Progress in the effect of inflammatory microenvironment on osteoarthritis

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Osteoarthritis (OA) is the most common chronic joint degenerative disease in the population, involving progressive focal cartilage degeneration, bone hypertrophy (osteoocyte formation and subchondral osteosclerosis), synovial joint inflammation, synovial sac thickening, and structural changes of periarticular ligaments and peripheral muscles [1], among which the degeneration of articular cartilage and joint inflammation are the main characteristics [2].

Globally, the age-standardized joint prevalence and annual incidence of OA in 2017 were 3,754.2 and 181.2 cases per 100,000 people, respectively, and are expected to grow [3]. However, the pathophysiology of OA remains unclear, and current ideas suggest that mechanical stimulation, inflammatory and metabolic factors are involved in the complex pathogenesis of OA, leading to the destruction of the joint [4]. OA has traditionally been classified as non-inflammatory arthritis, however, as research continues to develop, more and more people are recognizing the presence of synovitis in patients with primary OA and the presence of a large number of ongoing immune processes in the joints of patients with OA [5].

Inflammatory microenvironment in the joints is closely related to the occurrence and development of OA, which is composed of immune cells such as macrophages, T cells, dendritic cells and other immune cells, and inflammatory mediators, including inflammatory factors such as Interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-6, and anti-inflammatory factors such as IL-10 and transforming growth factor-β1 (TGF-β1) [6]. When inflammation occurs in joints and the tissues within them, activated macrophages (usually type M1) secrete a variety of cytokines involved in the inflammatory response, such as IL-1 and TNF-α [7]. The inflammatory response can disrupt the balance between cartilage matrix degradation and repair, resulting in excessive production of proteolytic enzymes that lead to cartilage rupture, and cartilage changes in turn exacerbate synovial inflammation, forming a vicious cycle [8]. Therefore, a comprehensive elucidation of the specific links between OA and the inflammatory microenvironment in the joints is helpful to further understand the progression of OA.

During the development of OA, macrophages are activated by inflammasome and immunoregulatory cytokines as well as abnormal mechanical forces, accumulate and polarize into different subtypes, classified as M1 and M2 macrophages [9]. M1 macrophages can produce a large number of pro-inflammatory cytokines, such as TNF-α, IL-1, IL-6, and IL-12, which can enhance host defense response on the one hand, but their overactivation can lead to aggravated OA [10]. M2 macrophages are mainly present in the phase of inflammation regression, producing anti-inflammatory cytokines and bone growth factors such as IL-10 and TGF-β1, promoting tissue repair [11]. Lu Y [12] et al. demonstrated that M1 polarization accelerated the progression of experimental OA through enhanced M1 or M2-polarized macrophages, while M2 polarization significantly reduced the development of OA. Inhibition of M1 macrophage polarization can significantly reduce the progression of OA, including joint synovitis and cartilage injury [13].

Abnormal T cell immunity promotes abnormal expression of inflammatory cytokines, leading to osteoclast-mediated bone erosion and osteoporosis formation in autoimmune arthritis [14]. T cells secrete Th1/Th2 cells. TH1 cells are induced by IL-12 and IFN-γ, and mainly produce IL-2, IL-12 and IFN-γ as effector cytokines [15], which have obvious pro-inflammatory and chondrogenic effects, and thus promote the development of OA [16]. In addition, TH1 cells induce macrophages to produce IL-1β, which in turn promotes the TH1 response.

Dendritic cells (DCs) originate from bone marrow hematopoietic stem cells and can efficiently absorb, process and present antigens [17]. Antigen presenting cells of DCs can express recognition receptors, such as releasing inflammatory mediators and cytokines, in response to inflammatory conditions and signals [18], and activate adaptive immune responses [19]. DCs, as a key initiator of the immune response [20], may play a key role, at least in part, in inflammation in the pathogenesis of OA, especially in the early stages of OA [21]. E Xiaojing et al. [21] found that in the early stage, with the progression of synovial inflammation, the number of DCs in the synovial membrane of OA of rabbits increased significantly.

In the progression of OA, the pro-inflammatory cytokines IL-1β, IL-6 and TNF-α play a key role in the pathogenesis of OA and contribute to the degradation of cartilage associated with inflammation. IL-1β in OA can effectively induce the production of matrix metalloproteinase-13, thus destroying the stability of cartilage and causing the destruction of articular cartilage [22, 23]. The destructive effect of IL-1β on articular cartilage is well established and has been used to establish the inflammatory environment in OA model animals [24, 25]. Local high concentration of IL-6 may stimulate leukocyte aggregation to joints, promote the maturation and activation of osteoclasts, inhibit chondrocytes, stimulate synovial proliferation, and eventually lead to joint injury [26]. E Xiaojing et al. [21] found that in the early stage, with the progression of synovial inflammation, the expressions of IL-1β and TNF-α in the synovial membrane of OA of rabbits significantly increased, and then decreased with the regression of synovial inflammation. The main anti-inflammatory cytokines are IL-10 and TGF-β1. IL-10 is mainly produced by immune cells such as T cells and macrophages, which can inhibit the innate and adaptive inflammatory response, and can inhibit the production of TNF-α, IL-2, IL-3, IL-6 and other pro-inflammatory factors [27]. TGF-β1 can enhance the function of bone marrow-derived mesenchymal stem cells, promote the formation and differentiation of chondrocytes, and down-regulate matrix-degrading enzymes, thus playing a role in cartilage protection and repair, helping to delay the development of OA [28].

Conclusion

The inflammatory microenvironment on OA is composed of immune cells and inflammatory mediators, which jointly regulate the occurrence and development of OA. Some pro-inflammatory cytokines in the inflammatory microenvironment on OA can directly stimulate and activate immune cells, and the activated immune cells indirectly promote the release of specific inflammatory factors, further aggravate the inflammatory immune response of the body, and jointly accelerate the development of OA. Understanding the inflammatory microenvironment on OA will help to develop a more comprehensive understanding of OA and provide references for exploring therapeutic
strategies of OA.

References


Competing interests

The authors declare no conflicts of interest.

Author Contribution

An-Lan Zhao and Ping Xin performed manuscript writing. Xin-Ju Li conceived and designed the article. Yi-Hua Fan critically revised the intellectual content of the article. Xiao-Hui Yang and Jia-Xin Yuan modified the language and checked the text. All authors contributed to the article and approved the submitted version.

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Abbreviations

OA, Osteoarthritis; IL, Interleukin; TNF, tumor necrosis factor; TGF-β1, transforming growth factor-β1; DCs, Dendritic cells.

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