Monoubiquitination: A dynamic tag for protein regulation

Ubiquitination is a post-translational modification (PTM) that involves the covalent attachment of an 8 kDa ubiquitin (Ub) peptide to one or more lysines of a target protein. Modification of a target protein may occur as a single Ub on a single lysine (monoubiquitination), a single Ub on multiple lysines (multibiquitination) or as ubiquitinated chains in which lysines on the initial protein-conjugated ubiquitin are extended through sequential rounds of ubiquitination (polyubiquitination). The fact that ubiquitin contains seven lysine residues and polyubiquitination has been demonstrated to occur through all of these gives this PTM the potential for highly diverse modifications of target proteins. It is also known that ubiquitination, through the action of deubiquitinating proteins (DUBs), is a rapidly reversible process, thus giving ubiquitination the potential to be a hugely versatile signaling moiety, far exceeding the complexity of more well-studied PTMs such as phosphorylation. While the critical role of ubiquitination in the proteasomal degradation of target proteins is well known, the non-degradative roles of ubiquitination are only beginning to be described. This newsletter focuses on several general, non-degradative processes regulated by monoubiquitination (Fig. 1).

Intramolecular Autoinhibition

PTMs such as phosphorylation are major regulators of protein autoinhibition. Evidence is emerging to suggest that protein monoubiquitination may serve a similar function. Several reports have shown that proteins containing ubiquitin binding domains (UBDs) are often monoubiquitinated (mUb), thereby suggesting a simple autoinhibitory mechanism via an intramolecular UBD-mUb interaction. Endocytic adaptor proteins such as Sts1, Sts2, and Eps15 provide the best examples of this type of regulation. Receptors, such as the epidermal growth factor receptor (EGFR), become ubiquitinated post-activation, which triggers internalization and degradation through the endosomal-lysosomal pathway, thereby attenuating the transduction signal. The endocytic adaptor proteins control the internalization and degradation of ubiquitinated cell surface receptors by binding the receptor’s Ub moiety in trans via the adaptor UBD domain and linking the receptor to endosomal trafficking proteins. In cases where the adaptor proteins are autoinhibited, and therefore blocked from recognizing their ubiquitinated receptor target, the transduction signal will continue to be propagated. In these cases, autoinhibition acts as a modulator of receptor-mediated signal transduction (Fig. 1).

There are twenty known families of UBDs and greater than 150 proteins that contain one or more UBD domains. The UBD proteins are involved in a wide range of cellular processes, including endocytosis, DNA repair, transcriptional regulation, transmembrane signaling, and cytoskeletal dynamics.
and signal transduction. Current evidence suggests that ubiquitin-mediated autoinhibition may play a major role in regulating these processes.

Intracellular Localization and Trafficking

Proper cellular localization of a protein is a primary means of regulating its activity and many strategies have evolved to ensure the fidelity of spatial regulation, including well-documented cases of PTM events such as farnesylation, palmitoylation, and phosphorylation. Monoubiquitination can act in conjunction with other PTMs to localize proteins such as small GTPases, cytoskeletal proteins, and scaffolding proteins to specific cellular compartments (Fig. 1). For example, the isoforms H-Ras, N-Ras, and K-Ras have all been shown to be substrates for monoubiquitination (and non-degradative diubiquitination in the case of H- & N-Ras). H-Ras ubiquitination appears to act in conjunction with farnesylation and palmitoylation to promote relocation of H-Ras from the plasma membrane to endosomal sites with a concomitant reduction in MAPK signaling. Interestingly, monoubiquitination of K-Ras, the Ras gene most commonly associated with cancer, appears to enhance GTP loading by modulating the affinity of K-Ras for downstream effectors. Similarly, signaling in response to VEGF also involves monoubiquitination. The monoubiquitinated form of the actin binding protein filamin B has been shown to regulate nuclear/cytoplasmic trafficking and cytoplasmic localization of HDAC7 in response to VEGF. Transient monoubiquitination of filamin B occurs in response to VEGF stimulation and binds to the nuclear localization signal (NLS) of HDAC7, thereby transiently preventing its re-entry into the nucleus and mitigating the transcriptional repressor activity of HDAC7 on the genes required for VEGF-mediated responses. Another structurally-related protein targeted for monoubiquitination is the Toll-like and interleukin-1 receptor complex scaffold protein TRAF4. This protein undergoes monoubiquitination as a prerequisite for localization at tight junctions where it is required for Rac1 activation and migration of normal breast epithelial and cancer cells.

Regulation of Protein Complex Formation

Monoubiquitination has been reported to regulate protein complex formation in a number of systems. For example, the process of transcriptional elongation is known to require nucleosomal rearrangement to remove the physical block from the transcribing RNA polymerase. The FACT (facilitates chromatin transcription) complex is a major player in this process and operates, in part, by displacing a histone H2A/H2B dimer from the nucleosome. An in vitro reconstitution system demonstrated that monoubiquitination of H2B is required for FACT-mediated displacement of the H2A/H2B dimer.

In conclusion, monoubiquitination, and non-degradative ubiquitination signaling in general, is rapidly becoming established as a versatile regulatory motif.

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