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 sub-
arachnoid hemorrhage, have multifactorial
etiology, and the significance of genetic
factors are increasingly recognized (8).

Theoretically, the role of arterial hyperten-
sion in aneurysm formation is important
and incidence of multiple aneurysms is re-
ported 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 symp-
tom of a ruptured aneurysm. Focal neuro-
logical deficits may also exist depending on
the site of the aneurysm (10).

Conventional surgical clipping is consid-
ered to be the most definite therapy by most
professionals (11-15). Damage to vital
structures during the operation of aneu-
rysms 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 un-
ruptured 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 metallopro-
teinase (MMPs) are important in the pro-
cesses of degradation and remodeling of the
vascular wall matrix which possess major
role in development and rupture of aneu-
rysms. Data from different reports on the
possible influence of MMP gene polymor-
phisms on susceptibility to intracranial aneu-
rysms are conflicting and such a possibil-
ity 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 des-
ignations MMP-1 to MMP- 28 are used for
classification (18).

Tissue remodeling associated with vari-
ous physiological and pathological process-
eses are influenced by MMPs. Example of
such processes are: morphogenesis, angi-
genesis, 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 osteo-
arthritis. Recent data suggests importance
of MMPs in the pathogenesis of aortic aneu-
rysms. 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 nerv-
sous system (CNS). Nevertheless there are
some exceptions, for example, high consti-
tutive 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 neuro-
logical disorders and after tissue injury.

Increased expression of plasmin and
MT1-MMP (membrane-type matrix metal-
loproteinase-1), and MMP-2 have been re-
ported in aneurysmal tissues in comparison
to normal cerebral arteries. These could be
due to excessive proteolytic activity and
resulting gelatin lysis which may cause fo-
cal 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 en-
zymes with proteolytic activity against
connective tissue proteins, including colla-
gens, 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-
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Östergaard JR, Høg E. Incidence of multiple in-


