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Translational regulation in stress biology

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Organisms must constantly respond to stress to maintain homeostasis, and the successful implementation of cellular stress responses is directly linked to lifespan regulation. In this Review we examine how three age-associated stressors—loss of proteostasis, oxidative damage and dysregulated nutrient sensing—alter protein synthesis. We describe how these stressors inflict cellular damage via their effects on translation and how translational changes can serve as both sensors and responses to the stressor. Finally, we compare stress-induced translational programmes to protein synthesis alterations that occur with age and discuss whether these changes are adaptive or deleterious to longevity and healthy ageing.

Stress is part of every level of life: cells, tissues and organisms face suboptimal environmental conditions and deleterious products of their own intrinsic biological processes and must sense the stressor, mount a response to mitigate and repair the damage, and return to normalcy once the danger has passed to maintain proper homeostasis. As organisms age, their stress response capabilities weaken, leading to accrual of damage that can cause functional decline and reduced lifespan[1]. The classical 'hallmarks of ageing' include several cellular stressors, such as loss of proteostasis and deregulated nutrient sensing[2], indicating the close connection between stress responses and healthy ageing.

Considerable work has been done to define transcriptional cellular stress responses, leading to the identification of highly conserved stress-specific programmes that directly regulate longevity, as has been reviewed extensively elsewhere[3–5]. However, the post-transcriptional response to stress has historically been less thoroughly explored despite the centrality of translation to cellular metabolism and proteome management. Translation is not only responsible for proteome synthesis but is also integral to its quality control[6], and the myriad translation machinery components make it a rapidly tunable signalling nexus (Box 1). Translation is intimately linked to ageing, as reductions in protein synthesis are a common means of extending lifespan in model organisms[7]. Protein synthesis is also one of the most energetically costly cellular processes, estimated to require approximately 75% of the cell's energy[8], and ribosomes alone comprise approximately 80% of all cellular RNA and up to 30% of total protein mass in growing yeast cells[9,10]. Given the high cost of translation, it is perhaps unsurprising that a common pattern shared across stress responses is decreased global protein synthesis coupled with selective translation of crucial stress response factors, thereby lowering the overall proteostatic burden while still synthesizing the genes needed to resolve the stress. In fact, the two pathways primarily responsible for this general translation inhibition and selective translation upregulation—the integrated stress response (ISR) and mTOR complex 1 (mTORC1) signalling (Box 2)—are involved in the responses to each stressor we will discuss in this Review. In addition to these shared core regulatory pathways, however, we are now beginning to appreciate the specificity of the cell's responses to distinct stressors. Technological advancements including ribosome profiling, which enable nucleotide resolution of translation activity, have now permitted detailed characterization of the subtleties of translation regulation across different stress conditions, revealing stress-specific translational perturbations and responses. In this Review we focus on three sets of cellular level ageing-associated stressors—proteotoxic stress, oxidative stress and nutrient-sensing dysregulation—and discuss the global translational changes that result from each stress, both adaptive and deleterious. For discussions of other ageing hallmarks, including genomic instability, we direct readers to other recent reviews[11–13]. We will highlight how gene-specific translational regulatory strategies are used to mount a successful stress response and present examples of how altered translation is used by the cell as a stress sensor. We then discuss how stress-induced translation patterns are reflected in, and differ from, protein synthesis alterations with ageing.

Proteotoxic stress

Loss of proteostasis is a hallmark of ageing, and accumulation of misfolded and aggregated proteins is a common feature of ageing-associated diseases, including neurodegenerative disorders. As the source of cellular proteins, translation is intimately tied to the proteostasis network, ensuring that peptides are accurately synthesized and properly folded or cleared by quality control machinery.

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BOX 1

Overview of translation initiation and elongation

Eukaryotic translation requires a carefully orchestrated cascade of interactions between the ribosome and a myriad of translation initiation and elongation factors, providing many opportunities for regulation by the cell. The canonical form of translation begins with the formation of a 43S preinitiation complex composed of the small (40S) subunit of the ribosome, multiple initiation factors (including eIF1A and the eIF3 complex) and the ternary complex (eIF2 bound to GTP and the initiator methionine tRNA)[164]. The 43S complex is recruited to mRNA by interactions between eIF3 and the eIF4F complex, which includes the scaffolding protein eIF4G, the helicase eIF4A and eIF4E, which binds the 5′ methylated guanine cap of mRNA. Once loaded onto the transcript, the 43S complex scans along the mRNA until the start codon base-pairs with the initiator tRNA anticodon, which causes eIF2 to hydrolyse its GTP, triggering its release from the ribosome. This is followed by recruitment of the large (60S) ribosomal subunit and dissociation of the other initiation factors, resulting in an 80S ribosome ready to proceed with translation of the transcript ORF. Elongation commences with the arrival of the next codon's cognate aminoacyl-tRNA, escorted by GTP-bound eEF1A, which after GTP hydrolysis and eEF1A release is properly accommodated into the ribosome to enable peptide bond formation, aided by the elongation factor eIF5A[165]. Although eIF5A has a general function in assisting peptide-bond formation, it plays a critical role when the amino acids are suboptimally positioned, such as during the translation of polyproline motifs[166]. Once the peptide bond has formed, eEF2–GTP assists with ribosomal translocation, thereby allowing the now deacylated tRNA to be released and the next aminoacyl-tRNA to continue the elongation cycle.

Both the initiation and elongation phases of translation can be reduced by changing the expression levels of these core translation factors, sequestering them away from the ribosome, or via post-translational modifications. Regulatory phosphorylation in particular tunes the activities of multiple initiation and elongation factors, including eIF2 and eEF2 (Box 2), permitting rapid and reversible reductions in protein synthesis in response to stress.

When misfolded proteins accumulate, the cell frequently responds by reducing protein synthesis to alleviate the proteostatic burden, while simultaneously upregulating the expression of chaperones and other stress response genes in a process known as the unfolded protein response (UPR)[4]. The precise response depends on the cellular compartment experiencing proteotoxic stress, with distinct modes of translational regulation following cytosolic, endoplasmic reticulum (ER) or mitochondrial stress. These pathways are interconnected—for instance, mitochondrial dysfunction can lead to accumulation of mitochondrial proteins in the cytosol, activating the cytoplasmic UPR machinery[14]—but for this Review we will address each compartment UPR individually.

Cytoplasmic proteotoxic stress

Unfolded cytoplasmic proteins trigger the highly conserved heat shock response (HSR), so termed due to its initial characterization in heat stress; however, it is activated by a broad array of protein-folding stressors. The HSR is a transcriptional feedback loop driven by the transcription factor HSF1, which is freed from inhibitory interactions with molecular chaperones (including HSP70 and HSP90) when the cellular misfolded protein burden rises and then promotes transcription of heat shock proteins, including the chaperones that restrict its own activity. Accordingly, once these chaperones are again expressed in excess of their clients, the HSF1 function is suppressed[3].

At the level of translation there is a graded response, with low stress still permissive to protein synthesis, probably to allow production of heat shock factors and replenishment of misfolded and degraded proteins, whereas high stress decreases translation[15,16]. This decrease is partly attributed to reduced translation initiation, including via the ISR[17] and mTORC1 (ref. 18 and Box 2), sequestering translation-initiation components into stress granules[19] and even disintegration of the nucleolus (the primary site of ribosome assembly) at high levels of heat stress[20]. In addition, components of the signal recognition particle, which canonically directs proteins containing signal peptides to be translated at the ER, inhibit protein synthesis during heat shock in mammalian cell culture, possibly by binding to 40S subunits of ribosomes to prevent their use in translation[21,22]. Surprisingly, the genes most impacted in their translation efficiency by signal-recognition-particle regulation during heat shock are not signal peptide-containing proteins but rather mitochondrial genes, which suggests that there may be alternative mechanisms of selectivity under stress conditions[23]. Translation is also decreased by restricted elongation: in heat-shocked mammalian cell culture, ribosomes pause within the first several hundred nucleotides of the coding sequence, specifically at regions encoding hydrophobic peptides predicted to rely on HSP70 for their proper folding[16]. This creates a reversible reduction in the synthesis of HSP70 clients, allowing their expression to resume once chaperone availability has increased (Fig. 1a). A similar ribosome pausing pattern was observed using chemical induction of proteotoxic stress or expression of a dominant-negative HSC70 (ref. 24), highlighting the importance of chaperone-assisted nascent chain folding for processive translation and its modulation by diverse sources of protein misfolding burdens.

How are chaperones such as HSP70 successfully translated under conditions of general translation repression? Multiple features of the HSP70 mRNA transcript promote translation, decreasing the reliance on canonical cap-dependent translation initiation mechanisms. A region of the 5′ untranslated region (UTR) of human HSP70 was found to promote translation during heat shock by triggering ribosome shunting, where the ribosome bypasses portions of the 5′ UTR instead of scanning its entire length to find the start codon[25]. Although this sequence is absent in the *Drosophila* HSP70 homologue Dm-hsp70, it was instead shown to have internal ribosome entry site activity[26], a mode of direct ribosome recruitment to the start codon independent of the 5′ cap. Increased N^6-methyladenosine (m^6A) RNA modifications have also been observed following heat stress in the 5′ UTR of mammalian HSP70 as well as other heat shock transcripts, which promote a cap-independent form of translation initiation based on recognition by the eIF3 initiation complex[27,28]. These findings indicate that multiple mechanisms have evolved to ensure the expression of HSP70 and other heat shock proteins under stress.

HSP70 levels increase in multiple ageing models, in keeping with age-associated accumulation of misfolded proteins[29]. However, the ability to activate the HSR to induce even higher HSP70 expression declines with age, preventing adaptation to further deteriorations in proteostasis[29,30]. Age-associated protein aggregates also directly inhibit translation machinery, further compounding translation decreases. Tau oligomers show increased ribosome association in brain samples from patients with Alzheimer's disease compared with controls and this interaction decreases translation in vitro[31]. Notably, this occurs with both wild-type and disease-associated mutant tau, suggesting that it results from aberrant aggregation and not a specific pathogenic mutation[31]. A specific case of cytoplasmic misfolded protein accumulation occurs in neurodegenerative diseases caused by mutations that render proteins intrinsically prone to aggregation.

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BOX 2

ISR and mTORC1 signalling as regulatory pathways responding to multiple stressors

The ISR is a pathway conserved across eukaryotes regulating translation initiation and expression of stress response genes. The ISR centres on phosphorylation of serine 51 (in the human sequence) of the α subunit of the GTPase eIF2 (eIF2α). This phosphorylation is catalysed by four kinases, each responsive to a different set of stimuli, that is, GCN2 (nutrient deprivation), PERK (unfolded proteins in the ER), PKR (double-stranded RNA; such as during viral infection) and HRI (mitochondrial stress and iron deficiency). This enables the ISR to be activated by a wide array of stressors. During translation initiation, eIF2 hydrolyses GTP to GDP (Box 1) and relies on its guanine nucleotide exchange factor, eIF2B, for its recycling for new rounds of protein synthesis. Phosphorylated eIF2α is converted into an inhibitor of eIF2B, thereby preventing ternary-complex formation and reducing global translation initiation. Simultaneously, however, phosphorylation of eIF2α stimulates the selective translation of ATF4 due to the presence of uORFs in its 5′ UTR. A uORF is a translated sequence initiated at a start codon upstream of the main ORF. Typically, uORFs sequester the translation machinery away from the main ORF, repressing its expression; when ternary-complex levels are low, ribosomes can scan past the inhibitory uORF and initiate at the main ORF instead[167]. ATF4 activates the transcription of stress response genes, including chaperones and other proteostasis machinery, amino acid synthesis and transport genes, antioxidants and autophagy genes. Several of these downstream genes also contain uORFs and rely on eIF2α phosphorylation for their translation, including the pro-apoptotic factor CHOP and GADD34, a regulatory subunit of the PP1 phosphatase that promotes dephosphorylation of eIF2α, creating a feedback loop to terminate the ISR[37].

The mTORC1 complex is one of two complexes centred around the kinase mTOR, which integrates cues from nutrient levels, growth factors, energy availability and oxygen levels to promote cell growth and proliferation. Activation of mTORC1, such as by growth hormones or abundance of specific amino acids such as leucine and arginine, inhibits autophagy and stimulates nucleotide, protein and lipid biosynthesis[114]. Activation of mTORC1 specifically promotes translation by phosphorylating eIF4E binding protein, which in its unphosphorylated form binds to eIF4E to prevent its use in translation. In addition, mTORC1 phosphorylates p70 S6 kinase (also known as S6K), which then in turn phosphorylates multiple downstream substrates to promote translation. These include a stimulatory modification on eIF4B (which promotes eIF4A function), a destabilizing modification on PDCD4 (an inhibitor of eIF4A) and an inhibitory modification on eEF2 kinase (eEF2K), a negative regulator of translation via its inhibitory phosphorylation of eEF2. mTORC1 activity also promotes ribosome biogenesis and the translation of mRNAs containing 5′ terminal oligopyrimidine elements, which are highly enriched for translational machinery components. Transcriptional activity of RNA polymerase III, which is responsible for tRNA and 5S rRNA synthesis, is also upregulated by mTORC1 signalling[168]. Inactivation of mTORC1, such as during nutrient deprivation, accordingly decreases the abundance of the translational machinery, reduces cap-dependent translation initiation via regulation of eIF4F components and inhibits translation elongation via eEF2K[169]. This in turn can influence gene-specific translation initiation based on differential sensitivity to eIF4E binding protein levels[170,171] and promote greater translation fidelity by slowing elongation rates[147,172].

In addition to overlapping stimuli that activate the ISR and repress mTORC1, there is complex crosstalk between the two pathways. ATF4 upregulates the transcription of amino acid synthetases and transporters, which during chronic stress can lead to increased mTORC1 activity[173]. Conversely, mTORC1 has been shown to upregulate ATF4 translation, probably via inhibition of eIF4E binding protein[174], to promote transcription of a subset of its target genes, including those for amino acid uptake and purine synthesis[175,176]. ATF4 target genes also include negative regulators of mTORC1, potentially leading to further pathway feedback[177]. In fact, ISR activation has been shown to lead to ATF4-dependent mTORC1 inhibition via upregulation of the mTORC1 inhibitors SESTRIN2 and DDIT4, resulting in mTORC1-mediated inhibition of RNA polymerase III to decrease transcription of tRNAs[178].

Pathogenic repeat expansions that create tracts of repeated nucleotides/amino acids, such as the CAG repeats/polyQ in the huntingtin gene and the G4C2/dipeptide repeats in C9orf72 (associated with frontotemporal dementia and amyotrophic lateral sclerosis), have been shown to decrease global protein synthesis[32,33]. In addition to activating translation inhibitory pathways such as the ISR, the pathogenic proteins themselves are direct translation repressors. Expanded C9orf72 dipeptide repeats bind in *trans* to the polypeptide exit tunnel of the ribosome and repress peptidyl transferase activity[34]. Increasing protein synthesis by overexpressing the translation initiation factor eIF1A alleviates C9orf72 expansion toxicity without altering dipeptide repeat abundance in *Drosophila*, indicating that reduced translation contributes to neurodegeneration[35]. Notably, eIF1A overexpression alone decreases lifespan[35], suggesting that eIF1A benefits neurodegenerative models by restoring translation to wild-type levels, but exceeding that is detrimental. Mutant huntingtin also binds to the translation elongation factor eIF5A, sequestering it away from the ribosome and thereby increasing ribosome stalling, particularly at motifs known to rely on eIF5A for efficient translation elongation[36]. As many of the genes most sensitized to eIF5A availability are components of the proteostasis network, this may contribute further proteotoxic strain on the cells.

UPR^{ER}

Protein-folding stress in the ER activates a specific mode of the UPR known as UPR^{ER}. The UPR^{ER} has three arms: two are transcriptional responses to increase ER protein-folding capacity, mediated by IRE1 and ATF6, whereas the third is activation of the ISR by ER stress sensor and eIF2α kinase PERK[4]. ISR activation decreases translation initiation globally, thereby decreasing the ER protein-folding burden while also increasing translation of ATF4, which activates adaptive transcriptional programmes and, if the stress is not successfully alleviated, a pro-apoptotic signalling cascade[4,37]. This adaptive-to-apoptotic transition makes ISR activation a double-edged sword, particularly in chronic ER stress conditions, with both beneficial and detrimental outcomes depending on the cellular context. Ageing itself represents a chronic ER stress condition, with age-associated increases in PERK activation and eIF2α phosphorylation, as well as downstream pro-apoptotic factors, reported in multiple model systems[37–39]. However, similar to the HSR, the UPR^{ER} loses its inducibility as

organisms age, leading to cellular damage following further increases in stress[40,41]. Increased ISR activation via PERK has also been reported for multiple neurodegenerative conditions but ISR manipulation, either genetically or by small molecules, has yielded conflicting results (reviewed in refs. 42,43). For instance, ISR inhibition ameliorated cognitive symptoms in mouse models of Alzheimer's disease[44], whereas increased ISR activation improved cell health in models of Parkinson's disease[45], amyotrophic lateral sclerosis[46,47] and Huntington's disease[48]. Even in models of healthy ageing there is context dependency: conditional loss of PERK or expression of phospho-null eIF2α in dopaminergic neurons led to abnormal cognitive and motor function[49], while treatment with the ISR inhibitor ISRIB improved memory in aged mice[50]. This suggests that there are shifts in the balance of adaptive versus apoptotic ISR signalling that vary across ages, cell types and disease states[38,39].

Beyond the ISR, there are additional mechanisms to decrease translational load at the ER in times of stress (Fig. 1b). The ER serves as a platform for synthesis of not only secretory-system components but also some cytosolic proteins via tethering of either the mRNA or the ribosome to the ER membrane. During ER stress, transcripts encoding ER-targeted proteins are selectively released from the ER, whereas mRNAs encoding cytosolic proteins maintain their ER localization, thereby selectively decreasing protein influx into the ER[51]. In addition, ER stress signalling through PERK leads to regulatory ubiquitylation of several 40S subunit ribosomal proteins[52] on stalled preinitiation complexes, triggering the degradation of the 40S subunit[53]. This may assist in lowering translation rates globally as a stress adaptation, given that mutation of these ribosomal protein residues to prevent modification sensitizes cells to ER stressors[52]. Interestingly, ribosome abundance reduces with age[54], but whether this pathway contributes to this loss remains to be determined. Finally, under chronic ER stress conditions, cells also activate an adaptive response that includes partial restoration of protein synthesis, probably to enable adequate expression of stress response genes while still keeping ER protein influx relatively low[55]. This modest recovery of translation rates relies on eIF3, but not other translation initiation factors, suggesting that this translational reprogramming utilizes a non-canonical eIF3 function to directly recruit transcripts to the ribosome for translation[56].

UPR^{MT}

Mitochondria are in the unique position of having their components encoded by more than one genome. Although diminutive in size, the mitochondrial genome encodes essential components of the electron transport chain that must be synthesized by mitochondrial ribosomes in the proper stoichiometries with their nuclear-encoded counterparts, which are translated by cytoplasmic ribosomes and imported into the mitochondria, to prevent orphan subunit aggregation[57]. When protein import or folding in mitochondria is perturbed, the cell activates the mitochondrial UPR (UPR^{MT}), a nuclear transcriptional programme to restore mitochondrial function[5]. Similar to the other UPR pathways, induction of the UPR^{MT} transcriptional programme attenuates with age[58] and its chronic activation can promote apoptosis[59].

Translation inhibition is a core component of the cellular response to mitochondrial dysfunction (Fig. 1c). In *Caenorhabditis elegans* the ISR acts as a parallel pathway to the UPR^{MT} to enable mitochondrial stress adaptation[60]. The ISR has a more central role in mammals, with the transcription factors ATF4, ATF5 and CHOP—which rely on ISR activation for their translation due to upstream open reading frames (uORFs) in their 5′ UTRs—promoting a transcriptional programme for mitochondrial stress response genes[61]. Although all four eIF2α kinases may contribute to ISR activation under various mitochondrial-stress conditions[61], HRI can be specifically activated by DELE1, a sensor of mitochondria-import dysfunction[62,63], and PKR by mitochondria-derived double-stranded RNA[64,65]. Interestingly, PKR demonstrated increased expression across tissues in aged mice[66]. In addition to cytosolic translation, mitochondrial translation is repressed to limit the proteostatic burden within the organelle[67]. Mitochondrial stress has been shown to reduce mitochondrial tRNA processing through lowered expression of MRPP3, a component of the mitochondrial RNase P complex[67]. In addition, nuclear-encoded mitochondrial ribosomal proteins exhibit decreased protein expression[68] and mitochondrial import[69] during stress, inhibiting mitochondrial ribosome biogenesis.

Notably, inhibition of translation at the mitochondrial surface can itself serve as a sensor of mitochondrial dysfunction (Fig. 1c). PINK1 promotes the localization and translation of nuclear-encoded oxidative-phosphorylation-complex transcripts at the mitochondrial outer membrane under conditions of mild mitochondrial damage, possibly to promote their repair[70,71]. When the damage is more severe, translation stalls on these transcripts, leading to recruitment of the translational quality control machinery known as the no-go decay pathway, including the ribosome recycling factor ABCE1 and the E3 ubiquitin ligase NOT4. Here NOT4 ubiquitylates ABCE1 and ubiquitylated ABCE1 facilitates the recruitment of the autophagy machinery, leading to mitophagy of the damaged organelles[71]. Accordingly, translation quality reflects mitochondrial quality, providing a rapid means of alerting the cytoplasmic quality control machinery of the damage within the mitochondria.

Oxidative stress

Oxidative stress occurs when the redox equilibrium of a cell is disrupted. Cells constantly produce reactive oxygen species (ROS) as a byproduct of metabolic processes, including mitochondrial respiration, but these are restrained by antioxidant defence mechanisms; when this balance is perturbed, ROS can directly damage cellular macromolecules. Accordingly, oxidative stress can impair both the protein and RNA components of the translation machinery. Oxidation of mRNA can cause ribosome stalls and reduce translation fidelity[72]. The rRNA can also be oxidized, leading to base adducts or even cleavage[73]. These modifications, especially when in the catalytic core of the ribosome, often inhibit translation—and intriguingly, increased rRNA oxidization and reduced translation are associated with neurodegenerative disease[74]—but this varies depending on the location on the ribosome[75]. Several oxidized rRNA species have been observed in actively translating ribosomes, which suggests they either are harmless or have more nuanced impacts on translation[75,76].

Fig. 1 | Translational response to proteotoxic stress. a, Cytoplasmic protein-folding stress reduces translation through the release of chaperone HSP70 from the ribosome, resulting in stalled translation at amino-terminal hydrophobic motifs that rely on HSP70 for their proper folding. HSP70 itself is translated in these conditions due to non-canonical translation-regulation elements in its 5′ UTR including m^{6}A base modifications that recruit eIF3 and ribosome shunting. **b**, ER stress reduces global protein synthesis by initiating the ISR through PERK activation by unfolded proteins in the ER as well as triggering the ubiquitylation and subsequent degradation of 40S small ribosomal subunits (right). Translation of ER-targeted proteins is specifically further reduced by the selective release of mRNA transcripts encoding ER proteins from the ER membrane, whereas cytoplasmic protein transcripts tethered at the ER are unaffected (left). Activation of the ISR response and alternative initiation mechanisms driven by eIF3 permit selective translation of stress response genes, including *ATF4* (centre). **c**, Mitochondrial dysfunction releases multiple ISR-activating cues into the cytoplasm, including DELE1 and double-stranded RNA, which lead to inhibition of cytosolic translation. This results in reduced mitochondrial import of nuclear-encoded mitochondrial translation machinery, thereby also decreasing mitochondrial protein synthesis. In addition, under mitochondrial stress, PINK1 recruits nuclear-encoded mitochondrial transcripts to the mitochondrial outer membrane. If translation of these transcripts stalls, the no-go decay (NGD) machinery is recruited and then polyubiquitylated, promoting the recruitment of mitophagy machinery to clear the damaged mitochondria. P, phosphorylation; Ub, ubiquitin.

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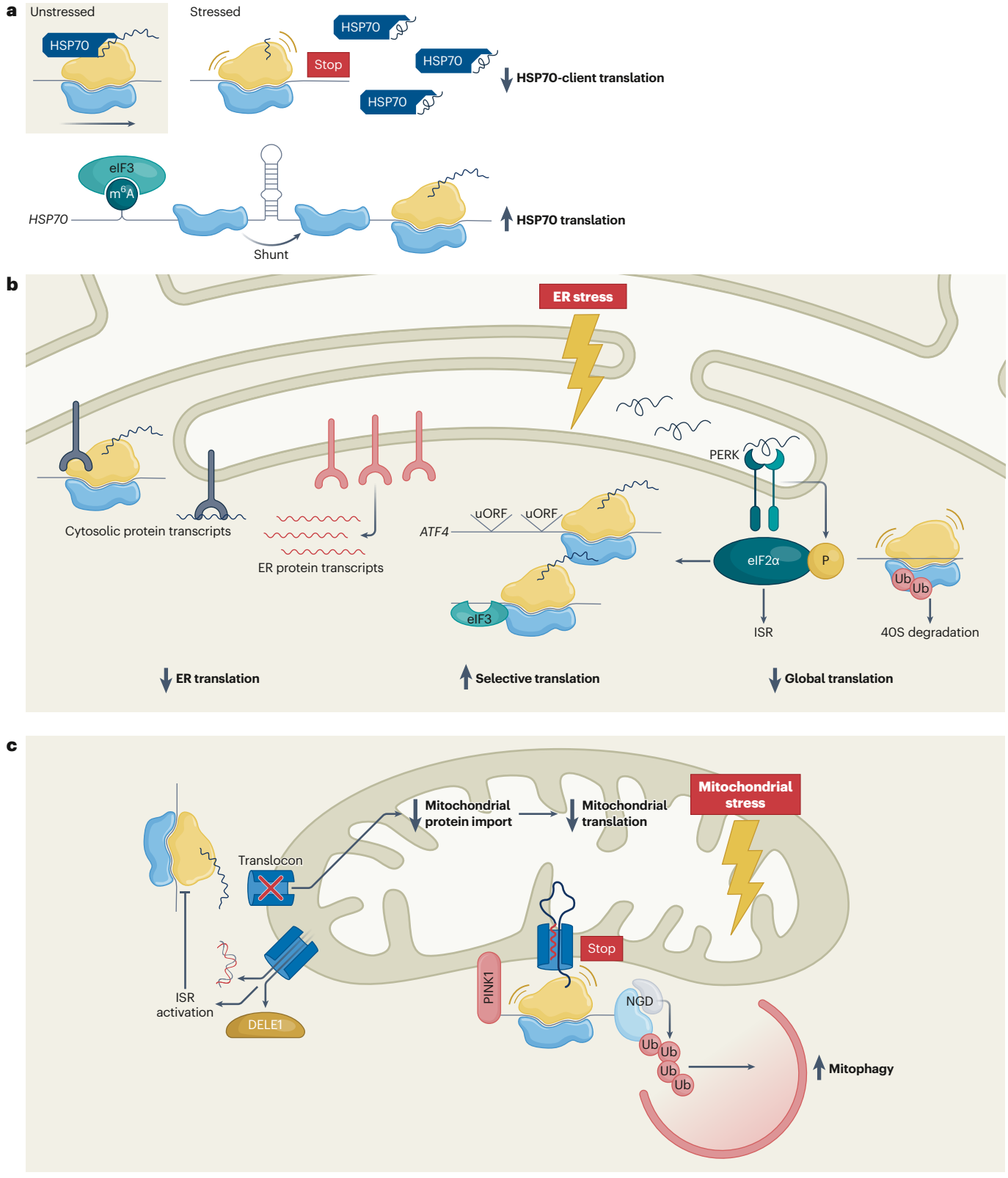
These tolerable rRNA modifications, particularly when present on the ribosome surface, could serve as signals of stress, alerting the cell of ribosome damage without fully abrogating protein synthesis[76]. Ribosomal proteins are frequently oxidized during stress[77], and several oxidized ribosomal proteins have been shown to be selectively removed from the ribosome and exchanged for freshly synthesized copies to repair ribosomal damage in yeast[78]. Oxidative stress may also lead to ribosome remodelling, with evidence of increased cytoplasmic ribosome incorporation for a distinct subset of ribosomal proteins in primary neurons treated with H_2O_2 (ref. 79). These may represent repair of ribosomes from oxidative damage or tuning of ribosome activity to meet the new cellular translational needs under stress.

These translational machinery modifications may underly the translational reprogramming observed during oxidative stress, which



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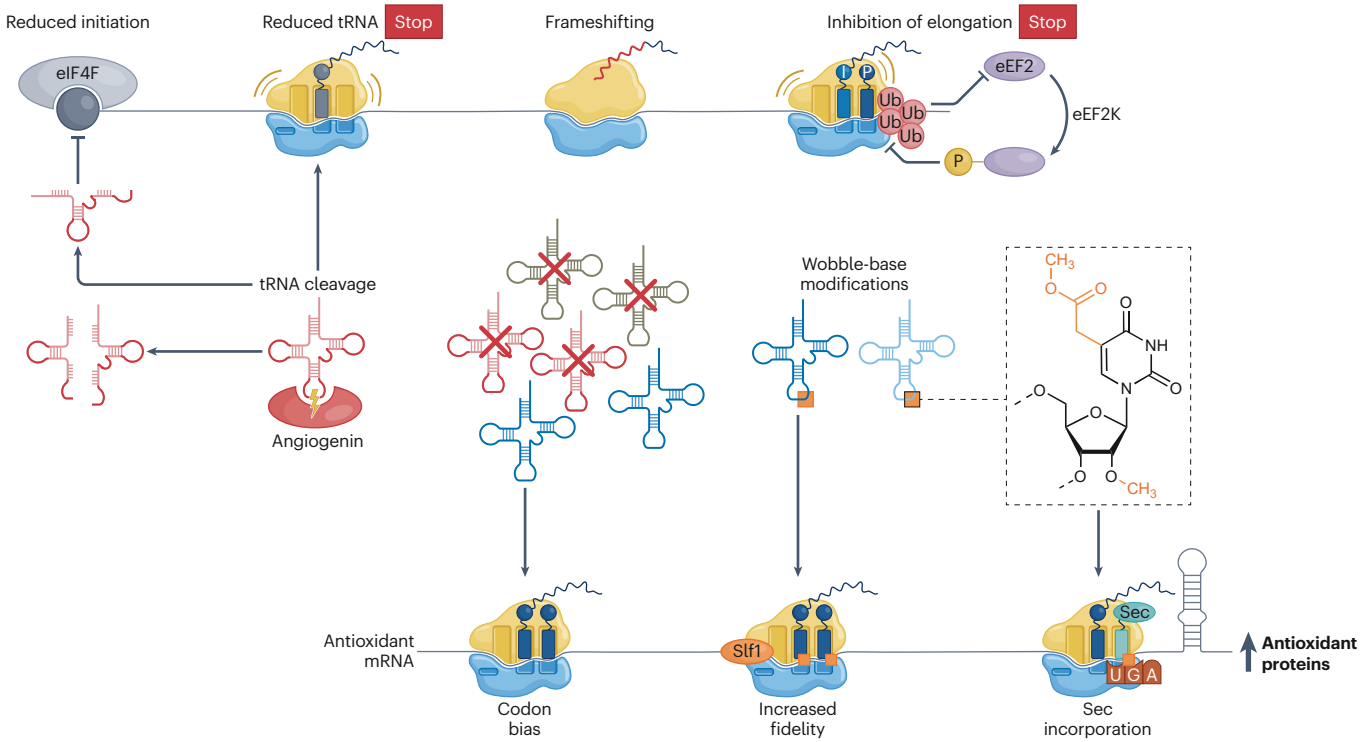

Fig. 2 | Translational response to oxidative stress. Oxidative stress reduces both the quantity and quality of translation via multiple mechanisms including reduced tRNA availability, generation of tRNA fragments that directly inhibit translation machinery and decrease in eEF2 activity due to its phosphorylation by eEF2K and altered interactions with the ribosome. The latter is driven by regulatory K63-linkage polyubiquitylation of ribosomal proteins, stalling the ribosome at specific sequence motifs. Antioxidant proteins are nevertheless synthesized in sufficient levels as they are enriched in codons whose cognate tRNAs are increased under oxidative stress and the recruitment of proteins such as Slf1 that prevent frameshifting when translation stalls. Many antioxidants additionally contain the amino acid selenocysteine (Sec), which can be incorporated at recoded UGA stop codons on mRNA that contains selenocysteine-insertion-sequence elements. The wobble-base tRNA modification that enables this recoding is upregulated by oxidative stress.

includes not just reduced protein synthesis—which is attributed in part to ISR activation and mTOR inhibition[77,80]—but also increased translation initiation within 5′ UTRs, stop codon read-through and frameshifting, suggesting substantial changes to start codon selection and translation fidelity[81] (Fig. 2). In addition, multiple ribosome profiling studies have revealed evidence of inhibited translation elongation, including increased ribosome occupancy at the beginning of ORFs, via several mechanisms[80–82]. The elongation factor eEF2 is phosphorylated in oxidative stress, decreasing its association with the ribosome and thereby slowing translocation[82–84]. During oxidative stress in yeast, the enzyme Rad6 reversibly stalls elongating ribosomes by modifying several ribosomal proteins with K63-linked polyubiquitin chains[85], causing ribosomes to halt at X (any amino acid)-isoleucine-proline motifs[86]. These modified ribosomes have structural changes at the sites of eEF2 binding, suggesting they may compromise eEF2 association or activity[87]. Once the stress has abated, these K63 polyubiquitin moieties are removed by the deubiquitinating enzyme Ubp2, allowing translation rates to recover[88]. Decreases in tRNA abundance have also been observed[89,90] but the levels vary depending on the specific tRNA species, as well as retrograde tRNA transport from the cytoplasm to the nucleus[91]. In mammals oxidative stress activates the endonuclease angiogenin to cleave tRNAs[92]. One reported cleavage event removes the 3′ CCA sequence required for aminoacylation, depleting the functional tRNA pool rapidly yet reversibly, as the CCA sequence can be restored enzymatically[93]. Angiogenin also cleaves tRNA in the anticodon loop to generate 5′ and 3′ tRNA halves, known as tRNA-derived stress-induced small RNAs (tiRNAs)[92]. Both 5′ tiRNA^{Cys} and 5′ tiRNA^{Ala}, which contain a terminal oligoguanine motif, can directly inhibit translation initiation by displacing eIF4F from mRNA[94,95].

Given the suboptimal translational environment created by oxidative stress, cells use several mechanisms to ensure proper translation of antioxidant mRNA (Fig. 2). In yeast, oxidative-stress-response genes are enriched for codons with high corresponding tRNA abundance in stress conditions, improving their translation efficiency[90]. Similarly, oxidative stress increases modifications at the wobble base of several tRNA anticodons, strengthening the affinity of specific codon–anticodon base pairs and increasing the synthesis of stress response proteins enriched for the cognate codons[96–98]. A notable example is the translation of selenoproteins, a set of antioxidant enzymes including glutathione peroxidases and thioredoxin reductases that contain the amino acid selenocysteine. Selenocysteine incorporation requires recoding of a UGA stop codon, demarcated by a selenocysteine-insertion-sequence element on the transcript. Modification of the selenocysteine tRNA^{UGA} wobble base (mcm^{5}U34m) increases following oxidative stress in mammalian cells and is required for efficient selenoprotein production[99,100]. The transcriptional master regulator of the oxidative-stress response NRF2 has also been reported to contain an internal ribosome entry site within its 5′ UTR, promoting translation during stress conditions when cap-dependent translation initiation is inhibited[101–103]. In addition, the yeast protein Slf1 was recently shown to bind to ribosomes stalled on antioxidant genes and prevent frameshifting, thereby increasing productive translation of key stress response proteins[104].

Oxidation is not universally negative, as ROS accumulation during development plays important signalling roles[105,106] and can improve oxidative-stress responses later in life in a process called hormesis[107,108]. Remarkably, targeted reductions in translation fidelity can also serve a beneficial role in oxidative-stress survival. In human cells oxidative stress triggers phosphorylation of methionyl-tRNA synthetase, which increases its misacylation of non-cognate tRNAs and causes a modest

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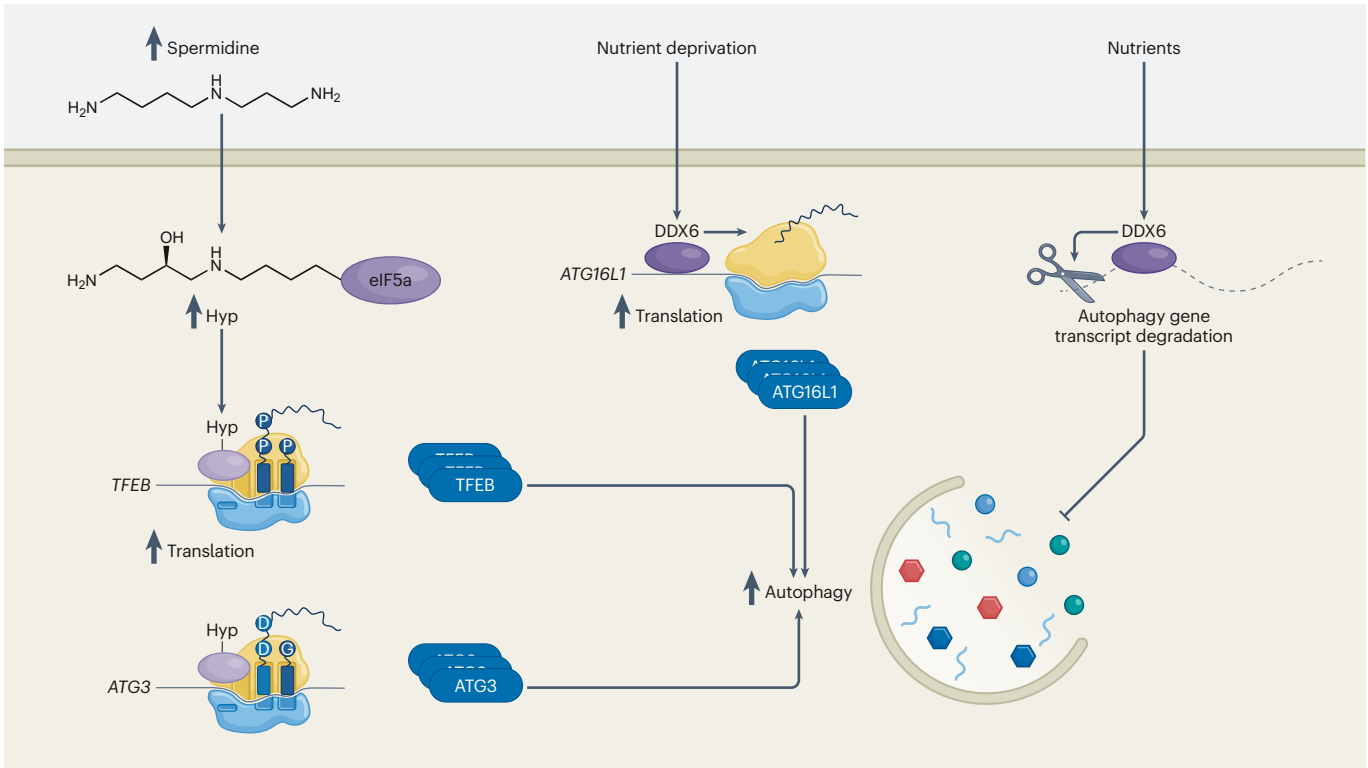

Fig. 3 | Translational regulation of autophagy. Spermidine is required for hypusination of eIF5A; this enables synthesis of autophagy genes, including *TFEB* and *ATG3*, which have tripeptide motifs that rely on hypusinated eIF5A for their efficient translation. Accordingly, spermidine supplementation increases autophagy induction (left). DDX6 additionally regulates autophagy gene expression in a nutrient-dependent manner: under conditions of nutrient deprivation, association of DDX6 with the autophagy gene *ATG16L1* promotes its translation, leading to increased autophagy (centre). In nutrient-replete conditions, DDX6 destabilizes autophagy gene transcripts, thereby inhibiting autophagy induction (right). Hyp, hypusine.

increase in methionine incorporation into the proteome[109]. Although detrimental for long-term viability, this process improves acute stress resistance[109], possibly due to the ability of methionine to serve as a sulfur-dependent ROS scavenger[110]. This suggests that typically harmful stress-induced translation changes can be co-opted for temporary improvement of survival.

Deregulated nutrient sensing and autophagy

Nutrient-sensing signalling networks are core regulators of longevity and reductions in their activity extend lifespan in multiple model organisms[2]. Inhibition of the insulin–IGF-1 signalling pathway, which promotes growth in response to nutrients and hormones, improves stress resistance and longevity through transcriptional regulation[111] and by decreasing translation via mTORC1 inhibition and ISR activation[112,113]. mTOR signalling itself integrates nutrient availability and other growth cues to promote multiple anabolic processes (Box 2). Reductions in amino acids (particularly the direct mTORC1 activators leucine, arginine and glutamine) inhibit mTORC1, leading to global translation repression[114]. Amino acid reductions also activate the ISR via GCN2 (Box 2); interestingly, this can occur through direct monitoring of translation with activation of GCN2 by stalling of elongating ribosomes[115]. In addition to reducing ternary-complex formation, ISR activation under nutrient deprivation can promote the degradation of small ribosomal subunits[116–118]. How individual amino acids change in abundance as organisms age, and whether their supplementation is beneficial or detrimental, varies across model systems and studies (reviewed in ref. 119). However, there are distinct impacts on translational regulation at the cellular level when specific amino acids are lacking. Leucine deprivation inhibits mTORC1 activity more strongly than arginine deprivation in human cell lines, with similar levels of ISR activation at early time points[120,121]. Arginine deprivation accordingly has been shown to permit more translation initiation, leading to exhaustion of the residual cellular pool of arginine-charged tRNAs and ribosome stalling on arginine codons[120]. This in turn further activates the ISR, resulting in a different balance of ISR activation/mTOR inhibition for arginine versus leucine deprivation and potentially enhancing repression of the synthesis of arginine-containing proteins. Whether this selective regulation of arginine-rich proteins is adaptive is unclear but cell viability is lower under arginine deprivation than leucine deprivation[120], which suggests that a stronger reduction in mTORC1 activity is preferable under these culture conditions. Interestingly, ribosome stalling on arginine codons increases with age in both yeast and *C. elegans* but whether this is due to decreased amino acid abundance has yet to be determined[122].

Several amino acid-derived metabolites also directly regulate translation in the context of ageing. Taurine (2-aminoethanesulfonic acid) can be synthesized from cysteine in mammalian cells or obtained from dietary sources. It has been shown that taurine levels decrease with age and taurine supplementation can improve healthspan[123]. Taurine is imported into mitochondria to produce the 5-taurinomethyluridine modification on the wobble base of mitochondrial tRNA, which promotes accurate decoding by stabilizing codon–anticodon base pairing[124]. Taurine supplementation was found to increase expression of the mitochondrially encoded electron transport chain component ND6 and the taurine-induced improvement of *C. elegans* health could be eliminated by treatment with the mitochondrial drug rotenone, suggesting that taurine's function in mitochondrial translation may contribute to its health benefits[123]. Another metabolite, spermidine, is a polyamine derived from arginine or methionine that is required for hypusination, a unique post-translational modification found on eIF5A (Fig. 3). Hypusination stabilizes the association of eIF5A with the ribosome and is necessary for eIF5A activity[125], with the hypusine modification itself inserted into the ribosomal P site, potentially contacting

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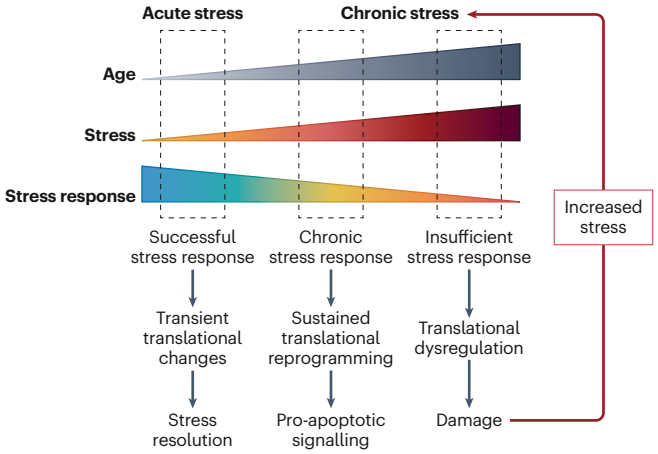

Fig. 4 | Stress responsiveness in ageing. Young organisms are capable of successfully mounting stress responses, allowing the stress to be resolved. Old organisms lose their ability to activate stress response pathways effectively, leading to chronic stress. Sustained stress-response-pathway signalling without stress resolution can activate pro-apoptotic pathways. Inability to activate protective cellular programmes leads to damage, which further increases the stress experienced by the cell, creating a positive-feedback loop of increasing stress and damage. All of these scenarios are accompanied by changes in translation but the causes and consequences—from regulated protein synthesis reduction to faltering translation machinery due to cellular damage—differ.

the tRNA[126,127]. Although eIF5A expression has been reported to remain stable with age, spermidine levels and eIF5A hypusination decrease[128], and spermidine dietary supplementation can increase eIF5A hypusination[128] and extend lifespan in multiple model systems[129,130]. Accordingly, the translation efficiency of proteins that especially rely on eIF5A activity for their synthesis, such as those with polyproline tracts[131], is likely to be reduced with age.

Intriguingly, several transcripts that depend on eIF5A for their translation are regulators of autophagy (Fig. 3). TFEB, a transcriptional master regulator of lysosome biogenesis and autophagy, contains two tri-proline motifs and was shown to rely on hypusinated eIF5A for its translation[132]. Reduced spermidine and corresponding eIF5A hypusination levels in B cells from aged mice lead to decreased TFEB translation, inhibiting autophagy; spermidine supplementation restores eIF5A hypusination and TFEB protein expression, thereby improving B cell function[132]. Knockdown of eIF5A in cell culture also inhibits autophagy and leads to decreased protein synthesis of several autophagy-related genes[133]. One of these genes, *ATG3*, was found to have a DDG stalling motif[131] that rendered its translation sensitive to hypusinated eIF5A levels. Accordingly, age-dependent reductions in eIF5A hypusination may underly the decrease in autophagy that are a hallmark of ageing[2]. Notably, this spermidine–eIF5A hypusination–autophagy axis has been proposed to underly the health benefits of dietary restriction: spermidine levels and hypusination of eIF5A increase in multiple model systems following fasting, and inhibition of spermidine synthesis or eIF5A modification reduce autophagic flux and prevent the lifespan extension and cardioprotective effects associated with dietary restriction[134]. In addition, other autophagy genes have been shown to be translationally regulated by RNA-binding proteins that recognize UTR elements, including Pub1 (TIA1 in mammals)-mediated regulation of Atg1 (ULK1 in mammals)[135]; regulation of Atg6 (Beclin in mammals)[136], ATG5, ATG12 and ATG16 by HuR[137]; and regulation of ATG5 by HuD[138]. A striking example is the bidirectional regulation by the DEAD box RNA helicase DDX6 (Dhh1 in yeast): under nutrient-replete conditions, DDX6 promotes the degradation of multiple autophagy gene transcripts; however, following nutrient deprivation, DDX6 enhances the translation of Atg1 and Atg13 in yeast as well as ATG16L1 in human cells[139,140]. This reveals an extensive network of translational regulation that tunes expression of the autophagy machinery in response to nutrient availability.

Translation in ageing

How does translation under stress compare with translation in ageing? Loss of proteostasis, oxidative stress and deregulated nutrient sensing are all faced by ageing organisms and accordingly their cells may enact the translational responses discussed earlier. However, stress-response-pathway activation diminishes with age, and organismal and cellular models of ageing often benefit from genetically or drug-induced forced stimulation of these pathways[2]. This suggests that a common feature of ageing is the experience of chronic stress accompanied by the inability to adequately respond (Fig. 4).

Global translation has been shown to decrease with age in many model systems[141] but the extent to which this is due to successful stress response implementation versus uncontrolled oxidative damage or protein misfolding remains unclear. ISR activation seems to increase with age across multiple model systems[37]; however, some studies have reported a switch from adaptive to pro-apoptotic ISR signalling with age, which can result in a decline in eIF2α phosphorylation due to induction of the GADD34 phosphatase[39]. Increased mTOR signalling is associated with ageing pathologies and inversely correlated with lifespan but the reported changes in mTOR signalling in healthy ageing have been mixed, possibly due to different measurement techniques[142]. It nonetheless seems probable that even if an increase in mTORC1 activity is not a universal driver of ageing, its levels may be optimized for increased growth and proliferation during development and are thus higher than optimal later in life[114,143]. Notably, decreased expression of the translation machinery is associated with ageing and this has been attributed in part to decreased translation of 5′ terminal oligopyrimidine-containing transcripts consistent with mTOR inhibition[144]. There are also reports of altered translation component stoichiometry at the whole-cell proteomics level[54], which is suggestive of dysregulated, rather than concerted, control of expression, although it is possible that some of these effects may be buffered at the level of mature assembled ribosomes[145].

Similarly to stress conditions, translation elongation rates decrease with age across mouse tissues[146]; although this may be expected to increase translation fidelity[147], it may also impact the kinetics of co-translational protein folding, which could add further proteotoxic strain[148]. Translation fidelity may indeed even decrease with age, possibly due to oxidative damage, as has been shown for increased stop codon read-through in aged mouse brain regions[149]. With age, chaperone release from the ribosome increases, a phenomenon also observed during proteotoxic stress[150]. However, the locations of ribosome stalling events seem to differ between ageing and stress: age-associated ribosome pause sites are not enriched at specific regions of the ORF but are specific for certain amino acid motifs, particularly lysine, arginine and proline[122]. As these sequences are considered difficult to synthesize under normal growth conditions[122,151], this suggests that aged translation machinery may be functionally compromised and therefore unable to overcome previously surmountable obstacles. Age-associated eIF5A hypusination loss may be responsible, especially for stalling at proline codons, but other translation machinery modifications, such as stoichiometric changes or oxidative damage, may also contribute. This suggests that although certain overarching trends of translational changes are shared across stress and ageing, such as decreased translation elongation, the specific mechanisms may differ.

Are these changes in translation an adaptive response to, or a detrimental consequence of, the stresses of ageing? The increase in longevity observed following mutations or drug treatments that decrease protein synthesis suggests this process is beneficial[7]. In fact, sequestration of translation initiation factors in processing bodies, which increases with both stress and ageing, has been shown to not

only lower protein synthesis rates but also promote stress resistance and longevity[152]. However, a decrease in translation can also be an early indicator of neurodegenerative disease[153], and interventions such as ISR inhibition that are likely to increase protein synthesis have shown benefits[33]. Clearly a balance must be struck; reducing the proteostatic burden of the cell is advantageous but chronic overactivation of the pathways that enable this can become toxic[4,154]. In addition, given that proteostasis-machinery components are themselves prone to aggregation, decreased translation may be a symptom of a runaway feedback cycle of proteostasis collapse: aggregates begin to sequester proteostasis components including ribosomal and proteasomal subunits, altering the stoichiometries of those complexes and impairing their function, leading to further proteotoxic stress[155]. Context may matter as different cell types have distinct translation requirements and accordingly different levels of either benefits or harm from stress-response-pathway activation. Cell non-autonomous effects may also be present that require optimal levels of translation not just in a cell but also in its neighbours or even distal tissues for organismal health. These features also may have different impacts on organismal health depending on their timing; it is possible that decreased translation is initially beneficial but can become maladaptive over time.

Conclusions

The past decade has seen remarkable strides in defining the post-transcriptional mechanisms that underly the cellular responses to stress and in carefully delineating the precise changes in protein synthesis at the global and gene-specific scales. From measurements of overall synthesis rates via metabolic labelling to assessment of translation kinetics on individual transcripts via ribosome profiling, our understanding of how cells use translation to sense and respond to diverse stressors has expanded. Increasingly, these techniques are being used to elucidate the molecular pathologies of ageing and yield new insights into the role of translation in proteostasis management and longevity regulation. This enables more nuanced comparisons of stressed and aged states, looking beyond broad phenotypes such as reduced translation, a shared feature of acute and chronic stress, to the underlying molecular causes and consequences, which may differ (Fig. 4). A limitation of our current understanding is the reliance on in vitro models as most molecular studies of translation under stress are performed in isolated cell culture systems instead of intact multicellular organisms. In addition, in vitro studies are necessarily more acute and often focus on a single source of stress, unlike the hyper-chronic and hyper-integrated stress experienced during organismal ageing. Conversely, ageing studies in animal models often use large swaths of tissue or even whole organisms as their experimental inputs, losing cell-type resolution. It is time to increase the complexity and to explore whether different cell types have unique stress sensitivities and translational responses, whether these translation alterations occur concertedly across tissues or if there is a cascading response through the organism and whether communication of stress-induced translational changes across tissues might orchestrate organism-wide adaptive responses. Advancements in single-cell technologies will aid this endeavour, particularly as improved low-input ribosome profiling protocols become available[156–158]. In situ translation measurement will also be invaluable, with the potential for spatial resolution both subcellularly and in intact tissue emerging from exciting progress in cryo-electron tomography, enabling visualization of ribosome structure and translational state[159–161], and the development of multiplexed imaging tools for mRNA translation efficiency quantification[162]. Finally, coupling these methods with proteomics approaches to measure protein synthesis fidelity[163] will further link translational changes to the quality of the final protein product. As our understanding of how the cell mitigates and responds to stress improves, we will be better able to apply these lessons to ageing, allowing us to more confidently determine what is a cause versus a consequence of ageing pathologies and thereby develop more targeted therapeutic interventions to improve healthy ageing.

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Competing interests

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