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CORBIS

PROTEIN DEGRADATION

Examining E1

Ubiquitin-activating (E1) enzymes catalyse the first step in the ubiquitylation cascade, which results in the addition of ubiquitin (Ub) and other ubiquitin-like proteins (Ubls) to target proteins. Briefly, an E1 enzyme binds a Ubl, adenylates its C terminus, and then transfers the Ubl to a Ub-conjugating (E2) protein for the next step in the ubiquitylation cascade. Although the general mechanism of E1 activity is known, the structure of E1 enzymes have been elusive. In *Cell*, Imsang Lee and Hermann Schindelin now report the crystal structure analysis of the *Saccharomyces cerevisiae* E1 enzyme, Uba1, bound to Ub.

The structure of Uba1 contains six modular domains: IAD, AAD, FCCH, SCCH, 4HB and UFD. Four of these domains, AAD, FCCH, SCCH and UFD, are packed together to form a large central canyon (~40-Å wide), one end of which accommodates Ub. The width of the canyon suggests that it may also accommodate the E2 protein. Notably, the structure also includes three flexible linkers that connect UFD, FCCH and SCCH to their respective adjacent domains.

By analysing the structure of Uba1, and by observing the effects of particular point mutations, the authors gleaned insight into the function and mechanism of E1 activity. E1 enzymes are highly specific, both for Ubls and E2 enzymes. In the crystal structure, three different faces of Ub interact with Uba1, and Uba1 provides residues that contact Arg72 of Ub, a key amino acid in Ub discrimination. Altogether, ~33% of the surface area of Ub is embedded in Uba1. The authors propose that these observations probably explain the specificity of E1 enzymes for Ubls. By introducing a point mutation in Uba1, the authors show that UFD has a key role in binding E2 proteins. Furthermore, the UFD seems primed for conformational changes, which the authors suggest are probably crucial for the handoff of Ub to an incoming E2 protein.

As E1 enzymes and Ubs from different organisms share extensive homology, UBE1, the mammalian homologue of Uba1, might adopt a similar architecture as Uba1 and might activate Ub in the same manner.

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ORIGINAL RESEARCH PAPER Lee, I. & Schindelin, H. Structural insights into E1-catalyzed ubiquitin activation and transfer to conjugating enzymes. *Cell* **134**, 268–278 (2008)