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PHARMACOTHERAPY FOR FAMILIAL CAVERNOUS MALFORMATION

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Abstract

Familial cerebral cavernous malformation (FCCM) is a hereditary vascular disorder characterized by multiple abnormal capillary lesions in the brain that can lead to seizures, hemorrhage, and neurological deficits. While surgical resection remains the primary treatment for symptomatic lesions, its effectiveness in FCCM is limited due to the presence of multiple and often surgically inaccessible lesions. Recent advances in molecular biology have improved understanding of the genetic and signaling mechanisms underlying FCCM, including mutations in the KRIT1 (CCM1), CCM2, and PDCD10 (CCM3) genes and dysregulation of pathways such as RhoA/ROCK, MEKK3–MEK5–ERK5, PI3K/mTOR, and oxidative stress signaling. These discoveries have led to the investigation of several potential pharmacological therapies, including rapamycin, ponatinib, fasudil, statins, propranolol, vitamin D_3, and antioxidants such as tempol. Preclinical and early clinical studies suggest that these agents may reduce lesion growth, improve endothelial stability, and decrease vascular permeability. However, most current evidence remains experimental, and significant challenges remain in translating these findings into effective clinical therapies. Further large-scale clinical trials are required to determine the safety and efficacy of targeted pharmacological treatments for FCCM.

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Keywords: Familial cerebral cavernous malformation, CCM1, CCM2, CCM3, RhoA/ROCK pathway, MEKK3–MEK5–ERK5 signaling, PI3K/mTOR pathway, pharmacotherapy, endothelial dysfunction, rapamycin.

Introduction

Cerebral cavernous malformations (CCMs) are hamartomas with endothelium-lined vascular chambers. CCMs lack developed vascular structures like elastic lamina, smooth muscle, or tight junctions; have no interspersed brain parenchyma; and have a border of nonfunctioning glial tissue. CCMs can lead to symptoms by causing uncontrolled seizures or through bleeding events, leading to focal neurologic deficits (Hoffman et al., 2022).

CCM disease can be broadly classified as either sporadic or familial. While sporadic CCMs typically present as solitary lesions in otherwise healthy individuals, familial CCMs typically present with a multiplicity of lesions and follow an autosomal dominant inheritance pattern (Snellings et al., 2021).

The overall prevalence of all CCMs has been estimated at 1/200 to 1/1,000 individuals. Familial cerebral cavernous malformation (FCCM) represents about 20% of all CCM cases with an estimated prevalence of 1/5,000 -1/10,000 and is therefore rare, contrarily to sporadic CCMs which are not (Orphanet, 2025).

Surgical resection remains the primary treatment modality for symptomatic cerebral cavernous malformations, particularly in cases of recurrent hemorrhage or drug-resistant epilepsy. However, this approach presents significant limitations in familial cerebral cavernous malformation (FCCM), where patients frequently harbor multiple lesions distributed throughout the brain. Complete surgical management is often impractical, especially when lesions are located in eloquent or deep brain regions. Given the genetic basis of FCCM, pharmacological strategies targeting molecular pathways have been proposed as a potential therapeutic alternative. Nevertheless, current evidence supporting pharmacotherapy remains limited, largely experimental, and insufficiently

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validated in large clinical trials. Consequently, an effective non-surgical treatment strategy for FCCM remains an unmet clinical need.

The aim of this review is to evaluate current evidence regarding pharmacological treatment strategies in familial cerebral cavernous malformation and to identify existing limitations and future therapeutic perspectives.

Genetic and Molecular Basis of Familial CCM

Mutations in the genes encoding CCM1, CCM2, and CCM3 have been associated with familial CCMs. These 3 proteins, present in vascular endothelial cells, form a complex that regulates signal transduction proteins associated with the maintenance of adjacent vascular endothelial cell-cell junctions. Dysfunction of these proteins results in the development of hemangiomas and abnormal intercellular junctions (Ishii et al., 2020).

Table 1. FCCM genes. Adapted from: Zafar., et al. (2019).

Locus Name	Gene	Chromosome locus	Protein	Function
CCM1	KRIT1	7q21.2	Krev interaction trapped protein 1	Regulate heart and vessel formation and angiogenesis. Inhibits endothelial cells, apoptosis, migration, and angiogenesis
			Alternative name(s): CCM 1 protein	
CCM2	CCM2	7p13	CCM 2 protein	Regulate heart and vessel formation and integrity
			Alternative name(s): Malcavernin	Stabilize the endothelial cell junctions
CCM3	PDCD10	3q26.1	Programmed cell death protein 10	Stimulate cell proliferation
			Alternative name(s): CCM 3 protein or TF-1 cell apoptosis-related protein 15	Regulates apoptotic pathway
				Increase mitogen- activated protein kinase and STK26 activity
				Involved with KDR/VEGFR2 signaling
				Regulate cardiovascular development and required for angiogenesis, vasculogenesis and hematopoiesis during development

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CCM Signaling Pathways.

Signaling Pathways Modulated by the Rho Family of GTPases.

The RhoA signaling pathway is one of the most important pathways controlled by CCM proteins. Normally, the CCM proteins KRIT1, CCM2, and PDCD10 work together to keep RhoA activity under control (Figure1). RhoA activates Rho-associated protein kinase (ROCK), which regulates the actin cytoskeleton and cell movement. KRIT1 forms a complex with several other proteins to stabilize endothelial cell junctions and reduce RhoA activity. CCM2 helps destroy excess RhoA through interaction with Smurf1, while PDCD10 regulates similar cytoskeleton pathways through other proteins. The interaction between KRIT1 and CCM2 is especially important for suppressing RhoA signaling.

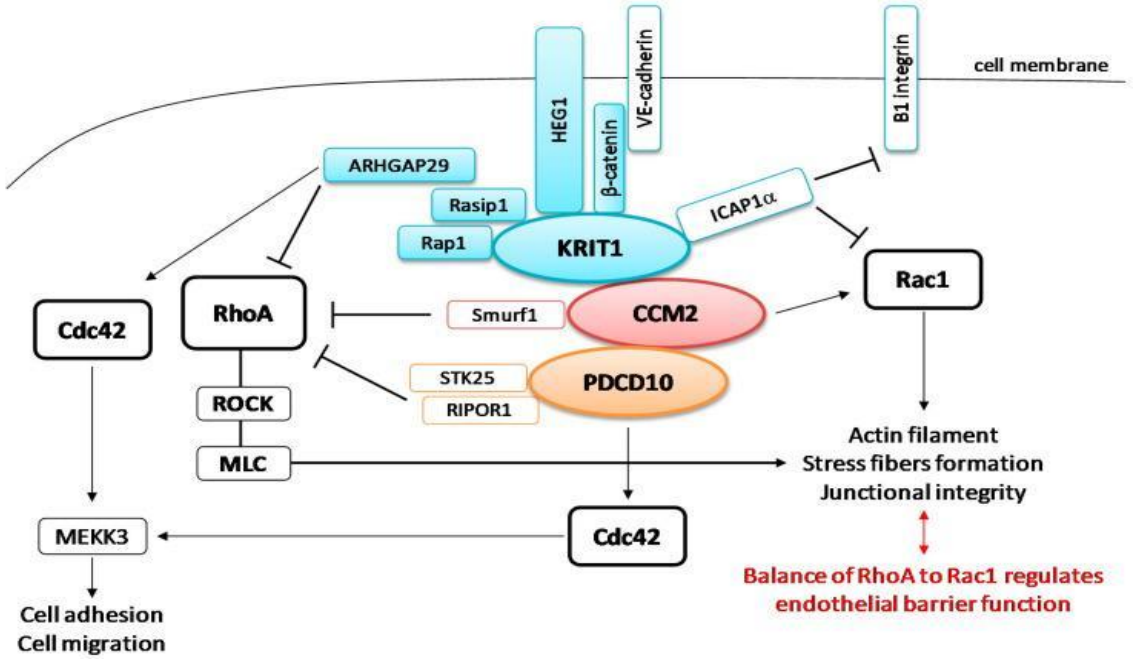

Figure 1. CCM signaling complex involved in Rho GTPase signaling. Adapted from Riolo, G., Ricci, C., & Battistini, S. (2021).

Because abnormal RhoA–ROCK activity contributes to CCM development, drugs that block this pathway are being studied as possible treatments. When

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CCM genes are damaged or inactive, RhoA becomes too active, which increases blood vessel permeability and causes the formation of stress fibers in endothelial cells. These changes weaken the connections between endothelial cells and make blood vessels more leaky, which contributes to the formation of CCM (Riolo et al., 2021).

MEKK3/MEK5/ERK5 signaling.

Deficiency of any of the CCM proteins (KRIT1, CCM2, or PDCD10) leads to hyperactivation of the MEKK3–MEK5–ERK5 signaling cascade, which plays a central role in the development of cerebral cavernous malformations. Normally, CCM2 interacts with MEKK3 and suppresses its activity to maintain vascular stability; however, disruption of the CCM complex removes this inhibition and results in activation of downstream kinases, including MEK5 and ERK5. Activated ERK5 translocates to the nucleus and increases the expression of the transcription factors KLF2 and KLF4, primarily through MEF2-mediated transcription.

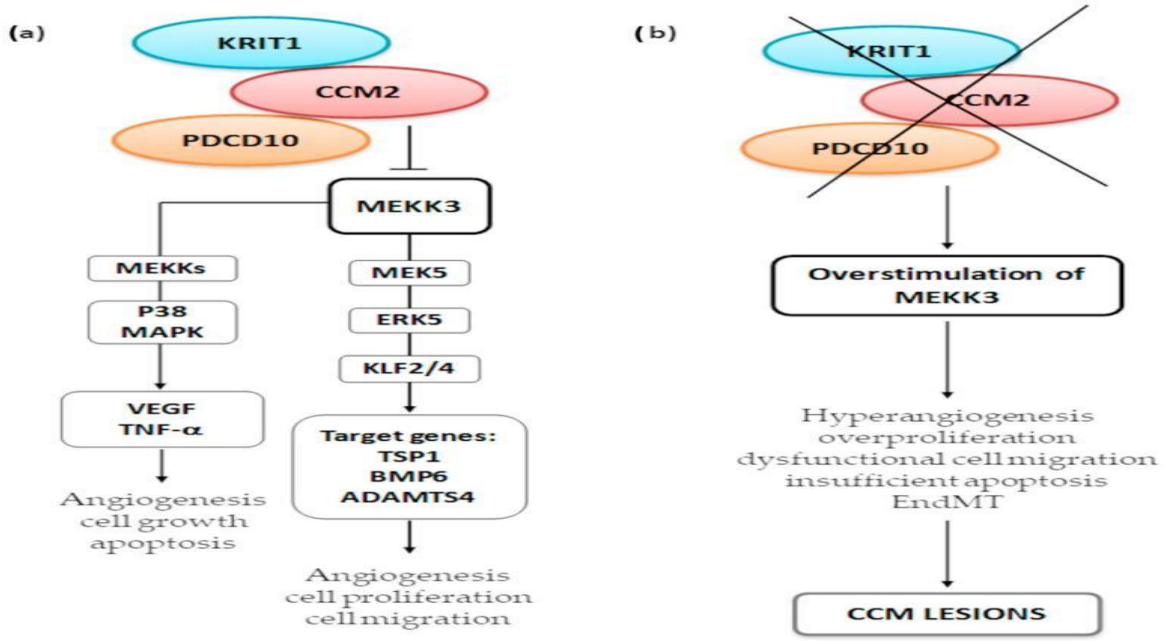

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Figure 2. MEKK3 signaling regulated by CCM2 in CS2 complex (**a**) and disrupted signaling due to CCM protein depletion (**b**). Adapted from Riolo, G., Ricci, C., & Battistini, S. (2021).

The MEKK3–KLF pathway is also influenced by inflammatory and environmental signals, including activation of Toll-like receptor 4 (TLR4) by bacterial lipopolysaccharides from the gut microbiome, linking immune signaling to CCM progression. Increased KLF2/4 expression subsequently regulates numerous downstream targets involved in endothelial function, angiogenesis, and coagulation, such as eNOS, thrombomodulin, thrombospondin-1, ADAMTS4/5, and VE-cadherin–regulating microRNA-27a (Figure 2). These changes disrupt endothelial junctions, promote abnormal angiogenesis, and may trigger endothelial-to-mesenchymal transition, ultimately contributing to CCM lesion formation and growth (Qi & Zheng, 2023).

PI3K-mTOR Signaling.

Recent mouse and human genetic studies have identified increased PI3K–mTOR signaling pathway as a key downstream mechanism in cerebral cavernous malformation development. Loss-of-function mutations in CCM genes—KRIT1, CCM2, and PDCD10—activate MEKK3-KLF2/4 signaling and enhance PI3K–mTOR activity in endothelial cells (Figure 3). However, CCM gene loss alone is insufficient for lesion formation; additional angiogenic signals are required. In mouse models, lesions form mainly in highly angiogenic regions such as the hindbrain and retina of neonatal mice, while later gene deletion results in minimal lesion development. Angiogenic stimulation through VEGFA or reduction of the anti-angiogenic factor THBS1 further promotes lesion formation. Moreover, activating mutations in PIK3CA, a strong activator of PI3K signaling, were identified in many human CCM lesions and occur within the same endothelial cells carrying CCM mutations. Experimental models show that CCM loss and PIK3CA activation individually have limited effects but act synergistically to produce typical cavernoma lesions (Snellings et al., 2021).

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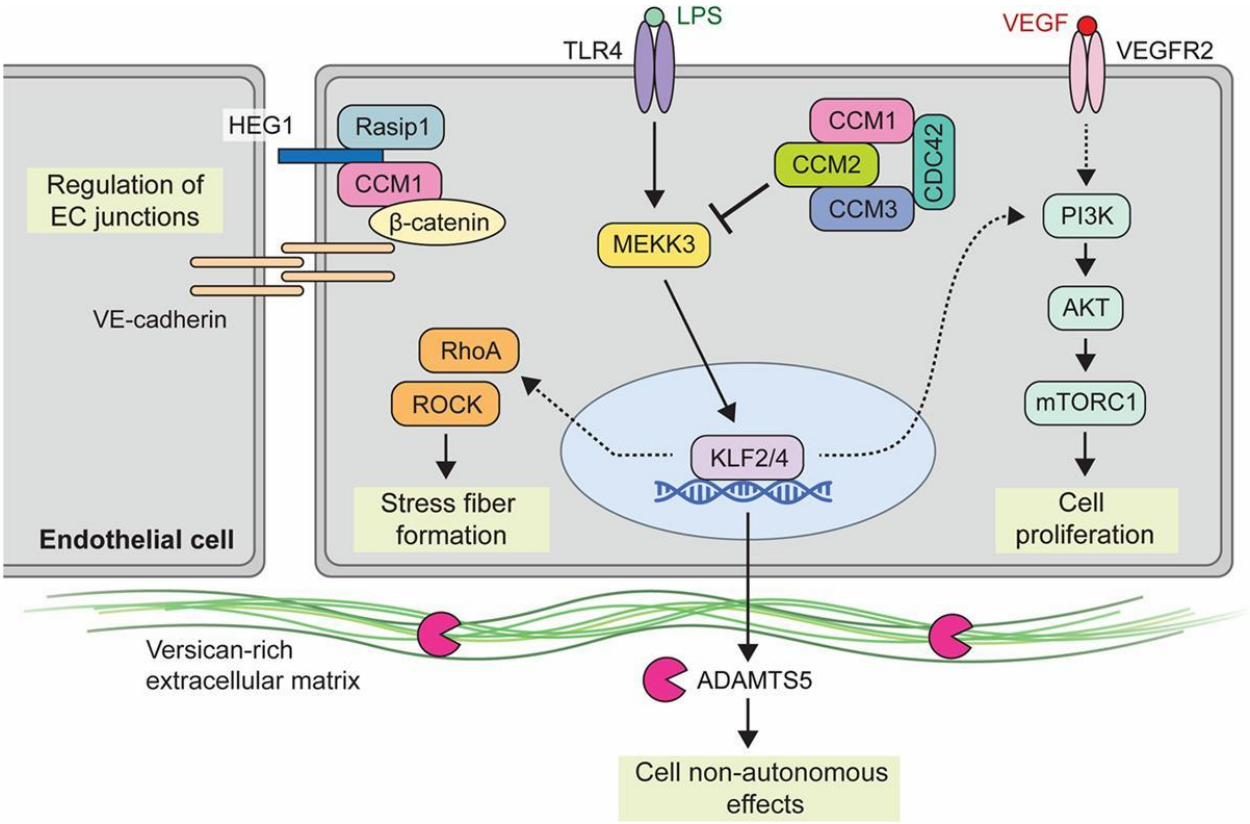

Figure 3. Adapted from "Cerebral cavernous malformation: From mechanism to therapy," by D. A. Snellings et al. (2021), Circulation Research, 129(1).

Pathophysiology of Lesion Formation

The cerebral cavernous malformation (CCM) is a common cerebrovascular anomaly predisposing patients to a lifetime risk of hemorrhagic stroke, seizures and other neurological sequela. CCM lesions consist of abnormal clusters of enlarged capillary vessels with aberrant angioarchitecture embedded in normal brain or spinal cord tissue found in 0.5–1% of the population. Some patients remain asymptomatic, while others are disabled from recurrent bleeds and/or high lesion burden. Early age of lesion onset, multiple hemorrhages and increased lesion burden have been correlated in various studies with chronic disease

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severity. Features of acute disease aggressiveness include clinically overt hemorrhage, CCM lesion growth and the genesis of new lesions (Girard et al., 2016).

The cellular processes of CCM lesion development include changes in stress fiber formation and the resulting tight junction and focal adhesion perturbation, endothelial to mesenchymal transition (EndMT) and the resulting proliferation and integrity disturbance, cytokine secretion and consequent angiogenesis and inflammation response, reactive oxygen species (ROS) homeostasis and the ensuing cell survival of endothelial cells (Qi & Zheng, 2023).

Familial CCMs are highly heterogeneous in clinical manifestation, and the disease progression and severity are not directly correlated with the type of germline mutations of CCM genes. Recent studies have demonstrated that environmental factors, such as the gut microbiome and the gut barrier, may contribute significantly to the formation of CCMs. Additional secondary local events following CCM germline mutation are also involved to synergize the progression of CCM pathogenesis, which worsen the stable CCMs becoming symptomatic manifestation and requires clinical management (Li et al., 2023).

Oxidative stress plays a central role in the pathophysiology of CCM, as previously reported for KRIT1 and PDCD10 mutations. In cell culture, loss of CCM2 increases reactive oxygen species (ROS) and decreases FOXO1 expression, suggesting a shared mechanism across CCM genes. In endothelial-specific CCM2 knockout mice, this oxidative stress impairs endothelial-dependent vasodilation and is associated with trends toward higher blood pressure and lower heart rates, reflecting systemic vascular dysfunction. These findings indicate that oxidative stress contributes not only to cellular dysfunction but also to broader vascular pathology in CCM, highlighting its critical role in lesion formation and vascular complications (Gibson et al., 2014).

Clinical severity is highly variable, but CCM1 gene mutations may cause the least severe clinical course, and PDCD10 (CCM3) mutations are associated with more

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severe disease manifestations. CCM3 mutation carriers have a greater chance of spontaneous mutation, an increased CCM burden, and a younger mean age of presentation, which is often associated with clinical hemorrhage. There is also a significant association with other manifestations including skin CCMs, scoliosis, spinal cord cavernous malformations, cognitive disability, and benign brain tumor including meningioma, vestibular schwannoma, and astrocytoma. Genotype does not entirely explain CCM clinical variability; investigation of possible genetic and environment modifiers is currently underway (Akers et al., 2017).

Current Pharmacological Targets

Rapamycin: In a preclinical study by Li et al. (2023), animals with CCM lesions between 0.5 and 1.0 mm were treated daily with either Rapamycin (3.3 mg/kg) or vehicle. In vehicle-treated mice, lesions grew rapidly, often exceeding the cranial window within 10 days, and some animals experienced severe neurological deficits or early death. In contrast, Rapamycin-treated lesions remained largely stable in size throughout the study period. Post-mortem visual and microCT analyses confirmed a dramatic reduction in lesion size in Rapamycin-treated animals ($P < 0.001$), accompanied by strong suppression of mTORC signaling as indicated by reduced phosphorylated ribosomal protein S6. Rapamycin treatment also decreased perilesional iron deposition, suggesting reduced hemorrhage, and improved blood flow within lesion cores as measured by FITC-dextran angiography ($P < 0.05$). Oral administration of Rapamycin produced similar reductions in lesion growth, supporting its potential as a long-term therapy to arrest CCM lesion progression. These findings underscore the value of Rapamycin as a gene-targeted therapy, directly acting on the mTORC1 pathway hyperactivated by CCM loss-of-function and PIK3CA gain-of-function mutations. By targeting this core mechanistic pathway, Rapamycin provides a promising pharmacological approach for patients with lesions that are not amenable to surgical resection.

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Ponatinib: Recent studies identify hyperactive MEKK3 signaling as a critical driver of CCM lesion formation. In this study, Ponatinib, an FDA-approved kinase inhibitor originally developed for leukemia, was shown to potently block MEKK3/ERK5 signaling and downstream targets including KLFs, eNOS, and ADAMTS genes. Preclinical data demonstrate that Ponatinib robustly inhibits CCM lesion initiation and progression in both Ccm1- and Ccm2-deficient mouse models, providing a rationale for its repurposing or for designing selective derivatives for CCM therapy. Although Ponatinib can target multiple kinases, our in vitro and zebrafish data suggest that MEKK3 is the primary mediator of its therapeutic effect, whereas MEKK2 and ABL1 play minor or negligible roles in CCM signaling. These findings establish Ponatinib as a promising candidate for targeted pharmacological intervention in CCM (Choi et al., 2018).

Statins: Statins are a promising therapy for CCM due to their widespread use and generally favorable safety profile. Preclinical studies suggest that they may reduce chronic hemorrhage and lower vascular permeability by inhibiting ROCK-mediated signaling, although their clinical efficacy remains uncertain and requires further investigation (Hoffman et al., 2022). Statins such as simvastatin and atorvastatin are particularly practical for drug repurposing, and clinical trials assessing their effectiveness in CCM are currently underway (Ishii et al., 2020).

Vitamin D_3: Cholecalciferol (vitamin D_3) has emerged as a potential therapeutic candidate for CCM due to its stabilizing effects on endothelial signaling pathways. Experimental studies show that vitamin D_3 can inhibit CCM2 knockdown–induced activation of key pathways involved in endothelial instability, including ARF6, RHOA, and phosphorylation of myosin light chain (pMLC), even at physiological concentrations, suggesting a rapid protective effect on endothelial function (Gibson et al., 2014). Vitamin D is also known to regulate inflammatory responses and vascular homeostasis, and deficiency has

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been associated with increased disease severity in several vascular and neurological disorders. In murine CCM2 models, vitamin D_3 supplementation reduced lesion burden, indicating potential disease-modifying effects (Girard et al., 2016).

Tempol: Tempol, a superoxide scavenger, effectively restores endothelial function in CCM2-deficient mice by rescuing impaired vasodilation. It also normalizes systemic vascular effects, such as elevated blood pressure and reduced heart rate, caused by oxidative stress. These results suggest that targeting ROS with tempol may offer a promising therapeutic strategy to mitigate both cellular and vascular pathology in CCM (Gibson et al., 2014).

Propranolol: Propranolol, widely used for treating infantile facial hemangiomas, has shown potential benefits for CCMs. Case reports and preclinical studies in mice suggest that propranolol may prevent CCM expansion and reduce vascular permeability (Lanfranconi et al., 2020). In a recent randomized, open-label, blinded end-point Phase II pilot trial (Treat_CCM), propranolol was found to be safe and well tolerated in individuals with FCCM. Although the study was not powered to evaluate efficacy, treatment was possibly beneficial in reducing the incidence of clinical events in symptomatic FCCM patients (Flemming et al., 2023).

Fasudil: Fasudil, a specific inhibitor of the Rho-associated kinase (ROCK) pathway, has been investigated as a potential therapy for CCM due to its role in regulating endothelial stability. Preclinical studies have shown that fasudil can significantly reduce lesion burden in CCM1 or CCM2 heterozygous mouse models, particularly when combined with genetic backgrounds such as Msh2 or p53 deficiency (Choi et al., 2018). By inhibiting RhoA kinase signaling, fasudil helps stabilize the interendothelial junctional complex and counteracts the

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vascular dysfunction associated with CCM lesions. In comparative studies, fasudil demonstrated greater efficacy than simvastatin in improving survival and reducing CCM lesion development, highlighting its promise as a targeted therapeutic strategy (Hoffman et al., 2022).

Clinical Trials and Translational Challenges

Rapamycin appears to act on a core mechanistic pathway associated with the two-hit model (CCM loss-of-function and PIK3CA gain-of-function), though its efficacy in lesions lacking PIK3CA mutations remains uncertain. Limitations include the short treatment duration, poor perfusion in nascent lesions, and the model's rapid lesion growth, which may not fully reflect the slower disease progression in humans. While Rapamycin effectively inhibits lesion growth, evidence for regression is lacking, and further studies in humans are needed to assess its potential for treating established lesions and reducing hemorrhage (Li et al., 2023).

The FDA has approved ponatinib for clinical use, but its use has been reported to cause significant adverse effects in the cardiovascular system. The exact cellular and molecular targets leading to these detrimental effects remain unknown. Whether other potent targets of ponatinib in addition to MEKK3 also play a potential role in CCM pathogenesis will require further investigation. While ponatinib can efficiently rescue the elevated p-ERK5 level in CCM-deficient endothelial cells, it had no effect on p38 MAPK signaling, although p38 MAPK is another pathway downstream of MEKK3. While the neonatal CCM mouse model closely mimics human disease, it does not fully recapitulate human conditions - CCM in humans typically manifests in adulthood and occurs throughout the brain, whereas in mice, gene deletion must be induced shortly after birth and lesions are largely restricted to the cerebellum. These differences mean that dosage, timing, and potential side effects will need careful evaluation in clinical trials. Long-term therapy may be required for human patients, and the

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effects on other kinases must be further investigated. Future chemical modifications to improve Ponatinib's target selectivity will be critical to develop a potent yet safe CCM therapy. Further investigations are required to translate the results from mouse models to the clinic (Choi et al., 2018).

One study using dynamic contrast-enhanced perfusion MRI did not observe a significant decrease in vascular permeability in CCMs treated with statins, although this may reflect limitations of the imaging method rather than a true lack of effect. Statins' pleiotropic effects, including lowering non-HDL cholesterol, raise concerns about a potential "lipid paradox," in which reduced lipid levels could paradoxically increase symptomatic risk, as observed in other inflammatory conditions. Nevertheless, there is no evidence that statins are harmful in CCM, and their overall benefit versus risk remains speculative. These questions should be addressed in targeted laboratory studies and carefully designed clinical trials (Girard et al., 2016; Hoffman et al., 2022).

There is currently no clinical evidence that vitamin D supplementation can prevent new lesion formation or modify disease course in familial CCM (FCCM) patients (Akers et al., 2017). No randomized controlled trials have been conducted to evaluate the efficacy or safety of vitamin D therapy in FCCM, leaving its clinical utility uncertain. Despite these limitations, maintaining adequate vitamin D intake is generally recommended for patients with FCCM, primarily for overall health, while the potential disease-modifying effects remain speculative and warrant further hypothesis-driven studies (Flemming et al., 2023).

Overall, differences between animal models and human pathology, such as timing of lesion development and lesion distribution, emphasize the need for careful consideration of disease dynamics when interpreting results. Variability in vascular responses, limitations of measurement techniques, and incomplete understanding of underlying molecular pathways further complicate clinical translation. Together, these observations underscore that while significant

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mechanistic insights have been gained, more rigorous and targeted studies are necessary to fully understand disease progression and to guide future clinical strategies.

Conclusion

Familial cerebral cavernous malformation (FCCM) is a genetically driven vascular disorder characterized by multiple cerebral lesions and a significant risk of hemorrhage, seizures, and progressive neurological deficits. Although surgical resection remains the standard treatment for symptomatic lesions, its effectiveness in FCCM is limited because patients frequently develop numerous lesions located in surgically inaccessible or eloquent brain regions. As a result, pharmacological therapy has emerged as an important area of investigation aimed at targeting the molecular mechanisms underlying lesion formation and progression.

Advances in the understanding of FCCM genetics and signaling pathways—including the RhoA/ROCK pathway, MEKK3–MEK5–ERK5 signaling cascade, PI3K/mTOR signaling, oxidative stress mechanisms, and endothelial dysfunction—have led to the identification of several potential pharmacological targets. Experimental and early clinical studies suggest that agents such as rapamycin, ponatinib, fasudil, statins, propranolol, vitamin D_3, and antioxidants like tempol may influence disease progression by stabilizing endothelial function, reducing lesion growth, or decreasing vascular permeability. Among these, rapamycin and fasudil show particularly strong mechanistic rationale due to their direct effects on pathways implicated in CCM pathogenesis.

Despite these promising findings, most evidence remains limited to preclinical studies or small clinical trials, and significant challenges remain in translating these results into effective therapies for patients. Differences between animal models and human disease, uncertainties regarding long-term safety, and incomplete understanding of drug targets highlight the need for further research.

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Large, well-designed clinical trials will be essential to determine the efficacy and safety of these pharmacological strategies.

Overall, while pharmacotherapy for FCCM remains largely experimental, growing insights into the molecular biology of the disease provide a strong foundation for the development of targeted treatments. Continued translational research may ultimately lead to effective non-surgical therapeutic options capable of slowing lesion progression, reducing hemorrhage risk, and improving long-term outcomes for patients with familial cerebral cavernous malformations.

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