Identification of the Second Membrane-type Matrix Metalloproteinase (MT-MMP-2) Gene from a Human Placenta cDNA Library

MT-MMPs FORM A UNIQUE MEMBRANE-TYPE SUBCLASS IN THE MMP FAMILY*

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Membrane-type matrix metalloproteinase (MT-MMP), which we have identified recently, is unique in its transmembrane (TM) domain at the C terminus and mediates activation of pro-gelatinase A on the cell surface (Sato, H., Takino, T., Okada, Y., Cao, J., Shinagawa, A., Yamamoto, E., and Seiki, M. (1994) Nature 370, 61–65; Takino, T., Sato, H., Yamamoto, E., and Seiki, M. (1995) Gene (Amst.) 115, 293–298). In addition to MT-MMP, a novel MMP-related cDNA of 2.1 kilobases was isolated from a human placenta cDNA library. The cDNA contains an open reading frame for a new MMP. The deduced protein composed of 604 amino acids was closely related to MT-MMP in the amino acid sequence (66% homology at the catalytic domains) and has a potential TM domain at the C terminus. Monoclonal antibodies raised against the synthetic peptide recognized a 64-kDa protein as the major product in the transfected cells. TIMP-1 fused with the potential TM domain was localized on the cell surface while native TIMP-1 is in the culture medium. Thus, we called the second membrane-type MMP, MT-MMP-2 and renamed MT-MMP, MT-MMP-1. MT-MMP-1 and -2 are thought to form distinct membrane-type subclasses in the MMP family since all the others are secreted as soluble forms. Like MT-MMP-1, expression of MT-MMP-2 induced protein composed of 604 amino acids was closely related to MT-MMP in the amino acid sequence and it turned out to be MT-MMP. Expression of MT-MMP in the transfected cells induced specific activation of gelatinase A, and it turned out to be MT-MMP. Expression of MT-MMP-2 in the transfected cells induced specific activation of gelatinase A in a cell-mediated manner. Appearance of the activated form of gelatinase A in the tissue is also a characteristic feature of invasive carcinomas. Expression of MT-MMP-2 mRNA was at the highest levels in the brain where MT-MMP-1 was at the lowest level compared to other tissues. MT-MMP-1 and -2 are thought to be utilized for extracellular matrix turnover on the surface of cells under different genetic controls.

Matrix metalloproteinases (MMPs)† are a family of enzymes that share a common domain structure composed of propeptide, catalytic, hinge, and hemopexin-like domains (exception is MMP-7-matrixlysin, which lacks a hemopexin-like domain) (3, 4). These enzymes are responsible for the turnover of extracellular matrix by degrading native macromolecules, including a variety of collagens and glycoproteins such as fibronectin and laminin, and play crucial roles in tissue remodeling during morphogenesis, wound healing, angiogenesis, and also in many pathological conditions such as tumor invasion and rheumatoid arthritis (5–10). 11 MMPs encoded by different genes are known as the MMP family members, and they have different substrate specificity against extracellular matrix macromolecules. 10 of them are produced by cells as a soluble zymogen form, but the last one, which we recently discovered, has a transmembrane domain at the C terminus and is expressed as a membrane protein (1, 2, 11). Thus, we called this ectoenzyme membrane-type MMP (MT-MMP).

All of the MMPs are expressed as inactive zymogens and need proteolytic activation for them to function. Although serine proteinases such as plasmin, neutrophil elastase, and trypsin can activate several MMP zymogens in a test tube (12, 13), little is known about the activators in tissue. MMP-2-gelatinase A cannot be activated by these serine proteinases (14, 15) but is activated on the surfaces of fibroblasts (16) and tumor cell lines treated with 12-O-tetradecanoylphorbol-13-acetate or concanavalin A (17–19). Thus, a unique activator on the cell surface was expected to be responsible for gelatinase A activation, and it turned out to be MT-MMP. Expression of MT-MMP in the transfected cells induced specific activation of gelatinase A in a cell-mediated manner. Appearance of the activated form of gelatinase A in the tissue is also a characteristic feature of invasive carcinomas (20, 21). Expression of MT-MMP was detected there, and the product was immunolocalized in and on the carcinoma cells (1). Since gelatinase A is an important enzyme for basement membrane invasion by degrading type IV collagen, MT-MMP on the tumor cell surface is thought to play a critical role in the invasive phenotype of tumor cells.

MT-MMP cDNA was isolated from a human placenta cDNA library using a MMP-related gene fragment as a probe (2). The probe with a possible new MMP gene sequence was obtained from the amplified cDNA fragments by polymerase chain reaction (PCR) using degenerate oligonucleotide primers corre-

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1 The abbreviations used are: MMPs, matrix metalloproteinases; mAb, monoclonal antibody; MT-MMP, membrane-type MMP; PCR, polymerase chain reaction; TIMP, tissue inhibitors of metalloproteinases; TM, transmembrane; DMEM, Dulbecco’s modified Eagle’s medium; kb, kilobase(s).
responding to the conserved sequences within the MMP family. The structural characteristic of MT-MMP is the transmembrane domain at the C terminus and two more additional insertions. One is the insertion of 8 amino acids in the catalytic domain, and the other is the insertion of 11 amino acids between the propeptide and the catalytic domain. MMP-11-stromelysin-3 (22) has a similar insertion of 10 amino acids between propeptide and catalytic domain, and RXXR sequences, potential recognition sites for subtilisin-like processing enzymes (23), are conserved between them. No insertion corresponding to the 8 amino acids of MT-MMP was found in the other members of the MMP family.

Both MT-MMP and stromelysin-3 were identified by cDNA cloning instead of the conventional biochemical purification of the enzymes. Thus, new MMP members may be obtained further by survey of the MMP-related genes. To identify yet unknown MMP members, we extended our previous study to survey the MMP-related cDNAs amplified from various human tissues by reverse transcription-PCR. In this study, we identified a fragment of another new MMP-related gene from a human melanoma tissue. This fragment was used as a probe to screen a human placenta cDNA library, and a cDNA fragment that encodes a new MMP having a TM domain at the C terminus was obtained. Thus, MT-MMPs form a distinct subgroup in the MMP family.

MATERIALS AND METHODS

Amplification of MMP cDNA Fragments and Molecular Cloning—Amplification of the MMP cDNA fragment was carried out as reported (2). Briefly, mRNA samples extracted from various sources were reverse transcribed with SuperScript reverse transcriptase (Life Technologies, Inc.) using random hexamers as primers. Aliquots of the reaction mixture were amplified using Taq polymerase with 30 rounds of PCR. Primers (5P-1 and 3P-2) were the previously reported degenerate primers designed from the conserved amino acid sequence GRRHRTCYCC in the catalytic enzyme domain. The PCR products (120–130 base pairs) were separated in a 10% polyacrylamide gel electrophoresis and subcloned into a plasmid. The nucleotide sequences of the inserts were determined using an automated sequencer (Applied Biosystems model 373A DNA sequenator). A possible new MMP gene deduced from one of the amplified cDNA fragment was tentatively designated as MMP-X2.

A human placenta cDNA library (Clontech), which was constructed using oligo(dT)- and random-primer cDNA was screened with the MMP-X2 DNA fragment as a probe.

Construction of the Expression Plasmid—A eukaryotic expression vector pSG5 (Stratagene) that has simian virus 40 early promoter was used to express the proteins and chimeric proteins in the transfected cells. C-terminal sequences between TIMP-1 (24) and the TM domains of MT-MMP-1 (TIMP/MT-1) (II) or MT-MMP-2 (TIMP/MT-2) were constructed as follows. cDNA fragments encoding the C terminus of MT-MMP-1 (Gly535 to Val582) containing the deduced TM domain (Ala539 to Phe562) or the C terminus of MT-MMP-2 (Ala556 to Val604) containing the deduced TM domain (Val559 to Phe584) were amplified by PCR. The amplified cDNA fragments were subcloned into a plasmid vector and sequenced.

Amplified cDNA fragments were subcloned into a plasmid vector and sequenced. Two of the seven cloned fragments were the interstitial collagenase gene and the one for gelatinase B. Two other fragments were identical and showed significant homology to the reported MMP genes (we tentatively called this fragment the MMP-X2 cDNA fragment). The remaining two showed no homology to the MMP genes.

By checking cDNA libraries from various sources by PCR, a human placenta library was found to contain MMP-X2 cDNA fragments and screened to isolate a longer size of the cDNA fragment. We isolated a 2.1-kb cDNA having a long open reading frame that potentially encodes a 604-amino acid protein (Fig. 1).

Sequence Characteristics of the Deduced MMP-X2 Protein—The protein deduced from the MMP-X2 cDNA was aligned well to the reported MMP sequences conserving the characteristic domain structure as a MMP member (Fig. 2). Comparison of the most conserved domain, the catalytic domain, revealed that conditioned media and cell lysates were incubated with monodonal antibodies (mAbs) against TIMP-1 (50-IH7) or MMP-2 (117-4E1, 117-138B). Antigen-antibody complexes were precipitated with protein A coupled to Sepharose beads (PharMacia, Uppsala, Sweden) by centrifugation. After being washed with lysis buffer, the immunoprecipitates were dissolved with sample buffer (50 mM Tris-HCl, pH 6.5, 10% glycerol, 5% SDS, 2% N-mercaptoethanol, 0.1% bromphenol blue), boiled for 3 min, and separated in 12% SDS-polyacrylamide gel electrophoresis with a discontinuous buffer system. The labeled complexes were visualized with a Bioimage Analyzer BAS1000 (Fuji Photo Film Co., Tokyo).

Indirect Immunofluorescence Staining—The procedure was performed as described (1). COS-1 cells were cotransfected with expression plasmids on coverslips. After 24 h, the cells were incubated with an mAb against TIMP-1 (5 μg/ml) at 37 °C for 40 min, washed three times with 3% bovine serum albumin/phosphate-buffered saline, and then dried by air and fixed with cold 95% acetone for 5 min. Then, the cells were rehydrated with 3% bovine serum albumin/phosphate-buffered saline and washed with 3% bovine serum albumin/phosphate-buffered saline followed by incubation with fluorescein isothiocyanate-conjugated goat anti-mouse IgG (Capel, Westchester, PA) for 30 min at 37 °C. These specimens were finally overlaid with glycerin and observed under an Olympus immunofluorescence microscope (1).

Activation of Pro-gelatinase A—COS-1 cells were cotransfected with plasmids for gelatinase A and MT-MMP-1, MT-MMP-2 plasmid, or vector plasmid, and HT-1080 cells were cotransfected with MT-MMP-1 plasmid and TIMP-1 plasmid, TIMP-2 plasmid, or vector plasmid, transfected with vector plasmid, and treated with concanavalin A. Cells were then cultured in serum-free DMEM for 24 h. Aliquots of media were mixed with sample buffer and analyzed by gelatin zymography.

Gelatin Zymography—Zymography was performed as described (26). Samples were mixed with SDS sample buffer in the absence of a reducing agent and incubated for 20 min at 37 °C and separated on a 10% polyacrylamide gel electrophoresis and stained into a plasmid. The gelatinolytic activity was detected as clear bands in the background of uniform staining.

Northern Blotting—RNA samples (10 μg) extracted from cells were separated by electrophoresis on a denaturing 1.0% agarose gel and transferred onto a nylon membrane Hybond-N (Amersham, Buckinghamshire, UK). Multiple Tissue Northern blot (Clontech) was used for analysis of MT-MMP-2 expression in human tissues. Hybridization and preparation of 32P-labeled probes were carried out as previously described (8). Radioactivity was analyzed by a Bioimage Analyzer BAS 1000.

RESULTS

Isolation of a cDNA Encoding a New Member of the MMP Family—An extension of our previous study to identify new MMP genes expressed in various human tissues, the mRNA sample extracted from an oral malignant melanoma was reverse transcribed and amplified by PCR using oligonucleotide primers designed from the conserved region of MMP genes (2). Amplified cDNA fragments were subcloned into a plasmid vector and sequenced. Two of the seven cloned fragments were the interstitial collagenase gene and the one for gelatinase B. Two other fragments were identical and showed significant homology to the reported MMP genes (we tentatively called this fragment the MMP-X2 cDNA fragment). The remaining two showed no homology to the MMP genes.

By checking cDNA libraries from various sources by PCR, a human placenta library was found to contain MMP-X2 cDNA fragments and screened to isolate a longer size of the cDNA fragment. We isolated a 2.1-kb cDNA having a long open reading frame that potentially encodes a 604-amino acid protein (Fig. 1).

Sequence Characteristics of the Deduced MMP-X2 Protein—The protein deduced from the MMP-X2 cDNA was aligned well to the reported MMP sequences conserving the characteristic domain structure as a MMP member (Fig. 2). Comparison of the most conserved domain, the catalytic domain, revealed that
the homology of MMP-X2 protein is the highest to MT-MMP (66%) (1, 2) and significantly to others, including MMP-12 and macrophage elastase (51%) (27), MMP-2 (72-kDa type IV collagenase) (50%) (28), MMP-9 (gelatinase B; 92-kDa type IV collagenase) (50%) (29), MMP-1 (interstitial collagenase) (49%) (30), MMP-3 (stromelysin-1) (48%) (31), MMP-10 (stromelysin-2) (48%) (32), MMP-8 (neutrophil collagenase) (47%) (33), MMP-11 (stromelysin-3) (46%) (22), and MMP-7.

MT-MMP has three characteristic insertions compared to other MMP family members. They are the 11-amino acid insertion (IS-1) between propeptide and catalytic domain, the 8 amino acids (IS-2) in the catalytic domain, and the 75 amino acids (IS-3) at the C terminus, having a TM composed of the 24 hydrophobic amino acids. All such insertions exist in MMP-X2 at the same positions with significant homology (Fig. 2B). In the first insertion, the RXKR sequence, a potential processing site for subtilisin-like enzymes, was conserved (23).
75 amino acids at the C terminus contain a potential TM domain composed of 24 amino acids with higher hydrophobicity. Thus, MMP-X2 is also expected to be a membrane-type MMP as well. Based on this structural homology to MT-MMP and the localization of the product on the cell surface as demonstrated in the following section, we will call the MMP-X2 gene product MT-MMP-2 and rename the previously identified MT-MMP as MT-MMP-1.

Identification of MT-MMP-2 Product—To identify MT-MMP-2, mAbs against a synthetic peptide unique to MT-MMP-2 (IS-2) were prepared (antibodies 117-4E1 and 117-13B6) and used for immunoprecipitation. COS-1 cells were transiently transfected with MT-MMP-2 expression plasmid and labeled with [35S]methionine. Cell lysate and culture medium were prepared and examined by immunoprecipitation using the mAbs (Fig. 3). Both mAbs precipitated a 64-kDa protein specifically from the lysate of cells transfected with the MT-MMP-2 plasmid but not from that of the control. The molecular size of the product was that of the deduced proMT-MMP-2 from the sequence. Three smaller immunoreactive bands (52, 33, and 30 kDa, respectively) were also detected only from the cells transfected with MT-MMP-2 plasmid. None of these proteins were detected in the culture medium. TIMP-1, which was coexpressed as a secretory protein, was detected in the medium as a 28-kDa band and weakly in the cell lysate. Thus, MT-MMP-2 was not a secretory protein like TIMP-1. The result is very similar to that with MT-MMP-1 where MT-MMP-1 is expressed on the cell surface and cannot be released into the culture medium at a detectable level.

Identification of MT-MMP-2 Gene and Product

![Domain structure of MT-MMP-2](https://example.com/fig2.png)

**Fig. 2.** Domain structure of MT-MMP-2. A, alignment of amino acid sequences of the MMP family members. The typical domains are indicated in the figure (signal, propeptide, catalytic, hinge hemopexin-like domains from the N terminus). Specific insertions characteristic to MT-MMPs are indicated by the upward arrows (IS-1 to IS-3). B, homology between the extra sequences characteristic to MT-MMPs are indicated. Asterisks are the conserved amino acids between the two.
Next, we examined whether the TIMP-1 portion of the chimeras was expressed on the cell surface. To show this, transfected cells were incubated with anti-TIMP-1 mAb without fixation, and then indirect immunofluorescence staining was carried out using fluorescein isothiocyanate-conjugated anti-mouse IgG (Fig. 4B). TIMP/MT-2-producing cells were stained positively as that of TIMP/MT-1, but TIMP-1 producer cells were negative. Thus, we concluded that MT-MMP-2 is the second member of the membrane-type MMP.

Effect of MT-MMP-2 on the Processing of Pro-gelatinase A—Since MT-MMP-2 conserves characteristic structural features of MT-MMP-1, we next examined whether it also induces activation of pro-gelatinase A. COS-1 cells were cotransfected with the expression plasmids for pro-gelatinase A and either MT-MMP-1 or -2. The culture medium was collected and analyzed by gelatin zymography (Fig. 5A). Gelatinase A activity was detected at a 68-kDa band corresponding to a pro-enzyme form when MT-MMPs were not expressed. MT-MMP-1 reportedly induced activation of pro-gelatinase A to the fully activated 62- and 64-kDa intermediate forms (1). Similar processing was induced by MT-MMP-2. This phenomena was not specific to COS-1 cells because the processing can also be seen by human fibrosarcoma HT1080 cells, which express pro-gelatinase A and B constitutively (Fig. 5B). Activation of pro-gelatinase A by MT-MMP-1 can be more efficiently inhibited by TIMP-2 than TIMP-1 as previously reported (1). This was also examined (Fig. 6B). MT-MMP-2 mRNA was detected in bladder carcinoma T24 and larynx carcinoma Hep2 cells, where MT-MMP-1 transcripts were detected at low levels. By contrast, MT-MMP-1 transcripts were predominant in squamous cell carcinoma OSC-19 and human embryonal lung fibroblasts where MT-MMP-2 mRNA levels were low. Thus, expression of the genes for MT-MMP-1 and -2 is regulated differently, although they share similar protein structures and functions in activating pro-gelatinase A.

DISCUSSION

In addition to MT-MMP-1 (MT-MMP in the previous paper), which we previously reported (1, 2), we identified a new MMP gene that was expressed in a human oral malignant melanoma and a human placenta. The isolated 2.1-kilobase pair cDNA contained a sufficient coding frame for MT-MMP-2. However, the transcript in tissues or cell lines was at 12 kb in size. Since the cDNA lacks the typical polyadenylation signal (AAATAAA), the 3‘-non-coding region of the gene is thought to be missing in the cloned fragment. MT-MMP-1 and -2 are approximately the same in their molecular weights, but they are encoded by 4.5- and 12-kb transcripts, respectively. The most plausible explanation for the difference in the mRNA sizes is the different length of non-coding regions at their 3‘-ends.

MT-MMP-2 is the most closely related to MT-MMP-1 in the amino acid sequence (66% homology at the catalytic domain) and in the characteristic insertions compared to other MMPs.
These insertions may be important for their function and regulation. For example, the first insertions (IS-1) between the propeptide and catalytic domain contain the conserved RXXKR sequences. A similar insertion also exists in stromelysin-3 but not in others (Fig. 2B). These sequences may be the recognition site for processing, since immediately downstream of the RXKR sequences is the reported N terminus of the processed forms of stromelysin 3 and MT-MMP-1 (34, 35). Since RXKR is the consensus sequence for subtilisin-like enzymes, autocatalytic activation mechanism, which is common for other MMPs, may not be applicable for these three MMPs. Indeed, 4-aminophenylmercuric acetate or SDS that induces autocatalytic activation of pro-MMPs cannot activate stromelysin-3 and MT-MMPs.

There exist 8 amino acid insertions (IS-2) in the catalytic domains of MT-MMP-1 and -2 at the same position. Three of the eight amino acids at both ends were conserved. Although the significance of this insertion is not clear, it may modulate substrate specificity of the enzymes from its position in the catalytic domain like the gelatin-binding domain of two gelatinases (36).

Additional sequences (IS-3) containing the TM domains are found downstream of the hemopexin-like domains of MT-MMPs. Both MT-MMPs are expressed as membrane proteins embedded in the plasma membrane through the TM domains at the C terminus. Thus, these two MMPs form a unique membrane-type subclass in the MMP family, while the others are expressed as a soluble form. We previously aligned the most C-terminal portion of the cysteine residue of MT-MMP-1 to that of the hemopexin-like domain of other MMPs and thought that the TM domain is an insertion in the hemopexin-like domain (1, 2). However, it is more appropriate that the IS-3 locate downstream of the hemopexin-like domains of MT-MMP-1 and -2 rather than splitting the domain as shown in the alignment in Fig. 2. With this alignment, it becomes possible for MT-MMPs to form a cysteine bridge in the hemopexin-like domain.
domain, the conserved structure among the MMPs, outside of the cells.

Expression of MT-MMP-2 in cells, like that of MT-MMP-1, induced activation of the pro-gelatinase A to the fully activated form (62 kDa) through the intermediate form (64 kDa). Thus, both MT-MMPs have similar biochemical activities at least in part, though it remains to be elucidated whether these MT-MMPs have different substrate specificity or not. If both MT-MMPs are similar in function, why are two separate genes required for the organism? The organism may have to utilize these MT-MMPs in different tissue environments or situations. Consistent with this idea, the tissue distribution of the MT-MMP-1 and MT-MMP-2 mRNAs was different in the human tissues. In contrast to MT-MMP-1, which is expressed widely in various tissues, MT-MMP-2 is expressed in only restricted tissues such as brain, heart, and placenta. In particular, brain tissue expresses MT-MMP-2 at the highest level but expresses MT-MMP-1 at the lowest level. The high level expression of MT-MMP-2 in brain may suggest a specific role of the product in the central nervous system. In cell lines, squamous cell carcinoma OSC-19 and human embryonal lung fibroblasts express MT-MMP-1 mRNA at higher levels but MT-MMP-2 mRNA at lower levels. The reverse was also the case; the MT-MMP-1 mRNA level was low in T24 cells where MT-MMP-2 mRNA was expressed predominantly.

Since MT-MMP-2 was originally detected in oral malignant melanoma, whether MT-MMP-2 is also involved in activation of gelatinase A in tumor tissues like MT-MMP-1 is of interest. Our preliminary findings with lung carcinomas where MT-MMP-1 was overexpressed indicated that MT-MMP-2 was not expressed frequently there.2

In addition to the activation of pro-gelatinase A, some of the proteins, such as β-amyloid precursor protein, tumor necrosis factor-α, and V-2 vasopressin receptor, are reported to be processed on the cell membrane by MMP-like activities (37–40). MT-MMPs may be responsible for the processing of many biologically important proteins on the cell surface as a regulator. These possibilities remain to be examined.

In this study, we reported MT-MMP-2 as a new member of the MMP family. Since both MT-MMP-1 and -2 have TM domain at the C terminus, we proposed a new subclass for MT-MMPs in the MMP family. Studies of MT-MMPs should provide clues to understand the cell surface events controlling extracellular matrix turnover and diverse biological responses.

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Note added in Proof—Two new MT-MMP-2s were reported at the Gordon Research Conference on Matrix Metalloproteinases (Andover, NH July 16–21, 1995). The one reported by Will et al. (Will, B., and Hinzmann, B. (1995) Eur. J. Biochem. 231, 602–608) was published just prior to this article. Thus, we agreed to rename MT-MMP-2 in this paper as MT-MMP-3.

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