Burns & Trauma, 2026, 14, tkag037
https://doi.org/10.1093/burnst/tkag037
Published: 21 May 2026
Review

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Mitochondrial unfolded protein response as a central stress-integration hub: mechanisms and implications in disease contexts

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Abstract

The mitochondrial unfolded protein response (UPR^{mt}) is a conserved mitochondrial stress response that is activated by mitochondrial dysfunction to maintain proteostasis. Although UPR^{mt} has been extensively studied in aging and cancer, its role in trauma and critical illness remains poorly understood. Here, we propose a unifying conceptual framework in which UPR^{mt} functions as a central stress-integration hub that senses and coordinates adaptive responses following acute injury. We systematically review the mechanisms of UPR^{mt} activation triggered by diverse insults and highlight how UPR^{mt} integrates mitochondrial-nuclear communication, and crosstalk with other stress-responses such as the integrated stress response and mitophagy. Beyond cell-autonomous regulation, UPR^{mt} also coordinates systemic adaptation through mitokine-mediated interorgan signaling. Importantly, we emphasize the context-dependent role of UPR^{mt} in trauma and critical illness. Moderate activation promotes mitochondrial recovery, limits reactive oxygen species accumulation, and supports immune cell function, thereby enhancing tissue resilience and repair. In contrast, sustained or dysregulated UPR^{mt} contributes to mitochondrial failure, sterile inflammation, and the progression to systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS). Furthermore, we discuss emerging evidence linking UPR^{mt} to immune regulation and inflammatory responses, and propose that targeting key regulatory nodes within this stress-integration network may offer novel therapeutic strategies for a broad spectrum of human diseases. Crucially, we synthesize how UPR^{mt} mechanisms contribute to post-traumatic mitochondrial damage, sterile inflammation, SIRS, and MODS. We propose that targeting key regulatory nodes within this stress-integration network may offer novel therapeutic strategies for trauma, burns, and critical illness.

Keywords UPR^{mt}proteostasis, Trauma, Immunity, MODS, SIRS

Highlights

- Mitochondrial unfolded protein response (UPR^{mt}) acts as a central mitochondrial stress-integration hub in trauma, ischemia–reperfusion injury, and critical illness.
- Dysregulated UPR^{mt} drives sterile inflammation, immune dysfunction, and the progression to systemic inflammatory response syndrome and multiple organ dysfunction syndrome.
- UPR^{mt} plays a context-dependent role in aging by maintaining mitochondrial proteostasis and metabolic homeostasis, thereby influencing longevity and age-related disease susceptibility.
- Precise and context-dependent modulation of UPR^{mt} represents a promising therapeutic strategy for trauma and organ dysfunction syndrome.

Received: 12 January 2026. **Revised:** 16 May 2026. **Accepted:** 19 May 2026
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Background

Mitochondria are double-membrane organelles of endosymbiotic origin that serve as central hubs of cellular metabolism and energy production. Beyond their well-established role in ATP generation through oxidative phosphorylation (OXPHOS) [1], mitochondria regulate a wide range of essential processes, including innate immunity [2, 3], calcium homeostasis [4, 5], cofactor biosynthesis [6, 7], and programmed cell death [8, 9]. The mitochondrial proteome comprises >1000 proteins, of which only 13 are encoded by mitochondrial deoxyribonucleic acid (mtDNA), while the vast majority are nuclear-encoded and imported into mitochondria via the TIM/TOM translocase system. The functional integrity of mitochondria therefore depends on tightly coordinated communication between the nuclear and mitochondrial genomes, as well as efficient protein folding, assembly, and quality control mechanisms.

Mitochondrial dysfunction and impaired OXPHOS are key factors leading to mitochondrial diseases, which exhibit significant heterogeneity and mainly affect neurons and muscle cells. The pathogenesis of mitochondrial diseases is closely related to mutations in genes encoding proteins related to OXPHOS, as well as mutations in genes involved in the assembly of respiratory chain and ATP synthase complex [10, 11]. With the increase of age, mitochondrial function gradually declines, which may be related to the accumulation of mtDNA damage, increased reactive oxygen species (ROS) production, toxin exposure, and the degradation of the organelle itself [12]. Mitochondrial dysfunction plays an important role in aging, and is closely linked to the decline of cellular function, muscle strength and neuronal function, such as in neurodegenerative diseases like Parkinson's disease and Alzheimer's disease [13–15].

In 1996, Hoogenraad's team first used ethidium bromide to deplete mtDNA and disrupt mitochondrial function in mammals [16]. They discovered a stress response mechanism against mitochondrial protein misfolding, which was later named the mitochondrial unfolded protein response (UPR^{mt}). Their study demonstrated that nuclear-encoded mitochondrial chaperonins, such as heat shock protein 60 (*Hsp60)* and heat shock protein 10 (*Hsp10*), have unique regulatory mechanisms: their genes are controlled by a bidirectional promoter, whose transcriptional activity is significantly enhanced when cells are exposed to mtDNA deletion or high temperature stimulation [17–19]. This breakthrough discovery demonstrated for the first time that mitochondria possess regulatory mechanism distinct from the classical heat shock response, maintaining mitochondrial protein homeostasis through a transmembrane signaling mechanism between mitochondria and the nucleus. Proteostasis imbalance arises from local ROS production during OXPHOS and the imbalance between mitochondrial- and nuclear-encoded proteins [20]. In addition, mutations in mtDNA and accumulation of damaged mtDNA can also adversely affect mitochondrial proteostasis [21]. The UPR^{mt} is a conserved mitochondrial stress response pathway that is activated to maintain mitochondrial proteostasis under conditions of mitochondrial dysfunction. It is triggered by the accumulation of unfolded or misfolded proteins within mitochondria, often resulting from imbalances between nuclear- and mitochondrial-encoded proteins, impaired protein import, or oxidative damage. Upon activation, UPR^{mt} induces a coordinated transcriptional program that upregulates mitochondrial chaperones and proteases, thereby enhancing protein folding capacity and promoting the clearance of damaged proteins, ultimately preserving mitochondrial function [22–24].

At present, the molecular mechanisms of partial mitochondrial stress have been systematically elucidated. Although protein accumulation significantly impacts mitochondrial function and cellular health, and has been extensively studied in nematodes, how mammals respond to mitochondrial protein disorder caused by accumulation of misfolded proteins remains unclear. In this review, we discuss the regulation and signal transduction of UPR^{mt} in nematodes and mammals, as well as its important role in aging, tumor, and other diseases, and elaborate the important role of UPR^{mt} in maintaining cellular homeostasis and prolonging lifespan. Our goal is to stimulate further research on UPR^{mt}-targeted therapy and deepen the mechanistic understanding to support future clinical translation and provide new perspectives for disease treatment. Here, we propose that UPR^{mt} functions as a central stress-integration hub, which senses and integrates multiple forms of mitochondrial perturbations—including proteotoxic, metabolic, and redox stress—and translates them into coordinated transcriptional, metabolic, and systemic outputs. Through this integrative architecture, UPR^{mt} governs context-dependent cellular outcomes, ranging from adaptive survival and metabolic reprogramming to immune modulation and cell death.

In this review, we reorganize current knowledge of UPR^{mt} from this perspective, highlighting how distinct signaling pathways and regulatory mechanisms converge within this hub to shape cellular and organismal responses in health and disease.

Review

To improve conceptual clarity, we have reorganized the current understanding of UPR^{mt} into a multi-layer regulatory framework. In this model, UPR^{mt} is not viewed as a collection of independent pathways, but as a coordinated stress-response program composed of distinct yet interconnected regulatory layers. Specifically, UPR^{mt} involves (i) a stress sensing layer that detects mitochondrial perturbations, (ii) a nuclear execution layer that translates these signals into transcriptional and epigenetic outputs, and (iii) a systemic amplification layer that extends stress signaling beyond individual cells. The following sections are organized to reflect these functional layers and their integration.

Stress sensing and nuclear priming of mitochondrial unfolded protein response

Stress sensing and initiation of mitochondrial unfolded protein response

This section describes the stress sensing layer of UPR^{mt}, in which diverse mitochondrial perturbations are converted into initial activation signals. These stimuli can be broadly categorized into four groups: pharmacological and chemical interventions, genetic perturbations, natural compounds, and physiological or environmental stresses. Despite their diversity, these stimuli converge on common mechanisms, including impaired protein folding, defective mitochondrial translation or import, and alterations in metabolic and redox homeostasis, ultimately leading to activation of the UPR^{mt} transcriptional program [25, 26]. These factors synergistically activate UPR^{mt} and provide key insights into its roles in

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development, aging, metabolic diseases, and neurodegenerative disorders [25, 27, 28].

Pharmacological and chemical interventions Pharmacological and chemical agents primarily induce UPR^{mt} by disrupting mitochondrial proteostasis, electron transport, or membrane potential. Tetracyclines (including doxycycline and tetracycline) are widely used mitochondrial translation inhibitors. These drugs suppress mitochondrial protein synthesis by binding to mitochondrial ribosomes, causing mito-nuclear proteome imbalance and accumulation of unfolded proteins in the matrix [29, 30].

Inhibiting the electron transport chain (ETC) is another effective strategy. Rotenone (complex I) and antimycin A (complex III) promote electron leakage and ROS generation [31, 32], similar to the severe oxidative protein damage induced by paraquat [33]. While oligomycin (ATP synthase inhibitor) and sodium azide (complex IV inhibitor) cause ATP depletion and membrane depolarization [34, 35]. The uncoupler CCCP depolarizes mitochondria and blocks protein import, rerouting regulators like ATF5/ATFS-1 to the nucleus to trigger the UPR^{mt} [36]. Together, these interventions are essential for dissecting UPR^{mt} signaling and have demonstrated the tissue-protective effects of UPR^{mt} activation in various animal models.

Genetic intervention Genetic perturbations activate UPR^{mt} by impairing mitochondrial protein quality control or respiratory chain function [37]. Zhao et al. first induced this response in mammalian cells by expressing a mutant form of ornithine transcarbamylase (ΔOTC) to force the accumulation of misfolded proteins in the mitochondrial matrix [18]. Similarly, RNAi-mediated knockdown of mitochondrial proteases (*spg-7*, the m-AAA protease subunit) or chaperones (*hsp-6*, mitochondrial Hsp70) disrupts protein degradation and folding, leading to constitutive UPR^{mt} activation [38, 39]. In addition, impairing energy metabolism through knockdown or mutation of respiratory chain subunits (cco-1, isp-1, and nuo-6) disrupts complex assembly and ATP production, which triggers a protective UPR^{mt} and extends lifespan in *C. elegans* [40–42].

Natural compounds Natural compounds modulate UPR^{mt} through metabolic reprogramming and enhancement of mitochondrial quality control. The nicotinamide adenine dinucleotide (NAD^+) precursors nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) increase cellular NAD^+ levels to activate sirtuins such as SIRT1 and SIRT3, which regulate metabolic enzyme and antioxidant protein activities through deacetylation, thereby triggering UPR^{mt} [43–45]. By restoring mitochondrial homeostasis, NR and NMN exhibit protective effects across models of aging, metabolic disorders, and neurodegenerative diseases [46–48].

Natural compounds, including resveratrol, honokiol, and urolithin A, maintain mitochondrial proteostasis by simultaneously promoting mitochondrial biogenesis and mitophagy [49–51]. Polyamine such as spermidine also support mitochondrial function by sustaining translation of nuclear-encoded mitochondrial genes. In addition, spermidine enhances mitophagy to clear damaged mitochondria, thereby alleviating the upstream protein folding stress associated with UPR^{mt} [52, 53]. These natural interventions provide a feasible strategy for transforming UPR^{mt} into potential therapeutic targets.

Physiological and environmental stresses Physiological and environmental stresses induce UPR^{mt} as an adaptive response to metabolic imbalance, infection, and aging-associated mitochondrial dysfunction. Nutrient limitation, such as glucose or amino acid restriction, can perturb cellular metabolism and tRNA modification, thereby triggering UPR^{mt} [54, 55]. Pathogen infection can directly damage mitochondria or activate inflammatory pathways, inducing UPR^{mt} to maintain mitochondrial mass and energy supply for host defense [56]. During aging, accumulation of mtDNA mutations, increased ROS, and decline in protein quality control lead to mitochondrial dysfunction, which may activate UPR^{mt} [12, 41]. Collectively, UPR^{mt} serves as a central mechanism preserving mitochondrial integrity under diverse stresses conditions.

These diverse stimuli converge on a unified stress-sensing framework that constitutes the initiation layer of the UPR^{mt} program. Diverse strategies, from direct pharmacological intervention to indirect metabolic regulation, and from genetic manipulation to physiological stress, can activate this protective response by disrupting mitochondrial proteostasis, energy metabolism, or redox balance. Despite this progress, important gaps remain in current understanding of the mechanisms of UPR^{mt} activation: are there qualitative differences in the transcriptome and function of UPR^{mt} triggered by different activation modalities? How do tissue-specific UPR^{mt} activation mechanisms differ? How does UPR^{mt} integrate with other cellular quality control pathways such as autophagy and mitophagy? With advancing understanding of UPR^{mt} activation and its physiological and pathological significance, intervention strategies targeting this pathway are expected to provide novel therapeutic approaches for mitochondrial dysfunction-related diseases, including neurodegenerative diseases, metabolic diseases, and aging itself. Future research should aim to elucidate the complete UPR^{mt} regulatory network, identify key nodal proteins as drug targets, and explore personalized activation strategies to maximize the therapeutic potential of UPR^{mt} (Figure 1).

Nuclear execution and chromatin remodeling

In addition to stress sensing, UPR^{mt} activation requires coordinated nuclear responses. Chromatin remodeling is increasingly recognized as an early regulatory event that facilitates UPR^{mt} activation, rather than a merely downstream consequence of mitochondrial stress signaling. These epigenetic mechanisms constitute an early nuclear execution layer, translating mitochondrial stress signals into chromatin remodeling and transcriptional regulation. When mitochondrial function is impaired, chromatin undergoes specific remodeling that promotes UPR^{mt} activation and extends lifespan [57, 58].

In *C. elegans*, this process is mediated through coordinated action of histone modifiers [57, 58]. The methyltransferase MET-2 and its cofactor LIN-65 promote global H3K9me2 deposition and chromatin compaction, whereas the demethylases JMJD-3.1 and JMJD-1.2 preserve transcriptionally permissive states at UPR^{mt} loci, thereby enabling selective gene activation within a repressive chromatin landscape [58]. Additional factors, including DVE-1 and UBL-5, further stabilize stress-induced chromatin architecture. Histone deacetylase HDA-1, a homolog of mammalian

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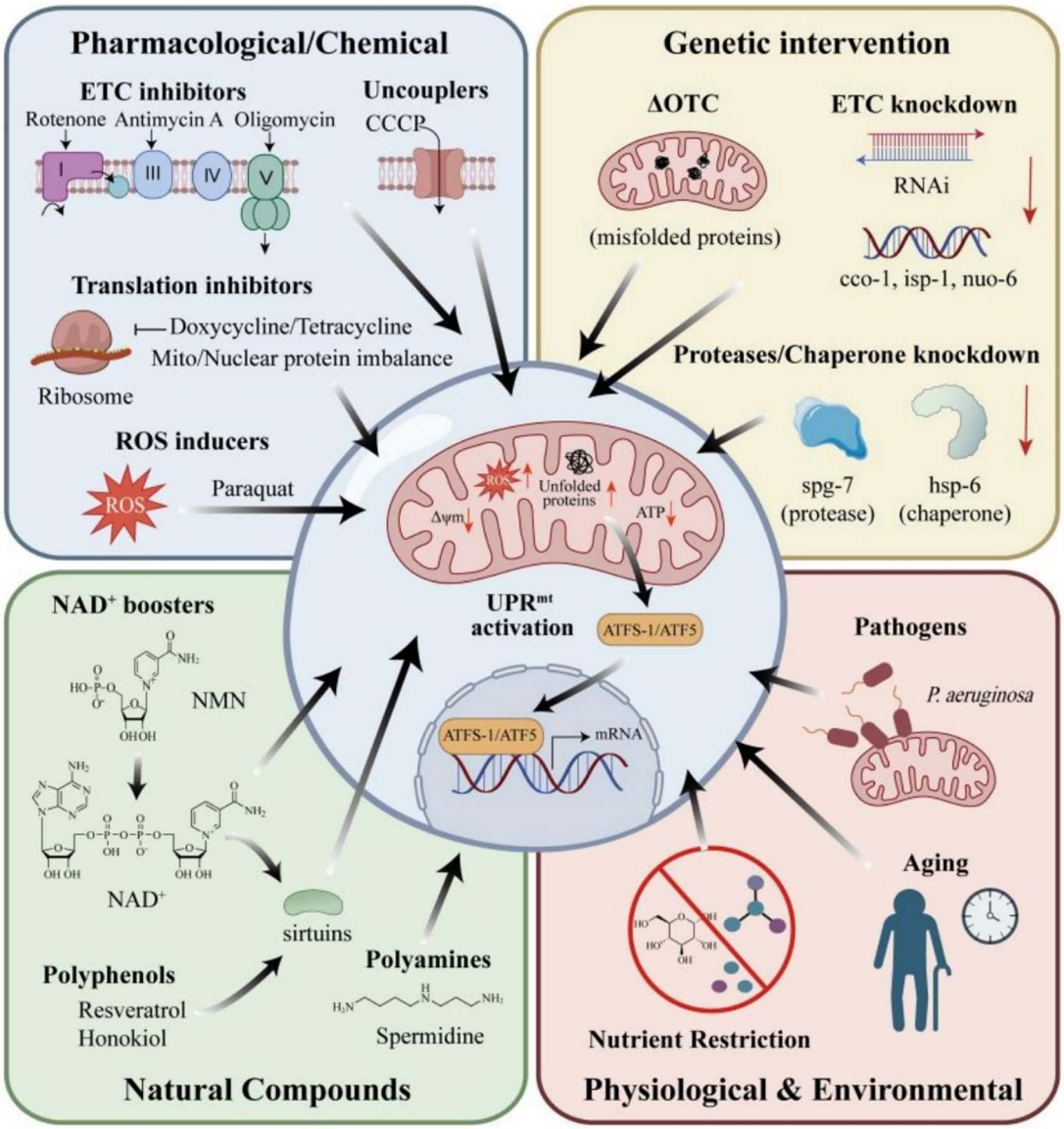


Figure 1 Diverse strategies for UPR^{mt} activation. Multiple factors can trigger the UPR^{mt} signaling pathway. These factors are mainly categorized into four types: pharmacological interventions (e.g. ETC inhibitors, uncouplers, translation inhibitors, ROS inducers), genetic manipulations [e.g. RNAi-mediated knockdown of specific genes, mutant of ornithine transcarbamylase (ΔOTC)], natural compounds (e.g. NAD^+ boosters and polyphenols), and physiological stressors (e.g. pathogen infection, nutrient restriction and aging). By inducing mitochondrial stress—such as ROS accumulation, unfolded protein aggregation and ATP depletion—these triggers ultimately converge to activate the core transcriptional regulators ATFS-1/ATF5, thereby initiating the cellular adaptive response to maintain mitochondrial proteostasis. *UPR^{mt}* mitochondrial unfolded protein response, *ETC* electron transport chain. Figure was created using BioRender and Adobe Illustrator

histone deacetylase (HDAC), synergizes with DVE-1 to promote UPR^{mt} activation [59].

This regulatory logic is evolutionarily conserved. In mammals, PHF8 and JMJD3 function as positive regulators of UPR^{mt} through modulation of H3K27 methylation, while HDAC1/2 and the DVE-1 ortholog SATB2 coordinate chromatin organization and mitochondrial homeostasis [60, 61]. In parallel, the acetyltransferase CBP/p300 axis promotes transcriptional activation of UPR^{mt} genes through enhanced histone acetylation [62].

In conclusion, UPR^{mt} activation is a coordinated, multi-layered process driven by diverse mitochondrial perturbations, including proteostasis imbalance, metabolic dysfunction, and genomic stress. Rather than functioning as an isolated mitochondrial response, UPR^{mt} operates as a central hub that integrates signals from mitochondrial damage with cytoplasmic quality-control systems, metabolic sensing pathways, and epigenetic regulation. This integrated network enables precise transcriptional and adaptive responses to cellular stress. Together, these findings suggest that UPR^{mt} activation is not a single-step event, but rather a coordinated process involving stress sensing and early nuclear priming, thereby setting the stage for downstream signaling and systemic adaptation.

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Signal integration and systemic coordination of mitochondrial unfolded protein response

Following activation in response to mitochondrial stress, UPR^{mt} does not function as a simple linear pathway but instead engages a complex network of downstream signaling events. These signals propagate from mitochondria to the nucleus and are further integrated with other cellular stress-response pathways, enabling coordinated transcriptional, translational, and metabolic adaptation. Moreover, UPR^{mt} signaling can extend beyond individual cells to mediate systemic communication. In this section, we focus on how UPR^{mt} signals are transmitted, integrated, and amplified across different regulatory layers.

Signal communication between mitochondria and nucleus

Transmission of stress signals from mitochondria to the nucleus serves as a critical bridge between stress sensing and nuclear execution, functionally linking different regulatory layers of the UPR^{mt} program. The maintenance of mitochondrial homeostasis relies on a finely regulated protein quality control network, in which mitochondrial retrograde signaling pathway plays a central role in sensing and responding to mitochondrial stress. Over the past decade, substantial progress has been made in elucidating the molecular mechanisms of the UPR^{mt} and its evolutionary and species-specific regulatory divergence, particularly regarding adaptive responses triggered by mitochondrial proteostasis stress, including defective protein folding, compromised protein import, and redox imbalance. The following sections focus on the core UPR^{mt} signaling mechanisms and their molecular regulatory networks in *C. elegans* and mammals.

In *C. elegans*, UPR^{mt} represents one of the best understood mitochondrial retrograde signaling pathways. Accumulation of unfolded or misfolded proteins within the mitochondrial matrix is considered the initial triggering event for UPR^{mt}. When the folding capacity of the molecular chaperone system is exceeded, these abnormal proteins are initially degraded into short peptides by the CLPP protease complex and subsequently transported to the mitochondrial intermembrane space (IMS) by the ATP-dependent transporter HAF-1 [60, 63]. This process reflects not only disruption of mitochondrial proteostasis but also changes the subcellular localization of the stress-related transcription factor ATFS-1 by restricting its import into mitochondria. ATFS-1 is the core transcriptional regulator of UPR^{mt} in *C. elegans*, which possesses both a mitochondrial targeting sequence (MTS) and C-terminal nuclear localization sequence (NLS) [64]. In the physiological state, ATFS-1 is mainly imported into the mitochondrial matrix and degraded by LON protease, thereby inhibiting UPR^{mt} activation [65]. However, under various mitochondrial stress conditions, including impaired OXPHOS, decreased mitochondrial membrane potential, or impaired protein import, the mitochondrial import efficiency of ATFS-1 is significantly reduced, leading to its cytosolic accumulation in the cytoplasm and subsequent nuclear translocation. In the nucleus, ATFS-1 binds to specific promoter regions to induce expression of molecular chaperones and proteases, thereby reshaping the mitochondrial proteostasis network [66].

In contrast to *C. elegans*, the mammalian UPR^{mt} is governed by a substantially more complex regulatory network, in which mitochondrial stress signaling is extensively integrated with other cellular homeostatic and stress-response pathways. Currently, ATF5 is recognized as the functional mammalian homolog of the *C. elegans* transcription factor ATFS-1 [67]. ATF5 also contains MTS and NLS, and is imported into mitochondria for degradation under normal conditions. However, disruption of mitochondrial proteostasis, loss of membrane potential, or impaired protein import limits ATF5 degradation within mitochondria, resulting in its nuclear accumulation and subsequent activation of UPR^{mt}-related gene transcription. Nuclear ATF5 cooperates with transcription factors such as ATF4 and CHOP to induce the expression of mitochondrial molecular chaperones including HSP60, HSP10, and mtHSP70, as well as proteases such as LONP1 and CLPP, thereby enhancing mitochondrial protein folding and proteolytic capacity [68]. Notably, ATF5 can also upregulate transcription of mitochondrial proteases such as LONP1 through a positive feedback mechanism, further strengthening the mitochondrial protein quality control system. This suggests that ATF5 functions not merely as a stress sensing factor, but also as an important executor of homeostasis remodeling during UPR^{mt} [69].

Beyond ATF5-mediated transcriptional regulation, mammalian UPR^{mt} is fine-tuned by multiple additional signaling pathways. Among these, antioxidant responses and IMS space protein quality control represent important complementary mechanisms. Under mitochondrial stress, the sirtuin family of deacetylases, especially SIRT3 and SIRT1, can indirectly participate in the maintenance of UPR^{mt} by regulating mitochondrial protein acetylation levels and redox homeostasis [70]. Activation of SIRT3 limits excessive mitochondria ROS accumulation and promotes its nuclear translocation by deacetylating transcription factor FOXO3A, thereby inducing expression of antioxidant enzymes such as superoxide dismutase 2 (SOD2) and catalase, mitigating secondary damage to mitochondrial proteins and DNA [71, 72].

In addition, disruption of IMS proteostasis can serve as an important trigger for UPR^{mt} activation. When misfolded proteins accumulate in the IMS, protein kinase AKT is activated and phosphorylates estrogen receptor (ERα), which in turn induces transcription of nuclear respiratory factor 1 (NRF1) and mitochondrial serine protease HTRA2. NRF1 coregulates mitochondrial biogenesis and expression of nuclear encoded mitochondrial genes [12], whereas HTRA2 participates in the clearance of abnormal proteins within the IMS [73], thereby enhancing mitochondrial protein quality control at multiple levels (Figure 2).

Furthermore, complex formation between heat shock transcription factor HSF1 and mitochondria single-strand DNA binding protein SSBP1 has also been implicated in UPR^{mt} regulation [74]. This complex can bind to promoters of a variety of mitochondrial molecular chaperone genes and further expand the transcriptional profile of UPR^{mt}. These findings suggest that mammalian UPR^{mt} is not a single linear pathway, but rather a network highly intertwined with metabolic, antioxidant, and inflammatory regulation [56, 68, 75].

Above all, UPR^{mt} acts as an evolutionarily conserved mitochondrial retrograde signaling pathway plays a central role in maintaining homeostasis, regulating metabolic adaptation, and resisting stress-induced injury. The *C. elegans* model reveals the basic framework and key regulatory logic of UPR^{mt}, while the

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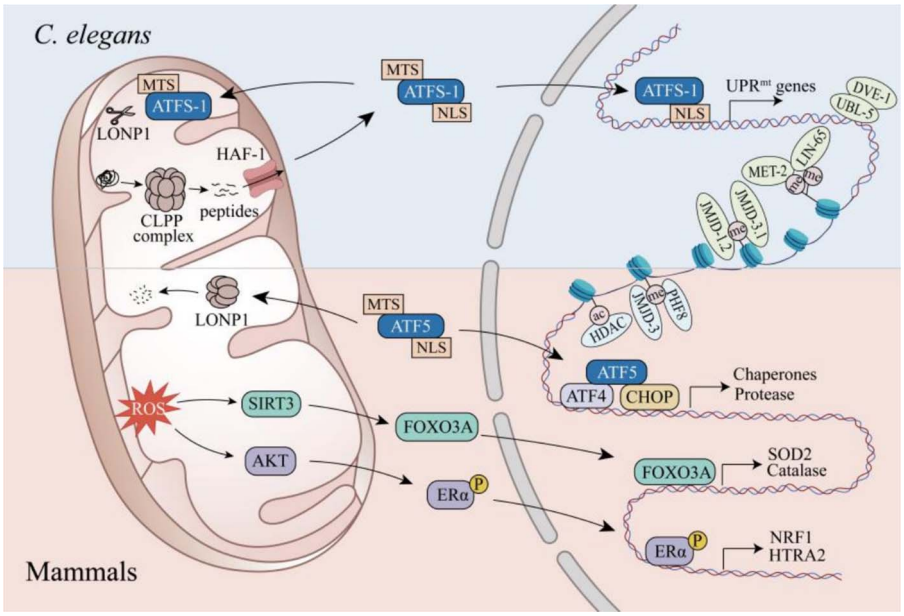


Figure 2 Schematic of UPR^{mt} signaling pathways in *C. elegans* and mammals. Top (*C. elegans*): under mitochondrial stress, accumulated unfolded proteins are cleaved by the CLPP protease complex into peptides, which are exported by HAF-1. This process inhibits the mitochondrial import of the transcription factor ATFS-1 (normally degraded by LONP1), causing it to translocate to the nucleus. There, ATFS-1 activates UPR^{mt} genes by coordinating with chromatin remodelers (such as MET-2 and JMJD-1.2/3.1) and co-factors (DVE-1, UBL-5) to establish a transcriptionally active chromatin state. Bottom (mammals): similarly, the mammalian factor ATF5 accumulates in the nucleus upon stress, working with ATF4, CHOP, and epigenetic regulators to drive protective gene expression. Concurrently, mitochondrial ROS triggers parallel signaling axes: the SIRT3-FOXO3A pathway upregulates antioxidant enzymes, while the AKT-ERα pathway promotes mitochondrial biogenesis and protease expression. *UPR^{mt}* mitochondrial unfolded protein response. Figure was created using BioRender and Adobe Illustrator.

mammalian system has developed a more complex regulatory network that is deeply integrated with other pathways. Given the important role of mitochondrial dysfunction in infection, trauma and multiple organ failure [76–78], comprehensive understanding of UPR^{mt} regulation in mammals will not only illuminate fundamental biological issues of cellular homeostasis maintenance, but also provide novel theoretical foundations and therapeutic targets for the intervention in related diseases.

Mitochondrial unfolded protein response communicates across organs

Beyond intracellular signaling, UPR^{mt} extends its influence across tissues. This non-cell-autonomous communication represents a systemic amplification layer, enabling organism-wide coordination of mitochondrial stress responses. UPR^{mt} functions as a systemic coordinator to communicate between cells and tissues through endocrine signals. Activation of non-autonomous UPR^{mt} in specific cells typically manifests as the release of secretory signaling factors (also known as mitokines) from neuronal mitochondria, which cross the tissue to activate the UPR^{mt} of the intestine, highlighting the importance of cross-cell mitochondrial quality regulation [40, 79, 80]. Andrew et al. found that neuronal expression of the Huntington disease-related protein PolyQ40 induces non-autonomous UPR^{mt} in distant tissues through Wnt signaling pathway [40]. Another study demonstrated that when neurons are subjected to proteotoxic stress, the neurotransmitter 5-hydroxytryptamine also mediates in mitochondrial stress communication from neurons to the intestine. Exogenous 5-hydroxytryptamine supplementation can rescue neuronal secretion defects and restore UPR^{mt} signaling, while impaired synthesis deficiency blocks the UPR^{mt} signal transmission to distant tissues, and this blocking effect can be reversed by exogenous 5-hydroxytryptamine supplementation [79]. Recent work from Tian's team further revealed that under long-term mitochondrial stress, neurons promote 5-hydroxytryptamine release through calcium oscillations, thereby activating intestinal UPR^{mt} and playing a key role in aging regulation [81]. These findings suggest that in neurodegenerative diseases such as Huntington's disease, a mechanistic association exists between mitochondrial proteostasis, endocrine signals, and peripheral metabolism. Additionally, CRISPR/Cas9-mediated knock out of mitochondrial genes *spg-7* and *cco-1* disrupting neuronal mitochondrial proteostasis, also activates intestinal UPR^{mt}. This strategy also led to discover the second secretory factor-the neuropeptide FLP-2, as well as the neuronal circuit involved in non-autonomous signal transmission [80]. Besides FLP-2 and 5-hydroxytryptamine, the Wnt signaling pathway is necessary for the activation of non-autonomous UPR^{mt}: *C. elegans* mitochondrial stress induces the secretion of Wnt ligand protein EGL-20 as a mitokine to induce UPR^{mt} in peripheral tissues [40].

To cope with dynamic environmental pressures, living organisms have evolved various cell-specific stress response mechanisms to maintain homeostasis. Specific cell types, such as neurons, can lead cross-organ coordination by integrating multi-tissue stress responses through non-autonomous signals. This phenomenon is particularly significant under pathological conditions, as mitochondrial dysfunction commonly observed in neurodegenerative diseases is frequently accompanied by metabolic reprogramming of distant tissues [82]. Therefore, comprehensive understanding of these intercellular and interorgan mitochondrial

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communication mechanisms will not only facilitate targeted regulation of protective stress responses, but also provide novel concepts for developing combined therapies for neurodegenerative diseases.

Mitochondrial unfolded protein response and the integrated stress response

UPR^{mt} does not function in isolation but is tightly integrated with other cellular stress pathways. The integrated stress response (ISR) acts as a key cross-pathway regulatory module, coordinating translational control and reinforcing UPR^{mt} signaling across different layers. Rather than functioning as an independent trigger of UPR^{mt}, the ISR primarily acts as a regulatory module that modulates the amplitude, specificity, and downstream outputs of UPR^{mt} signaling. Mitochondrial stress can also activate the ISR, an adaptive cellular program engaged in response to diverse stressors, including nutrient deprivation, hypoxia, viral infection, and the accumulation of misfolded proteins [83, 84]. Its core mechanism involves regulation of gene expression and protein synthesis, thereby assisting cells in restoring homeostasis and regulating cell fate. The key regulatory factor of the ISR is the eukaryotic translation initiation factor (eIF2α). eIF2α is phosphorylated by various kinases, including PKR-like endoplasmic reticulum kinase (PERK), heme-regulated inhibitor (HRI), general control nonderepressible 2 (GCN2), and protein kinase R (PKR). Phosphorylated eIF2α inhibits most protein synthesis, while activate expression of stress-related genes such as *ATF4*, *CHOP*, and *ATF5*. The mRNAs of these genes contains upstream open reading frame (uORF) in the 5′ non-coding region, enabling their preferential translation under stress conditions, thereby promoting cellular homeostasis restoration [85].

In *C. elegans*, mitochondrial dysfunction resulting from mutations in OXPHOS genes, such as *clk-1* and *isp-1*, leads to increased ROS production required for GCN2-mediated eIF2α phosphorylation. This process reduces cytoplasmic translation and new mitochondrial proteins generation [86]. Low levels of ROS participate in stress responses and exert protective effects [87]. Therefore, the activation of ISR is crucial for maintaining cellular homeostasis. GCN2 loss-of-function impairs mitochondrial function, enhances cellular sensitivity to mitochondrial stress, and subsequently leads to adverse consequences. In mammals, multiple mitochondrial stressors can activate the ISR. For instance, HTRA2 knock out in the mouse brain causes unfolded proteins accumulation on the inner membrane, thereby activating CHOP-dependent ISR and protecting neurons from death [88]. Additionally, the environmental toxin arsenite induces mitochondrial stress by promoting eIF2α phosphorylation and impairs the function of the mitochondrial protein import complex through the TIM23 core subunit Tim17A, and consequently activating a transcriptional program that maintains mitochondrial proteostasis [89].

In summary, the relationship between mitochondrial stress and ISR is dualistic, and may depend on the degree and duration of mitochondrial dysfunction. In some cells, inhibition of the mitochondrial OXPHOS subunits activates ATF4-dependent ISR and exerts protective effects [90]; however, in other cells, the activation of mitochondrial-dependent ISR may yield deleterious consequences, such as inhibiting cell proliferation or causing abnormal lipid metabolism [91, 92]. The phosphorylation of eIF2α is highly conserved evolutionarily, but this process is mediated by tissues-specific kinases. For instance, in pancreatic β cells, ISR is mainly regulated by PERK [93], while in hepatocytes, it mainly relies on GCN2 kinase [94]. Experimental evidence indicates that the ISR not only responds to mitochondrial stress signals but also constitutes a necessary condition for UPR^{mt} initiation. However, how the ISR-related kinases dynamically sense fluctuations in mitochondrial function under physiological conditions remains poorly understood. Collectively, the ISR should be understood not as an upstream trigger of UPR^{mt}, but as a higher-order regulatory module shaping its downstream effects. This additional layer of control highlights the importance of stress integration in determining context-dependent outcomes of mitochondrial dysfunction.

Mitochondrial unfolded protein response and mitochondrial turnover

As integral components of the mitochondrial quality control (MQC) network, UPR^{mt} and mitochondrial turnover—particularly mitophagy—operate in a highly coordinated, hierarchical manner to maintain cellular homeostasis. While UPR^{mt} acts as the first line of defense to repair stress by refolding or degradation of localized misfolded proteins, mitophagy serves as the ultimate clearance mechanism to eliminate severely or irreversibly damaged mitochondria [95].

Complex coordination exists between UPR^{mt} and mitophagy [96, 97]. In numerous physiological and pathological contexts, they function synergistically. For example, in myocardial ischemia–reperfusion injury (IRI), mitophagy and UPR^{mt} cooperate to protect cardiomyocytes [98]. Interventions utilizing natural compounds, such as urolithin A and spermidine, maintain mitochondrial proteostasis by simultaneously promoting biogenesis, UPR^{mt}, and mitophagy [52, 99].

These two pathways also exhibit reciprocal compensatory mechanisms [100]. UPR^{mt} serve as a compensatory survival signal when mitophagy is inhibited or impaired. This coordination mechanism is particularly important during aging and cellular senescence, where the decline in mitophagy efficiency represents a hallmark, and UPR^{mt} hyperactivation may compensate for this deficiency to maintain mitochondrial function. Conversely, excessive accumulation of unfolded proteins that overwhelms the capacity of the UPR^{mt} machinery inevitably triggers mitochondrial membrane depolarization, subsequently recruiting factors such as PINK1 and Parkin to initiate mitophagy [101]. Thus, understanding the spatial and temporal interplay between UPR^{mt} and mitophagy is crucial for developing therapeutic strategies that target mitochondrial turnover without disrupting the finely tuned proteostasis network.

Context-dependent roles of mitochondrial unfolded protein response in disease

Although UPR^{mt} has been implicated in a broad spectrum of diseases, this review focuses on representative and mechanistically distinct contexts: aging, cancer, immunity and trauma/IRI, which collectively capture key dimensions of mitochondrial stress responses in human pathophysiology. Aging provides a chronic stress background underlying multiple diseases, cancer represents a context of adaptive stress exploitation, and immunity reflects the role of UPR^{mt} in inflammatory and immune-mediated disorders. Trauma and IRI exemplify the consequences of acute, high-intensity metabolic crises that drive systemic organ dysfunction. We analyze UPR^{mt} across disease settings using a unified

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framework encompassing mitochondrial stress characteristics, activation mechanisms, and functional outcomes.

The role of mitochondrial unfolded protein response in aging

During aging, mitochondrial stress is typically chronic and cumulative, characterized by progressive mtDNA damage, redox imbalance, and declining mitochondrial protein quality control. Aging is a complex multifactorial process that constitutes a major risk factor for multiple age-associated diseases, including neurodegenerative, cardiovascular, and metabolic disorders. Senescent cells accumulate unfolded or misfolded proteins within mitochondria, linking mitochondrial proteostasis imbalance to age-related pathologies [69, 102–104]. Accordingly, mitochondrial dysfunction is widely recognized as a central driver of aging [105, 106], contributing to cellular senescence, chronic inflammation, and stem cell exhaustion [107–109].

NAD^+ metabolism plays a central role in this process. Declining NAD^+ levels-exacerbated by metabolic stressors such as high-fat or high-sugar diets-impair mitochondrial function and bioenergetics [110, 111]. Supplementation with NAD^+ precursors, including NR and NMN, activates SIRT1- and SIRT3-dependent pathways, thereby inducing UPR^{mt} and improving mitochondrial function across multiple models [112, 113]. For example, NR treatment rejuvenates muscle stem cells and alleviates age-associated decline in neural and melanocyte stem cells, while NMN supplementation partially rescues intestinal aging phenotypes through ATF5-mediated stress responses [114]. These chronic metabolic and proteotoxic perturbations activate UPRmt primarily through sustained mito-nuclear imbalance and NAD^+-dependent signaling pathways.

UPR^{mt} is increasingly recognized as a protective mechanism during aging, contributing to mitochondrial homeostasis and coordinating with metabolic and quality control pathways such as NAD^+ signaling and mitophagy. However, its beneficial effects are not unconditional. Evidence from *C. elegans* indicates that constitutive UPR^{mt} activation does not necessarily extend lifespan, highlighting the importance of activation timing and intensity [42]. Collectively, UPR^{mt} functions as a context-dependent compensatory mechanism that maintains mitochondrial homeostasis and modulates aging-related functional decline. Deeper understanding of UPR^{mt} molecular underpinnings during aging is expected to reveal novel targets for development of therapeutic interventions against age-related diseases. Future studies should aim to elucidate crosstalk between UPR^{mt} and other aging-related pathways, including inflammation and stem cell depletion, and to design strategies that selectively modulate UPR^{mt} activity to mitigate age-associated functional decline and promote healthy aging.

The role of mitochondrial unfolded protein response in cancer

In cancer, mitochondrial stress is dynamic and heterogeneous, arising from oncogenic signaling, metabolic reprogramming, hypoxia, nutrient deprivation, and elevated ROS levels within the tumor microenvironment. Although cancer cells exhibit the Warburg effect, mitochondrial function remains essential for supporting biosynthesis, redox balance, and metabolic flexibility. These conditions impose persistent bioenergetic and proteotoxic stress on mitochondria, making mitochondrial dysfunction a hallmark of malignant progression [115–118].

These stress conditions activate UPR^{mt} through multiple regulatory mechanisms, including ATF5-mediated mitochondrial-nuclear communication and integration with ATF4-dependent stress pathways such as the ISR. Upon activation, UPR^{mt} enhances mitochondrial proteostasis by upregulating chaperones and proteases, thereby preserving protein folding capacity and maintaining mitochondrial fitness under stress conditions. UPR^{mt} activation has been increasingly implicated in tumor adaptation to hostile microenvironments. By reinforcing mitochondrial quality control and metabolic resilience, UPR^{mt} supports cancer cell survival under hypoxia, nutrient limitation, and oxidative stress. In particular, UPR^{mt} promotes epithelial-mesenchymal transition (EMT), facilitating tumor cell migration and invasion [26]. Consistently, elevated UPR^{mt} expression predicts poor survival and disease progression in breast cancer [119], while its stress-induced activation promotes tumor invasion via mitokine GDF15 secretion in thyroid cancer [120].

UPR^{mt} exhibits dual roles in tumors: in early-stage malignancies and precancerous lesions, UPR^{mt} primarily acts as an adaptive, cytoprotective response to mitochondrial stress. By restoring mitochondrial proteostasis-through upregulation of chaperones and proteases-it mitigates apoptosis and supports tumor cell survival [121]. Within the tumor microenvironment, conditions such as hypoxia, nutrient deprivation, and elevated ROS further engage UPR^{mt} to maintain bioenergetic homeostasis and reinforce mitochondrial quality control, thereby promoting resistance to metabolic and oxidative stress [122]. Consistently, UPR^{mt} activation has been associated with chemotherapy resistance in multiple tumor models, including glioblastoma and colorectal cancer, thereby enhancing tumor cell resilience to oxidative and metabolic stress [123]. However, this protective effect is highly context-dependent. Under conditions characteristic of advanced disease-such as persistent oxidative stress or oncogenic alterations (e.g. KRAS activation or TP53 loss)-UPR^{mt} may exceed its compensatory capacity and become maladaptive, shifting toward pro-apoptotic signaling [124, 125]. Collectively, these findings suggest that UPR^{mt} functions as a threshold-dependent regulator of tumor cell fate, with the transition from pro-survival to pro-death determined by the intensity and duration of mitochondrial stress in cellular context.

Functionally, UPR^{mt} operates as a threshold-dependent regulator of tumor cell fate, shifting from cytoprotective adaptation to pro-apoptotic signaling depending on stress intensity, duration, and tumor context. Deeper understanding of crosstalk between UPR^{mt} and other organelle stress responses such as endoplasmic reticulum UPR (UPR^{er}) and metabolic reprogramming is essential for developing more effective and precise cancer treatment strategies. Future research should focus on identifying and exploiting specific regulatory mechanisms of UPR^{mt} in different cancer types to enable personalized tumor interventions.

The role of mitochondrial unfolded protein response in immunity

In immune-related conditions, mitochondrial stress is frequently acute and intense, driven by infection, inflammation, or trauma-induced metabolic overload. As energetic and signaling hubs of immune cells, mitochondria are highly vulnerable to immense

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metabolic and oxidative stress induced by severe infections or trauma. Dysregulated immune responses are central to a wide range of diseases, including chronic inflammatory disorders, autoimmune diseases, and infection-related pathologies such as sepsis and trauma-induced SIRS [68, 126–128]. Rather than merely supporting basal immune functions, we propose a synthesized model in which UPR^{mt} acts as a critical "metabolic rheostat" that dictates the trajectory and ultimate outcomes of immune responses in trauma and sepsis. In these critical settings, UPR^{mt} operates through a biphasic framework: governing the balance between adaptive immune clearance and maladaptive systemic inflammation.

These conditions activate UPR^{mt} primarily through proteotoxic stress, excessive ROS production, and integration with inflammatory and stress-response signaling pathways. In the early adaptive phase, moderate UPR^{mt} activation serves as an essential protective mechanism for immune cells. Activated macrophages and T lymphocytes require substantial bioenergetic bursts via OXPHOS to support phagocytosis, proliferation, and effector functions. By clearing misfolded proteins and restoring mitochondrial network integrity, UPR^{mt} sustains these energy demands. Furthermore, functional UPR^{mt} restricts excessive mitochondrial reactive oxygen species (mtROS) production, an important trigger for inflammasome activation. During lipopolysaccharide (LPS)-induced sepsis, UPR^{mt} coordinates with mitophagy to alleviate myocardial injury and limit excessive inflammatory responses [129, 130]. Thus, robust UPR^{mt} signaling enables immune cells to clear pathogens efficiently while avoiding hyper-inflammation.

Functionally, UPR^{mt} acts as a metabolic rheostat that determines the balance between effective immune responses and pathological inflammation, depending on the magnitude and persistence of mitochondrial stress. Conversely, during severe, sustained traumatic or septic stress, the immune response transitions into a maladaptive phase. When proteotoxic burden overwhelms UPR^{mt} machinery, mitochondrial networks in immune cells collapse, driving a dual pathology characteristic of MODS: immune paralysis: irreversible bioenergetic failure leads to metabolic exhaustion of T-cells and loss of macrophage phagocytic capacity, rendering the host highly susceptible to secondary infections. Amplification of sterile inflammation: the failure of UPR^{mt} directly leads to the irreversible opening of the mitochondrial permeability transition pore (mPTP) and the extrusion of damage-associated molecular patterns (DAMPs), such as mtDNA and cardiolipin, into the cytosol and circulation [131–134]. These DAMPs are potent activators of pattern recognition receptors in microglia and circulating macrophages, triggering the cGAS-STING pathway and robust NLRP3 inflammasome assembly. This creates a self-amplifying, vicious cycle of cytokine release and neuroinflammation [135, 136].

The role of mitochondrial unfolded protein response in trauma and ischemia–reperfusion injury

IRI represents a pivotal pathophysiological mechanism underlying severe clinical conditions-including trauma, sepsis, acute organ injury, and MODS. During ischemia, ATP depletion induces collapse of the mitochondrial membrane potential ($\Delta\Psi m$), intramitochondrial calcium overload, and impaired protein synthesis—leading to misfolding and aggregation of proteins within the mitochondrial matrix. Upon reperfusion, an abrupt ROS surge destabilizes protein conformation, creating a "high-risk proteotoxic burden". UPR^{mt} is rapidly engaged to restore proteostasis, orchestrating chaperone upregulation (HSP60, HSP10), protease activation (LonP1, ClpP), and nuclear-mitochondrial crosstalk (ATF5, ATF4), thereby preserving respiratory chain integrity and bioenergetic homeostasis [137, 138].

Persistent or systemic insults such as sepsis, traumatic brain injury, acute kidney injury, and post-transplant IRI can dysregulate UPR^{mt}, triggering a cascade of pathological consequences across multiple cellular layers. First, insufficient UPR^{mt} precipitates irreversible mPTP opening, sustained activation of pro-apoptotic effectors, cytochrome c release, $\Delta\Psi m$ collapse, and caspase-3 activation, collectively driving intrinsic apoptosis [139]. Second, mitochondrial dynamics are disrupted: although UPR^{mt} normally regulates fission proteins, chronic stress impairs this feedback, leading to excessive fragmentation, compromised fusion-mediated repair, and diminished OXPHOS efficiency [140, 141]. Third, UPR^{mt} becomes decoupled from mitophagy: although it may initiate PINK1/Parkin-dependent recognition of damaged mitochondria, defective autophagosome-lysosome fusion hinders clearance, causing accumulation of dysfunctional organelles and a self-amplifying loop of ROS production [137, 142]. Finally, sterile inflammation is exacerbated: mitochondrial protein aggregates and extruded mtDNA act as DAMPs, activating the cGAS-STING pathway and promoting NLRP3 inflammasome assembly and IL-1β/IL-18 maturation, thereby amplifying local and systemic inflammation and accelerating progression to SIRS and MODS [143, 144].

Collectively, these findings support a mechanistic framework in which dysregulated UPR^{mt} drives progression from mitochondrial dysfunction to sterile inflammation and immune dysregulation, ultimately contributing to SIRS and MODS. These findings suggest that targeting the UPR^{mt}-mitochondria-immune axis may offer promising avenues for precision intervention in trauma-related organ failure.

In summary, UPR^{mt} can be conceptualized as a context-dependent mitochondrial stress integrator that governs the balance between adaptation and pathology. Its functional outputs are not fixed but are dynamically shaped by stress intensity, duration, and cellular context. Whereas transient activation promotes proteostasis, metabolic flexibility, and tissue resilience, sustained or dysregulated UPR^{mt} drives bioenergetic failure, inflammatory amplification, and cell fate deterioration. This duality is particularly evident in trauma and critical illness, wherein UPR^{mt} lies at the intersection of mitochondrial dysfunction, immune dysregulation, and organ failure. Framing UPR^{mt} as a tunable threshold response rather than a binary pathway provides a unifying perspective for its diverse roles across aging, cancer, and immunity. Therapeutically, this highlights the need for precise, context-aware modulation of UPR^{mt} to restore mitochondrial homeostasis and improve clinical outcomes. Future research should focus on the specific role of UPR^{mt} in different immune cell subsets and strategies for precise UPR^{mt} regulation to achieve effective immune intervention, balance immune activation with immune tolerance, and improve disease prognosis (Figure 3).

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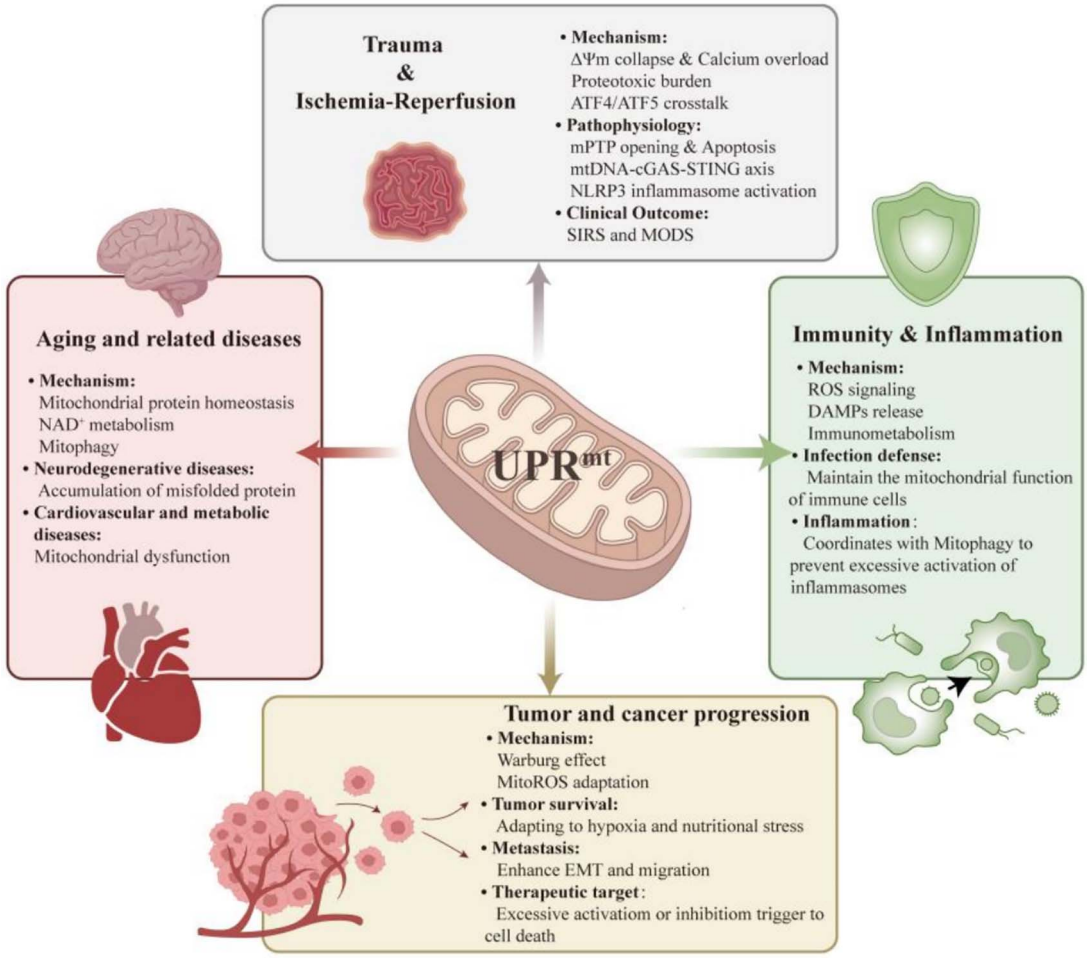


Figure 3 UPR^{mt} in various disease context. The diagram summarizes the functional impact of UPR^{mt} across three major physiological and pathological contexts. (Left) In aging and related diseases (including neurodegenerative, cardiovascular, and metabolic disorders), UPR^{mt} acts as a protective mechanism. It preserves mitochondrial proteostasis and coordinates with NAD^+ metabolism and mitophagy to counteract the accumulation of misfolded proteins and functional decline. (Bottom) In cancer, UPR^{mt} supports tumor survival and progression by facilitating adaptation to hypoxia and nutritional stress (the Warburg effect) and enhancing metastasis via EMT. However, regulating UPR^{mt} levels (excessive activation or inhibition) serves as a potential therapeutic strategy to induce cancer cell death. (Right) In immunity, UPR^{mt} maintains the mitochondrial function of immune cells for infection defense and modulates inflammation by regulating ROS signaling and DAMPs, preventing excessive inflammasome activation. (Top) In trauma and ischemia-reperfusion, UPR^{mt} responds to severe cellular stress characterized by mitochondrial membrane potential ($\Delta\Psi m$) collapse, calcium overload, and proteotoxic burden. This profound stress drives detrimental pathophysiological pathways, including mPTP opening, apoptosis, and severe inflammation through the mtDNA-cGAS-STING axis and NLRP3 inflammasome, ultimately contributing to critical clinical outcomes such as SIRS and MODS.
UPR^{mt} mitochondrial unfolded protein response, *EMT* epithelial-mesenchymal transition. Figure was created using BioRender and Adobe Illustrator

Therapeutic targeting of mitochondrial unfolded protein response: pharmacological modulators, challenges, and translational perspectives

Growing recognition of UPR^{mt} as a central stress-integration hub has stimulated increasing interest in its therapeutic modulation. However, despite frequent references to its potential as a drug target, systematic evaluation of pharmacological strategies and their translational implications remains limited.

Pharmacological modulators of mitochondrial unfolded protein response

Current pharmacological approaches to modulating UPR^{mt} can be broadly grouped into three categories (see Section 2.1.1 for detailed descriptions). Mitochondrial stress-inducing agents, such as tetracyclines, ETC inhibitors, and uncouplers, activate UPR^{mt} by disrupting mitochondrial proteostasis and bioenergetics [29, 36]. However, they are largely limited to experimental use due to toxicity and poor specificity. Metabolic modulators, including NAD^+ precursors such as NR and NMN, induce UPR^{mt} indirectly through sirtuin-dependent pathways and exhibit greater translational potential [48]. Natural compounds and mitochondrial quality control enhancers, such as resveratrol, urolithin A, and spermidine, promote mitochondrial homeostasis and engage UPR^{mt} as part of a broader adaptive network [53, 99, 145]. Notably, most available agents act indirectly, and specific pharmacological regulators targeting core UPR^{mt} components remain underdeveloped.

Challenges in therapeutic targeting of mitochondrial unfolded protein response

Despite its therapeutic promise, several major challenges complicate clinical translation of UPR^{mt}-targeted strategies. A key

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issue is tissue specificity. UPR^{mt} exerts divergent, and sometimes opposing, functions across tissues and disease contexts [146]. For instance, its activation may be protective in neurons or cardiomyocytes under stress [147], yet promote survival and metastasis in cancer cells [148]. Consequently, systemic modulation of UPR^{mt} may lead to unintended or even detrimental effects in non-target tissues.

Closely related is the challenge of context dependency, which represents a fundamental feature of UPR^{mt} biology. Moderate and transient activation of UPR^{mt} generally supports adaptive remodeling and stress resistance, whereas sustained or excessive activation may drive mitochondrial dysfunction, inflammatory signaling, or cell death. Conversely, in cancer, insufficient or excessive activation may have opposite therapeutic consequences [149]. These observations suggest that the therapeutic window for UPR^{mt} modulation is narrow and remains poorly defined. Another major limitation is the lack of target specificity of current pharmacological agents. Many commonly used UPR^{mt} activators are mitochondrial toxins or broad metabolic regulators, making it difficult to disentangle UPR^{mt}-specific effects from general mitochondrial stress responses. Development of selective modulators targeting defined components of the UPR^{mt} signaling network is therefore a critical unmet need.

In addition, the field lacks reliable biomarkers for monitoring UPR^{mt} activation in vivo. Without robust pharmacodynamic indicators-such as transcriptional signatures, mitokine levels, or mitochondrial proteostasis markers-it remains challenging to assess target engagement, optimize dosing, or stratify patients in clinical settings.

Future translational directions

Addressing these challenges will require a shift from empirical modulation toward mechanism-guided therapeutic strategies. Several key directions may facilitate clinical translation of UPR^{mt} targeting.

Precision delivery approaches, including mitochondria-targeted peptides and nanocarrier systems, may enable tissue- or organelle-specific modulation of UPR^{mt}, thereby minimizing off-target effects. Mechanism-informed patient stratification will be essential. Biomarkers such as mtDNA mutation burden, NAD^+/redox status, or circulating mitokines such as GDF15 may help identify patient populations most likely to benefit from UPR^{mt}-targeted interventions. Rational combination therapies may enhance therapeutic efficacy. Given extensive crosstalk between UPR^{mt} and other stress-response pathways, co-targeting mitophagy, the ISR, or inflammatory signaling may provide synergistic benefits. In oncology, for example, pushing UPR^{mt} beyond its adaptive capacity may selectively induce cytotoxic stress in tumor cells. Adaptive clinical trial designs incorporating early pharmacodynamic readouts and functional endpoints-such as metabolic profiling, cognitive assessment, or tumor imaging-will be critical for evaluating UPR^{mt}-targeted therapies in a context-dependent manner.

Conclusions

UPR^{mt} is not merely a stress response, but rather a central decision-making system that integrates mitochondrial stress signals and determines cellular and organismal outcomes. It operates through a hierarchical multi-layer regulatory architecture: stress sensing, nuclear execution, and systemic amplification. By maintaining mitochondrial proteostasis and coordinating metabolic and transcriptional remodeling, UPR^{mt} plays a central role in limiting cellular damage and preserving tissue function under injury-related conditions. In trauma, burns, and critical illness, UPR^{mt} emerges as a key determinant of disease trajectory: properly tuned activation preserves mitochondrial proteostasis, sustains immune cell bioenergetics, and tissue repair. In contrast, insufficient or prolonged activation leads to mitochondrial collapse, excessive release of DAMPs, and sterile inflammation, ultimately contributing to SIRS and multiple organ dysfunction syndrome. Importantly, the functional outcome of UPR^{mt} activation is highly context-dependent, underscoring the necessity of precise temporal and tissue-specific regulation. From a translational perspective, targeting UPR^{mt} represents a promising but challenging therapeutic opportunity. Future studies should focus on identifying context-specific UPR^{mt} signatures, developing reliable biomarkers, and designing precision strategies to modulate UPR^{mt} in a tissue- and context-dependent manner.

Acknowledgements

We thank BioRender (https://www.biorender.com/) and Adobe Illustrator for providing tools to create the figures in this manuscript.

Author contributions

Yanmin Xin (Writing—original draft [equal]), Yiting He (Writing—original draft [equal]), Xingguo Liu (Writing—original draft [equal], Writing—review & editing [equal]).

Conflicts of interest

The authors declare that they have no conflict of interest.

Funding

This work was financially supported by the National Key Research and Development Program of China (2024YFA0916400, 2022YFA1103800), the Strategic Priority Research Program of the Chinese Academy of Sciences (XDB0480000, XDB1410000), the National Natural Science Foundation projects of China (32488301, 92357302, 32261160376), Major Project of Guangzhou National Laboratory (GZNL2024A03006), CAS Project for Young Scientists in Basic Research (YSBR-075), the International Partnership Program of Chinese Academy of Sciences (188GJHZ2024048GC), Guangdong Province Science and Technology Program (2023B0303000023), Guangzhou Science and Technology Program (2025B03J0167), Human Cell Lineage Atlas Facility (CLAF) (DSS05010101), the Tianfu Jincheng Laboratory (TFJCPI20250043), Health@InnoHK funding support from the Innovation Technology Commission of the Hong Kong SAR, Major Research Project (GIBHMRP25–01) of Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences.

Data availability

Not applicable.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors read and approved the final manuscript.

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Burns & Trauma, 2026, 14, tkag037
https://doi.org/10.1093/burnst/tkag037
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