

Matrix Metalloproteinase Regulation in Intracerebral Hemorrhage

Jason J Chang, G. Morgan Jones, Anna Betlachin, Tayebah Pourmotabbed

Jason J Chang, Department of Neurology, University of Tennessee Health Science Center. Memphis, TN, the United States

G. Morgan Jones, Department of Pharmacology, University of Tennessee Health Science Center. Memphis, TN, the United States

Anna Betlachin, Keck School of Medicine. University of Southern California. Los Angeles, CA, the United States

Tayebah Pourmotabbed, Department of Microbiology, Immunology, and Biochemistry. University of Tennessee Health Science Center. Memphis, TN, the United States

Correspondence to: Tayebah Pourmotabbed, Professor, Department of Microbiology, Immunology, Biochemistry, University of TN Health Science Center, Memphis, TN, 38163, the United States.

Email: tpourmot@uthsc.edu

Telephone: +1-901-448 4361

Fax: +1-901-448-7360

Received: August 12, 2015

Revised: September 1, 2015

Accepted: September 3, 2015

Published online: December 1, 2015

ABSTRACT

Intracerebral hemorrhage remains a particularly devastating form of cerebrovascular disease with unchanged mortality rates despite several large studies that have targeted primary expansion of hematoma growth. A second, worthwhile target for improving clinical outcome after intracerebral hemorrhage may be neuroprotection through modulation of secondary mechanisms of brain injury. Matrix metalloproteinases represent a family of ubiquitous endopeptidase enzymes that can become pathologically activated and result in blood-brain barrier breakdown. In humans, high levels of matrix metalloproteinase have been associated with perihematomal edema, symptomatic hemorrhagic transformation, and worse clinical outcome. As a result, inhibition of matrix metalloproteinase in the acute phase of intracerebral hemorrhage may represent an efficacious strategy for improving clinical outcome. Current strategies for inhibiting matrix metalloproteinase in intracerebral hemorrhage are as follows: (1) direct inhibition, (2) transcriptional control of matrix metalloproteinase

expression, and (3) post-transcriptional control. Currently, the most clinically relevant form of matrix metalloproteinase inhibition lies with direct inhibition through broad-spectrum hydroxamate-class inhibitors and tetracycline-class antibiotics and the polymechanistic role of statins. Further trials are necessary to evaluate for possible roles of matrix metalloproteinase inhibition in improving clinical outcome after intracerebral hemorrhage.

© 2015 ACT. All rights reserved.

Key words: Cerebrovascular disease; Intracerebral hemorrhage; Inhibition; Matrix metalloproteinase; Neuroprotection

Chang JJ, Jones GM, Betlachin A, Pourmotabbed T. Matrix Metalloproteinase Regulation in Intracerebral Hemorrhage. *International Journal of Neurology Research* 2015; 1(4): 169-174 Available from: URL: <http://www.ghrnet.org/index.php/ijnr/article/view/1347>

INTRODUCTION

Stroke is the fifth leading cause of death in the United States, resulting in an estimated 130,000 lives lost annually^[1]. Intracerebral hemorrhage (ICH) remains a particularly devastating form of stroke with unchanged mortality rates ranging from 53-59%^[2]. Neuroprotection through modulation of secondary mechanisms of brain injury--including preservation of blood-brain barrier, up-regulation of inflammatory mediators, inhibition of apoptosis, and attenuation of cortical excitability^[3-5]--may be worthy targets to improve clinical outcome.

Matrix Metalloproteinases

Matrix metalloproteinases (MMP) are a family of ubiquitous zinc-dependent endopeptidase enzymes. Initially synthesized as inactive zymogens with negligible expression in normal conditions, MMPs become activated via proteolytic removal of a cysteine-zinc

interaction^[6]. While these enzymes play important roles in normal physiology, they have also been linked with pathologic processes such as multiple sclerosis, ischemic stroke and hemorrhagic transformation, amyloid angiopathy, intracerebral hemorrhage, and metastatic brain tumor^[7-9]. MMPs play a critical role in cerebrovascular disease by breaking down blood-brain barrier and activating inflammation through TNF- α and macrophages^[10].

MMP Pathophysiology

Several mechanisms for the pathological role of MMPs in cerebrovascular disease, validated in animal models and observed in humans, have been proposed. First, MMPs directly digest collagen type IV, laminin, and fibronectin, which serve as major components of the basal lamina surrounding blood vessels^[11,12]. Mechanistically, this is caused by inflammatory stimuli activation of MMP promoter regions, containing protein-1 and nuclear factor kB^[13]. Radiological studies in humans have also confirmed this relationship as MMP levels correlate with blood-brain barrier markers^[14]. Second, vascular endothelial growth factor (VEGF) has been proposed as an activator of MMPs, which creates a direct relationship between elevated MMP levels and larger hematoma volume via aberrant angiogenesis^[15].

In humans, high levels of MMP have been associated with perihematomal edema^[16,17], symptomatic hemorrhagic transformation^[18,19], and worse clinical outcome^[17]. As a result, regulation of MMPs in the acute phase may serve as an effective neuroprotectant in cerebrovascular disease. Extensive research has been done on strategies for MMP regulation in ischemic stroke with current phase 2 trials underway. However, less emphasis has been placed on the neuroprotective role of MMP regulation in ICH.

Endogenous MMPs are regulated at distinct levels, including direct antagonism with tissue inhibitors^[20], regulation of gene transcription, and post-transcriptional modification. The aim of this review is to explore the available evidence in both animal and human models for MMP regulation at these distinct levels and evaluate these strategies as efficacious neuroprotective agents in ICH.

STRATEGIES FOR REGULATING MMP ACTIVITY

1. Inhibition of MMP Activity

Broad-spectrum Hydroxamate-Class Inhibitors

The hydroxamate MMP inhibitors are a group of synthetic, broad-spectrum, collagen-like peptides that directly bind to the MMP active site. Although strongly inhibiting MMP-2, hydroxamate also has inhibitory effects on MMP-1 and MMP-3^[21]. These drugs were initially developed as antineoplastics, but have since been investigated as potential therapies for conditions ranging from autoimmune disorders to secondary brain injury following ischemic reperfusion^[22-26].

Rosenberg *et al* demonstrated that administration of BB-1101, six hours after ICH induction in a collagenase rat model, significantly decreased brain water and sodium content in regions distant from the primary lesion^[27]. Administration of another hydroxamate-class MMP inhibitor, GM6001, was shown to be neuroprotective in mouse models of ICH^[28,29]. Xue *et al* showed a significant reduction in neurotoxicity as assessed by brain injury area and neuronal cell death when GM6001 was administered simultaneously with autologous blood^[28]. A second study administered GM6001 at 24-hour intervals for 3 days following ICH and showed a dose-dependent reduction in neutrophil infiltration, reactive oxidative species production, injury volume, brain edema, and neuronal cell death^[29].

However, another hydroxamate inhibitor, BB-94, was shown

to have no effect on edema while increasing hemorrhage and cell death when administered twice daily to rats^[30]. It has been suggested that the observed differences between BB-94 and BB-1101 may be due to varying inhibition of tumor necrosis factor- α -converting enzyme (TACE)^[31]. In addition to causing cell death, TNF- α has been implicated in MMP-9 induction, and TACE modulation by MMP inhibitors may contribute to upstream regulation of MMP activity^[31,32].

Tetracycline-Based MMP Inhibitors

Minocycline, a second-generation tetracycline antibiotic, is a broad-spectrum inhibitor of MMPs. This small, highly lipophilic drug readily crosses the blood brain barrier more effectively than other medications in the same class, has high oral bioavailability, and exhibits a relatively narrow adverse effect profile^[33]. It has been shown in numerous animal studies to alleviate the negative effects of several neurologic disorders, including spinal cord injury, traumatic brain injury, and Parkinson's disease^[33]. In addition to inhibiting MMPs, minocycline has also been shown to be a potent inhibitor of microglial activation, apoptosis, and free-radical production, which may explain why it exhibits beneficial effects across numerous neurologic conditions.

To date, three major studies have evaluated the use of minocycline as an MMP inhibitor in individuals with ischemic stroke and demonstrated significantly improved clinical outcomes. Lampl *et al* demonstrated that 200 mg daily administration of minocycline to acute stroke patients significantly improved clinical outcomes^[34]. Similarly, Padma *et al* showed that 200 mg daily oral minocycline administration for 5 days to acute stroke patients significantly improved clinical outcome measures: 90-day National Institutes of Health Stroke Scale score, modified Rankin scores, and modified Barthel Index^[35]. Finally, in a multicenter randomized, controlled pilot study, Kohler *et al* showed that intravenous administration of minocycline to 47 patients with acute stroke increased the odds of handicap-free survival by a factor of 3 [odds ratio (OR) 2.99 (95% confidence interval (CI) 1.74-5.16)]; however, there was substantial heterogeneity among the available data (I^2 89.82)^[36].

In humans receiving intravenous tissue-plasminogen activator (tPA) for ischemic stroke, minocycline may also provide protection against hemorrhagic transformation by inhibiting MMP-9. Available evidence suggests that tPA may amplify MMP-9 and result in hemorrhagic transformation^[37]. MMP-9 levels were significantly reduced in all patients enrolled in the MINOS study, regardless of tPA administration. With previous data demonstrating a correlation between MMP-9 and hemorrhagic transformation after tPA^[8], the authors concluded that combining minocycline and tPA may prevent the adverse consequences of thrombolytic therapy and lead to reductions in hemorrhagic conversion after tPA administration^[38].

While use in ischemic stroke is more widely studied, there is limited data outside of animal models evaluating the effect of minocycline in ICH. Several models of minocycline injection in rats have shown various benefits in ICH, including reduced blood brain barrier damage^[39], edema formation, neurologic deficits, and brain atrophy^[40]. Power *et al* demonstrated that minocycline administration not only significantly decreased MMP expression but reduced glial activation and apoptosis after ICH in a collagenase-induced rat model of ICH^[10].

Dosing has shown to impact the neuroprotectant effects of minocycline in ICH. Xue *et al* conducted an in vitro study of human brain cells followed by an in vivo investigation in rat brains. They concluded that the neuroprotectant effects of minocycline are

improved by high concentrations delivered locally into the CNS with supplementation from systemic administration^[41]. Other studies have also suggested a benefit to minocycline use in ICH, but suggest administration must occur during a clinically relevant time for any beneficial effects to be observed^[42-44].

2. Transcriptional Control of MMP Expression

The role of MMPs across multiple inflammatory pathways allows for modulation at different levels and several MMP regulators are known to act as transcriptional modulators controlling MMP expression. MMP activity is known to be modulated via upstream regulation and have been studied in human cell lines and animal models. However, to date, no upstream regulator of MMP has been studied in humans.

NF- κ B acts as a transcription factor involved in cytokine and inflammatory cell upregulation and has been shown to increase MMP-9 levels in multiple cell types^[45-48]. Lee *et al* found that administration of pyrrolidine dithiocarbamate (PDTC), an NF- κ B inhibitor, in a vascular endothelial growth factor (VEGF) murine model of ICH suppressed MMP-9 activity downstream and attenuated ICH volume^[15].

The glucocorticoid dexamethasone may utilize a similar pathway to inhibit downstream MMP-9 activation by also modulating NF- κ B nuclear transcription. In a collagenase-induced ICH model, rats were acutely treated with dexamethasone for 3 days and showed a significant decrease in NF- κ B and MMP-9 levels. Imaging studies demonstrated a decrease in brain edema that peaked at day 5^[49]. Although glucocorticoid therapy may play a promising role in neuroprotection as an MMP-9 inhibitor, overwhelming evidence linking poorer outcome with hyperglycemia in cerebrovascular disease may limit its role^[50,51].

Geranylgeranylacetone (GGA) has also been investigated for neuroprotective effects that may be at least partially mediated through MMP downregulation^[52]. Treating rats with a single dose of GGA 48 hours prior to collagenase-induced ICH and daily treatment at 2 hours post injury significantly decreased brain water content. However, this improved brain edema was not seen in those who did not receive the combination of the pre- and post-injury doses^[52]. Using the same combined dosing regimen, GGA treatment resulted in decreased neuronal cell death and inflammatory cell migration at 72 hours post-ICH, as well as increased neurological function after ICH induction^[52]. Like PDTC and dexamethasone, GGA's effect on MMP-9 may be mediated through inhibition of NF- κ B; still, the exact mechanism remains uncertain since presently available research did not directly measure MMP-9 levels in the brain^[53,54].

Extracellular matrix glycoprotein osteopontin (OPN) may offer another upstream pathway of MMP-9 regulation. In a collagenase-induced ICH mouse model, animals pretreated with recombinant OPN 20 minutes prior to ICH induction had lower levels of MMP-9 and improved clinical outcomes^[54]. OPN inhibition of MMP-9 appears to occur through down regulation of inducible nitric oxide synthase, another known activator of MMP-9^[55]. There is also evidence to suggest that OPN may suppress NF- κ B, though this has not been demonstrated in the context of ICH^[56].

Imatinib, a platelet-derived growth factor receptor alpha (PDGFR- α) antagonist used in the treatment of chronic lymphocytic leukemia, has been shown to inhibit MMP-9, MMP-10, and MMP-13 activity in murine models of ICH. Imatinib in an autologous blood-induced murine model showed decreased ipsilateral brain edema and improved neurobehavioral functioning, while its administration in thrombin-induced murine ICH models resulted in decreased blood-brain barrier permeability^[57].

Various mechanisms have been proposed to explain the inhibitory effects of statins on MMP. Using human carcinoma cell lines, breast carcinoma and leukemia cells, treatment with cerivastatin and simvastatin, respectively yielded decreased levels of MMP-9 with presumed mechanisms being NF- κ B and p65 inhibition^[58,59]. Statins have shown similar results in animal models. Treatment with atorvastatin resulted in significant plasma MMP-9 reduction and brain water content on days 3 and 7 in a collagenase-induced ICH rat model^[60]. While statin use and its role in MMP inhibition in ICH has not been studied, the inhibitory effects of statins on MMP-9 levels has been demonstrated in humans receiving tPA for ischemic stroke. Humans taking statin pre-hospitalization were found to have significantly lower MMP-9 levels at hour 6, 12, 24, and 72 after tPA administration. However, this decreased MMP-9 level did not result in improved clinical outcome^[61]. While atorvastatin has previously been shown to correlate with reduced incidence^[62] and improved neurological outcomes in cerebrovascular disease, these results highlight the potential link between statins and serum MMP inhibition in neurologic injury^[63-66].

Sinn *et al* demonstrated that valproic acid (VPA) treatment in rats with ICH decreased levels of MMP-9 mRNA. VPA is thought to exert its neuroprotective effects by inhibiting histone deacetylase activity and suppressing the transcription of inflammatory cytokines such as MMP-9. Administration of VPA twice daily following ICH induction resulted in decreased levels of MMP-9 mRNA with inhibition of hematoma expansion, decreased perihematomal cell death, reduced inflammatory cell infiltration, and improved functional recovery^[67].

The N-methyl-D-aspartate (NMDA) receptor antagonist, memantine, may also function as an upstream modulator of MMP-9. Using a rat collagenase model, daily administration of memantine beginning 30 minutes post-ICH and continuing for 3 days showed a decrease in levels of MMP-9. Researchers also observed a reduction in hematoma expansion, apoptosis, inflammatory infiltration, and an improvement in functional recovery^[68]. Though the exact mechanism remains unclear, it has been proposed that memantine's effect on MMP-9 is through inhibition of glutamate excitotoxicity and suggested that glutamate may be another potential target in the upstream regulation of MMP-9^[68,69].

3. Post-transcriptional Control of MMP Expression

Small interfering RNA (siRNA) has been used for post-transcriptional control of MMP expression in vivo. The use of MMP siRNA in animal models has had the paradoxical effect of worsening clinical outcome. Rats injected with MMP-9 siRNA on days 7 and 10 following collagenase-induced ICH showed decreased neurogenesis and functional recovery^[70]. These results appear to corroborate the findings of Tang *et al*, who showed that MMP-9 knockout mice had increased hemorrhage, brain edema, early neurobehavioral deficits, and mortality in collagenase-induced ICH^[71]. However, this paradoxical effect of MMP-9 inhibition in a subacute time frame may actually highlight a dual purpose for MMP expression: a pathological acute phase that contributes to inflammation and cell death and a subacute neuroprotective phase highlighted by angiogenesis^[72]. Thus delayed inhibition may interfere with recovery after ICH

CONCLUSION

MMP regulation in ICH has the potential to be neuroprotective and improve clinical outcome. A summary of potential MMP regulators utilized in ICH is outlined in Table 1. Of the regulators described, direct inhibition of MMPs with minocycline and the poly-

Table 1 Potential Inhibitors of Matrix Metalloproteinase.

Inhibitor	Type	Mechanism	Study Population	Observed Effect
BB-1101	direct inhibition	direct chelation of MMP active site	rat collagenase	↓ brain edema
GM6001	direct inhibition	direct chelation of MMP active site	mouse autologous blood mouse collagenase	↓ brain edema ↓ neuronal cell death ↓ neutrophil infiltration
BB-94	direct inhibition	direct chelation of MMP active site	rat collagenase	↑ hemorrhage ↑ cell death
minocycline	direct inhibition	direct chelation of MMP active site	human	↓ brain edema ↑ functional outcome
pyrrolidine dithiocarbamate	upstream regulation	NF-κB inhibition	mouse VEGF	↓ hemorrhage
dexamethasone	upstream regulation	NF-κB inhibition	rat collagenase	↓ brain edema
geranylceranylacetone	upstream regulation	induction of heat shock protein 70 (HSP70)	rat collagenase	↓ neuronal cell death ↓ inflammation
osteopontin	upstream regulation	NF-κB inhibition iNOS/nitric oxide inhibition	mouse collagenase	↓ brain edema ↓ neuronal cell death
imatinib	upstream regulation	suppression of P38 MAPK pathway	mouse autologous blood	↓ brain edema ↓ BBB permeability
statin	upstream regulation	NF-κB inhibition, p65 inhibition	rat collagenase, human	↓ brain edema
valproic acid	upstream regulation	inhibition of histone deacetylase	rat collagenase	↓ hemorrhage ↓ neuronal cell death ↓ inflammation
memantine	upstream regulation	inhibition of glutamate toxicity	rat collagenase	↓ hemorrhage ↓ neuronal cell death ↓ inflammation
siRNA	post-transcriptional	RNA interference	rat collagenase	↓ neurogenesis ↓ neurobehavioral function

mechanistic regulation via statins have the most relevant clinical potential. Currently the Minocycline in Acute Cerebral Hemorrhage (MACH) Trial is evaluating the safety of minocycline use in ICH. In addition, the role and safety of MMP inhibition in ischemic stroke will be evaluated in The West Australian Intravenous Minocycline and TPA Stroke Study (WAIMATSS). The results of these studies may further substantiate the potential behind MMP regulation as an effective approach to treat ICH and cerebrovascular diseases.

CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

REFERENCES

- Leading Causes of Death. 2013. (Accessed April 8, 2015, at <http://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm>.)
- Flaherty ML, Haverbusch M, Sekar P, *et al* Long-term mortality after intracerebral hemorrhage. *Neurology* 2006;66:1182-6.
- Belur PK, Chang JJ, He S, Emanuel BA, Mack WJ. Emerging experimental therapies for intracerebral hemorrhage: targeting mechanisms of secondary brain injury. *Neurosurgical focus* 2013; 34: E9.
- Mun-Bryce S, Wilkerson A, Pacheco B, *et al* Depressed cortical excitability and elevated matrix metalloproteinases in remote brain regions following intracerebral hemorrhage. *Brain research* 2004; 1026:227-34.
- Qureshi AI, Suri MF, Ostrow PT, *et al* Apoptosis as a form of cell death in intracerebral hemorrhage. *Neurosurgery* 2003; 52:1041-7; discussion 7-8.
- Sternlicht MD, Werb Z. How matrix metalloproteinases regulate cell behavior. *Annual review of cell and developmental biology* 2001;17:463-516.
- Yong VW, Power C, Forsyth P, Edwards DR. Metalloproteinases in biology and pathology of the nervous system. *Nature reviews Neuroscience* 2001;2:502-11.
- Montaner J, Molina CA, Monasterio J, *et al* Matrix metalloproteinase-9 pretreatment level predicts intracranial hemorrhagic complications after thrombolysis in human stroke. *Circulation* 2003;107:598-603.
- Jung S, Moon KS, Jung TY, *et al* Possible pathophysiological role of vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs) in metastatic brain tumor-associated intracerebral hemorrhage. *Journal of neuro-oncology* 2006;76:257-63.
- Power C, Henry S, Del Bigio MR, *et al* Intracerebral hemorrhage induces macrophage activation and matrix metalloproteinases. *Annals of neurology* 2003;53:731-42.
- Rosenberg GA. Matrix metalloproteinases in neuroinflammation. *Glia* 2002;39:279-91.
- Parks WC, Wilson CL, Lopez-Boado YS. Matrix metalloproteinases as modulators of inflammation and innate immunity. *Nature reviews Immunology* 2004;4:617-29.
- Mun-Bryce S, Rosenberg GA. Matrix metalloproteinases in cerebrovascular disease. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism* 1998;18:1163-72.
- Barr TL, Latour LL, Lee KY, *et al* Blood-brain barrier disruption in humans is independently associated with increased matrix metalloproteinase-9. *Stroke; a journal of cerebral circulation* 2010;41:e123-8.
- Lee CZ, Xue Z, Zhu Y, Yang GY, Young WL. Matrix metalloproteinase-9 inhibition attenuates vascular endothelial growth factor-induced intracerebral hemorrhage. *Stroke; a journal of cerebral circulation* 2007;38:2563-8.
- Alvarez-Sabin J, Delgado P, Abilleira S, *et al* Temporal profile of matrix metalloproteinases and their inhibitors after spontaneous intracerebral hemorrhage: relationship to clinical and radiological outcome. *Stroke; a journal of cerebral circulation* 2004;35:1316-22.
- Li N, Liu YF, Ma L, *et al* Association of molecular markers with perihematomal edema and clinical outcome in intracerebral hemorrhage. *Stroke; a journal of cerebral circulation* 2013;44:658-63.
- Inzitari D, Giusti B, Nencini P, *et al* MMP9 variation after thrombolysis is associated with hemorrhagic transformation of lesion and death. *Stroke; a journal of cerebral circulation* 2013;44:2901-3.

19. Abilleira S, Montaner J, Molina CA, Monasterio J, Castillo J, Alvarez-Sabin J. Matrix metalloproteinase-9 concentration after spontaneous intracerebral hemorrhage. *Journal of neurosurgery* 2003;99:65-70.
20. Murphy G, Nagase H. Progress in matrix metalloproteinase research. *Mol Aspects Med* 2008;29:290-308.
21. Jani M, Tordai H, Trexler M, Banyai L, Patthy L. Hydroxamate-based peptide inhibitors of matrix metalloprotease 2. *Biochimie* 2005;87:385-92.
22. Davies B, Brown PD, East N, Crimmin MJ, Balkwill FR. A synthetic matrix metalloproteinase inhibitor decreases tumor burden and prolongs survival of mice bearing human ovarian carcinoma xenografts. *Cancer research* 1993;53:2087-91.
23. Liedtke W, Cannella B, Mazzaccaro RJ, *et al* Effective treatment of models of multiple sclerosis by matrix metalloproteinase inhibitors. *Annals of neurology* 1998;44:35-46.
24. Wallace GR, Whiston RA, Stanford MR, Wells GM, Gearing AJ, Clements JM. The matrix metalloproteinase inhibitor BB-1101 prevents experimental autoimmune uveoretinitis (EAU). *Clinical and experimental immunology* 1999;118:364-70.
25. Yang Y, Estrada EY, Thompson JF, Liu W, Rosenberg GA. Matrix metalloproteinase-mediated disruption of tight junction proteins in cerebral vessels is reversed by synthetic matrix metalloproteinase inhibitor in focal ischemia in rat. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism* 2007;27:697-709.
26. Mishiro K, Ishiguro M, Suzuki Y, Tsuruma K, Shimazawa M, Hara H. A broad-spectrum matrix metalloproteinase inhibitor prevents hemorrhagic complications induced by tissue plasminogen activator in mice. *Neuroscience* 2012;205:39-48.
27. Rosenberg GA, Navratil M. Metalloproteinase inhibition blocks edema in intracerebral hemorrhage in the rat. *Neurology* 1997;48:921-6.
28. Xue M, Hollenberg MD, Demchuk A, Yong VW. Relative importance of proteinase-activated receptor-1 versus matrix metalloproteinases in intracerebral hemorrhage-mediated neurotoxicity in mice. *Stroke; a journal of cerebral circulation* 2009;40:2199-204.
29. Wang J, Tsirka SE. Neuroprotection by inhibition of matrix metalloproteinases in a mouse model of intracerebral haemorrhage. *Brain: a journal of neurology* 2005;128:1622-33.
30. Grossetete M, Rosenberg GA. Matrix metalloproteinase inhibition facilitates cell death in intracerebral hemorrhage in mouse. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism* 2008;28:752-63.
31. Lin CC, Tseng HW, Hsieh HL, *et al* Tumor necrosis factor-alpha induces MMP-9 expression via p42/p44 MAPK, JNK, and nuclear factor-kappaB in A549 cells. *Toxicology and applied pharmacology* 2008;229:386-98.
32. Steenport M, Khan KM, Du B, Barnhard SE, Dannenberg AJ, Falcone DJ. Matrix metalloproteinase (MMP)-1 and MMP-3 induce macrophage MMP-9: evidence for the role of TNF-alpha and cyclooxygenase-2. *Journal of immunology* 2009;183:8119-27.
33. Yong VW, Wells J, Giuliani F, Casha S, Power C, Metz LM. The promise of minocycline in neurology. *Lancet neurology* 2004;3:744-51.
34. Lampl Y, Boaz M, Gilad R, *et al* Minocycline treatment in acute stroke: an open-label, evaluator-blinded study. *Neurology* 2007;69:1404-10.
35. Padma Srivastava MV, Bhasin A, Bhatia R, *et al* Efficacy of minocycline in acute ischemic stroke: a single-blinded, placebo-controlled trial. *Neurol India* 2012;60:23-8.
36. Kohler E, Prentice DA, Bates TR, *et al* Intravenous minocycline in acute stroke: a randomized, controlled pilot study and meta-analysis. *Stroke; a journal of cerebral circulation* 2013;44:2493-9.
37. Wang X, Tsuji K, Lee SR, *et al* Mechanisms of hemorrhagic transformation after tissue plasminogen activator reperfusion therapy for ischemic stroke. *Stroke; a journal of cerebral circulation* 2004;35:2726-30.
38. Switzer JA, Hess DC, Ergul A, *et al* Matrix metalloproteinase-9 in an exploratory trial of intravenous minocycline for acute ischemic stroke. *Stroke; a journal of cerebral circulation* 2011;42:2633-5.
39. Shi W, Wang Z, Pu J, *et al* Changes of blood-brain barrier permeability following intracerebral hemorrhage and the therapeutic effect of minocycline in rats. *Acta neurochirurgica Supplement* 2011;110:61-7.
40. Wu J, Yang S, Hua Y, Liu W, Keep RF, Xi G. Minocycline attenuates brain edema, brain atrophy and neurological deficits after intracerebral hemorrhage. *Acta neurochirurgica Supplement* 2010;106:147-50.
41. Xue M, Del Bigio MR. Intracerebral injection of autologous whole blood in rats: time course of inflammation and cell death. *Neuroscience letters* 2000;283:230-2.
42. Wasserman JK, Schlichter LC. Neuron death and inflammation in a rat model of intracerebral hemorrhage: effects of delayed minocycline treatment. *Brain research* 2007;1136:208-18.
43. Wasserman JK, Zhu X, Schlichter LC. Evolution of the inflammatory response in the brain following intracerebral hemorrhage and effects of delayed minocycline treatment. *Brain research* 2007;1180:140-54.
44. Szymanska A, Biernaskie J, Laidley D, Granter-Button S, Corbett D. Minocycline and intracerebral hemorrhage: influence of injury severity and delay to treatment. *Experimental neurology* 2006;197:189-96.
45. Bond M, Chase AJ, Baker AH, Newby AC. Inhibition of transcription factor NF-kappaB reduces matrix metalloproteinase-1, -3 and -9 production by vascular smooth muscle cells. *Cardiovascular research* 2001;50:556-65.
46. Ogawa K, Chen F, Kuang C, Chen Y. Suppression of matrix metalloproteinase-9 transcription by transforming growth factor-beta is mediated by a nuclear factor-kappaB site. *The Biochemical journal* 2004;381:413-22.
47. Rhee JW, Lee KW, Kim D, *et al* NF-kappaB-dependent regulation of matrix metalloproteinase-9 gene expression by lipopolysaccharide in a macrophage cell line RAW 264.7. *Journal of biochemistry and molecular biology* 2007;40:88-94.
48. Rhee JW, Lee KW, Sohn WJ, *et al* Regulation of matrix metalloproteinase-9 gene expression and cell migration by NF-kappa B in response to CpG-oligodeoxynucleotides in RAW 264.7 cells. *Molecular immunology* 2007;44:1393-400.
49. Yang JT, Lee TH, Lee IN, Chung CY, Kuo CH, Weng HH. Dexamethasone inhibits ICAM-1 and MMP-9 expression and reduces brain edema in intracerebral hemorrhagic rats. *Acta neurochirurgica* 2011;153:2197-203.
50. Baird TA, Parsons MW, Phan T, *et al* Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. *Stroke; a journal of cerebral circulation* 2003;34:2208-14.
51. Williams LS, Rotich J, Qi R, *et al* Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke. *Neurology* 2002;59:67-71.
52. Sinn DI, Chu K, Lee ST, *et al* Pharmacological induction of heat shock protein exerts neuroprotective effects in experimental intracerebral hemorrhage. *Brain research* 2007;1135:167-76.
53. Yoo CG, Lee S, Lee CT, Kim YW, Han SK, Shim YS. Anti-inflammatory effect of heat shock protein induction is related to stabilization of I kappa B alpha through preventing I kappa

- pa B kinase activation in respiratory epithelial cells. *Journal of immunology* 2000;164:5416-23.
54. Wu B, Ma Q, Suzuki H, *et al* Recombinant osteopontin attenuates brain injury after intracerebral hemorrhage in mice. *Neurocritical care* 2011;14:109-17.
 55. Gu Z, Kaul M, Yan B, *et al* S-nitrosylation of matrix metalloproteinases: signaling pathway to neuronal cell death. *Science* 2002;297:1186-90.
 56. Arafat HA, Katakam AK, Chipitsyna G, *et al* Osteopontin protects the islets and beta-cells from interleukin-1 beta-mediated cytotoxicity through negative feedback regulation of nitric oxide. *Endocrinology* 2007;148:575-84.
 57. Ma Q, Huang B, Khatibi N, *et al* PDGFR-alpha inhibition preserves blood-brain barrier after intracerebral hemorrhage. *Annals of neurology* 2011;70:920-31.
 58. Chen YJ, Chang LS. Simvastatin induces NFkappaB/p65 down-regulation and JNK1/c-Jun/ATF-2 activation, leading to matrix metalloproteinase-9 (MMP-9) but not MMP-2 down-regulation in human leukemia cells. *Biochemical pharmacology* 2014;92:530-43.
 59. Denoyelle C, Vasse M, Korner M, *et al* Cerivastatin, an inhibitor of HMG-CoA reductase, inhibits the signaling pathways involved in the invasiveness and metastatic properties of highly invasive breast cancer cell lines: an in vitro study. *Carcinogenesis* 2001;22:1139-48.
 60. Cui JJ, Wang D, Gao F, Li YR. Effects of atorvastatin on pathological changes in brain tissue and plasma MMP-9 in rats with intracerebral hemorrhage. *Cell biochemistry and biophysics* 2012;62:87-90.
 61. Zhao HD, Zhang YD. The effects of previous statin treatment on plasma matrix metalloproteinase-9 level in chinese stroke patients undergoing thrombolysis. *Journal of stroke and cerebrovascular diseases: the official journal of National Stroke Association* 2014;23:2788-93.
 62. Amarenco P, Bogousslavsky J, Callahan A, 3rd, *et al* High-dose atorvastatin after stroke or transient ischemic attack. *The New England journal of medicine* 2006;355:549-59.
 63. Yang D, Knight RA, Han Y, *et al* Vascular recovery promoted by atorvastatin and simvastatin after experimental intracerebral hemorrhage: magnetic resonance imaging and histological study. *Journal of neurosurgery* 2011;114:1135-42.
 64. Seyfried D, Han Y, Lu D, Chen J, Bydon A, Chopp M. Improvement in neurological outcome after administration of atorvastatin following experimental intracerebral hemorrhage in rats. *Journal of neurosurgery* 2004;101:104-7.
 65. Karki K, Knight RA, Han Y, *et al* Simvastatin and atorvastatin improve neurological outcome after experimental intracerebral hemorrhage. *Stroke; a journal of cerebral circulation* 2009;40:3384-9.
 66. Marti-Fabregas J, Gomis M, Arboix A, *et al* Favorable outcome of ischemic stroke in patients pretreated with statins. *Stroke; a journal of cerebral circulation* 2004;35:1117-21.
 67. Sinn DI, Kim SJ, Chu K, *et al* Valproic acid-mediated neuroprotection in intracerebral hemorrhage via histone deacetylase inhibition and transcriptional activation. *Neurobiology of disease* 2007;26:464-72.
 68. Lee ST, Chu K, Jung KH, *et al* Memantine reduces hematoma expansion in experimental intracerebral hemorrhage, resulting in functional improvement. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism* 2006;26:536-44.
 69. Lee ST, Chu K, Park JE, *et al* Memantine reduces striatal cell death with decreasing calpain level in 3-nitropropionic model of Huntington's disease. *Brain research* 2006;1118:199-207.
 70. Lei C, Lin S, Zhang C, *et al* Activation of cerebral recovery by matrix metalloproteinase-9 after intracerebral hemorrhage. *Neuroscience* 2013;230:86-93.
 71. Tang J, Liu J, Zhou C, *et al* Mmp-9 deficiency enhances collagenase-induced intracerebral hemorrhage and brain injury in mutant mice. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism* 2004;24:1133-45.
 72. Chang JJ, Emanuel BA, Mack WJ, Tsivgoulis G, Alexandrov AV. Matrix metalloproteinase-9: dual role and temporal profile in intracerebral hemorrhage. *Journal of stroke and cerebrovascular diseases: the official journal of National Stroke Association* 2014;23:2498-505.
- Peer reviewer:** Jiajun Chen, Professor, Neurology Department of China-Japan Union Hospital, Jilin University, Xiantai Street#126, Changchun City, 130033, China.