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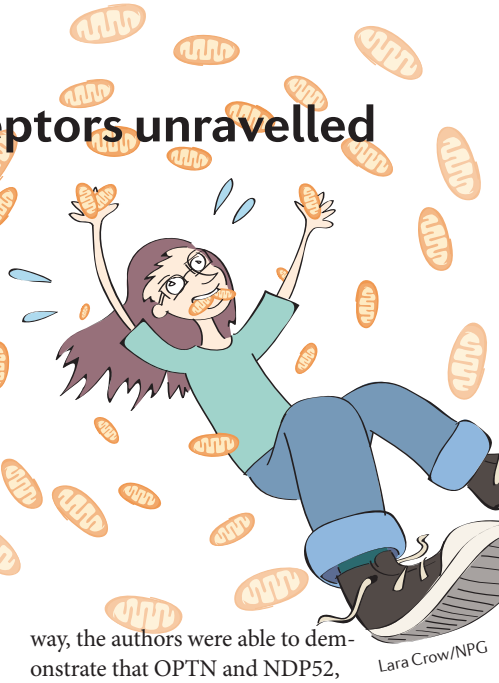
AUTOPHAGY

Mitophagy receptors unravelled



Lara Crow/NPG

> “OPTN and NDP52, but not p62, are directly recruited to phospho-ubiquitin on mitochondria”

During selective autophagy, specific cytosolic components are engulfed into autophagosomes and delivered to lysosomes for degradation. Cargoes destined for degradation are ubiquitylated and recognised by autophagy receptors, which bind to ubiquitin and to autophagosome-specific proteins such as LC3 (microtubule-associated protein 1 light chain 3). Youle and colleagues now find that NDP52 and optineurin (OPTN), two autophagy receptors that had previously been linked to xenophagy, are the primary receptors for mitophagy — the selective degradation of damaged mitochondria.

Mitophagy is initiated by the activation of the kinase PINK1, which becomes stabilized on the outer mitochondrial membrane, where it phosphorylates ubiquitin and activates the E3 ubiquitin ligase parkin that in turn assembles ubiquitin chains. Autophagy receptors such as p62 and OPTN have previously been shown to bind to ubiquitin chains on damaged mitochondria, but their roles were unclear.

The authors knocked out five autophagy receptors in HeLa cells — TAX1BP1, NDP52, NBR1, p62 and OPTN — which blocked mitophagy. Interestingly, only NDP52 and OPTN (and, to a lesser extent, TAX1BP1) were able to rescue mitophagy when re-expressed in the knockout cells lacking the five receptors. Moreover, whereas knocking out NDP52 or OPTN alone caused no defects in mitophagy, knocking out both receptors inhibited it, suggesting that they function redundantly in mitophagy. Furthermore, NDP52 or OPTN with a mutated or deleted ubiquitin-binding domain could not rescue mitophagy. Thus, binding of NDP52 and OPTN to ubiquitin is required for mitophagy.

Parkin-mediated mitophagy requires PINK1-dependent phosphorylation of ubiquitin Ser65 and of the ubiquitin-binding domain of parkin. To assess the role of parkin in mediating mitophagy, the authors expressed PINK1 on mitochondria in HeLa cells lacking parkin. In this way, the authors were able to demonstrate that OPTN and NDP52, but not p62, are directly recruited to phospho-ubiquitin on mitochondria independently of parkin, and that such recruitment is sufficient to initiate mitophagy.

Autophagy receptors are thought to function by bridging LC3 (on autophagosomes) and ubiquitylated cargoes. However, in cells lacking NDP52 and OPTN, two proteins involved in autophagosome formation upstream of LC3 (WIPI1 and DFCP1) and that are normally localized on or near mitochondria were undetectable. Thus, the receptors NDP52 and OPTN seem to be involved in the recruitment of these proteins and in early phases of autophagosome biogenesis.

This work shows that PINK1 induces mitophagy directly, through the phospho-ubiquitin-mediated recruitment of NDP52 and OPTN, and that these receptors have an early role in recruiting the autophagy machinery. Moreover, the authors suggest that parkin functions to amplify the mitophagy signal generated by PINK1, by assembling more ubiquitin chains that will be subsequently phosphorylated by PINK1.

Kim Baumann

ORIGINAL RESEARCH PAPER Lazarou, M. *et al.* The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. *Nature* **524**, 309–314 (2015)

FURTHER READING Youle, R. J. & Narendra, D. P. Mechanisms of mitophagy. *Nat. Rev. Mol. Cell Biol.* **12**, 9–14 (2011)