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REVIEW

Targeting Pericytes for Functional Recovery in Ischemic Stroke

Shuqi Hu[1] · Bingjie Yang[2] · Song Shu[1] · Xudong He[1] · Hongfei Sang[1] · Xuemei Fan[1] · Hao Zhang[1,2]

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Abstract

Pericytes surrounding endothelial cells in the capillaries are emerging as an attractive cell resource, which can show a large variety of functions in ischemic stroke, including preservation of the blood–brain barrier, regulation of immune function, and support for cerebral vasculature. These functions have been fully elucidated in previous studies. However, in recent years, increasing evidence has shown that pericytes play an important role in neurological recovery after ischemic stroke due to their regenerative function which can be summarized in two aspects according to current discoveries, one is that pericytes are thought to be multipotential themselves, and the other is that pericytes can promote the differentiation of oligodendrocyte progenitor cells (OPCs). Considering the neuroprotective treatment for stroke has not been much progressed in recent years, new therapies targeting pericytes may be a future direction. Here, we will review the beneficial effects of pericytes in ischemic stroke from two directions: the barrier and vascular functions and the regenerative functions of pericytes.

Keywords Pericytes · Ischemic stroke · Functional recovery · Blood–brain barrier · OPCs differentiation

Introduction

Globally, stroke is the second-leading cause of death and the third leading cause of death and disability combined in 2019 (GBD 2019 Stroke Collaborators, 2021). Ischemic stroke is the most common subtype of stroke. In 2019, approximately 73% of stroke cases are ischemic strokes in China (Ma et al., 2021), compared to 62% worldwide (GBD 2019 Stroke Collaborators, 2021). Although multiple innovative approaches to improve the prognosis of ischemic stroke (e.g., reperfusion therapy (Albers et al., 2018; Hacke et al., 2008; Ma et al., 2019; National Institute of Neurological Disorders & Stroke rt-PA Stroke Study Group, 1995; Nogueira et al., 2018; Suzuki et al., 2019; Thomalla et al., 2018; Yang et al., 2020), and neuroprotective therapy (Hill et al., 2020; Xu et al., 2021)) have flourished over the past few decades (Herpich & Rincon, 2020), the treatment of ischemic stroke has now reached a plateau. We have intensely and often been hindered in the translation of preclinical studies into successful clinical studies (Lyden, 2021), particularly in neuroprotective therapy (Paul & Candelario-Jalil, 2021). At the 2017 Stroke Treatment Academic Industry Roundtable X (STAIR X), the concept of Brain Cytoprotection was first proposed because stroke affects not only neurons but also the entire neurovascular unit and white matter (Savitz et al., 2019).

The Neurovascular Unit (NVU) was formalized in 2001 and has drawn attention to the interdependence between brain cells and cerebral blood vessels (Iadecola, 2017). The NVU consists of vascular components (pericytes, smooth muscle cells, endothelial cells), glial cells (astrocytes, oligodendrocytes, microglia), and neurons (Harder et al., 2002; Lo & Rosenberg, 2009; Lo et al., 2003). Interestingly, almost every neuron in the human brain has its own capillaries which account for more than 90% of the total blood vascular volume in the brain (Zlokovic, 2008). Therefore, impaired perfusion of the microvasculature after recanalization therapy can lead to lower-than-expected clinical outcomes (Ames et al., 1968; Goyal et al., 2016). As a member of the vascular part in the NVU, pericytes are present in small cerebral vessels including capillaries, pre-capillary

Shuqi Hu and Bingjie Yang have contributed equally to this work and share first authorship.

✉ Hao Zhang
syzhanghao@zju.edu.cn

[1] Department of Neurology, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou 310006, Zhejiang, China

[2] Department of Neurology, The Fourth Clinical School of Medicine, Zhejiang Chinese Medical University, Hangzhou 310053, Zhejiang, China

arterioles, and post-capillary venules (Winkler et al., 2011). Multiple studies have highlighted the important role of pericytes in the NVU (Sweeney et al., 2016), such as regulating Blood–Brain Barrier (BBB) permeability (Zlokovic, 2011), neuroinflammation (Rustenhoven et al., 2017), and cerebral blood flow (CBF) (Hall et al., 2014). While these studies focused on the barrier and vascular functions of pericytes, more recent studies have shifted attention to the pluripotent stem cell potential (Sakuma et al., 2016) and the promotion of white matter functions (Shibahara et al., 2020a).

Data show that in previous randomized trials, about 70% of patients treated with reperfusion successfully (modified Thrombolysis in Cerebral Infarction (mTICI) scale score 2b or 3), but only 27% of these patients were disability-free at 90 days (Goyal et al., 2016). This may be partly due to the irreversible injury of brain tissue before reperfusion occurred. Therefore, if pericytes have the ability to transform into other neurovascular unit components or promote white matter differentiation, then treatment of pericytes will play a key role in the recovery of motor, sensory, and emotional impairment after stroke.

In this review, we will start with the morphological structure and the vascular homeostatic functions of pericytes and then focus on the latest research on regenerative characteristics of pericytes which will provide new directions for the treatment of ischemic stroke.

Pericytes in Central Nervous System (CNS)

Since the pericytes were first discovered by Eberth (1871), described by Rouget (1873) as a cluster of contractible cells surrounding endothelial cells, and eventually named "pericytes" by Zimmermann (1923), the studies of pericytes have become increasingly popular in the last 50 years, especially in the brain due to the development of electron microscopy (Caporali et al., 2017). In vertebrates, pericytes are found in almost all tissues and located on the abluminal side of the endothelium in both continuous and fenestrated microvessels (Díaz-Flores et al., 2009). The morphology of pericytes is largely related to location (Joyce et al., 1984) and type of vessels (Armulik et al., 2011). In terms of the location of the pericytes, they can be divided into three types: precapillary, capillary, and postcapillary (Zimmermann, 1923). Usually, pericytes display an elongated, stellate morphology containing a cell body, nuclear region, or perinucleus, and produce a highly branched structure consisting of longitudinal and circumferential branching systems that wrap the endothelium. The primary (longitudinal) processes parallel to the long axis of the vessel, with smaller ones (circumferential) proportionally encircling the vessel wall (Díaz-Flores et al., 2009; Takahashi et al., 1997). Using Cre-recombinase driver mouse lines, Hartmann et al. identified that pericytes can be distinguished as helical pericytes and mesh pericytes in capillaries based on the morphology of the trunk and branches. The helical pericyte is the simplest form, with the primary trunk and branches being thin singular strands, approximately 2 μm in diameter, and the secondary processes branching off from the thin single strands, often present in pairs, forming a helical structure. As for its most complex form, is more commonly found in larger diameter microvessels (6–10 μm). The primary trunk of it shapes a mesh-like structure surrounding the entire vessel, hence comes the name mesh pericyte (Hartmann et al., 2015) (Fig. 1). Pericytes of the CNS and retina have the highest coverage ratio (Daneman et al., 2010). Using Electron Microscopy and 3D Reconstruction, Mathiisen TM et.al demonstrated that pericytes and their protrusions covered 37% of the endothelial tube circumference (Mathiisen et al., 2010), which can partially explain the important role of pericytes in the BBB permeability (Daneman et al., 2010). The ratio of pericytes to endothelial cells and the area of pericytes covering the endothelium are related to the tightness of the junctions between the endothelium, that is, the higher the number of pericytes and their coverage is, the better the microvascular barrier integrity works (Shepro & Morel, 1993).

The Temporal Dynamics of Pericyte Functions in Ischemic Stroke

In the acute phase of ischemic stroke, pericytes mainly exhibit the function of constricting blood vessels (Korte et al., 2022), which may further aggravate the injury of cerebral infarction and cause no-reflow phenomenon after reperfusion (Yemisci et al., 2009). Immediately after performing the vasoconstrictive function, pericytes die or separate from blood vessels (Hall et al., 2014), resulting in decreased pericyte coverage and increased BBB permeability in the acute phase. The function of mediating neuroinflammation also manifests after BBB disruption (Rustenhoven et al., 2017). 72 h after ischemic stroke, the coverage of pericytes recovers (Zhou et al., 2018a) and simultaneously exerts the protective effect of the BBB and the function of angiogenesis (Zhang et al., 2022). In the late recovery phase of ischemic stroke, the regenerative function of pericytes gradually appeared (Yang et al., 2017) (Fig. 2).

Barrier and Vascular Functions of Pericytes

Maintaining BBB Integrity

Pericytes share a basement membrane (BM) with endothelial cells and are also covered by a BM continuous with the BM of endothelial cells (Ayloo et al., 2022). This allows for

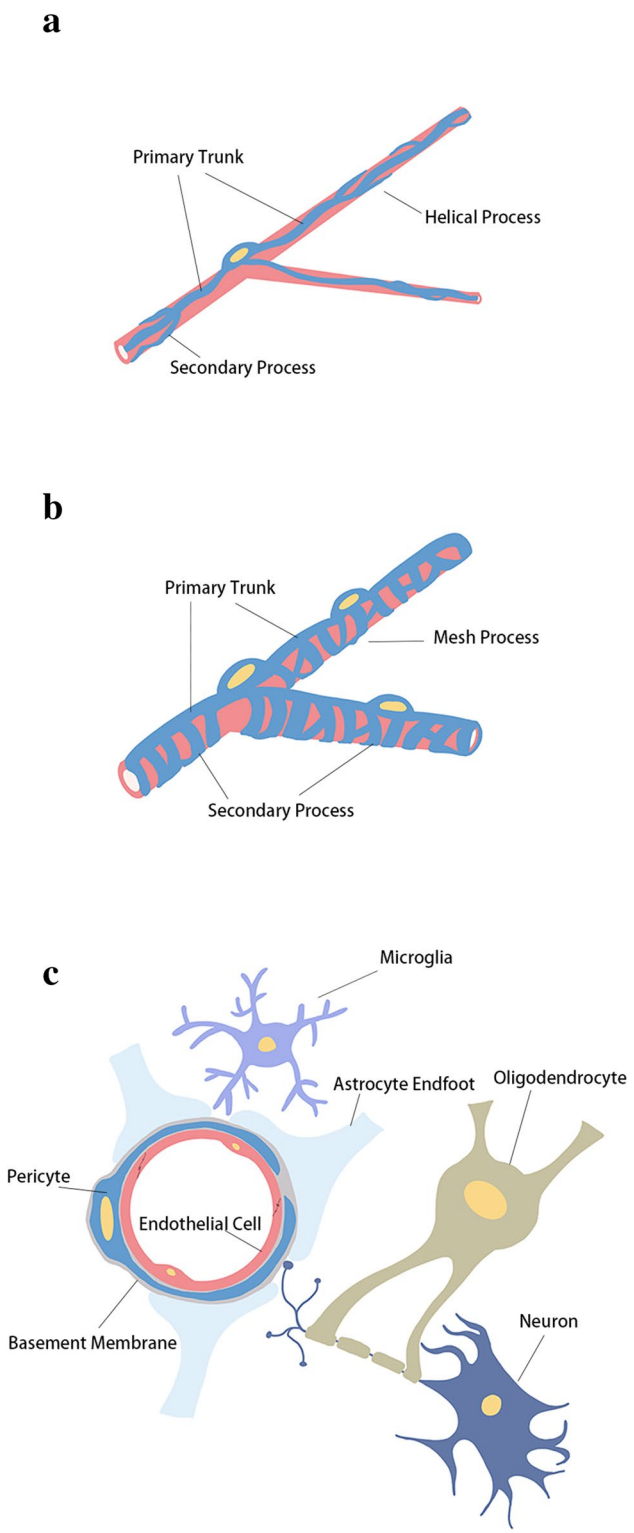

Fig. 1 Two types of pericytes and NVU. According to the morphology of the trunk and branches, pericytes can be distinguished as helical pericytes and mesh pericytes in capillaries. **a** The helical pericyte: the primary trunk and branches are thin singular strands, and the secondary processes branch off from the thin single strands, forming a helical structure. **b** The mesh pericyte: the primary trunk shapes a mesh-like structure surrounding the entire vessel, and is more commonly found in larger diameter microvessels (6–10 μm). **c** NVU: The NVU is composed of vascular components, glial cells, and neurons

sophisticated cell-to-cell interactions between two cells. In areas where the direct connection is absent, interdigitations of pericyte and endothelial cell membranes form peg-and-socket contacts (Sims, 1991) which contain tight-, gap-, and adherence junctions (Armulik et al., 2005). Although endothelial cells perform most of the properties of the BBB (Daneman, 2012), their presence alone does not keep the BBB functioning properly (Ayloo et al., 2022). The intricate connection between pericytes and endothelial cells determines the important role of pericytes in BBB. Also, previous studies have demonstrated that pericytes help regulate the BBB from embryogenesis (Armulik et al., 2010; Daneman et al., 2010). Platelet-derived growth factor-BB/platelet-derived growth factor receptor-beta (PDGF-BB/PDGFRβ) signaling and Angiopoietin (Ang)/Tie2 system have a critical role in BBB stabilization throughout growth and development (Sweeney et al., 2016). Lack of endothelial-secreted PDGF-BB or loss of pericyte PDGFRβ can lead to disruption of BBB integrity (Winkler et al., 2010), resulting in embryonic lethality or various neurological disorders. Angiopoietin-1 (Ang-1) has been shown to be constitutively expressed in pericytes and activates the Tie2 receptor in endothelial cells to prevent vascular leakage (Gurnik et al., 2016). While endothelial cell-derived angiopoietin-2 (Ang-2) is reported to increase both the paracellular and the transcellular permeability at the BBB in a mouse stroke model (Gurnik et al., 2016). N-cadherin plays a significant role in endothelial cell-pericyte interactions mediated by brain endothelial cells Smad4 and is thought to be an initial signal for BBB development and increases in angiogenic vessels (Li et al., 2011). Pericyte-endothelial cell interactions may not be unique. Ando et al. found that a pericyte contacts multiple endothelial cells and can extend to more than one capillary (Ando et al., 1999), which means it integrates signals along the length of one vessel and also communicates with other vessels (Bergers & Song, 2005).

In addition to maintaining the BBB through signaling with endothelial cells, the existence of pericytes can also reduce the transmembrane transport of endothelial cells. Mfsd2a$^{-/-}$ mice exhibit a sharp increase in vesicular transport under electron microscopy without variation of endothelial tight junctions, leading to leakage of BBB from embryonic to adult periods (Ben-Zvi et al., 2014). A recent study demonstrates that vitronectin-integrin α5 signaling from pericytes to endothelial cells maintains barrier integrity by actively inhibiting transcytosis in endothelial cells (Ayloo et al., 2022). A single-cell RNA analysis of pericytes-function-loss mice found that hotspot sites were hallmarked by low Mfsd2a and low Ang-2 expression (Mäe et al., 2021) (Fig. 3). Studies related to the interaction between pericytes and endothelial cells in ischemic stroke are also emerging. In oxygen deprivation models, pericytes have a stronger ability to maintain blood–brain barrier integrity than astrocytes

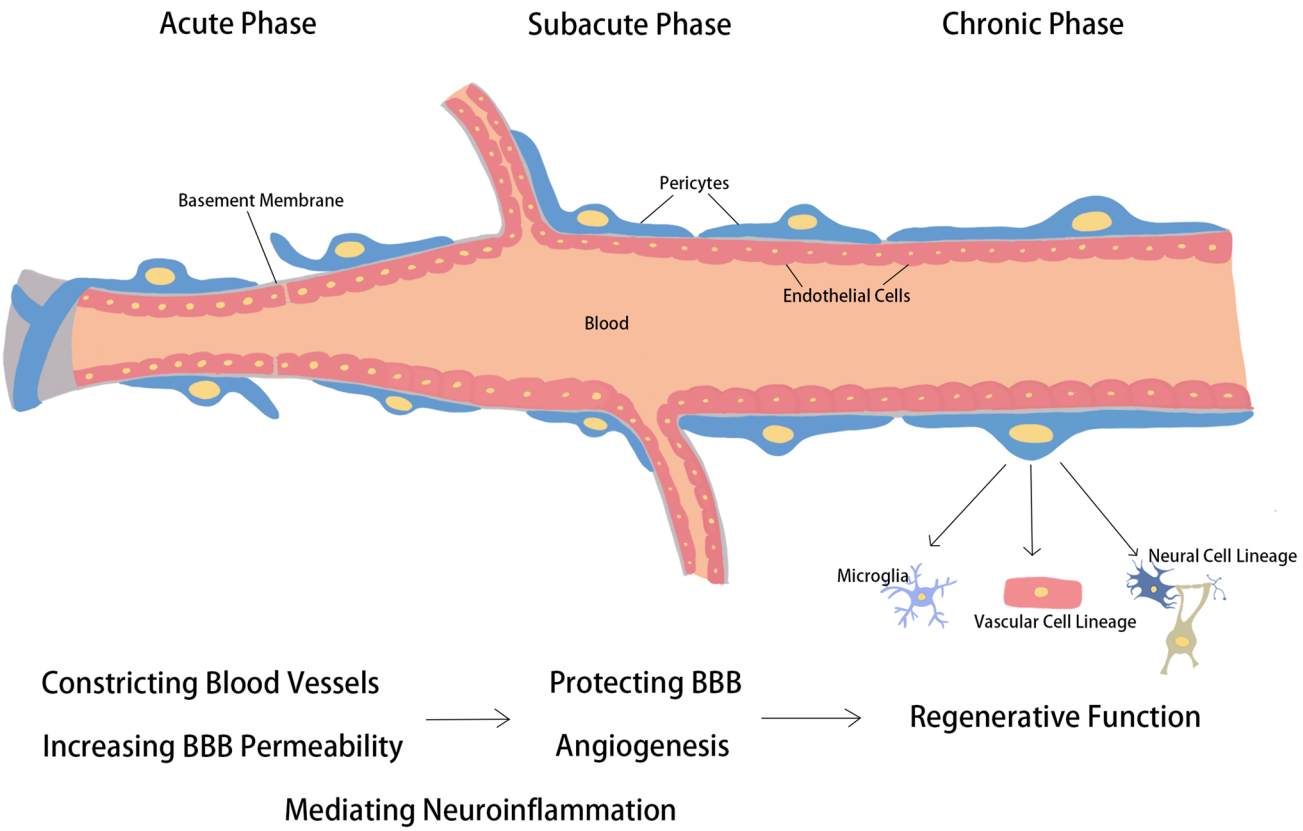

Fig. 2 The temporal dynamics of pericyte functions in ischemic stroke. Pericytes mainly exhibit the function of constricting blood vessels and increasing BBB permeability in the acute phase. Following vasoconstrictive action, pericytes die or separate immediately from blood vessels. The function of mediating neuroinflammation also manifests after BBB disruption and lasts a long time. In the subacute phase, pericytes exert the protective effect of the BBB and the function of angiogenesis. In the late chronic phase of ischemic stroke, the regenerative function of pericytes appeared

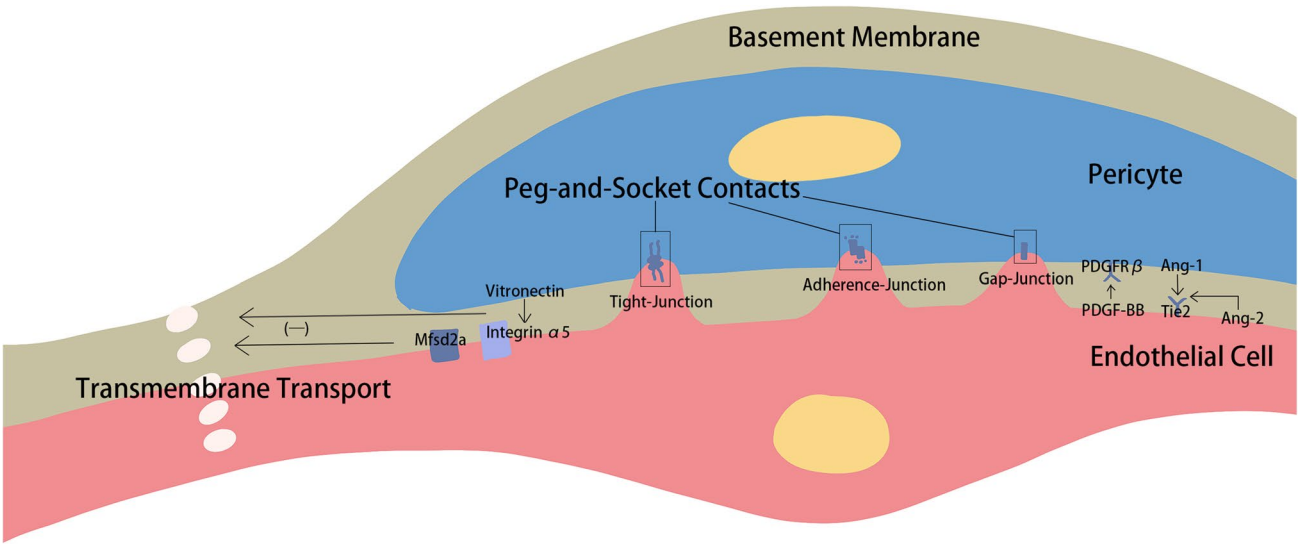

Fig. 3 Cell-to-cell interactions between pericytes and endothelial cells. Pericytes share a BM with endothelial cells and are also covered by a BM. PDGF-BB/PDGFRβ signaling and Ang/Tie2 system are the basis for maintaining the stability of the BBB. Cell-to-cell interactions between two cells keep the BBB functioning properly. In areas where the BM is absent, pericytes and endothelial cells membranes form peg-and-socket contacts. The transmembrane transport in endothelial cells can be reduced by the existence of pericytes through Mfsd2a and vitronectin-integrin α5 signaling

during severe and prolonged hypoxic conditions (Abbott, 2002; Al Ahmad et al., 2009). Fernández-Klett F el at. found that early pericyte death (within 24 h) preceded endothelial cell degeneration (after day 5) in the MCAO model (Fernández-Klett et al., 2013).

The crosstalk between pericytes and astrocytes also plays an important role in maintaining BBB integrity. Astrocytic end-feet express the water channel protein aquaporin-4 (AQP4), which plays a vital role in the integrity of the BBB (Abbott et al., 2006). Under normal conditions, pericytes regulate the distribution of AQP4 in the end-feet of astrocytes (Armulik et al., 2010; Gundersen et al., 2014). When pericytes are injured in ischemic stroke, the regulator of G-protein signaling 5 (RGS5) is upregulated before they detach from the blood vessels (Özen et al., 2014). And in a subsequent study, it was proved that the loss of RGS5 in pericytes contributes to the retention of AQP4 in the astrocyte end-feet and plays a neurovascular protective role (Özen et al., 2018). Similarly, astrocytes also help pericytes maintain BBB stability by secreting laminin (Yao et al., 2014). In contrast, semaphorin 4D (Sema4D) from astrocytes binds to PlexinB1 in pericytes and disrupts BBB integrity after stroke in rats (Zhou et al., 2018b.

Putting aside the association between pericytes and neighboring cells, only the pericytes themselves were taken out. Pericytes are an important source of extracellular matrix (ECM) in the BM (Xu et al., 2019). There are four major ECM proteins in the BM: collagen IV, laminin, nidogen, and perlecan (Yurchenco, 2011). Pericyte-derived laminin is associated with the maintenance of BBB permeability (Gautam et al., 2016). However, the effect of laminin on BBB is controversial in relation to the type of BBB. Lamininα5 and lamininα4 derived from mural cells may attenuate BBB damage during intracerebral hemorrhage by reducing transcytosis (Gautam et al., 2020). On the contrary, lamininα5 was demonstrated to play a negative role in ischemic stroke, and lamininα5-PKO mice exhibited milder neuronal injury and attenuated vascular damage, suggesting that inhibition of that signaling may have a neuroprotective effect (Nirwane et al., 2019). Also, it was found that endothelial cell-derived perlecan is upregulated in the BM, a process critical to the repair of BBB functions after ischemic stroke (Nakamura et al., 2019). Although current studies on pericyte-associated BM modifications after stroke mainly focus on laminin and perlecan, perhaps BM-targeted therapy is a path forward (Kang & Yao, 2020). HIF-1 once thought to be a protective factor, is produced under hypoxic conditions in the cardiovascular system (Bishop & Ratcliffe, 2015). However, HIF-1 loss-of-function in a model of cerebral ischemia shows less pericyte death, resulting in broader vascular coverage and better integrity in BBB. Therefore, that reduces the degree of infarction and cerebral edema post-stroke (Tsao et al., 2021). From a perspective other than molecular, Tunneling Nanotubes (TNT), open membranous channels for cell-to-cell communication (Rustom et al., 2004), were thought to show a functional role in the crosstalk among BBB. Ischemia-induced astrocyte apoptosis is reduced by TNT-mediated mitochondrial transfer of pericytes (Pisani et al., 2022), which allows for repair of the BBB after ischemic injury.

Recently, increasing studies have found pericytes to be heterogeneous (Dias Moura Park et al., 2016; Prazeres et al., 2017), implying that pericytes may exhibit different features after stroke. Type-1 pericytes are considered to be physiological capillary PCs, while type-2 pericytes are pathological. Type-2 pericytes were first described in skeletal muscle using Nestin-GFP/NG2-DsRed transgenic mice (Birbrair et al., 2013). And then they were claimed to be recruited during tumor angiogenesis (Birbrair et al., 2014). In the brain, PDGFRB + /SMA + /MYH11- (type-2) pericytes may be a cellular biomarker associated with the degree of BBB disruption, not limited to the disease state (Bohannon et al., 2020).

It has been proved that imperfect BBB recovery post-stroke may increase the risk of aftermath events and cognitive impairment (Taheri et al., 2011). Cerebral pericytes are integral components of the neurovascular unit, which governs the BBB (Ding et al., 2021). They are indispensable for BBB, so the opinion that maintaining pericytes function contributes to stroke recovery is increasingly reinforced.

Regulating Cerebral Blood Flow

Pericytes surround around blood vessels and constrict capillaries, leading to a decrease in CBF (Fernández-Klett et al., 2010; Peppiatt et al., 2006). In addition to the constrict ability, pericytes can be relaxed by neuronal activity and the neurotransmitter glutamate to dilate capillaries (Hall et al., 2014). However, the function of regulating CBF is unclear due to the difficulties in distinguishing pericytes from vascular smooth muscle cells (SMCs). What is clear is that SMCs on arterioles and ensheathing pericytes on pre-capillary arterioles (pre-capillary SMCs) control blood flow (Hill et al., 2015). To precisely identify these two types of cells, many markers have been studied in recent years and have been well reviewed (Bohannon et al., 2021; Grant et al., 2019; Zheng et al., 2020). Meanwhile, a technology to label pericytes in live models without marking SMCs was developed in 2017 (Damisah et al., 2017). In addition to difficulties in identification, the intrinsic connectivity of the cerebrovascular system hinders the certainty of pericyte regulation of CBF function of pericytes. Recently, the optical ablation of single capillary pericytes was used to isolate the effect of pericyte loss on local blood flow. The results suggest that capillary pericytes can modulate capillary diameter, influence blood flow in vivo, and establish basal capillary flow resistance

(Hartmann et al., 2021). Bohannon et al. demonstrated that pericytes first constrict the capillaries and then end up with death when capillaries are exposed to ischemia (Hall et al., 2014). After stroke, preventing pericytes from shrinking and dying may reduce long-term blood flow to injured neurons. Nonetheless, novel methods are needed to further study the role of pericytes in regulating blood flow.

Mediating Neuroinflammation

Neuroinflammation is involved in the pathophysiology of almost all neurological diseases (Rustenhoven et al., 2017). In ischemic stroke, this process probably includes oxidative stress, increased matrix metalloproteinase (MMP) production, infiltration of peripheral immune cells, and activation of microglia and astrocytes (Candelario-Jalil et al., 2022).

The role of pericytes in neuroinflammation has been studied for decades (Rustenhoven et al., 2017). Pericytes of the central nervous system were thought to have the ability to present antigens to T-lymphocytes (Balabanov et al., 1999). Then in vitro experiments which were stimulated with tumor necrosis factor (TNF) or lipopolysaccharide (LPS) demonstrated pericytes have the ability to detect inflammation because they have pattern recognition receptors (Guijarro-Muñoz et al., 2014; Stark et al., 2013). These studies reveal the active role of pericytes in innate immune responses, concluded to support immune surveillance.

Furthermore, in the experimental autoimmune encephalomyelitis (EAE) models, the infiltration of leukocytes into the CNS was negatively correlated with the coverage of pericytes in the vasculature (Török et al., 2021). However, it is not entirely clear whether CNS pericytes exhibit a pro- or anti-inflammatory profile (Rustenhoven et al., 2016). The polarity of pericytes may be similar to that of microglia in neuroinflammation under an ischemic environment (Ma et al., 2017). Therefore, more studies are needed to demonstrate the role of pericytes in neuroinflammation in ischemic stroke.

Promoting Angiogenesis

New blood vessels are formed through angiogenesis, a multifactory process requiring synchrony between endothelial cells and pericytes (Mastrullo et al., 2020). Angiogenesis after stroke can mitigate hypoxia-induced damage caused by ischemia (Ergul et al., 2012). And in theory, angiogenic therapy can save the ischemic border zone (Ergul et al., 2012). However, given the notion that treatments that promote angiogenesis may exacerbate stroke outcomes since new angiogenesis-induced vessels are more permeable than usual (Yang & Torbey, 2020). Accordingly, we speculate that the synergy of pericytes especially the function of promoting vascular maturation is important in this process.

In a newly formed blood vessel, pericytes are recruited through communication with endothelial cells, resulting in the formation of a new BM (Stratman et al., 2009). And PDGF-BB/PDGFRβ signal was thought to lead to pericyte recruitment and then stabilize the blood vessel (Gaengel et al., 2009). Also, angiogenesis and vascular integrity in the ischemic brain are partially modulated by pericyte-specific expression of vascular endothelial growth factor receptor 1 (VEGFR1) (Zechariah et al., 2013). When VEGF is present, Ang2/Tie2 signals make the system highly plastic, forming new vessels continuously (Ghori et al., 2022).

Regenerative Functions of Pericytes

Acting as Multipotent Stem Cells

The regenerative potential of pericytes has been discussed in various organs in addition to CNS. Since the discovery of the transformation of pericytes into microglia with the help of astrocytes in the cat cerebral cortex (Barón & Gallego, 1972), the debate on the potential of cerebral pericyte pluripotent stem cells has begun (Table 1).

Using cell markers, nestin/NG2-positive pericytes are considered to be a source of adult stem cells in vitro (Dore-Duffy et al., 2006). Under hypoxic conditions in vitro, human brain-derived pericytes were found to upregulate the expression of activated microglial mRNA, implying that they acquire a microglial cell phenotype (Özen et al., 2014). Furthermore, they showed that pericytes express microglia markers not only in vitro but also in human post-stroke brain tissue. In these observations, ischemia/hypoxia might enhance stem-like activity in brain pericytes, but we do not know which exact mechanisms are essential for their induction (Nakagomi et al., 2011). Reprogramming is reckoned as a pivotal process in transformation following the indications that after ischemia or hypoxia pericyte marker expression was downregulated, while stem cell-like marker was upregulated. Under oxygen/glucose deprivation, pericytes acquire the capacity of multipotential stem cells and can differentiate into major the BBB/neurovascular unit components because of reprogramming (Sakuma et al., 2016). This strategy could be used to induce pluripotency in pericytes to promote regeneration (Karow et al., 2018). Another possible mechanism was recently explained. Oxidative stress after ischemia with the expression of Nrf2 may trigger pericytes to acquire stemness (Sakuma et al., 2022). Similarly, in 2016, Sakuma R et al. revealed that pericytes show multipotent activity in MCAO models indicating that pericytes may be a novel source of microglia after ischemic stroke (Sakuma et al., 2016). Ischemia-induced multipotent stem cells (iSCs) in the human post-stroke brain were first isolated in 2017, and they are likely pericyte derivatives. More importantly,

Table 1 Studies of the multipotency of pericytes in cerebral ischemia

Year	Study type	Pericytic identity	Materials	Phenotype acquired	References
2011	In vitro	Circulating PDGFRβ (+) cells	The venous blood of stroke patients	Neural or vascular cell lineage	Jung et al. (2011)
2011	In vitro	PDGFRβ (+)	MCAO mice	Pial nestin-positive iNSPCs	Nakagomi et al. (2011)
2014	(1) In vivo (2) Ex vivo	Rgs5(+)	(1) MCAO $Rgs5^{gfp/+}$ mice (2) Post-stroke human brain tissues	microglial	Özen et al. (2014)
2015	Ex vivo	Nestin/PDGFRβ/NG2 (+) CD31 (-)	(1) iPCs from MCAO mice brains (2) Human PCs-OGD	Neural and vascular cell lineage	Nakagomi et al. (2015)
2016	Ex vivo	PDGFRβ(+)	(1) iPCs from MCAO mice brains (2) mice PCs-OGD	Microglial and multipotent VSC activity	Sakuma et al. (2016)
2017	Ex vivo	αSMA/NG2/PDGFRβ (+)	Post-stroke human brain tissues	Neural and vascular cell lineage	Tatebayashi et al. (2017)
2022	In vivo	PDGFRβ (+) $SMA^{low/undetectable}$	MCAO mice	Microglia-like and macrophage-like cells	Nirwane and Yao (2022)
2022	In vitro	αSMA/PDGFRβ/NG2 (+) CD31 (−)	MCAO mice	Neural cell lineage	Sakuma et al. (2022)

MCAO middle cerebral artery occlusion, *iNSPCs* ischemia-induced neural stem/progenitor cells, *iPCs* pericytes following ischemia, *VSC* vascular stem cells, *OGD* oxygen–glucose deprivation, *PCs-OGD* pericytes cultured under oxygen–glucose deprivation

they may help neural repair or regeneration in patients with ischemic stroke (Tatebayashi et al., 2017). The anti-ischemic effect of pericytes due to their multipotency has been used for limb ischemia (Yoshida et al., 2020). Recently, the lineage-tracing technique was used to trace pericyte fates after ischemic stroke. They found that $SMA^{low/undetectable}$ pericytes differentiated into both microglia and macrophages after the acute period of ischemic stroke (Nirwane & Yao, 2022). In conclusion, these studies suggest that pericytes not only have a strong migratory and proliferative response to ischemic brain injury but also serve as a source of neural lineage cells. While lineage-tracing experiments utilizing an inducible Tbx18-CreERT2 line insist that pericytes as well as vascular smooth muscle cells fail to contribute to other cell lineages, it is noteworthy that this study did not use an ischemia model (Guimarães-Camboa et al., 2017).

Furthermore, apart from transforming into neural lineage cells, pericytes are also revealed to be fibrotic activity. Type A pericytes were first proposed in models of spinal cord injury (Göritz et al., 2011). Blocking the proliferation of such cells will result in the inability to seal the damaged tissue. Interestingly, single-cell analyses later challenged this result suggesting such cells refer to fibroblast-like rather than pericytes (Vanlandewijck et al., 2018). Same to the previous work, Roth M et al. illustrated that the fibrotic ECM is not major coming from pericytes, so targeting pericytes to scar formation after stroke may be useless (Roth et al., 2020). However, type A pericytes were once again shown to be the source of fibrotic ECM, and this result is not limited to ischemic injury but is conserved across diverse central nervous system diseases (Dias et al., 2021). To further prove this idea, a single-cell RNA sequencing analysis was performed revealing that pathways related to fibrosis were enriched in pericytes of cardiac and cerebral ischemic injury (Pham et al., 2021).

The controversy over the presence of pluripotent stem cell potential in pericytes is mainly due to the lack of an appropriate marker for pericytes as well as multipotent pericytes if they existent (Yoshida et al., 2020). Further studies on this area need to be conducted.

Promoting OPCs Differentiation

It has been previously illustrated that more than two of third patients suffered disability after ischemic stroke even if they were successfully treated with reperfusion (Goyal et al., 2016). Cerebral white matter (WM) is particularly vulnerable to vascular occlusion. Numerous studies have demonstrated that WM damage after stroke is associated with long-term sensorimotor deficits and cognitive decline (Arai, 2020; Matute et al., 2013).

The WM is mainly composed of myelinated axons and glial cells. Multiple myelin sheaths produced by oligodendrocytes wrap the axons. Oligodendrocytes as important WM components are originally from OPCs (Bercury & Macklin, 2015). Myelin repair and oligodendrocyte formation in the adult brain are determined by OPCs (Menn et al., 2006) which comprise 5–8% of all the cells in the adult brain and are abundant in both grey and white matter areas (Dawson et al., 2000). Demyelination causes oligodendrocytes to split and differentiate, replacing lost oligodendrocytes with new ones (Levine et al., 2001). Therefore, targeting OPCs

to repair WM after ischemic stroke may promote functional recovery. Although there is a vast body of related research on glial cells such as microglia (Shi et al., 2021) and astrocytes (Miyamoto et al., 2015), it mostly falls into pericytes in this section.

It has been reported that in the perivascular region of cerebral WM, pericytes and OPCs may attach and support each other (Maki et al., 2015). Using pericyte-deficient mice, pericyte degeneration was found to disrupt WM microcirculation, which results in an accumulation of toxic blood-derived fibrinogen deposits leading to a loss of myelin, axons, and oligodendrocytes (Montagne et al., 2018). A variety of molecules secreted by pericytes may be required for OPC-to-oligodendrocyte renewal. A-Kinase Anchor Protein 12 (AKAP12) is thought to mainly express on pericytes and is necessary for OPCs function to keep WM homeostasis (Maki et al., 2018). Lama2 has also been identified as a pericyte-derived factor that promotes OPCs differentiation in multiple sclerosis (MS) (De La Fuente et al., 2017). It is shown to support OPCs differentiation into oligodendrocytes without affecting remyelination from OPCs in vivo. Besides functioning in demyelinating diseases, pericytes may promote peri-infarct oligodendrogenesis after ischemic stroke resulting in functional recovery (Shibahara et al., 2020a). The crosstalk between pericytes and macrophages may be critical for this procession in poststroke tissue repair (Shibahara et al., 2020b). However, the origin of pericytes in the infarct area should be further validated.

It is important to note that neurological disorders associated with cognitive dysfunction, cerebrovascular dysfunction, and WM lesions are characterized by a loss of pericyte coverage (Ding et al., 2020). Thus, the functional role of pericytes is not limited to vascular homeostasis but also includes modulating the progenitor cells of adult CNS regeneration.

Conclusions

We summarize the functions of pericytes after stroke as maintaining BBB, regulating CBF, mediating immune responses, promoting angiogenesis, acting as pluripotent stem cells, and promoting OPCs differentiation. Accordingly, pericytes are a promising source of cells for cell therapy and tissue engineering. In the acute phase, inhibiting the contractile function of pericytes and enhancing the function of protecting the BBB may help reduce the occurrence of hypoperfusion, edema, and increased infarct size after ischemic stroke. In subacute and late phases, focusing on the regenerative function of pericytes may contribute to neurological recovery. However, there is still much controversy surrounding the studies of pericytes. Firstly, accurate cellular markers for pericytes need to be identified so that the function of pericytes can be distinguished from vascular smooth muscle cells. Secondly, whether there is the heterogeneity of pericytes in the pathological process after stroke should be further studied. If pericytes, like microglia, are polarized, then drugs that target the polarization of pericytes may be effective in the treatment of stroke. Single-cell studies on pericyte heterogeneity are now available (Vanlandewijck et al., 2018). This may be the way forward as single-cell studies have the ability to differentiate between cell subpopulations (Liu & Zhang, 2022; Qiu et al., 2021). Finally, Research on pericytes after ischemic stroke is more limited to in vitro studies. In vivo, it remains unclear whether they differentiate into neural lineage cells. There is still a long way from clinical trials, so more attention should be paid to pericytes in ischemic stroke. Overall, based on the properties and functions that have been identified so far, further research on pericytes may provide new directions for the treatment of neurological recovery after stroke.

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Data availability Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Competing interest The authors have no competing interests to declare that are relevant to the content of this article.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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