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Potential Targets for the Treatment of Brain Arteriovenous Malformations

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Brain arteriovenous malformations (bAVMs) are a leading cause of neurological deficits and hemorrhagic stroke in children and young adults. Cases with bAVMs are generally present at all ages, with a mean age of 20 to 40 years. The prevalence of bAVMs is approximately 10–18 per 100,000 adults. The most devastating symptom of bAVMs is intracranial hemorrhage, which can cause long-term disability and death. Female sex may be associated with initial hemorrhage of AVM. The other symptoms include seizures with or without loss of consciousness, muscle weakness or complete paralysis, headache, nausea, vomiting, numbness, dizziness, mental confusion, hallucination, or dementia. The current treatments for bAVM include surgery, radiosurgery, or embolization. All are associated with considerable risks and not all patients can be offered treatment. There is not specific medical treatment available for treating bAVM patient.

The pathophysiology and pathogenesis of bAVMs are complex and unclear. More than 95% bAVMs cases are sporadic without family history. Although somatic mutations of genes in ras sarcoma virus (RAS)/microtubule-associated protein kinases (MAPK)/extracellular signal-regulated kinase (ERK) signaling pathway have been detected in some sporadic bAVMs [1], the pathogenesis of AVM is still not fully understood. Studies regarding a familiar form of bAVM, hereditary hemorrhagic telangiectasia (HHT), indicate that the initiation and progression of bAVMs need interplay among several factors including homozygous loss-of-function of causative genes in endothelial cells, angiogenic stimulation and participation of bone marrow–derived cells, inflammation, and hemodynamic changes. Mutations in genes coding for the TGF-β receptors, endoglin (ENG, HHT1) or the activin receptor-like kinase-1 (ACVRL1 or ALK1, HHT2), are found in more than 80% of HHT patients.

HHT mouse models have been largely used to dissect AVM mechanisms and test new therapies. These models are mostly generated through conditional knockout of *Alk1* or *Eng*

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gene. Common phenotypes in HHT mouse models include AVMs in the brain, in the retinas of neonates, around skin wound, and hemorrhages in the gastrointestinal tracts. Some of the phenotypes need to be induced by additional manipulation, such as stimulation of brain angiogenesis to induce bAVMs in adult mice and wounding to induce skin AVMs. Naturally, correction of Eng or Alk1 gene expression could be an effective and safe therapeutic strategy for treating HHT AVM. Using HHT mouse models, Kim et al. [2] investigated the therapeutic efficacy and potential risks of overexpression of Alk1 for HHT treatment. They found that overexpression or activation of Alk1 in endothelial cells alleviates the severity of AVMs in skin and retina in both *Alk1* and *Eng* deficient mice without any untoward effect. Therefore, overexpression of Alk1 in endothelial cells can be developed into an effective therapy for treating bAVMs in both HHT1 and HHT2 patients.

Through establishing and studying animal models and analyzing human bAVM specimens, some other potential therapeutic targets have been identified. Molecular and histopathological analyses have shown that the levels of angiogenic factors and inflammatory cytokines in mouse and human bAVMs are higher than that in the normal brain. Angiogenesis is necessary to induce bAVM in adult mice. Neyazi et al. found significant association between high numbers of carcinoembryonic antigen-related cell adhesion molecule-1 (CEACAM1)–positive cells and bAVM rupture, indicating a role of inflammation in the pathophysiology of bAVM [3]. Animal study showed that inhibition of angiogenesis through bevacizumab (Avastin, a humanized anti-VEGF antibody) treatment or adeno-associated viral mediated overexpression of extracellular domain of VEGF receptor (sFLT1) reduces bAVM severity [4, 5] and that doxycycline is effective in reducing bleeding risk in bAVMs via inhibition of matrix metallopeptidase 9 (MMP-9) [6]. Therefore, anti-angiogenesis and anti-inflammation are potential therapeutic targets for developing new therapies for treating bAVM.

In addition, vascular pericyte coverage is reduced in mouse and human bAVMs, which is associated with bAVM hemorrhage. Increase of pericyte coverage in mouse bAVM through increase in the expression of platelet-derived growth factor B reduced bAVM hemorrhage [7]. Thus, strategies that improve vascular pericyte coverage can also be used for developing new therapies for reduction of bAVM hemorrhage.

Nikolaev [1] et al. have identified somatic mutations: $KRAS^{G12V}$ and the $KRAS^{G12A}$ in sporadic bAVMs. A subsequent study showed that the prevalence of *KRAS/BRAF* mutations is 81% of bAVMs and 100% of spinal AVMs [8]. Further investigation of the downstream signaling pathways showed that MAPK-ERK is activated by *KRAS*-activating mutations. The level of ERK1/2 phosphorylation was increased in endothelial cells derived from bAVMs compared to that from normal brain vessels. Transduction of $KRAS^{G12V}$ gene to cultured endothelial cells enhanced their migratory behavior. Park et al. induced bAVM in mice through transduce $KRAS^{G12V}$ gene into mouse brain endothelial cells and showed that inhibition of MEK/ERK by trametinib treatment attenuated $KRAS^{G12V}$-induced bAVM growth in mice [9]. Similarly, endothelial-specific $HRAS^{V12}$ expression in mice resulted in the formation of dilated blood vessels in the brain, intracanal hemorrhage, and death [10]. Together, these data indicate that somatic mutations in KRAS are involved in bAVM

pathogenesis. Inhibition of KRAS downstream signaling is a promising target for developing new therapies for the treatment of bAVM.

The concept for the treatment of bAVM should be focused on stabilizing vascular wall and decreasing the risk of spontaneous intracranial hemorrhage. Therefore, in addition to identifying the pathways involved in the development of bAVMs, understanding their mechanisms and factors involved in vascular remodeling, integrity, and rupture of AVMs is crucial for developing strategies to stabilize the AVM vessel wall and to prevent AVM rupture. Further research is required to study how to translate the therapies tested out on animal models to clinical use to treat bAVM in patients.

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