mtUPR in Primary and Secondary Mitochondrial Diseases

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Mitochondrial dysfunction is a key pathological event in many diseases. Its role in energy production, calcium homeostasis, apoptosis regulation, and reactive oxygen species (ROS) balance render mitochondria essential for cell survival and fitness. However, there are no effective treatments for most primary and secondary mitochondrial diseases to this day. Therefore, new therapeutic approaches, such as the modulation of the mitochondrial unfolded protein response (mtUPR), are being explored. mtUPRs englobe several compensatory processes related to proteostasis and antioxidant system mechanisms. mtUPR activation, through an overcompensation for mild intracellular stress, promotes cell homeostasis and improves lifespan and disease alterations in biological models of mitochondrial dysfunction in age-related diseases, cardiopathies, metabolic disorders, and primary mitochondrial diseases. Although mtUPR activation is a promising therapeutic option for many pathological conditions, its activation could promote tumor progression in cancer patients, and its overactivation could lead to non-desired side effects, such as the increased heteroplasmy of mitochondrial DNA mutations. Researchers present the most recent data about mtUPR modulation as a therapeutic approach, its role in diseases, and its potential negative consequences in specific pathological situations.

mitochondria proteostasis mitochondrial unfolded protein response mitochondrial biogenesis

1. mtUPR and Aging

The decline in mitochondrial function is known to be a characteristic factor of aging, which is associated with the accumulation of mutations in mtDNA as well as with reductions in mtETC and ATP production [1]. This age-related mitochondrial dysfunction may be responsible for the loss of muscle and neuronal function; however, numerous studies have suggested that moderate mitochondrial stress associated with mtUPR activation could delay aging and lead to increased longevity in several biological models. Because aging cells generally accumulate a large amount of unfolded and damaged proteins, it is plausible that the mtUPR is intimately related to aging and age-related diseases [2].

Specifically, in *C. elegans*, it was observed that silencing the complex IV of the mtETC using RNA interference (RNAi) activates the mtUPR and extends its lifespan by approximately 50% [3]. Moreover, the mutation of *ATFS-1* in *C. elegans* shortened the lifespan [4]. The modulation of NAD+ cofactor levels in worms was also shown to

activate the mtUPR and extend the lifespan via the activation of *sir2.1*, the homolog of mammalian *SIRT1*, and *daf-16*, the homolog of *FOXO3A* [5]. In mice, damage to mitochondrial ribosomes genetically or pharmacologically and, consequently, the activation of the mtUPR also promoted longevity [6]. Wang et al. [7] suggested that mtUPR activation by itaconate increased healthy longevity in *C. elegans,* improving resistance to different types of stresses and worm motility. Likewise, cultured fibroblasts from the Snell dwarf model showed increased expression levels of Hsp60 and LonP1 [8]. Another example is a study in flies where the disruption of mitochondrial functions and the activation of the mtUPR promoted longevity [9].

On the other hand, it was proposed that the mtUPR has a protective role against osteoarthritis (OA). OA is an age-related disease whose prevalence is increasing worldwide, and, unfortunately, there is no effective treatment for it. Mitochondria play a key role in the pathogenesis of this disease since they are crucial for chondrocyte bioenergetics [10]. Zhou et al. [11] showed that the activation of the mtUPR with nicotinamide-protected mitochondria in an OA mouse model stressed chondrocytes as they presented correct structures, such as well-preserved cristae and double membranes, and mitochondrial respiration was restored and mitochondrial membrane potential also improved. In addition, they demonstrated that mtUPR activation alleviates OA pain because it reduces cartilage degeneration and improves chondrocyte survival. Moreover, cartilage tissue from OA patients showed mtUPR activation, which was associated with lower levels of inflammation or reduced chondrocyte death.

Therefore, there is sufficient evidence that the activation of the mtUPR could be beneficial in slowing aging and extending lifespans in different model organisms, as well as in the treatment of age-related diseases, such as osteoarthritis, although further studies are necessary.

2. mtUPR and Neurodegenerative Diseases

Given the relationship between aging and the mtUPR, the latter was proposed as a therapeutic option in the treatment of neurodegenerative diseases. Neurodegenerative diseases are characterized by the progressive loss of structures and functions of the nervous system, and a common feature of all of them is the appearance of unfolded proteins and their accumulation in different regions of the brain, depending on the pathology [12]. Furthermore, it was described that mitochondrial dysfunction occurs in neurodegenerative diseases [13]. In fact, it was shown that neurodegenerative disorders are associated with a reduction in the activity of mitochondrial respiratory complexes. In Parkinson's disease and Alzheimer's disease, a reduction in the activity of complex I and complex IV was observed, respectively [14]. Furthermore, in Huntington's disease, the decreased activity of complexes II and III were described [15]. Likewise, the reduction in the activity of α-ketoglutarate dehydrogenase was described in Alzheimer's and Parkinson's diseases [16]. Moreover, the pathogenesis of several neurodegenerative diseases was associated with an impaired balance between the mitochondrial fusion and fission processes which promote mitochondrial fragmentation as well as the downregulation of mitochondrial renewal by mitophagy [17]. Therefore, researchers could consider neurodegenerative diseases as secondary mitochondrial diseases since many lines of evidence suggest that mitochondrial dysfunctions play a key role in their pathomechanisms.

Recent studies suggested that the mtUPR is activated in the neurons of Alzheimer's disease (AD) patients. In fact, disturbances in the mitochondria, such as decreased mitochondrial respiration, aberrant mitochondrial morphology, or decreased import systems, are known alterations in AD. In the study by Sorrentino et al. [18], they observed that genes related to the mtUPR were upregulated in Alzheimer's disease, which may be related to a protective response during disease progression. Indeed, ATFS-1 depletion in a *C. elegans* Alzheimer's model led to a worsening of the disease signs. Furthermore, treatment with doxycycline for the activation of the mtUPR resulted in an increased clearance of Aβ aggregates and increased worm motility [18]. On the other hand, Perez et al. [19] obtained neurons from induced pluripotent stem cells knocked out with the *PITRM1* gene, which codes for pitrilysin metallopeptidase 1. A mutation in this protein generated an age-dependent progressive neurological syndrome, as this protein in humans is involved in the degradation of amyloid-β peptides, leading to an Alzheimer's disease phenotype. Neurons mutant for *PITRM1* induced mtUPR genes that could act as a protective mechanism for Alzheimer's disease, as the inhibition of this pathway with ISRIB, an inhibitor of the eif2α kinase, resulted in an increase in Aβ accumulation. Furthermore, treatment of these cells with NAD+ to activate SIRT3 mtUPR enhanced mitochondrial recovery and significantly decreased Aβ and phospho-tau aggregates. Otherwise, treatment with NAD+ or olaparib, an inhibitor of the PARP enzyme, decreased amyloid formation, mitochondrial dysfunction, and aging features in several models [20]. However, Counts et al. [21] suggested that the constitutive activation of the mtUPR could lead to neuronal cell death during the early stages of Alzheimer's disease. Likewise, Martínez et al. [22] demonstrated that the sustained induction of the mtUPR by introducing an ATFS-1 transcript with no mitochondrial localization signal in a *C. elegans* Parkinson's disease (PD) model resulted in the death of dopaminergic neurons in a non-caspase-mediated way. This result could be due to the hormetic role of the mtUPR, which could be beneficial in a specific context, but detrimental during its chronic activation. Indeed, the aberrant or prolonged activation of the mtUPR was described as a mechanism of constant mitochondrial recovery that causes the accumulation of deleterious mitochondrial genomes with point loss-of-function mutations or deletions, which is why the precise regulation of the mtUPR is necessary [23]. Nevertheless, in the study by Di Hu et al. [24], the authors observed that the activation of the mtUPR via the deletion of ornithine transcarbamylase in SH-SY5Y cells protected against mitochondrial damage and toxicity produced by MPP+ treatment. This MPP+ treatment initially also induced the mtUPR, but when it was sustained over time, it resulted in increased ROS production and mitochondrial dysfunction, which was mitigated by the overexpression of a vector with the ornithine transcarbamylase deletion. Another example that demonstrates the beneficial role of mtUPR activation in neurodegenerative diseases was provided by Liu et al. [25] in a model of Parkinson's disease in *Drosophila Melanogaster*. In this PTEN-induced kinase 1 (*PINK1*) mutant model organism, the treatment with ginseng, a Chinese herbal medicine, resulted in an increased lifespan, the rescue of dopaminergic neuron loss, a significant increase of dopamine in the brain, and a delayed onset of the Parkinson's phenotype. In one mouse model of α-synuclein A53T PD, the overexpression of ClPP ameliorated pathological symptoms via mtUPR activation [26].

Another of the best-known neurodegenerative diseases is Huntington's disease (HD), caused by the presence (in the majority of cases corresponding to full penetrance) of more than 39 CAG trinucleotide repeats (coding for glutamine) in exon 1 of the huntingtin gene. As a result, an aberrant protein is generated, which provokes its accumulation and leads to DNA damage and mitochondrial dysfunction [27]. There is evidence that the mtUPR is

related to the pathophysiology of HD. Thus, Fu et al. [28] observed a downregulation of the mtUPR associated with ROS overproduction and cell death in the striatal cells of a Huntington's disease mouse model, as well as in the fibroblasts derived from HD patients [29]. In human primary fibroblasts, the expression of the polyQ40 huntingtin gene caused the activation of the mtUPR, demonstrated by the increased expression of mitochondrial chaperones [4]. Naia et al. [30] proposed that SIRT3 activity was increased in HD models, and the translocation of this enzyme to the mitochondrion was also increased in mouse and human cell models. However, in postmortem HD tissues and late-symptomatic mice, there were no changes in SIRT3 activity in comparison with the controls, suggesting that increased SIRT3 activity could be an early adaptative mechanism of the disease. Moreover, the activation of SIRT3 with ε-viniferin improved mitochondrial elongation and anterograde transport in HD striatal neurons. These results were also confirmed in a fly model, demonstrating that SIRT3 and the activation of the mtUPR conferred neuroprotection in Huntington's disease [30].

Mitochondrial dysfunction was reported in amyotrophic lateral sclerosis (ALS). This disease is characterized by motor neuron death, and most cases are sporadic. However, 5–10% of cases are familial, and up to 20% are caused by mutations in the copper-zinc superoxide dismutase (*SOD1*) gene. The mutation in *SOD1* causes a disruption in the mitochondrial axonal transport in the neuron, leading to an alteration in mitochondrial function and dynamics. Mutant SOD1 is localized in several cell compartments, including the mitochondrion, both in the mitochondrial outer membrane, where it interacts with other proteins, such as VDAC and Bcl2, and in the mitochondrial intermembrane space, where it interrupts the correct folding of crucial mitochondrial proteins [31]. In the study by Riar et al. [32], a G93A-*SOD1* transgenic mouse was used as a model of ALS. In this experimental condition, the activation of the canonical mtUPR occurred as the protein levels of CHOP were greater in the mutant mice than in the control ones. In addition, they demonstrated that mutant SOD1, which accumulated in the IMS, provoked the activation of the ERα mtUPR axis since NRF1 and OMI increased their levels in mutant mice in comparison to the controls. This could be due to the protective mechanism that the cells activate to defend themselves against mitochondrial damage. Zhou et al. [33] proposed that the treatment of the mutant mice with nicotinamide riboside improved neurogenesis, promoted the clearance of the SOD1 mutant protein, and enhanced the mitochondrial function via the activation of the canonical mtUPR. Straub et al. [34] studied patient-derived fibroblasts with mutations in coiled-helix coiled-helix domain-containing protein 10 (CHCHD10), one protein localized in the mitochondrial intermembrane space whose mutation was recently identified as a genetic cause of familial and sporadic ALS. When they cultured these cells in a stress galactose medium, canonical and SIRT3 mtUPRs were activated, probably due to mitochondrial stress. However, the overactivation of the mtUPR by LonP1 downregulation caused the progression of the disease in ALS models [35].

Therefore, all these findings suggest that mtUPR decline is related to the development of neurodegenerative diseases, and its activation could be a potential therapeutic target. However, it was reported that its overactivation might produce several detrimental effects, such as dopaminergic neuronal death in Parkinson´s disease animal models [22], the worsening of disease symptoms in an ALS mouse model [35], or neuronal cell death in AD [21], among others.

3. mtUPR and Cardiovascular Diseases

Mitochondria play a key role in all tissues but especially in those that have higher requirements of energy, such as the myocardium. Cardiovascular diseases (CVDs) have been associated with mitochondrial oxidative phosphorylation defects [36]. In CVD, mitochondrial dysfunction leads to changes in mitochondrial structure, among them, the formation of megamitochondria due to the overactivation of fusion proteins or enlargement of individuals in restrictive cardiomyopathy or mitochondrial fragmentation and apoptosis in ischemic heart failure [37]. On the other hand, the uncoupling of the mtETC leads to ROS overproduction which promotes atherogenesis by promoting endothelial dysfunction, vessel inflammation, and the accumulation of low-density lipoproteins [38].

Since functional mitochondria are essential for cardiac health, the impairment of the mtETC and, consequently, ROS overproduction might be considered key features that result in cardiomyocyte death through apoptosis or necrosis. The mechanisms linking CVD and mitochondrial dysfunction are not entirely clear. However, it was suggested that the reduction in energy supply to the myocardium due to pathological alterations of the mitochondria is responsible for the failure of cardiac function [39][40][41]. For this reason, these pathologies could be considered secondary mitochondrial diseases.

The relationship between the mtUPR and cardiac disease is sustained since several genes related to the mtUPR were upregulated in both animals and humans with heart pathologies [42]. Likewise, the pharmacological treatment with mtUPR activators, such as choline, that induced the SIRT3 mtUPR axis promoted cardiomyocyte vitality and improved mitochondrial function in animal models of CVD [43]. In one mice model, the activation of the mtUPR with oligomycin or doxycycline alleviated ischemic injury, and this improvement did not occur in the mouse knockout for ATF5, suggesting that ATF5 is a factor necessary for the improvement of the pathophysiology via mtUPR activation [44]. Smyrnias et al. [42] showed that mtUPR activation with small-molecule agents alleviated mitochondrial dysfunction and contractile capacity in murine hearts and demonstrated that in patients with aortic stenosis, reduced plasma biomarkers of cardiac damage, such as levels of abnormal fibrosis or cardiomyocyte cell death, were presented in association with elevated levels of mtUPR-related genes. Therefore, mtUPR activation could also be a potential therapeutic target for the treatment of cardiovascular diseases. However, as well as in neurodegenerative diseases, it was reported that mtUPR overactivation promoted heart failure and cardiomyocyte apoptosis under hypoxic conditions [45][46][47].

4. mtUPR and Primary Mitochondrial Disease

Primary mitochondrial diseases, caused by mutations in both nDNA and mtDNA, are characterized by mitochondrial dysfunction with a consequent deficiency in ATP production and ROS overproduction [48]. Currently, a prevalence of 1:5000 is established for this type of disease. Unfortunately, probably due to the extreme variety of genes and proteins affected, most primary mitochondrial diseases still lack standard and effective treatments [49]. Moreover, the diagnosis of mitochondrial diseases is challenging due to their clinical heterogeneity and the existence of two genomes implicated in their pathogenesis.

Nargund et al. [50] showed that in an ATFS-1 mutant worm, mitochondrial genome transcripts increased in response to mitochondrial stress; however, in the wild-type worm, these transcripts only increased modestly, proposing that ATFS-1 is a negative regulator of mitochondrial genome transcript accumulation. Moreover, this factor was also involved in the correct assembly of mtETC complexes during mitochondrial stress by inducing the expression of mitochondrial molecular chaperones. ATFS-1 and, therefore, the mtUPR are essential for the proper transcription of mtDNA and the correct assembly of the complexes encoded by this genome during stressful situations in the mitochondria. Moreover, Suarez Rivero et al. [51], in line with previously published studies by Perry et al. [52], demonstrated that mtUPR activation via treatment with tetracyclines and broad-spectrum antibiotics, improved the pathophysiology of mitochondrial diseases. Specifically, in the study by Suarez Rivero et al., it was observed that treatment with tetracyclines in cell models of the G elongation factor mitochondrial 1 (*GFM1*) mutation increased mtUPR-associated proteins and improved cellular physiopathology. Furthermore, in the former study [52], the authors showed that the treatment with the tetracycline family of antibiotics, as well as the anti-parasitic agent pentamidine and the antibiotic retapamulin, all activators of the mtUPR, improved cell survival in MELAS cybrids and improved Leigh syndrome symptomatology in a complex I-deficient mouse model.

Another study by Suarez Rivero et al. [53] suggested that mtUPR activation with pterostilbene in combination with mitochondrial cofactors improved the mitochondrial pathophysiology of fibroblasts and induced neurons derived from patients with mitochondrial diseases. Pterostilbene was also reported as a survival and protective compound in several animal models [54] due to its antioxidant, anti-inflammatory, and neuroprotective functions. Moreover, Poveda-Huertes et al. [55] proposed that different stages of mtUPR activation stimulate protein import and cardiolipin remodeling, which could act as beneficial mechanisms in mitochondrial diseases.

5. mtUPR and Metabolic Diseases

Mitochondria also play key roles in the pathogenesis of many metabolic diseases due to their central role in essential metabolic pathways. In metabolic disorders, mitochondrial dysfunction induces ROS overproduction associated with a reduction in antioxidant capacity, decreased ATP production, and changes in mitochondrial dynamics [56]. One of the most important metabolic disorders is metabolic syndrome, a compilation of metabolic abnormalities, such as hyperglycemia, insulin resistance, abdominal obesity, hypertension, and atherogenic dyslipidemia [57]. These conditions occur together and increase the risk of cardiovascular diseases and type 2 diabetes (T2D). Several studies proposed a link between mitochondrial dysfunction and metabolic syndrome, although the pathological mechanisms are still unclear [58]. What is known, however, is that metabolic syndrome patients present depressed superoxide dismutase activity, increased lipid peroxidation and carbonylated proteins, as well as increased oxidative damage [59].

T2D, one of the comorbidities of metabolic syndrome, is characterized by insulin resistance in the peripheral tissues as well as elevated blood glucose, which in turn inhibits the function of chaperones and proteases, leading to the accumulation of unfolded and misfolded proteins. These conditions, together with oxidative stress in mitochondria, lead to mtUPR activation to correct these defects [60][61]. In addition, the mtUPR was reported to increase glucose metabolism through the induction of glycolytic enzymes [62]. In this regard, Wardelmann et al. [63]

suggested that the mtUPR was decreased in mice after a high-fat diet. However, intranasal treatment with insulin activated the mtUPR in the hypothalamus and reduced weight gain. Moreover, Hauffe et al. [64] demonstrated that reducing the Hsp60 gene protected against obesity and insulin resistance in high-fat dieted male mice. Consistent with the latter results, the LonP1 levels were found to be elevated in the visceral adipose tissue cells of obese individuals, and deficiency of this protease potentiated hepatic gluconeogenesis and caused insulin miss signaling [65]. Additionally, mitochondrial chaperones Hsp60 and Hsp70 also affect T2D since it was proposed that Hsp60 prevents the hyperglycemia characteristic of T2D and its deficiency leads to insulin resistance [66]. Likewise, other components of the mtUPR, such as the sirtuins family, have positive effects on insulin sensitivity [9]. Therefore, the mtUPR could be a potential therapeutic target for metabolic diseases, especially type 2 diabetes.

6. mtUPR and Cancer

Mitochondrial dysfunction is a hallmark of cancer and is associated with the increased invasiveness, metastatic potential, and drug resistance of cancer cells [67][68][69].

First, the mtDNA mutation rate is considerably higher than nDNA, mainly due to the proximity of mtDNA to ROS-generating sites in the mitochondrial electron transport chain. Thus, the accumulation of mtDNA mutations was identified in several cancer types and was associated with metastatic progression and chemoresistance [69][70][71][72] as well as with activating proliferative pathways, such as the AMPK [73] or MAPK [74] signaling pathways.

Furthermore, reductions in oxidative phosphorylation efficiency force cells to depend on glycolysis for ATP production even in the presence of oxygen, which is described as the Warburg effect [75]. However, when mitochondrial dysfunction becomes more severe, excessive ROS production may be lethal to tumor cells [76][77]. Moreover, it was described that mutations in the ND1, ND3, ND4, and ND6 genes of mtDNA promote tumorigenesis and metastasis as well as resistance to apoptosis, contributing to tumor progression [78].

In addition, several mutations in nuclear-encoded mitochondrial proteins are associated with cancer, i.e., mutations in isocitrate dehydrogenase promote leukemogenesis and glioma, and mutations in fumarate hydratase and succinate dehydrogenase facilitate tumor growth and progression via the induction of hypoxia-inducible factor 1α (HIF-1α) [79][80].

Due to proteotoxic stress produced in cancer cells by ROS and mutations which hamper the correct folding of proteins, the mtUPR is activated. It was demonstrated that ATF5 was upregulated in a wide range of cancers [81], such as lung cancer [82], pancreatic cancer [83], and carcinomas [84], including ovarian cancer [85], rectal cancer [86], leukemia [87], neural tumors [88][89], esophageal cancer [90], or astrocytoma [91]. Furthermore, ATF5 activation produced resistance to radiotherapy [81] and increased the invasiveness of cancer cells [92]. In addition, Hsp60 was also upregulated in several types of cancers [93], including mammary [94] and ovarian [95] carcinoma, prostate cancer [96], glioblastoma [97] and neuroblastoma [98], and colorectal [99], gastric [100] and pancreatic cancer [101] and this phenomenon is associated with reduced patient survival. Moreover, the knockdown of Hsp60 had beneficial effects, as demonstrated in glioblastoma, where a reduction in this heat shock protein reduced protein translation

and cell proliferation [97]. In concordance with these results, Hsp70, also called mortalin, had increased expression levels in different types of cancers [102]. Thus, Hsp70 was upregulated in cancers of the liver [103], ovary [104], and thyroid [105], and its overexpression was associated with lymph node metastasis, advanced tumor stage, and decreased survival [106][107]. Like Hsp60, the knockdown of Hsp70 reduced the migration, proliferation, and invasion of cancer [108]. Finally, LonP1 and ClPP proteases were also upregulated in several types of cancers [109][110][111][112][113][114]. Hence, the activation of the mtUPR is a common feature that occurs in most types of cancer (**Table 2**), and its inhibition could reduce cancer invasion. Moreover, it was demonstrated that the mtUPR SIRT3 axis is necessary for the invasion and metastasis of cancer cells [115]. For that reason, mtUPR inhibition could be considered a potential therapeutic target for cancer, inducing apoptosis and a reduction in tumor progression and metastasis, as well as increasing patients' survival.

Table 1. Summary of mtUPR factor activation in different types of cancer.

mtUPR Factor Activated	Type of Cancer	Reference
ATF5	Lung	[82]
	Pancreatic	[83]
	Carcinoma	[84]
	Ovary	[85]
	Rectal	[86]
	Leukemia	[87]
	Neural tumors	[88][89]
	Esophageal	[90]
	Astrocytoma	[91]
Hsp60	Mammary	[94]
	Ovary	[95]
	Prostate	[96]
	Glioblastoma	[97]
	Neuroblastoma	[98]
	Colorectal	[99]
	Gastric	[100]
	Pancreatic	[101]

mtUPR Factor Activated	Type of Cancer	Reference
Hsp70	Liver	[106]
	Ovary	[104]
	Thyroid	[105]
LonP1	Colon	[112]
ClpP	Mammary	[110]
	Leukemia	[114]

7. Conclusions

Mitochondrial biogenesis and the mtUPR are essential for mitochondrial survival and fitness, the main mechanisms of mitochondrial quality control. Moreover, different mtUPR pathways were proposed, among them, the canonical transcriptional pathway, where ATF4, ATF5, and CHOP participate as the main triggers, the mitochondrial intermembrane space UPR, carried out by ERα as the main participant, the sirtuin pathway, mainly involving SIRT3[69] and, finally, a translational response that would act when the damage is minor and has a smaller effect. These pathways could act in parallel and complementarily but are independent of each other. Moreover, the sirtuins family, specifically SIRT1 and SIRT3, interconnect mitochondrial biogenesis and the mtUPR via the deacetylation of two key transcription factors, PGC-1α and FOXO3a.

The maintenance of mitochondrial quality is essential since mitochondrial dysfunction may be considered the core of a wide range of pathologies, including primary mitochondrial diseases, metabolic disorders, age-related diseases, cardiopathies, and cancer. In addition, it was reported that mtUPR activation could be a potential therapeutic option for these disorders. Thus, mtUPR activation induces an improvement in physiopathological alterations and a delay in the development of the pathology in many disease models. Nonetheless, its overactivation could be detrimental and worsen both the pathology and symptoms of a wide range of diseases; therefore, precise regulation is necessary.

However, the situation in neoplastic diseases is the opposite. The activation of the mtUPR leads to the progression and invasion of malignant cells. For this reason, the therapeutic strategy in cancer is based on the targeted downregulation of mtUPR signal molecules instead of its activation. This approach aims to retard tumor growth and induce cell apoptosis.

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