Review Article

Matrix Metalloproteinase-9: Dual Role and Temporal Profile in Intracerebral Hemorrhage

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Background: Clinical outcome after intracerebral hemorrhage (ICH) remains poor. Recent trials in ICH, focusing on hematoma reduction, have not yielded significant clinical improvement. The modulation of matrix metalloproteinase (MMP)-9 may represent a potential therapeutic target for reducing perihematomal edema (PHE) and improving clinical outcome. *Methods:* We searched Cochrane Library, Ovid/Medline, and PubMed databases using combinations of the following MeSH search terms: "intracerebral hemorrhage," "matrix metalloproteinase," "minocycline," "inhibition," and "neuroprotection". *Results:* MMP-9 levels in animal models have largely shown detrimental correlations with mortality, clinical outcome, hematoma volume, and PHE. Animal models and clinical studies have established a timeline for MMP-9 expression and corresponding PHE that include an initial peak on days 1-3 and a secondary peak on day 7. Clinical studies evaluating MMP-9 levels in the acute phase (days 1-3) and subacute phase (day 7) of ICH suggest that MMP-9 may be detrimental in the acute phase through destruction of basal lamina, activation of vascular endothelial growth factor, and activation of apoptosis but assist in recovery in the subacute phase through angiogenesis. *Conclusions:* MMP-9 inhibition represents a potentially effective target for neuroprotection in ICH. However, as a ubiquitous protein, the inhibition of pathologic processes must be balanced against the preservation of neuroprotective angiogenesis. As the opposing roles of MMP-9 may have similar mechanisms, the most important factor may be the timing of MMP-9 inhibition. Further studies are necessary to delineate these mechanisms and their temporal relationship. **Key Words:** Matrix metalloproteinase—gelatinase B—intracerebral hemorrhage—neuroprotection—perihematomal edema—blood brain barrier.

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Introduction

Intracerebral hemorrhage (ICH) accounts for 10% of an estimated 795,000 new strokes each year[1] and is associated with worse clinical outcomes than ischemic stroke. Despite advances in stroke care, ICH mortality figures have failed to improve significantly over time. An ICH cohort study performed between 1998 and 2003 revealed unchanged 1-year mortality rates (53%-59%) across the observation period,[2] and Kaplan–Meier survival analysis documented 16-year cumulative survival rates of 3.2%-9.8%.[3]

Pathophysiology of ICH

Primary spontaneous ICH occurs in 2 pathophysiologic phases. The primary, acute phase consists of hematoma expansion. The secondary, subacute phase is characterized by propagation of perihematomal edema (PHE), direct cellular toxicity, blood–brain barrier (BBB) breakdown, upregulation of inflammatory mediators,[4] global depressed cortical excitability,[5] and apoptosis.[6]

Research on the primary phase demonstrates that early hematoma growth is associated with neurologic deterioration and worsened clinical outcomes.[7-10] Biomarkers and radiographic correlates of hematoma expansion have been studied. The computed tomography angiography "spot sign," or hyperdensity on contrast-enhanced computed tomography, is a reliable radiographic indicator of clot expansion in both the acute and delayed time intervals.[11-13] Early intensive blood pressure management (with goal systolic blood pressure <140 mm Hg) is feasible and has resulted in decreased hematoma growth.[14,15] Agents such as factor VII attenuated ICH growth and remained promising in small phase I-II clinical trials,[16] but carried substantial risk of thromboembolic complications in higher dosing groups,[17,18] and ultimately did not improve clinical outcome in a phase III trial.[19]

Despite advances in the control of primary hematoma expansion, therapies targeting the primary phase have largely been ineffective, and no definitive ICH trial has demonstrated significant improvement in clinical outcome or reduction in death or major disability. Therapeutic focus has shifted toward agents designed to target the secondary phase of ICH. Although relevant laboratory models exist and therapeutic agents have been developed, research has not yet translated to effective clinical therapies. Understanding the molecular mechanisms underlying secondary injury after ICH could guide the development and application of novel therapies. In this review, we will discuss matrix metalloproteinases (MMPs) as a potential therapeutic target for the secondary phase of ICH.

Role of MMPs in the Central Nervous System

MMPs are a family of ubiquitous zinc-dependent endopeptidase enzymes with 4 main classes—collagenases, stromelysins, gelatinases, and membrane-bound MMPs. Genome sequencing has identified 24 different human MMPs. Initially synthesized as inactive zymogens and negligibly expressed in normal conditions, MMPs become activated through the proteolytic removal of a cysteine–zinc interaction and are inhibited by tissue inhibitors of metalloproteinases.[20] MMPs play a critical role in the central nervous system (CNS) via breakdown of the BBB, demyelination, axonal injury, and activation of inflammation via tumor necrosis factor-alpha (TNF-α) and macrophages.[21] As a result, MMPs impact CNS pathology through neurogenesis, angiogenesis, apoptosis, and inflammatory modulation.[22]

Putative Role of MMP-9 in Hematoma Expansion and Formation of PHE

MMP-9, also known as gelatinase B, is produced by astrocytes in response to inflammation[23] and has been implicated in primary CNS pathologies, including ischemic stroke,[24] hemorrhagic transformation,[25] subarachnoid hemorrhage[26] amyloid angiopathy,[27] ICH,[28] and metastatic brain tumor hemorrhage.[29] Several putative mechanisms have implicated MMP-9 in secondary injury after ICH[1]: destruction of extracellular matrix and basal lamina,[2] activation by vascular endothelial growth factor (VEGF),[3] activation by thrombin, and[4] activation of apoptosis.

Activation of MMP-9 leads to digestion of collagen type IV, laminin, and fibronectin—major components of the basal lamina surrounding cerebral blood vessels.[30] The MMP-9 promoter region contains activator protein-1 and nuclear factor-κB both of which respond to inflammatory stimuli and specifically attack the basal lamina through the fibronectin binding domain.[31] Correlation between MMP-9 levels and radiological BBB disruption further suggests a role for MMP-9 in breakdown of the basal lamina.[32]

VEGF may also pathologically activate MMP-9, leading to a direct causal relationship between angiogenesis, primary hematoma expansion, and PHE. Lee et al[33] demonstrated that mice injected with adenoviral-mediated VEGF had both elevated MMP-9 levels and larger ICH volumes than those in controls ($P < .05$). Minocycline administration, however, completely inhibited this VEGF-induced MMP-9 activity and reduced ICH volume. The data suggest that VEGF induction of MMP-9 results in ICH volume expansion through destruction of the basal lamina of cerebral vessels, which increases vascular permeability and ruptures vascular walls. MMP-9 may also induce pathologic angiogenesis and hence larger ICH volume expansion through activation of latent insulin-like growth factor and tumor growth factor β1 and β2.[34]

Thrombin promotes coagulation and is essential for preventing continued bleeding after ICH. However, high dose thrombin, acting via G-protein coupled protease-activated receptors, is toxic to both neurons