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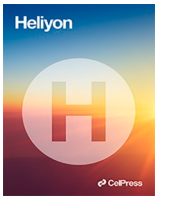

Review article

Potential significance of high-mobility group protein box 1 in cerebrospinal fluid

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ABSTRACT

High-mobility group protein box 1 (HMGB1) is a cytokine with multiple functions (according to its subcellular location) that serves a marker of inflammation. CSF HMGB1 could be the part of pathological mechanisms that underlie the complications associated with CNS diseases. HMGB1 actively or passively released into the CSF is detected in the CSF in many diseases of the central nervous system (CNS) and thus may be useful as a biomarker. Pathological alterations in distant areas were observed due to lesions in a specific region, and the level of HMGB1 in the CSF was found to be elevated. Reducing the HMGB1 level via intraventricular injection of anti-HMGB1 neutralizing antibodies can improve the outcomes of CNS diseases. The results indicated that CSF HMGB1 could serve as a biomarker for predicting disease progression and may also act as a pathogenic factor contributing to pathological alterations in distant areas following focal lesions in the CNS. In this mini-review, the characteristics of HMGB1 and progress in research on CSF HMGB1 as a biomarker of CNS diseases were discussed. CSF HMGB1 is useful not only as a biomarker of CNS diseases but may also be involved in interactions between different brain regions and the spinal cord.

1. Introduction

The cerebrospinal fluid (CSF) is a transparent and colorless fluid in the ventricles and subarachnoid space, and its total volume ranges from 130 to 150 ml. In adults, the volume of CSF secreted daily ranges from 400 to 600 ml, which is primarily generated by the choroid plexuses in the lateral ventricles and the tela choroidea in the third and fourth ventricles. The CSF is renewed about four times within 24 h, and its circulation is a dynamic process regulated to maintain brain homeostasis [1].The CSF is involved in regulating substance metabolism within the CNS and serves a crucial function in maintaining the homeostasis of the internal environment of the CNS. Previous studies have suggested that the CSF may facilitate the transportation of products of choroidal plexus secretion to their target locations, allowing for the modulation of activity in specific brain regions through circulation via the CSF [2]. Some neurodegenerative diseases are also characterized by an accumulation of catabolites in the brain and CSF [3]. Therefore, certain molecules or substances in the CSF have the potential as biomarkers of diseases. Biomarkers have various applications, such as diagnosing diseases,

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monitoring the progression and prognosis of illnesses, and assessing the safety and efficacy of newly developed drugs and therapies. There are several CSF biomarkers for CNS diseases, including neurodegenerative diseases, tumors, cerebrovascular diseases, traumatic brain injury (TBI), and traumatic spinal cord injury (TSCI) [4–8].

High mobility group box 1 protein (HMGB1) is a non-histone chromosomal protein that was identified in 1973. Its name is attributed to its high electrophoretic mobility on polyacrylamide gel electrophoresis [9]. As a cytokine, HMGB1 possesses numerous functions determined by its subcellular location and is considered an inflammation indicator. HMGB1 can be released in both active and passive ways. Upon cellular stimulation, HMGB1 undergoes acetylation or phosphorylation, translocates from the nucleus to the cytoplasm, and is then secreted into the extracellular environment. HMGB1 may also be released passively from damaged cells [10].

Once released through either of these mechanisms, HMGB1 binds to its receptors and activates downstream signaling pathways to exert its biological effects. As the disease develops and progresses, HMGB1 is frequently released into the blood and/or CSF following cellular stimulation or damage. Therefore, HMGB1 in the blood and CSF has the potential to serve as biomarkers. A prior investigation demonstrated that HMGB1 is a significant predictor of one-year mortality in patients suffering from TBI. Furthermore, HMGB1 is translocated to the cytoplasm from the nucleus during the early stages of TBI [11]. An increased serum/CSF HMGB1 ratio in humans is related to poor outcomes following TBI. Therefore, HMGB1 is a promising therapeutic target after TBI [12].

CSF HMGB1 is elevated in many CNS diseases, including traumatic CNS injury, epilepsy, subarachnoid hemorrhage (SAH), cerebral ischemia, meningitis, and Parkinson's disease (PD). Increased CSF HMGB1 was shown to be related to a poor prognosis in many diseases [13–16]. Although CSF HMGB1 levels are elevated in many CNS diseases, the underlying pathological mechanisms have rarely been studied. Therefore, the study of CSF HMGB1 is a promising research direction. It has been reported that HMGB1 can activate microglia to release inflammatory factors, damage neurons, and promote disease onset and progression [17]. Studies conducted on both spinal cord injury (SCI) patients and animal models have shown that there were pathological changes in the brain regions as a result of SCI. However, following SCI, it is still unclear which pathways can result in pathological alterations in distant brain regions. As HMGB1 is an endogenous danger signal or damage-associated molecular pattern (DAMP), and CSF acts as the transmission medium of the CNS, the release of HMGB1 into the CSF can result in pathological alterations in distant sites due to the circulation of CSF. It might account for the brain damage observed in patients with SCI. It could shed light on the pathological mechanisms of conditions like neuropathic pain, cognitive impairment, depression, and anxiety that SCI patients experience.

The present review provides a comprehensive overview of the current research on the role of CSF HMGB1 in disease and discusses the molecular mechanisms underlying the pathological alterations associated with it. Additionally, a new mechanism for the pathological alterations observed after SCI was proposed. It was speculated that after SCI, cells actively or passively release HMGB1 into the CSF, which then circulates throughout the brain via the CSF and causes pathological alterations that may be responsible for the neuropathic pain, cognitive dysfunction, depression, and anxiety associated with SCI. This hypothesis also applies to the interactions between different brain regions, including peripheral nerve damage. Simultaneously, HMGB1 in CSF may be used as a biomarker of CNS diseases to predict the occurrence, development and prognosis of diseases.

2. Literature search methods

The Web of Science, PubMed, and EBSCO electronic databases were used for the search, and the keywords were "HMGB1" and "cerebrospinal fluid". The search deadline was January 31, 2023. There were 126 articles in the Web of Science database, 67 in PubMed, and 52 in EBSCO that matched the search criteria. After duplicate reports were excluded, 147 literature reports were selected

Table 1
Changes of HMGB1 level in CSF.

Disease	Changes of HMGB1 level in CSF	Refences
Encephalitis	Increased	[32–35]
Meningitis	Increased	[36–38]
pIE	Increased	[39]
Neuroborreliosis and tick-borne encephalitis	Increased	[40]
NMO	Increased	[41–43]
MS	Increased	[43,44]
MS	Not increased	[45]
Guillain-Barré syndrome	Not increased	[46]
SAH	Increased	[15,47,48]
Brain ischemia	Increased	[16,49–52]
TBI	Increased	[13,53,54]
SNI	Increased	[55]
Epilepsy	Increased	[14,58–60]
Epilepsy	Increased but not statistically significant	[61]
Febrile seizure	Not increased	[62]
PD	Increased	[63,64]
SHR	Increased	[65]
OHCA	Increased	[66]

HMGB1 high mobility group box 1 protein, CSF cerebrospinal fluid, pIE pandemic H1N1 influenza-associated encephalopathy, NMO neuromyelitis optica, MS multiple sclerosis, SAH subarachnoid hemorrhage, TBI trauma brain injury, SNI spared nerve injury, PD Parkinson's disease, SHR spontaneously hypertensive rats, OHCA out-of-hospital cardiac arrest.

for this research. By reading the abstracts, irrelevant and non-English language articles were excluded, and 37 relevant articles were obtained. Changes of HMGB1 level in CSF are showed in Table 1. Fig. 1 shows a flow chart of the literature search and selection procedure.

3. Characteristics of HMGB1

The structure of HMGB1 is highly conserved across species, with 100 % identity at the protein level between rats and mice and 99 % between rodents and humans [18]. The HMGB1 gene has four introns and five exons and is located on chromosome 13q12 [19]. The A box and B box domains are arranged in series and are separated by a 30-amino acid glutamate- and aspartate-rich C-terminal tail and a short, flexible connector [20]. The B box has a pro-inflammatory effect, whereas the A box domain acts as an HMGB1 antagonist [21, 22]. In addition, the location of HMGB1 affects its functions. HMGB1 in the nucleus regulates critical nuclear activity, such as gene expression and chromatin remodeling [23]. Upon stimulation or damage, HMGB1 undergoes nucleus-to-cytoplasmic translocation and serves as an endogenous danger signal or DAMP through active or passive release. HMGB1 has been shown to be related to inflammatory response, cell proliferation, differentiation, invasion, cell autophagy, pyroptosis, and ferroptosis [10]. The posttranslational modification of HMGB1 is influenced by its localization and activity. It includes acetylation, N-glycosylation, ADP-ribosylation, phosphorylation, methylation, redox, and oxidation [10]. Actively or passively released HMGB1 must bind to its receptors to function. These include receptors for Toll-like receptor 2 (TLR2), TLR4, TLR9, advanced glycation end products (RAGE), chemokine receptor type 4 (CXCR4), and T cell immunoglobulin and mucin domain-3 (TIM-3) [24–28]. Upon binding to the receptor, HMGB1 activates downstream pathways, including nuclear factor-κB (NF-κB) and extracellular signal-related kinases 1/2, p38, and Jun amino-terminal kinases [29–32].

4. CSF HMGB1 in disease

4.1. Inflammatory diseases

HMGB1 is a widely distributed, highly conserved, relatively small protein known to be a potent innate inflammatory mediator. It can stimulate the activation of nuclear factor light chain enhancer of activated B cells and release cytokines following extracellular release [33]. A clinical study demonstrated that elevated levels of CSF HMGB1 were observed in patients with neurological infection/inflammation and Rasmussen's encephalitis [34]. As the HMGB1 protein in the CSF is associated with necrosis and inflammation, it has the potential to serve as a new marker for dogs with encephalitis [35]. Patients with healthcare-associated ventriculitis and meningitis (HAVM) were found to have significantly higher levels of CSF HMGB1 compared to those without HAVM. Therefore, HMGB1 is considered an accurate biomarker of HAVM patients, which improves the diagnostic significance of CSF-glucose measurements [36]. CSF levels of HMGB1 were considerably higher in patients with tuberculous meningitis and bacterial meningitis [37,

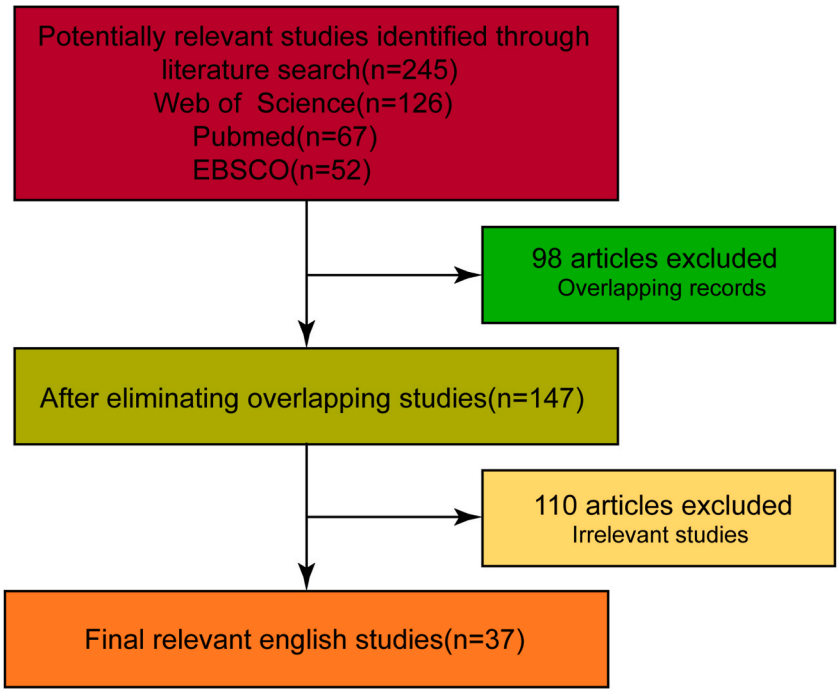

Fig. 1. Flow charts of literature search and selection.

38]. In another study, CSF HMGB1 levels were remarkably higher in meningitis patients, and CSF HMGB1 levels were related to those of interleukin (IL)-6 and IL-8 [39]. In patients with pandemic H1N1 influenza-associated encephalopathy (pIE), the levels of HMGB1 in cerebrospinal fluid were not elevated. However, a significant positive correlation was observed between serum HMGB1 levels and pIE. No such correlation was observed between CSF HMGB1 and IL-6 levels [40]. In addition, patients with neuroborreliosis and tick-borne encephalitis had significantly higher HMGB1 concentrations in the CSF than controls [41].

According to Ai et al., the levels of HMGB1 were elevated in the CSF of patients with Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. It indicated the presence of an underlying neuroinflammatory process [33]. High levels of CSF HMGB1 in patients with neuromyelitis optica (NMO) reflected neuroinflammatory processes [42–44]. Elevated concentrations of HMGB1 were observed in the CSF of patients with multiple sclerosis (MS) [44,45]. However, another study showed that the CSF HMGB1 levels were not elevated in samples from MS patients at clinical onset [46]. CSF HMGB1 levels were not notably different between patients with Guillain-Barré syndrome and those with noninflammatory neurological disorders [47].

To summarize, CSF HMGB1 levels are elevated in the majority of CNS inflammatory diseases and are positively correlated with inflammatory cytokine levels, which reflect neuroinflammatory processes. These findings suggested that HMGB1 may have significant implications in the pathophysiology of CNS infections.

4.2. Cerebrovascular diseases

Cerebrovascular diseases include hemorrhagic and ischemic cerebrovascular diseases, such as SAH, intracranial hemorrhage, and ischemic stroke. SAH is mainly caused by aneurysm rupture, which results in the death of large numbers of nerve cells. According to some research, SAH patients had higher levels of CSF HMGB1. There is a strong correlation between higher levels of HMGB1 in the CSF of SAH patients and poor outcomes, indicating that the level of CSF HMGB1 may serve as a useful and novel predictor of outcomes following SAH [15,48,49].

The pathological mechanism of brain injury induced by cerebral ischemia is complex. The levels of HMGB1 are elevated in both the CSF and serum during the initial and late stages of brain ischemia in mice and are thought to play a role in promoting brain damage [50]. Treatment with amlexanox or anti-HMGB1 antibody inhibits HMGB1 release in stroke-induced brain injury to protect against ischemic brain damage in mice [16]. Among rats with hyperglycemic stroke, the increased early extracellular release of HMGB1 may be a crucial mechanism underlying more severe ischemic damage, especially early blood-brain barrier (BBB) disruption [51]. Following ischemic injury of rats and mice, HMGB1 is released early from damaged neurons and activated inflammatory cells and may play a role in the early stages of the inflammatory response [52,53]. Therefore, SAH and cerebral ischemia induce brain injury, and the injured neurons and activated inflammatory cells subsequently release HMGB1 into the CSF, further exacerbating brain injury. The findings suggested that elevated CSF HMGB1 levels play a significant role in SAH and cerebral ischemia. However, there are no existing reports on intracranial hemorrhage, representing a potential future research direction.

4.3. Central and peripheral nervous system injury

TBI causes the death of large numbers of neurons and the activation of microglia, and CSF HMGB1 levels are elevated in TBI [54]. Elevated levels of HMGB1 and cytochrome *c* in CSF were found to be linked to unfavorable outcomes in infants and children following TBI [13]. Patients who developed moderate or severe TBI had increased levels of HMGB1 in their CSF, with the highest levels observed within the first 72 h following the injury. The findings suggested that the release of HMGB1 from neurons is triggered by the trauma of TBI, and is not merely a result of the accompanying increase in cerebral edema [55]. In a spared nerve injury (SNI) model, HMGB1 expression in the CSF of SNI rats was upregulated on days 7, 14, and 21 after the operation compared with the sham group [56]. Therefore, CSF HMGB1 levels are elevated in TBI and peripheral nerve injury. However, SCI is another traumatic disease of the nervous system, and CSF HMGB1 has not been reported in SCI. The previous study showed that the levels of HMGB1 expression in tissues increased following SCI [31,32]. Patients with acute or chronic SCI have been found to exhibit significantly elevated levels of plasma HMGB1. The outcomes indicated that HMGB1 might serve as a common, persistent, and early indicator of inflammation in SCI [57]. CSF HMGB1 may mediate brain remodeling after SCI [58]. Therefore, additional studies of CSF HMGB1 level and function in SCI are required.

4.4. Epilepsy and febrile seizures

The concentration of CSF HMGB1 in patients with epilepsy was found to be remarkably higher, and those who did not achieve remission had elevated levels of CSF HMGB1 at the 1-year follow-up. Furthermore, the levels of CSF HMGB1 were positively correlated with seizure frequency. These findings suggested that HMGB1 might play a crucial role in the onset of seizures and that the measurement of CSF HMGB1 levels could potentially be used to predict the etiology and prognosis of epilepsy [14]. CSF HMGB1 was shown to be significantly elevated in febrile infection-related epilepsy syndrome patients [59].

The CSF level of HMGB1 was significantly elevated in patients with suspected autoimmune epilepsy [60]. Children with febrile seizures have remarkably higher levels of HMGB1 in their CSF, indicating that the HMGB1 network could potentially play a role in the onset of febrile seizures in this population [61]. Although the differences were not statistically significant, both serum and CSF levels of HMGB1 were higher in patients with seizure disorders and neuropsychiatric systemic lupus erythematosus than in those with other neuropsychiatric symptoms [62]. However, another research reported that there was no significant increase in CSF HMGB1 levels during the early stages of febrile seizure patients [63].

4.5. Parkinson's disease

Santoro et al. reported an increase in HMGB1 levels in the CSF of PD patients, and HMGB1 may be linked to progressive dopaminergic degeneration and chronic neuroinflammation, which are considered to be key mechanisms underlying the progression of PD [64]. Another research has shown that the CSF concentration of HMGB1 is significantly higher in hemi-PD mice compared with the vehicle group, and HMGB1 plays a role in maintaining nociceptive symptoms in mice with hemi-PD by activating spinal microglia. Thus, central HMGB1 may have potential as a therapeutic target for pain associated with PD [65]. Therefore, HMGB1 levels are elevated in cerebrospinal fluid in both PD patients and mice, suggesting that CSF HMGB1 may play an important role in PD, although more studies are needed to confirm this.

4.6. Other diseases

CSF HMGB1 is not only used as a marker of CNS diseases, but also of various other diseases. Elevated levels of HMGB1 protein expression, IκB-α phosphorylation, TNF-α and IL-6 protein expression, and microglial activation were observed in the paraventricular nucleus of spontaneously hypertensive rats (SHR). Additionally, these rats exhibited elevated levels of HMGB1 in both their plasma and CSF [66]. The Glasgow-Pittsburgh Cerebral Performance Categories (CPCs) score, assessed six months after the return of spontaneous circulation (ROSC), was employed to determine if the presence of HMGB1 and S100B in the CSF and serum could predict neurological outcomes in patients resuscitated from an out-of-hospital cardiac arrest (OHCA). The results showed that HMGB1 and S100B in CSF were remarkably higher in the CPC≥3 group than CPC 1 and 2 groups. HMGB1 in CSF was strongly correlated with S100B [67]. The results suggested that CSF HMGB1 may also be useful to predict the prognosis in cases of non-neurological diseases.

5. Possible sources of CSF HMGB1

The CNS is mainly composed of brain and spinal cord tissue, blood and blood vessels, and CSF. Neurons and glial cells are the main components of the brain and spinal cord. Therefore, when disease occurs, HMGB1 is most likely to originate from neurons, glial cells, and blood vessels (Fig. 2).

5.1. Active or passive release from neurons and glial cells

Brain cells consist mainly of neurons and glial cells. Neurons are an important part of the nervous system. Nearly all diseases involving the nervous system are associated with neuronal activation or damage. HMGB1 is expressed in neurons and glial cells. HMGB1 is hypothesized to play a role in the pathogenesis of PD, stroke, TBI, epilepsy, autism, depression, MS, and amyotrophic lateral

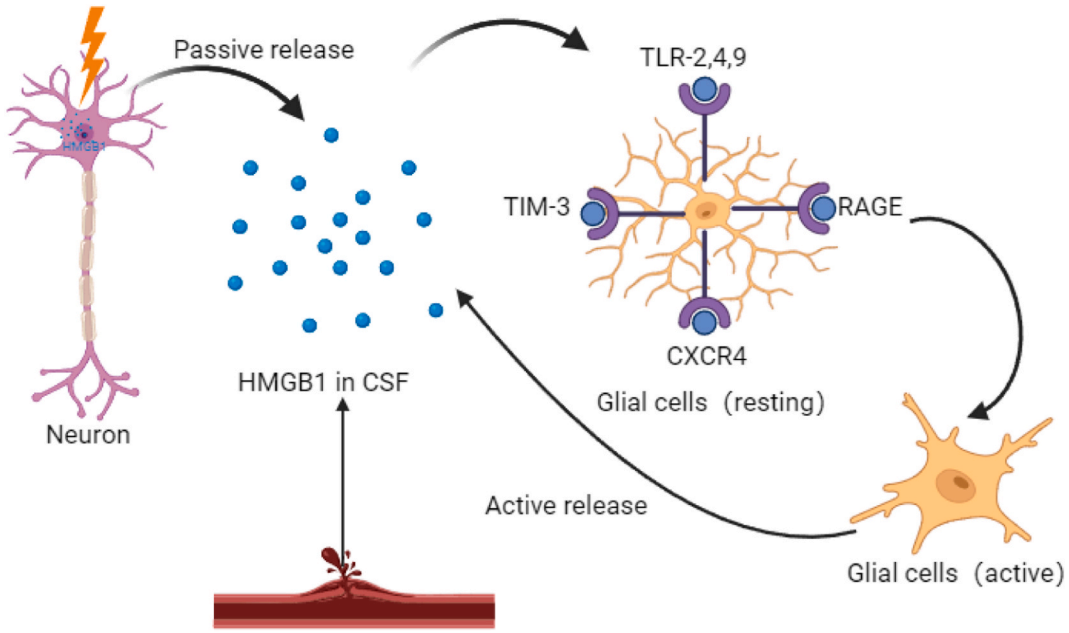

Fig. 2. Possible sources of high mobility group box 1 protein in cerebrospinal fluid (CSF HMGB1). CSF HMGB1 can be derived from various sources, including damaged neurons, activated glial cells, and ruptured blood vessels. Once it enters the CSF, it can bind to different receptors, including TLR-2/4/9, CXCR4, TIM-3, and RAGE receptors on glial cells. This binding activates glial cells to produce inflammatory factors and release more HMGB1 into the CSF. This figure was created with BioRender.

sclerosis, and is associated with neuroinflammation [21,42,68–74].

HMGB1 is actively released from neurons in response to optogenetic stimulation [75], and from neurons stimulated by TNF [76], or following ethanol exposure [77]. In addition, HMGB1 can be passively released from necrotic cells, such as neurons [78,79]. Therefore, neurons may be a major contributor to inflammation via the mechanism of releasing HMGB1. Numerous immune cell types, such as microglia and astrocytes, express HMGB1 and have the ability to secrete it in an active or passive manner [80,81]. Additionally, extracellular HMGB1 hinders CNS remyelination and directly suppresses the proliferation and differentiation of oligodendrocyte progenitor cells. It results in the development of disorders such as stroke, MS, and TBI [82–84]. HMGB1 actively or passively released into the extracellular environment causes microglia and other cells to actively secrete more HMGB1, thereby exacerbating inflammation and neuronal damage and contributing to inflammatory cascades. Therefore, HMGB1 is a key molecule in the interaction between glial and neuronal cells and an amplifier of neuroinflammation.

5.2. HMGB1 derived from brain or spinal cord Vasculature

When the brain or spinal cord is injured, the blood vessels are also damaged, and injured vascular smooth muscle cells and endothelial cells may release HMGB1. Human cerebral aneurysms have been demonstrated to express HMGB1, and ruptured aneurysms exhibit higher levels of HMGB1 expression than unruptured aneurysms [85]. The HMGB1/TLR4/NF-κB signaling pathway mediates the phenotypic transformation of vascular smooth muscle and endothelial cell dysfunction in the abdominal aortic aneurysm (AAA) [86,87]. Pannexin-1 channels on endothelial cells act as conduits for ATP release, stimulating macrophage activation via P2X7 receptors and mitochondrial DNA release, thus resulting in increased IL-1β and HMGB1 secretion [88].

Interestingly, a recent study showed that the HMGB1 level was elevated in acute lung injury and that HMGB1 accumulates in the abdominal aorta through blood circulation, which leads to AAA [89]. These findings suggested that HMGB1 released from damaged blood vessels or injured tissues may circulate to other sites. In addition, HMGB1 mediates the breakdown of the BBB in many CNS diseases [90]. Therefore, HMGB1 may be derived from vascular smooth muscle cells or endothelial cells and intrude into the CSF directly or enter the brain tissue and CSF by breaking down the BBB via blood circulation.

6. Time course of CSF HMGB1 expression and release

In an SNI model, CSF HMGB1 increased significantly on day seven after surgery and continued to increase until the end of the experiment on day 21[56]. The HMGB1 level was significantly increased in the CSF of individuals with simple and complex febrile seizures between 6 months and six years of age compared to controls [61]. In a study of SAH, the HMGB1 level was measured in CSF samples collected from patients on days 1, 5, and 10 after injury. The HMGB1 levels were significantly different between days 1 and 5, and the difference between days 1 and 10 was almost significant [15]. There was no increase in the HMGB1 level in CSF from patients with acute encephalopathy, febrile seizure, or fever without neurological complications at early time points (1–12 h after onset of symptoms). In contrast, individuals with bacterial and aseptic meningitis had CSF that showed a substantial rise in HMGB1. These findings revealed that in patients with encephalopathy at the early stages, damaged neural cells may not release HMGB1 into the CSF [63]. CSF HMGB1 levels did not change over time when examined 0–24, 25–48, 49–72, and >72 h after TBI, but both the mean and peak CSF HMGB1 levels were significantly elevated compared with controls [13]. HMGB1 exists as three different redox isomers with different functions: fully reduced HMGB1 (fr-HMGB1), which induces cell migration; disulfide HMGB1 (ds-HMGB1), a TLR4 ligand, with proinflammatory effects; and sulfonyl HMGB1 (ox-HMGB1), which has lost its proinflammatory characteristics and cannot induce cell migration or cytokine production [91]. HMGB1 has been reported to show distinct roles in CNS injury, with inflammatory effects in the early stages and anti-inflammatory effects in the later stages, suggesting that HMGB1 has distinct effects at different periods [92]. In acute cerebrovascular diseases, HMGB1 released by astrocytes at the late stage of stroke promotes the activity and migration of endothelial progenitor cells, thereby repairing neurovascular units, generating angiogenesis around the site of infarction, and improving neurological function [93,94]. When the subacute stage has passed, HMGB1 in the CSF may promote the regeneration of neuronal cells, vascular remodeling, and recovery of nerve function. The predominant isomer of HMGB1 may change over the course of the disease, allowing it to perform a different function. Therefore, it is interesting to explore the dynamics of different isoforms of HMGB1 in CSF during the time course of the disease and how they contribute to the initial damage. Further studies of the time courses of CSF HMGB1 expression and release in CNS diseases will allow for more accurate prediction of disease progression and aid the development of more effective interventions. In addition, CSF HMGB1 levels are generally elevated in most CNS diseases, although there are some exceptions. The exact cause of this discrepancy remains unclear and may be attributed to various factors such as the timing of the sampling, the small sample size, or the severity of the disease. These factors may contribute to lower levels of HMGB1 in the CSF.

7. Sampling, preservation, and assessment of CSF

CSF samples can be obtained from patients by lumbar puncture [14,34,38,47,61,67] or endoventricular drainage [13,15,49]. However, CSF has been collected from the cisterna magna of mouse, rat, and dog brains and samples were stored at −80 °C until assay [16,35,50–53,65]. The concentration of HMGB1 in CSF was determined by means of an enzyme-linked immunosorbent assay.

8. Perspectives

Although the level of HMGB1 in CSF following SCI has not been reported, patients with acute or chronic traumatic SCI have systemically higher serum levels of HMGB1 [57]. A review of the literature showed that CSF HMGB1 levels are elevated in many CNS diseases, which predicts a poor prognosis. Therefore, further studies of CSF HMGB1 are warranted to ascertain how an injury at one site can cause a pathological alteration at a distant site.

Remote hippocampal damage occurring after focal damage has been observed in many nervous system diseases, including TBI, SCI, and nerve injury. After experiencing a controlled cortical impact brain injury, there is a delayed onset of histopathological damage in the corpus callosum and hippocampus that can take several months to appear. This damage is accompanied by progressive depression and memory loss. Similar alterations are also observed in humans following TBI [95]. Region-specific glial fibrillary acidic protein disturbances and ionized calcium-binding adaptor molecule 1 transcript protein levels in higher brain regions are seen as early as 24 h post-SCI [96]. Nerve ligation activated microglia predominantly in the contralateral hippocampus [97]. However, a different study revealed that mice that underwent partial sciatic nerve ligation (PSNL) demonstrated elevated levels of the HMGB1 protein and microglial activation in their frontal cortex at the 8-week mark [98]. The study demonstrated that intracerebroventricular administration of recombinant HMGB1 (rHMGB1) induced microglial activation and anxiodepressive-like behavior in naïve mice. Additionally, it was found that blocking HMGB1 in mice with PSNL using glycyrrhizic acid or anti-HMGB1 antibody led to an attenuation in microglial activation and anxiodepressive-like behavior. These outcomes demonstrated that HMGB1 likely plays a role in developing PSNL-induced anxiodepressive-like behavior [98]. These findings indicated that HMGB1 might be crucial for communication between

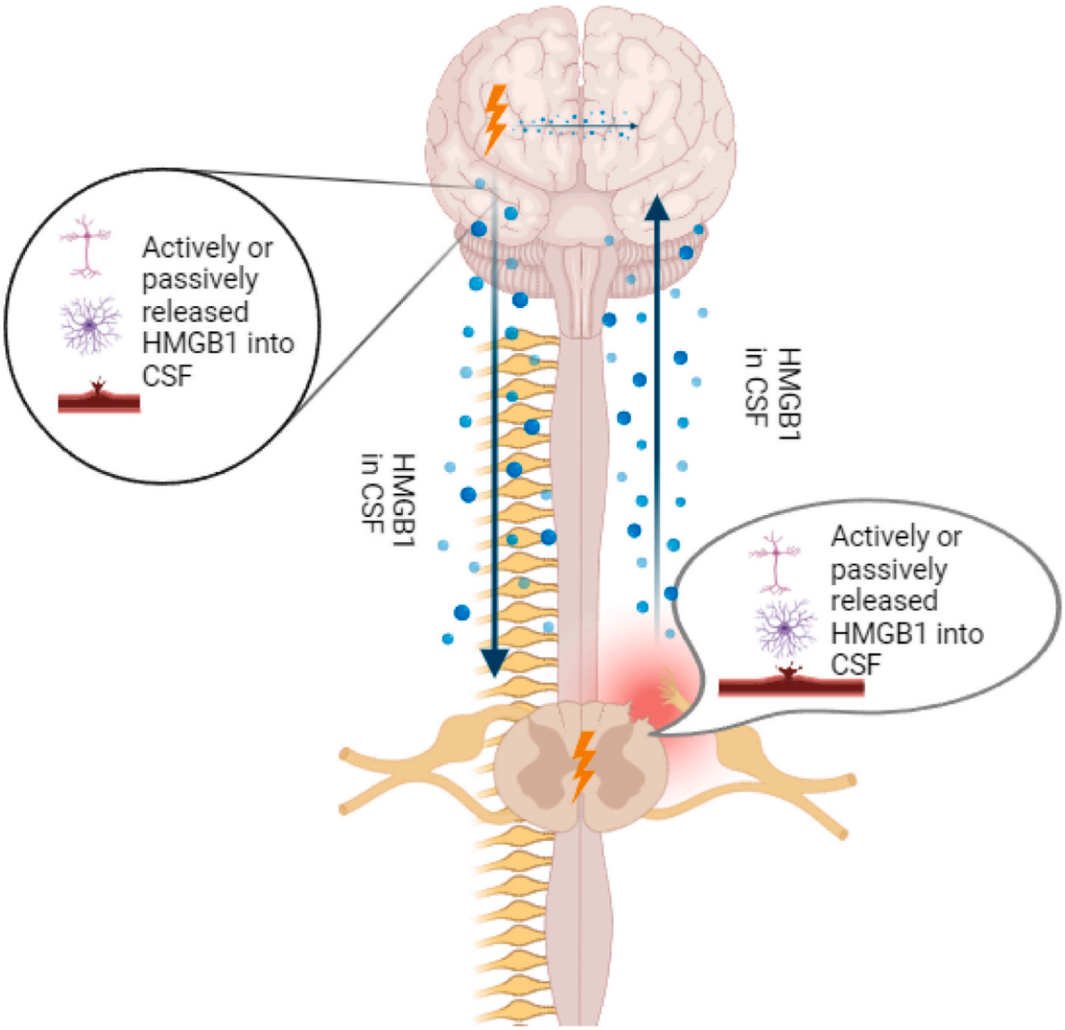

Fig. 3. Schematic diagram showing the bridging function of high mobility group protein box 1 in cerebrospinal fluid (CSF HMGB1) allowing communication between different brain regions, as well as between the brain and spinal cord. After spinal cord injury (SCI) or peripheral nerve injury (PNI), CSF HMGB1 can induce pathological changes in the brain, thus leading to disease. CSF HMGB1 can also cause pathological changes in other brain regions and the spinal cord after a focal brain lesion. This figure was created with BioRender.

the brain and spinal cord.

Interactions between different brain regions and between SCI and brain regions, as well as the associations between peripheral nerve injury and various brain regions, have not been fully elucidated. CSF HMGB1 level is elevated in many CNS diseases. Intraventricular injection of anti-HMGB1 antibody reduces HMGB1 expression in the brain, with an anti-inflammatory effect contributing to the improvement of the disease. Anti-HMGB1 monoclonal antibody therapy may be effective for various CNS and peripheral nervous system diseases [99]. Central HMGB1 induced mechanical hypersensitivity through spinal microglial activation in a mouse hemi-PD model [65]. Therefore, it is reasonable to conclude that CSF HMGB1 may serve a crucial role in mediating the interactions between different regions. It can also explain the pathological alterations seen in brain regions caused by SCI (Fig. 3). This provides a basis for studying the connection between the brain and the spinal cord.

Recent research on CSF HMGB1 has focused mainly on its role as a biomarker for predicting disease progression and prognosis and has not considered its full potential. The role of HMGB1 in CSF remains understudied, with current research primarily focused on its expression levels in relation to disease diagnosis and prognosis. Studying the molecular mechanism of CSF HMGB1 is a very interesting research direction in the future. Possible speculate that CSF acts as a transmitter, transporting HMGB1 to distant sites where it binds to surface receptors on microglia cells or astrocytes, leading to inflammatory reactions that can damage neurons. The release of HMGB1 from damaged neurons can activate glial cells, and HMGB1 may play a key role in the interaction between glial cells and neuronal cells. HMGB1 is widely distributed in the brain through the flow of CSF, and this may result in the activation of border-associated macrophages or widespread meningeal or parenchymal inflammations. However, further studies are necessary to confirm this hypothesis.

In sum, CSF HMGB1 is particularly valuable for CNS disease research. Basic experimental studies further confirmed that CSF HMGB1 could have inflammatory effects at distant sites, which sheds light on the mechanisms through which SCI causes neuropathic pain, depression, cognitive dysfunction, and other issues that are difficult to explain at present fully. These observations provide an experimental basis for the clinical application of HMGB1 inhibitors and neutralizing antibodies through the CSF pathway to treat various diseases.

9. Conclusion

HMGB1 is a transcription factor, however, it assumes cytokine role once released or actively secreted by immune cells during inflammation. HMGB1 is expressed in various cells of the CNS, including neurons and glial cells. When these cells are stimulated or injured, HMGB1 is released into the extracellular environment in an active or passive manner, exerting a proinflammatory effect and exacerbating tissue damage. The CSF is widely distributed in the brain and spinal cord. It plays a crucial role in regulating electrolyte balance, facilitating the circulation of active molecules, and removing catabolites, thus maintaining the homeostasis of the cerebral interstitial fluid and the neuronal environment. Elevated levels of CSF HMGB1 have been found in many CNS diseases and are associated with a poor prognosis; therefore, it has the potential as a biomarker. However, there are still unanswered questions about how lesions in one region can lead to pathological alterations in another, how SCI leads to pathological alterations in brain regions, how peripheral nerve injury leads to pathological alterations in various brain regions, and how hemi-PD causes spinal microglial activation and neuropathic pain.

Studies have shown that intraventricular injection of anti-HMGB1 neutralizing antibodies can reduce the expression of HMGB1, reduce inflammatory reactions, and improve disease prognosis. Hence, CSF HMGB1 may have significant implications for the pathogenesis of CNS diseases. In-depth studies of the role of CSF HMGB1 may explain the causes of pathological alterations in distant regions and provide a basis for clinical treatment of CNS diseases caused by intraventricular or lumbar cistern administration. To summarize, CSF HMGB1 serves not only as a biomarker of CNS disease but also as a bridge between different brain regions, as well as between the brain and spinal cord.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Data will be made available on request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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