Molecular Neurobiology
https://doi.org/10.1007/s12035-023-03563-w

Investigating the Potential Mechanisms and Therapeutic Targets of Inflammatory Cytokines in Post-stroke Depression

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Received: 5 May 2023 / Accepted: 7 August 2023

Abstract

Post-stroke depression (PSD) affects approximately one-third of stroke survivors, severely impacting general recovery and quality of life. Despite extensive studies, the exact mechanisms underlying PSD remain elusive. However, emerging evidence implicates proinflammatory cytokines, including interleukin-1β, interleukin-6, tumor necrosis factor-alpha, and interleukin-18, play critical roles in PSD development. These cytokines contribute to PSD through various mechanisms, including hypothalamic–pituitary–adrenal (HPA) axis dysfunction, neurotransmitter alterations, neurotrophic factor changes, gut microbiota imbalances, and genetic predispositions. This review is aimed at exploring the role of cytokines in stroke and PSD while identifying their potential as specific therapeutic targets for managing PSD. A more profound understanding of the mechanisms regulating inflammatory cytokine expression and anti-inflammatory cytokines like interleukin-10 in PSD may facilitate the development of innovative interventions to improve outcomes for stroke survivors experiencing depression.

Keywords Inflammatory cytokines · Stroke · Depression · Post-stroke depression

Introduction

Post-stroke depression (PSD) is a common complication affecting approximately one-third of stroke survivors [1]. Typically manifesting within three months following a stroke, PSD is believed to be precipitated by, or associated with, the ischemic event [2]. PSD has been connected to unfavorable outcomes in both inpatient and outpatient recovery settings, such as an elevated risk of subsequent stroke events, and ultimately increased mortality rates [3]. Women are more susceptible to PSD than men [4]. Various factors, including lesion locations, inflammatory mediators, and genetic factors, can influence PSD development [5]. Identifying and treating PSD is crucial, as it significantly impacts stroke recovery and patients' overall quality of life.

The precise mechanisms underlying PSD remain unclear. However, considerable evidence suggests that dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis, increased levels of pro-inflammatory cytokine, alterations in neurotransmitters, the neurotrophic hypothesis, and gene-related factors collectively contribute to PSD development [5, 6]. Cytokines, small proteins produced during the secondary immune response following acute focal brain injury in a stroke, play critical roles in regulating inflammatory responses [7]. Numerous studies have demonstrated that cytokine levels, such as IL-1β, IL-6, TNF-α, and IL-18, are significantly elevated in patients with PSD [8–10], suggesting that the presence of these cytokines in the brain following a stroke may contribute to PSD development. Table 1 provides a summary of the cytokine signatures implicated in PSD, with evidence gathered from animal models, human studies, and genetics research.

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Published online: 17 August 2023

Table 1 Cytokine signatures of post-stroke depression (PSD): evidence from animal models, human studies and genetics

Cytokines	Preclinical evidences	Observations in humans	Polymorphism
TNF-α		↑in patients with PSD [9, 11, 12]	TNF-α levels were significantly associated with PSD at 2 weeks in the presence of the − 850 T allele [8]
IL-1β	Rats with PSD showed an increased expression of IL-1β in the ischemic hippocampus [13]	↑in patients with PSD [14]	Individuals with the − 511 T allele and higher levels of IL-1β had a borderline significant association with PSD at two weeks after stroke [8]
IL-6		↑in patients with PSD [11, 15] ↑in blood [16]	
IL-10		↓in patients with PSD [17] ↑in patients with PSD [11]	IL-10 -1082A/A was associated with all PSD [18]
IL-18	Rats with PSD showed an increased expression of IL-18 in the ischemic hippocampus [13] ↑IL-18 in the whole brain and ischemic brain regions in a mouse PSD model [19]	↑blood in PSD [10, 15] IL-18 negatively correlate with depression [20]	

IL interleukin, *TNF* tumor necrosis factor, *PSD* post-stroke depression

The relationship between inflammatory cytokines and PSD is unclear and may involve multiple mechanisms, such as dysfunction of neuroendocrine pathway [21, 22], neurotoxic mediators pathway [23, 24], neurotransmitter pathway [25, 26], brain-derived neurotrophic factor (BDNF) levels [27], gut microbiota [28], and genetic factors [8, 18]. In addition, the direction of causality has not been conclusively determined, as depression itself can lead to increased cytokine production [29]. PSD is also associated with an increased risk of recurrent stroke and higher mortality [30]. The link between inflammatory cytokines and PSD underscores the importance of adopting a multifactorial approach to manage this condition. Targeting the underlying biological mechanisms may have the potential to improve outcomes for stroke survivors with depression.

This review is aimed at investigating the role of both proinflammatory cytokines, such IL-1, TNF-α, IL-6, and IL-18, and anti-inflammatory cytokines such as IL-10 in the development of PSD. Understanding the mechanisms that regulate the expression of inflammatory cytokines in PSD may also facilitate the modulation of these cytokines as potential therapeutic interventions for PSD.

Inflammatory Cytokines After Stroke

Overview of Inflammatory Cytokines

Stroke is a complex pathological event that involves brain tissue injury and subsequent systemic inflammatory reactions. Stroke-induced sterile inflammation is initiated by the release of damage-associated molecular patterns (DAMPs) from dying cells [31]. These DAMPs activate various pattern recognition receptors (PRRs), such as toll-like receptors (TLRs) on the surface of microglia, thus triggering the innate immune system [32–35]. DAMPs bind to PRRs through their specific ligands, and activate various signaling pathways, for example, the activation of nuclear factor-kappa B (NF-κB), which ultimately leads to the polarization of microglia to an M1 pro-inflammatory phenotype and production of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-18 [32, 36–38]. This process amplifies inflammatory cascades, resulting in concurrent tissue damage and the induction of both detrimental and cytoprotective adaptive immune responses [39]. These cytokines also promote leukocyte infiltration and exacerbate tissue damage [37]. This leads to further produce more DAMPs, fueling ongoing damage [37]. While microglia polarize to an M2 phenotype, they may produce anti-inflammatory cytokines, including IL-10, IL-4, and TGF-β, that can suppress inflammation and facilitate tissue repair [40, 41]. Notably, these cytokines act as crucial mediators of inflammatory signaling, occupying a central role in coordinating responses to injury and inflammation [42]. In the subsequent sections, we explicate the expression dynamics of inflammatory cytokines following stroke events.

TNF-α in Ischemic Stroke

TNF-α is a vital pro-inflammatory cytokine and regulates inflammation both locally and systemically through its receptors, TNFR1 and TNFR2 [43]. Binding of TNF-α to the TNFR1 receptor induces inflammation and proapoptotic signaling, while the TNF-α attachment to TNFR2 is

anti-inflammatory and promotes tissue regeneration processes [44, 45]. Produced by a variety of cells, including mast cells, monocytes, T cells, neutrophils, keratinocytes, macrophages, and fibroblasts, TNF-α expression increases within hours of ischemic brain injury, potentially contributing to infarction progression during the post-ischemic period, either directly or by inducing neurotoxic mediators, such as nitric oxide [23]. Early TNF-α levels have been found to correlate with ischemic stroke severity [46]. TNF-α functions as a critical mediator in stroke's neuroimmunological development, exhibiting both neurotoxic and neuroprotective roles [47–50]. Following ischemic injury, TNF-α is initially produced by activated resident macrophages, such as microglia, impairing blood–brain barrier (BBB) function, potentially mediated by MMP-3 and MMP-9, increased oxidative stress and endothelial cells necroptosis [51, 52]. In animal stroke models, the increase of TNF-α in ischemic areas has been shown to lead to larger infarct zones and increased neuronal injury [53, 54]. Similarly, higher serum levels of TNF-α are associated with worse neurologic disability, skeletal muscle atrophy, delayed recovery, and poor prognosis in stroke patients [55–58]. Higher levels of TNF-α receptors TNFR1 and TNFR2 have been detected in the plasma of patients with ischemic stroke and may predict future intracerebral hemorrhage, poor functional outcome, and arterial stiffness [59–62]. Elevated TNFR1 has also been associated with increased risk of recurrent vascular events in patients who have suffered lacunar stroke [63]. Anti-TNF therapy has been shown to effectively reduce inflammation, provide neuroprotective effects, and improve stroke outcomes in both animal stroke models and human patients with stroke [52, 64–66]. In addition, the single nucleotide polymorphisms (SNPs) rs1800629 and rs1800610 in the TNF-α gene have been linked to stroke susceptibility [67, 68]. Thus, more evidence shows that TNF-α plays a significant role in the pathogenesis of stroke and may emerge as a promising target for developing novel stroke therapies.

IL-1β in Ischemic Stroke

The IL-1 family, comprising 11 cytokines, plays a central role in innate inflammatory and immune responses [69]. While all IL-1 family members exhibit biological significance, IL-1β is particularly noteworthy due to its association with auto-inflammatory diseases [70]. IL-1β, produced by macrophages, microglia, and monocytes following caspase-1 activation and cleavage of pro-IL-1β [71], shows an increased levels after acute ischemic stroke, with an initial increase within 24 h, followed by re-elevation at 144 h post-stroke [72]. This cytokine participates in various mechanisms exacerbating ischemic stroke-induced damage. For instance, IL-1β activates phospholipase A2, leading to blood–brain barrier dysfunction, vasogenic brain edema, and heightened microvascular permeability [73, 74]. Moreover, IL-1β amplifies inflammation by stimulating microglia, promoting leukocyte migration, and upregulating pro-inflammatory cytokines, such as IL-6 and TNF-α [75, 76]. Consequently, chronic inflammation ensues, hindering the recovery of damaged brain cells. IL-1β also induces excitotoxicity via glutamate-mediated apoptosis of impaired cells through the JNK/AP-1 pathway [77, 78]. The nucleotide-binding domain, leucine-rich repeat-containing protein (NLRP3) inflammasome-IL-1β pathway contributes to several post-acute ischemic stroke events [79], and recent evidence implicates IL-1β in the AIM2 inflammasome signaling cascade, resulting in immune suppression and secondary infection following stroke injury [80, 81].

Inhibition of IL-1 receptor 1, which binds IL-1 isoforms, reduces brain damage and preserves neurological function [82]. Striking a balance between IL-1β and its antagonist is crucial for determining its overall effect and role. Elevated IL-1β levels correlate with poorer prognosis and diminished long-term functional recovery [83], whereas increased interleukin-1 receptor antagonist (IL-1Ra) levels heighten infection risk post-ischemic stroke [84]. Thus, the IL-1β/IL-1Ra balance may serve as a valuable prognostic marker for patient outcomes following cerebral ischemia.

IL-6 in Ischemic Stroke

IL-6, a multifaceted soluble signaling molecule, modulates a range of physiological processes, encompassing inflammation, immune response, and hematopoiesis [85]. Following stroke onset, IL-6 concentrations exhibit a marked increase within 24 h and remain elevated for 5 to 7 days [86]. A positive correlation has been observed between IL-6 levels, infarct volume at day 7, and stroke severity [87]. IL-6 predominantly originates from neurons, microglia, astrocytes, and endothelial cells within the ischemic hemisphere, thus serving as an inflammation marker post-stroke [88, 89]. Among evaluated pro-inflammatory cytokines, IL-6 has been identified as a key mediator within the circulating cytokine network, responding to acute cerebral ischemia and significantly associating with both stroke severity and clinical outcome [90]. Heightened serum IL-6 levels correspond to an increased risk of incident stroke and futile reperfusion in patients with acute ischemic stroke and large vessel occlusion [91, 92]. Post-stroke release of IL-6 into the cerebrospinal fluid may impede cerebrovascular autoregulation and exacerbate histopathological manifestations [93]. Conversely, IL-6 also exhibits neurotrophic properties, promoting neurogenesis, angiogenesis, and neuronal differentiation [88], while attenuating excitotoxic damage and safeguarding neurons against apoptosis [94]. Local IL-6 production by brain-resident cells facilitates angiogenesis and confers long-term histological and functional protection

following ischemic stroke [95]. As a result, IL-6 is posited as the primary mediator within the pro-inflammatory cytokine network, displaying a dual effect in ischemic stroke: functioning as an inflammatory factor during the acute stage and a neuroprotective factor in subsequent phases [94, 95].

IL-10 in Ischemic Stroke

IL-10, an anti-inflammatory cytokine, plays a significant role in the context of stroke. Elevated IL-10 levels have been observed in experimental stroke models [96], while overexpression in transgenic mice resulted in reduced infarct size and decreased pro-inflammatory cytokine levels [97]. In contrast, IL-10 deficiency has been associated with poor stroke outcomes and exacerbated inflammatory responses [98]. The protective effects of IL-10 are mediated in part through the IL-10 receptor, PI3K/AKT and STAT-3 signaling pathways [99], as well as by inhibiting NF-κB [100]. T and B cells, crucial in mitigating neuroinflammation, modulate various cytokines and chemokines, with IL-10 being central to immunomodulation [101]. Moreover, IL-10 promotes neural stem cell proliferation and neurogenesis in the subventricular region of ischemic brain tissue, playing an essential protective role in stroke [102]. IL-10 restricts lesion size and encourages M2-type macrophage differentiation in stroke [24]. IL-10 production is critical for stroke outcomes, and regulatory T cells can limit neuroinflammation through IL-10 production [103]. However, regulatory T cells may worsen stroke during the acute phase by inducing microvascular dysfunction [104].

IL-18 and Ischemic Stroke

Interleukin-18 (IL-18), also known as interferon-gamma inducing factor, is a protein encoded by the human IL18 gene [105, 106]. It is synthesized by various cells, including macrophages, dendritic cells, lymphocytes, and non-immune cells [107], and expressed in neuronal cells during early phases and in microglia at later stages. Elevated IL-18 levels consistently correlate with unfavorable stroke outcomes [108]. Initially produced as an inactive cytokine in the cytoplasm, IL-18 requires caspase-1 proteolytic processing within the NLRP3 inflammasome for activation and secretion [109]. Concurrently released with IL-1β during pyroptosis, a caspase-1 activated cell-death program [110], IL-18 can also be produced via other caspase-mediated pathways, such as caspase-8 in Fas-mediated noncanonical maturation [111], and proteases including proteinase 3 [112], chymase [113], and granzyme B [114]. T cell receptor-independent IL-18 activation can occur through Fas/FasL signaling [115].

Patients with severe ischemic stroke exhibit higher IL-18 levels than those with moderate or mild ischemic stroke, rendering this biomarker a critical indicator for early detection and monitoring of ischemic stroke [108]. Increased intracranial pressure (ICP) may intensify neuroinflammation following ischemic stroke by activating the NLRP3 inflammasome in microglia [116]. Furthermore, IL-18 polymorphism has been associated with ischemic stroke risk [117].

Roles of Cytokines in PSD

Elevated levels of pro-inflammatory cytokines, including TNFα, IL-1β, and IL-6, have been associated with depression, resulting in a decrease in hippocampal neurogenesis and promotion of depressive-like behaviors [118, 119]. Inflammatory cytokines stimulate the HPA axis, leading to cortisol release and subsequent alterations in corticoid receptors and damage to stress-sensitive brain areas, particularly the hippocampus. This contributes to cognitive and depressive disorders [120, 121]. Prolonged elevated levels of cytokines may result in neurodegeneration and neuronal loss, leading to PSD [24]. Structural MRI findings in patients with major depressive disorder (MDD) reveal reductions in hippocampal and amygdala volume and enlarged lateral ventricles [122]. Chronic stress can activate microglial cells to release proinflammatory cytokines, causing neurotoxic effects, glutamate-mediated excitotoxicity, and disturbances in glutamate metabolism in specific brain regions such as the anterior cingulate cortex, prefrontal cortex, hippocampus, and insula, which play pivotal roles in the pathophysiology of depression [123]. Moreover, proinflammatory cytokines can directly impair adult hippocampal neurogenesis, resulting in inflammation in specific regions [124]. Investigating the correlation between SNPs in genes responsible for inflammatory molecules and PSD can enhance our understanding of the immuno-inflammatory mechanism underlying PSD [125, 126].

The symptoms of cytokine-induced depression and idiopathic depression in individuals demonstrate considerable overlap, suggesting that cytokines may target neurocircuits associated with psychomotor activity [127]. As a result, inflammatory cytokines may play a similar role in both depression and PSD.

TNF-α in Depression and PSD

Emerging research suggests a role for TNF-α in the pathogenesis of PSD, with numerous studies reporting elevated levels of this pro-inflammatory cytokine in patients diagnosed with MDD [128, 129]. Increased peripheral cytokines, such as TNF-α and its soluble receptors, have been found to correlate with higher glutamate concentrations in the dorsal anterior cingulate cortex and left basal ganglia, with depressive symptom severity positively associated with glutamate

concentration [130]. Moreover, TNF-α has been shown to increase blood–brain barrier permeability, potentially inducing depressive behavior and symptoms resembling depression in rodent models [131, 132].

Investigations specifically examining TNF-α levels in PSD have reported elevated levels in PSD patients and a higher TNF-α/IL-10 ratio [11]. Other studies have identified significantly increased levels of both IL-6 and TNF-α in the PSD group compared to the non-PSD group [9, 12]. Furthermore, TNF-α's inhibition of glutamate transporter activity may contribute to PSD pathogenesis by exacerbating glutamate neurotoxicity [133]. Elevated TNF-α levels have been associated with PSD at 2 weeks in the presence of the − 850 T allele, suggesting a role for genetic susceptibility in TNF-α occurrence during the acute phase of stroke in patients [8].

IL-1β in Depression and PSD

Depressed patients have been found to exhibit elevated IL-1β levels in both blood and cerebrospinal fluid, as demonstrated by multiple studies [134, 135]. A SNP in the IL1β gene (rs16944; 511C > T) has been associated with increased depression susceptibility in multiple sclerosis patients [136]. Furthermore, activation of the P2X7–NLRP3–IL-1β pathway has been correlated with depressive-like behaviors [137]. IL-1β is linked to the P2X receptor family, and P2X7 inhibition has been connected to antidepressant-like effects [138–140] . However, the relationship between elevated circulating IL-1β levels and depression may depend on patients' sex and age [141], with some studies reporting no significant difference in IL-1β levels or correlation with symptom severity [142, 143]. Interestingly, one study found that depressed individuals exhibited decreased IL-1β levels and increased IL-1RA levels [141]. Stress-induced IL-1β production and NLRP3 are implicated in depressive-like behaviors and depression-related cellular and molecular changes [144, 145]. Nonetheless, the role of IL-1β as a diagnostic or therapeutic biomarker for MDD remains debated, with conflicting results potentially attributable to patient variability.

In a study by using a rat PSD model, increased expression of IL-18, IL-1β, and the NLRP3 inflammasome was observed in the ischemic hippocampus [13]. Another investigation found a strong correlation between IL-1β and PSD in acute ischemic stroke patients up to six months post-stroke [14]. These findings imply that severe inflammation may contribute to the development of PSD. The CysLT2R antagonist HM3379 was found to alleviate PSD-induced neurological damage and depression-like behaviors in gerbils, potentially due to inhibition of the NLRP3 inflammasome/pyroptosis pathway and mature IL-1β/IL-18, as evidenced by both in vivo and in vitro studies [146]. Furthermore, individuals carrying the -511 T allele exhibited higher IL-1β levels associated with PSD at two weeks post-stroke, with a borderline significant interaction term, although no associations were detected with PSD at one year [8].

IL-6 in Depression and PSD

IL-6 has been implicated in depression, with monocyte-derived IL-6 associated with chronic stress-induced depression-like behavior [147]. Numerous preclinical studies and meta-analytic results demonstrate elevated IL-6 levels in patients with major depression [148–150], whereas IL-6 knockout mice show protection from stress-induced depression [151]. IL-6 disrupts the HPA axis, impairs synaptic neurotransmission, and reduces neurotrophic factors [152–154]. Furthermore, it enhances indoleamine 2,3-dioxygenase (IDO) activity, activating the kynurenine pathway and decreasing central serotonin availability [155], leading to the production of neurotoxic agonist quinolinic acid and 3-hydroxykynurenine, contributing to oxidative stress and neurodegeneration associated with MDD [156]. Additionally, pro-inflammatory cytokines can bind to microglial cells and diminish BDNF signaling in the synaptic cleft [157]. Lowering peripheral IL-6 is linked to increased total hippocampal volume [158]. However, Zhou et al. [159] discovered that hippocampal volume increase following ketamine administration was independent of peripheral inflammatory marker changes. Prefrontal cortex volume is significantly reduced in MDD patients [160–162] and negatively correlates with serum IL-6 levels [163]. Evidence suggests that IL-6 levels may serve as a predictive biomarker for therapeutic response, and IL-6 may impact depression via gut microbiota. IL-6 receptor blockade with MR16-1 antibody may have a rapid, lasting antidepressant effect by modulating immune system functions [164]. Although one study did not observe increased circulating IL-6 in MDD patients [128], a clinical Phase II study with IL6R antagonist tocilizumab is underway in depressed patients [165].

In PSD, elevated serum IL-6 levels persist up to one year post-stroke diagnosis [11]. Higher IL-6 levels independently associate with depressive disorders at two weeks and one year after stroke [15]. Plasma IL-6 levels in stroke patients significantly correlate with depressive symptom severity three months post-stroke, suggesting IL-6 as a potential PSD biomarker [16]. However, IL-6 levels in PSD patients remain constant and do not change after the acute period [166]. A study revealed a significant positive correlation between miR-221-3p and inflammatory cytokines IL-6 and TNF-α, indicating its potential involvement in the inflammatory response associated with IL-6 and TNF-α in PSD [167].

IL-10 in Depression and PSD

Decreased IL-10 levels have been associated with depression and more severe somatic depressive symptoms [168, 169], while increased IL-10 levels have been reported in MDD, potentially due to initial compensatory responses to acute inflammation and elevated mu-opioid receptor levels [170, 171]. Persistent inflammation, however, can diminish IL-10 levels over time. T lymphocytes contribute to resolving inflammation-induced depression via the IL-10-dependent pathway [172]. Increasing IL-10 levels may have anti-inflammatory effects and alleviated depressive-like behavior preclinical models [173, 174]. Although the precise mechanism underlying IL-10's potential benefits in MDD remains unclear, its anti-inflammatory effects in the peripheral and central nervous system and negative modulation of microglia activation may be involved [175].

Patients with lower IL-10 levels at 1-month follow-up after a stroke had a higher likelihood of developing PSD. IL-10 is associated with stroke severity, living ability, and functional outcomes, serving as an independent protective predictor for PSD [17]. The anti-inflammatory cytokine genotype IL-10 1082A/A has been linked to PSD within two weeks, supporting the cytokine hypothesis in PSD etiology [18]. However, one study found no correlation between serum IL-10 levels and PSD [176].

IL-18 in Depression and PSD

Elevated IL-18 levels have been detected in patients with MDD [177]. NLRP3 activation and IL-1β/IL-18 secretion may upregulate microglial IDO, implicated in MDD pathogenesis [178, 179]. Amitriptyline treatment reduced NLRP3 and caspase-1 gene expression, as well as IL-1β and IL-18 serum levels [180]. IL-18 significantly impacts HPA axis activation, which is reportedly dysregulated in MDD [181]. IL-18 may antagonize glucocorticoid signaling via NF-κB activation, disrupting glucocorticoid-dependent negative feedback on the HPA axis [182, 183]. Conversely, IL-18 deficiency has been shown to induce hippocampal abnormalities and depressive-like behavior [184], with some studies indicating decreased IL-18 blood levels in MDD patients [185].

Elevated IL-18 levels have also been linked to PSD. Chronic spatial restraint stress and middle cerebral artery occlusion are associated with depression-like behaviors due to increased IL-18 levels in the brain [19]. One study found significantly higher serum IL-18 levels in PSD patients on day 7, potentially predicting PSD risk at the acute stroke stage and six months post-stroke [10]. However, another study showed a negative correlation between IL-18 levels and depressive symptoms during acute stroke [20]. In a subsequent investigation, the PSD and oxygen–glucose deprivation/reoxygenation-induced BV2 cell models demonstrated microglial activation, which persistently facilitated the production of pro-inflammatory cytokines, such as IL-1β and IL-18 [146].

Mechanisms Linking Inflammatory Cytokines to PSD

Spalletta et al. introduced a cytokine hypothesis suggesting a link between proinflammatory cytokines and ischemic brain injury, with interleukins potentially playing a crucial role in specific depression subcategories [186]. Studies have demonstrated that inflammatory cytokines might induce PSD through several mechanisms, including BBB injury, microglial activation, NLRP3 inflammasome activation, neurotransmitter imbalances, kynurenine pathway modulation, reduced BDNF levels, gene polymorphisms, gut microbiota imbalances, and mitochondrial dysfunction.

Inflammatory cytokines in stroke can damage the BBB and worsen stroke outcomes [187]. Disruption of the BBB has been implicated in depression pathophysiology and heightened susceptibility to depression [188]. Classically activated microglia (M1) can release inflammatory cytokines [189], contributing to depression [190]. NLRP3 inflammasome activation mediates the effects of inflammatory cytokines, including IL-1β and IL-18, which are associated with depression [191]. Furthermore, increased NLRP3 levels in the hippocampus of PSD mice [192], suggest its involvement in PSD.

Cytokines and their signaling pathways substantially affect the metabolism of multiple neurotransmitters, such as serotonin, dopamine, and glutamate, by impacting their synthesis, release, and reuptake. This neurotransmitter system modulation leads to alterations in brain circuits, including the basal ganglia and anterior cingulate cortex, contributing to depression in susceptible individuals [193]. Pro-inflammatory cytokines can also enhance IDO activity, promoting tryptophan depletion and the kynurenine pathway. This results in neurotoxic metabolites that cause oxidative stress and decrease BDNF production, increasing vulnerability to depression [123, 124, 179, 194–196].

Polymorphisms in inflammatory cytokine genes have also been implicated in PSD development [8, 18].An imbalance of gut microbiota and reduced prevalence of Bifidobacterium are common in individuals with PSD, potentially leading to increased systemic inflammatory markers and contributing to PSD onset and progression after ischemic stroke [28]. One study found that disrupted homeostasis between pro-inflammatory and anti-inflammatory cytokines may result in PSD development over an extended period [11]. A recent study

supports the notion that TNF-α polymorphism is associated with indoleamine 2,3-dioxygenase 1 (IDO1) levels, and cytokines can regulate IDO1, representing a specific pathway linking immune-inflammatory processes with PSD pathophysiology [197].

Cytokines, such as TNF-α and IL-1β, impair mitochondrial oxidative phosphorylation and associated ATP production while stimulating mitochondrial reactive oxygen species production. These events lead to mitochondrial dysfunction and amplified inflammatory response [198, 199], potentially contributing to PSD development [200]. Here, we summarize the possible mechanisms of inflammatory cytokines in PSD (Fig. 1).

Possible Treatment for PSD Targeting Inflammatory Cytokines

PSD is predominantly treated with antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) [201]. However, SSRIs carry risks, including an increased likelihood of bone fractures, seizures, and gastrointestinal side effects [202, 203]. Alternative treatments may involve anti-cytokine modulators [204]. Timing is a critical consideration for future therapies. One meta-analysis found that anti-cytokine treatment could help treat depression in patients with chronic inflammatory conditions [205]. Inflammasomes may serve as targets

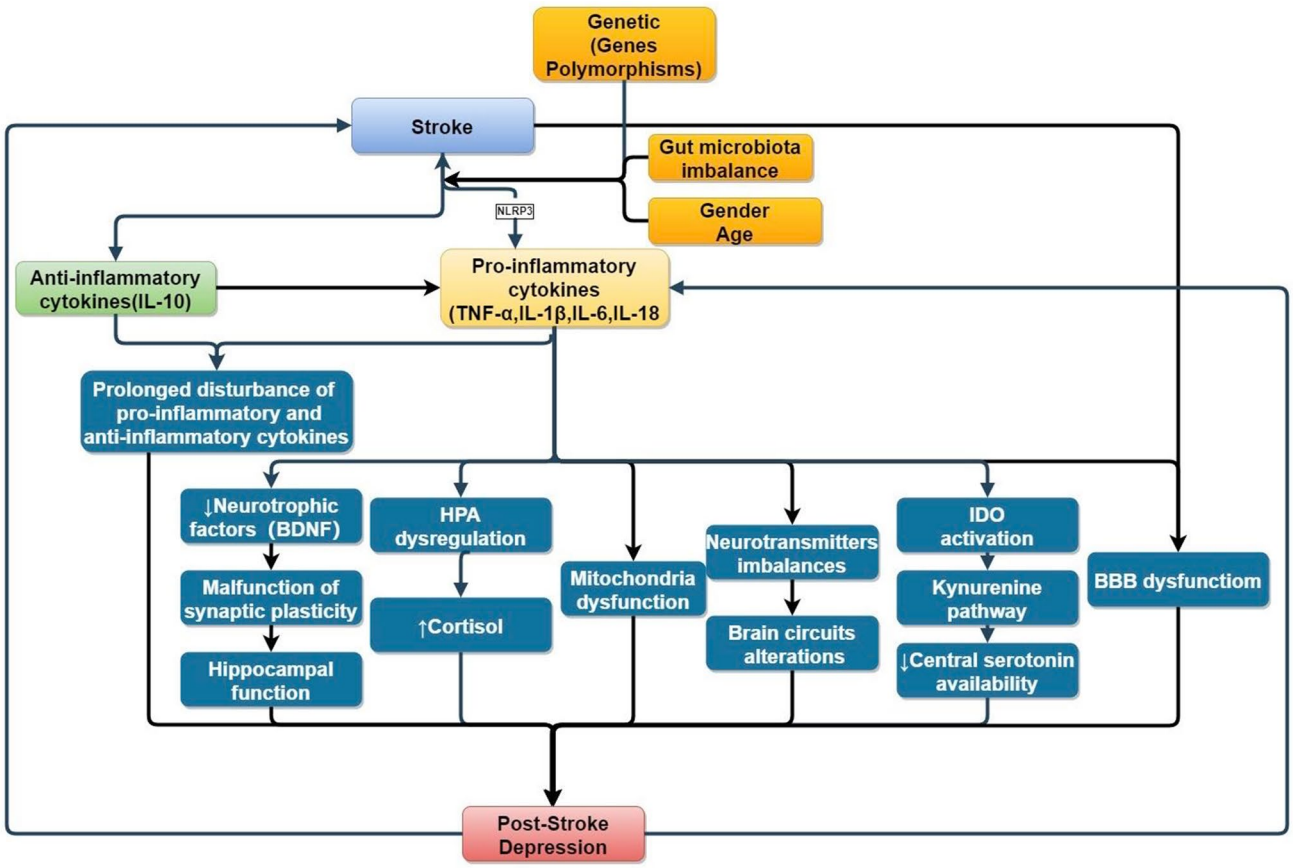

Fig. 1 Possible mechanisms of inflammatory cytokines in post-stroke depression. The diagram illustrates potential cytokine-driven pathways contributing to the development of post-stroke depression: polymorphisms in inflammatory cytokine genes are implicated in PSD development; an imbalance of gut microbiota and reduced Bifidobacterium prevalence may increase systemic inflammation, contributing to PSD; the levels of cytokines in PSD may be affected by factors such as patients' sex and age; Imbalances in inflammatory cytokine levels are associated with PSD; pro-inflammatory cytokines decrease BDNF signaling, causing impaired synaptic plasticity, hippocampal dysfunction, and ultimately depression; inflammatory cytokines activate the HPA axis, causing cortisol release, which leads to PSD; cytokines impair mitochondrial oxidative phosphorylation, resulting in mitochondrial dysfunction and an amplified inflammatory response, potentially contributing to PSD; cytokines affect neurotransmitter metabolism, altering brain circuits and increasing depression risk; pro-inflammatory cytokines enhance IDO activity, leading to neurotoxic metabolites, oxidative stress, and reduced BDNF levels; cytokines in stroke can damage the blood–brain barrier (BBB), increasing susceptibility to depression. IL, interleukin; TNF, tumor necrosis factor; BDNF, brain-derived neurotrophic factor; HPA, hypothalamic–pituitary–adrenal; IDO, indoleamine 2,3-dioxygenase; BBB, blood–brain barrier

for novel PSD therapies. A study demonstrated that Morinda officinalis oligosaccharides (MOOs) can alleviate depression in PSD rats by inhibiting the expression of IL-1β, IL-18, and NLRP3 inflammasome [13]. Nevertheless, further research is needed to assess the safety and tolerability of cytokine modulators in individuals with depression.

Cytokine Inhibitors

Elevated levels of TNF-α are associated with poor prognosis in stroke patients [57]. TNF-alpha inhibitors may be useful in treating PSD. Genetic deletion of TNFR1 and TNFR2 has been linked to antidepressant-like behavior in preclinical models [206]. Suppressing TNF-α activity in the periphery may effectively reduce brain inflammation and treat depression [207], with several TNF-α inhibitors demonstrating antidepressant effects in preclinical models and patients with autoimmune diseases [208, 209]. Anti-TNF-α compounds, such as etanercept and infliximab, show promise in treating both depression and stroke [65, 210, 211].

Interleukin-6 (IL-6) antibodies, such as sirukumab and siltuximab, have potential in treating inflammatory conditions and depressive symptoms [212]. Targeting IL-6 transsignaling mediators, like glycoprotein 130, may also be a promising approach, though further studies are needed [89].

Targeting the T lymphocyte/IL-10 resolution pathway may promote recovery from MDD [172]. Further investigations are warranted to determine the efficacy and safety of IL-10 agonists for the treatment of PSD, as a study has reported that administration of IL-10 can ameliorate depression-related impairments in mice [213].

Focusing on the IL-18 pathway, specifically the IL-18 receptor/Na–K-Cl cotransporter 1 signaling pathway, may present a promising strategy for preventing and treating PSD [19]. IL-18 pro-inflammatory activity is counteracted by constitutively secreted IL-18 binding protein, an intrinsic inhibitor of IL-18 [214].

Immunomodulatory Therapies

Pre-stroke statin treatment has been shown to reduce pro-inflammatory cytokine levels, such as IL-18, suggesting its potential as a preventive therapy for PSD [215]. Another finding indicates that the protective effects of statin use against PSD might be facilitated by its interactions with IL-6 [15]. The therapeutic potential of minocycline, a member of the tetracycline antibiotic class, has been explored for its capacity to mitigate pro-inflammatory cytokine levels [216], improve anxiety-like behaviors, and confer neuroprotective benefits following experimental ischemic stroke [217].

Other Strategies

Modulation of TNF-α-Stimulated Gene 6 pathways may also present a potential therapy for PSD [218]. Additionally, microRNA (miRNA)-based interventions, including miR-424 and miR-874-3p, exhibit potential as novel approaches for the treatment of stroke [219] and MDD [220], respectively. Phosphatidylserine liposomes have demonstrated efficacy in reducing TNF-α and IL-10 levels in the inflamed hippocampus of mice, thereby ameliorating PSD [221]. AMD3100 reduces IL-1β concentration and microglial activation, consequently improving neurological function after experimental stroke [222]. DL-3-n-butylphthalide also shows promise in attenuating post-traumatic brain injury, depressive behavior and proinflammatory cytokines, such as IL-1β and TNF-α [223]. One study suggested that Gadd45b could serve as a potential treatment for PSD, possibly involving the BDNF-extracellular signal-regulated kinase-cAMP response element-binding protein pathway and neuroinflammation [224].

Conclusions and Future Directions

In this review, we have emphasized the potential role of inflammatory cytokines in PSD development, which may arise from cytokine activity through various mechanisms, such as the activation of the HPA axis, neurotransmitter metabolism, BDNF, genetic influences, and inhibition of neurogenesis in the hippocampus. A meta-analysis has demonstrated that both established risk factors for MDD and potential neurologically related risk factors are predictive of PSD [225]. Furthermore, PSD has been identified as a form of vascular depression associated with large vessel occlusion [226]. Understanding the mechanisms and therapies of cytokines in MDD and vascular depression can help elucidate the role of inflammatory cytokines in PSD.

However, there is a scarcity of research investigating the genetic influences of cytokines on PSD. Further research is needed to identify unknown genetic polymorphisms that could help determine individuals vulnerable to developing this condition and fully elucidate its mechanism and potential treatments. Although substantial evidence supports the role of inflammation in PSD etiology, additional research is needed to precisely determine the contributions of inflammatory cytokines to PSD's underlying pathophysiology and mechanisms. Doing so could enable optimizing treatment approaches to yield the best outcomes for PSD, such as anti-cytokine therapies showing promise for treating depression or stroke.

Moreover, exploring miRNAs as a novel therapeutic approach presents exciting potential for managing PSD [227–229]. However, caution is warranted until more studies

prove their effects and safety before implementation. Investigating anti-inflammatory cytokine treatment at specific time points also shows promise, as some cytokines play dual roles in PSD pathogenesis. Ultimately, these findings highlight the need for ongoing research on the role of cytokines in PSD to discover new treatment options for improving outcomes in patients with this condition.

Author Contribution ZY and YY made the first draft. LH and FQ participated in the discussion of this manuscript and revised the part of this manuscript. XX and GW revised and finalized the paper. All authors read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

Data Availability Not applicable.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Yes.

Competing Interests The authors declare no competing interests.

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