European Review for Medical and Pharmacological Sciences 2020; 24: 8665-8674

Tra2β protects against the degeneration of chondrocytes by inhibiting chondrocyte apoptosis *via* activating the PI3K/Akt signaling pathway

C. ZHOU, K.-S. WANG, W. PENG, F.-L. YUAN, Z.-P. SI

Department of Orthopaedics, Affiliated Hospital of Jiangnan University (Wuxi No. 3 People's Hospital), Wuxi, China

Abstract. – OBJECTIVE: Osteoarthritis (OA) is a common disease in the elderly and seriously affects the quality of life of patients. Tra2β is a protein that has been found to activate PI3K/Akt in recent years. The purpose of this study was to explore the protective effects of Tra2β on chondrocytes and its mechanisms.

PATIENTS AND METHODS: The expression of Tra2β in knee cartilage tissue of patients with OA and normal people was compared. In addition, human primary chondrocytes were cultured, the expression of Tra2β in chondrocytes by cell transfection was changed, and its effects on extracellular matrix, inflammation, and apoptosis in chondrocytes were examined. LY294002 was also used to inhibit the activity of PI3K/Akt signaling pathway to verify the mechanism of Tra2β to protect chondrocytes.

RESULTS: The expression of Tra2β in the cartilage tissue of the OA group was significantly lower than that of the control group, and the IL-1β-induced chondrocytes also expressed the lower Tra2β. The overexpression of Tra2β increased the expression of extracellular matrix collagen II and decreased the expressions of MMP3/13, inflammatory factors (IL-6, IL-8 and TNF-α), and apoptotic factors (caspase3/9, Bax). In addition, the overexpression of Tra2β also increased expression and phosphorylation of PI3K and Akt. However, LY294002 attenuated the protective effect of Tra2β on chondrocytes by inhibiting the PI3K/Akt signaling pathway.

CONCLUSIONS: Tra2β activates the PI3K/Akt signaling pathway, reduces the degradation of extracellular matrix of chondrocytes, reduces the level of inflammation and apoptosis of chondrocytes, and thus, plays a role in the treatment of OA.

Key Words:
Osteoarthritis, Tra2β, Inflammatory, Apoptosis, PI3K/Akt signaling pathway.

Introduction

Osteoarthritis (OA) is a very common joint disease that occurs in the elderly and athletes. It is a degenerative disease of articular cartilage caused by various factors, accompanied by osteophyte formation in the joint cavity and synovium inflammation around the joint[1]. Clinically, the main manifestations are joint pain, swelling, and stiffness of the limbs. These symptoms greatly limit patient's mobility. OA in the late stage can lead to the complete loss of joint function, which makes the patient lose the ability to act, thus not only affecting daily work and life, but also seriously harming human health[2]. As the world is rapidly entering an aging society, the incidence of OA is also increasing year by year[3].

Chondrocytes are the only cells in articular cartilage. The stability of articular cartilage depends on chondrocytes, which in turn can maintain the balance of extracellular matrix[4]. Therefore, damage to the function and survival of chondrocytes will lead to damage of articular cartilage. Chondrocytes are responsible for the synthesis and renewal of the extracellular matrix, maintaining the integrity of the matrix. Chondrocyte apoptosis is one of the pathological factors of degenerative changes in the articular cartilage[5]. PI3K/Akt is an important anti-apoptotic pathway *in vivo*. Activation of receptor tyrosine kinase activates PI3K in a phosphorylated form, and phosphorylation of PIP2 to PIP3 by p-PI3K further phosphorylates and activates Akt. Then, the activated Akt can act on the TSC1/TSC2 dimer and depolymerize it, thereby releasing the inhibitory effect of the dimer on Rheb, and finally activates mTOR and the downstream transcription factor eIF4E and reg-

Corresponding Author: Chao Zhou, MM; e-mail: kkqmbnu@163.com

ulates the expression of apoptosis-related genes[6].

The transformer 2β (Tra2β) protein[7] is a member of the serine/arginine-like protein family and contains an RNA recognition domain and two serine/arginine domains. It is an important RNA-binding protein involved in alternative splicing. Ji et al[8] have shown that Tra2β is associated with various diseases, such as cerebral ischemia, nerve damage, and Alzheimer's disease. Tra2β is closely related to the PI3K/Akt signaling pathway. Ni et al[9] have shown that the silence of Tra2β can inhibit the proliferation of laryngeal squamous cell carcinoma and promote their apoptosis by inhibiting the PI3K/Akt signaling pathway. This suggests that Tra2β may activate the PI3K/Akt signaling pathway. However, the role of Tra2β in OA has not been studied. Therefore, human cartilage tissue and human primary chondrocytes were selected to detect the effect of Tra2β on chondrocytes to provide a new target for the clinical treatment of OA.

Patients and Methods

Patient Tissue Samples

Knee articular cartilage tissues of patients with knee OA and normal people were extracted to detect the expression levels of collagen II and Tra2β. For patients with severe OA requiring knee arthroplasty, a portion of the extracted knee cartilage tissue was taken for the study during surgery. The knee cartilage tissue of the normal control group was obtained from patients who required amputation due to trauma. For cartilage tissue removed during surgery, it was immediately placed in liquid nitrogen for storage. This study was approved by the Ethics Committee of the Affiliated Hospital of the Jiangnan University. 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 Saibaikang Bio Co., Ltd. (Shanghai, China). The medium used to culture the chondrocytes was Dulbecco's Modified Eagle's Medium (DMEM, Gibco, Rockville, MD, USA) containing 10% fetal bovine serum (FBS, Gibco, Rockville, MD, USA) and 1% penicillin plus streptomycin (Gibco, Rockville, MD, USA). We used Petri dishes (Corning, Corning, NY, USA) to incubate the cells in an incubator at 37°C and 5% CO_2. After the cell density reached 50-60%, the cells were transfected or treated with drugs. LY294002 (Selleck, Shanghai, China), an inhibitor of PI3K was used to inhibit the activity of the PI3K/Akt signaling pathway in chondrocytes, and recombinant human IL-1β (Lianke, Hangzhou, China) was used to stimulate degeneration of chondrocytes.

Lentiviral Transfection

When the cell density in the dish reached 50-60%, chondrocytes were transfected with Lenti-NC or Lenti-Tra2β. Lipofectamine 3000 (Thermo Fisher Scientific, Waltham, MA, USA) was used for transfection experiments. Then, lenti-Tra2β was used to increase the expression of Tra2β in chondrocytes, while Lenti-NC was used as a negative control.

Western Blot Analysis

After getting out human articular cartilage tissue or chondrocytes, protein lysate (NCM Biotech, Suzhou, China) was used to lyse the tissue or cells. Then, the bicinchoninic acid (BCA) kit (NCM Biotech, Suzhou, China) was applied to detect the concentration of protein in the protein lysate. Next, a solution containing 30 μg proteins was added to each well of the electrophoresis gel for sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE). After the end of the electrophoresis, the protein was transferred to the polyvinylidene difluoride (PVDF) membrane (Millipore, Billerica, MA, USA). Subsequently, the non-specific antigen was blocked on the PVDF membranes for one hour using 5% skim milk. Later, a primary antibody dilution (collagen II 1:3000, Rabbit, Abcam, Cambridge, UK, Tra2β, 1:5000, Rabbit, Abcam, Cambridge, UK, MMP3, 1:2000, Rabbit, Abcam, Cambridge, UK, MMP13, 1:1000, Rabbit, Abcam, Cambridge, UK, IL-6, 1:3000, Rabbit, Abcam, Cambridge, UK, TNF-α, 1:1000, Rabbit, Abcam, Cambridge, UK, caspase3, 1:5000, Rabbit, Abcam, Cambridge, UK, caspase9, 1:5000, Rabbit, Abcam, Cambridge, UK, PI3K, 1:3000, Rabbit, Abcam, Cambridge, UK, p-PI3K, 1:2000, Rabbit, Abcam, Cambridge, UK, Akt, 1:3000, Rabbit, Abcam, Cambridge, UK, p-Akt, 1:3000, Rabbit, Abcam, Cambridge, UK, β-actin, 1:3000, Rabbit, Abcam, Cambridge, UK) was used to incubate the PVDF membrane overnight at 4°C. After washing the PVDF membrane the next day, a secondary antibody dilution (Goat anti-rabbit, 1:3000, Abcam, Cambridge, UK) was used to incubate the PVDF membrane for 2 hours at room temperature. Fi-

nally, enhanced chemiluminescence (ECL) was adopted to observe protein expression.

Reverse Transcription-Polymerase Chain Reaction (RT-PCR)

TRIzol (Invitrogen, Carlsbad, CA, USA) was used to extract total RNA from human articular cartilage tissue and chondrocytes. After that, a spectrophotometer was used to detect the concentration of extracted RNA, and the SuperScript IV reverse transcription kit (Invitrogen, Carlsbad, CA, USA) was used to reverse RNA to cDNA. Then, cDNA was amplified using the SYBR Green kit (Invitrogen, Carlsbad, CA, USA). With glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as an endogenous control, $2^{-\Delta\Delta Ct}$ method was used to calculate relative expression level. The primer sequences of mRNA are shown in Table I.

Enzyme-Linked Immunosorbent Assay (ELISA)

Chondrocytes were cultured and subjected to passage into 6-well plates. When the cell density was 50-60%, the cells were treated. Then, the cell supernatant was taken, and the ELISA kit (Lianke, Hangzhou, China) was used to detect the contents of MMP3, MMP13, IL-6, and IL-8 in the supernatant according to the manufacturer's instructions.

Immunocytofluorescence (IF) Staining

Cell slides were placed in 24-well plates and passaged chondrocytes into 24-well plates. After the cells were treated, we took out the 24-well plates and discarded the medium. After washing the cells with phosphate-buffered saline (PBS), the cells were fixed with 4% paraformaldehyde. The cells were then immersed in 0.5% Triton-PBS for 15 minutes, and 10% goat serum was used to block non-specific antigens in the cells. Next, the chondrocytes were incubated with a primary antibody dilution (Tra2β, 1:500, rabbit, Abcam, Cambridge, UK; collagen II, 1:500, rabbit, Abcam, Cambridge, UK; caspase8, 1:500, rabbit, Abcam, Cambridge, UK; Akt, 1:500, rabbit, Abcam, Cambridge, UK) at 4°C overnight. After washing the cells in the next day, we incubated the cells for 1 hour at room temperature using a fluorescent sec-

Table I. RT-PCR primer sequences.

Name	sense/anti-sense	Sequence (5'-3')
Type Collagen II	sense	GGATGGCTGCACGAAAC
	anti-sense	CCCTATGTCCACACCGAAT
Tra2β	sense	CCGTTTTCCTCCAGTCC
	anti-sense	AAGCCGACAAATCCACAT
MMP3	sense	TTTTCTCCTGCCTGTGCT
	anti-sense	TTCACGCTCAAGTTCCCT
MMP13	sense	ATCTGAACTGGGTCTTCCAA
	anti-sense	GCCTGTATCCTCAAAGTGAAC
IL-6	sense	CAATAACCACCCCTGACC
	anti-sense	GCGCAGAATGAGATGAGTT
TNF-α	sense	CCCTCCTTCAGACACCCT
	anti-sense	GGTTGCCAGCACTTCACT
Caspase3	sense	CAGTGATGCTGTGCTATGAAT
	anti-sense	CAGATGCCTAAGTTCTTCCAC
Caspase9	sense	CAGGTTCTGGGGACAGG
	anti-sense	AGGATTCGCTCTTGCGT
Bax	sense	TGCGTCCACCAAGAAGC
	anti-sense	TCCAGTTCGTCCCCGAT
Bcl-2	sense	GCGGATTGACATTTCTGTG
	anti-sense	CATAAGGCAACGATCCCA
PI3K	sense	AGTACCTTGTTCCAATCCCA
	anti-sense	GTTCCTCTTTAGCACCCTTTC
Akt	sense	AAGCCCCAGGTCACGTC
	anti-sense	TCGCTGTCCACACACTCC
GAPDH	sense	CCTTCCGTGTCCCCACT
	anti-sense	GCCTGCTTCACCACCTTC

ondary antibody (Goat anti-rabbit-FITC, 1:500, Abcam, Cambridge, UK). After washing the cells, they were incubated for 10 minutes using 4′,6-diamidino-2-phenylindole (DAPI; Sigma-Aldrich, St. Louis, MO, USA). Finally, the cell slides were removed and fixed on glass slides, and then, the staining results were observed and recorded using a fluorescence microscope.

Flow Cytometry

Annexin V-fluorescein isothiocyanate (FITC) kit (Keygen, Nanjing, China) was used to detect the apoptosis level in chondrocytes. After the cells were treated, the medium was discarded and the cells were washed with PBS. Each group of cells was collected and added with 5 μl of Annexin V-FITC and 5 μl of propidium iodide (PI). Then, the cells were placed in the dark for 15 minutes. Finally, 400 μl of loading buffer was added to each group, and then, the apoptosis rate was measured by flow cytometry.

Statistical Analysis

SPSS 21.0 (SPSS IBM Corp., Armonk, NY, USA) was used in this study to analyze experimental data. The mean ± standard deviation is used to represent the measurement data. Comparison between multiple groups was done using One-way ANOVA test followed by post-hoc test (Least Significant Difference). All experiments were repeated more than three times. $p<0.05$ was considered to be statistically significant.

Results

Decreased Expression of Tra2β in Articular Cartilage Tissue of Patients with OA and IL-1β-Induced Chondrocytes

To examine the association between Tra2β and OA, the differential expression of Tra2β in articular cartilage tissue was compared between osteoarthritic patients and normal people. The results of Western blot (Figure 1A) and qRT-PCR (Figure 1B, 1C) showed that the expressions of collagen II and Tra2β in OA group were significantly lower than that in the control group, indicating that the articular cartilage of OA patients significantly degenerated and the expression of Tra2β decreased with degeneration. Chondrocytes were stimulated with recombinant human IL-1β (10 ng/ml) to cause degeneration of chondrocytes, and then, the changes in Tra2β expression were detected. The results of Western blot (Figure 1D) and qRT-PCR (Figure 1E, 1F) showed that the expressions of collagen II and Tra2β were decreased gradually with the prolongation of IL-1β stimulation time. In addition, the results of IF staining (Figure 1G) also showed that Tra2β decreased the expression of Tra2β in chondrocytes.

Overexpression of Tra2β Reduces IL-1β-Induced Inflammation of Chondrocytes and Degradation of Extracellular Matrix

Lenti-Tra2β was used to transfect chondrocytes to examine the effect of Tra2β on the extracellular matrix and inflammation of chondrocytes. The results of Western blot (Figure 2A) and qRT-PCR (Figure 2B-2F) showed that the expression of collagen II was significantly decreased after IL-1β stimulated chondrocytes, while the expressions of MMP3, MMP13, IL-6, and TNF-α were increased, indicating that IL-1β increased the inflammation level of chondrocytes and promotes the degradation of the extracellular matrix. However, overexpression of Tra2β attenuated IL-1β-induced degeneration of chondrocytes. The results of ELISA (Figure 2G-2J) also showed that Tra2β reduced the expression of MMP3, MMP13, IL-6, and IL-8. IF staining (Figure 2K) also verified this result.

Overexpression of Tra2β Reduces IL-1β-Induced Apoptosis of Chondrocytes

IL-1β was used to induce degeneration of chondrocytes and cause apoptosis. The results of Western blot (Figure 3A) and qRT-PCR (Figure 3B, 3C) showed that the expressions of caspase3 and caspase9 in chondrocytes were significantly increased after IL-1β induction, and the overexpression of Tra2β decreased their expression. The results of qRT-PCR (Figure 3D, 3E) also showed that overexpression of Tra2β reduced the expression of Bax and increased the expression of Bcl-2. The percentage of apoptosis of chondrocytes was detected by flow cytometry (Figure 3F). The results showed that the apoptosis rate of chondrocytes induced by IL-1β was significantly higher than that of the control group, while the overexpression of Tra2β significantly decreased the rate of apoptosis. IF staining (Figure 3G) detected the expression of caspase8, and the results showed that Tra2β can reduce the expression of caspase8 in chondrocytes.

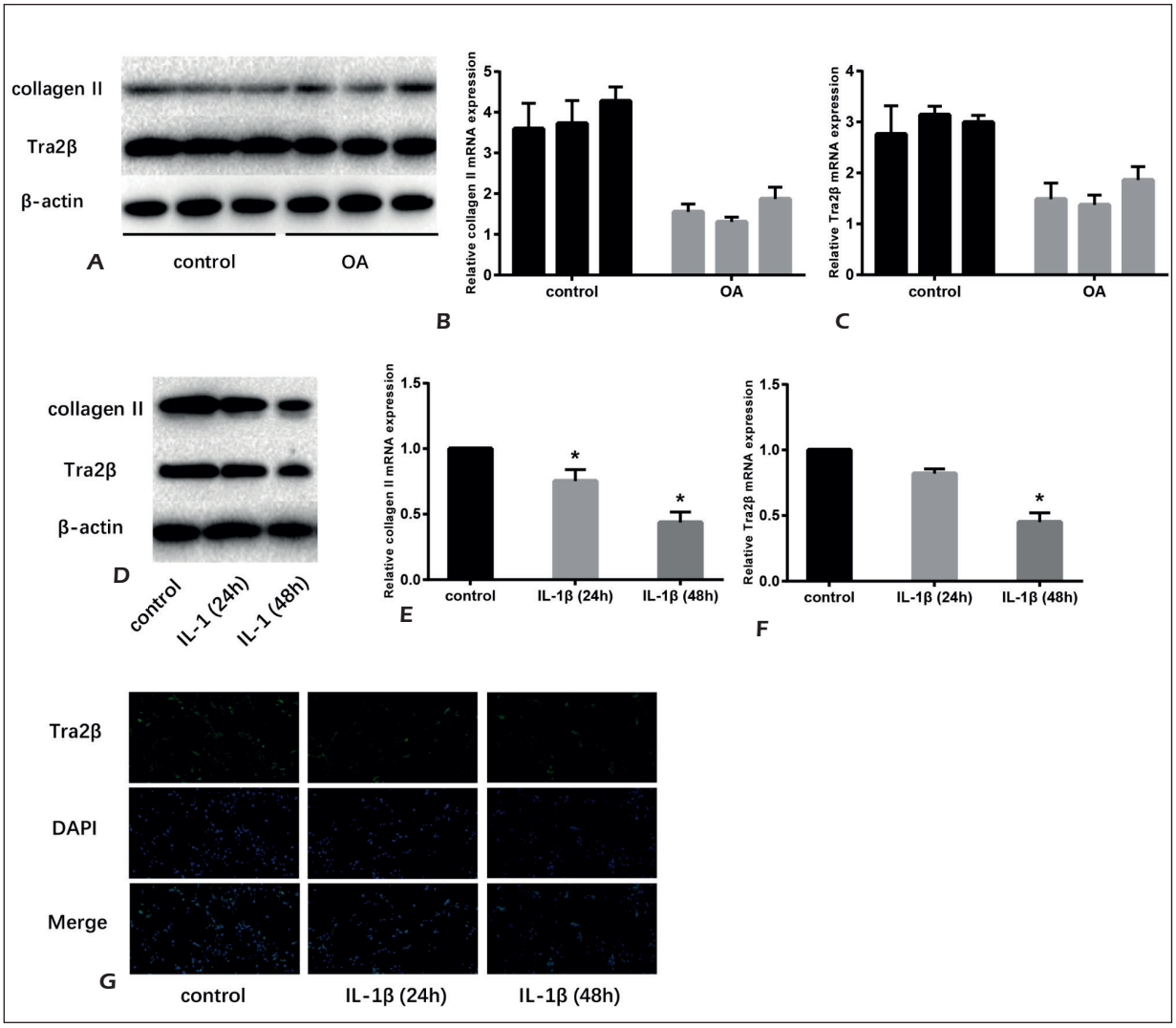

Figure 1. Decreased expression of Tra2β in articular cartilage tissue of patients with OA and IL-1β-induced chondrocytes. **A**-**C**, Expressions of collagen II and Tra2β in patients with OA and normal people are detected by Western blot (**A**) and RT-PCR (**B**, **C**). **D**-**F**, Expressions of collagen II and Tra2β in IL-1β-induced chondrocytes are detected by Western blot (**D**) and RT-PCR (**E**, **F**). **G**, IF staining detects the expression of Tra2β (magnification: 200x) ("*" means there is a statistical difference with the control group).

Tra2β Activates the Activity of PI3K/Akt Signaling Pathway in Chondrocytes

To verify whether Tra2β activates the PI3K/Akt signaling pathway in chondrocytes, the expression and phosphorylation levels of PI3K and Akt were examined. The results of Western blot (Figure 4A) and qRT-PCR (Figure 4B, 4C) showed that the overexpression of Tra2β significantly increased the expressions of PI3K and Akt, and the phosphorylation levels of PI3K and Akt were also increased. The results of IF staining (Figure 4D) also found that IL-1β reduced the expression of Akt, but overexpression of Tra2β attenuated the effect of IL-1β.

LY294002 Attenuates the Protective Effect of Tra2β on Chondrocytes

To determine whether Tra2β exerts a protective effect on chondrocytes by activating the PI3K/Akt signaling pathway, LY294002 was used to reduce the activity of the PI3K/Akt signaling pathway in chondrocytes. The results of Western blot (Figure 5A) and qRT-PCR (Figure 5B-5F) showed that the expressions of collagen II and Bcl-2 were significantly decreased after LY294002, while the expressions of IL-6, IL-8, and Bax were increased. These results indicate that LY294002 significantly attenuates the protective effect of Tra2β on the

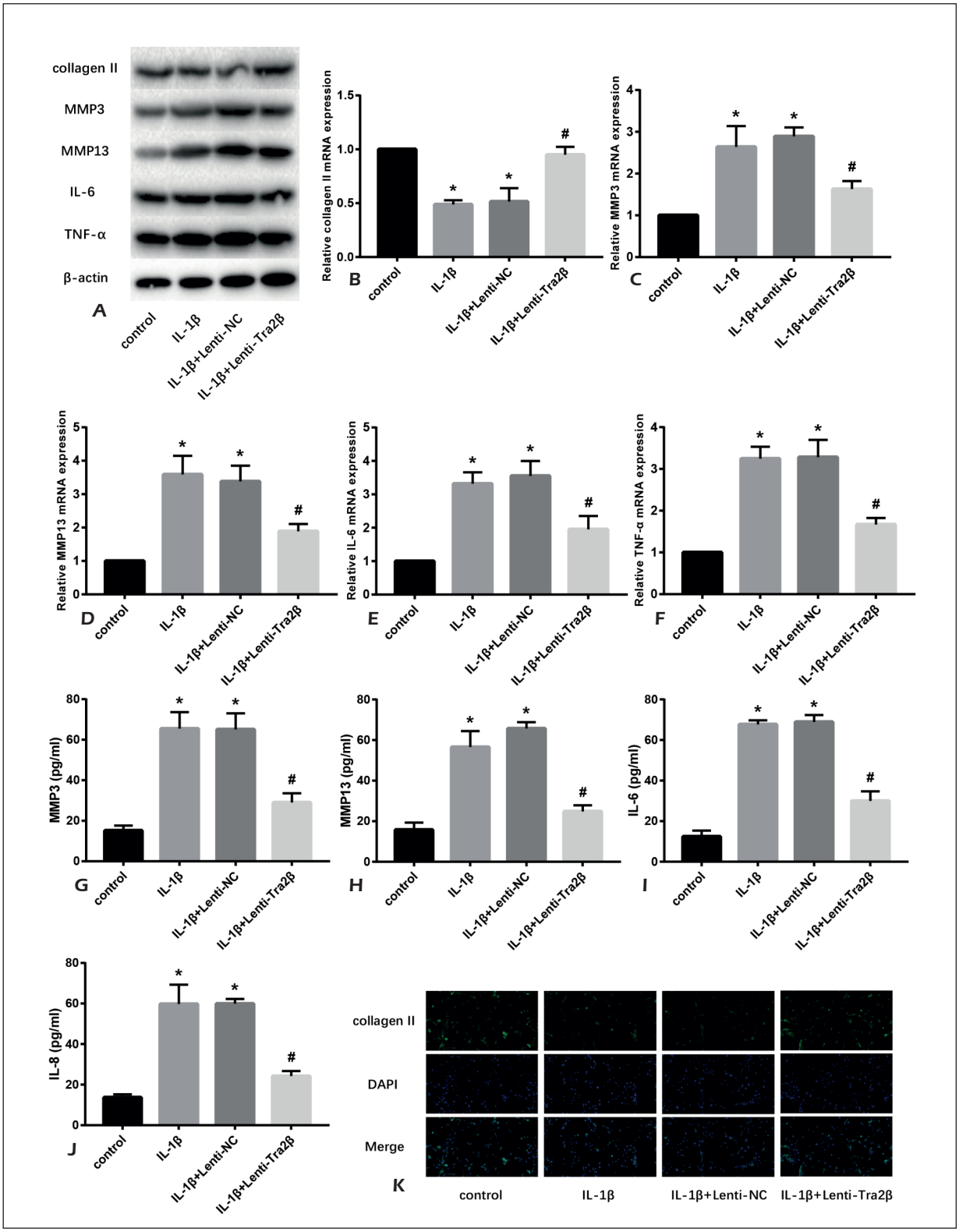

Figure 2. Overexpression of Tra2β reduces IL-1β-induced inflammation of chondrocytes and degradation of extracellular matrix. **A-F**, Expressions of collagen II, MMP3, MMP13, IL-6 and TNF-α in four groups are determined by Western blot (**A**) and RT-PCR (**B-F**). G-J, ELISA detects the expressions of MMP3, MMP13, IL-6 and IL-8. K, IF staining detects the expression of collagen II (magnification: 200x) ("*" means there is a statistical difference with the control group and "#" means there is a statistical difference with the IL-1β+Lenti-NC group).

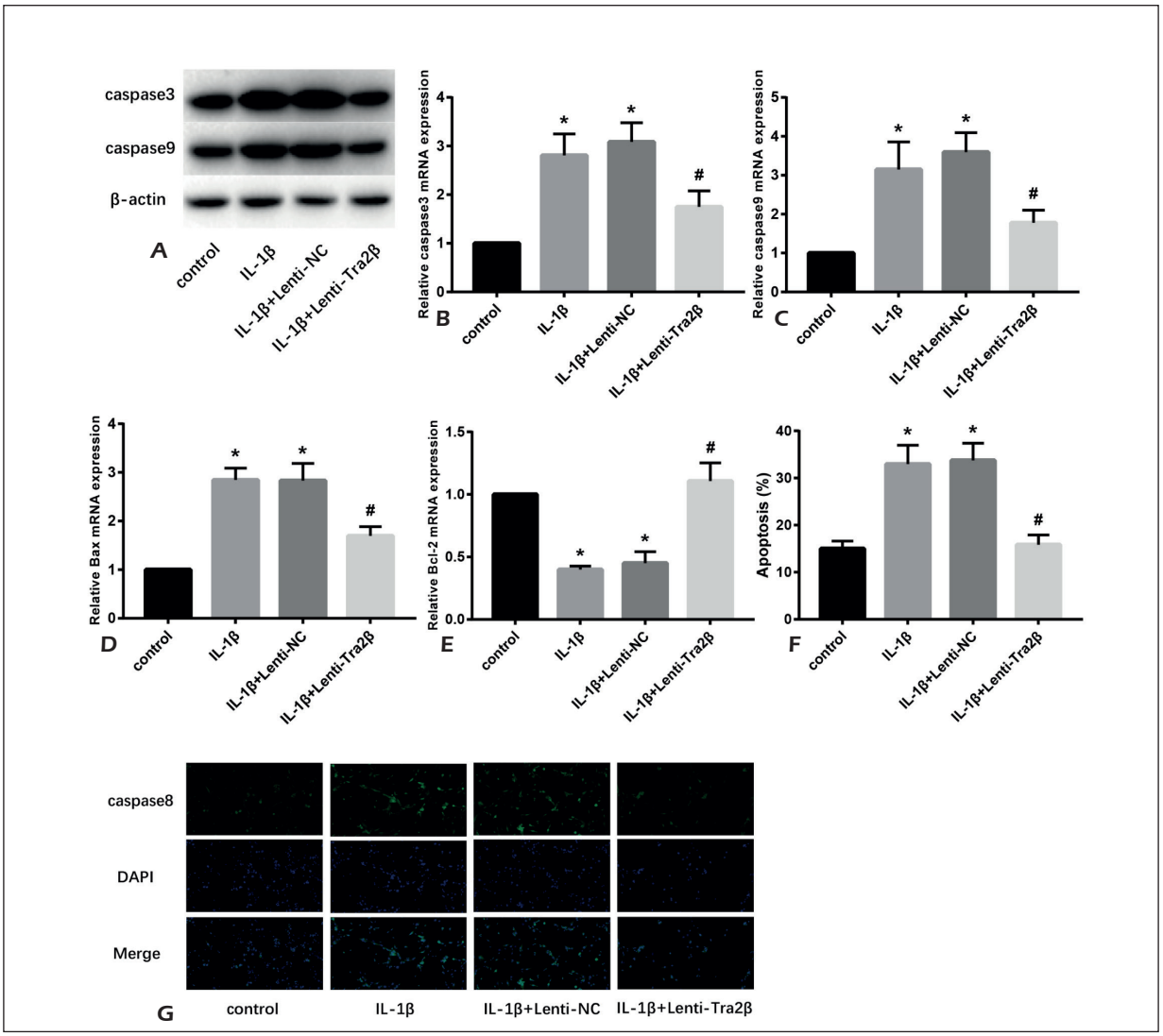

Figure 3. Overexpression of Tra2β reduces IL-1β-induced apoptosis of chondrocytes. **A**-**C**, Expressions of caspase3 and caspase9 in four groups are determined by Western blot (**A**) and RT-PCR (**B**, **C**). **D**, **E**, RT-PCR also detects the expressions of Bax (**D**) and Bcl-2 (**E**). **F**, Cell apoptosis rate is detected by flow cytometry. G, IF staining detects the expression of caspase3 (magnification: 200x) ("*" means there is a statistical difference with the control group and "#" means there is a statistical difference with the IL-1β+Lenti-NC group).

extracellular matrix of chondrocytes, as well as anti-inflammatory and anti-apoptotic effects.

Discussion

Apoptosis is one of the types of programmed cell death, including a series of morphological changes, such as nuclear pyknosis, nuclear lysis, and plasma membrane blebbing. In addition, it is accompanied by a series of changes in biochemical characteristics, such as permeabilization of mitochondrial outer membrane, activation of caspase effector molecules, and activation of metabolic enzymes[10]. Apoptosis is a highly controlled mode of adjustment involved in cell development, homeostasis, aging, and death. Disorders of apoptosis will lead to pathological conditions, such as cancer and some degenerative diseases[11]. The mechanism of apoptosis is divided into endogenous or mitochondrial pathways induced by intracellular signals, as well as exogenous or death receptor pathways triggered by extracellular signals, including activation of the death receptor family[12]. Studies have shown that death receptor Fas or TNFR1, cytokines, mechanical mechan-

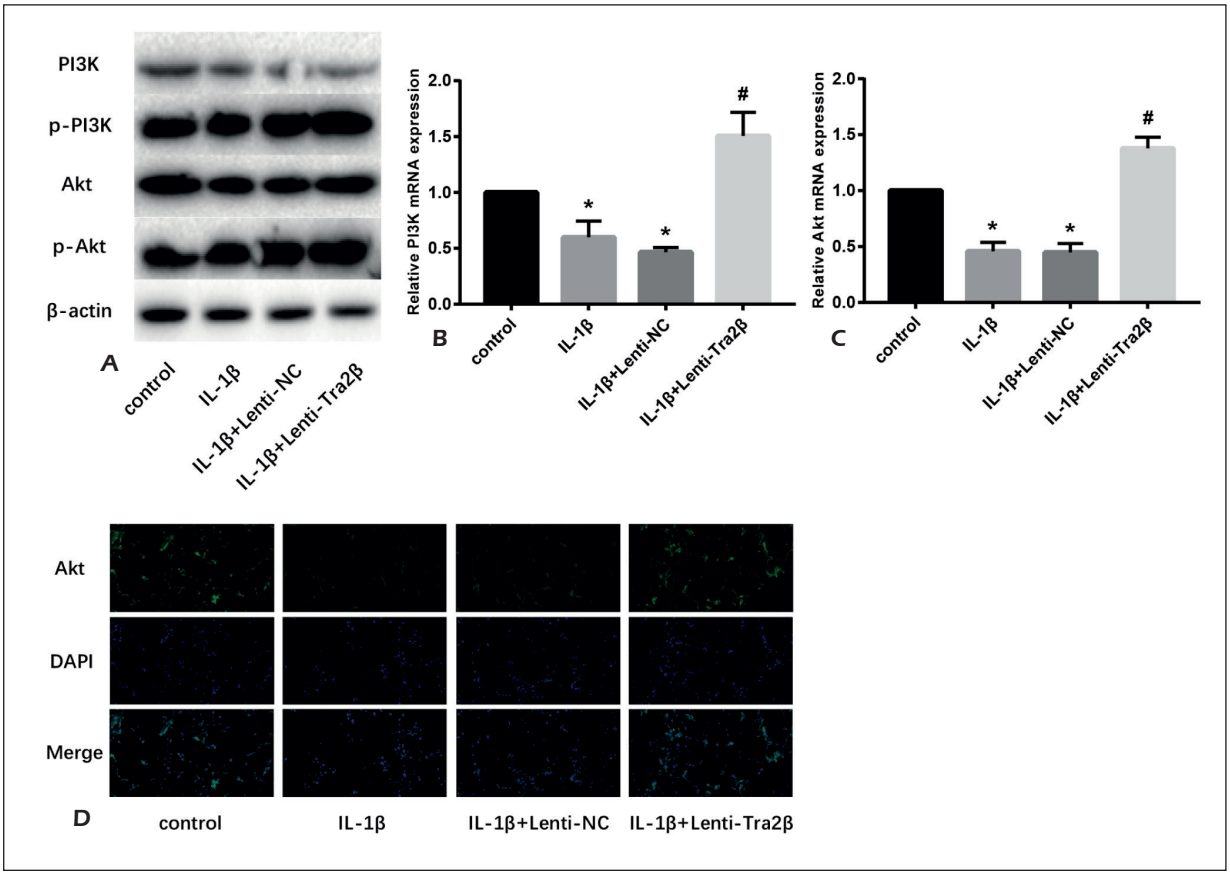

Figure 4. Tra2β activates the activity of PI3K/Akt signaling pathway in chondrocytes. **A-C**, Expressions of PI3K, p-PI3K, Akt and p-Akt in four groups are determined by Western blot (**A**) and RT-PCR (**B**, **C**). **D**, IF staining detects the expression of Akt in chondrocytes (magnification: 200x) ("*" means there is a statistical difference with the control group and "#" means there is a statistical difference with the IL-1β+Lenti-NC group).

ics, physicochemical, and other factors can trigger chondrocyte apoptosis. After the activation of the apoptotic signal, a variety of proteins and enzymes are involved to activate a variety of signaling pathways, including MAPKs, MEK/ERK, JNK, PI3K/Akt, JAKs/STAT1, and other signaling pathways. Cytochrome C and AIF released by chondrocyte mitochondria can induce apoptosis[13]. Reactive oxygen species (ROS) and oxidative stress are closely related to the promotion of OA processes. Oxidative stress can interfere with the balance of the antioxidant system, and ROS can lead to apoptosis and damage through the redox signaling pathway[14]. Therefore, the apoptotic pathway provides a potential target for the development of OA therapeutic drugs.

The PI3K/Akt signaling pathway is an important anti-apoptotic pathway in the cell, and its downstream transcription factor eIF4E can regulate the expression of various anti-apoptotic genes[15]. Bcl-2 is an important anti-apoptotic molecule in the mitochondrial apoptotic pathway, which can reduce the permeability of mitochondrial membrane to cytochrome c and inhibit the release of cytochrome c into cytoplasm in mitochondria. Bax is an antagonist of Bcl-2, and it can antagonize its anti-apoptotic effect after forming a heterodimer with Bcl-2[16]. Upon entry into the cytosol, cytochrome c is able to amplify the activation of caspase3 by cascade and cause apoptosis[17]. Our study found that Tra2β can reduce the expression of caspase 3/9, and Bax in chondrocytes, and increase the expression of Bcl-2, indicating that Tra2β has a significant anti-apoptotic effect on chondrocytes.

Inflammatory mediators are important upstream molecules that regulate the function of the PI3K/Akt signaling pathway, and multiple molecules in

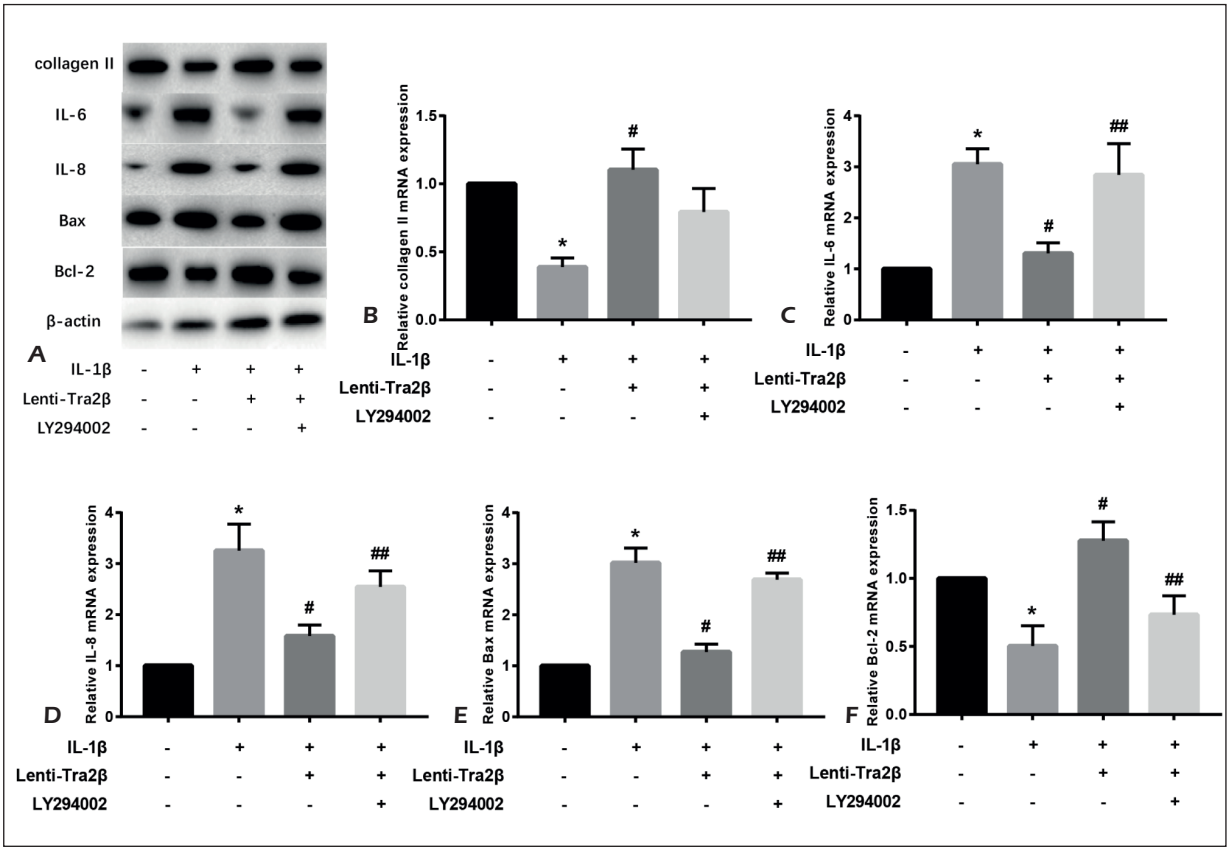

Figure 5. LY294002 attenuates the protective effect of Tra2β on chondrocytes. **A**-**F**, Expressions of collagen II, IL-6, IL-8, Bax and Bcl-2 in four groups are determined by Western blot (**A**) and RT-PCR (**B**-**F**). ("*" means there is a statistical difference with the control group, "#" means there is a statistical difference with the IL-1β+Lenti-NC group and "##" means there is a statistical difference with the IL-1β+Lenti- Tra2β+LY294002 group)

the interleukin family are closely related to the activation of the PI3K/Akt signaling pathway[18]. In the pathological process of OA, the inflammatory response mediated by interleukin plays an important role. Both IL-1β and IL-1α belong to the IL-1 family, which not only directly induces inflammatory reactions in articular cartilage, but also promotes the expression of ADAMTS-5, MMP13, etc., and causes degeneration of articular cartilage. IL-6 is the initiator of the regulation of articular cartilage inflammation and works synergistically with a variety of inflammatory mediators. In the pathological process of OA, the increase of MMP3 and MMP13 caused by inflammation has evident destructive effect on cartilage matrix[19]. We found that IL-1β-induced chondrocyte extracellular matrix collagen II was significantly reduced and MMP3 and MMP13 were significantly increased, suggesting that IL-1β promoted the degradation of extracellular matrix of chondrocytes. Overexpression of Tra2β significantly inhibited the destruction of chondrocytes by IL-1β. The inflammation level in chondrocytes is also significantly inhibited by Tra2β. In addition, in order to detect the effect of Tra2β on the PI3K/Akt signaling pathway in chondrocytes, we examined the expression levels and phosphorylation levels of PI3K and Akt. The results indicated that the overexpression of Tra2β significantly promoted the expression and phosphorylation of PI3K and Akt. Moreover, after the inhibition of PI3K/Akt signaling pathway by LY294002, the protective effect of Tra2β on chondrocytes was significantly reduced, demonstrating that the role of Tra2β in protecting chondrocytes may be caused by activation of PI3K/Akt signaling pathway.

To sum up, this is the first report on the role of Tra2β in OA. We believe that studying the effects and mechanisms of Tra2β on chondrocytes can provide a new direction and theoretical basis for clinical treatment of OA.

Conclusions

In degenerative human articular cartilage tissue and IL-1β-induced chondrocytes, the expression of Tra2β was significantly reduced. In addition, the overexpression of Tra2β significantly reduced the degradation of extracellular matrix and the levels of inflammation and apoptosis in chondrocytes. Moreover, the inhibition of PI3K/Akt signaling pathway can attenuate the protective effect of Tra2β on chondrocytes, indicating that Tra2β plays a role in protecting chondrocytes by activating PI3K/Akt signaling pathway.

Conflict of Interests

The authors declare that they have no conflict of interest.

References

1) Dequeker J and Luyten FP. The history of osteoarthritis-osteoarthrosis. Ann Rheum Dis 2008; 67: 5-10.
2) Scordino LE, Bernstein J, Nakashian M, McIntosh M, Cote MP, Rodner CM, Wolf JM. Radiographic prevalence of scaphotrapeziotrapezoid osteoarthrosis. J Hand Surg Am 2014; 39: 1677-1682.
3) Noskov SM, Lavrukhina AA, Shirokova KY, Pryanichnikova AA. [Strategy for the use of chondroprotectors in osteoarthrosis]. Ter Arkh 2013; 85: 92-94.
4) Pavelka K. [Therapy of osteoarthritis--from controlling the symptoms to preserving articular cartilage]. Cas Lek Cesk 2000; 139: 487-493.
5) Liu Y, Foreman SC, Joseph GB, Neumann J, Tien PC, Li X, Lane NE, Nevitt MC, McCulloch CE, Link TM. Is treated HIV infection associated with knee cartilage degeneration and structural changes? A longitudinal study using data from the osteoarthritis initiative. BMC Musculoskelet Disord 2019; 20: 190.
6) Malemud CJ. Negative regulators of JAK/STAT signaling in rheumatoid arthritis and osteoarthritis. Int J Mol Sci 2017; 18. pii: E484.
7) Liu J, Bian T, Feng J, Qian L, Zhang J, Jiang D, Zhang Q, Li X, Liu Y, Shi J. MiR-335 inhibited cell proliferation of lung cancer cells by target Tra2β. Cancer Sci 2018; 109: 289-296.
8) Ji L, Ni T, Shen Y, Xue Q, Liu Y, Chen B, Cui X, Lv L, Yu X, Cui Y, Lu X, Chen J, Mao G, Wang Y. Transformer 2beta (Tra2beta/SFRS10) positively regulates the progression of NSCLC via promoting cell proliferation. J Mol Histol 2014; 45: 573-582.
9) Ni HS, Hu SQ, Chen X, Liu YF, Ni TT, Cheng L. Tra2beta silencing suppresses cell proliferation in laryngeal squamous cell carcinoma via inhibiting PI3K/AKT signaling. Laryngoscope 2019; 129: E318-E328.
10) Elmore S. Apoptosis: a review of programmed cell death. Toxicol Pathol 2007; 35: 495-516.
11) Pistritto G, Trisciuoglio D, Ceci C, Garufi A, D'Orazi G. Apoptosis as anticancer mechanism: function and dysfunction of its modulators and targeted therapeutic strategies. Aging (Albany NY) 2016; 8: 603-619.
12) Kaminskyy VO, Zhivotovsky B. Free radicals in cross talk between autophagy and apoptosis. Antioxid Redox Signal 2014; 21: 86-102.
13) Charununtakorn ST, Shinlapawittayatorn K, Chattipakorn SC, Chattipakorn N. Potential roles of humanin on apoptosis in the heart. Cardiovasc Ther 2016; 34: 107-114.
14) Diwanji N, Bergmann A. An unexpected friend - ROS in apoptosis-induced compensatory proliferation: Implications for regeneration and cancer. Semin Cell Dev Biol 2018; 80: 74-82.
15) Fresno VJ, Casado E, de Castro J, Cejas P, Belda-Iniesta C, Gonzalez-Baron M. PI3K/Akt signalling pathway and cancer. Cancer Treat Rev 2004; 30: 193-204.
16) Maurya AK, Vinayak M. PI-103 attenuates PI3K-AKT signaling and induces apoptosis in murineT-cell lymphoma. Leuk Lymphoma 2017; 58: 1153-1161.
17) Jiang X, Wang X. Cytochrome C-mediated apoptosis. Annu Rev Biochem 2004; 73: 87-106.
18) Jiang X, Fang L, Wu H, Mei X, He F, Ding P, Liu R. TLR2 regulates allergic airway inflammation and autophagy through PI3K/Akt signaling pathway. Inflammation 2017; 40: 1382-1392.
19) Shi J, Zhang C, Yi Z, Lan C. Explore the variation of MMP3, JNK, p38 MAPKs, and autophagy at the early stage of osteoarthritis. IUBMB Life 2016; 68: 293-302.