AUTOPHAGY

Foundations of ER-phagy regulation

“
DDRGK1-mediated regulation of ER-phagy ... could coordinate quality control pathways of newly synthesized peptides entering the ER
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ER-phagy is a selective type of autophagy, whereby parts of the endoplasmic reticulum (ER) network (sheets or tubules) are engulfed by autophagosomes through specific ER-phagy receptors and then removed by lysosomal degradation. ER-phagy has been implicated in the response to ER stress, specifically in the unfolded protein response (UPR). Nevertheless, the mechanisms and regulation of ER-phagy remain elusive. In their work published in *Cell*, Liang et al. now identify 200 ER-phagy regulators and specifically dissect the role of two processes: one centred on mitochondrial oxidative metabolism and the other on protein UFMylation — a recently discovered ubiquitin-like post-translational modification.

The authors designed a genome-wide CRISPR–Cas9 screen to identify factors that are upregulated or downregulated during ER-phagy induced by starvation (the only currently known cue for ER-phagy induction). The screen returned 200 high-confidence genes, which coalesced into several functional groups, including ‘predictable’ factors, such as general autophagy mediators, components of secretory pathways

and regulators of ER homeostasis and stress. Less expectedly, among the genes most highly associated with ER-phagy disruption were those linked to mitochondrial oxidative metabolism, specifically oxidative phosphorylation (OXPHOS) and those implicated in UFMylation, which involves the transfer of the ubiquitin-like protein ubiquitin-fold modifier 1 (UFM1) onto Lys residues by the E1 enzyme UBA5, by the E2 enzyme UFC1 and by E3 UFM1-protein ligase 1 (UFL1).

Next, the authors focused on the roles of these two processes in ER-phagy. Stable depletion or chemical inhibition of OXPHOS components inhibited ER-phagy, without affecting bulk autophagy (macroautophagy). ER-phagy in response to OXPHOS perturbation was neither associated with increased mitochondrial quality control via mitophagy nor with activation of AMPK (a major sensor of cellular energy status and potent activator of macroautophagy). Overall, the exact mechanisms linking mitochondrial oxidative dysfunction to ER-phagy inhibition remain to be studied, but could involve various components, such as signalling pathways, metabolites and stress responses (including ER stress and UPR).

One of the factors identified as an ER-phagy regulator associated with UFMylation was DDRGK1, which was previously linked to ER homeostasis. DDRGK1 localized to the ER and interacted with UFL1, thereby targeting it to the ER. Reciprocally, this interaction was proposed to stabilize DDRGK1, as it was targeted for proteasomal degradation upon UFL1 depletion. Depletion of either DDRGK1 or UFL1 inhibited ER-phagy, which was specific for ER sheets.

Despite its interaction with UFL1, DDRGK1 was not UFMylated during ER-phagy. A proteomic screen for proteins UFMylated in a DDRGK1-dependent manner returned several high-confidence targets, including RPL26, a component of the large ribosomal subunit and known UFMylation substrate, and RPN1, a component of oligosaccharyl-transferase, which is a central enzyme involved in ER protein glycosylation that localizes to ER sheets in the vicinity of the SEC61 translocon complex (which serves in co-translational protein import into the ER and also harbours a known ER-phagy receptor for ER sheets, SEC62).

Depletion of DDRGK1, UFL1 or UFM1 resulted in UPR activation, with increased protein levels of the main ER stress sensor, IRE1α.

Collectively, these data revealed that DDRGK1 — through directing UFMylation to the ER — governs ER-phagy of ER sheets, which in turn opposes UPR activation. As DDRGK1-mediated regulation of ER-phagy involves UFMylation of ribosomal components and a key ER glycosylation enzyme at the SEC61 translocon, and taking into account that glycans instruct proper protein folding and quality control, this mechanism could coordinate quality control pathways of newly synthesized peptides entering the ER.

Further dissection of other regulatory factors identified in this study will pave the way towards deciphering the cellular and physiological roles of the still ‘mysterious’ process of ER-phagy.

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A genome-wide ER-phagy screen highlights key roles of mitochondrial metabolism and ER-resident UFMylation. *Cell* <https://doi.org/10.1016/j.cell.2020.02.017> (2020)

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