Zinc Signals in Cellular Functions and Disorders

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Editors

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Springer

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ISBN 978-4-431-55113-3 ISBN 978-4-431-55114-0 (eBook)
DOI 10.1007/978-4-431-55114-0
Springer Tokyo Heidelberg New York Dordrecht London

Library of Congress Control Number: 2014947521

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Foreword

Our understanding of the roles of the essential metal zinc in health and disease processes is advancing rapidly, as is evident from the remarkable studies presented in this book on zinc signaling mechanisms. Certainly many excellent scientists have contributed to the foundations of this field, and I trust that they will not be offended if I cannot mention them all in this limited space. However, I find the pioneering studies of several clinicians and molecular biologists particularly noteworthy of mention. The clinicians Ananda Prasad and Harold Sandstead traveled to Iran in the late 1950s and 1960s and found young adults who had failed to thrive and mature and then deduced that this was due to dietary zinc deficiency (Prasad 1984). By the early 1970s, Edward Moynahan identified acrodermatitis enteropathica as a genetic disease of zinc deficiency in humans (Moynahan 1974). These findings led the American National Academy of Sciences in the 1970s to realize that humans could, in fact, become zinc deficient and that zinc deficiency could cause disease.

The molecular biologist Richard Palmiter first described the mammalian metallothionein genes and demonstrated their dramatic transcriptional induction by zinc and then created mouse models which over-express or lack metallothioneins (MT-I and II) (Palmiter 1987; Masters et al. 1994). Subsequently Walter Schaffner identified and cloned the transcription factor MTF-1, which regulates metallothionein gene transcription in response to zinc (Radtke et al. 1993). These pivotal studies paved the way for thousands of subsequent studies. Although my group provided compelling data that the unique zinc-finger domain of MTF-1 functions as a zinc sensor (Laity and Andrews 2007), the structural basis for that mechanism remains to be resolved in detail. Nonetheless the concept that substantial changes in "available" zinc in higher eukaryotic cells and organisms are sensed by the cell was fundamental to our understanding of zinc biology and zinc homeostasis mechanisms. We now understand that zinc fluxes modify kinase signal transduction cascades and control the localization and stability of several zinc transporters. Using the MT over-expressing or knockout mice created by Richard Palmiter, we presented some of the first evidence that the mouse metallothioneins provide a biologically important labile pool of zinc (Dalton et al. 1996; Andrews and Geiser 1999). These proteins are now considered to function as zinc buffers. Richard Palmiter's contribution did not end with the metallothioneins.

He subsequently cloned the first mammalian zinc efflux transporter (ZnT1; Slc30a1), described the ZnT gene family, and created mouse models that lacked ZnTs (Palmiter and Findley 1995; Palmiter and Huang 2004). His ZnT3 knockout mouse model has been and continues to be employed in hundreds of neurobiology studies (Cole et al. 1999).

Another fundamental advance in the field was the identification of the first ZIP family member IRT-1 in Mary Lou Guerinot's laboratory (Eide et al. 1996). In collaboration with David Eide they showed that *Saccharomyces* ZRT zinc transporters (Zhao and Eide 1996) and *Arabidopsis* IRT1 iron transporters belong to a structurally related family of metal ion transporters, thus the acronym **Z**rt-**I**rt-like **P**roteins (Guerinot 2000). The ZIP proteins are found in all eukaryotes, and orthologues are found in bacteria. Since the identification of this family of metal ion transporters, there have been hundreds of publications on their structure, regulation, and functions. Pioneering studies by Jane Gitschier (Wang et al. 2002) and Sebastien Kury (Kury et al. 2002) identified *Zip4* mutations in patients with acrodermatitis enteropathica about 30 years after the description of this devastating zinc deficiency disease by Moynahan (1974). Among the 14 known ZIP family members, we now have mouse knockout models of over half of these genes. My group created mouse knockout models of *Zip1* through *Zip5* which includes mouse models of acrodermatitis enteropathica (Kambe et al. 2008; Dufner-Beattie et al. 2007; Geiser et al. 2012, 2013). Our studies revealed that expression of the *Zip4* gene in intestinal enterocytes and embryonic visceral endoderm in mice is essential for viability and that the loss of function of this gene causes a rapid shift from anabolic to catabolic metabolism in the animal accompanied by a devastating loss of intestinal integrity and impaired stem cell differentiation.

As you will see when you read this book, the field of zinc biology has matured rapidly in the past decade. The current availability of zinc-sensing fluorescent probes, zinc-transporter genes, and expression vectors, antibodies (still a weak point), and genetic mouse models allows investigators to probe mechanistic aspects of zinc metabolism in great depth. Evidence for functions of zinc and specific zinc transporters in several diseases has emerged, including functions in cancer as well as in normal growth and development. Studies of structure–function relationships in zinc transport proteins are rapidly progressing, and an active field of investigation involves understanding the biophysics of zinc–protein interactions in regulatory proteins and the multiple mechanism of cellular and organismal zinc sensing. We can look forward to many exciting and novel findings in this field over the next few years.

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Preface

More than five decades ago, Dr. Ananda S. Prasad discovered zinc (Zn) as the essential trace element for human life. Zn deficiency was the first discovery in Zn imbalance-related abnormality that causes growth retardation, immunodeficiency, hypogonadism, and neuronal and sensory dysfunctions. Human diseases including cancer, diabetes, osteoporosis, dermatitis, and auto-immune and neurodegenerative diseases have been shown to be associated with abnormal Zn status. Investigations of the biological roles of Zn, however, had been challenging because Zn compounds are normally colorless, and the natural status of Zn is stable as a divalent cation, unlike other bioactive metals such as iron and copper.

Until now, there have been at least four issues that advanced our knowledge about the significant roles of Zn in physiology and diseases. First: bioinformatics, which revealed that approximately 10 % of all proteins in humans may bind with Zn. Second: genetic approaches using animal models and human genetics, which contributed to demonstrating the physiological roles of Zn in cells, tissues, and the whole body. Third: investigation of Zn transporters and metallothioneins in vitro and in vivo, which provided a variety of information on the importance of Zn transportation within and between cells, which led us to the fourth issue: Zn indeed acts as a signaling factor like calcium, called "Zn signaling". Because this is a quite new field, we were motivated to introduce the current status of the study of Zn signaling and to review the whole scheme of this area to date.

The present book overviews up-to-date information on the study of Zn signaling, describing not only the essence of Zn signaling including its history, the molecular analysis of the structures and functions of Zn transporters and metallothioneins, and detection techniques for Zn signals, but also the involvement of Zn signaling in physiology and disease status as in brain function, immunity, inflammation, skeletogenesis, diabetes, and cancer. Besides the introduction of new insights in the study of Zn signaling, this book aims to address the many unsolved problems in the field. For this reason, we made a great effort to furnish educational contexts that will provide great introductions for students, young scientists, and clinical personnel. These contexts can also be valuable references for the pioneers and aficionados among researchers involved with Zn. So that all these goals would mesh, we as editors invited contributions from investigators who are world leaders in this field.

We believe the publication of this book is timely for reviewing the nature of Zn signaling, in which there is growing evidence that Zn signals regulate intra- and extracellular events leading to biological homeostasis, as all the authors will discuss. Also, we are confident that readers will find the book valuable for teaching, lecturing, and other outreach activities that can help make known to the public the importance of Zn itself. Finally, we express our heartfelt thanks to the splendid contributions of all authors, which will lead us to our goal.

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