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Review article

The role of matrix metalloproteinases in osteoarthritis pathogenesis: An updated review

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ABSTRACT

Extensive degeneration of articular cartilage (AC) is a primary event in the pathogenesis of osteoarthritis (OA) and other types of joint and bone inflammation. OA results in the loss of joint function, usually accompanied by severe pain, and are the most common type of arthritis, affecting more than 10% of adults. The characteristic signs of OA are progressive cartilage destruction and, eventually, complete loss of chondrocytes. A key enzyme responsible for these degenerative changes in cartilage is matrix metalloproteinase-13 (MMP-13), which is thought to be a major contributor to the degenerative process occurring during OA pathogenesis. The aim of the present review is to shed light on the general role of MMPs, with special emphasis on MMP-13, in the induction of OA and the general basis of OA treatment. The pathogenic mechanism of this highly prevalent disease is not clear, and no effective disease-modifying treatment is currently available. Any updated information about OA treatment in human patients will also benefit companion animals such as horses and dogs, which also suffer from OA. Selective inhibition of MMP-13 seems to be an attractive therapeutic strategy.

1. Introduction

Osteoarthritis (OA) is one of the most common chronic diseases affecting the elderly as well as middle-aged population; OA is rare in people under 40 years of age but is common in people over 65 years of age [1]. Projections indicate that by the year 2030, 20% of adults in Western Europe and North America will have developed OA [2]. The most prominent feature of OA is the destruction and fragmentation of articular cartilage (AC), including the synovial membrane, AC components (particularly type II collagen and aggrecan), subchondral bone, and periarticular soft tissues, accompanied by joint dysfunction [3,4]. OA may occur due to traumatic injury of the joint, infectious agents that induce joint destruction, and aging (wear and tear) and is associated with the stress of daily life. The major clinical signs of OA are knee pain, knee swelling and stiffness, gelling, tenderness, ankylosis, and bony enlargement (Osteophytosis) due to periarticular new bone formation or in some cases malignant tumors, resulting in limited activity or even an inability to move in more severe cases [1,5–7]. These signs may be largely related to the expression of microRNA (miR)-140-5. miR-140-5p is a novel non-coding miR expressed in OA (specifically IL-1 beta-induced OA) that can lead to a complex series of changes, such as synovitis, mesenchymal proliferation, and cartilage degradation [7]. The first sign of degeneration characteristic to OA is the onset of fibrillation (fibrillar protein deposition) at the surface of AC, which is ultimately damaged [4]; this fibrillation is followed by the characteristic depletion of chondrocytes and increased new bone formation under the perichondrium within the affected synovial joints [8]. In addition, OA induces degradation of the various components of the cartilage matrix, particularly collagen II (CII) and aggrecan, which is reversible in the early stage, but irreversible damage can subsequently occur [9]. In OA, the extracellular matrix (ECM) is degraded within synovial joints particularly those in the knee, hands and hips and is manifested by severe pain in patients with OA. Joint cells as well as immune cells produce numerous inflammatory mediators, such as tumor necrosis factor alpha (TNF-α) and interleukins (IL-1 and IL-7) [10]. These inflammatory mediators stimulate the production of matrix metalloproteinases (or matrix metalloproteases, MMPs), enzymes that can degrade all components of the ECM. The collagenases MMP-1 and MMP-13 have predominant roles in OA because they are rate-limiting in the process of collagen degradation. MMP-1 is produced primarily by synovial cells that line joints, and MMP-13 is a product of chondrocytes that reside in cartilage. In addition to degrading collagen, MMP-13 also degrades the proteoglycan molecule aggrecan, thus playing a dual role in matrix destruction. In addition, the expression of other MMPs, such as MMP-2, MMP-3 and MMP-9, is elevated in arthritis, and these enzymes degrade non-collagen matrix components of joints.

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This review aims to update the current knowledge about the role of MMPs in OA by considering the mechanisms of matrix degradation in OA, the role of MMP-13 in OA pathogenesis, and the strategies that have been employed to prevent or reduce the severity of OA.

2. Matrix degradation during OA

MMPs are zinc-dependent endopeptidases and are also called matrixins. MMPs are a major group of enzymes that regulate the cell–matrix composition and are considered the major proteases involved in ECM degradation [11]. Cartilage ECM is composed mainly of proteoglycans, including the major proteoglycan aggrecan and other minor proteoglycans (decorin, fibronectin, lumican, biglycan, etc.), and collagens, such as fibrillar type II collagen and other minor collagens (type IX, XI and VI collagens) [12]. Other MMP family members are adamalysins, serralysins, and astacins. MMPs are capable of degrading all kinds of ECM proteins, including fibrillar and non-fibrillar collagens, fibronectin, laminin and basement membrane glycoproteins, and are involved in the cleavage of cell surface receptors [13,14]. MMPs play a major role in cell behaviours such as proliferation, migration (adhesion/dispersion), differentiation, apoptosis and host defence [13]. MMPs participate in both physiological and pathological processes of tissue reconstitution, including wound healing, inflammation and cancer [15]. Moreover, individual MMPs regulate both normal and pathological inflammatory processes (cytokine and chemokine activity) [16]. Cellular sources of destructive metalloproteinases in articular joints of osteoarthritis and rheumatoid arthritis were illustrated in Fig. 1 and Table 1.

Metalloproteinases are a group of degradative enzymes closely related to tumor invasion of the cell membrane, stroma, and blood vessels and, finally, malignant metastasis. Metalloproteinases also play a role in tumor progression and specific steps in metastatic cascades [17]. Any change in the size and/or composition of the blood vessels that helps in adaption as well as repair mechanisms is called vascular remodelling. The absence of vascular remodelling due to, for example, cardiac diseases such as atherosclerosis and atheroma development could lead to ECM degradation by MMPs. Recently, MMPs have become players of interest in most physiological as well as pathological alterations in vivo and in vitro. Additionally, major drivers such as vascular remodelling, inflammation, injury and stressors involve MMP expression and activity

Table 1
Regulation of matrix Metalloproteinases production in joints.

MMP members	Stimulatory factor	Cellular sources
• MMP-1, MMP-3,MMP9-MMP-13	• IL-1 α • IL-1 β • TNF	• Macrophage • Chondrocytes • Synovial fibroblast
• MMP-1, MMP-3,MMP13-	• IL-17	• Chondrocytes • Synovial fibroblast
• MMP-1, MMP-3,MMP13-	• IL-18	• Synovial fibroblast
• MMP-13	• TGF-β	• Synovial fibroblast
• MMP-1, MMP-3, MMP-15	• VEGF	• Endothelial cells • Chondrocytes
• MMP-1, MMP-3,MMP8-MMP-13	• Histamine	• Chondrocytes • Synovial fibroblast
• MMP-13	• Ligands for RAGE	• Chondrocytes
• MMP-1, MMP-3	• EMMPRIN/CD147	• Fibroblast like synoviocytes
• MMP-1, MMP-3	• Serum amyloid A • β microglobin,	• Synovial fibroblast

MMP: matrix metalloproteinases; IL: interleukin; TNF: tumor necrosis factor; TGF: transforming growth factor; VEGF: vascular endothelial growth factor; RAGE: receptor for advanced glycation; EMMPRIN extracellular metalloproteinases inducer.

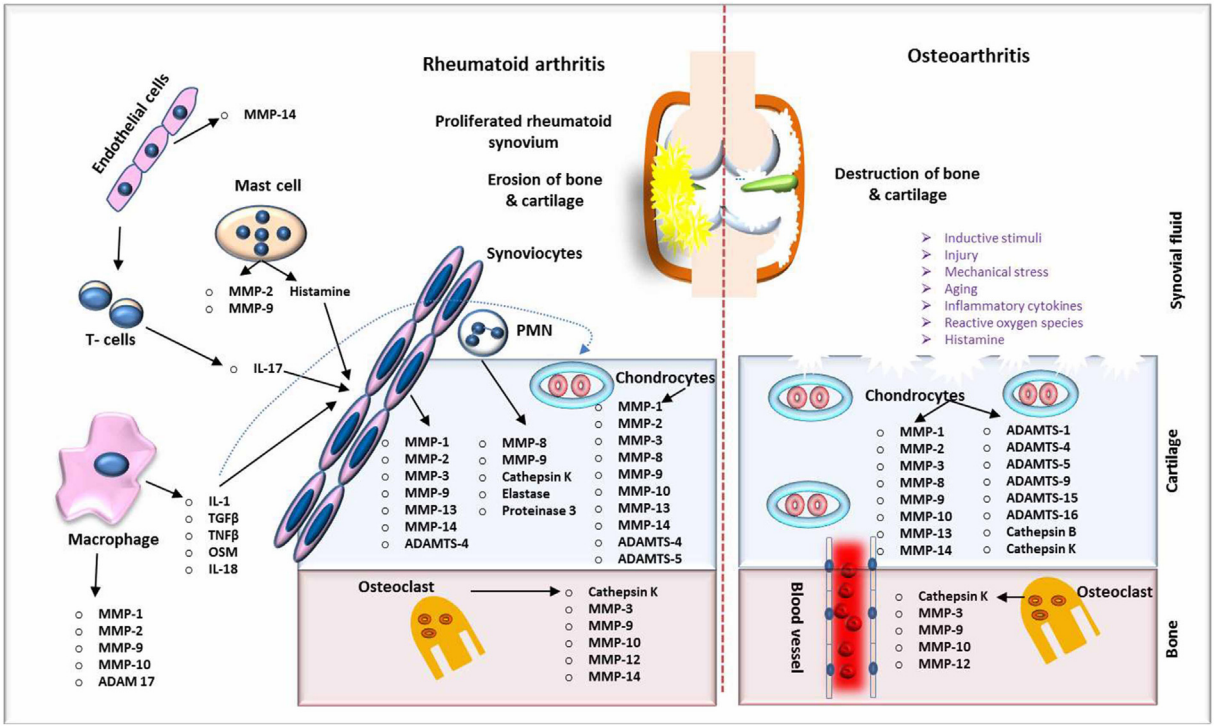

Fig. 1. Cellular sources of destructive metalloproteinases in articular joints of osteoarthritis and rheumatoid arthritis. In osteoarthritis (right side), chondrocytes are the primary cellular source for destructive proteinases, where they produced in response to inductive stimuli including mechanical stimuli, injury, reactive oxygen species, aging, and inflammatory cytokines. Bone erosion occurred due to migration of osteoclasts from blood vessels into the bony region. In rheumatoid arthritis (left side), tissue inflammation recruits inflammatory cells including lymphocytes, mast cells, and macrophages to the synovium. These cells produce histamine and inflammatory cytokines, which in turn induce production of MMPs and ADAMTSs from chondrocytes and synoviocytes.
ADAM: a disintegrin and metalloproteinase; PMN: polymorphonucleocyte; ADAMTS: a disintegrin and metalloproteinase with thrombospondin motifs; MMP: matrix metalloproteinases; TGF: transforming growth factor; TNF: tumor necrosis factor; OSM: oncostatin M; IL: interleukin.

Table 2
Functions and description of MMPs family members.

Gene	Name	Aliases	Location	Description	Substrate	Function	References
MMP1	Interstitial collagenase	CLG, CLGN	Secreted	Substrates include Col I, II, III, VII, VIII, X, gelatin	Collagen I, II, III, VII, VIII, X, gelatin, aggrecan, α1-antitrypsin inhibitor, α1-antichymotrypsin, casein, entactin, IGF-BP-3, IGFBP-5, IL-Iβ, 2-macroglobulin, nidogen, ovostatin, perlecan, proteoglycan link protein, Lselectin, pro-TNFα, SDF-1, serpins, tenascin-C, versican	• MMP-1 breaks down the interstitial collagens, types I, II, and III.	Brinckerhoff et al. [26] and Shalini et al. [27]
MMP2	Gelatinase-A, 72 kDa gelatinase		Secreted	Substrates include Gelatin, Col I, II, III, IV, Vii, X	Collagen I, II, III, IV, V, VII, X, XI, IV, gelatin, active MMP-9 and MMP-13, aggrecan, elastin, fibronectin, FGF-RI, IGF-BP-3, IGF-BP-5, IL-1β, laminin, nidogen, proteoglycan link protein, pro-TNF-α, TGF-β, versican	• Proteins of the matrix metalloproteinase (MMP) family are involved in the breakdown of ECM in normal physiological processes and disease processes, such as arthritis and metastasis. • This gene encodes an enzyme which degrades type IV collagen • Plays a role in endometrial menstrual breakdown, regulation of vascularization and the inflammatory response.	Devarajan et al. [28] and Samuel et al. [29]
MMP3	Stromelysin 1	CHDS6, MMP-3, SL-1, STMY, STMY1, STR1	Secreted	Substrates include Col II, IV, IX, X, XI, gelatin	Collagen II, III, IV, V, IX, X, XI, gelatin, aggrecan, α1-antichymotrypsin, antithrombin III, E-cadherin, casein, decorin, elastin, fibronectin, fibrinogen, Page 9 of 139 Accepted Manuscript 7 IGF-BP-3, laminin, nidogen, ovostatin, perlecan, proteoglycan, proteoglycan link protein, α1-proteinase inhibitor, pro-HB-EGF, pro-IL-β, pro-MMP-1, pro-MMP-8, pro-MMP-9, pro-MMP-13, L-selectin, SDF-1, pro-TNFα, versican	• The MMP-3 enzyme degrades collagen types II, III, IV, IX, and X, proteoglycans, fibronectin, laminin, and elastin. • MMP-3 can also activate other MMPs such as MMP-1, MMP-7, and MMP-9, rendering MMP-3 crucial in connective tissue remodelling. • The enzyme is also thought to be involved in wound repair, progression of atherosclerosis, and tumor initiation.	Eriksson et al. [30] and Zuo et al. [31].
MMP7	Matrilysin, PUMP 1	MMP-7, MPSL1, PUMP-1	Secreted	Membrane associated through binding to cholesterol sulfate in cell membranes, substrates include fibronectin, laminin, Col IV, gelatin	Collagen I, II, III, IV, V, X, aggrecan, casein, decorin, Ecadherin, elastin, enactin, Fasligand, β4 integrin, laminin, nidogen, plasminogen, proteoglycan link protein, pro-MMP-2, pro-MMP-7, pro-MMP-8, pro-TNFα, transferrin, tenascin, syndecan, versican	• It digests components of the extracellular matrix • Cleaves the α 2 chain of gelatin more rapidly, and digests the B chain of insulin at Ala-Leu, and Thyr-Leu. • MMP4 is inhibited by α 2-macroglubulin and TIMP. • The activated MMP7 can also cleave the propeptides of proMMP2 and proMMP9 to facilitate tumor invasion	Yokoyama et al. [32]
MMP8	Neutrophil collagenase	CLG1, HNC, MMP-8, PMNL-CL	Secreted	Substrates include Col I, II, III, VII, VIII, X, aggrecan, gelatin	Collagen I, II, III, V, VII, VIII, X, gelatin, aggrecan, α2-antiplasmin, elastin, fibronectin, laminin, 2-macroglobulin, nidogen, pro-MMP-8, serpins		Hasty et al. [33] and Devarajan et al. [34].
MMP9	Gelatinase-B, 92 kDa gelatinase	CLG4B, GELB, MANDP2, MMP-9	Secreted	Substrates include Gelatin, Col IV, V	Collagen IV, V, VII, X, XIV, gelatin, aggrecan, CXCL5, fibrillin, fibronectin, IL-1β, IL2-R, laminin, nidogen, osteonectin 2, plasminogen, proteoglycan link protein, pro-TNFα, SDF-1, TGF-β, versican		Wang and Tsirka [35] and Vandooren et al. [36]
MMP10	Stromelysin 2	SL-2, STMY2	Secreted	Substrates include Col IV, laminin, fibronectin, elastin	Collagen III, IV, V, aggrecan, casein, gelatin, elastin, fibronectin, laminin, nidogen, pro-MMP-1, pro-MMP-7, pro-MMP-8, pro-MMP-9, pro-MMP-10, pro-MMP-13	• MMP10 has been linked to cancer stem cell vitality and metastasis. • MMP10 is a potential prognostic biomarker for oral cancer	Justilien et al. [37]
MMP11	Stromelysin 3	SL-3, ST3, STMY3	Secreted	MMP-11 shows more similarity to the MT-MMPs, is convertase-activatable and is	Aggrecan, α1-antitrypsin, fibronectin, IGF-BP-1, laminin, α1-proteinase inhibitor		

(*continued on next page*)

Table 2 (*continued*)

Gene	Name	Aliases	Location	Description	Substrate	Function	References
				secreted therefore usually associated to convertase-activatable MMPs. Substrates include Col IV, fibronectin, laminin, aggrecan			Boulay et al. [38] and Perret et al. [39].
MMP12	Macrophage metalloelastase	HME, ME, MME, MMP-12	Secreted	Substrates include elastin, fibronectin, Col IV	Collagen IV, gelatin, casein, elastin, fibrillin, fibronectin, laminin, plasminogen, vitronectin		Shapiro et al. [40] and Belaaouaj et al. [41]
MMP13	Collagenase 3	CLG3, MANDP1, MMP-13	Secreted	Substrates include Col I, II, III, IV, IX, X, XIV, gelatin	Collagen I, II, III, IV, V, IX, X, XI, XIV, gelatin, aggrecan, casein, fibronectin, laminin, perlecan, plasminogen activator 2, pro-MMP-9, pro-MMP-13, SDF-1, tenascin		Yamamoto et al. [42,43]
MMP14	MT1-MMP	MMP-14, MMP-X1, MT-MMP, MT-MMP 1, MT1-MMP, MT1MMP, MTMMP1, WNCHRS	Membrane-associated	Type-I transmembrane MMP; substrates include gelatin, fibronectin, laminin	Collagen I, II, III, gelatin, aggrecan, CD44, dermatan sulfate proteoglycan, gCIqR, elastin, fibrin, fibrillin, fibronectin, αvβ3 Integrin, laminin, 2-macroglobulin, nidogen, perlecan, tenascin, pro-MMP-2, pro-MMP-13, pro-TNFα, SDF-1, tissue transglutaminase, vitronectin		Sato et al. [44].
MMP15	MT2-MMP	MT2-MMP, MTMMP2, SMCP-2, MMP-15, MT2MMP	Membrane-associated	Type-I transmembrane MMP; substrates include gelatin, fibronectin, laminin	Collagen I, II, III, gelatin, aggrecan, fibronectin, laminin, nidogen, perlecan, pro-MMP-2, pro-MMP-13, tissue transglutaminase, tenascin, vitronectin		Sato et al. [45] and Mattei et al. [46].
MMP16	MT3-MMP	C8orf57, MMP-X2, MT-MMP2, MT-MMP3, MT3-MMP	Membrane-associated	Type-I transmembrane MMP; substrates include gelatin, fibronectin, laminin	Collagen I, III, gelatin, aggrecan, casein, fibronectin, laminin, 2-macroglobulin, perlecan, proteoglycans, pro-MMP-2, proMMP-13, vitronectin		Takino et al. [47].
MMP17	MT4-MMP	MT4-MMP, MMP-17, MT4MMP, MTMMP4	Membrane-associated	Glycosyl phosphatidylinositol-attached; substrates include fibrinogen, fibrin	Gelatin, fibrin, fibrinogen, fibronectin, TNFα precursor		Puente et al. [48].
MMP18	Collagenase 4, xcol4, xenopus collagenase		–	No known human orthologue	Collagen I, II, III, gelatin, α1-antitrypsin		Clark [49] and Takino et al. [47]
MMP19	RASI-1, occasionally referred to as stromelysin-4	MMP18, RASI-1, CODA	–		Collagen I, IV, gelatin, aggrecan, casein, fibronectin, laminin, nidogen, tenascin		Kolb et al. [50].
MMP20	Enamelysin	AI2A2, MMP-20	Secreted		Collagen V, aggrecan, amelogenin, cartilage oligomeric protein		Llano et al. [51].
MMP21	X-MMP	MMP-21, HTX7	Secreted		Gelatin, α1-antitrypsin		Marchenko and Strongin [52]
MMP23A	CA-MMP	MIFR, MIFR-1, MMP22, MMP23A	Membrane-associated	Type-II transmembrane cysteine array	Gelatin		Clark [49] and Takino et al. [47].
MMP24	MT5-MMP	MMP-24, MMP25, MT-MMP 5, MT-MMP5, MT5-MMP, MT5MMP, MTMMP5	Membrane-associated	Type-I transmembrane MMP	Gelatin, N-cadherin, chondroitin sulfate, dermatan sulfate, fibrin, fibronectin, pro-MMP-2, pro-MMP-13		Kinoh et al. [53].
MMP25	MT6-MMP	MMP-25, MMP20, MMP20A, MMPL1, MT-MMP 6, MT-MMP6, MT6-MMP, MT6MMP, MTMMP6	Membrane-associated	Glycosyl phosphatidylinositol-attached	Collagen IV, gelatin, fibrin, fibronectin, pro-MMP-2, α-proteinase inhibitor		Kojima et al. [54].
MMP26	Matrilysin-2, endometase		–		Collagen IV, gelatin, casein, fibrin, fibrinogen, fibronectin, β1-proteinase inhibitor, TNF-α converting enzyme (TACE), vitronectin, pro-MMP-2		Park et al. [55] and de Coignac et al. [56].
MMP27	MMP-22, C-MMP	MMP-27	–		Gelatin, casein		Cominelli et al. [57]
MMP28	Epilysin	EPILYSIN, MM28, MMP-25, MMP-28, MMP25	Secreted	Discovered in 2001 and given its name due to have been discovered in human keratinocytes. Unlike other MMPs this	Casein		Lohi et al. [58] and Marchenko and Strongin [52].

(*continued on next page*)

Table 2 (*continued*)

Gene	Name	Aliases	Location	Description	Substrate	Function	References
				enzyme is constitutively expressed in many tissues (Highly expressed in testis and at lower levels in lung, heart, brain, colon, intestine, placenta, salivary glands, uterus, skin). A threonine replaces proline in its cysteine switch (PRCGVTD).			

[18]. In addition, MMPs participate in angiogenesis and tumor metastasis. MMPs are secreted by neoplastic tissues or the surrounding stroma [11]. MMP-13 proteins are involved in the breakdown of the ECM during normal physiological processes such as embryonic development, reproduction, and tissue remodelling, as well as in disease processes such as arthritis and metastasis [19]. AC has a simple vascular structure with an abundance of ECM and a small number of chondrocytes and is the major tissue targeted for destruction in both rheumatoid arthritis (RA) and OA [12,20]. A series of MMPs, including MMP-13, MMP-2/MT1-MMp and MMP-3, play key roles in cartilage destruction in OA through the degradation of aggrecan and collagens [21,22]. Among the most classic collagenases (MMP-1, MMP-8 and MMP-13), MMP-13 is thought to be the most important for the degradation of collagen within cartilage due to its preferential digestion of type II collagen over type I and III collagens [23–25]. The functions and descriptions of MMP family members are summarized in Table 2.

3. Role of MMP-13 in OA pathogenesis

MMP-13 is the enzyme responsible for the degeneration of the cartilage ECM and the degenerative process of OA pathogenesis. The major collagenase-producing cells are mesenchymal cells such as fibroblasts and chondrocytes, which synthesize and secrete these enzymes, a process that is affected by cytokines produced by mononuclear cells. These cytokines act primarily through cell surface receptors, and their signalling is mediated by complexes of nuclear oncoproteins, leading to the activation of pro-collagenase gene transcription [18]. Increased collagenase-3 (MMP-13) activity plays an important role in the induction and pathogenesis of OA; MMP-13 causes AC degradation and pathological changes in joints, manifested as synovial hyperplasia and synovitis with diffuse mononuclear cell infiltration in synovial joints, in addition to cartilage erosion and ulceration [59].

In addition, MMP-13 plays a critical role in the induction of OA [60]. In 2012, Wang and colleagues found that OA progression was decelerated in Mmp13 cKO mice 8, 12 and 16 weeks post-surgery, as evidenced by histological grading. Mmp13 cKO mice exhibited increased type II collagen and aggrecan expression following meniscal–ligamentous injury (MLI). Additionally, Neuhold et al. [61] reported that increased MMP-13 plays an important role in the pathogenesis of OA and that the pathological changes in the AC of mice following MLI are similar to those observed in human OA. Excessive MMP-13 activity can result in AC degradation and joint pathology similar to that in OA, suggesting that excessive proteinase activity of MMP-13 can lead to OA. Regarding the matrix expression of MMPs, MMP-13 is particularly expressed in the cartilage of human OA patients and is not expressed in normal adult cartilage. MMP-13 is the major collagenase in OA and has the higher activity toward CII than toward other collagens. Therefore, compared to saline treatment, intraperitoneal injection of CL82198 (an MMP-13 inhibitor) decelerated MLI-induced OA progression, as it increased the levels of type II collagen and proteoglycans and inhibited chondrocyte apoptosis, as determined by OA grading, histology, histomorphometry, immunohistochemical staining, and TUNEL [9,60]. Additionally, MMP-13 irreversibly degrades the collagen matrix of cartilage ECM, playing an important role in OA progression and the inflammatory process by activating transcription factor 3 (TCF3), which indirectly affects MMP13 expression [10]. MMP-13 has proteolytic capacity, suggesting that it is a powerful, potentially destructive proteinase; thus, MMP-13 was long believed not to be produced in most adult human tissues in the steady state. However, recent studies have revealed that although human chondrocytes isolated from healthy adults constitutively express and secrete MMP-13, MMP-13 is rapidly endocytosed and degraded by chondrocytes, suggesting the key role of autophagy in the regulation of the MMP-13 protein [42,43]. The pathological changes and cellular responses in AC during OA progression are shown in Figs. 2 and 3.

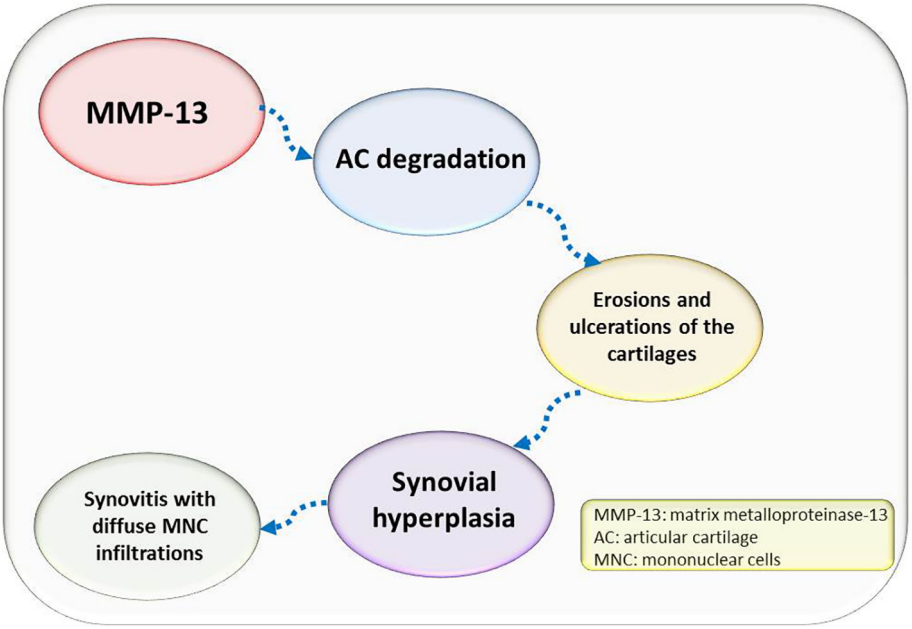

Fig. 2. Pathological changes in OA due to MMP-13.

4. MMP-13 inhibitors as a novel therapeutic strategy

MMP-13 is the major collagenase in OA cartilage, has the highest activity against CII and is a central node in the cartilage degradation network [1]. Baragi et al. [62], reported the design and synthesis of several non-hydroxamic acid-containing compounds that showed a high degree of potency for MMP-13 and selectivity against other MMPs. Littel [63] stated that MMP-13 inhibitors might be useful in arresting cartilage erosion in OA. Erosion results from the breakdown of cartilage components, including aggrecan (caused by a disintegrin and

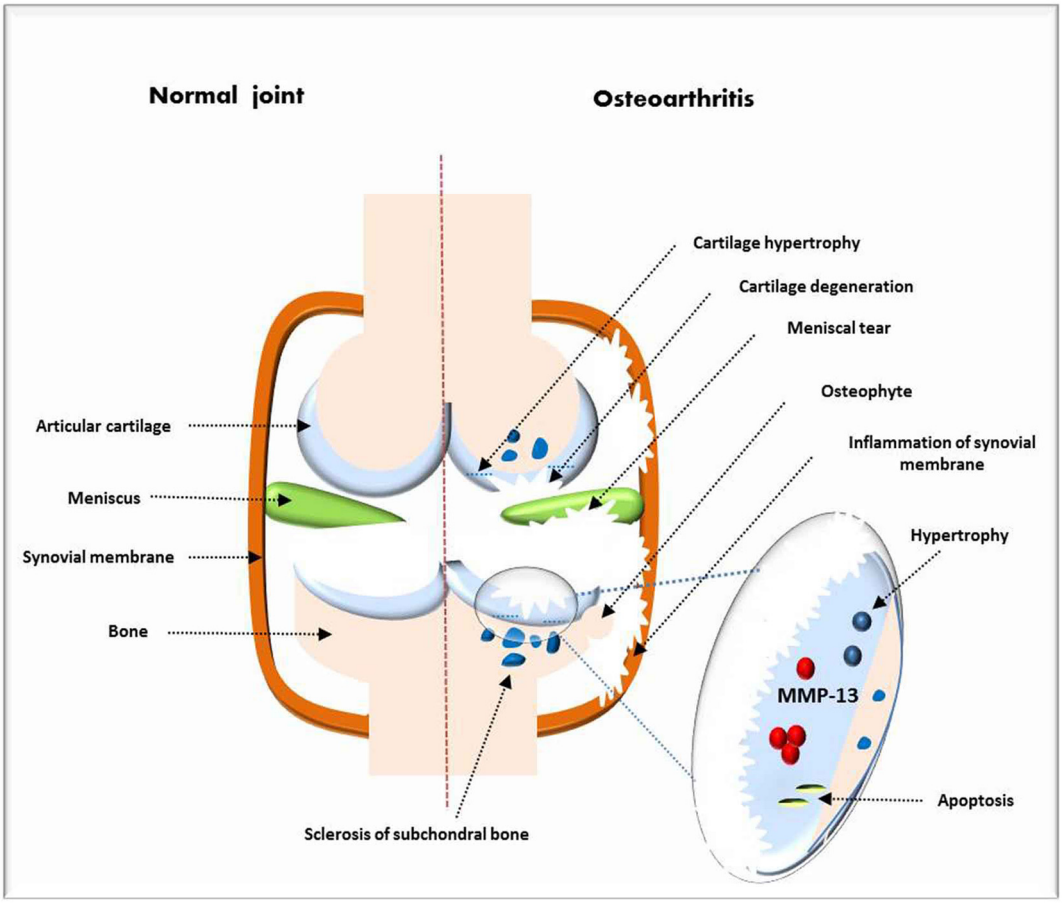

Fig. 3. Pathological changes and cellular responses in AC during OA progression.

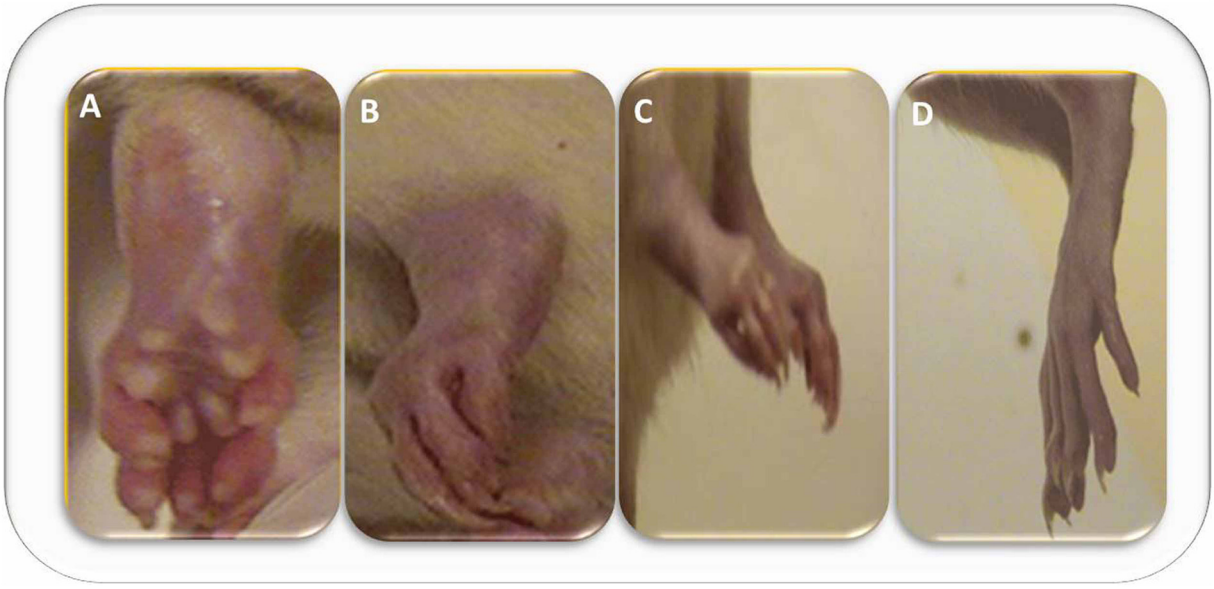

Fig. 4. Gross pathological changes of rats limbs from CII (a, b), CII + vitamin E (c), and CII + vitamin C (d) -treated groups showed: (a, b) severe inflammatory reaction, redness, edema, yellowish tubercle-like nodules in the joints of the lower limbs, swelling and transformation of the smooth contour of the joint surface. (c, d) Less severe inflammatory reaction, indicating severe inflammatory reactions [67]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

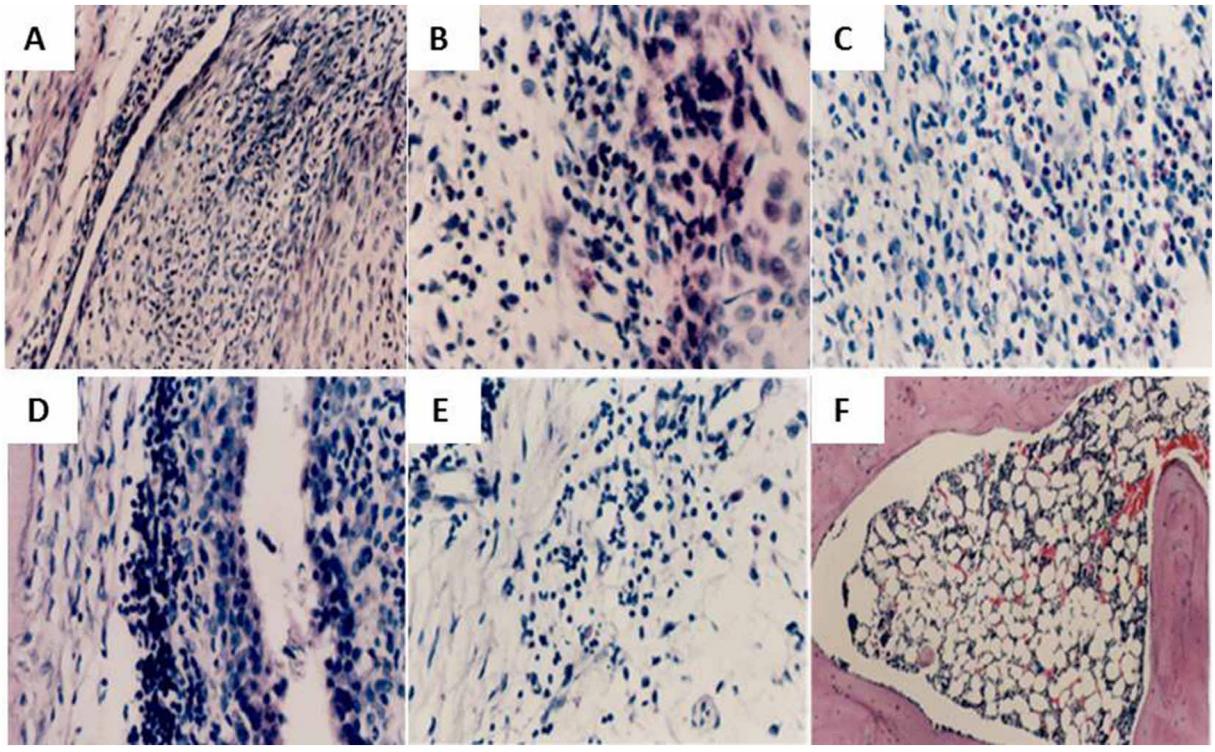

Fig. 5. Pathological alterations of rats limb from CII (a–d), CII + vitamin E (e), and CII + vitamin C (f) - injected groups showing: (a) synovial membrane with edema, necrosis and inflammatory cells infiltration. (b) Sub synovial stroma showing macrophage, giant cells, and (c) extensive eosinophil infiltration. (d) Synovial lining cells showing hyperplasia, hypertrophy, necrosis, and lymphocytic aggregates. (e) Mild to moderate leukocyte cells infiltrations in synovial stromal membrane. (f) Subchondral bone showing nearly normal bone and normo-cellular bone marrow.

metalloproteinase with thrombospondin motifs (ADAMTS) enzymes), the collagen network (caused by MMPs) and ECM proteins. Severe inflammatory conditions are modulated by collagenase production mediated by interactions with surrounding inflammatory cells; for example, monocyte-macrophages produce a stimulatory factor with homology to IL-1, which increases the synthesis of collagenase and PGE2 [64]. In synovitis induced by OA, collagenase is probably responsible for collagen degradation in the ECM and distortion of the architecture and function of the joints [10]. The increased production of MMP-13 is the result of a cascade of cellular effects involving both complex interactions between different ligands and signal amplification [65]. A noticeable increase in the level of denatured type II collagen is seen in early OA, with loss of these molecules by collagenase degradation, and is accompanied by an increase in the synthesis of matrix

molecules such as type II collagen and aggrecan [1]. However, the newly synthesized molecules are often damaged, compromising and preventing any repair of the damaged cartilage ECM. Additionally, the limited proliferation of chondrocytes due to the physical bulk of the large damaged collagen fibrils that occupy much of the ECM is important [66]. Hesham et al. [67] performed a comparative pathological study on the effect of different antioxidants on arthritis induced in rats. Sixty male albino rats were divided into 6 groups: the control group, CII-induced rheumatoid arthritis group (CII group), CII group treated with allopurinol (CII + Allo), and CII group treated with green tea extract (GTE) (CII + GTE). After 6 weeks of antioxidant treatment, the CII-treated group exhibited severe pathological changes, with marked inflammatory and destructive processes in the joints (Figs. 4 and 5). MMP inhibitors also have therapeutic effects in blocking the enzymes that facilitate tumor metastasis [17]. Recent studies have used MMP-13 inhibitors to treat OA, with an emphasis on their enzyme inhibitory properties [68]. Several trials were performed to protect cartilage from exposure to the destructive effects of the protease (MMP-13) [8]. MMP-13-mediated regulation may improve or inhibit the onset of OA through the functions of interacting factors, the autophagy process, and epigenetic modifications [1]. Paeoniflorin downregulates the expression of MMPs and increases the expression of tissue inhibitor of metalloproteinases-1 (TIMP-1) and other proteins in IL-beta-induced rat chondrocytes. Treatment of chondrocytes with paeoniflorin blocked the activation of the nuclear factor (NF)-κB pathway, suggesting that paeoniflorin plays an anticatabolic role in the pathogenesis of OA and may be an effective preventative treatment for OA [69].

5. Conclusion

MMPs are a group of enzymes that regulate the ECM composition and are considered the major proteases involved in ECM degradation. MMPs have an important role in cell behaviours, such as proliferation, migration, differentiation, apoptosis and host defence. MMPs participate in both physiological and pathological processes of tissue reconstitution, including wound healing, inflammation and cancer. MMP-13 is the major collagenase in OA cartilage, has the highest activity against CII and is a central node in the cartilage degradation network. Therefore, selective inhibition of MMP-13 seems to be an attractive therapeutic strategy. However, limited data are available on the role of MMP-13 inhibitors in the treatment of OA, and scientists are encouraged to accelerate their research in this area.

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Declaration of competing interest

The authors declare no conflicts of interest.

References

[1] L. Heng, D. Wang, Y. Yuan, J. Min, New insight on the MMP-13 regulatory network in the pathogenesis of early osteoarthritis, Arthritis. Res. Ther. 19 (2017) 248–251.
[2] I.F. Petersson, L.T. Jacobsson, Osteoarthritis of the peripheral joints, Best Pract. Res. Clin. Rheumatol. 16 (5) (2002) 741–760.
[3] M.B. Goldring, S.R. Goldring, Osteoarthritis, J. Cell. Physiol. 213 (2007) 626–634.
[4] J.E. Rana, M. Saeed, S. Khaled, B. Hossein, B. Yousefi, Melatonin in regulation of inflammatory pathways in rheumatoid arthritis and osteoarthritis: involvement of circadian clock genes, BJP 175 (16) (2018) 3230–3238.
[5] P. Brooks, Impact of osteoarthritis on individuals and society: how much disability? Social consequences and health economic implications, Curr. Open Rheumatol. 14 (2002) 573–577.
[6] G. Nuki, Pathophysiology of Osteoarthritis: Role of Mechanical Factors in the Etiology, Pathogenesis and Progression of Osteoarthritis, Springer, Berlin, 1999, pp. 101–114.
[7] L. Weihao, S. Zhao, H. Yang, Y. Xu, Y. Ding, Potential novel prediction of TMJ-OA: MIR-140-5P regulates inflammation through Smad/TGF-beta signaling, Front. Pharmacol. 10 (2019) 15.
[8] H. Deshmukh, C. Barroga, L. Dellamary, Y. Yazici, A small-molecule inhibitor of the Wnt pathway (SMO4690) as a potential disease modifying agent for the treatment of osteoarthritis of osteoarthritis of the knee, Osteoarth. Cartil. 26 (1) (2017) 18–27.
[9] N.G. Li, Z.H. Shi, Y.P. Tang, J.A. Duan, New hope for the treatment of osteoarthritis through selective inhibition of MMP-13, Curr. Med. Chem. 18 (7) (2011) 977–1001.
[10] M.C. Chun, M.D. Christopher, J.L. Gary, D.R. Andrew, Cytokin-induced MMP13 expression in human chondrocytes is dependent on activating transcription factor 3 (ATF3) regulation, J. Biol. Chem. 292 (5) (2016) 1625–1636.
[11] A. Jabłońska-Trypuć, M. Matejczyk, S. Rosochacki, Matrix metalloproteinases (MMPs), the main extracellular matrix (ECM) enzymes in collagen degradation, as a target for anticancer drugs, J. Enzyme Inhib. Med. Chem. 31 (1) (2016).
[12] T. Hironari, K. Tokuhiro, D. Seema, D. Armeino, Joint diseases and matrix metalloproteinases: a role for MMP-13, Curr. Pharm. Biotechnol. 9 (1) (2008) 47–54.
[13] M.W. Slawomir, R.B. Paraga, J.H. Michael, Matrix metalloproteinase inhibitors, Investig. New Drugs 15 (1) (1997) 61–75.
[14] L.P. Van, C. Lbert, Chemokine and cytokine processing by matrix metalloproteinases and its effect on leukocyte migration and inflammation, J. Leukoc. Biol. 82 (6) (2007) 1375–1381.
[15] H. Birked, Proteolytic remodeling of extracellular matrix, Curr. Opin. Cell. Biol. 7 (1995) 728–735.
[16] M.M. Anne, K.M. John, Matrix metalloproteinases as modulators of inflammation, Semin. Cell Dev. Biol. 19 (1) (2009) 34–41.
[17] R.N. Amy, F. Barbara, L.R. Mace, M.S. Matrisian, Matrix metalloproteinases: biological activity and clinical implication, Clin. Oncol. 18 (5) (2016) 1135–1145.
[18] S.G. Zorina, J.K. Jaikirshan, Matrix metalloproteinases in vascular remodeling and atherogenesis, Circ. Res. 90 (2018) 251–262.
[19] C. Bonnans, J. Chou, Z. Werb, Remodelling the extracellular matrix in development and disease, Nat. Rev. Mol. Cell Biol. 15 (12) (2015) 786–801 (2014 Dec).
[20] Y. Okada, E.D. HarrisJ. (Ed.), Kelley's Textbook of Rheumatology, WB Saunders Company, Philadelphia, 2005, pp. 63–81.
[21] P.G. Mitchell, H.A. Magna, S.A. Yocum, et al., J. Clin. Invest. 97 (1996) 761–768.
[22] D.J. Shlopov, R.W. Lie, K.A. Hasty, et al., Arthritis Rheum. 40 (1997) 2065–2074.
[23] K. Imai, S. Ohta, T. Matsumoto, Y. Okada, Am. J. Pathol. 151 (1997) 245–256.
[24] S. Ohta, K. Imai, K. Yamashita, Y. Okada, Lab. Investig. 78 (1998) 79–87.
[25] Y. Okada, M. Shinmei, O. Tanaka, H. Nagase, Lab. Investig. 66 (1992) 680–690.
[26] C.E. Brinckerhoff, P.L. Ruby, S.D. Austin, M.E. Fini, H.D. White, Molecular cloning of human synovial cell collagenase and selection of a single gene from genomic DNA, J. Clin. Invest. 79 (2) (1987).
[27] Y.R. Shalini, N. Hideak, K.A. Ravi, Crystal structure of an active form of human MMP-1, J. Mol. Biol. 362 (1) (2006) 78–88.
[28] P. Devarajan, J.J. Johnston, S.S. Ginsberg, H.E. Van Wart, N. Berliner, Structure and expression of neutrophil gelatinase cDNA. Identity with type IV collagenase from HT1080 cells, J. Biol. Chem. 267 (35) (December 1992) 25228–25232.
[29] H.A. Samuel, B. Evan, B. Vesna, F.P. Carlos, Identification of a novel heart-liver axis: matrix metalloproteinase-2 negatively regulates cardiac secreted phospholipase A2 to modulate lipid metabolism and inflammation in liver, J. Am. Heart Assoc. 4 (11) (2015) e002553.
[30] P. Eriksson, A. Hamsten, M. Kurkinen, S.E. Humphries, A.M. Henney, Progression of coronary atherosclerosis is associated with a common genetic variant of the human stromelysin-1 promoter which results in reduced gene expression, J. Biol. Chem. 271 (22) (May 1996) 13055–13060.
[31] X. Zuo, P. Wen, T. Feng, J. Dai, Matrix metalloproteinase 3 promotes cellular anti-dengue virus response via interaction with transcription factor NFKB in cell nucleus, PLoS One 9 (1) (2014) e84748.
[32] Y. Yokoyama, F. Grünebach, S.M. Schmidt, A. Heine, M. Häntschel, S. Stevanovic, H.G. Rammensee, P. Brossart, Matrilysin (MMP-7) is a novel broadly expressed tumor antigen recognized by antigen-specific T cells, Clin. Cancer Res. 14 (17) (2008) 5503–5511.
[33] K.A. Hasty, T.F. Pourmotabbed, G.I. Goldberg, J.P. Thompson, D.G. Spinella, R.M. Stevens, C.L. Mainardi, Human neutrophil collagenase. A distinct gene product with homology to other matrix metalloproteinases, J. Biol. Chem. 265 (20) (1990) 11421–11424.
[34] P. Devarajan, K. Mookhtiar, H. Van Wart, N. Berliner, Structure and expression of the cDNA encoding human neutrophil collagenase, Blood 77 (12) (1991) 2731–2738.
[35] J. Wang, S.E. Tsirka, Neuroprotection by inhibition of matrix metalloproteinases in a mouse model of intracerebral haemorrhage, Brain 128 (7) (2005) 1622–1633.
[36] J. Vandooren, P.E. Van den Steen, G. Opdenakker, Biochemistry and molecular biology of gelatinase B or matrix metalloproteinase-9 (MMP-9): the next decade, Crit. Rev. Biochem. Mol. Biol. 48 (3) (2013) 222–272.
[37] V. Justilien, R.P. Regala, I.C. Tseng, M.P. Walsh, J. Batra, E.S. Radisky, N.R. Murray, A.P. Fields, Matrix metalloproteinase-10 is required for lung cancer stem cell maintenance, tumor initiation and metastatic potential, PLoS One 7 (4) (2012) 35–40.
[38] A. Boulay, R. Masson, M.P. Chenard, et al., High cancer cell death in syngeneic tumors developed in host mice deficient for the stromelysin-3 matrix metalloproteinase, Cancer Res. 61 (5) (2001) 2189–2193 (PMID 11280785).
[39] A.G. Perret, R. Duthel, M.J. Fotso, et al., Stromelysin-3 is expressed by aggressive meningiomas, Cancer 94 (3) (2002) 765–772.
[40] S.D. Shapiro, D.K. Kobayashi, T.J. Ley, Cloning and characterization of a unique elastolytic metalloproteinase produced by human alveolar macrophages, J. Biol. Chem. 268 (32) (1993) 23824–23829.
[41] A. Belaaouaj, J.M. Shipley, D.K. Kobayashi, D.B. Zimonjic, N. Popescu, G.A. Silverman, S.D. Shapiro, Human macrophage metalloelastase. Genomic

organization, chromosomal location, gene linkage, and tissue-specific expression, J. Biol. Chem. 270 (24) (1995) 14568–14575.
[42] K. Yamamoto, H. Okano, W. Miyagawa, S. Santamaria, MMP-13 is constitutively produced in human chondrocytes and co-endocytosed with ADAMTS-5 and TIMP-3 by the endocytic receptor LRPI, Matrix Biol. 56 (2016) 57–73.
[43] K. Yamamoto, H. Okano, W. Miyagawa, S. Santamaria, MMP-13 is constitutively produced in human chondrocytes and co-endocytosed with ADAMTS-5 and TIMP-3 by the endocytic receptor LRPI, Matrix Biol. 56 (2016) 57–73.
[44] H. Sato, T. Takino, Y. Okada, J. Cao, A. Shinagawa, E. Yamamoto, M. Seiki, A matrix metalloproteinase expressed on the surface of invasive tumour cells, Nature 370 (6484) (1994).
[45] H. Sato, M. Tanaka, T. Takino, M. Inoue, M. Seiki, Assignment of the human genes for membrane-type-1, -2, and -3 matrix metalloproteinases (MMP14, MMP15, and MMP16) to 14q12.2, 16q12.2-q21, and 8q21, respectively, by in situ hybridization, Genomics 39 (3) (1997) 412–413.
[46] M.G. Mattei, N. Roeckel, B.R. Olsen, S.S. Apte, Genes of the membrane-type matrix metalloproteinase (MT-MMP) gene family, MMP14, MMP15, and MMP16, localize to human chromosomes 14, 16, and 8, respectively, Genomics 40 (1) (1997) 168–169.
[47] T. Takino, H. Sato, A. Shinnagawa, Identification of the second membrane–type matrix subclass in the MMP family, J. Biol. Chem. 270 (1995) 23013–23020.
[48] X.S. Puente, A.M. Pendas, E. Llano, C. Lopez-Otin, Localization of the human membrane type 4-matrix metalloproteinase gene (MMP17) to chromosome 12q24, Genomics 54 (3) (1999) 578–579.
[49] M.I. Clark, Matrix Metalloproteinase Protocols, Human Press, Totowa, New Jersey, 2001.
[50] C. Kolb, S. Mauch, H.H. Peter, U. Krawinkel, R. Sedlacek, The matrix metalloproteinase RASI-1 is expressed in synovial blood vessels of a rheumatoid arthritis patient, Immunol. Lett. 57 (1–3) (1997) 83–88.
[51] E. Llano, A.M. Pendas, V. Knauper, T. Sorsa, T. Salo, E. Salido, G. Murphy, J.P. Simmer, J.D. Bartlett, C. Lopez-Otin, Identification and structural and functional characterization of human enamelysin (MMP-20), Biochemistry 36 (49) (1998) 15101–15108.
[52] G.N. Marchenko, A.Y. Strongin, MMP-28, a new human matrix metalloproteinase with an unusual cysteine-switch sequence is widely expressed in tumors, Gene 265 (1–2) (2001) 87–93.
[53] H. Kinoh, H. Hayashita, M. Kajita, A. Okada, M. Seiki, Assignment of the genes for membrane-type-4 matrix metalloproteinase (Mmp17, MMP17) to mouse chromosome 5, human chromosome band 12q24.3 and membrane-type-5 matrix metalloproteinase (Mmp24, MMP24) to mouse chromosome 2 and human chromosome band 20q11.2-q12, respectively, by radiation hybrid and in situ hybridization, Cytogenet. Cell Genet. 97–98 (1999) (1999) 87.
[54] S. Kojima, Y. Itoh, S. Matsumoto, et al., Membrane-type 6 matrix metalloproteinase (MT6-MMP, MMP-25) is the second glycosyl-phosphatidyl inositol (GPI)-anchored MMP, FEBS Lett. 480 (2–3) (2000) 142–146.
[55] H.I. Park, J. Ni, F.E. Gerkema, D. Liu, V.E. Belozerov, Q.X. Sang, Identification and characterization of human endometase (matrix metalloproteinase-26) from endometrial tumor, J. Biol. Chem. 275 (27) (2000) 20540–20544, https://doi.org/10.1074/jbc.M002349200. PMID 10801841.
[56] A.B. de Coignac, G. Elson, Y. Delneste, G. Magistrelli, P. Jeannin, J.P. Aubry, O. Berthier, D. Schmitt, J.Y. Bonnefoy, J.F. Gauchat, Cloning of MMP-26. A novel matrilysin-like proteinase, Eur. J. Biochem. 267 (11) (2000) 3323–3329.
[57] A. Cominelli, M. Halbout, F. N'Kuli, P. Lemoine, P.J. Courtoy, E. Marbaix, D. Tyteca, P. Henriet, A unique C-terminal domain allows retention of matrix metalloproteinase-27 in the endoplasmic reticulum, Traffic 15 (4) (2014) 401–417.
[58] J. Lohi, C.L. Wilson, J.D. Roby, W.C. Parks, Epilysin, a novel human matrix metalloproteinase (MMP-28) expressed in testis and keratinocytes and in response to injury, J. Biol. Chem. 276 (13) (2001) 10134–10144.
[59] A.N. Lisa, K. LOran, Z. Weiguang, D. Louis, Postnatal expression in hyaline cartilage of constitutively active human collagenase-3 (MMP-13) induces osteoarthritis in mice, J. Clin. Invest. 107 (1) (2001) 35–44.
[60] M.S. Wang, H. Jin, O. Ke, D. Chen, MMP13 is a critical target genes during the progression of osteoarthritis, Arthritis Res. Ther. 8 (1) (2013) 15, https://doi.org/10.1186/ar4133.
[61] A. Neuhold, L. Killar, W. Zhao, L.J. Degennaro, Postnatal expression in hyaline cartilage of constitutive active human collagenase-3 (MMP-13) induces osteoarthritis in mice, J. Clin. Invest. 107 (1) (2001) 35–44.
[62] V.M. Baragi, G. Becher, A.M. Bendele, B. Xia, A new class of potent matrix metalloproteinase 13 inhibitor s for potential treatment of Osteoaethritis: evidence of histologic and clinical efficacy without musculoskeletal toxicity in rat models, Arthritis Rheum. 60 (2) (2009) 1–18.
[63] C.B. Little, Matrix metalloproteinase 13–deficient mice are resistant to osteoarthritis cartilage erosion but not chondrocyte hypertrophy or osteophyte development, Arthritis Rheum. 60 (2009) 3723–3733.
[64] S.M. Kranr, Collagenases collagen degredation, J. Invest. Dermatol. 1 (1982) 83s–86s.
[65] S.M. Kranr, W. Conca, M.L. Stephenson, M.B. Goldring, Mechanisms of matrix degradation in rheumatoid arthritis, Ann. N. Y. Acad. Sci. 580 (1990) 340–354.
[66] R.A. Poole, M. Kobayashi, T. Yasuda, Wu, Type II collagen degradation and its regulation in articular cartilage in osteoarthritis, Ann. Rheum. Dis. 61 (2002) II78–II81.
[67] S.A. Hesham, E.E. Mehana, M. Abdel-Raheim, Comparative pathological study of the effect of different antioxidants on arthritis–induced in rats, Assiut Med. J. 32 (2) (2008) 60–78.
[68] X.W. Xie, R.Z. Wan, Z.P. Liu, Recent research advances in selective matrix metalloproteinase-13 inhibitors as anti-osteoarthritis agents, ChemMedChem 12 (15) (2017) 1157–1168.
[69] P.F. Hu, F.F. Sun, L.F. Jiang, L.D. Wu, Paeoniflorin inhibits IL-1B-induced MMP secretion via the NF-KB pathway in the chondrocytes, Exp. Ther. Med. 16 (2) (2018) 1513–1519.