Translational Reprogramming of mRNA in Oxidative Stress and Cancer

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Abstract

Oxidative distress is a hallmark of cancer. Neoplastic cells produce elevated levels of reactive oxygen species that trigger signaling pathways and specific gene expression to aid cancer cell proliferation and activate stress responsive, adaptive cellular metabolic programs. Among other steps, the final stage of gene expression comprising of protein synthesis is extensively and dynamically modulated in response to stress and in cancer. This chapter first outlines

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the process of mRNA translation and its regulation followed by how this is reprogramed in cellular stress and during oncogenesis, especially in the context of oxidative stress. Targeting mRNA translation for cancer therapeutics is an emerging field that has enhanced possibilities for combination therapy. Owing to the intimate links between oxidative stress and remodeling of cellular mRNA translation, the chapter concludes by emphasizing the necessity to investigate outcomes of combining standard of care anti-oxidants/ROS enhancers with translation inhibitors in treatment of difficult to cure cancers.

Keywords

Protein synthesis · eIF4F · eIF-2α phosphorylation · Stress adaptation · tRNA cleavage · tRNA modification · Reactive oxygen species · Redox homeostasis · Targeted therapy

Introduction

Gene expression is a multistep cellular process starting with transcription of a gene and culminating in synthesis of the corresponding protein, regulated tightly at each step. In eukaryotes, mRNA translation comprises of decoding information carried in mRNAs from nucleus to cytosol in order to build amino acid chains held together by peptide bonds. This process of polypeptide chain synthesis is highly energy consuming and involves a complex machinery composed of core proteins and ancillary factors that are under the stringent control of cellular signaling cascades. This enables prompt and dynamic rewiring of mRNA translation, bringing rapid but specific changes to the proteome in response to various extrinsic and intrinsic stimuli. Defects in the expression of translation factors or in cellular signaling that control mRNA translation often lead to disease states like cancer and neurodegeneration (Lehmkuhl and Zarnescu 2018; Fabbri et al. 2021) Recently, deregulation of mRNA translation in cancer has been identified as a vulnerability that is being exploited for therapeutic advances (Fabbri et al. 2021). This has led to increased interest in exploring the mechanisms of translational regulation under inherent cellular or microenvironmental stress and diseased conditions.

Cells are constantly exposed to various adverse conditions, and they strive to adapt to such stresses by conserving energy and repairing the stress-induced damage. This is achieved in part by reprogramming mRNA translation in addition to other reforms in cellular metabolism. Stress generally imposes reduction in global rate of cellular protein synthesis but enhances translation of specific mRNAs. This enables reshaping of the cellular proteome and reprogramming of signaling cascades to adapt and promote cell survival programs by fine tuning gene expression. The mechanisms of regulation of mRNA translation in stress are complex and manifold. These include alterations in expression, activity, and availability of core translation factors, RNA binding proteins (RBPs), ribosomal proteins, and non-coding RNAs. Stress-induced

alterations in RNA modifications, RNA secondary structures, use of upstream open reading frames (uORFs), and codon usage bias are other significant mechanisms impacting translational outcome (Advani and Ivanov 2019).

During cellular metabolism, reactive oxygen species (ROS) are often generated as by-products. Though toxic at high levels, ROS at moderate amounts specifically regulate signaling pathways. Cells therefore need to balance their redox state in order to maintain active signaling without accumulating cytotoxic levels of ROS. Imbalance in ROS levels or dysfunctional anti-oxidation mechanisms give rise to oxidative stress in cells. Oxidative stress is associated with grave pathophysiological conditions including initiation and progression of cancer (Hayes et al. 2020). Cancer cells manifest anomalous Redox homeostasis with ROS having pleiotropic functions in these cells. ROS up to a certain threshold promotes neoplastic growth exceeding which cells are targeted for senescence (Reczek and Chandel 2017). This susceptibility has been exploited in developing cancer therapeutics. Since tumor cells generate high levels of ROS, they gear up anti-oxidation mechanisms to tackle the oxidative burden and support proliferation. Translational reprogramming is instrumental in achieving this feat underscoring the importance of regulation of mRNA translation in oxidative stress for cancer progression.

This chapter attempts to first describe the process of canonical mRNA translation, the general mechanisms of translational regulation operating in stress, and then focusses on regulatory mechanisms specifically pertinent in oxidative stress mostly in a cancer context. Finally, the emerging role of translation inhibitors in cancer therapeutics has been highlighted.

An Outline of mRNA Translation

mRNA Translation Initiation

Translation of mRNA is classically categorized into four steps comprising of initiation, elongation, termination, and ribosome recycling. Of all the steps, translation initiation is the most regulated and is the rate-limiting step. Initiation is the process of recruiting 80S ribosome and initiator methionyl-transfer RNA (Met-tRNAi) to the open reading frame (ORF) of an mRNA with the help of several eukaryotic initiation factors (eIFs). Most mRNAs undergo cap-dependent translation (Sonenberg and Hinnebusch 2009; Jackson et al. 2010). There are other less frequently occurring alternative modes of translation initiation that have also been described (Sriram et al. 2018). In cap-dependent translation (schematically explained in Fig. 1), mRNA 5′ cap binding protein eIF4E binds the 5′ 7-methylguanosine cap of mRNA (m^7G) in the nucleus and is exported. In the cytoplasm, eIF4E is sequestered by an abundant small protein 4EBP1 to prevent initiation of translation. Signaling through mTORC1 phosphorylates 4EBP1 causing its dissociation from eIF4E. This enables binding of a large scaffolding protein eIF4G to eIF4E at the same binding site as of 4EBP1. PolyA binding proteins (PABPs) that bind the 3′ end of poly-adenylated mRNA also interact with eIF4G, resulting in circularization of

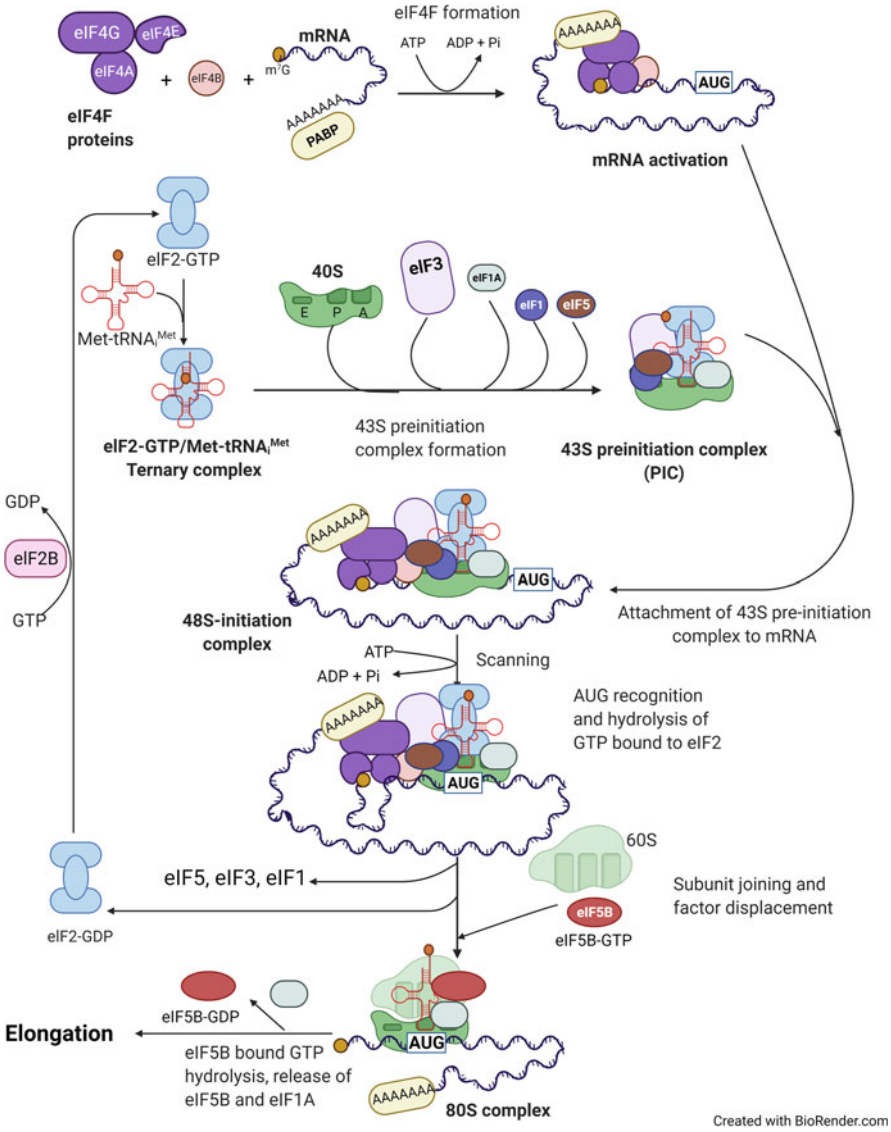

Fig. 1 Cap-dependent translation initiation: mRNA is activated for recruitment to 43S pre-initiation complex (PIC) by eukaryotic translation initiation factors eIF4E, eIF4G, and eIF4A together called eIF4F complex and eIF4B. 43S PIC consists of a 40S small ribosomal subunit, eIF3, eIF5, eIF1, eIF1A, and a ternary complex composed of an initiator methionyl tRNA (Met-tRNA$_i$) and GTP-bound eIF2. Association of eIF4F-bound mRNA to 43S PIC marks the formation of 48S initiation complex that scans the mRNA 5′ untranslated region (UTR) for an initiation codon (usually the AUG). Upon start codon recognition, the 48S complex changes its conformation triggering GTP hydrolysis from eIF2-GTP and the release of eIF2-GDP and other factors such as eIF1, eIF5, and eIF3. eIF2B recycles eIF2-GDP back to the ternary complex. The 60S ribosomal subunit is recruited by eIF5B-GTP. An elongation competent 80S complex is finally formed by joining of ribosomal subunits which potentiates GTP hydrolysis and release of the initiation factors eIF5B-GDP and eIF1A. m^{7}G:7-methylguanosine

the mRNA. An RNA helicase eIF4A, which is also bound to eIF4G then unwinds the complex secondary structures on the mRNA 5′ UTR to facilitate 43S pre-initiation complex association. The activity of eIF4A is enhanced by eIF4B and is inhibited by PDCD4, both controlled by the mTOR signaling pathway. eIF4E, eIF4G, and eIF4A together form the eIF4F cap binding complex. A 43S pre-initiation complex (PIC) then joins the mRNA bound eIF4F. 43S PIC consists of a 40S small ribosomal subunit, eIF3, eIF5,eIF1, eIF1A, and a ternary complex composed of an initiator methionyl tRNA (Met-tRNA$_i$) and GTP bound eIF2. The 43S PIC is recruited to eIF4F at the mRNA 5′ end through eIF4G–eIF3 interaction, resulting in a 48S initiation complex. The 5′UTR of the mRNA is scanned by the 48 complex until it finds an AUG (or AUG-like) start codon. On reaching AUG, the 48S complex changes conformation to establish base pairing between Met-tRNAi anticodon (bound at the 40S ribosomal P-site) and the AUG codon on mRNA releasing eIF2-GDP, phosphate (Pi), and other initiation factors. A GTP-bound eIF5B then helps to recruit the 60S ribosomal subunit. An elongation competent 80S complex is finally formed by joining of ribosomal subunits which potentiates GTP hydrolysis and release of the initiation factors eIF5B-GDP and eIF1A.

Translation Elongation and Termination

tRNA can bind at three sites on the ribosome: P (peptidyl), A (aminoacyl), and E (exit). During initiation, Met-tRNA$_i$ remains bound at the P site. Elongation (described schematically in Fig. 2) begins by recruitment of another aminoacyl tRNA to the A site of ribosome by base pairing with the second mRNA codon. Aminoacyl tRNAs are escorted to the A site by the GTP-bound eukaryotic elongation factor 1A (eEF1A-GTP). As the correct aminoacyl tRNA is inserted into the A site, strongly base-pairing with the mRNA codon at its anti-codon site, GTP is hydrolyzed and eEF1A-GDP is released. This is a proofreading and rate-limiting step for elongation that allows accurate incorporation of an amino acid corresponding to an mRNA codon. Release of eEF1A-GDP promotes peptide bond formation that causes methionine transfer from the tRNA$_i$ at P site to form a peptidyl tRNA with the aminoacyl tRNA at the A site, leaving tRNAi uncharged at the P site. The ribosome now moves three nucleotides along the mRNA, setting the next codon at a vacant A site in a process called translocation, with the help of GTP-coupled eukaryotic elongation factor 2 (eEF2) and requires hydrolysis of the GTP. This therefore results in the peptidyl tRNA translocation from the A to P site and uncharged tRNA translocation from the P to E site. A new aminoacyl tRNA binding to the A site induces uncharged tRNA release from the E site, and the steps of elongation are continued allowing the polypeptide chain to grow until the ribosome arrives at a stop codon (UAA, UAG, or UGA). No aminoacyl tRNAs correspond to stop codons, instead, eukaryotic release factors (eRFs) are recruited to the ribosomal A site that aid hydrolysis of the tRNA-polypeptide chain bond at P site, discharging the completed polypeptide chain and marking the termination of translation. This is followed by tRNA release and dissociation of ribosomal subunits

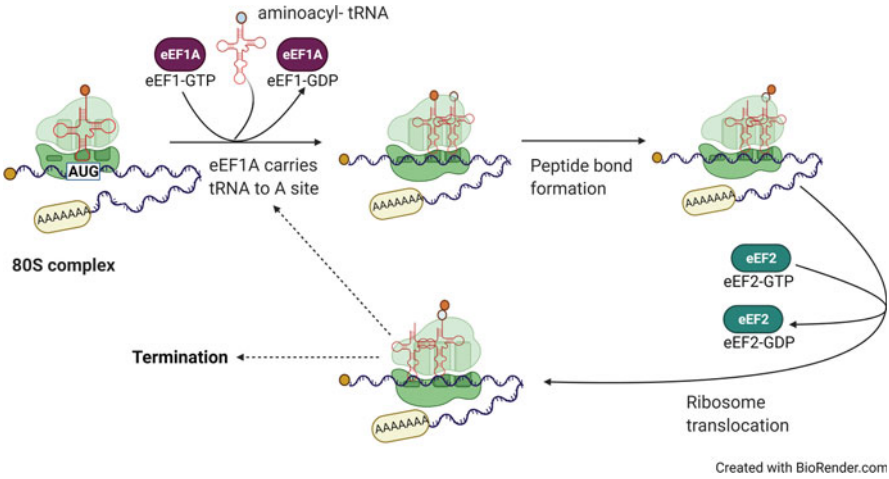

Fig. 2 Translation elongation is marked by decoding of triplet nucleotide codons following the start codon. Aminoacylated tRNAs are transported to the ribosomal A site by the eukaryotic elongation factor 1A (eEF1A)-GTP. tRNA anticodon–mRNA codon pairing induces hydrolysis of eEF1A-GTP, and eEF1A-GDP is removed from the A site. This is followed by ribosome-mediated peptide bond formation and subsequent ribosomal translocation mediated by the eEF2-GTP hydrolysis and change in ribosomal conformation that allows the next aminoacyl-tRNA to enter the A site. The process of elongation continues until the ribosomal A site encounters an in-frame stop codon, resulting in termination of translation

from the mRNA template which are recycled to participate in another round of protein synthesis (reviewed by Dever and Green 2012).

Regulation of mRNA Translation Under Stress

Integrated Stress Response Involves Rewiring of mRNA Translation

Cells trigger the integrative stress response (ISR) pathway when confronted with stresses (such as hypoxia, nutrient deprivation, ultraviolet radiation, viral infection, oxidative damage, and endoplasmic reticular stress) that marks dynamic reprogramming of gene expression to channelize anabolic energy toward adaptation and restoration of cellular homeostasis. Translational reprogramming is an integral part of ISR. This involves arrest of global translation initiation but augmented synthesis of specific proteins that orchestrate stress adaptation (Advani and Ivanov 2019). Stress-induced phosphorylation of the serine 51 residue of eIF2 α-subunit inhibits ternary complex formation that reduces its availability for 43S PIC assembly. eIF2B-regulated GDP/GTP exchange on eIF2α is prevented when eIF2α is phosphorylated. eIF2α phosphorylation (eIF2α-P) is accomplished by four different kinases in mammals that sense distinct stress signals. The heme-regulated inhibitor kinase (HRI) is triggered by low levels of heme, heat shock, and oxidative stress.

Protein kinase RNA (PKR) is triggered by RNA double strands playing important role in innate immune response during viral infections. The general control non--repressible-2 (GCN2) is actuated in response to UV radiation or amino acid deprivation resulting in uncharged tRNA accumulation, and finally the PKR-like ER kinase (PERK) is stimulated by ER stress in unfolded protein response. Therefore, eIF2α is phosphorylated in response to most stresses inhibiting global translation owing to the four eIF2α kinases that are sensitive to one stress or the other (Wek 2018). eIF2α-P however stimulates translation of the activating transcription factor 4 (ATF4), a vital ISR regulatory gene implicated in transcription of other stress responsive genes. The uORFs on the 5′UTR of ATF4 mRNA normally prevents translation initiation from the primary ORF marking the coding sequence (CDS) by initiating ribosomes on them that terminate before reaching the CDS. However, phosphorylated eIF2α (eIF2α-P) decreases ternary complex availability, preventing initiations at the 5′uORFs, thereby allowing the scanning 40S ribosomes to reach the CDS and initiate translation at the AUG in the context of a strong Kozak sequence (Vattem and Wek 2004).

mTOR Signaling Mediates Stress Adaptation by Controlling mRNA Translation

Translation initiation is also inhibited under stress by the regulation of signaling through the protein kinase mammalian target of rapamycin (mTOR) complexed with other factors to form the multi-subunit mTORC1 complex. mTORC1 is sensitive to changes in cellular nutritional (amino acid levels) and energy (ATP:AMP ratio) status. During stress, mTORC1 is inactivated and does not phosphorylate 4EBPs, allowing sequestration of eIF4E. eIF4E is a lowly expressed translation factor. Its sequestration by 4EBP1 further reduces its availability for eIF4F formation, hindering cap-dependent translation initiation (Mader et al. 1995). mTORC1 also controls phosphorylation of S6 kinases that in turn phosphorylate a 40S subunit component; ribosomal protein S6 (RPS6) and eIF4B; an activator of the RNA helicase eIF4A. Inactivation of mTORC1 in stress therefore affects the activity of multiple translation factors. In addition, mTORC1 inhibition also impacts protein expression of many translation factors and ribosomal proteins that bear the 5′-terminal oligopyrimidine (5′TOP) motifs defined by a cytosine next to the 5′mRNA cap, followed by a tract of 4–15 nucleotide pyrimidine residues, resulting in a short and unstructured 5′UTR. Other mRNAs containing 5′TOP like motifs have also been found to be mTORC1 sensitive (Gandin et al. 2016).

Translational Repression Induces Stress Granule Formation

Stress-induced repression of cap-dependent translation initiation is marked by the dissociation of polysomes and accumulation of messenger ribonucleoprotein complexes (mRNPs) in membraneless subcellular compartments designated as stress

granules by associating with RBPs like G3BP1 and TIA1. Stress granules are formed when stress-induced signaling pauses the initiation of translation but allows the continuation of elongation and termination, resulting in accumulation of mRNPs that gather into discrete foci by RNA–RNA, RNA–protein, and protein–protein interactions. Stress granules are dynamic structures formed during stress and are disassembled when stress is released. They serve as storage for translationally halted mRNAs sorting them for translational re-initiation or degradation. Detailed discussion on stress granule and translation can be found in Ivanov et al. (2019).

tRNA Metabolism, Modification, and Cleavage Under Stress Impact mRNA Translation

tRNAs are the second most abundant among cellular noncoding RNAs, and their expression is highly regulated. Availability and abundance of specific tRNAs shape the cellular proteome by impacting codon usage. Inflections in specific tRNA pools at times of stress dynamically control the rate and fidelity of mRNA translation. tRNAs are transcribed by RNA polymerase III that can be controlled under stress in an mTOR-MAF1-dependent manner to abate the synthesis of a group of tRNAs (stress responsive) while not affecting the rate of synthesis of another group (housekeeping tRNAs). This leads to change in cellular tRNA stoichiometry and distribution under stress, thereby impacting codon usage (Orioli 2017). Besides synthesis, tRNAs are regulated during processing, maturation, and aminoacylation, determining their availability for protein synthesis. All these steps may be affected by stress. Trm4- and Trm9-mediated methylation of tRNA wobble base in the presence of stress regulates the abundance of specific tRNA pools for mRNA translation underpinning the importance of tRNA wobble modifications in generating codon bias (Johansson et al. 2008; Chan et al. 2012). Transcripts enriched in degenerate codons displaying distinct codon usage profile are stabilized under stress and code for stress response proteins. tRNAs also encourage miscoding as an adaptive mechanism in stress. Miscoding is defined as the unconventional decoding of an aminoacyl tRNA to a mRNA codon at the ribosomal A site. The disincorporation of amino acid residues in the resulting polypeptide chain enhances its stress responsive function (Netzer et al. 2009). Yet another mechanism of translational regulation is through cleavage of some tRNAs by the stress-induced ribonuclease Angiogenin to form tRNA-derived stress-induced RNAs (ti-RNAs) (Ivanov et al. 2011). Angiogenin cleavage results in tRNA halves called 5′-tiRNAs and 3′-tiRNAs of which some 5′-tiRNAs interfere with translation initiation. $tRNA^{Ala}$- and $tRNA^{Cys}$-derived 5′-tRNAs have motifs called 5′ terminal oligo guanidine (5′-TOG) that are able to form G-quadruplexes and displace eIF4F from the mRNA 5′cap. Cap complex dissociation from mRNA induces stress granule formation via eIF2α phosphorylation and is mediated by the protein YB-1 that can bind to 5′-TOG motifs of 5′tiRNA (Lyons et al. 2016). Other smaller tRNA-derived fragments (tRFs) formed by Angiogenin or Dicer cleavage of pre or mature tRNA under stress

act similar to microRNAs and inhibit translation of specific proteins. Some tRFs have also been shown to act in a sequence-independent fashion to inhibit global translation (reviewed by Advani and Ivanov 2019).

Oxidative Stress and Translational Reprogramming

Oxidative Stress Induces Specific mRNA Translation Programs

Global translation initiation is attenuated in oxidative stress by mechanisms similar to that in other stresses as described in the previous section. However, selective mRNA translation programs are operational to help cells adapt. Few examples include phosphorylation of eIF4E under oxidative stress by MNK kinase to promote specific translation of mRNAs with highly structured 5′UTR in macrophages and resident vascular cells (Duncan et al. 2005) and activation of HRI-mediated phosphorylation of eIF2α inhibiting globin mRNA translation while enhancing translation of ATF4 mRNA to induce stress response genes in erythroid precursors (Suragani et al. 2012).

During stress, mRNAs are sequestered by RBPs into RNA granules to attenuate their translation. A study on transcript partitioning under stress showed that brief arsenite-induced oxidative stress in prostate cancer cells altered the association of mRNAs to the stress granule (SG)-nucleator protein G3BP1 and mRNA association with polysomes (PS). G3BP1-associated transcripts that were depleted in PS correlated with decrease in mitochondrial protein expression, G3BP1-dissociated proteins enriched in PS demonstrated increased expression of proteins involved in cell cycle and cytoprotection while G3BP1-associated and PS-enriched transcripts encoded various stress response pathway proteins, thereby highlighting the role of G3BP1 in guiding transcript partitioning for reprogramming of mRNA translation as part of cellular adaptation to stress (Somasekharan et al. 2020). Another study on pluripotent stem cell's (PSC's) capacity for self-renewal and differentiation in response to oxidative stress and the role of stress granules in it demonstrated SG formation post eIF2 phosphorylation in response to sodium arsenite (SA). SG proteins such as TIAR, G3BP, eIF4E, eIF4G, eIF4A, eIF3B, and PABP are localized in PSC SGs during stress, but these granules disappeared after the release of stress. Expression of only specific pluripotent protein markers such as NANOG and L1TD1 was reduced due to SA treatment in PSCs (Palangi et al. 2017).

tRNA Metabolism Is Altered in Oxidative Stress

Human epithelial cell growth is inhibited in response to oxidative stress by tyrosine tRNA ($tRNA^{Tyr}_{GUA}$) fragmentation. Huh and colleagues have recently shown that oxidative stress-induced fragmentation of pre-$tRNA^{Tyr}_{GUA}$ depletes the cellular pool of mature $tRNA^{Tyr}_{GUA}$ that impair translation of growth-related mRNAs rich in

tyrosine codon such as USP3, EPCAM, and SCD. It also induces exoribonuclease DIS3L2-mediated cleavage of $tRNA^{tyr}_{GUA}$ to form tRNA fragments (tRF^{Tyr}_{GUA}) that sequester hnRNPA1 protein from binding to 3′UTRs of growth-associated mRNAs triggering their destabilization. This is conserved in evolution as they observed similar events in *C. elegans* (Huh et al. 2021). Mis-charging of tRNA in oxidative stress is also an evolutionarily conserved phenomenon observed in both yeast and human cells. In Hela cells, ROS prompted methionine misacylation (acylation to non-cognate tRNAs) in almost 1% of tRNAs promoting methionine incorporation in proteins that contributed to improved cell viability (Netzer et al. 2009). Another layer of translational regulation imposed by oxidative stress is through rewiring the tRNA epitranscriptome. ROS induces the Alkbh8 gene in murine embryonic fibroblast (MEF) cells that promote the expression of enzymes containing selenocysteine for ROS detoxification such as glutathione peroxidase and thioredoxin reductase. Mechanistically, Alkbh8-dependent recoding of UGA stop codon by 5-methoxycarbonylmethyl-2′-*O*-methyluridine (mcm^5Um) modification of wobble uridine on selenocysteine tRNA ($tRNA^{UGA\text{-}SEC}$) is enhanced in response to ROS promoting selenocysteine protein expression and thereby ROS detoxification (Endres et al. 2015).

Oxidative Stress Responsive Factors Modulate mRNA Translation

During oncogenesis, many tumor cells rewire cellular metabolism to support antioxidant processes that promote tumor progression (DeNicola et al. 2011; Son et al. 2013). One such master regulator of antioxidant gene expression is NRF2/Nrf2 (Nuclear factor erythroid 2 Related Factor 2) that is found constitutively activated in many cancers including *Kras*-mutated pancreatic cancers where its expression facilitates cells to cope with oxidative damage promoting pancreatic cancer development (DeNicola et al. 2011). Loss of NRF2 increased cysteine oxidation in response to peroxide, and this was enriched in proteins involved in mRNA translation (DeNicola et al. 2015). Protein variants of the initiation factor eIF3J and the elongation factor eEF2 were later found to be targets of cysteine oxidation that were sensitive to NRF2 expression levels and contributed to decrease in translation efficiency of proteins. This was demonstrated in Nrf2-deficient $Kras^{G12D}$-p53 mutant (KP) organoids where oxidative damage decreased polysomal association of mRNA and reduced S^{35} methionine incorporation into proteins (Chio et al. 2016). NRF2 protein synthesis is also augmented under mild oxidative stress. This was attributed to interaction of eEF1A with a G quadruplex structure on the 5′ UTR of NRF2 in response to oxidative stress promoting NRF2 translation (Lee et al. 2017).

A p53 family transcription factor TAp73 shows homeostatic ability and also contributes in cellular response to oxidative stress by regulating protein synthesis. Depletion of Tap73 was associated with anomalous rRNA processing, decreased translation elongation, and impaired translation. Concomitantly, its knockdown escalated cellular sensitivity to oxidative stress and 5′ adenosine monophosphate-activated protein kinase (AMPK) hyperactivation. TAp73

Table 1 Translation inhibitors in development as anti-cancer drugs

Target	Inhibitor	Stage of drug development
PI3K and mTOR	Gedatolisib (PF-05212384)	Phase III CT for AML, Phase I/II for breast cancer and NSCLC[a]. Satisfactory safety and anti-tumorigenic properties observed for advanced solid tumors in Phase I CT (Shapiro et al. 2015). Moderate activity and tolerance in patients with recurrent endometrial cancers in Phase II CT (Del Campo et al. 2016)
mTORC1	Bimiralisib (PQR309)	Phase I/II CT for breast cancer, Phase II for glioblastoma, lymphoma, head and neck cancer[a].
	Paxalisib (GDC0084)	Active Phase II CT for glioblastoma, Phase I for glioma and meningeal carcinomatosis[a].
	Everolimus (RAD001)	FDA approved for the treatment of advanced RCC, neuroendocrine tumors of pancreatic, gastrointestinal, or lung origin, and for breast cancer[b]. Active Phase III CT for liver cancer, Phase I/II for several other cancers[a].
	Temsirolimus	FDA approved for advanced RCC[b] Marketed for mantle cell lymphoma[a]. Active Phase II CT for AML, Glioblastoma, bladder cancer, Hodgkin's disease, Non-Hodgkin's lymphoma, glioma, thyroid cancer, and Phase I/II CT for follicular lymphoma, head and neck cancer[a]
mTORC1 and mTORC2	Sapanisertib (INK 128)	Active Phase II CT for bladder, endometrial, fallopian tube ovarian, peritoneal, thyroid and urogenital cancers, glioblastoma, neuroendocrine tumors, Precursor cell lymphoblastic leukemia-lymphoma and soft tissue sarcoma. In phase I trial for liver cancer and MCC[a]
MNK1/2	Tomivosertib (EFT508)	Phase II for breast, colorectal, and liver cancers, DLBCL, and solid tumors[a]
EIF4E	ISIS EIF4E Rx (LY2275796)	Phase I/II CT for solid tumors and irinotecan-refractory colon cancer. Stable disease observed in 47% patient who were progressing before administration of ISIS EIF4E Rx + irinotecan (Duffy et al. 2016)
EIF4E–mRNA 5′cap binding	Ribavirin	Active Phase I trials for AML, follicular lymphoma, mantle cell lymphoma, HPV-related malignancies, tongue squamous cell carcinoma, and advanced refractory liver cancer[a]
EIF4E–Hsp27 interaction	Phenazine14	Effective in vitro and in vivo models of castration resistant prostate cancer (Ziouziou et al. 2017)
EIF4E–EIF4G interaction	EGPI-1	Autophagy, ROS generation, apoptosis in A549 lung cancer cells, and tumor shrinkage in A549 mouse xenografts with good safety and pharmacokinetic properties (Wang et al. 2019)
EIF4A1 inhibition	Zotatifin (EFT226)	Phase1/II CT for advanced solid tumors[a]
EIF2α dephosphorylation	Salubrinal	Mimic estrogen-mediated apoptosis response in breast in ER+ breast cancer ex vivo model and

(continued)

Table 1 (continued)

Target	Inhibitor	Stage of drug development
		synergizes with 4-hydroxytamoxifen (Sengupta et al. 2019)
Translation elongation		
First peptide bond formation	Omacetaxine mepesuccinate	FDA approved for CML[b] in Phase II trials for AML and myelodysplastic syndromes
Amino acid pools	Asparaginase Erwinia chrysanthemi	FDA approved for ALL[b] in trial for other Leukemias

CT clinical trial, *RCC* renal cell carcinoma, *TCC* transitional cell carcinoma, *NSCLC* non-small-cell lung cancer, *MCC* Merkel cell carcinoma, *DLBCL* diffuse large B-cell lymphoma, *HPV* human papilloma virus, *CML* chronic myeloid leukemia, *ALL* acute lymphoblastic leukemia
[a]Based on information from https://clinicaltrials.gov/ and/or https://adisinsight.springer.com/. References in the table: Shapiro et al. (2015), Del Campo et al. (2016), Duffy et al. (2016), Ziouziou et al. (2017), Wang et al. (2019), and Sengupta et al. (2019)
[b]Drug information from https://www.cancer.gov/

maintained active translation of mitochondrial transcripts in oxidative stress, thereby sustaining mitochondrial function and aiding stress adaptation (Marini et al. 2018).

Controlling mRNA Translation: A Remedial Avenue in Cancer Therapeutics

The primary challenge in developing anti-cancer drugs is to walk the line between drug efficacy in cancer cells and toxicity in normal cells to establish a therapeutic window. mRNA translation is an essential process for cancer cell survival with most oncogenic programs converging on it and its deregulation is often associated with resistance. The past few years have seen the advent of several small molecule inhibitors that target either the constituents of signaling pathways regulating translation or the components of the translation machinery itself. These molecules alone or in combination with frontline therapies have shown to greatly improve patient outcome. Table 1 lists the translation inhibitors in routine use or in active development as cancer therapeutics. Since protein synthesis is at the nexus of multiple ROS regulated pathways, it could be intriguing to investigate the effects of combining ROS modulating drugs with translation inhibitors. Indeed, Chio and colleagues have shown that glutathione synthesis inhibitor buthionine sulfoximine (BSO) together with MK2206, an AKT inhibitor effective in pancreatic cancer preclinical settings by decreasing the rate of protein synthesis (Chio et al. 2016). More such studies will enable identification of effective treatment strategies for difficult to cure cancers.

Conclusions

Regulation of mRNA translation is increasingly being recognized as vital for cancer progression and therapy resistance. The links between oxidative stress, translational remodeling, and cancer are also becoming evident from emerging studies that point to the importance of exploring the therapeutic potential of combining ROS inducers/scavengers with mRNA translation inhibitors. However, greater understanding of how ROS levels correlate with translational rewiring in different cancer contexts is required to exploit this vulnerability effectively for personalized therapy.

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