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Review article ■

Cerebral Cavernous Malformations: New Insight in Mechanisms of Disease

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SUMMARY

Cerebral cavernous malformations (CCMs) are the most common vascular malformations in the brain, and occur at a rate of approximately 0.6 per 100.000 people. Recognized as familial or sporadic cases, CCMs are characterized as single or multi clusters of enlarged capillary-like channels with a single layer of endothelium and without intervening brain parenchyma. There are specific alterations in brain endothelial barrier components that ultimately lead to vascular hyperpermeability, extravasation of red cells and inflammatory response within brain parenchyma. Patients with CCMs may have seizures, focal deficits, or nonspecific headaches. The most common complication is hemorrhagic stroke.

In the recent years, significant progress was made in understanding the cellular mechanism of the cerebrovascular defect in CCMs. This paper reviews the recent findings about the mechanism of CCMs as well as the new therapeutic strategies in the treatment of sporadic and familiar cerebral cavernous malformations.

Key words: **cerebrovascular defect, blood brain barrier, tight junction, angiogenesis**

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INTRODUCTION

Cerebral cavernous malformations (CCMs) are vascular malformations which can be found in any region within the CNS as multiple and bilateral lesions (genetic) or solitary (sporadic) lesions (1). The prevalence of CCMs based on the magnetic resonance imaging is 0.4-0.9%. CCMs are thought to comprise 10-20% of all vascular lesions and occur equally in males and females. The mean age of clinical presentation is 20-40 years. Nearly 50-80% of patients with CCMs have the sporadic form with a negative family history, while 8-19% have positive family history (1,2). The patents with CCMs lesion are subject to a 1-5% cumulative risk (estimated 50-70% of lifetime risk) of hemorrhagic stroke (develops in 15% of patients and in 20% of pediatric stroke cases), seizures, epilepsy (develops in 30% of patients), nonspecific headaches (5% of patients) and other neurological sequels (weaknesses in arms or legs and vision, balance, memory and attention problems, 25% of patients) (3). In most of the cases, the CCMs symptoms are highly variable among individuals; in some cases no symptoms may be present. However, when symptoms do manifest themselves, they often depend on the location of the CCMs lesion. The high incidence of stroke in children is associated with existence of CCMs lesions, and in particular CCM3 lesions (3). In this review, the current literature regarding genetical dysfunction is discussed, ultrastructural and angioarchitecture of CCMs as well as the current hypotheses regarding the immunological response in CCMs pathology. Understanding the molecular biology of CCMs is critical for development of novel diagnostic modalities as well as the potential targets for drugs that may inhibit the progression and consequence of lesion.

Histology and gross anatomy

Grossly, CCMs have a mulberry-like configuration consisting of thin-walled vascular sinusoids lined by a thin endothelium (1, 4, 5). These sinusoidal structures lack smooth muscle, elastin and intervening parenchyma, and can be thrombosed as well as surrounded by hemosiderin deposits and gliosis resulting from previous hemorrhage (1, 4). Histologically, CCMs have poorly formed tight junction between adjacent endothelial cells, with gaps often noted between individual cells (4, 5). Pericytes, the precursors to smooth muscle cells, are scant (1, 4). In addition, no astrocytic foot processes and no normal nervous tissues are present within the lesion (6, 7) (Figure 1).

The CCMs appear to grow by process of cavern proliferation in the setting of repetitive lesional hemorrhages, hemorrhagic proliferative dysangiogenesis. The CCMs are also only CNS vascular malformation in which the pathological substrate is associated with alterations in the microvasculature and blood brain barrier (BBB) (1, 6, 7). Paracellular hyperpermeability of the BBB, due to the alteration of tight junction complex between brain endothelial cells is considered as the key event for developing the hemosiderosis, inflammatory response and hemorrhagic type of stroke (4, 5, 8).

The major structural impairment occurs at the level of tight junctional complex. The ultrastructural and immunohistochemical analysis however indicates an alteration in transmembrane Tight junction protein occludin, adherence junction protein Ve-cadherin and CD31 -(PECAM) adhesion molecule are responsible for the interaction with leukocytes. These three proteins showed increased expression in CCMs lesion as a compensatory reaction on disorganization of intracellular junction complex (7) (Figure 1).

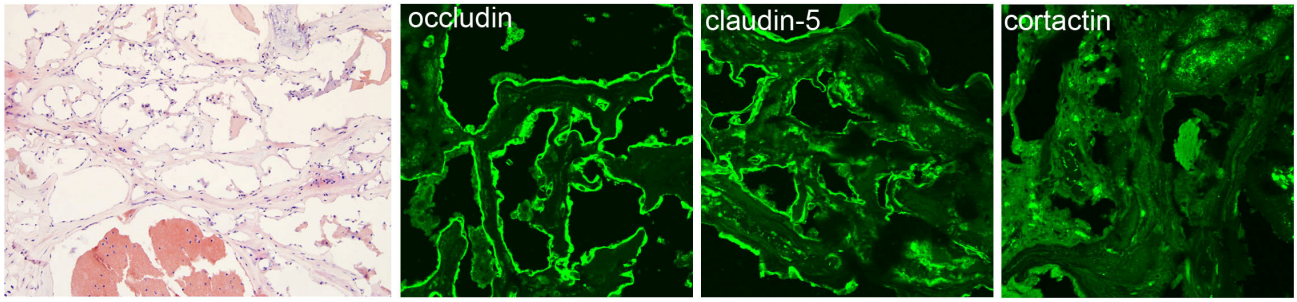

***Figure 1**. Human cerebral CCM3 lesion. A) Hematoxylin-eosin (H&E) staining indicated the typical mulberry-like and thrombosed structure. Mag. 10x. B) and C) Immunofluorescence staining for two transmembrane Tj proteins occludin (anti-occludin antibody, Invitrogen, USA) and claudin-5 (anti-claudin-5 antibody, Invitrogen, USA). There are not any specific changes in expression and localization of occludin and claudin-5. D) Immunofluorescence staining for cortactin (anti-cortactin antibody, Abcam, USA). Cortactin is a "bridge" protein between actin cytoskeletal filaments and tight junction proteins, colocalized with Tj proteins on the cell-cell border. Cortactin showed dislocation and low expression. This indicated the lost association between Tj protein and actin cytoskeletal structure and defect in Tj complex assembly. Confocal images were obtained on LSM 510 Confocal Laser Scanning Microscope (Molecular Imaging Laboratory Department of cell and Development Biology, University of Michigan, Ann Arbor). Mag . 40X*

Genetical approach regarding the CCMs

There has been great progress in the understanding of the pathogenesis of CCMs over the past two decades. Three separate genes have been identified in association with familial CCMs: CCM1 on 7q21-q223-5 accounts for 40% of the cases, CCM2 on 7p13-p15 for 20%, and CCM3 at 3q25.2-q27 for 40%. Each exhibits a Mendelian autosomal dominant inheritance due to a heterozygous loss-of-function mutation at 1 of 3 distinct loci with incomplete clinical and neuroradiological penetrance (9). Individuals usually become symptomatic between 20 and 40 years of age, although lesions have been described in all age groups with no gender predominance. All three genes are expressed through the neuronal cell layer during the development and adulthood as well as within the developing blood vessels in mid-gestation (9, 10). The respective encoded proteins Krit1 (CCM1) *MGC4607 (CCM2)*, and *PDCD1 (CCM3)* appear to interact with cytoskeletal and interendothelial cell junction proteins. The proportion of familial cases has been estimated to be as high as 50% in Hispanic CCM patients and close to 10-40% in Caucasian patients. The clinical phenotype of multiple lesions in familial cases and single lesions in sporadic cases, the preponderance of nonsense mutations, and the structure of the protein suggest that CCM may be caused by somatic mutations of the remaining functional gene in familial cases in a tumor suppressor-like mechanism (10).

Structure and function of CCM1/KRIT1, CCM2/MGC4607, and CCM3/PDCD1

The *CCM1* gene contains 16 coding exons for K-Rev interaction trapped 1 (Krit1), a 736-amino acid (84 kDa) scaffold protein containing three ankyrin domains and one band of 4.1 ezrin radixin moesin (FERM) domain (3, 10, 11). FERM domain, a signature of membrane binding proteins like talin, ezrin, radixin or moesin, is composed of three subdomains: F1-F3 with phosphotyrosine binding (PTB) domains for a canonical NPXY/F motif (3, 11). In addition to its FERM domain, Krit1 possesses three N-terminal NPXY/F motifs. This, structural organization allows the N- and C-terminal halves of Krit1 to interact with each other generating the Krit1 closed and open conformation *in vivo*, resulting from either intramolecular folding or dimerization (3, 10, 11). Three ankyrin repeats are present between the NPXY/F motifs and the FERM domain, and until now no partner interacting with Krit1 ankyrin repeats has been found (3, 12). Krit1 was identified as a partner of the small G-protein Krev-1/Rap1 protein. Besides Rap1, Krit1 interaction with integrin cytoplasmic domain associated protein-1a (ICAP1a) was also described and vie this interaction Krit1 participate in integrin β1 mediated cell adhesion and migration (11, 12). The interactions of β1 integrin and KRIT1 with ICAP1a occur through an NPxY motif/PTB domain, suggesting that integrin signaling plays a role in CCM pathogenesis (11, 12). ICAP1a and KRIT1 possess a functional nuclear localization sequence and both of them have the capacity to shuttle between the cytoplasm and the nucleus (12). It seems that KRIT1 acts as an intracellular signaling molecule through extracellular/adhesion signals, which may be important for the activation of differentiation programs that determine arterial identity (12). CCM1 is expressed in astrocytes and endothelial cells, and can be associated to microtubules, membranes, and adherens junctions, but also the nucleus (3, 8) (Figure 2).

CCM2, a 10-exon gene, encodes for the 51 kDa, *Osmosensing Scaffold for MEKK3 - OSM*, *Malcavernin*, or MGC4607 protein (3, 8, 11). Similar to CCM1, the CCM2 protein contains a PTB binding domain, but no other known domain (10). This PTB domain is indicated to play an important role in Krit1 and malcaverin interaction and a common functional pathway. Indeed, KRIT1 -malcavernin interaction was pinpointed to contribute to CCM pathogenesis, possibly by its regulation of KRIT1 shuttling to and from the nucleus. Furthermore the murine orthologue of malcavernin, OSM (osmosensing scaffold for Mekk3), was shown to modulate the Mekk3 dependent p38Mapk activation induced by hyperosmotic shock (10, 11). The Krit1 was identified in a ternary complex with malcavernin and MEKK3, suggesting a possible function of the CCM1/2 complex in p38MAPK activation (11). Besides that, CCM2 function was also linked to RhoGTPase activity (RhoA, Rac1 and Cdc42) through which CCM2 may regulate the tight junction complex stability and process of angiogenesis (13). CCM2 mRNA is expressed in neurones and astrocytes, in embryonic and adult stages and it is transiently observed in meningeal and parenchymal cerebral vessels (13) (Figure 2).

CCM3 includes seven exons, which encode for Programmed Cell Death 10 (PDCD10), a small protein (25kDa) without any known conserved functional domain. PDCD10 is involved in apoptosis and is upregulated in fibroblasts exposed to specific apoptosis inducers, such as staurosporine, cycloheximide and tumor necrosis factor-α (3, 10, 11). CCM3 mRNA expression is present in neuronal cells at embryonic and adult stages and similarly to CCM2, the CCM3 also can be seen in meningeal and parenchymal cerebral vessels. CCM3 interacts with CCM2 but their respective interaction sites are not known. However, the three possible CCM2 mutations cited can impair binding to CCM1/Krit1 but none of them affect CCM3 biding (11, 12). There is also no binding affinity between CCM1 and CCM3, and it is proposed that CCM2 play the role of linker protein that brings together Krit1 and CCM3 (10, 11). However, recent proteomic analysis suggests that CCM3 protein resides within a large multiprotein assembly, referred as the STRIPAK (striatin - interacting

phosphatase and kinase complex), which assembles phosphatases and kinases arranged around a protein phosphatase 2A core (14). Interestingly, neither Krit1 nor CCM2 was detected in the STRIPAK complex while CCM3 in the larger portion (~80%) is associated with that complex (14). This suggest that CCM3 is associated with two complexes CCM1/CCM2/CCM3 and STRIPAK and through them could be involved in biogenesis of CCMs lesion (Figure 2).

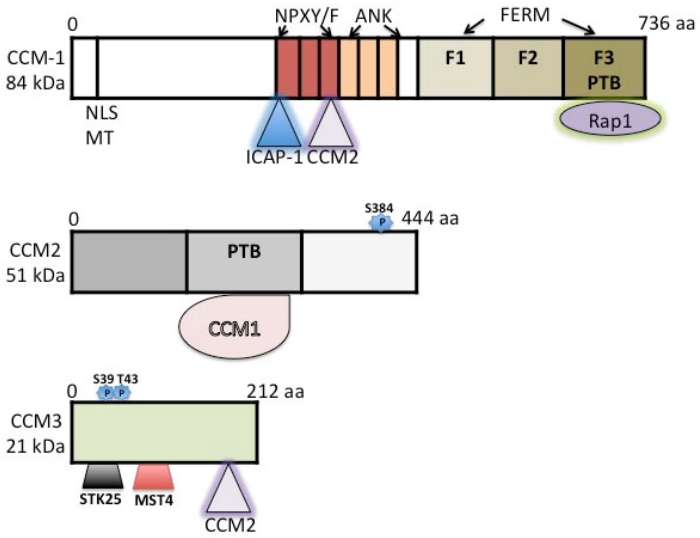

***Figure 2**. Structural domains of CCM1, CCM2 and CCM3 proteins. (Adapted from Faurobert and Albiges-Rizo, FEBS J. 2010;277(5):1084-96.)*

Current hypothesis about developing CCM1, CCM2 and CCM3 lesions

In general, at the cellular level, there are two ongoing process associated with CCMs lesion for all described forms of CCMs: pathological angiogenesis and /or alterations in the Tj complex.

An increasing body of evidence indicates that CCM proteins are associated with the plasma membrane, regulated formation of cell-cell junctions, cell shape and polarity, and most likely cell adhesion to the extracellular matrix. Both cell-cell adhesion and cell polarity require the assembly of two specialized intercellular interactions - tight and adherence junctional complex that regulate vascular permeability. Tight junctional complex is a specialized structure that seals the interendothelial cleft forming a continuous blood vessel and providing the high endothelial electrical resistance, in the range of 1500-2000 $\Omega.cm^2$ (pial vessels), as compared to 3-33 $\Omega.cm^2$ in other tissues (15). The adherence junctions on the other hand is important for initiating and maintaining endothelial cell-cell contact and during the vasculogenesis support the forming of tight junctions. The brain endothelial Tj complex is composed of a combination of transmembrane integral proteins and cytoplasmic accessory proteins (15). The major structural BBB Tj proteins of are: (i) claudins, (claudin-5 predominantly and claudin 3, 12), tissue-specific proteins that form the primary Tj seal, (ii) occludin, an integral membrane protein involved in regulating electrical resistance across the BBB and paracellular permeability and (iii) JAMs (1-3), a single membrane spanning protein which belongs to the immunoglobulin superfamily, that is mostly involved in leukocyte-endothelial cell interaction and leukocyte transendothelial migration (15). The TJs accessory proteins are multidomain cytoplasmic molecules, which form structural support for the TJ (ZO-1, -2, -3, Af6) as well as being involved in signal transduction (cingulin, 7H6 and atypical protein kinase C) (15). In addition, actin filaments are extended into the TJs (linked to ZO-1 and occludin), coupling the structural and dynamic properties of the paracellular barrier. To obtain a tightly sealed TJ, trans-interaction between transmembrane Tj proteins (particularly claudin-5), as well as a stable support/interaction with adaptor proteins (ZO-1, -2) and actin filaments (15) are essential. In this way, the TJ junction complex acts as a dynamic structure and any alteration in the function of these components may lead to paracellular gap formation (15). The major transmembrane protein of endothelial AJs is Ve-cadherin, whereas AJ cytoplasmic plaque proteins include proteins of the catenin family ($\alpha\beta$, γ, p120) (15). Vascular endothelium cadherin (Ve-cadherin) is an important determinant of microvascular integrity and together with catenin forms the complex that initiates the brain endothelial cells interaction (15). The last component of junctional complex is brain endothelial cytoskeleton, which plays critical role in establishing the interendothelial junctional integrity. The cytoskeleton is composed of three primary

elements: actin microfilament, intermediate filaments and microtubule. The actin microfilament system is focally linked to multiple membrane adhesive proteins such as cadherin of occludin, glycocalix components, functional intercellular proteins like zona occludens (ZO) and catenins and focal adhesion complex. Short radial bands of F-actin and TJ and AJ actin-associated proteins assemble to form a structure denoted as the actin-rich adhesion belt (15). Besides a supporting role, actin structure is also involved in endothelial cells tension force generated via myosin light chain phosphorylation and actin stress fiber formation. The second major element of brain endothelial cytoskeletal structure is microtubule, and their role is in rapid assembly of actin filaments and focal adhesion, isometric cellular contraction and/or increased transendothelial leucocytes migration (15). Some recent studies suggested that these functions are realized via interactions of microtubules with microfilaments (15).

How does the CCMs protein affect the Tj complex formation? There are three ongoing models of CCMs action (Figure 3).

CCM1 (Krit1) is localized on cell-cell junctions and in direct binding and activation of Rap1 regulated AF-6/afadin, β-catenin and p120-catenin (11,12). Absence of Krit1 leads to disruption of β-catenin localization to adherens junctions and increases the permeability of the monolayer barrier (11, 12). Thus regulating β-catenin localization in adherens junction, Krit1 is likely to be involved in the formation and maintenance of the endothelial barrier. The CCM2 on the other hand is localized on endothelial cell cytoskeletal architecture and its activity is associated with signaling molecule RhoA (13). CCM2 loss leads to an increased number of actin stress fibers and enhanced permeability of the endothelial layer, and this was associated with increased activity of RhoA. Therefore, a physiological function of CCM2 is considered to be limited on regulation /inhibition of RhoA activation. In line with that, the study by Crose et al. has identified the new CCM2 biding partner E3 ubiquitin ligase Smurf1, which interaction with CCM2 leads to loss of RhoA activity (16). The current proposed hypothesis is that CCM2 regulate proteosomal degradation of RhoA and participate in spatially restriction of small G-protein signaling (Figure 3). The role of *CCM3* in regulation of cell junctional complex is least understood. Two recent studies shed a potential role of CCM3, pinpoint the CCM3 binding to GCK-III family of sterile 20-like serine/threonine kinases (STKs) STK24 and STK25 which in turn directly regulate the activity of moesin, negatively regulate Rho activity, and consequently with that the endothelial cell-cell junctions (17) (Figure 3).

Consistent with their involvement in the same pathology, CCM1, CCM2 and CCM3 are able to interact in ternary complex. In this complex, there is a direct biding between CCM1 and CCM2 proteins, while CCM3 only interacts with CCM2 protein. Taking into consideration the CCM1, CCM2 and CCM3 function and interaction (RhoAGTPases, MAP kinases, cell junctions, and the cytoskeleton), this complex is hypothetically localized on cell junctions poised to mediate the key aspects of vascular stability. The emerging experimental and clinicopathological data suggest that CCM proteins, and in particular Krit1-CCM2, are involved in the spatiotemporal tuning of RhoA GTPases. For example, mouse brain endothelial cells with insufficient (Krit1 (-/-), CCM2 (-/-) or haploinsufficient Krit1 (+/-) or CCM2 (+/-), as well as both Krit1 (+/-) and CCM2 (+/-) mice exhibited sustained activity of RhoA and its effector Rho kinase (ROCK), and the increased leakage was reversible by fasudil, a ROCK inhibitor (18). Furthermore, in sporadic and familial human CCM, ROCK hyperactivity was also present in human CCM endothelium as judged by increased phosphorylation of myosin light chain and by beneficial effect of fasudil (the inhibitor of ROCK activity in amelioration of both, CCM disease and vascular leak), (13, 18). The specific type of pathology was mostly associated with CCM1 and CCM2 proteins.

However, some very recent studies pinpoint that CCM3, besides a close interaction with CCM2, may also be involved in some other complexes such as binding to STRIPAK. Association with STRIPAK complex puts CCM3 in a position of close interaction with PIP2A enzymes and association with membrane phospholipids like PIP2 and PIP3 that play prominent role in tight junction complex assembly (14). This new role of CCM3, in regulating permeability, awaits further clarification.

Besides the effect on TJ complex stability and assembly there is accumulating evidence that CCM1-3 can also affect vasculogenesis/angiogenesis, which could be good substrate for developing CCM lesion (19, 20). In line with that, the CCM1 protein Krit1 with the binding partner ICAP-1 may regulate the β1 integrin function affecting the process of blood vessels branching and sprouting, extracellular matrix remodeling, growth factor delivery, lumen formation and the recruitment of mural cells. The CCM2 on the other side, via regulation of RhoGTPase Rac1 and Cdc42, regulates the brain endothelial cell migration, cell polarization and lumen formation. The absence of CCM2 also affects the Cdc42 and Rac1 activation and the Pak2, Pak4 and PAR complex which in turn guides to the vacuolization of blood vessels lumens (13, 19). The CCM3 also affects the angiogenesis by increasing antiapoptotic potency of endothelium and promoting the endothelial cells proliferation. In addition to that the CCM3 deletion reduced vascular endothelial growth factor receptor 2 (VEGFR2) signaling in embryos and endothelial cells. In response to VEGF stimulation, CCM3 may recruit and stabilize VEGFR2 (20). Indeed, the CCM3 mutants found in human patients lacking the carboxyl-terminal domain were labile and were unable to stabilize and activate VEGFR2.

The current working hypothesis of CCM onset is a "two-hit" hypothesis in which one germline mutant allele is inherited and the remaining somatic allele undergoes a spontaneous mutation, experiences an environmental

insult such as osmotic stress, or an inflammatory response that alters the stability of the endothelial cells (18). Although there is lack of solid experimental and clinical evidence for this hypothesis, the further investigation regarding the role of CCM proteins in vasculogenesis/angiogenesis and TJ assembly should clarify this issue.

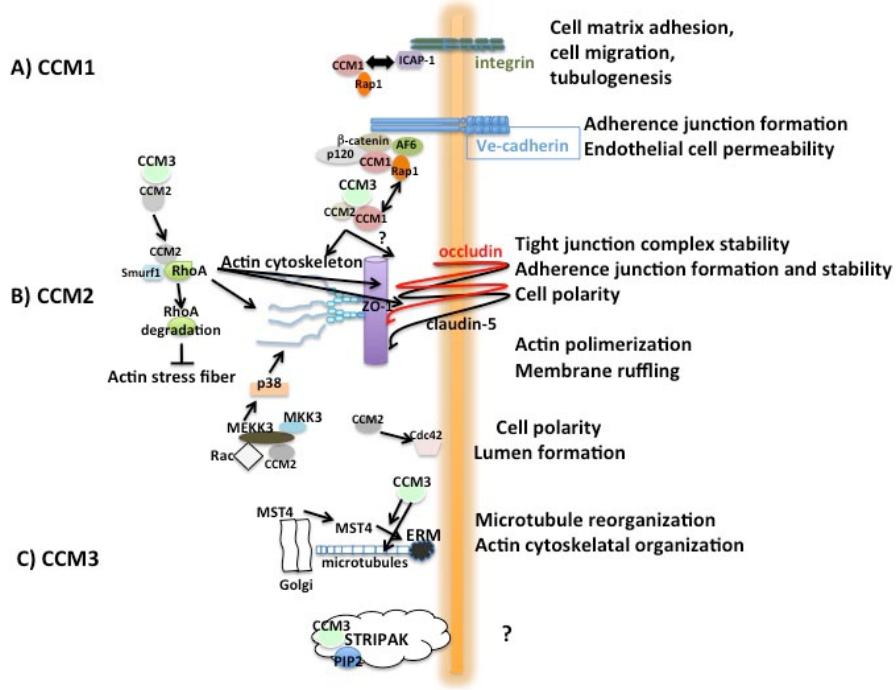

Figure 3. *Signaling pathways and vascular process controlled by CCM1 (A), CCM2 (B) and CCM3 (C). (Adapted from Faurobert and Albiges-Rizo, FEBS J. 2010;277(5):1084-96.)*

Inflammatory aspect of CCM lesion

A potential role of the immune response in CCMs has not been demonstrated previously, but due to unique antigenic milieu of CCM lesions with leaky blood-brain barrier, and the numerous examples of immune mediators in controlling angiogenesis in other disease states, the inflammatory response could be accounted for triggering and progression of CCM lesion (21). Histopathological analysis of CCMs lesion indicated wide infiltration of the immune cells, mostly B- and T-lymphocytes and macrophages, in particularly during the bleeding phase of CCMs lesion. Intriguingly, there were significantly more B-lymphocytes in CCMs lesion associated with venous anomaly while T cells were more present in solitary lesion. There is also specific cell type infiltration dependent on age of CCM patients, with high prevalence of T cells and less macrophage present in CCMs from younger subjects (21). However, robust B and plasma cell infiltration and oligoclonal IgG immune responses have been demonstrated in CCM lesion but not in sera of the same patents. Most of lesion have also specific IgG isotype such as expression IgM and IgA, with IgM predominance over IgA correlating with recent CCM growth. Oligoclonality was shown in IgG mRNA from CCM lesion, with only eight CDR3 sequences. There is also a correlation between an antigen-directed oligoclonal IgG immune response and clinical CCM activity. Apparently there are differences in immune response in younger patients and in lesions with recent growth. However, a causal relationship between immune response and lesion growth of CCMs cannot be still proven (21).

Finally, the inflammatory cytokines, including tumor necrosis factor-α and some interleukins (IL-1β, IL6), are potent stimulators of both angiogenesis and BBB breakdown and could contribute to lesion progression and rupture (21). The solid data regarding cytokines effect is still lacking.

Therapy and new strategy

The CCMs patients mostly have benefited from a pharmacological therapy and neurosurgical treatment. Brain surgery or radiation treatment has been the only option for CCM patients although the most of these patients received also the treatment for associated symptoms (epilepsy, thrombosis, headache). However, due to significant risk of surgical operation, the recent therapeutic strategy was redirecting towards the pharmacological treatment.

Two clinical trials regarding the treatment of CCMs lesion have recently come out. Testing the hypo-

thesis that inhibition of Rho activity, Whitehead and his collaborators demonstrated that statin (widespread use of drugs for lowering cholesterol), specifically simvastatin were effective in reducing the leakiness of blood vessels in mice that were bred to have the Ccm2 genetic mutation.

However, the recent study by Stockton and Ginsburg has identified another medication, generically known as fasudil, as being effective at reducing leaky blood vessels in mice bred with the Ccm1 genetic mutation (22). Fasudil is a "Rho Kinase inhibitor" and works on cavernous angiomas in a way that is similar to statins by blocking the RhoA/Rho kinase pathway to reduce the BBB leakage. Fasudil has been used in Japan for more than 15 years to treat cerebral vasospasm and in the USA is currently undergoing clinical trials to gain approval to be used in the treatment of pulmonary hypertension and other conditions.

Another option for treatment of CCMS came from the study of Wüstehube and colleagues (19). Sorafenib, known as antiangiogenic drug is mostly used to slow the spread of cancer in individuals with advanced primary kidney cancer and with advanced primary liver cancer. Sorafenib was shown to shrink cavernous angiomas in mice bred without immune systems that had received a transplant of human CCM1-mutated endothelial cells, attacking the angiogenic process (19). The identification of sorafenib, however, has opened the door to a different class of medications that can be explored. The arising question regarding the pharmacological approach in the treatment of CCMs is how much are the statins, fasudil and sorafenib, specific to these mutations, or will they work for all types of cavernous angiomas?

This is a question without a solid answer. All of the CCM proteins (CCM1, CCM2, and CCM3) that cause the hereditary form of the illness have been shown to be a part of the same system. Sporadic cavernous angioma lesions are indistinguishable from those in the inherited forms of the illness. It may be that a medication that works for CCM1 could also work for CCM2, CCM3 and sporadic cases. However, the more researchers learn about the function of the CCM proteins, the more they find that each has additional unique functions that can tune the current approach and open a new therapeutic avenue for treatment of CCMs.

References

1. Gault J, Sarin H, Awadallah NA, Shenkar R, Awad IA. Pathobiology of human cerebrovascular malformations: basic mechanisms and clinical relevance. Neurosurgery 2004;55(1):1-16.
2. Shenkar R, Venkatasubramanian PN, Zhao JC, Batjer HH, Wyrwicz AM, Awad IA.Advanced magnetic resonance imaging of cerebral cavernous malformations: part I. High-field imaging of excised human lesions. Neurosurgery 2008;63(4):782-9; discussion 789.
3. Shenkar R, Sarin H, Awadallah NA, Gault J, Kleinschmidt-DeMasters BK, Awad IA. Variations in structural protein expression and endothelial cell proliferation in relation to clinical manifestations of cerebral cavernous malformations. Neurosurgery 2005;56(2):343-54.
4. Frischer JM, Pipp I, Stavrou I, Trattnig S, Hainfellner JA, Knosp E.Cerebral cavernous malformations: congruency of histopathological features with the current clinical definition. J Neurol Neurosurg Psychiatry 2008; 79(7):783-8.
5. Abe M, Fukudome K, Sugita Y, Oishi T, Tabuchi K, Kawano T.Thrombus and encapsulated hematoma in cerebral cavernous malformations.Acta Neuropathol. 2005;109(5):503-9.
6. Clatterbuck RE, Eberhart CG, Crain BJ, Rigamonti D. Ultrastructural and immunocytochemical evidence that an incompetent blood-brain barrier is related to the pathophysiology of cavernous malformations. J Neurol Neurosurg Psychiatry 2001;71(2):188-92.
7. Burkhardt JK, Schmidt D, Schoenauer R, Brokopp C, Agarkova I, Bozinov O, Bertalanffy H, Hoerstrup SP. Upregulation of transmembrane endothelial junction proteins in human cerebral cavernous malformations. Neurosurg Focus 2010;29(3):E3.
8. Gore AV, Lampugnani MG, Dye L, Dejana E, Weinstein BM. Combinatorial interaction between CCM pathway genes precipitates hemorrhagic stroke. Dis Model Mech 2008;1(4-5):275-81.
9. Labauge P, Denier C, Bergametti F, Tournier-Lasserve E. Genetics of cavernous angiomas. Lancet Neurol 2007;6(3):237-44.
10. Stahl S, Gaetzner S, Voss K, Brackertz B, Schleider E, Sürücü O, Kunze E, Netzer C, Korenke C, Finckh U, Habek M, Poljakovic Z, Elbracht M, Rudnik-Schöneborn S, Bertalanffy H, Sure U, Felbor U. Novel CCM1, CCM2, and CCM3 mutations in patients with cerebral cavernous malformations: in-frame deletion in CCM2 prevents formation of a CCM1/CCM2/CCM3 protein complex. Hum Mutat 2008;29(5):709-17.
11. Faurobert E, Albiges-Rizo C. Recent insights into cerebral cavernous malformations: a complex jigsaw puzzle under construction. FEBS J 2010;277(5):1084-96.
12. Glading AJ, Ginsberg MH Rap1 and its effector KRIT1/CCM1 regulate beta - catenin signaling.. Dis Model Mech 2010;3(1-2):73-83.
13. Whitehead KJ, Chan AC, Navankasattusas S, Koh W, London NR, Ling J, Mayo AH, Drakos SG, Jones CA, Zhu W, Marchuk DA, Davis GE, Li DY. The cerebral cavernous malformation signaling pathway promotes vascular integrity via Rho GTPases. Nat Med 2009; 15(2):177-84.
14. Goudreault M, D'Ambrosio LM, Kean MJ, Mullin MJ, Larsen BG, Sanchez A, Chaudhry S, Chen GI, Sicheri F, Nesvizhskii AI, Aebersold R, Raught B, Gingras AC.A

PP2A phosphatase high density interaction network identifies a novel striatin-interacting phosphatase and kinase complex linked to the cerebral cavernous malformation 3 (CCM3) protein. Mol Cell Proteomics 2009; 8(1):157-71.
15. Bazzoni G, Dejana E.Endothelial cell-to-cell junctions: molecular organization and role in vascular homeostasis. Physiol Rev 2004;84(3):869-901.
16. Crose LE, Hilder TL, Sciaky N, Johnson GL. Cerebral cavernous malformation 2 protein promotes smad ubiquitin regulatory factor 1-mediated RhoA degradation in endothelial cells. J Biol Chem 2009; 284 (20):13301-5.
17. Zheng X, Xu C, Di Lorenzo A, Kleaveland B, Zou Z, Seiler C, Chen M, Cheng L, Xiao J, He J, Pack MA, Sessa WC, Kahn ML. CCM3 signaling through sterile 20-like kinases plays an essential role during zebrafish cardiovascular development and cerebral cavernous malformations. J Clin Invest 2010;120(8):2795-804.
18. McDonald DA, Shenkar R, Shi C, Stockton RA, Akers AL, Kucherlapati MH, Kucherlapati R, Brainer J, Ginsberg MH, Awad IA, Marchuk DA. A novel mouse model of cerebral cavernous malformations based on the two-hit mutation hypothesis recapitulates the human disease. Hum Mol Genet 2011;20(2):211-22.
19. Wüstehube J, Arne Bartol A, Liebler SS, Brütsch R, Zhu Y, Felbor U, Sure U, Augustina HG, and Fischer A. Cerebral cavernous malformation protein CCM1 inhibits sprouting angiogenesis by activating DELTA-NOTCH signaling. PNAS 2010 (in press).
20. Zhu Y, Wu Q, Xu JF, Miller D, Sandalcioglu IE, Zhang JM, Sure U. Differential angiogenesis function of CCM2 and CCM3 in cerebral cavernous malformations. Neurosurg Focus 2010;29(3):E1.
21. Shenkar R, Shi C, Check IJ, Lipton HL, Awad IA. Concepts and hypotheses: inflammatory hypothesis in the pathogenesis of cerebral cavernous malformations. Neurosurgery 2007;61(4):693-702; discussion 702-3.
22. Stockton RA, Shenkar R, Awad IA, Ginsberg MH. Cerebral cavernous malformations proteins inhibit Rho kinase to stabilize vascular integrity. J Exp Med 2010; 207 (4):881-96.

CERABRALNE KAVERNOZNE MALFORMACIJE: NOVI UVID U MEHANIZAM BOLESTI

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Sažetak

Cerebralne kavernozne malformacije (CKM) su najčešće vaskularne malformacije mozga, i stopa javljanja je 0.6 osoba na 100.000 ljudi. Bilo da su nasledne ili se javljaju kao sporadični slučajevi, cerebralne kavernozne malformacije se javljaju kao pojedinačne ili višebrojne grupe kapilarolikih kanala prekrivenih jednim slojem endotela, bez zahvatanja moždanog parenhima. U komponentama moždane endotelne barijere dolazi do specifičnih promena koje na kraju dovode do vaskularne hiperpropustljivosti, ektravazacije eritrocita i inflamatornog odgovora unutar moždanog parenhima. Bolesnici sa CKM imaju napade, fokalne deficite ili nespecifične glavobolje. Najčešća komplikacija je moždani udar.

U poslednjih nekoliko godina napravljen je značajan pomak u poimanju celularnog mehanizma cerebrovaskularnog defekta kod CKM. Rad pruža pregled novije literature o mehanizmima CKM i terapeutske strategije u lečenju sporadičnih i naslednih cerebralnih kavernoznih malformacija.

Ključne reči: **cerebrovaskularni defekt, krvno-moždana barijera, tesni spoj, angiogeneza**