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Editorial: Are Mitochondrial Therapeutics the Next Disruptor in Molecular Healthcare?

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Mitochondrial therapeutics are not new [1]; however, one might think so if the reader followed only the paucity of announcements from the Food and Drug Administration (FDA) or listings on ClinicalTrials.gov—but I get ahead of myself. What is meant by mitochondrial therapeutics?

Most scientists would define mitochondrial therapeutics as compounds that are used or are in development for correcting aberrations in primary mitochondrial disorders, caused by mitochondrial mutations. Conditions include mitochondrial encephalopathy syndrome (MELAS), myoclonic epilepsy with ragged red fibers (MERRF), Leber hereditary optic neuropathy (LHON), neuropathy, ataxia, and retinitis pigmentosa (NARP), Leigh syndrome, and Kearns-Sayre syndrome (KSS), to name the common ones [2]. In addition to the primary mitochondrial disorders are a collection of age-related and/or acquired types of mitochondrial dysfunction [3, 4] that are much more familiar. These include cancer, diabetes, heart disease, lupus, Parkinson's disease, Alzheimer's disease, and even aging, to name a few. Interestingly, as of this writing, there are no FDA-approved mitochondrial medicines, and few clinical trials have been attempted to test mitochondrial therapeutics. For the last decade or more, most work has actually focused on rare primary mitochondrial disorders and not the larger world of mitochondrial dysfunction in age-related disease.

Given the field is advancing so rapidly, the above definition of mitochondrial therapeutics is also no longer complete. The emerging number of subfields (and private companies) within mitochondrial therapeutics is exploding and includes mitochondrial pharmacology, mitochondrial replacement therapy, nutritional management, physical therapy, nanotechnology, medical devices, gene therapy, mitoceuticals, MitoChips, and mitochondrial transfusion, transfer, and/or transplantation. One can see that treatment for primary mitochondrial disorders or acquired mitochondrial dysfunction can vary tremendously. The approaches in some cases focus on drugs, in other cases on genetic manipulation, and in still other cases on improving bioenergetics.

In this editorial, I want to focus mainly on the mitochondrial bioenergetics approach. The science of bioenergetics started in the eighteenth century with the pioneering work of Antoine Lavoiser and Joseph Preistly who characterized aspects of cellular respiration and photosynthesis [5]. Other discoveries followed, but it was not until the 1940s with the work of Lehninger, Green, and Kennedy that realized that the enzymes of the citric acid cycle, fatty acid oxidation, and oxidative phosphorylation are in the mitochondria [6]. Then, in 1961, Peter Mitchell publishes the chemiosmotic coupling hypothesis that was refined over the next few years [7]. Following this, the human mitochondrial genome was determined by a group of scientists in Cambridge [8]. These were disrupting discoveries.

In my opinion, the next disruptor for molecular healthcare is how to modulate mitochondrial bioenergetics to treat disease. Some of these methods so far have included methods of transplantation or transfusion, which can be lumped together—at least for now. The end result for these interventions is an enhancement in mitochondrial bioenergetics. Mitochondria are the powerhouse of the cell and the *energy currency* that the cell utilizes via the generation of adenosine triphosphate (ATP). A plethora of reviews and studies have already been written that describe the biology, physics, and chemistry of mitochondrial bioenergetics, and the reader is encouraged to read these as a primer [9–11].

So, what is mitochondrial transplantation or transfusion? To date, animal studies and human interventions mostly on heart or brain have been attempted with great success. Mitochondrial transplantation is a therapeutic approach that involves the injection of isolated healthy mitochondria into body regions that have damaged or diseased tissue or organs [12]. Many different routes of administration and delivery

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are being tried. In essence, damaged mitochondria are being replaced with healthy mitochondria so that the increase in healthy mitochondria is substantial and beneficial. New studies continue to examine mitochondrial transfer, internalization, movement, and compartmentalization and their potential risks in other cellular organelles.

The transplantation story begins a few years ago with applications in the cancer field [13], but more recently had a significant increase in activity due to the work by McCully et al. [14] who successfully transplanted healthy heart mitochondria into ischemic regions of the heart in a pediatric patient and improved clinical outcome. Other recent advancements by the Boilard lab in Quebec, Canada, include work with platelet-derived extracellular mitochondria that have been shown to improve health [15]. For example, in their recent studies in mice, activated platelets were shown to produce extracellular vesicles (EVs) that contain mitochondria (aka mitlets [16]) that improve mitochondrial bioenergetics in immune cells [17].

The Boilard lab and a collaborative industrial partner called Mitrix Bio call this concept HISET therapy (Human Immune System Energetics Transplant). The group sees it as a potentially "general purpose" immune system booster, which might be administered in combination with the usual antiviral or anti-bacterial drugs, boosting the strength and vigor of the white blood cells temporarily, or to help an elderly patient fight off COVID or the flu.

In another recent paper led by my former postdoctoral fellow, Dr. Aida Adlimoghaddam, and co-authored by myself and Mitrix Bio. [18], we provided evidence for a similar approach, that is, upregulating the respiratory machinery to enhance the available energy for the brain. In this work, we transplanted mitochondria from 1-month-old C57BL6 mice into 12-month-old C57BL6 mice, who had been previously studied and shown to have presumptive energy depletion as they aged given that significant decreases in the expression of mitochondrial complex protein subunits (I–V) were found. In the 12-month-old mice, following transfusion, we found significant increases in mitochondrial complex II protein subunit SDHB in the hippocampus, suggesting the possibility for energy improvement in a key location for memory encoding. Similar work by my collaborators was recently conducted (Benson et al. biorxiv, 2023. https://doi.org/10.1101/2023.09.08.556161), where platelet extracellular vesicles and their mitochondrial content significantly improved survival and cytokine levels when transfused into mice with sepsis or H1N1 infections. The results of this study also implied that immune senescence is a function of reduced mitochondrial energy production and thus can be reversed, which is intriguing. Overall, these studies suggest that transplants of young mitochondria appear to reverse key age-related factors of the immune system.

Others have also reviewed the literature on the prospects of mitochondrial transplantation in various diseases and organs [19]. In their review, Hosseinian et al. point out not only the excitement around mitochondrial transplantation but also the challenges that need to be addressed before this approach is used in the clinic, for example, concerns such as high concentrations of calcium ions, increases in inflammatory mediators, organ-specific challenges, effects on storage of mitochondria, auto-immune responses, the possibility of short-lived benefit, routes of administration, and overall safety concerns, to name a few. Another practical concern is the limited supply of donor-quality mitochondria for this procedure to work in the clinic; in other words, in order to treat age-related diseases, clinics would require a larger supply than what is currently available. One strategy that some investigators are working on is to develop bioreactor technology to grow health mitochondria in large numbers, similar to the way stem cells are grown—an approach that Mitrix Bio is using.

All of these papers highlight new possibilities for mitochondrial therapeutics using transplantation approaches, but more importantly, they highlight an understudied area in the biological and pharmaceutical sciences. Taken together, the studies mentioned above provide evidence that transplanted mitochondria can replace deficient mitochondria and can be beneficial in various disease states. Future studies are still needed with transplanted mitochondria to address specific questions related to processes of mitochondrial exchange, potential bioenergetic enhancements, roles in repairing damage from inflammatory conditions, whether transfusion contributes to adverse effects, applicability to human cells, and routes of administration, to name a few.

Declarations

Conflict of Interest BCA is a scientific advisor for Mitrix Bio and the Intracell Research Group Consortium.

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