

SUMOylation and Ubiquitination

Current and Emerging Concepts

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Preface

The discovery of ubiquitin and the ubiquitin-proteasome system in the late 1970s provided elegant insight into protein degradation as the biochemical process for removing damaged or unwanted proteins. This seminal discovery that polyubiquitination of substrate proteins directed them to the proteasome for subsequent degradation led to the Nobel Prize in 2004 for Drs Aaron Ciechanover, Avram Hershko and Irwin Rose. During the roughly 25 years between the discovery of this process and the award of the Nobel Prize there was an explosion of research demonstrating the breadth and importance of this post-translational modification system. One of the perhaps less expected and more slowly recognized features was the role of polyubiquitin-mediated degradation as a regulatory mechanism for controlling the functional levels of individual proteins and of multi-protein complexes. Proteasomal degradation became not simply a device to remove ageing or defective proteins, but also a powerful system to control levels of functional proteins in complex pathways and thus rapidly modulate the activity of these pathways. In addition, like phosphorylation, ubiquitination became appreciated as a versatile modification that could affect substrate functions in non-degradative ways. Combined with the discovery of mono- and multi-ubiquitination, along with multiple types of linkages for branched forms of polyubiquitin, it became clear that the ubiquitin addition was highly complex with enormous combinatorial capacity. Some of this complexity also stems from the large number of distinct enzymes and co-factors involved in ubiquitin processing and transfer to substrates, with several hundred proteins known to function in this process. Because of this biochemical complexity and diversity of components it is not surprising

that, nearly 40 years later, we are still uncovering the novel features of the ubiquitin system, identifying more and more substrates, and elucidating key cellular regulatory steps controlled by this small, yet profoundly important, protein.

A second exciting chapter in the ubiquitin story was the discovery in the late 1980s that there were a number of other ubiquitin-related proteins that together comprise the ubiquitin superfamily. Like ubiquitin, the other *Ubiquitin-like* proteins (Ubls) are covalently attached via their C-terminus to lysine residues in substrate proteins (although for a few family members ligation to substrates has not yet been established). Each member of the superfamily has its own specific set of enzymes that mediate the addition of the modifier to the substrate, although biochemically all members of the family undergo the same scheme of processing, activation, conjugation and eventual ligation to the substrate. Several members of the superfamily are still poorly characterized and several have fairly limited realms of substrates. However, one member of this superfamily, the *Small Ubiquitin-like Modifier* (SUMO) proteins, has been prominently investigated. In humans, there are five related SUMO proteins, SUMOs 1–5. SUMOs 1–3 are widely expressed and well characterized, whereas SUMOs 4 and 5 are more restricted and less is known about their functional roles. In contrast to the ubiquitin system, the SUMO system has far fewer components involved in processing and substrate modification. Nonetheless, sumoylation collectively has been shown to have a large and broad range of substrates (well over 3000 identified) and to be a critical modification during development, as well as for many normal cellular processes. Importantly, there is now well-established crosstalk between the ubiquitin and

SUMO systems through multiple mechanisms, including competition for the same target lysine in substrates, modification of substrates with both modifiers at different lysines, formation of mixed SUMO–ubiquitin polymers on some substrates, and degradation of substrates through targeting of ubiquitin to sumoylated proteins through SUMO-targeted ubiquitin ligases (STUbLs). The ability of these two modification pathways to function both independently or cooperatively on thousands of substrates is a remarkable observation that underscores just how widespread and entrenched this type of post-translational modification is in cell biology.

In late 2017 I was approached about putting together a book on current and emerging concepts in the fields of sumoylation and ubiquitination. The previous 5 years had seen an explosion of new technologies for identifying substrates and mapping modification sites, so there was a wealth of novel biochemical, molecular and biological data about these two systems. All of these new data were perfect fodder for a book project, especially one

focused on the interplay between these systems, so the timing was ideal. Although certainly not all-inclusive, I tried to identify topic areas for the book for which there were significant recent advances and/or strong evidence for a functional role of both SUMOs and ubiquitin. I would like to thank all of the authors who so graciously agreed to address these topics and provide chapters for this book. Your individual contributions to the book were uniformly excellent and provided wonderful reviews of your research areas. I hope that this final compilation will prove useful to both novice and seasoned investigators in these fields, and that future readers will learn as much about sumoylation and ubiquitination as I did.

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