Allergy and Immunology

AIMS Allergy and Immunology, 6(4): 228–247.
DOI: 10.3934/Allergy.2022017
Received: 13 October 2022
Revised: 08 November 2022
Accepted: 10 November 2022
Published: 16 November 2022

http://www.aimspress.com/journal/Allergy

Review

Mast cells: A dark horse in osteoarthritis treatment

Anastasiia D. Kurenkova[1,*] and Peter S. Timashev[1,2]

[1] Institute for Regenerative Medicine, I.M. Sechenov First Moscow State Medical University (Sechenov University), 8, Trubetskaya st., Moscow, 119991, Russian Federation
[2] World-Class Research Center "Digital Biodesign and Personalized Healthcare", Sechenov First Moscow State Medical University (Sechenov University), 8, Trubetskaya st., Moscow, 119991, Russian Federation

* **Correspondence:** Email: n_kurenkova@mail.ru.

Abstract: Mast cells are best known for their involvement in the pathogenesis of allergic reactions and inflammation. Due to the wide variety of activation methods and the various mediators that mast cells can synthesize and store, they can regulate all stages of the inflammatory process. There are a large amount of data describing the role of mast cells in the development of autoimmune rheumatoid arthritis, but their role in the development of inflammatory traumatic osteoarthritis remains poorly described. However, non-autoimmune cartilage damage is the main reason for joint replacement surgeries. As important regulators of the inflammatory process, mast cells could be an interesting target for the treatment of osteoarthritis. Herein, we summarize the knowledge about the role of mast cells in the pathogenesis of osteoarthritis and outline various approaches that, to varying degrees, seem promising for the correction of the disease.

Keywords: mast cells; inflammation; osteoarthritis; cartilage damage; targeted therapy

1. Introduction

Mast cells (MCs) are myeloid tissue cells containing a large number of basophilic granules, known for their important role in the development of allergies, as well as in the regulation of the inflammatory process. MCs granules contain pre-stored mediators that are released in response to a stimulus, such as histamine, proteoglycans, or proteases [1]. Moreover, when stimulated, MCs begin to synthesize mediators *de novo*, such as various cytokines, chemokines, and growth factors [1]. It

should be noted that MCs are characterized by a differential release of their mediators; depending on the stimulus, a different set of factors are synthesized and secreted by cells [1,2]. Due to this and a unique set of mediators, mast cells are involved in all stages of inflammation, from its initiation to wound healing [3].

Osteoarthritis (OA) is a common cause of population disability. Regardless of the reasons for the disease initiation, whether it be trauma, aging, obesity or genetic causes, OA is largely inflammatory [4,5]. The important signs of joint inflammation are infiltration by immune cells, the growth of catabolism enzymes and the synthesis of pro-inflammatory cytokines and chemokines [5,6]. And a large role in the regulation of the inflammatory process belongs to MCs, which, due to the large spectrum of regulatory molecules and the presence of differential secretion, can "orchestrate" other cells [3].

In the joint, MCs are located in the subintima of the synovial membrane, capsule, and periarticular fat, and generally play a negative role in the development of OA [7]. Genetic and pharmacological depletion of MCs leads to a decrease in the severity of symptoms in experimental OA models [8]. Moreover, injection of MCs causes histopathological changes of OA in cartilage, although without pain and swelling [9]. Injection of MCs after the development of OA aggravates the disease, and this effect is leveled by the membrane stabilizer Tranilast [9].

With the development of OA, an increase in the number of both degranulated and intact MCs has been shown [7]. At the same time, there is a clear positive correlation between the amount of MCs and synovial inflammation, as well as pain assessed by the visual analog scale (VAS) and Knee injury and Osteoarthritis Outcome Score (KOOS) scores [10–12]. It has also been noted that the number rather than the percentage of degranulated MCs correlates with pain and cartilage damage [11].

Recruitment of new MCs seems to occur due to the secretion of stem cell factor (SCF) by various synovial cells, including fibroblasts, monocyte/macrophages, and endothelial cells [13]. SCF binds to the c-kit receptor, which is present only on MCs in adulthood, causing progenitor division, maturation, and chemotaxis [13,14]. Drugs targeting c-kit and MCs maturation such as Imatinib [8] and Sorafenib [15] have been shown to reduce experimental OA.

In osteophytes developing in OA, an increase in the number of MCs has been shown, mainly due to migration of the precursors from the bloodstream; however, recruitment from the subchondral bone is also possible, and the differentiation and maturation of MCs are largely provided by the components of synovial fluid [16]. Apparently, the environment that forms in osteoarthritis causes additional recruitment of MCs, which creates a vicious circle of inflammation.

Thus, a clear correlation between the MCs number, their morphological and functional status and the degree of OA development strongly suggests that MCs play a significant role in the pathogenesis of OA. Below we will consider in more detail which pathways of MCs activation and which of their mediators may be involved in this process. We also summarized which MCs-targeted pharmacological approaches have already shown some success in experimental or clinical studies and could already be used to treat OA.

2. Mast cell activation

2.1. Immunoglobulin E (IgE)

IgE is widely known as an activator of MCs in immediate hypersensitivity (type I) allergic reaction. However, the role of IgE and its ability to activate MCs cannot be underestimated in OA. In a model of experimental OA, cartilage damage, osteophyte formation, and synovitis were significantly less expressed in IgE-deficient and anti-IgE neutralizing antibody recipient mice [8]. Pilot clinical trials in humans have shown the efficiency of anti-IgE therapy [17]. A similar effect has been detected in mice with a deficit of the IgE high-affinity receptor (FcεRI) and in pharmacological inhibition of downstream signaling caused by the Syk agonist PRT062607 [8].

Activation of IgE receptors on MCs causes the calcium-dependent release of pre-stored mediators from granulae, which is reviewed hereinafter [8]. At the same time, phosphoinositide 3-kinases (PI3K), extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinases (JNK), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and protein kinase C (PKC) are also activated, initiating the synthesis of mediators *de novo*, the first being metabolites of arachidonic acid, cytokines, chemokines, NO, and reactive oxygen species (ROS) [1,18].

In spite of the great role of IgE in its pathogenesis, OA does not appear to be a typical allergic reaction, and the problem of antigen for immunoglobulin is still open. Some authors suppose that exogenous allergens or cartilage breakdown products may become antigens [8]. On the contrary, MCs activation mechanisms by IgE not bound with antigens have been described [19]. It is interesting that the general level of IgE (particularly *Dermatophagoides farinae*-specific IgE) in serum correlates with an increased risk of OA development [20], and allergy cases appear more often in patients with OA [21]. It seems that the presence of IgE, both free and bound with antigens, may increase OA development whilst not being its initiator.

2.2. Damage-associated molecular patterns (DAMPs)

The development of traumatic osteoarthritis occurs after trauma and tissue damage, and DAMPs that are released in damaged tissues play the main role in initiating this process [22]. DAMPs include components of destroyed extracellular matrices, high-mobility group box 1 protein (HMGB1), heat shock proteins (HSPs), uric acid, altered matrix proteins, and S100 proteins. DAMPs play an important part in the initiation and development of OA (for detail, see [23]). Briefly, activation of the receptor for advanced glycation end-products (RAGE) and Toll-like receptors (TLRs) causes the release of matrix metalloproteinases (MMPs), ROS, cytokines, and chemokines by innate immunity cells, which are present in the synovial membrane. This causes a further increase in the inflammatory response. There are different types of TLRs on the membrane of MCs, and their activation causes the *de novo* synthesis and secretion of cytokines, chemokines, and phospholipid metabolites [24]. It has been shown that extra domain A of fibronectin (FN-EDA), which is gained by protease-infused fibronectin breakdown, is a ligand for TLR4 and causes dose-dependent secretion of tumor necrosis factor α (TNFα), interleukin 6 (IL-6), and IL-1β [25]. In experimental OA, an intra-articular injection of the inhibitor of TLR4 TAP2 has been shown to decrease cartilage degeneration and reduce pain [26]. It is interesting that lubricin (proteoglycan 4, Prg4), produced by the surface cells

of cartilage, may concurrently bond with TLR2 and TLR4, thus being capable of inhibiting the inflammatory process in OA [27,28].

Another important DAMP receptor, RAGE, bonds with glycation end-products (AGEs), besides its reaction to such DAMPs as HMGB1, S100 proteins, and amyloid-β protein. RAGE activation causes noticeable exocytosis and histamine secretion by MCs and increases ROS production, while the cytokine profile remains unchanged [29]. Blocking RAGE with anti-RAGE monoclonal antibody (mAb) causes a dose-dependent reduction in exocytosis [29].

NLRs are "non-classic" DAMP receptors because, rather, they are sensors of pathogen-associated molecular patterns. Nucleotide-binding oligomerization domain (NOD)-, leucine-rich repeat (LRR)-, and pyrin domain-containing protein 3 (NLRP3), alongside other proteins, form a multimeric structure named "the inflammasome," and its activation depends on the TLR activation on a cell [30]. Apparently, NLRP3 plays an important role in the development of OA and synovial inflammation (for detail, see [31]). NLRP3, similar to other DAMP sensors, is expressed in many cells of the synovial membrane, although it is not particularly shown for MCs. However, there is information about the presence of NLRP3 in endometrium MCs, and its activation increases the inflammatory response [32].

2.3. Complement

The complement system is known primarily for its antimicrobial activity, but more and more information is accumulating about the regulatory influence of individual components in non-inflectional inflammation. Components C3, C5, C7, and C9 are found in the synovial fluid of patients with OA [33]. The formation of the last C5b–C9 membrane–attack complex (MAC) enhances the inflammatory response, and the genetic depletion of the C5 and C6 components reduces the severity of cartilage destruction in experimental OA [33]. The complement anaphylatoxins C3a and C5a can be MCs activators and chemoattractants [34,35]. It is interesting that the mechanism of MCs degranulation differs from that of IgE during complement activation and is associated with the fusion of individual granules with the membrane and the weaker production of cytokines [34]—although, at the same time, the complement potentiates IgE-dependent mast cell activation and degranulation [36].

It has also been shown that MCs themselves can synthesize and secrete complement components C1q, C3, and C5, while secreted tryptase and chymase can cleave C3, converting it into the active form C3a [37]. In general, preliminary *in vitro* experiments have shown success in preserving chondrocytes by inhibition of C3a with antibodies [38], as well as in reducing cartilage degeneration and inflammation in experimental OA using chondroitin sulfate (CS) E oligosaccharides due to inhibition of the MAC by targeting C5 [39].

2.4. Nerve growth factor (NGF)

As already noted, the number of MCs positively correlates with pain in OA. An important role is played by the activation of MCs by NGF. During inflammation in the joint, NGF production is increased by various cells of the synovial membrane, and the expression of its tropomyosin receptor kinase A (TrkA) receptor on MCs and sensory neurons also increases; in OA, there is a noticeable clustering of peptidergic fibers and MCs. In response to TrkA activation, MCs synthesize prostaglandin D2 (PGD2), which, by activating the DP1 receptors on neurons, leads to the

emergence of an action potential and pain sensations [40]. In addition, activation of TrkA on MCs themselves leads to their secretion of histamine, which causes pain hypersensitivity [1,41].

A systematic analysis of anti-NGF therapy (tanezumab) showed a decrease in pain in patients; however, in some cases, cartilage deterioration was observed, and animal studies have provided conflicting results depending on the timing and dose of the drug [42]. The use of the TrkA blocker AR786 has also been shown to lead to a reduction in pain and, in general, contributed to the reduction of synovitis, although it had no effect on the cartilage itself [43]. Apparently, NGF is not one of the main factors in the development of cartilage damage in OA, although it significantly affects pain.

2.5. Substance P

An important polypeptide neurotransmitter responsible for the appearance of pain is substance P, secreted mainly by afferent fibers, as well as by MCs themselves [44]. A clear colocalization of nerve endings containing substance P with MCs has been shown in OA [45]. Interestingly, the activation of TK by substance P does not occur through interaction with canonical neurokinin-1 receptor (NK1R), but rather through Mas-related G-protein-coupled receptor 2 (MRGPRX2), which leads to the secretion of PGD2, cytokines, and chemokines, attracting more inflammatory cells to focus [1,46]. In general, this is indirectly confirmed by conflicting data on the use of NK1R blockers for the treatment of OA and the relief of pain [47]. At the same time, MRGPRX2 antagonists clearly prevent the activation of MCs, although their action for the treatment of OA has not yet been shown [48].

3. Pre-stored mediators

3.1. Biogenic amines

The main mediator pre-stored in MCs granules is histamine. Histamine has many biological functions that depend on its receptor, the primary ones being provided through H1R: Vasodilation, increased vascular permeability, platelet aggregation, and the stimulation of the production of adhesion molecules, cytokines, and chemokines [49]. In the joint, histamine receptors are located on chondrocytes, synovial fibroblasts, various immune cells, and the endothelium [49]. Cross-sectional analysis has shown that H1R blocker intake is associated with a decrease in the severity of OA in patients [50]. Another retrospective study also showed a decreasing trend in structural progression in knee OA while taking antihistamines [51]. However, convincing prospective studies on the effectiveness of antihistamine therapy in OA, including animal models, have not been conducted.

Another important biogenic amine of MCs is serotonin, and it plays an important role in pain formation. Interestingly, serotonin has both hyperalgesic and analgesic effects, depending on the cell type and location. At the periphery, serotonin predominantly potentiates pain, and many of its receptors may be involved in this process [52]. In an adjuvant-induced arthritis model, serotonin depletion reduced the severity of the disease, which may rather indicate a negative role for serotonin [53]. There is also evidence that serotonin is associated with increased pain in rheumatoid arthritis (RA) [54,55]. In part, this effect may be due to an increase in prostaglandin E2 (PGE2) synthesis by synovial cells [56]. However, the role of serotonin and the regulation of its activity in OA has not yet been studied.

3.2. Proteoglycans

Mast cell proteoglycans are stored in granules and are ionically bound to proteases such as tryptase, chymase, and various exopeptidases. Interestingly, during secretion, the protease–proteoglycan complex remains intact, although tryptase more often dissociates at a neutral pH (for more detail, see [57]). Heparin itself has a known anticoagulant property, although the level of activation of the coagulation pathway increases in arthritis [58]. As a thrombin blocker, heparin may also have a therapeutic effect on OA, although endogenous amounts from MCs are insufficient to detect significant effects [59]. Chondroitin sulfate and hyaluronic acid are important components of the cartilage extracellular matrix and can be used to treat OA [60,61]. At the same time, it has been shown that chondroitin sulfate and hyaluronic acid are able to stabilize MCs, prevent pro-inflammatory mediator secretion, and reduce their proliferation [62,63].

3.3. Enzymes

According to the content of neutral proteases, MCs are divided into several subtypes. Tryptase-chymase MCs (MC_{TC}) contain tryptase, chymase, and cathepsin G, and there are also tryptase-only MC_T and chymase-only MC_C. MC_C are localized mainly in the mucous membranes of the gastrointestinal tract, skin, and bronchi [64]. Normally, 60% of all MCs present in the joint are MC_{TC}, but in OA, an increase in MC_T is observed, although MC_{TC} remains the same in absolute numbers [65]. In OA, tryptase is primarily known for destroying the extracellular matrix, chondrocyte apoptosis and stimulation of pro-inflammatory molecules secretion by synovial cells [8,66].

Tryptase has two isoforms, α and β, and β-trypatase has protease activity, while the α form is proteolytically inactive [67]. Interestingly, in OA, the level of β-trypatase in the synovial fluid increases to a greater extent than in RA, and this positively correlates with the level of histamine, which may indicate anaphylactic degranulation of MCs [68]. However, tryptase activity in the synovial fluid has been noted to still be higher in RA than in OA, although tryptase is equally elevated in the synovial membrane [69]. Apparently, in OA, the greater amount of tryptase is compensated by a decrease in its activity.

Interestingly, the expression of protease-activated receptor (PAR)-2 on the MCs in OA is very low, that is, tryptase does not additionally activate MCs, stimulating them in the synthesis of pro-inflammatory mediators, such as IL-8 [69]. However, in OA, PAR-2 expression is increased in chondrocytes, apparently after activation by pro-inflammatory cytokines IL-1β, TNFα, and transforming growth factor β (TGFβ) [70]. In turn, this increases cartilage degradation, premature aging, and chondrocyte death [71]. The use of the PAR-2 antagonist AZ3451 or monoclonal antibodies prevents this effect and reduces the severity of OA in animals [71,72]. In addition, PAR-2 is present on osteoblasts and osteoclasts of subchondral bone, and its activation leads to an imbalance in osteogenesis and bone resorption [73]. Inhibition of tryptase itself by APC366 has been shown to significantly reduce cartilage damage, osteophyte formation, and synovitis in experimental OA [8].

The enzymes secreted by MCs also include arylsulfatases, carboxypeptidase A, kinogenases, MMPs, peroxidases, and phospholipases, which actively degrade the extracellular matrix. In general, MCs are not a unique source of these enzymes, as they are also produced by synovial membrane cells, chondrocytes themselves, blood cells, etc. At the same time, therapy aimed at suppressing the activity of proteases has therapeutic potential in OA (discussed in more detail in [74,75]).

3.4. Polypeptides

As part of MCs granules, various polypeptides involved in the regulation of the inflammatory response are stored. In general, these polypeptides are not a unique product of MCs and are synthesized by many other types; however, the pathophysiological effect of these mediators cannot be ignored. It has been shown that the concentration of CRH [76], endothelin-1 [77], and bradykinin [78] increases in the synovial fluid of patients with OA. Endothelin-1 has a catabolic effect on cartilage, increasing the secretion of MMP-1 and -13, and NO by articular chondrocytes and synoviocytes [79–81], and blockade of the ETB receptor alleviates the OA-like cartilage phenotype [82]. Bradykinin is a pro-inflammatory mediator and induces the secretion of PGE2, IL-6, and IL-8 by synoviocytes and chondrocytes, and blockade of its B2 receptor by Icatibant and Fasitibant has a therapeutic effect in OA [78,83].

Some of the MCs peptide mediators may be protective in OA. Somatostatin and its chimeric peptide with a growth hormone fragment have therapeutic potential in OA, with the latter even reducing cartilage degradation to a greater extent than hyaluronic acid [84,85]. Urocortin is able to inhibit the induced apoptosis of chondrocytes, and the mechanism seems to be related to the influence on Ca2+ influx and regulation of the mechanosensitive channel by the Piezo1 channel [86,87]. Vasoactive intestinal peptide, which is also produced by nerve endings, plays a role in the pathogenesis of pain in OA. On the one hand, there are data showing the pro-inflammatory effect of VIP, which consists of sensitizing nerve endings, as well as stimulating the production of pro-inflammatory cytokines, but on the other hand, its modulating effect on the CRH system, particularly on increasing the expression of urocortin, shows its anti-inflammatory side [88]. Interestingly, the MCs tryptase and chymase can cause degradation of VIP and substance P, which makes the system of interaction between various MCs mediators even more complex [89].

4. *De novo* synthesized mediators

When activated, MCs, like many other immune cells, also begin to synthesize and secrete various inflammatory mediators, such as cytokines, chemokines, growth factors, arachidonic acid metabolites, and nitric oxide. The role of most of these in the development of OA deserves a separate detailed consideration; herein, we briefly consider their main functions.

4.1. Cytokines

The most powerful inducers of cartilage degradation are the members of the IL-1 family IL-1α and IL-1β. In OA, IL-1 stimulates the synthesis of MMPs and inhibits the synthesis of type 2 collagen and proteoglycans by chondrocytes, providing a catabolic effect, and stimulates the secretion of IL-6 and TNFα, providing a pro-inflammatory effect. The use of recombinant interleukin 1 receptor antagonist (IL-1RA), a protein of the IL-1 family that has an inhibitory effect on IL-1α and IL-1β signaling, has shown a pronounced protective effect in animal models, although it has failed in clinical trials [90,91].

The second most important cytokine involved in the pathogenesis of OA is TNFα. Its catabolic and pro-inflammatory effects are well known [92,93]. The use of various approaches for TNFα

inhibition may improve the state of patients with OA, as well as improve the results of other therapies [94].

In cartilage, MCs are one of the main sources of IL-17, although the production of the cytokine itself increases to a greater extent in RA [95]. Nevertheless, the pro-inflammatory effects of IL-17 have been described [96], partly due to its tandem action with IL-1 [97].

IL-6 is usually referred to as a pro-inflammatory cytokine; however, its role in OA is not actually so clear. On the one hand, an increase in its amount in synovial fluid in OA and its concomitant catabolic effects are clearly shown [98], but on the other hand, it is able to inhibit other pro-inflammatory agents, which partly determines its protective effect (for detail, see [99]). Nevertheless, the blockade of IL-6 itself or its receptor with antibodies may be a promising strategy for the treatment of OA [99].

Interferon γ (IFNγ) can suppress the synthesis of MMPs by chondrocytes [100], as well as reduce the IL-1β-stimulated production of IL-8 and IL-10 [101]. However, synergistically with IL-1, IFNγ enhances the production of IL-6, NO, and PGE2, which can be attributed to the pro-inflammatory effect of the cytokine, which makes its role in the pathogenesis of OA also ambiguous [101].

IL-3 is an anti-inflammatory MCs mediator, although it is also secreted extensively by T cells and monocytes/macrophages. In OA, IL-3 is able to reduce the secretion of MMPs by chondrocytes and, in an *in vivo* model of OA, reduce cartilage and subchondral bone degeneration [102]. The anti-inflammatory cytokines IL-4 and IL-10, secreted by a wide variety of immune cells, also have chondroprotective and analgesic effects [103]. IL-13, which is also produced in large amounts by T-helpers, reduces the secretion of IL-1β and TNFα in the synovial membrane [104] and can also presumably reduce the expression level of adamalysin metalloproteinase 15 (ADAM15) [105].

4.2. Growth factors

In addition to a wide range of cytokines, MCs secrete various growth factors that are responsible for the regulation of the inflammatory process and tissue remodeling. The action of growth factors such as SCF, which is responsible for mast cell recruitment, and NGF, which mediates pain, have been described above.

Granulocyte–macrophage colony-stimulating factor (GM-CSF) appears to play a significant role in the pathogenesis of OA, particularly in pain. GM-CSF blockade with monoclonal antibodies reduces pain and cartilage degradation in experimental OA, although therapy should be continual in the later developmental stages [106,107]. The mechanism of pain development during GM-CSF stimulation is not associated with a direct effect on neurons, but with an effect on macrophages, which release factors that activate nociception [108].

The concentration of basic FGF (FGF2) increases in the plasma and synovial fluid of patients with OA and positively correlates with the degree of cartilage damage, as well as with the number of MCs in the synovial tissue [109–111]. FGF2 is able to activate the synthesis of MMP-13 by chondrocytes, which leads to the degradation of the cartilage extracellular matrix [112]. On the contrary, exogenous FGF2 is used to repair joint tissues, especially in the focal defect model, where it is able to increase the expression of collagen-2 and aggrecan, although it strongly promotes fibrosis, which makes it unpromising for the treatment of articular cartilage diseases [113–115]. It is assumed that the difference in the effects of FGF depends on the balance between the expression of its two

receptors: FGFR1 seems to mediate catabolic activity, and FGFR3 is responsible for anabolic prochondrogenic effects [116].

Another important growth factor secreted by MCs is vascular endothelial growth factor (VEGF). In general, its most important effects include stimulation of the secretion of IL-1, IL-6, and MMPs, which have a catabolic effect, as well as stimulation of vascular growth, which promotes osteogenesis and osteophyte formation [117]. Inhibition of VEGF by monoclonal antibodies is considered a potential therapy for OA [118].

4.3. Phospholipid metabolites

One of the most important signaling molecules activated during inflammation is phospholipase A2 (PLA2) and activation of the downstream metabolism of arachidonic acid. As a result of cyclooxygenase-2 (COX-2) activity, prostaglandins and thromboxanes are formed, and as a result of lipoxygenase activity, leukotrienes (LT) are formed [119]. This pathway is characteristic of many cell types, including MCs that predominantly secrete LTB4, LTC4, and PGD2 [120].

LTB4 and its metabolite LTC4 have not been shown to be clearly involved in the pathogenesis of OA *in vivo*, although some of its pro-inflammatory properties, consisting of increased neutrophilic inflammation, have been described for RA [121,122]. Targeted therapy directed against LTB4 has not shown much effectiveness in RA [121], and in OA, no significant effect of LTB4 on chondrocytes has been observed [123]. Experiments with synovial membrane explants have shown that LTB4 is able to stimulate the synthesis of IL-1β and TNFα [124].

PGD2 is synthesized by MCs in greater amounts in RA than in OA; however, in both cases, it has a pro-inflammatory effect, partly mediated by neutrophil recruitment [125], as well as costimulation of the production of COX-2 by chondrocytes [126]. The role of PGD2 in the pathogenesis of pain induced by NGF and substance P has been described above. On the contrary, when acting on chondrocytes themselves, PGD2 can reduce IL-1-induced MMP-1 and MMP-13 expression [127] and NO synthesis [128]. Moreover, deletion of the DP1 receptor leads to a worsening of OA [129]. This difference in effects seems to be determined by the concentration of PGD2 [128].

In general, COX-2 blockers (non-steroidal anti-inflammatory drugs) reduce pain and have a chondroprotective effect [130], while steroid drugs that block PLA2 activity seem to be effective only for a short period of time [131].

4.4. Nitric oxide (NO)

During inflammation in the joint, NO synthesis is triggered by both the chondrocytes themselves and the cells of the synovial membrane, including MCs. Inhibition of inducible NO synthase (iNOS) leads to a decrease in the synthesis of MMPs, IL-1β, and COX-2 [132]. Moreover, the effects of NO include a decrease in the synthesis of collagen-2 and proteoglycans and an increase in the synthesis of MMP-9 by chondrocytes, and can also stimulate apoptosis, largely due to the combination with superoxide anions and the formation of peroxynitrite (for more detail, see [133]). Recent data confirm that NO blockade is able to reduce COX-2 and MMP-3 expression and increase collagen-2 and aggrecan expression in chondrocytes, as well as prevent cartilage degradation in experimental OA [134].

5. Conclusions

MCs play a significant role in the pathogenesis of OA. It is worth noting that in addition to regulating the progression of the disease itself, MCs appear to be largely responsible for the initiation of inflammation in trauma and the onset of pain. MCs-targeted therapy, especially affecting the individual links in mast cell activity, may be promising for the treatment of OA (Figure 1). Moreover, new therapies can be directed at different parts of the MCs response, and can be different in time, simulating the dynamics of the inflammatory response development. Various nanoparticles, microspheres, hydrogels, liposomes, etc. can be suitable for this [135,136]. Thus, it is possible to develop drug systems that differentially regulate only the activity of MSs and thereby affect other links of the inflammatory response.

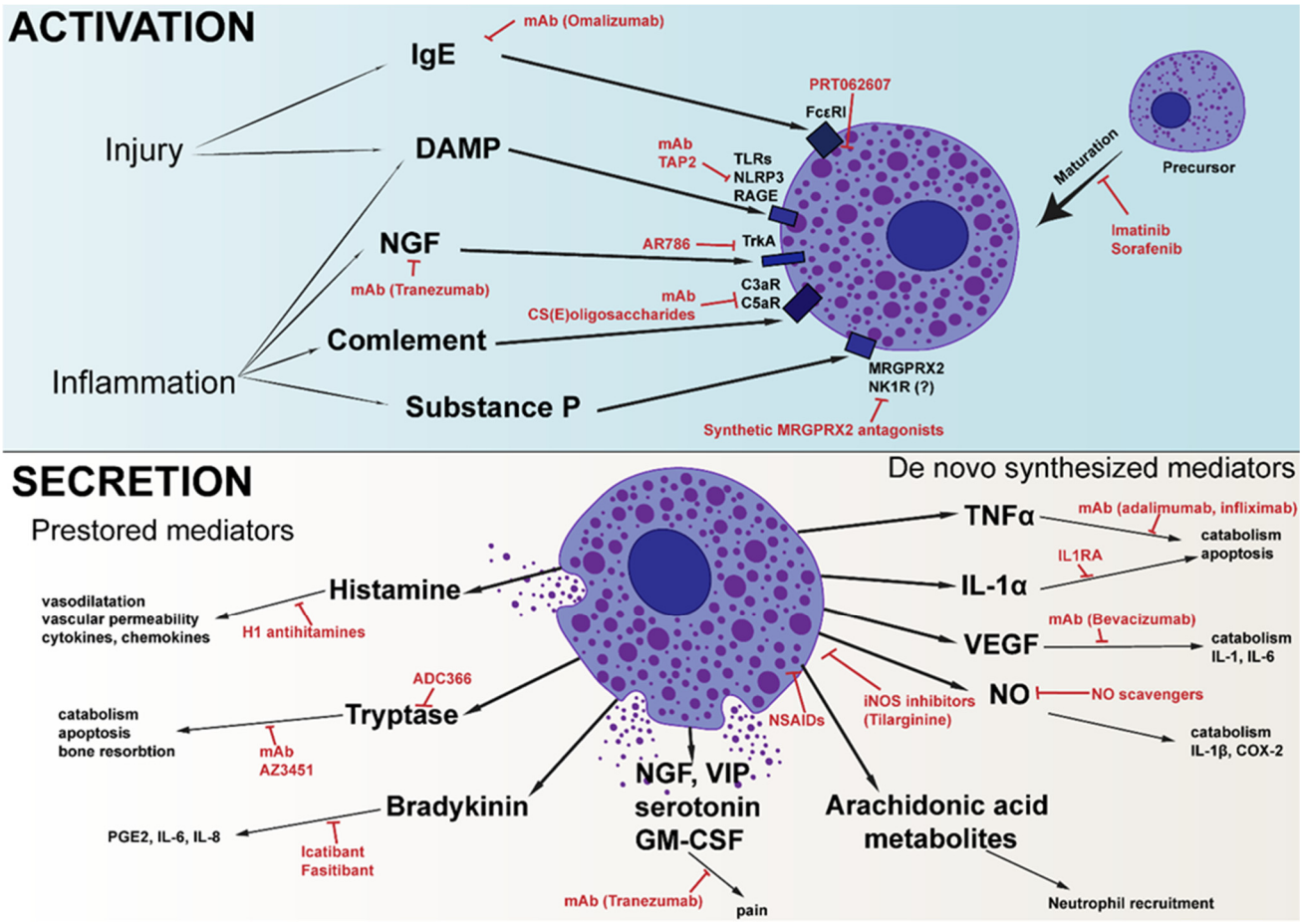

Figure 1. Pharmacological approaches for MCs secretory activity regulation in osteoarthritis (indicated by red font and arrows). IgE: immunoglobulin E; DAMP: damage-associated molecular patterns; NGF: nerve growth factor; mAb: monoclonal antibodies; TLRs: Toll-like receptors; NLRP: nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing protein 3; RAGE: receptor for advanced glycation end-products; TrkA: tropomyosin receptor kinase A; MRGPRX2: Mas-related G-protein-coupled receptor 2; NK1R: neurokinin-1 receptor; VIP: vasoactive intestinal peptide; GM-CSF: granulocyte–macrophage colony-stimulating factor; VEGF: vascular

endothelial growth factor; IL: interleukin; COX: cyclooxygenase; NSAIDs: non-steroidal anti-inflammatory drugs; TNF: tumor necrosis factor; PGE: prostaglandin E.

Acknowledgments

This work was supported by the Russian Science Foundation (Grant No. 21-75-10082).

Conflict of interest

The authors declare no conflict of interest

Author contributions

A.D.K.—original draft preparation; P.S.T—review and editing. All authors have read and agreed to the published version of the manuscript.

References

1. Moon TC, Befus AD, Kulka M (2014) Mast cell mediators: Their differential release and the secretory pathways involved. *Front Immunol* 5: 569. https://doi.org/10.3389/fimmu.2014.00569
2. Theoharides TC, Kempuraj D, Tagen M, et al. (2007) Differential release of mast cell mediators and the pathogenesis of inflammation. *Immunol Rev* 217: 65–78. https://doi.org/10.1111/j.1600-065X.2007.00519.x
3. Abraham SN, St John AL (2010) Mast cell-orchestrated immunity to pathogens. *Nat Rev Immunol* 10: 440–452. https://doi.org/10.1038/nri2782
4. He Y, Li Z, Alexander PG, et al. (2020) Pathogenesis of osteoarthritis: Risk factors, regulatory pathways in chondrocytes, and experimental models. *Biology (Basel)* 9: 1–32. https://doi.org/10.3390/biology9080194
5. Chow YY, Chin KY (2020) The role of inflammation in the pathogenesis of osteoarthritis. *Mediators Inflamm* 2020: 8293921. https://doi.org/10.1155/2020/8293921
6. Sokolove J, Lepus CM (2013) Role of inflammation in the pathogenesis of osteoarthritis: Latest findings and interpretations. *Ther Adv Musculoskelet Dis* 5: 77–94. https://doi.org/10.1177/1759720X12467868
7. Dean G, Hoyland JA, Denton J, et al. (1993) Mast cells in the synovium and synovial fluid in osteoarthrhis. *Rheumatology* 32: 671–675. https://doi.org/10.1093/rheumatology/32.8.671
8. Wang Q, Lepus CM, Raghu H, et al. (2019) IgE-mediated mast cell activation promotes inflammation and cartilage destruction in osteoarthritis. *Elife* 8: e39905. https://doi.org/10.7554/eLife.39905
9. Dan J, Izumi M, Habuchi H, et al. (2021) A novel mice model of acute flares in osteoarthritis elicited by intra-articular injection of cultured mast cells. *J Exp Orthop* 8: 75. https://doi.org/10.1186/s40634-021-00391-6
10. Sellam J, Berenbaum F (2013) Is osteoarthritis a metabolic disease? *Joint Bone Spine* 80: 568–573. https://doi.org/10.1016/j.jbspin.2013.09.007

11. de Lange-Brokaar BJE, Kloppenburg M, Andersen SN, et al. (2016) Characterization of synovial mast cells in knee osteoarthritis: Association with clinical parameters. *Osteoarthr Cartilage* 24: 664–671. https://doi.org/10.1016/j.joca.2015.11.011
12. Farinelli L, Aquili A, Mattioli-Belmonte M, et al. (2022) Synovial mast cells from knee and hip osteoarthritis: histological study and clinical correlations. *J Exp Orthop* 9: 13. https://doi.org/10.1186/s40634-022-00446-2
13. Ceponis A, Konttinen YT, Takagi M, et al. (1998) Expression of stem cell factor (SCF) and SCF receptor (c-kit) in synovial membrane in arthritis: correlation with synovial mast cell hyperplasia and inflammation. *J Rheumatol* 25: 2304–2314.
14. Dahlin JS, Hallgren J (2015) Mast cell progenitors: Origin, development and migration to tissues. *Mol Immunol* 63: 9–17. https://doi.org/10.1016/j.molimm.2014.01.018
15. Gözel N, Çakirer M, Karataş A, et al. (2018) Sorafenib reveals anti-arthritic potentials in collagen induced experimental arthritis model. *Arch Rheumatol* 33: 309. https://doi.org/10.5606/ArchRheumatol.2018.6652
16. Kulkarni P, Harsulkar A, Märtson AG, et al. (2022) Mast cells differentiated in synovial fluid and resident in osteophytes exalt the inflammatory pathology of osteoarthritis. *Int J Mol Sci* 2022: 541. https://doi.org/10.3390/ijms23010541
17. Aquili A, Farinelli L, Bottegoni C, et al. (2017) The effect of anti-IgE therapy in knee osteoarthritis: a pilot observational study. *J Biol Regul Homeost Agents* 31: 1–5.
18. Theoharides TC, Alysandratos KD, Angelidou A, et al. (2012) Mast cells and inflammation. *Biochim Biophys Acta Mol Cell Res* 1822: 21–33. https://doi.org/10.1016/j.bbadis.2010.12.014
19. Bax HJ, Keeble AH, Gould HJ (2012) Cytokinergic IgE action in mast cell activation. *Front Immunol* 3: 229. https://doi.org/10.3389/fimmu.2012.00229
20. Park S, Choi NK (2020) Association between serum immunoglobulin E levels and knee osteoarthritis in Korean adults. *Osteoarthr Cartilage* 28: 462–467. https://doi.org/10.1016/j.joca.2020.02.830
21. Nishioka M, Ioi H, Matsumoto R, et al. (2008) TMJ osteoarthritis/osteoarthrosis and immune system factors in a Japanese sample. *Angle Orthod* 78: 793–798. https://doi.org/10.2319/091407-438
22. Riegger J, Brenner RE (2020) Pathomechanisms of posttraumatic osteoarthritis: chondrocyte behavior and fate in a precarious environment. *Int J Mol Sci* 21: 1560. https://doi.org/10.3390/ijms21051560
23. Foell D, Wittkowski H, Roth J (2007) Mechanisms of disease: A 'DAMP' view of inflammatory arthritis. *Nat Clin Pract Rheumatol* 3: 382–390. https://doi.org/10.1038/ncprheum0531
24. Sandig H, Bulfone-Paus S (2012) TLR signaling in mast cells: common and unique features. *Front Immunol* 3: 185. https://doi.org/10.3389/fimmu.2012.00185
25. Gondokaryono SP, Ushio H, Niyonsaba F, et al. (2007) The extra domain A of fibronectin stimulates murine mast cells via Toll-like receptor 4. *J Leukocyte Biol* 82: 657–665. https://doi.org/10.1189/jlb.1206730
26. Park H, Hong J, Yin Y, et al. (2020) TAP2, a peptide antagonist of Toll-like receptor 4, attenuates pain and cartilage degradation in a monoiodoacetate-induced arthritis rat model. *Sci Rep* 10: 1–13. https://doi.org/10.1038/s41598-020-74544-5

27. Flannery CR, Zollner R, Corcoran C, et al. (2009) Prevention of cartilage degeneration in a rat model of osteoarthritis by intraarticular treatment with recombinant lubricin. *Arthritis Rheum* 60: 840–847. https://doi.org/10.1002/art.24304
28. Alquraini A, Garguilo S, D'Souza G, et al. (2015) The interaction of lubricin/proteoglycan 4 (PRG4) with Toll-like receptors 2 and 4: an anti-inflammatory role of PRG4 in synovial fluid. *Arthritis Res Ther* 17: 1–12. https://doi.org/10.1186/s13075-015-0877-x
29. Sick E, Brehin S, André P, et al. (2010) Advanced glycation end products (AGEs) activate mast cells. *Brit J Pharmacol* 161: 442–455. https://doi.org/10.1111/j.1476-5381.2010.00905.x
30. Swanson KV, Deng M, Ting JPY (2019) The NLRP3 inflammasome: molecular activation and regulation to therapeutics. *Nat Rev Immunol* 2019 198 19: 477–489. https://doi.org/10.1038/s41577-019-0165-0
31. McAllister MJ, Chemaly M, Eakin AJ, et al. (2018) NLRP3 as a potentially novel biomarker for the management of osteoarthritis. *Osteoarthr Cartilage* 26: 612–619. https://doi.org/10.1016/j.joca.2018.02.901
32. Guo X, Xu X, Li T, et al. (2021) NLRP3 inflammasome activation of mast cells by estrogen via the nuclear-initiated signaling pathway contributes to the development of endometriosis. *Front Immunol* 12: 3909. https://doi.org/10.3389/fimmu.2021.749979
33. Wang Q, Rozelle AL, Lepus CM, et al. (2011) Identification of a central role for complement in osteoarthritis. *Nat Med* 17: 1674. https://doi.org/10.1038/nm.2543
34. Gaudenzio N, Sibilano R, Marichal T, et al. (2016) Different activation signals induce distinct mast cell degranulation strategies. *J Clin Invest* 126: 3981. https://doi.org/10.1172/JCI85538
35. Elieh Ali Komi D, Shafaghat F, Kovanen PT, et al. (2020) Mast cells and complement system: Ancient interactions between components of innate immunity. *Allergy* 75: 2818–2828. https://doi.org/10.1111/all.14413
36. Schäfer B, Piliponsky AM, Oka T, et al. (2013) Mast cell anaphylatoxin receptor expression can enhance IgE-dependent skin inflammation in mice. *J Allergy Clin Immunol* 131: 541–548. https://doi.org/10.1016/j.jaci.2012.05.009
37. Lubbers R, van Essen MF, van Kooten C, et al. (2017) Production of complement components by cells of the immune system. *Clin Exp Immunol* 188: 183–194. https://doi.org/10.1111/cei.12952
38. Bollmann M, Colombo F, Marco P, et al. (2018) Inhibition of the complement system component C5 as possible treatment in OA. *Osteoarthr Cartilage* 26: S108. https://doi.org/10.1016/j.joca.2018.02.236
39. Yu C, Zang H, Yang C, et al. (2021) Study of chondroitin sulfate E oligosaccharide as a promising complement C5 inhibitor for osteoarthritis alleviation. *Mat Sci Eng C-Bio S* 127: 112234. https://doi.org/10.1016/j.msec.2021.112234
40. Sousa-Valente J, Calvo L, Vacca V, et al. (2018) Role of TrkA signalling and mast cells in the initiation of osteoarthritis pain in the monoiodoacetate model. *Osteoarthr Cartilage* 26: 84–94. https://doi.org/10.1016/j.joca.2017.08.006
41. Obara I, Telezhkin V, Alrashdi I, et al. (2020) Histamine, histamine receptors, and neuropathic pain relief. *Brit J Pharmacol* 177: 580. https://doi.org/10.1111/bph.14696
42. Miller RE, Block JA, Malfait AM (2017) Nerve growth factor blockade for the management of osteoarthritis pain: what can we learn from clinical trials and preclinical models? *Curr Opin Rheumatol* 29: 110–118. https://doi.org/10.1097/BOR.0000000000000354

43. Nwosu LN, Mapp PI, Chapman V, et al. (2016) Extended report: Blocking the tropomyosin receptor kinase A (TrkA) receptor inhibits pain behaviour in two rat models of osteoarthritis. *Ann Rheum Dis* 75: 1246. https://doi.org/10.1136/annrheumdis-2014-207203
44. Okamura Y, Mishima S, Kashiwakura J, et al. (2017) The dual regulation of substance P-mediated inflammation via human synovial mast cells in rheumatoid arthritis. *Allergol Int* 66: S9–S20. https://doi.org/10.1016/j.alit.2017.03.002
45. Henry CH, Wolford LM (2001) Substance P and mast cells: Preliminary histologic analysis of the human temporomandibular joint. *Oral Surg Oral Med O* 92: 384–389. https://doi.org/10.1067/moe.2001.117811
46. Green DP, Limjunyawong N, Gour N, et al. (2019) A mast-cell-specific receptor mediates neurogenic inflammation and pain. *Neuron* 101: 412–420. https://doi.org/10.1016/j.neuron.2019.01.012
47. Ko KR, Lee H, Han SH, et al. (2022) Substance P, a promising therapeutic target in musculoskeletal disorders. *Int J Mol Sci* 23: 2583. https://doi.org/10.3390/ijms23052583
48. Ogasawara H, Noguchi M (2021) Therapeutic potential of MRGPRX2 inhibitors on mast cells. *Cells* 10: 2096. https://doi.org/10.3390/cells10112906
49. Thangam EB, Jemima EA, Singh H, et al. (2018) The role of histamine and histamine receptors in mast cell-mediated allergy and inflammation: The hunt for new therapeutic targets. *Front Immunol* 9: 1873. https://doi.org/10.3389/fimmu.2018.01873
50. Shirinsky I, Shirinsky V (2018) H1-antihistamines are associated with lower prevalence of radiographic knee osteoarthritis: a cross-sectional analysis of the Osteoarthritis Initiative data. *Arthritis Res Ther* 20: 1–6. https://doi.org/10.1186/s13075-018-1619-7
51. Bihlet AR, Miller CP, Byrjalsen I, et al. (2022) OP0230 antihistamine use and structural progression of knee OA: a post-hoc analysis of two phase III clinical trials. *Ann Rheum Dis* 81: 152. https://doi.org/10.1136/annrheumdis-2022-eular.4425
52. Sommer C (2010) Serotonin in pain and pain control, *Handbook of Behavioral Neuroscience*, Amsterdam: Elsevier, 457–471. https://doi.org/10.1016/S1569-7339(10)70096-5
53. Harbuz MS, Perveen-Gill Z, Lalies MD, et al. (1996) The role of endogenous serotonin in adjuvant-induced arthritis in the rat. *Rheumatology* 35: 112–116. https://doi.org/10.1093/rheumatology/35.2.112
54. Kopp S, Alstergren P (2002) Blood serotonin and joint pain in seropositive versus seronegative rheumatoid arthritis. *Mediators Inflamm* 11: 211. https://doi.org/10.1080/09629350290000069
55. Wan M, Ding L, Wang D, et al. (2020) Serotonin: A potent immune cell modulator in autoimmune diseases. *Front Immunol* 11: 186. https://doi.org/10.3389/fimmu.2020.00186
56. Seidel MF, Fiebich BL, Ulrich-Merzenich G, et al. (2008) Serotonin mediates PGE2 overexpression through 5-HT2A and 5-HT3 receptor subtypes in serum-free tissue culture of macrophage-like synovial cells. *Rheumatol Int* 28: 1017–1022. https://doi.org/10.1007/s00296-008-0564-1
57. Stevens RL, Adachi R (2007) Protease-proteoglycan complexes of mouse and human mast cells and importance of their β-tryptase-heparin complexes in inflammation and innate immunity. *Immunol Rev* 217: 155–167. https://doi.org/10.1111/j.1600-065X.2007.00525.x
58. So AK, Varisco PA, Kemkes-Matthes B, et al. (2003) Arthritis is linked to local and systemic activation of coagulation and fibrinolysis pathways. *J Thromb Haemost* 1: 2510–2515. https://doi.org/10.1111/j.1538-7836.2003.00462.x

59. Chou PY, Su CM, Huang CY, et al. (2014) The characteristics of thrombin in osteoarthritic pathogenesis and treatment. *Biomed Res Int* 2014: 1–9. https://doi.org/10.1155/2014/407518
60. Migliore A, Procopio S (2015) Effectiveness and utility of hyaluronic acid in osteoarthritis. *Clin Cases Miner Bone Metab* 12: 31. https://doi.org/10.11138/ccmbm/2015.12.1.031
61. Bishnoi M, Jain A, Hurkat P, et al. (2016) Chondroitin sulphate: a focus on osteoarthritis. *Glycoconj J* 33: 693–705. https://doi.org/10.1007/s10719-016-9665-3
62. Takano H, Furuta K, Yamashita K, et al. (2012) Restriction of mast cell proliferation through hyaluronan synthesis by co-cultured fibroblasts. *Biol Pharm Bull* 35: 408–412. https://doi.org/10.1248/bpb.35.408
63. Theoharides TC, Patra P, Boucher W, et al. (2000) Chondroitin sulphate inhibits connective tissue mast cells. *Brit J Pharmacol* 131: 1039. https://doi.org/10.1038/sj.bjp.0703672
64. Crivellato E, Beltrami CA, Mallardi F, et al. (2004) The mast cell: an active participant or an innocent bystander? *Histol Histopathol* 19: 259–270.
65. Buckley MG, Gallagher PJ, Walls AF (1998) Mast cell subpopulations in the synovial tissue of patients with osteoarthritis: selective increase in numbers of tryptase-positive, chymase-negative mast cells. *J Pathol* 186: 67–74. https://doi.org/10.1002/(SICI)1096-9896(199809)186:1<67::AID-PATH132>3.0.CO;2-D
66. Takata K, Uchida K, Mukai M, et al. (2020) Increase in tryptase and its role in the synovial membrane of overweight and obese patients with osteoarthritis of the knee. *Diabetes Metab Syndr Obes* 13: 1491–1497. https://doi.org/10.2147/DMSO.S253147
67. Marquardt U, Zettl F, Huber R, et al. (2002) The crystal structure of human α1-tryptase reveals a blocked substrate-binding region. *J Mol Biol* 321: 491–502. https://doi.org/10.1016/S0022-2836(02)00625-3
68. Buckley MG, Walters C, Wong WM, et al. (1997) Mast cell activation in arthritis: Detection of α- and β-tryptase, histamine and eosinophil cationic protein in synovial fluid. *Clin Sci* 93: 363–370. https://doi.org/10.1042/cs0930363
69. Nakano S, Mishiro T, Takahara S, et al. (2007) Distinct expression of mast cell tryptase and protease activated receptor-2 in synovia of rheumatoid arthritis and osteoarthritis. *Clin Rheumatol* 26: 1284–1292. https://doi.org/10.1007/s10067-006-0495-8
70. Xiang Y, Masuko-Hongo K, Sekine T, et al. (2006) Expression of proteinase-activated receptors (PAR)-2 in articular chondrocytes is modulated by IL-1β, TNF-α and TGF-β. *Osteoarthr Cartilage* 14: 1163–1173. https://doi.org/10.1016/j.joca.2006.04.015
71. Huang X, Ni B, Xi Y, et al. (2019) Protease-activated receptor 2 (PAR-2) antagonist AZ3451 as a novel therapeutic agent for osteoarthritis. *Aging* 11: 12532. https://doi.org/10.18632/aging.102586
72. Ferrell WR, Kelso EB, Lockhart JC, et al. (2010) Protease-activated receptor 2: a novel pathogenic pathway in a murine model of osteoarthritis. *Ann Rheum Dis* 69: 2051–2054. https://doi.org/10.1136/ard.2010.130336
73. Lucena F, McDougall JJ (2021) Protease activated receptors and arthritis. *Int J Mol Sci* 22: 9352. https://doi.org/10.3390/ijms22179352
74. Smith RL (1999) Degradative enzymes in osteoarthritis. *Front Biosci* 4: 704–712. https://doi.org/10.2741/A388

75. Meszaros E, Malemud CJ (2012) Prospects for treating osteoarthritis: enzyme–protein interactions regulating matrix metalloproteinase activity. *Ther Adv Chronic Dis* 3: 219. https://doi.org/10.1177/2040622312454157
76. Crofford LJ, Sano H, Karalis K, et al. (1993) Corticotropin-releasing hormone in synovial fluids and tissues of patients with rheumatoid arthritis and osteoarthritis. *J Immunol* 151: 1587–1596.
77. Zhao Z, Li E, Cao Q, et al. (2016) Endothelin-1 concentrations are correlated with the severity of knee osteoarthritis. *J Invest Med* 64: 872–874. https://doi.org/10.1136/jim-2015-000030
78. De Falco L, Fioravanti A, Galeazzi M, et al. (2013) Bradykinin and its role in osteoarthritis. *Reumatismo* 65: 97–104. https://doi.org/10.4081/reumatismo.2013.97
79. Roy-Beaudry M, Martel-Pelletier J, Pelletier JP, et al. (2003) Endothelin 1 promotes osteoarthritic cartilage degradation via matrix metalloprotease 1 and matrix metalloprotease 13 induction. *Arthritis Rheum* 48: 2855–2864. https://doi.org/10.1002/art.11247
80. Sin A, Tang W, Wen CY, et al. (2015) The emerging role of endothelin-1 in the pathogenesis of subchondral bone disturbance and osteoarthritis. *Osteoarthr Cartilage* 23: 516–524. https://doi.org/10.1016/j.joca.2014.11.002
81. Khatib AM, Siegfried G, Messai H, et al. (2002) Mechanism of inhibition of endothelin-1-stimulated proteoglycan and collagen synthesis in rat articular chondrocytes. *Cytokine* 17: 254–261. https://doi.org/10.1006/cyto.2001.1001
82. Au M, Liu Z, Rong L, et al. (2020) Endothelin-1 induces chondrocyte senescence and cartilage damage via endothelin receptor type B in a post-traumatic osteoarthritis mouse model. *Osteoarthr Cartilage* 28: 1559–1571. https://doi.org/10.1016/j.joca.2020.08.006
83. Tenti S, Pascarelli NA, Cheleschi S, et al. (2016) The emerging role of bradykinin in the pathogenesis of osteoarthritis and its possible clinical implications. *Curr Rheumatol Rev* 12: 177–184. https://doi.org/10.2174/1573397112666160331143305
84. Montjean R, Escaich S, Carelli C, et al. (2019) Chimeric peptide combining both growth hormone and somatostatin sequences (REG-O3) improves function and prevents cartilage degradation in rat model of osteoarthritis. *Osteoarthr Cartilage* 27: S428. https://doi.org/10.1016/j.joca.2019.02.449
85. Silveri F, Morosini P, Brecciaroli D, et al. (1994) Intra-articular injection of somatostatin in knee osteoarthritis: clinical results and IGF-1 serum levels. *Int J Clin Pharmacol Res* 14: 79–85.
86. Intekhab-Alam NY, White OB, Getting SJ, et al. (2013) Urocortin protects chondrocytes from NO-induced apoptosis: a future therapy for osteoarthritis? *Cell Death Discov* 4: e717. https://doi.org/10.1038/cddis.2013.231
87. Lawrence KM, Jones RC, Jackson TR, et al. (2017) Chondroprotection by urocortin involves blockade of the mechanosensitive ion channel Piezo1. *Sci Rep* 7: 1–12. https://doi.org/10.1038/s41598-017-04367-4
88. Jiang W, Wang H, Li YS, et al. (2016) Role of vasoactive intestinal peptide in osteoarthritis. *J Biomed Sci* 23: 1–6. https://doi.org/10.1186/s12929-016-0280-1
89. Caughey GH, Leidig F, Viro NF, et al. (1988) Substance P and vasoactive intestinal peptide degradation by mast cell tryptase and chymase. *J Pharmacol Exp Ther* 244: 133–137.
90. Vincent TL (2019) IL-1 in osteoarthritis: Time for a critical review of the literature. *F1000Research* 8: 1–8. https://doi.org/10.12688/f1000research.18831.1
91. Florián AM (2011) IL-1 and its role in osteoarthritis. *Open J Med* 1: 1–6.

92. Li H, Xie S, Qi Y, et al. (2018) TNF-αincreases the expression of inflammatory factors in synovial fibroblasts by inhibiting the PI3K/AKT pathway in a rat model of monosodium iodoacetate-induced osteoarthritis. *Exp Ther Med* 16: 4737–4744. https://doi.org/10.3892/etm.2018.6770
93. Hu G, Zhao X, Wang C, et al. (2017) MicroRNA-145 attenuates TNF-α-driven cartilage matrix degradation in osteoarthritis via direct suppression of MKK4. *Cell Death Discov* 8: e3140–e3140. https://doi.org/10.1038/cddis.2017.522
94. Chisari E, Yaghmour KM, Khan WS (2020) The effects of TNF-alpha inhibition on cartilage: a systematic review of preclinical studies. *Osteoarthr Cartilage* 28: 708–718. https://doi.org/10.1016/j.joca.2019.09.008
95. Suurmond J, Dorjée AL, Boon MR, et al. (2011) Mast cells are the main interleukin 17-positive cells in anticitrullinated protein antibody-positive and -negative rheumatoid arthritis and osteoarthritis synovium. *Arthritis Res Ther* 13: R150. https://doi.org/10.1186/ar3466
96. Mohamed SA, Neseem NO, Metwally SS, et al. (2018) IL-17 in primary knee osteoarthritis and its relation with severity of the disease. *Int J Clin Rheumtol* 13: 364–369. https://doi.org/10.4172/1758-4272.1000212
97. Na HS, Park JS, Cho KH, et al. (2020) Interleukin-1-interleukin-17 signaling axis induces cartilage destruction and promotes experimental osteoarthritis. *Front Immunol* 11: 730. https://doi.org/10.3389/fimmu.2020.00730
98. Liao Y, Ren Y, Luo X, et al. (2022) Interleukin-6 signaling mediates cartilage degradation and pain in posttraumatic osteoarthritis in a sex-specific manner. *Sci Signal* 15: eabn7082. https://doi.org/10.1126/scisignal.abn7082
99. Wiegertjes R, van de Loo FAJ, Davidson ENB (2020) A roadmap to target interleukin-6 in osteoarthritis. *Rheumatology* 59: 2681–2694. https://doi.org/10.1093/rheumatology/keaa248
100. Ahmad R, El Mabrouk M, Sylvester J, et al. (2009) Human osteoarthritic chondrocytes are impaired in matrix metalloproteinase-13 inhibition by IFN-γ due to reduced IFN-γ receptor levels. *Osteoarthr Cartilage* 17: 1049–1055. https://doi.org/10.1016/j.joca.2009.02.008
101. Henrotin YE, Zheng SX, Labasse AH, et al. (2000) Modulation of human chondrocyte metabolism by recombinant human interferon. *Osteoarthr Cartilage* 8: 474–482. https://doi.org/10.1053/joca.1999.0323
102. Kour S, Garimella MG, Shiroor DA, et al. (2016) IL-3 decreases cartilage degeneration by downregulating matrix metalloproteinases and reduces joint destruction in osteoarthritic mice. *J Immunol* 196: 5024–5035. https://doi.org/10.4049/jimmunol.1500907
103. van Helvoort EM, van der Heijden E, van Roon JAG, et al. (2022) The role of interleukin-4 and interleukin-10 in osteoarthritic joint disease: A systematic narrative review. *Cartilage* 13: 194760352210981. https://doi.org/10.1177/19476035221098167
104. Jovanovic D, Pelletier JP, Alaaeddine N, et al. (1998) Effect of IL-13 on cytokines, cytokine receptors and inhibitors on human osteoarthritis synovium and synovial fibroblasts. *Osteoarthr Cartilage* 6: 40–49. https://doi.org/10.1053/joca.1997.0091
105. Yang CY, Chanalaris A, Bonelli S, et al. (2020) Interleukin 13 (IL-13)-regulated expression of the chondroprotective metalloproteinase ADAM15 is reduced in aging cartilage. *Osteoarthr Cartil Open* 2: 100128. https://doi.org/10.1016/j.ocarto.2020.100128

106. Cook AD, Pobjoy J, Steidl S, et al. (2012) Granulocyte-macrophage colony-stimulating factor is a key mediator in experimental osteoarthritis pain and disease development. *Arthritis Res Ther* 14: 1–9. https://doi.org/10.1186/ar4037
107. Lee KMC, Prasad V, Achuthan A, et al. (2020) Targeting GM-CSF for collagenase-induced osteoarthritis pain and disease in mice. *Osteoarthr Cartilage* 28: 486–491. https://doi.org/10.1016/j.joca.2020.01.012
108. Tewari D, Cook AD, Lee MC, et al. (2020) Granulocyte-macrophage colony stimulating factor as an indirect mediator of nociceptor activation and pain. *J Neurosci* 40: 2189–2199. https://doi.org/10.1523/JNEUROSCI.2268-19.2020
109. Honsawek S, Yuktanandana P, Tanavalee A, et al. (2012) Correlation between plasma and synovial fluid basic fibroblast growth factor with radiographic severity in primary knee osteoarthritis. *Int Orthop* 36: 981. https://doi.org/10.1007/s00264-011-1435-z
110. Takata K, Uchida K, Takano S, et al. (2021) Possible regulation of bFGF expression by mast cells in osteoarthritis patients with obesity: A cross-sectional study. *Diabetes Metab Syndr Obes* 14: 3291–3297. https://doi.org/10.2147/DMSO.S319537
111. El-Fetiany AE, Kassem EM, El-Barbary AM, et al. (2017) Evaluation of plasma basic fibroblast growth factor (bFGF) in primary knee osteoarthritis patients. *Egypt Rheumatol* 39: 33–37. https://doi.org/10.1016/j.ejr.2016.03.006
112. Im HJ, Sharrocks AD, Lin X, et al. (2009) Basic fibroblast growth factor induces matrix metalloproteinase-13 via eRK MAP kinase-altered phosphorylation and sumoylation of Elk-1 in human adult articular chondrocytes. *Open Access Rheumatol Res Rev* 1: 151–161. https://doi.org/10.2147/OARRR.S7527
113. Li X, Su G, Wang J, et al. (2013) Exogenous bFGF promotes articular cartilage repair via up-regulation of multiple growth factors. *Osteoarthr Cartilage* 21: 1567–1575. https://doi.org/10.1016/j.joca.2013.06.006
114. Chuma H, Mizuta H, Kudo S, et al. (2004) One day exposure to FGF-2 was sufficient for the regenerative repair of full-thickness defects of articular cartilage in rabbits. *Osteoarthr Cartilage* 12: 834–842. https://doi.org/10.1016/j.joca.2004.07.003
115. Khan SN, Muhammad H, Scammahorn JJ, et al. (2018) Fibroblast growth factor 2 promotes regeneration of cartilage by attracting mesenchymal stem cells to the site of cartilage injury. *Osteoarthr Cartilage* 26: S37. https://doi.org/10.1016/j.joca.2018.02.090
116. Vincent TL (2011) Fibroblast growth factor 2: Good or bad guy in the joint? *Arthritis Res Ther* 13: 1–2. https://doi.org/10.1186/ar3447
117. Murata M, Yudoh K, Masuko K (2008) The potential role of vascular endothelial growth factor (VEGF) in cartilage: How the angiogenic factor could be involved in the pathogenesis of osteoarthritis? *Osteoarthr Cartilage* 16: 279–286. https://doi.org/10.1016/j.joca.2007.09.003
118. Hamilton JL, Nagao M, Levine BR, et al. (2016) Targeting VEGF and its receptors for the treatment of osteoarthritis and associated pain. *J Bone Miner Res* 31: 911–924. https://doi.org/10.1002/jbmr.2828
119. Wang B, Wu L, Chen J, et al. (2021) Metabolism pathways of arachidonic acids: mechanisms and potential therapeutic targets. *Signal Transduct Target Ther* 6: 1–30. https://doi.org/10.1038/s41392-020-00443-w
120. Theoharides TC, Kalogeromitros D (2006) The critical role of mast cells in allergy and inflammation. *Ann NY Acad Sci* 1088: 78–99. https://doi.org/10.1196/annals.1366.025

121. Miyabe Y, Miyabe C, Luster AD (2017) LTB4 and BLT1 in inflammatory arthritis. *Semin Immunol* 33: 52–57. https://doi.org/10.1016/j.smim.2017.09.009
122. Wittenberg RH, Willburger RE, Kleemeyer KS, et al. (1993) In vitro release of prostaglandins and leukotrienes from synovial tissue, cartilage, and bone in degenerative joint diseases. *Arthritis Rheum* 36: 1444–1450. https://doi.org/10.1002/art.1780361017
123. Hansen AK, Indrevik JT, Figenschau Y, et al. (2015) Human articular chondrocytes express functional leukotriene B4 receptors. *J Anat* 226: 268–277. https://doi.org/10.1111/joa.12275
124. He W, Pelletier JP, Martel-Pelletier J, et al. (2002) Synthesis of interleukin 1beta, tumor necrosis factor-alpha, and interstitial collagenase (MMP-1) is eicosanoid dependent in human osteoarthritis synovial membrane explants: interactions with antiinflammatory cytokines. *J Rheumatol* 29: 546–553.
125. Mishima S, Kashiwakura J, Toyoshima S, et al. (2021) Higher PGD2 production by synovial mast cells from rheumatoid arthritis patients compared with osteoarthritis patients via miR-199a-3p/prostaglandin synthetase 2 axis. *Sci Rep* 11: 1–14. https://doi.org/10.1038/s41598-021-84963-7
126. Zayed N, Chabane N, Elmansouri FE, et al. (2010) Prostaglandin D2 enhances interleukin-1β-induced cyclooxygenase-2 expression in osteoarthritic cartilage. *J Transl Med* 25: 945. https://doi.org/10.1096/fasebj.25.1_supplement.945.15
127. Zayed N, Afif H, Chabane N, et al. (2008) Prostaglandin D2 inhibits interleukin-1β-induced matrix metalloproteinase-1 and -13 production by human osteoarthritic chondrocytes. *Arthritis Rheum* 58: 3530. https://doi.org/10.1002/art.23958
128. Dave M, Amin AR (2013) Yin-Yang regulation of prostaglandins and nitric oxide by PGD2 in human arthritis: Reversal by celecoxib. *Immunol Lett* 152: 47–54. https://doi.org/10.1016/j.imlet.2013.04.002
129. Fahmi H, Ouhaddi Y (2017) Deletion of the prostaglandin D2 receptor DP1 exacerbates aging-associated and instability-induced osteoarthritis. *Osteoarthr Cartilage* 25: S153–S154. https://doi.org/10.1016/j.joca.2017.02.255
130. Timur UT, Caron MMJ, Jeuken RM, et al. (2020) Chondroprotective actions of selective COX-2 inhibitors *in vivo*: A systematic review. *Int J Mol Sci* 21: 1–15. https://doi.org/10.3390/ijms21186962
131. McCabe PS, Maricar N, Parkes MJ, et al. (2016) The efficacy of intra-articular steroids in hip osteoarthritis: a systematic review. *Osteoarthr Cartilage* 24: 1509–1517. https://doi.org/10.1016/j.joca.2016.04.018
132. Pelletier JP, Lascau-Coman V, Jovanovic D, et al. (1999) Selective inhibition of inducible nitric oxide synthase in experimental osteoarthritis is associated with reduction in tissue levels of catabolic factors. *J Rheumatol* 26: 2002–2014.
133. Abramson SB (2008) Osteoarthritis and nitric oxide. *Osteoarthr Cartilage* 16: S15–S20. https://doi.org/10.1016/S1063-4584(08)60008-4
134. Shang X, Wang Y, Cai D, et al. (2022) An inducible nitric oxide synthase dimerization inhibitor prevents the progression of osteoarthritis. *Front Pharmacol* 13: 2627. https://doi.org/10.3389/fphar.2022.861183
135. Han Y, Yang J, Zhao W, et al. (2021) Biomimetic injectable hydrogel microspheres with enhanced lubrication and controllable drug release for the treatment of osteoarthritis. *Bioact Mater* 6: 3596–3607. https://doi.org/10.1016/j.bioactmat.2021.03.022

136. Huang H, Lou Z, Zheng S, et al. (2022) Intra-articular drug delivery systems for osteoarthritis therapy: shifting from sustained release to enhancing penetration into cartilage. *Drug Deliv* 29: 767. https://doi.org/10.1080/10717544.2022.2048130

AIMS Press