

Review

Neuroinflammation and Post-Stroke Depression: Focus on the Microglia and Astrocytes

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ABSTRACT: Post-stroke depression (PSD), a frequent and disabling complication of stroke, has a strong impact on almost thirty percent of stroke survivors. The pathogenesis of PSD is not completely clear so far. Neuroinflammation following stroke is one of underlying mechanisms that involves in the pathophysiology of PSD and plays an important function in the development of depression and is regarded as a sign of depression. During the neuroinflammation after ischemic stroke onset, both astrocytes and microglia undergo a series of morphological and functional changes and play pro-inflammatory or anti-inflammatory effect in the pathological process of stroke. Importantly, astrocytes and microglia exert dual roles in the pathological process of PSD due to the phenotypic transformation. We summarize the latest evidence of neuroinflammation involving in PSD in this review, focus on the phenotypic transformation of microglia and astrocytes following ischemic stroke and reveal the dual roles of both microglia and astrocytes in the PSD via modulating the neuroinflammation.

Key words: ischemic stroke, PSD, microglia, astrocyte, neuroinflammation

1. Introduction

As a medical emergency, ischemic stroke frequently leads to severe neurological dysfunctions and other sequelae. PSD is a prevalent one among all neurological sequelae for it is experienced by approximate one-third of stroke patients [1, 2]. The reduced quality and expectancy of a patient's life with PSD are related to multiple factors, containing cognitive decline, increased fall risk, increased suicide rate, poor response to rehabilitation and dysfunction [3]. In addition to the decreased quality of depression patients' life, depression is likewise associated with higher mortality and a shorter interval to recurrent stroke [4, 5]. The underlying molecular pathways involved in depressive disorders contain neuroinflammation hypothesis, monoamine neurotransmitter hypothesis, neurotrophic hypothesis, and hypothalamus-pituitary-adrenal axis (HPA) dysfunction hypothesis [6].

In the neuroinflammation hypothesis, high levels of inflammatory mediators, containing cytokines and

chemokines and reactive oxygen species, are closely correlated with the development of PSD [7]. Many individuals with cerebrovascular ischemic events have been found to present a long-term and persistent pro-inflammatory background [8].

The immediate activation of central and peripheral immune inflammatory responses after acute stroke is followed by a significantly increased expression of pro-inflammatory cytokines, containing tumor necrosis factor (TNF)- α , interleukin (IL)-1, IL-6, etc. The increment of pro-inflammatory cytokines leads to the amplification of inflammatory response [9] and induces the overactivity of the HPA axis, as well as induces the noradrenergic dysfunction and widespread activation of indoleamine 2,3-dioxygenase. These actions exacerbate the depletion of 5-hydroxytryptamine (5-HT) in the temporal cortex and left frontal, which eventually leads to the depression [10]. Therefore, neuroinflammation following ischemic stroke plays important roles in the pathological process of PSD.

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The present review focused on the relationship between neuroinflammation and PSD to reveal the duality of microglia and astrocytes in the pathological process of PSD and provide the potential therapeutic targets of PSD.

2. Post-stroke depression (PSD)

PSD is associated with sleep disorders, disability, cognitive impairment, poor rehabilitation outcomes, social withdrawal and isolation, and increased mortality [11]. The depression has been a focus since treatise “Depressive States in Old age”, which was reported by Gaupp et al. in 1905 [12]. The link between depression and atherosclerotic disease was firstly founded in 1955, the researcher described that atherosclerotic disease can lead to depressive disorders [13]. Subsequently, depression is found to be markedly more common in stroke patients [14], which attracts more attention of researches.

2.1 The definition and diagnosis of PSD

PSD is diagnosed and defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. A person must present at least five out of following nine symptoms: feelings of guilt, a sad mood, decreased energy levels, insomnia, decreased appetite, decreased concentration, changes in psychomotor activity (decreased or increased), and recurrent thoughts of self-harm or suicide and loss of interest in pleasurable activities (anhedonia) that lasts for at least 2 weeks [15]. Nevertheless, DSM-5 is not used for some exceptional cases when diagnosing patients do not exhibit typical psychological symptoms and cannot describe their psychological conditions coherently [16]. Therefore, it is often challenging for medical practitioners to diagnose such exceptional cases as PSD after a stroke. After decades of improvement and development, Hamilton Depression Rating Scale (HDRS) has been proved validity and reliability in screening for depressive symptoms among stroke patients [17]. In addition, Patient Health Questionnaire-9 (PHQ-9) has been justified and confirmed useful in measure depressive symptoms [18, 19].

2.2 The frequency of PSD

PSD occurs at any time point following stroke. A clinical study about 186 acute stroke patients in hospitals have reported that 31.72% of these patients were identified as suffering from depression within 2 weeks after stroke onset [15]. Mitchell et al. have reported in their comprehensive meta-analysis that one-third stroke patients had depressive disorders after a stroke [20]. 39%

to 52% of stroke patients have at least one episode of depression within 5 years after stroke [5]. This variation is considered to be associated with differences in the diagnostic method of PSD, time point of depression assessment and study population [21].

2.3 The frequency of PSD and lesion location

The relationship between PSD and lesion characteristics has aroused considerable interest of researchers. Among the several hypotheses about the frequency of PSD and lesion location, one suggests that there are differences in the frequency of PSD between lesions in the right and left hemispheres [22]. Importantly, it has been suggested that stroke occurred in the left hemisphere cortex, particularly in frontal region, is related to higher risk for depression. In a clinical study, researchers have reported that female gender, left-sided stroke lesions and the absence of hypertension are statistically significant predictors of early onset of PSD [23]. Bekhbat et al. have confirmed that women with stroke are more likely to be diagnosed with PSD [24].

A clinical study has reported that higher incidence of depression tends to be associated with left hemisphere lesion and the severity of PSD is obviously correlated with the lesion to the frontal pole in the left anterior. Meanwhile, the frequency of depression in stroke patients with left posterior lesion is higher than that in patients with right anterior lesion [17]. Besides, Starkstein et al. have found that stroke patients with left subcortical or cortical anterior lesion have more serious depression and greater frequency than patients with lesion in other parts of the brain. Furthermore, a strong correlation between the lesion to the frontal pole and severity of depression was observed in both left cortical and subcortical lesions [25].

Accumulating studies have revealed that left hemisphere, particularly the left basal ganglia and frontal lobe, are key regions for PSD development [26, 27]. Klingbeil et al. have confirmed the significant association between PSD and the infarcts in the left ventrolateral prefrontal cortex [28]. A study involving 243 stroke patients have revealed that the severity of PSD is closely correlated with the extent of damage in the bilateral basal ganglia and left frontal lobe [29]. Thus, the incidence rate of PSD is strongly related to the location of lesion that triggers stroke.

Terroni and others have found the correlation between depression pathophysiology and dysfunction of the medial prefrontal cortex and of the left limbic-cortical-striatal-pallidal-thalamic (LCSPT) circuit in 2011 [30]. This hypothesis has been proposed by another study in 2021 that damage in LCSPT circuit predisposes to PSD [31]. The LCSPT circuits are of particular interest due to their vital role in the major depressive disorder (MDD)

[32]. LCSPT circuit might likewise be disturbed indirectly by subsequent degeneration if it is outside the main ischemic lesion. Brain regions such as substantia nigra and the ipsilateral thalamus would exhibit delayed shrinkage on account of synaptic connections to the initial lesion location. For instance, anterograde degeneration results from basal ganglia lesions, retrograde degeneration results from cortical lesions [33].

Robinson et al. have found that PSD is related to the ischemic lesion of amine-containing axons, which is ascending from the brainstem to the left cerebral cortex and induces the decreased synthesis of norepinephrine (NE) and 5-HT in the limbic areas of frontal and temporal lobes and basal ganglia [17, 30, 34, 35]. Nevertheless, it must be pointed out that PSD is influenced by plenty of factors beyond stroke characteristics alone. The severity and development of PSD are related to the individual factors, containing pre-existing depression, post-stroke functional impairments, age, and disease duration [36-38].

3. The PSD and neuroinflammation

Accumulating evidence supports that inflammation is the dominant presence in depressive disorders [39]. Signs of systemic inflammation have been found in atypical depression, including higher circulating levels of IL-1 β , TNF- α and C-reactive protein, as well as containing the dominance of IL-2 positive Th1 lymphocytes. In addition to the increased circulating proinflammatory cytokines, the typical systemic acute-phase reaction has likewise been described in the depression [40]. The pro-inflammatory factors perpetuate the nitrosative and oxidative stress in the central nervous system (CNS), which results in the consumption of glutathione, coenzyme Q10, n-3 polyunsaturated fatty acids (n-3 PUFA), and antioxidant capacity. These actions lead to significant activation of N-methyl-D-aspartate (NMDA) receptor and reduce 5-HT level [39].

Astrocytes and microglia in the CNS play vital roles in the pathological process of PSD via producing the cytokines, containing IL, TNF and interferon (IFN). Inflammation triggers depression via affecting the synthesis and secretion of monoamine neurotransmitters [41, 42]. Spalletta et al. explore and put forward the “cytokine hypothesis”, the investigators find that pro-inflammatory cytokines such as IL-1 β , TNF- α and IL-18 interact with 5-HT, which results in the amplification of inflammatory processes in the limbic region and activates the indoleamine-2,3-dioxygenase (IDO) [43]. Activation of IDO in the limbic region promotes the conversion of tryptophan to kynurenine, which then leads to 5-HT depletion in the paralimbic structures. 5-HT depletion-induced physiological dysfunction is closely related to the occurrence of PSD [44].

3.1 Cytokines and PSD

3.1.1 Pro-inflammatory cytokines and PSD (Fig. 1)

In an ischemic stroke, pro-inflammatory cytokines, containing IL-1 β , IL-6, and TNF- α , are released from glial cells and/or neurons and trigger the inflammation [45-47]. Cerebral ischemia-induced inflammation directly exacerbate the pathologies via injuring the blood-brain barrier (BBB) and promoting neuronal cell death [45, 47]. Accumulating literatures have explored the relationship between the cytokines and PSD [48-52]. IL-18, a novel biomarker for PSD, is independently associated with depressive symptoms after stroke [48, 52, 53]. The inactive precursor protein of IL-18 is constitutively expressed in nearly all cells [54]. IL-18 is activated when it is cleaved by caspase-1 upon appropriate stimuli, and further secreted into extracellular space [54]. The activated IL-18 promotes the production of IFN- γ and the other pro-inflammatory cytokines via binding to the receptor of IL-18 (IL-18R). However, the pro-inflammatory activity of IL-18 can be antagonized by a constitutively secreted IL-18 binding protein (IL-18BP), which is intrinsic inhibitor of IL-18 [55].

IL-18 is expressed in ependymal cells, astrocytes, microglia, and a limited subpopulation of neurons in brain regions under physiological conditions [56, 57]. After cerebral ischemia, increased level of IL-18 mRNA has been found in rat brain tissues [58, 59]. The roles of IL-18 in PSD were well demonstrated by Wu et al. The researchers found that increased IL-18 induces the depression-like behaviors of mice via promoting the IL18 receptor/ sodium-potassium-chloride co-transporter 1 (NKCC1) signaling pathway [60]. The primary function of NKCC1 is maintaining intracellular Cl⁻ concentrations in cells via transporting the Na⁺, K⁺ and Cl⁻ ions into cells [61]. Dysfunction of NKCC1 is associated with various psychiatric disorders including depression [62]. Membrane NKCC1 in the CNS is new player in mediating depressive behaviors induced by repeated stress via reversing gamma-aminobutyric acid (GABA) inhibition and reducing Cl⁻ concentrations in cells [63]. Inhibiting IL-18 and its downstream NKCC1 is a potential strategy for the prevention and treatment of PSD [60].

IL-1 β is linked to the P2X receptor family, activation of the P2X7-NLRP3-IL-1 β pathway is connected with depressive-like behaviors [64], and inhibition of P2X7 is connected with antidepressant-like effects [65]. Enhanced expressions of IL-1 β , IL-18 and the NLRP3 inflammasome were found in the ischemic hippocampus of PSD model rats [66]. In PSD, increased IL-6 levels in sera of patients persist up to one year post-stroke diagnosis [67]. Higher IL-6 levels in plasma of stroke patients prominently correlate with symptom severity of

depression three months post-stroke, suggesting that IL-6 can be used as a potential PSD biomarker [68]. Increased IL-6 impairs synaptic neurotransmission, disrupts the HPA axis, and reduces the neurotrophic factors [69-71].

Furthermore, IL-6 enhances IDO activity, decreases central 5-HT availability and activates the kynurenine pathway [72].

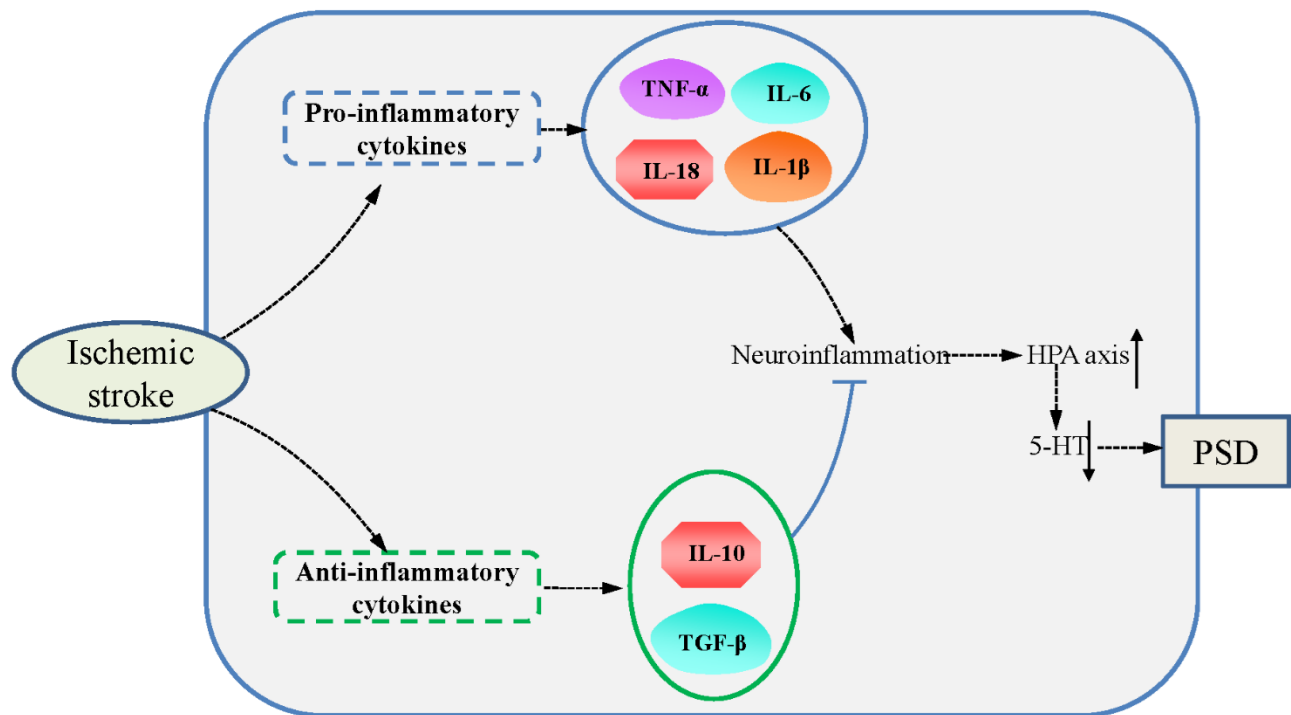


Figure 1. Cytokines and PSD.

3.1.2 Anti-inflammatory cytokines and PSD (Fig. 1)

Decreased level of IL-10 is associated with depression and more severe somatic depressive symptoms [73]. Whereas, increased level of IL-10 has been reported in the MDD, potentially due to initial compensatory responses to acute inflammation [74]. IL-10 has inhibitory effects on the inflammation and can alleviate the depressive-like behavior in preclinical models [75, 76]. Patients with lower level of IL-10 have a greater possibility in developing PSD at one month after a stroke. Thus, IL-10 serves as an independent protective predictor for PSD [17]. The anti-inflammatory effects of IL-10 in the central nervous and peripheral system may be involved in the underlying mechanism of IL-10's potential benefits in MDD [77].

Clinical studies have revealed that decreased IL-10 following stroke is associated with a decline in neurologic condition [78]. Chi et al. have found that IL-10 levels reduce markedly in patients with severe stroke compared to those with lighter stroke [79]. The researchers revealed a negative correlation between IL-10 levels and Hamilton rating scale for depression (HAMD) scores, and suggested

that IL-10 can be used as a predictor for predicting PSD at a 1-month follow-up [79]. In addition, therapeutic potential of IL-10 is shown in patients with depression, inhibition of IL-10 signaling via administrating the neutralizing antibody against IL-10 led to prolonged depression-like behaviors in mice, suggesting that promoting IL-10 signaling may be a novel and efficacious therapeutic strategy to promote the resolution of depression [80].

Besides, another anti-inflammatory cytokine, transforming growth factor- β (TGF- β) is also connected with depression. Although there is controversy regarding TGF- β level in depression, researches have revealed that patients with MDD exhibit reduction of TGF- β network-associated gene transcripts in the choroid plexus [81] and reduced levels of TGF- β in serum [82, 83]. Importantly, the pro-inflammatory factors and the anti-inflammatory factors are antagonistic and bound up with the development direction of PSD [79, 84, 85]. For instance, Bensimon et al. reveal that pro-/anti-inflammatory ratios of IL-18/IL-10, IFN- γ /IL-10, and IL-1 β /IL-10 are increased in sera of patients with moderately severe PSD [86]. The use of pro-/anti-inflammatory ratios

(IL-1 β /IL-10, TNF- α /IL-10, IL-18/IL-10, IL-6/IL-10, IFN- γ /IL-10) are also supported by Levada et al., they propose that the pro-/anti-inflammatory ratios might be used to differentiate PSD patients from non-PSD subjects [87]. Therefore, up-regulation of anti-inflammatory factors can antagonize the pro-inflammatory mediators on the PSD development and may be used to intervene PSD.

3.2 Microglia and PSD (Fig. 2)

As the resident immune cells in the CNS, microglia constantly monitor the surrounding microenvironment [88]. The ischemia stimuli after ischemic stroke induce the microglia activation, afterwards, microglia undergo

physical and biochemical changes, including cell migration, phagocytosis, cell proliferation, and production of cytokines [89]. The dynamic alterations of microglia are associated with distinct functions and specific cytokines being secreted [90, 91]. Activated microglia have been defined as ‘M1 vs M2’ phenotypes. M1 microglia exhibit proinflammatory effect and M2 microglia possess anti-inflammatory function [92]. Promoting the microglial polarization to the M2 phenotype exhibits the neuroprotective effects in the ischemic stroke [93-95]. Besides, polarization of M1/M2 microglia is closely associated with psychiatric disorders [96].

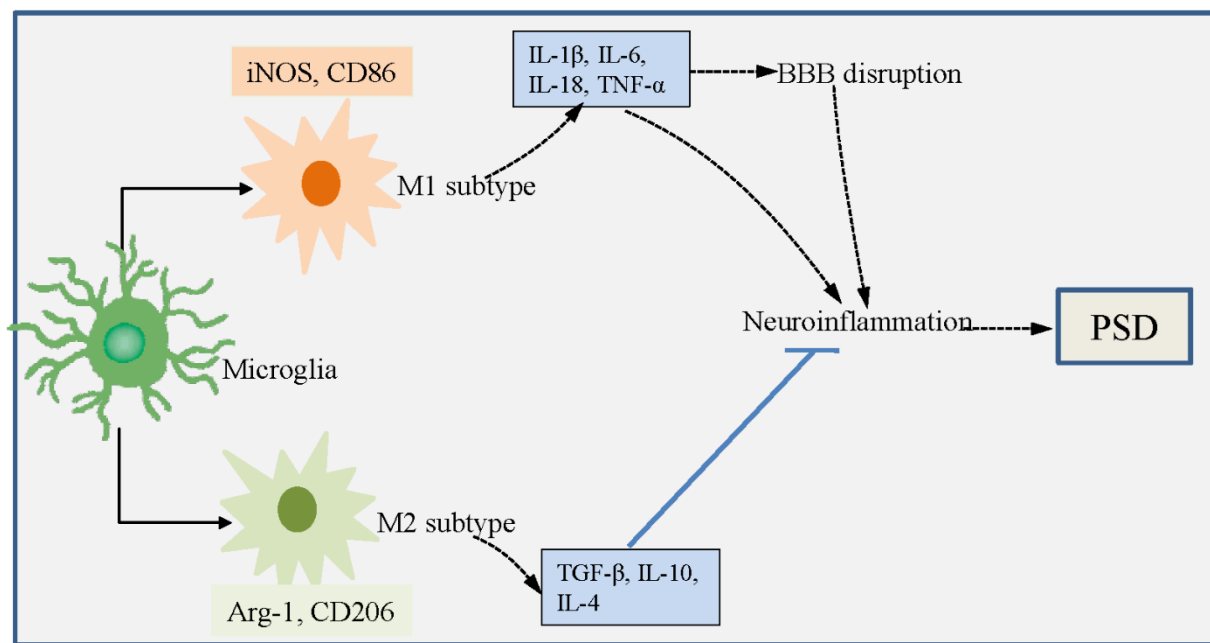


Figure 2. Dual roles of microglia in the PSD.

The main signal pathways that participating in the M1 microglial polarization: (1) helper T cells 1 (Th1)-secreted IFN- γ promotes the transformation of microglia into M1 subtype via activating STAT and JAK1/JAK2 pathways [97]. (2) Activation of M1 microglia can be induced by another pathway triggered by lipopolysaccharide (LPS) or damage-associated molecular patterns (DAMPs) stimulation of TLR4. Subsequently, an “activation complex” is formed, which contains nuclear factor- κ B (NF- κ B), p65, p38, myeloid differentiation factor 88 (Myd88), and interferon regulatory factor 3 (IRF3). This complex in turn contributes to the polarization of M1 microglia [98]. The high number of TGF- β , IL-4, IL-10, regulatory T cells, and intracellular signaling via cAMP response element-binding protein (CREB) promote the differentiation of M2 microglia [99].

3.2.1 M1 (pro-inflammatory) microglia and PSD

Microglia are polarized to M1 subtype within a short period of time after ischemic stroke, thereby secreting various pro-inflammatory factors, including IL-1 β , IL-6, IL-18 and TNF- α . These pro-inflammatory cytokines recruit immune cells from blood to the damaged brain tissue, which can exacerbate the neuroinflammation and deteriorate the brain injury [100, 101]. Therefore, M1 microglia polarization promotes neuroinflammatory and immune reaction after ischemic stroke.

Inflammation after cerebral ischemia directly hinders the neural repair and exacerbates subsequent pathologies via deteriorating the BBB dysfunction and promoting neuronal cell death [45]. Among the cytokines related to PSD, IL-18 is mainly secreted by M1 microglia at a later

phase and by neurons at early stage in mice model of depressive-like behaviors induced by LPS [102]. As aforementioned above, IL-18 is independently associated with depressive symptoms after stroke, and IL-18 level in sera of patients is a biomarker for PSD [48].

In addition to the vital roles of IL-18 on the PSD, cytokine hypothesis of PSD shows associations between PSD and the other microglia-produced TNF- α , IL-6, and IL-1 β [85]. Serum levels of IL-6 were significantly higher in patients with PSD than in those without PSD [49]. Similarly, significant evaluation of IL-6, TNF- α , and IFN- γ levels has been found in PSD patients one year after stroke [67]. Kang et al. have reported that higher IL-6 and IL-18 levels in a sample of 286 participants were independently associated with depression within 2 weeks and at one year after stroke [48]. Inhibition of M1 microglial polarization can reduce the release of IL-1 β , TNF- α and IL-6 [103]. Therefore, inhibiting the polarization of M1 microglia can reduce the occurrence of PSD.

3.2.2 M2 microglia and PSD

The polarization of M2 microglia is characterized by the increased expressions of anti-inflammatory factors, containing TGF- β , IL-10 and IL-4 [104]. M2 microglia can be identified by detecting the expressions of arginase-

1 (Arg-1) and CD206 [105]. In addition to the anti-inflammatory roles of IL-10 in the inflammatory response after stroke [106], IL-10 is also a negative regulator of pro-inflammatory cytokines TNF- α , IL-1 β and IL-6 [107].

Zhang et al. have reported that intracerebroventricular administration of recombinant TGF- β improves the social isolation-exacerbated PSD and post-stroke anxiety (PSA), and promotes the hippocampal neurogenesis and cognitive functions [108]. Li et al. have revealed the enhanced expression of M1 microglia markers (iNOS, CD86, TNF- α and IL-1) in the rat hippocampal region in the PSD group than those in sham and poststroke groups. Besides, authors revealed that the M2 microglia marker Arg1 is prominently up-regulated in the PSD group than in the poststroke group [109]. Considering the distinct effects of M1 and M2 microglia in the depression, we proposed that inducing the phenotypic transformation of microglia to the M2 subtype is a potential therapeutic target for PSD.

3.3 PSD and astrocyte (Fig. 3)

Astrocytes are strongly associated with depression, and rapidly undergo morphological changes following ischemic stroke, such as hypertrophy and hyperplasia [110].

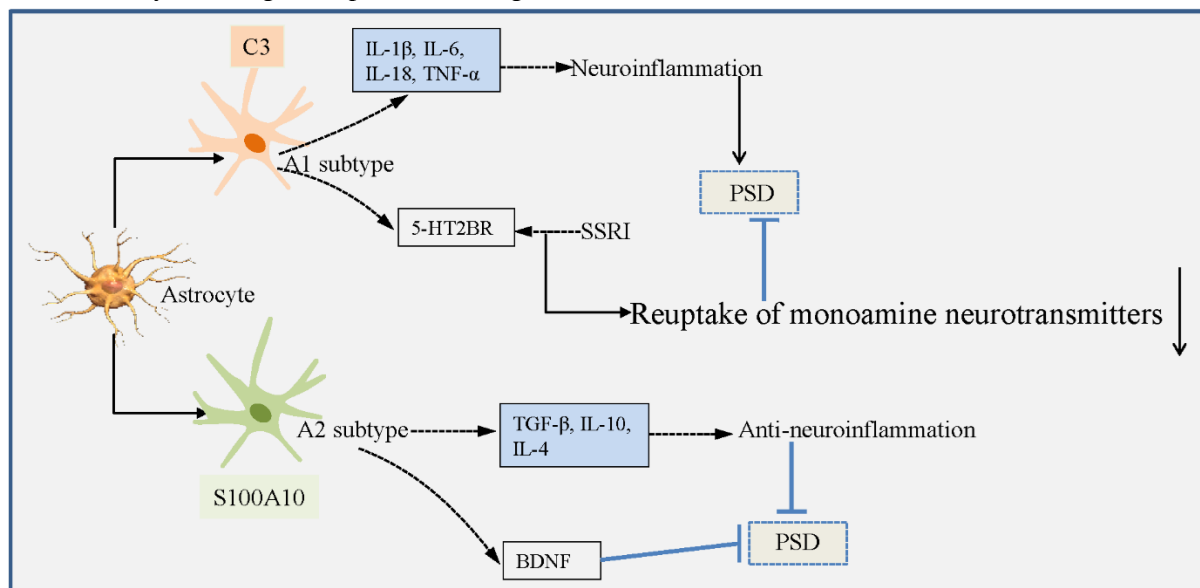


Figure 3. Dual roles of astrocytes in the PSD.

Ischemia stimuli and microglia-mediated inflammatory reaction trigger the activation of astrocytes, which then polarize into A1 subtype identified by C3 expression and A2 subtypes identified by S100A10 expression [111, 112]. A1 astrocytes-secretd IL-1 β , IL-6, IL-18 and TNF- α aggravate the neuroinflammation and

deteriorate the brain tissue damage [113, 114]. Whereas, A2 astrocytes produce brain-derived neurotrophic factor (BDNF), which is known as neurotrophic factor and provide neuroprotection against cerebral ischemia injury [115-117]. BDNF is essential for the differentiation of

neural stem cells (NSCs), and promote neuronal growth and maturation [118, 119].

Astrocyte markers would change in relation to emotion in brain regions of depressed patients. For instance, the decreased expression of glial fibrillary acidic protein (GFAP) is found in dorsolateral prefrontal cortex [120], ventrolateral prefrontal cortex (vPFC) [121], hippocampus [122], and prefrontal cortex [123] of depressed patients. In addition, there is increased level of S100 β produced by A1 astrocytes [124] in serum [125], cerebrospinal fluid (CSF) [126], PFC [127] and hippocampus [128]. Importantly, the lower density of GFAP immunoreactive cells is found in the brain tissues of young patients compared with age-matched controls, this change does not exhibit in older patients with depression. Therefore, the changes of astrocyte markers are age dependent in depression patients [122, 129]. Effective treatment of depressive disorder could promote the proliferation of astrocytes [130, 131]. Whereas, dysfunction of astrocytes in medial prefrontal cortices leads to the depression like behaviors in rodents model [132, 133].

3.3.1 Negative roles of astrocytes in PSD

The monoamine hypothesis of PSD suggests that underlying pathophysiologic basis of PSD occurrence is closely related to the reduced syntheses of monoamine neurotransmitter and correlated with conduction block in the basal ganglia, frontal, and temporal regions following ischemic brain injury. For example, 5-HT levels in serum and CSF of PSD patients are less than those in serum and CSF of stroke patients without depression [134, 135]. Single-nucleotide polymorphisms in genes of 5-HT transporter and 5-HT receptor have been found to be related to PSD [136]. Importantly, antidepressants such as selective 5-HT reuptake inhibitors (SSRIs), 5-HT and norepinephrine reuptake inhibitors (SNRIs) relieve the PSD symptoms via targeting the monoamine [137, 138].

Recent studies have revealed that A1 astrocytes participate in acute stress and LPS-induced depression-like behaviors. Besides, both 5-HT transporters and 5-HT receptors expressed in A1 astrocytes are targets of monoamine antidepressants [76, 139]. Other researches have revealed that 5-HT receptor modulators and SSRI mediate the activity of 5-HT_{2B} receptor (5-HT_{2BR}) and downregulate the 5-HT receptor type-7 (5-HT_{7R}) and 5-HT_{1A} receptor (5-HT_{1AR}) in astrocytes [140, 141], these actions reduce the expressions of connexin 43 (Cx43) on the plasma membrane of astroglia and decrease glutamate diffusion.

Fang et al. have revealed that inhibition of A1 astrocytes response participates in the antidepressant action of fluoxetine in a mouse model of MDD through

astrocytic 5-HT_{2BR}/ β -arrestin2 signaling [142]. Thus, A1 astrocytes may be targets of antidepressants. Furthermore, A1 astrocytes-produced pro-inflammatory cytokines, containing IL-1 β , IL-6, IL-18 and TNF- α [143], are likewise closely associated with the mechanisms of PSD [76, 144, 145].

3.3.2 Positive roles of astrocytes in PSD

Glutamate excitotoxicity is found to be related to PSD development. Enhanced content of glutamate are found in the serum and PFC of PSD patients [146], which is similar to the result obtained from rodent models that increased level of glutamate and decreased level of GABA play a crucial role in the occurrence and development of PSD [147, 148]. Meanwhile, blood glutamate scavengers such as pyruvate and oxaloacetate can alleviate the depressive symptoms in the animal models of PSD [149]. Astrocytes participate in balancing the secretion and uptake of glutamate [150]. Excitatory amino acid transporter 2 (EAAT2) shared by astrocytes and neurons is a glutamate transporter and clear 90% of glutamate overflow in the synaptic cleft in the mammalian brain [151, 152]. In rodents, glial glutamate transporter-1 (GLT-1) is responsible for glutamate clearance. The expression of GLT-1 in astrocytes was significantly decreased in a rat model for PSD compared with control rats [151]. Therefore, astrocytes are involved in the PSD development via disrupting the glutamate circulation.

In addition, astrocytes likewise ameliorate the PSD by releasing BDNF [153]. The level of BDNF in serum from PSD patients at 3-6 months after stroke onset is lower than that from control stroke patients, suggesting that BDNF level in serum may be used as a predictor of PSD [154]. Moreover, the results of meta-analysis studies have shown that BDNF concentrations in patient sera significantly decrease during the early period of stroke and can predispose the patients to PSD [155, 156].

Further studies have confirmed that BDNF is released by A2 astrocytes but not by A1 astrocytes [157], and the reduced BDNF is related to the development of PSD, which is evidenced by the findings that PSD patients have reduced BDNF levels compared with stroke patients without depression [158, 159]. Besides, a reduced serum BDNF level has been found to enhance the PSD risk in the acute phase of stroke [160]. Moreover, the relationship between BDNF expression and antidepressants has been extensively explored. BDNF levels in sera of patients are increased after antidepressants treatment, containing SSRIs, monoamine oxidase inhibitors, tricyclic agents, serotonin-norepinephrine reuptake inhibitors, as well as including specific serotonergic antidepressants [161-163]. Importantly, injecting the exogenous BDNF into hippocampus can ameliorate the depression symptoms

[164]. Not surprisingly, BDNF depletion can abolish the protective effects of antidepressants [161]. Inversely, overexpression of BDNF in hippocampus of rats can effectively alleviate the depression-like behaviors after stroke [165].

4. PSD and neurotransmitters

The neurotransmitter theory, a theory of the depression pathogenesis, posits the biological basis of PSD, which is related to the imbalance of the 5-HT, dopamine (DA), and NE systems [166]. During PSD, axons containing DA, NE and 5-HT between the brainstem and cerebral cortex might be impaired, leading to neurotransmitter production imbalances throughout the brain [34, 167]. Increased DA can lead to the dopaminergic activation, which promotes the synaptic plasticity and ameliorates the cognitive impairment [168]. DA neurons highly express neurotrophic factor Neuregulin 1 (NRG-1) receptors throughout development into adulthood. NRG-1 likewise affects the DA neurotransmission via raising extracellular DA levels [169].

The NE system in the CNS integrates inputs from lots of brain regions, it likewise projects widely to these brain regions [170]. The NE projections promotes the regrowth processes of 5-HT after neurotoxin treatment [171]. As aforementioned, SSRIs (selective 5-HT reuptake inhibitors) and SNRIs (5-HT and NE reuptake inhibitors) relieve the PSD symptoms via targeting the 5-HT and NE [137, 138]. In a mice model of PSD after a stroke in the left medial prefrontal cortex (mPFC), the authors have found that Fluoxetine-mediated behavioral and cognitive recovery is associated with promoting the NE and 5-HT and NE axonal plasticity in these regions [172].

5. Conclusion

PSD impacts almost one-third of stroke survivors, impairing the recovery of patients. Neuroinflammation is one of the essential factors involved in the pathogenic mechanisms of ischemic stroke. Besides, neuroinflammation exerts an important role in the development of depression and is regarded as a sign of depression. Astrocytes are known as underlying therapeutic targets for depression and stroke due to their important roles in modulating neurotrophic factor expression, neurotransmission, and inflammation. In addition, microglia can monitor the CNS microenvironment and remove dead and dying neurons in time, which contributes to the supportive roles of microglia in the CNS homeostasis. Under the cerebral ischemia stimuli, both astrocytes and microglia undergo phenotypic transformation to different subtypes, A1/A2 and M1/M2, respectively. The different subtypes of

microglia and astrocytes exert distinct (harmful or beneficial) roles in the PSD. Promoting the A2 astrocytes or M2 microglia polarization can offer opportunities for developing effective interventions for PSD.

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