frontiers in Aging Neuroscience

MINI REVIEW
published: 11 September 2020
doi: 10.3389/fnagi.2020.581849

The Mitochondrial Unfolded Protein Response: A Hinge Between Healthy and Pathological Aging

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Aging is the time-dependent functional decline that increases the vulnerability to different forms of stress, constituting the major risk factor for the development of neurodegenerative diseases. Dysfunctional mitochondria significantly contribute to aging phenotypes, accumulating particularly in post-mitotic cells, including neurons. To cope with deleterious effects, mitochondria feature different mechanisms for quality control. One such mechanism is the mitochondrial unfolded protein response (UPR^{MT}), which corresponds to the transcriptional activation of mitochondrial chaperones, proteases, and antioxidant enzymes to repair defective mitochondria. Transcription of target UPR^{MT} genes is epigenetically regulated by Histone 3-specific methylation. Age-dependency of this regulation could explain a differential UPR^{MT} activity in early developmental stages or aged organisms. At the same time, precise tuning of mitochondrial stress responses is crucial for maintaining neuronal homeostasis. However, compared to other mitochondrial and stress response programs, the role of UPR^{MT} in neurodegenerative disease is barely understood and studies in this topic are just emerging. In this review, we document the reported evidence characterizing the evolutionarily conserved regulation of the UPR^{MT} and summarize the recent advances in understanding the role of the pathway in neurodegenerative diseases and aging.

Keywords: mitochondrial unfolded protein response, neurodegenerative diseases, aging, mitochondria, epigenetic regulation, stress response

OPEN ACCESS

Edited by:
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Reviewed by:
Karen Schmitt, Central Institute of Mental Health (ZI), Germany
Merja Jaronen, University of Eastern Finland, Finland

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Received: *10 July 2020*
Accepted: *24 August 2020*
Published: *11 September 2020*

Citation:
Muñoz-Carvajal F and Sanhueza M (2020) The Mitochondrial Unfolded Protein Response: A Hinge Between Healthy and Pathological Aging. Front. Aging Neurosci. 12:581849. doi: 10.3389/fnagi.2020.581849

UPR^{MT} MACHINERY AND MITOCHONDRIAL HOMEOSTASIS REGULATION

Mitochondria are the main energy producers within the cell and the coordinators of several pathways that control essential metabolites, which include not only ATP and NAD^+, but also acetyl-CoA and S-adenosyl methionine for protein acetylation and methylation, respectively (Teperino et al., 2010; Menzies et al., 2016). Mitochondria are unique in that they have an independent genome (mtDNA), which encodes 2 rRNAs, 22 tRNAs, and 13 proteins that constitute the OXPHOS complexes (Wallace and Chalkia, 2013). Remaining mitochondrial proteins are encoded in the nucleus, so the function of the organelle heavily depends on the coordinated regulation of nuclear and mitochondrial genomes (Couvillion et al., 2016). Imbalances in protein expression in any of these two sources activate

an anterograde regulation of mitochondrial function (from the nucleus towards mitochondria) that adjusts its activity to match cellular needs (Cui et al., 2006; Kaarniranta et al., 2018). Mitochondria can also control the expression of nuclear genes through a retrograde regulatory mechanism (Lin and Haynes, 2016). This bidirectional communication between mitochondria and the nucleus forms a molecular network that maintains cellular homeostasis. Part of the network that synchronizes the cellular adaptation to a variety of stressors is termed the mitochondrial unfolded protein response (UPR^{MT}). Thus, UPR^{MT} is the transcriptional program that stabilizes mitochondrial homeostasis and reduces misfolded protein amount in the organelle, increasing the mitochondrial response capability to stress stimuli (reviewed in Jensen and Jasper, 2014; Shpilka and Haynes, 2018; Gomez and Germain, 2019; Tran and Van Aken, 2020). Known activators of UPR^{MT} include the impairment of the Electron Transport Chain (ETC), alteration of mitochondrial dynamics, accumulation of unfolded proteins, deletion of mitochondrial DNA (mtDNA), inhibition of mitochondrial chaperones or proteases, and the increase of reactive oxygen species (ROS) levels (Nargund et al., 2012; Pimenta de Castro et al., 2012; Runkel et al., 2013; Qureshi et al., 2017). Despite the mechanisms underlying the UPR^{MT} are less understood than endoplasmic reticulum UPR (Hetz et al., 2020), this mitochondrial stress pathway is emerging as an important response that guarantees the organelle function.

UPR^{MT} was originally observed in mammalian cells, where mitochondrial stress was induced by mtDNA deletions (Martinus et al., 1996) and by aggregation of mutant ornithine transcarboxylase (ΔOTC) (Zhao et al., 2002). Both stress stimuli upregulated the expression of mitochondrial chaperones Hsp60, Hsp10 under the control of the transcription factor CHOP (Zhao et al., 2002; Horibe and Hoogenraad, 2007). Three nuclear components were then identified in *C. elegans* as UPR^{MT} regulators: ATFS-1, DVE-1, and UBL-5. These proteins are part of the UPR^{MT}-ATF5 axis, an ATFS-1/ATF5 dependent response that is the most characterized UPR^{MT} pathway (**Table 1**, Kenny and Germain, 2017; Ji et al., 2020). ATFS-1, a leucine zipper protein, carries a nuclear localization sequence and a mitochondrial targeting sequence. Under mitochondrial stress, ATFS-1 normal transport towards mitochondria is blocked and translocates instead to the nucleus where it interacts with DVE-1 and UBL-5 (**Figure 1**; Nargund et al., 2012, 2015). In mammals, the CHOP target ATF5 was identified as the functional ortholog for ATFS-1, which also contains targeting sequences for mitochondria and nucleus and upregulates UPR^{MT} genes (Teske et al., 2013; Fiorese et al., 2016). On the other hand, DVE-1 is a DNA binding protein that together with its coregulator UBL-5, interacts with chromatin regions to maintain an ATFS-1-dependent active transcription of UPR^{MT}-related genes (Benedetti et al., 2006; Haynes et al., 2007; Tian et al., 2016). The coordinated action of these three proteins upregulates the expression of mitochondrial chaperones hsp-60, hsp-6, and protease clpp-1 (**Table 1**, Haynes and Ron, 2010).

Two other pathways have been associated with this stress response (**Figure 1**). The UPR^{MT}-ERα axis, a pathway dependent on the activation of the estrogen receptor α (ERα), was described as associated with the accumulation of proteins in the mitochondrial intermembrane space (Papa and Germain, 2011). Mitochondrial stress and ROS production trigger the phosphorylation of the protein kinase AKT and consequently, the activation of ERα. This cascade increases the transcription of protease HTRA2 and the mitochondrial biogenesis regulator NFR1, which translates in an increased proteasome activity independent of activation of the UPR^{MT}-ATF5 axis (**Table 1**, Papa and Germain, 2011). Finally, the UPR^{MT}-SIRT3 axis is based on the activation of Sirtuin 3 that modulates the expression of SOD1, SOD2, and catalase, through activation of FOXO (Papa and Germain, 2014; Kenny et al., 2017). The UPR^{MT}-SIRT3 axis has been validated also in worms and mammalian cells, supporting the high evolutionary conservation of the pathway (Mouchiroud et al., 2013). Importantly, both ERα- and SIRT3-UPR^{MT} axes work independently of CHOP (Papa and Germain, 2014), upholding the idea of three parallel paths coordinating the same stress response (**Figure 1**).

Chromatin remodeling has been shown to play a central role in UPR^{MT} regulation. Histone 3 is a target for methylation catalyzed specifically by methyltransferase MET-2 in *C. elegans* (ortholog of human SETDB1). Activation of UPR^{MT} requires the dimethylation of lysine 3 of histone 3 (H3K9), which translates into a compacted and overall silenced chromatin state. At the same time although, other chromatin portions remain loose, favoring the binding of UPR^{MT} regulators such as DVE-1 (Tian et al., 2016). Also required for UPR^{MT} activation are the conserved demethylases JMJD-3.1 and JMJD-1.2, which reduce the chromatin compaction by removing methylation from H3K9 and H3K27 (**Figure 1**; Merkwirth et al., 2016; Sobue et al., 2017). Interestingly, chromatin remodeling acts independently of ATFS-1, as its downregulation does not affect the nuclear localization of DVE-1 (Tian et al., 2016). It is known that besides genes encoding chaperones and proteases, UPR^{MT} activation increases the expression of glycolysis and amino acid catabolism genes, and represses TCA-cycle and OXPHOS encoding genes (Nargund et al., 2015; Gitschlag et al., 2016; Lin and Haynes, 2016). To date, it is not clear whether UPR^{MT} can activate any other quality control mechanism such as mitochondrial fission, fusion, and mitophagy. It has been reported, however, that the same mitochondrial stressors can activate mitophagy and UPR^{MT} (Nargund et al., 2012; Pimenta de Castro et al., 2012; Jin and Youle, 2013; Runkel et al., 2013; Lin et al., 2016). Organisms that have adapted after constant exposure to low doses of these stressors (misregulation of ETC components and low doses of the UPR^{MT} activator paraquat) exhibit a hormetic phenotype as they show increased longevity despite their mild mitochondrial dysfunction (Yoneda et al., 2004; Owusu-Ansah et al., 2013). This homeostatic regulation is particularly important in post-mitotic cells such as neurons.

THE ROLE AND REGULATION OF UPR^{MT} IN AGING

Aging is defined as the time-dependent functional decline that increases vulnerability to different forms of stress, ultimately

TABLE 1 | Mitochondrial UPR regulators and their function in conserved species.

Name	CE	DM	MM	HS	Function	References
UPR^{MT}-ATF5 axis						
Activating Transcription Factor 5	Atfs-1	crc	Atf5	ATF5	Transcription factor with basic leucine zipper domain. Carries an MTS in the N-term and an NLS in the C-term.	Yoneda et al. (2004), Nargund et al. (2012), Fiorese et al. (2016) and Wu et al. (2018)
Special AT-Rich Sequence-Binding Protein 2	dve	DVE	Satb2	SATB2	DNA binding protein. Stabilizes open chromatin for UPR^{MT}-associated transcription.	Haynes et al. (2007) and Tian et al. (2016)
Ubiquitin Like 5	UBL-5	ubl	Ubl5	UBL5	Protein binding. Binds DVE to activate transcription of Hsp60	Benedetti et al. (2006)
ATP Binding Cassette Subfamily B Member 10	haf-1	CG3156	ABCB10	ABCB10	Mitochondrial inner membrane transporter. Exports peptides from the matrix.	Haynes and Ron (2010) and Yano (2017)
Caseinolytic Mitochondrial Matrix Peptidase Proteolytic	clpp-1	ClpP	ClpP	CLPP	Mitochondrial ATP-dependent protease. Its attenuation reduces the UPR^{MT} activation and the formation of the UBL/DVE complex.	Haynes et al. (2007) and Al-Furoukh et al. (2015)
Translocase of Inner Mitochondrial Membrane 23	timm-23	Tim23	Timm23	TIMM23	Protein transmembrane transporter. Required for full induction of UPR^{MT} mediated by ATFS-1.	Rainbolt et al. (2013)
Lon Peptidase 1	, lonp-1	Lon	Lonp1	LONP1	Mitochondrial protease. Degrades ATFS-1 when imported to mitochondria under stress conditions.	Nargund et al. (2012)
Heat Shock Protein Family D (Hsp60) Member 1	hsp-60	Hsp60A Hsp60B Hsp60C	Hspd1	HSPD1	Mitochondrial heat-shock protease. Upregulated upon mitochondrial stress.	Zhao et al. (2002), Yoneda et al. (2004), Haynes et al. (2007) and Owusu-Ansah et al. (2013)
Heat Shock Protein Family A (Hsp70) Member 9	hsp-6	Hsc70–5	Hspa9	HSPA9	Mitochondrial heat-shock protease. More sensitive to oxidative stress than unfolded protein stress.	Yoneda et al. (2004), Benedetti et al. (2006) and Merkwirth et al. (2016)
UPR^{MT}- ERα axis						
Estrogen Receptor 1	nhr-107	ERR	Esr1	ESR1	Ligand-activated transcription factor. Regulates the expression of Htra2 and NRF1 after Akt phosphorylation.	Papa and Germain (2011) and Riar et al. (2017)
HtrA Serine Peptidase 2	psmd-9	HtrA2	HtrA2	HTRA2	Serine protease. Protein import checkpoint in IMS. Increased expression upon stress.	Papa and Germain (2011)
Nuclear respiratory factor 1	-	-	Nrf1	NRF1	Transcription factor.	Papa and Germain (2011)
UPR^{MT}- SIRT3 axis						
Sirtuin 3	Sir-2.1	Sirt2	Sirt3	SIRT3	NAD$^+$ dependent deacetylase. Regulates the activity of FOXO3 upon oxidative stress in the mitochondria.	Mouchiroud et al. (2013); Papa and Germain (2014); Gariani et al. (2016) and Kenny et al. (2017)
Forkhead box	daf-16	foxo	Foxo3	FOXO3	Transcription factor. Translocate to the nucleus to activate transcription of SOD1, SOD2, and Catalase.	Mouchiroud et al. (2013); Gariani et al. (2016) and Kenny et al. (2017)
Superoxide dismutase 1	sod-1	Sod	Sod1	SOD1	Superoxide dismutase. Soluble cytoplasmic isoenzyme.	Mouchiroud et al. (2013); Gariani et al. (2016) and Kenny et al. (2017)
Superoxide dismutase 2	sod-2	Sod2	Sod2	SOD2	Superoxide dismutase. Mitochondrial isoenzyme.	Mouchiroud et al. (2013); Gariani et al. (2016) and Kenny et al. (2017)

(Continued)

TABLE 1 | Continued

Name	CE	DM	MM	HS	Function	References
UPR^{MT} epigenetic regulators						
SET Domain Bifurcated Histone Lysine Methyltransferase 1	met-2	eggless	Setdb1	SETDB1	Histone methyltransferase. Loci protected by H3K9 contains genes upregulated upon mitochondrial stress.	Tian et al. (2016)
Abnormal cell lineage.65	lin-65	-	-	-	Nuclear co-factor. Highly unstructured protein involved in chromatin remodeling. Necessary for the incorporation of MET-2 to the nucleus.	Tian et al. (2016)
Euchromatic Histone Lysine Methyltransferase 1	SET-6	CG4565	Ehmt1	EHMT1	Histone methyltransferase. Upregulated during aging to inhibit UPR^{MT} activation.	Yuan et al. (2020)
Lysine Demethylase 6A	JMJD-3.1	Utx	Kdm6A	KDM6A	Histone demethylase. Positive regulator of lifespan upon mitochondrial stress. Needed to activate the UPR^{MT}	Merkwirth et al. (2016)
Bromodomain Adjacent to Zinc Finger Domain 2B	Baz-2	tou	Baz2b	BAZ2B	Transcription factor. Neuronal Epigenetic Reader upregulated during aging acting with SAT-6 to inhibit the UPR^{MT} during aging by regulating methylation of H3K9.	Yuan et al. (2020)

CE, Caenorhabditis elegans; DM, Drosophila melanogaster; MM, Mus musculus; HS, Homo sapiens; MTS, mitochondrial targeting sequencing; NLS, nuclear localization signal; IMS, mitochondrial intermembrane space.

leading to death (Kennedy et al., 2014). Aging has particularly severe consequences for organs composed mostly by post-mitotic cells, such as the heart and brain (Kowald and Kirkwood, 2000; Terman et al., 2010). For instance, aging is the major risk factor for the onset of chronic, brain-related, and neurodegenerative diseases (ND). Current studies in the field introduced critical questions aiming to understand the physiological sources of time-dependent damage, the compensatory cellular responses that reestablish homeostasis, and their interconnection to find potential targets to intervene and delay aging. Seven cellular pillars of aging have been described, including among others, alterations to proteostasis, epigenetics, metabolism, and adaptation to stress (Kennedy et al., 2014). Mitochondrial dysfunction is a common factor for these events, suggesting a role of mitochondrial reparative machinery in aging progression. Furthermore, it is accepted that aging in model organisms is functionally associated with mitochondrial decline, contributing to the time-dependent tissue malfunction (Chistiakov et al., 2014; Kim et al., 2018). Therefore, activation of UPR^{MT}, as one of the mitochondrial mechanisms against different forms of aging-causing damage, could be in part bridging the adaptation to stress and other pillars of aging as proteostasis and epigenetics.

Current evidence highlights an age-dependent effect of UPR^{MT} on lifespan. For instance, activation of UPR^{MT} triggered by downregulation of ETC complexes I and IV promotes longevity (Dillin et al., 2002; Durieux et al., 2011; Mouchiroud et al., 2013). Histone demethylases JMJD-1.2 and JMJD-3.1 mediate in part that extension, as their overexpression is sufficient to extend the lifespan of worms (Merkwirth et al., 2016). On the other hand, reducing the expression of nuclear effectors ATFS-1, UBL-5 and DVE-1, or demethylases JMJD-1.2 and JMJD-3.1, suppresses the lifespan extension (**Table 1**, Durieux et al., 2011; Houtkooper et al., 2013; Merkwirth et al., 2016; Lan et al., 2019). It is interesting that UPR^{MT} activation after exposure to mitochondrial stress is strongly responsive only during development and not in later stages of the lifespan (Dillin et al., 2002; Copeland et al., 2009; Durieux et al., 2011; Houtkooper et al., 2013). UPR^{MT} appears less active in adult organisms, so there is no increased lifespan as a response to mitochondrial stressors, as observed in developmental stages in worms and flies (Dillin et al., 2002; Owusu-Ansah et al., 2013; Jensen et al., 2017).

Decreased chromatin accessibility of target UPR^{MT} genes in aged organisms is a potential explanation for the differential UPR^{MT} activation. This was recently confirmed in a study where the methyltransferase SET-6 and the neuronal epigenetic reader BAZ-2, mediated specifically an age-dependent regulation of UPR^{MT}. Both proteins when overexpressed in aged worms increased the levels of H3K9Me3, the triple methylated state of the protein, thus inhibiting UPR^{MT} activation in the H3K9-protected loci (**Figure 1**). Loss of function of SET-6 or BAZ-2 increased healthspan but not longevity, a phenotype that was inhibited downregulating UBL-5 or ATFS-1 (Yuan et al., 2020). Histone 3 methylation appears then as a key epigenetic mediator for UPR^{MT} throughout the lifespan (Merkwirth et al., 2016; Tian et al., 2016; Ono et al., 2017). Longitudinal studies have proved that H3K9Me3 increases during aging in mice

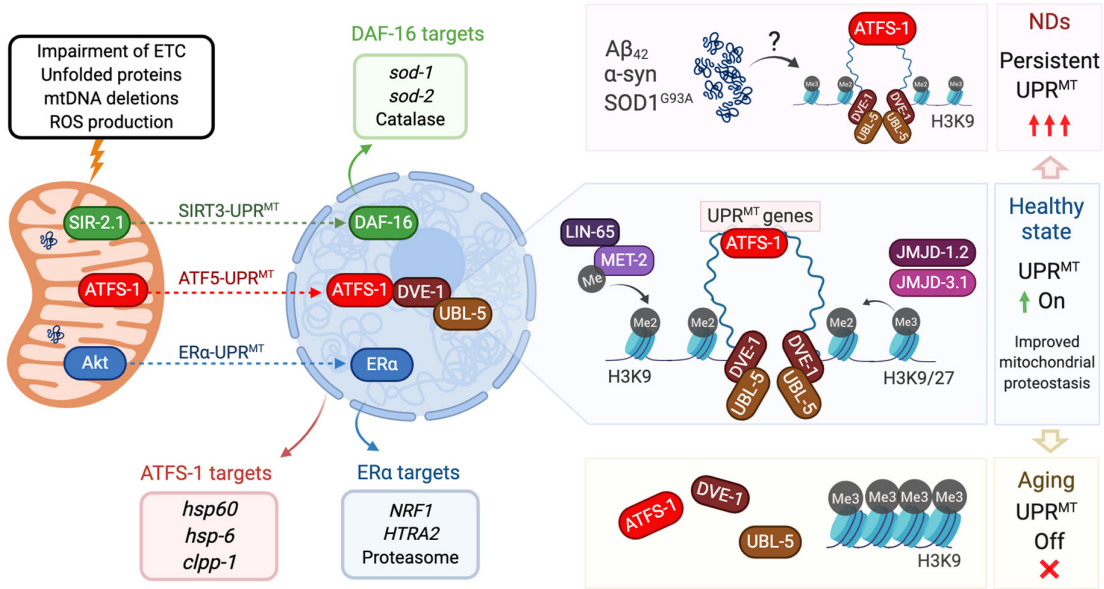

FIGURE 1 | Mitochondrial unfolded protein response (UPR) and its regulation in aging and neurodegeneration. Insults to mitochondria (top left) activate three different axes of the UPR^{MT} program. The SIRT3-UPR^{MT} axis (green arrow) increases the transcription of superoxide dismutases and catalase, after the activation of DAF-16/FOXO3 by the deacetylase SIR-2.1/SIRT3. In the ATF5-UPR^{MT} axis (red arrow), the transcription factor ATFS-1/ATF5 relocalizes from mitochondria to nucleus to upregulate mitochondrial proteostasis related genes (red box) after the interaction with the chromatin stabilizers DVE-1 and UBL-5. In the ERα-UPR^{MT} axis (blue arrow) the estrogen receptor is activated by the kinase Akt, to increase the expression of the protease HTRA2 and mitochondrial biogenesis regulator NRF1. On a healthy state (center right), ATF5-UPR^{MT} activation requires chromatin reorganization. Dimethylation of Histone 3 by MET-2, and presence of demethylases JMJD-1.2 and JMJD-3.1, allow the binding of DVE to facilitate the ATFS-1-dependent expression of UPR^{MT} genes and improve mitochondrial proteostasis. In neurodegenerative states triggered by accumulation of Aβ$_{42}$ (AD), α-syn (PD) or SOD1^{G93A} (ALS, top right), UPR^{MT} could be persistently activated, affecting mitochondria proteostasis and neuron viability. In aging cells (bottom right), Histone 3 is preferentially trimethylated, which blocks DVE and ATFS-1 biding to compacted DNA. Lack of expression of UPR^{MT}-related genes decreases mitochondrial response to aging-causing damage. All protein names are taken from *C. elegans*, except the ones from the ERα axis, which has only been described in mammalian cells.

hippocampus, and inhibition of this methylation state was sufficient to block aging-associated cognitive decline in mice (Snigdha et al., 2016). Advanced knowledge of the loci carrying UPR^{MT} genes on them, will contribute to further understand the lack of UPR^{MT} activation during aging.

UPR^{MT} IN AGING NEURONS AND NEURODEGENERATIVE DISEASES

Several factors influence mitochondrial homeostasis in neurons during aging, such as oxidative damage, neuronal localization, and quality control mechanisms. Compared to mitotic cells, neurons are more sensitive to the accumulation of oxidative damage and defective mitochondria (Kowald and Kirkwood, 2000; Terman et al., 2010). Neuronal unique shape, on the other hand, generates a differential mitochondrial distribution required to provide energy at specific compartments (Obashi and Okabe, 2013). Indeed, evidence shows that at nerve terminals, mitochondria are more prone to age-related dysfunction and oxidative damage compared to non-synaptic mitochondria (Lores-Arnaiz et al., 2016; Olesen et al., 2020). Importantly, aging aggravates the difference between these two populations of mitochondria (Borrás et al., 2010; Lores-Arnaiz et al., 2016). The decreased ability of neurons to renew their pool of healthy mitochondria and the lower activity of quality control mechanisms, act synergistically to trigger deleterious consequences in neurons not only in aging but also at earlier stages. In the etiology of the most prevalent ND, shared critical mitochondrial stressors include misfolded and aggregated proteins, impaired mitophagy, and oxidative stress (Niedzielska et al., 2016; Bakula and Scheibye-Knudsen, 2020; Weidling and Swerdlow, 2020). Considering also the number of ND-causative genes associated with mitochondrial dysfunction (Masters et al., 2015; Hardiman et al., 2017; Poewe et al., 2017), quality control mechanisms such as UPR^{MT} emerge as key intervention targets for age-related diseases. However, compared to other mitochondrial response programs (Pellegrino and Haynes, 2015; Pernas and Scorrano, 2016; Misgeld and Schwarz, 2017) or even UPR^{ER} (Hetz et al., 2020), the studies linking UPR^{MT} and NDs are just emerging.

Parkinson's disease (PD) is caused by decreased dopamine secretion from damaged dopaminergic neurons (reviewed in Poewe et al., 2017). PD pathomechanism is strongly connected to mitochondrial dysfunction and only recently to UPR^{MT} (Franco-Iborra et al., 2018; Chen et al., 2019). Two proteins encoded by PD-causative genes, serine-threonine kinase PINK1 and E3 ubiquitin ligase Parkin, work together to unclutter dysfunctional mitochondria through mitophagy. PINK1 or

Parkin downregulation induces decreased mitochondrial respiration and ATP synthesis, degeneration of dopaminergic neurons, and reduced lifespan (Zhu et al., 2013; Moisoi et al., 2014; Tufi et al., 2014; Choi et al., 2015). In *C. elegans*, the downregulation of their orthologs (*pink-1* and *pdr-1*) activates UPR^{MT} as a mitigation mechanism. Without atfs-1 dependent UPR^{MT} activation, lifespan decreases, and dopamine neurons degenerate (Cooper et al., 2017).

PINK1 also interacts with the ERα target HTRA2, mediating its phosphorylation and activation (Plun-Favreau et al., 2007). Interestingly, mutant alleles of HTRA2 were found in PD patients (Strauss et al., 2005; Unal Gulsuner et al., 2014).

PD pathogenesis is strongly connected to the accumulation of α-synuclein (Poewe et al., 2017). αSyn^{A53T} preferentially accumulates in the mitochondria and interacts with the UPR^{MT}-regulator ClpP, suppressing its peptidase activity. Overexpression of the protease is sufficient to decrease αSyn^{A53T}-associated pathology in mice (Hu et al., 2019). Despite the previous evidence, reports are suggesting a toxic role of UPR^{MT} over-activation. Expression in dopaminergic neurons of an active form of ATFS-1 lacking the mitochondrial target sequence mimics stress conditions with a constant nuclear expression of UPR^{MT} targets. Over-activation of UPR^{MT} shortens lifespan and promotes faulty mitochondria accumulation, a phenotype synergistically increased overexpressing mutant αSyn^{A53T} (Martinez et al., 2017). From the epigenetic point of view, α-synuclein expression in *Drosophila* led to an upregulation of the methyltransferase EHMT2, with an overall H3K9 dimethylation effect (Sugeno et al., 2016). It would be interesting to study whether chromatin remodeling linked to the H3K9Me2 epigenetic mark in this PD model modifies UPR^{MT} activation as previously reported (Merkwirth et al., 2016; Tian et al., 2016).

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease and its complex etiology is explained by the almost 30 causative genes that have been linked to familial cases (reviewed in Hardiman et al., 2017). Among these genes, mutations in the superoxide dismutase SOD1 initially unveiled a link between ALS and mitochondrial dysfunction (Rosen et al., 1993). Post-mortem samples of ALS patients show the altered activity of ETC complexes (Bowling et al., 1993), while SOD1 overexpression in transgenic mice causes dysregulated ETC activity, increased ROS production, and diminished mitochondrial Ca^{2+}-buffering (Mattiazzi et al., 2002; Brookes et al., 2004). Mutant SOD1^{G93A} localizes in the mitochondrial intermembrane space, which is sufficient to activate two axes of UPR^{MT} *in vivo* (Gomez and Germain, 2019). CHOP is transiently activated in mice's spinal cord, followed by Akt-dependent phosphorylation of ERα that upregulates NRF1 and proteasome activity (Riar et al., 2017; Gomez and Germain, 2019). This is consistent with recent reports showing that UPR^{MT} activation precedes the onset of ALS and its activity increases throughout disease progression (Pharaoh et al., 2019). Dysregulation of TDP-43, another ALS causative gene, impairs mitochondria in ALS patients, suppresses ETC complex I and activates UPR^{MT} in cellular and animal models. Downregulation of the UPR^{MT} protease LonP1 increased TDP-43 levels, mitochondrial damage and neurodegeneration (Wang et al., 2019). A third ALS-linked mitochondrial protein is CHCHD10, which has an unknown function but its mutant aggregates in mitochondria causing proteotoxic stress, mitochondrial dysfunction and upregulation of the UPR^{MT} regulators CHOP and ATF5 (Anderson et al., 2019). These reports suggest that the accumulation of ALS-associated mutant proteins in mitochondria persistently over activates UPR^{MT}, which could be triggering detrimental effects on already stressed neurons (**Figure 1**).

Alzheimer's disease (AD) is characterized by key neuropathological hallmarks such as the abnormal accumulation of the amyloid-β (Aβ) peptide (reviewed in Masters et al., 2015). Evidence indicates that oxidative damage and mitochondrial dysfunction have a key role in AD pathogenesis (Butterfield and Halliwell, 2019; Weidling and Swerdlow, 2020), but the relationship between UPR^{MT} and AD has only been recently explored. Aβ accumulation activates UPR^{MT} in human cells and mice (Shen et al., 2020). In *C. elegans*, the sirtuin-activator resveratrol reduced the Aβ-induced toxicity on a Ubl-5 dependent manner, decreasing the amount of Aβ aggregates (Regitz et al., 2016). Further characterization of this finding could provide clues of a potential connection between the two UPR^{MT} axes, and their association to AD. On the other hand, deficiency of the mitochondrial protease PITRM1 induces UPR^{MT}, increased Aβ accumulation, and triggered AD-like phenotypes. These were exacerbated by pharmacological inhibition of UPR^{MT} suggesting a protective role of the pathway on Aβ-associated toxicity (Pérez et al., 2020). The expression of UPR^{MT}-related genes appear highly increased in post mortem samples of the prefrontal cortex of AD patients (Beck et al., 2016). It would be noteworthy to determine the temporality of this increased expression to understand whether it is an early program persistently activated throughout the disease progression, or a late response triggered by an overall mitochondrial dysfunction. This is especially relevant considering that the expression of the epigenetic regulators of UPR^{MT} EHMT1 and BAZ2B, and therefore inhibition of UPR^{MT}, correlates positively with the progression of AD (Zhang et al., 2013; Yuan et al., 2020). Therefore, future studies should try to clarify whether both inhibition and persistent activation of UPR^{MT} contribute to ND pathomechanisms.

FUTURE PERSPECTIVES

Mitochondrial dysfunction is a hallmark of aging and age-related neurodegenerative diseases (Kennedy et al., 2014). As UPR^{MT} activation extends mitochondrial function, further characterization of the pathway will provide stronger hints to understand neuronal homeostasis and healthspan extension. So far, it seems that UPR^{MT} activation is partially modulated by the age-dependent methylation levels of Histone 3. As H3K9 is differentially methylated in specific brain regions (Snigdha et al., 2016), regulation of the UPR^{MT} could differ in distinct neuronal types. This fact raises concerns when thinking about therapeutic approaches since systemic inhibition of UPR^{MT}

could be beneficial for cell types with a dysregulated activation of UPR^{MT}, but detrimental for another that requires its activation. Therefore, the fine-tuning of UPR^{MT} in different pathogenic contexts will be a crucial consideration for future studies. In the case of PD, AD and ALS, incipient evidence has emerged in the last years highlighting also an over-activation of UPR^{MT} as contributors of the ND pathomechanisms. Future studies on this topic should focus on determining whether known ND causative genes are associated to UPR^{MT} components on an early neurodegenerative stage, or whether UPR^{MT} is only activated on a late, non-reversible stage as a consequence of an overall neuronal decay. Precise pharmacological modulation of the mitochondrial stress response could bring new alternatives to restore compromised neuronal functions, with a prospective increase in the life quality of ND patients and the elderly population.

AUTHOR CONTRIBUTIONS

FM-C and MS planned, researched, and wrote the manuscript.

FUNDING

This work was supported by Comisión Nacional de Investigación Científica y Tecnológica (CONICYT) Subvención a la instalación a la academia (PAI77180059—MS) and Center for Integrative Biology, Universidad Mayor (FM-C).

ACKNOWLEDGMENTS

We want to thank Dr. Natalia Salvadores and Dr. Felipe Court for their feedback and comments.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.