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RECEIVED 03 August 2025

ACCEPTED 03 October 2025

PUBLISHED 21 October 2025

CITATION

Ouyang H, Gu H, Cai Y and Wang C (2025)
Mechanisms and potential therapeutic
molecular targets in blood–brain barrier
disruption following subarachnoid
hemorrhage: a review of early brain injury.
Front. Neurol. 16:1678839.
doi: 10.3389/fneur.2025.1678839

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Mechanisms and potential therapeutic molecular targets in blood–brain barrier disruption following subarachnoid hemorrhage: a review of early brain injury

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Subarachnoid hemorrhage (SAH) is a devastating stroke characterized by acute onset, severe symptoms, and a poor prognosis. A series of pathological changes occur within 72 h after SAH, leading to early brain injury (EBI). Blood–brain barrier (BBB) disruption is a key factor contributing to the EBI progression. When the BBB is compromised, detrimental substances and immune cells have the potential to infiltrate brain tissues, and a range of mechanisms contribute to the disruption of the BBB following SAH. This review provides a comprehensive overview of the current knowledge regarding the underlying mechanisms and potential therapeutic targets in BBB disruption during EBI following SAH. It focuses on the dysfunction of endothelial cells, tight junctions, astrocytes, and pericytes; the specific molecular targets for EBI after SAH; and new emerging treatments for BBB disruption in EBI after SAH.

KEYWORDS

hemorrhagic stroke, intracranial aneurysm, brain edema, neuron apoptosis, brain herniation, endothelial cells, pericytes, astrocytes

Introduction

Subarachnoid hemorrhage (SAH) is a critical form of hemorrhagic stroke resulting from the rupture of pathological blood vessels, leading to the direct influx of blood into the subarachnoid space within the brain (1). The prevalence of SAH was approximately 10 per 100,000 individuals in the general population, accounting for 5–10% of all stroke cases, while the incidences were more evident in specific countries (Finland and Japan), elderly, women, black races, family history of SAH and some heritable connective-tissue disorders (2, 3). An underlying intracranial aneurysm rupture is the primary etiology in approximately 80–85% of cases of spontaneous SAH (4). Brain injury induced by SAH could be divided into early brain injury (EBI) and delayed brain injury. EBI is the primary prognostic factor for aneurysmal SAH, which can occur within minutes to 72 h after the initial bleeding. EBI is characterized by increased intracranial pressure, resulting in global cerebral ischemia or the presence of extravasated blood (5, 6). Multiple physiological disturbances cause EBI, and various pathological changes occur within 72 h after SAH, potentially leading to secondary brain tissue damage (7). In clinical practice, surgical clipping or endovascular coiling used for early aneurysmal obliteration are widely applied to prevent rebleeding and improve the

prognosis of SAH. Moreover, intensive medical care should be used to manage delayed cerebral ischemia after ruptured aneurysm is successfully treated, irrespectively for cerebral vasospasm (CVS), and other various medical complications status. Furthermore, it is crucial to closely monitor and effectively manage surrogate markers for early brain injury (EBI) in order to enhance the prognosis of subarachnoid hemorrhage (SAH). These markers include the initial clinical severity, extent of subarachnoid hemorrhage, and the presence of global cerebral edema (5).

Studies have shown that the disruption of the BBB is a significant factor in the development of brain edema caused by EBI (8). An increased intracranial pressure following SAH is strongly correlated with reduced cerebral blood flow and widespread cerebral ischemia. This is accompanied by the extravasation of blood and degradation products, which can impact the advancement of brain injury. The disruption of BBB permeability significantly contributes to death within 72 h after SAH, as it could induce brain edema, increase intracranial pressure, cause secondary neuron apoptosis, and result in brain herniation (9). The BBB in the cerebrovascular system is composed of neurons, endothelial cells, pericytes, astrocytes, microglia, and vascular smooth muscle cells (VSMC) (10). The BBB regulates brain homeostasis by restricting the entry of neurotoxic plasma components, blood cells, and pathogens from the systemic circulation (11). Preclinical SAH studies have demonstrated that BBB permeability increases at 24–36 h, peaks at 48 h, and normalizes at 72 h. Disruption of the BBB function is closely correlated with damage to the basal lamina and microvasculature (12, 13). Thus, inhibiting of BBB disruption could be considered as an effective strategy to improve the prognosis of EBI after SAH.

Considering the complexity of SAH and the difficulty in identifying effective treatments, exploring new therapeutic approaches for EBI is crucial to improving the prognosis of SAH. Therefore, it is necessary to perform a thorough review of the literature in order to evaluate the underlying mechanisms and identify potential molecular targets for therapeutic interventions in BBB disruption following EBI after SAH.

Mechanisms of EBI after SAH

A intracranial pressure (ICP) peak after SAH could arrest in intracranial circulation (14), and severe global ischemic injury could be caused by temporary intracranial circulatory arrest via hemostasis, which was associated with autoregulation loss, lower cerebral perfusion pressure (CPP) or cerebral blood flow (CBF), and elevated secondary ICP (15). Moreover, the cytotoxic edema could be affected by hypoxic state via energy failure in neurons and glia (16). Furthermore, ischemia can

trigger the apoptosis of BBB cells, leading to an augmented permeability of serum from the blood vessels into the cerebral tissues, which is primarily attributed to the death of endothelial cells and perivascular astrocytes (17). The astrocytes and microglia were activated after SAH, which could induce the up-regulation of pro-inflammatory cytokines, and then the brain parenchyma was affected (18). Finally, the pathophysiological changes during the EBI period after SAH within 72 h included raised ICP, reduced CPP and CBP, BBB disruption, acute vasospasm, autoregulation dysfunction, brain swelling, and brain edema (16). Multiple mechanisms have been shown to be involved in cell death and subsequent dysfunction following SAH, and the specific details are illustrated in Figure 1 (19–22). In summary, EBI after SAH is a synergistic outcome of multiple mechanisms, including elevated ICP, reduced CBF/CPP, ion disturbance, and molecular alterations. These processes collectively induce cell death in neurovascular units, laying the pathological foundation for BBB disruption. The details of mechanisms for EBI after SAH are summarized in Table 1.

Among the multiple pathological processes of EBI, BBB disruption is a pivotal link connecting upstream insults (e.g., ischemia, oxidative stress) to downstream damage (e.g., brain edema). The integrity of BBB directly determines the extent of fluid and toxic substance infiltration into brain tissue, thereby governing the development of cerebral edema. Thus, the following section focuses on the association between BBB integrity and brain edema.

BBB integrity and brain edema

BBB disruption after SAH could induce various pathophysiological processes, and the endothelial cell apoptosis was involved (23). The presence of blood breakdown products, such as oxyhemoglobin, and the associated oxidative stress have been linked to the advancement of blood–brain barrier (BBB) disruption. Additionally, the activation of inflammatory cytokines, including TNF- α , IL-1 β , and thromboxane A₂, can induce BBB disruption by promoting endothelial cell death and activating matrix metalloproteinases. Furthermore, various mechanisms are involved in BBB disruption, including matrix metalloproteinase-9 (MMP-9)—which degrades the extracellular matrix of the basement membrane (e.g., collagen IV, laminin) and directly cleaves tight junction proteins (occludin, ZO-1) to increase BBB permeability (23), and tight junction (TJ) proteins between endothelial cells (24). Cerebral edema may occur when blood components and inflammatory factors infiltrate the brain following disruption of the BBB. Study has indicated that aquaporin 4 (AQP4) is implicated in the development of brain edema after SAH. Inhibiting AQP4 has been associated with amelioration of cerebral edema, as it plays a crucial role in regulating water balance within brain tissue following SAH (25). To conclude, BBB disruption is the core pathogenesis of cerebral edema in EBI, with oxidative stress, inflammatory cytokines, and MMP-9 activation as key mediators. Targeting these pathways to preserve BBB integrity may effectively alleviate brain edema.

Mechanical impact

During the acute phase of SAH, a decrease in CPP and an increase in ICP play a significant role in reducing CBF. The reasons for a

Abbreviations: BBB, Blood–brain barrier; SAH, Subarachnoid hemorrhage; EBI, Early brain injury; CVS, Cerebral vasospasm (CVS); ICP, Intracranial pressure; CPP, Cerebral perfusion pressure; CBF, Cerebral blood flow; MMP-9, Matrix Metalloproteinase-9; TJ, Tight junction; AQP4, Aquaporin 4; ROS, Reactive oxygen species; NOS, Nitric oxide synthase; eNOS, Endothelial nitric oxide synthase; nNOS, Neural nitric oxide synthase; iNOS, Inducible nitric oxide synthase; TLR4, Toll-Like receptor 4; NF- κ B, Nuclear factor- κ B; JAK/STAT, Janus kinase/signal transducer and activator of transcription; PI3K/Akt, Phosphatidylinositol 3-kinase/protein kinase B.

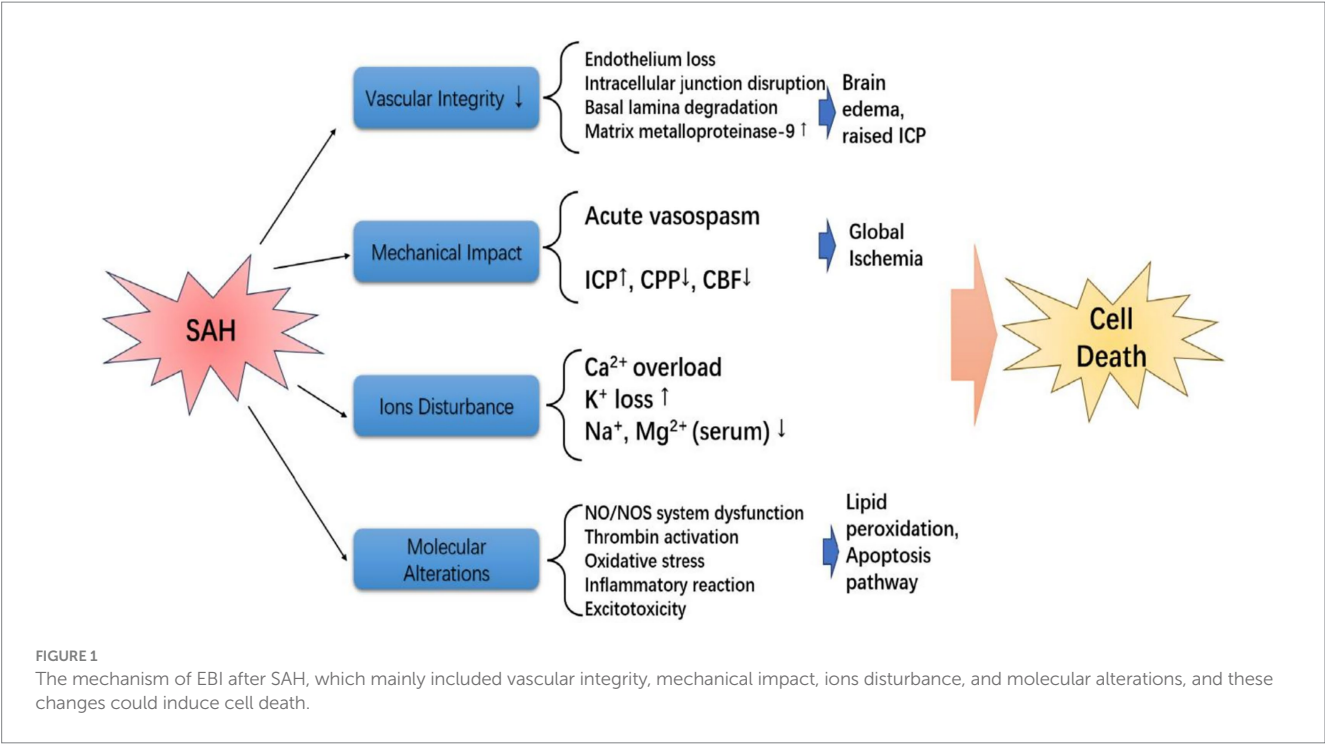


TABLE 1 Potential mechanism for early brain injury after SAH.

Components	Molecular mediators	Targets
Vascular integrity	Endothelial cell apoptosis, TNF- α , IL-1 β , and thromboxane A2	BBB disruption (23)
	MMP-9, TJ proteins between endothelial cells	BBB disruption (24, 28)
	AQP4	Cerebral edema (25)
Mechanical impact	CBF, ICP, and CPP	Brain's microcirculation (12)
	MMP-9	Platelet aggregation (28)
	CMRO2	Oxygen and glucose metabolism (29)
Ions disturbance	Intracellular calcium, potassium, sodium, and magnesium	CSD (30–33)
Molecular alterations	Ras-MAPK-NF- κ B, JAK/STAT, and TLR4/NF- κ B	IL-1, IL-6, and TNF- α (35–37)
	Lipid peroxidation and protein oxidation	Oxidative stress (39)
	NOS	ROS, oxidative stress (40)

decrease in CPP and increase in ICP included cerebral edema, cerebrovascular dysfunction causing congestion, and hematomas blocking cerebrospinal fluid circulation, and the levels could return normal or slightly elevated quickly. However, the pathophysiological mechanisms, such as disruption of the BBB, constriction of microvessels, formation of microthrombi, and impaired autoregulation, prolonged the time needed for the recovery of cerebral blood flow (12). Study found the arterioles' reactivity to endothelin-1 was increased after blood injection (26). Furthermore, ultrastructural examination revealed the presence of partially collapsed capillaries, enlarged astrocyte foot processes, and protrusions from endothelial cell lumens within 1 h following SAH (27).

The progression of microthrombi can be influenced by platelets, with arterial damage and active bleeding playing a significant role in promoting platelet aggregation and the formation of microthrombi. The potential mechanism involved the liberation of serotonin, ADP, and platelet-derived growth factor subsequent to SAH, leading to

potential alterations in cerebral perfusion. Moreover, the collagenases release, such as MMP-9 was associated with BBB disruption, while the inflammatory damage could exacerbate via lymphatic cells adhering to microvessels. Furthermore, the brain energy metabolism included oxygen and glucose metabolism. The decrease in cerebral metabolic rate of oxygen (CMRO₂) after SAH is significantly related to lower CBF and elevated ICP (28). An increase in high-glucose anaerobic glycolysis has been found to be associated with a decline in neurological function score, particularly in relation to anaerobic metabolism (29).

Ions disturbance

After SAH, there are several alterations observed in the brain microenvironment, including fluctuations in intracellular levels of calcium, potassium, sodium, and magnesium. These dynamic changes

are closely linked to brain tissue injury, such as disruption of nerve electrical activity, constriction of blood vessels, and the occurrence of chronic delayed effects. Nowadays, the etiology of cerebral ischemic injury after SCH was considered induce cortical spreading depression (CSD) caused by ion imbalance combined with the secondary cortical spreading cerebral ischemia (CSCI). Possible targets for intervention to address ion imbalance involve increasing the threshold for CSD by enhancing NO availability, utilizing magnesium ion antagonism, NMDA receptor antagonists, or maintaining high perfusion pressure, all of which have been associated with shorter duration of CSD (30–33).

Molecular alterations

The immune-inflammatory response plays a significant role in brain injury and CVS following SAH. Additionally, the activation of inflammatory cells, increased expression of immune molecules, and release of inflammatory mediators have been observed following disruption of the BBB, which may be a response to the presence of blood-derived antigens—referring to blood components (e.g., hemoglobin breakdown products, platelet-derived factors) that are normally sequestered by the BBB and enter brain tissue after disruption. It should be clarified that this inflammatory response is not a traditional antibody–antigen specific immune reaction, but rather a result of blood components acting as damage-associated molecular patterns (DAMPs) to activate innate immune pathways (34). Studies has indicated that during the acute stage of SAH, there is an increase in the levels of IL-1, IL-6, and TNF- α , and the production of these inflammatory factors involves the activation of the Ras-MAPK-NF- κ B, JAK/STAT, and TLR4/NF- κ B pathways (35–37).

Oxidative stress can be triggered by the breakdown products of hemoglobin that are released into the subarachnoid space following a SAH. This oxidative stress can be further intensified by cerebral ischemia–reperfusion. Oxidative stress leads to lipid peroxidation and protein oxidation, which are associated with DNA damage, cell apoptosis, and the activation of inflammatory cascade reactions. Oxidative stress induces endothelial cell apoptosis, degrades tight junction proteins, and damages the basement membrane, directly exacerbating BBB disruption (38). Thus, interventions targeting oxidative stress (e.g., inhibiting ROS production, activating antioxidant pathways) can protect endothelial function, maintain TJ integrity, thereby alleviating BBB disruption and ultimately reducing EBI severity (39).

The production of reactive oxygen species (ROS) following SAH is mediated by heme oxygenase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and nitric oxide synthase (NOS). NO generated by NOS was significantly reduced owing to acute cerebral vasospasm (CVS)—a pathological vasoconstriction of cerebral arteries after SAH, whereas it was dramatically increased after 24 h. Thus, NOS and NO contributed a crucial role in brain damage caused by oxidative stress (40). Studies have shown that reducing the factors that lead to the production of ROS and inhibiting ROS generation can result in enhanced antioxidant responses, which are correlated with reduced oxidative stress-induced damage (41, 42). Endothelial nitric oxide synthase (eNOS) knockout is associated with larger infarct size in cerebral infarction models (43), but in SAH, eNOS knockout is

associated with less microvascular damage and exerts neuroprotective effects (44).

BBB disruption after SAH

Disruption of the BBB, a prominent pathological feature, is strongly correlated with unfavorable outcomes following SAH. Unlike ischemic stroke (mainly caused by focal ischemia) and intracerebral hemorrhage (mainly caused by extravasated blood components), BBB disruption after SAH is multifactorial: it results from transient global cerebral ischemia after aneurysm rupture, delayed cerebral ischemia, and the toxic effects of extravasated blood components (45–47).

BBB disruption leads to the infiltration of blood components and inflammatory factors into brain tissue, triggering cerebral edema and neuroinflammation. Approximately 8–67% of SAH patients are diagnosed with global cerebral edema on admission, and nearly 12% develop delayed cerebral edema within 2 weeks (48). Elevated BBB permeability and global cerebral edema in the acute phase of SAH are significantly associated with poor prognosis and are considered important manifestations of EBI (48). Additionally, SAH comorbidities (e.g., infection, electrolyte disturbance) can further worsen BBB disruption and clinical outcomes (45).

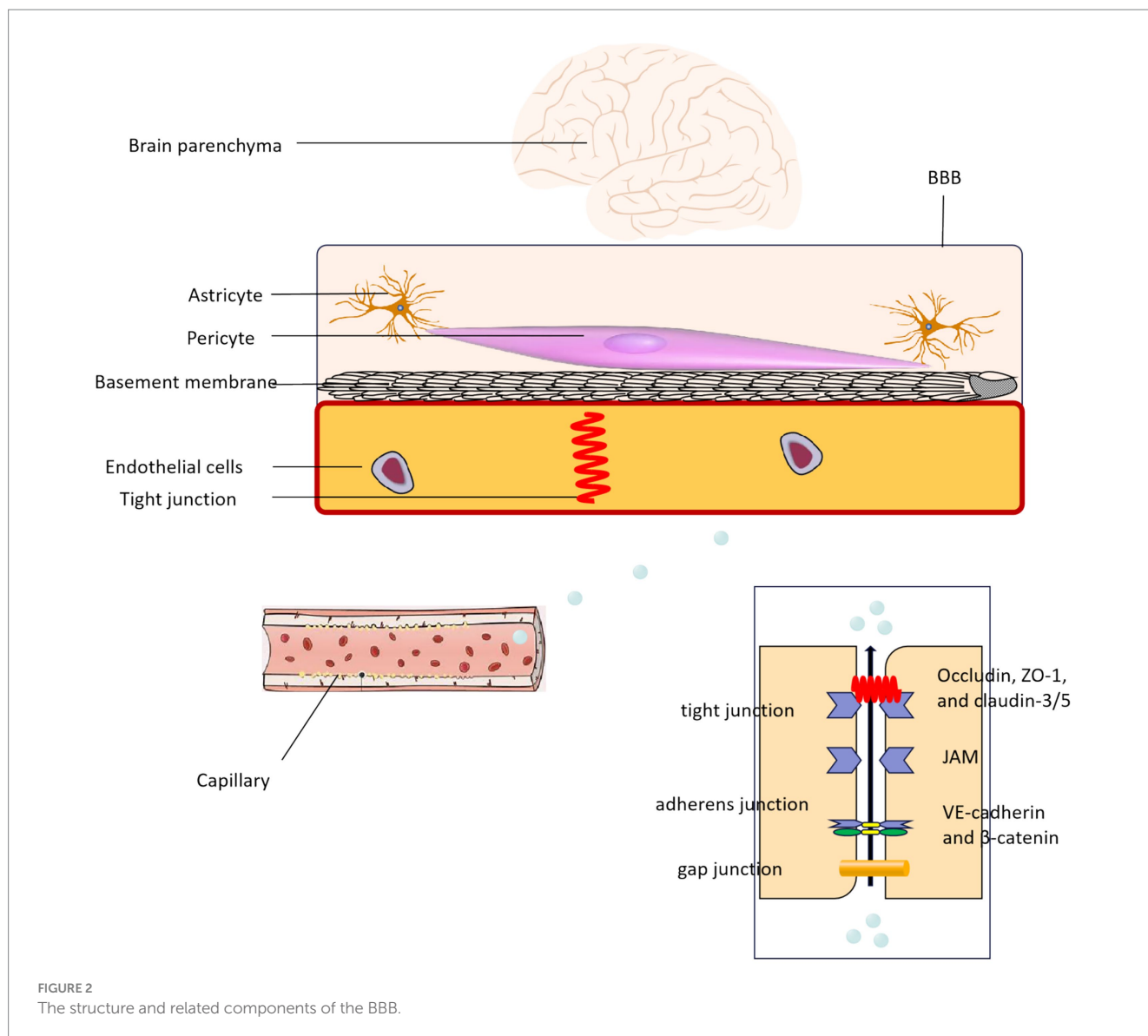
BBB component dysfunction and its association with EBI

The BBB serves as the interface between the bloodstream and the central nervous system, facilitating the communication of substances from the peripheral blood to the brain (49). The key constituents of the BBB comprise microvascular endothelial cells, TJs, astrocytes, and pericytes. The integrity and functionality of the BBB are influenced by these components (Figure 2) (50). Moreover, the components of the BBB can undergo modifications based on the specific needs of various brain regions and blood vessels. These modifications encompass alterations in glial cells, the extracellular matrix, and VSMC (51).

In addition to the classic components of the blood–brain barrier (BBB), emerging evidence in recent years has highlighted the critical role of the glymphatic drainage system in brain waste clearance (52). This system facilitates the elimination of neurotoxic substances β -amyloid (A β) through glymphatic fluid flow mediated by aquaporin-4 (AQP4) expressed in astrocytic end-feet (53). Following subarachnoid hemorrhage (SAH), disruption of AQP4 polarity may impair glymphatic function, leading to A β accumulation (54). Similar mechanisms have been observed in Alzheimer's disease (AD), where glymphatic dysfunction is recognized as an early pathological hallmark (55). Thus, SAH-induced early brain injury may accelerate neurodegenerative progression by interfering with glymphatic clearance pathways (56).

Microvascular endothelial cell dysfunction and EBI

Microvascular endothelial cells, which are connected by TJs, adherens junctions, and gap junction proteins, constitute the primary constituent of the BBB and serve as the initial protective barrier in the



brain (57–60). Cerebral endothelial cells establish a barrier through the expression of TJ proteins, which limit vesicle-mediated transcellular transport or transporter-mediated transport (61). These cells facilitate the transportation of proteins and molecules to reach brain tissues, and the activity of vesicle transport in endothelial cells as well as the components of the plasma membrane can influence transcellular transport (62–64). Endothelial cells are widely used in BBB models, but the transporters and cellular machinery differ between polarized endothelial cells' luminal and abluminal sides (62).

The BBB disruption caused by SAH was associated with the progression of EBI and cerebral vasospasm (CVS), depending on the response of endothelial cells (65, 66). Within 24 h following SAH, there is evidence of the presence of oxyhemoglobin, excessive iron, and oxidative stress resulting from the breakdown of red blood cells. These factors are known to contribute significantly to the apoptosis of endothelial cells (67–69). The free radicals induced by oxidative stress could cause cellular damage by accelerating DNA fragmentation, protein breakdown, and lipid peroxidation. These changes are significantly related to pathological changes in endothelial cells,

leading to increased permeability of the BBB (70–73). Disruption of the basal lamina and development of cerebral vasospasm (CVS) contribute significantly to the advancement of EBI through endothelial cell damage (74, 75). Nevertheless, there are mechanisms that can suppress endothelial cell death. The presence of ApoE has a strong correlation with the inhibition of EBI in SAH. ApoE levels increase significantly after 6 h, reach their peak after 48 h, and return to normal after 72 h in SAH. This elevation of ApoE may hinder the activation of the inflammatory cyclophilin A (CypA)-NF-κB-MMP-9 pathway, thereby preserving the integrity of the BBB (76). Furthermore, the Janus kinase 2 (JAK2)/STAT3 signaling pathway has been found to partially regulate endothelial cell apoptosis, and activation of the JAK2/STAT3 cascade can result in increased expression of anti-apoptotic genes such as B-cell lymphoma 2 (Bcl-2) and Bcl-xL (77–79).

The activation of the Nrf2-ARE signaling pathway in endothelial cells following SAH is crucial for preserving BBB integrity by inhibiting endothelial cell apoptosis and countering the effects of oxidative stress. This pathway regulates the expression of detoxifying

enzymes and antioxidative proteins, thereby mitigating the detrimental effects of SAH-induced oxidative stress on the BBB (80–82). The level of v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 4 (ErbB4) is upregulated in endothelial cells 72 h after SAH. ErbB4 triggers the activation of the yes-associated protein (YAP)/phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit beta (PIK3CB) signaling pathway, resulting in enhanced expression of occludin and claudin-5. This pathway promotes endothelial cell survival under oxidative stress and stabilizes intercellular junctions, thereby maintaining BBB integrity and reducing brain edema (83).

The integrity of BBB could be affected by the endothelial cytoskeleton. Studies have demonstrated that increased expression of myosin light chain kinase (MLCK) is linked to heightened phosphorylation of myosin light chain (MLC), resulting in reorganization of the cytoskeleton, disrupted cell–cell interactions in endothelial cells, compromised BBB integrity, and the development of vasogenic brain edema following SAH (84). Moreover, the integrity of endothelial TJs plays a crucial role in preventing platelet adhesion to extracellular collagen, thus maintaining the delicate equilibrium between hemostasis and thrombosis. However, the dysregulation of this equilibrium occurs due to the upregulation of vascular endothelial growth factor (VEGF) expression following vasospasm subsequent to SAH (85–87). In the acute phase of SAH, the increased expression of VEGF may impact platelet adhesion and disruption of endothelial TJ through the regulation of collagen IV exposure and its binding to platelet glycoprotein Ia-II (88, 89). These alterations can affect the entry of platelets into the brain, triggering neuroinflammation and EBI following SAH (90–92). Furthermore, insufficient NO production by endothelial cells failed to effectively inhibit platelet adhesion and aggregation, thus potentially contributing to the development of ischemic brain injury following SAH (93). The enhanced protein kinase C (PKC) expression was regarded as the primary mechanism for vasospasms, and the PKC family was significantly related to S100 calcium-binding protein during cerebral vasospasm (CVS) after SAH (94). SAH could change transport mechanisms among endothelial cells, and P-glycoprotein (P-gP) was reduced after SAH (95). Vesicular trafficking in endothelial cells and changes in Mfsd2a expression and TJ proteins have a significant impact on BBB permeability following SAH (96).

Studies have already demonstrated that BBB integrity could be assessed using the von Willebrand factor (vWF), thrombomodulin (TM), and endothelin 1 (ET-1). The expression of these markers increases after SAH, demonstrating disrupted BBB (97). The p38 MAPK-p53/NF- κ B (p65) signaling pathway involved TM's role on endothelial TJ proteins after SAH (98). Moreover, the expression of ET-1 could affect the role of endothelial cells on VSMC (99). In vascular smooth muscle cells, the binding of ET-1 to the ETA receptor can trigger the activation of the ERK1/2 pathway and the Kruppel-like transcription factor 4 (KLF4), leading to the transition of VSMCs from a contractile phenotype to a synthetic phenotype, thereby inducing KLF4 activation (100, 101). Studies have indicated that the expression level of endothelin-1 increases after subarachnoid hemorrhage, and the activation of endothelial nitric oxide synthase (eNOS) can provide negative feedback on the expression of endothelin-1 (102). In addition, lipoxin A4 (LXA4) plays a vital role in endothelial cells by inhibiting neutrophil infiltration and pro-inflammatory cytokines. It exerts regulatory control over the NF- κ B signaling pathway through the

inhibition of ERK1/2 phosphorylation, resulting in reduced levels of pro-inflammatory cytokines and decreased neutrophil infiltration (103).

Tight junction disruption and EBI

The TJs, adherens junctions, and gap junctions constituted the intercellular junctional complexes among endothelial cells (64). TJs are composed of several proteins, such as occludin, zonula occludens-1 (ZO-1), and claudin-5 (104). These TJ proteins exhibited structural similarity as phosphoproteins, and their interaction, redistribution, and transmembrane protein localization could be modified through phosphorylation (104, 105). The TJ system, which is a part of the immunoglobulin superfamily, includes the junctional adhesion molecules (JAMs). JAMs play a role in facilitating leukocyte migration across endothelial cell layers through homotypic and heterotypic interactions with other members of the JAM family. These interactions have an impact on endothelial cells (106). Furthermore, the disassembly of TJs was associated with an elevated BBB permeability, then the BBB disruption was occurred, which could cause brain edema formation after SAH. The transport of materials across the BBB includes paracellular and transcellular pathways. The paracellular pathway depends on the integrity of intercellular junctions (e.g., TJs, adherens junctions)—SAH-induced TJ degradation opens this pathway, allowing macromolecule leakage. The transcellular pathway is mediated by vesicular transport (e.g., receptor-mediated endocytosis)—SAH activates abnormal vesicular trafficking, further increasing BBB permeability (64).

The expression of TJ proteins (claudin-3 and claudin-5) can be regulated by sphingosine-1-phosphate receptor-1 (S1P1) proteins, which activate the PI3K/Akt signaling pathway. This activation leads to the inhibition of glycogen synthase kinase 3 β (GSK3 β) and the stabilization of β -catenin. S1P1 is primarily located in endothelial cells, and its expression level decreases 24 h after SAH, leading to changes in TJ protein expression (107). The activation of S1P1 by PAR-1 involves the regulation of endothelial protein C receptor (EPCR) and activated protein C (APC) (98). The expression of adhesion molecules on the luminal surface of endothelial cells was increased in response to the presence of blood in the subarachnoid space (108–112). These molecules facilitate the communication between endothelial cells and leukocytes, promoting the recruitment, adhesion, and migration of white blood cells to the site of bleeding (113–115). In addition, it has been observed that neutrophils infiltrate the brain within the first 10 min following SAH, which is strongly associated with a decrease in cerebral NO levels due to the activity of the neutrophil-derived enzyme myeloperoxidase. Research studies have indicated that neutrophil infiltration contributes to the disruption of the BBB after SAH by releasing ROS, elastases, proteases, collagenase, and matrix metalloproteinase-9 (MMP-9) (116).

The disruption of TJs between endothelial cells triggers the activation of the NF- κ B inflammatory signaling pathway, resulting in the development of posthemorrhagic vasogenic edema (117). The primary cause of EBI observed within 24 h after SAH is believed to be alterations in the expression levels of TJ proteins. Moreover, a decrease in the levels of various TJ proteins, such as ZO-1, occludin, claudin-5, JAM-A, and adherens junction protein VE-cadherin, has been observed between 24 and 48 h following SAH (118). Studies have

reported a significant correlation between elevated permeability and reduced expression levels of tight at 3 h and 72 h after SAH (104). T2-weighted MRI hyperintensities could be observed after SAH, indicating increased BBB permeability in the early stages of SAH (89, 119). The loss of collagen IV mediates perturbations in the microvascular basal lamina after SAH, promoting the progression of BBB disruption. The levels of MMP-9 and collagenase activity reach their highest point 3–6 h after SAH, whereas the expression of collagen IV decreases in two distinct phases (13, 120). The alterations in collagen IV expression paralleled the biphasic alterations observed in the TJ proteins ZO-1 and occludin (104). Collagen IV decreases in two phases: first at 3–6 h post-SAH (driven by initial MMP-9 activation) and second at 24–48 h (due to sustained inflammation), consistent with TJ protein changes. Furthermore, laminin—a substrate for MMP-9—decreases at 24 h post-SAH, and endothelial MMP-9 upregulation coincides with reductions in laminin, occludin, and collagen IV (121–123).

The NF- κ B-MMP-9 molecular signaling pathway is implicated in the regulation of pathophysiological cascades within cerebral endothelial cells following SAH (124). Inflammation contributes to the induction of BBB disruption, as indicated by the increased expressions of toll-like receptor (TLR)-4 and high-mobility group box 1 (HMGB1) following SAH (125, 126). Furthermore, the elevation of MMP-9 levels can be triggered by the activation of p53 expression through the NF- κ B signaling pathway in brain endothelial cells 24 h post-SAH. This activation can lead to the degradation of collagen IV and laminin, subsequently resulting in the degradation of occludin and disruption of the basal lamina (127). The inflammatory-induced disruption of TJ proteins contributes to the onset of vasogenic brain edema 24 h following SAH (128).

Astrocyte activation and EBI

Astrocytes, which are the predominant cell type in the central nervous system, play crucial roles in the maturation, viability, metabolic support, and neurotransmission of neuronal activities (129). They maintain and repair the BBB by releasing various effector molecules that induce barrier properties, transporter polarization, and overall BBB function (130–132). Astrocytes also serve as a cellular link between neuronal activity and blood vessels, modulating cerebral blood flow and brain water content in response to neuronal activity (133, 134). Astrocytic end-feet undergo polarization—functional proteins (e.g., AQP4) are directionally distributed on the membrane contacting vessel walls. This polarization is regulated by pericyte-derived signals, forming a functional interface of the BBB (135).

After SAH, astrocytes exhibit morphological alterations characterized by dilated end-feet and endothelial protrusions—these changes compress capillary lumens and disrupt cerebral ultrastructure (136). These changes lead to compression of the capillary lumen and disruption of cerebral ultrastructure (136). Astrocytes react to damage-associated molecular patterns (DAMPs) originating from the perivascular area, resulting in the production of pro-inflammatory cytokines, chemokines, growth factors, as well as the attraction and activation of immune cells from the periphery (137). Astrocytes express Toll-like receptor 4 (TLR4), which plays a crucial role in the progression of neuroinflammation (138–140). This function is exemplified by the increased expression of myeloid differentiation

primary response protein 88 (MyD88), a crucial mediator for delivering TLR signals to NF- κ B (141). Stimulation of the TLR4/MyD88 signaling pathway leads to the ubiquitination of tumor necrosis factor receptor-associated factor 6 (TRAF6). The ubiquitylation of TRAF6 leads to the degradation of ULK1 or the prevention of ULK1 phosphorylation. This process exacerbates brain injury after SAH by inhibiting autophagy (142, 143). Activation of NF- κ B can trigger the upregulation of p65, TNF- α , and IL-1 β via the TLR4/MyD88 signaling pathway. The PI3K/Akt signaling pathway, which is downstream of the angiogenic factor with G-patch and FHA domain 1 (Aggfl), attenuates the expression of these pro-inflammatory molecules. Aggfl in astrocytes exerts a significant influence on the PI3K/Akt signaling pathway following SAH (144).

Astrocytes have the ability to differentiate into two distinct phenotypes following SAH: the pro-inflammatory/harmful A1 phenotype and the anti-inflammatory/beneficial A2 phenotype (145). The A1 polarization in response to SAH is triggered by the activation of microglia and the release of pro-inflammatory cytokines (146, 147). TNF- α induces astrocyte differentiation towards the detrimental A1 phenotype via NF- κ B activation. Conversely, TNF- α promotes astrocyte differentiation towards the advantageous A2 phenotype through the induction of neuronal-derived prokineticin 2 (PK2) expression, activating the STATA3 cascade (148). Moreover, the diminished capacity of astrocytes to remove glutamate from the synaptic cleft following SAH is attributed to the decreased expression of glutamate transporter 1 (GLT-1) and EAAT-2 on the astrocytic membrane, leading to subsequent neuronal harm (149). The SAH-associated decrease in Akt phosphorylation could explain this decrease in EAAT-2 expression of GLT-1, which could be affected by histone deacetylase 2 (HDAC2) (150). These alterations may exert a detrimental effect on hippocampal synaptogenesis and lead to cognitive impairment following SAH (151).

Astrocytes play a role in brain damage via an elevated ET-1 expression after SAH, as they are the major source of ET-1 production (152, 153). However, ET-1 exerts positive effects by promoting the synthesis of BDNF, GDNF, and NT3 (100)—these neurotrophic factors support neuronal survival, axon regeneration, and synaptic remodeling, offsetting SAH-induced neuronal damage. Furthermore, the levels of glial fibrillary acidic protein (GFAP) and heme oxygenase 1 (HO-1) were found to be elevated in astrocytes following SAH. This increase can be attributed to the passage of PDGF released by platelets through the endothelium and basal lamina into the brain tissue (149). Ferritin expression in astrocytes plays a cytoprotective role by attenuating neuronal Hb toxicity (154). CD163 receptors present on microglia and neurons are capable of uptaking haptoglobin-Hb complexes, thereby extracting iron from astrocytes following SAH, leading to the initiation of brain damage (154–156).

Pericyte dysfunction and EBI

Pericytes are located on the outer surface of microvessels and are integrated into the vascular basement membrane. They establish connections with endothelial cells through various types of junctions, including gaps, adherens junctions, and peg-and-socket junctions (157, 158). The pericytes in cerebral tissue were higher than in peripheral tissues, which could regulate angiogenesis and the extracellular matrix deposition to maintain the endothelial

cell monolayer (157). Moreover, pericytes were essential for tight junctions and BBB function in the brain, and pericytes' contractility could regulate cerebral blood flow by altering capillary diameter (158–160).

Given the multifaceted functions of pericytes, which play a crucial role in the intricate pathophysiology following SAH due to their unique characteristics (161), picytes can express alpha-smooth muscle actin (α -SMA) to enhance the constriction of capillary lumens after SAH (162, 163). Additionally, pericytes with an α -SMA phenotype can release factors that compromise the integrity of the BBB (164, 165). The release of Hb from ruptured red blood cells within pericytes can trigger microvascular constriction through the scavenging of NO during the initial phase following SAH. Reduced levels of NO after SAH are strongly associated with pericyte contraction. However, during the later stages after SAH, pericyte contraction is induced by decreased expression of eNOS (166, 167).

The upregulation of MMP-9 in pericytes following SAH may be attributed to the activation of protease-activated receptors (PARs) by thrombin. This activation triggers the activation of G-protein coupled receptors and subsequent signaling through the PKC θ -Akt and PKC δ -ERK1/2 pathways (168–171). Additionally, MMP-9 expression could be induced by ROS through the activation of the NF- κ B inflammatory pathway (172). Pericytes play a significant role in the pathophysiological cascade by secreting cyclophilin A (CypA), and the elevated expression of CypA was co-localized with pericyte markers (173). Moreover, greater ferritin was localized in pericytes after SAH, suggesting that pericytes store iron and are associated with low oxygen tension, high ROS, and acidosis. Fe²⁺ could accelerate ROS production under SAH or ischemic conditions and induce electrolyte imbalance (174). The DAMPs in the perivascular spaces could activate pericytes and initiate a local pro-inflammatory response, which could be related to the infiltration of leukocytes and the degradation of tight junctions (161).

Therapeutic targets in the BBB

In preclinical models, multiple therapeutic strategies have been identified to enhance BBB integrity following SAH. However, the mechanisms underlying these treatments and their specific targets for BBB disruption have not been examined. Several molecular mediators, including MMP-9 (175), Nrf2 (176, 177), TLR4 (178, 179), VEGF (180, 181), and ZO-1 (5), have been observed to contribute to BBB disruption in SAH-induced EBI. Many studies have explored the mechanisms and possible therapeutic targets for BBB disruption in EBI following SAH, and these findings have been summarized in Table 2.

Microvascular endothelial cells dysfunction

Cerebral capillary endothelial cells maintain BBB function. However, BBB disruption could occur because of injuries to endothelial cells caused by aneurysmal rupture. Endothelial cell apoptosis may be triggered within 24 h of SAH by factors such as oxidative stress, oxyhemoglobin, and iron overload (68, 91). Oxyhemoglobin exerts cytotoxic effects on endothelial cells by activating caspase-3, caspase-8, caspase-9, and MMP-9, elevating intracellular Ca²⁺ and free radicals (68). Oxidative stress injury, excessive free radicals, extracellular hemoglobin, and iron overload following SAH were associated with several endothelial cell damage. Furthermore, the overproduction of ROS could activate proapoptotic signals, accelerating cell apoptosis and aggravating BBB disruption through p53, caspase-3, and caspase-9 (182). Furthermore, the factors implicated in endothelial cell damage following SAH encompass heme, thrombin, platelets, fibrinogen, and leukocytes, which have the potential to activate microglia and TLR4. TLR4 could recognize damage and induces inflammatory cascades through activation of

TABLE 2 Potential therapeutic targets and agents for early brain injury in the blood–brain barrier.

Components of the BBB	Molecular mediators	Potential therapeutic agents
Microvascular endothelial cells dysfunction	MMP-9	ApoE-mimetic peptide (193)
	ALOX15	Cepharanthine (194)
	Caspases	XIAP, VX-765, and Z-VAD-FMK (195)
Disruption of tight junctions	Ang-1, MAPK, VEGF-A	Recombinant osteopontin (198)
	ATF6/CHOP	Apelin-13 (209)
	RIP3/MLKL	Necrostatin-1 (211)
	VASP, occludin, AQP	JNJ16259685 (213)
	MMP-9, RIP3, MLKL	Celastrol (175)
	HIF-1 α , MMP-9, and VEGF	2-Methoxyestradiol (215)
	ZO-1, caspase-3, Bax, Bcl-2, TLR2, and TLR4	Cerebrolysin (216)
Astrocytes and pericytes	APQ4	Hydrogen sulfide, β -hydroxybutyrate (54, 217)
	Nrf2, ho-1, phospho-Akt, Bcl-2, Bcl-2-related X protein	Gastrodin (219)
	STAT3	Ponesimod (221)
	Cdk5	Roscovitine (222)
	PI3K/AKT	Recombinant GBP2 protein and LY294002 (223)
	ERR γ /PGC-1 α /SIRT3	DY131 (225)

NF- κ B, activator protein-1, or both mediated by MAPKs (46, 141). ErbB4, a member of the EGFR tyrosine kinase family, also plays a role in regulating the guidance of axons, the outgrowth of neurites, and the signaling between synapses (183). Study has demonstrated that ErbB4 can enhance the survival of endothelial cells and maintain the integrity of the BBB in the presence of oxidative stress injury (184). The activation of ErbB4 enhances the expression of tight junction proteins, including occludin and claudin-5, and promotes protective effects through the ErbB4/YAP/PIK3CB signaling pathway (83). Focal adhesion kinase (FAK) plays a crucial role in regulating the function of endothelial cells and maintaining the integrity of the endothelial barrier. When FAK is absent in endothelial cells, it can lead to the disruption of barrier integrity and abnormal distribution of vascular endothelial cadherin (185).

EBI can occur due to the leakage of blood into the subarachnoid space and subsequent dissemination through the cerebrospinal fluid surrounding the brain. This can lead to a sudden increase in intracranial pressure, reduced cerebral blood flow, cerebral edema, acute vasospasm, global cerebral ischemia, and impaired autoregulation (186, 187). These instabilities are significantly associated with the prognosis of SAH (5, 188). The large and small cerebral vessel constriction occurs immediately after SAH, and the vasoconstriction-mediating endothelial cell receptors, endothelin B or serotonin receptors (5-HT_{1B}), were upregulated. However, the expression of the vasodilator NO in the cerebral arteries was reduced (189–191). The hyper-responsive endothelial cells could activate smooth muscle cells (192). Several studies have illustrated the underlying molecular changes of endothelial cell dysfunction for EBI (193–195). Pang et al. (193) discovered that the administration of ApoE-mimetic peptides could effectively suppress endothelial cell apoptosis and enhance the prognosis of EBI. This treatment approach resulted in several beneficial outcomes, including decreased brain edema and neuronal apoptosis, enhanced cerebral glucose uptake, and improved neurological functions. These effects were achieved by inhibiting the pro-inflammatory activators of MMP-9. Gao et al. (194) provided evidence of ferroptosis induction in microglia and endothelial cells following SAH, accompanied by an upregulation of 15-lipoxygenase-1 (ALOX15) expression. Cepharranthine exerts an inhibitory effect on ferroptosis by suppressing the expression of ALOX15. Finally, caspases were involved in endothelial cell apoptosis at the early stages after SAH, and caspase inhibitors (XIAP, VX-765, and Z-VAD-FMK) could ameliorate EBI after SAH (195).

Disruption of tight junctions

The integrity and permeability of the BBB may be compromised due to endothelial cell contraction and disassembly of TJs, leading to the development of brain edema following SAH (68). Substances transport across the BBB through the paracellular and transcellular pathways. The disruption of TJs may result in the leakage of exudate into the brain's extracellular space, leading to the accumulation of extracellular fluid (196). The phosphorylation of TJ proteins can modulate the interaction, redistribution, and subcellular localization of transmembrane proteins, such as occludin, ZO-1, and claudin-5 (104). The downregulation of occludin and ZO-1 in tight junctions could cause capillary leakage, thereby increasing BBB permeability (186, 197). The role of MMP-9 in the early stages of BBB disruption

after SAH has been illustrated. Inflammatory cytokines and ROS can stimulate the production of MMP-9, which can result in the breakdown of the extracellular matrix surrounding cerebral microvessels and the disruption of TJ proteins between endothelial cells (121). NF- κ B activation facilitates the transcription of MMP-9 and tissue inhibitor of MMP-1. The dynamic interplay between MMP-9 and tissue inhibitor of MMP-1 plays a crucial role in determining the extent of BBB disruption following SAH (198, 199). Additionally, the activation of MAPK signaling pathway may facilitate the activation of MMP-9, while the disruption of ZO-1 in endothelial cells could lead to the upregulation of tenascin-C and periostin matricellular proteins (200–202). Furthermore, galectin-3 could activate MMP-9 in endothelial cells and affect BBB disruption through the MAPK signaling pathway (203, 204).

Heat shock protein 70 (HSP 70) significantly reduces MMP-9 activity, and BBB disruption and cell death could be mediated via aberrant proteolysis, which regulates inflammation and brain edema during EBI (205). Moreover, NF- κ B and MAPKs could be activated by TLR4 after SAH, resulting in the upregulation of pro-inflammatory cytokines and mediators (201). Studies have demonstrated that several molecules can be stimulated at different phases of BBB disruption, such as VEGF-A, VEGF-B, angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2), MAPKs, and MAPK phosphatase-1 (206). VEGF-A has the potential to disrupt the BBB, whereas VEGF-B and Ang-1 have the ability to counteract the effects of VEGF-A by regulating MAPK signaling pathway. MAPK phosphatase-1 is recognized as an intrinsic inhibitor of MAPK, while Ang-2 functions as an endogenous antagonist of Ang-1 (207, 208). Thus, the decrease in Ang-1 and MAPK phosphatase-1 expression, along with the increase in MAPKs and VEGF-A expression, contributed to the disruption of the BBB following SAH. Conversely, the upregulation of MAPK phosphatase-1, inactivation of MAPKs, and downregulation of VEGF-A could ameliorate BBB damage (206). These molecules could be regulated by recombinant osteopontin to restore BBB function, whereas Ang-2 and VEGF-B were not altered (206). Additionally, BBB disruption could be regulated by the hypoxia-HIF-1 α -LCN2-VEGF-A signaling pathway (119, 208). The expression of activating transcription factor 6 (ATF6) is strongly associated with BBB disruption and is increased during EBI. On the other hand, the administration of apelin-13 has been shown to suppress the ATF6/CHOP signaling pathway, thereby ameliorating BBB damage (209). The activation of the Wnt/ β -catenin signaling pathway could be a potential therapeutic target for enhancing the integrity of the BBB. β -catenin, an adherens junction protein and a transducer of the Wnt pathway, plays a role in the endogenous protective mechanism that regulates BBB function. Disruption of β -catenin is associated with decreased levels of tight junction proteins, which are crucial for maintaining BBB integrity. However, activation of the Wnt/ β -catenin signaling pathway can attenuate this disruption and promote the expression of tight junction proteins, thereby improving BBB integrity (210). The tropomyosin-related kinase receptor B (TrkB) activation could ameliorate EBI by restoring the TJ protein ZO-1 via the activated Wnt/ β -catenin signaling pathway (196).

Recent studies have elucidated the underlying molecular changes in tight junction disruption during EBI. The utilization of necrostatin-1, a selective inhibitor of receptor-interacting protein kinase 1 (RIP1), may mitigate albumin leakage and degradation of TJ

proteins, serving as a neuroprotective agent following SAH through the inhibition of RIP3/MLKL signaling pathway activity (211, 212). The administration of the metabotropic glutamate receptor 1 (mGluR1) negative allosteric modulator JNJ16259685 via intraperitoneal injection at 72 h post-SAH could lead to an increase in phosphorylation of the vasodilator-stimulated phosphoprotein (VASP) and occludin, as well as a reduction in aquaporin (AQP) levels (213). In addition, celastrol has the potential to improve the leakage of albumin and degradation of TJ proteins in order to preserve the integrity of the BBB. This is achieved by inhibiting the expression of MMP-9 and exerting anti-neuroinflammatory effects. Furthermore, celastrol has the ability to decrease the levels of RIP3 and MLKL, which are proteins associated with necroptosis, and reduce the presence of propidium iodide-positive cells in the basal cortex (175). The inhibition of NLRP3 was linked to reduced cerebral edema, preservation of tight junction integrity, prevention of microthrombosis, and modulation of microglial reactive morphology (214). Hu et al. (215) discovered that the administration of 2-Methoxyestradiol demonstrated a potential to ameliorate the disruption of tight junction proteins and suppress the expression of HIF-1 α , MMP-9, and VEGF. Consequently, this led to an improvement in the inflammatory response to EBI and BBB disruption following SAH. Finally, cerebrolysin could upregulate ZO-1 levels, reduce the protein expression of caspase-3 or Bax, and increase the Bcl-2 expression level. The TLR2 and TLR4 levels were also reduced after cerebrolysin treatment (216).

Astrocytes and pericytes

Astrocytes and pericytes are crucial for maintaining the integrity of the BBB. However, there is limited research on the mechanisms and potential therapeutic targets involving astrocytes and pericytes in EBI following SAH. Hydrogen sulfide has the potential to reduce the formation of brain edema by protecting the BBB and reducing the expression of AQP4 on astrocytes through the inhibition of glial cell activation and the secretion of pro-inflammatory cytokines (217).

Moreover, the pathological process of EBI after SAH could be affected by Nox4, whereas there is no overlay effect of Nox2 inhibition and Nox4 inhibition for preventing EBI after SAH (218). SAH could induce microglial activation, astrocyte activation, and neuronal apoptosis, and the use of gastrodin could suppress these molecular changes. Additionally, it could reduce oxidative stress and inflammatory response, upregulate the Nrf2, ho-1, phospho-Akt, or Bcl-2, and downregulate the Bcl-2-related X protein and cleaved caspase-3 (219). Promoting PK2 expression and utilizing recombinant PK2 can selectively regulate astrocytic polarization, inducing a protective phenotype following SAH (148). The upregulated expression of the calcium-sensing receptor in neurons, astrocytes, and microglia after SAH could promote EBI via the CaMKII/NLRP3 signaling pathway (220). Furthermore, ponesimod could prevent astrocytic polarization to the A1 phenotype, and ponesimod could mediate astrocytic response via the STAT3 signaling pathway (221). The expression of cyclin-dependent kinase 5 (Cdk5) was observed in both neurons and astrocytes following SAH. Treatment with roscovitine resulted in the improvement of EBI and reduction of cerebral edema after SAH by inhibiting the activity of Cdk5 (222). The 6-gingerol could activate PI3K/AKT signaling pathway, and

recombinant GBP2 protein and LY294002 (PI3K inhibitor) could reverse the effects of 6-gingerol (223). Furthermore, miR-26b may exacerbate EBI and the inflammatory response following SAH, promoting hemoglobin-induced apoptosis in astrocytes. Conversely, the suppression of miR-26b could alleviate EBI after SAH by modulating the KLF4/STAT3/HMGB1 signaling pathway (224). Activation of Estrogen-related receptor γ (ERR γ) using DY131 may enhance the reduction of oxidative stress and neuronal apoptosis following SAH through the ERR γ /PGC-1 α /SIRT3 signaling pathway. This pathway could potentially be targeted as a novel therapeutic approach to mitigate EBI after SAH (225).

The regulatory pathways of pericyte involved in SAH include the PDGF pathway (226), the Notch pathway (227), the canonical Wnt/ β -catenin pathway (228), and new players in the pericyte signaling pathway, such as miRNA, exosome, and lncRNA (161). Moreover, the pericyte α -SMA phenotype could inhibit the NO/cGMP signaling pathway to mediate acute microvessel constriction after SAH, and the eNOS or the pericyte α -SMA phenotype could be considered therapeutic targets (167). ApoE deficiency could activate the CypA-NF- κ B-MMP-9 pathway and induce the degradation of N-cadherin, resulting in greater pericytes loss, which is significantly associated with EBI after SAH (229). Furthermore, the glial limitans formation and neurological function could be regulated by pericytes through EphA4/EphrinB2 signaling pathway, and the intervention should be applied as a novel treatment target for improving EBI after SAH (230).

Glymphatic system impairment and EBI

Subarachnoid hemorrhage (SAH) impairs meningeal lymphatic system function. Evaluations using gadopentetate dimeglumine distribution reveal reduced cerebrospinal fluid inflow post-SAH, more prominently in the ipsilateral hemisphere, persisting for 1 week with partial recovery by the second week. Under physiological conditions, gadopentetate dimeglumine rapidly fills regions like the olfactory bulb and optic nerve, while SAH induces delayed and diminished outflow in these areas, indicating lymphatic clearance dysfunction. Additionally, intermittent cerebellomedullary cistern cerebrospinal fluid drainage markedly improves glymphatic and meningeal lymphatic system function following SAH (56).

A study integrating single-cell RNA sequencing, spatial transcriptomics, and *in vivo/in vitro* experiments delineated the spatial and cellular alterations of meningeal lymphatic vessels (mLVs) in the early phase after SAH. It demonstrated that THBS1 overexpression and its interaction with CD47 may induce meningeal lymphatic endothelial cell (mLEC) apoptosis via the STAT3/Bcl-2 signaling pathway. Concurrently, S100 α 6 was identified as associated with poor prognosis, potentially serving as a novel biomarker for meningeal lymphatic injury, with a linear relationship to THBS1 expression (231).

Th17 cells are linked to post-SAH brain injury, though their cerebral clearance mechanism remains unclear (232). SAH model mice exhibit significant behavioral abnormalities, brain injury, and cerebral immune cell accumulation. Further investigations show that laser ablation of the meningeal lymphatic system or CCR7 knockout leads to meningeal Th17 cell accumulation, reduced neurological scores, and elevated inflammatory factor levels. Conversely, VEGF-C

or CCL21 protein injection promotes Th17 cell drainage to lymph nodes, improves neurological scores, and lowers inflammatory factor levels (233).

Another study reported increased aquaporin 4 (AQP4) expression post-SAH (234). Notably, SNTA1 knockout reduces AQP4 polarization, implying a association between AQP4 polarization and SNTA1 expression (235). Western blot and immunofluorescence analyses indicated that post-SAH, AQP4 expression increases while polarization decreases, with concurrent SNTA1 upregulation. BHB treatment restores AQP4 polarization by upregulating SNTA1, enhances meningeal lymphatic system function, mitigates neuroinflammation, and thereby ameliorates neurological deficits in SAH mice (54).

Meningeal lymphatic vessels also play a key role in Alzheimer's disease (AD) by modulating β -amyloid ($A\beta$) clearance, microglial activation, and immunotherapeutic efficacy (236). Post-SAH early brain injury and delayed cerebral ischemia trigger neuroinflammatory responses, which are closely linked to AD neurodegeneration (237, 238). Deep cervical lymphatic-venous anastomosis (LVA) is safe and effective, significantly improving AD patients' cognitive function as evidenced by pre- and post-surgical Mini-Mental Status Examination, though its long-term efficacy requires verification through large-scale clinical trials and prolonged follow-up (55, 239).

Perspective

There are multiple pathological and molecular processes that contribute to the breakdown of the BBB following SAH, while the precise mechanisms and potential therapeutic targets for EBI after SAH in the BBB are still not fully understood. Currently, the majority of therapeutic interventions aim to enhance endothelial cell dysfunction and restore TJ integrity following SAH, but these interventions have not yet been successfully translated into clinical practice. Moreover, the complex pathogenesis of BBB disruption after SAH and its role in causing EBI makes it difficult to alleviate by inhibiting a single pathway or molecule. Therefore, it is essential to investigate the underlying mechanisms and identify potential therapeutic molecular targets for the BBB to enhance EBI following SAH. Additional studies should be performed to identify potential therapeutic targets against BBB disruption and improve the EBI after SAH. Notably, the neurodegenerative process in Alzheimer's disease (AD) is closely linked to that following subarachnoid hemorrhage (SAH). Deep cervical lymphatic-venous anastomosis (LVA), as an emerging therapeutic technique for improving cognitive function in

AD patients, remains to be validated through large-scale clinical trials and long-term follow-up investigations.

Author contributions

HO: Writing – original draft. HG: Writing – review & editing. YC: Writing – review & editing. CW: Visualization, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This research was funded by the Huzhou Municipal Bureau of Science and Technology (Grant No. 2024GY20).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Lawton MT, Vates GE. Subarachnoid hemorrhage. *N Engl J Med*. (2017) 377:257–66. doi: 10.1056/NEJMcp1605827
2. Hoh BL, Ko NU, Amin-Hanjani S, Chou SH-Y, Cruz-Flores S, Dangayach NS, et al. 2023 guideline for the management of patients with aneurysmal subarachnoid hemorrhage: a guideline from the American Heart Association/American Stroke Association. *Stroke*. (2023) 54:e314–70. doi: 10.1161/STR.0000000000000436
3. Robba C, Busl KM, Claassen J, Diring MN, Helbok R, Park S, et al. Contemporary management of aneurysmal subarachnoid haemorrhage. An update for the intensivist. *Intensive Care Med*. (2024) 50:646–64. doi: 10.1007/s00134-024-07387-7
4. Schertz M, Mehdaoui H, Hamlat A, Piotin M, Banydeen R, Mejdoubi M. Incidence and mortality of spontaneous subarachnoid hemorrhage in Martinique. *PLoS One*. (2016) 11:e0155945. doi: 10.1371/journal.pone.0155945
5. Rass V, Helbok R. Early brain injury after poor-grade subarachnoid hemorrhage. *Curr Neurol Neurosci Rep*. (2019) 19:78. doi: 10.1007/s11910-019-0990-3
6. Lauzier DC, Jayaraman K, Yuan JY, Diwan D, Vellimana AK, Osbun JW, et al. Early brain injury after subarachnoid hemorrhage: incidence and mechanisms. *Stroke*. (2023) 54:1426–40. doi: 10.1161/STROKEAHA.122.040072
7. Osgood ML. Aneurysmal subarachnoid hemorrhage: review of the pathophysiology and management strategies. *Curr Neurol Neurosci Rep*. (2021) 21:50. doi: 10.1007/s11910-021-01136-9
8. Li T, Xu W, Gao L, Guan G, Zhang Z, He P, et al. Mesencephalic astrocyte-derived neurotrophic factor affords neuroprotection to early brain injury induced by subarachnoid hemorrhage via activating Akt-dependent prosurvival pathway and

- defending blood–brain barrier integrity. *FASEB J.* (2019) 33:1727–41. doi: 10.1096/fj.201800227RR
9. Chen J, Chen G, Li J, Qian C, Mo H, Gu C, et al. Melatonin attenuates inflammatory response-induced brain edema in early brain injury following a subarachnoid hemorrhage: a possible role for the regulation of pro-inflammatory cytokines. *J Pineal Res.* (2014) 57:340–7. doi: 10.1111/jpi.12173
10. Solár P, Zamani A, Lakatosová K, Joukal M. The blood–brain barrier and the neurovascular unit in subarachnoid hemorrhage: molecular events and potential treatments. *Fluids Barriers CNS.* (2022) 19:29. doi: 10.1186/s12987-022-00312-4
11. Sweeney MD, Zhao Z, Montagne A, Nelson AR, Zlokovic BV. Blood–brain barrier: from physiology to disease and back. *Physiol Rev.* (2019) 99:21–78. doi: 10.1152/physrev.00050.2017
12. Tso MK, Macdonald RL. Subarachnoid hemorrhage: a review of experimental studies on the microcirculation and the neurovascular unit. *Transl Stroke Res.* (2014) 5:174–89. doi: 10.1007/s12975-014-0323-4
13. Schöller K, Trinkl A, Klopotoski M, Thal SC, Plesnila N, Trabold R, et al. Characterization of microvascular basal lamina damage and blood–brain barrier dysfunction following subarachnoid hemorrhage in rats. *Brain Res.* (2007) 1142:237–46. doi: 10.1016/j.brainres.2007.01.034
14. Grote E, Hassler W. The critical first minutes after subarachnoid hemorrhage. *Neurosurgery.* (1988) 22:654–61. doi: 10.1227/00006123-198804000-00006
15. Sarwal A, Robba C, Venegas C, Ziai W, Czosnyka M, Sharma D. Are we ready for clinical therapy based on cerebral autoregulation? A pro-con debate. *Neurocrit Care.* (2023) 39:269–83. doi: 10.1007/s12028-023-01741-1
16. Ostrowski RP, Colohan AR, Zhang JH. Molecular mechanisms of early brain injury after subarachnoid hemorrhage. *Neurol Res.* (2006) 28:399–414. doi: 10.1179/016164106X115008
17. Stafford P, Mitra S, Debot M, Lutz P, Stem A, Hadley J, et al. Astrocytes and pericytes attenuate severely injured patient plasma mediated expression of tight junction proteins in endothelial cells. *PLoS One.* (2022) 17:e0270817. doi: 10.1371/journal.pone.0270817
18. Alsbrook DL, Di Napoli M, Bhatia K, Biller J, Andalib S, Hinduja A, et al. Neuroinflammation in acute ischemic and hemorrhagic stroke. *Curr Neurol Neurosci Rep.* (2023) 23:407–31. doi: 10.1007/s11910-023-01282-2
19. Ayer R, Zhang J. Connecting the early brain injury of aneurysmal subarachnoid hemorrhage to clinical practice. *Turk Neurosurg.* (2010) 20:159–66. doi: 10.5137/1019-5149.JTN.2714-09.0
20. Li X, Zeng L, Lu X, Chen K, Yu M, Wang B, et al. Early brain injury and neuroprotective treatment after aneurysmal subarachnoid hemorrhage: a literature review. *Brain Sci.* (2023) 13:1083. doi: 10.3390/brainsci13071083
21. Chou SH, Feske SK, Simmons SL, Konigsberg RG, Orzell SC, Marckmann A, et al. Elevated peripheral neutrophils and matrix metalloproteinase 9 as biomarkers of functional outcome following subarachnoid hemorrhage. *Transl Stroke Res.* (2011) 2:600–7. doi: 10.1007/s12975-011-0117-x
22. Sehba FA, Pluta RM, Zhang JH. Metamorphosis of subarachnoid hemorrhage research: from delayed vasospasm to early brain injury. *Mol Neurobiol.* (2011) 43:27–40. doi: 10.1007/s12035-010-8155-z
23. Li Y, Wu P, Bihl JC, Shi H. Underlying mechanisms and potential therapeutic molecular targets in blood–brain barrier disruption after subarachnoid hemorrhage. *Curr Neuropharmacol.* (2020) 18:1168–79. doi: 10.2174/1570159X18666200106154203
24. Cornejo-Olivas M, Griswold AJ, Saldarriaga-Mayo A, Mena PR, Rodriguez RS, Adams LD, et al. Basic science and pathogenesis. *Alzheimers Dement.* (2024) 20:e090818. doi: 10.1002/alz.090818
25. Bordoní L, Thoren AE, Gutiérrez-Jiménez E, Åbjörnsbråten KS, Bjørnstad DM, Tang W, et al. Deletion of aquaporin-4 improves capillary blood flow distribution in brain edema. *Glia.* (2023) 71:2559–72. doi: 10.1002/glia.24439
26. Park IS, Meno JR, Witt CE, Chowdhary A, Nguyen TS, Winn HR, et al. Impairment of intracerebral arteriole dilation responses after subarachnoid hemorrhage. Laboratory investigation. *J Neurosurg.* (2009) 111:1008–13. doi: 10.3171/2009.3.JNS096
27. Crobbedu E, Pilloni G, Tardivo V, Fontanella MM, Panciani PP, Spena G, et al. Role of nitric oxide and mechanisms involved in cerebral injury after subarachnoid hemorrhage: is nitric oxide a possible answer to cerebral vasospasm? *J Neurosurg Sci.* (2016) 60:385–91.
28. Sunny A, James RR, Menon SR, Rayaroth S, Daniel A, Thompson NA, et al. Matrix Metalloproteinase-9 inhibitors as therapeutic drugs for traumatic brain injury. *Neurochem Int.* (2024) 172:105642. doi: 10.1016/j.neuint.2023.105642
29. Barcelos GK, Tholance Y, Grousseau S, Renaud B, Perret-Liaudet A, Dailler F, et al. Outcome of poor-grade subarachnoid hemorrhage as determined by biomarkers of glucose cerebral metabolism. *Neurocrit Care.* (2013) 18:234–44. doi: 10.1007/s12028-012-9810-1
30. Bosche B, Graf R, Ernestus RI, Dohmen C, Reithmeier T, Brinker G, et al. Recurrent spreading depolarizations after subarachnoid hemorrhage decreases oxygen availability in human cerebral cortex. *Ann Neurol.* (2010) 67:607–17. doi: 10.1002/ana.21943
31. Song B, Jiang M, Zhang Y, Xu Y, Wu C, Wu D, et al. Research hotspots and frontier trends of neuroprotective effects of magnesium from 1999 to 2023: a bibliometric analysis. *CNS Neurosci Ther.* (2024) 30:e14597. doi: 10.1111/cns.14597
32. Peeters M, Gunthorpe MJ, Strijbos PJ, Goldsmith P, Upton N, James MF. Effects of pan- and subtype-selective N-methyl-D-aspartate receptor antagonists on cortical spreading depression in the rat: therapeutic potential for migraine. *J Pharmacol Exp Ther.* (2007) 321:564–72. doi: 10.1124/jpet.106.117101
33. Sukhotinsky I, Yaseen MA, Sakadzić S, Ruvinskaya S, Sims JR, Boas DA, et al. Perfusion pressure-dependent recovery of cortical spreading depression is independent of tissue oxygenation over a wide physiologic range. *J Cereb Blood Flow Metab.* (2010) 30:1168–77. doi: 10.1038/jcbfm.2009.285
34. Weng W, Cheng F, Zhang J. Specific signature biomarkers highlight the potential mechanisms of circulating neutrophils in aneurysmal subarachnoid hemorrhage. *Front Pharmacol.* (2022) 13:1022564. doi: 10.3389/fphar.2022.1022564
35. Galea J, Ogungbenro K, Hulme S, Patel H, Scarth S, Hoadley M, et al. Reduction of inflammation after administration of interleukin-1 receptor antagonist following aneurysmal subarachnoid hemorrhage: results of the subcutaneous interleukin-1Ra in SAH (SCIL-SAH) study. *J Neurosurg.* (2018) 128:515–23. doi: 10.3171/2016.9.JNS16615
36. Xu YZ, Deng XH, Bentivoglio M. Differential response of apoptosis-regulatory Bcl-2 and Bax proteins to an inflammatory challenge in the cerebral cortex and hippocampus of aging mice. *Brain Res Bull.* (2007) 74:329–35. doi: 10.1016/j.brainresbull.2007.07.002
37. Kılıç G, Engin BE, Halabi A, Tuncer C, Sungur MA, Alpay M, et al. Mitigating post-subarachnoid hemorrhage complications: anti-inflammatory and anti-apoptotic effects of Anakinra in an experimental study. *J Clin Med.* (2025) 14:1253. doi: 10.3390/jcm14041253
38. Higashi Y, Maruhashi T, Noma K, Kihara Y. Oxidative stress and endothelial dysfunction: clinical evidence and therapeutic implications. *Trends Cardiovasc Med.* (2014) 24:165–9. doi: 10.1016/j.tcm.2013.12.001
39. Endo H, Nito C, Kamada H, Yu F, Chan PH. Reduction in oxidative stress by superoxide dismutase overexpression attenuates acute brain injury after subarachnoid hemorrhage via activation of Akt/glycogen synthase kinase-3beta survival signaling. *J Cereb Blood Flow Metab.* (2007) 27:975–82. doi: 10.1038/sj.jcbfm.9600399
40. Andrianov VV, Kulchitsky VA, Yafarova GG, Bazan LV, Bogodvid TK, Deryabina IB, et al. Investigation of NO role in neural tissue in brain and spinal cord injury. *Molecules.* (2023) 28:7359. doi: 10.3390/molecules28217359
41. Loftspring MC. Iron and early brain injury after subarachnoid hemorrhage. *J Cereb Blood Flow Metab.* (2010) 30:1791–2. doi: 10.1038/jcbfm.2010.139
42. Ostrowski RP, Tang J, Zhang JH. Hyperbaric oxygen suppresses NADPH oxidase in a rat subarachnoid hemorrhage model. *Stroke.* (2006) 37:1314–8. doi: 10.1161/01.STR.0000217310.88450.c3
43. Kubota H, Tsutsui M, Kuniyoshi K, Yamashita H, Shimokawa H, Sugahara K, et al. Alleviated cerebral infarction in male mice lacking all nitric oxide synthase isoforms after middle cerebral artery occlusion. *J Anesth.* (2024) 38:44–56. doi: 10.1007/s00540-023-03271-8
44. Wu J, Jia J, Ji D, Jiao W, Huang Z, Zhang Y. Advances in nitric oxide regulators for the treatment of ischemic stroke. *Eur J Med Chem.* (2023) 262:115912. doi: 10.1016/j.ejmech.2023.115912
45. Jiang X, Andjelkovic AV, Zhu L, Yang T, Bennett MVL, Chen J, et al. Blood–brain barrier dysfunction and recovery after ischemic stroke. *Prog Neurobiol.* (2018) 163–164:144–71. doi: 10.1016/j.pneurobio.2017.10.001
46. Suzuki H, Fujimoto M, Kawakita F, Liu L, Nakatsuka Y, Nakano F, et al. Tenascin-C in brain injuries and edema after subarachnoid hemorrhage: findings from basic and clinical studies. *J Neurosci Res.* (2020) 98:42–56. doi: 10.1002/jnr.24330
47. Keep RF, Zhou N, Xiang J, Andjelkovic AV, Hua Y, Xi G. Vascular disruption and blood–brain barrier dysfunction in intracerebral hemorrhage. *Fluids Barriers CNS.* (2014) 11:18. doi: 10.1186/2045-8118-11-18
48. Ivanidze J, Ferraro RA, Giambrone AE, Segal AZ, Gupta A, Sanelli PC. Blood–brain barrier permeability in aneurysmal subarachnoid hemorrhage: correlation with clinical outcomes. *AJR Am J Roentgenol.* (2018) 211:891–5. doi: 10.2214/AJR.17.18237
49. Abbott NJ, Rönnbäck L, Hansson E. Astrocyte-endothelial interactions at the blood–brain barrier. *Nat Rev Neurosci.* (2006) 7:41–53. doi: 10.1038/nrn1824
50. Suzuki H, Nakano F. To improve translational research in subarachnoid hemorrhage. *Transl Stroke Res.* (2018) 9:1–3. doi: 10.1007/s12975-017-0546-2
51. Ueno M. Molecular anatomy of the brain endothelial barrier: an overview of the distributional features. *Curr Med Chem.* (2007) 14:1199–206. doi: 10.2174/092986707780597943
52. Chachaj A, Gąsiorowski K, Szuba A, Sieradzki A, Leszek J. The lymphatic system in the brain clearance mechanisms—new therapeutic perspectives for Alzheimer's disease. *Curr Neuropharmacol.* (2023) 21:380–91. doi: 10.2174/1570159X20666220411091332
53. Murdock MH, Yang CY, Sun N, Pao PC, Blanco-Duque C, Kahn MC, et al. Multisensory gamma stimulation promotes glymphatic clearance of amyloid. *Nature.* (2024) 627:149–56. doi: 10.1038/s41586-024-07132-6

54. Tan X, Li X, Li R, Meng W, Xie Z, Li J, et al. β -Hydroxybutyrate alleviates neurological deficits by restoring glymphatic and inflammation after subarachnoid hemorrhage in mice. *Exp Neurol.* (2024) 378:114819. doi: 10.1016/j.expneurol.2024.114819
55. Ma YN, Wang Z, Tang W. Deep cervical lymphaticovenous anastomosis in Alzheimer's disease: a promising frontier or premature enthusiasm? *Biosci Trends.* (2025) 19:144–9. doi: 10.5582/bst.2025.01108
56. Wang J, Lv T, Jia F, Li Y, Ma W, Xiao ZP, et al. Subarachnoid hemorrhage distinctively disrupts the glymphatic and meningeal lymphatic systems in beagles. *Theranostics.* (2024) 14:6053–70. doi: 10.7150/thno.100982
57. Begley DJ, Brightman MW. Structural and functional aspects of the blood–brain barrier. *Prog Drug Res.* (2003) 61:39–78. doi: 10.1007/978-3-0348-8049-7_2
58. Wolburg H, Noell S, Mack A, Wolburg-Buchholz K, Fallier-Becker P. Brain endothelial cells and the blood–vascular complex. *Cell Tissue Res.* (2009) 335:75–96. doi: 10.1007/s00441-008-0658-9
59. Tietz S, Engelhardt B. Brain barriers: crosstalk between complex tight junctions and adherens junctions. *J Cell Biol.* (2015) 209:493–506. doi: 10.1083/jcb.201412147
60. Hansen CE, Hollaus D, Kamermans A, de Vries HE. Tension at the gate: sensing mechanical forces at the blood–brain barrier in health and disease. *J Neuroinflammation.* (2024) 21:325. doi: 10.1186/s12974-024-03321-2
61. Reese TS, Karnovsky MJ. Fine structural localization of a blood–brain barrier to exogenous peroxidase. *J Cell Biol.* (1967) 34:207–17. doi: 10.1083/jcb.34.1.207
62. Rhea EM, Banks WA. Role of the blood–brain barrier in central nervous system insulin resistance. *Front Neurosci.* (2019) 13:521. doi: 10.3389/fnins.2019.00521
63. Deng J, Huang Q, Wang F, Liu Y, Wang Z, Wang Z, et al. The role of caveolin-1 in blood–brain barrier disruption induced by focused ultrasound combined with microbubbles. *J Mol Neurosci.* (2012) 46:677–87. doi: 10.1007/s12031-011-9629-9
64. Stamatovic SM, Keep RF, Andjelkovic AV. Brain endothelial cell–cell junctions: how to “open” the blood–brain barrier. *Curr Neuroparmacol.* (2008) 6:179–92. doi: 10.2174/157015908785777210
65. Gürses L, Seçkin H, Simşek S, Senel OO, Yigitkanli K, Oztürk E, et al. Effects of raloxifene on cerebral vasospasm after experimental subarachnoid hemorrhage in rabbits. *Surg Neurol.* (2009) 72:490–4. doi: 10.1016/j.surneu.2008.11.007
66. Stevanovic D, Zhang D, Blumenstein A, Djuric D, Heinle H. Effects of hydroperoxides on contractile reactivity and free radical production of porcine brain arteries. *Gen Physiol Biophys.* (2009) 28:93–7.
67. Marbacher S, Anderegg L, Neuschmelting V, Widmer HR, von Gunten M, Takala J, et al. A new rabbit model for the study of early brain injury after subarachnoid hemorrhage. *J Neurosci Methods.* (2012) 208:138–45. doi: 10.1016/j.jneumeth.2012.05.010
68. Peeyush Kumar T, McBride DW, Dash PK, Matsumura K, Rubi A, Blackburn SL. Endothelial cell dysfunction and injury in subarachnoid hemorrhage. *Mol Neurobiol.* (2019) 56:1992–2006. doi: 10.1007/s12035-018-1213-7
69. Shafeeqe CM, Harmanci AO, Thomas S, Dinel AC, McBride DW, Peeyush KT, et al. Gene expression changes in human cerebral arteries following hemoglobin exposure: implications for vascular responses in SAH. *Front Physiol.* (2025) 16:1529113. doi: 10.3389/fphys.2025.1529113
70. Sen O, Caner H, Aydin MV, Ozen O, Atalay B, Altinors N, et al. The effect of mexiletine on the level of lipid peroxidation and apoptosis of endothelium following experimental subarachnoid hemorrhage. *Neurol Res.* (2006) 28:859–63. doi: 10.1179/016164106X115099
71. Yan J, Chen C, Hu Q, Yang X, Lei J, Yang L, et al. The role of p53 in brain edema after 24 h of experimental subarachnoid hemorrhage in a rat model. *Exp Neurol.* (2008) 214:37–46. doi: 10.1016/j.expneurol.2008.07.006
72. Yilmaz C, Cansever T, Kircelli A, Ozen OI, Aydemir F, Akar A, et al. The effects of proanthocyanidin on vasospasm after experimental subarachnoid hemorrhage in rats. *Turk Neurosurg.* (2018) 28:667–74. doi: 10.5137/1019-5149.JTN.14781-15.3
73. Hernandes MS, Xu Q, Griendling KK. Role of NADPH oxidases in blood–brain barrier disruption and ischemic stroke. *Antioxidants.* (2022) 11:1966. doi: 10.3390/antiox11101966
74. Yamaguchi-Okada M, Nishizawa S, Mizutani A, Namba H. Multifaceted effects of selective inhibitor of phosphodiesterase III, cilostazol, for cerebral vasospasm after subarachnoid hemorrhage in a dog model. *Cerebrovasc Dis.* (2009) 28:135–42. doi: 10.1159/000223439
75. Callewaert B, Gsell W, Lox M, Himmelreich U, Jones EAV. A timeline study on vascular co-morbidity induced cerebral endothelial dysfunction assessed by perfusion MRI. *Neurobiol Dis.* (2024) 202:106709. doi: 10.1016/j.nbd.2024.106709
76. Pang J, Wu Y, Peng J, Yang P, Kuai L, Qin X, et al. Potential implications of Apolipoprotein E in early brain injury after experimental subarachnoid hemorrhage: involvement in the modulation of blood–brain barrier integrity. *Oncotarget.* (2016) 7:56030–44. doi: 10.18632/oncotarget.10821
77. Chen G, Zhang S, Shi J, Ai J, Hang C. Effects of recombinant human erythropoietin (rhEPO) on JAK2/STAT3 pathway and endothelial apoptosis in the rabbit basilar artery after subarachnoid hemorrhage. *Cytokine.* (2009) 45:162–8. doi: 10.1016/j.cyto.2008.11.015
78. Chen G, Wu J, Sun C, Qi M, Hang C, Gong Y, et al. Potential role of JAK2 in cerebral vasospasm after experimental subarachnoid hemorrhage. *Brain Res.* (2008) 1214:136–44. doi: 10.1016/j.brainres.2008.03.085
79. Duan ZD, Zheng LY, Jia QY, Chen HL, Xu DY, Yang YJ, et al. Effect of scutellarin on BV-2 microglial-mediated apoptosis in PC12 cells via JAK2/STAT3 signalling pathway. *Sci Rep.* (2024) 14:13430. doi: 10.1038/s41598-024-64226-x
80. Wang Z, Chen G, Zhu WW, Zhou D. Activation of nuclear factor-erythroid 2-related factor 2 (Nrf2) in the basilar artery after subarachnoid hemorrhage in rats. *Ann Clin Lab Sci.* (2010) 40:233–9.
81. Zhao XD, Zhou YT, Zhang X, Wang XL, Qi W, Zhuang Z, et al. Expression of NF-E2-related factor 2 (Nrf2) in the basilar artery after experimental subarachnoid hemorrhage in rabbits: a preliminary study. *Brain Res.* (2010) 1358:221–7. doi: 10.1016/j.brainres.2010.08.035
82. Wang X, Yu JY, Sun Y, Wang H, Shan H, Wang S. Baicalin protects LPS-induced blood–brain barrier damage and activates Nrf2-mediated antioxidant stress pathway. *Int Immunopharmacol.* 96:107725. doi: 10.1016/j.intimp.2021.107725
83. Qian H, Dou Z, Ruan W, He P, Zhang JH, Yan F. ErbB4 preserves blood–brain barrier integrity via the YAP/PIK3CB pathway after subarachnoid hemorrhage in rats. *Front Neurosci.* (2018) 12:492. doi: 10.3389/fnins.2018.00492
84. Luh C, Feiler S, Frauenknecht K, Meyer S, Lubomirov LT, Neulen A, et al. The contractile apparatus is essential for the integrity of the blood–brain barrier after experimental subarachnoid hemorrhage. *Transl Stroke Res.* (2019) 10:534–45. doi: 10.1007/s12975-018-0677-0
85. Joško J. Cerebral angiogenesis and expression of VEGF after subarachnoid hemorrhage (SAH) in rats. *Brain Res.* (2003) 981:58–69. doi: 10.1016/S0006-8993(03)02920-2
86. Joško J, Gwóźdź B, Hendryk S, Jedrzejowska-Szypułka H, Słowiński J, Jochem J. Expression of vascular endothelial growth factor (VEGF) in rat brain after subarachnoid haemorrhage and endothelin receptor blockage with BQ-123. *Folia Neuropathol.* (2001) 39:243–51.
87. Sun BL, Hu DM, Yuan H, Ye WJ, Wang XC, Xia ZL, et al. Extract of *Ginkgo biloba* promotes the expression of VEGF following subarachnoid hemorrhage in rats. *Int J Neurosci.* (2009) 119:995–1005. doi: 10.1080/00207450902815842
88. Liu ZW, Zhao JJ, Pang HG, Song JN. Vascular endothelial growth factor promotes platelet adhesion to collagen IV and causes early brain injury after subarachnoid hemorrhage. *Neural Regen Res.* (2019) 14:1726–33. doi: 10.4103/1673-5374.257530
89. Germanò A, d'Avella D, Imperatore C, Caruso G, Tomasello F. Time-course of blood–brain barrier permeability changes after experimental subarachnoid haemorrhage. *Acta Neurochir.* (2000) 142:575–80. doi: 10.1007/s007010050472
90. Friedrich V, Flores R, Muller A, Sehba FA. Escape of intraluminal platelets into brain parenchyma after subarachnoid hemorrhage. *Neuroscience.* (2010) 165:968–75. doi: 10.1016/j.neuroscience.2009.10.038
91. Friedrich V, Flores R, Sehba FA. Cell death starts early after subarachnoid hemorrhage. *Neurosci Lett.* (2012) 512:6–11. doi: 10.1016/j.neulet.2012.01.036
92. Sehba FA, Mostafa G, Friedrich V Jr, Bederson JB. Acute microvascular platelet aggregation after subarachnoid hemorrhage. *J Neurosurg.* (2005) 102:1094–100. doi: 10.3171/jns.2005.102.6.1094
93. Friedrich V, Flores R, Muller A, Sehba FA. Luminal platelet aggregates in functional deficits in parenchymal vessels after subarachnoid hemorrhage. *Brain Res.* (2010) 1354:179–87. doi: 10.1016/j.brainres.2010.07.040
94. Lefranc F, Decaestecker C, Brothi J, Heizmann CW, Dewitte O, Kiss R, et al. Co-expression/co-location of S100 proteins (S100B, S100A1 and S100A2) and protein kinase C (PKC- β , - η and - ζ) in a rat model of cerebral basilar artery vasospasm. *Neuropathol Appl Neurobiol.* (2005) 31:649–60. doi: 10.1111/j.1365-2990.2005.00682.x
95. Enkhjargal B, McBride DW, Manaenko A, Reis C, Sakai Y, Tang J, et al. Intranasal administration of vitamin D attenuates blood–brain barrier disruption through endogenous upregulation of osteopontin and activation of CD44/P-gp glycosylation signaling after subarachnoid hemorrhage in rats. *J Cereb Blood Flow Metab.* (2017) 37:2555–66. doi: 10.1177/0271678X16671147
96. Zhao C, Ma J, Wang Z, Li H, Shen H, Li X, et al. Mfsd2a attenuates blood–brain barrier disruption after sub-arachnoid hemorrhage by inhibiting caveolae-mediated transcellular transport in rats. *Transl Stroke Res.* (2020) 11:1012–27. doi: 10.1007/s12975-019-00775-y
97. Chen JH, Wu T, Yang LK, Chen L, Zhu J, Li PP, et al. Protective effects of atorvastatin on cerebral vessel autoregulation in an experimental rabbit model of subarachnoid hemorrhage. *Mol Med Rep.* (2018) 17:1651–9. doi: 10.3892/mmr.2017.8074
98. Xu T, Zhang WG, Sun J, Zhang Y, Lu JF, Han HB, et al. Protective effects of thrombomodulin on microvascular permeability after subarachnoid hemorrhage in mouse model. *Neuroscience.* (2015) 299:18–27. doi: 10.1016/j.neuroscience.2015.04.058
99. Sercombe R, Dinh YR, Gomis P. Cerebrovascular inflammation following subarachnoid hemorrhage. *Jpn J Pharmacol.* (2002) 88:227–49. doi: 10.1254/jjp.88.227
100. Hostenbach S, D'haeseleer M, Kooijman R, De Keyser J. The pathophysiological role of astrocytic endothelin-1. *Prog Neurobiol.* (2016) 144:88–102. doi: 10.1016/j.pneurobio.2016.04.009

101. Zhang Z, Chen H, Liu L, Zhao G, He J, Liu H, et al. ETAR silencing ameliorated neurovascular injury after SAH in rats through ERK/KLF4-mediated phenotypic transformation of smooth muscle cells. *Exp Neurol*. (2021) 337:113596. doi: 10.1016/j.expneurol.2021.113596
102. Munakata A, Naraoka M, Katagiri T, Shimamura N, Ohkuma H. Role of cyclooxygenase-2 in relation to nitric oxide and Endothelin-1 on pathogenesis of cerebral vasospasm after subarachnoid hemorrhage in rabbit. *Transl Stroke Res*. (2016) 7:220–7. doi: 10.1007/s12975-016-0466-6
103. Liu L, Zhang P, Zhang Z, Hu Q, He J, Liu H, et al. LXA4 ameliorates cerebrovascular endothelial dysfunction by reducing acute inflammation after subarachnoid hemorrhage in rats. *Neuroscience*. (2019) 408:105–14. doi: 10.1016/j.neuroscience.2019.03.038
104. Li Z, Liang G, Ma T, Li J, Wang P, Liu L, et al. Blood–brain barrier permeability change and regulation mechanism after subarachnoid hemorrhage. *Metab Brain Dis*. (2015) 30:597–603. doi: 10.1007/s11011-014-9609-1
105. Dithmer S, Blasig IE, Fraser PA, Qin Z, Haseloff RF. The basic requirement of tight junction proteins in blood–brain barrier function and their role in pathologies. *Int J Mol Sci*. (2024) 25:5601. doi: 10.3390/ijms25115601
106. Kealy J, Greene C, Campbell M. Blood–brain barrier regulation in psychiatric disorders. *Neurosci Lett*. (2020) 726:133664. doi: 10.1016/j.neulet.2018.06.033
107. Zuo S, Ge H, Li Q, Zhang X, Hu R, Hu S, et al. Artesunate protected blood–brain barrier via sphingosine 1 phosphate receptor 1/phosphatidylinositol 3 kinase pathway after subarachnoid hemorrhage in rats. *Mol Neurobiol*. (2017) 54:1213–28. doi: 10.1007/s12035-016-9732-6
108. Chaichana KL, Pradilla G, Huang J, Tamargo RJ. Role of inflammation (leukocyte-endothelial cell interactions) in vasospasm after subarachnoid hemorrhage. *World Neurosurg*. (2010) 73:22–41. doi: 10.1016/j.surneu.2009.05.027
109. Gallia GL, Tamargo RJ. Leukocyte-endothelial cell interactions in chronic vasospasm after subarachnoid hemorrhage. *Neurol Res*. (2006) 28:750–8. doi: 10.1179/016164106X152025
110. Rothoerl RD, Schebesch KM, Kubitz M, Woertgen C, Brawanski A, Pina AL. ICAM-1 and VCAM-1 expression following aneurysmal subarachnoid hemorrhage and their possible role in the pathophysiology of subsequent ischemic deficits. *Cerebrovasc Dis*. (2006) 22:143–9. doi: 10.1159/000093243
111. Sehba FA, Friedrich V. Early micro vascular changes after subarachnoid hemorrhage. *Acta Neurochir Suppl*. (2011) 110:49–55. doi: 10.1007/978-3-7091-0353-1_9
112. Sills AK Jr, Clatterbuck RE, Thompson RC, Cohen PL, Tamargo RJ. Endothelial cell expression of intercellular adhesion molecule 1 in experimental posthemorrhagic vasospasm. *Neurosurgery*. (1997) 41:453–60. doi: 10.1097/00006123-199708000-00025
113. Baybek M, Polin R, Kwan AL, Arthur AS, Kassell NF, Lee KS. Monoclonal antibodies against ICAM-1 and CD18 attenuate cerebral vasospasm after experimental subarachnoid hemorrhage in rabbits. *Stroke*. (1998) 29:1930–6. doi: 10.1161/01.STR.29.9.1930
114. Polin RS, Baybek M, Shaffrey ME, Billups K, Bogaev CA, Kassell NF, et al. Detection of soluble E-selectin, ICAM-1, VCAM-1, and L-selectin in the cerebrospinal fluid of patients after subarachnoid hemorrhage. *J Neurosurg*. (1998) 89:559–67. doi: 10.3171/jns.1998.89.4.0559
115. Pradilla G, Wang PP, Legnani FG, Ogata L, Dietsch GN, Tamargo RJ. Prevention of vasospasm by anti-CD11/CD18 monoclonal antibody therapy following subarachnoid hemorrhage in rabbits. *J Neurosurg*. (2004) 101:88–92. doi: 10.3171/jns.2004.101.1.0088
116. Friedrich V, Flores R, Muller A, Bi W, Peerschke EIB, Sehba FA. Reduction of neutrophil activity decreases early microvascular injury after subarachnoid haemorrhage. *J Neuroinflammation*. (2011) 8:103. doi: 10.1186/1742-2094-8-103
117. Hayman EG, Wessell A, Gerzanich V, Sheth KN, Simard JM. Mechanisms of global cerebral edema formation in aneurysmal subarachnoid hemorrhage. *Neurocrit Care*. (2017) 26:301–10. doi: 10.1007/s12028-016-0354-7
118. Keep RF, Andjelkovic AV, Xiang J, Stamatovic SM, Antonetti DA, Hua Y, et al. Brain endothelial cell junctions after cerebral hemorrhage: changes, mechanisms and therapeutic targets. *J Cereb Blood Flow Metab*. (2018) 38:1255–75. doi: 10.1177/0271678X18774666
119. Toyota Y, Wei J, Xi G, Keep RF, Hua Y. White matter T2 hyperintensities and blood–brain barrier disruption in the hyperacute stage of subarachnoid hemorrhage in male mice: the role of lipocalin-2. *CNS Neurosci Ther*. (2019) 25:1207–14. doi: 10.1111/cns.13221
120. Sehba FA, Mostafa G, Knopman J, Friedrich V, Bederson JB. Acute alterations in microvascular basal lamina after subarachnoid hemorrhage. *J Neurosurg*. (2004) 101:633–40. doi: 10.3171/jns.2004.101.4.0633
121. Guo Z, Sun X, He Z, Jiang Y, Zhang X, Zhang JH. Matrix metalloproteinase-9 potentiates early brain injury after subarachnoid hemorrhage. *Neurol Res*. (2010) 32:715–20. doi: 10.1179/016164109X12478302362491
122. Guo Z, Xu L, Wang X, Sun X. MMP-9 expression and activity is concurrent with endothelial cell apoptosis in the basilar artery after subarachnoid hemorrhaging in rats. *Neurol Sci*. (2015) 36:1241–5. doi: 10.1007/s10072-015-2092-6
123. Uekawa K, Hasegawa Y, Ma M, Nakagawa T, Katayama T, Sueta D, et al. Rosuvastatin ameliorates early brain injury after subarachnoid hemorrhage via suppression of superoxide formation and nuclear factor- κ B activation in rats. *J Stroke Cerebrovasc Dis*. (2014) 23:1429–39. doi: 10.1016/j.jstrokecerebrovasdis.2013.12.004
124. Khan D, Cornelius JF, Muhammad S. The role of NF- κ B in intracranial aneurysm pathogenesis: a systematic review. *Int J Mol Sci*. (2023) 24:14218. doi: 10.3390/ijms241814218
125. Xiong L, Sun L, Zhang Y, Peng J, Yan J, Liu X. Exosomes from bone marrow mesenchymal stem cells can alleviate early brain injury after subarachnoid hemorrhage through miRNA129-5p-HMGB1 pathway. *Stem Cells Dev*. (2020) 29:212–21. doi: 10.1089/scd.2019.0206
126. Zhang T, Su J, Guo B, Wang K, Li X, Liang G. Apigenin protects blood–brain barrier and ameliorates early brain injury by inhibiting TLR4-mediated inflammatory pathway in subarachnoid hemorrhage rats. *Int Immunopharmacol*. (2015) 28:79–87. doi: 10.1016/j.intimp.2015.05.024
127. Lee TH, Chen JL, Tsai MM, Wu YH, Tseng HC, Cheng LC, et al. Protective effects of Sophoraflavanone G by inhibiting TNF- α -induced MMP-9-mediated events in brain microvascular endothelial cells. *Int J Mol Sci*. (2023) 25:283. doi: 10.3390/ijms25010283
128. Zou Z, Dong YS, Liu DD, Li G, Hao GZ, Gao X, et al. MAP4K4 induces early blood–brain barrier damage in a murine subarachnoid hemorrhage model. *Neural Regen Res*. (2021) 16:325–32. doi: 10.4103/1673-5374.290904
129. Garcia-Caceres C, Quarta C, Varela L, Gao Y, Gruber T, Legutko B, et al. Astrocytic insulin signaling couples brain glucose uptake with nutrient availability. *Cell*. (2016) 166:867–80. doi: 10.1016/j.cell.2016.07.028
130. Alvarez JI, Dodelet-Devillers A, Kebir H, Ifergan I, Fabre PJ, Terouz S, et al. The hedgehog pathway promotes blood–brain barrier integrity and CNS immune quiescence. *Science*. (2011) 334:1727–31. doi: 10.1126/science.1206936
131. Bell RD, Winkler EA, Singh I, Sagare AP, Deane R, Wu Z, et al. Apolipoprotein E controls cerebrovascular integrity via cyclophilin a. *Nature*. (2012) 485:512–6. doi: 10.1038/nature11087
132. Yamazaki Y, Kanekiyo T. Blood–brain barrier dysfunction and the pathogenesis of Alzheimer's disease. *Int J Mol Sci*. (2017) 18:1965. doi: 10.3390/ijms18091965
133. Daneman R, Prat A. The blood–brain barrier. *Cold Spring Harb Perspect Biol*. (2015) 7:a020412. doi: 10.1101/cshperspect.a020412
134. Battini S, Cantarutti N, Kotsalos C, Roussel Y, Cattabiani A, Arnaudon A, et al. Modeling of blood flow dynamics in rat somatosensory cortex. *Biomedicine*. (2024) 13:72. doi: 10.3390/biomedicine13010072
135. Armulik A, Genové G, Mäe M, Nisancioglu MH, Wallgard E, Niaudet C, et al. Pericytes regulate the blood–brain barrier. *Nature*. (2010) 468:557–61. doi: 10.1038/nature09522
136. Østergaard L, Aamand R, Karabegovic S, Tietze A, Blicher JU, Mikkelsen IK, et al. The role of the microcirculation in delayed cerebral ischemia and chronic degenerative changes after subarachnoid hemorrhage. *J Cereb Blood Flow Metab*. (2013) 33:1825–37. doi: 10.1038/jcbfm.2013.173
137. Soung A, Klein RS. Astrocytes: initiators of and responders to inflammation In: T Spohr, editor. *Glia in health and disease*. London: IntechOpen (2019)
138. Lin S, Yin Q, Zhong Q, Lv FL, Zhou Y, Li JQ, et al. Heme activates TLR4-mediated inflammatory injury via MyD88/TRIF signaling pathway in intracerebral hemorrhage. *J Neuroinflammation*. (2012) 9:46. doi: 10.1186/1742-2094-9-46
139. Hanafy KA. The role of microglia and the TLR4 pathway in neuronal apoptosis and vasospasm after subarachnoid hemorrhage. *J Neuroinflammation*. (2013) 10:83. doi: 10.1186/1742-2094-10-83
140. Kwon MS, Woo SK, Kurland DB, Yoon S, Palmer A, Banerjee U, et al. Methemoglobin is an endogenous toll-like receptor 4 ligand-relevance to subarachnoid hemorrhage. *Int J Mol Sci*. (2015) 16:5028–46. doi: 10.3390/ijms16035028
141. Okada T, Suzuki H. Toll-like receptor 4 as a possible therapeutic target for delayed brain injuries after aneurysmal subarachnoid hemorrhage. *Neural Regen Res*. (2017) 12:193–6. doi: 10.4103/1673-5374.200795
142. Dou Y, Shen H, Feng D, Li H, Tian X, Zhang J, et al. Tumor necrosis factor receptor-associated factor 6 participates in early brain injury after subarachnoid hemorrhage in rats through inhibiting autophagy and promoting oxidative stress. *J Neurochem*. (2017) 142:478–92. doi: 10.1111/jnc.14075
143. Chen J, Wu X, Shao B, Zhao W, Shi W, Zhang S, et al. Increased expression of TNF receptor-associated factor 6 after rat traumatic brain injury. *Cell Mol Neurobiol*. (2011) 31:269–75. doi: 10.1007/s10571-010-9617-6
144. Zhu Q, Enkhjargal B, Huang L, Zhang T, Sun C, Xie Z, et al. Aggf1 attenuates neuroinflammation and BBB disruption via PI3K/Akt/NF- κ B pathway after subarachnoid hemorrhage in rats. *J Neuroinflammation*. (2018) 15:178. doi: 10.1186/s12974-018-1211-8
145. Chang J, Qian Z, Wang B, Cao J, Zhang S, Jiang F, et al. Transplantation of A2 type astrocytes promotes neural repair and remyelination after spinal cord injury. *Cell Commun Signal*. (2023) 21:37. doi: 10.1186/s12964-022-01036-6
146. Liddlelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*. (2017) 541:481–7. doi: 10.1038/nature21029
147. Zhang ZY, Sun BL, Liu JK, Yang MF, Li DW, Fang J, et al. Activation of mGluR5 attenuates microglial activation and neuronal apoptosis in early brain injury after

experimental subarachnoid hemorrhage in rats. *Neurochem Res.* (2015) 40:1121–32. doi: 10.1007/s11064-015-1572-7

148. Ma M, Li H, Wu J, Zhang Y, Shen H, Li X, et al. Roles of prokineticin 2 in subarachnoid hemorrhage-induced early brain injury via regulation of phenotype polarization in astrocytes. *Mol Neurobiol.* (2020) 57:3744–58. doi: 10.1007/s12035-020-01990-7

149. van Dijk BJ, Vergouwen MD, Kelfkens MM, Rinkel GJ, Hol EM. Glial cell response after aneurysmal subarachnoid hemorrhage—functional consequences and clinical implications. *Biochim Biophys Acta.* (2016) 1862:492–505. doi: 10.1016/j.bbdis.2015.10.013

150. Feng D, Wang W, Dong Y, Wu L, Huang J, Ma Y, et al. Ceftriaxone alleviates early brain injury after subarachnoid hemorrhage by increasing excitatory amino acid transporter 2 expression via the PI3K/Akt/NF- κ B signaling pathway. *Neuroscience.* (2014) 268:21–32. doi: 10.1016/j.neuroscience.2014.02.053

151. Tao K, Cai Q, Zhang X, Zhu L, Liu Z, Li F, et al. Astrocytic histone deacetylase 2 facilitates delayed depression and memory impairment after subarachnoid hemorrhage by negatively regulating glutamate transporter-1. *Ann Transl Med.* (2020) 8:691. doi: 10.21037/atm-20-4330

152. Koyama Y. Endothelin ET_B receptor-mediated astrocytic activation: pathological roles in brain disorders. *Int J Mol Sci.* (2021) 22:4333. doi: 10.3390/ijms22094333

153. Yeung PK, Shen J, Chung SS, Chung SK. Targeted over-expression of endothelin-1 in astrocytes leads to more severe brain damage and vasospasm after subarachnoid hemorrhage. *BMC Neurosci.* (2013) 14:131. doi: 10.1186/1471-2202-14-131

154. Regan RF, Kumar N, Gao F, Guo Y. Ferritin induction protects cortical astrocytes from heme-mediated oxidative injury. *Neuroscience.* (2002) 113:985–94. doi: 10.1016/S0306-4522(02)00243-9

155. Chen-Roetling J, Regan RF. Haptoglobin increases the vulnerability of CD163-expressing neurons to hemoglobin. *J Neurochem.* (2016) 139:586–95. doi: 10.1111/jnc.13720

156. Liu R, Cao S, Hua Y, Keep RF, Huang Y, Xi G. CD163 expression in neurons after experimental intracerebral hemorrhage. *Stroke.* (2017) 48:1369–75. doi: 10.1161/STROKEAHA.117.016850. Epub 2017 Mar 30

157. Bonkowski D, Katyshev V, Balabanov RD, Borisov A, Dore-Duffy P. The CNS microvascular pericyte: pericyte-astrocyte crosstalk in the regulation of tissue survival. *Fluids Barriers CNS.* (2011) 8:8. doi: 10.1186/2045-8118-8-8

158. Winkler EA, Bell RD, Zlokovic BV. Central nervous system pericytes in health and disease. *Nat Neurosci.* (2011) 14:1398–405. doi: 10.1038/nn.2946

159. Daneman R, Zhou L, Kebede AA, Barres BA. Pericytes are required for blood-brain barrier integrity during embryogenesis. *Nature.* (2010) 468:562–6. doi: 10.1038/nature09513

160. Hamilton NB, Attwell D, Hall CN. Pericyte-mediated regulation of capillary diameter: a component of neurovascular coupling in health and disease. *Front Neuroenerg.* (2010) 2:5. doi: 10.3389/fnener.2010.00005

161. Chen Y, Li Q, Tang J, Feng H, Zhang JH. The evolving roles of pericyte in early brain injury after subarachnoid hemorrhage. *Brain Res.* (2015) 1623:110–22. doi: 10.1016/j.brainres.2015.05.004

162. Liu Z, Li Q, Cui G, Zhu G, Tang W, Zhao H, et al. Blood-filled cerebrospinal fluid-enhanced pericyte microvasculature contraction in rat retina: a novel in vitro study of subarachnoid hemorrhage. *Exp Ther Med.* (2016) 12:2411–6. doi: 10.3892/etm.2016.3644

163. Yemisci M, Gursay-Ozdemir Y, Vural A, Can A, Topalkara K, Dalkara T. Pericyte contraction induced by oxidative-nitrosative stress impairs capillary reflow despite successful opening of an occluded cerebral artery. *Nat Med.* (2009) 15:1031–7. doi: 10.1038/nm.2022

164. Thanabalasundaram G, Pieper C, Lischper M, Galla HJ. Regulation of the blood-brain barrier integrity by pericytes via matrix metalloproteinases mediated activation of vascular endothelial growth factor in vitro. *Brain Res.* (2010) 1347:1–10. doi: 10.1016/j.brainres.2010.05.096

165. Thanabalasundaram G, Schneidewind J, Pieper C, Galla HJ. The impact of pericytes on the blood-brain barrier integrity depends critically on the pericyte differentiation stage. *Int J Biochem Cell Biol.* (2011) 43:1284–93. doi: 10.1016/j.biocel.2011.05.002

166. Haefliger IO, Zschauer A, Anderson DR. Relaxation of retinal pericyte contractile tone through the nitric oxide-cyclic guanosine monophosphate pathway. *Invest Ophthalmol Vis Sci.* (1994) 35:991–7.

167. Li Q, Chen Y, Li B, Luo C, Zuo S, Liu X, et al. Hemoglobin induced NO/cGMP suppression deteriorate microcirculation via pericyte phenotype transformation after subarachnoid hemorrhage in rats. *Sci Rep.* (2016) 6:22070. doi: 10.1038/srep22070

168. Fumoto T, Naraoka M, Katagai T, Li Y, Shimamura N, Ohkuma H. The role of oxidative stress in microvascular disturbances after experimental subarachnoid hemorrhage. *Transl Stroke Res.* (2019) 10:684–94. doi: 10.1007/s12975-018-0685-0

169. Oztop-Cakmak O, Solaroglu I, Gursay-Ozdemir Y. The role of pericytes in neurovascular unit: emphasis on stroke. *Curr Drug Targets.* (2017) 18:1386–91. doi: 10.2174/1389450117666160613104523

170. Machida T, Takata F, Matsumoto J, Takenoshita H, Kimura I, Yamauchi A, et al. Brain pericytes are the most thrombin-sensitive matrix metalloproteinase-9-releasing cell type constituting the blood-brain barrier in vitro. *Neurosci Lett.* (2015) 599:109–14. doi: 10.1016/j.neulet.2015.05.028

171. Machida T, Dohgu S, Takata F, Matsumoto J, Kimura I, Koga M, et al. Role of thrombin-PAR1-PKC θ /8 axis in brain pericytes in thrombin-induced MMP-9 production and blood-brain barrier dysfunction in vitro. *Neuroscience.* (2017) 350:146–57. doi: 10.1016/j.neuroscience.2017.03.026

172. Yang CC, Hsiao LD, Tseng HC, Kuo CM, Yang CM. Pristimerin inhibits MMP-9 expression and cell migration through attenuating NOX/ROS-dependent NF- κ B activation in rat brain astrocytes challenged with LPS. *J Inflamm Res.* (2020) 20:325–41. doi: 10.2147/JIR.S252659

173. Pan P, Zhao H, Zhang X, Li Q, Qu J, Zuo S, et al. Cyclophilin A signaling induces pericyte-associated blood-brain barrier disruption after subarachnoid hemorrhage. *J Neuroinflammation.* (2020) 17:16. doi: 10.1186/s12974-020-1699-6

174. Li Y, Yang H, Ni W, Gu Y. Effects of deferoxamine on blood-brain barrier disruption after subarachnoid hemorrhage. *PLoS One.* (2017) 12:e0172784. doi: 10.1371/journal.pone.0172784

175. Xu H, Cai Y, Yu M, Sun J, Cai J, Li J, et al. Celastrol protects against early brain injury after subarachnoid hemorrhage in rats through alleviating blood-brain barrier disruption and blocking necroptosis. *Aging.* (2021) 13:16816–33. doi: 10.18632/aging.203221

176. Zhang T, Xu S, Wu P, Zhou K, Wu L, Xie Z, et al. Mitoquinone attenuates blood-brain barrier disruption through Nrf2/PHB2/OPA1 pathway after subarachnoid hemorrhage in rats. *Exp Neurol.* (2019) 317:1–9. doi: 10.1016/j.expneurol.2019.02.009

177. Zhang T, Su J, Guo B, Zhu T, Wang K, Li X. Ursolic acid alleviates early brain injury after experimental subarachnoid hemorrhage by suppressing TLR4-mediated inflammatory pathway. *Int Immunopharmacol.* (2014) 23:585–91. doi: 10.1016/j.intimp.2014.10.009

178. Wang CX, Xie GB, Zhou CH, Zhang XS, Li T, Xu JG, et al. Baincalein alleviates early brain injury after experimental subarachnoid hemorrhage in rats: possible involvement of TLR4/NF- κ B-mediated inflammatory pathway. *Brain Res.* (2015) 1594:245–55. doi: 10.1016/j.brainres.2014.10.014

179. Nishikawa H, Suzuki H. Possible role of inflammation and galectin-3 in brain injury after subarachnoid hemorrhage. *Brain Sci.* (2018) 8:30. doi: 10.3390/brainsci8020030

180. Agre P. The aquaporin water channels. *Proc Am Thorac Soc.* (2006) 3:5–13. doi: 10.1513/pats.200510-109JH

181. Kim ID, Cave JW, Cho S. Aflibercept, a VEGF (vascular endothelial growth factor)-trap, reduces vascular permeability and stroke-induced brain swelling in obese mice. *Stroke.* (2021) 52:2637–48. doi: 10.1161/STROKEAHA.121.034362

182. Chen S, Feng H, Sherchan P, Klebe D, Zhao G, Sun X, et al. Controversies and evolving new mechanisms in subarachnoid hemorrhage. *Prog Neurobiol.* (2014) 115:64–91. doi: 10.1016/j.pneurobio.2013.09.002

183. Shamir A, Kwon OB, Karavanova I, Vullhorst D, Leiva-Salcedo E, Janssen MJ, et al. The importance of the NRG-1/ErbB4 pathway for synaptic plasticity and behaviors associated with psychiatric disorders. *J Neurosci.* (2012) 32:2988–97. doi: 10.1523/JNEUROSCI.1899-11.2012

184. Lok J, Sardi SP, Guo S, Besancon E, Ha DM, Rosell A, et al. Neuregulin-1 signaling in brain endothelial cells. *J Cereb Blood Flow Metab.* (2009) 29:39–43. doi: 10.1038/jcbfm.2008.94

185. Zhao X, Peng X, Sun S, Park AYJ, Guan JL. Role of kinase-independent and -dependent functions of FAK in endothelial cell survival and barrier function during embryonic development. *J Cell Biol.* (2010) 189:955–65. doi: 10.1083/jcb.200912094

186. Fujii M, Duris K, Altay O, Soejima Y, Sherchan P, Zhang JH. Inhibition of Rho kinase by hydroxyfasudil attenuates brain edema after subarachnoid hemorrhage in rats. *Neurochem Int.* (2012) 60:327–33. doi: 10.1016/j.neuint.2011.12.014

187. Kanamaru H, Suzuki H. Therapeutic potential of stem cells in subarachnoid hemorrhage. *Neural Regen Res.* (2025) 20:936–45. doi: 10.4103/NRR.NRR-D-24-00124

188. Guo ZD, Sun XC, Zhang JH. Mechanisms of early brain injury after SAH: matrix metalloproteinase 9. *Acta Neurochir Suppl.* (2011) 110:63–5. doi: 10.1007/978-3-7091-0353-1_11

189. Hansen-Schwartz J, Hoel NL, Xu CB, Svendgaard NA, Edvinsson L. Subarachnoid hemorrhage-induced upregulation of the 5-HT_{1B} receptor in cerebral arteries in rats. *J Neurosurg.* (2003) 99:115–20. doi: 10.3171/jns.2003.99.1.0115

190. Hansen-Schwartz J, Hoel NL, Zhou M, Xu CB, Svendgaard NA, Edvinsson L. Subarachnoid hemorrhage enhances endothelin receptor expression and function in rat cerebral arteries. *Neurosurgery.* (2003) 52:1188–94.

191. Morone PJ, Yan W, Adcock J, Komalavilas P, Mocco J, Thompson RC, et al. Vasorelaxing cell permeant phosphopeptide mimetics for subarachnoid hemorrhage. *Eur J Pharmacol.* (2021) 5:174038. doi: 10.1016/j.ejphar.2021.174038

192. King DR, Sedovy MW, Eaton X, Dunaway LS, Good ME, Isakson BE, et al. Cell-to-cell communication in the resistance vasculature. *Compr Physiol.* (2022) 12:3833–67. doi: 10.1002/jc.2040-4603.2022.tb00235.x

193. Pang J, Chen Y, Kuai L, Yang P, Peng J, Wu Y, et al. Inhibition of blood–brain barrier disruption by an Apolipoprotein E-mimetic peptide ameliorates early brain injury in experimental subarachnoid hemorrhage. *Transl Stroke Res.* (2017) 8:257–72. doi: 10.1007/s12975-016-0507-1
194. Gao S, Zhou L, Lu J, Fang Y, Wu H, Xu W, et al. Cepharranthine attenuates early brain injury after subarachnoid hemorrhage in mice via inhibiting 15-lipoxygenase-1-mediated microglia and endothelial cell Ferroptosis. *Oxid Med Cell Longev.* (2022) 2022:4295208. doi: 10.1155/2022/4295208
195. Wu Y, Liu Y, Zhou C, Wu Y, Sun J, Gao X, et al. Biological effects and mechanisms of caspases in early brain injury after subarachnoid hemorrhage. *Oxid Med Cell Longev.* (2022) 2022:3345637. doi: 10.1155/2022/3345637
196. Qi X, Liu J, Wu J, Bi Y, Han C, Zhang G, et al. Initiating TrkB/Akt signaling cascade preserves blood–brain barrier after subarachnoid hemorrhage in rats. *Cell Transplant.* (2019) 28:1002–8. doi: 10.1177/0963689719857649
197. Liu G, Wang Q, Tian L, Wang M, Duo D, Duan Y, et al. Blood–brain barrier permeability is affected by changes in tight junction protein expression at high-altitude hypoxic conditions—this may have implications for brain drug transport. *AAPS J.* (2024) 26:90. doi: 10.1208/s12248-024-00957-z
198. Suzuki H, Ayer R, Sugawara T, Chen W, Sozen T, Hasegawa Y, et al. Protective effects of recombinant osteopontin on early brain injury after subarachnoid hemorrhage in rats. *Crit Care Med.* (2010) 38:612–8. doi: 10.1097/CCM.0b013e3181c027ae
199. Ahmadihykolaei H, Lambert JA, Raeeszadeh-Sarmazdeh M. TIMP-1 protects tight junctions of brain endothelial cells from MMP-mediated degradation. *Pharm Res.* (2023) 40:2121–31. doi: 10.1007/s11095-023-03593-y
200. Okada T, Kawakita F, Nishikawa H, Nakano F, Liu L, Suzuki H. Selective toll-like receptor 4 antagonists prevent acute blood–brain barrier disruption after subarachnoid hemorrhage in mice. *Mol Neurobiol.* (2019) 56:976–85. doi: 10.1007/s12035-018-1145-2
201. Liu L, Kawakita F, Fujimoto M, Nakano F, Imanaka-Yoshida K, Yoshida T, et al. Role of periostin in early brain injury after subarachnoid hemorrhage in mice. *Stroke.* (2017) 48:1108–11. doi: 10.1161/STROKEAHA.117.016629
202. Shiba M, Suzuki H. Lessons from tenascin-C knockout mice and potential clinical application to subarachnoid hemorrhage. *Neural Regen Res.* (2019) 14:262–4. doi: 10.4103/1673-5374.244789
203. Nakatsuka Y, Shiba M, Nishikawa H, Terashima M, Kawakita F, Fujimoto M, et al. Acute-phase plasma osteopontin as an independent predictor for poor outcome after aneurysmal subarachnoid hemorrhage. *Mol Neurobiol.* (2018) 55:6841–9. doi: 10.1007/s12035-018-0893-3
204. Nishikawa H, Liu L, Nakano F, Kawakita F, Kanamaru H, Nakatsuka Y, et al. Modified citrus pectin prevents blood–brain barrier disruption in mouse subarachnoid hemorrhage by inhibiting galectin-3. *Stroke.* (2018) 49:2743–51. doi: 10.1161/STROKEAHA.118.021757
205. Shao A, Zhou Y, Yao Y, Zhang W, Zhang J, Deng Y. The role and therapeutic potential of heat shock proteins in hemorrhagic stroke. *J Cell Mol Med.* (2019) 23:5846–58. doi: 10.1111/jcmm.14479
206. Suzuki H, Hasegawa Y, Kanamaru K, Zhang JH. Mechanisms of osteopontin-induced stabilization of blood–brain barrier disruption after subarachnoid hemorrhage in rats. *Stroke.* (2010) 41:1783–90. doi: 10.1161/STROKEAHA.110.586537
207. Nag S, Manias JL, Stewart DJ. Pathology and new players in the pathogenesis of brain edema. *Acta Neuropathol.* (2009) 118:197–217. doi: 10.1007/s00401-009-0541-0
208. Manukjan N, Majcher D, Leenders P, Caiment F, van Herwijnen M, Smeets HJ, et al. Hypoxic oligodendrocyte precursor cell-derived VEGFA is associated with blood–brain barrier impairment. *Acta Neuropathol Commun.* (2023) 11:128. doi: 10.1186/s40478-023-01627-5
209. Xu W, Gao L, Li T, Zheng J, Shao A, Zhang J. Apelin-13 alleviates early brain injury after subarachnoid hemorrhage via suppression of endoplasmic reticulum stress-mediated apoptosis and blood–brain barrier disruption: possible involvement of ATF6/CHOP pathway. *Neuroscience.* (2018) 388:284–96. doi: 10.1016/j.neuroscience.2018.07.023
210. Tran KA, Zhang X, Predescu D, Huang X, Machado RF, Göthert JR, et al. Endothelial β -catenin signaling is required for maintaining adult blood–brain barrier integrity and central nervous system homeostasis. *Circulation.* (2016) 133:177–86. doi: 10.1161/CIRCULATIONAHA.115.015982
211. Chen J, Jin H, Xu H, Peng Y, Jie L, Xu D, et al. The neuroprotective effects of necrostatin-1 on subarachnoid hemorrhage in rats are possibly mediated by preventing blood–brain barrier disruption and RIP3-mediated necroptosis. *Cell Transplant.* (2019) 28:1358–72. doi: 10.1177/0963689719867285
212. Liu C, Cao Y, Wang HX, Zhao L, Chen YX, Zhong KH, et al. Necrostatin-1 decreases necroptosis and inflammatory markers after intraventricular hemorrhage in mice. *Neural Regen Res.* (2022) 17:2710–6. doi: 10.4103/1673-5374.339488
213. Zhang C, Jiang M, Wang WQ, Zhao SJ, Yin YX, Mi QJ, et al. Selective mGluR1 negative allosteric modulator reduces blood–brain barrier permeability and cerebral edema after experimental subarachnoid hemorrhage. *Transl Stroke Res.* (2020) 11:799–811. doi: 10.1007/s12975-019-00758-z
214. Dodd WS, Noda I, Martinez M, Hosaka K, Hoh BL. NLRP3 inhibition attenuates early brain injury and delayed cerebral vasospasm after subarachnoid hemorrhage. *J Neuroinflammation.* (2021) 18:163. doi: 10.1186/s12974-021-02207-x
215. Hu Q, Du Q, Yu W, Dong X. 2-Methoxyestradiol alleviates neuroinflammation and brain edema in early brain injury after subarachnoid hemorrhage in rats. *Front Cell Neurosci.* (2022) 16:869546. doi: 10.3389/fncel.2022.869546
216. Lu W, Zhu Z, Shi D, Li X, Luo J, Liao X. Cerebrolysin alleviates early brain injury after traumatic brain injury by inhibiting neuroinflammation and apoptosis via TLR signaling pathway. *Acta Cir Bras.* (2022) 37:e370605. doi: 10.1590/acb370605
217. Cao S, Zhu P, Yu X, Chen J, Li J, Yan F, et al. Hydrogen sulfide attenuates brain edema in early brain injury after subarachnoid hemorrhage in rats: possible involvement of MMP-9 induced blood–brain barrier disruption and AQP4 expression. *Neurosci Lett.* (2016) 621:88–97. doi: 10.1016/j.neulet.2016.04.018
218. Zhang L, Li Z, Feng D, Shen H, Tian X, Li H, et al. Involvement of Nox2 and Nox4 NADPH oxidases in early brain injury after subarachnoid hemorrhage. *Free Radic Res.* (2017) 51:316–28. doi: 10.1080/10715762.2017.1311015
219. Wang X, Li S, Ma J, Wang C, Chen A, Xin Z, et al. Effect of gastrodin on early brain injury and neurological outcome after subarachnoid hemorrhage in rats. *Neurosci Bull.* (2019) 35:461–70. doi: 10.1007/s12264-018-00333-w
220. Wang C, Jia Q, Sun C, Jing C. Calcium sensing receptor contribute to early brain injury through the CaMKII/NLRP3 pathway after subarachnoid hemorrhage in mice. *Biochem Biophys Res Commun.* (2020) 530:651–7. doi: 10.1016/j.bbrc.2020.07.081
221. Zhang L, Guo K, Zhou J, Zhang X, Yin S, Peng J, et al. Ponesimod protects against neuronal death by suppressing the activation of A1 astrocytes in early brain injury after experimental subarachnoid hemorrhage. *J Neurochem.* (2021) 158:880–97. doi: 10.1111/jnc.15457
222. Ding Y, Zhang L, Zhou W, Lu H, Gao X, Li J, et al. Role of cyclin-dependent kinase 5 in early brain injury following experimental subarachnoid hemorrhage. *Exp Ther Med.* (2022) 23:147. doi: 10.3892/etm.2021.11070
223. Tang H, Shao C, Wang X, Cao Y, Li Z, Luo X, et al. 6-Gingerol attenuates subarachnoid hemorrhage-induced early brain injury via GBP2/PI3K/AKT pathway in the rat model. *Front Pharmacol.* (2022) 13:882121. doi: 10.3389/fphar.2022.882121
224. Huang Z, Liu J, Xu J, Dai L, Wang H. Downregulation of miR-26b attenuates early brain injury induced by subarachnoid hemorrhage via mediating the KLF4/STAT3/HMGB1 axis. *Exp Neurol.* (2023) 359:114270. doi: 10.1016/j.expneurol.2022.114270
225. Guo Y, Hu Y, Huang Y, Huang Y, Huang L, Kanamaru H, et al. Role of estrogen-related receptor γ and PGC-1 α /SIRT3 pathway in early brain injury after subarachnoid hemorrhage. *Neurotherapeutics.* (2022) 20:822–37. doi: 10.1007/s13311-022-01330-8
226. Ma Q, Huang B, Khatibi N, Rolland W II, Suzuki H, Zhang JH, et al. PDGFR- α inhibition preserves blood–brain barrier after intracerebral hemorrhage. *Ann Neurol.* (2011) 70:920–31. doi: 10.1002/ana.22549
227. Hofmann JJ, Iruela-Arispe ML. Notch signaling in blood vessels: who is talking to whom about what? *Circ Res.* (2007) 100:1556–68. doi: 10.1161/01.RES.0000266408.42939.e4
228. Coombs GS, Covey TM, Virshup DM. Wnt signaling in development, disease and translational medicine. *Curr Drug Targets.* (2008) 9:513–31. doi: 10.2174/138945008784911796
229. Pang J, Wu Y, Peng J, Yang P, Chen L, Jiang Y. Association of pericyte loss with microthrombosis after subarachnoid hemorrhage in ApoE-deficient mice. *Front Neurol.* (2021) 12:726520. doi: 10.3389/fneur.2021.726520
230. Zhou J, Guo P, Duan M, Li J, Ru X, Li L, et al. EphA4/EphrinB2 signaling mediates pericyte-induced transient glia limitans formation as a secondary protective barrier after subarachnoid hemorrhage in mice. *Exp Neurol.* (2023) 360:114293. doi: 10.1016/j.expneurol.2022.114293
231. Wang X, Zhang A, Yu Q, Wang Z, Wang J, Xu P, et al. Single-cell RNA sequencing and spatial transcriptomics reveal pathogenesis of meningeal lymphatic dysfunction after experimental subarachnoid hemorrhage. *Adv Sci.* (2023) 10:e2301428. doi: 10.1002/adv.202301428
232. Kebir H, Kreymborg K, Ifergan I, Dodelet-Devillers A, Cayrol R, Bernard M, et al. Human TH17 lymphocytes promote blood–brain barrier disruption and central nervous system inflammation. *Nat Med.* (2007) 13:1173–5. doi: 10.1038/nm1651
233. Gao D, Zou B, Zhu K, Bi S, Zhang W, Yang X, et al. Enhancing Th17 cells drainage through meningeal lymphatic vessels alleviate neuroinflammation after subarachnoid hemorrhage. *J Neuroinflammation.* (2024) 21:269. doi: 10.1186/s12974-024-03252-y
234. Hou C, Li J, Wang B, Liu Q, Zhao Y, Zhang H, et al. Dynamic evolution of the glymphatic system at the early stages of subarachnoid hemorrhage. *Front Neurol.* (2022) 13:924080. doi: 10.3389/fneur.2022.924080
235. Mestre H, Hablitz LM, Xavier AI, Feng W, Zou W, Pu T, et al. Aquaporin-4-dependent glymphatic solute transport in the rodent brain. *eLife.* (2018) 7:e40070. doi: 10.7554/eLife.40070
236. Da Mesquita S, Papadopoulos Z, Dykstra T, Brase L, Farias FG, Wall M, et al. Meningeal lymphatics affect microglia responses and anti- $\alpha\beta$ immunotherapy. *Nature.* (2021) 593:255–60. doi: 10.1038/s41586-021-03489-0

237. Aydin S, Peker S. Long-term cognitive decline after subarachnoid hemorrhage: pathophysiology, management, and future directions. *Stroke*. (2025) 56:1106–11. doi: 10.1161/STROKEAHA.124.049969
238. Seyfried KS, Kremer B, Conzen-Dilger C, Veldeman M, Bertram U, Blume C, et al. Mapping inflammatory markers in cerebrospinal fluid following aneurysmal subarachnoid hemorrhage: an age- and sex-matched analysis. *Int J Mol Sci*. (2025) 26:1302. doi: 10.3390/ijms26031302
239. Chen JY, Zhao DW, Yin Y, Gui L, Chen X, Wang XM, et al. Deep cervical lymphovenous anastomosis (LVA) for Alzheimer's disease microsurgical procedure in a prospective cohort study. *Int J Surg*. (2025) 111:4211–21. doi: 10.1097/JS9.0000000000002490