

Preface

The ubiquitin system has two major functions in eukaryotic cells: it regulates protein degradation, which is essential for normal cellular function and for the removal of potentially harmful, damaged, or misfolded proteins, and it controls protein activity by regulating protein–protein interactions and subcellular localization. The ubiquitin system is thus involved in processes as diverse as cell cycle progression, signal transduction, gene transcription, and DNA repair. Not surprisingly, defects in the ubiquitin system have been linked with numerous diseases such as cancer, inflammation, central nervous system disorders, and metabolic dysfunction.

Ubiquitin is a highly conserved 76-amino acid protein which is transferred to its target protein in an ATP-dependent manner. This post-translational modification takes place in a hierarchical, three-step fashion involving an E1 ubiquitin-activating enzyme, an E2 ubiquitin-conjugating enzyme, and an E3 ubiquitin ligase. Substrate specificity is predominantly controlled by members of a large family of E3 enzymes, which form complexes with the proteins that will be modified. This ultimately leads to the covalent attachment of the C-terminus of ubiquitin to usually an ϵ -amino group of a lysine residue in the targeted protein. Additional ubiquitin transfer to lysine-48 of ubiquitin itself will form a polyubiquitin chain, which usually targets the conjugate for degradation by the proteasome. By contrast, mono- or polyubiquityla-

tion involving lysine-63 is normally involved in the control of protein activity. Ubiquitylation can be reverted by deubiquitylating enzymes, of which approximately 95 exist in mammals.

Following the approval of the first proteasome inhibitor for the treatment of multiple myeloma, efforts in both academia and industry have focused on the identification of novel drug targets within the ubiquitin pathway. Since numerous enzymes and co-factors are implicated in the addition or removal of ubiquitin, there is hope that appropriate targets can be found in the near future, opening the way for the identification of selectively blocking compounds.

The remarkable pace of developments in the area of ubiquitin research prompted us to organize a workshop to discuss the relevance of the ubiquitin pathway in health and disease. We believe we were successful in bringing together an outstanding group of international experts in this field. We are grateful to all of them for their excellent presentations and lively discussions. Their contributions to this book are also greatly appreciated. We sincerely hope that the proceedings of the workshop will lead to a better appreciation of the prominent and resourceful role of the ubiquitin system in many physiological processes and in numerous human diseases.

Finally, we wish to express our gratitude to the Ernst Schering Foundation for their excellent organization of the workshop, which undoubtedly helped to make it a great success. Special thanks also go to the Berlin-Brandenburg Academy of Sciences and Humanities and to Prof. G. Stock for hosting the meeting on their premises.

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