MS08-P01 | Regulation Of P97 ATPase Activity By Cofactor-Mediated Remodeling And Post-Translational Modification

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AAA proteins are ATPases associated with diverse cellular activities. The abundant human ATPase p97 is functionally regulated by a family of ubiquitin regulatory-X (UBX) domain-containing cofactors. We demonstrated that the UBX protein ASPL (alveolar soft-part sarcoma locus) modifies p97 function by remodeling p97 hexamers into p97:ASPL heterotetramers with reduced ATPase activity [1]. This activity depended on the presence in ASPL of an extended UBX (eUBX) domain with N-terminal lariat that wraps around the p97-N domain, disrupting the functional p97 hexamer and reducing its ATPase activity.

A database search for eUBX sequence signatures identified the *Arabidopsis thaliana* protein PUX1 protein. By biochemical studies and crystal structure analysis of the *A. thaliana* p97 ortholog CDC48 and a p97:PUX1 complex we provided evidence for an ATPase remodeling process in plants analogous to p97 remodeling by ASPL.

Further, we observed that the conversion of p97 into p97:ASPL heterotetramers led to the surface exposure of peptide segments deeply buried inside functional p97 hexamers, some of which harbored post-translationally modified residues. We hypothesized that structural remodeling by ASPL or homologous proteins might facilitate the modification of these residues and tested this hypothesis by studying the trimethylation of p97 Lys315 by the protein lysine methyltransferase METTL21D. Biochemical evidence and the crystal structure of heterotetrameric p07:ASPL:METTL21D complex confirmed our hypothesis and suggested a novel mode of functional regulation of p97 and, possibly, related ATPases by coupling of structural remodeling and post-translational modification.

[1] Arumughan, A. et al. (2016) Nat. Commun. 7, 13047 (2016).