Role of matrix metalloproteinases in the pathogenesis of intracranial aneurysms

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Intracranial aneurysms (IAs) are a result of complex interactions between biochemical and mechanical forces and can lead to significant morbidity if they rupture and cause subarachnoid hemorrhage. This review explores the role of matrix metalloproteinases (MMPs) in the pathogenesis and progression of IAs. In addition to providing a review of the normal function of MMPs, it is intended to explore the interaction between inflammation and abnormal blood flow and the resultant pathological vascular remodeling processes seen in the development and rupture of IAs. Also reviewed is the potential for the use of MMPs as a diagnostic tool for assessment of aneurysm development and progression.

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INTRACRANIAL aneurysms (IAs) are characterized by localized structural changes to the arterial vessel wall that lead to weakened wall integrity and vessel dilation at the point of weakness. IAs are often found near vessel bifurcations, probably as a result of turbulent flow at those areas. Unruptured IAs have a prevalence of 1%–5% in the population older than 30 years of age.^{53,56} Known risk factors for IA formation and rupture include cigarette smoking, hypertension, and familial history.⁵⁶ IA rupture results in subarachnoid hemorrhage (SAH), a condition with high rates of morbidity and mortality. In patients with SAH secondary to rupture of an IA, 12% die prior to receiving medical attention, and of those who are admitted to the hospital, 40% die within the first month.^{29,57} One-third of the individuals who survive SAH have significant permanent neurological deficits.⁵⁶

Histopathologically, IAs exhibit loss of the internal elastic lamina (IEL), atrophy of the media, and abnormal patterns of extracellular matrix (ECM) expression.⁹ Although the mechanisms underlying these histopathological changes are poorly understood, there is growing evidence that inflammation plays an important role in the disease process.¹³ Matrix metalloproteinases (MMPs) are molecules of particular interest, not only because they

are upregulated in inflammatory states but also because of their intrinsic ability to degrade ECM components and their role as the main effector molecules in ECM remodeling. Numerous studies have demonstrated that MMP-2 and MMP-9 play a significant role in aneurysm formation and progression.^{5,7,36} As gelatinases, MMP-2 and MMP-9 are responsible for the degradation of major components of the vascular ECM and IEL, including elastin and collagen types I and III.

Despite the significant public health implications of IAs, preventive management of these lesions has been hindered by the limited understanding of the mechanisms of their formation, growth, and rupture. Further elucidating the role that MMPs play in the pathogenesis of IAs may help facilitate the development of screening tools for early intervention, as well as potentially stratifying IAs according to risk of rupture.

MMP Biology

First discovered in 1962 as a collagenase that mediated the resorption of the tadpole tail, MMPs are a family of structurally related proteins that mediate a wide variety of biological processes through enzymatic activity.²³ MMPs

ABBREVIATIONS AAA = abdominal aortic aneurysm; ECM = extracellular matrix; IA = intracranial aneurysm; IEL = internal elastic lamina; IL = interleukin; MMP = matrix metalloproteinase; SAH = subarachnoid hemorrhage; TIMP = tissue inhibitor of metalloproteinases; TNF α = tumor necrosis factor- α ; VSMC = vascular smooth muscle cell; WSS = wall shear stress.

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play a significant role in eliciting changes in the micro-architecture of tissues and also contribute to the development of cell lines. These functions include initiating structural changes to proteins within the ECM and affecting chemotaxis, cell survival, and proliferation. MMPs are classified into 6 groups based on their functionality: collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs, and others.^{62,63} The majority of the proteins found in the ECM are known to be substrates of MMPs. Specifically, MMP-9 has been demonstrated to degrade elastin, and MMP-2 has been shown to degrade collagen types I and III.^{1,38} In addition, MMPs and their cleaved products can modify the downstream effects of cell-signaling molecules such as growth factors, cell adhesion molecules, cytokines, and other MMPs. Although functionally different, all MMPs share a high degree of structural homology that includes a propeptide, a catalytic domain, a hinge region, and a hemopexin domain (Fig. 1).

MMPs are synthesized and secreted into the bloodstream as zymogens (pro-MMPs) by vascular smooth muscle cells (VSMCs), macrophages, and fibroblasts.^{15,20,21} The conversion from pro-MMPs to enzymatically active MMPs requires the proteolytic cleavage of the propeptide.⁶⁰ Levels and activities of proteinases, including other MMPs and MMP inhibitors, tightly regulate this process.^{12,62} A variety of factors also regulate the expression of MMPs, including inflammatory cytokines such as tumor necrosis factor- α (TNF α) and interleukin-1 β (IL-1 β); vascular factors such as endothelin A; ECM proteins; and mechanical forces such as stretch and shear stress.^{3,6,32,33,49} The main endogenous inhibitors of MMP activity are tissue inhibitors of metalloproteinases (TIMPs), which function by binding the C-terminal domain of MMPs.^{62,63} Thus, the complex interplay between inducers of *MMP* expression and activation and TIMPs has a key role in the development and pathogenesis of IAs.

Vascular Remodeling in IAs

The development of cerebral aneurysms can be divided into 3 stages: initiation, growth, and rupture.⁵⁶ Although the pathophysiology behind each stage of aneurysm development has not been clearly delineated, abnormal blood flow and inflammation have been recognized to play key roles in IA pathogenesis.^{14,22} The initiation phase of aneurysm development is thought to be due to the effect of abnormal blood flow on a blood vessel that is already predisposed to aneurysm formation.⁵⁶ This predisposition is known to be influenced by a combination of genetic, physiological, and environmental factors.³⁵ It is well known that individuals with genetic defects of collagen production (e.g., Ehlers-Danlos syndrome type IV) or those who smoke cigarettes are at increased risk for the development of aneurysms.^{40,52} Sites of aneurysm formation are generally localized to areas of vessel bifurcation curvatures, and aneurysms are thought to be due to intimal injury secondary to altered laminar blood flow in these areas.²² Blood flow exerts pressure and wall shear stress (WSS) on endothelial cells lining vessel lumens. In studies of human and animal subjects, WSS has been

FIG. 1. MMP domain structures. All MMPs share a high degree of structural homology that includes a propeptide, a catalytic domain, a hinge region, and a hemopexin domain. **Upper:** Collagenases, stromelysins, and other MMPs. **Lower:** Gelatinases (MMP-2, MMP-9). Copyright Department of Neurosurgery, University of Utah. Published with permission.

found to be significantly greater at vessel bifurcations.^{11,59} Changes in WSS can be detected by mechanically sensitive endothelial cells, leading to the initiation of the vascular remodeling process.⁵⁹

A hallmark of vascular remodeling in IAs is atrophy of the tunica media—a layer of smooth muscle responsible for providing structural support to the arterial wall—leading to localized weakening of the arterial wall and the possibility of vessel dilation. This phenomenon is believed to be mediated by the apoptosis and migration of the primary cellular component of the tunica media, VSMCs.^{24,42,55} Kondo and colleagues⁴¹ elucidated the process of atrophy of the tunica media during aneurysm formation by ligating the common carotid arteries of rats and inducing prolonged hypertension over several months. Histopathological analysis of the vessel walls demonstrated that shortly after the disappearance of the IEL, an early marker of vascular remodeling prior to vessel dilation, VSMC density remained the same between control and experimental groups. Corresponding with progressive vessel wall dilation, the VSMCs became more disorganized and displayed decreased intracellular volume and a reduction in cellular density. In the mature aneurysm, VSMC density was vastly reduced and the remaining cells were poorly organized with irregular cellular morphology. By using terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) staining and light microscopy, the authors further showed that the VSMCs demonstrated the cardinal signs of apoptosis: cell shrinkage, chromatin condensation, and formation of apoptotic bodies within the cells.⁵⁵ Although compelling, the above results have not

FIG. 2. MMPs mediate IA formation via a process of vascular remodeling. Intimal injury and increased WSS leads to recruitment and infiltration of inflammatory cells into the vessel wall. Release of free radicals, proinflammatory chemokines, and cytokines, and activation of the complement cascade mediate upregulation of MMP-2 and MMP-9. The consequent proteolytic process results in the degradation of the ECM within the tunica media and altered structure of the vessel wall with IA formation. Copyright Department of Neurosurgery, University of Utah. Published with permission.

been replicated in human studies. Large studies of human aneurysm wall samples demonstrate variable VSMC density among different aneurysms and even within the same aneurysm.^{17,37,43} In some samples there is a higher density of VSMCs in the aneurysm wall than in the parent vessel.^{16,17}

The causes of apoptosis and remodeling of VSMCs are multifactorial; however, oxidative stress in the vessel wall also clearly plays a significant role.^{43,61} Mechanical stress has been shown to increase production of free radicals in the affected vessel walls.³⁰ Free-radical formation in cerebral arteries is driven by nicotinamide adenine dinucleotide phosphate oxidase (NADPH) and cyclooxygenases. Although these substrates are functionally active in healthy endothelial cells, the increased production of free radicals (superoxide and hydrogen peroxide) can lead to activation of inflammatory cascades, resulting in increased migration of MMP-releasing monocytes and macrophages and the activation of pro-MMPs. Increased regional MMP activity ultimately contributes to vessel

wall remodeling and weakening and to eventual aneurysmal dilation (Fig. 2).⁶¹

MMPs and Aneurysm Development and Rupture

Role of MMPs in Abdominal Aortic Aneurysm Pathogenesis

Several studies have linked *MMP* expression to aneurysm development and progression in the setting of abdominal aortic aneurysms (AAAs). At a cellular level, Ishii and Asuwa³¹ reported increased MMP-2 and MMP-9 immunohistochemical staining at the sites of intimal tears in patients with acute aortic dissection. Observational studies have further supported this association between elevated *MMP* expression at the tissue level and the presence of progressive AAA.^{50,65} Furthermore, gene knockout models have confirmed the critical role of MMPs in the development of AAAs—MMP-9 knockout models were unable to develop AAAs despite the presence of a chemi-

cal stimulus. Interestingly, transfection of the *MMP-9* gene restored the ability to express MMP-9 and the subsequent development of AAAs.⁴⁵

Circulating levels of MMPs have been shown to be elevated in patients with AAA; plasma levels of MMP-9 are higher in patients with AAA than in normal or athero-occlusive controls.^{27,47} In patients with smaller AAAs (3–5 cm), plasma levels of MMPs were predictive of the expansion of these lesions.⁴⁴ Furthermore, Wilson et al.⁶⁴ demonstrated significantly increased levels of MMP-1 and MMP-9 in patients with ruptured AAAs when compared with individuals with nonruptured AAAs.

Role of MMPs in IA Pathogenesis

Pathophysiology and Experimental Studies

Elevated levels of macrophages and lymphocytes found within aneurysm walls support the theory that inflammation plays a key role in IA formation.^{14,18} Chyatte et al.¹⁴ noted that the number of macrophages assembled on the endothelium and within the adventitia increased with propagation of aneurysmal formation. Infiltration of the vascular wall by macrophages due to damage and free-radical release leads to the recognition of ECM components by macrophage cell surface receptors, stimulating increased production of proinflammatory molecules from macrophages.⁶¹ Among these molecules are TNF α and IL-8, both of which are potent inducers of MMP-2 and MMP-9 expression and production.⁴⁸ Induction of MMP activity can be triggered by other factors at the site of an aneurysm. Mechanical stretch from abnormal blood flow or hypertension is sensed by endothelial cells, which can produce TNF α , a proinflammatory cytokine and potent stimulator of MMP-2 expression.^{30,58} Mechanical stretch also leads endothelial cells to produce free radicals and nitric oxide, leading to the conversion of pro-MMP-9 to active MMP-9.^{46,61}

The central role of MMPs in IA pathogenesis has been demonstrated and validated in numerous experimental studies. Using a rat model of IA, Aoki and colleagues⁷ found that aneurysm growth was closely associated with MMP-2 and MMP-9 expression and that selective inhibition of these MMPs can prevent aneurysm progression. Furthermore, using the same rodent model, Kanematsu and colleagues³⁶ demonstrated that aneurysm formation was decreased by systemic depletion of macrophages, which are potent producers of MMP-2 and MMP-9. Conversely, inhibitors of MMP such as *TIMP-1* and *TIMP-2* have a protective effect against aneurysm initiation and growth. TIMPs inhibit proteolytic activity of MMPs through the formation of protein complexes with their specific partners (i.e., *TIMP-1* and MMP-9, *TIMP-2* and MMP-2).¹⁰ In a rat model of cerebral aneurysms, genetic knockout of *TIMP-1* or *TIMP-2* genes both resulted in increased MMP-2 and MMP-9 enzymatic activity and increased rates of aneurysm formation.⁸ Conversely, in a rat model of AAA, local overexpression of *TIMP-1* at the site of the aneurysm prevents its degradation and rupture.⁴ Subsequent studies illustrated that *TIMP-1* and *TIMP-2* are primarily found in VSMCs and are highly expressed in cerebral aneurysms, suggesting that the apoptosis and

migration of VSMCs away from tunica media potentially leads to a shift in MMP/TIMP balance favoring increased MMP enzymatic activities, ECM degradation, and eventually aneurysm progression and possibly rupture.⁸

Clinical Studies

Evidence for an association between *MMP* expression and IA predisposition, development, and subsequent rupture has been demonstrated in human clinical studies. Genetic predisposition to increased production of MMPs has been tied to an increased propensity to develop IAs. Peters et al.⁵¹ demonstrated that a polymorphism in the promoter of MMP-9 was associated with the presence of IA in a small population of people with a familial history of ruptured and unruptured IAs. Additionally, in a case-control genetic association study, the presence of a single nucleotide polymorphism (rs243865 C > T) leading to an increased transcription of the *MMP-2* gene was associated with the presence of ruptured IAs, even after controlling for smoking and hypertension status, thus supporting the role of *MMP* expression in both the development and rupture of IAs.²

Local and systemic MMP activity may also contribute to IA development and, more importantly, rupture. Kim and colleagues³⁹ found a localized increase in MMP-9 levels in IA wall samples compared with both the patient's own plasma samples and samples from control patients. Jin et al.³⁴ noted higher serum and aneurysm wall levels of MMP-2 and MMP-9 among patients with ruptured IAs compared with those with unruptured aneurysms. These findings corroborated the results of a previous study by Gaetani et al.,¹⁹ which found a difference in the activity of the MMPs elastase and collagenase in the aneurysm walls of patients with aneurysmal SAH compared with those with unruptured aneurysms. In contradistinction, Rojas et al.⁵⁴ found a significantly higher serum level of MMP-9 in patients with any IA compared with controls, but they did not find a difference in levels when comparing patients with ruptured versus unruptured IAs.

Interestingly, medications known to decrease inflammation and block MMP production and activation have been shown to be associated with decreased aneurysm rupture rates.^{13,26,35} In fact, recently published data have suggested that patients taking daily aspirin may have a lower risk of aneurysm rupture.^{13,26,35} Although the exact pathophysiological mechanism remains unknown, current theory relies on aspirin's inhibition of cyclooxygenase-2 (COX-2), which may lead to downstream effects by decreasing the expression of immune modulators that contribute to IA rupture.²⁵ Moreover, aspirin has been demonstrated to inhibit the expression of MMP-2 and MMP-9 in macrophages, and it may upregulate the expression of TIMPs.²⁸

Future Directions

Given that differential expression of MMPs has been demonstrated between ruptured and unruptured aneurysmal samples, it stands to reason that MMP concentrations could potentially be used for diagnostic purposes. Quantitative levels of circulating MMPs might potentially serve

as serum biomarkers for both the presence and rupture status of cerebral aneurysms. Furthermore, falling plasma concentrations of these enzymes might be used as a surrogate for successful endovascular treatment (Weiner G, Kattar N, Grandhi R: Matrix metalloproteinases as serum biomarkers for the presence, evolution, and indication of successful endovascular treatment of cerebral aneurysms, presentation at the AANS/CNS Cerebrovascular Section Joint Meeting, Nashville, TN, 2015), as has been shown after endovascular AAA repair.⁴⁹ Future studies involving the assessment of MMP levels within intracranial blood and peripheral blood as well as microRNA and proteomic expression within the walls of aneurysms, both ruptured and unruptured, may help determine whether aneurysm presence, evolution, and rupture are due to a systemic, local, or combined process. Indeed, such studies may lead to the identification of targets for the prevention of aneurysm growth and rupture while also stratifying rupture risk, thus enabling physicians to determine which patients are at highest risk for experiencing a life-threatening hemorrhage.

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Disclosures

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