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Review

A Ribosomal Perspective on Proteostasis and Aging

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As the first and most direct process influencing the proteostasis capacity of a cell, regulation of translation influences lifespan across taxa. Here we highlight some of the newly discovered means by which translational regulation affects cellular proteostasis, with a focus on mechanisms that may ultimately impinge upon the aging process.

Introduction

In response to stress, cells rely on a highly conserved network of mechanisms to protect the proteome from damage. The ability of cells to maintain proteostasis in the face of intrinsic cellular and environmental insults that accumulate over time is a major determinant of lifespan. The expansive proteostasis network functions on many levels to maintain a healthy proteome (Wolff et al., 2014), but for individual proteins, life begins on the ribosome.

Ribosomes are tasked with the critical process of building proteins from amino acids. This job is no small feat; transcripts from all three RNA polymerases and over 200 accessory proteins are required to bring the machinery together. Altogether, the synthesis of a typical protein consumes the amount of energy stored in several thousand molecules of ATP (Lane and Martin, 2010). Considering that there can be upward of a billion protein molecules per cell, the amount of energy and coordination devoted to this process is staggering. It is not surprising, therefore, that evolution has generated a multitude of mechanisms for regulating the process of protein synthesis (Hinnebusch and Lorsch, 2012).

Translation is the first and most direct process influencing the proteostasis capacity of a cell; consistently, its regulation influences lifespan in multiple model organisms (Kennedy and Kaeberlein, 2009). Due in large part to advancements in technology, exciting new research has uncovered layers of translational regulation that have escaped decades of intense research. Here we highlight some of the newly discovered means by which translational regulation affects cellular proteostasis, with a focus on mechanisms that may ultimately impinge upon the aging process.

Protein Synthesis Affects Lifespan

In the last decade, researchers have established that mutation or depletion of translational machinery can impact the lifespan of evolutionary disparate organisms. In yeast, worms, and flies, mutation or depletion of many ribosomal proteins or translation factors can significantly extend lifespan (Curran and Ruvkun, 2007; Hansen et al., 2007; Kaeberlein et al., 2005; Kapahi et al., 2004; Pan et al., 2007; Rogers et al., 2011; Steffen et al., 2008; Syntichaki et al., 2007; Tohyama et al., 2008; Zid et al., 2009). These factors do have limitations; for example, the intervention must occur post-development to confer beneficial effects on lifespan. While the exact functions of these factors are quite diverse, their mutation or depletion appears to commonly result in globally decreased translation and altered translation of specific mRNAs. Further bolstering the evolutionary conservation of reduced or altered translation in modulating lifespan across taxa, epistasis analyses suggest that these interventions may act downstream of the highly conserved, nutrient-responsive target of rapamycin (TOR) signaling pathway (Johnson et al., 2013). Consistently, the TOR inhibitor rapamycin results in lifespan extension in mice, as does mutation of the TOR substrate ribosomal protein S6 kinase (S6K) (Harrison et al., 2009; Selman et al., 2009).

While the lifespan-extending mechanisms invoked by interventions that alter the translation machinery are not fully understood, two outcomes that are common among them, namely, decreased global translation and enhanced translation of specific mRNAs, are features shared with ancient evolutionarily conserved stress response pathways. Researchers have postulated that either, or a combination of both, of these processes could be the major determinant of lifespan extension. In support of the former, several theories have been proposed, including that reducing global translation would limit hyperfunction—the activity of processes that were useful in youth but become detrimental during aging (Gems and Partridge, 2013). Several studies have provided evidence of the latter, in which particular mRNAs required for lifespan extension exhibit increased translation, despite the global reduction in protein synthesis. Among these genes are stress response factors (Rogers et al., 2011), mitochondrial components (Zid et al., 2009), and the highly conserved transcription factor *ATF4* or its ortholog, *GCN4* (Li et al., 2014; Steffen et al., 2008). ATF4 is best known for its role as a canonical translationally regulated gene involved in the integrated stress response (ISR).

Ancient Stress Response Pathways Modulate Lifespan

The point at which translational control has been best understood is initiation, the first and most complex phase of protein synthesis. In order to initiate translation of an mRNA, eIF4F, which is composed of the eIF4G scaffold protein, the helicase eIF4A, and eIF4E, which is responsible for recognizing the 7-methyl guanosine 5′ cap structure on the mRNA, recruits the 43S pre-initiation complex. The 43S pre-initiation complex, itself consisting of the 40S ribosomal subunit, a ternary complex of

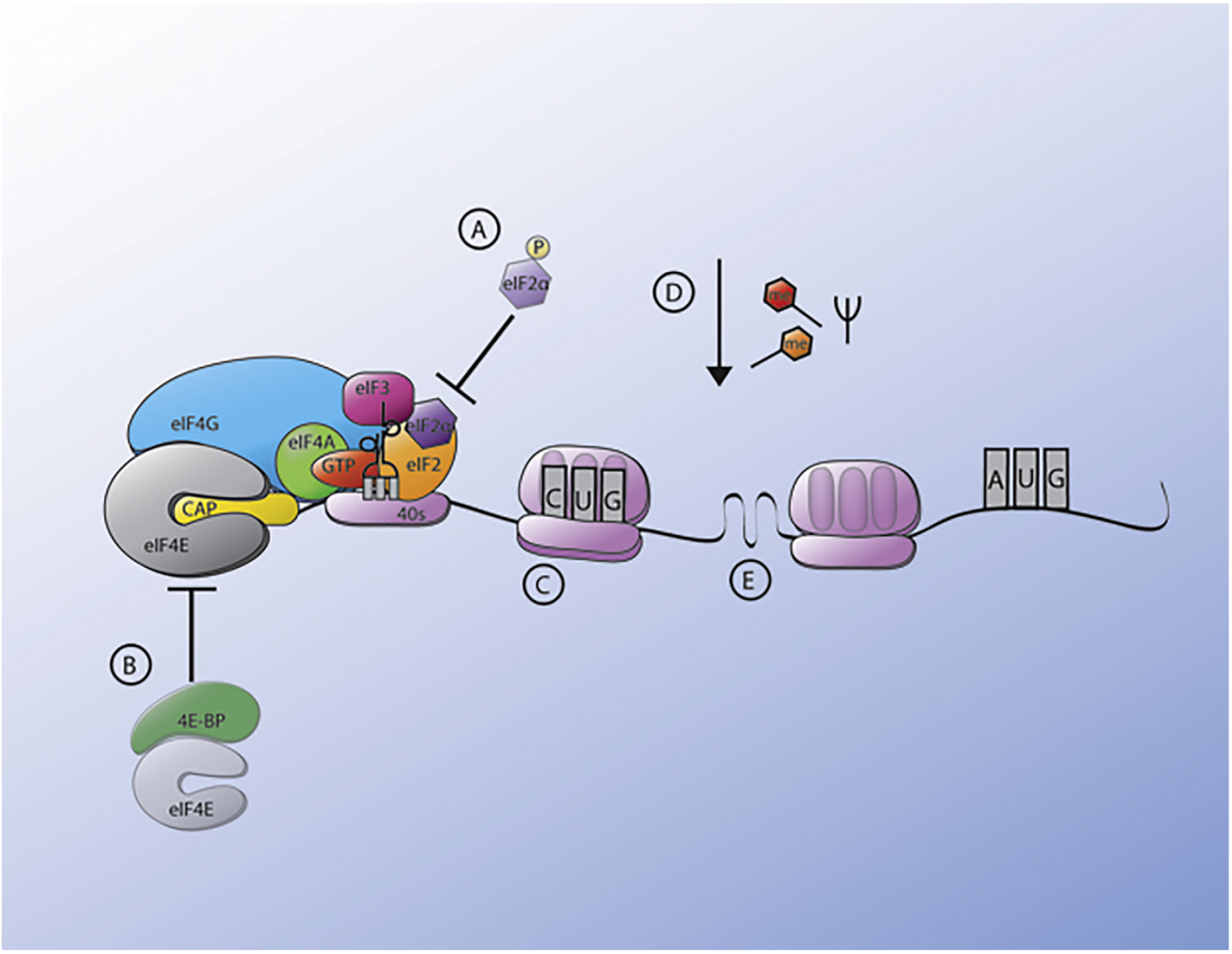

Figure 1. Conserved Stress Response Pathways Alter Translation Initiation in Ways that May Influence Longevity
(A and B) eIF2α phosphorylation (A) or 4E-BP activation (B) inhibit cap-dependent translation initiation.
(C) Stress alters the ratio of translation initiation events at AUG to non-AUG codons.
(D) Stress influences the methylation or pseudouridylation (Ψ) of mRNA, leading to altered translation efficiency.
(E) Stress allows more frequent translation initiation at non-canonical sites, including uORFs, internal ribosome entry sites (IRESs), or translation-enhancing elements.

GTP, a methionine loaded initiator tRNA, and eIF2, scans along the 5′ untranslated region (5′ UTR) of a message to find the initiating AUG, where the 60S subunit joins to form the 80S ribosome. Such a complex process presents a plethora of opportunity for regulation. Two well-studied events that control translation initiation are phosphorylation of the alpha subunit of eIF2 (eIF2α) and inhibition of eIF4F via the activity of the eIF4E binding protein (4E-BP), a substrate of TOR (Figure 1).

When faced with a variety of distinct stresses, cells cope by invoking the ISR (Harding et al., 2003; Wek et al., 2006). The ISR is initiated by activation of one of four stress-specific protein kinases that phosphorylate Serine51 of eIF2α, which effectively inhibits ternary complex formation, thereby globally repressing eIF2-dependent mRNA translation (Figure 1). Importantly, a subset of messages escapes this repression, and key messages are actually translated better under these conditions. The transcription factor *ATF4* is the best known of these messages; its 5′ leader sequence encodes upstream open reading frames (uORFs) that inhibit translation of the *ATF4* coding sequence during normal conditions when eIF2α is active. Upon phosphorylation of eIF2α, the *ATF4* message becomes translated, resulting in transcriptional activation of ATF4 target genes that promote recovery from stress (Lu et al., 2004; Vattem and Wek, 2004).

Interestingly, enhanced translation of *ATF4* is a common feature of multiple lifespan extension paradigms in mammals. Calorically restricted or methionine-restricted mice that exhibit lifespan extension upregulate the translation of *ATF4*, as do mice treated with rapamycin (Li et al., 2014). Consistently, Gcn4, an ortholog of ATF4, modulates yeast lifespan extension (Steffen et al., 2008).

A second conserved mechanism to regulate translation is via activation of 4E-BP (Figure 1). During nutrient-replete conditions, TOR phosphorylates 4E-BP, but inhibition of TOR causes 4E-BP hypophosphorylation, allowing it to bind and sequester eIF4E,

broadly limiting cap-dependent translation. In a manner reminiscent of the ISR, particular mRNAs are capable of escaping this translational repression. 4E-BP is activated during dietary restriction in *Drosophila*; under these conditions, translation of particular messages encoding mitochondrial components is enhanced, a phenomenon that is key to lifespan extension (Zid et al., 2009). In *C. elegans*, RNAi knockdown or mutation of eIF4E extends lifespan, as do other mutations that limit cap-dependent translation initiation (Hansen et al., 2007; Pan et al., 2007; Rogers et al., 2011; Syntichaki et al., 2007; Tohyama et al., 2008). Furthermore, enhanced 4E-BP1 activity in skeletal muscles protects mice from age-associated metabolic dysfunction, supporting the role for evolutionary conservation of 4E-BP activity in ameliorating age-associated phenotypes (Tsai et al., 2015).

These data suggest that interventions that alter translation may alleviate the chronic stress of aging by manipulating cells to activate ancient mechanisms evolved to tolerate stress, thereby extending lifespan. Indeed, stress response pathways are commonly intertwined with those that regulate proteostasis and aging, and researchers have been remarkably successful at taking advantage of the beneficial effects of activating these pathways to positively influence lifespan (Epel and Lithgow, 2014).

Regulated Non-canonical Translation Initiation

Before protein synthesis begins, the translation machinery must be recruited to the mRNA it is meant to translate. For a vast majority of messages, this is accomplished via the cap-dependent mechanism described above. However, some mRNAs can be translated independently of the cap structure, and this happens more frequently during times of stress. Many of these instances depend on internal ribosome entry sites (IRESs), complex secondary structures within 5′ UTRs that can directly recruit ribosomes. More generally defined cap-independent, translation-enhancing elements may be quite common in the human genome, as an in vitro screen has identified over 12,000 such instances, 12 of which function as human IRES sequences (Wellensiek et al., 2013).

Mounting evidence suggests that translation outside annotated coding regions, particularly within 5′ leader sequences of mRNAs, occurs at much higher rates than previously thought (Ingolia et al., 2011; Lee et al., 2012). Surprisingly, more than half of initiation events may occur on ribosomes occupying non-AUG codons (most often at the near-cognate CUG codon), having obvious implications for the diversity of protein coding potential in the genome (Gao et al., 2015; Ingolia et al., 2011; Lee et al., 2012). Importantly, the use of non-AUG start sites is regulated in response to nutritional stress; upon amino acid depletion or expression of a phosphor-mimetic of eIF2α, hundreds of genes exhibit altered ratios of translation initiation at non-AUG codons as compared to canonical AUGs (Gao et al., 2015) (Figure 1). Such a phenomenon occurs in vivo as well, as liver homogenates isolated from mice fasted overnight also exhibit altered frequency of initiation at non-AUG codons (Gao et al., 2015).

Consistent with these findings, translation occurring within 5′ leader sequences appears to be a common feature of mRNAs that are capable of escaping ISR-dependent global repression of translation (Andreev et al., 2015). By mechanisms similar to that of the *ATF4* message, upstream translation appears to limit translation of canonical coding sequences during normal conditions. Using a clever approach that takes advantage of the ability of T cells to detect small peptides, previously uncharacterized peptides resulting from translation of uORFs have been identified (Starck et al., 2016). Interestingly, it appears that several of the uORFs present in the many chaperone-encoding messages that escape stress-induced translational repression may generate major histocompatibility complex class I peptides active in adaptive immunity (Starck et al., 2016).

Finally, another activity that can influence the initiation of translation is association of microRNAs (miRNAs), which form the RNA-induced silencing complex (RISC) with additional effector factors, and act to repress translation of target messages by multiple mechanisms (Fabian and Sonenberg, 2012). Biochemical studies in both *Drosophila* and human cells support a "pure" translational repression mechanism involving disruption of the eIF4F complex by inducing dissociation of eIF4A (Fukao et al., 2014; Fukaya et al., 2014). Numerous miRNAs display age-associated alterations in expression, and the activities of many miRNAs have been shown to modulate aging (Smith-Vikos and Slack, 2012).

Chemical Modifications of mRNA Influence Translation

Chemical modifications have been identified on each of the RNA bases, and while tRNAs and rRNAs are generally more decorated with modifications than mRNA, recent large-scale studies have uncovered important functional roles for chemical modifications of mRNA bases in influencing translation (Figure 1). The most common mRNA modification is N6-methyladenine (m^6A), which shows widespread and dynamic distribution that can be influenced by diverse cellular stresses, including heat, ultraviolet radiation, and exposure to interferon-γ (Dominissini et al., 2012; Meyer et al., 2012, 2015). Using classical biochemistry coupled with high-throughput sequencing approaches, a stress-responsive mechanism whereby m^6A modification of bases in 5′ leader sequences promotes cap-independent translation of mRNAs has been uncovered (Meyer et al., 2015).

Newly developed sequencing approaches have also identified a role for methylation of the N1 position of adenine (m^1A) in influencing mRNA translation (Dominissini et al., 2016). This modification appears to occur at adenine residues very close to translation initiation start sites, and its correlation with protein production is consistent with a role in promoting translation. Importantly, m^1A is highly dynamic in response to nutritional cues, including amino acid and glucose starvation (Dominissini et al., 2016).

In yet another example of the power of novel high-throughput sequencing approaches for studying RNA modifications, recent studies have uncovered a regulated role for pseudouridine (Ψ) modification of mRNA in response to environmental cues such as nutrient deprivation in cells as well as in mammalian tissues (Carlile et al., 2014; Li et al., 2015; Schwartz et al., 2014). Although the functional consequences of naturally occurring Ψ-modification in mRNA are yet to be determined, artificial pseudouridylation of mRNA has the ability to alter the genetic code by allowing non-canonical base pairing in the decoding center of the ribosome (Fernández et al., 2013; Karijolich and

Yu, 2011), revealing the potentially dramatic impact this modification could have on proteostasis.

Regulatory Roles for tRNA

The process of translation requires accurate and efficient delivery of amino acids to the A-site of the translating ribosome. This responsibility, effectively bridging the worlds of nucleic acids and amino acids, is the job of tRNA. Despite there being only 64 possible codons and 20 amino acids, most organisms, including humans, encode hundreds of tRNA genes (506 in hg19 human genome) (Chan and Lowe, 2009), and the information encoded in the genome is only a fraction of what mature tRNAs possess, as tRNAs exhibit the most numerous and chemically diverse modifications of all nucleic acids.

The functional consequences of tRNA modifications are most apparent when the modification occurs on bases within the anticodon. For example, 5-methylcytosine (m^5C) is a common modification on tRNAs, but only in leucine $tRNA^{CAA}$ does it occur at the anticodon wobble position (Chan et al., 2010). m^5C modification of this tRNA, which occurs in response to oxidative stress, results in the preferential translation of mRNAs enriched for UUG relative to the wobble codon. Interestingly, several individual UUG-enriched ribosomal protein genes, but not their paralogs, are among the set of genes preferentially translated during oxidative stress (Chan et al., 2012).

The wobble anticodon position 34 is frequently enriched for chemical modifications that enhance codon binding in vitro (Agris et al., 2007). In fact, U34 is almost always modified (Grosjean et al., 2010), and when U34 modifications are inhibited, codon-specific ribosome pausing is observed (Nedialkova and Leidel, 2015; Zinshteyn and Gilbert, 2013). Such codon-specific pausing illustrates the fact that the pool of functional tRNAs can dictate the kinetics of codon-specific translation. Local ribosome elongation rate is thought to be important to support folding of the nascent polypeptide (Pechmann and Frydman, 2013); consistently, protein aggregation results from limiting U34 modifications (Nedialkova and Leidel, 2015).

As the pool of functional tRNAs can dictate the efficiency with which translation occurs, cell types whose transcriptomes differ markedly express a similarly altered pool of tRNA; specifically, there appears to be a pool of tRNAs that are induced in differentiated cells that is distinct from the tRNA pool expressed in proliferative cells (Gingold et al., 2014). Interestingly, the matching of a tRNA anticodon supply to the mRNA codon demand also extends to developmental programs, at least in embryonic development of mice (Schmitt et al., 2014). Another way to alter the pool of available tRNAs is by inducing their endonucleolytic cleavage, which occurs under oxidative stress conditions (Thompson and Parker, 2009). tRNA cleavage events give rise to small RNA species that may function as secondary stress signals (Saikia and Hatzoglou, 2015).

Perhaps the most obvious process affected by tRNAs is building the nascent polypeptide chain. Fidelity of this process depends on the ability of aminoacyl tRNA synthetases to accurately charge tRNAs, a process that can go awry during stressful conditions. Misacylation of methionine tRNAs occurs at about ten times the normal frequency when cells are faced with innate immune or oxidative stress (Netzer et al., 2009). Interestingly, translational fidelity assays reflecting accurate charging of tRNAs, as well as the subsequent steps, indicate that fidelity is increased in fibroblasts isolated from the long-lived naked mole rat relative to those from laboratory mice (Azpurua et al., 2013). In a similar assay, translational fidelity was inversely correlated with TOR activity in a model where TOR repression reduces translation elongation rates, a process mediated by S6K and resulting in enhanced accuracy of translation (Conn and Qian, 2013).

Translational Regulation Post-initiation

Using pulse-chase experiments to determine the kinetics of protein synthesis of a single gene three decades ago, researchers estimated that translation occurred at a rate of six amino acids per second (Boström et al., 1986). More recently, genome-wide ribosome profiling data were used to make the same estimate, which yielded a remarkably similar result: 5.6 amino acids per second (Ingolia et al., 2011). However, alterations in the rate of global protein synthesis have been observed; for example, diminished expression of *FMR1*, the gene encoding fragile X syndrome-associated FMRP, binds RNA and represses translation; the resulting increase in polypeptide elongation rate is critical to the disease phenotype (Darnell et al., 2011; Feng et al., 1997; Udagawa et al., 2013). Interestingly, estimated rates of phenylalanyl-tRNA binding to ribosomes in poly(U)-translating cell-free extracts from aged organisms led to the conclusion that the rate of protein elongation declines up to 80% during aging (Rattan, 1996). Consistently, in vivo studies have reported up to a 2-fold decrease in elongation rate in aged rat tissues relative to youthful counterparts (Khasigov and Nikolaev AYa, 1987; Merry and Holehan, 1991).

In cells, protein damage accumulates with age and is linked to many age-associated pathologies, such as Parkinson's and Alzheimer's diseases. As proteins are being synthesized on the ribosome, Hsp70 molecular chaperones are present to guide proper folding of the nascent chain (Beckmann et al., 1990; Frydman, 2001; Nelson et al., 1992). Recent data suggest that under conditions of proteotoxic stress, the ribosome-associated Hsp70 chaperone can be sequestered to aid in protein folding away from the ribosome, causing elongating ribosomes to stall (Liu et al., 2013; Shalgi et al., 2013). The proposed model implies that ribosome-associated Hsp70 will abandon its post to preferentially associate with clients elsewhere, suggesting that ribosome-associated Hsp70 could be affected by the accumulation of misfolded proteins in aged cells (Figure 2).

A recently discovered quality control mechanism is capable of recognizing ribosomes that stall during translation, directing their disassociation and recycling, as well as removal of the associated truncated polypeptide (Brandman and Hegde, 2016). The ribosome quality control (RQC) complex, which includes a highly conserved E3 ubiquitin ligase, listerin (Ltn1 in yeast), targets the aberrant polypeptide for clearance (Brandman et al., 2012; Defenouillère et al., 2013). Rqc2, a key component of the RQC complex, can uniquely catalyze the addition of a C-terminal stretch of alanine and threonine residues (CAT tail) onto truncated polypeptides associated with stalled ribosomes (Shen et al., 2015), conferring their potential to form aggregates, which may be important for the activation of a distinct ribosomal stress response (Yonashiro et al., 2016). Perturbation of listerin has been linked to neurodegeneration in mice (Chu et al., 2009),

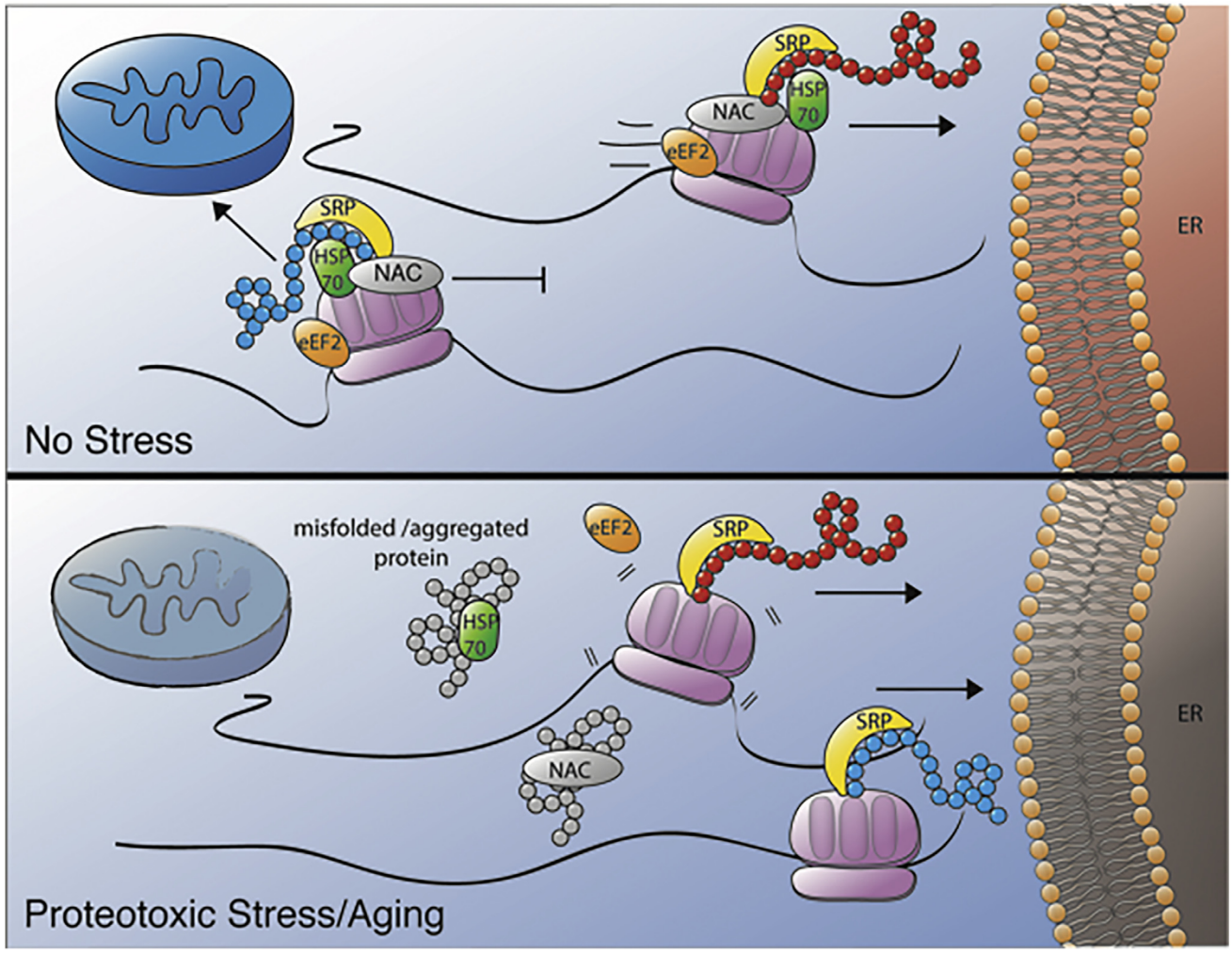

Figure 2. Translational Regulation Post-initiation
Under conditions of proteotoxic stress, the normally ribosome-associated Hsp70 (top panel) instead associates with cytosolic misfolded proteins, resulting in ribosome stalling (bottom panel). Under normal conditions (top panel), NAC inhibits non-secretory mitochondrial proteins (blue chain) from being sorted to the ER, to which ER proteins (red chain) are properly directed. When NAC is depleted, SRP targets both mitochondrial and ER proteins to the ER, resulting in ER and mitochondrial stress (bottom panel). During aging or proteotoxic stress, NAC associates with aggregated proteins (gray disordered chain, bottom panel). The translation elongation factor eEF2 is repressed during stress, resulting in disassociation from ribosomes (bottom panel).

highlighting the importance of future work to understand the relevance of this pathway to aging biology.

Several other highly conserved protein complexes associate with translating ribosomes and their emerging polypeptides, including the nascent polypeptide-associated complex (NAC) and the signal recognition particle (SRP) (Figure 2). SRP has long been known for its role in sorting secretory proteins to the ER; it binds hydrophobic signal sequences on nascent polypeptides as they emerge from the ribosome, then delivers the translating complex to the Sec61 import translocon at the endoplasmic reticulum (ER) membrane (Siegel and Walter, 1988). Mounting evidence now supports a similar role for NAC in coordinating proper localization of newly synthesized proteins by ensuring the exclusion of non-secretory cargo from associating with the Sec61 translocon (Wiedmann et al., 1994; Gamerdinger et al., 2015) (Figure 2). When NAC is depleted, many non-secretory cargo proteins are mistargeted to the ER; mitochondrial proteins were particularly sensitive to this mistargeting. Under these conditions, proteostasis of both the ER and the mitochondria collapses and lifespan is severely limited (Gamerdinger et al., 2015). Interestingly, in *C. elegans*, both the alpha and beta subunits of NAC become insoluble and instead associate with protein aggregates during aging (Kirstein-Miles et al., 2013) (Figure 2). Together, these data imply that age-induced depletion of NAC at the ribosome may result in mislocalization of mitochondrial proteins to the ER.

Importantly, both the ER and the mitochondria have distinct organellar proteomes that are essential to maintaining the function of these structures. Proximity-specific ribosome profiling has highlighted localized protein synthesis as an important mechanism for ensuring that proteins associated with these structures are present at the site they are needed (Jan et al., 2014; Williams et al., 2014). Both the ER and mitochondria have their own compartmental-specific stress responses, not

surprisingly involving translational regulation (Baker et al., 2012). Roles for both these stress responses in mediating longevity have been established in *C. elegans* (Durieux et al., 2011; Taylor and Dillin, 2013).

Interestingly, the conserved longevity modulator TOR has distinct roles in regulating translation elongation in addition to its well-known roles in influencing initiation. The translation elongation factor eEF2 is inhibited by phosphorylation of eEF2K, a kinase whose activity is negatively regulated by TOR (Redpath et al., 1996). eEF2 is also known to be repressed under a variety of stress conditions relevant to aging, including ER stress, hypoxia, and nutrient deprivation (Proud, 2015) (Figure 2). In addition, eEF2 is repressed by another highly conserved nutrient-responsive kinase, AMPK (Browne et al., 2004), whose increased activity extends lifespan in model organisms (Apfeld et al., 2004; Stenesen et al., 2013; Ulgherait et al., 2014).

Despite the known links between modulators of aging and their roles in translation elongation, it is important to note that our understanding of the mechanisms regulating translation elongation is severely limited relative to what is known about translation initiation. Recent studies, some of which are highlighted here, have begun to illuminate the myriad ways in which control of translation post-initiation can influence proteostasis and, potentially, aging.

Specialized Protein Synthesis

Just as the subcellular localization of proteins determines their function within the cell, the coordination of multiple cell types determines their ability to function within an organism. It has long been postulated that the translational machinery may vary to meet the needs of specific cells or tissue types. In support of this idea, ribosomopathies, which are diseases that can result from genetic mutations in core ribosomal components, manifest as distinctly cell-type-specific defects (Danilova and Gazda, 2015). Making use of newly developed chemistry, quantification of protein synthesis in vivo in distinct somatic stem cell lineages revealed levels of protein synthesis that varied by up to 10-fold (Signer et al., 2014). Cell-type-specific phenotypes may, in part, be influenced by abundance of translational machinery. Surprisingly, genes encoding individual ribosomal proteins, which are required in equimolar amounts in ribosomes, are expressed at highly variable levels among tissue types in mice (Kondrashov et al., 2011). The abundance of tRNAs also varies in different tissues (see above), and remarkably, at least one tRNA is cell-type specific with functional consequences related to its specificity (Ishimura et al., 2014).

A recent study examining the underlying mechanism for mutagenesis-induced neurological pathology in mice identified a gene encoding a ubiquitous ribosome release factor (Ishimura et al., 2014). However, this mutation was only pathological in combination with a mutation in the arginine $tRNA^{UCU}$. Consistent with the pathology, expression of this mutant tRNA was surprisingly confined to the CNS. Despite the mutation's location in the stem-loop structure of the tRNA, away from the anticodon, the combination of these two mutations caused stalling of ribosomes at the cognate mRNA codon, resulting in neurodegeneration (Ishimura et al., 2014).

Implications for Aging Research

For cells to survive under harsh conditions, the cellular resources invested in generating a proteome must not be squandered. It is of utmost importance that gene expression programs, ultimately governed at the level of mRNA translation, support their needs. With recent advances in sequencing technology, we now have the ability to gain unprecedented resolution into how these programs are regulated. The studies highlighted here illustrate the speed with which we can uncover new insights into how cells regulate protein synthesis, alluding to the possibility that we may have only seen the tip of the iceberg.

Most certainly, the stress response pathways described here have evolved to deal with transient stresses, but aging poses a different problem: chronic, prolonged stress. The prolonged activation of stress response pathways is not likely to have been under selective pressure, thereby adding an element of unpredictability in regard to what we might learn about how these programs act during aging. Understanding the functional consequences of these processes will aid in the identification of candidate pathways to target for the benefit of aging individuals.

Aging researchers have good reason to look forward to the functional characterization of translational regulatory mechanisms, as many lifespan extension paradigms engage pathways that govern these processes. Researchers have historically been quite successful at harnessing the beneficial effects of stress response pathways to extend lifespan in model organisms (Epel and Lithgow, 2014), and it seems there will soon be many new potential targets for this goal.

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