

## Matrix Metalloproteinases in Coronary Artery Disease: A Review

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**ABSTRACT** Atherosclerosis plays an important role in coronary artery disease (CAD). The atherosclerotic plaque progression occurs through structural changes of the myocardium leading to accumulation of smooth muscle cells, lipids, extra cellular matrix (ECM) proteins etc. in the intima of the coronary artery. Several proteinases are implicated in ECM degradation among which matrix metalloproteinases (MMPs) form the most important enzymes, which are regulated by a variety of physiological signals like growth factors, cytokines etc. These are multi-domain proteins and are regulated by TIMPs. This review focuses on the members of MMP family and their genetic variants in relation to the pathology of CAD. Functional polymorphisms in the MMP genes (MMP-1, MMP-3 and MMP-9) contribute to the interindividual differences in susceptibility and /or progression of CAD.

### INTRODUCTION

Atherosclerosis, the underlying pathology of coronary artery disease (CAD), is a common multi factorial disorder with both genetic and environmental components. Atherosclerosis begins early in life and its evolution usually occurs slowly over decades. The atherosclerotic lesion occurs as an accumulation of lipoprotein particles in the intima of the coronary artery and evolves to fibrous plaque containing smooth muscle cells, lipids and fibrous tissue consisting predominantly of extra cellular matrix proteins. The principal matrix proteins in plaques are types I and III collagens, proteoglycans and elastin, with collagens accounting for up to 60% of the total protein content (Ye et al. 2003). The cellular constituents of atherosclerotic lesions, particularly macrophages, also express a number of proteolytic enzymes, matrix metalloproteinases (MMPs), that are thought to influence rates of atherogenesis and the stability of atherosclerotic plaques (Galis et al. 2002; Humphries et al. 2002). The rupture of these intimal

plaques may cause narrowing of coronary arteries as well as thrombosis resulting in sudden complete coronary artery occlusion.

During the developmental stages of atherosclerosis in coronary arteries, genetic differences may predispose or protect an individual from CAD risk, as the major risk factors such as hyperlipidemia, arterial hypertension and diabetes mellitus are influenced by genetic and environmental factors.

To date a large number of genes and gene products are suggested to contribute to the development and severity of CAD among which MMPs represent a potential candidate gene system.

### MATRIX METALLOPROTEINASES

MMPs play an important role in normal tissue remodeling, however increased expression has been identified in pathological processes, such as tumor angiogenesis and metastasis, rheumatoid arthritis, vascular neointimal hyperplasia, plaque rupture etc. (Hansen et al. 1993; Nelson et al. 2000). They degrade most of the ECM components and constitute a family of zinc-dependent enzymes that are more than 20 species and are secreted in a latent proform which undergo activation for proteolysis.

Their activity and expression is tightly regulated and have endogenous tissue inhibitors called TIMPs (Esther et al. 2001). Membrane bound and secreted are two principal types of MMPs.

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### Membrane Type MMPs (MT-MMPs)

These are recently described class of MMPs and are involved in ECM proteolytic degradation. They undergo intracellular activation through a proprotein convertase pathway (Murphy and Knauper 1997; Miyamori et al. 2000) and can also activate other MMPs within the ECM (Murphy and Knauper 1997; Nagase and Woessner 1999).

### Secreted MMPs

These are released into the extracellular space in a latent or proenzyme state and are activated by serine proteases, such as plasmin, as well as with other MMP species. Majority of MMPs fall into this category and are subdivided based on their substrate specificity into 3 groups: Collagenases, Gelatinases and Stromelysins.

The fibrillar collagens (types I, II, and III) which are extremely resistant to cleavage by most proteinases are fragmented by the collagenases, including MMP-1 (interstitial collagenase), MMP-8 (neutrophil collagenase), and MMP-13 (collagenase-3), into single  $\alpha$ -chains, called gelatins. These gelatins are degraded by second group, gelatinases (MMP-2 and MMP-9) which are also capable of degrading type IV collagen in basement membranes.

Third group includes stromelysins (MMP-3, -10, and -11), active against a broad spectrum of ECM components, including proteoglycans, laminins, fibronectin and some types of collagens.

### Regulation of MMPs

In certain physiological and pathological remodeling processes expression of MMPs is highly upregulated by a variety of inflammatory cytokines, hormones, and growth factors, such as interleukin-1 (IL-1), IL-6, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), epidermal growth factor (EGF), platelet-derived growth factor (PDGF) and CD40 etc. (Malik et al. 1996; Schonbeck et al. 1997).

Inflammatory cytokines, such as interleukin (IL)-1, IL-4 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), coordinately induce a broad range of MMPs, including MMPs-1, -3, and -9. Cytokines act synergistically with growth factors, such as platelet-derived growth factor (PDGF) and fibroblast growth factor-2 (FGF-2).

The presence of both inflammatory mediators and growth factors in injured and atherosclerotic blood vessels could therefore drive the production of MMPs with the ability to efficiently remodel both basement membranes and many components of the interstitial matrix (Andrew 2005).

In addition an intimate interaction between T lymphocytes and macrophages may also regulate the production of macrophage-derived MMPs. The CD-40 ligand on T cells can bind to the CD-40 receptor on macrophages, a process which has been shown to induce MMP synthesis (Fan and Watanabe 2003). Schonbeck et al. (1999) reported that cell contact with T-lymphocyte membranes and addition of recombinant CD40 ligand induce MMPs-1, -3, -8, and -9 in VSMC which implies a relationship between immune activation and wide-ranging matrix remodeling.

The expression of MMPs is regulated at both pre and post transcriptional levels and is also influenced by TIMPs.

### Endogenous MMP Inhibitors: The TIMPs

TIMPs inhibit MMPs by interacting with the zinc-binding site within the catalytic domain of active MMPs. The family consists of four structurally related members, TIMP-1, -2, -3 and -4 expressed by a variety of cell types and are influenced by factors like stretch, injury, inflammation and immune activation (Esther et al. 2001; Newby 2005; Sugioka et al 2010).

Although the role of TIMPs is clearly important in the prevention of excessive matrix degradation by MMPs, recent advances in TIMP research suggest that TIMP-1 and TIMP-2 are multifunctional proteins with more diverse biological actions. It has been reported that TIMP-1 and TIMP-2 exhibit growth factor-like activity and can inhibit angiogenesis (Hayakawa et al. 1992, 1994; Thorgeirsson et al. 1996) whereas TIMP-3 has been implicated in apoptosis (Baker et al. 1998) and TIMP-4 inhibits MMP-1, -3, -7, and -9 and shows a high level of expression in adult human cardiac tissue (Greene et al. 1996; Liu et al. 1997).

Several factors either individually or in combination are capable of potentially driving MMP/TIMP balance in vascular smooth muscle cells (VSMC) towards proteolysis, suggesting that MMP activity may not be completely abolished

by TIMP binding but could be confined temporally or spatially to the pericellular region surrounding VSMC.

The balance between MMPs and its tissue inhibitors play a vital role in maintaining the integrity of healthy tissues. Disturbance in balance of MMPs and TIMPs is found in various pathological conditions, including CAD, rheumatoid arthritis, periodontitis, cancer, etc. Therefore, elucidation of TIMP inhibition mechanisms may also provide new insights for therapeutic intervention (Nagase et al. 2006).

### MMP Gene Polymorphisms in CAD

Earlier studies have found that MMP-1 (interstitial collagenase), MMP-3 (stromelysin-1) and MMP-9 (92-kD gelatinase or gelatinase B) are expressed in atheroma at high levels compared with normal vessel walls (Jones et al. 2003; Andrew 2005). Ketelhuth and Bäck (2011) suggested that MMP-1 and MMP-9 seem to play a pro-atherothrombotic role while MMP-3 has been shown to be involved in plaque stabilization and fibrous cap formation and it has also been reported that except MMP-3 levels, all other MMPs have been found to be increased in the blood of patients at risk for CAD.

According to the important role of MMPs in the atherogenesis it has been shown that genetic variation affecting the expression of MMPs influence the susceptibility and/or progression of cardiovascular diseases (Ye 2000).

Among the best characterized is MMP-1 (collagenase-1) which plays an important role in the degradation of collagen types I, II and III. The promoter region of MMP1 contains a guanine insertion/deletion polymorphism (1G/2G polymorphism) at position -1607. Individuals who were homozygous for the 2G allele of the MMP-1 gene compared to those who were homozygous for the 1G allele resulted in reduced risk of CAD (Tower et al. 2002; Ye et al. 2003).

An association between the MMP3 5A/6A promoter polymorphism and atherosclerosis was first described in 1995. Functional studies showed that the 6A allele was associated with two-fold lower transcriptional activity of MMP-3 and the 6A homozygous genotype was associated with greater progression of coronary atherosclerosis.

Studies have been carried out in Koreans (Kim 2002), Caucasians (Beyzade 2003), Japa-

nese (Hirashiki 2003), Taiwanese, British and Finnish (Abillera et al. 2006), Indians (Shalia et al. 2010) and data provide evidence for the role of MMP3 polymorphism in plaque destabilisation.

MMP-9 is one of the MMPs found to be highly expressed in the vulnerable regions of atherosclerotic plaques, and for this reason it has been suggested to be causally involved in the remodeling processes associated with atherogenesis and plaque rupture (Galis et al. 2002) Zhang et al. (1998) described a functional -1562C/T polymorphism in the promoter region of MMP9 and also suggested that the T-1562 allele carriers are predisposed to the development of coronary atherosclerosis .

### CONCLUSION

Accumulating data suggests that the MMP gene variations are one of the strong candidate genetic factors for coronary artery disease with a multifactorial and polygenic aetiology. Recent studies on MMP genotyping accounts for inter-individual differences in susceptibility and in response to treatment .Therefore, there is a need for devising genetic tests for identifying the individuals with favourable or adverse effects for the treatment and for also identifying the asymptomatic individuals at risk of the disease for early therapeutic interventions.

Hence studying MMPs and their inhibitors (TIMPs) not only are relevant to the understanding of the progression and pathogenesis of atherosclerosis but may also find utility in new therapeutic strategies.

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