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Original Article

miR-137 suppresses cell growth and extracellular matrixdegradation through regulating ADAMTS-5 in chondrocytes

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Abstract: Osteoarthritis (OA) is the most common degenerative joint disease. microRNAs (miRNAs) have been shown to act critical roles in several diseases including OA. However, the involvement and underlying mechanism of miR-137 in development of OA remains unkown. In our study, we firstly showed that IL-1β decreased the expression of miR-137 in the chondrocytes and we demonstrated that the miR-37 expression level was lower in the OA cases than in the control patients. Dual-luciferase reporter analysis was performed to confirm that ADAMTS-5 was a direct target gene of miR-137. Furthermore, we indicated that elevated expression of miR-137 decreased the protein expression of ADAMTS-5 in the chondrocytes. In additional, we showed that IL-1β induces the ADAMTS-5 expression in the chondrocytes. The ADAMTS-5 expression level was higher in the OA cases than in the control patients. We showed that the expression of ADAMTS-5 was negatively correlated with the miR-137 expression level in OA tissues. Overexpression of miR-137 suppressed cell growth, extracellular matrix (ECM) degradation and inflammation in chondrocytes. These preliminary data elucidated that miR-137 suppressed OA progression via inhibiting cell growth, inflammation and ECM degradation.

Keywords: Osteoarthritis, miR-137, ADAMTS-5, extracellular matrix

Introduction

Osteoarthritis is one age-correlated disorder of joint-bone that causes disability and pain in older and middle people worldwide [1-3]. As one degenerative illness, articular cartilage degeneration acts crucial roles in the development and pathogenesis of osteoarthritis [4-6]. The degeneration of articular cartilage owns to lack of balance of the extracellular matrix (ECM) components including proteoglycan and collagen [2, 7, 8]. A lot of factors conduce to articular cartilage degeneration such as strain, aging, obesity, inflammation, congenital malformation and trauma [9-11]. Thus, it is crucial to explore the regulatory mechanism and pathophysiology of osteoarthritis.

MicroRNAs (miRNAs) are non-coding, endogenous and small RNAs that modify protein coding gene expression via binding to 3'-UTR (untranslated region) of mRNA (messenger RNA), resulting in inhibition of enhancement or translation of target mRNA degradation [12-15]. Several studies suggested that miRNAs act crucial roles in diverse cellular and biological processes such as differentiation, apoptosis, proliferation and metabolism [16-20]. A number of miRNAs are found to be aberrantly altered in diverse diseases including neurological disorders, diabetes, heart failure, autoimmune disease, pulmonary hypertension, and cancer and disc degeneration [21-27]. Growing evidences also found that miRNAs act critical roles in the development of osteoarthritis [5, 28, 29]. A series of studies suggested that miR-137 played important functional roles in the development of several diseases [30-32]. For instances, Qi et al. [33] reported that the expression of miR-137 was downregulated in melanoma cell lines and tissues and miR-137 knockdown suppressed melanoma cell invasion and migration partly through regulating PIK3R3 expression. However, the involvement and underlying mech-

anism of miR-137 in development of OA remains unknown.

Here, we monitored miR-137 expression in the OA cases and normal control patients. We firstly showed that IL-1β decreased the expression of miR-137 in the chondrocytes and the miR-37 expression level was lower in the OA cases than in the control patients. Overexpression of miR-137 suppressed cell growth, ECM degradation and inflammation in chondrocytes.

Materials and methods

Human samples

The normal control cartilage tissues were contained from patients that were taken amputation without OA history or rheumatoid arthritis. OA cartilage tissues were collected from the OA patients that underwent total knee arthroplasty (AKT). Our study was approved by Ethics Informed consent of our hospital and informed consent was collected from all cases.

Cell culture and treatment

Chondrocytes were isolated from OA cartilage samples and cultured following to previous study [34]. These Chondrocytes cells were cultured in the Dulbecco's modified Eagle's medium (DMEM) containing 10% FBS. miR-137 mimic and miR-137 control miR-NC were obtained from Shanghai GenePharma (Shanghai, China) and was transfected into chondrocytes cells with Lipofectamine-2000 (Invitrogen, USA) according to information of manufacturer.

RNA extraction and quantitative real-time PCR

Total RNAs of tissues or cells were isolated by using TRIzol Reagent (Life Technologies). mRNA and miRNA expression was determined with qRT-PCR. qRT-PCR analysis was performed by using SYBR RT-PCR Reagent (Takara) and stem-loop RT primers on the ABI PRISM 7900 (Applied Biosystems, Foster City, USA). U6 and GAPDH were performed as the internal control for miRNA and mRNA expression respectively. These primers which used in this study were shown as following: miR-137, forward, 5'-GTGACGGGTATTCTTGGGT-3' and reverse 5'-GACTACGCGTATTCTTAAGCAA-3' and U6, forward, 5'-CGCTTCGGCAGCACATATAC-3' and reverse 5'-TTCACGAATTTGCGTGTCAT-3' and GAPDH forward, 5'-GGAATCCACTGGCGTCTTCA-3' and reverse 5'-GGTTCACGCCCATCACAAAC.

CCK-8 assay

Cell growth was measured by exploiting CCK-8 (Cell Counting Assay Kit-8) (Dojindo, Gaithersburg, MD) following to protocol of manufacturer. Cells were cultured in the 96-well plate and then transfected with miR-137 mimics. These cells were detected at the 24, 48 and 72 hours respectively. Ten mL CCK-8 kit was added into each 96-well and there cells continued to incubate for 2 hours. The absorbance at 450 nm was measured with microplate reader.

Western blot

Cell lysates were established in the RIPA buffer and the concentration of protein was measured with BCA kit (Pierce). Cell protein lysate was separated with 12% SDS-PAGE and then transferred to polyvinylidene fluoride (PVDF) membranes. After blocking with non-fat milk with 2 hours, the membranes were incubated with anti-ADAMTS-5 and anti-GAPDH overnight. These membranes were detected by chemiluminescent detection (ECL) kit. GAPDH was used as the internal control.

Dual luciferase activity assay

The human ADAMTS-5 3'UTR and mutant 3'UTR luciferase reporter vector was cloned into 3'UTR region of the pMIR-Report vector (Promega). Cell were cultured in the 24-well plate and co-transfected with miR-137 mimic or scramble, ADAMTS-5 3'UTR or mutant ADAMTS-5 3'UTR by using Lipofectamine 2000 (Invitrogen) according to protocol of manufacturer. After 24 hours, the luciferase activity was determined by using Dual-Luciferase Reporter System (Promega) following to the instructions of manufacturer.

Statistical analysis

Data were expressed as means ± SD (standard deviation). SPSS statistical (Inc., Chicago, USA) was used to analyze the significant difference. Statistically difference was detected with Two-tailed Student's t test. $P < 0.05$ was indicated as statistically significant.

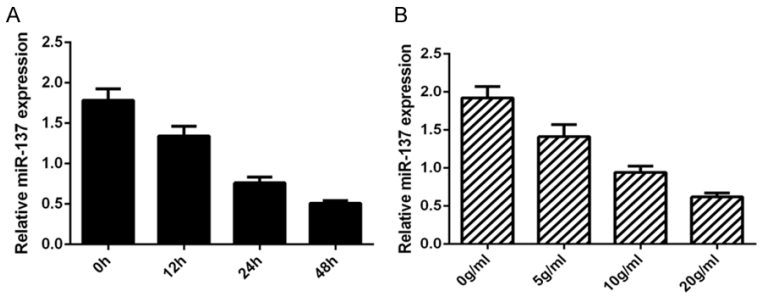

Figure 1. IL-1β decreased the expression of miR-137 in the chondrocytes. A. The expression of miR-137 was detected by qRT-PCR assay and U6 was used as the internal control. B. The miR-137 expression level was downregulated after treatment with 0 (as a control), 5, 10 and 20 ng/ml IL-1β.

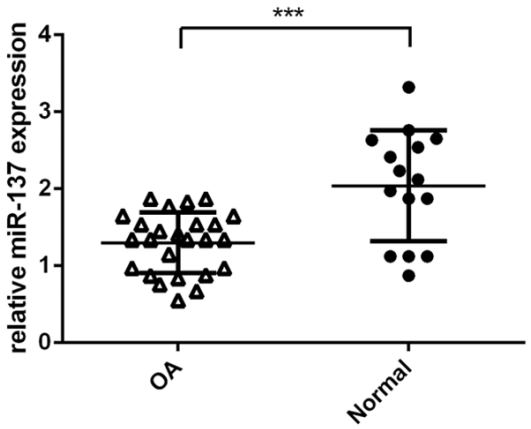

Figure 2. miR-137 expression was downregulated in the OA issues. The expression level of miR-137 in the OA cases and normal control patients was measured by qRT-PCR assay. ***P < 0.001.

Results

IL-1β decreased the expression of miR-137 in the chondrocytes

Firstly, we study the expression of miR-137 in the chondrocytes after treatment of inflammatory mediator IL-1. Our result showed that IL-1β (10 ng/ml) suppressed the miR-137 expression in the chondrocytes at the time-dependently (**Figure 1A**). In additional, we demonstrated that the miR-137 expression level was downregulated after treatment with 0 (as a control), 5, 10 and 20 ng/ml IL-1β (**Figure 1B**).

miR-137 expression was downregulated in the OA issues

Next, we determined the expression level of miR-137 in the OA cases and normal control patients. Our data suggested that the miR-37 expression level was lower in the OA cases than in the control patients (**Figure 2**).

ADAMTS-5 was a direct target gene of miR-137 in the chondrocytes

To further study the mechanism of miR-137 in OA, the software targetscan (http://www.targetscan.org/vert_72/) was utilized to find the target gene interacted with miR-137. As shown in the **Figure 3A**, we demonstrated that ADAMTS-5 contained potential binding sites with miR-137. Moreover, we showed that the miR-137 expression was upregulated in the chondrocytes after treatment with miR-137 mimic (**Figure 3B**). Dual-luciferase reporter analysis was done to confirm whether ADAMTS-5 was a direct target gene of miR-137. Our results proved that ectopic expression of miR-137 significantly suppressed luciferase activity of ADAMTS-5-WT vector but not the ADAMTS-5-MUT (**Figure 3C**). Furthermore, we indicated that elevated expression of miR-137 decreased the protein expression of ADAMTS-5 in the chondrocytes (**Figure 3D**).

IL-1β induces the ADAMTS-5 expression in the chondrocytes

Then, we study the expression of ADAMTS-5 in the chondrocytes after treatment of inflammatory mediator IL-1β. Our result showed that IL-1β (10 ng/ml) enhanced the ADAMTS-5 expression in the chondrocytes at the time-dependently (**Figure 4A**). In additional, we demonstrated that the ADAMTS-5 expression level was downregulated after treatment with 0 (as a control), 5, 10 and 20 ng/ml IL-1β (**Figure 4B**).

ADAMTS-5 expression was upregulated in the OA issues and was negatively correlated with miR-137 in OA

Next, we investigated the expression level of ADAMTS-5 in the OA cases and normal control patients. Our data suggested that the ADAMTS-5 expression level was higher in the OA cases than in the control patients (**Figure 5A**).

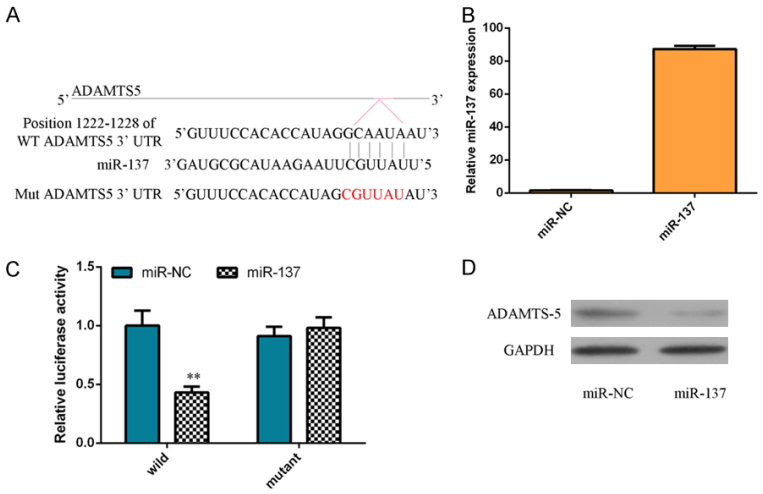

Figure 3. ADAMTS-5 was a direct target gene of miR-137 in the chondrocytes. A. ADAMTS-5 contained potential binding sites with miR-137 by using the software targetscan (http://www.targetscan.org/vert_72/). B. miR-137 expression was upregulated in the chondrocytes after treatment with miR-137 mimic. C. Ectopic expression of miR-137 significantly suppressed luciferase activity of ADAMTS-5-WT vector but not the ADAMTS-5-MUT. D. Elevated expression of miR-137 decreased the protein expression of ADAMTS-5 in the chondrocytes.

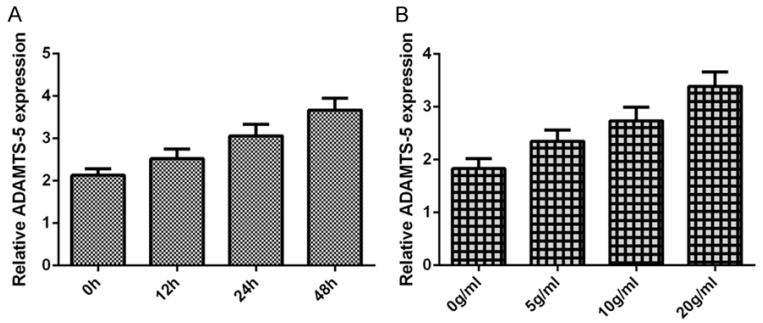

Figure 4. IL-1β induces the ADAMTS-5 expression in the chondrocytes. A. The expression of ADAMTS-5 was measured by qRT-PCR assay and GAPDH was used as the internal control. B. The miR-137 expression level was downregulated after treatment with 0 (as a control), 5, 10 and 20 ng/ml IL-1β.

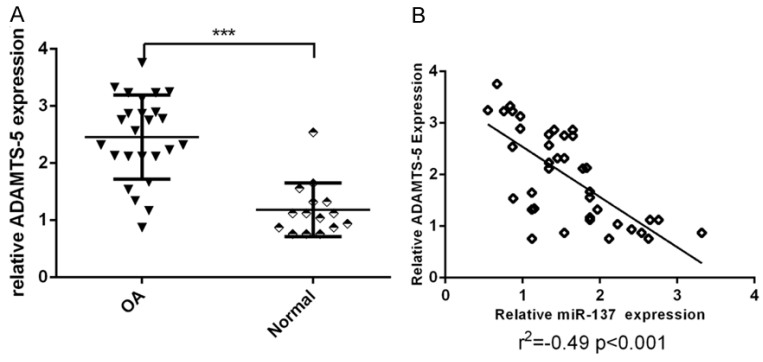

Figure 5. ADAMTS-5 expression was upregulated in the OA issues and was negatively correlated with miR-137 in OA. A. The ADAMTS-5 expression level was higher in the OA cases than in the control patients. B. The expression of ADAMTS-5 was negatively correlated with the miR-137 expression level in OA tissues. ***P < 0.001.

Moreover, we showed that the expression of ADAMTS-5 was negatively correlated with the miR-137 expression level in OA tissues (**Figure 5B**).

Overexpression of miR-137 suppressed cell growth, ECM degradation and inflammation in chondrocytes

We demonstrated that ectopic expression of miR-137 suppressed cell growth in the chondrocytes (**Figure 6A**). Then, we showed that overexpression of miR-137 inhibited the IL-1 expression in the chondrocytes (**Figure 6B**). In addition, miR-137 overexpression promoted the aggrecan expression in the chondrocytes (**Figure 6C**). Ectopic expression of miR-137 enhanced type X collagen expression in the chondrocytes (**Figure 6D**). Moreover, we demonstrated that overexpression of miR-137 suppressed the ADAMTS-4 (**Figure 6E**) and MMP-13 (**Figure 6F**) expression in chondrocytes.

Discussion

Identification of pivotal miRNAs correlated with pathogenesis of OA may assist to OA prognosis and diagnosis. In our study, we firstly showed that IL-1β decreased the expression of miR-137 in the chondrocytes and we demonstrated that the miR-37 expression level was lower in the OA cases than in the control patients. Dual-luciferase reporter analysis was performed to confirm that ADAMTS-5 was a direct target gene of miR-137. Furthermore, we indicated that elevated expression of miR-137 decreased the protein expression of ADAMTS-5 in the chondrocytes. In additional, we showed that IL-1β

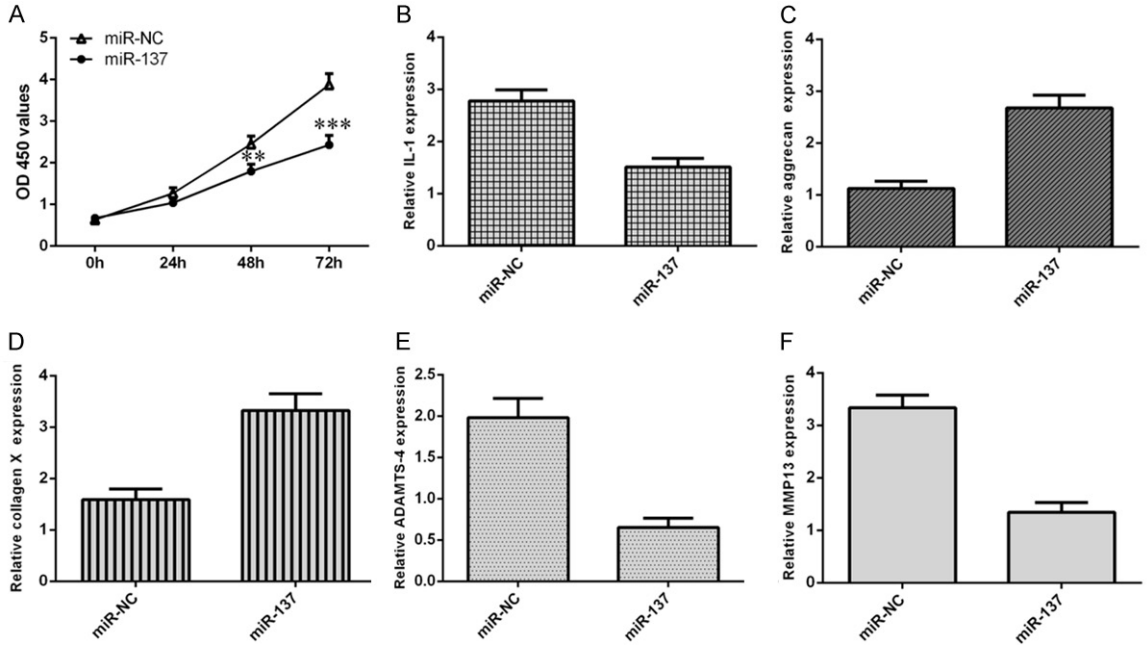

Figure 6. Overexpression of miR-137 suppressed cell growth, ECM degradation and inflammation in chondrocytes. A. CCK-8 assay was performed to detect the cell growth. B. Overexpression of miR-137 inhibited the IL-1 expression in the chondrocytes. C. miR-137 overexpression promoted the aggrecan expression in the chondrocytes. D. Ectopic expression of miR-137 enhanced type X collagen expression in the chondrocytes. E. Overexpression of miR-137 suppressed the ADAMTS-4 expression in chondrocytes. F. The expression of MMP-13 was detected by qRT-PCR assay and GAPDH was used as the internal control. $^{**}P < 0.01$ and $^{***}P < 0.001$.

induces the ADAMTS-5 expression in the chondrocytes. The ADAMTS-5 expression level was higher in the OA cases than in the control patients. We showed that the expression of ADAMTS-5 was negatively correlated with the miR-137 expression level in OA tissues. Overexpression of miR-137 suppressed cell growth, ECM degradation and inflammation in chondrocytes. These preliminary data elucidated that miR-137 suppressed OA progression via inhibiting cell growth, inflammation and ECM degradation.

A series of researches indicated that miR-137 played critical functional roles in the development of several tumors [35-37]. For instances, Qi et al. [33] reported that the expression of miR-137 was downregulated in melanoma cell lines and tissues and miR-137 knockdown suppressed melanoma cell invasion and migration partly through regulating PIK3R3 expression. Huang et al. [38] indicated that miR-137 expression was decreased in hepatocellular carcinoma cell lines and overexpression of miR-137 suppressed hepatocellular carcinoma cell migration and invasion via inhibiting EZH2 expression. Bi et al. [39] showed that miR-137 expression level was downregulated in colon cancer cells and ectopic expression of miR-137 decreased the colon cancer cell invasion, proliferation and migration by modulating TCF4 expression. However, the involvement and underlying mechanism of miR-137 in development of OA remains unknown. In the present study, we investigated the expression of miR-137 in the OA cases and normal control patients. Our results suggested that the miR-137 expression level was lower in the OA cases than in the control patients. Moreover, we showed that IL-1β decreased the expression of miR-137 in the chondrocytes. Ectopic expression of miR-137 suppressed cell growth in the chondrocytes. Furthermore, we indicated that overexpression of miR-137 suppressed the ADAMTS-4 and MMP-13 expression. These results suggested that that miR-137 suppressed OA progression via inhibiting cell growth, inflammation and ECM degradation.

Previous studies indicated that miRNAs involved in cell physiological and pathological processes by modulating several target genes expression and their signal pathways [40, 41]. ADAMTS-5, one member of ADAMTS family,

played pivotal roles in the development of OA [42-44]. Glasson et al. [45] indicated that erosion of cartilage and aggrecan early loss was decreased by depletion of ADAMTS-5 in one murine model of the OA. This result suggested that ADAMTS-5 played important roles in the progression of OA. However, the modulation of ADAMTS-5 functioning in the progression of OA remains unclear. In our study, we used software targetscan (http://www.targetscan.org/vert_72/) to predict the target gene interacted with miR-137. We found that ADAMTS-5 contained potential binding sites with miR-137. Dual-luciferase reporter analysis was performed to confirm that ADAMTS-5 was a direct target gene of miR-137. Ectopic expression of miR-137 significantly suppressed luciferase activity of ADAMTS-5-WT vector but not the ADAMTS-5-MUT. Furthermore, we indicated that elevated expression of miR-137 decreased the protein expression of ADAMTS-5 in the chondrocytes.

In summary, our data identified that IL-1β decreased the expression of miR-137 in the chondrocytes and miR-137 expression level was lower in the OA cases than in the control patients. Overexpression of miR-137 suppressed cell growth, ECM degradation and inflammation in chondrocytes. ADAMTS-5 was a direct target gene of miR-137. These preliminary data elucidated that miR-137 suppressed OA progression via inhibiting cell growth, inflammation and ECM degradation.

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Disclosure of conflict of interest

None.

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