

Structure of the Human Type IV Collagenase Gene*

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The structure of the gene for human 70-kDa type IV collagenase (gelatinase) was determined. Three overlapping genomic clones were isolated and shown to contain 0.4 kilobase (kb) of the 5'-flanking region, the 27-kb structural gene, and 4.5 kb of the 3'-flanking region. The gene has 13 exons that vary in length from 110 to 901 base pairs (bp) and 12 introns that range from 175 to 4350 bp. Alignment of intron locations demonstrated that introns 1-4 and 8-12 of the type IV collagenase gene coincide with intron locations in the interstitial collagenase and stromelysin genes, indicating a close structural relationship of these metalloproteinase genes. Exons 5-7 are each 174 bp in size, and each codes for one complete internal repeat that resembles the collagen-binding domains of fibronectin. The transcription initiation site was determined by primer extension and S1 nuclease analyses. Analysis of the 0.4-kb 5'-flanking region of the gene showed that, in contrast to the genes of interstitial collagenase and stromelysin, there is no TATA box or 12-O-tetradecanoylphorbol-13-acetate-responsive element present in the promoter region, whereas there are two GC boxes. There is no CAAT box, but a potential binding site (CCCCAGGC) for the transcription factor AP-2 is located in the first exon.

Type IV collagenase (gelatinase) is a 70-kDa protein that belongs to a family of mammalian extracellular neutral metalloproteinases that are able to degrade a number of matrix proteins (1, 2). Other well-characterized members of the family are interstitial collagenase (3) specific for fibrillar collagens and stromelysin (transin) (4) that can degrade several non-collagenous matrix components in addition to type IV collagen. The existence of a 92-kDa type IV collagenase (gelatinase) has also been reported (5). The metalloproteinases share a high degree of structural homology, including a conserved sequence at the Zn^{2+} -binding site which is considered to be a part of the active center of these enzymes. They are secreted as inactive proenzymes than can be activated by proteinases such as plasmin or by organomercurials. The active enzyme forms can all be inhibited by the tissue inhibitor of metalloproteinases (6). The metalloproteinases participate in normal remodeling of the matrix during embryogenesis and regeneration processes, and enhanced activity is frequently associated

with pathological states such as inflammation and malignant growth.

Type IV collagenase degrades type IV collagen, the major structural component of basement membranes, in a specific manner, and it also has gelatinase activity (7-9). The type IV collagen molecule is an ~400-nm-long triple helical rod with a large globular noncollagenous domain (NC-domain) at the carboxyl terminus. Type IV collagenase cleaves this substrate molecule at a single site 121 ± 12 nm from the amino terminus into $\frac{1}{4}$ and $\frac{3}{4}$ size fragments (10). The actual cleavage site has not been determined, but it is believed to be Gly-Ile and Gly-Leu bonds that are located within the same region of the $\alpha 1(IV)$ and $\alpha 2(IV)$ chains, respectively (11). The 92-kDa enzyme has also been shown to generate similar cleavage fragments (5). Type IV collagenase is synthesized as a preproenzyme of 660 residues with a 29-residue signal peptide and an 80-residue propeptide (9, 12). The calculated molecular weight of the proenzyme form is 70,984 and that of the active enzyme is 62,067. The proenzyme can be converted to an active form by proteolytic cleavage or with organic mercurials (7, 8). The amino acid sequence is partially homologous to that of interstitial collagenase (13) and stromelysin (4, 14), also known as transin (15), but there are also distinct differences. The resemblance involves 456 residues of the 631-residue type IV procollagenase, i.e. a 192-residue amino-terminal end sequence and a 264-residue carboxyl-terminal end sequence (9, 12). Together, these 456-residue sequences have a significant identity to the entire sequences of interstitial collagenase (469 residues) and stromelysin (477 residues). However, type IV collagenase differs from the other enzymes in that it has a unique 174-residue central domain that consists of three internal repeats that resemble the collagen-binding domains of fibronectin (9, 16). Type IV collagenase is presumably required for the turnover of basement membranes *in vivo*, but increased secretion has also been shown to be linked with the invasive potential of tumor cells (1, 2, 17). The latter may significantly facilitate the penetration of disseminating tumor cells through tissue compartments of the body.

The genes for interstitial collagenase and stromelysin are not only structurally related, but, additionally, their gene loci are linked on the long arm of chromosome 11 (18). In contrast, we have recently shown that the type IV collagenase gene is located on 16q21 (12). This difference may in part explain the divergence of the type IV collagenase gene from the other metalloproteinase genes.

Knowledge about the structure and regulation of the gene is a prerequisite for a fundamental understanding of the role of type IV collagenase in normal and pathological states. In this study, we have isolated and determined the complete structure of the human type IV collagenase gene. The data show that the exon/intron structure resembles that of the gene for interstitial collagenase but that it also has features

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The nucleotide sequence(s) reported in this paper has been submitted to the GenBank™/EMBL Data Bank with accession number(s) J05471.

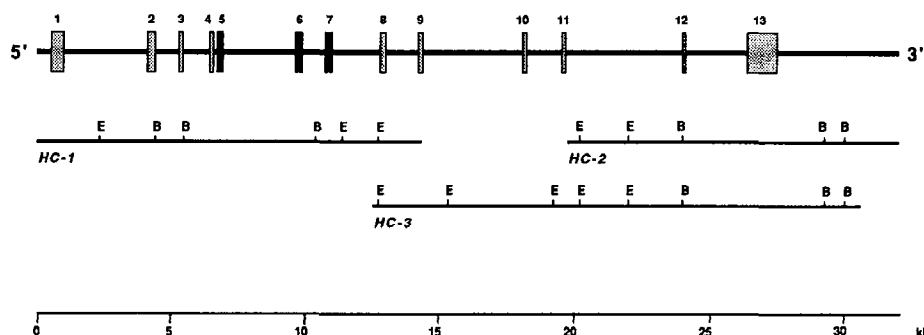


FIG. 1. Structure of human type IV collagenase gene. Three overlapping human genomic clones (HC-1, HC-2, and HC-3) that span over 30 kb were isolated and characterized as described under "Experimental Procedures." Top, the exons are depicted by boxes, and they are numbered starting from the 5'-end of the gene. The black boxes correspond to the exons coding for the three internal repeats. The introns and flanking sequences are depicted as a solid line. Middle, genomic clones were subjected to restriction analysis, and restriction sites for *EcoRI* (E) and *BamHI* (B) are indicated. A scale in kilobases is shown below.

Exon/Intron number	Exon-Intron junctions	Exon size (bp)	Intron size (bp)
1	ATG GAG GCG ... TTG GCA GTG Met Glu Ala ... Leu Ala Val 1 51	5'untranslated 290 +153	3170
2	tttttttttag CAA TAC CTG ... ATC ACA TAC AG gtacgaagac Gln Tyr Leu ... Ile Thr Arg R(rg) 52 126	227	900
3	ccacccttag G ATC ATT GGC ... GGC GCG TGG G gtacgaagaa (A)rg Ile Ile Gly ... Gly Arg Trp G(ly) 127 177	149	970
4	gtgtgttag AG CAT GGC GAT ... GAA GGC CAA G gtacgaagag (G)lu His Gly Asp ... Glu Gly Gln Val 178 219	129	175*
5	caactcttag TG CTC CCT GTG ... CCC CAT GAA G gtacgaatcc (Val Val Arg Val ... Pro His Glu A(ly) 220 277	174	2790
6	ccacccttag CC CTG TTC ACC ... CCT GAG ACC G gtacgaagcc (A)la Leu Phe Thr ... Pro Glu Thr A(ly) 278 335	174	950
7	taacccttag CC ATG TCA ACT ... CCT GAG CAA G gtacgaagcc (A)la Met Ser Thr ... Pro Asp Glu G(ly) 336 393	174	1890
8	aaacccttag GG TAC AGC CTG ... GAG CTC TAT G gtacgaatcc (G)ly Tyr Ser Leu ... Glu Leu Tyr G(ly) 394 445	156	1250
9	ttctacccttag GG GGC TCT CCT ... TTC AAG GAC CG gtacgaagag (G)ly Ala Ser Pro ... Phe Lys Asp R(rg) 496 490	136	3800
10	ctctcttag G TTC ATT TGG ... TTC TTT GCA G gtacgaagag (A)rg Phe Ile Trp ... Phe Phe Ala G(ly) 491 536	126	1270
11	tccacccttag GG AAT GAA TAC ... AAA TTC TGG AG gtacgaagag (G)ly Asn Glu Tyr ... Lys Phe Trp R(rg) 537 589	160	4350
12	tttttttag A TAC AAT GAG ... CAG GGC GGC G gtacgaagcc (A)rg Tyr Asn Glu ... Glu Gly Gly G(ly) 590 626	110	2400
13	tctatcccttag GT CAC AGC TAC ... CTA GGC TGC tga..... (G)ly His Ser Tyr ... Leu Gly Cys *** 627 660	102 + 3'untranslated 799	

FIG. 2. Summary of exon/intron structure of human type IV collagenase gene. Nucleotide sequences at the intron (lower-case letters) and exon (upper-case letters) boundaries and the derived amino acid sequences are shown with the corresponding position numbers in the polypeptide chain below. The exons are numbered beginning from the 5'-end of the gene. The exon/intron structure was determined by sequencing and heteroduplex analysis as described under "Experimental Procedures." The stop codon (TGA) is marked (***). The length of the fourth intron (asterisk) was verified by nucleotide sequencing.

similar to a part of the fibronectin gene. Analysis of the 5'-flanking region indicates that the regulation of this gene differs from that of interstitial collagenase and stromelysin.

EXPERIMENTAL PROCEDURES

Isolation and Characterization of Genomic Clones—Human genomic libraries in λ phage EMBL3 (HL1006 and HL1067J, Clontech) were screened using the 32 P-labeled human type IV collagenase cDNA clone pK191 (12) as probe, and positive clones were isolated using standard methods (19). Three positive overlapping genomic clones

were further characterized by restriction mapping, and suitable fragments were subcloned into M13 derivatives for sequencing. The exon/intron structure was analyzed by nucleotide sequencing and heteroduplex electron microscopy.

DNA Sequencing—The DNA sequence was determined from single-stranded DNA subcloned in M13 derivatives by the dideoxy sequencing method (20) using Sequenase and Taq DNA polymerase enzymes according to the procedure recommended by the manufacturer (United States Biochemical Corp.). Either M13 universal primer or specific oligonucleotide primers derived from appropriate regions of the cDNA clones (12) were used in the sequencing reactions.

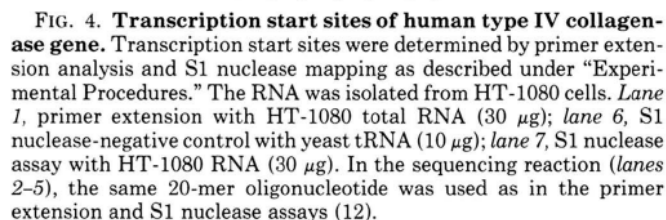
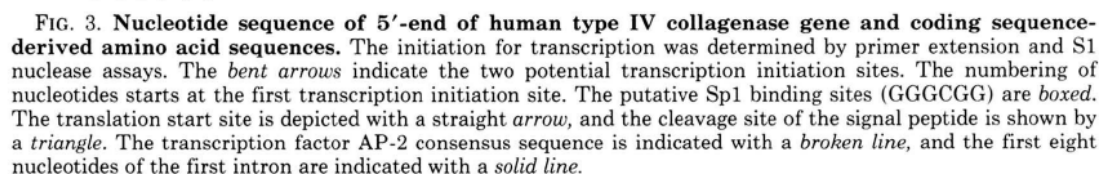
Heteroduplex Analysis—Genomic DNAs (HC-1, HC-2, and HC-3) were purified from phage using standard methods (19). The cDNA clone pK191 (12) was linearized with *SalI*, which cuts in the vector. The asymmetric localization of the cDNA in the vector allowed an unambiguous determination of the orientation of exon/intron segments in the heteroduplexes. The phage DNAs and the cDNA were denatured with NaOH, neutralized with Tris-HCl, and renatured in 50% (v/v) formamide, 0.1 M Tris-HCl, pH 8.5, 0.01 M EDTA at room temperature. The resulting heteroduplexes were mounted onto parlodion grids, contrast-enhanced, and visualized by electron microscopy as described previously (21, 22). Length standards were circular single-stranded ϕ X174 DNA and renatured linear pK191 DNA in the same electron photograph.

Primer Extension and S1 Nuclease Mapping—Primer extension analysis was performed using an end-labeled 20-mer oligonucleotide complementary to the human type IV collagenase mRNA sequence (nucleotides 204–233) as primer and total RNA (30 μ g) isolated from HT-1080 cells as template for reverse transcription (23). The primers were extended with reverse transcriptase under standard conditions (23). In the S1 nuclease protection assay, single-stranded M13 template DNA, containing a 2.3-kb¹ *SalI*-*EcoRI* genomic fragment spanning the 5'-end of the type IV collagenase gene, was hybridized (24) with the same oligonucleotide used for the primer extension. The extension was carried out using Klenow enzyme and [α - 32 P]dCTP as the labeled nucleotide. The 640-nucleotide single-stranded radioactive probe was isolated from a denaturing agarose gel after *SalI* digestion. For hybridization, 100,000 cpm of the probe was incubated with HT-1080 total RNA (30 μ g) at 55 °C for 18 h, and the S1 nuclease reactions were performed for 1 h at 37 °C (24). Yeast tRNA (10 μ g) was used as negative control. The primer-extended products and the protected fragments from the S1 nuclease assays were run on a sequencing gel along with sequencing reactions of the *SalI*-*EcoRI* fragment that contained the first exon using the same oligonucleotide used in the primer extension and S1 nuclease assays as primer.

RESULTS

Characterization of Genomic Clones—Three overlapping genomic λ phage clones (HC-1, HC-2, and HC-3) that together span ~32 kb of genomic DNA were isolated (Fig. 1) using cDNA clones coding for human type IV collagenase as a probe

¹ The abbreviations used are: kb, kilobase(s); bp, base pair(s); TPA 12-O-tetradecanoylphorbol-13-acetate.



Exon/Intron Structure—The nucleotide sequences of the exons were primarily determined using "exon hopping" (25) with synthetic oligonucleotide primers that were designed based on sequences known from the cDNA clones. Additionally, electron microscopic analysis of heteroduplexes between the genomic clones and the cDNA clones was used to determine the complete exon/intron pattern of the gene. These analyses established that the human type IV collagenase gene contains 13 exons that vary in size from 110 to 901 bp and introns ranging in size from 175 to 4350 bp (Figs. 1 and 2). With the exception of exon 2, all translated exons start with the second or third base of a codon. Primer extension and S1 nuclease mapping analyses (see below) and nucleotide sequencing revealed that exon 1 contains 443 bp. Exons 3 and 4 code for a region of the protein that is related to the amino-terminal end of the interstitial collagenase and stromelysin proenzymes. Exons 5–7 are all 174 bp in size, and each of them codes for one complete internal repeat that resembles the collagen-binding domains of fibronectin. Exon 8 contains sequences for the putative zinc-binding region.

Sequencing analysis of the 5'-end untranslated region and of 415 bp of the flanking region (Fig. 3) revealed several interesting features of this gene. There was no TATA or CAAT box. However, there were two GGGCGG consensus sequences (GC boxes) for the binding of the transcription factor Sp1 (27). One GGGCGG sequence started at position -89 and a second one at position -69 (Fig. 3). We could not identify a transcription factor AP-1 binding sequence that can confer TPA induction (28), and, furthermore, a computer search did not reveal consensus sequences (see Ref. 29) for the glucocorticoid-response element, transcription factor C/EBP, cAMP inducibility (CREB), the octamer transcription factors OCT-1 and OCT-2, or the serum-response element. However, a potential binding site consensus sequence (CCCCAGGC) for the transcription factor AP-2 (30) was present in exon 1 starting at position +157 (Fig. 3).

Characterization of the structural gene for human 70-kDa type IV collagenase demonstrates both differences from and similarities to the genes for mammalian interstitial collagenase and stromelysin. The type IV collagenase gene has 13 exons as opposed to 10 in the two other genes (Fig. 5). The gene is 27 kb, which is more than three times larger than the human (31) and rabbit (32) interstitial collagenase genes, and it is also significantly larger than the rat stromelysin (transin) genes (33, 34). The size difference is obviously not due only

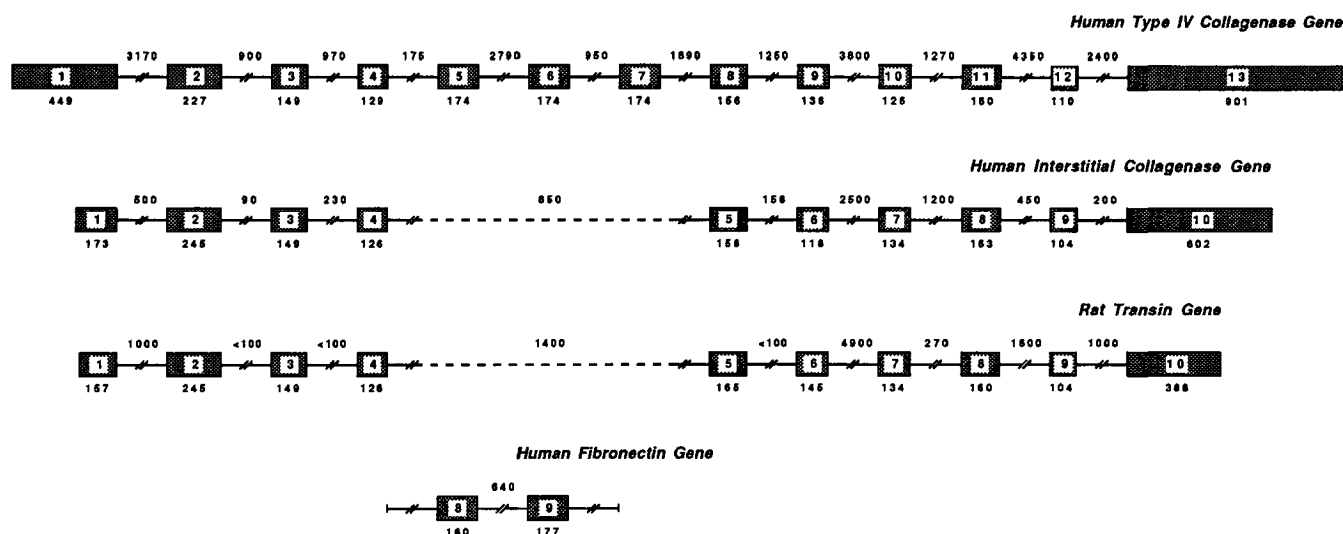


FIG. 5. Comparison of structure of human type IV collagenase gene with those of human interstitial collagenase (31), rat stromelysin (transin) (33), and human fibronectin (16, 35) genes. The exons are shown as shaded boxes numbered from the 5'-end, and the introns are depicted by broken lines. Exons corresponding to each other are aligned. Sizes of exons (in base pairs) are indicated below the boxes, and sizes of introns (in base pairs) are indicated above the introns. The intron sizes of the stromelysin and fibronectin genes are approximated from Refs. 33 and 35, respectively.

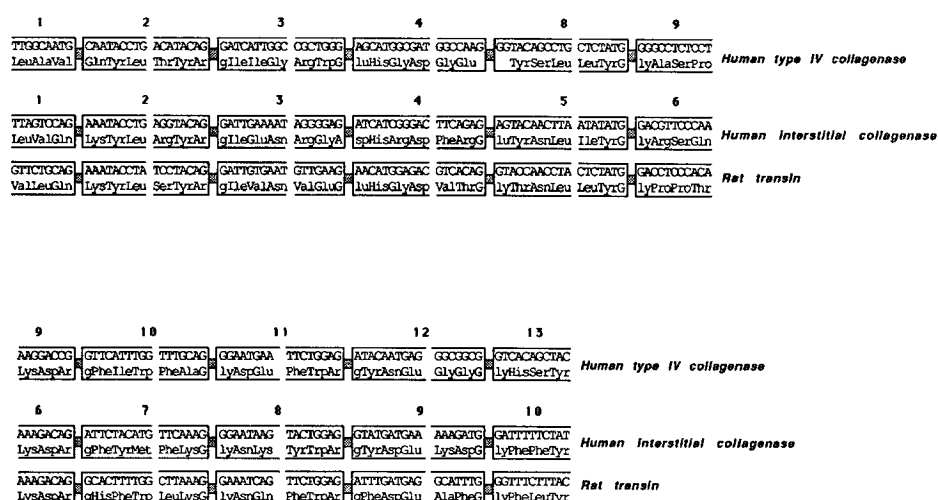


FIG. 6. Illustration of conserved location of intervening sequences in human type IV collagenase, human interstitial collagenase, and rat stromelysin (transin-1) genes. Nucleotide sequences of exons at the intron junctions are shown in open-ended boxes, with the derived amino acid sequences shown below. The introns are depicted by shaded boxes. Sequences of the interstitial collagenase and stromelysin genes are taken from Refs. 31 and 33, respectively.



FIG. 7. Comparison of amino acid sequences encoded by exons 5-7 in type IV collagenase gene with those encoded by exons 8 and 9 in human fibronectin gene. The two fibronectin type II repeats (FN II-1 and FN II-2) contain 1 and 2 more amino acids, respectively, than the three repeats (CLG4-1, CLG4-2, and CLG4-3) in type IV collagenase. Amino acids conserved in all repeats are boxed, with the cysteine residues in shaded boxes.

to the presence of the unique domain consisting of internal repeats, but also to the larger intron sizes. For example, introns 1-3, 8, 11, and 12 in the type IV collagenase gene are all considerably longer than their counterparts in the other metalloproteinase genes. Despite these differences, the genes

clearly belong to the same family based on structural similarities in the parts of the genes that code for homologous regions of the proteins. Alignment of sequences at intron junctions (Fig. 6) demonstrates that introns 1-4 and 8-12 of the type IV collagenase gene all coincide with locations in the inter-

stitial collagenase and stromelysin genes (31–34). The slight differences in the sizes (Fig. 5) of exons depend on whole codons that have been either inserted or deleted.

This study demonstrates that the three 58-residue internal repeats that resemble the collagen-binding domains of fibronectin are each encoded by a single 174-bp exon. Fibronectin contains two internal repeats of this type (type II domains), each of which is encoded by separate exons (35). The sequence identity among the three repeats in type IV collagenase is ~50%, which is of the same order as the sequence identity to the type II domains in fibronectin (Fig. 7). The cysteine residues are conserved in all repeats. It seems likely that the divergence of the type IV collagenase gene has involved an uptake of such elements from another locus. The function of the internal repeats in type IV collagenase is not known, but they possibly confer substrate specificity to the enzyme by providing binding sites for type IV collagen and gelatin.

This study shows that, despite the close intergene relationship, the 5'-flanking region of the type IV collagenase gene differs considerably from those of the genes for human and rabbit interstitial collagenase and human and rat stromelysin (32–34, 36, 37). These differences may provide an explanation for their differential gene expression. For example, cultured human melanoma cells (A2058) and fibrosarcoma cells (HT-1080) express type IV collagenase (9), but not stromelysin (4). Even the tumor promoter TPA does not induce expression of stromelysin in these cells (4). Furthermore, normal human bronchial epithelial cells that become malignant after transfection with the Ha-ras oncogene express type IV collagenase, but not stromelysin or interstitial collagenase (9). These observations support previous findings about linkage between type IV collagenase and the malignant phenotype (9, 17, 38–40). However, type IV collagenase is also expressed to some extent in cultured human endothelial cells, keratinocytes, and fibroblasts (9, 41).

One striking finding was that the type IV collagenase gene does not contain a TATA box, which is present in the interstitial collagenase and stromelysin genes. The lack of a TATA box has been observed in most but not all housekeeping genes, the polyoma virus late promoter, the adenovirus 2 DNA-binding protein promoter, and the SV40 late promoter (42–46). Also, genes for the basement membrane proteins, type IV collagen (47) and laminin B1 (48) and B2 chains (49), do not have a TATA box. Promoters without TATA boxes generally have heterogeneous initiation sites for transcription, as was also shown to be the case for the type IV collagenase gene in this study. Another feature of the type IV collagenase gene is the presence of two Sp1 binding sequences (GGCGG) in the 5'-flanking region, whereas there are no such sequences in the other two metalloproteinase genes. All three metalloproteinase genes are similar in that they lack a CAAT box.

Interestingly, the type IV collagenase gene lacks the TPA-response element sequence (TGAGTCAG) that can serve as a binding site for the nuclear transcription factor AP-1 (28). This consensus sequence is present in both the interstitial collagenase and stromelysin genes at the same location, starting ~40 bp upstream from the TATA box and ~70 bp from the start site for transcription (36, 37). Both interstitial collagenase and stromelysin expression are directly induced in fibroblasts by TPA, an effect that is mediated through the AP-1 protein (28). The effects of TPA on type IV collagenase expression are as yet controversial. TPA has been reported to increase both type IV collagenase activity (41) and mRNA levels (50) in human skin fibroblasts, but the absence of induction has also been reported (9). The possible role of the AP-2 binding site (CCCCAGGC) in the first exon of the type

IV collagenase gene remains to be determined. The AP-2 protein appears to mediate transcription activation through phorbol esters such as TPA and protein kinase C as well as cAMP-dependent protein kinase A (30).

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