



# Translational control in brain pathologies: biological significance and therapeutic opportunities

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## Abstract

Messenger RNA (mRNA) translation is the terminal step in protein synthesis, providing a crucial regulatory checkpoint for this process. Translational control allows specific cell types to respond to rapid changes in the microenvironment or to serve specific functions. For example, neurons use mRNA transport to achieve local protein synthesis at significant distances from the nucleus, the site of RNA transcription. Altered expression or functions of the various components of the translational machinery have been linked to several pathologies in the central nervous system. In this review, we provide a brief overview of the basic principles of mRNA translation, and discuss alterations of this process relevant to CNS disease conditions, with a focus on brain tumors and chronic neurological conditions. Finally, synthesizing this knowledge, we discuss the opportunities to exploit the biology of altered mRNA translation for novel therapies in brain disorders, as well as how studying these alterations can shed new light on disease mechanisms.

**Keywords** mRNA translation · RNA-binding proteins · Neurodegenerative diseases · Brain tumors · eEF2 kinase · Translation control

## Introduction

Francis Crick, a pioneer in molecular biology, had the fortuitous intuition that RNA molecules worked as “adaptors” in the transfer of genetic information from DNA to amino acids (Crick 1957, On protein synthesis). Subsequent work would confirm this notion, and led to the unraveling of details into the structure, function, and regulation of the translation machinery [76]. In light of recent advances, alterations in mRNA translation are increasingly recognized in human pathogenesis. Indeed, it is estimated that translation control determines ~ 50% of protein levels, making this process a far better predictor of protein levels than mRNA expression [156]. Although informative publications discuss various aspects of mRNA translation in synaptic function and brain diseases, a comprehensive review focusing on the role of mRNA translation control in central nervous system disorders is currently lacking. Although biologically very different diseases, and typically studied by distinct research communities, neurodegenerative disorders and brain tumors are both characterized by alterations of the translational machinery. As discussed in detail below, such alterations are typically disease specific, but we believe that a better understanding of translational modifications in different diseases

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will have cross-cutting benefits to the research community. With this as the underlying theme, this review outlines major findings regarding translation control across different brain pathologies and discusses their therapeutic implications.

## An overview of mRNA translation and its regulatory mechanisms

Protein synthesis is regulated at multiple steps, including transcription (amounts of mRNA generated) and translation (efficiency of mRNA translation), in addition to protein stability and posttranslational modifications. Given the relatively long half-life (> 6 h) of mRNAs in mammalian cells [156], translation control is extremely relevant particularly when cells face the need to quickly respond to rapid micro-environmental changes via new protein synthesis [168]. In addition, translational control is exploited by specific cell types, such as neurons, to achieve timely and spatially heterogeneous protein synthesis.

Traditionally, studies into the regulation of eukaryotic translation have focused primarily at the initiation step, as mediated by reactions involving the ribosomal subunits, eukaryotic initiation factors (eIFs) such as eIF3 and eIF4F (comprising the cap-binding complex), and engagement of the start codon [165]. Emerging evidence suggests that subsequent reactions during nascent polypeptide elongation also act as critical regulatory steps, with important implications for adaptation to cell stress and neurological diseases [39, 62]. A detailed overview of the translation machinery and its regulation is beyond the scope of this work, and the reader is referred to notable reviews published elsewhere [73, 84]. Briefly, three consecutive steps, each comprising multiple molecular interactions and reactions, constitute mRNA translation, namely (1) initiation, (2) elongation, and (3) termination.

### Translation initiation and its canonical regulation

A crucial first step in translation initiation is the formation of the *ternary complex* between a methionyl transfer RNA (Met-tRNA<sub>i</sub>), encoding the first amino acid, Met, and the GTP bound eIF2 (eIF2-GTP, Fig. 1a). Once formed, the ternary complex binds to eIF1A and the 40S ribosomal subunit in complex with eIF3, constituting the so-called 43S *pre-initiation complex* (PIC; Fig. 1b). At the same time, the 5' cap of an mRNA to be translated is bound by members of the eIF4F complex (Fig. 1b), constituted by the DEAD-box RNA helicase eIF4A, the cap-binding protein eIF4E, and the scaffold protein, eIF4G. As a result, eIF4F bound to the target message associates with the preinitiation complex, forming the *initiation complex* (Fig. 1c). The initiation complex then scans the bound mRNA 5' untranslated region

(5'-UTR) until the initial AUG start codon is recognized, followed by recruitment of the 60S ribosomal subunit, allowing Met-tRNA<sub>i</sub> engagement with the start codon to initiate translation. This, coupled with the hydrolysis of eIF5-bound GTP to GDP, constitutes an irreversible step, such that ribosomal subunits will not dissociate until protein synthesis is complete (Fig. 1d).

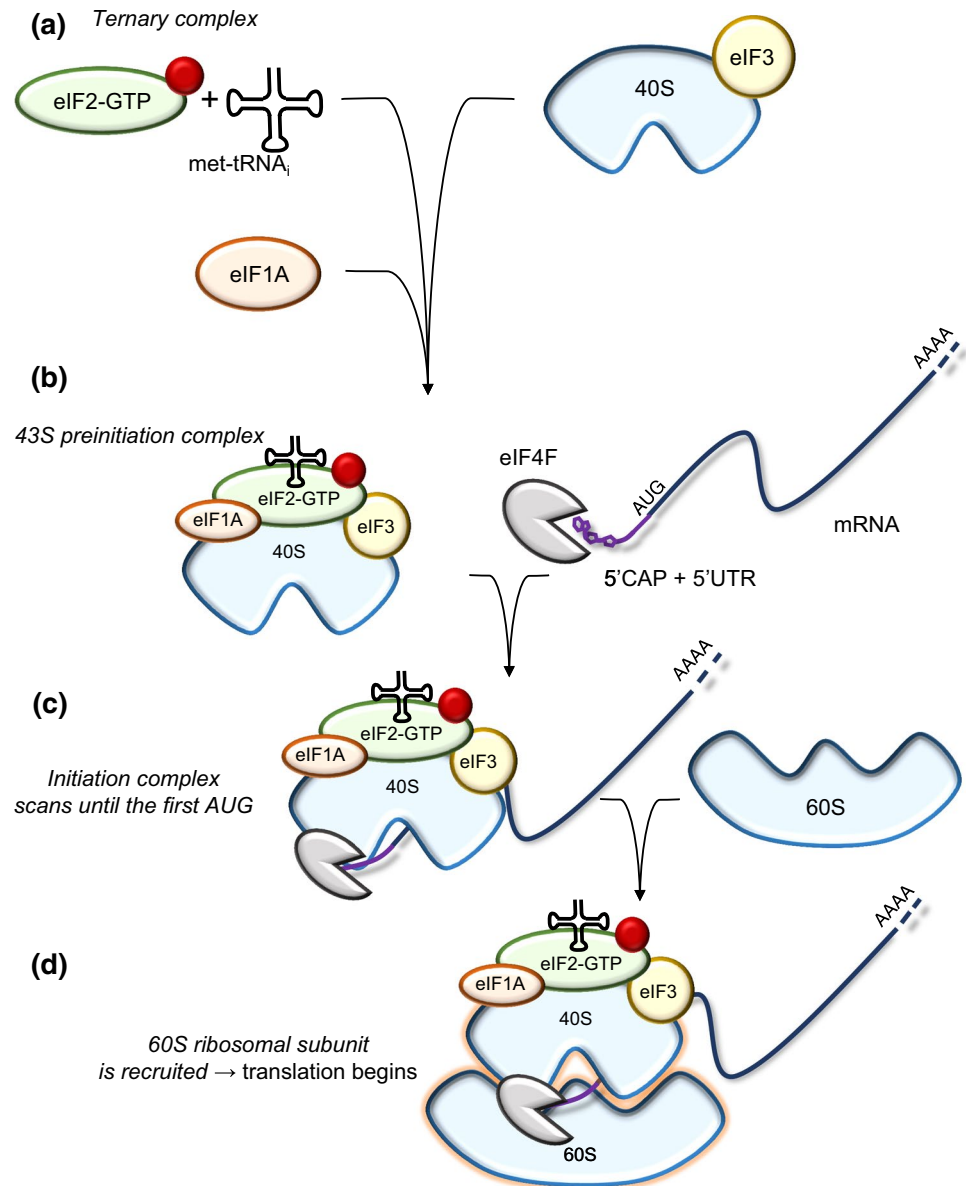
Several highly conserved mechanisms regulating translation initiation have been well documented, such as phosphorylation of the  $\alpha$  subunit of the heterotrimeric eIF2 complex at Ser51. This increases affinity of the eIF2 complex for the guanine exchange factor eIF2B, limiting the conversion of inactive eIF2-GDP to active eIF2-GTP and inhibiting global translation [129]. Four stress activated kinases are known to phosphorylate eIF2 $\alpha$  as part of the so-called integrated stress response (ISR), to limit protein synthesis under stress: PKR [protein kinase R, activated in response to double-stranded (ds)RNA], HRI (heme-regulated inhibitor, in response to oxidative stress), GCN2 (general control nonderepressible 2, in response to amino acid deprivation), and PERK (PRKR-like endoplasmic reticulum kinase, in response to ER stress) [129]. Although eIF2 $\alpha$  phosphorylation inhibits global translation, a subset of mRNAs containing upstream open-reading frames (uORFs) within their 5'-UTR remains preferentially translated under stress [74] (described further below).

Another critical regulator of translation initiation and protein synthesis is the serine/threonine kinase mammalian target of rapamycin complex 1 (mTORC1), a well-known nutrient/energy sensor. Under nutrient replete conditions, mTORC1 is activated and phosphorylates the eIF4E-binding proteins, 4E-BP1/2, thereby releasing them from eIF4E to promote eIF4E binding to the cap, leading to enhanced cap-dependent translation [165]. In contrast, under nutrient deprivation and certain other stresses, mTORC1 is inactivated and 4E-BPs remain hypophosphorylated, allowing them to sequester eIF4E to limit translation initiation [165].

Recruitment and translation efficiency of a given mRNA is also determined by distinct structures within the 5'-UTR, such as complex stem-loops, 5' terminal oligopyrimidine (5' TOP) motifs, and uORFs. These mechanisms have been reviewed in detail elsewhere [74] and are beyond the scope of the current review. It is also well known that a subset of eukaryotic mRNAs can be translated in a 5' cap-independent manner (Fig. 2), in part through sequences called internal ribosome entry sites (IRESs) that directly bind translation factors called IRES trans-acting factors (ITAFs, [101, 106]).

RNA modifications are also emerging as potentially major regulators of translation initiation. The m<sup>6</sup>A (6-methyladenosine) modification of mRNA is the best-studied eukaryotic post-transcriptional mRNA modification. In eukaryotes, this modification is dependent on the METTL3 enzyme, whereas the FTO demethylase is a key enzyme

**Fig. 1** Different stages of cap-dependent translation initiation. **a** eIF2-GTP and met-tRNA<sub>i</sub> (the *ternary complex*) bind to eIF1A and to the 40S ribosomal subunit complexed with eIF3, constituting the *43S preinitiation complex* (**b**). **c** The eIF4F complex, bound to the 5' cap of the mRNA to be translated, associates with the preinitiation complex, forming the *initiation complex*. **d** The initiation complex then scans the bound mRNA until the first AUG start codon is recognized. The subsequent recruitment of the large 80S ribosomal subunit, coupled with the hydrolysis of the eIF5 bound GTP to GDP, results in mRNA translation



for mRNA demethylation [87]. While the biological functions of m<sup>6</sup>A are incomplete, recent studies have implicated m<sup>6</sup>A-modified mRNAs (see also below) in cap-independent translation, through direct binding of translation initiation factors, such as eIF3 subunits [124].

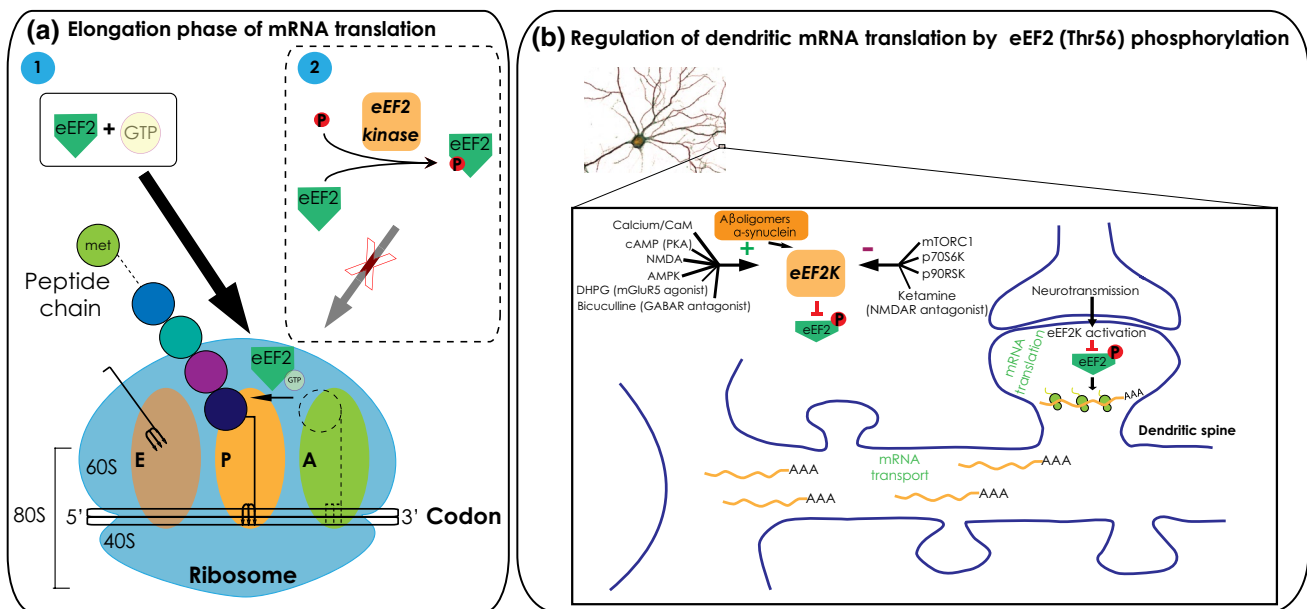
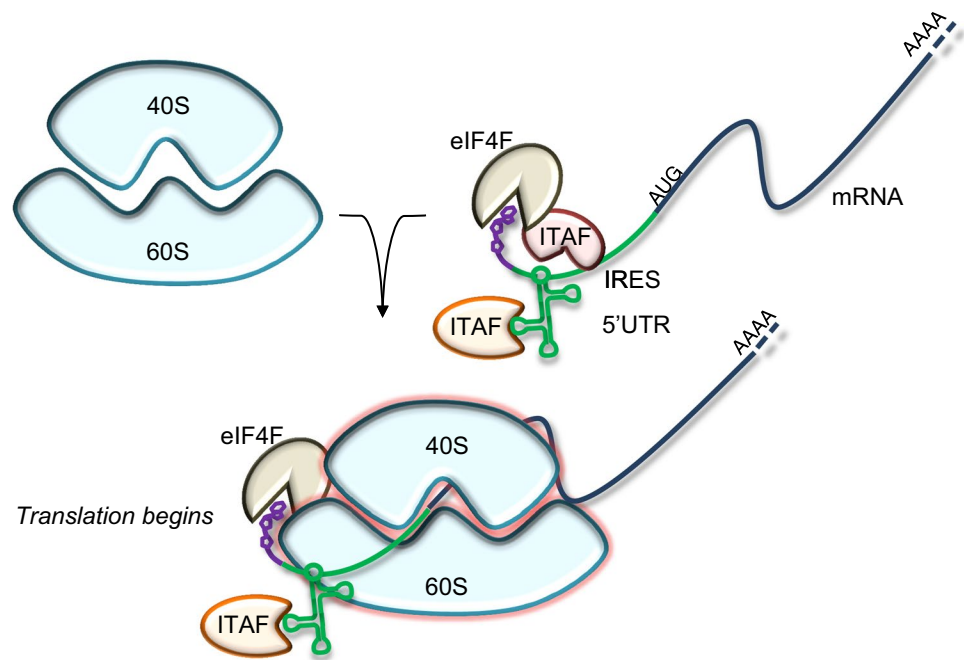
### Translation elongation and its regulation

Following initiation, peptide chain extension occurs in a process known as translation elongation. This process is relatively simple compared to initiation, and mainly mediated by eukaryotic elongation factors 1 and 2 (eEF1 and eEF2). Briefly, once the Met-tRNA has been delivered to the P site of the ribosome, the next aminoacyl-tRNA bound to eEF1-GTP comes to the A site. GTP hydrolysis leads to

a conformational change in the ribosome, and Met forms a peptide bond to aminoacyl-tRNA in the P site. Ribosome translocation to the next codon is regulated by the hydrolysis of GTP bound to eEF2 (Fig. 3a). This cycle of events repeats as the ribosome moves along the mRNA being translated, and the nascent polypeptide chain elongates. Translation terminates when a stop codon (UAA, UGA, or UAG) enters the ribosome and is recognized by release factors such as eRF1 [43], in a step called translation termination. Subsequent reactions result in separation of the polypeptide chain from the tRNA and protein release.

Elongation is traditionally under-appreciated in translational control, compared to the control of initiation. However, emerging evidence highlights an important regulatory role for control of ribosome transit (elongation) [39, 62,

**Fig. 2** Cap-independent translation initiation. A subset of eukaryotic mRNAs can be translated in a 5' cap-independent way, due to sequences called internal ribosome entry sites (IRESs) that facilitate direct binding of translation initiation factors called IRES-transacting factors (ITAFs)



**Fig. 3** eEF2 kinase controls the elongation phase of mRNA translation by phosphorylating eEF2 on Thr56. **a** During translation elongation, aminoacyl-tRNA located on the A site (aminoacyl or acceptor site) forms a peptide bond with the peptidyl-tRNA occupying the P site (peptidyl or polypeptide site), resulting in the attachment of the growing peptide chain to the tRNA in the A site. Then, GTP bound eEF2 mediates translocation of peptidyl-tRNA from the A site (dashed cartoon) to the P site (solid cartoon), and the now deacylated-tRNA leaves the ribosome on E site (exit site). The grow-

ing peptide chain is depicted as beads on a string with methionine (met) as the first amino acid in the chain. eEF2K phosphorylates and inactivates eEF2, preventing its binding to the ribosome. **b** Phosphorylation of eEF2 Thr56 in neurons, reflecting neuronal eEF2K activity is increased in response to several stimuli. Negative regulators of eEF2 phosphorylation (Thr-56)/eEF2K activity include mTORC1, p70RS6K, and p90RSK. We reported that human amyloid- $\beta$  ( $A\beta$ ) or alpha-synuclein also increase eEF2 Thr56 phosphorylation, suggesting increased eEF2K activation [85, 86]

83, 109]. Eukaryotic translation elongation is mainly regulated by eukaryotic elongation factor 2 kinase (eEF2K, also

known as calcium/calmodulin-dependent kinase III, CamKIII) [96], a crucial molecule linking the energy sensors

AMP-Activated Protein Kinase (AMPK) and mTORC1 to translation. Activation of the AMPK–eEF2K pathway slows polypeptide chain elongation, as eEF2K inactivates eEF2 by phosphorylation of its Thr56 residue (Fig. 3a) [152]. AMPK is a master cellular energy sensor, as increased AMP:ATP ratios lead to AMPK activation [61]. In addition, three upstream kinases, LKB1 (liver kinase B1), CaMKK $\beta$  (Ca<sup>2+</sup>/calmodulin-dependent kinase kinase  $\beta$ ), and TAK1 (transforming growth factor  $\beta$ -activated kinase 1), activate AMPK to fine tune AMPK–eEF2K activity [97]. Activated AMPK suppresses energy consuming processes (e.g., protein and fatty acid synthesis) and promotes energy production via glycolysis, lipid metabolism, and increased glucose uptake [20]. Regulation of eEF2K is also mediated by calmodulin binding in response to changes in cellular calcium levels and positive regulation by autophosphorylation [17]. Finally, recent work suggests a tight interplay between initiation and elongation control, as activated mTORC1 blocks eEF2K via S6 kinase (S6K) mediated eEF2K inhibitory phosphorylation, thus enhancing elongation rates during anabolic growth [48]. In addition, ribosome stalling during translation promotes eIF2 $\alpha$  phosphorylation to inhibit translation initiation [82]. While a recent review has extensively summarized the role of mTORC–AMPK signalling in brain [52], mechanisms of translation elongation control unique to neuronal cells are discussed in “[Translational control in normal brain function](#)”.

### Translational control through RNA granules

In addition to control of initiation and elongation, eukaryotic cells have evolved other sophisticated mechanisms to regulate translation. An important example is the formation RNA granules, including stress granules (SGs) and processing bodies (P-bodies) in somatic cells, neuronal granules in neurons, and germinal granules in germ cells [2]. Due to their relevance to neuronal function and CNS pathology, this review will mainly focus on SGs (discussed below) and neuronal granules (discussed in “[Translational control in normal brain function](#)”).

Diverse cellular stresses such as heat shock, oxidative stress, hypoxia, nutrient deprivation, or viral infections lead to a rapid translational inhibition and disassembly of translationally active polysomes [168]. Under these conditions, translationally stalled complexes consisting of the 40S ribosome, silenced polyadenylated mRNAs, translation initiation factors, and distinct RNA-binding proteins (RBPs) aggregate into membrane-less organelles called SGs [2]. Previous studies indicate that eIF2 $\alpha$  phosphorylation is necessary for SG formation [93], suggesting that, along with the above-mentioned ISR, SG formation might contribute to stress-induced global translation inhibition. However, other studies have brought this notion into dispute. First, SGs are reported to

form in the absence of eIF2 $\alpha$  phosphorylation [123]. Second, a detailed analysis of SG-associated mRNAs suggests that only ~10% of cellular mRNAs reside in SGs under stress [98]. In addition, no specific functional mRNA classes are significantly over- or under-represented in SGs, and the only consistent features of these mRNAs are longer lengths and higher translational inefficiency scores [98]. This calls into question whether SGs actually function to reduce global translation. Additional functional studies are necessary to uncover the role of these perplexing structures in translation regulation.

### Translational control in normal brain function

Neurons are morphologically unique, highly polarized cells, with the ability to integrate excitatory and inhibitory stimuli from hundreds to thousands of synaptic inputs. Changes in protein synthesis necessary for synaptic activity must occur very rapidly, which is biologically challenging for neurons, given the distance (in the range of hundreds of micrometers or even millimeters) between cell body and axonal or dendritic terminals. Although de novo protein synthesis in neuronal cell bodies is important, emerging evidence suggests that hundreds of mRNAs are localized at synaptic terminals [23, 198], and that local translation at the dendritic terminal is key to synaptic functions. Furthermore, localized mRNA translation appears critical for processes such as synaptic development, synaptic plasticity, and memory formation [19, 33, 166].

The strengthening of a synapse, a process also called long-term potentiation (LTP), and the long-lasting decrease in synaptic strength, long-term depression (LTD), are thought to be key mechanisms mediating a number of critical brain functions, including learning and memory formation [30, 135]. Strong evidence supporting a role for localized mRNA translation at the dendritic terminal relies on seminal neurobiology work, indicating that LTP and LTD occur even when the neuronal body is physically disconnected from the synapse [80, 91].

### Translation initiation control

Translation initiation control by the above-mentioned eIF2 $\alpha$  pathway, acting as a negative regulator, is critical for memory function. Indeed, genetically engineered mice deficient in eIF2 $\alpha$  phosphorylation (+/S51A) display increased memory capacity [31]. In contrast, increased eIF2 $\alpha$  phosphorylation in mouse hippocampus reduces long-term memory [89]. Mechanistically, eIF2 $\alpha$ -mediated translational control appears to inhibit the progression from transient to persistent LTP [142] and to induce LTD [45], both phenomena

requiring de novo protein synthesis. Thus, it is likely that these processes are mediated by eIF2 $\alpha$ -induced decreases in translation of a subset of mRNAs, a few of which (e.g., oligophrenin-1) have been identified [45].

The highly conserved mTOR enzyme is ubiquitously expressed in neuronal cells, where its activity is also linked to synaptic function and cognition [107]. The activity of mTOR and its downstream targets is also critical for memory formation, as extensively reviewed [32]. This is supported by the finding that mTORC1 inhibition negatively impacts LTP and memory formation [169]. Hippocampal LTP induces the expression of eukaryotic elongation factor 1A (eEF1A), the mRNA of which contains a 5'TOP motif, within five minutes after stimulation [179]. This is preserved in dendrites disconnected from their cellular bodies, but is impaired by the mTOR inhibitor rapamycin, suggesting that the mTOR pathway controls the rapid synthesis of proteins during LTP formation at the dendritic terminals. However, these studies did not address whether changes in dendritic protein expression induced by rapamycin are required for LTP. The process of LTD also requires selective mRNA translation and localized dendritic protein synthesis, which appears to be mostly mediated by activation of the PI3K–Akt–mTOR pathway at dendritic terminals [197].

### Translation elongation control

Translation control at the level of elongation is also critical for synaptic plasticity. In addition to the regulation of elongation by the AMPK–eEF2K–eEF2 pathway under nutrient deprivation, ample evidence implicates additional mechanisms regulating neuronal eEF2K activation in response to synaptic activity (Fig. 3b) [69]. For instance, chemical stimulation of metabotropic glutamate receptors mGluR5 using (*S*)-3,5-dihydroxyphenylglycine (DHPG), depolarization by potassium chloride bath application, and treatment with the gamma-aminobutyric acid (GABA<sub>A</sub>) antagonist bicuculline increase eEF2K activity (i.e., p-eEF2 Thr56) in cultured neurons (Fig. 3b) [69, 97]. Instead, ketamine-mediated suppression of NMDA receptors (NMDAR) activity suppresses eEF2K and induces eEF2 dephosphorylation [128]. The significance of eEF2K activity and eEF2 phosphorylation in synaptic plasticity, such as LTP and LTD, has been reviewed elsewhere [69]. In brief, eEF2K mediates activity-dependent changes in dendritic mRNA translation, particularly postsynaptic changes in protein synthesis in response to acute or prolonged NMDAR and mGluR signaling [69]. Although eEF2K activation inhibits general mRNA translation in dendrites, some studies suggest that translation of messages encoding brain-derived neurotrophic factor (BDNF), activity-regulated cytoskeletal-associated protein (Arc), the alpha subunit of calcium/CaM-dependent kinase II (CaMKII), microtubule-associated protein

1B (MAP1B), and other microtubule-associated proteins is actually increased in response to eEF2K activation [95, 184]. In addition, translational control of Arc synthesis by the eEF2K–eEF2 axis is lost in Fragile X disease mice, suggesting an unexpected coordinated control of Arc translation by eEF2K and the Fragile X mental retardation protein FMRP [138]. These processes are linked to diverse forms of synaptic plasticity including recycling and internalization of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [69, 138]. Finally, eEF2K activation inhibits GABAergic synaptic transmission, thus interfering with the GABA<sub>A</sub> activation/inhibition balance and decreasing resistance to epileptic seizures [70].

### Translation control by neuronal RNA granules

Neuronal granules constitute the major contributors to the spatio-temporal regulation of mRNA translation and protein synthesis in neurons. Serving as motile macromolecular entities that translocate mRNA from the nucleus to synaptic terminals within neurons, neuronal granules are composed of mRNA, translation initiation factors, small and large ribosomal subunits, and RBPs [2, 102]. While neuronal granules are mostly considered to package and transport silenced mRNA, recent literature has suggested that some components of neuronal granules might also promote translation of subsets of mRNAs [191]. At the dendritic terminal, membrane depolarization leads to a redistribution of mRNAs from neuronal granules to actively translating polysomes [62, 102]. Accordingly, neuronal RNA granules appear to directly contribute to localized dendritic mRNA translation. Recent evidence also suggests that local translation of specific mRNAs, such as  $\beta$ -actin, might contribute to synaptic plasticity upon granule disassembly [21]. For additional discussion on translational control in memory and normal brain function, we refer the readers to recent review works [56, 166, 187].

### Translational control in brain tumors

Since the discovery that proliferating cells rely on increased translation rates for enhanced protein synthesis, it has become clear that mRNA translation plays a critical role in cell transformation and tumor progression [177]. However, translation control in cancer has been historically overlooked in favor of the other steps regulating protein expression, such as control of transcription. A growing body of literature indicates that transcript abundance does not predict protein level for a wide variety of genes in different tumors [193], including brain cancer [49, 149]. For comprehensive reviews on translation control in cancer, we refer the reader to other specific work [178]. In the present review, we will

focus exclusively on work that has shed light on translational control in brain tumors. The two most common and most aggressive primary brain tumors, which have been extensively dissected through genomics, epigenomics, and transcriptomic studies over the last decade, are glioblastoma (GBM, [189]) and, in childhood populations, medulloblastoma (MB, [175]). While the most important alterations of mRNA translation in brain tumors are discussed below, a summary is also presented in Table 1.

### Translation initiation control

A limited number of studies of the translational state of brain tumors have been reported, and largely in the context of GBM. To investigate in vivo translation regulation in brain tumors, Helmy et al. applied a method of ribosome-bound mRNA immunoprecipitation followed by deep sequencing to a genetically engineered glioma mouse model [72]. By comparing ribosome-bound mRNA to total mRNA levels, the authors measured the translation efficiency of single mRNAs in vivo. They found that >60% of all genes were differentially represented in the ribosome-bound and non-bound mRNA sets, suggesting a high degree of protein biosynthesis regulation at the level of translation. Compared to non-neoplastic cells, the most efficiently translated genes belonged to the broad class of cell division and biosynthetic pathways. In addition, deletion of Phosphatase and Tensin

homolog (PTEN, mutated or deleted in 36% of GBM, [24]) was found to translationally downregulate a set of genes involved in cellular respiration, consistently with the switch towards anaerobic glycolysis observed in PTEN-deleted tumors [13]. Combining a RiboTag system with ribosome profiling, Gonzalez et al. measured genome-wide ribosomal mRNA occupancy and translation rates in an in vivo glioma model [60]. They found that translation efficiency is highly cell-dependent, with remarkable differences between tumor and non-tumor cells. As opposed to non-transformed cells, there were high ribosome densities at the 5'-UTRs of mRNAs in glioma cells, suggesting that these cells have higher translation rates for the existing mRNAs. Among the genes highly translated in tumor cells, many were associated with cell motility, cell adhesion, and regulation of angiogenesis. These studies highlight translational control as an important phenomenon which should not be overlooked in the study of brain cancer.

The PI3K-Akt pathway is frequently hyperactive in GBM [189]. Oncogenic transformation in mouse derived GBM cells by Ras and activation of Akt signaling was shown to increase the translation of existing mRNAs, rather than altering transcript expression [144]. In particular, pharmacological inhibition of Akt leads to a decrease in the polysome-bound mRNA fraction, as opposed to the levels of total mRNA, of several target genes. Some of these genes, such as ATM (Ataxia-Telangectasia Mutated), Miz1, VEGF, and

**Table 1** mRNA translation alterations in brain tumors

Tumor	Subtype/pathway	mRNA translation alteration	Evidence	References
Glioma	<i>PTEN</i> mutant	Decreased translation of mRNAs involved in cellular respiration	Mouse model	[72]
	PDGF-B, Trp53 <sup>flox/flox</sup>	Increased translation of mRNAs involved in cell motility, cell adhesion, and regulation of angiogenesis	Mouse model	[60]
	Active Kras	Increased global mRNA translation, including ATM, Miz1, VEGF, Notch1	Mouse derived glioma cells	[144]
	High AKT activity	Decreased IRES-dependent translation of cyclin D1 and c-Myc	Cell line	[159]
	IDH1/2 mutant	Increased mTOR signalling and cap-dependent translation	Cell line	[25]
	–	Increased c-Jun IRES translation	Primary tumors and cell lines	[12]
	–	Increased eEF2K activity	Transcriptomic data sets	[109]
Medulloblastoma	Group 3	Decreased mTOR signaling	Transcriptomics, proteomics and phospho-proteomics on primary tumors	[49]
		Increased eEF2K activity	Transcriptomic data sets	[109]
		Increased eEF2K activity	Proteomics and phospho-proteomics on primary tumors	[5]
	SHH	Increased eEF2K activity	Mouse model	[109]
		Upregulation of translation elongation factors eEF2 and EEF1A2	Mouse model	[54]

This table summarizes the alterations of the canonical mRNA translation machinery that have been reported for the most studied brain tumors, medulloblastoma and glioblastoma

Notch1, are well known to be involved in GBM pathogenesis. The PI3K–Akt pathway is also known to stimulate cap-dependent protein synthesis, via activation of mTORC1, and to inhibit IRES-dependent translation. This effect is mediated by direct phosphorylation of the multifunctional RNA-binding heterogeneous nuclear ribonucleoprotein (hnRNP) A1 by Akt [121]. As a consequence, inhibition of mTORC1 by rapamycin in GBM is ineffective in inhibiting the translation of IRES mRNAs critical for cell cycle progression, such as Cyclin D1 and c-Myc [159]. However, co-targeting of IRES- and cap-dependent translation (i.e., by IRES-J007 and PP242, respectively) reduces tumor growth in a pre-clinical model of GBM [77]. IRES-dependent translation in GBM occurs also for c-Jun, a transcription factor that stimulates cell cycle progression [12], and accumulation of the c-Jun protein results from increased translatability of the transcript, rather than from upregulated mRNA levels. Additional links between GBM pathogenesis and translation control are suggested by the fact that isocitrate dehydrogenases 1 and 2 (IDH1/2) mutations, which are frequent in WHO grade 2 and 3 astrocytomas, oligodendrogliomas and secondary GBM [189], have been reported to modulate mTOR signaling [25]. Mechanistically, the oncometabolite R-2-hydroxyglutarate (2HG), produced by IDH1/2 gain of function mutations, inhibits the activity of the  $\alpha$ -ketoglutarate-dependent enzyme Lysine-specific demethylase 4A (KDM4A). This enzyme normally promotes the demethylation of di- and tri-methylated H3K9 and H3K36. Inhibition of KDM4A results in a drastic decrease in levels of DEPTOR, an mTOR inhibitor; this stimulates mTOR signalling, in turn, increasing cap-dependent translation rates and protein synthesis [25]. This suggests that the potential therapeutic benefit for mTOR inhibition specifically in IDH-mutant glioma should be examined. Collectively, these results underscore deregulation of mRNA translation in glioma as a critical component of the disease. Further mechanistic studies are required to fully elucidate how translation control contributes to the aggressive behavior of GBM, and how targeting of this process might result in effective therapeutic strategies.

### Translation elongation control

As discussed above, cellular stress reduces translation rates and protein synthesis [110]. The classic view is that acute cellular stress impairs the survival of normal cells, but adaptive mechanisms in cancer cells help them to survive in harsh milieus, such as under O<sub>2</sub> and nutrient deprivation. Our recent data support the notion that processes regulating elongation are altered in tumor cells, and that such adaptation confers a survival advantage. We reported that the AMPK–eEF2K–eEF2 axis is part of a highly conserved pathway hijacked by cancer cells to overcome nutrient deprivation [109], a stress form typical of the tumor

microenvironment. As stated earlier, under acute cellular stress, such as nutrient deprivation, phosphorylation of eEF2 (Thr56) by eEF2K reduces translation elongation rates and protein synthesis [152], a highly energy demanding cellular process. Indeed, mouse embryonic fibroblasts lacking eEF2K show lower polysome-associated mRNA levels under acute nutrient deprivation, suggesting that eEF2K stalls polyribosomes on mRNAs to help cells preserve energy and survive under nutrient deprivation. This mechanism seems particularly relevant for tumors driven by c-MYC or MYCN, such as pediatric MB and neuroblastoma, as transformation by these oncogenes renders cells hypersensitive to nutrient starvation [41, 42]. Indeed, in these tumors, as well as in GBM, eEF2K is upregulated, hyperactive, and linked to worse clinical outcome [42, 109]. Consistent with this, recent phospho-proteomic data reveal that in Group 3 MB, typically characterized by c-MYC overexpression, eEF2K is one of the most active kinases [5]. While detailed mechanistic studies are currently lacking, it is tempting to speculate that tight translation elongation control by eEF2K is critical for MYC-driven tumors, and that the effects of a loss of this process become phenotypically evident under conditions of cellular stress. Although the effects on translation were not examined, making it difficult to understand the significance, upregulation of translation elongation regulatory proteins such as eEF2 and eukaryotic translation elongation factor 1 $\alpha$  (EEF1A2) is also linked to oncogenic transformation in genetically engineered mouse models of MB [54]. Collectively, these observations suggest that, by altering the rate of translation elongation, the AMPK–eEF2K–eEF2 pathway is critical for the survival and growth of brain tumors [42, 109]. While the role of this pathway in inhibiting bulk translation is well established, it remains to be deciphered if the same pathway is used by cancer cells for preferential translation of mRNAs required for survival and adaptation in their microenvironment.

### Additional mechanisms of translation control

SG formation might influence tumor biology by altering the cellular translation landscape under stress, through silencing of SG-sequestered mRNA molecules [143]. In this context, a recent study reported increased SG formation in MB, leading to impaired global translation, due to frequent mutations of the DEAD-box RNA helicase DDX3X gene [54]. In addition, phospho-proteomics data suggest important differences in the activity of pathways regulating mRNA translation across distinct MB subgroups, including differential expression of RBPs, SG proteins, and mTOR pathway components [49]. While these results are preliminary, further mechanistic studies should help to further elucidate the role of SGs formation in brain tumors. A better understanding of how tumor cells exploit these mechanisms to survive and



progress in their microenvironment will likely uncover new therapeutic opportunities.

## Translational control in neurodevelopment and mental retardation disorders

Given the role of dendritic mRNA translation in synaptic function, it stands to reason that a number of neurological disorders result from altered mRNA translation. Fragile X syndrome is the most prominent monogenic cause of autism spectrum disorders and is probably the first neurological disease linked to alterations in translation [183]. Napoli et al. reported that FMRP, an RBP, inhibits translation initiation at the dendritic terminal through its binding partner, CYFIP1, which acts as a 4E-BP to block eIF4E activity [133]. An additional role for FMRP in this disease is suggested by the finding that mutations in the RNA-binding domain of FMRP impair its ability to bind to polyribosomes to alter translation elongation, underlying the Fragile X phenotype in mice and humans [192]. High-throughput sequencing of RNAs bound to FMRP revealed that FMRP reversibly stalls polyribosomes specifically on its target mRNAs, thus inhibiting their translation [39]. There was strong overlap between autism candidate genes, such as *NLGN3*, *NRXN1*, *SHANK3*, and FMRP target mRNAs, suggesting that loss of translation inhibition of specific mRNAs by FMRP in neurons may be the etiologic basis for the disease. It will be important to uncover whether these mechanisms are complementary or mutually exclusive, and what their exact functional significance is in Fragile X phenotype. Alterations of other components of the translation initiation machinery, such as hyperphosphorylation of eIF4E, also contribute to the pathogenesis of Fragile X syndrome [57]. In addition, knockout of eIF4E-binding protein 2 (4EBP2) induces autistic-like behavior in mice, due to increased translation of neuroligins, which have been previously linked to this disease [58]. As mentioned, recent studies have implicated m<sup>6</sup>A modifications in cap-independent translation [124], and loss-of-function mutations of the FTO gene are described as leading to growth delay and mental retardation [14]. Additional mechanisms of RNA-mediated neurotoxicity are beyond the scope of this article and have been extensively reviewed elsewhere [10].

Although mTOR activity is essential for synaptic plasticity, overactive mTOR signaling can also hamper synaptic function and cognition, as can be witnessed in tuberous sclerosis complex (TSC) disease [35]. This rare disorder is caused by mutations in tumor suppressors *TSC1* or *TSC2*, encoding hamartin and tuberin, respectively [37]. These proteins constitute a complex downstream of the PI3K-Akt pathway to stimulate the GTPase activity of the RAS family member RHEB (Ras Homolog Enriched in Brain), inducing

GTP hydrolysis and conversion of RHEB into its inactive GDP-bound form [81]. Active RHEB localizes at the lysosome and induces phosphorylation and activation of mTOR [65]. Therefore, hyperactive mTOR signaling induced by genetic mutations in either *TSC1* or *TSC2* likely represents a crucial pathogenic mechanism for neuronal dysfunction in the TSC syndrome.

## Translational control in neurodegenerative diseases

Neurodegenerative diseases represent a significant burden on the healthcare system. Alzheimer disease (AD) is the most common cause of dementia worldwide [78], while Parkinson disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington disease (HD) represent leading neurodegenerative causes of motor disability [46]. Given that mRNA translation and protein synthesis are vital in the maintenance of synaptic structure and function, it is not surprising that defects in translation control are increasingly linked to these diseases [92]. Accordingly, a number of reports have shown that aberrations of translation regulation, including ribosomal recruitment, ribosomal components, RBPs, and metabolic pathways are common in neurodegenerative diseases [113].

### Translation initiation control

As mentioned, eIF2 $\alpha$  phosphorylation inhibits protein synthesis and is cytoprotective under acute stress, as part of the ISR [137]. Several reports have shown that eIF2 $\alpha$  phosphorylation is elevated in AD and PD brains, pointing to persistent defects in protein synthesis and pathologically overactive stress responses in these diseases [117, 170]. Further evidence supporting defective mRNA translation in neurodegenerative diseases, possibly due to amyloidogenic protein aggregates, comes from studies on misfolded prion proteins [67, 130]. These works report that prion protein self-assembly induces translational repression through eIF2 $\alpha$  phosphorylation, and restoration of mRNA translation efficiency in mouse hippocampi rescues neuronal loss and symptoms. One of the proposed mechanisms of pathology involves chronic eIF2 $\alpha$  phosphorylation and consequent induction of SG formation, as discussed further below.

In regard to translation initiation control, mTOR and its downstream signaling targets have widely been studied in AD and PD pathology [1, 36, 136, 141], and in models of ALS [154] and HD [145]. These studies indicate that mTOR activity is increased in AD and PD brains, as reviewed elsewhere [36, 141]. In brief, phosphorylation of mTOR (Ser2481), 70S6K (Thr389 or Thr421/Ser424), eIF4E (Ser209), and 4EBP1/2 (Thr70 and Ser65) are elevated in

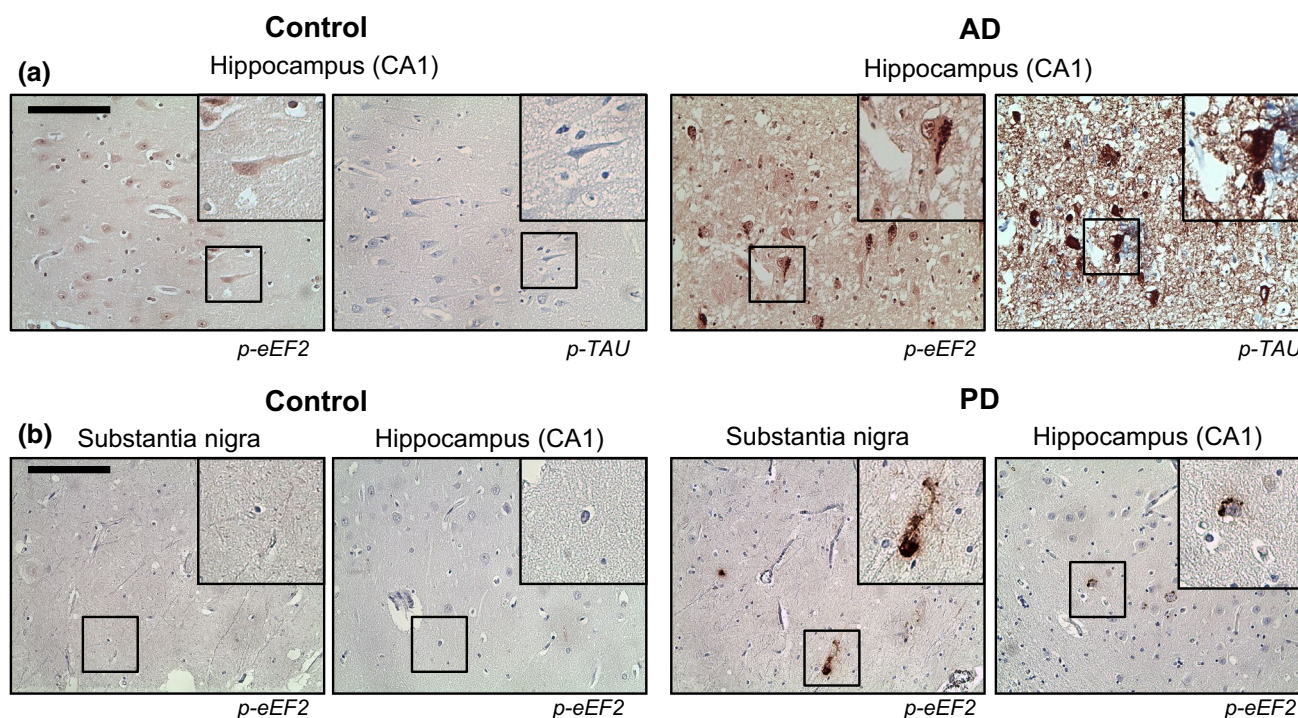
postmortem AD medial temporal cortex [1, 111]. Similar observations of aberrant mTOR and eIF2/eIF4 signaling have also been reported in PD midbrain substantia nigra [51]. Cell culture studies and transgenic animal models suggest that mTOR activity may also be involved in pathological processes triggered by aggregation of disease-associated proteins, such as amyloid- $\beta$  (A $\beta$ ) and tau in AD [1, 22, 196], and alpha-synuclein in PD [167]. This is not surprising, since mTOR acts as a negative regulator of autophagy, a known factor in neurodegenerative diseases, and possibly affects the clearance of aggregated amyloidogenic proteins [141].

Selective mRNA translation affecting neuronal survival in neurodegenerative diseases is also supported by studies showing decreased expression of the tumor suppressor HACE1 in HD. Expression of this protein, an HECT family E3 ligase that controls cellular oxidative stress [40], is decreased in HD striatal neurons [151]. HACE1 protects neurons from mutant huntingtin toxicity by increasing translation and activity of the nuclear factor erythroid 2-related (NRF2), an antioxidant master regulator [151]. Additional evidence for translation initiation alterations in neurodegenerative disease comes from the observation that some allelic variants of FTO demethylase that normally affect m<sup>6</sup>A modifications and, hence, cap-independent translation

are associated with increased risk of developing dementia/AD [94]. However, detailed mechanistic studies on this topic are currently lacking.

### Translation elongation control

Defective translation elongation control is also emerging as a crucial factor in the pathogenesis of many neurological disorders. In this regard, altered AMPK–eEF2K signaling is increasingly recognized in AD, PD, and HD (Fig. 4). AMPK signaling has been shown to decline with age, and may contribute to metabolic dysfunction and altered energy homeostasis in aging or age-related diseases [148, 153]. In AD and other tauopathies, phosphorylation of AMPK at Thr172, indicating increased activity, is found in cerebral neurons and to a lesser extent in astrocytes [186]. In these pathologies, p-AMPK immunohistochemical (IHC) localization is particularly abundant in neurons bearing pretangles and tangles, and in close proximity to dystrophic neurites surrounding amyloid plaques [186]. Similarly, increased p-AMPK is reported in the midbrain of chemical (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP) induced parkinsonism [27], and in the striatum of mutant huntingtin expressing R6/2 transgenic mice [126]. Interestingly, AMPK also stimulates autophagy by direct phosphorylation of ULK1, and



**Fig. 4** Activity of eEF2 kinase is increased in Alzheimer's (AD) and Parkinson's (PD) disease brains. **a** Immunohistochemical detection of phospho-eEF2 (Thr56), as a readout of eEF2K activity, and phospho-TAU was performed on postmortem serial sections of the CA1 hip-

pocampal region in control and AD brains, as previously described [86]. **b** Immunohistochemistry for phospho-eEF2 (Thr56) was performed on sections of the substantia nigra and Hippocampus in control and PD brains, as previously described [85]. Scale bar = 80  $\mu$ m

there is evidence that AMPK negatively regulates mTOR activity and vice versa [158]. Altered translation elongation in neurodegenerative diseases is also highlighted by the observation that, in a subset of the autosomal dominant spinocerebellar ataxias, a single-nucleotide variant results in a P596H amino acid substitution in eEF2 [71]. This mutation impairs the ability of eEF2 to maintain binding to the mRNA reading frame and results in impaired ribosome translocation during elongation. Moreover, Ishimura et al. identified a single nuclear polymorphism in the T loop stem of *n-Tr20*, a tRNA isodecoder, as inducing neurodegeneration in mice, when combined with loss *Gtpbp2*, part of the ribosome stalling detection system [83]. Ribosome profiling experiments in mutant mice revealed that the *n-Tr20* mutation stalls ribosomes specifically on AGA codons of mRNA. The lack of other AGA isodecoders in the brain suggests that the expression of the *n-Tr20* tRNA isodecoder is required for correct translation elongation in mammals.

Recent reports, including our own data, show that the expression and/or activity of eEF2K are increased in AD brain. Earlier studies by Li et al. reported that eEF2K activity, as assessed by IHC detection of eEF2 (Thr56) phosphorylation or by Western blots, is increased in postmortem AD mesial temporal cortex [111]. They also demonstrated decreased eEF2 levels in AD brain, particularly in AD cases neuropathologically diagnosed as stages IV–VI of Braak neurofibrillary tangle pathology [111]. Ma et al. confirmed these observations and found increased eEF2 (Thr56) phosphorylation in homogenates of postmortem AD mesial temporal cortex [116]. Expanding these studies to gain further mechanistic insights, we found that eEF2 (Thr56) phosphorylation is particularly increased in the hippocampal fields, cornu ammonis 1–3 (CA1–CA3), and in cortical layers III–V in postmortem AD brains [86] (Fig. 4a). Furthermore, eEF2 phosphorylation is significantly increased in the hippocampus of aged transgenic AD mice, although with conflicting evidence that this was due to changes in AMPK activity [86, 116]. In a follow-up report, we found, by IHC analysis, that eEF2 phosphorylation was markedly increased in postmortem PD midbrain (neurons of substantia nigra and periaqueductal gray), and to a lesser extent in hippocampus sections (CA1 and CA2) [85] (Fig. 4b). It remains to be determined whether aberrant AMPK–eEF2K signaling is also involved in other neurodegenerative diseases such as HD and ALS.

Overall, the anticipated effect of these alterations is the global shutdown of protein synthesis, except for mRNAs required for stress adaptation and survival, and suppression of long-term plasticity [69]. It is possible that, in the short term, these changes represent adaptive responses of neurons and may have some survival advantages in the face of disease processes such as protein aggregation (e.g., tau in AD and alpha-synuclein in PD). However, prolonged and/or chronic reduction in translation and protein synthesis may

seriously hamper synaptic function and lead to synaptic and neuronal loss. Taken together, alterations in translation elongation control appear to contribute to the pathogenesis of several neurodegenerative diseases. Nevertheless, further studies are required to determine the exact molecular determinants of these aberrations, how they contribute to symptomatology and whether therapeutic targeting will have any beneficial effect on the disease course.

## Repeat-associated non-AUG (RAN) translation in neurodegeneration

Nucleotide repeat expansions have been extensively studied in relation to their potential to produce insoluble protein aggregates toxic to neurons, which is the mechanistic basis of several neurodegenerative diseases, as extensively reviewed elsewhere [105]. Until recently, it was considered that this class of mutations encodes proteins only when retained as an open-reading frame within an annotated protein coding region. The recent discovery of repeat-associated non-AUG (RAN) translation has shed further light on the pathogenesis of microsatellite repeat diseases [199].

RAN translation occurs across expanded repetitive RNA repeats even in the absence of an AUG start codon, and was initially described in association with CAG repeats in spinocerebellar ataxia type 8 (SCA8) [199]. Loss of the canonical requirements for translation initiation results in six possible reading frames: CAG repeats can be read as CAG, AGC, GCA, and the antisense CUG, UGC, GCU [140], which can be translated into potentially toxic proteins containing homopolymeric polypeptides of polyglutamine, polyserine, polyalanine, polyleucine, polycysteine, and polyalanine. Expressed proteins resulting from RAN translation, characterized by dipeptide repeats, display an increased tendency to self-aggregate and induce neurodegeneration [140, 157]. This form of aberrant translation has been described for multiple-nucleotide repeat sequences, including but not limited to CGG repeats in Fragile X Tremor Ataxia Syndrome (FXTAS) [176], GGGGCC and GGCCCC repeats in *C9orf72* ALS and frontotemporal dementia (FTD) [53, 122, 131, 132, 155, 195, 200], and CAG repeats in HD [8], as extensively reviewed [29].

The potential mechanistic basis of RAN translation initiation is complex and depends on the disease, mutated gene, and nucleotide repeat, as extensively reviewed elsewhere [29, 64]. For example, some reports show that GGGGCC repeats in *C9orf72* form complex RNA G-quadruplex structures [146], thus possibly indicating an effect of these structures on translation initiation efficiency. Experiments in cell free in vitro systems also show that translation of GGGGCC repeats depends on a close-cognate codon and is regulated by an uORF [172]. However, a different model,

where translation starts at uncapped repeat-containing intronic regions, is supported by data in cellular systems [26]. In addition, a role for eIF2 $\alpha$  phosphorylation under chronic cellular stress in promoting selective translation of microsatellite-containing transcripts in *C9orf72* ALS/FTD has recently been proposed [26, 63]. In contrast, translation efficiency of CGG repeats in FXTAS seems to be dependent on the reading frame, with repeats resulting in the expression of polyglycine and polyalanine but not polyarginine in cell culture [176]. It is clear from different model systems that aberrant proteins resulting from RAN translation are neurotoxic and induce neurodegeneration [50, 122, 125, 182, 195]. Hence, elucidating the molecular basis of RAN translation may offer novel opportunities for its targeting, as reviewed elsewhere [29, 150].

### Stress granules in neurodegenerative diseases

As discussed above, RBPs containing a prion-like low complexity domain (LCD), such as TIA1, G3BP1, TDP-43, FUS, EWSR1, and hnRNPA1, self-assemble into SGs along with mRNAs by the process of phase separation, occurring when a solution oversaturated with multiple components spontaneously separates into a solid and a liquid phase [15, 127, 139]. Self-assembly and recruitment into SGs is accelerated by pathologic mutations in the LCDs of several RBPs, and inappropriate phase separation leading to pathological self-assembly is linked to the development of neurodegenerative diseases associated with mutations in RBPs, including TDP-43 and FUS in ALS and FTD [68, 127, 139]. Consistent with this notion, an increasing number of mutations in RBPs (e.g., hnRNPA1, FUS, TDP-43, Atx2, and TIA1) that promote their self-assembly are being discovered in ALS/FTD, as recently reviewed [11].

In ALS, after the discovery that neuronal protein aggregates contain the TDP-43 protein [134], more than 30 different disease-linked mutations in the *TDP-43* gene have been identified [104, 120]. Most mutations induce TDP-43 localization in the cytoplasm and its association into SGs [112]. Several other disease-causing mutations, such as *C9orf72* repeat expansions [108, 118] and mutant *hnRNPA2/B1* and *hnRNPA1* [99], have been described to induce SG formation. Moreover, polyGly-Arg and polyPro-Arg dipeptide repeats resulting from RAN translation of *C9orf72* expansions directly interact with SGs and promote their assembly [108], and RNA self-assembly induced by pathogenic dipeptide repeats promotes SG formation [180]. In addition to SG hyperformation, alterations in SG dynamics and inhibition of their dissociation have also been proposed to induce neurodegeneration in ALS. SG clearance in mammalian cells is linked to autophagy, and is impaired by the inhibition of

valosin-containing peptide (VCP) [18]. Interestingly, VCP mutations predispose to several neurodegenerative diseases, including ALS [90]. Moreover, a P362L mutation in the prion-like domain of TIA1, inducing phase separation and impaired SG disassembly, has been recently identified in ALS/FTD familial cases [75, 119]. Intermediate length polyQ expansions (27–33 glutamines) of the Ataxin-2 gene (*ATX2*), promoting protein self-assembly and interaction with TDP-43, are another common finding in ALS patients [47].

While multiple mechanisms of neurotoxicity have been proposed in ALS/FTD (as extensively reviewed [174, 182]), ample literature argues that mutations in RBPs also affect their RNA-binding ability, possibly altering mRNA translation. Most of this evidence comes from studies in *Drosophila*, where mutations that prevent the RNA-binding capacity of FUS attenuate its neurotoxicity [38]. In mice, expression of ALS-linked FUS mutations impairs local protein synthesis in neurons without inducing protein aggregates, suggesting that mutant FUS affects mRNA translation [115]. Similarly, the RNA-binding capacity of TDP-43 contributes to neurodegeneration [7], suggesting a role for RNA sequestration in the disease. Consistent with this notion, restoring translation of target mRNAs of TDP-43, such as *futsch/*MAP1B, decreases neurodegeneration in ALS [34]. VCP and FUS were recently shown to directly interact with ribosomes in cell culture, pointing to potential roles in controlling translation [163]. In the context of *C9orf72* expansions, SG formation was reported to impair translation in both cell culture [108] and mouse models [194]. It should also be mentioned that not all the genetic mutations identified in ALS/FTD have been linked to SGs assembly [16]. Nevertheless, the existence of multiple disease-linked mutations in RBPs, promoting their self-assembly into SGs, supports a mechanistic model whereby pathological SG assembly over time impairs motor neuron function, at least partially by altering mRNA translation. Future studies are required to fully understand this process and potential targets for therapy.

In other chronic neurodegenerative diseases, SG proteins such as TIA1, eIF3, TDP-43, and polyA binding protein (PABP) have been observed to co-localize with neuropathological markers in postmortem brain tissue in AD [4, 79, 181, 190]. In cell culture, tau, huntingtin, and misfolded prion protein (PrP<sup>Sc</sup>) associate with SGs and to modulate their formation [59, 188], suggesting a potential role for SGs in pathogenic mechanisms of these diseases. Studies demonstrating interactions between tau and SG proteins also suggest that SG formation increases tau phosphorylation, indicating that SGs might contribute to tau pathology [88, 181]. In PD, TDP-43 inclusions have been reported in postmortem tissue [55] and the antioxidant protein DJ-1, frequently mutated in PD, was also shown to associate with

SGs during neurodegeneration [147]. It is important to distinguish between the self-assembly of SG proteins during stress, and the aggregation of amyloid-forming proteins such as tau in AD. In this context, Wolozin has proposed a model of regulated protein aggregation in neurodegenerative diseases, in which SG formation in neurons is an adaptive stress response to the toxicity of mutant proteins (i.e., TDP-43 and FUS) and/or to the pathological excess of amyloidogenic proteins such as tau [190]. Based on this model, transient formation of SGs in neurons may be protective, but unregulated and overactive SG formation may cause deleterious effects by sequestering crucial transcripts and/or proteins needed for efficient plasticity and neuronal survival. It is also plausible that transiently overactive SG assembly is triggered by aggregation of amyloidogenic proteins (e.g., tau), and SGs may help to sequester toxic amyloidogenic oligomers. However, stable (i.e., pathological) SG structures may provide a nidus for the nucleation of these amyloid-forming proteins, and, hence, represent a vicious cycle in the formation and propagation of neurotoxic oligomeric aggregates. While further studies are required to fully elucidate the role of SGs in the pathogenesis of neurodegenerative diseases other than ALS/FTD, it is reasonable to postulate a model whereby protein aggregation, chronic oxidative stress, and neuronal injury activate the cellular stress responses, inducing eIF2 $\alpha$  phosphorylation and the formation of SGs. Supportive of this model is the common finding of phosphorylated eIF2 $\alpha$  in neurodegenerative diseases, as well as recent studies showing that misfolded prion proteins [130] and TDP-43 [100] induce chronic eIF2 $\alpha$  phosphorylation, and inhibition of this pathway mitigates TDP-43 toxicity [100]. Whether modulating this response might represent a therapeutic approach to these pathologies will be a relevant topic for future investigations, as discussed in the therapy section below.

### Therapeutic targeting of aberrant translation in brain tumors

The following discussion will focus exclusively on emerging concepts on therapeutic targeting of brain tumors with a special emphasis on SG biology, eIF2 $\alpha$  phosphorylation, and the AMPK–eEF2K–eIF2 axis. As mentioned, SG formation represents an important component of the adaptive response of cells to acute stress. Consistently with this notion, blocking SG formation renders cells highly sensitive to apoptosis under oxidative stress conditions [6, 173]. Furthermore, we reported that blocking SG significantly attenuates the metastatic and invasive capacity of pediatric sarcomas [164]. Although early literature suggests that SG assembly inhibition *in vitro* in GBM sensitizes cells to chemotherapeutic agents [185], the role of SGs in brain tumor progression,

invasive capacity, and antioxidant response remains largely unexplored. Investigation of this field will be of particular interest in deciphering chemoresistance, since chemotherapeutic agents (e.g., vincristine) used in the therapy of brain tumors are reported to promote SG formation [171]. In addition, drugs inhibiting SG formation, such as nocodazole [103], should be evaluated for their capacity to inhibit brain tumor progression and invasion.

As discussed above, four different kinases (PKR, HRI, GCN2, and PERK), activated by distinct stress forms, phosphorylate eIF2 $\alpha$  on Ser51 as part of the ISR [129]. The small molecule ISRIB, an activator of the guanine nucleotide exchange factor eIF2B, has recently been shown to render cells resistant to the effects of eIF2 $\alpha$  phosphorylation without affecting eIF2 $\alpha$  phosphorylation itself [160, 162]. ISRIB is a potent inhibitor of SG formation and promotes the disassembly of preformed SGs [161]. In addition, the small size of this molecule and its ability to penetrate the blood–brain barrier [66] makes it an ideal candidate for SG inhibition in brain tumors.

As also previously discussed, the AMPK–eEF2K axis is critical for adaptation of cancer cells to diverse acute micro-environmental stresses [109, 110]. In this context, we have shown that MYC overexpressing tumors are particularly sensitive to eEF2K inhibition in combination with caloric restriction diets [41, 42]. Despite the challenge of identifying and developing inhibitors for an atypical  $\alpha$ -kinase such as eEF2K, several drugs have been described as eEF2K inhibitors, with conflicting opinions regarding their specificity [44], and this topic is reviewed elsewhere [114]. Testing the efficacy of eEF2K inhibition, particularly in combination with caloric restriction mimetics, glycolysis, or mTOR inhibitors, will be of interest in MYC-driven cancers, such as neuroblastoma, MB, and pediatric GBM.

### Therapeutic targeting of aberrant translation in neurodegenerative diseases

Although many studies have explored the potential benefits of targeting translation in tumors, similar therapeutic approaches for neurodegenerative diseases remain largely unexplored. Given the complex etiology of neurodegenerative diseases discussed in this review, it may be challenging to design clinically beneficial therapeutic agents targeting more than a single mechanism in translation regulation (i.e., translation initiation or elongation). However, it is not unlikely that the neuronal dysfunction and neuronal loss induced by amyloid aggregation and/or deleterious effects of rare disease-causing mutations (e.g. APP in AD, and alpha-synuclein in PD) on neuronal protein synthesis could be mitigated. For example, clearance of SGs by autophagy has been proposed as a possible therapeutic approach in

neurological diseases characterized by pathologic accumulation of SGs and RBPs [18], and it is possible that a moderate reduction in SG formation may prove beneficial in chronic pathological conditions [3]. More mechanistic studies are, however, needed to determine the therapeutic value of targeting pathways relevant to SG formation in neurological diseases. In this context, decreasing expression or activity of the eIF2 $\alpha$  kinases GCN and PERK in transgenic AD mice (expressing the mutant human APP and presenilin 1-APP/PS1) prevented synaptic deficits and improved performance in tasks of spatial memory [117]. Consistent with the notion that eIF2 $\alpha$  acts as an important memory repressor, preventing the effects of eIF2 $\alpha$  phosphorylation with the small molecule ISRIB significantly improves hippocampal-dependent memory function in a mouse model of traumatic brain injury [28]. Further studies are needed to fully explore the effectiveness of ISRIB as a therapeutic strategy in neurodegenerative diseases.

With regard to the potential therapeutic utility of targeting pathological hyperactivity of the AMPK–eEF2K–eEF2 axis in neurodegenerative diseases, genetic deletion of the AMPK $\alpha$ 2 subunit, treatment with a small molecule inhibitor of AMPK (compound C), or exposure to a small molecule inhibitor of eEF2K prevented the detrimental effects of A $\beta$  on LTP in hippocampal slices and improved protein synthesis [116]. In line with these observations, we have explored the potential benefits of eEF2K inhibition in models of neurotoxicity induced by amyloidogenic proteins, specifically A $\beta$  and alpha-synuclein in neuronal cultures. Indeed, eEF2K inhibition, by pharmacological and genetic approaches, prevented the toxic effects of A $\beta$ 42 oligomers on neuronal viability and dendrite maturation in neuronal cultures [86], and these types of results were recently confirmed in a transgenic mouse model of AD [9]. Furthermore, we observed that eEF2K inhibition reduced oxidative stress in cultures of dopaminergic neuroblastoma N2A cells by promoting NRF2 antioxidant response, and prevented the oxidative stress associated with application of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) treatment [86]. Taken together, these data support the notion that targeting defective mRNA translation and protein synthesis represents a promising strategy in chronic neurodegenerative diseases.

## Conclusions and perspectives

Emerging evidence suggests that loss of translation control is a common pathologic hallmark across diverse neurological disorders, including CNS tumors, neurodevelopmental and mental retardation disorders, and neurodegenerative diseases. In this article, we set out to review the role of mRNA translation in different brain diseases, and how different alterations in one pathway may contribute to very distinct

pathologies. The knowledge acquired from a better understanding of the biological basis of one disease could open unexpected therapeutic opportunities for a different one. For example, unraveling the basis of RAN translation in repeat expansion diseases may suggest novel mechanisms of translation exploited by cancer cells to adapt to their microenvironment. A better understanding of how translation control impacts brain pathologies is critical for the development of novel and targeted therapies for these diseases.

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## Compliance with ethical standards

**Conflict of interest** The authors declare no conflicts of interest.

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