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The evolving roles of pericyte in early brain injury after subarachnoid hemorrhage

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Abstract

Despite accumulated understanding on the mechanisms of early brain injury and improved management of subarachnoid hemorrhage(SAH), it is still one of the serious and refractory health problems around the world. Traditionally, pericyte served as capillary contraction handler, is recently considered as the main participant of microcirculation regulation in SAH pathophysiology. However, accumulate evidences indicate pericyte is much more than we already know. Therefore, we briefly review the characteristics, regulation pathways and functions of pericyte, aim to summarize the evolving new pathophysiological roles of pericyte that are implicated in early brain injury after SAH and to improve our understanding in order to explore potential novel therapeutic options for patients with SAH.

Keywords

pericyte; subarachnoid hemorrhage; early brain injury; vascular neural network

1. Introduction

Subarachnoid hemorrhage(SAH) is usually defined as a devastating cerebrovascular disease after bleeding into subarachnoid space(Suarez et al., 2006). For a long time, vasospasm and following delayed cerebral ischemia are thought to be the majority cause of SAH(Macdonald et al., 2007). But, disappointingly, treatment with clazosentan, an endothelin receptor antagonist that effectively reverses angiographic vasospasms, has failed to reduce mortality and neurological outcome after SAH(Chen et al., 2011; Macdonald et al., 2011; Wong and Poon, 2011). On the other hand, early brain injury, which occurs within 72

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Conflicts of interest
None

hours after SAH, becomes a common sense in recent studies to be the most important pathogenic factor in SAH patients (Cahill and Zhang, 2009; Sehba et al., 2012). Despite accumulated understanding on the mechanisms of early brain injury and improved management of SAH, it is still one of the serious and refractory health problems around the world (Sehba et al., 2011; Sehba et al., 2012). Among the cells of the vascular neural network in our brain (Leak et al., 2013; Zhang et al., 2012), pericyte served as capillary contraction handler, is recently considered as the main participant of microcirculation regulation in SAH pathophysiology (Hall et al., 2014; Ostergaard et al., 2013; Tso and Macdonald, 2014). However, accumulate evidences indicate pericyte is much more than we already know. Therefore, we briefly review the characteristics, functions and cell interactions of pericyte, aim to summarize the evolving new pathophysiological roles of pericyte that are implicated in early brain injury after SAH and to improve our understanding in order to explore potential novel therapeutic options for patients with SAH.

2. Characteristics of pericyte in brain

2.1 Location of pericyte

Pericytes are usually present on the outside surface of endothelial cells of capillaries, as well as arterioles and venules (Dore-Duffy and Cleary, 2011; Farrell et al., 1987; Frank et al., 1990). Pericytes cover about quarterly cerebral capillary surface and postcapillary venules tend to have more pericytes than capillaries (Allt and Lawrenson, 2001). The location of pericytes on the microvessel is not random but appears to be functionally determined (Allt and Lawrenson, 2001). In a typical neurovascular unit, pericyte is surrounded by two layers of basal membranes, one layer separates pericytes from endothelial cells, whereas another layer serves to compartmentalize pericytes from astrocyte endfeet (Sa-Pereira et al., 2012).

Electron microscopy studies have found that the interaction between endothelial cells and pericytes has three ways: (1) gap junction; (2) tight junction; (3) Adherence junctions (Cuevas et al., 1984; Gerhardt et al., 2000; Gerhardt and Betsholtz, 2003). This area was called peg-socket contacts which represent membrane invaginations extending from either cell type (Caruso et al., 2009). In their adhesion plaques, the intercellular space between the two cell types is maintained and contains fibronectin deposits (Courtoy and Boyles, 1983). Therefore, pericytes appear to be arranged to facilitate and integrate cell communication. And a single pericyte often contacts with several endothelial cells through these specialized contacts, they may integrate and coordinate neighboring endothelial cell responses. Furthermore, a lot of experiments revealed the five canonical signaling pathways between those two cells: TGF- β signaling pathway, Angiopoietin-Tie2 signaling pathways, PDGF- β / PDGFR- β signaling pathway, S1P/Edg signaling pathway and Notch signaling pathway (Armulik et al., 2005). These interactions play a vital role in blood vessel formation, stability and permeability.

2.2 Cellular feature of pericyte

Based on the presence or absence of cytoplasmic, lysosome-like granules of variable size and appearance, there are two types of pericytes exist in cerebral microvasculature, granular and agranular. However, agranular pericytes only constitute less than 5% of the

population(Farrell et al., 1987). Granular pericyte morphology(Figure 1) is characterized by a stellate appearance with long cytoplasmic processes(Fisher, 2009; Li et al., 2013). Pericyte granularity is associated with extent of cytoplasmic lysosomes, and human brain pericytes appear to be exclusively granular with high content of acid phosphatase(Allt and Lawrenson, 2001).

2.3 Identification of pericyte

For a long time, researchers are looking for specific immunochemical markers of pericyte. So far, attempts to identify pericyte typically require stains with a combination of positive and negative immunoreactivity. To be specific, pericyte is immunoreactive for α -smooth muscle actin, nestin, alkaline phosphatase, γ -glutamyl transpeptidase vimentin, neuroglial cell 2 chondroitin sulfate proteoglycan(NG-2) and the platelet derived growth factor-beta(PDGF- β) receptor(Armulik et al., 2011)(Figure 2). On the other hand, pericyte shows no immunoreactivity for von Willebrand factor and glial fibrillary acidic protein, markers for endothelial cells and astrocytes, respectively(Armulik et al., 2011; Guillemin and Brew, 2004). However, it is gratifying that Bondjers et al's work may shed new light on pericyte identification. By using brain microvessels from mice mutant without PDGF- β or the PDGF- β receptor, they found that brain pericytes expressed the adenosine triphosphate sensitive potassium channel Kir6.1, and more importantly, this expression seemed to be limited to the pericytes of the brain(Bondjers et al., 2006).

3 Regulation pathways of pericyte involved in SAH

3.1 PDGF pathway

At the very beginning of angiogenesis, PDGF- β is the crucial factor of sprouting capillaries recruiting pericytes, which highly express PDGF- β receptor. And PDGF- β , secreted by endothelial cells, contains a specific sequence to combine with chondroitin sulfate proteoglycan, in order to maintain its local high concentration at spouting area and enhance the effect of pericyte recruiting(Hellstrom et al., 1999; Winkler et al., 2010). PDGF- β deficient mouse embryos were found to lack microvascular pericytes. And they developed numerous capillary microaneurysms that ruptured at late gestation. Endothelial cells of the sprouting capillaries in the mutant mice appeared to be unable to attract PDGF- β receptor positive pericyte progenitor cells(Lindahl et al., 1997).

Secreted PDGF could build up five different disulphide-linked dimers, act via two tyrosine kinases receptor, PDGF receptors alpha and beta(Fredriksson et al., 2004). After combined with PDGF- β receptor, PDGF-BB cause receptor to be self-phosphorylated on tyrosine residues, result in inducing several classic signal cascades, such as mitogen-activated protein kinase(MAPK)/ extracellular signal-regulated kinase(ERK) pathway, phosphoinositide 3-kinase(PI3K)/ protein kinase B(AKT) pathway, phospholipase C gamma(PLC- γ)/protein kinase C(PKC)/calcium pathway, and mediating cell proliferation, survival and migration(Andrae et al., 2008). Early after SAH, a significant release of PDGF was reported and higher levels of PDGF were found in cisternal cerebrospinal fluid of patients being operated within 72 hours after SAH(Gaetani et al., 1997). In our previous studies, by targeting PDGF- α receptor, we found that PDGF signaling may contribute to blood brain

barrier impairment and neurological deficits, bring about the early brain injury in both SAH and intracerebral hemorrhage (Ma et al., 2011; Zhan et al., 2015).

3.2 Notch pathway

Notch signaling pathway has well defined to play a critical role in the development and homeostasis of the neurovascular system (Hofmann and Iruela-Arispe, 2007). In general, there are four different heterodimeric receptors, Notch1-Notch4, and five ligands, delta-like 1 (DLL1), delta-like 3 (DLL3) and delta-like 4 (DLL4) and jagged 1 (Jag1) and jagged 2 (Jag2). Of the four receptors, Notch1 and Notch4 have being reported to predominant in the endothelial cells, whereas Notch1 and Notch3 are present in smooth muscle cells. And the five ligands, DLL1, DLL4 and Jag1 are the most popular in the endothelial cells, while Jag1, Jag2 and DLL1, also being found on smooth muscle cells (Li and Baker, 2004). After ligand-receptor binding, subsequently proteolytic effect releases the Notch intracellular domain, which translocates to the nuclear and binds to the transcription factor recombination signal binding protein J κ (RBP-J κ), leading to downstream transcriptional activities (Weinmaster, 2000).

Recent studies showed that Notch1 and Notch3 receptor are also presented in cerebral pericytes (Gu et al., 2012; Guichet et al., 2015; Regan and Majesky, 2009; Walshe et al., 2011), and implied that Notch signaling could be important for pericyte attachment to endothelial cells and survival (Li et al., 2011; Liu et al., 2009; Liu et al., 2010; Stewart et al., 2011; Winkler et al., 2011b). For example, specifically inhibit RBP-J κ in endothelial cell was reported to impair pericyte adhesion, leading to reduced pericyte coverage and perinatal intracerebral hemorrhage (Li et al., 2011; Winkler et al., 2011a; Winkler et al., 2011b). Some other studies have suggested that Notch3 receptor could be crucial in pericyte survival (Liu et al., 2010; Walshe et al., 2011) and Notch ligand DLL4 maybe functional in pericyte differentiation (Stewart et al., 2011). Underline with these evidences between Notch signal and pericyte, Notch inhibition treatment could significantly decrease Notch1 receptor expression and attenuate the neurological deficits after SAH (Yang et al., 2010). However, we are still far from the therapeutic modulation of Notch signaling in SAH patients (Andersson and Lendahl, 2014), more work is needed to establish the exact mechanism of Notch signaling in pericytes and other possible pathophysiology of SAH.

3.3 Canonical Wnt/ β -catenin pathway

Wnt pathway is a highly conserved cellular communication system that is mediated cell proliferation, migration, polarization, apoptosis, and stem cell differentiation (Klaus and Birchmeier, 2008). Nineteen different Wnt ligands were reported existence, which could potentially bind to and signal through 10 members of the Frizzled family receptors. Depend on Wnt/Frizzled receptor interaction and differences in co-receptors, Wnt downstream signal can be distinguished into three pathways, canonical β -catenin pathway, non-canonical calcium and planar cell polarity pathway (Coombs et al., 2008; Reis and Liebner, 2013). In the canonical Wnt pathway, when ligands bind to Frizzled receptors, there will be an inhibition of β -catenin degradation in proteasome. Then, β -catenin accumulates in cytoplasm, translocates into the nuclear, binds to T cell factor/lymphoid enhancer factor and initiates downstream protein transcription (Liebner et al., 2008; Logan and Nusse, 2004).

It was reported that pericyte also expresses one of the Frizzled receptor, Frizzled-4 (Kirton et al., 2007), which may be vital to canonical Wnt signal mediating neural tube and retinal vascularization and maintains the blood brain barrier and blood retinal barrier (Obermeier et al., 2013; Stenman et al., 2008; Zhou et al., 2014). And endothelial β -catenin also plays a central role in embryonic and postnatal blood brain barrier maturation by regulating tight junction proteins and adherent junction proteins (Liebner et al., 2008; Zhou et al., 2014). However, Wnt protein has widely expression in different tissues and non-specifically effects, which are tricky to be manipulated, upregulation could cause high bone mass and even cancer, but downregulation could lead to osteoporosis and heart failure (Liebner et al., 2008). Thus, find the right target of Wnt pathway and making sure it acts on the target and nowhere else is vital to not trigger off-target side effects (Coombs et al., 2008). Due to the central nervous system specific expression (Daneman et al., 2009; Junge et al., 2009; Ohlmann et al., 2012), we used Norrin proteins in our recent studies (Chen et al., 2015b) to activate Frizzled-4 receptor and downstream canonical β -catenin pathway, managed to reduce brain edema, protect blood brain barrier integrity and eventually improve neurological function after SAH. Besides, we also found Wnt inhibition maybe a promising treatment to alleviate subarachnoid fibrosis after cerebral hemorrhage (Meng et al., 2014).

3.4 New players in pericyte signaling

It can be sure that there are still other pathways involved in pericyte physiology, such as transforming growth factor- β signal in induction of pericyte differentiation and adhesion (Gaengel et al., 2009; Lebrin et al., 2005; Sieczkiewicz and Herman, 2003; Walshe et al., 2009), p38-mitogen-activated protein kinase pathway in upregulating matrix metalloproteinase 9 (Takahashi et al., 2014), nitric oxide and calcium signal in pericyte contraction (Kamouchi et al., 2004; Yemisci et al., 2009), et al. Moreover, recent studies indicated some novel participants in pericyte interactions (Table 1).

3.4.1 MicroRNA—MicroRNA (miRNA) is a recently discovered group of small, genome-encoded endogenous RNAs that are transcribed but are not translated into proteins (Lagos-Quintana et al., 2001). It was reported to play an key regulatory role in many cellular functions, including cell growth, proliferation, differentiation, lineage determination and metabolism (Zhang, 2009). In central nervous system, miRNA was well established to be vital in neurogenesis (Li and Jin, 2010), neural development (Cochella and Hobert, 2012), differentiation (Lau and Hudson, 2010) and synaptic plasticity (Goldie and Cairns, 2012). Moreover, recent studies demonstrated that miRNAs are involved in responses to hypoxia and ischemia (Fasanaro et al., 2010; Yan et al., 2013a), and in ischemic tolerance induced by ischemic precondition (Lusardi et al., 2010).

As we reviewed before, SAH patient suffers in a global ischemia at the early stage of stroke onset (Chen et al., 2014). Recently, Truettner, et al used microarray to analysis the changes of miRNA in cortex pericytes under hypoxia, and found miR-322, miR-345-5p, miR-145, miR-150, miR-140, miR-126, miR-376b-3p and to a lesser degree of miR-222 were significantly upregulated, but other miRNAs such as miR-24, miR-140 and miR-199a were suppressed (Truettner et al., 2013). These changes are associated with hypoxia inducible factor-1 α (Ghosh et al., 2010; Gu and Chan, 2012), transforming growth factor-

β 1 (Bakhshandeh et al., 2012; Davis-Dusenbery et al., 2011; Pais et al., 2010) and vascular endothelial growth factor (Chamorro-Jorganes et al., 2011; Jafarifar et al., 2011; Lichner et al., 2012; Zhu et al., 2011), all of them are known as pericyte regulators (Du et al., 2008; Greenberg et al., 2008; Takata et al., 2007). In addition, miR-145 was found existence in pericytes. By targeting the hematopoietic transcription factor Fli1 miR-145 could block pericyte migration in response to the growth factor gradients (Larsson et al., 2009). Moreover, miR-132 secreted by exogenous saphenous vein-derived pericyte progenitor cells could stimulate endothelial tube formation and enhance angiogenesis (Katara et al., 2011).

3.4.2 Exosome—Exosomes are types of nano extracellular vesicles, naturally released from different kinds of living cells, can be taken up by recipient cells (Qin and Xu, 2014). Faure et al. described the release of exosomes by neuron in vitro (Faure et al., 2006). And Taylor et al. reported the secretion of exosomes by astrocytes, also in vitro (Taylor and Gercel-Taylor, 2011). Furthermore, exosomes can also be found in cerebral spinal fluid in animal models (Bachy et al., 2008; Vella et al., 2008), which might be a reminder of its vital role in brain physiologies.

Exosome has been recently known as intermediate link in cell-cell communication, with the capability of transferring the proteins, DNAs, microRNAs, non-coding RNAs and lipids with or without direct contact (Ailawadi et al., 2015). Xin et al. demonstrated exosomes secreted by mesenchymal stem cells can transfer microRNA-133b into neurons, resulting in the induction of synaptic growth (Xin et al., 2012). Morel et al. showed that neuron secretes microRNA-124a via exosomes, which subsequently transport into astrocytes, then indirectly increasing protein expression (Morel et al., 2013). Taken together, these finds support the hypothesis that exosome could mediate cell-cell communication in central nervous system.

Determined by the content of exosomes, it has been reported to involve in various pathophysiologies, such as neuroinflammation (Horstman et al., 2007), neurodegeneration (Kalani et al., 2014), vascular plasticity (Xin et al., 2013). However, it is still unclear about whether or what types of exosomes secreted by pericyte (Chivet et al., 2012). But, emerging evidences suggest exosome based interventions and technologies maybe promising in central nervous system disease diagnostic (Colombo et al., 2012; Felder et al., 2013; Kucharczyk et al., 2013; Rao et al., 2013). And their simple structure and ability to cross the blood-brain barrier makes exosome-based cell and gene therapies a bright prospects in the future (Braccioli et al., 2014; Li et al., 2014; O'Loughlin et al., 2012; Xin et al., 2014).

3.4.3 Long non-coding RNA—Long non-coding RNA (lncRNA) is a classic non-coding RNA with transcript frame longer than 200 nucleotide, usually in cytoplasm or nuclear, being well transcribed but lack of protein-coding capability (Ponting et al., 2009). At the beginning, lncRNA was considered to be the accessory substance of RNA polymerase II transcription, with no meaningful biological function. But, growing evidences suggests lncRNA maybe prevalent in cerebral cortex, hippocampus and olfactory bulb in central nervous system, involve in cell differentiation, cellular transportation, cell-cycle regulation, stem cell reprogramming and other molecular genetical and cellular functions (Clark and Mattick, 2011), and play an important role in various pathologies including

neurodevelopment, neuroinflammation, neurodegeneration, primary brain tumors and psychiatric diseases(Guennewig and Cooper, 2014; Qureshi et al., 2010).

Moreover, cerebral LncRNA expression profiles are significantly changed after ischemic brain injury(Dharap et al., 2012). With 62 stroke-positive LncRNA, they might also control chromatin modifications(Gupta et al., 2010), transcription factor activity(Khalil et al., 2009) and apoptosis(Huarte et al., 2010) as previously reported. To be specific in pericyte, it was showed that one of the stroke-positive LncRNA, metastasis-associated lung adenocarcinoma transcript 1(MALAT1) knockdown could ameliorate pericyte loss(Liu et al., 2014b) and endothelial dysfunction(Michalik et al., 2014). These results suggest LncRNA-MALAT1, along with other unveiling LncRNAs, are still needed to be studied in the future, and be clarified inherent mechanisms with early brain injury after SAH.

4 Multiple functions of pericyte in subarachnoid hemorrhage pathophysiology

Pericyte has substantial range of functions in central nervous system physiology, along with multiple effects in early brain injury pathophysiology. Based on increasing observations both in vivo and in vitro, these functions include as follow (Figure 3):

4.1 Contractile function

As we review in Section 2, pericyte locates around arterioles, capillaries and venules, with α -smooth muscle actin expression. The distribution of α -smooth muscle actin as well as the expression of endothelin receptor(Dehouck et al., 1997) in pericytes imply contractile function of pericytes with blood flow regulatory capabilities(Peppiatt et al., 2006).

Pericyte can be dilated and constricted by neurotransmitters in vitro(Puro, 2007). Extracellular transforming growth factor- β signal and intracellular Rho GTPase signal were previously reported to be involved in pericyte contractile(Bertolino et al., 2005; Kolyada et al., 2003; Kutcher and Herman, 2009). However, the specific mechanisms are still poorly understood, and the situations in vivo are much more complicated. First, previous evidences suggested global ischemia after SAH significantly constricts pericyte and reduces blood flow in microcirculation. But, wired against common sense, dilated pericyte may not reverse the blood flow, as we called as 'no-reflow phenomenon'(Greif and Eichmann, 2014; O'Farrell and Attwell, 2014). Second, in SAH and other brain injuries pathophysiology, pericyte contraction usually along with pericyte programmed cell death, leaves reduced capillary density and microcirculation maintaining shut down(Johshita et al., 1990; Ohkuma et al., 1997; Uhl et al., 2003). Third, even if pericyte in arteriole and capillary can be dilated after intervention, because of our ignorance with post-capillary and venule, where these pericytes are hard to response(Takahashi et al., 1994) and lumen in these areas is easy to be compressed(Ostergaard et al., 2013; Sehba and Friedrich, 2013; Uhl et al., 2003), blood flow are still not harmony in arterial and venous system(Chen et al., 2015a; Yemisci et al., 2009). Therefore, the whole vascular neural network is still barren, and worse still is that brain will be put in a danger place with edema and substantial hemorrhage.

4.2 Immune and phagocytic function

In central nervous system, besides microglia, pericyte is thought to be the second kind of macrophage and the first line of defense because of its antigen presentation capability and closest direct contractions with microvascular (Balabanov et al., 1999; Guillemin and Brew, 2004). It was reported that pericytes could detach from basal lamina and migrate into perivascular space without functional differences to perivascular inherent macrophages and reactive microglia (Guillemin and Brew, 2004). When pericyte presenting antigens, it may initiate a local pro-inflammatory response mediated by the increased expression of adhesion molecules (intercellular adhesion molecule-1 and vascular cell adhesion molecule-1) near endothelial cells and circulating cytokines and chemokines which contribute to neutrophil infiltration and tight junction degradation (Arima et al., 2013; Kovac et al., 2011). Furthermore, large number of acid phosphatase expressed by pericyte lysosomes indicates potential phagocytic function of pericytes (Allt and Lawrenson, 2001).

Despite so many researches on the role of neuroinflammation in early brain injury and delightful achievements of anti-inflammation treatment after SAH (Sercombe et al., 2002), they practically focused on microglia while pericyte involvement is still little to known (Hurtado-Alvarado et al., 2014). Under these circumstances, we recently studied the role of milk fat globule-epidermal growth factor-factor 8/Integrin $\beta 3$ pathway, a well-known adaptive immune responses and inflammation signal (Deroide et al., 2013; Hanayama et al., 2004), in early brain injury after SAH, and found it could significantly alleviate early brain injury and improve neurological deficits after SAH (Liu et al., 2014a). With these similar inflammatory effects on apoptotic antigen presentation, apoptotic neuron clearance and reduced inflammation mediators, compared to pericyte function, we believe further studies may shed light on the mechanism of pericyte in neuroinflammation after SAH (Poon et al., 2014; Uchiyama et al., 2014).

4.3 Angiogenesis

Pericytes have an important regulatory role in angiogenesis via PDGF/PDGF- β receptor, transforming growth factor- β , vascular endothelial growth factor, angiopoietin-1/Tie-2, and sphingosine-1 phosphate signaling pathways (Dore-Duffy and LaManna, 2007; Orlova et al., 2011; Ribatti et al., 2011). Pericyte could modulate the proliferation, migration and differentiation of endothelial cells, co-cultured pericytes with endothelial cells and astrocytes could establish a stable capillary-like structure (He et al., 2014; Obermeier et al., 2013). In their efforts of orchestrating initiation, sprout connection and termination in angiogenesis, pericytes secreted vascular endothelial growth factor and interleukin-6 facilitate maturation of endothelial cells and microvessels sprouting, which contribute a pivotal role in the initial stage of angiogenesis (Hagedorn et al., 2004). And transforming growth factor- β binds to its receptor in endothelial cell and pericyte, to self-regulate and induce perivascular mesenchymal cell differentiating into pericyte and smooth muscle cells (Sinha et al., 2004). Meanwhile, PDGF pathway, as we review in Section 3.1, is the crucial factor of sprouting capillaries recruiting pericytes. And angiopoietin-1 from pericyte binds to Tie-2 of endothelial cell will enhance pericyte surrounding new blood spout, increase the vessel stability (Gaengel et al., 2009). Then activation of sphingosine-1 phosphate pathway in

endothelium, pericyte and mesenchymal cell, could promote intercellular adhesion by enhancing the connections between N-cadherin and VE-cadherin(Paik et al., 2004).

4.4 Contribution to blood-brain barrier

Based on the intimate connections between pericytes and endothelial cells, it is easy to understand that the pericytes have a substantial role in the development of blood brain barrier tight junctions and paracellular permeability(Lai and Kuo, 2005). Even pericytes itself could form intercellular blood brain barrier tight junction(Shimizu et al., 2008). These functions are mediated in part through pericyte secreted transforming growth factor- β and angiopoietin-1(Guillemain and Brew, 2004; Lai and Kuo, 2005). And pericytes also contribute to basal lamina formation by synthesizing type IV collagen, glycosaminoglycans and laminin(Allt and Lawrenson, 2001). Besides, in pericyte deficit mouse, blood brain barrier permeability is significantly increased without changing in endothelium markers, suggests that pericyte may regulate endocytosis transportation in blood brain barrier(Daneman et al., 2010).

Since blood brain barrier is one of the major pathophysiologies of early brain injury after SAH(Cahill and Zhang, 2009; Fujii et al., 2013), a lot efforts were made to induce angiogenesis and protect blood brain barrier(Altay et al., 2012; Suzuki et al., 2010; Yan et al., 2013b; Zhan et al., 2015), but it is still far from clinical implication. Recently, our studies successfully stimulate tight junction and adherin junction proteins by activating Frizzled-4 receptor, a canonical Wnt signal receptor with expression also on pericyte(Chen et al., 2015b), suggesting pericyte maybe a promising target to maintain blood brain barrier integrity and functions in SAH treatment(Chen et al., 2014).

4.5 Stem cell function

Pericyte purified from different organs was proved capability to differentiate into other mesenchymal cell, such as adipocyte, chondrocyte, osteocyte, fibroblast and smooth muscle cells(Crisan et al., 2008). In fact, pericyte shares multiple features of mesenchymal stem cells, like origination from mesoblast, immunohistochemical markers and differentiation capability(Caplan, 2008; Lamagna and Bergers, 2006). Some pericytes were also proved to be neural progenitor cells, by responding to basic fibroblastic growth factor signal, they expresses neuronal and glial cell markers, suggesting that pericyte in central nervous system have capacity to serve as neural stem cell(Dore-Duffy et al., 2006; Kamouchi et al., 2011). However, there are few studies working on the pericyte's stem cell potential in SAH, with which it could participate in various neurological disorders and become the promising therapeutical targets in the future(Chen et al., 2014; Lange et al., 2013).

5 Prospective

Giving the fact that we currently only have limited information, and limited approaches in elucidating pericyte function in vivo, the better understanding how pericyte may response to SAH and affect SAH pathophysiology, the better chances we could develop corresponding therapies and drugs to specifically regulate pericyte's functions. Why are pericytes, unlike other cell types, particularly vulnerable to ischemia-induced cell death? Can pericytes death

be prevented and sequentially reduce the no-reflow phenomenon? And how to induce the potential capacity of pericytes to repair the brain injuries after SAH? Most importantly, the connections and unique characteristics of pericytes should be clarified in the future studies. For clinical, imaging examination still could not directly measure the changes of pericytes, but strategies which observing the cerebral microcirculation in vivo could be helpful for the studies of pericyte in SAH patients at current time. Furthermore, the therapeutical strategies towards pericytes should be considered in the future.

6 Conclusion

Despite extensive research and vast efforts, patient outcomes following SAH are still unsatisfied. More recently, early brain injury has emerged as a new frontier and requires further studies in devising therapeutic strategies for improving SAH outcomes. Pericyte, as the novel and outlooked cellular constituent of vascular neural network, worth to have a better understanding about its functions and mechanisms in identifying potential therapies to ameliorate SAH injury. Multiple roles of pericyte may provide a critical platform for the future successful translation of basic science research into human trials of SAH.

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Highlights

This article explored a potential role of pericytes in early brain injury after subarachnoid hemorrhage

Multiple signaling pathways of pericytes were summarized including PDGF, Notch, Canonical Wnt, and beta catenin

New and emerging factors in pericyte regulation are discussed such as MicroRNA, Exosome, and Long non-coding RNA

Pathophysiology of pericyte in subarachnoid hemorrhage are presented in contraction, immune, phagocytic function, angiogenesis, blood-brain barrier, and stem cell function

Figure 1.
Representative image of rat pericytes from in vitro cell culture.
Scale bar=25 μ m

Figure 2. Representative immunofluorescence images of the markers of rat pericytes in brain cortex. Scale bar=15 μ m. α -SMA: α -smooth muscle actin, PDGFR- β : platelet derived growth factor receptor beta.

Figure 3.

Schematic of pericyte in subarachnoid hemorrhage pathophysiology. Pericyte has multiple effects in early brain injury pathophysiology after SAH, such as contractile function, immune and phagocytic function, angiogenesis, along with its contribution to blood-brain barrier formation and stem cell potential.

VEGF: vascular endothelial growth factor, IL-6: interleukin-6, TGF- β : transforming growth factor- β , ANG-1: angiopoietin-1, PDGF: platelet derived growth factor, S1P: sphingosine-1 phosphate, GAG: glycosaminoglycans.

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Table 1

New players involved in pericyte signaling

Type	Participator	Physiological function	Reference
microRNA	miR-145	Block pericyte migration	Larsson et al, 2009
	miR-132	Stimulate endothelial tube formation and enhance angiogenesis	Katare et al, 2011
	miR-322 miR-199a	Vascular remodeling and angiogenesis	Ghosh et al, 2010 Gu and Chan, 2012
	miR-140 miR-376b	Target TGF- β pathway to intervene pericyte differentiation and adhesion	Paris et al, 2010 Gaengel et al, 2009 Bakhshandeh et al, 2012
	miR-126 miR-150	Target VEGF pathway and stimulate angiogenesis	Zhu et al, 2011 Zhang et al, 2010
	miR-345	Regulate cell cycle progression, maintain pluripotent capacity of pericytes, anti-apoptosis	Wu et al, 2010 Dore-Duffy et al, 2008 Tang et al, 2011
	miR-222	Cell survival and development	Decembrini et al, 2009
	miR-24	Downregulate vascularization and pro-apoptosis	Fiedler et al, 2011
lncRNA	MALAT1	Pericyte loss and endothelial dysfunction	Liu et al, 2014 Michalik et al, 2014
Exosome		Act as cargo, variety functions depends on what's inside	Chivet et al, 2012 Ailawadi et al, 2015