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Metalloproteinases and atherothrombosis: MMP-10 mediates vascular remodeling promoted by inflammatory stimuli

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1. ABSTRACT

Atherosclerosis is the common pathophysiological substrate of ischemic vascular diseases and their thrombotic complications. The unbalance between matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) has been hypothesized to be involved in the growth, destabilization, and eventual rupture of atherosclerotic lesions. Different MMPs have been assigned relevant roles in the pathology of vascular diseases and MMP-10 (stromelysin-2) has been involved in vascular development and atherogenesis. This article examines the pathophysiological role of MMPs, particularly MMP-10, in the onset and progression of vascular diseases and their regulation by pro-inflammatory stimuli. MMP-10 over-expression has been shown to compromise vascular integrity and it has been associated with aortic aneurysms. MMP-10 is induced by C-reactive protein in endothelial cells, and it is over-expressed in atherosclerotic lesions. Additionally, higher MMP-10 serum levels are associated with inflammatory markers, increased carotid intima-media thickness and the presence of atherosclerotic plaques. We have cloned the promoter region of the MMP-10 gene and studied the effect of inflammatory stimuli on MMP-10 transcriptional regulation, providing evidences further supporting the involvement of MMP-10 in the pathophysiology of atherothrombosis.

2. INTRODUCTION

Atherosclerosis development involves a series of stages in which inflammatory and proteolytic activities are fundamental determining plaque stability and rupture (1). Vulnerable (high risk) plaques are characterized by a big necrotic core, thin fibrous cap and an inflammatory infiltrate mainly composed by monocyte/macrophages, neutrophils and lymphocytes. Atherosclerotic plaque rupture causes 75% mortality after acute myocardial infarction (2).

Matrix metalloproteinases (MMPs) are proteolytic enzymes that carry out highly selective cleavage of specific substrates, degrading extracellular matrix (ECM) components and modulating tissue remodeling. MMPs, alone or in combination with the fibrinolytic system, are key factors in vascular remodeling associated to atherosclerosis. It has been assumed that these enzymes favor local cell migration and neointima formation, contributing to atheromatous plaque destabilization (3). Recently, MMP-10 (also known as stromelysin-2) over-expression has been reported in various carcinomas and tumors (4), and it has also been proposed to be involved in vascular pathologies. MMP-10 degrades multiple components of the ECM or stromal connective tissue, such as proteoglycan, laminin, fibronectin, and collagen III and IV (5). MMP-10 has been proposed to participate in

Table 1. Characteristics and specificity of main MMPs

MMPs	Name	Substrate
Colagenases		
MMP-1	Collagenase-1	Collagen I,II,III,VII,VIII and X, gelatin, proteoglycan, tenascin.
MMP-8	Collagenase-2	Collagen I,II, III, V, VIII and X, gelatin, aggrecan
MMP-13	Collagenase 3	Collagen I,II,III, IV, IX, X and XIV, gelatin, tenascin, fibronectin, aggrecan, osteonectin
Gelatinases		
MMP-2	Gelatinsa A	Collagen I,IV,V,VII,X,XI and XIV, gelatin, elastin, fibronectin, laminin, aggrecan, versican, osteonectin, proteoglycan
MMP-9	Gelatinase B	Collagen IV,V, VII, X and XIV, gelatin, elastin, aggrecan, versican, proteoglycan, osteonectin
Stromelysins		
MMP-3	Stromelysin-1	Collagen III,IV,V and IX, gelatin, aggrecan, versican, proteoglycan, tenascin, fibronectin, laminin, osteonectin
MMP-10	Stromelysin -2	Collagen III, IV, V, gelatin, casein, agrecan, elastin, proteoglycan
MMP-11	Stromelysin -3	Collagen IV, casein, laminin, fibronectin, gelatin, transferrin
MT-MMPs		
MMP-14	MT1-MMP	Collagen I, II and III, casein, elastin, fibronectin, vitronectin, tenascin, proteoglycan, laminin, entactin
MMP-15	MT2-MMP	Tenascin, fibronectin, laminin
MMP-16	MT3-MMP	Collagen III, gelatin, casein, fibronectin
MMP-17	MT4-MMP	ND
MMP-24	MT5-MMP	ND
MMP-25	MT6-MMP	ND
Others		
MMP-7	Matrilysin	Collagen IV and X, gelatin, aggrecan, proteoglycan, fibronectin, laminin, tenascin, casein transferrin, Iβ4, osteonectin, elastin
MMP-12	Metalloelastase	Collagen IV, gelatin, elastin, casein, laminin, proteoglycan, fibronectin, vitronectin, entactin
MMP-20	Enamelysin	Amelogenin
MMP-23A	MMP-21	ND
MMP-23B	MMP-22	ND
MMP-26	Matrilysin-2	Collagen IV, fibrinogen, fibronectin, casein
MMP-27	ND	ND
MMP-28	Epilysin	Casein

MMPs: metalloproteinases; MT-MMPs: membrane-type MMPs; Iβ4: integrin β4; ND: non determined

physiological processes like bone growth, being actively expressed by osteoclasts and at resorption sites in developing human bone, and wound healing, where tightly regulated expression level of MMP-10 is required for limited matrix degradation at the wound site, thereby controlling keratinocyte migration (6). In this paper we examine the pathophysiological role of MMPs, particularly MMP-10, in the onset and progression of vascular diseases and their regulation by pro-inflammatory stimuli.

3. METALLOPROTEINASES IN ATHEROSCLEROSIS

3.1. MMP structure and function

MMPs are a family of at least 24 zinc-dependent proteases, encoded by different genes and secreted as zymogens that are proteolytically activated by other proteases. MMPs share certain degree of homology, containing a catalytic domain that possesses a zinc-binding consensus sequence and an N-terminal regulatory domain responsible for the inactivation of the enzyme. A number of additional structural domains condition the binding to ECM proteins, among them, the hemopexin carboxy-terminal domain determines substrate specificity and the interaction with tissue inhibitors of metalloproteinases (TIMPs), although there are two matrilysins (MMP-7, MMP-26) that lack the hemopexin C-terminal domain. There is also a subfamily of MMPs bound to the membrane through intracytoplasmic and transmembrane domains (MT-MMP). Main MMP subfamilies participating more actively in ECM catabolism are: collagenases (MMP-1 and -8), gelatinases (MMP-2 and -9), stromelysins (MMP-3, -10 and -11) and MT-MMPs (Table 1) (7). MMP activity is tightly regulated at both intracellular and extracellular levels. Growth factors, cytokines, hormones and tumor promoters induce MMP expression at the transcriptional level, while heparin, transforming growth factor-beta (TGF-beta) and corticosteroids have an inhibitory effect. Extracellular activation of the latent pro-enzymes, mainly by plasmin, represents the second level of control.

MMPs are involved in the pathologic tissue destruction associated to rheumatoid arthritis, cancer and certain vascular diseases. At cellular level, MMPs favor cell migration and proliferation associated with tumor growth and invasion (8), and at molecular level they may act as modulators of the biological activity of ECM proteins, cytokines, latent growth factors, cell surface receptors and adhesion molecules (7, 9).

3.2. MMPs in the atherosclerotic vascular wall

It has been demonstrated that the expression and activity of several MMPs (MMP-1, -2, -3, -7, -8, -9, -11, -12, -13 and -14), ADAMS 9 and 15, neutrophil elastases, proteins of the fibrinolytic system and cathepsins (K,S and V) increase in the atherosclerotic plaque. Main sources for these enzymes are endothelial cells (ECs), vascular smooth muscle cells (VSMC) and macrophages (10). Vascular lesions that undergo expansive remodeling, like aneurysms and plaques responsible for the acute coronary syndromes, exhibit an increase in MMP-2 and -9 activities (11). Indeed, the degradation of interstitial collagen (the major contributor to the mechanical strength of the fibrous cap of the plaque) requires the initial proteolysis of collagens I and III by interstitial collagenases (MMP-1, -8 and -13), and by gelatinases (MMP-2 and -9) in the latter steps (12). The presence of MMP-3 (stromelysin-1) and MMP-14 (MT-MMP-1) has also been documented in human atherosclerotic plaques. Studies conducted in apolipoprotein E deficient (apoE-/-) mice, an animal model

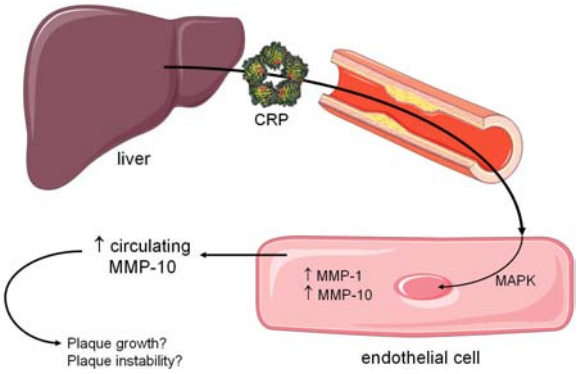

Figure 1. Inflammation induces MMP-10 in the vessel wall. Circulating CRP may exert direct vascular effects inducing endothelial cell expression of MMP-1 and MMP-10. Elevated plasma levels of MMP-10 are associated with increased carotid IMT and with the presence of atherosclerotic plaques in asymptomatic subjects and hence, it has been proposed that MMP-10 could be related to plaque progression and instability.

that develops atherosclerosis, have shown that MMP-3 can contribute to plaque destabilization and promotion of aneurysm formation by degrading the elastic lamina. In this model, it has been also shown that MMP-9 deficiency reduces the atherosclerotic load and diminishes macrophage infiltration during aneurysm formation. Besides, TIMP-1 deficiency accelerates plaque destruction and aneurysm formation, while its over-expression reduces lesion size (3). Therefore, experimental evidences suggest that MMPs may become a therapeutic target for the treatment of restenosis or atherosclerosis following a strategy addressed to stabilize the atheromatous plaque.

3.3. MMP inhibitors

In addition to the regulation of MMPs at transcriptional level and by proteolytic processing, a further level of control of MMP activity involves the binding of MMPs to specific TIMPs. The four TIMPs characterized so far (TIMP-1, -2, -3 and -4) share similar structural features and, usually, their transcriptional regulation parallels to that of MMPs. Therefore, overall proteolytic activity depends on the relative concentration of the active enzymes and their inhibitors.

Because of their potential in therapeutical approaches, MMP inhibitors (natural and synthetic) have been tested in experimental models of vascular human diseases. Data from genetically altered mice (both transgenic and knockout mice) has strengthened the view that MMPs are key players in vascular pathologies. However, as these are chronic processes, long-term treatments are required and this kind of studies in animal models do not always reflect the situation in humans. Neointima formation has been shown to be increased in TIMP-1 deficient mice and, in agreement with this, broad spectrum MMP inhibitors such as GM6001 and marimastat were able to inhibit in-stent intimal hyperplasia, while batimastat and marimastat inhibited constrictive arterial remodeling after balloon angioplasty (13). However, negative results obtained in a clinical study with batimastat-coated stents indicate that non-selective MMP inhibition is not a useful therapeutical strategy for vascular disease in humans, suggesting a more complex role for MMPs in vascular remodeling. The fact that mice deficient in MMP-11 or MMP-3 exhibit augmented neointima and larger atherosclerotic lesions further supports this idea (13).

4. MMP-10 IN ATHEROSCLEROSIS

4.1. Inflammation induces endothelial MMP-10 expression

Vascular inflammation plays a key role in the onset, progression and thrombotic complication of atherosclerotic lesions (1). Inflammation heightens production of biomarkers, such as C-reactive protein (CRP), which provide information about the risk of developing cardiovascular disease. CRP is a powerful and independent predictor of myocardial infarction, stroke and vascular death in a variety of clinical settings (14). In addition, multiple studies suggest that CRP has direct pro-atherosclerotic effects on cellular functions implicated in atherosclerotic lesion formation: promotes EC activation, uptake of low density lipoproteins (LDL) by macrophages and expression of angiotensin II type 1 receptor by VSMC (15). Recently, we have shown that CRP induces endothelial MMP-1 and -10 expression (Figure 1), both at the mRNA and the protein level, without modifying the expression of other MMPs (MMP-2, -3, -7, -8, -9, -11, -12 or -13) (16). The null effect of CRP on the endothelial expression of any of the TIMPs could explain the increase in the proportion active protein/zymogen of MMP-1 and MMP-10 (16). Mitogen-activated protein kinase (MAPK) signaling pathways (extracellular-regulated kinase 1/2 [ERK1/2], p38 MAPK and c-Jun N-terminal kinase [JNK]) seem to be the main pathways mediating the effect of CRP on MMP-1 and MMP-10 production by ECs (16) and other cell types (17).

4.2. MMP-10 is expressed in the atherosclerotic vessels

In general, MMP over-expression in human plaques colocalizes with macrophages and VSMC proximal to the fibrous cap. The presence of MMP-10 in the atherosclerotic plaque has been revealed immunohisto-chemically in vascular sections from 15 advanced atherosclerotic lesions (obtained from patients with >75% stenosis undergoing carotid endarterectomy), showing intense staining in macrophage-rich areas and endothelium, co-localizing with CRP (Figure 2, A-E), while a much weaker signal has been observed in mammary artery (16). Interestingly, CRP and MMP-10 colocalize within regions previously described as rupture-prone, in areas particularly abundant in macrophages. Similarly, advanced murine atheromas from apoE$^{-/-}$ mice exhibit a marked staining for MMP-10 (Figure 2, F-G) that it is absent in the healthy vascular wall from wild-type mice. MMP-10 expression in the atherosclerotic lesion is restricted to the neointima, mainly in cells with macrophage-like morphology. Given the importance of MMPs in weakening atherosclerotic plaques (10), increased local and systemic MMP activation may contribute to the association of CRP with cardiovascular events caused by plaque complication.

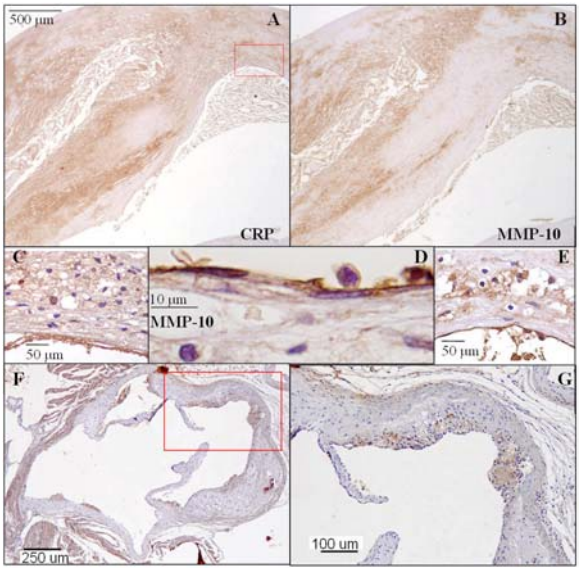

Figure 2. Representative immunohistochemical analysis of MMP-10 expression in human and murine atherosclerotic arteries. Strong immunostaining for MMP-10 (B, D, E) and CRP (A, C) was observed in advanced lesions from human carotid endarterectomy specimens, with a high degree of co-localization. Details at higher magnification show CRP and MMP-10 immunostaining in macrophage rich areas and endothelial cells (C, D, E). For a more detailed description of patients characteristics see reference 16. Panels F and G show MMP-10 staining in atherosclerotic lesions from apoE$^{-/-}$ mouse aorta, where MMP-10 appears to be localized predominantly in macrophage-rich areas of the neointima.

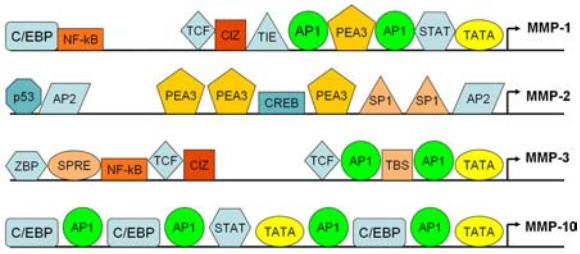

Figure 3. Regulatory elements in the promoter regions of human MMP genes. The functional activity of most of the indicated binding sites has been experimentally demonstrated. The relative positions of the different elements are not drawn to scale. Putative response elements present in MMP-10 promoter have been identified by *in silico* analysis using the TransFac software.

4.3. MMP-10 compromises vascular integrity

It has been suggested that a tightly regulated expression level of MMP-10 is required for limited matrix degradation in wound healing. MMP-10 is expressed in keratinocytes of skin wounds and it has been shown to enhance migration of cultured keratinocytes. Transgenic mice expressing a constitutively active MMP-10 mutant in keratinocytes showed a reduced deposition of new matrix and increased cell apoptosis in the wound healing epithelium (6).

MMP-10 is also over-expressed and active in tumors like lung carcinoma, prostate cancer or the earlier stages of transitional cell carcinoma of the bladder. However, unlike most MMPs, MMP-10 has not been associated with either tumor aggression or invasion, or with the clinicopathological characteristics of the tumor (18, 19). While MMP-10 has been related to wound healing and oncological processes, there are scarce reports regarding the involvement of MMP-10 in vascular pathophysiology. It has been shown that histone deacetylase 7 (HDAC7) is specifically expressed in the vascular endothelium during early embryogenesis, where it maintains vascular integrity by repressing MMP-10 expression, thus preventing ECM degradation. This extent was further proved by disrupting the HDAC7 gene in mice, which results in embryonic lethality due to a failure in EC adhesion and the consequent dilatation and rupture of blood vessels. HDAC7 represses murine MMP-10 gene transcription by associating with myocyte enhancer factor-2 (MEF2), a direct activator of MMP-10 transcription and essential regulator of blood vessel development. The adenoviral-mediated misexpression of MMP-10 in cultured human umbilical vein ECs (HUVECs) impaired the angiogenic ability of HUVECs, and the combined effect of TIMP1 knockdown and MMP-10 over-expression was very similar to the effect of HDAC7 knockdown, indicating that MMP-10 and TIMP1 could be involved in the regulation of vascular integrity (20). These observations are also in agreement with other reports suggesting that genetic variations in MMP-10 and TIMP1 genes may contribute to the pathogenesis of abdominal aortic aneurysms, a vascular disease characterized by histological signs of chronic inflammation, vascular destructive remodeling of ECM, and depletion of VSMC (21).

4.4. Circulating MMP-10 as a biomarker

Among asymptomatic subjects with CV risk factors, those with higher CRP levels (CRP > 3 mg/L) and increased cardiovascular risk (22), showed higher plasma MMP-1 and MMP-10 levels and augmented carotid intima-media thickness (IMT) (16). Raised serum MMP-10 levels are associated with both systemic inflammatory markers and increased carotid IMT, as well as with the presence of carotid plaques in a series of subjects free from clinical cardiovascular disease. The association was independent from traditional atherosclerotic risk factors, inflammatory markers (fibrinogen, hs-CRP and von Willebrand factor [vWF]) and medical therapy (23). These data suggests a close relationship between ongoing inflammatory markers and systemic proteolytic activation with subclinical atherosclerosis, and extend previous data showing that elevated CRP also predicts recurrent instability and mortality in patients with coronary disease (24).

4.5. Transcriptional regulation of MMP-10 expression

MMP gene expression is mainly regulated at the transcriptional level and many of the MMP promoters share a certain degree of similarity (Figure 3) that, however, does not help to explain different MMP expression patterns in

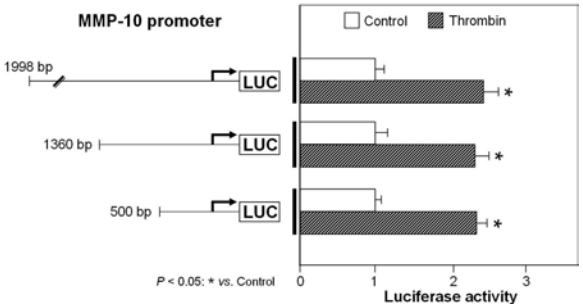

Figure 4. Thrombin induces MMP-10 transcriptional activity. MMP-10 promoter activity was evaluated in human umbilical vein endothelial cells (HUVEC) transfected with different luciferase MMP-10 promoter constructs in the presence or in the absence of thrombin (10 U/mL for 10 h). As shown serial deletion analysis of MMP-10 promoter region indicates that thrombin-mediated MMP-10 regulation is dependent on elements located within the 500 bp near the transcriptional start site.

specific cell types. For example, MMP-10 overexpression and activation by several serine proteases has been associated with capillary tubular network collapse and regression in 3D collagen matrices (25). Looking for additional inflammatory mediators able to modulate MMP-10 in human ECs, we focused on thrombin. Thrombin is a multifunctional serine protease generated at the site of vascular injury that transforms fibrinogen in fibrin, activates blood platelets and elicits multiple effects on ECs and VSMC including a proinflammatory activity. Indeed, the reorganization of the endothelial cytoskeleton induced by thrombin promotes the discharge of Weibel-Palade bodies (WPBs) that act as cellular stores for vWF and P-selectin, but also for a myriad of molecules involved in coagulation, fibrinolysis and inflammation such as factor VIII, tissue-type plasminogen activator (t-PA), interleukin-6 (IL-6), IL-8 and endothelin-1. In addition, thrombin modulates the expression of multiple genes involved in the inflammatory response among them several MMPs (26, 27).

We have generated a luciferase reported construct containing a 2 kbp DNA fragment corresponding to the region upstream the transcription start site of the MMP-10 gene. HUVEC transiently transfected with this putative promoter exhibited a 2.5-fold increase in luciferase activity upon stimulation with 10 U/ml thrombin for 12 h (Figure 4). Furthermore, deletion studies revealed that thrombin-regulation is mediated by response elements located within the 500 bp near the transcriptional start site. These results suggest that thrombin modulates MMP-10 expression, activity and secretion in ECs by a mechanism that operates primarily at transcriptional level. Further studies are needed to establish the transcription factors involved in this effect and determine its pathophysiological consequences.

5. SUMMARY AND PERSPECTIVES

The experimental findings discussed in this article clearly show the relevance of MMPs in atherosclerosis, paying particular attention to MMP-10 as a new player in the field of vascular disease. MMP-10 reveals as a potential biomarker and a relevant molecule in atherosclerotic vascular remodeling. New experiments are being conducted in genetically-modified animal models (transgenic and knockout mice) in order to improve our current knowledge of MMP-10 involvement in atherosclerosis. Further studies, both in experimental animal models and in the clinical setting, are required in order to elucidate whether systemic MMP-10 levels may represent a new biomarker of atherosclerotic risk in asymptomatic subjects, and to better define the role for MMP-10 in atherosclerosis development and plaque rupture.

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Abbreviations: MMP: matrix metalloproteinase; TIMP: tissue inhibitor of metalloproteinase; ECs: endothelial cells; VSMCs: vascular smooth muscle cells; IMT: intima-media thickness; ECM: extracellular matrix; MT-MMP: membrane-type MMP; TGFbeta: transforming growth factor beta; CRP: C-reactive protein; MAPK: mitogen-activated protein kinase; ERK1/2: extracellular-regulated kinase 1/2; JNK: c-Jun N-terminal kinase; HDAC7: histone deacetylase 7; MEF2: myocyte enhancer factor-2; WPBs: Weibel-Palade bodies; t-PA: tissue-type plasminogen activator; IL: interleukin; HUVEC: human umbilical vein endothelial cells; AP: activator proteins; C/EBP: CCAAT/enhancer-binding protein; CIZ: CAS-interacting zinc-finger protein; CREB: cAMP response-element binding protein; KRE: keratinocyte differentiation-factor responsive element; NF-κB: nuclear factor of κB; PEA3: polyomavirus enhancer-A binding-protein-3; SPRE: stromelysin-1 platelet-derived growth factor-β responsive element; STAT: signal transducer and activator of transcription; TATA: TATA-box; TBS: TEL (translocation-ETS-leukaemia) binding site; TCF: T-cell factor; TIE: transforming growth factor-β inhibitory element; ZBP: binding site for 89-kDa zinc-binding protein.

Key Words: MMPs, atherosclerosis, MMP-10, Endothelial Cells, Transcriptional Regulation, Review

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