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Long non-coding RNA H19 modulates proliferation and apoptosis in osteoarthritis via regulating miR-106a-5p

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Osteoarthritis (OA), a type of joint diseases, could result in breakdown of joint cartilage and underlying bone. Accumulating evidences suggested that long non-coding RNAs play important roles in OA progression. However, the underlying mechanism of H19 in OA is still not fully explored. The expression levels of H19 and miR-106a-5p in OA samples from patients or cultured chondrocytes were examined by quantitative real time polymerase chain reaction. Cell proliferation and apoptosis were analysed by MTT assay and flow cytometry, respectively. Western blotting was employed to detect the expression levels of PCNA, CyclinD1, Caspase 3 and Cleaved Caspase 3. StarBase database, luciferase assay and RNA immunoprecipitation were introduced to confirm the relationship between H19 and miR-106a-5p. The correlation of H19 and miR-106a-5p was analysed by Spearman rank analysis. H19 expression was upregulated, while miR-106a-5p level was downregulated in OA samples and IL-1β-treated chondrocytes. H19 overexpression inhibited the proliferation and induced apoptosis in IL-1β-treated chondrocytes, while H19 knockdown induced the opposite effect. Luciferase and RIP assay demonstrated that miR-106a-5p was a direct target of H19. miR-106a-5p overexpression led to proliferation promotion and apoptosis inhibition in chondrocytes treated by IL-1β and it reversed the effect of H19 addition. We conclude that H19 could regulate proliferation and apoptosis of chondrocytes treated by IL-1β in OA via sponging miR-106a-5p.

Keywords. Apoptosis; H19; miR-106a-5p; osteoarthritis; proliferation

1. Introduction

Osteoarthritis (OA) is the most commonly diagnosed chronic arthritis in the elderly (Cross *et al.* 2014; Glyn-Jones *et al.* 2015), which is characterized by gradual degradation of articular cartilage, inflammation (Urban and Little 2018) and pain leading to disability (Hunter and Bierma-Zeinstra 2019). Many factors contribute to the degradation of articular cartilage in OA by directly or indirectly regulating the catabolism of cartilage matrix (Felson *et al.* 2000; Mobasheri *et al.* 2017), including genetic factors (Warner and Valdes 2017) and inflammatory cytokine (Abramson 2004; Benito *et al.* 2005). Recently, long non-coding RNAs were demonstrated to play important roles in OA (Shen *et al.* 2018).

Long non-coding RNAs (lncRNAs) are a class of RNAs which are longer than 200 nucleotides in length and are not capable of coding protein (Ponting *et al.* 2009). LncRNAs are involved in many biological processes, including cell proliferation, cell cycle, metabolism, apoptosis and differentiation (Geisler and Coller 2013). Mechanically, lncRNAs can regulate the transcription by promoting or preventing the binding of transcription factors to promoter which functions as *cis*- or *trans*- acting modulators (Feng *et al.* 2006; Ng *et al.* 2013). LncRNAs can also regulate RNA splicing or decay (Gong and Maquat 2011; Tripathi *et al.* 2010). Recent studies revealed that lncRNAs may act as competing endogenous RNAs (ceRNAs) which harbor complementary sequence to microRNA (miRNA) thereby sequestering and preventing miRNA from binding to the mRNA target (Cesana *et al.* 2011; Salmena *et al.* 2011). Disrupted lncRNAs are involved in human diseases, including OA (Liu *et al.* 2016; Shen *et al.* 2018; Wang *et al.* 2017; Xu and Xu 2017). Moreover, lncRNAs in diseases have unveiled new

diagnostic and therapeutic opportunities (Brunner *et al.* 2012). LncRNA H19 has been reported to be involved in regulation of cell progresses, including proliferation, apoptosis, migration and inflammation in disorders (Cao *et al.* 2019; Gan *et al.* 2019). More importantly, previous studies revealed that H19 knockdown could relieve cartilage cells injury in OA (Steck *et al.* 2012; Hu *et al.* 2019). However, the underlying mechanism of H19 in OA progression remains poorly understood.

Apoptosis is a programmed cell death which is highly regulated in development and homeostasis (Andreoli 1999; Häcker 2000). Dysregulated apoptosis leads to development of multiple diseases, such as developmental anomalies, degenerative disease and even cancer (Fadeel and Orrenius 2005). Previous studies demonstrated that apoptosis of chondrocytes is involved in OA, which may lead to the degeneration of cartilage and failed regeneration of the cartilage (Adams and Jr 1998; Zamli and Sharif 2011).

The chondrocytes treated by IL-1β were widely used as cellular model of OA (Xue *et al.* 2019; Zhang *et al.* 2019). In the present work, we investigated the effect of H19 on proliferation and apoptosis of chondrocytes challenged by IL-1β and explored the potential mechanism.

2. Methods

2.1 *Patient samples*

A total of 37 OA cartilage tissues were obtained from People's Hospital of Tongchuan. Normal cartilage tissues were collected from 15 patients who were underwent the amputation without OA or rheumatoid arthritis (RA) history. All the experiments were approved by the ethics committees of People's Hospital of Tongchuan and all donors signed the written informed consents.

2.2 *Cell line and culture*

Cartilage samples were obtained from normal donors and cut into small pieces, followed by subjecting to digestion with 0.1% trypsin (Invitrogen, Carlsbad, CA, USA) for 30 min and then digested with 0.15% collagenase II (Millipore, Billerica, MA, USA) for 16 h at 37°C. The suspension was filtered with a 100 μm nylon cell strainer (BD Falco) and then cultured in Dulbecco's modified Eagle's medium (DMEM) (HyClone, Logan, UT, USA) at 37°C. After centrifuge, chondrocytes were obtained and cultured in DMEM containing 10% fetal bovine serum (HyClone) and antibiotics (100 U/ml penicillin and 100 μg/ml streptomycin) (Invitrogen) at 37°C with 5% CO_2. The culture media were changed every 2 days.

2.3 *Transient transfection*

H19 overexpression vector, negative control (NC), siRNA against H19 (si-H19), siRNA negative control (si-NC), miR-106a-5p mimic (miR-106a-5p), miRNA negative control (miR-NC), miR-106a-5p inhibitor (anti-miR-106a-5p) and inhibitor negative control (anti-NC) were purchased from Ribobio Co. (Guangzhou, China). All vectors and oligos were transfected into chondrocytes using FuGENE HD (Promega, Madison, WI, USA) according to the manufacturer's instructions. Cells were subsequently cultured about 48 h for further study.

2.4 *IL-1β treatment*

Chondrocytes were maintained at 2.5 or 5×10^5 cells per well in 1 or 2 ml medium in 6 or 12-well plates and stimulated with recombinant human IL-1β (10 ng/ml; R&D Systems, Minneapolis, MN, USA) for the indicated time.

2.5 *Dual-luciferase reporter assay*

Wild-type or mutated H19 (H19-WT, H19-MUT) containing binding sites of miR-106a-5p predicted by starBase were cloned into the pGL3-basic vectors (Promega, Madison, WI, USA), respectively. Chondrocytes were seeded into 24-well plates (Corning), co-transfected with H19-WT or H19-MUT, and miR-NC, miR-106a-5p, anti-miR-106a-5p or anti-NC for 48 h. Cells were collected and analyzed with the Dual-luciferase reporter assay system according to the manufacturer's instructions (Promega).

2.6 *RNA isolation and quantitative real-time polymerase chain reaction (qRT-PCR)*

Total RNA was extracted from OA tissues and cultured chondrocytes using TRIzol (Invitrogen) and RNA concentration was detected by NanoDropND-1000 spectrophotometer. The TaqMan miRNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, USA) and qScript cDNA Synthesis Kit (QuantaBio, Beverly, MA, USA) were applied to reverse transcription. H19 and miR-106a-5p expression levels were determined using SYBR® Green (Promega, Madison, WI, USA) according to the manufacturer's protocol. U6 small nuclear RNA was used as reference gene for miR-106a-5p. 18s rRNA was used as reference gene for H19. Fluorescence was detected in iQTM5 Multicolor Real-Time PCR Detection System (Bio-Rad, Hercules, CA, USA). The relative expression levels of H19 and miR-106a-5p were calculated by the $2^{-\Delta\Delta Ct}$ method. Primer sequences are:

H19 forward 5′-TGCTGCACTTTACAACCACTG-3′
Reverse 5′-ATGGTGTCTTTGATGTTGGGC-3′
MiR-106a-5p forward 5′-GATGCTCAAAAAGTGCTTACAGTGCA-3′
Reverse 5′-TATGGTTGTTCTGCTCTCTGTCTC-3′
U6 forward 5′-TGACACGCAAATTCGTGAAGCGTTC-3′

Reverse 5′-CCAGTCTCAGGGTCCGAGGTATTC-3′
18s forward 5′-GTAACCCGTTGAACCCCATT-3′
Reverse 5′-CCATCCAATCGGTAGTAGCG-3′

2.7 *Cell viability assay*

Cell viability was assayed by using (4-5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) assay. Cultured chondrocytes with different treatments were incubated in 96-well plate (Corning) at cell density of 1×10^5 cells per well in 150 μl medium for 24 h prior to insult of 5 mg/ml MTT (Sigma-Aldrich, Louis, MO, USA) for another 4 h, followed by the addition of 150 μl of DMSO to dissolve the generated formazan crystals. The absorbance at a wavelength of 490 nm was detected using a microplate reader.

2.8 *RNA immunoprecipitation*

RNA immunoprecipitation (RIP) was applied to further validate the direct binding between H19 and miR-106a-5p using the EZMagna RIP kit (Millipore) according the manufacturer's protocol. The chondrocytes cells were transfected with miR-106a-5p for 48 h and then incubated with anti-Ago2 antibody and IgG (Millipore). Samples were incubated with Proteinase K with shaking to digest the protein. qRT-PCR was used to detect the expression of H19.

2.9 *Western blotting*

Total protein from cultured chondrocytes was extracted with RIPA Reagent (Beyotime Institute of Biotechnology, Nanjing, China). Equal amount of protein was loaded into 8-10% sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), and run for 120 min at 100 V. Then proteins were transferred onto a polyvinylidene fluoride (PVDF) membrane (Millipore), and blocked with 5% nonfat milk for 1 h at the room temperature. Then, membranes were incubated with primary antibody against PCNA (1:1000, CST, #13110), CyclinD1 (1:1000, CST, #2922), Caspase 3 (1:1000, CST, #9662), Cleaved Caspase 3 (1:1000, CST, #9664) and β-actin (1:1000; CST, #3700) overnight at 4°C. After being incubated with a horseradish peroxidase (HRP)-conjugated secondary antibody (Santa Cruz) at room temperature for 1 h, the membranes were visualized by the enhanced chemiluminescence (ECL) reagent (Millipore) on chemiluminescence instrument. The quantification analysis was conducted by Image J.

2.10 *Statistical analysis*

The data were presented as mean ± SD (standard deviation) from three biological replicated experiments. The analysis of results was exhibited and plotted using GraphPad Prism 7.0 (GraphPad Software, San Diego, CA, USA). All group comparisons were carried out using the Student t-test. The *P* values less than 0.05 was regarded as statistically significant.

3. Results

3.1 *H19 expression is increased in OA*

Firstly, we obtained 37 cartilage tissues from OA patients and 15 tissues from normal volunteers and detected H19 expression. qRT-PCR results showed that H19 in OA tissues increased 4-fold compared with that in normal tissues (figure 1A). To further confirm the expression of H19 *in vitro*, we used IL-1β to treat chondrocytes at the concentration of 10 ng/ml to mimic OA. It was obvious that H19 level was upregulated in a time-dependent manner (figure 1B). The results suggested that H19 expression was enhanced in OA which means that H19 may be involved in OA progression.

3.2 *H19 inhibits cell proliferation and induces apoptosis in chondrocytes treated by IL-1β*

To explore the function of H19 in OA, we overexpressed H19 in chondrocytes and then cells were treated with 10 ng/

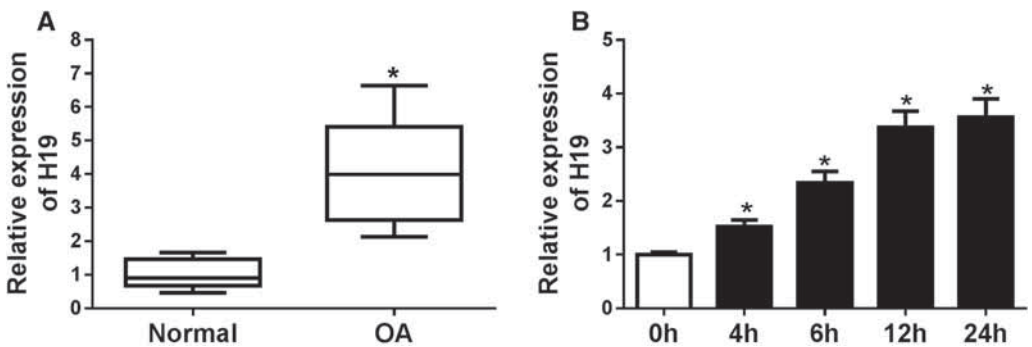

Figure 1. The expression of H19 in OA. (**A**) The expression of H19 in normal (n = 15) and OA tissues (n = 37). (**B**) The expression of H19 in chondrocytes after IL-1β treatment (10 ng/ml) on 0, 4, 6, 12, 24 h. *P<0.05.

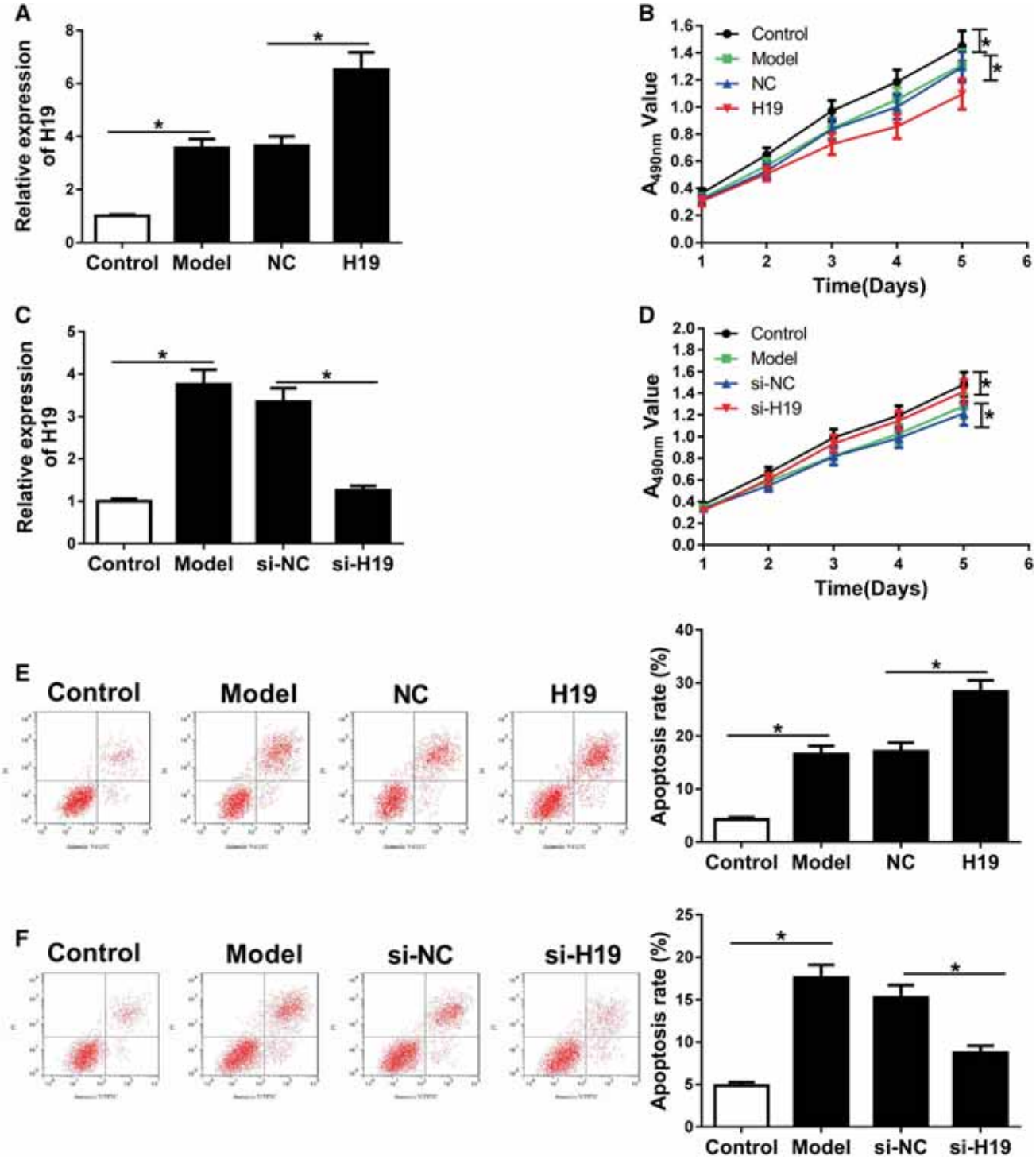

Figure 2. H19 affected cell proliferation and apoptosis in OA. (**A**) Expression of H19 in chondrocytes, chondrocytes + IL-1β, chondrocytes + NC + IL-1β, chondrocytes + H19 + IL-1β. (**B**) The proliferation curve of chondrocytes, chondrocytes + IL-1β, chondrocytes + NC + IL-1β, chondrocytes + H19 + IL-1β. (**C**) Expression of H19 in chondrocytes, chondrocytes + IL-1β, chondrocytes + si-NC + IL-1β, chondrocytes + si-H19 + IL-1β. (**D**) The proliferation curve of chondrocytes, chondrocytes + IL-1β, chondrocytes + si-NC + IL-1β, chondrocytes + si-H19 + IL-1β. (**E**) Apoptosis in chondrocytes, chondrocytes + IL-1β, chondrocytes + NC + IL-1β, chondrocytes + H19 + IL-1β. Annexin V positive cells were considered as apoptotic cells. (**F**) Apoptosis in chondrocytes, chondrocytes + IL-1β, chondrocytes + si-NC + IL-1β, chondrocytes + si-H19 + IL-1β. Control, no treatment; Model, chondrocyte treated with IL-1β; NC, chondrocyte treated with empty vector and IL-1β; H19, chondrocyte treated with H19 vector and IL-1β; si-NC, chondrocyte treated control siRNA and IL-1β; si-H19, chondrocyte treated with siRNA-H19 and IL-1β. * $P<0.05$.

ml IL-1β. As shown in figure 2A, the H19 abundance was upregulated after IL-1β treatment, and H19 transfection indeed increased the level of H19 about 1.5-fold in the OA model. Moreover, MTT assay revealed that IL-1β treatment significantly inhibited the chondrocyte proliferation on day 5, which was exacerbated by overexpression of H19 (figure 2B). Then we knocked down the expression of H19 in chondrocytes (figure 2C), and found that H19 knockdown significantly increased the proliferation inhibited by IL-1β (figure 2D).

Apoptosis is one cause of impaired proliferation. Thus, we used flow cytometry to detect the apoptotic status in the different treatment groups. IL-1β treatment induced apoptosis in chondrocytes (figure 2E and 2F). Meanwhile, overexpression of H19 in chondrocytes could further aggravate apoptosis compared with NC group after IL-1β treatment (figure 2E), while H19 knockdown abated the apoptosis (figure 2F).

Moreover, the makers of proliferation and apoptosis (PCNA, CyclinD1 and Caspase 3) were checked. As shown in figure 3A, after treatment of IL-1β, the protein levels of PCNA and CyclinD1 were reduced and Cleaved Caspase 3 level was enhanced, but total Caspase 3 abundance was not changed. However, silencing H19 caused an opposite effect on these protein expression (figure 3B). These data suggested that H19 could repress proliferation and induce apoptosis in IL-1β-treated chondrocytes.

3.3 *MiR-106a-5p is a target of H19*

Recent studies suggested that lncRNAs could act as a competitive endogenous RNA (ceRNA) or molecular sponges for specific miRNAs and regulate their biological functions. starBase online software was used to predict the

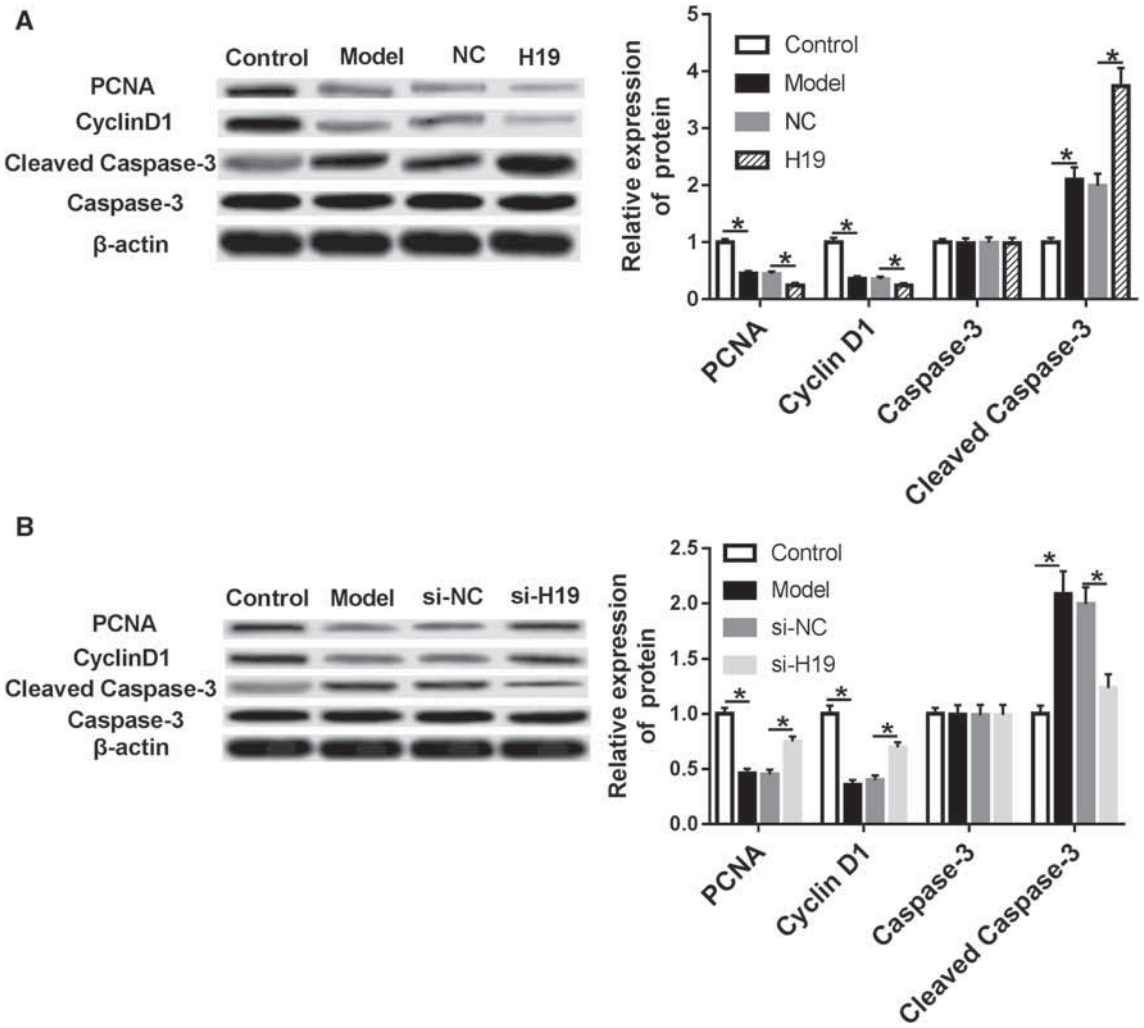

Figure 3. H19 inhibited PCNA, cyclinD1 and activated Caspase 3 in OA. (**A**) The expression of PCNA, CyclinD1, Caspase3, Cleaved Caspase 3 in chondrocytes after H19 overexpression and IL-1β treatment. (**B**) The expression of PCNA, CyclinD1, Caspase3, Cleaved Caspase 3 in chondrocytes after H19 knockdown and IL-1β treatment. Control, no treatment; Model, chondrocyte treated with IL-1β; NC, chondrocyte treated with empty vector and IL-1β; H19, chondrocyte treated with H19 vector and IL-1β; si-NC, chondrocyte treated control siRNA and IL-1β; si-H19, chondrocyte treated with siRNA-H19 and IL-1β. *$P<0.05$.

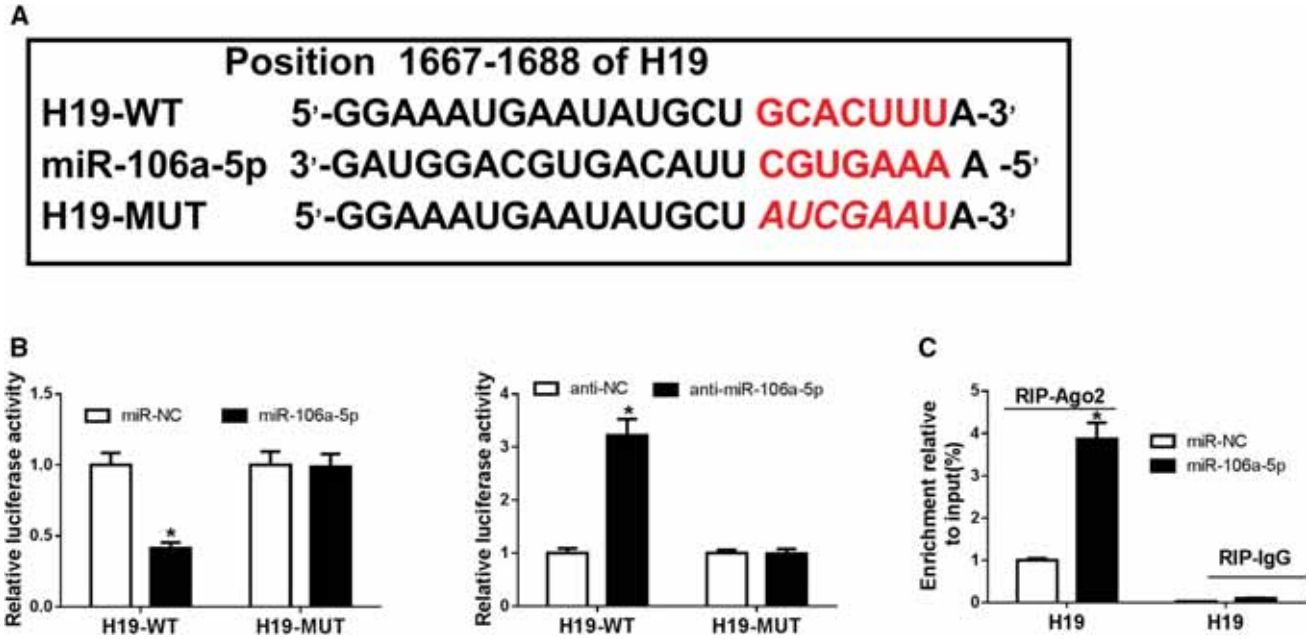

Figure 4. MiR-106a-5p was a direct target of H19. (**A**) StarBase was used to predict the relationship between H19 and miR-106-5p. (**B**) Luciferase assay of miR-106a-5p or anti-miR-106a-5p and H19-WT or H19-MUT in chondrocytes. (**C**) RNA immunoprecipitation was used to confirm the relationship between H19 and miR-106-5p. **P*<0.05.

target miRNA of H19 and the result suggested that miR-106a-5p was a potential target which contains complementary sequence with H19 at position 1681-1687 (figure 4A). To confirm the relationship between miR-106a-5p and H19, luciferase assay was employed. As displayed in figure 4B, the luciferase activity was significantly decreased by miR-106a-5p overexpression but increased by miR-106a-5p knockdown in H19-WT group, but unchanged in H19-MUT group. In addition, an anti-Ago2 RIP assay was also introduced to identify the endogenous interaction between H19 and miR-106a-5p in chondrocytes. The level of H19 enriched by Ago2 RIP was significantly enhanced via miR-106a-5p overexpression (figure 4C). The results demonstrated that miR-106a-5p was a target of H19.

3.4 *miR-106a-5p promotes cell proliferation and decreases cell apoptosis in chondrocytes treated by IL-1β*

Then, we checked the expression of miR-106a-5p in OA patients and found that it was downregulated in OA tissues compared with that in normal group (figure 5A). Similarly, miR-106-5p expression was gradually decreased in chondrocytes stimulated by IL-1β (figure 5B). Furthermore, the spearman analysis showed that miR-106a-5p level in OA tissues was negatively correlated with H19 ($r = -0.896$, $P<0.05$) (figure 5C). Moreover, H19 overexpression decreased the expression of miR-106a-5p in chondrocytes treated by IL-1β (figure 5D) and H19 silencing increased miR-106-5p expression (figure 5E). Additionally, miR-106a-5p overexpression led to obvious proliferation promotion and apoptosis suppression in chondrocytes treated by IL-1β (figure 5F, G). These results suggested that miR-106a-5p overexpression induced proliferation promotion and apoptosis suppression in IL-1β-treated chondrocytes.

3.5 *miR-106a-5p reverses the role of H19 in chondrocytes treated by IL-1β*

To explore whether H19-mediated chondrocytes processes was regulated by miR-106a-5p, we co-transfected miR-106a-5p and H19 in chondrocytes. As shown in figure 6A, H19 transfection inhibited miR-106a-5p expression while H19 and miR-106a-5p co-transfection partially increased miR-106a-5p expression. Moreover, the proliferation of chondrocytes inhibited by H19 overexpression was elevated by miR-106a-5p addition (figure 6B). Meanwhile, cell apoptosis induced by H19 was obviously reduced by addition of miR-106a-5p (figure 6C). In addition, miR-106a-5p overexpression significantly attenuated the effect of H19 on the protein levels of PCNA, CyclinD1 and Cleaved Caspase 3 (figure 6D). These results suggested that miR-106a-5p could partially reversed the effect of H19 in chondrocytes.

4. Discussion

Osteoarthritis (OA) is a common degenerative disease in the elderly, which is characterized by degradation of cartilage. LncRNAs were suggested to be involved in OA

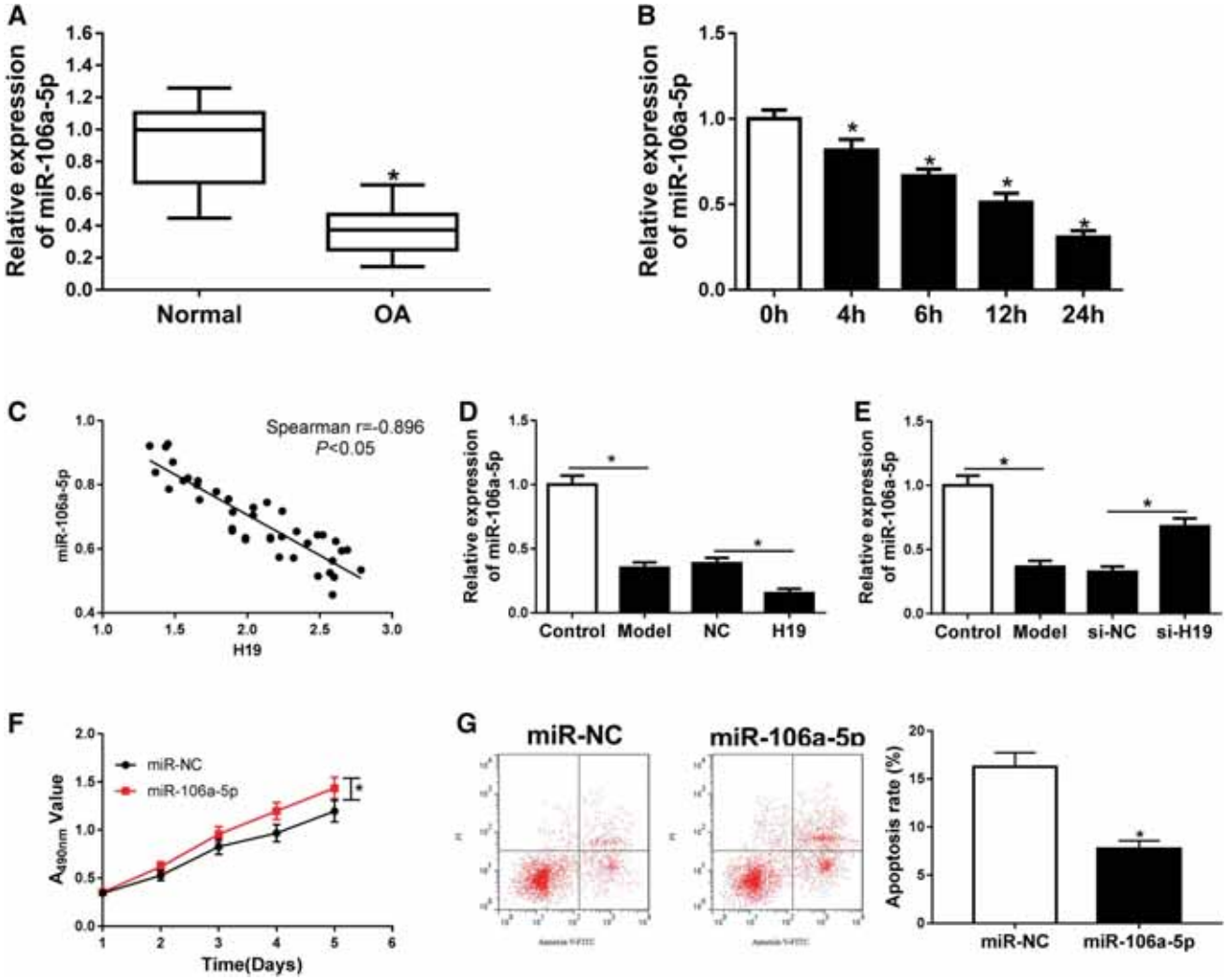

Figure 5. MiR-106-5p regulated cell proliferation and apoptosis in OA. (**A**) The expression of miR-106-5p in normal (n = 15) and OA tissues (n = 37). (**B**) The expression of miR-106-5p in chondrocytes after IL-1β treatment (10 ng/ml) on 0, 4, 6, 12, 24 h. (**C**) The Spearman rank correlation of H19 and miR-106-5p in human normal and OA samples. (**D**) miR-106-5p expression after H19 overexpression. (**E**) miR-106-5p expression after H19 knockdown. (**F** and **G**) Cell proliferation and apoptosis of chondrocytes in miR-NC or miR-106a-5p group. Control, chondrocyte treated with IL-1β. NC, chondrocyte treated with empty vector and IL-1β; H19, chondrocyte treated with H19 vector and IL-1β; si-NC, chondrocyte treated control siRNA and IL-1β; si-H19, chondrocyte treated with siRNA-H19 and IL-1β; miR-NC, chondrocyte treated with miR-NC and IL-1β; miR-106a-5p, chondrocyte treated with miR-106a-5p mimic and IL-1β. * $P<0.05$.

development (Pearson and Jones 2016). Long non-coding RNA H19 is transcribed by RNA polymerase II, spliced and polyadenylated, but not available to be translated (Brannan *et al.* 1990). It was reported that H19 was involved in tumor progression, such as gastric cancer (Li *et al.* 2014), colorectal cancer (Liang *et al.* 2015), prostate cancer (Zhu *et al.* 2014), breast cancer (Sun *et al.* 2015), laryngeal squamous cell cancer (Wu *et al.* 2016), bladder cancer (Hua *et al.* 2016) and other types of cancer. However, it was seldom focused on OA. In our study, we found that lncRNA H19 was upregulated in OA tissues and in IL-1β-treated chondrocytes, which is also in agreement with previous studies (Steck *et al.* 2012; Hu *et al.* 2019).

Chondrocytes are the highly specialized resident cells in cartilage and are involved in the formation, maintenance of extracellular matrix proteins (Muir 1995). Thus, the regulation of chondrocyte viability is significantly important. However, a previous study demonstrated that chondrocytes undergo apoptosis during aging in C57BL mice and Wistar rat using a *in situ* technique to detect the fragmented DNA (Adams and Jr, 1998). *In vitro* experiments, apoptosis could be induced by different stimuli in chondrocytes including starvation, Fas ligand, etc. (Aigner *et al.* 2010; Heraud et al. 2000). In present work, the apoptosis was increased and Caspase 3 was activated in chondrocytes after 10 ng/ml IL-1β treatment. Knockdown of H19 could attenuate the apoptosis and activation of Caspase 3. Besides, H19 overexpression also inhibited PCNA and CyclinD1 expression and led to proliferation block.

LncRNAs usually act as miRNA sponges or ceRNA in human cancers and diseases. In the present study, we

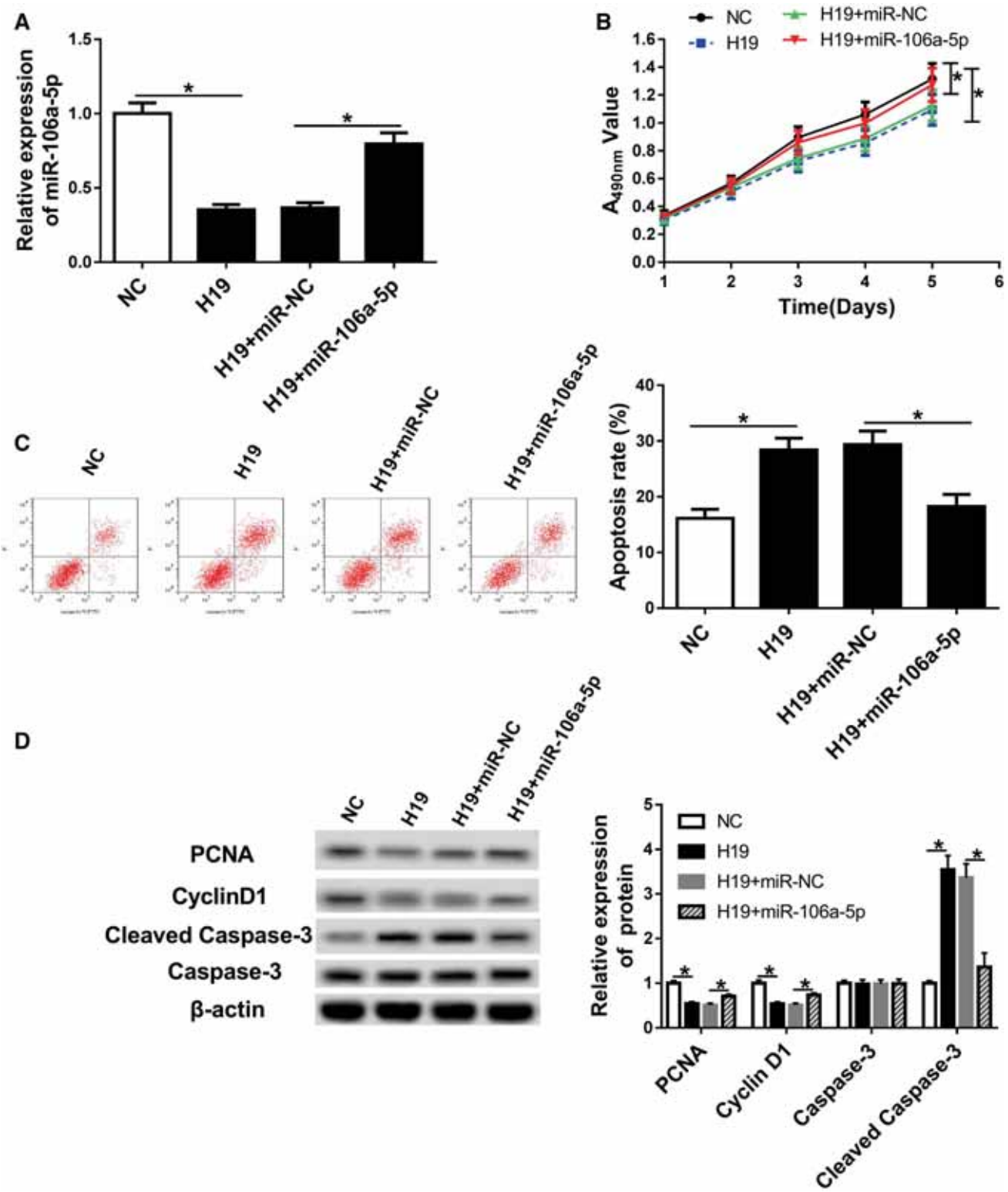

Figure 6. MiR-106a-5p mitigated the promoting effect of H19 in OA. (**A**) miR-106a-5p expression in NC, H19, H19 + miR-NC and H19 + miR-106a-5p groups. (**B**) The proliferation curve of NC, H19, H19 + miR-NC and H19 + miR-106a-5p groups. (**C**) Apoptosis in NC, H19, H19 + miR-NC and H19 + miR-106a-5p groups. (**D**) PCNA, CyclinD1, Cleaved Caspase 3 and Caspase 3 expression in NC, H19, H19 + miR-NC and H19 + miR-106a-5p groups. NC, chondrocyte treated with empty vector and IL-1β; H19, chondrocyte treated with H19 vector and IL-1β; H19+miR-NC, chondrocyte transfected with H19 and miRNA control and treated with IL-1β; H19+miR-106-5p, chondrocyte transfected with H19 and miR-106-5p and treated with IL-1β. *P<0.05.

confirmed H19 as a sponge of miR-106a-5p in chondrocytes by luciferase assay and RIP. Here we found that miR-106a-5p expression was decreased in OA and its overexpression protected against chondrocytes damage in OA, which is consistent with former work (Ji *et al.* 2018). Furthermore, introduction of miR-106a-5p abated the promoting role of H19 in chondrocytes injury induced by IL-1β, indicating that miR-106a-5p was responsible for the regulatory mechanism of H19 in OA. Moreover, target of miR-106a-5p might be helpful for better understanding the regulatory mechanism. TargetScan database predicted that TCF4 has the similar miR-106a-5p binding sites with H19. Meanwhile, previous studies suggested that TCF4 could promote IL-1β-induced chondrocytes injury (Ma *et al.* 2013; Xue *et al.* 2019). Hence, we hypothesized that TCF4 might be responsible for H19/miR-106a-5p axis in osteoarthritis, which should be confirmed in future.

In conclusion, we first found that H19 was upregulated in OA tissues. Then we used 10 ng/ml IL-1β to treat chondrocytes so as to mimic OA *in vitro* and H19 was increased in treated chondrocytes in a time-dependent manner. Next, we overexpressed H19 in chondrocytes and the proliferation was inhibited while cell apoptosis was promoted. In addition, the proliferation marker PCNA and cell cycle protein CyclinD1 expression was inhibited and Caspase 3 was activated by H19 overexpression. In contrast, knockdown of H19 rescued the proliferation, inhibited cell apoptosis, upregulated PCNA and CyclinD1 expression and inhibited Caspase 3 activity to some extent. Subsequently, we confirmed that miR-106a-5p was a target of H19 and it was downregulated in OA tissues and IL-1β-treated chondrocytes. Finally, overexpression of miR-106a-5p could partially reversed the effect of H19 *in vitro*. In brief, H19/miR-106a-5p axis was involved in the progression of OA which provides a novel and promising therapeutic target for treatment of OA.

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