

Role of damage-associated molecular patterns in the pathogenesis and therapeutics of traumatic brain injury

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Abstract

Traumatic brain injury (TBI) is a serious condition that poses a significant threat to human health globally. It is typically caused by direct trauma to the brain due to external forces such as impact or compression. The progression of TBI occurs in two stages based on physiological and pathological changes: primary and secondary brain injury. During the secondary stage, a large number of damage-associated molecular patterns (DAMPs) are released from injured cells into the extracellular space. These DAMPs trigger or exacerbate pathological conditions, including neuroinflammation, brain edema, diffuse axonal injury, and programmed cell death. The three main types of neural cells—neurons, microglia, and astrocytes—facilitate intercellular communication and functional crosstalk through the release and transmission of DAMPs. This forms the cellular foundation of secondary brain injury pathology. In the later stages of TBI, DAMPs are transported to various organs throughout the body via extracellular vesicles, leading to systemic changes and secondary injuries. Recent research has increasingly recognized the correlation between TBI and specific DAMPs. However, there remains a lack of comprehensive reviews exploring this relationship from a broader perspective. This review summarizes the primary pathological changes that occur after TBI, the types of DAMPs and their related signaling pathways, the role of DAMPs in mediating intercellular communication and neuronal crosstalk, and the relationship between DAMPs and systemic changes following TBI. This study also highlights that DAMPs represent promising targets for clinical diagnosis and treatment, which emphasizes the critical role of DAMPs in TBI.

Keywords: Traumatic brain injury; Damage-associated molecular patterns; Neuroinflammation; Neurons; Glial cells

Highlights

- DAMPs are consistently implicated in the development of TBI, ranging from the state of primary injury to the state of secondary injury.
- The crosstalk among different DAMPs is important in the progression of TBI, particularly in neuroinflammation.
- DAMPs serve as a crucial mediator in coordinating neurons and glial cells for the delivery of inflammatory signals, playing a role in various pathological processes associated with TBI.
- DAMPs are also involved in the systemic damage caused by TBI, and therapeutic strategies targeting DAMPs are a promising approach for overcoming TBI.

Background

Traumatic brain injury (TBI) refers to brain damage or alterations in brain function caused by a sudden physical impact on the head, which often results in temporary or permanent neurological impairment [1]. Over 50 million individuals worldwide experience TBI annually, with many suffering multiple incidents over their lifetime. Patients with TBI have high mortality rates. Therefore, TBI represents a major global public health challenge and is a leading cause of severe neurological disability. Trauma following TBI is

typically divided into primary and secondary stages. Primary injuries usually involve the physical displacement of brain structures, while secondary injuries involve a range of processes, including blood–brain barrier (BBB) dysfunction, oxidative stress, neuroinflammation, and cell death. These processes are interconnected, often worsening each other in a cyclical manner [2]. Following trauma, glial cells in the central nervous system (CNS), such as microglia, macrophages, and reactive astrocytes, release inflammatory factors that can both contribute to cell death and protect brain function. This

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intricate pathological response, known as neuroinflammation [3], is integral to disease progression and plays a crucial role in the progression of TBI from its onset to its conclusion [4].

Damage-associated molecular patterns (DAMPs) are endogenous molecules released by damaged, stressed, or dying cells. They can trigger the innate immune response and induce sterile inflammation when the cells encounter stress or infection [5]. After they bind to pattern recognition receptors (PRRs), initiating the release of pro-inflammatory mediators and activating the innate immune response [6]. Direct physical damage from primary brain injury to neurons, the meninges, and the BBB causes tissue and cellular destruction, releasing large amounts of DAMPs. The continuous release and accumulation of these DAMPs at the injury site results in a degree of damage [7]. This damage is not solely due to their increased presence but also due to their delayed clearance [8, 9]. Following TBI, many neurons undergo cell death and release DAMPs. In the short term, DAMPs activate glial cells, which are closely linked to the innate immune system. Over time, DAMP-activated glia cells and monocytes experience reduced autophagic capacity, leading to inefficient DAMP clearance and their accumulation, which worsens inflammatory responses after TBI [10]. This process can be evidenced by microglia, one of the most important immune cells in the CNS [3]. Microglia rapidly respond to DAMPs *via* sensors, such as Toll-like receptors (TLRs) and purinergic receptors (PRs) [11–14]. Microglial activation releases chemokines and inflammatory factors, exacerbating the inflammatory state [15]. These effects lead to the occurrence and aggravation of pathological processes in multiple secondary brain injury stages, such as BBB breakdown and cytotoxic brain edema. As these pathological processes worsen, neuronal damage and loss become more severe, potentially leading to diseases, such as neurodegenerative diseases. In addition to neurodegeneration, other late-stage consequences of TBI also include systemic effects [16]. As neuroinflammation worsens in severe brain injury, extracellular vesicles (EVs) carrying DAMPs may spread from the CNS to the rest of the body, resulting in multi-organ damage—a particularly undesirable outcome.

In the two injury stages after TBI, especially in the second stage, the cells of the CNS are stimulated by inflammation, oxidative stress, or mechanical injury, releasing DAMPs that participate in various neuroinflammation-related pathological processes [17]. Recent research has increasingly recognized the correlation between TBI and specific DAMPs. A prospective study analyzing ventricular cerebrospinal fluid (vCSF) samples from 50 patients with traumatic and nontraumatic acute brain injury revealed that specific DAMP expression patterns could distinguish between traumatic and nontraumatic brain injuries [18]. Another study found that high-mobility group box 1 (HMGB1), a classical DAMP, induced microglial pyroptosis and ferroptosis during stroke and secondary brain injury [19]. However, there remains a lack of comprehensive reviews exploring this relationship from a broader perspective. In this study, we aimed to address this gap by examining the relationship between TBI and DAMPs. It begins with a brief overview of the two stages of TBI, followed by a discussion of the functions and mechanisms of several classical and novel DAMPs involved in TBI. We then discuss the roles and damage suffered by various neural cells during TBI, as well as the systemic changes and multi-organ damage that occur in the later stages. This review aims to

provide a macro perspective on the multifaceted roles DAMPs play in TBI. This study also highlights that DAMPs represent promising targets for the clinical diagnosis and treatment of TBI.

Review

Primary and secondary brain injury in traumatic brain injury

TBI is typically categorized into two stages: the primary injury and the secondary injury. Primary brain injury occurs immediately after TBI, which is triggered by the initial physical impact on the head, causing rapid and widespread tissue damage. Secondary brain injury occurs within minutes, with neuroinflammation being one of the main pathological processes, leading to long-term damage and deterioration [20]. Table 1 listed the classification of TBI and common treatment strategies [21–30].

Primary brain injury

Primary brain injury refers to immediate damage to brain tissue caused by the initial physical impact and subsequent shear forces, resulting from the displacement of the brain within the skull. This can lead to skull fractures, vascular tears, hemorrhages, and axonal injuries [20]. The severity and nature of the trauma determine the extent of injury. Primary brain injury mainly includes intracranial hematomas, skull fractures, and both coup and contrecoup injuries.

Intracranial hematomas. Intracranial bleeding is a common consequence of primary brain injury, with three types of hematomas depending on the location of blood accumulation. Epidural hematoma refers to blood accumulation between the dura mater and skull, often due to tears in dural veins or arteries passing through the skull. Temporal bone fractures that rupture meningeal arteries are common causes of this type of hematoma [1]. Subdural hematoma arises from ruptured veins that cause bleeding in the subdural space, classified as acute or chronic. Both types result in low-pressure bleeding, with blood accumulating between the dura mater and arachnoid membrane. Subdural hematomas develop more slowly than epidural hematomas but pose a higher risk of neuronal damage [31, 32]. Intraparenchymal hemorrhage refers to bleeding within the brain parenchyma, which is often accompanied by cortical contusions. Contusion-related bleeding occurs at the site of a direct impact, typically in areas where the brain surface meets the inner surface of the skull, such as the frontal and temporal lobes [33].

Skull fractures. Skull fractures are present in over 30% of adolescents with head injuries, with closed-head trauma accounting for ~90% of these cases [22]. Skull fractures are closely linked to cranial nerve injuries, intracranial hematomas, and exacerbation of brain damage. After TBI, especially in cases involving skull fractures, facial nerve damage can lead to facial muscle paralysis [33]. In addition, skull base fractures increase the risk of cerebrospinal fluid (CSF) leakage. Classic signs of skull base fractures include periorbital ecchymosis (raccoon eyes), mastoid ecchymosis (Battle's sign), and clear nasal discharge (rhinorrhea), indicating CSF leakage [34]. CSF leakage into the intracranial space may result in a subdural hygroma. If air or bacteria enter the skull through the ears

Table 1. The classification of TBI and treatment strategies

TBI stages	Disease	Causes	Pathological manifestations	Treatment	Ref
Primary brain injury	Intracranial hematoma	Large and small blood vessels bleed rapidly, and the blood is wrapped by the tough dura mater, pia mater, and arachnoid mater, which have not yet ruptured.	Blood accumulates between the meninges and the skull or brain tissue, forming a hematoma that causes cerebral edema.	Small hematomas do not require treatment; The large and deep hematomas can be removed by surgery.	[21]
	Skull fracture	Open or closed injury.	1. Skull fractures damage the cerebral blood vessels, causing intracranial hematoma; 2. Fracture fragments that cut the skin can cause infection; 3. Depressed fractures may expose brain tissue to the outside world, leading to intracranial infection.	Remove the foreign matter by surgery and put the skull fragments back in place.	[22]
Secondary brain injury	Coup and Contrecoup Contusions Edema	Physical impact causes the brain tissue to be repeatedly impacted within the skull. Vasodilation and imbalance of osmotic pressure inside and outside cells.	Physical damage to axons.	N/A	
			1. Cytotoxic edema: Dysfunction of water channels and ion channels such as AQP4 and NMDA-R will disrupt the osmotic pressure balance in nerve cells and cause brain parenchymal edema; 2. Vasogenic edema: When cytotoxic edema occurs in endothelial cells or astrocytes associated with the BBB or blood vessels, vasogenic edema is triggered, and the reflex dilation of blood vessels will further aggravate the edema.	Osmotherapy, surgical decompression.	[23]
	DAI	1. The damaged neuronal cell structure and the destroyed axonal cytoskeleton; 2. The protein accumulation and axon rupture caused by axonal transport dysfunction.	1. Axonal swelling; 2. Disrupted neuronal calcium homeostasis; 3. Neuroinflammation; 4. Wallerian degeneration.	Bepridil and Dynasore	[24, 25]
	BBB dysfunction	Increased BBB permeability and loss of tight junction proteins (TJ).	1. The destruction of the blood–brain barrier allows too many inflammatory factors to enter the brain tissue, aggravating neuroinflammation; 2. The influx of large-molecular-weight substances such as albumin and thrombin aggravates brain edema.	Basic fibroblast growth factor (bFGF) and Catechin	[26]
	Cell death	Induced by caspases, apoptosis complexes, inflammatory factors, and DAMPs.	Neurons undergo a series of cell death modes such as apoptosis, pyroptosis, ferroptosis, and necrosis. 1. The appearance of neurons collapses, such as swelling, dissolution, and protein denaturation. 2. More DAMPs are released outside the cells, triggering further neuroinflammation and other pathological changes such as BBB destruction, excitotoxicity, apoptosis, and microglia polarization.	Minocycline and recombinant erythropoietin (rhEPO)	[27]

(continued)

Table 1. Continued

TBI stages	Disease	Causes	Pathological manifestations	Treatment	Ref
	Neuroinflammation	DAMPs, inflammatory factors, and ROS released by tissue damage.	BBB disruption, excitotoxicity, apoptosis, and polarization of microglia.	Minocycline	[28]
	Excitotoxicity	Glutamate and glutamate metabolites bind to glutamate receptors and activate excitotoxicity.	Intracellular Ca^{2+} and Na^{+} overload and cell apoptosis.	D exanabinol, amantadine, and bromocriptine.	[29]
	Oxidative stress	Elevated levels of free radicals	Enhanced intracellular Ca^{2+} and destroyed cell membrane.	Ciclosporin A (CsA) and Methylprednisolone.	[30]

AQP4 aquaporin 4, NMDA-R n-methyl-D-aspartate receptor, BBB blood–brain barrier, DAI diffuse axonal injury, DAMP damage-associated molecular pattern

or nose, serious infectious complications, such as pneumocephalus, brain abscesses, and meningitis, can occur.

Coup and contrecoup injuries. After the initial TBI impact, the brain may continue to move within the skull due to inertia, causing secondary damage opposite the impact point—a phenomenon known as the “coup-contrecoup mechanism” [35]. Cortical contusions typically occur at both the coup and contrecoup sites, which are the sites of subsequent secondary inflammation. Brain contusions cause damage to brain tissue and cerebral blood vessels [36]. This type of primary injury was previously considered to be a simple twice impact between the brain and the skull. However, some recent studies have found that in severe TBI [37], CSF cavitation formed at the concussion site. The shock wave generated after the cavitation explosion might cause more damage to nerves and blood vessels locally than direct impact [38], which explains why contrecoup contusion sites show more oxidative damage, mitochondrial dysfunction, and synaptic protein loss compared to surrounding areas [39, 40].

Secondary brain injury

After primary brain injury, brief physical damage quickly leads to multiple pathological changes of secondary brain injury. This secondary injury can persist for minutes to years after the initial trauma and is closely linked to delayed cellular function, metabolism, and other post-TBI changes [41]. The long-term pathological and physiological changes in secondary brain injury significantly contribute to severe neurological deficits and neurodegenerative changes in the later stages of TBI. Herein, we review several secondary brain injuries, including cerebral edema, diffuse axonal injury (DAI), BBB disruption, and cell death.

Cerebral edema. Cerebral edema is defined as a pathological increase of water content in the brain interstitium. Structural damage from primary brain injury leads to changes in the brain osmotic pressure, resulting in brain edema [42]. Brain edema can be broadly classified into two types: cytotoxic and vasogenic. This often manifests through two progressive phases post-TBI. First, cytotoxic edema occurs during the period when BBB structural integrity remains intact, but excess fluid accumulates in cellular compartments observed as early as 1 h post-TBI [43]. Multiple CNS cell types are severely affected during cytotoxic edema onset. In TBI, persistently activated $\text{Na}^{+}\text{-K}^{+}\text{-2Cl}^{-}$ cotransporter (NKCC) 1 facilitates massive ion influx into cells, not only exacerbating cellular swelling but also collaborating with AQP4 to

mediate astrocytic edema-induced release of inflammatory factors like interleukin-1 beta ($\text{IL-1}\beta$) and IL-6 [44]. During this phase, sulfonyleurea receptor 1 (SUR1) bound to transient receptor potential melatonin 4 (TRPM4) interacts with AQP4 to aggravate cytotoxic edema, promoting matrix metalloproteinase (MMP)-9. MMP-9 is a key molecule causing BBB disruption. In the second phase, vasogenic edema features BBB rupture, causing transendothelial leakage of water, proteins, electrolytes, and blood components [45]. In vasogenic edema, macromolecules and water accumulate extracellularly due to dysfunctional BBB regulation, elevating cerebral blood flow and intracranial pressure and worsening cytotoxic edema while increasing risks of infarction-related disorders during TBI recovery [46]. If untreated, it can result in elevated intracranial pressure, predominantly caused by the edema itself. This elevated pressure can lead to irreversible brain damage, cerebral herniation, and ultimately, brain death [47]. Thus, brain edema after TBI is mainly confined to the CNS in the early stages of secondary brain injury. However, for long-term TBI, cerebral edema is very likely to cause systemic edema and uneven fluid osmotic pressure under the influence of sympathetic nerves and hormones. These effects extend to the peripheral nervous system (PNS) and may increase acute kidney injury risk [48].

Diffuse axonal injury. TBI is a common cause of DAI, and DAI is the most common form of diffuse brain injury [49]. DAI results from shear forces on axons caused by rapid brain movement following impact. The distribution of DAI after TBI is mainly in the CNS. DAI consists of multiple, scattered, small hemorrhagic or nonhemorrhagic lesions distributed in a relatively narrow white matter area [50]. The shear force generated after primary brain injury causes excessive stretching of white matter axons and blood vessels, resulting in axonal swelling, interruption of axonal transport, and disorder of cell scaffolds. In severe cases, axons may be directly broken, which is called “primary axonal severance” [51]. However, only a small number of patients with TBI experience axonal damage during primary brain injury. In most patients with DAI, the injury process unfolds in what is referred to as “secondary axotomy,” which arises from abnormalities in neurotransmitter transport, disruption of membrane homeostasis, and molecular and cellular cascades [52]. The two main causes of secondary axotomy are the breakdown of axonal microtubules (MTs) and an increase in intracellular calcium ion concentration [53]. The influx of calcium ions also induces changes in mitochondrial membrane permeability and the opening of membrane pores, resulting in excessive

uptake of small molecules, mitochondrial swelling, and eventual rupture, releasing mitochondrial DAMPs (mtDAMPs). These processes also initiate caspase-mediated progressive cell death [54]. Glial cells in the CNS are also involved in this process. After DAI, activated glial cells engulf and degrade particles released from the site of injured axons, extending and filling the damaged lacunae. However, as DAI advances, overactivated glial cells release proinflammatory cytokines, such as IL-1 β and tumor necrosis factor- α (TNF- α). High concentrations of TNF- α impair the ability of microglia to clear glutamate, leading to neuronal excitotoxic damage [10]. Apoptotic oligodendrocytes not only affect the subsequent regeneration and repair of myelin but also affect the clearance of myelin debris [55]. The accumulated myelin debris acts as a stimulus to overactivate microglia and astrocytes [56]. Therefore, TBI is amplified and exacerbated during the secondary brain injury phase, emphasizing the importance of interventions that target the secondary brain injury process.

Blood-brain barrier disruption. BBB dysfunction/disruption represents a critical node during TBI secondary injury phase, accelerating progression of cerebral edema, neuroinflammation, and cell death [57]. When the BBB is damaged, patients with TBI may experience clinical manifestations such as cerebral edema, brain herniation, and thrombosis [21]. The BBB is formed by brain endothelial cells, which are tightly connected by adherens junction (AJ) and tight junction (TJ) proteins [58]. Its physiological functions primarily include controlling peripheral immune cell entry, toxic substance clearance, and regulation of molecular interactions between the circulating blood and brain environment. Following TBI, primary brain injury causes endothelial cell damage and reduces cerebral blood flow, resulting in BBB breakdown. In the acute phase of TBI, the extravasation of serum proteins, fibrinogen, and immunoglobulins has been observed in the brains of both deceased patients and some survivors [59]. This phenomenon mainly arises from two causes: TJ protein loss and increased transendothelial cell (EC) transcytosis, both contributing to enhanced BBB permeability. As secondary brain injury progresses, the entry of albumin from the periphery triggers the activation of innate immune cells, particularly microglia, altering BBB permeability and the distribution of TJ proteins. Activated microglia release cytokines such as IL-1 β , TNF- α , transforming growth factor- β (TGF- β), and monocyte chemoattractant protein-1 (MCP-1), which further affect BBB permeability and TJ protein distribution [60]. Downstream pathways, such as Rho-associated protein kinase (ROCK), protein kinase C (PKC), and mitogen-activated protein kinases (MAPKs), are also activated by cytokines released by microglial cells, increasing the paracellular permeability of the BBB [61]. Communication between endothelial cells and astrocytes also influences BBB permeability [62], which relies on AQP4 distributed on astrocytes [63]. Compared to physiological BBB functions, post-TBI BBB impairment allows peripheral immune cell infiltration into brain parenchyma, triggering neuroinflammation [64]. Moreover, BBB disruption may also cause focal motor epilepsy [65] and Alzheimer's disease (AD) following TBI [66].

Cell death. Cell death is an inevitable outcome of a series of pathological changes associated with secondary brain injury. Neuronal and oligodendrocyte apoptosis, in particular, has

emerged as a hallmark of secondary brain injury [67]. Irrespective of the excessive release of excitatory amino acid neurotransmitters, moderate mechanical damage from primary brain injury, or subsequent tissue damage due to ischemia or hypoxia, cell death in the form of necrosis can occur [68]. Apoptosis, on the other hand, mainly affects glial cells and neurons that maintain cellular morphology throughout the traumatic phase, with causes including intracellular calcium accumulation, free radicals, and excitotoxicity, as well as alternative pathways identified through *in vitro* experiments [69]. Iron-dependent cell death, also known as ferroptosis, is a newly identified mode of cell death characterized by lethal iron-catalyzed lipid damage and exhibits distinct differences from existing cell death pathways [70]. In TBI, ferroptosis mainly arises due to abnormalities in iron, lipid, and glutathione metabolism, as well as GPX4 inactivation [71–73].

In conclusion, TBI damage is mainly categorized into primary and secondary brain injury. The primary injury is short, while the secondary injury involves a long and complex process. The various pathological changes that occur during secondary brain injury can have severe consequences. Therefore, it is essential to control this stage to prevent further damage. A growing body of evidence demonstrates that DAMPs are involved in the various manifestations of secondary brain injury, particularly the neuroinflammation in TBI. Accordingly, the role of DAMPs in TBI warrants more attention.

Damage-associated molecular patterns in traumatic brain injury

DAMPs are endogenous molecules that are released from host cells in response to infection or stress. They are frequently identified as “alarming signals” [74]. When cells are damaged or dead, they are released to the extracellular space, causing pathological processes, such as sterile inflammation, oxidative stress, or various programmed cell death (PCD) [75, 76]. These molecules include, but are not limited to, adenosine triphosphate (ATP), HMGB1, heat shock proteins (HSPs), S-100 proteins, hyaluronic acid (HA), mtDAMP, and others [77]. DAMPs originate from extracellular matrix (ECM) and intracellular compartments, with the latter further subdivided into cytoplasmic, nuclear, mitochondrial, endoplasmic reticulum, and cytoplasmic membrane sources [78]. DAMPs can be classified in various ways. For example, human DAMPs are classified as protein-type (HMGB1, S100B, histones) and nonprotein-type (ATP, hyaluronic acid) [74]. Another way is to divide DAMPs into constitutive DAMPs (cDAMPs) and inducible DAMPs (iDAMPs) [79]. Alternative classifications exist based on release mechanisms or receptor families, providing flexible categorization for research needs.

Following TBI, multiple nerve cells may undergo PCDs, leading to DAMP release [80]. Once in the extracellular fluid, DAMPs can cause additional damage to surrounding nerve cells and initiate further PCD [3]. During early secondary injury under sterile conditions, DAMPs directly initiate sterile inflammation accompanied by various forms of PCD, causing expanded damage [6]. Simultaneously, DAMP production influences immune cell polarization (e.g. T cells) and directional immune responses, serving crucial roles in adaptive immunity mediating tissue repair and damaged cell clearance [81]. The extensive effects of DAMPs on secondary brain injury are based on their interactions with PRRs and non-PRRs, which are widely distributed across CNS cells [82].

DAMPs play a critical role in the pathophysiology of TBI described in Figure 1, and this section provides an overview of the effects of several key DAMPs following TBI. Moreover, Table 2 listed the function of various types of DAMPs in TBI [11, 71, 83–112].

Adenosine triphosphate

ATP is the primary energy source for cellular functions and is typically stored in the vesicles and granules of neurons and glial cells. It supports nerve impulse propagation and facilitates various cellular processes under normal physiological conditions. ATP is released into the extracellular space at low concentrations and acts as a vital component of intercellular communication mechanisms [113]. However, under pathological conditions, such as compromised plasma membrane integrity, extracellular ATP (eATP) concentrations rise significantly, amplifying its role in initiating innate immune responses following TBI [114–116].

When neurons and glial cells are injured, ATP is rapidly released into the extracellular environment, where it serves as a chemoattractant for microglial cells. This release is closely associated with poor TBI prognosis [117]. The action of ATP is also partially regulated by glial cells, which gradually convert ATP from adenosine diphosphate to adenosine, resulting in the binding of different downstream receptors: P1 PRs bind to adenosine, while P2 receptors bind to adenosine diphosphate (ADP). When ATP is released into the extracellular space, it activates PRs, such as ionotropic P2X and metabotropic P2Y, triggering the release of pro-inflammatory cytokines. P2X7 participate in the signaling pathway that activates inflammasomes, leading to K⁺ efflux and activation of PRRs, such as nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) [118]. Following TBI, ATP can synergize with other DAMPs, such as HMGB1, HSP70, and chromogranin A, inducing caspase-1 and NLRP3-mediated IL-1 β secretion and thereby cell pyroptosis [119]. High concentrations of eATP typically act as stimulants and pro-inflammatory agents in neuroinflammation, but ATP also serves as the main precursor to adenosine, a nucleotide with neuroprotective effects. Adenosine's anti-inflammatory effects are achieved not only by inhibiting neurotransmitter release (such as glutamate and ATP) but also by reducing presynaptic voltage-dependent calcium channels and P2X7R plasma channels [120, 121].

ATP's dual roles in TBI secondary injury primarily diverge at concentration thresholds, thereby activating different receptors or pathways. Among PRs, P2X7R requires high micromolar/millimolar eATP concentrations (concentration for 50% of maximal effect (EC₅₀) $\geq 100 \mu\text{mol/L}$) to activate caspase 1-mediated pyroptosis [122, 123]. In the CCI mouse model, it was found that the eATP level was closely related to the level of neuroinflammation, which reveals the possibility of using eATP as a biological indicator of TBI severity [124]. However, low concentrations of ATP may also cause inflammation or nerve damage. During zinc excitotoxicity in secondary brain injury, persistent poly (ADP-ribose) polymerase-1 (PARP-1) activation and inhibited glyceraldehyde-3-phosphate dehydrogenase (GAPDH) suppress glycolysis, causing low concentrations of ATP and cellular necrosis [125]. In stroke/TBI-related studies, low concentrations of ATP activate SUR, which combines with TRPM4 and AQP4 to form SUR1–TRPM4–AQP4 complexes that are key contributors to post-TBI edema [126].

Beyond concentration, prolonged ATP exposure induces P2X7R pore dilation permitting large cation (e.g. N-methyl-D-glucamine [NMDG⁺]) passage, suggesting P2 receptor-mediated macromolecule exchange potential [122, 127].

Taken together, the role of ATP following TBI is dual-faceted. It can have beneficial effects, such as promoting tissue repair, reducing cellular edema, and exerting anti-inflammatory actions, or it may have detrimental effects, such as exacerbating neuroinflammation and causing white matter damage. The function of ATP in this context depends on various factors, including its extracellular concentration, the receptors it binds to, and whether it is hydrolyzed by nucleotidases.

HMGB1

HMGB1 was first identified in 1973 in the calf thymus as a nonhistone protein involved in the assembly of DNA into chromosomes within the cell nucleus. Decades of research have shown that HMGB1 is expressed at varying levels in both the cytoplasm and extracellular space [128]. In the cytoplasm, HMGB1 acts as a nucleic acid-induced immune response sensor and an endogenous initiator of autophagy. Once released outside the cell, HMGB1 functions as a mediator of inflammatory immunity and metabolism, participating in various pathological processes as a member of the DAMP family. HMGB1 has been considered one of the earliest pro-inflammatory factors released after TBI, earning the designation “master switch” of neuroinflammation [129, 130].

Elevated HMGB1 levels have been observed in various neuroinflammatory diseases, including TBI. High concentrations of HMGB1 have been detected in the CSF of patients with TBI but are absent in patients with normal-pressure hydrocephalus, suggesting the potential of HMGB1 as a TBI-specific biomarker and emphasizing its specificity [131]. Following TBI, HMGB1 translocates from the nucleus to the cytoplasm and is secreted. This nucleocytoplasmic translocation and extracellular release of HMGB1 are fundamental to the role of microglia in immune and inflammatory responses as the first responder cells after TBI. It is also an initiating factor of subsequent inflammatory responses and other pathological processes in secondary brain injury. In the Feeney DM-TBI model, immunofluorescence showed that HMGB1 was upregulated in the cytoplasm of neurons, microglia, and astrocytes, and the number of NeuN-positive neurons was reduced [132]. HMGB1 resides in nuclei and cytoplasm. Under physiological conditions, nuclear HMGB1 needs to be acetylated before it can be actively secreted [132, 133], whereas nonacetylated HMGB1 passively leaks from damaged cells [134]. Experimental evidence shows rapid nonacetylated HMGB1 release from necrotic neurons postinjury [134]. Extracellular HMGB1 oxidizes into disulfide-HMGB1, showing low initial concentrations (within 2 h) followed by sustained elevation in murine stroke models [135]. In pediatric TBI CSF, disulfide-HMGB1 peaks between 24 and 72 h without significant subsequent changes. Another study demonstrated that low HMGB1 concentrations (0.1–1 ng/ml) protected oligodendrocyte progenitor cells (OPCs) and promoted remyelination/neural repair, effects absent at high concentrations [136]. Thus, concentration and temporal patterns jointly determine HMGB1's role in TBI.

HMGB1 also involves multiple downstream pathways. For example, disulfide-HMGB1 binds membrane TLR2/TLR4 or RAGE. TLR2/TLR4 engagement activates the MyD88

Table 2. The function of DAMPs

DAMPs	Distribution	Expression	TBI patients or TBI models	Involved molecules	Affected signaling pathways	Disease-related pathological changes	Ref
ATP	Cytoplasm, Mitochondria	Increased	CCI mouse model	P2X7R, P2Y6, P2Y2, P2Y12, and caspase 1	NLRP3/Caspase-1 p20/GSDMD pathway	The increase of ATP stimulates the expression of cell pyroptosis signaling pathway and promotes cell pyroptosis.	[83, 84]
	Mitochondria	Increased, decreased	CCI rat model	Cytosolic GTPase and dynamin-related protein 1 (Drp1)	Oxidative phosphorylation pathway	1. Mitochondrial fusion can increase ATP production. 2. Mitochondrial lysis can reduce ATP production and increase the production of ROS and apoptotic factors.	[85]
	Mitochondria	Increased	Modified weight-drop rat model	Sodium/potassium ATPase	Oxidative phosphorylation pathway	ATP addition increases the intracellular calcium concentration, leading to mitochondrial swelling and depolarization, which, in turn, causes excessive mitochondrial ROS production, resulting in vascular dysfunction.	[86]
HMGB1	Cytoplasm, extracellular	Increased	ATP-induced cortical injury mouse model	P2YR and K ⁺ channel	N/A	Excess ATP affects changes in membrane potential of microglia and neurons.	[87]
	Extracellular, Cytoplasmic	Increased	Patient blood samples/weight-drop mouse model	Neutrophil extracellular trap (NET)	NETosis	Activated platelets release HMGB1, which promotes the formation of NETs on neutrophils. NETs promote coagulation and may induce coagulopathy.	[88]
	Extracellular	Increased	Feeney's weight drop rat model	RAGE, TLR, and sirutin (SIRT)1	HMGB1/NF-κB pathway	SIRT1 inhibits the pro-inflammatory effect of HMGB1/NF-κB pathway by promoting the deacetylation level of HMGB1.	[89]
	Extracellular, cytoplasmic	Increased	Weight-drop mouse model	TLR	HMGB1/TLR4 pathway	Oxidative stress and neuroinflammation activate microglia, causing them to release HMGB1, which then binds to TLRs and releases proinflammatory factors and chemokines.	[90]
	Cytoplasm	Increased	CCI mouse model	TLR4 and RAGE	HMGB1/NF-κB pathway	Activation of the HMGB1/TLR 4 or HMGB1/RAGE-specific pathways leads to activation of NF-κB, thereby aggravating the inflammatory cascade.	[91]
	Cytoplasm	Increased	CCI mouse model	HSP-organizing protein (HOP)	N/A	HSP90 and its cochaperones are responsible for tau folding and hyperphosphorylated tau, whereas the HSP70 chaperone complex mediates tau degradation.	[92]

(continued)

Table 2. Continued

DAMPs	Distribution	Expression	TBI patients or TBI models	Involved molecules	Affected signaling pathways	Disease-related pathological changes	Ref
HSP	N/A	Increased	TBI patient blood samples	N/A	N/A	N/A	[93, 94]
	Cytoplasm	Increased	Neuronal trauma cortical neuron model	CDC37 protein and RIPK3	HSP90 α /RIPK3 pathway	The complex formed by HSP90 and CDC37 promotes RIPK3 activation and necroptosis, inducing neuronal necroptosis	[95]
	Cytoplasm	Increased	CCI rat model	NF- κ B, IL-6, and synapsin I	HSP70/NF- κ B/IL-6/synapsin I pathway	HSP70 exerts neuroprotective effects by increasing the expression of IL-6.	[11]
	Cytoplasm	Increased	FPI rat model	Brain-derived neurotrophic factor (BDNF) and functional receptor tropomyosin-related kinase B (TrkB)	HSP20/BDNF/TrkB pathway	The accumulation of A β can downregulate the function of TrkB receptor and BDNF, and phosphorylated HSP20 can bind to A β . Increasing the expression of HSP20 can alleviate the cognitive deficits caused by TBI by increasing the expression of BDNF and TrkB ratio in the rat cortex and play a neuroprotective role.	[11]
S100B	Cytoplasm	Increased	FPI rat model/astrocyte stretch injury model	RAGE	S100B/RAGE pathway	1. Activation of S100B/RAGE signaling promotes endothelial glycocalyx shedding by enhancing the expression, translocation, and activity of the shedding enzyme ADAM17 in endothelial cells. 2. Damage to the endothelial glycocalyx aggravates BBB dysfunction and systemic vascular hyperpermeability, leading to secondary brain and lung damage.	[96]
HA	Cytoplasm	Increased	CCI rat model	RAGE and HMGB1	HMGB1-S100B/RAGE pathway	S100B and HMGB1 jointly induce the interaction between pericytes and endothelial cells through RAGE, destroying the BBB function and inducing brain edema.	[97]
	Extracellular	Increased	Controlled weight drop mouse injury	N/A	N/A	N/A	[98]
	Mitochondria	Increased	TBI patient blood samples	N/A	N/A	During TBI, mtDNA increases in human serum, with >90% of mtDNA present in EVs.	[99]
mtDNA	Extracellular	Increased	CCI rat model	Hyaluronan synthases (HAS1, HAS2, and HAS3) and CD44	HA/CD44 pathway	The interaction between HA and CD44 can stimulate T cells to chemotaxis to the inflammatory site, induce endothelial cell activation, and reduce tissue damage.	[100]
	Mitochondria, cytoplasm	Increased	CCI mouse Model	Cyclic guanosine monophosphate–adenylate synthase (cGAS) and stimulator of interferon genes (STING)	mtDNA/cGAS/STING pathway	mtDNA activates STING through cGAS, promoting cell apoptosis and necrosis.	[101]
	Mitochondria, Extracellular	Increased	CCI rat model	N/A	N/A	N/A	[102]

(continued)

Table 2. Continued

DAMPs	Distribution	Expres- sion	TBI patients or TBI models	Involved molecules	Affected signaling pathways	Disease-related pathological changes	Ref
CL	Mitochondria, extracellular	Increased	CCI rat model	Cytochrome C (Cyt C)	cyt c/CL pathway	Cyt c binds to CL, induces mitochondrial oxidation, and promotes mitochondrial apoptosis	[103, 104]
ROS	Mitochondria, cytoplasm	Increased	CCI mouse model	N/A	N/A	The accumulation of intracellular iron and ROS causes mitochondrial atrophy and stimulates the occurrence of ferroptosis.	[71]
IL-1	Cytoplasm	Increased	Explosion impact mouse model CCI mouse model	IL-1RI N/A	IL-1/IL- 1RI/Myd88/NF- κ B pathway N/A	IL-1 α expression increases after TBI and aggravates retinal damage after binding to IL-1RI.	[105]
				N/A		IL-13, IL-1 α , and IL-1 β increase with inflammation after TBI.	[106]
Histone	Nuclear	Increased	CCI mouse model	TLR2/4	NETosis pathway	Histones induce the formation of NETs, which accelerate cell apoptosis. The formed NETs are excreted from the cell, carrying a variety of DAMPs including histones.	[107]
			RB photothrombotic rat model	RAGE	NETosis pathway	HMGB1 stimulates histone citrullination through RAGE, induces NET formation, and stimulates brain damage in photothrombotic stroke model rats.	[108]
exRNA	Nuclear	Increased	CCI mouse model	NLRP3	NLRP3-p38/MAPK pathway	miRNA initiates pyroptosis and inflammatory response by activating NLRP3.	[112]
			Nuclear	Optic atrophy-1 (OPA1)	EV-miR-382-5p- OPA1 pathway	miRNA-382-5p leads to mitochondrial damage by inhibiting the expression of OPA1, releasing more ROS, triggering oxidative stress and neuroinflammation.	[109]
	Nuclear		N/A	TLR2/TLR6	TLR2/TLR6/NF- κ B pathway	18S rRNA forms a complex with Pam 2 CSK 4 (Pam2) and binds to TLR2/TLR4 to activate the NF- κ B inflammatory pathway.	[110]
CIRP	Nuclear	Increased	FPI mouse model	TLR4	TLR4/histone H3/ α 7nAChR	Extracellular CIRP (eCIRP) promoted neuronal apoptosis through the TRS pathway, regulated microglial M1/M2 polarization through the TLR4/histone H3/ α 7nAChR signaling pathway, and induced inflammation in TBI.	[111]

NLRP3 NLR Family Pyrin Domain Containing 3, GSDMD Gasdermin D, ATP adenosine triphosphate, ROS reactive oxygen species, CCI mouse model, controlled cortical impact mouse model, FPI mouse model, fluid percussion injury mouse model, NETosis neutrophil extracellular trap formation, RAGE receptor for advanced glycation end-products, TLR toll-like receptor, HMGB1 high-mobility group box 1, NF- κ B nuclear factor kappa-light-chain-enhancer of activated B cells, HSP heat shock protein, RIPK3 Receptor-Interacting Protein Kinase 3, A β amyloid beta, S100B S100 Calcium Binding Protein B, HA hyaluronic acid, mtDNA mitochondrial DNA, CL cardiolipin, CIRP cold-inducible RNA-binding protein

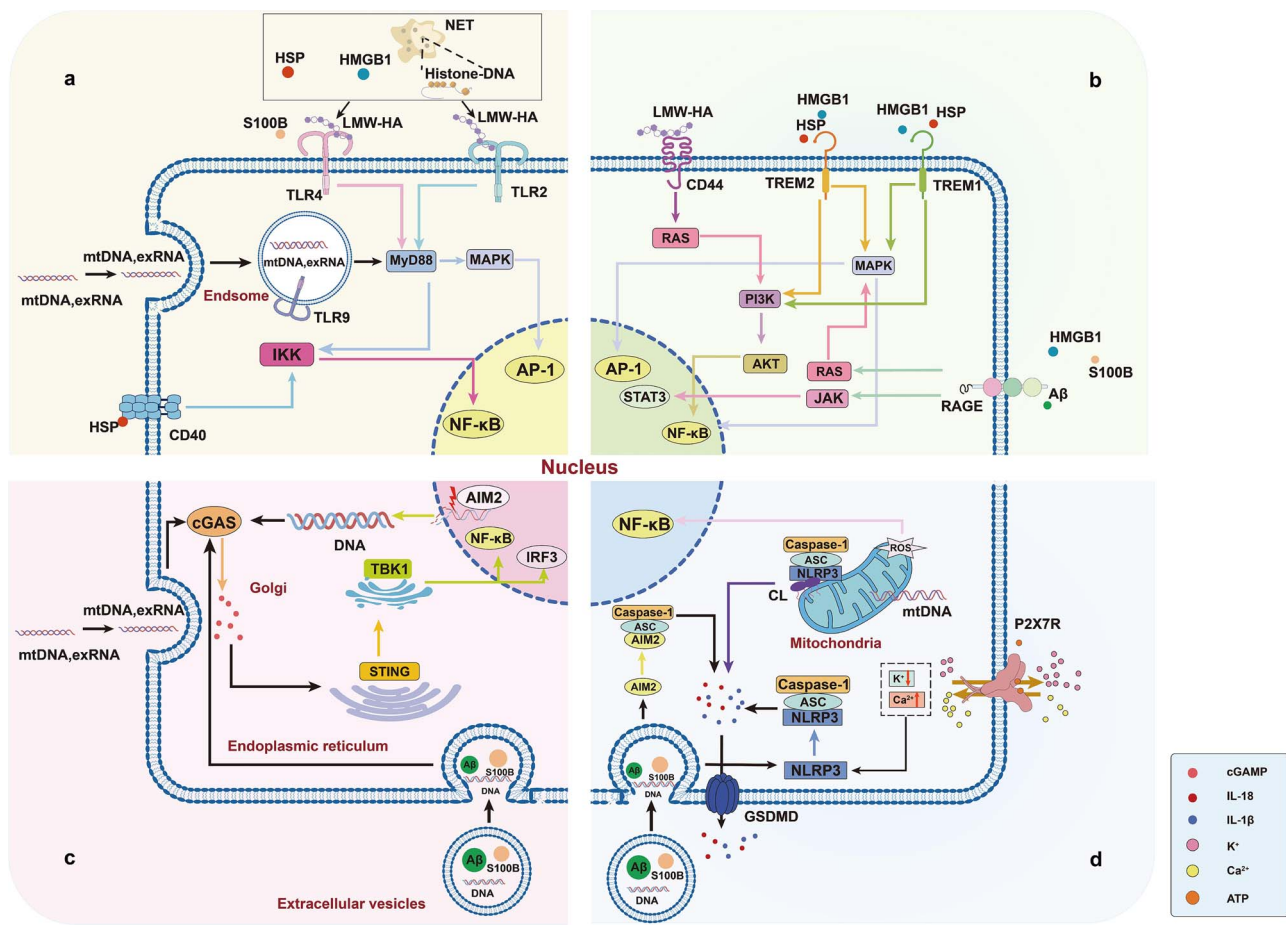


Figure 1. Signaling pathways related to the mechanism of action of DAMPs after TBI. Following TBI, various nerve cells—including neurons, microglia, and astrocytes—endogenously release a range of DAMP proteins into the extracellular space. **(a)** These DAMPs can bind to specific receptors, such as membrane-bound TLRs. TLR2 and TLR4 are recognized by intracellular proteins (e.g. HMGB1, HSPs, and histones) as well as extracellular matrix components (e.g. LMW-HA). Free mtDNA, outside the cell, is delivered into the cell by endosomes through endocytosis, subsequently binding to TLR9 on the endosomal membrane. Upon activation by these DAMPs, TLRs initiate downstream signaling cascades via the adaptor protein MyD88. MyD88 then activates MAPKs and IKKs, leading to the production of inflammatory cytokines by nuclear transcription factors, such as AP-1 and NF-κB; additionally, after HSP binds to CD40, it activates IKK, thereby inducing the NF-κB inflammation-related pathway. **(b)** Exogenous HMGB1, S100B, and Aβ can drive pro-inflammatory responses by binding to the RAGE, subsequently initiating multiple signaling pathways, including the MAPK and JAK–STAT pathways. These pathways further influence various transcription factors, including NF-κB, AP-1, and STAT3, promoting the expression of pro-inflammatory genes and regulating cell migration, proliferation, and apoptosis; within the TREM family, TREM1 and TREM2 are key receptors activated by HMGB1 and HSP, which leads to further activation of the AKT–NF-κB pathway through PI3K or the NF-κB or AP-1 pathways via MAPK. LMW-HA activates the PI3K–AKT–NF-κB signaling pathway by binding to CD44, promoting neuroinflammation. **(c)** When nuclear DNA is damaged or exogenous DNA fragments are transported into cells via EVs, AIM2 is activated, initiating the assembly of AIM2 inflammasomes and inducing nonclassical pyroptosis pathways. Excessive tissue damage leads to the leakage of DNA fragments into the cytoplasm, including exogenous mtDNA that enters the cell via endocytosis and exogenous DNA that enters via EVs. These fragments can all activate the cGAS signaling pathway, promoting the production of the second messenger cGAMP that binds to the STING, located in the ER. STING then activates TBK1 and IKK on the Golgi apparatus, leading to the production of interferons and inflammatory cytokines through transcription factors IRF3 and NF-κB. **(d)** The NLRP3 inflammasome can be activated by various DAMPs, including CL from mitochondria, extracellular Aβ, and S100B, which is transported into cells via EVs, resulting in the secretion of IL-1β and IL-18 through GSDMD and inducing classic pyroptosis; the activation of P2X7R by extracellular ATP triggers the formation of nonselective pores, leading to calcium influx and potassium efflux, which may promote NLRP3 inflammasome activation; the color of the arrows corresponds to that of the molecule from which the arrow originates. TLRs toll-like receptors, HMGB1 high-mobility group box protein 1, HSPs heat shock proteins, LMW-HA low-molecular-weight hyaluronan, mtDNA mitochondrial DNA, MyD88 myeloid differentiation primary response 88, MAPKs mitogen-activated protein kinases, IKKs IκB kinases, AP-1 activator protein 1, NF-κB nuclear factor κB, EVs extracellular vesicles, AIM2 absent in melanoma 2, CL cardiolipin, Aβ β-amyloid protein, GSDMD gasdermin D, cGAS cyclic guanosine monophosphate–adenylate synthase, STING stimulator of interferon genes, ER endoplasmic reticulum, TBK1 TANK-binding kinase 1, RAGE receptor of advanced glycation endproducts, NLRP3 NLR Family Pyrin Domain Containing 3

pathway via MD-2, while RAGE binding initiates JAK–STAT through Ras. Both pathways activate NF-κB to trigger neuroinflammation and IL-1β/IL-6 release [137]. N-methyl-D-aspartate subtype 2 B (NR2B) mediates HMGB1 release from necrotic neurons, exacerbating brain edema after TBI, leading to increased intracranial pressure.

HMGB1's role in this process involves upregulating the expression of AQP4 through TLR4, and the role of AQP4 has been confirmed by administering a TLR4 receptor antagonist in animal models [138].

More recent studies have shown that HMGB1 can cooperate and interact with other DAMPs such as histones or

ATP, reflecting the potential of HMGB1 as a novel biomarker or therapeutic target for TBI. However, the transition from experimental findings to clinical application is still challenging, which requires further research.

Heat shock protein

The heat shock response (HSR) is a common endogenous reaction to various external stressors, including oxidative stress, metabolic disturbances, ischemia, and reperfusion. HSPs are a family of proteins produced by heat shock factors (HSFs) during the HSR [139]. The HSP family is categorized based on molecular weight and function. Constitutive HSPs such as HSP90, HSP40, and HSP70 play cellular chaperone roles, while inducible HSPs, primarily HSP70, include subtypes such as HSP70i and HSP72 [140]. As molecular chaperones, HSPs assist in refolding proteins whose spatial configurations are disrupted by environmental stressors [141]. This function enables HSPs to support the self-repair mechanisms of damaged cells following TBI. However, when protein conformations and structure cannot be restored, HSPs, along with their associated molecular chaperones, facilitate the degradation of these irreparable proteins *via* proteolysis or autophagy. This degradation process is another mechanism by which HSPs protect the CNS after TBI [142].

Numerous animal models and clinical studies have documented increased expression of various HSP subtypes. For instance, in TBI mice subjected to fluid percussion injury (FPI), HSP70 mRNA levels increased significantly within 2–6 h, while HSP60 mRNA and protein levels showed two peaks of upregulation at 4 and 24 h [143]. This suggests that HSP70 could serve as a marker of cellular stress and injury and predict poor TBI outcomes. In CCI rat models, HSP90/HSC70 significantly increased at 24 h post-TBI but returned to baseline within 2 weeks. HOP expression similarly peaked at 24 h but declined markedly after 1 week [92]. Notably, male animals showed earlier chaperone elevation compared to females, indicating sex-dependent HSC70/HOP expression differences [92, 144].

Among HSPs, HSP70 and HSP90 have been extensively studied, particularly for their neuroprotective functions. Under conditions of oxidative stress and injury caused by TBI, the synergistic effect of HSP40 and HSP90 with ATP activates HSP70, which primarily exerts its neuroprotective function by inhibiting multiple cell death pathways and mitigating neuroinflammatory effects. In the caspase-dependent apoptosis, TBI-induced oxidative stress opens mitochondrial permeability transition pores, releasing cytochrome c into the cytoplasm [145]. HSP70 exerts neuroprotection by reducing cytochrome c release and blocking caspase-3 [146]. In the caspase-independent pathway, B-cell lymphoma 2 (Bcl-2) prevents the release of cytochrome c and apoptosis-inducing factors (AIFs), while HSP70 could enhance Bcl-2 expression in certain disease models [147]. During inflammation, HSP70 also inhibits NF- κ B nuclear translocation while preventing I κ B phosphorylation [142, 148]. In animal models with TBI, mice overexpressing HSP70 manifested better neurological outcomes following controlled cortical impact than wild-type and HSP70-deficient mice [149]. *In vitro* studies have shown that endothelial cells release EVs containing HSP70 that promote neuronal growth, migration, and protect from ischemia/reperfusion-induced secondary brain injury [150]. This suggests that HSP70 interrupts inflammatory signaling pathways at multiple levels and plays an active role in

anti-inflammatory processes. Other HSP subtypes can exhibit contrasting functions. In ethanol-induced brain injury models, HSPB1 (HSP27/25) is an ATP-independent chaperone that promotes I κ B phosphorylation/degradation and reduces TGF- β 1 expression, enhancing inflammatory responses [151]. HSP72 also activates neutrophils through TLR4, inducing inflammation [152]. Some members of HSP70 may have pro-inflammatory effects in different disease models and pathways, such as glucose regulatory protein 78 (GRP78) [153]. Therefore, the role of HSPs post-TBI cannot be solely defined as neuroprotective or pro-inflammatory, as their effects depend on the specific HSP subtypes and their spatial expression patterns.

S100B

S100B is a member of the S100 family, a group of small calcium-binding cytoplasmic proteins first identified in 1965. This dimeric protein is primarily produced by astrocytes [154]. Under normal conditions, astrocyte-derived S100B does not cross the BBB, and its concentration in CSF is $\sim$ 100 times higher than in serum [155]. However, during the secondary brain injury phase following TBI, BBB disruption and damaged neural cells rapidly increase S100B levels in the bloodstream. At this stage, elevated serum S100B levels induce astrocytes to adopt a pro-inflammatory phenotype, promoting neuronal death.

In experimental TBI models, such as the rat FPI and controlled cortical impact injury (CCI) model, both mRNA and protein expression levels of S100B increase near the lesion site to varying degrees [156]. Clinically, blood S100B levels have been validated and utilized as a reliable marker for TBI. Its use may reduce radiation exposure in patients with mild TBI (mTBI) [155]. As a DAMP, S100B plays a crucial role in secondary brain injury by interacting with receptors for RAGE. The contrasting effects of S100B at different concentrations are closely associated with RAGE expression, which, in turn, influences S100B function. S100B exerts neuroprotective effects in low concentrations [157]. However, when the concentrations and molecular densities of S100B and RAGE reach the submicromolar and micromolar levels, S100B activates the autocrine loop of RAGE in astrocytes [158], triggering the NF- κ B signaling pathway. This amplifies RAGE expression, exacerbating neuroinflammation during the secondary brain injury phase of TBI [159, 160]. Recent studies have recognized activation of the S100B/RAGE signaling pathway as a key mediator of TBI damage. Notably, soluble RAGE (sRAGE) levels in serum increase after TBI [159]. Therefore, based on these findings, some studies have proposed S100B as a potential therapeutic target for TBI [161]. The S100B inhibitor polydatin has been shown to exert therapeutic effects in severe TBI by reducing oxidative stress and inflammatory factor release while promoting the recovery of pulmonary vascular permeability, thereby mitigating neuronal damage and secondary lung injury following TBI [162]. Similarly, treatment with a RAGE antagonist suppressed S100B expression [96]. These interventions effectively alleviated brain injury caused by TBI and reduced astrocyte activity after stretch injuries.

While S100B is a well-established clinical biomarker, its use faces challenges, such as lack of specificity and sensitivity. Moreover, as a potential therapeutic target, S100B also shows promise in neurodegenerative diseases such as AD, Parkinson's disease (PD), and amyotrophic lateral sclerosis

(ALS). Accordingly, the association between neurodegenerative diseases and TBI warrants further investigation to better understand S100B's role.

HA

The ECM constitutes ~10%–20% of brain volume, making it a significant component of the CNS [96]. HA is a proteoglycan that is essential for ECM function. In a rat CCI model, HA levels significantly increased in the ipsilateral brain following injury. After 1–3 days, HA levels in the contralateral brain also showed an upward trend. One week later, CD44, HA's primary receptor, sharply increased near the lesion site [163–165].

HA functions vary depending on its molecular weight. High-molecular-weight (HMW) HA, which naturally occurs in extracellular spaces, reaches megadalton sizes. Following TBI, HMW-HA undergoes degradation into HA fragments (HAFs) of various sizes through processes, such as hyaluronidase activity or reactions with ROS during inflammatory cascades [166–168]. The population of HAFs with a size of 20–500 kDa is called low-molecular-weight (LMW) HA. LMW-HA is released from the damaged ECM and acts as a DAMP to promote pro-inflammatory signaling [169]. LMW-HA binds CD44/TLR2/4 to activate the Ras-Raf-MEK-ERK-NF- κ B axis, inducing IL-6 release and inflammation [170]. HMW-HA competitively binds these receptors, engaging CD44 to activate the SUR1-TRPM4-AQP4-Hippo pathway through MST kinase, inhibiting inflammation and cell apoptosis [171]. This differential effect is thought to arise from distinct conformational changes in CD44 activated by HA of different molecular weights [170]. Tumor necrosis factor-stimulated gene 6 (TSG-6), which binds to HA, is upregulated after TBI [172]. TSG-6 plays a role in inducing the activation of reactive astrocytes in TBI models or inhibiting microglial activation [173, 174]. While the underlying mechanisms remain unclear, it has been found that TSG-6 catalyzes the binding of the inter- α -trypsin inhibitor (α I) heavy chain (HC) to HA, with the binding to HMW HA being reversible, while binding to LMW HA is irreversible. Therefore, the fragment size of HA is likely to be closely related to the activation and phenotypic changes in immune cells following TBI [175].

However, compared to other well-documented DAMPs, such as HMGB1, research on the precise role of HA in TBI as a DAMP remains limited. Some studies only indicated that the clinical application of HA in treating TBI is mainly related to its role in bioengineering with materials, such as gel or collagen [176–178]. Considering that the function of HA in TBI is complex and depends on its molecular weight, receptors, and other factors, future research may explore whether HA can be effectively cleaved to obtain HMW HA with neuroprotective and anti-inflammatory effects while preventing its degradation into pro-inflammatory HA in TBI. Such studies have significant clinical translational potential.

Mitochondrial damage-associated molecular pattern

During secondary brain injury in TBI, pathological processes like excitotoxicity and cell death severely impair mitochondrial function. Numerous studies report that brain mitochondria exhibit functional abnormalities following TBI, including

calcium overload, mitochondrial DNA damage, and morphological changes [179]. Uncontrolled mitochondrial dysfunction leads to mitochondrial autophagy, necrosis, apoptosis, and fusion, resulting in the excessive release of mitochondrial contents termed mtDAMPs, including ATP, mtDNA, mitochondrial reactive oxygen species (mtROS), mitochondrial unfolded protein response (mtUPR), cardiolipin (CL), mitochondrial calcium ions, and iron ions [180].

Due to the loss of the complete double membrane structure of the inner and outer mitochondrial membranes, these mtDAMPs are excessively released into the cell or its external environment, triggering neuroinflammation and various forms of PCD [181–184]. After TBI, mitochondrial redox dysfunction results in excessive ROS production and changes in mtDNA expression related to ROS. This occurs because mtDNA, due to the substantial ROS production during oxidative phosphorylation (OXPHOS), is more susceptible to oxidative damage [185]. Under normal physiological conditions, defective mitochondria and mtDNA initiate autophagic degradation. However, after TBI, when the mitochondria sustain extensive damage, rupture of the inner and outer membranes releases mtDNA into the extracellular space as DAMPs, thereby regulating inflammation. TLR9 is activated by mtDNA, which mediates inflammation through the MAPK and NF- κ B pathways. Activation of NLRP3 inflammasomes by mtDNA and mtROS promotes the production of IL-18 and IL-1 β , intensifying the inflammatory response [186]. At this stage, mtDNA released into the cytoplasm further exacerbates inflammation through the activation of the cyclic GMP-AMP synthase (cGAS)-cGAMP-stimulator of the interferon gene (STING) pathway. The mitochondrial electron transport chain and NADPH oxidase (NOX) are the main sources of mitochondrial ROS production [187]. CL, a unique component of the inner mitochondrial membrane, plays a crucial role in mitochondrial and cellular apoptosis. In the CCI rat TBI model, the CL content in the contusion and surrounding areas decreases after TBI, but specific CL levels in the blood increase 24 h later, thereby CL molecules could serve as biomarkers for assessing TBI severity [179]. Furthermore, mitochondria have long been considered key organelles in the regulation of PCD. As research on TBI and PCD has deepened, the link between mitochondria and TBI has received increasing attention. Whether in the context of neuroinflammation after TBI or in other neurodegenerative diseases caused by neuroinflammation, mtDAMPs should be considered an important direction of research.

IL-1

In addition to the aforementioned DAMPs, numerous DAMPs play significant roles in post-TBI pathological processes, such as the IL-1 protein family. IL-1 was initially identified as an endogenous pyrogenic mediator in humans [188]. Subsequent research has expanded this protein family to ligands such as IL-1 α , IL-1 β , and IL-18 [189]. Recent studies have further identified new members, like IL-38 [190]. Under physiological conditions, the IL-1 family primarily maintains ion balance, signal transduction, and neurotrophic activation in the CNS. Following TBI, these molecules are activated through distinct pathways. In a unilateral PBBI rat TBI model, NLRP3 activation occurred within 6 h postinjury, with IL-1 β elevation observed as early as 4 h [191]. Activated IL-1 β binds IL-1R1 to recruit MyD88, which associates with interleukin-1 receptor-associated kinases (IRAK1/2/4)

and TNFR-associated factor 6 (TRAF6), subsequently activating AP-1 *via* JNK or the IKK complex (composed of IKK α , IKK β , and IKK γ). The IKK complex triggers NF- κ B nuclear translocation and initiation of inflammatory responses [192]. Furthermore, IL-1 β directly stimulates MMP-9 production, influencing post-TBI cerebral edema and BBB dysfunction [193]. Emerging family members like IL-38 exhibit functional diversity: acting as an IL-1RA-like competitor for IL-1R1 and IL-36R, IL-38 downregulation was observed in ethanol-induced TBI rat models [194], while its neuroprotective effects *via* IL-36R antagonism were confirmed in analogous mouse models [195]. Notably, the IL-1 family continues to expand with ongoing research, which creates opportunities to identify new IL-1 family members that may govern more modulation of post-TBI inflammatory responses.

Histones

Histones are present in eukaryotic cells [196]. After TBI, histones in the nucleus are passively released into the extracellular space and act on neighboring cells and circulating immune cells through PRR, exerting inflammatory or cytotoxic effects. The main classifications of histones include H1, H2A, H2B, H3, H4, and H5, which are found in the cell membrane or cytoplasm of neurons, Schwann cells, and microglia after stress response [197]. Extracellular histones often bind to TLR2/4/9 to activate the Myd88–IRAK–TRAF6–IKK–NF- κ B pathway to induce an inflammatory response or directly act as one of the extensive stimulators of NLRP3 to stimulate the formation of NLRP3 inflammasomes and recruit neutrophils to the site of inflammatory damage [198]. Compared to treating histone as an individual DAMP, more studies have focused on the role of neutrophil extracellular traps (NETs) in TBI, which are closely related to histones. NETs are special DNA structures carrying histones and nucleoproteins [199], which capture and kill bacteria, viruses, and other microorganisms through oxidation or nonoxidation to exert immune functions [200]. The process of NET formation accompanying cell death is called NETosis. NETosis is divided into suicidal and vital NETosis. The former is the mechanism of releasing NETs when cells are damaged and die, which is also the main mechanism of NET formation after TBI. After the early injury after TBI, a large number of stimuli (such as histones and other DAMPs) trigger neutrophil elastase (NE) to dissociate from various membrane structures of the cell [201]. After NE enters the nucleus, it degrades chromatin by cleaving histones [202]. Through the cell pores opened by GSDMD, NETs containing histones are released outside the cell, further inducing destruction and inflammatory responses of other cells [203]. In TBI patients and CCI mice, high expression of NETs and neuronal apoptosis caused by ER stress were observed [204, 205], indicating a close relationship between NETs and brain edema. In addition, modifications of histones are related to TBI, such as methylation of histones by methyltransferases. In the CCI rat model and the weight-drop rat model, it has been widely found that the methylation level of histones is reduced [206, 207]. Dietary or universal methyl (-CH₃) group donor S-adenosylmethionine (SAM) supply alleviates the neurological damage after TBI to varying degrees [208]. Therefore, the precise role of histones in DAMP. Histone deacetylase (HDAC) associated with histone acetylation is another new area of research TBI should be clearly deciphered in the role of HDAC and its related inhibitors' future, especially in the NETosis pathway and the posttranslational modifications of histones.

Extracellular RNA

Extracellular RNA (exRNA) is defined as RNA that is passively or actively released from damaged or dead cells under various pathological conditions [209], including long non-coding RNA (lncRNA), circular RNA (circRNA), microRNA, mRNA, and ribosomal exRNA (rexRNA). After TBI occurs, most exRNAs are released from cells by endocytosis under physical or inflammatory stimulation [210]. The released exRNA could bind to PRRs on the cell membrane directly [210, 211], whereas EVs can allow exRNA to enter the cytoplasm by docking and fusing with the target cell membrane, activating the receptors in the cytoplasm [210]. The TLR family is one of the main PRRs that bind to exRNA. rRNA–PAMP complexes activate the Myd88–IRAK–TRAF6–IKK–NF- κ B inflammatory pathway by binding to TLR1/2/6 [212]. rRNA internalized into the cell can also activate the same pathway through TLR7/8 to induce an inflammatory response [213]. By studying postmortem brain samples of patients with TBI and the FPI rat TBI model, the authors discovered that the expression of miR155 and miR142 was increased. When primary cultured astrocytes of TBI model mice were overexpressing miR142, high levels of TNF- α expression and activated pro-inflammatory signaling pathways of NF- κ B were observed [214]. In another recent study, human mesenchymal stem cell-derived (hMSC) EVs were used to specifically inhibit multiple miRNAs known to activate NLRP3 in the CCI mouse TBI model, preventing the overactivation of the NLRP3–p38–MAPK signaling pathway [112]. Although the exact mechanisms are still unknown, the role of exRNA should be given more attention in the scenario of TBI.

Crosstalk between damage-associated molecular patterns

It is noteworthy that the functional interaction among different DAMPs in the development of TBI needs further discussion. Some DAMPs initiate inflammatory responses through the same receptor or different receptors, playing a synergistic pro-inflammatory role. However, a small number of DAMPs may inhibit the pro-inflammatory pathways but activate other signaling pathways and display an antagonistic effect. Using exRNA to coculture damaged astrocytes, the inflammatory factors were increased, while RNase treatment reduced the level of inflammation [215]. Since exRNA binds to TLR2 as a PRR, it can be speculated that the two DAMPs may show a synergistic role by acting on TLR2. Besides, in the NETosis-related pathway after TBI, HMGB1 and histones can promote the recruitment of neutrophils through the TLR4 receptor and accelerate the formation of NETs [88, 216]. HMGB1 inhibition can effectively reduce the concentration of histones and NETs in blood samples of patients with TBI [88]. Similarly, S100A aggravates inflammation through the recruitment of neutrophils and the generation of ROS. ROS generated through the AMPK–Nrf2–HO-1–ROS signaling pathway activates PAD4 and accelerates the formation of NETs [217, 218]. Therefore, HMGB1, histones, and S100A play a synergistic role in NETosis after TBI. In a recent study, IL-1 α binding to IL-1R exerted proinflammatory effects in an inflammatory model of astrocytes and macrophages through activated P2Y₁₁R. Meanwhile, high concentrations of eATP (a DAMP signal) inhibited the P2Y₇R–TLR-related inflammatory pathway. In this process, antagonism was created

between the proinflammatory effects of IL-1 α and the anti-inflammatory effects of eATP [219]. Therefore, different signaling pathways of the same DAMP may play different roles, and the synergistic or antagonistic effects between DAMPs require in-depth research in TBI.

Overall, DAMPs play an important role in multiple pathological processes in TBI. Numerous types of DAMPs released by neural cells participate in this process, indicating that they are one of the regulators in the complex mechanism of TBI development.

Crosstalk between neurons and glial cells mediated by damage-associated molecular patterns after TBI

Neurons

Neurons play a crucial role in maintaining the structural integrity and normal functioning of the nervous system, making them significantly affected by TBI. Neuronal injuries resulting from TBI can be categorized as mechanical or chemical trauma, corresponding to the primary and secondary phases of brain injury, respectively. Mechanical trauma involves direct physical impact, causing structural damage to neurons [220]. The most direct consequence of this is traumatic axonal injury (TAI) [221]. Additionally, physical impact induces “mechanoporation,” which directly leads to the release of DAMPs.

In the secondary brain injury phase, excitotoxicity occurs due to BBB collapse and neuronal cell death. This breakdown leads to the excessive release of excitatory amino acids from synaptic terminals, which are not reabsorbed. These amino acids bind to ligand-gated ion channels on neurons, causing an excessive influx of Ca²⁺ into the cells, triggering neuronal membrane depolarization. The accumulated Ca²⁺ in neurons activates various apoptosis-related proteins, such as caspases, and triggers the accumulation of ROS, another DAMP, thereby impairing mitochondrial function [29].

TBI contributes to neuronal loss underlying complex pathological conditions, particularly the neurodegenerative changes observed in the later stages of chronic brain injury [222]. Prolonged TAI often leads to chronic traumatic encephalopathy (CTE) and various neurodegenerative diseases. Histopathological examinations of TBI frequently reveal characteristics similar to those of AD, particularly the accumulation of β -amyloid protein (β) [223]. Impaired axonal transport may contribute to amyloid protein accumulation, while neuroinflammation induced by DAMPs from damaged cells exacerbates β misfolding. In this context, HMGB, a downstream molecule of β , is activated and upregulated by β , promoting the production of inflammatory mediators through the RAGE/TLR4 signaling pathway and aggravating neuroinflammation. HMGB1 also hinders β degradation and clearance [224]. Therefore, it is speculated that the long-term pathological process of TBI lays the foundation for the development of neurodegenerative diseases.

Damaged neurons have a certain ability to regenerate themselves. The core mechanism of nerve regeneration is called neuroplasticity, which is the ability of the nervous system to reorganize its structure and function in response to stimulation and reconnect intermittently [225]. This function can support complete nerve regeneration in the PNS because the myelin sheath of the PNS is composed of Schwann cells, which remain active after nerve rupture and can engulf myelin debris. However, in the CNS, since oligodendrocytes that make up the myelin sheath do not have this function, neurons

cannot fully regenerate extensively [226, 227]. Therefore, effectively removing broken cell fragments, controlling the growth of glial scars, and controlling neuroinflammation help CNS nerve regeneration [227]. In the CCI mouse model, cognitive and memory function were improved by clearing accumulated DAMPs and may restore the autophagic function of microglia and macrophages to assist neuron regeneration [10, 228]. Therefore, neuroinflammation and DAMPs are not only involved in the process of neuronal injury or neurodegeneration but also implicate in the neuron regeneration after TBI.

Glial cells

Glial cells in the CNS include oligodendrocytes, astrocytes, ependymal cells, and microglia. Microglia, which act as macrophages in the CNS, are critical in neuroinflammation as innate immune cells. Although astrocytes are not part of the innate immune system, they are the most abundant cell type in the CNS, outnumbering neurons. Astrocytes are stimulated by various inflammatory factors, including DAMPs, and undergo complex reactive changes after CNS injury, potentially altering the tissue structure and leading to scar formation. Figure 2 illustrates the changes in glial cells during TBI.

Microglia. Microglia are resident immune cells in the CNS, constituting 5%–20% of all glial cells. Under physiological conditions, they participate in several neural activities, such as continuous monitoring of the brain microenvironment, synaptic remodeling, phagocytosis, and removal of cell debris [229]. Following TBI, microglia become activated, gain mobility, and undergo morphological changes. They rapidly proliferate and migrate to the injury site, often within minutes of TBI, suggesting that they serve as the first line of defense in the CNS. This response may persist for several months or longer, depending on the severity of TBI [230, 231]. This long-term activation may indicate ongoing secondary brain injury and an increased risk of neurodegenerative diseases.

Upon reaching the injury site, microglia become polarized due to various molecular pathways and stimuli. Although their functions are complex and diverse, they are typically classified into two main phenotypes: the pro-inflammatory M1 and anti-inflammatory M2. These phenotypes play crucial roles in antioxidant responses, tissue remodeling, and angiogenesis [232]. The polarization into M1 or M2 phenotypes is influenced by different stimuli; for example, exogenous particles, bacteria, interferon- γ , and cell debris induce M1 polarization, while IL-4 and IL-13 stimulate M2 polarization [233]. Classic signaling pathways involved in this polarization include TLR4/NF- κ B, Janus kinase/Signal Transducers and Activators of Transcription (JAK/STAT) [234], HMGB1-related pathways, and MAPK pathways. The TLR4/NF- κ B and HMGB1/TLR4/RAGE pathways primarily induce M1 polarization [235]. Reports suggest that in the FPI mouse model, the application of anti-HMGB1 monoclonal antibodies (mAbs) can shift microglia from M1 to M2 [232], modulating neuroinflammation and affecting the progression and prognosis of diseases such as TBI, PD, and epilepsy [236–238]. Additionally, c-Jun N-terminal kinase (JNK), a member of the MAPK family, drives M1 polarization by interacting with DAMPs, such as HSP, S100B, and HMGB1. In a CCI mouse model, the use of bazedoxifene to inhibit the JNK/NF- κ B pathway reduced BBB damage [239, 240].

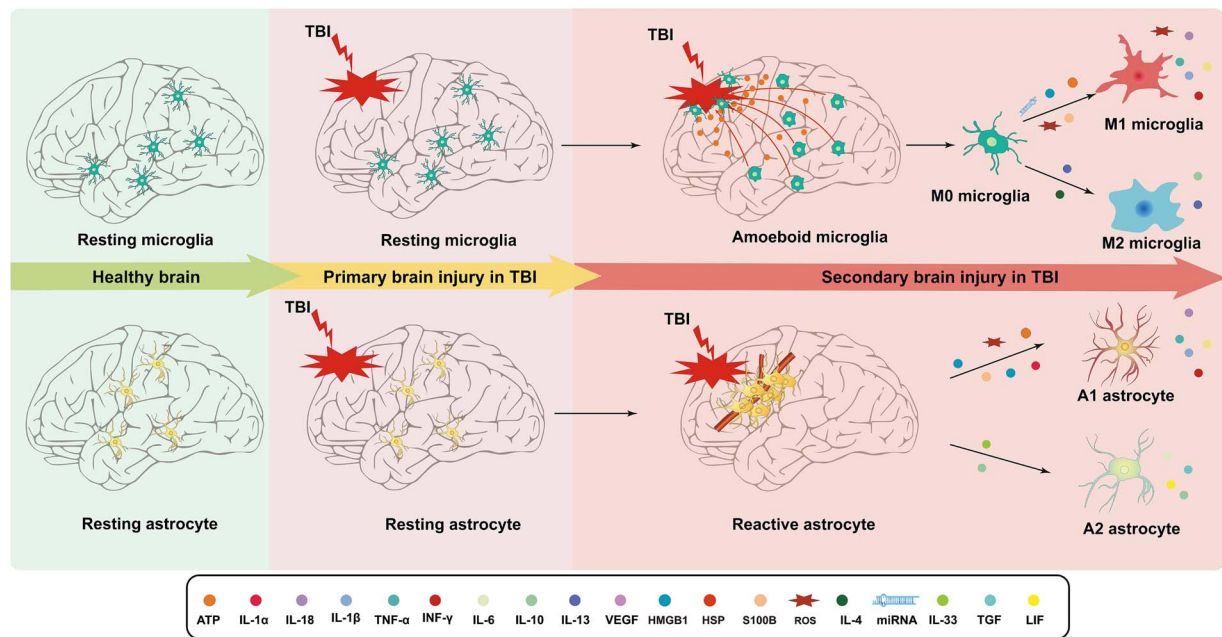


Figure 2. Temporal dynamic changes of glial cells after TBI. In TBI secondary brain injury, resting microglia are stimulated by ATP released from damaged tissues, and the tips of the protrusions expand and become spherical. The cells appear irregularly spherical and follow the ATP concentration gradient to move toward the damaged site. These microglia are called amoeba-like microglia. When amoeba-like microglia arrive at the site of injury, they polarize to the pro-inflammatory M1 phenotype or the anti-inflammatory M2 phenotype according to the DAMP or other stimuli they receive. After TBI, resting astrocytes are stimulated by inflammatory factors, proliferate and increase in size, and form glial scars around the injury. Under the stimulation of DAMPs or other factors, they polarize to the cytotoxic A1 phenotype and the A2 neuroprotective phenotype. *TBI* traumatic brain injury, *DAMP* damage-associated molecular pattern, *ROS* reactive oxygen species, *TNF* tumor necrosis factor, *VEGF* vascular endothelial growth factor, *HMGB1* high-mobility group box 1, *HSP* heat shock protein, *TGF* transforming growth factor, *LIF* leukemia inhibitory factor

Regardless of their phenotype, as a mediator, DAMP is involved in the intercellular communication or functional crosstalk among neurons and glia cells following TBI shown in Figure 3. After TBI, the direct clinical phenotype is headache, dizziness, nausea, vomiting, convulsions, or epileptic seizures. When TBI affects multiple organs in the body in the middle and late stages, there will be gastrointestinal-related digestive dysfunction. Skull fracture and impact force damage nerves and blood vessels. The hematoma caused by bleeding directly exacerbates the subsequent cerebral edema [241]. The imbalance of local perfusion pressure caused by cerebral edema forms ischemia and hypoxia. Hypoxia directly causes the accumulation of ROS and leads to oxidative stress, and damaged neurons release various DAMPs that attract microglia to lesion sites [242]. For instance, ATP released by neurons and astrocytes creates a concentration gradient that attracts microglia, guiding them to phagocytose axonal and myelin debris caused by Wallerian degeneration (WD) [243]. Under normal conditions, the CX3CL1-CX3CR1 signaling pathway maintains neuronal-microglia communication and inhibits microglial activation. However, these functions are impaired following TBI. In the CCI model, CX3CR1 knockout mice showed reduced sensory-motor defects and neuronal damage compared to wild-type mice after 4 days, but this improvement was reversed after 5 weeks. This indicates that the CX3CL1-CX3CR1 signaling pathway plays varying roles at different time points [244]. Although inducing a shift from M1 to M2 microglia may seem beneficial, long-term neuroinflammation can lead to an increase in the number of M1 microglia and a decrease in the number of M2 microglia, which is detrimental. This imbalance contributes to various

forms of PCD, the accumulation of Aβs, and other pathological changes associated with neurodegenerative diseases [245]. Therefore, microglia and neuroinflammation are significant contributors to TBI-induced neurodegenerative diseases.

Astrocytes. Astrocytes and oligodendrocytes play indispensable roles in neuroinflammation and immune responses [246]. Under normal physiological conditions, astrocytes maintain glucose metabolism in the CNS, regulate synaptic function, support BBB integrity as a component of the BBB, and contribute to the development of gray and white matter [247, 248]. In response to injury, astrocytes undergo morphological and functional changes, becoming known as reactive astrocytes [249]. Functionally, reactive astrocytes are categorized into two phenotypes: A1 astrocytes, which exhibit neurotoxic effects, and A2 astrocytes, which exhibit neuroprotective properties. Notably, controversy exists regarding the current M1/M2 nomenclature of microglia and the A1/A2 nomenclature of astrocytes. This classification may no longer fully describe the newly discovered functions of glial cells. Therefore, a new nomenclature for microglia has been suggested. However, considering that no acknowledged standards exist for these names, creating more precise classification according to existing M1/M2 or A1/A2 nomenclature is reasonable rather than introducing new naming systems to avoid misunderstanding.

Glial fibrillary acidic protein (GFAP) is a key marker of reactive astrocytes and indicates astrocyte activation [249]. Clinically, GFAP levels in blood reflect the severity of TBI and the extent of intracranial damage [250]. Astrocytes thereby respond to both physical and biochemical damage post-TBI.

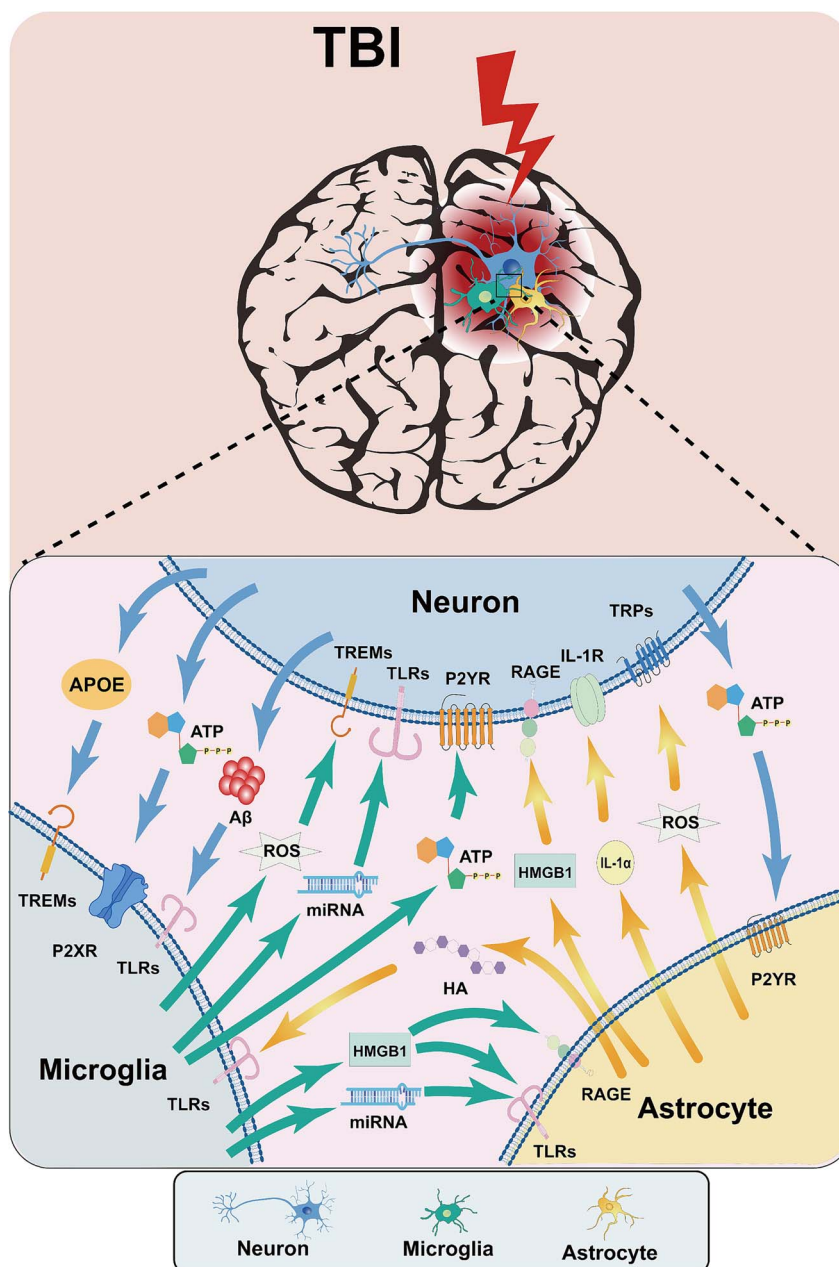


Figure 3. Neurons, microglia, and astrocytes use damage-associated molecular patterns (DAMPs) as mediators for intercellular communication and functional crosstalk following TBI. Neurons, microglia, and astrocytes communicate and engage in crosstalk through various mechanisms, including direct contact and paracrine signaling, which requires the release of signaling molecules and the presence of receptors on the nerve cells to facilitate signal transmission. After TBI, the signaling molecules involved in intercellular communication and functional crosstalk include most DAMPs, such as ATP, HMGB1, S100B, hyaluronan, Aβ, IL-33, miRNA, DNA, and Ca²⁺. The receptor types involved include TLRs, RAGEs, P2XR, P2YR, and TRP channels. Following TBI, neurons and astrocytes in the affected area release ATP, creating an ATP concentration gradient in the tissue. As the earliest responding immune cells, microglia utilize this ATP gradient as a chemotactic signal, primarily through P2Y12R and P2X4R located on microglia, to migrate toward the damaged area. During this process, receptors such as RAGE, TLR2, and TLR4 on microglia bind DAMPs, including HMGB1, S100B, and APOE released by neurons or astrocytes, or inflammatory mediators, such as TNF-α, IL-18, and IL-1β, inducing microglia to polarize toward the pro-inflammatory M1 phenotype. Microglia also respond to fibrinogen and cytochrome c released by neurons through TLR4, activating NOX in microglia. This promotes the generation of ROS, exacerbating oxidative stress after TBI, and affecting astrocytes and neurons. Similarly, astrocytes respond early to injury after TBI. ATP and Ca²⁺ released from microglia and neurons activate the JAK2-STAT3 pathway through P2Y1R in astrocytes, leading to the polarization of astrocytes to the pro-inflammatory A1 phenotype. A1 astrocytes release inflammatory factors, such as IL-6 and INF-γ, further aggravating inflammation, or release Aβ to induce microglia to adopt the M1 phenotype. The transmission of hyaluronan between microglia and astrocytes via receptors such as IL-33 and CD44 affects the morphology and chemotaxis of both cell types during neuroinflammation. IL-33 and HMGB1 exhibit self-feedback loops in astrocytes and microglia, respectively, stimulating these cells to produce inflammatory factors that amplify the inflammatory response and lead to the release of additional IL-33 and HMGB1. Throughout this crosstalk process, neurons continuously exchange DAMPs, such as ATP, HMGB1, S100B, Aβ, and HSP, with glial cells through receptors, including TLR, RAGE, and TREM, resulting in various pathological changes, e.g. synaptic inhibition, inflammatory damage, oxidative stress, and programmed cell death. Therefore, DAMPs facilitate intercellular communication and functional crosstalk between neurons and glial cells during the secondary brain injury stage. While they may exacerbate pathological reactions, they can also provide neuroprotective effects in certain contexts. Taken together, the influence of DAMPs at the cellular level after TBI remains critically important. *P2XR* P2X receptors, *P2YR* P2Y receptors, *TRP* transient receptor potential, *APOE* apolipoprotein E, *NOX* NADPH oxidase, *ROS* reactive oxygen species, *TBI* traumatic brain injury, *DAMP* damage-associated molecular pattern, *TNF* tumor necrosis factor, *HMGB1* high-mobility group box 1, *IL* interleukin, *INF* interferon

During the primary injury phase, mechanical forces disrupt the flexible network of intermediate filaments in astrocytes [251]. This disruption activates mechanosensitive ion channels and receptors. The activation of these channels leads to a significant influx of calcium ions into astrocytes [252]. Elevated intracellular calcium levels trigger ATP release [253], which reactivates nearby microglia and astrocytes through PRs, such as P2Y1, initiating a cascade that exacerbates neuroinflammation by releasing additional purines [254, 255]. Furthermore, astrocytes exert anti-inflammatory effects primarily through the STAT3 signaling pathway, which is activated by brain-derived neurotrophic factor (BDNF), glycoprotein 130 (gp130), and interferon (IFN) [254, 256]. In an FPI brain injury model, intraventricular S100B injection accelerates neuroregeneration in hippocampal neurons and improves cognitive recovery [257]. Inhibiting GFAP in mouse models of entorhinal cortex injury facilitated hippocampal neurorepair and synaptic regeneration [258]. Thus, astrocytes play a complex role in promoting and inhibiting inflammation, neural repair, and synapse formation post-TBI.

The interaction between microglia and astrocytes is well studied. After TBI, microglia respond rapidly and rely on eATP concentration. Astrocytes release purines *via* PRs, which stimulate microglia, exacerbate neuronal damage, and accelerate microglial recruitment. Using purine receptor antagonists at this stage may reduce ATP-induced microglial chemotaxis. Microglia also release EVs containing HMGB1, IL-6, and other inflammatory factors that cause astrocyte swelling and destruction [16]. Astrocytes repair neuronal axonal damage by releasing ECM molecules, including HA, which promote axonal sprouting and synaptic regeneration [259]. Therefore, future studies should consider the roles of astrocytes at various injury stages and their interactions with other cell types such as microglia and neurons in the progression of TBI.

In summary, the function of neurons and glial cells is closely linked to TBI, with DAMPs playing an essential role in this cell-to-cell communication within the TBI progression, potentially contributing to the systemic damage discovered in TBI.

Secondary brain injury causes systemic damage with damage-associated molecular patterns

The prolonged accumulation of DAMPs and inflammatory factors, exacerbated by BBB disruption, affects multiple organs through blood circulation or axonal transport. EVs, which are double-layered vesicle structures secreted by or released from damaged cells, serve as crucial carriers in this process [260]. These EVs contain various substances, including DAMPs, and are present in nearly all body fluids [261]. Therefore, the alteration of DAMPs after TBI may contribute to multi-organ pathological and systemic changes, as shown in Figure 4.

In the secondary brain injury phase of TBI, cortisol (with glucocorticoids being the main effectors) and catecholamines released by the hypothalamic–pituitary–adrenal (HPA) axis and the autonomic nervous system (ANS) lead to neuroinflammation and excitotoxicity, which is considered to be one of the main causes of severe multi-organ dysfunction after TBI [262–265]. Glucocorticoids released by the HPA axis during the acute phase of TBI play a proinflammatory role when overactivated and induce microglial transformation to the M1 phenotype, further exacerbating cell death in the

late phase of TBI [266]. Furthermore, an imbalance in the HPA axis also affects the ANS. Excessive ANS activation results in a surge of catecholamines [267]. Therefore, patients experiencing HPA axis imbalance and ANS dysfunction can be considered harmed by the dual effects of stress and secondary brain injury. Upon activation, paroxysmal sympathetic hyperactivity (PSH, or sympathetic storm) manifests across multiple organs [260]. Thus, after initially serving a protective role in maintaining organ blood flow, prolonged sympathetic nervous system activity ultimately leads to poor adaptation and multi-organ dysfunction. Moreover, EVs are secreted in large quantities during stress and neuroinflammation. EVs from neurons and glial cells are loaded with various DAMPs, including HMGB1, HSP, ATP, CL, and DNA, transporting them throughout the whole body and causing damage to multiple organs [268].

The lung becomes one of the injured organs after TBI [269]. The most discussed theory between TBI and acute lung injury (ALI) is the neural–respiratory–inflammasome axis, which emphasizes the connection with inflammasomes [270]. Serum EVs from CCI mice were injected into normal mice, and increased levels of ALI with pulmonary endothelial cell pyroptosis were observed [271, 272]. When EVs from blood samples of patients with TBI were used to culture pulmonary endothelial cells, the level of pulmonary endothelial cell pyroptosis was also significantly increased, further causing pulmonary edema [273]. These results indicate that EVs, as important carriers of DAMPs are critical in the neural–respiratory–inflammasome axis, linking CNS damage and lung injury after TBI. Besides, various organs also affect each other and transmit inflammatory and injury-related factors. In the recent “triple hit” theory, microbial dysbiosis causes intestinal damage after TBI and the intestinal flora migrates to the lungs through the respiratory tract, lymphatic vessels, portal vein system, or systemic circulation, aggravating the level of ALI-related inflammation and pulmonary fibrosis [274], forming a mutual influence between the brain, lungs, and intestines [275, 276].

Apart from the lung, injuries in other organs, such as the heart [277], liver [278], gut [279], and kidney [280], may occur following TBI. In a clinical analysis of 491 patients with TBI, ~19.8% of patients developed acute kidney injury (AKI) within the first 3 days of admission [281]. Up to 74% of patients with TBI in the intensive care unit may experience diarrhea, which indirectly proves the importance of the brain–gut axis constructed by the brain and gastrointestinal tract after TBI [282]. Dysfunction of the brain–gut axis after TBI may affect multiple systems, including the circulatory system. EVs from CNS can transport various DAMPs across the blood–brain and intestinal barriers *via* the circulatory system to the gastrointestinal tract [283], thereby inducing intestinal dysbiosis, intestinal gliosis, and macrophage polarization after TBI [284, 285]. Moreover, disturbances in the gut flora may release more lipopolysaccharides, which, in turn, enter the CNS *via* the circulatory system to exacerbate neuroinflammation in TBI [286]. This process was also demonstrated to facilitate the synthesis and accumulation of A β in microglia, increasing the risk of neurodegenerative disease after TBI [287]. Furthermore, in a cohort study of 29 570 patients with TBI, the long-term risk of heart failure and coronary heart disease was significantly increased after TBI [288]. In the CCI mouse model, researchers found that neuroinflammation after TBI may lead to accelerated atherosclerosis through

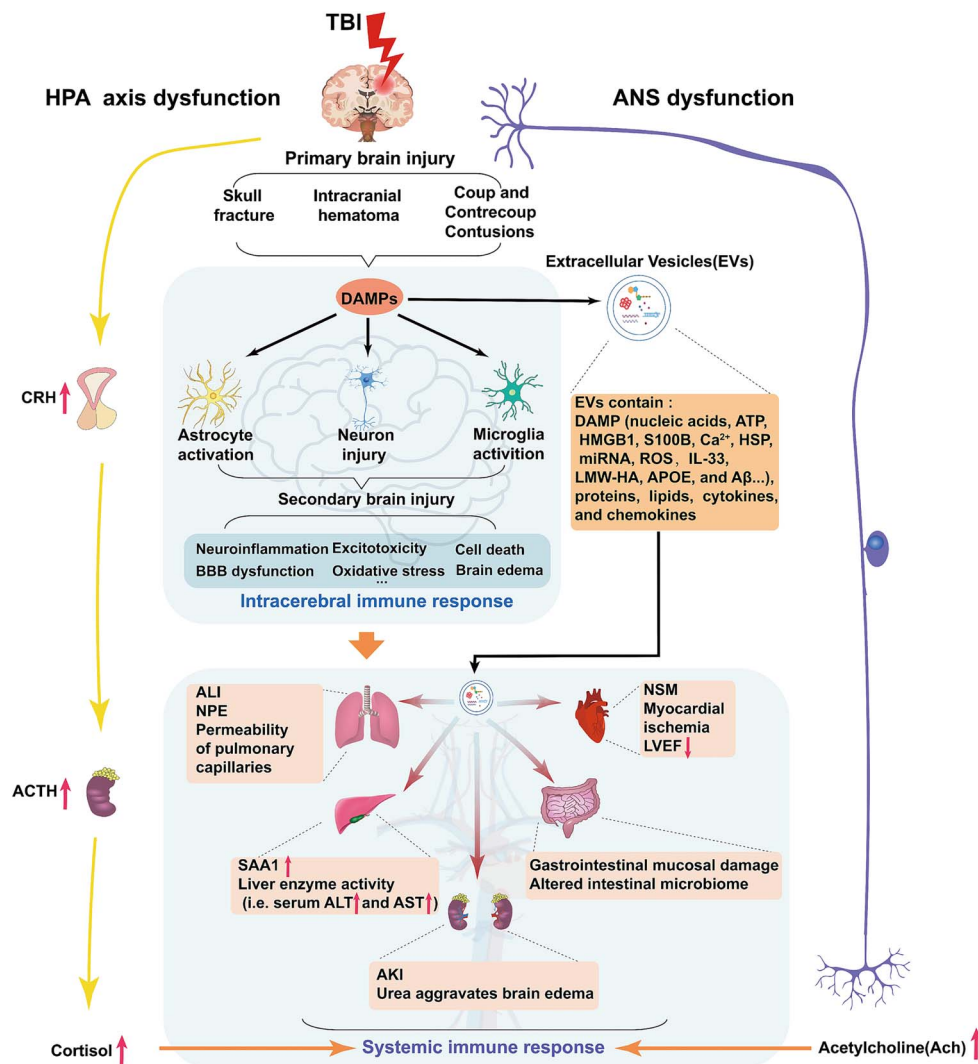


Figure 4. Alteration of DAMPs after TBI leads to multi-organ pathological and systemic changes. The primary injury in TBI leads to the overproduction of DAMPs. This excessive release of DAMPs triggers an inflammatory response that is detrimental to brain cells. The activation of microglia and astrocytes, alongside neuronal injury, further exacerbates secondary brain injury, manifesting as oxidative stress, cell death, excitotoxicity, BBB dysfunction, brain edema, and neuroinflammation. During the early stages of secondary brain injury, the immune response in the brain predominates; however, the peripheral immune response subsequently influences the entire body. The HPA axis and ANS may affect the immune response following TBI. On one hand, neurohormones weaken innate immunity and increase the risk of bacterial or aseptic infections in patients with TBI. On the other hand, extracellular vesicles (EVs) carrying DAMPs released by nerve cells can be distributed through various bodily fluids, including blood, lymph, and urine, leading to systemic pathological changes. Pulmonary complications are often among the most serious and frequent consequences of TBI. Respiratory failure associated with ALI has a notably high mortality rate. NPE exacerbates dyspnea in patients with TBI, potentially linked to the MAPK-NFκB inflammatory pathway triggered by S100B and HMGB1 in the lungs; changes in liver function following TBI are characterized by increased SAA1. As hepatocytes are the primary source of SAA1, its elevation serves as a damage marker in patients with TBI. Furthermore, within 12–24 h post-TBI, increased liver enzyme activity (ALT and AST) reflects hepatic injury. Numerous experimental and clinical studies indicate that, during acute and chronic hepatitis, the expression of HMGB1 and IL-33, along with that of their receptors RAGE and ST2, respectively, is significantly upregulated. It can be speculated that, in the long-term pathological phase of secondary brain injury, the onset and progression of hepatitis are related to the transport of DAMPs from the CNS to the entire body via EVs after TBI; TBI also impacts kidney function, where elevated renal load following systemic vasoconstriction may heighten the risk of AKI. Impaired kidney function could disrupt fluid balance within the body, exacerbating cerebral edema and increasing the risk of systemic edema. Kidney diseases that are closely associated with the overexpression of multiple HSP subtypes, including HSP70, HSP90, and HSP27, include chronic glomerulonephritis, ischemic and toxic AKI, and obstructive nephropathy. EVs laden with DAMPs can circulate throughout the body via various fluids, underscoring the close relationship between post-TBI renal functional changes and DAMP transport; the heart is subject to numerous cardiovascular abnormalities, including ECG changes, arrhythmias, and the release of cardiac injury biomarkers. Severely affected patients with TBI may exhibit LVD, reduced left ventricular ejection fraction, NSM, and abnormal heart rates, indicating persistent autonomic dysfunction. The binding of HMGB1 to TLR4 on cardiomyocytes and endothelial cells is a significant contributor to hypertension following TBI; gastrointestinal function after TBI is primarily characterized by mucosal damage and intestinal flora imbalance. The inflammatory factors and chemokines released into the gastrointestinal tract due to heightened neuroinflammation are critical causes of mucosal damage. The imbalance of intestinal flora is also influenced by the ANS, hindering the digestion and absorption processes in patients with TBI, prolonging disease duration, and negatively impacting prognosis. Consequently, TBI involves multi-organ damage throughout the body via the HPA axis, ANS, and immune system. Importantly, DAMPs within the brain can be transported to various organs via EVs, which play a crucial role in this process. *HPA* hypothalamic–pituitary–adrenal axis, *ANS* autonomic nervous system, *EVs* extracellular vesicles, *ALI* acute lung injury, *NPE* neurogenic pulmonary edema, *SAA1* serum amyloid protein A1, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CNS* central nervous system, *RAGE* receptor of advanced glycation, *BBB* blood–brain barrier, *DAMPs* damage-associated molecular patterns, *TBI* traumatic brain injury, *HPA* hypothalamic–pituitary–adrenal, *ANS* autonomic nervous system, *EVs* extracellular vesicles, *NPE* neurogenic pulmonary edema, *AKI* acute kidney injury, *ECG* electrocardiogram, *LVD* left ventricular dysfunction, *NSM* neurogenic stunned myocardium

neural and endocrine connections [289]. These studies illustrate the crosstalk between the brain and heart in TBI. In a mouse model of intracerebral hemorrhage (ICH), inhibition of liver X receptor (LXR) reduced brain damage and promoted neurological recovery after ICH [290], suggesting the relationship between the liver and the brain in TBI. DAMPs also play an important role in isolated injuries of other organs. mtDNA induces and aggravates AKI through multiple pathways including cGAS–STING, TLR9–Myd88–NF- κ B, and NLRP3 inflammasomes [291]. Neutrophil-derived S100A8/A9 amplifies granulocyte production after myocardial infarction, activates the NLRP3 inflammasome, and promotes IL-1 β secretion, increasing the risk of pericarditis after myocardial infarction [292]. Although the clear mechanism of multiple organ injuries following TBI remains unknown, given the role of DAMPs contained in EVs in lung injury after TBI, it is reasonable to speculate that EVs may be involved in injury signal transmission among various organs. Therefore, more experiments could be designed to test brain-derived EVs in these organs after TBI.

Although there is no clear research regarding DAMPs as biomarkers of systemic multi-organ damage after TBI, certain DAMPs have been associated with the organ injury in the progression of human diseases, such as the expression of S100A8/A9 is highly correlated with the mortality rate and oxygen demand rate of patients with COVID-19 [293]. Accordingly, whether DAMP may become a potential indicator for predicting multi-organ injury after TBI is worthy to be explored.

Besides, the change of DAMPs may also aggravate TBI by affecting PNS. DAMPs play important roles in both the CNS and the PNS through different pathways. The functional changes of CNS pathways after TBI occur. The DAMPs released by damaged or destroyed nerve cells may induce and aggravate neuroinflammation, oxidative stress, and various forms of PCDs. Neuroinflammation lasts throughout the entire process and is closely related to other pathological processes. The role of DAMPs in the PNS is evident in the destruction of the BBB after TBI, allowing EVs to transport DAMPs from the CNS into the PNS through the blood circulation. This process induces secondary injuries after TBI, including ALI and inflammatory bowel disease [294]. In the latest research, mast cells may affect the ANS (part of PNS) after IL-33 activation from the CNS, regulating multiple processes, including the heart rate and blood pressure circadian rhythm [295]. During the secondary injury phase in various organs, the damaged organs also release DAMPs, exacerbating systemic damage after TBI [296]. Meanwhile, oxidative stress after TBI releases ROS, Ca²⁺, and other factors that lead to excessive excitation of the ANS and activation of the HPA axis [297]. The excitation of the ANS releases excessive catecholamines, which lead to capillary contraction to induce pulmonary edema, discovered in patients with TBI [264]. HPA axis disorders lead to the loss of control of hormone substances, including glucocorticoids, which directly affects the ENS (one of the components of the PNS) [287, 298]. Therefore, DAMPs may contribute to changes in the PNS, which aggravate inflammation and multiple organ injuries after TBI by simultaneously regulating the nervous, endocrine, and circulatory systems.

Therapeutic prospects targeting damage-associated molecular patterns in traumatic brain injury

As shown in Figure 5, targeting DAMPs presents significant therapeutic potential, which makes them a central role in responding to cellular stress and tissue damage, ultimately helping to restore homeostasis through adaptive and innate immune responses [299]. The therapeutic approaches include the direct administration of antagonists to regulate the concentration or state of specific DAMPs, inhibition of precursor molecules or proteins that indirectly promote or generate DAMPs, or blocking the interaction between DAMPs and their receptors, such as PRRs, to suppress downstream inflammatory responses and inflammasome activation [79].

Directly reducing the expression of DAMPs after TBI is an effective therapeutic approach. For example, gene knockout of HDACs or cGAS inhibits the inflammatory response and brain injury of the mtDAMP-cGAS-STING pathway through a new signaling pathway HDAC3-p65-cGAS [300]. Nicotinamide *n*-oxide (NAMO) reduces the level of ROS to reduce neuroinflammation in the weight-drop mouse model [301]. Arundic acid (AA) reduced BBB damage after TBI by inhibiting the S100B expression [96, 302]. An RAGE antagonist, FPS-ZM1, has been shown to reduce S100B and RAGE expression, thereby mitigating brain and lung damage following TBI [96]. On the other hand, given that multiple DAMPs can act through the same receptor, blocking only one DAMP may not be enough to be useful. Thus, inhibiting DAMP-related receptors or downstream factors is also an option. For example, CX-01 (2-O, 3-O desulfated heparin) exerts anti-inflammatory effects and reduces multi-organ damage after TBI by inhibiting the binding between HMGB1 and RAGE [303]. Anti-HMGB1 antibodies have an effect on multi-organ damage, such as liver and lung edema after TBI, by reducing the expression of RAGE [304]. The application of AZ11645373 (antagonist of P2X7 receptor) and 5-BDBD (antagonist of P2X4 receptor) reduced the binding of ATP to purine receptors, which effectively reduced the occurrence of secondary epilepsy after TBI [305].

So far, no DAMP targeting therapy has been approved to clinical trials for TBI treatment. However, this therapy has been tested in clinical trials for other human diseases, such as treating myeloproliferative syndrome (MPS) with HSP inhibitors (NCT02873832). Moreover, the pharmacological clinical trials in healthy people using the HMGB1 inhibitor SB17170 (NCT05795192) indicated the feasibility for TBI treatment. Nevertheless, the side effects of the drugs should also be carefully considered. For example, glycyrrhizin is an inhibitor of the HMGB1/TLR pathway, with toxic effects that may cause pseudoaldosteronism [306]. Additionally, high doses and long-term use of glycyrrhizin may cause hypertension, hypokalemia, or rhabdomyolysis [307], which becomes one of the obstacles to its clinical application. Although it has undergone clinical trials for tumors and COVID-19, its toxicological effects could not be neglected [308]. Re-designing medication based on its effective composition or combining application with some potassium-sparing drugs, including aldosterone blockers or angiotensin-converting enzyme inhibitors, may counteract some of glycyrrhizin's side effects [309, 310].

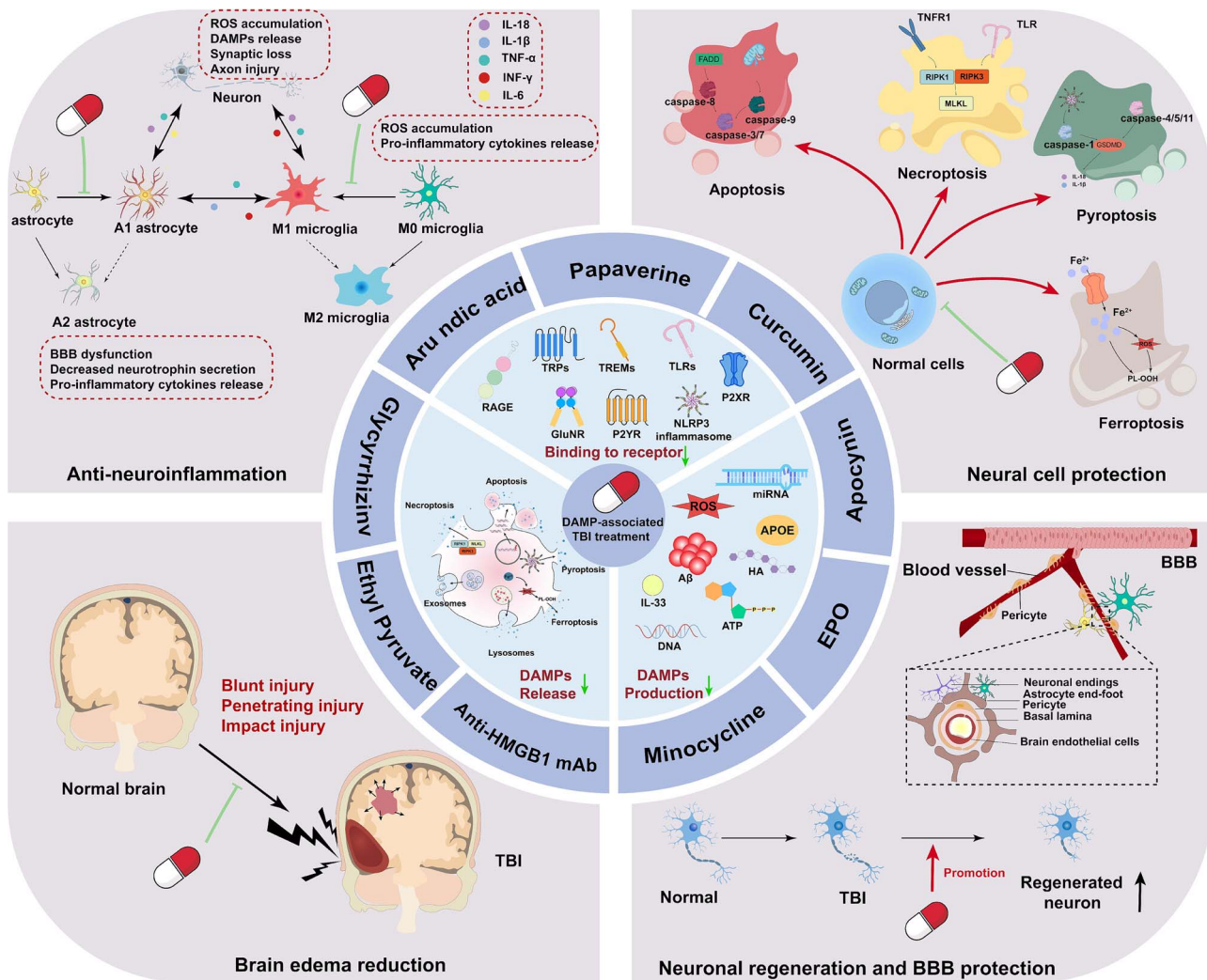


Figure 5. TBI treatment strategy and treatment effect based on DAMPs. Given the connection between DAMPs and TBI, several pharmacological agents have been explored in clinical or experimental settings, resulting in DAMP-related treatment strategies. The primary mechanisms of these strategies include: reduction of DAMP production: This can be achieved by decreasing the expression of related DAMP precursors or of DAMPs themselves, utilizing agents such as apocynin and minocycline; inhibition of DAMP binding to receptors: Competitive or noncompetitive inhibitors can block downstream signaling pathways, as demonstrated by compounds such as arundic acid, papaverine, and curcumin; decreased release of DAMPs from cells: This can be accomplished by targeting the primary DAMP release pathways, such as those related to exosomes, lysosomes, necroptosis, apoptosis, pyroptosis, ferroptosis, and DAMP translocation, by using agents such as glycyrrhizin and ethyl pyruvate. The reported effects of these treatment strategies include: anti-neuroinflammation: This involves reducing the release of inflammatory factors, minimizing axonal damage, decreasing ROS accumulation, limiting DAMP release, and preserving synapses. Furthermore, these strategies inhibit the decline of neurotrophic factors in microglia and astrocytes, preventing their polarization toward the pro-inflammatory M1 microglial and A1 astrocyte phenotypes, respectively, while promoting an anti-inflammatory/neuroprotective M2 microglial and A2 astrocyte phenotype, respectively. For instance, glycyrrhizin administered via intravenous injection in the fluid percussion injury rat model achieved anti-neuroinflammatory effects and improved neurocognition. In a lipopolysaccharide-induced TBI mouse model, curcumin reduced the release of inflammatory mediators and inhibited neuronal apoptosis. Anti-brain edema: This entails reducing the severity of brain edema through the mitigation of inflammation, oxidative stress, and regulation of ATP and Ca²⁺ levels. For example, in a weight-drop mouse model, papaverine competitively binds to RAGE, resulting in reduced brain edema, neuroinflammation, apoptosis, and neuroprotection while also inhibiting upstream S100B expression. Similarly, apocynin was used to lower NOX2 expression, an enzyme responsible for ROS generation, indirectly reducing ROS levels and achieving multiple therapeutic effects, including diminished brain edema, cell apoptosis, neuronal death, and inflammatory factor release. Promoting neuronal and myelin repair and maintaining blood–brain barrier integrity: For instance, EPO has been shown to reduce neuroinflammation by activating pathways that lower ROS levels, thereby promoting neuronal regeneration and repair and mitigating microglial activation. Anti-neuronal programmed cell death: This includes inhibition of cell death mechanisms, such as apoptosis, necroptosis, pyroptosis, and ferroptosis. For example, in the weight-drop TBI mouse model, apocynin effectively reduced NOX2 expression, indirectly lowering ROS generation and achieving therapeutic effects, such as a reduction in brain edema, cell apoptosis, neuronal death, and inflammatory factor release. *DAMPs* damage-associated molecular patterns, *TBI* traumatic brain injury, *ROS* reactive oxygen species, *RAGE* receptor of advanced glycation endproducts, *S100B* S100 Calcium Binding Protein B, *NOX2* NADPH oxidase 2, *EPO* erythropoietin

Similarly, resveratrol is an inhibitor of HMGB1 expression but has clinical side effects, such as diarrhea, vomiting, and abdominal distension in the gastrointestinal tract [311]. AA or polydatin in the FPI model directly inhibited S100B

expression in astrocytes and reduced the expression of downstream RAGE [96, 162]. AA was used to treat stroke and patients with AD, but it may increase the risk of depression [312]. Therefore, it is necessary to conduct psychological

assessments of the subjects regularly to ensure the safety of participants and the side effects of these drugs should also be fully considered in the experimental design.

Moreover, the barriers between existing experimental TBI models and clinical practice are the primary problem for clinical application. In an ICH marmoset model, researchers used a humanized anti-HMGB1 mAb (OKY001) to achieve an effective protective effect [313]. However, considering the differences between this model and TBI, as well as the differences in the time window of therapeutic drugs in the rat ICH model and the marmoset ICH model described by the researchers. Additionally, since rodent brains are predominantly lissencephalic while human brains are gyrencephalic, this difference in physiological structure may result in variations in treatment responses between animal models and human patients [314, 315]. There is still a gap between lab research and the clinical application of anti-HMGB1 mAb for TBI treatment as well. Therefore, the data and results obtained from experiments and animal models need to be rigorously and carefully evaluated for clinical application. Another limitation is the BBB penetration of drugs. The existing DAMP-related therapeutic drugs have not fully considered the BBB permeability of drugs in experimental studies [316]. Considering that the BBB has been damaged in the TBI animal model before administration, it is impossible to detect the BBB permeability of these drugs. It is recommended to employ the emerging TBI models to help verify the BBB permeability in future research, including transwell models of single culture or coculture, 3D microfluidic models, neurovascular microfluidic models, or BBBs-on-chips [317]. Moreover, there are currently no efficient and targeted biomarkers that reflect the effects of these drugs. As an inhibitor of HMGB1, resveratrol exhibits rapid metabolism and low systemic availability; thereby, the altered biomarker could be detected when a higher concentration is reached, but high concentrations usually lead to side effects [311]. Therefore, it is also necessary to search for new biomarkers with high sensitivity.

As of 2021, completed or ongoing TBI clinical trials registered on [ClinicalTrials.gov](https://clinicaltrials.gov) used related drugs such as phenytoin sodium, dexamethasone, and propranolol [318]. The results of existing TBI clinical drug trials are not ideal [319]. This situation can be improved by using reasonable machine learning algorithm models to classify patient populations [320].

Inhibitory DAMPs or self-associated molecular patterns (SAMPs) are a class of molecules that exert anti-inflammatory effects after binding to receptors. SAMPs include E2 glycoprotein, sialic acid polysaccharide, and pro-resolving mediator (SPM) [321, 322]. SAMPs released by tumor cells in tumors can interrupt the immune response and obtain immune escape [323, 324]. The special feature of sepsis and COVID-19 is that pro-inflammatory and anti-inflammatory reactions exist almost at the same time, and the sustained release of SAMP in them effectively helps control the inflammatory response [325]. The normal order of inflammation response in the body is that DAMP induces inflammation, and then SAMP exerts an anti-inflammatory effect. So far, there are no reports on the use of SAMP in TBI treatment. Considering its anti-inflammatory effect in COVID-19, in the early neuroinflammation of TBI, DAMP-targeted treatment can be considered to limit excessive inflammation levels. When entering the mid-to-late chronic inflammation period, SAMP treatment

might be used as supplementary treatment for DAMP-targeted therapy. The use of this combined treatment strategy also requires estimating the DAMP level and the SAMP level under physiological conditions to maintain a reasonable ratio. Too low DAMP levels or too high SAMP levels may cause immunosuppression and increase the risk of infection [326]. Reasonable maintenance of DAMP concentrations and inhibition of SAMP when necessary, and appropriate maintenance of inflammation levels to maintain immune response are also options for this treatment plan.

Overall, targeting DAMPs is a potential approach for TBI treatment. However, many challenges remained to be addressed before the actual clinical application.

Conclusions

In multiple pathological processes of TBI, a large number of CNS neurons undergo cell death and release DAMPs. Due to the destroyed BBB, DAMPs may also affect various organs apart from the brain by the ANS and HPA axes, and the EVs carrying DAMPs can enter the circulatory system, thus causing systemic damage. Given the large amount of evidence supporting DAMPs' involvement in TBI, there are still some questions. First, the mechanism of DAMP activity in the process of TBI is not fully understood. Multiple factors, such as the concentration, the molecular weight, or the location in the brain microenvironment of DAMPs, may affect their functions. Further research is needed to clarify the signaling pathways and molecular mechanisms. Apart from TBI experimental models, clinical samples should be also employed, such as blood samples from patients with TBI. These clinical samples can be analyzed using mass spectrometry or 3D imaging of solvent-cleared organs profiled by mass spectrometry (DISCO-MS), to track the movement trajectory, concentration changes, and detailed pathological changes of DAMPs in TBI. This may be more conducive to the clinical trials for the novel therapeutic approach. Second, after TBI, neurons and glial cells in the CNS undergo morphological and physiological changes under the influence of multiple DAMPs and they may interact with each other. Therefore, future research should focus on the functional crosstalk between different neural cell types, rather than studying the changes of a single cell type. The TBI model that combines neurons, astrocytes, microglia, and oligodendrocytes should be utilized. Moreover, the combined application of various bioinformatic technologies, such as genomic and transcriptomics, is necessary for exploring the dynamic change of DAMPs in the diverse stages of TBI, which will provide novel insights into their role in disease progression. Third, the development of DAMP-targeted drugs is still in an early phase, which cannot be translated into clinical practice. Therefore, multiple animal and cell models should be combined to explore the role of DAMPs in TBI, while the results ought to be re-evaluated strictly before clinical needs. Moreover, emerging models should also be employed. For those drugs that have been included in clinical trials for other diseases but only in animal model experiments for TBI, it is also necessary to examine the side effects of these drugs and the differences between different disease models ensure the safety of clinical application. Finally, not all DAMPs have been identified. For instance, the cold-induced RNA-binding protein was discovered in 1997 but only recognized as a DAMP in 2016. Therefore, further research is needed to determine whether novel DAMPs are involved in TBI development. In

conclusion, DAMPs serve as key indicators of the pathological processes in TBI. Increasing attention is definitely necessary to be paid to deepen our understanding of DAMPs' involvement in TBI. DAMPs may become key regulators for the multiple organ injury, and targeting DAMPs is a promising therapy for the treatment of TBI.

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Author contributions

X.X., C.Z., and J.W. conceived and designed the study; B.S. and J.Z. wrote the paper. B.S. and Z.L. designed the figures. X.X. revised the draft. All the authors reviewed the manuscript and approved the submitted version. Bowen Sun (Writing—original draft [equal]), Jiarui Zhang (Writing—original draft [equal]), Zhiqiang Li (Writing—original draft [supporting]), Jialu Wang (Writing—review & editing [equal]), Chuansheng Zhao (Writing—review & editing [equal]), and Xiaoxue Xu (Writing—review & editing [equal]).

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors read and approved the final manuscript.

Conflict of interest

None declared.

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Data availability

Not applicable.

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