PREFACE

The journey from discovering cell volume regulation of euryhaline fish to the identification of key mechanisms of cell volume homeostasis

Following the observation in the 1960s that cells from euryhaline fish species recover their volume during adaptation from sea water to fresh water, and that this basic property could be found in all cells throughout evolution, an international community of scientists formed around the theme of *Cell Volume Regulation* (CVR). Meetings dedicated to this research area started in the early 1980s and have been held regularly for the past 30 years. The latest meeting was organized by us in August 2016 in Chicago. This volume of *Current Topics in Membranes* gathers a group of experts that contributed to the success of the Chicago meeting. Note that a volume (volume 30) of *Current Topics in Membranes,* titled "Cell Volume Control: Fundamental and Comparative Aspects in Animal Cells," was published in 1987, some 30 years ago. It was edited by Raymond Gilles, Arnost Kleinzeller, and Liana Bolis. While this first volume details the basic phenomenology of cell volume regulation, many of the transport processes and regulatory molecules had yet to be identified at the molecular level. Obviously, in 30 years, significant advances have been made in the field, even if some fundamental questions still remain, including the identity of the volume sensing mechanism or process that links cell volume to the activation of ion channels and transporters.

The current volume summarizes the phenomenology, highlights landmark papers, and provides ample historical data (e.g., in Chapter by Delpire & Gagnon). It then discusses in detail our current understanding the mechanisms at play, including the properties of biological membranes and the sponge-like nature of the cell's interior. As thoroughly discussed in Sergei Orlov's chapter, the central question that remains a "holy grail" in our field is whether changes in cell volume are detected at the plasma membrane, at membrane–cytoskeleton interaction sites, or at the level of the cytoplasm and macromolecules. In addition, the role of intracellular ions and interacting proteins as "sensors" cannot be excluded. To this latest possibility, we know that phosphorylation and dephosphorylation are the mechanisms by which volume-sensitive transporters are activated or inhibited, and different kinases have now been identified that seem to respond differentially to changes in intracellular ions (e.g., Cl^-) and changes in cell volume (see Chapter by de los Heros, Pacheco-Alvarez, & Gamba). The chapter of Model & Petrucelli is dedicated to methods to quantify intracellular macromolecules.

One of the major advances in the field in the last decade highlighted in the two chapters of this volume, by the groups of Yasunobu Okada and Zhaozhu Qiu, was establishing the molecular identity of the volume-sensitive anion channel, a key mechanism in regulatory volume decrease, the ability of cells to recover their volumes under hypotonic stress. The question of the molecular identity of these channels has been a source of major controversy for decades with multiple molecular candidates being identified and then discovered to be false positives. The pioneering work of Qiu and coworkers leading to the discovery of the new channel, *Swell1*, is described in detail in the chapter by Osei-Owusu et al.

The volume also addresses a current controversy about the role of mechanical cues in cell volume regulation. The original premise that cell volume regulation is initiated by mechanical signals was based on the expectation that cell swelling should result in membrane stretch and increase in membrane tension, which in turn would activate mechanosensitive ion channels and other mechanosensitive mechanisms. However, a new detailed analysis of membrane tension and elastic modulus during cell swelling described here by Ayee & Levitan shows that this is not the case and that cell swelling is not accompanied with an increase in membrane tension. Instead, the authors discuss work from their lab and from other investigators showing that cell swelling increases cell stiffness/elastic moduli raising the question of whether intracellular hydrostatic pressure rather than membrane tension may be critical for cell volume regulation. A novel idea of membrane tension homeostasis and its role in cytotoxic swelling is introduced by Catherine Morris in her chapter describing this relationship in different types of excitable cells. Two chapters, by Fred Sachs and Sergei Orlov, also described growing evidence that cytoskeleton has a gel-like properties and may absorb water during cell swelling thus serving as a protective reservoir. Further studies are needed to establish whether incorporation of water into the cytoskeleton gel may also be a signaling event and initiate enzymatic cascades.

In addition, one chapter is dedicated to cell volume regulation in nervous system. Wilson & Mongin describe unique aspects of cell volume maintenance in neurons and astrocytes and cover the consequences of water and ion dysregulation in conditions of hyponatremia, epilepsy, hepatic encephalopathy, and stroke. Two chapters also address the role of extracellular water around epithelial cells: Dey & Bradbury focus on intestinal cells, whereas Webster & Taran highlight the importance of cell surface and mucus hydration in the airway epithelium.

Together, these assays provide a comprehensive analysis of what is known today about Cell Volume Regulation.

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