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# Putative targeting of matrix metalloproteinase-8 in atherosclerosis

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ABSTRACT

There is compelling evidence indicating that some members of the matrix metalloproteinase (MMP) family play important roles in the pathogenesis of atherosclerosis and related vascular and cardiac conditions such as atherosclerotic plaque rupture leading to myocardial infarction, heart failure after myocardial infarction, neointima formation following angioplasty, and abdominal aortic aneurysm. Studies have shown that administration of MMP inhibitors can deter some of these conditions in experimental animal models, but few pertinent human clinical trials have been reported to date. Clinical studies of broad-spectrum MMP inhibitors in cancers and arthritis, however, have reported considerable side effects that are likely to be related to the lack of selectivity of these inhibitors. Since different members of the MMP family can have divergent and even opposing functions, it is believed that selective MMP inhibitors that specifically target particular MMPs that are key in the disease pathogenesis will likely have greater efficacy and less adverse effects. In recent years there has been accumulating evidence indicating an important role of MMP8 in atherosclerosis and the associated conditions mentioned above. This article will review findings from studies examining MMP8 in relation to these conditions and discuss rationale of targeting MMP8 as a potential therapeutic strategy.



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## 1. Introduction

Coronary artery disease (CAD) and stroke are leading causes of mortality and morbidity in Western countries, and their prevalence has been increasing in the populations in many developing countries in recent years due to changes toward more urban lifestyles, such as high-fat intake and insufficient physical activities, which are well-established risk factors for cardiovascular diseases (Nichols, et al., 2013; Nowbar, et al., 2014; Yang et al., 2012).

*Abbreviations:* AAA, Abdominal aortic aneurysm; ADAM10, A-disintegrin-and-metalloproteinase-domain-10; Ang I, Angiotensin I; Ang II, Angiotensin II; CAD, Coronary artery disease; CI, Confidence interval; LDLc, Low-density-lipoprotein-cholesterol; LV, Left ventricular; MMP, Matrix metalloproteinase; MI, Myocardial infarction; VCAM1, Vascular cell adhesion molecule-1.

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CAD is primarily caused by atherosclerosis in coronary arteries (Libby, 1995b; Naghavi et al., 2003a; ,Naghavi et al., 2003b). The atherosclerotic plaque can clog the coronary artery, resulting in reduced blood and oxygen supply to the myocardium, and consequently the patient can experience angina pectoris. In more severe cases, the atherosclerotic plaque can fissure or rupture, which can trigger blood coagulation and thrombosis in the coronary artery, resulting in its blockage and consequently causing myocardial infarction (MI) or sudden death. Following MI, the myocardium undergoes remodeling that can lead to left ventricular (LV) dilatation and heart failure (Cohn, Ferrari et al., 2000). A commonly used procedure to widen the stenotic coronary artery with atherosclerosis is coronary angioplasty. Although this treatment is very effective in relieving symptoms in patients with CAD, restenosis due to neointima formation occurs in a significant proportion of patients, resulting in the return of symptoms (Babapulle, et al., 2004; Hoffmann and Mintz, 2000).

Similarly, many ischemic stroke cases are underlain by atherosclerosis in the arteries of the cerebral circulation. For instance, carotid artery atherosclerosis can lead to cerebral or cerebellar ischemia or infarction, resulting from carotid artery stenosis due to the carotid atherosclerotic plaque or from embolism caused by dislodged thrombi/tissues from the carotid atherosclerotic plaque (Grotta, 2013).

Furthermore, there is evidence indicating that atherosclerosis plays a major role in the pathogenesis of abdominal aortic aneurysm (AAA) (Golledge & Norman, 2010). Rupture of AAA is also an important cause of deaths in men aged over 65 years (Daugherty & Powell, 2014) (Golledge & Norman, 2010).

There is substantial evidence indicating that elevated expression and activity of members of the matrix metalloproteinase (MMP) family plays an important role in the pathogenesis of atherosclerosis, plaque rupture, post-MI heart failure, neointima formation, and AAA. Administration of various MMP inhibitors has been shown to exert protective effects against these conditions in experimental animal models. As the different members of the MMP family have divergent and even opposing functions, selective MMP inhibitors that specifically target particular MMPs that are key in the disease pathogenesis are likely to have greater efficacy and less adverse effects, than broad-spectrum MMP inhibitors.

This review article will focus on findings from studies that examined MMP8 in the context of atherosclerosis, plaque rupture, post-MI heart failure, post-angioplasty restenosis, and AAA (Fig. 1), and discuss rationale of targeting MMP8 as a potential therapeutic strategy.

## 2. MMP8

### 2.1. The matrix metalloproteinase family

MMPs are a family of zinc-dependent proteases belong to the metzincin superfamily (Nagase & Woessner, 1999; Nagase, et al., 2006). Based on the degrees of similarity in their amino acid sequences and substrate specificities, the MMPs have been classified into several groups, i.e. collagenases (MMP-1, -8, and -13), gelatinases (MMP-2 and -9), stromelysins (MMP-3, -10, and -11), matrilysins (MMP-7 and -26), membrane-type MMPs (MMP-14, -15, -16, -17, -24, and -25), enamelysin (MMP-20), and others (MMP-19, -21, -23, -27 and -28) (Nagase & Woessner, 1999; Nagase et al., 2006).

MMPs are best known for their ability to degrade extracellular matrix proteins (Birkedal-Hansen et al., 1993; Nagase & Woessner, 1999; Nagase et al., 2006). The different members of this family are specialized in degrading different sets of matrix proteins, although their substrate specificities overlap. Additionally, MMPs can also cleave a variety of non-matrix proteins including cytokines, adhesion molecules, growth factors, lipoproteins, and clotting factors, leading to their shedding, activation or inactivation (Page-McCaw, et al., 2007; ,Sternlicht and Werb, 2001).

The levels of MMPs are usually very low in normal adult tissues, but their expression is increased in tissues with inflammation or undergoing active remodeling in certain physiological processes or pathological conditions (Birkedal-Hansen et al., 1993; Sternlicht & Werb, 2001). The expression of most MMPs is primarily regulated at the transcriptional level, with the different MMPs having varying temporal and spatial expression patterns (Birkedal-Hansen et al., 1993). MMPs are produced as zymogens and hence require activation to become active proteases (Birkedal-Hansen et al., 1993). They can form complexes with TIMPs (Tissue Inhibitors of MMPs) that hinder MMP activation or with other endogenous inhibitors that sequester activated MMPs (Birkedal-Hansen et al., 1993). Therefore, MMPs are controlled at the transcriptional level as well as at the protein level by their activators and inhibitors.

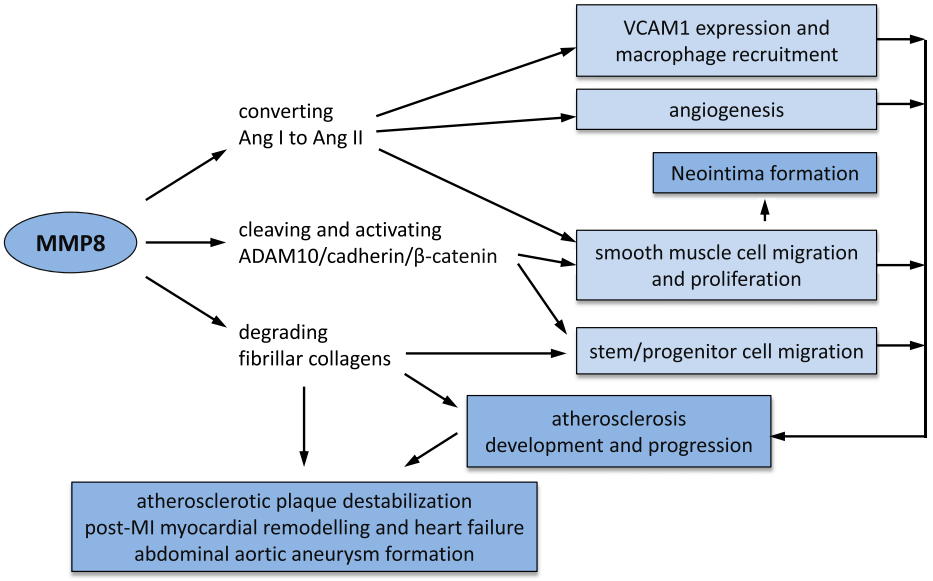


**Fig. 1.** MMP8 is involved in atherosclerosis and a number of associated vascular and cardiac conditions. MMP8 has been implicated in atherosclerosis pathogenesis and progression, atherosclerotic plaque destabilization, myocardial remodeling and heart failure after myocardial infarction, neointima formation following vascular injury, and abdominal aortic aneurysm development and expansion. Possible mechanisms involved are illustrated in the diagram.