

# Protein Profile



## Lysosomal Cysteine Proteinases

SECOND EDITION

**Heidrun Kirschke, Alan J. Barrett  
and Neil D. Rawlings**

# Lysosomal Cysteine Proteases

**Nathalie Vergnolle, Michel Chignard**



## **Lysosomal Cysteine Proteases:**

Lysosomal Cysteine Proteinases and Their Role in Visceral Yolk Sac Mediated Nutrition and Embryotoxicity Jeffrey Lee Ambroso, 1994      Role of Proteases in the Pathophysiology of Neurodegenerative Diseases Abel Lajtha, Naren L. Banik, 2007-05-08

Researchers seeking problems that offer more hope of success often avoid subjects that seem to be difficult to approach experimentally or subjects for which experimental results are difficult to interpret. The breakdown part of protein turnover in vivo particularly in nervous tissue was such a subject in the past it was difficult to measure and difficult to explore the mechanisms involved. For factors that influence protein metabolism it was thought that protein content, function and distribution are controlled only by the synthetic mechanisms that can supply the needed specificity and response to stimuli. The role of breakdown was thought to be only a general metabolic digestion/elimination of excess polypeptides. We now know that the role of breakdown is much more complex; it has multiple functions, it is coupled to turnover and it can affect protein composition, function and synthesis. In addition to eliminating abnormal proteins, breakdown has many modulatory functions: it serves to activate and inactivate enzymes, modulate membrane function, alter receptor channel properties, affect transcription and cell cycle, form active peptides and much more. The hydrolysis of peptide bonds often involves multiple steps, many enzymes and cycles such as ubiquitination and often requires the activity of enzyme complexes. Their activation, modification and inactivation can thus play an important role in biological functions with numerous families of proteases participating. The specific role of each remains to be elucidated.

**The Role of Lysosomal Cysteine Proteases in Endocytosis-mediated Retinal Degeneration** Ronald D. Kinser, 2012

Many retinal degenerative diseases result in blindness. The causes and clinical progression of these diseases are heterogeneous in nature. In many instances the genes involved are known yet the molecular mechanisms leading to blindness still require elucidation. Our lab utilizes the *norpA* mutant which undergoes light dependent retinal degeneration as a cell death model. Previous characterization of *norpA* has shown that rhodopsin and arrestin form stabilized complexes that are internalized into the cell body in response to light. Furthermore, this mass endocytosis of rhodopsin leads to its aggregation and accumulation in the late endosome. Accumulation of proteins in the endosomal system has been shown to lead to the permeabilization of endosomes and lysosomes subsequently allowing translocation of the resident cathepsins to the cytosol. Cathepsins are lysosomal proteases that have been shown to mediate cell death when translocated from the endosomal system. In this thesis I describe the role of the lysosomal cysteine proteases in endocytosis mediated retinal degeneration. Using a combination of techniques in genetics, cell biology and biochemistry we show the specific involvement of the cathepsin L like protease CP1. Retinal degeneration in *norpA* retinas can be blocked by mutation of the *Cp1* gene or expression of the pan cysteine cathepsin inhibitor cystatin. Conversely, retinal degeneration can be accelerated in *norpA* retinas by overexpressing CP1. Interestingly, there is a decrease in CP1 immunofluorescence accompanied by a decrease in rhodopsin colocalization in the *norpA* mutant compared to wild.

type suggesting a CP1 redistribution event in norpA retinas in response to light We also examined cathepsin involvement in a broader range of neurodegenerative disorders Although cathepsins were not implicated in many we discovered a role for cathepsins in the retinal degeneration observed in Drosophila trafficking mutants This suggests that cathepsins may be involved in a broader group of retinal degenerative disorders caused by defects in endosomal trafficking Lastly we identified a novel role for the Toll signaling pathway in endocytosis mediated cell death as mutations to Toll and dorsal block retinal degeneration These data represent a novel molecular pathway leading to cell death in Drosophila A potential link between Toll activation and cathepsins function is discussed Biology of the Lysosome John B. Lloyd, Robert W. Mason, 2012-12-06

Volume 27 provides a comprehensive review of current knowledge of lysosome function in mammalian cells The book's unique contribution is its series of chapters that offers unparalleled treatment of the metabolic activities of lysosomes

*Mechanism for Selective Secretion of a Lysosomal Cysteine Protease/cathepsin L by Transformed Mouse Fibroblasts*

Jianming Dong, Sackler School of Graduate Biomedical Sciences, 1990 Mechanisms of Protease Action Laszlo

Polgar, 1989-01-31 A uniform treatment of the four protease groups and a discussion of the differences and similarities in their action is presented in this important new publication Serine cysteine aspartate and zinc proteases are systematically discussed by nomenclature evolution specificity and their regulatory role The chemistry of the peptide bond including the catalysis of ester and peptide hydrolyses is explained For each protease group the emphasis is placed on the structure and function Kinetics enzyme modifications isotope effects subzero temperature investigations nuclear magnetic resonance measurements X ray diffraction data binding of transition state analogs zymogen activation and site specific mutagenesis are combined to rationalize the action of proteases Both natural and synthetic inhibitors are considered because of their importance in mechanistic studies and drug design **Proteases: Structure and Function** Klaudia Brix, Walter

Stöcker, 2014-01-21 Proteolysis is an irreversible posttranslational modification affecting each and every protein from its biosynthesis to its degradation Limited proteolysis regulates targeting and activity throughout the lifetime of proteins Balancing proteolysis is therefore crucial for physiological homeostasis Control mechanisms include proteolytic maturation of zymogens resulting in active proteases and the shut down of proteolysis by counteracting endogenous protease inhibitors Beyond the protein level proteolytic enzymes are involved in key decisions during development that determine life and death from single cells to adult individuals In particular we are becoming aware of the subtle role that proteases play in signaling events within proteolysis networks in which the enzymes act synergistically and form alliances in a web like fashion Proteases come in different flavors At least five families of mechanistically distinct enzymes and even more inhibitor families are known to date many family members are still to be studied in detail We have learned a lot about the diversity of the about 600 proteases in the human genome and begin to understand their physiological roles in the degradome However there are still many open questions regarding their actions in pathophysiology It is in this area where the development of small

molecule inhibitors as therapeutic agents is extremely promising Approaching proteolysis as the most important irreversible post translational protein modification essentially requires an integrated effort of complementary research disciplines In fact proteolytic enzymes seem as diverse as the scientists working with these intriguing proteins This book reflects the efforts of many in this exciting field of research where team and network formations are essential to move ahead

*Lysosomal Cysteine Proteases* Heidrun Kirschke, Alan J. Barrett, Neil D. Rawlings, 1998 This volume examines each known cathepsin in turn examining gene structure and localization precursors purification activation and inhibition and hydrolysis of synthetic substrates polypeptides and proteins

**Proteases and Their Receptors in Inflammation** Nathalie Vergnolle, Michel Chignard, 2011-08-03 Proteases are everywhere from prokaryotes to eukaryotes from virus to bacteria and in all human tissues playing a role in many biological functions Among these functions the inflammatory reaction is of particular interest In inflamed tissues proteases can have a microbial and or host origin and are involved not only in tissue remodeling but also in specific signaling to resident or inflammatory cells thereby contributing to the innate immune response This volume presents all advances in our knowledge of the role proteases and their inhibitors play in various diseases associated with inflammatory response Mechanisms involved in protease signaling to cells are presented and the different types of proteases that are present at inflammatory sites and their effects on the course of inflammation are discussed Finally the evidence for considering proteases and their receptors as potential molecular targets for therapeutic interventions in the treatment of inflammatory diseases is discussed in the context of specific organ inflammatory pathologies the lung gastrointestinal tract skin joints etc

**Proteases in Apoptosis: Pathways, Protocols and Translational Advances** Kakoli Bose, 2015-08-06 This book provides a comprehensive overview of the proteases involved in programmed cell death It presents a focused yet extensive discussion on proteolytic enzymes such as caspases HtrAs granzymes calpains and cathepsins as well as laboratory protocols related to enzymology and apoptosis Mouse model systems and non invasive imaging techniques in apoptosis related diseases such as cancer and neurodegeneration are also covered in this book While slowly unravelling the complexities of apoptosis in chapter one the next three chapters individually elaborate on different classes of proteases that play key roles in the initiation progression and execution of programmed cell death The last two chapters complete this discussion by describing different laboratory methodologies and therapeutic advances involving apoptotic proteases Protocols portraying in vitro and ex vivo colorimetric and fluorescence based enzyme kinetic studies as well as cell death assays are explained in the fifth chapter Preclinical in vivo models and non invasive imaging in apoptosis to understand the complexities of disease progression and their contribution toward therapeutics is recounted in the last chapter The book spans topics related to both fundamental and applied biology It would therefore be equally appealing and informative to scientists working in the field of apoptosis and those who are investigating mechanisms of proteases and enzymes in general The protocols would certainly benefit both graduate and undergraduate students working in the related fields and provide

useful leads for drug design to translational biologists involved in neurodegeneration and cancer research

**Pathophysiological Aspects of Proteases in Cancer** Sajal Chakraborti, Srijit Das, Cheorl-Ho Kim, 2024-10-22

Pathophysiological Aspects of Proteases in Cancer provides a comprehensive overview of the multifaceted field of proteases in the cellular environment and focuses on the recently elucidated functions of complex proteolytic systems in physiology and pathophysiology. The book both gives insights on the general aspects of the role of proteases in cancer, their role as diagnostics and prognostics biomarkers, their impact on chemoresistance, and the future cutting edge technologies like cocktail therapies and Cyber Knife technology. Given the breadth and depth of information covered in the respective contributions, the book will be immensely useful for researchers in oncology and working to identify targets for drug development. Multidisciplinary in scope, the book bridges the gap between fundamental and translational research with applications in the biomedical and pharmaceutical industry, making it a thought provoking read for basic and applied scientists engaged in biomedical research. Gives insight into the spectrum of proteases, protease inhibitors and protease interactors involved at the cellular and molecular level in cancer development. Gives a comprehensive overview of the role of proteases in modulating cellular metabolism and chemoresistance to better understand how proteases play in early to the end point in cancer development and metastasis. Provides a multidisciplinary approach demonstrating the biochemical and signal transduction mechanisms associated with dysregulation of proteases leading to the manifestation of various diseases. Highlights the roles and regulation of different types of proteases as well as their synthetic and endogenous inhibitors. Bridges the gap between fundamental and translational research with applications in the biomedical and pharmaceutical industry.

Proteases in Human Diseases Sajal Chakraborti, Tapati Chakraborti, Naranjan S. Dhalla, 2017-07-13 This book bridges the gap between fundamental research and biomedical and pharmacological applications on proteases. It represents a comprehensive overview of the multifaceted field of proteases in cellular environment and highlights the recently elucidated functions of complex proteolytic systems in different diseases. Several established investigators have elucidated the crucial role of proteases in biological processes including how proteolytic function and regulation can be combined to develop new strategies of therapeutic interventions. Proteases form one of the largest and most diverse families of enzymes known. It is now clear that proteases are involved in every aspect of life functions of an organism. Under physiological conditions, proteases are regulated by their endogenous inhibitors; however, when the activity of proteases is not regulated appropriately, disease processes can result. So there is absolute need for a stringent control of proteolytic activities in cells and tissues. Dysregulation of proteases may cause derangement of cellular signalling network resulting in different pathophysiological conditions such as vascular remodelling, atherosclerotic plaque progression, ulcer and rheumatoid arthritis, Alzheimer disease, cancer metastasis, tumor progression and inflammation. Additionally, many infective microorganisms require proteases for replication or use proteases as virulence factors which have facilitated the development of protease targeted therapies for a

variety of parasitic diseases

**Proteases in Physiology and Pathology** Sajal Chakraborti, Naranjan S. Dhalla, 2017-09-14

Using a multidisciplinary approach this book describes the biochemical mechanisms associated with dysregulation of proteases and the resulting pathophysiological consequences. It highlights the role and regulation of different types of proteases as well as their synthetic and endogenous inhibitors. The role of proteases was initially thought to be limited to general metabolic digestion. However, we now know that the role of protein breakdown is much more complex and proteases have multiple functions: they are coupled to turnover and can affect protein composition, function, and synthesis. In addition to eliminating abnormal proteins, breakdown has many modulatory functions, including activating and inactivating enzymes, modulating membrane function, altering receptor channel properties, affecting transcription and cell cycles, and forming active peptides. The ubiquity of proteases in nature makes them an important target for drug development. This in-depth, comprehensive resource is a valuable resource for researchers involved in identifying new targets for drug development. With its multidisciplinary scope, it bridges the gap between fundamental and translational research in the biomedical and pharmaceutical industries, making it thought-provoking reading for scientists in the field.

Frontiers in Protein Structure, Function, and Dynamics Dev Bukhsh Singh, Timir Tripathi, 2020-07-02 This book discusses a broad range of basic and advanced topics in the field of protein structure, function, folding, flexibility, and dynamics. Starting with a basic introduction to protein purification, estimation, storage, and its effect on the protein structure, function, and dynamics, it also discusses various experimental and computational structure determination approaches, the importance of molecular interactions, and water in protein stability, folding, and dynamics. Kinetic and thermodynamic parameters associated with protein-ligand binding, single-molecule techniques, and their applications in studying protein folding and aggregation, protein quality control, the role of amino acid sequence in protein aggregation, muscarinic acetylcholine receptors, antimuscarinic drugs, and their clinical significances. Further, the book explains the current understanding on the therapeutic importance of the enzyme dopamine beta-hydroxylase, structural dynamics and motions in molecular motors, role of cathepsins in controlling degradation of extracellular matrix during disease states, and the important structure-function relationship of iron-binding proteins, ferritins. Overall, the book is an important guide and a comprehensive resource for understanding protein structure, function, dynamics, and interaction.

Proteases: New Perspectives Vito Turk, 2012-12-06 This book provides an account of the recent advances in our understanding of the role of proteases under physiological and pathological conditions. It reviews the contributions that have been made in the fields of biochemistry, molecular biology, medicine, agriculture, and ecology. In addition, there is an account of the growing number of practical applications in biotechnology, reflecting the fact that peptidases are major targets for medical and agricultural purposes. The book shows how the numerous protease structures are essential for drug design. The contributions place special emphasis on cysteine, aspartic, and metalloproteases and their role in physiological and certain pathological states. Another focus is the classification and nomenclature of peptidases and a review of those proteases

currently under the most intensive investigation The book provides an informative introduction for teachers and newcomers to the field such as graduate students while providing a valuable source of material and ideas for the academic and industrial researcher in areas including biochemistry medicine agriculture and biotechnology     The Serpin Family Margarethe Geiger,Felix Wahlmüller,Margareta Furtmüller,2015-11-13 The book provides an comprehensive overview on biology genetics and cellular functions of serpins serine protease inhibitors in health and disease With over 1000 members serpins are the most diverse family of protease inhibitors Latest groundbreaking research findings are presented and broaden the understanding on inhibitory and non inhibitory serpins not only in mammalian organisms but also in insects worms plants and viruses     Cell Apoptosis Research Advances Carter R. Kettleworth,2007 Apoptosis is the regulated form of cell death It is a complex process defined by a set of characteristic morphological and biochemical features that involves the active participation of affected cells in a self destruction cascade This book presents research from around the world     **Medical Aspects of Proteases and Protease Inhibitors** Nobuhiko Katunuma,1997 The work presents articles on proteases and their inhibitors as mediators of biological functions Topics addressed cathepsin B and L MHC and peptide interaction procathepsin L cysteine proteinases selective neuronal cell death HIV and influenza virus tumor invasion gingivitis bacterial infection Readers professionals in the area of molecular medicine biochemists molecular biologists clinical pharmacologists pharmaceutical companies     *Cumulated Index Medicus* ,1985     **Handbook of Muscle Foods Analysis** Leo M.L. Nollé,Fidel Toldra,2008-11-10 In today s nutrition conscious society there is a growing awareness among meat scientists and consumers about the importance of the essential amino acids vitamins and minerals found in muscle foods Handbook of Muscle Foods Analysis provides a comprehensive overview and description of the analytical techniques and application methodologies for t



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