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Mini Review

Subcellular Transplantation for Cardiac Ischaemia - The Exciting Future Unfolds

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Abstract

Mitochondria known as power house of the cell are intimately linked to cellular origin and existence, enabling the conversion of oxygen to energy. Ischaemia ranks as a forerunner in mitochondrial damage leading to cell death. Replacing mitochondria in ischaemia situations like stroke or myocardial infarction opens up multitude of possibilities in treatment domain. To mitigate cellular dysfunction, mitochondrial transplantation is now an acceptable form of treatment of ischaemia reperfusion injury [1]. Real world applications in pediatric ischaemia reperfusion has been showed by the Boston Group [2]. Usefulness of this mode of treatment now extends to graft function improvement in transplantation scenarios too. From tissue samples following an automated system harvest vectors transport the mitochondria for target cell incorporation by endocytosis. A newer treatment modality has now emerged flaring hopes of successful treatment in areas of cardiovascular domain with significant morbidity and mortality. In addition to cell based therapies that are emerging in the form of stem cells, cellular organelle transplantation now opens up the domain of sub cellular transplantation too.

Keywords: *Subcellular Transplantation; Cardiac Ischaemia; Mitochondria*

Introduction

Hypoxia triggers cell death as energy production is impaired. As far as cardiac muscle is concerned minutes is muscle- emphasizing the importance of time scale of ischaemia in myocardial damage. With acute shortage of donor organs, the statistics that 1 out of 3 cardiac donations are to be discarded emphasizes the need to counter ischaemic damage with alternative novel forms of treatment. Even in renal transplants ischaemia induced delayed graft dysfunction is noted in upto 50% of cases. With about a lakh in the renal transplantation waiting list, newer modalities of treatment like mitochondrial transplantation would pave way for enormous reduction in health care burden too. Energy is the core of life. Reinvigorating energy failing cellular energy metabolism by replacing and reinvorgating stunned

cells is an exciting research concept that rolls out from bench to bed side. It has been compared with jump starting a car. Technology like the Nespresso machine makes this dream a reality. Commercial viability is expected by around 2026 by companies like Cellvie. Direct infusion or vascular injection to end organs is currently advocated. Following injection into coronary arteries they move like magnets into the injured cells [3].

Surviving the extracellular transfer, reaching the target cell in sufficient numbers they must produce adequate ATP to trigger cellular contraction. For this the endothelial barrier is crossed followed by interstitial migration and reaching the target dysfunction cell. Animal model validation of this theory has already been done [4,5]. Augmented ATP levels are noticeable even upto a month after injection of mitochondria. This is due to upregulation of enzymes involved in mitochondrial energy production. A significant reduction in infarct size (13 - 5%) is also noticeable [6]. Figure 1 explains how mitochondrial transplantation works.1.8mM concentrations of calcium in extracellular fluids could pose permeability problems and osmotic burst mitochondria. Tracking mitochondria that were injected with MRI in porcine hearts survival upto 1 month has been demonstrated [7]. High quality physiological buffer solutions can be used for assessment of donor mitochondrial function. More scientific studies are needed in this sector.3-7% of transplanted mitochondria are internalized [8,9]. How whole heart AT P production is augmented is still an enigma considering the internalized percentage. Here again additional experimental work would be needed. For the human pediatric evaluation mitochondria obtained from rectus abdominis is given by intracoronary route in patients on ECMO more than 24hrs after cardiac surgery. An improvement of 40% mortality in ECMO patients has been claimed by this group [10]. Treatment for this group was from 2-15 days after ischaemic damage. Animal studies provide the transplantation within a minute of reperfusion. So, there is a question raised on lack of similarity between the human and animal trials.

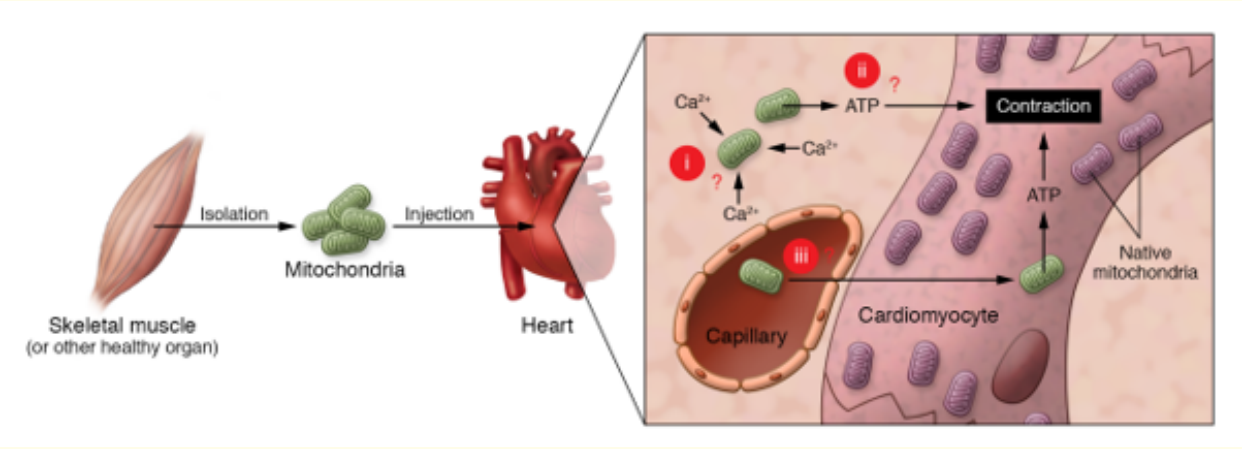

Figure 1: *How mitochondrial transplantation works.*

More clinical trials that are randomized and prospective with proper quantification if cardiac ischaemia and ventricular function prior to ischaemia, comparing to a control group is needed to further substantiate the translational effects of mitochondrial transplantation. Putative mechanisms of benefit still remain speculative and lot more is to the revealed in further clinical research.

Conclusion

Possibility of therapeutic interventions of transplantation going to sub cellular levels is a novel and exciting concept that would be validated by our better understanding of cell functions in future.

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