Mechanisms and interventions in aneurysmal subarachnoid hemorrhage: Unraveling the role of inflammatory responses and cell death in early brain injury (Review)

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Abstract. Aneurysmal subarachnoid hemorrhage (aSAH) is a subtype of stroke associated with high morbidity and mortality rates worldwide, posing challenges in developing effective treatment strategies. The present review aimed to summarize the role of inflammation and pyroptosis in early brain injury (EBI), a key determinant of outcomes in aSAH, the interplay between oxidative stress, neuroinflammation and cell death and the immune-inflammatory response and oxidative stress as central components in the pathogenesis of aSAH. Key signaling pathways include toll-like receptor 4/NF-κB and NLR family pyrin domain-containing 3/gasdermin D pathways, which regulate inflammatory responses and pyroptotic cell death. Additionally, current and traditional Chinese therapeutic approaches to mitigating EBI and improving patient outcomes are summarized, demonstrating the potential roles of salvianolic acid B, pterostilbene, luteolin and electro-acupuncture. The findings of the present review underscore the necessity for continued research into the molecular mechanisms underlying aSAH to translate these insights into clinical practice, enhancing patient survival and recovery.

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Contents

1. Introduction

In the aging population, stroke has become a global concern (1). Subarachnoid hemorrhage (SAH) is the third most common subtype of stroke (2). The global mortality rate 25-35% (3). There are severe long-term neurological sequelae as cognitive ability may decline by >20% 1 year post-injury (4,5). Aneurysmal (a)SAH affects 6-9/100,000 individuals/year (6). According to the World Health Organization, the fatality rates 1, 2 and 7 days after the onset of SAH are 37, 60 and 75%, respectively (7). The cumulative mortality at 28 days in Australia is 26.7% (8) and 20-38% in Europe (9-11). The incidence rate of SAH in China is 2/100,000 individuals/year (12); additionally, it is estimated that the cumulative mortality at 28 days of aSAH in China is 16.9% (13). Considering the high mortality rate, it is important to pay attention to the complications following the SAH that contribute to mortality. Early case fatality are high across the world, which may increase by 50% in 2050 (1).

The pathophysiological mechanism of SAH is complex and multifactorial. Early brain injury (EBI) and delayed cerebral ischemia are key pathological processes following aSAH (14). Numerous clinical trials (14) have been conducted to improve outcomes for patients with aSAH, but there are challenges in aSAH prevention and the development of lower-risk

treatments, these challenges persist in translating promising preclinical findings into effective low-risk treatments, partly due to issues with drug delivery across the blood-brain barrier and the multifactorial nature of early brain injury. The present aimed to summarize the pathogenesis and treatment for aSAH.

2. Pathology in the development of aSAH

SAH is primarily divided into two stages: The pathophysiological changes with the first 72 h after SAH are called 'EBI' and the second pathological process that occurs 72 h after EBI involves delayed cerebral ischemia (DCI) which typically occurs days after the initial hemorrhage (15,16). EBI is the key factor affecting the prognosis of SAH (2,17). EBI primarily describes the pathological changes 72 h after aneurysm rupture: Blood leaks into the subarachnoid space following aneurysm rupture, followed by the rapid increase in intracranial pressure, acute vasospasm, decreased cerebral blood flow, disruption of brain autoregulation and brain swelling (15-17). It is triggered by primary disturbances such as hemorrhage, increased intracranial pressure, vasospasm, and decreased cerebral blood flow. These factors activate downstream pathological mechanisms, including oxidative stress, apoptosis, autophagy, and immune inflammation (14). These mechanisms lead to the formation of pro-inflammatory signals and metabolic disturbances in the brain, which are focal points for early neuroprotective strategies (18,19). EBI manifests via various secondary pathological cascades triggered by the primary insults of hemorrhage including microvascular dysfunction, blood-brain barrier (BBB) disruption, cerebral edema, neuroinflammation, oxidative stress, and neuronal death, leading to acute neurological deficit (17,18).

For example, the breakdown of heme releases toxic substrates that catalyze reactive oxygen species (ROS) production and activate neuroinflammation, further contributing to neuronal death (12). Additionally, blood in the subarachnoid space activates toll-like receptor 4 (TLR4) via the TLR4/NF-κB signaling pathway, which mediates neuroinflammation (20).

The upregulation of inflammatory cytokines enhances the expression of matrix metalloproteinase-9 (21,22), an enzyme that degrades tight junction proteins such as zonula occludens-1 (23). This degradation compromises the integrity of tight junctions, accelerating BBB disruption (24). Compromised BBB further promotes neuroinflammation, creating a cycle that exacerbates BI. Understanding these pathological mechanisms is essential for developing targeted therapeutic strategies to mitigate the impact of EBI and improve patient outcomes following aSAH.

3. EBI-associated inflammation responses

TLR4 serves a key role in recognizing danger-associated molecular patterns (DAMPs), which are released following an aneurysm rupture. DAMPs markedly contribute to the increased permeability of the damaged BBB, leading to white blood cell infiltration, tissue edema and exacerbated BI (25). The activation of TLR4 initiates a series of signaling cascades that result in leukocyte activation and proliferation (26), further enhancing the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-8 and IL-12 (27).

Hemoglobin (Hb) degradation pathway, or the Hb-heme-iron axis, contributes to EBI. Hb degrades into heme, which breaks down into bilirubin and free iron (28). Free iron catalyzes ROS (29,30) production, and ROS-induced NLRP3 inflammasome activation triggers inflammatory responses (31). Excessive ROS production, coupled with decreased antioxidant defenses, results in cellular damage. Yue *et al* (30) revealed that in an intravascular perforation mouse model of SAH, ROS induces pyroptosis of neural stem cells (NSCs) by activating the NLRP3/gasdermin D (GSDMD) pathway. These findings indicate that Hb-induced NSCs may hinder nerve regeneration following SAH (32-35). Chang *et al* (36) used a mouse model of SAH to reveal that triiodothyronine (T3) treatment decreases mitochondrial ROS release, inhibiting neuronal apoptosis. These findings suggest that ROS is a potential therapeutic target for treating EBI following SAH (34,35). Studies (31,32) indicate that antioxidant treatment is an effective approach to mitigate EBI (Fig. 1).

4. Inflammation signaling pathways in EBI: The TLR4/NF-κB signaling pathway

TLR4 is the most well studied TLR and is widely expressed in the central nervous system (37-40). TLR4 serves out an important role in stroke-related inflammation (41). It is activated by the extravasated blood components in myeloid differentiation primary response-88/Toll/interleukin-1 receptor-domain-containing adapter-inducing interferon-β (MyD88/TRIF)-dependent pathway (42) after SAH. Transcription factors initiated by the activation of TLR4, such as NF-κB, mitogen-activated protein kinase and interferon regulatory factor that regulate the expression of proinflammatory cytokine genes cause brain damage after SAH (43,44). These factors collectively regulate the expression of pro-inflammatory cytokine genes, which contribute to brain damage post-SAH (45-47).

Moreover, NF-κB is a key driver of inflammation, which increases the expression of inflammatory markers and matrix metalloproteinases (48) and contributes to the pathogenesis of intracranial aneurysm (IA) (49). In addition, NF-κB activation can lead to endothelial dysfunction (50,51). Furthermore, TLR4-mediated inflammation fosters smooth muscle cell phenotype switching (52-54) and promotes the infiltration of inflammatory cells in arterial walls, potentially leading to the occurrence and progression of IAs, which may result in rupture (55). Therefore, targeting the TLR4/NF-κB pathway presents a promising therapeutic strategy to mitigate EBI and delay BI associated with neuroinflammation following SAH, ultimately improving patient prognosis (47,49).

5. Pyroptosis signaling pathways in EBI: The NLRP3/GSDMD signaling pathway

NLRP3-dependent signaling pathway serve a role in almost every mechanism of cell death, including pyroptosis (24,56-58). The NLRP3 inflammasome serves a role in the progression of injury following SAH (59,60). NLRs are a family of intracellular sensors of microbial motifs and 'danger signals' that serve as key components of innate immune responses and inflammation (61). Inflammasomes are multiprotein

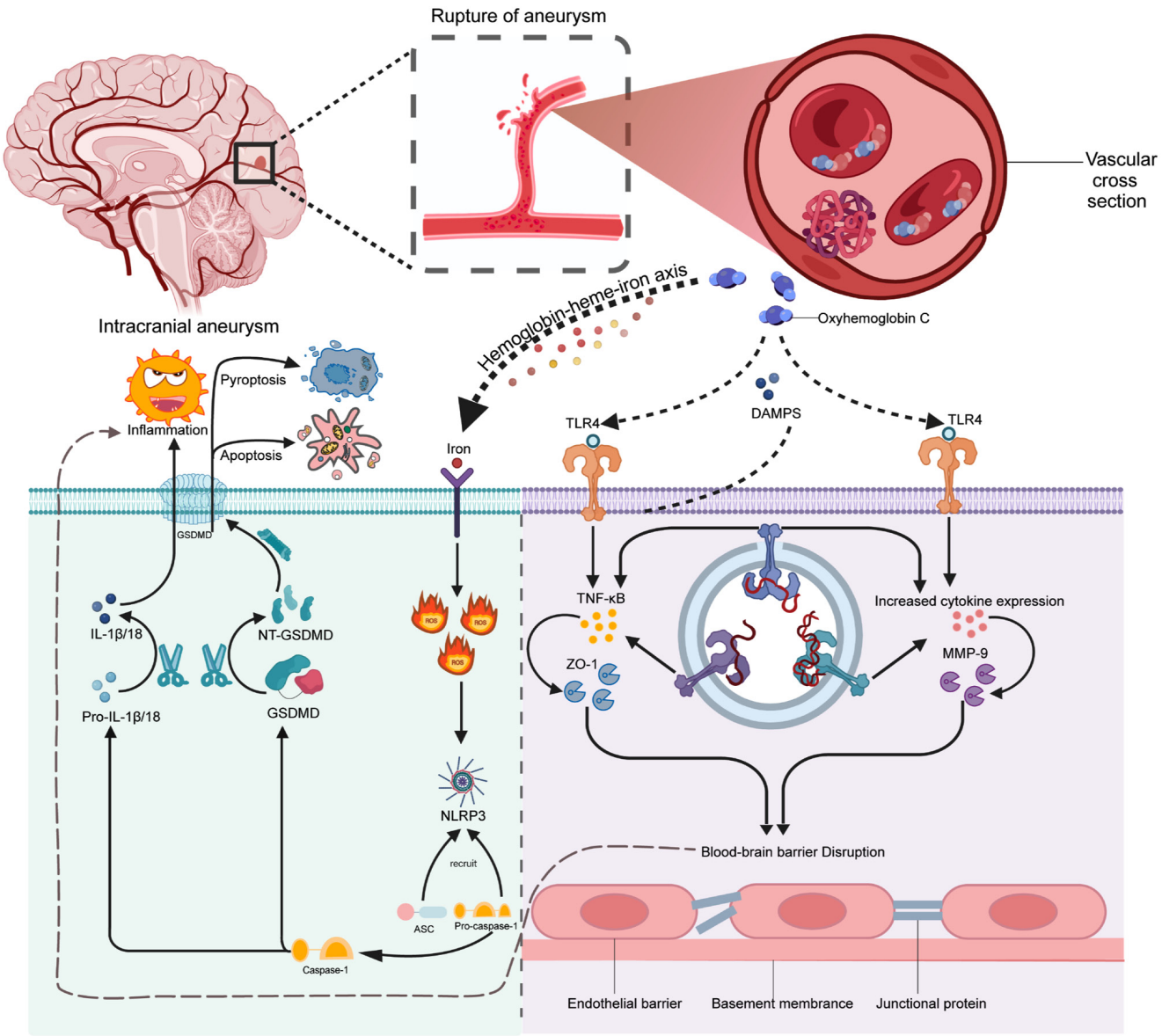

Figure 1. Inflammation signaling pathways in early brain injury. After intracranial aneurysm ruptures, blood enters the subarachnoid space and red blood cells release oxygen, hemoglobin and other breakdown products as DAMPs. TLR4 recognizes DAMPs and triggers immune cascade reactions. Inflammatory cytokines upregulate MMP-9, ZO-1 and other structure proteins, which damages the tight junction of BBB; disrupted BBB will further lead to increased neuroinflammation. Meanwhile, hemoglobin through the hemoglobin metabolite axis of hemoglobin-heme-iron further decomposes into heme, and heme further decomposes bilirubin and free iron. The free iron catalyzes the production of ROS, and ROS induces NLRP3 inflammasome, which leads to the activation of caspase-1. This active caspase-1 then triggers the activation of GSDMD and the cellular inflammatory response, the activated GSDMD induces apoptosis and pyroptosis. DAMP, damage associated molecular pattern; zonula occludens-1, ZO-1; BBB, blood brain barrier; ROS, reactive oxygen species; NLRP3, NLR family pyrin domain containing 3; GSDMD, gasdermin D; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain.

complexes that activate caspase-1. They process proinflammatory cytokines such as IL-1β. For a functional NLRP3 inflammasome, key components include a sensor protein (like an NLR), the adaptor protein ASC, and pro-caspase-1. ASC contains a CARD domain, which is important for recruiting pro-caspase-1 (62-64) and caspase-1 (65). GSDMD, a 53 kDa protein, is an inactive prerequisite protein in the cytoplasm, primarily composed of two domain groups, the C-terminal domain (CT-GSMD) and the T-terminal domain (NT-GSMD), which are connected by a flexible interdomain linker (66). After the aneurysm ruptures, heme groups of unstable extracellular Hb spontaneously oxidize to ferric methemoglobin and release superoxide in the reaction (67), which contributes to the production of ROS (68). The SAH model suggests that NLRP3 is activated by a common pathway of ROS (69,70). Activated NLRP3 inflammasomes recruit ASC and pro-caspase-1, further decompose and convert pro-caspase-1 into caspase-1 (71). Studies have demonstrated that caspase-1 can cleave the active linker (62,65,72), leading to the activation of the GSDMD protein and stimulating the secretion of the pro-inflammatory cytokines IL-1β and IL-18. The GSDMD protein also leads to the secretion of the pro-inflammatory cytokines IL-1β and IL-18 (71), as well as apoptotic and pyroptotic cell death (73). In addition, GSDMD is essential for both canonical and non-canonical inflammasome pathways (74) (Table I).

Table I. Signaling pathways in EBI.

First author/s, year	Signaling pathway	Role in EBI	Intervention	(Refs.)
Kwon *et al*, 2015	TLR4/NF-κB	Activation of proinflammatory cytokines	Anti-inflammatory drugs, specific inhibitors	(27)
Suzuki *et al,* 2020	NLRP3/GSDMD	Inflammation, apoptosis, pyroptosis	Caspase inhibitors, compounds such as pterostilbene	(39)

EBI, early brain injury; TLR4, toll-like receptor 4, NLRP3, NOD-like receptor pyrin domain-containing protein 3; GSDMD, gasdermin D.

Table II. Therapeutic strategies for EBI after SAH.

First author/s, year	Therapeutic strategy	Mechanism of action	Outcomes and potential	Evidence from clinical trials/studies	(Refs.)
Xu *et al*, 2021; Pradilla *et al*, 2010; Wang *et al*, 2020; Hu *et al*, 2021	Antioxidant agents	Decreasing oxidative stress and ROS production	Decreases neuronal death and improves neuroprotection	Inhibits oxidative stressand	(24,26, 43,50)
Kwon *et al*, 2015; Thilak *et al*, 2024; Suzuki *et al*, 2020	Anti-inflammatory drugs	Inhibiting inflammatory cytokines and pathways	Decreases inflammation and mitigates EBI	Inhibits the pathways of TLR4/NF-κB and NLRP3/GSDMD	(27,31, 39)
Wang *et al*, 2022 Okada *et al*, 2019	Caspase inhibitors	Preventing apoptosis and pyroptosis	Decreases cell death and neuroinflammation	Attenuates apoptosis and inflammation	(46,47)
Kirseborn *et al*, 2019	Neuroprotective drugs	Inhibiting the activity of the RIP3/MLKL signaling pathway	Prevents blood-brain barrier disruption	Necrostatin-1improves albumin leakage and degradation of tight junction proteins	(52)
Kairmy *et al*, 2020	SIRT1 activators	Enhancing SIRT1 and activating Nrf2 signaling	Decreases apoptosis and inhibit OS production	SalB promotes neuroprotection and decreases EBI	(42)
Ahmed *et al*, 2021; Klepinowski *et al*, 2023; Liu *et al*, 2020	Electro-acupuncture therapy	Modulating neuroinflammation, promoting neuronal survival.	Alleviates EBI, enhances neurological recovery	Alleviates EBI, enhancing recovery	(53-55)

EBI, early brain injury; SAH, subarachnoid hemorrhage; ROS, reactive oxygen species; TLR4, toll-like receptor 4; NLRP3, NLR Family Pyrin Domain Containing 3; GSDMD, gasdermin D; RIP3, receptor-interacting serine/threonine-protein kinase 3; MLKL, mixed lineage kinase domain-like protein; SIRT1, salb also activates sirtuin 1; Nrf2, nuclear factor erythroid 2 related factor 2; OS, oxidative stress; SalB, Salvianolic acid B.

6. Treatments for aSAH

Current drugs targeting EBI. Salvianolic acid B (SalB) is a polyphenolic compound extracted from the Chinese herb *Salvia miltiorrhiza* (75). It possesses antioxidant and neuroprotective properties, demonstrating effectiveness in decreasing oxidative damage (76) and neuronal apoptosis post-SAH (77). SalB operates via the Nrf2 pathway (78), enhancing the expression of antioxidant proteins and improving neurological functions. Experimental studies (78-80) have demonstrated

that the knockout of Nrf2 negates the protective effects of SalB, indicating its key role in the mechanism of action of SalB. SalB also activates Sirtuin 1 (SIRT1), a protein that modulates the Nrf2 signaling pathway (78). By enhancing SIRT1 activity, SalB indirectly promotes Nrf2 signaling, amplifying its neuroprotective effects. SIRT1 is known for its role in cellular stress resistance and metabolic regulation, making it a key component in neuroprotection (77-79). Furthermore, SalB has been shown (79) to exert anti-inflammatory effects in microglia, the immune cells of the brain. By regulating microglial activation and decreasing the release of pro-inflammatory cytokines (such as TNF-α and IL-1β), SalB helps to alleviate neuroinflammation, which is a contributor to EBI following SAH (80).

Therapeutic drugs targeting oxidative stress. Pterostilbene treatment reduces neuronal apoptosis by inhibiting NLRP3 inflammasome and Nox2-associated oxidative stress (81). This intervention not only mitigates neuronal death but also addresses the inflammatory response that often exacerbates BI after SAH.

Inhibitors of caspase family enzymes. Studies (82-86) have demonstrated that caspase family enzymes are involved in both neuronal and endothelial cell apoptosis in the primary stage following SAH. Activation of caspase post-SAH is complex, involving intrinsic and extrinsic pathways of apoptosis, endoplasmic reticulum stress-induced apoptosis and necroptosis (82). The intrinsic pathway is triggered by internal cellular stress signals, such as oxidative stress and mitochondrial dysfunction (83). It leads to the release of cytochrome *c* from the mitochondria, which activates initiator caspases such as caspase-9 (84). By contrast, the extrinsic pathway is activated by external signals, primarily through death receptors on the cell membrane, such as TNF receptors. Activation of these receptors leads to the formation of the death-inducing signaling complex, which activates initiator caspases such as caspase-8 (85). This activates downstream effector caspases (such as caspase-3), culminating in cell death (86). Caspase inhibitors, such as x-linked inhibitor of apoptosis protein (XIAP) (83), Z-VAD-FMK[carbobenzoxy-valyl-alanyl-aspartyl-(O-methyl)-fluoromethylketone] (84) and VX-765 (also known as Belnacasan), a potent caspase-1 and caspase-4 inhibitor (85), decrease the impacts of EBI by decreasing apoptosis and inflammation associated with caspase activation (86).

Luteolin (LUT) exerts biological functions beneficial to cerebrovascular diseases (87,88). In SAH rats (89), LUT markedly inhibits neuroinflammation via the Nrf2-dependent pathway. LUT decreases microglial activation (90), neutrophil infiltration and the release of pro-inflammatory cytokines, while also ameliorating oxidative damage and restoring the endogenous antioxidant system. Furthermore, LUT markedly ameliorates SAH-induced oxidative damage and restores the endogenous antioxidant system. Fluoxetine decreases neuroinflammation in EBI after SAH by regulating the TLR4/MyD88/NF-κB signaling pathway (91,92). This regulation helps to modulate inflammatory responses, providing a protective effect against neuronal damage.

The neuroprotective effect of necrostatin-1 (93) in SAG rats may stem from its ability to prevent BBB disruption by inhibiting the RIP3/MLKL signaling pathway (94). Administration of necrostatin-1 improves albumin leakage and tight junction protein degradation (95).

Electro-acupuncture (EA) therapy. EA has been revealed to regulate the balance between pro-apoptotic and anti-apoptotic proteins (96-98), decreasing levels of cleaved caspase-3 and inflammatory cytokines such as TNF-α, IL-1β and IL-6. Additionally, EA decreases the M1 polarization of activated microglia, suggesting an anti-inflammatory effect that improves outcomes in EBI. In summary, EA is a potential therapy for the treatment of SAH (Table II).

The aforementioned therapies illustrate a multi-faceted approach to mitigating EBI following SAH. By targeting oxidative stress, inflammatory pathways and apoptotic processes, these drugs aim to enhance neuronal survival and improve clinical outcomes. Understanding the mechanisms of these treatments may aid in developing more effective therapeutic strategies for patients with SAH.

7. Conclusion

aSAH is a severe cerebrovascular event characterized by complex and multifaceted pathophysiological mechanisms, leading to high rates of morbidity and mortality. The present review summarized understanding of pathophysiology of aSAH and therapeutic strategies targeting the molecular pathways involved. Further research is required to translate these findings into clinical practice and improve outcomes for patients affected by aSAH.

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Authors' contributions

RL conceived the study and wrote and edited the manuscript. SG conducted the literature review and wrote and edited the manuscript. JW and MH performed the literature review and wrote the manuscript. MF substantial intellectual contributions to the analysis and interpretation of the existing literature, critically shaping the review's key arguments and conclusions, conceptualized and designed the illustrative figures and comprehensive tables and provided language polishing assistance. JXW and NZ wrote and revised the manuscript. XZ revised the manuscript. JL contributed significantly to the intellectual content of the review and participated in the drafting and finalization of the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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