Mitochondria breathe for autophagy

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The EMBO Journal (2011) 30, 2095–2096. doi:10.1038/emboj.2011.149

Proper mitochondrial structure and function are established by continuous cycles of fusion and fission, and a unidirectional pathway of autophagy-mediated degradation. In this issue of *The EMBO Journal*, Graef and Nunnari (2011) demonstrate that autophagy requires healthy mitochondria in cells under amino-acid starvation. Defects in mitochondrial respiration cause activation of cAMP-dependent protein kinase A (PKA), an evolutionarily conserved regulator that inhibits autophagic flux. This study reveals a crucial interplay between mitochondrial function and autophagy, and raises the possibility that deregulation in one of these processes simultaneously compromises the other to potentiate risks for various human disorders.

Mitochondria are double membrane-bound compartments that function as chemical factories for manifold metabolic reactions, and as communication platforms for diverse signalling pathways. In many cell types, this multi-tasking organelle forms a dynamic structure, frequently changing its number, size, shape, and distribution. Studies in the last decade have defined a fundamental principle that the integrity of mitochondrial structure and function is regulated by fusion and fission, two opposing events conserved among almost all eukaryotes (Westermann, 2010). Constant cycles of these events are physiologically relevant to the maintenance of mitochondrial DNA (mtDNA) and respiratory chains, and the partitioning of mitochondria. Recently, a large body of evidence implicates mitophagy, autophagic degradation of mitochondria, as a quality control mechanism (Youle and Narendra, 2011). This process is selective for dysfunctional mitochondria that are segregated from the fusion–fission cycle (Twig *et al*, 2008), suggesting that mitophagy directly contributes to regulation of mitochondrial integrity. Moreover, autophagy, but not mitophagy, is critical for mtDNA maintenance in yeast under nitrogen starvation (Suzuki *et al*, 2011). Thus, this bulk, non-selective recycling system also has a vital role in mitochondrial homeostasis. Notably, defects in autophagy are associated with human diseases, such as aging, cancer, and neurodegeneration, which are also linked to mitochondrial dysfunction (Wallace, 2005; Mizushima *et al*, 2008). This means that mitochondrial function and autophagy could be interdependent. What if bad mitochondria impact autophagy? Now, Jodi Nunnari and Martin Graef demonstrate that this is indeed the case in yeast cells starved for amino acids (Graef and Nunnari, 2011).

Upon starvation, autophagy is activated via several nutrient signalling pathways, and the autophagy-related proteins

cooperatively mediate *de novo* formation of double membrane-bound structures termed autophagosomes. Subsequently, cytosolic constituents are sequestered by the autophagosome, transported to the lysosome (vacuole in yeast), and degraded by hydrolytic enzymes for recycling. Graef and Nunnari assayed autophagy induction and autophagic flux by monitoring the expression and vacuolar transport of Atg8, an ubiquitin-like protein that localizes to the autophagosome, and found that both processes are impaired in cells lacking mtDNA. Similar results were also seen in the absence of functional respiratory chain complexes. Notably, cells treated with antimycin A, an inhibitor that specifically blocks the respiratory chain complex III, displayed defects in autophagy and loss of mitochondrial membrane potential; however, the ATP levels were similar to those of untreated cells. These results suggest that mitochondrial membrane potential has a role in autophagy regulation.

How does mitochondrial dysfunction affect the autophagic response? In the yeast *Saccharomyces cerevisiae*, the protein kinase target of rapamycin complex 1 (TORC1) and

Figure 1 Model for PKA-mediated regulation of autophagy and mitochondrial function. In yeast cells under glucose-rich conditions, PKA is highly activated to repress both autophagy and mitochondrial respiration. When mitochondria are compromised, PKA is also activated, thereby suppressing autophagic flux. Whether defects in autophagy cause activation of PKA and subsequent reduction of mitochondrial activity has not yet been investigated.

cAMP-dependent PKA act in two major nutrient signalling cascades, and negatively regulate autophagy by suppressing localization of the Atg1–Atg13 kinase complex to the pre-autophagosomal structure (PAS), a putative protein assembly for autophagosome formation (He and Klionsky, 2009; Stephan *et al*, 2009). Graef and Nunnari found no significant changes in TORC1 activity in amino-acid-starved cells lacking mtDNA, excluding the possibility that loss of mitochondrial function downregulates autophagy via the TORC1 pathway. In contrast, the authors detected activation of PKA and impairment of the Atg1–Atg13 PAS localization in respiratory-deficient cells. Importantly, specific inhibition of PKA activity in cells lacking mtDNA resulted in stimulation of autophagic flux at levels similar to those in wild-type cells. Together, these observations support the idea that mitochondria influence autophagy through the PKA pathway. Intriguing, unsolved issues are how dysfunctional mitochondria suppress autophagy induction under amino-acid starvation, which appears to be independent on the TORC1 and PKA pathways, and how mitochondrial membrane potential regulates PKA activity.

It is noteworthy that PKA reciprocally controls mitochondria (see Figure 1). For example, PKA phosphorylates Tom70, a preprotein import receptor on the surface of mitochondria,

in order to inhibit its receptor activity in yeast cells under non-respiring conditions (Schmidt *et al*, 2011). In this way, PKA negatively regulates mitochondrial biogenesis, thereby reducing mitochondrial activity. It is, therefore, conceivable that defects in autophagy could activate PKA, and then lessen mitochondrial respiration. This PKA-mediated interplay between mitochondrial function and autophagy is likely to serve, perhaps together with other pathways, as a smart coordinator for cellular metabolism.

Acknowledgements

We apologize for not being able to cite all of relevant contributions, owing to space limitations. KO acknowledges grant-in-aid from the Ministry of Education, Culture, Science and Technology of Japan for Scientific Research on Priority Areas (22020012), Scientific Research on Innovative Areas (23113717), and Scientific Research (C) (20570144), Special Coordination Funds from Osaka University Life Science Young Independent Researcher Support Program for Promoting Science and Technology, and grants from the Mochida Memorial Foundation for Medical and Pharmaceutical Research, and the Sumitomo Foundation.

Conflict of interest

The author declares that he has no conflict of interest.

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