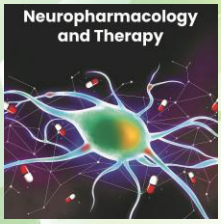

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REVIEW ARTICLE

Brain Pericytes — Crucial Regulators of Neuroinflammation in Ischemic Stroke

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Abstract

Inflammation is a key element in the pathophysiology of ischemic stroke. The current effective treatments for ischemic stroke are almost exclusively based on reperfusion of occluded vessels. An increasing number of studies are attempting to develop better treatment strategies for ischemic stroke by investigating the involvement of neuroinflammation in the pathogenesis. There is a growing focus on the inflammatory response of glial cells within the neurovascular unit (NVU) in ischemic stroke, while pericytes, despite their central position within the NVU and having interactions with all cellular components through direct contact or signaling pathways, have been less studied in terms of the related inflammatory mechanisms. Pericytes regulate blood flow, modulate the entry of peripheral immune cells into the brain parenchyma, and contribute to the integrity of the blood-brain barrier (BBB), which situates pericytes in a unique position to significantly influence NVU function. This article discusses the potential inflammatory mechanisms of pericytes in ischemic stroke from three perspectives: pericytes and innate immunity in the brain; pericytes and infiltration of peripheral inflammatory cells; and pericytes and BBB repair mechanisms. The goal is to better understand the role of pericytes in the pathogenesis of ischemic stroke and to provide new insight for research and treatment.

Keywords: pericytes, ischemic stroke, inflammatory mechanisms, BBB, therapeutic strategy

1. INTRODUCTION

Stroke is the second leading cause of death worldwide. With population growth and aging, the burden of stroke has increased dramatically [1]. Ischemic stroke has a high disability and mortality rate [2,3]. Ischemic stroke, characterized by a sudden interruption of blood flow, leads to ischemia and hypoxia in the damaged brain and failure to maintain normal physiologic functions [4,5]. Inflammation has a significant link to the pathophysiology of ischemic stroke [6], in which cerebral ischemia triggers a severe neuroinflammatory response that leads to blood-brain barrier (BBB) disruption, release of inflammatory factors, and infiltration of peripheral immune cells, further worsening brain injury [7,8]. The effective treatment options for ischemic stroke are limited and are almost entirely based on reperfusion of the occluded vessels [9-11]. However, it is increasingly evident that the impact of vascular reperfusion on stroke outcomes is largely dependent on the functionality of neurovascular unit (NVU) components [12]. In recent years researchers have focused on the NVU to explore potential therapeutic targets and strategies [13-15] (Fig 1). The NVU is composed of neurons, endothelial cells (ECs), pericytes, astrocytes, microglia, and the basement membrane (BM). The biological functions of pericytes are related to cerebral blood flow, BBB permeability, cerebrovascular formation, and neuroinflammation, making pericytes closely related to cerebrovascular diseases [16]. Perivascular macrophages also participate in immune surveillance, waste clearance, and vascular permeability in ischemic stroke [17]. Pericytes, are situated in the center of NVU, have a crucial role in regulating NVU function.

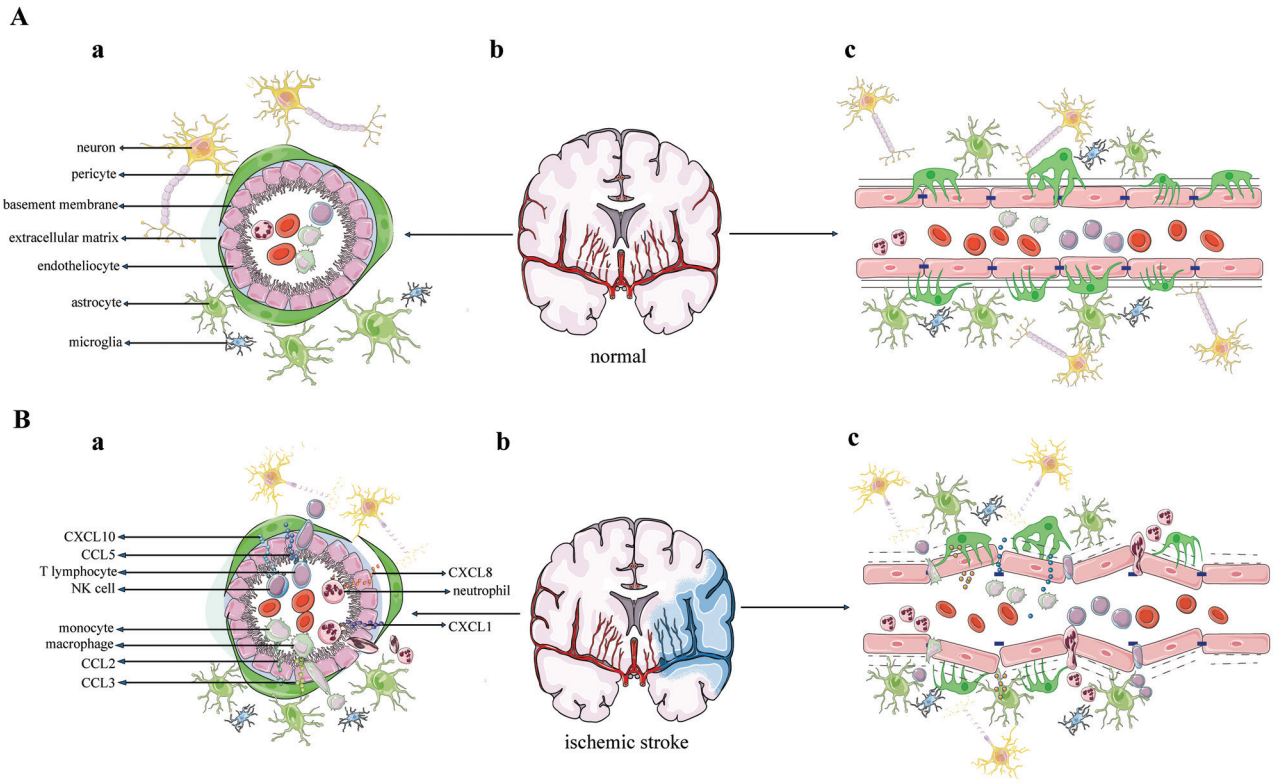

Figure 1 | (A) Normal state: (a) The role of brain pericytes in the neurovascular unit (NVU). The NVU is composed of neurons, endotheliocytes, pericytes, astrocytes, microglia, the basement membrane, and extracellular matrix. (b) Cerebral blood supply in the normal state; (c) Pericytes are involved in maintaining BBB integrity and stability in the normal state. (B) Ischemic stroke: (a) NVU is destroyed and pericytes secrete inflammatory factors to mediate the infiltration of inflammatory cells into the brain parenchyma. Pericytes are shed and neurons are damaged. (b) Cerebral blood supply in ischemic stroke; (c) Pericytes secrete inflammatory factors to mediate the infiltration of inflammatory cells into brain parenchyma. Pericytes are shed, TJs are broken, BBB integrity is destroyed, and neurons are damaged.

Moreover, pericytes play are involved in the occurrence and progression of ischemic stroke [18,19].

A number of studies [18,20-24] have focused on pericyte function in ischemic stroke, attempting to determine the role of pericytes at different stages of ischemic stroke and to develop better methods for treating ischemic stroke. The inflammatory mechanisms in which pericytes are involved may provide a breakthrough for the treatment of ischemic stroke. This article summarizes the immune function of pericytes in ischemic stroke and discusses the inflammatory mechanisms of pericytes in ischemic stroke. We believe that targeting pericytes and their associated inflammatory mechanisms may lead to new perspectives for the research and treatment of ischemic stroke.

2. ORIGINS AND FUNCTIONS OF PERICYTES

The perivascular cell was first named the 'Rouget cell' by Charles-Marie Benjamin Rouget in 1898 and was described as a "contractile element" surrounding the ECs of small blood vessels. In 1923 Zimmermann coined them "pericytes" according to the morphology and location within the vasculature. Pericytes have different origins within the same tissues. Quail-chick chimerization experiments demonstrated that brain pericytes are derived from different progenitor cells. While pericytes in the forebrain are generated from neural crest cells, pericytes in the midbrain, brainstem, spinal cord, and peripheral organs are derived from mesodermal cells [25-28].

Pericytes are situated within capillaries, post-capillary venules, and precapillary arterioles in the brain. The three subtypes of central nervous system (CNS) pericytes can be distinguished based on location, shape, and protein expression. Pericytes located at the arteriolar end of the capillary bed express more α-smooth muscle actin (α-SMA) and undergo more circumferential processes. Pericytes have an essential role in the regulation of blood flow. The pericytes at the center of the capillary beds express less α-SMA. The integrity of the BBB depends on these pericytes. Pericytes at the venule end of capillaries primarily orchestrate peripheral immune cell trafficking into the brain parenchyma [22,29,30] (Fig 2). Armulik showed that pericytes regulate BBB function by controlling BBB-specific gene expression in endothelial cells and polarization of astrocyte end-feet [31]. Pericytes interact with astrocytes in the CNS to maintain functional integrity of the BBB [32]. Pericytes also work together with other components of the NVU (ECs, astrocytes, and neurons) to

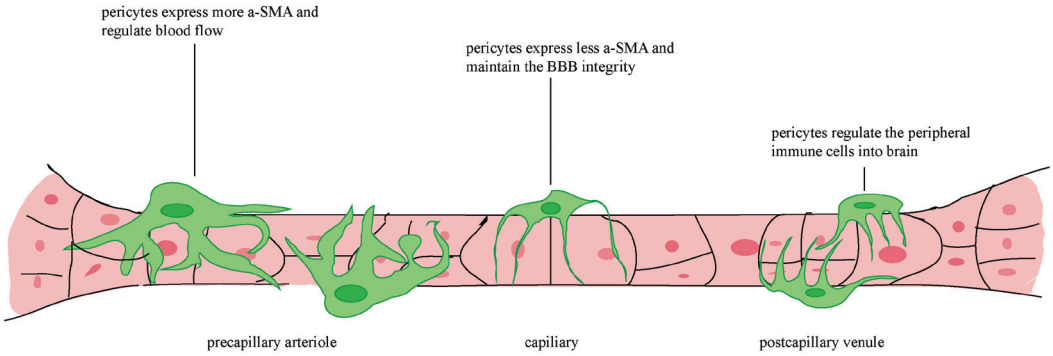

Figure 2 | Topology and morphology of brain pericytes. Pericytes located at the arteriolar end of the capillary bed express more α-smooth muscle actin (α-SMA) and undergo more circumferential processes. Pericytes have an essential role in the regulation of blood flow. Pericytes at the center of the capillary bed express less α-SMA. The integrity of the BBB depends on these pericytes. Pericytes at the venule end of capillaries primarily control the trafficking of peripheral immune cells into the brain parenchyma.

fine-tune adaptations to promote tissue survival [33]. In addition, pericytes respond to and express inflammatory molecules, present antigens, and have phagocytic ability [34]. Pericytes participate in immune responses by secreting cytokines, modulating phagocytosis, and promoting gliocyte activity in response to inflammatory mediators [35]. An increasing body of evidence has identified novel roles of pericytes in the CNS involving neuroinflammation and immune responses that could broaden the therapeutic targets for ischemic stroke.

2.1. Immunologic functions of pericytes

Pericytes participate in immune responses by upregulating cell adhesion molecules, secreting immunoregulatory cytokines (Table 1), phagocytosis, presenting antigens, trafficking immune cells into the brain, and affecting other cells of the NVU during disease pathogenesis [53,54].

Pericytes express several adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), which are involved in leukocyte adhesion and immune cell trafficking across vessel walls [36,37]. Tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) stimulation of human brain pericytes can enhance the expression of ICAM-1 and VCAM-1, leading to a significant increase in T cell adhesion to pericytes [55,56]. Interferon-γ (IFN-γ) upregulates the expression of ICAM-1 and VCAM-1 in pericytes [57]. A large number of clinical trials showed that higher serum ICAM-1 levels upon admission may increase the risk of adverse outcomes in acute ischemic stroke [58] and

Table 1 | Pericytes-derived factors modulate neuroinflammation.

Factors	Mechanisms	References
ICAM-1 and VCAM-1	involved in leukocyte adhesion and immune cell trafficking across vessel walls	[36,37]
IL-6	activate polymorphonuclear leukocyte	[38]
IL-8	promote the migration of neutrophils	[39]
TGF-β	lead to brain damage by activating the Smad2 signaling pathway and promote further maturation of the BBB	[40,41]
IP-10	increase immune cell recruitment and induce neurotoxicity	[42]
MCP-1	promote the infiltration of blood-derived monocytes and lymphocytes into the ischemic area	[43]
MIP-1	enhance microglial activation	[44]
MMPs	promote the shedding of neutrophils attached to pericytes	[39]
MMP-2 and MMP-9	permit pericytes to move away from the BM and into newly created blood vessels and aid in repairing the damaged BBB	[25,45-47]
VEGF	promote angiogenesis and decrease BBB integrity	[48]
Ang 1	enhance occludin expression in CNS ECs and reduce BBB integrity	[49]
G-CSF and GM-CSF	promote the migration of macrophages into the CNS parenchyma	[50]
CXCL10	lead to increased migration of monocytes across the BBB	[51]
CX3CL1	regulate microglia-mediated immune response	[52]
prostaglandins and NO	lead to vasodilation	[37]

early identification could aid in primary prevention of ischemic stroke [59,60]. However, therapeutic inhibition of ICAM-1 with enlimomab in ischemic stroke patients did not improve the pathologic outcomes of the acute phase [61]. Another study involving animals showed that the absence of ICAM-1 did not inhibit neutrophil accumulation in the brain and did not improve the pathologic outcomes of acute phase ischemic stroke after reperfusion [62]. Although ICAM-1 is considered to be a key factor in neutrophil recruitment after ischemic stroke [63], therapeutic inhibition of ICAM-1 has not been successful in clinical practice. This finding possibly reflects the multifactorial and multistep nature of ischemic stroke. Targeting a single factor may not lead to effective treatment, which necessitates a comprehensive understanding of the relevant mechanisms to guide treatment. A prospective study showed that sVCAM-1 levels could predict the prognosis of ischemic stroke early on in patients [64] and the risk of ischemic lesions increases with elevated serum VCAM-1 levels, suggesting that VCAM-1 may serve as a biomarker for acute ischemic stroke [65].

Studies have shown that pericytes secrete numerous proinflammatory factors, such as monocyte chemoattractant protein-1 (MCP-1), IL-6, IL-8, and four chemokine subfamilies (β-chemokine [CXC], α-chemokine [CC], δ-chemokine [CX3C], and γ-chemokine [XC]), in response to inflammation in human pericyte cultures, which can attract circulating leukocytes to the brain and promote neovascularization [34,37,66,67]. Pericytes express pro-inflammatory cytokines, such as IL-1β and TNF-α, which can induce a pro-inflammatory state in astrocytes, microglia, and endothelial cells, and aid in leukocyte recruitment [50]. Post-stroke inflammation is characterized by increased levels of inflammatory mediators, including interleukin-6 (IL-6) [68], which is positively correlated with stroke recurrence and adverse clinical outcomes [69,70], Elevated IL-6 levels in the acute phase of stroke are associated with larger stroke volumes and poor prognosis after one year [71]. Elevated IL-8 may be involved in the pathophysiologic process of stroke by activating polymorphonuclear leukocytes (PMNLs) early after ischemia [38]. IL-8 may participate in infarct evolution and disease progression in ischemic stroke patients through neutrophil-mediated inflammatory responses and serum IL-8 levels may serve as a prognostic indicator for ischemic stroke [72]. Cultured pericytes express two chemokines (interferon gamma-induced protein 10 [IP-10] and MCP-1), which can increase immune cell recruitment and induce neurotoxicity [42]. Numerous studies using animal models of stroke have shown that MCP-1 participates in the inflammatory process by promoting the infiltration of blood-derived monocytes and lymphocytes into the ischemic area [43]. A study that compared 23 ischemic stroke patients with 15 tension headache patients (controls) showed that MCP-1 has a role in the early inflammatory response of ischemic stroke by inducing monocyte/macrophage infiltration [73]. Chemokine-chemokine ligand 2 (CCL2), which belongs to the CC subfamily, is the chemokine that most often causes neovascularization. Duan et al. reported that CCL2 regulates neuronal activity and recruits immune cells from the brain periphery [74,75]. Research involving a rat model of middle cerebral artery occlusion/reperfusion (MCAO/R) showed that CCL2 expression was elevated with significant neurologic damage and ischemic infarction in brain tissue. Inhibitors of CCL2 significantly suppress the inflammatory response, alleviate nerve damage, and reduce the area of ischemic infarction in MCAO/R rats [76]. Analysis of plasma IL-8 expression and peripheral blood leukocyte expression of CXC chemokine receptor 2 (CXCR2) in ischemic stroke patients indicated that CXCR2 expression was positively correlated with granulocytes and natural killer (NK) cells, which in turn were recruited by IL-8 [72]. Niu et al. demonstrated that the release of CXCL10 from brain pericytes was critical for the transmigration of monocytes across the brain endothelium in cocaine-exposed mice [51]. TNF-α stimulates the release of MIP-1 and IL-6 from pericytes and can enhance microglial activation [44]. Under TNF-α, IL-1β, or IFN-γ induced stimulation, pericytes generate inflammatory prostaglandins and nitric oxide (NO) by upregulating cyclooxygenase-2 (COX-2), which leads to vasodilation [37].

In addition to the expression of inflammatory mediators, pericytes enriched in culture and isolated microvessels express several macrophage markers, including ED-2 and the integrin subunit, CD11b (αM) [77]. Pericytes also express macrophage-like characteristics upon stimulation by inflammatory factors. Studies have shown that the phagocytosis rate of primary porcine brain capillary pericytes (PBCPs) increase when stimulated by TNF-α and IFN-γ. Following INF-γ activation, expression of major histocompatibility complex II (MHC II) and cluster of differentiation 68 (CD68) mRNA in PBCPs increases. CD68 is a typical marker of macrophages [78]. Studies have shown that BBB-associated pericytes clear amyloid-β (Aβ) aggregation via a low-density lipoprotein receptor-related protein-1 (LRP1)/apolipoprotein E (apoE) isoform-specific mechanism [79]. Cultured pericytes phagocytose small molecules, such as fluorescent latex. By suppressing the expression of the scavenging receptors (CD36, CD47, and CD68) the inflammatory factor (TGF-1) reduces the phagocytic action of pericytes and inhibits microglia-mediated immune response by decreasing the expression of CX3CL1 in pericytes [52]. Using flow cytometry analysis, Nirwan et al. reported that α-SMA$^{low/undetectable}$ pericytes transform towards microglia and macrophages on day 7 following a stroke [80]. Pericytes can acquire a microglial phenotype to phagocytose cellular debris and participate in post-stroke inflammation and immunity [81]. Pericytes exhibit weaker phagocytosis than microglia, which has a key role in the clearance of pathogenic substances from the brain parenchyma [52].

3. POSSIBLE MECHANISMS BY WHICH BRAIN PERICYTES REGULATE NEUROINFLAMMATION IN ISCHEMIC STROKE

Inflammation is a key element of the pathophysiology of ischemic stroke [6,82-84]. In this section, we will discuss the possible mechanisms by which pericytes are involved in neuroinflammation in ischemic stroke (Fig 3).

3.1. Pericytes and innate immunity in the brain

Pattern recognition receptors (PRRs), which are key regulators of innate immunity against pathogens [85], are the first responders to CNS injury and are responsible for detecting microorganisms and endogenous substances generated during microbial and cellular damage. PRRs can be classified into pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [86]. Among the five PRR families, toll-like receptors (TLRs) and nucleotide-binding oligomerization-like receptors (NLRs) have been the most studied [87] (Table 2).

TLRs and NLRs are involved in coordinating innate immunity after an ischemic stroke. Activation of innate immunity in the brain leads to an increase in leukocyte infiltration and exacerbation of tissue damage by producing more DAMPs and laying the foundation for adaptive immunity [84]. By expressing functional PRRs, secreting cytokines, chemokines, and adhesion molecules, and activating the complement system, pericytes participate in regulating innate immunity in the ischemic brain. Because the brain is a sterile organ, endogenous DAMP molecules must be released from the necrotic brain to activate the infiltrating immune cells. High mobility group box 1 (HMGB1) is an essential DAMP in the hyperacute phase of ischemic brain injury that can increase the permeability of the vasculature and aggravate the destruction of the BBB during ischemia-reperfusion injury for 2–4 hours [95].

TLRs are expressed on a wide range of cells, including immune cells, ECs, pericytes, astrocytes, neurons, and gliacytes, which are all part of the NVU [96]. Among the 10 known human TLRs, pericytes express TLR2, TLR4, TLR5, TLR6, and TLR10 [97]. TLR2 and TLR4 are more important than other TLRs in the pathologic progression of cerebral ischemia-reperfusion and are involved in the expansion of cerebral infarction and exacerbation of ischemic brain injury [88]. Studies have shown that inhibiting the expression of TLR2/4 in the ischemic hemisphere can reduce the expression of MyD88, NF-kappaB, IL-1β, and IL-6 in the inflammatory pathway, as well as reduce the expression and activity of inducible nitric oxide synthase (iNOS) and COX-2, thereby alleviating the inflammatory response and reducing brain edema and the ischemic area

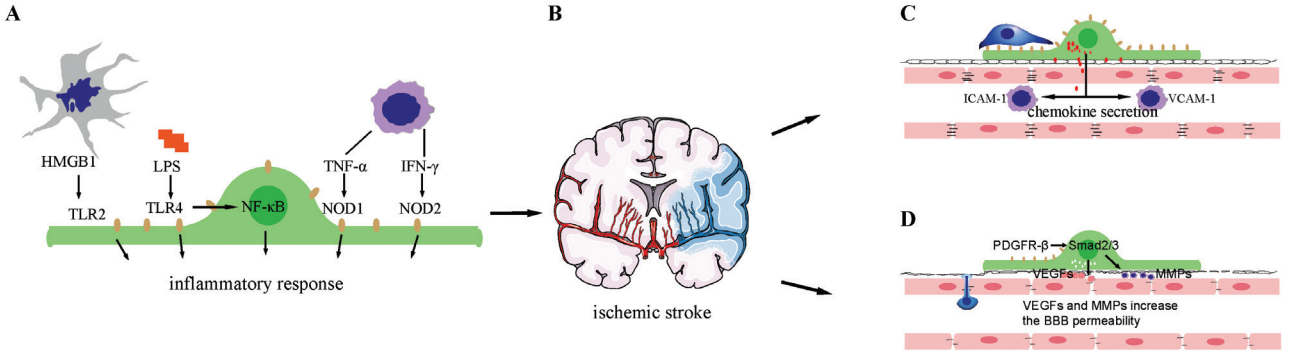

Figure 3 | Possible mechanisms by which brain pericytes regulate neuroinflammation in ischemic stroke. (A) Pericytes express TLRs and NLRs. HMGB1 and LPS stimulate the expression of TLR2 and TLR4 in pericytes. Inflammatory mediators stimulate the expression of NOD1 and NOD2. (B) Ischemic stroke has occurred. (C) Chemokine secretion by pericytes acts to recruit circulating leukocytes to the CNS. ICAM-1 and VCAM-1 guidance aids leukocytes in crawling to gaps in the pericyte coverage, allowing entrance to the brain parenchyma. (D) After cerebral ischemia, PDGFR-β is highly expressed in pericytes, which activates the Smad2/3 pathway and secretes more permeability factors, including VEGFs and MMPs. VEGF secretion and MMP expression promotes breakdown of the BBB.

Table 2 | Pericytes express receptors regulating neuroinflammation.

Receptors	Mechanisms	References
ED-2 and CD11b (αM)	express macrophage-like characteristics	[77]
low/undetectable SMA	transform towards both microglia and macrophages	[80]
TLRs	involved in the expansion of cerebral infarction and exacerbation of ischemic brain injury	[88-90]
NLRs	promote inflammation, accelerate neuronal apoptosis, and worsens neuronal functional damage	[91-93]
PDGFR-β	promote the secretion of TGF-β from brain pericytes and participate in maintaining the function and integrity of the BBB	[94]

in ischemia/reperfusion (I/R) rats [89,90]. Compared to the sham operation group, I/R can upregulate the expression of TLR2 and inhibition of TLR2 can inhibit the expression of IL-1β, TNF-α, IL-17, and IL-23, thereby reducing inflammation and ischemia reperfusion injury [98]. In a transient focal cerebral ischemia model, the infarct volume in TLR2-deficient mice was significantly smaller than wild-type mice [99]. These studies indicate that upregulation of TLR2 and the TLR2 signaling cascade are important events in focal cerebral ischemia, triggering inflammatory cascades and exacerbating brain damage.

Guijarro-Muñoz et al. showed that pericytes express TLR4 and secrete a variety of chemokines, cytokines, and cellular adhesion molecules once bound to the TLR4 ligand, HMGB1, and lipopolysaccharide (LPS). LPS stimulates the production of IL-6, IL-8, and CXC ligands (CXCL1, CXCL2, CXCL3, CCL2, SELE, ICAM-1 and VCAM-1) via activation of the nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) signaling pathway. HMGB1 stimulates the secretion of CXCL1, CXCL2, CXCL3, IL-8, and CCL2. In addition, HMGB1 and other DAMPs stimulate TLR2 and TLR4 expression in pericytes [100]. The TLR4 agonist, LPS, increases the volume of cerebral infarction and degree of cerebral edema, and aggravates the inflammatory response in MCAO rats [101]. Recent studies have shown that by inhibiting the HMGB1-mediated TLR4/NF-kB pathway and reducing the activation of caspase-3, cell apoptosis can be prevented, thereby reducing I/R-induced brain injury [102,103]. Another study showed that HMGB1-mediated inhibition of TLR4/MyD88/TNF receptor-associated factor 6 (TRAF6) expression reduced neuronal cell damage and the inflammatory response [104]. Studies have shown that a TLR2 or TLR4 deficiency significantly alleviates ischemic brain injury on day 1 after ischemia-reperfusion in mice and inhibits inflammatory cytokine expression in infiltrated immune cells [105]. Therefore, pericytes can be considered as participants in the ischemic stroke inflammatory cascade [100]. Inhibiting the TLR4 signaling pathway may be a potential neuroprotective treatment strategy by providing potential targets for the treatment of brain I/R injury. Most studies have focused on the role of TLR expression on microglia and TLR-related signaling pathways in I/R. Pericytes, as an important member of the NVU, also express TLR receptors and may co-participate in the ischemic stroke inflammatory response with microglia, which has broadened our thinking for further exploring the inflammatory mechanisms related to ischemic stroke.

Pericytes express TLRs and NLRs. NLRs are cytosolic receptors that sense microbial motifs, endogenous byproducts of tissue injury, and environmental signals, which are important for maintaining tissue and immune homeostasis. When dysregulated, NLRs can lead to inflammatory diseases [91]. NOD1 and NOD2 are two important NLRs that recognize distinct fragments of peptidoglycans (PGNs). PGNs are components of the gram-positive bacteria cell wall [92]. Baseline levels of innate immune receptor (NOD1, NOD2, NLRC5, NLRP1-3, NLRP5, NLRP9, NLRP10, and NLRX) mRNA expression were detected in untreated pericytes. NOD1 is upregulated by 1.5–2-fold in TNF-α- or IFN-α-stimulated pericytes. Similarly, inflammatory cytokines in pericytes stimulate NOD2 expression [97]. However, Navarro et al. reported that NOD1 is expressed in pericytes and TNF-α and IFN-γ upregulate the expression of NOD1 in human brain pericytes, while NOD2 expression is essentially undetectable. The NOD1 agonist, C12-iE-DAP, induces pericytes to express genes encoding IL-6 and IL-8, and releases cytokines into the culture supernatant [93]. NOD1 and TLR4 induce proinflammatory responses synergistically through different signaling pathways [93]. Analysis of I/R rat and H/R cell models has shown that the levels of NLRP3, TLR4, LC3, TNF-α, IL-1, IL-6, and IL-18 expression are significantly increased in I/R-induced rats or H/R-induced cells, and knocking down TLR4 significantly inhibits expression, thereby suppressing cell apoptosis. These data suggest that upregulation of TLR4 induces cerebral ischemia/reperfusion (CI/R) injury through stimulation of the NLRP3 inflammasome and autophagy [106]. Another study using the MCAO mouse model showed that inhibiting the TLR4/NF-kB signaling pathway in microglial cells suppresses activation of the NLRP3 inflammasome [107]. He et al. reported that inhibiting the TLR4/NLRP3 signaling pathway suppresses the inflammatory response induced by CI/R [108]. Similarly, inhibiting the TLR4-p38-NF-kappaB-NLRP3 signaling pathway reduces neuronal apoptosis, alleviates neurologic deficits, reduces brain edema, and decreases the cerebral infarction size in MCAO/R rats [109].

Brain pericytes express TLRs and NLRs. TLRs and NLRs produce more DAMPs during ischemic stroke, which activates TLR2/4 and NOD1/2 and other downstream inflammatory pathways, promotes inflammation, accelerates neuronal apoptosis, worsens neuronal functional damage, promotes brain edema, and expands the infarct area. In theory, by targeting TLR2/4 inhibition, NOD1/2 on pericytes may provide new therapeutic targets for the treatment of ischemic stroke.

3.2. Pericytes and peripheral inflammatory cell infiltration

Neuroinflammation is an important factor in stroke occurrence and development. Peripheral inflammatory cell infiltration persists in ischemic tissue after acute ischemia, which triggers neuroinflammation [110], induces brain tissue injury, and leads to an increase in neurodegeneration in the peri-infarction area [111]. During homeostasis and autoimmune neuroinflammation, pericytes limit leukocyte infiltration into the CNS [36]. Studies have increasingly highlighted the significance of pericytes as sensors and regulators of neuroinflammation. If pericytes are absent, the NVU allows leukocytes to enter the CNS, which leads to increased neuroinflammation. Pericytes may have a unique role in immune infiltration because pericytes can "instruct" immune cell extravasation, assist leukocyte

crawling through blood vessels by providing adhesion substrates, and alter pericyte morphology to promote neutrophil extravasation [112]. Pericytes secrete various adhesion molecules and chemokines/cytokines that contribute to the recruitment and migration of monocytes, T cells, eosinophils, and neutrophils [34,78,100]. Pericytes can induce the expression of key adhesion molecules (ICAM-1 and VCAM-1), chemokines (CXCL1, CXCL8, CXCL10, MIF, CCL2, CCL3, and CCL5), and pro-inflammatory molecular receptors (TNFRI, TNFRII, IL-1R, TLRs, and NOD-like receptors) [113]. The neutrophil surface receptors, CXCR1 and CXCR2, interact with chemokines (CXCL8 and CXCL1) [114]. Monocyte surface CCR2 is bound by CCL2. CXCR3, which is a highly expressed cell surface receptor on Th1, CD8, and NK cells, is bound by CXCL10. CCL3 and CCL5 bind to monocytes, macrophages, Th1, CD8, and NK cell receptors (CCR1 and CCR5) to regulate immune cell migration [37,115].

Pericytes provide an adhesive substrate for neutrophils crawling on the venous wall. This response is mediated by the interaction of ICAM-1 expressed by pericytes with the macrophage-1 antigen (Mac-1) and lymphocyte function-associated antigen-1 (LFA-1) on neutrophils. In addition, other mechanisms that promote leukocyte migration include "thinning" of the BM, which may be caused by changes in pericyte shape or different traction forces exerted on the BM by other physical and enzymatic processes [113]. Studies involving pericyte-deficient adult mice have shown that pericyte deficiency leads to increased expression of leukocyte adhesion molecules (LAMs) in the brain vascular system of adult mice, which results in leukocyte extravasation into the brain (primarily monocytes, dendritic cells, and T lymphocytes). However, the increase in infiltrating leukocyte subpopulations in the brain is not due to an increase in the number of blood or peripheral organ leukocytes. The regional differences in pericyte coverage of capillaries in the CNS determine the extent to which leukocytes are allowed to enter the CNS under steady-state conditions [36]. Under stimulation by LPS, TNF-α, and IL-1β, pericytes respond to inflammatory signals by secreting IL-8, thereby promoting the migration of neutrophils [39]. Stimulation by the inflammatory cytokines, IL-1β and IFN-γ, induce pericytes to secrete granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-5, and IL-6, which promotes the migration of macrophages into the CNS parenchyma [50]. Exposure of human brain vascular pericytes to cocaine promotes secretion of more CXCL10 by pericytes, leading to increased migration of monocytes across the BBB [51]. Moreover, migration of monocytes in a BBB model consisting of human brain endothelial cells and pericytes was significantly reduced compared to a BBB model consisting of brain ECs alone. Additionally, the inflammatory cytokines, TNF-α and IL-1β, enhance the expression of adhesion molecules in pericytes and increase the adhesion of monocytes to pericytes [116]. Matrix metalloproteinases (MMPs), which are secreted not only by endothelial cells but also by pericytes, have a key role as regulators of adhesion between neutrophils and pericytes during neutrophil migration. Under the stimulation of TNF-α, IL-1β, or LPS, MMP-9 promotes the shedding of neutrophils attached to pericytes, while inhibition of MMP-9 enhances the adhesion of neutrophils to pericytes [39].

LPS promote the expression of ICAM-1 and VCAM-1 in human brain pericytes, which promotes adhesion of peripheral lymphocytes to pericytes [100]. Years ago it was suggested that the VCAM-1/VLA-4 interaction mediates T cell infiltration into the CNS [117]. Stimulation of pericytes with IL-1β increases the expression of VCAM-1 [112]. Upon stimulation by inflammatory mediators, NG2(+) pericytes upregulate the expression of ICAM-1 and release chemoattractant migration inhibitory factor (MIF), which is involved in extravasation of neutrophils and macrophages [118]. In pericyte cultures, infection with Japanese encephalitis virus activates pericytes, increases the secretion of IL-6 and prostaglandin E2 (PGE2), initiates and amplifies inflammatory factor expression, regulates EC and leukocyte function, and facilitates leukocyte infiltration into the CNS [85]. In contrast, the transcription factor, CCAAT/enhancer binding protein δ (C/EBp-δ), in human brain pericytes has an anti-inflammatory role that limits infiltration of peripheral immune cells and prevents further inflammatory responses in the brain [119]. TGF-β1 induces pericyte inflammatory gene expression and limits the infiltration of peripheral immune cells into the CNS by decreasing the expression of VCAM-1 and MCP-1 [52].

Neuroinflammation drives fibrotic scar formation, which is a major obstacle to CNS regeneration [120]. Pericytes are considered the main source of fibroblasts that form scars [121]. Pericytes have been identified as the main cell type forming glial scars in spinal cord injury models [122]. Pericytes proliferate and migrate to the damaged area to participate in scar formation [123]. Reducing pericyte proliferation significantly improves the long-term prognosis of spinal cord injury [124]. Platelet-derived growth factor receptor-β (PDGFRβ$^+$) pericytes have been shown to trigger a fibrotic response in the CNS during ischemic injury, with PDGFRβ$^{+/-}$ mice showing reduced fibrosis, decreased fibronectin deposition in the ischemic area, and increased infarct volume. This finding indicates that PDGFRβ signaling-induced fibronectin production is essential for the ischemic stroke repair process [125]. In experimental and human stroke there is a significant proliferation of the PDGFRβ$^+$ stromal cell population and fibrotic scars with PDGFRβ$^+$ cells constitute tissue remodeling after stroke [126]. Pericytes and perivascular fibroblasts have been shown to promote fibrotic scar formation in a region-dependent manner in mice after traumatic injury [127].

Due to the specific distribution of pericytes in the NVU, complete pericyte coverage in ischemic stroke can limit leukocyte infiltration into the CNS, which protects the brain from inflammatory cell attack. In contrast, pericytes

secrete various adhesion molecules, chemokines, and inflammatory cytokines in ischemic stroke, which promotes leukocyte infiltration and exacerbates brain injury. Finding a balance between these two outcomes is essential to minimize the secretion of adhesion molecules, chemokines, and inflammatory cytokines while maintaining pericyte coverage as much as possible. Additionally, the significance of fibrotic scarring in ischemic injury repair should also be considered and may become a new direction for the treatment of ischemic stroke.

3.3. Pericytes and BBB repair mechanisms

The BBB, which consists of cerebral microvascular ECs, pericytes, astrocytes, and neurons, establishes a protective interface between the CNS and peripheral blood circulation and is essential for CNS homeostasis. The brain is an immunoprivileged site due to the BBB physical defense function [128]. However, harmful substances, peripheral antigens, and peripheral immune cells can invade the brain parenchyma through a damaged BBB, leading to the activation and exacerbation of neuroinflammatory cascades after an ischemic stroke [129]. In fact, BBB breakdown is a key determinant of infarct volume enlargement after acute cerebral ischemia [130].

Pericytes secrete angiopoietin-1 (Ang1), TGF-β, endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF) to regulate the BBB. Loss of pericytes results in the breakdown of EC tight junctions (TJs), which can lead to BBB damage [67,131]. Studies have shown that TGF-β and Ang-1 secreted by pericytes enhance occludin expression in CNS ECs and reduce BBB integrity [49]. BBB dysfunction leads to brain damage via the secretion of TGF-β by pericytes, which activates the Smad2 signaling pathway [40]. Lei et al. demonstrated that bone morphogenic protein 3 (bmp3) regulates BBB integrity in zebrafish embryos by promoting pericyte coverage, which likely involves the TGF-β/BMP signaling pathway [132]. However, other studies have shown that pericyte coverage does not affect BBB permeability. The BBB has low permeability due to the significant loss of pericytes in specific brain regions, which may be caused by changes in transcytosis across brain ECs [133].

Following cerebral ischemia, pericytes highly express PDGFR-β, which in turn promotes the secretion of TGF-β from brain pericytes, activates the Smad2/3 pathway, and participates in maintaining the function and integrity of the BBB [94]. TGF-β induces pericyte differentiation into the α-SMA-positive phenotype and secretes more permeability factors, including VEGF, MMP-2, and MMP-9, which promote angiogenesis and decrease BBB integrity, while basic fibroblast growth factor (bFGF) induces pericyte differentiation into the α-SMA-negative phenotype that stabilizes the BBB [48]. However, it has also been shown that pericytes expressing CD146 promote further maturation of the BBB by secreting TGF-β1 [41]. MMP-2 (gelatinase A) and MMP-9 (gelatinase B) have been widely confirmed to contribute to BBB damage in stroke and MMP-dependent BBB destruction is caused by degradation of the basal lamina and tight junction proteins (TJPs) by active MMPs [7]. After brain injury and under inflammatory conditions, MMP-2 and MMP-9 are secreted by pericytes, which may aid in the breakdown of the extracellular matrix (ECM) [25,45] and permit pericytes to move away from the BM and into newly created blood vessels. This process is helpful in repairing the damaged BBB after ischemic stroke [46,47]. Administration of MMP inhibitors after cerebral ischemia reduces BBB opening and stroke injury [134]. During vascular stabilization, pericytes express MMP inhibitors, such as tissue inhibitors of MMP-3, which inhibits ECM degradation and promotes vascular maturation and BBB repair [25]. Oxidative stress causes pericytes to release MMP-9 during the acute stage of ischemic stroke. Activated MMP-9 then causes pericyte injury, shedding, and migration, exacerbating BBB destruction [130]. In a mouse model of ischemic stroke, MMP-9 knockout reduces the degradation of TJPs, thereby alleviating BBB damage [135].

Upregulation of PDGFR-β has an important role in BBB repair during ischemic stroke with the possible involvement of pericytes. PDGFR-β acting on MCAO mice helps regulate pericyte recruitment, which promotes BBB repair and maintenance [136]. After transient middle cerebral artery occlusion (tMCAO), PDGFR-β (+/-) mice with a pericyte deficiency have a significantly increased brain infarct volume and brain edema compared to wild-type mice with exacerbation of BBB disruption and an increase in the number of degenerating neurons [137]. Additionally, inflammatory factors are involved in the processes in which brain pericytes regulate the BBB. Inflammatory factors (IL-1β, TNF-1α, and IL-6), LPS, and reactive oxygen species (ROS) stimulate pericytes, which lead to morphologic changes and induce separation from the basal lamina, thereby increasing BBB permeability [138,139]. In response to α-synuclein, pericytes release inflammatory factors, including IL-1β, IL-6, MCP-1, TNF-β, and MMP-9, which leads to BBB dysfunction in endothelial cell and pericyte co-cultures [140]. Pericytes control blood flow within capillaries, maintain the basal lamina, and regulate BBB permeability. In mouse models lacking functional pericytes, blood vessel control is lost and tight junction regulation is disrupted, highlighting the important role of pericytes in maintaining BBB integrity [49]. Yao et al. showed that binding of astrocyte laminin to integrin α2 receptors maintains BBB integrity by regulating pericyte differentiation and prevents pericyte differentiation from the quiescent to the systolic phase [141].

Brain pericytes interact with ECs to regulate BBB formation, angiogenesis, and vascular function [142]. PDGFRβ is mainly expressed on brain pericytes [143,144] and PDGF-BB released by ECs activate PDGFRβ, which promotes recruitment of pericytes to newly formed vessels [143,145,146]. Surrounding ECs can produce more PDGF-BB to activate PDGFR-β in ischemia, which induces Akt phosphorylation in pericytes and leads to anti-apoptotic responses and

cell proliferation [23]. In contrast, PDGF-BB/PDGFR-β signaling is crucial for brain microcirculation and BBB development [144]. PDGFRβ expression is significantly increased on pericytes after 48 h of MCAO [147]. OGD and brain ischemia upregulate PDGFR-β expression [94]. Inactivation of the PDGF-BB/PDGFRβ signaling pathway leads to pericyte deficiency and reduced microvasculature [143]. Mice lacking PDGFβR or the PDGFβR ligand, PDGFβ, lack brain pericytes, ultimately resulting in embryonic or perinatal lethality, CNS microbleeds, and increased vascular permeability [148]. PDGFR-β signaling has a protective role in recovery of BBB function and integrity after brain ischemia [94]. Pericyte-secreted angiopoietin 1 (Ang-1) activates the Ang-1 receptor (Tie-2) on ECs to mediate formation of TJs [149]. Pericyte-derived Ang-1 binds to Tie2 on ECs, which stimulates pericyte coverage and BCM protein deposition, thereby reducing vascular permeability [150]. Ang-1-driven Tie2 phosphorylation mediates activation of downstream pathways involved in survival, proliferation, migration, and anti-inflammatory signals [151]. Expression of Ang-1 and Tie2 in pericytes increases with hypoxia-induced VEGF elevation, which stimulates Akt1 levels and acts on VEGF [152]. Therefore, regulation of Ang/Tie2 signaling is crucial for maintaining post-stroke neovascularization and BBB stability.

Numerous studies have shown that pericyte coverage affects BBB integrity, while some studies have found that pericyte coverage does not affect BBB integrity. This discrepancy may be related to the different locations of pericytes in the capillary bed because pericytes expressing less α-SMA in the middle of the capillary bed are involved in maintaining BBB integrity. The maintenance of BBB integrity by pericytes also depends on the differentiation stage of pericytes, with pericytes at different differentiation stages having different effects on the BBB. Resting pericytes are involved in maintaining BBB integrity, which provides new insight for ischemic stroke treatment strategies. Knocking out the MMP-9 gene alleviates pericyte damage, reduces the degradation of TJPs, and prevents BBB damage during the acute phase of an ischemic stroke. Inhibiting MMP-9 expression in the acute phase of an ischemic stroke may be a good ischemic stroke treatment strategy. The interaction between pericytes and ECs on the BBB should be recognized. Targeting the PDGF-BB/PDGFRβ and Ang/Tie2 signaling pathways may provide new insight for ischemic stroke.

4. PERICYTES AS A THERAPEUTIC TARGET FOR ISCHEMIC STROKE

Pericytes are involved in the maintenance of cerebral vascular function and have an important role in the pathophysiologic process of ischemic stroke. Therapeutic methods targeting pericytes in ischemic stroke, such as repairing the BBB and reducing immune inflammation, may facilitate the treatment of ischemic stroke. The treatment methods targeting pericytes in ischemic stroke are summarized in Table 3, with an attempt to find new breakthroughs in the treatment of ischemic stroke.

Yang et al. found that atorvastatin promotes angiogenesis around infarction sites, stabilizes neovascularization, and maintains BBB integrity by promoting endothelial TJP formation. Proliferating perivascular pericytes expressing neural-glial antigen 2 (NG2) mediates the effect of atorvastatin in BBB maturation by regulating endothelial

Table 3 | Pericytes related mechanisms in the treatment of ischemic stroke.

Medicine/therapy/target	Mechanisms	References
Atorvastatin	pericytes promote BBB maturation by regulating the formation of endothelial TJPs	[153]
RGS5	activated pericytes express RGS5, loss of RGS5 in pericytes contributes to an increase in the number of pericytes, maintains the integrity of TJs in ECs, and significantly reduces BBB damage	[81,154]
HIF-1	inhibiting HIF-1 activation of pericytes can reduce pericyte death and maintain BBB integrity	[155]
Perlecan	pericyte recruitment through the synergistic activity of PDGFR-β and integrin α5β1 to promote BBB maintenance and repair	[136]
SGLT2	inhibit SGLT2 increases the number of mitochondria, pericyte ischemic tolerance, and contribute to the treatment of ischemic brain injury	[156]
Itakalim	inhibit formation of the SUR2/EPAC1 complex can inhibit pericyte contraction, reduce the number of obstructed capillaries, and improve cerebral microcirculation	[157]
Imatinib	selective blocking the PDGFRβ signaling pathway can suppress pericyte-fibroblast transformation, alter pericyte microvascular coverage, reduce inflammation, and decrease microvascular leakage	[158]
VEGF-B	encourage the communication between pericytes and ECs, reduce neuronal injury and inflammation, and stimulate the formation of stable cerebral microvessels in the injured area	[159]
Intravenous injection hPSC-CNC PCs	alleviate cerebral edema and neuronal apoptosis, reduce infarct size, restore the integrity of the BBB, and promote the recovery of neurologic function	[160]
ADPs transplantation	promote neurovascular remodeling	[161]

TJP formation [153]. Regulator of G-protein signaling-5 (RGS5) is expressed on activated pericytes during the ischemic response. RGS5 is an important regulator of pericyte detachment and is involved in the transformation of pericytes from a vascular to a parenchymal phenotype. Loss of RGS5 in pericytes during the acute stage of stroke contributes to an increase in the number of pericytes, maintains the integrity of TJs in ECs, and significantly reduces BBB damage. Thus, RGS5 may be a novel therapeutic target of ischemic stroke [81,154]. Inhibiting hypoxia-inducible factor-1 (HIF-1) can maintain vascular coverage and suppress vascular remodeling to maintain barrier integrity by reducing pericyte death. Itakalim, which targets K-ATP channels, is a promising treatment for improving the microvascular status after ischemic stroke by inhibiting pericyte contraction [155]. Perlecan regulates pericyte recruitment via the synergistic activity of PDGFR-β and integrin α5β1 to promote BBB maintenance and repair after ischemic stroke [136].

Antidiabetic sodium-glucose cotransporter 2 (SGLT2) has received attention for cardiorenal protective properties and glucose-lowering effect. Recent studies have shown that SGLT2 is mainly expressed in brain pericytes and the SGLT2 inhibitor, luseogliflozin, activates AMP-activated protein kinase α and increases mitochondrial transcription factor A expression and the number of mitochondria. Inhibition of SGLT2 before stroke increases pericyte ischemic tolerance and contributes to the treatment of ischemic brain injury [156]. Itakalim promotes opening of the K-ATP channel by inhibiting formation of the SUR2/EPAC1 complex, calcium influx, and ET-1 release, thereby promoting the recovery of cerebral blood flow after cerebral ischemia-reperfusion, preventing pericyte shrinkage, reducing the number of obstructive capillaries, and improving cerebral microcirculation. Itakalin, which targets K-ATP channels, could be an effective therapy for ischemic stroke because itakalin inhibits pericyte contraction and improves microvascular disorders after ischemic stroke [157]. Additionally, imatinib targets pericytes to alleviate neuroinflammation. Studies have shown that imatinib, by selectively blocking the PDGFRβ signaling pathway, inhibits the survival and proliferation of PDGFRβ-positive cells, suppresses pericyte-fibroblast transformation, alters pericyte microvascular coverage, reduces inflammation, and decreases microvascular leakage [158]. Jean LeBlanc et al. concluded that delaying the intranasal administration of VEGF-B in MCAO model mice significantly encourages the communication between pericytes and ECs, reduces neuronal injury and inflammation, increases the number of cerebral microvessels in ischemic tissue, and stimulates the formation of stable cerebral microvessels in the injured area. Thus, VEGF-B-mediated angiogenesis is a promising and safe treatment option for ischemic stroke [159].

The intravenous injection of human pluripotent stem cell-cranial neural crest-derived pericyte-like cells (hPSC-CNC PCs) in mice with transient tMCAO alleviates cerebral edema and neuronal apoptosis, reduces infarct size, restores the integrity of the BBB, and promotes the recovery of neurologic function in mouse models of ischemic stroke [160]. Adipose-derived pericyte (ADP) transplantation significantly improves neurologic status and promotes neurovascular remodeling in rats following ischemic stroke [161]. Pericyte transplantation provides new insight into cell therapy in patients with ischemic stroke.

Although our understanding of pericytes and related mechanisms in ischemic stroke has improved, there are still many key issues to be addressed. Most of the treatment strategies for pericytes are based on animal studies and further research is needed to investigate the safety, dosage, and administration routes for ischemic stroke. A better understanding of pericytes will contribute to the exploration of ischemic stroke treatment.

5. CONCLUSION

In recent years, with increasing attention to the NVU, the focus of ischemic stroke research has gradually shifted from neuroprotection to the interaction of various components of the NVU. Pericytes participate in innate immunity within the brain, mediate inflammatory cell infiltration and fibrotic scar formation, and are involved in BBB disruption and repair after ischemic stroke. Additionally, pericytes contribute to stabilizing the BBB by releasing neurotrophic factors and promoting angiogenesis. Therefore, pericytes are promising therapeutic targets for ischemic stroke.

Herein we discussed the potential inflammatory mechanisms of pericytes in ischemic stroke to explore treatment strategies for ischemic stroke. Targeting the inhibition of TLR2/4 and NOD1/2 expression on pericytes could significantly reduce the post-stroke inflammatory response, at least in theory, which can provide new therapeutic targets for ischemic stroke. If it is possible to reduce the secretion of adhesion molecules, chemokines, and inflammatory factors of pericytes while maintaining pericytes coverage as much as possible to alleviate the inflammatory response and reduce brain damage, new directions may emerge for the treatment of ischemic stroke. At the same time it is also necessary to conduct in-depth research on the impact of pericytes at different locations and stages of differentiation on the BBB and to inhibit the differentiation of pericytes from the resting phase to the contracting phase as much as possible to maintain the integrity of the BBB. Additional clinical studies are needed to validate the effectiveness and safety of treatment strategies targeting MMP-9 in the treatment of ischemic stroke.

Currently, targeting pericytes for treatment involves regulating RGS5, HIF-1, PDGFR-β, SGLT2, and VEGF-B to modulate pericyte proliferation and maintain BBB stability. Additionally, pericyte transplantation significantly improves the neurologic status of ischemic stroke rats and promotes neurovascular remodeling. Further research is needed to evaluate the therapeutic effects of pericyte transplantation. Despite advances in understanding pericytes

and related mechanisms in ischemic stroke, there are still many key issues to be addressed. First, pericytes are a diverse cell population and different types of pericytes may have different roles in ischemic stroke. Second, the potential impact of solely targeting pericytes on interactions with other components of the NVU needs to be considered. Moreover, most therapeutic strategies targeting pericytes are based on animal studies and further research is needed to assess the safety, dosage, and administration routes for ischemic stroke. Better understanding of pericytes contributes to exploring treatments for ischemic stroke. In conclusion, further research on the inflammatory mechanisms of pericytes in ischemic stroke will contribute to a better understanding of the pathogenesis of cerebrovascular diseases and provide new insight and approaches for the treatment of related diseases.

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CONFLICT OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Katan M, Luft A. Global burden of stroke. Semin Neurol. 2018;38:208-211.
2. Collaborators GBDS. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol. 2021;20:795-820.
3. Saini V, Guada L, Yavagal DR. Global epidemiology of stroke and access to acute ischemic stroke interventions. Neurology. 2021;97:S6-S16.
4. Li Q, Khatibi N, Zhang JH. Vascular neural network: the importance of vein drainage in stroke. Transl Stroke Res. 2014;5:163-166.
5. Hatano S. Experience from a multicentre stroke register: a preliminary report. Bull World Health Organ. 1976;54:541-553.
6. Endres M, Moro MA, Nolte CH, Dames C, Buckwalter MS, Meisel A. Immune pathways in etiology, acute phase, and chronic sequelae of ischemic stroke. Circ Res. 2022;130:1167-1186.
7. Candelario-Jalil E, Dijkhuizen RM. Neuroinflammation, stroke, blood-brain barrier dysfunction, and imaging modalities. Stroke. 2022;53:1473-1486.
8. Chamorro A, Hallenbeck J. The harms and benefits of inflammatory and immune responses in vascular disease. Stroke. 2006;37:291-293.
9. Linfante I, Cipolla MJ. Improving reperfusion therapies in the era of mechanical thrombectomy. Transl Stroke Res. 2016;7:294-302.
10. Hafez S, Coucha M, Bruno A, Fagan SC, Ergul A. Hyperglycemia, acute ischemic stroke, and thrombolytic therapy. Transl Stroke Res. 2014;5:442-453.
11. Lapchak PA. Critical early thrombolytic and endovascular reperfusion therapy for acute ischemic stroke victims: a call for adjunct neuroprotection. Transl Stroke Res. 2015;6:345-354.
12. Posada-Duque RA, Barreto GE, Cardona-Gomez GP. Protection after stroke: cellular effectors of neurovascular unit integrity. Front Cell Neurosci. 2014;8:231.
13. Morrison HW, Filosa JA. Stroke and the neurovascular unit: glial cells, sex differences, and hypertension. Am J Physiol Cell Physiol. 2019;316:C325-C339.
14. Sato Y, Falcone-Juengert J, Tominaga T, Su H, Liu J. Remodeling of the neurovascular unit following cerebral ischemia and hemorrhage. Cells. 2022;11:2823.
15. Cao H, Seto SW, Bhuyan DJ, Chan HH, Song W. Effects of thrombin on the neurovascular unit in cerebral ischemia. Cell Mol Neurobiol. 2022;42:973-984.
16. Liu Q, Yang Y, Fan X. Microvascular pericytes in brain-associated vascular disease. Biomed Pharmacother. 2020;121:109633.
17. Gerganova G, Riddell A, Miller AA. CNS border-associated macrophages in the homeostatic and ischaemic brain. Pharmacol Ther. 2022;240:108220.
18. Sen J, Chen R, Yang S, Jin H, Zhu Y, Wan Y, et al. Diverse functions and mechanisms of pericytes in ischemic stroke. Int J Mol Sci. 2017;15:892-905.
19. Zhou SY, Guo ZN, Zhang DH, Qu Y, Jin H. The role of pericytes in ischemic stroke: fom cellular functions to therapeutic targets. Front Mol Neurosci. 2022;15:866700.
20. Carlsson R, Özen I, Barbariga M, Gaceb A, Roth M. STAT3 precedes HIF1α transcriptional responses to oxygen and oxygen and glucose deprivation in human brain pericytes. PLoS One. 2018;13:e0194146.
21. Cao L, Zhou Y, Chen M, Li L, Zhang W. Pericytes for therapeutic approaches to ischemic stroke. Front Neurosci. 2021;15:629297.
22. Cai W, Liu H, Zhao J, Chen LY, Chen J, Lu Z, et al. Pericytes in brain injury and repair after ischemic stroke. Transl Stroke Res. 2017;8:107-121.
23. Arimura K, Ago T, Kamouchi M, Nakamura K, Ishitsuka K, Kuroda J, et al. PDGF receptor β signaling in pericytes following ischemic brain injury. Curr Neurovasc Res. 2012;9:1-9.
24. Berthiaume AA, Hartmann DA, Majesky MW, Bhat NR, Shih AY. Pericyte structural remodeling in cerebrovascular health and homeostasis. Front Aging Neurosci. 2018;10:210.
25. Winkler EA, Bell RD, Zlokovic BV. Central nervous system pericytes in health and disease. Nat Neurosci. 2011;14:1398-1405.
26. Etchevers HC, Vincent C, Le Douarin NM, Couly GF. The cephalic neural crest provides pericytes and smooth muscle cells to all blood vessels of the face and forebrain. Development. 2001;128:1059-1068.
27. Korn J, Christ B, Kurz H. Neuroectodermal origin of brain pericytes and vascular smooth muscle cells. J Comp Neurol. 2002;442:78-88.
28. Trost A, Lange S, Schroedl F, Bruckner D, Motloch KA, Bogner B, et al. Brain and retinal pericytes: origin, function and role. Front Cell Neurosci. 2016;10:20.
29. Attwell D, Mishra A, Hall CN, O'Farrell FM, Dalkara T. What is a pericyte? J Cereb Blood Flow Metab. 2016;36:451-455.
30. Hall CN, Reynell C, Gesslein B, Hamilton NB, Mishra A, Sutherland BA, et al. Capillary pericytes regulate cerebral blood flow in health and disease. Nature. 2014;508:55-60.
31. Armulik A, Genove G, Mae M, Nisancioglu MH, Wallgard E, Niaudet C, et al. Pericytes regulate the blood-brain barrier. Nature. 2010;468:557-561.
32. Dias Moura Prazeres PH, Sena IFG, Borges IDT, de Azevedo PO, Andreotti JP, de Paiva AE, et al. Pericytes are heterogeneous in their origin within the same tissue. Dev Biol. 2017;427:6-11.
33. Bonkowski D, Katyshev V, Balabanov RD, Borisov A, Dore-Duffy P. The CNS microvascular pericyte: pericyte-astrocyte crosstalk in the regulation of tissue survival. Fluids Barriers CNS. 2011;8:8.
34. Rustenhoven J, Jansson D, Smyth LC, Dragunow M. Brain pericytes as mediators of neuroinflammation. Trends Pharmacol Sci. 2017;38:291-304.
35. Bhattacharya A, Kaushik DK, Lozinski BM, Yong VW. Beyond barrier functions: roles of pericytes in homeostasis and regulation of neuroinflammation. J Neurosci Res. 2020;98:2390-2405.
36. Torok O, Schreiner B, Schaffenrath J, Tsai HC, Maheshwari U, Stifter SA, et al. Pericytes regulate vascular immune homeostasis in the CNS. Proc Natl Acad Sci USA. 2021;118:e2016587118.
37. Navarro R, Compte M, Alvarez-Vallina L, Sanz L. Immune regulation by pericytes: modulating innate and adaptive immunity. Front Immunol. 2016;7:480.

38. Grau AJ, Reis A, Buggle F, Al-Khalaf A, Werle E, Valois N, et al. Monocyte function and plasma levels of interleukin-8 in acute ischemic stroke. J Neurol Sci. 2001;192:41-47.
39. Pieper C, Pieloch P, Galla HJ. Pericytes support neutrophil transmigration via interleukin-8 across a porcine co-culture model of the blood-brain barrier. Brain Res. 2013;1524:1-11.
40. Sun Z, Gao C, Gao D, Sun R, Li W, Wang F, et al. Reduction in pericyte coverage leads to blood-brain barrier dysfunction via endothelial transcytosis following chronic cerebral hypoperfusion. Fluids Barriers CNS. 2021;18:21.
41. Chen J, Luo Y, Hui H, Cai T, Huang H, Yang F, et al. CD146 coordinates brain endothelial cell-pericyte communication for blood-brain barrier development. Proc Natl Acad Sci USA. 2017;114:E7622-E7631.
42. Jansson D, Rustenhoven J, Feng S, Hurley D, Oldfield RL, Bergin PS, et al. A role for human brain pericytes in neuroinflammation. J Neuroinflamm 2014;11:104.
43. Arakelyan A, Petrkova J, Hermanova Z, Boyajyan A, Lukl J, Petrek M. Serum levels of the MCP-1 chemokine in patients with ischemic stroke and myocardial infarction. Mediat Inflamm. 2005;2005:175-179.
44. Matsumoto J, Takata F, Machida T, Takahashi H, Soejima Y, Funakoshi M, et al. Tumor necrosis factor-alpha-stimulated brain pericytes possess a unique cytokine and chemokine release profile and enhance microglial activation. Neurosci Lett. 2014;578:133-138.
45. Medina-Flores F, Hurtado-Alvarado G, Deli MA, Gomez-Gonzalez B. The active role of pericytes during neuroinflammation in the adult brain. Cell Mol Neurobiol. 2023;43:525-541.
46. Zozulya A, Weidenfeller C, Galla HJ. Pericyte-endothelial cell interaction increases MMP-9 secretion at the blood-brain barrier in vitro. Brain Res. 2008;1189:1-11.
47. Takata F, Dohgu S, Matsumoto J, Takahashi H, Machida T, Wakigawa T, et al. Brain pericytes among cells constituting the blood-brain barrier are highly sensitive to tumor necrosis factor-alpha, releasing matrix metalloproteinase-9 and migrating in vitro. J Neuroinflamm. 2011;8:106.
48. Thanabalasundaram G, Schneidewind J, Pieper C, Galla HJ. The impact of pericytes on the blood-brain barrier integrity depends critically on the pericyte differentiation stage. Int J Biochem Cell Biol. 2011;43:1284-1293.
49. Smith BC, Tinkey RA, Shaw BC, Williams JL. Targetability of the neurovascular unit in inflammatory diseases of the central nervous system. Immunol Rev. 2022;311:39-49.
50. Shi X, Kaushik DK, Bhattacharya A, Lozinski BM, Wee Yong V. 2021 Pericytes as mediators of infiltration of macrophages in multiple sclerosis. Cells. 2021;18:301.
51. Niu F, Liao K, Hu GK, Sil S, Callen S, Guo ML, et al. Cocaine-induced release of CXCL10 from pericytes regulates monocyte transmigration into the CNS. J Cell Biol. 2019;218:700-721.
52. Rustenhoven J, Aalderink M, Scotter EL, Oldfield RL, Bergin PS, Mee EW, et al. TGF-beta1 regulates human brain pericyte inflammatory processes involved in neurovasculature function. J Neuroinflamm. 2016;13:37.
53. Cheng J, Korte N, Nortley R, Sethi H, Tang Y, Attwell D. Targeting pericytes for therapeutic approaches to neurological disorders. Acta Neuropathol. 2018;136:507-523.
54. Sa-Pereira I, Brites D, Brito MA. Neurovascular unit: a focus on pericytes. Mol Neurobiol. 2012;45:327-347.
55. Rudziak P, Ellis CG, Kowalewska PM. Role and molecular mechanisms of rericytes in regulation of leukocyte diapedesis in inflamed tissues. Mediators Inflamm. 2019;2019:4123605.
56. Pieper C, Galla HJ. Ultra structure analysis of cell-cell interactions between pericytes and neutrophils in vitro. Biochem Biophys Res Commun. 2014;445:180-183.
57. Balabanov R, Beaumont T, Dore-Duffy P. Role of central nervous system microvascular pericytes in activation of antigen-primed splenic T-lymphocytes. J Neurosci Res. 1999;55:578-587.
58. Wang L, Chen Y, Feng D, Wang X. Serum ICAM-1 as a predictor of prognosis in patients with acute ischemic stroke. Biomed Res Int. 2021;2021:5539304.
59. Wang D, Zhang FH, Zhao YT, Xiao XG, Liu S, Shi HB, et al. Association of polymorphism in ICAM-1 (K469E) and cytology parameters in patients' initial blood test with acute ischemic stroke. Genet Mol Res. 2015;14:15520-15529.
60. Nepal G, Yadav JK, Kong Y. Association between K469E polymorphism of ICAM-1 gene and susceptibility of ischemic stroke: an updated meta-analysis. Mol Genet Genomic Med. 2019;7:e00784.
61. Enlimomab Acute Stroke Trial I. Use of anti-ICAM-1 therapy in ischemic stroke: results of the enlimomab acute stroke trial. Neurology. 2001;57:1428-1434.
62. Enzmann GU, Pavlidou S, Vaas M, Klohs J, Engelhardt B. ICAM-1(null) C57BL/6 mice are not protected from experimental ischemic stroke. Transl Stroke Res. 2018;9:608-621.
63. Connolly ES Jr, Winfree CJ, Springer TA, Naka Y, Liao H, Yan SD, et al. Cerebral protection in homozygous null ICAM-1 mice after middle cerebral artery occlusion. Role of neutrophil adhesion in the pathogenesis of stroke. J Clin Invest. 1996;97:209-216.
64. de Araujo MCM, Alfieri DF, Lehmann A, Luz TF, Trevisani ER, Nagao MR, et al. Baseline severity and soluble vascular cell adhesion molecule 1 (sVCAM-1) as biomarker predictors of short-term mortality in acute ischemic stroke. Metab Brain Dis. 2023;38:657-670.
65. Peycheva M, Deneva T, Harizanova Z, Zlatareva D. The role of cell adhesion molecules (ICAM-1 and VCAM-1) in acute ischemic stroke. Ceska Slovenska Neurol Neurochir. 2022;85:168-174.
66. Rustenhoven J, Smyth LC, Jansson D, Schweder P, Aalderink M, Scotter EL, et al. Modelling physiological and pathological conditions to study pericyte biology in brain function and dysfunction. BMC Neurosci. 2018;19:6.
67. Sharma K, Zhang Y, Paudel KR, Kachelmeier A, Hansbro PM, Shi X. The emerging role of pericyte-derived extracellular vesicles in vascular and neurological health. Cells. 2022;11:3108.
68. Whiteley W, Jackson C, Lewis S, Lowe G, Rumley A, Sandercock P, et al. Inflammatory markers and poor outcome after stroke: a prospective cohort study and systematic review of interleukin-6. PLoS Med. 2009;6:e1000145.
69. Switzer JA, Sikora A, Ergul A, Waller JL, Hess DC, Fagan SC. Minocycline prevents IL-6 increase after acute ischemic stroke. Transl Stroke Res. 2012;3:363-368.
70. Li J, Lin J, Pan Y, Wang M, Meng X, Li H, et al. Interleukin-6 and YKL-40 predicted recurrent stroke after ischemic stroke or TIA: analysis of 6 inflammation biomarkers in a prospective cohort study. J Neuroinflamm. 2022;19:131.
71. Waje-Andreassen U, Krakenes J, Ulvestad E, Thomassen L, Myhr KM, Aarseth J, et al. IL-6: an early marker for outcome in acute ischemic stroke. Acta Neurol Scand. 2005;111:360-365.
72. He Q, Shi X, Zhou B, Teng J, Zhang C, Liu S, et al. Interleukin 8 (CXCL8)-CXC chemokine receptor 2 (CXCR2) axis contributes to MiR-4437-associated recruitment of granulocytes and natural killer cells in ischemic stroke. Mol Immunol. 2018;101:440-449.
73. Losy J, Zaremba J. Monocyte chemoattractant protein-1 is increased in the cerebrospinal fluid of patients with ischemic stroke. Stroke. 2001;32:2695-2696.
74. Duan L, Zhang XD, Miao WY, Sun YJ, Xiong G, Wu Q, et al. PDGFRβ cells rapidly relay inflammatory signal from the circulatory system to neurons via chemokine CCL2. Neuron. 2018;100:183-200.e8.
75. Rafalski VA, Merlini M, Akassoglou K. Pericytes: the Brain's very first responders? Neuron. 2018;100:11-13.
76. Li L, Lou W, Li H, Zhu Y, Huang X. Upregulated C-C motif chemokine ligand 2 promotes ischemic stroke via chemokine signaling pathway. Ann Vasc Surg. 2020;68:476-486.
77. Balabanov R, Washington R, Wagnerova J, Dore-Duffy P. CNS microvascular pericytes express macrophage-like function, cell surface integrin alpha M, and macrophage marker ED-2. Microvasc Res. 1996;52:127-142.

78. Pieper C, Marek JJ, Unterberg M, Schwerdtle T, Galla HJ. Brain capillary pericytes contribute to the immune defense in response to cytokines or LPS in vitro. Brain Res. 2014;1550:1-8.
79. Ma Q, Zhao Z, Sagare AP, Wu Y, Wang M, Owens NC, et al. Blood-brain barrier-associated pericytes internalize and clear aggregated amyloid-β42 by LRP1-dependent apolipoprotein E isoform-specific mechanism. Mol Neurodegener. 2018;13:57.
80. Yang QW, Nirwane A, Yao Y. SMA(low/undetectable) pericytes differentiate into microglia- and macrophage-like cells in ischemic brain. Cell Mol Neurobiol. 2022;79:264.
81. Ozen I, Deierborg T, Miharada K, Padel T, Englund E, Genove G, et al. Brain pericytes acquire a microglial phenotype after stroke. Acta Neuropathol. 2014;128:381-396.
82. Ceulemans AG, Zgavc T, Kooijman R, Hachimi-Idrissi S, Sarre S, Michotte Y. The dual role of the neuroinflammatory response after ischemic stroke: modulatory effects of hypothermia. J Neuroinflamm. 2010;7:74.
83. Tian D, Pan Y, Zhao Y, Wang H, Tian Y, Yang L, et al. TCRalphabeta(+)NK1.1(-)CD4(-)CD8(-) double-negative T cells inhibit central and peripheral inflammation and ameliorate ischemic stroke in mice. Theranostics. 2023;13:896-909.
84. Iadecola C, Anrather J. The immunology of stroke: from mechanisms to translation. Nat Med. 2011;17:796-808.
85. Chang CY, Li JR, Ou YC, Lin SY, Wang YY, Chen WY, et al. Interplay of inflammatory gene expression in pericytes following Japanese encephalitis virus infection. Brain Behav Immun. 2017;66:230-243.
86. Dolasia K, Bisht MK, Pradhan G, Udgata A, Mukhopadhyay S. TLRs/NLRs: shaping the landscape of host immunity. Int Rev Immunol. 2018;37:3-19.
87. Brubaker SW, Bonham KS, Zanoni I, Kagan JC. Innate immune pattern recognition: a cell biological perspective. Annu Rev Immunol. 2015;33:257-290.
88. Tu XK, Yang WZ, Chen JP, Chen Y, Ouyang LQ, Xu YC, et al. Curcumin inhibits TLR2/4-NF-kappaB signaling pathway and attenuates brain damage in permanent focal cerebral ischemia in rats. Inflammation. 2014;37:1544-1551.
89. Ling Y, Jin L, Ma Q, Huang Y, Yang Q, Chen M, et al. Salvianolic acid A alleviated inflammatory response mediated by microglia through inhibiting the activation of TLR2/4 in acute cerebral ischemia-reperfusion. Phytomedicine. 2021;87:153569.
90. Tu XK, Yang WZ, Shi SS, Chen Y, Wang CH, Chen CM, et al. Baicalin inhibits TLR2/4 signaling pathway in rat brain following permanent cerebral ischemia. Inflammation. 2011;34:463-470.
91. Trindade BC, Chen GY. NOD1 and NOD2 in inflammatory and infectious diseases. Immunol Rev. 2020;297:139-161.
92. Inohara N, Ogura Y, Chen FF, Muto A, Nunez G. Human Nod1 confers responsiveness to bacterial lipopolysaccharides. J Biol Chem. 2001;276:2551-2554.
93. Navarro R, Delgado-Wicke P, Nunez-Prado N, Compte M, Blanco-Toribio A, Nunez G, et al. Role of nucleotide-binding oligomerization domain 1 (NOD1) in pericyte-mediated vascular inflammation. J Cell Mol Med. 2016;20:980-986.
94. Yang E, Cai Y, Yao X, Liu J, Wang Q, Jin W, et al. Tissue plasminogen activator disrupts the blood-brain barrier through increasing the inflammatory response mediated by pericytes after cerebral ischemia. Aging. 2019;11:10167-10182.
95. Shichita T, Ago T, Kamouchi M, Kitazono T, Yoshimura A, Ooboshi H. Novel therapeutic strategies targeting innate immune responses and early inflammation after stroke. J Neurochem. 2012;123 Suppl 2:29-38.
96. Kigerl KA, de Rivero Vaccari JP, Dietrich WD, Popovich PG, Keane RW. Pattern recognition receptors and central nervous system repair. Exp Neurol. 2014;258:5-16.
97. Nyul-Toth A, Kozma M, Nagyoszi P, Nagy K, Fazakas C, Hasko J, et al. Expression of pattern recognition receptors and activation of the non-canonical inflammasome pathway in brain pericytes. Brain Behav Immun. 2017;64:220-231.
98. Sun W, Ding Z, Xu S, Su Z, Li H. Crosstalk between TLR2 and Sphk1 in microglia in the cerebral ischemia/reperfusion-induced inflammatory response. Int J Mol Med. 2017;40:1750-1758.
99. Ziegler G, Harhausen D, Schepers C, Hoffmann O, Rohr C, Prinz V, et al. TLR2 has a detrimental role in mouse transient focal cerebral ischemia. Biochem Biophys Res Commun. 2007;359:574-579.
100. Guijarro-Muñoz I, Compte M, Álvarez-Cienfuegos A, Álvarez-Vallina L, Sanz L. Lipopolysaccharide activates toll-like receptor 4 (TLR4)-mediated NF-κB signaling pathway and proinflammatory response in human pericytes. J Biol Chem. 2014;289:2457-2468.
101. Chen X, Yao Z, Peng X, Wu L, Wu H, Ou Y, et al. Eupafolin alleviates cerebral ischemia/reperfusion injury in rats via blocking the TLR4/NF-kappaB signaling pathway. Mol Med Rep. 2020;22:5135-5144.
102. Saeedan AS, Abdel-Rahman RF, Soliman GA, Ogaly HA, Abdel-Kader MS. Amentoflavone attenuates oxidative stress and neuroinflammation induced by cerebral ischemia/reperfusion in rats by targeting HMGB1-mediated TLR4/NF-kappaB signaling pathway. Saudi Pharm J. 2023;31:101798.
103. Xu Y, Zhang J, Gao F, Cheng W, Zhang Y, Wei C, et al. Engeletin alleviates cerebral ischemia reperfusion-induced neuroinflammation via the HMGB1/TLR4/NF-kappaB network. J Cell Mol Med. 2023;27:1653-1663.
104. Zhang B, Shen J, Zhong Z, Zhang L. PKM2 aggravates cerebral ischemia reperfusion-induced neuroinflammation via TLR4/MyD88/TRAF6 signaling pathway. Neuroimmunomodulation. 2021;28:29-37.
105. Shichita T, Hasegawa E, Kimura A, Morita R, Sakaguchi R, Takada I, et al. Peroxiredoxin family proteins are key initiators of post-ischemic inflammation in the brain. Nat Med. 2012;18:911-917.
106. Mao L, Wu DH, Hu GH, Fan JH. TLR4 enhances cerebral ischemia/reperfusion injury via regulating NLRP3 inflammasome and autophagy. Mediat Inflamm. 2023;2023:9335166.
107. Liu J, Ma W, Zang CH, Wang GD, Zhang SJ, Wu HJ, et al. Salidroside inhibits NLRP3 inflammasome activation and apoptosis in microglia induced by cerebral ischemia/reperfusion injury by inhibiting the TLR4/NF-kappaB signaling pathway. Ann Transl Med. 2021;9:1694.
108. He J, Wu H, Zhou Y, Zheng C. Tomentosin inhibit cerebral ischemia/reperfusion induced inflammatory response via TLR4/NLRP3 signalling pathway - in vivo and in vitro studies. Biomed Pharmacother. 2020;131:110697.
109. Yang B, Sun Y, Lv C, Zhang W, Chen Y. Procyanidins exhibits neuroprotective activities against cerebral ischemia reperfusion injury by inhibiting TLR4-NLRP3 inflammasome signal pathway. Psychopharmacology. 2020;237:3283-3293.
110. Wang H, Zhang S, Xie L, Zhong Z, Yan F. Neuroinflammation and peripheral immunity: focus on ischemic stroke. Int Immunopharmacol. 2023;120:110332.
111. Jones KA, Maltby S, Plank MW, Kluge M, Nilsson M, Foster PS, et al. Peripheral immune cells infiltrate into sites of secondary neurodegeneration after ischemic stroke. Brain Behav Immun. 2018;67:299-307.
112. Smyth LCD, Rustenhoven J, Park TI, Schweder P, Jansson D, Heppner PA, et al. Unique and shared inflammatory profiles of human brain endothelia and pericytes. J Neuroinflammation. 2018;15:138.
113. Nourshargh S, Alon R. Leukocyte migration into inflamed tissues. Immunity. 2014;41:694-707.
114. Liu R, Lauridsen HM, Amezquita RA, Pierce RW, Jane-Wit D, Fang C, et al. IL-17 Promotes neutrophil-mediated immunity by activating microvascular pericytes and not endothelium. J Immunol. 2016;197:2400-2408.
115. Griffith JW, Sokol CL, Luster AD. Chemokines and chemokine receptors: positioning cells for host defense and immunity. Annu Rev Immunol. 2014;32:659-702.
116. Persidsky Y, Hill J, Zhang M, Dykstra H, Winfield M, Reichenbach NL, et al. Dysfunction of brain pericytes in chronic neuroinflammation. J Cereb Blood Flow Metabol. 2016;36:794-807.

117. Verbeek MM, Westphal JR, Ruiter DJ, de Waal RM. T lymphocyte adhesion to human brain pericytes is mediated via very late antigen-4/vascular cell adhesion molecule-1 interactions. J Immunol. 1995;154:5876-5884.
118. Stark K, Eckart A, Haidari S, Tirniceriu A, Lorenz M, von Bruhl ML, et al. Capillary and arteriolar pericytes attract innate leukocytes exiting through venules and 'instruct' them with pattern-recognition and motility programs. Nat Immunol. 2013;14:41-51.
119. Rustenhoven J, Scotter EL, Jansson D, Kho DT, Oldfield RL, Bergin PS, et al. An anti-inflammatory role for C/EBPdelta in human brain pericytes. Sci Rep. 2015;5:12132.
120. Fernández-Klett F, Priller J. The Fibrotic scar in neurological disorders. Brain Pathol. 2014;24:404-413.
121. Dias DO, Kalkitsas J, Kelahmetoglu Y, Estrada CP, Tatarishvili J, Holl D, et al. Pericyte-derived fibrotic scarring is conserved across diverse central nervous system lesions. Nat Commun. 2021;12:5501.
122. Göritz C, Dias DO, Tomilin N, Barbacid M, Shupliakov O, Frisén J. A Pericyte origin of spinal cord scar tissue. Science. 2011;333:238-242.
123. Dias DO, Kim H, Holl D, Solnestam BW, Lundeberg J, Carlén M, et al. Reducing pericyte-derived scarring promotes recovery after spinal cord injury. Cell. 2018;173:153–165.
124. Yokota K, Kobayakawa K, Saito T, Hara M, Kijima K, Ohkawa Y, et al. Periostin promotes scar formation through the interaction between pericytes and infiltrating monocytes/macrophages after spinal cord injury. Am J Pathol. 2017;187:639-653.
125. Makihara N, Arimura K, Ago T, Tachibana M, Nishimura A, Nakamura K, et al. Involvement of platelet-derived growth factor receptor β in fibrosis through extracellular matrix protein production after ischemic stroke. Exp Neurol. 2015;264:127-134.
126. Fernández-Klett F, Potas JR, Hilpert D, Blazej K, Radke J, Huck J, et al. Early loss of pericytes and perivascular stromal cell-induced scar formation after stroke. J Cereb Blood Flow Metabol. 2013;33:428-439.
127. Holl D, Hau WF, Julien A, Banitalebi S, Kalkitsas J, Savant S, et al. Distinct origin and region-dependent contribution of stromal fibroblasts to fibrosis following traumatic injury in mice. Nat Neurosci. 2024;27:1285–1298.
128. Parvez S, Kaushik M, Ali M, Alam MM, Ali J, Tabassum H, et al. Dodging blood brain barrier with "nano" warriors: novel strategy against ischemic stroke. Theranostics. 2022;12:689-719.
129. Cho YE, Lee H, Bae HR, Kim H, Yun S, Vorn R, et al. Circulating immune cell landscape in patients who had mild ischaemic stroke. Stroke Vasc Neurol. 2022;7:319-327.
130. Nishimura A, Ago T, Kuroda J, Arimura K, Tachibana M, Nakamura K, et al. Detrimental role of pericyte Nox4 in the acute phase of brain ischemia. J Cereb Blood Flow Metab. 2016;36:1143-1154.
131. Shimizu F, Sano Y, Abe MA, Maeda T, Ohtsuki S, Terasaki T, et al. Peripheral nerve pericytes modify the blood-nerve barrier function and tight junctional molecules through the secretion of various soluble factors. J Cell Physiol. 2011;226:255-266.
132. Lei D, Jin X, Wen L, Dai H, Ye Z, Wang G. bmp3 is required for integrity of blood brain barrier by promoting pericyte coverage in zebrafish embryos. Curr Mol Med. 2017;17:298-303.
133. Villasenor R, Kuennecke B, Ozmen L, Ammann M, Kugler C, Gruninger F, et al. Region-specific permeability of the blood-brain barrier upon pericyte loss. J Cereb Blood Flow Metab. 2017;37:3683-3694.
134. Yang C, Hawkins KE, Doré S, Candelario-Jalil E. Neuroinflammatory mechanisms of blood-brain barrier damage in ischemic stroke. 2019;316:C135-C153.
135. Asahi M, Wang X, Mori T, Sumii T, Jung JC, Moskowitz MA, et al. Effects of matrix metalloproteinase-9 gene knock-out on the proteolysis of blood-brain barrier and white matter components after cerebral ischemia. J Neurosci. 2001;21:7724-7732.
136. Nakamura K, Ikeuchi T, Nara K, Rhodes CS, Zhang P, Chiba Y, et al. Perlecan regulates pericyte dynamics in the maintenance and repair of the blood-brain barrier. J Cell Biol. 2019;218:3506-3525.
137. Wang Y, Kisler K, Nikolakopoulou AM, Fernandez JA, Griffin JH, Zlokovic BV. 3K3A-Activated protein C protects the blood-brain barrier and neurons from accelerated ischemic injury caused by pericyte deficiency in mice. Front Neurosci. 2022;16:841916.
138. Yamanaka G, Takata F, Kataoka Y, Kanou K, Morichi S, Dohgu S, et al. The neuroinflammatory role of pericytes in epilepsy. Biomedicines. 2021;9:759.
139. Gautam J, Cao Y, Yao Y. Pericytic laminin maintains blood-brain barrier integrity in an age-dependent manner. Transl Stroke Res. 2020;11:228-242.
140. Dohgu S, Takata F, Matsumoto J, Kimura I, Yamauchi A, Kataoka Y. Monomeric alpha-synuclein induces blood-brain barrier dysfunction through activated brain pericytes releasing inflammatory mediators in vitro. Microvasc Res. 2019;124:61-66.
141. Yao Y, Chen ZL, Norris EH, Strickland S. Astrocytic laminin regulates pericyte differentiation and maintains blood brain barrier integrity. Nat Commun. 2014;5:3413.
142. ElAli A, Theriault P, Rivest S. The role of pericytes in neurovascular unit remodeling in brain disorders. Int J Mol Sci. 2014;15:6453-6474.
143. Lindahl P, Johansson BR, Leveen P, Betsholtz C. Pericyte loss and microaneurysm formation in PDGF-B-deficient mice. Science. 1997;277:242-245.
144. Winkler EA, Bell RD, Zlokovic BV. Pericyte-specific expression of PDGF beta receptor in mouse models with normal and deficient PDGF beta receptor signaling. Mol Neurodegener. 2010;5:32.
145. Bjarnegard M, Enge M, Norlin J, Gustafsdottir S, Fredriksson S, Abramsson A, et al. Endothelium-specific ablation of PDGFB leads to pericyte loss and glomerular, cardiac and placental abnormalities. Development. 2004;131:1847-1857.
146. Gaengel K, Genove G, Armulik A, Betsholtz C. Endothelial-mural cell signaling in vascular development and angiogenesis. Arterioscler Thromb Vasc Biol. 2009;29:630-638.
147. Renner O, Tsimpas A, Kostin S, Valable S, Petit E, Schaper W, et al. Time- and cell type-specific induction of platelet-derived growth factor receptor-beta during cerebral ischemia. Brain Res Mol Brain Res. 2003;113:44-51.
148. Daneman R, Zhou L, Kebede AA, Barres BA. Pericytes are required for blood-brain barrier integrity during embryogenesis. Nature. 2010;468:562-566.
149. Qi LJ, Wang F, Sun XJ, Li H, Zhang K, Li JA. Recent advances in tissue repair of the blood-brain barrier after stroke. J Tissue Eng. 2024;15:20417314241226551.
150. Armulik A, Genove G, Betsholtz C. Pericytes: developmental, physiological, and pathological perspectives, problems, and promises. Dev Cell. 2011;21:193-215.
151. Qin D, Trenkwalder T, Lee S, Chillo O, Deindl E, Kupatt C, et al. Early vessel destabilization mediated by Angiopoietin-2 and subsequent vessel maturation via Angiopoietin-1 induce functional neovasculature after ischemia. PLoS One. 2013;8:e61831.
152. Gurnik S, Devraj K, Macas J, Yamaji M, Starke J, Scholz A, et al. Angiopoietin-2-induced blood-brain barrier compromise and increased stroke size are rescued by VE-PTP-dependent restoration of Tie2 signaling. Acta Neuropathol. 2016;131:753-773.
153. Yang Y, Yang LY, Salayandia VM, Thompson JF, Torbey M, Yang Y. Treatment with atorvastatin during vascular remodeling promotes pericyte-mediated blood-brain barrier maturation following ischemic stroke. Transl Stroke Res. 2021;12:905-922.
154. Roth M, Gaceb A, Enstrom A, Padel T, Genove G, Ozen I, et al. Regulator of G-protein signaling 5 regulates the shift from perivascular to parenchymal pericytes in the chronic phase after stroke. FASEB J. 2019;33:8990-8998.
155. Tsao CC, Baumann J, Huang SF, Kindler D, Schroeter A, Kachappilly N, et al. Pericyte hypoxia-inducible factor-1 (HIF-1) drives blood-brain barrier disruption and impacts acute ischemic stroke outcome. Angiogenesis. 2021;24:823-842.
156. Takashima M, Nakamura K, Kiyohara T, Wakisaka Y, Hidaka M, Takaki H, et al. Low-dose sodium-glucose cotransporter 2 inhibitor ameliorates ischemic brain injury in mice through

pericyte protection without glucose-lowering effects. Commun Biol. 2022;5:653.
157. Guo RB, Dong YF, Yin Z, Cai ZY, Yang J, Ji J, et al. Iptakalim improves cerebral microcirculation in mice after ischemic stroke by inhibiting pericyte contraction. Acta Pharmacol Sin. 2022;43:1349-1359.
158. Yao F, Luo Y, Liu YC, Chen YH, Li YT, Hu XY, et al. Imatinib inhibits pericyte-fibroblast transition and inflammation and promotes axon regeneration by blocking the PDGF-BB/PDGFRbeta pathway in spinal cord injury. Inflamm Regen. 2022;42:44.
159. Jean LeBlanc N, Guruswamy R, ElAli A. Vascular endothelial growth factor isoform-B stimulates neurovascular repair after ischemic stroke by promoting the function of pericytes via vascular endothelial growth factor receptor-1. Mol Neurobiol. 2018;55:3611-3626.
160. Sun J, Huang Y, Gong J, Wang J, Fan Y, Cai J, et al. Transplantation of hPSC-derived pericyte-like cells promotes functional recovery in ischemic stroke mice. Nat Commun. 2020;11:5196.
161. Mukouyama YS, Yamada Y, Ogay V. Improvement of neurological function in rats with ischemic stroke by adipose-derived pericytes. J Cell Biol. 2020;29:963689720956956.

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