

Research Progress of Traditional Chinese Medicine Intervention on HIF-2 α in the Prevention and Treatment of Knee Osteoarthritis

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Abstract: Knee osteoarthritis (KOA) is the most common chronic, degenerative and progressive osteoarthritis in clinical practice, which mainly manifests as knee pain, deformity and even joint function loss. With the advent of the global aging era, its incidence continues to increase, seriously occupying the medical resources of various countries. Its pathogenic factors are complex and its pathogenesis is not clear. How to effectively prevent and cure it has always been a hot topic in the medical field. Recent studies have found that the expression level of hypoxia inducible factor (HIF) -2 α plays an important role in regulating chondrocyte homeostasis, which is involved in the degradation of chondrocyte extracellular matrix and the generation of subchondral bone vessels, and accelerates cartilage degeneration. Studies have shown that the active ingredients of traditional Chinese medicine can regulate the expression of HIF-2 α and slow down the development of knee osteoarthritis. This article reviews the related research on the prevention and treatment of knee osteoarthritis by the intervention of traditional Chinese medicine on HIF-2 α expression, so as to provide scientific clinical basis and treatment plan for the later research on the treatment of KOA with traditional Chinese medicine.

1. Introduction

KOA is a chronic degenerative cartilage disease induced by trauma, aging, hormones, obesity, genetics and other factors [1, 2]. The pathological features are articular cartilage injury, subchondral bone sclerosis, osteophyte formation, synovial inflammation and ligament lesions, leading to the clinical manifestations of knee pain, stiffness, swelling, deformity and limited mobility. Recent epidemiological surveys show that KOA is more common in middle-aged and elderly women, with a high disability rate [3]. With the acceleration of population size and aging, its incidence rate increases rapidly, which seriously reduces people's quality of life and increases the country's medical investment. The pathogenesis of KOA has not been elucidated. Most scholars believe that KOA is related to metabolic disorders of articular chondrocytes caused by non-physiological mechanical load stimulation and local inflammatory response. Study found HIF plays an important

role in cell metabolism regulation, it through the activation or inhibition of upstream and downstream gene transcription maintains steady cartilage cells, which HIF - 2 alpha as metabolic regulation factor, can pass to VEGF, MMP, NAMPT and Fas gene activation, involved in the degradation of extracellular matrix of cartilage, subchondral bone is the formation of blood vessels, It is closely related to the degeneration of articular cartilage and plays an important role in the pathophysiology of KOA [4]. Chinese medicine considers KOA as "arthralgia syndrome", "bone arthralgia" and other diseases. In recent years, Chinese medicine has a good clinical effect on KOA with few side effects, which is widely accepted by clinicians and patients. With the development of multi-disciplinary integration of Chinese medicine and pharmacology, the mechanism of action of Chinese medicine monomer effective components in the treatment of diseases has become a research hotspot [5]. Many studies have explored the intervention of Chinese monomers, drug pairs and extracts on HIF-2 α protein expression level. This article summarizes the characteristics of HIF-2 α protein and its relationship with KOA, as well as the mechanism of traditional Chinese medicine monomers and drugs to intervene HIF-2 α in the treatment of KOA.

2. HIF - 2 alpha

Under hypoxia, the human erythropoietin gene is activated by a DNA-binding protein that promotes transcription, named hypoxia-inducible factor. HIFs is considered to be the main regulatory factor of body tissues and cells adapting to oxygen environment under hypoxia or hypoxia environment, and belongs to the basic helical loop helix (bHLH) per-Arnt-SIM (PAS) transcription factor family. HIFs is a heterodimeric protein complex composed of α and β subunits (hif- α and hif- β). Hif- α is the functional group with a molecular weight of 120kD, and its stability is regulated by oxygen concentration. Hif- β , also known as Aryl hydrocarbon re-ceptor nuclear translocator (ARNT), has a molecular weight of 91-94kD. It is located in the Q21 region of human chromosome 1 and plays a structural role. Stable intracellular expression is independent of oxygen concentration. Each subunit has three subtypes (HIF-1, HIF-2 and HIF-3), which are α -subunit (HIF- α , including HIF-1 α , HIF-2 α /EPAS1 and HIF-3 α) and β -subunit (HIF- β , including HIF-1 β /ARNT1, ARNT2 and ARNT3) [6, 7].

Under normoxic conditions, hydroxylation of the HIF-2 α subunit is catalyzed by Prolyl hydroxylase domain (PHD), which is further ubiquitylation by ubiquitin ligase E3 including VHL (Vonhippel-Lindau) factor, and is finally degraded by the proteasome. Under hypoxia or hypoxia, PHD enzyme activity decreases, HIF-2 α cannot be modified by hydroxylation and ubiquitination, is activated and expressed, and rapidly accumulates, transfers to the nucleus, and binds to HIF- β . By binding to the hypoxia-responsive element (HRE), the transcription of target genes is activated so that cells can adapt to the current hypoxia or hypoxia microenvironment [8]. Studies have found that HIF-2 α plays an important role in brain and cardiovascular development [9, 10], but it can also induce a series of diseases. For example liver adipose disease, tumor and so on. Recently, with the in-depth study of domestic and foreign scholars, it has been found that HIF-2 α can inhibit chondrocyte maturation and play a role as a catabolic regulator in bone remodeling, which is crucial for maintaining bone homeostasis [11-13]. This may become a research direction for the treatment of bone metabolic diseases.

3. HIF - 2 alpha and KOA

KOA is a degenerative disease of articular cartilage in middle-aged and elderly people, which is mainly caused by abnormal mechanical stimulation, inflammation and immune changes. Although the pathogenesis of KOA is still unclear, domestic and foreign scholars believe that the pathogenesis of KOA is caused by the imbalance between synthesis and degradation of articular

chondrocytes, chondrocyte extracellular matrix, and subchondral bone. With the development of multidisciplinary crossover, various molecules and signaling pathways have been shown to be involved in the pathophysiology of KOA [14]. Articular cartilage consists mainly of chondrocytes and cartilage matrix (type ii collagen and proteoglycans). Articular cartilage is a highly differentiated connective tissue that does not contain blood vessels, lymph and nerves. Cartilage cells of oxygen and nutrients can only rely on synovial fluid and the subchondral bone peripheral vascular proliferation, but a large number of studies have shown that the joint cavity is a closed group, generally in the inferior vena at low oxygen environment, including cartilage surface around the oxygen concentration is often oxygen under 6% ~ 10% only, and the middle and deep cartilage chondrocytes oxygen content is only 1% ~ 6% [15]. At the same time, abnormal mechanical load stimulation causes a large number of inflammatory cells to migrate and aggregate, which seriously reduces the oxygen content in the joint cavity. Pressure can up-regulate the expression of HIF, and hypoxia can activate the expression of HIF [16]. Recent studies have found that the expression level of HIF-2 α protein has a major regulatory effect on chondrocyte homeostasis and significantly promotes the development of KOA. Among them, infiltration of inflammatory factors, degradation of cartilage extracellular matrix and generation of subchondral bone vessels are considered to be the primary factors of KOA [17]. Liu et al. [18] found that high expression of HIF-2 α could promote the expression of MMP-13 in articular cartilage and accelerate the degradation and degeneration of cartilage matrix. Moreover, the expression level of HIF-2 α significantly promotes the expression of VEGF, leading to the formation of subchondral bone vessels, and both of them synergistically promote the development of KOA. Study found that in KOA cartilage ZhongYan amide phosphoribosyltransferases transferase (nicotinamide phosphoribosyltransferase, NAMPT) is nicotinamide purine nucleotides (nicotinamide guanine dinucleotide, NAD⁺) remedies the rate-limiting enzyme in the synthesis pathway and acts as an inflammatory cytokine [19]. As a direct target of HIF-2 α , NAMPT can directly up-regulate MMP-3, MMP-2 and MMP-13 in articular chondrocytes, thereby activating the activities of downstream catabolic factors of HIF-2 α . It has been confirmed that eNAMPT level is closely related to the pathogenesis of KOA. ENAMPT accelerated the progress of KOA by inhibiting proteoglycan synthesis and increasing the expression of metalloproteinases in human articular cartilage. Fatty acid synthase (Fas) is a member of tumor necrosis factor family, which can promote chondrocyte apoptosis, and it was confirmed that HIF-2 α accelerates chondrocyte destruction in KOA patients by directly upregulating the expression of Fas gene. Upregulated HIF-2 α contributes to the development of osteoarthritis by mediating primary ciliary loss [20]. Zhou et al. [21] induced mice to form a KOA model by intrarticular injection of HIF-2 α overexpression vector, and detected increased expression of HIF-2 α in cartilage, indicating that HIF-2 α is a key mediator of cartilage destruction and KOA development.

Studies have shown that inhibiting the expression level of HIF-2 α can reduce the expression of MMP and subsequently reduce cartilage degradation. Studies have found that osteopontin (OPN) inhibits the expression of HIF-2 α mRNA in OA chondrocytes and plays an important role in maintaining chondrocyte homeostasis. Studies have found that Mithramycin A (MitA) is an aureus-type antitumor antibiotic and an inhibitor of HIF-2 α protein expression, thereby reducing the expression of MMP, reducing the degradation of chondrocytes and improving the process of KOA [22]. The IKK inhibitor BMS-345541 can regulate the development of OA induced by knee surgery in mice. Immunohistochemical analysis of the treated cartilage showed that the phosphorylation of I κ B α was significantly inhibited, and the expression of HIF-2 α was also significantly inhibited. Slowing down the development of KOA [23]. In conclusion, the expression level of HIF-2 α protein can maintain the normal process of synthesis and degradation of chondrocytes, and the intervention of HIF-2 α signaling pathway may be a novel method to prevent and treat KOA.

4. Intervention of traditional Chinese medicine on HIF-2 α

4.1. Traditional Chinese Medicine monomer

Curcumin (Cur) is a polyphenolic compound extracted from turmeric root. Modern pharmacological studies have found that Curcumin has strong antioxidant, anti-microbial, anti-inflammatory and anti-cancer activities [24]. It's often used to treat cancer. Recent studies have found that [25] curcumin can promote the proliferation of chondrocytes, inhibit the apoptosis of chondrocytes, inhibit the destruction of cartilage by inflammatory factors, regulate the oxidative stress response of cartilage matrix, and maintain the balance of the internal environment of articular cartilage. Curcumin can be used as a preventive and therapeutic drug for KOA. Studies have shown that curcumin can promote cell viability. Cell experiments have found that curcumin can reduce the content of HIF-2 α in a dose-dependent manner, proving that curcumin improves cartilage destruction by promoting the production of collagen 2A1. It also inhibited the phosphorylation of HIF-2 α , matrix metalloproteinase 3, RUNT-related transcription factor 2, vascular endothelial growth factor, I κ B α and NF- κ B p65. It was demonstrated that curcumin inhibits the activation of NF- κ B/HIF-2 α signaling pathway to regulate ECM homeostasis and inhibit chondrocyte apoptosis to alleviate the development of KOA [26]. The pathological features of KOA are cholesterol accumulation in chondrocytes, cartilage degeneration, extracellular matrix (ECM) destruction and joint dysfunction [27]. And curcumin, a chemical that lowers cholesterol levels in people with KOA, can also inhibit the progression of KOA. However, high concentrations of curcumin can also induce apoptosis in normal chondrocytes. Further studies are needed to determine the safe and effective dose of curcumin.

Osmanthus, also known as methoxy-parvaxol, is the highest content of coumarin in dried and mature fruits of umbel plant *Cnidium monnieri* (L.) Cuss. Traditional medicine believes that osmanthus has the effect of warming the kidney and strengthening the Yang, removing wind and dampness. Modern pharmacological studies have shown that osmanthus has anti-arrhythmia, anti-thrombosis, anti-osteoporosis, anti-inflammatory, anti-oxidation and hormone-like effects [28]. Recently, osmanthus has been found to have a protective effect on articular cartilage. Osmanthus may be considered as a potential component in the treatment of KOA. The chondroprotective effect of osmanicin in a mouse model of MIA-induced osteoarthritis (OA) can be explained by inhibiting OA-induced upregulation of NF- κ B and HIF-2 α and downregulating COX-2 and RUNX2, leading to downregulation of MMP-13, Syndecan IV and ADAMTS-5 [29]. In addition, osmanthus may have anti-inflammatory and analgesic effects due to COX-2 inhibition. The specific mechanism of the treatment of KOA needs to be further studied, and its efficacy and safety should be tested.

D-mannose has anti-inflammatory effect and has therapeutic effect as a non-antibiotic treatment for recurrent urinary tract infection [30]. OA mouse model induced by anterior cruciate ligament transection (ACLT) in vivo and chondrocytes in KOA microenvironment induced by interleukin-1 β (IL-1 β) exposure were studied in vitro. Combined with the gain and loss of *Epas1* gene function, histological, immunofluorescence, quantitative RT-PCR, Western blotting, cell viability and flow cytometry experiments showed that D-mannose played a protective role in cartilage by attenuating the sensitivity of chondrocytes to iron death and reducing the progression of OA [31]. Hif-2 α was identified as the central mediator of D-mannose-induced chondrocyte iron death resistance. In addition, overexpression of HIF-2 α by intra-articular injection of AD-EPAS1 in chondrocytes abolished the chondroprotective effect of D-mannose during OA progression and abolished the effect of D-mannose as an inhibitor of iron death. It is suggested that D-mannose alleviates the development of osteoarthritis by inhibiting the HIF-2 α -mediated sensitivity of chondrocytes to iron death.

4.2. Traditional Chinese medicine pairs

Traditional Chinese medicine thinks that KOA is mostly for liver and kidney deficiency, Qi stagnation and blood stasis syndrome, traditional Chinese medicine treatment is mainly to tonifying kidney and promoting blood circulation. Traditional Chinese medicine believes that the Chinese medicine Panax notoginseng has the effects of nourishing and strengthening the body, promoting blood circulation and removing blood stasis, reducing swelling and relieving pain, and stopping bleeding. The cooked rehmannia rehmannia has mild temperature and sweet taste, and has the effects of nourishing Yin and nourishing blood, enriching essence and filling pulp. Jhun et al. [32] gavage the extract YH23537 of Panax notoginseng and Rehmanniae rehmanniae into the rat KOA model, observed histopathology, immunohistochemistry and random polymerase chain reaction analysis, and found that compared with the normal group, the degree of cartilage damage in rats was reduced. YH23537 inhibited the increased expression of metalloproteinase 3, nitrotyrosine, IL-1 β and IL-6 in KOA joints. Furthermore, the protein levels of NF- κ BP65 and HIF-2 α in joint tissues were decreased, and the tissue inhibitors of metalloproteinase TIMP-1 and TIMP-3 were up-regulated. It is suggested that the extract YH23573 of Rehmannia rehmannia plays an analgesic and cartilage protective role in KOA by inhibiting oxidative damage, inflammatory mediators and inducing anabolic factors.

5. Summary and outlook

With the aging of the population, the incidence of KOA is increasing rapidly, and there is no effective treatment. Its treatment is mostly analgesic, such as oral acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) and glucosamine, corticosteroid injections and hyaluronic acid (HA) injections by intra-articular injection. Although with the rapid development of biological tissue engineering, stem cells and exosome injection therapy have also achieved certain effects, the current technology is still imperfect and the high cost makes it difficult to apply it into clinical practice on a large scale [33]. In the end stage of KOA, joint replacement surgery has to be chosen to improve the quality of life. However, the risk, cost and duration of prosthesis use make the choice of treatment questionable. With the 2019 Nobel Prize in physiology or medicine for the heterogeneous dimers hypoxia inducing factor (HIF) since the groundbreaking discovery, mechanism of how HIF mediated diseases get in-depth exploration of the researchers at home and abroad, the study found that HIFs can regulate the expression of related genes and proteins involved in, maintain steady [34] cartilage cells. As a metabolic regulator, HIF-2 α can degrade chondrocyte extracellular matrix, induce chondrocyte apoptosis and accelerate the formation of subchondral bone blood network through the activation of VEGF, MMP, NAMPT and Fas genes, leading to cartilage sclerosis and degeneration and aggravating the process of KOA. Interestingly, HIF-1 α , another member of the HIF family, is highly expressed under hypoxia or hypoxia, and can promote mitophagy in chondrocytes to inhibit the degradation of extracellular matrix and maintain the cell phenotype [35], which have exactly opposite effects on chondrocytes. Does downregulation of HIF-2 α inhibit the expression of HIF-1 α and destroy chondrocyte homeostasis, resulting in cartilage degeneration [36]? Regulation of the level of HIF-1 α and HIF-2 α may be a way to treat KOA. Regulation of HIF may be a therapeutic option for KOA. Chinese medical treatment of knee osteoarthritis has its own unique views, in the treatment of a clear therapeutic effect. Some scholars have found that traditional Chinese medicine can regulate the expression of HIF-2 α [37], which may be one of the important mechanisms for the prevention and treatment of knee osteoarthritis in Chinese medicine.

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