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SPOTLIGHT

Tunnel traffic: Import stress induces bidirectional mitochondrial transfer between cells

Konstanze F. Winklhofer[1,2] and Johannes M. Herrmann[3]

Stressed cells can exchange mitochondria through intercellular tunneling nanotubes. In this issue of the *JCB*, Glover et al. (https://doi.org/10.1083/jcb.202511211) describe two functionally different tunnels: one for exporting dysfunctional mitochondria and another for retrieving respiration-active healthy mitochondria.

Mitochondria are essential eukaryotic organelles implicated in energy production, metabolism, signaling, and cell-fate decisions. Mitochondrial dysfunction threatens cellular fitness and is associated with various diseases, including neurodegenerative, metabolic, and inflammatory diseases. Mechanisms that maintain mitochondrial function long-term are particularly important for long-lived, nondividing cells, such as neurons. Several stress response programs, including the integrated stress response and the mitochondrial unfolded protein response, were recently identified that allow cells to efficiently respond to mitochondrial defects by modulating the transcription, translation, and stability of individual gene products (1, 2). Moreover, degrading damaged or dysfunctional mitochondria or parts thereof by selective autophagy, called mitophagy, contributes to the maintenance of a healthy mitochondrial population. In this issue of *JCB*, the group of Ian Collinson in Bristol describes an alternative cellular response that relies on the formation of ultrathin nanotubes through which mitochondria are shipped back and forth between compromised and healthy cells (3) (Fig. 1).

Mitochondrial biogenesis relies on the import of about 1,500 different precursor proteins from the cytosol into the organelle. Defects in protein translocation result in the depletion of mitochondrial mass over time and compromised mitochondrial function. However, presumably even more relevant in the context of diseases, such as neuropathies, is another consequence of such import defects: the accumulation of nonimported mitochondrial precursor proteins in the cytosol. Such nonimported mitochondrial proteins can have profound negative consequences for cellular proteostasis outside of mitochondria, as they strongly burden the chaperone and proteasome systems (4). In addition, several nonimported mitochondrial precursor proteins serve as signaling molecules that elicit distinct types of stress response programs (5, 6, 7). "Clogger" proteins that jam the mitochondrial import pores proved to be very efficient to trigger such responses (8).

Glover et al. used such clogger constructs composed of a mitochondrial targeting sequence, different types of fluorescent proteins, and a dihydrofolate reductase (DHFR) domain. The addition of the folate analog methotrexate induces rapid and stable DHFR folding, preventing the successful translocation of these DHFR fusion proteins through mitochondrial protein translocases. The authors observed that cells responded to the expression of the DHFR cloggers by the formation of nanotubes, long ultrathin tunnels formed by the plasma membrane that connect the cytoplasm of neighboring cells.

Next, they cocultured clogger-expressing cells containing import-defective mitochondria with import-competent cells expressing a mitochondria-targeted fluorescent protein of a different color. They then made a surprising observation: neighboring import-defective and import-competent cells formed two functionally distinct types of nanotubes that both transferred mitochondria.

The inhibition of mitochondrial protein import induced the fragmentation of mitochondria. These fragmented, functionally compromised mitochondria were tunneled to cells with uncompromised mitochondria. Once they reached the healthy cells, the mitochondrial fragments did not fuse with the mitochondrial network of the recipient cells. Instead, they were rapidly engulfed by isolation membranes and degraded by lysosomes. Similar observations had been reported before (reviewed in reference [9]), and it is assumed that healthy cells use this form of transmitophagy to support their stressed neighbors in degrading nonfunctional mitochondria.

However, the second type of tunnel, which transported mitochondria in the opposite direction, was unexpected. These counterflux nanotubes transferred healthy mitochondria into cells with import-defective mitochondria, where the import-competent mitochondria segregated into large clusters that the authors termed "mitochondrial degradation bodies (MDBs)." In some unknown way, the clogger-expressing cells seem to send signals to their healthy neighboring cells, which stimulates them to send respiration-active mitochondria in the counterflux tunnels.

[1]Department of Molecular Cell Biology, Institute of Biochemistry and Pathobiochemistry, Ruhr University Bochum, Bochum, Germany; [2]Cluster of Excellence RESOLV, Ruhr University Bochum, Bochum, Germany; [3]Cell Biology, RPTU, University of Kaiserslautern, Kaiserslautern, Germany.

Correspondence to Johannes M. Herrmann: hannes.herrmann@biologie.uni-kl.de.

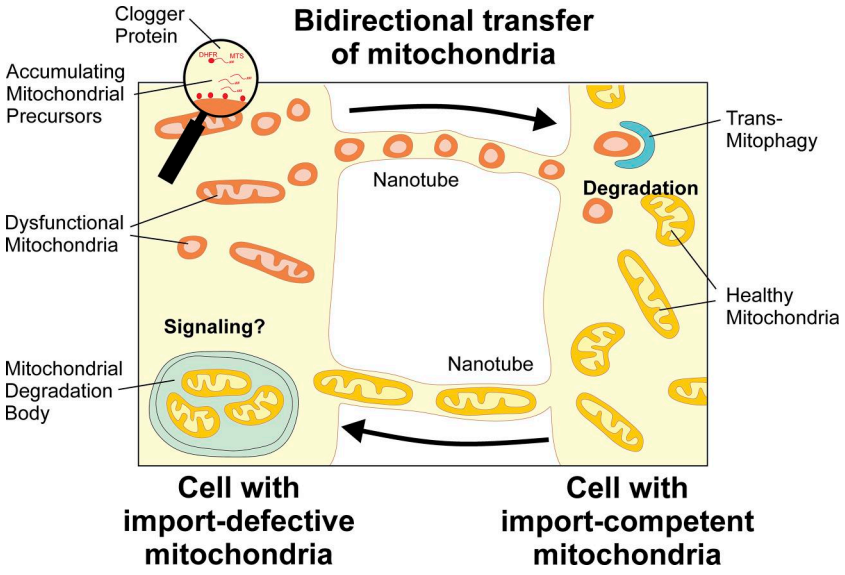

Figure 1. **Ian Collinson and coworkers identified two distinct nanotube types that mediate mitochondrial exchange between cells (1).** Healthy cells with import-competent mitochondria were cocultured with import-defective cells expressing a mitochondrial import clogger. These clogger constructs consist of a MTS and a rapidly folding DHFR domain. Clogger-expressing cells transferred compromised fragmented mitochondria to neighboring healthy cells for degradation. Unexpectedly, respiration-active mitochondria were sent back from healthy cells using a second type of nanotubes. In the compromised cells, the freshly received healthy mitochondria are not used for respiration but are degraded in specific structures which the authors termed MDBs. MTS, mitochondrial targeting sequence.

Interestingly, the import-competent mitochondria showed increased levels of reactive oxygen species (ROS) when located in the cell periphery of the donor cells, indicative of high metabolic activity. These ROS may act as signaling molecules in the receiving cells because ROS quenching inhibited MDB formation. Surprisingly, the healthy mitochondria within MDBs rapidly underwent lysosomal degradation in the import-deficient recipient cells. It appears that the counterflux tunneling is not used to directly replenish the pool of mitochondria in the compromised cells. Therefore, it remains unclear whether and how the recipient cells benefit from the formation of MDBs.

So far, the authors only studied the formation of these two types of nanotubes in galactose-grown HeLa cells and rat primary astrocytes. It will be important to show that similar tunnels are formed in living tissues, for example, between glial cells and neurons. Moreover, using the clogger is clearly not a physiological situation, even though the accumulation of nonimported mitochondrial precursors has recently been linked to a variety of diseases that are caused by mitochondrial dysfunction (10).

Several questions remain open. Are different types of nanotubes required for the bidirectional mitochondrial transport between the donor and recipient cells? Is unidirectional traffic a strategy to avoid traffic jam within individual tunnels? Which cues govern cargo selectivity and directionality? What are the specific signals to initiate tunnel formation from cells with import-competent versus import-defective mitochondria? Does the signal come from the donor cell or are cooperative signals from both the donor and recipient cells required? How are MDBs formed and why are mitochondria within MDBs degraded? Are transmitophagy and the removal of mitochondria within MDBs ubiquitin-dependent or ubiquitin-independent processes? Are selective autophagy receptor proteins involved? It will be exciting to unravel these processes in more detail in the future.

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