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MODERN VIEW ON THE IMMUNE MECHANISMS OF OSTEOARTHRITIS FORMATION

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Abstract:

Osteoarthritis is both a general medical and socio-economic problem, characterized by the development of functional disorders in the joints, loss of working capacity, disability of patients and, thereby, a decrease in their quality of life, significant financial costs. The review article presented by the authors systematizes modern research by foreign authors, including metabolic shifts, inflammatory processes, immune disorders.

Keywords: Osteoarthritis, immune mechanisms, pathogenesis, severe syndrome

Osteoarthritis (OA) is the most common disease of the musculoskeletal system and occurs in a third of patients aged 45 to 64 years and in 60-70% of patients over 65 years. The social significance of osteoarthritis is determined by the associated high level of disability and a significant decrease in the quality of life of patients due to limited mobility and the severity of concomitant pain syndrome. Pathogenetic mechanisms in osteoarthritis include metabolic shifts, inflammatory processes, and immune disorders [2].

On the one hand, it is believed that it is the immuno-inflammatory component that leads to disorders in collagen metabolism and the development of a degenerative process in articular tissues. On the other hand, it is known that pathological immunological reactions in OA lead to an aggravation of the severity of anatomical disorders and contribute to the chronization of the pathological process. Innate immunity is an important component of the immune response in OA, which has been proven by numerous studies. At the same time, the question of the dependence of the indicators of innate immunity on the size of the tibial condyle defect in patients with gonarthrosis is completely not covered in the modern literature [9].

Lesions of the musculoskeletal system belong to the most common pathology, among which OA is of particular importance. OA is both a general medical and socio-economic problem, characterized by the development of functional disorders in the joints, loss of working capacity, disability of patients and, thereby, a decrease in their quality of life, significant financial costs. The problem of OA has been actively developed in adults for several decades. There is an opinion that this pathology is characteristic of mature and elderly people. Significant recent achievements in the study of OA in adults relate mainly to the advanced stages of the disease, but it is important for the diagnosis, timely appointment of adequate treatment to determine the early manifestations of OA and the mechanisms of its development at the initial stages of formation [5].

Unlike systemic diseases, OA was initially considered not an inflammatory disease of the joints, but over time, ideas about this pathology have changed. It was determined that the pathogenesis of OA is based on the release of cytokines interleukin-1 (IL-1) and tumor necrosis factor (TNF / TNFa), which stimulates the inflammatory reaction of synovial tissue that occurs after injury with hemorrhage into the joint cavity. The available data on the morphohistochemical features of post-traumatic osteoarthritis (PTOA) allow us to characterize this disease as an acutely ongoing process with the rapid development of fibrosis, early degradation of the matrix of articular cartilage and cell membranes, the products of which penetrate into the synovial fluid in large quantities and initiate an immune process affecting both cartilage and synovial membrane. Acute joint injury is closely associated with elevated levels of IL-6, gamma interferon, monocyte chemoattractant protein and other pro-inflammatory factors. It is believed that together with the accumulating reactive oxygen species, cytokines (IL-1, -2, -6, -8, TNFa, interferon γ) trigger mechanisms such as cell apoptosis and expression of catabolic enzymes in chondrocytes, thereby contributing to progressive degeneration of the extracellular matrix, which leads to a violation of cartilage homeostasis [3].

The intensification of the study of pathological mineralization processes observed in the last decade, on the one hand, is due to the obvious need to find answers to questions related to the lack of explanation of all pathological changes in articular cartilage within the existing concepts of OA, on the other hand, initiated by the emergence of high-tech equipment

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that allows you to look at the deep processes of pathophysiology of OA from the standpoint of biomineralization [2].

Microcrystallization of articular cartilage, the pathogenesis of which has yet to be clarified, is a proven participant in the pathogenesis of OA. The phenomenon of apoptosis of chondrocytes undergoing pathological differentiation is a way to prevent the development of microcrystalline stress. The appearance of hydroxyapatite crystals in the intercellular matrix is associated with hypertrophic differentiation of chondrocytes, a decrease in their proliferation under conditions of multiple stress [4].

The most significant risk factors are considered to be the gender and age of patients. Generalized OA is more common in women and is hereditary. Knee joint OA is associated with the female sex and overweight (body mass index > 30), and hip joint OA affects mainly men. Data indicating the ability of sex hormones to influence metabolic processes in cartilage have been obtained. In particular, estrogens are able to influence cytokines (interleukin-2 – IL-2, tumor necrosis factor-α – TNF-α) and growth factors. A decrease in the level of estrogens in postmenopause contributes to the early appearance of OA and its rapid progression. It was also found that women with radiologically pronounced knee joint OA are significantly more likely to have lower levels of estradiol in serum and its metabolite 2-hydroxyestrone in urine. OA is attributed to age-dependent diseases. The development of OA in all joint zones progressively increases with age. So, if degenerative changes in cartilage occur in 95% of cases at the age of 40-50 years, then at the age of over 50 years – already in 100% of people. It was found that the incidence of manifest OA of the knee joints progressively increases from 0.1% in patients aged 25-34 years to 10-20% in patients aged 65-74 years [10].

Matrix metalloproteinases (MMPs) belong to the family of zinc metalloprotenases, whose function is associated with the exchange of proteins of the intercellular matrix. These enzymes play a crucial role in the development of such physiological processes as morphogenesis, tissue resorption and remodeling, embryogenesis, tissue repair, neoangiogenesis, as well as in pathological conditions (rheumatoid arthritis, glomerulonephritis, osteoarthritis, etc.). MMPs are synthesized and secreted by a number of cells: fibroblasts, chondrocytes, epithelial cells, phagocytes, lymphocytes and oncogenically transformed cells [7].

In numerous experiments, a direct correlation has been established between the development of osteoarthritis and the level of various MMPs(-1, -2, -3, -7, -9, -13). This paper examines the role of metalloproteinases, which have the greatest impact on the joint, in the pathogenesis of osteoarthritis. According to the literature, one of the most important roles in the pathogenesis of osteoarthritis is played by MMP-1 (intracranial collagenase). MMP1 is produced by chondrocytes, the synthesis is stimulated by various agents, such as epidermal growth factor, cytokines, among which tumor necrosis factor alpha (TNF–α) plays a leading role, as well as chemical compounds such as cAMP and forbol esters. MMP-1 is inhibited by tissue inhibitors of metalloproteinases (Tissue inhibitors of metalloproteinases – TIMP-1 and -2), as well as α2-macroglobulin. Normally, MMP-1 participates in many physiological processes in the human body, such as keratinocyte migration, platelet aggregation, cell proliferation, including collagen degradation and remodeling of the extracellular matrix of cartilage. Obviously, MMP-1 plays one of the key roles in the pathogenesis of osteoarthritis. As evidenced by numerous experimental data reflecting an increase in the level of expression of interstitial collagenase in OA [11].

OA has a significant impact on the quality of life. Patients with OA need more time for daily activities. They largely depend on the help of family and friends, spend more financial resources on treatment and examinations than the general population. OA is one of the main causes of total knee (CS) and hip joint replacement. In Europe, surgical interventions are performed every 1.5 minutes to replace the affected joint. Approximately 500 thousand joint replacement surgeries are performed annually in the USA [8].

The stimulating effect of leptin on the synthesis of extracellular matrix (collagen and proteoglycans) indicates the direct influence of leptin on the formation of cartilage and proves a new role of leptin in the growth and development of the skeleton [1].

The direct effect of leptin on chondrocytes is realized synergistically together with interferon-γ (IFN-γ) and interleukin-1β (IL-1β) by promoting the synthesis of nitric oxide, which induces a wide range of proinflammatory cytokines, is a proinflammatory mediator in joint cartilage and promotes the activation of metalloproteinases and apoptosis of chondrocytes. A high level of insulin-like growth factor-1 (IGF-1) and transforming growth factor-β (TFR-β) was detected in the synovial fluid (CSF) and in the cartilages of patients with OA, as well as in animal models of OA. In people with OA, chondrocytes demonstrated the production of leptin and growth factors depending on the severity of the degenerative process. Growth factors play an important role in the regenerative

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processes in the cartilage that can occur with OA. However, in addition to their protective role, they can also cause connective tissue degeneration. In particular, excessive and prolonged exposure to TFR-β leads to the development of damage similar to that observed in mice with spontaneous OA. Growth factors are also involved in the formation of osteophytes, which are a characteristic feature of OA. Thus, TFR-β and IGF-1 are found in osteophytes, and repeated injections or overexpression of TFR-β in the knee joints of mice leads to the development of osteophytes [6].

CONCLUSION: Osteoarthritis is considered as a multifactorial disease. Its development and progression is influenced by many factors, among them it is customary to distinguish endogenous (gender, age, heredity) and exogenous (excessive mechanical stress and obesity). It has been established that leptin may be involved in regulating the anabolic activity of chondrocytes in OA, especially in the early stages of the disease, which is associated with an increase in the synthetic activity of chondrocytes. Growth factors (especially TFR-β) have a dual effect on cartilage tissue.

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