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Investigation of the Intervention Mechanism of Traditional Chinese Medicine in Knee Osteoarthritis Based on the Focal Cell Death Theory

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Abstract: ***Knee osteoarthritis (KOA) is a common orthopaedic disease in middle-aged and elderly people, and its pathogenesis has not been fully understood. Cellular pyroptosis, a non-apoptotic programmed cell death, is widely implicated in the onset, development and progression of many diseases. TCM intervenes in the treatment of KOA by inhibiting the production of cellular pyrolysis to reduce osteoarthritis, chondrocyte death and synovial tissue lesions. In this paper, we will review the pathway of cellular pyroptosis, cellular pyroptosis-related factors mediating the development of KOA, and Chinese medicine intervention in KOA based on the theory of cellular pyroptosis according to the relevant studies at the domestic and international level, so as to provide new ideas for Chinese medicine intervention in the treatment of KOA.***

Keywords: Knee osteoarthritis, Cell pyroptosis, Traditional Chinese Medicine, Intervention mechanism**.**

1. Introduction

Knee osteoarthritis (KOA) is a common disease in orthopaedics that is mainly characterised by joint swelling and pain, reduced mobility and a high disability rate. Studies have shown that the prevalence of this disease in the population is as high as 8.1% [1], and the prevalence of this disease in women is 10.3%, which is significantly higher than the prevalence in men, which is 5.7% [2], but its aetiology and pathogenesis are still not clear. KOA belongs to the category of 'bone paralysis' in Chinese medicine, and the cause of the disease is deficiency of the liver and kidney, A deficiency of qi and blood and the reappearance of pathogens from the wind, cold and damp [3]. Some scholars [4] believe that wind, cold and dampness pathogens are the external causes of KOA, and the internal causes of the disease is due to prolonged strain on the human body, which damages the vital energy and leads to the insufficiency of the liver and kidneys. Therefore, TCM treatment of KOA is mainly based on nourishing the liver and kidneys, tonifying the emptiness and treating the root cause, supplemented by dispersing the wind pathogen and removing dampness pathogen, invigorating the blood circulation and removing blood stasis, as well as treating the branch symptoms. Pyroptosis is a specific non-apoptotic mode of pro-inflammatory programmed cell death, a natural immune response mediated by cysteine aspartate protease (Caspase) [5], Cellular pyroptosis was first discovered in 1992 and the concept of 'pyroptosis' was introduced in 2001 [6,7], which is manifested by continuous swelling of cells, formation of pyroptotic vesicles, rupture of cell membranes and release of inflammatory factors, resulting in an immune response, such as the release of interleukin-1β (IL-1β) and interleukin-18 (IL-18), causing severe inflammatory reactions [8].

Cellular death has been found to be present in the development of many diseases, including cardiovascular and cerebrovascular diseases and KOA, and plays an important role in the evolution of such diseases [9, 10]. Currently, there is a lack of international research on the correlation between cellular death theory and KOA. This paper will provide new clinical ideas and references for the prevention and treatment of KOA by TCM from the perspective of combining cellular death theory and traditional Chinese medicine.

2. Pathways of Cellular Pyrokinesis

2.1 Classical Pathway

The classical pathway of cellular pyroptosis is mainly based on Caspase-1 of the Caspase family, which is a key link in the assembly of inflammatory vesicles, thus further inducing the occurrence of cellular pyroptosis [11]. Inflammatory vesicles, are composed of pattern recognition receptors (PRRs), apoptosis-associated speck-like proteins (ASCs) and the effector protein pro-caspase-1 (caspase-1 precursor) [12]. Inflammasome assembly ultimately cleaves pro-caspase-1 to catalytically active cysteine protease 1 (caspase-1) and cleaves Gasdermin D (GSDMD) protein to release its lipolytic N-terminal structural domain (GSDMD-N) to induce perforation of the cell membrane and release of cellular contents [13, 14]. In addition, caspase-1 activated by inflammatory vesicles cleaves IL-1β and IL-18 precursors, generates active IL-1β and IL-18, and then releases them to the extracellular compartment through the cell membrane pore, causing inflammatory cell aggregation and inducing cellular cellular death, which contributes to the development of inflammation [15].

2.2 Non-classical Pathways

The non-classical pathway is mediated by caspase-4/-5/-11, a lipopolysaccharide (LPS) that activates caspase-4/-5/-11 [16], which shears and activates the GSDMD, forming a plasma membrane pore and causing cellular death. Activated caspase-11 cleaved the N-terminal domain of GSDMD, and the N-terminal side of GSDMD directly aggregated on the cell membrane to rupture the cell membrane, causing cell death; On the other hand, the active protein formed through the

N-terminal structural domain of GSDMD activates the inflammatory vesicle NLRP3 to activate caspase-1, which mediates the production of inflammatory factors, such as IL-1β and IL-18, and causes an inflammatory response [17].

3. Cellular Pyroptosis-related Factors Mediate the Development of KOA

DONG W [18] et al. found that the pathological process of KOA was closely related to the occurrence of cellular pyroptosis through their study. KOA is a common chronic aseptic inflammatory disease with a complex pathomechanism involving a variety of joint tissues, including cartilage and synovium, which undergo abnormal changes and can affect the entire joint structure [19].

3.1 NLRP3 Mediates KOA Development

NLRP3, a key protein in cellular pyroptosis, is present during the development of KOA. Synovial tissue is a connective tissue that connects bones, muscles, joint capsules, menisci and tendons in the joints [20], and is capable of secreting synovial fluid, lubricating and repairing joint injuries, as well as protecting the soft tissues mentioned above [21]. In the stage of KOA, synovial lesions may arise earlier than in other affected tissues [22], and the inflammatory response induced by the pathological mechanism is closely related to cellular pyroptosis. NLRP3 protein levels were shown to be more than 5-fold higher in KOA patients than in study controls [23]. NLRP3, which is present in synovial fluid, is closely associated with synovial histopathology [24] and is capable of inducing synovial inflammation, which is the classic pathway of cellular pyroptosis via NLRP3 inflammatory vesicles. NLRP3 can promote the activation of caspase-1, which in turn produces a large number of inflammatory factors such as IL-1β and IL-18, resulting in the aggregation of inflammatory cells, which promotes the death of cells and leads to inflammation, causing joint swelling and pain, and accelerating the progression of KOA; Cartilage is a special connective tissue composed of chondrocytes, and one of the main functions of cartilage is to absorb and dissipate mechanical loads. In KOA, when abnormal mechanical stresses stimulate cartilage, damage-associated molecular patterns can be generated through mitochondrial dysfunction and other pathways(Damage-Associated Molecular Patterns, DAMPs). which can be recognised by PRR and activate the assembly of intracellular NLRP3 inflammatory vesicles [25], resulting in activated NLRP3 to further promote the self-cleavage and cleavage maturation of pro-Caspase-1 to form catalytically active Caspase-1, which then promotes the inflammatory response through the classical pathway of cellular pyrolysis. However, the above process produces active NLRP3, which can induce the secretion of matrix metalloproteinase 3 (MMP-1) and matrix metalloproteinase 13 (MMP-13), which are capable of degrading the cartilage matrix, leading to chondrocyte damage, and the damaged chondrocytes will cause the generation of the pyroptosis reaction again [26], resulting in the worsening of clinical symptoms.

3.2 IL-1β Mediates KOA Development

IL-1β inflammatory factors, whether classical or non-classical pathways, are present as important proteins in the process of cellular cell death. It is a typical inflammatory cytokine, the synthesis and secretion pathway mainly rely on the production of activated monocytes and macrophages [27], has a wide range of biological activities. In the normal physiological state only in a small amount of synovial fluid and the surface layer of chondrocytes in the presence of expression, induces inflammation, repair damaged cells and tissues in the body and scavenging pathogenic microorganisms. In KOA, IL-1β is also considered to be one of the critical inflammatory factors leading to KOA [28], which can induce the generation of inflammatory response alone or co-mediate the inflammatory response in concert with other substances [29]. High IL-1β expression was found in synovium, synovial fluid and cartilage of patients with KOA [30]. Cartilage lesions are a major cause of KOA, and abnormal chondrocyte damage or death leads to dysregulation of chondrocyte metabolic responses and degradation of the cartilage matrix [31]. The cartilage matrix produces a large number of proteases and collagenases, which in turn induce the production of inflammatory factors and promote the inflammatory response [32], and a large amount of IL-1β is expressed in the chondrocytes and cellular matrix of the upper and middle layers of the knee joint, and activated IL-1β induces inflammatory cell aggregation causing cellular pyropoiesis to produce an inflammatory response, This leads to the aggravation of the clinical manifestations of KOA; IL-1β also induced the production of MMP-1 and MMP-13 in synoviocytes. MMP-1 belongs to the collagenase subfamily of MMPS and is capable of degrading type II collagen, which is the main component of the cartilage matrix, while MMP-13 belongs to the same family of collagenases and is more efficient at hydrolysing proteins than MMP-1.Therefore, the large amount of MMP-1 and MMP-13 produced by sliding membrane cells induced by IL-1β, accelerates the degradation of cartilage matrix and the destruction of cartilage [33]. IL-1β also induces synovial hyperplasia and promotes chondrocyte secretion of prostaglandin E2, a potent proinflammatory agent, resulting in elevated expression of adhesion factors in synoviocytes, causing synovial inflammation [34], and the synovial inflammatory response in turn promotes the progression of KOA. At the same time, IL-1β is highly expressed in synovial fluid, inhibiting the synthesis of proteoglycans by chondrocytes, affecting and leading to the loss of cartilage matrix [35], resulting in the destruction of chondrocytes, generating an inflammatory response, which in turn stimulates the production of IL-1β resulting in joint swelling, pain, and unfavourable activities, stimulating accelerated progression of KOA, and lowering the quality of life of patients.

4. Research based on the Theory of Focal Cell Death for Chinese Medicine Intervention in KOA

4.1 KOA Single Agent Intervention Study based on Focal Cell Death Theories

It was found that single herbs and drug-containing serums that nourish the liver and kidneys are effective in the treatment of KOA. Shi Jiyuan et al [36], by establishing a rat model of OA, set Icariin as the experimental group, and injected it into the knee joint cavity of rats, and found that Icariin further

inhibited LPS-induced non-classical pathway by inhibiting NLRP3 and caspase-1 transduction, and reduced chondrocyte damage and cellular pyroclasmic response, and further alleviated the OA of the knee joint of rats. Li Yuguo [37] extracted primary chondrocytes from the knee joints of newborn mice and cultured them, simulated the inflammatory environment of osteoarthritis by TNF-α stimulation in vitro, and used ginsenoside as the experimental group, dripped into chondrocytes, and found that ginsenoside could reduce the expression of MMP-13 induced by IL-1β, and further reduce the degradation of collagen type II and aggrecan, reduce the damage to chondrocytes, maintain the stability of cartilage, and inhibit the activation of NLRP3 inflammatory vesicles, block the generation of cellular focal response, protect the knee joint and slow down the progression of KOA.HU et al [38], based on the study of strychnosine to enhance cartilage degeneration and osteoarthritis development in OA mouse model by inhibiting chondrocyte pyroptosis, found that strychnosine could reduce the levels of MMP-3 and Caspase-1, decrease the degradation of cartilage matrix and the generation of cell pyroptosis, and inhibit the progression of KOA.

4.2 KOA Formulation Intervention Study Based on Cellular Scorch Death Theory

Ma Fuhai et al [39], found that the expression of NLRP3, Caspase-1 signaling pathway-related proteins and inflammatory factors were significantly reduced in KOA rats even under the intervention of low concentration of Yi-Shen Qubi Pills,, Yishen-Qubi Pills were able to inhibit the cellular death of the classical pathway, and prevented the progression of the disease in KOA rats; Jin Linglu et al [40], using Aconitum soup in KOA rats, found that the inflammatory indexes in cartilage tissues of KOA rats increased significantly compared with normal rats, but the expression of proteins, such as Caspase-1, IL-1β, IL-18, etc., was significantly reduced in the cartilage of KOA rats after the intervention of Aconitum soup, suggesting that Aconitum soup may inhibit the cellular death response and protect the chondrocytes of KOA rats, thus producing a therapeutic effect on KOA, using Aconitum soup in KOA rats. Zhang Li et al [41] found that the synovial tissue of KOA rats was in a state of hypoxia and could lead to the elevation of HIF-1α, which further induced the generation of fibrotic synovial cell pyrolysis. However, oral administration of knee palsy improved the hypoxic state of the synovial tissue of the knee joint and regulated the expression of HIF-1α, which could inhibit cell pyrolysis, and attenuate the synovial fibrosis.

4.3 Research on KOA's External Chinese Medicine Intervention Based on Cellular Focalization Theory

Some scholars use acupuncture, moxibustion and other external treatment methods of traditional Chinese medicine, through the inhibition of cell death and intervention in the KOA, the treatment will produces significant results, Zhang Wei et al [42] found that electroacupuncture specific points can inhibit the expression of NLRP3 inflammatory vesicles in the knee joint of the rat and reduce the cell death response to further protect the cartilage and other tissues. Yu Yinan et al [43], by setting up a rat model of knee osteoarthritis KOA, found that electroacupuncture on the points of "inner XI-yan" and "Du-Bi" effectively reduced the levels of IL-1β and IL-18 inflammatory factors in the serum, and NLRP3 protein expression in the synovium, reduced the inflammatory response, thus inhibiting the occurrence of cellular death, which had a certain degree of therapeutic effect on KOA. Wang [44] and others established a KOA rat model and used Moxibustion as a treatment, and found that IL-1β, NLRP3, GSDMD, GSDMD-N and other inflammatory factors and proteins were less expressed in the serum of the Moxibustion group compared with that of the sham-operated group, which concluded that Moxibustion could down-regulate the p38 MAPK signaling pathway and effectively inhibit NLRP3 inflammatory vesicle-mediated chondrocyte cell death to achieve the protective effect on the cartilage.

5. Summary and Future Prospects

In summary, significant progress has been made in the study of the correlation between cellular pyroptosis and KOA. Cellular pyroptosis is present throughout KOA and can lead to inflammation induced by lesions in cartilage, subchondral bone and synovial tissue. According to the research findings of many scholars mentioned above, Chinese medicine relies on the inhibition of cellular pyroptosis to protect the knee joint, maintain its normal physiological state, and delay the progression of KOA. Specifically on the chondrocyte level, TCM can regulate Caspase-1, NLRP3, IL-1β and other related proteins and inflammatory vesicles, reduce the degradation of cartilage matrix and inflammatory response, inhibit chondrocyte cell pyrolysis, and block the progression of KOA; At the level of synovial tissue, it effectively improved the elevation of HIF-1α caused by synovial tissue hypoxia, inhibited the generation of fibroblast-like synovial cell death, prevented synovial fibrosis, and alleviated the symptoms of KOA. Obviously, the use of TCM in the treatment of KOA has important scientific and clinical value in alleviating patients' pain and improving their quality of life. However, its specific mechanism of action, especially the active ingredients or targets of TCM, has not been completely clarified. Therefore, the author believes that, from the cellular death theory, the recognition of the targeted intervention of TCM on KOA should become the in-depth direction of future research, and the enhancement of TCM therapeutics with precise target therapeutic effect on KOA will provide new theories and bases for the prevention and treatment of KOA.

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