HHS Public Access

Author manuscript

Crit Rev Biochem Mol Biol. Author manuscript; available in PMC 2018 June 01.

Published in final edited form as:

Crit Rev Biochem Mol Biol. 2017 June ; 52(3): 304–313. doi:10.1080/10409238.2017.1291577.

Integrating the UPR^{mt} into the Mitochondrial Maintenance Network

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Abstract

Mitochondrial function is central to many different processes in the cell, from oxidative phosphorylation to the synthesis of iron-sulfur clusters. Therefore, mitochondrial dysfunction underlies a diverse array of diseases, from neurodegenerative diseases to cancer. Stress can be communicated to the cytosol and nucleus from the mitochondria through many different signals, and in response the cell can effect everything from transcriptional to post-transcriptional responses to protect the mitochondrial network. How these responses are coordinated have only recently begun to be understood. In this review we explore how the cell maintains mitochondrial function, focusing on the UPR^{mt}, a transcriptional response that can activate a wide array of programs to repair and restore mitochondrial function.

Graphical abstract

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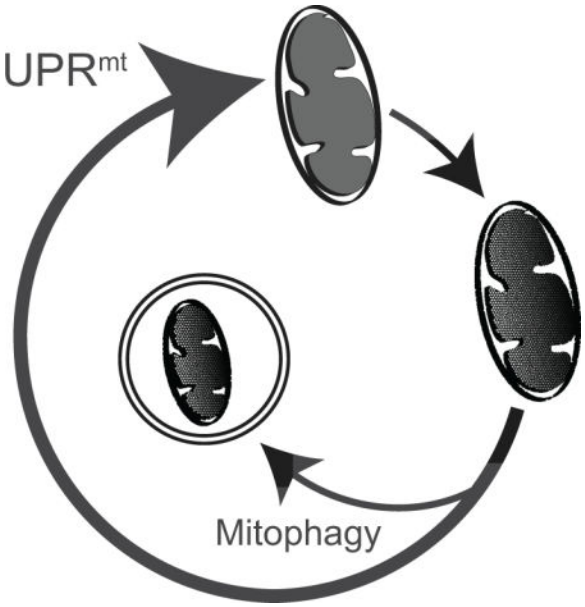
Declarations of Interest

The authors report no declarations of interest



Mitochondria: More than energy production

Mitochondria are organelles descended from an endosymbioitic α-proteobacteria that was engulfed by pre-eukaryotic cells over a billion years ago (Allen, 2003, Lane and Martin, 2010, Gray, 2012). This engulfment event allowed energy production to be specialized to one area of the cell and contributed to the explosion of multicellular complexity found in metazoans. While mitochondria are associated with energy production, these organelles also serve important roles for production of essential metabolites and co-factors such as fatty acids (Osman et al., 2011), amino acids (Wellen and Thompson, 2012), and iron-sulfur clusters (Lill and Mühlenhoff, 2008). In addition to being a hub for the cell's anabolic and catabolic reactions, mitochondria also serve as a signaling platform central for many processes in the cell, for example in the activation of apoptosis (Xiong et al., 2014). Because of these diverse functions, the preservation of mitochondrial homeostasis is vital to cellular and organismal health. Failure to maintain mitochondrial function results in a diverse array of diseases, from Parkinson's disease (Vafai and Mootha, 2012) to cancer (Nunnari and Suomalainen, 2012).

Although the mitochondrial genome (mtDNA) is small in animals, about 16 kilobases in mammals, with a small number of genes encoded therein: 13 protein-coding, 22 tRNA, and 2 rRNA genes (Gray, 1999). In animal mtDNA there is a core of gene products always present that encodes components of the oxidative phosphorylation (OXPHOS) machinery that produce the majority of energy for the cell (Falkenberg et al., 2007). Transcription is polycistronic, producing two transcripts known as the heavy and light strands. While mitochondria harbor machinery to produce mtDNA gene products, the proteins encoded by mtDNA comprise only about 1% of the mitochondrial proteome. The other 99% of proteins located in mitochondria are encoded by the nuclear genome and synthesized in the cytosol. Because mitochondria are double-membrane bound organelles, proteins produced in the cytosol require a channel to be imported into mitochondria. This channel, a complex of

proteins known as the translocase of the outer/inner membrane, transports unfolded proteins through the outer and inner membranes. Transport of a protein is dependent on the presence of a mitochondrial targeting sequence (MTS), the mitochondrial inner membrane potential ($\Delta\Psi$), ATP and molecular chaperones located within the mitochondrial matrix (Chacinska et al., 2009).

Mitochondrial defects affect a wide range of cellular processes and are associated with neurodegenerative disorders, cardiomyopathies, metabolic syndrome, cancer, and obesity. Mitochondrial disorders can manifest in any organ, ands at any age, depending on whether the mutations are autosomal, inherited from the X chromosome, or from the maternal line (Nunnari and Suomalainen, 2012). Furthermore, mtDNA mutations have pleiotropic effects due in part to heteroplasmy of mtDNA, the particular mix of wildtype and mutated mtDNA in a cell, and the severity of the mtDNA mutation (Wallace and Chalkia, 2013).

Cancer cells and mitochondrial dysfunction have long been linked, first in the description of the Warburg effect (Koppenol et al., 2011). The Warburg effect describes a phenomenon where glucose is fermented into lactic acid despite the ready availability of oxygen, often in cancer cells. While Warburg initially proposed that this phenomenon was due to mitochondrial dysfunction, the reality of how mitochondrial dysfunction interacts with cancer biology is now known to be much more complicated than previously hypothesized. Mitochondrial function is required for cancer cell viability, and depletion of functional mitochondria impairs tumor cell growth (Weinberg et al., 2010). MtDNA mutations are also associated with tumor growth, as many different types of cancers accumulate mtDNA mutations as they grow and some tumors contain homoplasmic mtDNA mutations (Polyak et al., 1998, Petros et al., 2005). These mutations can affect OXPHOS efficiency, and increase the production of reactive oxygen species (ROS) by mitochondria (Ralph et al., 2010, Ishikawa et al., 2008). Further evidence that mtDNA mutations drive cancer formation suggests that efficient mitochondrial function is tumor suppressive in some cases (Santidrian et al., 2013). While intriguing, it should be noted that the role of mtDNA mutations in cancer remains controversial as considerable data indicates that the mutations have little impact on cancer growth or survival (Ju et al., 2014).

Transcriptional Responses To Mitochondrial Dysfunction

As mitochondria are responsible for many essential cellular functions, maintenance of these organelles is critical. Mitochondrial activity is monitored by multiple mechanisms including mitochondria to nuclear communication, which occurs through several known pathways. Signals that convey mitochondrial status to the nucleus include calcium fluctuations (Biswas et al., 1999, Amuthan et al., 2001), ROS (Johnson et al., 2008), mitochondrial protein import efficiency (Nargund et al., 2012), metabolites (Mouchiroud et al., 2013), and energy production (Martinez-Reyes et al., 2012).

In yeast, mitochondrial dysfunction is signaled to the nucleus via the retrograde response (RTG). Mitochondrial stress caused by mtDNA depletion activates the transcription factors Rtg1 and Rtg3 (Liao and Butow, 1993, Jia et al., 1997). In the absence of mitochondrial stress, the Rtg1-Rtg3 complex is phosphorylated and sequestered in the cytosol. During

stress, the phosphatase Rtg2 is activated resulting in dephosphorylation of Rtg1-Rtg3 and the transcription factors translocate to the nucleus and activate the RTG response. RTG activation causes induction of a number of metabolic genes including *CIT2*, a key enzyme in the glyoxylate cycle, which allows the cell to use alternate carbon sources for energy that can be processed independent of mitochondrial function (Butow and Avadhani, 2004, Liu and Butow, 1999). However, a pathway orthologous to the RTG pathway has not been found in metazoans. Rather, the RTG response seems to be fulfilled by multiple pathways. The transcription factors NRF1 and NRF2 control expression of OXPHOS genes, the voltage-dependent anion channel (VDAC), and mitochondrial transcription factors A and B (mtTFA and mtTFB) in mammals (Scarpulla, 2002). Peroxisome proliferator activated receptor (PPAR) α and γ control expression of genes involved in fatty acid metabolism and β-oxidation (Puigserver and Spiegelman, 2003) and PPARγ coactivator-1 (PGC-1) regulates mitochondrial biogenesis in tissues such as brown fat and skeletal muscle cells (Wu et al., 1999).

The UPR^{mt} in Worms, Mice, and Humans

The mitochondrial unfolded protein response (UPR^{mt}) is an adaptive transcriptional response that was initially described as a mechanism for cells to maintain mitochondrial protein homeostasis during mitochondrial dysfunction, as these organelles are constantly importing and processing proteins in an unfolded state. Hoogenraad and colleagues first described the pathway in rat hepatoma cells in which mtDNA had been depleted through ethidium bromide (EtBr) treatment (Martinus et al., 1996) and later found similar results when mitochondrial stress was caused by overexpression of a terminally misfolded mitochondrial protein (Zhao et al., 2002). However, many of the studies to determine how the UPR^{mt} is regulated have been carried out in *Caenorhabditis elegans* (Figure 1). The UPR^{mt} in *C. elegans* can be activated by conditions similar to those in mammalian cells that cause mitochondrial stress, such as depletion of mtDNA (Yoneda et al., 2004), OXPHOS components (Durieux et al., 2011), mitochondrial proteases (Nargund et al., 2012), perturbation of mitochondrial ribosomes (Moullan et al., 2015), or exposure to reagents that generate ROS (Yoneda et al., 2004). Genetic screens have identified multiple components required for UPR^{mt} activation including the mitochondrial protease ClpP, the homeobox transcription factor DVE-1 (Haynes et al., 2007), the ubiquitin like protein UBL-5 (Benedetti et al., 2006), the mitochondrial peptide transporter HAF-1 (Haynes et al., 2010), multiple chromatin regulatory factors, (Merkwirth et al., 2016, Tian et al., 2016) and the transcription factor ATFS-1 (Nargund et al., 2015). Consistent with the UPR^{mt} preserving mitochondrial function, worms lacking UPR^{mt} components have impaired growth and survival during mitochondrial stress (Gatsi et al., 2014, Liu et al., 2014, Nargund et al., 2012).

Mitochondrial protein import efficiency, which is reliant on mitochondrial protein homeostasis and OXPHOS, of the bZip transcription factor ATFS-1 regulates the UPR^{mt}. ATFS-1 is imported into the mitochondrial matrix via an N-terminal MTS where it is degraded by the Lon protease under normal conditions (Nargund et al., 2012). However during stress, import efficiency is reduced and a percentage of ATFS-1 accumulates in the cytosol. It then translocates to the nucleus via its nuclear localization sequence (NLS). This

arrangement of two compartmental localization sequences within a single transcription factor couples activation of the UPR^{mt} to mitochondrial import efficiency. Thus, mitochondrial import efficiency of ATFS-1 acts as a surrogate for the functional status of the entire mitochondrial network. Once activated, ATFS-1 upregulates over 400 genes involved in processes such as mitochondrial protein homeostasis, ROS detoxification, glycolysis, and interestingly, xenobiotic detoxification and innate immunity (Nargund et al., 2012). Perturbation of vital cellular functions activates an immune response, as multiple pathogens interfere with these vital functions (Melo and Ruvkun, 2012, Liu et al., 2014). Among those bacteria that activate the UPR^{mt} are several that impair mitochondrial function. For example, exposure to the pathogen *Pseudomonas aeruginosa* activates the UPR^{mt} as *P. aeruginosa* produces the OXPHOS inhibitor cyanide as a virulence factor resulting in activation of an innate immune response (Pellegrino et al., 2014, Liu et al., 2014).

Many of the genes upregulated by ATFS-1 contain a 14 base-pair sequence in the promoter region, termed the UPR^{mt} element (UPR^{mt}E), to which ATFS-1 directly binds. In addition to the genes that ATFS-1 upregulates, ATFS-1 limits transcription of genes encoding tricarboxylic acid (TCA) cycle enzymes, and OXPHOS components encoded by both the mitochondrial and nuclear genomes (Nargund et al., 2015). This potentially allows time for the recovery of mitochondrial protein homeostasis and regulates expression and efficient assembly of the highly expressed TCA cycle and OXPHOS complexes. In addition to these findings, during mitochondrial stress in mammals synthesis of mtDNA-encoded proteins is reduced (Munch and Harper, 2016).

In addition to transcriptional adaptions, mitochondrial stress during development affects long-term chromatin changes, and these epigenetic marks contribute to activation of the UPR^{mt} in worms and mammals that maintains a “youthful” state (Tian et al., 2016, Merkwirth et al., 2016). Specifically, mitochondrial stress results in di-methylation of the histone H3K9, mediated by the methyltransferase *met-2* and the nuclear factor *lin-65*. This change causes global silencing of chromatin, but opens up chromatin in regions associated with UPR^{mt} activation and is required for DVE-1 and ATFS-1 to bind the appropriate promoters (Tian et al., 2016). Furthermore, two histone lysine demethylases, the Jumonji family proteins *jmjd-1.2* and *jmjd-3.1* are required for UPR^{mt} activation and mitochondrial stress mediated longevity in worms (Merkwirth et al., 2016). The homologs of these proteins in mammals, PHF8 and JMJD3 respectively, positively correlate with methylation status, mRNA, and protein expression of UPR^{mt} associated genes.

Interestingly, UPR^{mt} activation can be communicated in a cell non-autonomous manner (Durieux et al., 2011, Berendzen et al., 2016). For example, mitochondrial dysfunction in neuronal cells activates a neuronal UPR^{mt}, which in turn leads to activation of the UPR^{mt} in intestinal cells. While the cell-to-cell communication is not completely understood, considerable data indicates a requirement for serotonin (Berendzen et al., 2016) and the secreted neuropeptide FLP-2. Furthermore, FLP-2 signaling involves a neural sub-circuit that includes two sensory neurons with environmental exposure and an interneuron. The sensory neurons communicate mitochondrial stress to the interneuron, which releases FLP-2 to signal to downstream neurons to activate the UPR^{mt} in distal tissues (Shao et al., 2016), although how the intestinal cells receive the signal remains to be determined. Cell non-

autonomous signaling potentially allows for metabolic coordination between cells (Berendzen et al., 2016) or pre-emptive UPR^{mt} activation in distal cells in response to systemic mitochondrial stress, such as during bacterial infection.

ATF5 regulates a Mammalian Mitochondrial UPR

While *C. elegans* has proven useful to identify UPR^{mt} signaling components, the initial observations were made in mammalian cells. Those studies used a mutated form of ornithine transcarbamylase (ΔOTC), a protein that is terminally misfolded following import into mitochondria (Zhao et al., 2002) resulting in mitochondrial stress. ΔOTC expression results in upregulation of mitochondrial chaperones and proteases such as Cpn60 (HSP60) and ClpP. The transcription factor CHOP, which is also induced by ΔOTC expression, has been proposed to regulate the UPR^{mt} but the mechanism by which CHOP is stimulated by mitochondrial stress and regulates UPR^{mt} genes is unclear (Aldridge et al., 2007).

Using a combination of *C. elegans* and mammalian genetics, we found the mammalian bZIP transcription factor ATF5 to be required for UPR^{mt} activation during a variety of mitochondrial stresses (Figure 2). ATF5, in addition to sharing homology with ATFS-1 and containing a putative MTS, is transcriptionally upregulated in several mitochondrial diseases such as the neurological disease spinocerebullar ataxia 28 (SCA28), which is caused by a mutation in the mitochondrial m-AAA protease *AFG3L2* (Mancini et al., 2013). In addition, ATF5 is induced in a mouse model of mitochondrial myopathy caused by a dysfunctional mitochondrial helicase, Twinkle, which causes accumulation of mtDNA deletions (Tyynismaa et al., 2004, Tyynismaa et al., 2010). Similarly, ATF5 is induced in mice harboring a deletion in the mitochondrial aspartyl-tRNA synthetase DARS2, which results in mitochondrial stress (Tyynismaa et al., 2004, Dogan et al., 2014).

Consistent with conservation of the UPR^{mt} between worms and mammals, expression of ATF5 rescues UPR^{mt} signaling in worms lacking *atfs-1* (Fiorese et al., 2016). ATF5 is required for the increase of mitochondrial-protective transcripts in response to mitochondrial stress, such as the ROS-generating molecule paraquat, OXPHOS inhibition and transgenic expression of ΔOTC. And, transcriptional activation by ATF5 requires the same UPR^{mt}E promoter element to which ATFS-1 binds in worms during mitochondrial stress (Nargund et al., 2015). And intriguingly, the promoters of those genes induced in the Twinkle mouse model of mitochondrial myopathy were enriched for the same UPR^{mt}E (Tyynismaa et al., 2010).

In *C. elegans*, ATFS-1 responds to mitochondrial stress when mitochondrial protein import becomes impaired. It is well documented that ATF5 accumulates in the nucleus when activated (Monaco et al., 2007, Dalton et al., 2013), but in the absence of stress ATF5 accumulates in mitochondria in worm, mice, and human cells suggesting ATF5 is also regulated by mitochondrial import efficiency. Lastly, ATF5 is required for mitochondrial function and cellular recovery from a variety of mitochondrial perturbations including ΔOTC expression, mtDNA depletion and exposure to the ATP synthase inhibitor oligomycin (Fiorese et al., 2016). Thus, ATF5 is conceptually and experimentally similar to *C. elegans* ATFS-1.

It is important to note however, that differences between UPR^{mt} signaling in worms and mammals are emerging. For example ClpP, a component required for UPR^{mt} signaling in worms is likely dispensable for UPR^{mt} signaling in mice and humans (Seiferling et al., 2016, Gispert et al., 2013). ClpP knockout in a DARS2 knockout model of cardiomyopathy has no effect on the induction of UPR^{mt} genes. In fact, ClpP deletion seems to improve OXPHOS function and even extended the lifespan of DARS2 knockout mice, through a mechanism that results in decreased protein synthesis within mitochondria and increased protein turnover rates.

Additionally, there is the question of how ATF5 interacts with other proposed regulators of the UPR^{mt}. For example ATF5 and CHOP have been show to regulate each other (Watatani et al., 2007, Teske et al., 2013), but how these two components interact during mitochondrial stress remains to be investigated. Additional transcription factors affected by mitochondrial stress include the estrogen receptor and FOXOA3, which upregulate expression of the mitochondrial protease Omi (Papa and Germain, 2011) and induce antioxidant genes (Papa and Germain, 2014) respectively. It will be interesting to determine how these pathways integrate with ATF5 and the UPR^{mt}.

A Role for the Integrated Stress Response During Mitochondrial Stress

The integrated stress response (ISR) is characterized by the phosphorylation of eIF2α by one of four eIF2α kinases that are activated by different forms of stress. Endoplasmic reticulum stress activates the kinase PERK (Shi et al., 1998, Harding et al., 1999), PKR is activated by the accumulation of double stranded RNA in the cytosol (Meurs et al., 1990), general control nonderepressible 2 (GCN2) is activated by amino acid depletion and ROS (Harding et al., 2003, Shenton et al., 2006), and the heme regulated inhibitor kinase (HRI) is activated during heme depletion (Lu et al., 2001). Regardless of the upstream stressor, all four kinases phosphorylate eIF2α which represses global protein synthesis, but promotes translation of mRNAs harboring upstream open reading frames (uORFs) in the 5′ untranslated region (UTR) such as *ATF4* and *ATF5* (Lu et al., 2004, Zhou et al., 2008).

Interestingly, PKR (Rath et al., 2012), PERK (Hori et al., 2002) and GCN2 (Martinez-Reyes et al., 2012, Baker et al., 2012) can be activated during mitochondrial dysfunction although the respective modes of activation are unclear. Consistent with both mRNAs containing uORFs ATF4 and ATF5 are preferentially synthesized when eIF2α is phosphorylated (Harding et al., 2000, Zhou et al., 2008). As described above, ATF5 regulates expression of mitochondrial protective transcripts, as does ATF4. For example, ATF4 induces expression of *LONP1*, components of one carbon metabolism (Harding et al., 2003, Bao et al., 2016) as well as the endocrine hormone fibroblast growth factor 21 (FGF21) in the serum, which promotes metabolic coordination between tissues (Kim et al., 2013a, Kim et al., 2013b, Dogan et al., 2014).

Thus, considerable evidence in mammals supports a role for the ISR in the response to mitochondrial dysfunction, potentially through the UPR^{mt}. In *C. elegans*, the ISR is not required for UPR^{mt} activation as worms lacking all homologous eIF2α kinases are still able to activate the UPR^{mt}. In fact, GCN2 promotes mitochondrial function during mitochondrial

stress independent of ATFS-1, most likely by reducing protein synthesis and reducing the protein folding load on dysfunctional mitochondria (Baker et al., 2012). However, it should be noted that like *ATF5*, some *atfs-1* mRNAs contain uORFs and some do not, suggesting ATFS-1 may be regulated by the ISR under specific stress conditions. Furthermore, most cultured mammalian cells only express the *ATF5* splice variant harboring the uORF, thus requiring eIF2α phosphorylation to be translated. However, in mouse tissues such as liver, ATF5 mRNA and protein are expressed at relatively high levels likely due to relatively high steady state levels of eIF2α phosphorylation dependent of Gcn2 (Zhang et al., 2002, Fiorese et al., 2016, Pascual et al., 2008). Going forward, it will important to understand the contribution of the individual eIF2a kinases during mitochondrial stress, but also the role of each splice isoform of ATF5 and ATFS-1 both in tissue culture models, but more importantly in vivo.

Mitochondrial Quality Control

In addition to transcriptional adaptations to mitochondrial stress, cells also employ a number of quality control pathways that can degrade damaged mitochondrial proteins or whole organelles (Figure 3). The ubiquitin-proteasome system degrades outer membrane mitochondrial proteins as well as mitochondrial-targeted proteins that fail to be imported into mitochondria (Neutzner et al., 2008) while mitophagy sequesters mitochondria for degradation (Narendra et al., 2010).

During mitochondrial dysfunction, a reduction in protein import efficiency results in an accumulation of mislocalized mitochondria-targeted proteins in the cytosol. In response to this accumulation of precursor proteins, processes known as the unfolded protein response activated by mistargeted proteins (UPRam) (Wrobel et al., 2015), and mitochondrial precursor over-accumulation stress (mPOS) (Wang and Chen, 2015) are activated. Impressively, these programs increase cytosolic proteasome activity and reduce protein synthesis to rescue otherwise lethal mitochondrial dysfunction that impairs of mitochondrial protein import.

Mitophagy is a process to recognize and degrade mitochondria when the organelles have become severely damaged. The protein kinase PINK1 is a mitochondrial-localized protein that in the absence of stress is imported and degraded (Narendra et al., 2010). During stress, mitochondrial import is impaired causing PINK1 to accumulate on the outer membrane where it phosphorylates ubiquitin (Kane et al., 2014, Koyano et al., 2014, Ordureau et al., 2015). Decoration of mitochondrial proteins with ubiquitin serves to recruit the ubiquitin ligase Parkin, which in turn is phosphorylated and activated by PINK1 (Kazlauskaite et al., 2014). Parkin further ubiquitinates mitochondrial outer membrane proteins (Tanaka et al., 2010, Sarraf et al., 2013) leading to the recruitment of the autophagy receptors Optineurin (OPTN) and NDP52, which serves as a bridge between the cargo and the autophagosome. OPTN binds to polyubiquitin chains and recruits the kinase TBK1 to phosphorylate the autophagy receptors, which increases the affinity of the autophagy receptor for the autophagosome component LC3 and increases autophagic clearance (Lazarou et al., 2015, Richter et al., 2016, Heo et al., 2015, Ordureau et al., 2015). Thus, PINK1 initiates an

amplification loop to increase mitophagy signaling ensuring the specific recognition and degradation of the least fit organelles.

Conclusion and Perspectives

Several strategies by which cells respond to mitochondrial stress have emerged in recent years including the UPR^{mt}, mitophagy and pathways that protect the cytosol from mis-localized mitochondrial proteins. While the individual quality control pathways are still being elucidated, it will be interesting to understand how each pathway (Figure 3) integrates or interacts with one another to coordinate a successful defense against mitochondrial stress and maintenance of the mitochondrial network. The UPR^{mt}, UPRam/mPOS, and mitophagy are all regulated by mitochondrial import efficiency. Do these pathways directly or indirectly antagonize each other, and what is the tipping point from recovery of mitochondrial function through the UPR^{mt} and UPRam/mPOS to turnover of mitochondria via mitophagy?

The mammalian UPR^{mt} appears to be regulated similarly to the *C. elegans* UPR^{mt}, with ATF5 fulfilling many of the same roles as ATFS-1 in the worm. ATF5 localizes to mitochondria, and during mitochondrial stress translocates to the nucleus and upregulates mito-protective genes. However, much remains unknown about the UPR^{mt}. For example, how does the UPR^{mt} interact with the ISR? Perhaps it is through eIF2α kinases, many of which are activated by mitochondrial stress. Of particular interest are those known to signal downstream to ATF5 and ATF4, such as GCN2 (Zhou et al., 2008), PERK (Dalton et al., 2013), and PKR (Rath et al., 2012). Furthermore, additional mitochondrial stress activated transcriptional responses involving the estrogen receptor alpha and FOXOA3 have been identified (Papa and Germain, 2011), (Papa and Germain, 2014). It will be interesting to understand how these responses coordinate to promote cellular and organismal health.

The physiologic roles for the described pathways are expanding rapidly. Considerable data supports roles for the UPR^{mt} during mitochondrial dysfunction associated with aging (Houtkooper et al., 2013), toxin exposure (Gatsi et al., 2014) and infection by pathogenic bacteria that perturb mitochondrial function (Pellegrino et al., 2014). However, recent work has demonstrated that prolonged UPR^{mt} activation has potential negative consequences. In *C. elegans*, the UPR^{mt} promotes the maintenance and propagation of deleterious mtDNAs in both aging somatic cells as well as between generations (Lin et al., 2016, Gitschlag et al., 2016). The UPR^{mt} appears to both counter the mitophagy pathway in this respect, which serves to clear deleterious mtDNA, as well as promote deleterious mtDNA propagation directly. Furthermore, overexpression of Parkin eliminates mutant mtDNA in mammalian cells (Suen et al., 2010). It remains to be seen if the mammalian UPR^{mt} fufills a similar role to the worm UPR^{mt} in the maintenance of deleterious mtDNA.

ATF5 expression is required for survival of many transformed cells such as glioblastomas (Arias et al., 2012, Monaco et al., 2007), which are also affected by mitochondrial dysfunction (Deighton et al., 2014). How does ATF5, and by extension the UPR^{mt} allow transformed cells to survive and grow in environments they normally would not? Cancer cells can gain advantage by aberrant activation of stress response pathways in other contexts

(Paolicchi et al., 2016), and the UPR^{mt} is an attractive candidate to target with inhibitors to prevent cancer cells from benefitting from this stress response pathway.

Acknowledgments

This work was supported by grants from the NIH (R01HL127891 and R01AG047182 to C.M.H.)

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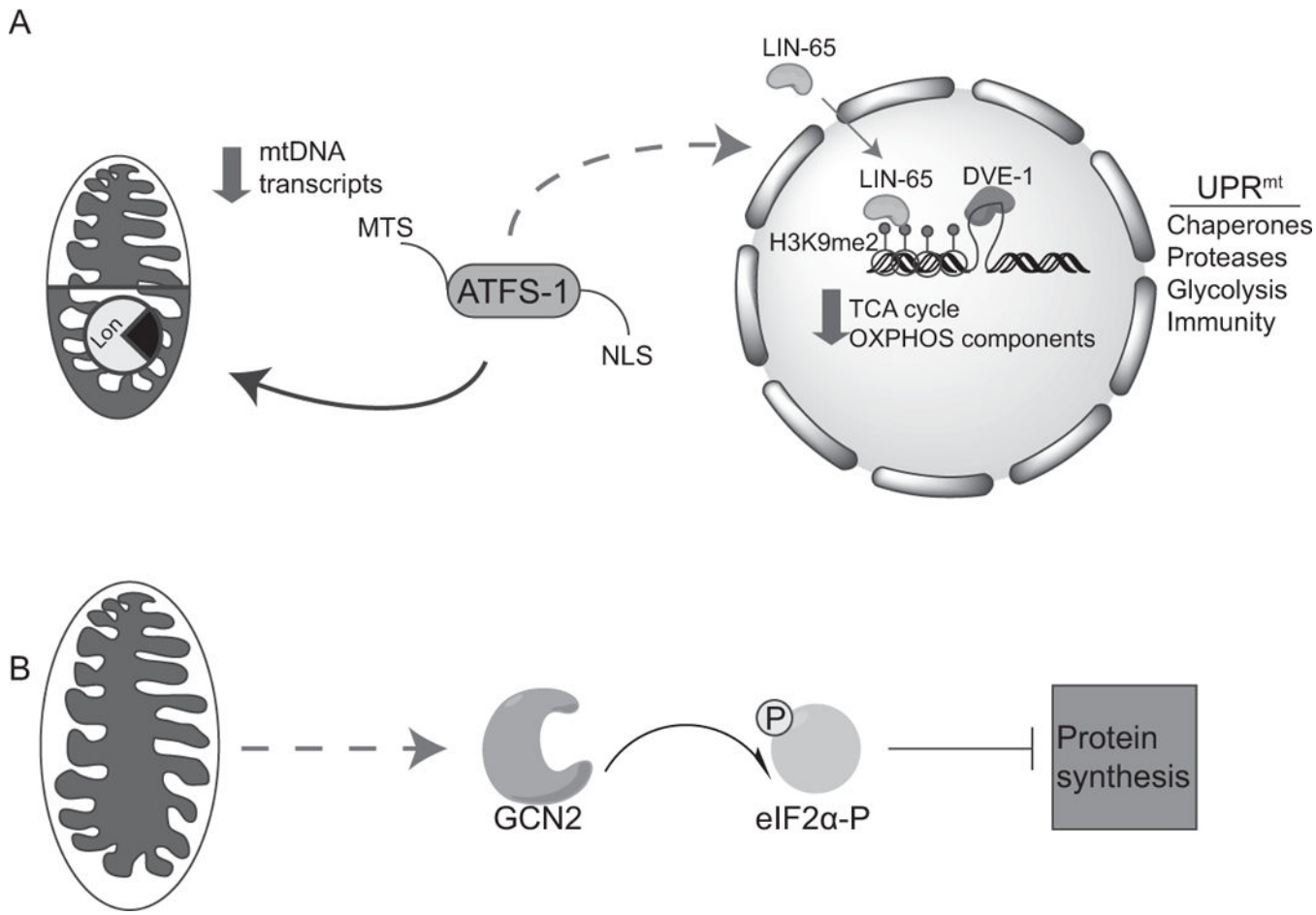

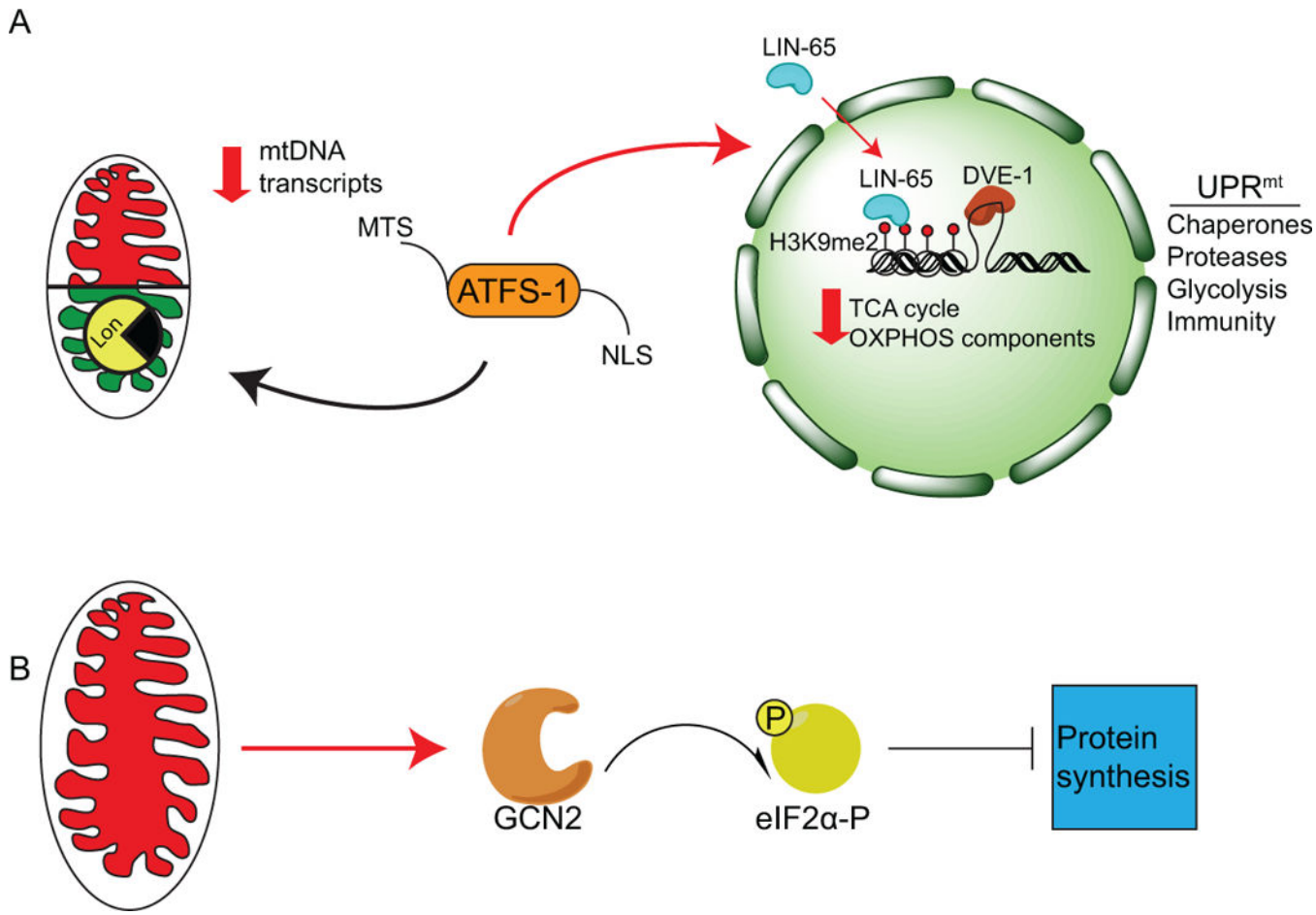

Figure 1. Regulation of the UPR^{mt} in *C. elegans*

(A) The mitochondrial unfolded protein response (UPR^{mt}) is regulated by the mitochondrial import efficiency of the transcription factor ATFS-1, which contains a mitochondrial targeting sequence (MTS) and a nuclear localization sequence (NLS). In the absence of stress, ATFS-1 is imported into mitochondria and subsequently degraded by the Lon protease. During stress import efficiency is reduced, and a percentage of ATFS-1 accumulates in the cytosol. ATFS-1 then translocates to the nucleus and activates a broad range of genes encoding mitochondrial chaperones and proteases as well as glycolysis and innate immune components, while limiting transcription of tricarboxylic acid (TCA) cycle genes, as well as oxidative phosphorylation (OXPHOS) genes encoded by both the nucleus and mitochondria. In addition to ATFS-1 signaling, the nuclear factor LIN-65 translocates to the nucleus during stress as well to modify chromatin, specifically the methylation of lysine 9 of histone H3 (H3K9me1/2) to allow the transcription factors DVE-1 and ATFS-1 to bind the promoters of UPR^{mt} associated genes for transcription.

(B) In parallel, the eIF2α kinase GCN2 is activated during mitochondrial dysfunction and phosphorylates eIF2α reducing protein synthesis and the load of unfolded proteins in the stressed organelles. NB: Color version of this figure is available online.

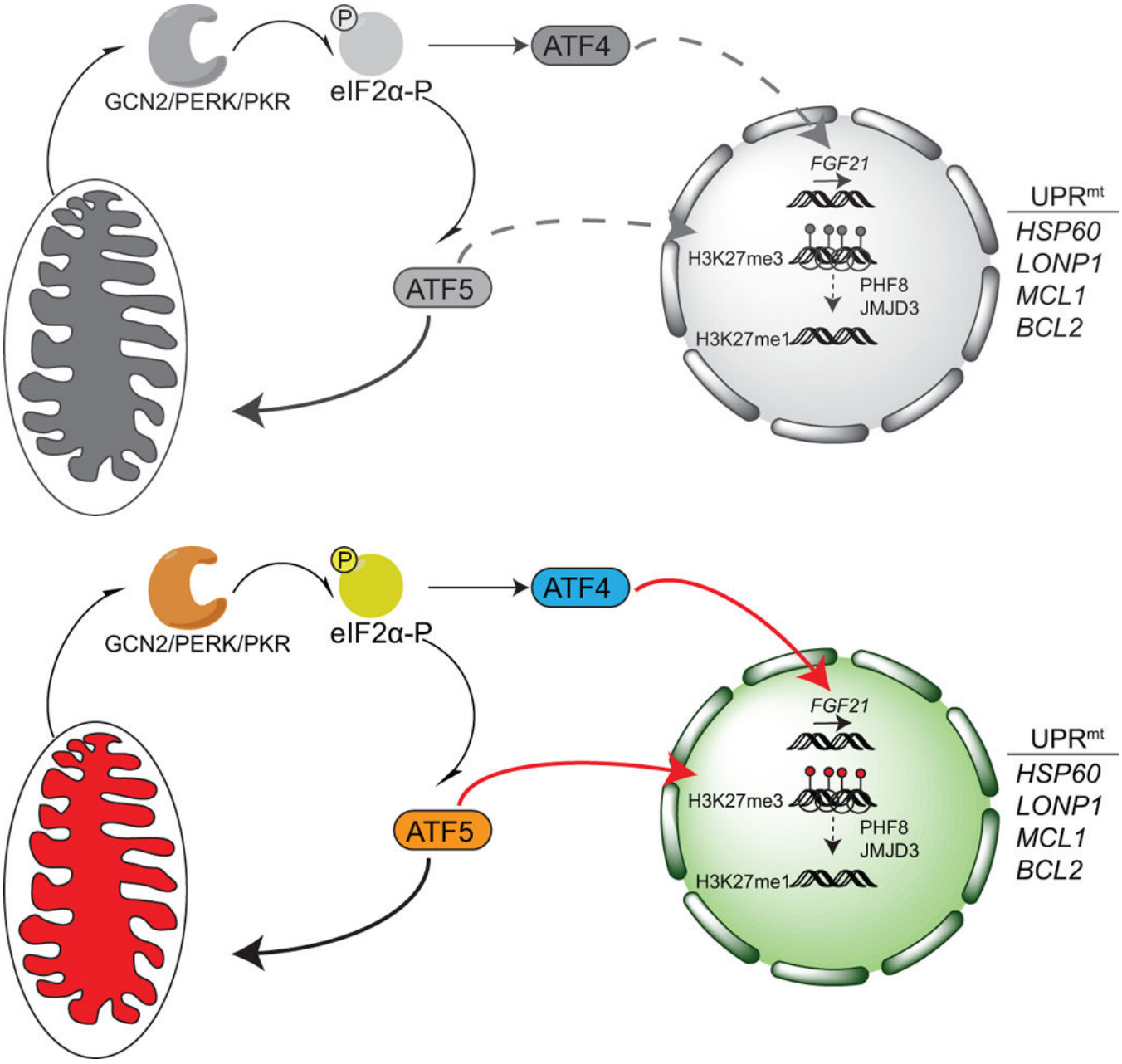

Figure 2. Regulation of a mammalian UPR^{mt}

The bZIP transcription factor ATF5 has homology to ATFS-1 and localizes to mitochondria in the absence of stress. During mitochondrial stress, ATF5 translocates to the nucleus and upregulates chaperones (*HSP60*) and proteases (*LONP1*) associated with the UPR^{mt} as well as anti-apoptotic genes like *MCL1* and *BCL2*. ATF5 is also regulated by eIF2α–phosphorylation due to the presence of upstream open reading frames (uORFs) in one of the *ATF5* mRNA splice variants, The eIF2α kinases GCN2, PERK, and PKR all phosphorylate eIF2α during mitochondrial stress but how they are activated is unclear. Thus, ATF5 activation is regulated by import efficiency and the Integrated Stress Response (ISR) to promote the recovery of dysfunctional mitochondria. The transcription factor ATF4 is also

activated during mitochondrial stress via the ISR, which upregulates expression of the endocrine *FGF21*, which regulates metabolic changes in the organism. Like ATF5, the ATF4 transcript contains uORFs in the 5′ UTR of the transcript. Furthermore, mitochondrial stress results in chromatin reorganization by the histone demethylases PHF8 and JMJD3, which modify the methylation status of lysine 27 on histone H3 (H3K27me3/1) and mediate UPR^{mt} gene expression. NB: Color version of this figure is available online.

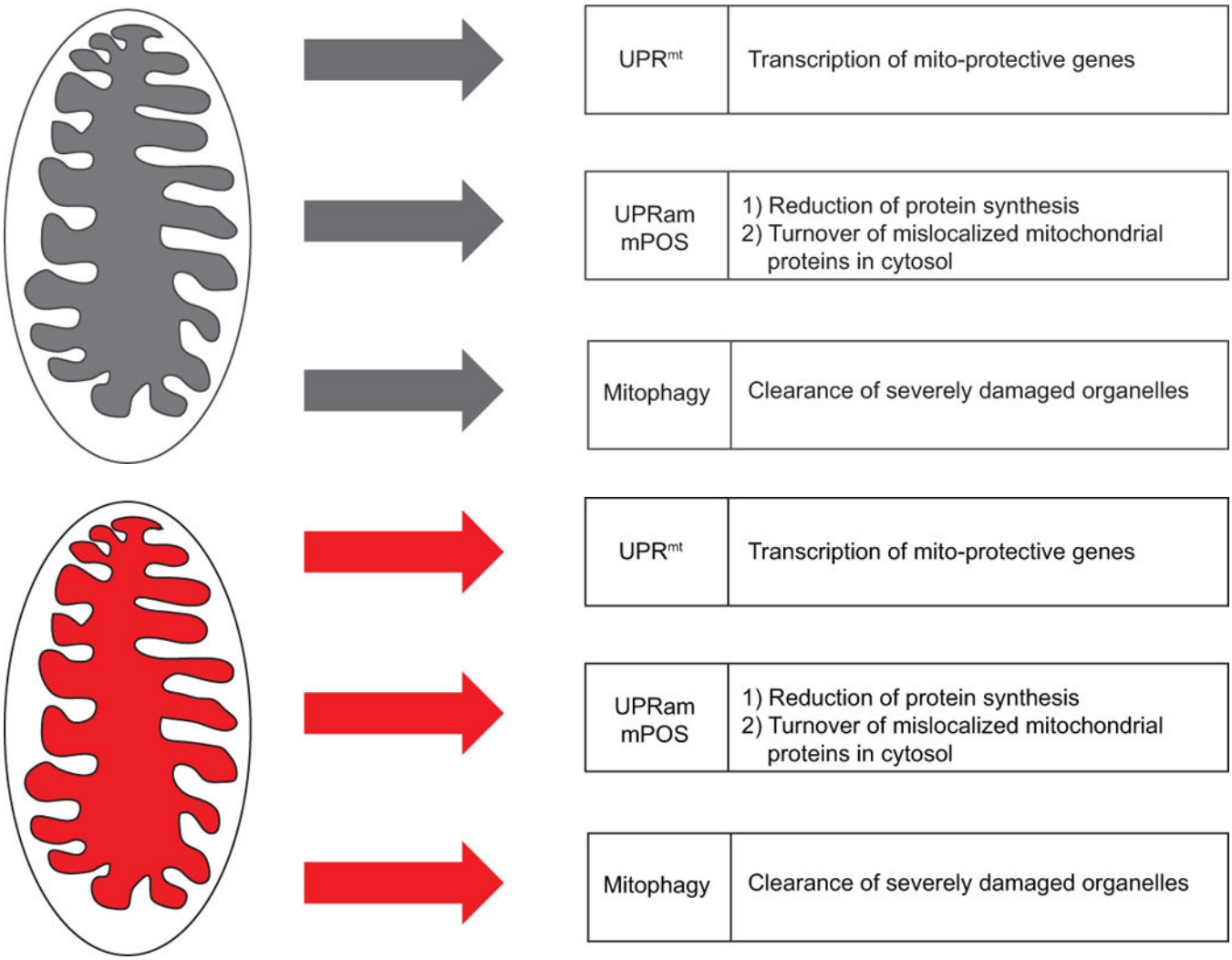

Figure 3. Responses to mitochondrial dysfunction

Mitochondrial stress activates quality control pathways such as the UPR^{mt}, the UPRam/mPOS, and mitophagy. Once mitochondria are damaged, the UPR^{mt} activates a transcriptional response to recover mitochondrial function, while the unfolded protein response activated by mistargeted proteins (UPRam) and mitochondrial precursor over-accumulation stress (mPOS) serve to reduce cytosolic protein synthesis and degrade mislocalized mitochondrial proteins that fail to be imported. The kinase PINK1 accumulates on the mitochondria outer membrane where it phosphorylates ubiquitin which recruits Parkin, leading to the clearance of severely damaged mitochondria via lysosome-dependent degradation. Coordination of these three pathways promotes the recovery of the mitochondrial network and cellular health. NB: Color version of this figure is available online.