Nature Reviews Molecular Cell Biology | AOP, published online 21 January 2015; doi:10.1038/nrm3942

PROTEIN FOLDING

PHOSPHORYLATION REGULATES IDP FOLDING

Intrinsically disordered proteins (IDPs) can transition between disordered and ordered states to mediate their biological function. Bah *et al.* reveal a new means by which this can be controlled, showing that phosphorylation regulates the folding, and thus biological function, of the IDP eukaryotic translation initiation factor 4E-binding protein 2 (4E-BP2).

4E-BP2 competes with eukaryotic translation initiation factor 4G (eIF4G) for eIF4E binding to suppress cap-dependent translation initiation; both bind to eIF4E through their canonical YXXXXLΦ motif (in 4E-BP2, this motif starts at Tyr54). Although it was clear that phosphorylation of 4E-BP2 (at Thr37, Thr46, Ser65, Thr70 and Ser83) reduces its affinity for eIF4E, the mechanism was unknown.

The authors showed that residues Pro18–Arg62 of 4E-BP2 become folded following Thr37 and Thr46 phosphorylation, while the rest of the protein remains disordered. Further analysis showed that this phosphorylation causes Pro18–Arg62 to form a four-stranded β-fold in which the YXXXXLΦ motif is sequestered, explaining why phosphorylation reduces 4E-BP2–eIF4E binding.

As phosphorylation of 4E-BP2 at Thr37, Thr46, Ser65, Thr70 and Ser83 reduces its affinity for eIF4E more than phosphorylation at Thr37 and Thr46 alone, the authors propose that phosphorylation at Ser65, Thr70 and Ser83 stabilizes the fold.

Thus, this study presents phosphorylation as a new mechanism by which IDPs can control biological function. It also provides insight into 4E-BP-mediated control of translation initiation.

Katharine H. Wrighton

ORIGINAL RESEARCH PAPER Bah, A. *et al.* Folding of an intrinsically disordered protein by phosphorylation as a regulatory switch. *Nature* http://dx.doi.org/10.1038/nature13999 (2014)
FURTHER READING Wright, P. E. & Dyson, H. J. Intrinsically disordered proteins in cellular signalling and regulation. *Nature Rev. Mol. Cell Biol.* **16**, 18–29 (2015)

© 2015 Macmillan Publishers Limited. All rights reserved