Research Progress on the Application of Icariin in Osteoarthritis Treatment

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Abstract: Osteoarthritis (OA) is a multifaceted bone and joint disease with degenerative changes of articular cartilage. Therefore, the current research on the etiology of OA mainly focuses on the etiology of articular cartilage degeneration. Clarifying the pathogenesis of OA from the molecular level has become an important research topic in the field of orthopedics. Its main pathological features are the decrease of chondrocyte metabolic activity, cartilage matrix degradation, and osteophyte formation. Icariin (ICA) is the main active monomer of epimedium, a traditional Chinese medicine, and the pharmacological research has revealed favorable effects of ICA on the bone system. ICA can promote the proliferation of chondrocytes and inhibit the apoptosis of chondrocytes, alleviate the degradation rate of cartilage matrix, and effectively protect articular cartilage. This review also expounds the mechanism of promoting cartilage repair.

Keywords: Osteoarthritis; Articular cartilage; Icariin; Cartilage cells

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1. Pathogenesis of osteoarthritis

The histological changes of articular cartilage in osteoarthritis (OA) are the significant characteristics of the disease, mainly including bone and cartilage structural changes that start from the edge of the skeletal component of the joint to induce significant changes to the skeletal appearance, proteoglycan, and the cellular matrix degeneration [1]. When OA occurs, chondrocytes undergo changes in proliferation, viability and secretory characteristics. In addition, cytokines, growth factors and other factors are related to the pathogenesis of OA [2].

2. Pharmacological analysis of icariin

Modern pharmacological research is mainly carried out from the aspects of cardiovascular system, reproductive system, bone metabolism and so on. As the most effective monomer of epimedium, icariin (ICA) can promote the proliferation and differentiation of osteoblasts and induce osteoclast apoptosis. ICA can repair cartilage well, promote chondrocyte proliferation, inhibit chondrocyte apoptosis and inhibit the expression of inflammatory cytokines [3]. Studies found that ICA can inhibit OA by inhibiting NLRP3/caspase-1 signal transduction-mediated apoptosis in NL model in vivo and in vitro [4]. This study suggests that ICA has a good therapeutic effect on the pathogenesis of OA.
3. Effect on chondrocytes
The formation and maintenance of articular cartilage depend on chondrocytes. In mature tissues, chondrocytes account for less than 10% of the total tissue volume and are responsible for maintaining the matrix. As a static and fully differentiated cell, chondrocytes maintain the homeostasis of human articular cartilage, and when chondrocytes degenerate, OA would eventually be resulted [5]. Chondrocytes are metabolically active and can respond to many environmental stimuli, including growth factors, interleukin (IL), matrix molecules and so on. Although chondrocytes are generally in a stable state, the response to some factors can lead to matrix degeneration, such as IL-1.

3.1. Promoting chondrocyte proliferation
ICA can promote chondrocyte proliferation and inhibit apoptosis by promoting Wnt/β-catenin signaling pathway. Thus, ICA promotes chondrocyte proliferation in a concentration- and time-dependent manner. Experiments have shown that ICA can increase the viability of chondrocytes and the synthesis of extracellular matrix. ICA promotes the viability of chondrocytes mainly by promoting hypoxia-inducible factor 1-alpha (HIF-1α) expression and anaerobic glycolysis [6]. It has been demonstrated that ICA upregulated HIF-1α expression and glycolysis in chondrocytes, and maintained chondrocyte phenotype. Another member of the HIFs family, HIF-2α, also plays an important role in OA, but the mechanism remains unclear.

3.2. Inhibiting chondrocyte apoptosis
Zhao [7] cultured human osteoarthritis chondrocytes in vitro and treated the chondrocytes with different concentrations of ICA. The measured results showed that the apoptosis rate of human osteoarthritis chondrocytes was significantly reduced after ICA treatment at 0 µg/mL, 100 µg/mL, and 150 µg/mL, indicating that ICA could inhibit chondrocyte apoptosis. Nuclear factor kappa B (NF-κB) can induce the expression of a series of genes after being stimulated by pro-inflammatory factor, leading to OA. Therefore, a comprehensive understanding of the function or regulation of NF-κB in OA pathology will contribute to the development of targeted therapeutic strategies [8].

4. Effect on bone cells
Subchondral bone is the auxiliary structure of joint. Recent studies have found that abnormal subchondral bone remodeling plays a great role in the occurrence and pathogenesis of OA, and this process occurs before articular cartilage lesions. The results showed that ICA inhibited the differentiation of osteoclast precursor cells into osteoclasts and the expression of various genes related to osteoclast formation and bone resorption. Under normal conditions, osteoclasts are the only cells that can absorb bone. Osteoblasts are mainly responsible for bone formation, and they jointly dominate subchondral bone remodeling [9]. Jiang et al. [10] selected logarithmic growth mouse precursor osteoblast cell line (MC3T3-E1) through in vitro cell experiment, intervened with different concentrations of ICA (10⁻⁶-10⁻³ mmol/L), determined the optimal concentration of ICA, and then treated the MC3T3-E1 cells with optimal concentration, which were divided into three groups: control group, ICA group, and ICA + 3-mA group (autophagy inhibitor). The results showed that ICA could promote osteoblast differentiation by improving autophagy.

5. Effect on bone mesenchymal stem cells
At present, among the many methods for the treatment of OA, soft tissue engineering is a very promising technology. Bone mesenchymal stem cells (BMSCs) are mesenchymal stem cells isolated from skeletal muscle and play a very important role in cartilage repair [11]. A certain concentration of ICA can promote the proliferation of BMSCs and promote osteogenic differentiation by activating Wnt classical pathway.
Li et al. [14] used density gradient centrifugation to isolate bone marrow mononuclear cells and routinely subculture rabbit BMSCs. The second-generation rabbit cells were used for experiments, and different concentrations of ICA were given as intervention. The proliferation was analyzed by MTT method, the extracellular alkaline phosphatase activity of the supernatant was measured, and the differentiated osteoblasts were measured by alizarin red. The results showed that 48 hours of ICA treatment enhanced bone marrow mesenchymal stem cells and improved the differentiation ability of BMSCs. Based on the results, ICA at the concentration of 1 μmol/L is the best.

6. Effect on cell matrix
Extracellular matrix is a noncellular three-dimensional polymer network composed of collagen, proteoglycan/glycosaminoglycan, elastin, fibronectin, laminin and several other glycoproteins. It provides structural support for cells and tissues, provides nutrition for chondrocytes, provides conduction signals for cells, and is remodeled by several matrix degrading enzymes under pathological and normal conditions [15-16]. Matrix metalloproteinases (MMP), as a large class of protease with similar structure, can cause extracellular matrix degradation, induce cartilage degradation, accelerate the decomposition of collagen reticular structure, and further accelerate cartilage degeneration, all of which eventually lead to OA [17]. The study of Zeng et al. [18] showed that when IL-1β was applied to SW1353 chondrosarcoma cells to simulate the microenvironment of OA, ICA was used to treat the cells and the expression of MMP-1, MMP-3 and MMP-13 was evaluated by quantitative reverse transcription method. The results showed that ICA could inhibit the expression of MMP-1, MMP-3 and MMP-13 through MAPK pathway, so as to protect cartilage.

7. Summary and prospect
As a time-related joint degenerative disease that aggravates with age, it is believed that the incidence rate of OA will become higher, which will seriously affect the quality of life of the middle-aged and elderly populations. The main pathological feature of OA is the degeneration and regression of articular cartilage. However, the formation and maintenance of articular cartilage depend on chondrocytes. Compared with the matrix, chondrocytes have fewer cells, so their metabolic activity is low and they have no self-healing ability. Therefore, OA degeneration is a challenging medical problem. Also, surgical treatment is not suitable for everyone, and the search for new drugs has become increasing imperative. Traditional Chinese medicine monomers are safe and effective in the treatment of OA. It is applicable to a wide range of people, and has been gaining traction. ICA can promote the proliferation and differentiation of chondrocytes, inhibit the apoptosis of osteoclasts, and prevent OA by regulating relevant inflammatory factors, inhibiting the degradation of extracellular matrix and promoting the osteogenic differentiation of bone marrow mesenchymal stem cells. In view of the above, we understand that many problems still remain to be solved, such as the optimal range, concentration, optimal action time of the therapeutic compounds of interest.

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Disclosure statement
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