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REVIEW ARTICLE

ADVANCES IN RESEARCH ON THE PATHOGENESIS OF OSTEOARTHRITIS

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ABSTRACT

Osteoarthritis（OA）is one of the most common joint disorders. OAseriously threatens human health and life, it has been an important subject of orthopaedic science. Although the investment in the early treatment of osteoarthritis and inhibiting the developing direction is largerin the past20 years, it has not obtained great progress in drug treatment. In spite of thearticular cartilage of physiology, biochemistry and metabolism of chondrocyte have a certain understanding, but the etiology and pathogenesis of osteoarthritis is still not very clear. So for, its early diagnosis and treatment of the lack of a clear direction. The pathogenesis of osteoarthritis is caused by a variety of factors, including genetic heritage, biomechanical factors, cartilage nutritional and metabolic abnormalities, chondrocyte apoptosis, etc. Now, in this paper we reviewed the pathogenesis of osteoarthritis from the structure of the articular cartilage, cytokines theory, theory of free radicals, miRNA and STAT3.

INTRODUCTION

Osteoarthritis (OA) is a kind of chronic joint disease. The pathological features of osteoarthritis isarticular cartilage degeneration and loss, bone regeneration of joint edge and the subchondral bone. The commonparts of osteoarthritis are the knee, hip, elbow and small joints, etc. The cause of OA is unclear, but withsimilar biology, morphology and clinical features. OA is mainly involving the articular cartilage, subchondral bone, joint capsule and ligaments, synovial membrane and the surrounding muscles. OAoccurs in the elderly, more women than men. With the coming of aging society, osteoarthritis patients number will gradually rise. By 2020, the elderly population for a quarter of the total population in developed countries, half of all chronic diseases that suffered from by the elderly over the sixty-five age will be for “osteoarthritis”. There areabout 130 million OA patients older than sixty age in China, accounting for about 30% of the total population.

the structure of Articular Cartilage: Cartilage tissue is histologically divided into hyaline cartilage, fibrocartilage and elastic cartilage, while articular cartilage is hyaline cartilage, the surface is smooth and shiny, milky white light blue translucent. Articular cartilage can be divided into four layers from the joint to the deep: shallow layer, transition layer, radiation layer and calcified layer (Wong, 2013).

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Articular cartilage consists of chondrocytes and cartilage matrix. Chondrocytes are differentiated from mesenchymal cells (Buckwalter, 1998). The cartilage matrix is mainly composed of fiber, proteoglycan and water.Water flows in the extracellular matrix and accounts for more than 50% of the dry weight of cartilage. Type II collagen is the main molecular component. Other collagen fibers, such asIII、VI、IX、X、XIand XII type collagen, also participate in maturation. The composition of the matrix (Eyre, 2002). The collagen fibers in the calcified layer are polymerized into small fiber bundles to travel perpendicularly to the cartilage surface, and then reach the middle layer and then scatter to form a fiber network structure, which is arched. This structure allows the cartilage to adapt to shear forces mainly in the superficial layer, the pressure is mainly carried out by the middle layer and the deep layer, and the pressure in the lower part of the cartilage is reduced, and the separation of the metaphysis is reduced. The other major component of the matrix is proteoglycan, which, in combination with collagen fibers, has a fixed and compressive action to stabilize the matrix. The tension formed by the proteoglycan's absorption of moisture and the stress of the collagen structure network are in a dynamic equilibrium, in which water travels.

The Pathogenesis of OA

Changes in the biomechanical properties of joints: multiple small doses of shock or a single impact of more than 25 MPa can cause irreversible damage to articular cartilage (Chen, 2011), Yu *et al* (2002), removed the medial meniscus of the

rabbit and changed the normal trajectory of the joint. The pressure on the joint was too concentrated, the pressure was too high, and the frame structure of the articular cartilage tissue was destroyed. The cell was damaged and the matrix synthesis was blocked. Articular cartilage continues to degenerate and necrosis, forming a vicious circle until OA is formed. Egloff *et al* (Egloff, 2012) studied the weight-bearing mechanism of lower limb weight-bearing joints, and showed that increasing mechanical movement and biomechanical changes are important factors in the pathogenesis and development of OA.

Joint trauma and braking: Intra-articular fractures and other injuries often cause articular cartilage damage. Studies (Kim, 2002 and Mckinley, 2010) found that the rate of chondrocyte apoptosis in the fracture area increased significantly, indicating that the chondrocytes lost abnormal protection after matrix protection and nutrition. The experiment found that superficial cartilage damage, 24 h after chondrocyte death, peripheral chondrocyte division, matrix synthesis, catabolic enzyme activity increased, this change only lasts for a few days. Deep injury to the articular cartilage will affect the subchondral bone and its blood supply. The response is hematoma, granulation tissue and new bone formation and fibrosis. Whether oa can occur after the articular cartilage is damaged is also related to factors such as joint activity and braking.Excessive activity after injury can cause degeneration of articular cartilage.If the joint is fixed for too long, the cartilage will undergo an inevitable degeneration, which will lead to the occurrence of oa (Stuart, 2017).

Mechanism of action of cytokines in OA: Normally, the apoptosis and proliferation of articular chondrocytes and the degradation and synthesis of extracellular matrix are in a dynamic equilibrium, thus maintaining the stability of the structure and function of articular cartilage. This dynamic balance is involved and accomplished by a variety of cytokines. Cytokines involved in bone metabolism can be divided into three categories: cytokines of catabolism include IL-1, TNF-α, IL-6, IL-17, IL-18, etc.; cytokines that inhibit metabolism: IL-4, IL- 10. IL-11, IL-13, IFN-γ; anabolic cytokines include TGF-β, FGF, IGF, BMP, and the like. IL-1 is a cytokine with a wide range of biological activities and is a major pro-inflammatory factor. Normal joint fluid contains trace amounts of IL-1 and is mainly IL-1β.IL-1 has two high-affinity receptors: IL-1RI and IL-1RII.IL-1α has high affinity with IL-1RI, while IL-1β and IL-1RII have strong binding ability [10].The study found that the expression of IL-1β in the joint fluid of patients with OA was elevated, and it was positively correlated with articular cartilage injury (Marks, 2005). Aigner *et al*. Reported that under the influence of IL-1β, 19 genes of human chondrocytes changed significantly, including IL-1β itself. In OA, IL-1 can inhibit the synthesis of type II and IV collagen fibers, which are characteristic collagen of hyaline cartilage, promote the synthesis of type I and III collagen fibers, inhibit the synthesis of proteoglycans, and cause degeneration of chondrocytes. Inhibition of chondrocyte proliferation (Chen, 2011). In OA, the anabolic cytokine expression is reduced or increased much less than the catabolic factor is another factor in metabolic imbalance.IGF-1 can regulate the synthesis of chondrocyte proteoglycan during the development of OA, and plays a key role. It is a medium for cartilage synthesis, reducing cartilage degradation and increasing the synthesis of proteoglycans (Martel-Pelletier, 1998). IGF-2 The non-differentiation phase is called a stimulant for cartilage synthesis and promotes the synthesis of proteoglycans by chondrocytes (Bhaumick, 1991). TGF-β can induce mesenchymal cells to differentiate into chondrocytes and express cartilage phenotype. It can also stimulate bone matrix synthesis and reduce inflammation, promote the synthesis of proteoglycans and TIMPs, and increase the expression of IL-1 receptor antagonist protein. Thereby, the expression of the IL-1 receptor is reduced, and the calcification of the matrix (Bertrand, 2010) is reduced. BMPs can stimulate the transformation of bone marrow stromal stem cells into chondrocytes, increase the synthesis of type II collagen and proteoglycan in articular cartilage, and promote the healing of full-thickness cartilage injury (Scimeca, 2017).

The mechanism of action of immune response in OA: Recent studies have confirmed that articular cartilage can induce the body's immune response and continue to play a role (Scimeca, 2017). Genetic, metabolic or mechanical factors cause the initial cartilage damage leading to the release of some specific cartilage autoantigens, triggering the activation of the immune response. Immune cells include joint tissues infiltrated by T cells, B cells, and macrophages. Different types of cells in the joint release cytokines and chemokines, the complement system is activated, and cartilage degeneration factors such as matrix metalloproteinases (MMPs) and prostaglandin E2 The release of (PGE2) further damages the articular cartilage (Haseeb, 2013). Yuan *et al*. (2003), believe that autoimmune reaction can occur in cartilage tissue components, which can up-regulate the expression of degrading enzymes and inflammatory factors, causing further damage of cartilage, causing more cartilage tissue to be exposed to the immune system, forming a malignant cascade, thus forming OA. Experimental studies have shown that the expression of TIMP-1, VEGF and MMP-13 in OA is accompanied by increased activation of $CD8^+$ T cells (Hsieh, 2013), indicating that $CD8^+$ T cells play an important role in the pathogenesis of OA. In the application of type II collagen-induced rat joint model, it was found that there was deposition of IgG and complement C3 on the cartilage surface, indicating that humoral immune response was involved in the formation of OA. When the rats were removed by type II collagen and found to be free of complement C3, only IgG deposition was observed, and no inflammatory manifestations and cartilage damage were found, indicating that the damage of articular cartilage requires complement-mediated antigen-antibody reaction.

Mechanism of action of miRNAs in OA: miRNAs are a family of single-stranded small RNAs of endogenous, non-coding proteins, about 19-25 nt in length, widely found in animals, plants and microorganisms, first in the early 1990s. Found in the online worm. Studies have shown that in the occurrence and development of OA, a variety of miRNAs are involved, confirmed by gene chip, qRT-PCR and in situ hybridization, miR-483, miR-22, miR-377, etc. in human knee joint OA The expression of 9 miRNAs was up-regulated, while the expression of 7 miRNAs such as miR-140, miR-29a and miR-25 was down-regulated. Dimitrios Iliopoulos *et al* [22] confirmed that miR-22 directly acts on BMP-7 and PPARA mRNA in OA, inhibiting the expression of two proteins, increasing the expression of IL-1 and MMP-13, leading to degeneration of chondrocytes and Matrix degradation. Yamasaki *et al*. (Yamasaki, 2009) showed that IL-1β induces high expression of miR-146a in the early stage of OA, miR-146a can inhibit the inflammatory response by down-

regulating the expression of IRAK1 and TRAF6, and negative feedback regulates the expression of MMP-13, thereby inhibiting cartilage. Catabolism.miR-140 is a cartilage-specific miRNA that plays an important role in embryonic development of cartilage and bone (Si, 2017). Miyaki *et al*. (Miyaki, 2010). (Miyaki, 2010), developed miR-140$^{-/-}$ mice by gene knockout technique, although its bone structure is consistent with normal mice, but its development is small, and age-related OA appears in articular cartilage.mi-R-483 was found in 2007 and humans are highly homologous.mi-R-483 is an intron mi-RNA whose gene is located in the second intron of IGF-2.Mature mi-R-483 is divided into two groups, mi-R483-5p and mi-R-483-3p.Studies have shown that the intron miR-483 is up-regulated in mouse OA, which plays an important role in gene regulation in the early and late stages of OA.Recent studies have shown that miR-93-5p can inhibit OA chondrocyte apoptosis and progression through its target gene TCF4 (Xue, 2019). In recent years, various techniques have been used to confirm and confirm that many miRNAs promote or inhibit chondrocyte degeneration and mechanism degradation by regulating the expression of certain genes, breaking through the previous understanding of the regulation pattern of gene expression, explaining from a new perspective. The regulation mechanism of gene expression of OA provides a new direction for the diagnosis and treatment of OA.

The role of STAT3 in OA: STAT3 (signal transducer and activator of transcription3) is an acute-phase response factor (APRF) in interleukin-6 (IL-6) signaling in 1994. Purified to induce transcription of a limited set of target genes.STAT3 is widely expressed in different types of cells and tissues, and is involved in the regulation of physiological functions such as cell growth, malignant transformation and apoptosis (Jeffries, 2017). In the field of orthopedics, scholars have begun to pay attention to the regulation of STAT3 in the pathogenesis of OA (Hoey, 1999). Suemoto *et al*. (2007) showed that the knockdown of the Trps1 gene in rats will result in dysplasia of the cartilage characterized by decreased proliferation and apoptosis of growth plate chondrocytes. Trps1 is an inhibitor of STAT3 expression, which in turn regulates chondrocyte proliferation and survival by regulating the expression of cyclin D1 and Bcl-2.Trps1 is a novel regulatory mechanism that regulates the proliferation and survival of chondrocytes by regulating the expression of STAT3.Krejci *et al* (Krejci, 2009), showed that activated fibroblast growth factor receptor 3 (FGFR3) can cause attenuation of cartilage growth.Members of the transcription factor STAT family, STAT1, 3, 5, and 6, are thought to be involved in the FGFR3 signaling pathway in cartilage, however the molecular mechanisms of this behavior are poorly understood. Demoulin *et al* (1998) studied the IL-2 signal transduction pathway and confirmed that IL-2 binds to the receptors on the surface of T lymphocytes and activates JAK1 and JAK3 coupled to the receptor, which in turn causes STAT3 and STAT5. Phosphorylation, a series of reactions downstream of the initiation pathway. Xiong *et al* (Xiong, 2005) pointed out that when IL-2 is present in the environment, the degree of tyrosine phosphorylation of STAT3 in T lymphocytes inside the joint of OA patients is increased. This amplified or prolonged phosphorylation reaction will directly affect the next level of transcription, leading to an increase in the transcriptional level of various genes regulated by STAT3 in the nucleus, thereby amplifying or prolonging the action of IL-2 on T lymphocytes. The various biological effects that can be produced include promoting the proliferation of various types of T lymphocytes, and inducing or enhancing the cytotoxic activity of T lymphocytes, and to a certain extent, maintaining the survival of T lymphocytes and inhibiting their withering. Death (Janssen, 2000).

Other: Insulin promotes so4 into chondrocytes, which is beneficial to the synthesis of proteoglycans.Experiments have shown that androgen promotes OA, and estrogen has an inhibitory effect on oa.Nfat1 (nuclear factor 1) may play an important role in the pathogenesis of OA (Zhang, 2019).

Conclusions

The pathogenesis of OA is not a single one, but a complex, multi-factor interleaving result. Mechanism research has evolved from macroscopic biomechanics to microscopic cytokine levels to current gene levels, but it is still not very clear. The treatment of osteoarthritis is also a difficult problem. The effect of general medication on the changes of osseous hyperplasia is not obvious, and joint replacement has the problems of high cost, high risk, loosening of the prosthesis and infection. At present, in the gene therapy of OA, it is still in the stage of animal experimentation in the world, and it is a new topic worthy of study. These studies provide more theoretical basis for the pathogenesis of OA, and research and design a signal transduction pathway as a target molecule. Drugs and treatments provide new thinking that will eventually open up a new avenue for OA prevention and treatment, maximizing the suffering of OA patients.

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