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Cytokine Regulation of Metalloproteinase Gene Expression

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Abstract Matrix metalloproteinases belong to a family of zinc-dependent enzymes capable of degrading extracellular matrix and basement membrane components. Their expression is greatly modulated by cytokines and growth factors and involves the gene products of the Fos and Jun families of oncogenes. After extra(peri)cellular activation, their activity can be further controlled by specific tissue inhibitors of metalloproteinases. A correct balance between these regulatory mechanisms is necessary to ensure matrix remodeling in normal physiological processes such as embryonic development, but the overexpression of these enzymes may initiate or contribute to pathological situations such as cartilage degradation in rheumatoid arthritis or to tumor progression and metastasis. Delineation of the mechanisms of metalloproteinase and metalloproteinase inhibitors gene expression, understanding of their mode of interactions, and characterization of their patterns of expression in various tissues in normal and pathological states will lead to new therapeutic strategies to counteract the deleterious effects of matrix metalloproteinases in human disease.

Key words: metalloproteinases, cytokines, gene expression, extracellular matrix, growth factors

Matrix metalloproteinases (MMPs) form a family of enzymes capable of degrading various extracellular matrix (ECM) components that are expressed in normal remodeling of connective tissue, such as that occurring during embryonic development, uterine resorption, and wound healing, as well as in disease states, such as in rheumatoid arthritis or tumor invasion. MMPs are produced by mesenchymal cells as well as by monocyte/macrophages and tumor cells in response to a variety of stimuli, including tumor promoters, growth factors, oncogenes, cytokines, heat shock, and physiological substances such as urate crystals, metal ions, or serotonine [reviewed in Emonard and Grimaud, 1990; Woessner, 1991].

The MMP family of enzymes, capable of degrading the macromolecules of the ECM, comprises three subclasses with respect to their specific substrates: collagenases, stromelysins, and gelatinases. All members of this family share amino acid sequences and various structural domains and are secreted as zymogens requiring activation for proteolytic activity. In vitro, the latent MMPs can be activated by organic mercurides, chaotropic agents, or proteases. They contain a zinc ion, require Ca^{++} for full activity, and are inhibited by chelating agents [reviewed in Harris et al., 1984]. Furthermore, they are inhibited by specific tissue inhibitors of metalloproteinases (TIMPs).

So far, nine different MMPs have been identified by cDNA cloning and sequencing. The different members of this family of enzymes are listed in Table I. The MMPs present a high degree of conservation between each type of enzyme across several mammalian species (about 80% similarity between collagenases and stromelysins), as demonstrated by cDNA-predicted amino acid sequences alignment. The similarity between types is lower but still highly significant (50%) [Murphy et al., 1991]. Different domains with apparent specific functions can be delineated within the sequences, including a propeptide domain lost during activation, a metallic zinc and calcium binding domain, and domains with sequence similarities to a number of extracellular

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TABLE I. The Family of Matrix Metalloproteinases*

MMP #	Name	MW (kDa)	ECM substrate	Distribution	Regulator TPA	TGF-β	IL-1	TNF-α	Others
Collagenases									
1	Interstitial collagenase (Human/ rabbit)	52.5	Fibrillar collagens (I, II, III, V, VII, X)	Connective tissue cells Monocyte/macrophages Endothelial cells	+	−	+	+	PDGF, bFGF, EGF (+) LR, LT (+) IFN-γ (+/−) IL-6 (+/−/=) IL-4 (−)
8	Neutrophil collagenase	75	Fibrillar collagens (I, II, III) Gelatin	Neutrophils (PMN)	+				
Gelatinases									
2	72 kDa gelatinase (gelatinase A) Type IV collagenase	72	Gelatin Collagens IV, V, VII, X, XI FN, elastin	Most cell types Tumor cells	+	+	+	+	
9	92 kDa gelatinase (gelatinase B) 92 kDa Type V collagenase	92	Same as gelatinase A	Connective tissue cells Monocyte/macrophages Tumor cells	+	+	+	+	LT (+) IL-4, IFN-γ (−)
Stromelysins									
3	Stromelysin-1 (rat transin)	57/60	Proteoglycans, FN Laminin Collagens III, IV, V, IX Gelatins Activates MMP-1	Same as MMP-1 Tumor cells	+	−	+	+	LR (+) PDGF, EGF (+) IFN-γ (−)
10	Stromelysin-2 (rat transin-2)	53	Same as MMP-3 but lower activity	Macrophages Tumor cells					
7	Matrilysin (Pump-1)	28	Gelatins FN, proteoglycans Collagen IV (?) elastin	Immature monocytes, Connective tissue cells Tumor cells					
Others									
	Stromelysin-3	54.6[a]	Unknown	Stromal cells of tumors					
	Metalloelastase	21	Elastin, FN	Macrophages					

*,+ indicates a stimulatory effect of the regulator, − indicates an inhibitory effect, and = indicates no effect. This table is a compilation of published data. Original references may be found throughout the literature cited in this paper.
[a]The molecular weight has been estimated from the cDNA.

matrix structural proteins, such as type V collagen, fibronectin, or vitronectin. The function and structure of the various domains are described in detail in recent reviews [Woessner, 1991; Murphy and Docherty, 1992].

MODULATION OF THE COLLAGENASE AND STROMELYSIN PROMOTER ACTIVITY: ROLE OF AP-1 IN TRANSCRIPTIONAL REGULATION

The promoter regions of the genes encoding for stromelysin-1 and interstitial collagenase have been sequenced and exhibit common features important for transcriptional regulation. These promoters contain a TATA box, about 30 nucleotides upstream from the transcriptional start site, a tumor promoter-responsive element (TRE) [Angel et al., 1987], and a PEA3-binding site within a short distance further upstream [Gutman and Wasylyk, 1990]. Mutation within these regulatory elements has shown that both the TRE and the PEA3-binding element regulate the basal activity of the collagenase promoter as well as its inducibility by a variety of agents [Gutman and Wasylyk, 1990]. Other elements further upstream may also participate in the regulation of the promoter activity, but their exact role is still obscure [Brinckerhoff and Auble, 1990]. The TRE (TGAGTCA) binds the transcription factor AP-1, composed of dimers of protein products encoded by the families of oncogenes, Fos and Jun. The PEA3-binding site interacts with the proto-oncogene product c-*ets*. It is, therefore, conceivable that the stimulation of the expression of these oncogenes by a variety of effector molecules would lead to increased transcription of the metalloproteinase genes. In fact, all of the potent stimulators of collagenase and stromelysin gene expression—for example, 12-*O*-tetradecanoylphorbol-13-acetate (TPA), interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), or leukoregulin (LR)—induce the expression of oncogenes of the Jun and Fos families [Schönthal et al., 1988; Brenner et al., 1989; Krane et al., 1990; Mauviel et al., 1992a,b]. The induction of MMP gene expression by these cytokines is prevented by treatment of the cells with cycloheximide, demonstrating the requirement of ongoing protein synthesis. Furthermore, the induction is down-regulated by glucocorticoids and retinoic acid, which have been shown to interact with the transcription factor AP-1 and block its binding to the TRE by as yet unclear mechanisms [Nicholson et al., 1990; Jonat et al., 1990]. Also, other studies have shown that the induction of the stromelysin and collagenase genes by TPA and cytokines requires the expression of the Fos gene [Schönthal et al., 1988]. Thus, these results collectively suggest that the TRE is involved in the upregulation of collagenase and stromelysin-1 gene expression.

On the other hand, transforming growth factor-β (TGF-β) has been shown to reduce collagenase gene expression and activity in cultured cells. This inhibition results from two distinct mechanisms: 1) TGF-β reduces the expression of the collagenase genes, and 2) the expression of TIMP is elevated by TGF-β [Edwards et al., 1987]. This growth factor has also been shown to inhibit rat stromelysin-1 (transin) gene expression, and this inhibition is mediated by the binding of a Fos-containing protein complex to the TGF-β inhibitory element (TIE) present in the transin promoter region [Kerr et al., 1990]. Although the rat transin promoter is very similar to that of human collagenase and stromelysin, no direct evidence of a functional role for the consensus TIE of the latter promoters has been described so far. Since IL-1, TNF-α, and TPA as well as TGF-β have been shown to induce c-*fos* gene expression, and since these cytokines exert opposite effects on MMP gene expression, it can only be concluded that the synthesis of c-*fos* is an essential factor for modulation of the expression of collagenase and stromelysin genes. This bifunctional role of c-*fos* is further established by experiments in which induction of Fos protein by oncogenes, TPA, or platelet-derived growth factor (PDGF) was blocked by the expression of antisense c-*fos* RNA. The subsequent induction of collagenase and/or stromelysin gene expression was also blocked, demonstrating the absolute requirement for c-*fos* in the stimulation of MMP mRNA synthesis [Schönthal et al., 1988]. In view of these studies, it appears that c-*fos* is involved in both positive and negative regulation of metalloproteinases gene expression. However, antisense *fos* sequences can block PDGF-induced transin gene expression, whereas their effect on epidermal growth factor (EGF)–stimulation is cell type specific [Kerr et al., 1988; McDonnell et al., 1990].

The complexity of the transcriptional system involving the binding of the transcription factor AP-1 to the TRE is further accentuated by the fact the known members of the Jun and Fos gene families all code for proteins capable of interacting with the TRE and have closely related recognition sites, but with different affinities. While the Jun proteins can form homodimers, the Fos proteins only interact with

the TRE as part of heterodimers with various members of the Jun family [Vogt and Bos, 1990]. Moreover, different transcriptional activities of two members of the Jun family of oncogenes (e.g., c-*jun* and *jun*-B) have been reported [Chiu et al., 1989; Schütte et al., 1989]. Whereas c-*jun* is an efficient activator of the c-*jun* and collagenase promoters which contain a single TRE, *jun*-B is not. Furthermore, *jun*-B inhibits activation of these promoters by c-*jun*. However, like c-*jun*, *jun*-B is a potent activator of constructs containing multimeric TREs. These differences in the biological properties of the two Jun proteins are due to intrinsic differences in the properties of their activation domains and allow a fine tuning of the regulation of TRE-driven genes. Furthermore, since *jun*-B is capable of both repressing and activating transcription in a manner that depends on the number of binding sites within the responding promoters, different classes of genes may show a differential response to *jun*-B expression.

The regulatory role of these different Jun proteins is further suggested by the fact that the corresponding genes are not coordinately expressed in various tissues [Wilkinson et al., 1989], suggesting a tissue-specific transcriptional regulation of TRE-driven target genes. Therefore, data suggest that, in different inducible systems, increased specificity and precise regulation of TRE-driven transcriptional activation is achieved by interactions between positive and negative transcription factors that belong to the same gene family. One could also speculate that these genes are differentially regulated by various cytokines and growth factors, which would allow them to either cooperate with or antagonize each other to modulate the expression of TRE-driven genes such as those coding for interstitial collagenase or stromelysin-1. In fact, we recently observed that TGF-β, which down-regulates IL-1, TNF-α, and LR-driven fibroblast collagenase gene expression, induces the expression of *jun*-B without affecting that of c-*Jun;* and we have demonstrated, using antisense *jun*-B vectors in transfection experiments, that *jun*-B is required for TGF-β induced inhibition of collagenase gene expression [Mauviel et al., in press].

It should be noted that in most of the studies performed on the regulation of collagenase and/or stromelysin by proinflammatory cytokines (e.g., IL-1, TNF-α, or LR), there is a major discrepancy between the dramatic elevation of mRNA levels and the significantly lower level of transcription of the corresponding gene. This may be due to increased mRNA stability, as suggested for TPA, or EGF [Brinckerhoff et al., 1986; Delany and Brinckerhoff, 1992]. IL-1, TNF-α, and LR stimulation may also result in increased mRNA stability. Other evidence suggests that additional mechanisms other than TRE *trans*-activation may be involved in the upregulation of MMP gene expression. For example, IL-1β mutant has been shown to induce the expression of *c-Fos* and *c-Jun* in fibroblasts, but not that of collagenase and stromelysin, suggesting an altered signal transduction which would not allow the expression of late genes [Conca et al., 1991].

The understanding of signal transduction pathways and the characterization of second messengers involved in growth factors and cytokine regulation of MMP genes is still very preliminary. Calmodulin seems to be required for IL-1–induced TIMP expression, but it is a suppressor for the synthesis on MMP-1 and -3 [Ito et al., 1991]. By contrast, activation of protein kinase C may be a prerequisite for EGF stimulation of transin gene expression [McDonnell et al., 1990]. Also, okadaic acid, a protein phosphatase inhibitor, up-regulates collagenase gene expression, through pathways which are different from those used by IL-1 [Kim et al., 1990].

REGULATION OF GELATINASE GENE EXPRESSION BY CYTOKINES AND GROWTH FACTORS

Contrasting with the extensive knowledge on the molecular biology of MMP-1 and MMP-3, studies on the regulation of gelatinase gene expression started only a few years ago. Although their substrate specificity is very similar, the regulation of the two forms of gelatinase appear to be quite different.

Analysis of the 5′-flanking region of the type IV collagenase gene has revealed striking differences with the MMP-1 promoter. For example, the type IV collagenase promoter contains no TATA box and contains several potential SP-1 binding sites within 120 bp upstream of the transcription start site, not found in the interstitial collagenase gene. Furthermore, there is no TRE in the type IV collagenase promoter. Other structural features include an adenovirus E1A oncogene-repressible enhancer element, located about 1,650 bp upstream of the start site, and a strong silencer downstream of this element, which may contribute to the cell-specific expression of the gene [Frisch and Morisaki, 1990].

Recent studies have shown that cytokines and growth factors can modulate the expression of type IV collagenase, but eventual responsive elements have not been characterized as yet.

The type IV collagenase gene, which can be induced in epithelial cells by *ras* transformation, does not respond to TPA treatment in either the normal or the tumorigenic cell lines tested [Collier et al., 1988]. Neither does it respond to IL-1 in these cell lines, but this may be cell specific since other reports have shown elevation of type IV collagenase gene expression in response to IL-1.

Interestingly, while IL-1β, TNF-α, lymphotoxin (LT), PDGF, and bFGF all stimulate fibroblasts to produce interstitial collagenase, only TNF-α, LT, and IL-1β are capable of inducing the expression of the 92 kDa gelatinase. LT, furthermore, has no effect on the 72 kDa gelatinase mRNA levels, whereas IL-1β and TNF-α elevate its expression [Unemori et al., 1991].

TGF-β has been shown to up-regulate both 92 kDa and 72 kDa gelatinase activities in cultured fibroblasts, thus contrasting with its inhibitory effect on MMP-1 and MMP-3 gene expression. The effect of TGF-β on MMP-2 expression appears to result from an elevation of the corresponding mRNA levels through a transiently increased transcription of the gene and increased stability of the message [Overall et al., 1991]. A similar or even somewhat higher elevation of gelatinase A and B expression by TGF-β has also been reported in cultured keratinocytes [Salo et al., 1991].

Contrasting with the upregulatory effect of TGF-β on gelatinase gene expression, IL-4, which is another potent suppressor of monocytic functions as well as a B cell growth factor, suppresses the release of both interstitial collagenase and 92 kDa gelatinase by human alveolar macrophages without affecting the expression of TIMP [Lacraz et al., 1992]. The effect of IL-4 on MMP expression takes place at the pre-translational level by reduction of the corresponding mRNA steady-state levels and may be a prostaglandin E_2-mediated cAMP dependent mechanism [Corcoran et al., 1992]. Interferon-γ also suppresses constitutive expression of macrophage 92 kDa gelatinase [Shapiro et al., 1990].

REGULATION OF METALLOPROTEINASE ACTIVITY

Although transcriptional regulation is obligatory for zymogen production, matrix degradation requires the proenzymes to be activated by catalytic cleavage. These activation steps have been described in detail by Harris et al. [1984]. It is now generally accepted that the endogenous activator of MMPs is plasmin, the product of plasminogen proteolytic cleavage by plasminogen activators (PAs), the latter being controlled by plasminogen activator inhibitors (PAIs) [reviewed in Vassalli et al., 1991]. Therefore, the modulation of MMP activity by cytokines may be regulated through the plasmin/PA/PAI system (Fig. 1). In fact, phorbol esters, EGF, IL-1, TNF-α, and IFN-γ have been shown to upregulate PA and PAI expression, whereas TGF-β and glucocorticoids inhibit PA expression, therefore slowing down the activation of MMPs in addition to downregulating their expression.

In addition to secreting MMPs, various cell types also produce TIMP, a 25 kDa protein which binds collagenase and stromelysin stochiometrically and inhibits their ECM degradative potential by as yet unknown mechanisms. TIMP is expressed constitutively at high levels in fibroblasts, and its regulation is independent of that of MMPs. IL-1, TNF-α, and phorbol esters, which stimulate collagenase and stromelysin gene expression, also upregulate TIMP expression, but TGF-β and retinoic acid which repress MMP-1 and MMP-3 gene expression are potent activators of TIMP expression. The biological importance of TIMP is strongly evidenced by the disruption of its gene by homologous recombination in pluripotent mouse embryonic stem cells, which leads to an increased invasive behavior of primitive mesenchymal cells in vitro, suggesting that MMP activity can be rate limiting for cell invasion [Alexander and Werb, 1992].

PERSPECTIVES

Although the understanding of MMP biology has greatly improved during the past 10 years, thanks to the enormous development of cellular and molecular biology, the exact role of MMPs in the pathogenesis of degradative diseases, tumor invasion, or diseases associated with excessive deposition of ECM remains to be elucidated.

Studies on the regulation of MMP-1 and MMP-3 gene expression have emphasized the importance of the target sequence TGAGTCA (TRE), which binds the transcription factor(s) AP-1, composed of products of the Fos and Jun gene families. The Fos family has four characterized members, *Fra-1, Fra-2, c-fos,* and *Fos-B,* whereas the Jun family has three known members, namely *c-Jun, Jun-B,* and *Jun-D.* This multiplicity can lead to a variety of dimeric

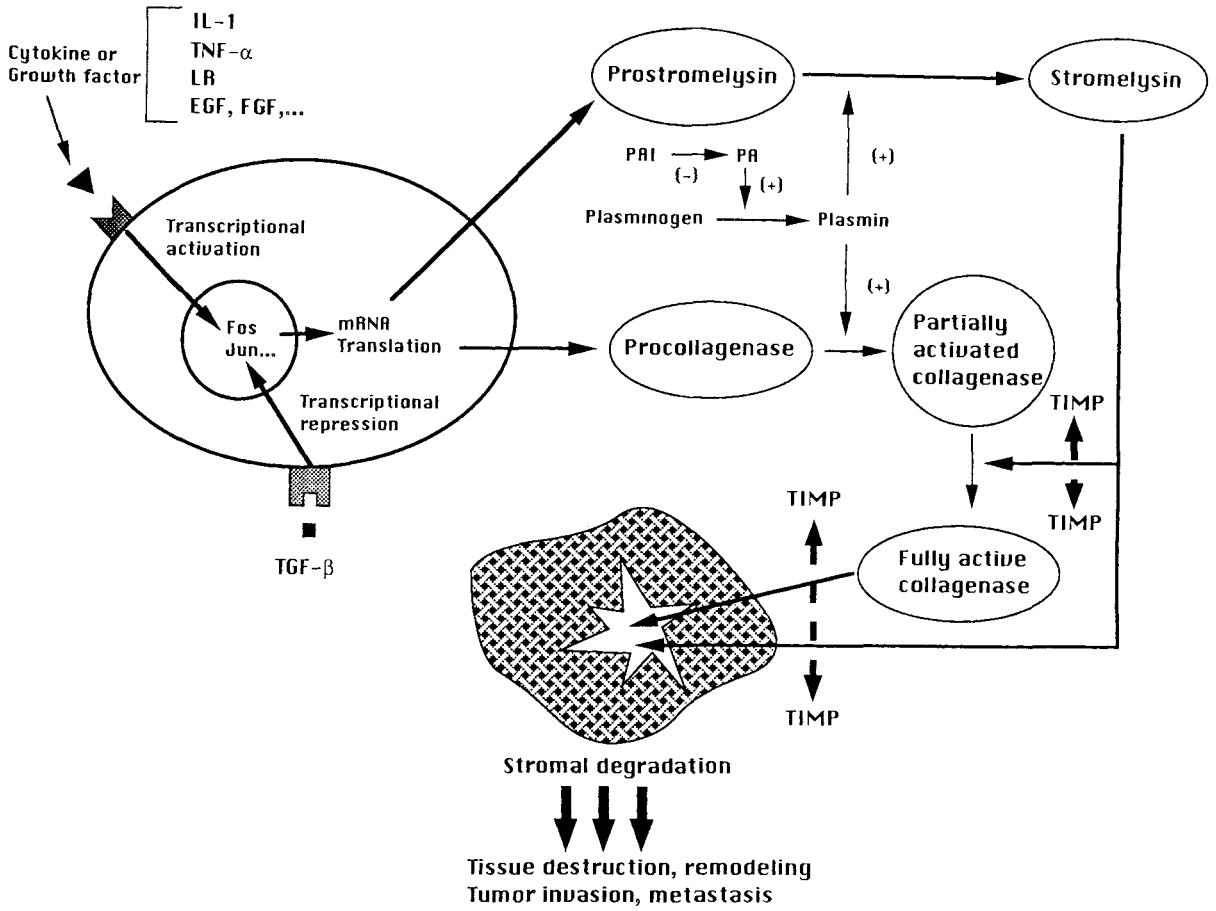

Fig. 1. Schematic representation of the different steps involved in the regulation of MMP-1 and MMP-3 activities.

combinations capable of binding the TRE and possibly the TIE (see previously), and their respective transcriptional activities in relation to the MMP genes remain to be determined. Furthermore, characterization of the pattern of oncogenes induced by the different cytokines is essential to understand, and eventually control, the resulting MMP expression. Also, in this context, increased understanding of how oncogenes modulate their own expression may help to better control this regulatory pathway.

Another key control of MMP activity is the balance between proteinases and their inhibitors, the TIMPs. The exact mechanisms by which TIMPs can abolish MMP activity is not fully understood. Their expression can be modulated by growth factors, which may, therefore, represent a way to modulate the ECM degradation. The growing family of MMPs suggests that additional inhibitors remain to be discovered. Understanding their mode of action will allow the design of molecules capable of specifically interacting with MMPs to block their deleterious effects on the ECM. In fact, this approach may be much more efficient than the recent clinical trials intended to block specific cytokines with either soluble receptors, antibodies, or receptor antagonists, since the excessive production of MMPs in pathological states, such as rheumatoid arthritis, is, in all likelihood, not the result of a single cytokine but of the concerted action of a plethora of factors.

Another area of human pathology in which cytokines may play an essential role in modulating MMP gene expression is cancer, and more specifically tumor invasion and metastasis. The spreading of tumor cells throughout the body involves degradation of the stromal extracellular matrix of various organs and the passage through the endothelium of blood vessels. In fact, tumor invasion and metastatic processes are often associated with the expression of MMPs, in both tumor cells and stromal cells. Stromelysin-1 and -2 and PUMP expression have been correlated with tumor progression, whereas TIMP levels inversely correlate with the invasive potential of mouse fibrosarcoma cells [Alexander and Werb, 1992]. Moreover, antisense

TIMP RNA induces cell invasiveness through the human amnion and metastatic tumors in nude mice, suggesting that the invasive phenotype is dependent on MMP activity [Khokha et al., 1989].

Recently, the existence of a tumor-cell membrane-associated putative receptor for the 72 kDa type IV collagenase was demonstrated [Emonard et al., 1992]. This receptor was described in two human breast adenocarcinoma cell lines which are unable to release the 72 kDa type IV collagenase. This suggests that their metastatic phenotype may be due to their capacity to bind exogenous 72 kDa type IV collagenase, produced by the peritumor stromal fibroblasts. Such interactions between stromal and tumor cells have been described for the urokinase-type plasminogen activator, produced by stromal cells and which binds to a specific receptor on the tumor cells [Pyke et al., 1991]. Also, stromelysin-3 gene expression is detected in stromal cells but not in tumor cells of breast adenocarcinomas [Basset et al., 1990]. However, in this case, its function as a MMP is still under investigation.

Recently, the expression of 92 kDa type IV collagenase was studied in various human skin tumors, such as benign tumors of sweat glands, basal cell carcinomas, baso-squamous cell carcinomas, and squamous cell carcinomas. Its expression is exclusively restricted to stromal cells and is never observed in the tumor epithelium [Karelina et al., 1993]. Interestingly, the tumor cells themselves have been shown to secrete cytokines capable of inducing fibroblasts to produce collagenase [Golsen et al., 1985]. How cytokines and growth factors can regulate the expression of MMPs and TIMPs in the metastatic processes requires further investigation and may lead to new approaches in the immunotherapy of cancer.

Transgenic mice expressing the human collagenase transgene in their lungs under the control of the haptoglobin promoter develop pulmonary emphysema [D'Armiento et al., 1992], implicating interstitial collagenase as a possible etiological agent in the disease. Future development of additional experimental models allowing the tissue-specific overexpression of MMPs should allow major advances in the understanding of the pathogenesis of various diseases characterized by ECM destruction.

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