Review

MMP-1 polymorphism and its relationship to pathological processes

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Matrix metalloproteinases (MMPs) are a family of zinc (Zn)-dependent endopeptidases that are collectively capable of cleaving virtually all extracellular matrix (ECM) substrates and play an important role in diverse physiological and pathological processes. The activity of MMPs is regulated at multiple levels. The transcriptional regulation of MMP appears to represent the key step in MMP regulation. There are diverse types of MMPs that differ structural and functionally. MMP-1 is the most ubiquitously expressed interstitial collagenase and has a prominent role in initial cleavage of the ECM. The level of MMP-1 expression can be influenced by different single-nucleotide polymorphisms (SNPs) in the promoter region. A functional polymorphism at position –1607 has been shown to alter the transcriptional activity of MMP-1 and was associated with diverse pathological processes. The aim of our review was to discuss some topics related to MMP in physiological and pathological processes, with a focus on MMP-1 polymorphism.

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1. Introduction

Extracellular matrix (ECM) macromolecules are important for creating the cellular environments required during development and morphogenesis of tissues and serves as a scaffold for normal biological functions. The matrix is basically composed of fibrous proteins such as collagen and elastin, and elongated glucoproteins such as fibronectin and laminin, whose function is to provide cell matrix adhesion. In addition, glucoaminoglycan and proteoglycan form a bed of gel, in which there are all the constituents of the matrix (Alberts 1997). The matrix comprises varying proportions of proteins and polysaccharides organised in networks, which are responsible for the morphological, functional and pathological diversity of tissues, and provide the appropriate substrate for growth and differentiation of diverse cell types (Bornstein and Sage 2002).

A family of metalloenzymes, the matrix metalloproteinases (MMPs), is largely responsible for degradation of the ECM (Kerrigan *et al*. 2000). MMPs are zinc (Zn)-dependent metallopeptidases belonging to the subfamily M10A (Barret *et al*. 2004) which are collectively capable of cleaving virtually all ECM substrates, including collagens, laminin, fibronectin, vitronectin and proteoglycans (Egeblad and Werb 2002). Like other peptidases in subclan MA(M), the peptidases of family M10 are synthesised as inactive precursors (zymogens) and their activation occurs in the tissue by cleavage of the N-terminal pro-peptide domain by other proteinases (Murphy and Knauper 1997).

MMPs have important roles in diverse physiological and pathological processes, as they regulate various cell behaviours such as angiogenesis, cell proliferation, apoptosis, alteration of cell motility, effects on the immune system and host defence, and modulation of the bioactivity

Keywords. Metalloproteinases; pathological process; polymorphism

Abbreviations used: ECM, extracellular matrix; MMP, matrix metalloproteinase; MMPIs, inhibitors of different MMPs; PEA-3, polyoma early promoter activator-3; SNP, single-nucleotide polymorphism; TIMP, tissue inhibitors of MMP; Zn, zinc

of chemokines (Cauwe *et al*. 2007). In fact, MMPs are expressed in response to specific stimuli by resident connective tissue cells as well as the major inflammatory cell types that invade the tissue during remodelling events (Birkedal-Hansen 1993).

There are diverse types of MMPs that differ structurally and functionally. MMP-1 is an important member that initially cleaves the ECM. The aim of our review was to discuss some topics related to MMP in physiological and pathological processes, with a focus on MMP-1.

2. MMP

In the MMP family, at least 24 human members have been identified till date, and these enzymes are classified according to their substrate specificity and structural similarities. MMPs are grouped into five main classes (collagenases, gelatinases, stromelysins, membrane-type and others, including matrilysin).

To be classified as an MMP, a protein must have at least the conserved prodomain and catalytic domain, which ligate the active site of Zn^{2+}. Additionally, MMPs have a flexible proline-rich hinge region and a haemopexin-like C-terminal domain, which functions in substrate recognition (with the exceptions of MMP-7, -23, and -26).

Some extra domains or short inserts can be found attached to the common structure in several subgroups of MMPs (Woessner 1998; Baker *et al*. 2002), such as transmembrane and cytosolic domains in most of the membrane-type MMPs and gelatin-binding domains that resemble similar motifs in fibronectin in MMP-2 and -9 (Ra and Parks 2007). In addition to a remarkably common 3-D structure (Massova *et al*. 1998), MMPs share a similar gene arrangement, suggesting that they arose by duplications of an ancestor gene. At least eight of the known human MMP genes (MMP-1, -3, -7, -8, -10, -12, -13 and -20) are clustered on chromosome 11 at 11q21-23. Other MMP genes are scattered among chromosomes 1, 8, 12, 14, 16, 20, and 22 (Shapiro 1998).

Several reports in recent years have demonstrated that various MMPs act on non-matrix proteins, such as cytokines, chemokines, receptors and antimicrobial peptides (Meng *et al*. 2008). Thus, MMPs should not be viewed solely as proteinases for matrix catalysis, but rather as extracellular processing enzymes involved in regulating cell–cell and cell–matrix signalling events, typically gain-of-function processing of latent proteins (Page-McCaw *et al*. 2007).

Each type of MMP participates in some normal remodelling processes such as embryonic development, post-partum involution of the uterus, bone remodelling, ovulation and wound healing (Woessner 1991). Alteration in the activity of MMPs has been related to a number of important diseases such as cartilage destruction and bone erosion in rheumatoid arthritis (Ye *et al*. 2007), osteoarthritis (Barlas *et al*. 2009), acute myocardial infarction (Koh *et al*. 2007), and in carcinogenesis (Egeblad and Werb 2002), invasion and metastasis of tumour cells (Basset *et al*. 1997; Johnsen *et al*. 1998).

The activity of MMPs is regulated at multiple levels, including conversion of proenzyme to the activated form, inhibition by tissue inhibitors of MMPs (TIMPs) and regulation of transcription.

2.1 *Activated form*

MMPs are translated as zymogens and contain a signal sequence peptide for targeting to secretory vesicles. MMPs are secreted or anchored to the cell surface, thereby confining their catalytic activity to membrane proteins or proteins within the secretory pathway or extracellular space (Ra and Parks 2007).

ProMMPs are kept in a catalytically inactive state by interaction between the thiol of the conserved prodomain cysteine residue and the zinc ion of the catalytic site, so that the prodomain covers the catalytic cleft, thereby barring an interaction with a protein substrate. The thiol–Zn^{2+} interaction must be disrupted for a proMMP to become catalytically active (Van Wart and Birkedal-Hansen 1990). The thiol–Zn^{2+} interaction can be broken by three mechanisms: (i) direct cleavage of the prodomain by another proteinase such as furin; (ii) reduction of the free thiol by oxidants or non-physiological reagents such as alkylating agents, heavy metal ions, and disulphides (Springman *et al*. 1990); and (iii) allosteric perturbation of zymogen anchored to other macromolecules, such as integrins and proteoglycans (Ra and Parks 2007). Thiol reduction and allosteric controls would lead to inter- or intramolecular autolytic cleavage of the prodomain (Ra and Parks 2007).

2.2 *Relationship between TIMP and MMP*

A family of four specific inhibitors, the TIMPs, has been described (Baker *et al*. 2002). They share substantial sequence homology and structural identity at the protein level. TIMPs have basically two structural domains: an N-terminal domain consisting of six conserved cysteine residues forming three disulphide bridges, which possesses MMP-inhibitory activity, and a C-terminal domain that also contains six conserved cysteine residues and forms three disulphide bridges (Tuuttila *et al*. 1998).

By definition, all members of the TIMP family inhibit MMP activity. This is accomplished through coordination of the Zn^{2+} of the MMP active site by the amino and carbonyl groups of the TIMP N-terminal cysteine residue. However, selective inhibition of some members of the MMPs has been observed (Stetler-Stevenson 2008).

Control over MMP and/or TIMP activity *in vivo* occurs at different levels and involves factors such as regulation of gene expression, activation of zymogens and inhibition of active enzymes by specific inhibitors. Many MMPs and TIMPs are regulated at the level of transcription by a variety of growth factors, cytokines and chemokines (Yan and Boyd 2007).

Although originally characterised by their ability to inhibit MMP activity, TIMPs have additional biological activities such as regulation of a number of cellular processes including cell growth, migration and apoptosis (Massarotti *et al*. 2002). However, despite mounting evidence that suggests direct cell signalling capacity for the TIMPs, the requirement for MMP-inhibitory activity in mediating these cellular activities of the TIMPs remains controversial (Stetler-Stevenson 2008).

2.3 *Transcriptional regulation*

The transcriptional regulation of MMP appears to represent the key step in MMP regulation since most MMP genes are expressed only when active physiological or pathological tissue remodelling takes place (Matrisian 1990; Fini *et al*. 1998).

The promoters of many MMP genes (including MMP-1, -3, -7, -9, -10, -12 and -13) encompass an AP-1 consensus element and one or two copies of the polyoma early promoter activator-3 (PEA-3) element; the former interacts with the Fos and Jun families and the latter with the Ets family of transcription factors. A large number of studies have demonstrated that these two *cis*-elements play an important role in the regulation of MMP gene expression, both at the basal level and in response to various stimuli including phorbol ester, cytokines and growth factors (Angel *et al*. 1987; Gaire *et al*. 1994).

Spontaneous sequence variations in the promoters of MMPs could influence critical steps in binding to transcription factors or overall transcriptional efficiency, which results in discrepancy in the expression of MMPs in different individuals. In fact, genetic polymorphisms can alter the binding sites of some functional regulating factors and influence the level of MMP expression.

3. MMP-1

MMP-1 is the most ubiquitously expressed interstitial collagenase, a subfamily of MMPs that cleaves stromal collagens. It is also called collagenase-1 or peptidase M10.001 in the MEROPS classification, and has a prominent role in collagen degradation.

MMP-1 is a major proteinase of the MMP family that specifically degrades type I collagen, which is a major component of the extracellular matrix, as well as other fibrillar collagens of types II, III, V, IX (Ziober *et al*. 2000; Kerkela and Saarialho-Kere 2003) and X at neutral pH (Vincenti *et al*. 1996). As these collagen types are the most abundant proteins in the body, MMP-1 is critical for modelling and remodelling of the extracellular matrix (Vincenti *et al*. 1996).

The MMP-1 gene is localised on chromosome 11q22 and expressed in a wide variety of normal cells, such as stromal fibroblasts, macrophages, endothelial and epithelial cells, and in various tumour cells (Brinckerhoff *et al*. 2000). It is constitutively expressed at low levels under normal physiological conditions; however, its expression may increase markedly in pathological conditions. Increased expression of MMP-1 has been associated with a poor prognosis in several cancers such as colorectal cancer (Woo *et al*. 2007), bladder cancer (Tasci *et al*. 2008), oral carcinoma (Shimizu *et al*. 2008; Nishizawa *et al*. 2007), nasopharyngeal carcinoma (Nasr *et al*. 2007), hip arthroplasty (Godoy-Santos *et al*. 2009), implant failure (Leite *et al*. 2008), and occlusive peripheral arterial (Flex *et al*. 2007) and coronary artery disease (Horne *et al*. 2008).

4. Polymorphism of MMP-1

Polymorphism represents natural sequence variants (alleles), which may occur in more than one form. These appear in at least 1% of a population and are considered biologically normal (Thompson *et al*. 1991). Approximately 90% of DNA polymorphisms are single-nucleotide polymorphisms (SNPs) due to a single base exchange (Ra and Park 2007). Although the majority of DNA polymorphisms are probably functionally neutral, a proportion of them can exert allele-specific effects on the regulation of gene expression or function of the coded protein, which underlie individual differences in various biological traits and in susceptibility to disease (Ye 2000).

Recently, DNA polymorphisms have been found in the promoter region of several MMPs; these promoter regions control gene transcription. Such genetic polymorphisms are important because they can be used as biomarkers that herald various diseases and thus facilitate early intervention in patients at high risk.

The level of MMP-1 expression can be influenced by different SNPs in the promoter region. An insertion/deletion of guanine at position –1607 has been identified in the promoter of the human MMP-1 gene and creates two different alleles: one having a single guanine (1G) and the other having two guanines (2G) (Rutter *et al*. 1998). Promoter assays have indicated that this is a functional polymorphism. The two guanines together with an adjacent adenosine create a core-binding site (5′-GGA-3′) for the Ets family of transcription factors, leading to a higher

expression of MMP-1. It has been demonstrated that the 2G allele binds substantially larger amounts of recombinant Ets-1 transcription factor and has significantly higher transcriptional activities than the 1G promoter in normal fibroblasts and melanoma cells (Rutter *et al*. 1998).

This polymorphism has been associated with susceptibility to diverse diseases (table 1). The overexpression of MMP-1 is implicated in tumour invasion and metastasis (Rutter *et al*. 1998). The above findings indicate that patients carrying the 2G allele are predisposed to the development of several types of cancers and/or their rapid progression (Ye 2000; Cao and Li 2006; Nishizawa *et al*. 2007; Tasci *et al*. 2007; Woo *et al.* 2007), degenerative disc disease (Song *et al*. 2008), endobronchial tuberculosis (Kuo *et al*. 2008), arthritis (Massarotti *et al*. 2002), arteriosclerosis (Orbe *et al*. 2003), periodontitis (de Souza *et al*. 2003), failure in osseointegration of implants (Leite *et al*. 2008; Santos *et al*. 2004), coronary heart disease in diabetes mellitus patients (Drzewoski *et al*. 2008); and other pathological conditions. The 2G allele in polymorphism –1607 of MMP-1 potentially increases the level of protein expression. This mechanism provides the molecular basis for a more intense degradation of ECM, which is important in tissue remodelling and repair during development and inflammation.

On the basis of the some studies, no significant association has been found for isolated MMP-1 polymorphisms, while the specific MMP haplotype may contribute to diverse pathological processes. Haplotype is a combination of alleles at multiple loci which are transmitted together on the same chromosome. For example, Su *et al.* (2006) put together the MMP-1 –1607 1G/2G, MMP-3 –1171 5A/6A,

Table 1. Polymorphisms in the –1607 MMP-1 gene associated with some diseases

Polymorphism-allele	Disease	Population number of test group/ control group (country)	Reference
2G	Implant failure	44 / 60 (Brazil)	Leite *et al* 2008
2G	Severe chronic periodontitis	102 / 98 (Turkey)	Pirhan *et al* 2008
2G	Brain astrocytoma	221 / 266 (China)	Lu *et al* 2007
2G	Peripheral arterial occlusive disease	157 / 206 (Italy)	Flex *et al* 2007
2G	Bladder cancer	102 / 94 (Turkey)	Tasci *et al* 2007
2G	Colorectal cancer	185 / 304 (Korean)	Woo *et al* 2007
2G	Oral carcinoma	170 / 164 (Japan)	Nishizawa *et al* 2007
2G	Oral carcinoma	96 / 120 (China)	Cao and Li 2006
2G	Colorectal cancer	201 (France)	Zinzindohoué *et al* 2005
2G	Glioblastoma	81 / 57 (USA)	McCready *et al* 2005
2G	Colorectal cancer	60 / 164 (Italian)	Ghilardi *et al* 2001
2G	Ovarian cancer	163 (Japan)	Kanamori *et al* 1999
1G/2G	Nasopharyngeal carcinoma	174 / 171 control (Tunisia)	Nasr *et al* 2007
1G	Degenerative disc disease	378 / 122 (Southern China)	Song *et al* 2008
1G	Endobronchial tuberculosis	38 of 101 pulmonary TB (Taiwan)	Kuo *et al* 2008
1G	Oral cancer	156 / 141 (Greece and Germany)	Vairaktaris *et al* 2007
1G	Sclerosing cholangitis	165 / 346 (Norway)	Wiencke *et al* 2004
2G/2G - A/A (MMP-1 – IL-8)	Tongue carcinoma	69 / 91 (Japan)	Shimizu *et al* 2008
2G/1G - 6A/5A (MMP-1 – MMP-3)	Coronary artery disease	1967 / 1122 (USA)	Horne *et al* 2007
2G/2G - 6A/6A (MMP-1 – MMP-3)	Colorectal cancer	302 / 568 (France)	Liévre *et al* 2006
1G-6A-82A-1082G(MMP-1-MMP3 - MMP12)	Lung cancer	2014 / 1323 (USA)	Su *et al* 2006

MMP-12 –82 A/G and MMP-12 1082 A/G polymorphisms, which suggested that the *1G-6A-82A-1082G* haplotype may be associated with a higher risk of lung cancer among never smokers. In fact, carcinogenesis, like most diseases, is a multicellular and multistage process, and different genes that metabolise different types of proteins may be involved at various stages.

Despite the fact that –1607 is the most important MMP-1 polymorphism, other polymorphic sites in MMP-1 have been described. Polymorphism at the –519 position consists of a guanine to adenine substitution (Jurajda *et al*. 2002). The authors observed linkages between these two polymorphisms: the A allele in –519 was more often found with the 2G allele in –1607. Nho *et al*. (2008) suggested a protective role of the MMP-1 –1607 G allele and MMP-1 –519 A allele together against increase of body mass index in the Korean population. Our group showed that haplotypes arranged at these polymorphic sites as alleles and genotypes were associated with dental implant loss, while A–519G polymorphism individually does not show a significant relationship with implant loss. Haplotype allele GGG in the successful implant groups was only 12.5%, while in the implant failure group, 28.8% were GGG. The haplotype genotype AG/GGG was observed in 11.7% of individuals with successful implants, and in 35.6% with failed implants (Leite *et al*. 2008). This suggests that haplotype combinations of polymorphisms in the MMP-1 gene can influence the osseointegration process, suggesting that MMP-1 gene variation contributes to interindividual variability in osseointegration.

Therefore, haplotype effects may provide more complete and reliable information than the single polymorphism analysis, which may contribute only partially to the MMP pathway. It appears that there are at least two reasons that might explain why a phenotype can be associated with a haplotype but not with the individual polymorphisms that make up the haplotype. First, a functional effect on gene expression can be dependent on the interaction between two or more polymorphisms (Terry *et al*. 2000); second, haplotypes generally have a higher probability than individual polymorphisms of showing useful linkage disequilibrium with an unknown casual variant (Garner and Slatkin 2003). However, a complete explanation depends on an analysis to characterise the nuclear proteins involved and their interactions.

Correlations between –1607 SNP in MMP-1 and diverse diseases have been described by several studies. However, some representative studies show conflicting results, since this SNP generally displays ethnic variations (Ju *et al*. 2007). To determine whether a true difference exists between the genotype distributions in different races, Ju *et al*. (2007) compared the genotype distribution of the MMP-1 –1607 SNP in different populations from Korea, Japan, Taiwan, the USA, the UK, France, Italy, Poland and Brazil. The results showed that the allele frequencies of MMP-1 –1607 SNP in Asians showed no significant difference, but significant differences between allele frequencies were seen in white populations (Ju *et al*. 2007), highlighting that ethnic variations exist between Asians and Caucasians.

Therefore, in order to clarify the contribution of genetic polymorphisms to the development and progression of disease, it is important analyse the genotype distribution and allele frequency between diverse races, which would help to confirm the positive correlation reported in different populations.

Excessive or inappropriate expression of MMP-1 may contribute to the pathogenesis of tissue-destructive processes in a wide variety of diseases. The discovery of genetic markers related to various pathological processes could be clinically invaluable in identifying susceptible individuals. Some active, low molecular-weight inhibitors of different MMPs (MMPIs) have been developed. These MMPIs have been effective in controlling cancer progression in animals, but not in human patients with cancer (Zucker and Vacirca 2004). MMPIs of MMP-1 have not yet been evaluated. Nevertheless, the development of individual therapeutics with MMPIs in order to provide successful treatment appears promising.

It is important to consider that the effect of an isolated SNP could be buffered by polymorphisms present in the same or another gene that participates in the complex network of interactions causing disease in different ethnic groups. To do this, it is important examine studies involving different diseases and ethnic groups to better understand the molecular influence of each polymorphism.

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