Review

Balanced actions of protein synthesis and degradation in memory formation

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Storage of long-term memory requires not only protein synthesis but also protein degradation. In this article, we overview recent publications related to this issue, stressing that the balanced actions of protein synthesis and degradation are critical for long-term memory formation. We particularly focused on the brain-derived neurotrophic factor signaling that leads to protein synthesis; proteasome- and autophagy-dependent protein degradation that removes molecular constraints; the role of Fragile X mental retardation protein in translational suppression; and epigenetic modifications that control gene expression at the genomic level. Numerous studies suggest that an imbalance between protein synthesis and degradation leads to intellectual impairment and cognitive disorders.

The brain stores and recalls information throughout life in the form of memories. For long-term storage, learned information should be "consolidated" into neural circuits through dynamic gene regulatory events in the brain (Kandel 2001). Through de novo protein synthesis during certain time windows (~1–3 h after learning) (Bourtchouladze et al. 1998), learned information is believed to be solidified into the brain and permanently stored as a long-term memory that is relatively insensitive to disruption (Kandel 2001).

Long-term potentiation (LTP), initially identified as a sustained increase in synaptic efficacy at the hippocampal synapses (Bliss and Gardner-Medwin 1973; Schwartzkroin and Wester 1975; Bliss and Collingridge 1993; Huang et al. 1996), has been suggested as the cellular substrate of hippocampal memory formation. LTP is triggered by activation of the *N*-methyl-D-aspartate receptors (NMDAR). NMDAR-dependent LTP can be classified as early-phase LTP (E-LTP) and late-phase LTP (L-LTP), each including mechanistically distinct features. High-frequency stimulation to the hippocampal Schaffer collateral pathway induces short-term potentiation that is rapidly decayed in several minutes, followed by a sustained phase of elevated synaptic transmission lasting for hours in vitro and days to months in vivo (Abraham et al. 2002; Abraham 2003). This sustained phase of synaptic potentiation can be subdivided based on dependency on protein kinase A (PKA) and protein synthesis (Park et al. 2014b). E-LTP, which is insensitive to inhibitors of PKA and protein synthesis, involves modifications of preexisting synapses through NMDAR-dependent Ca^{2+} signaling. L-LTP requires PKA-dependent signaling, subsequent activation of gene transcription, and new protein synthesis (Huang et al. 1996; Matsushita et al. 2001; Abraham 2003). Due to its sensitivity to protein synthesis blockers, the molecular mechanisms underlying L-LTP are similar to those of long-term memory formation (Bourtchouladze et al. 1998).

Despite these notions, another line of studies has provided evidence that protein degradation is also involved in LTP. In 1993, Bliss laboratory demonstrated that in vivo LTP induction in the rat hippocampus results in either an increase or decrease in protein expression levels by utilizing two-dimensional gel electrophoresis technique (Fazeli et al. 1993). Consistent with findings of proteolysis-dependent *Aplysia* long-term facilitation (LTF) (Hegde et al. 1993, 1997; Chain et al. 1999), treatments with the proteasome inhibitor such as lactacystin could produce impaired long-term memory (Lopez-Salon et al. 2001) and disrupted L-LTP (Fonseca et al. 2006) in the rodent brain. Since then, the importance of the suppression of protein synthesis or protein degradation for synaptic plasticity and memory formation has been supported by accumulating evidence (Lee et al. 2008a, 2012).

Long-term synaptic plasticity and increased protein level through BDNF signaling

Similar to that in other nonneuronal cells, protein synthesis in neuronal cells is regulated by general translation processes. During new protein synthesis in response to learning or L-LTP triggering stimuli, the role of the brain-derived neurotrophic factor (BDNF) is prominent. BDNF is a member of the neurotrophin family of secretory proteins that not only acts as a survival factor for peripheral neurons but also mediates diverse activity-dependent processes, such as neuronal differentiation and growth, synapse formation and plasticity, and learning and memory, through signaling pathways dependent on a high-affinity receptor, tyrosine receptor kinase B (TrkB) (Chao 2003; Reichardt 2006). Since neural activity directly controls either the expression or secretion of BDNF through Ca^{2+}-dependent signaling (Poo 2001; Matsuda et al. 2009; Park and Poo 2013; Park et al. 2014a), L-LTP-inducing stimuli can elicit activity-dependent BDNF secretion at the synapses, leading to structural and functional enhancements of the synapses, such as enlargement of the synaptic structures correlated with L-LTP maintenance and sustained enhancement of the presynaptic release, through local TrkB activation (Aicardi et al. 2004; Tanaka et al. 2008; Harward et al. 2016). Conversely, retrograde transport of the neurotrophin-Trk complexes to the soma could exert their transcriptional regulation of activity-dependent genes, such as *Arc* (Cohen et al. 2011; Yamashita and Kuruvilla 2016), indicating

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the capability of local BDNF signaling to induce a cell-wide enhancement of neural functions.

After BDNF secretion, the subsequent activation of TrkB stimulates the phosphoinositide 3-kinase (PI3K) and extracellular-signal-regulated kinase (ERK) signaling pathways (Fig. 1; Costa-Mattioli et al. 2009). The PI3K-Akt pathway can induce either the eukaryotic translation initiation factor 4F (eIF4F)- or the mechanistic target of rapamycin-ribosomal protein S6 (mTOR-S6) kinase-dependent initiation of translation processes (Roux and Topisirovic 2012). ERK up-regulates translation processes by phosphorylation of the eIF4B or eIF4E, leading to an increased translation rate of 5′CAP-mRNAs (Roux and Topisirovic 2012). In addition, phosphorylation of the eIF4E-binding protein 1 (4EBP1) through the Akt- and ERK-signaling pathways leads to its decreased binding with eIF4E and a consequent decrease in the 4EBP1-mediated inhibition of translation, resulting in increased protein synthesis (Ruvinsky and Meyuhas 2006; Roux and Topisirovic 2012). Translation elongation steps could also be influenced by BDNF signaling. The eukaryotic elongation factor 2 (eEF2) kinase, whose activity is controlled by the S6 kinase or mitogen-activated protein kinase (MAPK), down-regulates the actions of eEF2, a member of the guanosine triphosphate (GTP)-binding translation elongation factor family, by phosphorylating eEF2 (Heise et al. 2014). In vivo BDNF infusion into the hippocampus could promote a rapid and transient increase in eEF2 phosphorylation (Kanhema et al. 2006), which can decrease overall protein synthesis. In contrast, activation of eEF2 in the cortex was induced by BDNF treatment (Takei et al. 2009), suggesting that the effect of BDNF signaling on translation elongation is brain area-specific.

Rather than affecting global protein synthesis, BDNF signaling seems to play a selective role in regulating protein expression. When rapid changes in the synaptic proteome were analyzed using a multidimensional protein identification technology, BDNF-induced proteins were classified as translation factors, proteins involved in synaptic structure maintenance and remodeling, and vesicle formation and movement (Liao et al. 2007). Confirming the alteration of the expression level of the translation machinery, another study additionally demonstrated BDNF-induced up-regulation of the ubiquitin-proteasome system (UPS)-related proteins such as 26S proteasome subunits (Psmd7, Psma2) or ubiquitin carboxy-terminal hydrolase 14 (USP14) (Manadas et al. 2009). Since ubiquitination of synaptic proteins could be tightly regulated by neural activity or BDNF signaling (Jia et al. 2008), these results suggest that BDNF-dependent L-LTP involves not only new protein synthesis but also protein degradation.

Memory formation by disinhibiting molecular constraints

Memory formation and disruption have been correlated with protein synthesis and degradation, respectively. Indeed, many studies have demonstrated that the decrease in memory is dependent on protein degradation. Memory destabilization during memory retrieval required proteasome-dependent protein degradation (Lee et al. 2008a, 2012), and synaptic destabilization by autophagy induction was sufficient for disrupting already consolidated memories (Shehata et al. 2018).

However, to store learned information in the neural circuits, the inhibitory mechanisms hindering activity-dependent facilitation of structural and functional enhancements of synapses need to be removed (Abel et al. 1998). These inhibitory molecular constraints appear to be conserved mechanisms. One possible way of removing such "memory suppressor proteins" is to relieve their inhibitory functions without affecting protein expression levels (Fig. 1). In invertebrates, such as *Aplysia* and *Drosophila*, inhibitory forms of cAMP response element binding protein (CREB2) suppress the CREB1-dependent transcription during basal states; however, repetitive activation of specific *Aplysia* 5-HT receptors (Lee et al. 2009) triggers either PKA-dependent CREB1 phosphorylation (Bartsch et al. 1998) or mitogen-activated protein kinase (MAPK)-dependent phosphorylation of CREB2 (Bartsch et al. 1995; Michael et al. 1998), leading to up-regulation of CREB1-dependent transcription that is necessary for LTF (Liu et al. 2008, 2011). Similarly, a mammalian homolog of inhibitory CREB2, activating transcription factor 4 (ATF4), was also reported to repress the transcription of memory genes, and this repression is relieved by LTP- or learning-inducing stimuli (Chen et al. 2003; Pasini et al. 2015).

Degradation of memory suppressor proteins has also been shown to be effective for long-term memory formation. During serotonin-induced LTF of the sensory-motor neuron synapses in *Aplysia*, facilitation of PKA-dependent synaptic release, activation of CREB1, and induction of gene transcription (Kaang et al. 1993; Kandel 2001; Lee et al. 2008b), as well as an UPS-dependent degradation of the regulatory subunits of cAMP-dependent PKA were demonstrated (Hegde et al. 1993). Since the rapid induction of ubiquitin carboxy-terminal hydrolase, which interacts with the proteasome, was elicited by an LTF-triggering neurotransmitter, serotonin (Hegde et al. 1993, 1997), learning stimuli could evoke such protein degradation mechanism during memory formation. Such protein degradation is able to induce constitutive activation of the catalytic subunits of PKA without an increase in cAMP concentration (Chain et al. 1999), leading to facilitation of PKA-dependent presynaptic release and activation of CREB1 (Greenberg et al. 1987; Hegde et al. 1993; Hegde 2017).

UPS-dependent memory formation has also been observed in the mammalian brain. Infusion of lactacystin, a UPS inhibitor, into the CA1 area of the rat hippocampus impaired long-term memory formation (Lopez-Salon et al. 2001). Accordingly, treatment with lactacystin enhanced the induction but inhibited the maintenance of L-LTP (Dong et al. 2008). Collectively, these results clearly demonstrate that the UPS-dependent protein degradation of memory suppressor proteins is essential for maintaining of synaptic plasticity that is crucial for long-term memory. The detailed mechanisms of memory consolidation targeted by the protein degradation pathways remain to be elusive; however, there is evidence that synaptic plasticity is dependent on the UPS proteolytic activity. Proteasome-mediated augmentation of the early phase of L-LTP required activation of NMDAR and PKA as well as protein synthesis, whereas CREB-dependent transcription of BDNF was blocked by the same treatment due to inhibition of the degradation of ATF4, a CREB repressor (Dong et al. 2008). These results indicate that the LTP maintenance in the hippocampal slices was dependent on proteasome activation (Fonseca et al. 2006; Dong et al. 2008). In addition, an NMDAR- and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII)-dependent increase in local protein degradation was required for activity-induced new spine growth (Hamilton et al. 2012). Since the activity-dependent remodeling of the molecular composition of the postsynaptic density was UPS-dependent (Ehlers 2003), it is possible that the molecular constraints existing at the synaptic regions are the main target of the UPS-dependent down-regulation during memory formation.

In addition to UPS, other protein degradation pathways are also involved in memory consolidation. Another line of evidence suggests a calpain-mediated removal of inhibitory constraints for long-term memory formation. At the hippocampal CA3-CA1 synapses, it was reported that activity-induced accumulation of proteolytic fragments in the stimulated dendrites is induced by calpain, a protein that belongs to the family of Ca^{2+}-dependent nonlysosomal systemic proteinases (Vanderklish et al. 1995). Theta burst stimulation (TBS)-induced LTP in the cultured or

acute hippocampal slices was dependent on calpain expression (Vanderklish et al. 1995; Zhu et al. 2015), raising the possibility that long-term memory formation requires the actions of calpain at the synaptic level. The molecular targets of calpains are largely unknown, but μ-calpain-mediated degradation of suprachiasmatic nucleus circadian oscillatory protein (SCOP), a negative ERK regulator, was demonstrated to be induced during the early phase of TBS-induced LTP (Wang et al. 2014).

Additionally, an autophagy-dependent regulation of memory formation was recently demonstrated. The autophagy flux was increased by learning stimuli, and inhibition of this activity-induced autophagy in the hippocampal neuron was sufficient for producing deficits in TBS-induced LTP and long-term memory formation, with no alteration of the memory stability (Glatigny et al. 2019). These studies collectively indicate that memory formation is mediated by well-balanced actions of activity-dependent protein synthesis and degradation, although the list of molecular targets remains incomplete (Ehlers 2003; Fonseca et al. 2006; Bingol and Sheng 2011; Jarome and Helmstetter 2014; Hegde 2017).

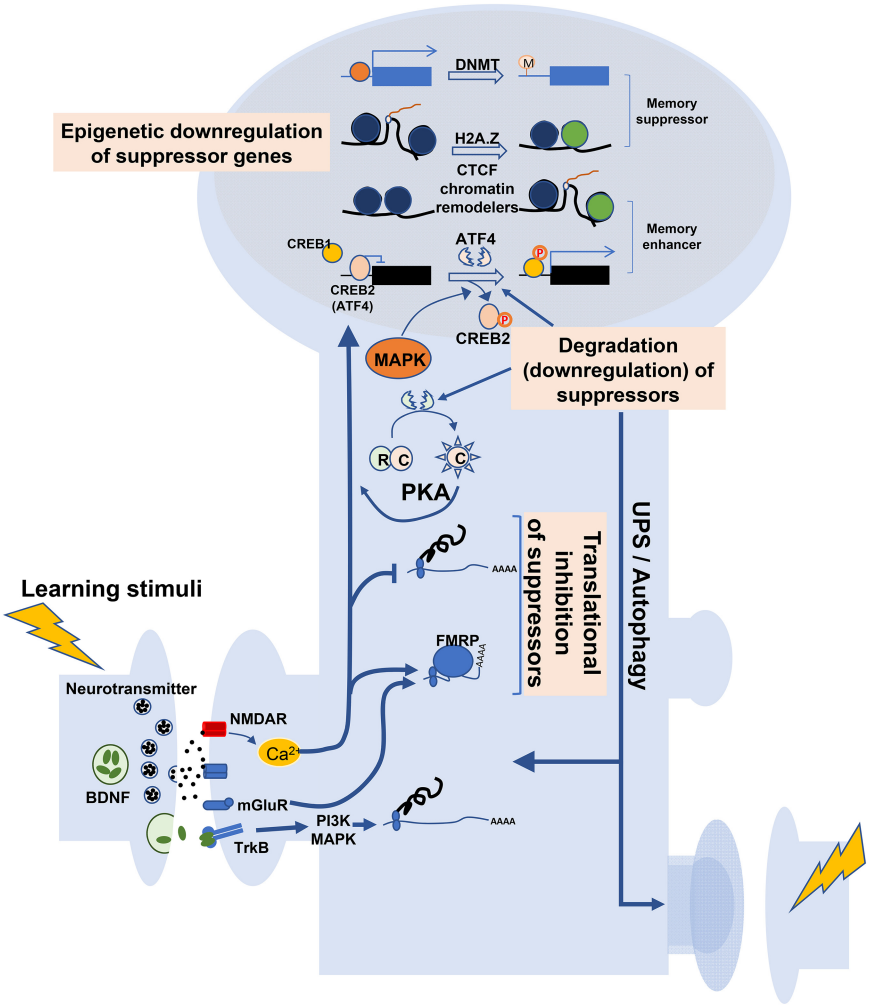

Figure 1. Schematic diagram showing protein synthesis and degradation involved in memory consolidation. Learning stimuli trigger the presynaptic release of neurotransmitters and BDNF, leading to activation of NMDARs and TrkB receptors, respectively. Secreted BDNF activates TrkB signaling linked with PI3K and MAPK, resulting in increased de novo protein synthesis. Presynaptic neurotransmitters activate NMDARs and subsequent NMDAR-dependent Ca^{2+} elevation, which not only activates signaling pathways increasing gene transcription and translation but also induces activity-dependent translational suppression of mRNAs that encode memory suppressor proteins, by reducing translation rates or FMRP-dependent inhibition of mRNA translation (*Translational inhibition of suppressors*). On the other hand, learning stimuli enhance expression and activities of proteolysis mechanisms mediated by UPS or autophagy, leading to degradation of the PKA regulatory subunit (R), ATF4, or other memory suppressor proteins. Degradation of PKA R subunit produces the constitutively active form of PKA catalytic (C) subunit, which triggers diverse molecular mechanisms required for long-term synaptic plasticity. Down-regulation of CREB2 activity is known to induce CREB1-dependent transcription of memory enhancer genes (*Degradation or down-regulation of suppressors*). Finally, learning stimuli lead to epigenetic down-regulation of memory suppressor genes by suppressing transcription via DNMT-dependent DNA methylation, H2A.Z incorporation to histone complexes, or CTCF-mediated alteration of gene expression. In some cases, such epigenetic modulation was reported to produce an increase in expression of memory enhancer genes, suggesting that epigenetic modulation of transcription is gene-specific (*Epigenetic down-regulation of suppressor genes*).

Translational suppression for memory formation

The reduction in protein expression could be also mediated by translational suppression, and there is evidence that such translational suppression is implicated in memory consolidation. A fragile X metal retardation protein (FMRP) protein, encoded by the *FMR1* gene, is known to be a key negative regulator of the mRNA translation (Laggerbauer et al. 2001; Li et al. 2001). As an RNA binding protein, FMRP represses either the initiation or the elongation of translation, and its activity is modulated by bidirectional regulation of phosphorylation through the activity-dependent actions of S6 kinase and protein phosphatase 2A (PP2A) (Bagni and Greenough 2005; Bhakar et al. 2012). Moreover, exposure to enriched environments as well as learning stimuli could transiently increase the expression and dendritic localization of FMRP via metabotropic glutamate receptor (mGluR) signaling (Weiler et al. 1997; Irwin et al. 2000; Gabel et al. 2004), suggesting that the FMRP protein plays a role in long-term synaptic plasticity and memory formation (Fig. 1).

To screen mRNAs that are translationally suppressed during memory consolidation, a recent study utilized the technique that quantitatively measures translating mRNA levels by ribosome profiling (RPF)-mediated RNA deep sequencing (Cho et al. 2015). Contextual fear conditioning elicits translational suppression of a subset of genes in the hippocampus, including the ribosomal protein-coding genes, as well as *Nrsn1* and *Mapk6*. Overexpression of the *Nrsn1* gene resulted in deficits in hippocampal long-term memory tasks (Cho et al. 2015), supporting the idea that long-term memory consolidation requires reduced translation of a subset of mRNAs (Fig. 1). This translational suppression was mediated by NMDAR-dependent, but mTOR-independent signaling (Cho et al. 2015). The exact mechanisms underlying NMDAR-dependent translational repression during memory consolidation remain to be elucidated.

Epigenetic inhibition for memory consolidation

Although changes in the rates of protein synthesis/degradation directly contribute to the expression level of proteins during memory formation, the relatively high protein turnover rates (hours) induced by these mechanisms do not fully explain the lifelong endurance of memory traces. Hence, epigenetic regulation of gene expression is believed to be as a part of the mechanism achieving sustained up- or down-regulation of the gene products affecting memory storage. Two major epigenetic modifications are known to be involved in memory formation and maintenance: DNA methylation and posttranslational modification of histone proteins. There are numerous reports showing a sustained increase in the memory-promoting genes via epigenetic mechanisms (Levenson and Sweatt 2005; Day and Sweatt 2011; Yu et al. 2011; Peixoto and Abel 2013; Zovkic et al. 2013; Kim and Kaang 2017). In this review, we will focus on epigenetic inhibition of the memory suppressor proteins during memory formation (Fig. 1).

One of the epigenetic modifications of DNA, methylation, refers to the covalent addition of a methyl group to the cytosine base of DNA and is mediated by actions of DNA methyltransferases (DNMTs). Hippocampal *Dnmt* gene expression was shown to be up-regulated following contextual fear conditioning, and the inhibition of DNMT activation was sufficient for blocking memory formation; however, it did not affect memory retrieval (Miller and Sweatt 2007). Among the target genes of DNMT is a protein phosphatase 1 (PP1), which plays an inhibitory role in learning and memory (Genoux et al. 2002; Miller and Sweatt 2007). Learning-induced methylation of another suppressor, calcineurin (CaN), was also reported (Malleret et al. 2001), and persistent methylation of CaN in the cortex was necessary for consolidation of remote memory in the prefrontal cortex (Miller et al. 2010). These findings are consistent with the notion that the removal of molecular constraints is essential for memory consolidation and suggest the importance of epigenetic down-regulation of memory suppressor proteins for inducing and maintaining long-term memory.

In addition to DNA methylation, the exchange of histone proteins in the nucleosome plays a role in memory consolidation by regulating the gene expression. A replacement of canonical histones with other variants regulates the DNA accessibility of transcription factors, through alterations of the chromatin structures around the transcription initiation sites, caused by the incorporation of histone variants. Among histone proteins, the histone 2A (H2A) family consists of the largest number of variants with the highest sequence divergence at their carboxy-terminal domain (Bönisch and Hake 2012). One of the H2A variants, H2A.Z, is included in the nucleosomes near the transcription start site (TSS) and plays either a positive or a negative role in transcription by influencing the accessibility of genomic DNA to the transcription regulator proteins (Marques et al. 2010; Bargaje et al. 2012). Whether the H2A.Z. is associated with transcriptional activation or repression during memory consolidation appears to be gene-specific. In the mouse brain, chromatin immunoprecipitation (ChIP) analysis demonstrated that the learning stimulus by contextual fear conditioning induces dissociation of H2A.Z from the first nucleosome (+1 nucleosome), upstream of the TSS of memory-promoting genes, such as *Npas4*, *Arc*, and *Egr1*. In contrast, the same fear conditioning stimulus elicited incorporation of H2A.Z into +1 nucleosome of the memory suppressor genes, such as *Ppp3ca* (the α isoform of a subunit of calcineurin), resulting in reduced gene expression (Zovkic et al. 2014). Since the binding of H2A.Z to the +1 nucleosome was transient and returned to the baseline level within ∼2 h after learning, the repressive role of H2A.Z in memory suppressor gene expression seems to be selective to the memory consolidation process (Zovkic et al. 2014).

Alteration of the 3D chromatin architecture is also reported to be required for remote memory formation. The binding of CCCTC-binding factor (CTCF) to DNA is involved in transcriptional regulation, insulator activity, and regulation of the chromatin architecture (Phillips and Corces 2009). Conditional knockout of CTCF in the forebrain excitatory neurons of adult male mice caused selective deficits in the L-LTP and spatial memory (Sams et al. 2016; Kim et al. 2018), and the effect of CTCF in remote memory was more profound than that in recent memory (Kim et al. 2018). Because CTCF conditional knockout mice exhibited disrupted cortical, but normal hippocampal LTP (Kim et al. 2018), a major function of CTCF in the cortex appears to be to preserve remote memory. RNA sequencing of neurons with deficient CTCF expression revealed that target genes that are implicated in synaptogenesis were down-regulated, whereas the expression of several genes, such as *RIN1* or *HDAC3*, both of which were reported as negative regulators for LTP and memory formation, was up-regulated (Dhaka et al. 2003; McQuown et al. 2011). These findings suggest that the CTCF-dependent chromatin remodeling and regulation of gene expression are critical for regulating remote memory formation. Other chromatic remodeling factor such as neuronal Brm/Brg-associated factor (nBAF) complexes, a mammalian homolog of the yeast SWI/SNF complex, and its regulatory functions in memory formation or drug addiction behavior have been also demonstrated (Wu et al. 2007; Vogel-Ciernia et al. 2013; Alaghband et al. 2018). Neurobiological mechanisms underlying nBAF complex-dependent gene expression and memory regulation were discussed recently (Choi et al. 2015).

Abnormal learning and memory by imbalanced protein synthesis and degradation

We have discussed the importance of balanced synthesis and degradation of proteins for LTP and memory consolidation (Fig. 1). A representative example for an imbalanced protein expression-mediated memory disruption could be found in studies about FMRP-mediated regulation of the translational control. Since *FMR1* gene is silenced in Fragile X syndrome, the symptoms of which are intellectual disability and autism, the *Fmr1* KO mouse model has been utilized for studying how learning and memory are altered by the FMRP-mediated translational control (The Dutch-Belgian Fragile X Consortium et al. 1994). *Fmr1* KO results in increased levels of protein synthesis, due to the inhibitory actions of FMRP on the translation process. Indeed, protein synthesis- and mGluR-dependent long-term depression (LTD) was selectively enhanced in *Fmr1* KO mice, with no alteration of NMDAR-dependent LTD (Huber et al. 2002; Hou et al. 2006). Furthermore, a recent study demonstrated that a rat with *Fmr1 KO* generated by CRISPR/Cas9 displayed impaired synaptic plasticity and spatial memory, as well as a deficit in social interaction (Tian et al. 2017).

Abnormal protein degradation is also linked to neurodegenerative diseases and related cognitive defects. It appears that postmitotic neurons are more vulnerable to misaccumulated proteins than the proliferating cells, due to the lack of dilution of misaccumulated proteins by cell division. Thus, proper protein turnover is not only critical for cellular health but also essential for remodeling of synapses during long-term synaptic plasticity. Regulated proteolysis in the neuron is mediated by various proteolytic pathways, including UPS, lysosome-, and autophagy-dependent protein degradation, and defects in any of these proteolytic pathways can lead to generating abnormally large protein complexes composed of aggregate-prone proteins, such as β-amyloid, tau, α-synuclein, and polyglutamine-repeat proteins. For example, malfunctioning of the UPS is known to be linked with an accumulation of intracellular inclusions enriched with aggregations of ubiquitinated

proteins and associated with the development of Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) (Ciechanover and Kwon 2015; Gentier and van Leeuwen 2015; Zheng et al. 2016; Hegde 2017).

Molecular evidence for neurodegeneration due to abnormal proteolysis has been well established. For instance, mice with ablation of *Atg7* or *Atg5*, essential autophagy genes, showed behavioral defects and reduced lifespan (Komatsu et al. 2006). Deletion of such autophagy genes not only caused impaired axonal membrane trafficking and turnover (Hara et al. 2006; Komatsu et al. 2007) but also resulted in accumulation of polyubiquitinated proteins in the inclusion bodies, without loss of proteasome function. Similarly, blocking the lysosomal proteolysis by inhibiting the lysosomal acidification of cathepsin triggered a slowed cargo-specific axonal transport of endosomes and lysosomes, accompanied by dystrophic swelling of the axons (Lee et al. 2011a,b). This lysosome-dependent axonal dystrophy was found to be associated with accumulation of ubiquitin, APP, and hyperphosphorylated neurofilament proteins, all of which are also found in mouse models of AD (Lee et al. 2011a). In accordance with these findings, it was recently shown that neurons derived from human patients with AD displayed accumulated autophagosomes in the axons, due to the amyloid β oligomer-mediated disruption of the interaction between dynein motor proteins and autophagosomes, leading to a delayed axonal retrograde transport of the autophagosome for fusion with the mature lysosomes (Tammineni et al. 2017).

A defective turnover of certain synaptic proteins is also known to be implicated in the development of pathological sensitization of nociception. Abnormal chronic pain, induced by a peripheral injury and subsequent cortical synaptic plasticity, shares similar features with those of protein synthesis-dependent L-LTP maintenance (Bliss et al. 2016). Similar to learning stimuli, a peripheral injury could induce alterations of the protein turnover rates in the anterior cingulate cortex (ACC), resulting in protein synthesis-dependent spine structural changes and synaptic potentiation (Ko et al. 2018). Among the candidate proteins in the ACC showing rapid synthesis and degradation induced by the peripheral injury, the neuronal cell adhesion molecule 1 (NCAM1) played an essential role in regulating the structural plasticity involved in behavioral sensitization in response to the peripheral nerve injury (Ko et al. 2018).

Age-related memory loss is also suggested to be controlled by autophagy. An age-related memory decline is found during normal aging, and this is believed to be mediated by the reduced hippocampal plasticity (Burke and Barnes 2010; Grady 2012). As discussed earlier, autophagy is induced by learning stimuli and is required for memory formation (Glatigny et al. 2019); however, reduced autophagy biogenesis and reduced expression of autophagy essential genes were found to be correlated with age-related memory decline (Rubinsztein et al. 2011; Stavoe and Holzbaur 2018). Consistently, selective impairment of autophagy in the *Drosophila* mushroom body produced similar alterations of associative olfactory memory, neuronal structures, and neuropeptide signaling (Bhukel et al. 2019). Boosting autophagy levels in the hippocampus of the aged mice was sufficient for reversing memory deficits (Glatigny et al. 2019), suggesting that memory impairment can be restored by manipulating the autophagy levels.

Summary and future perspectives

Accumulating evidence suggests that protein degradation as well as protein synthesis are not only critical for memory formation but also underlie cognitive impairments and numerous psychiatric disorders. Any intervention to specifically control the protein synthesis/degradation could be a good therapeutic target to restore cognitive disorders. Future studies should provide greater insight for the understanding of the following: (1) how protein synthesis/degradation are regulated in molecular terms, both in the local synaptic structures and in the cell nucleus; and (2) how these two regions, that is, nucleus and synapse, communicate to produce activity-dependent Hebbian plasticity (Choi et al. 2018).

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