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RESEARCH ARTICLE

MATRIX METALLOPROTEINASES IN CARDIOLOGY PRACTICE

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ABSTRACT

Matrix metalloproteinases, their structure and classification is considered. The meaning of MMPs in cardiovascular disease atherosclerotic lesions and diabetes is described in details.

INTRODUCTION

Matrixmetalloproteinase's (MMP), ormatrixins are functioning in extracellular medium of cells and destroy both matrix and extra matrix proteins. They play central role in morphogenesis, wound healing, tissue restoration and reconstruction in response to damage i.e. after myocardium infarction. Also they participate in progression of such pathological conditions as a thermo a, arthritis, cancer and chronic ulcers. MMP are the multi-domain proteins and their activity is regulated, among other, by tissue inhibitors of metalloproteinase's (TIMP). In this article we will try to review the classification, structure and functions of metalloproteinase's, their biological role in certain pathological conditions.

Mpp functions

Timely destruction of extracellular matrix (ECM) is an important specific of development, morphogenesis, restoration and remodeling of thet issue. In normal physiological conditions those processes are in equilibrium, but disruption of their regulation and subsequent imbalance is a reason for a number of pathologies, such as arthritis, nephrites, cancer, encephalomyelitis, chronic ulcers, fibrosis etc. The inseparable part of such cardiovascular diseases as atherosclerosis, left ventricle hypertrophy, heart failure, heart aneurism[1-3],is the uncontrolled remodeling of extracellular matrix (ECM) of myocardium and vascular tissue. Multiple types of proteinases participate in degradation of ECM, but it is thought that the key role is played by matrix metalloproteinases [4]. 24 genes in human genome are responsible for synthesis of matrixins. However, gene MMP-23 is doubled, and thus 23 MMP exist in human organism. Activity of the majority of matrixins in physiological conditions and tissues is very insignificant and their production is to large extent controlled by inflammatory cytokines, growth factors, hormones, intercellular and cell-matrix interaction [5]. The activity of matrixins is also controlled by activation of precursor pro-enzymes and suppressing activity of internal inhibitors -tissue inhibitors of metalloproteinases (TIMP).Thus the balance between MMP and TIMP is deciding for subsequent extracellular remodeling in the tissues.

It is thought that destruction and removal of molecules of extracellular matrix from the tissue is the main function of matrixins. At the same time wider recognition is achieved by

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hypothesis that the destruction of molecules of extracellular matrix or cellular surface molecules affects intercellular and cell-matrix interactions, and production of growth factors related to extracellular matrixes makes cell receptors sensitive to matrixins. Also, multiple cells of NON-extracellular matrix are the potential substrate for matrix metalloproteinases. I.e. the effect of MMP may lead to cellular migration, differentiation, growth, inflammatory processes, neovascularization, apoptosis etc.

Structure of MMP

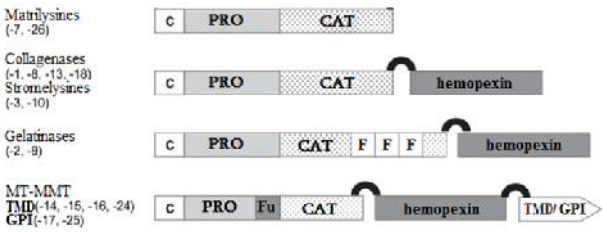

Fig.1. Structure and classification of matrix metalloproteinases: S – signal site; PRO – propeptide domain, CAT - catalytic domain; hemopexin – hemopexin domain; F – fibronectin-linking site; TMD – transmembrane domain; GPI – glycophosphatidylinositol; Fu – furin-cleaved site.

Standard MMP consists of propeptide approximately 80 amino acids long, catalytic domain approximately 170 amino acids long, linking peptide of different length (sometimes called "link" region)and hemopexin-like domain consisting of approximately 200 amino acids. ExceptionsincludeMMP-7 (matrilysin -1), MMP-26 (matrilysin -2)andMMP-23 – they lack linking peptide and hemopexin-like domain, and MMP-26 has unique cystein-rich domain and immunoglobulin-like domain after catalytic domain. Two gelatinases, gelatinase A (MMP-2) and gelatinaseB (MMP-9), have three repeating fibronectin-II-like motif in catalytic domain. Zinc-bindingmot if HEXXHXXGXXH incatalyticdomain and mot if PRCGXPD ("cystein switch") in propeptide are the typical sequences where three histidin residues in zinc-binding motif and cystein in propeptide bind catalytic zinc ion. ComplexCystein-Zn^{2+}prevents binding of zinc atom to water molecule necessary for catalysis which allows to keep pro MMP inactive. The catalyticdomainalsocontains methionine residue forming the so-called Met-turn sites after zinc-binding motif [6]. Zinc-binding motif and Met-turn also exist in families of ADAM-proteases (*A Disintegrin And Metalloproteinase),* ADAMTS-proteases (*A Disintegrin And Metalloproteinase* with *Thrombospondin Motifs*), as tacinsfamily, serralysines family, protozoan peptidase leishmanolys in and pregnancy associated protein-A (PAPP-A), due to which all the above mentioned compounds are included in the metzincins group[6].

Based on the domain structure and biological function MMP are divided intocollagenases, gelatinases, stromelysines, matrilysines, membrane type matrix metalloproteinase (MMP-MT) and other [65].

Classification so FMMP

MMP are classified as sub family of matrixes of family of zinc-containing metalloproteinase's M10 in peptidases catalogue MEROPS. The MMP of vertebrates are numbered, butat the same time some of them have generic names. MMP-4, MMP-5, MMP-6 and MMP-22 are absent in the list of metalloproteinases since they were proven to be identical with other compounds in the list. Matrix metalloproteinases are normally the extracellular protein, but in the recent studiesMMP-1 [7], MMP-2 [8] andMMP-11 [9]were found in intracellular space as well, due to which it is presumed they can affect intracellular proteins.

Collagenases

ThegroupincludesMMP-1, MMP-8, MMP-13 andMMP-18 (notfoundinhuman, foundinXenopus clawed frogs). The key particularity of the proteases is the capability to cleave interstitial collagens of types I, II and III in specific site near N-terminal. Also the collagenases may destroy multiple other molecules of extracellular and NON-extracellular matrix.

Gelatinases

The group includes gelatinase A (MMP-2) and gelatinaseB (MMP-9). They easily cleave denaturized collagen and gelatins. As was mentioned above, the proteases have the site with three repeating fibronectin-II-like motif in catalytic domain, binging to gelatin, collagen and laminin [10].MMP-2 (butnotMMP-9) cleaves collagen of I, II and III types [11,12]. DespitethefactthatlaboratorymicewiththelackofMMP-2

Develop without any visible pathology [13], mutations in humans leadingto the absence of active form of the protease are related to hereditary multicentric osteolysis – rare autosomal-recessive genetic disease leading to destruction and resorption of damaged bones [14]. This fact confirms the participation of MMP-2 in osteogenesis [14].

Stromelysines

Stromelysin-1 (MMP-3) andstromelysin-2 (MMP-10) have similar biological functions, but proteolytic activity of MMP-3 in general is higher than in MMP-10. Other than cleavage of extracellular matrix elements, MMP-3 activates some pre-MMP. Forexample, itseffectonpre-MMP-1 is a decisive factor leading to formation of fully functional form of MMP -1 [15].MMP-11 has generic name stromelysine-3 but is often included in the group of non-classified MMP due to different structure and different biological function. I.e. comparedtoMMP-3 it seffectonextracellularmatrixis much weaker [16], but at the same time it actively cleaves serpins (serine protease inhibitor) [17]–proteins, inhibiting serin protease. Also, as was already noted, MPP-11 displays the activity in intracellular space [29].

Matrilysines

The particularity of matrilysines is the absence of hemopexin-like domain. The representatives of the group include matrilysin-1 (MMP-7) and matrilysin-2 (MMP-26) [18], also known asendometase. Other than molecules of extracellular matrix, MMP-7 interacts with the molecules of cellular surface,

such as pro-alpha-defensin, fas-ligand, pro-TNF-α, and E-cadherin.

Membrane type matrix metalloproteinase (MMP-MT)

There are six types of MMP-MT: four are type I transmembranous proteins (MMP-14, MMP-15, MMP-16 and MMP-24), and two (MMP-17 and MMP-25) are the proteins with glycophosphatidylinositol(GPI)-anchor [66]. Except for MMP-MT4 all of them are capable of activation of pro-MMP-2. Those proteins also can cleave the molecules of extracellular matrix and MMP-MT1 destroys collagen of type I, II and III [19].

Laboratory mice with the absence of MMP-MT1 demonstrate the abnormal skeletal development in postnatal period which is likely related to collagenolytic activity of MMP-MT1 [20].MMP-MT1 also plays the important role in angiogenesis [21].MMP-MT5 is brain-specific and mostly secreted in cerebellum [22].MMP-MT6 (MMP-25) is produced almost exclusively in WBC of peripheral blood, as well as in anaplastic astrocytomas and glioblastomas, but not in meningiomas [23-24].

Other MMP

Seven MMP (together with MMP-11, which, as was said above, sometimes is classified as a stromelysine) are the so-called non-classified MMP.

Metalloelastase (MMP-12) is synthesized mostly in macrophages [25] and is the necessary factor of its migration [26]. Other than elastin it destroys other types of protein as well.

MMP-19 was found in lymphocytes and in the plasma of patients with rheumatoid arthritis and was recognized as autoantigen in patients with rheumatoid arthritis and systemic lupus erythematosis [27]. However it is widely found in many organs including proliferating keratinocytes in healing wounds [28].

Enamelysin (MMP-20), which cleaves amelogenin is mostly found in freshly formed dental enamel. Mutation of the gene site responsible for synthesis of MMP-20 causes genetic diseaseAmelogenin imperfect, which includes the defects of enamel development [29].

MMP-23 is most frequently found in reproductive tissues [30]. It is presumed that this is a type II membrane protein carrying the transmembranous domain in N-terminal part of propeptide. Sincethe propeptide MMP-23 contains motif recognized by furin enzyme it is cleaved in Golgi apparatus and is extracted into extracellular space as active enzyme [31].

MMP-27 was first detected in embryo fibroblasts of chicken [32]. Chicken MMP-27 cleaves gelatin and casein and causes autolysis of enzyme, but presently the data on activity of the enzyme in mammals is scarce.
The last representative of MMP family isepilys in or MMP-28 which issynthe sized mostlyinkeratinocytes[33-34]. Comparison of content of MMP-28 in intact and damaged skin signifies the participation of the protease in tissue homeostasis and participation in reparation [33, 34, 35].

MMP As Markers Of Cardiovascular Pathology

There are several plasma and/or serum proteins which are closely associated with heart failure and are classified as the markers of left ventricle remodeling. Such markers involve extracellular matrix markers- collagen, matrix metalloproteinases [70] and tissue inhibitors of metalloproteinases; inflammatory markers – C-reactive protein (CRP), TNF-αandinterleukins (IL) – 1,6 and 18; oxidative stress markers – homocystein and myeloperoxidase; neurohormonal activation markers– renin, angiotensin-II andaldosterone; myocardium damage markers – cardiospecific troponins and creatinine kinase; myocardium stress markers-brain natriuretic peptide (BNP) and N-terminalpro-BNP [36]. Presentlymultiplebiomarkersinthebloodcirculationmaybeviewe daspredictors of remodeling of the left ventricle or heart failure, however use of only one marker is not enough for precise diagnostics and determination of grade and degree of disease progression. For example, while the average level of BNP is increased in the patients with heart failure, individual level smayvary from 100 to 1,400 ng/ml. BNP concentration does not always correlate with degree of heart failure, and its level may also be increased due to concomitant diseases such as renal failure [37].Thus the level of BNP may vary to such large extent that it is often difficult to differentiate the patients with cardiac pathology from the ones without it [38]. Considering abovementioned it is more reasonable to use multimarker diagnostics which would have included several criteria such as stage of disease, degree of progression etc. One of such biomarker scan be MMP-9

which is the marker of myocardium remodeling [67].

In 2003 Blankenberg *et al* performed first comprehensive clinical study where MMP-9 was proposed as a new prognostic biomarker for persons with increased risk of cardiovascular mortality [39]. There was shown the correlation between MMP-9 and proteins of acute inflammatory phase IL-6, CRP and fibrinogen which indicates that MMP-9 may have its own pathophysiological role in cardiovascular mortality. Squire *et al* added to the study by demonstrating that increase in MMP-9 level is proportional to the increase in LV volume and deterioration of myocardium function after myocardium infarction [40]. Sundstrom *et al*, upon studying the patients from Framingham Heart Study, also noted the relation between increased level of MMP-9 and increased LV volume and heart walls thickness [40]. Hlakty *et al* showed that the level of MMP-9 is related to the myocardium infarction, [41]. Fertin *et al* studied 112 correlations among 52 different biomarkers. The most informative markers related to the remodeling of the left ventricle were related either to extracellural matrix or to neurohormonal activation. They included MMP-9, as well as collagen peptides and BNP [42].

MMP In Atherosclerosis And Plaque Rupture

It is known that atherosclerotic plaque consists of lipid nucleus, external fibrosis “coat” and a mixture of inflammatory cells.

Fibrous coat consists mostly of smooth muscle cells and components of extracellular matrix [71]. The components include collagen responsible for flexibility and elastin responsible for durability. When plaque grows or diminishes, fibrous cover is destroyed and reconstructed again which is a typical remodeling process [72]. In normal conditions destructive and constructive processes are balanced and the coat protects the lumen of vessel from the underlying thrombogenic material. How everinpro-inflammatory conditions there modeling process shifts towards matrix resorption which leads to dangerous weakening of fibrous coat resulting in plaque rupture.

Presently there is proven presence of MMP in active the roscleroticplaques [69]. Both animal studies and study of samples of coronary atherosclerosis in humans display joint localization of MMP-9 and MMP-3 in the edges of atherosclerotic plaques[43].Detected MMP are often related to inflammatory cells such as macrophages or T-lymphocytes [44].Localization of MMP shows weak spots in plaque where the ruptures are the most frequent [45]. It is interesting that the natural inhibitors of MMP, TIMP, were also found in atherosclerotic plaques [44].Sites with increased concentration of TIMP are frequently characterized by vascular calcification [43]. It shows that the vascular calcification is the natural method for stabilization of remodeling processes. Thus the prevalence of MMP activity over TIMP aids in vascular remodeling and increased atherogenesis [45].

Local activation of MMP leads to destruction of collagen and elastin, weakens plaque structure and aids its rupture. Presence of inflammatory cells such as macrophages and T-cells accelerates this process [45].

StudiedusingtransgenicmicewithMMP-9

Deficiency showed that initsbreeding with mice lacking Apolipoprote in E (possessing potent anti-atherosclerotic effect), atherosclerotic load was significantly less than in mice with normal MMP-9 [46]. The similar experiment with MMP-12-deficient mice failed to achieve such result.

It is interesting that Lee *et al* have proven [47], than MMP may directly influence the inflammatory process itself. For example, activation of MMP may lead to local production of growth factor. Changes of matrix in connection with mitogenic factors aid migration of smooth muscle cells in intima and its transformation in macrophage-like structures. Thus activation of MMP creates vicious circle of increased inflammation, increased cells transformation aiding the growth of atherosclerotic plaque, as well as stimulating potential rupture of newly formed plaques [47].

It is also worth to note that the majority of risk factors lead to MMP activation. Smoking, diabetes, hyper homocysteinemia lead to oxidative stress of intima and media of the blood vessel which in turn leads to MMP activation. In addition, the presence of lipids (especially oxidized LDL) stimulates the release of cytokines from activated macrophages leading to increased expression and activity of MMP [68].

MMP And Diabetes Mellitus

Increased level of glucose in vivo affects the MMP activation in different types of cells [48].While acute (24-hours) hyperglycemia in vitro does not cause gelatinolytic activity, chronic increase in glucose level leads to increased MMP activity in the endothelial cells culture while at the same time exerting slight effect on smooth muscle cells and macrophages[49].Said effect was not related to changes in os morality caused by hyperglycemia since similar result was not achieved in equimolecular concentrations of mannose.

In addition to the described aboveroleinrupture of atherosclerotic plaques the observed increase of MMP-9 activity is also very significant for development tof vascular complications related to diabetes mellitus. I.e. Ebihara *et al* have shown [50] that increase in MMP-9 level may serve as predictor of possible microalbuminuria in patients with diabetes. Recent studies have established the necessity of MMP-activity for angiogenesis [51-52]. Thus the increase in MMP-9 level may play the decisive role in such microvascular complications as neovascularization of retina in proliferative diabetic retinopathy [53].

Shiro Uemura *et al* in their study showed than when affecting endothelial cells in conditions of chronic hyperglycemia with antioxidants (PEG-SOD, NAC), their MMP-9 activity decreased, confirming the fact that oxidative stress participates in induction of MMP-9 in diabetes mellitus [49].

As was already said, regulation of MMP is performed on the level of transcription of genes and activation of pro-MMP. Multiple factors, including growth factors, cytokines, chemical agents (phorbol esters) and mechanical stress induce the expression of MMP gene [48, 54, 55]. Promoter area of MMP-9 gene contains nuclear factor-κB (NF-kB), activator protein-1 (AP-1), stimulatory protein-1, and phorbol esters-sensitive elements [56].Li N *et al* in their study showed that NF-kB and AP-1 are sensitive to changes of oxidation-reduction equilibrium [57], which explains the mechanism of regulation of transcription and activity of MMP-9 in glucose-induced oxidative stress.

There is presumed central role of proteinkinaseC (PKC) in activation of MMP-9. It also increases the secretion of MMP-9 in different cells, for example, endotheliocytrs of blood vessels. In addition hyperglycemia promotes the formation of active forms of oxygen in endothelium and smooth muscle cells [58]. At the same time, Shiro Uemura *et al* in their study showed that glucose-induced activity of MMP-9 wasn't changes under effect of PKC antagonists (Staurosporine) [49]. The described paradoxical effect of staurosporine on activity of MMP-9 was previously seen in human B-lymphocytes [59].This question may be answered by most recent study of interaction of signal pathways of active oxygen forms and protein kinaseC. For example, phorbol 12-myristate 13-acetate (PMA) activates specific subunit NADPH-N oxidase and regulates subsequent production of superoxide-anion [60, 61]. Inturn, absorbers of free radicals may decrease PMA- and cytokine-induced activity of PKC in fibroblasts and smooth muscle cells in blood vessels [62, 63]. In the same way, as was stated above, PEG-SOD and

NAC inhibit PMA- and glucose-induced activity of MMP-9 and its expression [49].Thus the capability of PMA to induce MMP-9 may be related to its effect on free radicals and not only to its effect on PKC [49].

In conclusion we can say that expression and activity of MMP-9 in endothelial cells increases with the blood sugar increase, which signifies new mechanism, via which the hyperglycemia may negatively affect the development of atherosclerotic damage. Also, oxidative stress plays key role in glucose-induced activity of MMP-9 showing that antioxidant therapy is useful for treatment of diabetes mellitus [49]

CONCLUSION

Matrixm etalloproteinases were first discovered in 1962. While just over half a century passed since then, it's early to say that they are fully studied. As was described above, new MMP are discovered, their functions are described in details and the changes are made to the existing classification. Detailed study of behavior of MMP in XXI century will answer many questions set by the science of the XX century.

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