Review

Translating from cancer to the brain: regulation of protein synthesis by eIF4F

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Formation of eukaryotic initiation factor 4F (eIF4F) is widely considered to be the rate-limiting step in cap-dependent translation initiation. Components of eIF4F are often up-regulated in various cancers, and much work has been done to elucidate the role of each of the translation initiation factors in cancer cell growth and survival. In fact, many of the basic mechanisms describing how eIF4F is assembled and how it functions to regulate translation initiation were first investigated in cancer cell lines. These same eIF4F translational control pathways also are relevant for neuronal signaling that underlies long-lasting synaptic plasticity and memory, and in neurological diseases where eIF4F and its upstream regulators are dysregulated. Although eIF4F is important in cancer and for brain function, there is not always a clear path to use the results of studies performed in cancer models to inform one of the roles that the same translation factors have in neuronal signaling. Issues arise when extrapolating from cell lines to tissue, and differences are likely to exist in how eIF4F and its upstream regulatory pathways are expressed in the diverse neuronal subtypes found in the brain. This review focuses on summarizing the role of eIF4F and its accessory proteins in cancer, and how this information has been utilized to investigate neuronal signaling, synaptic function, and animal behavior. Certain aspects of eIF4F regulation are consistent across cancer and neuroscience, whereas some results are more complicated to interpret, likely due to differences in the complexity of the brain, its billions of neurons and synapses, and its diverse cell types.

Beginning with the first experiments injecting the antibiotic and translation elongation inhibitor puromycin into mice, translation has been known to be important for the formation of long-term memory (Flexner et al. 1963). Since that initial study, which was published in 1963, many of the mechanisms of translation have been discovered, including initiation, ribosome recruitment, elongation, and the regulation of the translation factors involved in each step. These translational control pathways have proved to be important in both cancer and neuronal signaling, providing the basis for cancer cell growth and the signaling required for long-term synaptic plasticity and memory formation, respectively. One such critical translational control point is the eukaryotic initiation factor 4F (eIF4F) complex, which binds to mRNA and is crucial for cap-dependent translation initiation. Many of the factors that are components of the complex have been investigated extensively for cancer therapies, but the precise details of how eIF4F and other translation machinery are regulated in the brain are not well understood. Here, we follow the progression of studies on eIF4F, from the role the complex and its associated factors have in cancer, to their role in neuronal signaling, synaptic plasticity, and memory formation. We focus on findings that have been shown to be transferable across fields, as well as findings that appear more complicated and nuanced in the diverse cell types and experimental models utilized to study the brain.

eIF4F complex formation and regulation

The eIF4F complex consists of eukaryotic initiation factor 4E (eIF4E), the cap-binding protein, eukaryotic initiation factor 4G (eIF4G), which binds the other translation factors in the complex, and eukaryotic initiation factor 4A (eIF4A), the DEAD-box RNA helicase, along with additional accessory proteins (Fig. 1; Sonenberg et al. 1979; Tahara et al. 1981). eIF4E was the first eIF4F component that was discovered (Sonenberg et al. 1979), but it is also less abundant than the other factors in the complex, and is thus considered to be the limiting factor for translation initiation (Duncan and Hershey 1983). Because eIF4E binds to the m^7GTP cap of mRNAs, its main role is to direct other eIF4F factors and translation machinery to the 5′ end of mRNAs (Raught and Gingras 1999).

The scaffold protein, eIF4G, binds to both eIF4E and eIF4A and helps to anchor all of the eIF4F complex proteins together. This binding by eIF4G ensures that all three of the eIF4F proteins are in proximity to one another, even though there is no direct interaction of eIF4E with eIF4A. eIF4G exists as two isoforms, encoded by two different genes, *eIF4G1* and *eIF4G2*, which share a similarity of 46% at the amino acid level, although the eIF4G1 is the more prevalent isoform (Gradi et al. 1998). eIF4G binds directly to eIF4A (Imataka and Sonenberg 1997), and formation of the complex with eIF4E permits eIF4G to increase the helicase activity of eIF4A (Feoktistova et al. 2013). eIF4G also can bind to the poly (A)-binding protein (PABP), which recognizes the tail end of the mRNA and circularizes it, facilitating translation (Tarun and Sachs 1996). The interaction between eIF4G and PABP is considered to be a stimulatory one (Borman et al. 2002; Kahvejian et al. 2005; Park et al. 2011).

The last translation factor of the core eIF4F complex is the helicase eIF4A, which helps to unwind the secondary structure of

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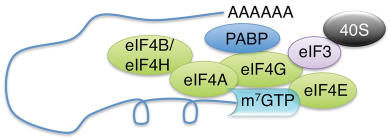

Figure 1. The eIF4F translation initiation complex. The main components of the eIF4F translation initiation complex are eIF4A, the DEAD-box helicase, eIF4G, the scaffolding protein, and eIF4E, the cap-binding protein. eIF4G binds to both eIF4A and eIF4E, and it also helps to recruit eIF3, which then recruits the 40S ribosomal unit. eIF4G binds to PABP, which binds to the poly-(A) tail of mRNA and helps to circularize it. eIF4A helicase activity helps resolve mRNA secondary structure and is stimulated by eIF4B and eIF4H, which share a common binding site allowing only one of these factors to bind to eIF4A at a time.

mRNAs. Similar to eIF4G, eIF4A also exists in two isoforms, eIF4A1 and eIF4A2, which have 90% similarity at the amino acid level despite being encoded by two different genes on different chromosomes (Nielsen and Trachsel 1988; Conroy et al. 1990). Both isoforms of eIF4A can bind to eIF4G and incorporate into the cap-binding complex (Yoder-Hill et al. 1993), but previous studies have implied that eIF4A1 is the most important isoform for translation, as knockdown of eIF4A2 in cultured cells did not have an appreciable effect on overall translation (Galicia-Vazquez et al. 2012). In addition, the expression of the two isoforms switches from predominantly eIF4A1 to predominantly eIF4A2 in cells that are not dividing (Williams-Hill et al. 1997; Galicia-Vazquez et al. 2012). The activity of eIF4A can be modulated by the accessory proteins eukaryotic initiation factor 4H (eIF4H) and eukaryotic initiation factor 4B (eIF4B), both of which can stimulate the helicase activity of eIF4A by altering the interaction of eIF4A and ATP (Rogers et al. 1999, 2001; Rozovsky et al. 2008; Marintchev et al. 2009). eIF4B and eIF4H share a common binding site, suggesting that only one can be bound to eIF4A at a time (Marintchev et al. 2009).

A critical level of control for eIF4F is via the inhibition of factors in the complex by binding partners that regulate their function. For example, eIF4E is bound by eukaryotic initiation factor 4E-binding protein (4E-BP), which sequesters eIF4E from eIF4G and the cap-binding complex, thereby inhibiting translation initiation (Fig. 2; Pause et al. 1994; Haghighat et al. 1995; Marcotrigiano et al. 1999). There are multiple isoforms of 4E-BP that are expressed preferentially in different tissues, but each isoform inhibits eIF4E by binding to the same site that eIF4G binds (Tsukiyama-Kohara et al. 2001; Banko et al. 2005). When 4E-BP becomes phosphorylated by mechanistic target of rapamycin complex 1 (mTORC1), it no longer binds eIF4E, thereby allowing for eIF4E integration into the cap-binding complex (Gingras et al. 1999, 2001). Similar to eIF4E and 4E-BP, eIF4A is bound by programmed cell death 4 (PDCD4), which inhibits the helicase activity of eIF4A and its interaction with eIF4G by binding to one of two interaction sites it has with eIF4G (Yang et al. 2003; Suzuki et al. 2008). PDCD4 is phosphorylated at serine 67 by p70 ribosomal S6 kinase 1 (S6K1), which itself is phosphorylated and activated by mTORC1 (Dorrello et al. 2006). PDCD4 also can be phosphorylated at serine 76 by p90 ribosomal S6 kinase (RSK) (Galan et al. 2014). The disinhibition of eIF4A is not via a direct inactivation of PDCD4. Instead, the phosphorylation of PDCD4 on either serine 67 or serine 76 results in its ubiquitination and degradation by the ubiquitin proteasome pathway (Dorrello et al. 2006; Galan et al. 2014).

In addition to inhibition by other proteins, the activity of the translation factors in the cap-binding complex are regulated by phosphorylation at specific amino acid residues. eIF4B can be phosphorylated at serine 422 by both S6K1, via phosphorylation and activation by mTORC1, and by RSK, via phosphorylation and activation by mitogen-activated protein kinase (MAPK), which is also referred to as extracellular signal-regulated kinase (ERK) in the literature. Although eIF4A activity does not appear directly affected by phosphorylation of eIF4B, phosphorylated eIF4B interacts with eukaryotic initiation factor 3 (eIF3), which helps to recruit the ribosome to mRNA (Shahbazian et al. 2006; Kroczynska et al. 2009). Similarly, eIF4E can be phosphorylated downstream from ERK by MAPK-interacting protein kinase 1 (Mnk1) at serine 209 (Joshi et al. 1995). Mnk1 binds to eIF4G, which brings Mnk1 into proximity with eIF4E to allow for its phosphorylation (Pyronnet et al. 1999; Waskiewicz et al. 1999). The phosphorylation of eIF4E is thought to increase translation by increasing its affinity for mRNA, but paradoxically, it has been shown to decrease affinity of eIF4E for the cap, which may instead increase the rate of eIF4E recycling through the complex (Scheper and Proud 2002; Scheper et al. 2002; Zuberek et al. 2003). There is evidence that the phosphorylation eIF4G1 is regulated by multiple signaling pathways, as it can be phosphorylated at serine 1093 by protein kinase C beta II (PKCβII) and at serine 1232 by cyclin dependent kinase 1 (Cdk1) (Dobrikov et al. 2014, 2018). The phosphorylation of eIF4G1 at these two serine residues modulates translation initiation in opposite directions, with phosphorylation of serine 1093 being conducive (Dobrikov et al. 2018) and phosphorylation of serine 1232 being inhibitory for translation (Dobrikov et al. 2014). Although phosphorylation of serine 1232 increases the interaction of eIF4G1 with eIF4A, it decreases the affinity of mRNA for the two factors (Dobrikov et al. 2014), thereby decreasing translation initiation.

More recently, multiple components of eIF4F were shown to be modified by O-GlcNAcylation, which can affect the activity of the proteins. eIF4A is modified at serine 322/323 and eIF4G is modified at serine 61, which results in different effects on translation. The O-linked β-*N*-acetylglucosamine (O-GlcNAc) modification on eIF4A results in less binding to eIF4G, as well as a reduced helicase activity and translation. On the other hand, the O-GlcNAc modification on eIF4G increases translation through its interaction with poly(A)- binding protein (PABP) and mRNA (Li et al. 2019).

For a process that is critical for cell survival, it makes sense that translation is a heavily regulated step with multiple levels of control. Within the eIF4F complex alone there are many regulatory mechanisms, including proteins that can either bind the core

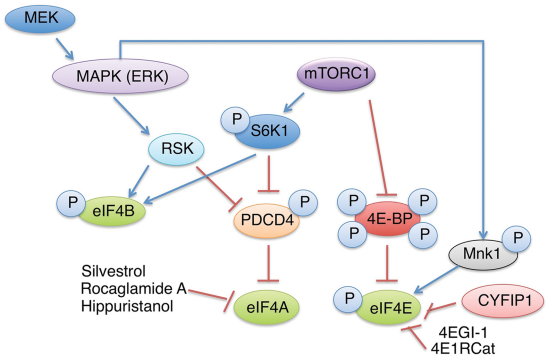

Figure 2. The mTORC1 and MEK-ERK signaling pathways regulate eIF4F activity and assembly. 4E-BP is phosphorylated and inactivated by mTORC1, which frees eIF4E and allows it to bind to eIF4G and incorporate into the complex. eIF4E also is phosphorylated by Mnk1, which activates it, and is bound by CYFIP1, which sequesters it from the eIF4F complex. PDCD4 and eIF4B are both phosphorylated by S6K1 and RSK, which are downstream from mTORC1 and MEK-ERK, respectively. The phosphorylation of eIF4B results in its activation and the phosphorylation of PDCD4 results in its inactivation via ubiquitination and degradation by the proteasome pathway, resulting in decreased repression of eIF4A.

components of eIF4F or modify their activity via posttranslational modifications, including phosphorylation and O-GlcNAcylation. There also are different upstream signaling pathways that can regulate eIF4F, including the mTORC1 and ERK pathways. All of these levels of regulation allow checkpoints for sensing when something goes awry in the cell, but concurrently allows for processes that cells can hijack when they are working abnormally, as they are in cancer or in neurological disorders.

eIF4F and cancer

Cancer studies have provided the framework for much of our knowledge about the mechanisms of translation initiation and have fostered further studies of translation in many different tissues and organs, including the brain. Much of the research centered on eIF4F, including details of how the complex assembles and what individual components do, was first studied in cancer cell lines (see Pelletier et al. 2015 for an excellent review that focuses on the role of eIF4F in cancer). The eIF4F factors, particularly eIF4E, have been shown to be up-regulated in a variety of cancers and cancer cell lines from lymphomas to breast cancer, which is thought to increase the translation of other procancer proteins (Kerekatte et al. 1995; Miyagi et al. 1995; Anthony et al. 1996; Rosenwald et al. 1999; Wang et al. 1999; Bauer et al. 2001, 2002; Seki et al. 2002; De Benedetti and Graff 2004; Ruggero et al. 2004; Lin and Aplan 2007; Wendel et al. 2007; Horvilleur et al. 2014; Modelska et al. 2015; Jaiswal et al. 2018; Oblinger et al. 2018; Wen et al. 2007). Conversely, targeting eIF4F factors in cancer has been shown to decrease the translation of cancer-relevant proteins, decrease tumor growth, and/or make cancer cells more susceptible to cell death, with promising preclinical results. Targeting translational control pathways, particularly eIF4F, remains a promising field in cancer therapeutics.

One of the first papers demonstrating the importance of eIF4F in cancer showed that increasing the expression of eIF4E in NIH-3T3 cells and fibroblasts causes their transformation. Subsequently, a similar transformation result was observed with overexpression of eIF4G (Lazaris-Karatzas et al. 1990; Fukuchi-Shimogori et al. 1997), and later with eIF4H, in NIH-3T3 cells (Vaysse et al. 2015). The implication of the results of these studies is that the eIF4F proteins are oncogenes themselves and are responsible for transforming cells. Overexpression of eIF4E in a transgenic mouse line confirmed this as it causes a variety of cancers including lymphomas, angiosarcomas, lung carcinomas, and hepatomas, beginning at 16 mo of age (Ruggero et al. 2004). Mouse lines with other eIF4F-related factors perturbed in a way to facilitate translation can cause similar changes, as was observed in a PDCD4 knockout mouse that develops lymphomas (Hilliard et al. 2006). These studies show that increasing eIF4F activity in some way either facilitates or causes cancer, which makes it an attractive target for potential therapies. In fact, many cancer studies have attempted to target eIF4F, either by knocking down or inhibiting eIF4F members and their associated factors, in order to limit translation and tumor growth. These studies have taught us about the complex functions of eIF4F and its accessory proteins, and which steps in its formation and regulation are either vital or dispensable for normal function.

Many cancer studies have targeted eIF4E using small molecules to block its function, with promising results. A class of histidine triad nucleotide binding protein (HINT)-dependent pronucleotides that are able to inhibit eIF4E binding to the cap inhibited the epithelial to mesenchymal transition, which is a critical step in epithelial cancer (Ghosh et al. 2009). The same small molecule also sensitized breast and lung cancer cell lines to the cancer drug gemcitabine (Li et al. 2013). A different class of drugs, 4EGI-1 and 4E1RCat, which both displace eIF4E from binding to eIF4G, were shown to induce cell death and inhibit the growth of several cancer cell lines, as well as sensitizing cells to proapoptotic DNA damage (Moerke et al. 2007; Cencic et al. 2009). These studies strongly suggest a critical role for eIF4E in cancer progression.

Additional methods to genetically target and knockdown expression of eIF4E have shown similar results to the small molecule inhibitors of eIF4E, while also highlighting that there may be differential requirements for eIF4E in normal, untransformed cells. eIF4E-specific antisense oligonucleotides (ASOs) that decrease the amount of eIF4E mRNA are able to affect xenograft growth without affecting normal functions such as body and organ weight. Notably, although there was a knockdown of ~80% of eIF4E, overall cap-dependent protein synthesis only decreased by ~20% (Graff et al. 2007). A similar method using an shRNA model for eIF4E knockdown also showed tumor formation delay with some intestinal degeneration that was reversed after the shRNA was no longer expressed (Lin et al. 2012). A constitutive eIF4E heterozygous knockdown mouse with 50% of eIF4E expressed showed decreased cellular transformation without a noticeable effect on either overall cap-dependent translation or normal function (Truitt et al. 2015). These studies show that although eIF4E is crucial for cancer development and its overexpression can cause transformation, its requirement may be lower for normal function.

eIF4A also has been shown to be important for cancer cell growth. A class of drugs has been discovered that inhibit eIF4A, either by preventing it from binding to RNA, such as hippuristanol, or by causing it to bind unproductively to RNA, such as pateamine A and silvestrol (Bordeleau et al. 2005, 2008; Kuznetsov et al. 2009; Tsumuraya et al. 2011). Both types of eIF4A-targeting drugs have been tested in cancer with promising results. Silvestrol has been shown to decrease the amount of eIF4A in the eIF4F complex, and to decrease cap-dependent protein synthesis and tumor growth in a breast and prostate xenograft cancer model (Cencic et al. 2009). Silvestrol and its analog CR-31-B were shown to decrease translation by preferentially targeting mRNAs with G-quadruplex structures in T-cell acute lymphoblastic leukemia cells (Wolfe et al. 2014). Silvestrol also was able to decrease cell growth in leukemic cells (Lucas et al. 2009). Although hippuristanol prevents eIF4A binding to mRNA, Rocaglamide A, which is in the same family of drugs as silvestrol, was shown to actively inhibit translation by causing eIF4A1 to clamp onto specific sequences of mRNA and prevent the translation from occurring (Iwasaki et al. 2016). These studies suggest that blocking eIF4A function is a promising therapeutic approach to treating cancer, with the most robust effects observed with eIF4A inhibitors that cause active inhibition of mRNA targets of eIF4A.

Although there have not been as many studies investigating the contribution of the eIF4F accessory factors in cancer, there is some evidence that eIF4B and eIF4H can play an important role in the disease. Knocking down eIF4B in cancer cell lines using RNAi decreased translation and proliferation, and increased the rate of cell death. In addition, treatment of a lymphoma cancer line with siRNAs for eIF4B also decreased the amount of translation (Shahbazian et al. 2010). Knocking down eIF4H using shRNAs in lung cancer cells had similar effects, decreasing tumor growth, cell migration, and translation of key mRNAs, while increasing sensitization to chemotherapy (Vaysse et al. 2015).

The role of eIF4E phosphorylation in eIF4F formation and translation in normal cells is somewhat ambiguous, but its role in cancer growth has been well established. A knock-in mouse in which eIF4E cannot be phosphorylated exhibited resistance to tumoriogenesis in prostate cancer (Furic et al. 2010). Upstream of eIF4E, a Mnk1/2 double knockout mouse and a dominant-negative Mnk1 mouse both displayed decreased eIF4E phosphorylation with resistance to tumor proliferation (Wendel et al. 2007; Furic et al. 2010). Cercosporamide, a Mnk inhibitor, was shown to

induce apoptosis in cancer cells and suppress metastasis and xenograft tumor growth (Altman et al. 2013). The same Mnk inhibitor also suppressed primitive leukemic progenitors growth in acute myeloid leukemia (Altman et al. 2013).

Taken together, the studies described thus far have demonstrated that the eIF4F complex is important for the progression and treatment of cancer; however, its relevance for normal growth is less clear. Many of the mouse lines targeting either eIF4F or its associated factors exhibited normal development even though cancer cell growth was impaired. This is not all that surprising given that cancer cells, as highly replicating cells, may have a higher need for translation to maintain their growth. Knockdown of eIF4E via ASOs, shRNA, or in a heterozygous knockout mouse line all showed normal weight and growth, with overall translation largely unaffected. Although the constitutive deletion of eIF4E is lethal, decreasing the level 50%–80% did not appear to negatively impact normal tissue (Graff et al. 2007; Lin et al. 2012; Truitt et al. 2015). Similarly, a mouse knockout of Mnk1/2, which was shown to exhibit almost no eIF4E phosphorylation, clearly had decreased cancer progression, but again exhibited normal growth and development (Ueda et al. 2004; Furic et al. 2010). Normal cells exhibited greater resistance to multiple drugs that inhibit translation in comparison to transformed cells (Pelletier et al. 2015). It is possible that there are other eIF4F-associated factors that will prove to be more critical for development and growth in vivo. The current model that we have for eIF4F function begs for a more definitive answer to the question: Is the necessity of translation different in noncancerous cells, and is this true for all tissues and cell types?

eIF4F in neuroscience

In neuroscience, studies demonstrating the importance of eIF4F in neuronal and brain function are relatively recent in comparison to the cancer field. Similar to the cancer literature, most studies in neuroscience have focused on eIF4E, the cap-binding protein widely considered to be the limiting factor for translation initiation, and its inhibitor 4E-BP, although there have been studies on other eIF4F-related pathways. Unlike cancer cells, neurons are polarized cells with specialized compartments that allow them to form and alter their connections to other cells during development and in response to activity, including during memory formation. Neurons also are postmitotic cells that are no longer dividing, but can grow processes, in the form of axons and dendrites, which allow them to form connections with other neurons via synapses, all of which require de novo translation (Biever et al. 2019). Because of the complex structural network of neurons and the relevance to behavior, the type of experiments conducted to examine translational control in a neural context can often be different than that in other cells and tissues. Cancer studies typically examine cell growth rate, tumor formation, total translation, and eIF4F complex formation. It is clear that eIF4F complex formation and de novo translation are critical for the normal function of neuronal cells, but disruption of key points of translational control can also have dramatic effects on synaptic function and behavior without affecting overall de novo translation, presumably because translation of only a few critical mRNAs is impacted (see Table 1 for summary). Moreover, there is a substantial diversity of neurons in the brain that may exhibit cell type-specific differences, or even subcellular differences in either the regulation of the translation machinery or in the rate of de novo translation in response to activity. These questions are only now beginning to be addressed.

Multiple threads of research have shown that translation in neuronal processes is important for synaptic function and behavior. Translation machinery, including all of the eIF4F factors, was shown to be present in dendrites and synapses of neurons (Tang et al. 2002; Wang et al. 2002; Asaki et al. 2003). Brain-derived neurotrophic factor (BDNF), which stimulates translation in neurons, was observed to increase the phosphorylation of 4E-BP and S6K1 in the cell body and at the synapse, including in dendrites separated from the cell body (Takei et al. 2004). eIF4E was observed to colocalize with PSD-95 in dendrites and increase with neuronal stimulation by KCl (Moon et al. 2009). Overexpression of either 4E-BP1 or an RNA interference (RNAi) against S6K1 decreased the amount of dendrite outgrowth and branching measured in cultured neurons, and the basal dendrite number in organotypic cultures (Jaworski et al. 2005). Blocking both pathways also attenuated increased axon growth caused by activation of mTORC1 in utero electroporated animals (Gong et al. 2015). Conversely, knocking out 4E-BP in neurons that were electrophysiologically silent allowed them to refine without postsynaptic activity (Chong et al. 2018). Thus, eIF4F machinery is present in neuronal processes and the translation appears important for their growth.

A genetic model knocking out the eIF4F-associated factor 4E-BP has demonstrated the importance of eIF4F for synaptic function and behavior. Knockout mice that do not express 4E-BP2, which is the primary 4E-BP isoform in the brain, were shown to have altered synaptic plasticity and multiple abnormal behaviors. For example, early phase LTP (E-LTP) was converted to late phase LTP (L-LTP), but conversely, L-LTP induced with traditional stimulation paradigms was inhibited in area CA1 of hippocampal slices from mice that lack 4E-BP2. The 4E-BP2 knockout mice also were shown to have increases in both amplitude and frequency of spontaneous miniature excitatory postsynaptic currents (mEPSCs) in area CA1 and increased excitatory postsynaptic currents generated with minimum stimulation. The increase in postsynaptic currents was found to be α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)-mediated and due to increased translation of the GluA1/GluA2 AMPAR subunits (Ran et al. 2013). 4E-BP2 mutant mice were shown to display a number of behavioral phenotypes, including impaired spatial learning and memory, and deficits in long-term contextual threat memory (Banko et al. 2005). The 4E-BP2 mutant mice also had deficits in motor coordination and learning in the rotarod task, impaired working memory in the spontaneous alteration task, and enhanced memory for conditioned taste aversion (Banko et al. 2007).

In addition to the phenotypes described above, increased eIF4E signaling has been shown to cause autistic-like phenotypes in mice akin to mouse models with other upstream genetic perturbations that increase mTORC1 signaling (Sato 2016). The 4E-BP2 knockout mice showed autistic-like phenotypes that were correlated with increased excitatory-inhibitory balance. Although there were no differences in overall cap-dependent translation in the mice, the translation of specific mRNAs were dysregulated. In particular, several of the autistic-like behaviors in the 4E-BP2 were shown to require increased neuroligin 1 translation (Gkogkas et al. 2013). Transgenic mice that overexpress eIF4E phenocopied the autistic-like behaviors of the 4E-BP2 knockout mice, including repetitive and perseverative behaviors, as well as social interaction deficits that likely originate in the striatum and medial prefrontal cortex, respectively (Santini et al. 2013). In contrast to the 4E-BP2 knockout mice, the eIF4E overexpressing mice did exhibit a net increase in de novo translation in the striatum. Notably, the autistic-like behaviors in both the 4E-BP2 knockout and eIF4E overexpressing mice were reversed by reducing eIF4E–eIF4G interactions with 4EGI-1 (Gkogkas et al. 2013; Santini et al. 2013). Taken together, these findings suggest that dysregulated translation due to increased eIF4F complex formation can result in wide range of synaptic dysfunction and aberrant behaviors, some of which are consistent with autism.

The role of eIF4F complex formation has also been examined in memory consolidation in rodents. Infusion of 4EG1-1 into the

Table 1. Summary of studies of the role of eIF4F in cancer and neuroscience

Protein (modification)	Cancer literature	Neuroscience literature	Cancer references	Neuroscience references
eIF4E (overexpression)	↑ cell transformation ↑ variety of cancers in the mouse model	↑ autistic-like phenotypes ↑ total translation	Lazaris-Karatzas et al. 1990; Ruggero et al. 2004	Santini et al. 2013
eIF4E (knockdown)	↓ xenograft growth, ↓ tumor formation, ↓ cellular transformation	N/A	Graff et al. 2007; Lin et al. 2012; Truitt et al. 2015	N/A
4E-BP (knockdown)	N/A	Synaptic plasticity deficits ↓ spatial learning and memory ↓ contextual threat memory ↓ motor coordination ↓ working memory ↑ conditioned taste aversion ↑ autistic-like behaviors ↑ translation of specific mRNA targets	N/A	Ran et al. 2013; Banko et al. 2005, 2007; Gkogkas et al. 2013
eIF4E inhibition (4EGI-1)	↑ cell death ↓ growth of cancer cells Sensitized cells to DNA damage	↓ consolidation of auditory threat memory ↓ reconsolidation of auditory threat memory (also requires inhibition of S6K1) ↓ L-LTP and ↓ L-LTP-induced de novo translation ↓ polyribosomes	Moerke et al. 2007; Cencic et al. 2009	Hoeffer et al. 2011; Huynh et al. 2014; Hoeffer et al. 2013; Ostroff et al. 2017; Gkogkas et al. 2013; Santini et al. 2013
eIF4E (decreased phosphorylation)	↓ tumorigenesis and proliferation ↑ Apoptosis ↓ Metastasis	↓ LTP in the DG ↓ BDNF-induced increase in translation (with Mnk inhibitor) ↓ serotonin ↑ depression-like symptoms no change in total de novo translation (p-eIF4E mutant)	Furic et al. 2010; Wendel et al. 2007, Altman et al. 2013	Panja et al. 2014; Genheden et al. 2015; Amorim et al. 2018; Aguilar-Valles et al. 2018
eIF4G	Overexpression: ↑ cell transformation	Knockdown eIF4G2: ↓ density of dendritic filopodia ↓ spine formation	Fukuchi-Shimogori et al. 1997	Kar et al. 2013; Srivastava et al. 2012
eIF4H	Overexpression: ↑ cell transformation Knockdown: ↓ translation ↓ tumor growth/ migration ↑ sensitization to chemotherapy	Knockout mice: ↓ body weight and brain size altered brain morphology ↓ number and complexity of neurons ↓ spatial learning and auditory threat memory	Vaysse et al. 2015	Capossela et al. 2012
eIF4A	Silvestrol: ↓ eIF4A in complex ↓ cap-dependent protein synthesis ↓ tumor growth	Hippuristanol: ↓ HFS- and DHPG-induced L-LTP ↓ de novo translation With HuD: ↑ translation, ↑ neurite outgrowth Binding to eIF3 for dendritic pruning in Drosophila	Cencic et al. 2009; Wolfe et al. 2014; Lucas et al. 2009	Hoeffer et al. 2013; Ran et al. 2009; Fukao et al. 2009; Rode et al. 2018
eIF4B	Knockdown ↓ translation and proliferation ↑ cell death	dephosphorylated by stimulation causes ↑ translation, Indirectly, S6K1 knockout shows mild behavioral impairments but can rescue FXS	Shahbazian et al. 2010; Antion et al. 2008	Bettegazzi et al. 2017; Antion et al. 2008; Bhattacharya et al. 2012
PDCD4	Knockout ↑ lymphomas ↑ cap-dependent translation in splenocytes	Mediate ethanol-induced: ↓ translation ↑ death in neurons Knockdown: ↑ translation Suppression by microRNA-21: ↑ neurite outgrowth	Hilliard et al. 2006	Narasimhan et al. 2013; Jiang et al. 2017

lateral amygdala was shown to block the consolidation, but not the reconsolidation, of associative threat memories in rats (Hoeffer et al. 2011). 4EGI-1 treatment in the same brain region during memory consolidation also decreased the amount of polyribosomes in dendritic shafts and prevented up-regulation of polyribosomes in spine heads, but not bases and necks of the spines (Ostroff et al. 2017). Notably, in mice, concomitant activation of both eIF4E and S6K1 were shown to be necessary for blocking threat memory reconsolidation and inhibition of S6K1 alone destabilized long-term memory 10 d after reactivation of the memory (Huynh et al. 2014). Taken together, these studies show that eIF4E-mediated translation is required for memory consolidation,

but is not sufficient for reconsolidation, which may have a higher requirement for multiple arms of the eIF4F pathway.

eIF4F complex formation also has been shown to be necessary of long-lasting hippocampal synaptic plasticity. 4EGI-1 blocked both L-LTP and de novo translation induced by L-LTP-inducing high-frequency stimulation (HFS). Similarly, hippuristanol, which inhibits eIF4A, blocked both L-LTP and increased de novo translation induced by L-LTP-inducing HFS (Hoeffer et al. 2013). L-LTP induced by DHPG in individual CA1 oriens-alveus interneurons also was inhibited by hippuristanol and was facilitated in 4E-BP2 knockout mice (Ran et al. 2009). Thus, both eIF4A and eIF4E signaling appear to be essential for inducing long-term synaptic plasticity.

Phosphorylation of eIF4E has been studied in both invertebrate and mouse models. The earliest studies of eIF4E phosphorylation in neurons were done in Aplysia and suggested that it was important for synaptic plasticity. The level of phosphorylated eIF4E correlated with translation in Aplysia, but treating with serotonin, which stimulates translation in Aplysia neurons, increased phosphorylation of eIF4E in some neurons while decreasing it in others. The phosphorylation of eIF4E appeared to be dependent on p38 MAPK rather than MEK-ERK signaling, but inhibiting p38 MAPK did not have an effect on general de novo translation (Dyer and Sossin 2000). Treatment of cultured neurons with brain-derived neurotrophic factor (BDNF) resulted in increased phosphorylation of eIF4E that was correlated with increased de novo translation, both of which were prevented with a Mnk inhibitor. In addition, BDNF-induced eIF4E phosphorylation and increased de novo translation were absent in cultured neurons prepared from Mnk1 knockout mice (Genheden et al. 2015). Increased eIF4E phosphorylation has been observed in hippocampal area CA1 due to the convergence of the ERK and mTORC1 signaling pathways in response to stimulation of group 1 metabotropic glutamate receptors (Banko et al. 2004, 2006). Increased phosphorylation of eIF4E also was observed in association with β-Adrenergic receptor-enhanced LTP that was prevented with inhibition of MEK (Gelinas et al. 2007). Finally, increased phosphorylation of eIF4E was observed in hippocampal area CA1 in association with HFS-induced L-LTP, which was absent in MEK1 dominant-negative mice. The MEK1 dominant-negative mice also displayed defects in L-LTP, activity-dependent translation, spatial memory, and contextual threat memory (Kelleher et al. 2004).

Increased eIF4E phosphorylation also has been observed in response to BDNF signaling induced by HFS of the dentate gyrus (DG) of the hippocampus. Treatment with a Mnk inhibitor abrogated HFS-induced LTP in the DG when treated within 2 h of stimulation, but this effect is impossible to separate from the impact of Mnk inhibitors on cytoplasmic fragile X mental retardation interacting protein 1 (CYFIP1) and eIF4E interactions, since that pathway was also affected (Panja et al. 2014). In mice, mutation of serine 209 on eIF4E to an alanine that cannot be phosphorylated by Mnk, did not cause the impairments in L-LTP, spatial memory, or contextual threat memory that were shown in the dominant negative MEK1 mouse model. Instead, the eIF4E phosphomutant mice exhibit increased inflammatory response and a decrease in serotonin levels that was accompanied by depressive symptoms as assessed by forced swim, tail suspension, and novelty suppressed feeding tests, while total de novo translation was not affected. The eIF4E mutant mice also displayed anxiety-like behaviors measured in an elevated plus maze and the open field test (Amorim et al. 2018). The same effect on depressive behavior mediated by serotonin also was observed by a different group studying a Mnk1 knockout mouse (Aguilar-Valles et al. 2018).

Fragile X syndrome (FXS) subjects were shown to have an increase in phosphorylated eIF4E (Hoeffer et al. 2012). Targeting either Mnk1 or eIF4E phosphorylation, either pharmacologically or genetically, was able to alleviate multiple phenotypes in FXS model mice, including increased translation, increased stubby dendritic spines, enhanced metabotropic glutamate receptor-dependent long-term depression (mGluR-LTD), and several behavioral phenotypes. However, the Mnk1 knockout and the eIF4E phospho-mutant mice themselves did not have many observable behavioral phenotypes, other than reduced social novelty behavior. The rescue of phenotypes displayed in FXS model mice by either genetically or pharmacologically inhibiting eIF4E phosphorylation was attributed to reducing increased MMP-9 translation. Both eIF4E phosphorylation and MMP-9 levels were up-regulated in FXS model mice, and increasing MMP-9 itself caused similar phenotypes to the FXS mice (Gkogkas et al. 2014).

Most of the studies that have investigated eIF4E phosphorylation in neurons have used indirect methods such as upstream inhibitors of either MEK or Mnk, which have additional targets and can affect CYFIP/eIF4E binding. These studies have examined eIF4E phosphorylation state as a readout in addition to other downstream effectors and translation factors, but typically have not differentiated between the separate function of the two. This makes interpretation of these studies complicated because it is difficult to determine which part of the translation machinery impacted by inhibition of either MEK or Mnk is essential for the synaptic and/or behavioral changes. For example, the synaptic and behavioral changes caused by inhibition of either MEK or Mnk1 could be due to either decreased eIF4E phosphorylation alone or due to the inhibition of the parallel signaling through MEK/Mnk to CYFIP1 (McKendrick et al. 2001; Ueda et al. 2004; Gkogkas et al. 2014).

Although not particularly well studied in cancer, CYFIP1 is an important protein that binds to both fragile X mental retardation protein (FMRP) and eIF4E. When CYFIP1 is bound to eIF4E, it inhibits translation initiation. The binding of CYFIP1 to eIF4E is activity-dependent and stimulation with either BDNF or the group 1 mGluR agonist DHPG causes the release of CYFIP1 from eIF4E (Napoli et al. 2008). BDNF stimulation was shown to activate Mnk1 and the BDNF-induced release of eIF4E from binding to CYFIP1 was Mnk1-dependent (Panja et al. 2014; Genheden et al. 2015). The increase in eIF4E–eIF4G binding that resulted from decreased eIF4E inhibition up-regulated translation of specific transcripts, which were reported to be FMRP-regulated (Genheden et al. 2015). Moreover, inhibiting eIF4E–eIF4G interactions with 4EGI-1 also rescued multiple hippocampal phenotypes in FXS model mice via the CYFIP1-related pathway. By decreasing eIF4E–eIF4G interactions, eIF4E was able to bind to CYFIP1, which prevented altered actin dynamics normally observed in FXS model mice as a result of reduced CYFIP1 interaction with several other complexes. The change in eIF4E/CYFIP1 binding partners in the FXS model mice rescued several phenotypes including exaggerated mGluR-LTD, increased spine density, and deficits in contextual threat discrimination memory (Santini et al. 2017). The findings described above indicate that CYFIP1/eIF4E interactions are important for normal neuronal function and are dysregulated in FXS model mice.

Although the consequences of altering the interactions of eIF4E with 4E-BP and eIF4E with eIF4G have been relatively well studied, there is a paucity of studies on either eIF4G (outside of eIF4G/eIF4E binding) or eIF4A in either neurons or in the brain. In addition, investigation of the accessory factors eIF4B, eIF4H, and PDCD4, the inhibitor of eIF4A, have not been well studied in the context of synaptic function and behavior, even though both PDCD4 and eIF4B are known to be phosphorylated by S6K1, which has been the focus of studies in synaptic plasticity, memory (Antion et al. 2008), and several brain disorders (Bhattacharya et al. 2012; Oddo 2012).

Although eIF4G1 is the more highly expressed isoform of eIF4G, eIF4G2 was shown to have a role, along with 4E-BP2, in axonal growth and local protein synthesis (Kar et al. 2013). In addition, CaMKI-dependent phosphorylation of serine 1156 on eIF4G2 increased with neuronal activity, and the resulting increase in cap-dependent translation required two CaMKI isoforms, β and γ, as well as NMDA receptor activity. Knockdown of eIF4G2 decreased the density of dendritic filopodia and spine formation, but did not affect dendritic arborization (Srivastava et al. 2012). These studies suggest that eIF4G is required or normal neuronal development, but there is little else known about eIF4G and its role in neuronal function.

Similar to eIF4G, there is little known about the role of eIF4H in synaptic function and behavior. The *EIF4H* gene is allocated to a large gene region associated with Williams–Beuren syndrome, a neurodevelopmental disorder causing cardiovascular issues, cerebral dysplasia, and cognitive abnormalities. Thus, it is possible that deletion of eIF4H would result in altered synaptic function and behavior. eIF4H knockout mice exhibited decreased body weight and brain size, as well as altered brain morphology and a reduction in the number and complexity of neurons. The eIF4H mutant mice also exhibited impairments in spatial learning and associative auditory threat memory. The behavioral phenotype caused by deletion of eIF4H is consistent with impaired translation, but the mice did not have altered polysome profiles. However, no other assays for translation were performed, so it is possible that only specific targets that are eIF4A-dependent would have been affected by the lack of eIF4H (Capossela et al. 2012).

eIF4A and eIF4B have been indirectly investigated in studies of dendritic brain cytoplasmic RNAs (BC RNAs). BC RNAs are small cytoplasmic RNAs that are noncoding, but regulate translation initiation and downstream neuronal excitability. One of these RNAs, BC1, binds to eIF4B and interferes with its binding to 18s rRNA. BC1 also binds to eIF4A and inhibits its helicase activity allowing for another level of regulation (Eom et al. 2011). Consistent with other translation inhibitors, knockout of BC1 caused neuronal hyperexcitability, increased responses to activation of group 1 mGluRs, and audiogenic-induced seizures (Zhong et al. 2009). Although different from the traditional S6K1-mediated serine 422 phosphorylation site, eIF4B dephosphorylation at serine 406 decreased its binding to BC1 RNA and thereby permitted more translation to occur. Serine 406 on eIF4B is dephosphorylated in response to both depolarization with KCl and stimulation with DHPG, both of which have been shown to increase translation (Eom et al. 2014). All together, these studies show that regulation of eIF4B via phosphorylation regulates its interactions with BC1 RNA to regulate translation in neurons.

eIF4B has other important phosphorylation sites. eIF4B was shown to be phosphorylated in neurons at serine 504 in response to blocking inhibitory synaptic transmission with bicuculline. This effect was mediated by casein kinases 1 and 2, and by conventional isoforms of PKC, but not by S6K1. Serine 504 on eIF4B was also shown to exhibit increased phosphorylation in a rat model of epilepsy (Bettegazzi et al. 2017). eIF4B phosphorylation by S6K1 at the serine 422 site has been studied indirectly by investigating upstream S6K1 function in neurons. Although eIF4B phosphorylation was not directly examined, S6K1 knockout mice exhibited a deficit in short-term contextual threat memory, a modest impairment in spatial learning, and hypoactive exploratory behavior. Otherwise, S6K1 knockout mice exhibit normal behavior, as well as normal gross brain morphology and L-LTP (Antion et al. 2008). However, deletion of S6K1 was shown to rescue a number of synaptic and behavioral phenotypes in FXS model mice that was correlated with a normalization of eIF4B phosphorylation and net de novo translation. The genetic deletion of S6K1 in the FXS model mice also rescued impaired mGluR-LTD and multiple behavioral phenotypes, although S6K1 knockout mice themselves showed a social novelty deficit (Bhattacharya et al. 2012). In addition to eIF4B phosphorylation, S6K1 would presumably also effect the phosphorylation of PDCD4, which should affect translation via increased eIF4A inhibition. However, PDCD4 phosphorylation and the levels of PDCD4 in FXS model mice were not examined in this study.

PDCD4 and eIF4A, the RNA helicase that it inhibits, are largely unstudied in the context of neuroscience. As mentioned above, there has been a study suggesting that eIF4A was the mediating factor by which BC1 RNA exerts its inhibition of translation. In addition, the eIF4A inhibitor hippuristanol was shown to prevent L-LTP (Hoeffer et al. 2013). eIF4A also was shown to mediate the ability of the RNA-binding protein HuD to increase cap-dependent translation via direct interaction and the ability of HuD to promote neurite outgrowth necessitated eIF4A binding (Fukao et al. 2009). Dendritic pruning during metamorphosis in Drosophila is associated with inhibited translation via 4E-BP, but requires eIF4A translation. In this model, eIF4A binds to the eIF3 complex, as opposed to eIF4G, to mediate translation of genes that are involved in the pruning process (Rode et al. 2018). PDCD4 has been shown to facilitate translation suppression by binding to eIF4A, resulting in less eIF4A bound to the m^7GTP cap. Knocking out PDCD4 resulted in increased de novo translation and resolved the negative effect of ethanol on translation (Narasimhan et al. 2013). PDCD4 suppression by microRNA-21 also was shown to promote neurite outgrowth after spinal cord injury in rats (Jiang et al. 2017). These studies suggest that eIF4A and PDCD4 may have an important role in synaptic plasticity, and perhaps learning and memory, although more direct studies are needed to confirm this idea.

Conclusions

The eIF4F complex is clearly important for cancer progression and cell growth, but this does not always translate seamlessly to understanding its role in synaptic function and behavior. Key nodes in translational control pathways that are important for cancer progression appear to play a more specialized role in the brain. For example, eIF4E phosphorylation appears to be important for behaviors associated with depression, whereas CYFIP1/eIF4E appears to be more critical for learning and memory. These effects are more nuanced than the effect of eIF4E phosphorylation in cancer paradigms where eIF4E phosphorylation decreases tumorigenesis and proliferation while increasing apoptosis, akin to other translation inhibitors. Preventing eIF4F complex formation by interfering with eIF4E–eIF4G interactions prevents memory consolidation and L-LTP, but either deletion of 4E-BP2 or overexpression of eIF4E can result in autistic phenotypes and memory impairments. In a cancer context, increasing eIF4E causes cell transformation while decreasing its expression or inhibiting its function causes similar effects to eIF4E phospho-mutants by increasing cell death and decreasing proliferation. Other eIF4F translation factors have been studied less rigorously than eIF4E, but the results of studies that have been conducted already show similar trends. As an example, inhibiting eIF4A causes decreases in cell and tumor growth but in neurons it decreases L-LTP and is important for dendritic pruning, once again showing context-specific intricacies in its role in cellular function.

As research progresses in the translation field and more studies are conducted to examine the role of eIF4F in brain, there will surely be a more nuanced understanding of its role in neuronal development and synaptic plasticity, especially with respect to how eIF4F functions in specific subtypes of neurons to drive behavior. In cancer cells, disrupting eIF4F and its associated factors typically results in decreases in translation and cell/tumor growth, and can

also increase the rate of cell death. Although specific eIF4F manipulations may have a greater impact on particular cancers, the results of these studies thus far are more homogeneous than the range of alterations on synaptic plasticity and behaviors observed in mice. Moreover, although overall de novo translation may not be observably different in the brains of many of the eIF4F mutant mouse models, the translation of specific crucial mRNAs might be preferentially affected. These specific mRNAs likely will play a role in altered synaptic plasticity and behavior. It is unlikely, however, that the mRNA targets regulated by eIF4F in cancer cells and neurons are identical given the difference in proteins that are expressed in these dissimilar cell types that most certainly have different requirements for growth and survival. Earlier mechanistic studies in cancer are an important reference to use for informing neuronal signaling studies, but it is important to note that there may still be discrepancies between these models as research moves forward.

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