

# Mitochondrial proteostasis in the context of cellular and organismal health and aging

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As a central hub of cellular metabolism and signaling, the mitochondrion is a crucial organelle whose dysfunction can cause disease and whose activity is intimately connected to aging. We review how the mitochondrial network maintains proteomic integrity, how mitochondrial proteotoxic stress is communicated and resolved in the context of the entire cell, and how mitochondrial systems function in the context of organismal health and aging. A deeper understanding of how mitochondrial protein quality control mechanisms are coordinated across these distinct biological levels should help explain why these mechanisms fail with age and, ultimately, how routes to intervention might be attained.

The decline in the health of an organism over time derives from dysfunction at the cellular level, which largely arises from the progressive accumulation of damage to proteins and organelles (Fig. 1A). Work over the past decades has identified the mitochondrion as an organelle whose function imparts a significant effect on aging. Here, we review a set of underlying pathways and molecular machines that are central to the mitochondrial contribution to aging.

The key functions mitochondria are tasked with—energy homeostasis, metabolism, and apoptosis—rely upon an elaborate network of proteins, many of them multisubunit complexes. Several challenges face the mitochondrion with respect to establishing and maintaining a functional proteome. First, having descended from an ancestral bacterium, the mitochondrial proteome and genome are separated from the rest of the cell by inner and outer membranes (Fig. 1B). Only ~13 of its ~1,100 resident proteins are encoded by the mitochondrial genome (mtDNA) (1); therefore, a vast majority of mitochondrial proteins have to be folded following translation in the cytoplasm and import into mitochondria. Moreover, once imported into the organelle, mitochondrial proteins are physically separated from the cytoplasmic protein-folding machinery, therefore requiring mitochondrion-localized machinery for their maintenance. The second challenge is that a number of key mitochondrial protein complexes

contain subunits encoded by both the nuclear and mitochondrial genomes, and an imbalance in the expression from these two genomes can be detrimental to mitochondrial protein homeostasis. A third challenge is that the primary energy-producing process inside the mitochondrion, oxidative phosphorylation (OXPHOS),<sup>4</sup> creates damaging reactive oxygen species (ROS) as a by-product of the electron transport chain (ETC). These ROS threaten not only the OXPHOS machinery but also other mitochondrial proteins, lipids, and the mtDNA.

To defend against these proteomic challenges, mitochondria employ several mechanisms to maintain protein homeostasis, or “proteostasis” within the organelle. In general terms, proteostasis mechanisms exist to monitor and control all steps in the life of a protein, including biogenesis, folding, localization, and degradation. Proteostasis of mitochondrial proteins includes mitochondria-localized chaperones and proteases that re-fold or degrade individual mis-folded proteins, as well as bulk mitochondrial organelle degradation, inter-organellar communication, and trans-cellular signaling, all of which impact the quality of proteins functioning within mitochondria. Defects in these mitochondrial proteostasis defense pathways in these different layers of biological complexity can have substantial impacts on organismal health and aging. A number of mutations in genes encoding mitochondrial proteostasis machinery result in accelerated proteostatic collapse, and many eventually manifest in age-associated diseases (Table 1). In addition, acute environmental insults, such as exposure to mitochondria-targeted pesticides, herbicides, and antibiotics are thought to increase the proteostatic burden on mitochondria and are known to be pathogenic to humans (2). An increased focus on mitochondrial proteostasis as it connects to cellular and organismal health should yield a more informed perspective on the etiology and treatment of aging and aging-related disease.

## Mitochondrial proteostasis at the organellar level

### Types of damage that accumulate in mitochondria

To trace the connection between mitochondrial proteostasis and organismal health, we first review the types of damage to

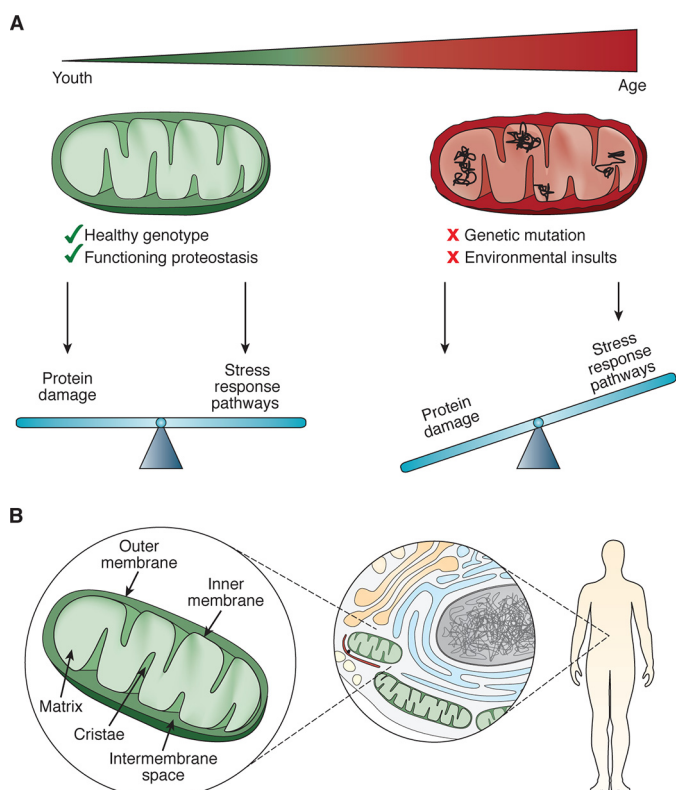
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<sup>4</sup> The abbreviations used are: OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; ETC, electron transport chain; PD, Parkinson's disease; IMS, intermembrane space; AD, Alzheimer's disease; mtUPR, mitochondrial unfolded protein response; ER-UPR, unfolded protein response of the ER; ER, endoplasmic reticulum; MDV, mitochondria-derived vesicle; MDC, mitochondria-derived compartment; MAM, mitochondria-associated ER membrane; MCSR, mitochondrial-to-cytosolic stress response.



**Figure 1. Factors that impact mitochondrial proteostasis.** *A*, mitochondria must balance the damage that occurs to its proteins with activation of pathways evolved to counteract this damage. *B*, mitochondrial proteostasis occurs at multiple scales: at the level of the mitochondrion, the mitochondrion's interaction with the rest of the cell, and with the organism as it impacts metabolism, health, and life span.

**Table 1**  
**Genetic mutations in mitochondrial protein quality control factors associated with disease and age-related disorders**

Protein	Function	Associated disorder
PINK1	Signaling in mitophagy	Parkinson's disease (96)
Parkin	E3 ubiquitin ligase in mitophagy	Parkinson's disease (96); ovarian cancer (152)
mtHsp60	Matrix-localized protein folding chaperonin	Spastic paraplegia 13 (24)
<i>m</i> -AAA, various subunits	Inner membrane-localized metalloprotease facing matrix	Spastic paraplegia 7 (23); spino-cerebellar ataxia type 28 (25)
CipP	Matrix-localized peptidase	Perrault Syndrome (22)
TRAP1	Matrix-localized mtHsp90 chaperone	Parkinson's disease (29)
OPA1	IMS-localized; mitochondrial fusion	Autosomal dominant optic atrophy (52)
MFN2	Outer membrane-localized GTPase; membrane fusion	Charcot-Marie Tooth disease (53)

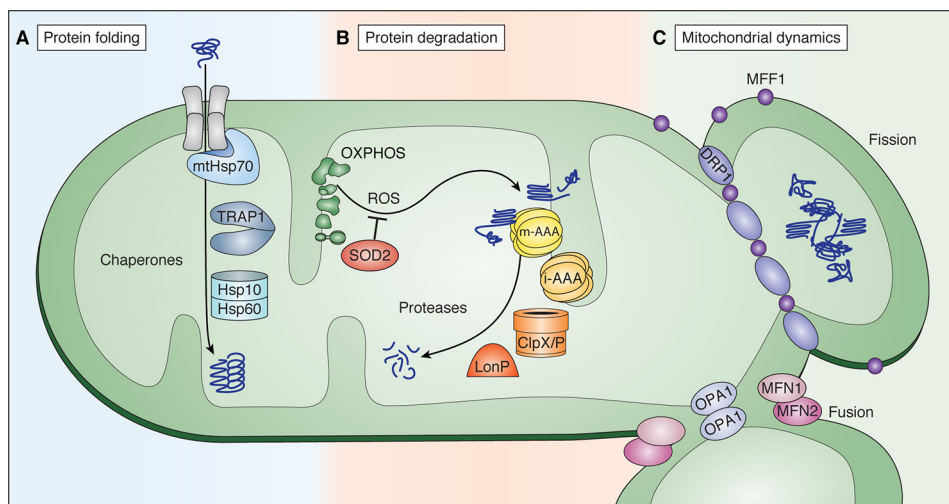
the mitochondrial proteome and the molecular machines that function within the organelle to repair this damage. Much like other cellular proteins, mitochondrial proteins misfold, misassemble in protein complexes, and aggregate over time, and these events all pose a threat to proteostasis if left unresolved. In some cases, this type of damage can be reversed locally through

protein-folding molecular chaperones. In contrast, terminally damaged proteins, such as those containing carbonylated residues due to exposure to ROS (3), must be degraded. In addition to direct protein damage, the mitochondrial proteome can be adversely affected by mutations or deletions in the mitochondrial genome. Each mitochondrion carries multiple copies of mtDNA, and a mutation in even a fraction of these copies can result in the synthesis of misfolded proteins. Mutations and deletions in mtDNA can also perturb mitochondrial proteostasis because they affect ATP production and increase ROS production (4–8).

The accumulation of mitochondrial proteome damage directly impacts organismal health and aging. Compromised OXPHOS proteins perturb the overall structure and function of mitochondria, particularly in organisms of advanced age (9). Carbonylation of mitochondrial proteins from ROS damage has been observed to increase with age in multiple model organisms (3), and inducing excessive ROS in mice or humans causes Parkinson's disease (PD)-like symptoms (2). Furthermore, mutations in mtDNA accumulate with age, resulting in dysfunction of its encoded proteins, which can have direct physiological consequences. For example, mtDNA mutations have been observed in the substantia nigra of the midbrain and are more prevalent in PD patients compared with age-matched controls (10, 11). In addition, mutations in *POLG*, the gene encoding the mitochondrial DNA polymerase responsible for replication, cause deletions in, and copy number variations of, mtDNA and correlate with inheritance of parkinsonism (12), as well as a diverse panel of progressive neurological and muscular symptoms (13). The relevant mouse model of *Polg* mutation, termed the mutator mouse, accumulates mutations and deletions and exhibits premature aging phenotypes (7).

### Mitochondria-localized mechanisms to combat damage

The canonical cytoplasmic proteostasis systems, such as the proteasome and heat-shock proteins, do not function inside mitochondria. For this reason, the mitochondrion has evolved a dedicated set of molecular machines, such as a network of resident chaperones, proteases, and other quality control factors, whose function is to protect the proteome (Fig. 2). The mitochondrion in particular bears a substantial burden with respect to protein folding, because all imported polypeptides must be folded immediately upon import and integrated into elaborate protein complexes that function inside the mitochondrion. Molecular chaperones are essential to correctly fold proteins after they are imported as nascent polypeptides into mitochondria and to re-fold any unfolded or misfolded proteins that may cause proteotoxic damage (Fig. 2A). A key chaperone, the mitochondrial Hsp70 (mtHsp70) is associated with the inner membrane import complex on the matrix side and actively mediates the import and folding of nascent proteins (14). In addition, a mitochondrial isoform of the heat-shock protein TRAP1 (mtHsp90) and the large chaperonin Hsp60/10 complex also contribute to the folding of matrix-localized polypeptides that require additional assistance (15–17). Separately, SOD2 in the matrix and SOD1 in the intermembrane space (IMS) convert damaging ROS into less toxic H<sub>2</sub>O<sub>2</sub> and O<sub>2</sub> before they can damage proteins (18, 19).



**Figure 2. Protein quality control machines at work within mitochondria.** *A*, protein folding chaperones that function in the mitochondrial matrix to fold nascent polypeptides or repair mis-folded proteins. *B*, proteins can be damaged by the ROS generated by components of the OXPHOS machinery. Proteases in the intermembrane space and matrix degrade these damaged proteins. *C*, fission and fusion work dynamically to alter the shape of the mitochondrial network to dilute or segregate areas of damage.

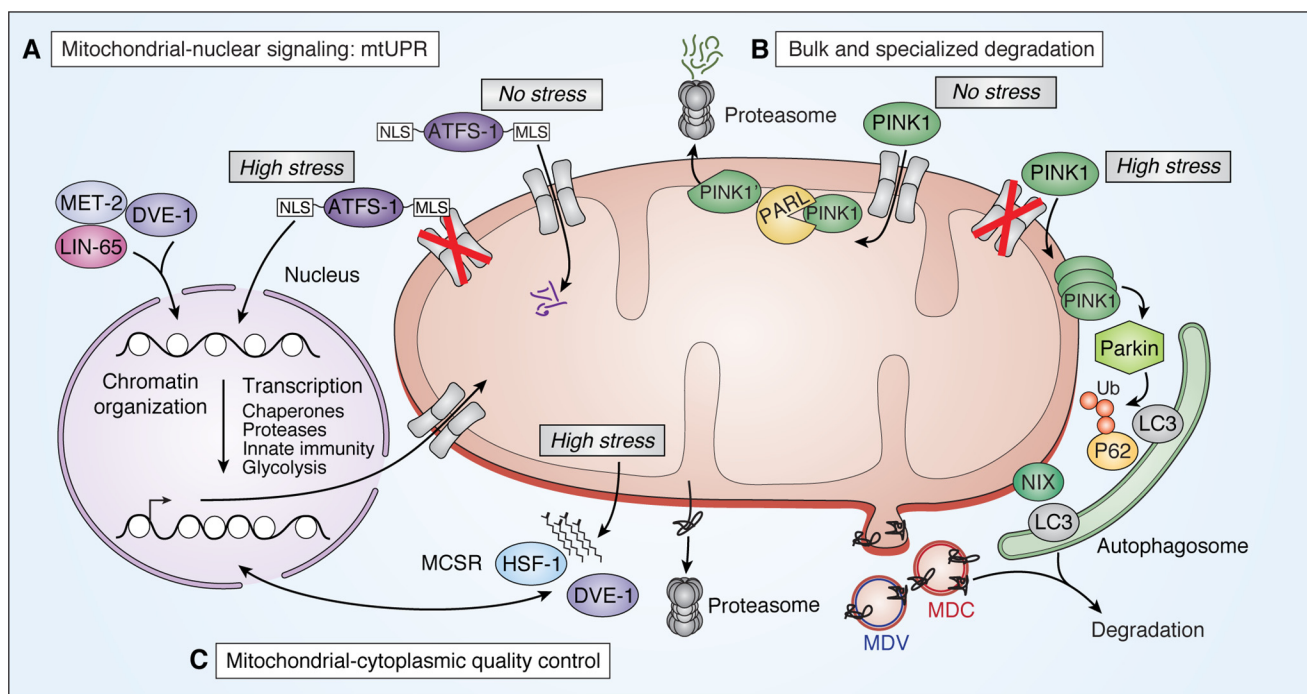
In parallel with chaperone-mediated protein folding and repair, mitochondrial proteostasis also relies on a set of dedicated proteases to resolve irreversible protein damage through degradation (Fig. 2*B*). The mitochondrial proteome has a high turnover rate: measurements from yeast reveal that as much as 6–12% of the mitochondrial proteome is degraded in each generation (20). Proteins with terminal damage or orphan subunits from multimeric complexes are frequent targets for the mitochondrion's numerous proteases. In the matrix, these include LonP and ClpP, whereas the inner membrane contains two protease complexes, m-AAA (AFG3L2, AFG3L1, and SPG7) and i-AAA (YME1L), which face the matrix and IMS, respectively (21). These inner-membrane proteases are especially important for functional integrity of the OXPHOS machinery, which are particularly susceptible to oxidative damage due to their ROS-releasing activity.

Defects in these chaperone and protease machines are associated with diverse organismal pathologies (Table 1). In some cases, loss of mitochondrial quality control machinery causes severe organismal pathology starting in early or mid-life: mutations in the *CLPP* protease have been associated with Perrault syndrome, resulting in neonatal or early childhood sensorineural hearing loss (22). In addition, two degenerative hereditary spastic paraplegias can be caused by mutations in the mitochondrial protease *SPG7* or the chaperone *HSP60* (23, 24), and spinocerebellar ataxia type 28 results from mutations in the m-AAA component, *AFG3L2* (25). Mutation in, or decreased expression of, mitochondrial chaperones is also associated with aging-related diseases such as PD and Alzheimer's disease (AD) (26–28). For example, loss of TRAP1 by mutation has been associated with late-onset PD, as well as decreased OXPHOS activity and loss of membrane potential in patient cells (29). In addition, *SOD2* is up-regulated in both AD (30) and PD patients (31), presumably in response to oxidative stress within mitochondria from these diseases. As an organism ages, its capacity to fight proteostatic insults appears to decrease: for example, basal *Lonp* expression decreases with age in mice (32); similarly,

the ability of mice and *Caenorhabditis elegans* to induce expression of mitochondrial chaperones decreases with age (33, 34). There is an unfortunate paradox in these data, since the need for such protective measures increases with age. Inherited neurological disorders are not the only pathology derived from loss of mitochondrial quality control; the mitochondrial matrix protease *CLPP* is highly expressed in leukemias (35) and multiple tumors (36), suggesting that cancer cells may experience a high proteotoxic burden within mitochondria.

Beyond managing their internal proteome, mitochondria continuously undergo opposing fusion and fission events, and this dynamic process is necessary for maintaining a healthy mitochondrial network (Fig. 2*C*). In healthy cells, mitochondria are fused into a large network, with multiple copies of the mtDNA and contiguous inner and outer membranes (37). Mitochondrial fusion, which mixes contents of different mitochondrial membranes as well as soluble components, relies on MFN1/MFN2 and OPA1 for outer and inner membrane fusion, respectively (38, 39).

In healthy cells, fusion dilutes the effects of small amounts of damage within the larger network (40). In fact, some stresses promote hyper-fusion in a process involving MFN1, OPA1, and the scaffolding inner membrane protein, SLP2 (40). Such hyper-fusion has been shown to be vital to cell survival during stresses like starvation (41) and may stave off fission-induced apoptosis. In contrast, mitochondrial fission partitions damaged mitochondria away so the health of the overall mitochondrial network can recover (42). Mitochondrial fission is driven by the dynamin-related protein DRP1/DNM1 and OMA1 (43–45). DRP1/DNM1 is recruited to mitochondrial fission sites by several identified outer mitochondrial membrane receptors, such as FIS1 and MFF (46–48). Under conditions of stress, OMA1 induces mitochondrial fragmentation by proteolytically cleaving OPA1 (49, 50). In addition to recovering the mitochondrial network, mitochondrial fission also plays a critical role in mitophagy (see below) and the initial steps of apoptosis, or programmed cell death (51).



**Figure 3. Mitochondrial proteostasis mechanisms that function at the level of the cell.** *A*, mitochondrial–nuclear communication as described in *C. elegans*. Mitochondria signal proteotoxic stress to the nucleus to up-regulate genes that will aid in restoring mitochondrial health as well as enact epigenetic changes across the genome. We focus on the ATFS-1 and LIN-65/MET-2/DVE-1 pathways. During basal conditions (*No stress*), the MLS targets ATFS-1 for mitochondrial import and subsequent degradation. During mitochondrial stress (*High stress*), low mitochondrial membrane potential and blocked mitochondrial import impairs mitochondrial targeting of ATFS-1, instead allowing NLS-dependent nuclear localization of ATFS-1, where it activates various gene transcription pathways. *NLS*, nuclear localization sequence; *MLS*, mitochondrial localization sequence. For a complete summary of all identified mtUPR players, we direct the reader to two recent mtUPR-focused reviews (154, 155). *B*, mechanisms of mitochondrial degradation via mitophagy for bulk degradation (*top*) or specialized, vesicle-dependent degradation (*bottom*). Mitophagy by either the PINK1/Parkin or NIX pathways in humans requires recognition of defective mitochondria, followed by recruitment and engulfment by an autophagosome membrane, and shuttling to the lysosome. Under basal conditions (*No stress*), PINK1 is targeted to the mitochondria and rapidly degraded. In one described mechanism, this occurs via mitochondrial import and N-terminal cleavage by the inner membrane protease PARL (99). N-terminally cleaved PINK1 (*PINK1'*) is then shuttled to the cytoplasm for proteasomal degradation. MDC (*Saccharomyces cerevisiae*) and MDV (humans) have both been shown to selectively target mitochondrial protein and other metabolite cargo for degradation. *C*, mitochondrial–cytoplasmic quality control mechanisms include the MCSR from *C. elegans* and proteasome-dependent degradation of mitochondrial outer membrane proteins. *HSF-1*, heat-shock factor 1.

Mutations in several components of the mitochondrial dynamics machinery also yield organismal pathologies, particularly neurological disorders. Mutation of *OPA1* causes dominant optic atrophy (52), and mutations of *MFN2* that disrupt the morphology and distribution of the mitochondrial network can cause Charcot-Marie-Tooth syndrome type 2A, characterized by dystrophy of peripheral muscle (53, 54). Remarkably, a knockout of *Mfn2* in the mouse leads to specific loss of dopaminergic neurons, a phenotype observed in PD patients (55, 56).

### A cellular perspective: mitochondrial proteostasis in the context of the cell

The mitochondrial genome has lost the vast majority of its protein-coding genes, and its proteome is therefore derived overwhelmingly from nuclear transcription, cytoplasmic translation, and polypeptide import into the mitochondrion. For this reason, whereas mitochondrial chaperones, proteases, and fusion/fission machinery act internally to maintain mitochondrial proteostasis, the overall integrity of mitochondrial function requires cooperation and communication with other cellular compartments.

#### Mitochondrial–nuclear communication: mtUPR

Originally identified in mammalian cells (57), the mitochondrial unfolded protein response (mtUPR) has been established

as a prominent line of defense for mitochondrial proteotoxic stress in mammals, *Drosophila*, and *C. elegans* (57–60) (Fig. 3A). In a pathway named after the unfolded protein response of the endoplasmic reticulum (ER–UPR) (61), the mtUPR senses proteotoxic stress within mitochondria and enacts a gene expression program to recover organellar proteostasis. Like the ER–UPR, the mtUPR up-regulates target genes that include organelle-specific chaperones and proteases. An additional goal of the mtUPR is to alleviate the demands on stressed mitochondria by shifting metabolism away from mitochondrial-dependent OXPHOS and toward cytoplasmic glycolysis (62).

Activation of the mtUPR arises from a wide range of proteotoxic stresses, including blocking mitochondrial translation (60), depletion of mtDNA (63, 64), targeted impairment of mitochondrial chaperones or proteases (65, 66), excessive ROS (67), ETC impairment (58), or expression of a misfolded protein (57). It is unclear how misfolded or damaged proteins are recognized by mtUPR machinery. One possibility is through the oligopeptides generated by the protease ClpP (66) after degrading compromised proteins. However, many of the stresses that induce the mtUPR converge on decreased mitochondrial protein import. To this end, work in *C. elegans*, where the mtUPR is best-studied, showed that the transcription factor ATFS-1, a primary activator of the mtUPR (68), is highly sensitive to

mitochondrial import efficiency. As a primary activator of the mtUPR, ATFS-1 is uniquely suited to communicate mitochondrial stress to the nucleus as it contains both mitochondrial and nuclear localization sequences that are differentially utilized under basal and stressed conditions. Under basal conditions when mitochondrial membrane potential is high and protein import is robust, the N-terminal mitochondrial targeting sequence routes the nascent ATFS-1 protein to the mitochondrial import machinery. Immediately following import, it is rapidly degraded to undetectable levels by LonP (Fig. 3A, *No stress*) (68). However, during mitochondrial stress, protein import is compromised; this causes the ATFS-1 protein to accumulate in the cytoplasm, allowing its C-terminal nuclear localization sequence to access the nuclear import machinery (Fig. 3A, *High stress*). Once in the nucleus, ATFS-1 activates the transcription of genes to restore mitochondrial health such as chaperones, protein import machinery, ROS detoxification genes, as well as innate immunity and glycolysis factors to improve mitochondrial and cellular health (62). Consistent with ATFS-1 transcription factor activity being sensitive to import efficiency, a direct block in protein import, thereby limiting ATFS-1 import into mitochondria, leads to activation of the mtUPR (68).

Beyond ATFS-1, evidence suggests that additional methods for mtUPR activation also occur: of the 700 transcripts found to be induced during mitochondrial stress, only ~400 required *atfs-1* for induction (68). This additional regulation may come, in part, from the histone demethylases JMJD-1.2 and JMJD-3.1, which facilitate access to mtUPR response gene promoters (69), as well as the transcription factor DVE-1 and its ubiquitin-like cofactor UBL-5 (Fig. 3) (66, 70). The joint action of DVE-1 and UBL-5 is additionally driven by H3K9 dimethylation by MET-2 and its cofactor LIN-65 to up-regulate the mtHsp70 and Hsp60 chaperones upon mitochondrial stress (71). These chromatin factors promote nuclear localization of DVE-1 and enact the epigenetic changes required for mitochondrial stress signaling (71). How independent the ATFS-1 and DVE-1/LIN-65/MET-2 branches of mtUPR activation are is not fully known.

Although best-studied in *C. elegans*, the mtUPR was first discovered in mammalian cells (57) and remains an active area of investigation. Notably, a mammalian ortholog of ATFS-1, ATF5, has been shown to regulate the mtUPR in mammalian cells and to up-regulate transcription of mammalian orthologs of many *C. elegans* quality control genes in response to mitochondrial stress (72). Although such evolutionary conservation of function is noteworthy, it is clear that the mammalian mtUPR involves additional factors, such as the transcription factors CHOP and CEBPB (*C/EBPβ*), which have binding sites in many mtUPR-responsive genes (57, 73), including *ATF5* itself (74). Furthermore, recent evidence has suggested that the mtUPR works closely alongside the integrated stress response in responding to mitochondrial stress, and that this may be a prominent mechanism for responding to stress in mammalian systems (75, 76). Finally, although the majority of mtUPR-described mechanisms focuses on proteotoxic stress in the mitochondrial matrix, an unfolded protein response specific to the IMS in human cells has also been reported (77).

An important aspect of the mtUPR is its close relationship to aging and organismal health. In *C. elegans*, *Drosophila*, and mice, mitochondrial stresses that activate the mtUPR can extend life span and improve health (58, 60, 69, 78, 79). For example, disrupted balance of expression from the mitochondrial and nuclear genomes, via altered expression of a mitochondrial ribosomal subunit, strongly correlates with increased longevity in mice (60). Furthermore, higher expression of *jmjd-1.2/Phf8* or *jmjd-3.1/Jmjd3* correlates with life span extension in both *C. elegans* and mice (69). In *Drosophila*, knockdown of ETC components to activate mtUPR promotes expression of genes regulated by the FoxO transcription factor to extend life span (78). In a recent study, knockout of *Clpp* in mice led to a compensatory mitochondrial stress response that increased insulin sensitivity and protected mice from diet-induced obesity (79). Finally, a recent study points to the mammalian mtUPR as a component of hematopoietic stem cell regeneration (80). There can, however, be a fitness compromise associated with this mtUPR-mediated extended life span. *C. elegans* animals often become developmentally delayed or less reproductively fit upon mtUPR activation (81, 82). In addition, ectopic activation of the mtUPR in dopaminergic neurons can cause cell death (83), suggesting that chronic activation of the mtUPR may be detrimental to cell survival. Rather than be interpreted as a longevity panacea, mtUPR-mediated effects for promoting health span may be context-dependent, highlighting the need for further investigation.

#### **Mitophagy: removal of proteotoxic damage in bulk**

During stresses such as accumulation of misfolded proteins or loss of membrane potential, the mtUPR up-regulates a host of mitochondrial proteases that degrade aberrant proteins. However, when these stresses induce too much damage within an individual mitochondrion, the entire organelle can be degraded in a process known as mitophagy (mitochondrial-specific autophagy) (Fig. 3B). Although healthy mitochondria rapidly re-fuse back into the network following fission (84, 85), unhealthy mitochondria are poor at fusion, remain separated from the network, and are recognized by the mitophagy machinery. This segregation and pruning approach allows mitochondria harboring mutant mtDNA or with a critically high burden of misfolded proteins to be degraded, thereby facilitating the recovery of the rest of the network. Many stresses that activate the mtUPR also activate mitophagy, leading to the idea that the mtUPR and mitophagy are complementary: the mtUPR may act as a first line of defense to combat insults to mitochondrial proteostasis, whereas mitophagy acts to remove the unsalvageable mitochondria (86).

The precise mechanisms by which the mitophagy machinery recognizes defective mitochondria remain incompletely understood, but they are generally thought to target mitochondria with reduced membrane potential (85), increased ROS (87), blocked mitochondrial protein import (88), or excess misfolded proteins (89). Although the exact molecular players differ between yeast and mammalian systems, general principles of mitophagy involve recognition of a damaged mitochondrion, subsequent engulfment by the autophagosomal membrane, and shuttling to the lysosome, or vacuole in yeast, for degradation.

In yeast, where mitophagy mechanisms have been best studied, autophagosome components Atg11 and Atg8 recognize the outer membrane mitochondrial protein Atg32 (90, 91). In mammalian systems, mitophagy mechanisms are more complex, involving at least two distinct pathways (Fig. 3B). Much of what is known about mitophagy in mammals focuses on BNIP3L (NIX)-driven mechanisms, in which the outer membrane protein NIX binds to the autophagosomal protein MAP1LC3A (LC3) to initiate mitophagy (92–94). Interestingly, NIX is also up-regulated during hypoxia (95), suggesting that NIX is broadly involved in restoring mitochondrial proteostasis through mitophagy during stress. An additional mechanism of mitophagy in mammalian cells is the PINK1/PRKN (Parkin) pathway. PINK1 and Parkin have gained special attention from the discovery that mutations in both proteins result in autosomal-recessive forms of PD (Table 1) (96). Similar to ATFS-1, PINK1 recognition of defective mitochondria is also regulated by mitochondrial protein import. In the absence of stress, PINK1 is imported and constitutively degraded; this occurs either by protease degradation in the mitochondrial matrix (97, 98) or by cleavage by the IMS-localized protease PARL followed by translocation to the cytoplasm and N-end rule pathway degradation by the proteasome (Fig. 3B, *No stress*) (99, 100). During stress, mitochondrial import efficiency decreases, and PINK1 accumulates on the mitochondrial surface (Fig. 3B, *High stress*) (101). This PINK1 accumulation recruits the E3 ubiquitin ligase Parkin to the mitochondrial surface, where it polyubiquitinates outer membrane proteins (102–104). It has been proposed that the autophagosome recognizes ubiquitylated mitochondria through the ubiquitin-binding protein SQSTM1 (p62), as it has been observed to accumulate on mitochondria and bind LC3 (105), but the exact mechanism of autophagic recognition remains unclear (103, 106).

NIX and PINK1/Parkin homologs have also been found to regulate mitophagy in *C. elegans* (107). Importantly, they have been shown to interface with other genetic pathways such as SKN-1, the transcription factor that regulates mitochondrial biogenesis, and the DAF-16 insulin/IGF-1 pathway to regulate aging (107). In mice, a PINK1 knockout exhibits impaired mitochondrial respiration and synaptic plasticity (108). Overall, mitophagy is an essential pathway that eliminates defective organelle activated under high levels of mitochondrial proteostatic stress to promote steady-state mitochondrial integrity and healthy aging.

#### **Asymmetric cell division: controlling mitochondrial inheritance**

Mitochondrial fission followed by mitophagy eliminates the damaged fraction of the mitochondrial network. However, another opportunity to eliminate damaged mitochondria occurs during the process of cell division. Typically, during mitosis, cytoskeletal components strategically organize mitochondria to equally split the mitochondrial network between the two daughter cells (109, 110). However, individual mitochondria can be actively segregated to either the mother or the daughter cell based on their quality. This active parsing of mitochondria has been demonstrated in systems as diverse as budding yeast and human mammary stem cells (111, 112) with

substantial impacts on the health and life span of the daughter cells. In budding yeast, the healthiest mitochondria are passed to the daughter cell to promote longer replicative life span (111, 113, 114). The underlying mechanism involves mitochondrial interactions with the actin cytoskeleton (115) and mitochondrial fusion: only mitochondria that undergo fusion at the bud tip are retained and passed on to the daughter cell (116). In higher eukaryotes, segregation of healthy from unhealthy compartments is critical to maintain cellular and tissue homeostasis (117, 118). A recent study demonstrated that mammalian epithelial stem-like cells divide asymmetrically to retain the newest mitochondria and pass older mitochondria on to the differentiating daughter cell (112). Interestingly, only the mitochondria, and not other subcellular components such as the lysosome, ribosome, or Golgi apparatus, were asymmetrically apportioned, suggesting there is a crucial aspect of mitochondrial homeostasis required for stem cell maintenance.

#### **Inter-organellar proteostasis**

Mitophagy evolved as a mechanism to degrade an entire mitochondrion, but smaller-scale degradation mechanisms that transport damaged mitochondrial components for processing elsewhere in the cell are an emerging area of investigation. Two prominent mechanisms that have recently been described are mitochondria-derived vesicles (MDVs) and compartments (MDCs), which transport protein- and other metabolite-containing vesicular bodies to other organelles in the cell. MDVs have been reported to transport specific mitochondrial cargo to the peroxisome (119) as well as oxidized mitochondrial proteins for degradation in the lysosome (120). Although the formation and lysosomal targeting of these vesicles seem to be independent of mitochondrial fission and canonical mitophagy mechanisms, intracellular MDV trafficking relies on both Parkin and PINK1 and can be triggered by mitochondrial oxidative stress (120, 121). In yeast, a different vesicular body, the MDC, is involved in the direct removal of mitochondrial proteins for degradation in the vacuole (122). In contrast to MDVs in human cells, MDC release relies directly on the fission and autophagy machinery. Recent evidence for direct mitochondria–lysosome contacts in mammalian cells further highlights the importance of understanding this inter-organellar communication (123).

The role of these mitochondria-derived vesicular bodies in physiological contexts remains to be defined. However, growing evidence suggests that direct mitochondrial contacts with the endoplasmic reticulum (ER) impact human health: disturbance of these contact sites in the brain is observed in numerous neurodegenerative diseases (124, 125) and in primary human myotubes from patients with type 2 diabetes (126). These ER–mitochondria contact sites (also called mitochondria-associated ER membranes, or MAMs), have recently emerged as mediators of mitochondrial homeostasis. One of the primary roles of MAMs is coordinating  $\text{Ca}^{2+}$  signaling and lipid metabolism between the ER and mitochondria, which regulate OXPHOS and apoptosis (127–129). How MAMs as inter-organellar contact sites impact mitochondrial proteostatic health is an area of new investigation. ER–mitochondria contact sites are enriched for stress-induced cytoplasmic protein aggregates, which are later captured by mitochondria for degradation

(130). In addition, MAMs have been shown to directly control mitochondrial homeostasis by regulating mitochondrial fission sites and mtDNA replication (131, 132). The functional homology of ER–mitochondria contact sites from yeast to humans (129, 133) highlights the importance of mitochondrial communication in signaling and cellular homeostasis.

### **Proteostasis through mitochondrial–cytoplasmic communication**

A burgeoning area of research is in the coordination of proteostasis mechanisms among different cellular compartments. In one such mechanism discovered in *C. elegans*, termed mitochondrial-to-cytosolic stress response (MCSR), mitochondrial proteotoxic stress from pathogenic protein aggregates up-regulates not only the mtUPR but the cytosolic unfolded protein response as well, including heat-shock protein 1 (*hsp-1*) (Fig. 3C). This occurs via changes in lipid biosynthesis that act as the signal between the mitochondria and cytosol and serves to protect the cell as a whole from proteotoxic insults (134). Importantly, the MCSR was conserved in a cell culture model of Huntington's disease, suggesting a broad evolutionary need to coordinate intracellular stress-response pathways.

There may also exist mechanisms for coordinated protein degradation between mitochondrial and cytoplasmic compartments. The cytoplasmic proteasome has been implicated in extracting and degrading misfolded proteins from the mitochondrial outer membrane (135, 136). Additionally, it was proposed that cytosolic protein aggregates may be targeted to mitochondria for degradation by mitochondrial proteases (137). Although these mechanisms remain to be further explored, it is interesting to consider why the cell may route damaged proteins to different compartments of the cell and what the physiological consequences may be in aging.

### **Global effects of a local process: the whole-organism impact of mitochondrial proteostasis**

Aging is a phenotype visible to the naked eye but is intricately connected to mitochondrial dysfunction at the cellular and subcellular levels. Studies of mitochondrial proteostasis offer an interesting and clear example of this connection. A remarkable set of studies established that dysfunction in the ETC (81, 138–140) or induction of ROS (141) can lead to life span extension. Interestingly, there is only a small window during development in which this effect can occur (81), providing nuance to the long-standing hypothesis that the level of ROS generated over the lifetime of an organism directly correlates with its rate of aging (142). Rather, these newer findings suggest that during development, the organism senses energy-production capacity and permanently adjusts organismal physiology to ultimately impact life span. Connection between mitochondrial output and altered life span depends on two histone demethylases (69), suggesting that mitochondrial dysfunction in early development can alter the epigenomic landscape that regulates gene expression during adulthood.

These findings prompted the question of whether the entire organism or, rather, specific tissues are responsible for sensing mitochondrial health and orchestrating the downstream effects that impact life span. Remarkably, studies in *C. elegans* have shown

that mitochondrial dysfunction in neurons alone is sufficient to account for the life span extension (58). Furthermore, up-regulation of the mtUPR in one tissue (neurons) was sufficient to activate the mtUPR in another (the intestine). These data point to a cell-nonautonomous mechanism for communication among mitochondria in separate tissues and prompted the hypothesis that neuronal mitochondria communicate as master regulators with the rest of the organism via a currently unidentified molecule termed a “mitokine” (58). Studies in *C. elegans* have proposed that this mitokine may derive from secreted neuropeptides (143, 144).

In mice, two separate instances of trans-cellular mitochondrial communication by mitokine have been reported that appear to rely on a mechanism distinct from the one observed in *C. elegans*. Specifically, a block in mitophagy in muscle cells caused these cells to secrete an FGF21 mitokine into the serum (145). Follow-up in C2C12 cells showed that *FGF21* expression is induced as part of an ATF4-dependent integrated stress response, as the *FGF21* promoter contains ATF4-binding sites (120). Independently, a GDF15 mitokine was shown to be released from muscle cells upon perturbation of mitochondrial translation or mutation of *POLG*, and it was confirmed in a muscle cell culture model that *GDF15* is up-regulated in a CHOP-dependent but ATF4-independent manner (146). It was recently reported that patients with mtDNA mutations that cause mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) exhibit abnormally high levels of GDF15, which the authors suggest could be used as a biomarker for mitochondrial disease (147). At the organismal level, both of these muscle mitokines suppress sensitivity to insulin, highlighting the powerful impact of tissue-specific stress on the metabolic state of the entire organism. In a separate study, it was shown that mitochondrial dysfunction in *Drosophila*, when combined with mutation in Ras, leads to cell nonautonomous progression of tumor growth via the IL6 and WNT signaling pathways (148), suggesting that the mitochondria in the tumor microenvironment can impact severity of tumorigenesis.

Although the biochemical and physiological specifics of these three examples—from *C. elegans*, mice, and *Drosophila*—are distinct, they clearly demonstrate how mitochondria in a single tissue can communicate the state of their proteome across the organism. Thus, although the mitochondrion is not typically thought of as a major component of the endocrine system, these recent data prompt a new perspective of considering mitochondria in organismal signaling.

A separate cell-nonautonomous mechanism impacting mitochondrial proteostasis is the transfer of mitochondria between cells (149), suggesting that the mitochondrial proteostatic burden can be relieved through transfer or exchange of organelles between cells. For instance, it has been reported that healthy mitochondria can be sent through tunneling nanotubes from untreated PC12 cells to UV-irradiated cells to rescue these cells and avoid apoptosis (150). However, in a process termed trans-mitophagy, depolarized mitochondria can be extruded from optical ganglion cells at the optic nerve head and subsequently engulfed and degraded by surrounding astrocytes (151). It is an interesting notion that in diseases such as PD, in which mitophagy is an important regulator of disease progression, trans-mitophagy may also play a role.

## Concluding remarks

The phrase “the mitochondrion is the powerhouse of the cell” is both an educational truism and a misrepresentation of the sophistication of this organelle. In reality, the mitochondrion is not an isolated factory, tirelessly and reliably feeding energy to the rest of the cell. Instead, its function is tightly integrated with that of the rest of the cell, and a set of dedicated circuits has evolved to sense and resolve mitochondrial stress. Failure to do so, whether due to genetic or environmental insults, has profound effects on the entire organism.

At the foundation of robust cell function is a set of mechanisms for surveillance of mitochondrial proteomic integrity. These mechanisms face unique challenges because of the physical and genetic separation of the mitochondrion from the rest of the cell. As a consequence, not one but multiple mechanisms at different layers of biological complexity have evolved to regulate mitochondrial proteostasis. Initial control is imposed by intra-organelle machinery composed of a network of chaperones and proteases that fold and degrade mitochondrial proteins and complexes, as well as coordinated mitochondrial dynamics operating through fission and fusion.

Importantly, mitochondrial proteostasis is also maintained by factors beyond the organelle: coordination with other organelles is crucial in maintaining mitochondrial and cellular health. These recent discoveries point to a new perspective of mitochondria as not only a regulator of metabolism but also of cellular proteostasis. Genetic evidence connects dysfunction within every tier of mitochondrial proteostasis to aging and age-related disease, especially to those of the central nervous system. One challenge is to understand why such defects in mitochondrial proteostasis, which presumably occur systemically, can have such tissue-specific effects. Equally compelling is the emerging role for mitochondrial proteomic health in the progression of certain cancers (152, 153). In principle, these mitochondrial proteostasis pathways contain a wealth of drug-gable circuits. Given how integrated the mitochondrion is into overall cell and organismal function, an additional challenge is to understand how to selectively regulate mitochondrial function without unwanted cellular and organismal effects. Finally, recent evidence on the cell nonautonomous coordination of mitochondrial proteostasis suggests that assessing the role of mitochondrial dysfunction in aging requires an understanding of the mitochondrial signaling circuits that operate across different tissues. Implicit in this line of reasoning is the tantalizing notion that targeted control over mitochondrial proteostasis in one tissue may result in a systemic improvement in health.

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*Note added in proof*—While this manuscript was under review, Zhang *et al.* (156) reported that neuronal mitochondrial stress can be communicated via the canonical Wnt pathway to distal tissue.

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