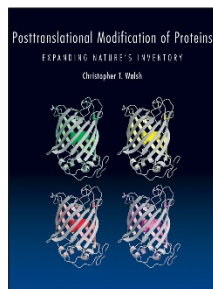


## The protein modification repertoire

**Posttranslational Modifications of Proteins: Expanding Nature's Inventory**

By Christopher T Walsh

Roberts and Co. Publishers, 2006

576 pp, hardcover, \$98.00

ISBN 0974707732

Reviewed by Wilfred A van der Donk

The enormous progress over the past decade in analytical techniques to study large macromolecules has revealed a much greater diversity in protein primary structure than predicted based on the use of the 20 common proteinogenic amino acids. X-ray crystallographic and mass spectrometric studies, in particular, have expanded the repertoire of co- and posttranslational modifications (PTMs) well beyond long-known examples such as phosphorylation, glycosylation and proteolytic processing. Together with variations in mRNA splicing, the diversity of these modifications greatly enlarges the accessible functional and structural space from the at-first-glance surprisingly small human genome. In *Posttranslational Modifications of Proteins*, Christopher Walsh provides the first comprehensive treatment of the modification processes and their biological consequences. The publication of this treatise is timely, given the rapidly increasing interest in systems biology and efforts to map proteomes. Its clearly laid-out content should appeal to both specialists and general readers.

Although the text is not meant to be encyclopedic, the book covers an impressive inventory of modifications that will provide many surprises for most readers. No less than 15 of the 20 common amino acids receive modifications in addition to rearrangements of the protein backbone. With a few exceptions, Walsh does not cover covalent modifications that occur during catalytic turnover of enzymes, but modifications that can be undone by counterbalancing enzymes are included. In the introductory chapter, concepts and trends are discussed as well as a survey of the techniques used to study PTMs. The scope of known modifications, both with respect to structural diversity and combinatorial complexity, is also covered. This chapter is followed by fourteen chapters organized by characteristic chemical features of PTMs, with many chapters describing multiple structurally distinct modifications. A superficial survey of the topics (phosphorylation, sulfation, Cys/Met oxidation, methylation, N-acetylation, lipidation, proteolysis, ubiquitylation, glycosylation, ADP-ribosylation, hydroxylation, automodification, carboxylation, and modification with biotin, lipoate and phosphopantetheine) does not do full justice to the many fascinating 'hidden gems' in each chapter. Many readers will have some familiarity with the categories listed, but few

will realize the diversity within each class with respect to structure, mechanism and function.

In a style reminiscent of that of his previous books, Walsh uses chemical rigor in numerous clearly drawn illustrations to describe the intricacies of the mechanisms for installation of the modified structures. The book should appeal to the chemical biologist, who will appreciate the attention paid to physicochemical details, such as changes in  $pK_a$  upon modification, and equilibrium constants derived from reaction free energies. At the same time, by choosing appropriate and recent examples, Walsh succeeds in providing the reader with a broader perspective of the biological role of the pertinent modification. Covered are the effects that each PTM has on structure, chemical reactivity, cellular localization, regulation of protein lifetime and temporal control over cellular processes. Like the descriptions of chemical mechanisms, the discussions of these functional roles are illustrated with excellent figures and diagrams, some of which are taken from the primary literature. Clearly, for anyone interested in the complex networks of signal transduction, chromatin remodeling or proteomics in general, this book will be a powerful and indispensable resource.

Organizationally, the book serves well as a reference for the reader interested in a subset of modifications. Each chapter stands on its own, telling one or more independent stories, and, combined with the introductory chapter and a final chapter on "Diversification of Proteomes," places the pertinent modification in a larger context. On the other hand, the book makes for a fascinating read when perused from cover to cover. The author provides insightful links between the various modifications and their roles. Chemical analogy is often pointed out, for instance in the amplification of the reactivity of amides to achieve N-glycosylations, protein splicing, biotinylation or repair of isoaspartate linkages. Similarly, the common intermediacy of thioesters in diverse processes like transamidation, protein splicing, ubiquitylation and proteolysis by Cys proteases is discussed. The chemical logic of phosphorylations versus sulfations is explained nicely, as are the different strategies used by phosphatases and sulfatases based on the inherently different reactivity of their substrates. Walsh also provides numerous cross-references for proteins that may undergo multiple different modifications in their lifetimes, such as the Rho family of GTPases, which undergo five distinct modifications, and histones, which undergo at least seven different types of modifications. In the latter example, the combination of N-acetylation (which removes positive charge), N-methylation (which is charge neutral) and phosphorylation (which introduces negative charge) can be used to modify the local charge context.

Walsh notes that additional PTMs undoubtedly will be discovered. Certainly, daunting challenges remain even for known modifications, such as establishing the details of the kinome and the ubiquitylated proteome, and deciphering the histone code. With its clarity and comprehensive coverage, this book will be a valuable handbook for students who will engage in such endeavors. Furthermore, it promises to be an excellent textbook for a variety of courses. For instance, it would be a great starting point for an enzymology course focusing on enzymes with protein substrates rather than the more common small-molecule substrates or for a course on proteomics. For a wide audience interested in enzyme catalysis, proteomics, structural biology and cell biology, this monograph is a precious addition to one's bookshelf. ■

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