Experimental Cell Research 394 (2020) 112161

Contents lists available at ScienceDirect

Experimental Cell Research

journal homepage: www.elsevier.com/locate/yexcr

Translational quality control and reprogramming during stress adaptation

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ARTICLE INFO

Keywords:
Translation
Quality control
tRNA

ABSTRACT

Organisms encounter stress throughout their lives, and therefore require the ability to respond rapidly to environmental changes. Although transcriptional responses are crucial for controlling changes in gene expression, regulation at the translational level often allows for a faster response at the protein levels which permits immediate adaptation. The fidelity and robustness of protein synthesis are actively regulated under stress. For example, mistranslation can be beneficial to cells upon environmental changes and also alters cellular stress responses. Additionally, stress modulates both global and selective translational regulation through mechanisms including the change of aminoacyl-tRNA activity, tRNA pool reprogramming and ribosome heterogeneity. In this review, we draw on studies from both the prokaryotic and eukaryotic systems to discuss current findings of cellular adaptation at the level of translation, specifically translational fidelity and activity changes in response to a wide array of environmental stressors including oxidative stress, nutrient depletion, temperature variation, antibiotics and host colonization.

1. Introduction

It is not surprising that the word "stress" can be defined in multiple different ways as it is a well-used concept in many biological fields including psychology, ecology and cell biology. In general, stresses are considered any environmental factors which could cause damaging changes to a system. Some of the more common stressors which affect cellular viability include heat shock, oxidative stress, and nutrient depletion. Stress is also crucial because it can provide selections which encourage the evolutionary process [1]. It is essential for cells to be able to adapt rapidly under different environmental changes to maintain fitness and viability. As proteins are responsible for catalyzing most biochemical reactions in cells, gene expression and protein synthesis are tightly regulated under stress. There are multiple pathways to fine-tune cellular protein levels and properties, including pre-mRNA splicing [2], mRNA structure [3], tRNA-modification [4], post-translational modification [5] and protein degradation [6]. This review will focus on how prokaryotic and eukaryotic systems adapt to injurious conditions through translational control. Specifically, we will discuss current understandings of how cells respond and defend themselves through stress by optimizing the fidelity and robustness of translation.

2. Translational fidelity and quality control

Faithful translation of genetic information to active proteins is crucial for cellular viability. As errors in protein synthesis can lead to the accumulation of misfolded and aberrant proteins, cellular protein homeostasis will be disrupted, resulting in the formation of protein aggregates [7]. Terminally differentiated cells such as neurons are especially susceptible to aggregated proteins, hence mistranslation has been associated with many neurodegenerative disorders [8–11]. To deal with these problems, cells have developed multiple steps of quality control mechanisms to ensure correct amino acids are incorporated during translation. Mutations in genes involving these quality control activities are detrimental. For example, the loss of alanyl-tRNA synthetase (AlaRS) aminoacylation quality control in mice is reported to be embryonic lethal [12], and the same aaRS defect in *Escherichia coli* results in a global proteomic dysregulation [13]. Errors in translation can occur during the stage of aminoacylation or ribosomal decoding. In this section, we will discuss the quality control activities each of the stage employs for maintaining translational fidelity.

2.1. Aminoacyl-tRNA quality control

The first step to ensure translational fidelity is the formation of

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https://doi.org/10.1016/j.yexcr.2020.112161
Received 31 May 2020; Received in revised form 26 June 2020; Accepted 29 June 2020
Available online 30 June 2020
0014-4827/

accurate aminoacyl-tRNAs [14]. The aminoacylation reaction is catalyzed by aminoacyl-tRNA synthetases (aaRS) through a two-step process. First, cognate amino acids are activated by their respective aaRSs, forming aminoacyl-adenylates. The activated amino acids are later transferred to the corresponding tRNAs, generating aminoacyl-tRNAs, which could be sampled by EF-Tu/eEF1A along with GTP to form ternary complexes [15]. Although aaRSs have very specific activation domains for amino acid selections, errors can still occur due to the structural and chemical similarities shared by some amino acids [16,17]. For example, LeuRS is known to activate not only leucine but also isoleucine, valine, methionine and other non-canonical amino acids such as norvaline and homocysteine (reviewed in Refs. [18]). To prevent mischarged tRNA accumulation, many aaRSs have evolved with proofreading mechanisms, in which misactivated amino acids or misacylated tRNAs will be hydrolyzed [19]. These steps are termed as pre-transfer editing and post-transfer editing respectively (Fig. 1). The post-transfer editing activity of aaRS can occur both in *cis* and *trans*. It is worth noting that the same aaRS in different organisms may employ different editing strategies. For example, *E. coli* AlaRS deacylates mischarged Ser-tRNA^{Ala} in a tRNA dependent fashion, while human AlaRS is capable of clearing misactivated Ser-AMP and Ser-tRNA^{Ala}, suggesting the existence of species-specific proofreading mechanisms [20,21].

In addition to aaRSs, the fidelity of the cellular aa-tRNA pool can also be maintained by *trans*-editing factors. The most well studied of these factors are the free standing editing-domain homologs which are found in all domains of life [22]. For example, AlaXP possess the proofreading domain of AlaRS, and is able to hydrolyze Ser-tRNA^{Ala} [22,23]; ProXP-Ala and Ybak are homologs of the INS editing domain of ProRS, and are able to clear mischarged Ala-tRNA^{Pro} and Cys-tRNA^{Pro} respectively [22,24,25]. Aside from the editing domain homologs, D-aminoacyl-tRNA deacylase (DTD) prevents the accumulation of D-aa-tRNAs and plays an important role in deacylating Gly-tRNA^{Ala} [26]; A DTD variant, Animalia-specific tRNA deacylase (ATD), was also identified in higher eukaryotes to deacylate mischarged Ala-tRNA^{Thr} [27]. Besides proofreading of misacylated tRNAs, misaminoacylation can also be prevented by interrupting the transfer of misactivated amino acid to tRNAs. For example, the vertebrate specific ANKRD16 facilitates pre-transfer editing of AlaRS by hydrolyzing misactivated Ser-adenylate in an ATP dependent manner [28].

2.2. Quality control of ribosomal decoding

If mischarged aa-tRNAs avoid the previously described quality control activities, they can still be subjected to a series of proofreading mechanisms before participating in translation elongation. One check point is the formation of ternary complexes, which consist of the bacterial EF-Tu or the eukaryotic eEF1A, in complex with aa-tRNA and GTP [29,30]. Ternary complexes deliver aa-tRNAs to the ribosomes, allowing the tRNA accommodation to occur at the ribosomal A site without premature deacylation [31]. The interactions between EF-Tu and aa-tRNAs are thermodynamically regulated to minimize the delivery of incorrectly charged tRNAs [32–34].

A recent proteomics study showed that most amino acid misincorporation events occur during the stage of ribosomal decoding [35]. The selection of tRNA by ribosome is accomplished in two steps to ensure accuracy. First, initial selection based on the codon-anticodon

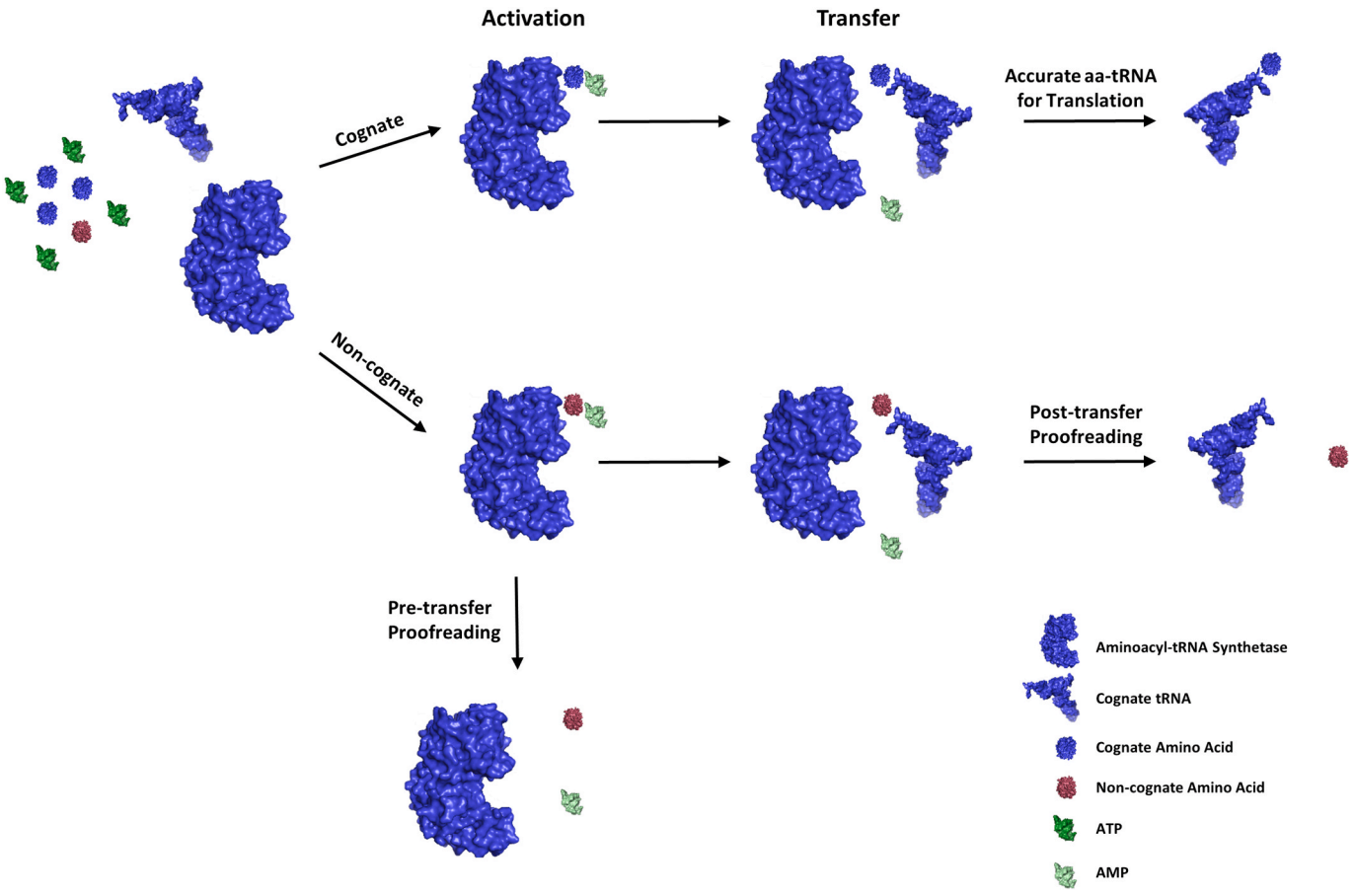

Fig. 1. Aminoacyl-tRNA synthetase activities. Aminoacyl-tRNA synthetases function in two steps. First, cognate amino acids are activated with ATP creating an aminoacyl-adenylate. Second, the amino acid is transferred to the cognate tRNA to be used in translation. Due to the similarities between many amino acid substrates in the cell, some aaRSs have evolved secondary activities to prevent mis-acylation on tRNAs. Pre-transfer proofreading occurs by hydrolyzing the mis-activated amino acid. Alternatively, mis-aminoacylated tRNA substrates can be hydrolyzed following the transfer onto tRNA.

interaction occurs in the decoding center of the small ribosomal subunit (SSU). Once the correct codon-anticodon complex is formed, a conformational change is induced in EF-Tu favoring the active state for GTP hydrolysis [36]. After GTP is hydrolyzed, EF-Tu makes another conformational change favoring the binding of GDP and loses affinity for aa-tRNA. The cognate aa-tRNA is then accommodated into the A site [37]. Some near-cognate aa-tRNAs may escape the initial selection, but will be rejected during the subsequent proofreading step, due to the instability of the codon-anticodon base pair [38,39]. In addition to ribosomal proofreading, EF-Tu has recently been demonstrated to have the capacity of reforming new ternary complexes using the aa-tRNA within the ribosomal A site, suggesting a potential mechanism of cognate or near-cognate aa-tRNA proofreading at the expense of GTP futile cycling [40].

3. Stress adaptation associated with translational fidelity

Among all steps in the central dogma of biology, translation has the highest error rate, with the frequency of one mistake every 1000 to 10,000 codon translated [35,41]. In contrast, the frequency of errors during DNA replication and mRNA transcription are 10^{-8} and 10^{-6} respectively [42–45]. Based on the reported translational error frequency, if the average protein in *E. coli* is assumed to be 500 amino acid long, then one fourth of the putative protein population in *E.coli* would host at least one misincorporated amino acid [46]. Indeed, it was later demonstrated by using a missense suppression system that *E. coli* is capable of tolerating around 10% mistranslated proteins without showing significant growth defects [47]. These results showed that errors in translation are unexpectedly well tolerated, opening the discussion that mistranslation might even provide benefits in some instances. Nevertheless, mistranslation is still generally expected to be detrimental to proteome homeostasis and cellular viability. In this section, we will discuss our current understandings of translational fidelity regulation under different stresses, including oxidative stress, changes in temperature, antibiotic exposure and host interaction. Next, we will examine the instances of how mistranslation affects cellular stress responses.

3.1. Stress-associated fidelity regulation

3.1.1. Oxidative stress

Reactive oxygen species (ROS) are natural byproducts of aerobic metabolism [48]. They are highly reactive, and damaging to nucleic acids, fatty acids and proteins. An imbalance of ROS and antioxidants is called oxidative stress, which has been associated with pathologies including cancer [49], chronic inflammation [50], neurodegeneration [51] and aging [52,53]. Therefore, it is crucial for cells to maintain redox homeostasis for optimal survival.

Regulating translational fidelity is one of the strategies to protect cells against oxidative damage. In the mammalian system, oxidative stress and innate immune response enhance Met misincorporation at non-Met codons up to 10-fold by increasing the affinity of MetRS toward non-cognate tRNAs [54] (Fig. 2e). The promiscuity of MetRS is regulated by post-translational phosphorylation upon oxidative stress [55]. Met is readily oxidized by ROS to form methionine sulfoxide, which can be reduced by methionine sulfoxide reductase in most cells. Hence increasing Met content in the proteome is beneficial to cellular viability under oxidative stress as Met acts as a scavenger to excess oxidants [56]. In *E. coli*, ROS decreases the fidelity of ThrRS by oxidizing a critical cystine residue in the editing domain, resulting in the production of mischarged Ser-tRNA^{Thr} [57] (Fig. 2f). This was suggested as a

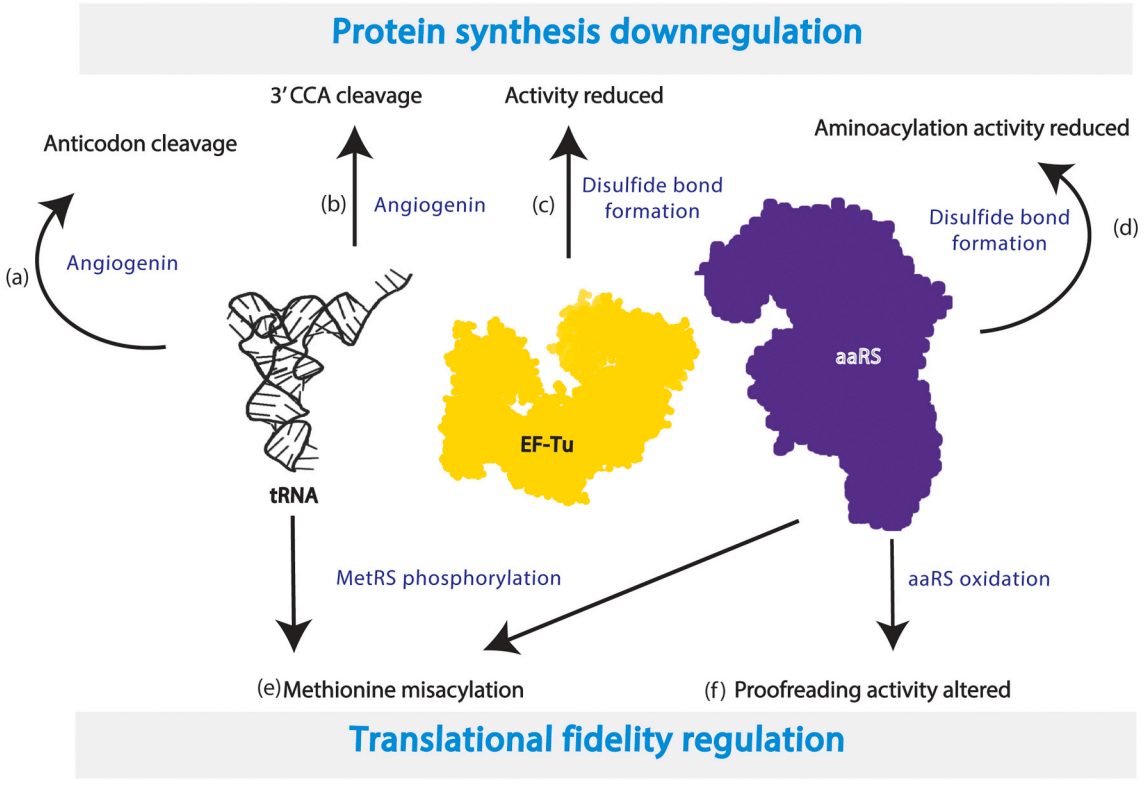

Fig. 2. Translational response to oxidative stress. Oxidative stress has been reported to affect the translational machinery in both prokaryotic and eukaryotic systems. The translational response during oxidative stress can be categorized as global downregulation of the translational machinery and the alteration of translational quality control. (a)(b) In mammals, angiogenin cleaves the anticodon loop or the 3′ termini of tRNAs, resulting in the reduction of active tRNA pool. (c)(d) ROS can also repress translation by forming reversible inter or intramolecular disulfide bonds in EF-Tu and aaRS. (e) MetRS misacylates non-cognate tRNAs with Met, allowing proteins with Met misincorporation to act as ROS scavengers. In addition to reducing the aminoacylation activity in yeast mtPheRS, (f) aaRS oxidation also alters the editing activity in bacteria.

mechanism for bacterial cells to sense environmental redox level.

ROS has also been shown to increase the fidelity of some bacterial aaRSs. For example, the editing activity of *Salmonella enterica* PheRS increases when oxidized, allowing robust deacylation of mischarged Tyr-tRNA^{Phe} and meta-Tyr-tRNA^{Phe} (m-Tyr-tRNA^{Phe}) [58] (Fig. 2f). m-Tyr is a non-proteinogenic amino acid (NPA) generated from Phe oxidation, and the accumulation of m-Tyr-tRNA^{Phe} is toxic in both prokaryotic and eukaryotic cells [59,60]. As *Salmonella* frequently experiences oxidative stress in its natural habitat, this may be a protective mechanism to minimize potentially harmful misincorporation events in the proteome.

3.1.2. Antibiotics and host colonization

Mistranslation also provides phenotypic heterogeneity for pathogens to adapt under stressful conditions. For example, *Mycobacterium* species utilize GatCAB-dependent mistranslation to develop phenotypic resistance against rifampicin [61,62]. GatCAB is an enzyme complex performing transamidation to produce correctly charged tRNA^{Gln} and tRNA^{Asn} from naturally mischarged Glu-tRNA^{Gln} and Asp-tRNA^{Asn} [63,64]. Clinical Mycobacterial isolates were identified with SNPs in the GatCAB complex which minimize its enzymatic proofreading activities, resulting in elevated mistranslation [62]. Mistranslation contributing to antibiotic resistance was also observed in the prokaryotic model organism *E. coli*. During anaerobiosis and antibiotic exposure, mismethionylation increased in *E. coli*, providing the organism tolerance to antibiotics and other stressors [65]. In *Candida albicans,* $tRNA_{CAG}$ can be recognized by both SerRS and LeuRS, resulting in Ser misincorporation at Leu (CUG) codons [66]. The CUG codon misincorporation is crucial for *C. albicans* cellular surface variability [67] morphology plasticity and adherence [68] (reviewed in Refs. [69]), providing diverse niches for its colonization.

Additionally, many intracellular organisms including *Microsporidia* and *Mycoplasma* were identified with degenerated aaRS proofreading mechanisms [70,71]. For example, *Mycoplasma* species were reported with degenerated PheRS, ThrRS and LeuRS, which allows them to produce mischarged tRNAs, resulting in elevated amino acid misincorporation [71–73]. A recent report shows that bacterial genome decay positively correlates with aaRS degeneration, suggesting a gain of fitness by losing the editing activities [74]. However, whether the advantage is due to protein heterogeneity or simply a strategy to conserve energy is still unclear.

3.1.3. Temperature

Temperature fluctuation is a stressor for many microorganisms. For example, the growth temperature of *Aeropyrum pernix*, a thermophilic archaeon, ranges from 70 °C to 100 °C [75]. Under low growth temperature, global Leu to Met misincorporation was identified in *A. pernix* due to MetRS mismethionylation of tRNA^{Leu} [76]. Interestingly, the mistranslated proteins naturally produced under low temperature growth showed greater activities at low temperature than the correctly translated counterparts, suggesting that mistranslation provides cellular adaptive fitness upon temperature changes [76]. Additionally, it was recently reported that all strains in the archaeal family Sulfolobacea were identified with LeuRS duplication including one copy exhibiting a degenerated editing domain (LeuRS-I), where critical residues were substituted, abolishing its editing function [77]. Although its functions and mechanisms are still unknown, LeuRS-I was shown to be required upon temperature fluctuation, suggesting that it plays an important role for *Sulfolobus* optimal growth [77].

3.2. Mistranslation alters stress responses

Artificial error-prone ribosomal mutations in *E. coli* have demonstrated that mistranslation could trigger different cellular stress responses. It has been shown that moderate mistranslation increases the tolerance of *E. coli* toward oxidative stress by activating RpoS, the general stress response transcriptional regulator, leading to the upregulation of genes involving antioxidation such as catalase *katE* and peroxidase *osmC* [78]. Mistranslation also protects cells from heat stress by activating the heat stress sigma factor RpoH, which increases the mRNA levels of proteases and chaperones, resulting in the degradation and refolding of misfolded proteins [79]. Furthermore, it was recently reported that mistranslation induces bacterial SOS response by a Lon protease mediated mechanism [80]. The induction of SOS response increases bacterial survival under DNA damage and heat shock, further emphasizing the association between proteotoxicity and stress response (Fig. 3b–e).

Amino acid starvation is monitored by the accumulation of mischarged tRNA in both prokaryotic and eukaryotic organisms. When the intracellular amino acid levels are low, deacylated tRNA will be more likely to enter the ribosomal A site, resulting in transient ribosomal pausing and RelA activation in bacteria [81]. Activated RelA will synthesize alarmone (p)ppGpp and trigger stringent response, in which amino acid biosynthesis pathways are upregulated and translational machinery is downregulated to avoid actively utilizing the limiting amino acids resources [82]. In yeast, amino acid starvation signaling is regulated by the general amino acid control pathway (GAAC). Similar to the bacterial stringent response, GAAC also depends on the intracellular deacylated tRNA levels to monitor amino acid starvation (mechanism reviewed in [83]). When bound with uncharged tRNA, the protein kinase general control non-depressible 2 (Gcn2p) will be activated, resulting in a global decrease of translation and elevating the expression of GCN4, which is responsible for regulating amino acid biosynthesis [83].

As deacylated tRNA is such an important factor in sensing amino acid starvation, the loss of aaRS quality control has been shown to misregulate this stress response. In *E. coli*, PheRS proofreading deficiency leads to the accumulation of mischarged tRNA, which subsequently leads to less uncharged tRNAs to accurately sense cognate Phe starvation [84] (Fig. 3a). Similarly, editing deficient yeast cells failed to correctly activate the GAAC pathway during amino acid stress [85], showing that aminoacylation fidelity can control cellular sensitivity toward amino acid stress.

4. Stress induced translation reprogramming

As previously described, one mechanism for cells to cope with environmental stressors is to downregulate the rate of protein synthesis and increase the selective expression of certain genes for stress adaptation. Translation consists of three stages: initiation, elongation and termination. A complex pool of proteins is responsible for the regulation at each step, and initiation is usually considered as the rate limiting step. In this section, we will discuss current knowledge on stress-regulated translational reprogramming that is independent of fidelity, specifically we will focus on the regulation in the initiation and elongation steps.

4.1. Stress-induced translational downregulation

A ubiquitous strategy for cells to overcome stress under unfavorable condition is to slow down global protein synthesis and upregulate the expression of stress-related genes. In addition to stress responses, cells can also downregulate translation by modulating the level of active translation components. For instance, under oxidative stress, oxidized mitochondrial PheRS (mtPheRS) loses its aminoacylation activity due to the formation of reversible disulfide bonds [86] (Fig. 2d). This was suggested as a protective mechanism for mitochondria to reduce potentially toxic protein synthesis, until the oxidative stress is alleviated. In addition to modulation of aaRS activity in response to environmental stressors, it has been shown that post-translational modification of aaRSs can also alter aaRS activity. Post-translational lysine acetylation in *E. coli* has been shown to decrease the canonical

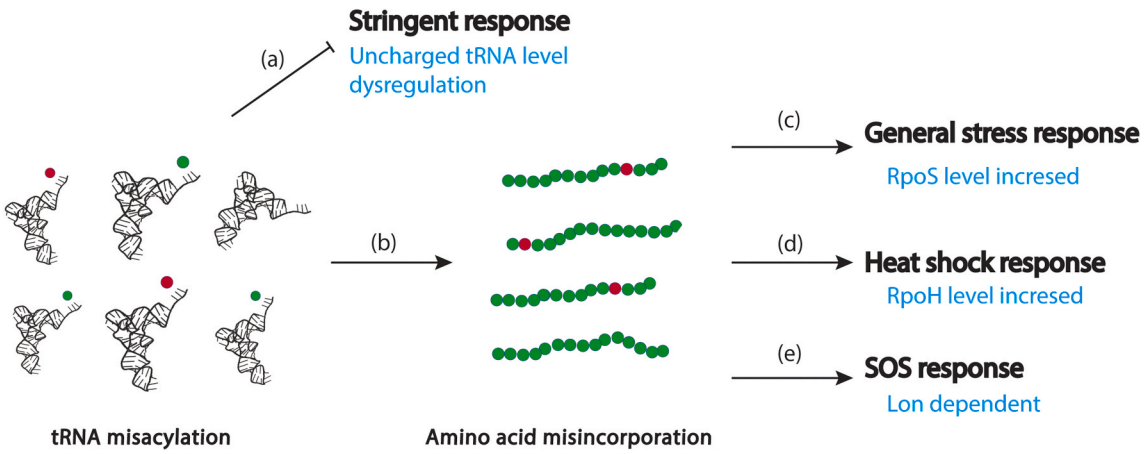

Fig. 3. Translational fidelity affects different cellular responses in *E. coli*. The fidelity of protein synthesis is strictly regulated, however errors can still occur at low frequency. Red circles represent non-cognate amino acids while green circles represent cognate amino acids. (a) Defects in aaRS quality control result in the dysregulation of the charged/uncharged tRNA pool, which can desensitize the stringent response, delaying cells to correctly respond to amino acid starvation. (b) Misacylated tRNAs can also be used in protein synthesis, which leads to the production of mistranslated proteins. These aberrant proteins are subject to misfolding, which triggers other stress responses. For example, (c) RpoS level can increase and activate the general stress response, which can enhance tolerance towards oxidative stress. (d) Similarly, RpoH level may increase, allowing cells to respond quickly to heat stress. (e) Mistranslation can also activate the SOS response in a Lon protease-dependent manner, suggesting an unclear association between protein homeostasis and DNA repair. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

activity of Class I aaRSs, TyrRS [87], CysRS [88], and HisRS [88], and on the Class II aaRSs, AlaRS [89] and ThrRS [88]. Acetylation of K73 in AlaRS led to a decrease in cognate activity, similar to those observed from the Class I aaRSs. These findings suggested that aaRS activity is dynamically regulated and can contribute crucial roles to adjust the level of protein synthesis.

In addition to aaRS regulation, global translation can also be downregulated by adjusting the activities of ternary complexes and translation factors. For example, under hyperosmotic stress, translational elongation rate are decreased in *E. coli* due to the reduction of binding between the ternary complex and the ribosome [90]. In cyanobacteria, EF-G and EF-Tu are inactivated by ROS due to the formation of intramolecular and intermolecular disulfide bonds respectively [91,92] (Fig. 2c). In the eukaryotic system, eIF2 phosphorylation regulates global translation by decreasing the initiation rate under stresses such as amino acid starvation (GCN2), ER stress (PERK) and the presence of dsRNA (PKR), heme deficiency (HRI) and interferon (reviewed in Ref. [93]). The recycling of eIF2-GDP to eIF2-GTP requires the facilitation of guanine nucleotide exchange factor eIF2B [94]. However, when eIF2 is phosphorylated at the alpha subunit, it will act as a competitive inhibitor to eIF2B, which diminishes its activity [95,96]. This results in the reduction of translational initiation rate due to the limitation of ternary complex availability [95]. Another mechanism for global protein synthesis regulation is the inhibition of m^7G cap recognition. The eukaryotic cap-initiation complex consists of eIF4E, the cap binding protein; eIF4G, the scaffold protein; eIF4A, the RNA helicase and eIF3, a multiprotein complex that binds to the ribosomal 40S subunit [97]. Cap dependent initiation is inhibited by eIF4E binding proteins, 4E-BPs, and the affinity is abolished when they are phosphorylated [98,99]. mTor is known to hyperphosphorylate 4E-BP1, which inhibits 4E-BP1 affinity toward eIF4E, resulting in the upregulation of protein synthesis (reviewed in Ref. [100]). Under hypoxic conditions, in addition to eIF2 phosphorylation by PERK [101], cap-dependent translation is also reduced due to mTor inhibition [102].

tRNA-derived stress-induced fragment (tiRNA) production is another common mechanism for eukaryotic cells to modulate translation under stress. tiRNAs are products of secreted ribonucleases such as RNY1 in yeast [103] and angiogenin in humans [104]. These enzymes recognize the single strand CA sequence, which targets the anticodon loop of some tRNA species, leading to the production of 5′ halves and 3′ halves tRNA fragments. Under oxidative stress, the production of tiRNAs increases in both human and yeast cells, but the full-length tRNA levels are not significantly altered [105] (Fig. 2a). This suggested that tRNA fragmentation may possess other functions rather than simply decreasing the pool of competent tRNAs to alter translation. Indeed, it was later reported that the angiogenin induced 5′ tRNA halves, specifically the ones with 5′ terminal oligoguanine motifs such as $tRNA^{Ala}$ and $tRNA^{Cys}$, inhibit translation initiation by displacing eIF4E and eIF4G [106]. Although not many tRNAs fulfill the criteria of 5′ oligo-G motif and CA sequence in the anticodon loop, all active tRNAs consist of the 3′ CCA sequence. In fact, it was found that during severe oxidative stress, all tRNAs were deactivated due to angiogenin cleavage of their CCA termini, allowing a rapid downregulation of protein synthesis [107] (Fig. 2b). In addition to eukaryotic organisms, tRNA cleavage was observed in some bacterial species including uropathogenic *E. coli* (UPEC) [108] and *Burkholderia* [109] as a strategy for interbacterial competition in the bacterial contact dependent growth inhibition (CDI) system [110]. tRNA pool downregulation under oxidative stress was also found in *E. coli*, which leads to the reduction of translation elongation rate and subsequently results in growth arrest [111]. These findings showed that in addition to tiRNA, limiting active elongator tRNAs also plays an important role in downregulating protein synthesis under stress.

4.2. Stress-induced selective protein synthesis

In addition to global translational decline, stresses can also induce selective variation of the tRNA pool for reprogramming protein synthesis. One example is during viral infection, where the cellular tRNA pool is optimized for viral translation [112,113]. Influenza A virus (IVA) and Vaccina Virus (VV) were found to significantly change the polysome-associated tRNA pool in HeLa cells upon infection, and the changes of tRNA abundance reflects the codon usage of the virus [112]. Bacterial phages utilize a different approach to cope with the differences in host codon usage, where they encode tRNA genes corresponding to the codons which are enriched in phages but rare in the hosts [114]. In yeast, genes enriched in codons that are translated by rare tRNAs were found to be upregulated under stressful conditions [115]. This was later elucidated to be a consequence of tRNA abundance rearrangement, which allows yeast cells to selectively translate stress-associated

transcripts [116]. These findings emphasize the dynamic changes of the cellular tRNA pool upon stress exposure and raised questions on how the abundances of tRNAs are regulated.

Recently, Schlafen 11 (SLFN11) was found in human cells to present a novel ribonuclease activity to bind and degrade many Type II tRNAs [117]. SLFN11 belongs to the SLFN protein family, which is limited to mammals, and have been associated with cellular immune responses [118,119]. Interestingly, it was found in humans to abrogate the protein synthesis of HIV in a retrovirus specific manner [113]. The mechanism of this inhibition was later elucidated by the finding of their ribonuclease activities toward Type II tRNAs, especially $tRNA^{Leu}$ -TAA [117]. The TTA codon is enriched in genes involving in DNA repair, DNA damage signaling and HIV-viral genes [117]. These findings showed that selective tRNA cleavage plays an important role in regulating gene expression under stressful conditions.

In addition to tRNA pool reprogramming, ribosome heterogeneity also promotes the translation of specific mRNA subsets. For example, kasugamycin triggers the production of 61S ribosomes in *E. coli*, which selectively translate leaderless mRNA [120]. In yeast, where most ribosomal proteins (RPs) are produced from duplicated genes, it was reported that stress can change the ribosomal composition by selectively integrating different RP paralogs [121]. Post-translational modifications of RPs were also recently found to participate in generating ribosome heterogeneity. In mammalian cells, phosphorylated RPL12 was found to be enriched in the monosome fraction but not the polysome fraction by polysome profiling [122]. Moreover, RPL12 phosphorylation was shown to selectively regulate the translation of mitotic-related genes, suggesting that this modification is involved in differential gene expression [122]. Besides post-translational modification, rRNA modification such as 2′-O-ribose-methylation, pseudouridylation and methylation have also been shown to promote the heterogeneity of ribosomes (reviewed in Ref. [123]).

In addition to ribosome heterogeneity, inactive dimerized ribosomes have also been associated with stress adaptation. They have been identified in both bacteria and mammalian cells (100S and 110S respectively), and are considered as a reservoir for ribosomes under unfavorable conditions [124,125]. The level of factors associated with the formation of 100S, including ribosome modulation factor (RMF) and hibernation promoting factor (HPF) are regulated under stress. For example, (p)ppGpp upregulates the transcription of *rmf* [126], and the loss of *rmf* renders *E. coli* susceptible toward environmental stresses such as acid [127], heat [128] and nutrient deficiency [129]. It was recently reported that the expression of some transcripts are more regulated by the 100S ribosomes, however the mechanism behind this differential regulation is still unclear [130]. These findings demonstrated the active role of ribosomes in regulating protein synthesis for environmental adaptations.

5. Outlook

As we discussed in this review, translational regulation plays an important role for stress adaptation in both eukaryotic and prokaryotic organisms. There has been growing evidence showing how the fidelity of translation is altered under unfavorable conditions [131]. Nevertheless, it remains a question why some mistranslation events are more tolerated than the others. For example, Met misincorporation seems to be a mechanism for adaptive translation under multiple stresses [65,132], while Ala to Ser misincorporation can be extremely detrimental for cellular growth [133]. It would also be important to understand how naturally error-prone organisms tolerate NPAs, as NPAs are in general more toxic than proteinogenic amino acids [134]. Similar to tRNAs, the level of NPAs also fluctuate upon environmental changes. For example, m-Tyr accumulation was found when cells are exposed to oxidative stress [59], and norvaline and norleucine were shown to accumulate under anaerobic conditions [135,136]. These findings suggested that there is more to explore on how translational fidelity changes correspond to NPA abundance fluctuation under stress.

It is also worth noting that cells are able to fine-tune their translational regulation depending on the severity of the environmental stress. For instance, under moderate oxidative stress, eukaryotic cells downregulate translation by producing tiRNAs [105]; While under severe oxidative stress, angiogenin reduces the active tRNA pool by tRNA 3′ cleavage [107], resulting in a more rapid downregulation of protein synthesis. In addition to intensity-oriented stress responses, viral infection shows species specific regulation of the host translational mechanism. For example, HIV, VV and IVA were found to modulate host cell tRNA abundance for viral protein expression, while flavivirus infection increased aaRS expression in the brain [137]. These results demonstrated the variability of mechanisms virus can employ for propagation, and many questions remain on how the host tRNA and aaRS are regulated upon viral infection. As viruses, especially RNA viruses, have high mutation rates [138], understanding potential drug targets is crucial for future viral therapeutics development.

Persister cells are bacteria which enter dormant states to adapt under antimicrobial stress (reviewed in Ref. [139]). Once the stress is relieved, the growth will be resumed. Persister formation is stochastic but has been shown to correlate with (p)ppGpp accumulation [140]. As mistranslation can alter intracellular (p)ppGpp production in bacteria as a consequence of aa-tRNA pool dysregulation [84], it would be insightful to understand whether translational fidelity plays an important role in persister cell formation.

A major unresolved question in the field is whether mistranslation results in mutagenesis or just phenotypic heterogeneity. One of the hypotheses is that mistranslation can lead to the production of malfunctional proteins involved in DNA replication, such as DNA polymerase, resulting in hypermutagenesis. Another hypothesis is that mistranslation may increase mutagenesis through the recABC dependent pathway. Different groups have demonstrated that mistranslation in bacteria can enhance SOS response, allowing cells to rapidly adapt when exposed to DNA damaging agents [80,141], however whether this results in higher mutation rate is still under debate.

6. Conclusion

Although accurate translation is crucial for cellular viability, we have discussed in this review that translational fidelity can be modified as a response towards stress adaptation. Mistranslation leads to the production of mistranslated proteins and dysregulate the intracellular aa-tRNA pool, which result in the alteration of stress responses (Fig. 3). Additionally, the level of protein synthesis is dynamically regulated under different environmental stressors both globally and selectively via the modulation of tRNAs, aaRSs, translation factors and ribosomes. Some stressors such as ROS can trigger multiple different strategies for cellular stress adaptation, indicating the complexity of translational regulation (Fig. 2).

CRediT authorship contribution statement

Nien-Ching Han: Conceptualization, Writing - original draft. **Paul Kelly:** Conceptualization, Writing - review & editing. **Michael Ibba:** Supervision, Writing - review & editing, Funding acquisition.

Acknowledgements

This work was supported by funding from the National Science Foundation (MCB-1715840 to MI).

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