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Dysregulated translational control in brain disorders: from genes to behavior

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Control of protein synthesis (mRNA translation) is essential for proper brain development and function. Perturbations to the mechanisms governing mRNA translation have repeatedly been shown to constitute a neurodegenerative, neuropsychiatric, and neurodevelopmental disorder risk factor. Developing effective therapeutics for brain disorders will require a better understanding of the molecular mechanisms underlying the control of protein synthesis in brain function. Studies using transgenic animal models have been invaluable towards this end, providing exciting new insights into the genetic basis of brain disorders with hopeful prospects for new and effective treatment options.

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Neurological disorders and mRNA translation

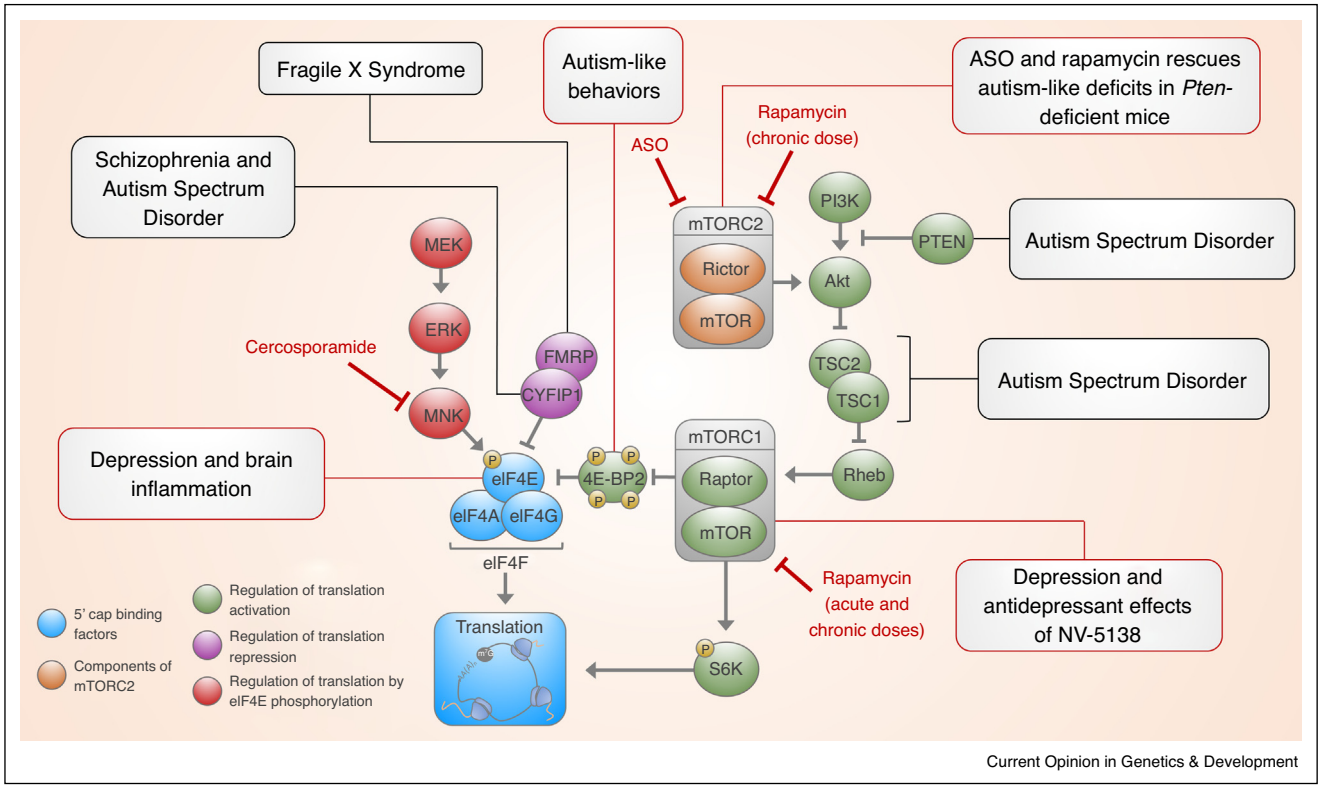
Gathering genetic information from patients using techniques such as genome-wide linkage analysis (GWLA), genome-wide association studies (GWAS), and whole genome sequencing (WGS) is becoming cheaper and more accessible. As a result, hundreds of genes and genetic loci have been linked to various neurological disorders thereby helping to uncover their etiology. These studies, in addition to the known monogenic causes of some neurological disorders, have revealed interesting patterns in the types of genes often mutated. Among these, the genes encoding for proteins involved in regulating mRNA translation are afflicted by disruptive mutations [1]. These include the regulators of the mTOR pathway (e.g. PTEN and TSC1/2) and cap-dependent mRNA translation (e.g. eIF4E, FMRP, and CYFIP1). Overactivation of the integrated stress response pathway (i.e. eIF2) has also been observed in numerous neurological disorders. Using transgenic animal models, exciting progress has been made towards understanding how these proteins govern brain function and how their dysregulation underlies brain disorders.

The mTOR pathway: mTORC1 and mTORC2

The mechanistic target of rapamycin (mTOR) is a protein serine/threonine kinase present in two distinct functional complexes. mTOR complex 1 (mTORC1), contains as the indicative subunit the regulatory associated protein of mTOR (Raptor) and is sensitive to inhibition by rapamycin [2]. mTOR complex 2 (mTORC2) instead contains as a subunit the rapamycin-insensitive companion of mTOR (Rictor). In the brain, mTORC1 integrates synaptic signals through a variety of postsynaptic receptors such as the NMDA receptors (glutamate) and TrkB receptors (BDNF and NGFs). Downstream of these receptors, phosphatidylinositol 3-kinase (PI3K) and the tuberous sclerosis complex (TSC) proteins TSC1 and TSC2 activate the Ras homolog enriched in brain (Rheb), which in turn stimulates mTORC1 [2]. The negative regulator phosphatase and tensin homolog (PTEN) directly counteracts PI3K activity, thereby attenuating mTORC1 function (Figure 1). There are many direct downstream targets of mTORC1, of which the best studied are ribosomal protein S6 kinases (S6Ks) and the eukaryotic initiation factor 4E (eIF4E)-binding proteins (4E-BPs). Activation of mTORC1 results in phosphorylation of the S6Ks and 4E-BPs (see below, and legend to Figure 1 for details) to promote mRNA translation.

Conditions associated with abnormal mTORC1 function, aptly named 'mTORopathies', define a large class of neurodevelopmental disorders. The function of mTORC1 in neurodevelopmental disorders like autism spectrum disorder (ASD) has been extensively reviewed [3–5]. Individuals with ASD harbor mutations in the upstream mTORC1 regulating proteins *TSC1*, *TSC2* and *PTEN*. Mice lacking the genes *Tsc1*, *Tsc2*, or *Pten* either full-body or in specific cell types exhibit abnormally high mTORC1 activity and recapitulate ASD-related behavioral deficits observed in patients. Treatment of these mice with rapamycin rescued the observed impairments [6–8]. However, chronic treatment of rapamycin also inhibits mTORC2 along with mTORC1 [9]. Building on this, Chen *et al.* discovered that

Figure 1



Neurological disorders linked to regulation of cap-dependent translation initiation. Initiation of translation requires binding of the eukaryotic initiation factor (eIF) 4F (eIF4F) complex to the 5' end of the mRNA. eIF4F is composed of eIF4E, the 5' cap-binding protein, eIF4G, a scaffolding protein, and eIF4A, an RNA helicase. eIF4E is a downstream effector of MAPK-interacting serine/threonine-protein kinases (MNKs), mechanistic target of rapamycin complex 1 (mTORC1), and the fragile X mental retardation protein (FMRP)-cytoplasmic FMR1 interacting protein 1 (CYFIP1) complex. MNKs can phosphorylate eIF4E at Ser 209 to regulate the translation of a subset of mRNAs. Phosphorylation and therefore activity of the eIF4E-binding protein 2 (4E-BP2) is regulated by mTORC1 (inhibited by rapamycin) in response to various complex upstream signaling pathways. FMRP/CYFIP1 regulate translation by forming the FMRP-eIF4E-CYFIP1 complex at the 5' end of the mRNA, repressing translation. Abbreviations: Mitogen-activated protein kinase kinase (MEK); extracellular signal-regulated kinases (ERK), regulatory-associated protein of mTOR (Raptor), mechanistic target of rapamycin (mTOR), ribosomal protein S6 kinase (S6K), phosphoinositide 3-kinase (P13 K), phosphatase and tensin homolog (PTEN), mechanistic target of rapamycin complex 2 (mTORC2), protein kinase B (Akt), tuberous sclerosis 1 (TSC1), tuberous sclerosis 2 (TSC2), ras homolog enriched in brain (Rheb). Neurological disorders associated with factors that control cap-dependent translation initiation from recent patient and animal model studies (in black bordered boxes) or from animal studies only (in red bordered boxes) are presented.

mice lacking *Pten* exclusively in excitatory neurons displayed autism-like behaviors that were not rescued by co-deletion with mTORC1 but only with co-deletion of mTORC2 [10••]. Further, chronic rapamycin treatment of mice that lack both *Pten* and mTORC1 in excitatory neurons rescued the observed impairments, indicating an mTORC1-independent role for rapamycin-mediated treatment of *PTEN*-related mTORopathies. However, it is not clear what role mTORC2 plays in ASD that is not *PTEN* mutation associated, given that deletion of *Pten* in mice is itself known to increase mTORC2 activity [2]. The inhibitory neuron-specific role of mTORC1 and mTORC2 also remains to be evaluated to fully understand the individual contributions of the two mTOR complexes in ASD-related behaviors.

Over the last decade, a new role for mTORC1 has emerged in neuropsychiatric disorders, adding major depressive disorder (MDD) to a growing list of mTORopathies. Exposure of mice to chronic stress results in the reduction of mTORC1 signaling [11], which is consistent with findings that the antidepressant effect of ketamine, an anesthetic, in mouse models of MDD is mediated through mTORC1 activation [11–13]. Most recently, Kato *et al.* used the new drug NV-5138, which is the first brain-selective mTORC1 activator [14•], in a mouse model of MDD [15]. Treatment with NV-5138 using a single dose was sufficient to reverse depressive-like behaviors in the mouse model, similar to ketamine. Importantly, infusion of rapamycin before NV-5138 treatment rendered the depressive-like behavior in the mice non-reversible, indicating that mTORC1

activation is required for the antidepressant effects of NV-5138 [15].

Cap-dependent mRNA translation: eIF4E and 4E-BP2

Most eukaryotic mRNAs require binding of eIF4E to the 5' cap to initiate translation. Together with an RNA helicase, eIF4A, and a scaffolding protein, eIF4G, these proteins form the eIF4F complex, which facilitates the attachment of the 43S preinitiation complex to the mRNA [16]. Being the least abundant initiation factor, eIF4E activity is rate-limiting for translation initiation and constitutes a key translational regulatory mechanism (Figure 1). For example, eIF4E activity is regulated via phosphorylation on serine (Ser) 209 by upstream MAPK-interacting serine/threonine-protein kinases (MNKs) [17,18]. This mechanism is important for controlling the translation of a subset of mRNAs and impacts oncogenesis [19]. Little was known about how eIF4E phosphorylation regulates brain function until two studies demonstrated that mice containing an eIF4E with a Ser 209 mutation to alanine (Ala), thereby preventing eIF4E phosphorylation, exhibit depressive-like behavior and exaggerated brain inflammatory responses via increased production of tumor necrosis factor α (TNFα) [20,21]. Treating eIF4E mutant mice with a dominant negative TNFα rescued depression-like behaviors and restored serotonin responsiveness in the dorsal raphe nucleus [20]. Importantly, these phenotypes were consistent with deletion of the MNKs or by pharmacologically inhibiting the phosphorylation [20]. Taken together, these data suggest that deregulation of p-eIF4E is a potential underlying pathology mediating brain inflammation and depression.

Another mechanism regulating eIF4E activity is through competitive binding of the 4E-BPs for a conserved sequence shared by the 4E-BPs and eIF4G, thereby inhibiting translation initiation [22] (Figure 1). Several studies have implicated eIF4E overactivity through enhanced expression of eIF4E [23] or by deletion of 4E-BP2 [24,25], the predominant 4E-BP isoform in the brain, in the development of autistic-like features, including behavioral deficits reminiscent of ASD. Interestingly, deletion of 4E-BP2 only in GABAergic interneurons was sufficient to elicit many of the core behavioral deficits observed in full-body knockout (KO) mice [26]. This finding suggests that translational control via 4E-BP2 in selective cell types might be more critical than others in regulating complex behaviors. Consistent with this notion, other studies have documented an important role for mTOR signaling in somatostatin neurons, which constitute a subset of GABAergic neurons, in synaptic plasticity and memory [27•]. In the case of fragile X mental retardation protein (FMRP) translational regulator 1 (*Fmr1*) KO mice, chemogenetic stimulation of parvalbumin-specific GABAergic interneurons using designer receptors exclusively activated by designer drugs (DREADDs) reversed behavioral impairments [28]. These findings prompt the utilization of cell-type-specific protein analysis techniques to further elucidate the role of translational control in brain function and behavior.

Cap-dependent mRNA translation: FMRP and CYFIP1

FXS is the leading monogenic cause of ASD, which is engendered by >200 CGG trinucleotide repeats in the promoter region of the *FMR1* gene, leading to hypermethylation and gene silencing [29]. *FMR1* encodes the RNA binding protein FMRP, which functions in part to inhibit eIF4E and translation initiation [30] (Figure 1). Using the FXS mouse model (*Fmr1* KO mice), progress has been made in identifying differentially translated genes with techniques such as ribosome footprinting [31•], translating ribosome affinity purification (TRAP) [32], and biorthogonal non-canonical amino-acid tagging (BONCAT) [33]. Using cell-type-specific TRAP and RNA-Seq, Thomson *et al.* demonstrated that deletion of FMRP in CA1 pyramidal neurons of the hippocampus resulted in differential translation of 121 mRNAs with the muscarinic acetylcholine receptor 4 (M_4) being significantly overexpressed [32]. Interestingly, positive allosteric modulation of M_4, rather than inhibition, normalized excessive protein synthesis and the exaggerated metabotropic glutamate receptor-mediated long-term depression (mGluR-LTD), and reduced the incidence of audiogenic seizures in *Fmr1* KO mice. This finding revealed that aberrant translation of some genes may be a protective adaptation, rather than a cause of the pathophysiology. Taking a different approach, the Darnell lab used conditional tagging of FMRP and UV cross-linking immunoprecipitation (FMRP cTag CLIP) to examine FMRP-associated mRNA targets in CA1 pyramidal neurons [34]. This technique utilizes the Cre-lox system to knock-in epitope tags on the RNA binding protein of interest for CLIP purification of protein-RNA complexes. The authors observed enriched binding of FMRP to autism candidate mRNAs as classified in the SFARI Gene database [34]. Interestingly, the CA1 hippocampal targets were not observed in cerebellar granule neurons suggesting that FMRP differentially regulates translation in specific cell types which may contribute to particular phenotypes associated with FXS [34]. Together these studies highlight the importance of investigating the cell-type-specific contribution of translation control mechanisms towards brain function, the results of which may inform more precise therapeutic interventions.

While much work has elucidated the cellular and molecular function of FMRP, current studies focus on drug discovery and the identification of novel FMRP targets, such as M_4 [32] and β-arrestin 2 [35]. The repurposing of FDA-approved drugs such as lovastatin [36,37] and metformin [38] have proven to be effective at reversing the

behavioral, electrophysiological and biochemical impairments in the FXS mouse model. Both lovastatin and metformin correct these deficits by normalizing exaggerated protein synthesis and extracellular signal-regulated kinase (ERK) 1/2 activity. Similarly, pharmacological inhibition of the PI3K catalytic isoform p110β ameliorated FXS-associated phenotypes in FMRP-deficient mice [39]. Taken together these findings suggest that drugs which rectify aberrations in the cell signaling pathways upstream of FMRP may be a potential therapeutic option for treating FXS patients. These drugs are currently being tested in clinical trials (Lovastatin: NCT02680379, NCT02998151, NCT02642653 and Metformin: NCT03722290, NCT04141163, NCT03862950, NCT03479476).

Unfortunately, some of the drugs that are effective in reversing phenotypes in the FXS mouse, such as mavoglurant and arbaclofen, failed to adequately improve FXS patients in clinical trials [40]. One possible explanation is that the age-point at which a drug is administered is critical in determining the effectiveness of the treatment. This was the case for the $GABA_B$ receptor agonist, arbaclofen, which manifested therapeutic effects in children, but not in young adults [41]. Similarly, Asiminas *et al.* found that treating *Fmr1* KO rats with lovastatin during an early stage of development (between 5 and 9 weeks of age), restored associative memory deficits observed in spatial memory tasks [42•]. Importantly, this rescue was sustained for several months after treatment further highlighting the necessity of therapeutic intervention during key developmental windows.

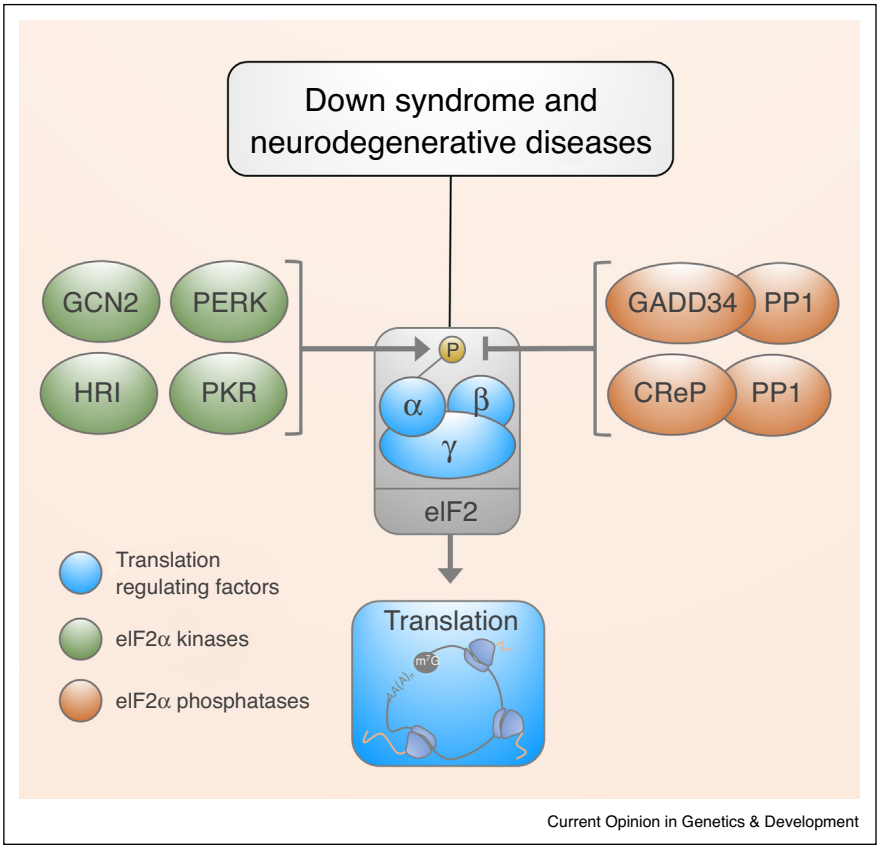
Translation repression by FMRP is achieved in part through physical interaction with cytoplasmic FMRP interacting protein 1 (CYFIP1) which directly binds to and sequesters eIF4E thereby inhibiting translation initiation [30]. CYFIP1 also interacts with the Rac1-Wave complex to regulate actin dynamics [43]. By shuttling between the FMRP-eIF4E and Rac1-Wave complexes, CYFIP1 activity links translation regulation with actin dynamics and dendritic spine morphology in a homeostatic balance [44], which is dysregulated in *Fmr1* KO mice. Since loss of FMRP also causes increased binding between eIF4E and eIF4G [45], Santini *et al.* hypothesized that blocking eIF4E-eIF4G interaction using the specific small molecule inhibitor, 4EGI-1, would increase the pool of available eIF4E to bind CYFIP1 [46]. Consistent with this hypothesis, the authors observed that loss of FMRP destabilizes the interaction between CYFIP1 and the 5' cap complex in the hippocampus. In addition, treatment of *Fmr1* KO mice with 4EGI-1 restored CYFIP1 interaction with the 5' cap, reversed hippocampal-dependent memory deficits, corrected aberrant spine morphology and restored exaggerated mGluR-LTD to control levels [46]. These results suggest that targeting eIF4F under conditions of dysregulated translation may be a potential therapeutic option for patients with neurological disorders.

In the human genome, *CYFIP1* resides in the 15q11.2 region for which copy number variants are associated with neurological/psychiatric disorders such as schizophrenia (SCZ) and ASD [47]. Polymorphisms and rare mutations in *CYFIP1* are also linked to SCZ [48] and ASD [49], further implicating disrupted CYFIP1 activity in neurological/psychiatric disorders. Since both microduplications and microdeletions in 15q11.2 are associated with these disorders, Davenport and colleagues sought to determine how CYFIP1 gene dosage affects neuronal function in rodents. They observed that either up or downregulation of CYFIP1 in hippocampal neurons resulted in alterations in the ratio of excitatory to inhibitory (E/I) currents [50]. However, a comprehensive behavioral study of CYFIP1 overexpression in mice did not reveal any ASD-associated behavioral impairments [51]. Instead, the mice presented mild learning deficits and an exaggerated fear response, suggesting that the E/I deficits observed with increasing CYFIP1 gene dose may not contribute to ASD-associated behaviors, but towards cognitive ability. Similarly, heterozygous deletion of CYFIP1 in both mice [52] and rats [53•] resulted in white matter thinning of the corpus callosal axons and the rats exhibited cognitive inflexibility. The mice, however, presented abnormalities in motor coordination, sensorimotor gating, and sensory perception which are consistent with the neuropsychiatric deficits observed in ASD and SCZ patients [52]. In summary, these findings suggest that CYFIP1 abundance is important for functional brain connectivity which may underlie the behavioral features in 15q11.2 patients, particularly for cognition.

Integrated stress response: eIF2

The integrated stress response (ISR) is a mechanism that evolved to halt the production of proteins in order to conserve energy during cellular stress. The ISR targets ternary complex (TC) availability in the cell. The TC comprises the initiator methionine-tRNA, GTP and the translation initiation factor eIF2, which contains 3 subunits (α, β, and γ) [54] (Figure 2). The cellular availability of the TC is controlled by the phosphorylation status of eIF2 at Ser 51 in its alpha (α) subunit [54]. Under conditions of cell stress, eIF2α is phosphorylated (p-eIF2α) by one of four kinases (general control nonderepressible 2, GCN2; protein kinase RNA-activated, PKR; protein kinase RNA-like endoplasmic reticulum kinase, PERK; or heme-regulated inhibitor, HRI), thereby inhibiting TC formation and arresting general translation, while paradoxically increasing translation of a subset of mRNAs containing 5′ upstream open reading frames (uORFs) [55]. Dephosphorylation of eIF2α is carried out by 2 protein complexes (PP1/CReP or PP1/GADD34), thus normalizing mRNA translation [55] (Figure 2).

Figure 2



Integrated stress-response related neurological disorders. Cellular stress results in activation of the integrated stress response (ISR) and phosphorylation of the eukaryotic initiation factor 2 (eIF2). eIF2 is composed of three subunits: α (eIF2α), β (eIF2β) and γ (eIF2γ). Phosphorylation of eIF2 occurs on the Ser 51 residue of eIF2α by one of four kinases: general control nonderepressible 2 (GCN2), PKR-like endoplasmic reticulum kinase (PERK), protein kinase RNA-activated (PKR) and heme-regulated inhibitor (HRI), each of which respond to different cell stressors (not shown). To attenuate levels of phosphorylated eIF2α, protein phosphatase 1 (PP1) bound to regulatory subunits growth arrest and DNA damage-induced protein (GADD34) or constitutive reverter of eIF2α phosphorylation (CReP) will remove the phosphate at Ser 51. Neurological disorders associated with eIF2α function from recent patient and animal studies are highlighted in boxes with black borders.

It is well established that genetic or pharmacological reduction of p-eIF2α enhances memory formation and long-term potentiation (LTP), and impairs mGluR-LTD [56–61]. In contrast, elevation of p-eIF2α impairs memory formation and LTP, but facilitates mGluR-LTD [57,60,62]. Importantly, eIF2α hyperphosphorylation is observed in neurodegenerative diseases that manifest deficits of learning and memory, such as Alzheimer's disease (AD), Parkinson's disease, Huntington's disease, and frontotemporal dementia [63,64]. In a mouse model of AD, pharmacological inhibition of p-eIF2α alleviated hippocampal-dependent memory deficits [65], highlighting the potential of targeting the ISR to treat neurodegenerative disorders.

More recently, Zhu *et al.* implicated the phosphorylation of eIF2α in Down syndrome (DS) [66••], a neurological condition caused by the presence of an extra copy of human chromosome 21 (ch 21) that results in hippocampal-dependent learning and memory deficits [67]. Here, the authors observed exaggerated levels of p-eIF2α in brain tissue and induced pluripotent stem cells (iPSCs) from individuals with DS as well as reduced general translation in the iPSCs. The authors show that a mouse model of DS, that contains 3 copies of the mouse gene orthologue of ch 21 (Ts65Dn mice), recapitulates exaggerated hippocampal p-eIF2α levels and decreased general translation. Consistent with DS, Ts65Dn mice displayed impaired hippocampal-dependent memory and LTP. Genetic deletion of the eIF2α kinase PKR in Ts65Dn mice normalized p-eIF2α and general translation, reversing the memory and synaptic plasticity impairments [66••]. Furthermore, Zhu *et al.* reversed memory and synaptic impartments in Ts65Dn mice by (1) genetically replacing the eIF2α Ser 51 residue with an Ala to reduce p-eIF2α levels and (2) pharmacologically

inhibiting the ISR [66••]. Thus, these findings implicate the ISR as a potential target for the treatment of DS.

Concluding remarks

The control of protein synthesis is essential for proper brain functioning and its dysregulation is a frequent cause of neurological disorders. We highlighted recent progress made in understanding how translational control modifies brain function, from the genetic to the behavioral level. Considering the challenges of translating basic neuroscience into clinical practice, these studies are imperative to provide the foundation for the discovery of novel treatments for neurological disorders.

Conflict of interest statement

Nothing declared.

CRediT authorship contribution statement

Shane Wiebe: Conceptualization, Writing - original draft, Writing - review & editing, Visualization. **Anmol Nagpal:** Conceptualization, Writing - original draft, Writing - review & editing, Visualization. **Nahum Sonenberg:** Writing - review & editing, Supervision, Funding acquisition.

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