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CLINICAL UPDATE

The Role of Matrix Metalloproteinases in the Progression and Vulnerabilization of Coronary Atherosclerotic Plaques

Diana Opincariu[1], Nora Rat[1,2], Imre Benedek[2]

[1] "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania
[2] Center of Advanced Research in Multimodality Cardiac Imaging, Cardio Med Medical Center, Târgu Mureș, Romania

ABSTRACT

Extracellular matrix (ECM) plays an important role in the development and progression of atherosclerotic lesions. Changes in the ECM are involved in the pathophysiology of many cardiovascular diseases, including atherosclerosis. Matrix metalloproteinases (MMPs) are a family of zinc-dependent proteases, also known as matrixins, with proteolytic activity in the ECM, being responsible for the process of tissue remodeling in various systemic pathologies, including cardiac and vascular diseases. MMPs play an important role in maintaining normal vascular structure, but also in secondary cardiovascular remodeling, in the formation of atherosclerotic plaques and in their vulnerabilization process. In addition to the assigned effect of MMPs in vulnerable plaques, they have a well-defined role in post-infarction ventricular remodeling and in various types of cardiomyopathies, followed by onset of congestive heart failure, with repeated hospitalizations and death. The aim of this manuscript was to provide a summary on the role of serum matrix metalloproteinases in the process of initiation, progression and complication of atherosclerotic lesions, from a molecular level to clinical applicability and risk prediction in patients with vulnerable coronary plaques.

Keywords: matrix metalloproteinases, extracellular matrix, acute coronary syndrome, vulnerable coronary plaques, atherosclerosis

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CORRESPONDENCE

Nora Rat
Str. Gheorghe Marinescu nr. 38
540136 Târgu Mureș, Romania
Tel: +40 265 215 551
E-mail: ratnora@gmail.com

INTRODUCTION

Extracellular matrix (ECM) plays an important role in the occurrence and progression of atherosclerotic lesions. Changes in ECM are involved in the pathophysiology of many cardiovascular diseases, including atherosclerosis, aneurysms, in-stent restenosis after percutaneous coronary angioplasty, but also in the vulnerabilization process of atherosclerotic plaques.[1-3] Studies from the last decade has led to an improved knowledge of the progression from endothelial lipid striae into mature atheroma, a special attention being directed to inflammatory cell infiltration, migration of vascular smooth muscle fibers (VSMF) and ECM remodeling. All these processes are dependent on the activity of a group of endogenous peptidases from the metalloproteinase matrix family (MMP).[4-6]

Diana Opincariu: Str. Gheorghe Marinescu nr. 38, 540136 Târgu Mureș, Romania. Tel: +40 265 215 551, E-mail: diana.opincariu@yahoo.ro
Imre Benedek: Str. 22 Decembrie 1989 nr. 76, 540124 Târgu Mureș, Romania. Tel: +40 265 217 333, E-mail: imrebenedek@yahoo.com

MATRIX METALLOPROTEINASES – CLASSIFICATION, STRUCTURE AND FUNCTION

Matrix metalloproteinases are a family of zinc dependent proteases, also known as matrixins, with proteolytic activity at the ECM level, which are responsible for the tissular remodeling process in various systemic disorders, including cardiac and vascular diseases.[7] The MMP family includes more than 28 members which modulate the reorganization and reconstruction of the vascular ECM, and also the release of cytokine and growth factors with are embedded in the ECM. From the 28 class representatives, 23 are expressed within various tissues and 14 are located at a vascular level (venous and arterial).[8] MMP2 are divided into 6 different categories as follows: collagenases (MMP-1, -8, -13, -18), gelatinases (MMP-2, -9), stromyelisins (MMP-3, -10, -11), matrilysins (MMP-7, -26), membrane (MMP-14, -15, -16, -17, -24, -25).[9] Expression of MMP-1, -2, -3, -7 and -9 respectively, has been detected at the site of endothelial cells, VSMF and fibroblasts. Furthermore, an array of MMP have been found in the vascular wall (membrane MMPs), leucocytes (MMP-2) and platelets (MMP-1, -2, -3, -14).[10]

All members of the MMP family are secreted as inactive forms, and have a similar biochemical structure that includes the N-terminal propeptide, catalytic domain, and C-terminal portion of the molecule.[11] MMPs are secreted by VSMF, endothelial cells, monocytes, macrophages, and T lymphocytes, as an inactive proenzyme. The initial level of MMP proenzymes is regulated by translational mechanisms, under the action of pro-inflammatory cytokines. Cytokine signals that include tumor necrosis factor alpha (TNF-α), interleukins or special extracellular inducers of MMP, platelet growth factors, or CD-40 ligands, increase the production of inactive MMPs in fibroblasts, smooth muscle fibers and myocytes, as well as their transport to the ECM.[12] Inactive MMPs are subsequently stored at the ECM. Here, the enzymatic activation locus is released under the action of additional activating signals (free oxygen radicals, ischemia, angiotensin converting enzyme).[13] This process is also catalyzed by membrane matrixins or other proteolytic enzymes (tissue plasminogen activators, plasmin), which are in turn activated by inflammation and coagulation cascade.[14]

Another mechanism for regulating MMP levels in tissues includes the counterbalancing action of tissue inhibitors of metalloproteinases (TIMPs). TIMPs are a family of specific MMP inhibitors, which are essential in the connective tissue remodeling and include 4 molecular types: TIMP 1, 2, 3, 4.[15] In addition to inhibition of MMP, the TIMP molecule family also promotes cell growth, via their antiapoptotic and antiangiogenetic effect.[16]

TIMP 1 is secreted by various cells in the connective tissue, mesangial cells and macrophages, causing an increase in cardiac fibroblasts and collagen production, but also regulating the activity of 14 of the 28 known MMPs. Preclinical studies have shown that expression of TIMP 1 is increased in various diseases characterized by an excess deposition of fibrous tissue, such as pulmonary fibrosis or diabetic nephropathy. This suggests the restrictive effect of TIMP 1 on ECM degradation.[17-20] TIMP 2 is closely related to MMP-2 expression, but a combination with MMP-14 is essential for its activation process.[21] TIMP 3 is a key modulator for inhibiting the ECM remodeling process. A low expression of TIMP 3 is associated with an increase in MMP activity, with a consequent increase in ECM degradation at different tissue levels.[22,23] Additionally, TIMP 3 deficiency has been associated with maladaptive cardiovascular remodeling in experimental animal models of myocardial infarction and hypertension.[24,25] TIMP 4 is the least studied family member, its role being attributed to MMP-14 inhibition and its anti-inflammatory properties.[26] There are data on the restrictive effect of TIMP 4 on MMP-based proteolysis in the fetal lung, female reproductive system or in transplanted tissues.[27-29]

The interaction between MMP and TIMPs determines the balance between accumulation and degradation of ECM. A number of other inflammatory cytokines and chemokines can influence extracellular matrix turnover by acting on the MMP/TIMP balance. TIMP can directly regulate ECM proteolysis by inhibiting MMP, but it can also control its turnover by controlling cell function, inflammation inhibition, controlled release of cytokines, and cytokine receptors in inflammatory cells.[21]

MMP AND PHYSIOPATHOLOGY OF ATHEROSCLEROSIS

Atherosclerosis is a chronic inflammatory disease, characterized by accumulation of lipids, proliferation of smooth muscle fibers, cellular apoptosis, necrosis and fibrosis. MMPs play an important role in all evolutionary stages of atherosclerosis, through vascular inflammation, endothelial dysfunction, VSMF migration, vascular calcification, ECM degradation and atheroma plaque stabilization.[30-32] Exposure of vascular wall cells to inflammatory mediators produced by chronic inflammation linked to atherosclerosis, causes excessive expression of MMP, with activation of leukocyte migration and endothelial invasion.[33] Migration of macrophages and subendothelial deposition

of oxidized LDL cholesterol particles, leads to initiation of atherosclerosis. Macrophage phagocytosis of oxidized cholesterol LDL particles results in the appearance of foam cells, and consequently the migration of VSMF into the vascular intima. Transmigration of inflammatory cells into the intima causes the secretion of pro-inflammatory cytokines, which additionally contributes to the recruitment of inflammatory cells and VSMF in the neointima. Subsequently, MMP and TIMP are secreted by monocytes, macrophages, but also by foam cells.[34-36] Endothelial dysfunction, characterized by a pro-inflammatory and prothrombotic status, causes an increase in vascular permeability, which facilitates additional infiltration with different inflammatory mediators. Endothelial MMP-2 activation can trigger endothelial dysfunction and damage. Inflammatory cells recruited at the intimal level cause remodeling of MEC and apoptosis of VSMF and endothelial cells.[37] Degradation of ECM by MMP contributes to intimal VSMF migration, under the influence of proinflammatory cytokines, with intimal vessel thickening and consecutive vascular remodeling. MMP stimulates neovascularization of atherosclerotic plaques by degradation of ECM and vascular basal membrane, but also by stimulating the production of endothelial vascular growth factor (VEGF).[38,39] Vascular calcification, representative of advanced, stable atherosclerotic plaques, is influenced by MMP. MMP-7 has been associated with the presence of carotid calcifications, MMP-2 contributes to the calcification of smooth muscle fibers, and MMP-10 activity has been directly associated with the degree of coronary calcification in subjects with subclinical atherosclerosis.[40-42]

MMPs play an important role in maintaining normal vascular structure, but also in secondary cardiovascular remodeling, in the formation of atherosclerotic plaques and in their vulnerabilization process.[43,44] MMP, and especially MMP-9 are responsible for ECM degradation in coronary atherosclerotic plaques, which can trigger acute fatal events. MMP facilitates transmigration of inflammatory cells and pro-inflammatory mediators at a tissue level, contributing to the process of vulnerability of atheroma plaques.[45,46]

A number of studies have shown that MMP levels and their proteolytic activity are increased in certain areas of the atherosclerotic plaque, or after the onset of acute coronary syndromes.[47,48] One study compared serum MMP levels in 53 patients with significant coronary atherosclerotic lesions (>50% degree of stenosis) and 133 healthy subjects. The results indicated that patients with significant coronary stenosis had a significantly higher serum level of MMP-9, while MMP-2 and MMP-3 levels were significantly lower.[49] Moreover, MMP-mediated extracellular matrix remodeling is also involved in the process of neo-atherosclerosis and in-stent restenosis after endoluminal revascularization procedures. Pleva *et al*. demonstrated, in a group of 111 patients with in-stent restenosis at 12 months after percutaneous coronary angioplasty, that an elevated level of MMP-3 (OR-1.01, p = 0.005) and MMP-9 (OR-1.01, p <0.0001) are significant predictors of intrastent neo-atherosclerosis.[50] Similar results were recorded by Katsaros *et al*. in a group of 85 patients in whom 159 pharmacologically active stents were implanted, who observed an increased serum level of MMP-9 (p = 0.008) and MMP-2 (p = 0.005) only in patients who had intrastent restenosis at a follow-up period of 6–8 months. These results suggest the efficacy of using these serum biomarkers to predict the risk of intrastent restenosis after percutaneous revascularization.[51]

SERUM MMPS – MARKER OR PROMOTER OF VULNERABLE PLAQUES

Atherosclerotic plaques consists of a necrotic lipid core, an external fibrous capsule and inflammatory cells, in this case foam cells. The fibrous cap, formed by the components of the extracellular matrix, collagen for resistance and elastin for flexibility, undergoes remodeling, with resorption and protein synthesis. These two stages of vascular remodeling are balanced under stable flow conditions and a relatively stable inflammatory status. Under conditions associated with an increased inflammatory response, the remodeling process may be shifted in favor of ECM resorption, with vulnerability of the fibrous cap and increased risk of plaque rupture.[14]

Rupture of coronary atherosclerotic plaques is mediated by the action of MMPs on the fibrous cap, which can progress to acute coronary syndromes or sudden cardiac death. MMP-9 and MMP-3 have been shown to be present in areas of plaque instability, and are often associated with the presence of inflammatory cells. MMP expression is higher in regions with potential vulnerability and risk of rupture, with excessive remodeling.[52-54] On the other hand, tissue inhibitors of MMP (TIMP) are also present in vulnerable plaques, being associated with a higher degree of calcification. Thus, the balance between MMP and TIMP determines the calcification of the lesion and stabilization if it is inclined towards TIMP activity, or progression towards remodeling and rupture if this balance is in favor of MMP activation.[55] MMP activity enhances production of local growth factors, with ECM alteration, accumulation of foam macrophages, necrotic core expansion, with ad-

ditional plaque vulnerability. Increased MMP production causes the development and maintenance of an inflammatory vicious circle, which contributes to plaque growth, but also promotes remodeling, with increased potential for rupture.[56] Changes in the coronary flow, subsequent to vascular remodeling, with the added persistent risk factors, further stimulates the secretion of MMP, with the release of pro-inflammatory cytokines, cell migration, and the occurrence of erosions in the fibrous cap. These erosions cause formation of non-occlusive thrombi in the vascular lumen and release of tissue activator plasminogen and plasmin which will in turn increase the production of MMP, maintaining this vicious circle.[14]

Circulating levels of MMP have been suggested to represent a prognostic marker for the stability of coronary atherosclerotic lesions, as well as for predicting the risk of cerebrovascular and coronary adverse events. MMP-9 was significantly more expressed in patients with unstable plaques compared to stable plaques, and MMP-9 levels were the only independent predictor of coronary plaque rupture in a study that included 47 patients with AMI, 23 with angina and 19 with stable angina pectoris, in which intravascular ultrasonography was performed to assess atheroma plaque rupture.[57] Serum MMP-9 was also significantly higher in patients with ST-segment elevation myocardial infarction those without non-ST-segment elevation MI or unstable angina, thus indication rupture or vulnerability of coronary plaques.[58]

MMP IN ACUTE CORONARY SYNDROMES

In addition to the assigned role of MMPs in the process of vulnerability of coronary atheromatous plaques, they have a well-defined role in post-infarction ventricular remodeling and various etiological forms of cardiomyopathies, with onset of congestive heart failure, repeated hospitalizations and death. MMP activity is directly proportional to the progression of heart failure.[12] Furthermore, in acute myocardial infarction, the level of MMP is significantly increased due to local cytokine activation and migration of inflammatory cells.[59] As the post-infarction reparative inflammatory response progresses, the level of MMP gradually decreases, but a subsequent a reactivation occurs, which is associated with worsening the ventricular remodeling and accelerated progression towards heart failure.[60] A study on 404 patients with AMI aimed to assess the relationship between structure and left ventricular function (measured by 2D echocardiography), and the level of MMP-9, TIMP-1, and the correlation of these biomarkers with the level of NTproBNP. The results identified a direct correlation between left ventricular volumes and plasma levels of MMP-9, TIMP-1 and NT-proBNP. TIMP 1 and MMP-9 were also significantly correlated with the postinfarction ventricular remodeling (assessed as the difference in ventricular volumes from baseline and follow-up). In addition, TIMP was a significant predictor for the composite endpoint of all-cause deaths and rehospitalization, with an area under the ROC curve of 0.811.[61]

The use of MMP inhibitors to prevent post-infarction ventricular remodeling is impeded by the biphasic character of MMP activation after MI. If the therapeutic target is to decrease ventricular rupture rates, the administration of MMP inhibitors should be performed in the initial phase. In order to modulate ventricular remodeling in a chronic setting, the inhibitors should target the second wave of MMP activation. However, excessive and prolonged administration of MMP inhibitors can lead to vicious scarring, with excessive fibrosis, which can result in diastolic heart failure.[14]

Matrix metalloproteinase 9, also called gelatinase B, is a proteolytic enzyme responsible for the degradation of type IV collagen and elastin.[62] Elevated plasma levels of MMP-9 have been previously reported in patients with acute coronary syndromes.[63-65] A study that evaluated the expression MMP-9 in a comparative study between patients with stable coronary heart disease, ACS and healthy controls, found that MMP-P levels were significantly higher in ACS patients compared to stable angina, and also significantly higher in patients with ACS with a poor outcome.[66] Another study that included 80 patients with AMI and stable coronary heart disease, assessed serum levels of MMP-2, -3, -9 at the time of the acute event, and at 3-months follow-up. The results showed that the level of MMP-3 evaluated in the acute phase was significantly higher in patients with AMI compared to those with stable angina (453 ng/L vs. 217 ng/L, $p = 0.01$). This difference was not maintained at the 3-month assessment, in terms of MMP-3 level ($p > 0.05$). Similar results were recorded for the level of MMP-9 which was significantly higher in those with acute myocardial infarction (412 ng/L vs. 168 ng/L, $p = 0.002$), but only in the acute phase, and not at 3 months after the acute event ($p > 0.05$).[67]

THE PROGNOSTIC ROLE OF MMP

In addition to the well-defined role on the development and progression of atherosclerotic lesions, but also of ventricular remodeling in various cardiovascular diseases, MMPs have also been studied as prognostic markers in various cardiovascular pathological scenarios. MMP plays

a central role in the process of rupture of vulnerable coronary plaques, but also in post-myocardial infarction remodeling, by degrading MEC, especially type IV collagen and elastin, and by facilitating the migration of inflammatory cells into tissues. It has been shown that MMP-9 levels are elevated after the acute phase of an ACS, but that it is also related to patient prognosis.[68] In a study that included 155 patients with AMI who underwent primary percutaneous coronary revascularization, the cut off value of 398.2 ng/L for MMP-9 was an independent predictor of in-hospital mortality.[69]

Moreover, persistently elevated MMP-9 levels beyond the acute phase in AMI, was associated with an altered cardiovascular prognosis over a 6-year follow-up period.[45] Another study that included 1,024 consecutive patients with AMI, aimed to assess the predictive capacity for adverse events of the serum level of MMP-2, -3, -9, determined on day 4 after the acute event. Adverse events included all-cause death, hospitalization for heart failure, and recurrent AMI over a mean follow-up period of 519 (134–1,059) days. The results revealed that MMP-2 and MMP-3 levels were significantly higher in patients who died compared to survivors ($p = 0.006$ and $p = 0.01$, respectively), but there were no statistically significant differences in the rate of hospitalization for heart failure or reinfarction. Also, the level of MMP-9 was not significantly different between survivors and those who had deceased during the follow-up period. However, the only independent predictor of all-cause mortality during the study period was the plasma level of MMP-2, after adjusting for the NT-proBNP level and the GRACE score.[70]

Another study evaluated the prognostic value of different plasma MMPs in 165 non-diabetic patients with stable coronary heart disease over a follow-up period of at least 6 months, with a primary endpoint consisting in cardiac death, non-fatal AMI, unscheduled coronary revascularization or hospitalization for unstable angina. The results showed that serum levels of MMP-2 (914.7 ± 13.2 ng/mL vs. 830.7 ± 31.9 ng/mL vs. 783.0 ± 28.4 ng/mL, $p = 0.002$), MMP-3 (129.5 ± 4.2 ng/mL vs. 116.8 ± 8.0 ng/mL vs. 91.7 ± 9.5 ng/mL, $p = 0.01$), and MMP-9 (31.4 ± 2.8 ng/mL vs. 11.4 ± 5.4 ng/mL vs. 6.7 ± 2.8 ng/mL, $p = 0.006$) were significantly higher in patients with significant atherosclerotic coronary heart disease compared with X coronary syndrome and healthy individuals. However, the only independent predictor for adverse cardiovascular events at follow-up was the MMP-3 level, after adjusting for the hs-CRP level and the number of coronary arteries with significant stenosis (hazard ratio 2.47, 95% CI 1.10–5.54, $p = 0.02$).[71]

CONCLUSIONS

The extracellular matrix plays an important role in the development and progression of atherosclerotic lesions. MMPs have proteolytic activity at the level of ECM and thus plays an important role in maintaining the normal vascular structure, but also in the secondary cardiovascular remodeling and in vulnerabilization of atherosclerotic plaques. In addition to the well-defined role on the development and progression of atherosclerotic lesions, MMP also has prognostic value in patients with acute myocardial infarction, for predicting the risk of heart failure, reinfarction or intrastent restenosis, therefore representing a potential prognostic biomarker that needs further validation.

CONFLICT OF INTEREST

Nothing to declare.

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