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Review

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Calm the raging hormone - a new therapeutic strategy involving progesterone-signaling for hemorrhagic CCMs

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Abstract

Cerebral cavernous malformations (CCMs), one of the most common vascular malformations, are characterized by abnormally dilated intracranial microvascular capillaries resulting in increased susceptibility to hemorrhagic stroke. As an autosomal dominant disorder with incomplete penetrance, the majority of *CCMs* gene mutation carriers are largely asymptomatic, but, when symptoms occur, the disease has typically reached the stage of focal hemorrhage with irreversible brain damage, while the molecular "trigger" initiating the occurrence of CCM pathology remain elusive. Currently, the invasive neurosurgery removal of CCM lesions is the only option for the treatment, despite the recurrence of worse symptoms frequently occurring after surgery. Therefore, there is a grave need for the identification of molecular targets for therapeutic treatment and biomarkers as risk predictors for hemorrhagic stroke prevention. Based on the various perturbed angiogenic signaling cascades mediated by the CCM signaling complex (CSC) reported, there have been many proposed candidate drugs, targeting potentially angiogenic-relevant signaling pathways dysregulated by loss of function of one of the CCM proteins, which might not be enough to correct the pathological phenotype, hemorrhagic CCMs. In this review, we describe a new paradigm for the mechanism of hemorrhagic CCM lesions and propose a new concept for the assurance of CSC stability to prevent the devastating outcome of hemorrhagic CCMs.

Keywords: Cerebral cavernous malformations, CCM signaling complex, progesterone, membrane progesterone receptors, CSC-mPRs-PRG signaling network, blood-brain barrier

INTRODUCTION

Cerebral cavernous malformations (CCMs) are characterized by abnormally dilated intracranial microvascular capillaries that result in increased susceptibility to stroke[1-5]. Familial CCMs are an autosomal dominant condition[1,6]. Three genes have been identified as culprits of most familial CCM cases[7-16]: *CCM1* at 7q11-22[11], *CCM2* at 7p15-23[12], and *CCM3* at 3q25.2-27[12]. These genes encode CCM proteins, including KRIT1 as CCM1[13,16-19], MGC4607 as CCM2[20], and PDCD10 as CCM3[21,22], that have been shown to interact with each other and form a core CCM triplex. In this triplex, CCM1 and CCM3 compete to bind to PTB domains of CCM2[23]. This core CCM triplex, in turn, interacts with other proteins[22,24-27] to form a complex referred to as the CCM signaling complex (CSC)[28,29]. Although the majority of *CCMs* gene mutation carriers are largely asymptomatic due to the incomplete penetrance of *CCMs*, when symptoms do occur, the disease has typically reached a serious stage of focal hemorrhage with irreversible brain damage. Currently, the invasive neurosurgical removal of CCM lesions is the only option for treatment, despite the recurrence of hemorrhagic events after surgery. Therefore, there is a grave need to understand the angiogenic functions of CSC in maintaining neurovascular integrity. Uncovering the mechanistic underpinnings of this signalosome may provide novel avenues for developing stroke prevention and vascular therapy techniques. Based on the various perturbed angiogenic signaling cascades reported, there have been many proposed candidate drugs, potentially targeting angiogenic-relevant signaling pathways dysregulated by loss of function of one of the CCM proteins, which might not be enough to correct the pathological phenotype, hemorrhagic CCMs. In this article, we propose a new concept for the assurance of CSC stability to prevent the devastating outcome of hemorrhagic CCMs.

FEMALE SEX STEROID HORMONES AND STROKE

The overall lifetime risk of stroke is similar between women and men[30]; however, postmenopausal women are at a much greater stroke risk, compared to premenopausal women. Women generally bear a notable lower risk of stroke during earlier life, until reaching their middle age, doubling the risk of stroke in women 10 years post-menopause[31-33]. This drastically increased stroke risk in women is caused by declining levels of circulating sex steroid hormones in the blood, especially estrogen[31,34]. Estrogen has been widely recognized as a beneficial factor for the integrity of vasculature[35-42] due to its actions on nuclear/membrane estrogen receptors (nERs/mERs)[37,43-45] in vascular smooth muscle cells[46,47] and endothelial cells[38,48-50]. Furthermore, sex steroids, estrogen, androgen, and glucocorticoid, have been evaluated, but no significant perturbation of CSC was found involving any of these sterols[51]. Increased stroke risk associated with altered levels of circulating female sex hormones has been well defined for several major female physiological events, including post-menopause, pregnancy, oral contraceptive regimens, and hormone replacement therapy[52]. It needs to be mentioned that the physiological changes during pregnancy, caused by the altered levels/composition of circulating female sex hormones, is a major risk factor for stroke in women[53-60]. Epidemiologic data in the United States indicate that approximately 87% of strokes are ischemic, and the remaining 13% are hemorrhagic strokes[61-63]. Interestingly, hemorrhagic stroke is the most dominant type (up to 74%) of strokes during pregnancy, much higher than that in the general population[64-71], suggesting an important correlation between altered progesterone (PRG) levels [Table 1] and elevated hemorrhagic stroke risk[72].

Although women and men have measurable amounts of PRG in the bloodstream, the levels and patterns of change of circulating PRG differ. Circulating PRG is approximately 0.5 ng/mL for males, while PRG levels

Table 1. Expected normal-range PRG values from serum/plasma samples in various age groups of both women and men

Physiological stages (women)	Values for ELISA kit detection
Follicular phase	0.2-1.4 ng/mL
Luteal phase	4.0-25 ng/mL
Menopause	0.1-1.0 ng/mL
Normal men	0.1-1.0 ng/mL

The dynamic range of PRG assay with human serum/plasma samples is 0-40 ng/mL. PRG: Progesterone.

vastly fluctuate between 4.0 and 25 ng/mL for premenopausal women during the luteal phase of their menstrual cycle [Table 1][72]. Only 2% of total blood PRG is in its free, active form, which has a very short half-life (5-10 min)[73]. Over 98% of PRG in the blood is believed to be physiologically inactive and passively transported by blood proteins[74], mainly by two major PRG-binding proteins: serpin A6 (binds ~18% of PRG) and albumin (binds ~80% of PRG)[75-77].

CSC COUPLES BOTH CLASSIC AND NON-CLASSIC PRG RECEPTOR SIGNALING

As a sex steroid hormone, PRG elicits its cellular responses through two major signaling pathways. PRG binds to either nuclear progesterone receptors (nPRs) to enact classic PRG effects[78] or to membrane progesterone receptors (mPRs/PAQRs)[79,80] and PRG receptor membrane components[81,82] to enact non-classic PRG effects. Currently, the intricate balance and switch mechanisms between these two signaling cascades remain unknown. Recently, we found that CSC can modulate PRG receptor-mediated signaling, coupling both classic and non-classic signaling by establishing crosstalk between them in nPR positive (+) breast cancer T47D cells. Based on our findings, under PRG actions, CSC stability is regulated by two major signaling cascades: (1) by the negative effects of PRG or its antagonist (nPRs only), mifepristone, via both classes of PRG receptors; and (2) by the positive effects of nPRs signaling[51]. This discovery reveals that the balance between classic and non-classic PRG signaling impacts CSC function and identifies CSC as an important mediator of nPR and mPR crosstalk in nPR(+) cells. Our observation is further supported by a previous finding that PRG can act simultaneously on both nPRs and mPRs, and the activation of mPR signaling can potentiate the hormone-activated nPR-2 isoform[78]. The intricate feedback regulation among the PRG-activated CSC-mPRs-PRG-nPRs (CmPn) signaling network in nPR(+) T47D cells can be summarized as a common mechanism that exists among the CmPn signaling network under steroid actions[51]. In this CmPn signaling network, PRG and its nPR-specific antagonist, MIF, work independently or synergistically to disrupt CSC through their common targets, mPRs, in a backward fashion (CSC←mPRs ←PRG) [Figure 1][51].

A COMMON REGULATORY MECHANISM UNDERLYING THE PROMOTIVE EFFECTS OF CSC ON MPRS IN BREAST CANCER CELLS

PRG can activate downstream signaling in both nPR(+) and nPR(-) cells by binding to mPRs[51,83-85]. Distinct from nPRs, mPRs represent a unique class of membrane steroid receptors that mediate non-classic PRG actions in nPR(+) and nPR(-) cells[78,86]. Numerous studies have implicated mPRs in breast cancer[87-95], especially nPR(-) breast cancers[84,88,93]. After defining the CmPn signaling network in nPR(+) breast cancer T47D cells[51], we shifted our focus to two nPR(-) breast cancer cells (MDA-MB231 and MDA-MB468), both of which are triple-negative breast cancer (TNBC) cells. Using these two nPR(-) cell models, we confirmed the presence of the CSC-mPRs-PRG (CmP) signaling network in nPR(-) breast cancer cells[96]. We also demonstrated that a common core mechanism exists among nPR(-) breast cancer cells, termed the CmP signaling network. In the CmP signaling network, CSC can stabilize mPRs under steroid actions in a forward fashion (CSC→mPRs), which overlaps with the CmPn signaling network in nPR(+) breast cancer

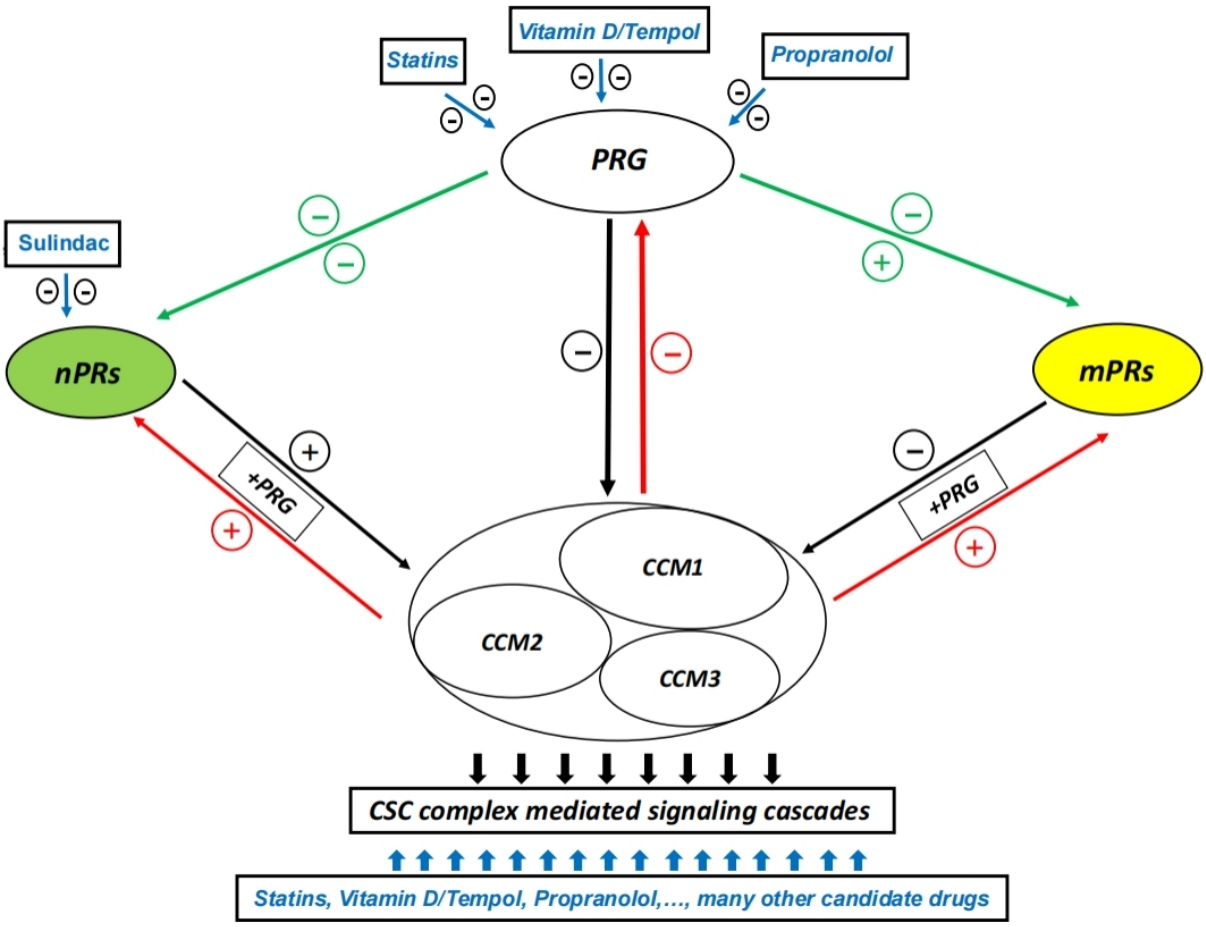

Figure 1. Schematic representation of the relationship among the CmPn network and potential candidate drug targets. The relationship among CSC, PRG, and two types of PRG receptors (nPRs and mPRs) is illustrated based on our current data. Candidate drug targeting points are presented with blue arrows, where candidate drugs are highlighted with blue letters within the box. Green arrow-lines indicate effects of PRG on PRG receptors, black arrow-lines indicate effects of PRG and its receptors on CSC, and red arrow-lines indicate effects of the CSC on biogenesis of PRG and its receptors. +PRG indicates under steroid actions. The + symbol indicates observed enhancement, while the - symbol demonstrates an inhibitory effect. CCM: Cerebral cavernous malformation; CSC: CCM signaling complex; PRG: progesterone; nPRs: nuclear progesterone receptors; mPRs: membrane receptors.

cells under steroid actions, regardless of nPR(+/-) cell type. This implicates a more essential role of CSC on the stability of mPRs in nPR(-) cells under steroid actions[96]. Our data support the previous findings that multiple mPRs can be co-expressed in various mammalian cell types[78,83,93,97,98] to perform multifaceted non-classic PRG signaling cascades among different nPR(+/-) mammalian cells[93].

ANGIOGENIC RESPONSES TO SEX STEROID ACTIONS THROUGH MPRS SIGNALING IN NPR(-) VASCULAR ENDOTHELIAL CELLS

CCMs are more common in women and become symptomatic during their reproductive period (in their 30s and 40s)[99,100]. Although no conclusive results have been found[101], hormonal changes during pregnancy have long been suspected as significant factors for increased bleeding[102-104], and female gender is a key risk factor for bleeding in CCM patients[102,105]. Increases in the size of CCM lesions[106-109] and the elevated frequency of hemorrhagic CCMs during pregnancy have been well documented[103,110-115], suggesting that pregnancy is associated with an increased risk of hemorrhagic CCMs. It has long been speculated that the flux of hormones during pregnancy may predispose CCMs to hemorrhage[102,111-114], and, furthermore,

increased PRG levels during early pregnancy[116,117] have been indicated to enhance the progression of lesions[118], possibly through the induction of structural changes within vessels[119]. Increased risk for acute CCM bleedings[101,103,104,113,115,120] or formation of a de novo CCM lesion[113,120,121] have also been reported during pregnancy. Collectively, these findings reinforce the idea that there is gender- and sex hormone-associated differences in hemorrhagic stroke pathophysiology and suggest that PRG-mediated signaling should be further investigated. Interestingly, nPR(+) endothelial cells (ECs) can only be found in the veins and lymphatics of the uterus and ovaries, where human umbilical vein endothelial cells (HUVECs) are derived[122]. Additionally, the MEKK3-KLF-ADAMTS signaling pathway has been implicated in CSC-mediated angiogenic activities[123]. KLFs are largely expressed in reproductive tissues and have been implicated as co-regulators and integrators of progesterone/progesterone receptor transactivity[124]. There are some associations between progesterone and ADAMTS-1 demonstrating ADAMTS as a transcriptional target of progesterone actions mainly in the ovaries of *nPR-KO* mice[125]. Additionally, in *Xenopus laevis* eggs and embryos, it was demonstrated that progesterone can stimulate JNK activation through both MEK/p42 MAPK-dependent and -independent pathways, and the addition of progesterone induced synthesis of MAPKKK c-Mos, leading to the activation of the MEK1-ERK-RSK cascade[126]. However, there is currently no available literature systemically demonstrating the effects of progesterone on the MEKK3-KLF-ADAMTS signaling pathway. The vast majority of vascular ECs derived from other tissues are nPR(-) and mPRs(+), where only non-classic actions of PRG have been reported[82]. When we used combined steroids (PRG + MIF) to treat four nPRs(-) microvascular ECs and nPRs(+) HUVECs, again, our data support a common regulatory mechanism underlying the inhibitory effects of PRG/MIF on CSC, independent of nPRs. In addition, the sex hormone inhibition of CCM1/3 protein expression in ECs is more dramatic than in non-endothelial-derived cell lines[51,127], reaffirming that steroid hormones have much stronger actions on the stability of CSC through mPRs in ECs.

PRG ACTIONS INCREASED PERMEABILITY OF EC MONOLAYER AND COMPROMISED BBB INTEGRITY

The haploinsufficiency of CCM proteins in microvascular ECs is an essential step in the pathogenesis of CCM lesions, as demonstrated by *in vivo* studies with zebrafish[128,129] and *Ccms* mice models[130-132], but it is insufficient to form hemorrhagic CCMs. Although the "two-hit" model, which creates a null condition in the lesion, can be used to explain familial CCM cases, it fails to account for sporadic forms of CCM, which make up 80% of all CCM cases[133]. Additional studies have demonstrated that haploinsufficiency condition of CCMs are insufficient in initiating hemorrhagic events of CCM lesions[134]. Since the "two-hit" model alone cannot explain CCM ruptures, there must be a molecular "trigger" that initiates the hemorrhagic events of CCM lesions. Therefore, we performed both *in vivo* and *in vitro* permeability assays demonstrating significantly increased blood-brain barrier (BBB) permeability among all Ccms (1, 2, 3) mutants only in the hormone treatment groups, compared to WT and/or untreated *Ccms* (1, 2, 3) mutants mice, which was further supported by *in vitro* permeability assays showing increased permeability of different EC lines under steroid actions, compared to vehicle controls[51,127]. This concordant BBB leakage among all Ccms mutant mice was not seen in other treatment groups, nor that of other tested organs, indicating that chronic steroid actions specifically increase BBB permeability, and it is the primary mechanism underlying CCM lesion formation. Therefore, we concluded that BBB integrity among individuals with CCMs deficiency is particularly susceptible to chronic and elevated sex steroid actions[51].

PARADIGM SHIFT FOR HEMORRHAGIC EVENTS IN CCMS OPENS UP NEW AVENUES OF RESEARCH

Hemorrhage is often rooted in defective endothelial cell junctions, and microvessel rupture is a result of compromised BBB integrity[135]. Currently, two major theories for the induction of hemorrhagic CCMs are

the anticoagulant vascular domain theory and the gut microbiota theory. In the anticoagulant vascular domain theory, local increases in the endothelial cofactors that generate anticoagulant activated protein C contribute to recurrent bleeding in CCM lesions[136]. In the gut microbiota theory, Gram-negative bacterial signaling through the lipopolysaccharide-activated innate immune receptor, Toll-like receptor 4, promotes hemorrhagic bleeding in both *Ccm1/2* mutant mice, indicating the important roles for the gut microbiome and innate immune signaling in the pathogenesis of CCMs[134]. The gut microbiota theory focuses on the importance of gut microbiota in influencing the interaction direction by inducing an inflammatory gut milieu, which leads to systemic inflammation that exacerbates the inflammatory response in the brain and promotes detrimental effects on the BBB[137]. However, lipopolysaccharide-induced *Ccms* hemorrhagic mice demonstrate massive bleeding, leading to lethality at the early stages of life, uncharacteristic of human CCMs. Nonetheless, neither of the previous theories addresses a key issue of gender discrepancies in CCM pathogenesis, demanding further evaluation for the underlying mechanisms of hemorrhagic stroke. Although it is still under debate[4,112,138], female dominance in CCM patients has long been suggested[3,113,139,140], and consensus has been reached on more severe bleeding with worse neurological outcomes in females[102,139]. This aggressive course of hemorrhagic lesions in females has been proposed to be a consequence of endocrine influences[3,113,139,140]. Our data demonstrate that enhanced PRG-mPRs signaling, due to perturbed homeostasis of PRG, leads to BBB disruption, in addition to evidence that long exposure to hormonal contraceptives increases the risk of cerebral venous sinus thrombosis[141], which is incongruent with the anticoagulant vascular domain theory[136]. Our findings that immunosuppression, caused by sex steroid actions in Ccms deficient mice, is associated with CCM bleeding also disagree with the gut microbiota theory[134]. Therefore, we propose a new paradigm for the mechanisms of initiating hemorrhagic CCMs. In nPR(-) ECs, the feedback loops among CSC-mPRs-PRG actions appear to be sensitive, and perturbation of this intricate balance [Figure 1][127], such as hormone therapy or hormonal contraception regimens, could result in an increased risk for BBB disruption, especially for human CCMs mutant carriers. Our new paradigm provides a theory that is in line with clinically observed CCM conditions and demonstrates the important functions of CSC and non-classic PRG actions in angiogenesis and vascular health.

CURRENT PHARMACOLOGICAL CANDIDATES TARGETING HEMORRHAGIC CCMS LINKED TO PRG HOMEOSTASIS

Since the molecular and cellular mechanism of the CmP network in microvascular ECs remains largely unknown, we recently investigated the CmP signaling network in nPR(-) ECs[127]. Our data indicate that nPR(-) ECs are different from nPR(-) TNBC cells (TNBC cells have extremely low CCM expression). Although nPR(-) ECs share a common core mechanism between the newly defined CmP network and the CmPn network in breast cancer cells, nPR(-) ECs also showed that steroids can disrupt CSC through their common targets, mPRs, in a backward fashion (CSC←mPRs←PRG), identical to nPR(+) breast cancer cells[51], indicating the significant impact of steroid actions on the stability of CSC.

Many candidate drugs have been identified and tested in animal models and even small clinical trials[142,143]. Ironically, the current pool of very diverse candidate drugs were collectively gathered as certain specific blockers for signaling pathways identified from different experiments using various *in vitro* and/or *in vivo* models[144-157]. Among them, statins and propranolol advanced into clinical trials[142,143,158], due to some promising data. Propranolol, one of the most commonly used β-adrenoceptor blockers (beta-blockers), was first used to successfully treat another common vascular condition, infantile hemangioma in 2008[159], and additionally with major success in three later cases of giant infantile cerebral cavernomas[160-162]. Utilizing *in vitro*, histological, and clinical findings, it was demonstrated that 20-60 mg/day of propranolol not only was effective in reducing previous hemorrhagic lesions, but it also prevented new hemorrhage in familial CCM

patients and reduced lesion size and edema in occipital CCM patients[144]. Additionally, it was also observed that propranolol therapy was effective in immediately stabilizing progressing lesions and preventing future bleeds in sporadic CCM patients[163]. Currently, there are two clinical trials actively recruiting patients to assess lesion burden and clinical events in both familial and symptomatic cerebral cavernous malformation patients[142]. Statin use has been shown to reduce both nonfatal and fatal strokes, improve functional outcomes after ischemic strokes, and reduce coronary death rate and primary and secondary cardiovascular events[164-167]. A randomized controlled trial involving the use of high-dose statin therapy demonstrated a 16% decrease in total stroke as well as a five-year absolute risk reduction in fatal and nonfatal strokes[167]. Despite the promising results seen with statin therapy, a *post hoc* analysis demonstrated a significant increase in intracerebral hemorrhage, suggesting that high-dose statin therapy may have contradictory results[167,168]. These results demonstrate a potential therapeutic use of statins for stroke prevention, but it should be tailored on an individual patient basis to ensure benefits are maximized while risks are minimized.

Intriguingly, by examining these candidate drugs, we found an interesting association of these candidates with the circulating levels of PRG, especially the ones with promising data in animal models. While tempol can alleviate increased PRG levels induced by dehydroepiandrosterone (DHEA, not statistically significant)[169], vitamin D, as a close physiological partner with PRG[170], is a strong inhibitor of PRG production[171], suggesting the inhibitory effect of vitamin D/tempol on PRG production. As an inhibitor for TGFβ/β-catenin signaling, sulindac inhibits the expression level of classic PRG receptors (nPRs)[172], while other TGFβ signaling inhibitors, such as K02288 (TGFβ/BMP6)[173], DMH1 (BMP6)[174], and SB431542 (BMP6)[173], have no effect on PRG levels, suggesting that TGFβ inhibitors might not be a good choice for PRG inhibition. Intriguingly, the two most promising candidates, which have been put in clinical trials, show strong inhibitory effects on PRG levels. While PRG can abolish the beneficial effects of atorvastatin on vascular EC functions[175], statins (atorvastatin, simvastatin, lovastatin, and mevastatin) can directly inhibit PRG levels[176,177]. Although the molecular mechanisms of its therapeutic action are still unknown, its known effect of vasoconstriction may be involved[178,179]. Propranolol has been reported to have an inhibitory effect on PRG levels, from both direct[180,181] and indirect[182,183] evidence, indicating the possibility of decreased PRG levels in this therapeutic process. Finally, although these two candidate drugs (statins and propranolol) show great potential for PRG inhibition[176,177,180-183], they might not be suitable drugs for the treatment and/or prevention of hemorrhagic CCMs. As common drugs for vascular conditions, both are highly effective and safe for most people, but they have been shown to have some side effects due to their wide spectrum of targets. Extensive clinical trials are needed to determine their real benefit and efficacy for hemorrhagic CCMs.

CONCLUSION

As mentioned above, the haploinsufficiency of *CCM* genes in microvascular ECs is an essential step in the pathogenesis of CCM lesions, as demonstrated by *in vivo* studies with zebrafish[128,129] and *Ccms* mice models[130-132], but it is insufficient to form hemorrhagic CCMs, mimicking the incomplete penetrance seen in human CCMs. However, when symptoms occur, the disease has typically reached the stage of focal hemorrhage (likely close to *CCM-null* condition at the genomic level and/or loss of function at the proteomic level) with irreversible brain damage. Following this rationale, we believe it could be strategic to suppress PRG actions on capillary ECs in order to prevent haploinsufficiency of *CCM* genes reaching similar levels observed in CCM loss-of-function for the initiation of a hemorrhagic event. Furthermore, it is not surprising to observe the widespread perturbation of almost all known signaling cascades involved in angiogenesis due to deficiency of CCMs, since CSC is an essential regulator of microvascular angiogenesis and perturbation of CSC will lead to disrupted angiogenesis in the most fundamental way[29,128,129,184,185]. For

this reason, efforts to try to correct any specific dysregulated angiogenic signaling, rooted from deficiency in any CCMs, to alleviate CCM lesion burden or even prevent hemorrhagic CCMs might eventually prove to be too little too late [Figure 1].

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Authors' contributions

Conceptualization, methodology, writing original draft preparation, reviewing and editing: Zhang J
Writing, reviewing and editing: Abou-Fadel JS

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Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Consent for publication

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