Preface

Because recapitulation of the historic developments within a scientific field usually helps, or may even be required, for understanding current paradigms and concepts, it appears important to begin with a condensed historic overview characterizing a research area, which has gained an impressive amount of attention due to its impact on various aspects of cell biology.

During the past decades, the concept of *store-operated Ca^{2+} entry* as a pivotal component of cellular signaling in a wide range of biological systems and as a process of particular importance for human pathology has emerged slowly and with several critical milestones being accomplished only after a tedious process of knowledge acquisition. All of this started with the perception of a Ca^{2+} transport process that appeared initially to be important only for the more or less direct refilling of intracellular storage compartments. Mobilization or, in other words, discharge of Ca^{2+} from these storage sites had already been recognized as a crucial signaling step for the control of cellular functions, and the mechanism of recharging of these signaling elements had been envisaged as a process similar to the charging of an electrical capacitator by the capacitative current. Thus, the initial term created to describe the phenomenon was "*capacitative Ca^{2+} entry*", originally coined by Jim Putney Jr. in 1986. The understanding that the Ca^{2+} store refilling mechanism is actually associated with highly relevant increases in cytosolic Ca^{2+} and the discovery of the striking dependency of the trans-plasmalemmal Ca^{2+} flux on the filling state of the endoplasmic reticulum, representing the primarily involved Ca^{2+} storage organelle, led to the concept of "store-operated Ca^{2+} entry" (SOCE) as a (patho)physiologically important signaling pathway.

Elucidation of the molecular basis of this cellular mechanism was promoted by the identification of the ion conductance mediating SOCE in mast cells. This conductance, which was originally designated as calcium release-activated calcium conductance (CRAC) by Markus Hoth and Reinhold Penner in 1992, was characterized as highly Ca^{2+} selective and mediated by an ion channel of particularly low unitary conductance, which suggested attempts to analyze the properties at the molecular, single channel level as barely feasible. Subsequent investigations in a wide range of tissues and cell types revealed ubiquitous expression of the signaling phenomenon, along with inconsistencies regarding the biophysical properties of the involved channels. Uncertainty about the pore features of store-operated membrane conductances, along with an even more disturbing uncertainty

regarding the mechanism(s) by which information on the filling state of the Ca^{2+} store is transferred to the Ca^{2+} entry channel has puzzled scientists in the field until the recent discovery of a paradigm SOCE channel.

A signal complex comprised of a highly Ca^{2+} selective pore protein (Orai1) and a Ca^{2+} sensor protein (STIM1) bridges the gap between plasma membrane and endoplasmic reticulum, and enables the information flow required for store-operated gating of the channels in immune cells and probably in many other tissues. This recently gained knowledge on the mechanistic principles underlying a classical SOCE pathway is currently promoting further expansion of the field and inspires investigators to fully elucidate the molecular mechanism of SOCE in different cell types, including rigorous analyses of the role of additional signaling molecules involved in these phenomena and elucidation of the crosstalk of SOCE with other Ca^{2+} signaling mechanisms. Moreover, recent progress in SOCE research, specifically the emerging general agreement on certain molecular concepts, has encouraged attempts to develop therapeutic strategies based on SOCE as a target. This research includes the extensive evaluation of the role of SOCE pathways in human pathology. At this point, having passed important milestones and in expectation of further expansion of SOCE research into a variety of biomedical fields, this book was intended to provide an overview on three main aspects SOCE research.

SOCE signaling is based on exceptional intracellular communication machinery, the key parts of which have just recently been uncovered, is introduced in Part I of this book. Part II provides information on how SOCE is currently seen as a component of cellular Ca^{2+} signaling networks and a pivotal determinant of organelle Ca^{2+} handling. Finally, current evidence for the (patho)physiological significance of SOCE in a selection of organ systems and tissues is outlined in Part III. Because molecular mechanisms, their integration within the cell's signaling network and (patho)physiological aspects of SOCE are highly integrated issues, the reader will recognize a certain degree of intended and potentially useful overlap, which is highlighted within the chapters by cross-references. Thereby, the book is expected to provide a valuable synopsis including the most relevant scientific points of view, specifically those of molecular biophysics, cell biology and pathology.

Finally, the editors would like to express their sincere thanks and appreciation to all contributors for their dedicated collaboration in this project and also to Karin Osibow for her support in editing this book.

We hope that the information provided by this book will be helpful for both students and advanced scientists that are new in the field as well as inspiring for researchers in a wide range of related areas.

Graz/Linz, November 2011 K. Groschner, W.F. Graier and C. Romanin

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