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The Structure of the APPBP1-UBA3-NEDD8-ATP Complex Reveals the Basis for Selective Ubiquitin-like Protein Activation by an E1. Helen Walden, Michael Podgorski, Brenda Schulman, Structural Biology, St Jude Children's Research Hospital, 332 N. Lauderdale, Memphis, TN 38105 USA.

E1 enzymes initiate ubiquitin-like protein (ubl) transfer cascades by catalyzing adenylation of the ubl's C-terminus. An E1's specificity for its cognate ubl is essential because the E1 coordinates the ubl with its correct downstream pathway. We report here the crystal structure of the 120 kDa ternary complex between human APPBP1-UBA3, a heterodimeric E1, and its ubl, NEDD8. The structure reveals that the E1 selectively recruits NEDD8 through a bipartite interface, involving both a domain common to all ubl activating enzymes including bacterial ancestors, and also eukaryotic E1-specific sequences. Modeling ubiquitin into the NEDD8 binding site identifies a single arginine in APPBP1-UBA3 that we demonstrate is responsible for preventing the misactivation of ubiquitin by NEDD8's E1. Residues in NEDD8 involved in the E1 interaction correspond to residues in ubiquitin important for interactions with CUE, UIM and UBA domains, suggesting that the conjugation and ultimate recognition machineries have coevolved for each specific ubl.