New Insights Into the World of Matrix Metalloproteinases

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The article by Carrel et al in the present issue of Circulation provides remarkable new insights into the matrix metalloproteinases (MMPs) and their effects on the remodeling of the vascular system in aortic atherosclerotic and aneurysmal lesions. The MMPs constitute a family of endopeptidases that have in common the presence of zinc in their active site, a dependency on Ca\(^{2+}\) for their activity, and the ability to react with specific tissue inhibitors of metalloproteinases (TIMPs) to form enzymatically inactive complexes. The MMPs show a wide range of specificity for different substrates, including native and partially degraded fibrillar collagens, basement membrane collagens, proteoglycans, elastin, and fibronectin. The ability of certain MMPs, such as MMP-2, MMP-3, MMP-9, and MMP-12, to hydrolyze elastin are of particular importance in terms of their effects on the vasculature. The “classic” MMPs are synthesized in an enzymatically inactive form, which requires activation by single or multiple steps, as well as by multiple mechanisms, in order to uncover their active site and thereby become biologically active. The “novel” MMPs (known as membrane-type matrix metalloproteinases or MT-MMPs) are synthesized in an active form and play important roles in the proteolytic activation of the classic MMPs. The MMPs are synthesized by a variety of parenchymal cells, connective tissue cells, and inflammatory cells.

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The importance of MMPs in the pathogenesis of vascular disorders is increasingly being recognized, particularly with respect to atherosclerotic lesions, aortic and cerebral aneurysm, and Marfan syndrome. In normal vascular tissues, endothelial cells, medial smooth muscle cells, and adventitial connective tissue cells are the main sources of MMPs, most of which are present in inactive form. However, the macrophages and other types of infiltrating cells are known to be important sources of MMPs in a wide variety of inflammatory conditions.

The activities of MMPs are controlled at three levels: gene expression, activation of the proenzyme forms of the MMPs, and inhibition by complexing with their specific TIMPs. The expression of MMPs is also controlled at the transcriptional level by cytokines, hormones, and growth factors. The activity of MMPs in macrophages is upregulated by a variety of factors, including reactive oxygen species, nitric oxide, and immunologic activation. Biochemical data indicate that the synthesis of individual MMPs is regulated by independent mechanisms.

Interest in the effects of the MMPs initially was centered on the alterations that these enzymes (particularly MMP-2 and MMP-9) produce in the basement membranes of preneoplastic and neoplastic epithelial cells. These observations demonstrated that lysis of basement membrane collagens is a critically important event in the spread of neoplasia and the development of metastases. Observations on the effects of MMPs on the pathogenesis of other disorders associated with destruction or structural remodeling of connective tissue followed, and the participation of MMPs in such processes is now widely recognized.

The classic MMPs are synthesized and secreted into the extracellular space as proenzymes, which require activation by one of the following mechanisms: (1) extracellular activation by other MMPs (including MT-MMPs); (2) extracellular activation by non-MMP proteins; (3) intracellular activation of MT-MMPs by furin; and (4) MT-MMP membrane-associated activation of MMP-2, which occurs in a series of complex events that take place at the cell surface. Plasmin, thrombin, and furin (a trans-Golgi network serine protease) are the most important non-MMP proteins capable of activating MMPs. These enzymes also can be activated in vitro by sulphydryl reagent.

During the past few years, several studies have demonstrated increases in the activities of various MMPs in atherosclerotic aortic aneurysms, and these observations have shown a good correlation with immunohistochemical findings of increased immunoreactivity for these components, particularly in macrophages, and with evidence of lysis of collagen and elastin in the walls of the aneurysm. However, the differences between stenotic and aneurysmal aortic lesions have not been clearly defined in terms of their MMP activity. In their article, Carrell et al have subdivided aortic sclerotic lesions into two categories, on the basis of whether they are characterized primarily by luminal stenosis, with a marked increase in the amount of collagen in the walls, or by an increase in luminal size with the formation of aneurysms that eventually undergo rupture. The finding of central interest in their study is the carefully documented observation, made with state-of-the-art molecular biology techniques, that both types of lesions are characterized by increases in the mRNA and protein expression of MMP-2, MMP-2, MMP-7, MMP-9, MMP-11, MMP-12, MMP-14, and MMP-17. Five other MMPs (MMP-8, MMP-10, MMP-13, MMP-15, and MMP-16) were not detected in either of the two types of aortic lesions. The aneurysmal lesions show a different pattern of expression of MMPs, as demonstrated by a marked selective increase in MMP-3.
The genetic implications of the finding of increased MMP-3 in aortic aneurysms also are of particular interest. To investigate the role of MMP-3, MMP-9, and plasminogen activator inhibitor-1 (PAI-1) in the development of abdominal aortic and intracranial aneurysms, Yoon et al performed genetic association studies using polymorphisms. This polymorphism is present in the promoter regions of the corresponding genes, with alleles that exhibit different transcriptional activities in vitro. Studies using these polymorphisms and DNA isolated from 47 patients with aortic abdominal aneurysms, 57 patients with intracranial aneurysms, and 174 control patients, all from Finland, showed that PAI-1 and MMP-9 were not associated with aneurysms, and that the frequency of the 5A MMP-3 allele was somewhat higher in patients with aortic aneurysms than in the control group. However, the MMP-3 allele frequencies in the intracranial aneurysm group did not differ from those in the control group. The authors concluded that the transcriptionally more active 5A MMP-3 allele might be a genetic risk factor for abdominal aortic aneurysms among Finns.

Consideration must be given to the possible effects of mechanical stretching of the aneurysmal walls on the production and activation of MMPs that can worsen the initial damage and contribute to additional disruption of the tissue architecture. Surprisingly, there have been only a few studies of the effects of the stretching of vascular smooth muscle cells, mostly in the context of changes developing in aortocoronary vein grafts. This event appears to be a generalized biological phenomenon, because changes of similar nature are induced by mechanical stretching of other types of cells, including scleral and cardiac fibroblasts, trabecular cells of the eyes, and glomerular mesangial cells. Furthermore, mechanical stretch also induces apoptosis in several of these cell types, including those in aortocoronary bypass graft, thus contributing further to the disorganization of the tissue. Increased production of MMP-3 in aortic aneurysms may occur at an early point in time, thus serving as an important mechanism of activation of other MMPs. However, this hypothesis needs to be examined critically.

For the reasons cited above, inhibition of MMPs is becoming an important issue in the pharmacological treatment of aortic aneurysms. Yoon et al have presented a review of studies showing the prevention of aortic aneurysms by drugs capable of inhibiting MMPs (RS132908, BB-94, amlodipine, doxycycline, tetracycline derivatives, and indomethacin) in various animal models.

Studies were made to determine the effects of CGS 27023A, a broad spectrum MMP inhibitor, on the aortic atherosclerotic and aneurysmal lesions that develop in LDL receptor-deficient mice fed a high-fat, cholic acid–enriched diet for 16 weeks. These animals developed advanced aortic atherosclerosis with destruction of elastic lamina and ectasia in the media underlying complex plaques. Lesion formation correlated with a 4.6-fold to 21.7-fold increase in the expression of MMP-3, MMP-12, and MMP-13. Treatment with CGS 27023A had no effect on the extent of aortic atherosclerosis, but caused a significant reduction in aortic medial elastin destruction and ectasia. These data suggest that therapy with MMP inhibitors may delay the progression of aneurysms.

Extensive biochemical studies of two types of MMP inhibitors have been reported by Parker et al. Both of these function as chelators of the zinc atom in the catalytic domain of MMP-3. The first of these, known as Galardin (Glycomed GM-6001) binds zinc to a hydroxamic acid group with a high degree of affinity. In contrast, the second type (PD180557 and PD166793) uses carboxylic acid groups to chelate the zinc. Hydroxamic acids undergo rapid metabolism in the liver, have limited aqueous solubility, and are subject to hydrolysis by peptidases in vivo. X-ray and NMR studies of the structure of complexes of several inhibitors with the catalytic domain of MMP-3 have shown that, in addition to chelation of zinc, they also can form hydrogen bonds to the peptide backbone of the enzyme. The exact location of these bonds appears to be an important determinant of the selectivity of the inhibition of MMP-3 compared with that of other MMPs and constitutes an important parameter in the design of new inhibitors. Nevertheless, these studies demonstrate the potential usefulness of MMP inhibitors in the management of abdominal aortic aneurysms, especially those in early stages. The application of the techniques of molecular biology developed by Carrel et al for the study of MMPs in aortic aneurysms holds great promise, especially with respect to the pathogenesis of other types of aortic aneurysms.

References


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