

MITOCHONDRIAL PHARMACOLOGY IN AGING AND DISEASE: MOLECULAR TARGETS, THERAPEUTIC STRATEGIES AND TRANSLATIONAL CHALLENGES

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ABSTRACT

In addition to producing energy, mitochondria influence innate immunological detection, calcium handling, redox signaling, and a cell's choice to survive or die. They are currently thought to be a contributing factor to aging, neurological, cardiovascular, metabolic, and cancerous diseases. In this review, we outline the several mechanisms that lead to mitochondrial dysfunction, including inadequate biogenesis, an imbalance between fission and fusion, deficient mitophagy, oxidative stress, telomere-linked signaling, and leakage of mitochondrial DNA. We also link each process to the medications that affect it. Respiratory-chain modulators, antioxidants that target mitochondria, metabolite-carrier modulators and insulin sensitizers, inducers of biogenesis (such as AMP-activated protein kinase activators, nicotinamide adenine dinucleotide precursors, and peroxisome proliferator-activated receptor agonists), regulators of mitochondrial dynamics, mild uncouplers, inhibitors of mitochondrial translation, and modulators of mitophagy and senescence. We also discuss genetic editing, diet, exercise, and mitochondrial transplantation. Clinical trials have yielded inconsistent results, while animal results are frequently impressive. The field is hampered by poor delivery to the organelle, species variations, reliance on surrogate end points, patient variability, and a lack of validated biomarkers. Biomarker-based patient selection, improved delivery chemistry, and thoughtful combination therapy will likely be key components of future advancements.

KEYWORDS: Mitochondrial dysfunction; Ageing; Mitophagy; Mitochondria-targeted antioxidants; Mitochondrial biogenesis; Senescence.

1. INTRODUCTION

Double-membrane organelles called mitochondria are descended from endosymbiotic bacteria. They still have a little genome called mitochondrial DNA (mtDNA), which codes for 13 respiratory chain subunits; the nucleus encodes all other mitochondrial proteins.^[1] They do more than just produce adenosine triphosphate (ATP). They also aid in the execution of apoptosis, buffer calcium (Ca²⁺), participate in lipid metabolism, and support immunological signaling.^[2] Over the past thirty years or so, the perception of mitochondria has changed from being passive power plants to organelles that may be targeted in common diseases.^[2,3]

There are two main types of mitochondrial malfunction. Leigh syndrome, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), and Leber hereditary optic neuropathy (LHON) are common instances of primary mitochondrial diseases (PMD), which are uncommon inherited illnesses of oxidative phosphorylation (OXPHOS). When another disease process disrupts mitochondrial homeostasis, as occurs in heart failure, neurodegeneration, diabetes, and cancer, secondary mitochondrial dysfunction (SMD) results. SMD is especially important as people age. There is mounting evidence that the loss of mitochondrial quality control actively accelerates the process rather than being a byproduct of aging.^[4,5]

The drug-based reactions have not evolved uniformly and are diverse. Numerous substances directly affect respiratory chain elements or the organelle's redox status. Newer theories seek to replace or repair the organelle itself, while others focus upstream on the nuclear regulators of mitochondrial gene expression. Here, we detail the primary medication classes and the clinical evidence supporting them, go over the mechanisms that lead to pharmacological targets in aging and age-related diseases, and talk about why so little of this has reached patients.

2. SCOPE AND APPROACH

This review is narrative in nature. It expands upon the major preclinical and clinical publications cited in recent thorough reviews. A literature search was carried out in PubMed/MEDLINE, Scopus and Google Scholar for articles published between January 2000 and October 2026, using combinations of the keywords "mitochondrial dysfunction", "aging", "senescence", "mitophagy", "mitochondrial biogenesis", "mitochondrial dynamics", "mitochondria-targeted antioxidants", "mitochondrial transplantation" and "clinical trial". Peer-reviewed, English-language articles were included if they reported preclinical or clinical data on pharmacological or non-pharmacological interventions directed at mitochondrial targets in aging or age-related disease, or if they were recent comprehensive reviews. Conference abstracts, non-peer-reviewed sources and reports without mitochondrial outcome data were excluded. Readers should visit trial registries for the most recent status because trial statuses are subject to change, and the information provided here is based on reports from the underlying sources.

3. MECHANISMS OF MITOCHONDRIAL DYSFUNCTION THAT DEFINE DRUG TARGETS

3.1 Bioenergetic failure and redox imbalance

One metabolic event can transform a functional respiratory chain into a source of harmful reactive oxygen species (ROS), as demonstrated by ischemia-reperfusion damage. During ischemia, succinate accumulates and is rapidly oxidized when blood flow resumes. As a result, electrons are forced back into complex I and superoxide is produced by reverse electron transport (RET), which keeps the ubiquinone pool small and the proton-motive force high.^[6] In mouse hearts, small compounds that prevent electron leak at complex I's quinone-binding site (S1QELs) reduced ROS generation and restricted ischemia-reperfusion injury while maintaining normal OXPHOS.^[7] It appears that the

dithiolethione OP2113 functions similarly.^[8] Findings like these favour blocking ROS formation at a defined site rather than scavenging indiscriminately, because ROS also do useful signalling work.

3.2 Declining biogenesis, mitophagy and the senescence phenotype

An energy deficiency often activates sirtuin 1 (SIRT1) and AMP-activated protein kinase (AMPK; EC 2.7.11.31), both of which increase the activity of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α). PGC-1 α stimulates mitochondrial transcription factor A (TFAM), which propels mtDNA transcription and replication, in conjunction with nuclear respiratory factors 1 and 2. As humans age, this axis becomes weaker. While telomere attrition or DNA damage activates p53, which represses PGC-1 α and PGC-1 β , higher activity of nicotinamide adenine dinucleotide (NAD⁺)-consuming enzymes like CD38 lowers NAD⁺ and dampens SIRT1 and SIRT3.^[8,9] At the same time, mitophagy decreases via both the receptor-mediated and PINK1-Parkin pathways, allowing damaged organelles remain in the cell.

There is more harm than just a lack of energy. The cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway and the NLRP3 inflammasome take up the mtDNA and cardiolipin that defective mitochondria release into the cytosol. Partial outer membrane permeabilization under sublethal apoptotic stress also releases mtDNA and contributes to the senescence-associated secretory phenotype (SASP).^[10] It has been observed that throughout aging, inducing mitophagy reduces this cytosolic mtDNA-driven cGAS-STING signaling.^[11] As a result, tissue aging and mitochondrial damage are reinforced by the SASP, which also increases inflammation and spreads senescence to other cells.^[12]

3.3 Imbalanced mitochondrial dynamics

Optic atrophy 1 (OPA1) and mitofusins 1 and 2 (MFN1/2) are necessary for fusion. Dynamin-related protein 1 (DRP1) is necessary for fission and is attracted by adaptors like FIS1 and mitochondrial fission factor (MFF). Senescent and aged tissues typically have increased DRP1 activity and fewer fusion proteins, resulting in fragmented mitochondria with less effective respiration. However, the image is not that straightforward. In the mouse heart and brain, loss of DRP1 results in hyperconnected mitochondria, heart failure, and dementia; excessive fusion also impedes clearance. Therefore, a medication must not only prevent fission but also restore equilibrium. A chimeric MFN2 agonist corrected axonal mitochondrial dysmotility in a mouse model of Charcot-Marie-Tooth disease type 2A.^[13] By contrast, mdivi-1, the fission inhibitor used in so many studies, turned out to be a reversible complex I inhibitor, which casts doubt on some of the earlier findings.^[14]

3.4 Calcium overload, permeability transition and metabolic reprogramming

The permeability transition pore opens when mitochondria are continuously overwhelmed with Ca²⁺. It is regulated by cyclophilin D (peptidylprolyl isomerase F; EC 5.2.1.8), and opening is a key step in cell death and reperfusion injury. Results from using ciclosporin to block the pore have been inconsistent. While AMPK/SIRT1/PGC-1 α signaling pulls in the other direction, hyperactive PI3K/AKT/mTOR signaling pushes metabolism toward a glycolytic, lipogenic state, suppresses fatty acid oxidation, and hinders mitophagy in senescent cells.

It's also unclear how lifespan and mitochondrial dysfunction are related. Deleting *sod-2* in *Caenorhabditis elegans* can extend life, while heterozygous *Sod2* mice are more susceptible to oxidative damage but still live as long as wild-type

animals. These findings serve as a cautionary tale against expecting that anything that reduces ROS will slow down aging.

3.5 Mitochondria as signalling hubs

Many pharmacological targets are located in their signaling networks rather than in the respiratory chain because mitochondria convert ions, nutrients, and energy status into transcriptional programs. Driven by the membrane potential, calcium enters through the mitochondrial calcium uniporter and activates the Krebs cycle's Ca^{2+} -sensitive dehydrogenases, increasing ATP production. After then, calcium is eliminated and the basal condition is restored via the $\text{Na}^{+}/\text{Ca}^{2+}$ exchanger NCLX. While NCLX overexpression and ischemic preconditioning reduced infarct size by 43%, deleting NCLX in the adult mouse heart resulted in heart failure and unexpected mortality. Since the endoplasmic reticulum and mitochondria's contact sites concentrate this calcium transport, they are also potential targets.^[2]

AMPK functions on multiple levels. PGC-1 α is phosphorylated, MFF is phosphorylated to promote fission, ULK1 and Parkin initiate mitophagy, and the uniporter is activated.^[2,4] mTORC1 promotes fission and apoptosis via MTFP1 and increases translation of nucleus-encoded mitochondrial mRNAs via 4E-binding proteins. NAD^{+} supply is linked to mitochondrial activity by the mitochondrial sirtuins SIRT3 to SIRT5. SIRT3 deacetylates OPA1 to promote fusion, SIRT4 eliminates lipoamide from the pyruvate dehydrogenase complex, and SIRT5 promotes antioxidant defense by desuccinylating IDH2. Mitophagy is also gated by nutrient condition. The receptor NLRX1 is kept in a closed, inactive state by acetyl-CoA, and its LC3-interacting motif is only revealed when fasting reduces acetyl-CoA.

Additionally, mitochondria serve as danger sensors. cGAS-STING, the NLRP3 inflammasome, and Toll-like receptor 9 recognize mitochondrial DNA, cardiolipin, and ROS. BAK/BAX macropores and VDAC oligomers allow mtDNA to escape; in one study, ciclosporin decreased cytosolic mtDNA by 30–40%, while an inhibitor of VDAC oligomerization decreased it by 50–60%.^[2] Therefore, anti-inflammatory strategies for aging may target these sensors.

3.6 Disease-specific pathophysiology

Neurodegeneration: Defective mitophagy is a common finding in Alzheimer disease, where amyloid- β interferes with the digestion of mitochondrial presequence peptides and causes fission through S-nitrosylation of DRP1. Aggregated α -synuclein interacts to TOM20, ATP synthase, and complex I in Parkinson PD, preventing protein import and promoting early permeability transition pore opening. Although Ndufs2-deficient mice exhibited progressive parkinsonism, conditional Ndufs4 deletion did not replicate the dopaminergic loss, raising doubts about whether complex I deficiency alone can cause parkinsonism.^[2] Alzheimer's, Parkinson's, Huntington's, and amyotrophic lateral sclerosis have all been linked to decreased PGC-1 α expression; in Parkinson models, NAD^{+} boosters such nicotinamide mononucleotide increased mitophagy and the mitochondrial unfolded protein response.

Cardiovascular disease: In addition to reperfusion injury (Section 3.1), 24-month-old mice's aging hearts have more FIS1 and DRP1 and less MFN1, MFN2, and OPA1, and PGC-1 α -deficient mice exhibit significant cardiac dysfunction under pressure overload.^[4] In ischaemia-reperfusion models, blocking the DRP1-FIS1 connection enhanced cardiac performance and decreased mitochondrial fragmentation, cytochrome c release, and ROS.

Metabolic disease: Diacylglycerol and acyl-CoA increase and fatty acid oxidation decreases in skeletal muscle with fewer or worse mitochondria. These trigger serine kinases that prevent GLUT4 translocation and phosphorylate insulin

receptor substrate-1. In the liver, mitochondria isolated from obese individuals with or without fatty liver demonstrated maximal respiration that was 4.3–5.0 times higher than that of lean controls; however, this adaptation vanished in non-alcoholic steatohepatitis (NASH), where respiration was 31–40% lower.^[2] PGC-1 α decreases in pancreatic β -cells in type 2 diabetes mellitus (T2DM), and insulin production is hampered by both excessive and insufficient fission, suggesting that balance is crucial.

Musculoskeletal disease and cancer: Sarcopenia goes with lower PGC-1 α , less fusion and impaired PINK1-Parkin mitophagy. In osteoarthritis, MFN2 is reduced in chondrocytes and loss of PINK1 worsens cartilage degeneration. Cancer shows the opposite dependence: PGC-1 α is raised in circulating tumour cells and supports invasion and metastasis, so strategies against ageing and against cancer can pull in different directions on this axis.

3.7 Telomere, epigenetic and metabolic links

Three pathways have been identified linking mitochondria and telomere attrition: ATM-AKT-mTOR-PGC-1 β , PARP1-NAD⁺-SIRT1, and telomere-p53-PGC-1 α/β . Both reduce biogenesis and increase reactive oxygen species (ROS), and mitochondrial dysfunction encourages telomere loss and telomere dysfunction-induced foci. Increased chromatin accessibility causes FOXC1-dependent networks associated with systolic dysfunction in cardiomyocytes with malfunctioning telomeres. The epigenome is also influenced by mitochondrial metabolites. Alpha-ketoglutarate and acetyl-CoA control histone marks, oxidative stress and NAD⁺ depletion alter DNA methylation, and non-coding RNAs increase the SASP via mitochondrial ROS. Sirtuin activators and NAD⁺ precursors work outside of bioenergetics for this reason.

3.8 Mitocytosis as an additional quality-control route

Damaged mitochondria can also be eliminated by migrating cells. During mitocytosis, depolarized, ROS-rich mitochondria are transported to the cell periphery by the motor protein KIF5B, anchored by myosin 19, cut off by DRP1, and packed into approximately 240 nm-long migrasomes, which are supported by TSPAN4 and cholesterol. The pathway's therapeutic potential has not been investigated, and it is especially important in highly motile cells like neutrophils.^[4]

4. PHARMACOLOGICAL STRATEGIES

4.1 Respiratory-chain modulators and antioxidants

The short-chain homologue of coenzyme Q10, idebenone [2-(10-hydroxydecyl)-5,6-dimethoxy-3-methylcyclohexa-2,5-diene-1,4-dione], dissolves more readily and serves as an antioxidant and electron carrier. Idebenone improved respiratory function in individuals with Duchenne muscular dystrophy (DMD) who were not receiving glucocorticoids in a placebo-controlled phase 3 trial,^[15] while a randomized trial in LHON revealed enhanced visual recovery.^[16] The outcomes for Friedreich ataxia^[17] and Alzheimer's disease^[18] have been mixed. Idebenone is one of the few mitochondria-directed medications to have made it to regulatory review, and it has both fast-track and orphan drug designations for DMD from the US Food and Drug Administration.

Up to 80% of superoxide and hydrogen peroxide production at complex I is inhibited by anethole trithione (OP2113) [5-(4-methoxyphenyl)-3H-1,2-dithiole-3-thione], whereas OXPHOS is unaffected. Although it has a human safety record from other applications, no clinical trials including mitochondrial dysfunction had been published at the time the sources were written.^[1]

The thioredoxin/peroxiredoxin system is affected by sonlicromanol (KH176). Phase 1 and phase 2 studies of patients with the m.3243A>G mutation found it to be safe and well tolerated; nevertheless, the major outcome metrics in that small study did not significantly improve.^[19] It is designated as an orphan for deafness and diabetes inherited from the mother. EPI-743 (vatiquinone), another antioxidant, has been investigated in relation to mitochondrial illness.

Mitochondria-targeted antioxidants: The idea behind MitoQ and SkQ1 is that lipophilic cations gather inside mitochondria due to the high inner membrane potential (-150 to -170 mV). Membrane potential has no effect on the cardiolipin-binding peptide SS-31 (elamipretide). MitoQ enhanced vascular function in healthy older persons^[20] but did not alter the course of Parkinson's disease.^[21] In phase 2 and phase 3 trials for dry eye condition, SkQ1 eye drops markedly enhanced corneal staining.^[22] While randomized trials in primary mitochondrial illness and amyotrophic lateral sclerosis found no meaningful difference on their primary scales, coenzyme Q10 has been examined in heart failure.^[23] In general, inadequate mitochondrial localization and disruption of normal ROS signaling impede global antioxidants.

4.2 Metabolite-carrier modulators and insulin sensitisers

Imeglimin improves mitochondrial function in the pancreas, liver and skeletal muscle of T2DM patients, although its precise mitochondrial mechanism is unknown. Added to metformin, it lowered glycated haemoglobin by 0.44% relative to placebo.^[24] At the time of the source its regulatory status was reported as the submission stage.^[1]

Mitochondrial pyruvate carrier (MPC) modulators: Thiazolidinediones inhibit the MPC. The derivative MSDC-0602K, which spares peroxisome proliferator-activated receptor gamma (PPAR γ), improved glycaemic parameters in patients with NASH but did not give a statistically significant histological improvement,^[25] so its likely niche is T2DM with liver involvement. PXL065 (deuterium-stabilised R-pioglitazone) is in phase 2 development, and the analogue MSDC-0160 improved cerebral glucose metabolism in a phase 2 study in Alzheimer disease. Pioglitazone [2,4-thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-] itself reduced hepatocellular injury and fibrosis in non-diabetic NASH^[26] and gave histological improvement in patients with prediabetes or T2DM.^[26, 27]

4.3 Inducers of mitochondrial biogenesis

PGC-1 α is hard to target directly because its regulation is so complex, so most strategies go through upstream sensors or downstream transcription factors.

PPAR agonists: Bezafibrate, an activator of all peroxisome proliferator-activated receptor (PPAR) isoforms, modestly improved cardiac function and reduced the number of COX-deficient muscle fibres in patients with mitochondrial myopathy over 12 weeks, without major adverse effects.^[28] Earlier work, however, had raised concern about long-term mitochondrial toxicity.^[1] REN001, a PPAR δ agonist, is being investigated for mitochondrial myopathy and fatty acid oxidation disorders.

AMPK activators: AMPK can be activated by 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), by metformin [N,N-dimethylimidodicarbonimidic diamide] and by the direct activator PXL770. The last restored mtDNA copy number in a mouse model of autosomal dominant polycystic kidney disease and is in phase 2 trials in NASH.

Sirtuin activation and NAD⁺ boosting: Sirtuins are NAD⁺-dependent protein deacylases (EC 2.3.1.286), and their activity drops as NAD⁺ declines with age. Resveratrol has given inconsistent clinical results, including opposite

outcomes in two Alzheimer disease trials.^[1] Nicotinamide riboside (3-carbamoyl-1- β -D-ribofuranosylpyridinium) was tested for safety in the NADPARK phase 1 trial in Parkinson disease,^[28,29] and it did not significantly improve peak oxygen uptake in chronic kidney disease. The NAD⁺ precursor acipimox (5-methylpyrazinecarboxylic acid 4-oxide) raised insulin sensitivity by about 27% and lowered hydrogen peroxide production by about 45% in T2DM, but did not improve mitochondrial oxidative capacity.^[30] The strong effects of NAD⁺ precursors in animals have not been reproduced consistently in people. Suggested reasons are complex metabolic regulation, tissue differences in target distribution and threshold effects.^[31] One encouraging exception is a randomised crossover trial in Werner syndrome, where nicotinamide riboside improved vascular and skin features.^[32]

4.4 Regulators of mitochondrial dynamics

Mdivi-1 protected the heart and neurons in preclinical models of ischaemia-reperfusion injury, dilated cardiomyopathy and neurotoxicity, but its off-target inhibition of complex I calls for caution. P110 selectively blocks the DRP1-FIS1 interaction and helped in models of Parkinson disease, Alzheimer disease, amyotrophic lateral sclerosis and myocardial infarction. Physiological fission is part of how the body adapts to exercise, and fission inhibitors reduced exercise capacity in animals. No Drp1 or MFN2 modulator has yet been tested for efficacy in humans.

4.5 Mild mitochondrial uncouplers

A small proton leak lowers ROS formation and raises energy expenditure, which makes mild uncoupling attractive in obesity, insulin resistance and fatty liver disease. 2,4-Dinitrophenol was abandoned after fatal overdoses and neurological toxicity. Safer designs include a controlled-release mitochondrial protonophore that reversed diabetes and steatohepatitis in rats.^[33] In a randomised phase 2a trial in adults with non-alcoholic fatty liver disease and a high body mass index, the uncoupler HU6 reduced liver fat compared with placebo; adverse effects were mild to moderate and included flushing, diarrhoea and palpitations.^[34]

4.6 Inhibitors of mitochondrial translation

Mitochondria kept a bacteria-like translation machinery, so some antibiotics can impair OXPHOS selectively in cancer cells that rely on mitochondrial metabolism, without stopping cytosolic protein synthesis. Tigecycline has entered trials in acute and chronic myeloid leukaemia, and preclinical data support activity in lymphoma, ovarian and lung cancer.^[35] Doxycycline and the tetracycline derivative COL-3 have been tried in solid and haematological tumours, and COL-3 showed limited efficacy on its own. RK-33, an inhibitor of the RNA helicase DDX3, is expected to enter trials in Ewing sarcoma and breast cancer.

4.7 Modulators of mitophagy and senescence

In aged auditory cells, the SIRT1 activator SRT2104 raised PINK1, Parkin, BNIP3 and LC3-II and lowered senescence markers.^[36] The terpenoids thymol and carvacrol stimulated PINK1-dependent mitophagy through SIRT3 and improved sarcopenia and epigenetic ageing markers in accelerated-ageing mice.^[37] Rapamycin inhibits mTOR and enhances mitophagy. Senolytic and senomorphic approaches include the BCL-2 family inhibitor ABT263 (navitoclax), which clears senescent cells through BCL-XL, as well as mitochondria-targeted antioxidants and metformin, which suppress SASP signalling.^[5] In cancer, the effect of modulating mitophagy depends on context. Losing mitophagy can promote early transformation, whereas more mitophagy can let tumour cells resist chemotherapy or KRAS inhibitors.

5. NON-PHARMACOLOGICAL AND ADVANCED STRATEGIES

5.1 Nutrition, caloric restriction and exercise

Carnitine, coenzyme Q, creatine and riboflavin are used to support patients with PMD, but most trials of supplements and diets are open-label rather than randomised. The ketogenic diet protects neurons in several preclinical models, yet prolonged exposure caused cardiac fibrosis and reduced mitochondrial biogenesis in rats.^[38] In a six-month human study, caloric restriction increased muscle mitochondrial biogenesis and reduced DNA damage.^[39] In rodents, however, lifelong restriction preserved oxidative capacity without raising mitochondrial content,^[40] which suggests that its benefit may lie in preserving the mitochondria already present. Regular exercise keeps respiratory capacity up in ageing skeletal muscle, increases PGC-1 α and fission-, fusion- and Parkin-related proteins in human muscle, and has been linked to a younger biological age.^[40]

5.2 Mitochondrial transplantation

In mitochondrial transplantation, isolated, respiration-competent mitochondria are placed into damaged tissue. Intravenous mitochondria from young mice improved cognitive and motor performance in aged mice,^[41] and autologous mitochondria injected into the ischaemic rabbit heart improved function after ischaemia.^[42] Better ventricular function has been reported in paediatric patients with ischaemia-reperfusion dysfunction,^[43] but a systematic review found only twenty animal and two human studies, with inconsistent results across biomarkers.^[44] The practical obstacles are considerable. Mitochondria lose function during isolation,^[45] the best donor source is unclear (autologous, allogeneic or xenogeneic), immune compatibility is a concern, and the routes of uptake, such as macropinocytosis, tunnelling nanotubes and gap junctions, are only partly understood. In aged mouse muscle, one transplantation raised basal ATP by about 65% and improved endurance.^[46] Tracking is a further problem, because mitochondrial dyes leak and give false-positive signals.

Preclinical uses cover ischaemia-reperfusion injury of heart, liver and brain, Parkinson and Alzheimer models (including intranasal delivery in 6-hydroxydopamine-lesioned rats), chemically induced liver injury, acute lung injury and spinal cord injury. Viability seems to matter. Frozen mitochondria, naked mitochondrial genomes and ATP-containing vesicles did not reproduce the benefit of living organelles. Transplanted mitochondria may partly work by activating PINK1-Parkin mitophagy in the recipient cells, so that damaged native organelles are cleared, although true integration with the host network has rarely been seen. Mitochondrial components carried in extracellular vesicles, such as mtDNA together with TFAM mRNA, offer an alternative to whole organelles.

5.3 Mitochondrial genome editing

No drug can correct an inherited mtDNA mutation. Base editors adapted for mitochondria (DddA-derived cytosine base editors and adenine base editors) can change single bases without double-strand breaks, and in a rat model of Leigh syndrome they restored wild-type mtDNA to about 53% with functional recovery.^[47] Off-target and bystander editing are still unresolved, and efficacy has so far been shown only in cells and animals.

6. SUMMARY OF SELECTED CLINICAL EVIDENCE

Table 1: Selected mitochondria-directed agents and representative clinical findings.

Sr. No.	Agent	Principal mechanism	Condition studied	Representative finding	Reference
1	Idebenone	Coenzyme Q10 analogue; electron carrier	DMD, LHON, Friedreich ataxia, Alzheimer disease	Improved respiratory function in DMD; benefit signals in LHON; inconsistent in ataxia and Alzheimer disease	[15-18]
2	Sonlicromanol	Thioredoxin/peroxiredoxin modulation	m.3243A>G disease	Safe; no significant improvement in primary outcomes	[19]
3	MitoQ	Mitochondria-targeted antioxidant	Parkinson disease; older adults	No disease modification; improved vascular function in older adults	[20,21]
4	SkQ1	Mitochondria-targeted antioxidant	Dry eye syndrome	Improved corneal staining in phase 2 and 3	[2,22]
5	Imeglimin	Mitochondrial function modulator	T2DM	HbA1c lowered 0.44% vs placebo as add-on to metformin	[24]
6	MSDC-0602K	MPC modulation	NASH	Glycaemic improvement; no significant histological benefit	[25]
7	Pioglitazone	PPAR γ agonist; MPC inhibition	NASH	Reduced liver injury and fibrosis in selected trials	[26,27]
8	Bezafibrate	Pan-PPAR agonist	Mitochondrial myopathy	Modest cardiac improvement; long-term toxicity concern	[1,28]
9	Acipimox	NAD ⁺ precursor	T2DM	Improved insulin sensitivity; no gain in mitochondrial capacity	[2,30]
10	Nicotinamide riboside	NAD ⁺ precursor	CKD; Parkinson disease; Werner syndrome	No gain in peak oxygen uptake in CKD; safety phase 1 in Parkinson disease; benefit in Werner syndrome	[2,29,32]
11	HU6	Mitochondrial uncoupler	NAFLD with high BMI	Reduced liver fat vs placebo; mild to moderate adverse effects	[34]
12	Tigecycline	Mitochondrial translation inhibitor	Myeloid leukaemia	Under clinical evaluation	[1,35]

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; DMD, Duchenne muscular dystrophy; HbA1c, glycated haemoglobin; LHON, Leber hereditary optic neuropathy; MPC, mitochondrial pyruvate carrier; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PPAR, peroxisome proliferator-activated receptor; T2DM, type 2 diabetes mellitus.

7. TRANSLATIONAL CHALLENGES

Heterogeneity and end points. PMD and SMD differ widely in cause, age of onset and the organs involved, which makes recruitment and trial design hard and tends to favour symptomatic rather than disease-modifying goals. Many ageing trials depend on surrogate end points such as insulin sensitivity or cytokine levels, and how these relate to healthspan and disability is still uncertain.^[4]

Delivery and bioavailability: Natural polyphenols are quickly converted to inactive conjugates, so the concentrations used in vitro are seldom reached in people. Mitochondria-targeted chemistry, using lipophilic cations or cardiolipin-binding peptides, improves localisation but does not solve the problem of tissue-specific exposure.

Species differences and safety: What works in mice has not always worked in humans, and several agents have dual or context-dependent effects, for example SIRT1 in cancer and mitophagy in tumour biology. Aggressive antioxidant or anti-fission therapy could, in theory, disturb physiological ROS signalling and adaptive fission.

Biomarkers: No single marker identifies every senescent cell or every pattern of mitochondrial dysfunction. Blood-based measures such as growth differentiation factor 15, circulating cell-free mtDNA and mitochondrial proteins in extracellular vesicles are being developed as less invasive alternatives to tissue biopsy.^[48]

8. FUTURE PERSPECTIVES

Future development will probably depend on sorting patients by their dominant defect, for example failed biogenesis, imbalanced dynamics or blocked mitophagy, and matching the treatment to it. Multi-omics profiling and non-invasive circulating biomarkers could help with this and would also let treatment response be followed. Combination therapy is a logical step, for instance pairing modulators of metabolic reprogramming with SASP inhibition.[†] Work on the contacts between mitochondria and other organelles, including the endoplasmic reticulum and lysosomes, may reveal further drug targets. Finally, organelle-level therapy and genome editing will need proof of safety and durability in large animals and early human studies.^[4]

9. CONCLUSION

Mitochondrial dysfunction ties together energy failure, oxidative stress, inflammation and cellular senescence, and it offers many targets that drugs could reach. A small number of agents, idebenone above all, have reached regulatory review, and several others have given encouraging early clinical signals. Most promising preclinical findings, though, have not yet been confirmed in humans. Real progress will need better delivery, validated biomarkers, patient stratification and trials built around clinically meaningful end points.

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