Review Article

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PI3K/Akt pathway and neuroinflammation in sepsis-associated encephalopathy

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Abstract

Background – Sepsis-associated encephalopathy (SAE) is a complex neurological complication of sepsis involving activation of microglia in the central nervous system (CNS), blood–brain barrier (BBB) dysfunction, neurotransmitter dysfunction, impaired brain metabolism, and mitochondrial dysfunction. Neuroinflammation is a critical component of the pathogenesis. The phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathway, as a key intracellular signaling pathway, plays a crucial role in regulating neuroinflammation, maintaining the integrity of the BBB, and promoting neuronal cell survival.

Objective – This review aims to summarize the role of the PI3K/Akt pathway in SAE-associated neuroinflammation and highlights potential therapeutic targets and strategies for its management.

Methods – We systematically reviewed recent basic and clinical studies on PI3K/Akt signaling pathway in neuroinflammation associated with SAE, as well as the development of pathway-specific agonists and inhibitors.

Results – The PI3K/Akt pathway serves as a crucial intracellular signaling axis involved in the regulation of neuroinflammatory processes. Accumulating evidence indicates that targeted modulation of this pathway may alleviate neuroinflammation associated with SAE and enhance neurological recovery.

Conclusion – Targeting the PI3K/Akt pathway represents a promising therapeutic approach for SAE. Advances in the development of specific agonists and inhibitors provide new opportunities for clinical translation and drug discovery in neuroinflammatory conditions.

Keywords: sepsis-associated encephalopathy, PI3K/Akt pathway, neuroinflammation, blood–brain barrier, cognitive dysfunction

1 Introduction

Sepsis is a systemic inflammatory response syndrome (SIRS) caused by infection, characterized by dysregulation of the body's immune response to infection. It is one of the key causes of death in critically ill patients in the intensive care unit [1]. Among these, sepsis-associated encephalopathy (SAE) is one of the most common complications of sepsis, with an incidence rate as high as 70% [2], which significantly increases the morbidity and mortality rate and diminishes the quality of life of the patients [3,4]. The pathogenesis of SAE is complex and multifactorial, with contributing key factors including activation of microglia in the central nervous system (CNS), blood–brain barrier (BBB) dysfunction, brain edema, neurotransmitter dysfunction, impaired brain metabolism, and mitochondrial dysfunction [5–8]. Additional mechanisms, such as the accumulation of amyloid-β and tau proteins, activation of the complement system, and direct neuronal injury, may also contribute to the development of SAE [9]. Overall, SAE results from the synergistic effects of multiple factors, rather than a single cause. Among these, neuroinflammation has been shown to play a crucial role throughout the SAE process and is closely associated with prognosis.

Neuroinflammation is an immune response activated by microglia and astrocytes in the CNS, usually occurring in response to CNS injury, infection, toxin stimulation, or autoimmunity [9]. Systemic inflammation induced by sepsis is mediated by the excessive release of proinflammatory cytokines – such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) – which increases the permeability of the BBB, thereby facilitating inflammatory factors to enter the brain and trigger an inflammatory response in the CNS. The sustained inflammatory response disrupts the BBB and facilitates the infiltration of peripheral immune cells. This exacerbates CNS

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injury, leading to neuronal damage [10,11], demyelination [12], impaired regeneration [13], and synaptic dysfunction.

Among the numerous molecular pathways implicated in neuroinflammation, the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathway has been extensively studied for its involvement in various physiological processes within the CNS, including cell survival, autophagy, neurogenesis, neuronal proliferation and differentiation, synaptic plasticity, anti-apoptosis, anti-oxidative stress, and neural repair [9,14]. Recently, several studies have confirmed that this pathway is closely related to the development of neurological diseases and plays an important role in modulating various pathological changes [15–17].

Based on the roles of neuroinflammation and PI3K/Akt pathway activation in the pathogenesis of SAE, this article aims to elucidate their specific roles and interrelationships in SAE development. The following sections will comprehensively describe the neuroinflammation triggered by sepsis, the underlying mechanisms of the PI3K/Akt pathway, its role in SAE, and the potential treatment of SAE through targeting the PI3K/Akt pathway.

2 Sepsis-induced neuroinflammation

The presence of neuroinflammation in SAE has been clearly demonstrated [18,19]. Autopsy studies of patients who died from sepsis revealed significantly increased expression of markers associated with acute neuroinflammation, suggesting that neuroinflammation may play a critical role in the progression of SAE [20]. While infection does not occur directly in the brain, peripheral inflammatory signals can trigger widespread neuroinflammation through both neuronal and humoral pathways [21]. Neuroinflammation is initiated by multiple biological mechanisms, including immune responses, oxidative stress, the release of inflammatory mediators, and damage to the BBB. Although neuroinflammation can initially have a protective effect, prolonged or excessive inflammation can result in neural tissue damage.

Neuroinflammatory responses can be classified into two categories: secondary inflammatory responses induced by peripheral immune cells and primary inflammatory responses triggered by resident immune cells. Initially, during sepsis, pathogens or their associated toxins – such as lipopolysaccharide (LPS) – stimulate the host immune system, leading to an exaggerated inflammatory response and the subsequent development of SIRS. These peripheral inflammatory signals affect the CNS through two main pathways: humoral and neuronal. Through the humoral pathway, elevated circulating pro-inflammatory factors (TNF-α, IL-1β, and IL-6) enter the brain via the disrupted BBB and directly activate CNS inflammation. In a septic environment, the intense secretion of inflammatory factors and chemokines recruits peripheral immune cells, such as neutrophils and macrophages, to the brain, thereby exacerbating neuronal damage [22,23]. Neuroinflammation can also be amplified through neurotransmission, with the vagus nerve upregulating pro-inflammatory gene expression by transmitting signals to the nucleus tractus solitarius of the medulla oblongata [24]. This central-peripheral inflammation cascade amplifies the inflammatory response. In sepsis, microglia become hyperactivated, releasing large amounts of pro-inflammatory cytokines (TNF-α, IL-1β) and chemokines (MCP-1). Overactivated microglia induce apoptosis and synaptic damage in neurons, stimulate reactive oxygen species (ROS) production [25], and further trigger oxidative stress and inflammatory cascades. Astrocytes are also activated [26], and synergize with microglia to exacerbate the inflammatory response. This includes breaking down matrix components in the BBB, leading to barrier disruption, and secreting large quantities of inflammatory factors (IL-6), which promote the spread of inflammation. Cytokines and chemokines also disrupt the integrity of the BBB by affecting the expression of tight junction proteins (Claudin, Occludin) [22,23,27]. The sepsis-induced immune response produces an abundance of pro-inflammatory factors (TNF-α, IL-1β), which bind to specific receptors and activate apoptotic signaling pathways such as Fas and Caspase [28,29]. This activation ultimately leads to neuronal and glial cell death, causing further damage to the nervous system. Additionally, activated inflammatory mediators and immune cells generate ROS and reactive nitrogen species, leading to increased oxidative damage [30,31]. These free radicals damage cell membranes, proteins, and DNA, which further contribute to neuronal dysfunction, apoptosis, and long-term neurological impairment. Sepsis-induced oxidative stress also disrupts mitochondrial function, compromising the cellular energy supply. Mitochondrial damage exacerbates neuronal apoptosis and creates a vicious cycle by releasing cytokines and activating neuroinflammatory pathways [32].

3 PI3K/Akt pathway and its role in brain tissue

The PI3K/Akt signaling pathway consists of two main components: phosphatidylinositol 3 (PI3K) and its downstream

serine/threonine protein kinase B (PKB, also known as Akt). PI3K is a class of intracellular lipid kinases, classified into types I, II, or III based on substrate specificity and sequence homology [33,34]. Akt is a proto-oncogene product that, upon activation, modulates a variety of downstream signaling molecules, including mammalian target of rapamycin (mTOR) [35] and glycogen synthase kinase-3 (GSK-3) [36], among others.

The PI3K/Akt signaling pathway is a central intracellular regulatory network involved in diverse biological processes, including cell survival, proliferation, metabolism, protein synthesis, immune regulation, and stress responses. By promoting proliferation, inhibiting apoptosis, and enhancing cell survival, this pathway plays a critical role in tumorigenesis and has emerged as a prominent target for cancer therapy [37–39]. Akt, a key effector of the PI3K/Akt pathway, regulates glucose and lipid metabolism, as well as cell differentiation and growth [40], and holds therapeutic potential for diabetes and metabolic disorders. The PI3K/Akt/mTOR pathway also plays a critical role in bone and joint diseases, such as osteoarthritis [41], and in erythroid hematopoiesis [40], suggesting its potential as a novel therapeutic target. In neurological disorders, the PI3K/Akt pathway regulates neuronal survival, mitigates inflammation, preserves BBB integrity, and exerts neuroprotective effects in conditions such as Alzheimer's and Parkinson's diseases [42,43]. Thus, the PI3K/Akt pathway holds broad clinical potential across various diseases, including cancer, metabolic disorders, neurological conditions, and osteoarticular diseases.

In normal brain tissues, the PI3K/Akt signaling pathway plays a crucial role in neuronal survival, synaptic plasticity, energy metabolism, BBB integrity, and neurodevelopment [44]. The activation of this pathway depends on upstream ligands such as derived brain-derived neurotrophic factor (BDNF) and insulin-like growth factor 1 (IGF-1), and mediates multiple regulatory effects on neuronal anti-apoptosis, resistance to oxidative stress, synaptic plasticity, and energy metabolism through downstream targets including mTOR, GSK-3β, and cAMP response element-binding protein 2 [45]. For example, Akt inhibits the mitochondrial apoptotic pathway by phosphorylating pro-apoptotic proteins such as BAD and Caspase-9, thereby preventing premature neuronal apoptosis and contributing to the maintenance of the functional integrity of brain tissue [46]. Akt exerts antioxidant effects by activating the Nrf2 pathway and scavenging ROS [47]. It also activates mTOR-dependent protein synthesis to support dendritic spine formation and long-term potentiation (LTP) [47], and promotes the membrane translocation of the glucose transporter GLUT4 to enhance neuronal glucose uptake. In addition, Akt plays a key role in stabilizing the intracerebral microenvironment by maintaining the expression of endothelial tight junction proteins, such as Zonula Cccludens-1 (ZO-1), at the BBB [48].

However, in the pathological state of SAE, the systemic inflammatory response and oxidative stress lead to inhibition of the PI3K/Akt signaling pathway. Proinflammatory cytokines, such as TNF-α and IL-1β, released during sepsis indirectly suppress the activity of the PI3K catalytic subunit p110 via activation of the nuclear factor kappa B (NF-κB) pathway [25]. Simultaneously, excessive ROS promote the conversion of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) to phosphatidylinositol 4,5-bisphosphate (PIP2) by activating the lipid phosphatase PTEN, a negative regulator of PI3K, thereby impairing Akt membrane localization and phosphorylation [49]. Mitochondrial dysfunction further exacerbates energy metabolism disorders and reduces the efficiency of Akt activation [25]. Akt inactivation results in the dephosphorylation of BAD, which in turn activates Bax/Bak-mediated mitochondrial cytochrome c release and triggers the caspase cascade, ultimately enhancing neuronal apoptosis. Additionally, GSK-3β disinhibition leads to Tau protein hyperphosphorylation, promoting the formation of neurofibrillary tangles and downregulating the expression of synapse-associated proteins such as PSD-95, contributing to synaptic damage [50]. Decreased Akt activity in endothelial cells also compromises tight junction integrity, aggravating brain edema and neuroinflammation.

In summary, the PI3K/Akt pathway plays a critical role in maintaining CNS homeostasis under normal conditions. However, in SAE, its expression and activity are markedly altered, resulting in the loss of its original protective functions and, in some cases, contributing to disease progression. Comparing the dynamic changes of this pathway between physiological and pathological states may help elucidate its role in SAE pathogenesis and provide a theoretical foundation for targeted therapeutic interventions. (Figure 1).

4 PI3K/Akt pathway and neuroinflammation in SAE

As discussed previously, sepsis-induced neuroinflammation is a core pathogenic mechanism of SAE. Within the pathophysiological framework of SAE, the PI3K/Akt pathway plays a dual regulatory role in both CNS injury and neuroprotection. It does so by modulating the expression of neuroinflammatory factors, regulating microglial activation, maintaining the integrity of the BBB, and controlling neuronal apoptosis. The PI3K/Akt pathway is a

classical signaling cascade that regulates neuronal survival and neurogenesis, making it a crucial player in the progression and potential treatment of SAE [40,51]. In the CLP mouse model, protein expression levels of PI3K and Akt in hippocampal tissues were significantly decreased [52–54], whereas activation of the PI3K/Akt pathway attenuated SAE-related damage [52–57].

4.1 Regulation of inflammatory factors

The PI3K/Akt pathway suppresses the excessive release of pro-inflammatory cytokines during sepsis through multiple mechanisms. First, it initiates a negative feedback regulatory loop that significantly reduces the overexpression and secretion of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6 [58–60]. Second, the pathway upregulates the expression of anti-inflammatory mediators, such as IL-10, which subsequently inhibits pro-inflammatory cytokine production via paracrine signaling [58]. Additionally, the PI3K/Akt pathway inhibits the activation and nuclear translocation of NF-κB, further modulating inflammation [61]. It also contributes to the regulation of the Th1/Th2 cytokine balance [62], thereby attenuating the inflammatory cascade. Clinical studies have confirmed that pharmacological agents like dexmedetomidine [63] and metformin [64] can activate the PI3K/Akt pathway, inhibiting pro-inflammatory cytokine release and improving sepsis-associated brain and lung injury.

4.2 Regulation of microglia polarization

The PI3K/Akt signaling pathway plays a crucial role in regulating microglia polarization. It modulates microglial M1/M2 polarization by influencing multiple signaling pathways [65], including NF-κB [66] and chemokine receptor CXCR7 [67], which promote the transformation of microglia to the M2 phenotype and enhance their anti-inflammatory properties. M2-polarized microglia secrete anti-inflammatory cytokines, such as IL-10 and TGF-β [68], thereby reducing the neuroinflammatory response. Agents like tretinoin and curcumin have been demonstrated to inhibit the activation of pro-inflammatory M1 microglia while promoting the anti-inflammatory properties of M2 microglia, presumably via activation of the PI3K/Akt pathway [69]. Furthermore, the PI3K/Akt pathway indirectly regulates microglial inflammation by modulating the neuron-derived BDNF-PI3K/Akt signaling axis [70,71]. Akt increases the secretion of BDNF from neurons by enhancing vesicular transport, which in turn strengthens the inhibitory effect of neurons on microglial inflammation. Compounds

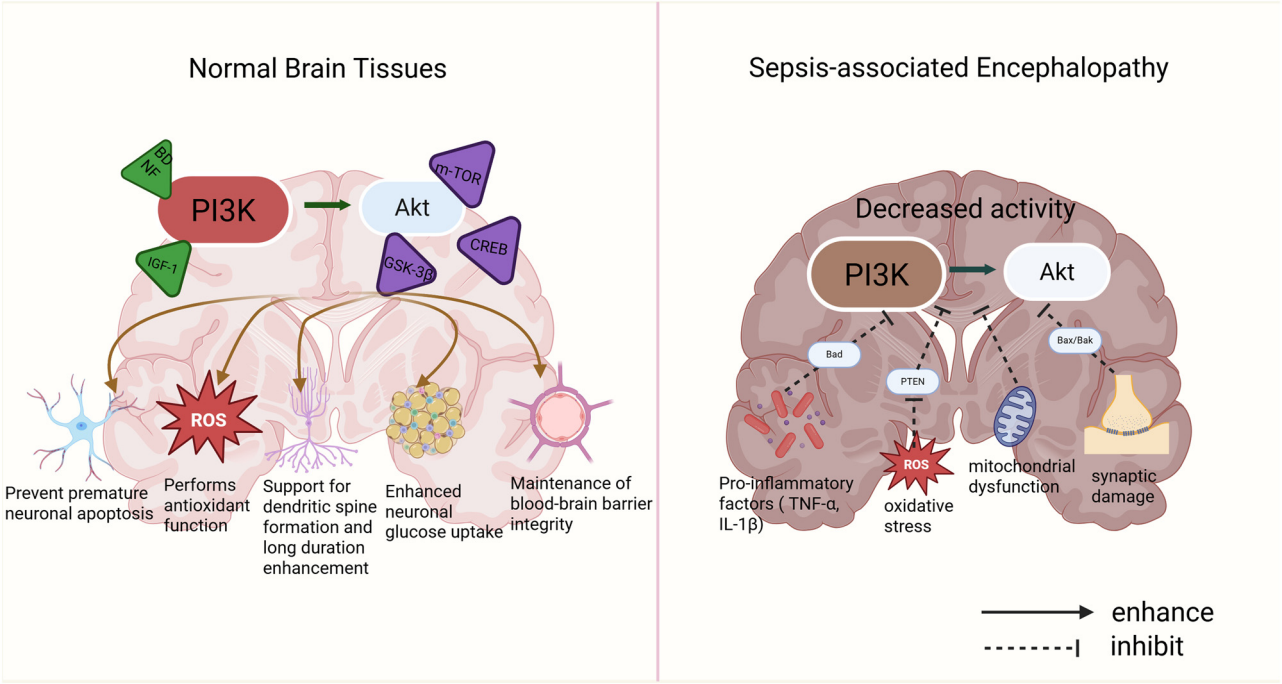

Figure 1: Differences in PI3K/Akt pathway in normal brain tissue and SAE conditions. ROS: reactive oxygen species.

like pineoside [72] and paeoniflorin [72] regulate the BDNF-PI3K/Akt axis, achieving a balanced regulation of microglia M1/M2 polarization and alleviating neuroinflammatory disorders such as SAE.

4.3 Maintenance of BBB integrity

The PI3K/Akt pathway plays a crucial role in maintaining the integrity of the BBB. Akt regulates the expression of tight junction proteins, such as Claudin, Occludin, and ZO-1, through the activation of the PI3K/Akt pathway, thereby preserving BBB structural integrity [73,74]. Chen et al. [75] demonstrated in an *in vitro* BBB model that activation of the PI3K/Akt pathway enhances the transcription and translation of tight junction proteins, resulting in decreased permeability of endothelial cell monolayers. Wang et al. [76] found that in a murine model of sepsis treatment with a PI3K-selective agonist significantly increased the expression of tight junction proteins in brain microvascular endothelial cells. Additionally, the PI3K/Akt pathway inhibits the TNF-α- and IL-1β-induced expression of matrix metalloproteinases, thereby reducing extracellular matrix degradation and protecting the BBB structure [77]. Zhi et al. [78] observed that selective PI3K agonist treatment significantly reduced levels of S100β and neuron-specific enolase in the cerebrospinal fluid of sepsis patients, along with other markers of BBB damage, and improved neurocognitive function scores. Gong et al. [79] reported that combined administration of a PI3K agonist and an anti-inflammatory agent significantly reduced the morbidity and mortality of patients with SAE, and the levels of tight junction protein degradation products, such as Occludin and Claudin-5 fragments, were notably lower in the peripheral blood of treated patients. This suggests that the combination regimen may exert neuroprotective effects by preserving BBB integrity.

4.4 Regulation of neuronal apoptosis

Neuronal apoptosis is a key pathological feature in sepsis-induced neuroinflammation, with its regulatory mechanisms linked to the PI3K/Akt pathway. First, the PI3K/Akt pathway inhibits neuronal apoptosis by regulating several downstream effector molecules. Activated Akt effectively blocks Bad-induced apoptosis by phosphorylating Bad at the Ser136 site, preventing its binding to Bcl-2. Additionally, the pathway upregulates the nuclear translocation of the antioxidant-related transcription factor Nrf2, which increases the expression of superoxide dismutase and catalase, thereby reducing oxidative stress-induced neuronal injury. Puerarin has been shown to reduce neuronal apoptosis by inhibiting oxidative stress through the PI3K/Akt/Nrf2 pathway [80]. Furthermore, the PI3K/Akt pathway promotes neural repair and regeneration. Akt-mTOR signaling enhances myelin sheath growth and stability during development by driving cap-dependent translation to facilitate myelin formation [81]. It has also been demonstrated that resveratrol can activate PI3K/Akt signaling to promote axonal regeneration and neurological recovery. Additionally, the PI3K/Akt pathway may play a role in regulating synaptic plasticity by modulating the reorganization of post-synaptic proteins, such as PSD-95 [82], and influences synaptic transmission efficiency as well as LTP [83]. Moreover, novel PI3K agonists have shown promising neuroprotective effects in animal models, providing new intervention targets for the treatment of SAE [84].

4.5 Discovery of new molecules

In recent years, several novel molecules have been identified as regulators of the PI3K/Akt pathway, with significant effects on the development and progression of SAE. Protein kinase N2 (PKN2), in particular, exerts a broad range of regulatory effects on the PI3K/Akt signaling pathway through mechanisms such as direct phosphorylation, modulation of membrane localization, and catalytic activity. PKN2 can directly phosphorylate the p85 regulatory subunit of PI3K [85], inducing a conformational change that alters its interactions with other signaling molecules. Furthermore, PKN2 affects the membrane localization of PI3K, thereby modulating its enzymatic activity [85]. Wang et al. [86] demonstrated that PKN2 overexpression activated the mTOR pathway in PC12 cells, reducing H_2O_2-induced oxidative damage and apoptosis. Additionally, PKN2 modulates Akt activity by phosphorylating its Ser473 site [87], a key step in regulating the function of Akt within the PI3K/Akt pathway. By phosphorylating Akt at this critical site, PKN2 influences the activity and substrate specificity of Akt, thereby affecting downstream signaling processes. In addition, PKN2 may play a role in regulating the integrity of the BBB [88]. Bai et al. [89] found that H_2 alleviates septic brain injury by activating PKN2 phosphorylation, which is associated with the PI3K pathway. While PKN2 exerts a broad range of regulatory effects on the PI3K/Akt signaling pathway, there are currently fewer studies focusing on its role in septic

encephalopathy. This presents an opportunity for future, more in-depth research. PTEN, as a negative regulator of the PI3K/Akt pathway, inhibits AKT activation by dephosphorylating PIP3 and converting it to PIP2 [90]. This action helps maintain normal neuronal function and survival, protecting against neuronal injury caused by dysregulated signaling. Furthermore, the signaling between PTEN-induced kinase 1 (PINK1) and the Parkin pathway is crucial in SAE. High expression of PINK1 can activate mitochondrial autophagy through up-regulation of Parkin, which reduces inflammatory responses, preventing neuroinflammation and alleviating cognitive impairments in SAE mice. In the absence of PINK1, there is a suppression of Ca^{2+} transients in the hippocampus, leading to elevated intracellular Ca^{2+} levels, which exacerbate sepsis-induced cognitive dysfunction in mice, highlighting the vital role of PINK1 in maintaining neuronal stability [91]. Girdin can inhibit the production of pro-inflammatory cytokines, promote neuronal survival, and prevent apoptosis by regulating the activation of the PI3K/Akt pathway, thereby alleviating neuroinflammation [92,93]. Phosphorylated Girdin enhances the activity of intracellular anti-apoptotic factors, such as Bcl-2 and mTOR, which reduce programmed cell death [94]. Additionally, Girdin regulates microglial activation, as overactivation of microglia exacerbates the neuroinflammatory response. Rheb (Ras homolog enriched in brain), a small GTP-binding protein, plays a key role in the PI3K/Akt/mTOR signaling pathway by directly activating mTOR, which is crucial for neuroprotection. In an LPS-induced neuroinflammation model, upregulation of Rheb was linked to astrocyte proliferation and neuronal apoptosis [95]. The Rheb-mTOR signaling pathway contributes to neuroinflammation-induced astrocyte activation and neuronal apoptosis through cell cycle activation [96]. Moreover, specific overexpression of Rheb in retinal ganglion cells significantly reduced cell death and effectively induced axonal regeneration [97], suggesting that Rheb promotes neural repair, potentially alleviating sepsis-induced neuroinflammation. Additionally, BAG3 is involved in regulating Akt downstream targets like mTORC1, affecting cellular autophagy processes. BAG3 forms a complex with CHIP (C-terminus of Hsc70 interacting protein) [98], which facilitates the ubiquitination and degradation of key inhibitors negatively regulating PI3K/Akt signaling, such as phosphatase and Tensin homolog deleted on chromosome 10 (PTEN), thereby positively regulating this pathway. Bcl-2-associated athanogene 3 (BAG3) also plays a protective role in sepsis-induced acute kidney injury (AKI), and studies have shown that sevelamer sodium can attenuate AKI in a rat sepsis model through inhibition of the PI3K/Akt pathway, with BAG3 involved in this protective mechanism. Although there are currently fewer studies directly examining these molecules in SAE, they play critical roles in the PI3K/Akt signaling pathway, which is integral to SAE pathogenesis. Future research should focus on how these molecules specifically contribute to SAE and whether they can be targeted for effective therapeutic interventions, potentially offering more effective treatments for patients with SAE (Figure 2).

5 Therapeutic potential of PI3K/Akt pathway modulators

IGF-1 attenuates the inflammatory response and ameliorates SAE by activating the PI3K/Akt pathway. Treatment with recombinant human IGF-1 significantly reduced serum levels of IL-1β, TNF-α, and IL-6 in patients with SAE, while also improving the Glasgow Coma Score (GCS), strengthening BBB integrity, reducing neuroinflammation, and enhancing cognitive function [99,100]. BDNF activates the PI3K/Akt signaling pathway through the TrkB receptor, upregulates the expression of the anti-apoptotic protein Bcl-2, and promotes the expression of synaptic plasticity-associated proteins (PSD95) [101,102]. BDNF has been shown to significantly ameliorate memory deficits in a mouse model of sepsis and reduce the expression of pro-inflammatory cytokines in the CNS. Several studies have shown that various naturally active compounds exert neuroprotective effects by modulating the PI3K/Akt signaling pathway. Curcumin significantly increased the level of phosphorylated Akt in neurons (the p-Akt/Akt ratio increased 2.1-fold), promoting the nuclear translocation of Nrf2 and enhancing cellular resistance to oxidative stress [103]. Resveratrol significantly reduced the volume of cerebral infarcts and neurological damage scores in cerebral ischemia/reperfusion rats, significantly lowering levels of myeloperoxidase, TNF-α, and upregulating p-Akt expression. The use of Akt inhibitors blocked the effects of resveratrol. Resveratrol was also shown to reduce neuronal apoptosis, as evidenced by an increase in the Bcl-2/Bax ratio and a decrease in the number of TUNEL-positive apoptotic cells [104]. Additionally, quercetin and rhodiola rosea glycosides synergistically activate PI3K/Akt downstream targets, significantly reducing pro-inflammatory factors and improving cognitive function [105,106]. Oleanolic acid [107] and dihydromyricetin (DHM) [108] inhibit oxidative stress through activation of the PI3K/Akt pathway, thereby exerting neuroprotective effects. Based on their role in other neuroinflammatory diseases, these natural compounds may have important therapeutic potential in SAE. In cases of overactivated PI3K/Akt

signaling, the PI3K-selective inhibitor LY294002 exerts a bidirectional modulatory effect, reducing inflammatory responses and neurotoxicity [104,109]. However, the targets of PI3K inhibitors need to be carefully selected to avoid inhibiting neuroprotective effects.

Several PI3K inhibitors have been developed for tumor therapy, such as PI-103, BKM120, and GDC-0941 [110,111]. These inhibitors block tumor cell proliferation and survival by targeting key nodes of the PI3K/Akt pathway, including PI3K, Akt, and mTOR. Some PI3K inhibitors have been approved for the treatment of specific hematologic malignancies. For example, Linperlisib, the first highly selective PI3Kδ inhibitor marketed in China, has been approved for the treatment of relapsed and/or refractory follicular lymphoma (FL), demonstrating significant clinical efficacy and good tolerability [112]. In addition, Duvelisib [113], a dual PI3Kδ and PI3Kγ inhibitor, has also been approved by the FDA for the treatment of adult patients with relapsed/refractory chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and FL who have received at least two prior therapies. Although these drugs have shown effectiveness in treating specific types of hematologic malignancies, their potential application in neuroinflammatory and neurological disorders requires further research and exploration. Although most compounds targeting the PI3K/Akt pathway – such as estrogen [114], resveratrol, curcumin [115], GDC-0941, duvelisib, and leniolisib [112] – have already entered clinical trials for other diseases (oncology, metabolic disorders, and neurodegenerative diseases), their clinical application in sepsis, especially SAE, remains largely unexplored or is still in its infancy. This suggests that, in the future, compounds with established clinical safety profiles could be prioritized for translational research in SAE, particularly through the use of animal models to verify their target specificity and neuroprotective efficacy (Table 1).

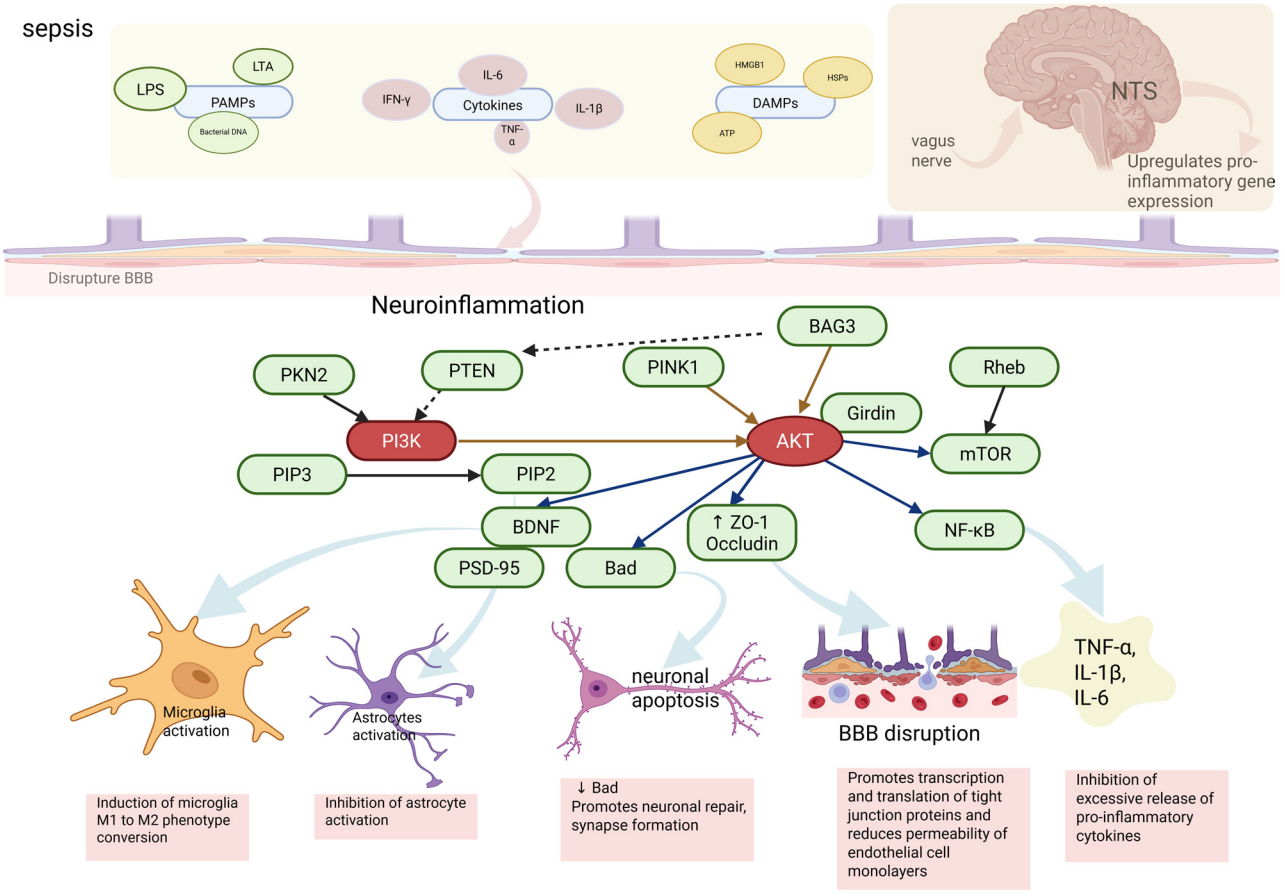

Figure 2: Inflammatory signaling regulates SAE through the PI3K/Akt pathway. PAMPs: pathogen-associated molecular patterns; DAMPS: damage-associated molecular patterns; LTA: lipoteichoic acid; NTS: nucleus tractus solitarius; BBB: blood–brain barrier.

Table 1: Major research models, mechanisms, and key findings of PI3K/Akt pathway agonists and inhibitors associated with SAEs

Compound	Mechanisms	Model	Key findings	Ref.
Recombinant human IGF-1	Activates PI3K/Akt pathway to reduce inflammation	C57BL/6 mice; sepsis induced by intratracheal instillation of *P. aeruginosa* (PA103 strain)	Decrease in serum IL-1β, TNF-α, IL-6 levels; increase in GCS score; enhancement of BBB function; decrease in neuroinflammation and improvement in cognitive ability	[99,100]
BDNF	Activates the PI3K/Akt pathway via TrkB receptors	SCID-Beige mice; NB xenograft model for metastasis	Improvement of memory deficits and reduction of pro-inflammatory cytokines in CNS	[101,102]
Estrogen	Activates PI3k/Akt, upregulates Bcl-2, and downregulates Bax and Caspase-3,8	VSC4.1 motor neuron cells	Antiapoptotic	[116]
Curcumin	Increases phosphorylated Akt (p-Akt) and promotes Nrf2 nuclear translocation	C57BL/6 mice; LPS-induced sepsis model; HL-1 cardiomyocytes; LPS stimulation	Enhanced antioxidant stress response and 2.1-fold increase in p-Akt/Akt ratio, promoting neuroprotection	[103]
Resveratrol	Increases p-Akt expression and inhibits oxidative stress	SD rats; MCAO-induced cerebral I/R injury model	Reduced cerebral infarct volume, improved neurologic scores, decreased MPO, TNF-α, increased p-Akt, and decreased apoptosis	[117]
Quercetin	Activates PI3K/Akt pathway, anti-inflammatory effects	C57BL/6 mice; *G. parasuis*-induced encephalitis model; mouse brain endothelial cells; *G. parasuis* stimulation	Significantly reduced inflammatory cytokines and improved cognitive function	[105,106]
Oleanolic acid	Activates PI3K/Akt pathway to inhibit oxidative stress and neuroinflammation	Rats; methylmercury-induced ALS model	Reduces oxidative stress and neuroinflammation	[107]
DHM	Activates the PI3K/Akt pathway to reduce oxidative stress	C57BL/6 mice; MPTP-induced Parkinson's disease model; MES23.5 cells; MPP^+ stimulation	Reduces oxidative stress and neuroinflammation and provides neuroprotection	[108]
PI-103 series	PI3K inhibitor targeting the PI3K/Akt/mTOR axis	Human tumor xenograft models (glioblastoma, breast cancer, leukemia, prostate cancer, etc.)	Inhibits tumor cell proliferation and survival by targeting the PI3K/Akt/mTOR pathway	[110,111]
BKM120 series	PI3K inhibitor targeting the PI3K/Akt pathway	Human tumor xenograft models (glioblastoma, breast cancer, leukemia, prostate cancer, etc.)	Inhibits tumor cell growth and survival by blocking PI3K/Akt signaling	[110,111]
GDC-0941	PI3K inhibitor targeting the PI3K/Akt pathway	Human tumor xenograft models (glioblastoma, breast cancer, leukemia, prostate cancer, etc.)	Inhibits tumor growth, metastasis, and survival in preclinical models by blocking PI3K/Akt signaling	[110,111]
Imperius	Highly selective PI3Kδ inhibitor	Refractory/relapsed FL	Approved for FL treatment in China; demonstrated significant clinical efficacy and tolerability	[112]
Duvelisib	Dual PI3Kδ/PI3Kγ inhibitor	Refractory CLL and FL	FDA approved for the treatment of CLL, SLL, and FL; effective in patients with relapsed/refractory disease	[113]
LY294002	PI3K inhibitor targeting the PI3K pathway	Rat astrocyte; LPS-induced astrocyte culture model used	Inhibits the PI3K/Akt pathway; shows bidirectional regulation in overactive pathways, reducing inflammation and neurotoxicity	[104,109]

6 Conclusion

Neuroinflammation is a key contributor to the pathogenesis of SAE, leading to CNS injury and adversely affecting cognitive function and patient survival. The underlying mechanisms primarily involve the activation of microglia and astrocytes, the release of pro-inflammatory cytokines and chemokines, disruption of the BBB structure, increased oxidative stress, and mitochondrial dysfunction. Among the numerous signaling pathways implicated in SAE, the PI3K/Akt pathway has emerged as a central regulator. This pathway plays a pivotal role in modulating neuroinflammatory responses, preserving BBB integrity, and promoting neuronal survival. Several studies have demonstrated that activation of the PI3K/Akt pathway by specific compounds can attenuate inflammation and neuronal damage, thereby alleviating SAE-related symptoms. However, the majority of these findings remain at the preclinical stage, and no PI3K/Akt-targeted agents have yet demonstrated clinical efficacy in SAE treatment.

As mentioned above, the PI3K/Akt signaling pathway plays a key role in regulating neuroinflammation, apoptosis, and BBB function, and holds great promise for clinical application. Activation of this pathway can reduce brain tissue damage and improve cognitive function, making it applicable to a variety of neurological diseases, including SAE. In addition, the PI3K/Akt pathway is closely related to immune system homeostasis. Moderate activation of this pathway can inhibit excessive immune responses and reduce systemic inflammation, which is particularly important in SAE, a condition characterized by a pathological "inflammatory storm." Currently, several drugs targeting this pathway have entered clinical trials for oncology and metabolic diseases and have demonstrated favorable safety profiles. As a potential therapeutic target, the PI3K/Akt pathway is expected to offer a novel intervention strategy for diseases such as SAE in the future.

Despite these advances, several critical knowledge gaps remain. The PI3K family comprises multiple isoforms – PI3Kα, PI3Kγ, and PI3Kδ – each with distinct cellular distribution and functions. For example, PI3Kγ, as a central driver of microglial inflammatory responses, promotes M1-type polarization through the activation of chemokine receptors (the CXCL12–CXCR4 axis), thereby inducing NLRP3 inflammasome activation and the infiltration of peripheral immune cells into the brain [118]. PI3Kα, on the one hand, maintains neuronal metabolism and anti-apoptotic functions via the Akt/mTOR pathway [119]; on the other hand, its overactivation may exacerbate mitochondrial autophagy disorders due to oxidative stress [120]. Current research on the roles of these isoforms in SAE is limited, fragmented, and lacks systematic comparison and precise localization. Moreover, most studies have been conducted in acute animal models or *in vitro* systems, and their clinical relevance and translational potential remain to be validated. Notably, the PI3K/Akt pathway is intricately linked with multiple other signaling cascades – including MAPK, JAK/STAT, NF-κB, mTOR, and NLRP3 – which can induce diverse, and sometimes opposing, biological outcomes. This complexity makes it challenging to predict the net effect of pathway activation or inhibition in the inflammatory milieu of SAE.

Future studies should aim to delineate the cell-type-specific and stage-specific roles of individual PI3K isoforms during SAE progression and evaluate their potential as therapeutic targets in terms of efficacy and safety. Additionally, integrating single-cell transcriptomics and multi-omics approaches may provide insights into the dynamic crosstalk between the PI3K/Akt pathway and other signaling networks. On this basis, the development of selective, brain-targeted PI3K modulators, and the investigation of combination therapies – such as anti-inflammatory agents paired with BBB-protective compounds – may accelerate the translation of preclinical findings into clinically viable interventions for SAE.

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