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PROTEIN DEGRADATION

Take a leaf from plants

The stability of the proto-oncogenic transcription factor c-Jun is known to be regulated by the ubiquitin–proteasome system, yet the identity of a c-Jun-specific ubiquitin ligase has been elusive. Taking a leaf from plant biology, Vishva Dixit and colleagues have now identified a human orthologue of *Arabidopsis thaliana* de-etiolated-1 (DET1), which regulates photomorphogenesis, and have found that human DET1 promotes the degradation of c-Jun by assembling a ubiquitin-ligase complex.

Dixit and colleagues found that two negative regulators of photomorphogenesis in *A. thaliana* — DET1 and constitutively photomorphogenic-1 (COP1) — are highly conserved in mammals. Given that DET1 and DNA-damage-binding protein-1 (DDB1) interact to regulate photomorphogenesis, and DDB1 associates with cullin 4A (CUL4A) and regulator of cullins-1 (ROC1) in mammalian ubiquitin-ligase complexes, the authors hypothesized that human DET1 might also bind ubiquitin-ligase components. This turned out to be the case — tagged human DET1 immunoprecipitated DDB1, CUL4A, ROC1 and COP1 .

A. thaliana COP1 provided a clue regarding the putative substrate(s) of this human multi-subunit ubiquitin ligase, which the authors named $DCX^{hDET1–hCOP1}$. The plant COP1 promotes the degradation of certain basic-region–leucine-zipper (bZIP) transcription factors, and indeed, human COP1, as well as a prevalent splice variant (COP1Δ24), binds c-jun, JunB and JunD, but not other members of the Jun family of bZIP transcription factors.

Next, Dixit and colleagues analysed $DCX^{hDET1–hCOP1}$-subunit interactions. In the absence of DDB1, the association between CUL4A and DET1 was reduced, which indicates that DDB1 bridges CUL4A and DET1. Similarly, decreasing DET1 expression reduced the association between COP1 and DDB1 — so, DET1 links COP1 to DDB1, and thereby recruits c-Jun to the $DCX^{hDET1–hCOP1}$ complex. However, COP1Δ24, which lacks part of the coiled-coil interaction domain, did not bind DET1 and, as a result, cannot associate with $DCX^{hDET1–hCOP1}$. Furthermore, the authors found that the COP1 RING finger is dispensable for c-Jun degradation, which implicates the ROC1 RING finger as the functional ubiquitin-ligase domain of the $DCX^{hDET1–hCOP1}$ complex.

To test the function of the $DCX^{hDET1–hCOP1}$ complex, Dixit and co-workers treated cells that were transfected with human DET1 and COP1 with a proteasome inhibitor, and found that this blocked c-Jun degradation. Ubiquitylation of c-Jun was detected only when the complete complex was assembled; indeed, COP1Δ24 did not promote effective ubiquitylation. Ablation of any subunit of $DCX^{hDET1–hCOP1}$ by RNA interference resulted in endogenous c-Jun accumulation — thereby confirming the physiological relevance of this c-Jun-specific ubiquitin-ligase complex.

So, the authors conclude that human DET1 promotes the ubiquitylation and degradation of c-Jun by promoting ubiquitin-ligase-complex assembly. And, coming back full circle to plants, given the conservation of the $DCX^{hDET1–hCOP1}$ components, a similar ubiquitin-ligase complex might explain how *A. thaliana* DET1 and COP1 regulate photomorphogenesis.

Arianne Heinrichs

References and links

ORIGINAL RESEARCH PAPER Wertz, I. E. *et al.* Human de-etiolated-1 regulates c-Jun by assembling a CUL4A ubiquitin ligase. *Science* 22 Jan 2004 (doi:10.1126/science.1093549)

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