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Cerebral cavernous malformations as a disease of vascular permeability: from bench to bedside with caution

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Abstract

Tremendous insight into the molecular and genetic pathogenesis of cerebral cavernous malformations (CCMs) has been gained over the past 2 decades. This includes the identification of 3 distinct genes involved in familial CCMs. Still, a number of unanswered questions regarding the process from gene mutation to vascular malformation remain. It is becoming more evident that the disruption of interendothelial junctions and ensuing vascular hyper-permeability play a principal role. The purpose of this review is to summarize the current understanding of CCM genes, associated proteins, and functional pathways. Promising molecular and genetic therapies targeted at identified molecular aberrations are discussed as well.

Keywords

cerebral cavernous malformation; genetics; angiogenesis; endothelial cell junction; CCM1; CCM2; CCM3

Cerebral cavernous malformations are vascular malformations consisting of a cluster of enlarged capillary-like channels with a single layer of endothelium and without intervening brain parenchyma.⁶³ They are among the most common vascular malformations of the brain and are detected in the population at a rate of approximately 0.6 per 100,000.^{4,39} Patients with CCMs may present with seizures, hemorrhage, focal deficits, or nonspecific headaches.^{2,6,21,50} Magnetic resonance imaging, particularly with gradient reversal acquisition techniques, reveals reticulated lesions surrounded by low-intensity signals from hemosiderin-laden macrophages, giving a classic “popcorn” or “mulberry” appearance.⁶²

Cerebral cavernous malformations are characterized by separate familial and sporadic forms of the disease that have been described in multiple reports over the past 4 decades.

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8,13,22,27,33,34,46 The familial form of the disease is inherited in an autosomal dominant pattern. It is involved in up to 30% of all cases and is present in a greater proportion of Hispanic Americans of Mexican descent than other ethnic groups.^{17,36,40} Familial CCMs are more likely to hemorrhage, grow, and form new lesions than sporadic CCMs.^{45,57} Sporadic CCMs are more likely to have a benign course and to be associated with developmental venous anomalies.^{10,56,57} Cerebral cavernous malformations have also been reported after brain irradiation.^{38, 51}

Treatment for CCMs is tailored to the symptoms, location, and hemorrhagic activity of a particular lesion. Authors of several case series have reported good outcomes with surgery for medically intractable seizures due to a CCM and for superficial lesions in patients who present with recurrent symptomatic hemorrhages.^{6,15,24,52,53,80} Surgery for deep-seated or brainstem lesions is less successful and is associated with an early morbidity rate of roughly 30%–70% and a mortality rate of 2%.³⁰ Stereotactic radiosurgery for these lesions remains controversial and its associated morbidity is significant.⁵⁹ The timing and choice of treatment is further complicated by the difficulty in predicting the natural history of specific lesions.⁶

There has been great progress in the understanding of vasculogenesis and the pathogenesis of CCMs over the past 2 decades.^{6,39} Three separate genes have been identified in association with familial CCMs: *CCM1/KRIT1*, *CCM2/MGC4607*, and *CCM3/PDCD10*.^{7,19,23,41} Each exhibits a Mendelian autosomal dominant inheritance due to a heterozygous loss-of-function mutation at 1 of 3 distinct loci. The respective encoded proteins appear to interact with cytoskeletal and interendothelial cell junction proteins.³⁹

There has been a concurrent progression in the identification of genetic targets and biotherapeutics for other human diseases, targeted at molecular defects or signaling pathways affected by disease mutations.^{1,47–49,64} Furthermore, it is anticipated that the identification of molecular disease pathways in familial cases will unlock pathobiological mysteries and reveal therapeutic opportunities for the sporadic form of the disease. The purpose of this review is to summarize current concepts of CCM pathogenesis including its genetic and molecular basis. The concept of vascular hyperpermeability as it relates to CCM pathobiology and potential therapeutic targets are discussed as well.

Throughout this review we have employed the conventional and distinct rules of nomenclature for disease, lesion, human gene, mouse gene, and protein. The human inherited disease cerebral cavernous malformation, or the vascular lesion that characterizes the phenotype, is abbreviated CCM. Human CCM genes are fully capitalized and italicized, *CCM1*, *CCM2*, and so forth. Similarly, murine genes are italicized and use both upper and lower case letters, as *Ccm1*, *Ccm2*, and so forth. To avoid confusion, we refer to the respective protein products in capitalized nonitalicized letters (CCM1, 2, or 3), or by their protein database names—KRIT1, malcavernin (or OSM), and PDCD10, respectively. With these clarifications, it should be evident whether the term in question refers to the disease, a vascular lesion, a gene (mouse or human), or a protein.

The CCM Genes

CCM1 (KRIT1)

CCM1 is located at chromosome locus 7q11–q22 and was the first gene identified in association with the familial form of CCMs.²³ Linkage studies have shown that a *CCM1* mutation is involved in 40% of familial CCMs and nearly half of those patients will have neurological symptoms before 25 years of age.^{6,21,61} The product of *CCM1*, named Krev interaction trapped 1 or KRIT1, is an ankyrin repeat–containing protein that interacts with RAP-1A (Krev-1), which is a member of the RAS family of GTPases.^{37,66} It has also been revealed that KRIT1 interacts with integrin cytoplasmic domain–associated protein-1a (ICAP-1), a protein involved in β 1-integrin–mediated signal transduction.⁸¹

Germline mutations in *CCM1* cause CCMs, and roughly 100 distinct mutations in this gene have been identified to date with familial CCM disease.^{11,31,35,37,44,61} Homozygous *Ccm1* knockout mice die in midgestation with gross dilations of the major arteries and heart chambers and narrowing of other arteries.⁷⁷ CCM lesions are not documented in mice with heterozygous *Ccm1* knockout alone but when coupled with *Trp53* mutation, vascular anomalies similar to CCMs can develop.^{60,67}

KRIT1 binds CCM2 and SNX17, a protein involved in endocytosis and the sorting machinery of transmembrane proteins.¹⁶ KRIT1 mRNA and protein have been found in vascular endothelium as well as in astrocytes, pyramidal cells, and epithelial cells.^{18,32} KRIT1 is predominantly localized in the cytoplasm but it can shuttle between the cytoplasm and nucleus.^{26,76} ICAP-1 also shuttles between the nucleus and the cytoplasm but is mainly found in the nucleus.^{81,82} KRIT1 and ICAP-1 have a synergistic role in β 1-integrin–mediated cell proliferation. KRIT1 also appears to modulate ICAP-1 regulation of β 1-integrin–mediated signal transduction.⁸¹ In addition, KRIT1 binds to RAP-1A, a GTPase involved in interendothelial junction integrity.²⁹ RNA-mediated depletion of KRIT1 impairs the ability of RAP-1A to stabilize endothelial junctions, and this may most directly explain the role of KRIT1 in the molecular pathogenesis of CCMs.²⁹

CCM2 (MGC4607)

CCM2 is localized at 7p15–13 and was initially identified by 2 independent teams using different approaches, gene sequencing and loss of heterozygosity mapping.^{19,41,61} *CCM2* mutations are involved in up to 40% of familial CCMs.^{19,42} Patients with *CCM2*-associated disease have a lower number of gradient-echo sequence lesions than those with *CCM1* or *CCM3* disease, and the number of lesions increases less rapidly with age than in patients with *CCM1* disease.²⁰ Homozygous deletion of *Ccm2* from mouse endothelial cells leads to morphogenic defects in major arteries and veins and ultimately midgestational death.⁹ Heterozygous mice with *Ccm2*[±] mutations do not form CCM lesions, unless sensitized by a second hit such as the loss of *P53* tumor suppression gene function.⁶⁷

The CCM2 protein, also referred to as malcavernin, shows similar temporal expression patterns as KRIT1, although KRIT1 is expressed in a greater variety of tissues.⁶⁵ Zawistowski and colleagues demonstrated that CCM2 binds to KRIT1 via a phosphotyrosine-binding domain, in a manner similar to ICAP-1, and is able to sequester

KRIT-1 in the cytoplasm.^{61,79} This suggests a common functional pathway and loss of the KRIT1-CCM2 interaction may result in CCM development. The KRIT1-CCM2 interaction also stabilizes endothelial cell junctions by suppressing a protein called RhoA and its effector protein ROCK that are involved in actin stress fiber formation and endothelial monolayer permeability.⁷⁰

CCM3 (PDCD10)

CCM3, localized at 3q25.2–q27, encodes programmed cell death protein 10 (PDCD10) and is the most recently discovered gene involved in familial CCMs.⁷ *CCM3* mutation carriers are less common than *CCM1* or *CCM2* carriers, but they are more likely to present with hemorrhage and to have symptom onset before 15 years of age.²⁰ The temporal expression of *CCM3* mRNA correlates with that of *CCM2* in meningeal and parenchymal cerebral vessels.⁵⁸ Both *CCM2* and *CCM3* proteins have been identified in developing placental endothelium, corroborating their role in vasculogenesis.⁷²

The exact function of *CCM3* has not been fully clarified. Chen et al.¹² found that overexpression of wild-type *CCM3* induces endothelial cell apoptosis. Induction of apoptosis by serum starvation of endothelial cells leads conversely to increased expression of *CCM3*, and siRNA-mediated inhibition of *CCM3* is responsible for decreased cell death.¹² These findings led the authors to suggest that aberrant apoptosis, in the endothelium or neural cells, may play a role in the pathogenesis of CCMs.¹² More recently, Fidalgo et al.²⁵ found that *CCM3* is located on the Golgi apparatus in a complex with proteins of the germinal center kinase III family (GCKIII). Depletion of *CCM3* leads to Golgi apparatus disassembly and impaired cellular migration.²⁵

Importantly, *CCM3* protein precipitates and colocalizes with *CCM2*.⁷⁵ Thus, all 3 CCM proteins interact to form a complex that then interacts with other proteins such as β 1-integrin and ICAP-1.^{6,61} Patients with *CCM1*, *CCM2*, or *CCM3* disease exhibit histologically indistinguishable CCM lesions and their respective mRNA expression patterns suggest closely linked functions and a common disease pathway.^{6,61} Interestingly, discrepancies in linkage data and the frequency of identified mutations have suggested the presence of an additional CCM gene that has yet to be identified.⁴³ This gene may account for some kindreds with clear familial inheritance that has not been linked to any of the 3 known loci.

Vascular Permeability and CCMs

More than a decade ago, one of the authors (I.A.A.) reported defective interendothelial cell junctions in human CCM lesions examined by electron microscopy.⁷⁸ That finding has since been corroborated by other investigators.^{14,74,78} The understanding of the cellular functions of the CCM proteins is slowly unfolding, and there is growing evidence that the ultimate cellular pathology in this disease lies in dysregulation of vascular development and endothelial permeability (Fig. 1).

It has been demonstrated that KRIT1 is localized, in part, to interendothelial cell junctions and that its loss results in disruption of junctional stability that leads to increased permeability in vitro and in vivo.^{29,70} Moreover, loss of malcavernin has similar effects on

endothelial cell junction stability.^{70,76} Importantly, although patients with familial CCM may be heterozygous for *CCM1*, *CCM2*, or *CCM3* mutations, the endothelial cells within CCM lesions appear to lack the relevant protein.⁵⁴ One of the authors (I.A.A.) and others have shown that this is often due to a somatic mutation of the remaining wild-type allele at the relevant locus.^{3,28} Loss of endothelial cell junctions readily explains the leakage of blood in CCMs and their associated hemosiderosis and can account for the observed inflammatory response in CCM lesions.^{68,69} (This concept of CCM protein impact on the interendothelial cell junction was recently illustrated in a compelling editorial by Patterson.⁵⁵)

Ccm2 knockout mice show a failure of angiogenesis and die in midgestation. Mice that lack CCM2 in the endothelium alone develop vascular defects and impaired vessel formation. Whitehead et al.⁷⁶ found that CCM2-deficient mice also develop impaired endothelial barrier function and increased actin stress fibers through RhoA GTPase activation. These investigators found that simvastatin, which is a known inhibitor of RhoA GTPase, was able to reverse CCM2-mediated barrier dysfunction.

The relationship of CCM proteins and RhoA has been investigated by the current authors' (I.A.A. and R.S.) team. Working with Stockton and colleagues, we have recently demonstrated that the loss of either KRIT1 or CCM2 disinhibits RhoA and ROCK activity leading to interendothelial barrier instability and vascular leaking.⁷⁰ We also discovered that administration of fasudil, a potent inhibitor of ROCK, reverses the vascular leak in vivo offering a potential therapy for CCM disease.

In this same work, we demonstrated markers of increased ROCK activity in endothelial cells lining sporadic and familial human CCM lesions that were excised surgically.⁷⁰ This suggests that a final common signaling aberration involving ROCK activation takes place in both sporadic and inherited lesions. Background hyperpermeability in familial cases may be one factor in lesion genesis. A second hit (that is, a focal somatic mutation) might lead to full-blown lesion genesis, likely through complete loss of CCM protein. This is then accompanied by more profound failure of the vascular barrier, hemorrhage, and reactive inflammation—all characteristic of the mature CCM lesion phenotype. The background hyperpermeability and the final CCM lesion both exhibit increasing activation of ROCK. It is possible that developmental venous anomalies and brain irradiation may also cause vascular hyperpermeability in the respective brain regions and predispose to CCM lesion genesis via a similar mechanism involving ROCK activation.⁷⁰

Development of CCM Therapies

The ultimate goal of cellular and genetic investigations of CCMs is the development of molecular or genetic therapies to alter the clinical phenotype.⁵ Identification of therapies that prevent lesion genesis or make lesions less likely to hemorrhage or more likely to regress will have a profound impact on the morbidity associated with CCMs. Other therapies might make the lesions more sensitive to apoptosis in reaction to ablative therapies or irradiation. One hurdle that has been cleared is the selectivity of gene therapy vectors for endothelial cells. Tan et al.⁷¹ developed a method of coupling antibodies to liposome-DNA complexes that are internalized by cells. They were also able to show that this vector can deliver a

selected gene to activated endothelial cells.⁷¹ In addition, Trepel et al.⁷³ have described a method of selective gene therapy delivery to specific vascular targets using an adenovirus vector.

Other therapies for CCM may not require selective vector delivery to endothelial cells. Early results with statin and fasudil, as discussed above, suggest that the background predisposition to CCM disease can be rescued by ROCK inhibition, a well-tolerated therapy in humans. Whether such treatment will in fact prevent lesion genesis remains to be demonstrated, and the advent of animal models with transgenic mice has offered new opportunities to test this hypothesis.^{60,67} It is unclear if such therapy can reverse markers of ROCK activation in actual, full-blown CCM lesions and what overall effect it might have on such lesions.

Conclusions, Implications, and Cautions to Patients

A number of discoveries regarding the cellular and molecular pathogenesis of CCMs have been unveiled over the past 2 decades. It is becoming more evident that the protein products of the CCM genes are associated within the cell and likely share a common final pathway, one that ultimately impairs endothelial cell-cell junctions and vasculogenesis. The development of molecular and genetic therapies for CCMs is still in its infancy; however, there is great hope that effective treatments will be found.

With these exciting research discoveries, there is now the genuine hope of vascular permeability therapy in this disease. Still, we do not know if such treatment will prevent lesions from forming or prevent existing lesions from growing or what other effects it might have. It is still unclear if one particular drug or class of drugs, such as the commonly available statins, is the best permeability therapy or if as-yet-undiscovered drugs might do better. We have no idea about the potential magnitude of any treatment effect (that is, how many lesions or bleeds are prevented per year, if any, per hundred patients treated) or if side effects, both known and unforeseen, will wipe out any potential benefit. The good news is that all these questions are answerable with careful research. Animal studies will attempt to define therapeutic effect on actual lesions so we can know better what effect to expect and pursue in humans. Better animal models are being developed that will allow such testing.

In the end, the only results that count are those recorded in human patients. It is certainly appropriate to attempt to define an effect on lesions in a carefully selected group of patients in an exploratory (Phase I) clinical trial in man or even a Phase I or II study that looks for the best dose, safety, and estimates of treatment effect. In a disease where there is no proven therapy to date, it is perfectly reasonable to pursue such exploratory trials with apparently safe drugs, such as statins. Controversies will arise over whom to include and exclude from these exploratory trials, what effects to look for (lesion number, lesion size, and/or bleeds), and how long to follow the treated and untreated cases to glean a potential benefit. If a convincing effect is shown in these exploratory trials, a more definitive prospective double-blinded randomized trial (Phase III) will be needed to prove effectiveness and alter the standard of clinical practice. A negative exploratory trial may not mean complete futility.

The same drug might work with a different group of patients or in combination with other interventions or with different outcome measures.

Additional research might suggest further therapeutic approaches, including other CCM signal–modulating, antiinflammatory, or blood vessel–modifying (antiangiogenesis) drugs. Enthusiasm or concern about each will need to be assessed based on potential risks and benefits of the individual therapy. Exploratory clinical trials will obviously be easier to justify if they involve safe drugs already in widespread clinical use. More powerful and potentially more risky therapies will require convincing proof of effect and safety in animals before trials can proceed in humans.

We are quite excited about the scientific promise of these advances, but proofs of benefit and safety on any aspect relevant to clinical CCM disease are not yet in hand. There will be disappointments, and good and bad surprises. Concerns about ethics and safety will deliberately slow the process down. Yet nothing will chill this research colder than a bad side effect in a human study participant or a false promise that causes unintentional harm through ill-advised exuberance for an ineffective treatment. False starts might threaten the enthusiasm toward more promising future research. Furthermore, no trial will include all CCM cases nor be automatically applicable to every patient. Ultimately, some treatments might work best at preventing lesion formation while others succeed at shrinking lesions or preventing growth and hemorrhage. Some treatments might work better in older or younger patients, in cohorts with more aggressive disease, in one genotype but not others, in combination with another therapy, or in genetic but not sporadic lesions or vice versa. Much research is still needed, but there are glimmers of hope on the horizon, none of which could have been imagined a short decade ago.

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Disclosure

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Abbreviations used in this paper:

CCM	cerebral cavernous malformation
ICAP-1	integrin cytoplasmic domain-associated protein-1a
KRIT1	Krev interaction trapped 1
PCDP10	programmed cell death protein 10

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Fig. 1.

Depiction of the current understanding of the CCM pathway. An unidentified ligand binds to a transmembrane receptor named heart of glass (HEG) that interacts with an intracellular protein complex comprised of the CCM proteins. This interaction leads to a number of processes, including the inhibition of a RhoA GTPase, that ultimately result in normal interendothelial cell junctions and vascular integrity.