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Cerebral Cavernous Malformations (CCM)

Methods and Protocols

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Humana Press

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ISSN 1064-3745 ISSN 1940-6029 (electronic)
Methods in Molecular Biology
ISBN 978-1-0716-0639-1 ISBN 978-1-0716-0640-7 (eBook)
https://doi.org/10.1007/978-1-0716-0640-7

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 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.

This Humana imprint is published by the registered company Springer Science+Business Media, LLC, part of Springer Nature.
The registered company address is: 1 New York Plaza, New York, NY 10004, U.S.A.

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.

Siena, Italy — *Lorenza Trabalzini*
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