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Cerebral Cavernous Malformations (CCM)

Methods and Protocols

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Cover Illustration Caption: Schematic representation of the major experimental approaches used for understanding the pathobiology of CCM disease, including genetics and molecular and structural biology research; studies on cellular models and blood vessels; biological and biomedical research in animal models of distinct species, such as nematode worm (*Caenorhabditis elegans*), fruit fly (*Drosophila melanogaster*), zebrafish (*Danio rerio*), and mouse (*Mus musculus*); and clinical and research studies in human beings. The artwork was conceived by Saverio Francesco Retta and realized by the graphic designer Fabio Zanchetta.

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Preface

Cerebral Cavernous Malformation (CCM) is a major cerebrovascular disease of proven genetic origin consisting of closely clustered, abnormally dilated and leaky capillary channels (caverns) lined by a thin endothelial layer.

CCM disease may arise sporadically or is inherited as an autosomal dominant condition with incomplete penetrance and highly variable expressivity. The familial form has been linked to loss-of-function mutations in any of three known CCM genes, *CCM1/KRIT1*, *CCM2* and *CCM3/PDCD10*.

CCM lesions exhibit a range of different phenotypes, including wide inter-individual differences in lesion number, size, and susceptibility to intracerebral hemorrhage. Lesions may remain asymptomatic or result in pathological conditions of various type and severity at any age, with symptoms ranging from recurrent headaches to severe neurological deficits, seizures, and stroke.

Although significant advances have been made toward understanding the natural history and pathogenic mechanisms of CCM disease, the clinical behavior in individual patients is highly unpredictable. Identification of modifiable risk factors of prognostic value associated with clinical severity of CCM disease is therefore needed to ultimately provide better options for disease prevention and treatment. In addition, novel pharmacological strategies are particularly needed to limit disease progression and severity and prevent de novo formation of CCM lesions in susceptible individuals, as to date there are no direct therapeutic approaches besides the neurosurgical excision of symptomatic and accessible lesions.

Useful insights into innovative approaches for CCM disease prevention and treatment are emerging from a growing understanding of the biological functions of the three known CCM proteins, *CCM1/KRIT1*, *CCM2* and *CCM3/PDCD10*. In particular, accumulating evidence indicates that these proteins play major roles in distinct signaling pathways, including those involved in cellular responses to oxidative stress, inflammation and angiogenesis, pointing to pathophysiological mechanisms whereby the function of CCM proteins may be relevant in preventing vascular dysfunctions triggered by these events.

Prepared for non-specialists as well as experienced researchers that may be interested in a multidisciplinary approach to study CCM disease, the book focuses on multidisciplinary experimental approaches aimed at addressing the multiple aspects of this cerebrovascular disease, including its clinicoepidemiological, neuroradiological, neurosurgical, histopathological, genetic, molecular and therapeutic features.

The volume is divided into four sections. Part I provides a general overview of the natural history, epidemiology, and pathogenetic mechanisms of CCM disease. Part II describes methods currently used for its diagnosis and treatment. Part III describes the production and analysis of distinct cellular and animal models of the disease. Part IV describes different methodological approaches to study the structure and physiopathological functions of CCM proteins, and the mechanisms of CCM disease onset and progression.

Each chapter is organized to include an introductory overview, a list of the materials and reagents needed to perform the experiment, a step-by-step, readily reproducible laboratory protocol, and a helpful notes section offering tips on troubleshooting and avoiding known pitfalls.

Besides constituting a comprehensive collection of multidisciplinary experimental procedures used in the CCM field and answering the need for standardized protocols, this detailed volume brings together for the first time articles of many of the leading researchers who have contributed significantly to the advancement of scientific knowledge on clinical, genetic and molecular aspects of CCM disease, including epidemiologists, neuroradiologists, neurosurgeons, geneticists, and molecular, cellular and developmental biologists. This authoritative and practical book may therefore serve as a valuable resource for experienced researchers in distinct but complementary clinical and basic research disciplines, but also for future investigators and young students starting to study this complex disease and its pathophysiologic correlates.

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Contents

<i>Preface</i>	<i>v</i>
<i>Contributors</i>	<i>xi</i>
PART I OVERVIEW OF CEREBRAL CAVERNOUS MALFORMATIONS	
1 From Genes and Mechanisms to Molecular-Targeted Therapies: The Long Climb to the Cure of Cerebral Cavernous Malformation (CCM) Disease	3
<i>Saverio Francesco Retta, Andrea Perrelli, Lorenza Trabalzini, and Federica Finetti</i>	
2 Incidence, Prevalence, and Clinical Presentation of Cerebral Cavernous Malformations	27
<i>Kelly D. Flemming</i>	
3 Natural History, Clinical, and Surgical Management of Cavernous Malformations	35
<i>Giovanni G. Vercelli, Fabio Cofano, Filippo Veneziani Santonio, Francesca Vincitorio, Francesco Zenga, and Diego Garbossa</i>	
PART II DIAGNOSIS AND TREATMENT OF CEREBRAL CAVERNOUS MALFORMATIONS	
4 Molecular Genetic Screening of CCM Patients: An Overview	49
<i>Elisabeth Tournier-Lasserre</i>	
5 Next Generation Sequencing (NGS) Strategies for Genetic Testing of Cerebral Cavernous Malformation (CCM) Disease	59
<i>Valerio Benedetti, Elisa Pellegrino, Alfredo Brusco, Roberto Piva, and Saverio Francesco Retta</i>	
6 Genome-wide Genotyping of Cerebral Cavernous Malformation Type 1 Individuals to Identify Genetic Modifiers of Disease Severity	77
<i>Hélène Choquet and Helen Kim</i>	
7 Clinical Imaging of Cerebral Cavernous Malformations: Computed Tomography and Magnetic Resonance Imaging	85
<i>Marc Mabray and Blaine Hart</i>	
8 Neuroradiology: Differential Diagnosis, Follow-Up, and Reporting	97
<i>Alessandra Splendiani, Federico Bruno, and Alfonso Cerase</i>	
9 Surgical Management of Brain Cavernous Malformations	109
<i>Marco M. Fontanella, Luca Zanin, Alessandro Fiorindi, Giannantonio Spena, Federico Nicolosi, Francesco Belotti, Pierpaolo Panciani, Claudio Cornali, and Francesco Doglietto</i>	

PART III ANIMAL AND CELLULAR MODELS OF CEREBRAL CAVERNOUS MALFORMATIONS

- 10 Generation of CCM Phenotype by a Human Microvascular Endothelial Model 131
Simona Delle Monache and Saverio Francesco Retta
- 11 Isolation and Purification of Mouse Brain Endothelial Cells to Study Cerebral Cavernous Malformation Disease 139
Preston Hale, Shady Ibrahim Soliman, Hao Sun, and Miguel Alejandro Lopez-Ramirez
- 12 Production of KRIT1-knockout and KRIT1-knockin Mouse Embryonic Fibroblasts as Cellular Models of CCM Disease 151
Luca Goitre, Claudia Fornelli, Alessia Zotta, Andrea Perrelli, and Saverio Francesco Retta
- 13 CRISPR/Cas9-mediated Generation of Human Endothelial Cell Knockout Models of CCM Disease 169
Konrad Schwefel, Stefanie Spiegler, Christiane D. Much, Ute Felbor, and Matthias Rath
- 14 Dissection of the Role of CCM Genes in Tubulogenesis Using the *Drosophila* Tracheal System as a Model 179
Alondra B. Schweizer Burguete and Amin S. Ghabrial
- 15 Generation and Analysis of CCM Phenotypes in *C. elegans* 191
Evelyn Popiel and William Brent Derry
- 16 Generation of Transgenic Lines of Zebrafish Expressing Fluorescently Tagged CCM Proteins to Study Their Function and Subcellular Localization Within the Vasculature 207
Stefan Donat and Salim Abdelilah-Seyfried
- 17 Vertebrate Models to Investigate CCM Pathogenesis: The Zebrafish and Mouse Model 225
Johnathan Abou-Fadel and Jun Zhang
- 18 Generation of Cerebral Cavernous Malformation in Neonatal Mouse Models Using Inducible Cre-LoxP Strategy 253
Jaesung P. Choi and Xiangjian Zheng
- 19 Isolation of Cerebral Endothelial Cells from CCM1/KRIT1 Null Mouse Brain 259
Nicholas Nobiletti and Angela J. Glading

PART IV CELLULAR AND MOLECULAR MECHANISMS OF CEREBRAL CAVERNOUS MALFORMATIONS

- 20 Identification of the KRIT1 Protein by LexA-Based Yeast Two-Hybrid System 269
Ilya G. Serebriiskii, Mohamed Elmekawy, and Erica A. Golemis

21	Crystallographic Studies of the Cerebral Cavernous Malformations Proteins	291
	<i>Oriana S. Fisher, Xiaofeng Li, Weizhi Liu, Rong Zhang, and Titus J. Boggan</i>	
22	Microscopy Techniques to Investigate CCM Pathogenesis	303
	<i>Johnathan Abou-Fadel and Jun Zhang</i>	
23	Preparation and Analysis of Protein Extracts to Investigate CCM Pathogenesis.	311
	<i>Johnathan Abou-Fadel and Jun Zhang</i>	
24	Systems Wide Analysis of CCM Signaling Complex Alterations in CCM-Deficient Models Using Omics Approaches	325
	<i>Johnathan Abou-Fadel and Jun Zhang</i>	
25	Study of Molecular Interactions of CCM Proteins by Using a GAL4-Based Yeast Two-Hybrid Screening	345
	<i>Federica Finetti and Lorenza Trabalzini</i>	
26	Study of CCM Microvascular Endothelial Phenotype by an In Vitro Tubule Differentiation Model	371
	<i>Simona Delle Monache and Saverio Francesco Retta</i>	
27	Bidimensional In Vitro Angiogenic Assays to Study CCM Pathogenesis: Endothelial Cell Proliferation and Migration	377
	<i>Federica Finetti and Lorenza Trabalzini</i>	
28	Measurement of Endothelial Barrier Function in Mouse Models of Cerebral Cavernous Malformations Using Intravital Microscopy	387
	<i>Angela J. Glading</i>	
29	Immunofluorescence of Cell–Cell and Cell–Extracellular Matrix Adhesive Defects in In Vitro Endothelial CCM Model: Juxtacrine Role of Mutant Extracellular Matrix on Wild-Type Endothelial Cells.	401
	<i>Sandra Manet, Daphné Vannier, Anne-Pascale Bouin, Justyna Lisowska, Corinne Albiges-Rizo, and Eva Faurobert</i>	
30	Detection of p62/SQSTM1 Aggregates in Cellular Models of CCM Disease by Immunofluorescence	417
	<i>Saverio Marchi, Saverio Francesco Retta, and Paolo Pinton</i>	
31	Notch Signaling in Familial Cerebral Cavernous Malformations and Immunohistochemical Detection of Cleaved Notch1 Intracellular Domain	427
	<i>Sana S. Hasan and Andreas Fischer</i>	
32	Measuring the Kinase Activity of GCKIII Proteins In Vitro	437
	<i>Juan Zalvide, Cristina Almengló, Sara Vázquez, Mar García-Colomer, Miriam Sartages, and Celia M. Pombo</i>	
33	Spectrophotometric Method for Determining Glyoxalase I Activity in Cerebral Cavernous Malformation (CCM) Disease	445
	<i>Cinzia Antognelli, Vincenzo Nicola Talesa, and Saverio Francesco Retta</i>	
34	Fluorescence Analysis of Reactive Oxygen Species (ROS) in Cellular Models of Cerebral Cavernous Malformation Disease	451
	<i>Andrea Perrelli and Saverio Francesco Retta</i>	

35	Library Preparation for Small RNA Transcriptome Sequencing in Patients Affected by Cerebral Cavernous Malformations.....	467
	<i>Souvik Kar, Robert Geffers, Amir Samii, and Helmut Bertalanffy</i>	
36	Affinity Purification and Preparation of Peptides for Mass Spectrometry from <i>C. elegans</i>	479
	<i>Evelyn Popiel and William Brent Derry</i>	
	<i>Index</i>	487

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