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
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 pre-synthetic region on chromosomes and their various substrate specificities. Number designsations 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 cer-
bral 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 demonstrat-
ed in abdominal aortic and intracranial an-
eurysms (19, 26-28) and its increment re-
results in formation of aneurysms by degra-
dation of type 4 collagen, proteoglycan
core protein and elastin, which are not de-
graded by some other MMPs. The MMP-9
is regulated mainly at the level of transcription in response to such regulatory mole-
cules as tumor necrosis factor-a, interleu-
kin-1, platelet-derived growth factor, and
epidermal growth factor (29, 30). Evidenc-
es reveal that imbalance in the local expres-
sion 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. How-
ever, aneurysmal progression and growth
may be arrested by local therapeutic modu-
lation of MMP-9 activity (25).

Role of MMP inhibitors

The MMP inhibitors may reduce the need
for invasive treatment and have major ad-
vantages for patients as well as socioeco-
nomic benefits (32).

Tetracycline has been shown to have
MMP inhibitor effects. Doxycycline, a tet-
racycline analogue, despite its unclear
mode of action is considered the main can-
idate. 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 pro-
found effect on the number of aortic wall
neutrophils, and a pronounced but selective
effect on the proteolytic balance in the ab-
dominal aneurysms. This remarkable and
novel observation suggests that doxycy-
cline may also be effective in other vascu-
lar conditions involving neutrophils, such
Behçet disease and Kawasaki disease, and
nonvascular conditions such as chronic ob-
structive pulmonary disease (33, 34).

It has been reported that MMP-2 expres-
sion from cultured human aortic smooth
muscle cells (SMCs) and abdominal aortic
aneurysm (AAA) tissue explants is inhibi-
ted 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 sug-
gest 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 rup-
ture in MFS-like mice (mouse model of
Marfan syndrome). The study shows that
the MMPs cause expansion of thoracic an-
eurysm in MFS (Marfan syndrome) and
that doxycycline may significantly inhibit
progression of the disease (42).

Doxycycline decreases parenchymal an-
giogenesis and stimulated cerebral MMP-9
activity. The decrease in MMP-9 activity is
associated with decreased micro vessel
counts. MMP inhibitors, including tetracy-
cline derivatives may modulate brain ab-
normalities that are caused by pathologi-
cally increased angiogenesis (43).

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

References

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