MS29.O04

Remodeling of the AAA+ ATPase p97 by the UBX Adaptor Protein ASPL

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The hexameric mammalian AAA+ ATPase p97, also known as VCP (valosin-containing protein; CDC48 in yeast), is a very abundant cytosolic protein and serves a wide variety of cellular functions. p97 is a central component in endoplasmic reticulum-associated degradation (ERAD) of proteins where it delivers ubiquitinated ERAD substrates to the proteasome. In addition, cellular roles of p97 in organelle membrane fusion, mitosis, DNA repair and suppression of apoptosis have been described. These different functions are linked to the binding of adaptor proteins to p97. Many of these adaptors contain ubiquitin regulatory X (UBX) domains. ASPL (alveolar soft part sarcoma locus, also known as TUG) was recenty identified as a p97 adaptor protein. As shown by crystal structure analysis, ASPL uses a substantially extended UBX domain for binding to the N domain of p97 where a lariat-like, mostly α-helical extension wraps around one subunit of p97. By this binding ASPL triggers the dissociation of functional p97 hexamers and the formation of p97:ASPL heterotetramers with 2:2 stoichiometry, leading to inactivation of the AAA+ ATPase. The p97-ASPL interaction in the heterotetramer is very tight, but p97 hexamer dissociation and heterotetramer formation may be suppressed by single-site mutations at p97-ASPL interfaces. p97 hexamer dissociation and p97-ASPL heterotetramer formation are linked to reduced ATPase activity of p97, cellular accumulation of ERAD substrates and apoptosis induction. To the best of our knowledge, this is the first time that the structural basis for adaptor protein-induced inactivation by hexamer dissociation of p97 and, indeed, any AAA+ ATPase has been demonstrated. This observation has far reaching implications for AAA+ ATPase-regulated processes.

Keywords: AAA+ ATPase, molecular machine, protein remodeling