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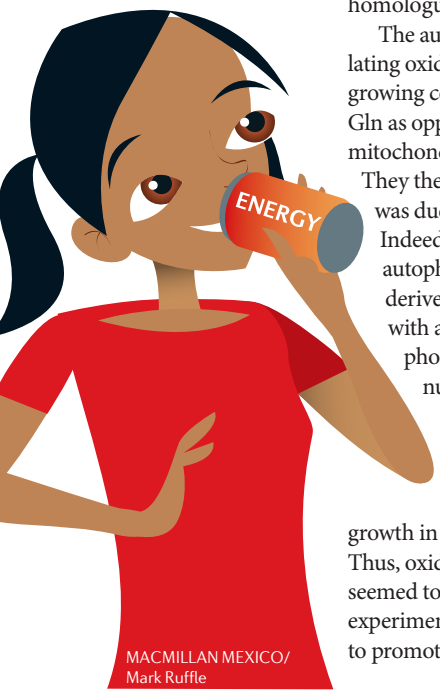
METABOLISM

Putting energy into mitophagy

> “oxidative phosphorylation induces mitophagy”



MACMILLAN MEXICO/ Mark Ruffle

Mitophagy is a selective form of autophagy by which mitochondria are degraded in autolysosomes (structures that form when autophagosomes and lysosomes fuse). Whether, and how, the bioenergetics of mitochondria are linked to mitophagy has been unclear. Now, Melser *et al.* show that oxidative phosphorylation enhances mitophagy to promote mitochondrial renewal, and that this is regulated by the small GTPase RHEB (RAS homologue enriched in brain).

The authors observed that stimulating oxidative phosphorylation, by growing cells in medium containing Gln as opposed to glucose, increased mitochondrial protein degradation. They therefore asked whether this was due to increased mitophagy. Indeed, levels of LC3-II, an autophagosome marker that is derived from LC3, increased with a rise in oxidative phosphorylation, as did the number of lysosomes and autophagosomes in the cell. Inhibiting mitophagy decreased mitochondrial protein degradation during growth in Gln-supplemented media. Thus, oxidative phosphorylation seemed to induce mitophagy. Further experiments revealed that, in order to promote mitophagy, Gln must be oxidized by the tricarboxylic acid (TCA) cycle, the process by which mitochondria produce energy from Gln.

So, what proteins might link the energy status of mitochondria to mitophagy? The authors observed that *RHEB* mRNA levels were decreased by 50% when oxidative phosphorylation was low and so investigated whether RHEB might have a role in energy-regulated mitophagy. RHEB overexpression in cells grown in medium containing Gln had decreased numbers of mitochondria and increased levels of LC3-II. Furthermore, RHEB overexpression was sufficient to induce mitophagy in cells grown in medium containing glucose, and liver-specific RHEB-knockout mice showed a twofold increase in mitochondrial proteins. Thus, RHEB promotes mitophagy in response to changes in oxidative phosphorylation.

How might RHEB achieve this? RHEB was found to localize to the outer mitochondrial membrane (OMM), where it was enriched under conditions of oxidative phosphorylation. Although RHEB is known to activate mammalian target of rapamycin complex 1, this pathway was not involved in oxidative phosphorylation-induced mitophagy. Instead, NIX (also known as BNIP3L), an OMM receptor that binds LC3 to promote mitophagy, was found to form a complex with RHEB and LC3, and Gln increased the interaction of RHEB with both NIX and LC3. Notably, knockdown of NIX reduced RHEB-induced mitophagy. Thus, a RHEB–NIX–LC3 complex seems to mediate mitophagy during changes in mitochondrial bioenergetics.

Finally, the authors asked how energy-regulated mitophagy influences mitochondrial physiology. Mitochondria produced more reactive oxygen species (ROS) in cells grown in oxidative as opposed to glycolytic conditions, and RHEB overexpression reduced ROS levels. Furthermore, RHEB overexpression increased the mitochondrial respiration rate and enhanced ATP production. The authors thus propose that “Rheb-dependent mitophagy is a degradation process that facilitates the constant renewal of mitochondria in order to maintain cellular bioenergetics efficiency, likely by preventing the accumulation of damaged mitochondria.”

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ORIGINAL RESEARCH PAPER Melser, S. *et al.* Rheb regulates mitophagy induced by mitochondrial energetic status. *Cell Metab.* 18 Apr 2013 (doi:10.1016/j.cmet.2013.03.014)
FURTHER READING Youle, R. J. & Narendra, D. P. Mechanisms of mitophagy. *Nature Rev. Mol. Cell Biol.* **12**, 9–14 (2011)

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