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ORGANELLE DYNAMICS

Fusing for stability

Fusion and fission are important for the function of mitochondria in all organisms studied. Fusion controls mitochondrion morphology, and impaired fusion is associated with neurodegenerative disorders and severe defects in cell respiration. Fusion has also been proposed to increase the tolerance of human cells to high levels of mutations in mitochondrial DNA (mtDNA), but how this may occur has not been examined. Now in *Cell*, Chen *et al.* show that impaired mitochondrial fusion causes muscle atrophy and that fusion is required for mtDNA stability and tolerance of mtDNA mutations in mice.

Mitochondrial fusion requires the coordinated fusion of the outer and inner membranes. Outer membrane fusion depends on the mitofusins MFN1 and MFN2, and inner membrane fusion requires the dynamin-like protein optic atrophy protein 1 (OPA1). Chen *et al.* found that mice in which *Mfn1* and *Mfn2* were specifically disrupted in skeletal muscle are severely undersized and die prematurely. Furthermore, Mfn-deficient muscles are small and have abnormal mitochondria, which are often fragmented or form aggregates that disrupt myofibril arrays.

When analysing mtDNA copy number, the authors found that Mfn-deficient muscles contain ~250 copies of mtDNA per nuclear genome instead of ~3,500 copies. This shows that mitochondrial fusion is required for mtDNA stability. This was also seen in OPA1-null cells, indicating that inner membrane fusion, and hence matrix content mixing, is necessary to preserve mtDNA. mtDNA depletion becomes apparent earlier than histological defects, suggesting that it might be at least in part responsible for muscle atrophy.

In addition, Mfn-deficient muscles accumulate a considerably high rate of mtDNA mutations and deletions. Interestingly, removal of MFN1 in mice carrying an error-prone mtDNA polymerase (which have a tendency to accumulate higher rates of mtDNA mutations) showed that fusion does indeed increase the tolerance to mtDNA mutations, as lethality was greatly accelerated in the absence of fusion.

By analysing the mitochondrial proteome, the authors found that a lack of Mfn proteins causes imbalance and protein content variability across the mitochondrial population and argue that this might be the underlying cause of mtDNA instability. However, the exact molecular mechanisms remain to be determined.

Kim Baumann

> “mitochondrial fusion … is required for mtDNA stability”

ORIGINAL RESEARCH PAPER Chen, H. *et al.* Mitochondrial fusion is required for mtDNA stability in skeletal muscle and tolerance of mtDNA mutations. *Cell* **141**, 280–289 (2010)
FURTHER READING Detmer, S. A. & Chan, D. C. Functions and dysfunctions of mitochondrial dynamics. *Nature Rev. Mol. Cell Biol.* **8**, 870–879 (2007)