Preface

Irina I. Serysheva

Intracellular Ca^{2+} signaling is a strictly controlled spatial and temporal event caused by the orchestrated mobilization of Ca^{2+} into the cytoplasm via Ca^{2+} channels, from the extracellular milieu (Ca^{2+} influx) or from the intracellular stores (Ca^{2+} release). The focus of this book is on ligand-gated Ca^{2+} channels that mediate release of Ca^{2+} from the intracellular stores such as the endoplasmic and sarcoplasmic (ER/SR) reticulum into the cytoplasm in response to appropriate messenger or protein interaction signals. These channels are essential to a wide variety of physiological processes, including muscle contraction, heartbeat, and brain function. Since the discovery of Ca^{2+} release channels about 30 years ago, intensive research efforts of numerous laboratories around the world were focused on studies of these channels to understand molecular mechanisms underlying their function. There have been major advances in the field of structure and function of Ca^{2+} release channels over the recent years. This book aims to provide a concise and informative overview of these developments in one volume. To achieve this goal, contributions from scientists at the forefront of their respective fields outline the most exciting discoveries, provide critical analysis of their implications, and give perspectives for future research on Ca^{2+} release channels.

Two families of intracellular Ca^{2+} release channels have been identified: the ryanodine receptor (RyR) and the inositol 1,4,5-trisphosphate receptor (IP_3R), that are reviewed in Part I and II of this book, respectively. RyRs are primary Ca^{2+} release channels in muscle cells and are key players in the generation of Ca^{2+} signals triggering muscle contraction. IP_3Rs are detected in all tissues and cell types with the highest density in the Purkinje cells of cerebellum. IP_3, primary cellular agonist of IP_3R channels, is generated in the cell as a result of phosphoinositide metabolism in response to numerous stimuli, such as hormones, growth factors, neurotransmitters, odorants, and light. Localized in the ER/SR membranes, Ca^{2+} release channels are the largest tetrameric ion channels, known to date, with a megadalton molecular mass. Both channel families share significant sequence homology that accounts for the many functional similarities between RyRs and IP_3Rs. The chapter by Clara Franzini-Armstrong, whose studies have provided the first glimpses of RyRs in the native membrane, discusses the ultrastructure of

RyRs in a variety of muscles. Current advances in the 3D structure determination of Ca^{2+} release channels are discussed by Terry Wagenknecht and Zheng Liu with the focus on RyR, and Steven Ludtke and Irina Serysheva provide the chapter on the structure of IP_3R. The chapters by Alan Williams and colleagues and by Darren Boehning are focused on molecular basis for the gating of Ca^{2+} release channels and review proposed mechanisms underlying the ion translocation through Ca^{2+} release channels across the cell membrane. The chapters by Derek Laver and Kevin Foskett and Don-On Daniel Mak are dedicated to the regulation of ion conduction properties of Ca^{2+} release channels by different intracellular modulators, while Colin Taylor and colleagues analyze the structural basis for the interaction between the IP_3 receptor and its naturally occurring high-affinity agonists, adenophostins, in their chapter. Regulation of Ca^{2+} release channels by protein kinases and redox active species is critically reviewed in the chapters by Gerhard Meissner, David Yule, and Suresh Joseph. The chapter by Manfred Grabner and Anamika Dayal is on the structure–functional relationships between the RyRs and their molecular partners in muscle cells, the voltage-gated L-type Ca^{2+} channels. Finally, the overview of human diseases related to the defects in Ca^{2+} release channels or to the modulation of their activity is given in two chapters by Robert Dirksen and Lan Wei (RyR-linked diseases) and Ilya Bezprozvany (IP_3R-linked diseases).

In attempt to cover the most topics in this active field of research within a single volume, it is inevitable that some areas are not presented in great detail or omitted due to the lack of space. Thus, we apologize in advance if some opinions and views are not discussed. Overall, this book should serve as a useful and an informative resource to a large group of research scientists including new researchers and students who are just entering the rapidly growing field of ion channels. Finally, it should provide an important reference for research-oriented clinicians aiding in novel drug discovery.

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