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REVIEW ARTICLE

Mitochondria-based medicine

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Abstract

At the balance between human health and disease (from the very first moments to the end of life), the mitochondrion is central players because of its metabolic role in adenosine triphosphate synthesis, cell signaling, immune response, and other processes of clinical interest. On the other hand, impairments at the optimal mitochondria function have important consequences in complex diseases, such as heart disease, diabetes, and cancer, among others. These mitochondrial impairments can occur at any age damaging multiple body systems, which have prompted the mitochondrial medicine development. Since mitochondrial diseases have great variability in their clinical manifestations, early studies were centered on mitochondriopathies, however nowadays, this focus has broadened to understand and encompass the mitochondrial role of in diseases development of both pediatric and adult age. The mitochondria potential to improve diagnostic, prognostic, and treatment response strategies has been revealed by experimental approaches using proteomics, genomics, and metabolomics to identify clinical biomarkers showing disease development. Thus, the perspective of mitochondria-based medicine recognizes the importance of generating scientific evidence related to mitochondria and their role in pathological conditions from a comprehensive approach.

Keywords: *Mitochondria. Mitochondrial diseases. Chronic non-communicable diseases. Metabolic diseases.*

Medicina basada en mitocondrias

Resumen

En el equilibrio entre la salud y la enfermedad de un individuo (desde los primeros instantes de su vida y durante el resto de ella), la mitocondria tiene un papel central en el correcto funcionamiento del metabolismo. Además, su papel es primordial en la síntesis de ATP, en la señalización celular, la respuesta inmune, entre otros procesos de interés clínico. Por otro lado, las afecciones al funcionamiento óptimo de la mitocondria tienen consecuencias importantes en las enfermedades complejas, tal es el caso de las enfermedades cardíacas, la diabetes y el cáncer, entre otras. Estas afecciones en la función mitocondrial pueden ocurrir a cualquier edad y dañar a múltiples sistemas del cuerpo lo que ha impulsado el desarrollo de la medicina mitocondrial, pues las enfermedades mitocondriales pueden presentar una gran variabilidad en sus manifestaciones clínicas. Inicialmente, el estudio se enfocó en las mitocondriopatías, actualmente su enfoque se ha ampliado para

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comprender y abarcar el papel de la mitocondria en el desarrollo de enfermedades, tanto de la edad pediátrica como de la edad adulta. El potencial de la mitocondria para mejorar las estrategias de diagnóstico, pronóstico y respuesta al tratamiento ha sido revelado por abordajes experimentales que emplean a la proteómica, la genómica y la metabolómica, para identificar biomarcadores con utilidad clínica que muestran el desarrollo de enfermedades. Por lo que la perspectiva de la medicina basada en mitocondrias reconoce la importancia de la generación de la evidencia científica relacionada con las mitocondrias y su papel en condiciones patológicas desde un enfoque integral.

Palabras clave: *Mitocondria. Enfermedades mitocondriales. Enfermedades crónicas no transmisibles. Enfermedades metabólicas.*

Introduction

The mitochondrion is the cellular organelle that regulates metabolism, cell signaling, and immune response; therefore, it requires coordination with other organelles and cellular niches to maintain cellular homeostasis. Disease disrupts this homeostasis or balance, and mitochondria register these changes, defining useful elements in recognizing and managing different diseases[1,2]. This relationship directly impacts medicine, as understanding the mitochondria-health-disease axis could improve decision-making and generate solutions in the context of mitochondria-based medicine.

Mitochondria possesses their own genome (mitochondrial DNA [mtDNA]); in humans, it contains 37 genes, 13 of which encode proteins related to oxidative phosphorylation (OXPHOS, the adenosine triphosphate [ATP] synthesis process)[3]; however, it contains a significant diversity of proteins (approximately 2000), such that the majority are encoded and imported from the nucleus[4]. mtDNA can also vary: a cell contains between 100 and 10,000 copies[3], which can have subtle differences and form populations (heteroplasmy) that could influence the health/disease phenotype. Furthermore, mitochondria communicate with virtually all cellular structures both intrinsically and extrinsically, as they make use of various extracellular structures (nanotubes, vesicles, and bloodstream) that allow them to establish long-distance communication; thus, they have also become attractive tools for the design of novel therapies[5,6].

Mitochondrial medicine

Initially, mitochondrial medicine focused on mitochondriopathies (inherited metabolic disorders that affect ATP synthesis)[7]. These diseases primarily present in childhood, although they can also appear in adults; they lack well-defined diagnostic criteria and treatment protocols, their symptoms are nonspecific, and the molecular defect is difficult to pinpoint, thus requiring different methodological strategies to resolve these ambiguities[8].

Mitochondriopathies are frequently confused with other pathologies (neuropathies, movement disorders, or heart diseases)[9,10], which can delay their diagnosis. For example, in cardiac diseases (one of the most frequent pediatric problems), mitochondrial alterations can go unnoticed and be treated inappropriately; hypertrophic cardiomyopathy[11] and tachycardias[12] associated with mitochondrial disease represent 20-40% of cases and present significantly higher mortality (71%) compared to patients without mitochondrial alterations (26%)[11]. This reveals that mitochondrial alterations are of utmost importance because, although they appear rare, their consequences can be substantial.

One of the most effective traditional approaches for determining mitochondriopathies is through catalytic activity assays that allow the identification of functional defects. However, these require various resources and involve invasive procedures (biopsies). At present, some strategies improve the diagnosis of mitochondriopathies; the proteins FGF21 and GDF15 (two mitokines found circulating in the blood) reflect mitochondrial damage and identify disease carriers[13]. Meanwhile, omic platforms define molecules that could guide a more accurate diagnosis and provide better monitoring of these diseases[14,15]. The diagnosis of a mitochondriopathy requires understanding the defect at the genetic level; conventional molecular biology strategies such as Sanger sequencing and polymerase chain reaction have relative success (≈6%) in determining genetic defects, in contrast to massive genome/exome sequencing strategies that achieve close to 45-60%, positioning themselves as the best diagnostic strategy[15,16].

On the other hand, proteomic analysis of primary human skin fibroblast cultures from patients with mitochondriopathy allows the detailing of the molecular mechanisms at the protein level[17]. Through metabolomics,

easily accessible biomarkers (metabolites) have been proposed with potential clinical utility in the development and treatment response of these diseases. Implementing these approaches improves the diagnosis of mitochondriopathies; however, their widespread use still requires corresponding clinical validation.

Mitochondrial alterations beyond mitochondriopathies

Non-communicable chronic diseases (NCDs) are long-term conditions and are the leading cause of death worldwide (80%)[18]. In these conditions, mitochondrial alterations can be found from their onset[19] and impact different processes that can be used to identify, monitor, or treat these diseases (Table 1), as well as extend diagnostic options and develop better mitochondria-targeted treatments (Table 2)[19,20].

This includes pediatric patients, as their main health conditions (obesity, diabetes, infections, among others) are related to mitochondria; therefore, the mitochondrial approach is very important in developing diagnostic tests and effective treatments. Mitochondria-related biomolecules (nucleic acids, proteins, and metabolites) can define useful elements in the stratification and pathophysiology of these diseases[21,22]. For example, in intractable childhood epilepsy, there are various mitochondrial aspects[23], such as variations between copy number and mtDNA damage[24,25] that are involved.

The outer mitochondrial membrane contains transporter complexes that activate the immune system: the translocase of the outer membrane, the sorting and assembly machinery and import machinery, as well as proteins sensitive to Damage Associated Molecular Patterns[26], whose alteration could indicate preferential signaling pathways associated with NCDs. Proteomic analysis of brain tumors in children and adults shows relevant participation of mitochondrial proteins; in fact, for glioblastomas, there are proposals for molecular classification that include mitochondrial categories[21,22]. Furthermore, in breast cancer, mitochondrial cristae are altered[27], and their evaluation could improve diagnosis and clinical monitoring, as their integrity and size are associated with the degree or advancement of malignancy[28]; in contrast, in gastric cancer, some mitochondrial proteins involved in energy metabolism (OXPHOS, TCA), mitochondrial dynamics (fusion/fission), and mitophagy[29] could function as early markers of the disease.

In cancer, energy metabolism (ATP synthesis) shifts in favor of anerobic glycolysis (Warburg effect) outside the mitochondria[30,31], such that mitochondria redirect their functions (Fig. 1)[30,32]. Based on this change, a bioenergetic signature was established to categorize prognosis in various types of cancer[33]. Furthermore, analysis of the mitochondrial proteome can distinguish different stages of cancer, with specific molecular events additional to this change in energy metabolism[34].

The distribution of mitochondria in the cell fluctuates and is found in different configurations, from bacteria-like units to tubular conglomerates extending and forming contact with other organelles[35]. Mitochondrial dynamics (fusion/fission processes) change notably in different pathologies, making their monitoring relevant in distinguishing health/disease. The mitochondrial arrangement reflects the metabolic-functional state and cellular health. A mitochondrial network increases oxidative capacity and is related to good health, while fragmentation into small units could indicate stress or the repair/degradation of damaged elements[35].

Mitochondrial dynamics is a quality control mechanism that requires specific proteins; some, like dynamin-like protein and dynamin-related protein, are related to processes involved in multiple pathologies[36]. Mitochondria continuously fluctuate in number, function, and form in response to inter- and intracellular stimuli, whether due to changes in location or metabolic rate (Fig. 1), grouping them according to energy demands[35].

Many pathologies involve mitochondrial dynamics; obesity, for example, has a particular interest in medical care as it is one of the main health problems in the pediatric population, and it implies and predicts other health problems such as infertility, hypertension, high cholesterol, and fatty liver, among others. Childhood obesity can lead to adult obesity with other health risks such as cardiovascular conditions and increased mortality rates[37]. It is interesting to note that these changes are described from the neonatal period and involve intrauterine processes since mothers with obesity during pregnancy have children who retain these changes after birth[38,39]. In this context, mitochondrial defects are usually found in energy metabolism, mtDNA mutations, increased oxidative stress, and, as mentioned, changes in mitochondrial dynamics. As a result, various therapeutic strategies targeting mitochondria have been proposed, such as the induction of thermogenesis or the use of natural molecules targeting mitochondria[40], like MOTS-c, which, in addition to decreasing body fat, regulates insulin sensitivity and metabolic homeostasis[41,42].

In this context, genomic variants and mitochondrial populations should be investigated considering their

Table 1. ECNTs with mitochondrial defects in their pathogenesis

Disease	Mitochondrial alteration	Cellular alterations
Obesity	Fragmentation, overproduction of mtROS, reduction of ETC components, decreased ATP synthesis, impaired membrane potential	Increased proliferation and differentiation, metabolic shift, and cell death.
Insulin resistance	Fragmentation, Ca+2 handling, mtROS production, MAM deregulation	Defective insulin-related signaling, decreased glucose uptake, GLUT4 translocation, defective insulin signaling, insulin resistance.
Type 2 diabetes mellitus	Respiratory uncoupling, decreased ATP synthesis, mitophagy, exacerbated fission/fusion	Decreased insulin secretion.
Cancer	Reduction of PGC-1α, increased mitophagy and glycolysis, moderate mtDNA mutations, metabolic hyperactivity	Metabolic shift, exacerbated biosynthesis, proliferation, tumorigenesis, aggressiveness, cell migration, and invasion.
Cardiovascular diseases	mtDNA damage, fragmentation, MAM deregulation, mtROS overproduction, Ca+2 handling defects, decreased oxygen consumption	Proliferation, hypertrophy, Ca+2 overload, energy crisis, impaired contractility, cell death.

mtROS: mitochondrial reactive oxygen species; ETC: electron transport chain; ATP: adenosine triphosphate; MAM: mitochondria-associated membranes; mtDNA: mitochondrial DNA (modified from 19).

Table 2. Treatment of NCDs through mitochondria-targeted molecules (*modified from 20*)

Type	Effect	Disease
Antioxidants	ROS neutralizers, SIRT activators based on CoQ	Neurodevelopment (Rett, Duchenne), Parkinson's, chronic kidney disease, among others.
Metabolism modulators	Niacin derivatives, metabolic (creatine, metformin), AMP kinase activators	Obesity, type 1 diabetes mellitus, myocardial infarction, liver disease (non-alcoholic).
PtPm inhibitors	Translocators, cyclophilin D	Acute kidney injury, Alzheimer's disease.

NCDs: non-communicable diseases; ROS: reactive oxygen species; SIRT: sirtuin; CoQ: Coenzyme Q; PtPm: permeability transition pore.

surroundings, as specific contacts with other organelles are established in the mitochondrial microenvironment. A mitochondrion can contact the endoplasmic reticulum (ER) and nucleus, with each interface involving different proteins[43]. The interaction with the ER is better understood where contacts occur through mitochondria-associated membranes (MAMs)[44]; the proteins located there are required for common activities (mitochondrial dynamics, calcium homeostasis, transport, among others) and become highly responsive metabolic platforms[44]. Regarding nucleus-mitochondria interaction, it has been observed that it regulates OXPHOS performance and determines somatic heteroplasmy dynamics[45].

MAMs participate in signaling and maintenance of cellular homeostasis44,46, contain regulatory proteins and tumor suppressors[47], and activate the immune system, as they harbor inflammasomes (Nlrp3: NOD-[nucleotide-binding oligomerization domain), LRR-Leucine rich repeats domain and pyrin domain-containing protein 3) which are activated during microbial infections or by interleukin secretion in the inflammatory response[48,49]. In common pediatric infections, such as *Mycobacterium tuberculosis*, *Proteus mirabilis*, *Escherichia coli*, *Salmonella enterica*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, and Plasmodium *falciparum*, there is generally an increase in reactive oxygen species, metabolic changes, and apoptosis, which occur through mitochondrial mediation; furthermore, it should be considered that various antibiotic treatments can damage mitochondrial function. Microbial pathogenicity is closely linked to mitochondrial damage, as many products derived from bacterial infections, such as nitric oxide, are respiratory complex inhibitors; the molecular and structural alterations of mitochondria caused by pathogens and treatments show great adaptability and therefore, their potential as therapeutic targets[50].

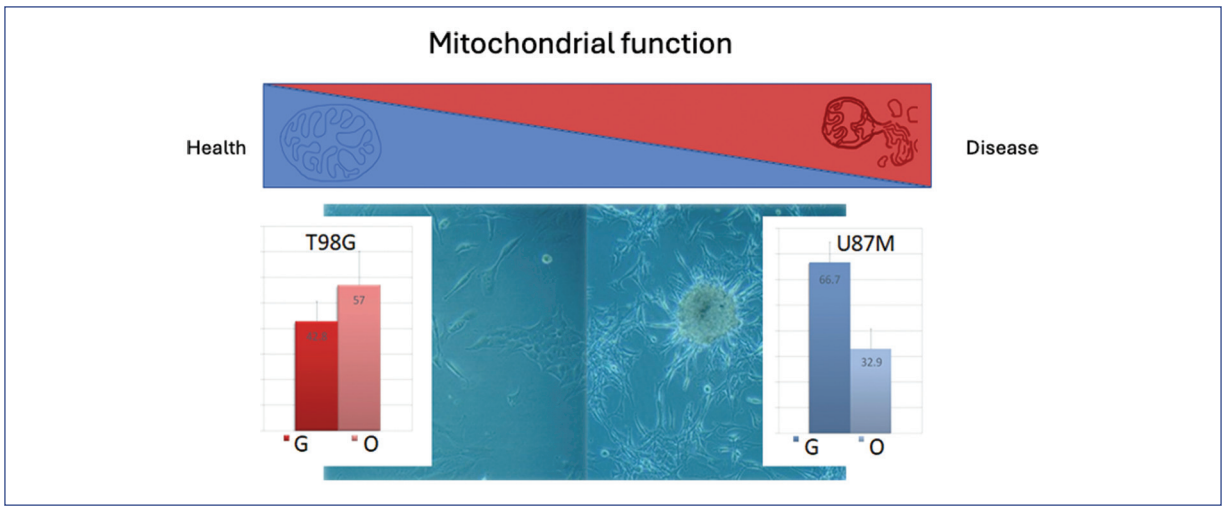

Figure 1. The transition to disease as a result of mitochondrial deterioration and resulting homeostatic loss. In cancer, mitochondria can follow the course of the disease and accompany disease progression (red triangle); the same occurs with non-communicable diseases, enabling the search for early markers of various diseases. In health, mitochondria are functional and structurally intact (blue triangle). In a glioblastoma cell model, less aggressive cancer (T98G cells) follows a more oxidative metabolism (O), as occurs in healthy cells, while advanced glioblastoma (U87 cells), where cells tend to form tumors, the metabolism becomes glycolytic (G), and mitochondrial structure is fragmented. This transition is associated with the dominance of certain metabolic pathways and structural changes in the mitochondria.

Other proteins in MAMs are involved in neurodegenerative diseases: Presenilin 1 and 2 (PSEN1 and PSEN2) in Alzheimer's; DJ1, Parkin (Park) 1 and 2, and Pink in Parkinson's; while AKT, mTORC2, GSK3b, and PTEN are involved in diabetes, and Sig1 in breast, liver, and colon cancer, among others[44].

MAMs also contain chaperones generated during the unfolded protein response (UPR), which is involved in stress response and the biogenesis of various pathologies where nucleus-mitochondria communication is established[51,52] and induces a response according to the stimulus. For example, when faced with a stressor, a transcriptional response can be activated, producing proteins safeguarded by chaperones while they achieve their functional structure. The UPR is distributed in MAMs[53,54] and regulates synthesis/alarm (apoptosis) cycles (Figs. 1 and 2), which is exacerbated in various diseases and infections[55]. Therefore, the UPR proteins involved could serve as biomarkers or therapeutic targets.

Therapeutic possibilities

There are several areas of interest for mitochondrial therapeutics, primarily focused on disease diagnosis, prognosis, and treatments. One of these approaches is through extracellular vesicles (EVs)[56], which function in biomolecule transport and communication between cells and tissues[57,58]. Their content varies according to biological conditions[5], and one advantage of EVs is that they are found in easily accessible fluids such as blood, saliva, and urine. The content of EVs can reach different tissues and influence the function, signaling, and regulation of various biological processes; they can also contain complete mitochondria or fragments, and there are even mitochondria-derived vesicles whose content has demonstrated diagnostic and therapeutic utility[59-61]. In experimental models, EVs correct the energy imbalance produced by ischemic, dilated, and hypertrophic heart diseases[62]. In disease, the number and diversity of EVs are exacerbated and affect different metabolic pathways[34,58,59,63], so identifying their content could benefit the clinical approach to various diseases[5,63,64].

Therapeutic targets for mitochondria-based medicine

Mitochondria-based medicine is founded on metabolic changes caused by disease[32,65,66], thus functioning as a sensor for different clinical phases and stages, which could help define various biomarkers to facilitate treatment selection. Regarding treatment, there is a wide variety of antioxidant reagents, both natural and designed, that can target mitochondria to prevent, modulate, or treat NCDs[67]. For example, mitocans prevent cancer

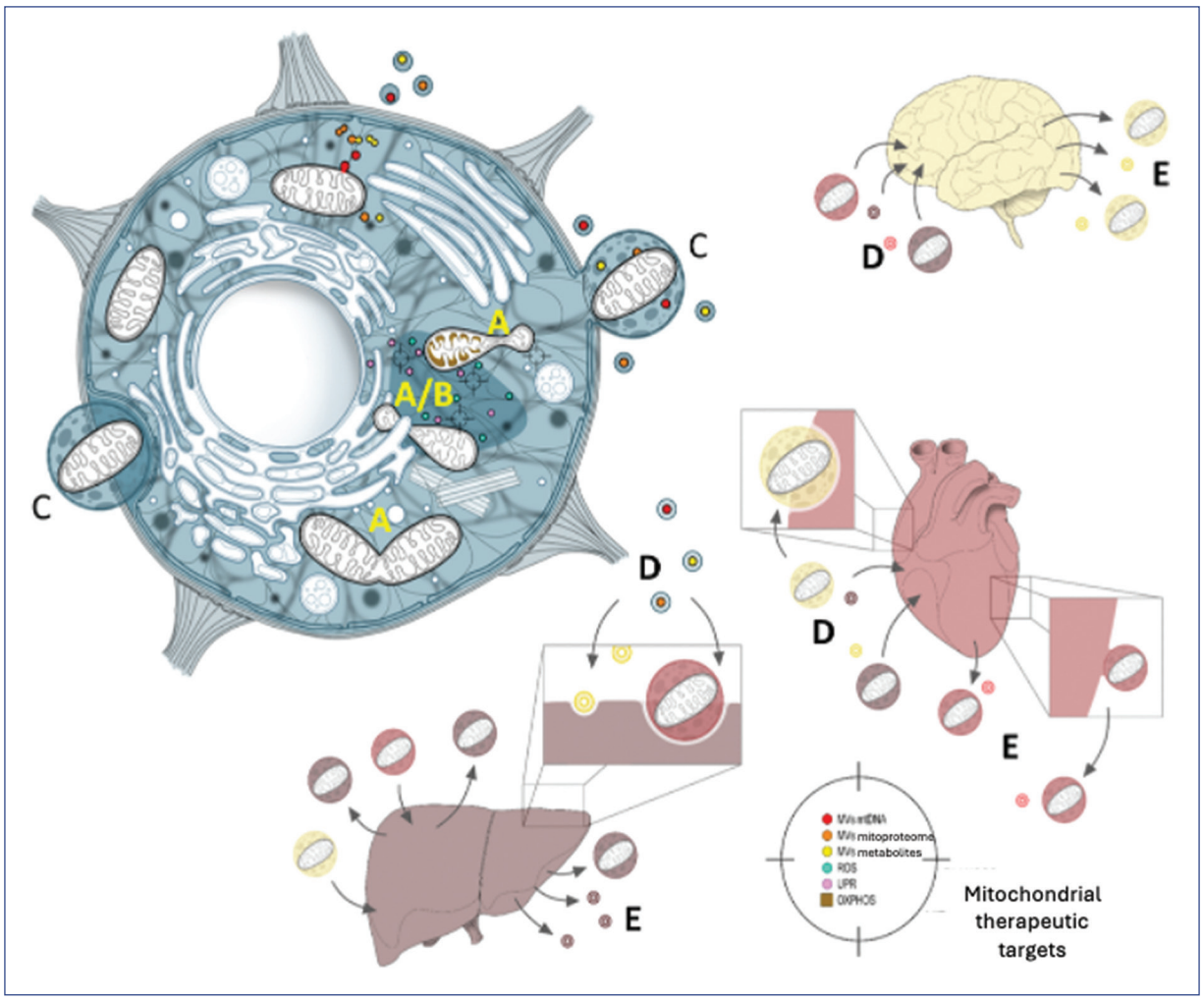

Figure 2. Mitochondria have great communication capacity at intra- and intercellular levels with various capabilities that can be used as therapeutic targets: At the intracellular level, fusion/fission (A/B) can signal different events in non-communicable disease pathogenesis as the damage caused leads to mitochondrial dysfunction. Likewise, mitochondria obtain information from the environment (unfolded protein response response, mitochondria-associated membranes), communicate with other cell organelles, and carry diverse information in extracellular vesicles (C, MVs) where they can even be contained completely and, in turn, can be directed to other targets or tissues such as brain, heart, or liver among others, through the bloodstream (D). The mitochondrial content they carry could activate (incoming arrows) a response to disease or release warning messages (E, outgoing arrows), a useful process in designing therapeutic strategies.

progression or drug resistance, and several of these can be easily manipulated[68,69]. Mitochondria have great inter- and intracellular communication capacity, making them novel therapeutic options, such as mitochondrial transplantation, which was conceived to restore or recover optimal functional and structural states of cells comprising the organ[70,71]. Mitochondrial transplantation emerges as a treatment strategy due to mitochondria's ability to transfer from one cell to another, particularly when mitochondrial damage exists. It could thus function as a treatment for diseases where typical therapies have not been effective. The process involves obtaining mitochondria (from adipose tissue, liver, or muscle) from a donor and transplanting them intranasally or by injection (systemic delivery) and has been tested primarily in murine models. Transfer can be facilitated using peptides that aid membrane absorption. At present, the technique's application focuses mainly on assisted reproduction to prevent transmission of mitochondrial diseases from mother to child; however, it has not been applied as a treatment for children who already have diseases[72]. Research is currently being conducted to evaluate its viability and safety as therapy for pediatric mitochondrial diseases[73,74] such as Leigh syndrome, Mitochondrial

Encephalopathy with Lactic Acidosis and Stroke-like episodes, Kearns-Sayre syndrome, Leber's Hereditary Optic Neuropathy, or mtDNA depletion syndrome.

There are still several challenges regarding mitochondrial transplantation for treating existing diseases, as ethical and biosafety considerations must be addressed. However, it is important to note that although the therapeutic potential is promising, widespread clinical application requires more research[75]. While the clinical potential of mitochondria is evident, there are limitations to their implementation. Much of our current information comes from biological models[76] or has only been determined in small population samples and may vary. In addition, proteins with multiple functions require further studies about their role. Such is the case of ATP synthase and its intrinsic inhibitor (IF1)[77] or sigma 1 receptor (a MAM chaperone)[78], which perform multiple functions according to their location or interactions. Therefore, the identification and validation of mitochondria-related biomarkers, as well as the development of targeted therapies, offer new perspectives in disease diagnosis and treatment, making mitochondria-based medicine a field of research and clinical application of growing relevance. Thus, information about mitochondrial function and its byproducts becomes central aspects in the health/disease balance that can be approached as potential therapeutic targets (Fig. 2).

Conclusions

Mitochondria-based medicine emerges as a promising field of research and clinical application for treating diseases acquired in childhood or NCDs. This approach focuses on understanding how mitochondrial alterations can trigger and contribute to developing these diseases. Mitochondria-based medicine contributes to developing options targeting these organelles, offering new perspectives on disease understanding and treatment, including personalized approaches.

In a context where complex and multifactorial diseases represent a significant challenge for contemporary medicine, mitochondria-based medicine opens new opportunities to advance patient care and quality of life.

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Conflicts of interest

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Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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