Commentary

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Mitochondria transplantation/transfer between single cells

Qin Hu[1], Jianfei Lu[1], Xiaohua Zhang[1], Ran Liu[2] and Shao-Hua Yang[2]

Abstract

Mitochondrial transplantation/transfer has been increasingly recognized as a potential way for cell and tissue revitalization. In a recent study, Gabelein et al. reported a novel method for single cells mitochondria transplantation using "nanosyringe". This technique combines atomic force microscopy, optical microscopy, and nanofluidics that enable intra- and intercellular organelle micromanipulation and cell-to-cell mitochondria transplantation with up to 95% success rate. The transferred mitochondria fuse to the host mitochondrial network and donor mtDNA incorporate into the recipient mitochondrial genome. The nanosyringe technique provides a novel tool for future mitochondrial research to offer insight into mitochondrial replacement therapy for stroke and fundamental mitochondrial biology.

Keywords

Mitochondria, mitochondrial transfer, mitochondrial transplantation, nanosyringe, revitalization

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Life is the interplay between energy and structure through metabolism, in which mitochondria serve as the central hub for both bioenergetics and biosynthesis. Consequently, mitochondrial dysfunction is highly implicated in a wide range of pathological conditions such as diabetes, cancers, neurodegenerative diseases, and stroke. Various therapeutic approaches have been developing for rescue mitochondrial function to improve the prognosis of these diseases. Pioneering studies indicate that mitochondrial transplantation might be a plausible approach to replenish the damaged mitochondria.[1–3] A variety of techniques, including microinjection, coincubation, and magnetomitotransfering have been attempted to improve the efficiency of mitochondrial transplantation. However, all currently established technologies have insufficient efficiencies and mitochondrial transplantation between single cells has not been possible to date.

In the March issue of PloS Biology, the team from Zurich, led by Julia A. Vorholt, established a single-cell technology based on fluidic force microscope (FluidFM) for inter- and intracellular micromanipulation of mitochondria.[4] FluidFM combines the high-precision force-regulated approach of an atomic force microscope with the volumetric dispensing of nanoscale pipets under optical inspection, providing the forces and volume control relevant for single-cell manipulation.[5] With this technology, they achieved tunable organelle extraction from single cultured cells without damage cytoplasmic membrane and rapid delivery of the fresh mitochondria to the recipient cells with a success rate up to 95% (Figure 1). Combined with fluorescent labeling, their research demonstrated that the nanosyringe approach preserves mitochondria viability, facilitates their internalization, and improves their incorporation into the mitochondrial network of the recipient cells.

[1]Department of Neurosurgery, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, P. R. China
[2]Department of Pharmacology and Neuroscience, University of North Texas Health Science Center, Fort Worth, TX, USA

Corresponding authors:
Qin Hu, Department of Neurosurgery, Renji Hospital, Shanghai Jiao Tong University School of Medicine, No. 1630, Dongfang Rd., Shanghai 200127, China.
Email: huqinle20010709@126.com

Shaohua Yang, Department of Pharmacology and Neuroscience, University of North Texas Health Science Center, 3500 Camp Bowie Blvd, Fort Worth, TX, 76107, USA.
Email: Shaohua.Yang@unthsc.edu

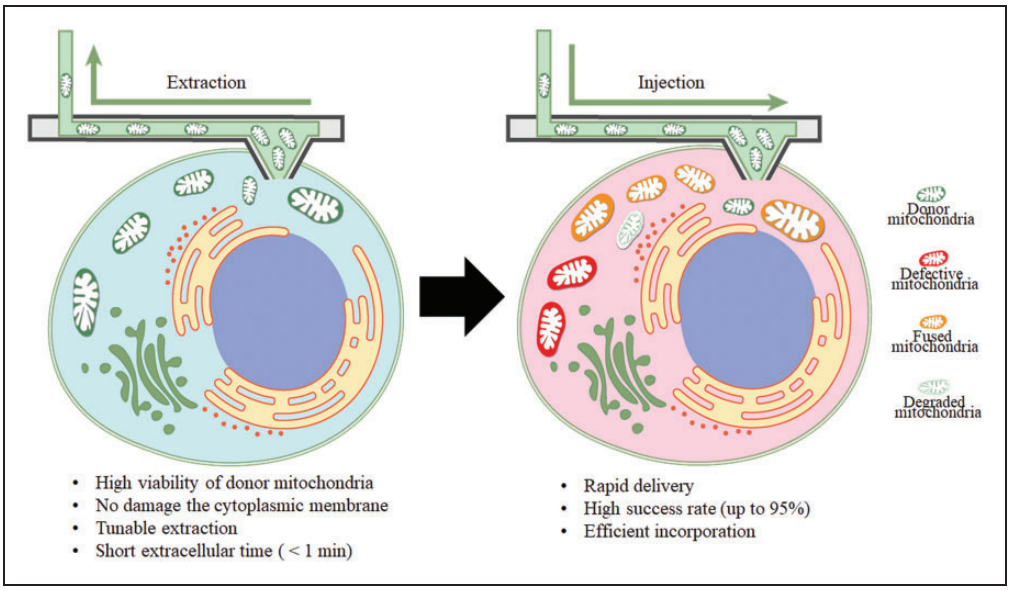

Figure 1. Therapeutic application of mitochondrial transplantation using the cell-to-cell nanosyringe. Mitochondria of a healthy donor cell are extracted and rapidly injected into a recipient cell. Most of the transplanted mitochondria will fuse with the recipient mitochondria network with a few degrade.

Using this nanosyringe approach, their study offers answers to several critical issues regarding mitochondrial transplantation/transfer therapy. As mitochondria are highly heterogeneous and display distinctive morphology and functional properties, mitochondria from different tissue may not be compatible to each other.[6] The established nanosyringe technique allows real time monitoring of mitochondrial dynamics and tracing mitochondrial fate in the recipient cultured cells. The current study presented that U2OS cells showed little selection for the mitochondria from organelle donor HeLa cells, and the transplanted mitochondria were fused with the mitochondrial network of the recipient cells. Primary human endothelia keratinocytes (HEKa) incorporate a majority of transplanted HeLa cell mitochondria into their network via mitochondrial fusion, and were capable to cope with damaged mitochondria upon transplantation. Interestingly, they found that the fusion or degradation of the transplanted mitochondria was not affected by either amount or state of transplant mitochondria. The host healthy HEKa cells response similar to small or large amount, depolarized or healthy mitochondria. The long-term studies of single cells mitochondrial transplantation over generations of host cells demonstrated the propagation of the transplanted mtDNA within the recipient cell's mitochondrial genome.

This nanosyringe-mediated cell-to-cell mitochondrial transfer provides a novel and efficient approach to treat neurological diseases, including stroke. Mitochondrial damage is one of the hall markers of stroke due to the insufficient supply of oxygen and glucose, and has been considered as a potential therapeutic target. [8] With the advantage of rapid replenishment of healthy mitochondria, this highly efficient and mini-invasive cell-to-cell mitochondrial transfer shows profound potential for the treatment of stroke. In addition, this technique can be used in conjunction with stem cells or induced pluripotent stem cells to generate healthy cells and reintroduce the cells into patients to improve stroke-induced neurological deficits.[8,9] However, there are additional issues need to be addressed before its wide application. Mitochondrial DNA are maternally inherited and closely interact with nuclear DNA. The introduction of allogenic mtDNA may interfere with the nuclear-mtDNA communication of the recipient cells, ultimately affect genomic expression and phenotype.[7] Future research using cell-to-cell mitochondria transplantation with single-cell sequencing technology may enable the identification of the metabolic and genetic factors that impact nuclear mitochondrial crosstalk. The transplanted mitochondria may induce immune response for their bacterial origin or mitochondrial damage-associated molecular patterns (DAMPs). Several studies have reported the increase of proinflammatory chemokines and cytokines after mitochondrial transplantation, and the underlying mechanisms still remains unknown.[10] It is plausible that degradation of the transplanted mitochondria in large amount upon mitochondria transplantation may elicit immune response through DAMPs. The cell-to-cell mitochondria transplantation presented in this paper provide a method that might fine-tune the condition of donor and recipient cells as

well as amount of mitochondria for transferring in long-term studies. Thus, this technique will facilitate future research and bring new perspective for mitochondria replacement therapy.

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Declaration of conflicting interests

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