Preface

This special volume of *Methods in Molecular Biology* covers precursor endoproteolysis as a mechanism of protein activation/inactivation in the secretory pathway. Initially identified in the late 1960s as a post-translational modification leading to the production of hormonal and neural peptides, this process was found through the years to be an intervening step in the activation, and sometimes inactivation, of a wide variety of functional proteins, in nearly all cells and living organisms, from viruses to mammals. Today, activation endoproteolysis of secretory proteins is recognized as a fundamental biological mechanism of spatial and temporal regulation of protein activity as well as of diversification of protein functions. It is described at varying lengths in most cell biology textbooks written in the last two decades.

Proprotein convertases, the enzymes mediating this endoproteolysis, constitute the central theme of this volume. These endoproteinases travel through, reside within, or cycle between the various compartments of the secretory pathway. Most of them are calcium-dependent serine proteases of the subtilase subfamily, collectively designated as proprotein convertases, subtilisin/kexin type (PCSKs), but other proteases, such as cathepsin L, also appear to be able to perform similar functions, in the brain at least. The nine known PCSKs are further subdivided into seven kexin-like convertases, which cleave after basic residues, and two non-kexin-like convertases, which do not. The enzymology of kexin-like PCSKs has been extensively studied in vitro using a variety of synthetic substrates. These studies have revealed specificities, preferences, and overlaps in cleavage motif recognition. The search for specific inhibitors for these enzymes is an active field of research which should lead to novel tools for altering their expression and/or activity for experimental or therapeutic purposes. The discovery of a non-enzymatic function to PCSK9 is the latest twist in the evolving story of the proprotein convertases. Acting as a binding protein for the low-density lipoprotein receptor (LDLR), PCSK9 promotes the degradation of this receptor, thus reducing hepatic clearance of blood LDL cholesterol and causing elevation of this lipid in circulation. PCSK9 is currently the subject of intense investigation as a target for inactivation in the treatment of hypercholesterolemia and associated atherosclerosis. A better grasp of its biosynthesis and cell biology should help in the design of potent and efficacious anti-PCSK9 drugs.

From a survey of the content of this volume, it is quite apparent that, collectively, the proprotein convertases are critical players in the network of intra- and intercellular signaling events that determine normal physiology. Alterations in their expression have been associated with illnesses such as infertility, obesity, diabetes, cardiovascular diseases, and cancer. These alterations may be caused by genetic lesions, epigenetic changes, or abnormal expression of proteins that modulate their biosynthesis and enzymatic activity.

The biological relevance of the proprotein convertases has been explored mostly by studying the developmental and physiological phenotypes of mice genetically engineered not to express them. Observations from mouse studies have been corroborated by clinical cases and by genome-wide association studies in human. They have also been enriched by findings from alternative experimental models such as the zebrafish, *Caenorhabditis*

elegans, and *Drosophila*. The targeted inactivation of proprotein convertase genes in mice has been either germline or somatic. Mice resulting from germline inactivation may represent useful models of inborn deficiency of a proprotein convertase in humans; those resulting from somatic inactivation, in contrast, may produce an organ- or a tissue-localized deficiency associated with a morbid phenotype mimicking human diseases caused by ageing or environmental injuries. Depending on the targeted enzyme, the phenotypes observed have ranged from developmental arrest to physical abnormalities, metabolic disturbances, and behavioral changes. The phenotyping of most of the targeted mice has been partial. Their complete and detailed characterization will undoubtedly require collaboration among many specialized fields of biology. In the meantime, comparative proteomics and peptidomics of tissues from mice expressing or not expressing the enzyme have begun to provide some insights into the nature of potential physiological substrates and the tightness of these enzymatic links, as well as the metabolic paths influenced by these enzymes. It will take refined cellular biological studies to elucidate the cascades, the cooperation, and redundancy that may be associated with the action of the proprotein convertases in the secretory pathway.

This special volume of *Methods in Molecular Biology* provides a timely assessment of the impact of activation/inactivation endoproteolysis in the secretory pathway on our current understanding of multiple physiological processes. In addition to reminiscences on the events surrounding the seminal discoveries that launched the concept in 1967, it describes the efforts that led to the elucidation in 1989 of the enzymes mediating this process as well as the evolution of the field since then. Furthermore, it offers a broader perspective on the biochemistry of the PCSKs by exploring structural and functional analogies with bacterial subtilisin and on the enzymology of endoproteolysis itself by describing the involvement in the process of non-PCSK type such as cathepsin L. Most of all, in line with the objective of the series, this volume contains a number of detailed protocols developed by prominent scientists from around the world who have been studying the biology of proprotein convertases.

This volume of *Methods in Molecular Biology* should represent an instructive and useful reference book for all scientists interested in endoproteolytic activation and/or inactivation of secretory proproteins through limited proteolysis, for experts in the field and newcomers to it as well.

Ottawa, Ontario ***Majambu Mbikay, PhD***
Montreal, Quebec ***Nabil G. Seidah, PhD***

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