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Synovial Macrophage Polarization in Knee Osteoarthritis: A Narrative Mini-review of an Emerging Biological Target

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ABSTRACT

Knee osteoarthritis (KOA) is increasingly recognized as a disease driven by low-grade inflammation in addition to mechanical degeneration. Among immune cells involved in joint homeostasis, synovial macrophages play a central role in modulating inflammatory responses. Recent evidence highlights the importance of macrophage polarization, particularly the imbalance between pro-inflammatory (M1) and anti-inflammatory (M2) phenotypes, in the progression of KOA. This narrative mini-review summarizes current insights into the role of synovial macrophage polarization in KOA, its molecular regulation, and its potential as a therapeutic target.

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Introduction

Knee osteoarthritis (KOA) has traditionally been considered a degenerative joint disease primarily driven by mechanical wear. However, growing evidence supports the concept that low-grade chronic inflammation within the synovium significantly contributes to disease progression [1, 2]. Among the cellular components of the synovial membrane, macrophages represent a dominant immune population that plays a critical role in maintaining joint homeostasis as well as mediating pathological inflammation. Recent advances in basic science have emphasized that not only the presence of macrophages but also their functional phenotype is crucial in determining disease outcomes.

Macrophages exhibit remarkable plasticity and can polarize into distinct functional phenotypes in response to environmental cues. Classically activated macrophages (M1) are induced by stimuli such as interferon-γ and lipopolysaccharide and are characterized by the production of pro-inflammatory cytokines, including interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) [3]. In contrast, alternatively activated macrophages (M2) are associated with anti-inflammatory functions, tissue repair, and the secretion of cytokines such as IL-10 and transforming growth factor-β (TGF-β) [4, 5]. In healthy joints, a balance between these phenotypes contributes to immune regulation and tissue maintenance.

In the osteoarthritic knee, this balance is disrupted, leading to a predominance of the M1 phenotype within the synovium [6, 7]. This shift promotes a pro-inflammatory microenvironment that enhances cartilage degradation by upregulating matrix metalloproteinases (MMPs) and aggrecanases. Moreover, M1 macrophages amplify inflammatory signaling pathways, such as nuclear factor kappa B (NF-κB), further exacerbating tissue damage [8]. Synovial inflammation mediated by M1 macrophages has also been associated with pain severity in KOA, suggesting a direct link between immune dysregulation and clinical symptoms [9-11].

Conversely, M2 macrophages play a protective role by promoting resolution of inflammation and supporting tissue repair. However, in KOA, the number and activity of M2 macrophages are often insufficient to counterbalance the pro-inflammatory effects of M1 cells [12, 13]. This imbalance not only sustains chronic inflammation but also impairs regenerative processes within the joint. Emerging evidence suggests that modulating macrophage polarization toward the M2 phenotype may represent a promising therapeutic strategy for osteoarthritis.

At the molecular level, several signaling pathways regulate macrophage polarization in the synovial environment. Key regulators include the NF-κB pathway, signal transducer and activator of transcription signaling, and hypoxia-inducible factors (HIFs), which respond to the hypoxic conditions in osteoarthritic joints [14-17]. In addition, metabolic reprogramming has been shown to influence macrophage phenotype, with M1 macrophages relying on glycolysis and M2 macrophages favoring oxidative phosphorylation [18-20]. These findings highlight the complex interplay between metabolic and inflammatory pathways in shaping macrophage function.

Recent studies have also identified the role of extracellular vesicles, particularly exosomes, in modulating macrophage polarization. Exosomes derived from mesenchymal stem cells have been shown to promote M2 polarization and reduce inflammation in experimental models of osteoarthritis [21, 22]. Furthermore, non-coding RNAs, including microRNAs, are increasingly recognized as key regulators of macrophage phenotype by targeting genes involved in inflammatory signaling [23, 24]. These advances open new avenues for targeted therapies to restore immune balance in osteoarthritic joints.

Overall, synovial macrophage polarization represents a critical but relatively underexplored aspect of the pathophysiology of KOA. The dynamic balance between M1 and M2 phenotypes not only influences inflammation and cartilage degradation but also determines the potential for tissue repair. Understanding the mechanisms that regulate this balance may lead to the development of novel disease-modifying therapies.

Conclusion

Synovial macrophage polarization plays a pivotal role in the pathogenesis of KOA by regulating the balance between pro-inflammatory and anti-inflammatory processes. The predominance of M1 macrophages contributes to chronic inflammation and cartilage degradation, while insufficient M2 activity limits tissue repair. Targeting macrophage polarization represents a promising and relatively underexplored therapeutic strategy that bridges basic immunology and clinical management of KOA.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflict of interest

The authors declared no conflict of interest.

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