Significance of Molecular Signaling for Protein Translation Control in Neurodegenerative Diseases

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Key Words

Double-stranded RNA-dependent protein kinase • Eukaryotic initiation factor 2 α • Protein translation control • microRNA

Abstract

It has long been known that protein synthesis is inhibited in neurological disorders. Protein synthesis includes protein transcription and translation. While many studies about protein transcription have been done in the last decade, we are just starting to understand more about the impact of protein translation. Protein translation control can be accomplished at the initiation or elongation steps. In this review, we will focus on translation control at initiation. Neurons have long neurites in which proteins have to be transported from the cell body to the end of the neurite. Since supply of proteins cannot meet the need of neuronal activity at the spine, protein locally translated at the spine will be a good solution to replace the turnover of proteins. Therefore, local protein translation is an important mechanism to maintain normal neuronal functions. In this notion, we have to separate the concept of global and local protein translation control. Both global and local protein translation control modulate normal neuronal functions from development to cognitive functions. Increasing lines of evidence show that they also play significant roles in neurodegenerative diseases, e.g. neuronal apoptosis, synaptic degeneration and autophagy.

We summarize all the evidence in this review and focus on the control at initiation. The new live-cell imaging technology together with photoconvertible fluorescent probes allows us to investigate newly translated proteins in situ. Protein translation control is another line to modulate neuronal function in neuron-neuron communication as well as in response to stress in neurodegenerative diseases.

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Introduction

Synthesis of proteins including transcription and translation involves thousands of molecules. Controlling protein translation can be accomplished at the initiation or elongation steps. There are several signaling pathways which can modulate protein translation processes. In fact, modulation of protein translation affects normal physiological functions of neurons as well as the degenerative processes in both acute and chronic neurological disorders. Back in 1978, Yanagihara [1] reported a decrease in protein synthesis including translation in an experimental gerbil stroke model. In 1992, increased phosphorylation of elongation factor 2 was reported in postmortem Alzheimer's disease (AD) brain sections, indicating inhibition of protein translation [2]. Thereafter, protein translation has received increasing attention in chronic neurodegenerative diseases. Furthermore, sig-

naling machinery controlling protein translation can also affect proapoptotic signaling, like that of stress kinases. Moreover, recent findings about unfolded protein responses leading to inhibition of protein translation, and the relationship between synaptic functions and local protein translation attract many investigators looking into protein translation control. This review summarizes how protein translation is controlled globally and locally in neurons, and how it affects the fate of neurons in neurodegenerative diseases. The scope of this review is to focus on protein translation control at the initiation step. We have studied a stress kinase controlling protein translation at initiation in AD. Therefore, we will start our review from this kinase, PKR.

Overview of PKR

The interferon-inducible, double-stranded RNA (dsRNA)-dependent protein kinase (PKR) is one of the four kinases to phosphorylate eukaryotic initiation factor 2 α (eIF2 α) [3, 4]. PKR is a serine/threonine protein kinase and consists of 551 amino acids (68 kDa) with two dsRNA-binding domains at the N-terminus and a kinase domain at the C-terminus [5]. Protein synthesis was observed to be inhibited in interferon-treated or vaccinia virus-infected cells [6, 7]. Furthermore, an inhibitor for protein translation with kinase property was discovered when dsRNA was incubated with rabbit reticulocyte lysates [8]. All this evidence led to the identification of PKR [9].

After binding of dsRNA, PKR is activated by dimerization and autophosphorylation. Activated PKR can phosphorylate eIF2 α on serine 51 to inhibit the initiation of global protein translation. The ability of activated PKR to inhibit the initiation of protein synthesis confers its antiviral [10, 11] and proapoptotic [12, 13] properties. Apart from the regulation of protein translation, PKR has been suggested to be involved in the control of cell growth for its tumor suppressor function [14]. PKR also takes part in the transcriptional control by phosphorylation of I κ B and activation of NF- κ B DNA binding activity in vitro [15].

Activation of PKR

As mentioned above, PKR is activated by dsRNA or interferon. In addition, PKR can be activated by polyanions such as heparin and chondroitin sulfate [16]; growth

factors and cytokines such as platelet-derived growth factor [17], tumor necrosis factor- α (TNF- α) [13, 17] and lipopolysaccharide [18]; cellular stresses such as depletion of Ca²⁺ from the endoplasmic reticulum (ER) [19], arsenite and H₂O₂ [20]. Moreover, a cellular protein activator of PKR, PACT (or its mouse homologue RAX), has been found to heterodimerize with PKR and activate PKR in the absence of dsRNA [20, 21]. Recent findings reveal that PKR can be activated by tyrosine phosphorylation via receptor-associated Janus kinase 1 and tyrosine kinase 2 [22]. Tyrosine phosphorylation can be a molecular switch to fully activate PKR [23]. Since PKR can mediate apoptosis via its activation by different stimuli such as depletion of Ca²⁺ from the ER, H₂O₂, lipopolysaccharides, TNF- α and serum starvation [24], PKR can be considered to be a stress kinase [25].

PKR and Protein Translation Control

Protein translation control is necessary for cells to reallocate resources in an effective way for continuous survival under stress conditions. In normal conditions, protein translation is carried out when the ribosome, the mRNA template and aminoacylated tRNAs can assemble together in a proper manner. Eukaryotic initiation factors (eIFs) bind to these components and facilitate the formation of the 80S initiation complex which is necessary for the 'switch-on' of protein synthesis [26]. The first step involved in the initiation of protein translation is the formation of a ternary complex [eIF2-GTP-Met-tRNA^f] that consists of eIF2-bound GTP that is associated with the initiating methionyl-tRNA (Met-tRNA^f). This ternary complex then binds to different ribosomal subunits, mRNA and initiation factors to form the complete 80S initiation complex, together with the generation of GDP from the hydrolysis of GTP. The eIF2-bound GDP must be exchanged for another molecule of GTP by the action of the guanine nucleotide exchange factor eIF2B before eIF2 can take part in another round of translation initiation [27, 28]. When there is a stress signal, eIF2 α is phosphorylated by its kinases, such as PKR, PKR-like ER-resident kinase, heme-regulated eIF2 α kinase or general control nonderepressible factor 2 kinase (GCN2), and it then forms a stable complex with GDP and eIF2B, thus inhibiting the guanine nucleotide exchange by eIF2B. Consequently, the initiation of protein translation is impaired [29, 30].

Since PKR can phosphorylate eIF2 α , it is one of the key regulators in the translation control. At present, the exact

mechanism of PKR in the regulation of protein translation is still unclear. However, there are increasing lines of evidence supporting that activation of PKR would mediate inhibition of protein translation. In a mouse model of temporal lobe epilepsy induced by pilocarpine, PKR has been found to be activated, followed by an increase in phospho-eIF2 α and inhibition of protein synthesis in the brain during status epilepticus [31]. In cultured neuronal cells, ethanol can activate the PKR-eIF2 α pathway inducing neuronal apoptosis [32]. Under the stimulation of okadaic acid in human osteoblastic MG63 cells, inhibition of translation occurred with a higher level of phosphorylated PKR and eIF2 α [33]. Similar observations were found in anti-Fas-mediated apoptosis in Jurkat T cells and TNF-mediated apoptosis in U937 cells [34].

PKR and Neurodegenerative Diseases

PKR has been suggested to play an important role in the pathogenesis of various neurodegenerative diseases. Our group is among the first to demonstrate that the immunoreactivity of both phospho-PKR and phospho-eIF2 α in AD brains is higher than that of age-matched controls [35]. Another two studies also showed similar findings about the protein level of activated PKR in AD subjects [36, 37]. We also found that activation of PKR and eIF2 α is crucial in β -amyloid (A β)-induced apoptosis in cultured cortical neurons [38], where extracellular accumulation of A β peptides is a key pathological hallmark of AD [39]. In a recent study, the levels of phospho-PKR and phospho-eIF2 α have been found to be elevated in lymphocytes of AD patients, and these changes were significantly correlated with the cognitive and memory test scores [40].

In addition to AD, activation of PKR has also been implicated in Huntington's disease (HD) and Parkinson's disease (PD). Intense staining of phospho-PKR was found in the striatum and globus pallidus in HD brain sections. Also, PKR preferentially bound to the expanded CAG region of mutant huntingtin RNA [41]. Another study also showed that brain tissues from HD and PD patients displayed strong induction of phospho-PKR in hippocampal neurons, in spite of the fact that this region is not the major degenerative site in HD and PD [42]. Besides these two neurodegenerative diseases, recent findings also show that PKR is activated in amyotrophic lateral sclerosis by proteomic study [43].

PKR and Related Signaling Pathways in Apoptosis

Several signaling pathways have been suggested to be related to PKR-mediated apoptosis. Our previous study showed that an early Ca²⁺ release from the ER as well as a mild activation of caspase-8 and -3 are involved in the upstream signaling events of PKR-eIF2 α activation in A β -triggered apoptosis [44]. Others also showed that caspase-dependent activation of PKR leads to phosphorylation of eIF2 α in anti-Fas-mediated apoptosis in Jurkat T cells as well as in TNF-mediated apoptosis in U937 cells [34]. On the other hand, activation of caspase-9 has been found in PKR-mediated apoptosis *in vitro* [45] and *in vivo* [46].

Apart from caspases, Fas-associated death domain (FADD) in the death receptor signaling pathway is also involved in PKR-mediated apoptosis. A study demonstrated the activation of FADD/caspase-8 in PKR-mediated influenza virus-induced apoptosis [47]. This group also showed that the mouse fibroblasts lacking FADD were almost completely resistant to PKR-mediated cell death [48].

Apoptosis signal-regulating kinase 1, which is a mitogen-activated protein kinase (MAPK) kinase kinase, has been shown to interact with PKR in PKR-mediated apoptosis in COS-1 cells [49]. In carcinoma, PKR enhances the transcription function of the tumor suppressor p53 and results in apoptosis [50].

Taken together, global protein translation control at initiation by the PKR-eIF2 α pathway plays an important role in normal neuronal functions as well as in determining the fate of neurons in neurodegenerative diseases. Apart from global translation control, protein translation can occur at the base of the spine. Therefore, local translation control at the spine should be considered to be another key step to modulate neuronal functions.

Local Protein Translation in Neurons

Owing to the unique and complex architecture of neurons, compartments in distal neurites or axons can be far away from the cell body. Efficient delivery of cellular constituents to the proper location for local needs is crucial to maintain the functions of neurons. Passive diffusion is efficient over a short distance; yet in many cases, it is not fast enough to deliver proteins or organelles to meet the needs in distal compartments. To solve this problem, a fast mode of transport which requires expenditure of energy is needed and a family of molecular motors and cy-

toskeletons to transport proteins synthesized from the cell body to distal compartments. The view that protein translation can take place locally in synapses is now well accepted. Local protein translation is important for the axonal guidance, synaptic plasticity, memory and development.

Since the discovery of polyribosomes at the base of spines under an electronic microscope by Steward and Levy [51], subsequent studies demonstrated the presence of both mRNA and protein translation machinery in dendrites [52–54] and in the axonal growth cone [55–57]. By using electron microscopy, ribosomes, ER and Golgi apparatus can be identified in the dendrites, which are essential structures required for protein translation, translocation of integral membrane proteins and posttranslational processing in the distal region of dendrites [55]. One can also use an *in situ* hybridization method to demonstrate the presence of mRNA encoding for various proteins such as microtubule-associated protein 2 [54], neurofilament light polypeptide [58], α -calcium/calmodulin-dependent protein kinase II (CaMKII α) [59], brain-derived neurotrophic factor (BDNF) [60], activity-regulated cytoskeleton-associated protein [61], β -actin [62], N-methyl-D-aspartate receptor [63], (alpha/symbol)-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor [64], glycine receptor [65] and InsP₃ receptor [66].

With the recent development of imaging technology, direct visualization of protein translation provides a powerful tool for the study of local protein translation in neurons. Aakalu et al. [67] developed a protein synthesis reporter by fusing green fluorescent protein with CaMKII α flanked by the 5'- and 3'-untranslated region (UTR) conferring both dendritic mRNA localization and translational regulation. The authors found that local protein translation is stimulated by BDNF. A new method has also been used to visualize local protein translation based on the fluorescence signal of the binding between a membrane-permeable biarsenical dye and tetracysteine (TA) tag. By genetic addition of TA tag to the intracellular carboxy domains of the target protein, local protein translation can be visualized by the fluorescence signal given out by the interaction of the TA tag and biarsenical dye [68, 69]. A recent study by Smith et al. [70] demonstrated a new protein synthesis reporter to detect endogenous protein translation in living hippocampal neurons, called fluorescein-dC-puromycin. This fluorescent probe relies on the peptidyl transferase inhibitor puromycin, a structural analog of an aminoacyl tRNA molecule that is covalently attached to the C-terminus of nascent proteins through a peptide linkage. By the use of the endogenous

protein translation reporter, the authors found that D1/D5 receptor activation stimulates local protein translation in the dendrites of cultured hippocampal neurons.

The Machinery of Translation Regulation and Relation to Neuronal Activity

Local protein translation occurs at the distal compartments far away from the cell body of neurons. Thus, the localization of the protein translation machinery to appropriate sites is regarded as the first level of local protein translation control. Recent studies have suggested that trafficking of these components is activity-dependent [60, 68, 71–73]. Indeed, transport of mRNA into dendrites is also regulated by neuronal activity [61, 74]. mRNAs are transported and docked at the appropriate destination to allow local protein translation. They are transported as RNA granules to prevent premature translation/degradation [75]. The localization of specific mRNAs is accomplished by recognizing *cis*-acting elements in the 3'-UTR to specific RNA-binding proteins whose transport involves kinesin motors [76–78]. For example, the zipcode sequence of β -actin is localized in the 3'-*cis*-acting sequence in the mRNA [71, 79]. Two zipcode-binding proteins (ZBP1 and ZBP2) bind to this sequence to facilitate the dynamic movement of filopodia in neurons [79–81]. ZBP is one of the members of the heterogeneous nuclear ribonucleoprotein (hnRNP) family that are associated with RNA transport in neurons [82]. Other proteins in the hnRNP family include ZBP1 [71, 79], staufen [76], hnRNP A2 [83], fragile X mental retardation protein (FMRP) [77] and Pur α [84].

Signaling pathways that are found to regulate global protein translation can play a role in local protein translation, mainly on initiation steps. For example, the extracellular signal-regulated kinase (ERK)-MAPK pathway and phosphatidylinositol 3-kinase (PI3K)-mammalian target of rapamycin (mTOR) pathway have been shown to play key roles in regulating the efficiency of protein translation and synaptic plasticity. Recent studies provide evidence showing that both long-term potentiation (LTP) and long-term depression (LTD) regulate cap-dependent initiation of protein translation [85]. For instance, the use of N-methyl-D-aspartate to induce LTP increases phosphorylation of MnK1, eIF4E, eIF4E-binding protein (4E-BP), and p70S6 kinase [85–89]. In contrast to LTP, treatment with (R,S)-3,5-dihydroxyphenylglycine leading to the induction of LTD also induces the phosphorylation of MnK1, eIF4E and 4E-BP [90]. In

these two situations, the formation of the eIF4F complex is upregulated enhancing initiation of protein translation as well as the translation rate [85]. Phosphorylation of MnK1 and eIF4E is regulated by ERK. For example, activation of protein translation by BDNF is partly mediated via stimulating ERK to phosphorylate eIF4E [89, 91]. BDNF can phosphorylate eIF4E and 4EBP1 through both the PI3K-mTOR pathway and ERK-MAPK pathway to initiate protein translation [89, 91–93]. Apart from ERK, PI3K and mTOR play significant roles in protein translation control. For example, phosphorylation of 4EBP is stimulated by PI3K and mTOR during LTD [90]. In agreement with these findings, inhibition of PI3K, mTOR or ERK attenuates LTP and LTD via inhibiting protein translation [86, 94–96].

Two recent reports demonstrated that the relationship of LTP and memory in the hippocampus is related to protein translation control at initiation. The 4E-BP2 knockout mice [87] and GCN2 (eIF2 α kinase) knockout mice [97] showed reduced LTP and a deficit in memory tasks. It is shown that inhibition of eIF2 α by GCN2 or a too great amount of eIF4E because of the lack of 4E-BP2 can lead to learning deficits. Besides, depolarization induced by KCl increases the localization of specific mRNAs [98] and ZBP1 [71] to neurites.

Increasing lines of evidence suggest that microRNA (miRNA) may also contribute to the regulation of local protein translation. Previous studies demonstrated that miRNAs are present in dendrites and FMRP interacts with miRNA, Dicer and Argonaute that can be found in dendrites [99] and developing axons and growth cones [100]. Schratt et al. [101] demonstrated that a brain-specific miRNA, miR-134, repressed protein translation of LIM-domain-containing protein kinase 1 in dendrites to regulate the spine structure. A recent study by Ashraf et al. [102] found that transport of mRNA for CaMKII and local protein synthesis are enhanced during the induction of a long-term memory that is regulated by the RNA-inducing silencing complex pathway. These findings suggest that protein translation control by miRNA is also regulated by neuronal activity. In addition, miRNA may be another regulatory tool to control local protein translation.

Local Protein Translation and Neurological Disorders

Transport of mRNA and local protein translation has played an important role in synaptic plasticity and axonal guidance. The regulation of local protein translation in-

volves various mechanisms. Several neurological disorders have emerged that could have resulted from dysregulation of local protein translation.

Fragile X Syndrome and FMRP

Fragile X syndrome is an inherited mental retardation caused by the loss of FMRP. FMRP is an RNA-binding protein that localizes in dendrites, axons and growth cones [103], where it modulates synaptic plasticity by regulating local protein translation. *FRM1* knockout mice exhibit excess filopodia, elongated spines along dendrites and reduction in the density of spine-like protrusion juxtaposed to presynaptic terminals [103]. Furthermore, activity-triggered protein synthesis for postsynaptic density protein-95 in cultured neurons from *FRM1* knockout mice does not function properly [104]. FMRP is associated with different mRNAs including those encoding proteins for regulating the cytoskeleton such as microtubule-associated protein 1b [105, 106] and small GTPase Rac1 in drosophila [107]. The loss of FMRP leading to dysregulation of local protein translation can greatly affect the morphology of neurons and synapses [108]. These studies suggest important roles of FMRP in regulating the cytoskeleton and architecture of synapses. As FMRP is important in local protein translation, elucidating its roles in synapses implicates the significance of local protein translation in the formation and functions of synapses.

Marie-Charcot-Tooth Disease and Internal Ribosome Entry Sites

In addition to the cap-dependent initiation of translation, a small subset of mRNA has the ability to recruit the 40S ribosome to the internal ribosome entry site (IRES) that is localized upstream from the initiation codon [109]. The IRES was first found in a virus that provides a mechanism for translating viral mRNA, while translation for proteins in host cells is inhibited. Therefore, initiation of translation can occur in the absence of some essential factors, for example, eIF4E. Several eukaryotic mRNAs have been found to contain IRES, such as activity-regulated cytoskeleton-associated protein, CaMKII, microtubule-associated protein 2, and FMRP [110, 111]. Dysregulation of IRES activity is related to a subtype of Marie-Charcot-Tooth disease. Marie-Charcot-Tooth disease is a nerve-specific disease caused by different mutations of genes expressed in Schwann cells. Mutation in the IRES in the 5'-UTR of connexin-32 has been related to the Marie-Charcot-Tooth disease [112]. Mutation in the IRES for connexin-32 abolished the function of IRES leading to the loss of connexin-32 translation. It has been shown

Fig. 1. Diagram showing the classification of protein translation control in neurodegenerative diseases. Translation control can be divided into two different levels: global and local. For global protein translation, there are two main regulatory pathways: one is the PI3K/mTOR, another is the PKR/eIF2 α pathway. For local protein translation control, several regulators/factors are involved: transport of mRNA, eIF2 α kinases, PI3K/mTOR, ERK and miRNA. PERK = PKR-like ER-resident kinase.

that an activity-dependent form of plasticity in neuroendocrine cells of *Aplysia* is switched from cap-dependent to cap-independent protein translation implicating that IRES regulation of protein translation may occur in dendrites during synaptic plasticity [113].

Spinal Muscular Atrophy and Small Nuclear Ribonucleoproteins

Spinal muscular atrophy is a neurodegenerative disease affecting motor neurons and causing infant death. Spinal muscular atrophy is caused by mutation of the survival of the motor protein gene (*SMN1*) [114]. As a result, the unstable isoform does not carry exon 7 in the C-terminus, whose function is the translocation of SMN from the nucleus to the cytoplasm [115]. SMN is part of a stable multiprotein complex that plays an essential role in the assembly of the spliceosomal small nuclear ribonucleoprotein [116]. SMN has been identified in axons of the spinal cord motor neuron [117]. The SMN complex directs the correct identity of target RNAs and facilitates small nuclear ribonucleoprotein assembly. Overexpression of truncated SMN (lacking exon 7) results in shorter neurites [118], implicating the importance of small nuclear ribonucleoprotein assembly and its localization in the functions of motor neurons.

AD and Local Protein Translation

Local protein synthesis is required for the persistence of synaptic change, including both LTP and LTD. It has been suggested that newly synthesized dendritic proteins

can consolidate early phase of LTP to late phase of LTP [85, 119]. Thus, inhibition of LTP may be caused by a dysregulation of local protein synthesis. It has been demonstrated that A β aggregate as a key pathological peptide in AD inhibits LTP, suggesting a possible involvement of local protein translation inhibition by accumulation of A β . Besides, an abnormal dendritic structure has been found in postmortem AD brains and in both in vivo and in vitro models of AD [120–124], implicating that the abnormalities of synaptic plasticity and synaptic structures in the pathogenesis of AD may be due to a dysfunction of localization and translation of mRNAs in synapses. Although there is no direct evidence addressing the involvement of local protein translation in the pathogenesis of AD, numerous elements of protein translation control are associated with AD. Enhanced phosphorylation levels of mTOR, 4EBP1, and eEF2 kinases have been found in AD brains [125] compared to controls. mTOR/p70S6k and PKR/eIF2 α signaling are also involved in A β toxicity in cultured neurons and postmortem AD brain sections [35, 36, 38, 44, 125–130]. Furthermore, a recent study of GCN2 knockout mice showed a deficit in hippocampal-dependent memory tasks, demonstrating the important role of eIF2 α regulation in synaptic plasticity, learning and memory [97]. It has been demonstrated that A β can induce phosphorylation of eIF2 α . Indeed, PKR, one of the eIF2 α kinases, was activated in AD brain sections and in an in vitro A β toxicity model [36, 38, 44, 127, 130]. In addition, impairment of axonal transport with the involvement of the kinesin motor protein has been impli-

cated in the pathogenesis of AD [131–134]. Translocation of mRNA to the appropriate destination also requires kinesin to regulate axonal transport, suggesting that axonal transport impairment may be important for local protein translation regulation in AD. The involvement of this translation control machinery acting locally in the synapse in the pathogenesis of AD is still unclear. It is interesting to study the dedicated control of local protein translation at the time before the global inhibition of protein translation.

Concluding Remarks and Future Study

Taken together, control in protein translation at initiation becomes an important issue for investigation. Fig. 1 summarizes the classification of the protein translation control in neurodegenerative diseases. With the modern molecular biology, live-cell imaging technology and new photoconvertible fluorescent probes, we are able to observe newly translated proteins at synapses to study local

protein translation. Increasing lines of evidence have shown us that local protein translation is related to normal synaptic functions as well as synaptic degeneration. Global protein translation can determine whether neurons will commit suicide via apoptosis. Besides, it can affect the formation of autophagosomes resulting in autophagy. Therefore, protein translation control becomes an important subject to be investigated. Furthermore, the signaling machinery in protein translation can modulate proapoptotic signaling. Modulation of those signaling molecules not only affects protein translation, but also apoptotic signaling. In this notion, it is not surprising that signaling of protein translation may become a biological target for pharmacological intervention against neurodegeneration in many diseases.

Acknowledgements

The work in this laboratory is supported by competitive earmarked research grants (HKU7699/05M and 7552/06M) and HKU Seed Funding for Basic Research.

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