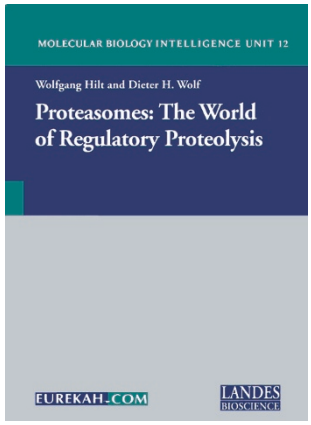
Protein purée



Proteasomes: The World of Regulatory Proteolysis
edited by Wolfgang Hilt and Dieter H. Wolf
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Several years ago, few biochemists or cell biologists would have predicted that the complexity of the pathways involved in protein degradation would rival those involved in protein synthesis. The repertoire of cellular proteins present within a cell at any one time can be altered rapidly by external signals, and it is now recognized that irreversible protein degradation is a critical component of this response system. Additionally, most protein breakdown requires energy, an important clue that this overall exergonic process might be highly regulated. Through characterization of the major system of protein degradation in eukaryotic cells, the ubiquitin–proteasome system, it is clear that this energy is used for the maintenance of a separate compartment in which degradation occurs (the proteasome) and for controlling access to this compartment through ubiquitination and substrate unfolding.

The range of biological processes in which ubiquitin-mediated proteolysis is known to have a crucial role is now incredibly broad. Indeed, Michael S. Brown, in his 2000 Lasker Award presentation to Aaron Chiechanover, Avram Hershko and Alexander Varshavsky for the discovery of the system, estimated that one in ten publications in present-day biology journals deal with the ubiquitin system. The amazing machine at the centre of this system, and the primary subject of the collection of reviews edited by Hilt and Wolf in this book, is the 26S proteasome. The other half of this amazing system is the complex array of enzymes whose job it is to define proteasome specificity by choosing which cellular proteins to ubiquitinate and — just as crucially — when to do so. The E1, E2 and E3 proteins form a pyramid of cooperating enzymes that generally link long chains of ubiquitin to substrates destined for degradation. Although the E1 and E2 enzymes are easily recognizable and their roles in the cascade are well defined, the ultimate diversity and number of E3 enzymes, which make ultimate contact with the substrates, remain unknown. In addition, the manner in which ubiquitin is attached to substrates is crucial and does not always lead to proteasomal degradation.

The last major broad review of the ubiquitin field was published in 1998 (*Ubiquitin and the Biology of the Cell*, Plenum Publishing, 1998); with significant advances on nearly all fronts since then, the job has only become more difficult. The present attempt is a success in most respects but at the same time reminds us that, like the proteasome, we should be careful not to bite off more than we can chew. Roughly half of the chapters focus on proteasomes themselves, opening up with a review of proteasomes in bacteria and archaea, which, although they do not function in recognizing ubiquitinated proteins, were nevertheless crucial in elucidating the structure and mechanism of both prokaryotic and eukaryotic proteasomes. Separate chapters on proteasome crystal structures, subunit arrangement, and assembly and mechanism give an excellent overview of the essential features of the proteasome core. From here, four chapters discuss the regulatory particles of the proteasome, both the 19S particle described above and an alternative regulatory particle (PA28/11S REG) whose precise biochemical function is unclear but is linked to generation of peptides for major histocompatibility complex (MHC) class I presentation. The discovery and characterization of specific inhibitors of the proteasome were key factors in the explosion of the field over the past few years, and the chapter by Lee and Goldberg is an excellent review of proteasome inhibitors. This is required reading for the many investigators eager to determine whether their favourite biological phenomenon requires proteasome function. Together, these chapters fit well together to give a coherent and comprehensive overview of the proteasome.

The compilation is not as strong with the second group of chapters, covering protein ubiquitination and phenomena controlled by the ubiquitin–proteasome pathway, in part because it is simply not possible to cover all the important aspects. In addition, most chapters contain few references to publications after 1998; much has happened since then, including the discovery of perhaps the largest class of E3 enzymes (the RING E3s) and the elucidation of several E2/E3 and E3/substrate X-ray crystal structures. Nevertheless, the first two chapters in this group of chapters provide a good overview of the signals within substrate proteins that confer targeting and of the ubiquitin system in yeast, which has been critical in the genetic dissection of the ubiquitin–proteasome system. Other chapters describe some specific examples of targeting of individual proteins, such as p53 and ornithine decarboxylase, the latter being the clearest example of a protein that does not have to be ubiquitinated to be degraded by the proteasome. A particularly lengthy chapter takes in the many aspects of cell cycle regulation that are regulated by ubiquitination; another covers the several human disease states that involve the ubiquitin system. Some areas, such as apoptosis and neurodegenerative diseases, with emerging links to the ubiquitin system are also highlighted, but the lack of molecular details in these areas, at least at the time at which they were written, makes these chapters largely descriptive. An overview of proteasome-dependent degradation of substrates within the endoplasmic reticulum is well presented, but again, recent advances in this field, such as the identification of an endoplasmic-reticulum-tethered E3 enzyme, are not captured in this volume.

Overall, this collection of reviews is highly recommended as an excellent reference for investigators interested in proteasome structure and mechanism. For mechanisms and functions of protein ubiquitination, however, a quick literature search would certainly yield a more current and comprehensive set of reviews in this rapidly expanding field. □

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