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AUTOPHAGY

Mitochondria encaged

During mitophagy, damaged mitochondria are ubiquitylated by the E3 ubiquitin ligase Parkin and subsequently bound by autophagy receptors and engulfed by autophagosomes for degradation. The removal of defective mitochondria is essential for cellular homeostasis, but how efficiency of mitophagy is achieved is unclear. Kruppa *et al*. now identify myosin VI (MYO6) as a new regulator of mitophagy.

MYO6 has been previously shown to interact with ubiquitin and mitophagy receptors, raising the possibility that it is involved in mitophagy. Indeed, following drug-induced mitochondria depolarization (a potent trigger of Parkin-mediated mitophagy) in cultured human epithelial kidney cells (HEK293 cells), MYO6 colocalized with Parkin on mitochondria, whereas it is normally found around intracellular vesicles in the cytosol and at the plasma membrane. Importantly, MYO6 recruitment to mitochondria was unaffected by the knockdown of mitophagy receptors, but was strongly impaired when its ubiquitin-binding region was mutated. Thus, following depolarization, MYO6 is targeted to mitochondria by binding to ubiquitin.

Apart from serving as actin-based motors, myosins also function in actin cytoskeleton reorganization. Within two hours after mitochondrial depolarization in HEK293 cells, actin formed cages around fragmented mitochondria; this encaging was blocked by ectopic expression of the MYO6 tail, which cannot interact with actin. Actin-caged mitochondria were smaller than mitochondria devoid of such cages, but ectopic expression of the MYO6 tail or interference with actin nucleation increased mitochondrial size and caused mitochondrial re-fusion. Thus, MYO6-mediated actin cages sequester mitochondria destined for mitophagy and prevent their re-integration into the functional mitochondrial network.

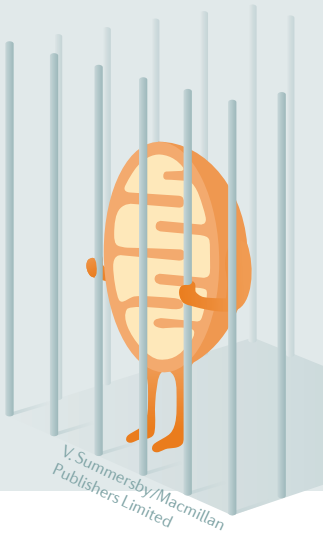
Mouse embryonic fibroblasts (MEFs) in which *Myo6* was deleted had increased numbers of mitochondria-containing autophagosomes induced by mitochondrial depolarization, indicating that in addition to sequestering damaged mitochondria before autophagosomal engulfment, MYO6 also promotes the timely clearance of mitochondria-loaded autophagosomes. Mitochondrial mass was increased in MYO6-deficient MEFs, but mitochondrial respiration was compromised. Mitochondrial function was also impaired in MYO6-depleted HEK293 cells, as they did not grow in medium containing the sugar galactose, which requires cells to rely on mitochondrial respiration for energy production.

In summary, MYO6 supports the clearance of dysfunctional mitochondria by mitophagy to maintain a healthy mitochondrial network, and it does so, at least in part, by inducing entrapment of damaged mitochondria into actin cages. These findings provide novel insights into mitophagy regulation by cytoskeletal components.

Paulina Strzyz

ORIGINAL ARTICLE Kruppa, A. J. *et al.* Myosin VI-dependent actin cages encapsulate Parkin-positive damaged mitochondria. *Dev. Cell* https://doi.org/10.1016/j.devcel.2018.01.007 (2018)

> MYO6-mediated actin cages sequester mitochondria



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