Review

Mitochondrial transfer and implications for muscle function in idiopathic inflammatory myopathies

J.A. Gonzalez Chapa[1], M. Barguil Macêdo[1], E. Naddaf[2], L.A. Saketkoo[3], C. Lood[1], for the International Myositis Health and Research Collaborative Alliance (MIHRA) Mitochondria Scientific Working Group

[1]*Division of Rheumatology, University of Washington, Seattle, WA;*
[2]*Department of Neurology, Mayo Clinic, Rochester, MN;*
[3]*Department of Medicine, Louisiana State University and Tulane University Schools of Medicine, New Orleans, LA, USA.*

*Jorge Amado Gonzalez Chapa, MD, PhD**
*Marina Barguil Macêdo, MD, MSc**
Elie Naddaf, MD
Lesley Ann Saketkoo, MD, MPH
Christian Lood, PhD

**Contributed equally to this paper.*

Please address correspondence to:
Christian Lood
Division of Rheumatology, Room E-545, University of Washington, 750 Republican Street, Seattle, WA 98109, USA.
E-mail: loodc@uw.edu

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ABSTRACT

Impairment in cellular bioenergetics as either the cause, consequence, or major contributor of tissue damage has drawn increasing scientific curiosity across aging and chronic health conditions, with mitochondrial dysfunction emerging as a central mechanism in the pathogenesis of a variety of inflammatory and degenerative disorders. Beyond bioenergetics, mitochondria play critical regulatory roles in programmed cell death of dysfunctional/defective cells as well as in metabolite synthesis and metabolic signalling. Further, extra-cellular exposure to fragmentation of injured mitochondria is associated with incitement of systemic and organ-based inflammation. Thus, mitochondrial function has recently drawn intense, spectral scientific interest as an integral component across maladies.

In muscle, mitochondrial dysfunction is clinically associated with atrophy and diminished endurance. Direct myohistopathological evidence characterising loss of mitochondrial integrity as a hallmark of muscle compromise was first noticed in inclusion body myositis (IBM). This was followed by the discovery of multiple deletions in mitochondrial DNA in sarcopenia, IBM, and other inflammatory myopathies, like dermatomyositis. Though fraught with bioethical considerations, the transplant technology of mitochondrial transfer is swiftly gaining prominence in cellular biology and muscle physiology to remediate mitochondrial diminution and dysfunction. Assembling seminal works and recent developments, this review ventures into the rapidly evolving landscape of mitochondrial transfer, focusing on its implications on muscle function, and offers an integrated perspective on the potential roles of mitochondrial transfer and its implications for preserving and restoring muscle health. Presented here is a consolidated viewpoint on mitochondrial transfer in idiopathic inflammatory myopathies.

Introduction

The term "mitochondria" was first introduced in 1898, in Greek *mito* meaning '*thread-like*', and *khondrion* meaning '*grain or granule*', possibly referring to each mitochondrion's plicated inner matrix, where much of its activity occurs (1). Mitochondria, passed down through generational matrilinear inheritance (2), harbour their own genome, distinct from that of the deoxynucleic acid (DNA) in the host's nuclei.

Tissue regeneration and repair, as well as the vital and regulatory function of each organ system, require tremendous energy from their constituent cells (3, 4). Depending on their resident tissue, this energetic heft is supplied by hundreds to thousands of mitochondria, except erythrocytes, which usually carry none (5). For this reason, mitochondria had been referred to as 'the powerhouse of cells' (6, 7) or 'bioblasts' (8), a term used historically by early cell biologists. Outside their primary function in bioenergetics, mitochondria are postulated to serve essential modulatory roles in the systematic eradication of aberrant or impaired cells, particularly in the context of apoptotic regulation (9). Additionally, they are implicated in the synthesis of metabolites and play a pivotal role in intra- and extra-cellular metabolic signalling (10, 11). Moreover, the external cellular milieu's exposure to fragmented portions of damaged mitochondria correlates with the

elicitation of inflammatory responses and injury (12).

Cellular bioenergetic dysregulation, particularly mitochondrial dysfunction, is increasingly acknowledged in scholarly research as a key factor in the aetiopathogenesis of various inflammatory and degenerative diseases (13, 14).

Mitochondrial culpability has been implicated across clinical syndromes and maladies such as chronic fatigue (15), chronic kidney disease (16), metabolic syndromes such as diabetes and obesity (17, 18), and oncogenesis (19). Particularly in muscle, mitochondrial diminution and dysfunction are demonstratively associated with sarcopenia (20), diminished muscle endurance (21, 22), muscle atrophy (23), and cardiac dysfunction (24), among many other syndromes (25). Idiopathic inflammatory myopathies (IIMs) are a spectrum of heterogeneous diseases that are often multi-system in nature, involving skin, joints, vascular, cardiac, gastrointestinal, pulmonary, and other extra-muscular manifestations. Though mitochondrial dysfunction has been implicated in the health of these organs, this review will focus on mitochondrial dysfunction in muscle.

Mitochondria comprise approximately 6% of muscle fibre volume (26-28), further corroborating the substantial role that mitochondrial impairment plays in muscle conditions like idiopathic inflammatory myopathies (IIM) (29). Direct evidence of loss of mitochondrial integrity as a hallmark of muscle compromise was first noticed in inclusion body myositis (IBM), in which cytochrome c oxidase (COX)-deficient fibres are commonly seen on muscle histopathology (30). This finding was followed by the discovery of multiple deletions in mitochondrial DNA (mtDNA), with an increase in heteroplasmy when compared to healthy individuals (31). Heteroplasmy refers to the presence of both normal and mutated mtDNA within a cell (32), for which proportionality can vary among individuals, and even among different tissues within the same individual (32-34). Clinically, the degree of heteroplasmy favouring mutated mtDNA often correlates with disease severity and symptomatology (33, 35). Perturbations in mtDNA are not exclusive to IBM, though, being also reported in dermatomyositis (DM) (36), and sarcopenia (37). A mismatch between increased energy demand, in face of stress conditions, and the failure of mitochondria to supply this demand could represent one of the final steps in all IIM, which eventually leads to muscle loss (29).

Mitochondrial transfer, a novel and promising approach in cellular and muscle biology, offers a solution to mitochondrial dysfunction and depletion. This review consolidates literature on the role of mitotherapy in IIM, focusing on its effects on muscle function and health.

The importance of mitochondria in cellular physiology and energy metabolism

Mitochondria, central to cellular energy dynamics, calcium homeostasis, and apoptosis, play a fundamental role in muscle tissues, where they cater to high-energy demands and foster muscle health (38, 39). Recent years have witnessed significant advances in our understanding of mitochondrial functions, chiefly the phenomenon of mitochondrial transfer, a process through which mitochondria are relocated between cells, indicating a new dimension in intercellular communication and cooperation for modulating inflammatory response (40-42). With its implications in muscle physiology, this transfer process hints at potential transformative approaches to muscle regeneration and repair, thereby inciting substantial research efforts aimed at delineating the pathways that facilitate these transfers and understanding their therapeutic ramifications (43, 44).

Mitochondria are the site of aerobic respiration, a crucial metabolic pathway that manufactures adenosine triphosphate, the cellular energy currency, via oxidative phosphorylation and, consequentially, mitochondria are also a main generator of reactive oxygen species (ROS) (45, 46). ROS are essential for signalling pathways and maintaining cellular balance; however, when cells are under stress, there is a notable increase in ROS levels (47). Given their reactivity, ROS can alter proteins, lipids, and other oxygen species, resulting in a state commonly referred to as oxidative stress (47), leading to mutations in mtDNA, impairing the mitochondrial respiratory chain, modifying membrane permeability, and affecting Ca^{2+} homeostasis (39, 48). Consequently, maintaining ROS levels within physiological limits is crucial for the optimal functioning of various cell types throughout the organism. Therefore, mitochondria serve as central regulators in the delicate balance between cellular survival and death, overseeing processes fundamental to the vitality and functionality of eukaryotic cells (49).

Clinical relevance of mitochondrial dysfunction, with emphasis on muscle function

Mitochondrial dysfunction stands as a pivotal culprit behind a spectrum of diseases and health conditions, encompassing neurodegenerative disorders (50), cardiovascular diseases (51), diabetes (17), chronic kidney disease (52), and other progressive chronic health conditions (40), acting as a silent orchestrator of cellular distress. The aging process is marked by a declining mitochondrial function, and a parallel surge in ROS production (53) associated with a lower mtDNA copy number, and increased heteroplasmy levels, especially evident in persons above 70 years old (33).

In the context of muscular physiology, the repercussions of mitochondrial dysfunction are clinically profound and multifaceted, culminating in muscle atrophy and impaired endurance (54). Of note, differential mitochondrial distribution between muscle fibres points towards the fibres' distinct metabolic needs and functional attributes, which consequently renders them either vulnerable or resilient to mitochondrial perturbations. Type I (slow-twitch) fibres, optimised for endurance and sustained activities, are generously endowed with mitochondria, underscoring their aerobic proficiency. In contrast, type II (fast-twitch) fibres, tailored for quick and explosive actions, have a comparatively diminished mitochondrial content (55).

In chronic presentations of polymyositis and DM, attenuated muscular endurance may be attributable to an insufficiency of oxidative, type I myofibres (56). Notably, an overrepresentation of type II myofibres is discerned in IIM, more so in longstanding cases, but remains less pronounced in untreated, newly onset patients (57). Pertinently, in conditions like DM, a multifarious effect on myofibre taxonomy is evident, elucidating the disparate histopathological shifts across these myopathies in which both Type I and II myofibres display perifascicular atrophy (58). Similarly, sarcopenia, an age-associated condition, demonstrates a fibre-type-specific reduction in muscle size, with a notable 10-40% diminution in Type II fibres, while Type I fibres remain largely unaltered (59). Cellular senescence reveals the potential for aging cells to rejuvenate through mitochondrial acquisition, offering prospects for strategies targeting age-associated disorders (60).

Evolutionary perspective of mitochondrial transfer

The concept of mitochondria being transferred between cells has its origins in observations of mitochondrial dynamics, including mitochondrial fusion and fission (61). Further, stem cells were observed to donate mitochondria to cells that had malfunctioning mitochondria (62), the same also applying to bone marrow-derived stromal cells, which could rescue neighbouring cells with mitochondrial dysfunction (63). In yet another facet, cancer cells could acquire mitochondria from surrounding stromal cells, possibly to enhance their metabolic capabilities (64). The exact mechanisms, significance, and implications of this transfer, especially in different disease contexts, are still areas of active research.

The primary hypothesis suggests that this capability arose as a survival mechanism, enabling cells to maintain cellular homeostasis and endure stressful conditions such as hypoxia (65, 66) and inflammation (67). By replacing damaged or malfunctioning mitochondria, cells can preserve their energy production, thereby enhancing the overall health and viability of a tissue or organism (63). This cellular exchange could be conceptualised as a manifestation of altruism at the microscopic level, serving to augment the collective vitality and resilience of a tissue or organism. Additionally, this mechanism may have its evolutionary roots in the symbiotic relationship formed between early eukaryotic cells and the progenitors of mitochondria. According to the endosymbiotic theory, mitochondria originated from a type of bacteria that was engulfed by eukaryotic cells, establishing a mutually beneficial relationship (68). This initial interaction may have driven the evolution of mechanisms for mitochondrial transfer between cells, enabling organelle sharing to enhance cellular survival and adaptability in varying environments.

Advantages apart, there is an inherent risk of propagating mitochondrial diseases via the transfer of dysfunctional organelles (69), and this process might also inadvertently sustain the life of cells destined for elimination, thereby potentially nurturing the persistence of cancer cells (70).

Mitochondrial transfer: basic biology, mechanisms, factors and consequences

Navigating through the intricate labyrinth of cellular dynamics, we encounter a variety of factors that serve as catalysts for mitochondrial transfer (63, 71). Scientists have stumbled upon an intriguing survival strategy that cells employ when faced with adversity. In conditions where oxygen becomes scarce, cells do not merely resign to their fate. Instead, they exhibit an almost neighbourly act of sharing essential organelles – their mitochondria (66, 71-73). The orchestration of mitochondrial transfer is also speculated to be influenced by inflammatory signals, with certain cytokines, inflammatory mediators, and cells such as macrophages (74) as key regulators of this process. Furthermore, metabolic fluxes and energetic demands of cells might be the guiding forces behind mitochondrial transfer (75, 76). Intriguingly, while calcium is central to cellular metabolism and intimately linked with mitochondria (77), its role in instigating mitochondrial transfers remains an enigma.

Many are the pathways by which mitochondria are delivered from one cell to another, but the one mechanism that stands as having greater biological relevance is by the formation of tunneling nanotubes (TNTs). Their composition, the regulatory elements dictating their formation, and the selectivity of the transfer process remains largely unknown (78, 79). Additionally, vesicular transport mechanisms such as microvesicles and exosomes (80-82), and direct contact and gap junction channels mediated by connexin 43, where mitochondria might traverse through direct cytoplasmic connections or through channels established between cells, may also serve as conduits (83, 84). More speculative mechanisms include cytoplasmic fusion (85), which can create a “kiss-and-run” (86) phenomenon involving direct and transient cellular contacts. Lastly, mitochondria, or their components, devoid of carriers, possess the capability to be expelled and subsequently internalised. This translocation occurs through the intricate mechanisms of exocytosis and endocytosis, whereby cellular materials are selectively exported and imported, facilitating the exchange of mitochondrial components without the necessity of a carrier (43).

Mitochondrial transfer technology

Mitochondrial transfer is a technique that refers to the delivery of either intact mitochondria, or mitochondrial components, such as RNA, DNA, or proteins, from one cell to another (40, 87). Preliminary studies have highlighted the significant potential of mitochondrial transfer for the regeneration of damaged tissues and alleviation of symptoms in various diseases and tissues, including the heart, skeletal muscle, and even immune cells (41, 44, 88). Mitochondrial transfer reduces ROS emissions and improves cellular respiration, suggesting that mitochondrial trafficking and bioenergetic reprogramming could be effective in maintaining tissue homeostasis and treating various diseases (89).

Various strategies have been employed in the pursuit of artificial mitochondrial transfer (90), from the seminal coincubation method used in 1982 (91) to more advanced techniques such as microinjection (92, 93) and photothermal nanoblade (94). Additional methods leverage the TOM22 receptor complex situated on the mitochondrial membrane as a tethering point to ease the internalisation of transferred mitochondria, illustrated by the Pep-1 (95, 96) and Magnetomitotransfer approaches which uses a magnet-mediated methodology, in which mitochondria, conjugated to paramagnetic beads, are translocated into target host cells (97). The MitoCeption technique, amalgamating thermal shock with centrifugation, serves to amplify the assimilation of mitochondria (98).

Whichever technique is adopted, one may keep in mind that mitochondrial transfer is, though on a microscopic level, a type of transplantation. Foreign mtDNA transfer into cells presents critical ethical and safety challenges, such as the risk of mitochondrial rejection and unforeseen genetic consequences, highlighting the vital importance of comprehensive, nuanced scientific research in the field of mitochondrial transfer (99).

Idiopathic inflammatory myopathies: time to shift the focus from the "inflammation" to the "myopathy" on their definition

Skeletal muscle functionality is critically dependent on mitochondrial energy production, as evidenced by muscle dysfunction being a primary symptom in mitochondrial pathologies (100). As such, the intricacies of mitochondrial dysregulation in primary mitochondrial myopathies have been much investigated, to achieve a better understanding of the pathogenesis behind this complex group of rare genetic diseases (101). On the other hand, mitochondria have been largely neglected by those exploring the field of idiopathic inflammatory myopathies (IIM). Loss of mitochondrial homeostasis as a core characteristic of IIM has been acknowledged just in the past two decades (102).

Treatment for IIM revolves essentially around immunosuppression, which usually leads to an initial good clinical response in up to three-fourths of patients (103, 104). Except for IBM (105), IIM are characteristically sensitive to immunosuppression or immunomodulatory therapy, to the point that, in dealing with non-responders, it becomes imperative to revise the primary diagnosis (106). Recurrence is frequent with glucocorticoid tapering, and a significant study indicates that prolonged disease duration (>5 years) correlates with increased dependence on walking devices, highlighting long-term disability (107). As the disease progresses, the final pathway for all IIM is, in varying degrees, muscle atrophy and fat replacement. Indeed, between 1 in 7 to 1 in 4 patients develop measurable muscle atrophy on imaging studies, and, on average, half of them show signs of fat replacement (108). Thus, even though quenching of the initial inflammatory process remains the focus of early disease treatment, innovative therapies directed against muscle fibre loss would be of great benefit by shifting the focus from the immune system to the impaired tissue – the muscle – and to the impaired organelle – the mitochondria.

The diverse and dynamic ways by which disruption of mitochondrial homeostasis is linked to the etiopathogenesis of IIM is outside the scope of this review, having been extensively outlined elsewhere (29). Within IIM, histopathological evidence of mitochondrial dysfunction is most significant and most commonly encountered in IBM (109-111). Indeed, deficiency of cytochrome c oxidase (COX) staining on histochemistry is a hallmark of IBM, though not pathognomonic (111). COX is one of the main enzymes responsible for the respiratory chain in the mitochondria christae, and three of its thirteen subunits are encoded by mitochondrial (as opposed to nucleic) DNA (112). It is conceivable that COX-deficient fibres may not exclusively function as an indicator of muscle compromise in IBM, but rather, there exists the plausible hypothesis that they could represent a prominent mechanistic pathway underlying the onset of muscle atrophy in this disorder.

In primary mitochondrial myopathies, the first described stop-codon mutation on mtDNA, inducing a decrease of over 90% of COX activity in muscle fibres, was reported in a patient with marked exercise intolerance and proximal myopathy (113). After that pivotal demonstration of inherited mutated mtDNA causing muscle dysfunction, interest has expanded to somatic mutations and polymorphisms of mtDNA in acquired myopathies. An enlarged number of deletions and duplications, increasing the level of heteroplasmy by 10 times or more than that of controls, has been described in muscle samples from IBM patients, in addition to a decrease of mtDNA copy number of 42% to that of controls (31). While one could argue that those findings merely represent cumulative damage of long-standing illness in an aged population, as the majority of the patients in that cohort had 3 or more years of disease duration, such an argument was put into check by another study from the same group of researchers. More recently, they evidenced a depletion of mtDNA copy number also in DM patients, most of them with a disease duration of only about 3 months (36). In face of the growing evidence of mtDNA perturbation as a prominent feature of IIM from the very beginning, and not only as a late manifestation, techniques, and therapies to lower the level of mtDNA heteroplasmy as a means to restore muscle homeostasis, have gained mounting interest.

Cellular enhancement through mitochondrial activity

Mitochondrial replacement therapy is promising for correcting the heightened heteroplasmy in diseased muscle cells by introducing healthy mitochondria, thus increasing the proportion of wild-type over-mutated mtDNA copies per cell (114). While mitochondria can be easily manipulated in *in vitro* models, the feasibility of successful transfer in *in vivo* models is more challenging, but even so attainable (40). The transfer of mitochondria between cells can occur in several ways, but the most relevant

one seems to be through TNTs, temporary connections made by a protruding cell membrane (70).

A study found that exposing astrocytes to hydrogen peroxide, a stressor, induces TNT formation. Stressed cells extend these filaments to unstressed cells, receiving healthy organelles, which then enhance their resistance to damage (115). In another study, exposure to pro-inflammatory cytokine tumor necrosis factor-alpha engaged TNT formation by epithelial cells, facilitating mitochondria donation from co-cultured mesenchymal stem cells (116). Contrary to the notion of altruistic intercellular support, Phinney et al.'s study suggests that mesenchymal stem cells expel depolarised mitochondria to boost their survival, with the recipient cells' bioenergetic improvement being an incidental benefit (80).

Restoring muscle function by reverting mitochondria dysfunction: what experimental models teach us

To replicate the observed intercellular mitochondrial movement *in vitro* and explore its implications, two conditions are essential: traceability of the mitochondria and measurability of their impact on the recipient cell. The former can be accomplished by tagging the mitochondria, for example, with a fluorescent protein (117), and the latter by several techniques, but one in particular deserves mention: the creation of cybrids (118).

Elimination of mtDNA from a cell can be achievable by adding ethidium bromide to the culture medium, which does not harm nucleic DNA, as it is protected against its deleterious effects by the presence of histones, which are lacking, however, in mtDNA (119). Cells depleted of mtDNA are named ϱ0 (rho) cells, and exogenous mtDNA can be implanted into them, generating the so-called cytoplasmic hybrids, or cybrids (120). This model permits, for instance, to unravel the function of a specific mitochondrial gene: as neatly demonstrated by Kagawa *et al.*, when wild-type mtDNA was inserted into fibroblasts collected from the skin of a patient suffering from MELAS (acronym from mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes), COX activity, which is defective in this syndrome, was promptly restored (121).

To fully understand mitochondrial transfer's biological significance, more complex models are needed. Experiments, mainly using rodents with tissue injuries, assess the effects of mitochondrial administration. The mitochondria originate from either the same animal or different cell lines, and their delivery varies, including direct injection into the injured tissue or intravenous administration (122). Those *in vivo* models, beyond merely reinforcing that an exogenous supply of mitochondria can mitigate organ damage in several conditions, also allow us to derive important conclusions about technical limitations, that would necessarily be rectified if we intend to advance in the field by transposing those findings into clinical practice (123). Proper storage of harvested mitochondria is vital for therapeutic success, given their susceptibility to cold injury; preservation by freezing can notably reduce their functionality (124). Bearing in mind those caveats, mitochondrial transfer as a modality of treatment for muscle impairment in IIM is not far from becoming a reality: in fact, a Korean clinical trial is currently actively enrolling DM patients to receive allogeneic mitochondria transplantation (Clinical Trials ID NCT04976140). The study intends to evaluate the effect of escalating doses of umbilical cord-derived mitochondria, administered intravenously, to the improvement of the standardised metric IMACS-TIS, 12 weeks after the injection. Results are eagerly awaited (125).

Exercising mitochondrial intervention in practice: exercise as a modality of mitotherapy

Although evidence on the applicability and usefulness of mitochondrial transfer in human disorders continues to evolve, practitioners can currently and confidently, prescribe a well-validated, and universally approved, modality of mitotherapy: exercise. The benefits of exercise to improve health-related quality of life (HRQoL) in patients with IIM are ubiquitously accepted and further emphasised by increasing evidence of endurance-based strength training improving mitochondrial enzyme activity leading to improved levels of inflammation, aerobic capacity as well as muscle endurance and strength in IIM patients (126, 127). The literature reiteratively asserts exercise as a disease-modifying intervention, irrevocably demoting the obsolete view of rest as a means of "sparing" inflamed muscle (128). The positive effects of keeping physically active by regular exercise cannot be overemphasised. Multiple are the mechanisms by which standardised exercise training improves muscle performance, and it is superfluous to mention that improvements are not restricted to the muscle, but a positive impact on psychological well-being and HRQoL are also noticed (129). Aerobic conditioning was demonstrated to increase mitochondrial enzymatic activity by 20%, and mitochondrial volume by 50%, in biopsies of the vastus lateralis muscle after a 14-week training, as reported by a prospective study that enrolled patients with mitochondrial myopathies (130). On a molecular level, exercise causes the remodeling of mitochondrial christae, stabilises mitochondrial respiratory complexes, and ultimately heightens the efficiency of electron flux (131). In effect, it has even been proposed that exercise can be a physiological way of propelling mitochondrial exchange: transfer of mitochondria from satellite cells to myocytes has been deemed one of the leading mechanisms through which resistance training enhances muscle function (132). Given all the summarised advantages to mitochondria and, consequently, to muscle performance, it is undeniable that exercise should be regarded as an essential part of the multimodal treatment of patients with IIM.

Future directions

Mitochondrial transfer is at a pivotal moment, poised to redefine regenerative medicine by establishing a direct connection between mitochondrial intervention and cellular repair. The

proposed mechanism involves an intercellular exchange of mitochondria, which could revitalise the function of mitochondria and tissue in IIM-affected muscle cells. *In vivo* mitochondrial transplantation, utilising either direct tissue injection or circulatory system infusion proximal to the target site has demonstrated therapeutic potential in ameliorating myocardial damage (105, 133). A crucial consideration in this approach is the source of the mitochondria, whether autologous, minimising the risk of immune rejection while keeping the protection of the recipient organ, as shown with the heart during ischaemic reperfusion injuries (134), or allogeneic, which might necessitate additional compatibility evaluations. IIMs muscle fibres, often characterised by mitochondrial dysfunction, play a significant role in muscle weakness and degeneration, and introducing healthy mitochondria could potentially boost their energy production and overall function. However, advancing mitochondrial transfer in IIMs necessitates mechanistic studies on donor cell selection, transfer mechanisms, regulatory processes, and immune responses in allogeneic transfers, along with refining techniques to ensure transferred mitochondria's long-term functionality.

Conclusion

The study of mitochondrial transfer is rapidly expanding, creating a rich foundation for new research and potentially revolutionary therapies, especially for conditions like myopathies. By exploring its mechanisms, triggers, and outcomes in greater detail, we can open doors to innovative diagnostic and therapeutic approaches, revealing previously undiscovered complexities in how cells communicate and cooperate. This emerging field has the potential to significantly advance our knowledge and application of cellular interaction, representing a significant development in biomedical science.

Take home messages

- Mitochondrial dysfunction plays an essential role in the aetiopathogenesis of IIM, albeit its importance has emerged only recently (29).
- Mitochondrial transfer between cells occurs as a physiological mechanism to supply energy in an increased demand state and seems to benefit both the donator and the recipient cell (43, 70).
- *In vitro* (ϱ0 cells and cybrids) and *in vivo* (exogenous mitochondrial transplantation) experimental models have propitiated advances in our knowledge about the role of mitochondria in disease modification and suggested the feasibility of mitochondrial transfer as a treatment modality for several conditions, including IIM (125).
- While we wait for clinical data to support the applicability of mitochondrial transfer in altering IIM disease course, one cannot overemphasise that physical exercise is, actually, a modality of mitotherapy, which could and should be prescribed to all patients suffering from IIM (128, 129).

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