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Review

Matrix Metalloproteinase-8 and Cardiovascular Diseases: A Narrative Review

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Abstract

Matrix metalloproteinases-8 (MMP-8), commonly known as neutrophil collagenase, is an MMP enzyme. MMPs break down extracellular matrix components, which support tissues. Skin, bones, and blood vessels contain collagen, which MMP-8 degrades. Researchers have linked higher MMP-8 levels to atherosclerosis, heart attacks, and heart failure (HF). MMP-8 damages the extracellular matrix in heart tissue and blood vessels, which can worsen cardiovascular diseases (CVDs) by altering the shape of artery walls, destabilizing plaques, and changing the shape of ventricles. MMP-8 breaks down collagen in the fibrous cap of atherosclerotic plaques, weakening it and increasing the likelihood of plaque rupture, which may lead to a heart attack or stroke. MMP-8 activity accelerates ventricular remodeling in heart failure, impairing cardiac function. MMP-8's role in CVDs is complex. Certain research suggests that MMP-8 may assist in the repair of injured tissue. How MMP-8 activity impacts CVDs overall depends on the efficiency of MMP-8 and its tissue inhibitors, or TIMPs, working together. MMP-8 inhibitors may reduce matrix breakdown and tissue damage in CVDs. MMP-8's importance in CVDs and its therapeutic potential requires further investigation. A trained healthcare professional should diagnose and treat CVDs and other medical conditions.

Keywords: Atherosclerosis, Cardiovascular diseases, Matrix metalloproteinases-8

INTRODUCTION

Matrix metalloproteinases (MMPs) are a family of enzymes that play a role in the remodeling and degradation of the extracellular matrix (ECM), which is the structural framework of tissues and organs in the body. Secreted as inactive enzymes (proMMPs), MMPs activate in response to various physiological and pathological stimuli. MMPs are involved in many physiological processes, such as embryogenesis, tissue repair, and tissue remodelling during normal development and growth. Pathological conditions such as inflammation, tissue injury, and cancer metastasis also implicate MMPs. MMPs are capable of degrading components of the ECM, including collagen, elastin, and proteoglycans, which are essential for maintaining tissue structure and function (1).

Fibroblasts, macrophages, neutrophils, and endothelial cells are just a few of the various cell types that produce and secrete MMPs. A complex interplay of activators and inhibitors tightly regulates their activity to prevent excessive tissue remodelling. Many diseases, including arthritis, tissue fibrosis, cardiovascular diseases (CVDs), and cancer metastasis, have implicated MMP dysregulation. Researchers have developed MMP inhibitors as potential therapeutic agents for these diseases, but the complex roles of MMPs in tissue remodelling and their potential side effects have limited their clinical use. Overall, MMPs are important enzymes involved in tissue remodelling and play a crucial role in both physiological and pathological processes in the body (1).

Matrix metalloproteinase-8 (MMP-8), also known as neutrophil collagenase, is a member of the matrix metalloproteinase family that specifically degrades collagen, which is a major component of the ECM in tissues. White blood cells known as neutrophils, which play a role in the immune response to infections, are the main producers of MMP-8. In the context of cardiovascular disease, MMP-8 has been implicated in the pathogenesis of atherosclerosis, which is a condition characterized by the accumulation of plaques in the

arterial walls. Atherosclerosis is a major risk factor for CVDs such as coronary artery disease, stroke, and peripheral artery disease. It is believed that MMP-8 contributes to atherosclerosis by breaking down the collagen fibers in the arterial walls, weakening the ECM's structural integrity and potentially causing plaque formation. Researchers have found that atherosclerotic lesions upregulate MMP-8, especially in the areas where plaques rupture, releasing their contents into the bloodstream and potentially triggering acute cardiovascular events (2).

The balance between MMPs and their tissue inhibitors (TIMPs) is critical for maintaining ECM homeostasis. If this balance is out of whack, with more MMP activity and/or lower TIMP levels, the ECM can break down too quickly, which can help heart diseases like atherosclerosis start and get worse. Several studies have suggested that MMP-8 may be a potential therapeutic target for CVDs. Preclinical and clinical studies have investigated MMP-8 inhibitors, but we are still evaluating their efficacy and safety in human subjects. Additionally, researchers are exploring other strategies as potential therapeutic approaches, such as modulating the activity of TIMPs or targeting other MMPs involved in CVDs. This review updates data suggesting that the neutrophilic collagenase MMP-8 may directly cause CVDs.

MMP-8 protein or mRNA is expressed higher in symptomatic unstable carotid plaques, abdominal aortic aneurysm aortas, rupture sites, and advanced shoulder atherosclerosis lesions. These findings implicate MMP-8 in matrix remodelling in atherosclerosis and unstable plaque rupture—the pathophysiology of acute coronary syndromes. It is rare to examine CVD serum or plasma MMP-8 levels, especially in a prospective manner. Plasma MMP-8 affects coronary artery disease, carotid plaque instability, morphology, and stroke delay. Congestive cardiac failure and cerebral ischaemia reduce plasma MMP-8. Small sample sizes and low statistical power may cause these disparities. Thus, the study's sample size, prospective population-based design, and extended follow-up are positives. A few CVD fatalities were analyzed. Solid outcomes. The male sample necessitates further investigation into MMP-8's role in women's CVD.

OVERVIEW

MMP-8 protein or mRNA is expressed higher in symptomatic unstable carotid plaques, abdominal aortic aneurysm aortas, rupture sites, and advanced shoulder atherosclerosis lesions. These findings implicate MMP-8 in matrix remodelling in atherosclerosis and unstable plaque rupture—the pathophysiology of acute coronary syndromes. It is rare to examine CVD serum or plasma MMP-8 levels, especially in a prospective manner. Plasma MMP-8 affects coronary artery disease, carotid plaque instability, morphology, and stroke delay. Congestive cardiac failure and cerebral ischaemia reduce plasma MMP-8. Small sample sizes and low statistical power may cause these disparities. Thus, the study's sample size, prospective population-based design, and extended follow-up are positives. A few CVD fatalities were analyzed. Solid outcomes. Due to the male sample, MMP-8's role in women's CVD needs more investigation (3,4).

Studies show subclinical atherosclerosis with carotid artery intima media thickness (IMT) above 1 mm. IMT increases stroke and MI. Males with IMT >1 mm exhibited multiple CVD risk factors, including elevated fibrinogen. Plasma fibrinogen concentrations significantly and positively correlated with serum MMP-8 and the MMP-8/tissue inhibitor of metalloproteinase-1 (TIMP-1) ratio after adjusting for key CVD risk variables. Inflammation raises fibrinogen, causing CVDs. A high fibrinogen concentration, with a multivariate RR of 1.65 (1.05 to 2.60, p= 0.029), predicted AMI in men without preclinical atherosclerosis, but not other endpoints or subclinical conditions. Smoking altered MMP-8 and fibrinogen levels. Smokers had slightly greater serum MMP-8 than nonsmokers, although urine nicotine metabolites and smoking years were unrelated (5,6).

Preclinical atherosclerosis may increase serum MMP-8. Periodontal bacteria inflaming tissues may produce MMP-8 in the blood. Researchers recently linked periodontitis severity and seropositivity to subclinical atherosclerosis. The combined serum antibody level to major pathogens is used as a confounding factor in the linear regression analysis. This is because periodontitis and seropositivity to periodontal pathogens are two different CVD risk factors. Antibody and MMP-8 levels were unrelated. In basic investigations, there was no significant difference in antibody levels to periodontal pathogens between subclinical atherosclerosis and IMT 1 mm. Blocking MMPs and TIMPs prevents plaque rupture (7). Widespread or subclinical atherosclerosis was associated with a worse cardiovascular prognosis and higher serum MMP-8 levels (8).

CORONARY ARTERY DISEASE

MMPs regulate collagen production and breakdown, which impacts plaque development, susceptibility, and vascular remodelling. Only MMP-1, MMP-8, and MMP-13 break collagen, leaving it vulnerable to further degradation by MMP-2 and MMP-9. MMP-8 destroys type I collagen, a key component of atherosclerotic plaques, 3-fold faster than MMP-1 and MMP-13. Atherosclerotic plaques upregulate MMP-1 and MMP-13, while neutrophils, which are rare in plaques, exclusively generate MMP-8. Endothelial cells, smooth muscle cells, and macrophages in human atherosclerotic plaques make MMP-8 mRNA and protein. These cells

are found in lipid-rich plaques with a thin fibrous cap. MMP-8 breaks down atherosclerotic plaque collagen, causing plaque vulnerability or vascular remodelling. We have not yet established a link between MMP-8 and coronary artery disease (CAD). Increased plasma MMP-8 levels independently correlate with CAD. MMP-8 concentration correlates with CAD severity, peaking in patients with 3-vessel disease. MMP-8 concentration independently causes three-vessel disease. High MMP-8 levels in CAD patients may target the adaptive remodeling of coronary arteries or plaque vulnerability (9).

Plaque vulnerability predicts unstable angina and myocardial infarction (MI) in angiography-detected complicated coronary lesions. Complex lesions are common in unstable angina and 10–20% in stable angina. Even after eliminating acute MI and unstable angina, complex lesions were present in 23% of CAD patients. Serum MMP-1 values in 185 stable CAD patients were similar, but high quantities were associated with complex coronary lesions. MMP-8 levels were higher in complex lesions, although not statistically significant. Plasma MMP-8 in stable CAD patients may indicate coronary atherosclerosis severity rather than plaque susceptibility (**Figure 1**). [10]. Coronary events were more common in high-hsCRP CAD patients. Independent of HsCRP levels, MMP-8 levels predicted CAD. Vascular MMP-9 activates diabetes [11]. High hyperglycemia in vascular cells enhanced MMP-1, MMP-2, and MMP-9 activity, according to Death et al. [12] Independent of diabetes, we linked high plasma MMP-8 levels to CAD, particularly 3-vessel disease. Statins lower rabbit atheroma MMP-1, MMP-3, and MMP-9 expression and CAD plasma MMP-9.

PULMONARY ARTERIAL HYPERTENSION

The lung upregulates MMP-8 after monocrotaline (MCT), but its role in pulmonary arterial hypertension (PAH) is uncertain. Severe PAH patients and three animal PAH models had elevated plasma MMP-8 (13). pulmonary vascular MMP-8 expression is linked to the severity of PAH, the development of PAH in mice exposed to hypoxia, and changes in the blood vessels. Mice without MMP-8 develop chronic hypoxia-induced PAH, vascular remodelling, and RV dysfunction. PAH development seems to include adaptive MMP-8 overexpression. Hypoxaemia, arrhythmia, and cardiac ischaemia may potentially cause mortality (14).

The activity of elastases and MMPs may directly improve the mitogenic activity of pulmonary artery smooth muscle cells (PASMCs) by releasing mitogens, revealing hidden integrin binding sites, or turning on mitogen receptors. MMP activity activates latent integrin-b3 binding sites by upregulating tenascin-C synthesis and deposition. Integrin-interacting matricellular proteins induce PAH. Osteopontin-expressing PAH patients had better outcomes (15,16). PASMCs and adventitial fibroblasts proliferate and undergo mitogenesis (17,18). Human PAH elevates thrombospondin-1, which correlates with severity and cardiac output, and significantly expresses in end-stage disease distal PAs (19-22). Thrombospondin-1 and integrin-b3 may increase PASMC migration and proliferation (23).

MMPs control integrin signaling. Gross MMP inhibition in cancer cell lines lowers traction pressures, cell rounding, and cell softness through integrin-B1 levels and localization (24). MMP-mediated integrin-b3 activation revealed no collagen-cleaved integrin binding sites. TIMP-1 activates integrin-b1 through CD63, whereas MMP-8 suppresses it in cancer cells (25-27). These results complement our observation that MMP-8 depletion enhances integrin signaling via integrin B3, not B1. Integrin-b3, crucial for shape signal transduction in SMCs, plays a role in SMC mobility, including chemotaxis (28,29). These signals are sent by Merlin, a Yes-associated protein/transcriptional co-activator with a PDZ binding motif (YAP/TAZ) regulator (30). PAH development increases pulmonary vasculature MMP-8, a new protective factor. MMP-8 disrupts PASMC integrin-β3/FAK, YAP/TAZ-dependent mechanical signaling, and matrix composition to resist pathologic mechanobiological feedback (31).

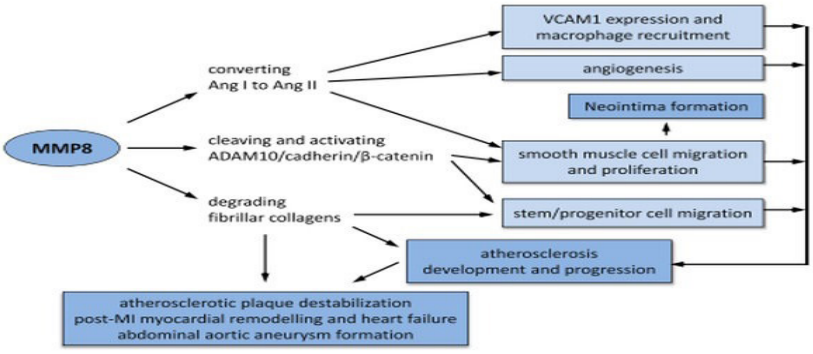

Figure 1. MMP8 causes atherosclerosis, plaque destabilisation, and myocardial remodelling. Mechanism diagrams. Other publication containing the figure in the manuscript include "Pharmacol Ther 2015;147:111-22".
MMP8: Matrix Metalloproteinase-8, Ang I: Angiotensin I, Ang II: Angiotensin II, ADAM10: A Disintegrin And Metalloproteinase 10, VCAM1: Vascular Cell Adhesion Molecule 1, MI: Myocardial Infarction

ATRIAL FIBRILLATION

Atrial fibrillation (AF) is a common cardiac arrhythmia characterized by rapid and irregular electrical activity in the atria, or upper chambers, of the heart. It is associated with an increased risk of stroke, heart failure, and other cardiovascular complications. Emerging evidence suggests that MMP-8, a member of the matrix metalloproteinase family, may be involved in the pathogenesis of atrial fibrillation. MMP-8 is a white blood cell type that is primarily responsible for producing the enzyme, and it participates in tissue remodelling by destroying the ECM. MMP-8 is associated with the structural remodelling of the atrial tissue, a hallmark of atrial fibrillation. The atrial ECM changes during structural remodelling. These changes include fibrosis (too much collagen buildup) and dilation (enlargement of the atria). These can stop the heart's normal electrical conduction and help AF start and stay active.

Researchers have found that patients with AF have upregulated MMP-8 in their atrial tissue, and they have correlated its expression with the severity of atrial fibrosis. Studies have also demonstrated that MMP-8 stimulates the breakdown of collagen in the atrial extracellular matrix (ECM), thereby exacerbating the atrial tissue's structural integrity and accelerating the onset of atrial fibrillation (AF). Apart from its involvement in structural remodelling, MMP-8 also plays a role in inflammation, oxidative stress, and the immune response, all of which can contribute to the pathophysiology of AF. MMP-8 can modulate the activity of other inflammatory molecules and enzymes, and its increased expression may lead to an imbalance in the inflammatory response in the atrial tissue promoting AF development. Targeting MMP-8 has emerged as a potential therapeutic strategy for AF, despite the incomplete understanding of the exact mechanisms through which MMP-8 contributes to AF pathogenesis and the need for further research. Preclinical studies have investigated MMP inhibitors, including specific inhibitors of MMP-8, and have shown promise in reducing atrial fibrosis and AF vulnerability in animal models. However, limited clinical studies in humans have yet to establish the safety and efficacy of MMP inhibitors for AF treatment.

ISCHEMIC STROKE

The pathophysiology of stroke has implicated MMP-8. Research has demonstrated an increase in MMP-8 levels in the brain tissue and blood of stroke victims. Studies have demonstrated that MMP-8 degrades the extracellular matrix in the brain, including the basement membrane of blood vessels, potentially leading to disruption of the blood-brain barrier and inflammation. MMP-8 can also activate other MMPs, leading to a cascade of matrix degradation and tissue damage. Animal models have demonstrated the role of MMP-8 in stroke progression, where a deficiency in MMP-8 leads to reduced brain injury and improved outcomes. Researchers have investigated MMP-8 inhibitors as potential therapeutic targets for stroke to reduce tissue damage and inflammation (32).

MMPs damage ischaemic stroke brains. Stroke patients' infarcted brains express higher MMP-1, -2, -3, -8, -9, -10, -13, and TIMP-1 than non-ischaemic areas (33). Microglia, macrophages, and neutrophils produce blood-brain barrier leakage and neurovascular abnormalities. Stroke therapy targets MMPs. We must carefully design treatment suppression because MMPs are essential for angiogenesis during recovery. MMP-9 is the most studied MMP in CVD; however, other MMP family members may have therapy potential. Stroke patients seldom study MMP-8 (34).

RECENT STUDIES

Neuropeptide Y upregulates MMP-8, which increases macrophage migration and neointima development (35). Iwańczyk et al. linked MMP-8 to aberrant coronary artery dilation (36). Zhang et al. found increased MMP-8 levels in aortic dissection patients (37). Having the MMP-8 promoter GTTT haplotype lowers the production of MMP-8 during inflammation and raises the risk of high blood pressure (38,39). Researchers have linked low blood levels of MMP-12 to ischemic stroke, low levels of MMP-1 and MMP-12 to large-artery stroke, and high levels of MMP-8 to lacunar stroke. cunar stroke (38,39). In their study, Yang et al. found that MMP8 from macrophages changes how AdSPC turns into SMC and how neointimal SMC grows after an injury (40). The study of MMP8's part in AdSPC differentiation and neointima development in angiographic restenosis could lead to the creation of new drugs that can stop this condition.

An imbalance in TIMP-MMP changes the structure of the extracellular matrix (ECM) and leads to the remodelling of dilated cardiomyopathy (DCM). This process could help researchers come up with new ways to treat DCM (41). MSSA pneumonia has implicated neutrophil proteases, including MMPs, in a rare aortic rupture (42). **Table 1** displays the main topics of recent studies.

CONCLUSION

Neutrophil collagenase (MMP-8) is an MMP enzyme. MMPs degrade the extracellular matrix, which supports tissues. MMP-8 breaks down collagen in skin, bones, and blood vessels. Higher MMP-8 levels are associated with atherosclerosis, heart attacks, and heart failure. MMP-8 breaks down the extracellular matrix in heart tissue and blood vessels. This changes the shape of the artery walls, makes plaques less stable, and changes the shape of the ventricles, all of which can lead to CVDs. MMP-8 destroys collagen in atherosclerotic plaques'

Table 1. The main topic points of recent studies.

Reference no.	Authors	Subjects	Main theme
Ref (16)	Mura et al.	Pulmonary arterial hypertension	Osteopontin (OPN) expression is closely linked with disease severity in severe PAH patients' lungs. PAH vascular remodelling may include OPN.
Ref (19)	Kumar et al.	Pulmonary arterial hypertension	TGF-β-dependent vascular disorders may be treated by targeting thrombospondin-1-dependent TGF-β activation.
Ref (22)	Rogers et al.	Pulmonary arterial hypertension	CD47 targets cMyc to boost endothelin-1 signalling in pre-clinical PH models. Clinical PH upregulates TSP1-CD47, which causes pulmonary arterial vasculopathy and dysfunction.
Ref (23)	Rogers et al.	Pulmonary arterial hypertension	Thrombospondin-1 and integrin-b3 may increase PASMC migration and proliferation
Ref (24)	Das et al.	Cancer cells	MMPs control integrin signalling. Gross MMP inhibition in cancer cell lines lowers traction pressures, cell rounding, and cell softness through integrin-b1 levels and localization.
Ref [26]	Ando et al.	Cancer cells	The TIMP-1- Yes-associated protein (YAP)/ transcriptional co-activator with PDZ binding motif (TAZ) axis may be a new cancer therapeutic target since it increases cell proliferation in cancer.
Ref (25)	Jia et al.	Ischemic Stroke	PAH development increases pulmonary vasculature MMP-8, a new protective factor. MMP-8 disrupts PASMC integrin-β3/FAK and YAP/ TAZ-dependent mechanical signalling and matrix composition to resist pathologic mechanobiological feedback
Ref (26)	Wu et al.	Mice	Neuropeptide Y upregulates MMP-8, which increases macrophage migration and neointima development.
Ref (36)	Iwańczyk et al.	coronary artery abnormal dilatation patients	MMP-8 to aberrant coronary artery dilation
Ref (37)	Zhang et al.	Mice	Increased MMP-8 levels in aortic dissection patients
Ref (38)	Maghajothi et al.	Hypertensive	MMP-8 promoter GTTT haplotype reduces NF-B-mediated MMP-8 production during inflammation and increases hypertension risk
Ref (39)	Cárcel-Márquez et al.	Ischemic Stroke	Lower serum MMP-12 levels to ischemic stroke, lower MMP-1 and MMP-12 to large-artery stroke, and higher MMP-8 to lacunar stroke.
Ref (40)	Yang et al.	Adventitia stem/progenitor cells	Macrophage-derived MMP8 modulates AdSPC-to-SMC differentiation and injury-induced neointimal SMC hyperplasia. The results on MMP8's role in AdSPC differentiation and neointima development in angiographic restenosis may help develop new medications to prevent it.
Ref (41)	Mitrut et al.	Dilated cardiomyopathy	TIMP-MMP imbalance disturbs ECM architecture and leads to dilated cardiomyopathy (DCM) remodelling, which may be utilised to design novel therapeutic treatments.
Ref (42)	Hashimoto et al.	Aortic dissection	In a rare aortic rupture caused by MSSA pneumonia, neutrophil proteases, including MMPs, were implicated

OPN: Osteopontin, PAH: Pulmonary Arterial Hypertension (Pulmoner Arteriyel Hipertansiyon), TGF-β: Transforming Growth Factor Beta, CD47: Cluster of Differentiation 47, cMyc: Cellular Myc (a proto-oncogene), TSP1: Thrombospondin-1, PASMC: Pulmonary Artery Smooth Muscle Cell, MMP: Matrix Metalloproteinase, TIMP: Tissue Inhibitor of Metalloproteinases, YAP: Yes-associated Protein, TAZ: Transcriptional Co-activator with PDZ-binding Motif, FAK: Focal Adhesion Kinase, NF-κB: Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells, AdSPC: Adventitial Stem/Progenitor Cell, SMC: Smooth Muscle Cell, ECM: Extracellular Matrix, DCM: Dilated Cardiomyopathy, MSSA: Methicillin-Sensitive Staphylococcus Aureus.

fibrous caps, weakening them and increasing the risk of plaque rupture, which may cause a heart attack or stroke. Heart failure impairs cardiac function due to MMP-8-induced ventricular remodelling. MMP-8 and CVDs are tricky. The equilibrium between MMP-8 and its tissue inhibitors, TIMPs, determines MMP-8's effect on CVDs. MMP-8 inhibitors may minimize CVD matrix breakdown and tissue injury. We need more research on MMP-8 and CVDs. Medical professionals should diagnose and treat CVDs and other illnesses.

DECLARATIONS

Ethics Committee Aproval: Since this study utilized publicly available literature, approval from the institutional review board was not obtained.

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