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Review

Signaling the mitochondrial unfolded protein response☆

Mark W. Pellegrino, Amrita M. Nargund, Cole M. Haynes *

Cell Biology Program, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA

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A B S T R A C T

Mitochondria are compartmentalized organelles essential for numerous cellular functions including ATP generation, iron-sulfur cluster biogenesis, nucleotide and amino acid metabolism as well as apoptosis. To promote biogenesis and proper function, mitochondria have a dedicated repertoire of molecular chaperones to facilitate protein folding and quality control proteases to degrade those proteins that fail to fold correctly. Mitochondrial protein folding is challenged by the complex organelle architecture, the deleterious effects of electron transport chain-generated reactive oxygen species and the mitochondrial genome's susceptibility to acquiring mutations. In response to the accumulation of unfolded or misfolded proteins beyond the organelle's chaperone capacity, cells mount a mitochondrial unfolded protein response (UPR^{mt}). The UPR^{mt} is a mitochondria-to-nuclear signal transduction pathway resulting in the induction of mitochondrial protective genes including mitochondrial molecular chaperones and proteases to re-establish protein homeostasis within the mitochondrial protein-folding environment. Here, we review the current understanding of UPR^{mt} signal transduction and the impact of the UPR^{mt} on diseased cells. This article is part of a Special Issue entitled: Protein Import and Quality Control in Mitochondria and Plastids.

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1. Introduction

Mitochondrial protein homeostasis is maintained through proper folding and assembly of newly translated polypeptides, as well as efficient trafficking and turnover of those proteins that fail to fold correctly [1–3]. The load of unfolded proteins in mitochondria must precisely match the chaperone protein-folding capacity. If the chaperone capacity is exceeded, each organelle becomes susceptible to the deleterious effects of protein misfolding and aggregation. However, during stress cells employ strategies to protect the protein-folding environment including organelle-specific quality control proteases to degrade the unfolded or misfolded proteins [4] and mitochondrial unfolded protein responses to increase chaperone capacity and re-establish homeostasis within the mitochondrial protein-folding environment [5]. Several factors challenge the mitochondrial protein-folding environment including complexities in mitochondrial biogenesis, DNA and protein damaging reactive oxygen species (ROS) that are generated within mitochondria, as well as environmental factors such as changes in temperature and exposure to toxins [6].

1.1. Complexities of mitochondrial biogenesis that threaten protein homeostasis

Mitochondria are double-membrane bound organelles composed of four compartments: the outer and inner membranes, the intermembrane space (IMS) and the matrix. Each compartment is a separate protein-folding environment, which must be maintained for efficient mitochondrial biogenesis and proper function. The mitochondrial proteome is composed of approximately 1200 proteins encoded by two separate genomes [7]. The mitochondrial genomes (mtDNA) are localized within the matrix and encode 13 essential components of the electron transport chain (ETC) and the ATP synthase as well as a number of mitochondrial-specific tRNAs. The remainder of the mitochondrial proteome is encoded by the nuclear genome, translated in the cytosol and imported into each mitochondrion [8,9]. Because ETC complexes I, III, IV and the ATP synthase are composed of components encoded by both genomes, it is imperative that expression from both genomes be coordinated to prevent the accumulation of orphaned subunits.

The mitochondrial protein-folding environment can be disturbed by excessive ROS generated from the ETC primarily via the NADH-ubiquinone oxidoreductase (complex I) and the ubiquinol cytochrome c oxidoreductase (complex III) [10,11], which directly perturb protein folding and structure. Additionally, mtDNA is prone to the accumulation of mutations, presumably because of its exposure to ROS and that it is not protected by histones [12,13]. Mutations that reduce expression of ETC components or perturb their ability to fold, compromise assembly of the individual complexes putting stress

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* Corresponding author at: Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box #390, New York, NY 10065, USA. Tel.: +1 212 639 3451; fax: +1 212 794 4342.

E-mail address: haynesc@mskcc.org (C.M. Haynes)

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on the protein-folding environment. Additionally, numerous toxins impair protein homeostasis such as paraquat, which causes high levels of ROS accumulation [14], and rotenone, which impairs complex I assembly and function [15].

1.2. Mitochondrial protein quality control: chaperones and proteases

To promote efficient mitochondrial protein folding and complex assembly, mitochondria have a dedicated repertoire of localized molecular chaperones located in both the IMS and matrix [1,9]. The Hsp60 chaperonin is in the matrix and consists of both Hsp60 and Hsp10 subunits which form a barrel-shaped complex. Hsp60 primarily facilitates the folding of relatively small, soluble monomeric proteins [16–18]. mtHsp70 also resides in the matrix where it performs multiple functions. At the translocase of the inner membrane (TIM23) channel, mtHsp70 functions in the multi-subunit PAM (Presequence Translocase-Associated Motor) where it interacts with the translocating polypeptides to drive their movement through the import channel into the matrix [9,19]. In a separate complex, mtHsp70 promotes protein folding and complex assembly of imported polypeptides while preventing aggregation [20–22]. Additionally, mtHsp70 is required for the biogenesis of iron–sulfur clusters within the matrix [23]. Mitochondria also contain an Hsp90 isoform known as TRAP-1 (TNF receptor-associated protein 1) that is thought to promote protein folding in a manner similar to the cytosolic isoforms of Hsp90 [24]. At present, no member of the Hsp60 or Hsp70 family of molecular chaperones has been observed in the IMS of mitochondria, however the Tim9-Tim10 complex promotes the import of highly hydrophobic membrane spanning proteins by preventing nonproductive protein–protein interactions as the polypeptides traverse the IMS [25].

In addition to molecular chaperones, mitochondria house several quality control proteases that recognize and degrade those proteins that fail to fold or assemble correctly. Both ClpXP and Lon are AAA proteases (ATPase Associated with diverse cellular Activities) located within the matrix that primarily degrade misfolded soluble proteins [3,4]. Interestingly, the Lon protease has been shown to preferentially degrade oxidatively-damaged proteins including aconitase [26]. Both Paraplegin (encoded by the *SPG7* gene) and YME1L are AAA proteases that are anchored within the inner membrane with their active sites facing the matrix and IMS, respectively. The primary role of YME1L and Paraplegin is to degrade misfolded or misassembled subunits of the ETC [27], although a recent role has been described for Paraplegin in mitochondrial ribosome biogenesis [28,29]. OMI/Htra2 resides in the IMS where it has been suggested to recognize and degrade soluble proteins that fail to fold correctly [30].

Numerous disease scenarios in which mitochondrial protein homeostasis is compromised emphasize the importance of maintaining the mitochondrial protein-folding environment [13,31,32]. Both paraquat and rotenone, as well as the *Htra2*-deletion cause Parkinson's-like symptoms in mice [15,33]. Mutations in the mitochondrial chaperonin Hsp60 and mitochondrial quality control protease Paraplegin cause the neurodegenerative disease spastic paraplegia [34]. In addition to a variety of diseases, loss of mitochondrial protein homeostasis has been closely associated with the aging process [6,13].

2. Compartment-specific unfolded protein response pathways

The cytosol, endoplasmic reticulum and mitochondria are all exposed to nascent polypeptides, thus each compartment requires dedicated protein-folding machinery, which constitutes each organelle's protein-folding capacity. Stress occurs when the quantity of unfolded or misfolded proteins exceeds a compartment's protein-folding capacity, rendering the organelle susceptible to catastrophic damage. To adjust folding capacity, eukaryotic cells have evolved organelle-specific signaling pathways known as unfolded protein responses (UPRs).

The heat shock response protects the cytosolic protein-folding environment and is regulated by the transcription factor Heat Shock Factor 1 (HSF1) [35]. In the absence of stress, HSF1 associates with the cytosolic chaperones Hsp70 and Hsp90. However, when unfolded proteins accumulate beyond the cytosolic chaperone capacity, HSF1 dissociates allowing it to trimerize and interact with the promoters of genes that constitute the heat shock response [36]. HSF1 mediates the expression of a number of chaperone genes that localize to the cytosol and nucleus including Hsp70 and Hsp90. Additionally, HSF1 induces the expression of a number of components of the ubiquitin-proteasome system to degrade terminally misfolded proteins and reduce the burden on the cytosolic protein-folding machinery [36]. Conditions that activate the heat shock response include increased temperatures and exposure to toxins such as arsenite that perturb protein folding in the cytosol [37,38].

The protein-folding environment of the ER is protected by a separate unfolded protein response (UPR^{ER}) [39]. The most conserved branch of the UPR^{ER} consists of the ER membrane spanning kinase Ire1 and the bZip transcription factor Xbp1. Ire1 monitors the protein-folding environment of the ER lumen and initiates URP^{ER} signaling by directly recognizing unfolded proteins [40]. If stress occurs in the ER, Ire1 oligomerizes [41] activating its cytosolic kinase domain. Once activated, the cytosolic domain of Ire1 splices an intron from the Xbp1 transcript [42] allowing translation of a functional bZip protein which traffics to the nucleus to induce the UPR^{ER}. The UPR^{ER} includes a number of ER-targeted protein-folding machineries including BiP, an ER-targeted Hsp70, protein disulfide isomerase and the glycosylation machinery [43]. Additionally, the UPR^{ER} activates expression of ERAD (ER-associated degradation) components which serve to recognize misfolded proteins, retrotranslocate them across the ER membrane to the cytosol where they are ubiquitylated and degraded by the proteasome [44].

In addition to increasing ER-specific protein folding and quality control machinery, a branch of the UPR^{ER} also briefly attenuates protein translation to reduce the load on ER folding capacity [39]. In response to ER stress, the ER membrane spanning kinase PERK (Pancreatic enriched ER kinase) dimerizes and phosphorylates the alpha subunit of eIF2 (eukaryotic initiation factor), which serves to attenuate protein translation [45].

Conceptually similar to the UPR^{ER} and heat shock response, accumulating evidence supports the existence of a UPR^{mt}; a mitochondria-to-nucleus signal transduction pathway that senses unfolded protein stress within the organelle and transmits a signal out of mitochondria, through the cytosol to the nucleus where the up-regulation of genes encoding mitochondrial chaperones and quality control proteases takes place to re-establish mitochondrial protein homeostasis [5].

3. Retrograde transcriptional responses from mitochondria suggested the presence of a UPR^{mt}

The survival of cells devoid of mtDNA (ρ^0 cells) suggested the activation of nuclear responses as compensation for severe mitochondrial dysfunction. Indeed, ρ^0 cells undergo a number of changes in nuclear gene expression including the induction of mitochondrial molecular chaperone and protease genes [46–49]. The absence of mtDNA places a considerable amount of stress on the mitochondrial protein-folding environment as those ETC components encoded by the nucleus are still imported into mitochondria but unable to assemble into stoichiometric complexes in the absence of their mtDNA-encoded binding partners. In addition to increasing the mitochondrial protein homeostasis machinery, cells down-regulate the expression of the ETC components in complex I, III and IV to protect the protein-folding environment but not the ATP synthase as it is

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