KRIT1: A Traffic Warden at the Busy Crossroads Between Redox Signaling and the Pathogenesis of Cerebral Cavernous Malformation Disease

KRIT1: a traffic warden at the busy crossroads between redox signaling and the pathogenesis of Cerebral Cavernous Malformation disease

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Abstract

Significance: KRIT1 (Krev interaction trapped 1) is a scaffolding protein that plays a critical role in vascular morphogenesis and homeostasis. Its loss-of-function has been unequivocally associated with the pathogenesis of Cerebral Cavernous Malformation (CCM), a major cerebrovascular disease of genetic origin characterized by defective endothelial cell-cell adhesion and ensuing structural alterations and hyperpermeability in brain capillaries. KRIT1 contributes to the maintenance of endothelial barrier function by stabilizing the integrity of adherens junctions and inhibiting the formation of actin stress fibers.

Recent Advances: Among multiple regulatory mechanisms proposed so far, significant evidence accumulated over the last decade has clearly shown that the role of KRIT1 in the stability of endothelial barriers, including the blood-brain barrier, is largely based on its involvement in the complex machinery governing cellular redox homeostasis and responses to oxidative stress and inflammation. KRIT1 loss-of-function has indeed been demonstrated to cause an impairment of major redox-sensitive mechanisms involved in spatiotemporal regulation of cell adhesion and signaling, which ultimately leads to decreased cell-cell junction stability and enhanced sensitivity to oxidative stress and inflammation.

Critical Issues: This review explores redox mechanisms that influence endothelial cell adhesion and barrier function, focusing on the role of KRIT1 in such mechanisms. We propose that this supports a novel model wherein redox signaling forms the common link between the various pathogenetic mechanisms and therapeutic approaches hitherto associated with CCM disease.

Future Directions: A comprehensive characterization of the role of KRIT1 in redox control of endothelial barrier physiology and defense against oxy-inflammatory insults will provide valuable insights into the development of precision medicine strategies.

1. Introduction

KRIT1 (Krev interaction trapped 1) is a ubiquitous scaffolding protein with several emergent functions and a critical role in vascular morphogenesis and homeostasis. It was originally identified in 1997 in a yeast two-hybrid screening for proteins interacting with Rap1, a small GTPase of the Ras family abundantly expressed in the mammalian brain and known also as Kirsten-ras-revertant 1 (Krev-1) (Serebriiskii et al. 1997). Loss-of-function mutations of the KRIT1 gene were subsequently discovered to underlie the pathogenesis of Cerebral Cavernous Malformation (CCM), a vascular disease affecting 0,3-0,5% of the population worldwide and characterized by defective endothelial junctions and the formation of abnormally enlarged and leaky capillary channels (caverns), which are referred to as CCM lesions (Laberge-le Couteulx et al. 1999, Sahoo et al. 1999). These can be effectively detected by magnetic resonance imaging (MRI) techniques (Mabray and Hart 2020) (Figure 1), and occur primarily in the central nervous system (CNS), where they can remain asymptomatic throughout the entire lifetime or unpredictably give rise to various clinical symptoms at any age, ranging from recurrent headaches to seizures, focal neurological deficits, and fatal intracerebral hemorrhage (ICH) (Clatterbuck et al. 2001, Batra et al. 2009, Rigamonti 2011, Fontanella 2015).

Within the brain, CCM lesions develop as a result of structural and functional alterations of the neurovascular unit (NVU), a complex multicellular entity composed of capillary endothelial cells surrounded by basal lamina, pericytes, and endfeet of perivascular astrocytes, which are intimately linked and cooperate to form the blood-brain barrier (BBB) and respond to changes in local microcirculation and metabolism (Abbott et al. 2006). In fact, brain CCM lesions are lined by a thin endothelium surrounded by an abnormal basal lamina and devoid of normal NVU structural components, such as pericytes and astrocyte foot processes (Clatterbuck et al. 2001), and may present with BBB disruption and oxy-inflammatory responses (Figure 1). They may occur as single or multiple lesions (even hundreds), ranging in size from a few millimeters to a few centimeters. Besides the CNS, CCM lesions have been found also in other organs, including skin, bone, eyes, and liver; however, there is not yet clear evidence of CCM specific symptoms or signs in such organs (Drigo et al. 1994, Toldo et al. 2009, Mabray and Hart 2020, Hart et al. 2021).

CCM disease is of proven genetic origin and may occur in both sporadic (sCCM) and familial (fCCM) forms, which account for about 70% and 30% of all CCM cases and are often characterized by single and multiple lesions, respectively. The familial form is inherited as an autosomal dominant condition with incomplete penetrance and highly variable expressivity, suggesting the involvement of both primary and secondary determinants of pathogenesis (Trapani and Retta 2015, Perrelli and Retta 2021). Besides *KRIT1* (also known as *CCM1*), whose mutations account for more than 50% of

the fCCM cases, CCM disease has been associated with mutations in other two genes, *CCM2* and *PDCD10* (also known as *CCM3*), which account for about 20% and 10% of the fCCM cases, respectively. However, up to 20% of fCCM cases could not be attributable to mutations in the three known CCM genes, suggesting the existence of yet unidentified causative genes or other unknown causes (Choquet et al. 2015, Tournier-Lasserve 2020). Consistently, using a next-generation-sequencing (NGS) approach, we have recently identified germline variants in *NOTCH3* and *PTEN* (phosphatase and tensin homolog deleted on chromosome 10) genes in fCCM cases devoid of mutations in known CCM genes, suggesting their potential involvement in CCM disease pathogenesis (Benedetti et al. 2022). Moreover, recent high-throughput sequencing analyses of surgical CCM specimens from patients affected by the sporadic form of CCM disease have led to the breakthrough discovery that mutations in the three known CCM genes are rarely present in sCCM lesions. Instead, these lesions are most frequently characterized by somatic mutations in genes implicated in the phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways, including *PIK3CA* and *MAP3K3*, which cause clinically indistinguishable phenotypes (Peyre et al. 2021, Weng et al. 2021, Hong et al. 2021), suggesting that the genetic basis of CCM disease can be more complex than previously thought.

Over the last decade there has been significant progress in understanding the structure and functions of proteins encoded by *CCM1*, *CCM2* and *CCM3* genes, providing useful insights into molecular mechanisms of CCM disease pathogenesis and the development of therapeutic approaches. In particular, the *CCM1*/*KRIT1* gene encodes for a 736 amino-acid protein containing distinct structural units, including a Nudix domain and three NPxY/F motifs at the N-terminus, four central ankyrin repeats, and a C-terminal clover-shaped FERM (band 4.1, ezrin, radixin, and moesin) domain (Fisher et al. 2020), which play fundamental roles in regulating KRIT1 molecular interactions, subcellular localizations, and functions (Francalanci et al. 2009, Fisher and Boggon 2014, De Luca et al. 2021) (Figure 2). In fact, these structural units form multiple protein binding sites, which have been implicated both in head-to-tail intramolecular interactions (Francalanci et al. 2009) and in intermolecular interactions with various binding partners, such as integrin cytoplasmic domain-associated protein-1 (ICAP1) (Zhang et al. 2001, Zawistowski et al. 2002), CCM2 (Zawistowski et al. 2005), Nd-1 (Guazzi et al. 2012), sorting nexin 17 (SNX17) (Czubayko et al. 2006), heart of glass 1 (HEG1) (Kleaveland et al. 2009), and Rap1 (Serebriiskii et al. 1997, Li et al. 2012). In turn, these multiple molecular interactions influence KRIT1 shuttling between distinct subcellular locations, including plasma membrane, cytoplasm and nucleus, suggesting that KRIT1 may act as a scaffold protein in different cellular compartments to control specificity, coordination, and branching in signaling pathways (Francalanci et al. 2009, Liu et al. 2011, Draheim et al. 2017, De Luca et al. 2021).

Consistent with a crucial role of KRIT1 in the regulation of endothelial cell adhesion, its loss-of-function affects major cell structures and molecular mechanisms involved in the formation and stability of cell–cell and cell–matrix junctions, including both cadherin- and integrin-mediated adhesions and actin cytoskeleton dynamics, which are required for the maintenance of endothelial barriers, such as the BBB (Glading et al. 2007, Glading and Ginsberg 2010, Stockton et al. 2010, Liu et al. 2011, Liu et al. 2013, Maddaluno et al. 2013, Faurobert et al. 2013, Macek Jilkova et al. 2014, Renz et al. 2015) (Figure 3 and Table 1). Accordingly, two established binding partners of KRIT1, Rap1 and ICAP1, were independently shown to exert a major role in the regulation of cell–cell and cell–matrix adhesions. The small GTPase Rap1 is crucially involved in the adhesive functions of both cadherins and integrins (Bos 2005, Boettner and Van Aelst 2009) and plays a pivotal role in their functional crosstalk (Balzac et al. 2005, Retta et al. 2006), whereas ICAP1 regulates β1 integrin-mediated adhesion and signaling (Degani et al. 2002, Bouvard et al. 2003).

On the other hand, data accumulated over the last decade have clearly shown that KRIT1 also plays an important role in key mechanisms involved in cellular redox homeostasis and defense against oxidative stress and inflammation, including reactive oxygen species (ROS) production and scavenging, autophagy, and antioxidant signaling, suggesting that its loss-of-function causes pleiotropic downstream effects by affecting such primary mechanisms (Goitre et al. 2010, Goitre et al. 2014, Marchi et al. 2015, Marchi et al. 2016a, Retta and Glading 2016, Marchi et al. 2016b, Goitre et al. 2017, Antognelli et al. 2018b, Antognelli et al. 2018a, Cianfruglia et al. 2019, Antognelli et al. 2020, Retta et al. 2020, Perrelli et al. 2021). In particular, a seminal paper published in 2010 showed that loss-of-function of KRIT1 led to an increase in intracellular ROS levels and an enhanced cell susceptibility to oxidative stress-mediated molecular and cellular dysfunctions (Goitre et al. 2010). Moreover, these effects were shown to be associated with decreased mitochondrial energy metabolism, activation of the PI3K/Akt signaling pathway, and downregulation of the transcription factor FoxO1 and some of its downstream targets, such as the antioxidant enzyme superoxide dismutase 2 (SOD2) (Goitre et al. 2010). Subsequent findings demonstrated that KRIT1 loss-of-function induces pro-oxidant and pro-inflammatory signaling pathways and mechanisms (Retta and Glading 2016, Retta et al. 2020), including upregulation of the redox-sensitive JNK/c-Jun/COX-2 axis (Goitre et al. 2014) and the NADPH oxidase/ROS/NF-κB cascade (Goitre et al. 2017). Furthermore, it was discovered that loss of KRIT1 activates the mechanistic target of rapamycin (mTOR) serine/threonine kinase and consequently downregulates autophagy, an essential cellular antioxidant system (Marchi et al. 2015, Marchi et al. 2016a, Marchi et al. 2016b) (Table 1). In turn, these molecular alterations were shown to impair microvessel barrier function and exacerbate vascular permeability triggered by inflammatory stimuli (Marchi et al. 2015, Goitre et al. 2017). More

recently, it has been shown that KRIT1 loss-of-function causes a chronic upregulation of NRF2 (nuclear factor E2-related factor 2), the master transcriptional regulator of antioxidant and cytoprotective responses (Antognelli et al. 2018b, Antognelli et al. 2018a), as well as an increased S-glutathionylation of redox-sensitive proteins (Cianfruglia et al. 2019) (Table 1). These data suggest the presence of multiple redox-dependent mechanisms that contribute to CCM disease pathogenesis (Antognelli et al. 2020, Retta et al. 2020). Accordingly, both hyperactivation of NRF2-mediated adaptive responses and perturbations in protein S-glutathionylation contribute to the etiology of chronic cardiovascular disorders (Vomund et al. 2017, Musaogullari and Chai 2020). Conversely, as a proof of concept of their redox dependence, the pathological phenotypes induced by KRIT1 loss-of-function could be rescued by the administration of either pro-autophagic drugs, such as the mTOR inhibitors rapamycin and torin 1 (Marchi et al. 2015, De Luca et al. 2018), or antioxidant compounds, including N-acetylcysteine (NAC), recombinant yeast avenanthramide (YAv) and tiron (Goitre et al. 2010, Goitre et al. 2014, Moglia et al. 2015, Goitre et al. 2017, Antognelli et al. 2018b, Antognelli et al. 2018a) (Table 2).

Overall, there is now compelling evidence that KRIT1 deficiency exerts pleiotropic effects in the vascular system by affecting key redox-sensitive molecular pathways and mechanisms that govern endothelial cell homeostasis and defenses against oxidative stress and inflammation, supporting a role for such pathways and mechanisms in the pathogenesis of CCM disease (Goitre et al. 2010, Goitre et al. 2014, Marchi et al. 2015, Marchi et al. 2016a, Antognelli et al. 2018b, Antognelli et al. 2018a, Cianfruglia et al. 2019). Indeed, a long-term impairment of redox homeostasis and antioxidant/anti-inflammatory responses, and the consequent increased susceptibility to endothelial dysfunction and barrier destabilization triggered by oxy-inflammatory insults, may explain the current evidence from studies in animal models and patient cohorts that loss-of-function mutations of CCM genes are not completely penetrant and only predispose to the development of CCM lesions (Trapani and Retta 2015, Retta and Glading 2016, Choquet et al. 2016, Goitre et al. 2017, Vieceli Dalla Sega et al. 2019, Retta et al. 2020). Accordingly, recent discoveries demonstrate that the consequences of KRIT1 loss-of-function extend beyond CCM disease pathogenesis, being also implicated in aortic endothelial dysfunction and atherosclerosis (Vieceli Dalla Sega et al. 2019), as well as in epithelial barrier dysfunction in the gastrointestinal tract (Wang et al. 2019). Furthermore, these findings and interpretations have been supported and complemented by the identification of genetic modifiers and risk factors associated with interindividual differences in susceptibility to CCM disease onset and severity, which opened up new perspectives for risk stratification (Choquet et al. 2016, Antognelli et al. 2020, Kim et al. 2020, Perrelli and Retta 2021, Flemming et al. 2020).

Taken together, the great advancements in the understanding of KRIT1 physiopathological functions and implications in CCM disease pathogenesis and severity have provided useful insights into the identification of biomarkers of prognostic and predictive value, and the development of personalized medicine strategies, including innovative approaches based on targeted multifunctional nanocarriers (Gibson et al. 2015, Moglia et al. 2015, Marchi et al. 2016a, Moglianetti et al. 2016, Perrelli et al. 2018, De Luca et al. 2018, Retta et al. 2020, Perrelli et al. 2021, Flemming 2017).

This review aims at providing a unifying scenario to the pleiotropic physiopathological functions of *KRIT1*, which have progressively emerged since its identification in 1999 as the major causative gene for CCM disease and exponentially expanded over the past two decades. Specifically, it provides a critical overview of the numerous and various biological functions and pathological effects to date attributed to the KRIT1 protein, highlighting the multiple lines of evidence that allow to contextualize them within the conceptual framework of redox biology, along with the plethora of putative pathogenetic mechanisms and therapeutic approaches so far associated with CCM disease.

While we are aware that alternative interpretations of existing data are possible, we hope that any controversial issues raised by our suggestive redox-centered view of KRIT1-related physiopathological processes may inspire new ideas and give hints for further investigations, thereby serving as a harbinger of important innovations and significant long-term benefits in terms of moving the field forward to a clearer understanding.

2. ROS metabolism and redox signaling in the vascular system

This section summarizes the basic mechanisms underlying ROS metabolism and biological effects in the attempt to provide a general conceptual framework that may serve to better contextualize the growing evidence for an important role of KRIT1 in redox biology. For a comprehensive knowledge of the specific reactive species and oxidative modifications involved in cellular redox homeostasis and signaling, and more in general in cell biology and physiology, the readers are referred to the diverse excellent review papers cited in the text, including those by Sies et al. (Sies and Jones 2020, Sies et al. 2022).

2.1 ROS metabolism

ROS are a highly reactive group of oxygen-containing molecules that are generated either constitutively or in response to various stimuli by distinct enzymatic and nonenzymatic sources in all cells. They include free oxygen radicals, such as superoxide anion ($O_2^{\bullet-}$) and hydroxyl radical ($OH^{\bullet}$), and peroxides, such as hydrogen peroxide (H_2O_2) and lipid hydroperoxide (LOOH), as well as other oxygen-containing reactive species (Sies and Jones 2020, Taverne et al. 2013). $O_2^{\bullet-}$ is a key

determinant of ROS physiopathological effects, being the precursor of most of the other major ROS found in biological systems. It can be dismutated to H_2O_2 and O_2 either nonenzymatically or by three superoxide dismutase (SOD) enzymes located in distinct cellular compartments, including cytoplasm and nucleus (SOD1/CuZnSOD), mitochondria (SOD2/MnSOD), and extracellular matrix (SOD3/ecSOD) (Faraci and Didion 2004, Fukai and Ushio-Fukai 2011). Moreover, it may be converted to $OH^{\bullet}$ by the Haber-Weiss reaction or to peroxynitrite ($OONO^-$) by reacting with nitric oxide (NO•), a biologically important free radical. In turn, H_2O_2 can be either converted to $OH^{\bullet}$ by the Fenton reaction, or reduced to H_2O by specific antioxidant enzymes, including catalase, glutathione peroxidases (GPx), and peroxiredoxins (Prx) (Faraci and Didion 2004, Fukai and Ushio-Fukai 2011).

2.2 Intracellular sources of ROS

Under physiological conditions the mitochondrial electron transport chain (ETC) is the major constitutive source of ROS, converting up to 5% of molecular O_2 to $O_2^{\bullet-}$ as a byproduct of aerobic metabolism due to unavoidable electron leakage from the ETC (Turrens 2003), and eventually contributing to approximately 45% of net cellular $O_2^{\bullet-}/H_2O_2$ production (Sies and Jones 2020). In particular, a total of 11 sites that produce $O_2^{\bullet-}$ and/or H_2O_2 as a consequence of electron leakage in the ETC have currently been identified in mammalian mitochondria (Brand 2016). These sites are located in the first three of the four ETC complexes (I, II, III, and IV) present in the inner mitochondrial membrane (IMM). The premature leak of electrons from them leads to one electron reduction of O_2 to $O_2^{\bullet-}$, which can then be dismutated to H_2O_2 by superoxide dismutase enzymes, including MnSOD (SOD2) in the matrix and Cu/ZnSOD (SOD1) in the intermembrane space. Under physiological conditions, it is estimated that 0.2-2% of the electrons in the ETC do not follow the normal transfer order but instead directly leak out of the ETC and interact with oxygen to produce $O_2^{\bullet-}$ (Turrens 2003, Chen et al. 2003). The rate of $O_2^{\bullet-}$ production from the ETC is dependent on the concentration of the one-electron donor at a particular site and the rate at which this redox active donor reacts with oxygen O_2, and is modulated by local factors, such as O_2 tension, protonmotive force (Δp), electron flux, and ATPase activity (Nolfi-Donegan et al. 2020). Interestingly, recent structural biology and biochemical studies revealed that ETC complexes can assemble into supramolecular structures known as supercomplexes (SCs), which confer several advantages, including stabilization of the structural integrity of ETC individual complexes, efficiency of substrate channeling and electron transfer, and prevention of excessive ROS formation (Maranzana et al. 2013).

Besides the mitochondrial source, $O_2^{\bullet-}$ and H_2O_2 are endogenously produced by specific ROS-generating enzymes located and activated in other subcellular compartments, including plasma

membrane, endoplasmic reticulum, peroxisomes and nucleus, as well as in redoxosomes, specialized redox-active endosomes that form in response to various extracellular stimuli, such as growth factors and cytokines, and contribute to the compartmentalization of ROS production and signaling (Ushio-Fukai 2009, Sies and Jones 2020). In particular, major enzymatic sources of $O_2^{\bullet-}$ and H_2O_2 are transmembrane NADPH oxidase (NOX) enzymes, which contribute about 40% of cellular $O_2^{\bullet-}/H_2O_2$ production in a timely and spatially regulated manner, thereby serving as important regulators of diverse physiological processes (Sies and Jones 2020) (Figure 4). There is in fact evidence that distinct subcellular localizations of NOX enzymes in specific signaling domains in the plasma membrane and endosomes are correlated with their differential roles in localized ROS production and oxidant signaling (Ushio-Fukai 2009, Ushio-Fukai 2006a, Wolin 2004, Hilenski et al. 2004).

Endothelial cells express four NOX isoforms, including NOX1, NOX2, NOX4, and NOX5, which are the major ROS sources in the cardiovascular system, acting as critical mediators of cardiovascular physiology and pathophysiology (Abid et al. 2007, Drummond et al. 2011, Lassègue et al. 2012). Indeed, the expression and activity of these enzymes are regulated by a variety of chemical and physical stimuli, including hormones, growth factors, chemokines, cytokines, neurotransmitters, metabolic factors, microorganism-derived pathogen associated molecular patterns (PAMPs), host cell-derived damage associated molecular patterns (DAMPs), shear stress and hypoxia, as well as aging (Park et al. 2004, Ushio-Fukai 2007, Chrissobolis and Faraci 2008, Goitre et al. 2012, Holmström and Finkel 2014, Chen et al. 2018). Once activated, they contribute to the regulation of diverse molecular and cellular mechanisms, such as calcium (Ca^{2+}) homeostasis, oxygen sensing, growth factor signaling, mechanotransduction, cell adhesion and cytoskeleton dynamics, autophagy, and angiogenic and inflammatory responses (Ushio-Fukai 2007, Ushio-Fukai 2009, Lassègue et al. 2012, Kim et al. 2017, Brandes et al. 2014a, Schröder 2014, Fukai and Ushio-Fukai 2020, Lee et al. 2011, Xu et al. 2017, Forte et al. 2017). Functional specificity is achieved through selective subcellular targeting and activation of NOX enzymes. These enzymes interact with signaling platforms in distinct subcellular compartments, including the nucleus, redoxosomes, plasma membrane microdomains (caveolae/lipid rafts), focal adhesions, adherens junctions, lamellipodial leading edges and membrane ruffles, thereby allowing spatiotemporally confined ROS production that controls activation of specific signal transduction pathways (Lassègue et al. 2012, Sies and Jones 2020, Ushio-Fukai 2009, Hilenski et al. 2004) (Figure 4). Accordingly, NOX enzymes were demonstrated to play a key role in the compartmentalization of ROS production and redox signaling in various cell types and tissues, including endothelial cells and cardiovascular tissues (Ushio-Fukai 2009, Lassègue and Griendling 2010, Brandes et al. 2014b).

Remarkably, while an abnormal increase in NOX activity has been shown to be responsible for excessive ROS production under a variety of pathological conditions, there is also evidence that elimination of NOX4 activity causes a marked reductive stress and consequent alteration of redox homeostasis and signaling. This reductive stress paradoxically promotes a net increase in mitochondrial ROS production and oxidative stress, leading to enhanced sensitivity to cardiovascular injury (Yu et al. 2014). Thus, both gain- and loss-of-function of NOX enzymes have deleterious effects on organisms, suggesting that NOX activity must be tightly maintained within optimal low and high threshold levels.

2.3 ROS as pleiotropic second messengers in cell redox signaling

Originally, ROS were characterized in terms of their harmful effects on biological molecules, cells and tissues, and implicated in aging and age-related diseases, including cardiovascular and neurodegenerative diseases (Taverne et al. 2013, Collin 2019). Indeed, consistent with the traditional view that ROS production was unregulated and their intracellular targets were random, oxidative stress originated by an imbalance between ROS production and antioxidant defense mechanisms has been clearly shown to cause a broad spectrum of molecular damage, such as abnormal oxidation of proteins, lipids, and nucleic acids, and contribute significantly to a wide range of pathologies, including cardiovascular and cerebrovascular diseases (Chrissobolis and Faraci 2008, Chrissobolis et al. 2011, Sena et al. 2018). However, whereas the critical impact of ROS on the development and progression of most human diseases has been widely confirmed and consolidated, it is now firmly established that ROS can also function as important mediators of intracellular physiological signaling implicated in major cell fate decisions (Holmström and Finkel 2014, Sies and Jones 2020). In particular, both NOX-derived ROS, $O_2^{\bullet-}$ and H_2O_2, have been suggested to function as pleiotropic physiological signaling messengers, acting similarly to Ca^{2+} (Holmström and Finkel 2014, Sies and Jones 2020), although the signaling role of $O_2^{\bullet-}$ is more likely as a precursor of H_2O_2 (Forman et al. 2010). Indeed, their production is spatially and temporally confined by the restricted subcellular localization and activation of NOX enzymes, and maintained in the low nanomolar concentration range by efficient removal systems, thus allowing spatiotemporal precision and specificity in redox regulation of target proteins and signaling pathways (Woo et al. 2010, Holmström and Finkel 2014, Sies and Jones 2020, Ushio-Fukai 2009). Consistently, it has been clearly demonstrated that NOX-derived ROS are crucially involved in the dynamic and coordinated orchestration of multiple redox-dependent signal transduction pathways that control essential biological processes, including physiological angiogenesis, vascular homeostasis, and barrier function (Griendling et al. 2000, Miller

et al. 2006, Ushio-Fukai 2007, Knock and Ward 2011, Ghosh et al. 2015, Byon et al. 2016, Kim et al. 2017, Obradovic et al. 2020) (Figure 4).

Physiological signal transduction mediated by ROS, known as "redox signaling", can be triggered by various endogenous and exogenous stimuli, and typically involves localized small bursts of $O_2^{\bullet-}/H_2O_2$ and reversible oxidative post-translational modifications (Ox-PTMs) of redox-sensitive proteins. Specifically, the reversible oxidation of protein cysteine residues is well recognized as a major regulatory mechanism in redox-dependent cell signaling (Paulsen and Carroll 2013). However, various Ox-PTMs of cysteine residues may occur, whose specific structural and functional impact is often poorly understood (Heppner et al. 2017, Dustin et al. 2019). In particular, both thermodynamic and kinetic considerations suggest that among possible oxidation states of cysteine, formation of sulfenic acid derivatives or disulfides can be relevant as thiol redox switches in the context of NOX-dependent signaling (Heppner et al. 2017, Dustin et al. 2019, Forman et al. 2010). Indeed, the first step in the reversible oxidation of cysteine thiols (Cys-SH) is their initial oxidation to a sulfenic acid (Cys-SOH). This process, termed sulfenylation, is mediated by two-electron oxidation by various biological ROS, and often influences protein function. However, a Cys-SOH is typically not stable within proteins and readily reacts with other cysteine thiols to generate a disulfide bond by reaction either with another cysteine within the same protein to form an intramolecular disulfide, with Cys-SH in a different protein to form an intermolecular disulfide, or with low-molecular weight thiols, such as free glutathione (GSH), to form protein S-glutathionylation adducts (Dustin et al. 2019). These disulfide intermediates can be reduced back to the original reduced thiol by oxidoreductases such as thioredoxins and glutaredoxins. On the other hand, C-SOH can be also subject to further oxidation to sulfinic acid (Cys-SO2H) or sulfonic acid (Cys-SO3H), which are irreversible Ox-PTMs that occur mainly in conditions of severe oxidative stress and are likely not involved in physiological cell signaling (Heppner et al. 2017, Dustin et al. 2019). Instead, the reversible nature of cysteine sulfenic acid, disulfide and S-glutathionylation makes them well suited to regulate protein function during cell signaling, although it is often unclear which oxidative modification is most critical for such regulation (Paulsen and Carroll 2013).

Among Ox-PTMs of redox-sensitive proteins, particularly important are thiol-based modifications of kinases, phosphatases, small GTPases, calcium handling proteins, cytoskeletal and cytoskeleton-associated proteins, cell adhesion proteins, metalloproteases, and transcription factors. In turn, redox-sensitive target proteins may serve as molecular switches in signal transduction pathways involved in specific cell responses (Sies and Jones 2020) (Figure 4). In particular, accumulating evidence points to protein tyrosine phosphatases (PTPs) and protein kinases as major redox-sensitive molecular targets of the intracellular messenger function of ROS (Tonks 2005,

Monteiro et al. 2008). PTPs are characterized by the presence in the active site of a highly conserved core CX5R catalytic motif containing a Cys residue that is essential for catalysis, and is very susceptible to reversible inactivating oxidation by ROS (Tonks 2005). In turn, oxidative inactivation of PTPs may promote various phosphorylation-dependent downstream signaling events, including modulation of cell-cell and cell-matrix adhesion and cytoskeleton dynamics (Young et al. 2021, Retta et al. 1996). Accordingly, oxidative inhibition of PTPs has been shown to be a sufficient stimulus for triggering both adherens junction disassembly and focal adhesion and actin stress fiber formation in adherent cells (Balzac et al. 2005, Retta et al. 1996). In addition, transient oxidation of cysteine residues in regulatory sites can directly activate both receptor and nonreceptor tyrosine kinases (PTKs), such as vascular endothelial growth factor receptor (VEGFR) and c-Src, respectively, as well as serine/threonine kinases, such as PKC, eventually contributing significantly to the activation of their downstream signaling pathways (Griendling et al. 2000, Nakashima et al. 2002, Knock and Ward 2011, Truong and Carroll 2013, Lee et al. 2011, Taverne et al. 2013, Heppner et al. 2018). In particular, there is compelling evidence that PKC can be activated by ROS independently of Ca^{2+} or diacylglycerol (Gopalakrishna and Anderson 1989, Knapp and Klann 2000). Notably, Ox-PTMs exert opposite effects on the enzymatic activity of protein phosphatases and kinases, the former being mainly inhibited and the latter activated by transient oxidation of thiol groups (Figure 5), suggesting that cellular signaling responses to stimuli are precisely coordinated and integrated by a fine-tuned crosstalk between redox-dependent and phosphorylation-dependent regulatory mechanisms (Chiarugi 2005, Chiarugi and Buricchi 2007).

The superfamily of small GTPases is another important group of signaling proteins known to be regulated by Ox-PTMs. There is evidence that distinct members of this superfamily, including Ras, Rac1, Cdc42, and RhoA, are directly activated by ROS through reversible oxidation of redox-sensitive cysteines. In turn, once activated, these small GTPases are capable to act as both regulators and effectors of redox signaling, eventually leading to the redox-dependent activation of downstream signaling proteins, such as MAPKs and Rho kinases (ROCKs), as well as to positive-feedback mechanisms that promote sustained ROS production (Griendling et al. 2000, Finkel 2006, Taverne et al. 2013, Mitchell et al. 2013, Hobbs et al. 2014, Ferro et al. 2014, Messina et al. 2019) (Figure 4 and 5).

Besides phosphatases, kinases, and small GTPases, a fourth important group of proteins implicated in redox signaling in the cardiovascular system is constituted by major redox-sensitive transcription factors, such as nuclear factor E2-related factor 2 (NRF2), nuclear factor-kappaB (NF-κB), activator protein 1 (AP-1), hypoxia-inducible factor-1 (HIF-1), and members of the forkhead

box O (FoxO) family (Liu et al. 2005, Brigelius-Flohé and Flohé 2011, Taverne et al. 2013, Marinho et al. 2014, de Keizer et al. 2011, Klotz et al. 2015, Checa and Aran 2020) (Figure 4).

3. Redox contextualization of the distinct molecular mechanisms linked to KRIT1

Perhaps the most clinically relevant effect of KRIT1 deficiency in endothelial cells is the loss of cell-cell contact. This event is thought to mediate the increased permeability of KRIT1-deficient microvessels and underlie the leakage of red blood cells and blood products into the surrounding tissue of the brain (Yadla et al. 2010, Clatterbuck et al. 2001). Indeed, hemorrhage of CCM lesions correlates closely with patient outcome and quality of life (Akers et al. 2017); therefore, controlling endothelial permeability should be a major goal for any putative CCM therapeutic. Unfortunately, our understanding of how KRIT1 and the other two CCM proteins stabilize endothelial cell-cell contacts remains rudimentary. Several years ago, we demonstrated that KRIT1 is a Rap1 effector associated with adherens junctions (AJs) (Glading et al. 2007) and that reduced expression of KRIT1 leads to loss of VE-cadherin-mediated adhesion and reduced localization of β-catenin and p120 catenin to AJs (Glading et al. 2007, Glading and Ginsberg 2010), suggesting for the first time that KRIT1 acts downstream of Rap1 to regulate endothelial cell-cell junctions and barrier integrity. Expression of the KRIT1 C-terminal FERM domain restores junctional stability as well as full-length KRIT1, suggesting that this domain is important to the ability of KRIT1 to stabilize cadherin adhesion (Glading et al. 2007). However, several other direct and indirect mechanisms have been proposed on the basis of the various effects known to be induced by KRIT1 loss-of-function (Table 1). Among others, these include:

1) activation of various signaling proteins, such as RhoA GTPase (Stockton et al. 2010), β1 integrin (Faurobert et al. 2013), vascular endothelial growth factor receptor 2 (VEGFR2) (DiStefano et al. 2014), mTOR (Marchi et al. 2015), and NADPH oxidase (NOX) enzymes (Goitre et al. 2017);
2) induction of transforming growth factor-beta (TGF-β)-mediated endothelial-to-mesenchymal transition (EndMT) (Maddaluno et al. 2013);
3) stimulation of β1 integrin-mediated Krüppel-like factor 2 (KLF2) proangiogenic activity (Renz et al. 2015);
4) upregulation of MAPK signaling, including the MAPK kinase kinase 3/MAPK kinase 5/extracellular signal-regulated kinase 5 (MEKK3/MEK5/ERK5) pathway, and consequent overexpression of KLF2 and KLF4 transcription factors (Zhou et al. 2016, Cuttano et al. 2016);
5) alteration of redox homeostasis and signaling, and concomitant downregulation of autophagy (Goitre et al. 2010, Goitre et al. 2014, Marchi et al. 2015, Marchi et al. 2016a, Retta and Glading 2016, Antognelli et al. 2018b, Antognelli et al. 2018a);

6) enhanced susceptibility to proinflammatory responses induced by cytokines and innate immune ligands, including interleukin-1β (IL-1β) and bacterial lipopolysaccharide (LPS) (Tang et al. 2017);
7) increased sensitivity to either low fluid shear stress conditions (Li et al. 2019) or absence of blood flow (Rödel et al. 2019).

One challenge to a better understanding of CCM pathogenesis is that these distinct mechanisms and signaling pathways have multiple downstream effects that could contribute to the loss of endothelial barrier function. However, consistent with our original finding that KRIT1 plays a major role in redox homeostasis and signaling, a major commonality is that both cadherin-mediated cell-cell adhesion and all the distinct mechanisms so far associated with KRIT1 loss-of-function are redox sensitive and can be simultaneously controlled by the pleiotropic effects of ROS-mediated cellular signaling. Accordingly, it is now well-established that ROS play a critical role in the coordinated and simultaneous regulation of multiple redox-sensitive signaling pathways and mechanisms necessary to ensure proper endothelial responses to various stimuli (Ushio-Fukai 2009, Holmström and Finkel 2014, Sies and Jones 2020).

3.1 Redox regulation of VE-cadherin-mediated cell adhesion

The AJ complex, comprising VE-cadherin and associated β-, α-, and p120-catenins, is of central importance for the formation and stabilization of endothelial cell–cell junctions and consequent regulation of vascular permeability. AJ stability requires the anchorage of VE-cadherin cytoplasmic domain to cortical actin bundles via α and β catenins, and is dynamically controlled through mechanisms that involve reversible protein phosphorylation mediated by kinases and phosphatases (Noda et al. 2010, Timmerman et al. 2012), as well as a fine-tuned interplay between Rap1 and Rho GTPases (Boettner and Van Aelst 2009, Cerutti and Ridley 2017, Citi et al. 2011, Noda et al. 2010, Spindler et al. 2010). Specifically, phosphorylation of VE-cadherin cytoplasmic domain and associated β-catenin by either receptor or nonreceptor tyrosine kinases, such as VEGFR2 and c-Src, results in disassembly of the AJ complex and internalization of VE-cadherin, which are accompanied by a concomitant increase in RhoA activity and vascular permeability. Conversely, dephosphorylation of VE-cadherin and β-catenin by VE-cadherin–associated PTPs, such Src homology-2 domain-containing tyrosine phosphatase 2 (SHP-2), and activation of the small GTPase Rap1 pathway, potentiate VE-cadherin–mediated cell–cell adhesion, leading to enhanced endothelial barrier function (Grinnell et al. 2010, Noda et al. 2010, Timmerman et al. 2012).

Remarkably, clear evidence shows that NOX-derived ROS can act as second messengers to regulate VE-cadherin-mediated AJ dynamics either through direct oxidative modification of

449 junctional proteins or indirectly through redox modification of associated regulatory proteins, such
450 as phosphatases, kinases and small GTPases (Tonks 2005, Ushio-Fukai 2009, Monaghan-Benson and
451 Burridge 2009, van Wetering et al. 2002, Lin et al. 2003, Nwariaku et al. 2004, Zhou et al. 2013)
452 (Figure 5). Specifically, ROS-dependent phosphorylation of VE-cadherin and catenins, and
453 subsequent disassembly of VE-cadherin/catenin complexes, have been demonstrated to occur in
454 response to the compartmentalized ROS-generating activity of NOX enzymes induced by angiogenic
455 growth factors, inflammatory cytokines, hypoxia and shear stress (van Wetering et al. 2002, Lin et
456 al. 2003, Nwariaku et al. 2004, Ikeda et al. 2005, Zhou et al. 2013, Marcos-Ramiro et al. 2014). ROS
457 generated by NOX enzymes can in fact modulate the activity of redox-sensitive kinases and
458 phosphatases that affect the conformation and function of AJ proteins, including VEGFR2, c-Src,
459 PKC, PTP-μ, VE-PTP, PTP1B, and SHP-2 (Griendling et al. 2000, Tonks 2005, Abid et al. 2007, Lee
460 et al. 2011) (Figure 4 and 5). Consistently, there is clear evidence for a tight interplay between NOX
461 enzymes and VEGFR2 in endothelial cells, which enhances VEGF-induced VEGFR2
462 autophosphorylation and signaling (Ushio-Fukai 2006b, Ushio-Fukai 2007), as well as for a
463 NOX/ROS-dependent oxidative activation of c-Src (Heppner et al. 2018). Conversely, antioxidant
464 compounds were demonstrated to strongly inhibit VEGF-mediated angiogenic responses, including
465 c-Src kinase activation, VE-cadherin and β-catenin tyrosine phosphorylation, and subsequent AJ
466 remodeling, suggesting that ROS are required for VEGF-induced microvascular permeability (Lin et
467 al. 2003, Monaghan-Benson and Burridge 2009).

468 VE-cadherin phosphorylation and subsequent disruption of AJ also occurs in response to other
469 stimuli, including pro-inflammatory factors, such as IL-1β, tumor necrosis factor-α (TNF-α), and
470 bacterial LPS (Angelini et al. 2006, Gong et al. 2008). Indeed, NOX-derived ROS play a central role
471 in the endothelial barrier dysfunction driven by these proinflammatory factors via their cognate
472 receptors, IL-1βR, TNF-α receptor (TNFR), and Toll-like receptor 4 (TLR4) (Park et al. 2004, Park
473 et al. 2006) (Figure 5). This is particularly noteworthy, as it has been proposed that activation of
474 endothelial TLR4 by gram negative bacteria and LPS contributes critically to both CCM disease
475 pathogenesis and its highly variable expressivity associated with KRIT1 loss-of-function mutations
476 (Tang et al. 2017). Specifically, signaling by IL-1β, a major proinflammatory cytokine capable of
477 inducing BBB breakdown, is known to be dependent on NOX-derived ROS and require the formation
478 of redox-active signaling endosomes (redoxosomes) containing its endocytosed heterodimeric
479 receptor (IL-1βR) and NADPH oxidase 2 (NOX2) (Oakley et al. 2009). Physical association of TNFR
480 and TLR4 with NADPH oxidase 1 (NOX1) and NADPH oxidase 4 (NOX4), respectively, is also a
481 prerequisite for ROS production downstream of TNF-α and LPS stimulation (Yazdanpanah et al.
482 2009). In turn, NOX-derived ROS have been directly linked to changes in the morphology and

functional properties of the endothelium induced by TNF-α (Li et al. 2005, Marcos-Ramiro et al. 2014) and LPS (Park et al. 2006, Singh et al. 2017, Yoo et al. 2020), being capable of coupling TNFR and TLR4 receptor triggering to the oxidative activation of c-Src, which leads to tyrosine phosphorylation and destabilization of cell-cell adhesion proteins and consequent enhanced microvascular permeability (Gong et al. 2008, Checa and Aran 2020) (Figure 5). To this regard, it is noteworthy that IL-1β- and TNF-α-induced endothelial barrier disruption is inhibited by compounds endowed with antioxidant activity, such as tiron, an $O_2^{\bullet -}$ scavenger (Li et al. 2005), apocynin, a NADPH oxidase inhibitor, and simvastatin (Freitas et al. 2020), some which have been proposed as potential therapeutic compound for CCM disease treatment.

Clearly, based on the above considerations it is reasonable to propose a contextual link between loss-of-function mutations in *KRIT1*, increased ROS/oxidative stress, and reduced VE-cadherin mediated adhesion.

3.2 Redox regulation of Rap1 and RhoA GTPases

A major role in KRIT1 loss-dependent destabilization of endothelial cell junctions and BBB integrity has been attributed to the modulation of small GTPases involved in cytoskeletal dynamics (Glading et al. 2007, Stockton et al. 2010). Indeed, apart from the phosphorylation status of VE-cadherin and catenins, the stability of AJs and permeability of endothelial barriers depend also on the architecture and dynamics of the junctional actin cytoskeleton, which are tightly controlled by the activity of small GTPases of the Ras and Rho families, including Rap1, RhoA, Rac1, and Cdc42 (van Buul and Timmerman 2016, Chrzanowska-Wodnicka 2017, Cerutti and Ridley 2017). In particular, Rap1 and RhoA exert crucial but antagonistic roles in the regulation of actin cytoskeletal rearrangements at VE-cadherin-based junctions, with consequent opposite effects on endothelial AJ dynamics and barrier permeability (Cerutti and Ridley 2017). In fact, while activation of Rap1 tightens cell-cell junctions by promoting AJ maturation and the formation of a cortical actin cytoskeletal belt (Kooistra et al. 2007, Boettner and Van Aelst 2009), activation of RhoA weakens cell-cell junctions by promoting AJ disassembly and the formation of contractile actin stress fibers (van Buul and Timmerman 2016, Cerutti and Ridley 2017). These opposite effects are mediated by distinct downstream effectors, including KRIT1, afadin/AF6, and Rac1/Cdc42 for Rap1, and Rho kinases (ROCKs) and mDia for RhoA (Boettner and Van Aelst 2009, Cerutti and Ridley 2017). Consistent with their antagonistic roles in the regulation of cell-cell adhesion, Rap1 inhibits leukocyte transendothelial migration (TEM) by promoting endothelial barrier function (Wittchen et al. 2005, Gaonac'h-Lovejoy et al. 2020), while RhoA promotes endothelial cell permeability to increase

leukocyte TEM in response to proinflammatory stimuli, such as TNF-α and bacterial LPS (Cernuda-Morollón and Ridley 2006, Cerutti and Ridley 2017).

Remarkably, the functions of Rap1 and RhoA have been shown to be reciprocally regulated (Moon et al. 2013, Birukova et al. 2013), and modulated by NOX-derived ROS (Wang et al. 2014, Mitchell et al. 2013, Hobbs et al. 2014), suggesting that these small GTPases engage in redox-dependent bidirectional crosstalk and feedback loops to orchestrate cell adhesion and cytoskeleton dynamics (Finkel 2006, Goitre et al. 2012, Ferro et al. 2014). Specifically, there is compelling evidence that active Rap1 increases endothelial barrier stability and inhibits TNF-α-induced angiogenesis by reducing NOX4 expression and NOX/ROS-dependent activation of NF-κB and β-catenin signaling (Wang et al. 2014, H. Wang et al. 2015, Wang et al. 2016, Li et al. 2018). On the other hand, the RhoA/ROCK1 signaling pathway is redox-sensitive and can be activated by NOX4-derived ROS (Meng et al. 2015, Huang et al. 2019). Consistently, apart from canonical regulators, such as guanine nucleotide exchange factors (GEFs), it has become apparent that RhoA can be directly activated by ROS through the reversible oxidation of critical cysteine residues located in a redox-sensitive motif within the conserved phosphoryl binding loop (p-loop) (Heo and Campbell 2005, Aghajanian et al. 2009). Moreover, RhoA activity is also regulated by the formation of specific redox-sensitive protein complexes in distinct subcellular compartments, which determine the precise spatiotemporal control of its multiple functions (Hodge and Ridley 2016, Navarro-Lérida et al. 2021). A major effect of the redox-dependent activation of RhoA is the activation of ROCK1 and the consequent formation of stress fibers, a well characterized readout of RhoA activity that affects fundamental cellular functions, such as cell-cell and cell-matrix adhesion, and plays a critical role in the pathogenesis of cardiovascular disorders, including CCM disease (Borikova et al. 2010, Stockton et al. 2010, Satoh et al. 2011, Hodge and Ridley 2016, Navarro-Lérida et al. 2021, Vannier et al. 2021).

The existence of a nexus between ROS generation and RhoA activation during endothelial barrier dysfunction and vascular remodeling has been indeed established (Karki and Birukov 2019), and is further supported by the finding that NOX4-derived ROS can activate the RhoA/ROCK1 signaling pathway (Meng et al. 2015, Huang et al. 2019) (Figure 5). In turn, given its major pathogenic role, the RhoA/ROCK pathway is considered an important therapeutic target in cardiovascular medicine (Satoh et al. 2011, Shi and Wei 2013, Shimokawa et al. 2016, Richardson et al. 2013, Shenkar et al. 2017). In fact, fasudil, a selective ROCK inhibitor, has been demonstrated to exert beneficial effects in many preclinical models of cardiovascular diseases, including CCM disease (Shi and Wei 2013, McDonald et al. 2012) (Table 2). However, growing evidence indicates that the protective effects of fasudil may be due to its strong antioxidant and anti-inflammatory activities,

including the capacity to suppress endothelial NOX upregulation and lipid peroxidation, to reduce the levels of inflammatory cytokines, and to induce eNOS expression and NRF2-mediated antioxidant responses (Higashi et al. 2003, Ma et al. 2011, Wang et al. 2018, Guan et al. 2018). Accordingly, there is evidence that ROCK1 can be directly downregulated by natural antioxidants, such as the phenolic compound protocatechuic acid (PCA) (Bai et al. 2021).

3.3 Redox regulation of integrin-mediated cell adhesion and actin cytoskeleton dynamics

The destabilization of AJs and increased endothelial permeability caused by KRIT1 loss-of-function was also linked to the upregulation of β1 integrin activation and consequent effects, including increased formation of β1 integrin–containing focal adhesions (FAs), enhanced RhoA-dependent endothelial contractility, and aberrant remodeling of the sub-endothelial extracellular matrix (ECM) (Faurobert et al. 2013) (Figure 3). Consistently, a characteristic feature of decreased endothelial barrier function is that the weakening of AJs is accompanied by increased formation of FAs and enhanced endothelial contractility and ECM remodeling, suggesting that these critical processes are controlled by integrated regulatory mechanisms, which likely include redox signaling (Ushio-Fukai 2009, Goitre et al. 2012, Sies and Jones 2020).

Accordingly, besides modulating VE-cadherin-mediated cell-cell adhesion, NOX-derived ROS are known to modulate also integrin-mediated cell-matrix adhesion, cytoskeleton dynamics and ECM remodeling (Ushio-Fukai 2009, Xu et al. 2017, Eble and de Rezende 2014, Vukelic et al. 2018, Balta et al. 2020), suggesting that they can orchestrate the established crosstalk between cadherins, integrins and the actin cytoskeleton (Balzac et al. 2005, Retta et al. 2006, Goitre et al. 2012) (Figure 5). Indeed, there is clear evidence that disassembly of cadherin-mediated AJs, formation of contractile actin stress fibers, and assembly of integrin-mediated FAs may occur synchronically through redox-dependent coupling mechanisms involving common regulatory proteins, including redox-sensitive kinases, phosphatases and small GTPases (Ushio-Fukai 2009, Goitre et al. 2012). In particular, either ROS-mediated inhibition of PTPs or activation of Src kinase have been shown to promote both AJ disassembly and FA assembly through increased phosphorylation of AJ and FA components, respectively (Lee et al. 2011, Knock and Ward 2011, Timmerman et al. 2012, Young et al. 2021). Furthermore, these events are coupled with activation of the RhoA/ROCK pathway and subsequent formation of contractile actin stress fibers, leading to increased endothelial cell contractility and vascular permeability (Chrzanowska-Wodnicka and Burridge 1996, Karki and Birukov 2019) (Figure 5). Consistent with their redox-dependent regulation, such molecular and cellular phenotypes can be reverted by ROS scavengers (Lin et al. 2003, Monaghan-Benson and Burridge 2009). In addition, there is evidence that integrin activation and outside-in signaling leads to a NOX4-mediated transient

584 increase in H_2O_2 production, which contributes to redox regulation of FA and stress fiber formation
585 (Vukelic et al. 2018). Accordingly, the formation of FAs requires the assembly of a redox signaling
586 platform involving multiple proteins, including integrins, growth factor receptors and NADPH
587 oxidases, which is essential for integrin adhesive and signaling functions (Ushio-Fukai 2009). In turn,
588 integrin-mediated activation of NOX/ROS signaling may affect cadherin adhesive functions via
589 multiple redox-sensitive regulatory proteins, suggesting potential mechanisms of redox-dependent
590 crosstalk between integrins and cadherins (Chiarugi et al. 2003, Usatyuk and Natarajan 2005, Goitre
591 et al. 2012, Ushio-Fukai 2009) (Figure 5).
592 In this context, it is relevant to consider the potential redox-dependent modulation of ICAP1, a
593 major binding partner and regulator of both KRIT1 and β1 integrin, which is known to dictate the
594 nuclear translocation of the ICAP1-KRIT1 complex (Draheim et al. 2017, Su et al. 2020), as well as
595 to inhibit β1 integrin-mediated adhesion and signaling (Degani et al. 2002, Bouvard et al. 2003, Liu
596 et al. 2013). Despite there is not yet evidence that ICAP1 is a target of redox signaling, the fact that
597 its subcellular localization and functions are controlled through regulatory phosphorylations mediated
598 by p21-activated kinase 4 (PAK4) and other protein kinases not yet identified (Chang et al. 1997, Su
599 et al. 2020) raises indeed the possibility that its functions are influenced at least indirectly by the
600 action of redox-sensitive kinases and/or phosphatases, a hypothesis that would warrant specific
601 investigation in future studies. Remarkably, consistent with an important regulatory role of redox
602 signaling in the nucleocytoplasmic shuttling of the ICAP1-KRIT1 complex, we have recently
603 demonstrated that PKC activation promotes a redox-dependent nucleocytoplasmic translocation of
604 KRIT1, whereas inhibition of PKC or treatment with the antioxidant N-acetylcysteine leads to KRIT1
605 nuclear accumulation (De Luca et al. 2021). Furthermore, we demonstrated that these redox-sensitive
606 effects rely on a PKC-dependent phosphorylation of the KRIT1 N-terminal region, which was
607 previously shown to play a major role in the open/closed conformation switch that regulates KRIT1
608 head-to-tail intramolecular interaction and intermolecular interactions with binding partners,
609 including Rap1, in a mutually exclusive manner (Francalanci et al. 2009). Further studies are needed
610 to test the interesting possibility that also KRIT1 intramolecular and intermolecular interactions are
611 redox-dependent.
612
613 **3.4 Redox regulation of endothelial-to-mesenchymal transition**
614 A major consequence of loss-of-function mutations of CCM genes in endothelial cells is an
615 enhanced tendency towards TGF-β-mediated endothelial-to-mesenchymal transition (EndMT)
616 (Maddaluno et al. 2013). EndMT is a process whereby endothelial cells loosen cell-cell junctions and
617 alter their cytoskeletal organization in response to a variety of stimuli. These include growth factors,

hypoxia, inflammation, oxidative stress, and abnormal shear stress, which eventually lead to a decrease in endothelial properties and the acquisition of mesenchymal features, such as a spindle-shaped morphology and contractile and migratory capacities (Bischoff 2019, Kovacic et al. 2019, Gao et al. 2020, Islam et al. 2021). TGF-β1 is considered the main EndMT inducer. However, other mechanisms besides the activation of the TGF-β pathway seem to be involved, including signaling pathways mediated by interleukin 6 (IL-6), bone morphogenetic protein (BMP), Wnt/β-catenin, and NOTCH, as well as alterations in fatty acid metabolism and autophagy deficiency (Rieder et al. 2011, Lin et al. 2012, Pérez et al. 2017, Piera-Velazquez and Jimenez 2019, Huang et al. 2021, Xiong et al. 2018, Takagaki et al. 2020). Initially observed to occur during cardiovascular development and tissue regeneration, EndMT is now recognized as a dynamic process that contributes to various human disorders, including inflammatory and cardiovascular diseases (van Meeteren and ten Dijke 2012, Kovacic et al. 2019, Piera-Velazquez and Jimenez 2019, Alvandi and Bischoff 2021, Huang et al. 2021).

Oxidative stress has emerged as a decisive factor in inducing EndMT through a TGF-β-dependent mechanism (Montorfano et al. 2014). Specifically, oxidative stress can promote EndMT by inducing expression, secretion and extracellular activation of TGF-β isoforms (Jobling et al. 2006, Montorfano et al. 2014). In turn, TGF-β has been shown to be a major inducer of NOX4 expression and activation in all cell types tested (Lassègue and Griendling 2010, Lassègue et al. 2012). Consistently, growing evidence indicates that NOX enzymes mediate many of the TGF-β effects and, in the opposite way, NOXs regulate TGF-β activity. This suggests the existence of a bidirectional crosstalk between TGF-β and NOX signaling (Figure 4), as well as potential feed-forward mechanisms between TGF-β and ROS in the development of human diseases (Crosas-Molist et al. 2015, Fernandez et al. 2015, Liu and Desai 2015, Thuan et al. 2018, Herranz-Itúrbide et al. 2021). Notably, EndMT can be attenuated or suppressed by either antioxidant compounds or autophagy inducers, suggesting that cellular antioxidant defenses, including activation of NRF2 signaling and autophagy, serve as cytoprotective mechanisms against EndMT (Chen et al. 2017, Zou et al. 2017, Ma et al. 2017, Takagaki et al. 2020, Giordo et al. 2021, Y. Li et al. 2021, Zhou et al. 2021). In particular, consistent with a major role of altered redox homeostasis and defective autophagy in CCM disease pathogenesis, both antioxidant compounds and autophagy inducers, such as tiron and rapamycin, were effective in rescuing EndMT phenotypes associated with KRIT1 loss-of-function (Marchi et al. 2016a, Retta and Glading 2016, Marchi et al. 2016b, Perrelli et al. 2021, Kim et al. 2020, Marchi et al. 2015, Goitre et al. 2017, Antognelli et al. 2018b, De Luca et al. 2018), and counteracting the burden of CCM lesions in animal models (Ren et al. 2021, Gibson et al. 2015).

3.5 Redox regulation of MAPK signaling

Another established mechanism elicited by loss-of-function mutations of CCM genes is the increased activation of mitogen-activated protein kinase (MAPK) signaling pathways, including JNK/c-Jun (Goitre et al. 2014) and MEKK3/MEK5/ERK5 (Cullere et al. 2015, Zhou et al. 2016, Cuttano et al. 2016), and consequent detrimental downstream effects, such as overexpression of COX-2 (Goitre et al. 2014) and KLF2/4 (Zhou et al. 2016, Cuttano et al. 2016), respectively (Table 1).

MAPK signaling cascades consist of three tier components, MAPK kinase kinase (MAPKKK), MAPK kinase (MAPKK) and MAPK, which are activated by sequential phosphorylations and eventually lead to the phosphorylation of target regulatory proteins. Four different MAPK cascades have been identified so far, and named after their MAPK components: ERK1/2, JNK, p38MAPK and ERK5. Remarkably, there is compelling evidence that ROS exert an important role in the sequential activation of all MAPK cascades. Indeed, distinct MAPK signaling pathways are activated by NOX-derived ROS via ROS-sensitive regulators, such as MAPK phosphatases (MKPs) (Kamata et al. 2005), being critically involved in cellular responses to various stimuli and environmental stresses (Torres 2003, Touyz et al. 2003, Veal et al. 2004, McCubrey et al. 2006, Taverne et al. 2013). In particular, the JNK, p38MAPK and ERK5 cascades have been shown to play a key role in redox signaling and cellular responses to oxidative stress (Torres 2003, Touyz et al. 2003, McCubrey et al. 2006, Lassègue and Griendling 2010, Taverne et al. 2013) (Figure 4). Both JNK and p38MAPK, also known as stress-activated protein kinases (SAPKs), can be activated by NOX4 (Djordjevic et al. 2005, Goettsch et al. 2009, Lassègue and Griendling 2010). In turn, redox regulation of these two major SAPKs has been implicated in ROS-dependent endothelial barrier dysfunction and vascular diseases (Usatyuk et al. 2003, Usatyuk and Natarajan 2004, Kyaw et al. 2001, Kyaw et al. 2002). Moreover, it has been shown that the activity of ERK5, also known as big MAP kinase 1 (BMK1), is induced to a greater extent by oxidants, including exogenous H_2O_2 and endogenous NOX-derived ROS, than by growth factors, suggesting that cellular redox signaling is a major driver of this pathway (Abe et al. 1996, Abe et al. 1997, Chao et al. 1999, Suzaki et al. 2002, Touyz et al. 2003, Zhao et al. 2011, Jiang et al. 2017). Furthermore, the MAPKKK apoptosis signal-regulating kinase 1 (ASK-1), an upstream regulator of JNK and p38MAPK signaling cascades, has been demonstrated to be preferentially activated by oxidative stress (Saitoh et al. 1998, Katagiri et al. 2010, Kim et al. 2008, Jarvis et al. 2012). Consistent with a crucial role of redox-dependent mechanisms, cell treatments with antioxidant compounds were effective in rescuing both the activating phosphorylation of JNK and ERK5, and the consequent upregulation of downstream targets, including respectively c-Jun and

KLF4 transcription factors, caused by KRIT1 loss-of-function (Goitre et al. 2014, Antognelli et al. 2018b).

4. CCM disease from a redox perspective: a unifying hypothesis for distinct pathogenetic mechanisms and therapeutic approaches

This review has been focused primarily on *CCM1*/*KRIT1*, the major causative gene for CCM disease, in the attempt to effectively highlight and comprehensively contextualize the compelling evidence for its pleiotropic physiopathological functions and significant involvement in redox biology. Indeed, in the light of the considerations set out in previous sections, it is possible to envisage a unifying scenario whereby KRIT1 exerts its crucial role in the maintenance of endothelial cell homeostasis and barrier function through the coordinated regulation of key redox-sensitive mechanisms, including NOX/ROS-dependent ox-PTMs of redox-sensitive proteins involved in the functional crosstalk between cadherins and integrins (Figure 6). These aspects could be easily extrapolated to the other two identified CCM proteins, CCM2 and CCM3, as they are known to form a molecular complex with KRIT1 and participate in almost the same regulatory mechanisms (Fisher and Boggon 2014). However, a brief overview of the existing evidence for a significant involvement in redox mechanisms of these and other proteins so far associated with CCM disease is also provided.

4.1 Existing evidence for the involvement of *CCM2* and *CCM3* in redox biology

Although the involvement of *CCM2* and *CCM3* genes in redox biology has been much less extensively and thoroughly examined, there are several lines of evidence that support such involvement. Specifically, the deficiency of either CCM2 or CCM3 proteins has been shown to cause defective autophagy, mitochondrial dysfunction and altered redox homeostasis similarly to KRIT1 deficiency (Marchi et al. 2015). Moreover, compounds endowed with ROS scavenging properties were identified by unbiased screenings as effective in rescuing major pathological phenotypes caused by the conditional knockout of *CCM2* in mouse models, including actin cytoskeleton and cell-cell adhesion alterations, enhanced vascular permeability, and formation of CCM lesions, suggesting that such CCM2 loss-of-function effects are indeed redox-dependent (Gibson et al. 2015). In addition, a specific role for CCM3 in protecting cells against oxidative stress was previously reported by Zalvide's research group, who demonstrated that CCM3 protects cells from apoptosis induced by oxidative stress and prevent the development of CCM lesions through the activation of serine/threonine kinases of the germinal center kinase III (GCKIII) family, including MST4/STK26, MST3/STK24 and SOK1/STK25 (Fidalgo et al. 2012, Sartages et al. 2022). Consistently, members of the GCKIII family, as well as other components of the striatin-interacting phosphatase and kinase

(STRIPAK) supramolecular complex in which they are involved together with CCM3, including the serine/threonine protein phosphatase 2A (PP2A), have been clearly implicated in cellular responses to oxidative stress and inflammation (Jiao et al. 2015, Elgenaidi and Spiers 2019, Pombo et al. 1996).

4.2 A unifying redox scenario for CCM disease pathogenesis and treatment: lessons from basic mechanisms and therapeutic approaches

ROS and the oxidative stress they produce have been extensively linked to vascular barrier function, vascular pathology, and the inflammatory response; thus, given the original discovery that KRIT1 loss-of-function leads to enhanced levels of intracellular ROS and cell susceptibility to oxidative stress (Goitre et al. 2010), it has been straightforward to predict that increased oxidative stress contributes to the loss of endothelial barrier function in CCM. In fact, several studies support the idea that blocking oxidative stress could be effective at preventing the increase in endothelial permeability caused by the loss of CCM proteins and affect the clinical impact of the disease. Vitamin D3, a well described antioxidant, restores barrier function of KRIT1 and CCM2 deficient cells and reduces CCM-like lesion formation in mouse models of CCM (Gibson et al. 2015). Tempol, a membrane-permeable radical scavenger and metal-independent SOD-mimetic, can similarly rescue endothelial barrier function and limit lesion formation (Gibson et al. 2015). In addition, we have shown that directly targeting the endothelium with antioxidant enzymes is sufficient to reverse the increased permeability in KRIT1 heterozygote mice, as does treatment with recombinant avenanthramides, a plant-based antioxidant (Goitre et al. 2017). These data indicate that limiting oxidative stress can restore endothelial barrier function and limit lesion growth in CCM protein-deficient cells and animals, and strongly suggest that antioxidants could be a fruitful pharmaceutical therapy for CCM.

Currently, the potential therapeutics in development for treatment of CCM disease target specific signaling pathways activated by the loss of CCM protein expression (Table 2). Yet many, if not all, of these therapeutics and their cognate pathways also impact, or are impacted by, the level of oxidative stress in the endothelium. For example, inhibition of RhoA and ROCK has been shown to restore endothelial barrier function and limit lesion formation in CCM deficient cells and animals. As described in section 3.2 above, RhoA is activated by ROS (Heo and Campbell 2005), and activates ROCK to promote the formation of contractile actomyosin stress fibers and the downregulation of cortical actin meshworks implicated in the dynamics of cell-matrix and cell-cell contacts (Marcos-Ramiro et al. 2014, Yao et al. 2010). It has been suggested that KRIT1 promotes a complex at the plasma membrane between ROCK2 and VE-cadherin that stabilizes cell-cell contacts and limits stress fiber formation downstream of ROCK1 (Lisowska et al. 2018). Therefore, in KRIT1 depleted cells,

activation of RhoA by ROS could trigger activation of ROCK1, leading to increased cellular contractility and subsequent loss of barrier function (Figure 6). Consequently, RhoA and ROCK inhibitors have attracted much attention as a possible treatment for CCM. The statin class of drugs, which inhibit HMG CoA reductase and block RhoA, have been extensively tested in pre-clinical models of CCM, but have had limited success at reducing lesion burden. However, an inhibitor of ROCK, fasudil, blocks stress fiber formation and reduces endothelial permeability in cells lacking KRIT1, CCM2, or CCM3 (Shenkar et al. 2019, Shenkar et al. 2017, Stockton et al. 2010, McDonald et al. 2012). *In vivo*, treatment of CCM3 deficient animals with fasudil reduces lesion formation and perilesional iron deposition, a marker of local hemorrhage and an indirect marker of endothelial barrier function (Shenkar et al. 2019). Notably, fasudil also exerts Rho-independent antioxidant effects on the endothelium *in vivo* by elevating the activities of antioxidant enzymes and reducing activation of NF-κB (Wang et al. 2018, Ma et al. 2011). Thus, the ability of fasudil to limit oxidative stress could also contribute to its ability to restoration of vascular homeostasis in CCM models. More recently, loss-of-function mutations in the Rho family GTPase Cdc42, which antagonizes RhoA and contributes to the formation of cortical actin structures that promote cell-cell contact stability (Wojciak-Stothard and Ridley 2002), has been show to stimulate MEKK3/ERK5/KLF signaling in brain endothelial cells and the formation of CCM-like lesions in mice (Castro et al. 2019). Cdc42, like RhoA, contains a conserved redox-sensitive motif that promotes nucleotide exchange, leading to GTPase activation (Heo and Campbell 2005); however, based on current knowledge, activation of Cdc42 by ROS would be predicted to promote barrier function and rescue CCM lesion formation. There may be a functional difference in ROS-dependent activation of these GTPases, as RhoA contains two redox-sensitive sites, and Cdc42 just one, and oxidative stress also activates RhoA by PKC-dependent phosphorylation and activation of p115RhoGEF (Chandra et al. 2012). Interestingly, Cdc42 also competes with the related GTPase Rac1 to bind to flavocytochrome b558 (Diebold et al. 2004), which antagonizes the ROS-producing capabilities of Rac1. Thus, loss of Cdc42 may also indirectly increase ROS production, however the contribution of such a signaling mechanism to the Cdc42-dependent formation of CCM-like lesions is not yet established.

Yet another redox-sensitive pathway active in CCM is the activation of VEGFR2 signaling (Abe et al. 2009), which regulates cell-cell contacts via both direct and indirect mechanisms. Distefano et al reported that loss of KRIT1 activates VEGFR2 signaling, leading to phosphorylation of β-catenin (DiStefano et al. 2014), a known direct mechanism regulating AJ stability. Inhibition of VEGFR2 activity reduced CCM-like lesion formation and lesion hemorrhage by 50%, and had an even stronger effect on vascular permeability, which it restored to wildtype levels (DiStefano and Glading 2020). Activation of VEGFR2 signaling likely occurs via up-regulation of VEGF-A

expression, which could occur downstream of increased β-catenin dependent transcription (DiStefano et al. 2014), or via upregulation of KLF2/4 (Y. Wang et al. 2015). VEGF-A expression is also increased by oxidative stress via the activation of NADPH oxidases NOX2 and NOX4. In turn, increased VEGFR2 signaling promotes activation of NOX2 via activation PI3K, which subsequently activates the small GTPase Rac1 (Monaghan-Benson and Burridge 2009). Thus, VEGF signaling is a critical nexus for the effects of oxidative stress in the endothelium, and is a potential target for CCM treatment.

Lastly, the MAPK cascades known to be activated upon deletion of CCM proteins are also regulated by ROS and oxidative stress, including p38MAPK (Usatyuk et al. 2003), JNK (Makarenko et al. 2014) and ERK5 (Foncea et al. 2000, Abe et al. 1996), and their activation has been shown to increase endothelial permeability downstream of ROS production. These parallel MAPK pathways are centrally regulated by CCM2, which binds to the respective upstream kinases MKK3 and MEKK3 (Zhou et al. 2016, Uhlik et al. 2003). Indeed, CCM2 was originally identified as a scaffold protein for MEKK3 activation induced by hyperosmotic shock (Uhlik et al. 2003), and subsequently shown to bind the N-terminal regulatory domain of MEKK3 in a complex with KRIT1, thereby interfering with its activation by autophosphorylation and resulting in a negative regulation of MEKK3-dependent signaling pathways, including the MEKK3-MEK5-ERK5 cascade (Cullere et al. 2015, Fisher et al. 2015, X. Wang et al. 2015). On the other hand, CCM2 deletion in endothelial cells leads to the spontaneous activation of MEKK3, owing to its ability to autophosphorylate critical residues necessary for its kinase activity (Fritz et al. 2006), with the consequent activation of ERK5 and downstream transcriptional program (Cullere et al. 2015). Remarkably, while these considerations suggest that MEKK3 activation requires the release of CCM2-dependent inhibitory restraint, there is compelling evidence that MEKK3 pathways can be activated by ROS independently of CCM2 deficiency (Son et al. 2011). Thus, despite these ROS-dependent activatory effects are likely limited, although not prevented, by CCM2 binding to MEKK3, they may potentially synergize with the effects of loss-of-function mutations in CCM genes, leading to a dramatically enhanced and sustained activation of MEKK3 signaling. On the other hand, activation of the MEKK3 effector kinase BMK1/ERK5 appears to be an important compensatory response to increased endothelial ROS, and limits the endothelial response to inflammatory stimuli (K. Wu et al. 2013). Indeed, there is evidence that ERK5 can act as a rheostat for varying levels of ROS, as endothelial treatment with low, but not high, levels of H_2O_2 promotes angiogenesis in an ERK5-dependent manner (Jiang et al. 2017). Furthermore, besides ERK5 (Chao et al. 1999), MEKK3 signaling is known to regulate gene expression through other downstream effectors, including p38MAPK and JNK (Deacon and Blank 1999), leading to the common activation of NF-κB-dependent transcription.

ERK5 also activates members of the Krüppel-like factor (KLF) family of transcription factors, including KLF2 and KLF4, which are thought to mediate most of the vasoprotective effects of ERK5 activation (Villarreal et al. 2010). KLF2/4 have been most commonly studied in the context of arterial endothelium, where they are up-regulated by shear stress, and confer vascular protection via regulation of gene programs that result in an anti-inflammatory, anti-coagulant, anti-adhesive, anti-oxidant state of the endothelium, thus serving as guardians of endothelial health against various stress conditions, including oxidative stress and inflammation (Chen et al. 2015, Hamik and Jain 2012). However, the consequence of up-regulation of KLF2/4 in brain microvessels is less clear. KLF4 is up-regulated in models of ischemic stroke and protects against cerebrovascular injury, likely via promoting claudin-5 expression (X. Zhang et al. 2020). Similarly, KLF2 overexpressing mice are protected against ischemic stroke and express higher amounts of the tight junction protein occluding (Shi et al. 2013). On the other hand, in CCM models, MEKK3-dependent upregulation of KLF2/4 has been associated with CCM lesion formation (Zhou et al. 2016) as well as with changes in intracellular signaling that may promote vascular dysfunction [e.g., increased β1 integrin activation (Renz et al. 2015), endothelial proliferation (Cuttano et al. 2016), and altered extracellular matrix deposition (Hong et al. 2020, Lopez-Ramirez et al. 2017)] (Table 1). However, it is noteworthy that only partial downregulation of MEKK3, including *Map3k3* haploinsufficiency in mice and 40% MEKK3 knockdown by low dose morpholinos in zebrafish, was effective in rescuing cardiovascular phenotypes associated with loss of CCM signaling (Zhou et al. 2015, Zhou et al. 2016), which leaves the data open to alternative interpretation. In particular, the KRIT1 loss-dependent and MEKK3-mediated upregulation of the anti-inflammatory transcription factors KLF2 and KLF4, two established and evolutionary conserved master regulators of endothelial homeostasis and defense against stressful conditions (Sweet et al. 2021), might be part of adaptive mechanisms that circumvent endothelial cell apoptosis by preventing positive feedback loops of abnormal ROS and inflammatory cytokine production. Indeed, similarly to the KRIT1 loss-dependent upregulation of the master antioxidant transcription factor NRF2 (Antognelli et al. 2018b, Antognelli et al. 2018a), the sustained upregulation of KLF2/4 and cytoprotective target genes might contribute to the ability of endothelial cells to counteract the development of a vicious circle between oxidative stress and inflammation, which would cause irreversible injury and subsequent cell death. Nonetheless, while preventing apoptosis, the chronic adaptive homeostasis promoted by cytoprotective transcription factors, including KLF2/4 and NRF2, may also cause side effects that eventually increase endothelial cell susceptibility to additional oxidative and inflammatory challenges (Antognelli et al. 2018a) (Figure 6). Consistently, miR27a, which downregulates VE-cadherin expression, was shown to be activated downstream of increased KLF2/4 signaling in CCM depleted cells (Li et al. 2020). Furthermore,

whereas there is evidence for synergistic activity of KLF and NRF2 transcription factors, which contributes to the expression of a cytoprotective transcriptome in endothelial cells (Fledderus et al. 2008), it is also known that recurrent oxidative stress and inflammation lead to cumulative damages, maladaptation and ultimately disease pathogenesis, despite the existence of such cytoprotective mechanisms (Alleman et al. 2014). Although the above considerations provide a plausible solution, the apparent contradiction between the role of KLF2/4 in the formation of CCM and the vasoprotective role of these transcription factors in other *in vivo* disease models remains a puzzle. It may be an important puzzle to solve, however, as statins, HMG CoA reductase inhibitors widely used to treat coronary artery disease and under consideration for treatment of CCM, upregulate KFL2/4 expression in at least some types of endothelial cells (K. Wu et al. 2013), and have demonstrated mixed effects in pre-clinical studies of CCM (Shenkar et al. 2017, Gibson et al. 2015). Furthermore, while a partial genetic downregulation of MEKK3/ERK5 signaling was effective at reducing lesion formation (Zhou et al. 2016), MEKK3 and ERK5 inhibitors have shown limited efficacy in pre-clinical models (Zhou et al. 2016, Choi et al. 2018).

4.3 Novel players in the CCM redox scenario

Aside from the implication of the distinct pathways mentioned above, recent reports showed that activating mutations in genes encoding the PI3K catalytic subunit alpha (PI3KCA) and the serine/threonine kinase Akt (also known as protein kinase B) are frequently found in sporadic CCM tissues in the absence of mutations in known CCM genes, suggesting that CCM lesions may occur either dependently or independently of loss-of-function mutations in CCM genes (Peyre et al. 2021, Weng et al. 2021, Hong et al. 2021, Ren et al. 2021). Consistently, whereas we previously showed that KRIT1 loss-of-function causes activation of the PI3K/Akt signaling pathway and Akt-mediated downregulation of FoxO1 (Goitre et al. 2010), one of these studies demonstrated that gain-of-function mutations in *PI3KCA* can drive CCM lesion formation in mice, pointing to a crucial implication of the PI3K/Akt/mTOR signaling pathway (Ren et al. 2021). Indeed, it was also reported that inhibition of the mTOR complex 1 (mTORC1) by rapamycin was highly effective in reducing CCM lesion burden (Ren et al. 2021), a consequence originally suggested by our previous studies demonstrating that mTORC1 inhibition by rapamycin reverts the molecular and cellular hallmarks of CCM disease (Marchi et al. 2015, De Luca et al. 2018). Not surprisingly, the PI3K/Akt/mTOR pathway is clearly implicated in redox signaling and oxidative stress. In particular, PI3K stimulates NOX2 activation via Rac (Monaghan-Benson and Burridge 2009) and mTORC1 increases ROS generation and pro-oxidant gene expression via activation of NF-κB (Reho et al. 2019). Conversely, it is well established that hyperactivation of the PI3K/Akt/mTOR signaling pathway can occur as a consequence of

NOX/ROS-mediated oxidative inactivation of its negative regulator PTEN, a critical redox-sensitive phosphatase that dephosphorylates phosphatidylinositol (3, 4, 5)-trisphosphate (PIP3) to phosphatidylinositol (4, 5)-bisphosphate (PIP2), thereby leading to inhibition of PI3K-dependent signaling (K. L. Wu et al. 2013, Y. Zhang et al. 2020). Redox regulation of PTEN by ROS is due to the presence of a cysteine residue in the active site, which can be oxidized by peroxides forming an intramolecular disulfide bond, and actually plays a crucial role in cellular signaling (Nguyen Huu et al. 2021). Furthermore, PI3K/Akt signaling can be enhanced also by oxidative inhibition of the redox-sensitive serine/threonine phosphatase PP2A, a negative regulator of Akt (Nguyen Huu et al. 2021, Raman and Pervaiz 2019) (Figure 4).

In this context, our recent identification of potentially causative germline variants in *PTEN* and *NOTCH3* genes in fCCM cases assumes considerable relevance (Benedetti et al. 2022). Indeed, loss-of-function mutations or oxidative inactivation of PTEN have been shown to cause the hyperactivation of Akt and consequent modulation of its downstream targets, including activation of mTOR and inhibition of FoxO1, leading to increased angiogenic responses and enhanced cell sensitivity to oxidative stress (Lee et al. 2002, Kwon et al. 2004, K. L. Wu et al. 2013, Shen et al. 2015, Y. Zhang et al. 2020, Nguyen Huu et al. 2021). In particular, there is evidence that oxidative inactivation of PTEN in response to increased production of mitochondrial H_2O_2 enhances PI3K/Akt signaling, leading to increased expression of VEGF and induction of the angiogenic switch, whereas PTEN overexpression prevents these effects (Connor et al. 2005). Accordingly, PTEN was reported to exert antioxidant effects by inactivating Akt and stimulating autophagy (Inglés et al. 2014, Kma and Baruah 2022, Chang et al. 2022). Remarkably, both mTOR activation and FoxO1 inhibition were originally demonstrated to be induced by loss-of-function of CCM proteins (Goitre et al. 2010, Marchi et al. 2015), suggesting that mTOR activation and FoxO1 inhibition consequent to mutational or oxidative inactivation of PTEN may indeed contribute to CCM disease pathogenesis.

On the other hand, whereas the downregulation NOTCH signaling has been clearly linked to CCM protein loss-of-function effects and CCM disease pathogenesis (Wüstehube et al. 2010, You et al. 2013, Schulz et al. 2015), there is also evidence that such a downregulation is redox dependent and can be rescued by antioxidant treatment (Vieceli Dalla Sega et al. 2019). Consistently, it has been recently reported that *NOTCH3* knockdown causes an increase in ROS and lipid peroxidation levels, accompanied by downregulation of glutathione peroxidase 4 (GPX4) and peroxiredoxin 6 (PRDX6) (Li et al. 2022). Furthermore, *NOTCH3* mutations have been shown to cause NADPH oxidase (NOX5) activation, superoxide production, and aberrant upregulation of the RhoA/ROCK pathway, leading to altered actin cytoskeleton organization and impaired pericyte-endothelial interactions (Neves et al. 2019) as well as to increased cell sensitivity to stressful conditions, including oxidative

stress (Takahashi et al. 2010). Intriguingly, the possibility that either *NOTCH3* or *PTEN* inactivating mutations contribute to CCM disease pathogenesis and severity is consistent with the recent discovery that NOTCH3 can transactivate PTEN and inhibit the PTEN downstream Akt/mTOR pathway (Zhang et al. 2021).

Overall, the recent identification of putative causative mutations in genes distinct from the three known CCM genes suggest that the genetic basis of CCM disease can be more complex than previously thought. On the other hand, taken together with the existing evidence that the proteins encoded by CCM genes and other genes so far associated with CCM disease share a common involvement in cellular redox homeostasis and/or signaling, the emerging complexity of CCM disease pathophysiology points to a unifying scenario where ROS and redox mechanisms take center stage to orchestrate the underlying molecular symphony.

Besides expanding the spectrum of potential causative genes linked to CCM disease, the recent findings described above raise also the intriguing hypothesis that CCM lesions may arise independently of gene mutations, mainly as a consequence of a combination between inter-individual genetic variability in sensitivity to oxy-inflammatory conditions and local increases in such conditions. Consistently, distinct genetic modifiers of endothelial cell responses to oxidative stress and inflammation, including polymorphic variants of distinct members of the CYP, MMP and TLR4 gene families, have been reported to impact the onset and severity of CCM disease (Hong et al. 2021, Fisher et al. 2020, Glading and Ginsberg 2010, Marchi et al. 2016a). Furthermore, whereas recent studies demonstrate that mutations in CCM genes rarely occur in human sporadic CCM lesions (Perrelli and Retta 2021, Choquet et al. 2015, Tournier-Lasserve 2020), we have recently suggested a major role for pro-inflammatory microenvironmental conditions generated by cerebral developmental venous anomalies (DVAs) in the secondary formation of sporadic CCM lesions, which are frequently associated with DVAs (Benedetti et al. 2022). In this context, it is noteworthy that the possibility that sporadic CCM lesions may develop independently of CCM gene mutations is also supported by the recent evidence that somatic mutations in CCM genes are rarely detected in the surgical specimens of human sporadic CCM lesions (Perrelli and Retta 2021, Choquet et al. 2015, Tournier-Lasserve 2020). Distinct genetic modifiers of endothelial cell responses to oxidative stress and inflammation, including polymorphic variants of distinct members of the CYP, MMP and TLR4 gene families, have been indeed reported to impact the severity of CCM disease (Hong et al. 2021, Fisher et al. 2020, Glading and Ginsberg 2010, Marchi et al. 2016a).

While further studies are required to address and clarify the role of the emerging new players in the complex molecular scenario underlying CCM disease pathogenesis, the comprehensive redox-

centered view provided by this review may pave the way forward to exploring their potential relationships.

4.4 A redox-centered view of the action of current therapeutic candidates for CCM disease

Overall, while the rescue of CCM-deficient phenotypes in cellular and animal models by a variety of novel or repurposed therapeutic candidates demonstrates a causal role for multiple signaling pathways in CCM disease pathogenesis, accumulated evidence suggests that such a rescue could be secondary to the normalization of defective autophagy and adaptive oxy-inflammatory responses. In turn, this may point to the need of any potential CCM treatment to promote such a normalization, and suggests that therapeutic evaluation of potential CCM treatments should incorporate assessment of their effect on redox homeostasis and signaling. Accordingly, the different therapeutic candidates for CCM disease proposed so far, including statins, fasudil, tempol, vitamin D, sulindac metabolites, rapamycin and propranolol, share potent antioxidant, anti-inflammatory, and/or pro-autophagic activities (Table 2), suggesting that their reported effectiveness in limiting CCM lesion formation and severity may be related to such properties (Retta et al. 2020, Perrelli et al. 2021, Marchi et al. 2016b). In particular, these biological activities are clearly exhibited by both atorvastatin (Lipitor) and propranolol, the two therapeutic candidates that are currently tested in exploratory clinical trials (Polster et al. 2018, Lanfranconi et al. 2020). In fact, it is well established that statins, including atorvastatin, promote potent systemic antioxidant and anti-inflammatory effects (Shishehbor et al. 2003, Davignon et al. 2004, Pignatelli et al. 2012), and can activate autophagy via the Akt/mTOR pathway (W. Wang et al. 2015, Zhang et al. 2012). Similarly, propranolol has potent antioxidant and anti-inflammatory capacities (Mak and Weglicki 2004, Lin et al. 2020), which are crucial for its anti-angiogenic activities (Lopes-Coelho et al. 2021), and has been shown to exert a protective effect against apoptosis by triggering autophagy (Zhao et al. 2020).

5. Concluding remarks and future perspectives

Since its original identification as an interactor of the small GTPase Rap1 (Serebriiskii et al. 1997), and the subsequent discovery of its implication in CCM disease pathogenesis (Laberge-le Couteulx et al. 1999, Sahoo et al. 1999), KRIT1 has progressively emerged as a key player in multiple molecular and cellular mechanisms involved in the maintenance of endothelial barrier integrity and function (Retta et al. 2020). Consistent with its pleiotropic functions, KRIT1 has been implicated in the functional modulation of various signaling proteins and transcription factors, including VE-cadherin/β-catenin, β1 integrin, RhoA/ROCK, NOTCH, VEGF/VEGFR2, TGF-β/BMP, NOXs, MAPKs, mTOR, KLFs, FoxO1, c-Jun, NF-κB, and NRF2 (Retta et al. 2020) (Table 1). However, the

mechanistic interconnection and causal prioritization between these molecular and cellular functions of KRIT1 have remained largely elusive. On the other hand, a unifying perspective has been unlocked over the past decade by original discoveries in cellular and animal models demonstrating a major involvement of KRIT1 in redox biology and suggesting that its loss-of-function affects redox-sensitive mechanisms that orchestrate the crosstalk between cadherins and integrins, including the NOX/ROS-dependent signaling network involved in AJ, FA and actin cytoskeleton dynamics (Goitre et al. 2010, Retta and Glading 2016, Retta et al. 2020) (Figure 6).

In this review we provide compelling evidence that virtually all the multiple signaling pathways and mechanisms hitherto implicated in KRIT1 functions and dysfunctional effects associated with CCM disease pathogenesis are redox-sensitive and may occur in a coordinated fashion through the pleiotropic action of redox signaling. In this light, it is now becoming clear that most effects of KRIT1 loss-of-function are part of an abnormal adaptive response to impaired redox homeostasis and defective autophagy (Retta and Glading 2016), including the sustained upregulation of transcription factors known to be cytoprotective in normal conditions, such as KLF2/4 (Cuttano et al. 2016, Zhou et al. 2016) and NRF2 (Antognelli et al. 2018b, Antognelli et al. 2018a) (Figure 6). In fact, growing evidence suggests that the persistent activation of antioxidant and anti-inflammatory transcription factors, including NRF2 and KLFs, can result in abnormal adaptive responses that paradoxically sustains oxidative stress effects despite the concomitant enhancement of antioxidant defenses, leading to increased cell susceptibility to additional oxidative and inflammatory insults and consequent pathological conditions (Antognelli et al. 2018a, Zucker et al. 2014, Retta and Glading 2016). Consistently, there is compelling evidence that when ROS levels deviate uncontrollably either above or below physiological thresholds, they may adversely affect cells and organisms, causing pathological conditions (Yu et al. 2014, Korge et al. 2015, Handy and Loscalzo 2017, Xiao and Loscalzo 2020, Schieber and Chandel 2014). This may explain some of the negative results from clinical trials in which large doses of exogenously administered antioxidants or hyperactivation of antioxidant pathways with electrophilic therapeutics failed to improve outcomes of vascular diseases or resulted in negative effects (Dodson et al. 2015, Johansen et al. 2005, Xiao and Loscalzo 2020).

The hormetic physiological response to ROS should be therefore carefully considered when interpreting experimental results and developing therapeutic strategies for CCM, including approaches based on the administration of pharmacological compounds endowed with antioxidant properties (Dodson et al. 2015, Johansen et al. 2005) (Figure 7). Emerging evidence demonstrates in fact that only intermediate levels and moderate activation of major regulators of antioxidant responses, including cytoprotective transcription factors and autophagy, are beneficial, with either excessive or insufficient activation being instead deleterious (Dodson et al. 2015, Vomund et al. 2017,

Forte et al. 2017) (Figure 7). These considerations may also explain the apparent paradox that both loss-of-function (Fisher et al. 2015) and gain-of-function (Zhou et al. 2016) of MEKK3, a major upstream regulator of KLF2/4, result in similar effects, including increased Rho/ROCK activity, impairment of neurovascular integrity, and brain blood vessel leakage, while intermediate levels seem to be beneficial for the homeostasis of brain vasculature (Zhou et al. 2016).

Regardless, the above considerations highlight the complexity of developing therapies that affect the intricately connected redox systems. Despite the potential beneficial effects of antioxidant and pro-autophagic compounds, precision medicine approaches are strictly required to ensure that activation of antioxidant responses and autophagy are restrained to moderate, protective levels (Dodson et al. 2015, Forte et al. 2017). In this light, combination therapy strategies based on the target delivery and controlled release of both antioxidant and pro-autophagic compounds through nanotechnology approaches might represent a promising option for a safe and effective pharmacological treatment (Retta et al. 2020, Perrelli et al. 2021). Future studies aimed at a better understanding of adaptive cellular control systems and hormetic responses to ROS and oxidative stress, including the role of CCM genes in the regulation of the complex interplay between autophagy, cytoprotective transcription factors, and oxy-inflammatory responses, should facilitate the development of innovative therapeutic strategies that maintain redox systems within the "Goldilocks Zone" (Alleman et al. 2014), thus avoiding adverse outcomes (Figure 7).

Abbreviations

AJ	adherens junction
AP-1	activator protein 1
ASK-1	apoptosis signal-regulating kinase 1
BBB	blood-brain barrier
BMP	bone morphogenetic protein
CCM	Cerebral Cavernous Malformation
DAMPs	damage associated molecular patterns
DUSPs	dual-specificity phosphatases
ECM	extracellular matrix
ERK5	extracellular signal-regulated kinase 5
FA	focal adhesion
FoxO1	forkhead box O1
HIF-1	hypoxia-inducible factor-1
ICAM-1	intercellular adhesion molecule-1
JNK	c-Jun N-terminal kinase
KLF	Kruppel-like factor
LPS	lipopolysaccharide
MAPK	mitogen-activated protein kinase
MEKK3	mitogen-activated protein kinase kinase kinase 3
MEK5	mitogen-activated protein kinase kinase 5
MKPs	mitogen-activated protein kinase phosphatases
mTOR	mechanistic target of rapamycin
NF-κB	nuclear factor-kappaB
NOX	NADPH oxidase
NRF2	nuclear factor E2-related factor 2
PAMPs	pathogen associated molecular patterns
PECAM-1	platelet endothelial cell adhesion molecule-1
PSKs	protein serine/threonine kinases
PSPs	protein serine/threonine phosphatases
PTEN	phosphatase and tensin homolog deleted on chromosome 10
PTKs	protein tyrosine kinases
PTPs	protein tyrosine phosphatases
ROS	reactive oxygen species

1076	SHP-2	Src homology-2 domain-containing tyrosine phosphatase 2
1077	SOD	superoxide dismutase
1078	TGF-β	transforming growth factor-beta
1079	TJ	tight junctions
1080	TLR4	toll-like receptor 4
1081	TNF-α	tumor necrosis factor-α
1082	VCAM-1	vascular cell adhesion molecule-1
1083	VEGF	vascular endothelial growth factor
1084	VEGFR2	vascular endothelial growth factor receptor 2

Acknowledgments

The authors are grateful to CCM Italia, the Italian Research Network for Cerebral Cavernous Malformation (https://www.ccmitalia.unito.it), and the Associazione Italiana Angiomi Cavernosi (AIAC) Onlus (https://www.aiac.unito.it), including its president Massimo Chiesa, for fundamental support. The authors gratefully acknowledge also Ing. Nicola Retta for his help in figure drawing, Dr. Luca Goitre, Cristina Panuzzo, Gaudenzio Inverso, Alessandra Bordon and Parisa Fatehbasharzad for significant research cooperation, and Francesca Retta, Alessandro Retta, Santa Barbaro, and Alberto Ragni for helpful discussion. This article is dedicated to the memory of Rosa Giunta, Fortunato Barbaro, and Piero Ragni.

Authors' Contributions

Study conception and planning: SFR; conceptualization: SFR and AG; writing-original draft preparation: SFR, AG and AP; figure preparation: CF, AP, EB and SFR; writing-review and editing: SFR, AG, and AP; supervision: SFR. All authors have read and agreed to the submitted version of the manuscript.

Financial Support and Sponsorship

This work was supported by the Telethon Foundation (grant GGP15219 to S.F.R.), the Fondazione CRT (Cassa di Risparmio di Torino) (project grant “Cerebro-NGS.TO” to S.F.R.), the Università degli Studi di Torino (Local Research Funding to S.F.R.), and the National Institutes of Health (HL117885 and HL141131 grants to AJG).

Conflict of interest

The authors declare no conflict of interest.

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