Molecular and cellular biology of cerebral arteriovenous malformations: a review of current concepts and future trends in treatment

***LEONARDO RANGEL-CASTILLA, M.D., JONATHAN J. RUSSIN, M.D.,
EDUARDO MARTINEZ-DEL-CAMPO, M.D., HECTOR SORIANO-BARON, M.D.,
ROBERT F. SPETZLER, M.D., AND PETER NAKAJI, M.D.**

Division of Neurological Surgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, Arizona

Object. Arteriovenous malformations (AVMs) are classically described as congenital static lesions. However, in addition to rupturing, AVMs can undergo growth, remodeling, and regression. These phenomena are directly related to cellular, molecular, and physiological processes. Understanding these relationships is essential to direct future diagnostic and therapeutic strategies. The authors performed a search of the contemporary literature to review current information regarding the molecular and cellular biology of AVMs and how this biology will impact their potential future management.

Methods. A PubMed search was performed using the key words “genetic,” “molecular,” “brain,” “cerebral,” “arteriovenous,” “malformation,” “rupture,” “management,” “embolization,” and “radiosurgery.” Only English-language papers were considered. The reference lists of all papers selected for full-text assessment were reviewed.

Results. Current concepts in genetic polymorphisms, growth factors, angiopoietins, apoptosis, endothelial cells, pathophysiology, clinical syndromes, medical treatment (including tetracycline and microRNA-18a), radiation therapy, endovascular embolization, and surgical treatment as they apply to AVMs are discussed.

Conclusions. Understanding the complex cellular biology, physiology, hemodynamics, and flow-related phenomena of AVMs is critical for defining and predicting their behavior, developing novel drug treatments, and improving endovascular and surgical therapies.

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KEY WORDS • molecular • cellular biology • arteriovenous malformation • medical treatment • future trends

ARTERIOVENOUS malformations (AVMs) are vascular lesions characterized by a tangle of abnormal arteries and veins that directly shunt blood from the arterial to the venous circulation. Cerebral AVMs occur most commonly sporadically but can be associated with genetic disorders.^{4,8,15,36,48,58} The reported incidence of AVMs is 1.34/100,000 person-years, with a prevalence of 10 to 18/100,000, and they account for approximately

1.4%–2% of all hemorrhagic strokes.^{10,36,46} Arteriovenous malformations are diagnosed incidentally in 0.05% of all neuroimaging studies.

Intracranial hemorrhage (ICH) is the most severe and most common clinical presentation of cerebral AVMs. Risk factors that have been associated with AVM rupture include certain genetic mutations, intranidal aneurysms, exclusive deep venous drainage, restricted venous outflow, and deep or infratentorial location.^{1,26,36} The annual risk of rupture is 2%–4%, manifesting as the initial symptom in 37%–71% of patients, with an incidence of 0.51/100,000. After hemorrhage, the risk of recurrent hemorrhage during the 1st year is 6%–18%, returning to 4% after this period. Mortality is reported at 10% after hemorrhage, and residual major disability occurs in 20%–30% of patients.^{7,9,10,14,15,18–20,29,36,40,44,55,57}

Feeding artery pressures, compartmentalization, venous drainage, flow phenomena, and vascular steal all contribute to the complex physiology of cerebral AVMs. Intranidal vessels are exposed to abnormally high blood flow and shear forces that activate molecular pathways in

Abbreviations used in this paper: ACVRL1 = activin receptor-like kinase 1; ANG = angiopoietin; ANGPTL = ANG-like; AVM = arteriovenous malformation; BDNF = brain-derived neurotrophic factor; BEC = brain endothelial cell; ENG = endoglin; HHT = hereditary hemorrhagic telangiectasia; ICH = intracranial hemorrhage; LPS/sTF = lipopolysaccharide and soluble tissue factor conjugate; MIF = macrophage migration inhibitory factor; miR-18a = microRNA-18a; MMP = matrix metalloproteinase; SNP = single nucleotide polymorphism; SRS = stereotactic radiosurgery; TGF = transforming growth factor; TSP-1 = thrombospondin-1; VEGF = vascular endothelial growth factor.

* Drs. Rangel-Castilla and Russin contributed equally to this work.

smooth muscle cells and brain endothelial cells (BECs), leading to proliferation and vascular remodeling.^{32,33,50,54} Microscopic animal models have shown that cerebral AVMs have a number of pathological changes present in nidus vessels. These changes include heterogeneously thickened vessel walls, splitting of the elastic lamina, thickened endothelial layers, endothelial cushions, lack of tight and adherent junctions, loss of endothelial continuity, and filopodia (microspikes) directed into the lumen.⁵¹

Over the last 2 decades, new genetic, molecular, and cellular factors have been demonstrated to be involved in the process of formation, growth, and rupture of AVMs. The goal of this work was to compile and analyze new evidence regarding these processes and investigate consequent potential future therapeutic alternatives.

Methods

A comprehensive review of English-language literature was performed on PubMed using the key words “brain,” “cerebral,” “arteriovenous,” “malformation,” “management,” “embolization,” “radiosurgery,” “rupture,” “genetic,” and “molecular.” Additional articles were located by cross-referencing articles encountered initially through PubMed searches. Inclusion criteria comprised articles (case reports, case series, meta-analyses, clinical trials, literature reviews, molecular studies, animal models, and guidelines) originating from peer-reviewed literature and discussing the molecular and cellular biology, the risk factors, clinical presentation, diagnostic tests, management, outcomes, and complications of patients with cerebral AVMs.

Conceptually, this review will examine the biology of syndromic AVMs for which there may be a more discernable pathway than for sporadic ones. Then the factors potentially involved in AVM formation will be reviewed. The processes involved in AVM progression, including the important events of growth and rupture, will be discussed. Current AVM treatment paradigms will next be covered. Lastly, potential treatment avenues that take advantage of AVM biology as it is currently known will be explored (Fig. 1).

Molecular and Cellular Biology Associated With Syndromic AVMs

The majority of cerebral AVMs are sporadic; however, a minority of patients will be diagnosed with a genetic mutation (e.g., hereditary hemorrhagic telangiectasia [HHT]).^{16,35,50} Identification of genetic mutations associated with cerebral AVM formation has facilitated the development of animal models that have provided new insights into the etiology of these lesions.^{9,34,39,50} Although inheritable mutations are most frequently discussed, environmental factors are also believed to play an important role in single allele mutations.²³

Osler-Weber-Rendu syndrome, or HHT, is the most common syndrome associated with AVMs. It is an autosomal-dominant vascular disease caused by haplo-insufficiency of the transforming growth factor (TGF)- β

pathway signaling genes *ENG*, *ACVRL1*, and *SMAD4*. It is characterized clinically by mucocutaneous telangiectasias, with the presence of single or multiple AVMs in 9%–25% of patients.^{35,42} The phakomatosis cerebrofacial arteriovenous metamerism syndrome (CAMS) consists of brain and orbit AVMs with retinal or retrobulbar lesions. Some patients with complete expression manifest high-flow maxillofacial or mandibular AVMs, manifesting life-threatening epistaxis or gingival hemorrhage.³ Cervical cutaneomeningospinal angiomas, or Cobb's syndrome, is a rare somatic disorder presenting with spinal AVMs and abnormal platelet endothelial cell adhesion molecule (PECAM-1), smooth muscle actin, VEGF (vascular endothelial growth factor), and matrix metalloproteinase (MMP)–9 expression.¹³ Other diagnoses less frequently associated with AVMs include ataxia telangiectasia, Sturge-Weber syndrome, and cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).^{33,46} While these represent a variety of associations with AVM formation, they do not yet define a common pathway.

AVM Formation

Arteriovenous malformations have been associated with several genetic mutations, resulting in their pathogenesis. These genetic mutations alter inflammatory factors, angiogenesis, vasculogenesis, and structural proteins.^{35,48} More than 860 genes are now known to be upregulated (300) and downregulated (560) in cerebral AVMs.³³ Single nucleotide polymorphisms (SNPs) are DNA sequence variations that differ between members of the same species. SNPs of certain angiogenic factors were first associated with sporadic cerebral AVMs and subsequently with their risk of rupture.³⁷ Some specific molecules affected by SNPs are TGF- β , an extracellular glycosylated protein that suppresses the effects of interleukins and is critical in de novo AVM formation;³² brain-derived neurotrophic factor (BDNF), a protein that supports survival, development, and function of neurons;⁵⁵ interleukin-6 (IL-6), which contributes to vascular wall instability by stimulating the release of MMP;^{32,33,38} and angiopoietin-like 4 (ANGPTL4), a glycoprotein believed to be involved in angiogenesis (Table 1).³¹ Vascular endothelial growth factor is a critical signaling molecule that regulates angiogenesis and is typically suppressed in normal adult vasculature. VEGF has a potent mitotic effect and is highly expressed in children with recurrent AVMs.⁶ Cerebral hypoxia and ischemia result in VEGF secretion by astrocytes. Following the release of hypoxia-induced factors, a response element contained in the VEGF gene promoters enables a 30-fold increase in VEGF within minutes.^{21,32} VEGF-A is primarily expressed in astroglia adjacent to the AVM nidus, while VEGF-C and VEGF-D are highly expressed within large nidi and are believed to contribute to development.

Angiopoietins (ANGs) are vascular growth factors that regulate pericyte and smooth muscle precursors involved in angiogenesis and vascular stability. ANG1 promotes cellular interaction providing vessel stability and has been found to have decreased levels in AVM patients. ANG2 has a role in deconstructive signaling, promoting

Fig. 1. Diagram showing different genetic, molecular, and cellular biology components that contribute to the formation, growth, and rupture of AVMs and experimental treatment. ACVRL1 = activin A receptor type II-like; ANGPTL-5 = angiopoietin-like 5; BDNF = brain-derived neurotrophic factor; BEC = brain endothelial cell; CAMS = cerebrofacial arteriovenous metamerism syndrome; ENG = endoglin; HHT = hereditary hemorrhagic telangiectasia; IL-6 = interleukin-6; LPS/sTF = lipopolysaccharide and soluble tissue factor conjugate; MIF = macrophage-migration inhibitory factor; miR-18a = microRNA-18a; MMP = matrix metalloproteinase; PECAM-1 = platelet endothelial cell adhesion molecule; SMAD = family member 4; SNP = single nucleotide polymorphism; TGF- β = transforming growth factor- β ; TIMP = tissue inhibitor of MMP-4; VEGF = vascular endothelial growth factor; $\downarrow$ = decreased; $\uparrow$ = increased.

TABLE 1: Single nucleotide polymorphisms associated with brain AVMs*

Molecule	SNP	Associated Effect
TGF- β 2	-879 G/G	increased risk for BAVM
TGFR- β 2	-875 A/G	increased risk for BAVM
IL-17A	-197 G/A	together with TGFR- β 2-875 A/G, increased risk for ICH
BDNF	rs6265 (Val66Met)	decreased BDNF secretion & poor outcome after neurological injury & worse surgical outcome in unruptured BAVMs
ANGPTL4	rs11672433	increased risk for BAVM
MMP-3	rs522616 (-709 A/G)	2-fold increased transcription
MMP-9	rs9509	highly associated w/ ICH
IL-1 α	-889 C>T	increased risk for BAVM
IL-6	-174 G/C	associated w/ TNF- α -238 G/A for increased risk of ICH
ACVRL1	IVS3-35 A/G	increased risk for BAVM
NA	rs1333040 C/T	located on 9p21 arm; associated w/ BAVM; deep venous drainage, seizures & ICH are more frequent

* ANGPTL4 = angiopoietin-like 4; ACVRL1 = activin receptor-like kinase 1; BAVM = brain AVM; BDNF = brain-derived neurotrophic factor; IL = interleukin; IVS = intervening space; MMP = matrix metalloproteinase; NA = not available; TGF = transforming growth factor; TGFR = TGF receptor; TNF = tumor necrosis factor.

remodeling, and vessel destabilization. It has been reported to be upregulated in cerebral AVM patients with ANG2 mRNA levels being increased by up to 30%. However, it is believed that to develop a cerebral AVM, ANG2 and VEGF work synergistically and both must be overexpressed.^{21,33}

Genes, molecules, and structural proteins located in BECs are believed to be intimately associated with the development of cerebral AVMs. Neurogenic locus Notch4 is a member of a family of transmembrane proteins with repeats of extracellular endothelial growth factor (EGF). Bone morphogenetic protein (BMP) signaling is linked to Notch4 modulation and it is thought that deviation from normal expression in this relationship can contribute to AVM formation. Deficiency of matrix Gla protein (MGP^{-/-}) in animal models induces expression of activin receptor-like kinase 1 (ACVRL1). ACVRL1 will inhibit BMP and induce Notch ligands, resulting in deregulation of endothelial differentiation and AVM development in MGP null animal models.⁵⁶ Activation of Notch4 (int-3) in the endothelium of animal models during brain development has been associated with AVM formation; it can be activated using a tetracycline-regulatable system. It has been demonstrated that int-3 activation alone is sufficient to induce and sustain the growth of abnormally large vasculature and shunting, which are the hallmarks of AVMs. Int-3 expression results in widespread enlargement of the microvasculature, which coincides with a reduction in the capillary density. The Notch pathway is a molecular regulator of brain AVMs pathogenesis in mice, and this connection offers hope that their regression might be possible by targeting the causal molecular pathway.³⁴

Aside from initiation, it is believed that cell-cell interactions may be important to AVM growth and progression. Integrins are heterodimeric transmembrane cell-surface adhesion receptors that mediate matrix and cell-cell interactions, transducing signals that regulate multiple vital cellular functions. Integrin $\alpha V\beta 3$ has increased expression in cerebral AVMs.^{16,33,43} Endoglin (ENG) is a glycoprotein located on cellular surfaces crucial for angiogenesis. High levels of endoglin enhance the effects of ACVRL1 over endothelial proliferation. Both proteins are part of the TGF- β complex, and genetic mutations on ENG and ACVRL1 are both associated with HHT and arteriovenous fistulas.^{7,33,43} Arteriovenous malformation BEC turnover has been described to be somewhere between normal BECs and those in developing tumors, with aberrant functions. These cells are believed to undergo rapid proliferation and migration, producing aberrant tubular structures, due to deregulation in vasculogenesis and angiogenesis.^{2,17,33,58}

AVM Growth and Rupture

A role for inflammation and extracellular matrix remodeling in AVM growth and rupture has been postulated. Inflammatory cells are frequently identified in the vascular wall of cerebral AVM vessels. Macrophages and neutrophils tend to invade AVM tissue even in the absence of radiographically evident hemorrhage. Relative neutrophilia and increases in macrophage migration inhibitory

factor (MIF) both appear to contribute to the instability of AVM nidus vessels, contributing to apoptosis and possibly rupture. Elevated MIF levels are primarily found in the vascular endothelium and adventitia, while apoptotic cells are concentrated in the smooth muscle layer.^{5,21}

Matrix metalloproteinases also appear to play a key role in the growth and rupture of cerebral AVMs.^{4,21,24,33,47} These are proteolytic enzymes that degrade pericellular substances, resulting in vascular destabilization and altered angiogenesis.^{18,33} Starke et al. found that plasma levels of MMP-9 were significantly elevated over controls at baseline, increased significantly immediately after surgery, and decreased to pretreatment levels during follow-up.⁴⁷ Single nucleotide polymorphisms of MMP-9 and tissue inhibitor of MMP-4 (TIMP-4) are also associated with increased risk of rupture in patients with cerebral AVMs. This was demonstrated in patients with AVM who underwent genotyping analysis.⁴⁹ VEGF has been associated with AVM rupture through an increased expression of MMP-9. Rupture of cerebral AVMs has also been associated with overexpression of MMP-3. It is believed that the binding of transcription factor C-MYB to the area around rs522616 SNP results in the overexpression of MMP-3.²¹ Table 1 summarizes the most relevant SNPs associated with cerebral AVMs and their risk for rupture.

Brain endothelial cells have a high proliferation rate with reduced apoptotic response to inflammatory mediators such as TGF- β . Angiogenic factors, like VEGF, are not normally produced by quiescent brain vasculature, but are by AVM-BECs.⁴³ In contrast to mature vessels, immature vessels are associated with a fibronectin-rich matrix deficient in laminin. The high concentration of laminin and the absence of fibronectin in AVM vessels favor the hypothesis that they are relatively mature vessels. This vessel maturity is believed to contribute to the vascular resilience in the face of hemorrhage. However, one observes clinically that while the vessels of AVMs are relatively robust, some are fragile to handling and do not coagulate normally, and clearly they develop areas of weakness, which results in clinical hemorrhage. It is likely that multiple mechanisms including inflammation, remodeling, and BEC abnormalities contribute to their tendency to exhibit hemorrhage.

AVM Treatment

Current Management

A recent meta-analysis presented by van Beijnum et al. included 13,698 patients with ruptured and unruptured cerebral AVMs.⁵³ They reported obliteration rates of 96%, 38%, and 13% by microsurgical resection, stereotactic radiosurgery (SRS), and endovascular embolization, respectively. Microsurgical resection is currently recommended for Spetzler-Ponce Class A or Spetzler-Martin Grade I or II AVMs based on pooled analysis.^{44,45} Spetzler-Ponce Class B or Spetzler-Martin Grade III lesions are a heterogeneous grouping and current recommendations are for resection with special consideration for combination therapy. For Spetzler-Ponce Class C or Spetzler-Martin Grade IV and V AVMs, palliative treatment is

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recommended in the setting of progressive neurological decline and/or recurrent hemorrhages. A combination of SRS, embolization, and microsurgery may be used in the palliative management of Spetzler-Ponce Class C lesions.^{15,22,36,41} Given that the large majority of high-grade lesions cannot be treated without relatively high morbidity and mortality using current surgical and radiosurgical paradigms, new cellular and molecular biological therapies are under development aiming toward radiosensitization, vascular targeting, and remodeling therapies.^{27,43} The current AVM treatment paradigm does not take into consideration any special factors related to the genetics or molecular constitution of the specific patient who has an AVM. It is reasonable to think at some point that a better understanding of regulatory factors and pathways may allow us to modify the natural history away from rupture.

Experimental Therapies

Given that the process of AVM rupture is believed to be related to the AVM's capacity for local vascular remodeling, drugs that impede this process form a group that are theoretically attractive as therapeutic agents. Tetracyclines are a class of antibiotics that have the potential to prevent pathological vascular remodeling and therefore potentially decrease the risk of AVM rupture.¹² Doxycycline has been shown to decrease cerebral MMP-9 activity and angiogenesis induced by VEGF.^{17,25} A model²⁵ of VEGF focal hyperstimulation delivered by an adenoviral vector (AdVEGF) showed inhibition of MMP-9 mRNA expression in response to doxycycline therapy. Doxycycline proved to be effective at very low doses, with good tolerance and acceptable complication rates.^{12,17} Although it remains a potential target, some authors have postulated that direct VEGF-oriented molecular therapy might be an ineffective or even detrimental alternative due to VEGF's inherent effect on normal vascular and neuronal cells.^{16,21,24,30,32,33}

Vascular endothelial growth factor is seen as a possible common pathway molecule in AVM pathogenesis. Thrombospondin-1 (TSP-1), a VEGF-A antagonist, has low levels in AVM-BECs. Inhibition of a TSP-1 transcription repressor, called "inhibitor of DNA-binding protein A" (Id-1), increases TSP-1 levels. Increasing TSP-1 will theoretically inhibit VEGF-A. Recently, microRNA-18a (miR-18a), a short noncoding RNA involved in post-transcriptional regulation of gene expression affecting stability and translation of RNA, was proven to increase TSP-1 in AVM-BECs by inhibiting its inhibitor (Id-1).^{11,58} Under shear arterial blood flow conditions, naked miR-18a significantly reduces VEGF-A and VEGF-D release in AVM-BECs and not in normal BECs, demonstrating tissue specificity. MiR-18a normalizes the behavior of AVM-BECs, leading to reduced proliferation and improved tubule formation, enhancing vascular structure and function. Moreover, miR-18a successfully penetrates target cells without additional reagents, allowing for intravenous or endovascular infusion, making it a promising therapeutic option.^{11,58}

The effect of radiation on the molecular process of AVM pathophysiology is of particular interest given its known ability, delivered as SRS, to drive endothelial pro-

liferation and ultimately AVM obliteration.⁴³ Radiation elevates proapoptotic factors, such as p53, p21Waf-1, and mdm-2 mRNA. Elevation of TGF- β and α -smooth muscle actin generates fibroblast transformation into myofibroblasts, possibly leading to shrinkage and obliteration of cerebral AVMs.^{27,28} Smooth muscle cell endothelialization with Weibel-Palade bodies is observed in arteries containing von Willebrand factor and P-selectin.⁵² Radiation causes endothelial cells to separate and become disrupted. Increased E-selectin, P-selectin, ICAM-1, and ET-1 lead to leukocyte and platelet increased adherence postirradiation. These adhesion molecules may be potential targets for biological strategies to accelerate intravascular thrombosis.²⁷

Using a lipopolysaccharide and soluble tissue factor conjugate (LPS/sTF) in an animal model of vascular targeting was recently described. In that study, 3 different treatment groups were compared. Results showed induced AVM thrombosis in 58% of subjects receiving SRS plus LPS/sTF, 12% in subjects undergoing SRS only, and 43% in those receiving LPS/sTF only. No systemic toxicity or intravascular thrombosis remote from the target region was detected in any of the animal groups. Human trials are still pending.³⁹

Conclusions

A large variety of genetic, molecular, and biological factors are involved in the process of AVM formation. In vivo models such as lines of endothelial cell cultures from AVM specimens are potential areas for research. Understanding molecular targets such as TGF, VEGF, ANGs, and integrins is important in the development of potential drug therapies. Structural and hemodynamic properties also have an effect on the growth and remodeling of AVMs. Interplay between vasculogenesis and flow through nidus vessels causes growth, remodeling, and hemorrhage of AVMs. In the near future, the development of drug therapies, endovascular technology, minimally invasive microsurgical techniques, and proper patient selection will optimize surgical results and clinical outcomes.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Nakaji, Rangel-Castilla, Russin. Acquisition of data: Rangel-Castilla, Russin, Martinez-del-Campo, Soriano-Baron. Analysis and interpretation of data: Rangel-Castilla, Russin, Martinez-del-Campo. Drafting the article: Nakaji, Rangel-Castilla, Russin, Martinez-del-Campo, Soriano-Baron. Critically revising the article: Nakaji, Rangel-Castilla, Russin, Spetzler. Reviewed submitted version of manuscript: Nakaji, Spetzler. Study supervision: Spetzler.

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Address correspondence to: Peter Nakaji, M.D., c/o Neuroscience Publications, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, 350 W. Thomas Rd., Phoenix, AZ 85013. email: neuropub@dignityhealth.org.