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The role of mural cells in hemorrhage of brain arteriovenous malformation

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Authors
Pan, Peipei
Shaligram, Sonali S
Do Prado, Leandro Barbosa
et al.

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Corresponding Author:	Hua Su, MD University of California San Francisco San Francisco, CA UNITED STATES
First Author:	Peipei Pan, PhD
Order of Authors:	Peipei Pan, PhD
	Sonali S Shaligram, PhD
	Leandro Barbosa Do Prado, PhD
	Liangliang He, MD
	Hua Su, MD
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September 26, 2020

Dear Dr. Zhang,

We would like to submit the enclosed review paper entitled “The role of mural cells in hemorrhage of brain arteriovenous malformation” for consideration for publishing in Brain Hemorrhages.

Brain arteriovenous malformation (bAVM) is one of the important causes of intracranial hemorrhage (ICH), expecially in young patients. However, the exact cause of bAVM bleeding and rupture is not yet fully understood. In this review, we discussed the role of mural cell in bAVM pathogenesis and the three major pathways that regulate mural cell function. We think the readers of this Journal will be interested in this topic.

All authors have read and approved the submitted manuscript; the manuscript has not been submitted elsewhere nor published elsewhere in whole or in part.

Thanks for your consideration.

Sincerely,

Hua Su, MD

Declaration of interest

All authors have no financial and personal relationships with other people or organizations that could inappropriately influence our work.

The role of mural cells in hemorrhage of brain arteriovenous malformation

Peipei Pan[1,2], Sonali S Shaligram[1,2,3], Leandro Barbosa Do Prado[1,2,3], Liangliang He[1], Hua Su[1,2,*]

[1]Department of Anesthesia and Perioperative Care, [2]Center for Cerebrovascular Research, University of California, San Francisco

[3]These authors contributed equally

[*]Correspondence author:

Hua Su, MD,

Department of Anesthesia and Perioperative Care,

University of California, San Francisco,

1001 Potrero Ave, Box 1363,

San Francisco, CA 94110.

Phone: (415)-206-3162

E-mail hua.su@ucsf.edu

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Peipei Pan[1,2], Sonali S Shaligram[1,2,3], Leandro Barbosa Do Prado[1,2,3], Liangliang He[1], Hua Su[1,2,*]

[1]Department of Anesthesia and Perioperative Care, [2]Center for Cerebrovascular Research, University of California, San Francisco

Short title: Mural cells in brain AVM hemorrhage

[3]These authors contributed equally

[*]Correspondence author:

Hua Su, MD,

Department of Anesthesia and Perioperative Care,

University of California, San Francisco,

1001 Potrero Ave, Box 1363,

San Francisco, CA 94110.

Phone: (415)-206-3162

E-mail hua.su@ucsf.edu

Abstract

Brain arteriovenous malformation (bAVM) is the most common cause of intracranial hemorrhage (ICH), particularly in young patients. However, the exact cause of bAVM bleeding and rupture is not yet fully understood. In bAVMs, blood bypasses the entire capillary bed and directly flows from arteries to veins. The vessel walls in bAVMs have structural defects, which impair vascular integrity. Mural cells are essential structural and functional components of blood vessels and play critical rols in maintaining vascular integrity. Changes in mural cell number and coverage have been implicated in bAVMs. In this review, we discussed the roles of mural cells in bAVM pathogenesis. We focused on 1) the recent advances in human and animal studies of bAVMs; 2) the importance of mural cells in vascular integrity; 3) the regulatory signaling pathways that regulate mural cell function. More specifically, the platelet-derived growth factor-B (PDGF-B)/PDGF receptor-β (PDGFR-β), EphrinB2/EphB4, and angiopoietin1/tie2 signaling pathways that regulate mural cell-recruitment during vascular remodeling were discussed in detail.

Keywords

Brain arteriovenous malformation; intracranial hemorrhage; mural cells; PDGF-B/PDGFR-β; EphrinB2/EphB4; angiopoietin1/tie2

Introduction

Brain arteriovenous malformations (bAVMs) are tangles of abnormal vessels, called Nidus, that connect arteries directly to veins. Arteriovenous shunts are hallmarks of bAVMs (Lawton et al., 2015; Rangel-Castilla et al., 2014; Yun et al., 2012; Zhang et al., 2016). The malformed vessels in bAVMs are tortuous and markedly dilated. The vascular wall structure is abnormal and thus is fragile and prone to rupture, leading to the life-threatening intracranial hemorrhage (ICH) and catastrophic neurological consequences (Gross and Du, 2013). ICH is the first clinical presentation in approximately half of all bAVM patients. Increasing evidence indicate that abnormal vascular remodeling and vascular instability are associated with bAVM the development and its abnormal phenotypes, including dilated perinidal capillaries (Attia et al., 2003; Sato et al., 2004; Tu et al., 2006), intranidal or feeding artery aneurysms (Gross and Du, 2013), microhemorrhage and rupture (Abla et al., 2015; Guo et al., 2012; Pekmezci et al., 2016). However, the exact mechanisms underlying bAVM bleeding remain unclear.

The cerebrovasculature contains several cell types, including endothelial cells, pericytes and vascular smooth muscle cells (vSMCs, Figure 1) (Pekmezci et al., 2016; Tu et al., 2006). Under normal circumstances, these cells coordinate to maintain the cerebrovascular integrity and function. Mural cells are no longer deemed as a passive cellular player, but rather as an integral part of the vessel wall playing various functions to maintain normal homeostasis. In the central nervous system (CNS), the vascular coverage and topographic density of mural cells are exceptionally high (Shepro and Morel, 1993). In fact, mural cells play a critical role in sustaining the blood-brain barrier (BBB) integrity (Daneman and Prat, 2015). The significant loss of mural

cells in bAVM vessels predisposes them to vascular leakage and microhemorrhage (Chen et al., 2013b). In this review, we discussed the role of mural cells and several pathways that regulate mural cell recruitment during angiogenesis and vasculogenesis in bAVM vascular instability and rupture.

1. Recent advances on bAVM-study: insights from patient cohorts to animal models

More than 95% of bAVM patients are sporadic cases without reported family history (Inoue et al., 2007). About 5% of bAVMs are familiar. Hereditary hemorrhagic telangiectasia (HHT; also called Osler-Weber-Rendu syndrome) is one of the major causes of the familiar form of bAVM. HHT is an autosomal dominant vascular disorder, affecting approximately 1 in 5,000 people, or 1.2 million people worldwide (Govani and Shovlin, 2009; Shovlin, 2010). It is characterized by recurrent epistaxis, chronic bleeding from telangiectases in the skin and gastrointestinal tract, and AVMs in various organs, e.g. brain, lungs, and liver (Shovlin, 2010).

It is known that HHT patients carries heterozygous mutations in endoglin (*ENG*, HHT1), Activin receptor-like kinase 1 (*ALK*1, also called *ACVRL1*, HHT2), or *SMAD4* (juvenile polyposis-HHT) genes (Johnson et al., 1996; Larsen Haidle and Howe, 1993; McAllister et al., 1994). HHT1 and HHT2 account for about 90% of all HHT cases (Richards-Yutz et al., 2010). Intriguingly, ENG, ALK1, and SMAD4 exert their functions in regulating the development of arteriovenous network, mainly in the endothelial cells (Mahmoud et al., 2010; Ola et al., 2018; Tual-Chalot et al., 2014), through transforming growth factor (TGF)-β and bone morphogenetic protein (BMP) signaling pathways. Genotype-phenotype studies in HHT patients have revealed that brain and pulmonary AVMs are more often associated with HHT1, while liver and gastrointestinal AVMs

are more prevalent in HHT2 patients (Bayrak-Toydemir et al., 2006) (Karlsson and Cherif, 2018).

The genesis of sporadic bAVM is starting emerging in recent years. Several studies showed a high prevalence of somatic activating mutations in KRAS/BRAF and MAP2K1/MER in sporadic bAVMs (Hong et al., 2019; Karlsson and Cherif, 2018; Nikolaev et al., 2018; Oka et al., 2019; Priemer et al., 2019), suggesting that the MER/ERK signaling pathways plays an important role in AVM pathogenesis.

Animal models has advanced research in bAVMs, which not only shedding light on the fundamental mechanisms but also providing scientific rationale for therapeutic target identification and test. Thus far, several animal models have been successfully established that have reproducible AVM phenotypes in adult mice by conditional knockout of *Eng* or *Alk1* genes, the two known HHT causal genes in combination with brain focal angiogenic stimulation (Chen et al., 2013b; Chen et al., 2014; Choi et al., 2014; Walker et al., 2011). Recently, Kim et al. have successfully established an inducible endothelial Alk1 overexpression mouse model (Kim et al., 2020). The authors demonstrated that ALK1-overexpression can rescue the AVM phenotypes in both *Alk1*- and *Eng*-inducible knockout (iKO) mice through normalizing the expression of SMAD and NOTCH target genes and resorting the effect of BMP9 on suppression of phosphor-AKT levels in ENG-deficient endothelial cells. ENG-overexpression could not inhibit the AVM manifestations in *Alk1*-iKO models. These findings suggest that the AVM development in HHT is caused by defects in the BMP9/10-ENG-ALK1-SMAD4 signaling pathways. In addition, animal models mimic sporadic bAVM have been established in mouse and zebrafish through

endothelial-specific gain of function mutations in *Kras* gene (Fish et al., 2020). Using these models, the authors demonstrated that activation of mitogen-activated protein kinase kinase 1 (MEK) instead of PI3K signaling is required for KRAS mediated AVM progression, and inhibition of MEK is a promising therapeutic target for the treatment of bAVM patients.

2. Pericytes and vascular smooth muscle cells (vSMCs) in bAVM hemorrhage

Mural cells consist of pericytes covering the endothelial cells and vSMCs. Pericytes are the predominant mural cell population of the cerebral microvasculature, containing roughly 90% of the abluminal side of the vessel wall (Bell et al., 2010; Winkler et al., 2012; Winkler et al., 2013). Pericytes exert significant modulatory influences on maintaining cerebrovascular integrity and functions, including the control of cerebral neovascularization, endothelial cells proliferation and migration, vascular diameter and cerebral blood flow; as well as maintaining microvascular stability and permeability. The function of pericytes are compromised in bAVMs. The vSMCs are circumferentially located in the medium part of the blood vessels, named *tunica media*, where they provide structural integrity to the vessel wall and regulate blood flow through regulating vessel dilation and contraction (Frosen and Joutel, 2018). In bAVM, vSMCs switch from a quiescent non-proliferative contractile phenotype to an active synthetic phonotype, accompanying with abnormal migration and growth of the cerebral blood vessels (Jaminon et al., 2019). Thus, the significant loss of pericytes and vSMCs in bAVMs vessels compromise vascular integrity, leading to increased vascular permeability and microhemorrhage.

Over the years, scientists have focused their attention mainly on the endothelial cell. The function of pericytes in vascular development and homeostasis has drawn increased attention lately. Pericytes are part of smallest diameter blood vessels such as arterioles, capillaries, and venules, and share their basal membrane with the endothelium. Pericytes play multiple roles in regulating angiogenesis, BBB integrity, and vascular stability (Armulik et al., 2011; Sweeney et al., 2016; Zhao et al., 2015). Pericytes have been shown to prevent hypoxia-induced BBB disruption *in vitro* (Hayashi et al., 2004). Changes in mural cell number, contractility or the attachment of mural cells to the endothelium is associated with diseases such as diabetic retinopathy, vascular malformation, and hereditary stroke (Chen et al., 2013b; Hammes, 2005; Yamamoto et al., 2020). Vascular malformations, such as bAVM, are characterized by reduced or incomplete alpha smooth muscle actin (αSMA) in the vSMC, as well as decreased elastin coverage in the internal elastin lamina (Davis et al., 2018). Recent works showed that both human and mouse bAVM vessels have fewer mural cell coverage compared to normal brain vessels (Winkler et al., 2018; Zhu et al., 2018b). In sporadic AVMs, pericyte number and coverage were reduced (Winkler et al., 2018). Reduction of pericytes is correlated with microhemorrhage in unruptured bAVM and faster blood flow rate through bAVM nidus. Overall, these suggest that loss of pericytes contributes to vascular fragility and hemodynamic changes in bAVMs (Winkler et al., 2018). However, pericyte deficiency is not just confined to bAVM, but also present in other neurological diseases that are associated with vascular abnormalities, such as Alzheimer's disease (Sagare et al., 2013), amyotrophic lateral sclerosis (Winkler et al., 2014), and Cavernous malformation (Schulz et al., 2015). Therefore, pericyte deficiency is a common denominator of reduced vascular stability in the brain.

The pericyte number and coverage can be quantified using membrane-bound markers, such as platelet-derived growth factor receptor-β (PDGFR-β), CD146, aminopeptidases A and N (CD13), and neuron-glial 2 (NG2) as well as commonly used cytoplasmic markers for pericyte identification, including αSMA, non-muscle myosin, desmin, vimentin, and nestin (Ribatti et al., 2011). Our group showed previously that Alk1-deficiency impairs vascular integrity through reduction of both α-SMA positive vSMCs and pericytes (Chen et al., 2013b). ALK1 regulates vSMC differentiation and recruitment during vascular development in the embryonic stage (Oh et al., 2000). Moreover, vascular endothelial growth factor (VEGF) stimulation in the Alk1-deficient brain reduces vascular integrity, which is associated with extravasation of intravascular components, such as fibrinogen, red blood cells, and inflammatory cells into the brain parenchyma around the bAVM vessels (Chen et al., 2013a).

The interaction of endothelial cells and pericytes is tightly controlled and modulated by several molecules, such as PDGF-B, transforming growth factor beta 1 (TGFβ1), VEGF, angiopoietins (Angs), Notch and ephrins. Pericytes maintain BBB function by releasing high levels of Ang-1 and TGFβ1 (Dohgu et al., 2005; Hori et al., 2004). Ang-1 derived from pericytes induces occludin expression via Tie2 receptor expressed by endothelial cells (Hori et al., 2004). Pericyte deficiency can lead to low levels of occludin in endothelial cells, which is associated with reduction of tight junction proteins and an increase of BBB permeability (Persidsky et al., 2006). Understanding the function of the factors involved in pericyte-endothelial cells interaction can help design therapies to prevent vascular permeability and destabilization in bAVM.

3. Signaling pathways: PDGF-B/PDGFR-β, EphrinB2/EphB4, and Angs/tie2

Several signaling pathways are involved in the abnormal phenotypes of bAVMs. In vascular development, a vascular fate, being arterial or venous, is determined by many signaling pathways (Walcott et al., 2016; Winkler et al., 2019). Below, we summarize the function of three major signaling pathways involved in this fate determination process: PDGF-B/PDGFR-β, EphrinB2/EphB4, and Angs/tie2 (Figure 2).

3.1 PDGF-B/PDGFR-β signaling

PDGFR-β is expressed in multiple cell types, including pericytes, vSMCs, and neurons (Fredriksson et al., 2004; Ishii et al., 2006). Its ligand, PDGF-B is secreted from the endothelial cells of angiogenic sprouts where it works as an attractant for comigrating pericytes. PDGF-B can also stimulate vSMCs proliferation (Abramsson et al., 2003; Hellstrom et al., 1999). PDGF-B -binds to PDGFR-β triggering receptor dimerization and phosphorylation, leading to activation of multiple downstream signal transduction pathways, which ultimately modulate survival, migration, apoptosis, proliferation, and differentiation of vascular cells. The PDGF-B/PDGFR-β are key elements in regulating pericyte recruitment and are important for an endothelium-to-mural cell paracrine signaling which maintains vascular integrity and stabilization (Gaengel et al., 2009; Shaligram et al., 2019). Homozygous deletion of *Pdgf-b* or *Pdgfr-β* in rodents results in high embryonic mortality due to widespread hemorrhage (Hellström et al., 2001). Maintenance of normal capillaries and BBB requires PDGF-B/PDGFR-β signaling. Genetic deletion of *Pdgf-b* in animals leads to pericyte loss and BBB breakdown (Armulik et al., 2010;

Hellstrom et al., 1999; Hirunpattarasilp et al., 2019). Disruption of PDGF-B/PDGFR-β signaling can also cause excessive vascular abnormalities and microaneurysms (Enge et al., 2002).

Abnormal expression of PGDF-B and PDGFR-β has been described in bAVMs in human and rodent (Barbosa Do Prado et al., 2019; Winkler et al., 2018; Yildirim et al., 2010). PDGFR-β expression was reduced in the bAVM lesions of Alk1-deficient mice, which was associated with a reduction of mural cell coverage, suggesting a possible crosstalk between ALK1 and PDGF-B/PDGFR-β signaling pathways (Chen et al., 2013b). Winkler et al. (Winkler et al., 2018) has shown that pericyte number and coverage are reduced in sporadic human bAVMs. Importantly, pericyte reductions are greatest in bAVMs with clinical hemorrhage and are associated with a higher microhemorrhage burden in unruptured cases, suggesting that reduction of pericytes contribute to bAVMs hemodynamic changes (Winkler et al., 2018). Upregulation of Pdgf-b expression via a lentiviral vector mediated gene transfer or thalidomide treatment reduced the number of dysplastic vessels and hemorrhage by increasing mural cell coverage in the bAVM lesions in mouse. These data demonstrate that PDGF-B/PDGFR-β signaling regulates mural cell plasticity and plays an important role in bAVM pathogenesis (Zhu et al., 2018a).

3.2 EphrinB2/EphB4 signaling

The Eph receptors (EphA1–EphA8, EphA10, EphB1–EphB4, and EphB6) and their ligands, Ephrins (ephrinA1–A5 and ephrinB1–B3) are crucial for multiple events in angiogenesis and vascular maturation, especially in embryonic angiogenesis and the formation of vascular architecture, including axon guidance, lymphatic and endothelia cell specification. Elevated

expression of Ephs and Ephrins was first reported in human carcinoma. Subsequent studies evolved their functions in angiogenesis and vasculogenesis (Himanen and Nikolov, 2003; Hirai et al., 1987; Salvucci and Tosato, 2012). Eph/Ephrin signaling allows short-distance endothelial cell-cell communication, which activates signaling pathways, modulates cellular cytoskeleton, and leads cell repulsion or adhesion. Therefore, multiple processes that changes cellular motility and/or morphology depend on Eph/Ephrin signaling (Barquilla and Pasquale, 2015; Kania and Klein, 2016; Vreeken et al., 2020).

Eph receptors are transmembrane proteins with an extracellular domain that contains a ligand-binding domain, a cysteine-rich region, and two fibronectin type-II domains. The intracellular domain of Ephrs contains two tyrosine residues, a protein tyrosine kinase domain, a sterile alpha motif (SAM), and a PDZ-binding domain. B-class Ephrins (ephrinB1-ephrinB3) have a transcellular and cytoplasmic domain with a PDZ-binding motif (Boyd et al., 2014; Vreeken et al., 2020). Ephrins binding to Ephs induces forward, reverse, parallel and antiparallel signalings by orchestrating the various functional domains, thereby allowing multiple signaling modes and modulatory mechanisms to be processed with high precision. Ephrin-Eph forward signaling works as classical ligands and receptors. In reverse signaling, the role of receptor and ligands of ephrin and Eph proteins are switched. When Eph receptors and Ephrins are located on the same cell membrane, they may act as ligands for Ephrins or Eph receptors, respectively, to activate signaling in the same direction (parallel signaling) or they can each function as receptors and ligands to activate signaling in alternative directions (antiparallel signaling) (Holland et al., 1996; Taylor et al., 2017).

Despite the complexity of Ephrin-Eph signaling, the regulation of angiogenesis and vasculogenesis is highly dependent on the specific EphrinB2/EphB4 signaling that has been implicated in the modulation of multiple vascular events, such as sprouting angiogenesis, vascular morphogenesis, and arteriovenous differentiation (Luxan et al., 2019; Pitulescu and Adams, 2010; Yang et al., 2016). In mural cells, EphrinB2 deletion causes embryonical lethality in mice with serious hemorrhage, edema, and vascular deficits in many organs. Cultured ephrinB2-deficient smooth muscle cells are defective in spreading, focal-adhesion formation and polarized migration with increase motility suggesting that EphrinB2 is important for vSMC recruitment and attachment to the vessel wall (Foo et al., 2006). In addition, EphrinB2 is a crucial regulator of PDGFR-β expression and internalization in vSMCs surface, and thereby acts as a molecular switch controlling the downstream signaling activity induced by PDGF-B/PDGFR-β. In particular, the EphrinB2 ablation enhances PDGF-B-induced MAPK and JNK activation, diminishes Tiam1/ Rac1 signaling, a pathway critical for cell migration, proliferation, and spreading (Nakayama et al., 2013).

EphrinB2 and EphB4 have been viewed as the primary molecular markers for endothelial arteriovenous specification. EphrinB2 is expressed exclusively by arterial endothelial cells and EphB4 by venous endothelial cells. Many studies indicate that EphrinB2/EphB4 signaling play roles in AVMs and other cerebrovascular disorders (Bai et al., 2014; Deloison et al., 2012; Gale et al., 2001; Long et al., 1974; Oike et al., 2002). Embryos harboring homozygous mutations in *Efnb2* and *Ephb4* exhibit vascular defects and arteriovenous malformations (Krebs et al., 2010). A study using an *in vitro* model of HHT2 showed that loss of *Alk1* gene blocked BMP9

signaling, resulting in reduced EphrinB2 expression, enhanced VEGFR2 expression, and dysregulated endothelial sprouting and anastomosis (Kim et al., 2012).

Whole exome sequencing studies in humans have identified mutations in EFNB2, EPHB4, and RASA1 in several congenital cerebrovascular disorders, including Vein of Galen malformation and capillary malformation-arteriovenous malformation (Amyere et al., 2017; Duran et al., 2019; Zeng et al., 2019), which corroborates the findings in model organisms. A recent study showed that dysregulation of the EphrinB2/EphB4 signaling cascade may play a role in AVM development, with potential utility as a diagnostic and therapeutic target (Fehnel et al., 2020).

3.3 Angs/tie2 signaling

Angs are growth factors that signaling through Tie receptor. Angs/Tie signaling pathway is essential for vascular maturation and vascular homeostasis (Akwii et al., 2019; Korhonen et al., 2016). The Ang family consists of 4 glycoproteins (Ang1-Ang4). The best-characterized members of the family are Ang1 and Ang2. Ang1 activates the Tie2 receptor, whereas Ang2 is a partial antagonist/agonist ligand for Tie2 receptor (Bilimoria and Singh, 2019; Maisonpierre et al., 1997). Ang1 is a constitutive paracrine agonist ligand for Tie2. It stimulates Akt-dependent phosphorylation and nuclear exclusion of the Forkhead box protein O1 (FOXO1) and its downstream signaling, which contributes to vascular development in the embryonic stage and maintenance of vascular stabilization. Ang2 is an autocrine ligand that functions as a context-dependent agonist or antagonist of Tie2. While Ang1 induces endothelial stabilization, Ang2 can antagonize Ang1 and block Tie2 activation, leading to vessel destabilization and regression

(Daly et al., 2004; Kim et al., 2016; Nicolini et al., 2019; Parikh et al., 2006; Sato et al., 1995). The balance between the levels of Ang1 and Ang2 partially determines the levels of Tie receptors and subsequent integrity of blood vessels, which are altered in various diseases, resulting in changes in the magnitude of Ang1 signaling (Iribarren et al., 2011; Ziegler et al., 2013). Besides endothelial cells, Tie2 expression and function have been established in other cell types, including neural cells, macrophages, hematopoietic stem cells, and mural cells (Androutsellis-Theotokis et al., 2009; Park et al., 2003; Teichert et al., 2017; Venneri et al., 2007).

Ang/Tie signaling controls the association of endothelial cells and pericytes (Yuan et al., 2009). Tie2 receptor in pericytes controls sprouting angiogenesis in spheroid assays. Moreover, silencing of Tie2 receptor results in a pro-migratory phenotype by downstream signaling through Calpain, Akt and FOXO3A (Teichert et al., 2017). Mice lacking pericytes present BBB disruption, increased vascular permeability and higher Ang2 levels, suggesting a possible role of Ang2 in pathological vascular permeability (Daneman et al., 2010).

Several studies have identified Ang/Tie2 signaling pathway as a key element on vascular malformations. Activating somatic Tie2 mutations in endothelial cells was observed in patients' vascular malformations (VM) lesions (Augustin et al., 2009; Limaye et al., 2009; Soblet et al., 2013; Wouters et al., 2010). Anti-Ang2 antibodies have been shown to alleviate AVM phenotype and normalize blood vessel diameter in preclinical models of HHT (Crist et al., 2019). PI3-Kinase signaling has been shown to be activated downstream of VEGF and Ang2 (Graupera et al., 2013). The therapeutic efficacy of PI3-Kinase inhibitors has been proven in preclinical HHT

models (Ola et al., 2016; Robert et al., 2020). Hashimoto et al. (Hashimoto et al., 2001) showed, for the first time, that the presence of abnormal balance in the Ang-Tie2 system is partially associated with the aberrant vascular phenotypes in bAVMs, which is likely due to loosening of cellular adhesion. In addition, next-generation sequencing analyses of human bAVM specimens revealed downregulation of Ang1 level, suggesting a relationship between Ang1 function and the pathophysiology of bAVMs.

Further, the reduction of Ang1 has been correlated with the reduced release of Ang11 by adjacent pericytes. Thess data are consistent with previous studies (Hashimoto et al., 2001; Hauer et al., 2020; Shenkar et al., 2003). In addition, polymorphisms in Ang4 were associated with a risk of bAVMs (Mikhak et al., 2011). Taken together, Ang/Tie2 pathway may play a key role in regulating mural cell plasticity. Dysregulation of this pathway contributes to the pathogenesis of bAVMs.

Summary

In this review, we discussed normal vascular structure, defects of bAVM vessels, and the association of mural cell-dysfunction with bAVM hemorrhage. We have also discussed the three major signaling pathways that regulate normal angiogenesis, vascular remodeling and endothelial specification, as well as their association with bAVM pathogenesis.

Due to the excess risks associated with invasive interventions (Mohr et al., 2017), the treatment selection for unruptured bAVM patients are debatable (Cenzato et al., 2017; Nisson et al., 2019). Thus, a safe and effective medical treatment for bAVM patients is urgently needed.

Understanding the signaling pathways involved in crosstalk of endothelial cells and mural cells might shed light on potential new targets.

One example is the PDGF-B/PDGFR-β signaling pathway, which plays an important role in regulating pericyte recruitment to newly formed vasculature. Endothelial-specific ablation of *pdgf-b* leads to pericyte loss and glomerular, cardiac and placental abnormalities (Bjarnegard et al., 2004). In HHT patients, thalidomide treatment can reduce the frequency and duration of nosebleed and the need for blood transfusion (Lebrin et al., 2010). Thalidomide treatment also reduced hemorrhage and improve mural cell coverage in mouse bAVMs, most likely through upregulation of Pdgf-b/Pdgfr-β signaling. Due to well-known adverse effects associated with thalidomide, it is difficult to be utilized in clinical settings. Our recent study showed that lenalidomide, one of the newer and safer derivatives of thalidomide, has similar effects to that of thalidomide. Increased mural recruitment was associated with reductions in dysplastic vessels and hemorrhage (Zhu et al., 2018a). Further, the mechanistic study revealed that effect of thalidomide and lenalidomide was through increasing endothelial Pdgf-b expression. Overexpression of Pdgf-b recapitulated the therapeutic benefit of thalidomide in mice.

Future studies are needed to understand the potential strategy for manipulating pericytes/mural cells in bAVMs therapy and establish better tools and mouse models to elucidate the role of pericytes in AVM pathogenesis.

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Declaration of interest

All authors have no financial and personal relationships with other people or organizations that could inappropriately influence our work.

Figure legends

Figure 1. A schematic diagram of a normal blood vessel and a bAVM vessel. The bAVM vessel has fewer mural cells than normal vessels which render the vessel prone to rupture.

Figure 2. Summary of key signaling pathways involved in the regulation of mural cell recruitment during angiogenesis and vasculogenesis and their association with bAVM phenotypes.

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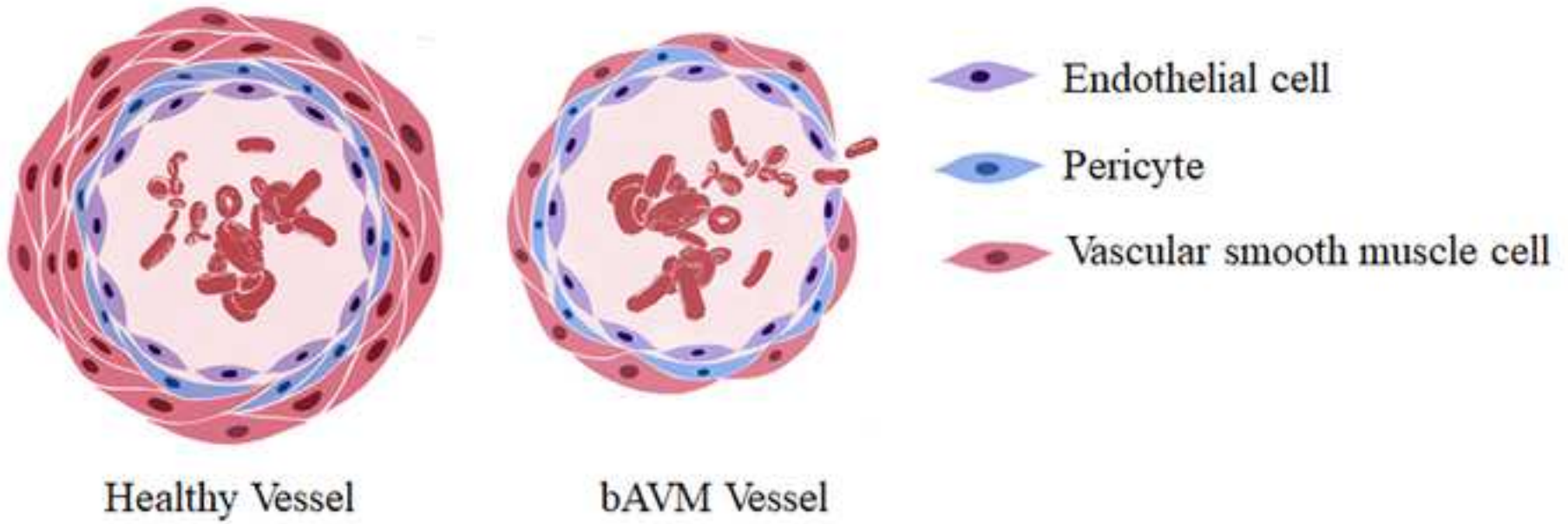
Figure



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