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The Influence of Pro-Inflammatory Factors on the Course of Osteoarthritis

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Annotation: The literature review summarizes modern ideas about the role of cytokines in the pathogenesis of osteoarthritis. Proinflammatory cytokines in joint tissue cause inflammation and damage ofvcartilage, leading to progressive joint degeneration.

Keywords: osteoarthritis; cytokines, pathogenesis, interleukin-1β, interleukin-6.

Introduction: Osteoarthritis belongs to the group of primary non-inflammatory diseases of the joints with various etiologies and can be considered as an anatomical and clinical syndrome, which is characterized by pain of a mechanical type in people over 45 years of age with corresponding radiological data. There is another definition, according to which osteoarthritis is a group of pathogenetically related diseases that have different etiologies, but lead to the same biochemical and clinical outcome, characterized by the progressive loss of hyaline cartilage and subchondral bone remodeling.

Prevalence of the disease: Osteoarthritis is one of the most common diseases, its prevalence is clearly related to age and gender. Almost every second patient over 50-years-old has clinical or radiological signs, and among people over 75-years-old, osteoarthritis is detected in everyone without exception. This disease is significantly more common in women than in men, which applies to any location. In women, both radiographic and clinical symptoms of osteoarthritis are more pronounced.

Primary pathogenetic signs of osteoarthritis: These include insufficient synthesis of proteoglycans and fragmentation of proteoglycan aggregates, increased catabolic processes, expression of superoxide radicals, activation of collagenase and phospholipase A2, reduced synthesis of hyaluronic acid, as well as hyperproduction of proinflammatory cytokines-interleukin (IL)-1 and factor tumor necrosis (TNF)–α. In addition, hyperproduction of prostaglandin is important, which leads to stimulation of osteoblasts and induction of cartilage degeneration. Osteoarthritis develops in cases where cartilage and subchondral bone are not able to adequately resist mechanical load, which is associated with limited reparative capabilities of these tissues. Hyaline cartilage serves as the primary locus for the initiation of pathological changes, characterized by a reduction in chondrocyte quantity and a concomitant decline in their metabolic activity. This leads to a decrease in the synthesis of collagen in the cartilage matrix and sulfated proteoglycans-chondroitin sulfate, keratan sulfate, proteoglycan-hyaluronic aggregates, as well as hyaluronic acid. The most important component of these changes is a deficiency in the synthesis of proteoglycans, the main structural component of the cartilage matrix. In osteoarthritis, not only the quantitative synthesis of proteoglycans decreases, but their qualitative composition also changes, namely the production of full-fledged proteoglycans with high molecular weight. Under the influence of mechanical stress (chronic overload of the joint), there is an increase in the synthesis and release of enzymes (metalloproteinases - collagenase, stromelysin and other proteases), which contribute to the destruction of proteoglycans and the collagen network, which ultimately determines the progressive degeneration of cartilage.

The expression of cytokines, primarily IL-1 and TNF-α, plays an important role in the development of morphological changes. Proinflammatory cytokines inhibit the formation of the cartilage matrix, stimulate the synthesis of metalloproteinases and reduce the production of tissue inhibitors of matrix proteinases. The importance of IL-1 in the pathogenesis of osteoarthritis is determined by the activation of synovial cells, osteoclasts and chondrocytes, which ultimately leads to inflammation,

degradation of subchondral bone and its reparative changes, as well as cartilage degradation. On the other hand, in osteoarthritis there is a deficiency of anti-inflammatory cytokines, such as transforming growth factor-β and plasminogen inhibitor-1, which inhibit anabolic processes in the affected cartilage. A certain role in the pathogenetic cascade of osteoarthritis is played by superoxide radicals, a decrease in the synthesis of hyaluronic acid by synoviocytes, as well as overproduction of prostaglandin E2, which, along with other factors, promotes inflammation in the joint tissues and induces fibroplastic degeneration of cartilage. Morphological changes in this disease include a decrease in hyaline cartilage mass, subchondral bone sclerosis with a hypertrophic reaction, and subchondral bone remodeling with the formation of marginal osteophytes. At the early stage of the disease, swelling of the extracellular matrix occurs, zones of quantitative decrease in chondrocytes appear, which are then replaced by foci of their proliferation.

Later, microcracks form in the extracellular matrix of the cartilage and destruction of the subchondral bone. One of the characteristic and obligate manifestations of osteoarthritis is the involvement of the subchondral bone. In experimental osteoarthritis, the expression of bone metabolism inhibitors has been shown. Osteoid is formed in the subchondral bone, which is actively mineralized, subchondral cysts and microfractures form, and all this leads to subchondral sclerosis, one of the characteristic signs of osteoarthritis. Changes in subchondral bone are thought to precede hyaline cartilage degeneration, with bone growth factors playing a significant role in bone remodeling and osteophyte formation. Specific changes in the architectonics of subchondral trabecular bone are a consequence of accelerated bone metabolism and lead to the development of osteophytes, the surface of which is covered with fibrillar cartilage. In osteoarthritis, degenerative changes predominate, but inflammation, which is localized in the synovial membrane, cartilage, subchondral bone and periarticular soft tissues, is of no less importance in the development of this disease. Persistent inflammation of the synovium is accompanied by nonspecific lymphoplasmatic and histiocytic infiltration, as well as overexpression of proinflammatory mediators.

Interleukin-1 beta (IL-1β) is considered one of the key cytokines involved in the pathogenesis of OA. It induces inflammatory reactions and catabolic effects in articular cartilage, subchondral bone, synovium, ligaments and other joint tissues. It is one of 11 members of the IL-1 family (IL-1F) [5]. Its synthesis by mononuclear cells present in the joint or penetrated there during the inflammatory reaction has a significant effect on the metabolism of chondrocytes, osteoblasts, osteoclasts and synovial cells [6]. Many studies have shown that patients with OA have increased levels of IL-1β in serum, synovial fluid, synovium, cartilage and subchondral bone [7]. Biological activation of cells by IL-1β is mediated by interaction with membrane receptor type 1 (IL-1R1), which can also bind to another IL-1α agonist and, in addition, to an IL-1ra receptor antagonist. In this case, the transmission of the activating signal into the cell occurs only during the assembly of the complex - IL-1β or IL1-α, IL-1R1 and the accessory protein of the IL-1AcP receptor. Then, interaction with the adapter protein MyD88 occurs, followed by activation of the IL-1RI-associated kinases IRAK4 and IRAK1. This leads to the initiation of MAP kinase cascades [10] and activation of the transcription factor NF-κB, which is accompanied by the expression of hundreds of genes responsible for the production of other cytokines, chemokines, adhesion molecules, other inflammatory mediators and enzymes [11]. In OA patients, the expression of the IL-1R1 receptor on the surface of chondrocytes and fibroblast-like synoviocytes increases, and the local concentration of IL-1β also increases significantly [9]. An increase in local levels of IL-1β shifts the regulatory balance in tissues in favor of the agonist, stimulating the development of inflammation through a mechanism similar to other inflammatory joint diseases. The effect of IL-1β is reflected in its significant influence on cell and extracellular matrix (ECM) metabolism [12]. During the course of the disease, the gradual loss of articular cartilage is of paramount importance. Many studies confirm that IL-1β blocks chondrocyte synthesis of ECM components by interfering with the synthesis of key structural proteins such as type II collagen and proteoglycans [13]. IL-1β also stimulates the synthesis of metalloproteinases (MMPs), mainly MMP-1, MMP-3 and MMP-13, which contribute to articular cartilage damage [14]. In addition to the induction of enzymes of the MMP family, IL-1β affects the production of

ADAMTS metalloproteinases by chondrocytes, which are responsible for the proteolysis of aggrecan molecules [15]. IL-1β, together with TNF-α, also stimulates chondrocyte apoptosis [16]. In addition, during exacerbation of the disease, IL-1β stimulates the formation of reactive oxygen species (ROS), which directly damage articular cartilage, which occurs while suppressing the expression and production of oxidative enzymes [17]. In addition to these direct effects, IL-1β induces the production of other cytokines, including IL-6, IL-8, and leukemia-inducing factor (LIF), which mediate additive or synergistic effects in the catabolic cascade. IL-1β also activates nociceptors by enhancing intracellular kinase activity and induces indirect sensitization by increasing the production of kinins and prostanoids. This relationship indicates the possibility of correlating cytokine levels with pain intensity and radiographic signs of disease progression in patients with OA.

Interleukin-6 (IL-6) is a pluripotent cytokine activating the immune system and enhancing the inflammatory response. IL-6 synthesis in the tissues of the affected joint usually occurs in response to IL-1β and TNF-α and is mainly carried out by chondrocytes, osteoblasts, macrophages and adipocytes. Increased concentrations of IL-6 are observed in both synovial fluid and serum and are positively correlated with the intensity of damage on radiological studies. There are two subtypes of IL-6R receptor, namely the membrane form mIL-6R and the soluble sIL-6R. The activity of IL-6 is realized through its high-affinity binding to the membrane receptor, which is expressed on the surface of B lymphocytes and other cells, the subsequent formation of a complex of the gp80 subunit of IL-6R with the homodimer of the transmembrane molecule gp130 and signal transmission into the cell. This results in activation of STAT3, phosphorylation of MAPK , and activation of the PI3 K/AKT pathway. Necessarily encoding IL-6 may determine the rate of development of pathological changes in OA. The effect of IL-6 on articular cartilage leads to a decrease in the production of type II collagen and an increase in the synthesis of enzymes from the MMPA group. Osteoblasts stimulated by IL-6, in turn, become additional sources of IL-1β, TNF-α and can also produce MMPs, exerting a destructive effect on cartilage located near the subchondral bone, which closes the circle of relationships between these three proinflammatory cytokines. A number of studies have noted the activation of afferent neurons with an increase in the level of IL-6, which indicates the important role of IL-6 in the spread of pain in OA. Thus, IL-6 is considered to be a key cytokine inducing changes in subchondral bone. Its effect is largely based on increasing osteoclast activity and therefore subchondral bone resorption. This circumstance makes IL-6, along with IL-1β and TNF-α, an important therapeutic target for rheumatoid arthritis and osteoarthritis.

Conclusion. Osteoarthritis encompasses a multifaceted progression of pathological processes resulting in the progressive degeneration of joints. It is characterized by cartilage degradation and destruction, subchondral bone structural damage and sclerosis, pathological formation of osteophytes, degeneration of the ligamentous and tendon apparatus, and associated muscle atrophy. Ultimately, the above processes make it impossible to carry out the most important function of the musculoskeletal system - movement! Hormonal imbalance, activation of adipokines in obesity, and disturbances in carbohydrate and purine metabolism in metabolic syndrome are of great importance in the development of OA. However, at the moment, the priority in the development of OA is inflammation, which occurs due to obvious deregulation in the cytokine network. In joints, inflammatory cytokines primarily have destructive effects on articular cartilage and subchondral bone. This is a multi-level effect, which is associated not only with the induction of chondrocyte apoptosis, but also with a decrease in the synthesis of key components of cartilage tissue.

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