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ORGANELLE DYNAMICS

Regulation of mitochondrial function by diet

> stearic acid … ensures proper mitochondrial fusion and function

Mitochondria undergo cycles of fusion (during which they form an integrated reticulum) and fission, but how this affects their function is not clear. Studying very-long-chain fatty acids, Senyilmaz *et al.* found that the metabolite stearic acid promotes mitochondrial fusion and function by inhibiting transferrin receptor protein 1 (TFR1; also known as TFRC) and its downstream signalling pathway.

Drosophila melanogaster flies lacking the factor elongation of very-long-chain fatty acids protein 6 (Elovl6), which catalyses the formation of stearic acid, die as early larvae. The serendipitous removal from fly food of antifungal agents, which are toxic to mitochondria, improved the survival of *Elovl6*$^-$ flies, which were found to have reduced mitochondrial respiratory function. Moreover, *Elovl6*$^-$ flies and Elovl6-depleted S2 cells were found to have hyper-fragmented mitochondria, and this was rescued by dietary supplementation with stearic acid. Removal of stearic acid from the medium of HeLa cells also caused mitochondrial fragmentation, indicating that stearic acid has a conserved role in the regulation of mitochondrial morphology.

To study how stearic acid may affect mitochondrial dynamics, the authors expressed the transmembrane GTPase mitofusin (Mfn; also known as Marf), which promotes mitochondrial fusion, in *Elovl6*$^-$ flies and in Elovl6-depleted S2 cells. Mfn rescued larval lethality and mitochondrial fragmentation. Furthermore, stearic acid did not induce fusion in the absence of Mfn, indicating that Mfn acts downstream of stearic acid to mediate mitochondrial fusion. To understand how stearic acid controls mitofusin proteins, the authors immunoprecipitated mitofusin 2 from HeLa cells growing without stearic acid and found it to be hyper-ubiquitylated. The depletion of the E3 ubiquitin ligase HUWE1 abolished mitofusin 2 hyper-ubiquitylation and mitochondrial hyper-fragmentation in these cells, as well as the lethality of *Elovl6*$^-$ flies. Furthermore, the phosphorylation of mitofusin 2 on Ser27 by c-Jun N-terminal kinases (JNK) is required for mitofusin 2 ubiquitylation, and indeed inhibition of JNK prevented mitochondrial fragmentation. Thus, the HUWE1- and JNK-mediated post-translational modification of mitofusin 2 inhibits its function and promotes mitochondrial fragmentation.

To examine whether stearic acid exerts its effects by 'stearoylation' (covalently binding to proteins), the authors pulled down stearic acid derivatives from cells and examined the coupled proteins by mass spectrometry. The most stearoylated protein was TFR1, which is known to activate JNK. Whereas addition of the TFR1 ligand gambogic acid induced rapid, JNK-dependent mitochondrial fragmentation in HeLa cells, addition of stearic acid suppressed this effect. Thus, stearic acid covalently binds to and inhibits TFR1.

As the authors noticed that including stearic acid in the diet of wild-type flies increased their mitochondrial fusion, they asked whether this could have clinical relevance. Fly mutants of Pink or Parkin, which are established Parkinson disease models, have impaired mitochondrial function, and supplementing their diets with stearic acid improved their mitochondrial and Parkinson-related defects.

The data show that stearic acid suppresses the ubiquitylation and inhibition of mitofusin 2 and thus ensures proper mitochondrial fusion and function. This is achieved by indirectly suppressing HUWE1 function through the inhibition of TFR1–JNK signalling by TFR1 stearoylation. Using stearic acid to improve mitochondrial fusion and function is potentially of clinical importance, but how deficient fusion causes a respiratory chain defect remains to be established.

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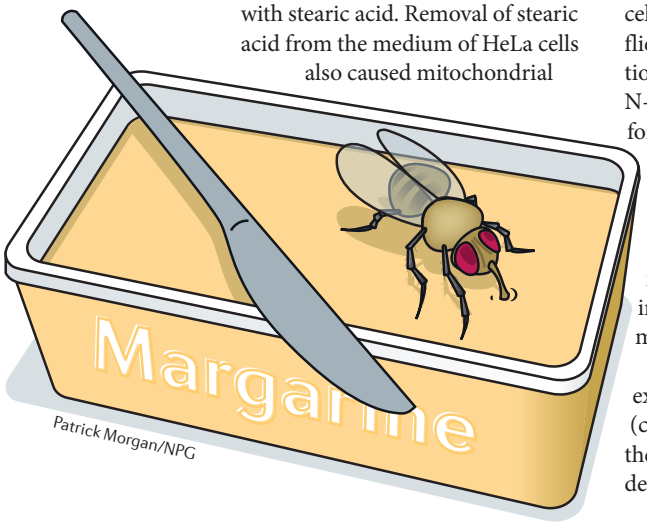

Patrick Morgan/NPG

ORIGINAL RESEARCH PAPER Senyilmaz, D. *et al.* Regulation of mitochondrial morphology and function by stearoylation of TFR1. *Nature* http://dx.doi.org/10.1038/nature14601 (2015)
FURTHER READING Mishra, P. & Chan, D. C. Mitochondrial dynamics and inheritance during cell division, development and disease. *Nat. Rev. Mol. Cell Biol.* **15**, 634–646 (2014)