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Role of matrix metalloproteinases (MMPs) and MMP inhibitors on intracranial aneurysms: a review article

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Abstract

Cerebrovascular disease is one of the leading causes of death in the world, and about one-fourth of cerebrovascular deaths are due to ruptured cerebral aneurysms (CA). Hence it is important to find a way to reduce aneurysm formation and its subsequent morbidity and mortality. Proteolytic activity capable of lysing gelatin has been shown to be increased in aneurysm tissue and expression of plasmin, membrane-type matrix metalloproteinase-1(MT1-MMP), and matrix metalloproteinase-2 (MMP-2) in aneurysmal wall is more than what we observe in normal cerebral arteries. MMP inhibitors such as doxycycline and statins may prohibit aneurysm formation and growth. MMPs are important in tissue remodeling associated with various physiological and pathological processes such as morphogenesis, angiogenesis, apoptosis and tissue repair. In this article we review the role of MMPs and MMP inhibitors in formation of aneurysm.

Keywords: Cerebral aneurysm, MMPs, MMP inhibitors, Doxycycline, Statins.

Introduction

The walls of normal arteries are made of three distinct layers: intima, media and adventitia. An internal elastic lamina, which provides mechanical strength, separates the intima from the media and layers of smooth muscle cells are seen in the media(1). There is no external elastic lamina between the media and adventitia in intracranial arteries (Unlike the extra cranial arteries) and adventitia is also very thin compared with vessels of similar diameter in other organs (2,3) . These peculiar characteristics of cerebral arteries make them suitable vessels for aneurysm formation and growth.

The prevalence of unruptured cerebral aneurysms is estimated to be as high as 5%. (4). Its prevalence in angiographic and autopsy studies, have been reported between 2 and 90 per 1000 (5,6). Methodological differences between studies probably lead to this wide range. If all available evidence with inherent overestimation and underestimation is taken together, aneurysms are found in approximately 2% in adults without risk factors for subarachnoid hemorrhage (7).

Intracranial aneurysms, which are the

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most common causes of spontaneous subarachnoid hemorrhage, have multifactorial etiology, and the significance of genetic factors are increasingly recognized (8). Theoretically, the role of arterial hypertension in aneurysm formation is important and incidence of multiple aneurysms is reported to be higher in hypertensive. In an unselected series of 737 aneurysm patients, it has been revealed that the major factor explaining multiplicity is the presence of hypertension, and the influence of age is not significant. Role of gender has been shown, indicating that females are more vulnerable to aneurysm formation (9).

Sudden, severe headache is a key symptom of a ruptured aneurysm. Focal neurological deficits may also exist depending on the site of the aneurysm (10).

Conventional surgical clipping is considered to be the most definite therapy by most professionals (11-15). Damage to vital structures during the operation of aneurysms can be prevented by localization of lesions by neuronavigation system (16). Interventional neuroradiological techniques offer minimally invasive procedures for these lesions. Embolization and coiling of aneurysms are the principal endovascular therapies. All patients with ruptured or unruptured aneurysms should be evaluated for endovascular procedures; nevertheless this therapy is not always the best approach for these patients.

Role of MMPs in the pathogenesis of aneurysm formation

The membrane – type matrix metalloproteinase (MMPs) are important in the processes of degradation and remodeling of the vascular wall matrix which possess major role in development and rupture of aneurysms. Data from different reports on the possible influence of MMP gene polymorphisms on susceptibility to intracranial aneurysms are conflicting and such a possibility is still controversial (17).

About 40% of MMPs family members have similar basic structures. Approximately 20 different types of MMPs have been known and classified based on their presynthetic region on chromosomes and their various substrate specificities. Number designations MMP-1 to MMP- 28 are used for classification (18).

Tissue remodeling associated with various physiological and pathological processes are influenced by MMPs. Example of such processes are: morphogenesis, angiogenesis, apoptosis, tissue injury , cirrhosis, arthritis, metastasis and brain tumors. It is thought that MMP-2 and MMP-9 are important in metastasis. MMP-1 is believed to be important in rheumatoid and osteoarthritis. Recent data suggests importance of MMPs in the pathogenesis of aortic aneurysms. Increased MMPs degrade the structural proteins of the aortic wall (19, 20).

Most MMPs are not expressed at high or detectable levels in the adult central nervous system (CNS). Nevertheless there are some exceptions, for example, high constitutive expression of MMP-11 and MMP-14 in the adult mouse brain have been revealed by RNase protection assays (RPA) (21). Polymerase chain reaction (PCR) technique has also revealed the expression of MMP-2,-3, -7, -9 and -13 in the normal rat spinal cord (22). As a whole, MMPs are mainly not detectable in the normal CNS and their excess has been observed in some neurological disorders and after tissue injury.

Increased expression of plasmin and MT1-MMP (membrane-type matrix metalloproteinase-1), and MMP-2 have been reported in aneurysmal tissues in comparison to normal cerebral arteries. These could be due to excessive proteolytic activity and resulting gelatin lysis which may cause focal degradation of the vascular extracellular matrix and may contribute to aneurysm formation and growth (23).

Matrix metalloproteinase-9 (MMP-9, gelatinase B or type 4 collagenase) gene is a member of the MMP gene family, which encodes a family of zinc-dependent enzymes with proteolytic activity against connective tissue proteins, including collagens, elastin, and proteoglycans. MMP-9 is

known to be produced by inflammatory cells, especially macrophages, and plays an important role in development and tissue remodeling (24). Increased levels of MMP-9 and tissue inhibitor metalloproteins (TIMP) have been revealed in the aneurysm wall in both extra cerebral and intracerebral arteries. Perturbations in MMP-9 levels that contribute to the matrix disruption and cerebral aneurysm formation are local rather than systemic and this local up-regulation is not the consequence of TIMP decrement (25).

The MMP-9 excess has been demonstrated in abdominal aortic and intracranial aneurysms (19, 26-28) and its increment results in formation of aneurysms by degradation of type 4 collagen, proteoglycan core protein and elastin, which are not degraded by some other MMPs. The MMP-9 is regulated mainly at the level of transcription in response to such regulatory molecules as tumor necrosis factor-a , interleukin-1, platelet-derived growth factor, and epidermal growth factor (29, 30). Evidences reveal that imbalance in the local expression of MMP-9 and tissue inhibitors of metalloproteinases is linked to genetic components contributes to the susceptibility to cerebral aneurysms (31).

Screening for presymptomatic aneurysms by the use of plasma MMP-9 activity is not possible due to the absence of increased systemic metalloproteinase activity, However , aneurysmal progression and growth may be arrested by local therapeutic modulation of MMP-9 activity (25).

Role of MMP inhibitors

The MMP inhibitors may reduce the need for invasive treatment and have major advantages for patients as well as socioeconomic benefits (32).

Tetracycline has been shown to have MMP inhibitor effects. Doxycycline, a tetracycline analogue, despite its unclear mode of action is considered the main candidate. It has been shown that doxycycline treatment, reduces MMP-8 and -9 levels and concentrations of tissue inhibitor of metalloproteinase-1 and cystatin C .This influence is considered to be through a profound effect on the number of aortic wall neutrophils, and a pronounced but selective effect on the proteolytic balance in the abdominal aneurysms. This remarkable and novel observation suggests that doxycycline may also be effective in other vascular conditions involving neutrophils, such Behçet disease and Kawasaki disease, and nonvascular conditions such as chronic obstructive pulmonary disease (33, 34).

It has been reported that MMP-2 expression from cultured human aortic smooth muscle cells (SMCs) and abdominal aortic aneurysm (AAA) tissue explants is inhibited by doxycycline at therapeutic serum concentrations. MMP activity contributes to degradation of extracellular matrix in AAAs and atherosclerotic plaque, hence doxycycline may have a potential value in treating these diseases (35).

There are convincing evidences that doxycycline prevents AAA formation in a variety of animal models (36-39), and the results from two small clinical studies suggest that doxycycline may also reduce the AAA expansion and growth in patients (40, 41).

There is a report which demonstrates that doxycycline inhibits expression of tissue MMP-2 and MMP-9, arrests degradation of the elastic matrix and delays aneurysm rupture in MFS-like mice (mouse model of Marfan syndrome). The study shows that the MMPs cause expansion of thoracic aneurysm in MFS (Marfan syndrome) and that doxycycline may significantly inhibit progression of the disease (42).

Doxycycline decreases parenchymal angiogenesis and stimulated cerebral MMP-9 activity. The decrease in MMP-9 activity is associated with decreased micro vessel counts. MMP inhibitors, including tetracycline derivatives may modulate brain abnormalities that are caused by pathologically increased angiogenesis (43).

In one study, excess MMP activity was detected in intracerebral aneurysm tissues, and the treatment with doxycycline signifi-

cantly reduced the incidence of intracranial aneurysms. It is noteworthy that the incidence of aneurysms was dramatically lower in MMP-9 knockout mice but not in MMP-2 knockout mice (26, 44).

Incidence of intracranial aneurysms were reduced to 10% in elastase-induced Intracranial Aneurysms in hypertensive mice treated by doxycycline (45).

In spite of the aforementioned studies , there is another experiment in rat model which does not confirm nonspecific inhibition of MMP with doxycycline decreases intracranial aneurysm formation (by ligation technique in common carotid artery) (46).

Elastase-induced rabbit aneurysm formation in right common carotid artery is accompanied by total elastin destruction. The reason for aneurysm formation in this model may be the initial infusion of elastase, rather than continuous destruction from endogenous proteases released by inflammatory cells. Aneurysmal formation in this experiment, was not inhibited by the administration of doxycycline(47).

Statins(hypolipidemic and antiatherosclerotic agents) are another kind of drugs that are considered the MMP inhibitors . In vitro incubation of mouse macrophages and HMs (human monocyte–derived macrophages) with fluvastatin or simvastatin have been reported to decrease the amount of MMP-9 secreted, suggesting that the effect on MMP-9 activity is affected by statins as a class of drugs (48).

Statins also have been shown to decrease MMP-3 and MMP-9 concentrations in AAAs in clinical trials. Recent observational studies in humans suggest that statins may have a role in abdominal aortic aneurysm (AAA) prevention or may even inhibit aneurysm progression and growth (49-51).

It has been reported that simvastatin reduces the risk of rupturing the intracranial aneurysms in mice. In addition, simvastatin reduces superoxide production and MMP-related gelatinase activity in aneurysmal walls. anti-inflammatory and anti-oxidative properties of simvastatin may have inhibitory effects on intracerebral aneurysmal rupture (52).

Conclusion

Considering the significant impact of MMPs on tissue remodeling associated with morphogenesis, angiogenesis, apoptosis, tissue repair and so on , and the observations in experimental models, it is probable that MMPs have some role in cerebral aneurysm formation and growth .Their role in abdominal aorta aneurysms have been studied more and convincing evidences prescribing anti MMPs in these patients was helpful. Influence of MMP inhibitors such as doxycycline and statins on cerebral aneurysms have also been studied in some experiments .These have revealed promising results but it seems that designation of more sophisticated studies to demonstrate their exact role are necessary.

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