Introduction

Stroke is a major life-threatening disease worldwide (Dal-Re, 2011), with a high disability and mortality rate, which places a huge burden on the economy and society (Bai et al., 2017). Ischemic stroke is the most common type, accounting for 87% of all strokes (Benjamin et al., 2018). The pathophysiological mechanisms of ischemic stroke are complex, involving microglia-mediated neuroinflammation, oxidative stress, excitotoxicity, and destruction of the blood-brain barrier (BBB) (Dirnagl et al., 1999; Allen and Bayraktutan, 2009; George and Steinberg, 2015). Thrombolytic therapy is currently recognized as the most effective method for the prevention and treatment of ischemic stroke, but it has a very narrow time window (Henderson et al., 2018). Thus, for patients who cannot receive thrombolytic therapy, we need to identify new therapeutic targets.

Numerous recent studies have shown that the microglia-mediated inflammatory response is an important pathological mechanism in ischemic stroke (Benaroch, 2013; Guruswamy and ElAli, 2017). Microglial cells derived from macrophages are important immune cells that play a critical role in the repair and regeneration of the central nervous system (CNS) (Xiong et al., 2016). Microglial cells are innate immune cells of the central nervous system (CNS) and are the main mediators of neuroinflammation (Amor and Woodroofe, 2014; Skaper et al., 2014). They can be activated by various stimuli to secrete factors that exert proinflammatory or anti-inflammatory effects (Herder et al., 2015; Xia et al., 2015; Yu et al., 2015). A recent study showed that M1 phenotype microglia have a destructive effect on the brain, while M2 phenotype microglia have neuroprotective effects (Hu et al., 2015). Therefore, it is beneficial for neuroprotection to promote the M2 phenotype and inhibit the M1 phenotype in microglia in ischemic stroke. Microglia are among the first cells to respond to stroke and other brain injuries (Streit et al., 2004; Kawabori and Yenari, 2015). Ischemic stroke and other brain injuries can cause local inflammatory responses, including activation of microglia (Heindl et al., 2018). In this review, we discuss the role of microglia in neuroinflammation and their impact on ischemic stroke. We also clarify the mechanisms underlying the role of microglia in stroke pathology, with a highlight on microglia-associated neuroinflammation, which may be a potential drug target. This review should provide new prospects and directions for the treatment of ischemic stroke.

Search Strategy

The articles included in this review were retrieved by an electronic search of the PubMed database from inception to 2020 for literature describing the role of microglia-associated neuroinflammation in ischemic stroke. Searches were conducted using the phrase “ischemic stroke” combined with the following key words: microglia, neuroinflammation, polarization, M1 phenotype, M2 phenotype, upstream factors, and therapeutic target. Articles were included if they were deemed to contribute to the understanding of the role of microglia-associated neuroinflammation in ischemic stroke.

Features of Microglial Cells

In the 1920s and 1930s, Pio del Rio-Hortega first investigated the characteristics of microglia and described their unique morphological phenotypes (Penfield, 1932). Microglia are the most abundant of the resident macrophage populations in the CNS (Ransohoff and Perry, 2009). Under physiological conditions, microglia are in a resting state, branching with

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Funding: This work was supported by the National Natural Science Foundation of China, Nos. 31871169 (to YT), 81600040 (to APW); Key Project of Department of Education of Hunan Province, China, No. 18A243 (to APW); Innovation Guidance Project of Hunan Province, China, No. 2018SK1606 (to SXG); the Natural Science Foundation of Hunan Province of China, No. 2017JJ3279 (to APW).

How to cite this article: Zhang W, Tian T, Gong SX, Huang WQ, Zhou QY, Wang AP, Tian Y (2021) Microglia-associated neuroinflammation is a potential therapeutic target for ischemic stroke. Neuro Regen Res 16(1):6-11.
small cell bodies and long protrusions (Michell-Robinson et al., 2015). However, resting microglia are not completely inert—although they do not display phagocytic functions, they can still move and pinocytose (Cherry et al., 2014; Prinz and Priller, 2014), and can secrete growth factors that nourish, support and protect the electrophysiological functions of neurons to maintain CNS homeostasis (Eyo and Dailey, 2013). In addition, microglia can also dynamically monitor synaptic function through synaptic contact. In the CNS, abnormal synaptic transmission or dysfunction can trigger microglia to respond. In addition to clearing dead cell debris, Wake et al. (2013) showed that glial cells also help maintain normal synaptic function, trimming or clearing damaged or redundant synapses. Stimulated by ischemia, infection and other factors, microglia can be activated within minutes, and then proliferate, migrate to the diseased site, shorten their cell body protrusions, and change from a branched to a round or amoeboid morphology. At this time, activated microglial cells proliferate, phagocytose and clear damaged and dead neurons (Jia, 2012). In the early stage of inflammation, microglia appear to be of the proinflammatory type, which is the classic activated (M1) type, secreting a variety of inflammatory factors. In the later stages of acute inflammation, these M1 microglia transform into the anti-inflammatory (M2) type, which secrete anti-inflammatory cytokines that contribute to neuroprotection (Liu et al., 2019). Microglia act as the first line of defense in the brain, and play a critical role in maintaining brain homeostasis (Perry et al., 2010; Xia et al., 2015). After an ischemic event, along with a reduction in cerebral blood flow, microglia undergo morphological changes in preparation for the upcoming immune response (Masuda et al., 2011). In a word, microglia are associated with neuroinflammation, which plays an important role in ischemic stroke.

Role of Microglia Associated
Neuroinflammation in Ischemic Stroke

Microglia are major immune system cells, and they play an important role in the repair and regeneration of the CNS (Hanisch and Kettenmann, 2007). In addition to their neuroprotective effects, microglia are also the main producers of proinflammatory cytokines, which can greatly inhibit brain repair and promote neurogenesis (Ekdahl et al., 2003). The inflammatory microenvironment has a great impact on microglial phenotypic changes, and can change gene expression patterns and biological functions in brain tissue (Xiong et al., 2016).

Neuroinflammation, the inflammatory reaction in the CNS, is a key pathological event after ischemic stroke, and can lead to secondary brain tissue injury and poor functional recovery. During ischemic injury, microglial cells are activated and release neuroinflammatory factors. In addition, the peripheral immune cell infiltration following BBB breakdown further amplifies the neuroinflammatory response, eventually leading to neuronal damage (Rajkovic et al., 2018).

In ischemic stroke, various proinflammatory factors, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6 and interferon-γ (IFN-γ), chemokines, nitric oxide, reactive oxygen species (ROS) and matrix metalloproteinase-9, activate microglia, further aggravating the neuroinflammatory reaction in the brain and exacerbating brain damage (Luo et al., 2016). After ischemic stroke, activated microglial cells exhibit distinct phenotypes, namely M1 or M2, according to the affected brain area, and the specific site and severity of injury, and respond differently, either exerting proinflammatory or anti-inflammatory effects (Skirving and Dan, 2001; Sieweke and Allen, 2013). The different microglial phenotypes represent the two extremes of their activation status. M1 phenotypic polarization causes the release of proinflammatory mediators that inhibit CNS recovery, while M2 phenotypic polarization leads to the release of anti-inflammatory cytokines that promote tissue regeneration and repair. M1 microglia mainly secrete proinflammatory factors, such as IL-1, TNF-α, IL-6 and IFN-γ, to increase expression of inducible nitric oxide synthase, which has cytotoxic effects on neurons, resulting in neuronal loss (Lan et al., 2019). This leads to disruption of the BBB and the degradation of the extracellular matrix (Haley and Lawrence, 2017). Subsequently, peripheral blood leukocytes, plasma fibrinectin, fibrinogen and other fibrinolytic factors enter the brain tissue (Dejongheere et al., 2011), aggravating tissue damage (Anrather and Iadecola, 2016).

Compared with M1 microglia, M2 microglia have a stronger ability to induce phagocytosis of dead neurons, which can curtail the secondary inflammatory response and promote tissue regeneration (Xia et al., 2015). The M2 phenotype can be divided into M2a, M2b and M2c subtypes, depending on function and stimulatory factors (Hu et al., 2012; Chhor et al., 2013; Sudduth et al., 2013; Franco and Fernández-Suárez, 2015; Latta et al., 2015). The M2a subtype is induced by IL-4 and IL-13 stimulation (Latta et al., 2015). The M2b subtype is an immunomodulatory phenotype that can be induced by lipopolysaccharide (LPS) and IL-1 receptor agonists (Chhor et al., 2013; Franco and Fernández-Suárez, 2015). The M2c subtype, called deactivated microglia, are stimulated by transforming growth factor-β, IL-10 and glucocorticoids (Franco and Fernández-Suárez, 2015). The M2 phenotype mainly secretes anti-inflammatory factors, such as IL-3, IL-4, IL-10, transforming growth factor-β and insulin-like growth factor-1, to inhibit inflammation (Xiong et al., 2016). M2 microglia also produce the antioxidative factors hemeoxygenase-1 and glutathione, which may inhibit the recognition of viable neurons, promoting viable neurons repair (Xia et al., 2015). It was found that activated M1 phenotypic microglia can be reactivated to the M2 phenotype under certain conditions. M1 polarized microglia can inhibit the actions of M2 polarized microglia to a degree. Therefore, microglia may produce proinflammatory or anti-inflammatory cytokines and chemokines (Lan et al., 2017), which have differential effects on neuroinflammation in ischemic stroke (Figure 1).

Proinflammatory response of microglial cells in ischemic stroke

Neuroinflammation is considered a major contributor to cerebral ischemia-induced brain damage. Neuroinflammation is initiated in response to ischemic stroke, and is usually characterized by microglial activation and collateral brain damage, and is caused by a strong inflammatory reaction. Excessive activation of microglial cells results in the release of a large number of proinflammatory factors that aggravate cerebral ischemia-reperfusion injury (Ekdahl et al., 2003; Xiong et al., 2016). Therefore, inhibiting the release of proinflammatory factors from microglial cells could be a major strategy for alleviating ischemic stroke (Lu et al., 2019). The proinflammatory M1 microglia can kill pathogens and promote tissue repair by enhancing phagocytosis. However, excessive release of IL-6, IL-1β, IL-12, IL-23 and TNF-α and the production of other proinflammatory factors such as inducible nitric oxide synthase and ROS can cause inflammation and aggravate brain damage (Xiong et al., 2016; Voet et al., 2018).

Studies have shown that the neuroinflammatory response mediated by microglia may be triggered by substances that stimulate M1 phenotypic microglia to produce proinflammatory factors (He et al., 2016, 2017). It is well known that LPS induces an inflammatory cytokine response in mice. LPS induces microglial activation through the mitogen-activated protein kinase pathway and increases the expression of proinflammatory cytokines (He et al., 2017; Ding et al., 2019). He et al. (2016) found that chemokine ligand 2 and chemokine ligand receptor 2 mediate the polarization of microglia into the M1 phenotype and promote the release of inflammatory factors during CNS inflammation. Indeed, inflammatory cytokines, such as IL-1β, IL-6 and TNF-α, are significantly increased in mice with...
Activated microglial cells secrete inflammatory cytokines. CCL2/CR2, sFasL, and LPS can activate M1 microglial cells, and activated M1 microglial cells can secrete inflammatory cytokines, such as IL-1β, IL-6, and TNF-α. PPARγ, SOCS1/JAK2/STAT3, AMPK, and IRF-4 can activate M2 microglial cells, and activated M2 microglial cells can secrete anti-inflammatory cytokines, such as IL-4, IL-10, and TGF-β. AMPK: Adenosine 5′-monophosphate-activated protein kinase; CCL2: chemokine ligand-2; CR2: chemokine ligand receptor-2; IFN-γ: interferon γ; IL-10: interleukin-10; LPS: lipopolysaccharide; PPARγ: peroxisome proliferator-activated receptor γ; SOCS1/JAK2/STAT3: suppressor of cytokine signaling 1/Janus kinase 2/signal transducer and activator of transcription 3; TGF-β: transforming growth factor-β; TNF-α: tumor necrosis factor α; TREM1-1: triggering receptor expressed on myeloid cells-1.

ischemic stroke (Hénaut et al., 2019). Among these cytokines, TNF-α is mainly secreted by microglia, and is an important factor contributing to ischemic/hypoxic injury. Microglia can stimulate the activation of inflammatory cells, such as neutrophils, and promote inflammatory responses (Wang et al., 2013). Chen et al. (2019) further demonstrated that M1 phenotypic microglia can cause BBB destruction after ischemic stroke, mainly because these cells secrete TNF-α, thereby promoting the inflammatory response. Therefore, finding an effective clinical drug to block microglial-associated neuroinflammation may reduce BBB breakdown and alleviate tissue damage after ischemic stroke.Triggering receptor expressed on myeloid cells 1 (TREM1), an amplifier of the innate immune response, is a critical regulator of inflammation. It has been found that TREM1 is upregulated after cerebral ischemic injury and accelerates the neuroinflammatory response (Xu et al., 2019). Soluble Fas ligand (sFasL) plays an important role in M1 microglial migration and the inflammatory response in the mouse model of middle cerebral artery occlusion. sFasL can increase M1 microglia, exacerbating neuroinflammation (Meng et al., 2016). Therefore, neutralizing sFasL is a potential new treatment strategy to inhibit post-stroke inflammation and M1 phenotypic microglial polarization, which may improve stroke prognosis. Papaverine inhibits the production of nitric oxide and proinflammatory cytokines by microglia stimulated by LPS by regulating various inflammatory signals (Lee et al., 2019). While the mechanisms by which microglia promote neuroinflammation remain unclear, the accumulating evidence suggests that M1 phenotypic microglial polarization promotes an inflammatory response and is a risk factor for ischemic stroke. Therefore, inhibiting the polarization of microglia into the M1 phenotype may have therapeutic potential for the treatment of stroke.

Anti-inflammatory effect of microglial cells in ischemic stroke
Activated microglial cells have different roles in the CNS inflammatory environment. The M2 phenotype microglial cells that are activated after ischemic stroke promote brain tissue repair mainly by of the removal of cell debris, the reduction of local inflammation, and the release of a large number of trophic factors (Hanisch and Kettenmann, 2007; Thored et al., 2009; Kwon et al., 2013; Miron et al., 2013). M2 microglia have an anti-inflammatory role and secrete anti-inflammatory mediators and neurotrophic factors, such as IL-10, IL-13, transforming growth factor-β, brain-derived neurotrophic factor, glial neurotrophic factor, to reduce inflammatory response, protect neurons, and promote tissue repair. Perego et al. (2011) showed that selectively activated M2 phenotypic microglia secrete various anti-inflammatory factors such as IL-4, IL-10, and transforming growth factor-β, which are of great significance to promote brain repair and neuron regeneration in ischemic stroke. Adenosine 5′-monophosphate-activated protein kinase (AMPK) is the main molecular switch that activates the M2 phenotype (Mounier et al., 2013). Activation of the AMPK pathway by synthetic or natural compounds can reduce inflammatory damage and promote microglial M2 polarization (Lu et al., 2010; Zhou et al., 2014; Zhu et al., 2019). ROS produced by NADPH oxidase in microglia play an important role in neuronal injury after ischemic stroke. The voltage-gated proton channel Hv1 is selectively expressed in microglia and is necessary for the production of ROS by NADPH oxidase in the brain. Compared with wild-type mice, mice lacking Hv1 exhibit reduced ROS production, and polarized microglia are transformed from the M1 to the M2 phenotype, which slows brain tissue damage (Tian et al., 2016). These observations suggest that microglial cells can reduce inflammation and tissue damage in the infarcted area.

Studies have demonstrated that inhibition of the suppressor of cytokine signaling 1 (SOCS1)/Janus kinase 2 (JAK2)/STAT3 signaling pathway promotes M2 phenotypic polarization, thereby reducing the neuroinflammatory response in rats with ischemic stroke (Qin et al., 2012; Tian et al., 2016; Wang et al., 2017b; Li et al., 2019a). The nuclear hormone receptor peroxisome proliferator-activated receptor γ is another transcription factor that regulates the differentiation of monocytes into M2 phenotypic microglia, and has anti-inflammatory effects, thereby reducing neuroinflammation (Bouhlel et al., 2007). The various subtypes of interferon regulatory factors play differing roles in microglial polarization. For example, interferon regulatory factor 4 is a key transcription factor that controls M2 polarization (Satoh et al., 2010) and reduces inflammation and tissue damage in the infarcted area. Further studies on the functional
characteristics of activated microglia are needed to determine how to polarize microglia toward the M2 phenotype and maintain them in an anti-inflammatory state in the brain. Finding a way to induce microglial cells to undergo M2 phenotypic polarization is therefore a potential new approach for the treatment of ischemic stroke (Figure 2).

### Upstream Regulators of Microglia-Associated Neuroinflammation in Ischemic Stroke

Microglial cells are highly plastic. Microglial polarization and microglial-associated neuroinflammation are dynamic processes. In the early stage of cerebral ischemia, inhibiting microglial polarization into the M1 phenotype and promoting their polarization into the M2 phenotype, to maintain the balance between anti-inflammatory and proinflammatory responses, is a potential new strategy for the treatment of ischemic stroke.

The signal transducer and activator of transcription (STAT) family of transcription factors play a key role in cytokine and immune regulation. For example, STAT6 is important in establishing the M2 phenotype following IL-13 and IL-4 stimulation (Kuroda et al., 2009). The STAT3 signaling pathway is thought to be an important pathway that regulates microglial phenotype and participates in the microglial-associated inflammatory response in ischemic stroke (Qin et al., 2012). Downregulation of the STAT3 signaling pathway can inhibit the death of neurons and promote microglial polarization into the M2 phenotype in ischemic stroke (Li et al., 2019a). sFasL activates microglia and promotes M1 polarization by phosphorylating the JAK2/STAT3/nuclear factor-kB (NF-kB) pathway in ischemic stroke, while AG490 (a JAK2 antagonist) not only inhibits STAT3/NF-kB phosphorylation, but sFasl-induced M1 phenotypic polarization and inflammation as well (Meng et al., 2016). Recent studies have shown that inhibiting the SOCS1/JAK2/STAT3 pathway can lower the loss of neural function and the apoptosis of neuronal cells, and may therefore serve as a new target for the clinical treatment of ischemic stroke. In addition, it has been reported that inhibition of the SOCS1/JAK2/STAT3 pathway reduces the neuroinflammatory response in the brain of rats with ischemic stroke (Wang et al., 2017b).

Exosomes are efficient tools for delivering gene-based drugs to the ischemic cortex. For example, exosomes loaded with miR-30d-5p can protect against ischemia and autophagy-mediated brain damage by promoting M2 microglial polarization. In the acute phase of stroke, the use of exosomes from adipose-derived stem cells overexpressing miR-30d-5p may reduce brain damage by inhibiting the inflammatory response (Jiang et al., 2018). Therefore, exosomes loaded with mir-30d-5p have the potential to be a therapeutic strategy for ischemic stroke by promoting M2 microglial polarization.

In ischemic stroke, class A scavenger receptor (SR-A) and cannabinoid 2 receptor are involved in the regulation of microglial-associated neuroinflammation. After ischemic stroke, the SR-A receptor promotes microglial M1 phenotypic polarization by activating NF-kB. The number of M1 microglial cells therefore increases rapidly, and the inflammatory response and brain damage worsen. In SR-A knockout mice, compared with control mice, the number of M1 microglial cells in ischemic tissue is decreased and the number of M2 microglial cells is increased (Xu et al., 2012). IL-10 is an anti-inflammatory cytokine that inhibits inflammatory responses and antigen presentation. For example, compared with normal mice, mice with IL-10 deficiency have larger and more severe lesions, and worse prognosis after brain injury. M2 microglia in mice lacking IL-10 are significantly decreased, suggesting that IL-10 promotes M2 polarization and neuronal recovery, and reduces the inflammatory response (De Córdoba et al., 2015).

Microglial-associated neuroinflammation is a complex process involving intricate molecular regulatory pathways. Therefore, identifying key targets upstream of microglial-associated neuroinflammation will likely contribute to more effective treatment of ischemic stroke.

### Therapeutic Targeting of Microglia-Associated Neuroinflammation in Ischemic Stroke

Ischemic stroke is a complex process involving multiple factors, interactions and targets. Therefore, the treatment of ischemic stroke is also a complex process involving multiple links and targets. Intravenous thrombolysis and mechanical thrombectomy are effective strategies for the treatment of ischemic stroke (Badhiwala et al., 2016). However, because of the narrow treatment time window, few patients can receive intravenous thrombolysis and mechanical thrombectomy. However, we can selectively develop new drugs and identify new targets for the prevention and treatment of ischemic stroke.

Table 1 summarizes the use of microglia in the treatment of ischemic stroke.
Inflammatory responses mediated by microglial activation play a key pathogenic role in ischemic stroke. Microglial cells can rapidly undergo morphological changes based on subtle changes in the brain environment. M1 phenotype microglial cells are associated with an increased inflammatory response through TLR4 during adolescence induces neuroinflammation by driving pro-inflammatory state of M1 microglia through TLR4 activation.

**Conclusion**

Inflammatory responses associated with microglial activation may play a key pathogenic role in ischemic stroke. Microglial cells can rapidly undergo morphological changes based on subtle changes in the brain environment. M1 phenotype microglial cells are associated with an increased inflammatory response, which damages the BBB by increasing the release of proinflammatory factors, thereby aggravating damage to ischemic brain tissue. In contrast, M2 phenotype microglia promote neuronal repair and regeneration by secreting anti-inflammatory and neurotrophic factors. Therefore, modulating microglial polarization in the different stages of ischemic stroke will be a good strategy for the treatment of ischemic stroke by reducing neural inflammation. However, the classification of macrophage polarization—new prospects for brain repair. Nat Rev Neurol 11:56-64.

**Author contributions:** Manuscript design: APW, YT; manuscript writing and table design: WZ, TT; data collection: SKG, WOM, QYZ; figure production: SKG, WOM, QYZ; manuscript and table revising: WZ, APW, YT. All authors contributed to read and commented on the manuscript.

**Conflicts of interest:** The authors declare no conflicts of interest.

**Financial support:** This work was supported by the National Natural Science Foundation of China, Nos. 31871169 (to YT), 81600040 (to APW); Key Project of Department of Education of Hunan Province, China, No. 18A243 (to APW); Innovation Guidance Project of Hunan Province, China, No. 2018SKS1606 (to SKG); the Natural Science Foundation of Hunan Province of China, No. 2017J3279 (to APW). The funding sources had no role in study conception and design, data analysis or interpretation, paper writing or deciding to submit this paper for publication.

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Penfield W (1932) Cytology & cellular pathology of the nervous system. New York: PB
Meng HL, Li XX, Chen YT, Yu LJ, Zhang H, Lao JM, Zhang X, Xu Y (2016) Neuronal soluble Masuda T, Croom D, Hida H, Kirov SA (2011) Capillary blood flow around microglial Li Q, Liu D, Pan F, Ho CSH, Ho RCM (2019b) Ethanol exposure induces microglia activation Li F, Zhao H, Han Z, Wang R, Tao Z, Fan Z, Zhang S, Li G, Chen Z, Luo Y (2019a) Xuesaitong Lee YY, Park JS, Leem YH, Park JE, Kim DY, Choi YH, Park EM, Kang JL, Kim HS (2019) Latta CH, Sudduth TL, Weekman EM, Brothers HM, Abner EL, Popa GJ, Mendenhall MD, Kuroda E, Hu X, Li P, Guo Y, Wang H, Leak RK, Chen S, Gao Y, Chen J (2012) Microglia/macrophage colocalization of microglia/macrophage phenotype following brain ischemic stroke. Prog Neurobiol 157:247-272.
McGuire C, Hagemeyer N, Martens A, Schroeder A, Wieghofer P, Daems C, Skirving DJ, Scott CL, Hoste E, Gonçalves A, Guilliams M, Lippens S, Libert C, et al. (2020) A20 critically controls microglia activation and inhibits inﬂammatory-dependent neurodegeneration. Nat Commun 9:3038.
Wang, X. Z., Cao Y., Ao G., Xu, Y., Liu, Y., Hu, L., Wu, J., Wang, X., Jin, M., Shen, Z., and Cao, H. (2017) Berberine facilitates angiogenesis against ischemic stroke through modulating histone deacetylase 1-dependent M1 microglial polarization. J Cell Mol Med 21:2295-2308.