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Astrocyte–microglia crosstalk in subarachnoid hemorrhage: mechanisms and treatments

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Subarachnoid hemorrhage (SAH) is a frequently encountered critical emergency characterized by the rupturing of an unhealthy blood vessel, resulting in high mortality and disability rates. Alterations in the neurovascular unit (NVU) are closely related to the pathogenesis of SAH. Microglia, the primary innate immune cells in the brain, and astrocytes, the most abundant cells in the brain, both play crucial roles in the response to SAH-associated cerebral injuries. Recently, the crosstalk between these two cells in the pathology and treatment of central nervous system (CNS) diseases, including SAH, has been revealed. Following acute brain insult, activated microglia and astrocytes can further activate each other, contributing to amplified neuroinflammatory reactions and thus inducing secondary brain injury. This review addresses the pathophysiological mechanisms of microglia and astrocytes in SAH, including neuroinflammation, neuronal damage, blood–brain barrier (BBB) disruption, vasospasm, and hematoma clearance. In addition, the newly identified therapeutic strategies against SAH by regulating astrocytes-microglia crosstalk through targeting damage-associated molecular patterns (DAMPs), immune mediators, and their receptors are also discussed. A thorough comprehension of microglia–astrocyte communication could provide novel ideas for future research and treatment of SAH.

1 Introduction

Subarachnoid hemorrhage (SAH) is a neurologic emergency caused by the rupture of a diseased vessel and following bleeding into the subarachnoid space. SAH ranks as the third most common type of stroke, with a mortality rate of almost 50%. Additionally, 30% of SAH survivors are unable to return to their previous way of life (1, 2). Hemorrhaging leads to a quick rise in intracranial pressure (ICP) and widespread cerebral ischemia, potentially resulting in death within minutes. Despite the availability of advanced interventional and microsurgical methods for securely closing aneurysms, patients who survive the initial period after SAH still face a high risk of morbidity and mortality (3). In addition to early brain injury (EBI) following SAH, delayed cerebral ischemia (DCI) is also closely related to

poor outcomes in SAH patients. Increasing evidence suggests that microcirculatory dysfunction, glymphatic impairment, inflammation, and neuroelectric disruption are the main pathological factors of SAH-associated DCI (4).

Maintaining the neurovascular unit (NVU) requires normal molecular crosstalk between the nervous and vascular systems (5). Following SAH, there is a broad spectrum of mild to severe neurovascular dysfunctions, including blood–brain barrier (BBB) damage, astrocytic and microglial activation, leukocyte infiltration, vasoconstriction, and astrocyte endfoot hypertrophy (6) (Figure 1). BBB injury disturbs the crosstalk among endothelial, vascular, glial, neural, and immune cells and leads to EBI and DCI (6, 7). During the first few hours after SAH, neurons, astrocytes, and parenchymal arterioles maintain normal communication (8). However, progressive impairment of NVC emerges after cerebral hemorrhage, which is considered a secondary pathological alteration (9). Astrocytes, the most abundant cells in brain, surround brain ECs with their endfeet and maintain BBB integrity, cerebral blood flow, nutrient uptake, and waste

clearance. They also regulate immune reactions and support BBB integrity (10, 11). However, SAH-mediated astrocytic activation contributes to altered BBB permeability by producing neurotoxic mediators (12, 13). SAH induces changes in calcium (Ca^{2+}) signaling within astrocytes, and astrocytic endfeet exhibit asymmetrical hypertrophy, resulting in a change in the neurovascular coupling response where vasodilation shifts to vasoconstriction. suggesting that astrocytes play an essential role in SAH-induced decreases in cortical blood flow (14). However, astrocytes also exert protective functions in SAH by mitigating endothelial cell (EC) dysfunction and BBB permeability (13).

Microglia are immune cells that originate from leptomeningeal mesenchymal cells. Under the stimulation of damage-associated molecular patterns (DAMPs) after SAH, microglia quickly become activated and polarized into different states (15). Classically activated microglia (also called "M1" microglia) can induce secondary brain injury by producing cytotoxic effectors, which aggravate neuronal damage and BBB disruption (16, 17). During the delayed phase of SAH, microglia dynamically polarize from the
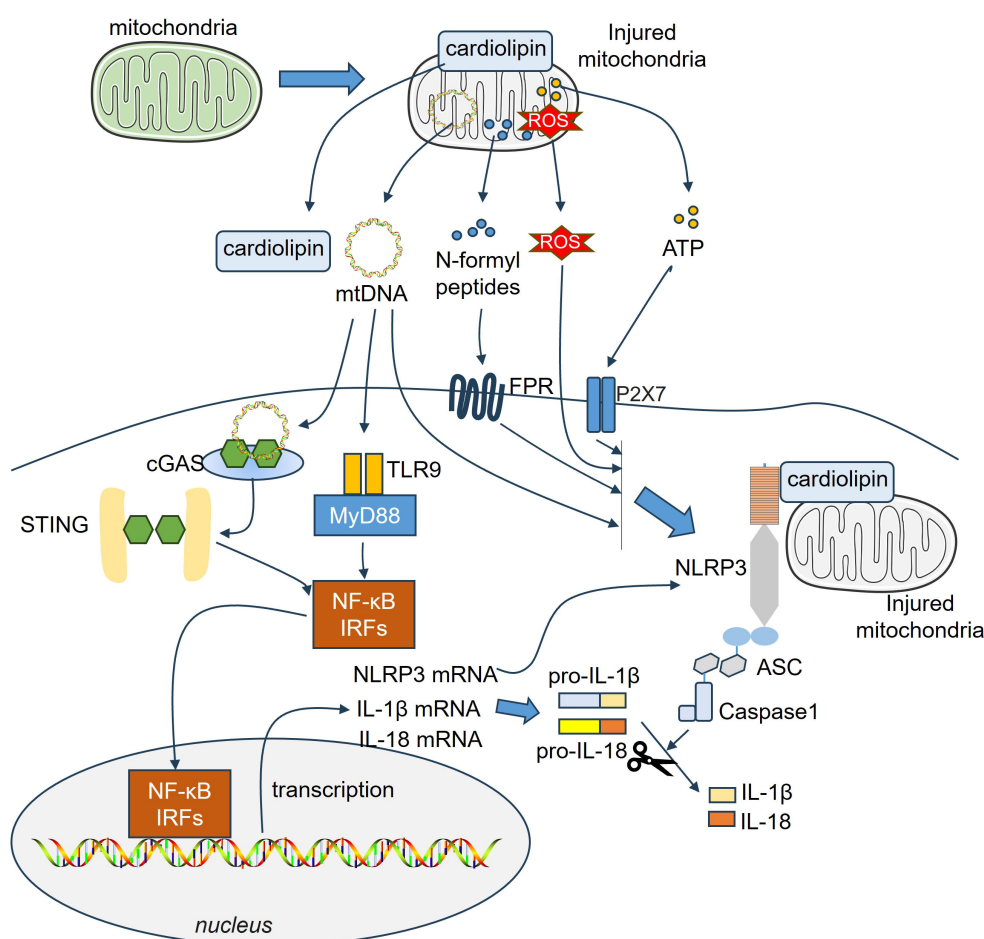
FIGURE 1

Astrocyte and microglia activation in the pathological changes of SAH. Following SAH, DAMPs are released from damaged cells, such as neurons, endothelial cells, RBCs. Those DAMPs stimulate astrocyte and microglia and induce their activation. Many mediators are involved in the interactions between activated astrocytes and microglia, which include cytokines, Ca2+, chemokines, ATP, growth factors, and so on. ATP, adenosine triphosphate; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; DAMPs, damage-associated molecular patterns; FGF2, fibroblast growth factor 2; GDNF, glial-derived neurotrophic factor; SAH, subarachnoid hemorrhage.

M1 to the M2 phenotype (18). M2 polarization of microglia significantly improves the inflammatory response, oxidative damage, neuronal degeneration, and BBB breakdown following SAH (19–21). Thus, dual roles are mediated by microglia in controlling BBB integrity. On the other hand, various studies have suggested that microglia–astrocyte crosstalk plays crucial roles in neurodevelopment, homeostasis, and central nervous system (CNS) disease progression (22, 23). Microglia react faster to pathological stimuli than astrocytes and then induce active astrocytes. However, astrocytes can also affect the activation of microglia (7). Following acute brain insult, activated microglia and astrocytes can further activate each other, contributing to amplified neuroinflammatory reactions and thus inducing secondary brain injury (24).

In our previous studies, we have reported that microglia and astrocytes exhibit swift reactions following stroke. Excessive reactive oxygen species (ROS) are generated via the mitochondrial and NADPH oxidase pathways, contributing to oxidative damage to microglia, astrocytes, and neurons (25). Many immune mediators, such as cytokines, chemokines, adenosine triphosphate (ATP), matrix metalloproteinases (MMPs), and growth factors, are altered following SAH (Table 1). They are essential for communication between microglia and astrocytes, thus maintaining brain homeostasis and mediating neuropathologies during different stages of SAH.

2 Dynamics of microglia/astrocyte activation in SAH

2.1 Dynamics of microglia activation in SAH

Microglia undergo a dynamic activation following SAH with spatiotemporal characteristics. At the early stage of SAH (0-3 days), microglia are rapidly activated in response to the presence of blood components and DAMPs. They change their morphology from a ramified, resting state to an amoeboid, activated state (43). Activated microglia can release a variety of pro-inflammatory cytokines and chemokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6). These molecules recruit immune cells from the periphery and initiate an inflammatory cascade, which can contribute to early brain injury (44). The NLRP3 (NOD-, LRR- and pyrin domain-containing 3)-ASC (apoptosis-associated speck-like protein containing a CARD) inflammasome activation plays an essential role in microglia activation, which mediates enhanced cytokine and chemokine concentrations. Within the early stage of SAH, the NLRP3-ASC inflammasome was increased in a time-dependent manner and peaked at 24 h after SAH (45).

Research on mice and rats revealed that microglia exhibited a phenotypic shift during the intermediate stage (3-5 days). They can adopt a more M2-like inflammatory phenotype, which is characterized by the release of cytokines such as interleukin-4 (IL-4) and transforming growth factor-beta (TGF-β). Microglia change morphologically from a ramified to an amoeboid form.

Those shifts are thought to be an attempt to resolve inflammation and promote tissue repair (18, 46, 47). During the late stage (5 days and later), microglia begin to phagocytose red blood cells, cell debris, and other foreign substances in the subarachnoid space. This process helps to clear the area of damaged tissue and potentially harmful substances (48). Iba1-labeled microglia/macrophages were significantly enhanced at 7-day and 14-day post-SAH, with elevated neuronal cell death (49). Though "M1" microglia are reduced in the perforated site and hippocampus during the intermediate stage, they are then enhanced at 10 days after SAH (18). Elevated productions of IL-6 and TNF-α can be detected 1 and 2 months after SAH, suggesting that chronic inflammation can persist. They may lead to further damage and potential long-term neurological deficits (49).

2.2 Dynamics of astrocyte activation in SAH

Astrocytes significantly contribute to the integrity of the BBB. Their endfeet surround the microvessel walls of the BBB, maintaining a structure that is essential for proper BBB function (50). GFAP-labeled astrocytes are activated 6 hours after SAH in the ventral cortex, and their activation in the dorsal cortex can be observed 24 hours after SAH (51). They change from a resting state to an activated state and show increased cell sizes and an upregulation of MMP9, which mediates BBB disruption (52). Over the course of the following week (days 1-7), MMP9 upregulation became detectable, starting from the cortical top layer towards the deeper layers (52). GFAP levels in the cerebrospinal fluid (CSF) from SAH patients were significantly enhanced and reached the highest on day 1 post-SAH. Higher GFAP levels were associated with poorer clinical outcomes of SAH patients (53). Astrocytes participate in the inflammatory response after SAH by secreting both proinflammatory and anti-inflammatory factors after the activation of distinct pathways. Neuroinflammation after SAH was very long-lasting and still present at day 21 (54–56). In the subacute and chronic stages, astrocytes gradually form a glial scar around the damaged area. The glial scar is mainly composed of astrocyte-derived extracellular matrix components and serves as a physical barrier to prevent the spread of inflammation and limit the invasion of immune cells and harmful substances. However, the glial scar may also hinder the regeneration of nerve fibers and affect the recovery of nerve function (57, 58).

3 DAMPs in microglia/astrocyte activation in SAH

Following tissue injury, host nuclear or cytoplasmic non-microbial molecules are released from cells, which are known as DAMPs. These DAMPs trigger the immune system, leading to a non-infectious inflammatory response that can result in systemic inflammation, organ damage, and potentially death (59). A wide

TABLE 1 The expressions and clinical associations of immune mediators in SAH patients.

Mediators	Source	Grouping		Expression	Clinical relevances	Ref.
IL-2, IL-6, IL-8, IL-10, and TNF-α	serum	poor prognosis group	good prognosis group	up	IL-2, IL-6, IL-8, and IL-10 levels were positively correlated with mRS scores	(26)
IL-4	serum and CSF	aSAH patients	healthy people	up	poor outcome, age, platelet-lymphocyte ratio (PLR), C-reactive protein (CRP), Hunt-Hess grade, mRS score, and World Federation of Neurological Surgeons score (WFNS), complications (intracranial infection, cerebral edema, hydrocephalus, and complications by DCI.	(27)
IL-6, CCL2, CCL11, CSF3, IL-8, IL-10, CX3CL1, and TNF-α	serum	higher clinical severity	lower clinical severity	up	Platelet-derived growth factor (PDGF)-AA, PDGF-AB/BB, soluble CD40 ligand, and tumor necrosis factor-α (TNF-α) increased over time. Colony-stimulating factor (CSF) 3, interleukin (IL)-13, and FMS-like tyrosine kinase 3 ligand decreased over time. IL-6, IL-5, and IL-15 peaked and decreased	(28)
IL-23 and IL-17	serum	aSAH patients	control patients	up	IL-23 and IL-17 showed differential correlations with post hemorrhagic complications	(29)
IL-1α, IL-18, IL-6 and IL-8	CSF	aSAH patients	control patients	up	IL-4 was higher in the CSF of patients who had delayed ischaemic neurological deficit. Day 3 plasma IL-6 levels predicted poor outcome at six months	(30)
IL-17	CSF	aSAH patients	control patients	down		
IL-6 and IL-8	Plasma	aSAH patients	control patients	up		
IL-1α	Plasma	aSAH patients	control patients	down		
CCL2, CCL4, CCL7, CCL11, CCL13, CCL19, CCL20, CXCL1, CXCL5, CXCL6 and CXCL8	CSF	poor outcome patients	good outcome patients	up	Higher levels of CCL11, CCL25, CXCL5 are associated with WFNS score, Fisher score or occurrence of delayed cerebral ischemia (DCI)/delayed ischemic neurological deficit (DIND)	(31)
CCL5	CSF and serum	aSAH patients	control patients	up	CSF CCL5 levels on post-aSAH day 1 were correlated with poor clinical outcome, however, serum CCL5 levels on post-aSAH day 7 were correlated with good clinical outcome.	(32)
CXCL12	serum	aSAH patients	control patients	up	Elevation of serum CXCL12 levels is associated highly with hemorrhagic severity and poor outcome after aSAH	(33)
FABP3 and CXCL-16	serum	poor outcome patients	good outcome patients	up	Early FABP3 and CXCL-16 levels are significantly associated with poor 30-day outcome in patients with aSAH	(34)
CRP	serum and CSF	poor outcome patients	good outcome patients	up	Patients with angiographic vasospasm had higher CRP measurements in serum and CSF	(35)
TNF-α	serum	poor outcome patients	good outcome patients	up	TNF-α over time are associated with poor outcome	(36)
HsCRP	blood	with vasospasm	without vasospasm	up	High plasma levels of HsCRP were significantly associated with angiographic vasospasm and clinical outcome	(37)
		poor outcome patients	good outcome patients	up		
E-selectin , ICAM-1, and VCAM-1	CSF	aSAH patients	control patients	up	Levels of E-selectin were associated with patients who later developed moderate or severe vasospasm	(38)
MMP-9	blood and CSF	poor outcome patients	good outcome patients	up	blood and CSF MMP-9 are associated with poor 3-month SAH clinical outcome	(39)

(Continued)

TABLE 1 Continued

Mediators	Source	Grouping		Expression	Clinical relevances	Ref.
IL-33	Serum	aSAH patients	control patients	up	High serum IL-33 concentrations have close relation to the inflammation, severity and poor outcome in aSAH	(40)
TGF-β1	CSF	SAH	control patients	up	TGF-beta1 in CSF after SAH are derived initially from blood and later from endogenous sources such as the choroid plexus	(41)
Factor III, Factor VII, fibrin,TAT, IL-1β , IL-2, IL-5, IL-6, IL-7, IL-8, IL-12, IL-17, G-CSF, GM-CSF, IFN-γ, CCL-2 , CCL-4, and TNF-α	CSF	severe cerebral edema	mild cerebral edema	up	TAT, fibrin, IL-1β, IL-2, IL-5, IL-7, and IL-4 were independently associated with severe cerebral edema; Factor VII, fibrin, IL-2, IL-5, IL-12, TNF-α, and CCL-4 were independently associated with chronic hydrocephalus	(42)

variety of endogenous molecules released upon brain injury are termed DAMPs, which cause the activation of microglia and astrocytes (60). For example, extracellular S100B (61) and high mobility group box 1 (HMGB1) (62) are dramatically elevated after brain injury and contribute to reactive gliosis in the injured brain through the activation of a receptor for advanced glycation end products (RAGE) or toll-like receptor (TLR)4 signaling. Other DAMPs, such as heat shock proteins (HSPs), adenosine triphosphate (ATP), purines, and peroxiredoxins, also play vital roles in the activation of the immune system early following brain insult, as reviewed in previous studies (63–66). The increased production of DAMPs in the serum or CSF following SAH is closely associated with the outcomes of SAH patients, and those DAMPs are promising diagnostic, prognostic, therapeutic, and drug therapy candidates for SAH (67) (Table 2). Notably, these DAMPs induce significant activation of microglia and/or astrocytes (Table 3), leading to further aggravated neurovascular dysfunctions in SAH.

3.1 HMGB1

HMGB1 is a nonhistone DNA-binding protein. In the brain, HMGB1 mediates neurite outgrowth and cell migration with a complex temporal and spatial distribution pattern (101). Clinical analysis revealed that the levels of HMGB1, along with those of IL-6 and TNF-α, are significantly increased in the cerebrospinal fluid (CSF) of patients with SAH (102) and in the serum of patients with intracerebral hemorrhage (ICH) (75). Notably, HMGB1 is positively correlated with these proinflammatory cytokines (75, 102). Under pathological conditions, such as cerebral ischemic stroke, HMGB1 can be released from injured neurons (103). As early as 2 h after experimental SAH, the mRNA and protein levels of HMGB1 were elevated. HMGB1 is translocated from the nucleus to the cytoplasm, which occurs mainly in neurons and, to a lesser extent, in microglia (104). In the hemoglobin (Hb)-induced in vitro SAH model, HMGB1 is rapidly produced from neurons in the medium (104). Murakami et al. reported that in the SAH model,

more than 90% of HMGB1-expressing cells were IBA1-labeled microglia/macrophages, suggesting that microglia/macrophages are potentially the major source of HMGB1 in SAH (105). HMGB1 can also be produced by pyroptotic endothelial cells in brain lesions, which further enhances macrophage pyroptosis, resulting in immune disorders (106). In the microcirculation of the brain, HMGB1 expression is upregulated on platelet microvesicles from acute ischemic stroke (AIS) patients and induces neutrophil extracellular trap (NET) formation. The latter significantly promoted procoagulant activity through tissue factor and platelet activation (107).

HMGB1 plays a vital role in microglial and astrocyte activation in SAH (Figure 2). Extracellular HMGB1 binds several pattern recognition receptors (PRRs). The most important receptors include TLR-2, TLR-4, and RAGE on immune cells to increase inflammation (108). RAGE is expressed mainly by neurons and microglia rather than astrocytes after SAH (109). TLR2 and TLR4 are mainly expressed in microglia after SAH (110, 111). HMGB1 release is elevated in traumatic brain injury (TBI) and mediates TLR4 signaling activation in microglia. Activated microglia produce IL-6, which enhances astrocytic expression of aquaporin-4 (AQP4) and ultimately contributes to posttraumatic brain edema (62). Direct treatment of primary cultured astrocytes from rats with HMGB1 did not increase the level of AQP4 mRNA, nor did it affect the nuclear transfer of NF-κB in astrocytes. With the help of microglia-derived IL-1β, AQP4 expression is upregulated in astrocytes (87), suggesting that HMGB1 can mediate astrocytic activation with the help of proinflammatory cytokines produced by activated microglia. In the absence of glial cells, HMGB1 failed to induce neurodegeneration in primary cultured cortical neurons. Glycyrrhizin-mediated HMGB1 blockade reduces neuronal degeneration, reactive astrogliosis, and microgliosis in the long term (88). Recently, Chi et al. reported that in spinal cord injury (SCI), HMGB1 promoted chemokine (C-C motif) ligand 5 (CCL5) expression and release from astrocytes by binding to TLR2/4 receptors. CCL5 mediates microglia/macrophage accumulation and M1 polarization in spinal lesions (89). These studies revealed that the detrimental effects of HMGB1 depend on microglial–astrocytic interactions.

TABLE 2 The expressions and clinical associations of DAMPs in SAH patients.

Mediators	Source	Grouping		Expression	Clinical relevances	Ref.
ex-mito	CSF	aSAH patients	control patients	up	higher mitochondrial membrane potentials in the CSF were correlated with good clinical recovery	(68)
mito-DNA	Serum	aSAH patients	control patients	up	mtDNA may directly or indirectly influence post-SAH complications and clinical outcome	(69)
	CSF and serum	aSAH patients	healthy people	up	Higher CSF DNA levels are associated with worse outcomes in patients with acute spontaneous aneurysmal SAH	(70)
HMGB1	CSF	SAH patients	control patients	up	Altered concentration of CSF HMGB1 correlates with outcome	(71)
	CSF	aSAH patients	control patients	up	CSF HMGB1 levels were positively associated with disease severity scores, IL-6 levels, DCI and 6-month poor outcome	(72)
	CSF	poor outcome	good outcome	up	CSF HMGB1 level was independently associated with unfavorable outcome at three months post-SAH	(73)
	Plasma	aSAH patients	control patients	up	plasma HMGB1 level was an independent predictor of poor functional outcome and mortality after 1 year, in-hospital mortality and cerebrovasospasm	(74)
	Serum	ICH patients	normal controls	up	Serum HMGB1 levels were significantly correlated with the levels of IL-6 and TNF-α and poor outcome of ICH patients	(75)
S100B	CSF and serum	poor outcome	good outcome	up	Serum S100B levels were significantly correlated with poor outcome of SAH patients	(76)
	CSF and serum	poor outcome	good outcome	up	CSF and Serum S100B levels were associated with poor outcome, intracranial hypertension and cerebral infarction of spontaneous SAH patients	(77)
	Serum	severe EBI	mild to moderate EBI		Early S100B seems to have a good diagnostic value to predict severe EBI.	(78)
	Serum	aSAH patients	healthy controls	up	Serum S100B levels predict the clinical prognosis of patients with aSAH	(79)
hemoglobin	Serum	poor outcome	good outcome	down	Higher HGB values are associated with improved outcomes after SAH at 14 days/discharge and 3 months.	(80)
	Serum	poor outcome	good outcome	down	Lower hemoglobin levels are associated with worse outcomes	(81)
	Serum	poor outcome	good outcome	down	SAH patients with higher initial and mean hgb values had improved outcomes	(82)
S100A8/A9	Serum	aSAH patients	healthy controls	up	Serum S100A8/A9 levels within 48 hours after onset was significantly correlated with poor outcome of aSAH patients	(83)
S100A12	Serum	poor outcome	good outcome	up	High serum S100A12 levels at admission are associated with inflammatory response and poor outcome of ICH patients	(84)
hemopexin	Serum	SAH patients	control patients	up	Higher hemopexin levels were associated delayed cerebral ischemia and poorer neurological outcome	(85)
ferritin	Serum	SAH patients	control patients	up	CSF ferritin level after SAH might be a new diagnostic marker	(86)

3.2 Hemoglobin/heme

Upon hemolysis, red blood cells (RBCs) release hemoglobin (Hb) into the circulation. Different Hb redox states and heme can act as DAMPs in the body (112). On the basis of clinical data, elevated Hb levels are associated with the clinical outcomes of SAH patients and predict less cerebral infarction, mortality, and vasospasm (80, 82, 113). However, increased Hb levels in the CSF of SAH patients are positively related to SAH-associated secondary brain injury (SBI), possibly by inducing an adaptive macrophage response and promoting vasoconstrictive and lipid peroxidation activities (114). When released from globin, heme is thought to be more toxic than hemoglobin, since it is highly lipophilic, easily intercalating into membranes and perturbing cellular function (115). Higher heme levels in the CSF have been found in SAH patients, with a positive association with the development of vascular injury and cerebral vasospasm (116).

Hb easily passes through the walls of cerebral arteries and the cortex, and there is a noticeable spatial relationship between blood clots and the accumulation of iron in the brain cortex (114, 117).

TABLE 3 The roles of DAMPs in microglia-astrocyte interactions.

DAMPs	Mechanisms		Ref.
	Microglia	Astrocyte	
HMGB1	HMGB1 enhances IL-1β expression from microglia	HMGB1 upregulates AQP4 expression with the help of microglia-derived IL-1β	(87)
	HMGB1 induces NF-κB activation by TLR2, TLR4, and RAGE	HMGB1 induces NF-κB activation in astrocytes with microglial cooperation	(88)
	HMGB1-induced release of CCL5 from astrocytes promotes microglia/macrophage accumulation and M1 polarization.	HMGB1 facilitates the production of CCL5 from astrocytes by binding with TLR2/4 receptors potently	(89)
hemoglobin	Hemoglobin promotes the expression of cytokines (ex. TNF-α, IL-1β, and IL-6) from microglia	Oxyhemoglobin activate the NF-κB pathway in astrocytes and increases the production of proinflammatory cytokines (including TNF-α, IL-1β, IL-6 and MMP9)	(90–94)
mitochondrial DNA	mtDNA promotes "M1" polarization of microglia via the activation of the STING and IRF3/NF-κB signaling pathways	Copper exposure caused the release of mtDNA and subsequent cGAS-STING pathway activation	(95, 96)
S100B	S100B stimulates microglial migration via the upregulation of chemokines and chemokine receptors and promotes proinflammatory reactions of microglia by S100B/RAGE-dependent activation of the JNK and NF-κB pathways	S100B promotes the NF-κB pathway activation dose-dependently and upregulates endogenous RAGE in astrocytes	(83, 97, 98)
Peroxiredoxin6	The peroxiredoxins 6 (PRDX6)-phospholipase A2 (iPLA2) axis is involved in the activation of microglia	PRDX6 is mainly expressed and produced by astrocytes	(99, 100)

Extracellular Hb is believed to have a crucial impact primarily on pathways associated with oxidative stress, inflammation, iron toxicity, and nitric oxide (118). Extracellular Hb/heme induces diverse toxic effects on neurons (119), pericytes (120), cerebral endothelial cells (121), and astrocytes (122). Compared with astrocytes, neurons are more susceptible to both hemoglobin and heme toxicity (123).

Accumulating evidence has shown that Hb/heme can mediate the microglial proinflammatory response by promoting the expression of cytokines (ex. TNF-α, IL-1β, and IL-6) and activate autophagy (90–92) (Figure 3). Microglia also have protective effects on ICH by accelerating hematoma clearance (80). For example, Hb promoted IL-10 expression in microglia and enhanced phagocytosis, which was dependent on the IL-10-regulated expression of CD36. The mice with IL-10 deficiency presented aggravated neuroinflammation, brain edema, iron deposition, and neurological deficits. The phagocytic ability of microglia is dampened due to decreased CD36 expression, leading to delayed hematoma clearance (124). CD163, a hemoglobin/haptoglobin scavenger receptor, can bind the hemoglobin-haptoglobin complex, thereby mediating extravasal hemolysis. CD163 also has potent anti-inflammatory effects on microglia/macrophages (125, 126). The absence of CD163 in the ICH mouse model resulted in reduced Hb, iron, and blood–brain barrier (BBB) disruption; increased astrogliosis; and neovascularization at 3 days. However, CD163 deficiency causes delayed injurious effects, as evidenced by enhanced iron and VEGF immunoreactivity (127). Damaged neurons can produce fractalkine (FKN) around the hematoma. FKN improves microglial erythrophagocytosis via the CD163/heme oxygenase-1 (HO-1) axis, thus mitigating neuroinflammation, hematoma size and Hb content and relieving neurological deficits in ICH mice (128, 129).

Astrocytes are involved in Hb- and haemin-mediated disorders during ICH (94, 130) (Figure 3). Hb pretreatment in astrocytes enhances the expression and nuclear translocation of Nrf2, thus preventing hemin-induced oxidative stress and apoptosis (131). However, Hb can promote pyroptosis and tissue factor production/release in primary astrocytes in SAH rats, which can be blocked by the caspase-1 inhibitor VX-765 (132). Oxyhemoglobin (OxyHb) promoted CD24 expression in hippocampal astrocytes, whereas knockdown of astrocytic CD24 contributed to impaired axons and dendrites of neurons cocultured with astrocytes (133). Astrocyte-derived glutathione (GSH) alleviated hemin-induced apoptosis in cerebral microvascular cells (134). Promoting the activation of Wnt5a/Ror2 signaling in astrocytes reduces heme-induced BBB damage after brain hemorrhage, and the underlying mechanism may depend on the nuclear accumulation of Nrf2 (135). Astrocytes can also affect neuroinflammation in ICH models. After exposure to OxyHb, astrocytes activate the NF-κB pathway and increase the production of proinflammatory cytokines (including TNF-α, IL-1β, IL-6 and MMP9) (93, 94). These effects were significantly reversed following the depletion of Nrf2 (93).

Excessive accumulated iron has been regarded as a hallmark of SAH-associated pathological changes. Iron-related brain injury is considered a major mechanism of intracranial hemorrhage as well as TBI (136). Recycling heme iron is an essential part of overall iron metabolism. Iron is freed from heme molecules with the help of enzymes called heme oxygenases (HOs), particularly HO-1 (137). Iron-rich red blood cells accumulate and lyse at the brain parenchyma following hemorrhagic stroke, thereby contributing to iron-induced lipid peroxidation and cell death (138). Iron deposition in the brain could also possibly modulate microglial activation and motility (139). Hepcidin is vital for iron homeostasis in the brain during neuronal iron loading and brain hemorrhage
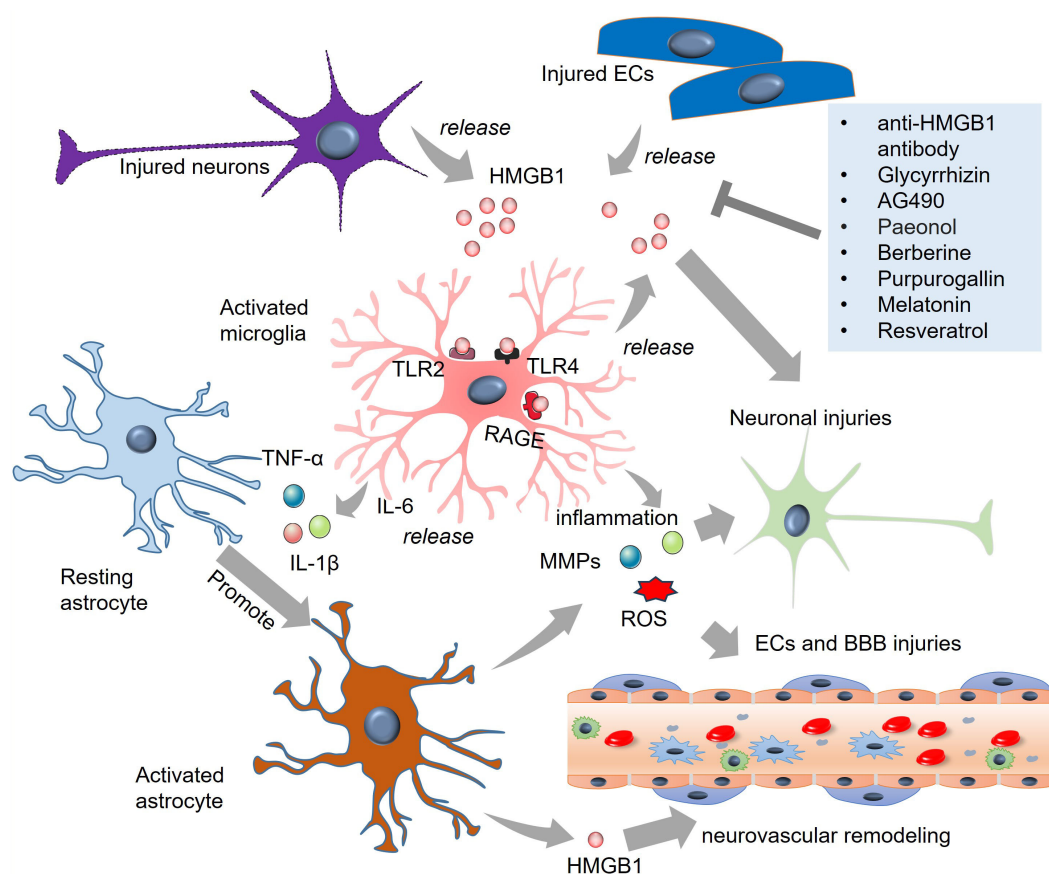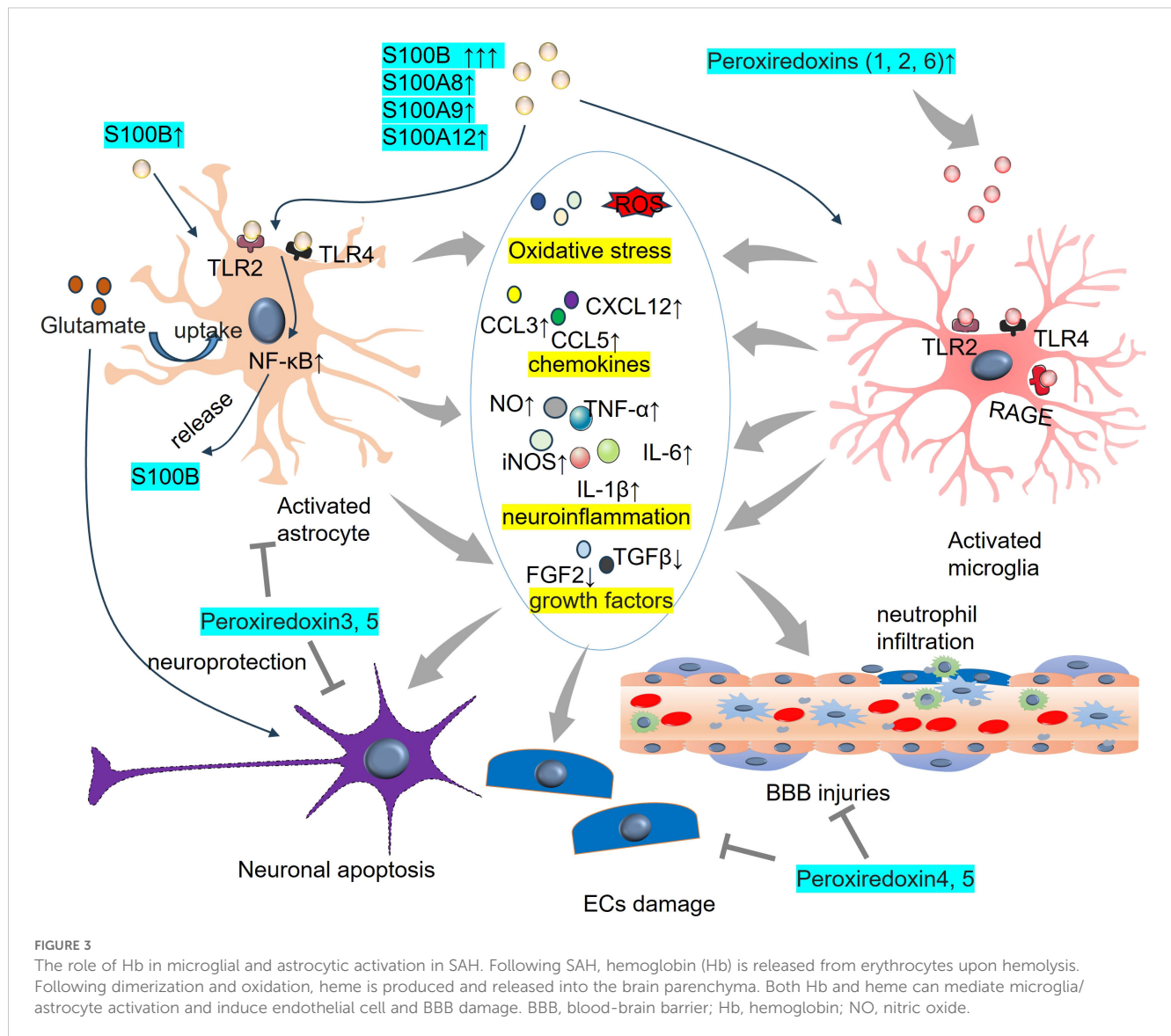
FIGURE 2

The role of HMGB1 in microglial and astrocytic activation in SAH. HMGB1 is released from injured neurons and endothelial cells. HMGB1 binds TLR-2, TLR-4, and RAGE on microglia and astrocytes and induces the activation of the two cells. Inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, MMPs, and ROS are produced from activated microglia and astrocytes, which promote secondary injuries to neurons and endothelial cells. Targeting HMGB1 via multiple strategies, such as anti-HMGB1 antibody and glycyrrhizin treatment, can mitigate HMGB1-mediated microglial and astrocytic activation. BBB, blood-brain barrier; ECs, endothelial cells; HMGB1, high-mobility group box-1; IL-6, interleukin-6; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; TLR, toll-like receptor; TNF-α, tumour necrosis factor-alpha.

(140). After SAH, there was an exacerbation in iron accumulation, as well as a decrease in ferroportin 1 (FPN1) in neurons and an increase in hepcidin in astrocytes. Downregulating astrocytic hepcidin enhances neuronal FPN1 levels and reduces iron accumulation (141). Elevated levels of hepcidin-25 were discovered in the serum and mainly in astrocytes following ICH. In mice with ICH, the absence of hepcidin helped reduce the release of brain iron, oxidative brain damage, and cognitive deficits. The TLR4/MyD88 signaling promotes hepcidin expression via the IL-6-signal transducer and activator of transcription 3 (STAT3) signaling pathway, suggesting that inflammation plays an essential role in mediating astrocytic hepcidin expression in the brain (142).

3.3 Damaged mitochondria, N-formyl peptides, and mitochondrial DNA

Accumulating evidence has shown that damaged mitochondria, or the release of N-formyl peptides and mitochondrial DNA (mtDNA) from mitochondria, can act as DAMPs that activate the innate immune system (143–145) (Figure 4). Mitochondrial N-formyl peptides are similar to bacterial N-formylated peptides, both serving as strong immune system activators. Hemorrhagic shock increased the plasma levels of mitochondrial N-formyl peptides in patients with lung damage. The antagonism of formyl peptide receptors (FPRs) ameliorated hemorrhagic shock-induced lung injury in rats (146). Endogenous mitochondrial-derived DAMPs (MTDs), including N-formyl peptides, cardiolipin (CL), and mtDNA, are used to treat HMC3 cells to test their effects on microglial activation *in vitro*. These MTDs fail to induce microglial activation toward a proinflammatory phenotype. However, mtDNA and CL markedly increase reactive oxygen species production in microglia (147). Circulating mitochondrial N-formyl peptides, which are endogenous ligands of FPR1, are augmented and correlated with the magnitude of brain edema in ICH patients. FPR1 is the most abundant DAMP receptor and is expressed mainly by microglia. Interactions of formyl peptides with FPR1-activated microglia increase neutrophil recruitment and aggravate neurological deficits in different ICH mouse models (148).

FIGURE 3
The role of Hb in microglial and astrocytic activation in SAH. Following SAH, hemoglobin (Hb) is released from erythrocytes upon hemolysis. Following dimerization and oxidation, heme is produced and released into the brain parenchyma. Both Hb and heme can mediate microglia/astrocyte activation and induce endothelial cell and BBB damage. BBB, blood-brain barrier; Hb, hemoglobin; NO, nitric oxide.

CL is a mitochondrial membrane phospholipid that supports mitochondrial function and metabolic processes and regulates neuronal and glial cell viability (149). Microglial phagocytosis and expression of neurotrophic factors are enhanced by extracellular CL while the release of inflammatory mediators and cytotoxins by activated microglia-like cells is reduced (150). In the traumatically injured brain, mitochondria are released from the systemic circulation, and the CL is exposed on its surface. Mitochondria exposed to CL exhibit a high level of procoagulant activity and contribute to the development of coagulopathy associated with TBI (151). TBI leads to increased mitophagy in the human brain and promotes oxidation of the CL, thus triggering neuronal apoptosis. CL is regarded as a marker of eliminating injured mitochondria, which in turn reduces neuronal death and decreases behavioral impairments (152). Extracellular mitochondria (Ex-mito) were detected in the CSF of the SAH rat model as well as in the CSF of patients with SAH. The mitochondrial membrane potential decreased following SAH. Higher mitochondrial membrane

potentials in the CSF were correlated with good clinical recovery 3 months after SAH onset (68). Moreover, reduced mitochondrial membrane potential in the CSF is also associated with DCI following SAH (153). Ex-mito can activate microglia and contribute to neuroinflammation (154). Considering the crucial role of the CL in mediating mitochondrial functions (149), it would be interesting to detect the CL and explore its role in mitochondrial functions in SAH.

The mitochondria have many copies of mtDNA, which carry instructions for making ribosomal and transfer RNAs, along with important proteins needed for oxidative phosphorylation (155). mtDNA resides in the mitochondrial matrix and is linked to the inner mitochondrial membrane. It acts as a DAMP via binding to toll-like receptor-9 due to unmethylated CpG motifs, leading to upregulation of inflammation (143). Additionally, mtDNA promotes innate immune response through other PRRs, including NLRP3-, NLRC4-, AIM2-, NLRP10-inflammasome complex (156–158), and cyclic GMP-AMP synthase (cGAS)-stimulator of
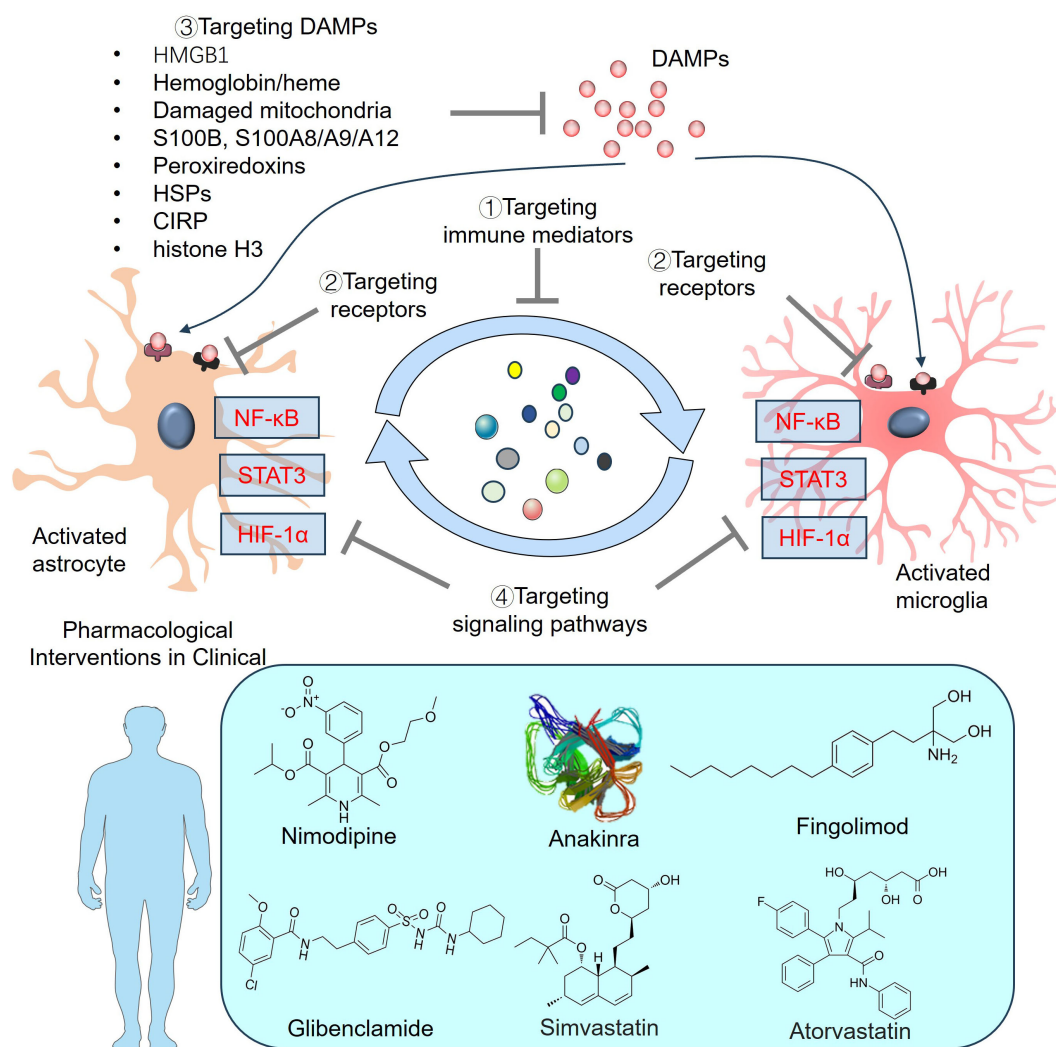
FIGURE 4

Mitochondria-related DAMPs on microglial and astrocytic activation. Endogenous mitochondrial-derived DAMPs, including N-formyl peptides, cardiolipin (CL), mtDNA and ATP are released from injured cells, which then bind different receptors and mediate inflammatory reactions. The downstream pathways, such as NF-κB, IRFs, NLRP3-ASC-Caspase1 inflammasome, become activated in astrocytes and microglia. ASC, apoptosis-associated speck-like protein a CARD; ATP, adenosine triphosphate; IRFs, Interferon regulatory factors; NF-κB, nuclear factor-kappaB; NLRP3, NACHT, LRR, and PYD domains-containing protein 3; ROS, reactive oxygen species.

interferon genes (STING) (159). As a unique type of PRRs, cGAS lacks DNA sequence specificity, and cannot effectively distinguish between self and foreign DNA. Therefore, mtDNA can bind cGAS upon entry into the cytoplasm, thus activating the downstream STING and mediating neuroinflammatory responses in CNS disorders (160). Chaudhry et al. analyzed the temporal profiles of three representative mitochondrial gene fragments, including Cytochrome B (CytB), D-Loop, and Cytochrome c oxidase subunit-1 (COX-1) in the serum of aSAH patients. They revealed that serum CytB, D-Loop and COX-1 were all significantly elevated following aSAH and correlated with post-SAH complications (69). Ischemic hypoxia triggers the growth of new mitochondria and elevates mtDNA levels, leading to oxidative stress and cell death (161, 162). For example, the protein levels of cGAS and p-STING were significantly elevated following MCAO in a time-dependent manner. mtDNA was released into the microglial cytoplasm in
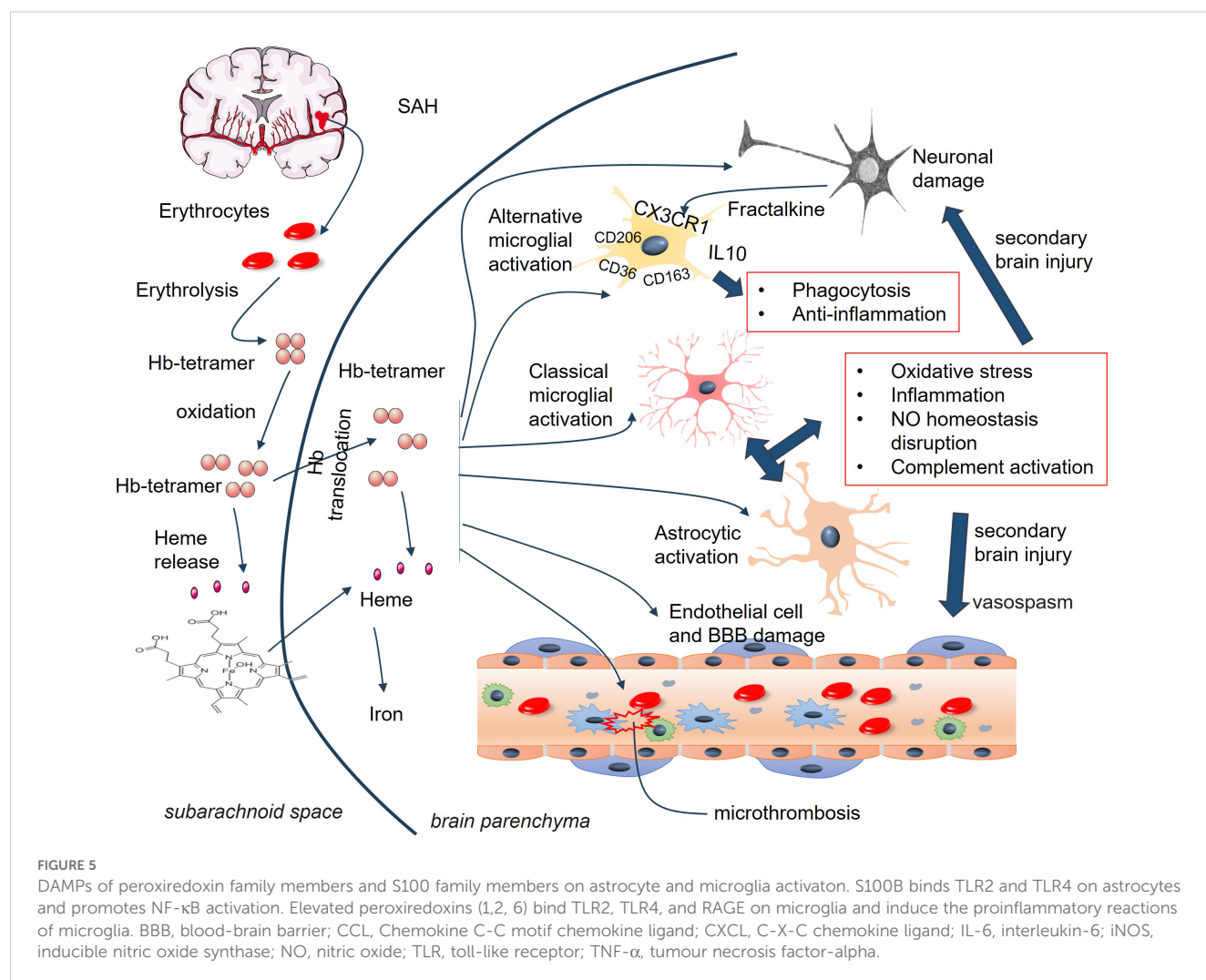
response to I/R injury and promoted "M1" polarization of microglia. mtDNA induced the activation of the cGAS-STING and IRF3/NF-κB signaling pathways. In turn, repressing STING via C-176 treatment markedly suppressed microglial mtDNA leakage (95). In the SCI model, the downregulation of mitofusin 2 (Mfn2) in microglia contributed to an imbalanced mitochondrial fusion and division. After that, mtDNA was released from microglia and activated the cGas-Sting signaling pathway (163). Gu et al. reported that oxyhemoglobin (OxyHb) increased cytosolic mtDNA levels in microglia. Microglia-derived mtDNA further activated the AIM2 inflammasome and IL-1β and IL-18 release following oxyHb stimulation. Suppressing AIM2 markedly relieved microglia-mediated neuroinflammation after ICH (164). Treatment with recombinant fibroblast growth factor 21 (rFGF21) improved neurological deficits and neural apoptosis by relieving microglia-mediated neuroinflammation. Specifically, rFGF21 restrained

microglial mtDNA release into the cytoplasm, thus dampening the activation of the cGAS-STING pathway (165). In copper-induced damage to astrocytes, mitochondrial ROS (mtROS) levels are increased, resulting in mitochondrial damage and mtDNA release into the cytoplasm. mtDNA activates the cGAS-STING pathway and induces NLRP3 inflammasome-associated pyroptosis (96). Therefore, mtDNA is considered a potent activator in both microglia and astrocytes.

3.4 S100 family members

There are more than 20 S100 family members. Among them, S100 calcium-binding protein B (S100B) is a Ca^{2+}-binding protein that is concentrated mainly in astrocytes and is selectively expressed in neurons and peripheral cells, where it exerts differential effects (166). S100B levels in the CSF and blood are significantly elevated following TBI or stroke and are associated with the severity of brain injury. Thus, S100B has significant potential as a diagnostic biomarker in these diseases (167–169). Moreover, increasing evidence now points to S100B as a DAMP that triggers a tissue reaction to damage (170) (Figure 5). The biological functions of

S100B in neurons in SAH are strongly linked to its concentration, leading to either neuroprotection or neurotoxicity (171). S100B is involved in cerebral vasospasm and brain damage in SAH (172–174). The S100B level is consistent with the development of reactive astrogliosis, and its role in mediating oxidative stress and neuroinflammation has been identified. For example, S100B expression and autocrine signaling in astrocytes are promoted by minimal hepatic encephalopathy in rats. Upon S100B stimulation, VEGF autocrine expression is facilitated and further contributes to the interaction between VEGFR2 and COX-2. The NF-κB pathway is activated, which eventually leads to inflammation and oxidative stress in MHE astrocytes (175). When astrocytes are stimulated by S100B, they are polarized into a proinflammatory phenotype with enhanced expressions of TLR2, inducible nitric oxide synthase (iNOS) and IL-1β. Thus, oxygen-glucose deprivation-induced neuron death is significantly aggravated. Moreover, S100B promotes the NF-κB pathway activation dose-dependently and upregulates endogenous RAGE in astrocytes (176). Moreover, high S100B stimulates microglial migration via the upregulation of chemokines (CCL3, CCL5, and CXCL12) and chemokine receptors (CCR1 and CCR5), which are dependent on RAGE expression (97). The proinflammatory reactions of microglia can

FIGURE 5
DAMPs of peroxiredoxin family members and S100 family members on astrocyte and microglia activaton. S100B binds TLR2 and TLR4 on astrocytes and promotes NF-κB activation. Elevated peroxiredoxins (1,2, 6) bind TLR2, TLR4, and RAGE on microglia and induce the proinflammatory reactions of microglia. BBB, blood-brain barrier; CCL, Chemokine C-C motif chemokine ligand; CXCL, C-X-C chemokine ligand; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; NO, nitric oxide; TLR, toll-like receptor; TNF-α, tumour necrosis factor-alpha.

also be accelerated by S100B/RAGE-dependent activation of the JNK and NF-κB pathways (98).

In addition to S100B, other S100 family members show significant alterations in ICH. For example, the level of calprotectin, a stable heteromorphic dimer complex of S100A8 and S100A9, was significantly greater in SAH patients than in healthy controls. Higher calprotectin levels predict poorer prognosis in SAH patients, and they are related to delayed cerebral ischemia and the complications of secondary pneumonia (83). Elevated levels of S100A12 are correlated with increased inflammation, greater hemorrhagic severity, and higher short-term mortality in patients with ICH (84, 177). S100A8/A9 and S100A12 represent prototypes of DAMPs in multiple diseases, such as myocardial infarction (178), COVID-19 (179), and atopic dermatitis (180). Recruited neutrophils to the infarct lesions produce specific alarmins of S100A8 and S100A9, which bind to TLR4 and prime the NLRP3 inflammasome activation in naïve neutrophils (178). S100A8 and S100A9 are also involved in intracranial hemorrhage (181–183). For example, S100A8 was significantly upregulated in microglia following SAH or OxyHb administration. Specific microglial S100A8 downregulation attenuated expressions of ferroptosis-related genes (including *ALOX15, ACSL4, PTGS2, NOX2* and *NOS2*), production of lipid peroxidation products, and ROS in microglia, and also relieved neural function deficits and neuronal apoptosis in SAH mice (181). Knocking out S100A9 exerted neuroprotective effects in SAH mice and mitigated SAH-induced neurogenic pulmonary edema (NPE). The TLR4/MYD88/NF-κB signaling pathway and the expression of inflammatory molecules (IL-1β and TNF-α) are downregulated by the knockout of S100A9 (182). Compared with those in the superficial temporal arteries, the gene levels of S100A8, S100A9, and S100A12 were upregulated in the aneurysmal domes of ruptured intracranial aneurysms. These three genes are associated with inflammatory and immune responses and phagocytosis (183). Recently, Wang et al. suggested that SAH patients had significantly higher CSF S100A9 level. S100A9 protein can activate the TLR4-NF-κB pathway and increase the activation of inflammation, and ultimately aggravate nerve injury (184).

3.5 Peroxiredoxin family members

Peroxiredoxins (Prxs, also known as PRDXs), a group of sulphhydryl-dependent peroxidases, have been identified as immune-modulating DAMPs in mammals (185). At least 6 PRDX family members (PRDX1-6) have been identified, all of which are altered during ischemic stroke or ICH (99, 186–190) (Figure 5). PRDX1 is believed to be a significant form of PRDX that is induced by hemorrhagic stress during the acute and subacute stages of ICH. Exogenous PRDX1 enhances the production of proinflammatory mediators (NO, TNF-α, and IL-6) in macrophages by activating the TLR4–NF-κB p65 axis. Within 72 hours of ICH, murine neurological deficits, cerebral edema, and various neuropathological changes, including neuron injury,

activation of astrocytes and microglia/macrophages, as well as invasion by neutrophils and T lymphocytes, are induced by ICH. Moreover, ICH stimulates PRDX1 expression and extracellular release (191). PRDX2 expression is elevated in the CSF of SAH patients and is associated with brain injury and prognosis (192). Prx2 can cause brain injury following ICH by inducing brain swelling, microglial activation, neutrophil infiltration, neuronal death, and neurological deficits via the TLR4/NF-κB pathway (193). PRX-2 upregulated lipocalin-2 (LCN-2) in ICH mice. However, LCN-2 knockout partly reduced the effects of PRX-2 on neutrophil infiltration and microglia/macrophage activation and ultimately brain damage (194). PRDX3 is located mainly in the mitochondria of neurons. Neuronal overexpression of PRDX3 prevents neuronal death via the mitochondria-mediated pathway in SAH rats (188). Following ICH, Txnrd2, Trx2 and Prx3 were increased in neurons and astrocytes. Txnrd2 downregulation facilitates ROS production, peroxidation and endoplasmic reticulum stress, which are associated with reduced Trx2 and Prx3 expression (195). Similarly, overexpression of Prx4 or Prx5 reduces BBB damage and has antioxidative stress and antiapoptotic effects in ischemic stroke and SAH models (189, 190). The release of astrocyte-produced PRDX6 contributes to neuroapoptosis in ischemic stroke (99). PRDX6 is expressed mainly in astrocytes, and PRDX6-phospholipase A2 (iPLA2) is involved in the activation of astrocytes and microglia. Further investigations revealed that PRDX6-iPLA2 worsens the production of ROS and activation of microglia caused by astrocytes through the activation of mitochondrial fission pathways dependent on Nox2 and Drp1 (100).

3.6 Other DAMPs

In addition to the abovementioned DAMPs, there are other DAMPs whose expression is elevated during stroke. These DAMPs, such as heat shock protein (HSP)70 (196), cold-inducible RNA-binding protein (CIRP) (197), and IL-33 (198), are significantly associated with the outcomes of stroke patients. These DAMPs have diverse functions, including mediating neuroinflammation, neuronal and endothelial cell damage, BBB integrity, and microglial and astrocytic activation (199–203). For example, CIRP levels are increased in the blood of ICH patients and are associated with poorer clinical outcomes. Knocking out CIRP significantly attenuated brain edema; neurological deficits; and the expression of proinflammatory cytokines (including IL-6, TNF-α, and IL-1β) and TLR4-NF-κB signaling (199). Neural-specific CIRP KO prevented neuronal apoptosis and alleviated glial cell activation in TBI mice. Neruon-derived secretion of extracellular CIRP (eCIRP) contributes to neural damage and glial-mediated inflammation (204). Histone H3 is one of the core histones responsible for binding DNA and regulating gene expression within the nucleus. Histone H3 can be released into the extracellular space by activated or damaged cells, where it then acts as a DAMP and triggers immune responses by interacting directly with TLRs and RAGE (205).

4 Crosstalk between microglia and astrocytes in SAH

Microglia are among the first nonneuronal cells on the scene of the innate immune response to ICH (206). Neves and colleagues also reported that the number of CD11+ microglia in the ipsilesional striatum and sensorimotor cortex was increased 6 h after ICH. The number of glial fibrillary acidic protein (GFAP)+ cells in the ipsilesional striatum increased 24 h after ICH. However, in the ipsilateral sensorimotor cortex, the number of GFAP+ cells was reduced 6 h after ICH, then gradually increased and peaked at 7 days post-ICH (207). Astrocyte–microglia communication can significantly affect their activation state, leading to further enhanced activation or attenuated activation. DAMPs and many other bioactive molecules are involved in their interaction, including cytokines, chemokines, chemokines, innate immune mediators (such as C3), growth factors, mitogenic factors, NO, reactive oxygen species, MMPs, neurotransmitters, gliotransmitters, tissue damage molecules (such as ATP), and metabolic mediators (such as glutamate and lactate) (208) (Table 3, Figure 6). Although most of these bioactive molecules can be expressed by both microglia and astrocytes, their expression levels, as well as their temporal and spatial characteristics, are significantly different after ICH (209–212).

4.1 Inflammatory cytokines

Following SAH, many inflammatory cytokines are elevated in the serum and CSF, including proinflammatory cytokines (e.g., IL-1α, IL-1β, IL-2, IL-6, IL-8, IFN-γ, TNF-α, IL-15, IL-17, and IL-18) and anti-inflammatory cytokines (e.g., IL-Ra, IL-4, IL-13, IL-10, and TGF-β) (Table 1). IL-1α and TNF-α are two representative neurotoxic cytokines produced by microglia in SAH (213, 214). Activated microglia exhibit increased release of IL-1α, TNF and C1q, which together promote A1 polarization of astrocytes and induce the death of neurons and oligodendrocytes (215). Administration of an IL-1 receptor antagonist (IL-1Ra) mitigated BBB breakdown in an SAH rat model. In addition, IL-1Ra completely reversed heme-induced cellular injury in organotypic slice culture (OSC) by blocking IL-1 signaling (214). Pure microglial cultures, but not pure astrocyte cultures, released IL-1ra in response to treatment with CM from injured primary neurons. Endogenous IL-1ra produced by microglia is neuroprotective in cerebral ischemia or excitotoxicity (216).

IL-1β and IL-18 are also members of the IL-1 family. These two proinflammatory factors can be released from activated microglia and astrocytes, where they mediate neurotoxic effects and BBB damage during ICH (217–219). The cultured human fetal astrocytes exhibit significant reactions to IL-1β produced by human fetal
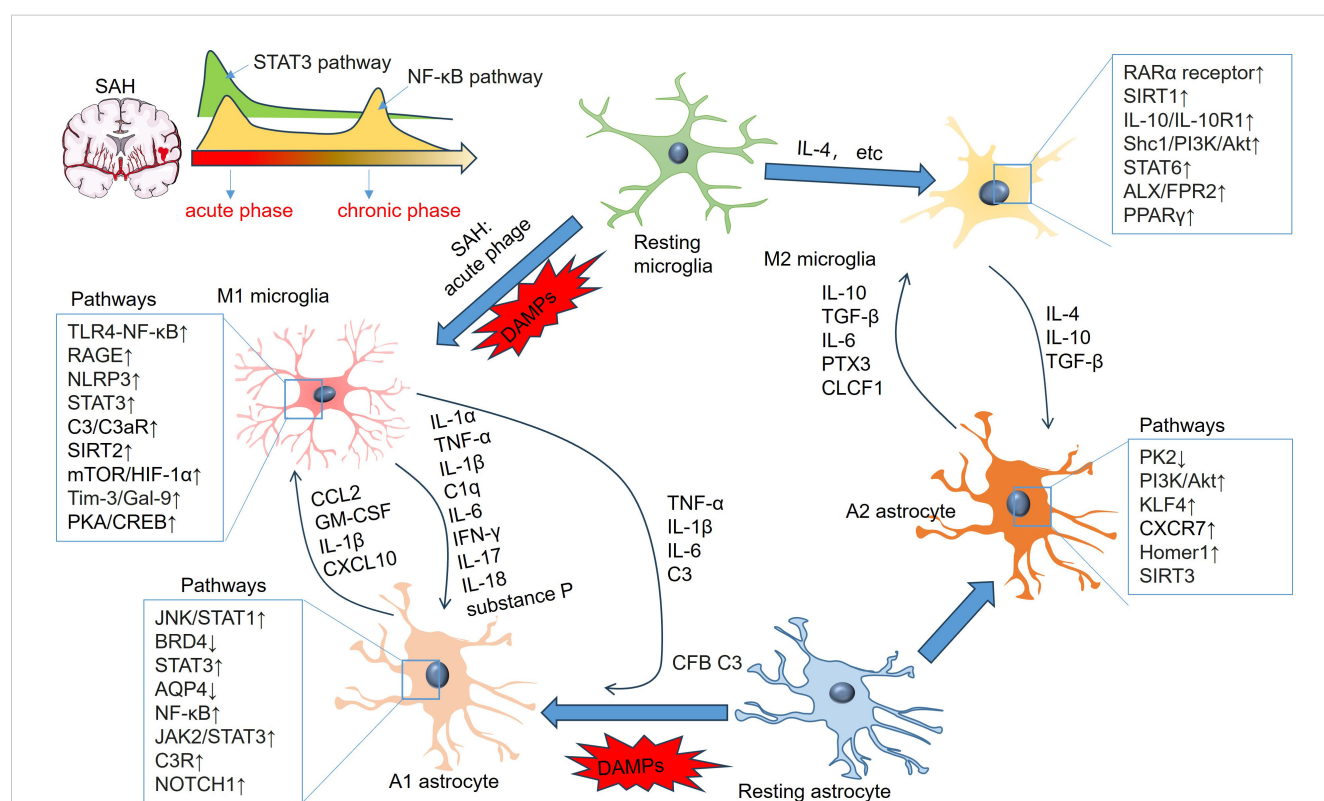

FIGURE 6
Signaling pathways involving microglial and astrocytic activation and inflammatory mediators in astrocyte-microglia crosstalk. "M1" microglia-produced TNF-α, IL-1β, IL-6, IFN-γ and IL-17 induce "A1" polarization of astrocytes. "A1" astrocytes-produced CCL2, IL-1β, and CXCL10 also mediate the proinflammatory reactions of microglia. "M2" microglia produce IL-4, IL-10, TGF-β and substance P, which promote "A2" polarization of astrocytes. "A2" astrocytes produce elevated IL-10, TGF-β, IL-6, PTX3, and CLCF1, which can mediate "M2" polarization of microglia.

microglia, but not the primary stimulus LPS (220). HMGB1 indirectly upregulates AQP4 expression in astrocytes through diffusible factor(s), such as IL-1β from microglia (87). These two studies indicate that astrocyte activation may be a secondary consequence of microglial activation. In an SAH rat model, the neutralization of IL-1β activity markedly attenuated the increase in the S-100B level (an astrocyte) and the number of leukocytes migrating into the CNS (221). IL-33 is another member of the IL-1 family (222). In the microglia–astrocyte circuit, IL-33 is produced by astrocytes, which activate ST2–AKT signaling in microglia, thus supporting microglial metabolic adaptation and phagocytic function during early development (223). Following SAH, IL-33 was primarily expressed by neurons and astrocytes rather than by microglia. Additionally, there is a notable correlation between the expression of IL-33 and IL-1β (224). In an ICH rat model, IL-33 attenuated short-term and long-term neurological deficits by reducing neuronal degeneration and transforming the "M1" to "M2" polarization of microglia (225). The results suggest that IL-33 could have a significant impact on the inflammatory reaction after SAH.

LPS (100 ng/ml) was treated with primary astrocytes and microglia for different durations (8 h or 24 h). Short-term LPS exposure induced bidirectional polarization of both microglia (M1 and M2) and astrocytes (A1 and A2). A longer duration of LPS exposure enhances proinflammatory and neurotoxic microglial and astrocytic polarization (M1/A1). However, the administration of IL-1 antagonists had no significant effect on the modulation of specific microglia or astrocyte activation pathways, suggesting that there are other mediators involved in microglia–astrocyte interactions (226). Recently, Shi et al. reported that IL-15 was significantly elevated in astrocytes from patients with ICH and wild-type mice subjected to experimental ICH. Brain water content and neurological disorders were facilitated by astrocytes with enhanced IL-15 expression, accompanied by increased microglial accumulation near astrocytes in perihematomal tissues. Moreover, there was a significant increase in microglial expression of CD86, IL-1β, and TNF-α in GFAP-IL-15[tg] mice after ICH. Additionally, the worsening of ICH injury in GFAP-IL-15[tg] mice was reduced by depleting microglia. The study showed that IL-15 plays a role in the communication between astrocytes and microglia, leading to worsened brain injury after ICH (227).

As a proinflammatory cytokine, IL-6 not only plays a major role in the pathobiology and pathophysiology of aneurysm formation and aneurysmal SAH (aSAH) but also has a close correlation with DCI/vasospasm and secondary brain injury (228). In the brain, IL-6 release is closely tied to reactive astrocytes, which are critical for blood product breakdown following SAH (229). Recently, Lucke-Wold et al. reported that IL-6 expression was elevated and peaked 3 days after SAH. Knocking out IL-6 in mice significantly mitigated vasospasm, secondary cascades, and the reduction in cerebral blood flow after SAH. The infiltration of macrophages occurred in regions of vasospasm adjacent to regions of microglial activation and increased the expression of IL-6 receptors. IL-6 blockade prevented vasospasm, improved neurologic performance,

inhibited "M1" polarization of microglia, and enhanced "M2" polarization. In addition, they indicated that the release of IL-6 at the endothelial border next to reactive astrocytes led to an elevation in Caveolin 3 levels. Caveolin 3 facilitates the BBB's preparation for peripheral macrophage diapedesis (230).

Several anti-inflammatory cytokines, such as IL-4, IL-10 and TGF-β, play essential roles in microglia–astrocyte interactions (231, 232). Following SAH, IL-4 can mediate hematoma resolution through activating STAT6/ST2 signaling in microglia/macrophages (233), and IL-10 has similar functions by regulating CD36 (124). IL-10-redirected astrocytes can relieve the activation of microglia by suppressing IL-1β expression and upregulating CX3CR1 and interleukin 4 receptor-α (IL-4Rα) in microglia. IL-10-mediated effects depend on astrocyte-derived TGF-β (234). Interestingly, Taylor et al. reported that TGF-β1 administration dampened the inflammatory reactions of microglia and improved functional outcomes in an ICH murine model (235). These authors suggested that astrocytes might provide an early source of TGF-β1 that initiates phenotypic modulation in microglia, considering that astrocytic TGF-β1 can restrain neuroinflammation and motor function deficits in an ischemic stroke mouse model (236).

There are more cytokines that mediate the interaction between microglia and astrocytes in other CNS diseases. For example, astrocyte-derived IL-3 induces microglia to undergo transcriptional, morphological, and functional changes that equip them with a rapid immune response, improved movement abilities, and the capability to gather and remove Aβ and tau accumulations. Thus, AD pathology and cognitive decline can be significantly mitigated (237). Following acute SCI, TLR4/p38 MAPK signaling promotes the production of elevated IL-18 by microglia, which stimulates IL-18R on astrocytes. IL-18R increases phosphorylated NF-κB level in astrocytes and causes GFAP upregulation (238). Radiation significantly promoted the expression of TNF-α, IL-1β and ICAM-1 in primary microglia. Lonizing radiation failed to induce ICAM-1 expression in astrocytes without microglia-produced TNF-α and IL-1β, suggesting that microglia-derived proinflammatory cytokines may be necessary for ICAM-1 expression in astrocytes during CNS radiation injury (239).

4.2 Chemokines

In patients with SAH, many chemokines, including CCL2, CCL4, CCL5, CCL7, CCL11, CCL13, CCL19, CCL20, CXCL1, CXCL5, CXCL6, CXCL8, CXCL12, and CXCL16, are upregulated in the CSF or serum. These chemokines are associated with poorer outcomes in SAH patients, indicating their potential roles in SAH pathology (31–34). Astrocytes play a major role in producing various chemokines, including CCL2, CXCL1, CXCL10, and CXCL12, while microglia express certain chemokine receptors like CCR2 and CXCR4 (216), which implies a strong association between microglia and astrocytes.

The CCL2–CCR2 chemotactic system is one of the major signaling pathways that induces inflammation and apoptosis in

the brain. Jin et al. conducted an *in vitro* study and reported that TNF-α stimulated CCL2 release from astrocytes. The conditioned medium of TNF-α-stimulated astrocytes increased the "M1" polarization and migration ability of microglia. The above effects were significantly reversed by knocking down CCL2 in astrocytes or inhibiting CCR2 in microglia (240). They later confirmed the involvement of the CCL2–CCR2 pathway in astrocyte–microglia interactions in rats with surgery-induced cognitive dysfunction. Targeting CCL2-CCR2 signaling significantly inhibited astrocyte-mediated microglial activation (241). In a collagenase-induced ICH mouse model, knocking out CCL2 or CCR2 can significantly decrease hematoma volume, BBB damage, microglial activation/migration, and leukocyte and neutrophil infiltration (242). Sphingosine-1-phosphate receptor 3 (S1PR3) and its ligand, sphingosine 1-phosphate (S1P), are dramatically increased following ICH. S1P upregulated the expression of CCL2 in astrocytes. CAY10444 (an S1PR3 antagonist) significantly attenuated CCL2 in astrocytes, improved neurological functions and BBB integrity, and suppressed microglial proliferation and M1 polarization in SAH rats (243).

CXCL10 is a vital chemokine produced by activated A1 astrocytes. A1 astrocyte-secreted CXCL10 enhances STAT3 phosphorylation in neurons via CXCR3, leading to ferroptosis-associated lipid peroxidation in epileptic brains (244). In the cuprizone model, CXCL10, CCL2, and CCL3 are three chemokines with distinct alterations. CXCL10, which is produced mainly by astrocytes, participates in the initiation of microglial activation. Early microglial activation was significantly reduced only in CXCL10-deficient mice but not in CCL2- and CCL3-deficient mice (245). Inhibiting astrocytic P2Y(1)R suppressed CXCL10 expression in astrocytes, thus decreasing infarct volume and improving motor functions in rats with cerebral ischemia (246). In the ICH mouse model, treatment with the colony-stimulating factor-1 receptor antagonist GW2580 repressed the proliferation and inflammatory response of microglia, after which astrocytes became activated and produced elevated CXCL10 around brain lesions. The CXCL10/CXCR3 axis is essential for the brain homing of regulatory CD8+CD122+ T cells, which exert synergistic anti-inflammatory effects with microglia (247).

CCL5 plays a critical role in initiating the intrinsic neuronal regeneration system following brain injury (248). CCL5 was among the genes whose expression was upregulated the most in astrocytes activated by IL-1α, TNFα, and C1q treatment. Following hemorrhagic stroke, CCL5 expression is elevated in the mouse brain. Knocking out CCL5 in astrocytes improved neurobehavioral outcomes and improved BBB integrity (249). CCL5 can enhance the proinflammatory reactions of microglia, as evidenced by both *in vitro* and *in vivo* experiments (250, 251). CCL5 and CCR5 (C-C chemokine receptor 5) expression increased after ICH and peaked at 24 hours. CCR5 was positively expressed in neurons, microglia, and astrocytes. CCL5/CCR5 axis activation aggravated neurological deficits in ICH mice by mediating neuronal pyroptosis, BBB disruption, and the activation of microglia, astrocytes and monocytes, partially through the CCR5/PKA/CREB/NLRP1 signaling pathway (252, 253).

4.3 Innate immune mediators

As vital mediators in the innate immune system, complement components have essential roles in several neurological disorders. The activation of this pathway occurs when the recognition protein C1q from the complement binds to the cell surface, resulting in the activation of C3 convertase and the cleavage of C3 into C3a and C3b fragments (254). In the CNS, C1q is principally produced by microglia, and C3 is produced by activated astrocytes (219, 255). Microglia-produced C1q can induce the A1 neurotoxic phenotype of astrocytes, which then produces elevated C3 and contributes to increased microglial activation via the C3–C3aR pathway (254). The microglia-mediated C3-C3aR pathway plays a crucial role in neuroretinal development by regulating developmental astrocyte and vascular network spatial patterning (256). Several studies have shown that intervening in C1q/C3-C3aR pathway-mediated astrocyte–microglia crosstalk has high potential for treating Parkinson's disease (257), posthemorrhagic hydrocephalus (PHH) (258), neuropathic pain (259, 260), and Alzheimer's disease (261).

Notably, excessive complement activation, including C1q/C3-C3aR signaling, also plays a prominent role in ICH (262). Higher complement C1q levels are associated with poorer outcomes in patients with acute ICH (263). Elevated C3a in the CSF correlates with delayed ischemic neurological deficits in SAH patients via activation of the coagulation system (264). C3 deficiency or C3aR inhibition effectively alleviated neurological deficits, brain edema, erythrolysis, inflammatory cell infiltration, and neuroinflammation following SAH (265–267). For example, inhibition of C3aR decreased abnormal microglial activation by reducing p53-induced death domain protein 1 (Pidd1) and protein kinase RNA-like ER kinase (PERK). In the subacute phase of SAH, intranasal administration of C3a, a proteolytically activated peptide of the complement component C3, significantly enhances "M2" polarization of microglia, suppresses astrocyte reactivity and improves cognitive function (268). Therefore, C3-C3aR signaling might also be involved in microglia–astrocyte crosstalk in SAH.

4.4 Growth factors

Several growth factors, such as insulin-like growth factor 1 (IGF1) (269) and VEGF (270), are involved in the pathologies of SAH, and they are potential mediators of microglia–astrocyte crosstalk. In a tri-culture composed of neurons, astrocytes, and microglia, microglia presented elevated IGF-1 expression and reduced caspase 3/7 activity. In response to LPS stimulation, astrocyte hypertrophy and neuron apoptosis are promoted by microglia, which increase the secretion of proinflammatory cytokines (e.g., TNF, IL-1α, IL-1β, and IL-6). During glutamate-induced excitotoxicity, microglia play a significant neuroprotective role in tri-culture by relieving reduced neuron loss and astrocyte hypertrophy (271). During the early stage of ICH, sustained microglial depletion induces disorganized astrocytic scarring, aggravates neutrophil infiltration, and impairs tissue repair.

Spatial transcriptomics (ST) analysis revealed that IGF1 produced by microglia mediates protective astrocytic scar formation, which is further facilitated by repopulating microglia (RMs). During the chronic stage of ICH, astrocytic scars exhibit destructive functions instead of primary protective effects. Delayed microglial depletion could partly reverse this phenomenon (210). Microglia play different roles in modulating proinflammatory and neurotoxic activities in astrocytes by producing TGFα and VEGF-B in an experimental autoimmune encephalomyelitis (EAE) mouse model. TGFα produced by microglia limits the pathogenic activities and development of EAE by acting through the ErbB1 receptor in astrocytes. On the other hand, VEGF-B released by microglia worsens EAE by activating FLT-1 signaling in astrocytes (272). In ischemic stroke, astrocyte-derived VEGFD, which acts on VEGFR3 in astrocytes and microglia, contributes to crosstalk dysfunction and proinflammatory activation of these two types of glial cells, thereby mediating neuronal damage (273). Hypertonic saline (HS) alleviates ischemic blood–brain barrier permeability in a cerebral ischemia rat model by suppressing the NLRP3/IL-1β signaling axis in microglia. In addition, HS inhibited VEGF expression in astrocytes by restraining the activation of the IL-1β/IL-1R1/NF-κB signaling pathway (274).

4.5 Extracellular vesicles

EVs have gained tremendous attention for the diagnosis and treatment of CNS disorders. EVs play important roles in intercellular communication, reparative processes, and as potential drug delivery vehicles. Due to their lipid membranes, EVs can easily cross the BBB and establish communication with target neurons and glia deep within the brain (275). Omics analysis revealed that many microRNAs (miRNAs) and proteins can be delivered by EVs, and their alterations are regarded as hallmarks of SAH (276–278). The administration of blood-derived EVs improved recovery after ICH (279). EV-enriched serum amyloid A1 (SAA1) is significantly increased in EVs from the plasma of ICH patients. SAA1 stimulation exacerbates neuroinflammation by increasing the accumulation of microglia and astrocytes (280). Previous studies have shown that EVs play a vital role in astrocyte–microglia communication (281, 282). For example, reactive astrocytes produce dual immunoglobulin domain-containing cell adhesion molecules (DICAMs), which are mainly secreted via extracellular vesicles (EVs). EV-delivered DICAM plays a significant role in modulating neuroinflammation by transforming microglia into the M2 phenotype (283). A2-reactive astrocyte-derived exosomes, which highly express miR-628, significantly attenuate pyroptosis and BBB damage following ischemic stroke and promote M2 microglial polarization (284). Following TBI, astrocyte-produced exosomes are enriched with miR-873a-5p, which mediates M2 microglial polarization by regulating extracellular regulated kinase (ERK) and NF-κB pathways (281). Homer scaffolding protein 1 (Homer1) has been found to play a protective role in ICH via the phenotypic conversion (A1 to A2) of astrocytes (285) as well as microglial activation (286).

A2 astrocytes can produce EVs that contain high levels of Homer1a. EV-encapsulated Homer1a enhanced the conversion of A1 to A2 astrocytes in ICH mice, improved neurological functions and reduced neuronal injuries through repressing the RAGE/NF-κB/IL-17 signaling pathway (287).

4.6 MMPs

Following SAH, MMPs exhibit altered expression and play a paramount role in pathological processes, such as BBB disruption, neuroinflammation and neuronal damage (39, 288–290). Knocking out TLR2 markedly attenuated MMP9 expression in astrocytes, thus mitigating BBB damage, neutrophil infiltration, and proinflammatory gene expression in brain lesions (291). Recently, Feng et al. reported that increased MMP-9 was derived mainly from reactive astrocytes after SAH. Downregulating NDRG2-PPM1A signaling inhibited MMP-9 expression in astrocytes after SAH and attenuated BBB damage (52). In the ICH mouse model, the expression of extracellular matrix metalloproteinase inducer (EMMPRIN) and MMP9 was elevated in both GFAP-labeled astrocytes and Iba1-labeled microglia. EMMPRIN inhibition by an anti-EMMPRIN (CD147) monoclonal antibody exhibited neuroprotective effects by suppressing MMP9 (292). The dipeptidyl peptidase (DPP4) inhibitor omarigliptin markedly decreased hematoma formation, neurobehavioral deficits, microglial/macrophage activation and neutrophil infiltration in ICH mice by repressing DPP4 expression. Omarigliptin also decreased the expression of DPP4 and MMP9 and inhibited CX43 expression in astrocytes (293). Therefore, MMP9 might be a potential mediator involved in astrocyte–microglia crosstalk in SAH.

4.8 Other bioactive molecules

OPN is a multifunctional extracellular matrix glycoprotein that is significantly induced in reactive astrocytes and capillary endothelial cells and peaks at 72 hours after SAH. OPN is necessary for repairing disrupted BBB after SAH (294). The administration of recombinant OPN has shown therapeutic effects by modulating diverse pathological processes in SAH, such as brain edema (295), neuroinflammation (296) and neutrophil infiltration (297). Notably, OPN altered microglial activation states from "M1" to "M2" polarization (296). Hematogenous macrophages infiltrating the inner border zone of infarcts can produce OPN and promote reestablishment of the BBB after ischemic stroke by mediating reactive astrocyte polarization (298).

Lipocalin-2 (LCN2) is a neutrophil gelatinase associated-lipocalin of the lipocalin superfamily. LCN2 can be produced by neurons as a "help-me" signal in the stroke-damaged brain. LCN2 can mediate microglia and astrocyte activation (299). In addition, astrocytes, as well as invading immune cells, are important sources of LCN2 in the peri-infarct region of the rat brain after ischemic stroke (300). LCN2-treated microglia presented increased IL-10

release and increased phagocytosis. In astrocytes, LCN2 upregulated BDNF and thrombospondin-1. The conditioned media from LCN2-treated microglia and astrocytes protected neurons against oxygen–glucose deprivation (299). Following SAH, microglia, astrocytes, and neurons all presented elevated LCN2 expression, which plays hazardous roles by mediating microglial ferroptosis-induced neural injury (301). The LCN2 receptor 24p3R is expressed in oligodendrocytes, astrocytes, endothelial cells, and pericytes in the white matter. LCN2 knockout improves BBB disruption caused by SAH (302). In addition, inhibiting the expression of microglial LCN2 early could help reduce ferroptosis-induced harm to oligodendrocytes and related neurological impairments, presenting a hopeful neuroprotective approach after ICH (303). Together, LCN2 might be a vital mediator of glial cell crosstalk in SAH.

4.9 Metabolic interactions

The brain is one of the most energy-consuming organs in the body. Astrocytes are considered an essential source of blood-borne glucose or its metabolites to neurons. Astrocytes and microglia can produce a large amount of mitochondrial ROS and transport glycolytically derived metabolites, like L-lactate, L-serine, and glutamate to neurons. These metabolites support energy requirements, maintain the balance of oxidation-reduction reactions, and influence neurotransmitter-receptor activity (304, 305). Following SAH, alterations in cerebral metabolism occur, along with the buildup of metabolites including glucose, lactate, pyruvate, and glutamate. These phenomena might disrupt oxidative metabolism within the brain. Such disruption can trigger secondary brain damage and is associated with an unfavorable prognosis (306–308). For instance, a decline in glucose levels and a sharp increase in glutamate were observed prior to the onset of DCI after SAH, accompanied by elevations in the lactate/pyruvate and lactate/glucose ratios. When cerebral microdialysis (CMD) monitoring was carried out outside the lesion area, the surge in glutamate was not evident, yet significant changes were still noted in glucose levels and the lactate/glucose (L/G) ratio. Therefore, glucose and the L/G ratio have the potential to prompt additional diagnostic evaluations or therapeutic interventions at an earlier stage (309).

Glucose transporter-1 (GLUT1) is the main astrocyte glucose transporter. Astrocytic GLUT1 has a pivotal role in mediating astrocyte insulin signaling and brain purinergic signaling, which are essential for sustaining metabolic and antioxidant support for neurons, and improving brain function and systemic glucose metabolism (310). Astrocyte-specific deletion of GLUT1 does not affect sensorimotor and memory functions in male mice suffering stroke. Astrocytes with GLUT1 deletion maintain normal resting glucose levels but exhibit a more than two-fold increase in glucose consumption, indicating enhanced metabolic activity (311). GLUT1 exhibits higher expression in microglia with LPS + IFNγ treatment. It acts as a main mediator in controlling glucose uptake and facilitating glycolysis in microglia, particularly under inflammatory conditions (312). After ICH, reduced glucose uptake of microglia was observed in

the perihaematomal region. The downregulation of GLUT1 and HK2 in microglia resulted in a reduced amount of glucose-6-phosphate (G-6-P), impaired early-stage glycolysis, and proinflammatory reactions of microglia after ICH (313). Elevated lactate can be produced by activated microglia. Its concentration is significantly increased in the core and penumbra regions of hemorrhagic foci (314). Lactate is not only beneficial for the proliferation, cell survival, migration, and phagocytosis property of the microglia (314), but also protects neurons from oxygen and glucose deprivation/reoxygenation (OGD/R) injury (315). Normally, lactate is transferred from astrocytes to neurons to match the neuronal energetic needs, and to provide signals that modulate neuronal functions, including excitability, plasticity and memory consolidation. However, increased brain lactate derived from astrocytes aggravates ischemic brain injury (316). Elevated lactate levels in stroke patients are inversely correlated with astrocytic mitochondria, which might affect astrocyte-to-neuron mitochondria transfer (317). Those studies suggest that lactate and other metabolites have potential roles in microglia-astrocyte crosstalk.

Pyruvate Kinase M2 (PKM2), a key glycolytic enzyme, has an essential impact on glial metabolic reprogramming and subsequent neuroinflammation (318, 319). PKM2 localizes in the cell body of neurons and mediates high levels of aerobic glycolysis, thus protecting against oxidative stress (320). In astrocytes, PKM2 is crucial for the astrocyte-neuron lactate shuttle, which helps maintain energy metabolism in neurons (319). PKM2 is upregulated in microglia in multiple CNS disorders, including ischemic stroke (321), TBI (322), and ICH (323), and it drives metabolic reprogramming, inducing microglial pro-inflammatory polarization and chemotaxis. TEPP-46 is a PKM2 activator by mediating the formation of the PKM2 tetramer and stabilizing PKM2 subunit interactions. In the TBI model, treatment with TEPP-46 improves the interaction between PKM2 and MFN2, enhances mitochondria, and reduces neuroinflammation (322). Following ICH, administering TEPP-46 significantly decreased PKM2 nuclear translocation, repressed the activation of microglia and astrocytes, and improved neurological functions of ICH mice (323). Hypoxia-inducible factor-1α (Hif-1α) mediated the nuclear translocation of PKM2 in ischemia-induced microglia. Therefore, PKM2 affected microglial polarization by associating with acetyl-H3K9 and upregulating the expression of microglial CCL2 in peri-infarct (324). Moreover, PKM2 knockdown inhibited NF-κB pathway-mediated microglial activation and production of inflammatory mediators (including C1q, TNF-α, and IL-1α), followed by reduced astrocyte C3 expression due to the C3-C3aR interaction (325). Collectively, those studies suggest PKM2 as a potential therapeutic target in stroke.

5 Strategies for SAH treatment by mediating astrocyte and microglial activation

After SAH, microglia and astrocytes exhibit a complex and specific response based on the stimulus, involving unique subpopulations of each cell type. Many strategies, including the

use of agonists or antagonists that target immune mediators, related receptors, related signaling pathways, inhibitors of DAMPs, anti-inflammatory drugs, stem cell therapy, and mitochondrial transfer, have been developed to treat SAH through the intervention of astrocytes and microglia (Figure 7).

5.1 Targeting immune mediators and related receptors

Neuroprotective effects can be achieved by administering antagonists of neurotoxic immune mediators or related receptors. For example, microglia-derived IL-1Ra reduced the expression of astrocytic CXCL1 caused by lack of oxygen and glucose, and also hindered the movement of neutrophils. In an ischemic stroke model, neutralizing antibody therapy against CXCL1 or the administration of recombinant IL-1Ra protein exhibited significant neuroprotective effects (326). Exogenously administered IL-1Ra can suppress IL-1β-mediated microglial astrocytic activation (327). Neurokinin 1 receptor (NK1R) is involved in the inflammatory reactions of microglia and astrocytes by mediating the release of IL-1β, IL-6, and TNF-α (328, 329). Aprepitant is a selective NK1R antagonist with the ability to cross the BBB. Aprepitant treatment significantly promoted hematoma clearance in a mouse model of ICH by suppressing M1 polarization while increasing M2 polarization of microglia (330). Aprepitant also improved the neurological functions of mice with ICH by decreasing neuronal pyroptosis, suppressing the expression of the NLRC4 inflammasome, and inhibiting the release of IL-1β and IL-18 (331). Targeting the S1P-S1PR3 axis could significantly mitigate brain injury by mediating the proinflammatory M1 polarization of microglia (332) and reactive astrocytes (333). Fingolimod (FTY720), an S1P antagonist, significantly decreases edema, apoptosis and brain atrophy in a mouse model of ICH (334) and restrains the expression of ICAM-1, INF-γ, and IL-17 in the brains of mice with ICH (335). CAY10444, an S1PR3 antagonist, significantly suppressed S1PR3, CCL2, TNF-α, and cleaved caspase-3 and relieved neuronal apoptosis following ICH (336). CAY10444 can also inhibit the expression of CCL2, p-p38 MAPK, and ICAM-1 in astrocytes and restrain the M1 polarization of microglia in an ICH model (243).
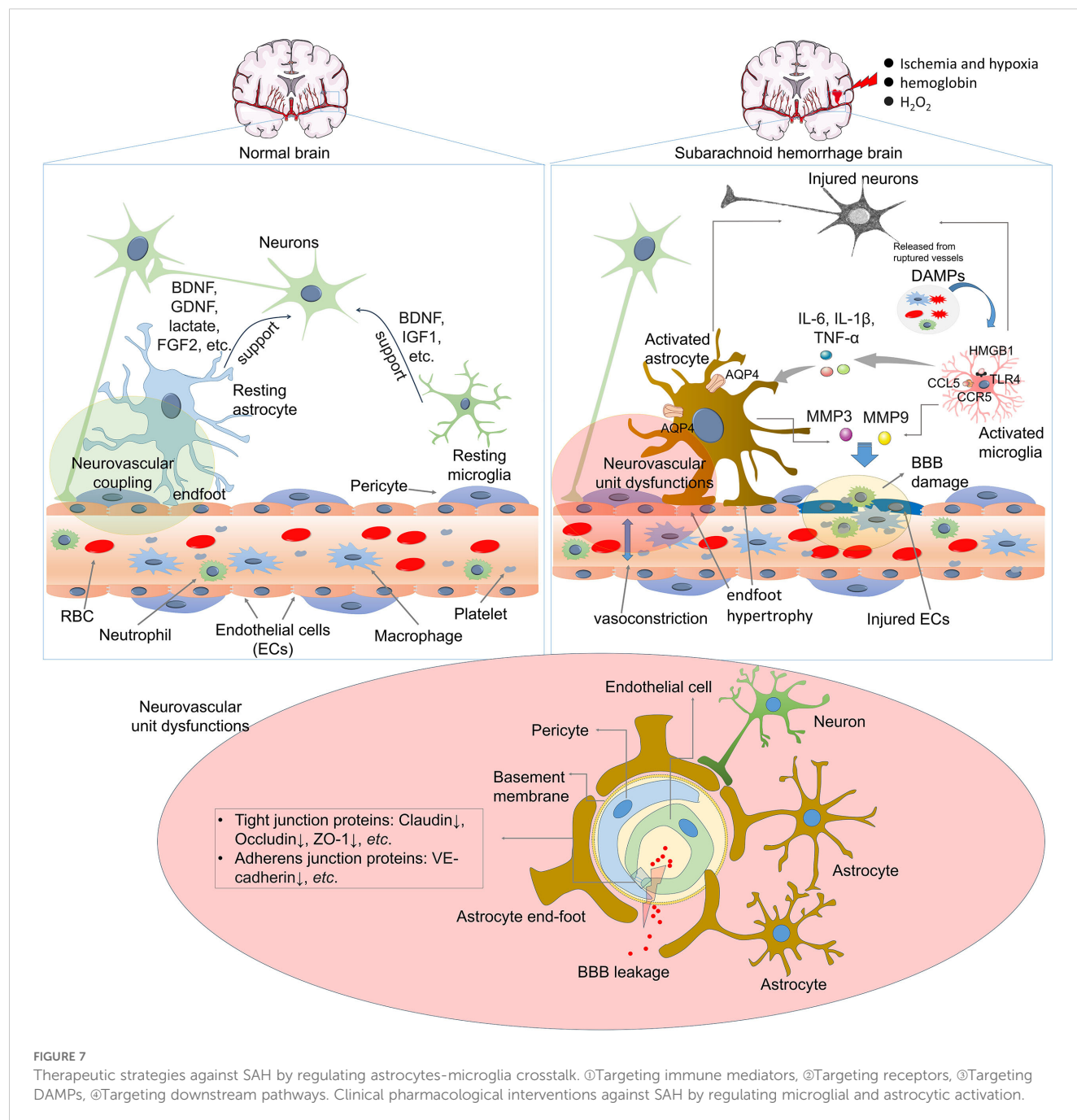
5.2 Targeting DAMPs and related receptors

DAMPs increase inflammation after binding to their cognate receptors on immune cells and underlie early and delayed brain injury after SAH. Thus, strategies have been developed to relieve the detrimental functions of DAMPs (337). Targeting HMGB1 with either an anti-HMGB1 antibody (338) or its inhibitors (e.g., glycyrrhizin) (339) can alleviate hemorrhage-induced brain injury by decreasing brain edema, protecting BBB integrity, reducing microglial activation and neuronal death, and suppressing the expression of inflammatory factors. Targeting RAGE and TLR4,

the two putative receptors of HMGB1, also has beneficial effects on SAH. For example, FPS-ZM1 is a selective RAGE inhibitor that specifically binds to the V domain of RAGE. FPS-ZM1 treatment significantly improved neurobehavioral functions and BBB permeability, inhibited the infiltration of inflammatory cells, and downregulated the expression of IL-1β, IL-6, IL-8R, COX-2, iNOS, and MMP-9 in the perihematoma after ICH (340–342). The TLR4 antagonist TAK-242 dampens neurological deficits and brain edema and inhibits the production of inflammatory factors as well as peripheral inflammatory cell infiltration in an ICH mouse model (343).

In addition to the proinflammatory functions in hemorrhagic stroke models, HMGB1 can also help cerebrovascular repair by regulating endothelial cell functions (337). For example, Hmgb1 is highly expressed in astrocytes at birth and then decreases rapidly during the first two postnatal weeks. Astrocyte-selective ablation of Hmgb1 at birth alters astrocyte morphology and endfoot placement and then disrupts the endothelial ultrastructure. In the adult mouse, a lack of astrocytic Hmgb1 impairs neurovascular coupling and behavior (344). Hayakawa et al. reported that astrocyte-derived HMGB1 helps in neurovascular remodeling, which is mediated by endothelial progenitor cells (EPCs) during stroke recovery (345). Astrocytes increase EPC accumulation in damaged white matter by increasing the migration and tube formation of EPCs. The HMGB1-RAGE axis plays a prominent role in astrocyte-EPC signaling (346). Most recently, Qi et al. reported that low-intensity focused ultrasound stimulation (LIFUS) promoted angiogenesis and synaptogenesis in transient MCAO mice, which was associated with increased HMGB1 expression in the ipsilateral hemisphere of the brain at 14 days after focal cerebral ischemia. Astrocytes were the main cells expressing HMGB1. Inhibition of HMGB1 expression aggravated microcirculation disturbance in the ischemic brain (347). In an SAH rat model, the administration of two HMGB1 inhibitors (including ethyl pyruvate and glycyrrhizin) and the Rage antagonist FPS-ZM1 effectively reduced HMGB1 and Rage expression. However, neurovascular recovery was prevented following those treatments. Oxidized HMGB1 failed to trigger the production of TNF. However, it could enhance brain recovery through the promotion of neurotrophin expression. Instead, recombinant HMGB1 can promote brain injury by stimulating proinflammatory cytokine expression. The authors suggested that HMGB1 in the oxidized state could enhance neurovascular recovery in the late stage of SAH (348). Therefore, HMGB1 functions as a powerful regulator in the processes of brain tissue reconstruction, neurovascular restoration, and inflammatory responses subsequent to SAH. Understanding the dynamics of redox states of HMGB1 holds great promise for its application as a biomarker and in the development of therapeutic strategies for SAH.

Extracellular Hb and heme are scavenged by the acute phase plasma proteins haptoglobin (Hp) and hemopexin (Hx), respectively, thus dampening their deleterious effects (349). As the body's first line of defense against the toxicity of extracellular Hb in SAH, the Hp level is low in the CSF, emphasizing the potential for therapeutic Hp supplementation (350). Functionally, the Hp concentrate was effective in preventing both EBI and cerebral

FIGURE 7

Therapeutic strategies against SAH by regulating astrocytes-microglia crosstalk. ①Targeting immune mediators, ②Targeting receptors, ③Targeting DAMPs, ④Targeting downstream pathways. Clinical pharmacological interventions against SAH by regulating microglial and astrocytic activation.

vasospasm by obstructing the penetration of Hb into brain tissues and enhancing the drainage of free Hb through the lymphatic system in a mouse model of SAH (351).

5.3 Targeting downstream signaling pathways

Many signaling pathways are involved in microglial and astrocyte activation following SAH (Figure 6). Transcription factors, including NF-κB (352, 353), STAT3 (354, 355), and HIF-1α (356, 357), are involved in the transcription of proinflammatory

genes such as TNF-α, IL-1β, and IL-6. In the SAH models, NF-κB activity showed a double elevation and peaks in rabbit brains and cultured neurons. The first NF-κB activity peak (at day 3) is involved in neuronal injury; however, the late peak (at day 10) might have no significant association with damaged neurons (358). The mRNA and protein level of STAT3 was enhanced following SAH, peaking at 24 h post-SAH (359). Over the first 24 hours post-SAH, the phosphorylations of ERK1/2 and STAT3 were enhanced at 1 h and remained elevated at 6 h and 24 h post-SAH. Though phosphorylated calcium calmodulin-dependent kinase II (CaMKII), focal adhesion kinase (FAK), and c-Jun were markedly increased at 1 h post-SAH, their levels were no longer significantly

regulated at 6 h and 24 h (360). Phosphorylated STAT3 at Tyr705 and Ser727 showed different characteristics post-SAH. p-STAT3 at Tyr^{705} had a 2.5-fold enhancement at 2 h after SAH, with a gradual decrease thereafter. Differently, p-STAT3 at Ser^{727} peaked at 1-2 d post-SAH during 1–2 d, then decreased by 7 days (361).

The inhibition of these transcription factors in microglia or astrocytes can significantly improve neurological functions and BBB integrity and mitigate inflammation and immune cell infiltration in animal SAH models. Minocycline is a promising anti-inflammatory, antiapoptotic, and neuroprotective compound for treating various CNS disorders, including SAH (362). Pretreatment with minocycline suppressed microglial/astrocytic activation; downregulated the expression of inflammatory mediators, including S100B, TNF-α, IL-6, iNOS, VCAM-1, ICAM-1, and MMP-9; and repressed TLR4–MyD88 pathway-mediated NF–κB p65 activation. These findings suggest that minocycline modulates neuroinflammatory reactions by interfering with the molecular crosstalk between reactive astrocytes and activated microglia (24). Our group also reported that minocycline relieves neurovascular injury and microglia/astrocyte activation in ICH by mediating multiple signaling pathways, including complement C1q/C3-CR3 signaling (363). Moreover, minocycline significantly modulates the Notch1 signaling pathway (364), TrkB/BDNF pathway (365), and DKK1-Wnt signaling (366) in SAH models. Iron overload in the brain is involved in brain injury after ICH by causing brain edema, neuronal death, and BBB disruption. Minocycline treatment reduced total serum iron and nonheme iron levels in the brain and suppressed ICH-induced upregulation of brain iron-handling proteins and neuronal death (367).

Following SAH, brain cells are exposed to different DAMPs, leading to the concerted activation of multiple inflammasomes, including NLRP3, AIM2, NLRC4, and NLRP1, which mediate the maturation of IL-1β and IL-18 and lead to pyroptosis. Suppressing these inflammasomes can significantly relieve SAH-associated brain injuries (368–371). MCC950 is a selective inhibitor of the NLRP3 inflammasome. MCC950 treatment has neuroprotective effects on SAH by improving the gut microbiota and corticospinal tract (CST) injury (372); relieving neurodeficits, perihematomal brain edema, leukocyte infiltration and microglial activation (373); and preventing early brain injury and delayed cerebral vasospasm (374). Three well-identified neuroprotective agents, resveratrol (375), melatonin (376), and minocycline (377), can prevent SAH-associated brain injury by suppressing NLRP3. Ozanimod, a novel selective S1P receptor modulator, improved the neurological functions of ICH model mice by suppressing microglial and AIM2 inflammasome activation through the regulation of the SIRT3/NF-κB axis (378).

STAT6 and PPAR-γ are two vital microglia-mediated neuroinflammation and efferocytosis factors (379–381). In the ICH model, IL-4-mediated STAT6 signaling activation promoted hematoma resolution and functional recovery (233). The ferroptosis inhibitor ferrostatin-1 (Fer-1) improved neurological function, promoted hematoma absorption, and enhanced the phagocytic function of microglia. Fer-1 mediates M2 polarization of microglia by activating the Fer-1-orchestrating

Janus kinase 1/STAT6 pathway (382). Treatment with the PPAR-γ agonist rosiglitazone or PPAR-γ overexpression further elevated PPAR-γ levels in microglia, reduced proinflammatory cytokines, and increased microglial phagocytosis in premature rabbits with intraventricular hemorrhage (383). On the other hand, STAT6 and PPAR-γ also play vital roles in mediating the inflammatory reactions of astrocytes (384, 385). LPS-stimulated microglia promoted "A1" polarization of astrocytes by releasing IL-1α, TNF-α and C1q. Telmisartan, a PPARγ agonist, reversed the microglia-mediated effects on astrocytes by inducing NF-κB p65 downregulation (386). Therefore, targeting STAT6/PPARγ is promising for SAH treatment because it alters microglia and astrocyte activation.

5.4 Progress of pharmacological interventions in clinic

Recently, accumulated clinical trials have strongly promoted the development of pharmacological treatments for SAH (387). Several drugs have been shown to have significant pharmacological effects on modulating immune inflammatory responses and the immune microenvironment in the brain, as well as the activation of microglia and astrocytes (Figure 7) (388).

Dexmedetomidine (DEX) is an α2-adrenergic agonist widely used for anesthesia, and also anti-inflammation, antioxidation, and anticell death (389). Based on the data from the MIMIC-IV database, DEX was a protective factor for in-hospital mortality of SAH patients (390). Glucocorticoids help to alleviate the inflammatory reaction in CNS diseases (391, 392). Güresir E et al. are conducting a randomized controlled trial to investigate the neuroprotective and anti-inflammatory effects of dexamethasone in treating aSAH patients. In this phase 3 clinical trial, 334 aSAH patients will be enrolled (393). The activation of the complement system plays a crucial role in neuroinflammation following SAH, and it is a key mediator in the pathophysiology of SAH-associated EBI and DCI (394). In a recently started clinical trial (ID. NCT06359782), Dr.Daan de Groot and his colleagues are going to investigate the safety and efficacy of C1-inhibitor Cinryze (an approved inhibitor of the complement system) in treating patients with SAH. In this Phase 2 clinical trial, the inflammatory markers (including TNF-alpha and ILs) in serum and CSF will be measured. In another clinical trial (ID. NCT06579274) enrolling 112 spontaneous SAH patients, the effects of parecoxib (a specific COX-2 inhibitor) in improving the clinical outcome, occurrence of symptomatic vasospasms, as well as occurrence of inflammation will be tested. Those clinical trials will provide more evidence of anti-inflammatory therapy in SAH.

Nimodipine, a lipophilic L-type calcium channel antagonist, is the only proven therapy for vasospasm (387). Nimodipine inhibits spreading depolarization and ischemic injury in mouse live brain slice preparations. Moreover, nimodipine suppressed neuronal damage and directly reduced reactive astrogliosis and microglial activation (395, 396). Anakinra, an IL-1 receptor antagonist (also known as IL-1Ra), can limit brain injury in an experimental SAH

model and reduce the levels of inflammatory mediators (214). Anakinra administration contributes to a reduction in IL-6, C-reactive protein, and fibrinogen levels in the blood of SAH patients (397).

Fingolimod is an immunomodulatory agent approved by the Food and Drug Administration (FDA) for treating multiple sclerosis. Studies have shown that fingolimod significantly attenuates SAH-related neurological deficits, brain edema, and neuroinflammation (398, 399). Fingolimod significantly alleviates brain injuries by suppressing neutrophil recruitment, microglia, and astrocyte activation in the brain (400–402). Clinical studies have shown that fingolimod effectively reduces secondary brain injury after ICH by modulating systemic inflammation and protecting vascular permeability (403, 404). Glibenclamide is an orally active ATP-sensitive K$^+$ channel (K$_{ATP}$) inhibitor that directly binds and blocks the SUR1 subunits of K$_{ATP}$. Glibenclamide treatment suppressed IL-1β and TNFα and inhibited microglial activation in the cortex of SAH rats (405). Glibenclamide also mitigated cerebral edema by suppressing astrocytic activation (406, 407). Oral administration of glibenclamide significantly reduces cerebral edema in SAH patients (408), mitigates ICH-associated perihematomal edema and improves the 90-day prognosis of patients (409).

Statins, such as simvastatin, may benefit some SAH patients by reducing the incidence of vasospasm and delayed ischemic events (410 –411). In an experimental ICH model, the administration of simvastatin improved hematoma absorption and neurological outcomes. Simvastatin upregulated CD36 expression, facilitated "M2" polarization of microglia and reinforced microglia-induced erythrocyte phagocytosis by inducing PPARγ activation (412). Both simvastatin and atorvastatin significantly reduce microglia and astrocyte activation and suppress IL-1β expression in acute brain injury models (413, 414).

5.5 Clinical translational challenges

While multiple animal studies have been widely investigated for treating SAH, their clinical translations remain challenging. Both experimental investigations and clinical observations have demonstrated that SAH inflicts significant damage on the capillary basement membranes and endothelial cells of the BBB. Elevated BBB permeability can be observed at 24-36 hours, peaking at 48 hours, and normalizing on day 3 (415). As a result, the passage of drugs and other substances across this barrier is affected. Depending on the circumstances, the permeability for drug penetration may either decrease, increase, or remain unaltered (416–419). For instance, phenytoin is a routinely prescribed prophylactic antiepileptic following aSAH. aSAH patients (grade 3 and 4) exhibited significantly decreased phenytoin concentration in the brain (420). Altered pharmacokinetics might contribute to unwanted effects of proposed treatments in SAH, which might be associated with clinical challenges in managing aSAH-associated vasospasm. For example, oral nimodipine is the mainstay of pharmacotherapy of cerebral vasospasm and DCI. However, nimodipine-induced hypotension is a serious concern, as blood pressure fluctuations have been associated with the development of focal deficits and worse outcomes (421). The short half-life, acute hypoxemia, armacokinetic variability, drug-drug interactions, and risk of vasoplegia are further shortcomings (422–424). Eicosapentaenoic acid, dapsone and clazosentan showed a good balance between effectiveness and favorable pharmacokinetics (422). Nicardipine and cilostazol, which have longer half-lives than nimodipine, had robust evidence of efficacy and safety (425, 426). Different administration methods, such as localized drug release implants, intracranial or intrathecal administration, can also provide investigational therapies for improving aSAH-associated vasospasm and DCI (427–429).

6 Perspectives

The cell–cell crosstalk within the brain is complex. Following ICH, pathological changes result in more complex cell–cell crosstalk in the NVU and neural–glia networks (430). Although the diagnosis and management of SAH have greatly improved in recent decades, substantial morbidity, mortality and burdens of SAH on the healthcare system still exist. Therefore, it is essential to improve current treatment protocols and create novel strategies for managing SAH (431).

Innovative progress in single-cell RNA-sequencing technology has enhanced our understanding of the brain microenvironment at a single-cell level, providing the opportunity to uncover communication between cells and enhance the treatment benefits resulting from complex interactions within the brain (432–434). Recently, scRNA-seq analysis has been conducted on experimental SAH models. For example, the results indicated that during the subacute stage following SAH, reparative microglia infiltrated and expanded clonally in white matter-enriched areas. Moreover, microglia-associated pleiotrophin (PTN) associated with microglia was found to play a role in regulating OPCs in SAH model mice by activating the mTOR signaling pathway. These results highlight the importance of interactions between microglia and OPCs through the PTN pathway, potentially aiding in white matter repair during the subacute phase after SAH (435). Zhang et al. performed a scRNA-seq analysis using perihematomal edema (PHE) from ICH patients. Twelve microglial subsets and 5 neutrophil subsets were identified in PHE tissues. The secreted phosphoprotein-1 (SPP1) pathway provides a foundation for microglial subclusters to communicate with each other as PHE advances. Furthermore, the osteopontin (OPN) produced by microglia can control the immune environment in PHE tissue by interacting with CD44-positive cells (436). Therefore, scRNA-seq analysis could offer more insights into the mechanism of SAH and the development of drugs that target specific cell subtypes.

Cerebral vasospasm is a persistent arterial narrowing typically observed during the 3–14 days following SAH, which is frequently associated with ischemic neurological deficits or even death, resulting in a poor prognosis for patients (437). Circulating immune cells, including neutrophils, lymphocytes and monocytes, as well as immune mediators, such as IL-6, MMP-9 and VEGF, are involved in

SAH-associated vasospasm (438–440). For example, our group reported that an elevated neutrophil-to-lymphocyte ratio (NLR) was significantly associated with poorer outcomes and DCI occurrence in SAH patients (441). Following early intracerebral infiltration and peripheral activation of innate immune cells, microglia and astrocytic activation are believed to occur at later time points and then induce secondary neurotoxicity (442, 443). Crosstalk between activated microglia and astrocytes can result in increased neuroinflammatory reactions (24). However, the protective effects of microglia and astrocytes in SAH should also be considered. They can mediate phagocytosis and release anti-inflammatory cytokines, which help with hematoma clearance, BBB repair and neurocognitive recovery (124, 444, 445). A promising strategy for preventing secondary injury involves mediating their crosstalk.

Stem cell therapy is a promising strategy for SAH because it involves multiple functions, including neuroregeneration, the modulation of astrocytes and microglia/macrophage activation, in the lesioned hemisphere (446–448). Notably, stem cell therapy can also mediate astrocyte–microglia crosstalk. Human umbilical cord mesenchymal stem cell (hUC-MSC) administration ameliorated the depression-like behaviors of chronic unpredictable mild stress model (CUMS) mice. hUC-MSCs promoted "M2" polarization while suppressing "M1" polarization of microglia. Moreover, hUC-MSCs inhibited the expression of complement C3a and C3aR in microglia. Thus, hUC-MSCs decrease and alleviate neuronal damage and synaptic deficits by restraining neuroinflammation (449). To overcome the shortcomings of MSC therapy (450), MSC-derived EVs are promising alternatives for SAH treatment because of their low or nonexistent immunogenicity and lack of tumorigenic potential (451). In addition, MSC-EVs have the capability to effectively pass through the BBB. They can also be modified to contain an excess of certain proteins or be filled with specific miRNAs in order to deliver desired therapeutic substances, enhancing their ability to reduce apoptosis and neuroinflammation (447).

Mitochondrial biogenesis, as well as fusion and fission processes, are essential for preserving mitochondrial function and balance. Mitochondrial dysfunctions are hallmarks of SAH and contribute to brain impairments by producing ROS, igniting apoptosis and inducing neuroinflammation (448–454). Mitochondrial transfer to damaged cells can help revive the energy of recipient cells. Accumulating evidence has shown that mitochondrial transplantation can replace impaired or dysfunctional mitochondria and exert significant therapeutic effects against ischemic stroke (455). For example, astrocytic mitochondria can be delivered into adjacent neurons following transient focal cerebral ischemia, and this entry amplifies cell survival signals (456). Microglia share healthy mitochondria with burdened neurons, reducing oxidative stress and normalizing gene expression (457). Astrocytes release both intact mitochondria and humanin, a small bioactive peptide normally transcribed from the mitochondrial genome. With the help of humanin, astrocyte-secreted mitochondria enter microglia, promote PPARγ expression, increase phagocytic activity toward red blood cells and suppress proinflammatory responses. Following ICH, the expression of humanin is significantly reduced. Intravenous administration of humanin reduced neurological deficits and improved hematoma clearance (458). Intravenously transplanted astrocytic mitochondria are transferred into neurons with the help of humanin, thus reducing ICH-associated brain injury (459). Thus, mitochondrial transfer between astrocytes and microglia is also a vital mechanism and therapeutic strategy in SAH.

7 Conclusion

The crosstalk between astrocytes and microglia is complex and plays essential roles in the pathological changes that occur during different stages of SAH. In this review, we discuss the effects of SAH-associated DAMPs on microglia and astrocytic activation and the intricate interplay between microglia and astrocytes and summarize the impacts of astrocyte–microglia crosstalk on the NVU as well as circulating immune cells. The extensive bidirectional crosstalk is initially mediated by DAMPs and then mediated by inflammatory cytokines, chemokines, and neurotrophic factors, which are mainly released by microglia/astrocytes and infiltrated immune cells. Moreover, we discuss strategies for SAH treatment by mediating astrocyte and microglia activation and their crosstalk. Further investigations to understand the detailed mechanisms mediating microglia–astrocyte interactions and their impact on the NVU are essential for developing effective therapeutic interventions. Nevertheless, our understanding of microglia/astrocyte communication relies mainly on data derived from research conducted on experimental animal models. Translating preclinical discoveries into the clinical application still faces challenges, partly due to limitations in current SAH animal models and an incomplete understanding of the pathophysiology of this intricate disease. Given that age, sex, and specific medical comorbidities (such as diabetes and obesity) can affect the progression of spontaneous SAH to a considerable extent, it is of great significance to develop SAH animal models that better mimic this clinical disease. Moreover, the systemic inflammation that occurs after SAH is the result of intricate interactions between the nervous and immune systems, impacting all organ systems significantly. Hence, it is crucial to identify and assess the level of systemic inflammation in SAH to identify possible therapeutic opportunities. While past studies have highlighted the benefits of different treatment strategies, more research is needed to fully comprehend the pathophysiological processes of systemic inflammation post aSAH and how they can be applied in clinical practice. Overall, we hope that the above summary can provide a better basis for SAH treatment and stimulate further research.

Author contributions

KY: Conceptualization, Data curation, Investigation, Software, Visualization, Writing – original draft, Writing – review & editing. WY: Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing. DW: Conceptualization, Data curation, Investigation, Software, Writing – original draft, Writing – review & editing.

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Glossary

AIS	acute ischemic stroke
AQP4	aquaporin-4
aSAH	aneurysmal subarachnoid hemorrhage
ATP	adenosine triphosphate
BBB	blood–brain barrier
BDNF	brain-derived neurotrophic factor
CaMKII	calcium calmodulin-dependent kinase II
CCL	Chemokine C-C motif chemokine ligand
CCR2	CC chemokine receptor 2
cGAS	cyclic GMP-AMP synthase
CL	cardiolipin
CNS	central nervous system
COX-1	Cytochrome c oxidase subunit-1
CSF	cerebrospinal fluid
CytB	Cytochrome B
DAMPs	damage-associated molecular patterns
DCI	delayed cerebral ischemia
DEX	Dexmedetomidine
EBI	early brain injury
Ex-mito	Extracellular mitochondria
GFAP	glial fibrillary acidic protein
FAK	focal adhesion kinase
FGF2	fibroblast growth factor 2
FPRs	formyl peptide receptors
GDNF	glial-derived neurotrophic factor
Hb	hemoglobin
HIF-1α	Hypoxia-inducible factor-1α
HO-1	heme oxygenase-1
HSP	heat shock protein
ICAM1	intercellular adhesion molecule-1
ICP	intracranial pressure
IL-6	interleukin-6
iNOS	inducible nitric oxide synthase;
IRFs	Interferon regulatory factors
LCN2	Lipocalin-2
MMPs	matrix metalloproteinases
mtROS	mitochondrial ROS
NET	neutrophil extracellular trap
NF-κB	nuclear factor-kappaB
NK1R	Neurokinin 1 receptor
NVU	neurovascular unit
NLRP3	NACHT, LRR, and PYD domains-containing protein 3
NO	nitric oxide
OxyHbm	oxyhemoglobin;
PRDXs	Peroxiredoxins
RBC	red blood cell
ROS	reactive oxygen species
S1P	sphingosine 1-phosphate
S1PR3	Sphingosine-1-phosphate receptor 3
SAH	subarachnoid hemorrhage
SBI	secondary brain injury
SCI	spinal cord injury
STAT6	Signal Transducer and Activator of Transcription 6
STING	stimulator of interferon genes
TLR	toll-like receptor
TBI	traumatic brain injury
TNF-α	tumour necrosis factor-alpha.