Mitochondrial Transfer between Airway Cells: Helping the Neighbors, or Sending Them Trash?

Mitochondrial homeostasis is essential for maintaining cell metabolism, function, and integrity. Mitochondrial dysfunction has been associated with aging and diverse chronic lung pathologies (1). Cells with high energy demand are more susceptible to mitochondrial dysfunction, which may lead to rapid cell exhaustion, senescence, or death. Cells respond to energy demands or stress with morphological and intracellular movement of the mitochondria. Recently, intercellular mitochondrial transfer between mammalian cells has been documented (2, 3). Mitochondria are recognized as endosymbiotic organisms whose noneukaryotic origin could facilitate their ability to be transferred from cell to cell (4). Even though stem cells are the most common donor cells among all the reported mitochondrial transfer cases, growing evidence suggests intercellular mitochondrial communication can be initiated by stromal cells such as cardiofibroblasts, vascular smooth muscle cells, and other cell types (5, 6). In this issue of the *Journal*, Frankenberg Garcia and colleagues (pp. 471–481) report on their investigation of mitochondria exchange between lung structural cells, specifically airway smooth muscle cells (ASMCs) from healthy ex-smokers and patients with chronic obstructive pulmonary disease (COPD) (7). The authors demonstrate that mitochondrial transfer does occur and that extracellular vesicles mediate mitochondrial transfer between ASMCs. They further reveal that there are no differences in the ability of ASMCs from healthy ex-smokers or patients with COPD to exchange mitochondria.

Several groups have already reported that the transfer of mitochondria helps not only to restore stressed cells and tissues but also to maintain physiological tissue homeostasis. For example, the transfer of mitochondria is a process required for somatic cell reprogramming (5). Under stress conditions, mitochondrial transfer can modulate inflammation (8), calcium dynamics, oxygen consumption, and ATP production (9). Notably, another aspect of intercellular exchange of mitochondria is that damaged mitochondria can be delivered to other cells for outsourced degradation, recycling, or even as a rescue signal, a process referred to as transmitophagy (10). Frankenberg Garcia and colleagues found autophagy-related proteins in the extracellular vesicles transporting mitochondria between ASMCs. This finding might suggest that mitochondria were targeted for degradation in the recipient cells. Transmitophagy has been described as a protective mechanism, preventing the release of mitochondrial damage-associated molecular patterns to the extracellular medium and preventing pathological inflammatory responses.

Because mitochondrial dysfunction observed in ASMCs from subjects with COPD does not impair the ability to exchange mitochondria, the authors were interested in investigating the effect of cigarette smoke. Cigarette smoke media (CSM) induces cellular stress and phenotypes associated with COPD *in vitro*. The authors found that ASMCs stressed by CSM increase the transfer of mitochondria in ASMCs from both healthy ex-smokers and subjects with COPD. Induction of mitochondrial depolarization by CSM or the electron transport chain uncoupler carbonyl cyanide m-clorophenyl hydrazone similarly enhances the donor's mitochondrial transfer to ASMC recipient cells. In concordance with these findings, studies have shown that conditions associated with high reactive oxygen species, mitochondrial dysfunction, and impaired mitophagy, such as aging or Alzheimer's disease, are associated with an increase in the intercellular transfer of mitochondria (11). Frankenberg Garcia and colleagues observed that CSM exposure increased mitochondrial transfer, leading to improvement of the bioenergetic capacity of the recipient cells and enhanced expression of *PGC-1*α gene (encoding peroxisome proliferator-activated receptor gamma coactivator 1-α protein), a key regulator of mitochondrial biogenesis. Unexpectedly, the bioenergetic benefit was similar in cells that uptake mitochondria from ASMCs from healthy ex-smokers and subjects with COPD. Although the status of the donated mitochondria was not defined by Frankenberg Garcia and colleagues, mitochondrial dysfunction is a common finding in COPD cells, opening the possibility that donation of mitochondria improves bioenergetics independently of their functional fitness. In concordance with this concept, studies in mesenchymal stem cells describe engulfment and degradation of damaged mitochondria as a potential trigger of mitochondrial biogenesis via activation of the heme oxygenase-1 signaling pathway (12). In addition, Phinney and colleagues showed that damaged mitochondria can be reused in recipient cells by fusion, increasing macrophage bioenergetics (10).

Although it was initially suggested that mitochondrial transfer was a salvage response (13), evidence has revealed that mitochondrial transfer can take place without stress in limited conditions (14). Frankenberg Garcia and colleagues propose that the transfer of mitochondria in ASMCs might constitute a homeostatic mechanism in the airways, independently of CSM exposure or disease state. Transferred mitochondria increase the bioenergetic capacity and mitochondrial biogenesis of the recipient cell, while at the same time reducing its proliferative potential. The potential signaling and reprogramming metabolic pathways involved in this shift have not been completely defined. However, the reduced proliferation might

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protect against hyperproliferation of ASMCs and small airway thickening, a common pathological characteristic in several lung diseases such as COPD and asthma.

This article defines critical new mechanisms of mitochondrial transfer in stromal cells; however, there are still some remaining questions. It is unknown if there are differences in the recycling process of healthy versus unhealthy mitochondria after being transferred to recipient cells. Similarly, it is not known whether the mitochondrial transfer affects other disease-relevant ASMC phenotypes, such as apoptosis, contractility, or secretion of inflammatory mediators. An important limitation of this study is using ASMCs from healthy ex-smokers as controls. Further work examining healthy never-smokers is needed to assess the impact of cigarette smoke exposure and disease.

Previous work has highlighted the importance of bone marrow–derived mesenchymal stem cells in transferring mitochondria to alveolar epithelial cells, leading to the improvement of energy, surfactant production, and protection from acute lung injury (15). The strength of the study by Frankenberg Garcia and colleagues is the demonstration that stromal ASMCs in healthy and COPD airways can exchange mitochondria. Furthermore, they showed that mitochondrial depolarization induced by stress conditions such as CSM exposure could lead to increased mitochondrial transfer, which improves the bioenergetic and biogenesis capacity in the recipient cell and ultimately leads to regulation of cellular proliferation. This work is especially exciting because it sheds light on new homeostatic mechanisms in lung stromal cells and suggests new potential therapeutic approaches, such as artificial mitochondrial transfer for lung diseases. ■

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