Matrix metalloproteinases (MMPs) are the primary mediators of extracellular remodeling and their properties are useful in diagnostic evaluation and treatment. They are zinc-dependent proteases. MMPs have been involved in the mechanisms of atherosclerosis in various arterial areas, ischemic heart disease and myocardial infarction, atrial fibrillation and aortic aneurysms. Recently, MMP9 has been implicated in dyslipidemia and cholesterol synthesis by the liver. Increased MMP expression and activity has been associated with neointimal arterial lesions and migration of smooth muscle cells after arterial balloon dilation, while MMP inhibition decreases smooth muscle cell migration in vivo and in vitro.

Key words: matrix metalloproteinases, atherosclerosis, ischemic heart disease

Matrix metalloproteinases (MMPs) are the main mediators of extracellular remodeling. Due to these properties attempts are being made to use them both in the diagnosis and treatment of cardiovascular diseases. Tissue remodeling and inflammation play an essential role in the onset and progression of atherosclerosis, ischemic heart disease and heart failure [1]. Myocardial extracellular matrix is not a static structure but it contributes to myocardial adaptation to stress and pathological remodeling [2]. Left ventricular hypertrophy alters the geometry of this ventricle. Myocardial extracellular matrix consists of a fibrillar collagen network, a basement membrane, proteoglycans and glycosaminoglycans [3]. Collagen types I and III ensure the integrity of myocytes and are essential for maintaining the structure and arrangement of myofibrils. Recently, MMP9 has been implicated in dyslipidemia and hepatic cholesterol synthesis [4]. Chronic inflammation plays a very important role in the pathogenesis of atherosclerosis, frequently complicated by myocardial infarction or stroke. Moreover, vascular smooth muscle cells and extracellular matrix proteins, especially collagen types I and III, and proteoglycans participate in atherosclerotic plaque formation [5].

MMPs are zinc-dependent proteases responsible for the degradation of extracellular matrix proteins. MMP8, also known as collagenase 2, is involved in the atherogenic process. Left ventricular remodeling after myocardial infarction or viral infection is also mediated by MMPs which act on collagen and elastin.

The extracellular matrix and the cardiovascular system

Recent progresses have highlighted the roles of extracellular matrix [1, 6, 7]; -promotes cell survival or apoptosis; -reservoir for growth factors and cytokines; -have a role in remodeling and inflammation. Although MMPs play an important role in physiological remodeling, they are also involved in many pathological processes: tumor angiogenesis, metastasis, rheumatoid arthritis, neointimal vascular hyperplasia, atheroma plaque rupture.

Liu P et al. described the members of the MMP family and their substrate for action.

MMPs classification and their action on substrate [1]:

Collagenases:
- MMP-1 (interstitial collagenase) - acts on collagen I, II, III, VII, gelatin, MMP2, MMP9;
- MMP-8 (neutrophil collagenase) - acts on collagen I, II, III, V, VII, X, gelatin;
- MMP-13 (collagenase-3) - acts on collagen I, II, III, IV, gelatin, fibronectin, laminin;

Gelatinases:
- MMP2 (gelatinase-A) - acts on gelatin, collagen I, IV, V, VII, X, XI, fibronectin, laminin, elastin;
- MMP9 (gelatinase-B) - acts on gelatin, collagen III, IV, V, VII, X, elastin, vitronectin;

Stromelysins:
- MMP3 (stromelysin-1) - acts on collagen III, IV, V, IX, X, gelatin, fibronectin, laminin, tenascin, MMP 1, 7, 8, 9, 13;
- MMP10 (stromelysin-2) - acts on collagen III, IV, V, IX, gelatin, laminin, casein, fibronectin, MMP1, 8;
- MMP11 (stromelysin-3) - acts on collagen IV, gelatin, fibronectin, laminin;

Membrane type MMPs:
- MMP14 (MT-1) - acts on collagen I, II, III, gelatin, fibronectin, laminin, vitronectin, proteoglycans, activates pro-MMP2 and pro-MMP13;
- MMP15 (MT-2) - activates pro-MMP2;
- MMP16 (MT-3) - activates pro-MMP2;
- MMP17 (MT-4) - activates pro-MMP2;
- MMP24 (MT-5) - activates pro-MMP2;
- MMP25 (MT-6) - gelatinolytic activity.
MMPs and vascular remodeling in atherosclerosis

Atheroma plaque formation involves structural alterations leading to the accumulation of cells, extracellular matrix and lipids in the arterial intima. Increased expression of MMPs and their activation results in the accumulation of smooth muscle cells in the atherosclerotic lesions [8, 9]. Increased MMP expression and activity has been associated with neointimal arterial lesions and migration of smooth muscle cells after arterial balloon dilation, while MMP inhibition decreases smooth muscle cell migration in vivo and in vitro.

There are still many unknowns about leukocyte infiltration in the intima; MMPs could also facilitate this step. MMP2 facilitates the interaction between T cells and extracellular matrix. Atheroma plaque initiation is determined by vascular leukocytes and invasion of smooth muscle cells into the subendothelial space. In the same way a neointimal hyperplasia is also formed after angioplasty and stenting. Plasminogen activator S3 and gelatinases are elevated after vascular injury.

Studies have shown an increased direct interaction between monocyte cells and a paraformaldehyde fixed layer and elevated MMPs in activated macrophages [10]. MMPs activity is also influenced by smoking. Smoking determines through MMPs emphysematous, as well as atherosclerotic lesions [11]. The epidemiology of cardiovascular diseases that have smoking as a risk factor, atherosclerotic lesions [11]. The epidemiology of cardiovascular diseases that have smoking as a risk factor, atherosclerotic lesions [11]. The epidemiology of cardiovascular diseases that have smoking as a risk factor, atherosclerotic lesions [11]. The epidemiology of cardiovascular diseases that have smoking as a risk factor, atherosclerotic lesions [11].

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to MMP family, enzymes capable of degrading the cardiac extracellular matrix. MMPs are essential in maintaining the balance between extracellular matrix formation and degradation, cavitary remodeling depending on it [24]. Inhibition of MMP actions has been shown to reduce pathological ventricular remodeling.

Kameda et al. raised the assumption of a link between oxidative stress, MMP activation, and left ventricular dilatation. The authors reported a significant positive correlation between left ventricular diastolic volume, MMP2 and MMP9 activity, and pericardial levels of 8-isoprostanand F2α, an oxidative stress marker.

MMPs have also been implicated in various aspects of vascular pathology. MMP collagensases degrade collagen within atherosclerotic lesions and may lead to atheroma plaque rupture. MMP2 and MMP9 gelatinases degrade the collagen fragments and may promote complication of the atheroma plaque [25-27].

Formation of thoracic and abdominal aneurysms is characterized by elastin degradation, collagen synthesis and accumulation of inflammatory cells. At the level of aortic aneurysms there are high concentrations of MMP2, MMP-9 and MMP-12. Experimental studies have demonstrated the elastolytic role of MMPs in aortic aneurysm formation. Increased collagen content causes increased arterial stiffness. However, MMP2 does not appear to be a convenient target in the prevention and therapy of aortic aneurysms [28,29].

Atherosclerotic coronary artery disease was associated with activation of MMP8 and MMP9. MMP activation was associated with high cardiovascular risk in general.

Conclusions

MMPs are a large family of enzymes involved in cardiac and vascular processes, which could be influenced by specific mediators with the goal of treating some cardiovascular disorders.

References

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