Signal Transduction and Targeted Therapy www.nature.com/sigtrans

REVIEW ARTICLE OPEN

Mitochondrial quality control in health and disease: mechanisms and therapeutic targets

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Mitochondria are essential for cellular homeostasis, integrating various signals to control key cellular functions such as metabolism, apoptosis, inflammation, cell proliferation and redox balance. Given their multifaceted functions, it is not surprising that mitochondrial dysfunction has been implicated as a key contributor to the pathogenesis of numerous human diseases. Consequently, preserving mitochondrial integrity and functionality is vital for overall organismal health. Mitochondrial health is safeguarded by a sophisticated and tightly regulated network of quality control systems. These include mitochondrial proteostasis, which ensures proper protein folding and degradation; mitochondrial biogenesis, which governs the synthesis of new mitochondria; mitochondrial dynamics, encompassing fusion and fission processes; and mitophagy, the selective autophagic removal of damaged mitochondria. Additionally, these core systems are intricately connected to other crucial mitochondrial processes, such as the maintenance of mitochondrial DNA integrity, the regulation of cristae architecture, and the control of mitochondrial permeability transition, all of which are indispensable for optimal mitochondrial performance. Preclinical and clinical studies consistently demonstrate a strong link between impairments in these quality control mechanisms and both aging and the development of a wide spectrum of diseases. These include cancer, metabolic disorders, cardiovascular conditions, neurodegenerative diseases and autoimmune pathologies. In this review, we explore the different facets of mitochondrial quality control and discuss their implications in disease progression and aging. Furthermore, we highlight recent advances in interventions and therapies aimed at modulating mitochondrial quality control, providing an overview of their potential to mitigate disease burden and promote healthy aging.

Signal Transduction and Targeted Therapy (2026)11:295 ; https://doi.org/10.1038/s41392-026-02813-2

INTRODUCTION

Mitochondria are indispensable and highly specialized organelles that perform a broad range of crucial roles in the cell. While best known for generating energy through oxidative phosphorylation (OXPHOS), their functions extend far beyond ATP generation. Mitochondria act as critical hubs for calcium buffering and signaling, integrate and regulate numerous metabolic pathways, govern intrinsic apoptosis, and participate actively in innate immune responses. These diverse activities underscore the complex, dynamic, and multifaceted nature of mitochondrial biology.

Given their centrality to cellular homeostasis, mitochondria are continuously exposed to metabolic, environmental, and physiological stresses that can compromise their function and ultimately threaten cellular health. To mitigate these risks, cells have evolved an intricate network of mitochondrial quality control (MQC) mechanisms tailored to monitor, repair, and, when necessary, eliminate damaged mitochondrial components. These MQC pathways operate at multiple levels, spanning molecular chaperones and proteases that maintain proteostasis, mechanisms of fusion and fission that segregate dysfunctional mitochondrial segments, mitophagy pathways that selectively remove damaged mitochondria and mitochondrial biogenesis programs that replenish the organellar population.

Mitochondrial dysfunction is a hallmark of aging and a major contributor to numerous age-related pathologies.[1] Importantly, disruptions in MQC mechanisms are implicated in aging and in various human diseases.[2–4] Consequently, unraveling the molecular mechanisms governing MQC has become a major focus in the fields of cellular biology, aging research, and disease pathogenesis. Defects in individual MQC components—ranging from dysregulated mitochondrial dynamics to impaired mitophagy—have been implicated in a wide spectrum of human diseases, including neurodegenerative disorders, metabolic and cardiovascular diseases, cancer, and autoimmune conditions. However, despite substantial progress in understanding individual MQC pathways, the full extent of their contributions to disease onset, progression and severity remains incompletely understood. Furthermore, the interplay among the various MQC mechanisms and how cells integrate these pathways in response to distinct stressors continue to be an area of active investigation.

The goal of this review is to provide a comprehensive and integrative overview of the current understanding of MQC mechanisms. We will summarize the major molecular pathways

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Received: 12 May 2025 Revised: 29 January 2026 Accepted: 13 May 2026
Published online: 29 July 2026

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that preserve mitochondrial integrity, including proteostasis systems, organelle dynamics, mitophagy, and biogenesis. In addition, we will discuss the implications of MQC in health and various disease contexts, such as metabolic syndrome, cardiovascular dysfunction, malignant transformation, neurodegenerative diseases, autoimmune disorders, and the aging process. Finally, we will examine emerging therapeutic strategies aimed at modulating MQC to prevent or ameliorate disease. By consolidating knowledge across these areas, this review aims to illuminate the central importance of MQC in maintaining cellular and organismal health and to identify potential avenues for clinical intervention.

MITOCHONDRIAL QUALITY CONTROL MECHANISMS

As essential organelles in maintaining cellular homeostasis, mitochondria require constant surveillance to ensure their proper functioning. MQC involves a diverse array of coordinated pathways operating at the molecular, organelle and cellular levels (Figs. 1–3). These pathways are activated depending on the type and severity of damage.[5] The key components of the MQC system are detailed below.

Mitochondrial protein quality control

Mitochondrial proteostasis (protein homeostasis) is essential for cellular function, energy production and signaling.[6] Given their central role in bioenergetics and metabolism, mitochondria require a tightly regulated balance of protein synthesis, folding and degradation to prevent dysfunction.[7] To achieve this proteostatic balance, mitochondria rely on specialized import and folding mechanisms (Fig. 1a). As nearly all mitochondrial proteins are encoded by the nuclear genome, they must be correctly imported into the mitochondria and then folded and assembled into functional complexes. The complex architecture of the mitochondrion, comprising the outer membrane, intermembrane space, inner membrane and matrix, necessitates precisely regulated mechanisms for protein import and assembly. Specialized translocase complexes, including the translocase of the outer membrane (TOM) and translocase of the inner membrane (TIM) complexes, manage protein import and assembly. The TOM complex serves as the primary entry point for nearly all nuclear-encoded mitochondrial proteins, whereas the TIM complex transports them to the mitochondrial matrix or inserts them into the inner membrane. For a more detailed view of mitochondrial protein import mechanisms and regulation, we refer to excellent reviews in the field.[8,9] Once inside the mitochondria, proteins are folded, assembled or degraded. At this step, MQC involves chaperones to assist with protein folding and proteases to degrade misfolded proteins.[10]

Mitochondrial chaperones play a vital role in maintaining proper mitochondrial function by ensuring correct protein folding, preventing aggregation and refolding misfolded proteins (Fig. 1a). Key players include the heat shock protein Hsp60/Hsp10 chaperonin complex in the matrix, which encapsulates unfolded or partially folded proteins and promotes their proper folding within a protected environment through an ATP-dependent mechanism.[11] Other chaperones, such as mitochondrial Hsp70 (mtHsp70), assist in protein translocation and folding upon import. mtHsp70 binds newly imported polypeptides, stabilizing and guiding them to their final destinations within the matrix or inner membrane, working in concert with the presequence translocase-associated motor (PAM).[12] In yeast, Hsp78 assists in refolding aggregated proteins under heat stress, working alongside Hsp70.[13] In the intermembrane space, small TIM chaperones ferry hydrophobic proteins with internal targeting sequences through the aqueous environment, preventing their release into the aqueous phase.[9] Small TIM chaperones are heterohexameric complexes that can be soluble (Tim9-Tim10 complex) or bound to the IMM (Tim9-Tim10-Tim12 complex). Critically, under conditions of cellular stress, mitochondrial chaperones not only support proper folding but also cooperate with MQC systems, directing irreversibly misfolded proteins for degradation. This prevents aggregation and preserves mitochondrial health.[10]

Mitochondrial protein quality control relies heavily on ATPases associated with diverse cellular activities (AAA+ proteases). These proteases reside in various mitochondrial compartments (Fig. 1a). Within the inner mitochondrial membrane (IMM), two permanently anchored AAA+ proteases, intermembrane space-AAA (i-AAA) and matrix-AAA (m-AAA), oversee protein turnover. The i-AAA protease, facing the intermembrane space, degrades unstable proteins at this location, whereas the m-AAA protease, with its active site facing the matrix, assists in assembling mitochondrial ribosomes and degrading nonassembled proteins.[14] i-AAA proteases form homo-oligomeric assemblies of Yme1 in yeast or Yme1-like ATPase (YME1L) in humans, whereas m-AAA proteases are hetero-oligomers of two subunits, Yta10 and Yta12 in yeast, or AFG3 ATPase family gene 3-like 2 (AFG3L2) and paraplegin in humans.[15] In the mitochondrial matrix, two other AAA+ proteases, LON peptidase 1 (LONP1) and caseinolytic mitochondrial matrix peptidase (ClpXP), primarily degrade oxidatively damaged proteins.[16,17] While the outer mitochondrial membrane (OMM) lacks dedicated proteases, it utilizes the ubiquitin–proteasome system to regulate its protein landscape. Outer membrane-bound ubiquitin ligases, such as membrane-associated ring-CH-type finger 5 (MARCH-V/MITOL) and mitochondrial ubiquitin ligase activator of NF-κB (MULAN), tag specific proteins for degradation, maintaining proteome stability.[18] The ubiquitin–proteasome system also influences protein management across mitochondrial compartments by controlling precursor stability in the cytosol,[19] highlighting its broader role in mitochondrial protein homeostasis.

Mitochondrial proteases not only degrade proteins and maintain quality control but also coordinate various MQC mechanisms. For example, YME1L works with the metalloprotease overlapping proteolytic activity with m-AAA protease 1 (OMA1) to cleave the mitochondrial dynamin-like GTPase, optic atrophy 1 (OPA1), a protein crucial for mitochondrial fusion, leading to mitochondrial fragmentation.[20] Importantly, stress can activate OMA1, which then cleaves the signaling peptide of DAP3-binding cell death enhancer 1 (DELE1), producing a short form. This truncated form accumulates in the cytosol and triggers the integrated stress response.[21,22] Additionally, two mitochondrial proteases, mitochondrial processing peptidase (MPP) and presenilin-associated rhomboid-like protease (PARL), are involved in mitophagy by processing and further degrading PTEN-induced kinase 1 (PINK1).[23]

Mitochondrial unfolded protein response

The mitochondrial unfolded protein response (mtUPR) is a transcriptional pathway activated in response to a wide range of mitochondrial stresses, including reactive oxygen species (ROS), protein import failure, blocked mitochondrial translation, mitochondrial DNA (mtDNA) depletion, electron transport chain impairment, and mito-nuclear protein imbalance (Fig. 1b). The mtUPR restores mitochondrial function by increasing the expression of nuclear-encoded chaperones and proteases involved in protein folding and degradation.[24] While initially characterized in mammalian cells,[25] the molecular components of the mtUPR have been extensively studied in *Caenorhabditis elegans*. In worms, the protease caseinolytic protease P (CLPP-1) is thought to detect and degrade misfolded or damaged mitochondrial proteins, generating oligopeptides that are then exported to the cytosol by the matrix peptide exporter HAF-1, activating the mtUPR.[26,27] Activating transcription factor associated with stress-1 (ATFS-1) is the primary messenger of mitochondrial stress to the nucleus in worms.[28] ATFS-1 contains both a nuclear localization sequence

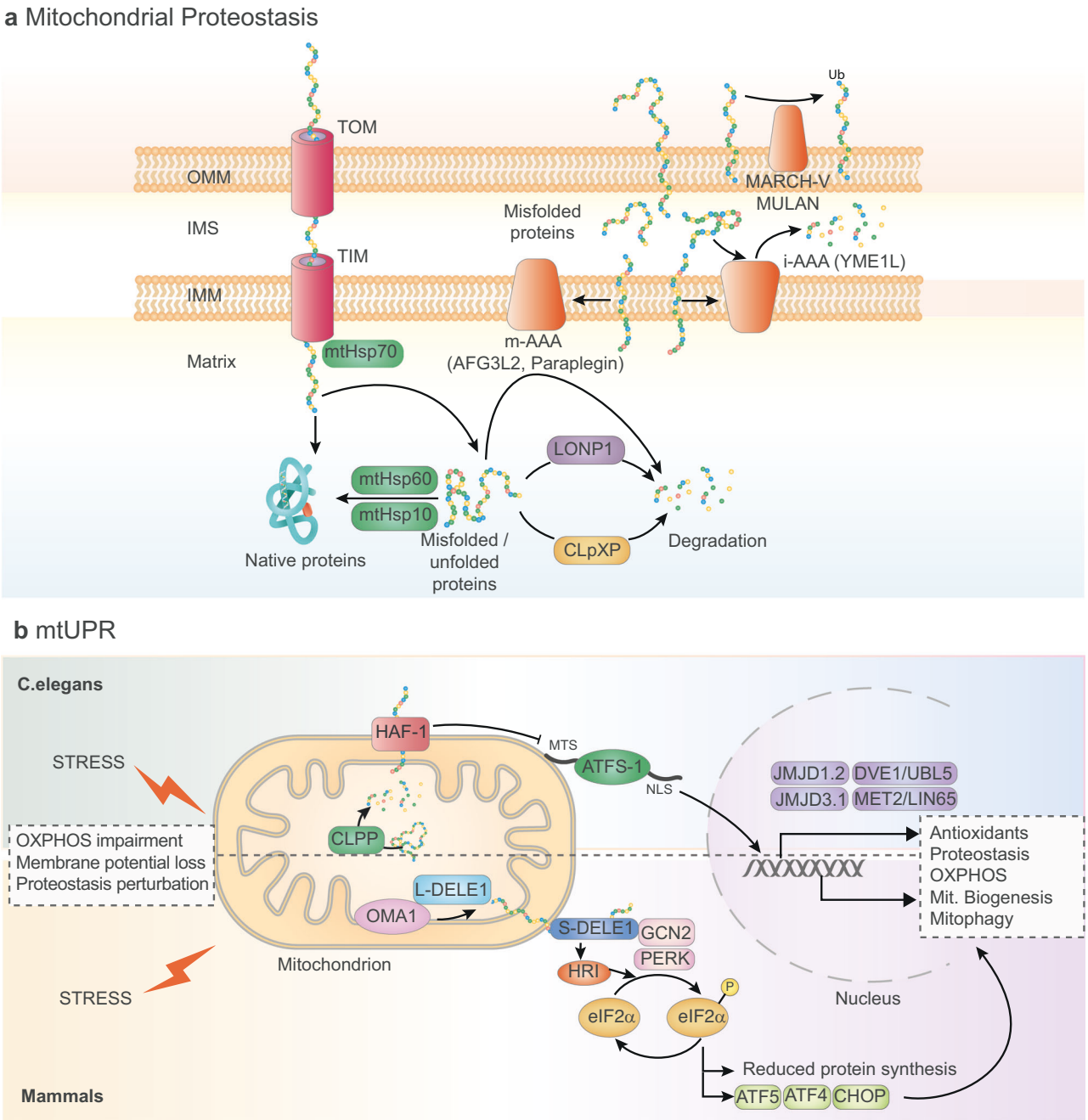


Fig. 1 Mitochondrial quality control mechanisms at molecular level. **a** Mitochondrial proteostasis. Nuclear-encoded mitochondrial proteins enter mitochondrial transported by TOM and TIM complexes, and mtHSP70 assists in their folding upon transportation. The mtHSP60/mtHSP10 chaperonin complex encapsulates unfolded or partially folded proteins and promotes their proper folding. Misfolded proteins that cannot be refolded are degraded by mitochondrial proteases such as LONP1 and ClpXP in the matrix, and m-AAA or i-AAA proteases are located in the inner mitochondrial membrane. Ubiquitin ligases such as MARCH-V and MULAN target outer mitochondrial membrane proteins for proteasomal degradation. **b** Mitochondrial UPR (mtUPR). In *C. elegans*, CLPP detects and degrades misfolded or damaged proteins, and the peptides generated are transported to the cytosol by HAF-1, activating the nuclear localization of ATFS-1, which, together with the action of the histone demethylases JMJD1.2 and JMJD3.1 and the transcription factors DVE-1/UBL-5 and MET-2/LIN-65, activates the transcription of a subset of genes to restore mitochondrial health. In mammals, mtUPR is activated by the phosphorylation of eIF2α by the action of different kinases (HRI, GCN2 and PERK). This leads to increased translation of ATF5, ATF4 and CHOP, which triggers the expression of genes involved in mitochondrial homeostasis

and a mitochondrial-targeting sequence. Under basal conditions, the mitochondrial-targeting sequence directs ATFS-1 to the mitochondria, where it is quickly degraded by LONP1. However, mitochondrial stress impairs protein import, causing ATFS-1 to accumulate in the cytosol. The nuclear localization sequence then directs ATFS-1 to the nucleus, where it activates genes that restore mitochondrial health (mitochondrial chaperones and proteases, protein import machinery and ROS detoxification).[29] While ATFS-1 is the key messenger, other factors also contribute to the nuclear response. For example, the histone demethylases JMJD-1.2 and JMJD-3.1 facilitate access to mtUPR gene promoters.[30] Additionally, the transcription factor defective proventriculus in Drosophila

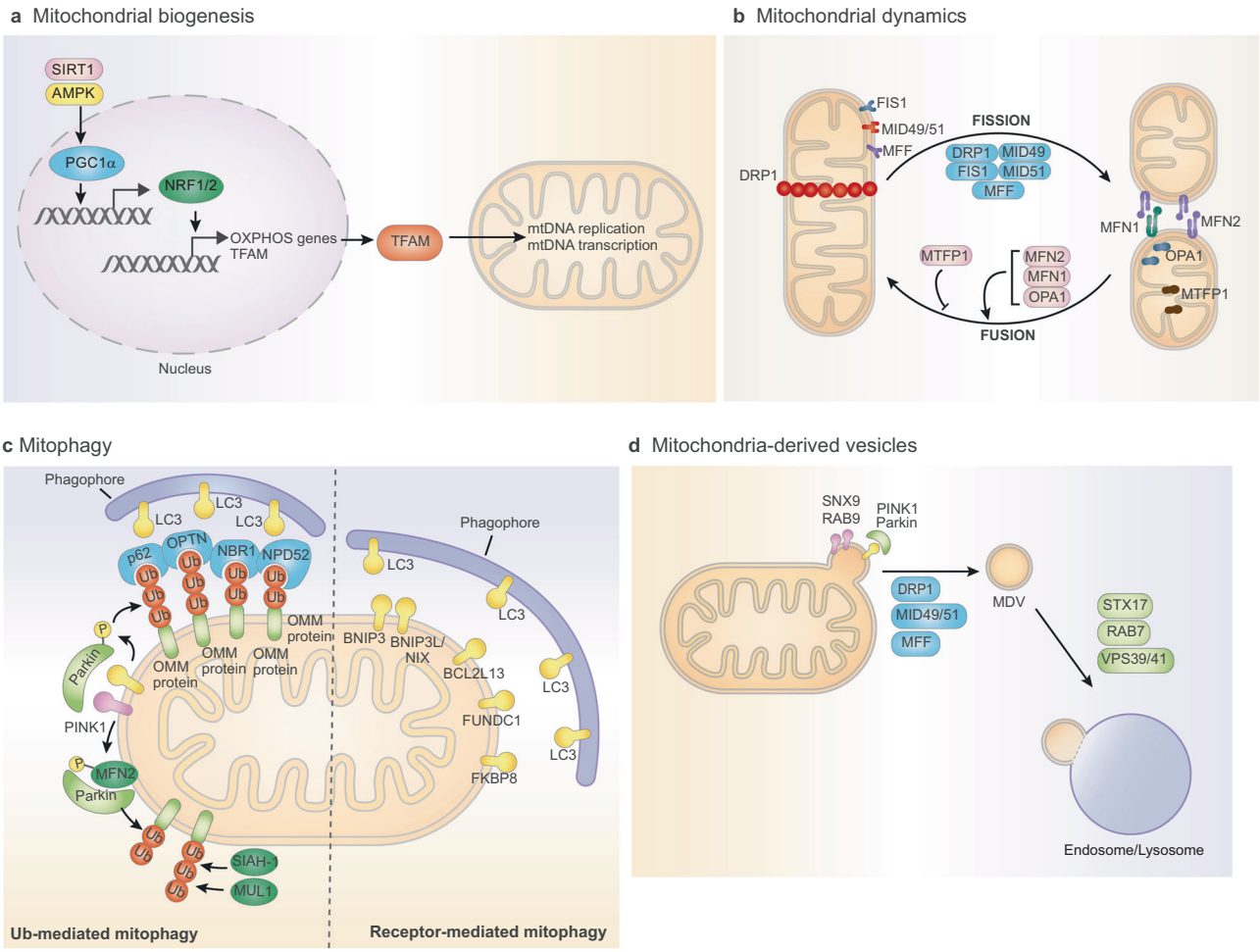


Fig. 2 Mitochondrial quality control mechanisms at the organellar level. **a** Mitochondrial biogenesis is regulated by PGC1α, which coactivates the transcription factors NRF1/2 to induce the expression of nuclear-encoded mitochondrial genes. TFAM controls mtDNA transcription and replication. **b** Mitochondrial dynamics is regulated by mitochondrial fusion and fission proteins. MFN1, MFN2 and OPA1 drive mitochondrial fusion, while MTFP1 inhibits it. On the other hand, DRP1, FIS1, MFF, and MID49/51 regulate mitochondrial fission. **c** Mitophagy can follow a Ub-dependent pathway or a receptor-mediated pathway. Ub-dependent mitophagy requires the ubiquitination of different mitochondrial proteins by PINK1-activated Parkin. Ubiquitinated proteins are recognized by different mitophagy adapters (p62, OPTN, NBR1, and NPD52), which bind to LC3 in the nascent autophagosome. Other Ub ligases, such as MUL1 and SIAH-1, have been described to participate in this type of mitophagy. Receptor-mediated mitophagy depends on the activation of mitophagy receptors (BNIP3, BNIP3L/NIX, BCL2L13, FUNDC1 and FKBP8), which interact with LC3 in the autophagosomal membrane. **d** Mitochondrial-derived vesicles (MDVs) originate from the action of PINK1 and Parkin or RAB9/SNX9 and are excised from mitochondria by the mitochondrial fission machinery. Once formed, they are delivered to the endosome or lysosome by the participation of STX17, RAB7 and VPS39/41

homolog 1 (DVE-1), its co-factor ubiquitin-like 5 (UBL-5), histone methyltransferase-like 2 (MET-2) and its co-factor abnormal cell lineage 65 (LIN-65) regulate the expression of mitochondrial chaperones.[26,31,32]

In mammals, the mtUPR relies on key transcription factors, including the mammalian ortholog of ATFS-1, activating transcription factor 5 (ATF5), ATF4 and C/EBP homologous protein (CHOP)[25,33] (Fig. 1b). The mammalian mtUPR is activated by the phosphorylation of eukaryotic translation initiation factor 2 subunit 1 (eIF2α) by eIF2α kinases 3 and 4 (EIF2AK3/PERK and EIF2AK4/GCN2). These kinases are activated by ROS, amino acid depletion and endoplasmic reticulum (ER) stress, suggesting that the mtUPR could also work alongside the integrated stress response.[34,35] Phosphorylation of eIF2α reduces global protein synthesis while promoting the translation of specific mRNAs, including those encoding CHOP, ATF4 and ATF5.[36,37] As previously mentioned, the mtUPR can also be triggered by the processing of the long form of DELE1 by OMA1, leading to the cytosolic accumulation of truncated DELE1, which activates EIF2AK1 (also known as HRI), which phosphorylates eIF2α.[21] In addition to activation of these mtUPR mechanisms by proteotoxic stress in the mitochondrial matrix, a separate mtUPR pathway responds to unfolded protein stress within the IMS. This IMS-specific pathway involves AKT phosphorylation and activation of the nuclear hormone receptor estrogen receptor alpha (ERα), which in turn increases the expression of the IMS protease HtrA2 and the transcription factor nuclear respiratory factor 1 (NRF1), a key regulator of mitochondrial biogenesis.[38]

Mitochondrial biogenesis

Mitochondrial biogenesis––the creation of new mitochondria––is a tightly regulated process essential for tissue development, adapting to energy stress and recovering from mitochondrial damage. This complex process requires coordinated gene expression from both the nucleus and the mitochondria, together with mitochondrial protein import, lipid synthesis and mitochondrial DNA (mtDNA) replication (Fig. 2a). A key regulator of this process is peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), often considered the "master regulator" of mitochondrial biogenesis. PGC-1α coactivates

transcription factors such as NRF1 and NRF2,[39] which then promote the expression of nuclear-encoded mitochondrial genes. This, in turn, drives the transcription of genes involved in OXPHOS, the machinery for importing proteins into the mitochondria and mtDNA replication.[40]

Another critical player in mitochondrial biogenesis is mitochondrial transcription factor A (TFAM), which controls mtDNA transcription and replication. Maintaining the mitochondrial genome and proper organelle function depends on TFAM activity.[41] Mitochondrial biogenesis is also tightly regulated by energy-sensing pathways. For example, AMP-activated protein kinase (AMPK) activates PGC-1α when energy levels are low.[42] Similarly, sirtuin 1 (SIRT1) activates PGC-1α (by deacetylation) in response to nicotinamide adenine dinucleotide (NAD+) levels, linking mitochondrial biogenesis to cellular metabolic states.[43] Finally, the mechanistic target of rapamycin (mTOR) supports mitochondrial biogenesis in nutrient-rich conditions by regulating protein synthesis and mitochondrial translation.[44]

Mitochondrial dynamics

When molecular MQC fails or mitochondrial damage exceeds a certain threshold, a second line of defense is activated––organellar quality control. This involves mitochondrial dynamics, continuous mitochondrial fusion and fission processes crucial for mitochondrial and cellular homeostasis (Fig. 2b). These dynamics allow mitochondria to adapt to cellular stress and are crucial for quality control.[45] Mitochondrial fusion merges individual mitochondria into larger, interconnected networks, distributing mitochondrial contents and mitigating localized damage while ensuring optimal mtDNA integrity. Fusion occurs in two steps: OMM fusion and IMM fusion. In mammals, OMM fusion is mediated by mitofusin 1 (MFN1) and mitofusin 2 (MFN2) GTPases located on the OMM. These proteins tether adjacent mitochondria and promote membrane merging by forming homotypic (MFN1-MFN1) or heterotypic (MFN1-MFN2) complexes.[46] MFN2 also tethers mitochondria to the ER, facilitating crucial interorganelle communication for lipid transfer and calcium homeostasis.[47,48] IMM fusion requires the activity of OPA1, which is located in the inner membrane. OPA1 exists in long (L-OPA1) and short (S-OPA1) forms. L-OPA1 anchors to the inner membrane, while s-OPA1 is generated by proteolytic cleavage of L-OPA1. This cleavage is mediated by OMA1 in response to mitochondrial depolarization, ATP depletion and other stresses or constitutively by YME1L, which is upregulated during OXPHOS stimulation.[49] The coordinated activity of both long and short OPA1 isoforms is critical for fusion. The specific functions of both isoforms are still under debate; however, L-OPA seems to be more important for mitochondrial fusion and s-OPA1 for sustaining energetic efficiency.[50] Beyond fusion, OPA1 maintains cristae architecture, preserving mitochondrial function and preventing cytochrome c release during apoptosis.[51] In addition to mitofusins and OPA1, phosphatidic acid (generated by mitochondrion-localized phospholipase D) and cardiolipin also play important roles in mitochondrial fusion.[52,53] Conversely, it has recently been demonstrated that the IMM protein mitochondrial fission process 1 (MTFP1) inhibits mitochondrial fusion, creating IMM subdomains targeted for fission and subsequent autophagic degradation.[54]

Mitochondrial fission, which involves cytosolic and mitochondrial proteins, cytoskeletal elements and regulatory pathways, is orchestrated by the large GTPase dynamin-related protein 1 (DRP1).[55] Inactive DRP1 resides in the cytosol, but mitochondrial stress or division signals trigger its recruitment to the OMM, mediated by adapter proteins, including mitochondrial fission protein 1 (FIS1), mitochondrial fission factor (MFF) and mitochondrial dynamics proteins of 49 and 51 kDa (MiD49 and MiD51).[56] Mitochondrial fission enables organelle redistribution during mitosis, facilitates apoptosis by segregating damaged mitochondria and supports mitophagy by preparing dysfunctional segments for removal.[57] Furthermore, DRP1 drives two different types of mitochondrial fission: midzone division, which promotes mitochondrial biogenesis, and peripheral division, which is associated with mitophagy.[58]

The mechanisms governing mitochondrial fusion and fission are complex and involve the coordinated action of the core mitochondrial dynamics machinery. This includes their structural characteristics and posttranslational modifications, mitochondrial membrane lipids and interactions with other organelles such as the ER. For a comprehensive review of the molecular mechanisms controlling mitochondrial dynamics, we refer the reader to a recent excellent review.[46]

Mitophagy

Mitophagy, the selective degradation of mitochondria *via* autophagy, involves a complex interplay of molecules and pathways that identify, isolate and breakdown defective mitochondria. This process begins with the identification of damaged mitochondria, which are then sequestered within autophagosomes and delivered to lysosomes for degradation. Mitophagy is broadly classified into two types based on the "eat me" signals that tag damaged mitochondria: ubiquitin (Ub)-mediated mitophagy and receptor-mediated mitophagy[59] (Fig. 2c).

Ubiquitin-mediated mitophagy involves the attachment of Ub chains onto damaged mitochondria by E3-ubiquitin ligases, which are recognized by autophagy adapter proteins, triggering the formation of the mitophagosome. One of the best-understood Ub-mediated mitophagy mechanisms is the PINK1-Parkin pathway. Under normal conditions, PINK1 is imported into healthy mitochondria *via* the TOM complex, where it is degraded by proteases such as PARL. However, when mitochondria lose membrane potential (a sign of dysfunction), PINK1 import is impaired, causing PINK1 to accumulate on the OMM.[60] This stabilized PINK1 then dimerizes and is activated by autophosphorylation. Active PINK1 phosphorylates serine 65 of Ub and Parkin, an E3 ubiquitin ligase, at specific residues, activating its ubiquitin ligase activity.[61] Interestingly, PINK1 can also phosphorylate MFN2, further promoting Parkin binding and ubiquitination.[62] Activated Parkin ubiquitinates numerous OMM proteins, including voltage-dependent anion channel 1 (VDAC1), creating docking sites for Ub-binding autophagy adapter proteins or autophagy receptors, such as p62/sequestosome 1 (SQSTM1), neighbor of BRCA1 gene 1 (NBR1), optineurin (OPTN), and calcium-binding and coiled-coil domain-containing protein 2 (CALCOCO2/NDP52).[63] These receptors, possessing both ub-binding domains and LC3-interacting regions, bridge damaged mitochondria to LC3-positive autophagosomal membranes. LC3-II, the lipidated form of LC3, localizes to the autophagosomal membrane and participates in autophagosome formation and elongation. Therefore, the interaction of adapter proteins with LC3 ultimately leads to the engulfment of damaged mitochondria within autophagosomes, which then fuse with lysosomes for degradation.[63] In addition to Parkin, other E3-Ub ligases, such as seven in absentia homolog (SIAH)-1 and mitochondrial Ub ligase 1/mitochondrial-anchored protein ligase (MUL1/MAPL), can drive mitophagy under specific contexts.[59]

Receptor-mediated mitophagy is driven by receptor proteins residing on the OMM, such as BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3), BCL2/adenovirus E1B 19 kDa protein-interacting protein 3-like (BNIP3L/NIX), BCL2-like 13 (BCL2L13/Bcl-rambo), FUN14 domain containing 1 (FUNDC1) and FK506-binding protein 8 (FKBP8). Each of these receptors contains an LC3-interacting region, enabling them to bind LC3-positive autophagosomal membranes and recruit damaged mitochondria for engulfment.[59] Because these receptors are constitutively present on the OMM, the key regulatory step in mitophagy is the upregulation or activation of the receptors themselves. For instance, BNIP3, NIX and FUNDC1 levels are regulated

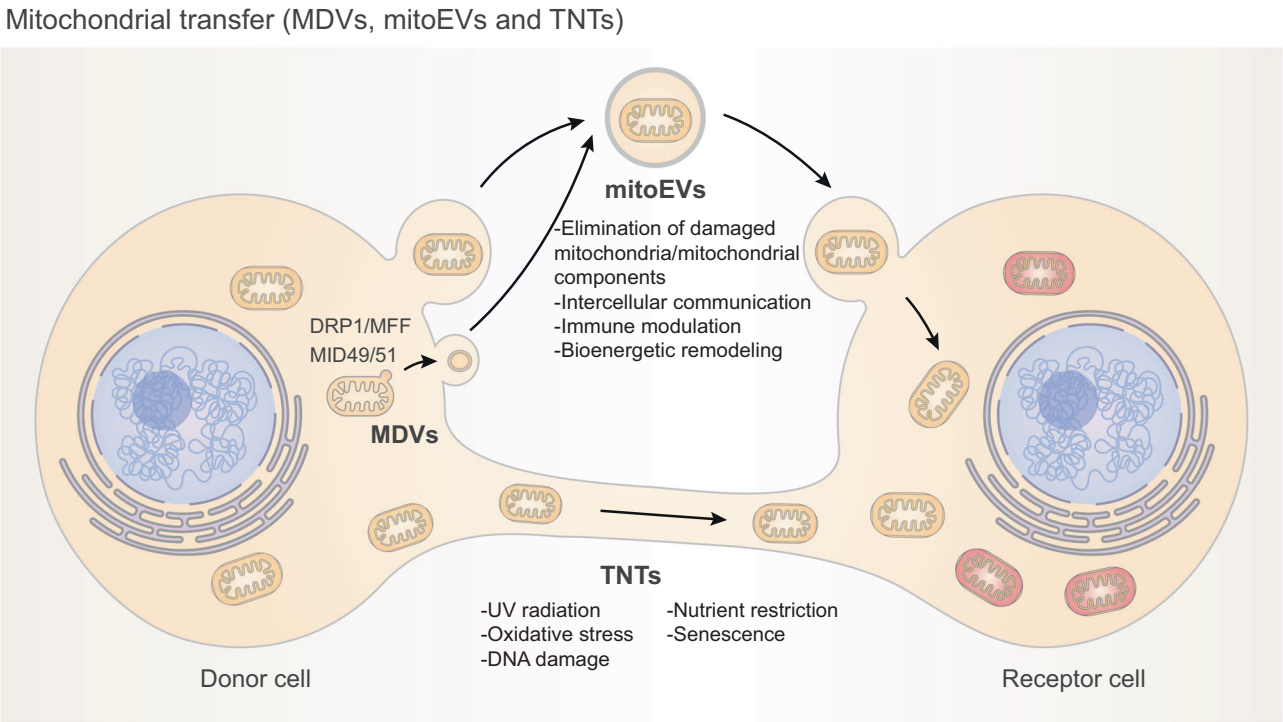


Fig. 3 Mitochondrial quality control at the cellular level. Mitochondrial transfer between cells occurs through extracellular vesicles (mitoEVs) or tunneling nanotubes (TNTs) as a novel mechanism to secrete and eliminate damaged mitochondria. Mitochondrial components can also be transferred through the generation of MDVs

transcriptionally and posttranslationally through ubiquitination and phosphorylation.[64–67] Receptor-mediated mitophagy contributes to both basal mitochondrial turnover and induced mitophagy in response to various cellular stresses and conditions, such as hypoxia, cellular differentiation, tissue remodeling and metabolic adaptation.[67–69] For a more detailed discussion of the molecular regulation and physiological functions of mitophagy, readers are directed to other comprehensive reviews.[59,70]

Mitochondrial-derived vesicles and mitochondrial transfer

Finally, other MQC systems have been described, including mitochondrial-derived vesicles (MDVs, Fig. 2d), the release of mitochondria in extracellular vesicles (EVs) and the transfer of mitochondria between cells (Fig. 3).

Mitochondria-derived vesicles are small, single- or double-membrane vesicles that bud from mitochondria and transport damaged mitochondrial components, such as oxidized proteins and lipids, to lysosomes for degradation or to peroxisomes for detoxification. While MDV formation occurs at a basal level under physiological conditions, it increases during mitochondrial stress.[71] This process begins with the identification of damaged mitochondrial regions, triggered by oxidative stress or mitochondrial depolarization. MDV formation and function involve several key molecules and complex processes that ensure proper cargo targeting and delivery.[4] For example, the retromer complex components vacuolar protein sorting ortholog 35 (VPS35) and VPS26A are involved in cargo selection.[72] PINK1 and Parkin initiate MDV biogenesis in response to mitochondrial stress,[73] while sortin nexin 9 (SNX9) and the small GTPAse RAB9 participate in inflammation-induced MDV formation.[74] The mitochondrial fission machinery, including DRP1 and its adapter proteins MFF, MiD49 and MiD51, regulates final MDV fission.[75] Finally, the SNARE protein syntaxin 17 (STX17) together with the small GTPase RAB7 and VPS39/VPS41 are required for delivering PINK1/Parkin-generated MDVs to the late endosome/lysosome.[76]

Mitochondrial transfer, the exchange of mitochondria between cells, occurs through various mechanisms, including EVs, tunneling nanotubes (TNTs) and direct engulfment. Cells can also secrete mitochondria as a (novel) quality control mechanism to eliminate damaged organelles. Although progress has been made in recent years, there is still relatively little knowledge about the molecular mechanisms that underlie the different intercellular mitochondria transfer axes. For a detailed view of the different mitochondrial transfer mechanisms, we direct the reader to another excellent review.[77] Recent studies have shown that diverse cell types, such as cardiomyocytes, adipocytes, astrocytes and mesenchymal stromal cells, release vesicles containing defective mitochondria.[78–81] These EVs, termed mitoEVs, can contain whole mitochondria or mitochondrial components. mitoEVs can originate from MDVs, representing a quality control pathway when lysosomal function is compromised.[82,83] Beyond mitochondrial homeostasis, mitoEVs also participate in intercellular communication, cell development, immune modulation and bioenergetic remodeling.[84] TNTs are actin-based bridges between cells, ranging from 50 to 1000 nm in diameter. These structures facilitate the direct transfer of intact mitochondria, allowing healthy organelles to be redistributed to recipient cells with dysfunctional mitochondria. This transfer can restore metabolic function and reduce oxidative damage.[85] While TNTs can form in healthy cells under normal conditions, their formation is also triggered by various stressors, including ultraviolet radiation, oxidative stress, DNA damage, nutrient restriction and senescence.[86] For example, TNT-mediated mitochondrial transfer has been observed between astrocytes and neurons, demonstrating neuroprotective effects in mice,[80] and between healthy and prostate cancer cells.[87]

Other aspects related to MQC: mtDNA integrity, cristae dynamics, and mitochondrial permeability transition pore (mPTP)

In addition to the main mechanisms of the MQC system, there are other aspects important for mitochondrial quality that need to be

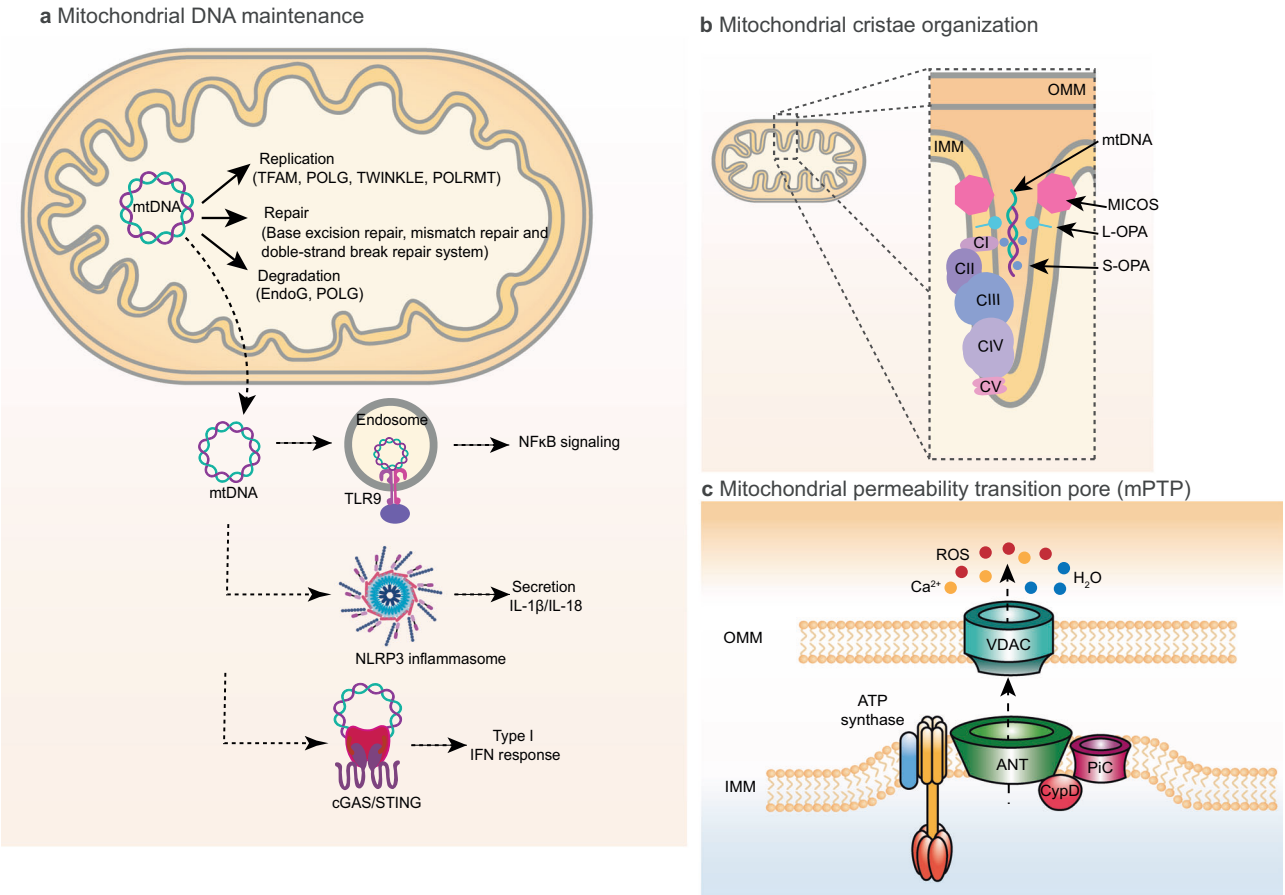


Fig. 4 Other aspects related to mitochondrial quality control. **a** Mitochondrial DNA (mtDNA) maintenance and integrity are preserved by the control of mtDNA replication by TFAM, POLG and TWINKLE; mtDNA repair systems (base excision repair (BER), mismatch repair and double-strand break repair systems); and mtDNA degradation carried out by POLG or EndoG. In addition, mtDNA mislocation outside mitochondria can trigger inflammatory responses through activation of the cGAS/STING pathway (type I interferon response), NLRP3 inflammasome (IL-1β and IL-18 secretion), or TLR9 (NFκB-induced inflammation). **b** Mitochondrial crista structure and organization. The MICOs complex and OPA1 protein are responsible for cristae structure and dynamics, which play an essential role in mitochondrial health. **c** Mitochondrial permeability transition pore (mPTP). The major components of mPTP are VDAC, ANT, PiC, ATP synthase and CypD

considered (Fig. 4). As described above, nuclear-encoded proteins such as TFAM, PGC1α, and NRF1/2 regulate mitochondrial biogenesis and are important for mtDNA replication under both basal and stress conditions.[39–41] In addition to these proteins, the core machinery of mtDNA replication includes DNA polymerase γ (POLG), TWINKLE helicase and mitochondrial RNA polymerase (POLRMT)[88] (Fig. 4a). Importantly, intrinsic errors of mtDNA replication caused by mutations in these genes can induce alterations in mtDNA, such as mutations or deletions, which are associated with mitochondrial dysfunction, metabolic alterations and the development of a number of different human diseases and aging.[89–91] In addition to alterations in mtDNA replication, defects in mtDNA repair are also associated with disease. For instance, mtDNA mutator mice, which have a POLG deficient in proofreading activity, accumulate high levels of point mutations, leading to multisystemic disease and premature aging.[92] To avoid the accumulation of mtDNA damage, mitochondria have different mtDNA repair mechanisms, such as base excision repair (BER), mismatch repair and double-strand break repair systems.[93] When the damage cannot be repaired or is persistent, mtDNA can be degraded by the action of endonuclease G (EndoG) or POLG.[94,95] Importantly, MQC mechanisms can be activated in response to mtDNA damage, such as mitochondrial fragmentation followed by mitophagy,[96] and the induction of the ISR via the OMA1-DELE1-HRI pathway in response to mtDNA double-strand breaks.[97] Interestingly, defects in some MQC mechanisms, such as mitophagy and mitochondrial dynamics, may promote the mislocation of mtDNA outside mitochondria, where it is a key signal triggering sterile inflammation.[98,99] In this regard, cytosolic mtDNA can engage with either cyclic GAMP synthase (cGAS), triggering the type I interferon response and the nuclear factor kappa B (NFκB)-dependent pathway,[100] or inflammasomes, promoting the secretion of interleukin 1β and 18.[101] In addition, endosomal localization of mtDNA can induce Toll-like receptor 9 (TLR9)-dependent activation of the NFκB inflammatory pathway[98] (Fig. 4a). In addition to mtDNA, other molecules released from damaged mitochondria, including mitochondrial RNA (mtRNA) and cardiolipins, have been shown to trigger inflammatory responses.[102]

The organization and structure of cristae (deep invaginations of the IMM) is essential for proper mitochondrial function. In this regard, crista shape is key for the activity of some Krebs cycle enzymes, the formation and elimination of ROS, OXPHOS supercomplex (SC) stability and assembly, and mitochondrial calcium sensing and signaling.[103] Different proteins have been described to be involved in the regulation of cristae structure and remodeling, such as the mitochondrial contact site and cristae organizing system (MICOS) and OPA1[104] (Fig. 4b). For a detailed view of the different IMM-shaping machineries and how they regulate cristae dynamics, readers are directed to another excellent review.[104] Alterations in these IMM-shaping machineries are associated with mitochondrial dysfunction and

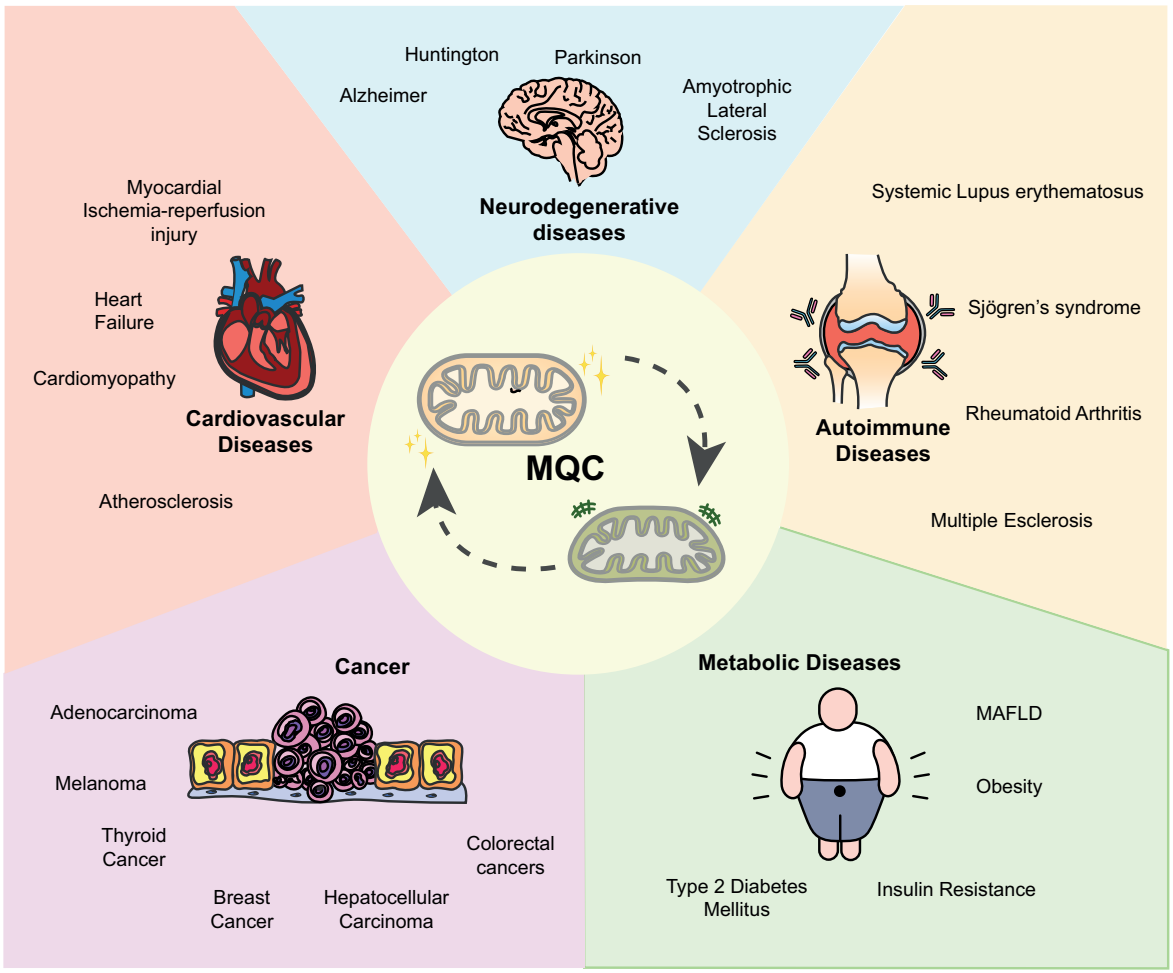


Fig. 5 Role of MQC in the development of disease. Alterations in different MQC systems are associated with the development of various diseases, including metabolic disorders, cardiovascular conditions, cancer, neurodegenerative diseases and autoimmune pathologies

the development of disease. In this regard, different studies have shown that cristae disorganization induced by the absence of different MICOS subunits is associated with alterations in OXPHOS complexes, mitochondrial fragmentation and dysfunction,[105,106] and the development of mitochondrial encephalopathy with liver disease.[107] Regarding OPA1, mutations causing dominant optic atrophy (DOA) lead to cristae morphology and OXPHOS defects,[108] and OPA1-dependent cristae remodeling is associated with the correct functionality of the OXPHOS system and protection from a range of pathological conditions in mice, such as muscular atrophy, heart and brain ischemia and reperfusion, and mitochondrial diseases.[109,110] In addition, OPA1 has been described to regulate SC formation and stabilization and therefore respiratory efficiency.[111]

The mPTP is a protein complex located in the IMM that, when activated, forms a mega-channel permeable to ions and low molecular weight solutes (up to 1500 Da in size). The molecular nature of mPTP is still under debate, but a group of proteins have been proposed to be responsible for its formation, including adenine nucleotide translocator (ANT), voltage-dependent anion channels (VDACs), mitochondrial inorganic phosphate carrier (PiC) and F_1/F_0 ATP synthase[112] (Fig. 4c). The channel is voltage-gated, activated by low mitochondrial membrane potential ($\Delta\psi m$) and inhibited by high $\Delta\psi m$, and it is physiologically activated by mitochondrial matrix calcium overload or excessive mitochondrial ROS production.[113] In addition, cyclophilin D (CypD), the most important mPTP-associated protein, binds to and activates the channel, and posttranslational modifications of this protein, such as phosphorylation and acetylation, have been described to modulate mPTP activity.[113] In addition, some mitochondrial chaperones, including HSP60 and HSP90, have been shown to interact with and inhibit CypD, conferring protection against mPTP opening and cell death.[114,115] Physiological and transient opening of the mPTP is important for calcium efflux from the mitochondrial matrix and therefore for the regulation of calcium-related metabolism, as well as for the extrusion of endogenous ROS into the cytoplasm. In contrast, persistent mPTP opening has a strong impact on mitochondrial activity since it causes the depletion of NADH and the disassembly of respiratory SCs, and prolonged pore opening in a large number of mitochondria in the cell can finally lead to cell death.[112,116,117] Interestingly, oxidized mtDNA can also be released from mitochondria via mPTP and trigger inflammatory responses.[118] Therefore, alterations in mPTP or its regulators have a profound impact on cellular metabolism and have been described to be linked with aging and disease.[119]

MITOCHONDRIAL QUALITY CONTROL AND DISEASE

Given the key role of mitochondria in cellular and tissue homeostasis, mitochondrial dysfunction has been associated with several diseases, many of which, as discussed below, are age-related conditions (Fig. 5). Consequently, we propose that disrupted MQC mechanisms contribute to the development of these diseases.

Table 1. Summary of metabolic alterations caused by genetic modulation of proteins involved in mitochondrial quality control in mice

	Targeted cell/tissue	Protein	Main effects at systemic level	References
mtUPR and proteostasis				
	Whole-body	↓ HSP60	Prevents overweight and insulin resistance	124
	Whole-body	↓ CLPP	Protects against overweight, abnormal glucose homeostasis, insulin resistance and hepatic steatosis	125
	Whole-body	↓ OMA1	Induces overweight, increased visceral adiposity and hepatic steatosis Alters lipid metabolism and glucose homeostasis Decreases energy expenditure	127
	Whole-body	↓ HSP72	Promotes obesity and insulin resistance Exacerbates diet-induced insulin resistance	121
	Liver	↑ mtHSP70	Prevents obesity and insulin resistance Decreases hepatic steatosis Improved dyslipidemia	120
	Skeletal muscle	↑ HSP72	Reduces body and fat pad weight gain Prevented diet-induced glucose intolerance and insulin resistance	122,123
		↓ LONP1	Confers resistance to diet-induced obesity and insulin resistance	126
Mitochondrial dynamics				
	Liver	↓ MFN2	Induces glucose intolerance and impairs insulin signaling	134
		↓ MFN1	Protects against diet-induced insulin resistance	144
		↓ DRP1	Protect from diet-induced obesity	152
	Skeletal muscle	↓ MFN2	Induces glucose intolerance and impairs insulin signaling	134,135
		↓ OPA1 ↓ DRP1	Protects against obesity and insulin resistance Enhances insulin sensitivity in diet-induced obesity	145,149,150
	White adipose tissue/ adipocytes	↓ MFN2	Increases food intake and adiposity Impairs glucose metabolism	137
		↓ OPA1	Induces glucose intolerance Reduces visceral adiposity by increasing hepatic steatosis	148
	Brown adipose tissue	↓ MFN2	Improves insulin sensitivity Confers resistance to obesity and hepatic steatosis	138,139
		↓ OPA1	Prevents diet induced obesity and IR Improves energy balance and thermoregulation	146
	POMC neurons	↓ MFN2/OPA1	Obesity Hyperphagia Hyperleptinemia and leptin resistance	140,141
		↓ MFN1 ↓ DRP1	Glucose intolerance Abnormal pancreatic insulin release Improved systemic glucose metabolism	142,153
	Agrp neurons	↓ MFN1	Prevents diet-induced obesity	143
		↓ MFN2	Decreased fat mass and leptin levels	143
Mitophagy				
	Whole-body	↓ FUNDC1	Aggravates severe diet-induced obesity and insulin resistance	161
	Whole-body	↓ Parkin	Overactivates brown adipose tissue thermogenic capacity Improves metabolic parameters	166
	Whole-body	↓ BNIP3	Reduces adiposity and increases liver steatosis Aggravates systemic insulin resistance	171
	Muscle Pancreas	↓ FUNDC1 ↑ FUNDC1	Protects against diet-induced obesity and insulin resistance Ameliorates insulin resistance and obesity	160,162
	Liver	↓ PARKIN	Accelerates the onset of key MAFLD disease features Increases hepatic steatosis and insulin resistance	164
		↓ BNIP3	Reduces hepatic glucose output	170
	BAT	↓ PINK1	Induces BAT dysfunction and obesity-prone phenotype	169

MQC and metabolic diseases

Role of mtUPR and proteostasis in metabolic disease. Several preclinical studies have demonstrated a role for mtUPR and proteostasis in metabolic disease (Table 1). Indeed, various mitochondrial chaperones have been implicated in insulin resistance. For example, lower levels of GRP75/mtHSP70 in the liver and white adipose tissue (WAT) are observed in insulin-resistant mice, while inducing GRP75/mtHSP70 expression prevents both obesity and insulin resistance.[120] Similarly, insulin-resistant humans show reduced HSP72 protein expression and increased c-Jun terminal kinase (JNK) phosphorylation in skeletal muscle,[121] and mice lacking HSP72 develop insulin resistance and obesity.[122] Conversely, overexpressing HSP72 in rodent skeletal muscle improves insulin sensitivity by increasing mitochondrial number and

oxidative capacity.[123] Interestingly, heterozygous whole-body HSP60 knockout mice fed a high-fat diet (HFD) exhibit lower body weight with reduced fat mass, along with improved insulin sensitivity and glucose tolerance. However, these same mice also display dysfunctional adipose tissue, characterized by altered metabolism, elevated insulin-independent glucose uptake, adipocyte hyperplasia and local insulin resistance.[124]

Mitochondrial proteases are also associated with metabolic disturbances. While some might be expected to support healthy metabolic function, their disruption can paradoxically improve certain metabolic parameters. For example, mice lacking the protease ClpP exhibit reduced adiposity, improved insulin sensitivity and protection against diet-induced obesity, glucose intolerance, insulin resistance and hepatic steatosis.[125] This protection is likely due to a compensatory increase in mitochondrial biogenesis and respiration in WAT. Similarly, deleting *Lonp1* specifically in muscle leads to an imbalance in mitochondrial proteostasis, triggering the mtUPR, which acts distally to activate thermogenesis in adipose tissue and decrease lipogenesis in the liver, ultimately conferring resistance to diet-induced obesity.[126] Conversely, mice lacking *Oma1*, a protease involved in OPA1 processing, develop obesity, hepatic steatosis and reduced thermogenesis. These effects are exacerbated by metabolic stress, such as HFD, demonstrating that a functional OMA1-OPA1 system is essential for appropriate metabolic adaptation to stress.[127]

Role of mitochondrial biogenesis in metabolic disease. Obesity and type 2 diabetes mellitus (T2DM) are often associated with decreased mitochondrial mass and/or function in skeletal muscle.[128] This is thought to be caused by impaired mitochondrial biogenesis, as evidenced by reduced expression of PGC1α and related genes. However, whether these alterations are linked with insulin resistance is still under debate.[129]

Role of mitochondrial dynamics in metabolic disease. Mitochondrial dynamics, which is closely linked to metabolism, adapt to metabolic needs[130] and is a key pathophysiological component of metabolic diseases.[131] In both humans and experimental models of obesity, insulin resistance is associated with impaired mitochondrial dynamics and altered levels of proteins that regulate fusion and fission in metabolically important tissues[132] (Table 1).

With regard to mitochondrial fusion, MFN2 expression in skeletal muscle is reduced in obesity and T2DM in humans and mouse models, and *Mfn2* mRNA levels in muscle correlate with insulin sensitivity in both nondiabetic individuals and those with T2DM.[133] Consistent with this, *Mfn2* deficiency in mouse skeletal muscle leads to insulin resistance in response to HFD and aging.[134,135] Similarly, human metabolic dysfunction-associated fatty liver disease is linked to decreased MFN2 expression, and *Mfn2* deficiency in mouse liver causes hepatic steatosis, insulin resistance and glucose intolerance early in life, progressing to fibrosis and liver cancer with age.[47,134] In human adipose tissue, biallelic *MFN2* mutations cause mitochondrial dysfunction, adipose tissue hyperplasia and impaired leptin expression,[136] and adult mice lacking MFN2 in white adipocytes showed increased food intake, adiposity and impaired glucose metabolism regardless of diet.[137] Conversely, *Mfn2* ablation in brown adipose tissue (BAT) blunts thermogenesis but protects against HFD-induced glucose intolerance, insulin resistance and hepatic steatosis.[138,139] Mitochondrial fusion is also important for central energy balance in the hypothalamus. In mice, specific ablation of *Mfn2* or *Opa1* in anorexigenic proopiomelanocortin neurons increases food intake and induces obesity and energy imbalance,[140,141] whereas *Mfn1* ablation impairs glucose homeostasis due to defective insulin secretion.[142] In contrast, *Mfn2* or *Mfn1* ablation in orexigenic agouti-related peptide neurons protects against diet-induced obesity.[143] Interestingly, deficiency of hepatic MFN1 also protects against diet-induced obesity and insulin resistance in mice,[144] possibly *via* compensatory improvements in mitochondrial function. Similarly, *Opa1* ablation in muscle or BAT protects against diet-induced obesity and insulin resistance through an FGF21-mediated compensatory mechanism.[145,146] In individuals with obesity, *OPA1* gene expression is significantly reduced in visceral adipose tissue, and ubiquitous mild induction of *Opa1* in diet-induced obese mice improves glucose tolerance and insulin sensitivity by increasing adipose tissue expandability and browning.[147] Finally, loss of function of *Opa1* in mouse white adipocytes reduces WAT mass and alters lipid handling, leading to hepatic steatosis and glucose intolerance, but surprisingly protects against diet-induced obesity.[148]

Mitochondrial fission is also associated with metabolic homeostasis. Studies in obese mice have shown that pharmacologically inhibiting DRP1 or specifically deleting *Drp1* in muscle improves insulin sensitivity.[149,150] In the liver, while one study found increased DRP1 expression in rats fed a high-fructose diet but not a HFD,[151] another found that liver-specific ablation of *Drp1* in mice actually protected against HFD-induced obesity by increasing energy expenditure, driven by ER stress and subsequent FGF21 production.[152] In the hypothalamus, deleting *Drp1* in proopiomelanocortin neurons enhanced their activity and improved systemic glucose metabolism.[153] Consistent with these findings, DRP1 expression in human adipose tissue correlates positively with obesity and insulin resistance.[154] Furthermore, DRP1 activity is regulated by posttranscriptional modifications. For example, whole-body and skeletal muscle-specific ablation of calcineurin, which dephosphorylates DRP1, increases phosphorylation of DRP1 at S637, leading to DRP1 inactivation, mitochondrial elongation and protection against HFD-induced obesity.[155] Similarly, mice with DRP1 S600A knock-in, which prevents DRP1 activation by phosphorylation at S600, show improved glucose tolerance and thermogenesis.[156] Interestingly, HFD-fed mice show increased expression and activity of the small GTPase RalA in WAT, which counteracts the inhibitory S637 phosphorylation of DRP1, promoting mitochondrial fission and contributing to weight gain and metabolic dysregulation.[154]

Role of mitophagy in metabolic disease. Mitophagy appears to be impaired in individuals with T2DM. This is supported by several observations, including decreased expression of mitophagy-related markers in peripheral blood mononuclear cells,[157] lower Parkin expression in myotubes[158] and reduced PINK1 expression in both muscle and adipose tissue.[159] While these findings suggest a link between impaired mitophagy and the development of metabolic disease, studies performed in different model organisms have yielded conflicting results about whether altering mitophagy is beneficial or harmful in the development of metabolic diseases (Table 1). These effects appear to depend on the specific tissue and the presence or absence of complementary mechanisms. For example, in mice, muscle-specific deletion of *Fundc1* protects against diet-induced obesity and insulin resistance by triggering muscle-adipose crosstalk to promote fat burning in adipose tissue through FGF21.[160] Conversely, whole-body ablation of *Fundc1* worsened diet-induced metabolic dysfunction by inducing WAT remodeling and inflammation.[161] Notably, overexpressing *Fundc1* specifically in the pancreas improved HFD-induced insulin resistance and obesity.[162]

The impact of PINK1/Parkin-induced mitophagy on metabolism has been investigated in various animal models. In skeletal muscle, activating the PINK1-Parkin pathway with brain-derived neurotrophic factor (BDNF) improves mitochondrial quality, whereas muscle-specific *Bdnf* deletion exacerbates HFD-induced metabolic dysfunction.[163] Similarly, *Hsp72* ablation impairs Parkin activity, leading to damaged mitochondrial accumulation and muscle insulin resistance.[122] Hepatic deletion of Parkin increases susceptibility to diet-induced steatosis, inflammation, fibrosis and insulin resistance.[164] Conversely, preserving Parkin-mediated mitophagy

improves β-cell function in diabetes models.[165] In BAT, increased Parkin levels correlate with thermogenic inactivation, and *Parkin* knockout mice exhibit enhanced thermogenesis and improved metabolic parameters under HFD,[166] potentially due to its role in thermogenic beige adipocyte retention.[167] However, other studies suggest that activation of the PINK1/Parkin pathway promotes thermogenesis,[168] as *Pink1* global or BAT-specific deletion in mice induces BAT dysfunction and an obesity-prone phenotype.[169] BNIP3-driven mitophagy also plays a role in metabolic dysfunction. Global *Bnip3* deletion increases inflammation and steatohepatitis-like features in mice fed a standard chow diet[170] and reduces adiposity but worsens liver steatosis and systemic insulin resistance in HFD-fed mice.[171] Interestingly, the mitophagy activator urolithin A ameliorates insulin resistance in obese rodents,[172] suggesting mitophagy as a potential therapeutic target for metabolic diseases.

Mitochondrial transfer and metabolic disease. Mitochondrial transfer can have complex metabolic effects. Transfer from a dysfunctional cell to a healthy cell can induce metabolic decline in the recipient, while transfer from a healthy cell to a dysfunctional cell can improve the metabolic state of the recipient. The role of this transfer in the context of metabolic diseases is now being explored. For example, both white and brown adipocytes can transfer mitochondria to macrophages, a process important for thermogenesis,[83] that is impaired in obesity.[173] In the heart, defective macrophage phagocytosis leads to impaired clearance of extracellular mitochondria and metabolic dysfunction.[79] Interestingly, mitochondria released in EVs from stressed adipocytes can signal to the heart,[78] demonstrating that mitochondrial transfer facilitates both intercellular and interorgan communication. While human data on mitochondrial transfer in metabolic disorders are limited, studies suggest a link between the release of mitochondrial components and T2DM. Lower circulating mtDNA levels are associated with T2DM,[174] and low blood mtDNA content correlates with impaired glucose-stimulated islet β cell function, HbA1c levels, fasting plasma glucose and age of onset in T2DM.[174,175]

Other aspects related to MQC and metabolic diseases. Loss of mtDNA integrity is associated with the development of mitochondrial diseases, a diverse group of inherited metabolic disorders that ultimately impair mitochondrial bioenergetics. Some of those are mitochondrial encephalopathy, lactic acidosis, stroke-like episodes (MELAS), Kearns-Sayre syndrome (KSS), Pearson syndrome, some cases of Leigh syndrome and chronic progressive external ophthalmoplegia (CPEO). These diseases can be caused by mtDNA mutations or deletions or by alterations in proteins involved in mtDNA maintenance, such as POLG, TWINKLE, and TFAM. For a comprehensive view of mitochondrial diseases, we direct the reader to a specific review on this topic.[91] Regarding metabolic diseases, different studies have shown that mice lacking different components of the mtDNA damage repair machinery are more prone to obesity, glucose intolerance, and insulin resistance.[176,177] In humans, a common polymorphism in the BER enzyme 8-oxoguanine DNA glycosylase OGG1 correlates with increased body mass index, total cholesterol, fasting blood glucose and incidence of T2DM.[178,179] In mice, alterations in cristae organization induced by dysregulation of MICOS components are associated with metabolic alterations, such as liver inflammation and liver fibrosis,[180] and mPTP opening has been found to contribute to insulin resistance in muscle.[181]

In summary, while alterations in different MQC mechanisms are clearly linked to metabolic disorders (Table 1), it remains unclear whether these anomalies are a cause or a consequence of mitochondrial dysfunction and whether they can trigger metabolic disease. The relationship between these alterations and metabolic disturbances likely depends on the activation of adaptive pathways, which are probably triggered by the degree of mitochondrial damage. Finally, the specific tissue- or cell-dependent signals and/or events that contribute to impaired MQC are not yet fully understood.

MQC and cardiovascular disease (CVD)

Role of mtUPR and proteostasis in CVD. Cardiovascular diseases, such as heart failure, cardiomyopathy, myocardial ischemia–reperfusion (I/R) injury and atherosclerosis, are characterized by mitochondrial damage and stress, such as unfolded and misfolded protein accumulation, calcium overload and oxidative stress. The mtUPR is known to play an important role in CVD development (Table 2). While mtUPR components can be down- or upregulated depending on the specific CVD, activating the mtUPR has shown promise as a therapeutic strategy. In rodent models of chronic pressure overload, pharmacologically boosting the mtUPR enhances cardiomyocyte survival and ventricular function.[182] Similarly, upregulating the mtUPR through dietary supplements, drugs or genetic manipulation protects against cardiac hypertrophy in cardiomyopathies and spontaneous hypertension[183,184] and cardiac injury in cardiometabolic syndromes.[185,186] Interestingly, the HSP60/HSP10 ratio has been proposed as a potential

Table 2. Summary of cardiac alterations caused by genetic modulation of proteins involved in mitochondrial quality control in mice

	Tissue/cell	Protein	Main effects at systemic level	References
mtUPR and proteostasis				
	Cardiac muscle	↓CLPP	Attenuates mitochondrial cardiomyopathy	189
	Cardiac muscle	↑ HSP70	Protects against acute cardiac stress	188
	Whole-body	↓OMA1	Protects from cardiomyocyte death in heart failure	190
Mitochondrial dynamics				
	Cardiac muscle	↓ MFN2	Exacerbates cardiac hypertrophy	199
		↓ MFN1/MFN2	Protects against acute I/R injury	200
	Whole-body	↓ OPA1	Leads to late-onset cardiomyopathy	205
	Whole-body	↑ OPA1	Protection from ischemic damage and cardiac hypertrophy	109
	Cardiac muscle	↓ DRP1	Induces cardiac dysfunction	211
Mitophagy				
	Whole-body	↓ PARKIN	Exacerbates diastolic dysfunction induced by high-fat diet and sensitivity to myocardial infarction	220
	Platelets	↓ FUNCD1	Increase susceptibility to infarct and cardiac dysfunction induced by ischemia–reperfusion	221

biomarker of CVD,[187] and enhancing HSP70 in the heart—through genetic or pharmacological approaches—protects against acute but not chronic cardiac stress in mice.[188] Regarding mitochondrial proteases, while loss of *Clpp* can alleviate mitochondrial cardiomyopathy, it does not appear to affect the mtUPR.[189] Ablation of the OMA1 protease has been shown to be protective in different mouse models of heart failure by protecting against cristae remodeling and cardiomyocyte death.[190] However, in a genetic mouse model of mitochondrial cardiomyopathy induced by cardiac-specific ablation of Cox10, activation of OMA1 results in activation of the DELE1-ATF4 signaling axis of the ISR, which confers protection from cardiomyopathy.[191]

Role of mitochondrial biogenesis in CVD. Mitochondrial biogenesis is disrupted early in the progression of heart failure.[192] Although increasing PGC-1α expression does not guarantee restored heart function, studies in different rodent models of heart failure have shown that stimulating mitochondrial biogenesis through different signaling pathways can improve cardiac performance and myocardial dysfunction.[193,194] Consistent with this, diabetic cardiomyopathy is characterized by reduced PGC-1α levels and decreased mitochondrial activity in cardiomyocytes, together with increased myocardial injury. In these cases, boosting the activity of SIRT1 and SIRT6 may offer a potential strategy to restore mitochondrial biogenesis.[195]

Role of mitochondrial dynamics in CVD. Cardiac tissue is highly oxidative, and proper mitochondrial function, dependent on a balanced fusion-fission process, is crucial for maintaining a healthy cardiovascular system and responding to stress (Table 2). Loss of MFN1/2, OPA1 and DRP1 in cardiomyocytes causes a profound shift in this fusion-fission balance that impacts cardiac performance. For example, reduced *Mfn2* expression is observed in experimental models of heart failure (induced by pressure overload) and diabetic cardiomyopathy and correlates with worsening cardiac abnormalities.[196,197] Studies using loss-of-function approaches have underscored the importance of fusion-related proteins for cardiovascular health. Mice with conditional, combined *Mfn1/2* knockout develop lethal dilated cardiomyopathy as adults.[198] Similarly, studies in cardiomyocytes specifically lacking MFN2 have demonstrated its essential role in maintaining heart function.[62,199] However, while combined *Mfn1/Mfn2* ablation impairs myocardial contractile function, it paradoxically protects mice from acute I/R injury.[200] This suggests that mitofusins play complex and context-dependent roles in heart physiology, potentially differing in response to short-term *versus* long-term stressors. A newly discovered pathway involving ubiquitin-specific protease 28 (USP28)-dependent activation of PPARα-MFN2 was found to restore mitochondrial function and improve cardiac structure and performance in diabetic hearts.[201] In humans, *MFN2* is downregulated in diabetic cardiomyopathy,[202] and a rare *Mfn2* mutation causing perinatal cardiomyopathy in mice is overrepresented in clinical cardiomyopathy.[203] The expression of OPA1 is decreased in failing human hearts (explanted at transplant) and rodent heart failure models,[204] and mice with a mutant version of *Opa1*, leading to a 50% reduction in OPA1 protein, develop late-onset cardiomyopathy.[205] Additionally, imbalanced OPA1 processing leading to accelerated OPA1 proteolysis and mitochondrial fragmentation has a causal role in heart failure development in mice.[206] Conversely, restoring OPA1 processing and reducing mitochondrial fragmentation in mice improves cardiac function,[207] and increased OPA1 levels in mice protect against I/R injury.[109] During I/R, left ventricle dysfunction is associated with DRP1 activation,[208] and acutely inhibiting DRP1 activity with Mdivi-1 protects against heart hypertrophy and preserves function after I/R injury[209] or myocardial infarction[210] in mice. However, chronic DRP1 dysfunction, in both mutant and cardiac-specific *Drp1* knockout mice, induces cardiac dysfunction, likely due to impaired mitophagy.[211] Some effects of MFN2 deficiency on the heart also stem from disrupted mitophagy,[62] reflecting the link between mitochondrial dynamics and mitophagy. Collectively, these findings indicate that maintaining the mitochondrial fusion-fission balance is essential for cardiomyocyte survival and heart function.

Role of mitophagy in CVD. In cardiac muscle, removal of damaged mitochondria is crucial for maintaining cardiac structure and function under normal conditions, and impaired mitophagy is associated with aging-induced cardiac abnormalities.[212] Human heart failure is associated with a downregulation of mitophagic genes in cardiac tissue.[213] Despite promising cardioprotective results with the mitophagy activator urolithin A in animal models, a recent randomized, double-blind, placebo-controlled crossover trial failed to find a positive effect of urothilin A supplementation in improving cardiac function in patients with heart failure.[214] However, activating mitophagy by pharmacological and/or genetic strategies has been shown to be effective against cardiac dysfunction in experimental models of cardiometabolic syndrome, heart failure and diabetic cardiomyopathy.[185,215,216] In the latter, the specific mitophagy mechanisms involved vary depending on the disease stage. In early phases, upregulation of Atg7-mediated mitophagy plays a key role in maintaining cardiac performance, while activation of Rab9-dependent alternative mitophagy becomes more important in later stages.[217,218] In pressure overload-induced cardiac hypertrophy, ULK1-mediated alternative mitophagy is the primary protective mechanism against cardiac dysfunction.[219] During I/R injury, clearing defective mitochondria is beneficial. In this regard, Parkin knockout mice have exacerbated infarct expansion,[220] and FUNDC1-dependent mitophagy offers protection.[221] Mitophagy also plays a role in age-related cardiac dysfunction. Mitophagy decreases with age in mouse hearts, and promoting Parkin-induced mitophagy alleviates aging-related decline in cardiac function.[222] One possible explanation for this decline in mitophagy is increased Shank3 levels in aging hearts. Shank3, a heart-enriched protein, inhibits Parkin-mediated mitophagy by binding to CaMKII and preventing its mitochondrial translocation.[223] Collectively, these findings suggest that mitophagy is essential for maintaining cardiac function and heart homeostasis under pathological or stressful conditions.

Mitochondrial transfer and CVD. Extracellular mitochondria are emerging as important regulators in CVD progression.[224] Cardiomyocytes can eject damaged mitochondria, which are then engulfed and eliminated by resident macrophages, a process amplified during cardiac stress and crucial for cardiac function.[79] Conversely, cardiomyocytes can also absorb mitochondria released by macrophages, triggering ferroptosis and cellular injury.[225] This bidirectional mitochondrial exchange between cardiomyocytes and macrophages highlights its importance for heart homeostasis and function. Consequently, mitochondrial transfer and EVs are being explored as potential CVD therapies. For example, intramyocardial injection of mitochondria-rich EVs from autologous stem cell-derived cardiomyocytes improves postmyocardial infarction cardiac function in animal models.[226] Similarly, cardiac-derived EVs have shown promise in mitigating I/R injury by delivering ATP synthase F1 subunit alpha (ATP5a1).[227]

Other aspects related to MQC and CVD. Alterations in mtDNA integrity are associated with the development of CVDs. Experiments using mDNA mutator mice demonstrated that mutations in mtDNA led to cardiac hypertrophy at the age of 6 months.[92] Indeed, cardiomyopathy has been shown to be present in 20% of patients with mitochondrial disease harboring different mutations in mtDNA.[228] Interestingly, circulating levels of mtDNA (possibly released from damaged mitochondria) have been described to be increased after myocardial infarction and to be associated with

increased mortality in heart failure.[229,230] Regarding mitochondrial crista organization, transgenic mice overexpressing the MICOS subunit MIC60/mitofilin show reduced type 1 diabetes-associated cardiomyopathy symptoms.[231] Finally, numerous studies have demonstrated a key role of mPTP opening in cardiomyocyte cell death during I/R.[232] In this regard, genetic ablation or pharmacological inhibition of CypD and ANT protects against heart damage during I/R.[233,234]

In summary, given the dependence of the heart on mitochondrial oxidative metabolism, disruption in MQC processes is believed to be a major driver of CVD and cardiac aging[235] (Table 2). However, further research is necessary to fully elucidate the mechanisms underlying these mitochondrial quality changes in CVD and to confirm their presence and relevance in humans.

MQC and neurodegenerative diseases

Role of mtUPR and proteostasis in neurodegenerative diseases. Neurons, with their high metabolic demand and complex morphology, rely heavily on intact mtUPR signaling and mitochondrial proteostasis. Accordingly, neurodegenerative diseases often exhibit evidence of either insufficient or maladaptive activation of these pathways. Mutations in the mitochondrial protease HTRA2/OMI have been found in sporadic cases of Parkinson's disease (PD), and *Htra2*-deficient mice show neurodegeneration and Parkinson-like phenotypes.[236] Mutations in paraplegin, a subunit of the m-AAA protease, cause hereditary spastic paraplegia (HSP),[237] and paraplegin-deficient mice recapitulate the symptoms of the disease.[238] Mutations in *Hsp60* and decreased expression of LONP1 and CLPP have also been documented in HSP patients,[239,240] and downregulation of *Hsp60* and *Clpp* mRNA has been found in fibroblasts derived from Huntington's Disease (HD) patients.[241] The mitochondrial protease Pitrilysin Metallopeptidase 1 (PITRM1), a matrix peptidase that clears amyloid-β (Aβ) fragments, is deficient in Alzheimer's Disease (AD) brains and model systems, leading to intramitochondrial Aβ accumulation and synaptic degeneration.[242] In addition, reduced expression of LONP1 has been found in experimental models of AD and in the brains of AD patients.[243] Consequently, LONP1 knockdown caused neuronal dysfunction, while restored neuronal expression of LONP1 in in vitro and in vivo models of AD rescued Aβ-induced mitochondrial alterations and cognitive deficits.[243] Interestingly, other studies have demonstrated an increase in mtUPR-associated genes in AD patients and mouse models, including mitochondrial chaperones and proteases, suggesting a protective response during disease progression.[244,245] Activation of mtUPR has also been described in PD models, which confers protection from neurotoxicity and neuronal death.[246] However, in HD patients and mouse models, mtUPR has been shown to be impaired due to the sequestration of ATF5 into mutant huntingtin (mHTT) aggregates.[247] In amyotrophic lateral sclerosis (ALS), the aberrant accumulation of the RNA-binding protein transactive response DNA-binding protein-43 kDa (TDP-43) or FUS leads to energy failure and proteostatic stress that activates mtUPR signaling,[248,249] and in models of ALS carrying SOD1 mutations, mtUPR has also been shown to be activated in a sex-specific manner.[250] In addition, ALS-linked mutations in the coiled-coil-helix-coiled-coil-helix domain containing 10 (CHCHD10) gene, which encodes a mitochondrial protein involved in cristae morphology, activate OMA1-dependent cleavage of OPA1, which disorganizes cristae and triggers the DELE1-HRI-eIF2α-dependent mtUPR.[251] Regarding protein import stress, in PD, misfolded α-synuclein binds the TOM20 receptor and interferes with TOM20-TOM22 cooperation, leading to protein import failure and mitochondrial dysfunction.[252] In HD, mHTT has been reported to engage the TIM23 import machinery and to produce a measurable defect in translocation of nuclear-encoded preproteins into the matrix/inner membrane, depleting imported respiratory subunits and contributing to OXPHOS compromise and neuronal vulnerability. However, the submitochondrial localization of mHTT and the universality of direct TIM23 blockade remain contested across models.[253,254]

Role of mitochondrial biogenesis in neurodegenerative diseases. Neurodegenerative disorders consistently display suppression of the mitochondrial biogenesis program, which is associated with a repression of PGC-1α signaling. Studies in AD patient brains and transgenic mouse models have documented reduced PGC-1α expression, accompanied by diminished mtDNA content and elevated Aβ levels. Experimental restoration of PGC-1α expression in these models was associated with decreased amyloid burden and improved mitochondrial function.[255,256] Genome-wide transcriptomic profiling of dopaminergic neurons and the substantia nigra of PD patients has also revealed coordinated downregulation of PGC-1α-responsive genes.[257] In HD, mHTT interferes with the coactivator function of PGC-1α and its downstream partners TFAM and NRF-1, leading to the repression of mitochondrial gene expression and increased vulnerability of striatal neurons.[258–260] Likewise, in ALS, reduced expression of PGC-1α and PGC-1α-regulated factors has been observed in both patient tissue and SOD1 mutant mice, and experimental restoration of PGC-1α in ALS models prolongs survival and improves motor performance.[261,262]

Role of mitochondrial dynamics in neurodegenerative diseases. Disruption of mitochondrial dynamics is a consistent feature of neurodegeneration and directly interfaces with other axes of MQC. Mutations in *OPA1* and *MFN2* are responsible for Charcot-Marie-Tooth 2 A and dominant optic atrophy neuropathies, respectively.[263–265] In addition, a mutation in *DRP1* has been associated with a severe type of infantile neurodegeneration, characterized by microcephaly, optic atrophy and abnormal brain development.[266] KO models of these genes in various organisms, including *Drosophila*, zebrafish, and mice, have yielded similar phenotypes.[267] In mice, specific ablation of *Mfn2* in the brain leads to degeneration of the cerebellum,[268] and neural cell-specific ablation of *Drp1* leads to premature death as a result of brain hypoplasia.[269]

Regarding neurodegenerative diseases, analyses of AD patient brains and neuronal models report increased levels of fission proteins (DRP1, FIS1) concurrent with decreased fusion proteins (MFN1/2, OPA1).[270] In addition, an increased interaction between DRP1 and Aβ or TAU has been observed in neurons from patients with AD,[270] together with nitrosylation of DRP1, induced by nitric oxide released from Aβ, which leads to excessive mitochondrial fission and neuronal synaptic damage, aggravating AD progression.[271] In HD, mHTT interacts with DRP1, enhancing its enzymatic activity and producing excessive mitochondrial fragmentation and defects in axonal mitochondrial transport and neuronal cell death.[272,273] Finally, in ALS, increased mitochondrial fission by hyperactivation of DRP1 in spinal cord motor neurons exacerbates the progression of the disease, whereas its negative modulation rescues neuronal cell death.[274]

Role of mitophagy in neurodegenerative diseases. Failures at multiple steps of mitophagy have been observed across several neurodegenerative disorders. Thus, loss-of-function mutations in *PINK1* or *PRKN* genes are responsible for early-onset hereditary PD, as they impair mitophagy, leading to the accumulation of damaged mitochondria.[275,276] Interestingly, Parkin inactivation results in the accumulation of PARIS, a Parkin-interacting substrate, which represses PGC-1α promoter activity, thereby leading to impaired mitochondrial renewal and contributing to neurodegeneration in PD.[277] Moreover, a recent study revealed that under conditions associated with PD, inactivated Parkin leads to NLRP3 inflammasome activation and promotes neuroinflammation.[278] In AD models, the TAU protein has been shown to inhibit mitophagy by binding to Parkin and blocking its translocation to

damaged mitochondria.[279] However, Parkin-mediated mitophagy has been found to be increased in neurons with TAU lesions in the early stages of AD and to impair synaptic function,[280] suggesting that mitophagy could be beneficial or detrimental depending on the stage of the disease. In HD, mHTT has been shown to impair Parkin translocation to mitochondria in a Drosophila model of the disease, and PINK1 overexpression counteracts the neurotoxicity of mHTT.[281] In ALS, mitophagy has been described to be activated in the spinal cord of SOD1 mutant mice, and Parkin genetic ablation delays disease progression, suggesting that Parkin-induced mitophagy is associated with the progression of ALS.[282] However, some ALS-linked mutations in TANK-binding kinase (TBK1), a kinase with an essential role in mitophagy, have been shown to inhibit mitophagy and contribute to disease pathogenesis.[283] Finally, cytoplasmic accumulation of TDP-43, a disease hallmark for many cases of ALS, is linked to Parkin reduction and cleaved PINK1 cytosolic accumulation in mouse primary neurons and an ALS mouse model.[284]

Mitochondrial transfer and neurodegenerative diseases. A few studies have described associations between intercellular mitochondrial transfer and neurodegenerative diseases. In PD, microglia have been shown to share healthy mitochondria with overburdened neurons via TNTs, restoring mitochondrial function and energy metabolism and alleviating cell death in neurons and PD-like symptoms in mice.[285] In addition, under PD-related stress, decreased FGF13 levels have been described to induce the transfer of damaged mitochondria from neurons to glia in part via EVs, promoting neuroinflammation.[286] In vitro *studies* have revealed that stressed astrocytes with accumulated α-synuclein oligomers extend TNTs to transfer them to healthy astrocytes, which, in turn, transfer mitochondria to assist with cellular function.[287] Finally, astrocytes can also rescue the degeneration of dopaminergic neurons through intercellular mitochondrial transfer.[288]

Other aspects related to MQC and neurodegenerative diseases. Alterations in mtDNA integrity have been linked to neurodegeneration. In this regard, mice lacking the mtDNA repair proteins MTH1 and/or OGG1 exhibited severe striatal neurodegeneration.[289] In humans, defects in POLG, higher levels of mtDNA deletions, or some polymorphisms in mtDNA repair enzymes have been reported in some cases of PD.[290–292] In addition, both mtDNA and mtRNA mislocation have been shown to play a role in the development of neurodegenerative diseases. Thus, in mouse models of HD, the release of mtRNA induced by mHTT is associated with innate immune signaling activation in spiny projection neurons,[293] and in ALS patient cells and disease models, TDP-43-induced release of mtDNA to the cytosol has been shown to drive neuroinflammation.[294]

Abnormal mitochondrial crista morphology is also observed in some neurodegenerative diseases. Several *MIC60/mitofilin* coding variants leading to altered crista morphology have been found in PD patients, and expression of this protein in PINK1-null flies rescues their behavioral defects and dopaminergic neurodegeneration.[295] Mitochondrial structure and cristae organization alterations have been described in fibroblasts from HD patients,[296] and in ALS, mutant variants of CHCHD10 have been shown to induce cristae disorganization by activating OPA1 cleavage.[251,297] Finally, alterations in mPTP have also been linked to neurodegenerative pathophysiology. In this regard, mPTP activation has been documented in mouse models of AD, PD and HD.[298–301] In AD, CypD deficiency has been shown to ameliorate neuronal alterations, learning and memory,[300] and reduced stability of F_1/F_0-ATP synthase leads to mPTP activation, mitochondrial dysfunction and synaptic injury in neurons.[301] Similarly, in PD, CypD ablation in mice delayed disease onset and extended lifespan.[299]

In summary, MQC in neurodegeneration is disrupted at multiple levels, from proteostasis and biogenesis to dynamics, mitophagy, and auxiliary pathways such as mitochondrial transfer. Together, these defects converge on the persistence of dysfunctional mitochondria and insufficient bioenergetic support in vulnerable neuronal populations, reinforcing the concept that MQC failure is a unifying mechanism of neurodegenerative disease (Table 3).

MQC and cancer

Role of mtUPR and proteostasis in cancer. Activation of the mtUPR has been frequently associated with tumor progression, although its effects may vary depending on tumor type and context. Several mtUPR effectors, including ATF4, ATF5, ERα, and the HSF1–SSBP1 axis, have been implicated in cancer progression or survival responses. For instance, ATF5 has been shown to suppress apoptosis and support invasive behavior, while HSF1 contributes to angiogenesis and tumor adaptation to stress.[302] Recently, several novel molecular players activated by mtUPR have been identified to play a role in cancer progression. For instance, in thyroid cancer, mtUPR activation induced by mitochondrial stress drives the release of growth differentiation factor 15 (GDF15), a well-characterized mitokine, inducing STAT3 activation and determining tumor progression.[303] Upregulation of β-catenin signaling by mtUPR promotes neuroendocrine prostate cancer,[304] and the ERα–SIRT3–mtUPR axis has been proposed as a modulator of breast cancer subtype–specific metabolic responses in an age-dependent manner.[305] mtUPR has also been associated with therapy resistance, particularly in response to oxidative stress–inducing agents.[302] Interestingly, a signature of mtUPR-related genes is able to predict therapy sensitivity and the prognosis of hepatocellular carcinoma (HCC).[306] Regarding mitochondrial proteases, their dysregulation or overactivation has been documented to contribute to tumor progression. In this

Table 3. Summary of neurological alterations caused by genetic modulation of proteins involved in mitochondrial quality control in mice

	Tissue/cell	Protein	Main effects at systemic level	References
mtUPR and proteostasis				
	Whole-body	↓HTRA2/OMI	Neurodegeneration and PD-like phenotypes	236
	Neurons	↓Paraplegin	Recapitulates hereditary spastic paraplegia symptoms	238
		↑ LONP1	Rescues cognitive deficits in AD	243
Mitochondrial dynamics				
	Brain	↓ MFN2	Degeneration of the cerebellum	268
	Neurons	↓ DRP1	Brain hypoplasia and premature death	269,272
		↑ DRP1	Exacerbates progression of ALS	
Mitophagy				
	Whole-body	↓ PARKIN	Delays ALS disease progression and prolongs survival	282

regard, knockdown of LONP1 decreased the proliferation, invasion, and migration of HepG2 cells, suggesting that upregulated LONP1 expression contributed to the malignant behaviors of HCC cells.[306] In addition, experimental strategies targeting mitochondrial proteases—such as HSP60, ClpP and LONP1—have been shown to impair cancer cell proliferation and invasion.[302,307]

Role of mitochondrial biogenesis in cancer. While glycolysis predominates in many tumors, several aggressive cancers—such as melanoma, prostate cancer, and HER2-positive breast cancer—or specific cellular subtypes within tumors show increased levels of PGC1α and enhanced mitochondrial biogenesis to sustain OXPHOS and support metastatic dissemination.[308,309] In this regard, a recent study has shown that the molecular chaperone TRAP1, which is overexpressed in most human colorectal cancers and correlates with poor clinical outcome, enhances mitochondrial biogenesis via PGC1α-TFAM signaling.[310] Additional evidence suggests a dual and context-dependent role of PGC1α in cancer, acting as both a transcriptional coactivator and a downstream target of oncogenic pathways to integrate diverse signals. For instance, different tumor-specific signaling axes—such as PML–PGC1α–PPARα and PGC1α–ERRα in breast cancer, MITF–PGC1α in melanoma, MYC–PGC1α in pancreatic ductal adenocarcinoma, and AR–PGC1α in prostate cancer—have been shown to regulate fuel flexibility and mitochondrial capacity.[311] Finally, stress conditions can also influence mitochondrial biogenesis in cancer cells. For instance, in HCC, hypoxia induces PGC1α and mitochondrial biogenesis, promoting tumor survival and proliferation.[312]

Role of mitochondrial dynamics in cancer. Several studies have pinpointed mitochondrial dynamics as a pivotal factor in cancer progression. Increased mitochondrial fission mediated by FIS1 or DRP1 has been reported in HCC and is associated with metabolic reprogramming, proliferation, and enhanced metastatic potential.[313,314] In other types of tumors, such as glioblastoma, DRP1-induced mitochondrial fission has also been associated with increased proliferative capacity and aggressiveness.[315] Succinylation of MFF, whose expression is increased in ovarian cancer cells and correlates with poor prognosis in patients, induces mitochondrial fission and enhances tumor growth.[316] Other studies highlight mechanisms involving transcriptional regulation of fission-related genes. In liver cancer stem-like cells (CSCs), the tumor suppressor YY2 negatively regulates *DRP1* transcription, maintaining the stem cell pool with tumor-initiating capacity,[317] and alternative *DRP1* splice variants identified in tumor samples have been shown to influence mitochondrial dynamics and impact tumor progression.[318] Interestingly, a broader systems biology approach has revealed fission-associated gene signatures associated with high risk and poorer prognosis in HCC.[319] Mitochondrial fusion proteins have been reported to be either upregulated or downregulated depending on the tumor type and cellular context. MFN2, initially known as hyperplasia suppressor gene (HSC), was shown to be reduced in hyperproliferative vascular smooth muscle cells (VSMCs) from arteries in different rodent models of hypertension, and its overexpression partially suppressed VSMC proliferation.[320] Further studies have shown that MFN2 stands out as an important inhibitory factor of tumor development and cell proliferation in ovarian cancer models.[321] Similar to MFN2, MFN1 has also been shown to exert tumor-suppressive functions across distinct tumor types. MFN1 has consistently been linked to the suppression of cancer cell dissemination, acting through both metabolic and structural mechanisms. In HCC, its downregulation favors epithelial–mesenchymal transition (EMT) and metabolic reprogramming, while in breast cancer, mitochondrial fragmentation increases metastatic capacity. In both contexts, MFN1 restoration impairs key steps of tumor progression, such as migration, invasion, and proliferation.[322,323] Finally, elevated *OPA1* gene expression has been documented to increase metastatic potential in breast cancer and to confer treatment resistance and increase CSC properties in lung adenocarcinoma.[324,325]

Role of mitophagy in cancer. Mitophagy plays a pivotal role in maintaining mitochondrial quality and supporting the metabolic demands of cancer cells. The functional impact of mitophagy alterations in cancer is largely determined by cancer type and microenvironmental context. Mitophagy induction driven by BNIP3 and BNIP3L/NIX has been found to be beneficial for tumor growth under hypoxia,[326] and Parkin-mediated mitophagy facilitates breast cancer cell survival under glucose starvation conditions.[327] Additional evidence further supports the tumor-promoting role of mitophagy in specific settings. In this regard, an increase in mitophagy and mitochondrial biogenesis has been shown to be important for oral cancer cells to adapt and survive,[328] and extracellular vesicles (EVs) released by highly metastatic tumor cells activate cancer-associated fibroblasts in lung cancer, which in turn enhance mtDNA release and trigger mitophagy, ultimately promoting metastasis.[329] However, a reduction in mitophagy has also been shown to be beneficial for tumor development and metastatic potential. Under normoxia, loss of BNIP3 in breast cancer cell lines impairs mitochondrial turnover, leading to mitochondrial damage, ROS accumulation, and a metabolic shift toward glycolysis, promoting metastasis.[330] In addition, a reduction in mitophagy during hypoxia induces an invasive phenotype of breast cancer cells and increases osteolytic bone metastasis.[331] Importantly, mitophagy has recently been recognized as a mechanism contributing to therapy resistance in cancer. Thus, increased mitophagy has been associated with chemotherapy resistance in human non-small cell lung cancer cells,[332,333] and PINK1-mediated mitophagy has been identified as a key mechanism for drug-tolerant persister cells during cancer therapy, highlighting its inhibition as a promising strategy to prevent relapse.[334] However, although mitophagy often favors cancer cell survival under therapeutic stress, some studies suggest that its activation may, in certain contexts, counteract chemoresistance. For example, the induction of PINK1-Parkin-mediated mitophagy suppresses chemoresistance in ovarian cancer.[335] Together, these findings highlight the dual role of mitophagy in either promoting or overcoming therapy resistance, depending on the tumor context and molecular regulators involved. Beyond its mechanistic contributions, recent bioinformatic analyses in triple-negative breast cancer have shown that mitophagy-related gene expression profiles can serve as prognostic markers and predictors of treatment response, reinforcing the potential of mitophagy as a therapeutic and stratification target in oncology.[336]

Mitochondrial transfer and cancer. Emerging research underscores mitochondrial transfer as a potent driver of intercellular signaling in the tumor microenvironment, enabling recipient cancer cells to boost metabolic flexibility, self-renewal, and aggressiveness. Tumor cells can acquire functional mitochondria from neighboring stromal fibroblasts, immune cells (e.g., T cells), platelets, endothelial cells, astrocytes, and cancer-associated stem cells through TNTs, extracellular vesicles, or direct cell–cell contacts.[77] Glioblastoma stem cells can receive astrocyte mitochondria via TNTs, substantially increasing tumor initiation capacity,[337] and cancer-associated neurons boost tumor metabolic plasticity by donating mitochondria to cancer cells, thereby enhancing stemness and metastatic potential.[338] In melanoma, the adapter protein Miro1 regulates horizontal mitochondrial transfer, whereas in hepatocellular carcinoma, hypoxia has been shown to induce TNT-mediated mitochondrial exchange.[339,340] Mitochondrial transfer has also been described to promote chemoresistance in different types of cancer, including breast and gastric cancer and glioblastoma.[341–343] In addition, the

transfer of mitochondria with mtDNA mutations from cancer cells to T lymphocytes has been shown to promote T-cell dysfunction and thereby chemoresistance due to immune evasion.[344] However, mitochondrial transfer is not always associated with benefits for tumor growth. In this regard, mitochondrial transfer from osteocytes to bone metastatic cancer cells has been shown to trigger a cGAS/STING-mediated antitumor response.[345]

Other aspects of MQC and cancer. Several mtDNA mutations and deletions have been reported in various types of cancers. For instance, a deletion in the region encoding NADH:ubiquinone oxidoreductase (complex I) has been demonstrated to be associated with renal cell carcinoma,[346] and a mutation in the Atp6 mitochondrial gene has been reported in prostate cancer cells.[347] However, it is difficult to establish whether these mtDNA alterations are drivers of the cancer phenotype or are secondary to cell transformation. In this regard, the accumulation of mtDNA mutations in intestine-specific mutator mice increased tumor burden, suggesting that mtDNA mutations could contribute to accelerated intestinal cancer development.[348] Interestingly, TFAM ablation in dendritic cells within the tumor microenvironment leads to mtDNA release and activation of the cGAS-STING pathway, enhancing antitumor immunity.[349] Release and transfer of mtDNA has also been observed in cancer cells. In colorectal cancer, the transfer of complete mitochondrial genomes to surrounding epithelial cells promotes tumor progression,[350] and VDAC-dependent release of mtDNA within EVs by senescent tumor cells leads to immunosuppression in the tumor microenvironment and thereby tumor progression.[351] Regarding mPTP, some studies have demonstrated that its opening status may influence cancer cell survival and death.[352] Different mPTP components, such as VDAC and ANT-2, are upregulated in cancer cells,[353,354] suggesting an enhanced probability of mPTP formation and cell death, which is counteracted by an increase in the expression of antiapoptotic proteins from the Bcl-2 family.[355]

In summary, the role of mitochondria in different key aspects of tumor biology, such as metabolic reprogramming, stress responses and intercellular communication, establishes them as key modulators of cancer development. However, the precise role of the different MQC mechanisms in tumor progression depends on the type of cancer cell, external conditions such as hypoxia or starvation, the tumor microenvironment and the intrinsic tumor heterogenicity.

MQC and autoimmune diseases

Role of mitochondrial biogenesis in autoimmune diseases. Several studies have documented a disruption in mitochondrial biogenesis associated with some autoimmune diseases. For example, PGC-1α levels and mitochondrial biogenesis are significantly reduced in the pyramidal neurons of the cortex in multiple sclerosis (MS) patients,[356] whereas PGC-1α overexpression in neurons increases mitochondrial mass and activity and protects against neurodegeneration in a mouse model of MS.[357] Interestingly, a striking upregulation of PGC-1α has been observed in reactive astrocytes from active demyelinating MS lesions, suggesting an endogenous astrocyte-driven protective mechanism to dampen oxidative damage and inflammation, thereby reducing neurodegeneration.[358] However, in PBMCs and T cells derived from rheumatoid arthritis (RA) patients, mitochondrial mass is maintained constant despite a decrease in respiratory activity,[359,360] which may be explained by reduced AMPK activation,[361] suggesting a coordinated reduction in mitochondrial biogenesis and mitophagy.

Role of mitochondrial dynamics in autoimmune diseases. Alterations in mitochondrial dynamics can contribute to the immune dysregulation, oxidative stress, and inflammation seen in autoimmune diseases. In RA, fibroblast-like synoviocytes (FLS) exhibit high invasiveness and proliferation, contributing to the progression of the disease. It has been found that the expression of DRP1, MiD49 and MiD51 is increased in FLS from RA patients, and their knockdown or inhibition can mitigate RA symptoms in mouse models of RA.[362,363] A similar scenario has been described in Sjögren's syndrome (SS), a common chronic inflammatory autoimmune disease affecting the salivary and lacrimal glands. The expression levels of DRP1 are increased in PBMCs from SS patients and submandibular glands from SS mice, and repression of mitochondrial fission alleviates the symptoms of the disease.[364] Furthermore, an increase in *MFF* gene expression has been observed in PBMCs from SS patients, together with a decrease in *MFN1*, *MFN2* and *OPA1* genes in salivary glands.[365,366] In MS, a disease characterized by demyelinating lesions in the central nervous system, overactivation of DRP1 has been observed in oligodendrocytes, the cells responsible for myelin production, while its inhibition improves disease progression in mice.[367] In this line, inhibition of mitochondrial fission by Mdivi-1 in T cells has also been shown to reduce demyelination and the severity of the disease in a mouse model of MS.[368] In contrast, in systemic lupus erythematosus (SLE), DRP1 expression has been found to be decreased in patient-derived peripheral blood lymphocytes, and an increase in DRP1 in T cells can delay the development of the disease in mice.[369] Additionally, the expression of *MFF* has been shown to be reduced in PBMCs from SLE patients compared to healthy subjects.[370]

Role of mitophagy in autoimmune diseases. Alterations in mitophagy have been proposed to contribute to the development of some autoimmune diseases. For example, in RA, FUNDC1 expression is decreased in FLS, and knockdown of PINK1 and Parkin has been shown to reverse the aggressive phenotype of these cells,[363,371] indicating that a decrease in mitophagy in FLS is associated with the progression of RA. In contrast, an increase in mitophagy in T cells has been observed in RA patients,[372] suggesting a cell-specific role of mitophagy in the pathophysiology of the disease. Disrupted mitophagic activity has been found in astrocytes in samples from MS patients, and activation of mitophagy in mouse primary and human embryonic stem cell-derived astrocytes is associated with improvements in an MS mouse model.[373] Supporting the protective role of mitophagy in MS, PINK1-deficient mice exhibit an earlier onset and more severe symptoms than control mice, although this effect is only observed in adult mice.[374] However, other studies have documented an increase in PINK1-Parkin-driven mitophagy in in vitro and in vivo MS models.[375,376] Interestingly, increased mitophagy-related elements such as Parkin, PINK1 and ATG5 have been found to be increased in serum and cerebrospinal fluid from MS patients.[377,378] These data suggest that mitophagy could constitute a compensatory mechanism aimed at removing damaged mitochondria in MS. Impairments in mitophagy are also linked to SLE pathogenesis. For instance, a failure in the autophagic degradation of mitochondria during erythroid cell maturation leads to the accumulation of red blood cells carrying mitochondria, which has been observed in SLE patients and is correlated with disease severity.[379] In addition, reduced mitophagy has also been described in other cell types from SLE patients, such as T $CD8^+$ cells and PBMCs.[369,380]

Mitochondrial transfer and autoimmune diseases. Few studies have proposed that mitochondrial transfer, by modulating immune and metabolic functions in recipient cells, might play a role in autoimmune diseases. For instance, mitochondrial transfer from mesenchymal stem cells (MSCs) to Th17 cells has been found to be reduced in RA, which contributes to increased IL-17 production and inflammation in RA synovitis.[381] However, the transfer of exogenous mitochondria to T $CD4^+$ cells from RA patients reduced the inflammatory profile and the development of RA symptoms in mice.[382] In SLE, mitochondrial transfer from

MSCs to T cells has been shown to decrease apoptosis in these cells, which has been proposed to play an important role in SLE treatment.[383]

Other aspects of MQC and autoimmune diseases. A number of studies have reported an association between alterations in mtDNA and the development of some autoimmune diseases. A reduction in mtDNA copy number has been linked to an increased risk of developing SLE and RA,[384,385] and several mtDNA polymorphisms are responsible for conferring susceptibility toward RA and SLE.[386,387] mtDNA-induced inflammation has also been shown to promote autoimmune disorders. In this regard, oxidative damage to mtDNA triggers an inflammatory response that is implicated in the development of SLE.[388] Interestingly, neutrophils in SLE undergo enhanced NETosis (neutrophil extracellular trap formation), a process during which oxidized mtDNA is extruded and further fuels IFN-I production, and provide a source of autoantigens for antibody generation.[389] In RA, TNF-induced mtDNA release, which activates the type I interferon response, promotes inflammation and the progression of the disease in mice.[390] Importantly, mtDNA levels are significantly elevated in the plasma of RA patients compared to healthy subjects, suggesting that plasma mtDNA can be used as a biomarker for autoimmune diseases.[391] Finally, mPTP has also been associated with autoimmune disorders, as revealed by the protective role of its inhibition in the development of MS in mice.[392,393]

In summary, numerous studies have highlighted the pivotal role of MQC in the regulation of immune cell homeostasis, activation and differentiation, and inflammatory cytokine production. Therefore, dysregulation of the different MQC systems is associated with the development of autoimmune diseases and could be a potential target for their treatment.

MITOCHONDRIAL QUALITY CONTROL AND ITS CONTRIBUTION TO AGING: FROM MODEL ORGANISMS TO HUMANS

Proper mitochondrial function depends on several MQC mechanisms, as described above. In this section, we examine how these mechanisms relate to aging in organisms ranging from simple models to humans.

Role of mtUPR and proteostasis in aging

Mitochondrial protein quality control, maintained by proteases and chaperones, declines with age, causing misfolded proteins to accumulate. Studies in the fungus *Podospora anserine* have shown that the absence of ClpP (catalytic subunit of the ClpXP complex) or i-AAA proteases leads to a reduction in lifespan, although the latter effect is temperature-sensitive.[394,395] In rodents, aging affects *Lonp1* expression differently in various tissues: it decreases in skeletal muscle but increases in the heart. This suggests a tissue-specific regulation of *Lonp1* expression during aging.[396] Regarding mitochondrial chaperones, overexpression or repression of HSP70 in *C. elegans* and HSP22 in *Drosophila melanogaster* leads to an increase or a decrease in lifespan, respectively.[397–400] Mitochondrial stress, such as electron transport chain disruption or mitonuclear protein imbalance, has been linked to lifespan extension in worms, flies and mice.[401–404] This longevity is largely attributed to the activation of the mtUPR.[401,403] However, the role of mtUPR as a pro-longevity effector depends on both time and context. In *C. elegans*, mtUPR promotes longevity only when triggered by early-life damage,[401,403,405] pointing to mtUPR activation as a surveillance mechanism, monitoring mitochondrial quality early in life and influencing the rate of aging during adulthood. Conversely, chronic mitochondrial dysfunction in mice is detrimental and shortens lifespan.[92] While it is unclear if persistent mitochondrial damage chronically activates mtUPR, its ectopic activation in *C. elegans* neurons causes cell death.[406] In addition, in *C. elegans*, activation of mtUPR only in some tissues but not in others has been shown to be associated with increased longevity,[401] indicating a tissue-specific role of this pathway in lifespan extension. Intriguingly, in worms and flies, mitochondrial stress in one tissue can trigger mtUPR activation in a cell-nonautonomous manner in distant tissues.[407,408] In mice, growth/differentiation factor 15 (GDF15) and fibroblast growth factor 21 (FGF21), two mtUPR-associated secreted factors, enhance healthspan and longevity.[409] These factors are also elevated during human aging,[410] indicating that mitochondrial stress and mtUPR can be propagated from a specific tissue to the rest of the organism, increasing stress resistance and promoting lifespan. In summary, while these adaptive responses to mitochondrial stress appear beneficial for lifespan in a time- and tissue-specific manner, much of the research relies on genetically modified lower organisms. It remains to be established whether age-related mitochondrial changes activate these pathways in higher organisms and whether their regulation plays a physiological role in aging and longevity.

Role of mitochondrial dynamics in aging

Mitochondrial dynamics, the balance between fusion and fission, changes with age, although this relationship is complex and varies across species and tissues.[2,411] Pioneering studies in lower organisms suggested a link between preservation of mitochondrial elongation and increased lifespan: elongated mitochondria correlated with longer lifespan in yeast [412] and *C. elegans*,[413] while fragmented mitochondria were associated with shorter lifespan in *Drosophila*.[414] In line with the pro-longevity effect of mitochondrial elongation, aging in worms was associated with mitochondrial fragmentation,[415] and different longevity-promoting pathways depended on mitochondrial fusion.[416] However, subsequent studies have challenged this simple correlation. For example, a recent study showed that overexpression of both mitochondrial fusion and fission genes in *C. elegans* extends longevity by conferring stress resistance.[417] In *Drosophila*, two independent studies showed that increased fission and fragmented mitochondria increased lifespan,[418,419] and both fusion and fission were required for the pro-longevity effects of AMPK activation or dietary restriction in *C. elegans*.[420] It has been proposed that maintaining mitochondrial network homeostasis through coordinated fusion and fission is more important for lifespan extension than simply favoring one process over the other.[420] In mice, both mitochondrial fusion and fission decline with age in various tissues and are implicated in age-related diseases.[135,411] Human aging also involves changes in the expression of proteins engaged in mitochondrial dynamics and morphological changes in muscle mitochondria.[99,421] Despite these clues, the independent contribution of mitochondrial dynamics to lifespan regulation in mice and humans remains unclear, although it likely plays a role in healthspan.

Role of mitophagy in aging

A growing number of studies show that mitophagy plays a crucial role in aging and longevity in different organisms. In *Drosophila*, loss of Parkin shortens lifespan,[422] whereas its overexpression extends it.[419] Similarly, inducing BNIP3-induced mitophagy in the adult fly nervous system also promotes organismal longevity.[423] In *C. elegans*, mitophagy is necessary for the extended lifespan observed in several long-lived mutants[424] and in response to mild mitochondrial stress induced by iron starvation.[425] In addition, activation of mitophagy by the natural compound urolithin A or distinct diamines also extends lifespan in worms.[426,427] In mice, the role of mitophagy in aging is more complex. It is generally accepted that mitophagy declines with age in different tissues; for example, mitophagy is decreased in heart and skeletal muscle from old mice compared with young counterparts,[135,222] correlating with the accumulation of dysfunctional mitochondria and tissue failure. Notably, however, inducing mitophagy by

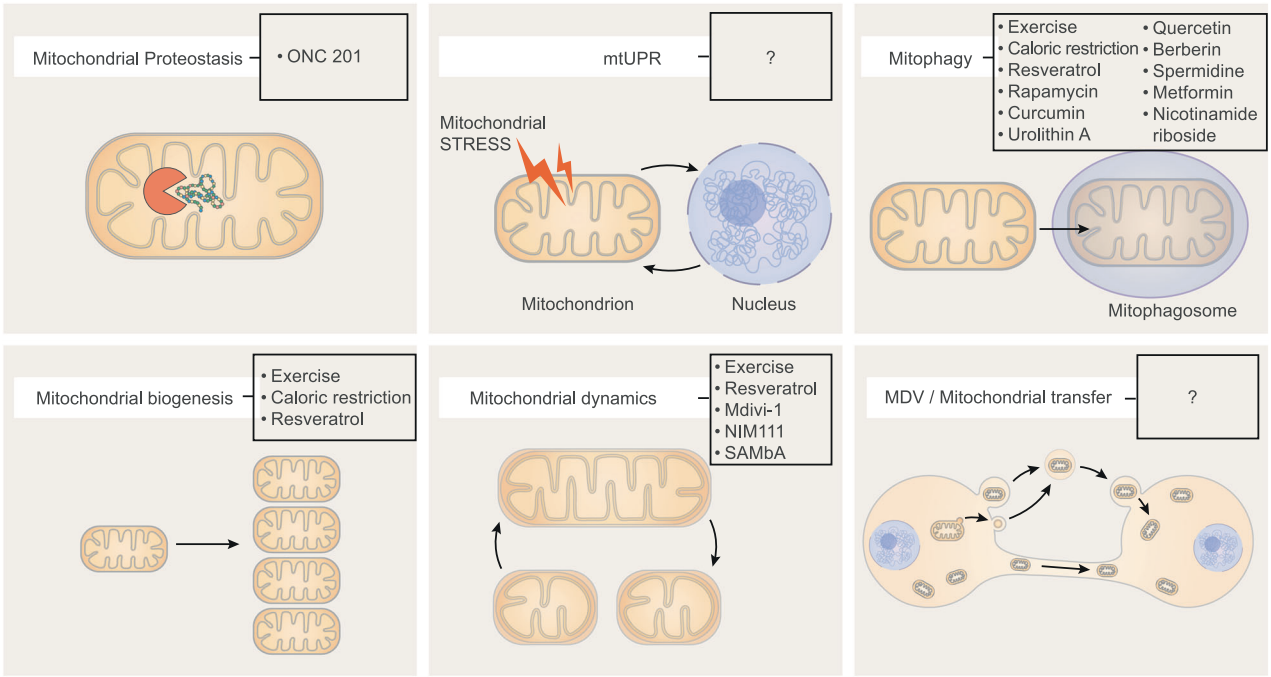


Fig. 6 Strategies targeting mitochondrial quality control. Summary of the different strategies and compounds described to target mitochondrial quality control mechanisms and to promote mitochondrial health

overexpressing the autophagy modulator TP53INP2 in mouse muscle mitigates sarcopenia and promotes healthy aging.[428] Defective mitophagy has been described in muscle satellite cells from aged mice and humans, contributing to the loss of muscle regenerative capacity.[429] However, studies using different mitophagy reporters have yielded conflicting results. One study observed reduced mitophagy associated with aging in the hippocampus of transgenic mice expressing the mitophagy reporter mt-Keima,[430] while a recent study using transgenic mice expressing the mitoQC mitophagy reporter found that aging is associated with stable or even increased mitophagy in multiple organs,[431] challenging the view of reduced mitophagy during aging and highlighting the potential influence of methodology on these findings. Human studies also present a mixed picture. While most studies report dysfunctional mitophagy in older individuals, often measured by the expression of mitophagy regulators, others find no significant differences.[3] For example, some studies have found reduced expression of several mitophagy-related genes (*PRKN*, *ATG7*, *BECN1* and *BNIP3*) in skeletal muscle from frail older women[432] and reduced Parkin levels in muscle from physically active old men.[433] However, other research has found no differences in the expression of Parkin, BNIP3 and p62 in muscle from sedentary older individuals.[434] Intriguingly, increased BNIP3 protein expression in the muscle of older individuals with healthy aging markers suggests that BNIP3-driven mitophagy may be protective.[435] Moreover, increased accumulation of p-Ub, a well-established marker of PINK1-Parkin-related mitophagy, in the hippocampus of aged individuals may suggest decreased mitophagy.[436] Despite these inconsistencies, several mitophagy modulators, such as urolithin A, spermidine and NAD^+ enhancers, have shown promise in models of aging and age-related diseases.[437–439]

Other aspects related to MQC and their role in aging

Genomic instability affecting mtDNA has been proposed to contribute to aging and age-related pathologies. The first proposed evidence for a causative role of mtDNA mutations in aging came from studies in the mtDNA mutator mouse model, which exhibited an accelerated aging phenotype and a 50% reduction in lifespan.[92,440] Further studies have proposed that mtDNA deletions and not point mutations act as drivers of aging in this mouse model.[441] However, the concept of loss of mtDNA integrity as a driver of aging has been challenged by different studies using mouse models deficient in proteins involved in mtDNA replication, which accumulate mtDNA mutations and deletions without significantly affecting lifespan.[442,443] Therefore, although mtDNA mutations have been shown to increase during aging across human tissues, their functional implication in the aging process remains unclear.[444] Another proposed role for mtDNA in aging is through its ability to induce inflammation. One of the hallmarks of aging is the development of a low-grade, chronic, sterile inflammatory state often called “inflammaging”. In this regard, as described above, defects in MQC systems can lead to mtDNA release from mitochondria and the induction of inflammation, which could participate in aging and age-related pathologies. Activation of either the NLRP3 inflammasome or cGAS-STING pathway, which can be activated by mtDNA, has been proposed as a major contributor to chronic inflammation and functional decline during aging.[445,446] In humans, unhealthy aging is characterized by reduced levels of the mitophagic protein BNIP3 and increased NLRP3 and inflammation in muscle.[435] Interestingly, in humans, circulating mtDNA has also been shown to increase with age and correlate with serum inflammatory markers.[447] Alterations in mitochondrial dynamics also induce inflammation by mislocation of mtDNA and activation of the NLRP3 or cGAS-STING pathways, which may explain the link between dysregulation of mitochondrial dynamics and some aging-related phenotypes.[98,99] Activation of mPTP is enhanced in aging and age-related diseases, suggesting a role of the pore as a driver of the aging process.[232] The mPTP opening threshold is lowered in mitochondria from old mice compared to young mice,[448] and spontaneous oscillations in mPTP activity are associated with aging in *C. elegans*.[449] Interestingly, mild inhibition of mPTP in heterozygous CypD KO mice, but not in homozygous mice, increased lifespan, suggesting that complete inhibition and loss of physiological roles of the mPTP could be detrimental.[450]

Remarkably, low mPTP activity is also required for the beneficial role of autophagy in lifespan extension in *C. elegans*.[451] Finally, in humans, an increased sensitivity to mPTP opening has been described in the atrophied muscle of older subjects.[433]

Overall, while manipulating MQC clearly impacts lifespan in lower model organisms such as flies and worms, its role in mice and humans appears more strongly associated with healthy aging and preventing age-related diseases. Further human studies are necessary to precisely define how these mechanisms influence aging and longevity.

THERAPEUTIC STRATEGIES TARGETING MQC

As described in the previous sections, mitochondrial quality is essential for cellular and organismal health, and its decline is strongly linked to aging and age-related diseases. Remarkably, studies in different experimental models have shown that improving mitochondrial health can extend lifespan and mitigate age-related pathologies. Consequently, MQC has become a promising therapeutic target to combat these diseases and promote healthy aging. Several mitochondrial health-promoting strategies have been identified, including lifestyle and dietary changes, as well as pharmacological therapies (Fig. 6).

Physical exercise is a potent catalyst for mitochondrial health, employing multiple mechanisms to enhance mitochondrial quality. Treadmill running activates AMPK and inhibits mTOR, triggering ULK1 activation and mitophagy in mouse muscle.[452] Similarly, acute exercise promotes Parkin translocation to mitochondria and increases mitophagic flux in mouse muscle,[453] a process dependent on PGC1α[454] and impaired with age.[453] Exercise rescues age-related mitochondrial dysfunction in both mouse muscle [99,455] and *C. elegans*[456] and boosts mitochondrial fission and mitophagy in mouse muscle *via* the PGC1α/FNDC5/irisin pathway.[457] However, the type and duration of exercise influences its effects on mitochondrial quality. In humans, endurance exercise,[434,458] but not resistance training[459] or acute exercise,[460] improves age-related alterations in mitophagy and mitochondrial dynamics protein expression in muscle. In mice, long-term endurance training increases muscle mitophagy marker expression and Parkin translocation but paradoxically reduces exercise-induced mitophagic flux,[461] possibly because improved mitochondrial function lessens the need for mitophagy. Beyond muscle, exercise may also enhance mitochondrial quality in other tissues, such as the heart and liver,[462,463] expanding the beneficial effects of exercise at the whole-body level.

Caloric restriction (CR)––reducing food intake without causing malnutrition––is considered a highly effective strategy for delaying age-related diseases across species.[464] In mice, CR promotes the expression and activation of PGC1α, sirtuins and AMPK, potentially contributing to the maintenance of mitochondrial biogenesis and mitophagy during aging.[420,465] Human studies on CR and mitochondrial function in muscle have yielded mixed results. One study found that CR increased mitochondrial function, linked to increased mitochondrial biogenesis[466]; however, another trial found improved mitochondrial function without changes in mitochondrial mass.[467]

While increased physical activity and reduced calorie intake are known to improve mitochondrial quality and delay age-related diseases, their effectiveness varies depending on factors such as individual adherence, age and genetic predisposition. Biomedical research is heavily invested in developing drugs that mimic these interventions, but such drugs face challenges such as tissue specificity, long-term safety and inconsistent human efficacy. Resveratrol, a natural polyphenol and CR mimetic, improves mitochondrial function by influencing mitochondrial biogenesis, mitophagy and mitochondrial dynamics in several aging and/or age-related disease models.[468] Similarly, the CR mimetic rapamycin promotes mitophagy in vitro by inducing PINK1, Parkin and BECN1.[469] Other natural compounds, including berberine, quercetin, curcumin and spermidine, have also shown promise in promoting mitochondrial quality and mitigating age-related changes in preclinical models.[470] However, human clinical evidence supporting their effects on mitochondrial health is limited. Urolithin A, a polyphenol metabolite derived from ellagic acid by gut bacteria, was found to increase longevity and reduce age-related disease by inducing mitophagy in preclinical models.[437] It also improved muscle performance and increased the mitophagy marker phosphorylated Parkin in the muscle of middle-aged overweight adults in a randomized trial.[471]

Several synthetic compounds, described as mitochondrial health boosters, have demonstrated potential benefits in age-related diseases. For example, metformin, a common hypoglycemic drug, promotes mitophagy through AMPK activation in peripheral blood mononuclear cells from patients with T2DM, both in vitro and in vivo.[472] Nicotinamide riboside, an NAD^+ precursor and a sirtuin activator, increases mitophagy and activates the mtUPR in different experimental models,[473–475] although its effects on human mitochondrial function are inconsistent.[476,477] Other compounds, such as modulators of the Kelch-like ECH-associated protein 1 (KEAP1) pathway[478] and SIRT1 activators,[479] influence mitophagy indirectly. Manipulating mitochondrial dynamics has also shown promise: inhibiting mitochondrial fission with Mdivi-1 (a chemical DRP1 inhibitor) or promoting mitochondrial fusion with small molecules targeting MFN2 (MiM111) or MFN1 (SAMβA) is protective in various diseases.[480–482] Finally, ONC201, an activator of the mitochondrial protease ClpP, reduces inflammation and ameliorates diet-induced steatohepatitis in mice.[483]

Mitochondrial transplantation constitutes an innovative cellular therapy approach for treating major diseases. It consists of the isolation and transplantation of healthy and functional mitochondria into defective cells to replace impaired ones. This approach has been proven to be effective in several disease models, including I/R injury in the heart or central nervous system[484,485] and in liver and kidney injury.[486,487] Additionally, a clinical study reported the effectiveness of mitochondrial transplantation in alleviating myocardial I/R injury.[488] In cancer, mitochondrial transplantation from nonmalignant cells has been shown to reverse malignant phenotypes. For instance, transplantation of gastric epithelial mitochondria into gastric cancer cells reduces cancer stemness and enhances chemosensitivity,[489] and transfer of mitochondria from bone marrow stromal cells to T $CD8^+$ cells enhances their antitumor efficacy.[490] In autoimmune diseases, treatment of T cells from RA patients with purified healthy mitochondria has been shown to restore the metabolic abnormalities of the recipient cells and to reduce the development of RA-like disease in a humanized mouse model.[382] Overall, these data suggest that administering cell-free mitochondria may have therapeutic potential. However, further studies are needed to assess the long-term safety, efficacy, potential side effects and ethical considerations.

These promising preliminary findings support the potential of targeting mitochondrial quality through diverse interventions for healthy aging. However, more research is needed to determine whether other MQC pathways (mtUPR, MDVs, mitochondrial transfer) can be effectively targeted. Furthermore, these preclinical results must be translated to human studies. Such studies should prioritize personalized approaches, combining lifestyle modifications with pharmacological interventions to maximize benefits for diverse populations.

CONCLUDING REMARKS

In recent decades, our understanding of mitochondrial biology has advanced significantly. While initially viewed primarily as energy producers, mitochondria are now recognized as central

hubs that integrate cellular information and coordinate appropriate responses to maintain homeostasis both in health and disease. Given their crucial role, cells have developed multiple MQC mechanisms to preserve mitochondrial integrity. Not surprisingly, disruptions in these MQC mechanisms have been linked to aging and many chronic diseases, reinforcing the idea that maintaining mitochondrial quality is essential for mitigating the effects of age-related diseases.

In this review, we have focused on different facets of MQC and its role in disease and aging. We have summarized recent advances in therapeutic interventions targeting these MQC processes, highlighting their potential for combating age-related diseases. While significant progress has been made using different experimental models, many questions remain regarding the link between mitochondrial quality and human disease. Key areas requiring further investigation include identifying all components of MQC mechanisms, understanding their interactions and determining whether age-related changes in MQC are a cause or consequence of disease. Critically, we must assess the translatability of these findings to humans to maximize the therapeutic potential of improving mitochondrial quality. This translation faces challenges, including limited access to human tissue samples and the lack of robust methods for assessing MQC in humans. Further research could confirm mitochondrial quality as a promising therapeutic target for age-related diseases and promote health.

ACKNOWLEDGEMENTS

Space constraints prevent us from including all relevant references for this expanding field. We apologize for any omissions. This study was supported by research grants PID2021-124645OB-100 funded by MICIU/AEI/10.13039/501100011033 and ERDF, EU; CNS2023-144685 funded by MICIU/AEI/10.13039/501100011033 and European Union NextGenerationEU/PRTR, and RED2022-134927-T funded by MICIU/AEI/10.13039/501100011033. A.C. is a recipient of a postdoctoral fellowship from MSCA-Sello de Excelencia ISCIII-HEALTH, funded by Instituto de Salud Carlos III and NextGenerationEU/PRTR (IHMC22/00034).

AUTHOR CONTRIBUTIONS

Conceptualization, D.S.; Writing—Original Draft, S.M., A.C., L.O., and D.S.; Writing—Review and Editing, D.S.; Funding Acquisition, D.S. All authors have read and approved the review article.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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