REVIEW ARTICLE

Mitochondria as a Therapeutic Target: Emerging Pharmacological Strategies in Chronic Diseases

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ABSTRACT
Mitochondria function as central regulators of cellular metabolism, redox homeostasis, and survival, making their impairment relevant to the development of several long-term diseases. Altered mitochondrial activity has been described in cardiovascular and metabolic disorders, neurodegenerative diseases, chronic hepatic and renal conditions, and cancer. The underlying abnormalities are diverse and may include defective oxidative phosphorylation, altered reactive oxygen species production, disruption of mitochondrial network remodelling, inadequate elimination of damaged organelles, and inappropriate activation of mitochondrial membrane permeability pathways. Persistent disturbance of these processes can impair energy availability, increase oxidative and inflammatory stress, and favour cellular injury or death. These observations have stimulated interest in pharmacological interventions that modify mitochondrial function at different levels. Investigational approaches include mitochondria-directed antioxidants, regulators of mitochondrial biogenesis and quality control, modulators of fission and fusion, agents affecting the mitochondrial permeability transition pore, and compounds that exploit altered mitochondrial metabolism in diseased cells. Although many of these strategies have produced encouraging experimental results, their clinical development remains limited by difficulties in achieving selective mitochondrial exposure, potential toxicity, inadequate biomarkers, and variability in treatment response among patients. Advances in mitochondrial drug delivery and biological marker development may improve the identification of suitable therapeutic targets and patient populations. A more disease-specific understanding of mitochondrial alterations may additionally support combination treatment strategies. This review examines the principal mechanisms through which mitochondrial dysfunction contributes to chronic disease, evaluates emerging pharmacological approaches directed at these abnormalities, and discusses the major challenges that must be addressed to achieve clinically useful mitochondria-based therapies.

KEYWORDS: mitochondrial dysfunction; oxidative stress; mitophagy; mitochondrial dynamics; permeability transition pore; mitochondria targeted drug delivery; chronic disease
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1. INTRODUCTION

1.1 Burden of Chronic Diseases

Chronic non communicable diseases, including cardiovascular disease, diabetes, chronic kidney and liver diseases, neurodegenerative disorders, and cancer, account for a substantial proportion of global morbidity and mortality. Although these diseases differ in their clinical presentation and affected organs, increasing evidence suggests that they share several cellular and metabolic disturbances [1]. One important example is the close relationship between cardiovascular, renal, and metabolic dysfunction. This relationship has led to the recognition of cardiovascular kidney metabolic syndrome, in which metabolic abnormalities, insulin resistance, organ dysfunction, and impaired cellular energy metabolism interact and contribute to disease progression [2]. The overlap between these conditions highlights the need to investigate common biological mechanisms that may provide therapeutic opportunities across different chronic diseases.

1.2 Mitochondrial Dysfunction in Disease Progression

Mitochondria are central to cellular energy metabolism, but their functions extend beyond ATP generation to include calcium regulation, provision of metabolic intermediates, redox signalling, and control of intrinsic apoptotic pathways. Evidence from multiple disease settings indicates that disruption of these functions can contribute directly to pathological progression rather than simply occurring as a secondary consequence of established disease [3]. In chronic neuroinflammatory and neurodegenerative conditions, mitochondrial abnormalities have been linked to altered inflammatory signalling, impaired neuronal function, and cell death, supporting their role as active participants in disease mechanisms [4]. The wider relationship between mitochondrial biology, metabolic regulation, aging, and degenerative disease has also been recognised through evidence connecting mitochondrial genetic and functional changes with diverse phenotypic outcomes across the lifespan [5].

1.3 Rationale for Targeting Mitochondria

The therapeutic interest in mitochondria arises from the convergence of several observations. Mitochondrial abnormalities are repeatedly observed across diverse chronic disorders, suggesting that disturbances in mitochondrial homeostasis may contribute to disease development rather than representing an incidental consequence of tissue injury [1]. In addition, key mitochondrial processes, including oxidative stress, energy metabolism, organellar quality control, and cell death signalling, can be influenced pharmacologically using small molecules, peptides, and other therapeutic platforms. A major challenge, however, is achieving adequate drug exposure within mitochondria. Several targeting approaches have therefore been developed, including lipophilic cations, mitochondria targeting peptides, and nanoparticle-based delivery systems, which can enhance intracellular and organelle specific accumulation of selected therapeutic compounds [6,7]. These approaches have expanded the practical feasibility of manipulating mitochondrial pathways and have strengthened the rationale for investigating mitochondria directed pharmacological interventions.

1.4 Scope and Objective of the Review

This narrative review examines the mechanistic basis of mitochondrial dysfunction as a therapeutic target and discusses emerging pharmacological approaches directed toward major mitochondrial processes, including bioenergetics, oxidative stress, mitochondrial dynamics, mitophagy, permeability transition, and metabolic regulation. The review further considers the application of these strategies across major chronic disease settings and evaluates recent advances in mitochondria targeted drug delivery. Particular emphasis is placed on the translational barriers that continue to limit clinical application, including drug delivery, safety, biomarker development, treatment timing, and the gap between preclinical efficacy and clinical benefit. The review concludes by outlining potential directions for developing more selective and clinically relevant mitochondrial therapies.

2. Mitochondrial Dysfunction as a Therapeutic Target

2.1 Impaired Mitochondrial Bioenergetics

Mitochondrial bioenergetics determines how efficiently cells convert metabolic substrates into usable energy through oxidative phosphorylation. Alterations in this process have been documented in metabolic disorders and may influence the development of impaired glucose and lipid metabolism. In an early study of skeletal muscle from patients with type 2 diabetes, Kelley et al. reported reduced activity of respiratory chain enzymes together with lower mitochondrial content, indicating that mitochondrial abnormalities can occur in human metabolic disease [8]. Further evidence came from studies of older individuals with insulin resistance, in whom diminished mitochondrial oxidative capacity was accompanied by greater accumulation of lipid within skeletal muscle cells [9]. Importantly, these changes were also observed in individuals without established diabetes, suggesting that mitochondrial alterations may occur relatively early during metabolic dysfunction. Nevertheless, the relationship between mitochondrial oxidative capacity and insulin resistance is complex and may vary according to tissue type, metabolic status, age, and stage of disease [10]. Thus, impaired mitochondrial energy metabolism should be considered as one component of the broader metabolic abnormalities associated with chronic disease rather than as an isolated cause of insulin resistance.

2.2 Mitochondrial Oxidative Stress

Reactive oxygen species generation is closely associated with mitochondrial electron transport and becomes particularly important when respiratory chain activity is disturbed. Under conditions of impaired electron transfer, a

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greater proportion of reducing equivalents may be diverted toward oxygen, resulting in increased formation of superoxide and related reactive species. When antioxidant defences are insufficient to maintain redox balance, these molecules can modify mitochondrial proteins, membrane lipids, and mitochondrial DNA, further impairing organelle function. Disturbances in calcium handling can aggravate this process by affecting metabolic reactions within mitochondria and altering energy production, thereby establishing an interaction between calcium imbalance and oxidative injury [11]. Human evidence also suggests that mitochondrial genomic damage can change in response to metabolic stress. For example, strenuous physical exercise has been associated with detectable alterations in circulating indicators of mitochondrial DNA damage [12]. Thus, mitochondrial oxidative stress should not be viewed solely as a downstream consequence of defective respiration. Under persistent stress conditions, increased reactive species production can itself contribute to further mitochondrial injury and may establish a cycle in which declining organelle function promotes additional oxidative damage.

2.3 Altered Mitochondrial Dynamics

Mitochondria are highly adaptable structures whose organisation changes continuously in response to metabolic requirements and cellular stress. This plasticity is achieved through opposing fusion and fission processes. Mitofusin 1 and mitofusin 2 participate in fusion of the outer mitochondrial membrane, while optic atrophy 1 contributes to fusion of the inner membrane. Mitochondrial division is largely mediated by dynamin related protein 1 (Drp1). Experimental genetic studies have demonstrated that disruption of mitofusin mediated fusion alters mitochondrial organisation and can impair normal development [13]. Loss of mitochondrial fusion has also been associated with heterogeneous organelle populations and functional abnormalities [14]. In contrast, changes in Drp1 activity can modify mitochondrial division and influence cellular responses to stress [15]. Alterations in these regulatory systems have also been reported in cardiovascular disease, where changes involving mitofusin 2 and fission related proteins have been associated with cardiac dysfunction [16]. These observations indicate that mitochondrial dynamics is more than a structural phenomenon. The balance between fusion and fission contributes to mitochondrial quality, metabolic adaptation, stress responses, and cellular survival [17,18].

2.4 Defective Mitophagy and Mitochondrial Quality Control

Removal of damaged mitochondria is an essential component of mitochondrial quality control. Mitophagy selectively directs dysfunctional organelles toward lysosomal degradation and thereby prevents their prolonged accumulation within cells. Among the pathways involved, the PINK1-Parkin system has been characterised extensively. Following mitochondrial damage, PINK1 becomes stabilised at the outer mitochondrial membrane and facilitates recruitment and activation of Parkin. Parkin then promotes ubiquitination of mitochondrial proteins, marking the damaged organelle for autophagic removal [19]. Mitochondrial turnover is not controlled exclusively by this pathway; receptor mediated mechanisms and interactions between mitochondrial dynamics and autophagy also contribute to mitochondrial quality maintenance [20]. Failure of these clearance mechanisms may allow defective mitochondria to persist and consequently increase oxidative stress, disrupt cellular metabolism, and promote accumulation of damaged mitochondrial components. Experimental disruption of PINK1 or Parkin signalling has been shown to alter mitochondrial turnover and increase cellular sensitivity to stress [21]. This quality control system is particularly important in neurons because of their high energetic requirements and limited capacity to replace damaged cellular components [22]. Changes in mitochondrial quality control associated with aging may further favour the accumulation of dysfunctional organelles and contribute to progressive cellular and tissue impairment [23]. These observations provide a rationale for investigating mitophagy and related mitochondrial quality control mechanisms as therapeutic targets in chronic disease.

2.5 Mitochondrial Mediated Apoptosis and Inflammation

The mitochondrial permeability transition pore (mPTP) is a high conductance channel associated with the inner mitochondrial membrane and plays an important role in determining whether stressed cells recover or progress toward cell death. Experimental studies showed that genetic deletion of cyclophilin D, an important regulator of mPTP activity, increased resistance to necrotic cell death while having a limited effect on apoptosis, providing evidence for a causal role of mPTP regulation in tissue injury [24,25]. Sustained mitochondrial calcium overload and oxidative stress are important triggers of persistent pore opening, linking disturbances in calcium homeostasis with the redox imbalance described earlier [26]. Prolonged mPTP opening can result in loss of mitochondrial membrane potential and severe impairment of mitochondrial function. Mitochondrial injury can also promote the release of cytochrome c, which contributes to activation of the intrinsic apoptotic pathway. In parallel, mitochondrial DNA released into the cytosol can act as a danger associated molecular signal and activate innate immune pathways, including the cGAS STING pathway, thereby connecting mitochondrial damage with inflammatory responses [27]. These mechanisms illustrate how disturbances in mitochondrial energy production, redox balance, dynamics, and quality control can converge on cell death and inflammation. The interaction among these processes and their contribution to chronic disease progression is illustrated in Figure 1.

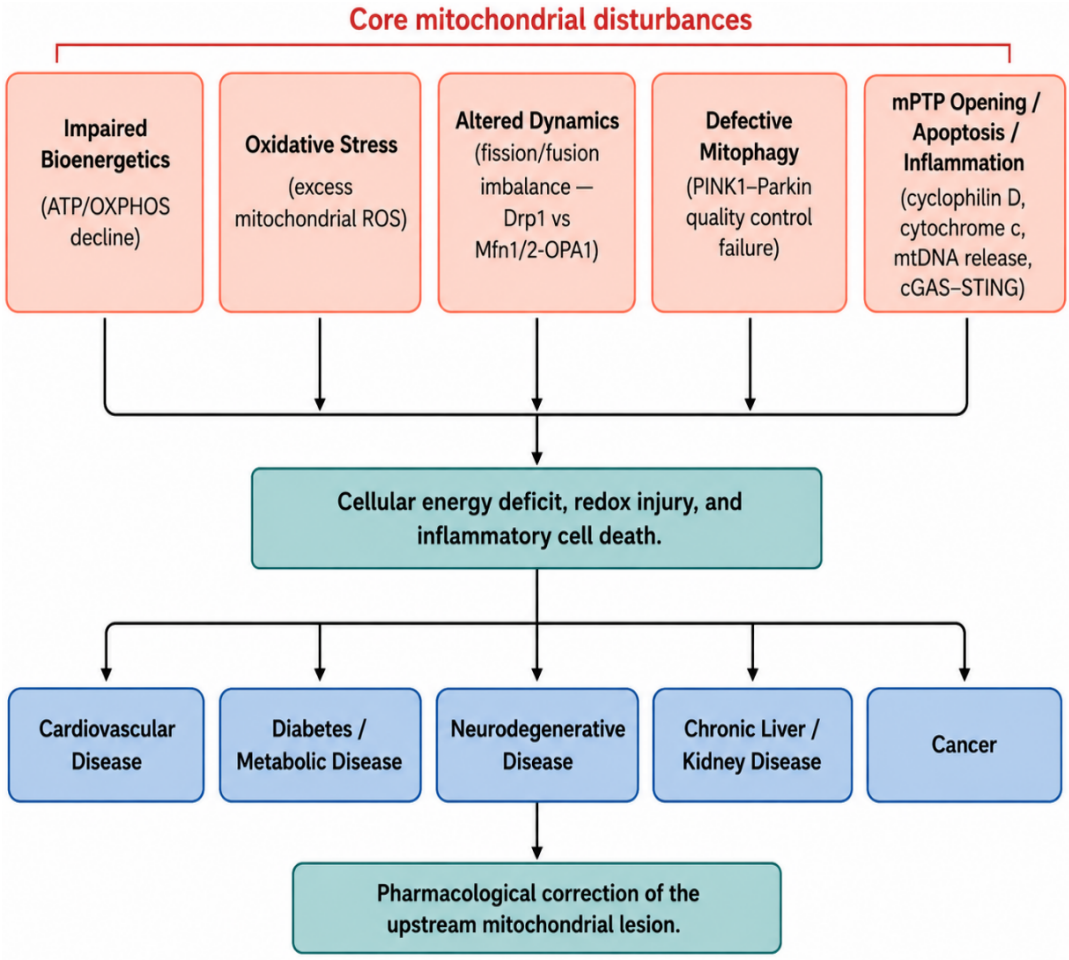

Figure 1. Mitochondrial Dysfunction as a Common Pathological Hub in Chronic Diseases

3. EMERGING PHARMACOLOGICAL STRATEGIES TARGETING MITOCHONDRIA

3.1 Mitochondria Targeted Antioxidants

Conventional antioxidants generally have limited access to mitochondria, which has encouraged the development of compounds designed to accumulate within the organelle. One widely investigated approach involves linking antioxidant molecules to lipophilic triphenylphosphonium cations, which can facilitate mitochondrial accumulation because of the negative membrane potential across the inner mitochondrial membrane [6]. However, this strategy also has limitations. At sufficiently high concentrations, triphenylphosphonium containing compounds may interfere with respiratory chain activity and increase mitochondrial proton leak, indicating that mitochondrial accumulation does not necessarily translate into a favourable therapeutic effect [28]. MitoQ is one of the most extensively investigated compounds in this class. Clinical studies have provided evidence of biological activity, including improvements in vascular endothelial function and reductions in markers of oxidative stress in older adults [29]. In experimental colitis, MitoQ has also been reported to reduce NLRP3 inflammasome activation, suggesting that its effects may extend beyond direct control of mitochondrial oxidative stress to include modulation of inflammatory signalling [30]. These findings support mitochondria targeted antioxidant therapy as a potential strategy, although the clinical relevance of these effects requires further evaluation across specific disease populations.

3.2 Modulation of Mitochondrial Biogenesis

Mitochondrial biogenesis provides another therapeutic avenue by promoting the generation and maintenance of functional mitochondria. Peroxisome proliferator activated receptor gamma coactivator 1 alpha (PGC 1α) is a major regulator of this process and coordinates transcriptional programmes involved in mitochondrial oxidative metabolism and respiratory chain function [31,32]. Its activity is influenced by cellular energy status, including activation through AMP activated protein kinase (AMPK), which links metabolic stress with increased mitochondrial biogenic signalling [33]. Sirtuin 1 (SIRT1) also contributes to this regulatory network, and pharmacological activation of SIRT1 related pathways has been associated with improved metabolic outcomes in experimental models [34]. Interest has also expanded toward interventions that combine mitochondrial quality control with renewal.

Urolithin A, a metabolite produced from dietary ellagitannins by the gut microbiota, has been shown to promote mitophagy and improve measures of mitochondrial and muscle function in experimental models [35]. A subsequent randomized controlled study in humans reported improvements in selected measures of muscle function and mitochondrial related biomarkers following supplementation [36]. These findings suggest that stimulating mitochondrial renewal and quality control may have therapeutic value, although the extent to which such interventions provide disease modifying effects in chronic disease remains to be established.

3.3 Regulation of Mitochondrial Dynamics

The continuous balance between mitochondrial fission and fusion has attracted considerable interest as a pharmacological target. Mitochondrial division inhibitor 1 (mdivi 1) was initially investigated as an inhibitor of dynamin related protein 1 (DRP1) and showed protective effects in several experimental models of mitochondrial injury [37]. However, subsequent biochemical studies challenged the assumption that its effects were primarily mediated through DRP1 inhibition. Mdivi 1 was found to inhibit mitochondrial complex I and alter mitochondrial reactive oxygen species production, while its direct inhibition of DRP1 was considerably weaker than previously proposed [38]. This finding is important when interpreting experimental studies involving mitochondrial dynamics inhibitors because a beneficial phenotype does not necessarily confirm the proposed molecular target. It also illustrates the need for rigorous target validation when developing pharmacological modulators of mitochondrial fission and fusion. Despite these limitations, the broader regulation of mitochondrial dynamics remains a potential therapeutic strategy, particularly because changes in mitochondrial morphology are closely linked to mitochondrial quality and cellular adaptation to stress.

3.4 Pharmacological Modulation of Mitophagy

Pharmacological modulation of mitophagy aims to improve the removal of dysfunctional mitochondria and thereby restore mitochondrial quality. However, the therapeutic effect of increasing mitophagy may depend on disease stage and the extent of existing mitochondrial damage. In an experimental model of Alzheimer's disease, activation of mitophagy through pharmacological or genetic approaches reduced pathological accumulation of amyloid beta and tau and improved associated cognitive abnormalities when treatment was initiated at an appropriate stage of disease progression [39]. These findings suggest that restoring mitochondrial clearance may be more effective before extensive and irreversible cellular damage has occurred. Reviews of mitochondrial quality control have similarly emphasized the importance of maintaining an appropriate balance between mitochondrial removal and replacement [22]. Therefore, future pharmacological approaches may need to consider not only whether mitophagy is increased, but also when and to what extent the pathway is activated. This temporal aspect may be particularly important when translating mitophagy based interventions from experimental models to chronic human disease.

3.5 Targeting Mitochondrial Apoptosis and mPTP

The mitochondrial permeability transition pore (mPTP) is another potential pharmacological target because sustained pore opening can lead to loss of mitochondrial membrane potential and contribute to cell death. Cyclophilin D is an established regulator of mPTP sensitivity, making it an important target for experimental pharmacological intervention [40]. In an experimental model of autoimmune encephalomyelitis, selective inhibition of cyclophilin D within mitochondria produced neuroprotective effects and was proposed as a way of limiting mitochondrial injury without exposing tissues to the broader immunosuppressive effects associated with systemic cyclosporine A [41]. However, the precise molecular composition and regulation of the mPTP remain incompletely resolved. Continued investigation of proposed pore components and their interactions is therefore necessary for the development of more selective mPTP modulators [42]. This uncertainty also emphasizes the importance of distinguishing between pharmacological effects associated with cyclophilin D inhibition and effects resulting from broader mitochondrial or cellular actions of the compounds used.

3.6 Modulation of Mitochondrial Metabolism

Direct modification of mitochondrial metabolism represents a different therapeutic strategy in which altered oxidative metabolism is used as a pharmacological vulnerability. This approach has received particular attention in cancer, where some tumour cells remain highly dependent on oxidative phosphorylation despite the metabolic adaptations commonly associated with malignant growth. IACS 010759, a potent inhibitor of mitochondrial complex I, demonstrated strong antiproliferative effects in preclinical models of glioblastoma and acute myeloid leukemia that showed substantial dependence on oxidative phosphorylation [43]. Its activity was associated with impaired cellular energy metabolism and reduced aspartate availability, which can limit nucleotide biosynthesis and thereby restrict tumour cell proliferation. These findings provide a mechanistic basis for targeting mitochondrial metabolism in selected cancers. However, because mitochondrial oxidative phosphorylation is also essential for normal tissues, therapeutic selectivity remains a major consideration. The clinical development of metabolic inhibitors will therefore depend on identifying disease contexts in which pathological cells have a sufficiently greater dependence on the targeted mitochondrial pathway than healthy tissues.

Table 1. Emerging pharmacological targets and therapeutic strategies for mitochondrial dysfunction

Mitochondrial target	Representative agent	Primary mechanism	Stage of development	Reference
Oxidative stress / mROS	MitoQ	TPP^+ conjugated antioxidant accumulation; NLRP3 suppression	Phase I/II completed	[29]
Mitochondrial biogenesis	Urolithin A	Mitophagy followed by PGC-1α mediated biogenesis	Randomised controlled trial	[36]
Mitochondrial dynamics	mdivi-1	Putative Drp1 inhibition; reversible complex I inhibition	Preclinical	[38]
Mitophagy	PINK1/Parkin activators	Selective clearance of depolarised mitochondria; stage dependent efficacy	Preclinical	[39]
mPTP / apoptosis	Cyclosporine A, mitochondrially restricted CypD inhibitors	Cyclophilin D inhibition; pore closure	Preclinical to failed Phase III	[41]
Mitochondrial metabolism	IACS-010759	Complex I inhibition; nucleotide biosynthesis impairment	Terminated Phase I	[43]

4. MITOCHONDRIAL THERAPEUTICS IN CHRONIC DISEASES

4.1 Cardiovascular diseases

Cardiomyocytes have a high mitochondrial content and depend heavily on oxidative phosphorylation to meet their continuous energy requirements. Consequently, disturbances in mitochondrial structure and function can affect cardiac energy production, contractile performance, and cell survival. Alterations in cardiolipin composition, mitochondrial fission and fusion, and permeability transition have been associated with both ischemic injury and chronic heart failure [44]. These findings have encouraged the development of therapies aimed at preserving mitochondrial structure and function. Elamipretide is a mitochondria targeted tetrapeptide that binds to cardiolipin and has been investigated for its ability to improve mitochondrial membrane stability and function. In a canine model of advanced heart failure, chronic treatment with elamipretide improved measures of left ventricular and mitochondrial function [45]. These findings provided a basis for subsequent clinical investigation, including a randomized placebo-controlled study in patients with heart failure with reduced ejection fraction, where treatment was associated with favourable changes in selected cardiac structural and functional measures [46]. Although these findings support mitochondrial targeting as a potential approach in cardiovascular disease, further studies are needed to establish whether improvements in mitochondrial function translate into sustained clinical outcomes.

4.2 Diabetes and Metabolic Disorders

Skeletal muscle is a major site of glucose disposal after meals, making its metabolic function particularly important in the development of insulin resistance. Mitochondrial abnormalities in skeletal muscle have therefore received considerable attention in type 2 diabetes. Reduced mitochondrial oxidative capacity, altered substrate metabolism, and impaired energy handling have been associated with insulin resistance, although the relationship between these abnormalities and disease progression is complex [10]. Oxidative stress may further influence this process by damaging mitochondrial components and disrupting metabolic signalling. A broader review of mitochondrial dysfunction in metabolic disorders has highlighted the interaction between oxidative stress, altered mitochondrial function, and metabolic impairment and has proposed mitochondrial pathways as potential therapeutic targets alongside conventional glucose lowering strategies [47]. These findings provide a rationale for investigating interventions that improve mitochondrial function, although the therapeutic relevance of targeting mitochondria in established metabolic disease requires stronger clinical evidence.

4.3 Neurodegenerative diseases

Neurons have high and continuous energy requirements and depend substantially on mitochondrial function to maintain membrane potential, synaptic activity, calcium homeostasis, and cellular survival. Mitochondrial impairment can therefore have pronounced consequences in neurodegenerative disorders. Evidence from studies of major neurodegenerative diseases indicates that oxidative stress and mitochondrial dysfunction are common features of neuronal injury, although their contribution differs between individual diseases and disease stages [48]. Parkinson's disease has received particular attention because abnormalities in mitochondrial quality control, oxidative metabolism, and cellular stress responses are

closely associated with neuronal vulnerability [49]. Mitochondrial dysfunction has also been incorporated into mechanistic models of Alzheimer's disease, in which impaired energy metabolism and mitochondrial stress may contribute to neuronal dysfunction before extensive neuronal loss occurs [50]. These observations provide a rationale for mitochondrial interventions in neurodegeneration, but the complexity of disease mechanisms and the limited regenerative capacity of neurons make it important to determine which mitochondrial abnormalities are therapeutically reversible.

4.4 Chronic Liver and Kidney Diseases

Mitochondrial dysfunction is increasingly recognized as an important component of chronic kidney disease. Renal tubular cells have substantial energy requirements and depend strongly on mitochondrial oxidative metabolism, particularly fatty acid oxidation. A systematic review identified impaired fatty acid oxidation, increased oxidative stress, and alterations in mitochondrial biogenesis among recurrent features of mitochondrial dysfunction in both diabetic and non-diabetic kidney disease [51]. As kidney function declines, these metabolic abnormalities may further compromise tubular function and contribute to progressive renal injury. Similar mitochondrial disturbances have been reported in chronic liver disease, where impaired energy metabolism, oxidative stress, and defective mitochondrial quality control may contribute to the progression from metabolic dysfunction toward inflammation and fibrosis. The parallel involvement of mitochondrial dysfunction in hepatic and renal disease supports further investigation of mitochondrial pathways as therapeutic targets, although disease specific differences in mitochondrial metabolism need to be considered when developing such approaches.

4.5 Cancer

Mitochondrial metabolism has emerged as an important therapeutic target in cancer because dependence on oxidative phosphorylation varies considerably between tumour types and cellular states. Although the Warburg effect established aerobic glycolysis as a prominent feature of cancer metabolism, subsequent research has shown that many tumours retain substantial oxidative phosphorylation capacity and that some tumour populations can become highly dependent on mitochondrial metabolism [52]. Reviews of mitochondrial metabolism in cancer have therefore identified respiratory chain activity, mitochondrial substrate utilization, and related metabolic pathways as potential therapeutic vulnerabilities [53,54]. Experimental evidence from a genetically engineered pancreatic cancer model further demonstrated that tumour cells surviving oncogene withdrawal can develop a strong dependence on mitochondrial oxidative metabolism for continued survival [55]. These observations provide a rationale for targeting mitochondrial metabolism in selected cancers rather than assuming that all tumours share the same metabolic phenotype. The therapeutic challenge is to exploit this metabolic dependence while preserving mitochondrial function in normal tissues, highlighting the importance of tumour selection and therapeutic selectivity.

Table 2. Mitochondrial targets and emerging therapeutic strategies across chronic diseases

Chronic disease	Predominant mitochondrial lesion	Representative strategy	Clinical status	reference
Cardiovascular disease	Cardiolipin loss, fission driven contractile decline	Elamipretide	Phase II clinical trials	[46]
Diabetes / metabolic disease	Reduced skeletal muscle oxidative capacity	Biogenesis and antioxidant support	Preclinical to early clinical	[47]
Neurodegenerative disease	mPTP driven neuronal death, chronic oxidative injury	Cyclophilin D inhibition	Preclinical to Phase II	[49]
Chronic liver / kidney disease	Impaired biogenesis, lipotoxic injury	Biogenesis activators	Preclinical to early clinical	[51]
Cancer	OXPHOS dependence in specific tumor subtypes	Complex I inhibition	Terminated Phase I	[55]

5. MITOCHONDRIA TARGETED DRUG DELIVERY

5.1 Challenges in Mitochondrial Drug Delivery

Mitochondria are surrounded by two membranes, and the inner mitochondrial membrane maintains a strong negative membrane potential that is essential for oxidative phosphorylation. This membrane potential also creates an opportunity for selective mitochondrial accumulation of appropriately designed compounds. However, reaching the mitochondrial matrix in therapeutically relevant concentrations remains challenging because drug distribution is influenced by factors such as molecular size, charge, and lipophilicity [56]. These properties can determine whether a molecule crosses cellular and mitochondrial membranes and whether it remains within the desired mitochondrial compartment. Therefore, successful mitochondrial drug delivery requires careful consideration of both intracellular transport and mitochondrial localization. The major barriers and targeting approaches are summarized in Figure 2.

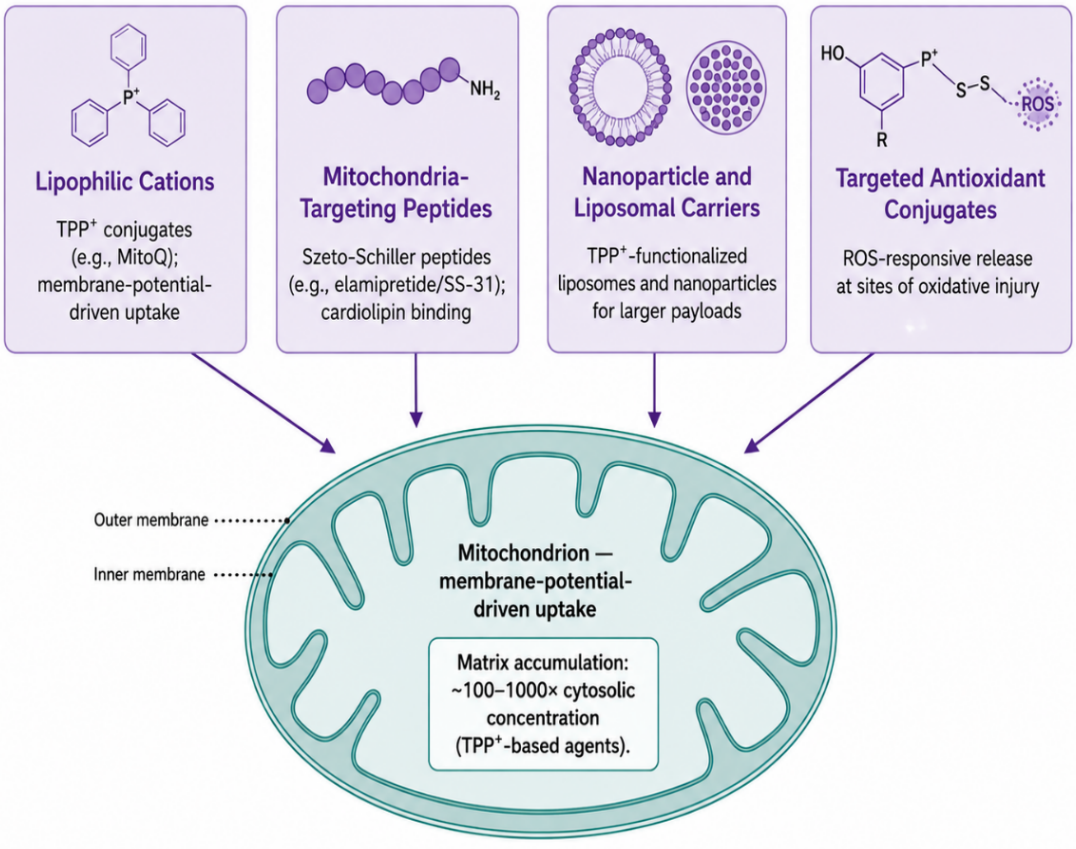

Figure 2. Emerging Strategies for Mitochondria Targeted Drug Delivery.

5.2 Lipophilic Cation Based Targeting

Lipophilic cations, particularly triphenylphosphonium based compounds, are among the most widely studied approaches for mitochondrial targeting. Their positive charge and lipophilic nature facilitate preferential accumulation within mitochondria in response to the negative membrane potential across the inner mitochondrial membrane [57]. This principle has been applied to the design of several mitochondria targeted compounds for therapeutic and diagnostic applications [58]. However, increasing mitochondrial accumulation may also increase the risk of unwanted effects. At high local concentrations, triphenylphosphonium compounds can interfere with respiratory chain activity and promote proton leakage across the inner membrane [28]. Therefore, the balance between efficient mitochondrial accumulation and preservation of normal mitochondrial function is an important consideration during the development of these compounds.

5.3 Mitochondria Targeting Peptides

Mitochondria targeting peptides represent another approach for directing therapeutic molecules to mitochondria. These peptides generally contain positively charged and hydrophobic amino acid residues that facilitate cellular entry and mitochondrial localisation. Elamipretide is a well-studied example that interacts with cardiolipin in the inner mitochondrial membrane and has been investigated for its ability to preserve mitochondrial structure and function [59,60]. This interaction provides an advantage over approaches that depend entirely on an intact mitochondrial membrane potential, as cardiolipin binding may allow the

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peptide to retain mitochondrial activity under conditions of partial membrane depolarisation. Clinical studies have investigated elamipretide in patients with primary mitochondrial myopathy and Barth syndrome, supporting continued evaluation of mitochondria targeting peptides as therapeutic platforms [61,62].

5.4 Nanoparticle and Liposomal Systems

Nanoparticle and liposomal systems provide a flexible platform for mitochondrial delivery, particularly for therapeutic molecules that are difficult to modify directly or are relatively large. These carriers can be engineered to incorporate mitochondrial targeting components and have been investigated for the delivery of antioxidants, anticancer agents, and other therapeutic payloads [63]. Experimental studies have demonstrated that nanoparticle-based systems can improve the intracellular delivery and mitochondrial localisation of selected therapeutic compounds compared with free drugs [64]. Mitochondria targeted liposomal formulations have also shown increased mitochondrial accumulation and enhanced cytotoxic effects in experimental models [65]. However, delivery of larger biological molecules, including nucleic acids and proteins, remains challenging because both cellular uptake and subsequent mitochondrial localisation must be achieved efficiently [66].

5.5 Targeted Antioxidant Delivery

Targeted antioxidant delivery is increasingly moving beyond simple mitochondrial accumulation toward strategies that regulate when and where the antioxidant is released. Stimulus responsive systems are being investigated to release antioxidant payloads in response to specific features of the diseased cellular environment, such as increased oxidative stress. Such approaches may help limit unnecessary exposure of healthy tissues while increasing drug availability at sites of mitochondrial injury. The rationale is particularly relevant to mitochondrial oxidative stress and permeability transition, where excessive reactive oxygen species can contribute to progressive mitochondrial damage [26]. Combining mitochondrial targeting with controlled or stimulus responsive release may therefore improve the therapeutic window of antioxidant interventions. However, these systems remain an emerging area, and their clinical usefulness will depend on demonstrating reliable mitochondrial targeting, predictable release, and acceptable safety in relevant disease models.

6. TRANSLATIONAL CHALLENGES AND FUTURE PERSPECTIVES

6.1 Pharmacokinetic and Pharmacodynamic Challenges

Even when a therapeutic agent is successfully directed toward mitochondria, its clinical performance remains influenced by conventional pharmacokinetic and pharmacodynamic factors. Drug absorption, distribution, tissue penetration, metabolism, clearance, and the time required to reach effective concentrations within target tissues can all affect treatment response. In mitochondrial pharmacology, dosing schedule and tissue equilibration are particularly relevant because adequate accumulation within the mitochondria does not necessarily occur immediately after administration [56]. These factors become more important when mitochondrial injury develops rapidly or varies considerably between disease stages. Peptide based agents such as elamipretide present an additional practical challenge because of their limited oral bioavailability and the resulting need for parenteral administration. This requirement may restrict long term use and reduce the feasibility of treatment outside supervised clinical settings.

6.2 Selectivity and Safety of Mitochondrial Targeting

Achieving selective mitochondrial targeting in diseased cells remains a major challenge because the mitochondrial membrane potential used by many targeting strategies is also present in healthy metabolically active cells. Consequently, a compound designed to accumulate efficiently in mitochondria may also affect normal tissues. This issue is particularly important for agents that directly inhibit mitochondrial respiration. The clinical development of complex I inhibitors in oncology illustrates the difficulty of achieving sufficient antitumour activity without producing unacceptable toxicity [43]. Similar concerns arise with systemic cyclophilin D inhibition. Although cyclosporine A can inhibit mitochondrial permeability transition, its broader pharmacological actions can produce clinically important immunosuppressive effects. More selective mitochondrial approaches may reduce such off-target effects, as demonstrated in experimental studies of mitochondria restricted cyclophilin D inhibition [41]. Future strategies therefore need to improve not only mitochondrial targeting but also disease and tissue selectivity.

6.3 Biomarkers for Mitochondrial Dysfunction

The limited availability of reliable and clinically accessible biomarkers remains an important barrier to the development of mitochondrial therapies. Many current clinical endpoints, such as symptoms, organ function, or structural changes, may not directly reflect mitochondrial target engagement and can change slowly during chronic disease. A useful biomarker should ideally provide information about mitochondrial dysfunction, identify patients with a relevant mitochondrial abnormality, and allow changes in mitochondrial activity to be followed during treatment. Development and prospective validation of such biomarkers could improve patient selection and help determine whether an investigational therapy is producing the intended biological effect. This would be particularly valuable in heterogeneous chronic diseases, where mitochondrial dysfunction may differ considerably between patients and disease stages.

6.4 Challenges in Clinical Translation

The clinical development of mitochondrial therapies has been complicated by differences between experimental models and the conditions encountered in patients. Therapeutic response may be influenced by the stage of

disease, the severity and reversibility of mitochondrial injury, patient characteristics, and the timing at which treatment is initiated. These factors may contribute to discrepancies between favourable preclinical findings and outcomes observed in clinical trials. The experience with cyclosporine A illustrates this difficulty. An early clinical investigation reported evidence of cardioprotection when cyclosporine was administered in the setting of acute myocardial infarction [67]. However, a subsequent larger randomised trial involving patients undergoing primary percutaneous coronary intervention failed to demonstrate a significant reduction in myocardial injury [68]. This contrasting evidence emphasises that successful translation requires more than confirmation of a plausible mitochondrial target. Future studies should carefully define the patient population, therapeutic window, disease stage, and degree of mitochondrial dysfunction most likely to respond to a particular intervention. Better alignment between experimental models and clinical disease may therefore be essential for improving the success rate of mitochondrial therapies.

6.5 Combination and Personalized Mitochondrial Therapies

The complexity of mitochondrial injury suggests that correction of an individual defect may not always be sufficient to restore cellular function. Disturbances in ATP production, redox regulation, mitochondrial remodelling, organelle clearance, and permeability control can coexist within the same disease state and may reinforce one another. This provides a basis for exploring therapeutic regimens that influence more than one mitochondrial process. An intervention designed to improve mitochondrial quality, for example, could potentially be paired with an antioxidant strategy to limit damage arising from persistent reactive oxygen species production. However, whether such combinations offer a clinically meaningful advantage over single-agent treatment remains to be demonstrated. The response to mitochondrial therapy is also likely to differ among patients because the type and severity of mitochondrial abnormalities can vary with disease phenotype and stage. Personalised treatment strategies should therefore incorporate information on mitochondrial status, clinical severity, and treatment response when selecting candidate interventions. Identifying the patients most likely to respond to a particular mitochondrial target, while avoiding unnecessary treatment in those unlikely to benefit, may improve both the effectiveness and safety of future mitochondrial therapies.

6.6 Future Research Directions

Future research should focus on translating the mechanistic understanding of mitochondrial dysfunction into clinically measurable and therapeutically useful strategies. Prospective validation of circulating and tissue-based biomarkers could improve patient selection and provide more direct measures of target engagement during clinical trials. Improving the oral availability and formulation of peptide based mitochondrial agents could also expand their potential use beyond hospital-based treatment. Another important priority is determining the appropriate timing of mitochondrial intervention. Experimental evidence suggests that the therapeutic response to approaches such as mitophagy activation and cyclophilin D inhibition may depend on when treatment is introduced relative to disease progression [22,39,41]. Future clinical studies should therefore consider disease stage, mitochondrial phenotype, and treatment timing together rather than evaluating mitochondrial therapies solely on the basis of molecular target selection. Such an approach may help identify patients most likely to benefit and improve the clinical development of mitochondria directed therapies.

Table 3. Translational challenges, current gaps, and potential solutions

Challenge	Current gap	Potential solution	reference
Pharmacokinetics	Poor oral bioavailability of peptide agents	Oral prodrug design; nanoparticle reformulation	[56]
Selectivity and safety	Shared membrane potential across healthy and diseased tissue	Mitochondrially restricted, disease site responsive conjugates	[28]
Biomarkers	Limited validation outside pediatric mitochondrial disease cohorts	Prospective biomarker qualification studies	[51]
Clinical translation	Preclinical cardioprotection not replicated in large trials	Improved model fidelity; earlier stage patient selection	[68]
Combination therapy	Monotherapy against single mechanistic nodes	Rational combination regimens targeting interdependent pathways	[3]

7. CONCLUSION

Mitochondrial dysfunction is increasingly recognized as an important contributor to chronic disease and as a potential target for therapeutic intervention. Evidence across bioenergetics, oxidative stress, mitochondrial dynamics, quality control, and cell death has provided a stronger mechanistic basis for targeting mitochondrial pathways. Several pharmacological approaches have progressed beyond experimental models into human studies, including mitochondria targeted antioxidants, strategies aimed at improving mitochondrial biogenesis, and cardiolipin stabilizing peptides. However, promising effects in preclinical studies have not consistently translated into clinical benefit. The experience with cyclosporine A in myocardial infarction and the toxicity associated with

potent complex I inhibition in oncology demonstrate that a well-defined molecular target alone does not guarantee therapeutic success. Future progress will require better mitochondrial targeting, reliable biomarkers for identifying suitable patients and treatment windows, and therapeutic combinations that address the interconnected nature of mitochondrial dysfunction. Integrating these approaches with disease specific biology may improve the likelihood of developing mitochondrial therapies that are both effective and clinically useful.

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