Int J Clin Exp Med 2020;13(11):8562-8569
www.ijcem.com /ISSN:1940-5901/IJCEM0115013

Original Article

Effect of platelet-rich plasma on infection markers and JAK/STAT pathway in rabbit models of knee osteoarthritis

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Received May 26, 2020; Accepted July 28, 2020; Epub November 15, 2020; Published November 30, 2020

Abstract: Objective: To investigate the effect of platelet-rich plasma (PRP) on infection and Janus-activated kinase/signal transducers and activators of transcription (JAK/STAT) pathway in rabbit models of knee osteoarthritis (KOA). Methods: Forty-five New Zealand white rabbits were randomly allocated into control group (n=15), model group (n=15) and PRP group (n=15). The left knee joints of rabbits in PRP group and model group were treated with modified Hulth to replicate OA models, while those in the control group only received articular exposure. In PRP group, 0.5 mL PRP prepared by Aghaloo method was injected into articular cavity at the first week after modeling. While in the control group and the model group, intra-articular injection of normal saline (5 mL) was carried out at the 5th week after modeling. Animals were sacrificed after 6 weeks of continuous injection. Infection markers, histological changes (Mankin score), mRNA levels of type II collagen, JAK-3 and STAT-3 in chondrocytes (quantitative real-time RT-PCR), apoptosis of chondrocytes (TUNNEL), and protein levels of JAK-3 and STAT-3 (western-blotting) were monitored. Results: After treatment, levels of infection markers in model group were remarkably higher than those in PRP group and control group; improvement of Mankin score in model group was remarkably lower than that in PRP group and control group; chondrocyte apoptosis in model group was remarkably higher than that in PRP group and control group; mRNA level of type II collagen in model group was remarkably lower than that in PRP group and control group, but protein levels of JAK-3 and STAT-3 were remarkably higher than those in the two groups. Conclusion: PRP effectively reduces the levels of infection markers in rabbit models of KOA and decreases the apoptosis of chondrocytes via activating JAK-STAT pathway.

Keywords: Platelet-rich plasma, knee osteoarthritis, infection marker, JAK/STAT pathway

Introduction

Knee osteoarthritis (KOA) is one of the main causes of joint dysfunction and physical disability in the elderly [1], characterized by articular cartilage degeneration, subchondral sclerosis, cyst and osteophyte formation [2]. These pathological changes generally lead to pain, swelling, and stiffness of the joints, resulting in severe disability and impaired quality of life of patients [3, 4]. Supportive therapies of analgesics, corticosteroids, and mucosal supplements alleviate the symptoms of KOA, but pose serious side effects [5, 6]. Therefore, seeking a treatment with high therapeutic effect is of great urgency.

Platelet-rich plasma (PRP) is an autologous blood product that delivers hyper-physiological concentrations of platelets, growth factors, leukocytes and bioactive proteins (chemokines, cytokines) to the injury site [7]. It has been widely used in sports and musculoskeletal medicine [8] and can restore intra-articular hyaluronic acid, stimulate the synthesis of glycosaminoglycan chondrocytes, as well as balance joint angiogenesis and serve as a scaffold for the migration of stem cells [9]. Janus-activated kinase/signal transducers and activators of transcription (JAK/STAT) pathway, a common intracellular signaling pathway, participates in cell immune regulation, proliferation, apoptosis, differentiation and provides a direct mechanism for extracellular factors to regulate gene expression [10]. It is associated with rheumatoid arthritis, cancer, and many human diseases. Matrine accelerates apoptosis of fibroblast-like synoviocytes in rheumatoid arthritis

Table 1. Primer sequence

	Forward	Reverse
Type II collagen	5'-GCCTTGGTGGAAACTTTG-3'	5'-CCTTGAAATCCTTGCGGT-3'
JAK-3	5'-ATCCTGCCCGTTTATCATTCG-3'	5'-GGTGACAGGTCTCCAGTCCAAA-3'
STAT-3	5'-TGGAAA AGGACATCAGTGGCA-3	5'-CGGGGCGA CAATACTTTCC-3'
GAPDH	5'-CCGTATTCAGCATTCTATGCTCTC-3'	5'-TGGATACACACTCTGGGGCT-3'

by inhibiting the activation of JAK-STAT pathway [11]. Besides, Genkwanin protects against adjuvant-induced arthritis in rats via suppressing the activation of nuclear factor-κB and JAK/STAT pathways, which reduces paw swelling and arthritis indexes, and also suppresses serum inflammatory cytokines [12]. Above all, we suspected that PRP played a protective role against KOA by activating JAK/STAT pathway.

We established rabbit models to observe the effect and mechanism of PRP on KOA, and to figure out the association between the protective effect of PRP and JAK/STAT pathway.

Material and methods

Animal data

MATERIALS: Forty-five healthy adult New Zealand white rabbits (average weight of 3.0-4.5 kg, Zhejiang Academy of Medical Sciences, Hangzhou, China) were raised in a clean environment with free access to water and food (Xietong Organism Jiangsu, China). This experiment was approved by the hospital ethics committee and followed the guidelines for the care and use of laboratory animals [13].

Model preparation

Forty-five New Zealand white rabbits were randomly allocated into control group, model group and PRP group with 15 rabbits each. Modified Hulth was adopted in the model group and PRP group [14]. The rabbits were anesthetized via the ear vein and fixed on the operating table. Following the aseptic protocols, skin preparation, disinfection and draping were carried out on the right knee joint. With the tibial medial condyle as the center, a 2-cm longitudinal incision was made. The skin, subcutaneous and superficial and deep fascia were cut in turn, and the medial collateral ligament was severed. The joint capsule was opened to expose the cavity. The anterior and posterior cruciate ligaments were severed carefully with an ophthalmic scissor, and the medial meniscus was removed. Care was taken not to damage the surface of articular cartilage during surgery. Afterwards, the articular cavity was flushed with 0.1 povidone iodine and 0.9% normal saline, and then the joint capsule, subcutaneous fascia and skin were sutured layer by layer. The wound was bandaged with sterile dressing without fixation. After surgery, 200,000 units of penicillin was injected intramuscularly every day. The dressing was changed for 7 consecutive days to prevent wound infection. On the 15th day after surgery, sutures were removed and the animals were forced to exercise twice a day for 30 min with a distance of ~100 m. The control group received artificial modeling, while preoperative preparation, anesthesia and disinfection procedures were the same as those in model group and PRP group. However, during the surgery, the medial collateral ligament was not severed. The incision was closed after checking whether there was primary disease in the articular cavity, and wound was sutured in the same way as performed in the model group and PRP group (**Table 1**).

PRP preparation

PRP was prepared with two-step centrifugation. 5 mL of arterial blood from rabbit was centrifuged at 1500×g and 4°C for 10 min. Red blood cells 2 mm below the buffy coat were discarded with a syringe. The rest was centrifuged again, and the upper 3/4 part of the serum layer was removed by a syringe, and the rest in the tube was PRP.

Treatment methods

Control group and model group: 0.7 mL of normal saline was injected into the joint from the first week after modeling, once a week for a total of 10 weeks/10 times.

PRP group: 0.5 mL of autologous PRP was injected into the joint from the first week after

modeling, once a week for a total of 10 weeks/10 times.

Outcome measures

Infection markers: Venous blood samples (5 mL) were centrifuged at 1500×g and 4°C for 10 min, and stored in a -70°C refrigerator. Enzyme-linked immunosorbent assay (ELISA) [20] was used to quantify the levels of interleukin-1 (IL-1), IL-6, tumor necrosis factor-α (TNF-α) with corresponding kits (Vector Science Technology Co., Ltd., Wuhan, China, EF0-17842; MultiSciences (Lianke) Biotech Co., Ltd., Hangzhou, China, 70-EK106/2; Jiahui Biotechnology Co., Ltd., Xiamen, China, IQP-163R).

Mankin score: All rats were monitored from the first injection, and Mankin scores were recorded at the 2nd, 4th, 6th, 8th and 10th week. Three rabbits were randomly selected from the two groups at each time point. After anesthesia, the rabbits were sacrificed by air embolism. Subcutaneous tissue was cut to expose the articular cavity and observe the general condition of cartilage at the joint of lateral and medial femoral condyles. Specimens were collected 3 mm from the posterior edge of the medial femoral condyle, along with articular cartilage and subchondral bone (stored in liquid nitrogen), and then the articular cartilage was peeled off. Afterwards, the specimens were fixed in 4% formaldehyde, washed in running water, then embedded in paraffin and sectioned, and stained with safranin-O-fast green for 15 min. After washing gently with deionized water for 3 times and drying, joint histology was scored with Mankin score.

mRNA levels of type II collagen, JAK-3, STAT-3: Quantitative real-time RT-PCR (qRT-PCR) was employed for measurement. Cartilage tissues were taken out and ground to obtain total RNA (TRIzol extraction kit, Xinfan Biotechnology Co., Ltd., Shanghai, China, XFR1030). Then reverse transcription was performed (Protein Innovation Co., Ltd., Beijing, China, BPI01030) in a 10-μL reaction system at 37°C for 20 min and 80°C for 5 sec. Using β-actin as internal reference, the amplification system was 25 μL, and the reaction conditions were 95°C for 3 min, 95°C for 35 s, 40 cycles at 58°C for 35 s and 73°C for 45 s, followed by 73°C for 5 min. The relative mRNA levels of type II collagen, JAK-3 and STAT-3 were calculated by $2^{-\Delta\Delta Ct}$.

Protein levels of JAK-3 and STAT-3: Western blotting was adopted in this section. Cartilage tissues from each group were lysed with 300 μL RIPA buffer (G-Clone Biotechnology Co., Ltd., Beijing, China, EX6020-100 mL) and rubbed for 10 min. After shaking well and standing for 10 min at 4°C, they were centrifuged (14000 r/min) for 8 min to obtain total proteins. Protein concentration was determined by BCA kit (Yuanye Biotechnology Co., Ltd., Shanghai, China, R21250). The total proteins were diluted in 1/5 volume of loading buffer and denatured at 95°C for 5 min. Western blotting steps: The denatured proteins were subjected to 12% SDS-PAGE (Gelatins Biological Engineering Co., Ltd., Shanghai, China, JK-R4883) and placed on a PVDF membrane. Afterwards, the membrane was blocked in 5% skimmed milk powder (Renold Biotech Co., Ltd., Suzhou, China, SL1330-100 mL). After an incubation with primary antibody (1:1000) at 4°C overnight, the membrane was washed to remove the primary antibody. Next, horseradish peroxidase-conjugated goat anti-rabbit secondary antibody (1:1000) was incubated at 37°C for 1 h, followed by three 5-minute PBS rinses. After development and fixing, an image analysis software was used to strictly analyze the gray value of the bands. The relative protein levels of JAK-3 and STAT-3 was the ratio of gray value of target protein and that of the control protein.

Chondrocyte apoptosis: The apoptosis assay was conducted with TdT-mediated dUTP nick end labeling (TUNEL) staining. Paraffin sections were routinely dewaxed and immersed in H_2O_2/methanol solution to inactivate endogenous peroxidase, and then washed and digested with distilled water and 0.1M TBS, respectively. Following labeling and blocking, routine sectioning, color development, hematoxylin re-dyeing, dehydration and mounting were carried out. Under a microscope, chondrocytes with brown granules in the nucleus were considered positive (apoptotic chondrocytes). Each specimen was monitored in 10 random fields of view under a 10×40 magnification microscope. The apoptotic rate of chondrocytes was calculated.

Statistical methods

GraphPad 6 was used for data analysis and graph building. All data were expressed by mean ± standard deviation ($\bar{x}$±sd). Multi-group comparisons were tested by one-way ANOVA

Table 2. General data [n (%)] ($\bar{x}$±sd)

Classification	Control group (n=15)	Model group (n=15)	PRP group (n=15)	F/χ^2	P
Sex				2.312	0.315
Male (%)	9 (60.00)	8 (53.33)	5 (33.33)		
Female (%)	6 (40.00)	7 (46.67)	10 (66.67)		
Age (weeks)	11.23±0.23	11.27±0.32	11.16±0.31	0.554	0.578
Body length (cm)	34.81±1.56	35.06±1.59	34.95±1.57	0.095	0.909
Indoor temperature (°C)	24.12±1.33	23.85±1.24	24.15±0.97	0.289	0.750
Indoor humidity (%)	51.32±2.44	50.77±1.96	50.71±1.93	0.376	0.688
Body mass before modeling (g)	221.43±10.35	227.23±10.55	219.53±9.23	2.385	0.105
Body mass after modeling (g)	209.32±7.12	212.34±7.65	208.73±7.57	1.013	0.371

Table 3. Comparison of infection markers ($\bar{x}$±sd)

Group	n	IL-1 (pg/ml)	IL-6 (pg/ml)	TNF-α (pg/ml)
Control group	15	21.54±5.23	12.49±3.14	10.63±3.18
Model group	15	42.46±8.37	65.23±14.23	78.23±15.35
PRP group	15	24.02±5.54	18.45±3.74	12.45±3.26
F	-	45.890	165.900	260.400
P	-	< 0.001	< 0.001	< 0.001

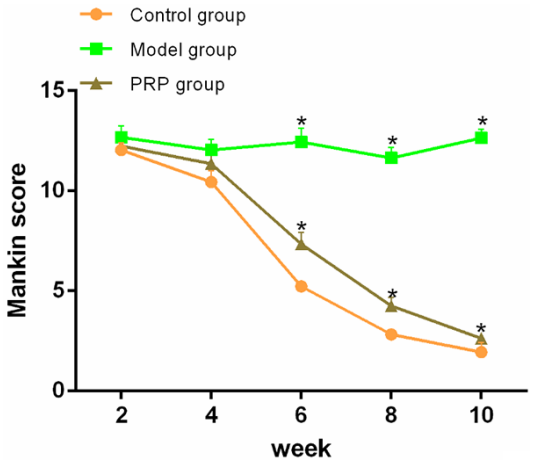

Figure 1. Comparison of Mankin score. The control group presents lower Mankin score than PRP group and model group at the 2nd, 4th, 6th, 8th and 10th week. There is no significant difference between PRP group and model group at the 2nd and 4th week, while that in PRP group is lower than model group at the 6th, 8th and 10th week. Note: *P < 0.05.

(denoted by F), and post-hoc pairwise comparisons by LSD-t test. Expressions at different time-points were analyzed by repeated measurement ANOVA (denoted by F), and post hoc test was conducted by Bonferroni. P < 0.05 indicated a statistically significant difference.

Result

General data

The sex, age, body length, indoor temperature, indoor humidity, and body mass showed no statistical significance before and after modeling in the control group, model group and PRP group (P > 0.05). See **Table 2**.

Comparison of infection markers

The levels of serum IL-1, IL-6 and TNF-α in model group increased, and were higher than those in control group and PRP group (all P < 0.01). See **Table 3**.

Comparison of Mankin score

There was no significant difference in Mankin score between model group and PRP group at the 2nd and 4th week (P > 0.05), but it was higher than that in control group (P < 0.05). The Mankin score in the three groups decreased over time. And it was lower in control group than that in PRP group and model group at the 6th, 8th and 10th week (P < 0.05), and PRP group was lower than model group (P < 0.05). See **Figure 1**.

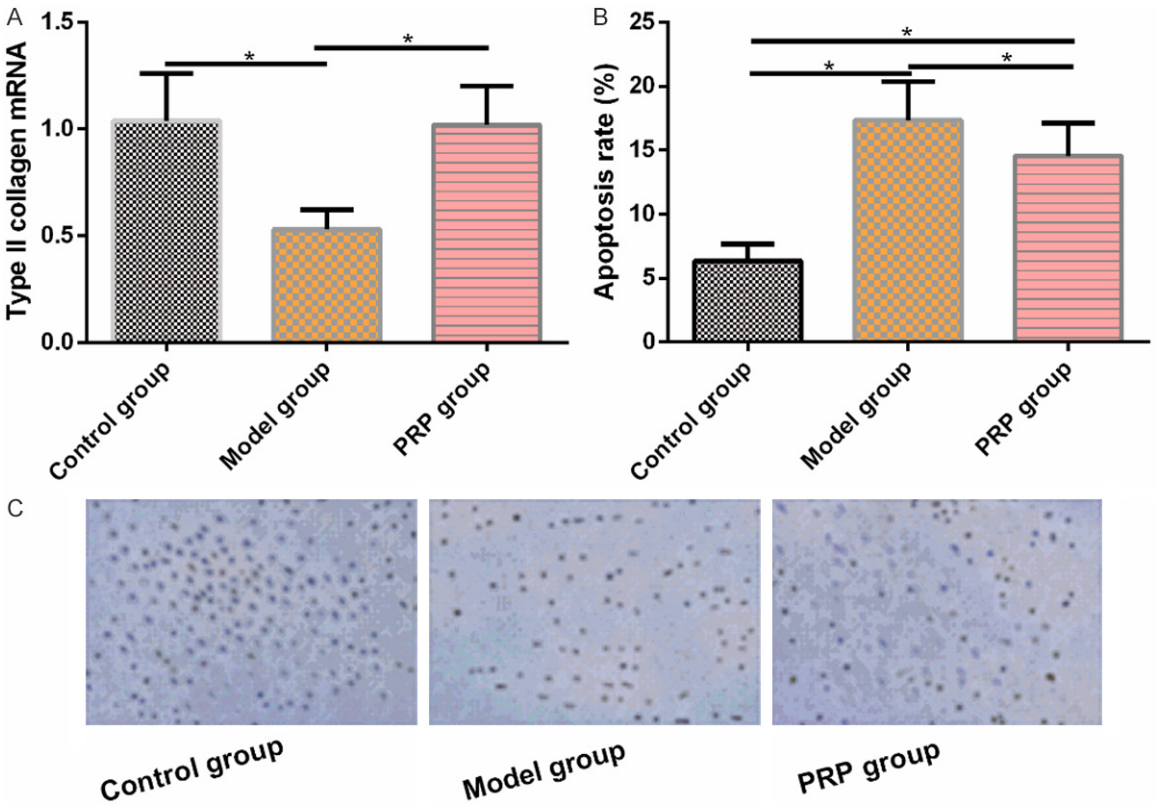

Figure 2. Comparison of mRNA level of type II collagen and chondrocyte apoptosis. A. The mRNA level of type II collagen in model group is significantly lower than that in control group and PRP group. B. The apoptotic rate in model group is significantly higher than that in control group and PRP group. C. Cell apoptosis. Note: *P < 0.05.

Comparison of mRNA level of type II collagen and chondrocyte apoptosis

As shown in qRT-PCR result, the mRNA level of type II collagen in model group was lower than that in control group and PRP group (P < 0.05). The apoptotic rate in model group was higher than that in other two groups (P < 0.05). See **Figure 2**.

Comparison of mRNA levels of JAK-3 and STAT-3

The qRT-PCR revealed that the mRNA levels of JAK-3 and STAT-3 in model group were higher than those in control group and PRP group (P < 0.05), and the level in control group was lower than that in PRP group (P < 0.05). See **Figure 3**.

Comparison of protein levels of JAK-3 and STAT-3

The qRT-PCR found that the protein levels of JAK-3 and STAT-3 in model group were higher than those in control group and PRP group (P < 0.05), and the level in control group was lower than that in PRP group (P < 0.05). See **Figure 4**.

Discussion

KOA, the most common arthritis worldwide, affects the hip, knee and other load-bearing joints and induces joint injury, leading to aggravation of joint structure and insufficient healing [15, 16]. At present, clinical treatments mainly aim to relieve pain and stiffness and maintain function with the assistance of conservative therapies (such as physical therapy, analgesia and surgery) [17]. In this study, PRP was injected into rabbit knees to evaluate its mechanism in KOA, thereby providing theoretical basis for the improvement of this disease.

PRP contains a variety of growth factors (vascular endothelial growth factors and fibroblast growth factors) that are effective chemical attractants and mitogens accelerating wound healing [18-20]. Intra-articular PRP alleviates the symptoms of patients and reduces proinflammatory cytokines by regulating the balance

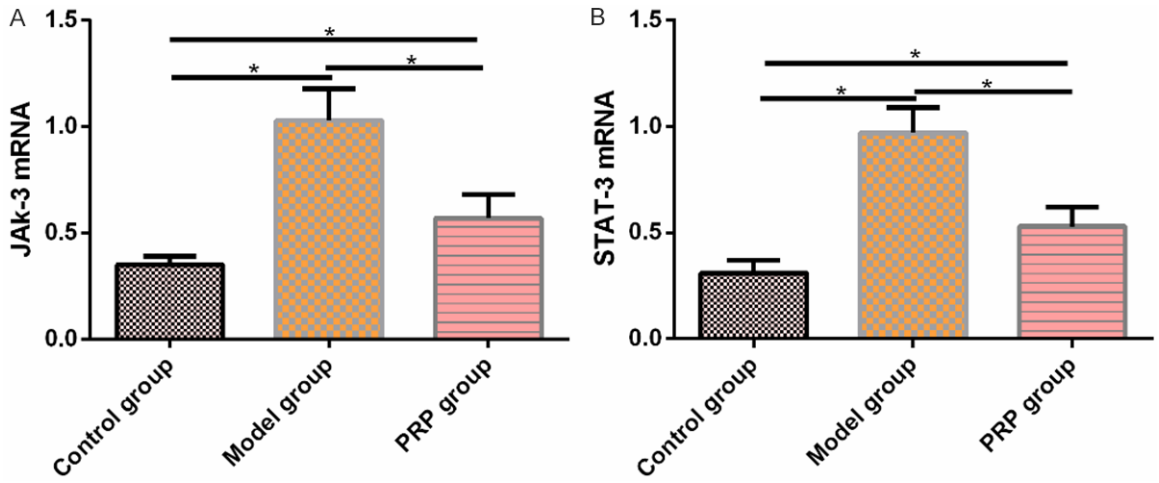

Figure 3. Comparison of mRNA levels of JAK-3 and STAT-3. The mRNA levels of JAK-3 and STAT-3 in model group are significantly higher than those in control group and PRP group, and the level in control group is significantly lower than that in the PRP group. Note: *P < 0.05.

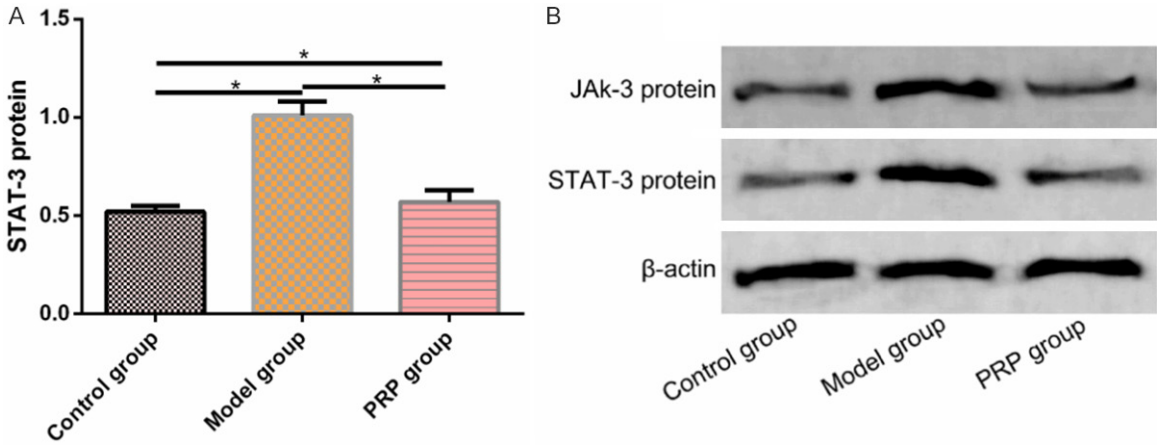

Figure 4. Comparison of protein levels of JAK-3 and STAT-3. The protein levels of JAK-3 and STAT-3 in model group are significantly higher than those in control group and PRP group, and the level in control group is significantly lower than that in PRP group. Note: *P < 0.05.

between pro-inflammatory and catabolic state and anti-inflammatory and anabolic state [21]. We confirmed in this study that the increased IL-1, IL-6 and TNF-α in the rabbit models of KOA were remarkably decreased after PRP intervention, indicating that PRP controls joint inflammation and disease progression by inhibiting the release of serum IL-1, IL-6 and TNF-α. Mankin score is used to identify manifestations of cartilage damage and degeneration, as well as structural integrity, cellularity, cloning and proteoglycan loss through individual parameters [22]. In this study, control group presented lower Mankin score at the 2nd, 4th, 6th, 8th and 10th week than PRP group and model group. The difference was not significant between PRP group and model group at the 2nd and 4th week, while that in the PRP group was significantly lower than model group at the 6th, 8th and 10th week. Therefore, PRP plays a role in repairing articular cartilage.

Type II collagen is closely associated with OA [23]. Our findings demonstrated that the mRNA level of type II collagen in model group was remarkably lower than that in control group and PRP group, suggesting that PRP down-regulates type II collagen in chondrocytes. Chondrocyte apoptosis was also evaluated in our study, and it turned out that the apoptotic rate in model

group was remarkably higher than that in control group and PRP group. This indicates that PRP reduces the apoptosis of chondrocytes and maintains joint structure. JAK-STAT pathway is essential in the pathogenesis of arthritis [24]. For example, Qiao et al. reported that JAK-STAT pathway can not only affect the proliferation and apoptosis of chondrocytes, but also mediate the release of various inflammatory factors [25]. The mRNA and protein levels of JAK-3, STAT-3 in the model group were found to be higher than those in the control group and PRP group, and control group was remarkably lower than PRP group. Thus, the enhancement of JAK-STAT pathway may be one of the causes leading to the increase of inflammatory cells in KOA, and PRP inhibits JAK-STAT pathway in the treatment process.

To sum up, PRP effectively reduces the levels of infection markers and decreases the apoptosis of chondrocytes in KOA via activating JAK-STAT pathway. However, there is still room for improvement. For example, there may be other ways to investigate the protective mechanism of PRP against KOA, which will be supplemented in the future explorations.

Conclusion

To sum up, PRP effectively reduces the levels of infection markers and decreases the apoptosis of chondrocytes in KOA via activating JAK-STAT pathway.

Disclosure of conflict of interest

None.

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