In This Issue

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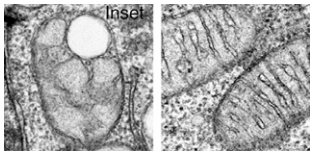
Mitochondrial fission is crucial for cristae remodeling



During the early stages of apoptosis, mitochondrial cristae swell up in a wild-type cell (left), but mostly remain flat in a cell lacking MiD49 and MiD51 (right).

Otera et al. reveal that the mitochondrial fission factor Drp1 and its receptors MiD49 and MiD51 promote apoptosis by remodeling mitochondrial cristae.

Early in apoptosis, mitochondrial cristae are remodeled so that cytochrome *c* enters the space between the inner and outer mitochondrial membranes, from where it can be released into the cytoplasm to initiate caspase activation and cell death. Cristae remodeling is facilitated by mitochondrial fission, a process driven by the dynamin-like GTPase Drp1 and its receptors on the outer mitochondrial membrane. Whether Drp1-mediated fission is required for cytochrome *c* release remains unclear, however.

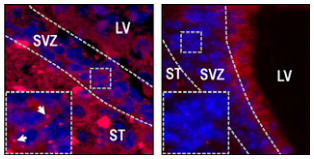
Otera et al. found that three Drp1 receptors—Mff, MiD49, and MiD51—have redundant roles in recruiting Drp1 and promoting mitochondrial fission. Knocking out Mff had little effect on cytochrome *c* release in apoptotic cells, but deleting MiD49, MiD51, or Drp1 itself prevented cristae remodeling and cytochrome *c* release during the early stages of apoptosis.

Cristae are thought to be stabilized by protein complexes containing long and short isoforms of the GTPase OPA1, and apoptotic signals are thought to induce cristae remodeling by initiating the proteolytic processing and disassembly of these complexes. Surprisingly, however, OPA1 complexes were still disrupted in remodeling-resistant MiD49/MiD51 knockout cells, indicating that OPA1 processing isn't sufficient to induce cristae reorganization.

Instead, says senior author Katsuyoshi Mihara, the results demonstrate a critical role for Drp1-mediated mitochondrial fission. The authors now want to investigate how MiD49 and MiD51 might interact with the cristae remodeling machinery.

Otera, H., et al. 2016. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201508099

p62 aggregation is a problem for neural stem cells



p62 (red) accumulates in *Fip200*-deficient NSCs (left), but not in *Atg5*-deficient precursors (right).

Wang et al. explain why loss of the autophagy-initiating protein Fip200 alters the fate of neural stem cells (NSCs).

Fip200 is required to induce the formation of autophagosomes that engulf and recycle cytoplasmic components. NSCs lacking Fip200 fail to self-renew or differentiate properly, possibly because, in the absence of autophagy, they accumulate mitochondria that emit increased amounts of reactive oxygen species. Fip200 has other, nonautophagic functions, however, so, to learn more about how its loss affects NSC fate, Wang et al. examined the effects of removing other genes required for autophagy.

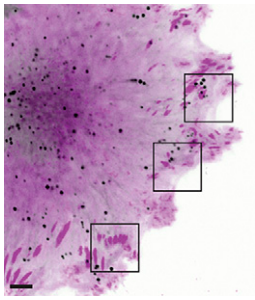
To their surprise, the researchers found that NSCs self-renewed and differentiated normally in the absence of *Atg5*, *Atg16L1*, or *Atg7*, even though, in each case, autophagy was impaired and the cells still accumulated mitochondria. One notable difference, however, was that only *Fip200*-deficient NSCs accumulated cytoplasmic aggregates of the selective autophagy receptor p62. Knocking out *p62* restored the ability of *Fip200*-null NSCs to self-renew and differentiate in vivo.

Wang et al. found that p62 aggregation impaired the activity of the enzyme superoxide dismutase 1 (SOD1), preventing the removal of superoxide species released from mitochondria. Restoring SOD activity lowered superoxide levels and rescued the defects of *Fip200*-deficient NSCs.

Senior author Jun-Lin Guan says it remains unclear why, at least in NSCs, p62 only accumulates in the absence of Fip200, but not other autophagy regulators. Fip200 might regulate p62 levels through a nonautophagic mechanism, or NSCs lacking *Atg5*, *Atg16L1*, or *Atg7* might retain some autophagic activity that can degrade the receptor.

Wang, C., et al. 2016. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201507023

NBR1 helps autophagosomes take a bite out of focal adhesions



Autophagosomes (black) target focal adhesions (magenta) at the leading edge of a migrating cell.

Kenific et al. identify a selective autophagy pathway that promotes cell migration by enhancing the turnover of focal adhesions.

Autophagy pathways target cytoplasmic components for degradation by engulfing them in a double-membraned autophagosome and delivering them to lysosomes. Inhibiting autophagy impairs cell migration, but the reasons for this are unclear. Kenific et al. noticed that autophagy-deficient cells had larger focal adhesions than wild-type cells, suggesting that their migration might be slowed because their attachments to the extracellular matrix are more stable.

Live imaging revealed that, indeed, adhesion turnover was slower in the absence of autophagy. In wild-type cells, autophagosomes targeted focal adhesions as they were being disassembled at the cells' leading edge, engulfing multiple adhesion components such as paxillin and vinculin. Autophagosomes can be selectively targeted to substrates by specific receptor proteins. Kenific et al. knocked down several autophagy receptors and found that autophagosomes weren't efficiently targeted to focal adhesions in cells lacking the receptor NBR1. Accordingly, these cells showed reduced rates of adhesion turnover and migrated more slowly than wild-type cells.

Overexpressing NBR1, in contrast, enhanced focal adhesion disassembly, an effect that depended on the protein's autophagosome- and cargo-binding domains. Senior author Jayanta Debnath now wants to identify which focal adhesion proteins are recognized by NBR1 and how this interaction is regulated. He speculates that autophagosomes may be particularly important for turning over long-lived focal adhesions that have grown too large to be disassembled by other mechanisms.

Kenific, C.M., et al. 2016. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201503075