mRNPs, polysomes or granules: FMRP in neuronal protein synthesis

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mRNA localization and regulated translation play central roles in neurite outgrowth and synaptic plasticity. A key molecule in these processes is the Fragile X mental retardation protein, FMRP, which is involved in the metabolism of neuronal mRNAs. Absence or mutation of FMRP leads to spine dysmorphogenesis and impairs synaptic plasticity. Studies that have mainly been performed on the mouse and *Drosophila* models for Fragile X Syndrome showed that FMRP is involved in translational regulation at synapses, but even 15 years after discovery of the *FMR1* gene, the precise working mechanisms remain elusive.

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Introduction

Mental retardation is a frequent cause of cognitive disability that includes a substantial genetic component. Mutations of the gene coding for FMRP (Fragile Mental Retardation Protein) are associated with an X-linked and syndromic form of mental retardation, the Fragile X Syndrome (FXS) [1•,2–5]. In the majority of cases, the syndrome is caused by expansion of a polymorphic CGG repeat located in the 5' UTR of the gene. The expansion causes transcriptional silencing of the *FMR1* gene, which occurs as a result of hypermethylation of the CGG repeats and the upstream CpG (region with at least 200 bp and with a GC percentage that is greater than 50%) islands [6].

The domain structure of FMRP includes three RNA-binding motifs that are typical of hnRNP (heterogeneous nuclear ribonucleoprotein) proteins, namely two ribonucleoprotein K homology domains (KH domains), and a cluster of arginine and glycine residues (RGG box). A fourth domain at the N-terminus that contains a helix-loop-helix–Tudor motif also binds RNA. This domain

structure suggests that FMRP is involved in messenger RNA (mRNA) biogenesis and metabolism [1•]. The absence of or mutations in FMRP lead to the defects in spine morphology that are found in FXS. Indeed, FMRP has been detected along dendrites [7] and at synapses [8] where it regulates synaptic protein synthesis [9]. mRNAs are localized and translated locally at the neurites, which spatially restricts gene expression within neurons, and thereby provides growth cones and synapses with the capacity to autonomously regulate their structure and function and to alter their individual protein composition. FMRP appears to be a key regulator of this process.

In this review, we summarize recent progress on the association of FMRP with different components and regulators of the translational machinery. Taking into account recent progress in translational control, we present a new perspective on the published literature.

Roles of FMRP in translation and molecular mechanisms

It has been hypothesized that FMRP has a role in the regulation of neuronal translation. mRNA translation (a process divided into several pre-initiation steps of initiation, elongation and termination) can be inhibited mainly at the initiation steps but also during elongation [10,11]. Because translation initiation complexes are smaller than a ribosome (80S; S: Svedberg unit), sedimentation on sucrose gradients, which measures complex size after ultracentrifugation, is traditionally taken as an indication of the translational status of an mRNP (messenger ribonucleoprotein) particle: if it is bigger than 80S, the mRNA is assumed to be associated with polyribosomes. However, some forms of stalled initiation complexes (mRNPs) tend to aggregate and become as big or even bigger than translating polyribosomes. Examples include stress granules [12], which contain stalled 48S initiation complexes, and P bodies, which contain an inhibitor of the very first step of translation complex formation [13–15].

To date, a very complex dataset concerning the distribution of FMRP along polysome gradients has been published [1•] with widely diverging results. Several studies show that FMRP primarily cofractionates with polyribosomes in both human and murine cultured cell lines and in two tissues, brain and liver [16,17]. However, other reports showed the cofractionation of FMRP primarily with mRNPs (mammalian and *Drosophila* cell lines and mouse brain) [9,18–20] or equally distributed between the two fractions (polyribosomes and mRNPs) in mammalian cell lines [21,22]. Although the conclusions of

these studies sometimes state that FMRP co-fractionates with one or the other fraction, the distribution in most cases is more heterogeneous.

A heterogeneous distribution on sucrose gradients can be observed when the protein is part of several different complexes or part of a large but labile complex so that the outcome is changed by the extraction protocol: whereas polyribosomes might partially dissociate during preparation, non-translating mRNPs can aggregate or remain aggregated (see above). The fact that FMRP forms both homo- and heterodimers [23], associates with a variety of other proteins [1[•]] and is present in an array of neuronal granules [24,25^{••},26[•]] strongly suggests that there are different FMRP-containing ribonucleoprotein particles. As putative FMRP target mRNAs are both up- and down-regulated [22,27], FMRP could serve as both an activator and a repressor of translation, and, therefore, sediment both in the mRNP and the polyribosome fraction, possibly depending on post-translational modifications [28]. We conclude that polysome gradients alone are not sufficient to elucidate the roles of FMRP in translation.

Therefore, the years of debate on the association of FMRP with polysomes and/or mRNPs unfortunately did not advance our knowledge on how FMRP represses translation. Instead, a different series of studies suggest that the population of FMRP associated with light mRNPs (the non-polysomal fraction) is involved in repression of translation initiation: large amounts of FMRP repress translation *in vitro* by inhibition of the 80S complex formation [29]. Furthermore, two molecular mechanisms, both based on non-coding RNAs, link FMRP to inhibition of translational initiation. First, FMRP is linked to the miRNA (microRNA) molecules that base pair to an mRNA target. As a consequence, the mRNA is translationally repressed [30] and can also be destabilized [31]. Both processes take place in a complex called RISC (RNA interference silencing complex). The purification of RISC from *Drosophila* tissue culture cells demonstrated that *Drosophila* FMRP (dfxr) is associated with RISC [32], whereas another group purified dfxr complexes from the same cells and found Argonaute 2, a RISC component, associated with the complex [20]. Mammalian FMRP also interacts with components of miRNA pathways, namely DICER, the Argonaute Ago1, and miRNAs [33[•]]. This link is further supported by the observation that synaptic protein synthesis associated with memory is regulated by the RISC pathway in *Drosophila* [34[•]]. Recently, it was also shown that mammalian miRNAs are present at synapses and regulate spine development [35^{••}]. miRNAs inhibit translation at the level of initiation [36[•],37[•]], and this appears to take place in the P-bodies [36[•],38–41], which are accumulations of non-translated mRNPs silenced at the initiation level [42[•]]. In fact, P-bodies contain proteins involved in the inhibition of translation initiation

[14,15]. We have observed FMRP in the P-bodies (Eleuteri B, Achsel T, unpublished observation). It remains to be seen whether all mRNAs in the P-bodies are blocked at the same stage of translation initiation, and how this reflects on the silencing mechanism that FMRP is involved in. The second finding that links FMRP to translation initiation is its association with the small non-coding RNA BC1 in brain [9,43[•]]. BC1 RNA has the potential to base pair to neuronal target mRNAs, connecting the mRNAs and FMRP. The binding of FMRP to BC1 was not observed in a study by Wang *et al.*, [44]. In this *in vitro* study the authors used protein constructs, preparations and assays different from those used in our studies [9,43[•]], which might be the cause of this discrepancy. However, the FMRP–BC1 interaction has been confirmed in other assays [43[•]], and in other laboratories both *in vitro* [45^{••}] and *in vivo* [46]. The FMRP–BC1 interaction is quite strong, with a K_d of 200 nM for baculovirus-produced protein at high salt [43[•]] and a K_d of 25 nM for *E. coli*-produced protein at lower salt concentrations, respectively [45^{••}]. In this latter study, the authors also show that FMRP has annealing, DNA-strand exchange, and unwinding activities. Moreover, deletions of the N-terminal region and of the two KH domains strongly reduce these activities [45^{••}]. Furthermore, FMRP binds through the N-terminus, a novel RNA binding domain, to the upper part of the BC1 5' stem loop [43[•]], while the rest of this stem loop anneals to mRNAs [9]. We propose a model in which FMRP binds to BC1 on one side of the stem, and its strand exchange activity facilitates annealing of the other side to the target mRNAs. Significantly, BC1 is implicated in inhibition of translation initiation: in *in vitro* assays, BC1 interacts with two initiation factors, eIF4A and PABP, and inhibits formation of the 48S pre-ribosomal complex on a non-neuronal reporter mRNA [47]. Thus, we think that FMRP and BC1 cooperate to accomplish tight regulation of the translation initiation.

Translational regulation is an important step that requires tight control. mRNAs can be simultaneously repressed by more than one miRNA species [48] and multiple mechanisms can work on the same mRNA. This is demonstrated in the case of the *Drosophila oskar* mRNA, which is regulated by both the miRNA and the Cup pathways [49]. In this case, RNA interference-mediated repression probably predominates early in oogenesis, whereas Cup-mediated repression functions late in oogenesis [49]. Similarly, FMRP could regulate mRNA translation during development and in the adult through different mechanisms and/or through a combination of pathways.

In conclusion, the population of FMRP on the light mRNP particles is probably involved in translation regulation. Furthermore, the protein has also been detected on the heavy part of sucrose gradients, which indicates an association with either polyribosomes or mRNA granules.

Granules can be P-bodies (see above), stress granules (in which FMRP can be detected after stress conditions) [50] or neuronal transport granules [24]. The first two are mRNP aggregates stalled at the initiation level [12,42*,51]; the latter contain, in addition to the transport-related factors, ribosomal components [25**,26*], and might thus be aggregates of polysomes. Finally, the FMRP population associated with polysomes is presumably bound to actively translated mRNAs, that is, those mRNAs that are not, at the given point, silenced (see below). Co-fractionation of FMRP with the polysomes can be disrupted by adding to brain extracts an RNA that binds to the KH2 domain (the 'kissing complex' RNA), but not by addition of RNAs that bind to the RGG box (the 'G-quartet' RNA) or to the N-terminus (BC1) [52]. It will be interesting to see which natural mRNAs contain a 'kissing complex' structure and the relevance for the co-sedimentation of FMRP with polysomes. Some groups claim that FMRP is associated exclusively with the polysomes. To reconcile this with the role of FMRP as translational repressor, a 'stalling ribosomes' model has been suggested [17,28], but mechanistic details have yet to be proposed.

Roles of FMRP in synaptic plasticity

The key deficit of FXS patients, similar to the situation in the mouse and fly models of the syndrome, is an immature — long and thin — appearance of the dendritic spines, which is thought to be the cause of the mental retardation [1*,53,54]. Spines are dynamic structures that mature during development and in response to stimulation, and this process requires local protein synthesis [55]. FMRP regulates synaptic protein synthesis [9]. To understand the mental retardation, it is, therefore, important to know which mRNAs are controlled by FMRP at the synapses. Despite the fact that FMRP has been reported to be associated with a large number of mRNAs *in vivo* and *in vitro* [1*], the majority of the dendritic targets remain elusive. More than 500 putative mRNAs have been isolated, but very few have been found in more than one independent study. Among these few, three are of particular interest for the development and function of the spines, namely microtubule-associated protein 1B [9,22,56,57], Rac1 (rho family, small GTP binding protein; [58], Zalfa F, Bagni C, unpublished), and calcium/calmodulin-dependent protein kinase II α mRNA [9,59]. These mRNAs encode key proteins involved in synaptic remodeling and strength.

Synaptic stimulation increases local translation [55], and similar stimuli provoke a relocation of the translation machinery into the spines [60]. Translation can be activated by dissociating FMRP from the regulated mRNA, by changing its function on the mRNA, or by bypassing its repression. The finding that mGluR (metabotropic glutamate receptor) activation actually increases FMRP levels [61] implies that FMRP itself is involved in

translation activation. Alternatively, several dendritic mRNAs contain internal ribosomal entry sites [62], which is a convenient way to bypass a specific block of translation initiation. Finally, rapamycin-sensitive translational initiation [63] and cytoplasmic polyadenylation [64,65] are upregulated after NMDA receptor stimulation — both increase translation. To elucidate which (combination) of the above mechanisms provides the main contribution to the release of FMRP repression, further studies are necessary. Recently, reports of very challenging techniques have been published [66–68], which we hope will lead to the answer of this question.

Conclusions

Mental retardation and dendritic spine dysmorphogenesis could reflect a lack of proper dendritically localized protein synthesis. Because FMRP is expressed not only during development but also in adulthood, it is tempting to hypothesize that in addition to a role in establishing new connections, FMRP also has a role in maintaining them throughout the lifetime of an organism. The future challenge that remains in order to find a therapeutical approach to Fragile X Syndrome is the identification of the precise role of FMRP in synaptic plasticity so that neuronal activity can be modulated in absence of FMRP.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Bagni C, Greenough WT: **From mRNP trafficking to spine dysmorphogenesis: the roots of fragile X syndrome.** *Nat Rev Neurosci* 2005, **6**:376–387.
- A comprehensive overview of spine dysmorphogenesis and its molecular basis.
2. Zhang YQ, Broadie K: **Fathoming fragile X in fruit flies.** *Trends Genet* 2005, **21**:37–45.
3. Crnic LS, Hagerman R: **Preface: fragile X syndrome: frontiers of understanding gene-brain-behavior relationships.** *Ment Retard Dev Disabil Res Rev* 2004, **10**:1–2.
4. Bear MF, Huber KM, Warren ST: **The mGluR theory of fragile X mental retardation.** *Trends Neurosci* 2004, **27**:370–377.
5. Chiurazzi P, Neri G, Oostra BA: **Understanding the biological underpinnings of fragile X syndrome.** *Curr Opin Pediatr* 2003, **15**:559–566.
6. Oberle I, Rousseau F, Heitz D, Kretz C, Devys D, Hanauer A, Boue J, Bertheas MF, Mandel JL: **Instability of a 550-base pair DNA segment and abnormal methylation in fragile X syndrome.** *Science* 1991, **252**:1097–1102.
7. Antar LN, Afroz R, Dichtenberg JB, Carroll RC, Bassell GJ: **Metabotropic glutamate receptor activation regulates fragile x mental retardation protein and FMR1 mRNA localization differentially in dendrites and at synapses.** *J Neurosci* 2004, **24**:2648–2655.

8. Feng Y, Gutekunst CA, Eberhart DE, Yi H, Warren ST, Hersch SM: **Fragile X mental retardation protein: nucleocytoplasmic shuttling and association with somatodendritic ribosomes.** *J Neurosci* 1997, **17**:1539-1547.
 9. Zalfa F, Giorgi M, Primerano B, Moro A, Di Penta A, Reis S, Oostra B, Bagni C: **The fragile X syndrome protein FMRP associates with BC1 RNA and regulates the translation of specific mRNAs at synapses.** *Cell* 2003, **112**:317-327.
 10. Gebauer F, Hentze MW: **Molecular mechanisms of translational control.** *Nat Rev Mol Cell Biol* 2004, **5**:827-835.
 11. Klann E, Dever TE: **Biochemical mechanisms for translational regulation in synaptic plasticity.** *Nat Rev Neurosci* 2004, **5**:931-942.
 12. Kedersha N, Anderson P: **Stress granules: sites of mRNA triage that regulate mRNA stability and translatability.** *Biochem Soc Trans* 2002, **30**:963-969.
 13. Marx J: **Molecular biology. P-bodies mark the spot for controlling protein production.** *Science* 2005, **310**:764-765.
 14. Andrei MA, Ingelfinger D, Heintzmann R, Achsel T, Rivera-Pomar R, Lührmann R: **A role for eIF4E and eIF4E-transporter in targeting mRNPs to mammalian processing bodies.** *RNA* 2005, **11**:717-727.
 15. Ferraiuolo MA, Basak S, Dostie J, Murray EL, Schoenberg DR, Sonenberg N: **A role for the eIF4E-binding protein 4E-T in P-body formation and mRNA decay.** *J Cell Biol* 2005, **170**:913-924.
 16. Khandjian EW, Huot ME, Tremblay S, Davidovic L, Mazroui R, Bardoni B: **Biochemical evidence for the association of fragile X mental retardation protein with brain polyribosomal ribonucleoparticles.** *Proc Natl Acad Sci USA* 2004, **101**:13357-13362.
 17. Stefani G, Fraser CE, Darnell JC, Darnell RB: **Fragile X mental retardation protein is associated with translating polyribosomes in neuronal cells.** *J Neurosci* 2004, **24**:7272-7276.
 18. Siomi MC, Zhang Y, Siomi H, Dreyfuss G: **Specific sequences in the fragile X syndrome protein FMR1 and the FXR proteins mediate their binding to 60S ribosomal subunits and the interactions among them.** *Mol Cell Biol* 1996, **16**:3825-3832.
 19. Siomi MC, Higashijima K, Ishizuka A, Siomi H: **Casein kinase II phosphorylates the fragile X mental retardation protein and modulates its biological properties.** *Mol Cell Biol* 2002, **22**:8438-8447.
 20. Ishizuka A, Siomi MC, Siomi H: **A drosophila fragile X protein interacts with components of RNAi and ribosomal proteins.** *Genes Dev* 2002, **16**:2497-2508.
 21. Feng Y, Absher D, Eberhart DE, Brown V, Malter HE, Warren ST: **FMRP associates with polyribosomes as an mRNP, and the I304N mutation of severe fragile X syndrome abolishes this association.** *Mol Cell* 1997, **1**:109-118.
 22. Brown V, Jin P, Ceman S, Darnell JC, O'Donnell WT, Tenenbaum SA, Jin X, Feng Y, Wilkinson KD, Keene JD *et al.*: **Microarray identification of FMRP-associated brain mRNAs and altered mRNA translational profiles in fragile X syndrome.** *Cell* 2001, **107**:477-487.
 23. Zhang Y, O'Connor JP, Siomi MC, Srinivasan S, Dutra A, Nussbaum RL, Dreyfuss G: **The fragile X mental retardation syndrome protein interacts with novel homologs FXR1 and FXR2.** *EMBO J* 1995, **14**:5358-5366.
 24. Krichevsky AM, Kosik KS: **Neuronal RNA granules: a link between RNA localization and stimulation-dependent translation.** *Neuron* 2001, **32**:683-696.
 25. Kanai Y, Dohmae N, Hirokawa N: **Kinesin transports RNA: isolation and characterization of an RNA-transporting granule.** *Neuron* 2004, **43**:513-525.
- The authors provide a thorough description of the composition of granules that contain FMRP and transport mRNAs. Tens of proteins including Staufen, FMRP, Pur α , Pur β , and other factors involved in protein synthesis, have been identified by mass spectrometry. The presence of α -CaMKII and ARC mRNAs in these granules was also detected.
26. Aschrafi A, Cunningham BA, Edelman GM, Vanderklisch PW: **The fragile X mental retardation protein and group I metabotropic glutamate receptors regulate levels of mRNA granules in brain.** *Proc Natl Acad Sci USA* 2005, **102**:2180-2185.
- The authors show that the quantity of mRNA granules that are heavier than the polysomes is regulated by FMRP and mGluR5. In particular, administration of an mGluR5 antagonist increases the granule content in Fmr1 knockout brain to the levels seen in wild type brain.
27. Miyashiro KY, Beckel-Mitchener A, Purk TP, Becker KG, Barret T, Liu L, Carbonetto S, Weiler IJ, Greenough WT, Eberwine J: **RNA cargoes associating with FMRP reveal deficits in cellular functioning in Fmr1 null mice.** *Neuron* 2003, **37**:417-431.
 28. Ceman S, O'Donnell WT, Reed M, Patton S, Pohl J, Warren ST: **Phosphorylation influences the translation state of FMRP-associated polyribosomes.** *Hum Mol Genet* 2003, **12**:3295-3305.
 29. Laggenbauer B, Ostareck D, Keidel EM, Ostareck-Lederer A, Fischer U: **Evidence that fragile X mental retardation protein is a negative regulator of translation.** *Hum Mol Genet* 2001, **10**:329-338.
 30. Filipowicz W, Jaskiewicz L, Kolb FA, Pillai RS: **Post-transcriptional gene silencing by siRNAs and miRNAs.** *Curr Opin Struct Biol* 2005, **15**:331-341.
 31. Bagga S, Bracht J, Hunter S, Massirer K, Holtz J, Eachus R, Pasquinelli AE: **Regulation by let-7 and lin-4 miRNAs results in target mRNA degradation.** *Cell* 2005, **122**:553-563.
 32. Caudy AA, Myers M, Hannon GJ, Hammond SM: **Fragile X-related protein and VIG associate with the RNA interference machinery.** *Genes Dev* 2002, **16**:2491-2496.
 33. Jin P, Zarnescu DC, Ceman S, Nakamoto M, Mowrey J, Jongens TA, Nelson DL, Moses K, Warren ST: **Biochemical and genetic interaction between the fragile X mental retardation protein and the microRNA pathway.** *Nat Neurosci* 2004, **7**:113-117.
- The authors show that mammalian FMRP is also linked to the RISC pathway.
34. Ashraf SI, McLoon AL, Scarsic SM, Kunes S: **Synaptic protein synthesis associated with memory is regulated by the RISC pathway in drosophila.** *Cell* 2006, **124**:191-205.
- In this paper, the authors demonstrate that components of the RNA interference (RISC) pathway in *Drosophila* regulate the transport of α -CaMKII mRNA to synapses.
35. Schratt GM, Tuebing F, Nigh EA, Kane CG, Sabatini ME, Kiebler M, Greenberg ME: **A brain-specific microRNA regulates dendritic spine development.** *Nature* 2006, **439**:283-289.
- In this study, the authors identify the first specific microRNA that regulates synapse function and one of its target mRNAs. This brain-specific microRNA, named miR-134, is localized to the synapses of rat hippocampal neurons and negatively regulates the translation of an mRNA encoding a protein kinase, Limk1, that controls spine development. miR-134 dependent inhibition in turn negatively regulates the size of dendritic spines, in this way contributing to synaptic development, maturation and/or plasticity.
36. Pillai RS, Bhattacharyya SN, Artus CG, Zoller T, Cougot N, Basyuk E, Bertrand E, Filipowicz W: **Inhibition of translational initiation by Let-7 MicroRNA in human cells.** *Science* 2005, **309**:1573-1576.
- See annotation to Humphreys *et al.* [37*].
37. Humphreys DT, Westman BJ, Martin DI, Preiss T: **MicroRNAs control translation initiation by inhibiting eukaryotic initiation factor 4E/cap and poly(A) tail function.** *Proc Natl Acad Sci USA* 2005, **102**:16961-16966.
- This study and that by Pillai *et al.* [36*] demonstrate that miRNAs in mammalian cells inhibit m⁷G-cap-dependent initiation, that is, the very first of the translational pre-initiation stages.
38. Sen GL, Blau HM: **Argonaute 2/RISC resides in sites of mammalian mRNA decay known as cytoplasmic bodies.** *Nat Cell Biol* 2005, **7**:633-636.
 39. Liu J, Rivas FV, Wohlschlegel J, Yates JR III, Parker R, Hannon GJ: **A role for the P-body component GW182 in microRNA function.** *Nat Cell Biol* 2005, **7**:1161-1166.

40. Liu J, Valencia-Sanchez MA, Hannon GJ, Parker R: **MicroRNA-dependent localization of targeted mRNAs to mammalian P-bodies.** *Nat Cell Biol* 2005, **7**:719-723.
41. Rehwinkel J, Behm-Ansmant I, Gatfield D, Izaurralde E: **A crucial role for GW182 and the DCP1:DCP2 decapping complex in miRNA-mediated gene silencing.** *RNA* 2005, **11**:1640-1647.
42. Collier J, Parker R: **General translational repression by activators of mRNA decapping.** *Cell* 2005, **122**:875-886.
Here, the authors show that mRNAs in the P bodies are silenced at the translational initiation level and that P body formation competes with polysomes.
43. Zalfa F, Adinolfi S, Napoli I, Kühn-Hölsken E, Urlaub H, Achsel T, Pastore A, Bagni C: **Fragile X mental retardation protein (FMRP) binds specifically to the brain cytoplasmic RNAs BC1/BC200 via a novel RNA-binding motif.** *J Biol Chem* 2005, **280**:33403-33410.
Here, the authors mapped the interacting domains of the FMRP-BC complex using independent methods. This study further underlined the specificity of this interaction and characterized a novel RNA binding domain in FMRP.
44. Wang H, Iacoangeli A, Lin D, Williams K, Denman RB, Hellen CU, Tiedge H: **Dendritic BC1 RNA in translational control mechanisms.** *J Cell Biol* 2005, **171**:811-821.
45. Gabus C, Mazroui R, Tremblay S, Khandjian EW, Darlix JL: **The fragile X mental retardation protein has nucleic acid chaperone properties.** *Nucleic Acids Res* 2004, **32**:2129-2137.
Analyzing the annealing and strand exchange activities of DNA oligonucleotides by FMRP, the authors show that this protein possesses all the properties of a potent nucleic acid chaperone. They show that FMRP is able to bind to BC1 and BC200 RNAs, suggesting that FMRP might regulate translation by acting directly on RNA-RNA interactions, helping and/or stabilizing these interactions and thus taking effect on the structural status of targeted mRNAs.
46. Johnson EM, Kinoshita Y, Weinreb DB, Wortman MJ, Simon R, Khalili K, Winckler B, Gordon J: **Role of Pur α in targeting mRNA to sites of translation in hippocampal neuronal dendrites.** *J Neurosci Res* 2006, **83**:929-943.
47. Wang H, Iacoangeli A, Popp S, Muslimov IA, Imataka H, Sonenberg N, Lomakin IB, Tiedge H: **Dendritic BC1 RNA: functional role in regulation of translation initiation.** *J Neurosci* 2002, **22**:10232-10241.
48. Doench JG, Sharp PA: **Specificity of microRNA target selection in translational repression.** *Genes Dev* 2004, **18**:504-511.
49. Wilhelm JE, Smibert CA: **Mechanisms of translational regulation in drosophila.** *Biol Cell* 2005, **97**:235-252.
50. Mazroui R, Huot ME, Tremblay S, Filion C, Labelle Y, Khandjian EW: **Trapping of messenger RNA by fragile X mental retardation protein into cytoplasmic granules induces translation repression.** *Hum Mol Genet* 2002, **11**:3007-3017.
51. Kimball SR, Horetsky RL, Ron D, Jefferson LS, Harding HP: **Mammalian stress granules represent sites of accumulation of stalled translation initiation complexes.** *Am J Physiol Cell Physiol* 2003, **284**:C273-C284.
52. Darnell JC, Fraser CE, Mostovetsky O, Stefani G, Jones TA, Eddy SR, Darnell RB: **Kissing complex RNAs mediate interaction between the Fragile-X mental retardation protein KH2 domain and brain polyribosomes.** *Genes Dev* 2005, **19**:903-918.
53. Zarnescu DC, Shan G, Warren ST, Jin P: **Come FLY with us: toward understanding fragile X syndrome.** *Genes Brain Behav* 2005, **4**:385-392.
54. Broadie K, Pan L: **Translational complexity of the fragile x mental retardation protein: insights from the fly.** *Mol Cell* 2005, **17**:757-759.
55. Steward O, Schuman EM: **Compartmentalized synthesis and degradation of proteins in neurons.** *Neuron* 2003, **40**:347-359.
56. Zhang YQ, Bailey AM, Matthies HJ, Renden RB, Smith MA, Speese SD, Rubin GM, Broadie K: **Drosophila fragile X-related gene regulates the MAP1B homolog Futsch to control synaptic structure and function.** *Cell* 2001, **107**:591-603.
57. Lu R, Wang H, Liang Z, Ku L, O'Donnell WT, Li W, Warren ST, Feng Y: **The fragile X protein controls microtubule-associated protein 1B translation and microtubule stability in brain neuron development.** *Proc Natl Acad Sci USA* 2004, **101**:15201-15206.
58. Lee A, Li W, Xu K, Bogert BA, Su K, Gao FB: **Control of dendritic development by the drosophila fragile X-related gene involves the small GTPase Rac1.** *Development* 2003, **130**:5543-5552.
59. Hou L, Antion MD, Spencer CM, Paylor R, Klann E: **Altered mGluR-LTD in the Fmr1 knock-out and FMR1 YAC mouse models of fragile X mental retardation. [abstract].** *Soc Neurosci Abs* 2005:382.10.
60. Ostroff LE, Fiala JC, Allwardt B, Harris KM: **Polyribosomes redistribute from dendritic shafts into spines with enlarged synapses during LTP in developing rat hippocampal slices.** *Neuron* 2002, **35**:535-545.
61. Weiler IJ, Irwin SA, Klintsova AY, Spencer CM, Brazelton AD, Miyashiro K, Comery TA, Patel B, Eberwine J, Greenough WT: **Fragile X mental retardation protein is translated near synapses in response to neurotransmitter activation.** *Proc Natl Acad Sci USA* 1997, **94**:5395-5400.
62. Pinkstaff JK, Chappell SA, Mauro VP, Edelman GM, Krushel LA: **Internal initiation of translation of five dendritically localized neuronal mRNAs.** *Proc Natl Acad Sci USA* 2001, **98**:2770-2775.
63. Tang SJ, Reis G, Kang H, Gingras AC, Sonenberg N, Schuman EM: **A rapamycin-sensitive signaling pathway contributes to long-term synaptic plasticity in the hippocampus.** *Proc Natl Acad Sci USA* 2002, **99**:467-472.
64. Wu L, Wells D, Tay J, Mendis D, Abbott MA, Barnitt A, Quinlan E, Heynen A, Fallon JR, Richter JD: **CPEB-mediated cytoplasmic polyadenylation and the regulation of experience-dependent translation of alpha-CaMKII mRNA at synapses.** *Neuron* 1998, **21**:1129-1139.
65. Wells DG, Dong X, Quinlan EM, Huang YS, Bear MF, Richter JD, Fallon JR: **A role for the cytoplasmic polyadenylation element in NMDA receptor-regulated mRNA translation in neurons.** *J Neurosci* 2001, **21**:9541-9548.
66. Aakalu G, Smith WB, Nguyen N, Jiang C, Schuman EM: **Dynamic visualization of local protein synthesis in hippocampal neurons.** *Neuron* 2001, **30**:489-502.
67. Goetze B, Grunewald B, Kiebler MA, Macchi P: **Coupling the iron-responsive element to GFP -an inducible system to study translation in a single living cell.** *Sci STKE* 2003, **2003**:PL12.
68. Hübener M, Bonhoeffer T: **Visual cortex: two-photon excitement.** *Curr Biol* 2005, **15**:R205-R208.