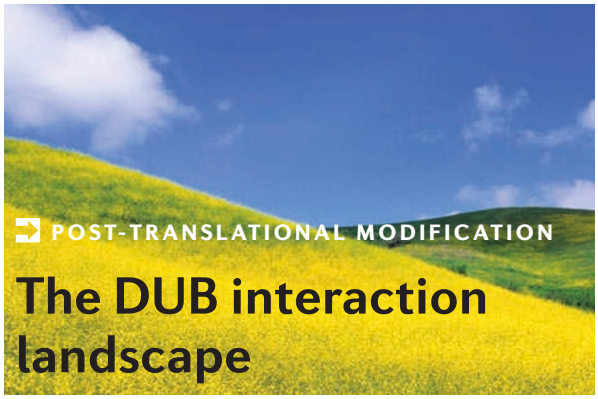

Whereas much progress has been made in understanding the function of the enzymes that conjugate ubiquitin to target proteins, little is known about those that remove this post-translational modification — the deubiquitylating enzymes (DUBs). Now, Wade Harper and colleagues report a global proteomic analysis that identifies 774 candidate interacting proteins for 75 of the ~95 DUBs that are encoded by the human genome. This study provides new insights into the function, regulation and targets of DUBs.

Using tagged versions of DUBs, the authors purified DUB-interacting complexes from a human cell line and analysed them by liquid chromatography–tandem mass spectrometry. To evaluate the proteomic data they developed the comparative proteomic analysis software suite (*CompPASS*), which uses an unbiased method to identify high-confidence candidate interacting proteins (HCIPs) and facilitates the functional dissection of interaction networks.

Gene ontology analysis, subcellular localization studies and the protein–protein interaction database tools of *CompPASS* were used to link DUBs and the 774 identified HCIPs to core cellular functions, such as the DNA damage response, transcription, RNA processing, protein turnover and endoplasmic reticulum-associated degradation (ERAD). Notably, 26 DUBs associate with protein domains that are found in various E3 ubiquitin ligases (the enzymes that conjugate ubiquitin to substrates), which suggests cross-regulation between ubiquitylation and deubiquitylation pathways.

To show the value of the data set for predicting the function of DUBs and the accuracy of *CompPASS*, the authors studied ubiquitin-specific protease 13 (USP13), a DUB of unknown function, and its HCIPs in more detail. USP13 interacts with p97 and other p97-interacting proteins, which have important roles in ERAD. Knockdown of *USP13* by small interfering RNA causes the accumulation of a model ERAD substrate and increases the sensitivity of cells to a drug that stimulates cell death through the unfolded protein response. So, as predicted by *CompPASS*, USP13 functions in the ERAD pathway.

Many more questions about the biological roles of DUBs remain unanswered, but this study, as the authors claim, "has allowed us to begin to define the Dub interaction landscape and to assign putative biological functions for previously unstudied Dubs."

Francesca Cesari

ORIGINAL RESEARCH PAPER Sowa, M. E. *et al.* Defining the human deubiquitinating enzyme interaction landscape. *Cell* 16 Jul 2009 (doi:10.1016/j.cell.2009.04.042)
FURTHER READING Komander, D. *et al.* Breaking the chains: structure and function of the deubiquitinases. *Nature Rev. Mol. Cell Biol.* **10**, 550–562 (2009)