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Kanwal K. Gambhir *

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Review Article

Potential Therapeutic Approaches to Metabolic Disorders Through the Tunneling Nanotubes

Washington A Jr [1], Morgan Gabrielle [3], Maurice Fluitt [1], Nunlee-Bland G [2], Gambhir Kanwal K [1,2]*

[1] Molecular Endocrinology Lab, Endocrinology / Metabolism Division, Department of Medicine.

[2] Diabetes Treatment Center, Howard University Hospital, 2041 Georgia Ave, N.W. Washington, D.C. 20060.

[3] Honors, Undergraduate Pre-med Student, Howard University College of Arts and Sciences, 2400 6th St NW Washington, D.C. 20059.

***Corresponding Author:** Kanwal K. Gambhir, Professor and Director Molecular Endocrinology Lab Division Endocrinology and Metabolism Department of Medicine, Bldg. HU Hospital 2041 Georgia Ave, N.W. Washington, DC 20060

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Abstract

Mitochondrial dysfunction is a common feature of many metabolic processes. Specifically, cellular oxidative stress is known to contribute to deleterious effects such as insulin resistance, obesity, and hypertension, due to mitochondria's centrality in bioenergetics and energy expenditures within the cell and throughout the collective organ systems. Furthermore, intercellular transfers of mitochondria via tunneling nanotubes (TNTs) and micro vesicles (MVs) are means in which metabolic needs of adjacent and distant cells can be supported in a cell-to-cell manner. Therefore, importance of mitochondrial intercellular transfer, such as by TNT is increasingly recognized due to its potential therapeutic usefulness. Considering this new paradigm of mitochondrial mobility within the organ and blood, novel approaches in controlling metabolic disorders such as obesity and insulin resistance are now in much need of further exploration. In this review, we briefly discuss the field of mitochondrial transfer and possible therapeutic approaches, specifically for metabolic disorders, by summarizing the potential regulators of TNT formation.

Key words: mitochondria; intercellular transfer; tunneling nanotubes; micro vesicles; insulin resistance; metabolic disorders; oxidative stress

Abbreviations

ADP: Adenosine Diphosphate

ATP: Adenosine Triphosphate

CD38: Cluster of Differentiation 38 (Cyclic Adenosine Diphosphate Ribose Hydrolase)

DAMP: Damage-associated Molecular Pattern

DNA: Deoxyribonucleic Acid

ER: Endoplasmic Reticulum

HDL: High-density Lipoprotein

HTN: Hypertension

IR: Insulin Resistance

mtDNA: Mitochondrial Deoxyribonucleic Acid

MV: Micro vesicle

PPAR: Peroxisome Proliferator-activated Receptors

PGC: Peroxisome Proliferator-activated Receptor-gamma coactivator

ROS: Reactive Oxygen Species

RNA: Ribonucleic Acid

siRNA: Small Interfering Ribonucleic Acid

rRNA: Ribosomal Ribonucleic Acid

tRNA: Transfer Ribonucleic Acid

TNT: Tunneling Nanotube

Introduction

Ever since the first ancestor alpha-proteobacterium achieved endosymbiosis within the eukaryotic cell, the mitochondrion – a biodynamic organelle with its own DNA and replicative capacity – has

provided a powerful cellular respiration reserve to match the energy needs of its host [1]. Of note, mitochondria do not have an autonomous existence; it is thought that mitochondria are dependent on eukaryotic cells for its existence and propagation [1]. However, it is more evident that eukaryotic cells are equally or more dependent on the mitochondrion for its wide-ranging functions: Not only a sensor of metabolic needs and provider of ATP, mitochondrion also facilitates clearance of damaged proteins and organelles, thereby upholding quality and longevity of the host cell [1].

It was long thought that mitochondria resided within the same cellular confinement of the entire host cell's existence. However, recent findings paint a hyperdynamic picture of intercellular mobility that allows various cell types to swap and share its resident mitochondria using tubes and vesicles [2-5]. As a result, it is increasingly suggestive that cells under metabolic stress have the means of replacing damaged mitochondria with less-damaged and healthy organelle. It is hypothesized that cells in such danger produce signals in the form of molecular patterns from damaged cellular products, flagging other competent cells to provide fresh mitochondria [2,4]. Emerging findings support the theory of mitochondrial transfer from the donor cells via tunneling nanotubes (TNT) and micro vesicles (MVs), both in supplying healthy machinery to help meet metabolic demands [2-6].

The history of direct cell-to-cell communication spans a century from the discovery of cells – described by Schleiden and Schwann in the 19th century as independent units of animal and plant tissue – to the discovery of membrane pores in the 20th century [6]. Finally, in the early 21st century, Rustom and his team proposed the existence of tube-like membranous structures, described as tunneling nanotubes (TNTs) that allowed for cell-to-cell transport of cytoplasmic organelles [7]. The last two decades have uncovered myriad details surrounding the organelle transfer processes, with developing discussions on the search for therapeutic approaches [2-5]. In this review, the concept of mitochondrial mobility is reviewed with the aim of summarizing key findings in ongoing studies and highlighting the potential for applications in metabolic disorders.

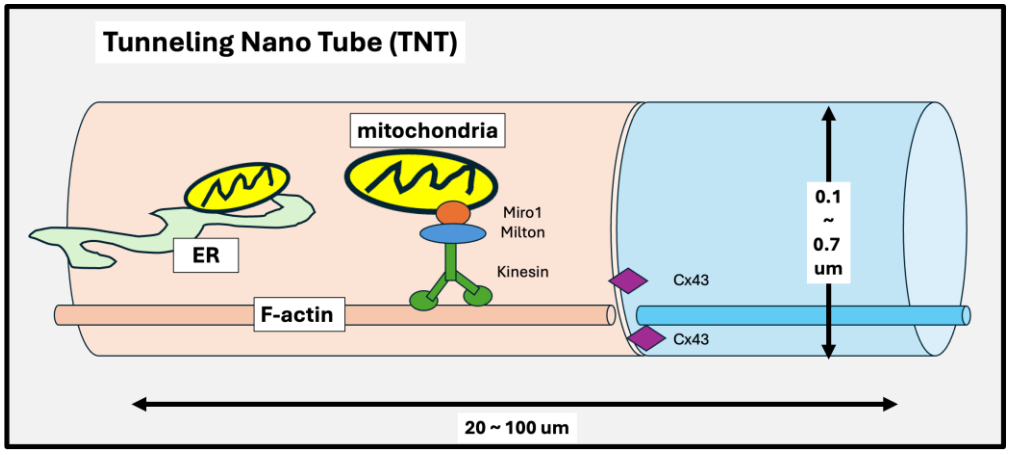

Figure 1: Tunneling nanotube (TNT) participants in the mitochondrial transfer. F-actin is the major building block that contributes to the highway where kinesin protein carries mitochondria and drives across the nanotube [2,12]. Key proteins such as Miro1 and Milton are associated strongly with mitochondrial transfer and are contributors to the process [5]. For example, Rho-GTPase Miro1 overexpression increases TNT mitochondria transfer from healthy to stressed cells [33]. It is thought that mitochondria tethers to the endoplasmic reticulum and is passed onto the kinesin for transport; therefore, ER can also be within these tubes, still tethered to mitochondria [4, 35]. Gap junction protein, Cx43 is found in edges of the open-ended TNT and facilitates formation [2,5,34]. The diameter of the tube is estimated at around under a micron, but the length is much larger in magnitude, reaching upwards of 100 microns [8,12].

Modes of Mitochondrial Mobility

1)Tunnel-mediated intercellular transfer

Tunneling nanotubes (TNTs) have gained recognition and attention in the past two decades since the seminal work by Rustom and colleagues [7]. Despite the relatively recent discovery, the structure seems to be an ancient feature of a eukaryotic cell, with an emerging hypothesis calling its presence predating the development of the brain [8]. TNT allows the process of horizontal mitochondrial transfer, which is now recognized as the most prevalent mode of intercellular sharing of mitochondria via cell-to-cell migration [2,3,9]. The tube can be long as 100 micron or more and can shuttle the mitochondrion at a speed of 50nm per second [8,10,11]. The life of the TNT is somewhat variable from minutes to hours and may be cell-dependent but is overall transient in nature [9-13]. The composition is mostly actin and cytosol surrounded by plasma membrane, although longer and thicker tubes may also be sustained by microtubules. The nanotube is a conduit for various cell components such as calcium, RNAs, proteins, pathogens, vesicles, and organelles. To this point, transfer of functional mitochondria from co-cultured cells prevents apoptosis in cells deficient in functional mitochondria in a TNT-dependent manner [10,13]. Emerging evidence increasingly make it clear that intercellular mitochondria transfer affects the recipient cells, impacting every physiological or pathological processes from homeostasis to tumorigenesis [5,7,11].

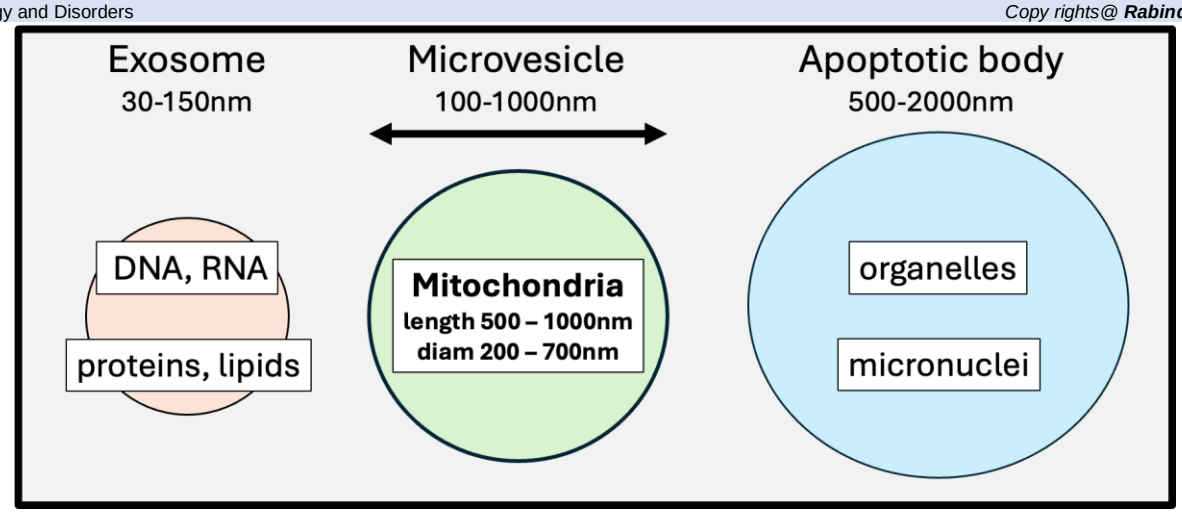

Figure 2: Extracellular vesicles in intercellular transfer. Microvesicles are between 100nm to 1000nm in size and have been shown to contain mitochondrion and other cellular organelles that are viably transferred from cell to cell [15-17,20]. Exosomes are generally under 150nm in diameter and can carry mitochondrial DNA (mtDNA) and other gene products and lipids [17,19]. Larger extracellular bodies resulting from apoptosis can generate vesicles ranging from 500nm to 2000nm, which can also contain larger organelles as well as mitochondria, but is thought more to be phagocytosed rather than transfer viable contents to recipients [16,17].

2) Microvesicle-mediated intercellular transfer

Similar to TNTs, microvesicles (MVs) aid in meeting the oxidative demands of recipient cells through the supplying of healthy mitochondria [14,15]. MVs are between 100nm to 1000nm in size and have been shown to contain mitochondrion and other cellular organelles that are transferred from cell to cell indirectly [16-19, Figure 2]. Much like TNT formation, exportation of MV-mitochondria seems to be driven by cellular stress events. Specifically, it utilizes the endosomal maturation pathways. For example, MV formation increases in number when cells encounter stress events that interrupt the endosomal maturation process, and furthermore, MV-mitochondria export may occur even without lysosomal degradation [20]. It is possible that TMTs and MVs may have overlapping signals and pathways that enhance or prioritize the mode of mitochondrial sharing depending on the cell type and instigating event [2,4, Figure 3].

Perhaps an ischemic/hypoxic event illustrates the power of MV-mitochondrial transfer best: In the brain, it is hypothesized that CD38 signaling through glial cells such as astrocytes mediate expression of cyclic ADP in mitochondrial membrane and promote extracellular release of mitochondria to proximal neurons [21]. Neurons receiving mitochondria survive better as a result, and interference of this process using Cd38 siRNA was consistent with worsened oxygen consumption in the brain, which implicated worsened ischemic damage from a stroke [21].

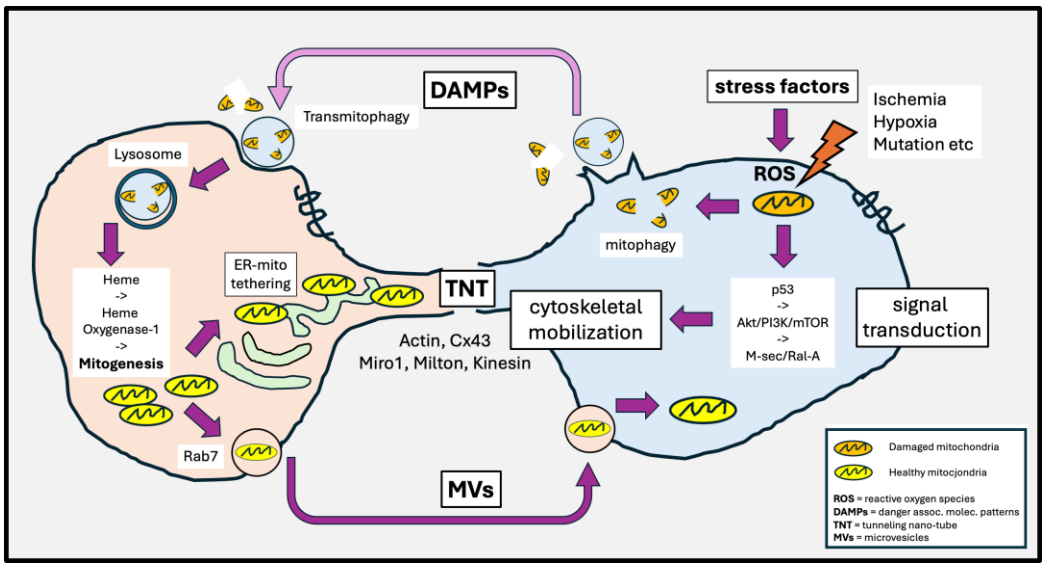

Figure 3: Tunneling nanotube (TNT) and micro vesicles (MV)-mediated mitochondrial transfer as means of sharing functional mitochondria. Stress factors such as ischemia and hypoxia lead to mitochondrial accumulation of reactive oxygen species [2-5]. Processes such as mitophagy lead to generation of signals in form of danger associated molecular patterns (DAMPs) that lead to mitogenesis [9,14,31]. Healthy intact mitochondria that traverse through tunneling nanotubes (TNTs) or sent in extracellular micro vesicles (MVs) can enter adjoining or distant cells to establish residency and contribute to respiratory needs of the cell [2-6].

Mitochondria and Metabolic Irregularities

Mitochondrial biology is increasingly recognized for key physiological undertakings in maintaining health, as dysfunction of mitochondria is indeed linked to many common human diseases, spanning: obesity, insulin resistance, metabolic syndrome, and cancer [22]. Although insulin resistance (IR) can be genetically associated with diseases such as myotonic dystrophy, ataxia-telangiectasia, and polycystic ovarian syndrome, IR for the most part is acquired, through aging, nutritional imbalance, and medications [23]. The American College of Endocrinology identifies risk factors of IR syndrome to include physiological changes such as inflammation, endothelial dysfunction, and elevated blood pressure [23,24].

Lifestyle and genetic makeup are also a recognized feature of metabolic dysfunction and IR risk, including being of non-white ethnicity, having sedentary lifestyle, and BMI over 25 kg/m2 [23]. In fact, the study of IR is complicated due to the many factors contributing simultaneously, ranging from micro-level factors such as adiposity and plasma triglyceride, to macro-level societal factors such as healthcare disparities and food/exercise access. Furthermore, it is becoming evident that some metabolic risk factors are salient in specific race and sex, while some are not. For example, recent investigation by Allister-Price et al. suggest insulin resistance in African American women is better predicted by HDL-cholesterol and plasma triglyceride, rather than adiposity [25]. Considering that adiposity is highly associated with insulin resistance in Caucasian women, biological differences merit closer scrutiny in understanding useful metabolic risk biomarkers. Considering the central role mitochondria has in metabolism, genetic differences in mitochondrial function are likely a fruitful venture in characterizing metabolic diseases and therapeutics.

Indeed, pathologic mutations in mitochondria have strong associations with wide ranging disorders spanning deafness to blindness, suggesting generalizable alteration in mitochondrial protein synthesis having far reaching systemwide consequences [22,26]. The oft mutated mitochondrial gene MT-TL1 codes for tRNA, and the most common mitochondrial disease is caused by the pathogenic m.3243 A>G MT-TL1 gene mutation leading to peripheral neuropathy, diabetic retinopathy, and nephropathy, known as maternally inherited diabetes and deafness, or MIDD (26,27). MT-TL1 mutation is in fact associated with a broad array of symptoms including cardiac and gastrointestinal, therefore pointing to the wide and dire consequences of compromised mitochondrial function [25,26].

In fact, disparities in the proclivity of African Americans to develop obesity, insulin resistance, and hypertension may in part be due to differences in the mitochondrial bioenergetics resulting in lower threshold to oxidative stress [27]. Outside of mitochondrial difference, it has been hypothesized that African American metabolism prefers glycolysis under fasted and fed state, whilst Caucasian metabolism prefer fatty acid oxidation under fasted, and reverts to glycolysis under fed state. Mitochondrial tRNA and 16S rRNA genes seem to have some role in blood pressure as well, as two separate older adult cohorts of African and European origin had higher baseline systolic and mean arterial pressure associated with the mitochondrial point mutation [28].

Potential Use of Mitochondrial Transfer for Metabolic Diseases

1)Mito-genesis enhancers

With emerging evidence for biodynamic role of mitochondria between healthy and damaged cells, therapeutic approaches on restoring mitochondrial function merits evermore focused investigation. For example, regulation of mitochondrial biogenesis has a far more reaching consequences considering the healthy mitochondria having not only positive impact on its host cell, but also to its non-adjacent neighboring cells. Some emerging drugs that target the mitochondrial biogenesis pathway has been explored, especially targeting the expression of PPAR system through use of bezafibrate and pioglitazone [29, 30]. In addition, Sirtuins and their upstream activators such as resveratrol and acipimox have also been explored and tested in trials but is less clear in effect. Therapeutic approaches that affect upstream event of mitochondrial biogenesis may have modulatory effect on the formation of TNTs and EVs.

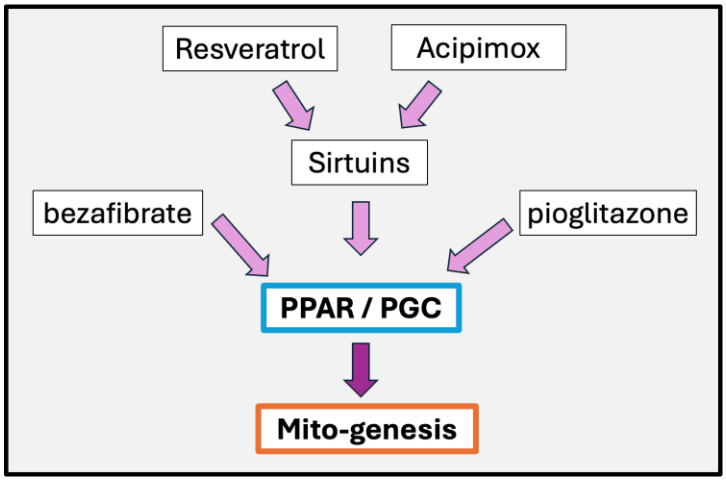

Figure 4: Peroxisome Proliferator Associated Receptor (PPAR) and Peroxisome proliferator-activated receptor-gamma coactivator (PGC)-mediated activators associated with mitochondrial biogenesis. Some emerging drugs that target the mitochondrial biogenesis pathway has been explored, especially targeting the expression of PPAR system through various means, such as by using fibrates and thiazolidinediones [29,30]. In addition, Sirtuins and its upstream activators such as resveratrol and acipimox have also been explored and are being tested in trials [30]. Therapeutic approaches targeting upstream of mitochondrial biogenesis may impact the downstream mitochondrial transfer events and the formation of TNTs and MVs [2-4, 31].

2)Mito-transplant strategies

Artificial uptake of isolated healthy mitochondria by cultured cells in vitro can be achieved through various approaches, such as the use of microinjection, co-incubation, and centrifugation, in addition to making the naked mitochondria physically more amenable to uptake by encapsulating the cell membrane with peptides and magnetic beads [3,4]. To this point, recent review by Chen and Chen highlights the challenges and promises of transplantation strategies that are anticipated in providing therapeutic avenues in metabolic disorders such as obesity, diabetes, and non-alcoholic fatty liver disease [3]. Practical questions to consider may center on the quality control of mitochondria and devising safe strategies to induce mitochondrial transfer from transplanted cells to targeted cells in the organ system.

In recent years, clinical trials have been performed to evaluate the usefulness of direct mitochondrial injection targeting the ischemic brain and heart [31]. One question concerning mitochondrial transfer may be whether healthy exogenous mitochondria reconstitute the cells beyond the injected area over time. To our knowledge, no clinical trials have been tried to apply the direct injection of mitochondrial products into humans specifically for metabolic disorders.

Conclusion

Mitochondria transfer to stressed and metabolically overburdened cells may restore homeostasis, quality control and wound healing. Although broadly speaking ROS is a driver of intercellular sharing of organelles, it is not clearly understood which specific signal is responsible for orchestrating the mitochondrial transfer [2-4]. The signal is most likely organ-specific, and likely to be initiated by a wide variety of physiological and pathological instigators. For example, in the brain, in vitro work shows that melatonin is sufficient to initiate mitochondrial transfer by TNT mechanism [32]. Much mechanistic understanding remains to unpack the black box encasing the details of intercellular mitochondria transfer. Altogether, the strong ties between mitochondria and metabolism make this venture an enticing one to find utility in treating metabolic dysfunction.

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