

PREFACE

In the last 50 years a wealth of information has allowed us to understand the contribution of various regulatory factors that alter mRNA and protein synthesis to a variety of physiological and pathological conditions. However, such regulation is only one of many factors that contribute to the levels of a given protein. One major factor that has been relatively obscure until recently has been the contribution of protein degradation to the regulation of the steady state level of protein expression and protein function. This rapidly evolving field has made a significant mark on the scientific community, as highlighted by the Award of the Nobel Prize in Chemistry for 2004 to Aaron Ciechanover, Avram Hershko and Irwin Rose for their pioneering work on the ubiquitin-proteasome system (UPS) of protein degradation, which is the subject of this volume. In recent years evidence has been accumulating that suggests a role for UPS function in both physiological and pathological settings. In particular, studies have implicated a central role for the UPS in cell cycle regulation, cancer and neurodegeneration. Two points are however worth bearing in mind: First, ubiquitin's function appears to extend far beyond the UPS and protein degradation; second, there are other important systems of intracellular protein degradation, most notably autophagic systems through the lysosomes, and these may also be involved in disease pathophysiology.

In parallel with this general surge of interest in the UPS, two other recent trends have enabled this volume to come into existence. Neurodegenerative diseases, once considered very distinct pathophysiological entities, have come closer together, as common threads between them are increasingly being recognized; and, with advances in genetics and animal modeling, neurobiology of disease is now largely based on facts, and not on hypothetical models that may or may not approximate disease states. This latter trend is highlighted by the inclusion of a new section, that of Neurobiology of Disease, in the *Journal of Neuroscience*, the *Journal of the Society for Neuroscience*.

Among the “common threads” holding the different neurodegenerative conditions together is the concept of impaired UPS function. How does the UPS relate to neurodegeneration? As outlined throughout this volume, converging genetic, pathological and biochemical data suggest that impairment of the UPS may underlie a number of neurodegenerative diseases states, or, at the very least, play a contributing role in neuronal dysfunction and death. It is this recurring theme that has galvanized us to create this volume, in which we have sought to present a wide range of information and opinions on the subject, tackling it from different angles. Authors who have been invited to contribute include internationally renowned experts in the field. Chapters represent a blend of the authors’ own research with thorough reviews of the respective fields. We have elected not to simply present the evidence linking the UPS to specific neurodegenerative disease states. This is indeed done in the last section of the book, where the potential link of the UPS to Parkinson’s disease, Alzheimer’s disease, Huntington’s disease, motor neuron diseases, prion diseases and aging is discussed in a critical fashion. In each one of these chapters, basic aspects of the pathophysiology of each of these conditions are discussed and their relationship to the new concepts related to the UPS is analyzed. In designing this book, we thought that this last and, in a sense, main section of the volume, should be buttressed by a number of other sections that are devoted to the subject of the UPS and neurodegeneration, irrespective of specific disease states, thus providing the wider framework in which to view this relationship. Thus, in total, there are 6 sections in this volume. In the introductory section, the main players in this system are introduced. One of the two chapters here is devoted to the yeast UPS, the study of which has proved invaluable in the deciphering of the structure, components and function of the proteasome. The other chapter is more tailored to the UPS in the context of the mammalian nervous system. We then have a second section devoted to the relationship between protein aggregation, inclusion formation and the UPS. This is a complicated subject, and one that is quite controversial. It is especially important, given the recent evidence that changes in protein conformation may underlie most cases of neuronal degeneration. We have tackled it by providing first a review of the topic that attempts to address the controversies in the field, and then two chapters that elaborate on specific experimental paradigms, which have offered insights into this relationship. The third section deals with the close relationship between the redox system and the UPS. Whereas the first chapter here tackles this relationship, and makes the point that it is reciprocal, and likely to be of great importance in neurodegeneration, the second introduces another player in the mix, inflammation, which may help to mediate interactions between the

two systems. The fourth section delves into the role of UPS in neuronal cell death. This again is a controversial topic, given that inhibition of the UPS has been linked both to neuronal survival and death. The two chapters here deal with these opposing, but not mutually exclusive, views. The fifth section addresses cellular and animal models of UPS dysfunction. Whereas the first chapter here deals with various pharmacological and molecular tools that can be used to model UPS dysfunction, the second is devoted to the *gad* mouse, a unique animal model that links defects in UPS to neurodegeneration.

We hope that this volume represents a comprehensive review of the role of the UPS in neurodegeneration. There are advantages and disadvantages in generating a book on a field that is as new and rapidly evolving as the field of UPS research. An obvious advantage is that the interest factor is high for neuroscientists of various backgrounds, for neurologists with an interest in the pathophysiology of neurodegeneration, and for biologists with an interest in protein degradation. A potential disadvantage is that the data presented here may be outshone by new developments. That is why we have emphasized critical appraisal of the literature, together with cutting-edge new advances. We believe that the concepts outlined here will be of relevance for many years to come, and are intended to generate interest in the nuances of the UPS system, and highlight new avenues for the understanding of the UPS and the generation of UPS-based therapies for the treatment of neurodegenerative diseases.

Jeffrey N. Keller
Leonidas Stefanis



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Stefanis, L.; Keller, J.N. (Eds.)

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