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Oxidative stress and inflammation in cerebral cavernous malformation disease pathogenesis: Two sides of the same coin

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ABSTRACT

Cerebral Cavernous Malformation (CCM) is a vascular disease of proven genetic origin, which may arise sporadically or is inherited as an autosomal dominant condition with incomplete penetrance and highly variable expressivity. CCM lesions exhibit a range of different phenotypes, including wide inter-individual differences in lesion number, size, and susceptibility to intracerebral hemorrhage (ICH). Lesions may remain asymptomatic or result in pathological conditions of various type and severity at any age, with symptoms ranging from recurrent headaches to severe neurological deficits, seizures, and stroke. To date there are no direct therapeutic approaches for CCM disease besides the surgical removal of accessible lesions. Novel pharmacological strategies are particularly needed to limit disease progression and severity and prevent *de novo* formation of CCM lesions in susceptible individuals.

Useful insights into innovative approaches for CCM disease prevention and treatment are emerging from a growing understanding of the biological functions of the three known CCM proteins, CCM1/KRIT1, CCM2 and CCM3/PDCD10. In particular, accumulating evidence indicates that these proteins play major roles in distinct signaling pathways, including those involved in cellular responses to oxidative stress, inflammation and angiogenesis, pointing to pathophysiological mechanisms whereby the function of CCM proteins may be relevant in preventing vascular dysfunctions triggered by these events. Indeed, emerging findings demonstrate that the pleiotropic roles of CCM proteins reflect their critical capacity to modulate the fine-tuned crosstalk between redox signaling and autophagy that govern cell homeostasis and stress responses, providing a novel mechanistic scenario that reconciles both the multiple signaling pathways linked to CCM proteins and the distinct therapeutic approaches proposed so far. In addition, recent studies in CCM patient cohorts suggest that genetic susceptibility factors related to differences in vascular sensitivity to oxidative stress and inflammation contribute to inter-individual differences in CCM disease susceptibility and severity.

This review discusses recent progress into the understanding of the molecular basis and mechanisms of CCM disease pathogenesis, with specific emphasis on the potential contribution of altered cell responses to oxidative stress and inflammatory events occurring locally in the microvascular environment, and consequent implications for the development of novel, safe, and effective preventive and therapeutic strategies.

1. Introduction

Cerebral Cavernous Malformations (CCM), also known as cavernous angioma or cavernoma, are vascular malformations consisting of closely clustered, abnormally dilated and leaky capillary channels (caverns) lined by a thin endothelial layer (Batra et al., 2009; Fontanella, 2015; Gault et al., 2004; Rigamonti, 2011). Lesions are devoid of normal vessel structural components, such as pericytes and astrocyte foot processes, but are surrounded by a thick, segmentally layered basal membrane (Clatterbuck et al., 2001). CCM lesions can occur anywhere in the body, but usually produce serious signs and symptoms only when they occur in brain and

Abbreviations: CCM, cerebral cavernous malformation; fCCM, familial form of CCM; sCCM, sporadic form of CCM; NVU, neurovascular unit; ICH, intracerebral hemorrhage; ROS, reactive oxygen species; COX-2, cycloxygenase-2; AJ, adherens junction; EndMT, endothelial-to-mesenchymal transition; TGFβ, transforming growth factor beta; BMP, bone morphogenetic protein; VEGF, vascular endothelial growth factor; KLF, Kruppel-like factor.

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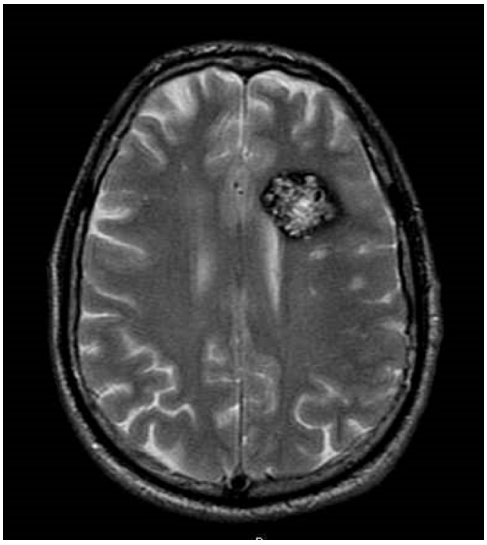

Fig. 1. MRI appearance of a Cerebral Cavernous Malformation.
Axial T2 FSE MRI of a CCM lesion in an affected patient (*image courtesy of Dr. Maria Consuelo Valentini, "Città della Salute e della Scienza" University Hospital of Torino, Italy*).

spinal cord, where they account for 5–15% of all vascular malformations. Retinal, skin, and liver lesions have also been occasionally reported in association with brain lesions. Within the brain, CCM can occur as single or multiple lesions (even hundreds), ranging in size from a few millimeters to a few centimeters. Lesions can remain clinically silent for a lifetime, or unpredictably give rise to various clinical symptoms including headaches, neurological deficits, seizures, stroke, and intracerebral hemorrhage (ICH) (Batra et al., 2009; Fontanella, 2015; Gault et al., 2004; Rigamonti, 2011).

Diagnosis is commonly made by magnetic resonance imaging (MRI) (Fig. 1), although detection is far more likely via gradient-echo (GRE) or susceptibility-weighted imaging (SWI), which can unmask small lesions (Campbell et al., 2010; Cooper et al., 2008; de Souza et al., 2008). Because of a large series of MRI and autopsy studies, CCM disease has been recognized as a common clinical entity. Indeed, the prevalence of CCM lesions in the general population has been estimated to be about 0.3%–0.5%, accounting for approximately 24 million people worldwide (Batra et al., 2009; Fontanella, 2015; Rigamonti, 2011). Nevertheless, knowledge and risk awareness of this disease is generally poor. Moreover, diagnosis is mainly possible only when lesions become symptomatic, because the majority of CCM lesions apparently remain clinically and biologically quiescent during most of the host's lifetime. Indeed, despite the high prevalence of CCM lesions, approximately only 30% of affected people will eventually develop clinical symptoms, which are extremely variable and may have a major impact on the quality of life. The initial presentation of symptoms may occur at any age without sex predominance, although the typical age of onset is between the second and fifth decades of life (Batra et al., 2009; Fontanella, 2015; Rigamonti, 2011).

CCM is a disease of proven genetic origin (OMIM 116860) that may arise sporadically or is inherited as an autosomal dominant condition with incomplete penetrance and variable expressivity (Cavalcanti et al., 2012; Riant et al., 2010). The sporadic form (sCCM) accounts for up to 80% of cases, whereas the familial form (fCCM) accounts for at least 20% of cases. Genetic studies have so far identified three genes whose mutation causes CCM: *KRIT1* (*CCM1*), *MGC4607* (*CCM2*) and *PDCD10* (*CCM3*), which account for about 50%, 20% and 10% of the fCCM cases, respectively. The remaining 20% of cases have been attributed either to other so far undetected genetic alterations in the three known CCM genes or to mutations of a fourth as yet unidentified CCM gene (Choquet et al., 2015; Riant et al., 2010). A genetic founder mutation in *KRIT1* (Q455X, also known as the common Hispanic mutation) is found in descendants of Hispanic-Americans who settled in the southwestern United States and northern Mexico states (Polymeropoulos et al., 1997), and today accounts for the largest population of fCCM worldwide, with thousands of affected patients and varying degrees of clinical severity (Choquet et al., 2014a; Sahoo et al., 1999). Recent studies of this population have facilitated the identification of genetic and environmental risk factors associated with CCM disease progression and severity (Choquet et al., 2014a, b, 2016). Like the common Hispanic mutation, most of the hundreds of distinct mutations identified so far in the three known CCM genes are loss-of-function mutations (Choquet et al., 2015; Riant et al., 2010). Notably, while the sporadic form of the illness typically presents as a solitary lesion, the familial form is characterized by the presence of multiple CCM lesions, which are associated with cutaneous and retinal vascular lesions in 9% and 5% of fCCM cases, respectively. Conversely, in contrast to fCCM cases, CCM lesions of sCCM cases are frequently associated with a developmental venous anomaly (DVA), suggesting the possibility of a different developmental mechanism (Meng et al., 2014; Petersen et al., 2010).

Despite the apparent higher disease severity in fCCM cases, up to 70% of mutation carriers remain asymptomatic or minimally symptomatic throughout life. Moreover, a large variability of disease severity is observed even among family members of similar ages carrying the same disease-associated genetic defect, including wide inter-individual differences in lesion number, size and susceptibility to ICH, suggesting that additional factors other than the disease-causing mutation can contribute to CCM disease pathogenesis (Trapani and Retta, 2015). Although significant advances have been made toward understanding the natural history and molecular basis of CCM disease (Batra et al., 2009; Fischer et al., 2013; Fontanella, 2015; Gault et al., 2004; Marchi et al., 2016b; Rigamonti, 2011), the clinical behavior in individual patients, including the development of numerous and large lesions, and the risk of serious complications such as ICH, remains highly unpredictable (Fontanella and Bacigaluppi, 2015). Furthermore, despite the long-held dogma that CCM lesions are congenital and the clear evidence that they may remain clinically and biologically quiescent during the host's lifetime, there are several instances where their *de novo* formation, increase in size, and recurrent phases of hemorrhage over time has been carefully documented by serial MRI scans (Acciarri et al., 2009; Jung et al., 2003; Yadla et al., 2010). A complete understanding of pathogenic mechanisms and risk factors associated with onset, clinical progression, and severity of CCM disease remains therefore a major clinical and research challenge. This challenge must be met in order to identify new pharmacological therapies and prognostic factors, thus ultimately providing better options for disease treatment and prevention. Indeed, while medications are available to treat some clinical symptoms caused by CCM lesions, including headaches and seizures, to date there are no direct therapeutic approaches for CCM disease, besides the surgical removal of accessible lesions in patients with intractable seizures or recurrent hemorrhage (Fontanella and Bacigaluppi, 2015). In particular, novel pharmacological strategies are specially needed for treating patients with severe symptomatic disease due to inoperable or multiple lesions, as well as for preventing *de novo* formation of CCM lesions and disease progression in susceptible individuals. In addition, the identification of specific risk and susceptibility factors for developing the most severe forms of CCM disease and appropriate biomarkers of disease progression and severity is required to allow accurate risk assessment and more specific diagnosis, thus providing useful insights into predictors of disease outcome, early therapeutic interventions, and surveillance of treatment effects.