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Journal club

MITOCHONDRIA: BACK TO THE FUTURE

Much of the first half of the 20th century was devoted to discovering metabolic pathways and processes, including those linked to the mitochondria. By the 1970s, there was a consensus as to how the mitochondria generate ATP and metabolites for macromolecule synthesis. Thus, the broader biology and medicine communities felt that there was not much more biochemical knowledge related to the mitochondria to be learned. Surprisingly, in the 1990s, research on mitochondria made a comeback, capturing the imagination of different fields ranging from cancer, to immunity, organismal metabolism and neuroscience — but how?

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There are likely a myriad of reasons that account for the comeback, but for me, there is one particular paper that stands out. This study has had an impact on the way I think about the role of mitochondria in biology and physiology.

In 1996, Xiaodong Wang and colleagues reported that the release of cytochrome *c* from the mitochondrial intermembrane space into the cytosol can initiate caspase-dependent apoptosis. As I was finishing my graduate studies on the dependence of cytochrome *c* oxidase on oxygen at the time, this was hard to digest. The dogma was that cytochrome *c* was functionally involved in the transport of electrons within the mitochondrial respiratory chain which generated a proton-motive force to produce ATP, that is, oxidative phosphorylation. Thus, we all viewed cytochrome *c* as essential for life, not for death!

This classic paper has stood the test of time (cited over 5000 times). Importantly, this study suggested that mitochondria, beyond ATP generation, could dictate cell fate or function by releasing cargo into the cytoplasm.

Inspired by these findings, we began to think of other methods by which mitochondria communicate with the cytosol to dictate cell function. In 1998, we showed that reactive oxygen species (ROS) could be released from mitochondria, not to cause cell death or damage, but for physiological adaptation to hypoxia. ROS were shown to induce expression of the hypoxia-inducible factor (HIF) target gene erythropoietin (EPO), which stimulates red blood cell production in the bone marrow.

More recently, mitochondrial release of ROS, which can occur under physiological conditions, has been linked to many processes including cell proliferation, differentiation, metabolic adaptation and immune function. Furthermore, there are multiple ways in which mitochondria communicate with the rest of the cell to dictate cell function, including the release of metabolites, mitochondrial DNA and mitochondrial-derived vesicles. An exciting emerging area of research is aimed at understanding how tricarboxylic acid cycle metabolites control chromatin and DNA modifications to regulate gene expression. Thus, it is clear that mitochondria are more than bioenergetic and biosynthetic organelles; they are also crucial signalling organelles.

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ORIGINAL ARTICLES Liu, X. *et al.* Induction of apoptotic program in cell-free extracts: requirement for dATP and cytochrome *c*. *Cell* **86**, 147-57 (1996) | Chandel, N.S. *et al.* Mitochondrial reactive oxygen species trigger hypoxia-induced transcription. *Proc. Natl Acad. Sci. USA* **95**, 11715-20 (1998)