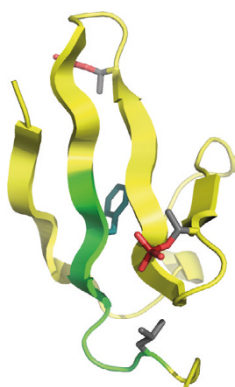


## Bringing phosphorylation into the fold

Intrinsically disordered proteins do not possess stable three-dimensional structures, but they can fold into ordered states upon interacting with partners such as ligands or other macromolecules. Although post-translational modifications have been known to regulate many intrinsically disordered proteins by stabilizing or destabilizing short localized secondary-structure segments, evidence of post-translational modifications mediating conformational transitions of intrinsically disordered proteins into folded states was lacking. Now Forman-Kay and colleagues show that phosphorylation of the intrinsically disordered protein 4E-BP2 at multiple sites induces a structured state with important functional implications. 4E-BP2 binds the translation initiation factor eIF4E to suppress cap-dependent translation initiation. Interaction of the nonphosphorylated form of 4E-BP2 with eIF4E causes a disorder-to-helix transition of its canonical YXXXXLΦ eIF4E-binding motif. Using a combination of NMR spectroscopy and isothermal titration calorimetry, the authors show that phosphorylation of 4E-BP2 at two sites, Thr37 and Thr46, induces folding of the region encompassing residues Pro18 to Arg62, which also includes the YXXXXLΦ motif, into a four-stranded β-domain while the rest of the protein remains disordered. The folding involves recruitment of the YXXXXLΦ motif into the fourth β-strand, and it results in reduced affinity for eIF4E as well as potential inhibition of the degradation-inducing ubiquitination of Lys57. This folded state is weakly stable, and the interaction with eIF4E—albeit diminished—leads to unfolding of the β-domain. Additional phosphorylation at three more sites (Ser65, Thr70 and Ser83) is required to stabilize the β-domain, with the fully phosphorylated 4E-BP2 having a 4,000-fold-reduced affinity for eIF4E. Thus, the transition into a folded state driven by phosphorylation provides a mechanism to regulate the biological activity of 4E-BP2 and suggests that post-translational modifications may have a role in mediating structural changes of other intrinsically disordered proteins into functionally relevant ordered states. (*Nature* doi:10.1038/nature13999, 22 December 2014) CD



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histone-acetylation motifs are more likely to perform structural roles, whereas rarer ones may transmit regulatory signals. To determine the contributions of lysine acetyltransferases (KATs) and deacetylases (KDACs) to the histone acetylome, the authors depleted 31 known or putative KATs and KDACs by RNA interference. In contrast to the widespread notion that KATs are fairly promiscuous enzymes, most KATs showed narrow substrate specificity that was influenced by adjacent acetylation and methylation. In contrast, KDACs were characterized by relaxed substrate specificity. Surprisingly, losses in histone acetylation upon ablation of KATs were usually accompanied by gains in other, sometimes unrelated, motifs. For example, loss of acetylated H4 Lys16, a mark with mainly structural functions, is accompanied by increased acetylation of the adjacent Lys12, a response conserved in human cells. These secondary effects can be interpreted as adaptations of a system that strives to compensate for a global change in acetylation state. Depletion of most KATs also led to changes in histone methylation, thus indicating an intricate co-regulated system. Further mining of this valuable data set will allow derivation of quantitative models and testable hypotheses about the functional cross-talk between histone-modifying enzymes, ultimately increasing knowledge of the systemic response of the chromatin-modification network. (*Mol. Cell* doi:10.1016/j.molcel.2014.12.008, 8 January 2015) AS

## Resolving stalled ribosomes

Fidelity in gene expression is maintained by a variety of mechanisms, including monitoring of mRNA templates and protein products. Although faulty mRNAs and the deviant polypeptides produced from them are usually subjected to accelerated degradation, ribosomes engaged in aberrant translation are probably recycled. Impediments that block ribosome translocation result in dissociation of the 40S ribosomal subunit and recruitment of the ribosome quality-control complex (RQC) to the peptide-bound 60S complex. The RQC guides tagging of the peptide for degradation via the Ltn1 E3 ligase and presumably mediates the release of the ribosomal subunit for reuse. Recent cryo-EM and functional studies by Weissman, Brandman, Frost and colleagues have uncovered a previously undefined role for the RQC component Rqc2 in mediating extension of nascent peptides in a template-independent manner. In the presence of an E3-deficient Ltn1 mutant, the authors were able to capture Rqc2-bound 60S subunits with nascent peptide chains in the ribosome exit tunnel. Rqc2 was located on the 40S-binding surface and appeared to associate with the peptidyl- and aminoacyl-site tRNAs, which were enriched for alanyl and threonyl tRNAs. Previous studies had shown the presence of extended polypeptides in an *ltn1Δ* strain. Here, the authors biochemically identified these extensions as Rqc2-dependent C-terminal 'CAT' tails comprising alanine and threonine residues. Interestingly, these CAT tails were required for the induction of a heat shock factor 1-dependent transcriptional response, which had previously been observed to occur upon the accumulation of stalled peptides in an Rqc2-dependent manner. In summary, Rqc2's ability to direct polypeptide chain extension provides a general mechanism whereby stalled nascent polypeptides can be marked in a sequence-independent manner. (*Science* 347, 75–78, 2015) SG

## Histone acetylome mapped

DNA packaging into chromatin requires a dynamic control of chromatin structure to allow regulated gene expression, which is achieved by a complex array of histone post-translational modifications (HPTMs). Histone acetylation, one of the most frequent HPTMs, recently celebrated the 50-year anniversary of its discovery, but despite this long history the precise combinatorial regulation of the histone-modification network and the interplay of enzymes that set these marks are far from being understood. Becker and colleagues have now optimized a mass spectrometry-based strategy to allow accurate quantification of HPTM motifs and have applied it to generate a comprehensive inventory of all acetylation sites and many combinatorial motifs for histones H3 and H4 in *Drosophila melanogaster* KC cells. The abundance of individual motifs differs greatly, suggesting separation of function. Highly abundant

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