The mitochondrial unfolded protein response: Signaling from the powerhouse

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Mitochondria are multifaceted and indispensable organelles required for cell performance. Accordingly, dysfunction to mitochondria can result in cellular decline and possibly the onset of disease. Cells use a variety of means to recover mitochondria and restore homeostasis, including the activation of retrograde pathways such as the mitochondrial unfolded protein response (UPRmt). In this Minireview, we will discuss how cells adapt to mitochondrial stress through UPRmt regulation. Furthermore, we will explore the current repertoire of biological functions that are associated with this essential stress-response pathway.

Mitochondria are double membrane organelles commonly associated with the production of cellular energy via oxidative phosphorylation (OXPHOS). Mitochondria are also required for the metabolism of nucleotides, amino acids, and lipids and have an essential function in regulating apoptosis. Maintaining mitochondrial integrity is therefore a key aspect in ensuring cellular and organismal viability. Consequently, a decline in mitochondrial function is frequently associated with the development of numerous diseases.

Mitochondria are dependent on a diverse compilation of proteins to carry out their vital functions. However, the mitochondrial proteome is faced with various challenges, most notably the partitioning of protein encoding genes between the mitochondrial and nuclear genomes. Remarkably, the human mitochondrial genome only encodes ~1% of the total mitochondrial proteome with the remaining proteins being encoded by nuclear genes. Sophisticated mechanisms have evolved to efficiently transfer nuclear-encoded mitochondrial proteins to their proper organelle destination following translation on cytosolic ribosomes. To accomplish this complex task, proteins are sorted to mitochondria via targeting sequences that form characteristic amphipathic helices composed of positively charged residues. Such mitochondrial targeting sequences (MTS) are recognized and translocated via the mitochondrial Tom–Tim complex to their respective sub-organelle compartment. The UPRmt is a mitochondrial stress signaling pathway discovered in mammalian cells (6), but much of what is known with regard to its regulation was discovered in C. elegans (Fig. 1A). Conditions that increase mitochondrial proteotoxicity such as mitochondrial DNA depletion, impaired mitochondrial protein quality control machinery, and OXPHOS perturbation elicit the UPRmt (7, 8). A number of UPRmt regulators have been discovered using genetic approaches, including the mitochondrial matrix protease ClpP, the ubiquitin-like protein UBL-5, the transcription factor DVE-1, the mitochondrial ABC transporter HAF-1, and the bZIP transcription factor ATFS-1 (9, 10). The current paradigm suggests that ClpP proteolytically degrades improperly folded mitochondrial proteins with a subsequent release of the resulting peptides from mitochondria via HAF-1 leading to UPRmt activation (9, 10). How mitochondrial peptide extrusion affects the activity of the UPRmt is unclear, but it is clear that HAF-1 is not essential for UPRmt activation.
and instead serves as a modulator that impacts the nuclear accumulation of the bZIP transcription factor ATFS-1, a pivotal regulator of the UPR\textsuperscript{mt} (7, 10).

ATFS-1 harbors two sorting signals able to target it to both mitochondria and the nucleus (7, 11). Under physiological conditions, the MTS directs the localization of ATFS-1 to mitochondria where it is degraded by the protease Lon (7). However, mitochondrial import efficiency is reduced during conditions that perturb mitochondrial function (7, 12–14), causing ATFS-1 to accumulate in the cytosol and subsequently be imported into the nucleus via its nuclear localization sequence. ATFS-1 regulates a diverse transcriptional response to recover mitochondrial function, including the induction of mitochondrial proteases and chaperones, xenobiotic and ROS-detoxifying genes, and metabolic regulators (7). The concept of mitochondrial import efficiency regulating the UPR\textsuperscript{mt} is reminiscent of Pink1 kinase regulation in the detection and removal of defective mitochondria by mitophagy (15). During mitophagy, damaged mitochondria are marked for removal by Pink1 leading to recruitment of the autophagic machinery (15). Pink1 is imported into unstressed mitochondria and degraded (16). However, mitochondrial dysfunction reduces the import efficiency of Pink1 allowing it to accumulate on the outer mitochondrial membrane where it initiates a cascade leading to mitochondrial clearance (17). Thus mitochondrial import efficiency may be used as a general indicator of perturbed mitochondrial function to activate mitochondrial recovery programs such as the UPR\textsuperscript{mt} and mitophagy.

Additional regulators of the UPR\textsuperscript{mt} have been identified that potentially shed light into the inputs of this protective program.

Using a genetic approach, two metabolic pathways were identified as important regulators of the UPR\textsuperscript{mt} (18). First, knockdown of components in the sphingolipid biosynthesis pathway, including the enzymes serine palmitoyltransferase and ceramide synthase, results in UPR\textsuperscript{mt} attenuation that can be rescued with ceramide supplementation. Interestingly, ceramide was found to accumulate at mitochondria prior to UPR\textsuperscript{mt} activation (18). Also, inhibition of the sphingolipid biosynthesis pathway could not block UPR\textsuperscript{mt} activation from a gain-of-function ATFS-1 that is constitutively nuclear irrespective of mitochondrial stress (18, 19). Therefore, ceramide accumulation at mitochondria may be an early step in the activation of the UPR\textsuperscript{mt}. In the same genetic screen, knockdown of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) synthase, a component of the mevalonate pathway, also blocked UPR\textsuperscript{mt} activation in the presence of mitochondrial stress (18). The mevalonate pathway is necessary for the synthesis of isoprenoids such as cholesterol. Interestingly, constitutive nuclear accumulation of ATFS-1 rescues the ill effects of statins, a class of cholesterol-lowering drugs that inhibit the mevalonate pathway (19) likely by increasing ubiquinone biosynthesis that is impaired by the statins. Intriguingly, statins block UPR\textsuperscript{mt} activation during mitochondrial stress suggesting that the side effects experienced while taking this drug may be due to an inability to sense and respond to conditions that perturb mitochondrial function (18). In addition to the synthesis of cholesterol, the mevalonate pathway is also important for the production of prenylated lipids such as farnesyl pyrophosphate that can be blocked with statin treatment (20). Protein prenylation involves the addition of the farnesyl moiety to client proteins (21), a reaction that is particularly crucial for the activity of small GTPases (22). Importantly, gain-of-function ATFS-1 animals are also resistant to the toxicity exerted by gliotoxin (19), which blocks the addition of farnesyl to small GTPases through the inhibition of farnesyl transferase. This suggests that impaired prenylation may contribute to the negative effects of statins. Perhaps GTPase prenylation is required for UPR\textsuperscript{mt} activation that can be mitigated through constitutive activation of ATFS-1. In support of this possibility, the small GTPase Rheb is required for UPR\textsuperscript{mt} activity (9).

Recent observations suggest that chromatin remodeling is also critically required for UPR\textsuperscript{mt} activity. In the first study, the histone lysine demethylases JMJD-1.2 and JMJD-3.1 were discovered in a genetic screen for positive UPR\textsuperscript{mt} regulators (23).

Both show specificity for histone H3K27me2/me3 and are required and sufficient for the UPR\textsuperscript{mt}. Consistent with mediating a mitochondrial protective transcriptional response, genes differentially expressed from JMJD-1.2 and JMJD-3.1 overexpression show significant overlap with expression profiles of mitochondrially stressed animals with perturbed OXPHOS (23). Analogous findings were also observed with the mammalian homologs of JMJD-1.2 (Phf8) and JMJD-3.1 (Jmdj3), suggesting a conserved mechanism of UPR\textsuperscript{mt} regulation (23). In the second study, the H3K9 methyltransferase MET-2 and the novel protein LIN-65 were found to positively regulate the UPR\textsuperscript{mt} (24). LIN-65 is initially cytosolic but localizes to the nucleus in the presence of mitochondrial stress in a MET-2-dependent manner (24), suggesting they are functionally
add an extra layer of complexity to the regulation of the UPRmt, representing sites of active gene expression (9, 24). These findings suggest that epigenetic modifications are a necessary step for the activation of this mitochondrial recovery program.

Remarkably, mitochondrial damage originating from one tissue can induce a UPRmt in distal tissues via cell non-autonomous signaling (Fig. 2) (25). For example, neuronal mitochondrial dysfunction can induce the UPRmt in the intestine through the production of secreted “mitokines” (25). Presumably, sensory neurons that are in contact with the external environment housing potentially damaging toxins would be ideal to relay mitochondrial stress signals to tissues, like the intestine, that are likely to be impacted by toxin exposure during feeding. Two recent advancements have been made into the identity of the mitokines that regulate the cell non-autonomous control of the UPRmt. In the first study, the bioamine neurotransmitter serotonin was found to be required for activation of the UPRmt in the intestine as a consequence of mitochondrial protein aggregate accumulation in neurons (26). In a parallel study, interneuron secretion of the neuropeptide FLP-2 was necessary and sufficient for UPRmt activation in the intestine (27). Flp-2 transcript levels are enhanced in the presence of neuronal mitochondrial stress, consistent with a role in the cell non-autonomous regulation of the UPRmt. Indeed, overexpression of FLP-2 specifically activates the UPRmt and not other stress responses (27). Together, these studies suggest that neuronal control of the UPRmt in distal tissues is likely complex involving the secretion of multiple mitokine signals. Going forward, it will be interesting to understand how these various mitokines are regulated in a coordinated manner in response to varying forms of mitochondrial dysfunction as well as their role in regulating whole-animal metabolism.

Mammals

The UPRmt was first discovered in mammalian cultured cells expressing a misfolded mitochondrial protein that resulted in increased expression of mitochondrial protein quality control genes in the nucleus (Fig. 1A) (6). This transcriptional response to mitochondrial dysfunction is thought to require the C/EBP transcription factor CHOP as the corresponding consensus binding site is present in multiple genes that are induced during the UPRmt (28, 29). Consistently, CHOP is transcriptionally induced during the UPRmt presumably by the transcription factor c-Jun (6, 28).

Inspired by the discovery of ATFS-1, Fiorese et al. (30) identified the bZIP transcription factor ATF5 as an additional regulator of the UPRmt response. Mitochondrial import efficiency appears to regulate ATF5 in a manner akin to ATFS-1 because ATF5 also contains a presequence that directs its localization to mitochondria in the absence of mitochondrial stress (30). Similar to ATFS-1, ATF5 transcriptionally regulates mitochondrial protective gene expression that is necessary for cell growth during mitochondrial stress (30). Interestingly, ATF5 can induce a UPRmt in C. elegans in the absence of ATFS-1 suggesting that it is a conserved mammalian homolog (30). However, there are still questions left unanswered with regard to ATF5 and the mammalian UPRmt. First, is ATF5 proteolytically degraded in healthy mitochondria by LONP1 similar to ATFS-1? LONP1 expression is transcriptionally induced during the UPRmt by ATF5 suggesting a functional relationship (30). Second, does ATF5 accumulation in the nucleus during the UPRmt require ClpP-derived peptide efflux via the mammalian homolog of HAF-1 (TAP)? Finally, how are ATF5 and CHOP coordinated during the UPRmt? Interestingly, the CHOP consensus sequence is present in some genes that are also regulated by ATF5 during the UPRmt (28, 30) suggesting some degree of overlap in target gene regulation. Further work is therefore needed to better understand the specific mechanisms of ATF5 regulation during the UPRmt.

The mitochondrial intermembrane space (IMS) contains its own suite of protein quality machinery and potentially distinct stress response. Perturbation to the IMS protein folding environment elicits a protective response through the phosphorylation of the estrogen receptor α by Akt (31). In a recent study, proteotoxicity to the mitochondrial matrix and IMS activated the deacetylase SirT3 to promote mitochondrial recovery through the activation of anti-oxidant machinery and the stimulation of mitophagy (32). Presumably, the SirT3 response during mitochondrial stress is mediated by the transcription factor FOXOA3 that accumulates in the nucleus following SirT3-mediated deacetylation (32).

Comparison of the UPRmt and UPRER

Much like mitochondria, the endoplasmic reticulum (ER) is prone to the accumulation of misfolded proteins and similarly responds to increases in proteotoxicity through the transcriptional up-regulation of ER chaperones and proteases to restore protein homeostasis via the UPRER (33). Although conceptually similar to the UPRmt, the UPRER possesses distinct signaling mechanisms that are involved in its regulation. There are three main regulatory pathways that govern the UPRER: the serine/threonine kinase/endonuclease Ire1; the bZIP transcription factor ATF6; and the kinase PERK. All three proteins are bound in an inactive state to the ER chaperone BiP and are released in
the presence of ER stress. Active IRE1 results in preferential mRNA splicing of the bZIP transcription factor XBP1 resulting in its activation and subsequent transcriptional up-regulation of proteostasis genes. ATF6 also positively regulates the expression of proteostasis genes following its activation by proteolytic cleavage.

In addition to transcriptionally regulating the expression of ER protective genes, the UPRER helps restore ER homeostasis by attenuating protein translation through PERK-dependent phosphorylation of the translation initiation factor eIF2α (34). PERK is among four kinases that constitute the integrated stress response (ISR) that diminishes protein translation in response to various cellular stresses (35). Interestingly, the ISR kinase GCN2 is activated by increased ROS during mitochondrial stress and helps restore mitochondrial homeostasis by lowering cytosolic protein translation via phosphorylation of eIF2α, thus reducing the load of incoming unfolded mitochondrial proteins (36). Although general protein translation is attenuated during the ISR, mRNAs containing upstream open reading frames (uORFs) are favorably translated. Intriguingly, ATF5 is among the uORF containing mRNAs that are preferentially translated following eIF2α phosphorylation during ER stress (37). Whether mitochondrial stress results in a similar preferential translation of ATF5 is still unknown.

It is noteworthy that the UPRmt and UPRER share some common regulatory proteins, suggesting a possible intersection in the regulatory inputs of both stress responses. For example, CHOP is also activated during ER stress downstream of the bZIP transcription factor ATF4 (38). In this context CHOP assumes a pro-apoptotic role by transcriptionally regulating ATF5, but whether a similar mode of regulation occurs during UPRmt activation is not known (39). In contrast to the pro-apoptotic role of CHOP and ATF5 during ER stress, these transcription factors adopt a pro-survival function during mitochondrial stress through the regulation of mitochondrial protective gene expression (6, 30). Possibly, CHOP and ATF5 undergo stress-specific post-translational modifications or heterodimerization that dictate their particular function.

Physiological roles of the UPRmt

**Protection against pathogen infection**

Mitochondria are desirable targets for bacterial pathogens during infection. For example, various pathogens manipulate mitochondrion-dependent cell death pathways to promote their own survival (40). Mitochondria also play an important role in regulating the innate immune response (41) that can be compromised during infection by certain pathogens (42). As such, bacterial pathogens have evolved various means to exploit mitochondrial function, including the precise targeting of protein virulence factors directly to mitochondria (43).

Host resistance to infection is dependent on innate and adaptive immune responses that limit the colonization of pathogenic microbes. In contrast, host tolerance during infection is defined as the ability to withstand the damage caused by harmful pathogens and possibly the self-damage inflicted by the host resulting from the inflammatory response (44). The UPRmt supports host tolerance by regulating mitochondrial recovery while additionally promoting host resistance through the transcriptional regulation of various innate immunity genes such as secreted anti-microbial peptides and lysozymes (Fig. 3A) (45). Various microbes such as the opportunistic pathogen *Pseudomonas aeruginosa* can activate the UPRmt through the production of mitochondrial toxins (18, 45). Consistent with a role in protecting the host from infection, ATFS-1 is required and sufficient for survival during *P. aeruginosa* infection (45, 46). Interestingly, the mitochondrial chaperone HSP-60 that is transcriptionally up-regulated during the UPRmt by ATFS-1 (7, 10, 11) promotes host resistance during infection by enhancing the PMK-1/p38 MAPK innate immunity pathway through direct binding and stabilization of SEK-1/MAPK kinase 3 (46).

The coupling of host tolerance and resistance to one stress-response pathway is an efficient means of protecting the host during infection considering that mitochondria are targeted by a number of pathogens (18, 43, 45). Furthermore, the UPRmt may be regarded as an additional sensor of infection from the damage that is inflicted by harmful microbes targeting mitochondrial function. It is unclear whether all metazoans couple the UPRmt to the regulation of innate immunity during infection. However, the homolog of ATFS-1 in the whiteleg shrimp induces the expression of antimicrobial peptides and is required for survival during pathogen infection suggesting that UPRmt-mediated regulation of host resistance may be conserved (47).

**Accumulation of deleterious mitochondrial genomes**

Deletions in mitochondrial DNA (mtDNA) occur as an organismic ages and contributes to various diseases (48). However, each cell houses hundreds of mitochondrial genomes as a mixture of wild-type and mutant forms, a phenomenon known as heteroplasmy (49), and accordingly the number of deleterious mitochondrial genomes only needs to exceed a certain threshold to be pathogenic (typically comprising more than 60% of the total number of mitochondrial genomes) (49). The mechanism that regulates the number of deleterious mitochondrial genomes has remained elusive until the discoveries made by
two recent independent studies (50, 51). Here, a C. elegans
heteroplasmic strain harboring mtDNA with a 3.1-kb deletion
(ΔmtDNA (52)) activated the UPRmt as a result of reduced
OXPHOS activity (50, 51). Surprisingly, loss of the UPRmt
through ATFS-1 inhibition reduced the number of ΔmtDNA
copies, whereas constitutive activation of ATFS-1 promoted
the accumulation of ΔmtDNA, further reducing OXPHOS effi-
ciency and causing impaired development (50, 51).

How does ATFS-1 promote the accumulation of deleterious
ΔmtDNA? Potentially, the UPRmt limits mitophagy by promot-
ing mitochondrial health, but ATFS-1 appears to preferentially
promote ΔmtDNA accumulation independent from mitophagy
(50, 51). ATFS-1 does promote the expression of genes involved
in mitochondrial biogenesis, including regulators of mtDNA
replication such as mtDNA polymerase and TFAM (51) as well
as transcriptionally regulating genes involved in mitochondrial
dynamics (7, 51). Reducing regulators of mtDNA replication
and mitochondrial dynamics attenuate the increased ΔmtDNA
number that is observed in constitutively active ATFS-1 ani-
mals suggesting that both are involved in the ATFS-1-depen-
dent propagation of ΔmtDNA (51). Together, these studies
reveal an unexpected toxic consequence of the UPRmt mito-
chondrial recovery program that expands ΔmtDNA through
the stimulation of mitochondrial biogenesis (Fig. 3B).

Metabolic adaptations

Paradoxically, in addition to nuclear accumulation, ATFS-1
also accumulates in mitochondria during stress despite reduced
mitochondrial import efficiency (7, 11). Multiple isoforms of
ATFS-1 are present in mitochondria during the UPRmt, but the
exact identity of these isoforms is still unknown. However, two
splice variants of ATFS-1 exist with a difference of just 16
amino acids (11). Although both the short and long ATFS-1
isoforms contain the MTS, it is not known which isoform accu-
mulates in mitochondria during stress. Within mitochondria
ATFS-1 binds the D-loop of mtDNA, an A-T-rich region resid-
ing in the control region adjacent to transcriptional regulatory
elements (11). Here, ATFS-1 limits the abundance of OXPHOS
transcripts encoded by the mitochondrial genome. ATFS-1
regulates mitochondrial OXPHOS transcript numbers poten-
tially through transcriptional repression via its association with
the D-loop region; however, its effects on transcript stability
have yet to be studied. Interestingly, ATFS-1 also negatively
regulates nuclear-encoded OXPHOS gene transcript abun-
dance through direct or indirect binding of their gene promot-
ers (11). Thus, ATFS-1 appears to transcriptionally attenuate or
limit OXPHOS biogenesis until the protein folding capacity is
restored as a means of promoting mitochondrial recovery. In
addition to repressing the abundance of OXPHOS transcripts,
ATFS-1 also transcriptionally induces the expression of genes
involved in glycolysis (7, 11). By positively regulating glycolysis
gene expression, ATFS-1 presumably ensures adequate ATP
levels in lieu of reduced OXPHOS activity in an effort to pro-
mote mitochondrial repair and cell survival (Fig. 3C).

Hematopoietic stem cell maintenance

Quiescent stem cells have relatively little mitochondrial
activity that increases during differentiation (53). In the study
by Mohrin et al. (54), the histone deacetylase SIRT7 was found
to reduce mitochondrial translation by complexing with the
central metabolic regulator of mitochondrial gene expression
NRF1 and repressing transcription of mitochondrial ribosomes
and translation factors. Loss of SIRT7 consequently results in
enhanced mitochondrial translation and biogenesis leading to
the activation of the UPRmt. Interestingly, inhibiting SIRT7 in
hematopoietic stem cells (HSC) enhances mitochondrial bio-
genesis and activates the UPRmt, thus reducing quiescence and
the ability to differentiate. Consistent with a role in maintaining
stem cell quiescence, SIRT7 levels are elevated during the qui-
escence stage and low in aged stem cell populations (54). Conse-
sequently, increasing SIRT7 levels in aged stem cells decrease
mitochondrial proteotoxicity and improve their differentiation
potential. Although it is still unclear whether specific loss of
UPRmt regulators impacts HSC maintenance, this study sug-
gests the importance of mitochondrial protein homeostasis in
stem cell vitality (Fig. 3D).

The future of the UPRmt

A decline in the mitochondrial function likely impacts a wide
range of cellular activities because of the essential nature of the
organelle. Consequently, mitochondrial stress presumably acti-
vates parallel cytoprotective pathways. For instance, mitochon-
drial stress results in the activation of multiple signaling mod-
ules in addition to the UPRmt, including the hypoxia-response
transcription factor HIF-1, the AMP-activated kinase pathway,
and the transcription factors TAF-4 and CEH-23 (55–57). As
well, increased mitochondrial ROS can activate an oxidative
stress response regulated by the transcription factor SKN-1
(58). Intriguingly, ATFS-1 regulates the expression of skn-1 as
part of the UPRmt transcriptional response (9). Finally, accumu-
lation of mitochondrial precursor proteins in the cytosol as a
result of impaired mitochondrial import elicits a separate
stress-response pathway involving reduced protein translation
and increased proteasome activity (12, 14). How the UPRmt
integrates with these and other cellular stress pathways is there-
fore an area worthy of further investigation.

Also, as the UPRmt is an important regulator of mitochon-
drial recovery, it may be an attractive therapeutic target for
those diseases that result from mitochondrial dysfunction. The
therapeutic potential of the UPRmt is particularly promising in
the field of cancer research. The relationship between mito-
chondrial dysfunction and cancer was first proposed based on
the observation by Otto Warburg that cancer cells utilize gly-
colysis in the presence of oxygen presumably due to a defect in
mitochondrial respiration and function (59). Although this
remains true with certain cancers, it can by no means be
generalized. Indeed, certain cancers display normal or even
enhanced mitochondrial function (60) suggesting a consider-
able heterogeneity in cancer subtypes. It is clear though that
some cancer cells express higher levels of mitochondrial chap-
erones indicative of an activated UPRmt (30, 61–63). The
UPRmt in this context could help support tumor survival from
the mitochondrial dysfunction that may arise from genetic
mutations (64) or through the increase in mitochondrial bio-
genesis used to support tumor growth and proliferation (65).
Interestingly, inhibiting mitochondrial chaperones or the
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UPR\textsuperscript{mt} regulator ATF5 increases tumor cell death while having little to no effect on healthy cells (30, 63, 66), supporting the targeting of the UPR\textsuperscript{mt} as an anti-cancer therapy. How the UPR\textsuperscript{mt} might be pursued for other mitochondrially related pathologies such as neurological disease and diabetes is still relatively unexplored and is likely to be an exciting avenue of research in the field.

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