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EDITORIAL COMMENT

The New Promise of Mitochondrial Transplantation for Myocardial Recovery*

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"There are times when a critic truly risks something, and that is in the discovery and defense of the new. The world is often unkind to new talent, new creations. The new needs friends."

—Anton Ego, in *Ratatoulle* (2007) (1)

Mitochondria are fascinating bacteria-like cellular organelles primarily located within subsarcolemmal, perinuclear, and intrafibrillar regions of the cardiomyocytes that regulate multiple cell processes, including calcium signaling, apoptosis, and cell metabolism in their hosts. We are just beginning to understand that these processes may be caused by altered expression of proteins that regulate mitochondrial dynamics in the form of fission, fusion, and autophagy, which are essential for energy production and structural integrity of the organelles (2). Indeed, altered mitochondrial biogenesis, fragmentation, and hyperplasia have long been observed in the failing myocardium, leading to the decreased capacity to oxidize fatty acid substrates seen in heart failure (3). Mitochondria contain their own circular genome encoding selected subunits of the oxidative phosphorylation complexes, and often leverage their host cells to generate the majority of their own protein components. Recent findings have revealed that mitochondria can even traverse cell boundaries, and can thereby horizontally transferred between cells. This has raised the possibility that transplantation of viable mitochondria into the injured tissues would replace or augment damaged mitochondria, allowing the potential "rescue" of a variety of cells (4). The hypothesis implies that autologous healthier mitochondria may "engraft" into the myocardium, or like mesenchymal stem cells, they might have paracrine effects that would benefit myocardial function. Even though earlier studies on this topic have provided much-needed proof of concept, logistics of direct tissue injection may be impractical beyond surgical approaches (5).

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In this issue of *JACC: Basic to Translational Science*, Shin et al. (6) extend their prior research in autologous mitochondrial transplant to direct myocardial injection and demonstrate that autologous mitochondrial transplantation with intracoronary delivery can potentially preserve myocardial blood flow in a swine ischemia-reperfusion model. Shin et al. (6) describe 3 sets of experiments and demonstrate that: 1) intracoronary autologous mitochondria can be safely administered and are taken up by the myocardium without hemodynamic consequences; 2) compared with nonviable or other cell types, autologous mitochondria transplantation leads to an increase in coronary blood flow, likely via inwardly rectifying potassium channels; and 3) autologous mitochondrial transplantation leads to a reduction in infarct size and cardiac remodeling in an ischemia-reperfusion model. The findings are indeed intriguing, although the proposed mechanistic benefits still need to explain the physiologic outcome differences, as the observed number of mitochondria taken up seemed relatively sparse. It would be helpful to better understand "uptake" dynamics and

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affinity of transplanted mitochondria toward the failing myocardium via this approach. Furthermore, it is not entirely clear how to reconcile the time course of the changes in the coronary blood flow, with transient effects seen in the nonischemic hearts versus sustained improvements observed in ischemia-reperfusion hearts. The premise would have stronger support if the effects of autologous mitochondrial transplant on coronary blood flow may somehow be negated with direct inwardly rectifying potassium channel inhibition. The lack of blinding of the measurements and the lack of randomization may have limited the confidence of the findings, and such observations would require independent external validation. Nevertheless, these intriguing findings have provided promise for mitochondrial transplantation as means for promoting myocardial recovery.

The potential for metabolic modulation and myocardial salvage with intracoronary injections in the setting of cardiogenic shock is not entirely new, as the impact of impaired myocardial energetics in the failing heart has been explored for over half a century. However, the prospects of autologous mitochondrial transplantation will likely be disruptive. It may create a unique opportunity to preserve or restore myocardial function via metabolic modulation with infusion of intact organelles, a concept that has largely been focused on modulating substrate availability and therapeutic targeting of myocardial energetic processes with small molecules. First, the opportunity to perform autologous transplantation of organelles to restore solid organ function captivates the potential of a therapeutic approach in the setting of cardiogenic shock that mirrors bone marrow transplantation in hematologic malignancies even in the acute setting. Second, there are potential applications in donor organ preservation with this approach, whereby donor mitochondria can be applied either in vivo (or potentially even ex vivo after harvest within portal organ perfusion systems) to reduce ischemic organ damage or even revive those that are otherwise unsuitable for transplantation. With improved myocardial viability, the potential for extending donor organ transfer ranges and cold-time durations may be expanded. Third, it is conceivable with multiple functions of mitochondria in the myocardium that replenishment of healthier mitochondria can be leveraged in various cardiotoxic settings besides ischemia-reperfusion injuries.

We have a lot to learn from understanding which patients may be benefit from such approaches, how many mitochondria are needed and whether they behave similarly in different conditions or settings, and how to maximize the uptake into myocytes and whether they can even be administered intravenously rather than through intracoronary approaches. The beneficial effects of autologous mitochondrial transplantation still demand rigorous human clinical investigations, including prospective randomization between treatment and placebo intracoronary infusions, and the need for stringent double-blind, multicenter study designs. Also, the validation process will demand replication of similar findings from other laboratories. Although it is tempting to follow the testimonies of promising observations such as those reported in this exciting report, we are reminded of the treacherous journeys of stem cell research that have taught us the importance balance of cautious optimism and careful scrutiny in clinical therapeutics development, especially for innovative new ideas such as this. The new does need friends.

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