

KLF11 protects chondrocytes *via* inhibiting p38 MAPK signaling pathway

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Abstract. – OBJECTIVE: The purpose of this study was to explore the effects of Kruppel like factors 11 (KLF11) on oxidative stress, apoptosis, and endoplasmic reticulum stress (ERS) in osteoarthritis (OA) and its mechanism.

PATIENTS AND METHODS: Human articular cartilage tissue was used to study the correlation between KLF11 and OA. Furthermore, human chondrocytes were used to explore the effects of KLF11 on oxidative stress, apoptosis, and ERS in chondrocytes by overexpressing KLF11 and using the OA inducer IL-1 β . The p38MAPK signaling pathway agonist P79350 was used to study the effect of KLF11 on the p38 MAPK signaling pathway.

RESULTS: Articular cartilage tissue in OA patients and IL-1 β -induced chondrocytes expressed higher KLF11. Overexpression of KLF11 significantly reduced oxidative stress levels, apoptosis levels, and activity of ERS-related pathways in chondrocytes. Moreover, P79350 attenuated the protective effect of KLF11 on chondrocytes by activating the p38MAPK signaling pathway.

CONCLUSIONS: KLF11 protects against OA by inhibiting oxidative stress, apoptosis, and ERS in chondrocytes by inhibiting p38MAPK signaling pathway.

Key Words:

Kruppel like factors 11, Osteoarthritis, Chondrocytes, Oxidative stress, Apoptosis, Endoplasmic reticulum stress.

Introduction

Osteoarthritis (OA) is a clinically common chronic degenerative bone and joint disease, also known as degenerative arthritis, senile arthritis, and hypertrophic arthritis¹. Its clinical manifestations are slow-developing joint pain, tenderness,

swelling, deformity, and joint stiffness¹. The disease is more common in middle-aged and elderly patients, and the prevalence rate of 60 years old and above can reach 50%, and 80% of those are over 75 years old. Therefore, OA seriously affects the quality of life of patients and has a high disability rate². At present, the cause of the disease is still unclear. Korochina et al³ believe that it may be related to age, obesity, inflammation, trauma, and genetic factors. However, its pathogenesis has not yet been elucidated.

Endoplasmic reticulum stress (ERS), an organelle with important biological functions in cells⁴, plays an important role in the pathogenesis of OA⁵. There is obvious ERS in the process of degenerative changes of articular cartilage. It has been found in animal studies that the ERS in the articular cartilage of OA model rats is over-activated, and the expression of various ERS genes is significantly increased⁶. In addition, the p38MAPK signaling pathway is involved in the pathological process of OA⁷. The p38MAPK signaling pathway can be activated by various extracellular stressors such as inflammatory factors and growth factors during OA pathology, then transmits signals to transcription factors, and regulates the expression of target genes⁸. In addition, this pathway can regulate chondrocyte proliferation and differentiation, regulate the synthesis of matrix metalloproteinase (MMP), and mediate the secretion of inflammatory factors and the production of pain media⁹. Therefore, p38MAPK signaling pathway plays a pivotal role in OA cartilage destruction.

Kruppel like factors (KLFs) are a class of zinc finger proteins that are widely distributed in mammals¹⁰. They participate in the transcriptional reg-

ulation of a variety of gene expression, involving a variety of physiological and pathological processes such as growth, differentiation, proliferation, apoptosis, metabolism, and inflammation¹⁰. The KLF11 gene, a member of the KLF family, can reduce the level of oxidative stress in cardiomyocytes¹¹. In addition, Fernandez-Zapico et al¹² constructed a pancreatic exocrine overexpressing KLF11 mouse model using the elastase 1 promoter and found that superoxide dismutase 2 (SOD2) and catalase 1 in the pancreas of the model mice decreased significantly. Richards et al¹³ indicate that KLF11 has anti-oxidation and anti-apoptosis effects. However, the role of KLF11 in OA has not been explored.

In this study, human chondrocytes overexpressing KLF11 were used to explore the effects of KLF11 on oxidative stress, apoptosis, and ERS in chondrocytes, and it was found that the protective effect of KLF11 on chondrocytes is related to the p38MAPK signaling pathway. The results of this study should help us better understand the role of KLF11 in the pathological process of OA.

Patients and Methods

Patient Tissue Samples

The knee cartilage tissues were extracted from OA patients who underwent knee arthroplasty and normal humans receiving amputation surgery due to trauma or tumor to detect the expression level of related indicators. All patients with OA were diagnosed by imaging, laboratory tests, signs, and symptoms. This investigation was approved by the Ethics Committee of Dalian Friendship Hospital. All patients provided written informed consent. This study was conducted in accordance with the Declaration of Helsinki.

Cells Culture and Drug Treatment

Human primary chondrocytes were purchased from Shanghai Yaji Biotechnology Co., Ltd. (Shanghai, China) and cultured in Dulbecco's Modified Eagle's Medium (DMEM) F/12 (Gibco, Rockville, MD, USA) medium containing 10% fetal bovine serum (FBS; Gibco, Rockville, MD, USA) and 1% penicillin plus streptomycin (Gibco, Rockville, MD, USA) in an incubator at 37°C and 5% CO₂. Recombinant human IL-1 β (Lianke, China) was used to stimulate chondrocyte degeneration to produce an OA model at the cellular level. P79350 (Invitrogen, Carlsbad, CA, USA), a

p38MAPK signaling pathway agonist, was used to activate p38MAPK signaling pathway.

Western Blot Analysis

Total protein was extracted from knee cartilage or chondrocytes to detect the expression of related indicators. The protein was electrophoresed by sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to a polyvinylidene difluoride (PVDF) membrane (Millipore, Billerica, MA, USA). After blocking the membrane with 5% skim milk, primary antibodies (collagen II, 1:3000, Rabbit, Abcam, Cambridge, MA, USA, KLF11, 1:3000, Rabbit, Abcam, Cambridge, MA, USA, p38, 1:1000, Rabbit, Abcam, Cambridge, MA, USA, SOD1, 1:3000, Rabbit, Abcam, Cambridge, MA, USA, SOD2, 1:3000, Rabbit, Abcam, Cambridge, MA, USA, Bcl-2, 1:4000, Rabbit, Abcam, Cambridge, MA, USA, Bax, 1:1000, Rabbit, Abcam, Cambridge, MA, USA, CHOP, 1:5000, Rabbit, Abcam, Cambridge, MA, USA, ATF-6, 1:3000, Rabbit, Abcam, Cambridge, MA, USA, GRP-78, 1:2000, Rabbit, Abcam, Cambridge, MA, USA, MMP13, 1:3000, Rabbit, Abcam, Cambridge, MA, USA, β -actin, 1:3000, Rabbit, Abcam, Cambridge, MA, USA) were used to incubate proteins at 4°C overnight. The next day, after washing the membrane with Tris-Buffered Saline and Tween-20 (TBST), a secondary antibody (Goat anti-rabbit, 1:3000, Abcam, Cambridge, MA, USA) was used for 2 hours of incubation at room temperature. Finally, chemiluminescence was applied to analyze the gray value of the bands.

Reverse Transcription-Polymerase Chain Reaction (RT-PCR)

TRIzol (Invitrogen, Carlsbad, CA, USA) was used to extract total mRNA from knee cartilage or chondrocytes, and a spectrophotometer (Molecular Devices, San Jose, CA, USA) was used to detect the concentration of the extracted RNA and configure equal amount of RNA according to the concentration. The reverse transcription system was 4 μ l 5 $\times$ First-Strand Buffer + 2 μ l 0.1M DTT + 1 μ l 40U/ μ l Ribonuclease inhibitor + 1 μ l 200U M-MLV reverse transcriptase (Beyotime Biotechnology, Shanghai, China). The reverse transcription product cDNA was stored in a refrigerator at 4°C. Then, different primers were applied to amplify cDNA to detect the expression of different indicators. The PCR reaction system

was 1 μ l cDNA Template + 5 μ l 10 $\times$ reaction buffer + 3 μ l 25 mM MgCl₂ + 3 μ l 2.5 μ M dNTP + 1 μ l 10 μ M Primer forward + 1 μ l 10 μ M reverse + 1 μ l 5U/ μ l Tap DNA polymerase (Vazyme, Nanjing, China). The number of cycles was set to 28 times. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used for normalization. The primers used for RT-PCR are shown in Table I. Relative mRNA expression levels were calculated by the $2^{-\Delta\Delta CT}$ methods.

Immunocytofluorescence Staining

The cells in the logarithmic growth phase were transferred to 12-well plates and treated. After removing the medium, cells were fixed with 4% paraformaldehyde for 30 minutes. Then, the cells were treated with 0.1% Triton for 20 min, and 10% of goat serum was used to block non-specific antigens. Next, the cells were covered with primary antibodies (KLF11, 1:500, rabbit, Abcam, Cambridge, MA, USA), SOD1, 1:500, rabbit, Abcam, Cambridge, MA, USA), MMP13, 1:500,

rabbit, Abcam, Cambridge, MA, USA)) dilution at 4°C overnight. The next day, after washing the cells three times with phosphate-buffered saline (PBS), cells were incubated with fluorescent secondary antibody (Goat anti-rabbit-FITC, 1:500, Abcam, Cambridge, MA, USA) for 1 h at room temperature and washed with PBS. Finally, DAPI-Fluoromount-G was used to mount. Fluorescence microscopy was used to observe and analyze the results.

Cell Viability Assay

The cells in the logarithmic growth phase were transferred to 96-well plates, and the cell density was adjusted to 5×10^6 per well. After the cells were treated, 10 μ l of Cell Counting Kit (CCK-8) reagent (Beyotime Biotechnology, Shanghai, China) was added to each well. The cells were then incubated in an incubator for 2 h. Finally, a microplate reader was used to measure the absorbance of each well.

Table I. Primer sequences for RT-PCR.

Name	sense/anti-sense	Sequence (5'-3')
collagen II	sense anti-sense	GGGAATGTCCTCTGCGATGAC GAAGGGGATCTCGGGGTTG
KLF11	sense anti-sense	GGGATGTCACCACCACTGT GGCTCTGAGGAGGAGTTATGC
p38	sense anti-sense	CACATGCCTACTTTTGCTCAG TAGGTCAGGCTTTTCCACTC
SOD1	sense anti-sense	GGTGAACCAAGTTGTGTTGTC CCGTCCTTTCCAGCAGTC
SOD2	sense anti-sense	CAGACCTGCCTTACGACTATGG CTCGGTGGCGTTGAGATTGTT
Prdx1	sense anti-sense	TTAACGGCAACCCTTGACACGAT ACCCGTATACGAGCGTACGAT
Prdx4	sense anti-sense	GCTATCGACGAATATGGCGCAT CTTGGCATCGACGACGATGTC
Bcl-2	sense anti-sense	AGTACCTGAACCGGCATCTG CAGCCAGGAGAAATCAAACAG
Bax	sense anti-sense	CCCCCGAGAGGTCTTC CGGCCCCAGTTGAAGTTG
CHOP	sense anti-sense	CAGCGACAGAGCCAGAATAAC ACCGTCTCCAAGGTGAAAGG
ATF-6	sense anti-sense	TTTACGGACTTGATGCACACGT TTGCAGCACTACGAGTAATCG
GRP-78	sense anti-sense	TACCCAGATTGAAGTCACCT TTCTCGGCGTCATTGACCA
MMP13	sense anti-sense	AGCTATCGATCATGCTACGACG ACGATCGACGTACGTACGTATCC
GAPDH	sense anti-sense	ACAACCTTGGTATCGTGGAAGG GCCATCACGCCACAGTTTC

Intracellular ROS Levels

DCFH-DA (10 μ M Keygen, Nanjing, China) fluorescent probes were used to detect endogenous ROS. Chondrocytes were transferred to 96-well plates at 10^4 cells per well. After treatment, the cells were placed in an incubator for 20 min. Finally, the fluorescence intensity of DCFH-DA was measured by flow cytometry and analyzed the results.

SOD Activity Assay

Chondrocytes were transferred to six-well plates. After treatment of the cells, the cells were lysed with lysate and centrifuged to remove the supernatant. Then, the SOD assay kit (Invitrogen, Carlsbad, CA, USA) was used to measure the SOD level in the cells according to the manufacturer's instructions.

Lentiviral Transfection

Chondrocytes were transfected with Lenti-NC and Lenti-KLF11, using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. The KLF11 gene was overexpressed by Lenti-KLF11.

Statistical Analysis

SPSS 20.0 (IBM, Armonk, NY, USA) was used to perform statistical analysis on the data. For measurement data, the mean $\pm$ standard deviation was used. Comparison between multiple groups was done using One-way ANOVA test followed by post-hoc test (Least Significant Difference). All experiments were repeated 3 times. $p < 0.05$ was considered to be statistically significant.

Results

Expression of KLF11 and p38MAPK Signaling Pathway in Articular Cartilage of Patients with OA

Protein and total RNA were extracted from articular cartilage in arthritic patients and normal people. Western blot results showed that the articular cartilage of patients in OA group expressed lower collagen II and KLF11, while the level of p38 increased (Figure 1A-1D). The results of RT-PCR were similar to those of Western blot (Figure 1E-1G). This indicates that the level of KLF11 in the articular cartilage of patients with OA is lower than that of normal people.

IL-1 β -Stimulated Chondrocytes Express Lower KLF11

Human chondrocytes were cultured and determined that 50 ng/ml of IL-1 β can effectively reduce the proliferation of chondrocytes by cell viability assay (Figure 2A), so that the OA model can be constructed at the cellular level. RT-PCR results showed that the expressions of collagen II and KLF11 gradually were decreased with the increase of IL-1 β concentration (Figure 2B, 2C). With the prolongation of IL-1 β stimulation time, the expressions of collagen II and KLF11 were also gradually decreased (Figure 2D, 2E). The results of immunofluorescence showed that the expression of KLF11 was decreased with stimulation of IL-1 β (Figure 2F).

Overexpression of KLF11 Reduces Oxidative Stress and Apoptosis in Chondrocytes

To study the effect of KLF11 on oxidative stress and apoptosis in chondrocytes, chondrocytes were transfected with Lenti-NC and Lenti-KLF11. Western blot (Figure 3A, B) and RT-PCR (Figure 3C-3F) results showed that IL-1 β could decrease the expressions of SOD1, SOD2, Bcl-2, Prdx1, and Prdx4 and increase the expression of Bax, while the overexpression of KLF11 could attenuate the effect of IL-1 β on oxidative stress and apoptosis of chondrocytes. The results of the SOD activity assay also verified this (Figure 3G). Flow cytometry to detect ROS levels also found that KLF11 inhibited oxidative stress of chondrocytes (Figure 3H). The results of cellular immunofluorescence indicated that KLF11 could effectively increase the expression of SOD1 (Figure 3I).

Overexpression of KLF11 Reduces ERS in Chondrocytes

ERS is involved in the progression of OA. Western blot (Figure 4A, 4B) and RT-PCR (Figure 4C-4E) results showed that the expressions of CHOP, ATF-6, and GRP-78 in the ERS-related signaling pathway in IL-1 β -stimulated chondrocytes were significantly increased, suggesting that ERS-related pathways are activated in chondrocytes stimulated by IL-1 β . Overexpression of KLF11 significantly reduced the expressions of CHOP, ATF-6, and GRP-78, suggesting that KLF11 can inhibit ERS in chondrocytes.

KLF11 Inhibits p38MAPK Signaling Pathway in Chondrocytes

The p38MAPK signaling pathway plays an important role in the progression of OA. Western blot analysis showed that the expressions of p38,

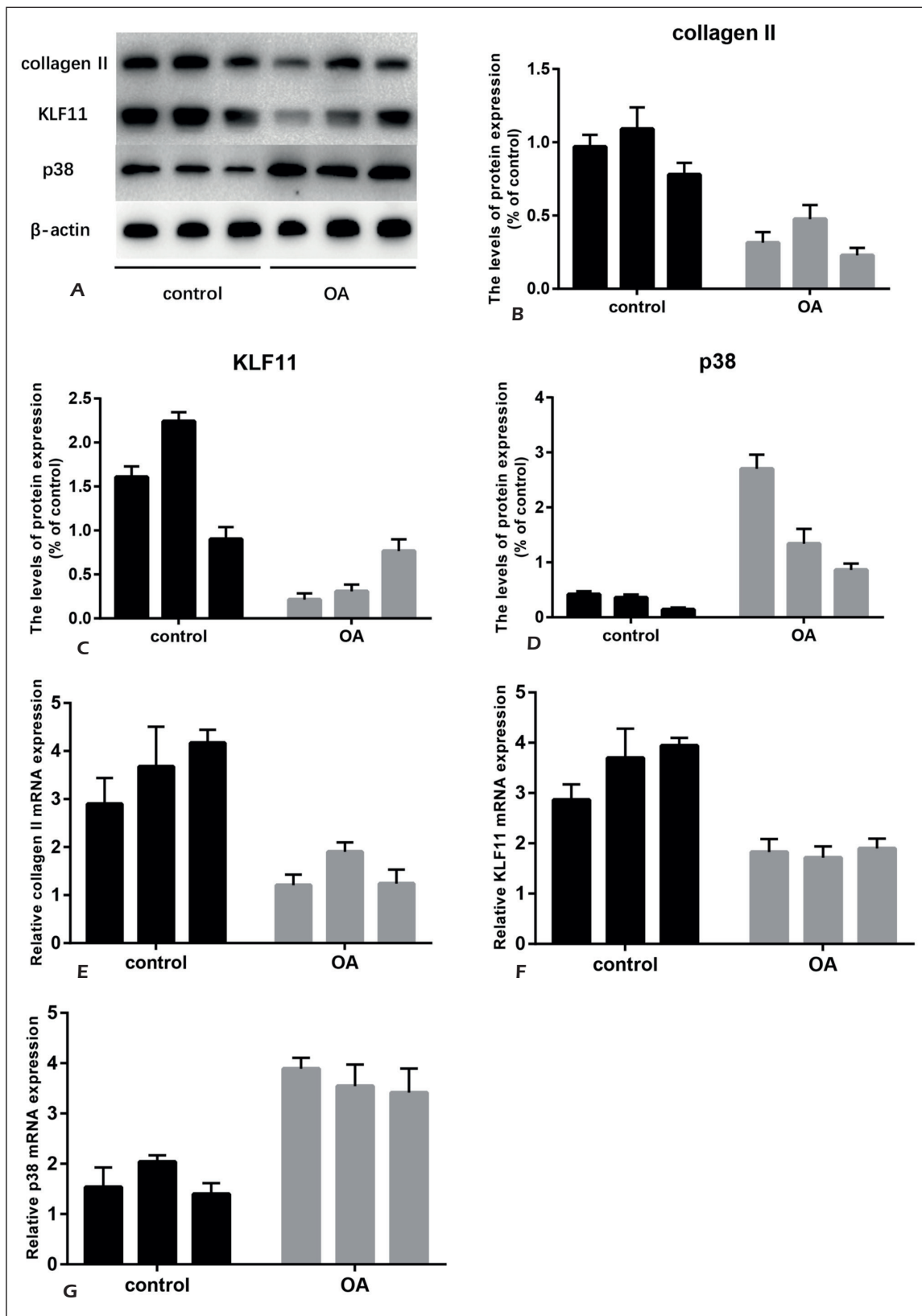


Figure 1. Expression of KLF11 and p38MAPK signaling pathway in articular cartilage of patients with OA. **A-G**, Western blot (**A-D**) and RT-PCR (**E-G**) determine the expressions of collagen II, KLF11, and p38 in control group and OA group.

p-p38, and MMP13 were significantly increased after IL-1 β stimulation, and KLF11 could inhibit their expressions (Figure 5A, 5B). RT-PCR results also confirmed this (Figure 5C, 5D). Cellular immunofluorescence results showed that overexpression of KLF11 significantly reduced the expression of MMP13 (Figure 5E).

Activation of the p38MAPK Signaling Pathway Attenuates the Inhibitory Effects of KLF11 on Oxidative Stress, Apoptosis, and ERS in Chondrocytes

P79350 was used to activate the p38MAPK signaling pathway. Western blot (Figure 6A-6C) and RT-PCR (Figure 6D-6J) showed that

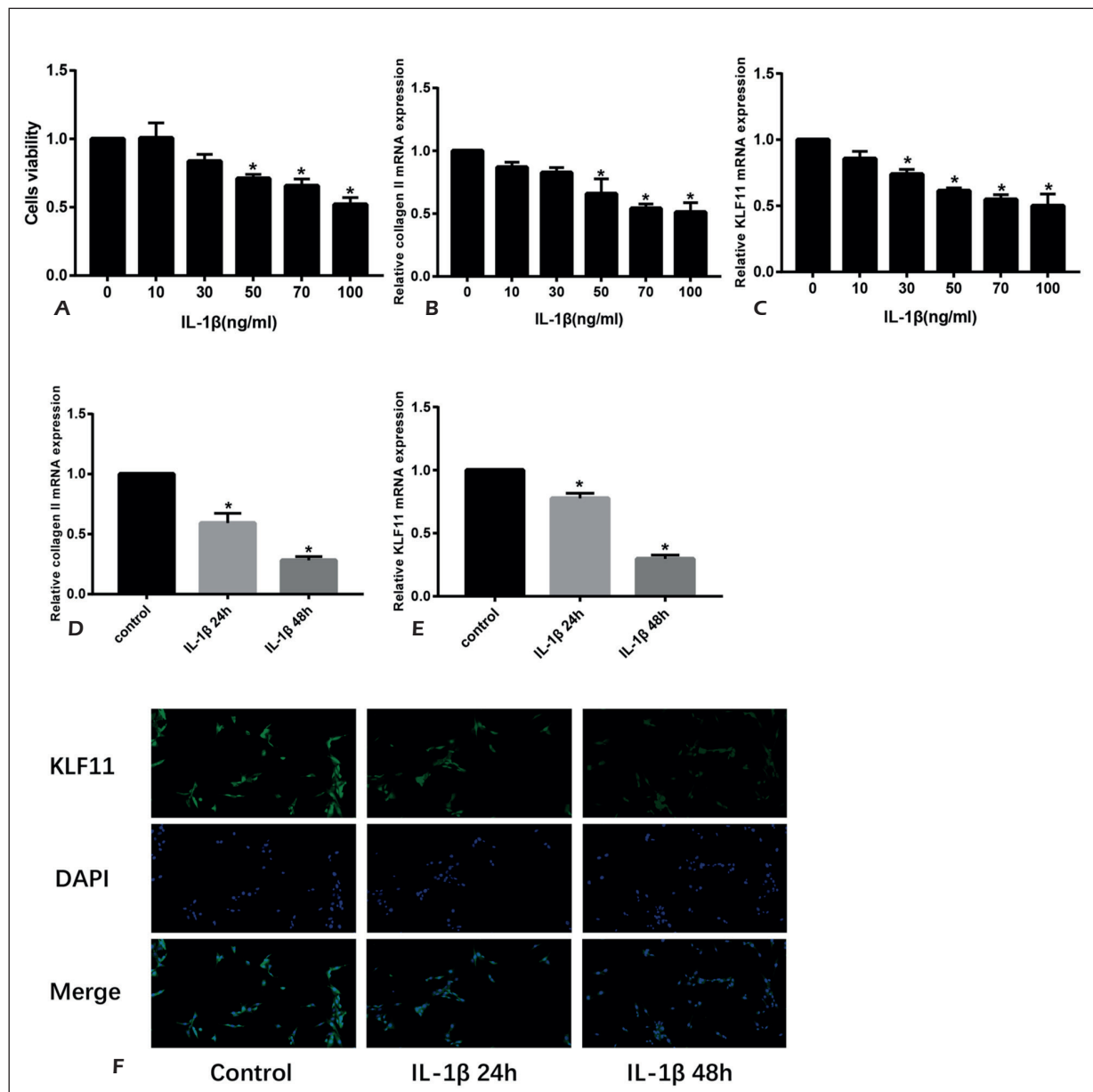


Figure 2. IL-1 β -stimulated chondrocytes express lower KLF11. **A**, Cell viability assay is used to determine the optimum working concentration of IL-1 β . **B, C**, 0, 10, 30, 50, 70, and 100 μ l IL-1 β is used to stimulate chondrocytes and the mRNA expressions of collagen II (**B**) and KLF11 (**C**) determined by RT-PCR. **D-F**, IL-1 β is used to stimulate chondrocytes for one or two day and the expressions of collagen II and KLF11 are determined by RT-PCR (**D, E**) and immunofluorescence (magnification: 100 $\times$) (**F**). (“*” means there is a statistical difference with the control group).

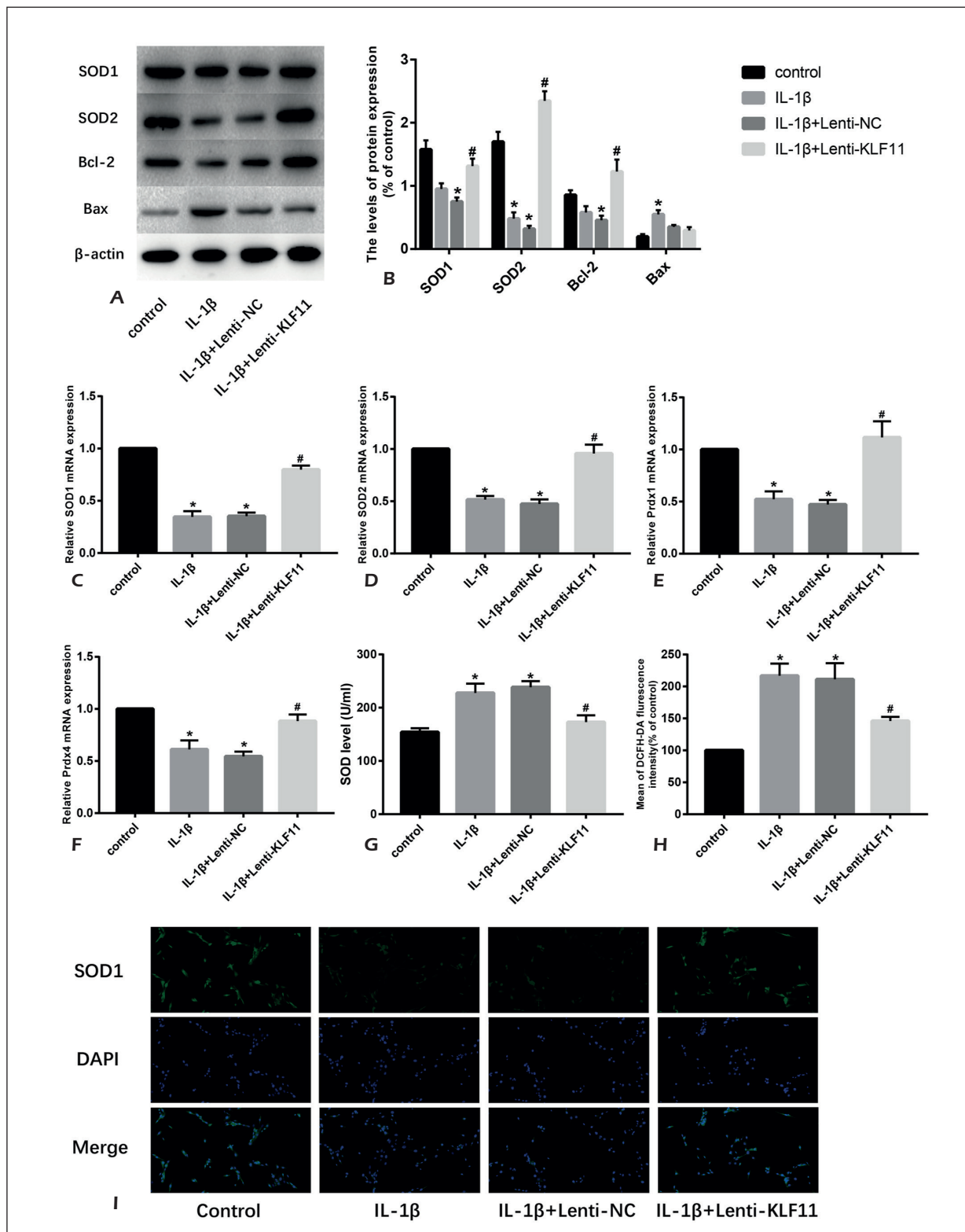


Figure 3. Overexpression of KLF11 reduces oxidative stress and apoptosis in chondrocytes. **A-B**, Expressions of SOD1, SOD2, Bcl-2, and Bax in four groups are determined by Western blot. **C-F**, Expressions of SOD1, SOD2, Prdx1, and Prdx4 in four groups are determined by RT-PCR. **G**, SOD level is determined by SOD activity assay. **H**, ROS level in four groups is detected by flow cytometry. **I**, Immunofluorescence is used to detect the expression of SOD1 (magnification: 100 $\times$). (“*”) means there is a statistical difference with the control group and “#” means there is a statistical difference with the IL-1 β +Lenti-NC group).

P79350 could effectively attenuate the anti-oxidative stress and anti-apoptotic effect of KLF11. Moreover, the inhibitory effect of KLF11 on the ERS-related signaling pathway was also attenuated by P79350.

Discussion

Knee and hip joints are the most common affected joints of OA¹⁴. The damage and destruction of articular cartilage is the most prominent pathological feature of OA, but the specific regulation mechanism is not clear. ERS is a newly discovered link closely related to the onset of OA in recent years. The ERS of cells is regulated by three transmembrane proteins PERK, IRE1, and ATF6. When unfolded proteins accumulate in cells, PERK, IRE1, and GRP78 are dissociated and activated by autophosphorylation, while ATF6 transfers into Golgi body and is activated

by the action of proteolytic enzymes. The activated PERK, IRE1, and ATF6 enhance the transcriptional activity of caspase-12 by up-regulating the downstream molecule CHOP. The highly expressed caspase-12 can mediate the cascade of apoptosis and cause cell damage⁶. Takada et al¹⁵ showed that increased ERS in chondrocytes during OA progression may increase chondrocyte apoptosis and reduce its protective response. This study evaluated the expression of ERS markers pPERK and ubiquitin (Ub), the expression of apoptosis markers CHOP and Pjnk, and expression of the protective markers GRP78 and XBP mRNA splices of ERS in a group of *in vitro* studies. As cartilage degeneration progresses, the expression of pPERK, Ub, CHOP, and caspase-3 suggests that chondrocyte apoptosis is increasing. In addition, XBP1S inhibits ERS-mediated apoptosis and major matrix degradation of OA, while ATF6 and IRE1 α regulate the coordinated expression of the endogenous XBP1S gene in OA cartilage.

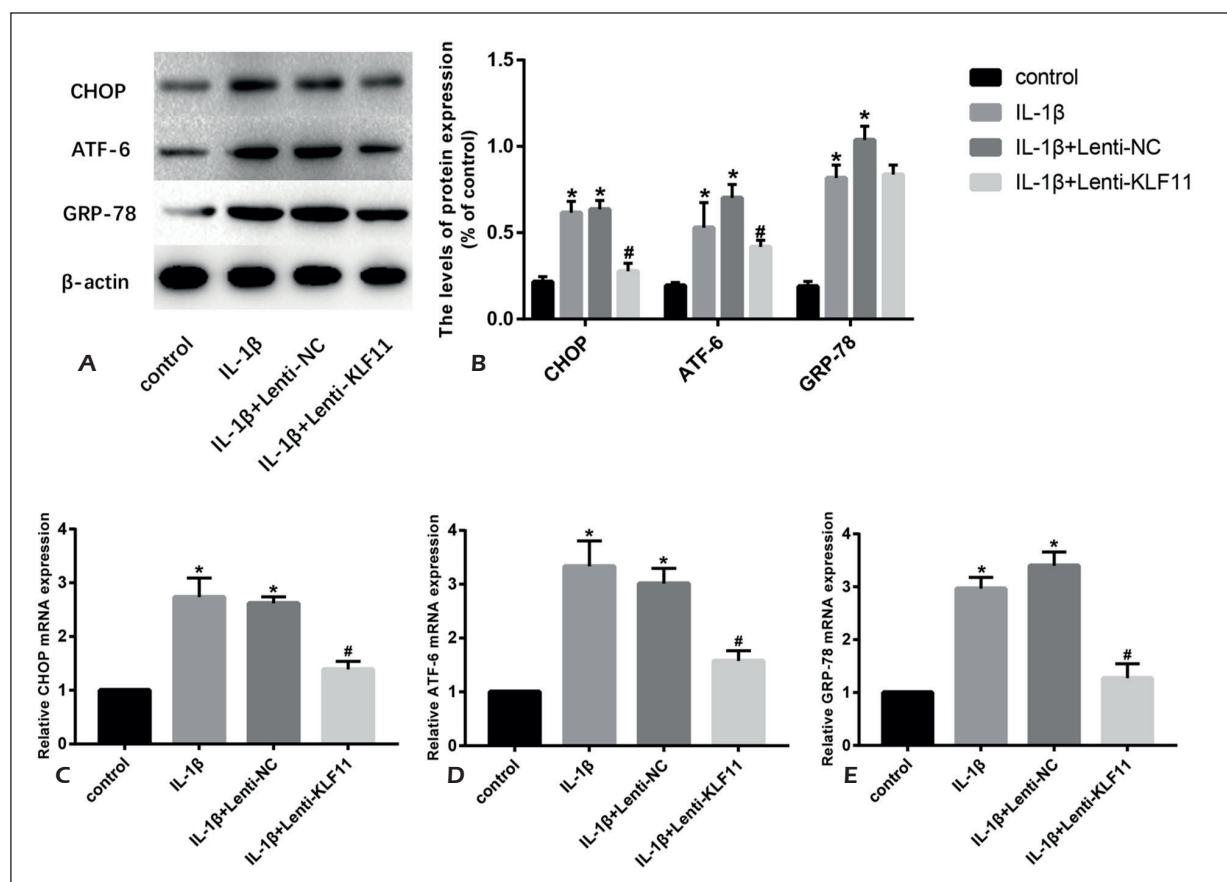


Figure 4. Overexpression of KLF11 reduces ERS in chondrocytes. **A-E**, Expressions of CHOP, ATF-6, and GRP-78 in four groups are determined by Western blot (**A-B**) and RT-PCR (**C-E**). (“*”) means there is a statistical difference with the control group and “#” means there is a statistical difference with the IL-1 β +Lenti-NC group).

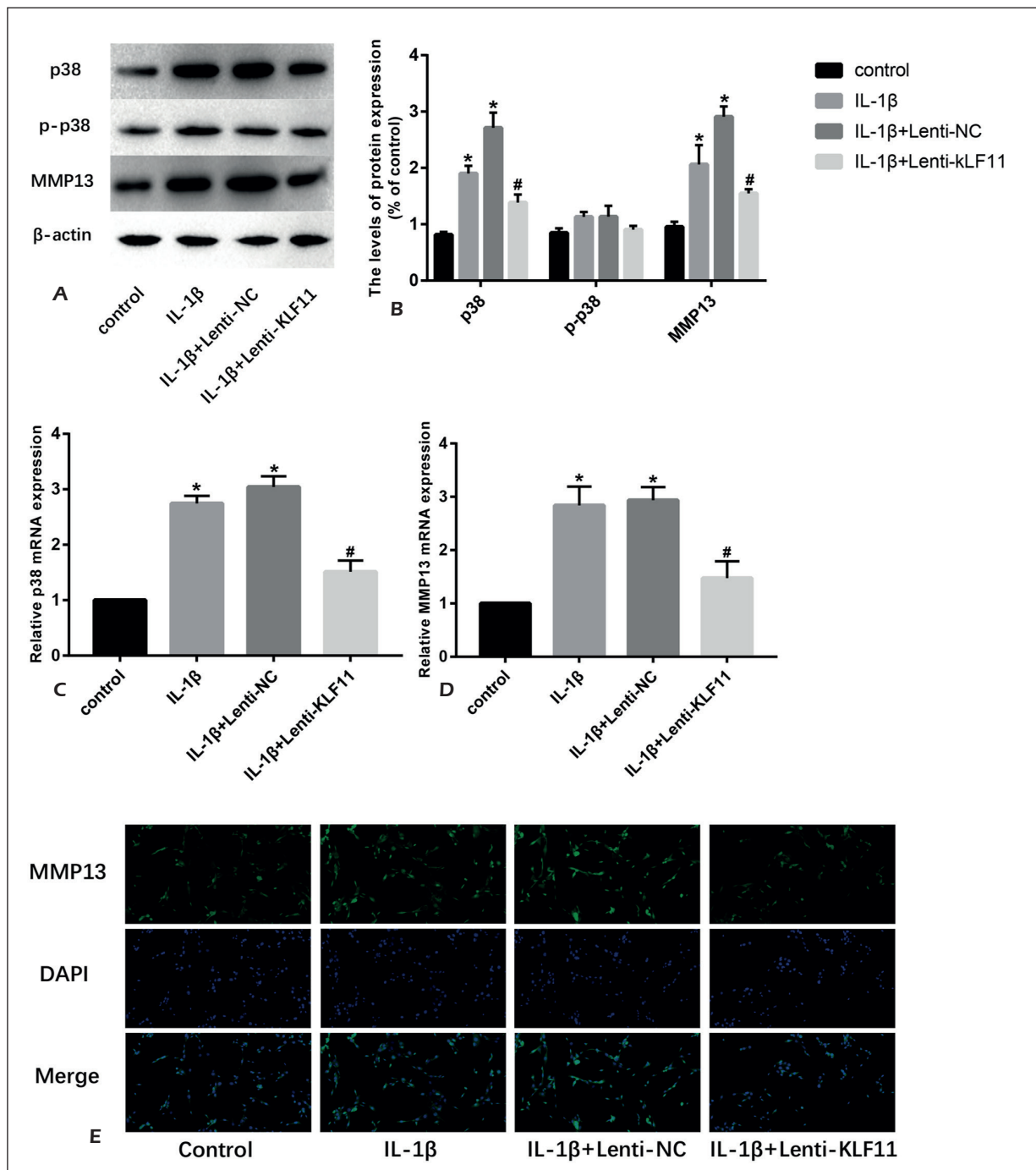


Figure 5. KLF11 inhibits p38MAPK signaling pathway in chondrocytes. **A-B**, Expressions of p38, p-p38, and MMP13 in four groups are determined by Western blot. **C-D**, The mRNA expressions of p38 (**C**) and MMP13 (**D**) are determined by RT-PCR. **E**, Immunofluorescence is used to detect the expression of MMP13 (magnification: 100×). (“*” means there is a statistical difference with the control group and “#” means there is a statistical difference with the IL-1β+Lenti-NC group).

ERS induces apoptosis of human chondrocytes cultured *in vitro* and inhibits the expression of proteoglycan and collagen II mRNA.

KLF11 was first cloned from the human pancreatic cell CFPAC1 in 1998 by the Raul Urrutia

laboratory¹⁶. At present, research on KLF11 shows that KLF11 is an important transcription factor involved in a series of important physiological processes, including cell growth and differentiation, glycolipid metabolism, and oxidative stress¹⁷. Har-

ris et al¹⁸ showed that KLF11 has protective effects on cerebral blood vessels after ischemic injury, and overexpression of KLF11 can inhibit cardiac hypertrophy and fibrosis in mice. Cullingford

et al¹⁹ found that KLF11 plays an important role in cardiomyocyte anti-oxidative stress. However, the role of KLF11 in OA has been rarely studied. In this study, the KLF11 gene was overexpressed

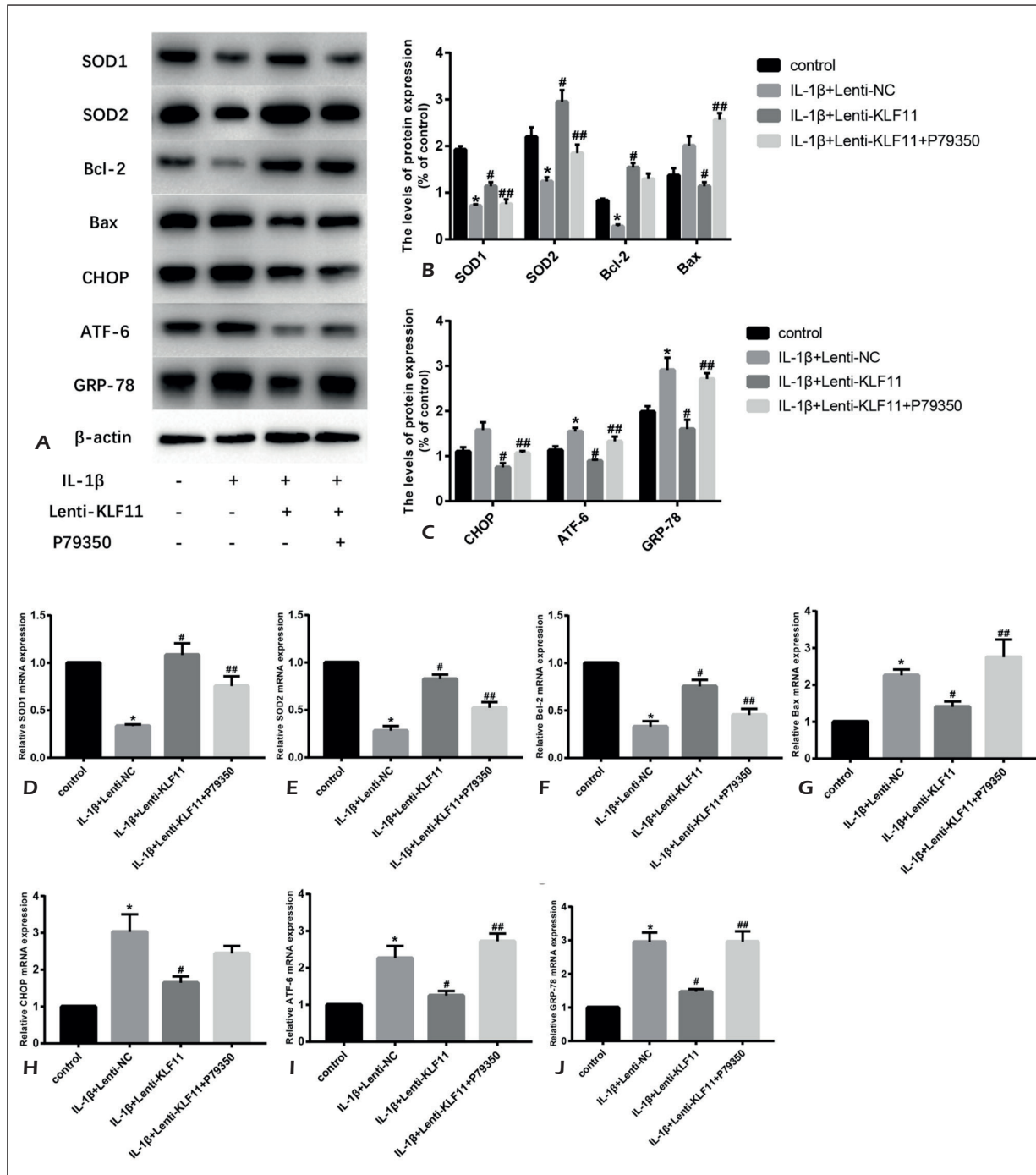


Figure 6. Activation of the p38MAPK signaling pathway attenuates the inhibitory effects of KLF11 on oxidative stress, apoptosis and ERS in chondrocytes. **A-J**, Expressions of SOD1, SOD2, Bcl-2, Bax, CHOP, ATF-6, and GRP-78 in four groups are determined by Western blot (**A-C**) and RT-PCR (**D-J**). (“*” means there is a statistical difference with the control group, “#” means there is a statistical difference with the IL-1 β +Lenti-NC group and “##” means there is a statistical difference with the IL-1 β +Lenti-KLF11 group).

in chondrocytes. It was found that overexpression of KLF11 significantly increased the expressions of SOD1 and SOD2, and inhibited the increase of oxidative stress level of chondrocytes induced by IL-1 β . In addition, KLF11 significantly reduced the expressions of CHOP, ATF-6, and GRP78, as well as the level of ERS in chondrocytes. Therefore, under the action of KLF11, the level of Bax in the chondrocytes was decreased and the level of Bcl-2 was increased, suggesting that the apoptosis of chondrocytes is decreased.

Many factors in articular cartilage can activate p38MAPK signaling pathway, such as various cytokines, inflammatory factors in synovial fluid, mechanical stress, and even X-rays²⁰. The pathway is involved in multiple processes related to OA, regulates the expression of target genes, transmits signals to transcription factors, participates in and regulates apoptosis, hypertrophy, calcification, and proliferation of chondrocytes, controls the regulation of MMPs synthesis, and mediates cellular inflammation. The p38 protein kinase plays a role in the inflammatory response in OA and activates the p38MAPK signaling pathway, resulting in overexpression of IL-1 β and TNF- α , and lead to damage to articular cartilage²¹. Adult articular cartilage has no blood vessels and no lymphatic vessels. The response to trauma and inflammation is mediated by cytokines secreted by chondrocytes and synovial tissue. The imbalance between cytokine synthesis and decomposition pathway is the basic in articular cartilage destruction of OA⁷. The study found that serum IL-1 β levels were significantly increased in patients with OA, and the degree of IL-1 β increase might be related to the degree of OA cartilage damage. IL-1 β can produce a large amount of NO by stimulating phosphorylation of p38, while NO can continue to activate the synthesis of IL-1 β converting enzyme and IL-1 β in chondrocytes, increase the levels of COX-2 and PGE 2, and further cause cartilage damage²². TNF- α can interact with p38 to form a positive feedback pathway. The study revealed that TNF- α can induce phosphorylation of p38, while inhibition of phosphorylation of p38 inhibits the production of TNF- α and IL-6²³. Therefore, the p38MAPK signaling pathway plays an important role in the pathological development of OA. We detected that overexpression of KLF11 significantly decreased phosphorylation of p38 in chondrocytes, suggesting that the p38MAPK signaling pathway is inhibited. However, after P79350 was used to activate the p38MAPK signaling pathway, KLF11's ability to resist oxidative

stress and reduce ERS was inhibited, suggesting that KLF11 protects chondrocytes by inhibiting the p38MAPK signaling pathway.

This study also has some limitations. The effect of KLF11 *in vivo* studies has not been verified. In the next study, KLF11 knockout mice will be constructed to explore the role of KLF11 in OA *in vivo* studies.

To our knowledge, this is the first study to report the role of KLF11 in OA, which should help us find new targets for the prevention and treatment of OA.

Conclusions

KLF11 inhibits oxidative stress, apoptosis, and ERS in IL-1 β -induced chondrocytes. In addition, KLF11 decreased the activity of the p38MAPK signaling pathway, while the p38MAPK agonist P79350 attenuated the effect of KLF11. This indicates that the protective effect of KLF11 on chondrocytes is achieved by inhibiting the p38 MAPK signaling pathway.

Conflict of Interests

The authors declare that they have no conflict of interest.

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