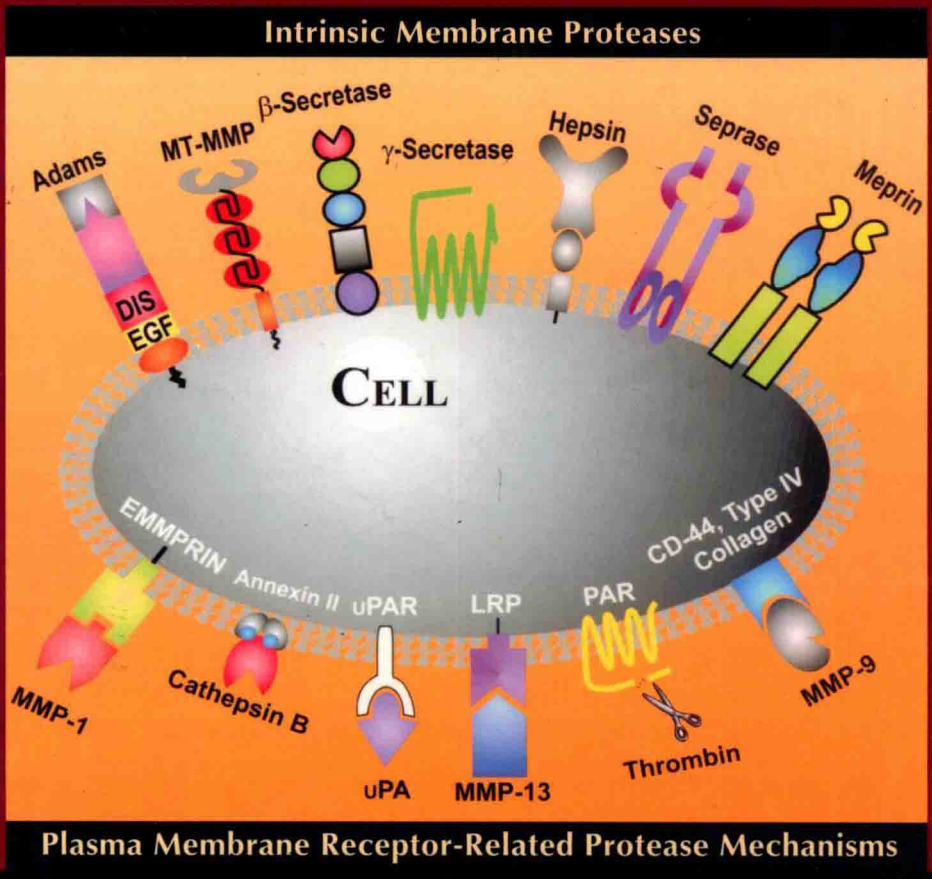
Cell Surface Proteases



Edited by

Stanley Zucker

Wen-Tien Chen

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Current Topics in Developmental Biology

Volume 54

Cell Surface Proteases

Edited by

Stanley Zucker
Professor of Medicine
Departments of Medicine/VA Medical Center
Northport, New York and State University
of New York at Stony Brook, Stony Brook, New York

and

Wen-Tien Chen
Professor of Medicine
Department of Medicine/Division of Neoplastic Diseases
State University of New York at Stony Brook
Stony Brook, New York

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Cell Surface Proteases

This book is dedicated to the vision of Fannie and Morris Zucker and the fulfillment of their dream to bring up their sons in a land of freedom and opportunity where education would open doors not available in their homeland.

Contributors

Numbers in parentheses indicate the pages on which authors' contributions begin.

Joaquín Arribas (125), Laboratori de Recerca Oncològica, Servei d'Oncologia Mèdica, Hospital Universitari Vall d'Hebron, Barcelona 08035, Spain

Wadie F. Bahou (343), Division of Hematology, State University of New York, Stony Brook, New York 11794-8151

J. David Becherer (101), Department of Biochemical and Analytical Pharmacology, GlaxoSmithKline Research Inc., Research Triangle Park, North Carolina 27709

Carl P. Blobel (101), Cellular Biochemistry and Biophysics Program, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center, New York, New York 10021

Judith S. Bond (145), Department of Biochemistry and Molecular Biology, The Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033-0850

Jian Cao (1), Department of Hematology, School of Medicine, State University of New York at Stony Brook, Stony Brook, New York 11794

Dora Cavallo-Medved (313), Department of Pharmacology, Wayne State University, School of Medicine, Detroit, Michigan 48201

Wen-Tien Chen (207), Department of Medicine/Division of Neoplastic Diseases, State University of New York at Stony Brook, Stony Brook, New York 11794-8154

Jacqueline M. Crisman (145), Department of Biochemistry and Molecular Biology, The Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033-0850

Vincent Ellis (263), School of Biological Sciences, University of East Anglia, Norwich, NR4 7TJ, United Kingdom

Rafael Fridman (77), Department of Pathology, School of Medicine, Wayne State University, Detroit, Michigan 48201

Giulio Ghersi (207), Department of Cellular and Developmental Biology, University of Palermo, Viale delle Scienze 90128 Palermo, Italy

Thomas Kelly (207), Department of Pathology, Arkansas Cancer Research Center, Little Rock, Arkansas 72205-7199

Carlos Lopez-Otin (1), Departamento de Bioquímica y Biología Molecular, Instituto Universitario de Oncologia, Universidad de Oviedo, 33071-Oviedo, Spain

Joseph A. Madri (391), Department of Pathology, Yale University School of Medicine, New Haven, Connecticut 06510

Gail L. Matters (145), Department of Biochemistry and Molecular Biology, The Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033-0850

Anna Merlos-Suárez (125), Laboratori de Recerca Oncològica, Servei d'Oncologia Mèdica, Hospital Universitari Vall d'Hebron, Barcelona 08035, Spain

Lourdes P. Norman (145), Department of Biochemistry and Molecular Biology, The Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033-0850

Duanqing Pei (1), Department of Pharmacology, University of Minnesota, Minneapolis, Minnesota 55455

Bonnie F. Sloane (313), Department of Pharmacology and Barbara Ann Karmanos Cancer Institute, Wayne State University, School of Medicine, Detroit, Michigan 48201

Bryan P. Toole (371), Department of Anatomy and Cellular Biology, Tufts University School of Medicine, Boston, Massachusetts 02111

M. Letizia Vittorelli (411), Dipartimento di Biologia cellulare e dello Sviluppo, Viale delle Scienze, Parco D'Orleans II, 90128-Palermo, Italy

0

Michael S. Wolfe (233), Center for Neurologic Diseases, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115

Qingyu Wu (167), Department of Cardiovascular Research, Berlex Biosciences, Richmond, California 94806

Stanley Zucker (1), VA Medical Center, Northport, New York 11768 and School of Medicine, State University of New York at Stony Brook, Stony Brook, New York 11794

Preface

This book represents the first book dedicated entirely to cell surface proteases, primarily of mammalian origin. The field has reached sufficient maturity to permit the presentation of 14 individual chapters. Membrane proteases that function primarily in other cell organelles beside the plasma membranes were not included in the book, i.e., pro-protein convertases that function in the Golgi apparatus. An attempt was made to describe interactions between different cell surface proteases and to avoid duplication wherever possible. In a few instances, the same topics were covered in more than one chapter, so as to present alternative points of views.

For anyone working in any single area related to cell surface proteolytic events, it is important to have an overview of the larger cast of characters that may be interacting on the cell surface. It is reasonable to speculate that none of the cell surface proteases functions alone and many important interactions remain to be elucidated. The importance of plasma membrane proteases in crucial aspects of cell function is only beginning to be appreciated. Not only are these enzymes involved in cleaving other membrane-bound and extracellular matrix proteins, but they are involved in processing physiologically important peptide substrates including growth factors, cytokines, chemokines, hormones, binding proteins, and apoptotic factors. As a result, membrane proteases are involved in a variety of cell functions, including metabolic regulation, immune response, cell growth, apoptosis, motility, and invasion. An important role for these proteases in embryonic development has been demonstrated throughout the phylogenetic tree. Furthermore, these proteases exhibit their multiple cell functions through interactions with other cell surface proteins such as receptors and integrins. The field is beginning to expand into new areas including protein localization, activation, inhibition, and three-dimensional structure. Inhibitors specific for plasma membrane proteases, including molecular inhibitors and naturalizing monoclonal antibodies, have been developed and tested *in vitro*. The involvement of cell surface proteases in disease represents an area of exciting new developments. The potential to treat disease with various categories of protease inhibitors is only beginning to be explored.

We thank the many authors for their thoughtful and timely contributions. The readers undoubtedly will appreciate the considerable amount of work and dedication required to put together such an extensive review of each of these subjects. Every one of these authors is an acknowledged expert in their field. As editors, we thank all of these contributors for their enthusiasm and patience. We thank our research colleagues for providing advice and editorial guidance (Michelle

Hymowitz) and the staff of Academic Press, especially Hilary Rowe, for their contributions to the development of this book. We extend our appreciation to the multitude of scientists who have made contributions to the field of cell surface proteases. This book is a tribute to their efforts. We apologize to those scientists whose work was not specifically mentioned or were misrepresented; space limitations prevented us from providing more extensive references.

We ask the readers to send along any corrections or missing information that can be corrected in future editions of this book.

We hope that this book will prove helpful for the large numbers of investigators and students who have an interest in cell surface proteolytic events and to the larger number of scientists interested in the plasma membrane.

Foreword

Recent years have seen an enormous expansion in the field of proteolytic enzymes, with a wealth of new knowledge of structures and mechanisms of the enzymes and the realization that a wide array of biological processes is controlled by proteolysis. Proteolytic events occur intracellularly, pericellularly, and extracellularly, but for many years the majority of studies have dealt with intracellular and extracellular proteolysis. Although the importance of pericellular proteolysis has long been recognized, it is only in the last several years that many cell surface anchored proteases have been discovered. These enzymes have rapidly become subjects of intense investigation as they play important roles in many biological processes. Some of the soluble proteases released from cells have shown to accumulate on the cell surface by binding to specific cell surface molecules. Localization of proteases on the cell surface either by a transmembrane domain or by other means serves to increase the local concentration of the enzymes, target proteolysis, enhance specificity, and also slow down reactions with endogenous inhibitors, thus regulating the protease action.

This is the first book that focuses on cell surface proteolysis. The Editors of this book, Stanley Zucker and Wen-Tien Chen, have long-standing interests in the role of pericellular proteolysis, especially in cell migration and cancer metastasis. The editors have chosen leaders in the field as contributors to the book. It covers metallo- (matrix metalloproteinases, ADAMs, meprins), serine (type II transmembrane serine proteases, dipeptidyl peptidase IV, seprase, plasminogen activators), cysteine (cathepsin B on the cell surface), and aspartic (memapsin 2/BACE, presenilins) proteases. Other subjects include protease-activated receptors, an MMP-inducing cell surface molecule of the Ig superfamily, emmprin, and shed membrane vesicles.

Many of the membrane-bound proteases are multidomain proteins and the noncatalytic domains often dictate the specificity of the enzymes as they allow the enzymes to interact with other cell surface or extracellular matrix molecules to express their biological activities. Such molecular assemblies on the cell surface may participate in cell–cell contacts and cell–matrix interactions. Each chapter, while describing biochemical and catalytic properties of a particular group of proteases, delineates biological and pathological implications of a specific group of cell surface associated proteases.

While the unified theme of this book is "Cell Surface Proteases," the functions of these proteases are diverse and therefore many avenues exist for medical applications. For example, membrane-bound MT1-MMP assists cells in migration

by cleaving cell surface adhesion molecules such as CD44, while ADAMs, which have more restricted substrate specificity, are involved in shedding of cell surface molecules, development, inflammation, and release of signaling molecules. Memapsin 2 and presenilins are associated with Alzheimer's disease. Membrane vesicles shed from cancer cells contain a number of proteases, integrins, and HLA molecules and they may alter cellular behavior.

The book is timely and comprehensive, covering substantial amounts of recently reported information. The reader will value the excellent reviews of each subject. At the same time, one may realize that there are many key questions yet to be addressed as only a small fraction of this area of biology has been unravelled to date. "Cell Surface Proteases" will provide a foundation on which future knowledge in the field will expand. It will also be valuable for identifying future research paths.

Hideaki Nagase
Professor of Matrix Biology
Kennedy Institute of Rheumatology Division
Imperial College of Science, Technology and Medicine
London, UK

Introduction

Although the biological importance of membrane-bound serine proteases was recognized more than a hundred years ago, interest in the field of cell surface proteases was slow to develop in comparison to proteases identified initially in serum (coagulation and complement factors), locally secreted by cells (plasminogen activators and matrix metalloproteinases), or intracellular compartments (cathepsins and calpains). It is of interest that the discovery of plasma-membrane-bound metalloproteinases (Chapters 1–5), serine proteases (Chapters 7–9), and cathepsins (Chapter 10) occurred about the same time in the mid-1980s. From a biological point of view, the late appreciation of this important class of enzymes may seem surprising. Technical difficulties in isolating and purifying proteases from plasma membranes contributed considerably to the delay. In the past decade, the field has rapidly progressed, as the reader will appreciate in reading this book. Undoubtedly, the identification of an extensive number of serine-, cysteine-, and metalloproteases that are displayed on the cell surface is not yet complete. The importance of plasma membrane proteases in crucial aspects of cell function as well as in health and disease (Chapters 11–14) is only beginning to be appreciated.

This book encompasses both intrinsic membrane proteases (Chapters 1–8) and plasma membrane receptor related protease mechanisms (Chapters 9–12). The figure on the book cover provides the reader with the sense of the close proximity of these various proteins displayed on the cell surface. A constant theme noted throughout this book is that the surface localization of proteases provides the cell with the capability to process a vast spectrum of surface precursor molecules, that once cleaved, play pivotal roles in normal cellular and tissue functions. Furthermore, co-localization of both the protease and the substrate as interacting molecule within specific regions of the plasma membrane, such as lipid rafts (Chapters 1, 2, and 9), invadopodia (Chapters 1, 2, 7, 10, and 12), caveolae (Chapter 9), and shed vesicles (Chapter 14), may increase their concentration, making regulatory events more efficient *in vivo*. Surface binding of intrinsic and soluble proteases also allows the cell to terminate proteolysis by rapid internalization of membrane-bound enzymes, thereby allowing the cells to fine tune its external environment (Chapters 1 and 2). These enzymes are involved in cleaving numerous extracellular matrix proteins (Chapters 1–10 and 14); they are also involved in processing peptide substrates including growth factors, cytokines, chemokines, hormones, and angiogenic factors (Chapters 1, 3–8, and 11). Cleavage of protease activated

receptors (PARs) at the cell surface by serine proteases generated by inflammatory or hemostatic pathways results in activation of signal transduction pathways that modulate numerous cellular activities (Chapter 11). Cleavage of proteins at the cell surface initiated by intrinsic plasma membrane proteases is also likely to activate intracellular signaling pathways; these events remain to be more thoroughly characterized.

The involvement of cell surface proteases in cell movement is an important new area of investigation (Chapters 1, 7, and 9–10). Cell migration requires constant modulation of the adhesive properties of a cell; this is achieved through numerous complex interactions between the extracellular matrix and the actin cytoskeleton mediated by transmembrane adhesion molecules. New clues have suggested that cleavage by membrane-type-MMPs (MT-MMPs), of adhesive-type proteins may provide a mechanism for enhancing cell migration and invasion (Chapter 1). Alternatively, association of seprase complexes with $\alpha 3\beta 1$ integrin localizes active molecules to invadopodia (Chapter 7). Chapter 9 deals with how migrating cells utilize the activity of the plasminogen activator system in the presence/absence of a transmembrane linkage between the glycolipid-anchored protein uPAR and the cytoskeleton. Considerable evidence indicates that serine peptidases and MT-MMPs accumulate at cell surface protrusions, termed invadopodia, that may have a prominent role in processing soluble factors (including growth factors, hormones, chemokines, bioactive peptides) in addition to the well-established role of invadopodia in degrading components of the extracellular matrix (Chapters 1 and 7). These membrane proteases may directly activate either themselves or soluble latent proteases such as MMP-2 and plasmin (Chapters 2 and 9). Different membrane proteases form complexes at invadopodia or other specialized locations that could provide distinct or overlapping functions (Chapters 10 and 14).

It has long been known that certain cell surface proteins can release their biologically active extracellular domains to the pericellular millieu through limited proteolysis. However, the broad recognition of this type of proteolysis (ectodomain shedding) as a general mechanism that regulates many functions of virtually all types of cell surface proteins has been relatively recent (Chapters 3–5, 11, and 14).

An important role for these proteases in embryonic development has been demonstrated throughout the phylogenetic tree. The cleavage of a cell surface protein (Notch) sequentially by ADAM family members, followed by the release of the cytoplasmic domain of Notch and transport to the nucleus, ultimately leading to control of gene expression, represents a fascinating effect of protease activity (Chapters 3 and 4). Knockout and transgenic mice have provided a fertile experimental model to delineate the function of various proteases.

Multiple interactions between cell surface proteases have complicated interpretation of the biological role of individual enzymes. A given membrane protease may have several functions and more than one protease or one protease family may mediate the same function (Chapter 7). For example, matriptase/MT-SP1,

a recently identified type II serine membrane protease, has been proposed to have a biological role in activating pro-uPA, as has the cysteine protease cathepsin B (see Chapters 6 and 9). Cross talk between cell surface receptors and ligands through cell surface proteolysis represents another mechanism through which plasma membrane proteases are involved in various cell functions (see Chapter 3). Another mechanism that cells have evolved to enhance protease activity at the cell surface is to have low affinity docking sites. For example, EMMPRIN, secreted tissue plasminogen activator, and cathepsin B binding to annexin II, a protein peripherally associated with the plasma membrane, provide for protein complex formation at the cell surface; the effect of these interactions needs to be better understood (Chapters 9, 10, and 12).

Interactions between membrane proteases and the lipid bilayer have not been studied in detail. The turnover of plasma membrane proteases involving cell surface shedding, endocytosis in clathrin-coated pits, and intracellular degradation in lysosomes and proteosomes has received scant attention. In sharp contrast, the fate and control of endocytosed plasma membrane receptors has become an area of intense scientific interest. The potential role of caveolae in regulating protease function at the cell surface, involving the presence of multiple proteases and their surface receptors including cathepsin B, uPAR, MT1-MMP, and MMP-2, is discussed in Chapters 1, 9, and 10.

The potential to treat disease with various categories of protease inhibitors is a burgeoning new field. Little is known definitively about the role of cell surface proteases in most diseases with the exception of tumor necrosis factor-α (TNF-α) converting enzyme (TACE). Because TNF-α plays a pivotal role in rheumatoid arthritis, several pharmaceutical companies have developed potent inhibitors of TACE that are effective anti-inflammatory agents in animal models (Chapter 3). Of considerable surprise, TACE has also been implicated in diabetes, as has DDPIV (Chapter 7) and meprin B (Chapter 5). The involvement of multiple cell surface proteases represents an area of exciting new development, as represented by Alzheimer's disease, where different types of surface proteases cleave the β-amyloid protein at different sites, leading to release of pathogenic soluble peptides (see Chapter 8). The involvement of membrane-bound serine proteases in cancer (matriptase and hepsin) and in heart failure (corin, the endogenous pro-atrial natriuretic peptide convertase) has been a strong impetus for pharmaceutical development of specific inhibitors for this category of enzymes (Chapter 6). Targeted strategies focusing on design of specific inhibitors of PARs have been initiated for possible applications in thrombotic/vascular diseases (Chapter 11).

Clinical trials of MMP inhibitors that effectively abrogate MT-MMPs as well as several other MMPs have been reported in advanced cancer; the lack of positive results in this setting suggests that these drugs were employed too late in the course of the disease. An alternative explanation is that MMPs may not be pivotal in cancer progression or that more specific inhibitors need to be developed to avoid interfering with proteases that might protect the host from disease (Chapter 13).

It is fair to predict that our understanding of cell surface proteases will likely evolve considerably over the next decade. A three-dimensional structure of a complete plasma membrane protease remains to be presented. Interactions between membrane proteases and the lipid bilayer need to be better understood. The role of individual proteases in health and disease needs to be better defined. These scientific advances will be eagerly anticipated.

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