Fragile X mental retardation protein: from autism to neurodegenerative disease

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INTRODUCTION

Fragile X mental retardation protein (FMRP) is a RNA binding protein, the absence of which due to silencing of the FMR1 gene causes fragile X syndrome, an X-linked neurodevelopmental disorder (Bassell and Warren, 2008; Bhakar et al., 2012; Santoro et al., 2012). FMRP regulates the transport, stability and translation of its mRNA targets. Loss of FMRP alters translational control and receptor-mediated signaling pathways, leading to aberrant dendritic spine dynamics, synaptic dysfunction and behavioral phenotypes in fragile X syndrome (Wang et al., 2012; Sidorov et al., 2013; Suhl et al., 2014). Since the identification of FMR1 as the causative gene for fragile X syndrome in 1991, studies have mainly focused on understanding the function of FMRP. More and more potential FMRP mRNA targets and interacting proteins have been identified in the mammalian brain, supporting the critical roles of FMRP in neurodevelopment, synaptic plasticity and other neurological disorders apart from fragile X syndrome (Wang et al., 2008b, 2012; Fasciuto and Bagni, 2014a; Suhl et al., 2014).

Fragile X syndrome, the most common monogenic cause of autism spectrum disorders (ASDs), has been leading the way for better understanding of autism and other neurodevelopmental disorders (Belmonte and Bourgeron, 2006; Benilova et al., 2012; Banerjee et al., 2014; Cook et al., 2014). Clinically, a substantial proportion of children with fragile X syndrome meets diagnostic criteria for ASDs (Budimirovic and Kaufmann, 2011). Genetically and biologically, many of the neuronal targets of FMRP overlap with genes associated with ASDs, suggesting the common pathways that are dysregulated and might be potential therapeutic targets for these neurodevelopmental disorders (Auerbach et al., 2013). Interestingly, studies in recent years have further revealed that FMRP regulates a multitude of synaptic proteins and components of signaling pathways that not only affect neurodevelopment, but also contribute to the pathogenesis of neurodegenerative diseases such as Alzheimer disease (AD), the leading cause for dementia in the elderly (Maller et al., 2010; Sokol et al., 2011; Westmark et al., 2011; Hamilton et al., 2014). FMRP may play a pivotal role in the association between neurodevelopmental and neurodegenerative disorders across lifespan.

FMRP AND AD PATHOGENESIS

AD is pathologically characterized by the presence of plaques comprised of β amyloid (Aβ) and neurofibrillary tangles (NFTs) containing hyperphosphorylated tau protein (Selkoe, 2011; Horlitzman et al., 2012; Ubbi and Masliah, 2013; Bloom, 2014). A considerable amount of evidence suggests that soluble Aβ oligomers are the predominant neurotoxic species of Aβ, with Aβ42 fragment as the particularly potent form (Klyubin et al., 2012; Masters and Selkoe, 2012; Klein, 2013). Aβ oligomers exert the toxic effects by binding to their receptors on neuronal synapses, disrupting normal synaptic signaling pathways, which further leads to synaptic damage accompanied by neuronal loss (Benilova et al., 2012; Sheng et al., 2012; Pozueta et al., 2013; Wang et al., 2013; Tu et al., 2014).

FMRP IN Aβ MEDIATED SYNAPTIC TOXICITY

A growing number of synaptic proteins have been proposed as potential Aβ receptors or coreceptors, which are believed to mediate Aβ induced synaptic dysfunction (Karran et al., 2011; Paulalima et al., 2013; Pozueta et al., 2013;
involves surface removal and endocytosis (other molecules which are closely linked to APP), ARC, STEP, PTEN, GSK3. Dysregulation of the translational mRNAs (Darnell and Klann, 2013; Sidorov). FMRP may regulate the balance of tau protein kinases, GSK3β, CaMKII, ERK1/2, and S6K1 are known to be FMRP targets (Figure 1A). The decrease in the levels or activity of protein phosphatase(s) that dephosphorylate tau also contributes to AD pathology (Braithwaite et al., 2012; Martin et al., 2013a); among these phosphatases, PP2A, STEP, and PTEN are FMRP targets (Figure 1A). FMRP, which is also a role in actin disorganization in AD (Wang et al., 2008b; Zhang et al., 2008; Lisman et al., 2012), supporting possible involvement of FMRP in glutamate receptor endocytosis (Figure 1A). The actin disorganization contributes to AD pathogenesis (Maloney and Bamburg, 2007; Bamburg and Bloom, 2009; Penuzes and Vanleeuwen, 2011). The actin disorganization regulates the balance between oligomeric Aβ and PrPC (Um et al., 2012; Boehm, 2013). Tau phosphorylation is regulated by a balance between tau kinase and phosphatase activities. Disruption of this balance by Aβ exposure is suggested to cause abnormal tau phosphorylation and thereby contributes to tau aggregation (Wang et al., 2007; Martin et al., 2013a,b). Of the tau protein kinases, GSK3β, CaMKII, ERK1/2, and S6K1 are known to be FMRP targets (Figure 1A). The decrease in the levels or activity of protein phosphatase(s) that dephosphorylate tau also contributes to AD pathology (Braithwaite et al., 2012; Martin et al., 2013a); among these phosphatases, PP2A, STEP, and PTEN are FMRP targets (Figure 1A). FMRP thus, might be involved in tau pathology through regulating those tau kinases and phosphatases. Hyperphosphorylated tau sequesters normal tau, and the other two major MAPs (MAP1 and MAP2), causing disruption of microtubules and misfolding of tau (Zempel and Mandelkow, 2014). Notably, both MAP1A and MAP2 are FMRP targets, further implicating FMRP in neurofibrillary degeneration (Figure 1A).

**FMRP IN Aβ STIMULATED APP SYNTHESIS**

Aβ is produced by the sequential proteolytic cleavage of APP by β- and γ-secretases via amyloidogenic pathway (Masters and Selkoe, 2012). The expression of APP can be upregulated upon mGluR5 stimulation. FMRP, which is also regulated by mGluR5 (Ronese and Huber, 2008; Wang et al., 2008a; Wang and Zhuo, 2012), binds to and represses the translation of APP mRNA due to mGluR5 activation (Westmark and Malter, 2007; Westmark, 2013).

The mGluR5 links FMRP with APP. It is known that mGluR5 acts as a coreceptor for Aβ oligomers bound to PrPC (Um et al., 2013). Aβ oligomers can stimulate APP synthesis through the mGluR5 and protein translation dependent pathway which involves FMRP, providing template for secretase cleavage to produce Aβ and other metabolites (Westmark and Malter, 2007; Westmark, 2013). Aβ oligomer interactions with mGluR5-PrPC may function to accelerate Aβ production through the FMRP dependent signaling pathway, suggesting that a positive feedback loop may
FIGURE 1 | Potential roles of FMRP in the pathogenesis of AD. (A) FMRP might be involved in oligomeric Aβ induced neurotoxicity. At pathological concentrations, Aβ oligomers may interact with multiple neuronal synaptic receptors such as mGluR5, NMDARs, AMPARs, and EphB2, triggering a series of toxic synaptic events which may involve FMRP and eventually lead (Continued)
FIGURE 1 | Continued
to synaptic dysfunction and neuronal loss. These events include: Aberrant activation of PI3K-Akt-mTORC1 and MEK-ERK signaling pathways linked to cap-dependent translation result in altered synthesis of synaptic proteins; Oligomeric Aβ exposure disrupts the balance between tau kinase (GSKß3), CaMKII, Akt, Fyn, and ERK1/2 and phosphatase (PP2A, STEP, and PTEN) activities, inducing tau hyperphosphorylation and aggregation; Stimulating EphB2-Rac1/PAK1 signaling by Aβ oligomers induces coflin phosphorylation and actin depolymerization, leading to actin network disorganization; Binding of Aβ oligomers to PrPc-mGluR5 activates Fyn kinase which phosphorylates not only tau, but also NR2B subunit of NMDARs, enhancing NMDAR activity and causing excitotoxicity; STEP is also activated, inactivates Fyn, and dephosphorylates AMPARs and NMDARs, resulting in endocytosis of glutamate receptors, a cellular process involves Arc, PSD-95, SAPAR and other synaptic proteins. Purple proteins are those whose mRNAs are FMRP targets (Darnell and Klann, 2013; Pasciuto and Bagni, 2014b; Santini and Klann, 2014); the blue ones are the interacting proteins of FMRP (Pasciuto and Bagni, 2014a). Proteins with red lines around them indicate those that have been successfully manipulated either pharmacologically or genetically to reverse molecular, cellular and/or behavioral phenotypes in animal models of AD (Zhang et al., 2010; Malinow, 2012; Caccamo et al., 2014; Feld et al., 2014; Hamilton et al., 2014; Llorens-Martin et al., 2014) as well as ASDs (Goebel-Goody et al., 2012; Guo et al., 2012; Won et al., 2012; Darnell and Klann, 2013; Osterweil et al., 2013; Wang and Doering, 2013; Wang, 2014). Proteins with black lines around them are the ones that have been reported to be potential targets for AD therapy (Griffin et al., 2005; Lafay-Chabassier et al., 2005; Ma et al., 2008; Cisse et al., 2011; Moriguchi, 2011; Chang et al., 2012; Gross and Bassell, 2014; Nygaard et al., 2014; Sontag and Sontag, 2014). (B) FMRP in APP synthesis. Aβ oligomers stimulate dendritic APP synthesis through PrPc-mGluR5 mediated protein translation dependent pathway, providing template for secretase cleavage to produce Aβ and other metabolites. A positive feedback may exist whereby production of APP results in increased substrate for amyloidogenic processing and release of Aβ, which then activates mGluR5 to further stimulate APP translation. In this process, FMRP competes with the other RNA binding protein hnRNP C to modulate APP translation. FMRP is a repressor of APP translation, whereas hnRNP C acts as an enhancer. The rate of APP synthesis is directly influenced by the relative association of each RNA binding protein (Lee et al., 2010). In signaling pathways, arrows indicate positive (green) or inhibitory (red) consequence on downstream components, but they do not necessarily represent direct interactions.

exist in AD, whereby translation of APP results in increased substrate for amyloidogenic processing and generation of Aβ which then stimulates mGluR5 signaling to induce further synaptic synthesis of APP (Westmark and Malter, 2007; Westmark, 2013) (Figure 1B). Thus, in addition to the established role in fragile X syndrome and autism, FMRP likely contributes directly to AD pathogenesis through mGluR5 dependent APP production.

FMRP TARGETS AND AD THERAPY
As discussed above, a number of signaling pathways, including PI3K-Akt-mTORC1, MEK-ERK and PAK1 pathways, have been found to be involved in the neurodevelopmental progression of AD. Therapies for AD might require the development of drugs targeting these aberrant signaling pathways, among which several key signaling proteins such as PI3K, mTOR, ERK and PAK1, are targets of FMRP. In addition, the FMRP targeted Aβ oligomer receptors including mGluR5 and NMDARs could be ideal therapeutic targets for AD (Figure 1A). Particularly, pharmacological inhibition or genetic deletion of mGluR5 was recently found to rescue learning deficits, or reduce Aβ oligomers and plaques in AD mice (Um et al., 2013; Hamilton et al., 2014).

Tau plays crucial roles in the neuronal cytoskeleton stabilization and is an important target for AD therapies (Gotz et al., 2012; Himmelstein et al., 2012; Giacobini and Gold, 2013). Interventions focused on preventing or reducing tau hyperphosphorylation and mislocalization may provide additional strategies for treatment of AD. The therapeutic tactics include Tau kinase inhibitors and phosphatase activators (Giacobini and Gold, 2013; Zempel and Mandelkow, 2014). The relevant kinases and phosphatases could be the FMRP targets such as GSKß3, ERK, S6K1, PP2A, PTEN, and STEP (Figure 1A). Although the tau based treatments are encouraging, additional work are undoubtedly needed to optimize each treatment for further development of safe and effective therapies.

Therefore, FMRP targeted signaling molecules not only provide therapeutic strategies for fragile X syndrome and other ASDs (Darnell and Klann, 2013; Santini and Klann, 2014), but may serve as potential targets for treatment of AD. Indeed, many components of altered signaling pathways in AD overlap with those in ASDs. A number of signaling proteins targeted by FMRP have been successfully manipulated either pharmacologically or genetically to reverse molecular, cellular and/or behavioral phenotypes in animal models of both ASDs and AD (Figure 1A). FMRP thus, acts as a molecular link between ASDs and AD through the common signaling pathways among the diseases. Developing novel therapies directed at FMRP targets may benefit both neurodevelopmental and neurodegenerative disorders.

FUTURE PERSPECTIVES
It is now known that FMRP controls signaling pathways that could be associated with both neurodevelopmental and neurodegenerative disorders. FMRP not only regulates gene expression at the translational level, but also interacts with a multitude of proteins at both presynaptic and postsynaptic sites (Pasciuto and Bagni, 2014a; Myrick et al., 2015). However, so far no systemic proteomic analysis of FMRP interactome in brain has been reported. Additionally, although many of the interacting proteins of FMRP such as transactive response DNA-binding protein-43 (TDP-43), survival of motor neuron 1 (SMN1) and CYFIP are known to be linked to neurological disorders (Abekhoukh and Bardoni, 2014; Pasciuto and Bagni, 2014a), the significance of the protein-protein interaction to individual proteins and diseases still need to be further characterized.

The AD animal or cell models are powerful tools for investigating the pathogenesis of the neurodegenerative disease. It will be useful to set up the transgenic AD mice/Aβ-treated primary neuronal culture which either lack or overexpress FMRP for further evaluating the pathological role of FMRP in AD. FMRP regulates specific mRNA/protein targets at different developmental stages and in different brain areas. Future studies will need to provide detailed information on FMRP mRNA targets and FMRP interactome in relevant brain areas at specific developmental
Alzheimer’s disease-like cognitive and pathological deficits by restoring hippocampal gene expression signature. *J. Neurosci.* 34, 7988–7998. doi: 10.1523/JNEUROSCI.0777-14.2014

Chang, P. K., Verbič, D., and McKinney, R. A. (2012). AMPA receptors as drug targets in neurological disease-advantages, caveats, and future outlook. *Eur. J. Neurosci.* 35, 1908–1916. doi: 10.1111/j.1460-9568.2012.08165.x

Chen, X., Nelson, C. D., Li, X., Winters, C. A., Azzam, R., Sousa, A. A., et al. (2011). PSD-95 is required to sustain the molecular organisation of the post-synaptic density. *J. Neurosci.* 31, 6329–6338. doi: 10.1523/JNEUROSCI.9687-10.2011

Chowdhury, S., Shephard, J. D., Okuno, H., Lyford, G., Petralia, R. S., Plath, N., et al. (2006). Arc/Arc3 interacts with the endocytic machinery to regulate AMPA receptor trafficking. *Neuron* 52, 445–459. doi: 10.1016/j.neuron.2006.08.033

Cisse, M., and Checler, F. (2014). Eph receptors: new players in Alzheimer’s disease pathogenesis. *Neurobiol. Dis.* 73C, 137–149. doi: 10.1016/j.nbd.2013.04.005

Cisse, M., Halabisky, B., Harris, J., Devizde, N., Dubai, D. B., Sun, B., et al. (2011). Reversing EphB2 depletion rescues cognitive functions in Alzheimer model. *Nature* 469, 47–52. doi: 10.1038/nature09635

Cook, D., Nuro, E., and Murai, K. K. (2014). Increasing our understanding of human cognition through the study of Fragile X Syndrome. *Dev. Neurosci.* 36, 417–443. doi: 10.1146/annurev-neuro-060909-153138

Bloom, G. S. (2014). Amyloid-beta and tau: the trigger and bullet in Alzheimer disease pathogenesis. *JAMA Neurol.* 71, 505–508. doi: 10.1001/jamaneurol.2013.50847

Boehm, J. (2013). ‘A danse macabre’: tau and Fyn in STEP with amyloid beta to facilitate induction of synaptic depression and excitotoxicity. *Eur. J. Neurosci.* 37, 1925–1930. doi: 10.1111/j.1460-9568.2012.07452.x

Caccamo, A., De Pinto, V., Messina, A., Branca, C., and Oddo, S. (2014). Genetic reduction of mammalian target of rapamycin ameliorates stages of AD animal models. The information will greatly help to further elucidate the pathogenesis of this neurodegenerative disease and develop relative therapeutic strategies.
Wang, T., Bray, S. M., and Warren, S. T. (2012). New perspectives on the biology of fragile X syndrome. Curr. Opin. Genet. Dev. 22, 256–263. doi: 10.1016/j.gde.2012.02.002

Waung, M. W., Pfeiffer, B. E., Nosyreva, E. D., Ronesi, J. A., and Huber, K. M. (2008). Rapid translation of Arc/Arg3.1 selectively mediates mGluR-dependent LTD through persistent increases in AMPAR endocytosis rate. Neuron 59, 84–97. doi: 10.1016/j.neuron.2008.05.014

Westmark, C. J. (2013). What’s hAPPening at synapses? The role of amyloid beta-protein precursor and beta-amyloid in neurological disorders. Mol. Psychiatry 18, 425–434. doi: 10.1038/mp.2012.122

Westmark, C. J., and Malter, J. S. (2007). FMRP mediates mGluR5-dependent translation of amyloid precursor protein. PLoS Biol. 5:e52. doi: 10.1371/journal.pbio.0050052

Westmark, C. J., Westmark, P. R., O’Riordan, K. J., Ray, B. C., Hervey, C. M., Salamat, M. S., et al. (2011). Reversal of fragile X phenotypes by manipulation of AbetaPP/Abeta levels in Fmr1KO mice. PLoS ONE 6:e26549. doi: 10.1371/journal.pone.0026549

Won, H., Lee, H. R., Gee, H. Y., Mah, W., Kim, J. I., Lee, J., et al. (2012). Autistic-like social behaviour in Shank2-mutant mice improved by restoring NMDA receptor function. Nature 486, 261–265. doi: 10.1038/nature11208

Zempel, H., and Mandelkow, E. (2014). Lost after translation: missorting of Tau protein and consequences for Alzheimer disease. Trends Neurosci. 37, 721–732. doi: 10.1016/j.tins.2014.08.004

Zhang, Y., Kurup, P., Xu, J., Garty, N., Fernandez, S. M., Nygaard, H. B., et al. (2010). Genetic reduction of striatal-enriched tyrosine phosphatase (STEP) reverses cognitive and cellular deficits in an Alzheimer’s disease mouse model. Proc. Natl. Acad. Sci. U.S.A. 107, 19014–19019. doi: 10.1073/pnas.1013543107

Zhang, Y., Venkitaramani, D. V., Gladding, C. M., Kurup, P., Molnar, E., Collingridge, G. L., et al. (2008). The tyrosine phosphatase STEP mediates AMPA receptor endocytosis after metabotropic glutamate receptor stimulation. J. Neurosci. 28, 10561–10566. doi: 10.1523/JNEUROSCI.2666-08.2008

Zoghbi, H. Y., and Bear, M. F. (2012). Synaptic dysfunction in neurodevelopmental disorders associated with autism and intellectual disabilities. Cold Spring Harb. Perspect. Biol. 4:a009886. doi: 10.1101/cshperspect.a009886

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