Microglia and neuroinflammation: the key drivers of sepsis-associated encephalopathy

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Abstract. Sepsis is a serious global health issue, and sepsis-associated encephalopathy (SAE) is one of the early complications of sepsis, with symptoms including neuronal and synaptic dysfunction, cognitive dysfunction and brain damage. Neuroinflammation has been identified as a significant pathogenic mechanism in the context of SAE, and microglia, as resident immune cells in the brain, playing a pivotal role in the development and progression of SAE by regulating unbalanced neuroinflammation. It is evident that microglia manifest heterogeneous characteristics at all stages of SAE. The basis for this heterogeneity is the alteration in gene expression profiles with the progression of the disease. This article reviews the recent progress of research on neuroinflammation in SAE and elucidate the specific changes in the function, phenotype, and gene expression profiles of microglia in SAE, revealing how microglia are involved in the onset and progression of SAE through regulating neuroinflammation. Finally, this review provides a comprehensive overview of the current therapeutic options for SAE, with a particular focus on the targeting of microglia and the neuroinflammation mediated by them, and puts forward the shortcomings and perspectives of the current research related to microglia and the neuroinflammation mediated by them in SAE, thus offering valuable insights for the development of relevant drugs and the subsequent advancement of basic research in this field.

Keywords: Sepsis-associated encephalopathy (SAE); microglia; neuroinflammation; heterogeneity; gene expression profiles; therapeutic targets.

1. Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection [1], classified as one of the global health issues by the World Health Organization (WHO) [2]. Epidemiological surveys show that in 2017, nearly 60.2 million cases of sepsis occurred worldwide, with a mortality rate of 19.7% [3]. In recent years, although the incidence of sepsis has increased, the mortality rate has decreased significantly [4].

Sepsis-associated encephalopathy (SAE) is an acute diffuse cerebral dysfunction that complicates the central nervous system (CNS) in patients in the early stages of sepsis. The prevalence rate of SAE is about 70% [5]. The clinical manifestations of SAE typically encompass a range of symptoms, including but not limited to: extensor tonus, peripheral nerve dysfunction, attention deficit, confusion, anxiety, lethargy, and coma. In severe cases, it can be fatal, and up to 30% of sepsis survivors suffer from long-term depression, anxiety, and post-traumatic stress disorder (PTSD) [6-8]. The pathophysiology of SAE encompasses a range of mechanisms, including neuroinflammation, disruption of the blood-brain barrier (BBB), alterations in cerebral ischemia and perfusion, mitochondrial dysfunction, oxidative stress and other factors [9]. An in-depth study of the pathological progression of SAE is imperative to reduce morbidity and mortality rates, and enhance patient survival outcomes.

As the major immune cells resident in CNS, microglia mediate a broad spectrum of immune responses and play an important role in regulating the inflammatory response in the CNS and maintaining normal brain function [10]. They also play an indispensable role in the onset and development of SAE [11]. Neuroinflammation triggered by CNS infection, injury, or autoimmunity is one of the most important pathogenic mechanisms of SAE, and microglia activation is an important feature of SAE. A large number of studies in recent years have found activation phenotypes such as microglia shape changes and CD68 positivity in the brains of patients died from

sepsis [12,13], and in the early stages of sepsis, the expression of genes related to inflammatory signal (e.g. NF-κB etc.) in microglia was also significantly up-regulated in the brains of patients [14]. Furthermore, certain studies have indicated that intracerebral minocycline administration has the capacity to inhibit microglia activation and attenuate cognitive dysfunction triggered by neuroinflammatory responses in patients with SAE, suggesting that modulation of neuroinflammation is one of the important mechanisms by which microglia play their role in SAE [15]. However, the mechanism by which microglia participate in SAE through neuroinflammation is complex, and the specific physiological process has not yet been fully clarified, necessitating further research. This article reviews the research on the role of microglia and their mediated neuroinflammation in SAE and the related therapeutic strategies, aiming to deepen the understanding of the mechanism of microglia and their mediated neuroinflammation in SAE, with a view to providing a theoretical basis for targeting microglia in the treatment of SAE.

2. Microglia in SAE

2.1 Functions of microglia

Microglia are resident immune cells in the CNS, accounting for approximately 0.5-16% of the total cell population in the human brain. They are primarily located in the hippocampus, substantia nigra, olfactory telencephalon, and basal ganglia, but less abundant in the brainstem and cerebellum [16]. It is evident that microglia fulfil a multitude of physiological functions in the CNS, there by playing pivotal roles in various aspects such as scavenging foreign antigens, regulating inflammatory responses in the CNS and maintaining normal brain functions. Firstly, microglia are responsible for a number of fundamental immune functions such as migration, phagocytosis, antigen presentation, inflammatory factor release, and the maintenance of homeostasis in the brain [17-20]. These functions serve to protect the CNS from both internal and external pathological factors. In addition, microglia play a vital role in the formation of neuronal circuits and the development of synaptic connections within the CNS. For example, ARG1+ microglia can influence hippocampal synaptic plasticity by modulating cholinergic neural input and IL-33-mediated microglia have been observed to promote synaptic remodeling by phagocytosis of extracellular matrix (ECM) [21,22]. But it has also been determined that microglia may be not essential for CNS synapses and neurogenesis [23]. Microglia have the capacity to induce programmed cell death via a CD11b-dependent pathway and to phagocytosis of cellular debris by triggering signaling of receptors on myeloid cell-2 (TREM2) [24,25]. Microglia also have neurotrophic functions, providing nutritional support to neurons and promoting oligodendrocyte development and myelin formation through the secretion of insulin-like growth factor-1 (IGF-1), transforming growth factor-β (TGF-β), and brain-derived neurotrophic factor (BDNF) [26,27].

2.2 SAE-associated microglia heterogeneity

In healthy organisms, microglia exist in the CNS in a stable state and are characterized by their small size, slender shape, and multiple and fine branches [28], performing physiological functions such as phagocytosis of synapses and cellular debris, pruning of synapses, and maintenance of homeostasis in the brain. In pathological conditions, microglia are rapidly guided by pathological factors to the site of infection or injury and are activated through receptor-ligand binding [29]. During the process, microglia become hypertrophied, with shortened and thickened branches, and are transformed into “amoeboid morphology”, accompanied by changes in labelling molecules and adaptive functions of gene transcription [16,30].

The majority of extant studies have classified activated microglia into two main phenotypes, namely classically activated phenotypes (M1 phenotype) and alternatively activated phenotypes (M2 phenotype) according to the stimuli conditions, molecular markers and function. The process of transforming the phenotype and function of microglia has also been referred to as microglia polarization [31]. In general, the M1 phenotype represents microglia with pro-inflammatory activity

and neurotoxicity, whereas the M2 phenotype is associated with anti-inflammatory response. The M1/M2 phenotype of microglia is not antagonistic, and microglia in inflammatory environments can undergo phenotypic and functional transformations under the combined influence of pro-inflammatory and anti-inflammatory mediators, with a variety of intermediate polarization states [32]. It has been demonstrated that pro-inflammatory reactive microglia can undergo a process of "depolarization" or polarization towards an anti-inflammatory reactive phenotype in response to anti-inflammatory mediators or neurotrophic factors [33], while anti-inflammatory reactive microglia, which are insensitive to 'depolarization', have been observed to express multiple polarization markers concurrently after treatment with pro-inflammatory mediators, suggesting that they may be in an intermediate state of polarization [34].

However, with the advent of single-cell RNA sequencing and multi-omics technologies, it has been found that the functional state of microglia is context-dependent and exists in a highly dynamic and plastic state. Microglia have been shown to sense the disruption of CNS homeostasis and alter their gene expression profiles at different stages of neurological diseases to achieve dynamic functional transitions, forming a highly heterogeneous population of cells, which implies that the traditional concept of the M1/M2 dichotomy is unable to accurately describe the heterogeneity of microglia. Recent studies have demonstrated a significant down-regulation in the expression of various internal homeostatic, phagocytic, and anti-inflammatory reactive genes, while the expression of pro-inflammatory reactive genes is significantly up-regulated in microglia activated by LPS, demonstrating that microglia in SAE perform a heterogeneous population of cells composed of multiple transcriptional and functional phenotypes, with pro-inflammatory reactive microglia predominantly, alongside anti-inflammatory reactive microglia and various intermediate reactive microglia [35,36]. Based on the results of scRNA-seq analysis, Keren-Shaul et al. identified disease-associated microglia (DAM), which can produce transcriptional and functional changes with the progression of Alzheimer's disease (AD) [37,38]. In addition to DAM, more and more microglia phenotypes such as lipid droplet accumulating microglia (LDAM) and monocyte-derived macrophages (DIMs) have been discovered and defined in recent years [39-41].

3. Microglia participate in SAE by regulating neuroinflammation

Neuroinflammation is one of the most important pathogenic mechanisms of SAE [42], which can be classified into primary and secondary inflammatory responses. Neuroinflammation is mediated by microglia under the combined influence of both intra- and extra-immune factors in the CNS [43]. Microglia trigger a primary inflammatory response via pattern recognition receptors (PRR) in response to endogenous infection or injury in the CNS. This results in releasing inflammatory factors and mediating the infiltration of peripheral inflammatory cells into the brain tissue, which in turn leads to the destruction of the BBB [44]. Excess pro-inflammatory mediators produced by the peripheral immune system can transmit inflammatory signals into the brain via the damaged BBB or through direct stimulation of the vagus and autonomic nervous systems, amplifying the microglial activation effect and inducing a secondary inflammatory response [42,43,45,46]. At different stages of SAE, microglia can undergo dynamic functional transformation by altering their gene expression profiles and form heterogeneous cell populations that exert generally pro-inflammatory and anti-inflammatory reactivities. However, pro-inflammatory reactive microglia predominate over the heterogeneous cell populations, which results in excessive and imbalanced neuroinflammation and the formation of a vicious cycle of inflammatory responses, leading to brain damage and cognitive deficits, among other SAE disorders [47], as shown in Figure. 1 below.

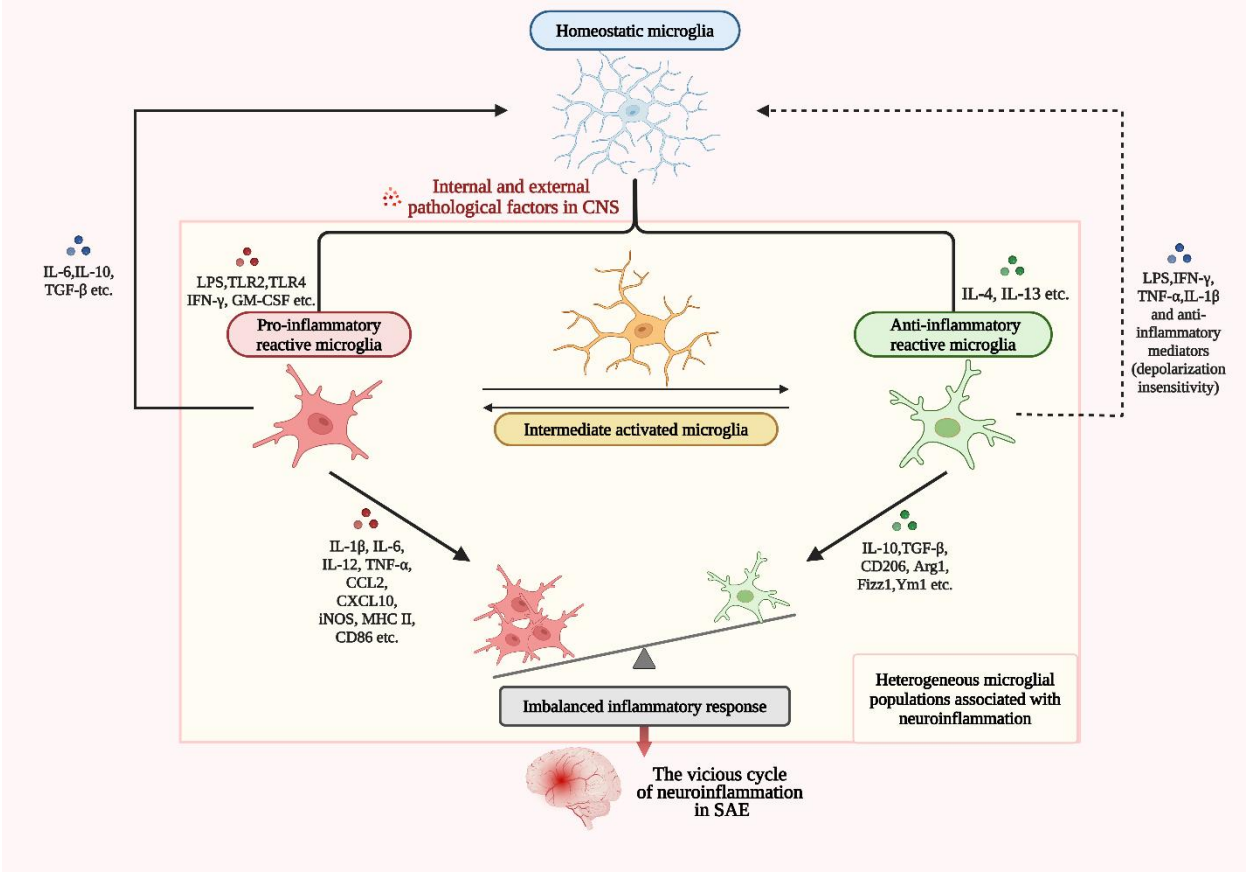

Figure. 1 Schematic representation of microglia activation, functional switching and heterogeneous microglia population-mediated neuroinflammatory response in SAE [11,34,48]. Created with BioRender.com.

3.1 Neuroinflammatory responses mediated by pro-inflammatory reactive microglia in SAE

Pro-inflammatory reactivity is one of the main functional properties of microglia in SAE, and pro-inflammatory reactive microglia dominate the heterogeneous microglia population in SAE. It has been shown that microglia in the brain parenchyma have been observed to develop pro-inflammatory reactivity within a time frame of 6-72 hours following stimulation by pro-inflammatory mediators within and outside the CNS [35,42,49], which include morphological changes, marker molecule changes and gene expression changes, accompanied by effects such as enhanced immune function and diminished phagocytosis. Pro-inflammatory reactive microglia functions express Toll-like receptors (TLR), nucleotide-binding oligomerization domain-like receptors (NLR), scavenger receptors (SRs) and chemokine receptors (CX3CR1, etc.) on their surfaces, among others [11,50], and can travel in the brain to receive bacterial lipopolysaccharides (LPS), interferon gamma (INF-γ), granulocyte-macrophage colony stimulating factor (GM-CSF) and other substances [34]. These processes activate multiple signal pathways such as NF-κB, JAK/STAT, and others, prompting the expression of pro-inflammatory reactive microglia surface marker molecules, such as Iba1, CD86, and MHC-II, etc.[16,51,52], and concurrently triggering microglia to express and release a large number of pro-inflammatory reactive mediators, such as pro-inflammatory reactive cytokines (e.g. interleukins, TNF-α, IFN-γ, etc.), chemokines and their receptors, as well as NADPH oxidase (NOX2, etc.), inducible nitric oxide synthase (iNOS), cyclooxygenase (COX), redox substances such as reactive oxygen species (ROS), reactive nitrogen species (RNS). Other molecules that have been observed to increase include prostaglandin E2 (PGE2), nitric oxide (NO), and others[11,53,54]. Table 1. details the functions of the pro-inflammatory mediators. Persistence of microglial pro-inflammatory reactivity can lead to a series of consequences. For example, substances such as NO, ROS and RNS have been shown to

inhibit electron transport chain, thereby disrupting mitochondrial function and promoting neuronal apoptosis [55,56]. Excessive pro-inflammatory reactivity further disrupts the BBB and exacerbates the accumulation of pro-inflammatory mediators in the brain, stimulating excessive neuroinflammation [44,57]. The result of neuroinflammation also include cerebral ischemia and interruption of cerebral perfusion. These consequences in turn drives a malignant cascade of neuroinflammatory responses and induces severe neuronal damage and synaptic dysfunction, resulting in neurological conditions such as long-term brain damage and cognitive dysfunction [58,59].

Table 1. List of key pro-inflammatory mediators released by microglia and their functions

Pro-inflammatory Mediators	Functions	References
	Cytokines	
IL-1α	Induces the production of pro-inflammatory cytokines, promotes the production of neurotoxic astrocyte, mediates immune cell infiltration, destroys the BBB and induces neuronal cell death.	[60,61]
IL-1β	Activates microglia, induces the production of pro-inflammatory mediators, inhibits hippocampal neural activity, induces neuronal apoptosis and synaptic dysfunction, involved in inflammatory vesicle activation	[62-64]
IL-6	Multipotent cytokine, activates microglia, destroys the BBB, mediates pathological pain and other symptoms, regulates chemokine and adhesion molecule production	[65-68]
IL-12	Promotes neuroinflammatory responses, regulates T cell function, mediates CNS autoimmune diseases	[68-70]
IL-17	Stimulates microglia to produce other pro-inflammatory mediators, enhances neuroinflammatory responses, promotes neutrophil infiltration of brain tissue, interferes with BBB function	[70,71]
IL-18	Can be produced by inflammasome activation, involved in microglia activation, induces the production of other pro-inflammatory mediators, inhibits LTP in hippocampus	[70,72,73]
IL-23	Promotes microglia and astrocyte activation, induces neuroinflammatory cascade response, induces IL-17 production, promotes lymphocyte infiltration, mediates brain injury.	[70,74]
IFN-γ	Activates microglia, up-regulates MHC molecule expression, promotes expression of IL-1β, IL-6, chemokine receptors, adhesion proteins, promotes proteasome formation, disrupts the BBB	[75,76]
TNF-α	Promotes activation of microglia and astrocytes, promotes neuroinflammatory response, increases BBB permeability, increases excitatory receptor expression on neuronal surface, produces excitotoxicity, promotes neuronal apoptosis, mediates brain injury.	[58,64]
	Chemokines	
CCL2, CXCL8, CXCL12, etc.	Activate glial cells, induce migration of leukocytes to the CNS and brain tissue infiltration of inflammatory cells, crosstalk neurons and glial cells, mediate BBB destruction and neuronal injury	[77,78]

Table 1. Cont.

Pro-inflammatory Mediators	Functions	References
	Redox substances	
NADPH oxidase	Transfer electrons from intracellular NADPH to extracellular,	[12,79,80]

(NOX2, etc.)	inducing a respiratory burst that generates reactive oxygen species and induces neuronal and synaptic damage	
iNOS	Synthesizes NO, mediating neuronal damage	[80,81]
COX	Synthesizes prostaglandins, amplifying neuroinflammatory responses	[82,83]
ROS, RNS	Mediates oxidative stress, BBB damage and mitochondrial dysfunction, promotes lipid peroxidation, disrupts membrane structure, induces severe neuronal and synaptic damage, activates inflammatory vesicles	[76,80,84,85]
Other inflammatory mediators		
NO	Dilates cerebral blood vessels, inhibits the electron transport chain, causes mitochondrial dysfunction, is neurotoxic, regulates synaptic function and neuronal signal	[86]
PGE2	mediates fever, strongly stimulates microglia to release pro-inflammatory mediators, produces excitotoxicity, increases cerebrovascular endothelial permeability, destroys BBB, mediates peripheral immune cell infiltration	[87]
ATP	Activates microglia, promotes the release of pro-inflammatory mediators, destroys the BBB, triggers a neuroinflammatory cascade, and worsens the outcome of brain injury	[60]
HMGB1	Promotes continued activation of microglia, promotes release of pro-inflammatory mediators, damages the BBB, mediates synaptic and neuronal damage, and produces cognitive dysfunction	[88-90]
S100 protein	Promotes pro-inflammatory reactivity of microglia and promotes neuroinflammatory responses	[49,91,92]

3.2 Neuroinflammatory responses mediated by anti-inflammatory reactive microglia in SAE

Anti-inflammatory reactivity is also a main functional property of microglia in SAE. Anti-inflammatory reactive microglia may account for a lower proportion of heterogeneous microglia populations and may exhibit a slower response to SAE. Anti-inflammatory reactive microglia have multiple functions such as down-regulating pro-inflammatory cytokine expression, restoring immune homeostasis in the brain, promoting neuronal development, facilitating tissue remodeling and cerebral vascular repair [93,94]. The polarization of microglia towards an anti-inflammatory reactive phenotype is mainly driven by anti-inflammatory mediators (mainly IL-4 and IL-13, along with BDNF, chemokines, etc.) .These agents stimulate the TLR, Fc γ receptor, and interleukin receptor, which in turn leads to the releases of IL-4, IL-10, IL-13, TGF- β , PPAR- γ , TREM2, and other anti-inflammatory mediators by initiating the signaling pathway such as JAK1/3-STAT6, etc. The result of this process enhances of phagocytosis, promote tissue repair and regeneration and reduce inflammatory cell activation [48,53,93]. The functions of each anti-inflammatory mediator are detailed in Table 2 below. Recently, researchers studying traumatic brain injury (TBI) have identified a type of microglia that exhibits a reparative effect on brain damage and cognitive impairment, but this type differs from conventional anti-inflammation reactive microglia, suggesting another reactive state in the heterogeneous population. In conclusion, microglia are able to regulate neuroinflammation through anti-inflammatory responses and exert neuroprotective effects, thus participating in the development of SAE.

Table 2. Major anti-inflammatory mediators released by microglia and their functions

Anti-inflammatory mediators	Functions	References
IL-4	Induction of anti-inflammatory reactive switch in microglia, inhibition of pro-inflammatory mediator release, up-regulation of anti-inflammatory mediator expression, and promotion of	[95,96]

	neuronal and synaptic regeneration	
IL-10	Induction of anti-inflammatory switching of microglia, prevention of their over-activation, enhancement of their phagocytosis, inhibition of pro-inflammatory cytokine release, and down-regulation of extracellular matrix protective proteins	[35,97]
IL-13	Induces conversion of anti-inflammatory function in microglia, inhibits inflammatory response, reduces inflammatory cell infiltration, promotes regeneration of neurons and other neuroglia, and promotes myelin remodeling	[70,98]
TGF-β	Inhibit inflammatory response, reduce the degree of brain tissue damage, promote the release of anti-inflammatory mediators, enhance the phagocytosis of microglia, promote the repair of damaged tissues and the reconstruction of synapses, and reduce the accumulation of intracellular lipid droplets in microglia	[99-101]
PPAR-γ	Inhibits pro-inflammatory cytokine release, attenuates oxidative stress damage and mitochondrial dysfunction, protects the BBB, promotes neurotrophic factor production, and improves memory and cognitive impairment	[102,103]
ARG-1	Promoting the conversion of L-arginine for brain injury repair	[104]
TREM2	Regulation of microglia proliferation, enhancement of microglia phagocytosis, inhibition of pro-inflammatory cytokine secretion, reduction of intracellular lipid accumulation in microglia, and promotion of DAM ontogeny and functional transformation	[105-107]

3.3 Microglia regulate neuroinflammation through altering gene expression profile in different stages of SAE

Microglia regulate neuroinflammation through altering gene expression, phenotypic and functional in different stages of sepsis, which in turn participates in SAE disease progression. In the homeostatic state of the brain, microglia highly express homeostatic genes such as Cx3cr1, P2ry12, and Tmem119 to facilitate maintenance of the homeostatic and surveillance states [35,108]. Microglia exhibit a response within 6h after LPS stimulation, as evidenced by the classical pro-inflammatory reactive genes such as Lcn2, Ccl3, Ccl5, Cxcl13, Il1b, and Tnf, as well as Itgax, Ch25h, Spp1, Saa3, Tnfaip3 and Cd40 are up-regulated, and the expression of homeostatic genes such as P2ry12, Tmem119 and HexB is down-regulated, in parallel with the down-regulation of the expression of genes mediating phagocytosis such as Trem2 and Tyrobp [35,108]. This suggests that microglia detach from homeostasis and exhibit pro-inflammatory reactivity during the early acute response phase of sepsis. In contrast, immune-related genes such as Tspo, Axl, Cd72 and Marco show up-regulation of expression only 24-48h after LPS stimulation, which may represent new pro-inflammatory reactive taxa. The expression of pro-inflammatory reactive genes is significantly up-regulated in the microglial cell population in the early stage of SAE, while the expression of anti-inflammatory reactive genes such as Arg1 is down-regulated [95,108,109], suggesting that pro-inflammatory reactive microglia are predominant in the population. It has been clarified that the enhancement of anti-inflammatory reactivity, which is caused by the up-regulation of the expression of a variety of anti-inflammatory reactive genes in the microglial cell population, mainly occurs in the late stage of SAE, whereby the heterogeneous population of microglial at the different stages of SAE triggered an unbalanced inflammatory response, which ultimately drives the development of SAE. The aforementioned neuroinflammation-associated reactive gene expression state is known to persist for a duration of 48h, while it will largely return to homeostasis after 7 days, but there is currently no evidence that the return of microglia to homeostasis occurs in parallel with the up-regulation of anti-inflammatory reactive gene expression [35]. In addition it has been found that there is an overlap of stage-specific gene expression in DAM or neurodegeneration-associated microglia (MGnD) and neuroinflammation-associated microglia within 48h-7d after LPS treatment, suggesting that SAE may induce secondary neurodegenerative

pathology and implies that the microglia dynamics that occur during the course of the SAE may be more enriched [110]. Specific gene expression is shown in Figure 2. below.

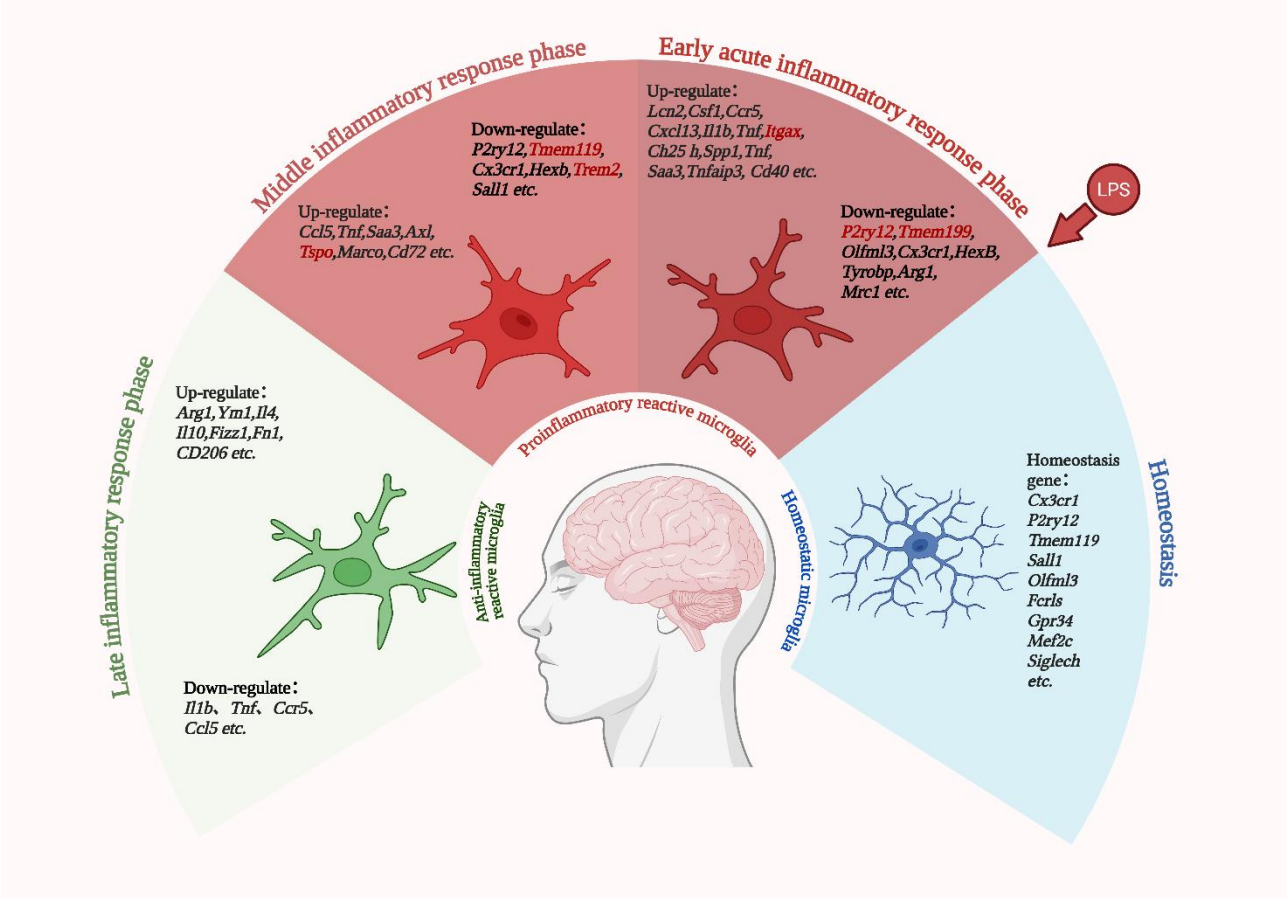

Figure 2. Gene expression profiles of microglia at each response stage after LPS stimulation [35,37,43,108,110]. Genes marked in red are the overlap of inflammation-associated microglia and neurodegenerative microglia stage-dependent gene expression. Created by BioRender.com.

4. Treatment strategies targeting Microglia and Neuroinflammation

As stated above, microglia-mediated neuroinflammation is one of the important pathogenic mechanisms of SAE and an important part of the occurrence of brain injury and cognitive dysfunction in SAE. Existing studies have shown that inhibition of microglia activation can ameliorate neurological symptoms and cognitive dysfunction to some extent in SAE [111]. Therefore, microglia and their mediated neuroinflammation can be an important target for SAE treatment with considerable potential for research and applications.

The process of microglia-mediated neuroinflammation is initiated by a series of pathological factors and intercellular crosstalk which in turn generates a rapid cascade of responses. The therapeutic potential of targeting microglia overactivation and their inflammatory responses is a promising avenue for research. Research has demonstrated that the suppression of the IL-10R and IL-17A pathways is critical for preventing microglia overactivation and neuroinflammation in SAE and alleviating cognitive impairment [35,71]. The colony-stimulating factor 1 receptor (CSF-1R) is a surface receptor of significance in the maintenance of microglia survival. Treatment with CSF-1R inhibitors or antagonists has been demonstrated to reduce LPS-stimulated neuroinflammation and inhibit aberrant excitation of hippocampal neurons in SAE in the mouse brain [112,113]. In addition, the inhibition of TNF- α and CCR2 signaling using inhibitors and monoclonal antibodies can impede sustained microglia activation, thereby suppressing the infiltration of inflammatory cells and attenuating neuroinflammatory responses. This approach may also be a potential target for the treatment of microglia-driven neuroinflammation [114,115]. A cyclin-dependent kinase 2 (CDK2)

inhibitor, BMS265246, has been shown to inhibit microglia-like cell hyperactivation, and a growth differentiation factor 15 (GDF15) antibody reduces microglial inflammatory responses and ameliorates sepsis-induced cognitive and memory deficits. These findings suggest that both of which are novel targets for SAE treatment [116,117]. Moreover, low-dose dexamethasone injections has been clarified to inhibit the pro-inflammatory reactivities of microglia, thereby improving cognitive function in juvenile SAE rats [118].

The enhancement of the anti-inflammatory reactivity of microglia is a principal therapeutic concept. TREM2 represents the current focal point of research endeavors aimed at enhancing microglia's anti-inflammatory reactivity. High expression of TREM2 can stimulate microglia to perform anti-inflammatory reactivity and enhance their phagocytosis, promote their transformation to DAM phenotype. Consequently, it may be used as a therapeutic target for the treatment of SAE in the future [106]. Nevertheless, a recent study identifies the presence of senescent microglia with high expression of TREM2. These cells have the potential to exacerbate neuroinflammation and cognitive deficits by secreting inflammatory factors and redox molecules. Consequently, the prospect of utilizing TREM2 as a therapeutic target for neuroinflammation or neurodegenerative diseases requires further research[119]. Targeted activation of α 7 nicotinic acetylcholine receptor (α 7nAChR) is demonstrated to promote the anti-inflammatory reactivity of microglia in the rat hippocampus, reduce the release of inflammatory factors, such as IL-6 and TNF- α , and ameliorate the neuroinflammation and oxidative stress after cerebral ischemia/reperfusion injury, which play a neuroprotective role in SAE [120].

In addition to the aforementioned therapeutic concepts, many researchers have underscored the efficacy of SAE therapeutic regimens that target inflammasome. The specificity of neuroinflammation in SAE is contingent upon the presence of NLRP3 inflammasome in microglia. The activation of microglia promotes NLRP3 gene expression, thereby initiating a neuroinflammatory cascade response that contributes to the formation of a vicious cycle of neuroinflammation [121]. Melatonin has also been found to inhibit the NLRP3-caspase-1-IL- β pathway in microglia, thereby suppressing neuroinflammation and reducing neuronal damage [122]. MCC950 (an NLRP3 inhibitor) have been demonstrated to inhibit SAE-induced NLRP3 expression and down-regulate the release of inflammatory factors in microglia, thereby inhibiting neuronal apoptosis and mitochondrial dysfunction [123]. Therefore, they may serve as an important target for targeting NLRP3 to treat microglia-mediated neuroinflammation. Palmitoylation is a post-translational modification of NLRP3. Inhibit the palmitoylation of NLRP3 can significantly reduce the activation of NLRP3 inflammasome. This, in turn, is demonstrated to play a role in the suppression of neuroinflammation [124]. It has also been determined that the modulation of the role of NLRP3-related partial microRNAs and long non-coding RNAs (lncRNAs) to regulate neuroinflammation at the gene level may also constitute a promising therapeutic strategy [121,125].

5. Conclusions and outlook

In summary, SAE is a serious complication in the early stage of sepsis, and neuroinflammation is one of the most important pathogenic mechanisms of SAE. Microglia, as important resident immune cells in the brain, play great role in the development of SAE by regulating neuroinflammation. In SAE, microglia adopt a dual role, exhibiting generally inflammatory and anti-inflammatory reactivity through heterogeneous cell populations. The cell populations mediate the generation of an imbalance inflammatory response, thereby establishing a vicious cycle of neuroinflammation and becoming an important mechanism driving the pathological process of SAE. The nature of microglia heterogeneity stems from the differentiation of gene expression, and its gene expression profile may demonstrate stage changes in accordance with the progression of SAE exhibiting overlap with that of neurodegenerative diseases. The extant research on SAE and microglia and their mediated neuroinflammation is still in its infancy. There are several deficiencies in the current research, for instance, there is a lack of clarity regarding the multiple interacting

pathogenic mechanisms, the traditional M1/M2 binary typing basis has certain defects and a new multidimensional research and classification frameworks have yet to be constructed. Therefore, microglia in SAE and their mediated neuroinflammation still need to be further in-depth and detailed research, and the regulation of microglial function and intervention in neuroinflammation should be developed based on such basic research. The development of pharmaceuticals or therapeutic strategies based on fundamental research to regulate microglia function and intervene in neuroinflammation is expected to reduce the incidence and mortality of SAE, provide effective therapeutic strategies, and improve the prognosis of patients, the quality of patients' survival, and reduce the burden on public health.

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