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Human stromelysin gene promoter activity is modulated by transcription factor ZBP-89

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Abstract Matrix metalloproteinase expression is under strict regulation in physiological conditions. Disruption of the regulatory mechanisms can lead to tissue destruction and is associated with tumour invasion and metastasis. Using the one-hybrid assay technique with a *cis*-element in the promoter region of the stromelysin (matrix metalloproteinase-3) gene, a cDNA encoding a transcription factor termed ZBP-89 was obtained. The interaction between ZBP-89 and the stromelysin promoter element was confirmed by electrophoretic mobility shift assays with a recombinant ZBP-89. Reporter gene expression under the control of the stromelysin promoter in transiently transfected cells was significantly increased when the cells were co-transfected with a ZBP-89 expression construct. These results indicate that ZBP-89 interacts with the stromelysin promoter and upregulates its activity. As ZBP-89 expression is known to be increased in gastric carcinoma cells, induction of stromelysin expression may be a significant factor in tumour metastasis.

Key words: Matrix metalloproteinase; Gene regulation; Transcription factor; Tumor invasion; Metastasis

1. Introduction

The matrix metalloproteinases (MMPs) are a family of zinc- and calcium-dependent enzymes which degrade a wide range of structural and adhesive extracellular proteins in neutral pH environments [1–4]. All members of the MMP family are secreted as a latent zymogen and are counteracted by tissue inhibitors of metalloproteinases (TIMPs). The MMPs play important roles in various physiological processes involving resorption and remodelling of extracellular matrix, such as tissue repair, cell migration, angiogenesis, tissue morphogenesis, and growth [1–3,5]. Under physiological conditions, the expression and activity of MMPs are tightly regulated. This is accomplished primarily through regulation of gene transcription, activation of zymogens and inhibition of proteolytic activity by TIMPs [2]. In a number of pathological situations, however, these regulatory mechanisms become disrupted, resulting in connective tissue destruction or excessive connective tissue accumulation. For example, over-expression and uncontrolled activity of MMPs play a major part in cancer invasion and metastasis, and are partly responsible for cartilage destruction in rheumatoid arthritis; whereas inadequate MMP expression and activity are associated with excessive accumulation of connective tissue in systemic sclerosis [1,2,6–8].

According to domain structure and substrate specificity, the MMPs are classified into four groups, namely the collagenases, the gelatinases, the stromelysins and the membrane-type MMPs [1–4]. Compared with other MMPs, stromelysin-1 (MMP3) has the broadest substrate spectrum, possessing proteolytic activity against collagens III, IV, IX, and X, gelatin, proteoglycans, elastin, fibronectin, laminin, casein, aggrecan, versican, and perlecan. It can also activate a number of other MMPs including interstitial collagenase, neutrophil collagenase, collagenase-3, gelatinase B, and matrilysin, therefore rendering itself crucial in connective tissue degradation and remodelling [3].

Regulation of stromelysin expression operates mainly at the level of transcription. A number of consensus *cis*-elements in the promoter region of the stromelysin gene have been shown to be important in the regulation of stromelysin transcription. These include a TATA box (−30 to −24), an activator protein-1 (AP-1) site (−70 to −64), two polyomavirus enhancer A binding protein-3 (PEA3) sites (−216 to −209 and −208 to 201), a stromelysin PDGF-responsive element (SPRE, −1576 to −1571), and a nerve growth factor-responsive element (−241 to −229) [9–12].

In previous work, we found that the sequence between −1626 and −1599 in the stromelysin gene promoter was also involved in the regulation of transcription [13]. Electrophoretic mobility shift assays and DNase I footprinting experiments showed an interaction of this promoter element with at least one nuclear protein. The identity of the nuclear protein(s) was, however, obscure. Reported here are results of our recent study showing interaction of this promoter element with a transcription factor, ZBP-89, which enhances the activity of the stromelysin gene promoter.

2. Materials and methods

2.1. Yeast one-hybrid assay

The MATCHMAKER One-Hybrid System from Clontech was used in this study. For these assays, the sequence from −1626 to −1599 of the stromelysin gene promoter (5′-AAGACATGG-TTTTTTCCCCCCATCAAAG-3′) was used as a 'bait' to identify the cDNA for the transcription factor(s) interacting with this promoter sequence. Three concatenated copies of this sequence were li-

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Abbreviations: ZBP-89, 89-kDa zinc binding protein; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinases; EGF, epidermal growth factor; PDGF, platelet-derived growth factor; NGF, nerve growth factor; IL-1, interleukin-1; AP-1, activator protein-1; PEA3, polyomavirus enhancer A binding protein-3; SPRE, stromelysin PDGF-responsive element; 3′-RACE, rapid amplification of 3′-cDNA end; EMSA, electrophoretic mobility shift assay; PMSF, phenylmethylsulphonyl fluoride

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gated into the *Eco*RI site of the pHISi and pLacZi plasmid vectors which, respectively, contain a histidine gene and a *LacZ* gene. The two resultant plasmid constructs were then sequentially used to transform a yeast strain (YM4271, the endogenous histidine gene in this yeast strain is inactive due to mutation) to create a dual reporter strain.

This dual reporter yeast strain was then used to screen a Gal4 activation domain/HeLa cell cDNA library (Clontech). The cDNA library (with 6×10^6 independent clones) was amplified to obtain 3.6× number of independent clones. Dual reporter yeast cells transformed with the cDNA library were cultured on histidine-dropout medium supplemented with 15 mM 3-aminotriazole. Positive colonies were then tested for β-galactosidase activity (due to expression of the 'nocked-in' *LacZ* gene) using 5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside as substrate. Plasmid DNA was then prepared from double positive colonies (positive both for histidine and *LacZ*), and used to transform electrocompetent *Escherichia coli* DH10B. Plasmid DNA prepared from the transformed DH10B was sequenced using a commercial cycle sequencing kit (Amersham).

2.2. Rapid amplification of 3′-cDNA end (3′-RACE)

To clone the 3′-end of the cDNA isolated from the one-hybrid assay, 3′-RACE was performed using a HeLa cell cDNA library from Clontech as template. Both ends of library cDNAs had been ligated with an adapter. Polymerase chain reaction (PCR) was carried out with the library DNA, a forward primer (5′-CCAGAACAGATCGTGTATTGAAACATAAACGTATGTG-3′) corresponding to the sequence from +792 to +828 relative to the start of translation of the human ZBP-89 gene, and a reverse primer (5′-CCATCCTAATACGACTCACTATAGGGC-3′) corresponding to part of the library adapter sequence. Two different species of PCR products (sized 1.6 kb and 1.8 kb respectively) detected on the agarose gel were sequenced using a commercial cycle sequencing kit (Amersham).

2.3. In vitro expression of recombinant human ZBP-89

A portion of the human ZBP-89 protein, containing the four zinc finger motifs suggested to be responsible for binding to its *cis*-element, was expressed using an in vitro expression system (QIAexpress system) from Qiagen. In these experiments, a partial cDNA sequence from position +180 to +1652 relative to the start of translation of the human ZBP-89 gene was cloned into the pQE30 vector which contained six consecutive histidine codons upstream of the multiple cloning site. Expression of the recombinant protein was performed in *E. coli* M15 cells following the manufacturer's instruction. To increase the solubility of the recombinant protein, zinc chloride was added to a final concentration of 1 mM in the culture, the isopropyl-β-thiogalactoside concentration was reduced to 0.1 mM and the culture was incubated for only 1 h at 30°C. The recombinant protein was purified by nickel-nitrilotriacetic acid-agarose resin affinity chromatography following the manufacturer's instruction.

2.4. Electrophoretic mobility shift assay

A double-stranded 28-mer oligonucleotide (sequence of top strand: 5′-AAGACATGGTTTTTTCCCCCCATCAAAG-3′) corresponding to the sequences from −1626 to −1599 in the stromelysin gene promoter was 5′ end-labelled with ^{32}P. A 3-μl aliquot of radiolabelled probe (3000 cpm/μl) was mixed with 5 μl of recombinant human ZBP-89, 10 μl 2× binding buffer (containing 10 mM Tris-HCl, pH 7.6, 5 mM zinc chloride, 0.5 mM dithiothreitol, 10% glycerol), 1 μl 500 ng/μl poly(dI-dC), and 1 μl of unlabelled oligonucleotide (specific or non-specific competitors). The mixture was incubated at room temperature for 20 min, and fractionated on a 7% non-denaturing polyacrylamide gel (acrylamide:bisacrylamide = 80:1) in 0.25×TBE buffer for 2 h at 200 V, room temperature. The gel was then dried and exposed to Hyperfilm-MP (Amersham) at room temperature without intensifying screen for 72 h.

2.5. Transfection experiments

Constructs used in these experiments were as follows: (1) pCI-ZBP89 which was prepared by cloning the full-length cDNA for ZBP-89 into a mammalian expression vector (pCI vector, Promega); (2) pGL-Str which was prepared by subcloning the stromelysin promoter from a previously reported chloramphenicol acetyltransferase reporter gene construct [13] into a firefly luciferase reporter vector (pGL3-basic vector, Promega); (3) pRL-TK (Promega) which expresses renilla luciferase by a thymidine kinase promoter and was used as a control for transfection efficiency.

Using the lipofection method as described previously [13], cultured rat smooth muscle cells (A10) were transiently transfected with 2.5 μg of pGL-Str, 0.4 μg of pRL-TK, and various amounts (2.5, 5 or 10 μg) of either pCI-ZBP89 or the pCI vector without the ZBP89 insert. Twenty-four hours after transfection, luciferase activities were measured using a commercial dual-luciferase assay system (Promega). Luciferase levels were denoted by the ratio of firefly luciferase activity over renilla luciferase activity.

3. Results

3.1. Identification of a cDNA encoding a transcription factor interacting with the stromelysin promoter

Our previous studies indicated that the sequence from −1626 to −1599 of the stromelysin gene promoter was recognised by at least one nuclear factor and involved in transcription regulation. In the present study, a yeast one-hybrid assay technique (see Section 2) was utilised to identify the nuclear factors. In these experiments, three concatenated copies of the promoter element (−1626 to −1599 relative to the start of transcription of the stromelysin gene) were used as a 'bait' to screen 6×10^6 independent clones of a HeLa cell cDNA library. As a result, a total of 19 highly positive colonies were obtained. Restriction enzyme digestion and DNA sequencing analyses revealed that all 19 clones contained the same partial cDNA sequence (approximately 1 kb) identical to a portion of the gene encoding a transcription factor cloned

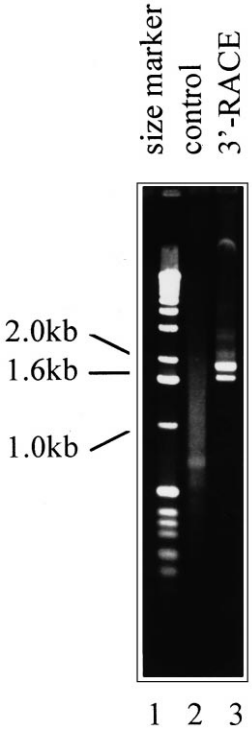

Fig. 1. Rapid amplification of 3′-cDNA end (3′-RACE) of ZBP-89. PCR templates were a HeLa cell cDNA library that had been ligated with an adapter. Lane 1, DNA size marker; lane 2, products of PCR with an oligonucleotide corresponding to part of the adapter sequence; lane 3, PCR amplicons from a primer as used in the PCR in lane 2 and a primer corresponding to the sequence from +792 to +828 relative to the start of translation of the human ZBP-89 cDNA.

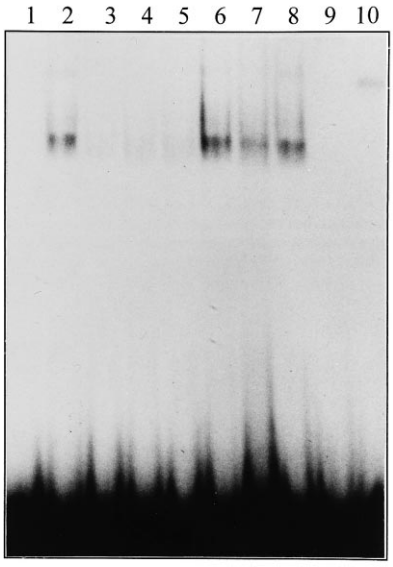

Fig. 2. ZBP-89 interacts with the sequence from −1626 to −1599 in the stromelysin gene promoter. Electrophoretic mobility shift assays were carried out using a ^{32}P-labelled double-stranded oligonucleotide probe corresponding to the sequence from −1626 to −1599 in the stromelysin gene promoter (AAGACATGGTTTTTTCCCCCCATCAAAG). Lane 1, ^{32}P-labelled probe alone; lane 2, ^{32}P-labelled probe incubated with recombinant ZBP-89 in the absence of competitors. Lanes 3–8, ^{32}P-labelled probe incubated with recombinant ZBP-89 in the presence of various competitors (100-fold excess), i.e. lane 3, AAGACATGGTTTTTTCCCCCCATCAAAG (unlabeled probe); lane 4, AAGACATGGTTTTTCCCCCCATCAAAG (M1); lane 5, AAGACATGGTT**GG**TTCCCCCCATCAAAG (M2); lane 6, AAGACATGGTTTTTTCC**TT**CCATCAAAG (M3); lane 7, AAGACAT**CTAAGTAT**CCCCCCATCAAAG (M4); lane 8, nonspecific competitor. Lane 9, $ZnCl_2$ omitted in the reaction buffer; lane 10, probe incubated with lysates from pCI-ZBP89-transformed *E. coli* uninduced with isopropyl-β-D-thiogalactoside.

by Wang et al. [14] and Law et al. [15], which was named htβ and ZBP-89 respectively. The partial cDNA sequence obtained in these experiments contained the coding sequence for the four zinc finger motifs of this transcription factor which were suggested to form the DNA binding domain of this transcription factor.

Multiple sequence alignment revealed 100% identity among the approximately 1-kb sequence obtained in these experiments and the corresponding region (+238 to +1164 relative to the start of transcription) of the sequences by Wang et al. (htβ, accession number L04282) and by Law et al. (ZBP-89, accession number AF039019) respectively. However, 3′ to this region, there were a number of discrepancies (substitutions and deletions) between the sequence by Wang et al. and that by Law et al., and the predicted protein by Law et al. was longer than that predicted by Wang et al. To further characterise the 3′ portion of this gene, 3′-RACE (see Section 2) was carried out, using a cDNA library as template, a PCR primer corresponding to the sequence from +792 to +828 relative to the start of translation, and a second primer corresponding to the sequence of an adapter that had been ligated to the cDNA library. Two different PCR products, sized 1.6 kb and 1.8 kb, were obtained (Fig. 1). DNA sequencing revealed that the 1.6-kb amplicon corresponded to a sequence from the position of the internal PCR primer to the first stop codon, whereas the 1.8-kb amplicon also began from the internal PCR primer but extended to a position approximately 200 bp beyond the first stop codon. Our sequence (accession number AJ236885) shared 99% similarity with the sequence by Law et al. (AF039019). The discrepancies between our sequence and that of Law et al. are shown in Table 1.

3.2. Characterisation of the DNA element in the stromelysin gene promoter interacting with ZBP-89

Electrophoretic mobility shift assays were carried out to confirm the interaction between ZBP-89 and the −1626 to −1599 sequence in the stromelysin gene promoter. A purified recombinant protein containing the four zinc finger motifs (the DNA binding domain) of ZBP-89 was incubated with a ^{32}P-labelled double-stranded oligonucleotide probe (5′-AAGACATGGTTTTTTCCCCCCATCAAAG-3′) corresponding to the −1626 to −1599 sequence in the stromelysin gene promoter, followed by polyacrylamide gel electrophoresis. As shown in Fig. 2, a DNA-protein complex was detected (lane 2), and the DNA-protein interaction was zinc-dependent (lane 9). The signal of the DNA-protein complex was significantly reduced in the presence of unlabelled double-stranded wild-type oligonucleotide (lane 3) and mutant oligonucleotides with a change of one or two bases outside the GC box (M1, lane 4; and M2, lane 5). The signal was also slightly reduced in the presence of a mutant oligonucleotide with a change of eight bases next to the GC box (M4, lane 7), but the reduction in band intensity was less pronounced as compared with the assays in lanes 3, 4 and 5. An oligonucleotide competitor with a mutation in the GC box did not decrease the signal of the DNA-protein complex (M3, lane 6), nor did a nonspecific competitor (lane 8).

3.3. ZBP-89 enhances stromelysin gene promoter activity

Transient transfection experiments were carried out to determine whether ZBP-89 had an effect on stromelysin promoter activity. For these experiments, a full-length ZBP-89

Table 1
Comparison of the ZBP-89 cDNA cloned in this study with that by Law et al. [15]

cDNA	Nucleotide position					
	1042	1438	1749	2127	2401	2449
Ye et al.	ctGttta	taCGttc	ccccAtc	aagtCac	gtg.aaa	actAtgt
	Val	Arg	Pro	Val	3′ UTR	3′ UTR
Law et al.	ctCttta	taGCttc	ccccGtc	aagtGac	gtgTaaa	actCtgt
	Leu	Ala	Pro	Val	3′ UTR	3′ UTR

Nucleotide positions are denoted in relation to the first ATG codon. Nucleotides that are different between the two sequences are shown in upper case.
GenBank accession numbers: Ye et al., AJ236885; Law et al., AF039019.

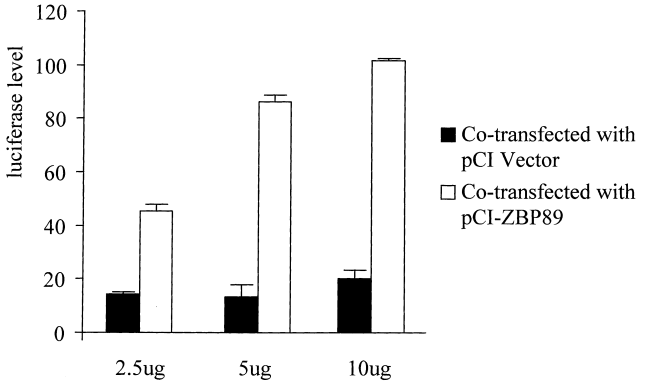

Fig. 3. ZBP-89 enhances stromelysin promoter activity. Transient transfection was performed on A10 cells. Open bars represent cells transfected with 2.5 μg of pGL-Str, 0.4 μg of pRL-TK, and various amount of pCI-vector as indicated. Closed bars represent cells transfected with 2.5 μg of pGL-Str, 0.4 μg of pRL-TK, and various amount of pCI-ZBP89 as indicated. Each transfection was done in duplicate. Data shown (mean+S.D.) are the ratios of firefly luciferase activity versus renilla luciferase activity using a dual-luciferase reporter assay system with each assay carried out in duplicate.

cDNA was cloned in a mammalian expression vector (pCI-vector). The resultant ZBP-89 expression construct (pZBP89-CI), together with a construct (pGL-Str) containing the stromelysin gene promoter linked to a firefly luciferase reporter gene, were co-transfected into cultured A10 cells. A plasmid (pRL-TK) expressing renilla luciferase under the control of the thymidine kinase promoter was also co-transfected to provide a reference for transfection efficiency. The level of firefly luciferase (after standardisation against renilla luciferase) in these transfectants was compared with the level of firefly luciferase (also standardised against renilla luciferase) in A10 cells transfected with pCI-vector (lacking the ZBP-89 insert), pGL-Str and pRL-TK. As shown in Fig. 3, firefly luciferase levels in cells co-transfected with the ZBP-89 expression construct were higher than those in cells co-transfected with the pCI-vector lacking the ZBP-89 insert, suggesting that ZBP-89 enhanced the activity of the stromelysin gene promoter. There also appeared to be a dose effect: a three-fold difference in standardised firefly luciferase was observed when comparing cells co-transfected with 2.5 μg of pZBP89-CI to cells co-transfected with the equivalent amount of pCI-vector; the difference increased to five-fold for cells transfected with 5 μg of either plasmid and 6.5-fold for cells transfected with 10 μg of plasmid.

4. Discussion

Expression of stromelysin is regulated by a variety of cytokines, growth factors, and hormones. For example, its expression is induced by epidermal growth factor (EGF), platelet-derived growth factor (PDGF), nerve growth factor (NGF), interleukin-1 (IL-1) and tumour promoters, but inhibited by transforming growth factor and glucocorticoid [10,12,16–20]. The effects of these regulatory agents on stromelysin expression largely operate at the level of transcription involving a number of *cis*-elements in the promoter region of the stromelysin gene. Substantial research has been undertaken into the role of the AP-1 site (−70 to −64) which is bound by transcription factors c-Fos and c-Jun, and the PEA3 elements (−215 to −201) recognised by transcription factor Ets [16–19,21]. These *cis*-elements and *trans*-factors have been found to be essential for the steady-state expression of stromelysin and for the response to various growth factors and cytokines such as EGF and IL-1 as well as tumour promoters such as phorbol esters [11,18,20,22]. In addition, a *cis*-element (termed SPRE) located further upstream (−1576 to −1571), which interacts with a transcription factor containing a leucine zipper region, has been reported to be involved in the response to PDGF stimulation [23,24], and an element (−241 to −229) bound by another member of leucine zipper gene family is involved in NGF induction [25].

Previously we showed that the sequence from −1626 to −1599 relative to the start of transcription was also involved in the regulation of stromelysin promoter activity. Interaction of nuclear factors with this promoter element was demonstrated by electrophoretic mobility shift assays and DNase I footprinting experiments. The identity of the nuclear factors binding to this region of the stromelysin gene promoter was, however, obscure. The data reported here indicate that transcription factor ZBP-89 interacts with this promoter element. Results of the transfection experiments also suggest that ZBP-89 enhances stromelysin gene promoter activity.

Transcription factor ZBP-89 has been shown to interact with promoter sequences containing a GC box in a number of different genes, including those in the genes encoding human T-cell receptor Vβ8.1 (CACCACCCCCAACTTC) [14], mouse T-cell receptor α silencer I (CACCCCACCCCCACCC) [14], human gastrin (CCCCCCACCCCGCCCC) [26], mouse type I collagen α2 (I) (TCCCTCCCCCCTCGGC) [27], mouse type I collagen α1 (I) (TCCTCCCCCCTCTT and GCGCCCCCCCTCCCGC) [27] and human ornithine decarboxylase (GCCCCTCCCCC) [15]. The results of this study indicate that it also interacts with the GC box within the sequence from −1626 to −1599 (GGTTTTTTCCCCCCATCAAA) in the stromelysin gene.

The effect of ZBP-89 on gene regulation appears to be dependent on the context of the relevant promoter. For example, it activates the human T-cell receptor gene promoter [14], but is repressive for the promoters of the human gastrin and ornithine decarboxylase genes [15,28]. In all these cases, regardless of whether it acts as an enhancer or repressor, ZBP-89 appears to compete with another transcription factor for binding to the promoter element. Where it competes with a transcription activator such as in the case of the gastrin [26] and ornithine decarboxylase [15] genes, ZBP-89 exerts a repressive effect. In contrast, where the competitor of ZBP-89 is a transcription silencer such as in the case of the T-cell receptor gene [14], ZBP-89 has an upregulatory effect.

Using a ZBP-89 cDNA probe, we have carried out Northern blot analyses with mRNA from various tissues including heart, brain, lung, liver, kidney, pancreas, skeletal muscle and placenta. Two RNA species, with estimated sizes of 4.1 kb and 7.5 kb respectively, were detected, which is consistent with the findings of Wang et al. [14]. Both transcripts were detectable in all tissues examined, indicating that ZBP-89 is an ubiquitous transcription factor. It is interesting that expression of ZBP-89 has been shown to be increased in gastric cancer tissues [29]. It is therefore plausible that in addition to other possible consequences, overexpression of ZBP-89 in neoplastic cells might lead to increased expression of stromelysin as the data reported here suggest that ZBP-89 enhances stromelysin gene promoter activity. If this is the case, upregu-

lation of stromelysin expression by ZBP-89 may be an important mechanism conferring cancer cells with the ability to invade and metastasise. Further studies are required to examine this possibility.

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