Subcellular Biochemistry

Volume 70

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Editors

The Biochemistry of Retinoic Acid Receptors I: Structure, Activation, and Function at the Molecular Level

Springer

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ISSN 0306-0225
ISBN 978-94-017-9049-9 ISBN 978-94-017-9050-5 (eBook)
DOI 10.1007/978-94-017-9050-5
Springer Dordrecht Heidelberg New York London

Library of Congress Control Number: 2014942450

Printed on acid-free paper

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

Foreword

The nutritional importance of liposoluble compounds, such as vitamin A, for good health has been known for a long time, but vitamin A itself, was only discovered 100 years ago. Since that time, vitamin A has been the focus of many scientific investigations aimed at understanding its mechanism of action. A number of epidemiologic studies performed with vitamin A-deficient populations of the Third World and with vitamin A-deficient animals have indicated that vitamin A is essential for vision, reproduction, growth, and development. The overall conclusion was that vitamin A maintains good health from birth to death by controlling the development and well-being of all tissues in a time and concentration dependent manner.

Early research in the field focused on vision, and in the 1940s, it was established that a metabolite of vitamin A, *11-cis*-retinaldehyde, is the visual chromophore. However, the mechanism of action of vitamin A in the regulation of cell proliferation and differentiation throughout life was not uncovered until 1987, when nuclear receptors for retinoic acid, another active derivative of vitamin A, were cloned. Since that time, there has been an explosion of new techniques and concepts that have revealed how retinoic acid and its receptors regulate gene expression at the molecular level and impact development and homeostasis. Some of these new findings have been summarized in recent specialized reviews, but it has been over 20 years since a comprehensive account of vitamin A function and metabolism has been published (*The Retinoids Biology, Chemistry and Medicine* edited by Sporn, Roberts and Goodman, Raven Press, New York 1993; *Vitamin A in Health and Disease*, edited by Rune Blomhoff, Dekker, New York, 1994).

In view of the recent explosion in this field, it is timely to publish a contemporary, comprehensive, book series recapitulating the most exciting developments in the field and covering fundamental research in molecular mechanisms of vitamin A action, its role in physiology, development, and continued well-being, and the potential of vitamin A derivatives and synthetic mimetics to serve as therapeutic treatments for cancers and other debilitating human diseases.

Here, we present the first volume of a multivolume series on Retinoic Acid Signaling that will cover all aspects of this broad and diverse field. One aim of Volume I is to present a compilation of topics related to the biochemistry of nuclear retinoic acid receptors, from their architecture when bound to DNA and associated with their coregulators to their ability to regulate target gene

transcription. A second aim is to provide insight into recent advances that have been made in identifying novel targets and nongenomic effects of retinoic acid.

Volume I is divided into ten chapters contributed by prominent experts in their respective fields. Each chapter starts with the history of the area of research. Then, the key findings that contributed to development of the field are described, followed by a detailed look at key findings and progress that is being made in current, ongoing research. Each chapter is concluded with a discussion of the relevance of the research and a perspective on missing pieces and lingering gaps that the authors recommend will be important in defining future directions in vitamin A research.

The volume begins with a retrospective of the vitamin A story and of the cloning of the nuclear retinoic acid receptors. Then, it is organized into three broad areas. The first area focuses on fundamental research covering the architecture of DNA bound RARs, the structural basis for coregulator interaction and exchange, the evolution of the receptors, and the role of the RXR heterodimerization partner. The second area addresses the complexity of the RAR-mediated transcriptional regulatory programs, focusing on the epigenetic changes at the gene promoters and on recent integrative genomics. The third area presents new mechanisms of action of RARs, including nongenomic effects, novel targets, and microRNAs.

We thank all of the authors for their efforts in preparing this volume. They comprehensively reviewed the literature and provided stimulating ideas that will serve to guide continued development of the retinoid field. They pointed out many questions that remain unsolved and noted that these answers will require new state-of-the-art techniques.

We also thank and acknowledge Meran Owen for his invitation to put together this “Retinoic Acid Signaling” book series, his assistant, Tanja van Gaans for her constant help, and Springer Publishing for its support of this project.

It is our hope that this book will serve as an illuminating introduction to the fascinating field of vitamin A biology for those who are not familiar with the amazing molecular intricacies of retinoic acid signaling, as well as a frequent reference for the current and next generations of scientists working in the field of retinoids and nuclear receptors.

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