Matrix metalloproteinases and cardiovascular disease

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This editorial refers to 'Prognostic value of tissue inhibitor of metalloproteinase-1 for cardiovascular death among patients with cardiovascular disease: results from the AtheroGene study' by E. Lubos et al., on page 150

Introduction

Matrix metalloproteinases (MMPs) are a group of endopeptidases with capacity to cleave components of extracellular matrix, such as collagen and elastin.1 The ability to modify the tissues is important for several aspects of normal and abnormal physiology. Approximately 20 different MMPs are identified, and they can be subdivided into different groups according to which components of the extracellular matrix they degrade. MMPs are secreted in a latent proform and require activation for proteolytic activity. The activity of MMPs is normally low in healthy tissue, but the increased expression and activity of several MMPs in a range of pathological processes, such as inflammation and ventricular remodelling after myocardial infarction, might indicate that they play a role in the pathophysiology and progression of atherosclerotic disease. The activity of MMPs is tightly regulated at gene transcription level and is also regulated by their secretion in an inactive zymogen form that requires extracellular activation and co-secretion of the tissue inhibitors of metalloproteinases (TIMPs).2 In healthy humans, MMP-2 and the inhibitory TIMP-1 and TIMP-2 are expressed across the vessel wall. Furthermore, focally increased expression of several MMPs and presence of MMP activity have been observed in diseased human arteries and in association with arterial morphological changes in experimental models of atherosclerosis.3 MMPs may influence the process of atherosclerotic lesion formation in different ways. MMP activity may contribute to the pathogenesis of atherosclerosis by facilitating migration of vascular smooth muscle cells through the internal elastic lamina into the intima of the vessel wall, where they proliferate and contribute to plaque formation.4 However, MMP activity may also diminish plaque volume by degrading extracellular matrix in the intima.5

Mechanisms

Ruptured plaques have been shown to have several histomorphological features that are different from stable plaques.6 Plaques that rupture tend to have a large lipid core, to have inflammatory cell infiltration of the fibrous cap and adventitia, to possess a thin cap depleted of smooth muscle cells. Depletion of matrix components from the fibrous cap caused by an imbalance between synthesis and breakdown leads to cap thinning. This predisposes the fibrous cap to rupture, either spontaneously or in response to haemodynamic or other triggers. Enhanced matrix breakdown has been attributed primarily to MMPs that are expressed in atherosclerotic plaques by inflammatory cells. MMPs may also be activated by thrombin in atherosclerotic plaques. In atherosclerotic plaques, thrombin could promote plaque instability by increasing the local matrix-degrading activity of MMPs. As acute plaque disruption leads to local thrombin production at the site of vascular injury, this may facilitate proteolytic activation of MMP, which may start a vicious circle with platelet aggregation and further generation of thrombin and then more MMP activation.

Clinical studies

MMP-2 levels are increased in patients with unstable angina or acute myocardial infarction compared with healthy control subjects6 and MMP-9 is increased in patients with three-vessel coronary artery disease compared with controls or patients with one or two vessel disease, implying that elevated levels of MMP-9 mirrors severity of coronary atherosclerosis. In another study, MMP-9 and TIMP-1 levels in patients with lesions in the left anterior descending artery were compared with normal subjects.7 Blood samples were obtained from the aorta and the great cardiac vein within 12 h of onset of symptoms in the myocardial infarction group and within 48 h in the unstable angina group. In both the acute myocardial infarction and unstable angina groups, the great cardiac vein–aorta difference was significantly increased for MMP-9 and TIMP-1 when compared with patient with stable angina pectoris and normal subjects. Therefore, it was concluded that during acute coronary syndrome, there is an increased production of MMP-9 and TIMP-1 in coronary arteries. This observation may suggest that MMP-9 and TIMP-1 act as markers of active plaque rupture. Lubos et al.8 report that TIMP-1 was an independent predictor for future cardiovascular
death in patients with suspected coronary heart disease participating in the AtheroGene study. The same study group has previously reported an increased risk for fatal coronary heart disease events in the same study group in subjects with elevated plasma levels of MMP-9. This association was independent of conventional cardiovascular risk factors. Furthermore, elevated TIMP-1 levels have been reported in patients with coronary heart disease and the Framingham study group has reported that elevated levels of TIMP-1 predict cardiovascular disease/death. MMP function may be influenced by pharmacological drugs. Nitroglycerin has been shown to increase the expression and the activity of different MMPs in isolated human macrophages and to decrease TIMP-1 protein and mRNA levels. The calcium channel blockers, amlodipine and diltiazem, have also been shown to increase the activity of MMP-1 and MMP-2 in cultured human vascular endothelial cells, and Losartan has been shown to increase MMP-2 activity in human vascular smooth cells.

Thus, MMPs are a complex group of endopeptidases with important roles in cardiovascular physiology and pathology. There are at least two possible future clinical applications of this research area. First, the reports from Lubos et al. and other previous observations within this field raise the interesting question of the possibility to develop non-invasive tests for detection of plaque vulnerability. At present, we are far away from the desired prognostic marker of ongoing processes contributing to ultimate plaque rupture. Secondarily, MMP function can be modulated to certain pharmacological drugs, as described earlier, and as MMP activity likely contributes to the development of acute coronary syndromes by making the plaques more vulnerable, MMPs may be an important therapeutic target for future drug development. This vision also appears to be far away in the future. More research is needed to better determine the pathophysiological roles of MMPs and TIMP.

Conflict of interest: none declared.

References