



β TrCP induces DEPTOR degradation, and ... DEPTOR must be phosphorylated ... to recruit β TrCP.



CELL SIGNALLING

mTOR targets its own inhibitor

Mammalian target of rapamycin complex 1 (mTORC1) and mTORC2 both contain, and are inhibited by, DEP domain-containing mTOR-interacting protein (DEPTOR). Upon serum stimulation, DEPTOR is degraded by the 26S proteasome to allow mTOR activation, but the ubiquitin E3 ligase driving this degradation was unknown. Three groups now report that, following its phosphorylation by specific kinases, DEPTOR is targeted for degradation by the Skp1–cullin 1–F box– β TrCP (SCF ^{β TrCP}) E3 ubiquitin ligase.

The authors of these papers all sought to identify the E3 ligase that triggers DEPTOR degradation. Gao *et al.* overexpressed DEPTOR in cells and, using mass spectrometry, identified the F box protein β -transducin repeat-containing protein 2 (β TrCP2) as a DEPTOR-interacting protein. Zhao *et al.* examined DEPTOR for consensus binding motifs of F box proteins and identified β TrCP1 and β TrCP2 (which are thought to function redundantly) as DEPTOR-interacting proteins. Duan *et al.* screened a library of F box proteins, revealing that DEPTOR interacts with β TrCP1 and β TrCP2. Thus, SCF ^{β TrCP} is a candidate E3 ligase for DEPTOR. Indeed, further experiments by these groups confirmed that β TrCP induces DEPTOR degradation, and that DEPTOR must be phosphorylated within its degradation motif (known as a degron; 286-SSGYFS-291) to recruit β TrCP.

But what kinases are required for DEPTOR degradation? Gao *et al.* and Duan *et al.* found that inhibitors of mTOR (the common active component of each mTORC) and casein kinase 1 (CK1) blocked β TrCP–DEPTOR interactions, degron phosphorylation and DEPTOR degradation. Furthermore, both groups found that mTOR induces initial ‘priming’ phosphorylations outside the DEPTOR degron, at Ser293 and Ser299, which is followed by CK1 α -induced phosphorylation of degron Ser residues and subsequent β TrCP recruitment.

Zhao *et al.* found that S6 kinase 1 (S6K1), a downstream target of mTOR signalling, and ribosomal S6K1 (RSK1) phosphorylate DEPTOR to enhance its β TrCP-mediated degradation; S6K1 seems to induce a priming phosphorylation for DEPTOR-targeted RSK1 activity. All of these results suggest that mTOR positively regulates its own activity by inducing the degradation of one of its key endogenous inhibitors, either directly or through its downstream target S6K1.

Finally, Zhao *et al.* and Gao *et al.* investigated how DEPTOR levels influence the ability of mTOR signalling to negatively regulate autophagy. Both groups found that glucose deprivation, which can trigger autophagy, increased DEPTOR protein levels, decreased mTORC1 activity and induced autophagy. Consistent with this, depletion of DEPTOR reduced autophagy induced by glucose limitation. Gao *et al.* also showed that an increase in DEPTOR, owing to β TrCP depletion, resulted in autophagy even in the presence of glucose. Interestingly, data from both groups also suggested that decreased mTORC1 activity, as a result of an increase in DEPTOR, might contribute to the chemotherapeutic resistance of cancer cells.

Together, these three papers reveal that mTOR signalling primes DEPTOR for phosphorylation by additional kinases, enabling SCF ^{β TrCP} to bind and trigger its degradation. Thus, mTOR can positively regulate its own activity to influence key biological responses, such as autophagy.

Katharine H. Wrighton

ORIGINAL RESEARCH PAPERS Gao, D. *et al.* mTOR drives its own activation via SCF ^{β TrCP}-dependent degradation of the mTOR inhibitor DEPTOR. *Mol. Cell* **44**, 290–303 (2011) | Zhao, Y., Xiong, X. & Sun, Y. DEPTOR, an mTOR inhibitor, is a physiological substrate of SCF ^{β TrCP} E3 ubiquitin ligase and regulates survival and autophagy. *Mol. Cell* **44**, 304–316 (2011) | Duan, S. *et al.* mTOR generates an auto-amplification loop by triggering the β TrCP- and CK1 α -dependent degradation of DEPTOR. *Mol. Cell* **44**, 317–324 (2011)

FURTHER READING Zoncu, R., Efeyan, A. & Sabatini, D. M. mTOR: from growth signal integration to cancer, diabetes and ageing. *Nature Rev. Mol. Cell Biol.* **12**, 21–35 (2011)