

# The role of high mobility group box 1 protein in acute cerebrovascular diseases (Review)

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**Abstract.** The occurrence and development of acute cerebrovascular diseases involves an inflammatory response, and high mobility group box protein 1 (HMGB1) is a pro-inflammatory factor that is expressed not only in the early-injury stage of disease, but also during the post-repair process. In the initial stage of disease, HMGB1 is released into the outside of the cell to participate in the cascade amplification reaction of inflammation, causing vasospasm, destruction of the blood-brain barrier and apoptosis of nerve cells. In the recovery stage of disease, HMGB1 can promote tissue repair and remodeling, which can aid in nerve function recovery. This review summarizes the biological characteristics of HMGB1, and the role of HMGB1 in ischemic and hemorrhagic cerebrovascular disease, and cerebral venous thrombosis.

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## 1. Introduction

High mobility group box protein 1 (HMGB1) is the non-chromosome-related group of proteins. It was first isolated in 1973 by Goodwin *et al* (1), and it is named after its rapid rate of electrophoresis in a polyacrylamide gel. HMGB1 is expressed in the nucleus of almost all eukaryotic cells and is encoded by the human HMGB1 gene (13q12) (2). HMGB1 is involved in stabilizing chromosomal structure in the nucleus, and in regulating the transcription of genes that are critical for maintaining basic life processes. When released from the cell, HMGB1 binds to its specific receptor under specific pathological or physiological conditions, which can mediate multiple inflammatory and autoimmune diseases (3).

In recent years, the high incidence of cerebrovascular disease has markedly affected the lives of patients (4). According to recently released data, in hospitalized patients aged between 55 and 63 years in the United States, the incidence of acute ischemic stroke is 202.5/10,000, the incidence of subarachnoid hemorrhage (SAH) is 11.9/10,000 and the incidence of intracerebral hemorrhage is 22.6/10,000 (4). Although treatment methods have improved over time, treatment remains invasive (5,6). Therefore, it is important to investigate the pathogenesis of cerebrovascular disease and to identify non-invasive treatment methods.

An increasing number of studies have demonstrated that the inflammatory response involving HMGB1 serves an important role in the course of acute cerebrovascular disease. This review summarized the structure, function, receptors and signaling pathways of HMGB1, and retrospectively analyzed the role of HMGB1 in ischemic cerebrovascular disease, hemorrhagic cerebrovascular disease and cerebral venous sinus thrombosis.

## 2. HMGB1

*The structure of HMGB1.* The sequence and structure of the HMGB1 protein are highly evolutionarily conserved. HMGB1 is composed of 215 amino acids, and has a molecular weight of ~25 kDa. HMGB1 includes three structural domains: Two relatively rigid DNA binding domains (A and B box) located at the N-terminal, which is termed the HMG box field, and a negatively charged acidic tail comprising 30 glutamic and

aspartic acids (7,8). The A box is located at the 1-79 loci of the HMGB1 molecular amino acid sequence and the B box is located at the 86-162 loci, and the amino acid homology rate of the two is >80%. The acidic tail between the B box and the C-terminal is connected by a flexible connection containing 24 amino acids (Fig. 1). Following HMGB1 being released to the outside of the cell, the B box is the main structural functional area that causes inflammation (7,9). The A box has an antagonistic effect on the inflammatory response caused by the B box, and this anti-inflammatory ability is enhanced following the fusion of the acidic C-terminal.

The HMGB1 molecule contains two nuclear localization sequences (NLS), respectively located in the A box (28-44) and the junction area of box B and the C tail (179-185). It also contains three cysteine residues, which are located separately at the 23 and 45 sites of the A box and the 106 locus of box B (Fig. 1) (8). Following stimulation, two cysteine residues can form a disulfide bond, and thus HMGB1 exists as three subtypes, the 'disulfide HMGB1', 'thiol HMGB1' and 'oxidized HMGB1' (10). Disulfide HMGB1 is the main subtype involved in the acute and chronic inflammatory response in the extracellular space and serum, which can further activate macrophages/monocytes to amplify the inflammatory response. The mechanism of HMGB1 is mainly involved in non-inflammatory responses and its mechanism has yet to be elucidated. Thiol HMGB1 can be released early and is able to repair cell damage by recruiting inflammatory cells (11).

**Secretion of HMGB1.** HMGB1 is secreted by two modes: Passive release and active secretion. The two secretory pathways differ in their molecular mechanism, release kinetics and downstream signaling pathway. Passive release occurs instantaneously upon the destruction of cellular integrity, as HMGB1 is not associated with nuclear DNA in living cells (8).

Under the stimulation of pathogen/microbe-associated molecular patterns and endogenous inflammatory mediators, including tumor necrosis factor (TNF), interleukin-1 (IL-1) and interferon- $\gamma$  (IFN- $\gamma$ ), macrophages, monocytes, dendritic cells, endothelial cells and other immune cells can actively secrete HMGB1 (8). HMGB1 can also induce its own release through pre-feedback regulation. Neurons, astrocytes, leukemia cells and neuroblastoma cells can also promote the active secretion of HMGB1 (8). Active secretion is much slower than passive release, and can be divided into two steps. To begin with, the HMGB1 in the nucleus is transferred to the cytoplasm through the internuclear pore. This process relies on the Janus kinase-signal transducer and activator of transcription signaling pathway and the super-acetylation of two key lysine residues in NLS (12), preventing HMB1 from entering the cytoplasm and returning to the nucleus, which may aid HMGB1 in accumulating in the cytoplasm. The second stage gradually induces the programmed death of inflammatory cells; alternatively, through secreted lysosomes, the intracellular HMGB1 is released from the cells (13).

**Biological functions of HMGB1.** Under physiological conditions, HMGB1 is involved in stabilizing chromosomal structure in the nucleus, maintaining gene stability, and induces DNA bending. In this process, box A of the two molecules of HMGB1 can form a special structure successively or

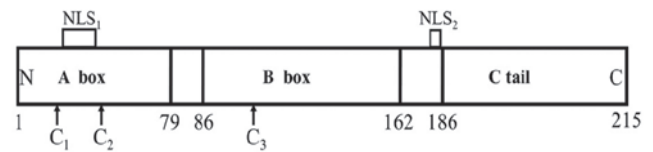


Figure 1. Structure of HMGB1. HMGB1 is comprised of 215 amino acids and has a molecular weight of ~25 kDa. HMGB1 includes three structural domains: A box, B box and an acidic tail. It contains two NLS, NLS1 (28-44 loci) and NLS2 (179-185 loci), and three cysteine residues, C1 (23 loci), C2 (45 loci) and C3 (106 loci). HMGB1, high mobility group box B1; NLS, nuclear localization sequences.

simultaneously with DNA, which causes the DNA to bend and reconstruct (14). In addition, HMGB1 can directly participate in the repair process of DNA damage following binding to DNA, namely in nucleotide, base excision, mismatch and double chain fracture repairs (15). The absence of HMGB1 can lead to increasing chromosomal instability (16).

Yanai *et al* (17), demonstrated that the absence of HMGB1 would weaken the response of the body to the extracellular signals associated with viral invasion, Toll-like receptor (TLR) ligands and PRRs. Therefore, HMGB1 may have a central role in early immunization activities. HMGB1 was one of the first members of its family to be identified. The downstream inflammatory ligands can induce the oligomerization of NOD-like receptor (NLR) and the assembly of inflammatory protein complexes (18). NLR molecules contain a leucine-rich repeat (LRR) domain, which has the functions of a combination of ligands. HMGB1 can also induce cell stress, mediating double-stranded RNA-dependent protein kinase autophosphorylation and promoting inflammatory cascade amplification in the process (19).

The HMGB1 in the cytoplasm can initiate autophagy, which is a self-protective process that removes damaged mitochondria and microbial invasions in the cell by combining with beclin-1 (20).

**The HMGB1 signaling pathway.** RAGE was the first identified receptor of HMGB1; it is a multifunctional transmembrane receptor of the immunoglobulin superfamily, which is involved in the maintenance of homeostasis and the occurrence of inflammation, and is encoded by a gene on chromosome 6p21.3 (21). When combined with HMGB1, it can activate p38 mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase 1 (ERK1) and ERK2, which in turn causes phosphorylation and degradation of the inhibitor of nuclear factor  $\kappa$ B (I $\kappa$ B) to activate NF- $\kappa$ B (22). HMGB1/RAGE can also induce the expression of MAPK, vascular cell adhesion molecule 1 and matrix metalloproteinase (MMP) (23).

The TLR is a member of the type I transmembrane superfamily, and consists of an extracellular LRR structural domain and a Toll/interleukin-1 receptor (TIR) structural domain in the cytoplasm (21). The TLR signaling pathway is divided into MyD88-dependent and MyD88-independent pathways. Following combining with a single ligand, TLR upregulates MyD88 or other adaptive molecules to induce the activation of downstream factors, including NF- $\kappa$ B, MAPK and IFN regulatory factors (24). HMGB1 interacts with

TLR-2, TLR-4 and TLR-9, triggering the activation of NF- $\kappa$ B and IRF pathways (25). Following the stimulation of TLR2, the downstream signal can be mediated by Rac1 and PI3K, increasing the adhesion of CD11b/CD18 and intercellular cell adhesion molecule-1 (ICAM-1), and Akt is activated directly by the p65 transcription complex or by the I $\kappa$ B kinase pathway; both of these pathways are able to activate NF- $\kappa$ B (22). Following the binding of TLR-4 to HMGB1, the interleukin-1 receptor-related kinase 1 can be phosphorylated, thereby activating the downstream signaling molecule NF- $\kappa$ B, and promoting MAPK by phosphorylating JNK, ERK, p38 and I $\kappa$ B (26). TLR9, normally located in the endoplasmic reticulum, can be transferred to the early endosomes in an HMGB1-dependent manner (27). TLR9 in endosomes and/or lysosomes can identify CpG DNA binding to HMGB1, and can then mediate NF- $\kappa$ B and its downstream inflammatory response (28). In recent years, it has been demonstrated that the combination of HMGB1 and TLR5 can also rely on MyD88 to activate the downstream signal (29).

C-X-C chemokine receptor 4 (CXCR4) is a member of the G protein-coupled receptor family, which has a low expression in normal tissues, but a significantly higher expression in tumor tissues (21). Recent studies have demonstrated that CXCR4 is also involved in inflammatory responses, and that thiol HMGB1 can form complexes with CXCL12 and activate CXCR4 to promote the production of inflammatory cells and cytokines (30).

### 3. HMGB1 and acute cerebrovascular disease

**Acute ischemic cerebrovascular disease.** Worldwide, ischemic cerebrovascular disease is the leading cause of disability and the third leading cause of mortality, and therefore is a heavy social and economic burden (31). Following cerebral ischemia, neuroinflammation and stress serve important roles in the pathogenesis of the disease (31). The inflammatory response in ischemic stroke consists of two stages: The early stage of destruction of the nerve tissue and the late stage of organizational reconstruction.

Following acute ischemic stroke, damaged brain tissue can release HMGB1, recruiting a variety of pro-inflammatory cytokines and chemokines, and increasing adhesion molecule expression, further activating brain cells and immune cells (32). Following cerebral ischemia, astrocytes and endothelial cells may be the early targets of HMGB1, which can be activated in this process. The former can directly transmit signals to neurons and blood vessels, and the latter upregulates ICAM-1 expression, recruiting immune cells into the ischemic area (33). The destruction of the blood brain barrier (BBB) is an important stage of ischemic brain injury, involving multiple cytokines. The activation of MMPs and the expression of various proteases results in the decomposition of the BBB, exacerbating leukocyte extravasation (34). HMGB1 can increase vascular permeability and promote BBB decomposition (35). Anti-HMGB1 antibody can inhibit the morphological and functional changes in the BBB induced by HMGB1 (36). Tsukagawa *et al* (32) demonstrated that quantitative serum HMGB1 levels could be used to evaluate the prognosis of ischemic stroke and may be more accurate than the existing evaluation methods.

Ischemic reperfusion injury can further aggravate functional metabolic disorders and structural damage in ischemic tissues. Apoptosis is strictly regulated by the MAPK family, and the c-Jun N-terminal kinase (JNK), ERK1/2 and p38 protein family in ischemia reperfusion injury is activated (37). The continuous activation of MAPK is associated with the death or apoptosis of neurons in the post-stroke stage of ischemic stroke (37). A study by Gong *et al* (38), demonstrated that glycyrrhizin can be used as a HMGB1 inhibitor to inhibit the JNK and p38 pathways in rats. Umahara *et al* (39), revealed that in the chronic stages of cerebral infarction, certain macrophages that were located in the ischemic region were positive for HMGB1. They hypothesized that there may be two reasons for this. One is that the HMGB1-associated inflammatory response in chronic cerebral infarction develops from acute cerebral infarction. Alternatively, HMGB1-positive macrophages may induce autophagy in the area of chronic ischemic injury, possibly due to the fact that HMGB1 can maintain autophagy (20).

In the recovery phase of ischemic stroke, HMGB1 may promote brain remodeling. Chen *et al* (40) and Wu *et al* (41), demonstrated that IL-6 and vascular endothelial growth factor (VEGF) mediate the reactive astrocyte release of HMGB1, and participate in the angiogenesis and neurogenesis in the late phase of stroke, promoting brain remodeling and neurological function recovery. Brain remodeling was inhibited following the administration of HMGB1 inhibitors. These studies have aided in improving the prognosis of ischemic stroke at different stages.

#### *Acute hemorrhagic cerebrovascular disease*

**Intracranial aneurysm and SAH.** Intracranial aneurysms are pathological local dilations caused by changes in local intracranial vessels. Among the various causes of SAH, spontaneous aneurysm rupture is the most common and requires attention. Zhang *et al* (42), demonstrated that HMGB1 was highly expressed on ruptured and unruptured aneurysm walls and, compared with the latter, the former had a higher level of expression. However, there is no significant association between the size of the aneurysm and the expression level of HMGB1. Through double immunofluorescence staining, Chalouhi *et al* (43) demonstrated that HMGB1 was expressed in the nucleus of smooth muscle cells, macrophages, lymphocytes and endothelial cells; these cells were involved in the remodeling of the aneurysm wall. NF- $\kappa$ B is highly expressed in the aneurysm wall, and the formation of the aneurysm is hindered by the application of NF- $\kappa$ B inhibitors (44). The incidence of intracranial aneurysms is associated with atherosclerosis and HMGB1 is involved in the formation of atheromatous plaques; following endothelial cell injury, activated NF- $\kappa$ B induces the activation of leukocyte adhesion molecules and a variety of cytokines, including HMGB1, and these signals can collect macrophages in the wall of blood vessels. Macrophages immersed in vessel walls can transform into foam cells and release HMGB1 again, forming a positive feedback inflammatory pathway (45). It has been demonstrated that in the formation and development of intracranial aneurysms, HMGB1 mediates the inflammatory response and participates in the formation of atherosclerotic plaques; as a result, the vascular wall is thickened or narrowed, and vascular remodeling increases the risk of rupture. Therefore, inhibition of HMGB1 may alleviate atheromatous plaque formation and reduce the risk of aneurysm rupture.



SAH is a life-threatening central nervous system disease. Cerebral vasospasm is one of the most important causes of the high morbidity and mortality of SAH. Previous study have demonstrated that 30-70% of patients with aneurysms and SAH will have vasospasm (46). It has been observed that this pathophysiological process is associated with inflammatory reactions, including leukocyte recruitment, infiltration and activation. Following SAH, HMGB1 participates in the inflammatory response and serves an important role in apoptosis and vascular spasm (47). Zhao *et al* (48), revealed that the artery endothelial cells and smooth muscle cells in the damaged brain region following SAH were activated to stimulate the secretion of HMGB1, which may promote intracranial arterial spasms. Umahara *et al* (39), conducted autopsies of patients with SAH and revealed that an HMGB1-like immunoreaction was observed in the cytoplasm of vascular smooth muscle cells in the hematoma. HMGB1 could not only promote the occurrence of cerebral vasospasm, but also increase the gene and protein expression levels of RAGE in neurons and microglia around the hematoma, and the number of microglia was also significantly increased. As a main downstream factor of RAGE, the main p65 subunit of NF- $\kappa$ B was significantly increased, indicating that RAGE promoted the activation of NF- $\kappa$ B at the early stage of SAH (49). Resveratrol, as an inhibitor of HMGB1, can relieve this pathophysiological change; the reason for this is that resveratrol may be involved in SAH-induced neuronal apoptosis, brain edema and nerve injury via inhibition of the HMGB1-mediated TLR4/MyD88/NF- $\kappa$ B pathway in the early stage of SAH (50). Clinically, patients with aneurysmal SAH may develop cerebral vasospasm and delayed cerebral ischemia, increased expression of HMGB1 during the course of disease, increased cerebral vasospasms and eventually an increased risk of cerebral infarction (51). Therefore, HMGB1 rapidly interacts with nerve cells and glial cells following SAH, and participates in cerebral vasospasm and apoptosis.

In the recovery phase of SAH, Tian *et al* (52) suggested that HMGB1 can promote neurological recovery and blood vessel regeneration via RAGE mediation, which further demonstrated that HMGB1 serves different roles at different disease stages.

**Intracranial hemorrhage (ICH).** ICH accounts for ~15% of all stroke cases and has a mortality rate close to 50% (53). Even patients who survive ICH often experience severe disability (53). The reaction that follows ICH is a complex process and involves a series of pathophysiological reactions, including excitotoxicity, free radical injury and inflammatory reactions (54). Hematoma can cause inflammatory reactions in the surrounding tissue, and can activate glial cells and neurons to aggravate cerebral injury (55). Following acute ICH, HMGB1 is released into the extracellular space by the damaged cell and, as a proinflammatory cytokine, it immediately causes a downstream inflammatory reaction (56), leading to brain damage, affecting neurobehavioral functioning, increasing the permeability of the BBB and aggravating brain edema (57). It has been reported that an anti-HMGB1 antibody can improve brain injury and nerve function defects following ICH in rats (58). In this process, HMGB1 triggers three specific downstream receptors,

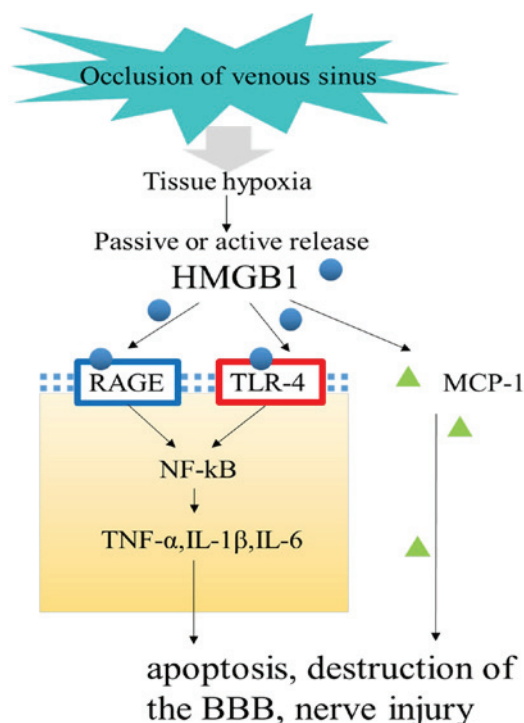


Figure 2. Signaling pathway of HMGB1 in cerebral venous sinus thrombosis. Following thrombosis, the pressure in the veins and capillaries is higher and blood return is limited, leading to tissue hypoxia. Subsequently, damaged tissue can actively or passively release HMGB1, triggering downstream inflammatory responses, participating in BBB disruption, apoptosis and nerve damage, and further aggravating brain damage. HMGB1, high mobility group box B1; BBB, blood brain barrier; TNF- $\alpha$ , tumor necrosis factor  $\alpha$ ; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; TLR-4, Toll-like receptor 4.

RAGE, TLR-2 and TLR-4, of which RAGE may be the most important. The use of RAGE antagonists alone hinders ICH-induced inflammatory cell infiltration, and decreases its downstream factors IL-1 $\beta$  and MMP-9 in the brain tissue around the site of the ICH (57). As a downstream factor of HMGB1, NF- $\kappa$ B is highly sensitive to oxidative stress in the surrounding area following ICH, and mediates downstream IL-1 $\beta$  and ICAM-1, which serve a key role in cell death following ICH, particularly in apoptosis (55).

At the end of the course of the disease, the brain begins to undergo a remodeling process, involving synaptic and vascular regeneration, which may aid in the recovery of nerve function following ICH. In this process, the progenitor cells of the subventricular region of the hippocampus migrate into the damaged brain region and differentiate into mature neurons and glial cells (59). HMGB1 serves an important role in promoting tissue recovery and remodeling at the late stage of disease. Following ICH, the expression levels of HMGB1 and VEGF are increased in surrounding brain tissue, and the inhibition of HMGB1 activity could significantly reduce the upregulation of VEGF (56). The ICH rat model induced by collagenase indicates that HMGB1 promotes angiogenesis mainly by mediating RAGE (56). In addition, HMGB1 can promote the expression of MMP-9, improve brain damage and restore nerve function (54). Therefore, when inhibiting the HMGB1-RAGE signaling pathway for ICH treatment, attention should be paid to the fact that early inhibition of this

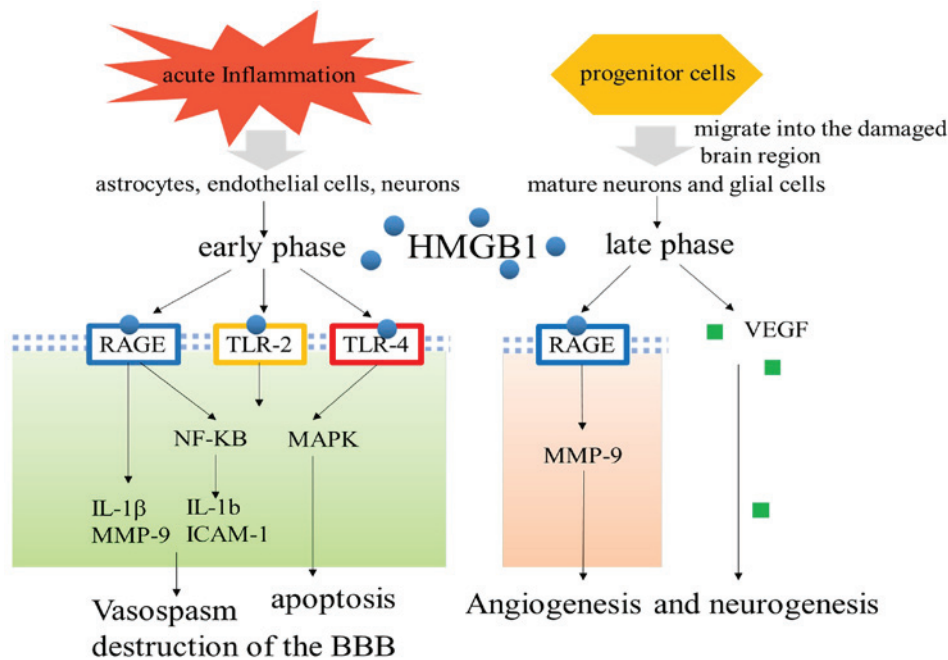


Figure 3. Signaling pathway of HMGB1 in the early and late phases of cerebrovascular disease. Following acute cerebrovascular disease, under the stimulation of inflammation, astrocytes, endothelial cells and neurons can actively secrete HMGB1, while passive release occurs instantaneously upon the destruction of cellular integrity. Extracellular HMGB1 interacts with neurons, endothelial cells and glial cells to participate in BBB disruption, vasospasm and apoptosis through mediating downstream inflammatory factors, which contribute toward cerebral edema and nerve injury. On the other hand, during the late phase, HMGB1 can promote brain repair and remodeling, participating in angiogenesis and neurogenesis, contributing toward the recovery of neurological function. HMGB1, high mobility group box B1; BBB, blood brain barrier; TLR, Toll-like receptor; VEGF, vascular endothelial growth factor; NF- $\kappa$ B, nuclear factor- $\kappa$ B; MAPK, mitogen-activated protein kinase; IL, interleukin; MMP, matrix metalloproteinase; ICAM-1, intercellular cell adhesion molecule-1.

pathway can improve the treatment of ICH, while later inhibition of this pathway could hinder the recovery of neurological function (57). These studies indicated that HMGB1 exerted different effects at different phases of intracranial hemorrhage; therefore, future studies need to focus on determining time frames.

**Cerebral venous thrombosis.** Cerebral venous sinus thrombosis is a relatively rare cerebrovascular disease, which accounts for 0.5-1% of the causes of stroke. A total of 50% of patients have venous cerebral infarction with a series of clinical manifestations, including headache, hemiplegia, epileptic seizures and intracranial hypertension. Its pathophysiological mechanism can be explained by the fact that, following thrombosis, the pressure in the veins and capillaries is higher and blood return is limited, leading to tissue hypoxia, which contributes toward brain edema and ICH. The increase in venous pressure also hinders the reabsorption of the cerebrospinal fluid and further aggravates the intracranial hypertension (60). Although an increasing amount of attention has been paid to CVST in recent years, little is known regarding the exact pathogenesis and progression of the disease.

In recent years, a number of studies have demonstrated that HMGB1 may be involved in the pathogenesis of CVST (Fig. 2): i) In a study undertaken by Gu *et al* (61), the protein and mRNA expression levels of HMGB1-RAGE were upregulated in the cerebral infarction area in rats following CVST. Recombinant human soluble (rhs)-TM was added to the model, which reduced the nerve injury and infarct volume, and reduced the expression level of HMGB1-RAGE and the proinflammatory cytokines TNF- $\alpha$ , IL-1 $\beta$  and IL-6 in the ischemic

penumbra; and ii) in the pathogenesis of CVST, venous return is blocked, but in view of the abundant collateral circulation of the cerebral venous system, there may be other mechanisms involved in the occurrence of cerebral edema following CVST. Nagai *et al* (62), demonstrated that following the occurrence of CVST, the concentration of monocyte chemoattractant protein-1 (MCP-1) increased. Meanwhile, HMGB1 could activate the expression of MCP-1 (23); therefore, HMGB1 may also be involved in the inflammatory response process of CVST in this way. A study undertaken by Yang *et al* (63), also demonstrated that apoptosis participated in the pathogenesis of CVST: caspase-3 served an important role in cellular apoptosis, and caspase-3 participated in the pathogenesis of CVST. Bax is a type of pro-apoptotic protein and Bcl-2 is one of the most active inhibitors of apoptosis. Bcl-2/Bax has been demonstrated to be essential for determining whether apoptosis has occurred, and the ratio of Bcl-2/Bax decreases significantly following the occurrence of CVST. HMGB1 can induce apoptosis via NF- $\kappa$ B by activating TLR-4 (47). The results of these studies suggested that HMGB1 serves an important role in the pathogenesis of CVST.

In general, following acute cerebrovascular incident, HMGB1 interacts with neurons, endothelial cells and glial cells to participate in BBB disruption, vasospasm and apoptosis through mediating downstream inflammatory factors, which contribute toward cerebral edema and nerve injury. On the other hand, during the recovery phase, HMGB1 can promote brain repair and remodeling, contributing toward the recovery of neurological function. Therefore, targeted therapy for HMGB1 may have a positive effect on acute cerebrovascular disease (Fig. 3).

#### 4. Conclusion

Due to the diversity of acute cerebrovascular diseases and complex pathophysiological mechanisms, it is very difficult to fundamentally cure acute cerebrovascular diseases by relying on the existing treatment methods. Gene therapy has the characteristics of high specificity, high biological activity and low toxicity, and can be targeted to improve or inhibit the expression of the target gene *in vivo*, so as to achieve the purpose of treating a disease. HMGB1 serves an important role in promoting the inflammatory response in acute cerebrovascular diseases. Gene therapy targeting HMGB1 may achieve satisfactory results in patients with acute cerebrovascular diseases.

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#### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

#### Authors' contributions

SWM researched literatures, and was a major contributor in writing the manuscript. YD researched literatures and edited the manuscript. SSW reviewed the manuscript. JJG reviewed the manuscript and approved the final version. All authors read and approved the final manuscript.

#### Ethics statement and consent to participate

Not applicable.

#### Patient consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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