [13]. In this study, miR-493-5p expression was downregulated in LPS-induced ATDC5 chondrogenic cells. Overexpression of miR-493-5p increased ATDC5 chondrogenic cell viability and decreased expression of inflammatory factors upon LPS-induced injury, indicating that miR-493-5p regulates OA disease development.

It has been shown that TAB2 can bind to several miRNAs. For example, miR-128 played a key role in TAB2-mediated NF-κB signaling leading to inhibition of the inflammatory response in miiuy croaker fish [14]. In addition, miR-149-5p binding to TAB2 mediated PM 2.5-induced inflammatory response via NF-κB and MAPK signaling *in vivo* and *in vitro* [15]. miR-23b binding to TAB2, TAB3, and IKK-α inhibited IL-17-mediated autoimmune inflammation [4]. Although no previous study has demonstrated any interaction between TAB2 and miR-493-5p, the ENCORI prediction website was used to reveal that miR-493-5P targets the 3 '-UTR of TAB2, and this interaction was verified through *in vitro* experiments. The miR-493-5p targets and inhibits TAB2 expression in LPS-induced ATDC5 chondrogenic cells.

It has been shown that TAB2 affects OA while, NLRP6 promotes the interaction between TAB2/3 and TRIM38 in fibroblast-like synoviocytes of rheumatoid arthritis [16]. In synovial fibroblasts of rheumatoid arthritis, TAB2 RNA expression was upregulated, which correlates with the VIP regulatory effect, and this TAB2 upregulation reverses TLR4-induced signaling [17]. Likewise, in this study, it has been observed that TAB2 overexpression reversed the suppression of TAB2 by miR-493-5p in LPS-induced ATDC5 chondrogenic cells.

CONCLUSION

MiR-493-5p expression decreases in LPS-induced ATDC5 chondrogenic cells, but its upregulation increases LPS-induced ATDC5 chondrogenic cell viability and decreases the expression of inflammatory factors. In addition, miR-493-5p targets and inhibits TAB2 expression in LPS-induced ATDC5 chondrogenic cells. Finally, TAB2 overexpression reverse the suppression of TAB2 by miR-493-5p in LPS-induced ATDC5 cells. These results show that miR-493-5p alleviates LPS-induced inflammation in ATDC5 chondrogenic cells by targeting TAB2. Thus miR-493-5p and TAB2 have potentials for use as clinical therapeutic targets for OA.

DECLARATIONS

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None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Xuan Chen designed the experiments and De Li carried them out. Mangmang Chen analyzed and interpreted the data and prepared the manuscript with contributions from all co-authors.

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