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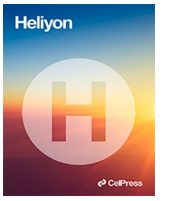

Review article

Synovial mast cells and osteoarthritis: Current understandings and future perspectives

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ABSTRACT

Osteoarthritis (OA) is a prevalent joint disease worldwide that significantly impacts the quality of life of individuals, particularly those in middle-aged and elderly populations. OA was initially considered as non-inflammatory arthritis, but recent studies have identified a substantial number of immune responses in OA, leading to the recognition of inflammation as a key factor in its pathogenesis. An increasing number of studies have found that mast cell (MC) and MC-secreted inflammatory mediators and cytokines are notably increased in the synovial fluid of OA patients, indicating a potential association between MCs and the onset and progression of synovial inflammation. The present review aims to summarize the significance and mechanism of MCs in the pathogenesis of OA. Meanwhile, we also discuss the clinical potential of using MCs as therapeutic target for OA therapy. Modulating the activities of MCs or the mediators of MCs in the synovial fluid inflammatory microenvironment will be promising new options for the treatment of OA.

1. Background

Osteoarthritis (OA) is an increasingly common joint disease worldwide, affecting estimated 240 million individuals [1]. Clinical manifestations of OA typically include joint pain, stiffness, and limited range of motion. The disease progression is usually gradual, but it can eventually lead to joint failure, resulting in persistent pain and disability [2]. While OA can impact any joint, it is most commonly observed in the knee. The development of OA may be associated with factors such as obesity, age, joint trauma, and biomechanical changes [3,4]. Interestingly, gender may also contribute to the pathogenesis of OA, as studies have shown a higher prevalence of OA in females than in males [5]. OA was initially thought to be a non-inflammatory form of arthritis, but as a large number of immune

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responses have been identified in OA, it has been increasingly recognized that inflammation is involved in the pathogenesis of OA [6–8]. The current treatment strategies for OA include drug therapy (NSAIDs), nondrug therapy (such as education, weight loss, exercise, and physical therapy) [9,10], and surgery. However, surgical treatment can be associated with complications and high costs [11]. In order to effectively treat the disease, it is crucial to focus on controlling the development of OA.

Mast cells (MCs) are key structural and functional components of the innate and adaptive immune systems and play an important role in responding to inflammation and infection [12]. Degranulation is the process by which various particles are released from MCs, serving as the primary allergic reaction of MCs. The particles primarily released during this process include histamine, serotonin, proteases, tryptase, lipid mediators (prostaglandins, leukotrienes), as well as cytokines, chemokines and reactive oxygen species [13]. When MCs are not activated properly, they can lead to various diseases, such as allergic diseases and autoimmune diseases [14,15]. MCs in OA were mainly divided into two subgroups according to protease content: the MC_T subgroup expressing tryptase and the MC_{TC} subgroup expressing tryptase, chymotrypsin and carboxypeptidase A3 (Cpa3) [16,17]. The number of MC_{TC} cells is dominant in normal joint tissues; however, in the tissue of patients with OA and other inflammatory disease, there is a significant increase in the number of cells in the MC_T subgroup [18,19]. This review aims to enhance the understanding of the biological significance and mechanism of MCs in OA. In addition, we summarized the role of MCs in the synovial fluid microenvironment, offering valuable insights for future OA treatments.

2. MCs and OA

2.1. MCs are involved in the pathogenesis of OA

Multiple studies have provided evidence supporting the involvement of MCs in the pathophysiology of OA. The number of MCs and the and the proportion of degranulation in the synovium of patients with OA were significantly increased, which was characterized by an increase in the release of histamine, Prostaglandin D2 (PGD2) and tryptase [20–22]. Besides, the number and degranulation status of MCs were positively correlated with the synovitis score and cartilage injury [23,24]. In addition to clinical data, experimental evidence also suggests that MCs have an impact on the progression of OA. Proteomics analysis revealed the accumulation of specific inflammatory proteins in MCs after 9 days of incubation in OA synovial fluid. This accumulation of inflammatory proteins in MCs may further exacerbate the inflammatory process associated with OA [20]. The injection of MCs exacerbated the development of monosodium iodoacetate-induced OA in mice and stimulated the release of inflammatory cytokines [25]. Genetic deficiency or pharmacologic inhibition of MCs has been shown to provide protection against the development of OA in mice [26,27]. These evidences indicate that activated MCs release inflammatory factors through degranulation, thus participating in the pathogenesis of OA.

2.2. Activation pathways of MCs in the pathogenesis of OA

In the microenvironment of osteoarthritis, inflammatory mediators activate MCs. Below we describe the pathways involved in MCs activation.

SCF/C-Kit Receptor Stem cell factor (SCF) is a growth factor expressed by endothelial cells and fibroblasts. It is transmembrane protein synthesized in a soluble or membrane-bound form by enzymatic cleavage of two alternatively spliced mRNAs [28]. SCF exerts its biological functions by binding to membrane tyrosine kinase receptors (C-Kit). The development and survival of MCs are critically dependent on SCF/C-Kit. SCF binds two c-Kit monomers and enables interactions between IgG-like domains 4 and 5 of adjacent c-Kit molecules. The homodimeric state of C-Kit is induced by SCF and subsequently stabilized by IgG 4/5-like domain interactions, allowing for efficient trans-phosphorylation in the lateral membrane region, kinase insert region, kinase domain, and terminal COOH tail. Subsequently, the phosphorylated residues act as docking sites for adjacent signaling molecules, including Src kinase, PI3K, Shc, and phospholipase Cγ (PLCγ). This interaction leads to the activation of the RAS-RAF-MAP kinase (MAPK) cascade, which in turn enhances the activation of transcription factors necessary for various biological functions, results in the promotion of MC proliferation [29,30]. Co-sensing of ATP and IL-33 results in the overactivation of MCs [31]. A study indicates that the activation of SCF/C-kit is essential for the cytokine response necessary for the co-sensing of ATP and IL-33, thereby facilitating the expansion of pro-inflammatory cytokines and eicosanoid production [32]. This mechanism may be crucial for mast cells in mediating heightened inflammatory responses. Besides, in inflammatory and tumor environment, SCF activates C-Kit receptor to induces MC degranulation, resulting in the expression and release of histamine, proinflammatory cytokines, and chemokines [33,34]. Inhibitor of the SCF/C-Kit pathway, such as RIN3 and β-eudesmol, markedly suppressed SCF-induced MCs migration and reduced MCs infiltration and inflammatory factor content in inflammatory sites [35,36].

IgE/FcεR1 A large number of studies have shown that immunoglobulin E (IgE) and MCs are key factors in the long-term pathophysiological process and tissue remodeling of allergic diseases [37,38]. According to the structure of FcεR1, the α chain serves as the IgE binding site, and the two γ subunits participate in the initiation and propagation of downstream signals of FcεR1. When bound to antigen, FcεR1 forms dimers. Cytoplasmic signaling is activated through the binding of the Src family protein tyrosine kinase Lyn and phosphorylation of the 'immunoreceptor tyrosine activator' (ITAM) located at the terminal of the β and γ subunits. Syk binds to the γ moiety of ITAM and facilitates the phosphorylation of multiple targets [39–41]. During a type I hypersensitivity, the release of IgE and its binding to FcεRI on the surface of tissue-resident MCs initiate the activation of the FcεRI signaling cascade. This process triggers degranulation and the subsequent release of pro-inflammatory cytokines of MCs [41,42]. Early studies have shown that inhibiting the IgE-activated MCs can decrease the release of inflammatory factors and the stimulation of chondrocytes, ultimately leading to improvements in pain and disability among patients with OA [43,44]. Subsequently, a study clarified that, MCs activated by IgE/FcεR1

pathway promote its downstream targets such as MAPK through Syk signaling pathway in OA, resulting in the release of multiple pro-inflammatory factors such as IL-1β, IL-6, CCL2, ADAMTS4 and MMP13, which is not only an important mechanism for the formation of inflammatory environment in osteoarthritis. It also leads to chondrocyte apoptosis, and cartilage breakdown [26].

IgG/FCγR Synovial MCs in patients with RA and OA express the IgG receptors FcγRI and FcγRII, but they do not express FcγRIII. When exposed to a specific stimulus, such as IFN-γ, the amount of FCγR on the MCs surface increases substantially [45,46]. FcγRI mediates the substantial MC degranulation and increase the production of cytokines such as PGD2, tumor necrosis factor (TNF)-α, granulocyte-macrophage colony stimulating factor (GM-CSF), IL-3, and IL-13. Besides, FcγRI activation of MCs through IgG promotes the expression of pro-survival protein A1/Bfl-1 [47,48]. In addition, IgG induces degranulation of MCs by binding to FcγRII, manifested by increased release of histamine and inflammatory substances [45]. Besides, IgG may be involved in TLR4-FcγR cross-talk, activating the Syk signaling pathway and mediating cytokine production [49]. Both IgE and IgG activate MAPK, which promotes inflammatory cytokines (IL-1 and TNF-α). Selective inhibition of MAPK can reduce the apoptosis of osteoblasts, thus exerting a positive effect on the treatment of OA [50].

Toll/TLRs Toll-like receptors (TLRs) are crucial receptors for pathogen recognition and innate immunity. Evidence suggests that TLR1-10 expression in addition to TLR8 has been identified on human mast cells [51]. Peptidoglycan (PGN) from Staphylococcus aureus stimulates mast cells to produce TNF-α, IL-4, IL-5, IL-6, and IL-13 in a TLR2-dependent manner. LPS from E. coli stimulates mast cells to produce TNF-α, il-1β, IL-6, and IL-13 in a TLR4-dependent manner [52]. All TLRs signaling pathways ultimately lead to activation of the transcription factor nuclear factor-κB (NF-κB), which controls the expression of many inflammatory cytokine genes [53]. Upon activation of TLRs and subsequent activation of NF-kB, various chemokines, including IL-8 and CCL5, as well as cytokines such as IL-1, IL-6, and TNF-α are produced. These molecules play a crucial role in the recruitment of macrophages, granulocytes, and lymphocytes into the synovium of patients with OA to increase local inflammation and cartilage degradation, playing a crucial role in the progression of OA [54,55]. In addition, TLRs has a synergistic effect with FcεRI, and the activation of TLRs sensitizes the MCs to stimulation through FcεRI. This mechanism may further accelerate the inflammatory response [56,57].

NGF/TrkA Receptor Nerve growth factors (NGF) belong to a family of neurotrophin compounds that play an important role in the survival of neurons damaged during development. It is also a potent factor in MC degranulation in vitro and in vivo [58]. MCs produce TrkA receptors in OA, which are activated by NGF, resulting in the upregulation and release of inflammatory mediators and adverse neuroimmune tissue reactions, resulting in hyperalgesia in patients [59]. NGF promotes the secretion of PGD2 from MCs by activating TrkA receptors to enhance the Ras, phosphoinositide-3 kinase (PI3K). The production of PGD2 may contribute to OA hypersensitivity by activating PGD2 receptor 1 in nociceptors [60,61]. This finding suggests that targeting the TrkA receptor of NGF in MCs could be a promising therapeutic approach for managing OA pain.

In summary, MCs play a role in the inflammatory process of OA through various pathways. By inhibiting MC activation or blocking the pathway between MCs and OA, it is possible to stabilize MCs to some extent, reduce the inflammatory response, and control the development of OA (Fig. 1).

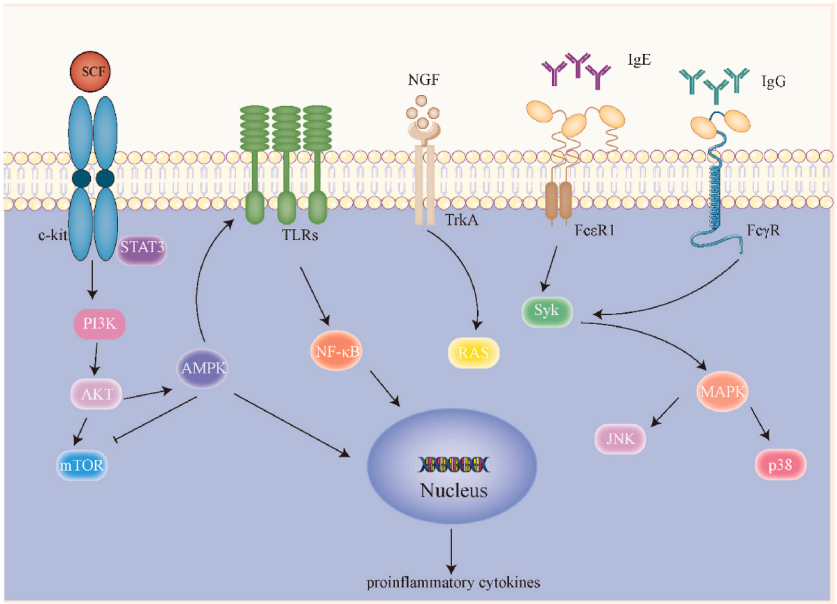

Fig. 1. The Pathways that MCs Activated in OA. MCs may participate in OA activation pathways, including stem cell factor/C-Kit receptor (SCF/C-Kit), immunoglobulin E/Fcε receptor 1 (IgE/FcεR1), immunoglobulin G/Fcγ receptor (IgG/FcγR), nerve growth factor/TrkA receptor (NGF/TrkA), and Toll-like cells/receptors (TLRs).

2.3. Mediators of MCs involved in OA

Traditionally, MC media is divided into pre-stored media and self-synthesized media. The latter is due to the rapid production and release of arachidonic acid metabolites and the slow production and secretion of cytokines [62]. Tryptase is a preformed mediator in MC granules, encoded by TPSB2 and TPSD1 gene. The expression of these genes was found to be upregulated in patients with OA compared to healthy synovium, indicating that MCs have enhanced transcriptional activity in synovium of OA [63]. Besides, the degranulation of MCs was found to be more pronounced in patients with OA, manifested by significantly increased levels of tryptase, eosinophil cationic protein and histamine [64]. The release of pro-inflammatory mediators by activated MCs can contribute to synovial inflammation and cartilage degeneration (Fig. 2). The available evidence indicates that the activation of MCs and their associated mediators contribute to the development of OA. The following section outlines the established effects of certain mediators on OA (see Table 1).

Tryptase Tryptases are proteases specifically secreted by MCs, serve as markers for MCs [65]. They can be classified into different forms, including α, β, γ and δ. β-Tryptase is the primary isoform found in MCs and has been extensively studied [66]. Multiple evidences proved that tryptase promotes inflammation response [67,68]. The extent to which tryptase contributes to the development of inflammatory processes and cartilage damage largely depends on its activation of the protease-activated receptor-2 (PAR-2) receptor. It stimulates the proliferation of synovial fibroblast-like cells (SFC) and triggers the release of pro-inflammatory cytokine IL-8 through PAR-2 [69,70]. In OA mice lacking PAR-2, cartilage degradation was reduced [71]. In addition, β-tryptases cleaved Proteoglycan 4 (PRG4), which is related to boundary lubrication and anti-inflammatory. Cleaved PRG4 activates the NF-κB, result in the progression of OA [72]. Tryptases are also matrix metalloproteinase (MMP) convertases. They are biologically active on MMP-1, MMP-2, MMP-3, MMP-9 and MMP-13. Tryptases activation of MMP leads to recombination of the intercellular matrix and degradation of fibrous collagens, proteoglycans and laminins. In OA, they mediate cartilage damage and proteolytic loss of aggrecan proteoglycans in arthritis by activating MMP-3 and MMP-13 [73,74]. Besides, it has been found that tryptases can induce further degranulation of MCs through a positive feedback mechanism, thus promoting further release of inflammatory mediators [75]. Tryptases increase microvascular permeability, neutrophilia in vivo, and stimulate MCs to release histamine [76,77].

Histamine The production of histamine in the synovial fluid of OA patients were significantly increased, and was significantly correlated with the number of MCs [21]. In OA patients, aberrant phenotype of OA chondrocytes express histamine receptors such as H1 and H2 [78]. Histamine can increase the histamine H1 receptor expression in synovial fibroblasts [79]. Treatment of mice with cetirizine, a histamine H1 receptor antagonist, reduced meniscus severity and OA-related mediators in mice. It was also demonstrated in a cross-sectional study that H1 antihistamines were associated with a reduced prevalence of OA in the knee [80], suggesting that the use of drugs to block histamine activity in MCs could be a therapeutic target for OA. Interestingly, H4 receptors are found to expressed on the surface of MCs, which mediate the release of pro-inflammatory cytokines and chemokines (TGF-β1, TNF-α, TNF-β, PDGF-BB, TIMP-2, M-CSF et al.) [81].

IL-1β and IL-6 Interleukin-1β (IL-1β) and Interleukin-6 (IL-6) are important pro-inflammatory cytokines in the pathogenesis of OA. They are secreted by MCs and are significantly increased in OA and are associated with the severity of OA [82–84]. In OA cartilage, IL-1β plays a crucial regulatory role in inducing chondrocyte apoptosis [85]. IL-1β promotes the degradation of cartilage by stimulating

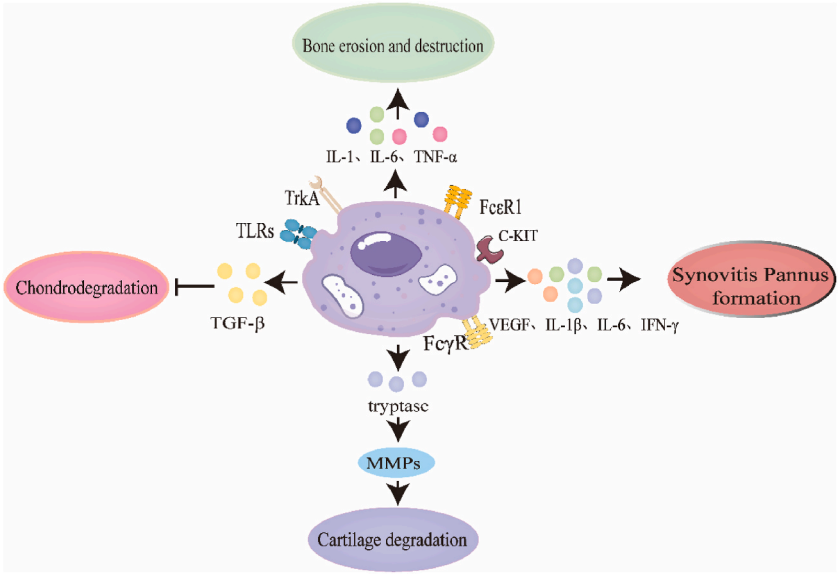

Fig. 2. Role of MC Mediators in OA. The activation of MCs leads to the production of cytokines that play a crucial role in the inflammatory process of OA. These cytokines, such as IL-1, IL-6, and TNF-α, are involved in bone erosion and destruction. Additionally, VEGF, IL-6, and IFN-γ contribute to the development of synovitis. Tryptase-induced MMPs promote cartilage degradation, while TGF-β helps inhibit cartilage destruction.

Table 1
Selected MCs mediators and their potential roles in OA.

Mediators	Potential Roles in OA	References
TNF-α	Stimulates osteoclast generation Promotes cartilage destruction Promotes neutrophil proliferation	[97–102,132]
IL-1β and IL-6	Promote the degradation of cartilage Induce apoptosis of chondrocytes Promote osteoclast generation Induce the Th17 cells differentiation	[76–81,123]
IFN-γ	Activates macrophages and white blood cells Increase FcεR1 of MCs	[87–89]
Tryptase	Promotes the development of inflammatory processes and cartilage damage Stimulate MCs degranulation	[59–67]
Histamine	Increases the release of inflammatory factors in OA Promotes osteoclast formation	[69–71,148]
NGF	Mediates pain and inflammation in OA Stimulates chondrocyte metabolism	[93,94]
VEGF	Induces angiogenesis Promote inflammation, chondrocyte hypertrophy and endochondral ossification	[107–111]
TGF-β	increases expression of proteases and induces proteoglycan degeneration TGF-β/Smad3 induces the development of OA	[115,116]

the expression of matrix MMPs and aggrecanases. It also induces the overexpression of MMP-13 through the p38, JNK, and NF-κB signaling pathways, leading to cartilage destruction [86,87]. Besides, IL-1β reduces the production of cartilage-specific macromolecules, such as type II collagen, by regulating the transcription factors Sp1 and Sp3(88). IL-6 can induce increased expression of the aggrecan-degrading enzymes ADAMTS-4 and MMP-3 and the collagen-degrading enzymes MMP-1 and MMP-13 and promote cartilage degradation [89]. IL-1 and IL-6 also promote osteoclast generation. IL-1β primarily inhibits the synthesis of extracellular matrix (ECM) proteins, promoting the generation and maturation of osteoclasts, and enhancing the inflammatory process of OA. The mechanism of IL-6 promoting osteoclasts is not clear. It may be related to the alterations in the ratio of RANKL to OPG and/or M-CSF expression [90,91]. In addition, IL-1β also regulates NGF expression in synovial fibroblasts, making it a potential target for the treatment of OA pain [92].

IFN-γ MCs have the ability to regulate the expression of interferon-gamma (IFN- γ) in the immune response. Its mechanism is mainly by stimulating other immune cells to release IFN, such as NK cells and T cells [93–95]. IFN-γ can be detected in the peripheral blood of OA patients [96]. Elevated levels of IFN-γ can activate macrophages and enhance the recruitment and activation of white blood cells, thereby exacerbating the inflammatory response in OA synovitis and promoting the inflammatory process [97,98]. In addition, IFN-γ itself is one of the factors that stimulate the increase of FcεR1 on the surface of MCs [99].

NGF NGF is significantly elevated in damaged or inflamed tissues and promotes pain sensory conduction in injury-inducing neurons through various mechanisms [100]. MCs have the ability to synthesize, store, and release NGF upon degranulation, thus playing a crucial role in pain conduction, nerve immunity, and tissue inflammation [101,102]. In an OA rat model, activated MCs increases NGF in synovial fluid and the sensitivity of NGF is increased by the upregulation of its receptor TrkA, promoting a persistent and intense pain response [103]. In addition, upregulated NGF in OA stimulates chondrocyte metabolism in the osteoarthritic process [104].

TNF-α Tumor necrosis factor–alpha (TNF-α) is pro-inflammatory mediators stored in granules of MCs. Its expression was significantly increased in the synovial tissue of early OA [105,106]. TNF-α promotes progression of OA through multiple mechanisms. For example, TNF-α has a detrimental effect on cartilage. TNF-α upregulates the expression of many factors, such as protein-2 (BMP-2), MMP-3 and a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 4 (ADAMTS-4), thereby promoting cartilage destruction [107–110]. It can also promote chondrocyte apoptosis, affect bone remodeling, stimulate the proliferation of osteoblasts, and activate osteoclasts [111,112]. In vitro studies have shown that the inhibition of TNF-α has a positive effect on the viability and proliferation of cartilage [113]. In addition, TNF-α may be key in the pain of OA. Clinical OA patient data showed that the level of TNF-α in synovial fluid was positively correlated with the pain score of knee OA [114].

VEGF As a classic angiogenic cytokine, Vascular endothelial growth factor (VEGF) may be stored and released from the cytoplasmic granules of mast cells [115]. VEGF is significantly increased in the synovial fluid of OA patients and is associated with pain [116]. Angiogenesis can promote inflammation, chondrocyte hypertrophy and endochondral ossification. VEGF actively promotes angiogenesis and neovascularization and promotes the development of OA inflammation [117–119]. The injection of VEGF into healthy mice resulted in synovial hyperplasia, increased calcification of the articular cartilage, osteosclerosis, and degradation of cartilage [120]. It also stimulates other inflammatory cells in the microenvironment to release angiogenic mediators, cytokines, and extracellular matrix-degrading proteases, thereby promoting angiogenesis [121]. In a rat model of OA, knocking down the expression of VEGF helps protect chondrocytes and delays the progression of OA [122].

TGF-β Mast cells also secrete Transforming growth factor-β (TGF-β) [123]. TGF-β is generally considered to protect against cartilage damage. For instance, IL1α-induced JAK/STAT signaling is antagonized by TGF-β [124]. However, recent research shows that TGF-β signaling has conflicting roles of in the development of OA. Synovial joint homeostasis depends on the complex control of TGF-β signal transduction pathways. In osteoarthritic joint, TGF-β activates p38 and Smad1/5/8, result in the increased expression of

proteases and proteoglycan degeneration, while the activation of Smad3 protects the cartilage degradation [125]. But another study proved that TGF-β/Smad3 induces the development of OA, indicating that the role of TGF-β relies upon intricate environment of synovium [126].

3. MCs and OA synovial fluid microenvironment

OA synovial fluid microenvironment often changes. For example, inflammatory cytokines, such as IL-17 and IL-22, are increasingly expressed [127]. Within the microenvironment of synovial fluid, various inflammatory cells contribute to the development of inflammation. We propose that crosstalk between MCs and synovial microenvironment plays an important role in OA. MCs interact with these inflammatory cells, leading to changes in the synovial fluid microenvironment and facilitate the progression of synovial inflammation (Fig. 3).

T Cells The increased expression of many T cell-related cytokines, such as IL-2, IL-6, IL-10, IL-17, IFN-γ, in patients with OA, indicating that T cell activation and differentiation play an important role in the pathogenesis of OA [128]. During the immune response of OA, immature dendritic cells capture allergens and, upon maturation, migrate to local lymph nodes where they present these antigens to naive T cells. This interaction promotes the differentiation of $CD4^+$ T cells into Th2 cells. Th2 cells subsequently secrete IL-4, which induces isotype switching in B lymphocytes from IgM class antibodies to IgE class antibodies, thereby activating mast cell IgE/FcεRI signaling [129]. In turn, MCs can present native antigens to human T cells, which can directly activate T cells and promote T cell proliferation [130,131]. For example, research shows that MCs secret IL-1β, TGF-β and IL-6 to induce $CD4^+$ T cells to differentiate into Th17 cells [132–134]. Although lower than that in RA patients, the number of Th17 cells in OA patients was significantly higher than that in healthy patients [135]. The Th17 increase the expression of IL-17, which enhances the inflammatory response in OA pathogenesis [136]. Therefore, the increase in Th17 correlates with the progression of OA [133,137]. In addition, MC-mediated IL-6 and histamine decrease Treg cells and inhibit their inflammatory suppressive activity [138].

Neutrophil There are varying levels of neutrophils present in the synovium of OA [139]. The role of neutrophils in OA may depends on the level of elastase and TGF-β [140]. MCs are capable of facilitating the release of PGD2 to recruit the neutrophils [140]. PGD2 induces lymphocytes to produce IL-8, recruiting more neutrophils into the synovial fluid [141]. The MC-restricted tryptase mMCP-6 helps recruit neutrophils to the site of bacterial infection and has a key immune role [142]. MCs can also produce many cytokines and growth factors that affect neutrophils, including TNF-α, IL-1β, GM-CSF, and IL-6 [143].

Fibroblast MCs may participate in joint destruction by inducing MMPs production to activate fibroblasts. Activation of synovial fibroblasts increases the expression of SCF, which promotes the survival and proliferation of MCs, leading to an increase in MCs in

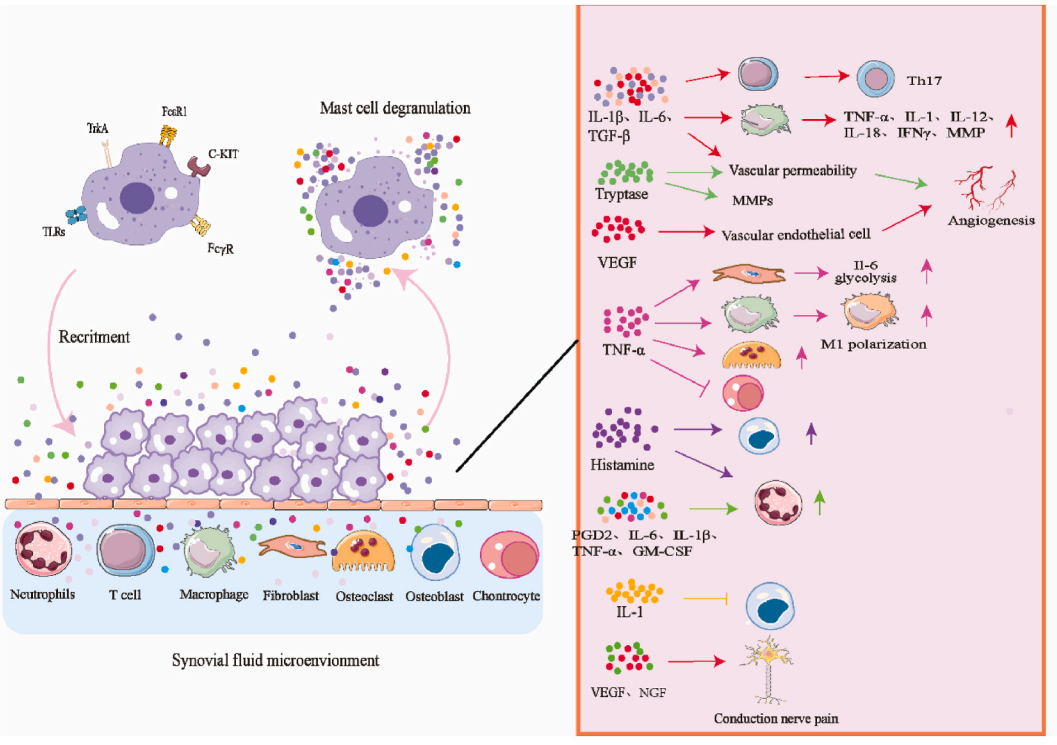

Fig. 3. The Role of MCs on Other Cells in the OA Synovial Fluid Microenvironment. In the stages of OA, MCs are recruited and activated in the synovial fluid microenvironment. These MCs release various cytokines that have an impact on other cells in the synovial microenvironment, including neutrophils, T cells, macrophages, fibroblasts, osteoclasts, osteoblasts, and chondrocytes.

synovial inflammation [144,145]. This interaction between MCs and synovial fibroblasts forms an important positive feedback loop that plays a crucial role in synovial inflammation in OA. The mediators produced by MCs have profound effects on fibroblasts. For example, TNF-α stimulates fibroblasts in the synovium of obese OA patients to secrete more lactic acid and aerobic glycolysis and produce more IL-6 [146]. TNF-α can also upregulate the expression of NGF in synovial fibroblasts and mediate the pain of OA to a certain extent [92]. MC-derived TNF-α and TGF-β1 also promote fibroblast proliferation [147]. In vivo studies have shown that the inhibition of TNF-α has a chondroprotective effect, further confirming the detrimental impact of TNF-α on cartilage [148]. In addition, animal studies have also shown that chymase can promote the proliferation of synovial fibroblasts [149].

Macrophage Macrophages play a crucial role in the initiation and development of OA through autocrine and paracrine effects by secreting inflammatory cytokines, growth factors, MMPs, and tissue inhibitors of metalloproteinases (TIMPs) [150]. Macrophages are typically classified into two types: classically activated/inflammatory (M1) type and alternatively activated/immunomodulatory (M2) type. When activated, macrophages can produce a significant amount of proinflammatory cytokines, which can lead to autoimmune diseases and tissue damage [151,152]. For instance, M1 macrophages produce IL-6, TNF-α, IL-1, and IL-12(153), while inducing macrophages polarize into M2 macrophages relieves the osteoarthritis [154]. MCs-produced IL-1β, TNF-α, and IL-6 can activate macrophages, causing them to produce large quantities of proinflammatory cytokines (TNF-α, IL-1, IL-12, IL-18, and IFN-γ), chemokines, and MMPs in the synovitis environment. This process ultimately leads to osteoclast formation, erosion, and progressive joint destruction [153,155].

Osteoclast and Osteoblast Osteoclasts have been shown to be important players in the pathogenesis of bone destruction and promote bone resorption [156,157]. Osteoblasts play a role in maintaining bone homeostasis. MCs directly act on osteoclasts, osteoclast precursors and osteoblasts by producing histamine and promote osteoclast generation through auto/paracrine signaling mechanisms [158,159]. The TNF-α, IL-6 and IL-1β produced by MCs can directly stimulate the precursors of osteoclasts, indirectly stimulate the formation and activation of osteoclasts [90,160,161]. In addition, MCs also produce proinflammatory cytokines (IL-1, IL-1β, IL-13, GM-CSF) to induce osteoclast production [162,163]. IL-1β increases the expression of NF-κB ligand (RANKL) receptor activator through osteoblasts, thereby indirectly inducing osteoclast production and maturation [90]. MCs can be involved in osteoclast differentiation and activation by producing a signaling system mediated by RANK, a member of the TNF receptor family [164]. TNF-α directly induces osteoclast differentiation independent of the ODF/RANKL-RANK interaction [165,166]. Additionally, IL-1α induces osteoblast apoptosis and inhibits osteoblast differentiation by activating the JNK and p38 MAPK pathways [167].

Chondrocyte The balance between anabolic and catabolic activities of articular chondrocytes is disrupted during active OA disease [168]. Besides, as individuals age, the decreased ability of cartilage cells to maintain and repair tissues may also lead to OA [169]. Chondrocytes have the ability to form an extracellular matrix primarily composed of aggrecan and type II collagen. TNF-α can promote the apoptosis of chondrocytes [111]. TLRs are increased in OA cartilage lesions, and the ligands of TLR-2 and TLR-4 induce chondrocyte decomposition [170]. TLRs are also expressed by synovial MCs, and further research is needed to investigate their potential impact on chondrocyte decomposition. The production of TGF-β secreted by MCs, plays a crucial role in regulating chondrocyte metabolism. It stimulates the synthesis of extracellular matrix (ECM) components and helps maintain the balance of chondrocyte activities [171]. In animal studies, cutting off TGF-β and OA signals leads to cartilage degradation and promotes OA development [172]. However, in OA environment, TGF-β increased MMP-13 and induced chondrocyte damage [125].

4. Clinical potential of targeting MCs for OA treatment

The current treatment of OA mainly includes medication for pain relief, patient self-management, exercise and weight loss. Total joint replacement is considered the gold standard of treatment for patients with OA who do not respond to conservative measures or experience a significant decline in their quality of life due to pain [173]. In addition, the new treatment involves the use of radiofrequency ablation [174] and intra-articular injection of platelet-rich plasma (PRP) or hyaluronic acid (HA) to repair cartilage [175–177]. However, unlike diseases such as cancer, the development of immune cell-based therapies for OA is very limited.

As MCs play a crucial role in inflammatory diseases, such as OA [178], targeting MCs could be an effective approach for OA patients. Disodium cromoglycate, widely described as a "MCs stabilizer," that is, a preparation that blocks the release of MCs mediators after proper cell activation, can be used to inhibit MCs releasing mediators, thereby controlling the development of inflammation [179–181]. MC-targeted therapy alleviates disease symptoms by blocking MC mediators, inhibiting activation receptors on MCs, neutralizing MC activation signals, silencing MCs and reducing the number of MCs.

Due to the high cost of researching new drugs, stabilizers for MCs are currently being studied more based on the reuse of drugs. Anti-IgE drugs can block the IgE-FcεR1 pathway activated by MCs, thereby reducing MCs numbers and controlling inflammatory allergic reactions [182]. For example, Statins inhibit MC-IgE response by blocking isoprene, thereby reducing the airway inflammation in asthma [183]. The H1 antihistamines associate with a lower prevalence of knee OA implies that it is possible for antihistamines to regulate the impact of MCs on disease management [184]. Monoclonal antibodies and humanized monoclonal antibodies represent a significant advancement in the development of MC stabilizers, offering high specificity and minimal side effects. There are three generations of anti-IgE monoclonal antibodies, which include omalizumab, ligelizumab, kilizumab, and UB-221. Each generation has seen improvements primarily focused on enhancing IgE affinity and reducing IgE production [185]. Besides, some monoclonal antibodies show potential in inhibiting MCs other receptor. For instance, CDX-0159 is an anti-Kit monoclonal antibody that inhibit activation of MCs through suppressing SCF/c-Kit. It has shown safety in animal studies and does not have adverse effects on the blood. In human experiments, the antibody can reduce plasma tryptase levels and inhibit MCs [186,187]. Several clinical studies have shown that injections of antibodies against NGF in patients with moderate to severe OA can be effective in relieving pain and restoring function [188–191].

The mechanism of OA control has positive significance for disease treatment. Efforts to identify new pathway inhibitors, such as tyrosine kinase Syk or mediator antagonists, may lead to new successes in this field. Most recently, Mrgprb-2 has been reported as a specific receptor for MC activation. Abnormal activation of PI3K-AKT and MAPK pathways in Mrgprb-2-deficient MCs may serve as a new target for therapy of OA [192].

5. Discussion and perspectives

Our review summarizes the crucial role and mechanism of MCs in the inflammation and progression of OA. The activation of MCs during OA leads to the release of pro-inflammatory mediators (histamine, tryptase, IL-1, IL-6, TNF-α, etc.), resulting in synovial inflammation and cartilage degeneration. The synovial microenvironment plays a crucial role in the progression of OA, particularly through the interaction of MCs with other inflammatory cells. Upon MC activation, the release of mediators can have diverse effects on various inflammatory cells, resulting in further intensification of local inflammation.

To date, the role of MCs in OA has been gradually explored. However, there is a lack of research on how MCs specifically affect factors such as gender, age, and obesity, which are important for the progression of OA [193,194]. Additionally, although MCs show potential as a target for OA treatment [195], many issues may need to be addressed before they can be applied in clinical settings. Currently, most studies on the development and function of MCs are based on murine MCs extracted from mice or from MC-deficient mice [196]. There is a need to explore new methods for obtaining human-derived mast cells to determine which mast cell functions are relevant to humans. Understanding mast cell development and heterogeneity through single-cell sequencing may enhance the application of MCs [197]. Furthermore, MCs not only play a pro-inflammatory role but also exhibit immunomodulatory and tissue homeostasis functions in certain contexts [198]. In the future, it will be essential to better identify the specific subtypes of MCs involved in various stages of OA. Concurrently, advancements in material technologies, including specialized polymers, lipids, and nanozymes, offer the potential to deliver drugs selectively to distinct subtypes of MCs by targeting specific surface receptors. This presents significant opportunities for progress in the development of MC-targeted therapeutic strategies.

CRediT authorship contribution statement

Guanghui Hao: Writing – original draft, Conceptualization. **Shanqian Han:** Writing – original draft, Conceptualization. **Zhangang Xiao:** Writing – review & editing. **Jing Shen:** Writing – review & editing. **Yueshui Zhao:** Writing – review & editing, Writing – original draft, Validation, Supervision, Funding acquisition, Conceptualization. **Qi Hao:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Data curation, Conceptualization.

Ethics approval and consent to participate

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

OA	Osteoarthritis
MCs	Mast Cells
RA	Rheumatoid Arthritis

Cpa3	Carboxypeptidase A3
SF	Synovial fluid
SCF	Stem cell factor
IgE	Immunoglobulin E
LTC4	Leukotriene C4
PGD2	Prostaglandin D2
TNF	tumor necrosis factor
GM-CSF	granulocyte-macrophage colony stimulating factor
MAPK	Mitogen-activated protein kinase
NGF	Nerve growth factor
TrkA	Tyrosine kinase receptor
TLRs	Toll-like receptors
SOD	Superoxide dismutase
CAT	Catalase
ROS	Reactive oxygen species
MMP	Matrix metalloproteinase
IL-1β	Interleukin-1β
IL-1	Interleukin-1
IL-3	Interleukin-3
IL-6	Interleukin-6
IL-13	Interleukin-13
TGF-β:	Transforming growth factor-β
IFN-γ:	Interferon-gamma
BMP-2	Bone morphogenetic protein-2
ADAMTS-4	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 4
VEGF	Vascular endothelial growth factor
TIMPs	Tissue inhibitors of metalloproteinases
ECM	Extracellular matrix
PRP	Platelet-rich plasma
HA	Hyaluronic acid
PAR-2	protease-activated receptor-2
PRG4	Proteoglycan 4

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