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Pathogenesis of non-hereditary brain arteriovenous malformation and therapeutic implications

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Abstract

Brain arteriovenous malformations have a high risk of intracranial hemorrhage, which is a substantial cause of morbidity and mortality in patients with brain arteriovenous malformations. Although a variety of genetic factors leading to hereditary brain arteriovenous malformations have been extensively investigated, their pathogenesis is still not well elucidated, especially in sporadic brain arteriovenous malformations. The authors have reviewed the updated data of not only the genetic aspects of sporadic brain arteriovenous malformations, but also the architecture of microvasculature, the roles of the angiogenic factors, and the signaling pathways. This knowledge may allow us to infer the pathogenesis of sporadic brain arteriovenous malformations and develop pre-emptive treatments for them.

Keywords

Arteriovenous malformation, non-hereditary, pathology, signal pathway

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Introduction

Brain arteriovenous malformations (bAVMs) are major causes of intracerebral hemorrhage. Treatments for bAVMs are mainly directed to reduce the risk of rupture, which could be fatal. Two mechanisms for bAVM formation have been postulated[1]: (1) abnormal sprouting angiogenesis leading to an anomalous direct arterial-venous connection and (2) the progressive dilation of existing capillary beds resulting in high-flow shunting from arterial to venous circulations. Both mechanisms have been described and appear specific to the rodent model,[2,3] but the pathogenesis of bAVM has still not been elucidated. bAVMs can occur as part of hereditary syndromes, such as hereditary hemorrhagic telangiectasia (HHT) and capillary malformation (CM)-arteriovenous malformation (AVM), where they result from germline mutations in genes that have known or plausible roles in angiogenesis and vascular remodeling, such as *ENG*, *ALK1*, *SMAD4*, and *RASA1*, among others.[4,5] Similarly, familial inheritance of sporadic bAVMs has been ascribed to mutations in *ALK1*.[6] Less is known about the cause of sporadic AVMs, which account for the majority of the disease burden in the general population.

Studies of AVM tissue suggest a dynamic and biologically active angiogenic and inflammatory lesion, rather than a static congenital vascular malformation.[7,8] Molecular biology and gene expression studies have been performed to investigate the nature of AVMs. Sporadic vascular malformations, including sporadic AVMs and cavernous malformations,[9,10] are much more common and seem to be associated with somatic mutations. In this communication, the formation of bAVMs, the architecture of microvasculature, the roles of the angiogenic factors, and the signaling pathways are reviewed. The emerging research geared toward a postulated genetic source for lesions once thought to be "sporadic" or without underlying genetic mutation is also summarized.

The rupture of bAVM

The underlying mechanisms for bAVM rupture are not fully understood. Hemodynamic factor (high flow shunt, restricted venous drainage, etc.) and vessel wall weakness are two main factors that may cause bAVM rupture. From the biological point of view, it is likely postulated that multiple mechanisms including inflammation,

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remodeling, and brain endothelial cell (EC) abnormalities contribute to bAVM's tendency to exhibit hemorrhage.[11] Several vascular wall cells, i.e. smooth muscle cells,[12] pericytes,[13] or both (mural cells),[14] may cause vessel wall fragility. Inflammatory cells (macrophages and neutrophils) have been detected in surgical specimens of human bAVM, even in those without a history of hemorrhage or previous embolization or radiosurgery.[15] Macrophages and neutrophils tend to invade AVM tissue even in the absence of radiographically-evident hemorrhage. Both relative neutrophilia and increases in macrophage migration inhibitory factor appear to contribute to the instability of bAVM nidus, contributing to apoptosis and possibly rupture. In the clinical scene, vessel wall magnetic resonance imaging may contribute to identify the rupture point in a ruptured bAVM.[16]

In addition, silent intralesional hemorrhage has been found in 30% of unruptured bAVMs.[17] Nearly one-third of patients without a clinical history of AVM hemorrhage had hemosiderin in surgical specimens, indicating silent bAVM hemorrhage.[18] Hemosiderin positivity was strongly associated with macrophages, suggesting that bAVMs with silent hemorrhage are more biologically active and inflamed lesions. These findings are consistent with the significantly higher risk of subsequent hemorrhage in patients with silent hemorrhage than in unruptured bAVM patients without it.[18]

Vasculogenesis and angiogenesis

During embryonic development, formation of blood vessel networks relies on two processes: vasculogenesis (de novo vessel formation during embryogenesis) and angiogenesis (the expansion of a pre-existing vascular network through sprouting or splitting of vessels).[19,20] Subsequent growth of the vertebrate vasculature occurs entirely by angiogenesis, the first phase of which involves vascular EC proliferation and migration; the second phase of angiogenesis is vascular stabilization, during which ECs form capillary tubes, strengthen their intercellular junctions, and recruit smooth muscles cells (SMCs) to their walls.[19–21]

Brain AVMs form at the interface between arterial and venous endothelium where capillary endothelium normally lies.[22] The angiogenic process, most severely disrupted by the vascular malformations, is that of vascular stabilization, the process whereby vascular ECs form capillary tubes, strengthen their intercellular junctions, and recruit SMCs to the vessel wall.[23,24] The AVM nidus expresses markers specific to arteries and veins, as well as capillaries. The AVM nidus is thought to consist of aberrant vessels that are not finally differentiated and inadequately matured,[25] and it histopathologically lacks a true capillary bed.[22]

Microvasculature

Cerebral blood vessels are anatomically comprised of ECs, vascular SMCs, and pericytes. To date, most bAVM research has focused on the endothelium. On histologic evaluation, significant endothelial heterogeneity has been described.[1] Disruption of the blood–brain barrier (BBB) is well documented,[13] and microhemorrhages are frequently observed in unruptured bAVMs and may predict future rupture.[18] Whether the function of vascular ECs and SMCs affects the phenotypic presentation of bAVMs is still unknown.

Endothelial cells

Brain ECs form the monolayer cell lining of the vascular lumen, serving as the vital interface between the blood and brain parenchyma known as the BBB. At a molecular level, ECs express higher levels of pro-angiogenic factors,[26,27] and, as a result, frequently assume a pro-angiogenic phenotype in bAVMs. ECs of bAVMs proliferate and migrate more rapidly and form aberrant vascular tubules in vitro.[28,29] The experimental models reproduce some features observed in human bAVMs (e.g. dilated vessels, an arteriovenous shunt, a high-flow lesion, and formation of a nidus).[30,31] In the mouse model, the combination of the EC-specific deletion of *ALK1* and administration of vascular endothelial growth factor (VEGF) in the brain causes a lesion similar to human AVM with dilated vessels and proliferation of ECs.[32] Adenovirus-mediated EC-selective *ALK1* deletion and overexpression of VEGF induce lesions resembling human bAVM as well,[3] suggesting involvement of changes in EC function and angiogenesis in the pathogenesis.

The endothelium in a bAVM also assumes a pro-inflammatory phenotype. Upregulation of endothelial adhesion molecules and cytokines and BBB breakdown facilitate the infiltration of circulating blood-derived inflammatory cells observed in bAVMs.[15,33] Whole-exome sequencing of bAVMs showed that some vascular ECs contained *KRAS* mutations,[10] and further investigation showed that cultured ECs that had the same mutation were phenotypically larger and elongated, demonstrated faster migration, and had more cytoskeletal actin projections.[10]

Smooth muscle cells

Vascular SMCs are the predominant cellular constituent of the vessel wall in arteries and veins. SMCs derived from bAVMs formed tubes in culture that were longer than those formed by normal brain vascular SMCs. The migration and proliferation of SMCs in bAVMs exceeded those of normal brain vascular SMCs.[34] The reductions in vascular SMCs in bAVMs have been described.[35] Wnt signaling was activated in vascular ECs and SMCs in low-flow bAVMs.[36]

Pericytes

Pericytes are embedded within a vascular basement membrane that is shared with the adjacent

endothelium. The close spatial proximity during vascular remodeling between sprouting ECs and neighboring pericytes suggests crosstalk and, potentially, a reciprocal signaling relationship between these two cell types during vascular remodeling.[37]

Pericytes are important in promoting vascular stability and maturation throughout the human body.[38,39] A reduction in pericytes has been described in both human bAVMs and rodent models,[13,14] and it is greatest in ruptured human AVMs.[13] In unruptured AVMs, the magnitude of pericyte loss correlates with the severity of BBB disruption and microhemorrhage.[13] Pericytes have important roles in angiogenesis and maintaining vessel stability through crosstalk with angiopoietin (ANGPT) signaling. Angiopoietin-2 (*Ang-2*) is overexpressed in bAVMs compared to controls.[27,40] Misregulated *VEGF-A* activity impairs pericyte coverage and distribution by disrupting pericyte migration.[41] The vascular abnormalities associated with bAVMs result, in part, from downstream defects in pericyte behaviors and their underlying signaling mechanisms.

Angiogenic factors

EC behavior during vascular development is regulated by prominent growth factor families such as VEGF, fibroblast growth factor (FGF), ANGPT, and transforming growth factor beta (TGF-β)/bone morphogenetic protein (BMP) families. One important pathway for EC-vascular SMC and pericyte crosstalk is the platelet-derived growth factor (PDGF)-B/PDGFRβ pathway. In addition to growth factors, vascular development and homeostasis are regulated by many other signaling inputs, including ligand-receptor signaling pathways such as Wnt and Notch.

Abnormal expressions of *PDGFB* and *PDGFRβ* have been described in bAVMs in rodent models and humans.[13,35,42] Recent work showed that both human and mouse bAVM vessels have less mural cell (vascular SMCs and pericytes) coverage than normal brain vessels,[13,14] suggesting abnormal vascular remodeling in bAVMs. Immunohistochemistry of AVM vessels has shown the abundant production of potent angiogenic factors, such as VEGF and other proliferative factors (e.g. basic FGF and TGF-α).[43,44] Significant overexpression of VEGF receptors and ANGPT receptors (e.g. Tie-1 and Tie-2) in ECs has been reported in surgically resected AVMs compared with controls.[40]

VEGF

VEGF is a potent EC mitogen that is thought to play a key role in angiogenesis,[45] and abnormal expression of VEGF has been repeatedly observed, making it increasingly more evident that a disruption in angiogenic signaling systems is involved in the formation and progression of bAVMs.[46,47] Increased VEGF expressions in the endothelium and other cells of the surgical specimens of bAVM implied that VEGF was involved in EC proliferation and angiogenesis in bAVMs.[26,27] Another study also demonstrated the abundant expression of VEGF and Ang-2 protein in human bAVM lesions compared with normal cerebral cortex.[48] Furthermore, the nidus size is larger in lesions positive for VEGF-A or Flt-1 (VEFR-A receptors) staining than in those without positive signals, suggesting the pathogenic role of VEGF-mediated angiogenesis in the enlargement of the lesion.[26] VEGF also plays an important role in maintaining the normal permeability of vessel walls.[49] Extrapolating from animal models, VEGF may contribute to the hemorrhagic tendency of bAVMs.[50,51]

Fatty acid binding protein 4

Fatty acid binding protein 4 (FABP4) is an intracellular lipid chaperone that is involved in cell proliferation and differentiation. FABP4 is potently induced by proangiogenic mediators, such as *VEGF*. FABP4 is not expressed in normal brain vasculature. However, FABP4 expression in EC and perivascular cells has been detected in 65% and 100% of AVM surgical specimens, respectively.[52,53]

TGF-β

TGF-β is a multifunctional cytokine that has multiple effects on brain vascular development implicated in vascular malformations, including both bAVMs and cavernous malformations.[39,54] In humans, it has been suggested that single nucleotide polymorphisms in *ALK1* or *ENG* may be associated with heightened risk of sporadic AVMs.[55,56] More recently, whole exome sequencing has identified a novel *SMAD9* mutation associated with a recurrent, sporadic AVM. Oligonucleotide-mediated knockdown in developing zebrafish confirmed formation of brain arterial-venous shunts, suggesting a causal role.[57] However, the role of TGF-β signaling in the formation of non-HHT, sporadic bAVMs remains to be defined.

Bone morphogenetic proteins

The BMPs are members of the TGF-β superfamily. BMP signaling plays a critical role in modulating the fates of the tip and stalk cells during sprouting angiogenesis. BMP and Notch signaling pathways are essential for vascular development and homeostasis, and disruption of these pathways is known to cause vascular diseases. Recent studies showed that lack of BMP inhibition induces the expression of Notch components in ECs, which results in bAVMs.[58,59] In human brain tissue, immunofluorescent staining demonstrated a vascular predominance of *SMAD9* at the protein level. Vascular *SMAD9* was markedly reduced in peri-nidal blood vessels of bAVMs, which was accompanied by decreased phosphorylated *SMAD4*, a downstream

effector protein of the BMP signaling pathway. In a zebrafish model, the morpholino splice site and translation-blocking knockdown of *SMAD9* resulted in abnormal brain artery-to-vein connections with morphologic similarities to human AVMs.[60]

Notch

The Notch pathway is a critical mediator of the differentiation of arteries and veins.[61,62] An AVM arises due to impaired arterial or venous differentiation during early angiogenesis consequent to imbalanced Ephrin proteins, particularly EPHB2 and EPHB4.

Notch components are considered to be critical mediators of EC fate decisions and vascular lumen formation,[63,64] and both loss-of-function and gain-of-function Notch mutations result in arteriovenous shunting.[65,66] Notch receptors and ligands are differentially expressed in arteries and veins, with *Notch1* and *Notch4* expressed on arterial ECs, and *Notch2* and *Notch3* expressed on venous ones.[67] In young mice, constitutive activation of the *Notch4* intracellular domain has led to the production of brain arteriovenous shunts.[2,68,69] Thomas et al. reported augmented expressions of *EphrinB2*, *Hey2*, and *DLL4* in the nidus structures of bAVMs when compared to normal brain arteries,[25] and they suggested that deregulated arterial specification signaling might have a significant role in the pathogenesis of AVM.

Recent work has suggested a role for Notch signaling in the formation of non-syndromic, sporadic bAVMs.[70] Elevated expressions of *Notch1* and *Notch* intracellular domain and increased activity of the ligands *Jagged-1* and *DLL-4* have been described in human bAVM specimens.[68,71] Other studies have shown that *Notch1*, but not *Notch4*, was overexpressed in ruptured AVMs compared to unruptured ones.[72] Polymorphisms of *Notch4* gene have also been associated with human AVM formation and hemorrhage.[73,74]

Wnt signaling

Gene ontology analysis identified that Wnt signaling, an important signaling pathway associated with embryonic angiogenesis, was involved in the development of bAVMs.[75] In vascular development, Wnt and Notch interact with each other to determine proper EC differentiation, vascular remodeling, and arteriovenous specification. Wnt signaling increases *Sox17* transcription, subsequently activating Notch and promoting arterial identity.[76] The *Sox17*-associated pathway is expressed in the bAVM nidus.[75] High expression of the *Sox17*-associated pathway in thick-walled veins indicates the process of arterialization in response to the hemodynamic stress. The increased activation of the *Sox17*-associated pathway in medium-sized and small arteries suggests that ECs in bAVMs are primarily abnormal.[75]

Gene mutations

The identification of gene mutations and genetic risk factors associated with bAVMs has enabled understanding of the genetics of this disease. The genetic hypothesis of the formation of AVMs is a ''two-hit'' mechanism, in which an inherited mutation in one copy of a cerebrovascular malformation gene is followed by a somatic mutation in a second counterpart.[19,77] The second ''hit'' could be environmental, in the form of a localized physiological or pathological perturbation.[19] Therefore, there is an interaction between hemodynamic factors and genetic factors in vasculogenesis.

KRAS

A recent study showed that the majority of sporadic bAVMs also harbored somatic activating *KRAS* mutations driving downstream mitogen-activated protein kinase (MAPK)–extracellular signal-regulated kinase (ERK) signaling.[10] Activating *KRAS* mutations were noted in 62.5% of 72 bAVMs, but in none of 21 paired blood samples.[10] The presence of activating *KRAS* mutations in more than half of bAVM tissue samples may indicate the pathogenic role of these *KRAS* mutations.[78] In sporadic bAVMs, *KRAS* mutations were also detected in 9 of 15 specimens (60%), and seven of them were *G12V* or *G12D* mutations.[79] Priemer et al. demonstrated the first reported instance of a *KRAS p.G12C* mutation in a bAVM.[80] The mean age of patients with *KRAS*-mutant bAVMs was lower than that of patients in the non-mutant group, and the mean size was larger. Histologic characteristics were equally distributed between *KRAS*-mutant and non-mutant groups.[80] They postulated that these mechanisms may result in potentially distinguishable clinical and/or histologic features between *KRAS*-mutant and non-mutant bAVMs.

KRAS mutations were detected in ECs from human bAVMs in vitro, and it was noted that mutant *KRAS* expression initiated increased ERK activity that was counteracted by inhibition of MAPK–ERK signaling.[10] Interestingly, *KRAS* is mostly implicated in tumorigenesis and cancer, where mutations promote unregulated activation of growth-promoting signal transduction pathways resulting in cell transformation and genomic instability.[81]

There is an opinion that cells with the mutated *KRAS* seem to be a therapeutic target in the treatment of bAVM.[82,83] On the other hand, Priemer et al. insisted that it may indicate that the histology of bAVMs is a reflection of MAPK–ERK activation in general, regardless of the initiating event. From another point of view, *KRAS G12D* mutation may be the result of a repair of ECs damaged by excessive hemodynamic force from arterial blood flow, which is usually diminished by intervening capillaries. They suggest that the presence of *KRAS* mutations within AVMs may be of little clinical or pathologic importance.[78–80]

BRAF

Hong et al. reported the first evidence of activating *BRAF* mutations in bAVMs and spinal AVMs (sAVMs). The total prevalence of *KRAS*/*BRAF* mutations was 87.1% (27 of 31 patients) in their cohort.[84] The prevalence of *KRAS*/*BRAF* mutations was 81.0% (17 of 21 patients) in bAVMs and 100% (10 of 10 patients) in sAVMs. *KRAS p.G12D* and *p.G12V* were mutation hotspots both in sAVMs and bAVMs, with a prevalence of 30.0% and 30.0% in sAVMs, and 52.4% and 19.0% in bAVMs, respectively, whereas *BRAF p.V600E* was rare and found in only one bAVM patient and one sAVM patient.[84] They found that mutation variant frequencies correlated negatively with nidus volumes and largest diameters, but not with age.[84]

Signaling pathways

Increased *KRAS* activity can potentially affect multiple downstream signal pathways (Figure 1). Most vascular malformations are associated with mutations commonly found in cancer, mainly in phosphoinositide 3-kinase (PI3K)–AKT–mammalian target of rapamycin (mTOR) in low-flow vascular malformations including venous and lymphatic malformations[85,86] and the RAS–MAPK–ERK pathway in high-flow lesions including bAVMs.[9,10,87] bAVMs without detectable *KRAS* mutations also had high levels of phosphorylated *ERK1*/*2*, suggesting that RAS–MAPK–ERK pathway activation is a hallmark of all bAVMs.[10] The PI3K signaling pathway is a critical regulator of the angiogenic process by controlling proliferation, migration, and survival of ECs.

Germline autosomal dominant *RASA1* mutations have been identified in 50% of CM-AVM1 patients, including those with Parkes Weber syndrome. *RASA1* encodes p120-RasGAP protein that inhibits activity of RAS protein. Loss of function mutations of *RASA1* may therefore lead to activation of RAS and increased downstream signaling via the MEK–ERK1/2 and PI3K–AKT–mTOR pathways that can be potentially targeted.[88]

Additional recent studies demonstrated autosomal dominant *EPHB4* mutations, named CM-AVM2.[89] This gene encodes a trans-membrane receptor expressed primarily in venous ECs during vascular development interacting with its ligand, EphrinB2, on arterial ECs. *EPHB4* also activates p120-RasGAP, and therefore exerts similar downstream effects on the MEK/ERK pathway as *RASA1*. The phenotypic similarity between CM-AVM1 and CM-AVM2 suggests that *RASA1* and *EPHB4* play an overlapping role in vascular development during embryogenesis.[90,91]

Mechanistically, endothelial BMP signaling is likely linked to the hemodynamic response, because blood flow potentiates *BMP9* signaling by inducing complex formation between *ENG* and *ALK1*. AVMs in *BMP9*, *ENG*, *ALK1*, and *SMAD4* mutants arise largely due to over-activation of PI3K–AKT signaling downstream of blood flow and VEGF-A signaling.[92,93] Reducing *VEGFR2* activity or PI3K–AKT largely normalized the AVM phenotype caused by disrupting *BMP9*/*ENG*/*ALK1*/*SMAD4* function.[92–94]

Somatic mutations have been noted in bAVMs, not only in the RAS–MAPK pathway, but in the PI3K pathway, as well as in other vascular malformations.

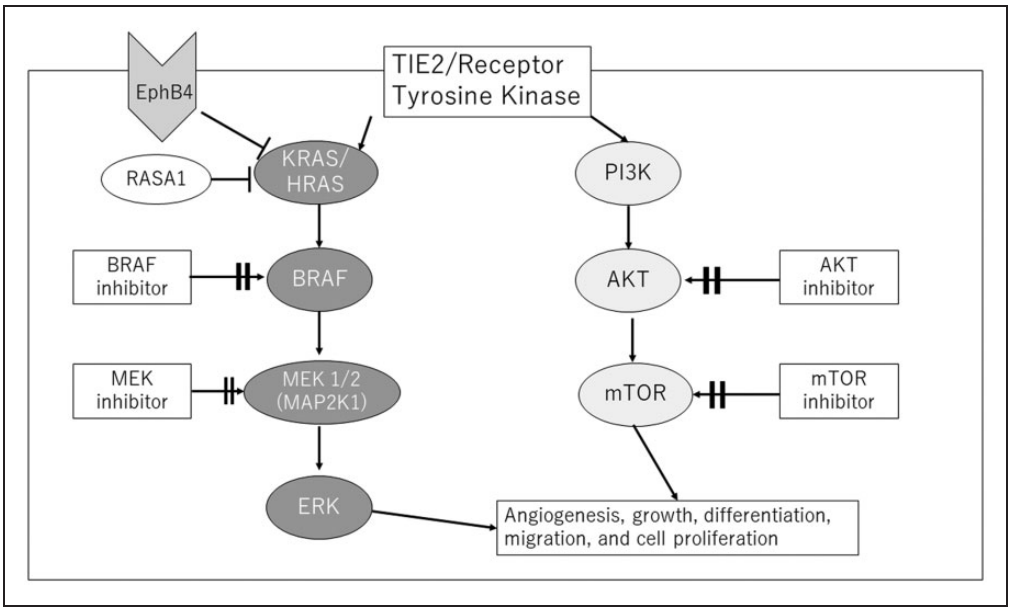

Figure 1. Signal transduction pathways in endothelial cells and the main genetic mutations associated with vascular malformations. Key signaling pathway PI3K/AKT/mTOR and RAS/RAF/MEK/ERK control cellular growth, apoptosis, and differentiation through complex transcriptional regulation. Potential treatments are shown in a square.
mTOR: mammalian target of rapamycin.

The RAS–MAPK signaling pathway is the most promising therapeutic target for bAVMs. The initiating events for AVMs without RAS mutations are uncertain. The PI3K–AKT–mTOR pathway has a possibility of being a therapeutic target for bAVMs, although the somatic mutations in the PI3K pathway in high-flow AVMs have not previously emerged. Further study will demonstrate the increasing importance of genetic diagnosis for both germ-line and somatic mutations for future molecular target therapies.[95]

Future therapeutic targets

There are multiple treatment options for bAVMs, including surgical resection, radiosurgery, embolization, or medical treatment, but these modalities are not without risk.

An ideal therapy would be non-invasive, immediate in action, and would be specific to the abnormal cells of the AVM without affecting adjacent blood vessels or brain. Considerable efforts have been made to use existing therapies to target molecular pathways disrupted in bAVMs, including TGF-β, Notch, and VEGF. For example, losartan, an angiotensin II receptor antagonist used for treatment of hypertension, decreased vascular dysplasia and arteriovenous-shunting in a zebrafish model of bAVMs induced through knockdown of the TGF-β receptor *ALK1*.[57] In HHT, treatment with thalidomide was shown to restore endothelial PDGFB expression, leading to recruitment of mural cells and vessel stabilization.[96] Thalidomide or lenalidomide treatment reduced the number of dysplastic vessels and hemorrhage, and increased mural cell (vascular SMCs and pericytes) coverage in bAVM lesion.[35]

Inhibitors of Notch signaling may represent another prospective therapy for future development. With extracranial vascular malformations, Notch inhibitors reduce the rate of endothelial migration and formation of vascular networks.[97] Direct targeting of pro-angiogenic pathways such as VEGF has also attracted attention for prospective therapeutic development in bAVMs.

VEGF neutralization prevented and normalized AVM in an animal model for HHT2, an autosomal-dominant disorder characterized by telangiectasia and AVMs in multiple organs.[98] Others have begun to explore a direct approach using bevacizumab, a humanized VEGF monoclonal antibody. Bevacizumab has an established safety profile and has been trialed as anti-angiogenic therapy in a number of neoplastic conditions, including glioblastoma.[99] In *ALK1*-deficient rodents with bAVMs, treatment with bevacizumab induced vascular apoptosis, reducing the number of proliferating vascular cells and dysplastic vessels.[45]

Malformations due to mutations affecting the RAS/BRAF/MEK/ERK pathway (e.g. CM, CM-AVM, bAVM, sAVM) could perhaps be targeted by a BRAF inhibitor (e.g. vemurafenib) and/or MEK inhibitors (e.g. trametinib, cobimetinib) that are available.[84,90,100,101] An AVM overlying the left scapular region in a child was treated by a genotype-guided approach. Exome sequencing from a specimen of the AVM and saliva showed in-frame deletion of *MAP2K1*; therefore, treatment with a *MEK* inhibitor, trametinib, was given, with a significant reduction in overall volume after six months.[102] Whether these agents may be repurposed to accelerate translation of a similar approach in human patients with bAVMs remains to be elucidated. Initial experiments with the MAPK–ERK pathway promoted vascular barrier properties and quiescence in patient-derived *KRAS*-mutant ECs in vitro.[10] Common MEK inhibitors are currently used for the treatment of melanoma.[103,104] A mutation of *MEK1* (downstream effector of *BRAF*) has been identified in more than 50% of cases of extracranial AVMs, though it has also been described in some cases of bAVM.[9,84,105]

Vascular anomalies with mutations affecting the PI3K–AKT–mTOR pathway (e.g. venous malformation, venous malformation cutaneo-mucosal, multifocal venous malformation, and lymphatic malformation) are known to respond to mTOR inhibitors (sirolimus, everolimus, and temsirolimus). In vivo animal models showed that sirolimus inhibits angiogenesis via downregulating the PI3K/AKT signaling pathway and the expression of VEGF.[106] All six head and neck AVM patients (four male and two female patients) responded favorably to the combination of sirolimus therapy followed by endovascular embolization, and four patients showed a near-complete response.[107] mTOR signaling has been shown to mediate angiogenesis via increased expression of VEGF.[108]

Only recently have the contributions of other cell-types, such as pericytes, vascular SMCs, and inflammatory cells, begun to be appreciated in bAVMs.[13] How molecular cross-talk among these cell types is disrupted remains poorly understood in bAVMs, and systematic characterization of other cell types, including astrocytes and resident microglia, has yet to be performed.[1] A more comprehensive understanding of the dysfunction of the neurovascular unit in its entirety will likely yield additional targets for therapeutic development.

Conclusions

The pathogenesis of non-hereditary bAVMs is not clearly understood, but the identification of gene mutations and genetic risk factors associated with bAVMs has enabled understanding of the genetics of this disease and provided new insights. Knowledge from several research aspects, such as gene mutations, signal pathways, and molecular cross-talk of microvasculature, may deepen our understanding of the pathogenesis and provide novel therapeutic approaches to bAVMs in the near future.

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