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Mitochondrial stress and aging: Lessons from *C. elegans*

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ABSTRACT

Aging is accompanied by a progressive decline in mitochondrial function, which in turn contributes to a variety of age-related diseases. Counterintuitively, a growing number of studies have found that disruption of mitochondrial function often leads to increased lifespan. This seemingly contradictory observation has inspired extensive research into genetic pathways underlying the mitochondrial basis of aging, particularly within the model organism *Caenorhabditis elegans*. The complex and antagonistic roles of mitochondria in the aging process have altered the view of mitochondria, which not only serve as simple bioenergetic factories but also as signaling platforms for the maintenance of cellular homeostasis and organismal health. Here, we review the contributions of *C. elegans* to our understanding of mitochondrial function in the aging process over the past decades. In addition, we explore how these insights may promote future research of mitochondrial-targeted strategies in higher organisms to potentially slow aging and delay age-related disease progression.

1. Introduction

Over 60 years ago, pioneering molecular biologist Sydney Brenner put forth the transparent tiny worm *Caenorhabditis elegans* as a model organism for studying developmental and neurobiological problems [1,2]. Over time, research using *C. elegans* has been extended to diverse biological fields including the genetic basis of aging [3,4]. Since the discovery of worm mutants exhibiting altered longevity phenotypes, extensive studies have been conducted to explore the genetic pathways responsible for controlling the rate of aging using *C. elegans* [5–9]. The first two mutants leading to increased lifespan were *age-1* and *daf-2*, which both function through the insulin growth factor-like pathway [10,11]. The discovery of the third long-lived mutant *clk-1,* a mitochondrial hydroxylase, which is required for the biosynthesis of ubiquinone, quickly linked mitochondrial stress to longevity, despite disruption to mitochondrial function [12,13]. Further studies have shown that a variety of mitochondrial perturbations may increase lifespan, including disruption of the mitochondrial electron transport chain (ETC) activity by RNA interference (RNAi) knock-down [14–17] and inhibition of mitochondrial mRNA translation [18]. However, certain mitochondrial mutations and knockdown of complex II subunits are short-lived, suggesting that not all mitochondrial stress has beneficial effects on longevity, with mild mitochondrial damage possibly promoting longevity [14,19,20].

In response to mitochondrial stress, the longevity pathway is genetically distinct from previously identified signaling pathways such as the insulin-like/IGF-1 pathways. It has been observed that the forkhead-box family transcription factor DAF-16, which is required to prolong the lifespan of *daf-2* mutants [21], is dispensable for the increased lifespan of *clk-1(e2519)* mutants [16,22]. Additionally, the lifespan extension of *clk-1* is additive when combined with the *daf-2* mutation. Another intriguing phenomenon is the critical timing window during development for mitochondrial stress to exert beneficial effects on the extension of lifespan in *C. elegans*, suggesting sustained cellular reprogramming. In this review, we provide an overview of the mitochondrial basis of aging, summarize emerging concepts, and underlying molecular mechanisms involved in mitochondrial stress-induced longevity with a focus on *C. elegans*.

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2. An overview of mitochondrial function during aging

As one of the most important organelles for the physiological activities in eukaryotes, mitochondria are semi-autonomous organelles that play important roles in material and energy metabolism, signal transduction, stem cell fate determination, and cell survival [23–28] (Fig. 1). Moreover, mitochondria are able to crosstalk with other cellular compartments, including the endoplasmic reticulum (ER), lysosome, peroxisome, and lipid droplets by physical binding or molecular signals [29,30]. These interactions not only regulate the functioning of these organelles but are also critical for the health and longevity of organisms [31–38]. Outside of metabolism and signal transduction, mitochondria are critical for the stemness maintenance, differentiation, and regeneration of stem cells [39–43], as well as defining immune cell subsets and important immune functions [44]. In recent years, an increased number of studies have suggested that mitochondria also act as signaling organelles to regulate various forms of cell death, including apoptosis, pyroptosis, necrosis, ferroptosis, and cuproptosis [28,45–47] (Fig. 1).

Mitochondrial dysfunction is a prominent biomarker of various diseases and is also associated with aging [48–50]. During aging, mitochondria exhibit significant network changes, accumulation of genetic mutations, loss of mitochondrial membrane potential (MMP), increased production of reactive oxygen species (ROS), decreased bioenergy synthesis capacity, and dysregulation of mitochondrial quality control machinery across humans and model organisms [51,52] (Fig. 1). Notably, it has been proposed that mitochondrial dysfunction is not only a concomitant event occurring throughout aging but also an important driving force of aging itself and aging-related diseases [53,54].

C. elegans serves as an excellent model for studying mitochondrial stress and aging due to a wide range of advantages, including a short lifespan, complete genome sequence, a wealth of genetic tools, and high genetic homology with humans [55,56]. Similar to mammals, a dramatic change in mitochondria can be observed in multiple tissues of *C. elegans* during aging [57]. Notably, restoring mitochondrial function and activating mitochondrial quality control pathways may delay aging in *C. elegans* [58,59].

3. Mitochondrial ROS and aging

Reactive oxygen species (ROS) are generally regarded as damaging signals causing oxidative stresses and the acceleration of aging [52,60,61]. Given that mitochondria contribute to the generation of over 90% of cellular ROS [62], it is natural to speculate upon the effect of decreased mitochondrial activity and whether this could suppress the production of mitochondrial ROS, thereby decreasing cellular damage during aging [63]. However, it was surprising to note that the loss of mitochondrial superoxide dismutase *sod-2,* which leads to reduced ROS degradation, significantly extends lifespan [64]. A subsequent study confirmed that long-lived *isp-1, nuo-6,* and *sod-2* mutants exhibited increased mitochondrial superoxide levels, and supplementation with antioxidants diminished the observed longevity phenotype [65]. Interestingly, the *sod-2* mutation further increased the lifespan of *clk-1* mutants [66]. Together, these results indicate that in opposition to the oxidative damage theory of aging, mitochondrial ROS could serve as a protective signal and elicit beneficial effects on lifespan [67–69].

It has been widely recognized that multiple signaling pathways are involved in the regulation of longevity in animals with elevated mitochondrial ROS [70–74], leading to the concept of mitohormesis, a term used to define the activation of an adaptive stress response that results in a beneficial effect on health and lifespan in response to low-level exposure of mitochondrial ROS. In *C. elegans,* both intrinsic and canonical apoptosis signaling pathways are required for increased lifespan caused by mitochondrial ROS signaling in *isp-1* and *nuo-6* mutants [72]. Moreover, both HIF-1 (hypoxia-inducible factor) and AMPK (AMP-activated protein kinase) mediate lifespan extension in *isp-1* mutants or animals treated with a low dose of paraquat [70,73]. Notably, activation of AMPK reduces the level of ROS, while activation of HIF-1 increases total ROS levels in long-lived animals [70], suggesting that the longevity caused by ROS is under the feedback and precise regulation by AMPK and HIF-1 (Fig. 2). Additionally, recent studies have shown that mitochondria-derived hydrogen peroxide (H_2O_2) promotes nuclear translocation of the transcriptional factor KLF-1 (Krüppel-like factor-1) via the p38 MAPK pathway. This strategy regulates the expression of xenobiotic detoxification genes and promotes lifespan extension in *C. elegans* [75,76] (Fig. 2).

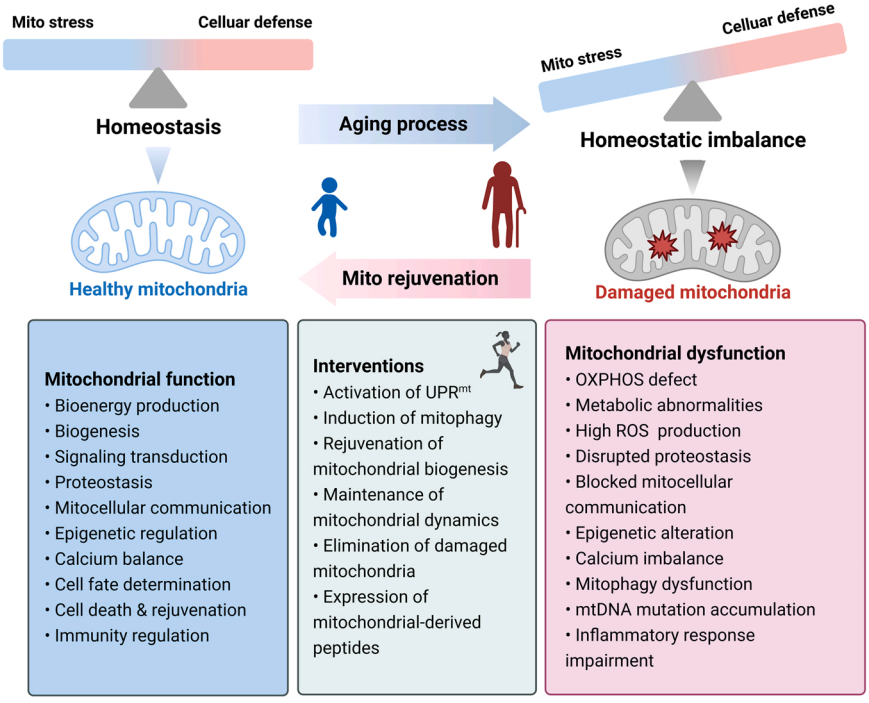

Fig. 1. Overview of mitochondrial function and decline throughout the aging process. Under physiological conditions, mitochondria act as cellular energy factories to produce bioenergy and regulators of signal transduction and intracellular proteostasis. In addition, mitochondria are also involved in cell fate and immune regulation. During the aging process, multifaceted structural alterations and functional declines take place in mitochondria thus disrupting systemic health. Notably, rescuing mitochondrial function through physiological interventions or medications can delay aging and aging-related disease progression. Created with BioRender.com.

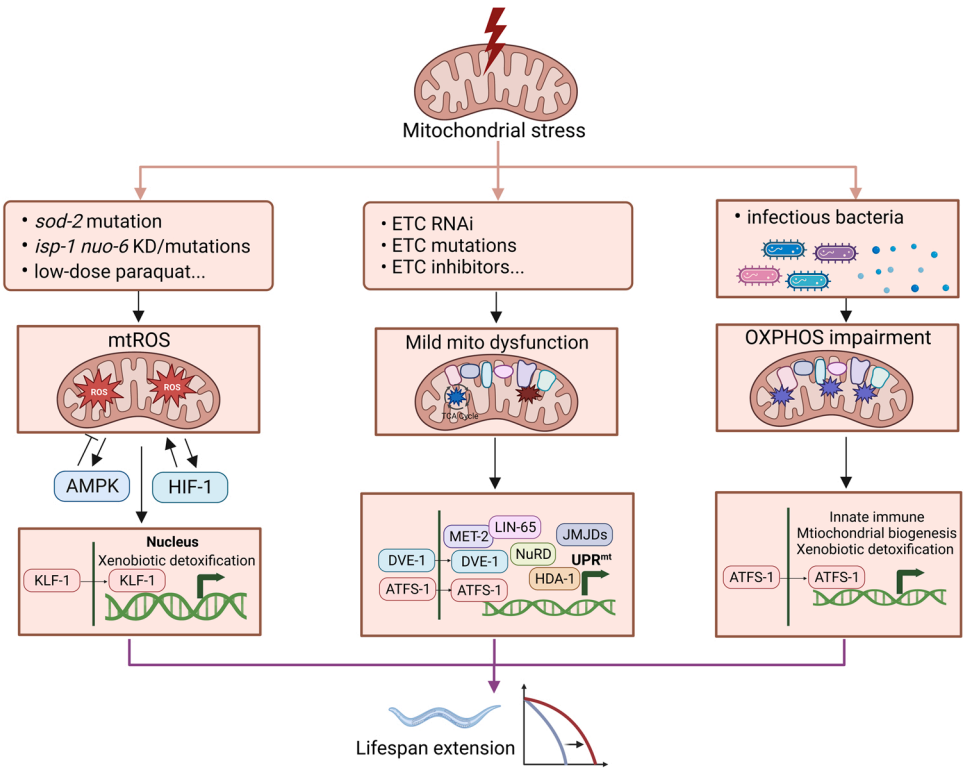

Fig. 2. Overview of mitochondrial stress-induced longevity pathways in *C. elegans*. Mild mitochondrial stress (including mutations, RNAi, drugs, and infections) can activate mitochondrial protective responses through disruption of the mitochondrial electron respiratory chain, releasing of mitochondrial ROS signals, and imbalance of mitochondria-nuclear proteostasis. These adaptive responses can promote mitochondrial repair and homeostasis, thereby extending lifespan. Created with BioRender.com.

Overall, these experiments suggest that while increased oxidative damage by ROS does indeed lead to aging, ROS in isolation may act as stress signals to activate multiple regulators and signaling pathways to enhance anti-oxidative abilities and promote longevity. Due to the compartment-specific effect on lifespan, future studies are required to identify specific mitochondrial regulators and analyze why and how these regulators sense the ROS signal. In addition, understanding how mitochondrial ROS act outside the organelle to impact cellular physiology may provide therapeutic targets to improve cellular fitness and ultimately lifespan without inducing mitochondrial damage.

4. Mitochondrial unfolded protein response and aging

4.1. Mitochondrial unfolded protein response (UPR^{mt})

The mitochondrial unfolded protein response (UPR^{mt}) was initially identified as an adaptive transcriptional response to promote mitochondrial proteostasis and maintain proper physiological activities in response to the accumulation of unfolded and misfolded proteins within mitochondria [77–80]. It was first reported that mitochondrial dysfunction could be caused by depleting mtDNA or interrupting proper protein folding and processing in cultured mammalian cells which led to elevated expression of mitochondria-specific chaperones and proteases [80,81]. While a high-frequency of mtDNA mutations was observed at single cell level [82], it was difficult to further investigate the molecular details in cultured cells due to limited tools and technologies. Taking advantage of *C. elegans* as a discovery tool, Drs. Haynes and Ron performed genetic screens via EMS mutagenesis and RNAi knockdown to identify key regulators of the UPR^{mt}. They demonstrated that the mitochondrial matrix protease CLPP-1 and mitochondrial matrix peptide exporter HAF-1 transduce the UPR^{mt} signal to nuclei via the transcription factor complex of DVE-1 (SATB1/2 homeobox transcription factor) and UBL-5 (ubiquitin-like protein), as well as the bZIP transcription factor ATFS-1 [83–86]. Further studies demonstrated that under normal conditions, ATFS-1 is transported into mitochondria where it is subject to LONP-1 protease-mediated protein degradation. However, under mitochondrial stress, the import efficiency is decreased in dysfunctional mitochondria and ATFS-1 enters the nucleus to regulate the expression of genes involved in OXPHOS, metabolism, and protein folding [87,88]. In parallel with the transcriptional activation of stress-related genes, mild mitochondrial dysfunction may also decrease general translation via GCN-2-mediated eIF2α phosphorylation [89]. Studies in *C. elegans* via genetic screens contribute greatly to our understanding of UPR^{mt} pathways and have accelerated the identification of bZIP transcription factors ATF4, ATF5, and CHOP as functional homologs involved in UPR^{mt} activation in mammalian cultured cells [81, 90,91]. Although the role of the UPR^{mt} is related to mitochondrial surveillance machinery and it is conserved across species, the molecular mechanism is more complex in higher organisms and requires further exploration across various physiological and pathological conditions [92,93].

4.2. UPR^{mt} regulation and aging

The link between UPR^{mt} activation and longevity was identified to explain why mutant worms with reduced ETC activity generally lived longer, despite a reduced body size and impaired mitochondrial function. Using genetic screening to identify long-lived mutants of *C. elegans*, Dillin et al. conducted large-scale RNAi screening of genes located on chromosome I and revealed that RNAi of various ETC components, including *atp-3, nuo-2,* and *cco-1*, all led to lifespan extension [16]. A similar screen consistently uncovered that RNAi of mitochondrial genes resulted in lifespan extension in *C. elegans* [17]. Thereafter, more studies demonstrated that multiple perturbations to mitochondria could elicit a beneficial effect on lifespan regulation and activate the UPR^{mt} [14,18, 94]. Elucidating the genetic pathways for UPR^{mt} regulation allowed investigating into the role of UPR^{mt} in mitochondrial stress-induced longevity. Researchers then uncovered that inhibition of the UPR^{mt} could partially suppress longevity in ETC mutants [14,95].

Another interesting phenotype of mitochondrial stress-induced longevity is the specific timing requirement during development to exert a beneficial effect on lifespan [16]. Animals exposed to *cco-1* RNAi

during development activated the UPR^{mt} and had an extended lifespan, whereas *cco-1* RNAi in adulthood did not activate the UPR^{mt} and elicited no effect on lifespan, suggesting that ETC-mediated longevity was positively correlated with the UPR^{mt} activation [16,96]. This result also indicated that an epigenetic memory in response to mitochondrial stress was constructed during development and maintained in adulthood [16].

Independent studies have revealed that many chromatin regulators required for transcriptional reprogramming of the UPR^{mt} are also essential for the epigenetic control of mitochondrial stress-induced longevity [97–99]. Dr. Tian performed large-scale genetic screens and found animals with mutations in *lin-65* that showed inhibition of the UPR^{mt} [100]. During mitochondrial stress, LIN-65 accumulates in the nucleus and requires the histone methyltransferase MET-2 to reorganize the chromatin structure and facilitate UPR^{mt} activation [100]. Meanwhile, Merkwirth et al. performed an RNAi screen and identified histone lysine demethylases JMJD-1.2 and JMJD-3.1 as key regulators of longevity in animals with reduced mitochondrial ETC activity. Consistently, PHF8 and JMJD3, mammalian homologs of JMJD-1.2 and JMJD-3.1, are positively correlated with UPR^{mt}-related genes through modulation of H3K27 methylation in cell lines and BXD mice [101]. In addition, it has been reported that mild mitochondrial stress results in reduced histone acetylation, which is required for UPR^{mt} activation and lifespan extension due to the limited production of acetyl-CoA and nuclear accumulation of histone deacetylase [102,103]. The histone acetyltransferase CBP-1 functions downstream of histone demethylases JMJD-1.2 and JMJD-3.1, but upstream of ATFS-1 to promote histone acetylation and thereby induce multiple beneficial effects upon mitochondrial stress [104] (Fig. 2).

Combined, these findings demonstrate that signaling communication between mitochondria and nuclei is required to restructure chromatin and activate the UPR^{mt} during chronic mitochondrial stresses, thus enabling long-lasting stress regulation that impacts lifespan [97]. Further studies should help to elucidate whether other epigenetic modifications are altered and involved in signaling transduction under mitochondrial stress, how metabolism changes within mitochondria are perceived by epigenetic modulators, and whether these epigenetic changes may be used to develop therapeutic targets for metabolic diseases.

4.3. Cell-non-autonomous UPR^{mt} regulation and aging

While ETC reduction across all tissues promotes longevity, it also results in damage to worms, including delayed growth, smaller size, and reduced fecundity. Interestingly, the knockdown of certain ETC components in neuronal cells extends lifespan and activates the UPR^{mt} in peripheral tissues without causing defects in growth and reproduction [95]. Later, studies have reported that various mitochondrial perturbations may cause similar inter-tissue communication in *C. elegans* [143,144]. For example, neuronal-specific expression of Tom20::KillerRed or polyglutamine (Q40), neuronal RNAi knockdown of mitochondrial protease *spg-7* or mitochondrial fusion regulator *fzo-1*, or ablation of neuronal epigenetic regulators all lead to the induction of the UPR^{mt} in the intestine, the major metabolic tissue in *C. elegans* [105–108] (Fig. 3). As there is no connection between *C. elegans* neurons and intestinal cells, it has been speculated that a "mitokine" signal may exist which is generated from the nervous system undergoing mitochondrial stress [95]. This signal is then released and perceived in distal tissues which have not been directly impacted by mitochondrial stress [95].

The neurotransmitter serotonin was the first identified neuronal signal to mediate cell non-autonomous UPR^{mt} activation [105]. In addition, the neuropeptide FLP-2 has been demonstrated in transducing a non-autonomous UPR^{mt} signal to the peripheral tissue [107]. However, overexpression of either serotonin or FLP-2 is not sufficient to extend worm lifespan (Fig. 3). Importantly, secreted Wnt signaling has been identified as essential for cell non-autonomous UPR^{mt} activation [109]. Further, overexpression of the gene encoding the Wnt ligand EGL-20 in neurons was sufficient to activate UPR^{mt} in the intestine and extend the lifespan of *C. elegans* [109]. The ER-located protein disulfide isomerase PDI-6 regulates the stability and secretion of EGL-20 under neuronal mitochondrial stress to coordinate inter-tissue UPR^{mt} activation and downstream lifespan extension [110] (Fig. 3). Neurotransmitters, neuropeptides, and insulin-like peptides are necessary for the

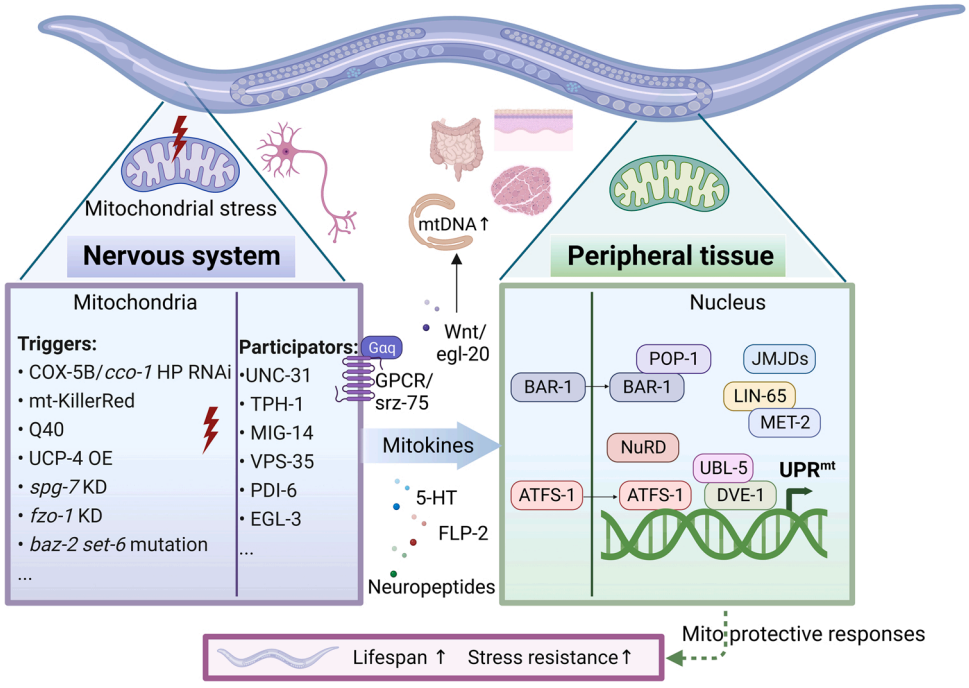

Fig. 3. The inter-tissue mitochondrial stress communication and mitokine signals. Under mitochondrial stress, neurons release mitokines to peripheral tissues including the intestine, germline, and others. These signaling molecules induce peripheral tissues to initiate mitochondrial protective responses, thereby regulating metabolism and increasing stress resistance, ultimately promoting systemic health. Created with BioRender.com.

activation of cell non-autonomous UPR^{mt} in animals with depleted neuronal *fzo-1* [106]. In addition, G-protein coupled receptor (GPCR) SRZ-75 acts in two chemosensory ADL neurons to coordinate the systemic mitochondrial stress response [111]. More importantly, activation of GPCR and downstream Gαq signaling in just two ADL neurons altered various distinct physiological characteristics in different distal tissues, including an altered metabolic state in the intestine, improved proteostasis in muscle cells, and increased stress resistance to pathogens [111] (Fig. 3). Besides, two conserved neuronal epigenetic regulators negatively regulated the mitochondrial function in peripheral tissues in *C. elegans* and led to accelerated aging [108]. Overall, multiple factors coordinate inter-tissue communication of neuronal mitochondrial stress with Wnt/EGL-20 as a strong candidate of mitokines which have an impact on lifespan regulation.

Outside of the neuron-intestine axis, perturbations of the germline could also non-autonomously activate UPR^{mt} in distal tissues. Reduced germline CYC-2.1, or cytochrome c, which functions between complex III and IV in the mitochondrial ETC, not only activates intestinal UPR^{mt} but also promotes longevity [112]. Aggregation of PGL-1, a germline-specific P granule regulator, promotes somatic mitochondrial fragmentation and aggregation, thereby inducing UPR^{mt} in peripheral tissues [113]. Therefore, it will be interesting to explore the identities of germline-produced mitokine signals and elucidate the downstream molecular mechanisms in future studies. It will also be interesting to investigate the impact of metabolic changes in peripheral tissues on mitochondrial function in neurons.

4.4. Debate on the relationship between UPR^{mt} and lifespan regulation

The relationship between the UPR^{mt} and longevity is controversial. Early studies have found that the activation of the UPR^{mt} accompanies lifespan extension in *C. elegans*. RNAi knockdown of the UPR^{mt} regulator UBL-5 partially suppresses the longevity of *isp-1(qm150)* and *clk-1 (e2519)* mutants or animals treated with *cco-1* or *mrps-5* RNAi [18,95]. However, a genome-wide RNAi screen of UPR^{mt} activation as measured by elevated expression of the *hsp-6p::gfp* reporter revealed that certain RNAi treatments can activate UPR^{mt} but cannot extend lifespan. Induction of the UPR^{mt} via inhibition of mitochondrial prohibitins (*phb-1* and *phb-2*), cytochrome b (*mev-1*), or NADH dehydrogenase (*gas-1*) is accompanied by reduced lifespan [20,114,115]. Additionally, ATFS-1 deficiency failed to reduce the lifespan extension in the *isp-1* mutant, and gain-of-function mutations of *atfs-1* are unable to induce lifespan extension, although they are sufficient for the activation of the UPR^{mt} [116]. Therefore, there appears to be no simple correlation between UPR^{mt} activation and longevity. It should also be noted that many studies relied upon the *hsp-6p::gfp* or *hsp-60p::gfp* reporters as the main output to measure UPR^{mt} activation. Considering the complexity of UPR^{mt} regulation and context-dependent mitochondrial stresses, it may be better to perform tissue-specific transcriptional analysis during mitochondrial stresses and develop new tools to monitor UPR^{mt} activation from multiple angles.

4.5. Mitochondrial DNA and aging

Mitochondrial DNA (mtDNA) consists of a small (16.6 kb) circular genome encoding 11 mRNAs (translated into 13 proteins in humans), 2 rRNAs, and 22 tRNAs [117]. The maintenance of mtDNA homeostasis is essential for mitochondrial function and therefore cellular activity [118, 119]. While the majority of mtDNA mutations have been linked with mitochondrial dysfunction and a wide range of age-related diseases, several mitochondrial haplogroups and populations that share similar mitochondrial polymorphisms have been associated with increased lifespan in humans [120,121].

Recent studies in *C. elegans* have made great contributions to our understanding of the role of mtDNA in aging. To comparatively analyze protein and nucleic acid compositions in intact and functional mitochondria, researchers developed a cell-specific mitochondrial affinity purification (CS-MAP) approach for the isolation of mitochondria from different tissues in *C. elegans* and found that the mtDNA copy numbers vary across different tissues. Moreover, the percentage of mutated mtDNA is higher within the germline than in somatic lineages [122]. This specific and robust mitochondrial purification approach could be used to analyze tissue-specific differences in mtDNA levels, protein compositions, and mitochondrial activity in worms as well as other model organisms.

As there are hundreds to thousands of copies of mtDNA in each cell, the composition of mtDNA is often heterogeneous, with different types of mtDNA haplotypes coexisting in a cell [123]. Recent studies in worms have extended our understanding of the maintenance and propagation of deleterious mtDNA under both normal and stress conditions. In animals containing both the wild-type and a 3.1 kb deletion within mtDNA, loss of the bZIP protein ATFS-1 significantly decreased the level of deleterious mtDNA [124]. Further studies have demonstrated that ATFS-1 and the mtDNA replicative polymerase (POLG) work together to promote replication of deleted mtDNA, while inhibiting the mitochondrial protease LONP-1 prevents the degradation of ATFS-1 in healthy mitochondria and increases wild-type mtDNA levels [125]. The mitochondrial location of ATFS-1 is required for mtDNA replication after prolonged starvation in *C. elegans* in coordination with the insulin-like receptor, DAF-2 [126]. These results indicate that ATFS-1 plays a crucial role in wild-type and mutated mtDNA replication under different cellular conditions. In addition, the level of deleterious mtDNA is also impacted by PINK1 and parkin activity, two main regulators for the mitophagy pathway. Tissues with reduced mitophagy levels are prone to accumulate deleterious mtDNA mutations in *C. elegans* [127]. Therefore, the maintenance of mutated mtDNA is often regulated by different mechanisms in *C. elegans*, and it will be interesting to examine the conservation of these mechanisms in mammals.

Although previous studies have showed that the mtDNA copy number decreases with age and higher mtDNA levels have been linked with increased physical and mental health among aged populations [128, 129], the detailed mechanism remains largely unknown. An interesting study revealed that neuronal mitochondrial stress signals could be transmitted to the offspring via a Wnt-mediated increase in mtDNA levels in germ cells, enabling offspring to inherit elevated copy numbers of mtDNA in *C. elegans* [130]. This strategy thereby confers increased stress resistance and lifespan extension to offspring [130–132]. Interestingly, *C. elegans* wild-type strains ED3011 and KR314 exhibited significantly higher copy numbers of mtDNA compared to the reference N2 strain. Inter-strain crosses between ED3011/KR314 and N2 demonstrated that F1 animals, which inherited mitochondria exclusively from ED3011 or KR314 retained higher levels of mtDNA, exhibited UPR^{mt} activation and displayed significantly longer lifespan compared with corresponding F1 counterpart animals generated from the reciprocal crosses [130]. With improved mitochondrial genome editing approaches, it will be interesting to address how specific mtDNA mutations impact health and lifespan in both *C. elegans* and mammals.

4.6. Targeting mitochondria to delay aging

Myo-inositol (MI), an endogenous metabolite, activates PTEN/DAF-18 and PINK1 to promote mitophagy and extend the lifespan of *C. elegans* [133]. Through induction of mitophagy, NAD^+ boosters (NMN; NR) and natural compounds (urolithin A; actinonin) delay the pathology and behavioral defects in worm models of Alzheimer's diseases [134,135]. Certain physiological interventions have similar effects. For example, exercise stimulates mitochondrial biogenesis signals and enhances mitophagy, thus maintaining mitochondrial homeostasis throughout the aging of mammalian skeletal muscle [136]. In *C. elegans*, swimming exercise prevents the fragmentation of body wall muscle mitochondria with aging and extends lifespan [136,137]. Moreover, dietary restriction extends the lifespan of *C. elegans* through a variety of

mitochondrial benefits, including mitophagy induction, mitochondrial network maintenance, mitochondrial respiration activation, and oxidative stress resistance [138–140]. Overexpression of mitochondria-derived peptide humanin also extends the lifespan of *C. elegans* [141,142]. Thus, *C. elegans* may be a useful model for screening interventions that target mitochondria to delay aging and promote health.

5. Conclusion

Taken together, studies using *C. elegans* as a model organism suggest that mitochondrial function is closely related to the aging process. However, it has both detrimental and beneficial effects on longevity. Whether mitochondrial dysfunction is associated with or causally linked to aging and age-related diseases remains controversial. Using an interdisciplinary approach including genetics, biochemistry, and in vivo imaging to further explore mechanisms of mitochondrial stress signaling in specific tissues at critical stages will allow for elucidation of the role of mitochondrial function in the normal aging process and various disease-related models.

6. Perspectives

While studies in *C. elegans* have identified a variety of essential regulators for increased lifespan as mentioned above, our understanding of mitochondrial stress and aging remains limited. The physiological consequences of mitochondrial stress signals, including mitochondrial ROS, UPR^{mt} activation, mitochondrial-derived metabolites, mtDNA copy numbers, and cellular stress response upon mitochondrial perturbations require further investigation in other organisms in more relevant physiological settings. Delaying aging is not simply related to extending lifespan. A healthy lifespan and improved cognitive function related to mitochondrial function is the research direction that should be adhered to in the future.

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Declaration of interests

The authors declare no financial competing conflicts of interest in relation to this work.

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