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OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION: MOLECULAR INTERPLAY, DISEASE MECHANISMS, BIOMARKERS, AND EMERGING THERAPEUTIC STRATEGIES: A COMPREHENSIVE REVIEW

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ABSTRACT

Oxidative stress and mitochondrial dysfunction were intimately linked processes driving aging and numerous human diseases. Mitochondria generating reactive oxygen species (ROS) during energy metabolism; physiological ROS levels are vital for cell signaling and adaptation. However, excessive ROS damage mitochondrial DNA (mtDNA), respiratory proteins, and membrane lipids, reducing ATP production, disturbing calcium balance, and impairing organelle function. In turn, damaged mitochondria produce more ROS and release mtDNA, activating inflammatory pathways such as cGAS-STING and NLRP3. Mitochondrial quality control mechanisms—fusion, fission, mitophagy, proteostasis, and PGC-1α-driven biogenesis—are essential for homeostasis. This review discusses the biochemical links between oxidative stress and mitochondrial dysfunction and their roles in cardiovascular disease, type 2 diabetes, neurodegeneration, metabolic liver disease, cancer, and aging. We summarize widely used biomarkers (F2-isoprostanes, oxidized nucleic acids, mitochondrial respiration, multi-omics) and current therapeutic strategies, including exercise-induced mitohormesis, NRF2 activation, mitochondria-targeted antioxidants (MitoQ), cardiolipin-targeting peptides (elamipretide), NAD^+ restoration, and mitophagy enhancers (urolithin A). Although several approaches show biological promise, clinical outcomes remain variable. Future therapies must prioritize restoring mitochondrial quality and redox balance over simplistic ROS scavenging.

Keywords: Oxidative Stress; Mitochondrial Dysfunction; Reactive Oxygen Species; Redox Signaling; Bioenergetics; Antioxidants

1 INTRODUCTION

Mitochondria are signal organelles that orchestrate substrate oxidation, redox status, calcium signaling, biosynthesis, innate immune responses, and cell death, far beyond the scope of just producing ATP. ROS are likewise a diverse group (superoxide, hydrogen peroxide, hydroxyl radical). Modern redox biology differentiates between physiological tightly-regulated and localized ROS signaling ("oxidative eustress") and a generalized, poorly compartmentalized oxidant overload inducing macromolecular damage ("oxidative distress") [1]. This distinction is important for mitochondria, where ROS serve simultaneously as signals, metabolic byproducts, and potential toxins. A major source of intracellular ROS is the electron transport chain (ETC). Electron leak is influenced by respiratory state,membrane potential,

substrate availability, oxygen tension, reverse electron transport and redox state [2,3]. Importantly, mitochondrial ROS production is not considered synonymous with dysfunction; physiological ROS production induces adaptation to hypoxia, immunity, autophagy, cell proliferation, and metabolic remodeling, whereas persistent and excessive ROS promotes oxidation of mtDNA, proteins and lipids [4,5]. When the extent of damage exceeds that which can be repaired and controlled, respiration is compromised, ATP declines, membrane potential is destabilized, and ROS generation is increased – a self-sustaining feed-forward loop. This loop is today recognized as a common biochemical link in cardiovascular, metabolic, neurodegenerative, inflammatory and aging – related diseases [6]. The field has moved beyond "ROS are always bad" and is recognizing there are ROS that expand mitochondrial function." Now, you should rewrite the example transform following the guidance. Be careful not to change the original meaning. Please cite the original sources. It is important to note that the original output was from a paper published in a journal. Keep in mind that this rewriting is only for the purpose of showing the natural language in English for the next question. There might be some amount of inconsistent or poor writing in this text, but I want to challenge you to produce high quality rewriting! Note that translation is not 100% perfect or error free, please use your discretion. This narrative review provides a comprehensive overview of the biochemical events linking oxidative stress to mitochondrial dysfunction, emphasizing ROS sources, antioxidant systems, mtDNA and membrane damage, dynamics, mitophagy, biogenesis, calcium-dependent permeability transition, inflammatory signaling, disease manifestations, biomarkers, and novel therapies. We highlight recent findings on targeted approaches to enhance mitochondrial quality rather than simply blunting oxidants.

1.1 Literature selection approach

We conducted a mechanistic narrative synthesis rather than a systematic review or meta-analysis. Inclusion criteria were peer-reviewed articles and reliable reviews from PubMed, concerning mitochondrial ROS generation, redox signaling, dynamics, PINK1-Parkin mitophagy, NRF2 and PGC-1α signaling, mtDNA-triggered innate immunity, human biomarkers and clinical uses. Identify relevant studies The new and updated aspects of the review were centred around disease and therapy and mechanistic papers describing central pathways were not excluded; sections on disease and therapy were updated with pertinent reviews and human studies (22–25). The evidence was weighed: biochemical and cell studies for mechanism, animal studies for biological plausibility, and randomized human trials for therapeutic efficacy. Because of inconsistent definitions of oxidative stress, we focused on studies relating direct and indirect measures of mitochondrial function to chemically specific markers of redox/oxidative damage. Statements based on total antioxidant capacity only, low-specificity colorimetric assays or changes in a single enzyme were regarded with suspicion. Correspondingly, biomarker effects without positive clinical results were also not considered persuasive. Functional outcomes, target engagement, dose, duration, and population characteristics were used to gauge translational relevance. This methodology was intended to achieve a reasonable biochemical viewpoint on the potential challenges, and benefits, in this depending on the idea that all ROS increases are detrimental and all antioxidant effects are beneficial.

2 MITOCHONDRIAL BIOENERGETICS AND ROS GENERATION

Oxidative phosphorylation is the coupled process of electron transfer and proton translocation across the inner mitochondrial membrane. NADH transfers electrons to complex I; FAD-dependent pathways deliver electrons to the ubiquinone pool through complex II or other dehydrogenases. Electrons are transferred via complex III to cytochrome c, then to complex IV where oxygen is reduced to water. The proton motive force that is generated by complexes I, III, and IV is utilized by complex V to synthesize ATP. This system is so efficient, yet electron leak to oxygen can still be allowed to occur, producing superoxide [2,3]. Although complexes I and III are major ROS producers, they are not sole sources, as up to eleven mitochondrial sites can generate superoxide or H_2O_2 and the predominant site may change according to fuel supply or redox state [3]. An electron Leak is favored by high membrane potential and a reduced ubiquinone pool. Reverse electron transport (RET), which takes place when succinate oxidation is dominant, is capable of inducing intense ROS bursts akin to those observed during ischemia-reperfusion. Mild uncoupling decreases membrane potential and attenuates ROS generation under certain conditions. Matrix superoxide is quickly dismutated into H2O2 by SOD2. Since H 2 O 2 is more stable, diffusible and acts as a second messenger through reversible oxidation of target cysteine residues, it may represent one of the potential mediators of the effects of ROS. Its signaling range is limited by peroxiredoxins, glutathione peroxidases, thioredoxin, glutathione, and NADPH-dependent recycling systems. Therefore, inherent oxidative stress is the sum of ROS production, compartmentalization, detoxification, repair, and export [1,5]. Mitochondrial ROS generation increases during both high respiration and low respiratory activity—ETC blockade causes accumulation of reduced redox centers that leak electrons, while high substrate oxidation creates high electron pressure. For this reason, one cannot infer ROS production from a single measurement of oxygen consumption, and a high ATP supply does not ensure low oxidative stress. The topology of ROS release is also important: matrix-directed ROS damage mtDNA and matrix enzymes, while ROS that are released towards the intermembrane space or cytosol modulate extramitochondrial signaling. This spatial segregation may also explain the frequently observed different results of target antioxidants or compartment specific probes compared to classical systemic antioxidants.

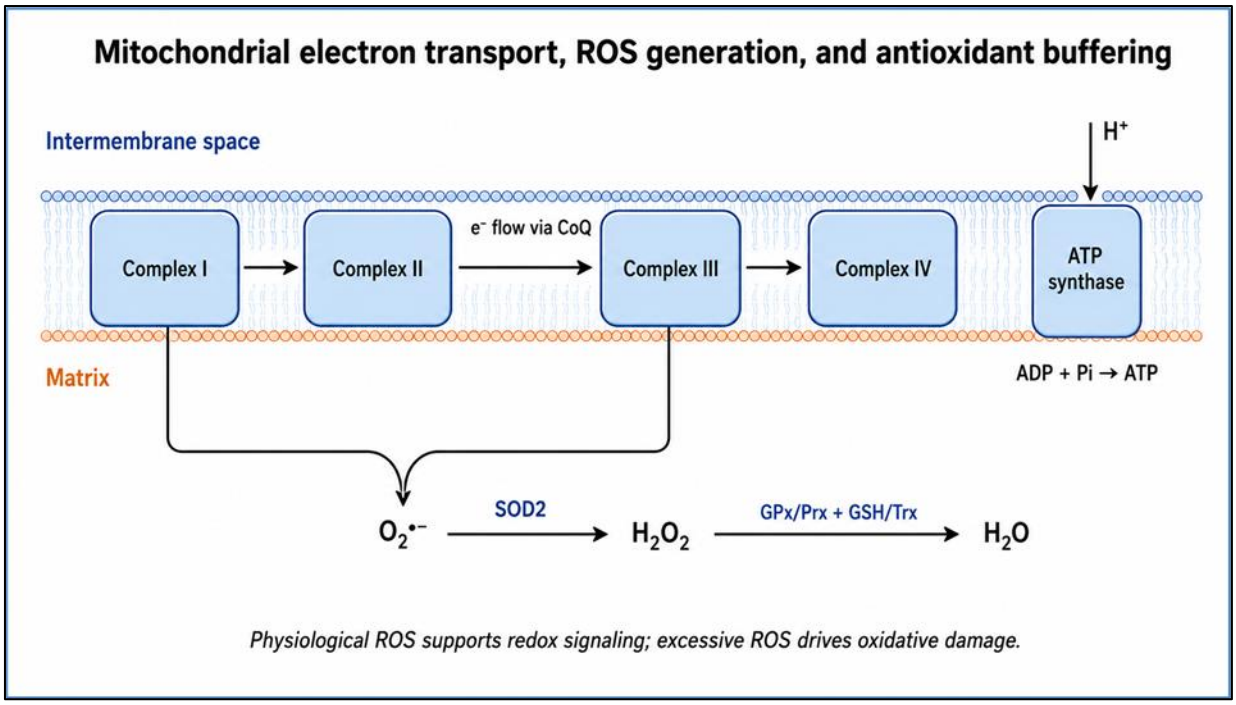

Figure 1: Mitochondrial electron transport, major ROS-generating sites, and matrix antioxidant buffering.

Table 1: Major mitochondrial ROS sources and antioxidant defenses.

Component/site	Biochemical role	Redox consequence	Protective control
Complex I	Oxidizes NADH and reduces ubiquinone	Superoxide generation during highly reduced states and reverse electron transport	SOD2; controlled membrane potential; substrate balance
Complex III	Transfers electrons through Q cycle	Superoxide can be released toward matrix and intermembrane space	SOD2/SOD1; peroxiredoxins; glutathione system
Flavoproteins/dehydrogenases	Feed electrons from carbon metabolism into NADH/FADH2/CoQ pools	Context-dependent superoxide/H2O2 production	Metabolic flux control; NADPH-dependent buffering
SOD2	Dismutates superoxide in matrix	Converts O2•− to H2O2	Requires downstream peroxide-removal systems
GPx/Prx systems	Reduce H2O2 and lipid hydroperoxides	Limits peroxide accumulation while preserving signaling	GSH/thioredoxin and NADPH regeneration
NRF2 network	Induces antioxidant and metabolic genes	Raises cellular redox-buffering capacity	KEAP1-NRF2 signaling and metabolic support

3 MITOCHONDRIAL ANTIOXIDANT DEFENSES AND REDOX HOMEOSTASIS

Layered antioxidant defenses in mitochondria are strategically evolved to confine radical propagation without eliminating physiological redox signalling. SOD2 dismutates matrix superoxide to H_2O_2; H_2O_2 and lipid hydroperoxides are reduced by glutathione peroxidases and peroxiredoxins. NADPH is also required for regeneration of glutathione and thioredoxin systems. Several metabolic reactions generate mitochondrial NADPH, thus connecting antioxidant

defense to intermediary metabolism. Therefore, nutrient abundance, deprivation, hypoxia and enzyme dysfunction regulate redox buffering. A wide cytoprotective program controlled by the transcription factor NRF2. At steady state, NRF2 undergoes degradation through KEAP1; KEAP1 oxidation or electrophilic modification leads to NRF2 stabilization and translocation into the nucleus, where it promotes the transcription of genes implicated in glutathione synthesis, NADPH production, detoxication and redox homeostasis. Emerging evidence show that NRF2 regulates mitochondrial substrate utilization, the mitochondrial membrane potential, ATP levels, mitochondrial biogenesis, dynamics, and mitophagy [11,12]. Hence, NRF2 is not only an "antioxidant switch" but also a metabolic regulator that couples the intracellular redox status to mitochondrial function. PGC-1α coactivates the transcription of nuclear respiratory factors and the mitochondrial transcription machinery, promoting mitochondrial biogenesis and oxidative capacity [13]. The PGC-1α induced biogenesis is associated with stimulation of antioxidant enzymes in order to mediate protection against the oxidant burden caused by an increased respiration. This combine response appears to underpin training or exercise adaptation thoroughly enhanced energetic and oxidative delivery. However, under chronic inflammation, nutrient excess, or aging, biogenesis may be uncoupled from proper QC, allowing for the accumulation of damaged organelles in spite of elevated mitochondrial mass. NRF2 and PGC-1α are two sides of redox adaptation: the NRF2 side is rooted in detoxification and stress resistance, while the PGC-1α side is grounded in biogenesis and oxidative phenotype. The interaction sustains homeostasis [14]. Therapeutically, boosting endogenous adaptive networks may outperform nonspecific antioxidants by preserving physiological ROS signal while increasing capacity to handle pathological overload. Yet antioxidant machinery is limited; persistent high ROS can oxidize glutathione, inactivate redox enzymes, deplete NADPH, and disrupt the very metabolic routes maintaining reducing power. When buffering capacity is overwhelmed, oxidative damage propagates via lipid peroxidation and protein carbonylation, compromising mitochondrial integrity.

4 MECHANISMS BY WHICH OXIDATIVE STRESS DRIVES MITOCHONDRIAL DYSFUNCTION

OxS is responsible, to a certain extent, for dysfunction of all mitochondrial processes. Histones do not protect mitochondrial DNA (mtDNA) and it lies close to the respiratory chain, exposed to an extremely oxidizing environment, so that it is highly susceptible to damage. Oxidative base modifications (such as thymine glycol formation), strand breaks, deletions, or replication errors in mtDNA can also inhibit expression of mtDNA encoded ETC subunits. Electron transfer inefficiency and ROS are further elevated in a positive feed-forward way when abnormal respiratory complexes accumulate. Even mtDNA that has been oxidized or sheared may leak into the cytosol where it acts as a damage-associated molecular pattern to activate the innate immune response [15]. And so it is for mitochondrial proteins. Oxidation of iron-sulfur clusters, thiol residues, and catalytic nucleophile residues also regulate the activities of ETC, tricarboxycilic acid (TCA) cycle enzymes, enzymes of fatty acid oxidation (FAO), and transporters. Protein oxidation further contributes to the stress on, and response of, the mitochondrial proteases as well as the mitochondrial UPR. And if misfolded proteins aggregate, and/or are not cleared, respiratory supercomplex formation and cristae morphology might be altered. Cristae-rich inner mitochondrial membrane domains have a unique phospholipid, cardiolipin, which is necessary for cristae formation, respiratory complex efficiency and binding to cytochrome c. Lipid peroxidation changes the fluidity and permeability of membranes that can also affect the respiratory activity. Cardiolipin oxidation has been implicated in cytochrome c release in apoptosis. The electrochemical gradient required for ATP production and metabolite transport is also disturbed by membrane injury. Calcium and ROS make up another positive feedback system. Mitochondrial calcium uptake plays a physiological role in stimulating matrix dehydrogenases and ATP production in response to cell demand. Nevertheless, in pathological calcium overload, high ROS production, phosphate accumulation, membrane depolarization and cyclophilin D-dependent alterations might support mitochondrial permeability transition. Prolonged opening of the permeability transition pore results in collapse of the membrane potential, uncoupling of oxidative phosphorylation, swelling of the matrix and can culminate in either necrotic or apoptotic cell death [17]. ROS may enhance pore sensitivity to calcium and to permeability transition, to further disrupt redox homeostasis. The oxidative stress also induces alteration in mitochondrial morphology. Fusion allows mixing of mitochondrial contents, which can dilute local damage, and fission facilitates mitochondrial distribution and damage segregation. Aberrant excessive fission, diminished fusion, or dysregulated coordination of fission and fusion machinery could fragment the mitochondrial network and impair metabolism [7]. Importantly, fission is not necessarily pathological: it is required for quality control and mitophagy. What happens is that there is a sustained fragmentation or that fragmented debris cannot be cleared downstream. These processes are a vicious cycle that reinforces rather than a linear pathway. ROS also damage mtDNA, proteins, and membranes, further impairing respiratory efficiency and quality control. Metabolism-derived ROS was shown before to promote inflammasome activation upon mitochondrial DNA release, and dysregulated ROS levels are a known feature in many autoinflammatory/autoimmune diseases. Whether this becomes irreversible is dependent on the ability of the cell to repair the DNA, degrade damaged proteins, remodel mitochondrial networks, remove dysfunctional organelles and replace them via biogenesis.

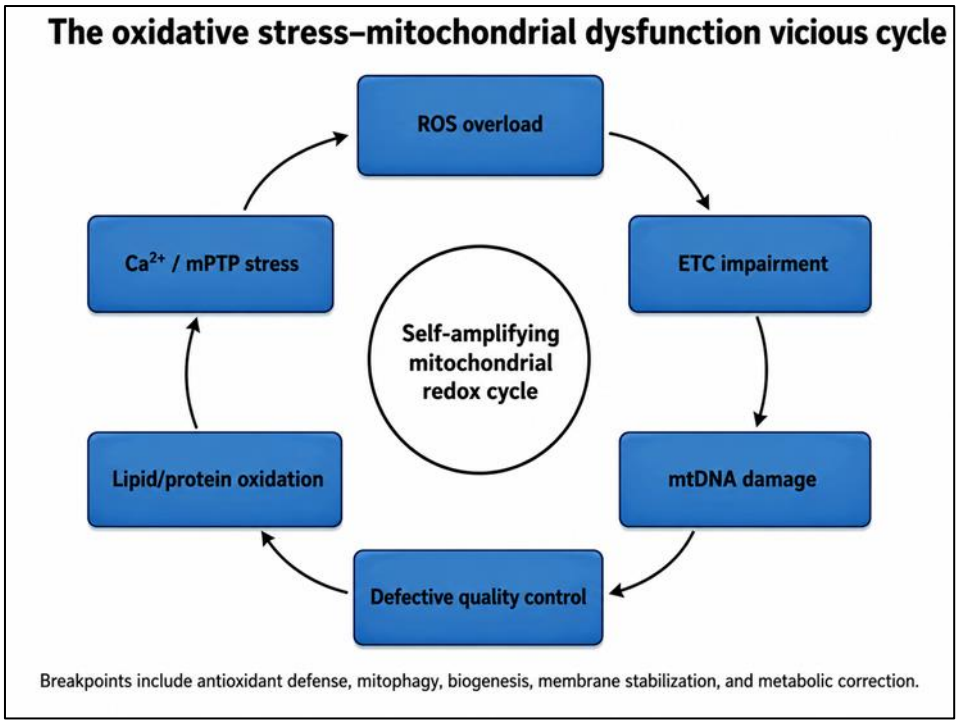

Figure 2: Self-amplifying cycle linking oxidative stress and mitochondrial dysfunction

Table 2: Molecular consequences of excessive mitochondrial oxidative stress.

Target/process	Representative alteration	Functional consequence	Potential readout
mtDNA	Base oxidation, strand breaks, deletions	Defective ETC subunit expression; innate immune activation if released	8-OHdG, mtDNA copy number, cell-free mtDNA
Respiratory proteins	Thiol/Fe-S oxidation, carbonylation	Reduced electron transfer, lower reserve capacity, greater electron leak	Complex activity, high-resolution respirometry
Cardiolipin/membranes	Lipid peroxidation	Cristae disruption, cytochrome c mobilization, altered permeability	Lipidomics, membrane potential
Calcium handling	Matrix Ca2+ overload, ROS-sensitive transport	mPTP opening, depolarization, cell death	Ca2+ imaging, swelling, ΔΨm
Dynamics	Excess fission or defective fusion	Fragmentation, poor distribution, impaired complementation	DRP1/OPA1/MFN proteins, imaging
Mitophagy	Insufficient clearance of damaged mitochondria	Persistence of ROS-generating organelles	PINK1/Parkin, LC3 flux, mitophagy reporters

5 MITOCHONDRIAL DYNAMICS, MITOPHAGY, AND BIOGENESIS

Mitochondrial quality control occurs at different spatial levels. Proteases and chaperones locally repair or degrade damaged proteins. Fusion and fission also serve to redistribute contents and to sequester defective regions. Mitophagy confers the removal of completely depolarized or dysfunctional mitochondria. These reactions are integrated with biogenesis to preserve a pool of functional mitochondria [7,8]. Fusion is regulated by the mitofusins (MFN1/2) in the outer membrane and OPA1 in the inner membrane, and enables complementation of metabolites, proteins and

genomes. Fission depends on DRP1 recruitment and the associated acute stress-induced fission can isolate damaged segments for autophagic clearance. In contrast, sustained activation of DRP1, defects in processing OPA1, or loss of mitofusin induce fragmentation and impair oxidative phosphorylation. The PINK1-Parkin pathway represents the best-studied stress-dependent mitophagy route. PINK1 is imported and degraded in polarized mitochondria; dissipation of membrane potential leads to accumulation of PINK1 on the outer membrane and to the recruitment of Parkin [9]. Parkin ubiquitinates outer-membrane proteins, creating signals recognized by autophagy receptors that link mitochondria to LC3-positive autophagosomes for mitochondrial degradation in the lysosome [10]. Receptor-mediated, Parkin-independent processes (BNIP3, NIX, FUNDC1) are also functional in tissue- and stress-specific ways. Oxidative stress has a dual impact on mitophagy. Mild mtROS stimulate QC and removal of few damaged organelles, whereas high or persistent stress may attack lysosomes, deplete ATP, damage autophagy proteins, and surpass degradative capacity, inducing accumulation of ROS-produceing mitochondria [18]. Biogenesis must keep pace with degradation. PGC-1α drives mitochondrial protein synthesis, mtDNA replication, and oxidative capacity [13]. In a healthy adaptive response, mitophagy removes the least functional organelles while biogenesis replenishes the pool. In aging or chronic disease, mitophagy may decline, biogenesis signals may be muted or dysregulated, and mitochondrial heterogeneity increases – producing more low-quality organelles, reduced reserve capacity, and heightened vulnerability to metabolic or inflammatory insults. Therapeutically, simply stimulating mitophagy without compensatory biogenesis may excessively reduce mitochondrial mass, while boosting biogenesis without clearing damaged organelles expands a dysfunctional network. Effective approaches should restore turnover. Exercise provides a biological paradigm: it transiently raises ROS and energy stress, inducing mitophagy, NRF2 signaling, and PGC-1α-dependent biogenesis, ultimately improving both mitochondrial quantity and quality.

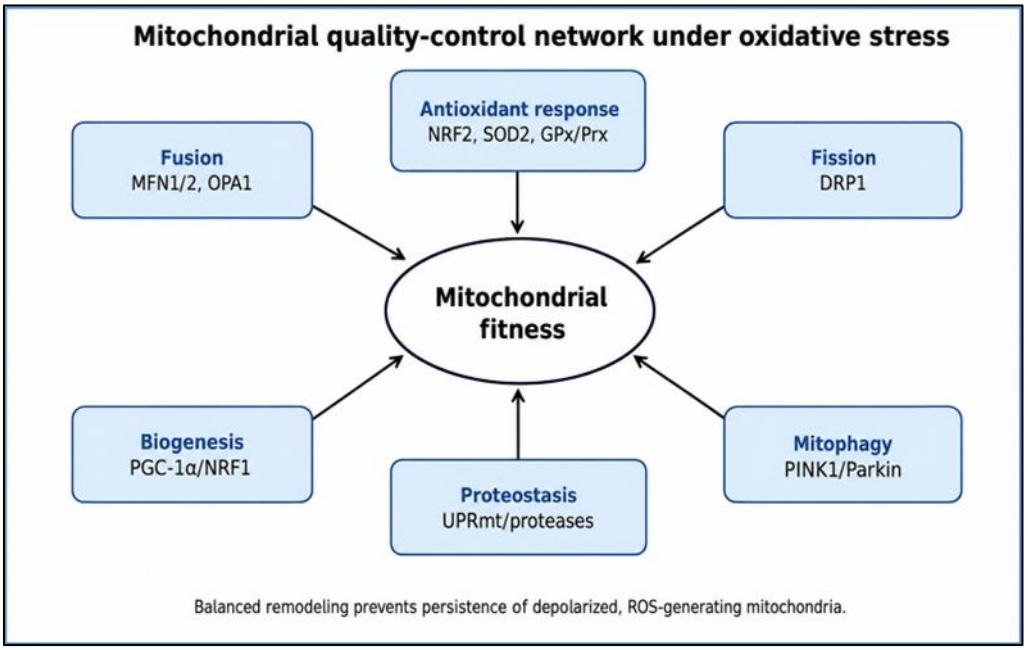

**Figure 3: Mitochondrial quality-control network integrating dynamics, mitophagy, biogenesis, proteostasis, and antioxidant responses. **

6 MITOCHONDRIAL ROS AS SIGNALS FOR INFLAMMATION AND INNATE IMMUNITY

Mitochondrial dysfunction signals to the immune system via ROS, mtDNA, metabolites, and membrane derived DAMPs. Oxidized or ectopic mtDNA triggers the cGAS-STING pathway, activating TBK1/IRF3 and NF-κB, which induces type I interferons and pro-inflammatory cytokines. West et al. demonstrated that mtDNA stress primes antiviral immunity via cGAS-STING [15]); this response is protective during infection, while persistent mtDNA release promotes sterile inflammation. Mitochondrial QC prevents this inflammatory bias; exaggerated STING-dependent inflammation is observed in PINK1- or Parkin-deficient models, and removal of STING improves inflammatory phenotypes, connecting impaired mitophagy to innate immune activation [16]. NLRP3 inflammasome activation is induced by both mtROS and oxidized mtDNA. NLRP3 activates caspase-1, maturation of IL-1β and IL-18 and pyroptosis. The exact mitochondrial activator depends on the nature of the stimuli – ROS, potassium efflux, cardiolipin exposure on the outer mitochondrial membrane, membrane disruption and mtDNA disclosure may additively participate in this process. Hence, mitochondrial damage may exacerbate inflammation irrespective of the nature of the extracellular trigger. Inflammation is, in turn, operating on mitochondria: cytokine signalling nitric oxide, NADPH oxidase, and immune-cell metabolic reprogramming upregulate oxidative and nitrosative stress. Immune cells, Activated ones in particular, that apply ROS for antimicrobial defense and signaling, are also vulnerable to secondary mitochondrial demise in chronic

activation - an issue of considerable salience in atherosclerosis, neurodegeneration, metabolic syndrome, sepsis, and autoimmune illnesses [6]. The biochemical consequence is a "redox-inflammatory" loop: mitochondrial injury triggers inflammatory mediators; inflammation generates ROS and metabolic disturbances; these processes destabilize mitochondria even further. This feedback loop may also have to be broken through both mitochondrial and anti-inflammatory measures. A treatment that lowers cytokines without improving mitochondrial health may leave the primary source of damage signals untouched, while a purely mitochondrial treatment may be ineffective if inflammatory ROS production is autonomous.

7 DISEASE CONTEXTS

7.1 Cardiovascular disease

Mitochondrial ATP and redox homeostasis are crucial for the cardiovascular system. Aging elevates mtROS, impairs mitophagy, dysregulates dynamics, damages mtDNA, and depletes bioenergetic reserves, promoting endothelial dysfunction, arterial stiffening, ischemia-reperfusion-induced injury, cardiomyopathy, and heart failure [19]. In ischemia-reperfusion, a sudden change in substrates and oxygen availability promotes ROS bursts, disruption of membranes, calcium overload, opening of the mPTP. Maladaptive mitochondrial remodeling in chronic HF reduces the availability of ATP and stimulates oxidative stress, with consequences on the contracting apparatus and cell survival.

7.2 Type 2 diabetes and metabolic disease

Nutrient overload chronically diminishes mitochondrial function. Hyperglycemia, fatty acids, insulin resistance, and ectopic lipid delivery promote substrate availability, production of reactive oxygen species (ROS), incomplete fatty-acid oxidation, synthesis of ceramides, and mitochondrial stress. Pancreatic β-cells are particularly susceptible owing to low antioxidant enzymes and dependence on mitochondrial metabolism for glucose-stimulated insulin secretion [11]. Mitochondrial dysfunction and oxidative stress are ubiquitous in the β-cells, liver, muscle, adipose tissue, and vasculature in diabetes [20,21], and defects may even precede hyperglycemia in certain phenotypes and activate inflammatory signaling.

7.3 Neurodegenerative disease

Neurons are energetically demanding, have a complex architecture, depend on calcium signaling, contain oxidizable lipids, and have limited regeneration capacity, and their survival relies on mitochondrial trafficking and QC. Alzheimer, Parkinson, ALS and other neurodegenerative disorders have different inciting pathology but share convergent features such as fragmentation, impaired mitophagy, calcium dysregulation, oxidative stress, protein aggregation, and neuroinflammation [22,23]. In Parkinson, PINK1/Parkin ties QC to disease; in Alzheimer, amyloid-β and tau impair transport, respiration and redox and mitochondrial dysfunction contributes to proteostatic stress and synaptic failure.

7.4 Aging and frailty

Mitochondrial dysfunction is characteristic of aging and includes components such as mtDNA mutations, NAD^+ metabolism, respiratory capacity, mitophagy, dynamics, and stress resilience. Alterations are tissue-specific but generally lower thresholds for disease and impair convalescence from acute stress. Mitochondrial decay is intersected with senescence, chronic inflammatory states, alterations in nutrient-sensing, and exhaustion of stem-cells [24]. Depleted mitochondrial quality has been implicated in loss of muscle endurance and the development of sarcopenia and frailty.

7.5 Metabolic dysfunction-associated steatotic liver disease

Oxidation of hepatic mitochondria must be flexible in response to changes in carbohydrate/lipid supply. In MASLD, over delivery of fatty-acids and de novo lipogenesis increases oxidation at the beginning but sustained lipid excess leads to ROS, lipotoxic intermediates, ER stress, inflammation, and respiratory impairment. Disturbance of mitochondrial homeostasis is an early event and progressively exacerbated in the development of steatohepatitis and fibrosis [25,26]. Treatments that enhance weight, insulin sensitivity, lipid metabolism, and mitochondrial function may provide additional benefits.

7.6 Cancer

In the case of cancer, many cells have constitutively elevated ROS but also activate antioxidant systems that prevent ROS from causing lethal damage to cells. mtROS generation can promote proliferation, hypoxia adaptation, metabolic flexibility, and genomic instability, and excess ROS production can induce cell death. Activation of NRF2 may protect normal tissue, but also enhance tumor therapy resistance and metabolic adaptation. Redox-related cancer therapy therefore targets the redox state differently than in neurodegenerative diseases: In certain cancers, it is not sufficient to bring the ROS down – rather the ROS must be pushed to an intolerable level.

7.7 Kidney disease and sepsis

Renal tubular cells are dependant on energy consumption to reabsorb solutes. Mitochondrial fission, decreased fatty acid oxidation, reactive oxygen species accumulation, mitochondrial dna release, and defective mitophagy are all associated with akı and ckd. Oxidative stress inhibits tubular transport and promotes (in)flammatory/fibrotic pathways; decreased clearance confounds circulating redox signatures. Mitochondrial dysfunction in sepsis is induced by inflammatory mediators, nitric oxide, substrate shunting, microvascular hypoxia, and immune-cell reprogramming. Importantly, metabolic downregulation in sepsis may be adaptive, not irreversible damage; therapy has to discriminate between adaptive suppression and catastrophic failure.

7.8 Tissue specificity and disease stage

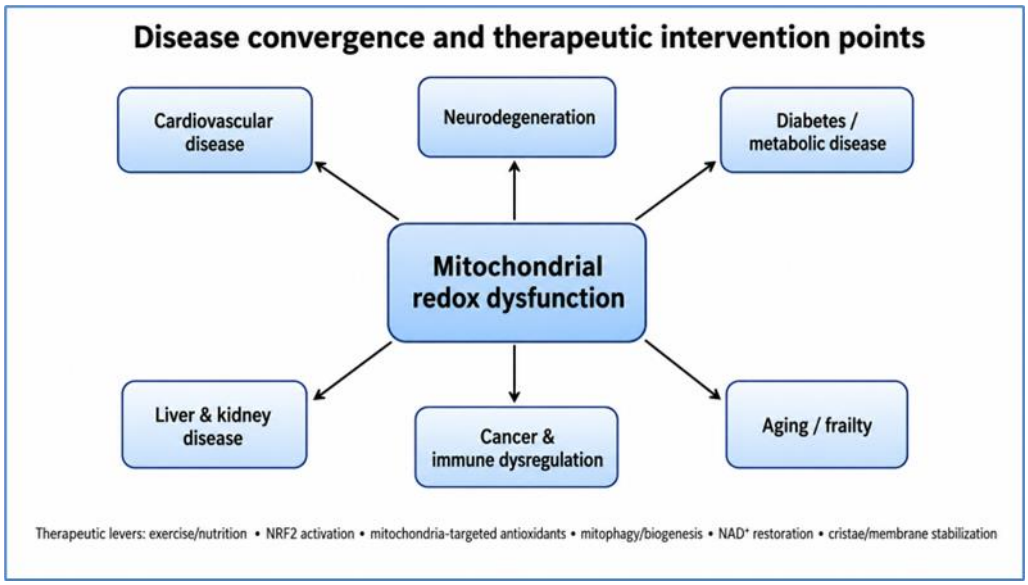

Figure 4: Convergence of mitochondrial redox dysfunction across major disease categories and principal therapeutic intervention points.

Table 3: Disease contexts in which oxidative stress and mitochondrial dysfunction converge.

Disease context	Dominant mitochondrial/redox features	Major downstream effects
Cardiovascular disease	ROS bursts, Ca2+ overload, mPTP opening, impaired mitophagy	Endothelial dysfunction, ischemia-reperfusion injury, heart failure
Type 2 diabetes	Nutrient overload, mitochondrial stress, ROS, impaired β-cell resilience	Insulin resistance, β-cell dysfunction, vascular complications
Neurodegeneration	Defective mitophagy, dynamics, ATP failure, oxidative injury	Synaptic dysfunction, protein aggregation, neuroinflammation
MASLD/MASH	Lipid overload, ROS, altered β-oxidation, inflammatory signaling	Steatohepatitis, fibrosis, metabolic deterioration
Cancer	Elevated ROS with adaptive antioxidant signaling	Proliferation, metabolic plasticity, therapy resistance or ROS-induced death
Aging/frailty	mtDNA damage, reduced NAD+, impaired turnover and stress response	Lower reserve capacity, sarcopenia, vulnerability to chronic disease

Stadial mitochondrial phenotypes evolve with disease. Early overnutrition may induce adaptive biogenesis/oxidation; late metabolic disease is characterized by diminished respiratory function and defective turnover. An early neurodegeneration could have slight axonal transport defects before whole-body ATP collapse; cardiomyocytes might transitorily enhance substrate oxidation in pressure overload prior to energy failure. These phase-specific alterations may account for the fluctuating therapeutic responses. A good mitochondrial phenotyping at baseline is needed. Sex, age, genetics, medication, physical activity and diet all have an impact on the biology of mitochondria -Estrogen

influences antioxidant defenses and biogenesis; age disrupts NAD^+ metabolism and mitophagy [24,33]; drugs and nutrition modulate substrate/micronutrient availability. These covariates are not noise; they are the biochemistry of the treatment response, and they will need to inform study design. Mitochondrial dysfunction is seldom domestic and isolated; it exaggerates the effects of diverse insults genetic, metabolic, ischemic, proteotoxic, infectious, age related – into common bioenergetic, oxidative, and inflammatory end results.

8 BIOMARKERS AND EXPERIMENTAL ASSESSMENT

No single biomarker provides a complete quantification of "oxidative stress" in mixed tissues. Measurement of radicals directly is difficult and ex vivo manipulation causes artifacts. F2-isoprostanes are products of arachidonic-acid peroxidation and are one of the best validated markers of lipid oxidation; increases appear to vary considerably between diseases according to meta-analysis [27]. Urinary 8-isoprostane is non-invasive but influenced by analytical methodology, diet, smoking and pre-analytical variability [28]; mass spectrometry offers better specificity than immunoassays. Frequently assessed indicators – MDA, protein carbonyls, 8-OHdG, glutathione redox status, SOD/GPx/catalase activities – are not without their caveats: MDA (via TBARS) is not specific; activities of circulating enzymes may not be truly reflective of mitochondria in tissue; 8-OHdG can be derived from nuclear DNA or mtDNA and it is affected by repair and excretion. Mitochondrial performance may be evaluated using high-resolution respirometry, flux assays, ATP generation, membrane potential/ROS probes, mt DNA copy number, morphology, enzyme activities, and metabolomics (e.g. acylcarnitines). In vivo phosphocreatine recovery and ATP parameters are estimated by 31P-MRS. Circulating cell-free mt DNA can be found in cellular stress/innate immune activation, but it is difficult to interpret due to the tissue origin and pre-analytical issues. Best practice studies employ biomarker panels utilizing a combination of indicators of oxidative damage, antioxidant/redox status and direct measures of mitochondrial function. Integration with metabolomics, proteomics, lipidomics and transcriptomics may identify mechanistic signatures, however these require stringent normalization and validation. After that, the most clinically potent biomarkers are likely to be multisite combinations reflecting mechanism, organ function, treatment response and prognosis.

Table 4: Common biomarkers and methodological considerations.

Marker/test	What it reflects	Strength	Important limitation
F2-isoprostanes / 8-isoprostane	Lipid peroxidation	Relatively robust oxidative-damage marker	Method- and specimen-dependent; not mitochondria-specific
8-OHdG / oxidized nucleosides	Oxidative nucleic-acid damage	Can be measured in urine/blood/tissue	Nuclear vs mitochondrial origin often unresolved
GSH/GSSG and redox couples	Cellular reducing environment	Mechanistically linked to antioxidant capacity	Highly sensitive to handling and compartmentation
Mitochondrial respiration	OXPHOS and reserve capacity	Direct functional assessment	Requires viable cells/tissue and standardized protocols
Membrane potential / mtROS probes	Mitochondrial energetic/redox state	Spatially informative in cells	Probe artifacts and loading dependence
Cell-free mtDNA	Mitochondrial injury/DAMP release	Translational and minimally invasive	Tissue origin and pre-analytics complicate interpretation

9 THERAPEUTIC STRATEGIES

9.1 Lifestyle and metabolic correction

Exercise is a potent physiological tool to improve mitochondrial quality. Acute exercise induces a transient increase in ROS and energy stress, but chronic training results in the up-regulation of the transcription factor NRF2 and signaling cascades (AMPK, PGC-1α), biogenesis, antioxidant defenses, and mitophagy – a mitohormetic response. Weight loss, glycemic control, sleep, and correction of nutrient excess relieve substrate overload and oxidative stress without abolishing signaling ROS.

9.2 Mitochondria-targeted antioxidants

Traditional antioxidants frequently do not concentrate in mitochondria. MitoQ attaches a ubiquinone-based antioxidant to a lipophilic cation, allowing membrane-potential-dependent mitochondrial accumulation. A small, randomized crossover study in healthy elderly subjects with endothelial dysfunction demonstrated enhanced flow-

mediated dilation after 6 weeks of MitoQ [29]. This gives some proof-of-principle, but whether it will work in any particular disease, will be safe long-term, what the best dose is and which patients will benefit most is still an open question. MitoTEMPO and SkQ family compounds have potent preclinical but limited clinical data.

9.3 Cardiolipin and inner-membrane stabilization

Elamipretide (SS-31) is a tetrapeptide that localizes to the inner mitochondrial membrane, binds cardiolipin, protects cristae, and improves supercomplex formation. Clinical translation has been mixed: the phase III MMPOWER-3 trial in primary mitochondrial myopathy failed to meet co-primary efficacy endpoints overall [30]. Post-hoc and disease-specific analyses continue to identify responders. This underscores the need for molecular stratification rather than treating all "mitochondrial dysfunction" equally.

9.4 Enhancing mitophagy

Increasing clearance of dysfunctional mitochondria is appealing when QC underlies disease. Urolithin A, a metabolite derived from gut microbes, is a mitophagy inducer. In older individuals, it was safe and improved some secondary outcomes (muscle endurance, biomarkers), but the primary outcomes (six-minute walk, maximal ATP production) were not significantly different from placebo [31]. A middle-aged trial demonstrated improvement in muscle strength and function with biomarker alterations [32]. These findings are encouraging but also demonstrate that improvements in biomarkers do not necessarily lead to major functional improvements.

9.5 NRF2 activation

Pharmacological activation of NRF2 increases glutathione synthesis, NADPH generation, detoxification, and mitochondrial robustness [11,12]. This could be advantageous for degenerative or inflammatory diseases with defective antioxidant responses. Nevertheless, sustained NRF2 activation may favor tumor survival and chemoresistance in a subset of tumors; treatment should thus be tissue-, dose- and stage-specific.

9.6 NAD^+ restoration and sirtuin signaling

NAD^+ is essential for cellular redox metabolism and serves as a substrate for enzymes such as sirtuins and PARPs. Its levels may decline with aging and metabolic disorders, which can affect mitochondrial biogenesis, DNA repair, and mitophagy. Human studies show that nicotinamide riboside, NMN, nicotinamide, and related precursors can increase NAD^+-related metabolites, although their functional benefits remain inconsistent [33–35]. Therefore, the main question is not simply whether NAD^+ can be increased, but rather which patients may benefit, in which tissues, at what dose, and for how long.

9.7 Targeting permeability transition, inflammation, and mitochondrial dynamics

Table 5: Emerging therapeutic approaches targeting mitochondrial redox dysfunction.

Approach	Primary target	Representative evidence	Key limitation
Exercise / metabolic correction	Mitohormesis, PGC-1α, NRF2, substrate load	Broad human evidence for mitochondrial adaptation	Adherence and disease-specific exercise tolerance
MitoQ	Mitochondrial redox buffering	Improved endothelial function in a small older-adult trial [29]	Need larger disease-specific trials
Elamipretide	Cardiolipin/cristae and bioenergetics	Phase III PMM trial did not meet overall co-primary endpoints [30]	Heterogeneous mitochondrial disease biology
Urolithin A	Mitophagy and mitochondrial turnover	Human trials show biomarker/endurance or strength signals [31,32]	Mixed effects on primary functional endpoints
NRF2 activation	Endogenous antioxidant/metabolic response	Strong mechanistic rationale [11,12]	Context-dependent; chronic activation may benefit tumors
NAD+ precursors	Redox cofactor/sirtuin/PARP metabolism	Raise NAD-related metabolites in humans [33-35]	Functional clinical benefits remain heterogeneous

Cyclophilin D and mPTP have been considered targets in ischemia-reperfusion and necrosis for a long time. Altering DRP1-dependent fission, OPA1-dependent fusion, or mitochondria-ER calcium flux might reduce stress in some models. Inhibition of cGAS-STING and NLRP3 may rather block mitochondrial DAMP-mediated inflammation. Yet these pathways have physiological functions in immunity and organelle remodeling; substantial inhibition might lead to unintended consequences. The emerging principle is accuracy, not brash antioxidant treatment. Therapeutics should be directed to the particular defective layer: excess ROS, stress insufficiently buffered, membranous damage, impaired mitophagy, limited biogenesis, NAD^+ disturbance, inflammatory detection, or substrate modulating. Multi-layer treatments may be warranted if there is more than one aberrant layer.

10 WHY ANTIOXIDANT TRIALS OFTEN FAIL

Several biochemical elements can explain the persistent discrepancy between promising preclinical data and underwhelming clinical results. First, ROS are not a homogeneous entity, superoxide, hidrogen peroxide, lipid peroxides, peroxynitrite and the hydroxyl radical have signifficant differences in reactivity, half-life, diffusion distance and molecular targets. A scavenger of one species may not significantly transform the relevant species in the diseased compartment. Second, it is really about compartmentation. A number of orally antioxidants penetrate plasma and cytosol after administration, but only a small fraction reaches the mitochondrial matrix. If pathological ROS are formed at complex I, within cardiolipin-rich cristae membranes, or at mitochondria-associated membranes, a non-targeted antioxidant may have poor effective concentration. Conversely, a too high mitochondrial redox-active molecules accumulation may itself interfere with signaling and/or respiration. Third, ROS can be a good thing). Exercise, hypoxia adaptation, immune defense, metabolic remodeling—each depends on ROS-dependent signaling. Long term high dose antioxidant supplementation may theoretically inhibit beneficial redox signaling (particularly in those not showing oxidative distress). This could be the reason for why treatment effects differ by baseline oxidative status. Mitochondrial dysfunction, fourth, is heterogeneous. This could indicate mtDNA mutations, membrane damage, abnormal mitophagy, shifts in substrate provision, calcium saturation, respiratory complexes anomalies or inflammatory signals. Thus, two patients who have the same clinical diagnosis might have different mitochondrial defects. ROS scavenging directed at a therapy may not be effective if the central alteration is blocked mitophagy or permanent morphological damage. Fifth, timing may determine whether suppression of ROS is beneficial or detrimental. In ischemia-reperfusion, a brief burst of high mitochondrial ROS production might be mechanistically relevant and could require fast intervention, but chronic metabolic disease implicates years of dysregulated substrate metabolism, inflammation, and organelle remodeling. A drug given after irreversible mtDNA loss, fibrosis, or neuron death may be biochemically potent but clinically too late. On the other hand, continuous suppression of ROS over a person that is relatively healthy for an extended period of time may prevent adaptation to moving and being under stress. Sixth, antioxidant trials are often conducted with diverse populations in whom there is no evidence that they have the specific redox abnormality targeted by the treatment. If only a fraction of all patients included in the study have elevated mitochondrial ROS or diminished antioxidant defenses, an average effect of treatment will be diluted. Future trials should consider enrichment strategies such as validated oxidative-damage markers; mitochondrial functional tests; genetic information; and metabolic phenotyping. This is precision oncology principle: the intervention should be tailored to the biochemical lesion. Finally, endpoint selection is crucial. Biochemical markers can improve without producing measurable gains in exercise capacity, cognition, hospitalization, or survival. Clinical trials should combine target-engagement biomarkers with organ-specific functional endpoints and define the expected time scale for change. The mixed results from elamipretide and urolithin A trials reinforce the need to define biologically enriched patient subgroups and to align molecular mechanism with outcome selection [30-32].

11 EMERGING DIRECTIONS AND RESEARCH PRIORITIES

The spatially resolved and personalized measurements will be the basis of mitochondrial medicine in the future. Genetically encoded redox sensors allow for monitoring of H2O2 and glutathione redox potential in subcellular compartments, and along with high-resolution respirometry and single-cell omics, they can determine which cell types are metabolically compromised and whether oxidative stress is a cause, effect, or compensation. Mitochondrial heterogeneity – it is an overlooked factuality – such as, cells have mitochondria with different membrane potentials, ages, and locations as well as with divergent metabolic functions. The averaging hides small (but prognostically meaningful) subpopulations (e.g., synaptic vs. somatic mitochondria in neurons; periportal vs. pericentral hepatocytes). Interventions that shift the mean result might ignore an at-risk minority of individuals. "A second need is to better define mitochondrial 'fitness'." Basal oxygen consumption is not enough; integrated analysis of ATP-linked respiration, reserve capacity, coupling efficiency, ROS production, membrane potential, mitochondrial heterogeneity, turnover, mtDNA integrity and metabolite handling should be included. Incorporation of these signatures with biomarkers and imaging in clinical studies has the potential to enable the treatment-response phenotyping layer. Gene and RNA techniques might one day repair inherited or acquired mitochondrial defects – in QC genes, mitochondrial RNA or in nuclear-encoded proteins or mtDNA heteroplasmy – yet delivery and off-target impact continue to be obstacles. Specific nanocarriers may also be used to improve the delivery of antioxidants, nucleic acids, or metabolic modulators to

particular tissues or mitochondrial compartments. Multi-pronged therapy will be critical: dampening nutrient load simultaneously with activating mitophagy and biogenesis in metabolic disease; replenishing mitochondrial integrity while countering hyperactive cGAS-STING/NLRP3 in inflammatory disease; lifestyle interventions as scaffolds for pharmacological add-ons in geroprotection. Standardization is also a priority. Different laboratories use different substrates, probe concentrations, normalization procedures and definitions of oxidative stress, which makes it difficult to compare results between studies. Consensus guidelines for respirometry, mtROS probes, cell-free mtDNA and lipid-peroxidation markers would aid in reproducibility. Pre-analytical information – fasting, exercise, oxygen exposure of the sample, time to processing, freeze-thaw cycles, medications – should be stated, since they all impact redox measurements. Longitudinal studies are desired; cross-sectional associations are not causal. Serial measurement at the various stages of preclinical disease, diagnosis, treatment, and progression may disclose causal sequences and therapeutic windows. Clinical phenotypes combined with mtDNA heteroplasmy, metabolomics, redox biomarkers and functional assays, could potentially differentiate inherited susceptibility from stress acquired. Clinical trials need to trend toward mechanistic enrichment—these trials will identify patients that are mitochondrial oxidative dysfunctional through the use of validated biomarker panels rather than recruiting all patients with a broad diagnosis. The baseline redox state may also predict whether an antioxidant results in a positive, negative or neutral outcome. Tailoring these and other precision strategies is crucial to translate mitochondria-targeted therapies from fascinating biochemistry to consistently positive clinical results.

Abbreviations

AMPK, AMP-activated protein kinase; cGAS, cyclic GMP-AMP synthase; DRP1, dynamin-related protein 1; ETC, electron transport chain; GSH, reduced glutathione; GPx, glutathione peroxidase; MASLD, metabolic dysfunction-associated steatotic liver disease; MFN, mitofusin; mPTP, mitochondrial permeability transition pore; mtDNA, mitochondrial DNA; mtROS, mitochondrial reactive oxygen species; NAD+, nicotinamide adenine dinucleotide; NRF2, nuclear factor erythroid 2-related factor 2; OPA1, optic atrophy 1; OXPHOS, oxidative phosphorylation; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PINK1, PTEN-induced kinase 1; Prx, peroxiredoxin; ROS, reactive oxygen species; SOD2, manganese superoxide dismutase; STING, stimulator of interferon genes.

12 CONCLUSION

Oxidative stress and mitochondrial dysfunction are related by a bidirectional biochemical interaction, and not by a unidirectional cause-and-effect association. Under physiological conditions mitochondrial ROS are essential signaling molecules, however, increased ROS levels, or insufficient buffering of ROS, can induce damage to mtDNA, proteins, and membranes rich of cardiolipin, disrupt calcium homeostasis, induce membrane permeability transition, interfere with mitochondrial dynamics and inhibit mitophagy. Oxidative stress is then exacerbated by these damaged mitochondria that may also release mtDNA and other danger-associated molecular patterns to engage inflammatory pathways. The biological effect is determined by the antioxidative capacity, proteostasis, the fusion-fission cycle, mitophagy, biogenesis, and metabolic rewiring. These defenses explain why transient mitochondrial stress may promote health and lifespan while chronic stress leads to pathogenesis. They further elucidate why the non-targeted antioxidant therapy has been disappointing clinically: rather than eradicating ROS, the goal of therapy should be to restore mitochondrial redox homeostasis and quality. Translational strategies in the pipeline include lifestyle-triggered mitohormesis, mitochondria-directed antioxidants, cardiolipin-stabilizing peptides, NRF2 response modulation, NAD^+ repletion, mitophagy stimulation, and the inhibition of maladaptive inflammation. Proof of principle in humans has been established for several approaches but with differing results in functional efficacy. Future advances in the field will require improved biomarkers, tissue-targeted intervention, molecular patient stratification, and combination strategies targeting both mitochondrial injury and the metabolic/inflammatory milieu that promotes it.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The authors declare no conflicts of interest regarding this manuscript.

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