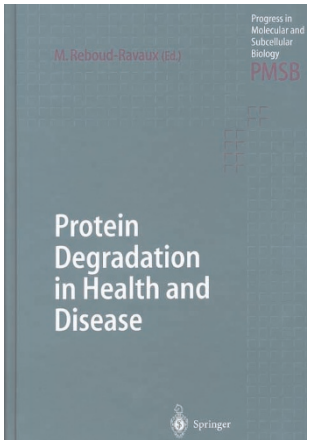
Benefits and hazards of protein destruction



Protein Degradation in Health and Disease
edited by M. Reboud-Ravaux
Spinger Verlag • 2002
Hardback, £48/$75

Peter Kloetzel

As a result of the advances in our understanding of the complex mechanisms that rule the life of a protein, and often the fate and the well-being of an entire organism, protein degradation has become an important area of research in cell biology and medical sciences. Various neurological and metabolic disorders, carcinomas, viral infections and certain autoimmune diseases (this list is not complete) are, in one way or another, related to disorders in protein metabolism. This may involve lysosomal, cellular and extracellular proteases or proteolytic systems. Calpains, cathepsins, matrix metalloproteases, caspases and the proteasome are all decisive in maintaining the critical balance between health and disease. For example, calpains have been shown to function in muscular dystrophy and cataractogenesis. Cathepsin K is involved in the degradation of collagen, different matrix metalloproteinases are important in tumor growth and vascular remodelling, whereas the function of several caspases is tightly connected with apoptotic pathways. Importantly, several proteolytic systems (proteasomes and caspases) function in a coordinated fashion, giving rise to greater flexibility and precision.

Among the existing different proteolytic enzymes and pathways, the proteasome system has been clearly established as the central cellular system that regulates cellular metabolism and cell fate. The regulatory function of the proteasome has been firmly established in processes that include cell cycle control, apoptosis, the activation or inactivation of transcription factors (such as NFkB), control of the inflammatory response, the elimination of proteins as part of the cellular quality control systems and the generation of peptides from viral or tumor antigens presented by major histocompatability complex (MHC) class I molecules. This is achieved by highly sophisticated signalling mechanisms, such as phosphorylation and dephosphorylation, the recognition and ubiquitination of protein substrates by ubiquitin ligases, controlled substrate binding by subunits of the multi-subunit proteasome complex and the consecutive complete or limited proteolysis of the substrates. In addition, a number of molecules exist whose synthesis is controlled by cytokines and that are known to modulate proteasome activity to provide an improved immune response. One can therefore imagine that interference with the proper function of the proteasome system will eventually result in certain disorders and pathophysiological states.

Considering the large number of different proteases, the complexity in the regulation of the different proteolytic systems and the numerous related diseases, the title of the book is very ambitious. Apparently, having understood the problems of composing a book with such a general topic and considering the wealth of knowledge on proteases, the editor decided to select articles that focus almost exclusively on progress in our knowledge of the proteasome system and its involvement in health and disease. As considerable cooperativity exists between different proteases or proteolytic systems, this restriction is somewhat unfortunate. Therefore, the book will only partially satisfy those readers who are interested in a more general introduction to protein breakdown and the function of such equally important proteases as calpains, caspases, cathepsins and matrix-metalloproteases in cell pathophysiology.

The editorial organization of the book and the content of the various chapters, which are of variable quality, are aimed at readers with a profound knowledge of this cellular pathway who do not require a general introduction into the proteasome field. Furthermore, the book lacks a comprehensive general introduction into the proteasome system at its beginning, as given by O.Coux towards the end of the book. The lack of a suitable introduction makes the very specialized and condensed chapters about E3 ligases and proteasome inhibitors relatively inaccessible for non-proteasome experts. Plemper and Hammond have written a chapter whose content comes closest to the expectations and the title of book. These authors try to summarize the whole spectrum of diseases associated with the ubiquitin/proteasome system. Although this is certainly the best chapter of the book, the space given to this article is too limited to allow a complete overview of ubiquitin/proteasome involvement in neurological and metabolic disorders, cancer, viral-induced malignancies and immune surveillance.

For a general readership, it would certainly have been a good idea to start the book with a detailed general introduction covering all the various components and aspects of the proteasome system, preferably accompanied with comprehensive illustrations. In this way, unnecessary redundancies in the subsequent chapters could have been avoided. Based on such an introduction, it would have been possible to include more detailed reviews discussing current literature and the importance of the proteasome system in the development and possible treatment of a variety of diseases, including cervical cancer (p53 and human papilloma virus), neurodegenerative diseases (Parkinson´s disease), Alzheimer´s or Huntington´s disease, to name just a few. In addition, any book dealing with the involvement of the proteasome in diseases ought to contain a separate chapter highlighting the increasing importance of proteasome inhibitors in the treatment of various cancers, inflammatory disorders or heart diseases. This chance was lost. □

Peter Kloetzel is in the Institute of Biochemistry-Charite, Humboldt-University Medical School, Monbijoustr.2, Berlin, D-10117, Germany*
**e-mail: p-m.kloetzel.charitie.de*