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The Role of Macrophage Polarization in OA: Insights for a Successful Strategy

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Abstract

Introduction: Osteoarthritis (OA) is the most prevalent joint pathology worldwide. OA is the leading cause of disability among older individuals. The medical and societal burden of OA makes the understanding of its pathogenesis and potential treatments paramount. **Objectives:** This narrative review seeks to explore the most up-to-date literature regarding the M1 - M2 macrophage transition that has been proposed as the possible solution for the pathogenesis of OA. **Methods:** PubMed was queried for "macrophages and the pathogenesis of OA", as well as "M1 to M2 transition in OA". Articles were included in our review if they focused primarily on the role of macrophages in OA pathogenesis and the specific role the M1 to M2 macrophage transition has in the development and resolution of osteoarthritis. We focused on key examples where the M1 - M2 transition could be exploited in the resolution of OA. **Results:** Aberrances in the physiologic M1 - M2 macrophage transition can promote the pathogenesis of osteoarthritis and a degenerative state. When there is a predilection for M1 pro-inflammatory macrophages in the joint, progression to OA may result. Conversely, when there is a predilection for M2 macrophages in the joint, OA is typically absent, and the induction of an M2 predominant state may alleviate symptoms and further joint destruction of OA. **Conclusion:** The M1 - M2 macrophage transition plays a key role in the pathogenesis and severity of OA. Exploiting biochemical pathways involved in this transition may prove to be a suitable treatment for patients with OA.

Keywords

Osteoarthritis, Macrophage Transition, Joint, Orthopaedics

1. Introduction

Osteoarthritis (OA) is the most common joint pathology worldwide [1]. It is esti-

mated that a total of 10% of men and 18% of women aged 60 and older have symptomatic OA [2]. From 1990 to 2019, the knee was found to be the most prominent location of disease, followed by the hip and the hand [3]. OA is the greatest cause of disability among older individuals [4]. Risk factors for disease include older age, obesity, prior trauma or injury to the joint, a variety of genetic factors, sex, and joint anatomy including shape and alignment [5]. The increasing life expectancy and higher obesity rates seen in the last few decades call for the need to better understand OA and its pathogenesis. The ultimate endpoint for many patients with advanced OA is joint arthroplasty surgery which is invasive, requires rehabilitation, and is costly [6]. The goal should be to mitigate the burden OA has on both patient quality of life and our growing society, in addition to the formulation of effective and less invasive therapies for those with active disease. OA is a degenerative disease of the joint that was once thought of as a disease of simply "wear and tear" that resulted from chronic use and loading [7]. However, in more recent years, there has been a greater understanding of the pathogenesis of OA as resulting from systemic inflammatory processes and the impact that some monocytes, cyto- and chemokines have on joint health in OA [8]. This paper seeks to explore the recent literature on the role of the M1 to M2 transition of macrophages in the pathogenesis and resolution of osteoarthritis.

2. Changes to the Joint in OA

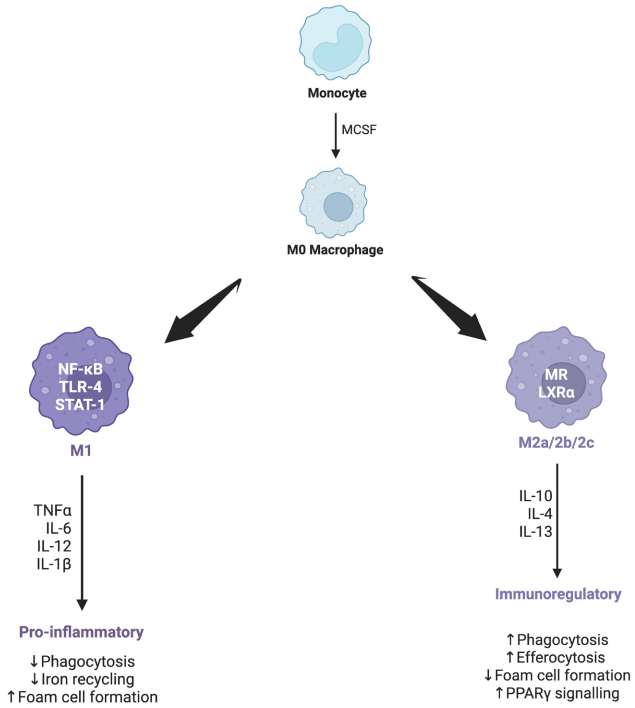
Osteoarthritis not only affects the articular cartilage of the joint, but also the subchondral bone, ligaments, capsule, synovial membrane, and surrounding muscles [9]. The joint synovium is an integral component of a joint that houses an abundance of macrophages which play an integral role in ensuring the synovium's health and longevity [10].

The articular cartilage covers the ends of bones of synovial or diarthrodial joints and serves as a weight-bearing and low-friction coating that can withstand a variety of forces at any given moment [9]. The functional unit or cell type of cartilage is the chondrocyte, which is a highly specialized cell that is responsible for both producing and maintaining the extracellular matrix of cartilage giving the tissue its structure and function [11]. Forces and loads acting on a joint are dissipated and transmitted to chondrocytes, thus maintaining the integrity of articular cartilage [12]. In a patient who has OA, the chondrocytes have diminished ability to restore articular cartilage to health. This leads to degradation of the cartilage surface, ultimately leading to joint pain and dysfunction that limits patient activity and quality of life [12]. After cartilage and extracellular matrix damage occur, the chondrocytes begin to proliferate and conglomerate [12]. These chondrocytes undergo phenotypic changes that lead to the formation of cartilage outgrowths that will eventually ossify and form bone spurs, also known as osteophytes [12]. As progressive damage occurs, chondrocytes undergo programmed cell death known as apoptosis, which affects the future of collagen production and mineralization in the joint, causing eventual subchondral bone thickening and subsequent di-

minished function. We now know that OA affects all joint tissues in addition to the articular cartilage—leading to vascular invasion of the articular surface, subchondral bone remodeling, osteophyte formation, and synovial inflammation [13]. Synovial inflammation has gained attention as having a significant connection with the pathogenesis, progression, and severity of OA [14]-[16].

3. Macrophage Role in Pathogenesis of OA

The importance of the role of macrophages in the pathogenesis of OA is debated [17] [18]. There are two main types of macrophages that function in the body-M1-like and M2-like macrophages [18]. Both types have a close relationship with various inflammatory responses but have differing functions. M1-like macrophages are predominantly involved in pro-inflammatory responses and are activated in response to signals from T helper 1 cells (Th1), while M2-like macrophages are predominantly involved in anti-inflammatory responses and act in response to Th2 cells (**Figure 1**) [18] [19]. Abnormal ratios of M1 to M2 macrophages, as well as differing activation states can lead to a host of diseases, one being OA [20]. Macrophage phenotype can cause a dependent modulation of the anabolic or catabolic responses that different cell types may have during the onset or progression of OA [19].



A scheme of macrophage immune signaling is shown beginning from the monocyte stage to either pro-inflammatory or immunoregulatory macrophages. Select chemical mediators and cytokines involved in each pathway are included. Created in BioRender. Milano, M. (2026) https://BioRender.com/0i0ro7n.

Figure 1. Macrophage immune signaling.

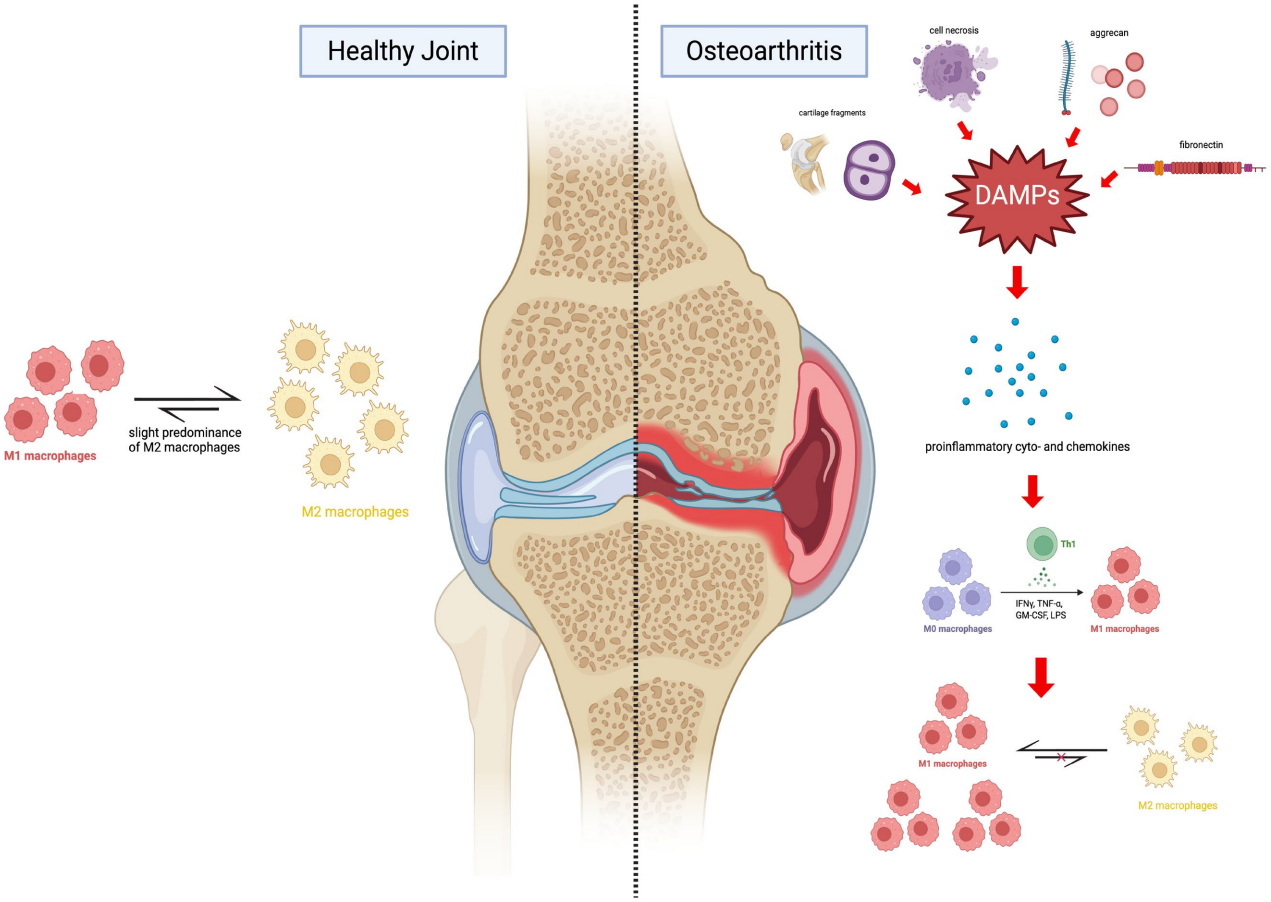
As aforementioned, synovitis has been found to be correlated with the pathogenesis and progression of OA [20]. The physiologic synovium is made up of two tissue layers, an intimal layer that consists of layers of macrophages and Fibroblast-Like Synoviocytes (FLSs). The other physiologic layer consists of the synovial sub-lining that is made of fibrous connective tissue and numerous blood vessels and lacks a substantial number of lymphocytes or macrophages [21]. These macrophages are considered tissue-resident, meaning they are embryonically derived, or non-tissue resident, meaning they are bone marrow derived. These macrophages can self-renew, but embryonically derived macrophages have the capability to persist in the synovium independent of hematopoiesis. Non-tissue resident macrophages are shorter lived and have the capacity to differentiate into either M1 or M2 macrophage phenotype depending on chemical signals received from surrounding tissue [22]. Such differentiation is crucial to predicting the fate of the synovium and joint overall in terms of health and functionality. Synovitis is denoted morphologically by an infiltration and accumulation of macrophages in the intimal lining, reconciling the correlation between synovitis and OA and the potential implication of macrophages in the pathogenesis of OA [14]-[16] [23]. Focus is often on chondrocytes and joint cartilage when discussing the effects and progression of OA, yet synovial pathology in OA is associated with both the onset and accelerated cartilage destruction in OA, making it of particular interest [24]. Furthermore, the symptomatology of OA also relies on synovial pathology and so understanding the interplay between synovium and macrophage polarization can be crucial in the emergence of OA therapies [24] [25].

As suggested by the existing literature and prior discussion, the distinction between M1 and M2 macrophages is important in understanding the pathogenesis of OA. Macrophage polarization is the process by which macrophages are signaled to become either M1 or M2 macrophages. Depending on the environment of the macrophages, different signals can impact their polarization. For example, in an infectious environment, lipopolysaccharide can signal macrophages to polarize into the M1 phenotype, whereas interleukin-4 can signal macrophages to polarize into the M2 phenotype [26] [27]. Furthermore, an important aspect of M1 and M2 polarization is the variation of cell surface markers expressed on the macrophages [28]. M1 macrophages have been found to express CD80, CD86, and CD 16/32 in excess, whereas M2 macrophages tend to express CD206 on their cell surface [29]. In addition, M1 macrophages have been found to express high levels of M1 genes including inducible Nitric Oxide Synthase 1 (NOS1), as well as secrete pro-inflammatory cytokines like tumor necrosis factor and interleukin-1. This differs from M2 macrophages which have elevated expression of arginase-1, mannose-receptor, interleukin-10, an anti-inflammatory cytokine, and chemokines CCL17 and CCL22 [28] [29]. These cell surface expression patterns are crucial for the determination of macrophage purpose and function in the environment in which they reside.

Macrophage polarization is a necessary component of proper macrophage function and utility in the body. However, as the literature suggests, when there is aberrant polarization, or a predilection for M1 polarization in the joint, osteoarthritis can result. Zhang *et al.* found that M1 macrophages were in abundance in human and mouse OA synovial tissue [20]. Additionally, Zhang and colleagues found that in mice that had a deletion in the myeloid lineage of Rheb, a GTP-binding protein that is largely involved in the mTOR pathway and the regulation of the cell cycle and had collagenase-induced OA or surgery to destabilize the medial meniscus to initiate OA, activating the Target Of Rapamycin Complex 1 (mTORC1), there was increased M1 polarization in synovial macrophages and resultant exacerbated OA [20]. However, mice with a deletion specifically in the myeloid lineage of Tuberous Sclerosis Complex 1 (TSC1), a gene that produces hamartin and regulates cell growth and division, showed an inhibition of mTORC1, increased M2 polarization, and an alleviation of collagenase-induced osteoarthritis [20]. These results emphasize the connection between macrophage polarization and progression of osteoarthritis. Furthermore, Liu and colleagues found that in patients with knee OA, the ratio of M1 to M2 macrophages was significantly higher than in patients without knee OA, further supporting the theory that a predilection for M1 macrophage polarization can lead to the pathogenesis and ultimate progression of OA [30].

Due to the degradative nature of OA, cartilage fragments, aggrecan, fibronectin, and intracellular proteins from necrotic cells present themselves as damage associated molecular patterns or DAMPs, which lead to recruitment and activation of macrophages, as well as encourage the production of inflammatory cytokines and chemokines (**Figure 2**) [31]. Damage-Associated Molecular Patterns (DAMPs) are sensed by innate immune receptors, triggering inflammatory signaling pathways that drive the development and progression of numerous inflammatory diseases. Unlike pathogen-induced inflammation, these responses are initiated by endogenous danger signals, resulting in a sterile inflammatory environment [32]. In contrast, classical T-cell activation involved in the adaptive immune response requires antigen-specific recognition by the T-cell receptor in conjunction with costimulatory signals provided by professional antigen-presenting cells, a process typically initiated in the context of infectious antigens rather than sterile tissue injury [33].

The presentation of DAMPs and production of proinflammatory cyto- and chemokines cause the M0 or resting macrophage to polarize into a proinflammatory M1 macrophage, leading to the eventual accumulation of such macrophages in the joint, exacerbating disease. Debris released from the subchondral bone and damaged menisci in a patient with OA can compound the inflammatory effects seen in the pathogenesis of OA by causing the release of even more inflammatory cytokines and metalloproteinases [31]. Further recruitment of macrophages damages the synovium and joint, increasing cartilage degradation, and causes the eventual destruction seen in OA.



The comparison between a healthy knee joint and an osteoarthritic knee joint shows a slight predominance for anti-inflammatory M2 macrophages in the healthy joint and a slight predominance for pro-inflammatory M1 macrophages in a joint with osteoarthritis. The impact of Damage Associated Molecular Proteins (DAMPs) in the pathogenesis of osteoarthritis is simplified into a flow diagram showing the favoring of M1 macrophages in a diseased joint. Created in BioRender. Milano, M. (2026) https://BioRender.com/hnqixjw.

Figure 2. Macrophage polarization in osteoarthritis.

It does not suffice to say that inflammatory signals cause an increase in the recruitment of M1 polarized macrophages in OA, but rather it is also the joint environment in OA that can potentially block the transition of proinflammatory damaging M1 macrophages to anti-inflammatory, repairing M2 macrophages. Kraus *et al.* found that when performing immunohistochemistry on the synovial fluid of OA patients, the synovial fluid of a particular patient demonstrated cells that had the co-localization of both TGF-β (an anti-inflammatory M2 macrophage marker) and iNOS (a pro-inflammatory M1 macrophage marker). The authors suggested a possible block in the transition of pro-inflammatory (M1) macrophages to anti-inflammatory (M2) macrophages [34]. This finding may prove to be significant in the further understanding of the pathogenesis of OA and the roles macrophages play. Additionally, Kraus *et al.* elucidate the idea that macrophages and inflammation are directly associated with joint symptoms and the disease severity seen on radiographs, whereas severity seen on radiographs is not

necessarily a reliable predictor of joint symptoms in patients with OA [34]. These findings are important in illustrating the overall impact that macrophages have not only on the pathogenesis of OA, but on its severity and progression.

More specifically, Fang *et al.* explored the effects of the triggering receptor expressed on the myeloid cell family (TREM) on the promotion of macrophage inflammation and polarization. They found that a receptor of the TREM family, TREM2 promotes the polarization from M1 to M2 macrophages in OA by regulating the NF-κB/CXCL3 axis [35]. Fang *et al.*'s findings further support the idea that it is a malfunction in the macrophage transition that can lead to the pathogenesis and progression of OA. Targeting the expression and harnessing the effects of TREM2 may prove to be a revealing path for researchers to take in the hopes of developing efficacious treatment for OA [35].

4. Exploiting the M1 to M2 Transition as a Therapeutic Strategy for OA

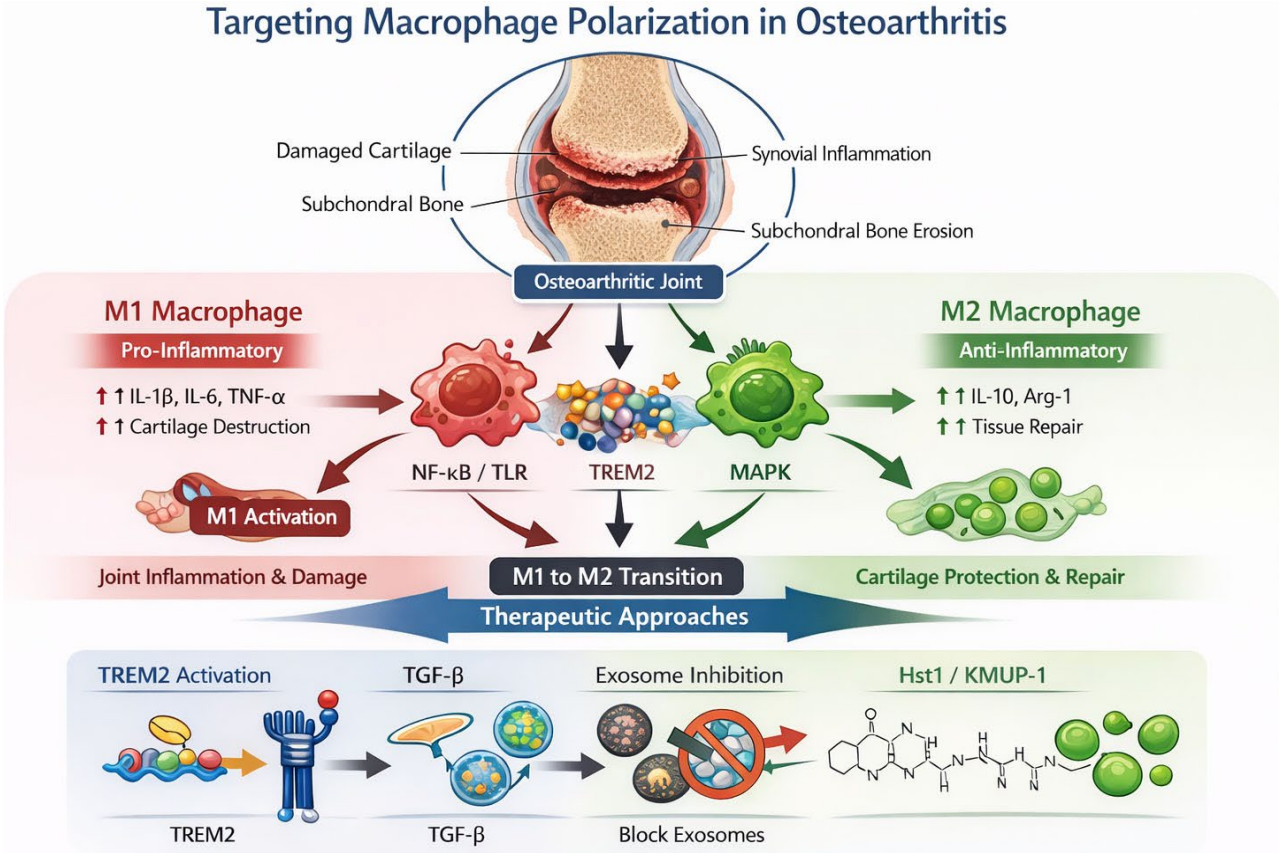


Figure 3. M1 and M2 macrophages in osteoarthritis and therapeutic strategies targeting macrophage polarization. Pro-inflammatory M1 macrophages (red) contribute to joint inflammation and cartilage destruction, while anti-inflammatory M2 macrophages (green) promote tissue repair. Therapeutic approaches include modulation of Nuclear Factor-kappa B (NF-κB), Mitogen-Activated Protein Kinases (MAPK), Toll-Like Receptors (TLRs), Transforming Growth Factor β (TGF-β) pathways, triggering receptor expressed on the myeloid cell family (TREM2) activation, and exosome inhibition. Figure created by authors.

Although there exist a few treatments for OA such as intra-articular injections,

surgery, platelet-rich plasma, and other cellular therapies, there remains a need for more effective and longer lasting therapies [17]. Intra-articular therapy may pose as an attractive treatment strategy for OA, but many challenges with intraarticular drug delivery exist including rapid clearance from the synovial cavity, poor penetration into cartilage tissue, and limited retention at target sites [36]-[38]. Rapid clearance occurs secondary to continuous synovial fluid turnover and drainage via the lymphatic system, with most drugs clearing from the joint space within hours to days [39]. Additionally, cartilage penetration proves to be another significant challenge in the efficacy of intra-articular treatments for OA. The dense, negatively charged extracellular matrix of cartilage, composed mostly of aggrecan and collagen II, restricts drug transport into the tissue where chondrocytes reside [40]. Furthermore, non-specific distribution within the joint space leads to an uneven drug distribution and inadequate accumulation of therapy at diseased sites [37] [38]. These challenges make it especially important for different modes of therapy to be explored in managing OA.

With recent literature highlighting the concept that macrophage polarization plays a crucial part in the pathogenesis and progression of OA, exploring ways to target and exploit this transition to favor polarization to the M2 anti-inflammatory subtype may prove to be helpful strategies to decrease the burden of OA on patients.

There are several biochemical pathways that have been studied in the search to find potential targets for OA treatment (**Figure 3**).

4.1. Pathway Inhibitors

One such pathway is the NF-κB signaling pathway. New evidence has been published supporting the idea that the NF-κB signaling pathway plays an integral role in M1 polarization and thus eventual inflammatory cytokine release, *i.e.*, the release of IL-1β, IL-6 and TNF-α [41]. Moreover, in OA, the DAMPs from damaged tissue activate Toll-Like Receptors (TLRs) which then lead to the M1 polarization, which is effectively regulated by the TLR/NF-κB signaling pathway [42]. These findings support the indication that targeting the NF-κB and TLR signaling pathway could provide patients with a new treatment for this disease. Furthermore, Wu *et al.* in an *in vivo* rat study, found that human salivary peptide Histatin-1 (Hst1), an immunomodulatory peptide which provides cell-activating functions like migration, adhesion, and differentiation, has the ability to downregulate the Mitogen-Activated Protein Kinases (MAPK) and NF-κB signaling pathways in M1 macrophages and initiates their switch to M2 macrophages [43]-[48]. This suggests that the MAPK signaling pathway has a role in OA and that Hst1 can potentially be used as a therapeutic trigger for the M1 - M2 transition via the mediation of the MAPK and NF-κB pathways [48]. Similarly, KMUP-1, a synthetic xanthine-based derivative developed by Yeh *et al.*, was found in Huang *et al.*'s study to have an anti-inflammatory effect on osteoarthritic rats by virtue of its ability to suppress the activation of the MAPK/NF-κB signaling pathway [49]. Huang *et al*'s *in vivo* rat study showed that KMUP-1 decreased mechanical hyper-

algesia, inflammation, and articular cartilage destruction in osteoarthritic rats [49]. These findings further emphasize the role that the MAPK and NF-κB pathways have on macrophage polarization and the subsequent pathogenesis of OA which can be further studied as a potential therapeutic target for treatment of OA [49].

4.2. Pathway Agonists

Conversely, upregulating the Transforming Growth Factor β (TGF-β) pathways may prove to be beneficial in treating OA. Recent literature has shown that macrophage polarization has a connection with the TGF-β pathways. Dai *et al.*'s in vitro study found that squid type II collagen was able to encourage M2 polarization of macrophages and encouraged such macrophages to express pro-chondrogenic genes like TGF-β [50]. Exploiting such a concept could allow researchers to formulate a therapeutic entity to help halt the progression and lessen the severity of OA, similar to how targeting the NF-κB and TLR signaling pathway would, although via different mechanisms. The translation of these findings to an *in vivo* study would be most suitable for determining the efficacy of squid type II collagen as a treatment modality for human osteoarthritis.

A promising *in vivo* rat study by Lee *et al.* concluded that TissueGene-C (TG-C), a new cell and gene therapy for OA, which consists of human allogeneic chondrocytes and cells formulated to overexpress TGF-β1, provides not only pain relief to patients with OA but also changes the structure of cartilage in rats [51]. In addition, Lee *et al.* found that the increased levels of TGF-β1 resulting from the introduction of TG-C led to increased expression of arginase 1, a marker of M2 macrophages, and conversely decreased the expression of CD86, an M1 macrophage marker [52]. The importance of such a study like Lee *et al.*'s is that the authors saw an improvement in cartilage structure in rats given TG-C. This means that there is potential for not only lessening symptoms of OA once they have started, but also the ability to modulate the effects that OA has had on the joint already. This study helped further elucidate the concept that increasing polarization from M1 to M2 macrophages can be advantageous for the joint microenvironment and ultimately for patients suffering from OA.

4.3. Exosomes as Potential Therapeutic Targets

Though many studies focus on the impact of macrophage development and polarization on the pathogenesis and progression of OA, few studies, like Liu *et al.*'s, which analyzed synovial fluid obtained from both human and mouse knees, have focused on the impact that exosomes have on the progression of OA by facilitating the M1 polarization. Inflammatory FLS-derived exosomes were found to enhance the M1 polarization of macrophages, which in turn would facilitate the initiation of OA, as well as accelerate the progression [53]. The facilitation is done with the encouragement of macrophage glycolysis. Stimulating these inflammatory exosomes leads to the accumulation of hypoxia-inducible factor 1-alpha (HIF1α)

which is a pro-glycolytic transcription factor. Upregulated glycolysis in macrophages satisfies the increased energy needs for the activation and progression of inflammation. These findings suggest that targeting exosomes for possible OA therapy may be fruitful and requires more exploration [53].

The inclusion of the aforementioned pathways serves to illustrate that even though the ways in which each pathway can be targeted may differ, they all share the common goal of treating OA symptoms and progression (Table 1).

Table 1. Therapies targeting macrophage polarization in OA.

Mechanism	Potential Therapeutic Agent	Target	Effect on Macrophage Polarization
Pathway Inhibitors	NF-κB pathway inhibitors	TLR/NF-κB signaling	Suppresses M1 polarization
	KMUP-1 (synthetic xanthine derivative)	MAPK/NF-κB signaling	
	Histatin-1 (Hst1)		Promotes M1→M2 transition
Pathway Agonists	Squid type II collagen	TGF-β signaling/expression	Promotes M2 polarization
	TissueGene-C (TG-C)		
Exosomes	Inhibition or modulation of FLS-derived exosomes	Exosome-mediated glycolysis, HIF-1α	Block promotion of M1 polarization

For example, it was discussed that targeting the NF-κB and TLR signaling pathway with the goal of blocking the pathway and its subsequent effects may prove to be an effective treatment for OA, whereas exploiting and potentiating the effects of TGF-β pathways in the joint may also be a suitable treatment for patients with OA. This demonstrates that targeting certain biochemical pathways in finding therapies for OA comes down to harnessing the ability to affect the macrophage polarization process, emphasizing the importance of macrophage polarization in not only the pathogenesis and progression of OA, but also in the potential treatment of the disease. More research needs to be done to further elucidate the impact that targeting these pathways, along with other pathways associated with macrophage recruitment and polarization, has on the progression and resolution of OA [31] [53] [54].

5. Conclusion

Osteoarthritis is a complex, multifactorial disease that affects not only articular cartilage but the entire joint, including subchondral bone, synovium, and surrounding tissues. Emerging evidence highlights the critical role of macrophages in OA pathogenesis, particularly the balance between pro-inflammatory M1 and anti-inflammatory M2 phenotypes. Aberrant M1 polarization, driven by damage-

associated molecular patterns, synovial inflammation, and dysregulated signaling pathways such as NF-κB and TLRs, contributes to cartilage degradation and joint dysfunction. Conversely, promoting M2 polarization through TGF-β pathway activation, cell and gene therapies like TG-C, or modulation of exosome-mediated signaling shows promise in reducing inflammation and supporting joint repair. These findings underscore that macrophage polarization acts both as a key mediator of OA progression and a potential therapeutic target. Further studies are needed to validate these strategies, optimize delivery approaches, and assess their long-term efficacy and safety in restoring joint homeostasis.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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