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REVIEW

Mitochondrial stress-dependent regulation of cellular protein synthesis

Ulrike Topf[1,2,*,‡], Barbara Uszczynska-Ratajczak[1,*] and Agnieszka Chacinska[1,3,‡]

ABSTRACT

The production of newly synthesized proteins is vital for all cellular functions and is a determinant of cell growth and proliferation. The synthesis of polypeptide chains from mRNA molecules requires sophisticated machineries and mechanisms that need to be tightly regulated, and adjustable to current needs of the cell. Failures in the regulation of translation contribute to the loss of protein homeostasis, which can have deleterious effects on cellular function and organismal health. Unsurprisingly, the regulation of translation appears to be a crucial element in stress response mechanisms. This review provides an overview of mechanisms that modulate cytosolic protein synthesis upon cellular stress, with a focus on the attenuation of translation in response to mitochondrial stress. We then highlight links between mitochondrion-derived reactive oxygen species and the attenuation of reversible cytosolic translation through the oxidation of ribosomal proteins at their cysteine residues. We also discuss emerging concepts of how cellular mechanisms to stress are adapted, including the existence of alternative ribosomes and stress granules, and the regulation of co-translational import upon organelle stress.

KEY WORDS: Cytosolic translation, Mitochondrial stress, Reactive oxygen species, Redox switches

Introduction

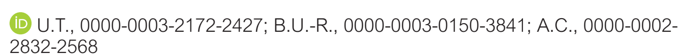
The mitochondrial genome encodes only ∼1% of mitochondrial genes. Thus, mitochondrial biogenesis largely depends on proteins that are encoded by nuclear genes, and need to be synthesized in the cytosol and imported into the organelle. The import of mitochondrial precursor proteins is regulated by a complex mitochondrial import machinery (Chacinska et al., 2009; Neupert and Herrmann, 2007). Mitochondrial precursor proteins enter mitochondria through the translocase of the outer membrane (TOM) complex (Walther and Rapaport, 2009) and are subsequently sorted into their destined subcompartment, i.e. mitochondrial outer membrane, mitochondrial inner membrane, intermembrane space (IMS) or matrix (Bolender et al., 2008; Mordas and Tokatlidis, 2015; Schulz et al., 2015; Stojanovski et al., 2012). Mitochondrial precursor proteins are mainly imported after they are entirely synthesized (post-translational import). However, recent studies provided evidence of coupling the translation of nuclear-encoded proteins with their import into mitochondria, similar to the process of translation-coupled import into the endoplasmic reticulum (ER; co-translational import; Gehrke et al., 2015; Gold et al., 2017; Jan et al., 2014; Lesnik et al., 2014, 2015; Williams et al., 2014). The dependence of mitochondrial function on non-mitochondrial protein production highlights the need for mitochondrion-derived mechanisms that coordinate protein expression of mitochondrial proteins in the cytosol based on current demands of the organelle. This is consistent with the emerging role of mitochondria as important signaling organelles that regulate non-mitochondrial cellular processes that participate in the maintenance of cellular homeostasis (Bohovych and Khalimonchuk, 2016; Chandel, 2015; D'Amico et al., 2017; Topf et al., 2016). Defects in the mitochondrial import machinery that result in decreased import efficiency were recently shown to activate non-mitochondrial responses, including activation of the proteasome and inhibition of cytosolic translation (Topf et al., 2018; Wang and Chen, 2015; Wrobel et al., 2015).

A complex machinery that comprises ribosomes as central components governs cytosolic protein synthesis. Ribosomes are large macromolecular complexes that consist of ribosomal RNA and ribosomal proteins. The process of protein synthesis (translation) proceeds in three phases: initiation, elongation and termination. These phases are followed by the recycling phase of ribosomal subunits. Each step of translation is controlled at various stages (Gebauer and Hentze, 2004; Hershey et al., 2012). Given the complexity of protein synthesis, mistakes can occur at any step of the process. Erroneous events during translation elongation can produce aberrant proteins and cause ribosome stalling (Joazeiro, 2017; Zurita Rendón et al., 2018). Stalled proteins can form aggregates, thereby imposing proteotoxic stress to the cell (Choe et al., 2016). Thus, maintaining a correctly folded proteome is vital for cellular homeostasis. The cell utilizes various surveillance mechanisms to control integrity of the synthesized polypeptide chain (Balchin et al., 2016; Hartl et al., 2011). Translation itself and its quality control mechanisms have been investigated in detail (Frank, 2017; Harms et al., 2001; Iwasaki and Ingolia, 2017; Ramakrishnan, 2002; Steitz, 2008), but the precise molecular processes that adjust protein synthesis to cellular needs still await elucidation. Recent advances in ribosome profiling techniques and developments in global redox proteomics have moved the field of translation regulation towards physiology, shedding light on the mechanisms that are important for recovery from pathological conditions, including mitochondria-derived dysfunctions (Gold et al., 2017; Jan et al., 2014; Topf et al., 2018; Williams et al., 2014).

In this Review, we discuss concepts of how cytosolic protein synthesis is regulated, with a focus on the impact of mitochondrial stress. We highlight recent findings on the ways in which mitochondria communicate with the cytosolic translation machinery. Furthermore, we conclude with a discussion of possible mechanisms that can resolve conditions of stress to restore cellular homeostasis.

[1]Centre of New Technologies, University of Warsaw, Banacha 2C, Warsaw 02-097, Poland. [2]Department of Genetics, Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Pawinskiego 5a, Warsaw 02-106, Poland. [3]ReMedy International Research Agenda Unit, University of Warsaw, Banacha 2C, Warsaw 02-097, Poland.
*These authors contributed equally to this work

‡Authors for correspondence (a.chacinska@cent.uw.edu.pl; utopf@ibb.waw.pl)


U.T., 0000-0003-2172-2427; B.U.-R., 0000-0003-0150-3841; A.C., 0000-0002-2832-2568

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Cytosolic translation regulation upon cellular stress

Protein homeostasis (proteostasis) is the balance between protein expression, folding and clearance in the cell (Sala et al., 2017). As individual components of this highly interconnected proteostasis network are affected during stress conditions, other components adjust accordingly to maintain normal cellular function (Klaips et al., 2018; Sala et al., 2017; Schneider and Bertolotti, 2015). A dysregulation of one or more components of proteostasis can lead to pathological conditions, such as neurodegenerative diseases, diabetes and cancer (Hadizadeh Esfahani et al., 2018; Labbadia and Morimoto, 2015; Mukherjee et al., 2015). The expression of many proteins is regulated in a post-transcriptional manner, which explains observed discrepancies between the transcriptome and proteome (Ghazalpour et al., 2011; Schwanhäusser et al., 2011). Indeed, multiple endogenous and exogenous stressors influence protein synthesis by initiating signaling cascades that lead to the attenuation of translation (Fig. 1; García et al., 2007; Grant, 2011; Harding et al., 1999, 2003; Liu et al., 2008; Rodrigues et al., 2018). Activation of the integrated stress response (ISR; Bernales et al., 2006; Harding et al., 2000) or inhibition of mechanistic/mammalian target of rapamycin (mTOR; Ben-Sahra and Manning, 2017; Hay and Sonenberg, 2004; Shimobayashi and Hall, 2014; Yoon, 2017) are well-established stress response pathways. ISR and mTOR modulate components of the initiation and elongation of translation that, upon diverse stressors, result in the attenuation of cytosolic translation (Fig. 1). Many excellent reviews have described these important stress response pathways in detail (for reviews on ISR, see Bernales et al., 2006; Donnelly et al., 2013; Pakos-Zebrucka et al., 2016; Ryoo and Vasudevan, 2017; Walter and Ron, 2011; for reviews on mTOR, see Caron et al., 2010; Ma and Blenis, 2009; Masvidal et al., 2017; Morita et al., 2015; Roux and Topisirovic, 2018; Thoreen, 2017; Zoncu et al., 2011). Thus, this Review focuses on response pathways that are activated upon mitochondrial stress (Fig. 1). Typically, mitochondrial stress signaling initiates responses at the level of transcription. Recent work suggests that mitochondrion-derived reactive oxygen species (ROS) can also modulate cytosolic protein synthesis, presumably through oxidative modification of ribosomal proteins (Fig. 2). Below, we summarize aspects of established mitochondrial stress responses and highlight emerging concepts on how mitochondria regulate protein synthesis.

Activation of the mitochondrial unfolded protein response

The mitochondrial unfolded protein response (UPR^{mt}) is a stress response pathway that has been described in flies, worms and mammals (Fig. 2A). It was originally discovered as a transcriptional response in the nucleus upon damage of mitochondrial DNA (Martinus et al., 1996) and accumulation of misfolded proteins inside mitochondria (Papa and Germain, 2011; Yoneda et al., 2004). When UPR^{mt} is activated, the expression of mitochondrial proteases and chaperones increases to restore mitochondrial protein homeostasis (Nargund et al., 2012; Owusu-Ansah et al., 2013; Wu et al., 2014; Zhao et al., 2002). Other stressors, such as impairment of mitochondrial ribosomes, inhibition of mitochondrial chaperones and proteases, oxidative phosphorylation (OXPHOS) perturbation, and high levels of ROS, also activate the UPR^{mt}. Mitochondrial stress that activates the UPR^{mt} often decreases mitochondrial import capacity. However, the depletion of mitochondrial membrane potential, i.e. the driving force for import of nuclear-encoded mitochondrial proteins into the mitochondrial matrix, is not necessary to activate the UPR^{mt} (Jin and Youle, 2013). Many of the genes that are required for UPR^{mt} activation were discovered in *Caenorhabditis elegans* (Benedetti et al., 2006; Liu et al., 2014). There, import of the stress-activated transcription factor 1 (ATFS-1) into mitochondria is blocked upon mitochondrial stress and, instead, ATFS-1 translocates into the nucleus, where it upregulates genes that promote mitochondrial stress relief (see Fig. 2A). A similar process has been observed for ATF5, the functional homologue of ATFS-1 in mammalian cells (Fiorese et al., 2016). In addition to ATF5 at least two other transcription factors, i.e. ATF4 and C/EBP homologous protein (CHOP, in mammals known as DDIT3) are involved in the activation of mammalian UPR^{mt}. The expression of ATF4 and CHOP depends on activation of the ISR pathway, which links activation of UPR^{mt} with the modulation of cytosolic translation (Fig. 2A). ISR is activated by mitochondrial stress, amino acid depletion, high levels of ROS and ribosome stalling (Baker et al., 2012; Barbosa et al., 2013; Haynes et al., 2013). The kinase EIF2AK4 (GCN2 in *C. elegans*)

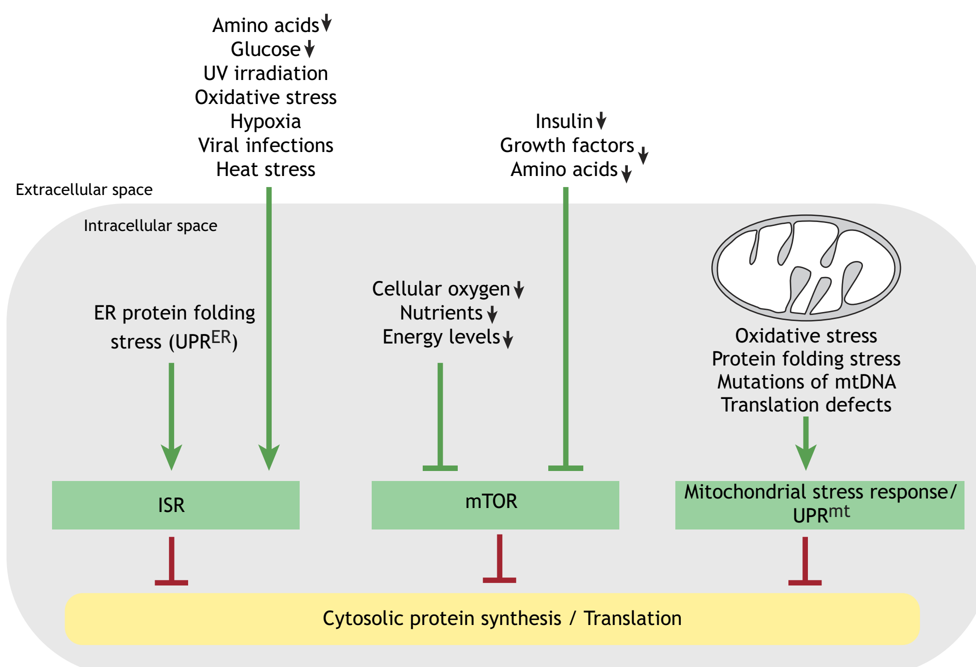

Fig. 1. Modulation of cytosolic translation upon stress. Cells are exposed to a wide variety of environmental and endogenous stressors (small black arrows indicate below-normal levels). Three main stress-signaling pathways modulate the response to diverse stressors by becoming activated (green arrows) or inhibited (green inhibitory arrows); they are the integrated stress response (ISR), the mTOR (mechanistic target of rapamycin) pathway and mitochondrial stress response pathways including the mitochondrial unfolded protein response (UPR^{mt}). All three lines of stress defense modulate protein translation, resulting in a decrease of protein synthesis within the cytosol (red inhibitory arrows). UPR^{ER}, unfolded protein response following ER stress.

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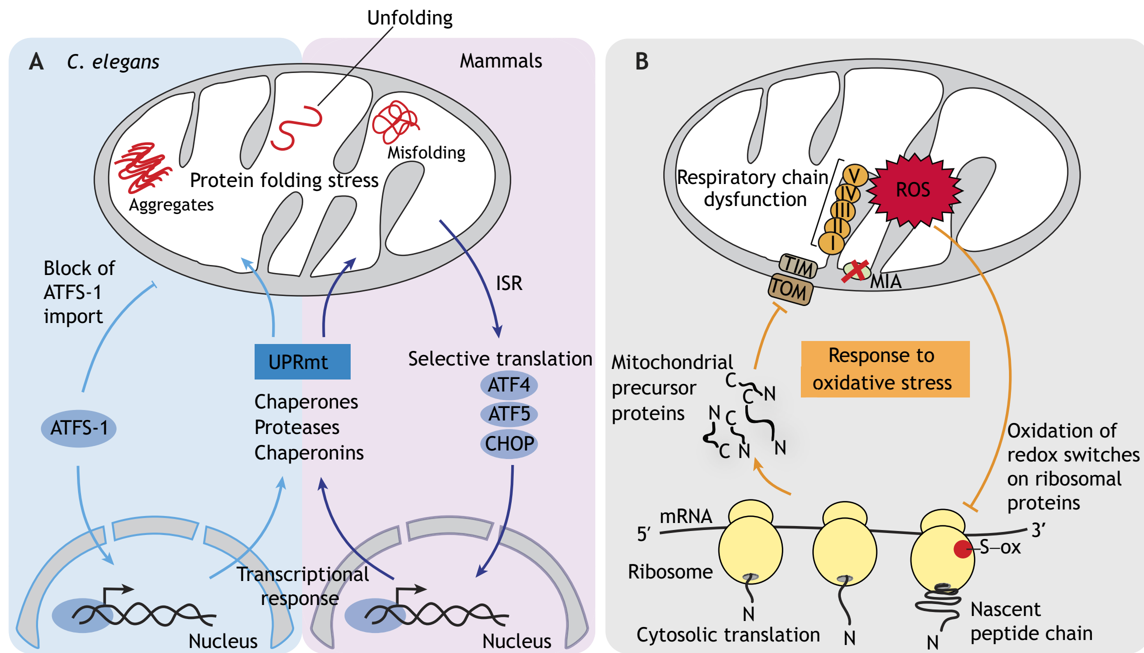

Fig. 2. Mitochondrial signals for the regulation of cytosolic translation. (A) Perturbation of protein folding in the mitochondria activates the mitochondrial unfolded protein response (UPR^{mt}). In the invertebrate *C. elegans* (left), the UPR^{mt} is predominantly regulated by the transcription factor ATFS-1. Upon mitochondrial protein-folding stress, ATFS-1 translocates to the nucleus, activating a transcriptional program, which results in the expression of mitochondrial proteins that increase folding capacity and can restore mitochondrial protein homeostasis. By contrast, in the mammalian system (right), the UPR^{mt} engages in crosstalk with the integrated stress response (ISR). Mitochondrial stress activates the ISR, which is required for expression of the transcription factors ATF4, ATF5 and CHOP. These, in turn, activate a transcriptional response, similar to that in *C. elegans*, to restore mitochondrial proteostasis. (B) Increased levels of reactive oxygen species (ROS) can be a signal to report the state of mitochondria to the cytosolic translation machinery. Defects in mitochondrial biogenesis caused by defective import of precursor proteins into mitochondria via translocase of the outer membrane (TOM), translocase of the inner membrane (TIM) and the mitochondrial inner membrane space assembly (MIA) pathway can result in defects of respiratory chain complexes I-V and subsequent increase in production of mitochondrial ROS. Thiols of cytosolic ribosomal proteins that are sensitive to ROS become oxidized (S-ox), presumably resulting in alterations of the ribosome and halting the elongation of translation.

phosphorylates eukaryotic translation initiation factor 2A (eIF2α), which leads to the attenuation of global translation by inhibiting the translation initiation step and, subsequently, by activating the selective translation of mRNAs yielding proteins, including ATF4, CHOP and ATF5 (Melber and Haynes, 2018). Similar observations were also made in *C. elegans* (Baker et al., 2012), where high levels of mitochondrion-derived ROS activate the GCN2-dependent phosphorylation of eIF2α; however, this is not required for activation of ATFS-1. Worms depleted of GCN2 still exhibited robust activation of the UPR^{mt}, which depended on ATFS-1. Thus, the UPR^{mt} in mammals depends on crosstalk with the ISR, whereas UPR^{mt} in *C. elegans* can also function independently of the attenuation of cytosolic translation (D'Amico et al., 2017). A decrease in overall translation also lowers the load of nuclear-encoded mitochondrial proteins that would need to be imported, and allows the restoration of mitochondrial proteostasis. Thus, mitochondrial stress that activates the UPR^{mt} also decreases overall cytosolic protein synthesis through crosstalk with the ISR (Fig. 2A).

Regulation of translation upon production of ROS

Activation of UPR^{mt} has not been described in the yeast *Saccharomyces cerevisiae*. However, we have recently identified a stress response upon decreased protein import into mitochondria in yeast, which resulted in the attenuation of cytosolic translation (Fig. 2B; Topf et al., 2018; Wrobel et al., 2015). The decrease in cytosolic translation was accompanied by unfolded protein response activated through mis-targeted proteins (UPR^{am}), which was characterized by increased activity of the proteasome (Wrobel et al., 2015). Importantly, this response did not increase mitochondrial protein-folding capacity (Wrobel et al., 2015), suggesting a mechanism that is distinct from the canonical UPR^{mt}. Instead, overexpression of certain ribosomal proteins and translation modulators rescued otherwise lethal mitochondrial defects, i.e. mitochondrial precursor over-accumulation stress (mPOS) (Wang and Chen, 2015). These responses to perturbations of the regulation of mitochondrial protein homeostasis in yeast might involve a common pathway. Mitochondria that are subjected to stress appear to transmit signals to the cytoplasm, resulting in attenuation of cytosolic translation and activation of a feedback mechanism to restore mitochondrial function (Fig. 2B). The mitochondrion-derived signal and possible molecular changes in the translation machinery that pauses protein synthesis remained unclear until recently. By using a quantitative proteomics approach, we identified components of the translation machinery located in the cytosol – including ribosomes – that undergo reversible thiol-oxidation mediated by mitochondrion-derived ROS (Topf et al., 2018). A decrease in global translation upon the exogenous application of hydrogen peroxide was observed previously (Shenton et al., 2006). However, a decrease in translation was subsequently shown to occur upon an increase in endogenous ROS levels that were caused by mitochondrial dysfunction (Topf et al., 2018). Importantly, attenuation of translation occurred independently of eIF2α phosphorylation (i.e. the main mediator of the ISR) and partially independent of mTOR signaling (Topf et al., 2018). The blockade of translation upon increase in ROS levels is likely to occur during the elongation and/or termination phase of protein synthesis. Ribosome profiling previously revealed that

polysomes are maintained upon the addition of hydrogen peroxide (Shenton et al., 2006). Polysome maintenance was also observed in mitochondrial import mutants that exhibited a decrease in cytosolic translation (Wrobel et al., 2015). The finding that nascent polypeptides are rescued upon blockade of translation when their degradation by the proteasome was inhibited supports the hypothesis that translation is blocked in the elongation phase (Topf et al., 2018). Further research is needed to uncover the molecular mechanisms of the attenuation of translation elongation upon oxidative stress. Among the identified proteins with ROS-sensitive thiols are ribosomal proteins (Brandes et al., 2011; Topf et al., 2018). One tempting speculation is that ribosomal proteins become oxidized upon mitochondrial stress, which temporarily disables ribosome function, thus behaving as redox switches. Redox switches are reversible post-translational oxidative modifications that occur most often at protein thiol residues (Groitl and Jakob, 2014). Interestingly, deletion of each of the identified ROS-sensitive ribosomal proteins resulted in resistance to the inhibition of translation upon oxidative stress. The concept of a ribosomal redox switch would limit the need for *de novo* ribosome assembly but also would prevent the ribosome from destruction (Fig. 2B). Redox switches have been identified and characterized in other proteins, such as enzymes, molecular chaperones and transcription factors (Georgiou, 2002; Groitl and Jakob, 2014). In fact, many proteins contain ROS-sensitive cysteine residues (Brandes et al., 2011; Erdos et al., 2019; Knoefler et al., 2012; Leichert et al., 2008; Menger et al., 2015; Rosenwasser et al., 2014; Shakir et al., 2017; Topf et al., 2018). However, the identification of biological function remains unexplored in most cases. We suggest that a mechanism involving thiol-based redox switches of ribosomal proteins can facilitate rapid and direct communication from mitochondria to the cytosolic translation machinery. This might be a mechanism that prevents an imbalance of cellular protein homeostasis and ensures the immediate continuation of global protein synthesis once stress conditions are resolved.

The attenuation of stress-induced global translation favors the selective synthesis of proteins that aid recovery from stress. Selective translation was shown to be an integral part of ISR and mTOR signaling (Nandagopal and Roux, 2015; Pakos-Zebrucka et al., 2016). Whether the attenuation of translation through a redox switch mechanism also allows selective translation is unknown. Analyses of mRNAs that remained bound to polysomes upon treatment of yeast cells with hydrogen peroxide revealed the enrichment of mRNAs that encode ROS-defense proteins, and proteins that are involved in ribosome biogenesis and rRNA processing (Shenton et al., 2006). This suggests a mechanism of selective production of proteins, which is triggered by oxidative stress. Further supporting selective protein production upon an increase in ROS levels was an analysis of deletion of the taffazin gene (*Taz1* in yeast), which caused defects in mitochondrial OXPHOS (de Taffin de Tilques et al., 2018). Deletion of taffazin was accompanied by an increase in ROS levels (Chen et al., 2008) and a partial decrease in cytosolic translation (de Taffin de Tilques et al., 2018). Interestingly, further mild inhibition of translation by chemical inhibition restored OXPHOS function and cell proliferation (de Taffin de Tilques et al., 2018). This suggests that a certain threshold of lower cytosolic translation must be reached to activate the recovery response. Importantly, the cellular response of translation attenuation in response to mitochondrion-derived oxidative stress appears to be preserved in higher eukaryotes (Topf et al., 2018). A recent study of mammalian cells implicated the transcription factor and p53 family member TAp73 (officially known as TP73) as a regulator of mRNA translation upon oxidative stress (Marini et al., 2018). Depletion of TAp73 resulted in aberrant ribosomal biogenesis and impairments in protein synthesis. TAp73 appeared to be especially important to maintain translation of mitochondrial transcripts under conditions of elevated ROS levels, thus suggesting its importance for homeostasis (Marini et al., 2018).

The proposed redox switches of ribosomal proteins occur under pathological conditions, such as mutant versions of proteins of the mitochondrial import machinery (Topf et al., 2018). One unresolved issue is whether attenuation of translation under changing physiological conditions also employs thiol switches of ribosomal proteins. Attenuation of translation is a common response to diverse stresses, many of them non-mitochondrial. This, presumably, serves as a means to lower the load of newly synthesized proteins in the cell, which would otherwise propel an imbalance of proteostasis. Proteostasis is crucial for cellular function and its collapse is a key event during the physiological process of aging (Taylor and Dillin, 2011; Walther et al., 2015). Activation of the UPR^{mt}, the inhibition of protein synthesis and the perturbation of mitochondrial function are independently linked with longevity (Higuchi-Sanabria et al., 2018; Jensen and Jasper, 2014; Riera et al., 2016; see Box 1). Multiple levels of stress-response regulation and numerous outputs often hamper precise determinations of the cause of lifespan extension. Unknown is whether the regulation of translation by redox switches of ribosomal proteins is a relevant molecular mechanism for longevity. A recent study in *C. elegans* showed that ribosome function is altered by the antibiotic minocycline, resulting in the inhibition of translation independently of the activation of stress-response pathways. This decrease in protein synthesis was shown to extend lifespan (Solis et al., 2018).

Box 1. Translation modulation during aging

Protein homeostasis collapses during aging. Many studies in different model organisms, including yeast, nematode and fruit fly, have applied genetic alterations to the translation machinery to decrease overall protein biosynthesis and extend the lifespan (Gonskikh and Polacek, 2017; Steffen et al., 2008; Taylor and Dillin, 2011). Such alterations have included depletion of ribosomal proteins (Chiocchetti et al., 2007; Hansen et al., 2007; Kaeberlein et al., 2005; Steffen et al., 2008) and decrease of translation initiation by knocking down initiation factors or overexpressing the translational repressor 4E-BP (Chen et al., 2007; Curran and Ruvkun, 2007; Hansen et al., 2007; Pan et al., 2007; Syntichaki et al., 2007; Zid et al., 2009). Consistent with the observation that a decrease of global protein synthesis extends the lifespan, the overexpression of translation initiation factor EIF4E induced cellular senescence in mammalian cells (Ruggero et al., 2004). Thus, lifespan extension upon decrease in translation is a phenomenon that is conserved across species. It remains unclear, however, whether translation attenuation is a cause of aging or a consequence of age-related physiological changes. Rapid protein biosynthesis is accompanied by the production of damaged proteins that, in healthy cells, are removed by protein quality-control mechanisms. However, protein quality-control mechanisms decline with age, which increases accumulation of damaged proteins that can induce proteotoxicity (Lopez-Otin et al., 2013). Thus, an overall reduction of translation may decrease the load of damaged proteins. Moreover, translation is one of the most energy-consuming cellular processes (Proud, 2002), and a decrease in translation can mobilize energy for cellular maintenance and repair processes (Tavernarakis, 2008). Finally, protein synthesis in general slows during aging, with a concomitant increase in the erroneous incorporation of amino acids into proteins (Gonskikh and Polacek, 2017). Recent work examined translation fidelity in rodents with different maximum lifespans, demonstrating that translation fidelity negatively correlates with lifespan (Ke et al., 2017). This raises the issue of whether a decrease in protein synthesis is also a regulated process during aging that initially counteracts an increase in stress conditions.

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In summary, the concept of redox switches of ribosomal proteins adds a new level of complexity to the modulation of translation, and expands the signaling capacity of mitochondria under pathological conditions and, potentially, physiological conditions (Fig. 2B).

Emerging concepts for restoring homeostasis upon translation attenuation

Along with discoveries of stress-response pathways are evolving that modulate translation and their initiation signals, concepts of mechanisms that contribute to restoring cellular homeostasis after translation is attenuated. As outlined above, mitochondrial homeostasis is inevitably linked to cellular homeostasis. Mitochondrial biogenesis depends on nuclear-encoded proteins that are produced by the cytosolic translation machinery. Below, we focus on recently described mechanisms that may be relevant to restoring cellular homeostasis upon mitochondrial stress.

Alternative routes for protein import into mitochondria

The dual origin of the mitochondrial proteome and structural complexity of mitochondria make their biogenesis logistically very challenging. The generation of fully functional mitochondria requires a fine-tuned balance between the biosynthesis and degradation of many cellular proteins. Dysfunctional mitochondrial protein import can have serious consequences for the cell, including energetic deficiencies with elevations of ROS levels and the accumulation of mis-targeted mitochondrial precursor proteins outside mitochondria (Fig. 2B). Consequently, cellular responses exist that decrease the accumulation of mis-targeted mitochondrial proteins in the cytosol (Topf et al., 2018; Wang and Chen, 2015; Wrobel et al., 2015). The mitochondrial compromised protein import response (mitoCPR) was shown to safeguard mitochondria by removing proteins that are close to the mitochondrial surface when import through the TOM complex in the outer mitochondrial membrane was blocked (Weidberg and Amon, 2018). Moreover, the ribosome quality control (RQC) complex, which controls integrity of newly synthesized nascent chains on cytosolic ribosomes, was found to be essential for the quality control of mitochondrial proteins that are inaccessible for ubiquitylation, in which they are likely to be co-translationally imported into mitochondria. Instead, the RQC component Vms1 facilitates import of mitochondrial polypeptides that stall on the ribosome during translation, which directs aberrant polypeptides to intra-mitochondrial quality control (Izawa et al., 2017).

Post-translational import, in which proteins are imported after being entirely synthesized in the cytosol, is considered to be a main route of transporting proteins into mitochondria (Fig. 3A). Although the machineries and mechanisms of mitochondrial import have been well-described, the cytosolic stage of this process is not fully understood. Evidence of alternative routes has been debated for a while. Electron microscopy (EM) studies confirmed the presence of cytosolic ribosomes on the surface of mitochondria (Crowley and Payne, 1998). *In vivo* studies that employed artificial C-terminal pre-sequences revealed that some proteins are targeted to their correct destination while still attached to the ribosome (Ni et al., 1999). In addition, numerous mRNAs that encode mitochondrial proteins were found either on the mitochondrial surface or in close proximity in both yeast (Corral-Debrinski et al., 2000; Egea et al., 1997; Gadir et al., 2011; Marc et al., 2002; Suissa and Schatz, 1982) and human cells (Gehrke et al., 2015; Matsumoto et al., 2012). Interestingly, our recent structural data in yeast showed that active cytosolic ribosomes are located at the outer membrane and that they can interact with the TOM complex (Gold et al., 2017). Furthermore, some mRNAs that are associated with mitochondria were shown to be active templates for protein synthesis (Tsuboi et al., 2019 preprint; Williams et al., 2014), suggesting that localized translation can also be coupled with the direct transport of synthetized proteins into mitochondria (Fig. 3B).

Recently, an unexpected pathway of targeting mitochondrial membrane proteins, termed ER-surface mediated protein targeting (ER-SURF), was discovered in yeast (Hansen et al., 2018). ER-SURF helps to retrieve mitochondrial proteins from the ER surface and transfers them to mitochondria (Fig. 3C). This is

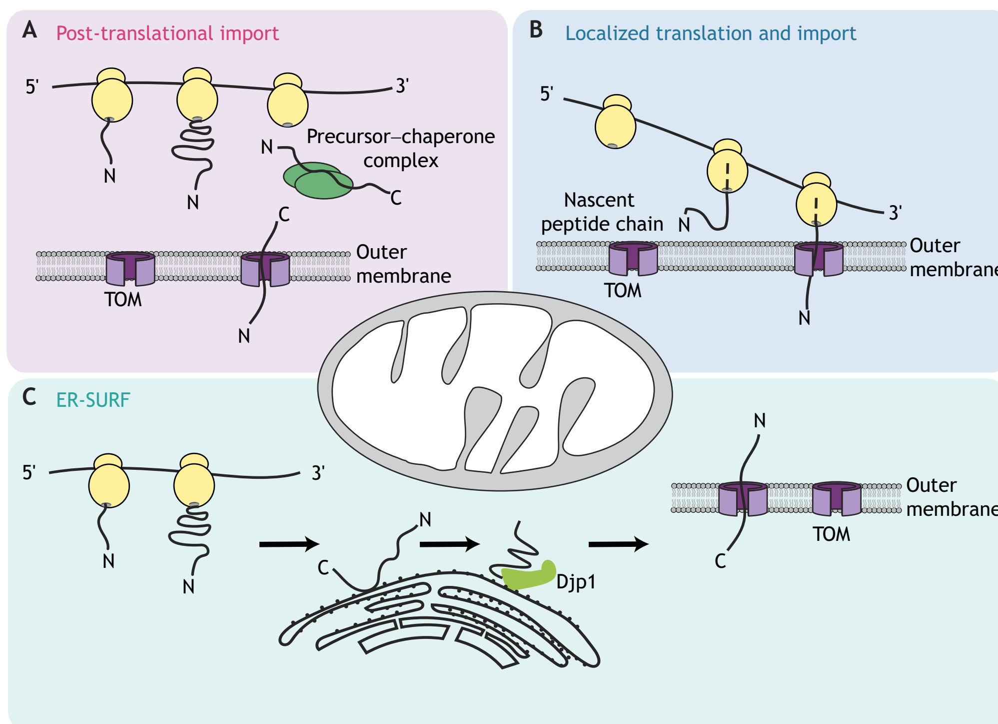

Fig. 3. Alternative routes for mitochondrial protein import. (A) In post-translational protein import, proteins are synthetized in the cytosol and then imported into mitochondria, accompanied by chaperones. (B) Localized translation occurs at the surface of mitochondria and may be directly coupled with the translocation of proteins into mitochondria. (C) In the ER-SURF-mediated pathway, mitochondrial proteins are retrieved from the ER surface and redirected into mitochondria in a Djp1-mediated interaction. TOM, translocase of the outer membrane.

promoted by the ER-localized chaperone Djp1 that cooperates with the mitochondrial pre-protein receptors Tom70 and Tom71 in this process. Through ER-SURF, Djp1 imports the inner membrane protein Oxa1 (in a precursor and import-competent state) into mitochondria (Hansen et al., 2018).

Various mechanisms protect cells from proteotoxic stress induced by the accumulation of precursor proteins in the cytosol, including the stabilization of precursor proteins by cytosolic chaperones and ubiquilins (Itakura et al., 2016; Young et al., 2003), and the proteasomal degradation of over-accumulated proteins (Wrobel et al., 2015). Alternative import pathways could have similar protective roles, in which localized translation and ER-SURF appear to be routes mainly for inner membrane proteins (Hansen et al., 2018; Williams et al., 2014). Because of the presence of hydrophobic transmembrane domains (TMDs) and signal sequences, inner membrane proteins are prone to aggregate in the cytosol or be erroneously integrated into other membranes. Therefore, alternative routes of mitochondrial protein import may reduce the accumulation of membrane proteins in the cytosol and minimize the proteotoxic stress response.

The role of specialized ribosomes in translation modulation

Increasing evidence supports the existence of ‘specialized ribosomes’ that have diverse compositions and post-translational modifications of subsets of ribosomal proteins, variations in rRNA, and bind to distinct ribosome-associated factors (Xue and Barna, 2012). Changes in the expression of ribosomal proteins across different cell types, tissues and developmental stages contribute to the heterogeneity of ribosomes (Bortoluzzi et al., 2001; Kondrashov et al., 2011). A recent study of embryonic stem cells identified and quantified subsets of ribosomes that are heterogeneous at the level of core ribosomal proteins (Shi et al., 2017). With regard to recovery from stress conditions, greater emphasis is being placed on changes in ribosome structures that mediate the selectivity of transcript translation (Gerst, 2018). Methodological advances in translation profiling have also allowed the identification of mRNAs that are enriched or depleted in heterogeneous ribosomes (Wang et al., 2009), and specific types of ribosome preferentially translate key regulators of cell metabolism, proliferation and survival (Shi et al., 2017). A recent study applied a nascent chain sequencing approach, i.e. puromycin-associated nascent chain proteomics (PUNCH-P; see Box 2), and found that specific paralogs of ribosomal proteins are important for the production of yeast mitochondrial proteins. In their absence, mitochondrial morphology and function are impaired (Segev and Gerst, 2018).

However, analyses of ribosome heterogeneity are complicated by the fact that many ribosomal proteins are encoded by more than one gene in yeast, plants and flies (Barakat et al., 2001; Marygold et al., 2007; Wolfe and Shields, 1997). For example, paralog gene pairs encode 59 of 79 yeast ribosomal proteins (Komili et al., 2007). Although these paralogs share high sequence identity, the deletion of either paralog can result in very different phenotypes (Enyenihi and Saunders, 2003; Haarer et al., 2007; Komili et al., 2007; Ni and Snyder, 2001). These results indicate that expression of paralogous ribosomal proteins adds a new layer to the modulation of translation, which could also matter for recovery from mitochondrial stress.

Stress granules and P-bodies

Under conditions of cellular stress, untranslated mRNAs are sequestered into membrane-less organelles, i.e. insoluble ribonucleoprotein protein (RNP) granules (Alberti et al., 2017; Rabouille and Alberti, 2017). Two such RNP granules are conserved cytoplasmic stress granules and processing bodies (P-bodies). Both structures are dynamic, exchange their content, and can be cleared by autophagy and degradation of lysosomal vacuoles (Protter and Parker, 2016). P-bodies contain mRNAs with translational repressors and mRNA decay machinery, whereas stress granules contain mRNA-associated RNPs that are stalled in the initiation phase of translation (Jain et al., 2016). This suggests that mRNAs in stress granules can be stored and that translation resumes promptly after recovery from stress. The biological function of stress granules is still poorly defined. Stress granules were found to enhance induction of the innate immune response and viral resistance (Protter and Parker, 2016). They might also promote interactions between mRNA and translation factors to enhance the formation of translation initiation complexes (Buchan et al., 2008). In addition to mRNA, stress granules also sequester numerous proteins that are involved in RNA physiology, metabolism and signaling (Arimoto et al., 2008; Thedieck et al., 2013). This might decrease the load of proteins from the bulk of the cytosol, which could contribute to preventing an imbalance of protein homeostasis. Support for this idea comes from studies that correlated impairments in stress granule formation with the development of several degenerative diseases and cancer (Anderson et al., 2015; Ramaswami et al., 2013). Cytoplasmic RNA sequestration was thought to be only a consequence of the inhibition of global translation upon stress (Decker and Parker, 2012). However, the existence of sequence-specific RNA-binding proteins suggests a more-specific recruitment of mRNAs (Harvey et al., 2017). In

Box 2. Advances in methodologies to identify mRNAs that are selectively translated upon global inhibition of translation.

High-throughput techniques, including RNA sequencing (RNA-seq), have revolutionized biology and medicine by allowing the analysis of thousands of genes and/or transcripts in parallel (Wang et al., 2009). RNA-seq is currently the most common method to investigate gene expression levels (Costa-Silva et al., 2017). However, to monitor translation rates by using RNA-seq is challenging. The technique of ribosome profiling has helped to overcome this limitation (Ingolia et al., 2009). Ribosome profiling (Ribo-seq) is a deep sequencing-based method that measures the translation rate at single-base resolution. A translating ribosome occupies ∼30 nucleotides of mRNA and protects them from nuclease activity. The deep sequencing of ribosome-protected fragments (ribosome footprints) provides information about the rate of protein synthesis, the position of ribosomes on mRNAs and the location of open reading frames. Ribo-seq can also be employed to investigate translation that is mediated by only a subset of ribosomes, such as those that are defined by their cellular location, for example, the outer membrane of the ER or of mitochondria (Jan et al., 2014; Williams et al., 2014). High-throughput analysis of proteins can also be performed by using mass spectrometry (MS). Pulsed stable isotope labeling by amino acids in cell culture (pSILAC) (Schwanhausser et al., 2009) is a popular method to investigate the rate of protein synthesis using MS. Cells are pulse-labeled with stable isotope-labeled amino acids that incorporate to newly synthesized proteins. This allows distinction of newly synthetized proteins from pre-existing ones. However, methods to measure the global translation of mRNAs, such as MS and Ribo-seq, often require substantial data analysis and computational resources. Puromycin-associated nascent chain proteomics (PUNCH-P) can be an alternative (Aviner et al., 2013). PUNCH-P is based on the incorporation of biotinylated puromycin into newly synthesized proteins under cell-free conditions, followed by streptavidin pull-down and liquid chromatography-tandem mass spectrometry analysis. The performance of this method was shown to be better than pSILAC with regard to the number of identified and quantified proteins per sample, but it was less efficient than ribosome profiling (Aviner et al., 2013).

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addition, stress granules were isolated from mammalian cells after exposure to different stresses, followed by analysis of their transcriptome. mRNAs of genes that are crucial for cell survival and proliferation were enriched in stress granules, and contained stress-specific targeting motifs (Namkoong et al., 2018). Thus, growing evidence suggests that the selective recruitment of mRNAs and, probably, of proteins, to RNP granules in a stress type-dependent manner contributes to recovery and the restoration of cellular homeostasis.

Multi-layered and increasingly interconnected signaling mechanisms provide a network of responses to mitochondrial stress, which we are just beginning to understand. Crosstalk between mitochondria and mechanisms in the cytosol is essential for mitochondrial biogenesis. By contrast, cellular homeostasis also depends on functional mitochondria. Thus, exploring feedback mechanisms in response to mitochondrial stress may also advance our understanding of cellular homeostasis (Fig. 4).

Conclusions and future perspectives

In response to various stressors, translation-modulating pathways (Fig. 1) form a network that combines transcriptional and post-transcriptional mechanisms to adjust to physiological changes and to overcome pathological conditions that can compromise protein homeostasis. Mitochondrial dysfunction has been linked to the attenuation of cytosolic translation, but the exact signals originating from mitochondria to halt protein synthesis have remained elusive. Mitochondrial perturbations can result in higher levels of ROS, powerful signaling molecules that can directly modify proteins and alter their function (D'Autreaux and Toledano, 2007; Finkel, 2011). The emerging concept of redox switches of ribosomal proteins as regulators of cytosolic translation may be a mechanism that allows mitochondria to regulate cytosolic protein synthesis (Fig. 4). A mechanism of thiol-based redox switches was found in yeast but is also relevant to higher eukaryotes (Topf et al., 2018). The concept of redox switches regulating the function of ribosomal proteins is an attractive model, but raises several questions about its mechanism. First, what kind of oxidative modification occurs? The identified oxidation-sensitive cysteine residues in ribosomal proteins are within a cysteine motif, in which four cysteine residues bind Zn^{2+} bind. The kinetically favored reversible oxidative form would be the formation of a disulfide bridge, although, sulfur oxidation states, such as glutathionylation, cannot be excluded. Second, are the redox switches directly oxidized by ROS or mediated by redox enzymes? Third, what are the structural consequences of oxidative modifications for the respective ribosomal proteins and the entire ribosome? Considering accumulating evidence of alternative ribosomes, redox switches could contribute to further heterogeneity within ribosomes. Fourth, are ribosomes located closer to mitochondria more susceptible to mitochondrion-derived ROS? Fifth, how is the oxidized state of ribosomal proteins maintained in the reducing environment of the cytosol and how are these redox switches reduced? Our experiments showed that translation quickly resumes upon the removal of oxidative stress conditions (Topf et al., 2018). And, last, in this context, are any enzymes involved in reducing the oxidized thiols of ribosomal proteins?

Another unresolved issue is the way in which redox switches of ribosomal proteins, which are most likely to affect translation elongation, can be placed in the context of previous findings that showed that UPR^{mt} activation inhibits cytosolic translation at initiation level by using mechanisms of the ISR (Baker et al., 2012). A dose dependence of hydrogen peroxide on the inhibition of translation initiation, based on eIF2α phosphorylation, was reported (Shenton et al., 2006). A yeast mutant with mitochondrial import defects exhibited a decrease in eIF2α phosphorylation, suggesting the inhibition of translation in an eIF2α-independent manner (Topf et al., 2018). Cells may have evolved to use different mechanisms to cope with acute and chronic stress but to define such transitions requires further experimental work. Finally, future research needs to focus on feedback mechanisms upon the attenuation of global

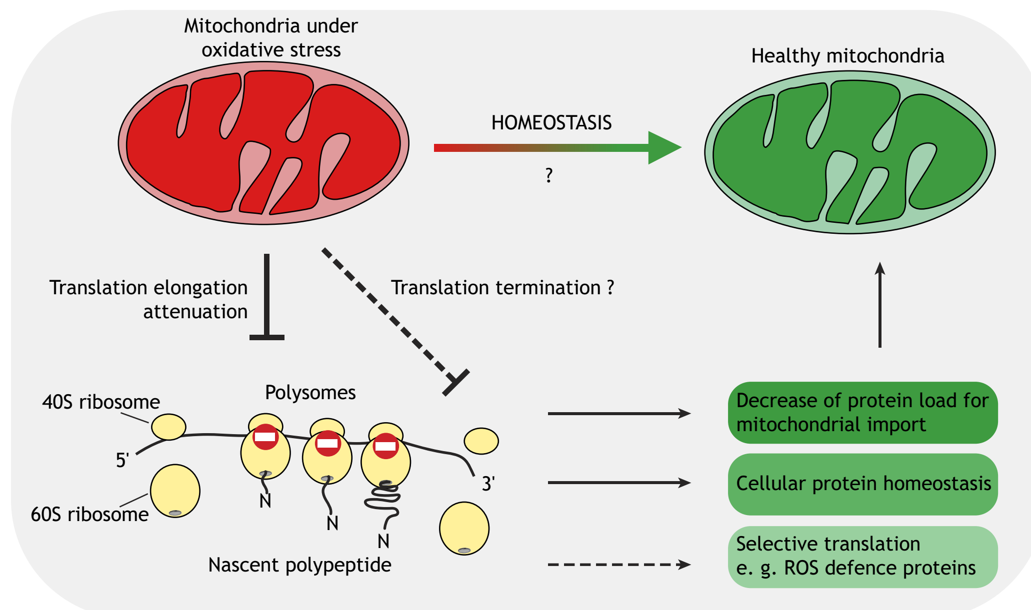

Fig. 4. Consequences of the modulation of cytosolic translation for recovery from mitochondrial stress. The feedback mechanisms that restore mitochondrial function upon the overproduction of mitochondrial reactive oxygen species (mROS) are mostly unknown. mROS can modulate thiol switches of cytosolic ribosomes, which might attenuate translation elongation. Pausing translation in the termination state is not excluded (dashed lines). Decreasing the load of newly synthesized proteins to be imported into mitochondria allows time to recover from mitochondrial dysfunction and helps restore cytosolic proteostasis. The mechanisms that are involved in recovery are unknown but could include the selective translation of mRNAs.

translation that is caused by mitochondrial dysfunction. For other stressors, selective translation is generally accepted to occur even when global translation pauses. Advances in methodologies applied to identify translated mRNAs on ribosomes are being used to identify selectively translated genome-wide transcripts and provide valuable insights into rescue mechanisms that are engaged upon mitochondrial stress. However, unbiased approaches should be implemented to uncover the potential diversity of recovery mechanisms that are engaged upon mitochondrial pathologies. Understanding the role of mitochondria as signaling organelles within the proteostasis network will increase our understanding of the dysregulation of cellular homeostasis in mitochondrial diseases and contribute to the development of therapeutic interventions.

Competing interests
The authors declare no competing or financial interests.

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