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MEMBRANE TRAFFICKING

The second job of ULKs

> neuronal degeneration ... relies on an alternative, autophagy-independent role of ULKs in regulating protein trafficking

Impairment of the process of autophagy underlies many neurodegenerative disorders. In mammals Unc51-like autophagy activating kinase 1 (ULK1) and ULK2 are the major inducers of autophagy, and thus their depletion from the brain would be expected to cause neuronal degeneration, dependent on the inhibition of the autophagic flux. Joo *et al.* show that brain-specific deletion of ULKs indeed results in neuronal degeneration, but that this phenotype relies on an alternative, autophagy-independent role of ULKs in regulating protein trafficking from the endoplasmic reticulum (ER), which is necessary to prevent ER stress.

To investigate the role of ULKs in the brain, the authors generated neuron-specific *Ulk1/2*-knockout mice. As expected, these mice presented with neuronal degeneration but, surprisingly, without impairment of autophagy. Interestingly, the authors noted that *Ulk1/2* deletion resulted in the expansion of the ER compartment, indicative of ER stress. Indeed, degeneration of the *Ulk1/2*-null neurons was associated with nuclear translocation of C/EBP-homologous protein (CHOP), which is a known transcriptional regulator of ER stress-mediated responses.

To understand how ULKs prevent ER stress, the authors undertook a proteomic approach, identifying SEC16A as a ULK-interacting protein. SEC16A facilitates the recruitment of coatamer protein complex II (COPII) vesicle components to so-called ER exit sites (ERES), thereby regulating protein trafficking between the ER and the Golgi. It was found that in mouse embryonic fibroblasts (MEFs), ULK1 co-localized with SEC16A and ULK1 depletion interfered with the cellular localization of SEC16A (as well as COPII vesicle subunits), suggesting that ULKs regulate ERES assembly. Importantly, one of the COPII cargoes — serotonin transporter (SERT; also known as 5-HTT) — was not efficiently transported to its final destination at the plasma membrane in *Ulk*-null cells (both *in vivo* in mouse platelets and *in vitro* in MEFs ectopically expressing SERT), demonstrating that the perturbation of ERES assembly resulting from ULK deficiency impaired vesicular trafficking. Furthermore, in MEFs, this trafficking defect was associated with increased levels of nuclear CHOP, thereby directly linking ULK deficiency to ER stress induction.

Finally, as ULKs are known kinases, it was investigated whether they regulate ERES assembly, and thereby vesicular trafficking, through phosphorylation. Indeed, it was found that both ULK1 and ULK2 were able to phosphorylate SEC16A *in vitro*, and that only the kinase-competent ULK1 or a phosphomimetic SEC16A variant was able to rescue ERES assembly and trafficking defects, as well as to prevent CHOP nuclear translocation in *Ulk1*-null MEFs.

In the future, it would be interesting to investigate how this autophagy-independent function of ULKs is controlled and co-regulated with the primary role of these proteins in autophagy.

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ORIGINAL ARTICLE Joo, J. H. *et al.* The noncanonical role of ULK/ATG1 in ER-to-Golgi trafficking is essential for cellular homeostasis. *Mol. Cell* **62**, 491–506 (2016)