PROGRESS IN

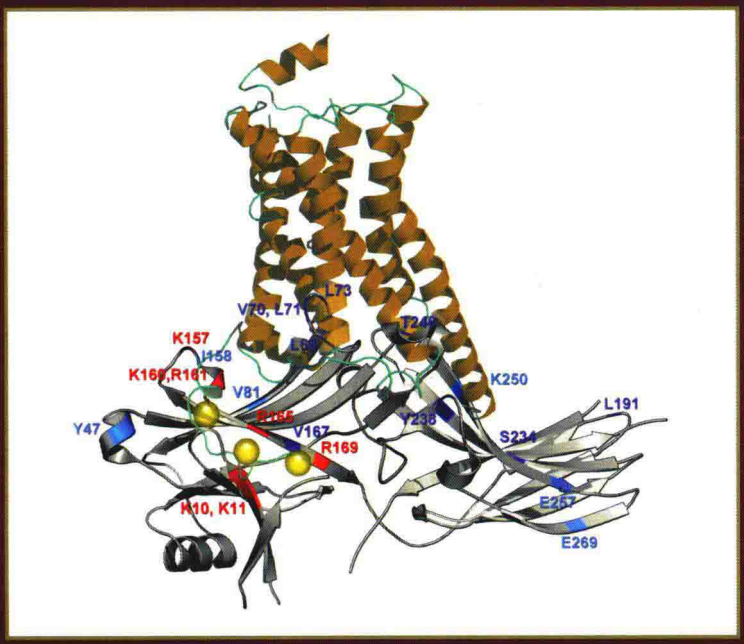
MOLECULAR BIOLOGY AND TRANSLATIONAL SCIENCE

VOLUME 118

THE MOLECULAR BIOLOGY OF ARRESTINS

EDITED BY

LOUIS M. LUTTRELL



VOLUME ONE HUNDRED AND EIGHTEEN

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The Molecular Biology of Arrestins

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LOUIS M. LUTTRELL

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AMSTERDAM • BOSTON • HEIDELBERG • LONDON
NEW YORK • OXFORD • PARIS • SAN DIEGO
SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO

Academic Press is an imprint of Elsevier

Academic Press is an imprint of Elsevier
The Boulevard, Langford Lane, Kidlington, Oxford, OX5 1GB, UK
32 Jamestown Road, London NW1 7BY, UK
Radarweg 29, PO Box 211, 1000 AE Amsterdam, The Netherlands
225 Wyman Street, Waltham, MA 02451, USA
525 B Street, Suite 1800, San Diego, CA 92101-4495, USA

First edition 2013

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN: 978-0-12-394440-5
ISSN: 1877-1173

Printed and Bound in the USA

13 14 15 12 11 10 9 8 7 6 5 4 3 2 1

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The Molecular Biology of Arrestins

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PREFACE

The arrestins, a small family of cytosolic proteins, have emerged as central players in the regulation of many facets of G protein-coupled receptor signaling. Originally discovered for their role in desensitization of the visual photoreceptor, rhodopsin, it soon became apparent that arrestin binding regulates the desensitization, internalization, and intracellular trafficking of nearly every G protein-coupled receptor. The subsequent discovery that arrestins serve as ligand-regulated signaling scaffolds added a new dimension to G protein-coupled receptor signal transduction. By binding and recruiting a host of catalytically active proteins to the receptor, arrestins function as alternative signal transducers, conferring novel G protein-independent signaling functions. It is increasingly apparent that the complementary desensitizing and signaling roles of arrestins are critical to many physiologic processes, from embryologic development to brain, cardiovascular, and immune system function, and to pathophysiologic processes such as cancer. Moreover, the finding that arrestin-mediated functions can be regulated independent of G protein signaling has made it possible to envision arrestin pathway-targeted therapeutics.

This volume represents an effort to present the full spectrum of arrestin biology, from structure–function relationships to translational applications for arrestin pathway-selective "biased" agonists. Beginning with a historical perspective and overview of the field written by 2012 Nobel Laureate in Chemistry Dr. Robert J. Lefkowitz (Chapter 1), the volume first covers the molecular biology of arrestins from high-resolution crystallographic structure, through molecular determinants of arrestin function, to mechanisms of arrestin-dependent G protein-coupled receptor desensitization and signaling (Chapters 2–8). The next section considers the physiological functions of arrestins in different organs and tissues, from embryologic development and metabolic regulation to roles in the eye, brain, bone, cardiovascular and immune systems, and cancer (Chapters 9–16). The volume closes with a glimpse of the future, discussing the analysis of arrestin function *in vivo* using large microarray and proteomic data sets and the opportunities and pitfalls of arrestin selectivity in drug design (Chapters 17 and 18). Hopefully, this compendium will provide a useful and enduring introduction to a rapidly expanding field of investigation that offers substantial translational potential.

LOUIS M. LUTTRELL

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Perspective—The Duality of Arrestin Function

CHAPTER ONE

Arrestins Come of Age: A Personal Historical Perspective

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Contents

Abstract

Visual arrestin and the two β-arrestins (1 and 2) were originally discovered 25–30 years ago in the context of their ability to desensitize phosphorylated G protein-coupled receptors (rhodopsin and the β2-adrenergic receptor, respectively). A fourth retinal-specific member of the family (X-arrestin) was discovered later. Over the past 10–15 years, however, it has become clear that these versatile molecules subserve a host of other roles in modulating and mediating the function of most GPCRs as well as other types of receptors. Functioning as multifunctional adaptor proteins, the β-arrestins also play prominent roles in receptor endocytosis, signaling, trafficking, and ubiquitination among others. Here, I provide a brief personal perspective on how the field has evolved since its inception and speculate on future directions.

Progress in Molecular Biology and Translational Science, Volume 118
ISSN 1877-1173
http://dx.doi.org/10.1016/B978-0-12-394440-5.00001-2