Translational Control in the Brain in Health and Disease

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Translational control in neurons is crucially required for long-lasting changes in synaptic function and memory storage. The importance of protein synthesis control to brain processes is underscored by the large number of neurological disorders in which translation rates are perturbed, such as autism and neurodegenerative disorders. Here we review the general principles of neuronal translation, focusing on the particular relevance of several key regulators of nervous system translation, including eukaryotic initiation factor 2 α (eIF2 α), the mechanistic (or mammalian) target of rapamycin complex 1 (mTORC1), and the eukaryotic elongation factor 2 (eEF2). These pathways regulate the overall rate of protein synthesis in neurons and have selective effects on the translation of specific messenger RNAs (mRNAs). The importance of these general and specific translational control mechanisms is considered in the normal functioning of the nervous system, particularly during synaptic plasticity underlying memory, and in the context of neurological disorders.

TRANSLATIONAL CONTROL IN MEMORY

Memory storage is widely thought to have a physical basis in long-lasting changes in synaptic function (Malenka and Bear 2004; Mayford et al. 2012; Neves et al. 2008). For instance, high activity in a given neural pathway can persistently increase the efficacy of synaptic connections in a process called long-term potentiation (LTP). The reverse is also true: reduced activity persistently lowers synaptic efficacy, resulting in long-term depression (LTD). These long-lasting changes in synaptic strength are forms of synaptic plasticity and require de novo protein synthesis (Sutton and Schuman

2006; Costa-Mattioli et al. 2009; Trinh and Klann 2013; Buffington et al. 2014). Pioneering work by Josefa and Louis Flexner showed that short-lasting and longer-lasting memories are differentiated by the requirement for protein synthesis only for the latter (Flexner et al. 1967; Squire and Davis 1981). Thus, the requirement for new protein synthesis underlies long-lasting changes in both synaptic plasticity and memory.

However, despite more than 50 years of research in the field, several important questions remain unanswered: What are the major translational control programs regulating synaptic plasticity and memory storage? Where in the neuron is protein synthesis important for mem-

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ory formation (cell soma vs. synapse; presynaptic axons vs. postsynaptic dendrites)? What is the nature of the messenger RNAs (mRNAs) whose translation is increased in response to a learning experience? Finally, is the translational control machinery dysregulated in cognitive disorders? If so, by specifically correcting the aberrant translational program, can we restore cognition in these brain disorders?

GENERAL VERSUS SPECIFIC PROTEIN SYNTHESIS

Two aspects of translational control are relevant for synaptic plasticity and memory: general translational control, which determines the overall rate of protein synthesis; and specific translational control, whereby selective regulatory mechanisms allow for translation of specific mRNAs.

When a memory is made, gene expression takes place selectively in a small number of neurons in a given brain area (Guzowski 2002; Reijmers and Mayford 2009). Growing evidence supports the idea that these are the neurons that encode the memory (Josselyn et al. 2015; Tonegawa et al. 2015). Currently, it is not known whether these neurons require (1) a general increase in translation, or (2) the translation of a specific subset of mRNAs to generate the long-lasting synaptic changes that encode memory.

Overall increases in the rate of protein synthesis after learning have been observed in a number of different learning paradigms (Davis and Squire 1984; Kelleher et al. 2004; Batista et al. 2016; Liu and Cline 2016). A general increase in translation rates could be important for the growth and stabilization of new synaptic connections formed in neurons that encode memory (Bailey and Kandel 2008; Xu et al. 2009; Yang et al. 2009; Ryan et al. 2015). The general activation of translation is associated with a number of processes that are discussed below, including decreased phosphorylation of the translation factors eukaryotic initiation factor (eIF)2 α and eukaryotic elongation factor 2 (eEF2) as well as activation of mechanistic target of rapamycin complex 1 (mTORC1).

By contrast, changes in the rate of translation of a subset of mRNAs may be sufficient for inducing or stabilizing changes at specific synapses. As we discuss below, the same pathways that regulate general translation can also regulate the synthesis of specific proteins. Thus, it is difficult to differentiate the relative importance of general and specific protein synthesis in the formation of a memory simply by identifying the regulatory pathway involved. Indeed, the two processes may be linked; for example, the specific translation of mRNAs with a 5' terminal oligopyrimidine tract (TOP mRNAs) (Tsokas et al. 2007; Gobert et al. 2008) promotes general protein synthesis.

DENDRITIC VERSUS SOMATIC PROTEIN SYNTHESIS

Memory is thought to require the strengthening of a specific subset of synapses. The requirement for both protein synthesis and synapse specificity does not necessarily imply a requirement for the activation of translation locally at the synapses. Proteins can also be synthesized in the soma of a neuron and then selectively transported to synapses. Nevertheless, several lines of evidence support the notion that local translation is required for LTP and LTD (Sutton and Schuman 2006). More than 2000 mRNAs are found in synaptic processes (Cajigas et al. 2012), presumably through selective transport of these mRNAs, and increases in protein synthesis can be seen locally at synapses (Aakalu et al. 2001; Wang et al. 2009). Moreover, in some cases, protein synthesis-dependent LTP and LTD can be observed when the soma is physically disconnected from the synapse (Kang and Schuman 1996; Huber et al. 2000; Liu et al. 2003; Cracco et al. 2005; Gelinis and Nguyen 2005), supporting the notion that local translation can mediate long-lasting forms of synaptic plasticity. However, it is not entirely clear whether local translation is used for memory storage. Local application of protein synthesis inhibitors to synaptic regions decreases, but does not completely block, long-lasting forms of synaptic plasticity (Bradshaw et al. 2003). Local protein synthesis may be required to generate high concentrations

of proteins locally at synapses to support basic synaptic functions (Cajigas et al. 2012), as opposed to the specific production of proteins to induce changes in synaptic plasticity. Indeed, many of the proteins that are known to be locally synthesized near synapses (e.g., calcium-calmodulin kinase II α [CAMKII α], β -actin, and protein kinase M ζ [PKM ζ]) have high basal levels at synapses, and for at least one of these, CAMKII α , the high basal levels require local protein synthesis (Miller et al. 2002). It is an open question how the small resultant change in concentration of these proteins can explain a functional change in synaptic strength. Furthermore, it is currently unknown how many out of the 2000 mRNAs found in synaptic processes are required for memory formation. In addition, so far, we have not been able to identify a translational control mechanism that takes place only at synapses (but not in the soma). Consequently, direct loss- or gain-of-function evidence that local translation is required for memory consolidation is still missing. Even if local translation is required for the synaptic plasticity underlying memory, it is still unclear whether this requires selective translational control of a few mRNAs or a general increase in the translation of all transported mRNAs. These are important issues in the field that require further research.

LATE-LTP AND SYNAPTIC TAGGING

Even if local translation produces proteins only near activated synapses, protein diffusion would allow these proteins to be accessible to many synapses situated nearby in the same neuron (Rangaraju et al. 2017). Therefore, it is difficult to envision mechanisms for these proteins to act only at activated synapses in the absence of additional changes that restrict the actions of the new proteins to these synapses. Activation of protein synthesis is thus rarely sufficient to increase synaptic strength in the absence of other changes, a concept formalized in the “synaptic tagging” model (Frey and Morris 1998). In this model, the learning stimulus that generates memory leads to both (1) the translation of plasticity-related proteins (PRPs) in the neuron, and

(2) the formation of a “synaptic tag,” which marks the activated synapse. The synaptic tag determines that the PRPs act only at the activated synapse. The production of PRPs is a conceptual framework that supports the necessity of specific protein synthesis for synaptic plasticity underlying memory but does not predict whether the PRPs are made locally or in the soma (Frey and Morris 1998).

There have been many suggestions to explain the molecular basis of the synaptic tag (Martin and Kosik 2002), including alterations in the actin cytoskeleton (Ramachandran and Frey 2009), slots for neurotransmitter-gated ion channels (Granger et al. 2013), and scaffold proteins that link persistently active kinases to their substrates (Hu et al. 2017). Candidates for the PRPs include persistently active kinases, such as truncated persistently active forms of protein kinase C, termed PKM (Sajikumar et al. 2005) and phosphorylated, constitutively active CAMKII α (Sajikumar et al. 2007; Sanhueza and Lisman 2013). Other candidates include neurotransmitter-gated ion channels and immediate early genes such as Homer and activity-regulated cytoskeleton-associated protein (Arc) (Martin and Kosik 2002). PKM ζ (Muslimov et al. 2004; Eom et al. 2014), CAMKII α (Ouyang et al. 1999; Aakalu et al. 2001), neurotransmitter-gated channels (Ju et al. 2004), and Arc (Steward et al. 2014) have all been shown to be synthesized locally at or near the synapse after stimuli that produce long-lasting synaptic changes and memory, whereas Homer is synthesized only in the soma (Okada et al. 2009).

PRESYNAPTIC VERSUS POSTSYNAPTIC PROTEIN SYNTHESIS

The vast majority of the work on neuronal protein synthesis has focused on local translation in the dendrite, the postsynaptic region of the neuron. These studies are driven by the assumption that ribosomes travel down dendrites, but not down axons to the presynaptic region of the cell. Indeed, the main evidence against presynaptic protein synthesis is the failure to visualize polysomes in presynaptic endings in electron microscopic (EM) studies (Twiss and Fainzilber

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2009). However, emerging evidence supports the notion that presynaptic protein synthesis is also important for synaptic plasticity. First, many studies have shown that during development, local translation in axonal growth cones is important for axon guidance, and in mature neurons local translation in the axon is important for response to injury (Jung et al. 2012). In GABAergic neurons, presynaptic protein synthesis is required for long-term plasticity (Younts et al. 2016). In invertebrates, many forms of plasticity depend on presynaptic protein synthesis (Martin et al. 2000; Costa-Mattioli et al. 2009). More recently, surveys of mRNAs found in the synaptic region have shown abundant presence of mRNAs for presynaptic proteins (Cajigas et al. 2012). Finally, whereas it has been difficult to identify polyribosomes at presynaptic sites by EM (Buxbaum et al. 2014), ribosomes and polysomes have been found in presynaptic endings from squid by electron spectroscopy and [^3H]-leucine labeling (Crispino et al. 1997). In future experiments, it would be interesting to determine whether the same translational control mechanisms operate in presynaptic and postsynaptic compartments.

eIF2 α -MEDIATED TRANSLATION: A MEMORY SWITCH

As discussed above, making new proteins is a critical step required for the generation of long-lasting memories. In particular, the eIF2 α signaling pathway plays a dominant role in regulating memory formation. Phosphorylation of the α subunit of eIF2 at Ser51 is tightly regulated by

four kinases: (1) the heme-regulated kinase HRI; (2) the double-strand RNA-dependent protein kinase R (PKR); (3) the PKR-like endoplasmic reticulum kinase (PERK); and (4) the highly conserved kinase general control nonderepressible 2 (GCN2). Dephosphorylation of eIF2 α is regulated by two phosphatase complexes: (1) the catalytic subunit protein phosphatase 1 (PP1) and the regulatory subunit PPP1R15A/GADD34, and (2) PP1 and the regulatory protein PPP1R15B/CreP (Fig. 1A) (Merrick and Pavitt 2018; Wek 2018). Behavioral training leads to a decrease in the phosphorylation of eIF2 α in the hippocampus (Costa-Mattioli et al. 2007), a brain structure crucially required for memory formation (Squire et al. 2015). Accordingly, heterozygous eIF2 $\alpha^{S/A}$ knock-in mice (where the single phosphorylation site at serine 51 is replaced by alanine in one allele), with reduced phosphorylation of eIF2 α in the hippocampus, show enhanced memory in a variety of behavioral tasks (Costa-Mattioli et al. 2007), indicating that eIF2 α phosphorylation normally serves as a memory repressor. Consistent with the results of the eIF2 $\alpha^{S/A}$ knock-in mice, genetic deletion of any of the eIF2 α kinases expressed in the brain, GCN2, PKR, or PERK, enhances memory formation (Costa-Mattioli et al. 2005, 2007; Zhu et al. 2011; Stern et al. 2013; Ounallah-Saad et al. 2014). However, using conditional knock-out mice in which PERK is removed only in the forebrain, deficits in behavior including increased repetitive behaviors and behavioral inflexibility were observed (Trinh et al. 2012). We speculate that this may be because PERK phosphorylates targets other than eIF2 α and/or mod-

Figure 1. Eukaryotic initiation factor (eIF)2 α bidirectionally regulates the two major forms of plasticity, long-term potentiation (LTP) and long-term depression (LTD) in the brain. (A) Regulation of translation by eIF2 α phosphorylation. (B) Increased eIF2 α phosphorylation prevents long-lasting LTP induced by four trains of high-frequency stimulation (arrows), but facilitates metabotropic glutamate receptors (mGluRs)-LTD. The strength of the synapse is measured by postsynaptic potentials (PSPs), or excitatory postsynaptic currents (ePSCs) normalized to the strength before induction of LTP or mGluR-LTD, respectively. (C) Decreased eIF2 α phosphorylation facilitates LTP induced by one high frequency stimulation but blocks mGluR-induced LTD. The strength of the synapse is measured by PSPs or ePSCs normalized to the strength before induction of LTP or mGluR-LTD, respectively. PKR, Protein kinase R; GCN2, general control nonderepressible 2; PERK, PKR-like endoplasmic reticulum kinase; PP1, protein phosphatase 1; mRNA, messenger RNA; uORF, upstream open reading frames; UTR, untranslated region.

Figure 1. (Legend on facing page.)

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ulates calcium dynamics (Zhu et al. 2016), because these perturbations have not been seen in the heterozygous eIF2 α ^{S/A} knock-in mice. Indeed, several targets of PERK other than eIF2 α that may regulate synaptic plasticity have recently been identified including CREB (Sen et al. 2017), calcineurin (Wang et al. 2013), and endoplasmic reticulum (ER)-mitochondrial tethering (van Vliet et al. 2016).

Pharmacological experiments also support the notion that eIF2 α phosphorylation is a memory suppressor. Pharmacological inhibition of either (1) PKR with a specific inhibitor (PKRi), or (2) derepression of the translational program controlled by eIF2 α with a recently discovered small-molecule inhibitor (integrated stress response inhibitor [ISRIB]), enhances memory formation in both mice and chicks (Zhu et al. 2011; Sidrauski et al. 2013; Stern et al. 2013; Batista et al. 2016), highlighting the evolutionarily conserved role of the eIF2 α signaling pathway in learning and memory. Thus, convergent genetic and pharmacological manipulations provide strong evidence that derepression of the translational program controlled by eIF2 α is sufficient to enhance memory.

The opposite is also true: increased eIF2 α phosphorylation in the brain impairs long-term memory. Administration of Sal003, an inhibitor of eIF2 α phosphatases, increases eIF2 α phosphorylation in both mice and chicks and prevents their ability to form long-term memory (Costa-Mattioli et al. 2007; Batista et al. 2016). Moreover, using an elegant pharmacogenetic approach to allow specific activation of engineered PKR in the hippocampus, Jiang and coworkers (2010) showed that increasing eIF2 α phosphorylation only in CA1 neurons of the mouse hippocampus was sufficient to block long-term memory. Importantly, in this study, the pharmacogenetic manipulation of eIF2 α phosphorylation did not affect general translation. In contrast, local application of low-dose anisomycin to the CA1 region significantly decreased overall translation without blocking memory formation. Thus, in this model, a strong argument could be made that specific translational changes downstream of eIF2 α phosphorylation are required for memory, as

opposed to a requirement for a general increase in translation.

During LTP, eIF2 α phosphorylation is reduced (Costa-Mattioli et al. 2005, 2007). However, an increase in eIF2 α phosphorylation occurs during a protein synthesis-dependent form of LTD associated with activation of metabotropic glutamate receptors, termed mGluR-LTD (Di Prisco et al. 2014; Trinh et al. 2014). Indeed, genetic reduction of eIF2 α phosphorylation (or treatment with ISRIB) enhances LTP (Costa-Mattioli et al. 2007; Zhu et al. 2011; Huang et al. 2016; Placzek et al. 2016) but blocks mGluR-LTD (Fig. 1B) (Di Prisco et al. 2014). By contrast, increased eIF2 α phosphorylation impairs LTP (Costa-Mattioli et al. 2007; Jiang et al. 2010; Huang et al. 2016) but induces mGluR-LTD (Fig. 1C) (Di Prisco et al. 2014). Taken together, eIF2 α phosphorylation bidirectionally controls two major forms of synaptic plasticity (LTP and LTD) and is thus crucial for memory formation.

Some of the proteins regulated by phosphorylation of eIF2 α during memory formation have been identified, including ATF4 (Costa-Mattioli et al. 2007) and oligophrenin-1 (OPHN1) (Di Prisco et al. 2014). Similar to other situations where eIF2 α regulation is important, these mRNAs contain upstream open reading frames (uORFs) in their 5' untranslated region (UTR) (Hinnebusch et al. 2016). However, there has not yet been a systematic examination of all the mRNAs in neurons that are regulated by the eIF2 α pathway in the brain. The use of translating ribosome affinity purification (Heiman et al. 2008), ribosome profiling (Ingolia et al. 2018), or a combination of both methods, will help to elucidate the translational state regulated by phosphorylation of eIF2 α in the brain.

TRANSLATIONAL CONTROL BY mTORC1

Treatment with the highly specific mTORC1 inhibitor, rapamycin (Tang et al. 2002; Bekinschtein et al. 2007) or direct pharmacogenetic inhibition of mTORC1 (Stoica et al. 2011) prevents the ability to elicit long-lasting LTP and form long-term memory (Costa-Mattioli and Monteggia 2013). mTORC1 integrates information

from various synaptic inputs and is believed to control the formation of memory by regulating translation via S6 kinase (S6K) and eIF4E-binding proteins (4E-BPs) (Sonenberg and Hinnebusch 2009; Proud 2018). S6K regulates translation initiation and elongation through phosphorylation of eukaryotic initiation factor 4B (eIF4B) and eEF2 kinase (eEF2K), respectively. By contrast, 4E-BPs exclusively repress translation initiation through binding to eIF4E. Although inhibition of mTORC1 blocks memory formation, activation of mTORC1 does not enhance memory formation (Graber et al. 2013). This is in contrast to eIF2 α phosphorylation, where as described above, memory formation is facilitated when levels of eIF2 α are reduced. Gain-of-function activation of mTORC1 by inhibiting upstream suppressors of mTORC1, tuberous sclerosis complex (Tsc) or phosphatase and tensin homolog (Pten), impairs, not enhances, synaptic plasticity and memory formation (von der Brelie et al. 2006; Ehninger et al. 2008; Sperow et al. 2012; Lugo et al. 2013). Similarly, whereas mice lacking 4E-BP2, the major 4E-BP isoform in the brain, show a lowered threshold for the induction of LTP (Banko et al. 2005), under normal learning conditions, 4E-BP2-deficient mice show impaired LTP and long-term memory (Banko et al. 2005). Thus, the correct balance of mTORC1 activation seems critical for normal memory formation.

The cap-binding factor eIF4E is normally inhibited by nonphosphorylated 4E-BPs (Sonenberg and Hinnebusch 2009). In nonneuronal cells, activation of mTORC1 promotes translation rates via phosphorylation of 4E-BPs (Hsieh et al. 2012; Thoreen et al. 2012; Proud 2018). However, in the adult brain, there are only low levels of phosphorylated 4E-BP2 (Bidinosti et al. 2009), the major 4E-BP form. The low levels of phosphorylation are associated with increased deamidation of 4E-BP2, which increases its association with the mTORC1 adaptor rapTOR, although the significance of this enhanced binding is still unclear (Bidinosti et al. 2009). Thus, it is unclear whether mTORC1 regulates translation in the adult brain through phosphorylation of 4E-BPs. It should also be noted that

mTORC1 regulates a variety of biological processes other than protein synthesis, including autophagy, metabolism, and lipid metabolism biosynthesis (Wullschlegel et al. 2006; Laplante and Sabatini 2012). Thus, it is not yet clear whether mTORC1 regulates memory formation by controlling protein synthesis or other biological processes.

REGULATION OF TRANSLATION ELONGATION

Interest in the role of regulating translational elongation in the nervous system has increased in recent years (Taha et al. 2013; Richter and Collier 2015). Although we have a good understanding of how translation initiation of specific mRNAs can be regulated by uORFs, structured 5'UTRs, and interactions between RNA-binding proteins and the initiation machinery (Sossin and Lacaille 2010; Darnell and Richter 2012), the role of elongation in controlling translation of specific transcripts is less clear.

There are two major elongation factors, the GTPases eEF1 and eEF2. eEF1 is comprised of eEF1A and eEF1B; eEF1A recruits aminoacylated transfer RNAs (tRNAs) to the A site in the ribosome and is complexed with eEF1B, its guanine nucleotide exchange factor (GEF) (Sasikumar et al. 2012). The translation of eEF1A mRNA is regulated by a TOP sequence in its 5'UTR. In neurons, eEF1A mRNA is translated locally at dendrites during memory formation and synaptic plasticity (Giustetto et al. 2003; Huang et al. 2005; Tsokas et al. 2005).

In contrast to eEF1, eEF2 is one of the few GTPases that does not require a GEF for activation. eEF2 ratchets the peptidyl-tRNA from the hybrid position on the ribosome after peptide bond formation to the P-site position (Kaul et al. 2011; Dever et al. 2018). There are reports of increased synthesis of eEF2 after induction of synaptic plasticity (Carroll et al. 2004; Takei et al. 2009) and eEF2, like eEF1A, is regulated through a TOP motif. Thus, because TOP mRNAs are regulated downstream of the mTORC1 pathway, one mechanism for mTORC1 regulation of elongation could be through increasing levels of elongation factors.

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REGULATION OF ELONGATION THROUGH eEF2K

Much attention has been devoted to studying eEF2 phosphorylation at Thr57 by eEF2K (Nairn and Palfrey 1987; Proud 2015; Dever et al. 2018). No other kinase appears to phosphorylate eEF2 at this site, as there is a complete lack of detectable eEF2 phosphorylation when eEF2K is genetically ablated (Heise et al. 2017). Phosphorylation of eEF2 reduces its binding to the ribosome and thus decreases elongation (Proud 2015, 2018). The impact of eEF2 phosphorylation on translation depends on whether (1) the rate of elongation is rate-limiting for translation overall, (2) the levels of eEF2 are rate-limiting for elongation, and (3) the extent of eEF2 phosphorylation. Increasing levels of eEF2 in cultured neurons decreased elongation times and increased protein synthesis, suggesting that eEF2 levels can be rate-limiting in neurons under some circumstances (Takei et al. 2009). However, increasing levels of active eEF2 by eliminating eEF2 phosphorylation through removal of eEF2K did not change the overall rate of protein synthesis in the brain (Heise et al. 2017).

A decrease in eEF2 phosphorylation in the hippocampus occurs after fear conditioning and after induction of long-term increases in synaptic strength in *Aplysia* neurons (Im et al. 2009; McCamphill et al. 2015). Preventing the decrease in eEF2 phosphorylation blocks long-term increases in synaptic strength in *Aplysia* (McCamphill et al. 2017), demonstrating that eEF2 dephosphorylation is required for long-term facilitation. Accordingly, in mice lacking eEF2K and with decreased eEF2 phosphorylation, long-term fear memory is impaired (Heise et al. 2017).

eEF2 phosphorylation is regulated by mTORC1 (Carroll et al. 2004; Inamura et al. 2005; McCamphill et al. 2015) through a conserved S6K phosphorylation site in eEF2K that inactivates the kinase (Wang et al. 2001; Weatherill et al. 2011). This site can also be phosphorylated by ERK through RSK2 (Wang et al. 2001).

Increased eEF2 phosphorylation has been shown in a number of synaptic plasticity and learning procedures, including novel taste learn-

ing (Belelovsky et al. 2005), LTP in the dentate gyrus (Panja et al. 2009), mGluR-LTD (Park et al. 2008), and a form of intermediate facilitation in *Aplysia* (McCamphill et al. 2015). Preventing the increase in eEF2 phosphorylation blocks both mGluR-LTD (Park et al. 2008) and intermediate facilitation in *Aplysia* (McCamphill et al. 2015), but eEF2 phosphorylation does not appear to be required for LTP in the dentate gyrus (Panja et al. 2009). It is not clear whether the increased eEF2 phosphorylation inhibits overall translation elongation rates in these situations, but it has been shown to be required for the increased translation of specific mRNAs including CAMKII α , brain-derived neurotrophic factor (BDNF), microtubule-associated protein (Map)1B and other cytoskeletal proteins (Fig. 2) (Scheetz et al. 2000; Davidkova and Carroll 2007; Park et al. 2008; Verpelli et al. 2010; Kenney et al. 2016; Heise et al. 2017).

There are two proposed mechanisms by which increased eEF2 phosphorylation could lead to the up-regulation of translation of specific mRNAs. When elongation is slow, the ribosome is slow to clear the initiation site; this decreases the rate of initiation on well-translated mRNAs, freeing rate-limiting initiation factors (reviewed in Sossin and Lacaille 2010). The second proposed mechanism involves eEF2 phosphorylation, which plays a role in the release of stalled polysomes. This proposal arose because of a correlation between synaptic plasticity events that specifically require eEF2 phosphorylation and those that are mediated by initiation-independent translation (i.e., forms of plasticity that are blocked by elongation inhibitors and resistant to translation inhibitors; see McCamphill et al. 2015). These forms of plasticity include mGluR-LTD in hippocampal neurons (Graber et al. 2013) and intermediate facilitation in *Aplysia* neurons (McCamphill et al. 2015).

Stalled polysomes have been suggested as an important mechanism for regulated transport of mRNAs to the synapse (Sossin and DesGroseillers 2006). mRNA initiation takes place in the cell soma; at some point elongation is stalled, and the stalled polysome is packaged into an RNA granule that is then transported to the syn-

Figure 2. Upstream and downstream of eukaryotic elongation factor 2 (eEF2) phosphorylation. In neurons, eukaryotic elongation factor 2 kinase (eEF2K) can be activated by calcium influx, metabotropic glutamate receptor (mGluR) activation, or protein kinases. The resultant increase in eEF2 phosphorylation increases translation of selective transcripts either by freeing up key initiation factors or by reactivating stalled polysomes. The increased synthesis of these proteins is linked to changes in synaptic strength (synaptic plasticity). In contrast, blockade of the *N*-methyl-D-aspartate receptor (NMDAR) or activation of the S6 kinase downstream of target of rapamycin complex 1 (TORC1) leads to a decrease in the activity of eEF2K. The resultant decrease in eEF2 phosphorylation causes an overall increased elongation rate with specific increases in the synthesis of several secreted factors, such as brain-derived neurotrophic factor (BDNF) in vertebrates and sensorin in *Aplysia*. The increased synthesis of these factors is linked to protein synthesis-dependent increases in synaptic strength (synaptic plasticity). PKA, Protein kinase A; PKC, protein kinase C.

apse. After the stall is relieved, translation from previously stalled polysomes is dependent only on elongation, but not initiation, similar to the forms of plasticity that require eEF2 phosphorylation noted above. The fragile X mental retardation protein (FMRP), the protein lost in fragile X syndrome in humans, is associated with stalled polysomes (Mazroui et al. 2002; Darnell et al. 2011; El Fatimy et al. 2016). FMRP can stall polysomes through direct binding to ribosomal RNA (Chen et al. 2014). The role of FMRP in stalling

polysomes is consistent with the role of FMRP in regulating mGluR-LTD (Hou et al. 2006; Nosyreva and Huber 2006; Graber et al. 2017). However, how phosphorylation of eEF2 regulates stalled polysomes is not immediately clear. One possibility is that the inactive phosphorylated form of eEF2 plays a role in stalling, and removal of this inactive form through eEF2 dephosphorylation is required for unstalling.

If mRNAs are transported to synapses in stalled polysomes, these polysomes would need

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to be protected from the ribosome-associated quality-control pathway that rescues stalled polysomes (Buskirk and Green 2017). Indeed, this rescue pathway is particularly important when levels of rare charged tRNAs are low, and the absence of this rescue pathway leads to neuronal degeneration (Ishimura et al. 2014). This may indicate that ribosomes are a limiting resource in neurons, which would be consistent with stalled polysomes, sequestering many of the ribosomes in dendrites and thus making the number of ribosomes rate-limiting for basal translation. A study examining changes in polysomes after learning (Ostroff et al. 2017) identified polysomes that are both sensitive and resistant to the initiation inhibitor 4EGI-1, which blocks the association of eIF4E and eIF4G, which is required for cap-dependent translation (Moerke et al. 2007). In this study, the sensitive and resistant polysomes were differentially distributed at distinct types of synapses (Ostroff et al. 2017). It was unclear in this study, however, whether the 4EGI-1-resistant polysomes were stalled or initiated in a cap-independent (and thus 4EGI-1-independent) manner.

TRANSLATIONAL CONTROL AND NEURODEVELOPMENTAL DISORDERS

Genetic perturbations impinging on translational control mechanisms have been associated with developmental disorders of the nervous system. In the last few years, it has been shown that specific translational control mechanisms are perturbed in these cases. The questions to be addressed are (1) whether restoration of translation reverses the cognitive decline in these disorders, and (2) whether drugs can be developed to target translation in the treatment of brain disorders.

PERTURBED TRANSLATIONAL CONTROL IN NEUROLOGICAL DISORDERS

How dysregulation of the signaling pathways impinging on translation contributes to the pathophysiology of several neurodegenerative diseases and neurodevelopmental disorders has been recently reviewed (Buffington et al.

2014; Huber et al. 2015; Kapur et al. 2017). One important context of translational regulation in neurological disorders is autism spectrum disorders (ASDs). The importance of translational control in ASD is underscored by the many neurological disorders in which mTORC1 activity is perturbed as a result of single gene mutations in mTORC1 upstream regulators (Pten, Tsc, or Fmr1). Indeed, in all three cases, enhanced translation rates have been postulated to cause ASD (Kelleher and Bear 2008). However, deletion of Pten or Tsc not only activates mTORC1, but also alters mTORC2 activity (Laplane and Sabatini 2012). Because mTORC2 is also required for LTP and mnemonic processes (Huang et al. 2013), it is currently unclear which mTOR complex drives the ASD pathology in these TORopathies. In addition, as we mentioned above, mTORC1 regulates other translation-independent processes (Proud 2018).

The strongest evidence that translation up-regulation leads to ASD-like behaviors emerged from studies of mice lacking 4E-BPs or over-expressing eIF4E. In both models, increased eIF4E-mediated translation leads to ASD-like behaviors (Gkogkas et al. 2013; Santini et al. 2013). Moreover, agents that modestly decrease translation rates, like rapamycin, metformin, or an inhibitor of the eIF4E kinase, MNK1, reverse ASD-like behaviors in FMRP-deficient mice (Busquets-Garcia et al. 2013; Gkogkas et al. 2014; Gantois et al. 2017), supporting the notion that enhanced overall translation contributes to the pathology associated with fragile X syndrome. Although most of these studies rescued the phenotypes in Fmr1-deficient mice by repressing initiation, in one study, reduction of the RNA-binding protein CPEB rescued pathology in Fmr1-deficient mice and this was associated with normalization of translation elongation rates (Udagawa et al. 2013).

These data suggest that increased translation may cause neuronal dysfunction in the fragile X syndrome. Accordingly, deletion of 4E-BP2 leads to an increase in the synthesis of the synaptic adhesion protein neuroligin-1, and preventing this increase ameliorates autistic-like behaviors in this rodent model (Gkogkas et al.

2013). Matrix metalloprotease 9 (Mmp9) is overexpressed in fragile X mice and decreasing its translation through reducing eIF4E phosphorylation rescues several autistic-like behaviors in this model (Gkogkas et al. 2014).

The second context in which translation dysregulation has been observed is neurodegenerative disease. In this case, a decrease in translation rates was reported in Alzheimer's disease (AD) (Langstrom et al. 1989), likely because of the activation of the integrated stress response (ISR), wherein eIF2 α phosphorylation is a central component (Wek 2018). Increased phosphorylation of eIF2 α has been observed in AD (Chang et al. 2002a,b; Hoozemans et al. 2005; Page et al. 2006), traumatic brain injury (Dash et al. 2015; Chou et al. 2017), and prion disease (Moreno et al. 2012). It is currently unclear whether translation dysregulation underlies, or is a downstream effector of, neurodegenerative disease. Nevertheless, increasing translation could ameliorate the disease. Indeed, both genetic reduction of eIF2 α phosphorylation (PKR or PERK knockout mice and GADD34-overexpressing vectors) or pharmacological correction of the abnormal translational program controlled by eIF2 α (e.g., using ISRIB and PKR inhibitors) reverses the cognitive decline associated with AD (Lourenco et al. 2013; Ma et al. 2013; Segev et al. 2015), traumatic brain injury (Chou et al. 2017), as well as the pathology associated with prion disease (Moreno et al. 2012).

Recently, eEF2 phosphorylation has also been reported to be elevated both in mouse models of AD and AD patients (Ma et al. 2014). Inhibiting eEF2K restored LTP that had been inhibited by β amyloid (Ma et al. 2014).

mTOR complexes have also been proposed to be targets for neurodegenerative diseases (Santos et al. 2011), although the proposed role for mTOR in neurodegenerative disease has mainly been through mTOR regulation of autophagy as opposed to direct regulation of protein synthesis.

Thus, perturbed eIF2 α phosphorylation (and possibly eEF2 phosphorylation), is responsible, at least in part, for some of the cognitive and cellular aspects underlying neurodegenerative disorders. Neurodegenerative diseases are

also caused by expansions of nucleotide repeats in proteins and these may also have an important contribution from dysregulated translation centered on those nucleotide repeats (Zu et al. 2018), further emphasizing the importance of translational control in neuronal disease.

CONCLUDING REMARKS

Regulation of mRNA translation initiation and elongation is essential for synaptic plasticity and memory formation. Moreover, alterations in translation rates resulting from mutations in signaling pathways regulating translation or activation of the ISR contribute to pathogenesis in a variety of neurological disorders. One of the most intriguing questions in the memory field, the identification of the nature of the proteins that are synthesized in response to a memory paradigm, remains largely unanswered. Given that memory is encoded in a small subset of neurons in a particular brain area, answering this question will require state-of-the-art intersectional molecular genetic approaches combined with translating ribosome affinity purification (TRAP) in the specific neurons that encode memories.

A better understanding of translational control in brain processes will require a full dissection at the cell-type level. The formation of memory is not only mediated by principal (pyramidal) neurons in a given brain area. In fact, other neuronal cell types, such as inhibitory or dopaminergic neurons, are crucially involved in memory formation. However, understanding the regulation of translation in these cell types is just beginning (Ran et al. 2009; Placzek et al. 2016).

From a therapeutic standpoint, it would be interesting to determine whether some of the very promising genetic manipulations blocking or activating translation can be replicated using pharmacology. Pharmacological agents that modulate translation rates by regulating the integrated stress response, such as PKRi and ISRIB, have been identified and initial results suggest the usefulness of these drugs in improving cognition (Zhu et al. 2011; Sidrauski et al. 2013; Chou et al. 2017). Their efficacy in multi-

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ple mouse models of disease remains to be examined before considering whether these drugs can be used to treat human disease. Drugs that act on other targets, including downstream effectors of TORC1, regulators of stalled polyosomes, and inhibitors and activators of eEF2K are also interesting candidates for ameliorating disease.

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