Transfer of mitochondria after stroke: a new hope for cardioprotection coming from the brain?

J. Fauconnier

Transfer of mitochondria after stroke: a new hope for cardioprotection coming from the brain?

Jérémy Fauconnier*

UMR CNRS 9214, INSERM U1046, Université de Montpellier, CHU Montpellier, 371 Avenue du Doyen Gaston Giraud, 34295 Montpellier Cedex, France

After his PhD, obtained in 2003 at the medical school of Montpellier University, Dr Jérémy Fauconnier joined the Muscle Physiology group of Prof. H. Westerblad at the Karolinska Institute (Stockholm, Sweden). After 2 years of postdoctoral research and following 3 years as a fellow of the National Institute for Medical and Health Research (France), Dr Jérémy Fauconnier was recruited as a permanent researcher by the French national center for scientific research (CNRS) at Montpellier University. Dr Jérémy Fauconnier, as a specialist in cellular electrophysiology and calcium imaging has published numbers of originals and review articles focusing on Calcium signalling, excitation–contraction coupling and mitochondrial function.
His contribution to the scientific community goes far beyond his research activities. He built up the national Young Investigator Group for Basic Cardiovascular Research with the aim to support scientific, educational, and advocacy activities of the French Society of Cardiology (GRRC/SFC). He is also a founding nucleus member of the Scientist of Tomorrow of the European Society of Cardiology and he belongs to several national and international scientific councils where he organizes workshop and scientific events dedicated to the Young Research community

Commentary on 'Transfer of mitochondria from astrocytes to neurons after stroke' by Hayakawa K *et al.*, Nature 2016.[1]

Mitochondria are dynamic organelles, interconnected and organized as a complex network within the cell. Intracellular fusion and fission are equilibrating processes that control mitochondrial turnover and allow the mitochondrial network to dynamically adapt to changes in metabolic demand. During the last decade, intercellular mitochondrial transfer has emerged as an additional mechanism for the replacement of damaged mitochondria. This new field of investigation in the mitochondrial community was marked by the initial observation that human mesenchymal stem cells (MSCs) could transfer healthy mitochondria to mitochondria-depleted cells (A549 ρ° cells) and rescue their aerobic respiration.[2] The *in vitro* transfer of mitochondria from MSCs to cell lines or primary cells, such as cardiomyocytes, endothelial cells, cancer cell, or pulmonary alveolar epithelial cells, has since been extensively documented.[3] All of these studies provide, voluntarily or not, a potential pathophysiological perspective of the endosymbiotic theory of the origin of mitochondria and the eukaryotic cell.

Despite the accumulation of studies demonstrating evidence of mitochondrial transfer, the mechanisms and signals allowing mitochondrial trafficking, transport and entry into the host cell are still unclear. One recurrent hypothesis proposed for mitochondrial transfer is by tunnelling nanotubes from the donor cell to the host cell. In this theory, the mitochondrial Rho-GTPase, Miro1, has been implicated in the movement of the mitochondria along the actin cytoskeleton of the nanotube to the host cell.[4] However, Hayakawa *et al.* recently demonstrated evidence supporting mitochondrial transfer by the release of extracellular vesicles containing mitochondria from the donor cell that may occur independently of an intercellular physical contact *per se*.[1] In this study, the authors demonstrated that cyclic ADP ribose-induced CD38 activation in astrocytes promotes mitochondrial vesicular formation and release. Transfer of these astrocytes-derived mitochondrial vesicles was shown *in vitro* to damaged cortical neurons after serum/glucose starvation. Similarly to other studies, Hayakawa *et al.* showed that mitochondrial transfer increased neurons viability and ATP synthesis *in vitro*. Mitochondrial vesicles were detected in neuroglia *in vivo* and mitochondria transfer was detected in peri-infarct neurons after stroke in a CD38 dependent

* Corresponding author. Tel: (+33) 4 67415222; fax: (+33) 4 67415242, E-mail: jeremy.fauconnier@inserm.fr

manner. This latter result supports a promising consequence: under ischemic injury *in vivo*, a native, donor cell can transfer healthy mitochondria to a damaged cell, possibly as a rescue mechanism. Whether reduction of mitochondrial transfer by CD38 knockdown is indeed responsible for a decreased post-ischemic neuroplasticity requires further investigation.

This novel aspect in intercellular mitochondrial transfer reinforces the concept of a trans-cellular organelle relocalization in response to tissue injury. This concept emerged from a report showing the *in vivo* transfer of mitochondria from bone marrow MSCs to alveolar epithelial cells following acute lung injury.[5] The mitochondrial transfer increased alveolar ATP synthesis and promoted protective adaptations. The establishment of connexin-43-containing gap junction channels between MSC and alveolar epithelium was a prerequisite to promote mitochondrial transfer and MSC mitochondria containing microvesicle formation. It is unknown if mitochondrial transfer from astrocytes to neurons utilize similar transfer mechanisms or other endocytic processes. Clarification of these mechanisms could provide protective approaches to optimize mitochondria transfer to damaged tissue.

From a cardiovascular point of view, the astrocytes-derived mitochondrial vesicles may also have some major functional implications. In the central nervous system, astrocytes are cellular components of the neurovascular units and cover the abluminal surface of the cerebral vessel wall. An increase in luminal blood pressure through mechanosensitive signalling is thought to increase intracellular calcium in astrocytes and the release of vasoactive molecules.[6] Accordingly, one could imagine that blood flow, and thus energy supply, could affect mitochondrial released in the central nervous system as reported in Hayakawa study[1] and also potentially in peripheral tissue. However, it is currently not know if such a mechanism occurs in the heart. One report demonstrated that intravenous injection of autologous mitochondria after a cardiac ischemia-reperfusion injury can improve mitochondrial respiration and post-ischemic myocardial function.[7] Interestingly, adult ventricular cardiomyocytes contain two populations of mitochondria based on their localization, sub-sarcolemmal and intra-myofibrillar mitochondria. Among the differences between these two populations, connexin-43 is present solely in sub-sarcolemmal mitochondria and its expression level has been associated with a cardioprotective effect against ischemia.[8] A possible link between the specific presence of connexin-43 sub-sarcolemmal mitochondria and connexin-43 associated transcellular mitochondrial transfer requires examination.

In parallel, the possibility of mitochondrial transfer *in vivo* between native cells in the context of cardiac ischemic injury raises several important questions: can resident non-cardiomyocytes cells release mitochondrial vesicles within the heart under ischemic injury? Could a paracrine mitochondrial transfer constitute an adaptive mechanism for ischemic injury and participate in pre- or post-conditioning? May mitochondrial transfer also affect sympathetic neurons plasticity within the heart? Could mitochondrial vesicular release provide a future biomarker of myocardial infarction? The biological implications of cardiac mitochondrial transfer are clearly and potentially broad.

To some extent, targeted transcellular mitochondrial transfer to rescue ischemic organs may sound somehow esoteric but mitochondrial dysfunction is associated with a broad range of pathophysiological conditions, and strategies to improve mitochondrial function, especially in cardiovascular diseases, are very few. An improved understanding of the mechanisms that orchestrate mitochondrial transfer from a donor cell to a host cell, from the trigger signals to the molecular processes allowing mitochondrial entry and integration, will open new opportunities to boost and stabilize mitochondria against tissue injuries.

Acknowledgement

The author thanks Amanda Finan-Marchi for the valuable discussions.

Conflict of interest: none declared.

References

1. Hayakawa K, Esposito E, Wang X, Terasaki Y, Liu Y, Xing C, Ji X, Lo EH. Transfer of mitochondria from astrocytes to neurons after stroke. *Nature* 2016;**535**:551–555.
2. Spees JL, Olson SD, Whitney MJ, Prockop DJ. Mitochondrial transfer between cells can rescue aerobic respiration. *Proc Natl Acad Sci U S A* 2006;**103**:1283–1288.
3. Berridge MV, McConnell MJ, Grasso C, Bajzikova M, Kovarova J, Neuzil J. Horizontal transfer of mitochondria between mammalian cells: beyond co-culture approaches. *Curr Opin Genet Dev.* 2016;**38**:75–82.
4. Ahmad T, Mukherjee S, Pattnaik B, Kumar M, Singh S, Kumar M, Rehman R, Tiwari BK, Jha KA, Barhanpurkar AP, Wani MR, Roy SS, Mabalirajan U, Ghosh B, Agrawal A. Miro1 regulates intercellular mitochondrial transport & enhances mesenchymal stem cell rescue efficacy. *EMBO J* 2014;**33**:994–1010.
5. Islam MN, Das SR, Emin MT, Wei M, Sun L, Westphalen K, Rowlands DJ, Quadri SK, Bhattacharya S, Bhattacharya J. Mitochondrial transfer from bone-marrow-derived stromal cells to pulmonary alveoli protects against acute lung injury. *Nat Med* 2012;**18**:759–765.
6. Filosa JA, Iddings JA. Astrocyte regulation of cerebral vascular tone. *Am J Physiol Heart Circ Physiol* 2013;**305**:H609–619.
7. Masuzawa A, Black KM, Pacak CA, Ericsson M, Barnett RJ, Drumm C, Seth P, Bloch DB, Levitsky S, Cowan DB, McCully JD. Transplantation of autologously derived mitochondria protects the heart from ischemia-reperfusion injury. *Am J Physiol Heart Circ Physiol* 2013;**304**:H966–982.
8. Schulz R, Gorge PM, Gorbe A, Ferdinandy P, Lampe PD, Leybaert L. Connexin 43 is an emerging therapeutic target in ischemia/reperfusion injury, cardioprotection and neuroprotection. *Pharmacol Ther* 2015;**153**:90–106.