Mod Rheumatol (2004) 14:197–204
DOI 10.1007/s10165-004-0292-7

REVIEW ARTICLE

Ginette Tardif · Pascal Reboul · Jean-Pierre Pelletier
Johanne Martel-Pelletier

Ten years in the life of an enzyme: the story of the human MMP-13 (collagenase-3)

Abstract In 1994, a new human matrix metalloproteinase (MMP) was identified and cloned. This enzyme displayed the structural characteristics of a collagenase and was named collagenase-3, or MMP-13 according to MMP nomenclature. This review describes the research advances in the understanding of the function/production of the human MMP-13 at the tissular, cellular, biochemical, and molecular levels. In contrast to many human MMPs, the MMP-13 distribution pattern is restrictive in normal tissues and selective in pathological conditions. This enzyme plays a premier role in tissue remodeling as well as in some pathological processes such as cancer and arthritis. MMP-13 demonstrates versatility in its substrate utilization. In addition to being highly active on type II collagen, MMP-13 cleaves other substrates, mostly macromolecules of the extracellular matrix, but also molecules such as connective tissue (CTGF) and fibrinogen. MMP-13 is controlled at multiple levels: i.e., the expression/synthesis, activation, and inhibition of the active enzyme. Unlike other MMPs, the human MMP-13 gene is transcribed into several transcripts which could yield proteins with activities and functions different from those of the original MMP-13. Activation of MMP-13 involves a proteolytic cascade including MMP-14 (MT1-MMP) and MMP-2. Transcription is regulated by numerous agents, mostly by growth factors, proinflammatory cytokines and mechanical stimuli. Cloning of the MMP-13 promoter revealed the presence of a number of binding sites implicated in transcriptional regulation: TATA box, AP-1, PEA-3, OSE-2, and the newly identified negative regulator, AGRE. MMP-13 constitutes a more complex system than was originally thought. Although our knowledge of MMP-13 biochemistry and regulation has greatly increased over the years, there is still much to discover.

G. Tardif · P. Reboul · J.-P. Pelletier · J. Martel-Pelletier (✉)
Osteoarthritis Research Unit, Hôpital Notre-Dame, Centre hospitalier de l'Université de Montréal, 1560 Sherbrooke Street East, Montreal, Quebec H2L 4M1, Canada
Tel. +1-514-890-8000 (ext. 26658); Fax +1-514-412-7582
e-mail: jm@martelpelletier.ca

Key words Arthritis · Cancer · Cartilage · Collagenase-3 · Matrix metalloproteinase (MMP)-13

Introduction

In 1994, Freije et al.[1] identified and cloned the gene of a new human matrix metalloproteinase (MMP) from a breast carcinoma. This novel enzyme displayed the structural characteristics of a collagenase and was designated collagenase-3, or MMP-13 according to MMP nomenclature. Collagenase-3 is the third member of the subfamily composed of collagenase-1 (interstitial or fibroblast collagenase or MMP-1) and collagenase-2 (neutrophil collagenase or MMP-8). Although MMP-13 was expressed in some breast tumor cells, it could not be detected in normal liver, placenta, ovary, uterus, prostate, parotid gland, or even breast tissues.

Shortly after the first publication, Reboul et al.[2] and Mitchell et al.[3] reported that MMP-13 was produced by chondrocytes in human cartilage. Its expression was upregulated in osteoarthritis (OA) and modulated by the two proinflammatory cytokines IL-1β and TNF-α. At about the same time, Wernicke et al.[4] identified an enzyme identical to MMP-13 from the synovial membrane of rheumatoid arthritis (RA) patients. They observed MMP-13 expression in RA and OA synovial membranes and, as also noted by Mitchell et al.,[3] that it could not be detected in normal brain, heart, lung, kidney, liver, muscle and pancreas tissues. A year later, the human MMP-13 promoter region was cloned by two groups.[5,6]

A few years prior to the discovery of human MMP-13, the sequence of the mouse and rat MMP-1[7,8] was published. At the time, it was reported that the rodent collagenase sequences diverged from the human MMP-1 sequence. Sequence homology analyses revealed that human MMP-13, but not human MMP-1, was homologous to the mouse collagenase. The human MMP-13 gene has 84% homology with both the mouse and rat collagenase genes. Although many publications have since been devoted to the study of

the rodent MMP-13 regulation, this review will focus mainly on human MMP-13 and its relevance to arthritic diseases such as OA and RA.

Biochemical properties

Activation and inhibition

MMPs are generally synthesized as proenzymes and must be processed by proteolytic cleavage at the N-terminus to be active. MMP-13 has 471 amino acids and is composed of distinct domains. There is a hydrophobic signal peptide which is necessary to the secretion of the enzyme, a prodomain associated with latency that has to be proteolytically cleaved to be active, a catalytic domain containing the zinc-binding site, and a hemopexin-like domain which is needed for collagenolytic activity as well as enzymatic activation.[1,9,10] In vivo, MMP-14 (MT1-MMP) and MMP-2 (gelatinase A) are the enzymes responsible for the activation of proMMP-13[11]; the activation requires the presence of the C-terminal domain.[9] Other enzymes, such as MMP-3 (stromelysin-1)[12] and the major isoenzyme of human tumor-associated trypsinogen, trypsin-2, can also activate MMP-13.[13]

MMP-13 activity is controlled physiologically by several naturally occurring inhibitors such as α_2-macroglobulins and tissue inhibitor of metalloproteases (TIMP).[14] α_2-macroglobulins are large proteins (750-kDa) produced by the liver and found in serum and synovial fluids. These proteins act as nonspecific inhibitors by trapping the enzymes and blocking their access to the substrate. TIMPs, on the other hand, inhibit MMPs by binding specifically to their active sites. Active MMP-13 is inhibited in a 1:1 stoichiometric fashion by TIMP-1, -2, and -3[12]; the ability of TIMP-4 to bind MMP-13 has not yet been reported.

TIMPs are effective inhibitors of MMP activity, but they do not specifically inhibit MMP-13. As therapeutic intervention based on MMP-13 inhibition is a promising avenue of research, there is an ongoing search for synthetic compounds that would specifically inhibit MMP-13 and spare other MMPs, and in doing so avoid unacceptable side-effects such as musculo-skeletal syndrome, which is observed with broad-spectrum MMP inhibitors. Compounds such as piperazine-based hydroxamic acids, and carboxylic and phosphinic acids are among the recently developed MMP-13 inhibitors. The piperazine-based dual MMP-13- and TNF-α–converting enzyme inhibitors are potentially interesting in arthritis treatment as they act on two different and important catabolic events.[15] The drawback of these inhibitors is their short in vivo half-life. Phosphinic acid-based MMP-13 inhibitors have recently been reported to spare both MMP-1 and -3, but not other MMPs[16]; these molecules have not yet been characterized in vitro and in vivo with respect to cartilage degradation. Among the MMP inhibitors, the carboxylate RS102481 is the best characterized in vitro. Its specificity for MMP-13 is very high compared with that of MMP-1, but it can also discriminate MMP-2, -3, -8, and -14. However, no in vivo studies have been published to date with this inhibitor. In vitro tests in human normal and OA articular cartilage,[17] as well as in basal and IL-1-stimulated bovine nasal and articular cartilages,[18] all showed inhibition of type II collagen breakdown. Although progress has been made towards achieving specific MMP-13 inhibition, similar inhibitors which have the right therapeutic and safety profiles are forthcoming.

Substrates

MMP-13 preferentially hydrolyzes type II collagen, the major collagen type of cartilage. This enzyme is 5–10 times more efficient than MMP-1 at cleaving this collagen type,[2,3] but is five times less active on types I and III collagens.[12] In contrast, MMP-1 preferentially cleaves type III collagen and MMP-8 type I collagen. MMP-13 is also active on other matrix components such as types IV, IX, X, and XIV collagens, and gelatin, fibronectin, and aggrecan.[1,3,19–21] It is noteworthy that the gelatinolytic activity of MMP-13 is about 44 times greater than that of MMP-1.[12]

Recent reports have broadened the list of molecules which are susceptible to digestion by MMP-13 to include connective tissue growth factor (CTGF) and fibrinogen. Vascular endothelial growth factor (VEGF) is a potent angiogenic mitogen. One of its isoforms, $VEGF_{165}$, binds the CTGF, which inhibits the angiogenic property of $VEGF_{165}$. Hashimoto et al.[22] have found that MMP-1, -3, -7, and -13 could restore the angiogenic property to $VEGF_{165}$ by cleaving CTGF and releasing $VEGF_{165}$ from the CTGF/$VEGF_{165}$ complex. This property may be important for VEGF-induced angiogenesis in arthritic tissues: the cleavage of the CTGF/$VEGF_{165}$ complex by the MMPs produced in the diseased joint could result in synovial membrane pannus invasion of the cartilage.

Fibrinogen is a glycoprotein that participates in both the cellular and the fluid phases of blood clot formation. It has been shown[23] that MMP-8, -12, -13, and -14 interact with the clotting system by proteolytically processing fibrinogen and, with the exception of MMP-8, also by inactivating Factor XII.

MMP-13 and pathologies

MMP-13 is expressed in hypertrophic chondrocytes and osteoblasts during human fetal development.[24,25] There is little or no expression of MMP-13 in normal adult tissues, but the enzyme is reexpressed in diseases where there is a need for tissue repair or remodeling. The very restricted distribution of MMP-13 in normal tissues, coupled with its ability to degrade type II collagen and other extracellular matrix components, make this enzyme an interesting target in arthritic diseases, especially OA, which is a disease characterized by the degradation of articular cartilage.

Several in vitro studies have demonstrated the importance of MMP-13 in human OA and RA.[2,3,19,26] In vivo

studies with animal models have confirmed the role of MMP-13 in OA progression. In one of these studies, Otterness et al.[27] injected active human recombinant MMP-13 intraarticularly into the knee joint of hamsters. Collagen cleavage was limited to a thin superficial band at the cartilage surface, probably because of the strong binding of the hemopexin-domain for collagen and gelatin. The injection of MMP-13 led to cartilage collagen damage with the release of measurable collagen fragments. In another study, Neuhold et al.[28] showed that the expression of a constitutively active human MMP-13 into hyaline cartilages and joints of transgenic mice resulted in erosion of the articular cartilage with excessive cleavage of type II collagen, loss of proteoglycan, and synovial hyperplasia, which are changes similar to those observed in human OA.

Immunohistochemistry and in situ hybridization methodologies have been used to localize MMP-13 in normal and OA cartilage, and variable results have been obtained. Shlopov et al.[29] showed that chondrocytes from areas surrounding OA lesions expressed more MMP-13 than the cells located further from the lesion. At the protein level, Moldovan et al.[30] found that the MMP-13 protein was preferentially localized in the lower intermediary and deep layers (deep zone) of human OA cartilage, while Tetlow et al.[31] associated the presence of MMP-13 at the superficial cartilage zone characterized by fibrillations and degenerative matrix changes. Freemont et al.[32] used in situ zymography to demonstrate that the distribution and amount of collagen II degrading activity varied with the extent of cartilage damage, being greatest in the deep zone and in cartilage lesions, and that MMP-13 mRNA expression co-distributed with the collagenase activity. Further evidence for the localization of MMP-13 in the deeper zone of diseased cartilage was shown by another immunohistochemical study of an experimental OA canine model. In this study,[33] the authors observed that MMP-13 was mostly located in the lower intermediary and deep layers of the cartilage, while MMP-1 was preferentially found at the superficial layers. The MMP-13 localization in diseased cartilage in the deep zone is of importance, since type II collagen fibers are largest in the deeper layers and chondrocytes are most able to reconstitute extracellular matrix.

MMP-13 has previously been reported to bind to a still unknown 170-kDa specific receptor on rat osteosarcoma cells; after binding, MMP-13 was internalized, processed, and excreted from the cells in degraded form.[34,35] Internalization required the low-density lipoprotein receptor-related protein. Recently, the same team[36] showed that, although the 170-kDa receptor is specific for MMP-13 in rodent cells, it can also bind MMP-1 and -3 on human chondrocytes. Moreover, the authors showed that OA chondrocytes and synovial fibroblasts have impaired the receptor-mediated removal of MMP-13, a mechanism that may lead to enhanced local degradation of cartilage.

MMP-13 is expressed in RA, an arthritic disease characterized by chronic inflammation and cartilage destruction. In this disease, MMP-13 has been detected in some synovial membranes,[4,37–42] and its expression correlated with elevated levels of systemic markers of inflammation, including erythrocyte sedimentation rate and C-reactive protein.[37] In these diseased synovial membranes, MMP-13 was localized at the lining and sublining layers and also at the membrane/cartilage interface.[37–39,42]

MMP-13 was originally found in breast carcinoma,[1] but is now associated with other types of human cancer: chondrosarcomas,[43] gastric cancer,[44] basal cell carcinomas,[45] and squamous cell carcinomas of the head and neck, larynx, vulva, and epithelium of the skin,[46–49] to name but a few. An extensive overview of MMP-13 expression in malignant tumors has been published by Pendas et al.[50] Because of its ability to degrade the components of the basement membrane, MMP-13 promotes tumor invasion and progression; MMP-13 expression enhances invasion of human squamous cell carcinomas[51] and of human fibrosarcoma HT-1080 cells.[52]

Some factors relevant to tumor progression are also regulators of MMP-13 expression. Endostatin, a 20-kDa collagen XVIII fragment, inhibits in vivo tumor growth. Nyberg et al.[53] suggested that this factor's inhibitory activity on human tongue carcinoma cell invasion occurs by blocking the activation and catalytic activity of some MMP, including MMP-2, -9, and -13. Another factor, named relaxin, appears to enhance the invasiveness of some breast cancer cell lines by up-regulating MMP-2, -9, -13, and -14 mRNA expression in these tissues.[54] Tumor hypoxia is a factor which contributes to the progression of a more malignant phenotype. Koong et al.[55] analyzed the changes induced by hypoxia in cell lines derived from squamous cell carcinomas and found that MMP-13 was among the induced genes.

Increased levels of MMP-13 have been associated not only with arthritis and tumors, but also with other pathologies, including adult periodontitis,[56] ocular surface diseases,[57] chronic ulcers,[58] and chronic inflammation of oral mucosal epithelium.[59] An enhanced expression of MMP-3, -12, and -13 mRNA has been detected in aortas of apolipoprotein E-deficient mice with advanced atherosclerosis.[60] Yoon et al.[61] reported a similar link between atherosclerosis and MMP-13. These authors discovered two polymorphisms in the MMP-13 promoter associated with atherosclerosis in the abdominal aorta of young black males. One polymorphism was associated with the PEA-3 site, but the mechanism for the polymorphism's action remains unknown.

Transcription and signaling

The MMP-13 gene is comprised of 10 exons and 9 introns spanning 12.5-kb on chromosome 11q22.3.[6,62] The transcription start sites have been mapped at 22 bp and 28 bp upstream from the ATG start codon.[5,6] Northern blots have revealed the presence of two major transcripts of 2.5 kb and 3 kb and a minor one of about 2/2.2 kb.[1,2] The difference in molecular weight of the two major transcripts is probably the result of different polyadenylation sites.[1,63] Other minor transcripts have recently been identified; they are derived from different transcription start sites, alternative splicing,

and internal deletion.[63] Interestingly, both the deleted and the alternatively spliced transcripts differ from the original sequence in the region coding for the hemopexin-like domain. This domain is necessary for MMP-13 to cleave native triple helical collagens, but its removal does not seem to affect activity on other substrates.[20] Hence, when translated, alternative MMP-13 proteins would probably result in enzymes with substrate specificities which are different from the original collagenase-3. Work is currently underway to study these proteins (G. Tardif and J. Martel-Pelletier, personal observation).

Promoter

The human MMP-13 promoter contains several binding sites for transcription factors.[5,6] There is a TATA box and AP-1, PEA-3, and OSE-2 sites in the proximal promoter region. The AP-1 site (TGACTCA) binds the Fos and Jun family of proteins; this site drives basal as well as induced transcription.[5,6] The PEA-3 site (AGGAGA) binds the Ets family of oncoproteins. In some cells, such as chondrocytes, there is a cooperative effect between the proteins binding the AP-1 and PEA-3 sites.[64,65] The OSE-2 site (ACCACA) binds CbfaI, a transcription factor implicated in bone formation.[6,66]

Recently, a novel negative regulatory element, namely AGRE, has been identified in the MMP-13 proximal promoter region.[67] The AGRE site (GAAAAGAAAAAG) acts as a repressor of basal transcription; it is composed of two AAAAG half-sites separated by one base, or alternatively, a repeat of the two GAAAA half-sites. Interestingly, the AGRE site is not found as such in the proximal promoter sequence of other human MMP genes. In some MMPs, the proximal promoter region contains AG-rich sequences or single copies of the pentanucleotide AAA AG, but their role has not yet been evaluated.

Other binding sites have been found in the more distal region of the MMP-13 promoter, but their functions are still undetermined. There is a TIE (TGF-β inhibitory element) site in the reverse orientation[6]; this site does not specifically bind nuclear proteins from human chondrocytes.[64] Two other sites that resemble consensus sequences for the Activin-response element and the Smad binding element specifically bind human chondrocytes nuclear proteins, but they do not seem to be implicated in the TGF-β-mediated regulation of MMP-13.[64] Three core motifs for hormone response elements and five consensus recognition sites for CCAAT DNA-binding proteins can be found in the more distal region of the promoter, but their role has not yet been investigated.

Several lines of evidence point to a role for the transcription factor p53 in MMP-13 regulation. The tumor suppressor p53 is implicated in cell-cycle control and apoptosis; it is inactivated in various types of malignant tumors and overexpressed in RA synovium. Sun et al.[68] have reported that p53 regulates MMP-13 expression in synoviocytes: expression of wild-type, but not mutant, p53 in these cells repressed transcription. Adenoviral delivery of the p53 gene was similarly found to repress MMP-13 expression in squamous cell carcinomas[51]; the repression was independent of the proapoptotic effect of p53. Finally, the joints of collagen-induced arthritic $p53^{-/-}$DBA/1 mice show greater MMP-13 and cytokine production and an increased severity of arthritis compared with the wild-type mice.[69] There is a 10-bp sequence recognized by p53 in the MMP-13 proximal promoter region. However, since p53 normally recognizes two copies of this motif, the inhibitory role of this element has yet to be determined.

Transcriptional regulation

MMP-13 was first reported to be up-regulated by IL-1β and TNF-α, two proinflammatory cytokines involved in arthritis.[2] Since then, the regulation of MMP-13 has been the subject of several reports. A number of pro- and anti-inflammatory molecules, growth factors, and mechanical stimuli have been found to control MMP-13 expression and some of the pathways by which these molecules signal are now identified.

The pathways by which IL-1β, TNF-α, and TGF-β signal to the MMP-13 gene have been well studied. TNF-α transduces its signal through the activation of the p38, ERK1/2, and JNK MAP kinases, as well as the AP-1 and NF-κB transcription factors in human chondrocytes.[70] The IL-1β-mediated induction also requires p38 and JNK MAP kinase activities and NF-κB translocation.[71,72] The activity through the p38 pathway occurs via the transcription factor Runx-2 (CbfaI) and the AP-1 site.[73]

Members of the Jun and Fos families of proteins that bind the AP-1 site were found to modulate the expression of MMP-13 in human OA chondrocytes differently. Indeed, although both proinflammatory cytokines IL-1β and IL-17 up-regulate MMP-13 expression, they activate different Fos proteins: IL-17 stimulates FosB, and IL-1β stimulates c-Fos.[65] As a higher concentration of IL-17 (10 ng/ml) is required to elicit a similar MMP-13 stimulation to IL-1β (100 pg/ml), these data suggest that the transactivating properties of the Jun/FosB complex are weaker than those of the Jun/c-Fos complex. Another AP-1 binding-protein, JunB, which has been found to negatively regulate MMP-1 expression,[74] is present in a greater amount in OA chondrocytes that have high basal levels of MMP-13 and low cytokine inducibility.[65] Because JunB's ability to make homodimers is less than that of c-Jun, increased levels of JunB may favor the preferential formation of heterodimers with decreased DNA-binding activity, thus making JunB a rate-limiting step in cytokine-induced MMP-13 production in OA chondrocytes.

TGF-β induces MMP-13 expression in several human cells, and the induction occurs through the activation of the Smad and p38 pathways as well as the AP-1 site.[75–78] In human OA chondrocytes, the induction requires both the AP-1 and PEA-3 sites for optimal response.[64] In human KMST fibroblasts, TGF-β induces MMP-13 through protein kinase C (PKC) and tyrosine kinase activities[79]; in these cells, the inductive effect of TGF-β is partially mediated by

the AP-1 site. The TGF-β-induced stimulation of MMP-13 in human gingival fibroblasts is dependent on the activation of Smad3 and p38α.[80] Smad3 and the MAP kinase pathways are also used in the human breast cancer cell line MDA-MB231.[81]

The hepatocyte growth factor (HGF) induces proliferation, motility, and morphogenesis. Reboul et al,[82] have recently shown that HGF stimulates MMP-13 in human OA chondrocytes. HGF mediates its effects through the SAP/JNK pathway and a sensitive p38 inhibitor cascade. Activation of c-Jun, JunD, and Fra-1 occurs in the process.

Fibronectin is a matrix glycoprotein involved in cell–matrix interactions through its binding to integrins, and fibronectin fragments are present in tissues and biological fluids in several diseases. Fibronectin fragments, but not intact fibronectin, mediate MMP-13 production in human chondrocytes. Binding of the fragments to $\alpha_5\beta_1$ integrins induces MMP-13 expression through the activation of PKC, the proline-rich tyrosine kinase-2 PYK2 and the ERK1/2, JNK, and p38 kinases.[83,84] Stimulation of MMP-13 in RA synovial fibroblasts by fibronectin fragments also requires the activation of the p38, JNK, and ERK1/2 pathways.[85]

Oncostatin M, a member of the IL-6 superfamily of cytokines, is elevated in patients with RA. This cytokine induces MMP-1, -3, and -13 in chondrocytes by activating JAK/STAT and MAP kinase signaling cascades in human and bovine chondrocytes.[86]

The potent vasoconstrictor peptide endothelin-1[87] was also found to stimulate MMP-13. In OA cells, its action appears to occur through activation of the p38 MAP kinase pathway and through protein kinase-dependent cyclic AMP (PKA).[88]

Other types of molecule that were found to stimulate MMP-13 transcription include basic calcium phosphate crystals, which are often associated with severe degenerative OA[89] and histamine.[90]

Many types of molecule stimulate MMP-13 transcription, but few have the ability to directly inhibit its synthesis. For example, IGF-1 and OP-1 (BMP-7) inhibit basal, fibronectin-, and IL-1β-induced MMP-13 expression in human chondrocytes.[91] The suppressive effect is due in part to the down-regulation of the expression of the proinflammatory cytokines and the activity of AP-1 and NF-κB. Activators of PPARγ have been reported to inhibit IL-1β-induced MMP-13 production in human chondrocytes; the inhibition occurs through a PPARγ-dependent pathway by interfering with the activation of AP-1.[92]

Among the few cytokines reported to inhibit MMP-13 expression are interferon-γ (IFN-γ) and IL-13. IFN-γ markedly inhibits basal expression of MMP-13 in transformed human epidermal keratinocytes[93]; this cytokine also abrogates the TNF-α- and TGF-β-mediated MMP-13 induction in these cells. The inhibition occurs through activation of ERK1/2 and STAT1. IL-13 inhibits MMP-13 production in human OA chondrocytes,[75] but the mechanism of action remains unknown.

Other molecules reported to inhibit MMP-13 transcription are bisphosphonates, which are used therapeutically to prevent bone resorption. Contradictory results are reported with clodronate. In one study, Lindy et al.[39] found that this bisphosphonate did not inhibit MMP-13-mediated degradation of type II collagen, but Heikkila et al.[94] later showed that clodronate inhibited MMP-13 and that the inhibitory effect was reduced by high Ca^{2+} levels. Alendronate, another bisphosphonate, is capable of inhibiting active MMP-13.[42] The mechanism by which the inhibition occurs has not yet been defined.

Factors such as mechanical stimuli also regulate MMP-13 expression. Sun and Yokota[95] observed that MMP-13 levels in RA synovial cells were transiently decreased by mechanical stress. Later, this group[96] reported that oscillatory shear reduced mRNA levels and the activities of both MMP-1 and -13. Furthermore, the induction of MMPs by IL-1β was suppressed by the oscillatory shear. The signaling pathways by which mechanical stimuli are relayed to the MMP-13 promoter are still unknown, but the transcription factor CITED2 may be part of the cascade. CITED2 is a nuclear regulator inducible by a number of stimuli, such as lipopolysaccharide, hypoxia, and cytokines such as IL-9 and IFN-γ. In the immortalized human chondrocyte cell line C-28/I2, CITED was found to be responsive to mechanical stimuli.[97] Flow shear as well as TGF-β increased CITED2 mRNA and protein levels and down-regulated MMP-1 and -13. Furthermore, overexpression of CITED2 repressed MMP-1 and -13 levels and activities.

CbfaI may be another transcription factor implicated in the regulation of MMP-13 expression by mechanical stimuli. Bovine chondrocytes exposed to cyclic tension and hydrostatic pressure showed that cyclic tension up-regulated CbfaI and MMP-13, while cyclic hydrostatic pressure down-regulated MMP-13.[98]

Translational regulation

The MMP-13 translational regulation has not been studied as extensively as its transcription. One study reported a posttranscriptional silencing of the MMP-13 gene.[99] The authors observed a discordance between mRNA levels and protein expression in human renal mesangial cells. Following IL-1β or TGF-β1 stimulation, MMP-13 mRNA levels increased significantly, whereas protein expression was absent. They also showed that an alternatively spliced form of T-cell-restricted intracellular antigen-related protein (TIAR) repressed MMP-13 translation by binding to the 3′-UTR.

Summary

Our knowledge of MMP-13 biochemistry and regulation has greatly increased over the years. MMP-13 is subjected to different levels of regulation and constitutes a more complex system than was originally thought. There are still some unanswered questions that need to be addressed, especially with respect to transcriptional and translational

control, since therapeutic intervention based on MMP-13 inhibition is under intensive investigation. Although we have learned much during the last decade, there is still much to be discovered.

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