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Selective role of the translin/trax RNase complex in hippocampal synaptic plasticity

Alan Jung Park^{1,5*}, Mahesh Shivarama Shetty^{2,3†}, Jay M. Baraban⁴ and Ted Abel^{1,2,3*} 

Abstract

Activity-dependent local protein synthesis is critical for synapse-specific, persistent plasticity. Abnormalities in local protein synthesis have been implicated in psychiatric disorders. We have recently identified the translin/trax microRNA-degrading enzyme as a novel mediator of protein synthesis at activated synapses. Additionally, translin knockout (KO) mice, which lack translin/trax, exhibit some of the behavioral abnormalities found in a mouse model of fragile X syndrome (fragile X mental retardation protein-FMRP-KO mice). Therefore, identifying signaling pathways interacting with translin/trax to support persistent synaptic plasticity is a translationally relevant goal. Here, as a first step to achieve this goal, we have assessed the requirement of translin/trax for multiple hippocampal synaptic plasticity paradigms that rely on distinct molecular mechanisms. We found that mice lacking translin/trax exhibited selective impairment in a form of persistent hippocampal plasticity, which requires postsynaptic protein kinase A (PKA) activity. In contrast, enduring forms of plasticity that are dependent on presynaptic PKA were unaffected. Furthermore, these mice did not display exaggerated metabotropic glutamate receptor-mediated long-term synaptic depression (mGluR-LTD), a hallmark of the FMRP KO mice. On the contrary, translin KO mice exhibited deficits in N-methyl-D-aspartate receptor (NMDAR) dependent LTD, a phenotype not observed in the FMRP knockouts. Taken together, these findings demonstrate that translin/trax mediates long-term synaptic plasticity that is dependent on postsynaptic PKA signaling and suggest that translin/trax and FMRP play distinct roles in hippocampal synaptic plasticity.

Keywords: Translin, Trax, Long-term potentiation, Long-term depression, Local protein synthesis, Hippocampal synaptic plasticity, FMRP, RNA-binding protein, microRNA, PKA

Introduction

Extensive evidence suggests that localization of key mRNAs in the vicinity of synapses and activity-mediated regulation of their translation contributes to persistent forms of synaptic plasticity related to long-term memory [1–4]. This synapse-specific, activity-dependent mechanism requires precisely regulated molecular signaling in presynaptic or postsynaptic compartments [2,

3, 5]. Several RNA-binding proteins (RBPs) take part in the trafficking and translational regulation of specific mRNAs and thus allowing diversity in the mechanisms engaged by different forms of plasticity [6–8]. The RNA-binding protein translin is an evolutionarily conserved brain-enriched protein, which regulates RNA trafficking and translational control [9–12]. Together with its partner protein, translin-associated factor X (trax), these proteins form a microRNA-degrading enzyme that can trigger protein synthesis by reversing microRNA-mediated silencing [13–15]. We have previously shown that the translin/trax RNase complex mediates activity-dependent local synaptic protein synthesis required for input-specific heterosynaptic plasticity (synaptic tagging and capture) and memory formation [15]. However, the

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mechanisms that regulate translin/trax activity within synaptic compartments have not been investigated.

Our previous findings suggest that translin/trax may interact with the cAMP-PKA signaling pathway. Specifically, the microRNA targets of translin/trax are predicted to regulate the expression of PKA-anchoring proteins, cAMP-degrading phosphodiesterases (PDEs), cAMP-producing Gs-coupled β 2-adrenergic receptors and adenylyl cyclases [15]. In fact, the cAMP-PKA signaling pathway is highly localized within presynaptic or postsynaptic compartments by PKA-anchoring proteins and mediates protein synthesis required for persistent synaptic plasticity and memory formation [16–20]. Therefore, investigating whether translin/trax interacts with PKA signaling within presynaptic or postsynaptic compartments can provide clues to understanding molecular mechanisms linking translin/trax to synaptic plasticity and memory formation.

In the present study, we determined the role of translin/trax in distinct forms of synaptic plasticity, which require presynaptic or postsynaptic PKA signaling. As trax protein is unstable in the absence of translin, in the current study we used translin KO mice, which lack both translin and trax proteins [15, 21].

Materials and methods

All experiments were performed according to the National Institutes of Health guidelines and were fully approved by the Institutional Animal Care and Use Committee at the University of Pennsylvania and at the University of Iowa.

Translin knockout (KO) mice

The generation and maintenance of translin KO mice (MGI: 2677496) were described previously [21, 22]. Mice were backcrossed to C57BL/6J for more than 15 generations. Heterozygous male and heterozygous female mice were mated to produce homozygous translin KO mice and wildtype littermates. Mice were maintained on a 12 h light/12 h dark cycle with lights on at 8 am (ZT0). Food and water were available ad libitum. All experiments were performed during the light cycle using translin KO mice and wildtype littermates as controls. 2- to 5-month-old mice were used for all experiments except for the LTD experiments in which 4- to 6-week-old mice were used.

Drugs

Forskolin (FSK, Molecular grade, Sigma), an adenylyl cyclase activator, was freshly prepared as a 50 mM solution in 100% ethanol and delivered at 50 μ M final concentration in artificial cerebrospinal fluid (aCSF) as described before [19]. (*RS*)-3,5-Dihydroxyphenylglycine (DHPG, Tocris), a potent agonist of group I metabotropic

glutamate receptors (mGluRs), was freshly prepared as a 10 mM solution in milliQ water and delivered at 100 μ M final concentration in aCSF as previously described [23].

Electrophysiology

Experiments were performed as described [15]. Briefly, both male and female 2–5-month-old mice (4–6 weeks old for LTD) were sacrificed by cervical dislocation and hippocampi were quickly collected in chilled, oxygenated aCSF (124 mM NaCl, 4.4 mM KCl, 1.3 mM $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$, 1 mM $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$, 26.2 mM NaHCO_3 , 2.5 mM $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ and 10 mM D-glucose) bubbled with 95% O_2 /5% CO_2 . 400 μ m-thick transverse hippocampal slices were prepared using a manual slicer (Stoelting) and placed in an interface recording chamber at 28 °C (Fine Science Tools, Foster City, CA). The slices were constantly perfused with aCSF at 1 ml/min (or 2.5 ml/min for the mGluR-LTD experiment). Slices were equilibrated for at least 2 h in aCSF. All the recordings were performed in the Schaffer collateral synapses in the CA1 stratum radiatum. The stimulus intensity was set to elicit ~40% of the maximum field-EPSP amplitude determined by an input–output curve in each experiment. The first 20-min baseline values were averaged, and the average was used to normalize each initial fEPSP slope. The input–output relationship was measured as previously described [15]. To electrically induce long-term potentiation (LTP), spaced 4-train (four 1 s 100 Hz trains delivered 5 min apart), massed 4-train (four 1 s 100 Hz trains delivered 5 s apart), theta-burst stimulation (TBS, 15 bursts of four 100 Hz pulses delivered for a total of 3 s at 5 Hz), and one-train (one 1 s 100 Hz train) stimulation were delivered after 20 min baseline recordings. To chemically induce LTP, 50 μ M of FSK in aCSF was bath applied to the slices for 15 min following 20-min baseline recordings. To chemically induce LTD, 100 μ M of DHPG in aCSF was bath applied to the slices for 10 min following 20-min baseline recordings. For the NMDAR-LTD experiments, the stimulus intensity was set to elicit ~50% of the maximal fEPSP amplitude determined by an input–output curve in each experiment and LTD was induced by a prolonged low-frequency stimulation (LFS) protocol (1 Hz, 15 min) [24, 25], following 20-min baseline recordings.

Western blotting

Hippocampal tissue homogenization, protein separation and transfer to polyvinylidene difluoride (PVDF) membranes were performed as previously described [26]. Membranes were blocked in 5% BSA or 5% non-fat milk in TBST and incubated with primary antibodies (translin, 1:100,000; FMRP, 1:10,000, Millipore) overnight at 4 °C. They were washed and incubated with appropriate

horseradish peroxidase-conjugated goat anti-mouse or anti-rabbit IgG (1:10,000, Santa Cruz) for 1 h in room temperature. Blots were exposed on a film by ECL and quantified using ImageJ. The density of signal was normalized to beta-tubulin levels (1:50,000, Sigma). Translin antibody was produced (New England Peptide, Inc.) based on the sequences provided previously [27]. The antibody synthesis was based on the C-terminal sequence of the human translin (CKYDLSIRGFNKETA).

Data analysis

Data analyses were performed using Statistica 10 and GraphPad Prism 8. The maintenance of LTP or LTD was analyzed using a two-way repeated-measures ANOVA test on the last 20-min of the recordings [15, 19]. The average of the normalized slopes over the last 20-min was compared between two groups using unpaired t-test. Western blotting data was analyzed using unpaired t-test. The 'n' used in all the experiments represents the number of mice. Differences were considered statistically significant when $p < 0.05$. Data are plotted as mean \pm S.E.M.

Results

Translin KO mice show deficits in a specific form of PKA-dependent long-lasting LTP

In our previous study, we found that translin knockout mice display normal basal synaptic transmission measured by paired-pulse facilitation and input–output curves. These mice also exhibit unaltered transient potentiation, induced by a single 100 Hz stimulation, that requires neither PKA activity nor protein synthesis [15]. In the present study, we first tested long-lasting forms of LTP induced by spaced 4-train (four 100 Hz trains of 1 s each, delivered 5 min apart) or massed 4-train (four 100 Hz trains of 1 s each, delivered 5 s apart) stimulation. The latter does not depend on PKA activation, whereas the former requires postsynaptic PKA activity [28–32]. Also, the massed 4-train LTP is less sensitive to protein synthesis inhibition by anisomycin as compared to spaced 4-train LTP [31]. Hippocampal slices from translin KO mice showed marked impairment in spaced 4-train LTP (Fig. 1b; $n = 5$ for each group, two-way repeated-measures ANOVA, $F_{(1,8)} = 34.43$, $p = 0.00038$). The average of the initial fEPSP slope over the last 20 min of the recordings was reduced in slices from translin KO mice compared to slices from wildtype littermates (wildtype littermates: $176.6 \pm 13.5\%$, $n = 5$; translin KO mice: $89.5 \pm 9.6\%$, $n = 5$, t-test, $p = 0.00037$). On the other hand, massed 4-train LTP was unaltered in slices from translin KO mice as shown in Fig. 1c ($n = 5$ for translin KO mice, $n = 5$ for wildtype littermates, two-way repeated-measures ANOVA, $F_{(1,8)} = 0.923$, $p = 0.365$). The average of the initial fEPSP slope over the last 20 min

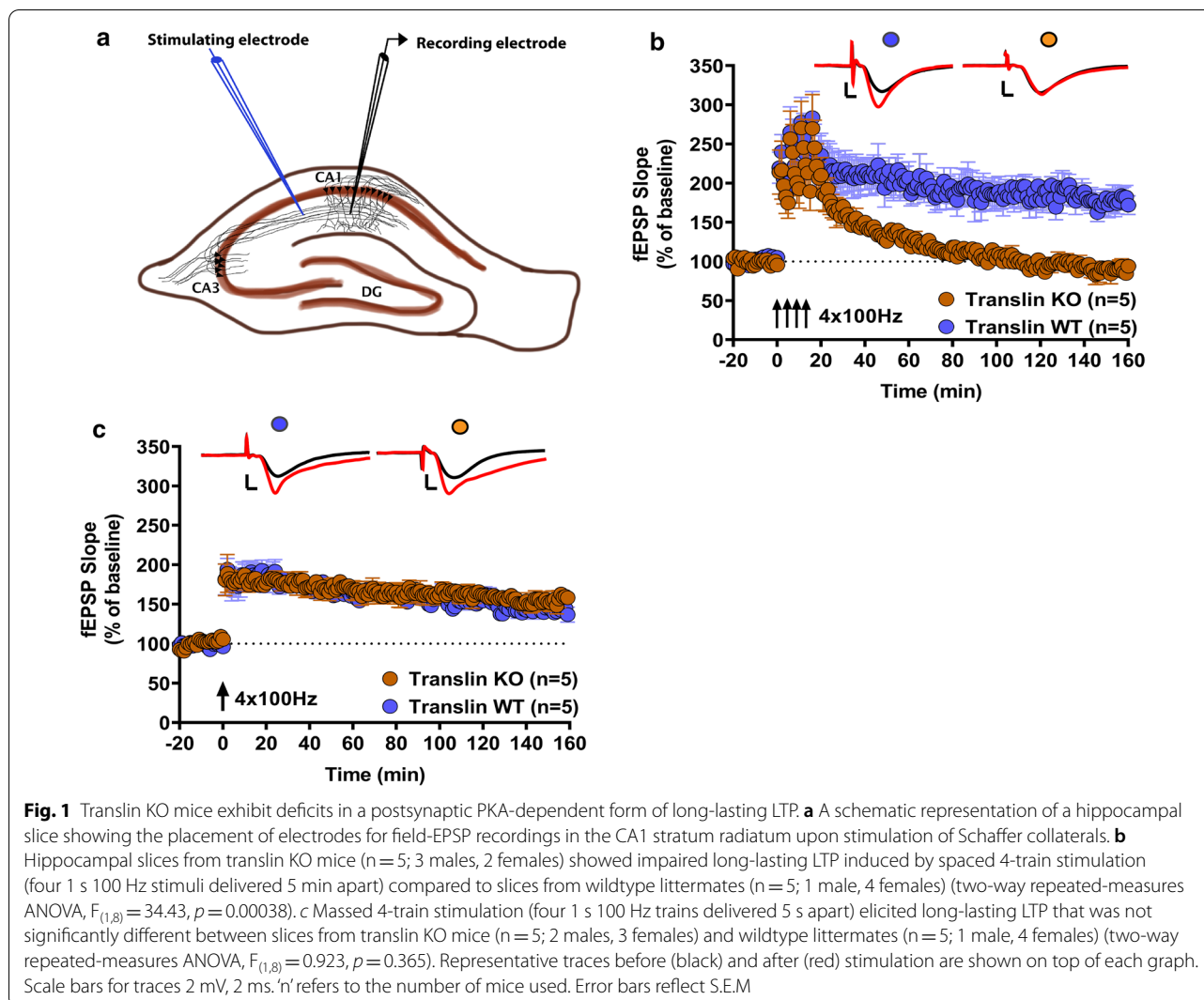
of the recordings was similar between slices from translin KO mice and wildtype littermates (wildtype littermates: $143.6 \pm 8.2\%$, $n = 5$; translin KO mice: $154.6 \pm 9.9\%$, $n = 5$, t-test, $p = 0.364$).

Next, we examined two other long-lasting forms of LTP induced by either theta-burst stimulation (TBS; 15 bursts of four 100 Hz pulses delivered at 5 Hz) or bath application of the adenylyl cyclase activator forskolin (FSK). These forms of LTP rely on increased transmitter release and require presynaptically compartmentalized PKA signaling [19, 30, 33–35]. TBS-LTP was unaffected in slices from translin KO mice (Fig. 2a; $n = 5$ for each group, two-way repeated-measures ANOVA, $F_{(1,8)} = 0.007$, $p = 0.94$). The average of the initial fEPSP slope over the last 20 min of the recordings was similar between slices from translin KO mice and wildtype littermates (wildtype littermates: $150.03 \pm 7.8\%$, $n = 5$; translin KO mice: $151.2 \pm 13.4\%$, $n = 5$, t-test, $p = 0.936$). Furthermore, slices from translin KO mice showed no impairment in the FSK-LTP compared to the WT mice (Fig. 2b; $n = 5$ for translin KO mice, $n = 6$ for wildtype littermates, two-way repeated-measures ANOVA, $F_{(1,9)} = 0.07$, $p = 0.79$). The average of the initial fEPSP slope over the last 20 min of the recordings was comparable between slices from translin KO mice and wildtype littermates (wildtype littermates: $180 \pm 14.3\%$, $n = 6$; translin KO mice: $180.4 \pm 11.8\%$, $n = 5$, t-test, $p = 0.982$).

Taken together, these data suggest that translin is selectively involved in mediating the long-lasting form of LTP induced by spaced tetanic stimuli, but not in LTP induced by massed stimuli, TBS or forskolin.

Translin KO mice exhibit unaltered mGluR-LTD and protein levels of hippocampal FMRP, but show deficits in NMDAR-dependent LTD

One of the most well-studied RBPs is fragile X mental retardation protein (FMRP). Exaggerated metabotropic glutamate receptor-mediated LTD (mGluR-LTD) is a well characterized phenotype of FMRP KO mice and has been proposed as an underlying mechanism of fragile X syndrome [36–38]. Because both translin/trax and FMRP mediate local protein synthesis [15, 38], we tested mGluR-LTD in hippocampal slices from translin KO mice. In contrast to the findings from FMRP KO mice, mGluR-LTD was unaffected in slices from translin KO mice (Fig. 3a; $n = 5$ for each group, two-way repeated measures ANOVA, $F_{(1,8)} = 0.08$, $p = 0.79$). The average of the initial fEPSP slope over the last 20 min of the recordings was comparable between slices from translin KO mice and wildtype littermates (wildtype littermates: $75.9 \pm 3.2\%$, $n = 5$; translin KO mice: $78.9 \pm 3.1\%$, $n = 5$, t-test, $p = 0.473$). We reasoned that if translin and FMRP are functionally independent, loss of



translin/trax should not cause a compensatory increase in FMRP protein levels. Indeed, Western blot analyses showed no changes in the protein levels of hippocampal FMRP in translin KO mice relative to wildtype littermates (Fig. 3b; translin KO mice: $102.5 \pm 0.4\%$, $n=6$; wildtype littermates: $100 \pm 4.3\%$, $n=6$, t-test, $p=0.36$).

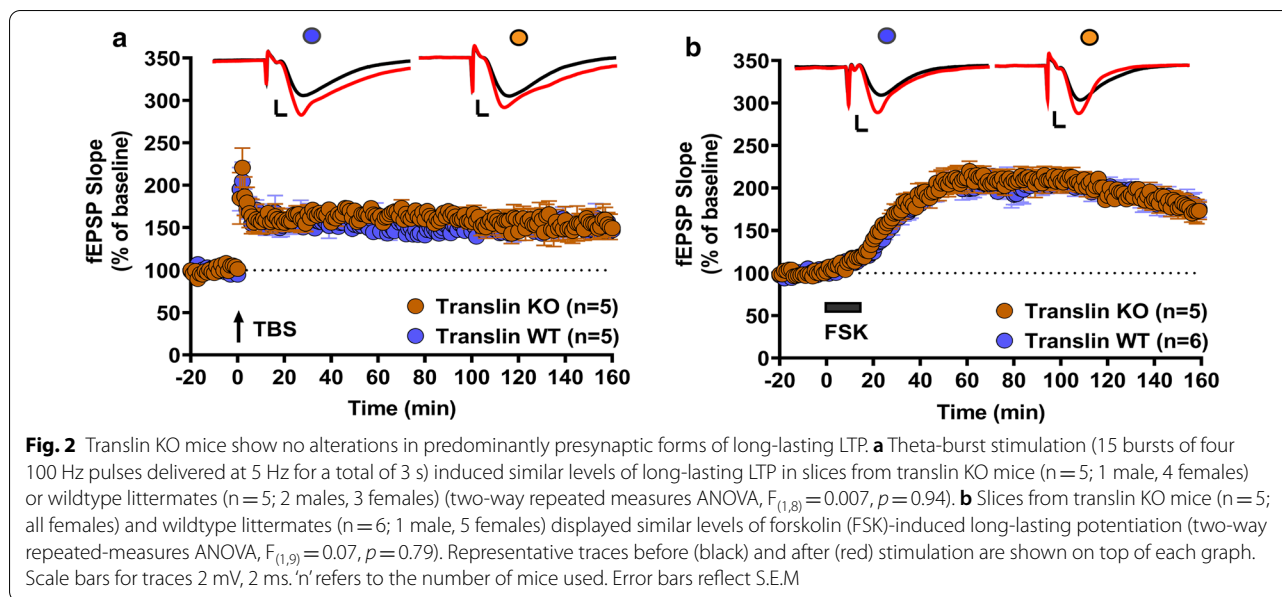
We then investigated NMDAR-dependent LTD induced by prolonged low-frequency stimulation [24, 25], because this form of LTD is mediated by anchored PKA signaling [39, 40] and is not affected in the FMRP KO mice [37]. We found that NMDAR-LTD induced by prolonged LFS was impaired in slices from the translin KO mice ($n=7$) compared to the wildtype littermates ($n=5$) (Fig. 3c; two-way repeated measures ANOVA, $F_{(1,10)}=5.342$, $p=0.043$). The average of the fEPSP slopes over the last 20-min recordings was significantly different between slices from translin KO mice and wildtype littermates (translin KO mice: $94.9 \pm 0.3\%$,

$n=7$; wildtype littermates: $71.2 \pm 0.3\%$, $n=5$; t-test, $p=0.043$).

Together, these data indicate that translin/trax and FMRP play distinct roles in hippocampal synaptic plasticity.

Discussion

The translin/trax complex is implicated in neuropsychiatric disorders [41]. However, the role of translin/trax in synaptic plasticity is largely unknown. In a previous report [15], we provided the first evidence that translin/trax mediates activity-dependent synaptic translation that is critical for synaptic tagging and capture, a form of heterosynaptic associative plasticity [42, 43], and long-term memory. The present study further determined that translin/trax is selectively required for spaced tetani-induced LTP, a long-lasting form of hippocampal



synaptic plasticity that is mediated by postsynaptic PKA activity, and also for NMDAR-mediated LTD.

We found that translin/trax is required for spaced 4-train-LTP that relies on postsynaptic PKA activity [30] but dispensable for TBS- and FSK-LTP that rely on presynaptic PKA activity [19, 30]. Further, massed 4-train LTP, which does not require PKA activation, was not affected by the loss of translin/trax. This suggests that massed 4-train LTP relies on mechanisms that do not require PKA and translin/trax for its persistence. Indeed, we have reported earlier that massed 4-train LTP is less sensitive to protein synthesis inhibition by anisomycin as compared to spaced 4-train LTP [31]. This indicates that although the persistence of massed 4-train requires protein synthesis, the mechanisms that activate protein synthesis could be different than those underlying spaced 4-train LTP. These findings highlight the role of translin/trax in postsynaptic PKA signaling-dependent persistent synaptic plasticity. Notably, synaptic tagging and capture is impaired in the absence of translin/trax [15] but is intact when postsynaptically compartmentalized PKA signaling is disrupted [19]. However, these studies used massed 4-train-LTP, which does not rely on PKA signaling, to induce synaptic tagging and capture. Considering this experimental caveat, multi-disciplinary approaches to manipulate localized translin/trax-PKA signaling with high spatiotemporal specification will further dissect the role of translin/trax in postsynaptic PKA signaling-mediated persistent synaptic plasticity.

We found that mice lacking translin/trax display electrophysiological phenotypes that are distinct from those observed in mice lacking FMRP, regardless of sharing

some common behavioral abnormalities [22]. Translin KO mice show deficits in spaced 4-train LTP (Fig. 1b) and high-frequency stimulation-induced synaptic tagging and capture [15], but FMRP KO mice do not exhibit these impairments [38, 44]. Exaggerated mGluR-LTD is the prominent phenotype of FMRP KO mice [37], but it was not observed in translin KO mice (Fig. 3a). Additionally, LFS-induced NMDAR-dependent LTD showed deficits in the translin KO mice (Fig. 3c) whereas it is unaffected in the FMRP KO mice [37]. These strikingly contrasting synaptic plasticity phenotypes observed in FMRP KO mice and translin KO mice suggest distinct roles of these proteins in hippocampal synaptic plasticity. Whereas FMRP seems to predominantly play a role in certain forms of synaptic depression, translin/trax complex appears to function in specific forms of both synaptic potentiation and depression. Given the requirement of PKA signaling and protein synthesis for the persistence of both the spaced 4-train LTP [28–32] and the LFS-induced NMDAR-LTD [39, 40, 45, 46] and that they are both impaired in the translin KO mice strongly suggest the role of translin/trax in PKA-dependent activation of protein synthesis. Thus, our study demonstrates a selective role for translin/trax in bidirectional synaptic plasticity and provides a foundation for future studies defining signaling pathways that enable distinct synaptic stimulation to trigger the activation of this microRNA-degrading enzyme and its targets.

Based on our published and current findings, we propose a working model in which translin/trax mediates persistent synaptic plasticity (Fig. 4). During basal synaptic transmission (Fig. 4a), the translin/trax

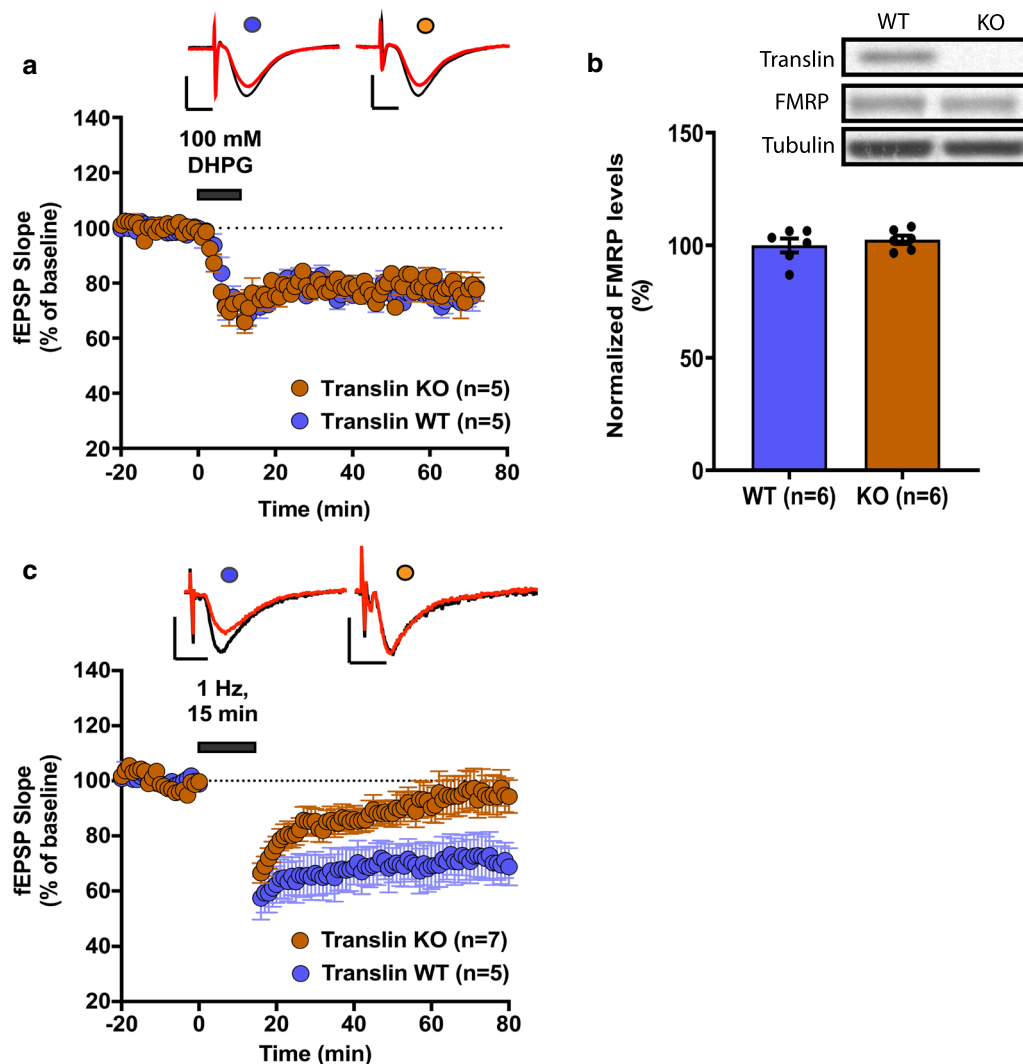
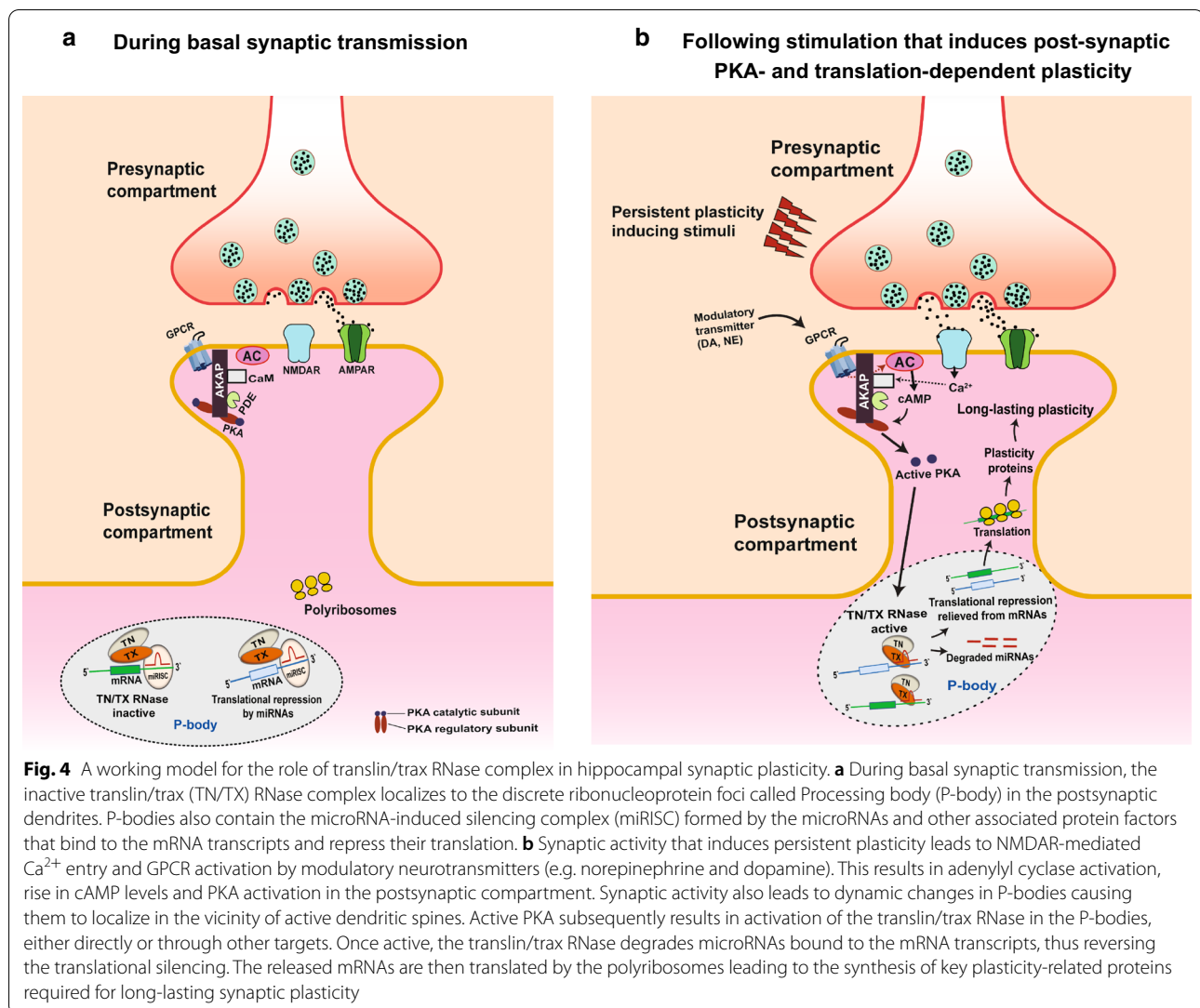


Fig. 3 Translin KO mice show unaltered mGluR-LTD and unchanged hippocampal protein levels of FMRP, but show deficits in NMDAR-dependent LTD. **a** Hippocampal slices from translin KO mice (n = 5; males) and wildtype littermates (n = 5; all males) displayed similar mGluR-LTD induced by bath application of 100 mM of DHPG for 10 min (two-way repeated measures ANOVA, $F_{(1,8)} = 0.08$, $p = 0.79$). **b** Hippocampal extracts from translin KO mice (n = 6) and wildtype littermates (n = 6) had similar protein levels of FMRP (t-test, $p = 0.36$). Beta-tubulin was used as the loading control and the expression level was normalized to the level of wildtype littermates. Representative blots are shown on top of the graph. **c** Hippocampal slices from translin KO mice (n = 7; 1 male, 6 females) showed deficits in NMDAR-dependent LTD induced by prolonged low-frequency stimulation (1 Hz, 15 min) compared to the wildtype littermates (n = 5; 3 males, 2 females) (two-way repeated measures ANOVA, $F_{(1,10)} = 5.342$, $p = 0.043$). Representative traces before (black) and after (red) stimulation are shown on top of the graphs. Scale bars for traces 2 mV, 5 ms. 'n' refers to the number of mice used. Error bars reflect S.E.M

microRNA-degrading enzyme is localized within the processing bodies (P-bodies) with its RNase inactive. This is supported by our previous data showing colocalization of trax with the P-body marker GW182 in hippocampal primary neuron dendrites [15]. Given that P-bodies also contain mRNAs translationally repressed by the microRNA-induced silencing complex (miRISC) [47–49], the translin/trax complex is well-positioned to degrade microRNAs. Following persistent plasticity-inducing

stimuli or learning (Fig. 4b), P-bodies are translocated to dendritic spines [50], and localized pools of PKA and the translin/trax complex are activated. Active translin/trax RNase then degrades microRNAs, relieving transcripts from translational repression. This allows the production of key plasticity-related proteins required for persistent plasticity. We have previously identified activin receptor type IC (ACVR1C) as one such plasticity-related protein [15]. Whether PKA directly activates the translin/trax



complex or acts through other targets warrants further investigation.

Taken together, these findings expand our understanding of the role of translin/trax in persistent synaptic plasticity. Future investigations are needed to directly validate the proposed model. First, the compartment-specific function of translin/trax needs to be further validated using hippocampal subregion-specific deletion of translin/trax using Cre-dependent viral strategies. Second, experiments are also needed to validate the dynamics of translin/trax localization in P-bodies following plasticity-inducing stimuli. Tagging a fluorescent reporter to translin or trax would enable tracking the localization of translin/trax but achieving this without affecting molecular interactions and RNase activity is challenging. Lastly, molecular assays to determine mechanisms by which translin/trax interacts with localized PKA signaling will

be required. Given the role of translin/trax in synaptic memory mechanisms, our findings pave the way for future research aimed at elucidating the pathophysiology of neuropsychiatric disorders.

Abbreviations

aCSF: Artificial cerebrospinal fluid; AC: Adenylyl cyclase; ACVR1C: Activin receptor type 1-C; AMPAR: α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CaM: Calmodulin; cAMP: Cyclic adenosine monophosphate; DHPG: (*RS*)-3,5-Dihydroxyphenylglycine; fEPSP: Field excitatory postsynaptic potential; FMRP: Fragile X mental retardation protein; FSK: Forskolin; GPCR: G-protein coupled receptor; LTP: Long-term potentiation; LTD: Long-term depression; mGluR: Metabotropic glutamate receptor; miRISC: MicroRNA-induced silencing complex; NMDAR: N-methyl *D*-aspartate receptor; PDE: Phosphodiesterase; PKA: Protein kinase A; RBP: RNA-binding protein; RNase: Ribonuclease; TBS: Theta-burst stimulation; TN/TX: Translin/trax; Trax: Translin-associated protein-X.

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Authors' contributions

AJP and TA designed the experiments. AJP performed the electrophysiology and western blotting experiments. MSS performed the NMDAR-LTD experiments. AJP and MSS performed data analysis. AJP and M.S.S prepared figures and wrote the manuscript with inputs from JMB and TA. All the listed authors have read and approved the manuscript for publication.

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Availability of data and materials

All the data supporting the conclusions of this article are included within the manuscript. Original data files and any supporting materials are available upon request, from the corresponding authors.

Ethics approval and consent to participate

All the experiments presented here were performed using mice. All experiments were performed according to the National Institutes of Health guidelines and were fully approved by the Institutional Animal Care and Use Committee at the University of Pennsylvania and the University of Iowa.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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