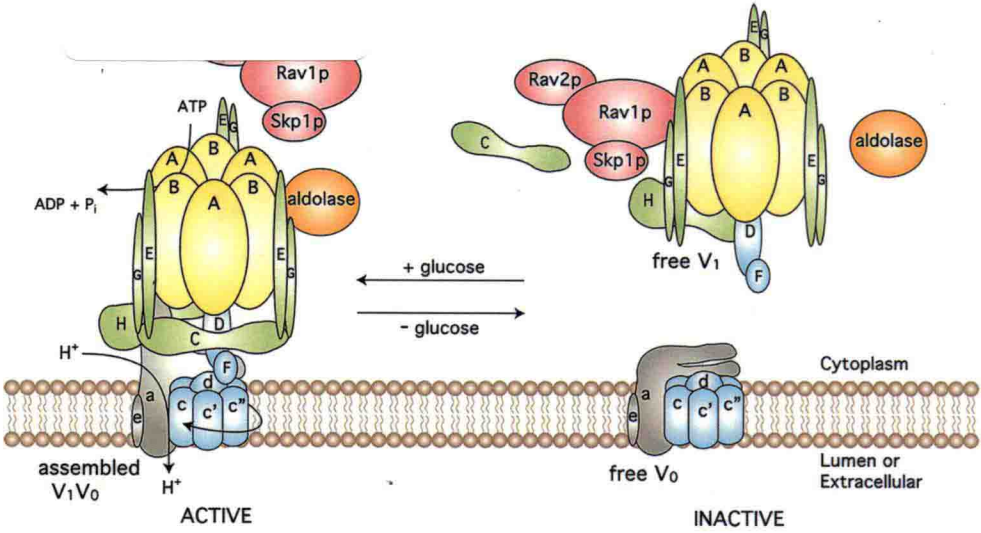

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H^+-ATPases

edited by
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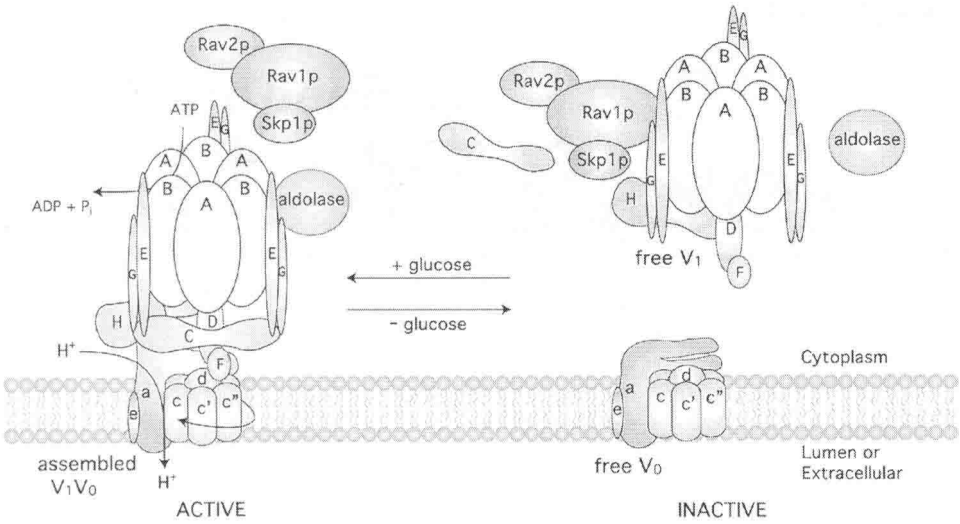

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Preface

Vacuolar-type H^+-ATPases (V-ATPases), which are found within the membranes of many organelles, such as endosomes, lysosomes, and secretory vesicles in eukaryotic cells, catalyze ATP hydrolysis to transport protons across intracellular and plasma membranes Plasma membrane H^+-ATPases, P-ATPases (E1E2-ATPases), which are found in bacteria, fungi eukaryotic plasma membranes and organelles, function to transport a variety of different ions across membranes. This book is dedicated to the scope of V-ATPases and P-ATPases by leading experts in the area of basic science and clinical medicine. This book presents recent findings on the structure and function of V-ATPase in glucose promoting assembly and in glucose signaling. It also describes the regulatory mechanisms of V-ATPases in yeast cells, neural stem cells, kidney cells, and cancer cells and under diabetic conditions. In addition, information on the role of V-ATPases on insulin secretion and cancer chemotherapy is also given in this book It also illustrates the activation of P-ATPases through glucose-induced calcium signaling in *Saccharomyces cerevisiae* yeast cells and the stimulation of proton–potassium pump (H^+–K^+-ATPase) by glucose in kidney cells.

V-ATPases are composed of two domains: the ATP hydrolysis V1 domain (subunits A, B, C, D, E, F, G, H) and the proton translocation V0 domain (subunits a, d, e, c, c′, c″ in yeast and subunits a, d, e, c, c″ and Ac45 in mammals). The activity of V-ATPase is largely controlled by the assembly state of the complex, which consists of two domains. Glucose has been shown to play a critical role in both the functional structure and activity of V-ATPase and, as discussed in this book, has also been shown to promote V-ATPase assembly and activation. There is much evidence to suggest that the glucosemodulated, glycolytic enzyme aldolase mediates the assembly, expression, and

activity of V-ATPase. Glucose signaling involves a number of different regulatory proteins including RAVE and protein kinase A, in order to control the assembly and disassembly of V-ATPase Glucose has also been shown to regulate cytosolic pH–promoted V-ATPase assembly in the field of nutrient sensing and signaling. Studies on cancer cells have shown that glucose withdrawal initiates reversible dissociation of V-ATPase, thereby shutting down its activity and leading to cell death; this suggests that glucose regulates V-ATPase in cancer cells.

It is also known that V-ATPase assembly can be regulated by other mechanisms such as angiotensin II or through certain extracellular factors. Angiotensin II is a peptide hormone that plays an endocrinological role in the regulation of blood pressure as well as fluid and electrolyte homeostasis. Angiotensin II is the major bioactive product of the renin–angiotensin system and it is involved in almost every pathophysiological process implicated in the development of diabetic nephropathy. Blocking the action of angiotensin II is a critical component in every therapeutic regimen designed to prevent and treat diabetic nephropathy. A study included in this book discusses how angiotensin II regulates the assembly of V0 and V1 domains through activation of P38 MAPKinase and PI3K pathways to form the active complex of V-ATPase. The activation of the PI3K/Akt pathway is responsible for glucose metabolism including glucose uptake and glycogenesis. It has been noted that V-ATPase assembly can also be regulated by other extracellular conditions through secondary messenger systems.

Several isoforms of the "a" subunit of V-ATPase have been identified including two "a" isoforms (Vph1p and Stv1p) that have been discovered in yeast. Vph1p is located in V-ATPase complexes of the vacuole while Stv1p is located in V-ATPase complexes of the Golgi and endosomes. Four different isoforms (a1–a4), encoded by different genes have been identified in mammalian cells; a1 (neural), a2 (endothelial and neural) a3 (osteoclasts, pancreatic β-cells and premature melanosomes), and a4 (renal and epididymis). The variants of the "a"subunit are generated by alternative splicing, with a1-I and IV being specifically expressed in the neurons of the brain while a3-III is expressed in the heart and lungs. Both a4-I and

a4-II have been found to be expressed in the kidneys, lungs, and testis. Additionally, a4-I is also located in heart and skeletal muscle while a4-II can be located in liver. The diversity of the "a" subunit isoforms is not only important for tissue specificity and targeting different membrane compartments but it could also result in the generation of V-ATPases with different functional properties.

Three chapters of this book discuss the functional activities of the isoforms of the "a" subunit of V-ATPase in cancer-related inflammation, pancreatic β-cells, and yeast cells. The a2 isoform of V-ATPase has been shown to be important in tumor progression and metastases. The studies discussed in this book suggest that the a2 isoform has the capacity to redirect its activity and to function as either an ATPase or to control acid hydrolysis on the cell surface. Research conducted on endocrine tissues has shown that mutant mice lacking the a3 isoform of V-ATPase have a significantly lower level of plasma insulin than their wild-type groups. This suggests that the a3 isoform of V-ATPase has a regulatory function in the exocytosis of insulin secretion. In yeast, key gluconeogenic enzymes such as fructose-1,6-bisphosphatase (FBPase), phosphoenolpyruvatecarboxykinase, malate dehydrogenase, and isocitratelyase are degraded in the vacuole during glucose refeeding. This prevents energy futile cycles that are detrimental to cells. Vacuole import and degradation (Vid) vesicles are intermediate vesicles that carry gluconeogenic enzymes to the vacuole. Stv1p and Vph1p of the V-ATPase are required for FBPase degradation. Vph1p is required for both Vid vesicles and vacuoles, while Stv1p is required for the proper function of the Vid vesicles.

V-ATPase plays an important role in both the cell surface and vesicular trafficking signaling mechanisms for cancer cells and cells under diabetic conditions. V-ATPase is believed to be largely responsible for supporting cancer growth by controling related inflammatory processes and subsequent angiogenesis. V-ATPase acts as a modulator of chemokines and cytokine expression through a released peptide, which is the *N*-terminal portion of the a2 isoform of a V-ATPase V-ATPases have also been shown to be related to tumor pH control, metastasis, tumor cell growth and survival, and multidrug resistance (MDR), and also possess possible therapeutic applications associated with the use of specific V-ATPase inhibitors.

In the kidney, the V-ATPase E-subunit interacts directly with the glycolytic enzyme aldolase while the a-subunit interacts with phosphofructokinase-1, thereby providing a functional coupling of V-ATPase with the glycolytic pathway.This book discusses the localization and function of renal V-ATPases and their role in intracellular pH (pHi) regulation, transepithelial proton transport and acid–base homeostasis, in addition to providing an overview of V-ATPase in distal renal tubular acidosis and diabetes.

Diabetic nephropathy is a progressive kidney disease caused by angiopathy of capillaries in the kidney glomeruli, which leads to end-stage renal disease (ESRD) and finally to kidney failure. One of the many aspects of the late stages of diabetic nephropathy is the diminished protein reabsorption by proximal tubules via the megalin/cubilin-mediated endosomal/lysosomal protein degradative pathway that leads to proteinuria. V-ATPase, cytohesins and Arf-family GTP-binding proteins (Arfs) are essential for vesicular trafficking of receptors and their signaling along endocytic pathway of eukaryotic cells. A study in this book has demonstrated a novel specific interaction of cytohesin-2 with V-ATPase and aldolase in the V-ATPase/Arf6/cytohesin-2/aldolase complex on early endosomes. High glucose levels may regulate the activities of the components of this complex and trafficking of receptors in the protein degradative pathway, and thus, contribute to the development of early stages of diabetic nephropathy.

The role of V-ATPase has also been examined in the regulation of phosphate transporters in rodents. The type II sodium phosphate cotransporter, Npt2a (SLC34A1), is one of three known sodium-coupled phosphate transporters responsible for the reabsorption of filtered phosphate from the lumen of the proximal renal tubule. It has been found that V-ATPases regulate Npat2a at multiple sites. Apical membrane V-ATPase which is activated during metabolic acidosis may contribute to the phosphaturia associated with metabolic acidosis by decreasing Npt2a transport function. V-ATPases are critical for the forward trafficking of Npt2a as well as physiological regulation of the Npt2a degradation pathway via the transport of proteins from the endosome to the lysosome and ultimately the degradation by lysosomal enzymes. These findings provide a possible link between Npt2a in the regulation of serum

phosphorus concentration and the risk of cardiovascular renal diseases.

Another study in this book shows that in neural stem cells of the mouse brain, V-ATPase is crucial for the transduction of Notch signaling and plays an important role for endosome acidification and endocytosis in signal transduction during neural stem cell differentiation and brain development.

The P-ATPases are a large group of transporter family–related ion and lipid pumps that can be divided into five subfamilies. H^+–K^+-ATPase in animal cells belongs to the type IIC subfamily while the P-ATPase is classified as type III in fungi. The relationship between glucose-induced calcium signaling and the activation of the P-ATPase in *S. cerevisiae* cells is discussed in this book We have also observed that glucose activates H^+–K^+-ATPase in kidney epithelial cells (our unpublished results).

We would like to thank our contributors and colleagues from around the world who have devoted a significant amount of time and effort into making this book as accurate and as useful as possible. Without their contributions, this project could not have possibly been as successful. Their expertise in biochemistry, cell biology, and pathophysiology has greatly added to our ability to bring the most recent results to our readers. I would also like to thank Ms. Shivani Sharma, Pan Stanford Publishing, for her professional assistance. We sincerely hope our readers will find this handbook beneficial and that the knowledge gained from the book will aid their future endeavors.

Suguru Nakamura
Winter 2013

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