THE ROLE OF MATRIX METALLOPROTEINASE-3 IN THE DEVELOPMENT OF ATHEROSCLEROSIS AND CARDIOVASCULAR EVENTS

Krintus Magdalena, Kuligowska Magdalena, Sypniewska Grazyna

Department of Laboratory Medicine, Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz, Head: Prof.Grazyna Sypniewska, PhD

1.1 Abstract

The matrix metalloproteinases are a family of peptidase enzymes responsible for the degradation of extracellular matrix (ECM). Alterations in the structure and composition of the ECM play a key role in the atherogenic process. Recent data suggest the important role of MMPs in the development of atherosclerosis and future cardiovascular events. Expressed at low levels in normal tissue, MMPs are upregulated in remodeling processes. Matrix metalloproteinase-3 (MMP-3) is present in atherosclerotic plaques and acts in the degradation of the fibrous cap of the atheroma. Many clinical studies reported that increased MMP-3 level and also the gene polymorphism of MMP were the independent cardiovascular risk factors. MMPs represent an attractive target to prevent matrix degradation, atherosclerosis and possible cardiovascular events.

Key words: matrix metalloproteinases, extracellular matrix, matrix metalloproteinase-3, remodeling, polymorphism, atherosclerosis

1.2 Characteristics of the MMPs family

MMPs were discovered in 1962, since there over 20 human MMPs have been cloned and sequenced (1). Metalloproteinases are a family of enzymes that degrade components of the extracellular matrix (ECM). These enzymes play an important role in various biological processes, both physiological and pathological, like for example cancer and atherosclerosis (2).

The MMPs family consists of at least 25 zinc-dependent endopeptidases. They are classified into 4 subgroups and include secretory enzymes such as: collagenases (MMP-1 and MMP-13), stromelysins such as MMP-3 and gelatinases, which include MMP-2 and MMP-9. There is also a member of MMP family characterized by being an integral part of the plasma membrane called MT-MMP (membrane type metalloproteinase) (3). Activated MMPs can completely degrade all extracellular matrix components. MMPs are produced by various cells including macrophages, fibroblasts, endothelial cells and smooth muscle cells (4).

Most MMPs are synthesized as inactive pro-enzymes (pro-MMPs). Various serine proteases activate latent pro-MMPs by cleaving the pro-peptide domain (5).

A large number of cytokines and growth factors can regulate the synthesis of MMPs. Il-1, PDGF and TNF stimulate, whereas TGF-ß, heparin and corticosteroids inhibit MMPs. The MMPs are more specifically inhibited by four naturally occurring enzymes called tissue inhibitors of matrix metalloproteinases (TIMPs) and also less specifically by a-2-macroglobulin and exogenous heparin. (3, 5). All TIMPs posses amino-terminal domain that interacts with the active zinc-binding sites of MMPs, blocking their access to substrate. Both TIMP-1 and TIMP-4 can interact and inhibit MMP-3 and MMP-9 (5). TIMP-1 is synthesized by most types of connective tissue cells including macrophages.

MMPs and TIMPs together contribute to both the inflammatory state and the extracellular remodeling that occurs during atherogenesis (6).

1.3 Metalloproteinases and vascular remodeling

Vascular remodeling plays an important role in many physiological processes requiring cell migration and degradation of extracellular matrix (ECM). There are two systems able to degradation of most ECM components: the plasminogen activator-plasmin and matrix metalloproteinase system (1). Connective tissue integrity depends on the balance between degradation and repair of the ECM. Activation or inhibition of degrading enzymes affects extracellular matrix remodeling (7).

Structural changes occurring during the growth of atherosclerotic plaque lead to accumulation of cells and lipids within the intimal layer of the diseased artery. The mechanism leading to an increased number of intimal smooth muscle cells in atherosclerotic lesions remains largely unknown, but the contribution of migration and proliferation of smooth muscle cells (SMCS) has been suggested. An increase of MMPs expression and activation were associated with development of subintimal arterial lesions and SMCS migration in experimental models. MMPs inhibition decreases SMCS migration in vitro (8).
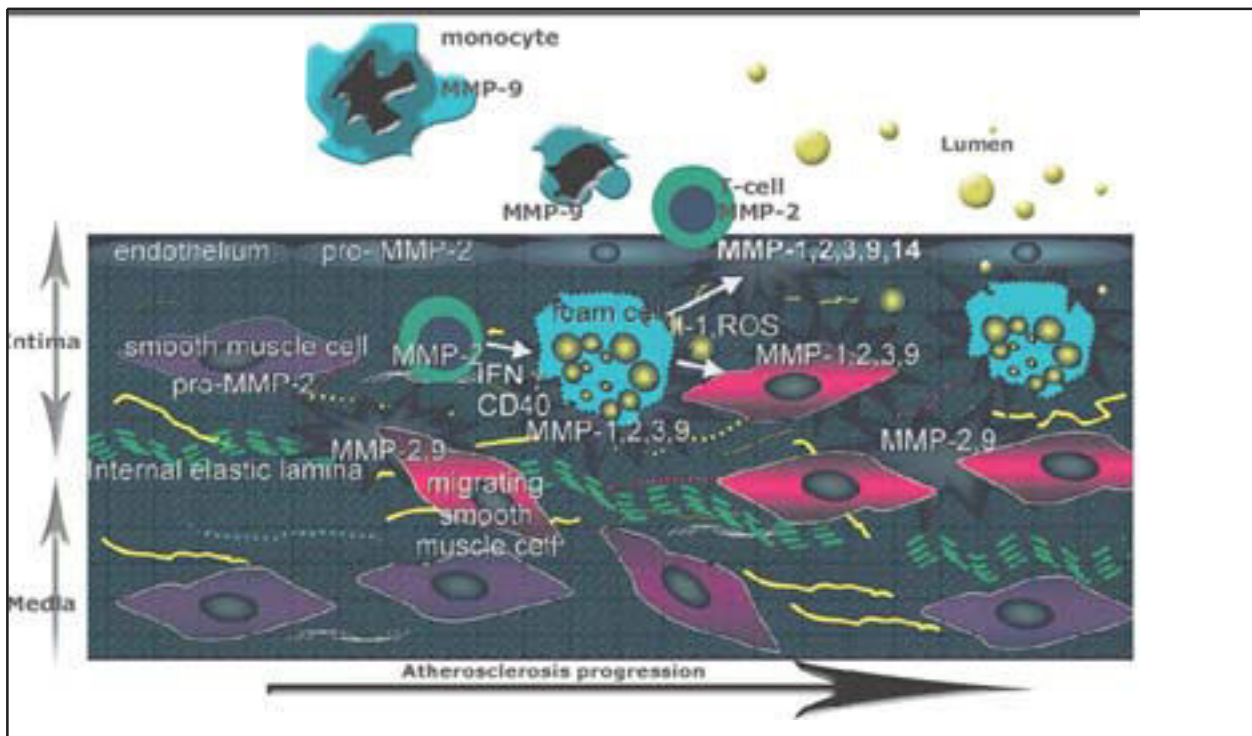
Figure 1. Cells within the vessel wall produce various MMPs. Degradation of matrix by activated MMPs in vessels undergoing remodeling is thought to weaken the arterial wall leading to progression of atherosclerosis (8- according to with small changes)

Expression of various pro-MMPs is increased in atherosclerotic lesions. Macrophages derived foam cells in unstable plaque, have been identified as a major source of MMPs including MMP-3, in human and experimental atherosclerotic lesions (9). Also some vascular smooth muscle cells have been shown to express stromelysin, which principally degrades proteoglycan core protein, laminin and basement membranes (10). Finally, MMPs are thought to weaken the arterial wall leading to destabilization and rupture of atherosclerotic plaques (8).

Regulation of matrix conservation and degradation by metalloproteinases determines the plaque stability and the risk of cardiovascular disease and stroke. MMPs activity is regulated at three levels: transcription, activation of zymogenes and interaction with specific inhibitors (1). The gene transcription of MMPs is under tight control. MMPs polymorphism has been identified for several of them. The most studied to date are polymorphism that occur in the promoter region of MMP-3 and lead to low- or high-transcription activity genotypes (10,11,12).

Recent studies identified genetic polymorphism of promoter regions of MMP-1 and MMP-3. There is a polymorphism at the -1171bp in the promoter region of MMP-3. The promoter region of MMP-3 is the 5A/6A allele and signifies a 5- or 6-adenine sequence. When the 5A allele occurs MMP-3 promoter activity is increased and in turn, MMP-3 levels are increased (12,13). The 6A allele has been associated with reduced activity of MMP-3 promoter and MMP-3 levels. First, Mizon-Gerad et al. identified a strong relationship between MMP-3 5A polymorphism and MMP-3 tissue level. They have assessed the possible effect of MMP-3 gene polymorphism on the clinical outcomes of patients with heart failure (HF). Their data suggest that MMP-3 and MMP-9 polymorphism is related to the occurrence of cardiac events in HF patients (14).

Many other clinical studies examined the relationship between MMP polymorphism and outcomes in cardiological patients.

Some investigators observed that MMP-3 polymorphism in patients with nonischaemic cardiomyopathy was an independent predictor of cardiac mortality (11,12,13).

In the Helsinki Sudden Death Study, Polannen discovered that high MMP-3 promoter activity (5A) represented a significant risk factor in the population of 300 Caucasian males aged 33-69 years. In this study, men with high promoter activity for both MMP-3 and MMP-9 loci were found to have the largest number of complicated lesions (13).

Recently, extracellular matrix metalloproteinase inducer (EMMPRIN) has been reported to induce and activate MMP expression. EMMPRIN is one of the factors involved in the production and activation of MMPs. EMMPRIN is a highly glycosylated transmembrane protein identified on the surface of human cancer cells. In one study, investigators found that EMMPRIN was expressed in human monocyte-derived macrophages. It was correlated with MMPs upregulation and colocalization with macrophages in atherosclerotic lesions. This data suggest that monocyte/macrophage-expressed EMMPRIN may play a key role in atherosclerotic lesions development, accumulation of macrophages and MMP production (6).

Other kind of control is an activation of latent proenzymes. Activation of MMPs can occur intra- or extracellulary through the action of other proteases. In the process of stepwise activation previously activated metalloproteinase can activate other, increasing their proteolytic activity fivefold to eightfold. In several studies MMP-3 has been shown to activate the zymogen form of: MMP-1, MMP-7, MMP-8, MMP-9 and MMP-13. Similarly, MMP-12 has been shown to activate pro-MMP-3 (3).

The inhibition of MMPs includes the interaction with specific tissue inhibitors of metalloproteinases.

1.4 MMP-3 and atherosclerosis

Stromelysin-1 (MMP-3) is a neutral proteinase secreted by connective tissue cells as an inactive zymogene (proMMP-3) and is capable of degrading many components of the extracellular matrix including collagen types I, and IV, fibronectin, laminin and proteoglycans. MMP-3 is also found as an activator for several other MMPs (5). MMP-3 is also capable to activate of interstitial procollagenase (proMMP-1) and progelatinase B (proMMP-9) (15).

Many molecular and cellular mechanisms link inflammation and haemostatic mechanism, for example atherosclerosis. Inflammation plays an important role in the initiation, progression and rupture of atherosclerotic plaques. Experimental data have established the key role of MMPs in atherogenesis (8). Elevated levels of several MMPs including MMP-3 have been demonstrated within atherosclerotic plaques (16). Macrophage-derived foam cells in unstable plaques have been shown as a major source of MMPs, including MMP-3 (4). MMPs activities facilitate migration of vascular smooth muscle cells through the internal lamina into the intimal space, where they proliferate and contribute to plaque formation (3). MMPs break down the components of fibrous cap of vulnerable atherosclerotic lesions. The fibrous cap contains collagen type I and III, and also elastin and proteoglycans (3).

Circulating levels of MMPs and their inhibitors (TIMPs) could reflect the atherosclerotic process occurring within the arterial wall and have been identified in normal and failing myocardium. Recent studies suggest that MMPs and TIMPs play a role in various cardiovascular diseases including atherosclerosis and ventricular remodeling observed in heart failure (17, 18).

In the field of cardiovascular disease increased levels of MMPs have been reported in patients with hypertension, unstable angina and acute myocardial infarction (17). In one study both serum MMP-3 and TIMP-2 levels were shown to be increased in heart transplant patients (17).

In the study of Beaudeux and colleagues it was found that mean circulating levels of MMP-3, MMP-9 and TIMP-1 were significantly elevated in patients with hyperlipidemia compared to normolipidemic, healthy subjects. Moreover, elevated serum levels of both MMP-3 and TIMP-1 were significantly associated with the presence of carotid atherosclerotic plaques in patients at high cardiovascular risk (4).

Wu et al assessed the prognostic value of different plasma MMPs in patients with stable coronary artery disease. In this study the number of diseased vessels, plasma hsCRP and MMP-3 level were associated with the development of cardiovascular events. However, only the plasma MMP-3 level was an independent prognostic marker for future cardiovascular events, suggesting its potential role in risk stratification of stable coronary artery disease (19).

Some investigators reported the positive effect of statin therapy on MMP-3 levels. The beneficial role of statins (3-hydroxy-3-methylglutaryl coenzyme-A inhibitors) in patients with coronary atherosclerosis has been established by a large number of clinical trials. They are also widely used for the treatment of hypercholesterolemia. The primary role of statins is lipid lowering but their pleiotropic effects are related also to vascular inflammation, plaque stability, endothelial function and oxidative stress (20, 21). Statins were shown to inhibit secretion of MMPs from human and animal smooth muscle cells and macrophages that could contribute to plaque stability (22). Recently, increasing evidence suggest that MMP-3 could be inhibited by statins thus decreasing a risk of cardiovascular events. Huang and colleagues observed that short-term effect of simvastatin treatment were different on serum hsCRP and MMP-3 levels in patients with hypercholesterolemia. Lipid profiles and serum hsCRP level were decreased while MMPs levels were unchanged. After withdrawal of statin lipids and CRP again increased while MMPs were still unchanged and MMP-3 was even lower. This suggested the prolonged effect of statin therapy on serum MMP-3 level, up to 120 days after simvastatin withdrawal (21).

MMP-3 lowering by statin therapy is an interesting target but further work is required.

References

1. Lijnen HR: plasmin and matrix metalloproteinases in vascular remodeling. Thromb Haemost (2001); 86(1), 324-333

2. Olewicz-Gawlik A, Hycaj P, Lacki JK: Metaloproteinazy w patogenezie zapalnych ukladowych chorób reumatycznych. Reumatologia (2005); 5, 280-285

3. Jones CB, Sane DC, Herrington DM: Matrix metalloproteinases: A review of their structure and role in acute coronary syndrome. Cardivasc Res (2003); 59, 812-823

4. Beaudeux JL, Giral P, Bruckert E, Bernard M, Foglietti MJ, Chapman MJ: Serum matrix metalloproteinase-3 and tissue inhibitor of metalloproteinases-1 as potential markers of carotid arherosclerosis in infraclinical hyperlipidemia. Atherosclerosis (2003); 169, 139-146

5. Pauschinger M, Chandrasekharan K, Poller J, Noutsias M, Tschope C, Schultheiss H: Inflammation and extracellular matrix protein metabolism: two sides of myocardial remodeling. Europ Heart Journal Suppl (2002); 4, 149-153

6. Liang L, Major T, Bocan T: Characterization of the promoter of human extracellular matrix metalloproteinase inducer (EMMPRIN). Gene (2002); 282, 75-86

7. Tengiz T, Ercan E, Aliyev E, Sekuri C, Duman C, Altuglu J: elevated levels of matrix metalloprotein-3 in patients with coronary aneurysm: A case control study. Current Controlled Trials in Cardiovascular Medicine (2004); 5, 10

8. Galis ZS, Khatri JJ: Matrix metalloproteinases in vascular remodeling and atherogenesis: the good, the bad, and the ugly. Circ Res (2002); 90: 251-262

9. Galis ZS, Sukhova GK, Kranzhofer R, Clark S, Libby P: Macrophage foam cells from experimental atheroma constitutively produce matrix degrading proteinases. Proc Natl Acad Sci USA (1995); 92, 402-406

10. Temo I, Torn K, Kan T: Circulating Matrix Metalloproteinase-1and-3 in Patients With an Acute Coronary Syndrome. Am J Cardiol (2003); 92, 1461-1464

11. Spinale FG: Matrix metalloproteinase gene polymorphisms in heart failure: new pieces to the myocardial matrix puzzle. Eur Heart J (2004), 25, 631-633

12. Nojiri T, Morita H, Imai Y, Maemura K: Genetic variations of matrix metalloproteinase-1 and -3 promoter regions and their associations with susceptibility to myocardial infarction in Japanese. Int J of Cardiol (2003); 92, 181-186

13. Pollanen PJ, Lehtimaki T, Mikkelsson J, Ilveskoski E, Kunnas T et al: Matrix metalloproteinase 3 and 9 gene promoter polymorphisms: joint action of two loci as a risk factor for coronary artery complicated plaques. Atherosclerosis (2005); 180, 73-78

14. Gerad-Mizon F, De Groote P, Lamblin N et al: Prognostic impact of matrix metalloproteinase gene polymorphism in patients with heart failure according to the etiology of left ventricular systolic dysfunction. Eur Heart J (2004), 25, 688-693

15. Masatoshi J, Hirondou J, Yoshihide A, Kenichi Y, Norihito Y, Kunihiko T: Serum matrix metalloproteinase-3 in systemic sclerosis, Arch Dermatol Res (2004); 296, 25-29

16. Prescott MF, Sawyer WK, Von Linden-Reed J: Effect of matrix metalloproteinase inhibition on progression of atherosclerosis and aneurysm in LDL-receptor-deficient mice overexpressing MMP-3, MMP-12, and MMP-13 and restenosis in rats after balloon injury. Ann NY Acad Sci (1999); 878, 179-190

17. Dorent R, Beaudeux JL, Tezenas S, Ghossoub JJ: Circulating Levels of Matrix Metalloproteinases in Heart Transplant Recipients, Transpl Proceed (2000), 32, 2750-2751

18. Dollery CM, Mc Ewan JR, Henney AM: Matrix Metalloproteinases and Cardiovascular Disease. Circulation Research (1995); 77, 863

19. Wu TC, Leu HB, Lin WT, Lin CP, Lin SJ, Cheu JW: Plasma matrix metalloproteinase-3 level is an independent prognostic factor in stable coronary artery disease. Eur J Clin Invest (2005); 35, 537-545

20. Wilson WR, Evans J, Bell PR, Thompson MM: HMG-CoA Reductase Inhibitors (Statins) Decrease MMP-3 and MMP-9 Concentrations in Abdominal Aortic Aneurysm. Eur J Vasc EndovascSurg (2005); 30, 259-262

21. Huang CY, Wu TC, Lin WT, Leu HB, Lin CP, Lin SJ, Chen JW: Effects of simvastatin withdrawal on serum matrix metalloproteinases in

hypercholesterolaemic patients. Eur J Clin Invest (2006); 36, 76-84

22. Luan Z, Chase AJ, Newby AC: Statins inhibit secretion of metalloproteinases-1, 2, 3, 9 from vascular smooth muscle cells and macrophages. Arterioscler Thromb Vasc Biol (2003); 23, 769-775