Multifaceted Control of mRNA Translation Machinery in Cancer

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Abstract

The mRNA translation machinery is tightly regulated through several, at times overlapping, mechanisms that modulate its efficiency and accuracy. Due to their fast rate of growth and metabolism, cancer cells require an excessive amount of mRNA translation and protein synthesis. However, unfavorable conditions, such as hypoxia, amino acid starvation, and oxidative stress, which are abundant in cancer, as well as many anti-cancer treatments inhibit mRNA translation. Cancer cells adapt to the various internal and environmental stresses by employing specialised transcript-specific translation to survive and gain a proliferative advantage. We will highlight the major signaling pathways and mechanisms of translation that regulate the global or mRNA-specific translation in response to the intra- or extra-cellular signals and stresses that are key components in the process of tumourigenesis.

Keywords: mRNA translation, translation machinery, protein synthesis, stress, signaling pathway, tumourigenesis, cancer, initiation, elongation, termination, ribosome recycling

1. Introduction

Beyond the regulation of transcription, post-transcriptional mechanisms of gene expression regulation, including mRNA translation, are pivotal for adjustment of the gene expression programme in response to intra- or extracellular signals. In fact, changes in the steady state of mRNA levels only partially correlate with variations in protein levels (Vogel, de Sousa Abreu et al. 2010, Ghazalpour, Bennett et al. 2011, Schwanhäusser, Busse et al. 2011), highlighting the crucial role of post-transcriptional mechanisms in determining the gene expression programme. Changes in the global or mRNA-specific translation rate govern fundamental biological processes including energy management, homeostasis, cell proliferation, survival and differentiation (Tanenbaum, Stern-Ginossar et al. 2015, Truitt, Conn et al. 2015, Leibovitch and Topisirovic 2018). Consequently, dysregulated translational control plays a key role in a plethora of diseases including cancers, wherein general or transcript-specific changes in mRNA translation are ubiquitously observed.

The intricate mechanism of regulation of mRNA translation allows quick acting and precise responses to the constantly changing environments. This is enabled by a complex network of translation factors, RNA-binding proteins (RBPs), non-coding RNAs, RNA modification, and the sequence features and secondary structures embedded within the mRNAs. Regulation of global translation in the cell is mainly achieved via post-translational modulation of translation factors through an array of signaling pathways, whereas transcript-specific translational control is mostly directed by the sequences embedded within the mRNA. In the following sections, we will review the process of mRNA translation in eukaryotes, with an emphasis on mammals and discuss the major mechanisms that control this process, along with anomalies that contribute to various aspects of tumourigenesis.

2. mRNA translation in higher eukaryotes

Eukaryotic mRNAs contain several key features that are critical for regulation of translation efficiency and stability. Nearly all nuclear-encoded cellular mRNAs contain a modified nucleotide at their 5´ terminus (m7GpppN, where m is a methyl group, and N is any nucleotide) termed the 5´ cap. The cap structure plays prominent roles in regulation of stability of mRNA by protecting against the 5´ to 3´ exonucleases (Furuichi, LaFiandra et al. 1977). Cap also facilitates translation initiation with the aid

of the eukaryotic Initiation Factor 4F (eIF4F) complex (Grifo, Tahara et al. 1983). A second feature of eukaryotic mRNAs is the presence of the 5′ Un-Translated Region (5´ UTR) located between the cap and translation START codon. The length of 5´ UTRs varies considerably among individual genes, ranging from a few to thousands of nucleotides (Mignone, Gissi et al. 2002) and in general has an inverse correlation with the mRNA translation efficiency (Kochetov, Ischenko et al. 1998). Presence of specific nucleotide sequences (*e.g.* terminal oligopremydine or TOP sequences (Iadevaia, Caldarola et al. 2008)) or features such as hairpin structures (Kozak 1986) also significantly impacts the translation efficiency of mRNAs and their sensitivity to variations in the activity of the translation machinery.

The open reading frame (ORF) that encodes the amino acid sequence begins with the START codon (typically AUG) and ends with the STOP codon (UAG, UAA, or UGA). The length and sequence of the 3´ UTR, located after the STOP codon, vary considerably among different genes and even different mRNA variants encoded by the same genes (Mignone, Gissi et al. 2002). RBP-binding sites and microRNAs (miRNAs)-recruitment elements are particularly enriched in 3´ UTRs. Another distinctive feature of eukaryotic mRNAs is the presence of a poly-Adenine stretch (poly(A) tail), which is the product of the endonucleolytic cleavage of the nascent transcript in the nucleus, followed by the template-independent synthesis of a poly(A) tail at their 3´ ends. Almost all mRNAs, with some notable exceptions such as the Histone mRNAs (Yang, Duff et al. 2011), contain a poly(A) tail. The typical poly(A) tails are ~60-80 nt long in human, and in addition to providing protection against 3´ to 5´ exonucleases, they increase the translation efficiency of the mRNA through recruitment of RBPs such as poly(A)-binding proteins (PABPs) (Kessler and Sachs 1998, Kahvejian, Svitkin et al. 2005). Notably, PABPs also interact with the components of the eIF4F complex, thus creating a distinctive circularised (closed-loop) conformation for mRNA that accelerates the recycling of the ribosomal subunits and translation factors that are released upon termination of translation (Wells, Hillner et al. 1998).

The process of mRNA translation consists of four stages: initiation, elongation, termination and ribosome recycling (**Fig. 1**). The first stage, termed “translation initiation” consists of two main events occurring in parallel: the formation of the 43S pre-initiation complex (PIC) and assembly of the eIF4F complex. The PIC is formed through assembly of the 40S ribosomal subunit with the eukaryotic initiation factors

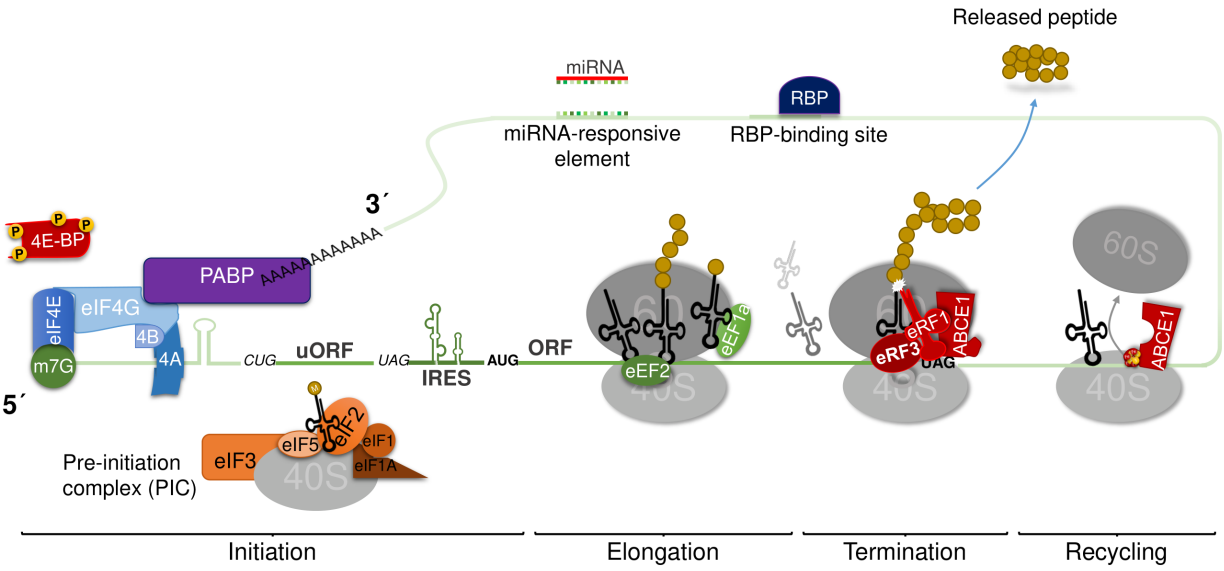
(eIFs); eIF1, eIF1A, eIF3 and eIF5 and the ternary complex (TC; consisting of eIF2, initiator methionyl-transfer RNA ($tRNA_i^{Met}$) and GTP). The eIF4F complex is formed by assembly of the cap-binding protein eIF4E, the scaffolding protein eIF4G and the DEAD box RNA helicase, eIF4A. Upon binding of this complex to the cap, the PIC is recruited to the mRNA through binding of eIF4G to eIF3 and scans the 5´ UTR in the 5´ to 3´ direction in order to identify the translation START codon (reviewed in (Shirokikh and Preiss 2018)).

The scanning process could be impeded by secondary structures, high GC content and RBPs that bind to this region (Babendure, Babendure et al. 2006). While the 5´ UTR of most vertebrate mRNAs have a typical length of 20-100 nt, it is estimated that around a quarter of mRNAs have a 5´ UTR longer than 100 nt. Notably, the majority of mRNAs encoding proto-oncogenes have long 5´ UTRs, making them particularly vulnerable to the impediment of the 40S ribosome scanning due to the presence of secondary structures (Kozak 1987). Scanning through such impediments is facilitated by RNA helicases. The eIF4A subunit of the eIF4F complex unwinds such secondary structures and is essential for translation of mRNAs with structured 5´ UTRs (Rubio, Weisburd et al. 2014). While translation initiation of most mammalian mRNAs is mediated by binding of the eIF4F complex to the 5′ cap, translation of many cellular mRNAs is not fully impaired in the absence or upon inactivation of eIF4F, due to the presence of alternative mechanisms of translation initiation (Weingarten-Gabbay, Elias-Kirma et al. 2016). The ability to function independently of the canonical cap-dependent translation initiation enables selective-mRNA translation when cap-dependent translation is inhibited (*e.g.* under stress conditions). Indeed, as discussed below, cancer cells heavily rely on non-canonical cap- or eIF4F-independent initiation mechanisms to avoid translational shut-down of important oncogenes under stress conditions.

Upon detection of the start codon by the PIC, the 60S ribosomal subunit is recruited to form the complete 80S ribosome and begin the “elongation” phase. The eukaryotic elongation factors 1 and 2 (eEF1 and eEF2) and eIF5A play major roles in this phase (Moldave 1985, CARLBERG, NILSSON et al. 1990). Firstly, the GTPase, eEF1, mediates the binding of the aminoacyl-tRNA (tRNA bound to the cognate amino acid) to the A site on the ribosome, powered by hydrolysis of GTP to GDP. This is followed by the transfer of the polypeptide chain from the peptidyl-tRNA in the P site to the aminoacyl-tRNA in the A site. eIF5A facilitates the substrate positioning for peptide

bond formation (Spahn, Gomez-Lorenzo et al. 2004, Taylor, Nilsson et al. 2007, Shoji, Walker et al. 2009, Ferguson, Wang et al. 2015, Ling and Ermolenko 2016). Next, the tRNA from the A site, now bound to the nascent polypeptide, translocates to the P site of the ribosome while the newly deacetylated tRNA in P site translocates to the E site. This process is aided by the GTPase, eEF2 (Moazed and Noller 1989, Budkevich, Giesebrecht et al. 2011, Behrmann, Loerke et al. 2015). Once a new aminoacyl-tRNA joins the now vacant A site, the deacyl-tRNA in the E site can exit the ribosome. Elongation continues until the ribosome arrives at one of the three stop codons, whereupon translation termination can occur.

Efficient translation termination relies on two main release factors (RFs), eRF1 and eRF3 (Stansfield, Jones et al. 1995, Zhouravleva, Frolova et al. 1995, Alkalaeva, Pisarev et al. 2006). The RFs form a ternary complex along with GTP, where the stop codon is recognised by eRF1, followed by hydrolysis of GTP by eRF3. This facilitates extension of the Gly-Gly-Gly motif of eRF1 towards the final peptidyl-tRNA where it can hydrolyse the nascent peptide to release it from the tRNA and enables its exit from ribosome (Atkinson, Baldauf et al. 2008). Following the release of the final polypeptide product, the last step of translation, recycling, takes place. At this stage, the 80S ribosomal subunit is bound to the mRNA, along with eRF1 in the A site and the deacylated tRNA in the P site (Korostelev, Asahara et al. 2008, Laurberg, Asahara et al. 2008, Weixlbaumer, Jin et al. 2008, Jin, Kelley et al. 2010). The first step of recycling is facilitated by a member of the ATP-binding cassette family, ABCE1, which



undergoes conformational change in its iron-sulphur cluster, rotation of which causes

the dissociation of the 60S subunit (Pisarev, Skabkin et al. 2010, Barthelme, Dinkelaker et al. 2011) followed by dissociation of the deacylated tRNA from the 40S subunit (reviewed in (Hellen 2018)).

Figure 1. Overview of mRNA translational in eukaryotes.
Cap-dependent initiation requires two parallel events: **i.** formation of the eIF4F complex, comprised of cap-binding protein, eIF4E; scaffold protein, eIF4G; and RNA-helicase, eIF4A, and **ii**. formation of the pre-initiation complex (PIC), comprised of the 40S ribosomal subunit, eIF2, bound to GTP and methionine-loaded initiator tRNA, eIF1, eIF1A, eIF3, and eIF5. Interaction of eIF4G with the poly(A)-binding protein (PABP) circularises the mRNA. PIC is recruited to the mRNA through interaction of eIF3 with eIF4G and scans the 5´ UTR aided by the RNA helicase eIF4A, until the recognition of the START codon. Once the start codon is recognised, the 60S subunit joins to form the 80S ribosome and begins the elongation stage. Elongation involves the possessive movement of the ribosome along the mRNA as the nascent polypeptide is synthesised and is aided by eEF1a and eEF2. Binding of aminoacyl-tRNAs to their corresponding codon at the A site is facilitated by eEF1a while eEF2 enables translocation of the peptidyl-tRNA through the ribosome and exit of the deacyl-tRNA from the ribosome. Termination begins when the STOP codon enters the ribosomal A site and is recognised by eRF1/eRF2/GTP complex. Movement of the stop codon from the A to P site causes polypeptide chain release through hydrolysis by eRF1. In concert witch eRF1, ABCE1-stimulated release of the 60S subunit leaves a 40S/mRNA/deacyl-tRNA complex. At this point, the 40S subunit can be ejected (recycled) to join a new mRNA or can remain bound to the same transcript and reinitiate for a new round of translation.

3. Dysregulated control of translation initiation in cancer

mRNA translation is the most energy consuming process in the cell (Buttgereit and Brand 1995). Therefore, in terms of energy conservation, it is intuitive that initiation is the stage at which the translation process is most heavily regulated to avoid the cells having to abrogate translation of an mRNA half-way. Multiple mechanisms involving a myriad of translation factors, specialised RNA sequences and structures, and regulatory pathways tightly control mRNA translation in both global and transcript-specific scales. Cancer cells frequently modify, escape or hijack these mechanisms in order to reprogramme the translatome and achieve a competitive advantage.

3.1. Regulation of cap-dependent initiation

Translation of the majority of eukaryotic mRNAs commences upon formation of the eIF4F complex on the cap (**Fig. 2A**). Formation of eIF4F complex on cap builds upon binding of eIF4G to the dorsal surface of eIF4E through a conserved canonical eIF4E-binding motif, YXXXXLΦ, where Φ is a hydrophobic amino acid and X is any amino acid (Mader, Lee et al. 1995). The 4E-binding proteins (4E-BP1-3), which also

contain the canonical eIF4E-binding motif, compete with eIF4G for binding to the eIF4E-binding motif (**Fig. 2B**).

3.1.1. 4E-BPs

While 4E-BP2 is mostly expressed in neural cells (Banko, Poulin et al. 2005), 4E-BP1 is the most abundant member in other cell types. 4E-BP3 is the least abundant paralog, although its expression is induced in certain conditions such as sustained mechanistic target of rapamycin (mTOR) inhibition (Tsukumo, Alain et al. 2016). The ability of 4E-BPs to eIF4F complex formation is negatively correlated with the phosphorylation of a few key amino acids (Gingras, Raught et al. 2001). 4E-BP1 and 2 are phosphorylated by mTOR on at least 4 amino acids (Thr-37, Thr-46, Ser-65, and Thr-70) in a sequential manner, (Thr-37 and Thr-46, followed by Thr-70 and Ser-65 phosphorylation) (Gingras, Gygi et al. 1999). Additional phosphorylation events, including Ser-83 (Fadden, Haystead et al. 1997), Ser-101 (HEESOM, AVISON et al. 1998), and Ser-112 (Wang, Li et al. 2003), have also been identified. Notably, besides disrupting the affinity of 4E-BPs for eIF4E, phosphorylation of 4E-BPs also results in their stabilisation (Yanagiya, Suyama et al. 2012), thus balancing the abundance and activity of these important regulatory proteins to maintain cellular homeostasis.

Expression and phosphorylation levels of 4E-BPs have significant impacts on tumourigenesis. Phosphorylation of 4E-BPs by mTORC1 promotes cell proliferation (Fingar, Richardson et al. 2004, Dowling, Topisirovic et al. 2010). Reduced 4E-BP1 expression (Wang, Feng et al. 2019) or its increased phosphorylation correlates with poor prognosis in several types of cancer (Armengol, Rojo et al. 2007, Rojo, Najera et al. 2007, O'Reilly, Warycha et al. 2009). 4E-BP1 phosphorylation also enables cancer cell resistance to stress and anti-cancer treatments. For instance, increased 4E-BP1 phosphorylation and cap-dependent mRNA translation is a potent mechanism by which the redox master regulator NRF2 promotes cell growth in response to oxidative stress in *Kras*-mutated pancreatic cancer cells (Chio, Jafarnejad et al. 2016). Similarly, treatment with active-site mTOR inhibitor MLN0128 (Mallya, Fitch et al. 2014) and combined AKT (AKTi) and MEK (PD0325901) inhibitors induce cancer cell apoptosis via repression of 4E-BP1 phosphorylation (She, Halilovic et al. 2010). In contrast, prostate cancer cells that express higher levels of 4E-BP1 are less sensitive to treatment with phosphoinositide 3 kinase (PI3K) inhibitor BKM120 and mTOR inhibitor

MLN0128 (Hsieh, Nguyen et al. 2015), underlying the cell type specificity in sensitivity to pharmaceuticals that modulate signaling pathways and translation machinery. These observations may also indicate the presence of a subpopulation of cancer cells with lower levels of protein synthesis, thus a lesser sensitivity to therapeutic agents that impinge on protein synthesis.

Interestingly, stem cells and cancer stem cells, a small subpopulation of dormant tumour stem cells, exhibit substantially lower mTOR activity (likely due to its proteasomal degradation (Spevak, Elias et al. 2020)) and dramatically reduced global translation compared to their differentiated progenies (Sampath, Pritchard et al. 2008, Signer, Magee et al. 2014, Blanco, Bandiera et al. 2016). 4E-BPs are required for maintenance of mouse embryonic stem cells (Tahmasebi, Jafarnejad et al. 2016). However, the contribution of 4E-BPs to the maintenance and lower translation rate observed in cancer stem cells remains unknown. The functional impact of 4E-BPs on cancer also depends on the genetic context. For instance, while mouse embryonic fibroblasts (MEFs) lacking 4E-BPs undergo p53-dependent senescence and are resistant to oncogenic transformation, depletion of 4E-BP1 and 2 in p53 knockout mice increased the rate of tumourigenesis (Petroulakis, Parsyan et al. 2009).

In addition to mTOR, phosphorylation of 4E-BP is also controlled by other signaling pathways (**Fig. 2A**). Cyclin-dependent kinase 1 (CDK1) phosphorylates 4E-BP1 at Thr-70, Ser-83, and Ser-65 (Shin, Wolgamott et al. 2014, Shuda, Velásquez et al. 2015, Velásquez, Cheng et al. 2016, Spevak, Elias et al. 2020) during mitosis, and sustains the global translation level in myeloid progenitor cells, wherein mTOR is targeted for proteasomal degradation (Spevak, Elias et al. 2020). Alternative pathways of 4E-BP phosphorylation, including GSK3 (Shin, Wolgamott et al. 2014), the Ser/Thr kinase Pim-2 (Fox, Hammerman et al. 2003), and Casein kinase 1epsilon (CK1e) (Shin, Wolgamott et al. 2014), have also been identified but their pathophysiological relevance are not well understood.

3.1.2. mTORC1: the central hub of translational regulation

mTOR functions as a focal point for coordinating fundamental cellular processes, such as mRNA translation, autophagy, cell growth and metabolism and due to its prominent role in translational control and implication in almost every type of cancer (Mossmann, Park et al. 2018), will be further examined here.

mTOR activity is stimulated via numerous intra- and extracellular inputs, such as hormones, cellular energy, oxygen, availability of amino acids, glucose, and growth factors (Saxton and Sabatini 2017). In general, mTOR activates anabolic processes (*e.g.* lipid and protein synthesis) and blocks catabolic processes, such as autophagy. mTOR is a highly conserved Ser/Thr kinase and found in two functionally distinct complexes associated with different co-factors. mTOR complex 1 (mTORC1), which is inhibited by Rapamycin, a natural allosteric inhibitor of mTOR, is composed of mTOR, the scaffolding protein Raptor (regulatory-associated protein of TOR), PRAS40 (proline-rich AKT substrate 40 kDa), mLST8, and Deptor (Peterson, Laplante et al. 2009, Aylett, Sauer et al. 2016). mTORC2 is not sensitive to Rapamycin and is composed of mTOR, Rictor (rapamycin-insensitive companion of TOR), Deptor, mLST8, mSIN1, and Protor (Frias, Thoreen et al. 2006, Jacinto, Facchinetti et al. 2006, Pearce, Huang et al. 2007, Thedieck, Polak et al. 2007, Woo, Kim et al. 2007, Fu and Hall 2020). mTORC1 and 2 govern distinct cellular processes and, while several mTORC1 substrates are directly involved in the regulation of translation, the role of mTORC2 in translational control is much less studied (Zinzalla, Stracka et al. 2011, Nayak, Feliers et al. 2013).

mTORC1 activity is regulated via several distinct, although often interconnected, mechanisms (**Fig. 2A**). The PI3K is a major upstream regulator that is activated in response to growth factors. PI3K activates AKT serine/threonine kinase (AKT), via recruitment of mTORC2 and pyruvate dehydrogenase kinase 1 (PDK1). Activated AKT phosphorylates both the PRAS40 subunit of mTORC1, as well as the mTOR inhibitor, tuberous sclerosis complex 2 (TSC2) thus repressing its association with TSC1 leading to inactivation of TSC2. TSC2 is a GTPase-activation protein (GAP) for the small G-protein Rheb, the GTP-bound form of which activates mTORC1 (Inoki, Li et al. 2002). The Ras-MAPK (mitogen-activated protein kinase) signaling pathway also activates mTORC1 via inhibitory phosphorylation of TSC2 (Ma, Chen et al. 2005) and the stimulatory phosphorylation of PRAS40 (Carrière, Cargnello et al. 2008). Inactivation of TSC2 can also occur due to its phosphorylation by IKKβ, a downstream kinase of the TNFα signaling pathway (Lee, Kuo et al. 2007), and the stress-activated kinase p38-activated kinase MK2 (MAPKAPK2) (Li, Inoki et al. 2003).

mTORC1 activity is also controlled via the intracellular level of amino acids, sensed by a variety of mechanisms, including the Rag GTPase complex (Sancak, Peterson et al. 2008), adenosine diphosphate ribosylation factor–1 GTPase (Arf1)

(Jewell, Kim et al. 2015), the lysosomal transmembrane protein SLC38A9 (Shen and Sabatini 2018), and the homotypic fusion and vacuole protein sorting (HOPS) complex (Hesketh, Papazotos et al. 2020). These factors recruit mTORC1 to the lysosomal surface, where it interacts with active Rheb GTPase (reviewed in (Saxton and Sabatini 2017, Mossmann, Park et al. 2018, Kim and Guan 2019, Peng and Jewell 2020)). In contrast, mTOR is inhibited by 5´-adenosine monophosphate-activated protein kinase (AMPK) under hypoxia and high AMP/ATP ratio, indicators of physical exercise and low energy availability (**Fig. 2B**). Activated AMPK directly phosphorylates TSC2 (on different residues than those phosphorylated by MAPK and AKT), thereby stabilise the TSC1-TSC2 complex, leading to mTORC1 inhibition (Inoki, Zhu et al. 2003). Activated AMPK also directly phosphorylates mTOR on Ser-2448, a nutrient-sensitive phosphorylation site that is located within the catalytic domain, leading to mTORC1 inactivation (Bolster, Crozier et al. 2002).

Other sources of stress, such as DNA damage, could also result in the inhibition of mTORC1 via the p53-dependent upregulation of AMPK (Feng, Hu et al. 2007). Similarly, the glycogen synthase kinase 3 (GSK3) directly inhibits mTOR pathway by phosphorylating TSC2 (Inoki, Ouyang et al. 2006). Besides the AMPK pathway, in hypoxic conditions the hypoxia-inducible REDD1 protein releases TSC2 from its growth factor-induced association with inhibitory 14-3-3 proteins, leading to repression of mTORC1 (DeYoung, Horak et al. 2008). Furthermore, the p38-regulated/activated kinase (PRAK) represses mTORC1 under energy starvation by direct phosphorylation of Rheb at Ser-130 and impairing its GTP-binding ability (Zheng, Wang et al. 2011) (**Fig. 2B**).

Besides phosphorylation of 4E-BPs, mTORC1 activity also controls translation initiation by regulation of several key substrates including, S6Ks, LARP1, and eIF4G.

3.1.3. S6Ks

The S6K1 protein was originally identified as a epidermal growth factor-activated ribosomal protein S6 kinase, the activation of which is directly controlled by phosphorylation (Jenö, Ballou et al. 1988). S6K2 was identified a decade later, and its activity was shown to be stimulated by serum stimulation and inhibited by Wortmannin (PI3 Kinase inhibitor) and mTOR inhibitor Rapamycin (Gout, Minami et al. 1998, Saitoh, ten Dijke et al. 1998), suggesting an mTOR-regulated mechanism of activation.

Utilisation of different translation start sites generates two isoforms for each protein (p70-S6K1 and p85-S6K1 and p54-S6K2 and p56-S6K2) (Grove, Banerjee et al. 1991, Gout, Minami et al. 1998). Whereas 4E-BPs mainly control the rate of cell proliferation downstream of mTOR, S6Ks predominantly affect the regulation of cellular and organismal size (Ohanna, Sobering et al. 2005, Dowling, Topisirovic et al. 2010).

Besides mTORC1, several other kinases including PDK1 (Pullen, Dennis et al. 1998), PKC (Valovka, Verdier et al. 2003), GSK3 (Shin, Wolgamott et al. 2011), MEK (Pardo, Arcaro et al. 2001), and receptor tyrosine kinases, such as platelet-derived growth factor receptor (PDGFR (Rebholz, Panasyuk et al. 2006)), all of which are critical components of oncogenic signaling pathways, can phosphorylate and regulate S6Ks activities. S6K1 and 2 have differential sensitivities to these upstream signals. While S6K1 is more sensitive to mTOR inhibition, S6K2 is more sensitive to MEK inhibition (Pardo, Arcaro et al. 2001). Similarly, leucine-deprivation, which is a strong environmental stimulus for repression of mTOR activity, reduced S6K1 but not S6K2 phosphorylation (Talvas, Obled et al. 2006).

S6Ks have profound impacts on several hallmarks of cancer, and amplification or overexpression of S6K1 and 2 has been observed in several types of cancer (Bärlund, Forozan et al. 2000, Van der Hage, van den Broek et al. 2004, Karlsson, Waltersson et al. 2011, Pérez-Tenorio, Karlsson et al. 2011). In ovarian cancer cells, expression of constitutively active forms of S6Ks increases invasiveness and migration by augmenting Matrix Metalloproteinase 9 (MMP-9) expression (Zhou and Wong 2006). Similarly, S6K1 induces expression of Hypoxia-inducible factor 1-alpha (HIF-1α) and Vascular endothelial growth factor (VEGF), two key drivers of angiogenesis, in multiple cancers (Skinner, Zheng et al. 2004). S6Ks also contribute to tumourigenesis through promoting cancer cell proliferation and resistance to apoptosis (Sridharan and Basu 2011), and chemo-resistance (Pardo, Wellbrock et al. 2006). Consistently, depletion of S6K1 prevented lung metastasis in a breast cancer xenograft model (Akar, Ozpolat et al. 2010), and reversed the epithelial to mesenchymal transition (EMT) (Pon, Zhou et al. 2008), as well as tumor growth and metastasis, in ovarian cancer cells (Ma, Kala et al. 2018).

Beside regulation of cells size, the substrates of S6Ks are also involved in various biological functions including metabolism (Um, Frigerio et al. 2004, Dagon, Hur et al. 2012, Kim, Pyo et al. 2012), apoptosis (Harada, Andersen et al. 2001), cell

proliferation (Goh, Pardo et al. 2010), cytoskeleton organization (Ip, Cheung et al. 2011), transcription (Ismail, Myronova et al. 2013) and mRNA translation. The best-known substrate of S6Ks, involved in mRNA translation, is their namesake ribosomal protein S6 (rpS6), a component of the 40S ribosomal subunit. There are 5 highly conserved phosphorylation sites—Ser-235, Ser-236, Ser-240, Ser-244, and Ser-247—located at the C terminus of rpS6 (Krieg, Hofsteenge et al. 1988). While phosphorylation of these residues is mainly attributed to the S6Ks (predominantly S6K2), phosphorylation at Ser-235 and Ser-236 is still observed in S6K1/2 double-knockout cells, likely due to the activity of the 90 kDa ribosomal s6 kinases (RSKs) (Pende, Um et al. 2004) (**Fig. 2A**). RSK1 as well as ERK 1/2 were shown to also phosphorylate the mTOR inhibitor TSC2, thus activating mTOR and its downstream signaling pathways and leading to increased cell proliferation and tumourigenesis (Ma, Chen et al. 2005), reflecting the multiple points of crosstalk between these two oncogenic pathways. Furthermore, S6Ks are part of an intricate negative feedback loop mechanism that dampens mTORC1 activity via phosphorylation of the mTORC2 components Rictor and Sin1. This in turn decreases the mTORC2-dependent phosphorylation of AKT (Dibble, Asara et al. 2009), or phosphorylation and inactivation of the Insulin Receptor Substrate 1 (IRS-1) upstream of PI3K/AKT (Smadja-Lamère, Shum et al. 2013).

Surprisingly, while S6Ks activate mRNA translation, MEFs, wherein all five serine residues in rpS6 are substituted with alanine ($rpS^{P-/-}$), exhibit elevated rate of protein synthesis and accelerated cell division, although they are significantly smaller than wild type MEFs (Ruvinsky, Sharon et al. 2005). Furthermore, while the impact of mutation of the rpS6 phosphorylation sites on cell sizes mirrors that of S6Ks-double knockout, its impact on general mRNA translation does not mimic that of S6Ks-depleted cells, in which global mRNA translation is only modestly reduced (Tang, Hornstein et al. 2001). Increased expression or phosphorylation of rpS6 has been observed in cancers such as non-small cell lung cancer (NSCLC) (Chen, Tan et al. 2015), pancreas (Hirashita, Hirashita et al. 2020), angiomyolipomas (Robb, Astrinidis et al. 2006), squamous cell carcinoma of the oral cavity (Chaisuparat, Rojanawatsirivej et al. 2013), and esophageal squamous cell carcinoma (Kim, Jang et al. 2013).

S6Ks also control translation initiation via phosphorylation of the translation initiation factors eIF4B and Programmed cell death 4 (PDCD4). Phosphorylation of eIF4B stimulates the helicase activity of eIF4A by enhancing the affinity of eIF4A for

ATP and mRNA (Rogers, Richter et al. 1999) and promotes mRNA translation. Phosphorylation of eIF4B on Ser-406 by MAPK and PI3K/mTOR induced by insulin also stimulates mRNA translation (Van Gorp, Van Der Vos et al. 2009). Expression of eIF4B is elevated in numerous malignancies such as lung cancer (Attar-Schneider, Drucker et al. 2016) and diffuse large B-cell lymphoma (DLBCL) (Horvilleur, Sbarrato et al. 2014). eIF4B-mediated upregulation of proto-oncogenes and anti-apoptotic proteins such as bcl-2 and XIAP, which harbor structured 5´ UTRs, hence are more sensitive to eIF4A helicase activity promotes cancer cell proliferation and survival (Wang, Begley et al. 2016, Kapadia, Nanaji et al. 2018). Conversely, depletion of eIF4B leads to decreased cell survival and proliferation (Shahbazian, Parsyan et al. 2010). PDCD4 is a tumour suppressor protein (Jansen, Camalier et al. 2005), expression of which is reduced in several types of cancer (Chen, Knösel et al. 2003, Chang, Miller et al. 2011). PDCD4 binds eIF4A and inhibits its activity by competing with eIF4G for binding to eIF4A (Yang, Jansen et al. 2003). S6Ks elevates eIF4A activity via phosphorylation and promoting degradation of PDCD4 (Dorrello, Peschiaroli et al. 2006).

3.1.4. LARP1

LARP1 is another key substrate of mTORC1 that increases the stability (Gentilella, Morón-Duran et al. 2017), while repressing the cap-dependent translation initiation, of TOP mRNAs (**Fig. 2C**) (Tcherkezian, Cargnello et al. 2014, Fonseca, Zakaria et al. 2015, Lahr, Fonseca et al. 2017, Philippe, Vasseur et al. 2018), which includes ribosomal proteins and the majority of translation factors (Iadevaia, Caldarola et al. 2008). LARP1 simultaneously binds to the cap and the poly(A) tail of TOP mRNAs (Aoki, Adachi et al. 2013, Hong, Freeberg et al. 2017, Al-Ashtal, Rubottom et al. 2019), thus preserves TOP mRNAs in a long polyadenylated state during long-term amino acid starvation, allowing the rapid resumption of their translation after addition of amino acids (Ogami, Oishi et al. 2019). mTORC1-dependent phosphorylation of LARP1 controls its affinity for the TOP motif and translation repressive function (Philippe, Vasseur et al. 2018). Considering the crucial role of ribosomes in protein synthesis and cell growth, the LARP1-mediated control of ribosomal proteins and translation factors by mTORC1 plays an important role in coordinating the production of ribosomes in response to environmental signals that promote cell growth (Hong,

Freeberg et al. 2017). As such, depletion of LARP1 reduces cancer cell growth and proliferation, cell migration, invasion, and tumorigenesis (Tcherkezian, Cargnello et al. 2014, Mura, Hopkins et al. 2015, Hong, Freeberg et al. 2017). Furthermore, LARP1 upregulation has been observed in several types of cancer (Xie, Huang et al. 2013, Kato, Goto et al. 2015, Mura, Hopkins et al. 2015, Ye, Lin et al. 2016, Xu, Xu et al. 2017). However, hitherto little information is available on the impact of LARP1 phosphorylation on tumourigenesis.

3.1.5. eIF4G

eIF4G (eIF4G1) is a phosphoprotein containing several phosphorylation sites sensitive to PI3K/mTOR (Raught, Gingras et al. 2000). eIF4G is also phosphorylated on Ser-1093 by the 40S ribosomal subunit protein, receptor for activated C kinase (RACK1), in association with the protein kinase C βII (PKCβII) (Dobrikov, Dobrikova et al. 2018). Upon recruitment of the 40S ribosome to the eIF4F complex, RACK1 phosphorylates eIF4G, possibly facilitating the dissociation and recycling of eIF4F complex. Interestingly, eIF4G is also phosphorylated on Ser-1186 by PKCα, which induces its interaction with the MAP kinase-interacting kinase 1 (Mnk1) and likely leads to enhanced phosphorylation of eIF4E by Mnk1 (Dobrikov, Dobrikova et al. 2011). Conversely, phosphorylation of eIF4G on S896D, by p21-activated protein kinase 2 (Pak2), results in loss of its interaction with eIF4E and reduced mRNA translation rate (Ling, Morley et al. 2005). Pak2 is activated under stress conditions such as serum deprivation, hyperosmolarity and ionising radiation, highlighting the complexity of parallel pathways that control mRNA translation initiation in response to environmental stresses.

While the functional significance of mTOR-mediated eIF4G phosphorylation events is not fully clear, depletion of eIF4G somewhat phenocopies inhibition of mTOR, causing a modest decreased in global protein synthesis (Ramírez-Valle, Braunstein et al. 2008). eIF4G depletion reduces translation of mRNAs involved in cell growth, proliferation, and bioenergetics, impairs cell proliferation and mitochondrial activity, and promotes autophagy (Ramírez-Valle, Braunstein et al. 2008).

Overexpression of eIF4G caused malignant transformation of NIH3T3 cells (Fukuchi-Shimogori, Ishii et al. 1997), and its upregulation is observed in several types of cancer (Brass, Heckel et al. 1997, Silvera, Arju et al. 2009). Disruption of

eIF4E:eIF4G interaction by peptides directed to the site of the interaction (Herbert, Fåhraeus et al. 2000), or the small molecule inhibitors 4EGI-1 (Moerke, Aktas et al. 2007), 4E1RCat (Cencic, Hall et al. 2011), and DDH-1 (Wang, Wang et al. 2020) significantly reduced expression of several proto-oncogenes, which led to inducing apoptosis, reducing tumourigenesis and acquiring resistance to chemotherapy in cancer mouse models.

3.1.6. eIF4E

The cap-binding protein eIF4E is the critical linchpin in the formation of the eIF4F complex and subsequent recruitment of ribosomes to the mRNA.

The function of eIF4E is regulated at multiple levels; expression, post-translational modification, protein-protein interaction, and competition with other cap-binding proteins, where numerous lines of evidence link these mechanisms to cancer. Transcription of eIF4E is upregulated by c-Myc (Jones, Branda et al. 1996) and stimulated under hypoxic condition (DeFatta, Turbat-Herrera et al. 1999). eIF4E mRNA exists in multiple forms due to the utilisation of alternative polyadenylation sites in different tissues, generating mRNA variants with varying length of 3´ UTRs (Jaramillo, Pelletier et al. 1991, Mrvová, Frydrýšková et al. 2018), the significance of which is discussed in Section **7**.

Expression of eIF4E is elevated in various cancers (Kerekatte, Smiley et al. 1995, Nathan, Liu et al. 1997, Franklin, Pho et al. 1999, Rosenwald, Chen et al. 1999, Wang, Rosenwald et al. 1999, Crew, Fuggle et al. 2000, Urtishak, Wang et al. 2019) and its overexpression induced transformed morphology, aberrant growth, and promotion of growth in soft agar (De Benedetti and Rhoads 1990, Lazaris-Karatzas, Montine et al. 1990, Lazaris-Karatzas and Sonenberg 1992, Ruggero, Montanaro et al. 2004). Conversely, reduction of eIF4E expression decreased the malignancy rate (De Benedetti, Joshi-Barve et al. 1991, Graff, Boghaert et al. 1995), and a haploinsufficient mouse model of eIF4E ($eIF4E^{+/-}$) revealed that a 50% reduction in eIF4E expression confers resistance to tumourigenicity, without any tangible impact on global protein synthesis and embryonic development (Truitt, Conn et al. 2015). Reducing eIF4E expression with antisense oligonucleotide (ASO) inhibited colorectal cancer cell proliferation in preclinical studies (Hong, Kurzrock et al. 2011, Duffy, Makarova-Rusher et al. 2016). Disrupting eIF4E binding to the cap via small molecule

inhibitors (4Ei-1) increased sensitivity to the chemotherapeutic reagent Gemcitabine in breast and lung cancer cells (Li, Jia et al. 2013).

eIF4E is phosphorylated on Ser-209 upon treatment of cells with growth factors, hormones, and mitogens (Joshi, Cai et al. 1995, Makkinje, Xiong et al. 1995) by Mnk1 and Mnk2, which in turn are regulated by MAPK/ERK signaling pathway (Pyronnet, Imataka et al. 1999, Scheper, Morrice et al. 2001) (**Fig. 2A**). Mnk1/2 are dispensable in cell growth and mouse development (Ueda, Watanabe-Fukunaga et al. 2004). However, Mnk1/2-deficient MEFs are resistant to Ras-induced transformation, and Mnk1/2 double knockout (Mnk-DKO) mice are significantly less prone to tumour development in a Pten-deficient lymphoma model. Furthermore, overexpression of a constitutively activate mutant Mnk1 promoted, while a dominant-negative MNK mutant inhibited, tumour cell proliferation in lymphoma mouse model (Wendel, Silva et al. 2007). Inhibition of Mnk1/2 activity by the small molecule inhibitors CGP57380(Grzmil, Morin et al. 2011), cercosporamide (Konicek, Stephens et al. 2011), eFT508 (Tomivosertib) (Xu, Poggio et al. 2019), and SEL201(Zhan, Guo et al. 2017), suppressed tumourigenesis and increased sensitivity to chemotherapy (Astanehe, Finkbeiner et al. 2012, Adesso, Calabretta et al. 2013, Kosciuczuk, Kar et al. 2019) in various tumour models. Several ongoing clinical trials are evaluating the efficacy of the Mnk1/2 inhibitor eFT-508 (NCT03616834, NCT03690141, NCT04261218) for treatment of cancer in combination with chemotherapy or other anti-cancer treatments.

Nonetheless, Ser-209 is located on the dorsal surface of the eIF4E, therefore is not close to the cap-binding site or the 4E-BPs/eIF4G-binding motif (Marcotrigiano, Gingras et al. 1997). Furthermore, the evidence for the impact of eIF4E phosphorylation on its affinity for cap are inconclusive (Minich, Balasta et al. 1994, Scheper, Van Kollenburg et al. 2002, Slepenkov, Darzynkiewicz et al. 2006), therefore the exact mechanism by which eIF4E phosphorylation affects mRNA translation is poorly understood. Increased phospho-Ser-209 of eIF4E has been observed in various types of cancer and inversely correlates with disease progression or patients' survival (Bianchini, Loiarro et al. 2008, Graff, Konicek et al. 2009, Yoshizawa, Fukuoka et al. 2010, Adesso, Calabretta et al. 2013, Guo, Peng et al. 2017). A knock-in mouse with Ser-209/Ala mutation in eIF4E is resistant to development of prostate cancer (Ueda, Watanabe-Fukunaga et al. 2004). Translation of several important proto-oncogenes, including the anti-apoptotic factor BIRC2, and VEGF-C, MMP-3 and MMP-9, is downregulated in eIF4E knock-in cancer cells (Furic, Rong et al. 2010).

Enhanced translation of MMP-3 and the transcription factor SNAIL by phospho-eIF4E was later shown to lead to the promotion of EMT and metastasis (Robichaud, del Rincon et al. 2015). Importantly, Ser-209 phosphorylation in non-tumour cells within the tumor microenvironment also impacts cancer progression. Accordingly, the eIF4E knock-in mice are resistant to the formation of lung metastases in a syngeneic mammary tumor model, due to the decreased expression of the anti-apoptotic proteins BCL2 and MCL1 in pro-metastatic neutrophils, leading to their reduced survival (Robichaud, Hsu et al. 2018).

3.1.7. eIF4E paralogs and other cap-binding proteins

In addition to the tight regulation of eIF4E availability (through 4E-BPs,) and activity (Ser-209 phosphorylation) that enable rapid modulation of translation in response to various signals, eIF4E binding to the cap is also subject to competition with other cap-binding proteins (**Fig. 2C**). This competition could have significant impacts on tumourigenesis. In mammals, eIF4E has two known paralogue proteins, eIF4E2 (also known as 4E-Homologous Protein; 4EHP) and eIF4E3. These 3 paralogs share 25-30% amino acid sequence identity (Joshi, Cameron et al. 2004). 4EHP is widely expressed, albeit 5-10 times less abundant than eIF4E, whereas eIF4E3 expression is barely detectable and largely restricted to hematopoietic cells (Rom, Kim et al. 1998).

Compared with eIF4E, 4EHP has a 30-100-fold weaker affinity for the cap due to substitution of two important Tryptophan residues in its cap-binding pocket (Zuberek, Kubacka et al. 2007). Affinity of 4EHP for the cap increases upon interaction with the 4E-T (4E-transporter) protein, directed by the miRNA-induced silencing machinery (Chapat, Jafarnejad et al. 2017) or modification with the ubiquitin-like molecule ISG15, which is activated by interferon, in response to genotoxic stress or pathogen infection (Okumura, Zou et al. 2007). Unlike eIF4E, 4EHP does not interact with eIF4G, therefore is unable to form the eIF4F complex and generally believed to repress mRNA translation (Joshi, Cameron et al. 2004). Thus, upon recruitment by the miRNA-induced silencing machinery (Chapat, Jafarnejad et al. 2017, Chen and Gao 2017) or triggering of the ribosome quality control (RQC) mechanism (Hickey, Dickson et al. 2020, Sinha, Ordureau et al. 2020) (discussed further in section **4.6**), 4EHP represses the translation of the target mRNAs through displacement of eIF4E from the

cap (Chapat, Jafarnejad et al. 2017, Chen and Gao 2017, Ruscica, Bawankar et al. 2019, Räsch, Weber et al. 2020). This mechanism is critical for promotion of cell growth and prevention of apoptosis in glioblastoma cells through mediating the miR-145-mediated repression of DUSP6, an ERK1/2-specific phosphatase (Jafarnejad, Chapat et al. 2018).

Interestingly, 4EHP may switch to a translation activator in certain stress conditions such as hypoxia. Accordingly, hypoxia stimulates the formation of a complex involving the RNA-binding protein RBM4, hypoxia-inducible factor 2α (HIF-2α), and 4EHP (**Fig. 2D**). This trimer replaces eIF4F to recruit ribosome and initiate mRNA translation on a limited list of hypoxic-response mRNAs (Uniacke, Holterman et al. 2012), although it is not clear how this complex recruits ribosome in the absence of eIF4G and eIF3. 4EHP-directed translation was shown to promote tumour formation in xenograft models (Uniacke, Perera et al. 2014) and drive cancer cell migration, invasion and adhesion through upregulation of the cell-cell adhesion molecule cadherin-22 (Kelly, Varga et al. 2018).

Strikingly, 4EHP was also shown to activate mRNA translation through association with the threonyl aminoacyl-tRNA synthetase (TARS) (Jeong, Park et al. 2019). Accordingly, the 4EHP/TARS dimer replaces eIF4E/eIF4G, and in cooperation with eIF4A, generates a pseudo-eIF4F complex and recruits PIC to the target mRNAs through direct interaction of TARS with eIF3 (**Fig. 2E**). Notably, this mechanism positively regulates the translation of mRNAs required for vertebrate development, particularly those involved in vasculogenesis and angiogenesis such as *Vegf* mRNA (Jeong, Park et al. 2019). Considering the pervasive function of aminoacyl-tRNA synthetase in non-canonical functions, besides their main roles in charging tRNAs with their cognate amino acids (Guo and Schimmel 2013, Jafarnejad, Kim et al. 2018), it would be interesting to assess the putative role of this mechanism in controlling mRNA translation in response to changes in amino acid levels.

The cap binding activity of eIF4E and 4EHP is achieved through the positively charged m7G cap and the negative π-electron clouds from two aromatic residues (Quiocho, Hu et al. 2000), which are missing in eIF4E3. Thus, it was believed that eIF4E3 lacks the ability to bind the cap (Joshi, Cameron et al. 2004). However, a later study reported that eIF4E3 binds the cap using a different spatial arrangement of residues to provide the necessary electrostatic and van der Waals contacts (Osborne, Volpon et al. 2013). Similar to eIF4E, eIF4E3 is able to interact with eIF4G and eIF4A,

thus generating an alternative eIF4F complex, in which eIF4E is replaced by eIF4E3 (Robert, Cencic et al. 2020). Furthermore, eIF4E3 replaces eIF4E in Mnk-depleted DLBCL cells, in which eIF4E3 expression is increased along with the reduction in eIF4E expression and Ser-209 phosphorylation. In this condition, eIF4E3 activates translation of several proto-oncogenes and sustains cell viability (Landon, Muniandy et al. 2014). In contrast, eIF4E3 was also shown to compete with eIF4E for binding to the cap and repress the translation of proto-oncogenes such as *Vegf*, *c-Myc*, *Cyclin D1*, and *Nbs1* mRNAs, thus it acts as a tumor suppressor (Osborne, Volpon et al. 2013). The precise function of eIF4E3 in regulation of mRNA translation and its role in tumourigenesis remain to be fully elucidated.

Interestingly, in addition to eIF4E paralogue proteins, several other cap-binding proteins have also been identified that modulate cap-dependent initiation by direct binding to the cap (**Fig. 2C**). The so-called "pioneer round" of translation initiation, *i.e.* the first round of translation on an mRNA that is exported from the nucleus to cytoplasm, requires the nuclear cap-binding complex (nCBC), a heterodimer of CBP80 and CBP20 (Ishigaki, Li et al. 2001). The pioneer round involves loading of one or more ribosomes to ensure that the mRNAs are properly processed (*e.g.* absence of non-spliced introns). This involves the nCBC-mediated recruitment of the 40S ribosome via eIF4G and eIF3 and is facilitated by the nCBC-dependent translation initiation factor (CTIF) (Maquat, Tarn et al. 2010) binds the ribosome-bound eIF3g (von Moeller, Lerner et al. 2013). This is however a temporary arrangement, since if the mRNA is deemed properly processed, it will be dissociated from the nCBC to eIF4E, which will subsequently initiate the bulk of translation in the cell. Improperly processed mRNAs will be degraded by the nonsense-mediated decay (NMD) pathway (Karousis and Mühlemann 2019).

Recent evidence also suggested the presence of an eIF4F-independent mechanism that stimulates translation of the mRNA encoding the proto-oncogene c-JUN through direct binding of eIF3D to the cap (Lee, Kranzusch et al. 2016). Protein/mRNA cross-linking assays showed that a ~62 kDa subunit of eIF3 (eIF3L or eIF3D) could directly bind to the cap (Kumar, Hellen et al. 2016). However, structural studies, using highly purified ribosomal complexes and electron cryo-microscopy, position eIF3D in the exit channel of the 40S ribosome, where it does not contact the mRNA (Eliseev, Yeramala et al. 2018). This result indicates the limited ability of eIF3D

to directly activate mRNA translation as a cap-binding protein. eIF3D was also suggested to facilitate cap-dependent translation of approximately 20% of mRNAs, including those involved in cell survival, motility, and DNA repair, via interaction with the eIF4G homologue protein DAP5 (eIF4G2) (de la Parra, Ernlund et al. 2018). Unlike eIF4G, DAP5 lacks the ability to bind to eIF4E, but instead interacts with eIF4A and eIF3D. This complex directly recruits PIC to the cap DAP5 (de la Parra, Ernlund et al. 2018, Haizel, Bhardwaj et al. 2020).

LARP1 is another recently identified cap-binding protein, which recognises the cap (Lahr, Fonseca et al. 2017, Philippe, Vasseur et al. 2018, Cassidy, Lahr et al. 2019) and its adjacent pyrimidine-rich sequence on TOP mRNAs (Iadevaia, Caldarola et al. 2008). Binding of LARP1 to the cap blocks the eIF4E binding to the cap, leading to the repression of the translation of TOP mRNAs, which encode ribosomal proteins and several key translation factors (Fonseca, Zakaria et al. 2015, Lahr, Fonseca et al. 2017, Philippe, Vasseur et al. 2018).

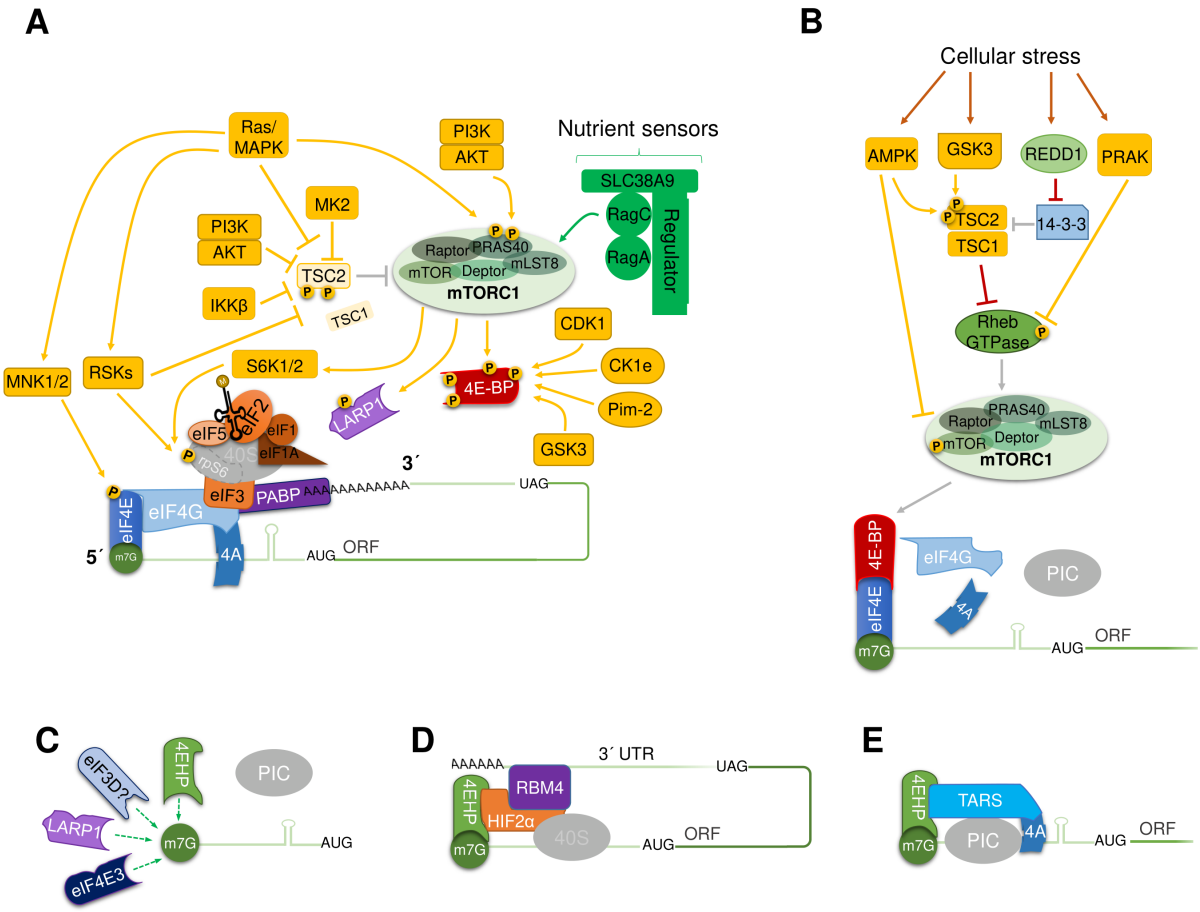


Figure 2. Regulation of translation initiation by cap-binding proteins.
(**A**) Binding of eIF4G to the dorsal surface of eIF4E, which is pivotal for the formation of eIF4F complex, can be interrupted by the eIF4E-binding proteins (4E-BP1-3) that compete with eIF4G for binding to eIF4E. Phosphorylation of 4E-BPs by mTOR alleviates their inhibitory function and enables eIF4F complex formation, followed by recruitment of PIC and scanning of the 5´ UTR. Besides mTORC1, several other kinases can also phosphorylate 4E-BPs to induce dissociation from eIF4E. Phosphorylation of LARP1 by mTORC1 relives the repression of mRNAs with 5´ terminal oligopyrimidine tract (TOP). In addition, eIF4E can be phosphorylated by the MNKs. Phosphorylation of the ribosomal protein rpS6 by mTORC1-activated S6Ks and MAPK-activated RSKs may control translation of mRNAs related to regulation of cell size. Phosphorylation of eIF4E on Ser-209, via Ras/MAPK-activated MNK1/2, stimulates selective translation of mRNAs involved. Activity of mTORC1, the central hub for regulation of initiation by cap-binding proteins, is regulated by a multitude of internal and external signals. The mitogen–activated Ras-MAPK pathway can also activate mTORC1 via the phosphorylation of its PRAS40 and TSC2, the inhibitor of the small GTPase protein Rheb, that in turn activates mTORC1. PI3K is activated in response to growth factors, where it in turn inactivates and phosphorylates TSC2 and PRAS40 via AKT. IKKß and p38-activated MK2 (MAPKAPK2) also phosphorylate TSC2 and inactivate it. mTORC1 is recruited to the ribosome and activated in response to the intracellular level of amino acids, sensed by several sensors including the Rag GTPase complex, the lysosomal transmembrane protein SLC38A9 and the regulator complex. (**B**) Under stress conditions, mTORC1 is inhibited through the stimulatory phosphorylation of its inhibitor TSC2 via AMPK and GSK3. Under hypoxic conditions, REDD1 releases TSC2 from its association with the inhibitory 14-3-3 proteins, leading to its activation. Energy starvation activates PRAK (p38β), which directly inhibits Rheb by phosphorylation, leading to inactivation of mTORC1. Inactivation of mTORC1 results in hypophosphorylation of 4E-BPs, which in turn bind eIF4E and interrupt the eIF4F complex. (**C**) eIF4F-mediated initiation from the cap is also subject to competition of eIF4E with other cap-binding proteins

for the cap. The eIF4E paralogue proteins 4EHP (eIF4E2) and eIF4E3, as well as LARP1 and possibly eIF3D subunit were also shown to bind the cap and prevent binding of eIF4E and canonical eIF4F complex formation. (**D**) 4EHP may activate the translation initiation of specific mRNAs under hypoxic stress, during which a complex formed by 4EHP, the RNA-binding protein RBM4, and oxygen-regulated hypoxia-inducible factor 2α (HIF-2α) recruit the 40S ribosome to the cap. It is not clear how this complex recruits the ribosome in the absence of eIF4G and eIF3. (**E**) 4EHP may also promote mRNA-specific translation through interaction with the threonyl aminoacyl-tRNA synthetase (TARS). The 4EHP/TARS dimer replaces eIF4E/eIF4G, and through direct interaction of TARS with eIF3, recruits PIC to target mRNAs. Arrows indicate activation, whereas bar-headed lines indicate inhibition. Yellow lines indicate phosphorylation, and grey lines indicate inactivation.

3.1.8. eIF4A and RNA helicases

5′ UTR scanning by PIC is significantly hampered in the presence of secondary structures (Babendure, Babendure et al. 2006), particularly in long and CG-rich 5′ UTRs of the proto-oncogene encoding mRNAs (Kozak 1987). G-rich sequences stabilised by stacked G–G–G–G tetrads (G-quadruplexes) and positioned adjacent to translation START codon (Patel, Phan et al. 2007), which are disproportionally more abundant in oncogenes compared to tumor suppressors (Eddy and Maizels 2006) also impede scanning. Thus translation of proto-oncogene encoding mRNAs is reliant on RNA helicases such as eIF4A (Rogers, Richter et al. 1999, Svitkin, Pause et al. 2001). Two eIF4A paralogs in mammalian cells, eIF4A1 and eIF4A2, which are ∼90% identical (Nielsen and Trachsel 1988), can participate in the eIF4F complex formation. However, while eIF4A1 is essential for efficient mRNA translation and cell viability, the absence of eIF4A2 does not affect cell viability, proliferation, or global mRNA translation (Galicia-Vázquez, Chu et al. 2015). A third paralog, eIF4A3 that is less similar to the other two isoforms (<65%), is implicated in NMD (Palacios, Gatfield et al. 2004, Shibuya, Tange et al. 2004).

Activity of eIF4A can be enhanced by eIF4E and other translation factors such as eIF4B and eIF4H (Rogers, Richter et al. 2001) and inhibited by direct interaction with the tumour suppressor PDCD4 (Yang, Jansen et al. 2003). It has also been suggested that miRNAs repress translation of their target mRNA via inactivation or displacement of eIF4A1 and eIF4A2 (Meijer, Kong et al. 2013, Fukao, Mishima et al. 2014), although the exact mechanism of interference with eIF4A function by miRNAs is disputed (Fukaya, Iwakawa et al. 2014, Kuzuoğlu-Öztürk, Bhandari et al. 2016). High-throughput analyses demonstrated that eIF4A stimulates translation of mRNAs with long and structured 5′ UTRs, or mRNAs that contain 12 G-quadruplexes including

those encoding many oncogenes, such as MYC, but not mRNAs with short 5´ UTRs (Rubio, Weisburd et al. 2014, Wolfe, Singh et al. 2014, Gandin, Masvidal et al. 2016). Consistently, overexpression of eIF4A is detected in several types of cancer (Shuda, Kondoh et al. 2000, Chen, Knösel et al. 2003, Oblinger, Burns et al. 2018) and, perhaps not surprisingly, inhibition of eIF4A activity by specific small molecule inhibitors such as Silvestrol (Bordeleau, Robert et al. 2008, Wolfe, Singh et al. 2014, Chan, Robert et al. 2019), Hippuristanol (Cencic, Robert et al. 2013, Ishikawa, Tanaka et al. 2013), and Pateamine A (Low, Dang et al. 2005, Kuznetsov, Xu et al. 2009) revealed promising anti-cancer activity.

eIF4A is a relatively weak helicase on its own (Rogers, Richter et al. 1999). Therefore, several other RNA helicases such as DHX29 (Pisareva, Pisarev et al. 2008), DDX3 (Lai, Lee et al. 2008), and RHA (DHX9) (Hartman, Qian et al. 2006) promote translation of mRNAs with complex 5´ UTRs and contribute to tumourigenesis (Clark, Coulson et al. 2008, Zoppoli, Regairaz et al. 2012, Oh, Flynn et al. 2016). Whereas majority of these helicases remove secondary structures in mRNAs without sequence specificity, certain RNA helicases facilitate translation by binding to specific RNA sequences. A typical example is DHX9, which promotes scanning through a two stem-loop structures called post-transcriptional control element (PCE), found in the mRNA encoding the proto-oncogene JUND (Hartman, Qian et al. 2006). YTHDC2 is a member of the YTH-domain family of proteins that bind N6 methylated adenosines (m^6A), the most common internal modification amongst the eukaryotic mRNAs post-transcriptional modifications (Hsu, Zhu et al. 2017). YTHDC2 possesses two DExD/H box motifs, conferring RNA helicase activity to it and enabling promotion of translation of mRNAs with m^6A by resolving mRNA secondary structures (Mao, Dong et al. 2019). YTHDC2 facilitates translation initiation of *HIF-1α* and *Twist1* mRNAs under hypoxic condition, and depletion of YTHDC2 reduced the *in vitro* and *in vivo* metastatic potential of colon cancer cells (Tanabe, Tanikawa et al. 2016). Importantly, m^6A also affects cap-independent translation initiation via other members of the YTH-domain family (discussed in section **3.4.2**).

Remarkably, certain RNA helicases repress translation of specific mRNAs. Depletion of DDX28 elevates *Hif-2α* mRNA translation and confers a proliferative advantage to hypoxic, but not normoxic glioblastoma cells (Evagelou, Bebenek et al. 2020). The RNA helicase DDX6 is extensively linked to the translational repression. Depletion of DDX6 increases *Vegf* mRNA translation under hypoxia, in a 5´ UTR-

dependent manner, leading to increased angiogenesis (de Vries, Naarmann-de Vries et al. 2013). Importantly, DDX6 is a critical component of the miRNA-induced silencing machinery (Rouya, Siddiqui et al. 2014, Radhakrishnan, Chen et al. 2016). The key role of DDX6 in cancer would be further appreciated in the context of the pivotal role of miRNAs in regulation of almost every aspect of tumourigenesis (Rupaimoole and Slack 2017).

3.2. Alternative cap-dependent initiation regulated by cis-elements

While recruitment of ribosome to the cap via eIF4F and 5´ UTR scanning by 40S is the most common mechanism of translation initiation, recent evidence highlighted alternative, albeit less common, mechanisms of cap-dependent initiation.

In mRNAs with short 5´ UTRs, a unique sequence termed translation initiator of short 5´ UTR (TISU) activates mRNA translation in a cap-dependent but 40S ribosome scanning-independent manner (Elfakess, Sinvani et al. 2011). The underlying mechanisms of translation of TISU mRNAs may involve interaction between eIF1 and eIF4G and eIF1A-directed binding of ribosomal proteins S3 and S10e to the TISU element (Haimov, Sinvani et al. 2017). TISU element is present in 4.5% of protein-coding mRNAs (Elfakess and Dikstein 2008), many of which encode mitochondrial proteins and impact cellular bioenergetics (Elfakess and Dikstein 2008). TISU-mediated translation enables continuous translation of these mRNAs under stress conditions such as nutrition deprivation (Sinvani, Haimov et al. 2015). However, translation of TISU mRNAs was shown to be negatively impacted by mTOR inhibition (Gandin, Masvidal et al. 2016) and was not enriched among the eIF1A-affected genes (Sehrawat, Koning et al. 2019), underscoring the complexities of this mode of translational regulation and the need for further investigation.

Ribosome “shunting”, mediated by the cap-independent translation enhancer (CITE) elements, is another alternative cap-dependent, but scanning-free initiation mechanism, that facilitates selective translation of several viral RNA genomes, as well as the cellular mRNAs encoding heat shock protein 70 (Hsp70) (Yueh and Schneider 2000), betasecretase 1 (Koh, Edelman et al. 2013), the proto-oncogenes Myc1 and Myc2 (Carter, Jarquin-Pardo et al. 1999), and cellular inhibitor of apoptosis 2 (cIAP2) (Nicholson, Jevons et al. 2017). While many mechanistic details of shunting remain to be understood, it involves direct interaction of the CITE elements with the 18S rRNA

in 40S ribosome, upon which PIC binds the cap and bypasses the 5´ UTR to reach the START codon (Yueh and Schneider 2000).

In addition to the main ORF, nearly half of all mRNAs in humans contain at least one upstream ORF (uORF) in their 5´ UTRs (Calvo, Pagliarini et al. 2009). uORFs are defined by a start codon that is out-of-frame with the downstream main ORF, and their presence significantly correlates with reduced translation of the main ORFs (Calvo, Pagliarini et al. 2009). This is due to the fact that initiation on uORF START codon and termination at the corresponding uORF STOP codon excludes the possibility of the PIC reaching the START codon of the main ORF. Thus, translation of the main ORF entails either a leaky scanning by the 40S ribosome, wherein it ignores the uORF START codon, or resumption of the translation at the downstream START codon after termination at the uORF STOP codon, in a process called “re-initiation”. Re-initiation requires the 40S ribosome to release the deacylated tRNA, remain associated with the mRNA, and recruit a new initiator tRNA. The mechanism of re-initiation is only partially understood. It involves several non-canonical initiation factors, such as density regulated protein (DENR) and multiple copies in T-cell lymphoma-1 (MCTS1) (Schleich, Strassburger et al. 2014) and the canonical translation factors eIF2D (Bohlen, Harbrecht et al. 2020) and eIF3h (Hronová, Mohammad et al. 2017). This mechanism is critical for translation of mRNAs encoding several proto-oncogenes such as ATF4, a-RAF, c-RAF, and CDK4 that contain uORFs (Bohlen, Harbrecht et al. 2020), under stress conditions.

3.3. Integrated stress response (ISR) pathway

During translation initiation, the GTP-bound eIF2α forms a ternary complex with Met-tRNAi^{Met}, and along with other initiation factors and the 40S ribosome, form the 43S pre-initiation complex (PIC). After recognition of the START codon by PIC, the GTPase activating protein (GAP) eIF5 induces hydrolysis of the GTP, leading to the dissociation of the GDP-bound eIF2α from the 40S ribosome (Paulin, Campbell et al. 2001). In order to participate in a new round of initiation, the GDP on eIF2 has to be exchanged for GTP, catalysed by the guanine nucleotide exchange factor (GEF) eIF2B (**Fig. 3A**). In response to various stress conditions, eIF2α is phosphorylated on Ser-51, converting it from a substrate to an inhibitor of the GEF subunit, eIF2B (Sudhakar, Ramachandran et al. 2000).

eIF2α phosphorylation under stress conditions results in reduced formation and activity of PIC, and declined rates of global translation initiation, enabling the cell to direct the recourses required for protein synthesis to more urgent processes. In mammals, four protein kinases are known to phosphorylate eIF2α Ser-51 in response to different upstream stimuli; general control non-derepressible 2 (GCN2) is activated by uncharged tRNAs that accumulate during amino acids starvation (Dong, Qiu et al. 2000, Sood, Porter et al. 2000), UV radiation (Deng, Harding et al. 2002), or ribosome stalling (Ishimura, Nagy et al. 2016), protein kinase RNA-like endoplasmic reticulum kinase (PERK) is activated by unfolded proteins in the endoplasmic reticulum (ER stress) (Shi, Vattem et al. 1998), protein kinase RNA-activated (PKR) is activated in response to the double-stranded RNAs in virus-infected cells (Meurs, Chong et al. 1990), and heme-regulated inhibitor (HRI) is activated under conditions of low haem, heat shock, osmotic shock and arsenite treatment (Lu, Han et al. 2001) (**Fig. 3B**). Thus, eIF2α phosphorylation is the culmination of the ISR pathway that coalesces signaling downstream of several types of stress, the outcome of which is reduced global translation and increased selective translation of mRNA encoding stress-response proteins.

Genome-wide translatome analysis revealed that mRNAs encoding stress-response proteins harbor a high number of uORFs (Ingolia, Ghaemmaghami et al. 2009). Nearly half of all mRNAs in humans (Calvo, Pagliarini et al. 2009) including the majority of proto-oncogenes (Kozak 1991) and other proteins involved in cellular processes such as differentiation, cell cycle, and stress response contain at least one uORF. Thus ISR/p-eIF2α-mediated regulation of translation has a major impact on homeostasis as well as tumourigenesis (**Fig. 3B**). A typical example for ISR/p-eIF2α-mediated translational regulation is the upregulation of the transcription factor ATF4 under starvation. The *Atf4* mRNA contains two uORFs, the second of which (uORF2) is overlapping and out-of-frame with the main ORF. In normal conditions, when eIF2α-GTP is abundant, translation of the main ORF is limited due to translation of uORF2. During stress, phosphorylation of eIF2α and reduction in the eIF2α-GTP levels increase the time required for the scanning ribosomes to re-initiate translation on uORF2. This delayed re-initiation allows for 40S to continue scanning and eventually initiate translation at the downstream main ORF (Vattem and Wek 2004) (**Fig. 3B**). The increased ATF protein level in turn triggers a cascade of transcriptional regulators including the transcription factors C/EBP homologous protein (CHOP) and ATF3,

leading to activation of a stress-response that is critical for metabolism, redox status of the cell, and survival (Harding, Zhang et al. 2003).

Interestingly, p-eIF2α also enhances translation of *Chop* mRNA, a key player in promoting cell death during chronic stress conditions by a similar mechanism (Han, Back et al. 2013). Repression of the uORF and simultaneous activation of main ORF by ISR/p-eIF2α under stress conditions has been reported for a relatively large number of mRNAs (Sidrauski, McGeachy et al. 2015).

Whereas AUG is the main translation START codon, another alternative but less common translation process is initiated at non-AUG codons; the near-cognate codons that differ by only one nucleotide, with CUG being most common. This is a highly regulated process that commonly leads to the synthesis of proteins involved in stress response and its impairment is linked to diseases including cancer. Nucleotide resolution ribosome profiling revealed the dramatic increase in ribosome occupancy of non-AUG uORFs during starvation (Ingolia, Ghaemmaghami et al. 2009, Zhou, Wan et al. 2018), exceeding the translation of canonical AUG uORFs as well as the main ORFs (Ingolia, Ghaemmaghami et al. 2009). A general mechanism for non-AUG initiation is utilisation of Leu-encoding codons (CUG and UUG) by eIF2α.

For instance, translation of the essential ER-resident chaperone, binding immunoglobulin protein (BiP) is enhanced upon ER stress due to eIF2α-mediated usage of UUG and CUG start codons (Starck, Tsai et al. 2016). Similarly, during oxidative stress, eIF2α promotes initiation from a CUG codon upstream of the main AUG codon in *PTEN* mRNA, which encodes an important tumour suppressor protein. This leads to production of an N-terminal extended isoform of named PTENα that induces cytochrome-c oxidase activity and ATP production in mitochondria, thus significantly reprograms the cellular metabolism (Liang, He et al. 2014). Notably, usage of an in-frame AUU codon upstream of the AUG initiation sequence for canonical PTEN leads to production of another N-terminal extended PTEN isoform, designated PTENβ. PTENβ localises in the nucleolus and regulates pre-rRNA synthesis and cellular proliferation (Liang, Chen et al. 2017). Furthermore, at higher cell densities and low availability of amino acids, particularly methionine, utilisation of an upstream in-frame CUG codon in *c-Myc* mRNA results in the production of a larger isoform with a distinct N-terminus (Hann, Sloan-Brown et al. 1992). This isoform contributes to the oncogenesis in Burkitt's lymphoma cells (Hann, King et al. 1988).

The mRNAs that are translationally repressed upon ISR activation are thought to partition into non–membrane compartments called Stress Granules (SGs) (Kedersha, Gupta et al. 1999). Within SGs the mRNAs are associated with 40S ribosomal subunits, along with their associated initiation factors (Kedersha, Stoecklin et al. 2005). Thus, accumulation of repressed mRNAs in SGs is reversible and upon recovery of the cell from a sub-lethal stress, the translation of these mRNAs could resume quickly due to their association with pre-initiation complex. Importantly, activation of ISR with different upstream stimuli leads to widespread, yet distinct translational responses which differ based on type of stress (Smirnova, Selley et al. 2005). The mechanism behind the preferential ISR-mediated translational reprogramming by different types of stress is not clearly understood but can be attributed to multiple reasons including; activation of transcriptional programmes that produce different transcriptomes in various conditions (Dey, Baird et al. 2010), spatially restriction of mRNA availability due to subcellular localization of mRNAs (Reid, Chen et al. 2014), and utilisation of alternative promoters and/or splicing patterns in the target mRNAs (Lehman, Cerniglia et al. 2015, Wek 2018).

Homozygous loss of eIF2α phosphorylation (eIF2α$^{S51A/S51A}$) in mouse leads to death within 18 hour after birth due to hypoglycemia but heterozygous (eIF2α$^{+/S51A}$) mice grow into healthy adults (Scheuner, Song et al. 2001). Phosphorylation of eIF2α is reversible and ends the ISR process. This is achieved by components of the protein phosphatase 1 (PP1) complex (Connor, Weiser et al. 2001, Jousse, Oyadomari et al. 2003) (**Fig. 3B**), depletion of key component of which in mouse (*Ppp1r15b*$^{-/-}$) results in severe growth retardation and early embryonic lethality. Notably, eIF2α^{S51A} mutation rescued these phenotypes (Harding, Zhang et al. 2009). The exact role of ISR in cancer is complex and likely context-dependent. Inactivation of ISR via mutations in PERK or inhibition of eIF2α phosphorylation by a dominant-negative PERK impaired cell survival under extreme hypoxia and tumourigenesis (Bi, Naczki et al. 2005). Oncogenic stress upon overexpression of c-Myc was also shown to activate the PERK/eIF2α/ATF4 pathway, leading to increased cell survival via the induction of cyto-protective autophagy (Hart, Cunningham et al. 2012). PERK/eIF2α axis also plays a key role in tumour cell survival under hypoxic conditions via increased glutathione synthesis, uptake of cysteine, and protection against ROS (reactive oxygen species) (Rouschop, Dubois et al. 2013).

The GCN2/eIF2α axis was also recently shown to engender a negative feedback loop that limits protein synthesis to prevent Myc-induced oncogenic stress and apoptosis in colorectal cancer cells (Schmidt, Gay et al. 2019). During EMT, cancer cells exhibit strong ER stress and activation of the PERK/eIF2α axis is required for EMT cells to invade and metastasise (Feng, Sokol et al. 2014). Altogether these studies indicate the requirement for a robust stress-response capacity mediated by the ISR pathway in cancer. However, contrary evidence also demonstrated the negative impact of long-term ISR activity on tumour growth and survival. In colon carcinoma cells, PERK-induced eIF2α phosphorylation is required for cell survival, but inducible activation of PERK resulted in quiescence (Ranganathan, Ojha et al. 2008).

Importantly, ISR/p-eIF2α pathway could be blunted by the small molecule inhibitor ISRIB (Sidrauski, McGeachy et al. 2015), which bolsters eIF2B GEF activity (Sekine, Zyryanova et al. 2015). Recent evidence demonstrated that ISRIB could inhibit the growth of tyrosine kinase receptors (RTK)-addicted hepatocellular cancer cells (Mahameed, Boukeileh et al. 2020), and attenuate the breast cancer plasticity induced by stimuli including hypoxia, mTOR inhibitors, and paclitaxel (Jewer, Lee et al. 2020). The potential efficacy of ISRIB in treatment of cancer needs further investigations.

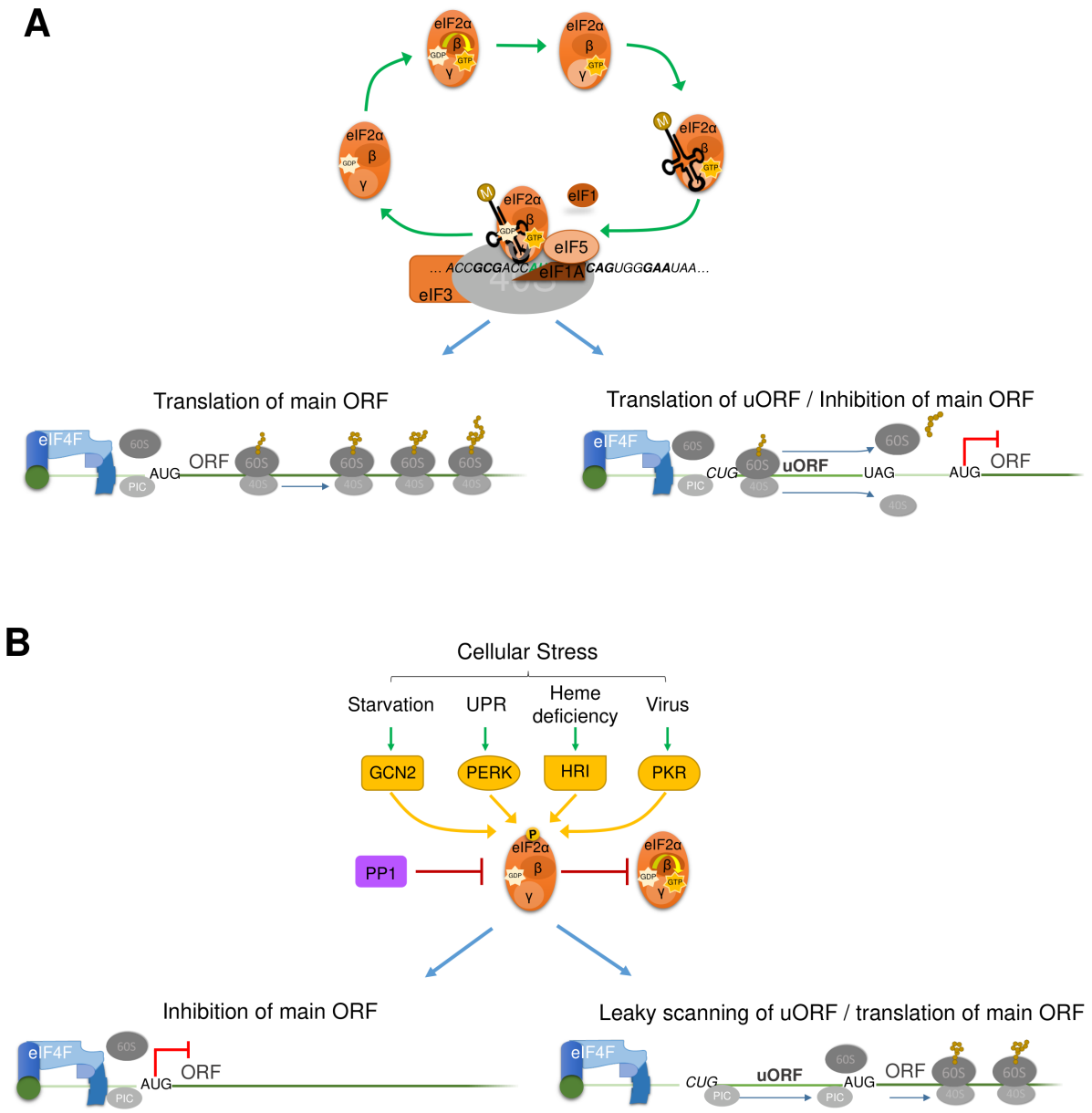


Figure 3. Integrated Stress Response pathway and translation of uORF-containing transcripts.

Cells activate the integrated stress response (ISR) to restore homeostasis in response to diverse types of stress. (**A**) The eukaryotic translation initiation factor 2 (eIF2) is comprised of 3 subunits, Met-tRNAi binding eIF2α, GEF eIF2β, and GAP eIF2γ. In its GTP-bound state, eIF2α binds to Met-tRNAi and forms the ternary complex (TC). TC participates in the formation of pre-initiation complex (PIC) along with 40S ribosome, eIF1 and eIF1A, eIF3, and eIF5 and scans the 5´ UTR to identify the translation START codon. In normal conditions, the main ORF (open reading frame) of mRNAs that contain uORFs (upstream ORF) will not be translated efficiently due to the fact that initiation of translation on uORF START codon and termination at the corresponding STOP codon excludes the possibility of the PIC reaching the START codon of the main ORF. (**B**) The core event in ISR pathway is the phosphorylation of eIF2α at Ser-51 by four kinases that are activated by specific stress signals. eIF2α phosphorylation converts it to an inhibitor of eIF2ß, resulting in repression of the global cap-dependent translation. However, ISR augments the transcript-specific translation of the mRNAs encoding stress-response proteins, which typically harbour one or more uORFs, due to inefficient initiation at the uORF START codon, allowing the continuous scanning of PIC until arrival at the START codon of the main ORF. ISR

terminates by the PP1 phosphatase complex that dephosphorylates eIF2α. By reducing general mRNA translation and enhancing the transcript-specific translation of mRNAs that encode key stress-response proteins, ISR maintains cellular homeostasis. Arrows indicate activation, bar-headed lines indicate inhibition, and yellow lines indicate phosphorylation. UPR, unfolded protein response

3.4. Cap-independent translation initiation

Cap-dependent translation initiation is maintained by mechanisms (*e.g.* mTORC1) that are inactivated in unfavorable growth and stress conditions. However, even under severe stress conditions, wherein general mRNA translation is repressed, translation of certain mRNAs that are required for the stress response or recovery from the stress is maintained in a cap-independent manner.

3.4.1. IRES

Internal Ribosomal Entry Sites (IRESs) promote cap-independent initiation, by bypassing the block in cap-dependent initiation and sustain the expression of proteins that are critical for cell survival under such conditions (**Fig. 4**). Several different types of IRES were originally identified in viruses, enabling the sustained translation of the viral RNAs despite the shutdown of the host cap-dependent translation (reviewed in (Lee, Chen et al. 2017)). Strikingly, an estimated 5-10% of cellular mRNAs can also recruit the ribosome through IRES (Spriggs, Stoneley et al. 2008, Weingarten-Gabbay, Elias-Kirma et al. 2016). However, compared with viral IRESs, cellular IRESs are less structured and defined, share less sequence conservation among them, and their mechanisms of action are largely unknown (Gilbert 2010, Jackson 2013). Cellular IRESs initiate translation via two general mechanisms; 1) certain mRNAs such as *c-Myc* (Stoneley, Subkhankulova et al. 2000) *and XIAP* (Thakor, Smith et al. 2017) contain structural elements or modifications (m^6A) that facilitate recruitment of 40S ribosomes via eIFs and RNA binding proteins known as IRES-transacting factors (ITAFs). 2) mRNAs, such as those encoding insulin-like growth factor 1 receptor (IGF1R) (Meng, Jackson et al. 2010) and NRF2 (Li, Thakor et al. 2010), contain a sequence resembling the bacterial Shine-Dalgarno motif, which recruits the ribosome directly to the mRNA (Dresios, Chappell et al. 2006).

IRESs can facilitate translation of key proteins for normal cellular processes and development. During mitosis, where the global translational efficiency is

dramatically reduced, translation of ~3% of mRNAs remain predominantly unchanged, at least partially due to presence of IRESs (Qin and Sarnow 2004). IRES elements in the mRNAs encoding Fibroblast growth factor-1 (FGF-1) and 2 (FGF-2) were shown to stringently control their spatiotemporal expression and play a role in myogenesis (Conte, Ainaoui et al. 2009) and neurogenesis (Audigier, Guiramand et al. 2008) respectively, and upregulate angiogenic growth factors after ischemic stress (Philippe, Dubrac et al. 2016). However, due to prevalence of stresses such as hypoxia, DNA damage, and starvation, which downregulate global translation, IRESs play a more prominent role in coping with such stresses in cancers (**Fig. 4B**). For instance, In hypoxic tumors and lymph nodes, VEGF-C expression is maintained via an IRES in its 5´ UTR (Morfoisse, Kuchnio et al. 2014).

"Oxidative stress", defined as a relative excess of ROS, is common in cancer cells (Hayes, Dinkova-Kostova et al. 2020), and can lead to impaired global translation through activation of the ISR pathway (Liu, Wise et al. 2008) and direct oxidation of specific translation factors (Gerashchenko, Lobanov et al. 2012, Chio, Jafarnejad et al. 2016). Cancer cells sustain expression of oxidative stress response proteins, such as the pivotal antioxidant response coordinator NRF2 through IRES-mediated translation (Li, Thakor et al. 2010). NRF2 protein in turn masterminds a gene expression programme that improves cellular fitness under stress (De La Rojo Vega, Chapman et al. 2018). IRESs also play a key role in the translation of *c-MYC* (SUBKHANKULOVA, MITCHELL et al. 2001), cellular inhibitor of apoptosis protein 1 (*c*-IAP)1 (VAN EDEN, BYRD et al. 2004), and *Bcl2* mRNAs that encode important pro-survival proteins (Sherrill, Byrd et al. 2004), in response to oxidative and genotoxic stress. Translation of several mRNAs encoding key proto-oncogenes such as *Snail1* (Evdokimova, Tognon et al. 2009), *Zeb2* (Beltran, Puig et al. 2008), and *Laminin B1* (Petz, Them et al. 2012) during EMT, a process which is imbued with multiple types of stress (Jiang, Wang et al. 2017) is also maintained by IRESs.

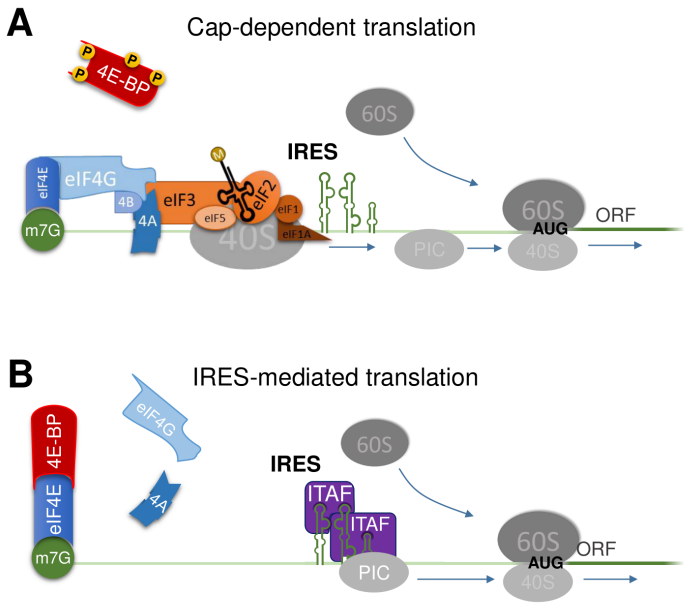
Furthermore, selective translational upregulation of anti-apoptotic genes by IRES is also linked to anti-cancer therapy resistance. IRES-mediated translation of the anti-apoptotic protein XIAP contributes to the human carcinoma cells resistant to γ-irradiation (Holcik, Lefebvre et al. 1999). Translation of BCL2-associated athanogene (BAG-1), which functions as a pro-survival protein and is associated with tumorigenesis and chemoresistance, is induced by IRES following treatment with

vincristine, a drug that blocks mitosis by interfering with microtubule polymerisation (Dobbyn, Hill et al. 2008).

RBPs play essential roles as ITAFs in translation of cellular IRESs, thus regulation of their expression and/or activity is a key mechanism in the regulation of IRES-dependent translation of these mRNAs (Mokrejš, Mašek et al. 2010). The exact mechanisms by which ITAFs control IRES-dependent translation are variable and, in many cases, largely unclear. The RBPs, Y-box-binding protein (Ybx-1) and polypyrimidine tract-binding protein 1 (PTBP1), act as ITAFs for the *c-Myc* mRNA IRES, and their overexpression results in enhanced c-MYC expression (Cobbold, Wilson et al. 2010). Furthermore, a C to T mutation in the *c-Myc* IRES, that is frequently observed in multiple myeloma patients, enhances the affinity of these ITAFs for the IRES and augments *c-Myc* mRNA translation (Cobbold, Wilson et al. 2010).

Under genotoxic stress conditions, IRES mediated translation of critical tumour suppressor protein, p53, is induced through synergistic phosphorylation of its ITAFs, HDMX and HDM2 by ataxia telangiectasia mutated (ATM) kinase. Phospho-HDMX first binds *p53* mRNA to promote a confirmation that supports binding of HDM2 and subsequent stimulation of IRES mediated translation (Malbert-Colas, Ponnuswamy et al. 2014). Interestingly, HDM2 also activate the IRES of the anti-apoptotic proto-oncogene *Xiap* mRNA and augment resistance to ionising radiation-induced apoptosis (Gu, Zhu et al. 2009).

While most ITAFs positively regulate their corresponding IRESs, a number of ITAFs (negative ITAFs) inhibit IRES activity. The PDCD4 tumour suppressor protein



directly binds to and represses the IRESs on *Xiap* and *Bcl-xL* mRNAs, thus prevents ribosome recruitment. S6Ks-mediated phosphorylation and subsequent degradation of PDCD4 leads to derepression of *Xiap* and *Bcl-xL* translation (Liwak, Thakor et al. 2012). The *Bcl-xL* mRNA IRES is also negatively regulated by hnRNPA1 during hypertonic stress, resulting in enhances apoptosis (Bevilacqua, Wang et al. 2010). Negative regulation of the IRES of the pro-apoptotic caspase-2 mRNA by HuR protein leads to resistance to doxorubicin and paclitaxel treatment in colon carcinoma cells (Badawi, Biyanee et al. 2018).

Figure 4. Cap-independent translation initiation mediated by Internal Ribosome Entry Sites (IRES).

(**A**) In normal conditions, initiation of translation of most mRNAs commences with cap–dependent recruitment of PIC to the mRNA via eIF4F complex. (**B**) Under stress conditions, wherein the global cap-dependent mRNA translation is repressed due to dismantling of eIF4F complex by hypo-phosphorylated 4E-BPs, translation of a subset of mRNAs is sustained due to the presence of IRES elements within their 5′ UTRs. The cellular IRESs recruit ribosomes via two distinct mechanisms; **i**. recruitment of 40S ribosomes via eIFs and RNA-binding proteins known as IRES-transacting factors (ITAFs), and **ii**. recruitment of 40S ribosome via a sequence resembling the bacterial Shine-Dalgarno motif, which directly binds to a sequence within the 18S rRNA. Cap-independent translation by IRESs is not subjected to many regulatory mechanisms that control cap-dependent translation, thus allows sustained expression of important stress-response pathways under stress conditions, such as hypoxia.

3.4.2. m^{6}A modifications

Besides IRESs, the m^{6}A mRNA modifications can also facilitate cap-independent translation initiation. m^{6}A is the most prevalent methylated nucleoside in eukaryotic mRNAs with more than 7000 mRNA in human and mouse containing m^{6}A in a non-stoichiometric and tissue-specific manner (Levanon, Eisenberg et al. 2004, Meyer, Saletore et al. 2012). m^{6}As serve as docking points for several important “readers” that control the stability and/or translation of the mRNA (Helm and Motorin 2017). While majority of m^{6}A modifications occur in 3′ UTRs or near the stop codons (Meyer, Saletore et al. 2012), m^{6}As in 5′ UTRs are also common and significantly affect translation. Initially, presence of m^{6}A in the 5′ UTR of an un-capped mRNA was shown to promote translation initiation in the absence of eIF4F complex (Meyer, Patil et al. 2015). Importantly, m^{6}A modifications in 5′ UTRs significantly increase during stress (Zhou, Wan et al. 2015), resulting in cap-independent translation and production of important stress-response proteins such as Hsp70 (Meyer, Patil et al. 2015), independent of structural IRES activity. Furthermore, translation of TOP mRNAs is

significantly enhanced by the presence of m^{6}A in the 5´ UTR, in a cap and IRES-independent manner (Coots, Liu et al. 2017).

The exact mechanism by which m^{6}A leads to ribosome recruitment independent of the cap and eIF4F complex is unclear and likely context-dependent. Efficient initiation on m^{6}A-containing mRNAs only requires eIF1, 1A, 2, and 3 (Meyer, Patil et al. 2015) and is likely mediated by METTL3 (Lin, Choe et al. 2016) or YTHDF1 (Wang, Zhao et al. 2015) proteins, which create a bridge between the m^{6}A and eIF3, thereby recruit PIC. METTL3 expression is elevated in lung adenocarcinoma and METTL3-mediated translation of m^{6}A-labelled mRNAs leads to translational upregulation of important proto-oncogenes including EGFR and the Hippo pathway effector, TAZ, as well as growth, survival, and invasion of lung cancer cells (Lin, Choe et al. 2016). Similarly, m^{6}A and METTL3 promote the translation of *c-Myc*, *Bcl2* and *Pten* mRNAs in the human acute myeloid leukemia cells (Vu, Pickering et al. 2017).

YTHDF1 expression is elevated in Hepatocellular carcinoma tissues, wherein it promotes cell proliferation and metastasis via enhanced translation of the *FZD5* mRNA that encodes a receptor for Wnt proteins (Liu, Qin et al. 2020). YTHDF1 is also frequently amplified in ovarian cancer, wherein it augments the translation of *eIF3C* mRNA in an m^{6}A-dependent manner and facilitates tumorigenesis and metastasis (Liu, Wei et al. 2020). Interestingly, YTHDF1-mediated translation of m^{6}A-bearing Cathepsins mRNAs in tumour microenvironment cells is also linked to enhanced tumourigenesis and resistance to PD-L1 checkpoint blockade in a mouse model of melanoma (Han, Liu et al. 2019). In contrast, m^{6}A was also shown to reduce translation efficiency of some mRNAs including *Atf4* under stress conditions, potentially through slowing the 40S ribosome scanning, which leads to enhanced translation at uORFs, thus repression of the main ORF (Zhou, Wan et al. 2018).

3.4.3. Cap-independent translation of circular RNAs

IRES structures and m^{6}A modification can also facilitate translation initiation on a class of RNAs termed circular RNAs (circRNAs). Human cells produce over hundred thousand circRNAs through back-splicing of exons in protein-coding genes (Ji, Wu et al. 2019), many of which are differential expression in cancer (Xia, Feng et al. 2018). Some circRNAs wield important regulatory functions in biological processes such as cell proliferation (Legnini, Di Timoteo et al. 2017) and immune response (Chen,

Satpathy et al. 2017). In most cases the role of circRNAs in tumourigenesis is attributed to their function as miRNA sponges, thus prohibiting the repression of proto-oncogenes by the corresponding miRNAs (Hansen, Jensen et al. 2013, Memczak, Jens et al. 2013, Sun, Xu et al. 2018). circRNAs also modify the function of regulatory proteins, such as the ternary complex between circFoxo3, p21 and CDK2, which is required for cell cycle progression (Du, Yang et al. 2016).

However, recent evidence also demonstrated the regulated translation of at least some circRNAs under stress conditions (Pamudurti, Bartok et al. 2017, Yang, Fan et al. 2017) and the direct role of circRNA-encoded proteins in tumourigenesis. For instance, the human papilloma virus HPV160-derived circE7 was shown to produce the E7 oncoprotein in cervical carcinoma cells. E7 blocks the function of the tumour suppressor Rb, thus circE7-depletion resulted in decreased cell proliferation and tumourigenicity (Zhao, Lee et al. 2019). However, due to absence of cap, ribosomes must be internally recruited onto the circRNAs through a natural IRES that initiates translation, in the case of circZNF609 (Legnini, Di Timoteo et al. 2017), or through m^6A modifications in sequences immediately before the START codon (Zhou, Molinie et al. 2017).

4. Dysregulated translation elongation in cancer

Although initiation has been at the forefront of research in the regulation of mRNA translation in health and diseases, emerging evidence also highlights the global as well as selective regulation of mRNA translation at the elongation phase. In contrast to the initiation phase, elongation requires only a minimal set of factors, including eEF1A, eEF2, and the elongation factor eIF5A, which was originally identified as an initiation factor (Saini, Eyler et al. 2009).

4.1. eEF1A

Vertebrates encode two eEF1A isoforms; eEF1A1 and eEF1A2, which share 98% amino acid homology. eEF1A1 is expressed in almost all tissues, however eEF1A2 is only expressed in the brain, heart, and skeletal muscle tissues that are composed of cells in permanent senescence (Lee, Francoeur et al. 1992). eEF1A activity is regulated via methylation on Lys-36 and methylation-deficient eEF1A

increase the translation efficiency on histidine codon but decrease efficiency on asparagine codons (Jakobsson, Małecki et al. 2017).

eEF1A1 overexpression has been observed in multiple types of cancers and protects the cancer cells in stress conditions (Scaggiante, Dapas et al. 2012, Liu, Chen et al. 2016, Lin, Beattie et al. 2018). Overexpression of eEF1A2 resulted in oncogenic transformation of NIH3T3 cells and enhanced their proliferation and ability to form tumour-like spheroids by ovarian carcinoma cells. Consistently, eEF1A2 is overexpressed in approximately 30% of ovarian tumours (Anand, Murthy et al. 2002) and is linked to tumourigenesis in several other types of cancer (Lee and Surh 2009, Li, Qi et al. 2010). Notably, plitidepsin, a drug approved for treatment of multiple myelomas, exerts its antitumor activity by targeting eEF1A2 (Losada, Muñoz-Alonso et al. 2016). However, considering the multitude of functions that eIF1A1/2 are implicated, besides their role in translation elongation, the contribution of their translational function in tumourigenesis is not always clear (Abbas, Kumar et al. 2015).

4.2. eEF2 and eEF2 kinase

eEF2 plays a pivotal role in translation elongation and is subject to several types of regulatory post-transcriptional modifications (**Fig. 5A**). A unique posttranslational modification of the eEF2 His-715 into diphthamide is essential for prevention of -1 frameshifting during elongation (Liu, Bachran et al. 2012). Although the direct role of this modification in cancer is not determined, depletion of OVCA1, a key enzyme in the process of diphthamide modification, increased the rate of spontaneous tumour development in mice (Chen and Behringer 2004). eEF2 is also heavily regulated through the phosphorylation of its Thr-56. This phosphorylation mediated by the eEF2 kinase (eEF2K) reduces the affinity of eEF2 for the ribosome (CARLBERG, NILSSON et al. 1990) and decreases the elongation rate (Ryazanov, Shestakova et al. 1988) (**Fig. 5B**). eEF2 is the only known substrate of eEF2K, and eEF2K is the only known kinase of eEF2 Thr-56, although recent evidence suggested a possible eEF2K-indepndent mechanism of increased eEF2 phosphorylation by AMPK (Kumar, Giles et al. 2020). Phosphorylation of eEF2 on Ser-595 by cyclin A–cyclin-dependent kinase 2 (CDK2) during mitosis also leads to inhibition of eEF2 activity by facilitating the recruitment of eEF2K and Thr-56 phosphorylation (Hizli, Chi et al. 2013) (**Fig. 5B**).

eEF2K is highly expressed in multiple types of cancer (Leprivier, Remke et al. 2013, Ashour, Gurbuz et al. 2014, Liu, Voisin et al. 2014) and promotes cancer cell survival during severe stress such as nutrient deprivation (Leprivier, Remke et al. 2013), anti-cancer drug treatment (Wu, Zhu et al. 2009, Cheng, Ren et al. 2011, Wang, Xu et al. 2019), and cell migration and tumour progression (Xie, Shen et al. 2018). eEF2K-knockout mice are viable (Chu, Liao et al. 2014) and preliminary studies with small molecule inhibitors of eEF2K have shown promising results in repressing tumour growth (Guo, Zhao et al. 2018, Kabil, Bayraktar et al. 2018, Li, Li et al. 2019). Activity of eEF2K is tightly controlled by a plethora of upstream stimuli including nutrient availability, hypoxia, and other types of stress. For instance, tumourigenicity and increased proliferation of APC-deficient colorectal cancer cells in response to insulin stimulation (Faller, Jackson et al. 2015) depends on phosphorylation of eEF2K Ser-366 by S6Ks, leading to reduced eEF2 phosphorylation (Wang, Li et al. 2001, Browne and Proud 2004) (**Fig. 5A**). Ser-366 could also be phosphorylated by the MAPK-regulated $p90^{RSK1}$ in response to treatment with mitogenic factors (Wang, Li et al. 2001). Stimulation of mTORC1 by amino acids can also repress eEF2K activity via cyclin-dependent kinase 1 (cdc2)-mediated phosphorylation of Ser-359 (Smith and Proud 2008). The Ser-359 residue is also phosphorylated by the stress-activated protein kinase 4 (SAPK4 also known as p38δ) (**Fig. 5A**), although the physiological relevance of inhibition of eEF2K and the subsequent increased elongation rate by SAPK4 is not fully understood (Knebel, Morrice et al. 2001).

In contrast, AMPK, the major sensor of low cellular energy levels, activates eEF2K activity by phosphorylation of the Ser-398 residue, resulting in reduced mRNA translation and preservation of energy (Browne, Finn et al. 2004). Similarly, the cAMP-dependent protein kinase, PKA activates eEF2K by phosphorylation of Ser-500 in response to increased levels of cAMP (Redpath and Proud 1993) (**Fig. 5B**). Under hypoxic conditions, reduced mTORC1 activity results in hypophosphorylation of 4E-BP1 as well as hypophosphorylation and stabilisation of eEF2K. This two-pronged mechanism results in simultaneous inhibition of translation initiation and elongation (Connolly, Braunstein et al. 2006). Hypoxic conditions also induce hydroxylation of eEF2K on Pro-98 by proline hydroxylases (PHDs), oxygen-dependent enzymes that are inactivated during hypoxia, leading to reduced activity of eEF2K without affecting its stability (Moore, Mikolajek et al. 2015) (**Fig. 5B**).

Depletion of eEF2K was shown to increase global protein synthesis, indicating a non-transcript specific regulation of translation by eEF2K-mediated eEF2 phosphorylation (Chu, Liao et al. 2014). However, recent evidence suggested that in prostate and lung cancer cells, eEF2K activity led to increased translation of the PD-L1, a pivotal immune-suppressant protein, by repressing the translation of an uORF, leading to the increased translation of the main ORF (Wu, Xie et al. 2020).

4.3. eIF5A and its unique hypusine modification

The third factor directly involved in translation elongation is eIF5A, which is encoded by two distinct genes; *EIF5A1* and *EIF5A2*. The two encoded proteins are 82% identical and while eIF5A1 is very abundant in most tissues, eIF5A2 is rare in normal tissues but overexpressed in many types of cancer malignancies (Guan, Sham et al. 2001). eIF5A is particularly critical for translation of stretches with consecutive proline residues, and its depletion results in ribosome stalling and impaired translation of polyproline-containing proteins *in vivo* (Gutierrez, Shin et al. 2013). A key feature of eIF5A proteins is the unusual post-translational modification of Lys-50 that results in formation of the amino acid hypusine. It has been proposed that upon localisation of eIF5A near the E site of the ribosome, the hypusine residue positions adjacent to the acceptor stem of the P site tRNA to stimulate the peptidyl transferase activity of poor substrates like Proline (Gutierrez, Shin et al. 2013). This unique modification is effected by two essential enzymes, deoxyhypusine synthase (DHPS), and deoxyhypusine hydroxylase (DOHH) (Park, Wolff et al. 1993), depletion of both of which in mouse is lethal (Meng, Kang et al. 2015, Pällmann, Braig et al. 2015).

eIF5A is a critical regulator of tumour cell growth through translation upregulation of key proto-oncogenes. Expression of eIF5A1 and eIF5A2 highly correlates with tumour progression and poor patient survival (Yang, Xie et al. 2009, He, Zhao et al. 2011, Tunca, Tezcan et al. 2013, Meng, Kang et al. 2015) and depletion of eIF5A inhibited tumor growth *in vivo* (Fujimura, Wright et al. 2014). eIF5A2 overexpression induces transformation in NIH3T3 cells (Guan, Fung et al. 2004) and promotes EMT and metastasis in several types of cancer (Tang, Dong et al. 2010, Li, Fu et al. 2014, Wei, Cao et al. 2014). Notably, expression of the DHPS and DOHH enzymes, which are responsible for eIF5A hypusinlation, also correlates with tumourigenesis (Bandino, Geerts et al. 2014). Moreover, small-molecule inhibitors that suppress eIF5A

hypusination also prevent tumourigenesis (Balabanov, Gontarewicz et al. 2007, Fujimura, Wright et al. 2014), creating a promising opportunity for cancer therapy considering that eIF5A is the only known hypusinated protein in humans.

Despite the prominent role of eIF5A in promotion of translation of polyproline-encoding mRNAs, recent genome-wide translatome analyses revealed that eIF5A facilitates global translation elongation, including many non polyproline-mRNAs (Pelechano and Alepuz 2017, Schuller, Wu et al. 2017). Interestingly, besides translation elongation, these analyses revealed that eIF5A also facilitates translation termination (Pelechano and Alepuz 2017, Schuller, Wu et al. 2017), likely through promoting eRF1 and eRF3 activity. Specific regulation of *Peak1* mRNA, encoding a non-receptor tyrosine kinase, as well as *RhoA* and *Rock2* mRNAs by eIF5A was also shown to promote the cell growth, invasive potential, and therapy resistance of pancreatic cancer (Fujimura, Wright et al. 2014, Fujimura, Choi et al. 2015). However, the mechanism by which eIF5A enhances transcript-specific translation is not understood.

4.4. eIF3

Besides recruiting the 40S ribosome to the eIF4F complex, the multi-subunit translation initiation factor eIF3 is involved in a multitude of non-canonical functions (Wolf, Lin et al. 2020). Interestingly, eIF3 was also found to associate with the elongating 80S ribosome and elongation factors, including eEF1A and eEF2 (Sha, Brill et al. 2009), where eIF3 remains associated with the 80S ribosome at least during the translation of the first 5–10 codons (Mohammad, Munzarová Pondělíčková et al. 2017). Recent studies revealed that eIF3 promotes selective mRNA translation elongation of select mRNAs encoding membrane proteins. Specifically, depletion of eIF3E subunit resulted in the accumulation of ribosomes in the first 25-75 codons (Lin, Li et al. 2020). This mechanism potentially affects the translation of thousands of mRNA, including mRNAs that encode membrane, secretory, and organelle-targeted proteins, and regulate the mitochondrial function and skeletal muscle health (Lin, Li et al. 2020).

4.5. Regulation of elongation by controlled abundance and modification of tRNAs

Availability and post-transcriptional modifications of tRNAs could significantly affect the rate of translation elongation. Abundance of codon-specific tRNAs is a major determinant of mRNA translation efficiency and accuracy (Drummond and Wilke 2008), and mRNAs that are enriched with codons biased towards the abundant tRNAs are translated more efficiently (Man and Pilpel 2007). Importantly, genes encoding cell growth and proliferation-related proteins use common codons, whereas those encoding stress-response proteins tend to use rare codons. Thus, a dynamic and rearranged tRNA pool dictates selective mRNA translation under normal or stress conditions (Torrent, Chalancon et al. 2018).

tRNAs are encoded by over 600 genes in humans, thus exhibit large sequence diversity (Berg, Giguere et al. 2019). Transcription of these tRNAs by RNA polymerase III is tightly controlled by the mTORC1 pathway, thereby coordinating the availability of tRNAs with the higher demand for them during active growth periods (Shor, Wu et al. 2010). Nevertheless, expression of tRNAs in response to environmental stimuli could be differentially regulated, hence changing the global tRNA expression profile in various conditions.

For instance, expression of tRNAs carrying anticodons that often correspond to a codon-usage signature characteristic of proliferation-related genes, such as $tRNAi^{Met}$, is induced in proliferating cells but repressed in differentiating/arresting cells. Conversely, tRNAs that harbour anticodons optimal for translation of codons found in differentiation-promoting mRNAs, such as selenocysteine tRNAs, are induced during differentiation (Gingold, Tehler et al. 2014). Consistently, overexpression of the $tRNAi^{Met}$ was shown to induce cell proliferation (Pavon-Eternod, Gomes et al. 2013), whereas reduction in selenoprotein levels resulted in increased tumourigenesis (Diwadkar-Navsariwala, Prins et al. 2006). Upregulation of Glu^{UUC} and Arg^{CCG} tRNAs was shown to promote metastasis through enhanced stability and translation efficiency of proteins enriched for their cognate codons such as *Exoc2* and *Gripap1* mRNAs, depletion of which abrogates the metastatic potential of breast cancer cells (Goodarzi, Nguyen et al. 2016).

Stress conditions also induce cleavage of tRNAs within the anticodon loop by the ribonuclease Angiogenin (ANG), which generates the 5´ and 3´ tRNA-derived stress-induced RNAs (tiRNAs) (Yamasaki, Ivanov et al. 2009). Importantly, some 5´-tiRNAs can inhibit cap-dependent translation by displacing eIF4F from the cap and partition

the target mRNAs to stress granules (Ivanov, Emara et al. 2011). Later evidence showed that production of these tiRNAs under hypoxic conditions suppressed breast cancer cells invasion, metastasis, and growth under serum-starvation by repressing translation of proto-oncogene encoding mRNAs (Goodarzi, Liu et al. 2015).

tRNAs are subject to extensive and diverse post-transcriptional modifications ranging from simple methylation to complex multistep modifications, involving a large number of enzymatic reactions (Pan 2018). On average each human tRNA contains an estimated 13 different modifications (Saikia, Fu et al. 2010) and while modifications are found along the entire 76-nucleotide length of the tRNAs, they most commonly occur at the wobble position and exert significant role in regulation of translation in response to environmental stress (Chan, Dyavaiah et al. 2010). For instance, increased m^5C modification of Leu^{CAA} following oxidative stress upregulates the translation of the ribosomal protein RPL22A and cell survival (Chan, Pang et al. 2012). Queuosine is a hyper-modified guanosine analog that is naturally produced by gut microbiota and occurs at the wobble position of Asp^{GUC}, His^{GUG}, Tyr^{GUA}, and Asn^{GUU}. Cytosine 38 methylation of tRNAs is promoted by Queuosine-containing tRNAs (Q-tRNA) leading to increased rate of translation elongation at codons decoded by Q-tRNAs and their near-cognate codons (Tuorto, Legrand et al. 2018). Importantly, loss of Q-modification results in production of unfolded proteins and triggering the ER stress and unfolded protein response (Tuorto, Legrand et al. 2018).

Dysregulated tRNA modifications and expression of tRNA-modifying enzymes, leading to differential mRNA translation, have been frequently observed in cancers (Close, Gillard et al. 2012, Begley, Sosa et al. 2013, Ladang, Rapino et al. 2015, He, Yang et al. 2020). The augmented expression of the tRNA modifying enzyme, NSun2, by Myc was shown to induce cancer cell proliferation and is upregulated in tumours (Frye and Watt 2006). In melanoma cases with $BRAF^{V600E}$ mutation, depletion of the U34 enzymes, which catalyse modifications of the wobble uridine 34 (U34) on tRNAs, led to increased cell death and reduced tumourigenesis. In these cells, PI3K pathway, a common mechanism of resistance to $BRAF^{V600E}$ inhibitors, induces the expression of U34 enzymes, which in turn promotes glycolysis through the direct, codon-dependent, elevation of *Hif1-α* mRNA translation (Rapino, Delaunay et al. 2018).

4.6. Ribosome stalling and quality control

In addition to slowed rates of translation elongation in stress conditions, the procession of the 80S ribosome along the ORF could also be halted, resulting in stalled ribosomes. “Ribosome stalling” could occurs due to various reasons including translation of poly(A) tracts (Dimitrova, Kuroha et al. 2009) and strong secondary structures (Doma and Parker 2006), damages to the mRNAs (*e.g.* oxidised nucleotides) (Simms, Hudson et al. 2014), deficiency in specific tRNAs (Ishimura, Nagy et al. 2014), or ribosome collisions in highly translated mRNAs (Juszkiewicz and Hegde 2017, Park and Subramaniam 2019). An unresolved stalled ribosome could have undesirable consequences such as aggregation and release of truncated proteins. The ribosome-associated quality control (RQC) mechanism recognises stalled ribosome and triggers a complex process that eliminates the nascent peptide as well as the aberrant mRNA (reviewed in (Joazeiro 2019)).

In brief, collision of a stalled ribosome with the trailing ribosome(s) is detected by the E3-ligase and RNA-binding protein ZNF598 (Juszkiewicz, Chandrasekaran et al. 2018). Facilitated by yet an unknown mechanism, detection of ribosome collision induces recruitment of the E2 ubiquitin ligase UBE2D3 by ZNF598, resulting in ubiquitination of several 40S ribosomal proteins (Garzia, Jafarnejad et al. 2017) and the dissociation of the 40S and 60S ribosomal subunits (Juszkiewicz, Speldewinde et al. 2020). The nascent peptide is ubiquitinated by the E3 ligase listerin and destined for proteasomal degradation. The aberrant mRNA is first cleaved by the endonuclease N4BP2 (D'Orazio, Wu et al. 2019), followed by degradation with 5´ and 3´ exonucleases (Joazeiro 2019). Recent evidence also showed that instead of outright degradation, RQC-target mRNAs could be translationally repressed by either of two alternative mechanisms; 1) the cap-binding protein and translation inhibitor 4EHP and its binding partner GIGYF2 are recruited to the stalled ribosome via either ZNF598 (Hickey, Dickson et al. 2020, Weber, Chung et al. 2020) or by EDF1 (Sinha, Ordureau et al. 2020) (**Fig. 5C**), 2) in yeast, recruitment of GCN2, likely through direct binding of GCN1 to the stalled/collided ribosomes (Pochopien, Beckert et al. 2020), induces ISR/p-eIF2α mediated translational repression (Wu, Peterson et al. 2020) (**Fig. 5D**), although it is not clear if a similar mechanism exists in humans and how p-eIF2α would specifically reduce translation of the aberrant mRNA without triggering a global translation shutdown.

Triggering RQC by stressors such as arsenate was also shown to partition the aberrant mRNA to stress granules (Moon, Morisaki et al. 2020), an indication of their

translational repression rather than decay. Altogether, these data highlight a coordinate mechanism of regulation of translation initiation and elongation that prohibits further rounds of translation of the aberrant mRNAs.

Severe neuromuscular and developmental deficiencies have been observed in mice with mutation in key components of RQC NEMF (Martin, Kigoshi-Tansho et al. 2020) and Listerin. However, the potential role of this mechanism in cancer has remained unexplored. Importantly, in the absence of RQC (*e.g.* depletion of ZNF598) or when RQC in overwhelmed under severe stress, a more expansive stress response pathway is activated. In such cases ZAKα, another sensor of collided ribosomes triggers apoptosis in a stress-activated protein kinases (SAPKs) dependent manner. ZAKα was previously shown to be required for SAPK-mediated ribotoxic stressor and chemotherapeutic agent doxorubicin-induced cell death (Sauter, Magun et al. 2010), further illustrating the potential importance of this mechanism in stress response pathway in cancer.

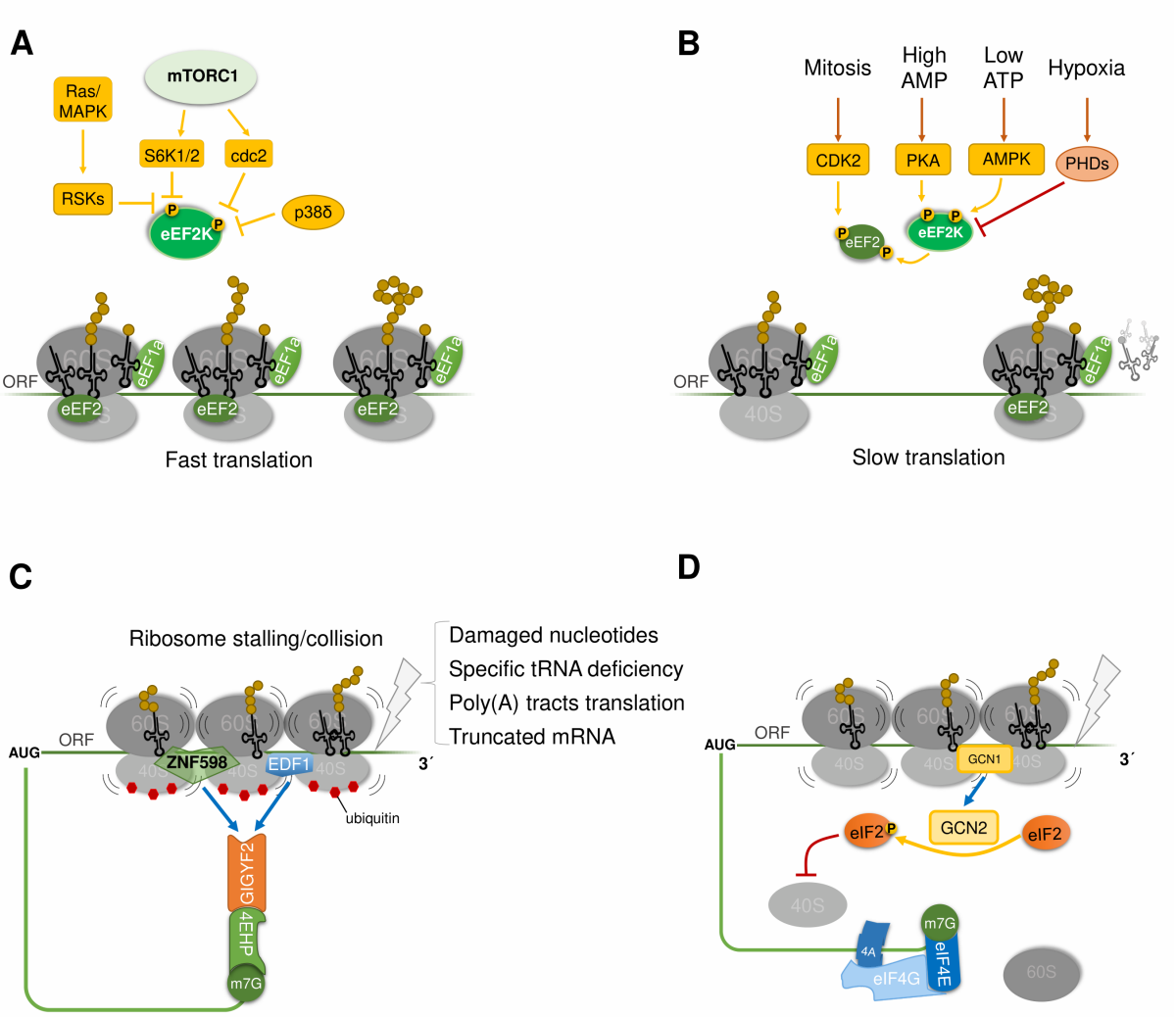


Figure 5. Regulation of translation elongation.

(**A**) The eukaryotic translation elongation factor 1a (eEF1a) facilitates binding of the aminoacyl-tRNAs to the A site of the ribosome. This is followed by peptide bond formation between the nascent polypeptide, which is bound to the peptidyl-tRNA in the P site, and the amino acid on the newly joined aminoacyl-tRNA causing transfer of the polypeptide chain. eEF2 facilitates, through GTP hydrolysis, translocation of the new peptidyl-tRNA in the A site to the P site, and the concomitant translocation of the newly deacetylated tRNA from the P site to the E site. Phosphorylation of eEF2 on Thr-56 by the eEF2 kinase (eEF2K) dramatically reduces the affinity of eEF2 for ribosome and reduced the rate of elongation. In normal conditions, eEF2K is phosphorylated on Ser-366 by S6Ks and RSK or Ser-359 by cdc2 and p38δ, leading to its repression and sustained activity of eEF2. (**B**) Under stress conditions, eEF2K becomes activated through hypo-phosphorylation of Ser-366 and Ser-359 residues due to repression of the upstream signaling pathways while simultaneously phosphorylated on Ser-398 and Ser-500 by AMPK and PKA, respectively, which leads to its activation and repression of eEF2 and reduces rate of global translation. In hypoxic conditions eEF2K is also hydroxylated on Pro-98 by proline hydroxylases (PHDs), which reduces its activity. Elongating ribosomes could stall before the stop codon is reached due to several causes such as damaged (oxidised nucleotides), truncated mRNA, presence of difficult secondary structures, deficiency in specific amino acids, or presence of poly(A) tract within ORF (open reading frame). The ribosome-associated quality control (RQC) mechanism resolves stalled ribosomes in order to avoid deleterious consequences, such as aggregation. During this process RQC blocks new rounds of translation on the aberrant mRNA via two proposed mechanisms: (**C**) collided ribosomes due to crashing of trailing ribosome with the stalled ribosome are detected by sensors of collided ribosomes ZNF598 or EDF1, which in turn recruit the 4EHP cap-binding protein and its binding

partner GIGYF2 to prepress new rounds of initiation on the cap, and (**D**) recruitment of GCN1 to the collided ribosomes activates the GCN2 kinase, which in turn phosphorylates eIF2α and represses mRNA translation via ISR pathway. Arrows indicate activation, bar-headed lines indicate inhibition, and yellow lines indicate phosphorylation.

5. Abnormal translation termination in cancer

Precise translation termination at STOP codon is crucial for the generation of functional proteins. Premature termination could result in production of truncated, nonfunctional, or deleterious proteins with dominant-negative or gain-of-function effects. Premature termination codons (PTCs) occur due to mutations such as nonsense mutations and frame-shift deletions/insertions, or aberrant splicing that generates mRNA variants with truncated reading frames. It has been estimated that one-third of alleles causing genetic diseases carry premature termination codons (Linde and Kerem 2008). Nonsense mutations, leading to inactivation of tumour suppressor genes, have been frequently observed. For instance, an estimated 83% of hereditary diffuse gastric cancer (HDGC) produce truncated E-cadherin proteins due to nonsense, splice-site, or frame-shift mutations (Carneiro, Oliveira et al. 2008). Similarly, >90% of colorectal cancer patients generate truncated APC (adenomatous polyposis coli) proteins due to nonsense or frame-shift mutations (Béroud and Soussi 1996).

Majority of PTC carrying mRNAs are detected and removed by NMD (reviewed in (Kurosaki, Popp et al. 2019)). Multiple pharmaceutical compounds enable translational readthrough of PTCs, thus restore the expression of the functional full-length protein (Dabrowski, Bukowy-Bieryllo et al. 2018). NB124, a synthetic aminoglycoside derivative, was shown to strongly induce apoptosis by promoting readthrough in human tumor cells that carry PTC in *p53* and *APC* mRNAs (Bidou, Bugaud et al. 2017). Similarly, 2,6-Diaminopurine (DAP), a naturally occurring compound in mushroom *Lepista inversa* enables readthrough of the UGA nonsense mutations in *p53* mRNA, leading to decreased growth of xenograft tumours (Trzaska, Amand et al. 2020).

Ineffective termination (STOP-codon readthrough) occurs through incorporation of an amino acid due to the recoding of the termination codon by a natural tRNA (**Fig. 6**). This could result in production of isoforms with extended C-terminus and possibly new functions. STOP-codon readthrough naturally occurs in ≈0.1% of STOP codons

(Schueren and Thoms 2016) and ribosome profiling assay revealed potential STOP-codon readthrough in 42 genes in primary human foreskin (Dunn, Foo et al. 2013). A common mechanism of STOP-codon readthrough is the incorporation of the naturally occurring non-canonical amino acid selenocysteine, mediated by the Sec^{UAG} tRNA that recodes the UGA STOP codon. Humans produce twenty-five known selenoproteins, the majority of which (e.g. glutathione peroxidases) are involved in antioxidant and anabolic processes (Labunskyy, Hatfield et al. 2014).

A secondary structure called the selenocysteine insertion sequence (SECIS) element (Berry, Banu et al. 1993) within the 3´ UTR of selenoprotein-encoding mRNAs facilitates the incorporation of selenocysteine by the unique GTP-binding elongation factor mSelB that recognizes the Sec^{UGA} tRNA and is required for efficient readthrough at UGA STOP codons (Fagegaltier, Hubert et al. 2000).

Other specific cis-acting mRNAs motifs were also shown to be important for STOP-codon readthrough in human. A specific CUAG motif positioned immediately after the UGA STOP codon is essential for STOP-codon readthrough in human *Sacm1l*, *Oprk1*, *Oprl1* and *Bri3bp* mRNAs (Loughran, Chou et al. 2014). A 63-nucleotide element in the 3´ UTR of *Vegf-A* mRNA was also shown to promote readthrough by recruiting the hnRNPA2/B1 RNA-binding protein, leading to production of a C-terminal extended protein called VEGF-Ax (Eswarappa, Potdar et al. 2014). Although it was initially shown that VEGF-Ax exhibits antiangiogenic and tumour suppressor activities (Eswarappa, Potdar et al. 2014), later evidence indicated the opposite mitogenic and angiogenic functions for VEGF-Ax (Xin, Zhong et al. 2016).

AGO1x is a product of STOP-codon readthrough of the *Ago1* mRNA that encodes Argonaute 1, a pivotal protein involved in miRNA-induced silencing. A short motif, located 10 nucleotides downstream of the canonical stop codon of the *Ago1* mRNA, was shown to be targeted by the let Let-7a miRNA, which in turn promotes STOP-codon readthrough. The resultant AGO1x protein functions as a dominant negative, due to its inability to interact with GW182, another key component of the miRNA-induced silencing pathway (Singh, Manjunath et al. 2019). Recent evidence demonstrated that AGO1x is produced in highly proliferative breast cancer cells, where it promotes cell growth and blocks induction of interferon-responses and apoptosis by inhibiting accumulation of double stranded RNAs (Ghosh, Guimaraes et al. 2020).

Binding of eIF3 translation factors to the pre-termination 80S ribosome, likely through interaction with the ribosomal protein uS3/Rps3 (Poncová, Wagner et al.

2019), was also shown to interfere with the eRF1-mediated decoding of STOP codons that are set in an unfavorable termination context (Beznosková, Wagner et al. 2015). This function is important for re-initiation of mRNAs with uORF and translation of important stress-response protein coding mRNAs such as *ATF4* under stress conditions (Hronová, Mohammad et al. 2017). The contribution of eIF3 in programmed STOP-codon readthrough at the main ORFs and its potential relevance to cancer remain to be addressed.

6. Ribosome recycling

The final stage of translation, recycling of ribosomes, is essential for maintenance of a pool of free ribosomes, hence for cellular homeostasis. In addition, un-recycled ribosomes could queue at stop codons and potentially re-initiate translation in 3´ UTRs in any of the three reading frames relative to the main ORF (Young, Guydosh et al. 2015). The generated polypeptides potentially impose significant and likely deleterious, effects. For instance, such novel peptides were observed on major histocompatibility complex (MHC) class I, with the ability to promote immune system reactivity (Schwab, Li et al. 2003), implying the importance of efficient and precise ribosome recycling in the maintenance of homeostasis and preventing cytotoxicity. However, information on ribosome recycling regulation and its implication in cancer are limited. Furthermore, the key proteins involved in the process of recycling, namely ABCE1, eIF3, and eIF6, are also involved in other aspects of translation (*e.g.* initiation and re-initiation), where the relative contribution of these functions to tumourigenesis has not been decoupled.

ABCE1 is an essential protein for the separation of the 60S and 40S subunits and has been linked to increased tumourigenecity. Ectopic expression of ABCE1 promoted clonogenicity, anchorage-independent growth, tumour growth, and metastatic potential of lung cancer cells (Tian, Tian et al. 2016). In neuroblastoma, ABCE1 expression strongly correlates with poor clinical outcome and depletion of ABCE1 reduces the growth, motility, and invasiveness of n-Myc-amplified neuroblastoma cells (Gao, Jung et al. 2020). Expression of ABCE1 is also upregulated in glioma tissues and its repression increases sensitivity of the glioma cells to the chemotherapeutic agent temozolomide (Zhang, Chen et al. 2018). Although it is unclear whether the

conspicuous oncogenic role of ABCE1 is due to its function in ribosome recycling, or else owed to an unidentified function, unrelated to ribosome recycling.

The translation initiation factor eIF6 increases the efficiency of ribosome dissociation and prohibits unproductive 80S formation without an mRNA (Valenzuela, Chaudhuri et al. 1982), thus maintaining the pool of free ribosomes. Consistently, expression of eIF6 is tightly regulated in accordance with the demand for ribosome and translational rate (Donadini, Giodini et al. 2001). eIF6 expression is positively correlated with cancer progression (GOLOB-SCHWARZL, PUCHAS et al. 2020), and its depletion limits the *in vivo* tumour growth (Gandin, Miluzio et al. 2008). Recent evidence also revealed a role for eIF3 in ribosome recycling. In yeast, the eIF3J was found as an accessory factor for ABCE1-catalysed ribosome dissociation. Accordingly, unrecycled 80S ribosomes can re-initiate translation in 3´ UTRs in eIF3J-deifiecnt cells (Young and Guydosh 2019). However, the potential role of human eIF3J in recycling is unclear.

Oxidative stress and ROS-inducing drugs were shown to reduce ribosome recycling efficiency and increase translation in 3´ UTRs, in an ABCE1-dependent manner (Sudmant, Lee et al. 2018, Zhu, Zhang et al. 2020) (**Fig. 6**). Given the prevalence of oxidative stress and ROS in cancer, targeting the ribosome recycling machinery could be a promising strategy to use in order to induce non-canonical translation events, with the potential for neo-antigens generation and reducing the free ribosome availability in cancer cells.

7. Versatile utility of 3´ UTR for translational control in cancer

3´ UTR have a profound impact on mRNA stability, subcellular localisation, translation efficiency, and protein-protein interaction of the nascent polypeptide, thus they significantly impact key cellular processes that affect cellular homeostasis and tumourigenesis. The main functions of 3´ UTR are affected via cis-acting motifs, which recruit trans-acting factors including miRNAs and RBPs. miRNAs are a large family of ~22 nucleotides regulatory RNAs, encoded by >2000 genes, which target an estimated 60% of protein-coding mRNAs in humans (Huang, Shi et al. 2019). miRNAs silence their target mRNAs by recruiting the miRNA-induced silencing complex (miRISC), which in turn engages the CCR4-NOT complex (**Fig. 6**) to repress target mRNAs by two mechanisms: repression of translation and promotion of mRNA decay

(Duchaine and Fabian 2019). While it has been suggested that the majority of miRNA-mediated repression is due to decay, several studies have demonstrated translational silencing in the absence of mRNA decay (Jin, Oda et al. 2017, Jafarnejad, Chapat et al. 2018). Dysregulated miRNA biogenesis and function have been frequently documented in almost all types of cancer and reviewed elsewhere (Hata and Kashima 2016).

RBPs are a large and heterogeneous family of proteins that contribute to the formation of different ribonucleoprotein complexes and play essential roles in sustaining cellular homeostasis as well as in diseases, including cancer. Human genome encodes >1500 RBPs (Gerstberger, Hafner et al. 2014), which affect various stages of mRNA life cycle, including maturation, transport, translation efficiency, stability and degradation (Hentze, Castello et al. 2018), illustrating the substantial and intricate roles of these proteins in almost every aspect of cellular physio/pathology. Similar to miRNAs, majority of RBPs bind to motifs located in the 3´ UTR (Mayr 2019). For instance, AU-rich elements (AREs), usually pentamers of the AUUUA, are present in 5-10% of all human mRNAs (Halees, El-Badrawi et al. 2008) and control stability and translation. Several RBPs such as AU-binding factor 1 (Brewer 1991), Tristetraprolin family (Blackshear, Lai et al. 2003), and ELAV/HuR family (Ma, Cheng et al. 1996) bind to AREs and control the stability and/or translation of their target mRNAs. Notably, while the majority of the ARE-binding proteins negatively impact the expression of target mRNAs by promoting decay or translational repression, ELAV/HuR proteins increase stability and/or translation of target mRNAs, at least partly by prohibiting the repression induced by other RBPs and miRNAs (Bhattacharyya, Habermacher et al. 2006). Dysregulated mRNA translation due to the aberrant expression and function of ARE-binding factors has been frequently observed in cancer (reviewed in (Bhattacharyya, Habermacher et al. 2006)).

Cancer cells employ two main strategies to circumvent the RBP- and miRNA-binding to the 3´ UTRs. Approximately 70% of mammalian mRNA-encoding genes use alternative polyadenylation sites to generate mRNA transcripts that differ in their 3´ UTR lengths, without changing the protein sequence (Derti, Garrett-Engele et al. 2012, Hoque, Ji et al. 2013). Proliferating (Sandberg, Neilson et al. 2008) and cancer cells (Mayr and Bartel 2009) commonly utilise alternative cleavage and polyadenylation sites to generate mRNA variants with shorter 3´ UTRs that lack the RBP- and miRNA-binding sites. For instance, expression of the shorter variants of the proto-

oncogenes *IGF2BP1, Cyclin D1, Cyclin D2, and FGF2* mRNAs, led to more oncogenic transformation compared with the expression of the full-length mRNAs (Mayr and Bartel 2009). Alternative splicing of mRNAs (3′ exon switching), leading to exclusion of the suppressive elements in mRNAs such as the proto-oncogene *Her2*, is another approach utilised to avert the RBP- and miRNA-induced silencing in cancer cells (Edwalds-Gilbert, Veraldi et al. 1997, Sandberg, Neilson et al. 2008, Mayr and Bartel 2009).

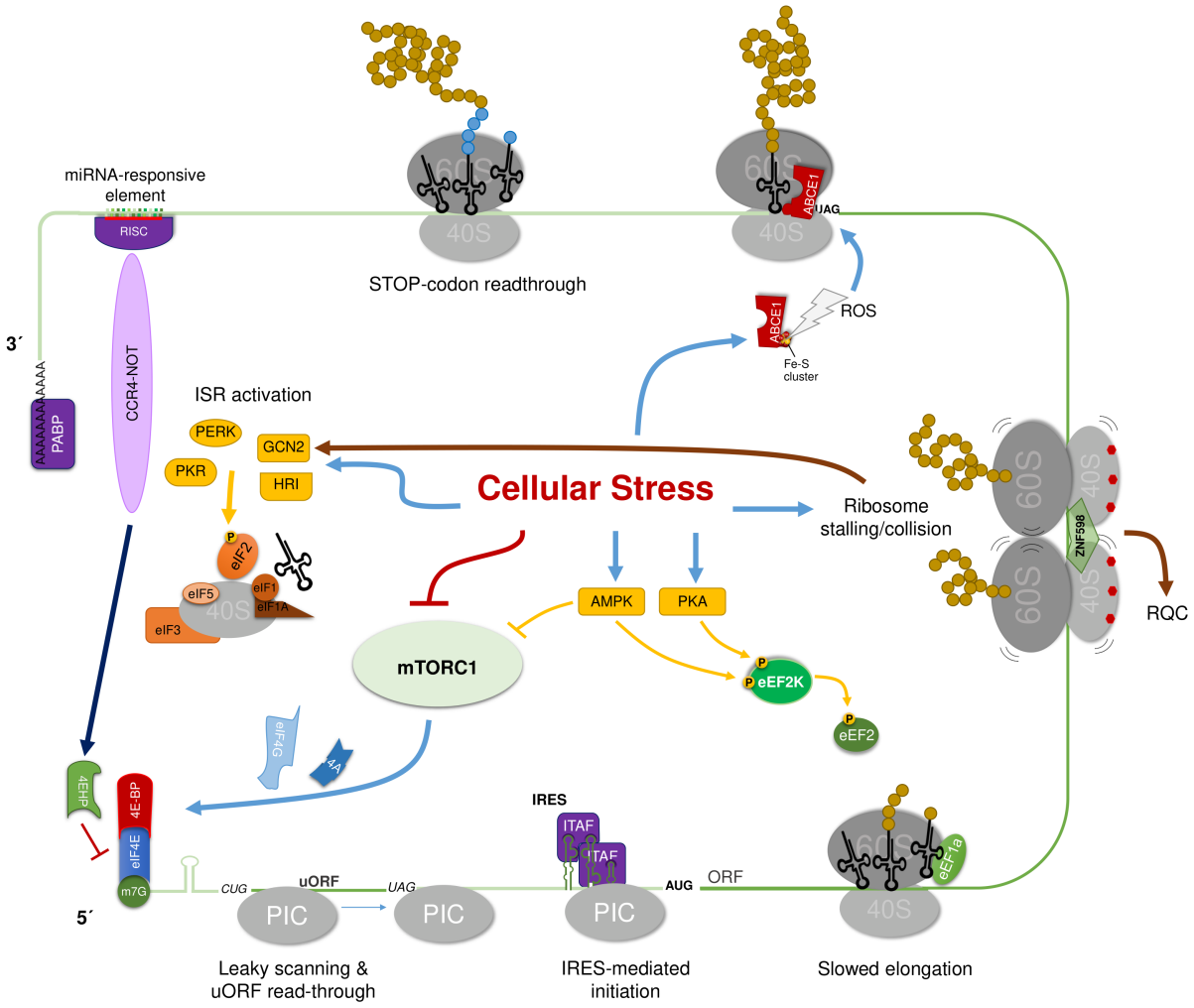


Figure 6. Overview of the multifaceted stress-induced regulation of mRNA translation
mRNA translation is highly influenced by various types of stress which (dys)regulate every stage of the translation process. In many cases, different types of stress could exert simultaneous and overlapping

effects on multiple stages of translation. Arrows indicate activation, bar-headed lines indicate inhibition, and yellow lines indicate phosphorylation.

8. Concluding remarks

Regulation of mRNA translation is a multifaceted mechanism involving an intricate network of translation factors, RBPs, non-coding RNAs, and signaling pathways. As highlighted frequently in this review, many signaling pathways simultaneously control multiple stages of translation. Furthermore, translation factors that we initially believed to be only involved in specific stages of translation have appeared to participate in more than one function (*e.g.* eIF3), illustrating the need for cautious interpretation of the outcomes of relevant mechanistic studies.

Furthermore, an important issue regarding the regulation of mRNA translation in cancer is the conspicuous context-dependency. This implies the unlikely chance of success for a one-size fits all approach and highlights the need for further informed, personalised procedures when selecting treatments involving translation-modulating reagents. Translation machinery and its associated regulatory pathways are highly amenable to treatment with drugs (Bhat, Robichaud et al. 2015), yet so far limited success has been achieved in "translating" that into clinic.

We discussed several major mechanisms that influence the global or transcript-specific regulation of mRNA translation in cancer. However, the growing list of novel regulatory mechanisms and non-canonical translation events provide exciting opportunities for further discoveries in this field as well as the possibility of significant advancement in the development of new forms of anti-cancer treatments.

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Declaration of Interest

The authors declare no conflict of interest.

References

Abbas, W., A. Kumar and G. Herbein (2015). "The eEF1A proteins: at the crossroads of oncogenesis, apoptosis, and viral infections." Frontiers in oncology **5**: 75.

Adesso, L., S. Calabretta, F. Barbagallo, G. Capurso, E. Pilozzi, R. Geremia, G. Delle Fave and C. Sette (2013). "Gemcitabine triggers a pro-survival response in pancreatic cancer cells through activation of the MNK2/eIF4E pathway." Oncogene **32**(23): 2848-2857.

Akar, U., B. Ozpolat, K. Mehta, G. Lopez-Berestein, D. Zhang, N. T. Ueno, G. N. Hortobagyi and B. Arun (2010). "Targeting p70S6K prevented lung metastasis in a breast cancer xenograft model." Molecular cancer therapeutics **9**(5): 1180-1187.

Al-Ashtal, H. A., C. M. Rubottom, T. C. Leeper and A. J. Berman (2019). "The LARP1 La-Module recognizes both ends of TOP mRNAs." RNA biology: 1-11.

Alkalaeva, E. Z., A. V. Pisarev, L. Y. Frolova, L. L. Kisselev and T. V. Pestova (2006). "In vitro reconstitution of eukaryotic translation reveals cooperativity between release factors eRF1 and eRF3." Cell **125**(6): 1125-1136.

Anand, N., S. Murthy, G. Amann, M. Wernick, L. A. Porter, I. H. Cukier, C. Collins, J. W. Gray, J. Diebold and D. J. Demetrick (2002). "Protein elongation factor EEF1A2 is a putative oncogene in ovarian cancer." Nature genetics **31**(3): 301-305.

Aoki, K., S. Adachi, M. Homoto, H. Kusano, K. Koike and T. Natsume (2013). "LARP1 specifically recognizes the 3′ terminus of poly (A) mRNA." FEBS letters **587**(14): 2173-2178.

Armengol, G., F. Rojo, J. Castellví, C. Iglesias, M. Cuatrecasas, B. Pons, J. Baselga and S. R. y Cajal (2007). "4E-binding protein 1: a key molecular "funnel factor" in human cancer with clinical implications." Cancer research **67**(16): 7551-7555.

Ashour, A. A., N. Gurbuz, S. N. Alpay, A. A. H. Abdel‐Aziz, A. M. Mansour, L. Huo and B. Ozpolat (2014). "Elongation factor‐2 kinase regulates TG 2/β 1 integrin/Src/u PAR pathway and epithelial–mesenchymal transition mediating pancreatic cancer cells invasion." Journal of cellular and molecular medicine **18**(11): 2235-2251.

Astanehe, A., M. Finkbeiner, M. Krzywinski, A. Fotovati, J. Dhillon, I. Berquin, G. B. Mills, M. Marra and S. Dunn (2012). "MKNK1 is a YB-1 target gene responsible for imparting trastuzumab resistance and can be blocked by RSK inhibition." Oncogene **31**(41): 4434-4446.

Atkinson, G. C., S. L. Baldauf and V. Hauryliuk (2008). "Evolution of nonstop, no-go and nonsense-mediated mRNA decay and their termination factor-derived components." BMC evolutionary biology **8**(1): 1-18.
Attar-Schneider, O., L. Drucker and M. Gottfried (2016). "Migration and epithelial-to-mesenchymal transition of lung cancer can be targeted via translation initiation factors eIF4E and eIF4GI." Laboratory investigation **96**(9): 1004-1015.
Audigier, S., J. Guiramand, L. Prado-Lourenco, C. Conte, I. G. Gonzalez-Herrera, C. Cohen-Solal, M. Récasens and A.-C. Prats (2008). "Potent activation of FGF-2 IRES-dependent mechanism of translation during brain development." Rna **14**(9): 1852-1864.
Aylett, C. H., E. Sauer, S. Imseng, D. Boehringer, M. N. Hall, N. Ban and T. Maier (2016). "Architecture of human mTOR complex 1." Science **351**(6268): 48-52.
Babendure, J. R., J. L. Babendure, J.-H. Ding and R. Y. Tsien (2006). "Control of mammalian translation by mRNA structure near caps." Rna **12**(5): 851-861.
Badawi, A., A. Biyanee, U. Nasrullah, S. Winslow, T. Schmid, J. Pfeilschifter and W. Eberhardt (2018). "Inhibition of IRES-dependent translation of caspase-2 by HuR confers chemotherapeutic drug resistance in colon carcinoma cells." Oncotarget **9**(26): 18367.
Balabanov, S., A. Gontarewicz, P. Ziegler, U. Hartmann, W. Kammer, M. Copland, U. Brassat, M. Priemer, I. Hauber and T. Wilhelm (2007). "Hypusination of eukaryotic initiation factor 5A (eIF5A): a novel therapeutic target in BCR-ABL–positive leukemias identified by a proteomics approach." Blood **109**(4): 1701-1711.
Bandino, A., D. Geerts, J. Koster and A. S. Bachmann (2014). "Deoxyhypusine synthase (DHPS) inhibitor GC7 induces p21/Rb-mediated inhibition of tumor cell growth and DHPS expression correlates with poor prognosis in neuroblastoma patients." Cellular Oncology **37**(6): 387-398.
Banko, J. L., F. Poulin, L. Hou, C. T. DeMaria, N. Sonenberg and E. Klann (2005). "The translation repressor 4E-BP2 is critical for eIF4F complex formation, synaptic plasticity, and memory in the hippocampus." Journal of Neuroscience **25**(42): 9581-9590.
Bärlund, M., F. Forozan, J. Kononen, L. Bubendorf, Y. Chen, M. L. Bittner, J. Torhorst, P. Haas, C. Bucher and G. Sauter (2000). "Detecting activation of ribosomal protein S6 kinase by complementary DNA and tissue microarray analysis." Journal of the National Cancer Institute **92**(15): 1252-1259.
Barthelme, D., S. Dinkelaker, S.-V. Albers, P. Londei, U. Ermler and R. Tampé (2011). "Ribosome recycling depends on a mechanistic link between the FeS cluster domain and a conformational switch of the twin-ATPase ABCE1." Proceedings of the National Academy of Sciences **108**(8): 3228-3233.
Begley, U., M. S. Sosa, A. Avivar‐Valderas, A. Patil, L. Endres, Y. Estrada, C. T. Chan, D. Su, P. C. Dedon and J. A. Aguirre‐Ghiso (2013). "A human tRNA methyltransferase 9‐like protein prevents tumour growth by regulating LIN9 and HIF1‐α." EMBO molecular medicine **5**(3): 366-383.
Behrmann, E., J. Loerke, T. V. Budkevich, K. Yamamoto, A. Schmidt, P. A. Penczek, M. R. Vos, J. Bürger, T. Mielke and P. Scheerer (2015). "Structural snapshots of actively translating human ribosomes." Cell **161**(4): 845-857.
Beltran, M., I. Puig, C. Peña, J. M. García, A. B. Álvarez, R. Peña, F. Bonilla and A. G. de Herreros (2008). "A natural antisense transcript regulates Zeb2/Sip1 gene expression during Snail1-induced epithelial–mesenchymal transition." Genes & development **22**(6): 756-769.
Berg, M. D., D. J. Giguere, J. S. Dron, J. T. Lant, J. Genereaux, C. Liao, J. Wang, J. F. Robinson, G. B. Gloor and R. A. Hegele (2019). "Targeted sequencing reveals expanded genetic diversity of human transfer RNAs." RNA biology **16**(11): 1574-1585.

Béroud, C. and T. Soussi (1996). "APC gene: database of germline and somatic mutations in human tumors and cell lines." Nucleic Acids Res **24**(1): 121-124.
Berry, M. J., L. Banu, J. W. Harney and P. R. Larsen (1993). "Functional characterization of the eukaryotic SECIS elements which direct selenocysteine insertion at UGA codons." Embo j **12**(8): 3315-3322.
Bevilacqua, E., X. Wang, M. Majumder, F. Gaccioli, C. L. Yuan, C. Wang, X. Zhu, L. E. Jordan, D. Scheuner and R. J. Kaufman (2010). "eIF2α phosphorylation tips the balance to apoptosis during osmotic stress." Journal of Biological Chemistry **285**(22): 17098-17111.
Beznosková, P., S. Wagner, M. E. Jansen, T. von der Haar and L. S. Valášek (2015). "Translation initiation factor eIF3 promotes programmed stop codon readthrough." Nucleic acids research **43**(10): 5099-5111.
Bhat, M., N. Robichaud, L. Hulea, N. Sonenberg, J. Pelletier and I. Topisirovic (2015). "Targeting the translation machinery in cancer." Nat Rev Drug Discov **14**(4): 261-278.
Bhattacharyya, S. N., R. Habermacher, U. Martine, E. I. Closs and W. Filipowicz (2006). "Relief of microRNA-mediated translational repression in human cells subjected to stress." Cell **125**(6): 1111-1124.
Bi, M., C. Naczki, M. Koritzinsky, D. Fels, J. Blais, N. Hu, H. Harding, I. Novoa, M. Varia and J. Raleigh (2005). "ER stress‐regulated translation increases tolerance to extreme hypoxia and promotes tumor growth." The EMBO journal **24**(19): 3470-3481.
Bianchini, A., M. Loiarro, P. Bielli, R. Busa, M. P. Paronetto, F. Loreni, R. Geremia and C. Sette (2008). "Phosphorylation of eIF4E by MNKs supports protein synthesis, cell cycle progression and proliferation in prostate cancer cells." Carcinogenesis **29**(12): 2279-2288.
Bidou, L., O. Bugaud, V. Belakhov, T. Baasov and O. Namy (2017). "Characterization of new-generation aminoglycoside promoting premature termination codon readthrough in cancer cells." RNA Biol **14**(3): 378-388.
Blackshear, P. J., W. S. Lai, E. A. Kennington, G. Brewer, G. M. Wilson, X. Guan and P. Zhou (2003). "Characteristics of the interaction of a synthetic human tristetraprolin tandem zinc finger peptide with AU-rich element-containing RNA substrates." J Biol Chem **278**(22): 19947-19955.
Blanco, S., R. Bandiera, M. Popis, S. Hussain, P. Lombard, J. Aleksic, A. Sajini, H. Tanna, R. Cortés-Garrido and N. Gkatza (2016). "Stem cell function and stress response are controlled by protein synthesis." Nature **534**(7607): 335-340.
Bohlen, J., L. Harbrecht, S. Blanco, K. C. von Hohenberg, K. Fenzl, G. Kramer, B. Bukau and A. A. Teleman (2020). "DENR promotes translation reinitiation via ribosome recycling to drive expression of oncogenes including ATF4." Nature communications **11**(1): 1-15.
Bolster, D. R., S. J. Crozier, S. R. Kimball and L. S. Jefferson (2002). "AMP-activated protein kinase suppresses protein synthesis in rat skeletal muscle through down-regulated mammalian target of rapamycin (mTOR) signaling." Journal of Biological Chemistry **277**(27): 23977-23980.
Bordeleau, M.-E., F. Robert, B. Gerard, L. Lindqvist, S. M. Chen, H.-G. Wendel, B. Brem, H. Greger, S. W. Lowe and J. A. Porco (2008). "Therapeutic suppression of translation initiation modulates chemosensitivity in a mouse lymphoma model." The Journal of clinical investigation **118**(7): 2651-2660.
Brass, N., D. Heckel, U. Sahin, M. Pfreundschuh, G. W. Sybrecht and E. Meese (1997). "Translation initiation factor eIF-4gamma is encoded by an amplified gene and induces an immune response in squamous cell lung carcinoma." Human molecular genetics **6**(1): 33-39.
Brewer, G. (1991). "An A + U-rich element RNA-binding factor regulates c-myc mRNA stability in vitro." Mol Cell Biol **11**(5): 2460-2466.

Browne, G. J., S. G. Finn and C. G. Proud (2004). "Stimulation of the AMP-activated protein kinase leads to activation of eukaryotic elongation factor 2 kinase and to its phosphorylation at a novel site, serine 398." Journal of Biological Chemistry **279**(13): 12220-12231.
Browne, G. J. and C. G. Proud (2004). "A novel mTOR-regulated phosphorylation site in elongation factor 2 kinase modulates the activity of the kinase and its binding to calmodulin." Molecular and cellular biology **24**(7): 2986-2997.
Budkevich, T., J. Giesebrecht, R. B. Altman, J. B. Munro, T. Mielke, K. H. Nierhaus, S. C. Blanchard and C. M. Spahn (2011). "Structure and dynamics of the mammalian ribosomal pretranslocation complex." Molecular cell **44**(2): 214-224.
Buttgereit, F. and M. D. Brand (1995). "A hierarchy of ATP-consuming processes in mammalian cells." Biochemical Journal **312**(1): 163-167.
Calvo, S. E., D. J. Pagliarini and V. K. Mootha (2009). "Upstream open reading frames cause widespread reduction of protein expression and are polymorphic among humans." Proceedings of the National Academy of Sciences **106**(18): 7507-7512.
CARLBERG, U., A. NILSSON and O. NYGÅRD (1990). "Functional properties of phosphorylated elongation factor 2." European journal of biochemistry **191**(3): 639-645.
Carneiro, F., C. Oliveira, G. Suriano and R. Seruca (2008). "Molecular pathology of familial gastric cancer, with an emphasis on hereditary diffuse gastric cancer." J Clin Pathol **61**(1): 25-30.
Carrière, A., M. Cargnello, L.-A. Julien, H. Gao, É. Bonneil, P. Thibault and P. P. Roux (2008). "Oncogenic MAPK signaling stimulates mTORC1 activity by promoting RSK-mediated raptor phosphorylation." Current biology **18**(17): 1269-1277.
Carter, P. S., M. Jarquin-Pardo and A. De Benedetti (1999). "Differential expression of Myc1 and Myc2 isoforms in cells transformed by eIF4E: evidence for internal ribosome repositioning in the human c-myc 5′ UTR." Oncogene **18**(30): 4326-4335.
Cassidy, K. C., R. M. Lahr, J. C. Kaminsky, S. Mack, B. D. Fonseca, S. R. Das, A. J. Berman and J. D. Durrant (2019). "Capturing the mechanism underlying TOP mRNA binding to LARP1." Structure **27**(12): 1771-1781. e1775.
Cencic, R., D. R. Hall, F. Robert, Y. Du, J. Min, L. Li, M. Qui, I. Lewis, S. Kurtkaya and R. Dingledine (2011). "Reversing chemoresistance by small molecule inhibition of the translation initiation complex eIF4F." Proceedings of the National Academy of Sciences **108**(3): 1046-1051.
Cencic, R., F. Robert, G. Galicia-Vazquez, A. Malina, K. Ravindar, R. Somaiah, P. Pierre, J. Tanaka, P. Deslongchamps and J. Pelletier (2013). "Modifying chemotherapy response by targeted inhibition of eukaryotic initiation factor 4A." Blood cancer journal **3**(7): e128-e128.
Chaisuparat, R., S. Rojanawatsirivej and S. Yodsanga (2013). "Ribosomal protein S6 phosphorylation is associated with epithelial dysplasia and squamous cell carcinoma of the oral cavity." Pathology & Oncology Research **19**(2): 189-193.
Chan, C. T., M. Dyavaiah, M. S. DeMott, K. Taghizadeh, P. C. Dedon and T. J. Begley (2010). "A quantitative systems approach reveals dynamic control of tRNA modifications during cellular stress." PLoS Genet **6**(12): e1001247.
Chan, C. T., Y. L. J. Pang, W. Deng, I. R. Babu, M. Dyavaiah, T. J. Begley and P. C. Dedon (2012). "Reprogramming of tRNA modifications controls the oxidative stress response by codon-biased translation of proteins." Nature communications **3**(1): 1-9.
Chan, K., F. Robert, C. Oertlin, D. Kapeller-Libermann, D. Avizonis, J. Gutierrez, A. Handly-Santana, M. Doubrovin, J. Park and C. Schoepfer (2019). "eIF4A supports an oncogenic translation program in pancreatic ductal adenocarcinoma." Nature communications **10**(1): 1-16.

Chang, K., N. Miller, E. Kheirelseid, H. Ingoldsby, E. Hennessy, C. Curran, S. Curran, M. Smith, M. Regan and O. McAnena (2011). "MicroRNA-21 and PDCD4 expression in colorectal cancer." European Journal of Surgical Oncology (EJSO) **37**(7): 597-603.
Chapat, C., S. M. Jafarnejad, E. Matta-Camacho, G. G. Hesketh, I. A. Gelbart, J. Attig, C. G. Gkogkas, T. Alain, N. Stern-Ginossar and M. R. Fabian (2017). "Cap-binding protein 4EHP effects translation silencing by microRNAs." Proceedings of the National Academy of Sciences **114**(21): 5425-5430.
Chen, B., Z. Tan, J. Gao, W. Wu, L. Liu, W. Jin, Y. Cao, S. Zhao, W. Zhang and Z. Qiu (2015). "Hyperphosphorylation of ribosomal protein S6 predicts unfavorable clinical survival in non-small cell lung cancer." Journal of Experimental & Clinical Cancer Research **34**(1): 126.
Chen, C.-M. and R. R. Behringer (2004). "Ovca1 regulates cell proliferation, embryonic development, and tumorigenesis." Genes & development **18**(3): 320-332.
Chen, S. and G. Gao (2017). "MicroRNAs recruit eIF4E2 to repress translation of target mRNAs." Protein & cell **8**(10): 750-761.
Chen, Y., T. Knösel, G. Kristiansen, A. Pietas, M. E. Garber, S. Matsuhashi, I. Ozaki and I. Petersen (2003). "Loss of PDCD4 expression in human lung cancer correlates with tumour progression and prognosis." The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland **200**(5): 640-646.
Chen, Y. G., A. T. Satpathy and H. Y. Chang (2017). "Gene regulation in the immune system by long noncoding RNAs." Nature immunology **18**(9): 962-972.
Cheng, Y., X. Ren, Y. Zhang, R. Patel, A. Sharma, H. Wu, G. P. Robertson, L. Yan, E. Rubin and J.-M. Yang (2011). "eEF-2 kinase dictates cross-talk between autophagy and apoptosis induced by Akt Inhibition, thereby modulating cytotoxicity of novel Akt inhibitor MK-2206." Cancer research **71**(7): 2654-2663.
Chio, I. I. C., S. M. Jafarnejad, M. Ponz-Sarvise, Y. Park, K. Rivera, W. Palm, J. Wilson, V. Sangar, Y. Hao and D. Öhlund (2016). "NRF2 promotes tumor maintenance by modulating mRNA translation in pancreatic cancer." Cell **166**(4): 963-976.
Chu, H.-P., Y. Liao, J. S. Novak, Z. Hu, J. J. Merkin, Y. Shymkiv, B. P. Braeckman, M. V. Dorovkov, A. Nguyen and P. M. Clifford (2014). "Germline quality control: eEF2K stands guard to eliminate defective oocytes." Developmental cell **28**(5): 561-572.
Clark, E. L., A. Coulson, C. Dalgliesh, P. Rajan, S. M. Nicol, S. Fleming, R. Heer, L. Gaughan, H. Y. Leung and D. J. Elliott (2008). "The RNA helicase p68 is a novel androgen receptor coactivator involved in splicing and is overexpressed in prostate cancer." Cancer research **68**(19): 7938-7946.
Close, P., M. Gillard, A. Ladang, Z. Jiang, J. Papuga, N. Hawkes, L. Nguyen, J.-P. Chapelle, F. Bouillenne and J. Svejstrup (2012). "DERP6 (ELP5) and C3ORF75 (ELP6) regulate tumorigenicity and migration of melanoma cells as subunits of Elongator." Journal of Biological Chemistry **287**(39): 32535-32545.
Cobbold, L., L. Wilson, K. Sawicka, H. King, A. Kondrashov, K. Spriggs, M. Bushell and A. Willis (2010). "Upregulated c-myc expression in multiple myeloma by internal ribosome entry results from increased interactions with and expression of PTB-1 and YB-1." Oncogene **29**(19): 2884-2891.
Connolly, E., S. Braunstein, S. Formenti and R. J. Schneider (2006). "Hypoxia inhibits protein synthesis through a 4E-BP1 and elongation factor 2 kinase pathway controlled by mTOR and uncoupled in breast cancer cells." Molecular and cellular biology **26**(10): 3955-3965.
Connor, J. H., D. C. Weiser, S. Li, J. M. Hallenbeck and S. Shenolikar (2001). "Growth arrest and DNA damage-inducible protein GADD34 assembles a novel signaling complex containing protein phosphatase 1 and inhibitor 1." Molecular and cellular biology **21**(20): 6841-6850.

Conte, C., N. Ainaoui, A. Delluc-Clavieres, M. P. Khoury, R. Azar, F. Pujol, Y. Martineau, S. Pyronnet and A.-C. Prats (2009). "Fibroblast growth factor 1 induced during myogenesis by a transcription–translation coupling mechanism." Nucleic acids research **37**(16): 5267-5278.
Coots, R. A., X.-M. Liu, Y. Mao, L. Dong, J. Zhou, J. Wan, X. Zhang and S.-B. Qian (2017). "m6A facilitates eIF4F-independent mRNA translation." Molecular cell **68**(3): 504-514. e507.
Crew, J., S. Fuggle, R. Bicknell, D. Cranston, A. De Benedetti and A. Harris (2000). "Eukaryotic initiation factor-4E in superficial and muscle invasive bladder cancer and its correlation with vascular endothelial growth factor expression and tumour progression." British journal of cancer **82**(1): 161-166.
D'Orazio, K. N., C. C.-C. Wu, N. Sinha, R. Loll-Krippleber, G. W. Brown and R. Green (2019). "The endonuclease Cue2 cleaves mRNAs at stalled ribosomes during No Go Decay." Elife **8**: e49117.
Dabrowski, M., Z. Bukowy-Bieryllo and E. Zietkiewicz (2018). "Advances in therapeutic use of a drug-stimulated translational readthrough of premature termination codons." Mol Med **24**(1): 25.
Dagon, Y., E. Hur, B. Zheng, K. Wellenstein, L. C. Cantley and B. B. Kahn (2012). "p70S6 kinase phosphorylates AMPK on serine 491 to mediate leptin's effect on food intake." Cell metabolism **16**(1): 104-112.
De Benedetti, A., S. Joshi-Barve, C. Rinker-Schaeffer and R. E. Rhoads (1991). "Expression of antisense RNA against initiation factor eIF-4E mRNA in HeLa cells results in lengthened cell division times, diminished translation rates, and reduced levels of both eIF-4E and the p220 component of eIF-4F." Molecular and cellular biology **11**(11): 5435-5445.
De Benedetti, A. and R. E. Rhoads (1990). "Overexpression of eukaryotic protein synthesis initiation factor 4E in HeLa cells results in aberrant growth and morphology." Proceedings of the National Academy of Sciences **87**(21): 8212-8216.
de la Parra, C., A. Ernlund, A. Alard, K. Ruggles, B. Ueberheide and R. J. Schneider (2018). "A widespread alternate form of cap-dependent mRNA translation initiation." Nature communications **9**(1): 1-9.
De La Rojo Vega, M., E. Chapman and D. Zhang (2018). "NRF2 and the Hallmarks of Cancer." Cancer Cell **34**: 21-43.
de Vries, S., I. S. Naarmann-de Vries, H. Urlaub, H. Lue, J. Bernhagen, D. H. Ostareck and A. Ostareck-Lederer (2013). "Identification of DEAD-box RNA helicase 6 (DDX6) as a cellular modulator of vascular endothelial growth factor expression under hypoxia." Journal of biological chemistry **288**(8): 5815-5827.
DeFatta, R. J., E. A. Turbat‐Herrera, B. D. Li, W. Anderson and A. De Benedetti (1999). "Elevated expression of eIF4E in confined early breast cancer lesions: possible role of hypoxia." International journal of cancer **80**(4): 516-522.
Deng, J., H. P. Harding, B. Raught, A.-C. Gingras, J. J. Berlanga, D. Scheuner, R. J. Kaufman, D. Ron and N. Sonenberg (2002). "Activation of GCN2 in UV-irradiated cells inhibits translation." Current Biology **12**(15): 1279-1286.
Derti, A., P. Garrett-Engele, K. D. Macisaac, R. C. Stevens, S. Sriram, R. Chen, C. A. Rohl, J. M. Johnson and T. Babak (2012). "A quantitative atlas of polyadenylation in five mammals." Genome Res **22**(6): 1173-1183.
Dey, S., T. D. Baird, D. Zhou, L. R. Palam, D. F. Spandau and R. C. Wek (2010). "Both transcriptional regulation and translational control of ATF4 are central to the integrated stress response." Journal of Biological Chemistry **285**(43): 33165-33174.
DeYoung, M. P., P. Horak, A. Sofer, D. Sgroi and L. W. Ellisen (2008). "Hypoxia regulates TSC1/2-mTOR signaling and tumor suppression through REDD1-mediated 14-3-3 shuttling." Genes Dev **22**(2): 239-251.

Dibble, C. C., J. M. Asara and B. D. Manning (2009). "Characterization of Rictor phosphorylation sites reveals direct regulation of mTOR complex 2 by S6K1." Molecular and cellular biology **29**(21): 5657-5670.
Dimitrova, L. N., K. Kuroha, T. Tatematsu and T. Inada (2009). "Nascent peptide-dependent translation arrest leads to Not4p-mediated protein degradation by the proteasome." Journal of Biological Chemistry **284**(16): 10343-10352.
Diwadkar-Navsariwala, V., G. S. Prins, S. M. Swanson, L. A. Birch, V. H. Ray, S. Hedayat, D. L. Lantvit and A. M. Diamond (2006). "Selenoprotein deficiency accelerates prostate carcinogenesis in a transgenic model." Proceedings of the National Academy of Sciences **103**(21): 8179-8184.
Dobbyn, H. C., K. Hill, T. L. Hamilton, K. A. Spriggs, B. M. Pickering, M. J. Coldwell, C. H. de Moor, M. Bushell and A. E. Willis (2008). "Regulation of BAG-1 IRES-mediated translation following chemotoxic stress." Oncogene **27**(8): 1167-1174.
Dobrikov, M., E. Dobrikova, M. Shveygert and M. Gromeier (2011). "Phosphorylation of eukaryotic translation initiation factor 4G1 (eIF4G1) by protein kinase Cα regulates eIF4G1 binding to Mnk1." Molecular and cellular biology **31**(14): 2947-2959.
Dobrikov, M. I., E. Y. Dobrikova and M. Gromeier (2018). "Ribosomal RACK1: protein kinase C βII modulates intramolecular interactions between unstructured regions of eukaryotic initiation factor 4G (eIF4G) that control eIF4E and eIF3 binding." Molecular and cellular biology **38**(19): e00306-00318.
Doma, M. K. and R. Parker (2006). "Endonucleolytic cleavage of eukaryotic mRNAs with stalls in translation elongation." Nature **440**(7083): 561-564.
Donadini, A., A. Giodini, F. Sanvito, P. C. Marchisio and S. Biffo (2001). "The human ITGB4BP gene is constitutively expressed in vitro, but highly modulated in vivo." Gene **266**(1-2): 35-43.
Dong, J., H. Qiu, M. Garcia-Barrio, J. Anderson and A. G. Hinnebusch (2000). "Uncharged tRNA activates GCN2 by displacing the protein kinase moiety from a bipartite tRNA-binding domain." Molecular cell **6**(2): 269-279.
Dorrello, N. V., A. Peschiaroli, D. Guardavaccaro, N. H. Colburn, N. E. Sherman and M. Pagano (2006). "S6K1-and ßTRCP-mediated degradation of PDCD4 promotes protein translation and cell growth." Science **314**(5798): 467-471.
Dowling, R. J., I. Topisirovic, T. Alain, M. Bidinosti, B. D. Fonseca, E. Petroulakis, X. Wang, O. Larsson, A. Selvaraj and Y. Liu (2010). "mTORC1-mediated cell proliferation, but not cell growth, controlled by the 4E-BPs." Science **328**(5982): 1172-1176.
Dresios, J., S. A. Chappell, W. Zhou and V. P. Mauro (2006). "An mRNA-rRNA base-pairing mechanism for translation initiation in eukaryotes." Nature structural & molecular biology **13**(1): 30-34.
Drummond, D. A. and C. O. Wilke (2008). "Mistranslation-induced protein misfolding as a dominant constraint on coding-sequence evolution." Cell **134**(2): 341-352.
Du, W. W., W. Yang, E. Liu, Z. Yang, P. Dhaliwal and B. B. Yang (2016). "Foxo3 circular RNA retards cell cycle progression via forming ternary complexes with p21 and CDK2." Nucleic acids research **44**(6): 2846-2858.
Duchaine, T. F. and M. R. Fabian (2019). "Mechanistic Insights into MicroRNA-Mediated Gene Silencing." Cold Spring Harb Perspect Biol **11**(3).
Duffy, A., O. Makarova‐Rusher, S. Ulahannan, O. Rahma, S. Fioravanti, M. Walker, S. Abdullah, M. Raffeld, V. Anderson and N. Abi‐Jaoudeh (2016). "Modulation of tumor eIF4E by antisense inhibition: A phase I/II translational clinical trial of ISIS 183750—an antisense oligonucleotide against eIF4E—in combination with irinotecan in solid tumors and irinotecan‐refractory colorectal cancer." International journal of cancer **139**(7): 1648-1657.

Dunn, J. G., C. K. Foo, N. G. Belletier, E. R. Gavis and J. S. Weissman (2013). "Ribosome profiling reveals pervasive and regulated stop codon readthrough in Drosophila melanogaster." Elife **2**: e01179.
Eddy, J. and N. Maizels (2006). "Gene function correlates with potential for G4 DNA formation in the human genome." Nucleic acids research **34**(14): 3887-3896.
Edwalds-Gilbert, G., K. L. Veraldi and C. Milcarek (1997). "Alternative poly(A) site selection in complex transcription units: means to an end?" Nucleic Acids Res **25**(13): 2547-2561.
Elfakess, R. and R. Dikstein (2008). "A translation initiation element specific to mRNAs with very short 5′ UTR that also regulates transcription." PLoS One **3**(8): e3094.
Elfakess, R., H. Sinvani, O. Haimov, Y. Svitkin, N. Sonenberg and R. Dikstein (2011). "Unique translation initiation of mRNAs-containing TISU element." Nucleic acids research **39**(17): 7598-7609.
Eliseev, B., L. Yeramala, A. Leitner, M. Karuppasamy, E. Raimondeau, K. Huard, E. Alkalaeva, R. Aebersold and C. Schaffitzel (2018). "Structure of a human cap-dependent 48S translation pre-initiation complex." Nucleic acids research **46**(5): 2678-2689.
Eswarappa, S. M., A. A. Potdar, W. J. Koch, Y. Fan, K. Vasu, D. Lindner, B. Willard, L. M. Graham, P. E. DiCorleto and P. L. Fox (2014). "Programmed translational readthrough generates antiangiogenic VEGF-Ax." Cell **157**(7): 1605-1618.
Evagelou, S. L., O. Bebenek, E. J. Specker and J. Uniacke (2020). "DEAD Box Protein Family Member DDX28 Is a Negative Regulator of Hypoxia-Inducible Factor 2α-and Eukaryotic Initiation Factor 4E2-Directed Hypoxic Translation." Molecular and Cellular Biology **40**(6).
Evdokimova, V., C. Tognon, T. Ng, P. Ruzanov, N. Melnyk, D. Fink, A. Sorokin, L. P. Ovchinnikov, E. Davicioni and T. J. Triche (2009). "Translational activation of snail1 and other developmentally regulated transcription factors by YB-1 promotes an epithelial-mesenchymal transition." Cancer cell **15**(5): 402-415.
Fadden, P., T. A. Haystead and J. C. Lawrence (1997). "Identification of phosphorylation sites in the translational regulator, PHAS-I, that are controlled by insulin and rapamycin in rat adipocytes." Journal of Biological Chemistry **272**(15): 10240-10247.
Fagegaltier, D., N. Hubert, K. Yamada, T. Mizutani, P. Carbon and A. Krol (2000). "Characterization of mSelB, a novel mammalian elongation factor for selenoprotein translation." Embo j **19**(17): 4796-4805.
Faller, W. J., T. J. Jackson, J. R. Knight, R. A. Ridgway, T. Jamieson, S. A. Karim, C. Jones, S. Radulescu, D. J. Huels and K. B. Myant (2015). "mTORC1-mediated translational elongation limits intestinal tumour initiation and growth." Nature **517**(7535): 497-500.
Feng, Y.-x., E. S. Sokol, C. A. Del Vecchio, S. Sanduja, J. H. Claessen, T. A. Proia, D. X. Jin, F. Reinhardt, H. L. Ploegh and Q. Wang (2014). "Epithelial-to-mesenchymal transition activates PERK–eIF2α and sensitizes cells to endoplasmic reticulum stress." Cancer discovery **4**(6): 702-715.
Feng, Z., W. Hu, E. De Stanchina, A. K. Teresky, S. Jin, S. Lowe and A. J. Levine (2007). "The regulation of AMPK β1, TSC2, and PTEN expression by p53: stress, cell and tissue specificity, and the role of these gene products in modulating the IGF-1-AKT-mTOR pathways." Cancer research **67**(7): 3043-3053.
Ferguson, A., L. Wang, R. B. Altman, D. S. Terry, M. F. Juette, B. J. Burnett, J. L. Alejo, R. A. Dass, M. M. Parks and C. T. Vincent (2015). "Functional dynamics within the human ribosome regulate the rate of active protein synthesis." Molecular cell **60**(3): 475-486.
Fingar, D. C., C. J. Richardson, A. R. Tee, L. Cheatham, C. Tsou and J. Blenis (2004). "mTOR controls cell cycle progression through its cell growth effectors S6K1 and 4E-BP1/eukaryotic translation initiation factor 4E." Molecular and cellular biology **24**(1): 200-216.
Fonseca, B. D., C. Zakaria, J.-J. Jia, T. E. Graber, Y. Svitkin, S. Tahmasebi, D. Healy, H.-D. Hoang, J. M. Jensen and I. T. Diao (2015). "La-related protein 1 (LARP1) represses terminal

oligopyrimidine (TOP) mRNA translation downstream of mTOR complex 1 (mTORC1)." Journal of Biological Chemistry **290**(26): 15996-16020.
Fox, C. J., P. S. Hammerman, R. M. Cinalli, S. R. Master, L. A. Chodosh and C. B. Thompson (2003). "The serine/threonine kinase Pim-2 is a transcriptionally regulated apoptotic inhibitor." Genes & development **17**(15): 1841-1854.
Franklin, S., T. Pho, F. W. Abreo, R. Nassar, A. De Benedetti, F. J. Stucker and C.-A. O. Nathan (1999). "Detection of the proto-oncogene eIF4E in larynx and hypopharynx cancers." Archives of Otolaryngology–Head & Neck Surgery **125**(2): 177-182.
Frias, M. A., C. C. Thoreen, J. D. Jaffe, W. Schroder, T. Sculley, S. A. Carr and D. M. Sabatini (2006). "mSin1 is necessary for Akt/PKB phosphorylation, and its isoforms define three distinct mTORC2s." Current Biology **16**(18): 1865-1870.
Frye, M. and F. M. Watt (2006). "The RNA methyltransferase Misu (NSun2) mediates Myc-induced proliferation and is upregulated in tumors." Current Biology **16**(10): 971-981.
Fu, W. and M. N. Hall (2020). "Regulation of mTORC2 Signaling." Genes **11**(9): 1045.
Fujimura, K., S. Choi, M. Wyse, J. Strnadel, T. Wright and R. Klemke (2015). "Eukaryotic translation initiation factor 5A (EIF5A) regulates pancreatic cancer metastasis by modulating RhoA and Rho-associated kinase (ROCK) protein expression levels." Journal of Biological Chemistry **290**(50): 29907-29919.
Fujimura, K., T. Wright, J. Strnadel, S. Kaushal, C. Metildi, A. M. Lowy, M. Bouvet, J. A. Kelber and R. L. Klemke (2014). "A hypusine–eIF5A–PEAK1 switch regulates the pathogenesis of pancreatic cancer." Cancer research **74**(22): 6671-6681.
Fukao, A., Y. Mishima, N. Takizawa, S. Oka, H. Imataka, J. Pelletier, N. Sonenberg, C. Thoma and T. Fujiwara (2014). "MicroRNAs trigger dissociation of eIF4AI and eIF4AII from target mRNAs in humans." Molecular cell **56**(1): 79-89.
Fukaya, T., H.-o. Iwakawa and Y. Tomari (2014). "MicroRNAs block assembly of eIF4F translation initiation complex in Drosophila." Molecular cell **56**(1): 67-78.
Fukuchi-Shimogori, T., I. Ishii, K. Kashiwagi, H. Mashiba, H. Ekimoto and K. Igarashi (1997). "Malignant transformation by overproduction of translation initiation factor eIF4G." Cancer Research **57**(22): 5041-5044.
Furic, L., L. Rong, O. Larsson, I. H. Koumakpayi, K. Yoshida, A. Brueschke, E. Petroulakis, N. Robichaud, M. Pollak and L. A. Gaboury (2010). "eIF4E phosphorylation promotes tumorigenesis and is associated with prostate cancer progression." Proceedings of the National Academy of Sciences **107**(32): 14134-14139.
Furuichi, Y., A. LaFiandra and A. J. Shatkin (1977). "5′ -Terminal structure and mRNA stability." Nature **266**(5599): 235-239.
Galicia-Vázquez, G., J. Chu and J. Pelletier (2015). "eIF4AII is dispensable for miRNA-mediated gene silencing." Rna **21**(10): 1826-1833.
Gandin, V., L. Masvidal, L. Hulea, S.-P. Gravel, M. Cargnello, S. McLaughlan, Y. Cai, P. Balanathan, M. Morita and A. Rajakumar (2016). "nanoCAGE reveals 5′ UTR features that define specific modes of translation of functionally related MTOR-sensitive mRNAs." Genome research **26**(5): 636-648.
Gandin, V., A. Miluzio, A. M. Barbieri, A. Beugnet, H. Kiyokawa, P. C. Marchisio and S. Biffo (2008). "Eukaryotic initiation factor 6 is rate-limiting in translation, growth and transformation." Nature **455**(7213): 684-688.
Gao, J., M. Jung, C. Mayoh, P. Venkat, K. M. Hannan, J. I. Fletcher, A. Kamili, A. J. Gifford, E. P. Kusnadi and R. B. Pearson (2020). "Suppression of ABCE1-Mediated mRNA Translation Limits N-MYC–Driven Cancer Progression." Cancer Research **80**(17): 3706-3718.
Garzia, A., S. M. Jafarnejad, C. Meyer, C. Chapat, T. Gogakos, P. Morozov, M. Amiri, M. Shapiro, H. Molina and T. Tuschl (2017). "The E3 ubiquitin ligase and RNA-binding protein

ZNF598 orchestrates ribosome quality control of premature polyadenylated mRNAs." Nature communications **8**(1): 1-10.
Gentilella, A., F. D. Morón-Duran, P. Fuentes, G. Zweig-Rocha, F. Riaño-Canalias, J. Pelletier, M. Ruiz, G. Turón, J. Castaño and A. Tauler (2017). "Autogenous control of 5′ TOP mRNA stability by 40S ribosomes." Molecular cell **67**(1): 55-70. e54.
Gerashchenko, M. V., A. V. Lobanov and V. N. Gladyshev (2012). "Genome-wide ribosome profiling reveals complex translational regulation in response to oxidative stress." Proceedings of the National Academy of Sciences **109**(43): 17394-17399.
Gerstberger, S., M. Hafner and T. Tuschl (2014). "A census of human RNA-binding proteins." Nat Rev Genet **15**(12): 829-845.
Ghazalpour, A., B. Bennett, V. A. Petyuk, L. Orozco, R. Hagopian, I. N. Mungrue, C. R. Farber, J. Sinsheimer, H. M. Kang and N. Furlotte (2011). "Comparative analysis of proteome and transcriptome variation in mouse." PLoS Genet **7**(6): e1001393.
Ghosh, S., J. C. Guimaraes, M. Lanzafame, A. Schmidt, A. P. Syed, B. Dimitriades, A. Börsch, S. Ghosh, N. Mittal, T. Montavon, A. L. Correia, J. Danner, G. Meister, L. M. Terracciano, S. Pfeffer, S. Piscuoglio and M. Zavolan (2020). "Prevention of dsRNA-induced interferon signaling by AGO1x is linked to breast cancer cell proliferation." Embo j **39**(18): e103922.
Gilbert, W. V. (2010). "Alternative ways to think about cellular internal ribosome entry." Journal of Biological Chemistry **285**(38): 29033-29038.
Gingold, H., D. Tehler, N. R. Christoffersen, M. M. Nielsen, F. Asmar, S. M. Kooistra, N. S. Christophersen, L. L. Christensen, M. Borre and K. D. Sørensen (2014). "A dual program for translation regulation in cellular proliferation and differentiation." Cell **158**(6): 1281-1292.
Gingras, A.-C., S. P. Gygi, B. Raught, R. D. Polakiewicz, R. T. Abraham, M. F. Hoekstra, R. Aebersold and N. Sonenberg (1999). "Regulation of 4E-BP1 phosphorylation: a novel two-step mechanism." Genes & development **13**(11): 1422-1437.
Gingras, A.-C., B. Raught and N. Sonenberg (2001). "Regulation of translation initiation by FRAP/mTOR." Genes & development **15**(7): 807-826.
Goh, E. T., O. E. Pardo, N. Michael, A. Niewiarowski, N. Totty, D. Volkova, I. R. Tsaneva, M. J. Seckl and I. Gout (2010). "Involvement of heterogeneous ribonucleoprotein F in the regulation of cell proliferation via the mammalian target of rapamycin/S6 kinase 2 pathway." Journal of Biological Chemistry **285**(22): 17065-17076.
GOLOB-SCHWARZL, N., P. PUCHAS, M. GOGG-KAMERER, W. WEICHERT, B. GÖPPERT and J. HAYBAECK (2020). "New Pancreatic Cancer Biomarkers eIF1, eIF2D, eIF3C and eIF6 Play a Major Role in Translational Control in Ductal Adenocarcinoma." Anticancer Research **40**(6): 3109-3118.
Goodarzi, H., X. Liu, H. C. Nguyen, S. Zhang, L. Fish and S. F. Tavazoie (2015). "Endogenous tRNA-derived fragments suppress breast cancer progression via YBX1 displacement." Cell **161**(4): 790-802.
Goodarzi, H., H. C. Nguyen, S. Zhang, B. D. Dill, H. Molina and S. F. Tavazoie (2016). "Modulated expression of specific tRNAs drives gene expression and cancer progression." Cell **165**(6): 1416-1427.
Gout, I., T. Minami, K. Hara, Y. Tsujishita, V. Filonenko, M. D. Waterfield and K. Yonezawa (1998). "Molecular cloning and characterization of a novel p70 S6 kinase, p70 S6 kinase β containing a proline-rich region." Journal of Biological Chemistry **273**(46): 30061-30064.
Graff, J. R., E. R. Boghaert, A. De Benedetti, D. L. Tudor, C. C. Zimmer, S. K. Chan and S. G. Zimmer (1995). "Reduction of translation initiation factor 4E decreases the malignancy of ras‐transformed cloned rat embryo fibroblasts." International journal of cancer **60**(2): 255-263.
Graff, J. R., B. W. Konicek, R. L. Lynch, C. A. Dumstorf, M. S. Dowless, A. M. McNulty, S. H. Parsons, L. H. Brail, B. M. Colligan and J. W. Koop (2009). "eIF4E activation is commonly

elevated in advanced human prostate cancers and significantly related to reduced patient survival." Cancer research **69**(9): 3866-3873.
Grifo, J., S. Tahara, M. Morgan, A. Shatkin and W. Merrick (1983). "New initiation factor activity required for globin mRNA translation." Journal of Biological Chemistry **258**(9): 5804-5810.
Grove, J., P. Banerjee, A. Balasubramanyam, P. Coffer, D. Price, J. Avruch and J. Woodgett (1991). "Cloning and expression of two human p70 S6 kinase polypeptides differing only at their amino termini." Molecular and cellular biology **11**(11): 5541-5550.
Grzmil, M., P. Morin, M. M. Lino, A. Merlo, S. Frank, Y. Wang, G. Moncayo and B. A. Hemmings (2011). "MAP kinase-interacting kinase 1 regulates SMAD2-dependent TGF-β signaling pathway in human glioblastoma." Cancer research **71**(6): 2392-2402.
Gu, L., N. Zhu, H. Zhang, D. L. Durden, Y. Feng and M. Zhou (2009). "Regulation of XIAP translation and induction by MDM2 following irradiation." Cancer cell **15**(5): 363-375.
Guan, X.-Y., J. M. Fung, N.-F. Ma, S.-H. Lau, L.-S. Tai, D. Xie, Y. Zhang, L. Hu, Q.-L. Wu and Y. Fang (2004). "Oncogenic role of eIF-5A2 in the development of ovarian cancer." Cancer research **64**(12): 4197-4200.
Guan, X.-Y., J. S. Sham, T. C. Tang, Y. Fang, K.-K. Huo and J.-M. Yang (2001). "Isolation of a novel candidate oncogene within a frequently amplified region at 3q26 in ovarian cancer." Cancer research **61**(9): 3806-3809.
Guo, M. and P. Schimmel (2013). "Essential nontranslational functions of tRNA synthetases." Nature chemical biology **9**(3): 145-153.
Guo, Y., Y. Zhao, G. Wang, Y. Chen, Y. Jiang, L. Ouyang and B. Liu (2018). "Design, synthesis and structure-activity relationship of a focused library of β-phenylalanine derivatives as novel eEF2K inhibitors with apoptosis-inducing mechanisms in breast cancer." European Journal of Medicinal Chemistry **143**: 402-418.
Guo, Z., G. Peng, E. Li, S. Xi, Y. Zhang, Y. Li, X. Lin, G. Li, Q. Wu and J. He (2017). "MAP kinase-interacting serine/threonine kinase 2 promotes proliferation, metastasis, and predicts poor prognosis in non-small cell lung cancer." Scientific reports **7**(1): 1-10.
Gutierrez, E., B.-S. Shin, C. J. Woolstenhulme, J.-R. Kim, P. Saini, A. R. Buskirk and T. E. Dever (2013). "eIF5A promotes translation of polyproline motifs." Molecular cell **51**(1): 35-45.
Haimov, O., H. Sinvani, F. Martin, I. Ulitsky, R. Emmanuel, A. Tamarkin-Ben-Harush, A. Vardy and R. Dikstein (2017). "Efficient and accurate translation initiation directed by TISU involves RPS3 and RPS10e binding and differential eukaryotic initiation factor 1A regulation." Molecular and cellular biology **37**(15).
Haizel, S. A., U. Bhardwaj, R. L. Gonzalez, S. Mitra and D. J. Goss (2020). "5′ -UTR recruitment of the translation initiation factor eIF4GI or DAP5 drives cap-independent translation of a subset of human mRNAs." Journal of Biological Chemistry **295**(33): 11693-11706.
Halees, A. S., R. El-Badrawi and K. S. Khabar (2008). "ARED Organism: expansion of ARED reveals AU-rich element cluster variations between human and mouse." Nucleic Acids Res **36**(Database issue): D137-140.
Han, D., J. Liu, C. Chen, L. Dong, Y. Liu, R. Chang, X. Huang, Y. Liu, J. Wang and U. Dougherty (2019). "Anti-tumour immunity controlled through mRNA m 6 A methylation and YTHDF1 in dendritic cells." Nature **566**(7743): 270-274.
Han, J., S. H. Back, J. Hur, Y.-H. Lin, R. Gildersleeve, J. Shan, C. L. Yuan, D. Krokowski, S. Wang and M. Hatzoglou (2013). "ER-stress-induced transcriptional regulation increases protein synthesis leading to cell death." Nature cell biology **15**(5): 481-490.

Hann, S. R., M. W. King, D. L. Bentley, C. W. Anderson and R. N. Eisenman (1988). "A non-AUG translational initiation in c-myc exon 1 generates an N-terminally distinct protein whose synthesis is disrupted in Burkitt's lymphomas." Cell **52**(2): 185-195.
Hann, S. R., K. Sloan-Brown and G. D. Spotts (1992). "Translational activation of the non-AUG-initiated c-myc 1 protein at high cell densities due to methionine deprivation." Genes & development **6**(7): 1229-1240.
Hansen, T. B., T. I. Jensen, B. H. Clausen, J. B. Bramsen, B. Finsen, C. K. Damgaard and J. Kjems (2013). "Natural RNA circles function as efficient microRNA sponges." Nature **495**(7441): 384-388.
Harada, H., J. S. Andersen, M. Mann, N. Terada and S. J. Korsmeyer (2001). "p70S6 kinase signals cell survival as well as growth, inactivating the pro-apoptotic molecule BAD." Proceedings of the National Academy of Sciences **98**(17): 9666-9670.
Harding, H. P., Y. Zhang, D. Scheuner, J.-J. Chen, R. J. Kaufman and D. Ron (2009). "Ppp1r15 gene knockout reveals an essential role for translation initiation factor 2 alpha (eIF2α) dephosphorylation in mammalian development." Proceedings of the national academy of sciences **106**(6): 1832-1837.
Harding, H. P., Y. Zhang, H. Zeng, I. Novoa, P. D. Lu, M. Calfon, N. Sadri, C. Yun, B. Popko and R. Paules (2003). "An integrated stress response regulates amino acid metabolism and resistance to oxidative stress." Molecular cell **11**(3): 619-633.
Hart, L. S., J. T. Cunningham, T. Datta, S. Dey, F. Tameire, S. L. Lehman, B. Qiu, H. Zhang, G. Cerniglia and M. Bi (2012). "ER stress–mediated autophagy promotes Myc-dependent transformation and tumor growth." The Journal of clinical investigation **122**(12): 4621-4634.
Hartman, T. R., S. Qian, C. Bolinger, S. Fernandez, D. R. Schoenberg and K. Boris-Lawrie (2006). "RNA helicase A is necessary for translation of selected messenger RNAs." Nature structural & molecular biology **13**(6): 509-516.
Hata, A. and R. Kashima (2016). "Dysregulation of microRNA biogenesis machinery in cancer." Crit Rev Biochem Mol Biol **51**(3): 121-134.
Hayes, J. D., A. T. Dinkova-Kostova and K. D. Tew (2020). "Oxidative stress in cancer." Cancer Cell.
He, L. R., H. Y. Zhao, B. K. Li, Y. H. Liu, M. Z. Liu, X. Y. Guan, X. W. Bian, Y. X. Zeng and D. Xie (2011). "Overexpression of eIF5A‐2 is an adverse prognostic marker of survival in stage I non–small cell lung cancer patients." International journal of cancer **129**(1): 143-150.
He, Q., L. Yang, K. Gao, P. Ding, Q. Chen, J. Xiong, W. Yang, Y. Song, L. Wang and Y. Wang (2020). "FTSJ1 regulates tRNA 2′-O-methyladenosine modification and suppresses the malignancy of NSCLC via inhibiting DRAM1 expression." Cell death & disease **11**(5): 1-12.
HEESOM, K. J., M. B. AVISON, T. A. DIGGLE and R. M. DENTON (1998). "Insulin-stimulated kinase from rat fat cells that phosphorylates initiation factor 4E-binding protein 1 on the rapamycin-insensitive site (serine-111)." Biochemical Journal **336**(1): 39-48.
Hellen, C. U. (2018). "Translation termination and ribosome recycling in eukaryotes." Cold Spring Harbor perspectives in biology **10**(10): a032656.
Helm, M. and Y. Motorin (2017). "Detecting RNA modifications in the epitranscriptome: predict and validate." Nature Reviews Genetics **18**(5): 275-291.
Hentze, M. W., A. Castello, T. Schwarzl and T. Preiss (2018). "A brave new world of RNA-binding proteins." Nat Rev Mol Cell Biol **19**(5): 327-341.
Herbert, T. P., R. Fåhraeus, A. Prescott, D. P. Lane and C. G. Proud (2000). "Rapid induction of apoptosis mediated by peptides that bind initiation factor eIF4E." Current Biology **10**(13): 793-796.
Hesketh, G. G., F. Papazotos, J. Pawling, D. Rajendran, J. D. Knight, S. Martinez, M. Taipale, D. Schramek, J. W. Dennis and A.-C. Gingras (2020). "The GATOR–Rag GTPase pathway inhibits mTORC1 activation by lysosome-derived amino acids." Science **370**(6514): 351-356.

Hickey, K. L., K. Dickson, J. Z. Cogan, J. M. Replogle, M. Schoof, K. N. D'Orazio, N. K. Sinha, J. A. Hussmann, M. Jost and A. Frost (2020). "GIGYF2 and 4ehp inhibit translation initiation of defective messenger RNAs to assist Ribosome-Associated quality control." Molecular cell **79**(6): 950-962. e956.
Hirashita, T., Y. Hirashita, Y. Iwashita, Y. Endo, M. Kiyonaga, S. Matsumoto, N. Hijiya, M. Moriyama, K. Murakami and M. Inomata (2020). "S6 ribosomal protein phosphorylation is associated with malignancy of intraductal papillary mucinous neoplasm of the pancreas." Annals of Gastroenterological Surgery **4**(5): 571-579.
Hizli, A. A., Y. Chi, J. Swanger, J. H. Carter, Y. Liao, M. Welcker, A. G. Ryazanov and B. E. Clurman (2013). "Phosphorylation of eukaryotic elongation factor 2 (eEF2) by cyclin A–cyclin-dependent kinase 2 regulates its inhibition by eEF2 kinase." Molecular and cellular biology **33**(3): 596-604.
Holcik, M., C. Lefebvre, C. Yeh, T. Chow and R. G. Korneluk (1999). "A new internal-ribosome-entry-site motif potentiates XIAP-mediated cytoprotection." Nature cell biology **1**(3): 190-192.
Hong, D. S., R. Kurzrock, Y. Oh, J. Wheler, A. Naing, L. Brail, S. Callies, V. André, S. K. Kadam and A. Nasir (2011). "A phase 1 dose escalation, pharmacokinetic, and pharmacodynamic evaluation of eIF-4E antisense oligonucleotide LY2275796 in patients with advanced cancer." Clinical Cancer Research **17**(20): 6582-6591.
Hong, S., M. A. Freeberg, T. Han, A. Kamath, Y. Yao, T. Fukuda, T. Suzuki, J. K. Kim and K. Inoki (2017). "LARP1 functions as a molecular switch for mTORC1-mediated translation of an essential class of mRNAs." Elife **6**: e25237.
Hoque, M., Z. Ji, D. Zheng, W. Luo, W. Li, B. You, J. Y. Park, G. Yehia and B. Tian (2013). "Analysis of alternative cleavage and polyadenylation by 3' region extraction and deep sequencing." Nat Methods **10**(2): 133-139.
Horvilleur, E., T. Sbarrato, K. Hill, R. Spriggs, M. Screen, P. Goodrem, K. Sawicka, L. Chaplin, C. Touriol and G. Packham (2014). "A role for eukaryotic initiation factor 4B overexpression in the pathogenesis of diffuse large B-cell lymphoma." Leukemia **28**(5): 1092-1102.
Hronová, V., M. P. Mohammad, S. Wagner, J. Pánek, S. Gunišová, J. Zeman, K. Poncová and L. S. Valášek (2017). "Does eIF3 promote reinitiation after translation of short upstream ORFs also in mammalian cells?" RNA biology **14**(12): 1660-1667.
Hsieh, A. C., H. G. Nguyen, L. Wen, M. P. Edlind, P. R. Carroll, W. Kim and D. Ruggero (2015). "Cell type–specific abundance of 4EBP1 primes prostate cancer sensitivity or resistance to PI3K pathway inhibitors." Science signaling **8**(403): ra116-ra116.
Hsu, P. J., Y. Zhu, H. Ma, Y. Guo, X. Shi, Y. Liu, M. Qi, Z. Lu, H. Shi and J. Wang (2017). "Ythdc2 is an N 6-methyladenosine binding protein that regulates mammalian spermatogenesis." Cell research **27**(9): 1115-1127.
Huang, Z., J. Shi, Y. Gao, C. Cui, S. Zhang, J. Li, Y. Zhou and Q. Cui (2019). "HMDD v3.0: a database for experimentally supported human microRNA-disease associations." Nucleic Acids Res **47**(D1): D1013-D1017.
Iadevaia, V., S. Caldarola, E. Tino, F. Amaldi and F. Loreni (2008). "All translation elongation factors and the e, f, and h subunits of translation initiation factor 3 are encoded by 5′ -terminal oligopyrimidine (TOP) mRNAs." Rna **14**(9): 1730-1736.
Ingolia, N. T., S. Ghaemmaghami, J. R. Newman and J. S. Weissman (2009). "Genome-wide analysis in vivo of translation with nucleotide resolution using ribosome profiling." science **324**(5924): 218-223.
Inoki, K., Y. Li, T. Zhu, J. Wu and K.-L. Guan (2002). "TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling." Nature cell biology **4**(9): 648-657.

Inoki, K., H. Ouyang, T. Zhu, C. Lindvall, Y. Wang, X. Zhang, Q. Yang, C. Bennett, Y. Harada and K. Stankunas (2006). "TSC2 integrates Wnt and energy signals via a coordinated phosphorylation by AMPK and GSK3 to regulate cell growth." Cell **126**(5): 955-968.
Inoki, K., T. Zhu and K.-L. Guan (2003). "TSC2 mediates cellular energy response to control cell growth and survival." Cell **115**(5): 577-590.
Ip, C., A. Cheung, H. Ngan and A. Wong (2011). "p70 S6 kinase in the control of actin cytoskeleton dynamics and directed migration of ovarian cancer cells." Oncogene **30**(21): 2420-2432.
Ishigaki, Y., X. Li, G. Serin and L. E. Maquat (2001). "Evidence for a pioneer round of mRNA translation: mRNAs subject to nonsense-mediated decay in mammalian cells are bound by CBP80 and CBP20." Cell **106**(5): 607-617.
Ishikawa, C., J. Tanaka, H. Katano, M. Senba and N. Mori (2013). "Hippuristanol reduces the viability of primary effusion lymphoma cells both in vitro and in vivo." Marine drugs **11**(9): 3410-3424.
Ishimura, R., G. Nagy, I. Dotu, J. H. Chuang and S. L. Ackerman (2016). "Activation of GCN2 kinase by ribosome stalling links translation elongation with translation initiation." Elife **5**: e14295.
Ishimura, R., G. Nagy, I. Dotu, H. Zhou, X.-L. Yang, P. Schimmel, S. Senju, Y. Nishimura, J. H. Chuang and S. L. Ackerman (2014). "Ribosome stalling induced by mutation of a CNS-specific tRNA causes neurodegeneration." Science **345**(6195): 455-459.
Ismail, H. M., O. Myronova, Y. Tsuchiya, A. Niewiarowski, I. Tsaneva and I. Gout (2013). "Identification of the general transcription factor Yin Yang 1 as a novel and specific binding partner for S6 kinase 2." Cellular signalling **25**(5): 1054-1063.
Ivanov, P., M. M. Emara, J. Villen, S. P. Gygi and P. Anderson (2011). "Angiogenin-induced tRNA fragments inhibit translation initiation." Molecular cell **43**(4): 613-623.
Jacinto, E., V. Facchinetti, D. Liu, N. Soto, S. Wei, S. Y. Jung, Q. Huang, J. Qin and B. Su (2006). "SIN1/MIP1 maintains rictor-mTOR complex integrity and regulates Akt phosphorylation and substrate specificity." Cell **127**(1): 125-137.
Jackson, R. J. (2013). "The current status of vertebrate cellular mRNA IRESs." Cold Spring Harbor perspectives in biology **5**(2): a011569.
Jafarnejad, S. M., C. Chapat, E. Matta-Camacho, I. A. Gelbart, G. G. Hesketh, M. Arguello, A. Garzia, S.-H. Kim, J. Attig and M. Shapiro (2018). "Translational control of ERK signaling through miRNA/4EHP-directed silencing." Elife **7**: e35034.
Jafarnejad, S. M., C. Chapat, E. Matta-Camacho, I. A. Gelbart, G. G. Hesketh, M. Arguello, A. Garzia, S. H. Kim, J. Attig, M. Shapiro, M. Morita, A. Khoutorsky, T. Alain, C. G. Gkogkas, N. Stern-Ginossar, T. Tuschl, A. C. Gingras, T. F. Duchaine and N. Sonenberg (2018). "Translational control of ERK signaling through miRNA/4EHP-directed silencing." Elife **7**.
Jafarnejad, S. M., S.-H. Kim and N. Sonenberg (2018). "Aminoacylation of proteins: New targets for the old arsenal." Cell Metabolism **27**(1): 1-3.
Jakobsson, M. E., J. Małecki, B. S. Nilges, A. Moen, S. A. Leidel and P. Ø. Falnes (2017). "Methylation of human eukaryotic elongation factor alpha (eEF1A) by a member of a novel protein lysine methyltransferase family modulates mRNA translation." Nucleic acids research **45**(14): 8239-8254.
Jansen, A. P., C. E. Camalier and N. H. Colburn (2005). "Epidermal expression of the translation inhibitor programmed cell death 4 suppresses tumorigenesis." Cancer research **65**(14): 6034-6041.
Jaramillo, M., J. Pelletier, I. Edery, P. J. Nielsen and N. Sonenberg (1991). "Multiple mRNAs encode the murine translation initiation factor eIF-4E." Journal of Biological Chemistry **266**(16): 10446-10451.

Jenö, P., L. M. Ballou, I. Novak-Hofer and G. Thomas (1988). "Identification and characterization of a mitogen-activated S6 kinase." Proceedings of the National Academy of Sciences **85**(2): 406-410.
Jeong, S. J., S. Park, L. T. Nguyen, J. Hwang, E.-Y. Lee, H.-K. Giong, J.-S. Lee, I. Yoon, J.-H. Lee and J. H. Kim (2019). "A threonyl-tRNA synthetase-mediated translation initiation machinery." Nature communications **10**(1): 1-15.
Jewell, J. L., Y. C. Kim, R. C. Russell, F.-X. Yu, H. W. Park, S. W. Plouffe, V. S. Tagliabracci and K.-L. Guan (2015). "Differential regulation of mTORC1 by leucine and glutamine." Science **347**(6218): 194-198.
Jewer, M., L. Lee, M. Leibovitch, G. Zhang, J. Liu, S. D. Findlay, K. M. Vincent, K. Tandoc, D. Dieters-Castator and D. F. Quail (2020). "Translational control of breast cancer plasticity." Nature communications **11**(1): 1-16.
Ji, P., W. Wu, S. Chen, Y. Zheng, L. Zhou, J. Zhang, H. Cheng, J. Yan, S. Zhang and P. Yang (2019). "Expanded expression landscape and prioritization of circular RNAs in mammals." Cell reports **26**(12): 3444-3460. e3445.
Jiang, J., K. Wang, Y. Chen, H. Chen, E. C. Nice and C. Huang (2017). "Redox regulation in tumor cell epithelial–mesenchymal transition: molecular basis and therapeutic strategy." Signal Transduction and Targeted Therapy **2**(1): 1-12.
Jin, H., A. C. Kelley, D. Loakes and V. Ramakrishnan (2010). "Structure of the 70S ribosome bound to release factor 2 and a substrate analog provides insights into catalysis of peptide release." Proceedings of the National Academy of Sciences **107**(19): 8593-8598.
Jin, H. Y., H. Oda, P. Chen, C. Yang, X. Zhou, S. G. Kang, E. Valentine, J. M. Kefauver, L. Liao, Y. Zhang, A. Gonzalez-Martin, J. Shepherd, G. J. Morgan, T. S. Mondala, S. R. Head, P. H. Kim, N. Xiao, G. Fu, W. H. Liu, J. Han, J. R. Williamson and C. Xiao (2017). "Differential Sensitivity of Target Genes to Translational Repression by miR-17~92." PLoS Genet **13**(2): e1006623.
Joazeiro, C. A. (2019). "Mechanisms and functions of ribosome-associated protein quality control." Nature Reviews Molecular Cell Biology **20**(6): 368-383.
Jones, R. M., J. Branda, K. A. Johnston, M. Polymenis, M. Gadd, A. Rustgi, L. Callanan and E. V. Schmidt (1996). "An essential E box in the promoter of the gene encoding the mRNA cap-binding protein (eukaryotic initiation factor 4E) is a target for activation by c-myc." Molecular and cellular biology **16**(9): 4754-4764.
Joshi, B., A.-L. Cai, B. D. Keiper, W. B. Minich, R. Mendez, C. M. Beach, J. Stepinski, R. Stolarski, E. Darzynkiewicz and R. E. Rhoads (1995). "Phosphorylation of eukaryotic protein synthesis initiation factor 4E at Ser-209." Journal of Biological Chemistry **270**(24): 14597-14603.
Joshi, B., A. Cameron and R. Jagus (2004). "Characterization of mammalian eIF4E‐family members." European journal of biochemistry **271**(11): 2189-2203.
Jousse, C., S. Oyadomari, I. Novoa, P. Lu, Y. Zhang, H. P. Harding and D. Ron (2003). "Inhibition of a constitutive translation initiation factor 2α phosphatase, CReP, promotes survival of stressed cells." The Journal of cell biology **163**(4): 767-775.
Juszkiewicz, S., V. Chandrasekaran, Z. Lin, S. Kraatz, V. Ramakrishnan and R. S. Hegde (2018). "ZNF598 is a quality control sensor of collided ribosomes." Molecular cell **72**(3): 469-481. e467.
Juszkiewicz, S. and R. S. Hegde (2017). "Initiation of quality control during poly (A) translation requires site-specific ribosome ubiquitination." Molecular cell **65**(4): 743-750. e744.
Juszkiewicz, S., S. H. Speldewinde, L. Wan, J. Q. Svejstrup and R. S. Hegde (2020). "The ASC-1 complex disassembles collided ribosomes." Molecular cell **79**(4): 603-614. e608.

Kabil, N., R. Bayraktar, N. Kahraman, H. A. Mokhlis, G. A. Calin, G. Lopez-Berestein and B. Ozpolat (2018). "Thymoquinone inhibits cell proliferation, migration, and invasion by regulating the elongation factor 2 kinase (eEF-2K) signaling axis in triple-negative breast cancer." Breast cancer research and treatment **171**(3): 593-605.
Kahvejian, A., Y. V. Svitkin, R. Sukarieh, M.-N. M'Boutchou and N. Sonenberg (2005). "Mammalian poly (A)-binding protein is a eukaryotic translation initiation factor, which acts via multiple mechanisms." Genes & development **19**(1): 104-113.
Kapadia, B., N. M. Nanaji, K. Bhalla, B. Bhandary, R. Lapidus, A. Beheshti, A. M. Evens and R. B. Gartenhaus (2018). "Fatty acid synthase induced S6Kinase facilitates USP11-eIF4B complex formation for sustained oncogenic translation in DLBCL." Nature communications **9**(1): 1-15.
Karlsson, E., M. A. Waltersson, J. Bostner, G. Pérez‐Tenorio, B. Olsson, A. L. Hallbeck and O. Stål (2011). "High‐resolution genomic analysis of the 11q13 amplicon in breast cancers identifies synergy with 8p12 amplification, involving the mTOR targets S6K2 and 4EBP1." Genes, Chromosomes and Cancer **50**(10): 775-787.
Karousis, E. D. and O. Mühlemann (2019). "Nonsense-mediated mRNA decay begins where translation ends." Cold Spring Harbor Perspectives in Biology **11**(2): a032862.
Kato, M., Y. Goto, R. Matsushita, A. Kurozumi, I. Fukumoto, R. Nishikawa, S. Sakamoto, H. Enokida, M. Nakagawa and T. Ichikawa (2015). "MicroRNA-26a/b directly regulate La-related protein 1 and inhibit cancer cell invasion in prostate cancer." International journal of oncology **47**(2): 710-718.
Kedersha, N., M. Gupta, W. Li, I. Miller and P. Anderson (1999). "RNA-binding proteins TIA binding proteins TIA binding proteins TIA-1 and TIAR link the phosphorylation of eIF TIAR link the phosphorylation of eIF-2 alpha to the assembly of mammalian stress ha to the assembly of mammalian stress granules. granules." The Journal of cell biology **147**: 1431-1442.
Kedersha, N., G. Stoecklin, M. Ayodele, P. Yacono, J. Lykke-Andersen, M. J. Fritzler, D. Scheuner, R. J. Kaufman, D. E. Golan and P. Anderson (2005). "Stress granules and processing bodies are dynamically linked sites of mRNP remodeling." The Journal of cell biology **169**(6): 871-884.
Kelly, N., J. Varga, E. Specker, C. Romeo, B. Coomber and J. Uniacke (2018). "Hypoxia activates cadherin-22 synthesis via eIF4E2 to drive cancer cell migration, invasion and adhesion." Oncogene **37**(5): 651-662.
Kerekatte, V., K. Smiley, B. Hu, A. Smith, F. Gelder and A. De Benedetti (1995). "The proto‐oncogene/translation factor eIF4E: a survey of its expression in breast carcinomas." International journal of cancer **64**(1): 27-31.
Kessler, S. H. and A. B. Sachs (1998). "RNA recognition motif 2 of yeast Pab1p is required for its functional interaction with eukaryotic translation initiation factor 4G." Molecular and cellular biology **18**(1): 51-57.
Kim, J. and K.-L. Guan (2019). "mTOR as a central hub of nutrient signalling and cell growth." Nature Cell Biology **21**(1): 63-71.
Kim, K., S. Pyo and S. H. Um (2012). "S6 kinase 2 deficiency enhances ketone body production and increases peroxisome proliferator‐activated receptor alpha activity in the liver." Hepatology **55**(6): 1727-1737.
Kim, S.-H., Y. H. Jang, G. C. Chau, S. Pyo and S. H. Um (2013). "Prognostic significance and function of phosphorylated ribosomal protein S6 in esophageal squamous cell carcinoma." Modern Pathology **26**(3): 327-335.
Knebel, A., N. Morrice and P. Cohen (2001). "A novel method to identify protein kinase substrates: eEF2 kinase is phosphorylated and inhibited by SAPK4/p38δ." The EMBO journal **20**(16): 4360-4369.

Kochetov, A. V., I. V. Ischenko, D. G. Vorobiev, A. E. Kel, V. N. Babenko, L. L. Kisselev and N. A. Kolchanov (1998). "Eukaryotic mRNAs encoding abundant and scarce proteins are statistically dissimilar in many structural features." FEBS letters **440**(3): 351-355.
Koh, D. C., G. M. Edelman and V. P. Mauro (2013). "Physical evidence supporting a ribosomal shunting mechanism of translation initiation for BACE1 mRNA." Translation **1**(1): e24400.
Konicek, B. W., J. R. Stephens, A. M. McNulty, N. Robichaud, R. B. Peery, C. A. Dumstorf, M. S. Dowless, P. W. Iversen, S. Parsons and K. E. Ellis (2011). "Therapeutic inhibition of MAP kinase interacting kinase blocks eukaryotic initiation factor 4E phosphorylation and suppresses outgrowth of experimental lung metastases." Cancer research **71**(5): 1849-1857.
Korostelev, A., H. Asahara, L. Lancaster, M. Laurberg, A. Hirschi, J. Zhu, S. Trakhanov, W. G. Scott and H. F. Noller (2008). "Crystal structure of a translation termination complex formed with release factor RF2." Proceedings of the National Academy of Sciences **105**(50): 19684-19689.
Kosciuczuk, E. M., A. K. Kar, G. T. Blyth, M. Fischietti, S. Abedin, A. A. Mina, R. Siliezar, T. Rzymski, K. Brzozka and E. A. Eklund (2019). "Inhibitory effects of SEL201 in acute myeloid leukemia." Oncotarget **10**(67): 7112.
Kozak, M. (1986). "Influences of mRNA secondary structure on initiation by eukaryotic ribosomes." Proceedings of the National Academy of Sciences **83**(9): 2850-2854.
Kozak, M. (1987). "An analysis of 5'-noncoding sequences from 699 vertebrate messenger RNAs." Nucleic acids research **15**(20): 8125-8148.
Kozak, M. (1991). "An analysis of vertebrate mRNA sequences: intimations of translational control." The Journal of cell biology **115**(4): 887-903.
Krieg, J., J. Hofsteenge and G. Thomas (1988). "Identification of the 40 S ribosomal protein S6 phosphorylation sites induced by cycloheximide." Journal of Biological Chemistry **263**(23): 11473-11477.
Kumar, E. A., D. Giles and K. Dalby (2020). "AMPK can stimulate eEF2 phosphorylation without regulating its cognate kinase eEF2K." The FASEB Journal **34**(S1): 1-1.
Kumar, P., C. U. Hellen and T. V. Pestova (2016). "Toward the mechanism of eIF4F-mediated ribosomal attachment to mammalian capped mRNAs." Genes & development **30**(13): 1573-1588.
Kurosaki, T., M. W. Popp and L. E. Maquat (2019). "Quality and quantity control of gene expression by nonsense-mediated mRNA decay." Nat Rev Mol Cell Biol **20**(7): 406-420.
Kuznetsov, G., Q. Xu, L. Rudolph-Owen, K. TenDyke, J. Liu, M. Towle, N. Zhao, J. Marsh, S. Agoulnik and N. Twine (2009). "Potent in vitro and in vivo anticancer activities of des-methyl, des-amino pateamine A, a synthetic analogue of marine natural product pateamine A." Molecular cancer therapeutics **8**(5): 1250-1260.
Kuzuoğlu‐Öztürk, D., D. Bhandari, E. Huntzinger, M. Fauser, S. Helms and E. Izaurralde (2016). "mi RISC and the CCR 4–NOT complex silence mRNA targets independently of 43S ribosomal scanning." The EMBO journal **35**(11): 1186-1203.
Labunskyy, V. M., D. L. Hatfield and V. N. Gladyshev (2014). "Selenoproteins: molecular pathways and physiological roles." Physiol Rev **94**(3): 739-777.
Ladang, A., F. Rapino, L. C. Heukamp, L. Tharun, K. Shostak, D. Hermand, S. Delaunay, I. Klevernic, Z. Jiang and N. Jacques (2015). "Elp3 drives Wnt-dependent tumor initiation and regeneration in the intestine." Journal of Experimental Medicine **212**(12): 2057-2075.
Lahr, R. M., B. D. Fonseca, G. E. Ciotti, H. A. Al-Ashtal, J.-J. Jia, M. R. Niklaus, S. P. Blagden, T. Alain and A. J. Berman (2017). "La-related protein 1 (LARP1) binds the mRNA cap, blocking eIF4F assembly on TOP mRNAs." Elife **6**: e24146.
Lai, M.-C., Y.-H. W. Lee and W.-Y. Tarn (2008). "The DEAD-box RNA helicase DDX3 associates with export messenger ribonucleoproteins as well astip-associated protein and participates in translational control." Molecular biology of the cell **19**(9): 3847-3858.

Landon, A. L., P. A. Muniandy, A. C. Shetty, E. Lehrmann, L. Volpon, S. Houng, Y. Zhang, B. Dai, R. Peroutka and K. Mazan-Mamczarz (2014). "MNKs act as a regulatory switch for eIF4E1 and eIF4E3 driven mRNA translation in DLBCL." Nature communications **5**(1): 1-15.
Laurberg, M., H. Asahara, A. Korostelev, J. Zhu, S. Trakhanov and H. F. Noller (2008). "Structural basis for translation termination on the 70S ribosome." Nature **454**(7206): 852-857.
Lazaris-Karatzas, A., K. S. Montine and N. Sonenberg (1990). "Malignant transformation by a eukaryotic initiation factor subunit that binds to mRNA 5'cap." Nature **345**(6275): 544-547.
Lazaris-Karatzas, A. and N. Sonenberg (1992). "The mRNA 5'cap-binding protein, eIF-4E, cooperates with v-myc or E1A in the transformation of primary rodent fibroblasts." Molecular and cellular biology **12**(3): 1234-1238.
Lee, A. S., P. J. Kranzusch, J. A. Doudna and J. H. Cate (2016). "eIF3d is an mRNA cap-binding protein that is required for specialized translation initiation." Nature **536**(7614): 96-99.
Lee, D.-F., H.-P. Kuo, C.-T. Chen, J.-M. Hsu, C.-K. Chou, Y. Wei, H.-L. Sun, L.-Y. Li, B. Ping and W.-C. Huang (2007). "IKKβ suppression of TSC1 links inflammation and tumor angiogenesis via the mTOR pathway." Cell **130**(3): 440-455.
Lee, K.-M., C.-J. Chen and S.-R. Shih (2017). "Regulation mechanisms of viral IRES-driven translation." Trends in microbiology **25**(7): 546-561.
Lee, M.-H. and Y.-J. Surh (2009). "eEF1A2 as a putative oncogene." Annals of the New York Academy of Sciences **1171**(1): 87.
Lee, S., A.-M. Francoeur, S. Liu and E. Wang (1992). "Tissue-specific expression in mammalian brain, heart, and muscle of S1, a member of the elongation factor-1 alpha gene family." Journal of Biological Chemistry **267**(33): 24064-24068.
Legnini, I., G. Di Timoteo, F. Rossi, M. Morlando, F. Briganti, O. Sthandier, A. Fatica, T. Santini, A. Andronache and M. Wade (2017). "Circ-ZNF609 is a circular RNA that can be translated and functions in myogenesis." Molecular cell **66**(1): 22-37. e29.
Lehman, S. L., G. J. Cerniglia, G. J. Johannes, J. Ye, S. Ryeom and C. Koumenis (2015). "Translational upregulation of an individual p21Cip1 transcript variant by GCN2 regulates cell proliferation and survival under nutrient stress." PLoS genetics **11**(6): e1005212.
Leibovitch, M. and I. Topisirovic (2018). "Dysregulation of mRNA translation and energy metabolism in cancer." Advances in biological regulation **67**: 30-39.
Leprivier, G., M. Remke, B. Rotblat, A. Dubuc, A.-R. F. Mateo, M. Kool, S. Agnihotri, A. El-Naggar, B. Yu and S. P. Somasekharan (2013). "The eEF2 kinase confers resistance to nutrient deprivation by blocking translation elongation." Cell **153**(5): 1064-1079.
Levanon, E. Y., E. Eisenberg, R. Yelin, S. Nemzer, M. Hallegger, R. Shemesh, Z. Y. Fligelman, A. Shoshan, S. R. Pollock and D. Sztybel (2004). "Systematic identification of abundant A-to-I editing sites in the human transcriptome." Nature biotechnology **22**(8): 1001-1005.
Li, S., Y. Jia, B. Jacobson, J. McCauley, R. Kratzke, P. B. Bitterman and C. R. Wagner (2013). "Treatment of breast and lung cancer cells with a N-7 benzyl guanosine monophosphate tryptamine phosphoramidate pronucleotide (4Ei-1) results in chemosensitization to gemcitabine and induced eIF4E proteasomal degradation." Molecular pharmaceutics **10**(2): 523-531.
Li, S., Y. Li and Y. Bai (2019). "What is the impact of eukaryotic elongation factor 2 kinase on cancer: A systematic review." European journal of pharmacology **857**: 172470.
Li, W., N. Thakor, E. Y. Xu, Y. Huang, C. Chen, R. Yu, M. Holcik and A.-N. Kong (2010). "An internal ribosomal entry site mediates redox-sensitive translation of Nrf2." Nucleic acids research **38**(3): 778-788.
Li, Y., L. Fu, J.-B. Li, Y. Qin, T.-t. Zeng, J. Zhou, Z.-L. Zeng, J. Chen, T.-T. Cao and X. Ban (2014). "Increased expression of EIF5A2, via hypoxia or gene amplification, contributes to

metastasis and angiogenesis of esophageal squamous cell carcinoma." Gastroenterology **146**(7): 1701-1713. e1709.
Li, Y., K. Inoki, P. Vacratsis and K.-L. Guan (2003). "The p38 and MK2 kinase cascade phosphorylates tuberin, the tuberous sclerosis 2 gene product, and enhances its interaction with 14-3-3." Journal of Biological Chemistry **278**(16): 13663-13671.
Li, Z., C.-F. Qi, D.-M. Shin, A. Zingone, H. J. Newbery, A. L. Kovalchuk, C. M. Abbott and H. C. Morse III (2010). "Eef1a2 promotes cell growth, inhibits apoptosis and activates JAK/STAT and AKT signaling in mouse plasmacytomas." PLoS One **5**(5): e10755.
Liang, H., X. Chen, Q. Yin, D. Ruan, X. Zhao, C. Zhang, M. A. McNutt and Y. Yin (2017). "PTENβ is an alternatively translated isoform of PTEN that regulates rDNA transcription." Nature communications **8**(1): 1-14.
Liang, H., S. He, J. Yang, X. Jia, P. Wang, X. Chen, Z. Zhang, X. Zou, M. A. McNutt and W. H. Shen (2014). "PTENα, a PTEN isoform translated through alternative initiation, regulates mitochondrial function and energy metabolism." Cell metabolism **19**(5): 836-848.
Lin, C.-Y., A. Beattie, B. Baradaran, E. Dray and P. H. Duijf (2018). "Contradictory mRNA and protein misexpression of EEF1A1 in ductal breast carcinoma due to cell cycle regulation and cellular stress." Scientific reports **8**(1): 1-12.
Lin, S., J. Choe, P. Du, R. Triboulet and R. I. Gregory (2016). "The m6A methyltransferase METTL3 promotes translation in human cancer cells." Molecular cell **62**(3): 335-345.
Lin, Y., F. Li, L. Huang, C. Polte, H. Duan, J. Fang, L. Sun, X. Xing, G. Tian and Y. Cheng (2020). "eIF3 associates with 80S ribosomes to promote translation elongation, mitochondrial homeostasis, and muscle health." Molecular Cell **79**(4): 575-587. e577.
Linde, L. and B. Kerem (2008). "Introducing sense into nonsense in treatments of human genetic diseases." Trends Genet **24**(11): 552-563.
Ling, C. and D. N. Ermolenko (2016). "Structural insights into ribosome translocation." Wiley Interdisciplinary Reviews: RNA **7**(5): 620-636.
Ling, J., S. J. Morley and J. A. Traugh (2005). "Inhibition of cap‐dependent translation via phosphorylation of eIF4G by protein kinase Pak2." The EMBO journal **24**(23): 4094-4105.
Liu, J. C., V. Voisin, S. Wang, D. Y. Wang, R. A. Jones, A. Datti, D. Uehling, R. Al‐awar, S. E. Egan and G. D. Bader (2014). "Combined deletion of P ten and p53 in mammary epithelium accelerates triple‐negative breast cancer with dependency on e EF 2 K." EMBO molecular medicine **6**(12): 1542-1560.
Liu, L., D. R. Wise, J. A. Diehl and M. C. Simon (2008). "Hypoxic reactive oxygen species regulate the integrated stress response and cell survival." Journal of Biological Chemistry **283**(45): 31153-31162.
Liu, S., C. Bachran, P. Gupta, S. Miller-Randolph, H. Wang, D. Crown, Y. Zhang, A. N. Wein, R. Singh and R. Fattah (2012). "Diphthamide modification on eukaryotic elongation factor 2 is needed to assure fidelity of mRNA translation and mouse development." Proceedings of the National Academy of Sciences **109**(34): 13817-13822.
Liu, T., Q. Wei, J. Jin, Q. Luo, Y. Liu, Y. Yang, C. Cheng, L. Li, J. Pi and Y. Si (2020). "The m6A reader YTHDF1 promotes ovarian cancer progression via augmenting EIF3C translation." Nucleic acids research **48**(7): 3816-3831.
Liu, X., L. Chen, J. Ge, C. Yan, Z. Huang, J. Hu, C. Wen, M. Li, D. Huang and Y. Qiu (2016). "The ubiquitin-like protein FAT10 stabilizes eEF1A1 expression to promote tumor proliferation in a complex manner." Cancer Research **76**(16): 4897-4907.
Liu, X., J. Qin, T. Gao, C. Li, B. He, B. Pan, X. Xu, X. Chen, K. Zeng and M. Xu (2020). "YTHDF1 facilitates the progression of hepatocellular carcinoma by promoting FZD5 mRNA translation in an m6A-dependent manner." Molecular Therapy-Nucleic Acids **22**: 750-765.

Liwak, U., N. Thakor, L. E. Jordan, R. Roy, S. M. Lewis, O. E. Pardo, M. Seckl and M. Holcik (2012). "Tumor suppressor PDCD4 represses internal ribosome entry site-mediated translation of antiapoptotic proteins and is regulated by S6 kinase 2." Molecular and cellular biology **32**(10): 1818-1829.
Losada, A., M. J. Muñoz-Alonso, C. García, P. A. Sánchez-Murcia, J. F. Martínez-Leal, J. M. Domínguez, M. P. Lillo, F. Gago and C. M. Galmarini (2016). "Translation elongation factor eEF1A2 is a novel anticancer target for the marine natural product plitidepsin." Scientific reports **6**: 35100.
Loughran, G., M. Y. Chou, I. P. Ivanov, I. Jungreis, M. Kellis, A. M. Kiran, P. V. Baranov and J. F. Atkins (2014). "Evidence of efficient stop codon readthrough in four mammalian genes." Nucleic Acids Res **42**(14): 8928-8938.
Low, W.-K., Y. Dang, T. Schneider-Poetsch, Z. Shi, N. S. Choi, W. C. Merrick, D. Romo and J. O. Liu (2005). "Inhibition of eukaryotic translation initiation by the marine natural product pateamine A." Molecular cell **20**(5): 709-722.
Lu, L., A.-P. Han and J.-J. Chen (2001). "Translation initiation control by heme-regulated eukaryotic initiation factor 2α kinase in erythroid cells under cytoplasmic stresses." Molecular and cellular biology **21**(23): 7971-7980.
Ma, J., S. Kala, S. Yung, T. M. Chan, Y. Cao, Y. Jiang, X. Liu, S. Giorgio, L. Peng and A. S. Wong (2018). "Blocking Stemness and Metastatic Properties of Ovarian Cancer Cells by Targeting p70S6K with Dendrimer Nanovector-Based siRNA Delivery." Molecular Therapy **26**(1): 70-83.
Ma, L., Z. Chen, H. Erdjument-Bromage, P. Tempst and P. P. Pandolfi (2005). "Phosphorylation and functional inactivation of TSC2 by Erk: implications for tuberous sclerosisand cancer pathogenesis." Cell **121**(2): 179-193.
Ma, W. J., S. Cheng, C. Campbell, A. Wright and H. Furneaux (1996). "Cloning and characterization of HuR, a ubiquitously expressed Elav-like protein." J Biol Chem **271**(14): 8144-8151.
Mader, S., H. Lee, A. Pause and N. Sonenberg (1995). "The translation initiation factor eIF-4E binds to a common motif shared by the translation factor eIF-4 gamma and the translational repressors 4E-binding proteins." Molecular and cellular biology **15**(9): 4990-4997.
Mahameed, M., S. Boukeileh, A. Obiedat, O. Darawshi, P. Dipta, A. Rimon, G. McLennan, R. Fassler, D. Reichmann and R. Karni (2020). "Pharmacological induction of selective endoplasmic reticulum retention as a strategy for cancer therapy." Nature communications **11**(1): 1-14.
Makkinje, A., H. Xiong, M. Li and Z. Damuni (1995). "Phosphorylation of eukaryotic protein synthesis initiation factor 4E by insulin-stimulated protamine kinase." Journal of Biological Chemistry **270**(24): 14824-14828.
Malbert-Colas, L., A. Ponnuswamy, V. Olivares-Illana, A.-S. Tournillon, N. Naski and R. Fåhraeus (2014). "HDMX folds the nascent p53 mRNA following activation by the ATM kinase." Molecular cell **54**(3): 500-511.
Mallya, S., B. A. Fitch, J. S. Lee, L. So, M. R. Janes and D. A. Fruman (2014). "Resistance to mTOR kinase inhibitors in lymphoma cells lacking 4EBP1." PloS one **9**(2): e88865.
Man, O. and Y. Pilpel (2007). "Differential translation efficiency of orthologous genes is involved in phenotypic divergence of yeast species." Nature genetics **39**(3): 415-421.
Mao, Y., L. Dong, X.-M. Liu, J. Guo, H. Ma, B. Shen and S.-B. Qian (2019). "m 6 A in mRNA coding regions promotes translation via the RNA helicase-containing YTHDC2." Nature communications **10**(1): 1-11.
Maquat, L. E., W.-Y. Tarn and O. Isken (2010). "The pioneer round of translation: features and functions." Cell **142**(3): 368-374.

Marcotrigiano, J., A.-C. Gingras, N. Sonenberg and S. K. Burley (1997). "Cocrystal structure of the messenger RNA 5′ cap-binding protein (eIF4E) bound to 7-methyl-GDP." Cell **89**(6): 951-961.
Martin, P. B., Y. Kigoshi-Tansho, R. B. Sher, G. Ravenscroft, J. E. Stauffer, R. Kumar, R. Yonashiro, T. Müller, C. Griffith and W. Allen (2020). "NEMF mutations that impair ribosome-associated quality control are associated with neuromuscular disease." Nature communications **11**(1): 1-12.
Mayr, C. (2019). "What Are 3' UTRs Doing?" Cold Spring Harb Perspect Biol **11**(10).
Mayr, C. and D. P. Bartel (2009). "Widespread shortening of 3'UTRs by alternative cleavage and polyadenylation activates oncogenes in cancer cells." Cell **138**(4): 673-684.
Meijer, H., Y. Kong, W. Lu, A. Wilczynska, R. Spriggs, S. Robinson, J. Godfrey, A. Willis and M. Bushell (2013). "Translational repression and eIF4A2 activity are critical for microRNA-mediated gene regulation." Science **340**(6128): 82-85.
Memczak, S., M. Jens, A. Elefsinioti, F. Torti, J. Krueger, A. Rybak, L. Maier, S. D. Mackowiak, L. H. Gregersen and M. Munschauer (2013). "Circular RNAs are a large class of animal RNAs with regulatory potency." Nature **495**(7441): 333-338.
Meng, Q.-B., W.-M. Kang, J.-C. Yu, Y.-Q. Liu, Z.-Q. Ma, L. Zhou, Q.-C. Cui and W.-X. Zhou (2015). "Overexpression of eukaryotic translation initiation factor 5A2 (EIF5A2) correlates with cell aggressiveness and poor survival in gastric cancer." PloS one **10**(3): e0119229.
Meng, Z., N. L. Jackson, O. D. Shcherbakov, H. Choi and S. W. Blume (2010). "The Human IGF1R IRES likely operates through a Shine–Dalgarno‐like interaction with the G961 loop (E‐site) of the 18S rRNA and is kinetically modulated by a naturally polymorphic polyU loop." Journal of cellular biochemistry **110**(2): 531-544.
Meurs, E., K. Chong, J. Galabru, N. S. B. Thomas, I. M. Kerr, B. R. Williams and A. G. Hovanessian (1990). "Molecular cloning and characterization of the human double-stranded RNA-activated protein kinase induced by interferon." Cell **62**(2): 379-390.
Meyer, K. D., D. P. Patil, J. Zhou, A. Zinoviev, M. A. Skabkin, O. Elemento, T. V. Pestova, S.-B. Qian and S. R. Jaffrey (2015). "5′ UTR m6A promotes cap-independent translation." Cell **163**(4): 999-1010.
Meyer, K. D., Y. Saletore, P. Zumbo, O. Elemento, C. E. Mason and S. R. Jaffrey (2012). "Comprehensive analysis of mRNA methylation reveals enrichment in 3′ UTRs and near stop codons." Cell **149**(7): 1635-1646.
Mignone, F., C. Gissi, S. Liuni and G. Pesole (2002). "Untranslated regions of mRNAs." Genome biology **3**(3): reviews0004. 0001.
Minich, W. B., M. L. Balasta, D. J. Goss and R. E. Rhoads (1994). "Chromatographic resolution of in vivo phosphorylated and nonphosphorylated eukaryotic translation initiation factor eIF-4E: increased cap affinity of the phosphorylated form." Proceedings of the National Academy of Sciences **91**(16): 7668-7672.
Moazed, D. and H. F. Noller (1989). "Intermediate states in the movement of transfer RNA in the ribosome." Nature **342**(6246): 142-148.
Moerke, N. J., H. Aktas, H. Chen, S. Cantel, M. Y. Reibarkh, A. Fahmy, J. D. Gross, A. Degterev, J. Yuan and M. Chorev (2007). "Small-molecule inhibition of the interaction between the translation initiation factors eIF4E and eIF4G." Cell **128**(2): 257-267.
Mohammad, M. P., V. Munzarová Pondělíčková, J. Zeman, S. Gunišová and L. S. Valášek (2017). "In vivo evidence that eIF3 stays bound to ribosomes elongating and terminating on short upstream ORFs to promote reinitiation." Nucleic acids research **45**(5): 2658-2674.
Mokrejš, M., T. Mašek, V. Vopálenský, P. Hlubuček, P. Delbos and M. Pospíšek (2010). "IRESite—a tool for the examination of viral and cellular internal ribosome entry sites." Nucleic acids research **38**(suppl_1): D131-D136.

Moldave, K. (1985). "Eukaryotic protein synthesis." Annual review of biochemistry **54**(1): 1109-1149.
Moon, S. L., T. Morisaki, T. J. Stasevich and R. Parker (2020). "Coupling of translation quality control and mRNA targeting to stress granules." J Cell Biol **219**(8).
Moore, C. E., H. Mikolajek, S. R. Da Mota, X. Wang, J. W. Kenney, J. M. Werner and C. G. Proud (2015). "Elongation factor 2 kinase is regulated by proline hydroxylation and protects cells during hypoxia." Molecular and cellular biology **35**(10): 1788-1804.
Morfoisse, F., A. Kuchnio, C. Frainay, A. Gomez-Brouchet, M.-B. Delisle, S. Marzi, A.-C. Helfer, F. Hantelys, F. Pujol and J. Guillermet-Guibert (2014). "Hypoxia induces VEGF-C expression in metastatic tumor cells via a HIF-1α-independent translation-mediated mechanism." Cell reports **6**(1): 155-167.
Mossmann, D., S. Park and M. N. Hall (2018). "mTOR signalling and cellular metabolism are mutual determinants in cancer." Nature Reviews Cancer **18**(12): 744-757.
Mrvová, S., K. Frydrýšková, M. Pospíšek, V. Vopálenský and T. Mašek (2018). "Major splice variants and multiple polyadenylation site utilization in mRNAs encoding human translation initiation factors eIF4E1 and eIF4E3 regulate the translational regulators?" Molecular Genetics and Genomics **293**(1): 167-186.
Mura, M., T. G. Hopkins, T. Michael, N. Abd-Latip, J. Weir, E. Aboagye, F. Mauri, C. Jameson, J. Sturge and H. Gabra (2015). "LARP1 post-transcriptionally regulates mTOR and contributes to cancer progression." Oncogene **34**(39): 5025-5036.
Nathan, C.-A. O., L. Liu, B. D. Li, F. W. Abreo, I. Nandy and A. De Benedetti (1997). "Detection of the proto-oncogene eIF4E in surgical margins may predict recurrence in head and neck cancer." Oncogene **15**(5): 579-584.
Nayak, B. K., D. Feliers, S. Sudarshan, W. E. Friedrichs, R. T. Day, D. D. New, J. P. Fitzgerald, A. Eid, T. DeNapoli and D. J. Parekh (2013). "Stabilization of HIF-2α through redox regulation of mTORC2 activation and initiation of mRNA translation." Oncogene **32**(26): 3147-3155.
Nicholson, J., S. J. Jevons, B. Groselj, S. Ellermann, R. Konietzny, M. Kerr, B. M. Kessler and A. E. Kiltie (2017). "E3 ligase cIAP2 mediates downregulation of MRE11 and radiosensitization in response to HDAC inhibition in bladder cancer." Cancer research **77**(11): 3027-3039.
Nielsen, P. J. and H. Trachsel (1988). "The mouse protein synthesis initiation factor 4A gene family includes two related functional genes which are differentially expressed." The EMBO journal **7**(7): 2097-2105.
O'Reilly, K. E., M. Warycha, M. A. Davies, V. Rodrik, X. K. Zhou, H. Yee, D. Polsky, A. C. Pavlick, N. Rosen and N. Bhardwaj (2009). "Phosphorylated 4E-BP1 is associated with poor survival in melanoma." Clinical Cancer Research **15**(8): 2872-2878.
Oblinger, J. L., S. S. Burns, J. Huang, L. Pan, Y. Ren, R. Shen, A. D. Kinghorn, D. B. Welling and L.-S. Chang (2018). "Overexpression of eIF4F components in meningiomas and suppression of meningioma cell growth by inhibiting translation initiation." Experimental neurology **299**: 299-307.
Ogami, K., Y. Oishi, T. Nogimori, K. Sakamoto and S.-i. Hoshino (2019). "LARP1 facilitates translational recovery after amino acid refeeding by preserving long poly (A)-tailed TOP mRNAs." BioRxiv: 716217.
Oh, S., R. A. Flynn, S. N. Floor, J. Purzner, L. Martin, B. T. Do, S. Schubert, D. Vaka, S. Morrissy and Y. Li (2016). "Medulloblastoma-associated DDX3 variant selectively alters the translational response to stress." Oncotarget **7**(19): 28169.
Ohanna, M., A. K. Sobering, T. Lapointe, L. Lorenzo, C. Praud, E. Petroulakis, N. Sonenberg, P. A. Kelly, A. Sotiropoulos and M. Pende (2005). "Atrophy of S6K1−/− skeletal muscle cells reveals distinct mTOR effectors for cell cycle and size control." Nature cell biology **7**(3): 286-294.

Okumura, F., W. Zou and D.-E. Zhang (2007). "ISG15 modification of the eIF4E cognate 4EHP enhances cap structure-binding activity of 4EHP." Genes & development **21**(3): 255-260.
Osborne, M. J., L. Volpon, J. A. Kornblatt, B. Culjkovic-Kraljacic, A. Baguet and K. L. Borden (2013). "eIF4E3 acts as a tumor suppressor by utilizing an atypical mode of methyl-7-guanosine cap recognition." Proceedings of the National Academy of Sciences **110**(10): 3877-3882.
Palacios, I. M., D. Gatfield, D. St Johnston and E. Izaurralde (2004). "An eIF4AIII-containing complex required for mRNA localization and nonsense-mediated mRNA decay." Nature **427**(6976): 753-757.
Pällmann, N., M. Braig, H. Sievert, M. Preukschas, I. Hermans-Borgmeyer, M. Schweizer, C. H. Nagel, M. Neumann, P. Wild and E. Haralambieva (2015). "Biological relevance and therapeutic potential of the hypusine modification system." Journal of Biological Chemistry **290**(30): 18343-18360.
Pamudurti, N. R., O. Bartok, M. Jens, R. Ashwal-Fluss, C. Stottmeister, L. Ruhe, M. Hanan, E. Wyler, D. Perez-Hernandez and E. Ramberger (2017). "Translation of circRNAs." Molecular cell **66**(1): 9-21. e27.
Pan, T. (2018). "Modifications and functional genomics of human transfer RNA." Cell research **28**(4): 395-404.
Pardo, O. E., A. Arcaro, G. Salerno, T. D. Tetley, T. Valovka, I. Gout and M. J. Seckl (2001). "Novel cross talk between MEK and S6K2 in FGF-2 induced proliferation of SCLC cells." Oncogene **20**(52): 7658-7667.
Pardo, O. E., C. Wellbrock, U. K. Khanzada, M. Aubert, I. Arozarena, S. Davidson, F. Bowen, P. J. Parker, V. Filonenko and I. T. Gout (2006). "FGF‐2 protects small cell lung cancer cells from apoptosis through a complex involving PKC ε, B‐Raf and S6K2." The EMBO journal **25**(13): 3078-3088.
Park, H. and A. R. Subramaniam (2019). "Inverted translational control of eukaryotic gene expression by ribosome collisions." PLoS biology **17**(9): e3000396.
Park, M. H., E. C. Wolff and J. Folk (1993). "Hypusine: its post-translational formation in eukaryotic initiation factor 5A and its potential role in cellular regulation." BioFactors (Oxford, England) **4**(2): 95.
Patel, D. J., A. T. Phan and V. Kuryavyi (2007). "Human telomere, oncogenic promoter and 5′-UTR G-quadruplexes: diverse higher order DNA and RNA targets for cancer therapeutics." Nucleic acids research **35**(22): 7429-7455.
Paulin, F. E., L. E. Campbell, K. O'Brien, J. Loughlin and C. G. Proud (2001). "Eukaryotic translation initiation factor 5 (eIF5) acts as a classical GTPase-activator protein." Current Biology **11**(1): 55-59.
Pavon-Eternod, M., S. Gomes, M. R. Rosner and T. Pan (2013). "Overexpression of initiator methionine tRNA leads to global reprogramming of tRNA expression and increased proliferation in human epithelial cells." Rna **19**(4): 461-466.
Pearce, L. R., X. Huang, J. Boudeau, R. Pawłowski, S. Wullschleger, M. Deak, A. F. Ibrahim, R. Gourlay, M. A. Magnuson and D. R. Alessi (2007). "Identification of Protor as a novel Rictor-binding component of mTOR complex-2." Biochemical Journal **405**(3): 513-522.
Pelechano, V. and P. Alepuz (2017). "eIF5A facilitates translation termination globally and promotes the elongation of many non polyproline-specific tripeptide sequences." Nucleic acids research **45**(12): 7326-7338.
Pende, M., S. H. Um, V. Mieulet, M. Sticker, V. L. Goss, J. Mestan, M. Mueller, S. Fumagalli, S. C. Kozma and G. Thomas (2004). "S6K1−/−/S6K2−/− mice exhibit perinatal lethality and rapamycin-sensitive 5′-terminal oligopyrimidine mRNA translation and reveal a mitogen-

activated protein kinase-dependent S6 kinase pathway." Molecular and cellular biology **24**(8): 3112-3124.
Peng, W. and J. L. Jewell (2020). "Amino acid sensing: architecture of mTORC1 on the lysosome surface." Current Biology **30**(2): R89-R91.
Pérez-Tenorio, G., E. Karlsson, M. A. Waltersson, B. Olsson, B. Holmlund, B. Nordenskjöld, T. Fornander, L. Skoog and O. Stål (2011). "Clinical potential of the mTOR targets S6K1 and S6K2 in breast cancer." Breast cancer research and treatment **128**(3): 713-723.
Peterson, T. R., M. Laplante, C. C. Thoreen, Y. Sancak, S. A. Kang, W. M. Kuehl, N. S. Gray and D. M. Sabatini (2009). "DEPTOR is an mTOR inhibitor frequently overexpressed in multiple myeloma cells and required for their survival." Cell **137**(5): 873-886.
Petroulakis, E., A. Parsyan, R. J. Dowling, O. LeBacquer, Y. Martineau, M. Bidinosti, O. Larsson, T. Alain, L. Rong and Y. Mamane (2009). "p53-dependent translational control of senescence and transformation via 4E-BPs." Cancer cell **16**(5): 439-446.
Petz, M., N. C. Them, H. Huber and W. Mikulits (2012). "PDGF enhances IRES-mediated translation of Laminin B1 by cytoplasmic accumulation of La during epithelial to mesenchymal transition." Nucleic acids research **40**(19): 9738-9749.
Philippe, C., A. Dubrac, C. Quelen, A. Desquesnes, L. Van Den Berghe, C. Ségura, T. Filleron, S. Pyronnet, H. Prats and P. Brousset (2016). "PERK mediates the IRES-dependent translational activation of mRNAs encoding angiogenic growth factors after ischemic stress." Science signaling **9**(426): ra44-ra44.
Philippe, L., J.-J. Vasseur, F. Debart and C. C. Thoreen (2018). "La-related protein 1 (LARP1) repression of TOP mRNA translation is mediated through its cap-binding domain and controlled by an adjacent regulatory region." Nucleic acids research **46**(3): 1457-1469.
Pisarev, A. V., M. A. Skabkin, V. P. Pisareva, O. V. Skabkina, A. M. Rakotondrafara, M. W. Hentze, C. U. Hellen and T. V. Pestova (2010). "The role of ABCE1 in eukaryotic posttermination ribosomal recycling." Molecular cell **37**(2): 196-210.
Pisareva, V. P., A. V. Pisarev, A. A. Komar, C. U. Hellen and T. V. Pestova (2008). "Translation initiation on mammalian mRNAs with structured 5′ UTRs requires DExH-box protein DHX29." Cell **135**(7): 1237-1250.
Pochopien, A. A., B. Beckert, S. Kasvandik, O. Berninghausen, R. Beckmann, T. Tenson and D. N. Wilson (2020). "Structure of Gcn1 bound to stalled and colliding 80S ribosomes." bioRxiv.
Pon, Y. L., H. Y. Zhou, A. N. Cheung, H. Y. Ngan and A. S. Wong (2008). "p70 S6 kinase promotes epithelial to mesenchymal transition through snail induction in ovarian cancer cells." Cancer research **68**(16): 6524-6532.
Poncová, K., S. Wagner, M. E. Jansen, P. Beznosková, S. Gunišová, A. Herrmannová, J. Zeman, J. Dong and L. S. Valášek (2019). "uS3/Rps3 controls fidelity of translation termination and programmed stop codon readthrough in co-operation with eIF3." Nucleic acids research **47**(21): 11326-11343.
Pullen, N., P. B. Dennis, M. Andjelkovic, A. Dufner, S. C. Kozma, B. A. Hemmings and G. Thomas (1998). "Phosphorylation and activation of p70s6k by PDK1." Science **279**(5351): 707-710.
Pyronnet, S., H. Imataka, A. C. Gingras, R. Fukunaga, T. Hunter and N. Sonenberg (1999). "Human eukaryotic translation initiation factor 4G (eIF4G) recruits mnk1 to phosphorylate eIF4E." The EMBO journal **18**(1): 270-279.
Qin, X. and P. Sarnow (2004). "Preferential translation of internal ribosome entry site-containing mRNAs during the mitotic cycle in mammalian cells." Journal of Biological Chemistry **279**(14): 13721-13728.
Quiocho, F. A., G. Hu and P. D. Gershon (2000). "Structural basis of mRNA cap recognition by proteins." Current opinion in structural biology **10**(1): 78-86.

Radhakrishnan, A., Y.-H. Chen, S. Martin, N. Alhusaini, R. Green and J. Coller (2016). "The DEAD-box protein Dhh1p couples mRNA decay and translation by monitoring codon optimality." Cell **167**(1): 122-132. e129.
Ramírez-Valle, F., S. Braunstein, J. Zavadil, S. C. Formenti and R. J. Schneider (2008). "eIF4GI links nutrient sensing by mTOR to cell proliferation and inhibition of autophagy." The Journal of cell biology **181**(2): 293-307.
Ranganathan, A. C., S. Ojha, A. Kourtidis, D. S. Conklin and J. A. Aguirre-Ghiso (2008). "Dual function of pancreatic endoplasmic reticulum kinase in tumor cell growth arrest and survival." Cancer research **68**(9): 3260-3268.
Rapino, F., S. Delaunay, F. Rambow, Z. Zhou, L. Tharun, P. De Tullio, O. Sin, K. Shostak, S. Schmitz and J. Piepers (2018). "Codon-specific translation reprogramming promotes resistance to targeted therapy." Nature **558**(7711): 605-609.
Räsch, F., R. Weber, E. Izaurralde and C. Igreja (2020). "4E-T-bound mRNAs are stored in a silenced and deadenylated form." Genes & development **34**(11-12): 847-860.
Raught, B., A. C. Gingras, S. P. Gygi, H. Imataka, S. Morino, A. Gradi, R. Aebersold and N. Sonenberg (2000). "Serum‐stimulated, rapamycin‐sensitive phosphorylation sites in the eukaryotic translation initiation factor 4GI." The EMBO journal **19**(3): 434-444.
Rebholz, H., G. Panasyuk, T. Fenton, I. Nemazanyy, T. Valovka, M. Flajolet, L. Ronnstrand, L. Stephens, A. West and I. T. Gout (2006). "Receptor association and tyrosine phosphorylation of S6 kinases." The FEBS journal **273**(9): 2023-2036.
Redpath, N. T. and C. G. Proud (1993). "Cyclic AMP-dependent protein kinase phosphorylates rabbit reticulocyte elongation factor-2 kinase and induces calcium-independent activity." Biochemical Journal **293**(1): 31-34.
Reid, D. W., Q. Chen, A. S.-L. Tay, S. Shenolikar and C. V. Nicchitta (2014). "The unfolded protein response triggers selective mRNA release from the endoplasmic reticulum." Cell **158**(6): 1362-1374.
Robb, V. A., A. Astrinidis and E. P. Henske (2006). "Frequent of ribosomal protein S6 hyperphosphorylation in lymphangioleiomyomatosis-associated angiomyolipomas." Modern pathology **19**(6): 839-846.
Robert, F., R. Cencic, R. Cai, T. M. Schmeing and J. Pelletier (2020). "RNA-tethering assay and eIF4G: eIF4A obligate dimer design uncovers multiple eIF4F functional complexes." Nucleic acids research **48**(15): 8562-8575.
Robichaud, N., S. V. del Rincon, B. Huor, T. Alain, L. A. Petruccelli, J. Hearnden, C. Goncalves, S. Grotegut, C. H. Spruck and L. Furic (2015). "Phosphorylation of eIF4E promotes EMT and metastasis via translational control of SNAIL and MMP-3." Oncogene **34**(16): 2032-2042.
Robichaud, N., B. E. Hsu, R. Istomine, F. Alvarez, J. Blagih, E. H. Ma, S. V. Morales, D. L. Dai, G. Li and M. Souleimanova (2018). "Translational control in the tumor microenvironment promotes lung metastasis: Phosphorylation of eIF4E in neutrophils." Proceedings of the National Academy of Sciences **115**(10): E2202-E2209.
Rogers, G. W., N. J. Richter, W. F. Lima and W. C. Merrick (2001). "Modulation of the helicase activity of eIF4A by eIF4B, eIF4H, and eIF4F." Journal of Biological Chemistry **276**(33): 30914-30922.
Rogers, G. W., N. J. Richter and W. C. Merrick (1999). "Biochemical and kinetic characterization of the RNA helicase activity of eukaryotic initiation factor 4A." Journal of Biological Chemistry **274**(18): 12236-12244.
Rojo, F., L. Najera, J. Lirola, J. Jiménez, M. Guzmán, M. D. Sabadell, J. Baselga and S. R. y Cajal (2007). "4E-binding protein 1, a cell signaling hallmark in breast cancer that correlates with pathologic grade and prognosis." Clinical Cancer Research **13**(1): 81-89.

Rom, E., H. C. Kim, A.-C. Gingras, J. Marcotrigiano, D. Favre, H. Olsen, S. K. Burley and N. Sonenberg (1998). "Cloning and characterization of 4EHP, a novel mammalian eIF4E-related cap-binding protein." Journal of Biological Chemistry **273**(21): 13104-13109.
Rosenwald, I. B., J.-J. Chen, S. Wang, L. Savas, I. M. London and J. Pullman (1999). "Upregulation of protein synthesis initiation factor eIF-4E is an early event during colon carcinogenesis." Oncogene **18**(15): 2507-2517.
Rouschop, K. M., L. J. Dubois, T. G. Keulers, T. van den Beucken, P. Lambin, J. Bussink, A. J. van der Kogel, M. Koritzinsky and B. G. Wouters (2013). "PERK/eIF2α signaling protects therapy resistant hypoxic cells through induction of glutathione synthesis and protection against ROS." Proceedings of the National Academy of Sciences **110**(12): 4622-4627.
Rouya, C., N. Siddiqui, M. Morita, T. F. Duchaine, M. R. Fabian and N. Sonenberg (2014). "Human DDX6 effects miRNA-mediated gene silencing via direct binding to CNOT1." Rna **20**(9): 1398-1409.
Rubio, C. A., B. Weisburd, M. Holderfield, C. Arias, E. Fang, J. L. DeRisi and A. Fanidi (2014). "Transcriptome-wide characterization of the eIF4A signature highlights plasticity in translation regulation." Genome biology **15**(10): 476.
Ruggero, D., L. Montanaro, L. Ma, W. Xu, P. Londei, C. Cordon-Cardo and P. P. Pandolfi (2004). "The translation factor eIF-4E promotes tumor formation and cooperates with c-Myc in lymphomagenesis." Nature medicine **10**(5): 484-486.
Rupaimoole, R. and F. J. Slack (2017). "MicroRNA therapeutics: towards a new era for the management of cancer and other diseases." Nat Rev Drug Discov **16**(3): 203-222.
Ruscica, V., P. Bawankar, D. Peter, S. Helms, C. Igreja and E. Izaurralde (2019). "Direct role for the Drosophila GIGYF protein in 4EHP-mediated mRNA repression." Nucleic acids research **47**(13): 7035-7048.
Ruvinsky, I., N. Sharon, T. Lerer, H. Cohen, M. Stolovich-Rain, T. Nir, Y. Dor, P. Zisman and O. Meyuhas (2005). "Ribosomal protein S6 phosphorylation is a determinant of cell size and glucose homeostasis." Genes & development **19**(18): 2199-2211.
Ryazanov, A. G., E. A. Shestakova and P. G. Natapov (1988). "Phosphorylation of elongation factor 2 by EF-2 kinase affects rate of translation." Nature **334**(6178): 170-173.
Saikia, M., Y. Fu, M. Pavon-Eternod, C. He and T. Pan (2010). "Genome-wide analysis of N1-methyl-adenosine modification in human tRNAs." Rna **16**(7): 1317-1327.
Saini, P., D. E. Eyler, R. Green and T. E. Dever (2009). "Hypusine-containing protein eIF5A promotes translation elongation." Nature **459**(7243): 118-121.
Saitoh, M., P. ten Dijke, K. Miyazono and H. Ichijo (1998). "Cloning and characterization of p70S6KβDefines a novel family of p70 S6 kinases." Biochemical and biophysical research communications **253**(2): 470-476.
Sampath, P., D. K. Pritchard, L. Pabon, H. Reinecke, S. M. Schwartz, D. R. Morris and C. E. Murry (2008). "A hierarchical network controls protein translation during murine embryonic stem cell self-renewal and differentiation." Cell stem cell **2**(5): 448-460.
Sancak, Y., T. R. Peterson, Y. D. Shaul, R. A. Lindquist, C. C. Thoreen, L. Bar-Peled and D. M. Sabatini (2008). "The Rag GTPases bind raptor and mediate amino acid signaling to mTORC1." Science **320**(5882): 1496-1501.
Sandberg, R., J. R. Neilson, A. Sarma, P. A. Sharp and C. B. Burge (2008). "Proliferating cells express mRNAs with shortened 3' untranslated regions and fewer microRNA target sites." Science **320**(5883): 1643-1647.
Sauter, K. A., E. A. Magun, M. S. Iordanov and B. E. Magun (2010). "ZAK is required for doxorubicin, a novel ribotoxic stressor, to induce SAPK activation and apoptosis in HaCaT cells." Cancer Biol Ther **10**(3): 258-266.
Saxton, R. A. and D. M. Sabatini (2017). "mTOR signaling in growth, metabolism, and disease." Cell **168**(6): 960-976.

Scaggiante, B., B. Dapas, S. Bonin, M. Grassi, C. Zennaro, R. Farra, L. Cristiano, S. Siracusano, F. Zanconati and C. Giansante (2012). "Dissecting the expression of EEF1A1/2 genes in human prostate cancer cells: the potential of EEF1A2 as a hallmark for prostate transformation and progression." British journal of cancer **106**(1): 166-173.
Scheper, G. C., N. A. Morrice, M. Kleijn and C. G. Proud (2001). "The mitogen-activated protein kinase signal-integrating kinase Mnk2 is a eukaryotic initiation factor 4E kinase with high levels of basal activity in mammalian cells." Molecular and cellular biology **21**(3): 743-754.
Scheper, G. C., B. Van Kollenburg, J. Hu, Y. Luo, D. J. Goss and C. G. Proud (2002). "Phosphorylation of eukaryotic initiation factor 4E markedly reduces its affinity for capped mRNA." Journal of Biological Chemistry **277**(5): 3303-3309.
Scheuner, D., B. Song, E. McEwen, C. Liu, R. Laybutt, P. Gillespie, T. Saunders, S. Bonner-Weir and R. J. Kaufman (2001). "Translational control is required for the unfolded protein response and in vivo glucose homeostasis." Molecular cell **7**(6): 1165-1176.
Schleich, S., K. Strassburger, P. C. Janiesch, T. Koledachkina, K. K. Miller, K. Haneke, Y.-S. Cheng, K. Kuechler, G. Stoecklin and K. E. Duncan (2014). "DENR–MCT-1 promotes translation re-initiation downstream of uORFs to control tissue growth." Nature **512**(7513): 208-212.
Schmidt, S., D. Gay, F. W. Uthe, S. Denk, M. Paauwe, N. Matthes, M. E. Diefenbacher, S. Bryson, F. C. Warrander and F. Erhard (2019). "A MYC–GCN2–eIF2α negative feedback loop limits protein synthesis to prevent MYC-dependent apoptosis in colorectal cancer." Nature cell biology **21**(11): 1413-1424.
Schueren, F. and S. Thoms (2016). "Functional Translational Readthrough: A Systems Biology Perspective." PLoS Genet **12**(8): e1006196.
Schuller, A. P., C. C.-C. Wu, T. E. Dever, A. R. Buskirk and R. Green (2017). "eIF5A functions globally in translation elongation and termination." Molecular cell **66**(2): 194-205. e195.
Schwab, S. R., K. C. Li, C. Kang and N. Shastri (2003). "Constitutive display of cryptic translation products by MHC class I molecules." Science **301**(5638): 1367-1371.
Schwanhäusser, B., D. Busse, N. Li, G. Dittmar, J. Schuchhardt, J. Wolf, W. Chen and M. Selbach (2011). "Global quantification of mammalian gene expression control." Nature **473**(7347): 337-342.
Sehrawat, U., F. Koning, S. Ashkenazi, G. Stelzer, D. Leshkowitz and R. Dikstein (2019). "Cancer-associated eukaryotic translation initiation factor 1A mutants impair Rps3 and Rps10 binding and enhance scanning of cell cycle genes." Molecular and Cellular Biology **39**(3).
Sekine, Y., A. Zyryanova, A. Crespillo-Casado, P. M. Fischer, H. P. Harding and D. Ron (2015). "Mutations in a translation initiation factor identify the target of a memory-enhancing compound." Science **348**(6238): 1027-1030.
Sha, Z., L. M. Brill, R. Cabrera, O. Kleifeld, J. S. Scheliga, M. H. Glickman, E. C. Chang and D. A. Wolf (2009). "The eIF3 interactome reveals the translasome, a supercomplex linking protein synthesis and degradation machineries." Molecular cell **36**(1): 141-152.
Shahbazian, D., A. Parsyan, E. Petroulakis, I. Topisirovic, Y. Martineau, B. F. Gibbs, Y. Svitkin and N. Sonenberg (2010). "Control of cell survival and proliferation by mammalian eukaryotic initiation factor 4B." Molecular and cellular biology **30**(6): 1478-1485.
She, Q.-B., E. Halilovic, Q. Ye, W. Zhen, S. Shirasawa, T. Sasazuki, D. B. Solit and N. Rosen (2010). "4E-BP1 is a key effector of the oncogenic activation of the AKT and ERK signaling pathways that integrates their function in tumors." Cancer cell **18**(1): 39-51.
Shen, K. and D. M. Sabatini (2018). "Ragulator and SLC38A9 activate the Rag GTPases through noncanonical GEF mechanisms." Proceedings of the National Academy of Sciences **115**(38): 9545-9550.

Sherrill, K. W., M. P. Byrd, M. E. Van Eden and R. E. Lloyd (2004). "BCL-2 translation is mediated via internal ribosome entry during cell stress." Journal of Biological Chemistry **279**(28): 29066-29074.
Shi, Y., K. M. Vattem, R. Sood, J. An, J. Liang, L. Stramm and R. C. Wek (1998). "Identification and characterization of pancreatic eukaryotic initiation factor 2 α-subunit kinase, PEK, involved in translational control." Molecular and cellular biology **18**(12): 7499-7509.
Shibuya, T., T. Ø. Tange, N. Sonenberg and M. J. Moore (2004). "eIF4AIII binds spliced mRNA in the exon junction complex and is essential for nonsense-mediated decay." Nature structural & molecular biology **11**(4): 346-351.
Shin, S., L. Wolgamott, P. P. Roux and S.-O. Yoon (2014). "Casein kinase 1ε promotes cell proliferation by regulating mRNA translation." Cancer research **74**(1): 201-211.
Shin, S., L. Wolgamott, J. Tcherkezian, S. Vallabhapurapu, Y. Yu, P. Roux and S. Yoon (2014). "Glycogen synthase kinase-3β positively regulates protein synthesis and cell proliferation through the regulation of translation initiation factor 4E-binding protein 1." Oncogene **33**(13): 1690-1699.
Shin, S., L. Wolgamott, Y. Yu, J. Blenis and S.-O. Yoon (2011). "Glycogen synthase kinase (GSK)-3 promotes p70 ribosomal protein S6 kinase (p70S6K) activity and cell proliferation." Proceedings of the National Academy of Sciences **108**(47): E1204-E1213.
Shirokikh, N. E. and T. Preiss (2018). "Translation initiation by cap‐dependent ribosome recruitment: Recent insights and open questions." Wiley Interdisciplinary Reviews: RNA **9**(4): e1473.
Shoji, S., S. E. Walker and K. Fredrick (2009). "Ribosomal translocation: one step closer to the molecular mechanism." ACS chemical biology **4**(2): 93-107.
Shor, B., J. Wu, Q. Shakey, L. Toral-Barza, C. Shi, M. Follettie and K. Yu (2010). "Requirement of the mTOR kinase for the regulation of Maf1 phosphorylation and control of RNA polymerase III-dependent transcription in cancer cells." Journal of Biological Chemistry **285**(20): 15380-15392.
Shuda, M., N. Kondoh, K. Tanaka, A. Ryo, T. Wakatsuki, A. Hada, N. Goseki, T. Igari, K. Hatsuse and T. Aihara (2000). "Enhanced expression of translation factor mRNAs in hepatocellular carcinoma." Anticancer research **20**(4): 2489.
Shuda, M., C. Velásquez, E. Cheng, D. G. Cordek, H. J. Kwun, Y. Chang and P. S. Moore (2015). "CDK1 substitutes for mTOR kinase to activate mitotic cap-dependent protein translation." Proceedings of the National Academy of Sciences **112**(19): 5875-5882.
Sidrauski, C., A. M. McGeachy, N. T. Ingolia and P. Walter (2015). "The small molecule ISRIB reverses the effects of eIF2α phosphorylation on translation and stress granule assembly." Elife **4**: e05033.
Signer, R. A., J. A. Magee, A. Salic and S. J. Morrison (2014). "Haematopoietic stem cells require a highly regulated protein synthesis rate." Nature **509**(7498): 49-54.
Silvera, D., R. Arju, F. Darvishian, P. H. Levine, L. Zolfaghari, J. Goldberg, T. Hochman, S. C. Formenti and R. J. Schneider (2009). "Essential role for eIF4GI overexpression in the pathogenesis of inflammatory breast cancer." Nature cell biology **11**(7): 903-908.
Simms, C. L., B. H. Hudson, J. W. Mosior, A. S. Rangwala and H. S. Zaher (2014). "An active role for the ribosome in determining the fate of oxidized mRNA." Cell reports **9**(4): 1256-1264.
Singh, A., L. E. Manjunath, P. Kundu, S. Sahoo, A. Das, H. R. Suma, P. L. Fox and S. M. Eswarappa (2019). "Let-7a-regulated translational readthrough of mammalian AGO1 generates a microRNA pathway inhibitor." Embo j **38**(16): e100727.
Sinha, N. K., A. Ordureau, K. Best, J. A. Saba, B. Zinshteyn, E. Sundaramoorthy, A. Fulzele, D. M. Garshott, T. Denk and M. Thoms (2020). "EDF1 coordinates cellular responses to ribosome collisions." Elife **9**: e58828.

Sinha, N. K., A. Ordureau, K. Best, J. A. Saba, B. Zinshteyn, E. Sundaramoorthy, A. Fulzele, D. M. Garshott, T. Denk, M. Thoms, J. A. Paulo, J. W. Harper, E. J. Bennett, R. Beckmann and R. Green (2020). "EDF1 coordinates cellular responses to ribosome collisions." Elife **9**.
Sinvani, H., O. Haimov, Y. Svitkin, N. Sonenberg, A. Tamarkin-Ben-Harush, B. Viollet and R. Dikstein (2015). "Translational tolerance of mitochondrial genes to metabolic energy stress involves TISU and eIF1-eIF4GI cooperation in start codon selection." Cell metabolism **21**(3): 479-492.
Skinner, H. D., J. Z. Zheng, J. Fang, F. Agani and B.-H. Jiang (2004). "Vascular endothelial growth factor transcriptional activation is mediated by hypoxia-inducible factor 1α, HDM2, and p70S6K1 in response to phosphatidylinositol 3-kinase/AKT signaling." Journal of Biological Chemistry **279**(44): 45643-45651.
Slepenkov, S. V., E. Darzynkiewicz and R. E. Rhoads (2006). "Stopped-flow Kinetic Analysis of eIF4E and Phosphorylated eIF4E Binding to Cap Analogs and Capped Oligoribonucleotides EVIDENCE FOR A ONE-STEP BINDING MECHANISM." Journal of Biological Chemistry **281**(21): 14927-14938.
Smadja-Lamère, N., M. Shum, P. Déléris, P. P. Roux, J.-I. Abe and A. Marette (2013). "Insulin activates RSK (p90 ribosomal S6 kinase) to trigger a new negative feedback loop that regulates insulin signaling for glucose metabolism." Journal of Biological Chemistry **288**(43): 31165-31176.
Smirnova, J. B., J. N. Selley, F. Sanchez-Cabo, K. Carroll, A. A. Eddy, J. E. McCarthy, S. J. Hubbard, G. D. Pavitt, C. M. Grant and M. P. Ashe (2005). "Global gene expression profiling reveals widespread yet distinctive translational responses to different eukaryotic translation initiation factor 2B-targeting stress pathways." Molecular and cellular biology **25**(21): 9340-9349.
Smith, E. M. and C. G. Proud (2008). "cdc2–cyclin B regulates eEF2 kinase activity in a cell cycle‐and amino acid‐dependent manner." The EMBO journal **27**(7): 1005-1016.
Sood, R., A. C. Porter, D. Olsen, D. R. Cavener and R. C. Wek (2000). "A mammalian homologue of GCN2 protein kinase important for translational control by phosphorylation of eukaryotic initiation factor-2α." Genetics **154**(2): 787-801.
Spahn, C. M., M. G. Gomez‐Lorenzo, R. A. Grassucci, R. Jørgensen, G. R. Andersen, R. Beckmann, P. A. Penczek, J. P. Ballesta and J. Frank (2004). "Domain movements of elongation factor eEF2 and the eukaryotic 80S ribosome facilitate tRNA translocation." The EMBO journal **23**(5): 1008-1019.
Spevak, C. C., H. K. Elias, L. Kannan, M. A. Ali, G. H. Martin, S. Selvaraj, W. S. Eng, A. Ernlund, V. K. Rajasekhar and C. M. Woolthuis (2020). "Hematopoietic Stem and Progenitor Cells Exhibit Stage-Specific Translational Programs via mTOR-and CDK1-Dependent Mechanisms." Cell Stem Cell **26**(5): 755-765. e757.
Spriggs, K. A., M. Stoneley, M. Bushell and A. E. Willis (2008). "Re‐programming of translation following cell stress allows IRES‐mediated translation to predominate." Biology of the Cell **100**(1): 27-38.
Sridharan, S. and A. Basu (2011). "S6 kinase 2 promotes breast cancer cell survival via Akt." Cancer research **71**(7): 2590-2599.
Stansfield, I., K. M. Jones, V. V. Kushnirov, A. Dagkesamanskaya, A. Poznyakovski, S. V. Paushkin, C. Nierras, B. S. Cox, M. Ter‐Avanesyan and M. F. Tuite (1995). "The products of the SUP45 (eRF1) and SUP35 genes interact to mediate translation termination in Saccharomyces cerevisiae." The EMBO journal **14**(17): 4365-4373.

Starck, S. R., J. C. Tsai, K. Chen, M. Shodiya, L. Wang, K. Yahiro, M. Martins-Green, N. Shastri and P. Walter (2016). "Translation from the 5′ untranslated region shapes the integrated stress response." Science **351**(6272).
Stoneley, M., T. Subkhankulova, J. P. Le Quesne, M. J. Coldwell, C. L. Jopling, G. J. Belsham and A. E. Willis (2000). "Analysis of the c-myc IRES; a potential role for cell-type specific trans-acting factors and the nuclear compartment." Nucleic acids research **28**(3): 687-694.
SUBKHANKULOVA, T., S. A. MITCHELL and A. E. WILLIS (2001). "Internal ribosome entry segment-mediated initiation of c-Myc protein synthesis following genotoxic stress." Biochemical journal **359**(1): 183-192.
Sudhakar, A., A. Ramachandran, S. Ghosh, S. E. Hasnain, R. J. Kaufman and K. V. Ramaiah (2000). "Phosphorylation of serine 51 in initiation factor 2α (eIF2α) promotes complex formation between eIF2α (P) and eIF2B and causes inhibition in the guanine nucleotide exchange activity of eIF2B." Biochemistry **39**(42): 12929-12938.
Sudmant, P. H., H. Lee, D. Dominguez, M. Heiman and C. B. Burge (2018). "Widespread Accumulation of Ribosome-Associated Isolated 3' UTRs in Neuronal Cell Populations of the Aging Brain." Cell Rep **25**(9): 2447-2456.e2444.
Sun, H.-D., Z.-P. Xu, Z.-Q. Sun, B. Zhu, Q. Wang, J. Zhou, H. Jin, A. Zhao, W.-W. Tang and X.-F. Cao (2018). "Down-regulation of circPVRL3 promotes the proliferation and migration of gastric cancer cells." Scientific reports **8**(1): 1-13.
Svitkin, Y. V., A. Pause, A. Haghighat, S. Pyronnet, G. Witherell, G. J. Belsham and N. Sonenberg (2001). "The requirement for eukaryotic initiation factor 4A (elF4A) in translation is in direct proportion to the degree of mRNA 5'secondary structure." Rna **7**(3): 382-394.
Tahmasebi, S., S. M. Jafarnejad, I. S. Tam, T. Gonatopoulos-Pournatzis, E. Matta-Camacho, Y. Tsukumo, A. Yanagiya, W. Li, Y. Atlasi and M. Caron (2016). "Control of embryonic stem cell self-renewal and differentiation via coordinated alternative splicing and translation of YY2." Proceedings of the National Academy of Sciences **113**(44): 12360-12367.
Talvas, J., A. Obled, P. Fafournoux and S. Mordier (2006). "Regulation of protein synthesis by leucine starvation involves distinct mechanisms in mouse C2C12 myoblasts and myotubes." The Journal of nutrition **136**(6): 1466-1471.
Tanabe, A., K. Tanikawa, M. Tsunetomi, K. Takai, H. Ikeda, J. Konno, T. Torigoe, H. Maeda, G. Kutomi and K. Okita (2016). "RNA helicase YTHDC2 promotes cancer metastasis via the enhancement of the efficiency by which HIF-1α mRNA is translated." Cancer letters **376**(1): 34-42.
Tanenbaum, M. E., N. Stern-Ginossar, J. S. Weissman and R. D. Vale (2015). "Regulation of mRNA translation during mitosis." Elife **4**: e07957.
Tang, D. J., S. S. Dong, N. F. Ma, D. Xie, L. Chen, L. Fu, S. H. Lau, Y. Li, Y. Li and X. Y. Guan (2010). "Overexpression of eukaryotic initiation factor 5A2 enhances cell motility and promotes tumor metastasis in hepatocellular carcinoma." Hepatology **51**(4): 1255-1263.
Tang, H., E. Hornstein, M. Stolovich, G. Levy, M. Livingstone, D. Templeton, J. Avruch and O. Meyuhas (2001). "Amino acid-induced translation of TOP mRNAs is fully dependent on phosphatidylinositol 3-kinase-mediated signaling, is partially inhibited by rapamycin, and is independent of S6K1 and rpS6 phosphorylation." Molecular and cellular biology **21**(24): 8671-8683.
Taylor, D. J., J. Nilsson, A. R. Merrill, G. R. Andersen, P. Nissen and J. Frank (2007). "Structures of modified eEF2· 80S ribosome complexes reveal the role of GTP hydrolysis in translocation." The EMBO journal **26**(9): 2421-2431.
Tcherkezian, J., M. Cargnello, Y. Romeo, E. L. Huttlin, G. Lavoie, S. P. Gygi and P. P. Roux (2014). "Proteomic analysis of cap-dependent translation identifies LARP1 as a key regulator of 5′ TOP mRNA translation." Genes & development **28**(4): 357-371.

Thakor, N., M. D. Smith, L. Roberts, M. D. Faye, H. Patel, H.-J. Wieden, J. H. Cate and M. Holcik (2017). "Cellular mRNA recruits the ribosome via eIF3-PABP bridge to initiate internal translation." RNA biology **14**(5): 553-567.
Thedieck, K., P. Polak, M. L. Kim, K. D. Molle, A. Cohen, P. Jenö, C. Arrieumerlou and M. N. Hall (2007). "PRAS40 and PRR5-like protein are new mTOR interactors that regulate apoptosis." PloS one **2**(11): e1217.
Tian, Y., X. Tian, X. Han, Y. Chen, C.-Y. Song, W.-J. Jiang and D.-L. Tian (2016). "ABCE1 plays an essential role in lung cancer progression and metastasis." Tumor Biology **37**(6): 8375-8382.
Torrent, M., G. Chalancon, N. S. de Groot, A. Wuster and M. M. Babu (2018). "Cells alter their tRNA abundance to selectively regulate protein synthesis during stress conditions." Science signaling **11**(546).
Truitt, M. L., C. S. Conn, Z. Shi, X. Pang, T. Tokuyasu, A. M. Coady, Y. Seo, M. Barna and D. Ruggero (2015). "Differential requirements for eIF4E dose in normal development and cancer." Cell **162**(1): 59-71.
Trzaska, C., S. Amand, C. Bailly, C. Leroy, V. Marchand, E. Duvernois-Berthet, J. M. Saliou, H. Benhabiles, E. Werkmeister, T. Chassat, R. Guilbert, D. Hannebique, A. Mouray, M. C. Copin, P. A. Moreau, E. Adriaenssens, A. Kulozik, E. Westhof, D. Tulasne, Y. Motorin, S. Rebuffat and F. Lejeune (2020). "2,6-Diaminopurine as a highly potent corrector of UGA nonsense mutations." Nat Commun **11**(1): 1509.
Tsukumo, Y., T. Alain, B. D. Fonseca, R. Nadon and N. Sonenberg (2016). "Translation control during prolonged mTORC1 inhibition mediated by 4E-BP3." Nature communications **7**(1): 1-13.
Tunca, B., G. Tezcan, G. Cecener, U. Egeli, A. Zorluoglu, T. Yilmazlar, S. Ak, O. Yerci, E. Ozturk and G. Umut (2013). "Overexpression of CK20, MAP3K8 and EIF5A correlates with poor prognosis in early-onset colorectal cancer patients." Journal of cancer research and clinical oncology **139**(4): 691-702.
Tuorto, F., C. Legrand, C. Cirzi, G. Federico, R. Liebers, M. Müller, A. E. Ehrenhofer‐Murray, G. Dittmar, H. J. Gröne and F. Lyko (2018). "Queuosine‐modified tRNAs confer nutritional control of protein translation." The EMBO journal **37**(18): e99777.
Ueda, T., R. Watanabe-Fukunaga, H. Fukuyama, S. Nagata and R. Fukunaga (2004). "Mnk2 and Mnk1 are essential for constitutive and inducible phosphorylation of eukaryotic initiation factor 4E but not for cell growth or development." Molecular and cellular biology **24**(15): 6539-6549.
Um, S. H., F. Frigerio, M. Watanabe, F. Picard, M. Joaquin, M. Sticker, S. Fumagalli, P. R. Allegrini, S. C. Kozma and J. Auwerx (2004). "Absence of S6K1 protects against age-and diet-induced obesity while enhancing insulin sensitivity." Nature **431**(7005): 200-205.
Uniacke, J., C. E. Holterman, G. Lachance, A. Franovic, M. D. Jacob, M. R. Fabian, J. Payette, M. Holcik, A. Pause and S. Lee (2012). "An oxygen-regulated switch in the protein synthesis machinery." Nature **486**(7401): 126-129.
Uniacke, J., J. K. Perera, G. Lachance, C. B. Francisco and S. Lee (2014). "Cancer cells exploit eIF4E2-directed synthesis of hypoxia response proteins to drive tumor progression." Cancer research **74**(5): 1379-1389.
Urtishak, K. A., L.-S. Wang, B. Culjkovic-Kraljacic, J. W. Davenport, P. Porazzi, T. L. Vincent, D. T. Teachey, S. K. Tasian, J. S. Moore and A. E. Seif (2019). "Targeting EIF4E signaling with ribavirin in infant acute lymphoblastic leukemia." Oncogene **38**(13): 2241-2262.
Valenzuela, D., A. Chaudhuri and U. Maitra (1982). "Eukaryotic ribosomal subunit anti-association activity of calf liver is contained in a single polypeptide chain protein of Mr= 25,500 (eukaryotic initiation factor 6)." Journal of Biological Chemistry **257**(13): 7712-7719.

Valovka, T., F. Verdier, R. Cramer, A. Zhyvoloup, T. Fenton, H. Rebholz, M.-L. Wang, M. Gzhegotsky, A. Lutsyk and G. Matsuka (2003). "Protein kinase C phosphorylates ribosomal protein S6 kinase βII and regulates its subcellular localization." Molecular and cellular biology **23**(3): 852-863.
Van der Hage, J., L. van den Broek, C. Legrand, P. Clahsen, C. Bosch, E. Robanus-Maandag, C. van de Velde and M. Van de Vijver (2004). "Overexpression of P70 S6 kinase protein is associated with increased risk of locoregional recurrence in node-negative premenopausal early breast cancer patients." British journal of cancer **90**(8): 1543-1550.
VAN EDEN, M. E., M. P. BYRD, K. W. SHERRILL and R. E. LLOYD (2004). "Translation of cellular inhibitor of apoptosis protein 1 (c-IAP1) mRNA is IRES mediated and regulated during cell stress." Rna **10**(3): 469-481.
Van Gorp, A., K. Van Der Vos, A. Brenkman, A. Bremer, N. Van Den Broek, F. Zwartkruis, J. Hershey, B. Burgering, C. Calkhoven and P. Coffer (2009). "AGC kinases regulate phosphorylation and activation of eukaryotic translation initiation factor 4B." Oncogene **28**(1): 95-106.
Vattem, K. M. and R. C. Wek (2004). "Reinitiation involving upstream ORFs regulates ATF4 mRNA translation in mammalian cells." Proceedings of the National Academy of Sciences **101**(31): 11269-11274.
Velásquez, C., E. Cheng, M. Shuda, P. J. Lee-Oesterreich, L. P. von Strandmann, M. A. Gritsenko, J. M. Jacobs, P. S. Moore and Y. Chang (2016). "Mitotic protein kinase CDK1 phosphorylation of mRNA translation regulator 4E-BP1 Ser83 may contribute to cell transformation." Proceedings of the National Academy of Sciences **113**(30): 8466-8471.
Vogel, C., R. de Sousa Abreu, D. Ko, S. Y. Le, B. A. Shapiro, S. C. Burns, D. Sandhu, D. R. Boutz, E. M. Marcotte and L. O. Penalva (2010). "Sequence signatures and mRNA concentration can explain two ‐ thirds of protein abundance variation in a human cell line." Molecular systems biology **6**(1): 400.
von Moeller, H., R. Lerner, A. Ricciardi, C. Basquin, W. F. Marzluff and E. Conti (2013). "Structural and biochemical studies of SLIP1–SLBP identify DBP5 and eIF3g as SLIP1-binding proteins." Nucleic acids research **41**(16): 7960-7971.
Vu, L. P., B. F. Pickering, Y. Cheng, S. Zaccara, D. Nguyen, G. Minuesa, T. Chou, A. Chow, Y. Saletore and M. MacKay (2017). "The N 6-methyladenosine (m 6 A)-forming enzyme METTL3 controls myeloid differentiation of normal hematopoietic and leukemia cells." Nature medicine **23**(11): 1369.
Wang, J., L. Wang, S. Zhang, J. Fan, H. Yang, Q. Li and C. Guo (2020). "Novel eIF4E/eIF4G protein-protein interaction inhibitors DDH-1 exhibits anti-cancer activity in vivo and in vitro." International Journal of Biological Macromolecules.
Wang, R.-X., X.-E. Xu, L. Huang, S. Chen and Z.-M. Shao (2019). "eEF2 kinase mediated autophagy as a potential therapeutic target for paclitaxel-resistant triple-negative breast cancer." Annals of translational medicine **7**(23).
Wang, S., I. B. Rosenwald, M. J. Hutzler, G. A. Pihan, L. Savas, J.-J. Chen and B. A. Woda (1999). "Expression of the eukaryotic translation initiation factors 4E and 2α in non-Hodgkin's lymphomas." The American journal of pathology **155**(1): 247-255.
Wang, X., W. Li, J.-L. Parra, A. Beugnet and C. G. Proud (2003). "The C terminus of initiation factor 4E-binding protein 1 contains multiple regulatory features that influence its function and phosphorylation." Molecular and cellular biology **23**(5): 1546-1557.
Wang, X., W. Li, M. Williams, N. Terada, D. R. Alessi and C. G. Proud (2001). "Regulation of elongation factor 2 kinase by p90RSK1 and p70 S6 kinase." The EMBO journal **20**(16): 4370-4379.

Wang, X., B. S. Zhao, I. A. Roundtree, Z. Lu, D. Han, H. Ma, X. Weng, K. Chen, H. Shi and C. He (2015). "N6-methyladenosine modulates messenger RNA translation efficiency." Cell **161**(6): 1388-1399.
Wang, Y., M. Begley, Q. Li, H.-T. Huang, A. Lako, M. J. Eck, N. S. Gray, T. J. Mitchison, L. C. Cantley and J. J. Zhao (2016). "Mitotic MELK-eIF4B signaling controls protein synthesis and tumor cell survival." Proceedings of the National Academy of Sciences **113**(35): 9810-9815.
Wang, Z., X. Feng, A. A. Molinolo, D. Martin, L. Vitale-Cross, N. Nohata, M. Ando, A. Wahba, P. Amornphimoltham and X. Wu (2019). "4E-BP1 is a tumor suppressor protein reactivated by mTOR inhibition in head and neck cancer." Cancer research **79**(7): 1438-1450.
Weber, R., M. Y. Chung, C. Keskeny, U. Zinnall, M. Landthaler, E. Valkov, E. Izaurralde and C. Igreja (2020). "4EHP and GIGYF1/2 Mediate Translation-Coupled Messenger RNA Decay." Cell Rep **33**(2): 108262.
Wei, J., J. Cao, D. Zhang, B. Liao, W. Zhong, J. Lu, H. Zhao, J. Zhang, Z. Tong and S. Fan (2014). "EIF5A2 predicts outcome in localised invasive bladder cancer and promotes bladder cancer cell aggressiveness in vitro and in vivo." British journal of cancer **110**(7): 1767-1777.
Weingarten-Gabbay, S., S. Elias-Kirma, R. Nir, A. A. Gritsenko, N. Stern-Ginossar, Z. Yakhini, A. Weinberger and E. Segal (2016). "Systematic discovery of cap-independent translation sequences in human and viral genomes." Science **351**(6270).
Weixlbaumer, A., H. Jin, C. Neubauer, R. M. Voorhees, S. Petry, A. C. Kelley and V. Ramakrishnan (2008). "Insights into translational termination from the structure of RF2 bound to the ribosome." Science **322**(5903): 953-956.
Wek, R. C. (2018). "Role of eIF2α kinases in translational control and adaptation to cellular stress." Cold Spring Harbor perspectives in biology **10**(7): a032870.
Wells, S. E., P. E. Hillner, R. D. Vale and A. B. Sachs (1998). "Circularization of mRNA by eukaryotic translation initiation factors." Molecular cell **2**(1): 135-140.
Wendel, H.-G., R. L. Silva, A. Malina, J. R. Mills, H. Zhu, T. Ueda, R. Watanabe-Fukunaga, R. Fukunaga, J. Teruya-Feldstein and J. Pelletier (2007). "Dissecting eIF4E action in tumorigenesis." Genes & development **21**(24): 3232-3237.
Wolf, D. A., Y. Lin, H. Duan and Y. Cheng (2020). "eIF-Three to Tango: emerging functions of translation initiation factor eIF3 in protein synthesis and disease." Journal of molecular cell biology **12**(6): 403-409.
Wolfe, A. L., K. Singh, Y. Zhong, P. Drewe, V. K. Rajasekhar, V. R. Sanghvi, K. J. Mavrakis, M. Jiang, J. E. Roderick and J. Van der Meulen (2014). "RNA G-quadruplexes cause eIF4A-dependent oncogene translation in cancer." Nature **513**(7516): 65-70.
Woo, S.-Y., D.-H. Kim, C.-B. Jun, Y.-M. Kim, E. Vander Haar, S.-i. Lee, J. W. Hegg, S. Bandhakavi, T. J. Griffin and D.-H. Kim (2007). "PRR5, a novel component of mTOR complex 2, regulates platelet-derived growth factor receptor β expression and signaling." Journal of Biological Chemistry **282**(35): 25604-25612.
Wu, C. C., A. Peterson, B. Zinshteyn, S. Regot and R. Green (2020). "Ribosome Collisions Trigger General Stress Responses to Regulate Cell Fate." Cell **182**(2): 404-416.e414.
Wu, H., H. Zhu, D. X. Liu, T.-K. Niu, X. Ren, R. Patel, W. N. Hait and J.-M. Yang (2009). "Silencing of elongation factor-2 kinase potentiates the effect of 2-deoxy-D-glucose against human glioma cells through blunting of autophagy." Cancer research **69**(6): 2453-2460.
Wu, Y., J. Xie, J. Xin, R. V. Lenchine, X. Wang, D. Fang, Z. D. Nassar, L. Butler, J. Li and C. G. Proud (2020). "eEF2K enhances expression of PD-L1 by promoting the translation of its mRNA." Biochemical Journal.
Xia, S., J. Feng, K. Chen, Y. Ma, J. Gong, F. Cai, Y. Jin, Y. Gao, L. Xia and H. Chang (2018). "CSCD: a database for cancer-specific circular RNAs." Nucleic acids research **46**(D1): D925-D929.

Xie, C., L. Huang, S. Xie, D. Xie, G. Zhang, P. Wang, L. Peng and Z. Gao (2013). "LARP1 predict the prognosis for early-stage and AFP-normal hepatocellular carcinoma." Journal of translational medicine **11**(1): 272.
Xie, J., K. Shen, R. V. Lenchine, L. A. Gethings, P. J. Trim, M. F. Snel, Y. Zhou, J. W. Kenney, M. Kamei and M. Kochetkova (2018). "Eukaryotic elongation factor 2 kinase upregulates the expression of proteins implicated in cell migration and cancer cell metastasis." International journal of cancer **142**(9): 1865-1877.
Xin, H., C. Zhong, E. Nudleman and N. Ferrara (2016). "Evidence for Pro-angiogenic Functions of VEGF-Ax." Cell **167**(1): 275-284.e276.
Xu, Y., M. Poggio, H. Y. Jin, Z. Shi, C. M. Forester, Y. Wang, C. R. Stumpf, L. Xue, E. Devericks and L. So (2019). "Translation control of the immune checkpoint in cancer and its therapeutic targeting." Nature medicine **25**(2): 301-311.
Xu, Z., J. Xu, H. Lu, B. Lin, S. Cai, J. Guo, F. Zang and R. Chen (2017). "LARP1 is regulated by the XIST/miR-374a axis and functions as an oncogene in non-small cell lung carcinoma." Oncology Reports **38**(6): 3659-3667.
Yamasaki, S., P. Ivanov, G.-f. Hu and P. Anderson (2009). "Angiogenin cleaves tRNA and promotes stress-induced translational repression." Journal of Cell Biology **185**(1): 35-42.
Yanagiya, A., E. Suyama, H. Adachi, Y. V. Svitkin, P. Aza-Blanc, H. Imataka, S. Mikami, Y. Martineau, A. R. Ze'ev and N. Sonenberg (2012). "Translational homeostasis via the mRNA cap-binding protein, eIF4E." Molecular cell **46**(6): 847-858.
Yang, G.-F., D. Xie, J.-H. Liu, J.-H. Luo, L.-J. Li, W.-F. Hua, H.-M. Wu, H.-F. Kung, Y.-X. Zeng and X.-Y. Guan (2009). "Expression and amplification of eIF-5A2 in human epithelial ovarian tumors and overexpression of EIF-5A2 is a new independent predictor of outcome in patients with ovarian carcinoma." Gynecologic oncology **112**(2): 314-318.
Yang, H.-S., A. P. Jansen, A. A. Komar, X. Zheng, W. C. Merrick, S. Costes, S. J. Lockett, N. Sonenberg and N. H. Colburn (2003). "The transformation suppressor Pdcd4 is a novel eukaryotic translation initiation factor 4A binding protein that inhibits translation." Molecular and cellular biology **23**(1): 26-37.
Yang, L., M. O. Duff, B. R. Graveley, G. G. Carmichael and L.-L. Chen (2011). "Genomewide characterization of non-polyadenylated RNAs." Genome biology **12**(2): 1-14.
Yang, Y., X. Fan, M. Mao, X. Song, P. Wu, Y. Zhang, Y. Jin, Y. Yang, L.-L. Chen and Y. Wang (2017). "Extensive translation of circular RNAs driven by N 6-methyladenosine." Cell research **27**(5): 626-641.
Ye, L., S.-t. Lin, Y.-s. Mi, Y. Liu, Y. Ma, H.-m. Sun, Z.-h. Peng and J.-w. Fan (2016). "Overexpression of LARP1 predicts poor prognosis of colorectal cancer and is expected to be a potential therapeutic target." Tumor Biology **37**(11): 14585-14594.
Yoshizawa, A., J. Fukuoka, S. Shimizu, K. Shilo, T. J. Franks, S. M. Hewitt, T. Fujii, C. Cordon-Cardo, J. Jen and W. D. Travis (2010). "Overexpression of phospho-eIF4E is associated with survival through AKT pathway in non–small cell lung cancer." Clinical Cancer Research **16**(1): 240-248.
Young, D. J. and N. R. Guydosh (2019). "Hcr1/eIF3j Is a 60S Ribosomal Subunit Recycling Accessory Factor In Vivo." Cell Rep **28**(1): 39-50.e34.
Young, D. J., N. R. Guydosh, F. Zhang, A. G. Hinnebusch and R. Green (2015). "Rli1/ABCE1 Recycles Terminating Ribosomes and Controls Translation Reinitiation in 3'UTRs In Vivo." Cell **162**(4): 872-884.
Yueh, A. and R. J. Schneider (2000). "Translation by ribosome shunting on adenovirus and hsp70 mRNAs facilitated by complementarity to 18S rRNA." Genes & Development **14**(4): 414-421.

Zhan, Y., J. Guo, W. Yang, C. Goncalves, T. Rzymski, A. Dreas, E. Żyłkiewicz, M. Mikulski, K. Brzózka and A. Golas (2017). "MNK1/2 inhibition limits oncogenicity and metastasis of KIT-mutant melanoma." The Journal of clinical investigation **127**(11): 4179-4192.
Zhang, P., X.-B. Chen, B.-Q. Ding, H.-L. Liu and T. He (2018). "Down-regulation of ABCE1 inhibits temozolomide resistance in glioma through the PI3K/Akt/NF-κB signaling pathway." Bioscience Reports **38**(6).
Zhao, J., E. E. Lee, J. Kim, R. Yang, B. Chamseddin, C. Ni, E. Gusho, Y. Xie, C.-M. Chiang and M. Buszczak (2019). "Transforming activity of an oncoprotein-encoding circular RNA from human papillomavirus." Nature communications **10**(1): 1-12.
Zheng, M., Y.-H. Wang, X.-N. Wu, S.-Q. Wu, B.-J. Lu, M.-Q. Dong, H. Zhang, P. Sun, S.-C. Lin and K.-L. Guan (2011). "Inactivation of Rheb by PRAK-mediated phosphorylation is essential for energy-depletion-induced suppression of mTORC1." Nature cell biology **13**(3): 263-272.
Zhou, C., B. Molinie, K. Daneshvar, J. V. Pondick, J. Wang, N. Van Wittenberghe, Y. Xing, C. C. Giallourakis and A. C. Mullen (2017). "Genome-wide maps of m6A circRNAs identify widespread and cell-type-specific methylation patterns that are distinct from mRNAs." Cell reports **20**(9): 2262-2276.
Zhou, H. Y. and A. S. Wong (2006). "Activation of p70S6K induces expression of matrix metalloproteinase 9 associated with hepatocyte growth factor-mediated invasion in human ovarian cancer cells." Endocrinology **147**(5): 2557-2566.
Zhou, J., J. Wan, X. Gao, X. Zhang, S. R. Jaffrey and S.-B. Qian (2015). "Dynamic m 6 A mRNA methylation directs translational control of heat shock response." Nature **526**(7574): 591-594.
Zhou, J., J. Wan, X. E. Shu, Y. Mao, X.-M. Liu, X. Yuan, X. Zhang, M. E. Hess, J. C. Brüning and S.-B. Qian (2018). "N6-methyladenosine guides mRNA alternative translation during integrated stress response." Molecular cell **69**(4): 636-647. e637.
Zhouravleva, G., L. Frolova, X. Le Goff, R. Le Guellec, S. Inge‐Vechtomov, L. Kisselev and M. Philippe (1995). "Termination of translation in eukaryotes is governed by two interacting polypeptide chain release factors, eRF1 and eRF3." The EMBO journal **14**(16): 4065-4072.
Zhu, X., H. Zhang and J. T. Mendell (2020). "Ribosome Recycling by ABCE1 Links Lysosomal Function and Iron Homeostasis to 3' UTR-Directed Regulation and Nonsense-Mediated Decay." Cell Rep **32**(2): 107895.
Zinzalla, V., D. Stracka, W. Oppliger and M. N. Hall (2011). "Activation of mTORC2 by association with the ribosome." Cell **144**(5): 757-768.
Zoppoli, G., M. Regairaz, E. Leo, W. C. Reinhold, S. Varma, A. Ballestrero, J. H. Doroshow and Y. Pommier (2012). "Putative DNA/RNA helicase Schlafen-11 (SLFN11) sensitizes cancer cells to DNA-damaging agents." Proceedings of the National Academy of Sciences **109**(37): 15030-15035.
Zuberek, J., D. Kubacka, A. Jablonowska, J. Jemielity, J. Stepinski, N. Sonenberg and E. Darzynkiewicz (2007). "Weak binding affinity of human 4EHP for mRNA cap analogs." Rna **13**(5): 691-697.