by introducing destabilizing mutants in the client, and, if so, are the predicted changes observed in the fitted ensembles? An obvious next step, given the importance of Spy-client electrostatic interactions, would be to use a somewhat higher-resolution model (multiple beads per residue), which would allow favorable and unfavorable electrostatic interactions between the client and chaperone to be modeled explicitly rather than implicitly via the statistical potential functions.

Molecular chaperones have long been regarded to be crucial contributors to successful protein folding *in vivo*, particularly under conditions of cell stress[21,22]. Yet despite three decades of active investigation, many details on exactly how these proteins function are still lacking. By focusing on an ATP-independent chaperone, these three new studies strip away some of the inherent complexity of chaperone mechanisms, highlighting the (still quite complex) crucial steps of client-protein recognition, binding and folding. Not surprisingly, results from these studies raise as many new questions as they resolve. The rapidity with which Spy binds its client brings up the issue of how the cell coordinates the much slower upstream steps necessary to position Spy for action. The striking contributions of electrostatics to this rapid binding lead to queries about the generality of this mechanism: is it used by Spy to recognize other clients? To what extent do other chaperones exploit electrostatics? Teasing apart the subset of partially folded conformations bound to Spy highlights the potential for using the new READ approach to test longstanding hypotheses regarding the specific hydrophobic interactions formed between these client conformations and the chaperone-binding surface. The answers may have important implications for developing a general understanding of chaperone-client interactions. Finally, it is important to bear in mind that these studies were performed under conditions in which Im7 can fold autonomously, and hence it remains to be determined how the crucial interactions are affected when client folding intermediates become prone to self-association (**Fig. 1**).

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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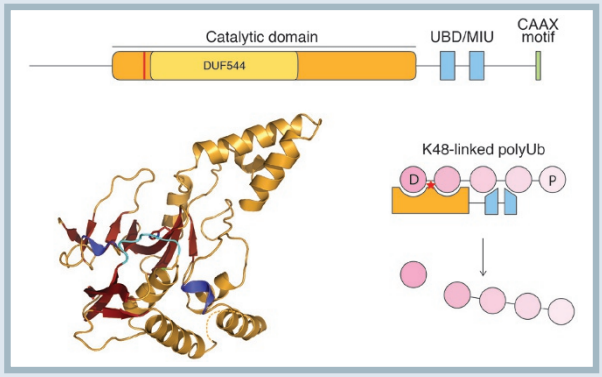
New DUBs on the block

Ubiquitination is a post-translational modification in which the ubiquitin protein (Ub) is attached to an acceptor lysine residue in the substrate. Ub itself has seven lysine residues and an N-terminal methionine that can serve as acceptors for another Ub; thus, chains with different linkages and different functional outcomes may form. In particular, K48-linked chains target their substrates for proteasomal degradation. Ub conjugates can be removed by deubiquitinating enzymes (DUBs), of which five families have been identified in the human genome.

Kulathu and colleagues have now identified a new DUB family, named MINDY (for MIU-containing novel DUB family), that has selectivity toward long K48 Ub chains (*Mol. Cell* doi:10.1016/j.molcel.2016.05.009).



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The authors started by investigating a previously uncharacterized protein, FAM63A, which bears tandem motifs interacting with Ub (MIUs; blue boxes in the domain-architecture schematics at top). A fragment containing the MIU motifs specifically binds K48 chains. FAM63A also contains a domain of unknown function, DUF544 (yellow box), and a conserved cysteine (red line), which together are part of a catalytic domain that displays cysteine protease activity with specificity toward K48 linkages. Other members of the family that were identified in humans and other eukaryotes on the basis of sequence similarity showed comparable properties *in vitro*.

To understand how FAM63A (renamed MINDY-1) recognizes and cleaves K48 Ub chains, the authors solved the crystal structure of its catalytic domain, both alone (model, bottom left) and in a covalent complex with a modified Ub moiety. The structures reveal a new cysteine protease folding variant that has no structural similarity to other DUB families; they also indicate how substrate binding activates the enzyme.

Furthermore, detailed biochemical analysis showed that MINDY-1 trims K48-linked Ub chains from the distal end. This activity requires chains with at least four Ub moieties, because the tandem MIU motifs bind a K48 di-Ub, and the catalytic domain binds another K48 di-Ub and cleaves the intervening linkage (bottom right). Importantly, coimmunoprecipitation assays on cell lysates demonstrated that MINDY-1 recognizes K48-linked polyubiquitinated proteins in a manner that requires the MIU motifs.

The identification of a new family of DUBs paves the way for functional studies to bring their cellular roles to the fore.

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