Cardiovascular Surgery International

ISSN 2692-7969

Mini Review

Concern for Mitochondrial Transplantation in Humans: "Another Opinion"

Robert L. Elliott[*] *and Xian-Peng Jiang*

Sallie A. Burdine Breast Foundation, USA

Abstract

In 2018, Edoardo Bertero et al published a paper in the Journal of Clinical Investigation entitled Mitochondrial transplantation in humans: "magical" cure or cause for concern? The authors were quite critical and skeptical of the research and therapeutic approach developed by McCully and colleagues to inject healthy mitochondria harvested from normal tissue into an ischemic organ of the subject. They are especially concerned about how isolated mitochondria survive in high extracellular calcium concentrations; produce ATP for energy and why results are not dose dependent. In this paper, we review evidences of evolutionary and early research and present our research data to support mitochondrial transplantation. Our data show the isolated mitochondria can survive in the media with 1.8 mM calcium (>physiological plasma calcium 1.3 mM to 1.5 mM) for 7 days. Also, the cultured mitochondria can easily enter into cancer cells after co-culture with cancer cells.

Keywords: Mitochondrial transplantation; Bacterial properties; Endoplasmic reticulum

Introduction

In 2018, Edoardo Bertero, Christoph Maack, and Brian O'Rourke published a paper in the Journal of Clinical Investigation entitled mitochondrial transplantation in humans: "magical" cure or cause for concern? [1]. after reading the paper, we decided to respond to the author's statements and some of their concerns. The authors were quite critical and skeptical of the research and therapeutic approach developed by McCully and colleagues to inject healthy mitochondria harvested from normal tissue into an ischemic organ of the subject [2].While reading the article it seemed the authors had some kind of ax to grind. They seemed more interested in criticism of the procedure than science and the actual results. The article was filled with sarcastic remarks: (a) "Mitochondria moved like magnets to the proper places in the cells and began supplying energy;"and (b) after infusion into the coronary arteries "somehow the organelles will gravitate almost magically to the injured cells that need them and take up residence". They imply that mitochondria must perform "magic tricks" to perform the mission [1].

Evolutionary and early research supporting mitochondrial transplantation

We believe the authors are familiar with the origin of mammalian mitochondria, but we encourage them to review the work of Margulis and Gray [3,4]. Mitochondria are evolutionary bacteria and though being intracellular for over a billion years; they still retain similar ribosomes and bacterial properties. Pathogenic bacteria enter humans, become intracellular and cause many severe infectious pathogenic conditions.

Citation: Elliott RL, Jiang XP. Concern for Mitochondrial Transplantation in Humans: "Another Opinion". Cardiovasc Surg Int. 2020;1(2):1007.

Publisher Name: Medtext Publications LLC

Manuscript compiled: June 05th, 2020

***Corresponding author:** Robert L. Elliott, Sallie A. Burdine Breast Foundation, Baton Rouge, LA 70806, USA, E-mail: drrobertelliott@cox.net

The authors have also ignored some great in vivo animal studies. Examples are:

1. "Transferring Xenogenic Mitochondria provides neural protection against Ischemic Stress in Ischemic Rat Brains" by Huang et al. [5]
2. "Mitochondrial transplantation strategies as potential therapeutics for central nervous system trauma" Gollihue et al. [6]
3. "Intravenous administration of mitochondria for treating experimental Parkinson's disease" Shi, Thao, Fu et al. [5-7] this is a start, but if they desire more evidence of efficacy there are many more examples. We will later briefly discuss some of our research evidence.

Response to doubts and questions

The authors do ask some important questions of why and how could this technology work? They are especially concerned about how isolated mitochondria survive in high extracellular calcium concentrations; produce ATP for energy and why results are not dose dependent. These are valid questions that need to be answered; however, sometimes we must accept a technology works without knowing the mechanism of action or exactly why. If the research is continued and explored, we may be able to answer these important questions. How mitochondria survive in high calcium concentrations are unknown, but we suspect it might be because isolated mitochondria have been disrupted from the endoplasmic reticulum. The Mitochondria Associated Membrane (MAM) an area of intimate contact between the endoplasmic reticulum and outer membrane of the mitochondria has been disrupted. The MAM is critical for calcium flux, lipid transfer and cellular homeostasis. Therefore, isolated mitochondria might not be so sensitive to flux in calcium concentrations. We cultured isolated mitochondria from a normal cell line in a media of calcium chloride concentrations 200 mg/L (1.80 mM) (higher than physiological plasma calcium 1.3 mM to 1.5 mM) for 7 days. They were stained with JC-1 and they still had a good membrane potential confirming the ability to still produce ATP. They were co-cultured with a cancer cell line and easily entered the cancer cells (Figures 1 and 2). If the

doubting authors want proof of mitochondrial intracellular location and survival, they should read references [5-7].

Doubts of the authors' mitochondrial transplantation experience

We did a Pub Med search on the mitochondrial research of the authors. O'Rourke was on 6 papers, Moack 4 and Bertero 3. To the best of our knowledge, none of the papers were concerned with mitochondrial transplantation. We were reminded of a statement by an English physician on patient care. We are not sure of the exact quote, but basically, he said: "Today we are constantly bombarded in the literature by a series of articles on patient care by experts whom have never seen patients; a most peculiar syndrome." Our gut feeling is this statement may be appropriate for these authors, as it seems they have not had or have had very little experience with this technology. We could be wrong but we sense a professional conflict and envy from the authors of the great work of McCully. We should praise Dr. McCully for his great contribution to this biotechnology, especially his tremendous isolation technique. We have had positive results of the technology in a neurodegenerative condition, ALS, and are convinced research should continue to bring this technology to a viable cellular biotherapy.

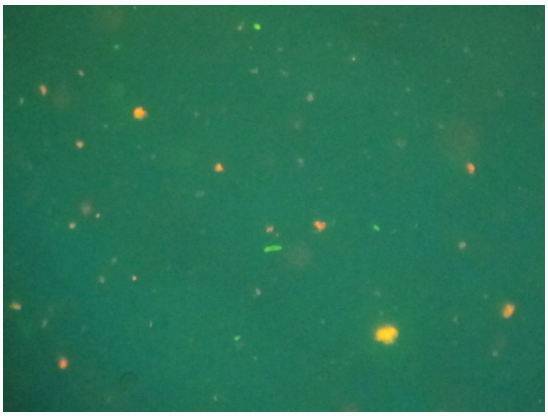

Figure 1: Fluorescent micrograph of MCF-12A isolated mitochondria stained with JC-1 showing good membrane potential after 7 days culture in a proprietary culture media.

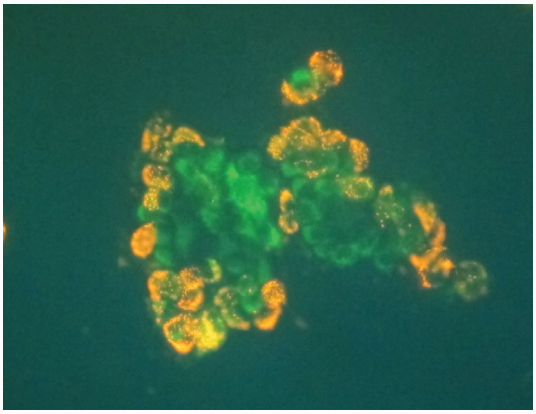

Figure 2: Fluorescent micrograph of MCF-7 mammary carcinoma cells after co-culture with MCF-12A isolated JC-1 stained cultured mitochondria. The 7-day cultured isolated mitochondria easily entered the cancer cell line.

Conclusion and Future Direction

We are in the embryonic stage of this technology and pray we can bring it to a beautiful birth. This is our opinion and there is evidence to prove it, as stated in our paper on Mitochondria and Neuro degeneration: "Could mitochondrial organelle transfer be a cellular biotherapy for neurodegenerative diseases?" [8]. our comments are only our opinion as we have no personal vendetta about the authors. We have never met them, but believe different views in research should be approached professionally without sarcastic criticism. This is especially true if those making the criticism have none or very little experience with the topic. However, we admit in this communication, we also may have slightly violated this rule. Therefore, it is imperative we continue to develop this technology for the potential it has to help patients with severe debilitating neurodegenerative diseases and cardiovascular emergencies.

References

1. Bertero E, Maack C, O'Rourke B. Mitochondrial transplantation in humans: "Magical" cure or cause of concern. J Clin Invest. 2018;128(12):5191-4.
2. Shin B, Cowan DB, Emoni SM, Del Nido PJ, McCully JD. Mitochondrial transplantation in myocardial ischemia and reperfusion injury. Adv Exp Med Biol. 2017:982:595-619.
3. Margulis L. origin of eukaryotic cells Origin of eukaryotic cells;: evidence and research implications for a theory of the origin and evolution of microbial, plant, and animal cells on the Precambrian earth. Yale University Press: New Haven CT. 1970.
4. Gray MW. Mitochondrial evoloution. Cold Spring Harb Perspect Biol. 2012.
5. Huang PJ, Kuo CC, Lee HC, Shen CI, Cheng FU, Wu SF, et al. Transferring Xenogenic Mitochondria Provides Neuroal protection against Ischemic stress in ischemic rat brains. Cell Transplant. 2016;25(5):913-27.
6. Gollihue JL, Patel SP, Rabchovsky AG. Mitochondrial transplantation strategies as potential therapeutics for central nervous system trauma. Neural Regen Res. 2018;13(2):194-7.
7. Shi X, Thao M, Fu C, Fu A. Intravenous administration of mitochondria for treating experimental Parkinson's disease. Mitochondrion. 2017;34:91-100.
8. Elliott RL, Jiang XP, Head JF. Mitochondria and neurodegeneration: "Could mitochondrial organelle transfer be a cellular biotherapy for neurodegenerative diseases?" SOJ Bio chem. 2016;2(1):1-5.