Matrix metalloproteinases: implication in vascular matrix remodelling during atherogenesis

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1. The matrix metalloproteinases are a family of at least 16 zinc-dependent endopeptidases possessing catalytic activity against extracellular matrix components. Some members of this family have been implicated in vascular matrix remodelling in the pathogenesis of atherosclerosis.

2. A common, naturally occurring variant has been identified in the promoter of the stromelysin gene with one allele having a run of five adenosines (5A) and the other having six adenosines (6A). Functional analyses have shown that the 6A allele has a lower promoter activity than the 5A allele, which is probably attributable to preferential binding of a putative transcriptional repressor protein.

3. In patients with coronary artery disease, the 6A allele has been found to be associated with progression of atherosclerosis assessed by sequential quantitative angiography.

4. In conclusion, the matrix metalloproteinases may be over-expressed in certain locations in atherosclerotic plaques, which might contribute to local destruction of connective tissue and thus plaque rupture. In the majority of lesional areas, however, matrix synthesis is likely to outstrip matrix degradation, because matrix accumulation is a major feature of most atheromas. This imbalance favoring matrix deposition is likely to be exacerbated in individuals with the 6A6A genotype in whom stromelysin expression is lower due to the weaker stromelysin promoter.

INTRODUCTION

Coronary artery disease and stroke are responsible for the majority of deaths in Western countries. These diseases are the consequences of atherosclerosis whose pathogenesis involves extensive vascular remodelling over a number of years, through the deposition of lipid, migration and proliferation of macrophages and smooth muscle cells, and accumulation of extracellular matrix proteins. A typical atheromatous plaque contains a core of lipid and a fibrous cap. However, pathological studies have revealed a wide variation in the morphology of atherosclerotic lesions [1]. At one end of the spectrum are the atherosclerotic plaques with a thick fibrous cap containing a substantial amount of extracellular matrix. The bulk of the plaque protrudes into the lumen, and restricts blood flow. At the other end of the spectrum are the lesions with a thin cap and a relatively well-preserved lumen. This type of plaque is less resistant to mechanical stress and more prone to rupture, the commonest cause of acute coronary ischaemic events.

The amount and distribution of extracellular matrix in atherosclerotic plaques will, therefore, have a significant impact on the outcome of the disease. The extent to which extracellular matrix proteins accumulate in the plaque will depend on the balance between their synthesis and degradation during atherogenesis. A number of studies in the last few years suggest that the matrix metalloproteinases (MMPs) play an important role in the degradation of lesional vascular matrix and that the levels of their expression influence plaque stability as well as disease progression.

MMPs

The MMPs constitute a family of 16 or more zinc-dependent endopeptidases which are generally expressed at low levels in normal adult tissue but are up-regulated during normal and pathological remodelling processes. All MMPs share the following common features that allow them to be classified as a family: (i) they degrade extracellular matrix components; (ii) they are secreted in a latent proform

Key words: atherosclerosis, matrix metalloproteinases, polymorphism, stromelysin.
Abbreviations: MMP, matrix metalloproteinase; MT-MMP, membrane-type matrix metalloproteinase; PG, proteoglycan; TIMP, tissue inhibitors of metalloproteinases.
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(zymogen) requiring activation for proteolytic activity; (iii) they contain Zn$^{2+}$ at their active sites and require Ca$^{2+}$ for stability; (iv) they function at neutral pH; and (v) they are inhibited by specific tissue inhibitors of metalloproteinases (TIMPs) [2].

Between them the MMPs can degrade all components of the extracellular matrix, but each enzyme has its substrate preferences (Table 1) [3, 4]. Based on their domain structures and substrate specificity, the MMPs are classically divided into three groups, i.e. the interstitial collagenases, the gelatinases and the stromelysins. Recently a new group of MMPs has been discovered, which are named membrane-type MMPs (MT-MMPs) because, instead of being soluble, the enzymes in this group contain a transmembrane domain and thus attach to the surface of the cell [5].

The amino acid sequences of MMPs deduced from cDNA data show approximately 70% similarity between the enzymes within a group, and about 50% similarity among different groups [6]. Apart from matrilysin, which is relatively small, each of the collagenases and stromelysins consists of five domains, including a signal peptide, a propeptide containing a cysteine residue that is bonded to Zn$^{2+}$ at the active site and is lost on activation, a catalytic domain that contains the catalytic machinery including the Zn$^{2+}$ binding site, a so-called 'hinge region' that bridges the catalytic domain and the COOH-terminal domain, and a haemopexin- or vitronectin-like COOH-terminal domain that appears to be responsible for conferring substrate specificity [7]. The two gelatinases also have this five-domain structure, but within their catalytic domain there are three fibronectin type II repeats which are thought to facilitate binding of gelatinases to their substrate [8, 9]. The MT-MMPs possess not only the five domains common to other MMPs, but also a unique transmembrane domain which anchors MT-MMPs to the cell surface [5].

All collagenase and stromelysin genes are located in a gene cluster on the long arm of chromosome 11, with the exception of stromelysin-3 gene which has been mapped to chromosome 22 [10–15]. The two gelatinase genes reside respectively on chromosomes 16 and 20, whereas the MT-MMP-1 gene is situated on chromosome 14 [8, 9, 16]. Comparison of the MMP genes has revealed a high degree of sequence similarity, with each of the collagenase and stromelysin genes containing ten exons and nine introns spanning 8 to 12 kbp of DNA, with the exception of matrilysin gene that lacks four exons corresponding to exons 7–10 of other genes in these two groups [17–19]. Compared with the genes for the collagenases and stromelysins, those encoding gelatinases A and B are considerably larger (26–27 kbp) and contain three additional exons which encode the three fibronectin-like inserts [8, 9].

The promoter regions of the MMP genes also share some common features. The genes encoding interstitial collagenase, gelatinase B, stromelysin, stromelysin-2, metalloelastase and matrilysin all contain one or more copies of the activator protein-1 binding site and the polyomavirus enhancer A-binding protein-3 site, which have been found to be important in the regulation of MMP gene expression [8, 9, 19–22]. The positions of these cis-elements relative to the transcription start site,

### Table 1. The matrix metalloproteinases (MMPs). Abbreviations: PG, proteoglycan; PMN, polymorphonuclear.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>Chromosomal location of MMP gene</th>
<th>Substrate</th>
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</thead>
<tbody>
<tr>
<td>Collagenases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial collagenase (fibroblast-type collagenase, MMP-1)</td>
<td>11q22</td>
<td>Collagen types I, II, III, (III &gt; &gt; I), VI, X, gelatins, PG</td>
</tr>
<tr>
<td>Neutrophil collagenase (PMN-type collagenase, MMP-8)</td>
<td>11q21</td>
<td>Same as interstitial collagenase (I &gt; &gt; III)</td>
</tr>
<tr>
<td>Collagenase-3 (MMP-13)</td>
<td>11q22</td>
<td>Gelatin, collagen types IV, V, VII, X, and XI, elastin, fibronectin, PG</td>
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<tr>
<td>Gelatinases</td>
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<tr>
<td>Gelatinase A (72 kDa Type IV collagenase, MMP-2)</td>
<td>16q21</td>
<td>Gelatin, collagen types IV, V, VII, X, and XI, elastin, fibronectin, PG</td>
</tr>
<tr>
<td>Gelatinase B (92 kDa Type IV collagenase, MMP-9)</td>
<td>20q11-q13</td>
<td>Gelatin, collagen types IV, V, elastin, PG</td>
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<tr>
<td>Stromelysins</td>
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<tr>
<td>Stromelysin (MMP-3)</td>
<td>11q22</td>
<td>PG, fibronectin, laminin, elastin, gelatin, collagen types II, IV, V, IX and X</td>
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<tr>
<td>Stromelysin-2 (MMP-10)</td>
<td>11q22</td>
<td>Same as stromelysin I</td>
</tr>
<tr>
<td>Stromelysin-3 (MMP-11)</td>
<td>22q11</td>
<td>Gelatin, fibronectin, PGs</td>
</tr>
<tr>
<td>Matrilysin (PUMP-I, MMP-7)</td>
<td>11q21-q22</td>
<td>Gelatin, fibronectin, laminin, collagen type IV, PG</td>
</tr>
<tr>
<td>Metalloelastase (MMP-12)</td>
<td>11q22-22</td>
<td>Elastin</td>
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<td>Membrane-type MMPs</td>
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<tr>
<td>MT-MMP-1 (MMP-14)</td>
<td>14q11-q12</td>
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<td>MT-MMP-2 (MMP-15)</td>
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<td>MT-MMP-3 (MMP-16)</td>
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<td>MT-MMP-4 (MMP-17)</td>
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<tr>
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<tr>
<td>MMP-19</td>
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however, differ between one gene and another, which may partly account for the differences in their expression patterns. The promoter of the gelatinase A gene lacks a TATA box and the activator protein-1 and polyomavirus enhancer A-binding protein-3 sites, but contains two copies of a GC box for binding of transcription factor SP1. This unique promoter profile of the gelatinase A gene might explain the fact that gelatinase A is constitutively expressed whereas other MMPs are mainly inducible [8].

Specializing in degrading extracellular matrix components, the MMPs are believed to play a crucial role in connective tissue remodelling in a variety of physiological processes such as angiogenesis and wound healing. To maintain the normal balance of tissue turnover, it is important that the activity of these enzymes is under tight control. This operates on at least three levels: transcription, activation of latent proenzymes, and inhibition of proteolytic activity by TIMPs. Disruption of the normal control in any of these steps can potentially lead to pathological consequences resulting from excessive accumulation or over-degradation of the extracellular matrix. It has been found that unregulated expression of MMPs is partially the cause of the accelerated breakdown of extracellular matrix in arthritic disease, tumour invasion and metastasis while, on the other hand, inadequate production of these enzymes is associated with the excessive accumulation of connective tissue in systemic sclerosis [3, 4, 23]. Recent studies have also indicated a connection between the MMPs and matrix remodelling in the pathogenesis of atherosclerosis [24–33].

VASCULAR MATRIX

The extracellular matrix is a major component of the normal blood vessel wall, accounting for up to 60% of the intimal volume. This matrix is predominantly composed of various types of proteoglycans and collagens, but also contains smaller amounts of elastin, fibronectin, laminin and a variety of plasma components [1, 34].

Proteoglycan (PG)

Proteoglycans are a diverse group of macromolecules, each of which possesses one or more linear glycosaminoglycan chains attached to serine residues along a core protein [35]. There are four types of proteoglycans present in the extracellular matrix of the blood vessel wall: chondroitin sulphate PG, heparan sulphate PG, dermatan sulphate PG and keratan sulphate PG, all of which are likely to be synthesized by endothelial and smooth muscle cells [34, 35]. In atherosclerotic lesions, there is a significant increase in the content of chondroitin sulphate and dermatan sulphate PGs can bind plasma low-density lipoprotein and thus enhance its retention in the intima [37, 38].

Collagen

Collagens are a large family of related proteins, consisting of at least 15 different types of collagen molecule [39]. Typically, each fibrillar collagen comprises three polypeptide chains (so-called x chains) wound around each other to confer the characteristic feature of a long, stiff, triple helical structure [40]. The majority of collagen in the normal arterial wall exists in the form of two fibrillar collagens, i.e. types I and III, which are thought to be produced by smooth muscle and endothelial cells. The amounts of both types of collagen significantly increase in advanced atherosclerotic lesions. In addition to types I and III, collagen types IV, V and VI are also found in the normal arterial wall but in a much smaller amount, accounting for only 0.5–1.0% of the total arterial collagen content [34].

Elastin

Elastin is the main component of the elastic fibres which give blood vessels their elasticity. Elastin molecules are secreted into the extracellular space where they become highly cross-linked, and then assemble with microfibrils into elastic fibres on the cell surface [39]. The normal vascular wall contains a substantial amount of elastin, which is mainly located in the media and the musculoelastic layer of the intima [34]. The content of elastin increases in advanced atherosclerotic lesions, but integration of the newly synthesized protein into a functional elastic fibre might be impaired [36, 41]. In addition, the elastic fibres in atherosclerotic lesions are split or frayed, and often appear to be closely associated with lipid and calcium deposits [42].

Other proteins

Fibronectin is a high-molecular-mass, multifunctional, adhesive glycoprotein and is present on cell surfaces, in extracellular matrices and in blood [39]. Laminin is another major non-collagenous glycoprotein. Along with heparan sulphate PG and type IV collagen, laminin is a major component of the basement membrane which underlies the endothelium and surrounds each smooth muscle cell [43]. Fibronectin and laminin are present in the extracellular matrix of normal intima, and are increased in atherosclerotic lesions [44, 45]. It has been suggested that fibronectin may induce neoointima formation by promoting smooth muscle cell migration, as well as monocyte and T-lymphocyte recruitment [46].
VASCULAR MATRIX REMODELLING

Connective tissue remodelling, involving the synthesis and degradation of matrix components, is an important physiological process associated with the maintenance of blood vessel integrity. As a functional component of the circulatory system, the blood vessel is under continual mechanical stress. In response to such haemodynamic conditions, the vessel wall is continually remodelling to repair and replace proteins that have become worn. It has been estimated that extracellular turnover of collagen in the normal adult canine cardiovasculature is approximately 0.6% per day [47].

The striking difference in the vascular structure between normal and atherosclerotic arteries suggests that atherogenesis involves extensive vascular remodelling. As accumulation of extracellular matrix is a major characteristic of the atherosclerotic lesion, it is likely that overall the synthesis of matrix proteins outstrips their degradation during atherogenesis. However, the rate of synthesis and degradation could vary between different lesional locations and the balance might possibly tip from one side to the other at different stages of the disease, as discussed below.

Matrix degradation and cell migration

It is widely accepted that atherosclerosis is initiated by chemical (e.g. irritants in tobacco smoke) and/or mechanical (e.g. shear stress in hypertension) injury to the endothelium, followed by trans-endothelial infiltration of circulating monocytes into intima where they become activated and elaborate a variety of cytokines and growth factors, such as platelet-derived growth factor and epidermal growth factor. In response to these stimuli, vascular smooth muscle cells migrate from the media to the intima and undergo proliferation [48]. For both the recruitment of monocytes and migration of smooth muscle cells, matrix degradation is a prerequisite, because in such manoeuvres, the cells have to traverse the extracellular barriers including the basement membranes (consisting of collagen type IV, laminin and heparan sulphate PGs) underlying the endothelium and surrounding each smooth muscle cell, as well as a dense mesh of interstitial PGs and collagen [43, 49].

Matrix deposition and plaque growth

Some growth factors and cytokines induce production of extracellular matrix proteins largely by smooth muscle cells. Although matrix deposition enlarges intimal volume, at the early stages of disease the lumen is well-preserved due to a phenomenon referred to as 'compensatory enlargement'; namely, the growth of the atherosclerotic plaque occurs by outward, abluminal expansion to accommodate the increasing intimal volume. Continuing matrix accumulation, however, will eventually outweigh the compensatory potential of the vessel and stenosis becomes inevitable [1, 48].

Matrix degradation and plaque rupture

Matrix accumulation may not be uniform across the entire atherosclerotic lesion. Plaque rupture, which is the commonest cause of acute ischaemic symptoms, is frequently found to correlate with loss of extracellular matrix at certain locations, often in the shoulder areas of the plaque. Focal destruction of extracellular matrix renders the plaque less resistant to the mechanical stresses imposed during systole and therefore vulnerable to rupture [24, 50].

Matrix deposition and fibrotic organization of mural thrombi

Plaque rupture exposes pro-coagulatory substances such as collagen and tissue factor to the local circulation and triggers the clotting cascade, leading to intraluminal and/or intraintimal thrombosis. While some thrombi are occlusive and contribute to acute ischaemic syndromes, many are small and can become fibroblastically organized. Fibrotic organization of thrombi involves migration of smooth muscle cells into the clot where they lay down various extracellular matrix proteins. Recurrent minor fissures with subsequent thrombus organization is an important mechanism contributing to progression of the atherosclerotic lesion [51].

MMPs AND VASCULAR MATRIX REMODELLING

In vitro studies suggest that MMP activity is required for the migration of smooth muscle cells. Using a Boyden chamber to study the ability of rat vascular smooth muscle cells to degrade a barrier of reconstituted basement membrane as they migrated towards a chemoattractant, namely platelet-derived growth factor B/B, Pauly et al. [49] showed that smooth muscle cells in a proliferating state readily migrated across the basement membrane barrier and this ability was inhibited by synthetic peptides that inhibited MMP activity. By Northern blotting and zymographic analyses, they found that gelatinase A was the only detectable MMP expressed and secreted by these cells, and that antisera capable of selectively neutralizing gelatinase A inhibited cell migration across the barrier. Newby et al. [43] studied rabbit smooth muscle cells and reported very similar findings.

There is evidence suggesting that MMP activity also contributes to destruction of connective tissue in the atherosclerotic lesion, leading to surface disruption. Plaque rupture commonly occurs in its shoulder regions where there is often accumulation
of macrophages that are probably derived from monocytes [52, 53]. Using in situ hybridization, Henney et al. [24] detected the presence of stromelysin-1 (MMP-3) transcripts in coronary atherosclerotic lesions, which were co-localized with large clusters of lipid-laden macrophages in the shoulder areas of the plaques. By in situ hybridization and immunohistochemistry, other researchers have detected the expression of several other MMPs including interstitial collagenase (MMP-1), gelatinase B (MMP-2), matrilysin (MMP-7) and metalloelastase (MMP-12) by macrophages located at the borders of the lipid core adjacent to fibrous caps and shoulder areas [25, 29, 30]. Galis et al. studied the expression of several MMPs concurrently and found that atherosclerotic plaques and lesion-free arteries had different patterns of MMP expression [26, 27]. In non-atherosclerotic arteries, gelatinase A together with TIMP-1 and TIMP-2 were found to be expressed by smooth muscle cells in all layers of the artery whereas gelatinase B, interstitial collagenase and stromelysin were not detected by the immunohistochemical method used. In contrast, atherosclerotic lesions showed immunoreactivity of all MMPs and TIMPs tested, with interstitial collagenase, gelatinase B and stromelysin being localized to macrophages, lymphocytes, smooth muscle cells and the endothelium in the fibrous cap and shoulders of the lesions. The regions expressing interstitial collagenase, gelatinase B and stromelysin also exhibited gelatinolytic and caseinolytic activity, suggesting that at least some of these enzymes were in their active form.

These studies suggest that matrix degradation may outstrip synthesis at certain locations in some atheromas, predisposing them to plaque rupture. In the majority of lesional areas, however, the balance between synthesis and degradation is likely to favour the former since there is a gain in the contents of matrix in all atheromas. This view is supported by the recent findings of Tyagi et al. [28] who studied the levels of MMPs in relation to the contents of the extracellular matrix in normal and atherosclerotic arteries and showed that, weight-for-weight, atherosclerotic vessels contained more collagen and PGs but had lower collagenolytic and elastinolytic activities than normal vascular tissues. There is also evidence to suggest that an imbalance favouring matrix deposition contributes to restenosis after angioplasty and endarterectomy [31].

**GENETIC VARIATION IN MMP-3 GENE**

Atherosclerosis is a multifactorial disorder resulting from the combined effects of common variation in a constellation of genes and a wide range of environmental factors. The epidemic of atherosclerosis-related diseases over the last few decades has been triggered by changes in lifestyle such as cigarette smoking and high dietary fat intake. However, different individuals respond to such environmental challenges in different ways mainly because of differences in the genes they have inherited [54]. A number of genetic variations at different loci have been detected and shown to be associated with higher risks of atherosclerosis and/or its intermediate traits. For example, several genetic polymorphisms in the fibrinogen gene cluster have been reported to be associated with differences in the plasma fibrinogen level, elevation of which is a strong risk factor for coronary artery disease [55].

Since the MMPs were implicated in atherogenesis, we recently carried out a genetic study to address whether sequence variation occurred naturally in the stromelysin (MMP-3) gene and, if so, what impact this might have on the expression or activity of the enzyme and on the development and progression of atherosclerosis [56]. Using the PCR-SSCP (polymerase chain reaction–single-strand conformation polymorphism) technique, a variant was detected in the 5' flanking region of the gene, arising from an insertion/deletion of an adenosine (A) at position approximately 1600 bp upstream from the start of transcription which results in one allele having a run of 6As and the other 5As.

Reporter gene constructs were then made in which a stromelysin promoter sequence with either 5A or 6A at the polymorphic site was cloned upstream of the chloramphenicol acetyltransferase reporter gene. Transient transfection experiments showed an allele-specific difference in promoter strength: reporter gene expression driven by the 5A allelic promoter was found to be approximately 2-fold greater than reporter gene expression directed by the 6A allelic promoter. The difference was consistently seen in two different cell types, i.e. human foreskin fibroblasts and rat vascular smooth muscle cells. Electrophoretic mobility shift assay and DNase I footprinting assay revealed the binding of one of more nucleoprotein(s) to the 5A/6A polymorphic site. The binding of one of these nuclear factors was more readily detectable in assays using a probe corresponding to the 6A allele than in assays using a probe corresponding to the 5A allele, suggesting that the difference in promoter strength between the two alleles as shown in the transient transfection experiments might be attributed to preferential binding of a transcriptional repressor protein to the 6A allelic promoter. Replacing the 5A/6A sequence with a random DNA sequence abolished the DNA–protein interaction in electrophoretic mobility shift assays, and resulted in increased reporter gene expression in transiently transfected cells [57].

Seventy-two men with coronary heart disease were genotyped using allele-specific oligonucleotide melting methods [56]. These men were participants in the St Thomas' Atherosclerosis Regression Study and were randomized to receive usual care (UC), dietary intervention (D), or diet plus cholestyramine (DC), with angiography at baseline and at approximately 39 months. In these patients the frequency of
the 6A allele was 0.51 (95% confidence interval 0.43–0.59) and was not significantly different from that in a sample of 354 healthy U.K. men. In the UC group, patients who were homozygous for the 6A allele showed greater progression of atherosclerosis than those with other genotypes: the minimum absolute width of coronary segments decreased by 0.04 (SEM 0.10) mm for 5A5A, 0.20 (0.07) mm for 5A6A, and 0.67 (0.19) mm for 6A6A ($P < 0.01$). The findings were similar but slightly less significant for the change in mean absolute width of coronary segments ($P < 0.05$). No significant associations were seen in patients in the D or DC groups. In data pooled from the three treatment groups, the 6A6A genotype was significantly associated with greater progression of coronary atherosclerosis in patients with baseline percentage diameter stenosis <20% ($P < 0.05$), but not in those with baseline percentage diameter stenosis ≥20%. These findings have recently been confirmed in an independent study on 494 patients with coronary heart disease (de Maat et al., unpublished work).

Based on these observations, a putative model is proposed to explain how the stromelysin polymorphism may affect progression of atherosclerosis. One of the major characteristics of atherosclerotic lesions is the accumulation of extracellular matrix proteins. This suggests that connective tissue turnover during atherogenesis favours the deposition of matrix: synthesis outweighs degradation. In individuals with the 6A6A genotype, this will be exacerbated because there will be a decrease in stromelysin expression due to the weaker stromelysin promoter. Consequently, extracellular matrix deposition in these individuals will be greater than in other genotypes where the activity of the stromelysin gene promoter is higher. Progression of atherosclerotic lesions will thus be more rapid in 6A homozygotes (Fig. 1).

**CONCLUSIONS**

Research over the last few years strongly suggests that the MMPs play an important role in vascular remodelling associated with atherogenesis. In addition, the MMPs have also been implicated in other biological processes relevant to the disease pathogenesis, such as platelet aggregation and activation of growth factors [58, 59]. However, more studies are required in order to understand the precise timing and location of expression of these enzymes during the evolution of atherosclerotic lesions, and how their expression is modulated by various stimulatory agents such as platelet-derived growth factor and epidermal growth factor which are likely to have an impact on the balance between connective tissue deposition and degradation during atherogenesis. It is also important to explore the possible inter-individual differences in these issues resulting from different genotypes, because such differences may affect the prognosis of the disease and the response to treatment.

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**During atherogenesis**

**5A5A or 5A6A**

- Collagens
- Proteoglycans
- Stromelysin-1
- Matrix synthesis
- Matrix degradation
- Lesion less fibrotic and occlusive
- Lesion progression slower

**6A6A**

- Collagens
- Proteoglycans
- Stromelysin-1
- Matrix synthesis
- Matrix degradation
- Lesion more fibrotic and occlusive
- Lesion progression more rapid

*Fig. 1. Effect of stromelysin polymorphism on progression of atherosclerosis: model for functional outcome*
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