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Review

Mito-nuclear communication: From cellular responses to organismal health

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SUMMARY

The co-evolution of mitochondria and the nucleus established constant mito-nuclear communication that is essential for both cellular and organismal homeostasis. At the cell-autonomous level, mitochondrial perturbations activate retrograde pathways such as the mitochondrial unfolded protein response (UPR^{mt}) and the mitochondrial integrated stress response (ISR^{mt}), which couple organelle dysfunction to nuclear transcriptional programs, thereby promoting mitochondrial function and preserving cellular integrity. Importantly, this communication is not confined to individual cells but extends across tissues to coordinate systemic adaptations. Stress signals can be sensed, broadcasted through secreted mitokines and neural circuits, and then interpreted by distal organs to coordinate systemic adaptations. These systemic responses integrate metabolism, immunity, and behavior, conferring resilience to stress and shaping the trajectory of aging. Understanding this multi-layered communication, from the organelle to the organism and its microbial ecosystem, promises new therapeutic strategies to enhance mitochondrial function, promote resilience, and extend healthspan.

INTRODUCTION

Over a billion years ago, an ancestral eukaryotic cell engulfed an α-proteobacterium, an event that forged an endosymbiotic partnership central to the evolution of complex life. Over time, massive gene transfer to the host nucleus rendered mitochondria dependent on nuclear-encoded proteins for the vast majority of their proteome, cementing an obligatory interdependence. This dependency necessitates a continuous bidirectional dialog for survival and prosperity, which is known as mito-nuclear communication.

Mito-nuclear communication operates along two primary routes. In the anterograde direction, the nucleus regulates mitochondrial biogenesis, composition, and function by encoding thousands of mitochondrial proteins. Conversely, retrograde signaling allows mitochondria to convey their functional state to the nucleus, using a diverse repertoire of messengers, including the ratios of AMP/ATP and NAD^+/NADH, reactive oxygen species (ROS), and other metabolites, which inform transcriptional and epigenetic programs to adapt to mitochondrial dysfunction.[1] Such retrograde communication underlies stress-responsive pathways, including the mitochondrial unfolded protein response (UPR^{mt}) and the mitochondrial integrated stress response (ISR^{mt}), which serve as canonical mechanisms to maintain mitochondrial functions under stress.[2,3] Beyond these protein-based mechanisms, mitochondrial nucleic acids (mtDNA and mtRNA) have also emerged as potent retrograde messengers that can be released into the cytosol under conditions such as pathogen infection or severe oxidative stress to engage innate immune sensors such as cGAS-STING. Although a detailed discussion of these nucleic acid-driven pathways is provided elsewhere in this issue (see review by Winklhofer and colleagues),[4] their recognition significantly expands the known landscape of mito-nuclear communication.

While these cell-autonomous pathways are foundational, emerging evidence suggests that mito-nuclear communication can occur beyond the cellular boundaries, activating systemic responses across tissues. Secreted factors known as mitokines, coupled with neuronal and germline circuits, establish an organism-wide signaling network that coordinates metabolism, modulates behavior, and influences longevity. Here, we review mito-nuclear communication across scales, beginning with cell-autonomous stress responses and extending to systemic regulation of physiology and aging. By linking mechanisms at the organelle level to outcomes at the organismal level, we aim to highlight both the evolutionary logic and the therapeutic potential of mito-nuclear communication.

MITO-NUCLEAR COMMUNICATION IN CELLULAR STRESS RESPONSES

Mitochondria are the central hubs of energy production and metabolic integration, and their performance depends on constant communication with the nucleus. Given that the majority of the mitochondrial proteome is encoded in the nuclear genome, cells rely on precise communication to monitor mitochondrial status and calibrate nuclear transcription

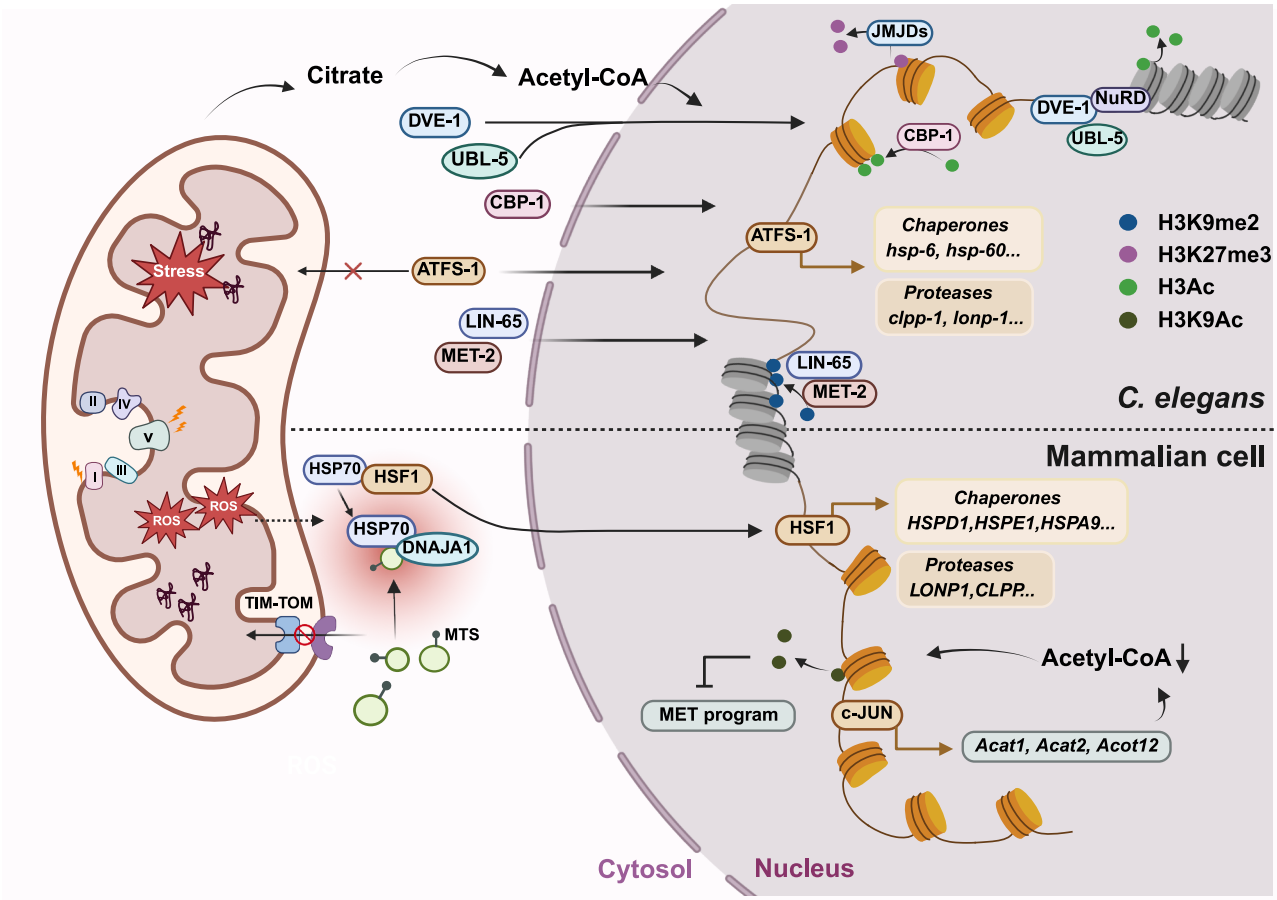

Figure 1. The UPR^{mt}

Mitochondrial stress impairs protein import and activates retrograde signaling to restore proteostasis. In *C. elegans*, ATFS-1 translocates to the nucleus upon compromised mitochondrial protein import to drive the expression of chaperones and proteases, a process facilitated by epigenetic remodeling of chromatin. In mammals, mtROS and unimported precursors activate DNAJA1-HSF1 signaling to drive similar transcriptional programs. Beyond proteostasis, the UPR^{mt} also links metabolic shifts to chromatin regulation and influences cell fate. Created in BioRender.

accordingly.[5–7] When mitochondria experience perturbations, which can arise from genetic defects, environmental stress, or aging, they activate retrograde signaling pathways that communicate their state to the nucleus. These retrograde pathways, collectively known as the mitochondrial stress response, not only restore proteostasis but also recalibrate metabolism, transcription, and cell fate to preserve overall cellular homeostasis.[8,9] Two principal branches exemplify this cell-autonomous communication: the UPR^{mt}, which couples impaired mitochondrial proteostasis to nuclear transcriptional programs, and the ISR^{mt}, which links mitochondrial dysfunction to the cytosolic ISR network to coordinate global adaptation.

The UPR^{mt} in *C. elegans*

Although the UPR^{mt} was first described in mammalian cells,[10,11] its molecular mechanisms have been most clearly defined in the nematode *Caenorhabditis elegans* (Figure 1).[12–14] The central regulator is the transcription factor ATFS-1, which provides a simple yet elegant model of import-based regulation. Under normal conditions, ATFS-1 is imported into mitochondria and degraded; however, when stress compromises mitochondrial protein import, ATFS-1 accumulates in the cytosol and translocates to the nucleus. There, together with partners such as DVE-1, it activates a transcriptional program of mitochondrial chaperones and proteases aimed at restoring proteostasis.[14–16] This adaptive response not only safeguards cellular function but also contributes to the extended lifespan observed under conditions of mild mitochondrial stress.[17,18]

Activation of the UPR^{mt} is accompanied by broad chromatin reorganization. Mitochondrial stress induces nuclear translocation of the histone methyltransferase MET-2 and its cofactor LIN-65, driving global reorganization of chromatin architecture.[19,20] Repression is then selectively relieved at UPR^{mt}-targeting loci by histone H3K27 demethylation catalyzed by Jumonji C domain-containing (JMJD) demethylases,[21] while permissive marks such as H3K27 and H3K18 acetylation are deposited by the coactivator CBP-1/p300.[22] Metabolic shifts further tune this process: for example, the nucleosome remodeling and histone deacetylace (NuRD) complex senses acetyl-coenzyme A (CoA) availability to modulate chromatin states,

linking mitochondrial activity directly to nuclear epigenetic regulation.[23,24] Together, these findings reveal that the UPR^{mt} is not merely a stress-induced transcriptional program but a highly integrated response, coupling mitochondrial proteostasis to the cell's epigenetic and metabolic state. This integration allows the UPR^{mt} to function as both a local repair mechanism and a regulator of long-term cellular adaptation.[25]

The UPR^{mt} in mammalian cells

In contrast to *C. elegans*, where ATFS-1 provides a clear mechanistic framework, the details of UPR^{mt} signaling in mammals have been more challenging to elucidate. The canonical mammalian UPR^{mt}, triggered by misfolded mitochondrial proteins, alleviates proteostatic stress through CHOP-ATF4- or ATF5-dependent transcriptional remodeling.[10,26–28] However, UPR^{mt} induction by ATF5 in ATFS-1-deficient *C. elegans* and HEK293T cells was not recapitulated in HeLa cells, suggesting that ATF5-dependent UPR^{mt} activation is highly context dependent.[27,29] Moreover, although ATF4 and CHOP are transiently induced, the loss of either does not impair UPR^{mt} activation, indicating that the ATF4 axis functions in parallel to the UPR^{mt} branch.[29] Unlike the import-dependent switch of ATFS-1 in worms, mammalian cells appear to rely on cytosolic surveillance mechanisms. A recent study identified two converging signals, mitochondrial ROS (mtROS) and unimported mitochondrial protein precursors (c-mtProt), as triggers of this response (Figure 1).[29] mtROS oxidize the cochaperone DNAJA1, which leads to the recruitment of HSP70 to c-mtProt and promotes the nuclear translocation of heat shock factor 1 (HSF1). Once in the nucleus, HSF1 induces mitochondrial chaperones and proteases, including *HSPD1*, *HSPE1*, and *LONP1*. This pathway reframes the mammalian UPR^{mt} as a cytosolic surveillance system, with DNAJA1 emerging as a potential hub for integrating diverse mitochondrial insults.

Beyond proteostasis, the mammalian UPR^{mt} influences cell fate and plasticity. During the early phase of somatic cell reprogramming, bursts of mtROS act as pivotal epigenetic regulators to promote pluripotency acquisition through modulating histone methylation.[30,31] The UPR^{mt} is transiently activated during somatic cell reprogramming, where it restricts mesenchymal-to-epithelial transition and reduces reprogramming efficiency.[32] Conversely, during differentiation, the UPR^{mt} facilitates epithelial-to-mesenchymal transition. These effects are linked to acetyl-CoA metabolism and histone acetylation, underscoring how mitochondrial stress reshapes the epigenetic landscape.[32] Collectively, the mammalian UPR^{mt} is best understood not as a linear stress pathway but as a multifaceted hub that links mitochondrial proteostasis, metabolism, and cell fate decisions.

The ISR^{mt}

While the UPR^{mt} provides a dedicated pathway for maintaining mitochondrial proteostasis, mammalian cells have also evolved a broader strategy to integrate mitochondrial dysfunction into global stress signaling. This complementary pathway, termed the ISR^{mt}, extends beyond proteotoxic stress to encompass diverse mitochondrial insults, including impaired oxidative phosphorylation (OXPHOS), membrane depolarization, and protein import defects.[33]

The ISR is an adaptive signaling network activated by diverse stimuli, including nutrient deprivation and proteostasis defects. This response is mediated by the phosphorylation of eIF2α by one of four kinases (GCN2, HRI, PERK, and PKR), leading to global translation attenuation and selective translation of stress-responsive mRNAs such as *ATF4* and *CHOP*.[33] As a branch of the ISR, the ISR^{mt} links mitochondrial dysfunction to canonical ISR machinery to coordinate transcriptional and translational programs that preserve cellular homeostasis.

The discovery of the OMA1-DELE1-HRI-ATF4 axis clarified how mitochondrial dysfunction engages this cytosolic network (Figure 2).[34,35] DELE1, a mitochondrial inner membrane protein, is cleaved by the metalloprotease OMA1 under conditions such as OXPHOS inhibition or membrane potential dissipation, releasing a C-terminal fragment (s-DELE1) that translocates to the cytosol.[34,35] There, its C-terminal tetratricopeptide repeat (TPR) domain mediates DELE1 oligomerization and binds to HRI, activating its kinase function and initiating the ISR^{mt} cascade.[36] Only oligomerized DELE1 efficiently triggers eIF2α phosphorylation,[36] and emerging evidence suggests additional molecules may fine-tune this interaction.[37] This activation leads to translational reprogramming and the upregulation of ATF4-dependent genes (e.g., *FGF21*, *GDF15*, *MTHFD2*, and *ATF5*). In the terminal phase of the ISR^{mt}, mild activation of ATF3 and the UPR^{mt} may also occur, thereby restoring redox balance and proteostasis.[38]

Importantly, DELE1 can also sense protein import stress. Under iron deficiency, unimported full-length DELE1 accumulates on the mitochondrial surface, where it directly recruits HRI independently of OMA1 cleavage.[39] Recent studies further show that DELE1 is processed at multiple cleavage sites[40] and by proteases other than OMA1.[41] These layers of regulation highlight its versatility as a context-dependent stress sensor, capable of distinguishing qualitatively distinct mitochondrial insults. Whether different cleavage products drive specialized transcriptional responses or converge on the common ISR^{mt} program remains an important open question.

Functionally, the ISR^{mt} supports recovery from severe mitochondrial insults. It promotes repair after mitochondrial DNA double-strand breaks (mtDSBs),[42] contributes to mitophagy,[43] and maintains redox homeostasis in cardiomyocytes.[43] Intriguingly, studies implicating HRI in this process have yielded conflicting results: one reports that HRI-driven eIF2α phosphorylation promotes mitophagy independently of the PINK1-Parkin pathway,[44] whereas another suggests HRI acts as a negative regulator of PINK1-dependent mitophagy.[45] These opposing outcomes highlight a context-dependent and still unresolved role of the ISR^{mt} in mitochondrial quality control. Loss of *Oma1* or *Dele1* exacerbates mitochondrial cardiomyopathy and myopathy,[46–48] while the sustained activation of the OMA1-DELE1-HRI axis improves cell growth, neuronal survival, mitochondrial structure, and even lifespan in models of spastic ataxia type 5 (SPAX5).[49] Notably, *Oma1*- or *Dele1*-knockout mice appear largely asymptomatic under basal conditions,[50] underscoring the ISR^{mt} as a stress-inducible safeguard rather than a housekeeping function.

Recent work has also revealed the ISR^{mt} as a driver of pathology in certain contexts. The progression of mitochondrial

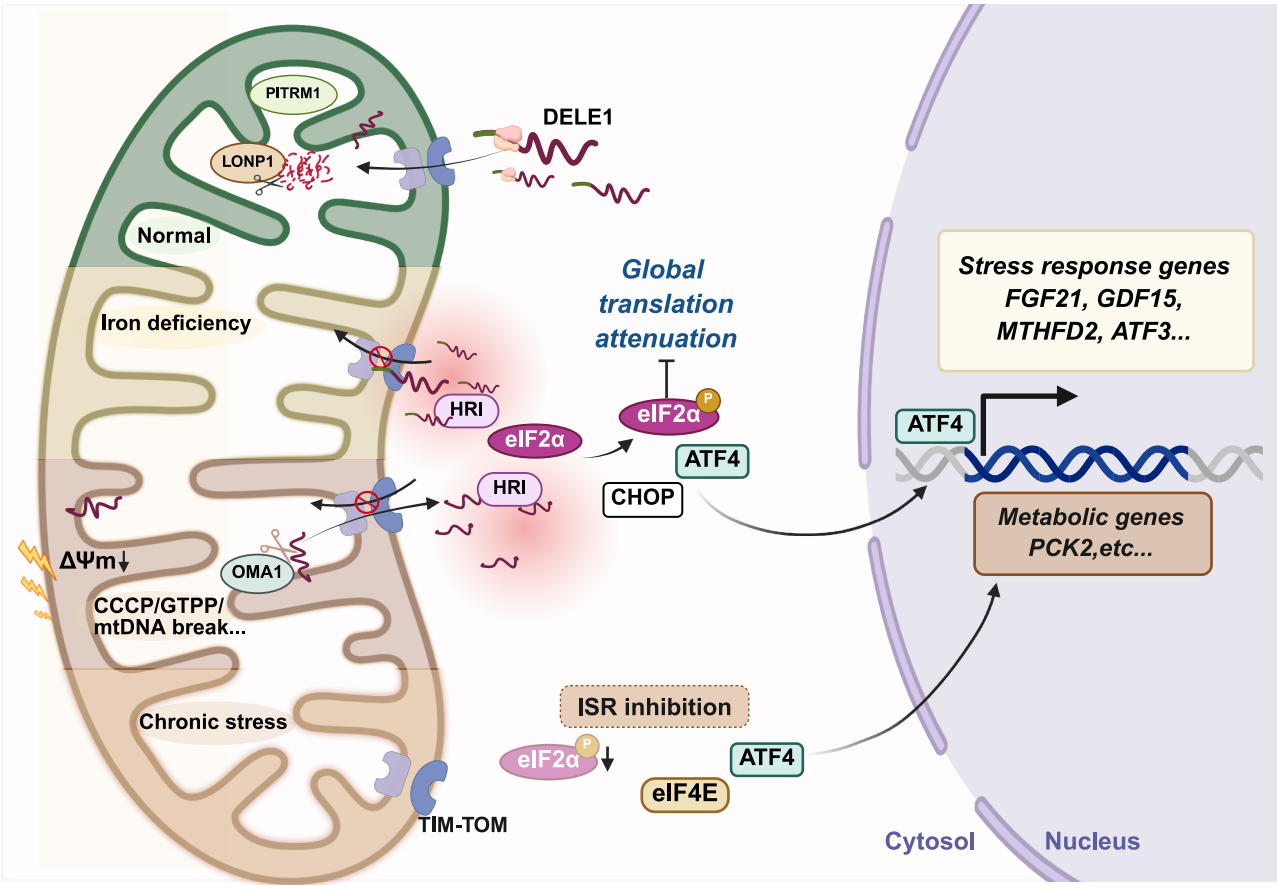

Figure 2. The ISR^{mt}

DELE1 acts as a versatile stress sensor that couples mitochondrial dysfunction to the cytosolic ISR. Under iron deficiency, unimported DELE1 accumulates on the mitochondrial surface to activate HRI. Acute insults trigger OMA1 cleavage, releasing s-DELE1 to bind HRI and induce eIF2α phosphorylation, which attenuates global translation while promoting ATF4-driven transcription. Under chronic stress, reduced ISR activity is buffered by eIF4E-mediated stabilization of ATF4, sustaining metabolic adaptation. Created in BioRender.

myopathy is accompanied by long-term induction of the ATF4-dependent ISR^{mt}, chronic upregulation of anabolic pathways, and secretion of mitokines such as GDF15 and FGF21.[51] In metabolic tissues, defects in mitochondrial quality control activate retrograde ISR^{mt} signaling, which remodels chromatin and reprograms transcription away from mature identity genes, thereby driving dedifferentiation and metabolic dysfunction.[52] The ISR^{mt} also emerges as a maladaptive regulator of tissue identity, and its pharmacological inhibition (e.g., by ISR inhibitor [ISRIB]) can restore pancreatic β-cell mass and function, highlighting its potential as a therapeutic target in metabolic disease.[52] The sustained ISR^{mt} activation in astrocytes enhances anabolic metabolism and promotes ciliary elongation, suggesting a potential link to the pathogenesis of ciliopathy-related mitochondrial neurodegenerative disorders.[53] These findings emphasize that the ISR^{mt} must be tightly regulated in duration and intensity to remain beneficial.

The discovery of DELE1 has raised several key questions. Since acute mitochondrial stress triggers strong ISR activation via eIF2α phosphorylation and ATF4 upregulation, whereas chronic mitochondrial dysfunction dampens ISR signaling but retains ATF4-dependent tuning of cytosolic translation to maintain long-term adaptation,[54,55] a key question arises as to how DELE1 discriminates between these acute and chronic mitochondrial stress states to tailor ATF4-dependent transcription. Another central question is whether s-DELE1 represents the sole mediator of ISR signaling and whether eIF2α phosphorylation constitutes the exclusive downstream effector. Although the ISR has traditionally been defined as a pathway activated through eIF2α phosphorylation, additional evidence indicates that this response can also be engaged independently of eIF2α kinases. Recent research divided the ISR into two different sensing modes: the canonical ISR driven by eIF2α phosphorylation sensing acute stress and the split ISR triggered by reduced eIF2B activity under chronic mitochondrial stress, which reprograms transcription via eIF4E to intersect during mitochondrial stress.[56] Futhermore, what feedback loops limit s-DELE1 persistent accumulation to prevent cytotoxicity? Understanding how the ISR^{mt} integrates mitochondrial signals into nuclear adaptation and how it might be harnessed therapeutically will be the key to elucidating the signaling crosstalk between mitochondria and nucleus.

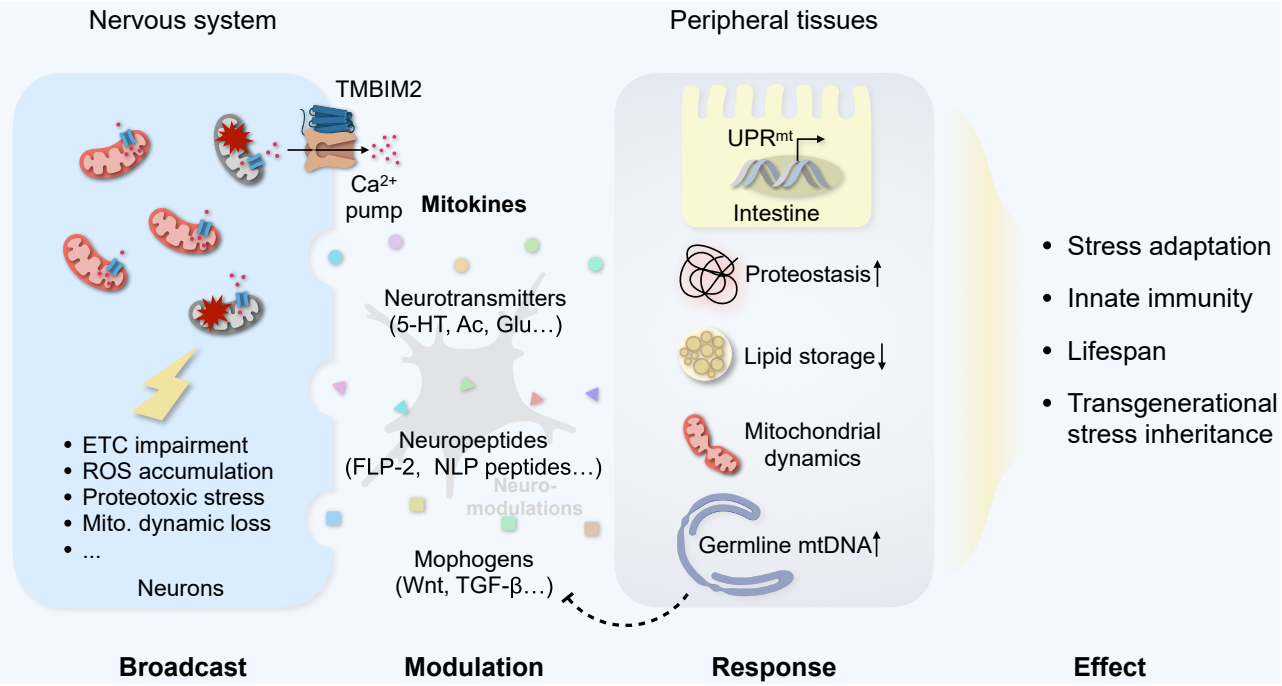

Figure 3. Systemic mito-nuclear communication coordinates organismal physiology

Local mitochondrial stress can be sensed and converted into secreted mitokines that broadcast signals across tissues. These systemic cues are integrated and modulated by neuronal circuits and suppressed by germline signals during aging. Distal tissues then decode the signals to mount adaptive responses, leading to organism-wide outcomes such as enhanced stress resilience, innate immunity, and longevity.

Together, the UPR^{mt} and the ISR^{mt} constitute the two principal arms of cell-autonomous mito-nuclear communication. Importantly, they also provide the mechanistic foundation for stress signals that can be amplified and transmitted beyond the single cell. In the following section, we consider how these local responses scale across tissues, forming systemic mito-nuclear communication networks that coordinate organismal physiology and aging.

SYSTEMIC MITO-NUCLEAR COMMUNICATION

While mito-nuclear communication is fundamental for maintaining homeostasis within individual cells, accumulating evidence shows that these signals are not confined by the plasma membrane. Mitochondrial stress can be sensed locally and relayed across tissues, giving rise to systemic mito-nuclear communication. This systemic communication coordinates multi-tissue stress responses that sustain metabolic balance, enhance resilience, and influence the aging process. In the following sections, we dissect this communication into three interrelated steps: the sensing and broadcasting of mitochondrial stress, its modulation through inter-tissue circuits, and its interpretation by distal organs (Figure 3).

Sensing and broadcasting

The initial discovery of systemic mito-nuclear communication came from *C. elegans*, where mitochondrial proteotoxic stress restricted to neurons was sufficient to induce the UPR^{mt} in the intestine.[18,57] Given that the nematode intestine lacks direct innervation, this finding implied the existence of secreted signaling molecules, now widely referred to as mitokines, that transmit mitochondrial stress beyond the originating cell to activate mito-nuclear communication pathways in peripheral tissues.[58–60] Subsequent work identified a diverse repertoire of such signals in worms, including morphogens like Wnt and the transforming growth factor beta (TGF-β) ligands[61–64]; classical neurotransmitters such as serotonin, acetylcholine, and glutamate[57,65]; and neuropeptides such as FMRFamide-like peptide (FLP)-2[66] and neuropeptide-like proteins (NLPs).[67]

A central question has been how mitochondrial dysfunction is translated into mitokine release. Recent work identified the conserved transmembrane protein TMBIM-2 as a key mediator.[68] During stress, reduced mitochondrial Ca^{2+} buffering promotes TMBIM-2 enrichment at the plasma membrane and synapses, where it interacts with the Ca^{2+} pump MCA-3 to generate sustained Ca^{2+} oscillations. These Ca^{2+} oscillations facilitate the Ca^{2+}-dependent neurotransmitter release, such as serotonin, which subsequently leads to UPR^{mt} activation in the intestine. Notably, *tmbim-2* expression declines with age across species, aligning with the reduction in Ca^{2+} oscillations over time. Restoring its expression in aged worms reversed the decline of pathogen-induced avoidance learning and extended lifespan.[68] This work illustrates how local mitochondrial stress is sensed, broadcast, and ultimately linked to organismal health.[69]

Orchestration and modulation

Systemic mito-nuclear communication is not a simple on/off switch but is shaped by multi-layered circuits that integrate

diverse inputs to fine-tune organismal responses. This principle is exemplified by the ASI-RIM neuronal axis in *C. elegans*.[62] Mitochondrial stress in ASI sensory neurons induces the secretion of the TGF-β homolog DAF-7, which acts on RIM interneurons to orchestrate the systemic UPR^{mt} in the intestine. This response is further modulated by opposing inputs, with dopamine positively regulating the systemic signaling, whereas GABA negatively regulates it.[62,70] A related study showed that RIM neurons respond to peripheral mitochondrial stress by secreting octopamine, which acts on AIY interneurons to integrate sensory input essential for aversive memory retrieval.[71] Together, these findings highlight the principle of neuronal computation: systemic mito-nuclear outputs are not simple reflexes but integrated physiological states shaped by a complex interplay of neuronal signals.

Modulation can also originate outside the nervous system, with the germline functioning as a central hub that gates systemic communication, particularly during aging.[72,73] With age, germline-derived signals actively suppress the somatic UPR^{mt}, contributing to the decline in stress resilience.[74] This reveals a fundamental trade-off between reproduction and somatic maintenance, positioning the germline as a pacemaker of aging. By controlling somatic stress resilience via systemic mito-nuclear communication, the germline shapes the balance between organismal longevity and reproductive success.

Receiving and responding

Once released, mitokines must be decoded by distal tissues to elicit adaptive responses. In *C. elegans*, mitokines released from neurons act at a distance to trigger the UPR^{mt} in the intestine, promote proteostasis in the muscle, and alter lipid metabolism, thereby reinforcing proteostasis and enhancing defense against pathogens.[57,67] This communication enhances intestinal stress resilience, with direct benefits for organismal health and lifespan.

Systemic mito-nuclear communication is often bidirectional, allowing the nervous system to monitor the metabolic state of peripheral tissues and adjust behavior accordingly. For instance, mitochondrial stress confined in peripheral tissues can trigger aversive learning, prompting animals to avoid potential hazards.[71] This adaptation relies on neuromodulators such as serotonin and octopamine,[75] illustrating how mitochondrial stress signals are integrated into coherent behavioral strategies that promote organismal fitness.

The germline also acts as a vital recipient of somatic stress, with effects that can be inherited across generations. Neuronal mitochondrial stress can be transmitted to the germline, increasing mitochondrial DNA (mtDNA) copy number via mitokine Wnt in a manner that is maternally inherited for over 50 generations.[76] This "stress memory" provides offspring with improved metabolic resilience and longevity but comes with tradeoffs like delayed development and reduced fecundity,[76,77] scaling the impact of mito-nuclear communication from organismal homeostasis to the fitness of a lineage.[78]

Systemic mito-nuclear communication in mammals

Although initially described in nematodes, systemic mito-nuclear communication is increasingly recognized in mammals, where a distinct suite of mammalian mitokines, including fibroblast growth factor 21 (FGF21),[79–81] growth differentiation factor 15 (GDF15),[82] and various mitochondrial-derived peptides,[83–85] mediates bidirectional signaling between neuron and peripheral tissue (Table 1; also see Zhang et al.[60] for a respective review on mammalian mitokines).

As in *C. elegans*, the mammalian brain can sense metabolic state and dispatch signals to regulate peripheral physiology. For example, a mild mitochondrial defect in hypothalamic proopiomelanocortin (POMC) neurons elicits cell non-autonomous effects that protect mice from diet-induced obesity and improve systemic glucose metabolism.[86] This neuroendocrine axis is mediated by the mitochondrial-derived peptide mitochondrial open reading frame of the 12S rRNA-c (MOTS-c), which promotes UPR^{mt} activation and thermogenesis in adipose tissue.[87] Physiologically, exercise stimulates hypothalamic MOTS-c expression, illustrating how local neuronal stress can be harnessed for systemic benefit.[87] By contrast, severe mitochondrial perturbations, such as the genetic ablation of OPA1, suppress lipolysis in white adipose tissue and promote obesity,[88] highlighting systemic mito-nuclear communication as a metabolic rheostat that translates mitochondrial status into distinct organismal outcomes.

Conversely, peripheral tissues can broadcast mitochondrial stress to the brain. GDF15, secreted from muscle during mitochondrial stress, acts on hindbrain receptors to suppress appetite and regulate energy homeostasis.[82] FGF21, induced by mitochondrial dysfunction in muscle or liver, circulates systemically to drive metabolic adaptations in target tissues (e.g., adipose, liver, and hippocampus).[89,90] Humanin, a peptide encoded by mtDNA, exerts robust neuroprotection and promotes cell survival.[84,91] Elevated levels of circulating mitokines, including GDF15, FGF21, and Humanin, are associated with exceptional longevity in humans,[92,93] underscoring their role in systemic resilience. The translational potential of these pathways is already evident, as GDF15 receptor agonists and FGF21 analogs are in clinical development for metabolic diseases.[94,95]

The role of the germline in acute systemic communication remains less explored in mammals. Whether a germline-soma mitokine axis actively coordinates stress responses, as in nematodes, represents a critical open question with broad implications for aging and metabolic health.

Physiological implications of systemic mito-nuclear communication

Together, current findings establish systemic mito-nuclear communication as a unifying mechanism that integrates mitochondrial stress across tissues to coordinate organismal physiology. This network influences metabolism by adjusting glucose and lipid balance,[86–88] shapes behavior by modulating appetite and aversive learning,[71,75,96] and regulates aging by maintaining proteostasis and resilience across the lifespan. Remarkably, its influence extends across generations: maternal mitochondrial stress can imprint heritable changes in germline mtDNA content, enhancing progeny resilience and linking these pathways to evolutionary fitness.[76,77]

By scaling local mitochondrial distress into organism-wide adaptations, systemic mito-nuclear communication provides a

Table 1. Mitokines in *C. elegans* and mammals

Mitokine	Transmission path	Local effects	Systemic effects
C. elegans			
Wnt/EGL-20	neurons → peripheral tissues	activates UPR^{mt} in the intestine	coordinates systemic stress resilience and extends lifespan
	neurons → germline	increases germline mtDNA copy number	confers offspring stress resilience and extends their lifespan
TGF-β/DAF-7	ASI → RIM → intestine	activates UPR^{mt} and depletes fat storage in the intestine	enhances pathogen tolerance and extends lifespan
Neuromodulators (serotonin and octopamine)	neurons → intestine	required for neuronal-to-intestinal UPR^{mt} activation	promotes aversive learning against hazards
Neuropeptides (FLP-2 and NLP peptides)	neurons → peripheral tissues	required for neuronal-to-intestinal UPR^{mt} activation	improves stress resilience
Mammals			
FGF21	liver/skeletal muscle → metabolic tissues (e.g., adipose and liver)/hippocampus	activates ISR^{mt} and induces metabolic adaptations (e.g., lipolysis and glucose uptake) in target tissues	increases energy expenditure; protects against diet-induced obesity and insulin resistance; drives weight loss
GDF15	skeletal muscle → hindbrain	activates hindbrain neurons to suppress appetite	drives weight loss while maintaining energy expenditure
MOTS-c	skeletal muscle (exercise-induced) → adipose/bone	adipose: promotes thermogenesis and brown fat activation; bone: promotes the differentiation of osteoblasts while inhibiting bone resorption	acts as an exercise-mimetic to improve metabolic health
	hypothalamic POMC neurons → adipose	activates UPR^{mt} and promotes thermogenesis	improves systemic glucose metabolism; prevents diet-induced obesity
Humanin	ubiquitous (mainly metabolic tissues) → neurons	inhibits neuronal cell death in Alzheimer's disease	provides neuroprotection

robust conceptual and therapeutic framework. Understanding how mitokines and tissue circuits interact to sustain resilience may open new avenues for interventions targeting metabolic disorders, neurodegeneration, and age-associated decline, ultimately offering strategies to extend healthspan.

CONCLUDING REMARKS

In this review, we describe mito-nuclear communication, ranging from cell-autonomous pathways that safeguard mitochondrial function to systemic networks that broadcast signals across tissues. Organized around the principles of sensing, broadcasting, modulation, and response, these pathways coordinate stress resilience, metabolic balance, and aging, positioning mito-nuclear communication as a fundamental pillar of organismal health.

Furthermore, this network may not be confined to the host's own cells, extending its reach to a ''meta-organismal'' scale shaped by the gut microbiota. Microbial metabolites such as peptidoglycans and lactate can be directly sensed by host mitochondria, triggering adaptive programs that influence physiology and longevity.[97–99] Conversely, host mitochondrial dysfunction can remodel microbial communities, creating feedback loops that affect health and disease.[100,101] These findings raise a provocative possibility: mitochondria may act as a crucial interface, translating microbial chemical cues into host nuclear responses, integrating the microbiome into the systemic communication network.

As discussed, while acute activation of mito-nuclear communication drives protective hormesis, chronic or dysregulated signaling can lead to pathology, such as metabolic dysfunction and neurodegeneration. This dual nature presents a significant challenge for translation. Looking forward, key challenges include unraveling the temporal dynamics of these pathways: how they are tuned during development, adapt to chronic versus acute stress, and decline with age. The therapeutic goal is not simply to activate or block these pathways but to fine-tune the conversation to differentiate beneficial mitohormesis from maladaptive chronic stress. By precisely modulating the duration and intensity of mitokine signaling to harness protective adaptations while avoiding the detriment of sustained activation, we may one day learn to rewrite mito-nuclear communication to extend healthspan and mitigate age-related disease.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used ChatGPT and Google Gemini in order to improve readability. After using the tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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