When proteins change partners

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Dieter Wolf, M.D., and colleagues at Burnham Institute for Medical Research (Burnham) have illuminated how competition between proteins enhances combinatorial diversity during ubiquitination (the process that marks proteins for destruction).

Using S. pombe fission yeast as a model, the Wolf laboratory uncovered an intricate relationship, in which an array of Fbox proteins alternately attach to and are kicked off of a cullin-RING ubiquitin ligase (CRL1) containing CUL1 and Skp1. Without the Fbox, CRL1 cannot attach to the protein substrate or recruit ubiquitin, potentially preserving aberrant proteins. The research was published in the journal *Molecular Cell* on September 11.

S. pombe expresses 16 different Fbox proteins, some of which are regulated by the COP9 signalosome (CSN). The study shows that these proteins attach to CRL1 but are kicked off by the competing protein CAND1. Fbox proteins and CAND1 continue to trade places until they come in contact with the appropriate substrate of the protein being degraded. This phosphorylated substrate recruits the protein N8, which attaches to the complex and stabilizes the Fbox protein. Then the complex can attach to the substrate and recruit ubiquitin. Once this process is completed, N8 is removed, Fbox is destabilized and the process begins again.

"The tension between CAND1 and Fbox gives more Fbox proteins the opportunity to attach to CRL1," says Dr. Wolf. "Without CAND1, more prevalent Fbox proteins would dominate the process. We also found that,

to bind to CRL1, the Fbox proteins must contain a specific proline residue. Only when the substrate is present can the Fbox protein be stabilized in the complex."

The laboratory tested eight of the 16 Fbox proteins. They found that five of the eight were regulated by the CSN and that CSN-insensitive proteins were missing a proline residue. They also found that the proline residue was required for CRL1 complex formation. The laboratory also determined that CAND1 deficiency and CSN deficiency produced different phenotypes, outlining the different roles they play in stabilizing CRL1.

Source: Burnham Institute (news : web)