Biology of Vascular Malformations of the Brain
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Biology of Vascular Malformations of the Brain NINDS Workshop Collaborators
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Background and Purpose—This review discusses recent research on the genetic, molecular, cellular, and developmental mechanisms underlying the etiology of vascular malformations of the brain (VMBs), including cerebral cavernous malformation, sporadic brain arteriovenous malformation, and the arteriovenous malformations of hereditary hemorrhagic telangiectasia.

Summary of Review—The identification of gene mutations and genetic risk factors associated with cerebral cavernous malformation, hereditary hemorrhagic telangiectasia, and sporadic arteriovenous malformation has enabled the development of animal models for these diseases and provided new insights into their etiology. All of the genes associated with VMBs to date have known or plausible roles in angiogenesis and vascular remodeling. Recent work suggests that the angiogenic process most severely disrupted by VMB gene mutation is that of vascular stabilization, the process whereby vascular endothelial cells form capillary tubes, strengthen their intercellular junctions, and recruit smooth muscle cells to the vessel wall. In addition, there is now good evidence that in some cases, cerebral cavernous malformation lesion formation involves a genetic 2-hit mechanism in which a germline mutation in one copy of a cerebral cavernous malformation gene is followed by a somatic mutation in the other copy. There is also increasing evidence that environmental second hits can produce lesions when there is a mutation to a single allele of a VMB gene.

Conclusions—Recent findings begin to explain how mutations in VMB genes render vessels vulnerable to rupture when challenged with other inauspicious genetic or environmental factors and have suggested candidate therapeutics. Understanding of the cellular mechanisms of VMB formation and progression in humans has lagged behind that in animal models. New knowledge of lesion biology will spur new translational work. Several well-established clinical and genetic database efforts are already in place, and further progress will be facilitated by collaborative expansion and standardization of these.

Key Words: angiogenesis ■ arteriovenous malformation ■ cerebral hemorrhage ■ genetics ■ physiologic ■ vascular malformations
pathological states may also provide fresh insights into the basic biology of the cerebral vasculature.

Cellular and Molecular Interactions Controlling Angiogenesis

The development of the vasculature occurs in 2 stages: vasculogenesis (de novo blood vessel formation during embryogenesis) and angiogenesis (the growth of new blood vessels from pre-existing ones). Vasculogenesis of the cerebral vasculature occurs outside the brain with the formation of the perineural plexus. Capillaries sprout from this plexus and penetrate the neural tube in a characteristic spatiotemporal pattern. Subsequent growth of the cerebral vasculature occurs entirely by angiogenesis, the first phase of which involves vascular endothelial cell proliferation and migration. A key mediator of these processes is vascular endothelial growth factor (VEGF), which is produced by developing neuroectodermal cells and their neural and glial progeny. In response to hypoxia, VEGF also upregulates capillary permeability, and developing capillaries are characterized by relatively high permeability and low levels of interendothelial junctional proteins.

The next phase of angiogenesis is vascular stabilization, during which endothelial cells form capillary tubes, strengthen their intercellular junctions, and recruit smooth muscle cells to their walls. Vascular stabilization involves reciprocal interactions between endothelial cells and pericytes, the precursors of vascular smooth muscle cells. Brain pericytes arise from mesoderm and neural crest and accompany capillary sprouts as they penetrate the brain. Pericyte differentiation and production of extracellular matrix are thought to be triggered by endothelial platelet-derived growth factor-B and transforming growth factor-β1 (TGF-β1). As pericytes differentiate, they act back on the vascular endothelium to suppress capillary sprouting, stimulate wall growth, and promote intercellular junction formation and cell-matrix adhesion. These actions are mediated in part through angiopeitoin-1; other mediators include tissue inhibitors of metalloproteinases and ephrin-B2. Loss of pericytes (in platelet-derived growth factor-B-deficient mice, for example) leads to vessel dilation, endothelial cell hyperplasia, and microaneurysm.

Brain angiogenesis subsides after birth but can be reactivated in response to physiological stimuli including exercise, sensory enrichment, chronic hypoxia, shear stress, and certain hormones. Dramatic, local upregulation of angiogenesis also occurs in response to pathological conditions such as tumor, stroke, or trauma. Adult angiogenesis is regulated by some of the same factors (eg, VEGF and angiopoietins) that regulate developmental angiogenesis but is also likely to involve unique mechanisms. Capillary sprouting in adulthood requires reactivation of quiescent endothelium and breakdown of previously stabilized vessel walls and often occurs in the context of inflammation. For example, recent work indicates that endothelial sprouting is induced by different Notch pathway genes during development and inflammation.

Figure 1. Schematic illustrations of (A) CCM and (B) AVM angioarchitecture.

Angiogenesis and VMB Formation

Cellular Pathology and Natural History of VMBs

VMBs form at the interface between arterial and venous endothelium, where capillary endothelium normally lies. A CCM is a cluster of dilated, capillary caverns that are low-flow and may contain thrombi (Figure 1A). An AVM is a mass of arteries and veins that appear to fuse without intervening capillaries and form a network of direct, high-flow arteriovenous shunts (Figure 1B). The generally accepted histopathologic conception of an AVM is that the nidus lacks a true capillary bed. However, the existence of dilated perinidal capillaries has long been appreciated, and recent studies suggest that these form a complex system that communicates directly with the nidus.

A common assumption has been that VMBs arise during embryonic development, but there is little direct evidence to support this idea. The mean age of presentation is approximately 34 years for CCM and 40 years for AVM. In addition, there is now clear evidence that active growth and de novo formation of CCMs and AVMs can occur. At the cellular level, the first step in the formation of both lesion types may be capillary dysplasia. In CCM, observations in the mouse suggest that multiple cavernous capillaries can sprout from the initial lesion. In AVM, it is possible that perinidal capillaries fuse to become part of the nidus.

VMB Genes and Angiogenesis

Most of the VMB genes and genetic risk factors discovered so far (Table) have demonstrated roles in vasculogenesis, angiogenesis, and vascular remodeling (formation or regression of vessels within a pre-existing vascular bed). An ongoing problem has been to understand which of these roles are most relevant to lesion formation. An additional conundrum arises from the focal nature of CCM and AVM lesions. Inherited CCM and AVM syndromes result from loss of function of one copy of the relevant gene in all of the cells that normally express the gene (eg, all endothelial cells in the case, for example, of CCM1), but lesions are seen only in discrete locations and not throughout the vasculature. This observation has led investigators to propose a genetic “2-hit” mechanism for VMB lesion formation, in which an inherited mutation in one copy of a VMB gene is followed by a somatic mutation in the second copy. Alternatively, the second “hit” could be environmental in the form of a localized physiological or pathological perturbation. These models and the
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Table. Genes Underlying Hereditary Forms of VMBs

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alternative Name(s)</th>
<th>Known or Putative Cellular Functions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCM 1</td>
<td>KRIT 1</td>
<td>Binds β-catenin, stabilizes interendothelial junctions associated with actin stress fibers</td>
<td>88</td>
</tr>
<tr>
<td>CCM 2</td>
<td>Malcavernin; osmosensing scaffold for MEKK3 (OSM)</td>
<td>Cellular responses to osmotic stress; modulates MAP kinase and RhoA GTPase signaling</td>
<td>89, 90</td>
</tr>
<tr>
<td>CCM 3</td>
<td>Programmed cell death 10 (PDCD10)</td>
<td>Cell proliferation and transformation (cancer cell lines); modulates extracellular signal-regulated kinase (ERK)</td>
<td>91</td>
</tr>
<tr>
<td>Endoglin</td>
<td>HHT1</td>
<td>TGFβ superfamily coreceptor; modulates signaling by TGFβ Type II receptor, ALK-1 and ALK-5</td>
<td>43</td>
</tr>
<tr>
<td>ALK-1</td>
<td>Activin A receptor type II-like 1 (ACVRL-1); HHT2</td>
<td>TGFβ Type I receptor</td>
<td>92</td>
</tr>
<tr>
<td>SMAD4</td>
<td>SMAD family member 4</td>
<td>Common downstream mediator of multiple TGFβ superfamily signaling pathways</td>
<td>92, 93</td>
</tr>
</tbody>
</table>

Ccm2+/− mice (i.e., mice in which a single copy of the Ccm2 gene is disrupted) show greater dermal vascular permeability in response to VEGF treatment in vivo than wild-type mice. Vascular permeability in Ccm2+/− and wild-type mice did not differ under normal conditions, however. This observation is consistent with a 2-hit model of CCM lesion development in which endothelial cells deficient in ccm2 protein function normally unless challenged with an environmental perturbation. In addition, enhanced vascular permeability may predispose to hemorrhage, a consistent pathological feature of CCM lesions. Interestingly, the in vivo dermal hyperpermeability seen in Ccm2+/− mice was reversed by the statin simvastatin (which inhibits RhoA isoprenylation and association with cell membranes), pointing to a possible CCM therapy.37

All 3 CCM genes are expressed in central nervous system neurons and glia as well as in vascular endothelium.33,38 However, studies in mice and zebrafish mutants have shown that Ccm1 and Ccm2 are specifically required in endothelial cells for normal vascular development and that selective knockout of Ccm2 function in neuroglial cells does not lead to obvious cerebrovascular defects.36,37,39 Finally, studies in zebrafish have shown that identical cardiovascular phenotypes result from knockdown of ccm1, ccm2, or ccm3, thus providing further evidence that the 3 genes operate in a single functional pathway.36,40

Figure 2. One possible model of genes and pathways involved in CCM signaling. CCM proteins form a molecular complex that interacts closely with cytoskeletal proteins and modulates interendothelial cell junctions. Mutations in one copy of a CCM gene may predispose to vascular permeability, which in turn may result in vascular leakage and vulnerability to form dysmorphic vessels. Somatic mutations in the same genetic pathway, immune responses, or altered capillary permeability after radiation injury all might act as “second hits” favoring CCM genesis or maintenance. β-catenin; ICAP-1, integrin cytoplasmic domain-associated protein-1; ITGβ1, integrin β1; JNK, JUN NH2-terminal kinase; MEKK3, mitogen-activated protein kinase kinase kinase 3; RAP-1, Ras-proximate-1.

Evidence for them are discussed in more detail in subsequent sections.

Cerebral Cavernous Malformation

Three CCM genes (CCM1, CCM2, and CCM3) have been identified to date. All 3 proteins are expressed in vascular endothelium33 and can bind into a single complex that associates with cytoskeletal and interendothelial junction proteins and components of certain signal transduction pathways (Table; Figure 2).34 The activity of the CCM protein complex may be regulated by the transmembrane receptor heart of glass, which is also expressed in vascular endothelium.35 The ligand for this receptor is currently unknown.

Mice and zebrafish with complete loss of Ccm1 or Ccm2 function (e.g., by gene knockout) show profound disruption of vascular development with severe and progressive dilation of major vessels followed by embryonic death.36,37 Mice with loss of a single copy of Ccm2 develop vascular lesions similar to those seen in human CCM.38 Recent work in mouse and zebrafish CCM models suggests that lesions result from defects in endothelial cytoskeletal dynamics and cell–cell adhesion.36,37 For example, mouse endothelial cells in which Ccm2 is knocked out in vitro show reduced intercellular contacts and barrier function together with failure of the actin redistribution that normally accompanies capillary tube formation. These deficits arise in part from loss of CCM2 interactions with RhoA, a GTPase that regulates the cytoskeleton.
Arteriovenous Malformation

HHT Types 1 and 2 result from loss-of-function mutations in one copy of the Endoglin (ENG) and Activin-like kinase receptor 1 (ACVRL1; ALK-1) genes, respectively. ALK-1 variants may also be associated with risk for sporadic AVM. Mutations in a third gene, SMAD4, were recently described in some cases of combined juvenile polyposis and HHT syndrome. ALK-1, endoglin, and SMAD4 all are components of TGF-β superfamily signaling pathways (Table; Figure 3).

Mice in which both copies of any of these genes are knocked out die as embryos. However, mice with mutations in just one copy of Eng or Alk-1 reproduce features of human HHT, including telangiectases and hemorrhage with unpredictable age of onset, severity, and location. Importantly, some of these mice spontaneously develop vascular dysplasias reminiscent of large-vessel AVMs.

How do reduced levels of ALK-1 or endoglin lead to vascular lesions? During development, both proteins are expressed most prominently in vascular endothelium. Both are downregulated in adulthood but induced during vascular repair. ALK-1 and endoglin have multiple actions on developing blood vessels, but their functions in vascular stabilization seem most central to disease etiology. ALK-1 or endoglin knockout mice establish relatively normal mature vasculature but have small-vessel malformations and loss of vascular smooth muscle. Defects in these mice resemble those in human HHT, in which dissociation of vascular smooth muscle cells is an early step, and sporadic brain AVM, in which there is reduced pericyte coverage of the perinidal capillaries.

Although ALK-1 and endoglin deficiencies manifest first histologically as defects of smooth muscle development, the disease process probably begins in the vascular endothelium. ALK-1, endoglin, and SMAD4 all are expressed in vascular endothelium, and ALK-1 and SMAD4 are specifically required there for smooth muscle recruitment. Thus, the primary defect in HHT may be an impaired endothelium-specific TGF-β signaling pathway with resulting smooth muscle defects. (Endoglin, however, is expressed not only in vascular endothelium, but also in vascular smooth muscle and monocytes and may be required there as well.)

Another potential cause of HHT lesions involves endothelial nitric oxide synthase. Endothelial cells of Eng+/− mice exhibit dysregulated endothelial nitric oxide synthase activity, leading to superoxide generation and impaired myogenic responses. Endothelial nitric oxide synthase malfunction could contribute to the small-vessel dilation seen at early stages of HHT, and superoxide may cause local endothelial damage and initiate capillary wall breakdown.

An unanswered question in AVM biology concerns the identity of the physiological ligand(s) for ALK-1 in vascular endothelial cells. This ligand was previously believed to be TGF-β1, which is expressed in developing vascular endothelium and known to regulate endothelial cell proliferation and migration. However, one study has indicated that deletion of TGF-βR2 (the ligand-binding TGF-β receptor) in endothelial cells does not affect vascular development and raised the possibility that the physiological ligand for Alk-1 is BMP9 or BMP10. Another mystery concerns the 10-fold difference in...
prevalence of brain AVMs in HHT1 (ie, *ENG* deficiency) versus HHT2 (ALK-1), which have approximate penetrances of 10% and 1%, respectively.

**VMBs and Vascular Patterning**
Another angiogenic process in which VMB genes have been implicated is arteriovenous specification. The arteries of mice with reduced levels of CCM1, ALK-1, or endoglin show wall thinning and dilation, fewer smooth muscle cells, and loss of artery-specific markers such as ephrinB2, suggesting either loss of arteriovenous identity or transformation toward a more venous phenotype. Recently, overexpression of Notch-4 (a gene involved in arteriovenous specification) in vascular endothelium of developing mouse brain caused cerebral vascular dysplasias resembling AVMs. However, studies of arteriovenous specification have so far focused on vessels outside the central nervous system; virtually nothing is known about how this process works in the brain. Another unexplored area concerns the development of vascular phenotypes that are specific to the brain or brain subregions. For example, 2 genes have been identified in zebrafish (βpix and pak2a) whose mutation causes failure of vascular wall stabilization and hemorrhage only in the head region. Better understanding of genes specific to the central nervous system vasculature could help illuminate VMB etiology and explain (for example) the different frequencies of brain AVMs in HHT1 and HHT2.

**Instigators and Abettors of VMB Formation and Progression**

**Genetic and Environmental Second Hits**
The focal nature of VMBs has suggested that lesion formation may require not only a mutation in one copy of a given VMB gene within a particular group of cells, but also a “second hit” that triggers the disease process in the region of the lesion. This second hit could be genetic, in the form of a somatic mutation to the second copy of that gene, or a mutation in another gene acting in the same cellular pathway. The possibility of a genetic 2-hit mechanism in CCM is supported by discoveries of coexistence of germline (ie, inherited) and somatic mutations in lesion tissue from subsets of patients with all 3 forms of inherited CCMs. In addition, it has been observed that CCM protein is lost from subsets of patients with all 3 forms of inherited CCMs. Finally, mice with mutations in one copy of the *Ccm1* gene do not normally develop lesions, but will do so if they also lack the tumor suppressor gene *p53* (a genetic background known to increase the rate of somatic mutations). It is not known how prevalent somatic mutations are in CCM or if a genetic 2-hit mechanism also operates in HHT or sporadic CCM or AVM.

Environmental factors, including angiogenic factors and inflammatory cytokines, could also act as second hits. For AVMs, hemodynamic factors such as high flow rates and the resultant high endothelial shear stress might also promote lesion formation and/or progression through direct mechanical effects on vessel walls, upregulation of angiogenic factors, or triggering inflammation. Hemodynamic factors are probably less important for CCM, because the lesions do not conduct high flows. Direct evidence that environmental second hits can initiate AVM lesion formation comes from studies of mice with mutations in one copy of either the *Eng* and *Alk-1* gene. Focal overexpression of VEGF greatly enhances the development of dysplasia in these mice, and this experimental dysplasia can be further exacerbated by regional increases in tissue perfusion.

**Angiogenic Factors**
VMBs exhibit activated angiogenesis, including upregulated expression of VEGF and other angiogenic factors and increased endothelial cell proliferation. Thus, it is possible VMBs escape the normal controls downregulating angiogenesis in adulthood and that lesion growth occurs through an autocrine-positive feedback loop. Angiogenic factor production by VMBs could also have adverse consequences for other cells of the neurovascular unit. For example, abnormal growth factor secretion by VMBs could cause inappropriate stimulation of neuronal or glial proliferation; indeed, there is evidence for the latter. In addition, VEGF and other angiogenic factors increase blood–brain barrier (BBB) permeability, which could in turn predispose vascular walls to rupture.

**Inflammation**
VMBs are also sites of active inflammation. Robust B and plasma cell infiltration and oligoclonal IgG immune responses have been demonstrated in CCMs. Neutrophils, macrophages, and inflammatory markers are seen in AVMs. Inflammatory cytokines, including tumor necrosis factor-α and some interleukins, are potent stimulators of both angiogenesis and BBB breakdown and could contribute to lesion progression and rupture. Consistent with this idea, polymorphisms in the tumor necrosis factor-α, interleukin-1β, and interleukin-6 genes are risk factors for intracerebral hemorrhage in sporadic AVM. Another link between inflammation and angiogenesis lies with endoglin, which is expressed in activated circulating monocytes. In postischemic heart, activated monocytes migrate to the infarct site, differentiate into endothelial cells, and contribute to vascular repair, but monocytes from HHT1 (*ENG*+/−) patients show reduced capacity to do so.

**Breakdown of the BBB**
BBB breakdown occurs in CCMs. Because loss of interendothelial contact and barrier function is also observed in Ccm2 mutant mice, BBB breakdown may be a primary defect in CCM. Alternatively, BBB breakdown in CCMs could be a symptom of activated angiogenesis and/or local inflammation. The BBB barrier has not been extensively studied in AVMs, but most intranidal vessels are of a caliber such that the capillary-level barrier would not be expected. Clinically, unless there is secondary injury from local mass effect or hemorrhage, imaging contrast agents do not pass into the extravascular space either in the nidus or in surrounding parenchyma.

**New Insights and Mysteries Remaining**
The past few years have shed considerable light on cellular mechanisms of VMB etiology. With regard to the roles of CCM and HHT disease genes in developmental angiogenesis,
it is now clear that both sets of genes are required specifically in endothelium and can act within common functional pathways. Several lines of evidence point to a critical requirement for these genes in vessel wall stabilization and smooth muscle recruitment and may eventually help explain how mutations in these genes render vessels vulnerable to rupture when challenged with other inauspicious genetic or environmental factors. Finally, there is now evidence of a genetic 2-hit mechanism operating in some CCM cases, as well as demonstration that environmental second hits can produce vascular lesions in mice bearing mutations in a single copy of a VMB gene.

Much still remains to be learned. Given that some (perhaps most) VMBs arise postnatally and into adulthood, we need to understand better how VMB genes function in adult angiogenesis and vascular repair and how their expression is affected by environmental perturbations. We also need to learn if mechanisms of lesion formation in sporadic VMB are the same as in familial forms. Other genes contributing to VMB syndromes should be identified, a quest that can be pursued not only in human populations, but also in C. elegans, Drosophila, or zebrafish.

With regard to experimental tools, more sophisticated animal models of VMB syndromes are being developed through conditional knockout, but currently available ones still have limitations; lesion frequency is low in heterozygous mutant mice and the available model systems do not precisely phenocopy either the angioarchitecture or the natural history of the human disease, especially with regard to intracranial hemorrhage. Better models might be generated by additional age- and cell type-specific knockouts, the use of different genetic backgrounds, or the identification of environmental triggers of lesion formation that can be applied easily and uniformly.

Finally, studies in humans have lagged behind those in animal models with regard to description of VMB etiology. Studies in human lesion tissue have been few and would be stimulated by the establishment of tissue repositories and standardized collection procedures. We still have no clear understanding of when lesion formation is initiated, how it typically progresses, or how progression is impacted by environmental risk factors. A critical step toward more sophisticated natural history studies and additional genetic studies will be the establishment of large cohorts of patients and databases of clinical information.

Translational Implications

Translational advances will include describing the biology underlying certain clinical behaviors, for example hemorrhagic risk. Although neither CCM nor AVM has a model that has been developed to the point of actually testing such questions, refinement of animal models that mimic disease onset and vascular repair and how their expression is understood will be important. In addition, understanding of when lesion formation is initiated, how it typically progresses, or how progression is impacted by environmental risk factors. A critical step toward more sophisticated natural history studies and additional genetic studies will be the establishment of large cohorts of patients and databases of clinical information.

Spatz, MD; Christian Stapf, MD; Guo-Yuan Yang, MD, PhD; Jun Zhang, PhD, ScD.

Appendix

Biology of Vascular Malformations of the Brain

National Institute of Neurological Diseases and Stroke Workshop Collaborators Workshop

Cochairs: Issam Awad, MD; and William L. Young, MD. Session Chairs: Mike Berg, MD; Michael Chopp, PhD; Nicholas W. Gale, PhD; Murat Gunel, MD; Eng H. Lo, PhD; Douglas Marchuk, PhD; Daniele Rigamonti, MD; and Elisabeth Tournier-Lasserve, MD. Speakers: Mike Berg, MD; Engolf E. Blasig, ScD, PhD; Nancy Boudreau, PhD; Michael Chopp, PhD; Nicholas W. Gale, PhD; Mark Ginsberg, MD; Kunlin Jin, MD, PhD; Gary L. Johnson, PhD; Helen Kim, PhD; Michael T. Lawton, MD; Michelle Letarte, PhD; Dean Y. Li, MD, PhD; Eng H. Lo, PhD; Douglas Marchuk, PhD; J. P. Mohr, MD, MS; Stephen Nishimura, MD; Douglas Noonan, PhD; Ludmila Pawlikowska, PhD; Karl H. Plate, MD; Daniele Rigamonti, MD; Robert Shenkar, PhD; and Elisabeth Tournier-Lasserve, MD. Participants: Rustam Al-Shahi Salman, PhD, MA, FRCP; Karen L. Ball; Marianne S. Clancy, MPA; Sander E. Connolly, Jr, MD, ME; Brent Derry, PhD; Eva Faurobert, PhD; Judith Gaul, PhD; Eugene Golanov, MD, PhD; Lisa Han Megan, NS, NP; Tomoki Hashimoto, MD; Richard F. Keep, PhD; Gabrielle G. Leblanc, PhD; Connie Lee, PsyD; Joseph McCarty, PhD; Leslie Morrison, MD; Ming-Ming Ning, MD; Michael F. Nunn, PhD; S. Paul Oh, PhD; Beth K. Plahn, RN, MHA; Charlotte A. Pratt, PhD; Wande B. Pratt, MD; Maria Spatz, MD; Christian Stapf, MD; Guo-Yuan Yang, MD, PhD; and Jun Zhang, PhD, ScD.

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