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Endocrine aspects of organelle stress — cell non-autonomous signaling of mitochondria and the ER

Robert Schinzel[1] and Andrew Dillin[1,2]

Organisms have to cope with an unpredictable and dynamic environment. It is crucial for any living being to respond to these changes by buffering the effects on cellular homeostasis. Failure to appropriately respond to stress can have severe consequences for health and survival. Eukaryotic cells possess several organelle-specific stress responses to cope with this challenge. Besides their central role in stress resistance, these pathways have also been shown to be important in the regulation of proteome maintenance, development and longevity. Intriguingly, many of these effects seem to be controlled by only a subset of cells implying a systemic regulation in a cell non-autonomous manner. The understanding of the nature of this stress communication across tissues, its mechanisms and impact, will be paramount in understanding disease etiology and the development of therapeutic strategies.

Addresses
[1] Department of Molecular and Cell Biology, The University of California, Berkeley, Li Ka Shing Center for Biomedical and Health Sciences, USA
[2] Howard Hughes Medical Institute, The University of California, Berkeley, USA

Corresponding author: Dillin, Andrew (dillin@berkeley.edu)

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Introduction

Living systems encounter an unpredictable and complex environment. Coping with ever-changing surroundings, they need to spend a considerable amount of their available energy to maintain homeostasis and to minimize the effects of stochastic events. The importance of buffering these challenges becomes apparent when efforts to sustain the balance fall short. An inappropriate cellular stress response has been associated with an ever-increasing variety of diseases, ranging from neurodegeneration to metabolic syndrome, from Alzheimer's disease to type 2 diabetes [1–5,6•].

Given this importance for the survival and proper function of every cell, it is not surprising that mechanisms to respond to cellular stress evolved very early, are highly conserved and can be found in all major evolutionary branches [7–10]. Furthermore, eukaryotic cells possess several organelle-specific stress responses, such as the heat shock response (HSR) for the cytosolic compartment, and the unfolded protein responses of the endoplasmic reticulum (ER) (UPR^{ER}) and mitochondria (UPR^{mito}) [11,12•,13•,14,15•,16].

Maybe surprisingly, in a range of model organisms, the activation of these pathways can lead to substantial increases in lifespan [17,18,19••,20]. In addition to longevity, the phenotypes of these animals almost always include increased stress resistance, altered metabolism, as well as delayed reproduction and development. These effects indicate a shift in the resource allocation strategy of the organism to another optimum — a tradeoff between reproduction and cellular maintenance [21–23]. Interestingly, the decision to alter the cellular investment and to delay development seems to be sensed and coordinated by only a subset of cells of the organism [19••,24••,25–27]. This indicates a cell non-autonomous mechanism of transmission of stress information. Again there seem to exist organelle specific endocrine signals to convey the cellular compartment affected.

The notion that stress responses and cellular homeostasis are to some degree under the regulation of cell non-autonomous neurosecretory mechanisms, was initially proposed for the HSR and the subject has been extensively reviewed recently [28,29]. Similarly, the topic of stress responses in general and the unfolded protein response in particular has a rich abundance of excellent reviews [12•,13•,15•,26]. We will therefore only briefly summarize the basic mechanisms of the UPR^{mito} and UPR^{ER} and instead focus in this review on the cell non-autonomous aspect of these two stress response pathways.

The unfolded protein response of the endoplasmic reticulum

The ER is important for a wealth of cellular processes including the folding and packaging of secretory as well as transmembrane proteins, the maintenance of intracellular Ca^{2+} levels, and lipid biosynthesis [30–32]. Besides this multitude of responsibilities, the ER is also intimately involved in maintaining cellular homeostasis. The ER is uniquely suited to this function because of its close association with every other membrane structure in the

cell, allowing the bidirectional transfer of lipids, proteins and ions throughout the cellular compartments [33•].

In the unfolded protein response (UPR^{ER}), the ER possesses an intricate system to sense and respond to various kinds of cellular stresses and physiological demands. Three principle signaling pathways of the UPR^{ER}, namely the IRE1, PERK and ATF6 branches, are able to respond to shifts in a range of biophysical parameters [12•,34]. For instance, the presence of unfolded or misfolded proteins, perturbations of membrane lipid composition, or imbalances in Ca^{2+} homeostasis are all able to strongly activate the UPR^{ER}. These changes indicate, at a molecular level, physiological or pathophysiological challenges that the cell is or will be encountering [2,33•,34–36]. Examples of these challenges include the takeover of the secretory pathway by pathogens, the presence of disadvantageous genetic alleles that cause chronic proteotoxic stress, or exposure to conditions such as hypoxia, nutritional scarcity or environmental toxins [12•,34,37,38]. Physiologically, the correct activation of the UPR^{ER} is necessary for proper cellular differentiation and essential for normal development [39–48].

Subsequent to the activation of the UPR^{ER}, a number of sophisticated mechanisms are triggered. At the transcriptional level, the upregulation of UPR^{ER} target genes, which include ER chaperones, ER-associated degradation factors or phospholipid biosynthesis proteins, takes place. This is supplemented by translational attenuation, an increased degradation of ER-associated mRNAs, the clearance of misfolded proteins from the ER to the lysosome, as well as activation of the protein degradation machinery [49–56]. These mechanisms aim to restore the correct protein-folding environment by strengthening folding capacity, reducing the protein burden and generally expanding ER size. Furthermore, each distinct UPR^{ER} branch, and combinations thereof, seems to be able to induce overlapping but divergent transcriptional responses [33•,50–52,57–60]. For instance, the selective and combined activation of the ATF6 and IRE1 branches in HEK293 cells, can each induce distinct transcriptional and proteomic profiles [50]. This points to the flexibility of the UPR^{ER} to match its response to various cellular needs, which may vary substantially due to differences in severity and duration of the insult as well as the kind of stress and cell type involved.

The difficult task of maintaining homeostasis in the ER, and in the cell as a whole, is exacerbated with increasing age. Not only does the cell face an increased burden through the surge in damaged and misfolded proteins, its ability to mount the appropriate stress responses seems to be reduced [61–63]. In the model organism *Caenorhabditis elegans* for instance, ER chaperones are downregulated and the ability to induce the UPR^{ER} diminishes with age [19••,60,64].

The cell non-autonomous regulation of the unfolded protein response of the ER

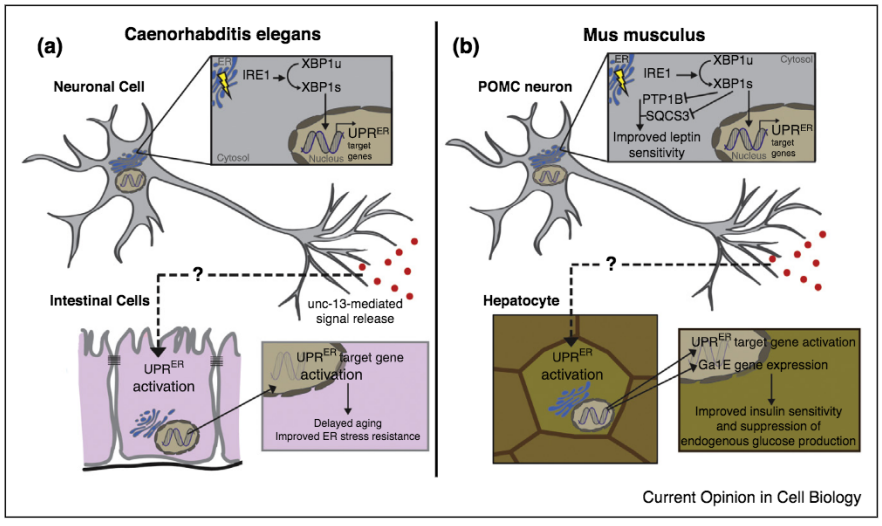
While the cell autonomous regulation of the UPR^{ER} has been extensively studied for decades, the realization that the UPR^{ER} can be subject to regulatory mechanisms across distal tissues is relatively new. Cellular differentiation or mounting an effective immune defense represent challenges to the ER environment and activate the UPR^{ER} strongly and extensively. While unmitigated ER stress generally causes an initiation of UPR^{ER}-associated apoptosis, the activation of apoptotic cell death under these circumstances would be detrimental [4,12•,65–69]. Therefore, a set of extracellular signaling cues seem to have evolved to suppress this effect in order to prepare cells for the upcoming challenge to ER homeostasis.

The activation of Toll-like receptors (TLR) through exposure of low dose lipopolysaccharide, for instance, attenuates the apoptotic response in cells undergoing prolonged ER stress. This effect has been suggested to promote survival in processes that involve a high level of protein synthesis, such as a host defense response mounted against invading pathogens [38,70,71]. Another example is the regulation of innate immunity and activation of UPR^{ER} target genes through OCTR-1 expression in neurons of *C. elegans*. Reducing the expression of the putative octopamine G protein-coupled receptor (OCTR-1) in a subset of neurons was able to increase the expression of a range of UPR^{ER} target genes in distal tissues involved in the immune response [72•,73].

Thyroid cells exposed to thyroid-stimulating hormones represent an example in which endocrine signals can activate expression of UPR^{ER} gene targets, apparently as a preparation for future secretory demands of the differentiating cells [74]. Moreover, tumor cells such as murine prostate cancer cells or mammary carcinoma cells, when subjected to toxins known to activate the UPR^{ER}, seem able to activate the UPR^{ER} in distal macrophages [75,76]. When exposed to the conditioned media of stressed cells, the macrophages showed an increased expression of UPR^{ER} target genes along with the initiation of secretion of tumor-promoting, pro-inflammatory and pro-angiogenic cytokines, which strongly suggests a role of aberrant UPR^{ER} signaling in tumor growth and progression [75,77].

Another instance of cell non-autonomous UPR^{ER} control became apparent through work investigating the consequence of the age-dependent decline of an appropriate UPR^{ER} activation. These experiments found that prolonged expression of the IRE1-pathway target XBP1s, even if just restricted to neuronal tissue, was sufficient to induce UPR^{ER} chaperone expression in distal tissues [19••] (Figure 1a). Along with the UPR^{ER} induction, the animals possessed an increased lifespan and improved stress resistance. This effect was subsequently shown to rely on *unc-13*, a mediator of small clear vesicle release

Figure 1



Overview of the cell non-autonomous regulation of the UPR^{ER} in *Caenorhabditis elegans* (a) and *Mus musculus* (b). **(a)** Upon activation of the IRE1 branch of the UPR^{ER}, the protein oligomerizes and activates its ribonuclease domain. Activated IRE1 catalyses the excision of a small intron in the XBP1u mRNA generating spliced XBP1s mRNA. As a consequence of the frame shift in the coding sequence, the XBP1s isoform is able to strongly activate the UPR^{ER} transcriptional program in a cell autonomous manner. The nervous system seem to be able to transmit the ER perturbation to other cells in the organism via an *unc-13* mediated signaling event. The mechanism of this transmission such as the signaling molecules involved, have yet to be identified. As a result of this cell non-autonomous ER stress signaling, distal tissues such as the intestine induce the UPR^{ER} target gene expression without directly being exposed to the stress themselves. Intriguingly, the animals subjected to this treatment possessed an improved ER stress resistance as well experienced a delay in aging. **(b)** In the mouse model, the selective activation of the IRE1 branch of the UPR^{ER} causes an activation of the UPR^{ER} response though XBP1s as well. In addition to the cell autonomous induction of UPR^{ER} target genes, expression of XBP1s in POMC neurons of the animals further suppresses the leptin-signaling blockers SOCS3 and PTP1B, thereby improving the ability of these neurons to response to leptin in times of ER stress. Again the activation of the UPR^{ER} in neurons is not restricted to the nervous system itself but is communicated to distal tissues via a yet to be defined signaling mechanism. Among other tissues, mouse hepatocytes respond to this cell non-autonomous signaling by upregulation of the UPR^{ER} and activation of an XBP1s-dependent postprandial transcriptional program though the activation of GalE. As a consequence of this activation the mice showed improved insulin sensitivity, reduced endogenous glucose release and lower glycemia.

(SCVs) in neurons, further supporting the involvement of cell non-autonomous regulation of the UPR^{ER} [19••,78–80]. In addition to these insights in *C. elegans*, recent evidence in the model system *Mus musculus* further underlined the importance of cell-non autonomous ER stress signaling. Here, the expression of XBP1s restricted to Pomc neurons in the hypothalamus, activated the UPR^{ER} in hepatocytes and adipocytes as well as induced metabolic changes which rendered the animals resistant to diet-induced obesity [81••] (Figure 1b).

In contrast to the earlier examples, which seem to involve the temporary modulation of stress tolerance in distinct tissues, the latter two cases indicate a coordinated shift in the activity of the stress response throughout an organism and its lifetime (Figure 1). The activation of the UPR^{ER} in this manner seems to accompany a fundamental change in the physiological state of the animal, including its proteome management, metabolic rate and lifespan and therefore provides the organism with a mechanism to respond to the presence of suboptimal genetic alleles or unfavorable environmental conditions which chronically disturb ER homeostasis.

While this change can be theoretically driven by a chronic exposure to the immune response modulators such as OCTR-1, the importance of the SCV indicates a central role for small molecule transmitters in this regulation. Intriguingly, this work suggests the possibility of multiple distinct cell non-autonomous signaling mechanisms, responding to various physiological, environmental or pathophysiological challenges. Future research will address whether non-cell autonomous UPR^{ER} signaling induces a similar diversity in UPR^{ER} target activation as the cell autonomous response can invoke.

The mitochondrial unfolded protein response

A vast majority of complex organisms rely on mitochondria to provide most of the energy necessary for cellular function. Crucial to this task is the electron transport chain (ETC), which allows the cell to generate an electrochemical gradient across the mitochondrial membrane and to utilize the thus-established membrane potential in the generation of ATP [82]. The ETC consists of various protein complexes, which are encoded by both nuclear and mitochondrial DNA [83]. While this genomic organization allows for local and immediate control of mitochondrial respiration, it nevertheless

requires the coordinated expression of both genomes to form functional ETC complexes [84–86].

In the mitochondrial unfolded protein response (UPR^{mito}), mitochondria possess a multifaceted quality control system to sense and respond to challenges to efficient mitochondrial function. The existence of the UPR^{mito} was first observed in experiments exposing cells to ethidium bromide. Besides depleting the mitochondrial genome, the treatment further induced the expression of a set of chaperones located specifically in mitochondria [87]. Subsequent work showed that a similar genetic program can be induced by the expression of a misfolded version of ornithine transcarbamylase, which causes the protein to accumulate in the mitochondrial matrix [88].

Besides the maintenance of the correct mitochondrial protein folding environment, the UPR^{mito} seems also responsible for monitoring the efficient ETC function. Challenges to the mito-nuclear balance of ETC components, such as reducing the expression of several nuclear-encoded mitochondrial ETC components via RNAi or interfering with mitochondrial ribosomal function, cause a strong activation of the UPR^{mito} [89,90,91••]. Further conditions able to induce the UPR^{mito} include shifts in AMP/ATP levels as well as changes in the NAD+/NADH ratio, thereby providing a mechanism to monitor mitochondrial function in general [91••,92•]. Causative to these imbalances at cellular level could be a range of pathophysiological conditions such as the presence of detrimental genetic alleles, a suboptimal match between mitochondrial and nuclear genomes or an exposure to harmful environmental conditions. Intriguingly, in the model organism *C. elegans*, the UPR^{mito} is also involved in the immune response triggered by microbial toxin-induced inhibition of host cellular function [93].

Two mechanisms are known to enable the UPR^{mito} to police the mitochondrial state. First, mitochondrial import efficiency is monitored through the protein ATSF-1, which, if not imported into the mitochondrial matrix, accumulates in the cytosol [94••]. From there, ATSF-1 transfers to the nucleus where it induces a genetic program characteristic to the UPR^{mito}, a process dependent on the transcription factors DVE-1 and UBL-5 [90,95•]. Since mitochondrial protein import is dependent on the presence of an electro-chemical gradient across the inner mitochondrial membrane, this provides a mechanism for the UPR^{mito} to assess mitochondrial function [96–98].

Alternatively, the UPR^{mito} can be induced by peptides generated as a consequence of stress-induced proteolytic breakdown of mitochondrial matrix proteins by the protease ClpP [99•]. In addition to ClpP, the peptide transporter HAF1 is essential for the activation of UPR^{mito} targets in this pathway, most likely by transporting peptides from the mitochondrial matrix to the cytosol. These peptides are thought to activate UPR^{mito} target gene expression through interaction with ATFS-1 [95•].

Once activated, the UPR^{mito} induces the expression of several genes important in reestablishing mitochondrial homeostasis such as mitochondria-specific chaperones, components of the mitochondrial protein import machinery, elements of the proteosomal-degradation system and subunits of the ETC [88,94••,100]. Additionally, some of the components of the UPR^{mito} transcriptional program seem to be central for the effect of mitochondrial stress on development, reproduction and longevity [24••].

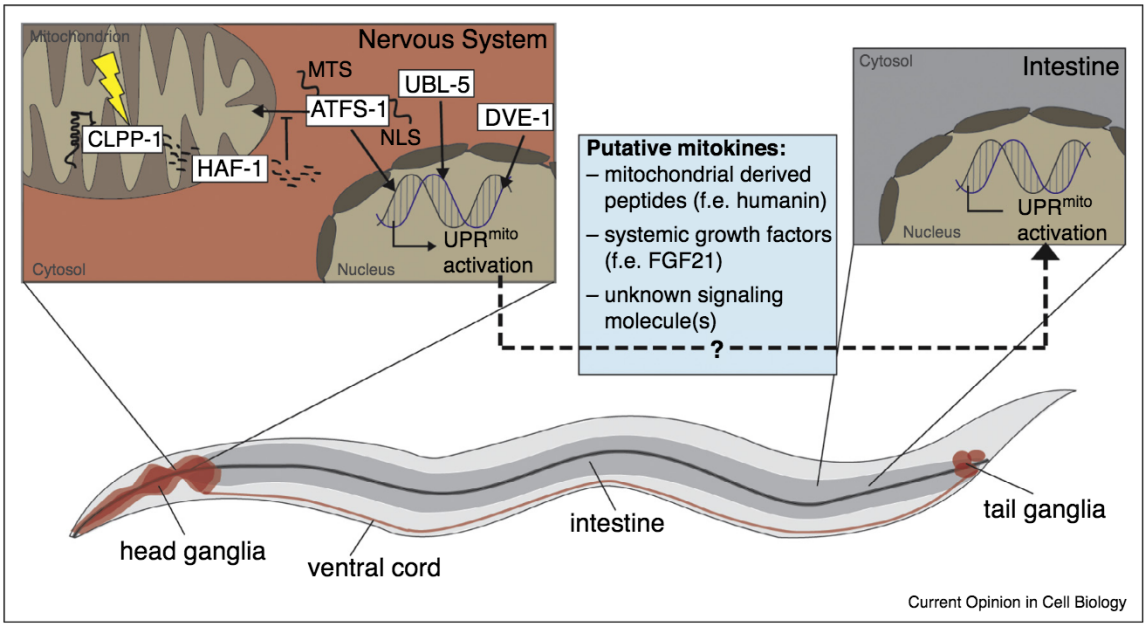
In a number of model organisms, mutations in genes that affect mitochondrial function have been found to increase the organism's lifespan and stress resistance. Work in *C. elegans* for instance, showed that reducing the expression of several nuclear encoded mitochondrial genes by RNAi is sufficient to extend the lifespan of the animal [101–103]. The role of mitochondria in the longevity of organisms has since been confirmed in the fruit fly *Drosophila melanogaster* and in rodents [91••,92•,104,105,106••]. Furthermore, a wide variety of mitochondrial stresses, which have the ability to induce the UPR^{mito}, are capable of extending organismal lifespan, including stoichiometric imbalances in mitochondrial proteins, increased NAD+ levels or exposure to mitochondria specific toxins [91••,92•,102].

The cell non-autonomous regulation of the mitochondrial unfolded protein response

Interestingly, not unlike cell non-autonomous UPR^{ER} signaling, the induction of the UPR^{mito} confined solely to the nervous system of *C. elegans* is sufficient to initiate a response throughout the entire organism. A restriction of the knockdown of ETC subunits to neuronal tissue, for instance, caused a lifespan extension similar to the knockdown in the entire animal [24••] (Figure 2). Furthermore, this treatment induced the expression of UPR^{mito} target chaperones in non-neuronal tissue independent of the UPR^{mito} transcriptional co-factor UBL-5 [24••]. This study suggests the involvement of a secreted signal molecule coordinating the UPR^{mito} across tissues. While the exact nature of this mitochondrial stress signal is yet to be determined, a few potential candidate molecules exist [78,107].

For example, the role of the peptide transporter HAF-1 in the cell autonomous UPR^{mito} activation suggests the possible involvement of a class of mitochondrial derived peptides (MDP), including the peptide humanin [13•,108]. Humanin is thought to be encoded by the mitochondrial genome, given its sequence similarities to the mitochondrial 16S rRNA, and its absence in cells depleted of mtDNA [109]. Interestingly, it has been shown to be stress responsive and to possess cytoprotective properties in an Alzheimer's disease model [110,111]. Nonetheless, it has yet to be

Figure 2



Current model of the cell non-autonomous regulation of the mitochondrial Unfolded Protein Response (UPR^{mito}) in *Caenorhabditis elegans*. Several mitochondrial perturbations such as a mito-nuclear protein imbalance of ETC components or the presence of misfolded proteins are able to efficiently induce the UPR^{mito} in a cell autonomous manner. For instance, when unfolded or misfolded proteins accumulate in the mitochondrial matrix, the protease CLPP-1 cleaves the proteins into peptides which subsequently are transported into the cytoplasma via the transporter HAF-1. This causes an inhibition of mitochondrial protein import and consequently to a reduction in the mitochondrial import of the transcription factor ATFS-1. As a result, ATSF-1 translocates to the nucleus, where it is able to activate the transcriptional response of the UPR^{mito} through interaction with the proteins UBL-5 and DVE-1. Intriguingly, the selective induction of the UPR^{mito} in the nervous system can be signaled to distal tissues of the animal. As a result of this cell non-autonomous ER stress signaling, UPR^{mito} target gene expression is induced and the lifespan of the animals in increased. The exact mechanism of the transmission of the stress signal, such as the signaling molecules involved is unknown, yet several candidates exist.

functionally connected to the UPR^{mito} or the global regulation of the mitochondrial stress response.

Another putative example of a cell non-autonomous stress signal molecule is FGF21. Transgenic mice, engineered to possess autophagy-deficient skeletal muscle cells, exhibited extensive mitochondrial dysfunction in their muscle tissue [112••]. This generated an increased expression of the signaling molecule FGF21 as well as an increase in FGF21 plasma concentrations in the animals. The observation that a similar FGF21 expression change is seen in C2C12 myotubes exposed to drugs inhibiting ETC function, and that patients suffering from mitochondrial ETC deficiencies also show increased FGF21 levels in their blood plasma, further strengthened the connection of mitochondrial dysfunction with FGF21 release [112••,113,114]. In addition to muscle atrophy and significantly reduced white adipose tissue (WAT) mass, the transgenic mice exhibited a range of beneficial phenotypes including a resistance to diet-induced obesity and improved insulin-resistance [112••]. Similar increases in FGF21 expression, blood plasma levels and resistance to diet-induced obesity was observed when the autophagy-deficiency was targeted to the liver of the mice instead of the muscle tissue [112••]. These results position FGF21 as a potential metabolic regulator and mitochondrial stress signaling molecule. Further research will show to what degree FGF21 is able to modulate UPR^{mito} or to coordinate the mitochondrial stress response at an organismal level, as for instance, ETC perturbation in neuronal tissue of *C. elegans* is able to achieve [24••].

Conclusion

Research on the UPR^{ER} and UPR^{mito} have yielded a wealth of exciting and promising results, providing the scientific community with an intricate understanding of how cells respond to challenges to homeostasis. The study of cell non-autonomous aspects of these mechanisms promises to extend our knowledge to the whole-organismal level, on how organisms adapt to homeostatic fluctuations, coordinate the stress response across tissues or cope with chronic proteotoxic and environmental challenges. Many questions remain to be answered, including the exact nature of the signaling molecules involved, their beneficial and detrimental effects in general as well as specifically to each tissue, and the extent of conservation across evolutionary boundaries.

While undoubtedly increasing the complexity of an already intricate subject, understanding the cell non-autonomous aspects of stress signaling may allow a regulation of the impact of cellular stress and its subsequent protective responses. And, given the involvement of aberrant stress responses in a host of severe diseases, these insights will almost certainly be valuable [1–5,6•,115–117].

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