



REVIEW

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Fragile X mental retardation protein and synaptic plasticity

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Abstract

Loss of the translational repressor FMRP causes Fragile X syndrome. In healthy neurons, FMRP modulates the local translation of numerous synaptic proteins. Synthesis of these proteins is required for the maintenance and regulation of long-lasting changes in synaptic strength. In this role as a translational inhibitor, FMRP exerts profound effects on synaptic plasticity.

Keywords: FMRP, Protein synthesis, Synaptic plasticity, Long-term depression, Long-term potentiation, Metabotropic glutamate receptor, Fragile X

Background

The long-term maintenance of many forms of synaptic plasticity requires the synthesis of new proteins. While the role of experience-dependent somatic gene transcription in long-term memory has been well studied [1], many mRNAs are trafficked to dendrites suggesting an additional role for local synaptic control of protein synthesis [2]. Indeed, activity-dependent translation of pre-existing dendritic mRNA at the synapse is necessary for the expression of multiple forms of synaptic plasticity [3-5]. Fragile X mental retardation protein (FMRP) influences this synaptic plasticity by functioning as a key regulator of mRNA translation [6-10].

FMRP was first characterized in the context of Fragile X syndrome. The *FMR1* gene is silenced in Fragile X (FX), and the consequent loss of FMRP leads to the symptoms of the disorder, often including intellectual disability and autism. In the *Fmr1* KO mouse model [11], loss of FMRP results in increased levels of protein synthesis [9,12]. The downstream consequences of this increase are believed to be at the core of FX pathophysiology [13-15]. Rapid progress has been made characterizing how loss of FMRP influences synaptic function and plasticity, and this knowledge has led to several strategies to correct the disorder that have been validated in animals and are now being tested in humans [16-19].

Here we briefly review the evidence, mostly from the *Fmr1* KO mouse, suggesting a role for FMRP in synaptic plasticity. Although the distinction is not always clear-cut, it is conceptually important to separate disruptions of synaptic plasticity that are *consequences* of altered brain development from those disruptions of synaptic plasticity that *cause* altered brain function in the *Fmr1* KO. While both are important for understanding disease pathophysiology, only the latter is relevant to the question of how FMRP contributes to synaptic plasticity in the wild-type brain.

FMRP regulates translation

FMRP is an RNA-binding protein and a repressor of translation which is well-conserved from mouse to human. FMRP associates with mRNAs through one of three RNA-binding domains [20,21], in some cases in conjunction with adaptor proteins [22,23]. There is evidence that FMRP can repress translation both by blocking initiation and elongation [15,24,25]. A point mutation in one FMRP/mRNA binding domain is sufficient to recapitulate plasticity phenotypes seen in the *Fmr1* KO mouse [26] and in at least one case FX in a human patient [27]. Thus it is likely that FMRP regulates plasticity mainly in its role as a repressor of translation.

FMRP is regulated by posttranslational modifications. Phosphorylated FMRP stalls ribosomal translocation and inhibits translation, whereas dephosphorylation of FMRP upregulates translation [28-30]. Bidirectional regulation of FMRP phosphorylation by the S6 kinase and protein

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phosphatase 2A (PP2A) in response to activity provide a potential link between synaptic stimulation and local translation [24].

FMRP is well-positioned to regulate synaptic plasticity

FMRP is well-positioned to be a key regulator of synaptic plasticity for three main reasons. First, the protein is found in dendritic spines [31-34], important postsynaptic sites of plasticity induction and maintenance. Secondly, FMRP regulates dendritic mRNA translation [16,17], which is required for multiple forms of plasticity [35]. Finally, FMRP itself is dynamically regulated by activity: experience and synaptic activation can trigger its local translation and rapid degradation, in addition to the posttranslational regulation mentioned above. Multiple experimental manipulations associated with synaptic plasticity have been shown to increase FMRP levels, including exposure to an enriched environment, a complex learning task, and pharmacological activation of group 1 metabotropic glutamate receptors (mGluRs) [31,36-38]. Importantly, FMRP is synthesized rapidly, on the same time scale (10–30 minutes) as induction of stable synaptic plasticity [37]. In hippocampal cultures, activity- and mGluR-dependent increases in dendritic FMRP may result from increased trafficking of existing FMRP, rather than *de novo* FMRP synthesis [33,39,40]. Either way, FMRP is an ideal candidate to be involved in regulating synaptic plasticity because of its rapid, transient rise in dendrites following well-characterized plasticity induction paradigms, as well as its role as an inhibitor of translation.

FMRP regulates mGluR-LTD via protein synthesis

Long-term potentiation (LTP) and long-term depression (LTD) are well-characterized forms of synaptic plasticity associated with learning and memory. These persistent changes in synaptic strength can be induced by a variety of manipulations and their expression mechanisms are diverse. Different induction protocols rely on different mechanisms for maintenance, including the requirement for protein synthesis. A particularly compelling example of a form of plasticity requiring local translation is metabotropic glutamate receptor-dependent LTD (mGluR-LTD) in the CA1 region of the hippocampus. Activation of group 1 mGluRs (mGluR1 and 5), either with paired-pulse low-frequency synaptic stimulation (PP-LFS) [4] or with the selective agonist (*S*)-3,5-dihydroxyphenylglycine (DHPG) [41-43], results in a persistent decrease in synaptic strength that is mechanistically distinct from classical NMDA receptor (NMDAR)-dependent LTD [41,44]. It is important to note that there are several mechanisms downstream of mGluR activation that can depress synaptic transmission, and these can be differentially expressed depending on the induction protocol, age, rearing history, and species (*e.g.*, [44-48]). However, under appropriate

experimental conditions the maintenance of mGluR-LTD requires rapid protein synthesis within minutes of induction [4,49]. This protein synthesis is likely to be synaptic, as mGluR-LTD can still be induced if the dendritic layer is physically severed from the cell body layer [4]. mGluR-LTD is expressed, in part, by the removal of AMPA receptors from synapses, which also requires rapid *de novo* translation [50]. The new protein synthesis may be instructive rather than merely permissive for synaptic plasticity since activation of group 1 mGluRs rapidly stimulates protein synthesis in hippocampal slices [12], dendrites and synaptoneuroosomes [51,52].

Fmr1 knockout mice show enhanced hippocampal mGluR-LTD [8,14,49,53] (Table 1). A subsequent study found a similar enhancement in cerebellar mGluR-LTD, which shares many of the same expression mechanisms [54]. Consistent with the electrophysiological data, loss of FMRP leads to excessive mGluR-mediated AMPAR internalization [55]. In addition, mGluR-LTD no longer requires new protein synthesis in the *Fmr1* KO mice [49,56]. These results, combined with what is known about FMRP function, suggest that FMRP acts to inhibit the synthesis of proteins required for mGluR-LTD. In the absence of FMRP, these “LTD proteins” are already available or over-expressed in dendrites resulting in enhanced magnitude and protein synthesis-independent persistence of this form of plasticity (Figure 1A) [13]. Conversely, postnatal overexpression of FMRP reduces the magnitude of mGluR-LTD in both wildtype and *Fmr1* KO neurons [49] and restores its protein synthesis dependence [57]. Moreover, reducing mGluR5 signaling in *Fmr1* KO mice restores both protein synthesis rates and LTD magnitude in the hippocampus to wildtype levels [53,58], suggesting that mGluR5 and FMRP act in functional opposition to maintain an optimal level of synaptic protein synthesis throughout development and into adulthood (Figure 1A).

L-LTP appears normal in *Fmr1* KO mice

While the effects of protein synthesis inhibition on mGluR-LTD can be seen within minutes, most forms of synaptic plasticity do not require *de novo* synthesis until several hours after induction. This is best characterized by late phase LTP (L-LTP), a persistent form of potentiation lasting at least 4 hours. The late maintenance phase of L-LTP requires protein synthesis but initial induction does not [59,60]. Due to FMRP's conjectured role in translation regulation, L-LTP was one of the first forms of plasticity studied in the *Fmr1* KO mouse [61]. Interestingly, no difference has been found in the magnitude of L-LTP in the *Fmr1* KO [61,62]. The fact that removal of FMRP affects protein synthesis-dependent LTD but not LTP suggests that FMRP may specifically regulate the translation of proteins required for the expression of

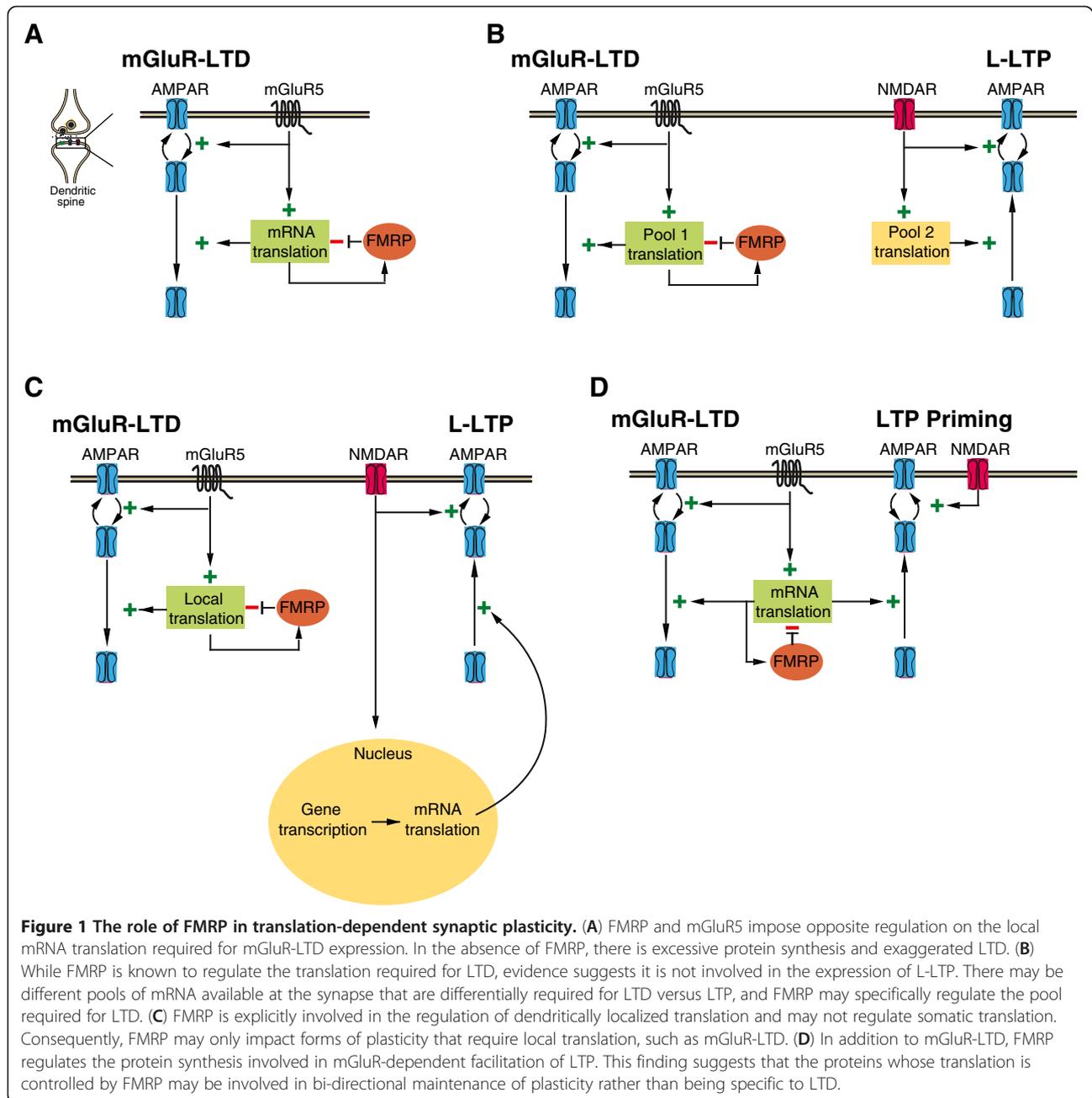
Table 1 Fragile X mouse synaptic plasticity phenotypes

Category	Region	Fragile X Mouse Phenotype	Age	References
mGluR LTD	hippocampus	enhanced	P25-30	Huber et al., 2002; Hou et al., 2006; Bhattacharya et al., 2012; Michalon et al., 2012
mGluR LTD	hippocampus	does not require new protein synthesis	4-12 wk	Nosyreva and Huber, 2006; Hou, et al., 2006; Zang et al., 2009**
mGluR LTD	hippocampus	*enhanced and not PS-dependent	P35-42	Iliff et al., 2012
mGluR LTD	cerebellum	enhanced	3-7 wk	Koekoek et al., 2005
mGluR LTD	hippocampus	enhanced and does not require new protein synthesis	3-7 wk	Volk et al., <i>J Neurosci</i> , 2007
LTP	hippocampus	NONE	20-26 wk; 8-10 wk; 3-12 month	Godfraind et al., 1996; Li et al., 2002; Larson et al., 2005
L-LTP	hippocampus	NONE	5-7 wk; 2-4 month	Paradee et al., 1999; Zhang et al., <i>J</i> 2009
LTP	hippocampus	deficient	2 wk; 6-8 wk	Hu et al., 2008; Shang et al., 2009
LTP	hippocampus	deficient with weak stimulus; normal with strong stimulus	2-3 month	Lauterborn et al., 2007
LTP	hippocampus	enhanced B-adrenergic-facilitated heterosynaptic LTP (PS-dependent)	3-4 month	Connor et al., 2011
LTP priming	hippocampus	does not require new protein synthesis (mGluR-dependent)	6-10 wk	Auerbach and Bear, 2010
LTP	anterior cingulate ctx	deficient	6-8 wk	Zhao et al., 2005; Xu et al., 2012
LTP	anterior cingulate ctx	impaired facilitation of LTP by 5-HT _{2A} R agonist	6-8 wk	Xu et al., 2012
LTP	somatosensory, temporal ctx	deficient	8-10 wk; 3 month	Li et al., 2002; Hayashi et al., 2007
LTP	somatosensory ctx	delayed window for plasticity	P3-10	Harlow et al., 2010
LTP	visual ctx	deficient (mGluR-dependent)	P13-25	Wilson and Cox, 2007
LTP	anterior piriform ctx	deficient in aged mice; normal in 3-6 mo mice	6-18 month	Larson et al., 2005
LTP	amygdala	impaired (mGluR-dependent)	6-8 wk; 3.5-6 mo	Zhao et al., 2005; Suvrathan et al., 2010
STD-LTP	somatosensory ctx	deficient with weak stimulus	P10-18	Desai et al., 2006
STD-LTP	prefrontal ctx	deficient with weak stimulus; normal with strong stimulus	P14-23	Meredith et al., 2007
homeostasis	hippocampus	deficient translation-dependent scaling	P6-7 slice culture	Soden and Chen, 2010
homeostasis	hippocampus	normal transcription-dependent scaling	P6-7 slice culture	Soden and Chen, 2010
experience-dependent	visual ctx (in vivo)	altered ocular dominance plasticity	LTD	Dolen et al., 2007
experience-dependent	somatosensory ctx	deficient experience-dependent plasticity (induced by whisker trimming)	LTD	Bureau et al., 2008

LEGEND: Fragile X mouse models have multiple altered forms of synaptic plasticity across multiple brain regions. The majority of phenotypes were assessed in the *Fmr1* KO mouse which lacks FMRP. *Assessed using a CGG knock-in mouse which models FX premutation. **Assessed using an FMRP point mutant mouse with disrupted FMRP-mRNA binding.

LTD (Figure 1B). However, while the magnitude of L-LTP is unchanged, it is possible that L-LTP is qualitatively different in its requirement for new protein synthesis when FMRP is absent, as is the case for mGluR-LTD (and LTP priming, see below). Therefore, it will be important to test the protein synthesis-dependency of L-LTP in *Fmr1* KO mice to show that FMRP truly does not play a role in regulating the persistence of LTP.

Alternatively, FMRP may be required for the regulation of local but not somatic translation in the context of L-LTP (Figure 1C). L-LTP is traditionally induced by multiple trains of high frequency tetanus or theta burst stimulation, protocols that rely on cell-wide transcription and translation [63-65]. L-LTP was characterized in the *Fmr1* KO mouse using these classical paradigms [61,62]. However, using a less intense induction protocol



results in L-LTP that is maintained specifically by local dendritic translation [5,66]. This form of L-LTP, similar to mGluR-LTD, is sensitive to inhibitors of translation but not transcription, and can be maintained in isolated dendrites. It will be interesting to determine if this locally expressed form of L-LTP is regulated by FMRP.

FMRP regulates LTP priming

While the role of FMRP in L-LTP is unclear, FMRP is known to be involved in LTP in other contexts. In particular, FMRP is involved in regulation of an mGluR-dependent form of metaplasticity that sets the threshold

for LTP. Originally described in rats [67], weak activation of group 1 mGluRs, in itself insufficient for LTD induction, facilitates the subsequent induction of LTP (“LTP priming”). As with mGluR-LTD, this facilitation requires translation but not transcription [68]. This prompted the examination of the role of FMRP in LTP priming [69]. mGluR-dependent priming of LTP is of comparable magnitude in WT and *Fmr1* KO mice; however, while LTP priming requires acute stimulation of protein synthesis in WT mice, it is no longer protein synthesis-dependent in the *Fmr1* KO. Thus, while mGluR-LTD and LTP priming are qualitatively different functional consequences of Gp1

mGluR-stimulated protein synthesis in the hippocampus, both processes are altered by the removal of FMRP (Figure 1D). These results suggest that the mRNA under translational control of FMRP may code for proteins required for bidirectional changes in synaptic strength. Thus, the proteins regulated by FMRP should be conceptualized as plasticity gatekeepers rather than solely “LTD proteins.”

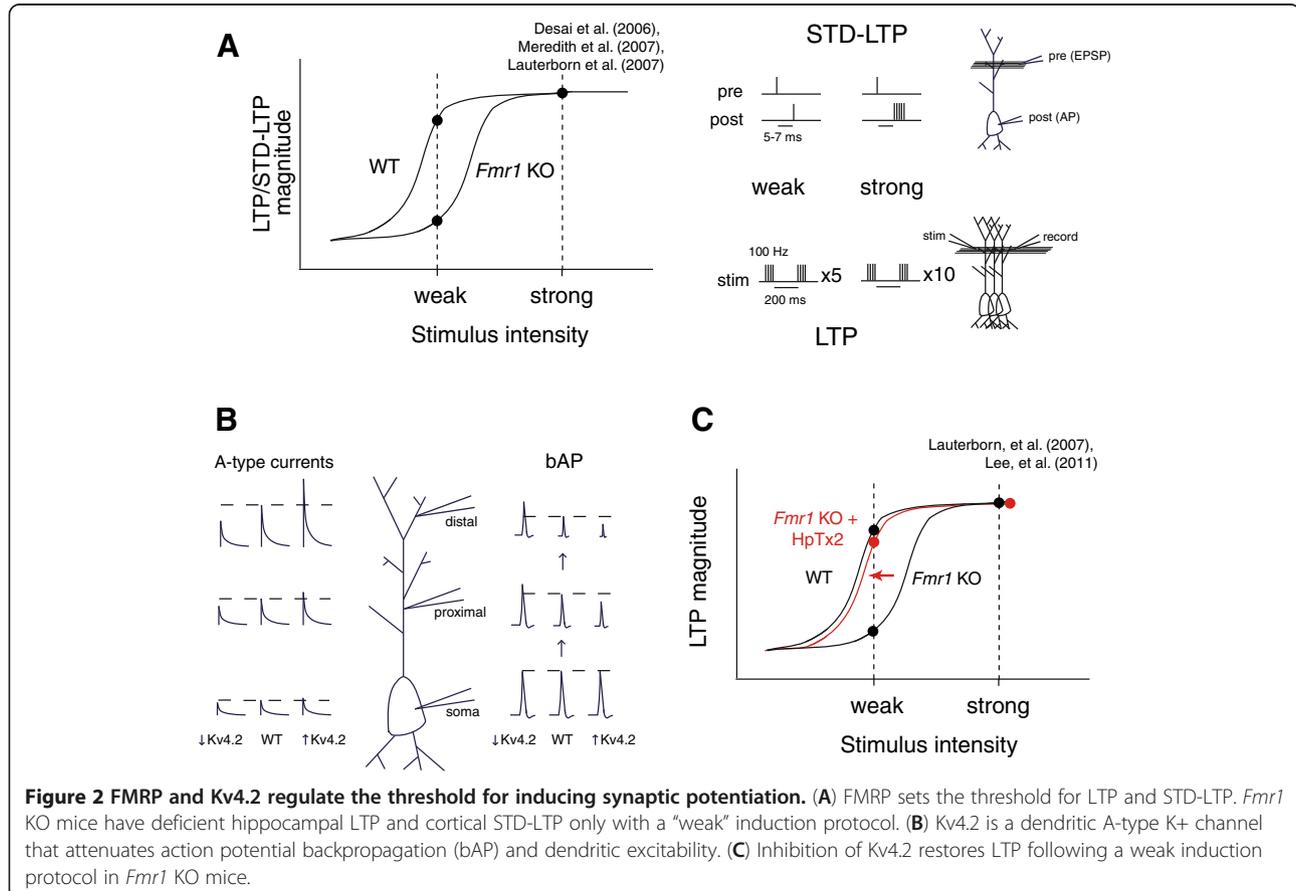
The induction threshold for LTP and STD-LTP is raised in *Fmr1* KO mice

In *Fmr1* KO hippocampal slices, LTP induction is deficient with a weak 5 theta burst protocol but is normal with a strong 10 theta burst protocol (Figure 2A) [70]. In addition, FMRP modulates the induction threshold for spike-timing dependent long-term potentiation (STD-LTP). This form of Hebbian plasticity is induced by temporally staggered presynaptic and postsynaptic activity within a very short window [71,72]. In somatosensory and prefrontal cortices, STD-LTP is deficient in *Fmr1* KO neurons [73,74]. However, if the postsynaptic stimulus strength is increased from a single spike to a burst of five spikes, STD-LTP does occur in KO neurons (Figure 2A) [74]. Therefore FMRP is not required for expression of STD-LTP, but the threshold is raised in its absence. A

possible mechanism for ongoing regulation of LTP thresholds by FMRP is discussed later in this review.

FMRP and other translation-dependent forms of plasticity

In addition to its role in translation-dependent forms of Hebbian plasticity, FMRP can also modulate some forms of homeostatic plasticity. Synaptic scaling is a form of homeostatic plasticity that acts to keep the strength of synapses within a functional range in response to extreme changes in activity. Broadly, a decrease in activity leads to a subsequent cell-wide increase in synaptic strength (“scaling up”) and an increase in activity leads to a decrement in synaptic strength (“scaling down”) [75]. Two types of scaling up have been described in hippocampal slice culture: one that requires transcription [76] and one that requires local translation [77]. Interestingly, only the translation-dependent form of synaptic scaling is deficient in neurons lacking FMRP. Postsynaptic viral expression of FMRP corrects deficient translation-dependent scaling up in *Fmr1* KO neurons [78]. Scaling down of synapses in response to high levels of activity (following prolonged blockade of inhibition) has also been observed [79] and requires mGluR5 activation [80,81]. However, the role of FMRP and local protein synthesis in scaling down has not been directly examined.



While the role of FMRP has been best characterized in mGluR-dependent forms of plasticity, it is not specific to these receptors. Removal of FMRP occludes TrkB-mediated increases in protein synthesis [12] and alters other forms of G protein-coupled receptor (GPCR)-dependent LTD and LTP [82,83]. The common thread between these processes is their reliance on local dendritic translation. Indeed, evidence suggests that FMRP may specifically be important for the regulation of local rather than somatic translation (Figure 1C), as removal of FMRP affects translation but not transcription-dependent forms of Hebbian and homeostatic plasticity.

FMRP and translation-independent plasticity

While many forms of translation-dependent synaptic plasticity are abnormal in *Fmr1* KO mice, other forms of hippocampal plasticity, including NMDAR-dependent LTD and early-phase LTP, are normal [8,61,69,84,85]. These observations suggest that FMRP regulates plasticity mainly in its role as a regulator of translation. However, removal of FMRP has also been shown to affect some forms of synaptic plasticity that do not require *de novo* translation, such as early-phase LTP in other brain areas, including the cortex and amygdala [61,85-89]. Some of these effects could be explained by FMRP modulation of protein synthesis-dependent plasticity thresholds; however it seems likely that many represent end-stage consequences of altered synaptic development in the *Fmr1* KO.

A case in point is altered LTP in the amygdala. A substantial deficit in basal transmission was reported at the same synapses that showed impaired LTP [88]. Reduced synaptic connectivity might have caused the defective LTP, and might have arisen as a consequence of increased FMRP-dependent protein synthesis during the development of amygdala circuitry.

Candidate plasticity gating proteins regulated by FMRP

In order to determine how FMRP regulates synaptic plasticity, we must identify the synaptic proteins whose translation is regulated by FMRP. FMRP has a wide variety of targets - it has been shown to selectively bind approximately 4% of the mRNA in the mammalian brain [90]. Recently, over 800 mRNA binding targets of FMRP were identified using a novel high throughput cross-linking immunoprecipitation (HITS-CLIP) assay [10]. These targets include genes coding for pre- and post-synaptically expressed proteins: 27% of pre-synaptic protein mRNAs (90 genes) and 23% of postsynaptic protein mRNAs (257 genes) are FMRP targets [10]. More specifically, the HITS-CLIP study found that 31% of mRNAs coding for proteins in the NMDAR complex (58 genes), 62% in the mGluR5 complex (32 genes), and 33% in the AMPAR complex (3 genes) are FMRP targets. These three receptor complexes are important for the induction and

maintenance of synaptic plasticity, suggesting that FMRP likely acts broadly as a translational regulator rather than solely regulating one or two "plasticity proteins."

The finding that many FMRP targets encode presynaptic proteins is interesting and illuminating. In the mature nervous system the evidence for local protein synthesis in axons or axon terminals is still sparse; however during early axon development and synapse formation local protein synthesis is believed to play an important role in pathway and target selection [91,92]. Thus, the absence of FMRP regulation of protein synthesis during early development very likely alters synaptic connectivity well before the onset of experience-dependent postnatal plasticity. In addition, outside the CNS, local control of translation in sensory afferent terminals plays a role in nociceptive sensitization and neuropathic pain [93]. FMRP is localized to these terminals and *Fmr1* KO mice show altered nociceptive sensitization [94]. These results suggest that in the spinal cord, presynaptic FMRP may inhibit local translation and can regulate pain plasticity even into adulthood.

We have discussed two major categories of plasticity defects in *Fmr1* KO mice: (1) forms of plasticity requiring FMRP/local translation for their maintenance (mGluR-LTD) and (2) forms of plasticity where FMRP regulates their induction threshold (STD-LTP). We will discuss a few proteins in both categories that are likely involved given their regulation by FMRP and their known roles in plasticity maintenance and threshold-setting in wild-type synapses. These "candidate proteins" are meant to serve as exemplars of how FMRP might regulate synaptic plasticity.

Plasticity maintenance proteins: MAP1B, Arc, and STEP

Recent work has identified proteins whose translation is regulated by FMRP and are involved in mGluR-LTD, including microtubule-associated protein 1B (MAP1B) and activity-regulated cytoskeleton-associated protein (Arc) [17,18]. MAP1B is required for mGluR-dependent AMPA receptor endocytosis [95], the mechanism by which mGluR-LTD is expressed. FMRP associates with MAP1B mRNA and represses its translation [90,96-98], and *Fmr1* KO mice show increased hippocampal MAP1B expression [49]. However, there may be mouse strain and region-specific variations in how FMRP regulates MAP1B translation. For example, in the cerebellum and hippocampus of FVB mice, FMRP may positively regulate MAP1B expression [99].

Arc is involved in AMPAR endocytosis [100] and is upregulated in dendrites following mGluR activation [101,102] and behavior [103]. Arc is required for hippocampal mGluR-LTD and L-LTP, which are both protein synthesis-dependent, and *Arc*^{-/-} mice have multiple learning deficits [101,102,104]. FMRP binds Arc mRNA

and suppresses its translation. As a result, Arc expression is increased in *Fmr1* KO dendrites [98,105,106]. Since (a) mGluR-LTD is increased in *Fmr1* KO mice, (b) Arc is increased in *Fmr1* KO dendrites, and (c) Arc is required for mGluR-LTD, it seems likely that FMRP regulates mGluR-LTD via Arc. This hypothesis was tested directly using *Fmr1*/Arc double knockout mice which show deficient (rather than exaggerated) mGluR-LTD [8,102]. This finding suggests that increased Arc expression may partially account for the enhanced mGluR-LTD seen in *Fmr1* KO mice.

Mechanistically, dephosphorylation of FMRP by the phosphatase PP2A is required for rapid mGluR-mediated increases in Arc protein. However in *Fmr1* KO neurons, Arc levels are basally increased, occluding a further effect of DHPG treatment. Acute viral reintroduction of FMRP into *Fmr1* KO neurons normalizes dendritic Arc levels and restores rapid mGluR-mediated Arc synthesis. This provides further evidence that the acute loss of FMRP, rather than developmental abnormality, underlies synaptic plasticity phenotypes in the *Fmr1* knockout mouse. eregulation of translation.

In addition to MAP1B and Arc, numerous other candidate LTD proteins have been identified in the *Fmr1* KO mouse. One interesting example is striatal-enriched protein tyrosine phosphatase (STEP). Translation of STEP is increased during mGluR-LTD [107,108], and STEP mRNA binds to FMRP [10]. Genetic reduction of STEP corrects behavioral phenotypes in the *Fmr1* KO mouse; but it is not known whether corresponding LTD phenotypes are affected [109]. Additional candidate proteins include APP [110,111], OPHN1 [112], CaMKII α [49,98,113], PSD-95 [113-115], and PI3K [116].

Plasticity threshold-regulating proteins: Kv4.2

A recent review discussing the role of potassium channels in Fragile X provides insight into how FMRP may regulate excitability [117]. FMRP directly regulates the translation of at least three potassium channels: Kv4.2, Kv3.1b, and Slack [118-122]. FMRP's control of Kv4.2 translation may have indirect consequences on regulating the threshold for LTP and STD-LTP induction.

Kv4.2 is an A-type potassium channel that regulates dendritic excitability and the extent of action potential backpropagation [123,124]. A-type currents act to dampen dendritic excitability and AP backpropagation (Figure 2B). By modulating the strength of backpropagation, Kv4.2 also has been shown to regulate the threshold for LTP and STD-LTP [123,125]. In the absence of Kv4.2, dendrites are more excitable and there is a decreased threshold for LTP induction [123,126].

Fmr1 KO mice have an increased threshold for LTP and STD-LTP induction, as discussed earlier (Figure 2A) [73,74]. One potential hypothesis for this phenomenon

is that FMRP inhibits the translation of Kv4.2, and *Fmr1* KO mice have excessive Kv4.2 protein synthesized in dendrites. Indeed, FMRP does directly associate with and negatively regulate the translation of Kv4.2 mRNA [118]. But does this account for the altered LTP/STD-LTP threshold in *Fmr1* KO mice? Pharmacological inhibition of Kv4.2 in *Fmr1* KO mice does correct deficient weak-stimulus hippocampal LTP while strong-stimulus LTP remains unchanged [118] (Figure 2C). This finding suggests that the increased threshold for LTP in the *Fmr1* KO mouse may be accounted for by increased translation of the potassium channel Kv4.2.

Interestingly, another group has recently shown that under their conditions, FMRP positively regulates the translation of Kv4.2 [119]. This study did not address the potential consequences of decreased Kv4.2 in the *Fmr1* KO on synaptic plasticity. One would expect increased dendritic excitability, which has been previously reported in other contexts [127], and a decreased LTP threshold. It will be important to determine the precise experimental and *in vivo* conditions under which each of these opposing patterns of regulation can occur, but it is clear that FMRP's regulation of Kv4.2 in either direction would have important consequences for plasticity.

FMRP, synaptic plasticity and learning

Long-lasting synaptic potentiation and depression have long been considered potential neural correlates of learning and memory. In conjunction with FMRP's role in synaptic plasticity in multiple brain areas, FMRP is also important for a wide range of behavioral learning tasks in mice. *Fmr1* KO mice show deficient amygdalar trace fear memory [87], cerebellar learning [54], inhibitory avoidance learning [58], and have difficulties with a prefrontal cognitive learning task [128]. *Drosophila* mutants lacking FMRP also have impaired long-term memory [129]. Overall, learning and memory deficits in the *Fmr1* KO mouse are a likely behavioral consequence of abnormal synaptic plasticity.

Conclusions

FMRP participates in the regulation of numerous forms of synaptic plasticity, including mGluR-LTD, LTP priming, and synaptic scaling. It seems that FMRP is particularly important for synaptic plasticity that requires dendritic translation, as these forms of plasticity all require local translation and FMRP is a well-established regulator of local translation. The current evidence suggests that FMRP plays an essential role in regulating the synaptic expression of proteins required for bidirectional changes in synaptic strength (Figure 1). It is likely that FMRP controls the expression of proteins not only acutely required for expression of synaptic plasticity, but also proteins that regulate the threshold for plasticity induction

(Figure 2). Therefore FMRP's role in synaptic plasticity is two-fold: it regulates the translation of proteins that directly participate in the induction and expression of plasticity as well as proteins that can indirectly modulate the properties of plasticity.

A key goal in the Fragile X field is to identify which proteins are regulated by FMRP and how increases or decreases in these proteins may account for phenotypes of the disorder. Determining the proteins that are regulated by FMRP (and altered in FX) will also lead to a better understanding of the neuronal processes that are essential for synaptic plasticity and learning/memory. The HITS-CLIP screen has identified hundreds of candidates and a significant number of these are putatively involved in synaptic plasticity. It is unlikely that there is one global "plasticity protein" - multiple proteins likely regulate different processes in parallel. Mapping which proteins are essential for which processes is the important next step for understanding the role of FMRP in the pathological and non-pathological brain.

The *Fmr1* KO mouse provides a model for assessing the role of FMRP in synaptic plasticity - but on their own, studies in *Fmr1* KO mice leave open the possibility that developmental rather than acute changes result in altered synaptic plasticity. In multiple contexts, acute manipulations of FMRP suggest that FMRP does actively regulate synaptic plasticity as a regulator of translation. There is ample evidence that FMRP can directly impact synaptic plasticity through its control of protein synthesis. Future work that allows for better temporal and spatial control of FMRP expression will help dissect the role of FMRP in development from its acute effects on synaptic plasticity.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors drafted, read, and approved the manuscript.

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