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The fragile X syndrome: exploring its molecular basis and seeking a treatment

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Fragile X syndrome (FXS) – the leading cause of inherited mental retardation – is an X-linked disease caused by loss of expression of the *FMR1* (fragile X mental retardation 1) gene. In addition to impairment of higher-cognitive functions, FXS patients show a variety of physical and other mental abnormalities. FMRP, the protein encoded by the *FMR1* gene, is thought to play a key role in translation, trafficking and targeting of mRNA in neurons. To better understand FMRP's functions, the protein partners and mRNA targets that interact with FMRP have been sought. These and functional studies have revealed links with processes such as cytoskeleton remodelling via the RhoGTPase pathway and mRNA processing via the RNA interference pathway. In this review, we focus on recent insights into the function of FMRP and speculate on how the absence of FMRP might cause the clinical phenotypes seen in FXS patients. Finally, we explore potential therapies for FXS.

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As early as 1943, Martin and Bell described a large pedigree of a sex-linked form of mental retardation (Ref. 1); much later, in 1969, with the advent of cytological studies, Lubs reported a peculiar constriction at the end of the long arm of the X chromosome in metaphase spreads from cultured cells obtained from patients with X-linked mental retardation (Ref. 2). This constriction at Xq27.3 turned out to be one of the chromosomal fragile sites that can be induced when cells are cultured in medium deficient in folic acid or thymidine, as described by Sutherland in 1977 (Ref. 3). Subsequently, this fragile X signature was confirmed through studies of families with X-linked mental retardation (Ref. 4).

The phenotypic hallmarks of fragile X syndrome (FXS) have been progressively defined. In addition to impaired higher-cognitive functions, various physical features are now recognised in males, including: large testicles (macro-orchidism); distinct craniofacial anomalies such as a long face, large and prominent jaws, elongated and everted ears, and a close interoccular distance; flat feet; and sometimes hyperextensible finger joints, hand calluses and strabismus. Cognitive deficits appear initially mild to moderate but older males seem more severely affected; indeed, a progressive decline of IQ in many affected boys has been observed (Ref. 5). In addition to mental retardation, speech and language skills are severely affected in males with FXS, who often exhibit autistic-like behaviour including poor eye contact, perseverative speech and behaviour, tactile defensiveness, shyness, social anxiety, and hand flapping and biting (Ref. 5).

FXS is the leading cause of inherited mental retardation, affecting approximately 1/7000 females and 1/4000 males worldwide. (Random inactivation of one of the two X chromosomes in females during embryonic development halves the chance of expression of the mutated allele.) The incidence of FXS is 10–20 times higher than other X-linked mental retardations, which affect 1/100 000 – 1/30 000 individuals, while the high incidences of other X-linked disorders such as Duchenne muscular dystrophy or Rett syndrome are accounted for by the presence of mutation hotspots and/or a very large gene mutation target size (Ref. 6).

The fragile site at Xq27.3 is due to a CGG triplet expansion of more than 200 repeats located within the 5' untranslated region of the *FMR1* (fragile X mental retardation 1) gene, and the concomitant hypermethylation of the CpG island in the promoter region of the gene, causing the silencing of *FMR1* (Refs 7, 8). In normal individuals the number of CGG triplets in the *FMR1* gene varies from 6 to 54, while alleles with 55 to 200 repeats are considered 'premutated' genes. The premutation is unstable during oogenesis, generating expansion, but is stable during spermatogenesis, meaning that the full mutation can be inherited only from the mother (Ref. 9). Individuals carrying the premutation have normal IQ but can be affected by fragile X tremor ataxia syndrome (FXTAS). Key clinical features of this late-onset syndrome are gait ataxia or intention tremor usually associated with Parkinsonism, peripheral neuropathy and autonomic dysfunction (Ref. 10). At the molecular level, FXTAS is characterised by the presence of nuclear inclusions in neurons, probably arising from an accumulation of the repeat-containing *FMR1* mRNA and its associated proteins, particularly those binding to the CGG expansion. Indeed, it has been shown that the amount of *FMR1* mRNA is increased in lymphocytes and in the brain of premutated individuals, while FMRP levels are reduced (Ref. 11). The FXTAS phenotype is more evident in men than in women. Conversely, around 20% of premutated women can suffer from premature ovarian failure (POF), and a large proportion of premutated females without POF have elevated gonadotropin levels (Ref. 12). More recently, it has also been speculated that *FMR1* premutation can be the molecular basis of some cases of autism, since young patients carrying premutations can show autistic features (Ref. 13).

A gene-family portait

The *FMR1* gene belongs to a small gene family that also includes the *FXR1* and *FXR2* (fragile-X-related 1 and 2) genes (reviewed in Refs 14, 15). Human *FMR1* is located on chromosome X at q27.3 (Ref. 3), whereas *FXR1* and *FXR2* are autosomal genes mapping at 3q28 and 17p13.1, respectively (Ref. 16). Inactivation of *FMR1* gene expression is the cause of the FXS in humans, but, so far, neither *FXR1* nor *FXR2* has been associated with any known pathology or defect. The corresponding proteins are structurally very similar and share a high degree of sequence homology in clustered regions (Fig. 1). They contain two KH domains and an RGG box that are characteristic motifs in RNA-binding proteins,

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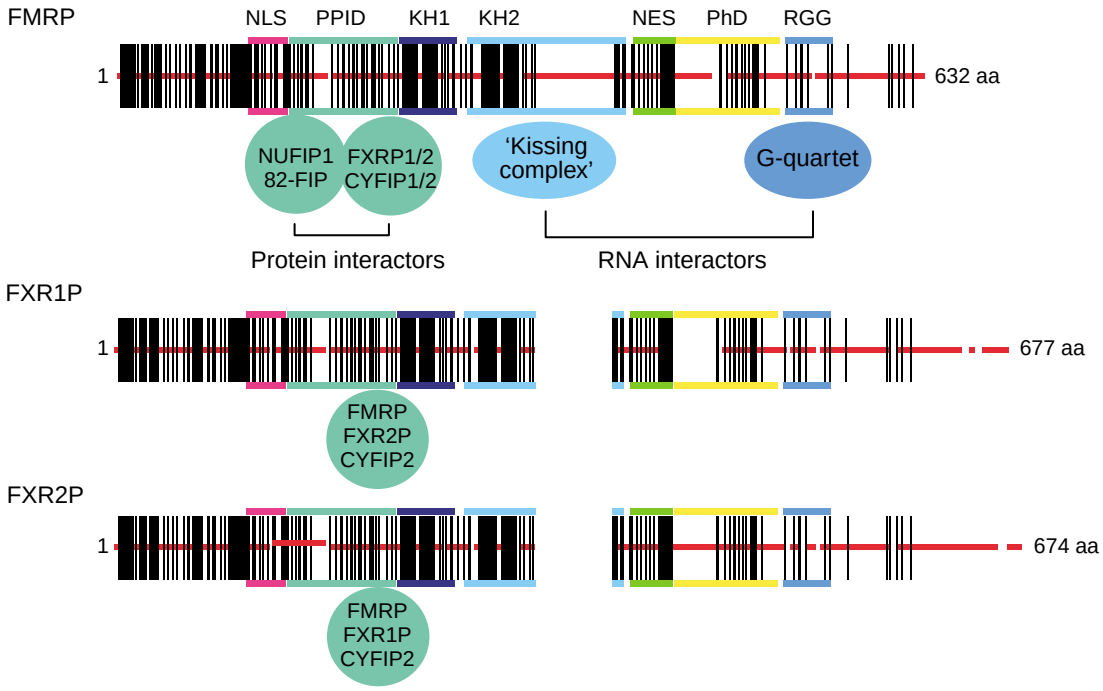

Structural comparison of members of the human fragile X protein family, and their known interactors

Figure 1. Structural comparison of members of the human fragile X protein family, and their known interactors. FMRP, the protein encoded by the fragile X mental retardation 1 gene, is the archetype of this small RNA-binding protein family; the related proteins FXR1P and FXR2P are encoded by the fragile-X-related genes 1 and 2, respectively. Vertical black bars indicate identical amino acids in the three proteins; horizontal red lines show divergent amino acid regions in FXR1P and FXR2P as compared with FMRP. The KH boxes and the RGG domain, which are motifs found in most RNA-binding proteins, as well as the nuclear localisation and export signals (NLS and NES), are conserved in the three proteins. (The KH domain was originally identified in the protein K associated with a heterogeneous nuclear RNP, hence KH for 'K Homologous', whereas the RGG box is a common domain rich in arginine (R) and glycine (G) residues that confer a positive charge with high affinity for negatively charged RNA molecules.) The phosphorylation domain (PhD) contains several serine amino acids that can be phosphorylated, and this post-translational modification can modulate the properties of the protein. Proteins that directly interact with FMRP (and its related proteins) (Ref. 15) are shown in green circles below the protein–protein interaction domain (PPID), whereas the recently documented 'RNA-kissing complex' (Ref. 76) and the G-quartet RNA structure (Refs 42, 43) that bind to FMRP are shown in blue. The RNA-kissing complex refers to a specific motif that presents a loop–loop pseudoknot, whereas the G-quartet is a secondary structure within an mRNA in which four guanines form hydrogen bonds in a symmetrical square planar layer; thus FMRP might recognise RNA structures rather than purely a sequence. Abbreviations: aa, amino acids; CYFIP1/2, cytoplasmic FMRP-interacting protein 1/2; 82-FIP, 82 kDa FMRP-interacting protein; NUFIP1, nuclear FMRP-interacting protein 1.

as well as nuclear localisation and export signals (NLSs and NESs, respectively) (Refs 14, 15, 16, 17, 18).

FMR1, *FXR1* and *FXR2* genes are highly conserved in evolution: orthologues are present in vertebrates, and *Drosophila* has a single related gene, *dfmr1* (Refs 19, 20). A related gene has even been found in the marine hydroid *Hydractinia echinata*, a member of the most ancient metazoan phylum Cnidaria (Ref. 21). In *Hydractinia*, hyFMR1 is expressed in neurons and neuronal precursors. Since the Cnidarians represent the

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most primitive living metazoans possessing a nervous system, this evolutionary conservation of one member of the *FXR* family raises the fascinating possibility that the FXR proteins have been conserved in evolution to accomplish ancestral functions related to the nervous system.

The proteins FMRP, FXR1P and FXR2P are expressed in a wide range of tissues in vertebrates (Ref. 22), albeit at different levels, and the highest levels of FMRP are found in brain and testis (Refs 23, 24), the two organs mainly affected in FXS. Interestingly, FMRP and FXR2P have not been detected in striated muscle although high levels of specific isoforms of FXR1P are present (Ref. 25). Like FMRP, FXR1P and FXR2P are mostly localised in the cytoplasm. However, because of their differential distribution in various tissues and cells, it is thought that the three related FMRP proteins, although structurally very similar, might have tissue-specific functions (Refs 26, 27) probably as a result of differential interactions with specific protein partners (Ref. 28). Whether FXR1P and FXR2P compensate, at least partially, for the absence of FMRP in fragile X cells remains an open question.

In search of FMRP functions

Cellular localisation of FMRP

In all cells grown in culture and in the majority of cells in human and animal tissues, except muscle, FMRP is detected in the cytoplasm, albeit at different levels. In neuronal cells, in addition to being present in the cell body, a small percentage is detected in synapses (Refs 29, 30) and also in association with trafficking granules present in neuronal processes such as neurites and dendrites (Refs 31, 32).

FMRP is associated with the translation machinery

The finding that FMRP is present in poly(A)$^+$ ribonucleoprotein complexes associated with the translation machinery (Refs 17, 33, 34, 35) has been critical in the understanding of its function. In all cell types so far studied, the majority of FMRP was detected in heavy sedimenting polyribosomes to which newly synthesised growing polypeptides chains are associated. Because of this specific cellular localisation, it has been inferred that FMRP plays a role in translation; however, little is known about its precise function(s) in translation control (see next section).

Although FMRP is particularly abundant in the brain as a result of its high expression in neurons (Refs 22, 23, 24), biochemical evidence for the presence of FMRP on brain polyribosomes was obtained only recently. Three independent studies have shown that FMRP is associated with polyribosomes prepared either from the cerebral cortex or from total brain using different extraction conditions (Refs 36, 37, 38, 39). To our knowledge, only a single report has claimed that FMRP is absent from polyribosomal mRNPs as it was reported to cosediment with small complexes (Ref. 40), and this result could not be reproduced by others (Refs 37, 38, 39).

FMRP RNA targets

The search for RNAs that bind to FMRP (FMRP RNA targets) has been performed in different laboratories and has resulted in the identification of a large number of mRNAs that direct the synthesis of different proteins with a variety of functions. Several in vitro approaches have been used to select brain mRNAs that have the highest affinity for FMRP. In general, two classes of brain mRNAs – containing either a G-quartet structure (Refs 41, 42, 43) or U-rich sequences (Refs 44, 45) – have been identified. However, although these targets bind with high affinity to naked FMRP, this binding likely does not reflect the situation in vivo. Miyashiro and colleagues (Ref. 46) have developed a new approach, called antibody-positioned RNA amplification (APRA), which aims to amplify RNA associated with FMRP by the use of primers coupled to anti-FMRP antibody. Using this approach, they identified some 80 new mRNAs, of which approximately 60% were directly associated with FMRP. They further showed that in the brain of the *Fmr1* knockout (KO) mouse, some of these mRNAs, as well as the corresponding proteins, display subtle changes both in location and abundance, pointing to a critical role for FMRP in targeting neurospecific mRNAs to be transported and translated at the synapse (Ref. 46).

Protein interactors

Comprehension of FMRP physiopathology also requires identification of FMRP-interacting proteins that, among other effects, might modulate its affinity towards its RNA targets (Ref. 15). FMRP can interact with a range of proteins either directly or indirectly (Table 1). Most of these interactors have been shown to be RNA-binding

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Table 1. FMRP protein partners in mammalian cells[a]

Interactors	Main cell localisation	RNA-binding?	Role	Ref.
Detected by yeast two-hybrid selection				
FXR1P	Cytoplasm	+	Translation regulation?	101
FXR2P	Cytoplasm	+	Translation regulation?	16
82-FIP	Cell-cycle-dependent localisation: cytoplasmic/nuclear	+	mRNA transport?	48
NUFIP	Nucleus and neuronal somatodendritic granules	+	Links transcription to mRNA export?	102
CYFIP1, CYFIP2	Cytoplasm	–	Cytoskeleton remodelling through Rho/Rac GTPase pathway	53
Ran-BPM	Nucleocytoplasmic	–	Nuclear trafficking, cell migration, regulation of transcriptional activity of steroid receptors	51
MSP58	Nucleocytoplasmic	+	Nucleolar transcription factor? RNP biogenesis? Translation regulation?	49
Detected by co-immunoprecipitation				
C23/Nucleolin	Nucleolus and cytoplasm	+	Chromatin structure, ribosome biogenesis (DNA transcription, rRNA maturation, ribosome assembly) and nucleocytoplasmic shuttling	103
YB-1/p50	Cytoplasm	+	Transcription factor, storage of repressed localised mRNAs in germ cells, translation regulator	104
mStaufen	Cytoplasm	+	Delivery of RNA to dendrites, transport of neuronal RNA granules, storage of repressed localised mRNAs in germ cells	50
Pur-α	Predominantly nuclear but also present in the somatodendritic compartment of neurons	+	DNA replication, gene transcription, dendritic mRNA transport and translation	50
Myosin Va	Neuronal somatodendritic compartment	–	Actin-based processive motor protein; transport of synaptic vesicles; regulation of vesicle exocytosis	50

[a] Direct interaction between FMRP and specific proteins has been documented using the power of the yeast two-hybrid selection method; other approaches such as co-immunoprecipitation allow detection of proteins that are associated with the ribonucleoprotein complexes but not a priori in direct contact with FMRP. Immunoprecipitation is a powerful tool to study proteins that are complexed to the targeted protein, and associated proteins are interpreted as reflecting the in vivo interactions. However, it has been shown that RNA-binding proteins might possibly re-associate with other components after cell lysis as a result of interaction of molecules in the cell extract, and so interactions identified by immunoprecipitation might not reflect the bone fide in vivo state of complexes (Ref. 105).
Abbreviations: CYFIP1/CYFIP2, cytoplasmic FMRP-interacting protein 1/2; 82-FIP, 82 kDa FMRP-interacting protein; FXR1P/FXR2P, proteins encoded by fragile-X-related genes 1 and 2; MSP58, microspherule protein 58; NUFIP1, nuclear FMRP-interacting protein 1.

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proteins, like FMRP itself. Direct interactions with FXR1P, FXR2P, NUFIP1 (nuclear FMRP-interacting protein 1), 82-FIP (82 kDa FMRP-interacting protein) and microspheruleprotein 58 (MSP58) have been described (Refs 15, 47, 48, 49). These proteins might modulate the affinity of FMRP for different classes of mRNAs by inducing structural changes in conformation, thus exposing the RNA-binding domains differentially. In addition, other RNA-binding proteins such as nucleolin, YB-1/p50, Pur-α and Staufen have been detected in complex structures containing FMRP, but it is not known whether they interact directly or indirectly with FMRP (Ref. 48). Only a few non-RNA-binding proteins have been shown to interact with FMRP, including: the actin-based motor protein myosin Va (Ref. 50); Ran-BPM (Ref. 51) and Lgl (Ref. 52), which are cytoskeleton-associated proteins; and CYFIP1 and CYFIP2, which link FMRP to the RhoGTPase pathway (Ref. 53) (see below).

FMRP function(s) in translation

Several experimental approaches have shown that when levels of FMRP are artificially increased, either in the rabbit reticulocyte lysate for synthesis of protein in vitro or in cell culture after transfection assays, translation repression occurs (Refs 54, 55, 56). However, FMRP might have multiple roles in translation control since, when absent, the polyribosomal distribution of many brain mRNAs is altered: some are increased and some are decreased in the heavy fractions corresponding to actively translating polyribosomes prepared from brains of *Fmr1* KO mice (Ref. 57) as well as from lymphoblastoid cells derived from FXS patients (Ref. 41). How might translation repression be achieved at the molecular level and how can such a function of FMRP be compatible with its predominant presence in the so-called actively translating polyribosomes?

FMRP as a nucleic acid chaperone

The demonstration that FMRP behaves as a nucleic acid chaperone has shed new light on a potent mechanism by which FMRP could exert its repressing activity (Ref. 58). Nucleic acid chaperones bind in a cooperative manner to one or several nucleic acid molecules to favour the most stable conformation, while at the same time preventing folding traps that might preclude function of the target nucleic acid. Once the most stable nucleic acid structure is reached, the continuous binding of the chaperone is no longer required to maintain the structure (Refs 59, 60). Classical approaches for characterising the chaperoning activities of various proteins were used to show that FMRP behaves as a nucleic acid chaperone (Ref. 58). First, FMRP promotes the hybridisation of cDNAs under low ionic strength conditions; second, FMRP directs the formation of a stable nucleic acid duplex structure by achieving strand exchange; third, FMRP enhances ribozyme-directed RNA substrate cleavage, a classical test used to characterise chaperones. Thus, FMRP possesses all the properties of a chaperone protein, with nucleic acid remodelling abilities. The chaperone activity of FMRP requires the presence of the protein–protein interaction domain as well as both KH motifs. These domains are also required for FMRP to be recruited into polyribosomal mRNPs in vivo, suggesting that binding to its cellular partners and KH integrity are necessary to achieve its chaperone activities (Ref. 61).

A model for FMRP function(s) related to its steady-state cellular levels has been proposed (Ref. 62). Based on its chaperone activities, we can envisage that the binding of one or a few FMRP molecules 'opens' the mRNA structure, favouring the initiation stage for protein translation; however, further binding of FMRP at a higher FMRP:mRNA ratio might 'close' the structure, hiding it from the translation apparatus. Thus, FMRP might regulate translation by acting on the structural status of mRNA, and the mRNA transition from a translatable to an untranslatable form would be due to an increase of bound FMRP molecules, inducing a densely packed structure of the mRNP complex (Fig. 2). In this way, FMRP would affect mRNA translation in a similar fashion to the manner by which histone-mediated chromatin condensation affects genomic DNA transcription.

Other possible mechanisms of translation repression

Another regulatory process that may be relevant to the function of FMRP is the RNA interference pathway (RNAi), which regulates the cleavage, degradation, and translation inhibition of mRNA. RNAi is triggered when a double-stranded RNA belonging to a novel class of untranslated small RNAs called microRNAs (miRNAs) is cleaved into small interfering RNAs (siRNAs) that are incorporated into the RNA-induced silencing

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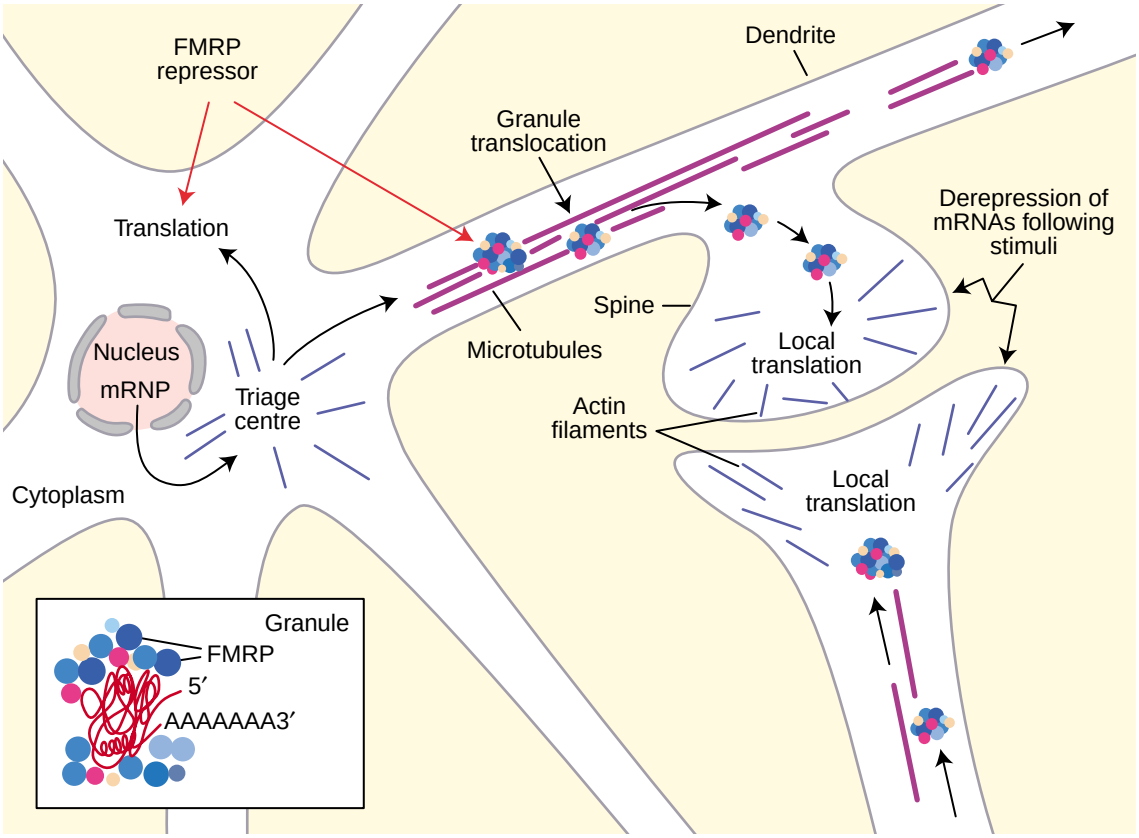
complex (RISC). The RISC uses siRNAs as guides to select mRNA substrates by complementary base-pairing, and drives their selective degradation or translation inhibition (for a review see Ref. 63). Interestingly, miRNAs are found on polyribosomes together with their cognate target mRNAs (Ref. 64). *Lin-4* is a prototypical miRNA that has been well characterised in *Caenorhabditis elegans*. Its target mRNAs (*lin-14* and *lin-28*) are translationally repressed but remain associated with polyribosomes, suggesting that translational inhibition occurs after translation initiation (Refs 65, 66).

In mammalian neurons, many miRNAs copurify with polyribosomes (Ref. 64). Moreover, Hammond's and Siomi's groups have independently reported that, in mammals and *Drosophila*, FMRP is associated with components of the RISC (Refs 67, 68), and Jin and colleagues therefore proposed that FMRP might regulate neuronal translation via miRNAs (Ref. 69). FMRP



Proposed model for mRNA repression and transport in neurons

Figure 2. Proposed model for mRNA repression and transport in neurons. FMRP, the protein encoded by the fragile X mental retardation 1 gene, enters the nucleus and interacts with the pre-messenger ribonucleoprotein (pre-mRNP) complexes to escort them to the cytoplasm. In neurons decorated with long extensions, once the mRNP complexes reach the cytoplasm, they are directed to a 'triage centre' where decisions are taken to send the mRNAs either to the translation apparatus to be decoded, or to translocate these mRNAs to distant locations. High levels of FMRP, as detected in neurons, in concert with other RNA-binding proteins such as FXR1P and FXR2P (encoded by the fragile-X-related genes 1 and 2), as well as other factors, might be necessary to saturate the mRNA and to repress its activity. The resulting granules are then sent along the dendrites, by 'sliding' on microtubule structures, to be delivered to the spines, where the repressed mRNA is reactivated under the right stimuli, in order to be locally translated. Note the high density of actin filaments (cytoskeleton) in the spine.

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could form a miRNP complex on its target mRNA on polyribosomes to allow a rapid and reversible translational control of certain mRNAs. Recent work has shown that the functional RISC complex is composed of Dicer, TRPB, Ago2 and pre-miRNA (Ref. 70), suggesting that FMRP may not be essential for RISC function; nevertheless, it is possible that FMRP participates in the driving of an RNA to the RISC processing apparatus, and interacts temporarily with the complex. Additional analyses will be necessary to understand the consequences of the absence of FMRP for the RISC machinery, and whether it is a necessary partner similar to GW 182, whose absence disrupts the cytoplasmic foci containing RISC (Ref. 71).

In the context of negative regulation of translation, it has been reported that BC1, a small non-translated RNA (Ref. 72), binds to FMRP to repress mRNA translation (Ref. 73). However, this interaction appears controversial (Refs 74, 75), and further discussions are beyond the scope of this review. Interestingly, FMRP can be removed from polyribosomes by RNA aptamers (synthetic oligonucleotides) presenting a loop–loop pseudoknot specific motif or 'kissing complex', whereas other proteins are not (Ref. 76). However, it is not known whether the kissing complex is relevant to understanding the role of FMRP in translation. It will also be interesting to search for proteins that are able to bind specific motifs to drive FMRP out of the polyribosome structures.

Precedents for repression on polyribosomes

Recent studies support the notion that mRNAs can be repressed on polyribosomes. In *Drosophila melanogaster* oocytes, *nanos* mRNA is found on polyribosomes but is translationally repressed at the level of elongation by the homologue of the β-subunit of nascent polypeptide-associated complex encoded by the *bicaudal* gene (Refs 77, 78). In yeast, the mRNA of the transcription factor Hac1p, which controls the unfolded-protein response, is stably associated with polyribosomes but still is not translated, suggesting that the ribosomes engaged on the mRNA are stalled. This polyribosomal pool of *HAC1* mRNA is a substrate for splicing. The presence of a non-excised intron apparently leads to polyribosomes stalling by complementary base-pairing with the 3' UTR of the mRNA (Ref. 79).

FMRP function in neurons: synaptic architecture and plasticity

Dendritic spines constitute the post-synaptic compartment of most excitatory synapses in mammalian brain. During normal development, maturation of dendritic spines leads to a shrinking and consolidation of dendritic spines bearing functional synapses and a progressive elimination of inactive or supernumerary synapses. Absence of FMRP in cortical neurons of FXS patients and of the *Fmr1* null mouse model correlates with a high density of immature dendritic spines (Refs 80, 81), which are longer and thinner than normal.

Following these observations, it has been proposed that in the absence of FMRP, a defect in the morphological development and maturation of dendritic spines, coupled with a failure in normal elimination of supernumerary dendritic spines, results in abnormal brain circuitry development, ultimately leading to mental retardation. Impaired higher-cognitive functions as observed in FXS patients and *Fmr1* null mice might thus result from altered synaptic plasticity. FMRP might be required for synaptic development and plasticity at two interconnected levels: first, biochemical modifications at synapses involving local de novo protein synthesis; and second, as a consequence, morphological modifications at synapses involving local actin-cytoskeleton remodelling. But what is the precise role of FMRP in neuronal maturation and development? And how can we explain the morphological defects observed macroscopically at the molecular level?

Regulation of synaptic protein synthesis

Soon after the observation that FMRP was associated with heavy sedimenting polyribosomes (Ref. 33), Weiler and colleagues (Ref. 30) reported that *Fmr1* mRNA was present in isolated synaptosomes purified from rat brain, and that this mRNA was rapidly taken up into polyribosomes and translated in response to stimulation by agonists for phosphoinositide-coupled group I metabotropic glutamate receptors (mGluRs). FMRP may normally counter mGluR-stimulated translation-dependent long-term depression and elongation of dendritic spines (see below). Thus, in fragile X, exaggerated mGluR-dependent translation may result in synaptic changes that are proximal causes of cognitive impairment (Ref. 82). Based on these observations, the mGluR5-specific antagonist MPEP [2-methyl-6-(phenylethynyl)pyridine] has

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been proposed as a pharmacological treatment for fragile X syndrome (see below).

Absence of FMRP can alter protein synthesis of key proteins essential for synaptic development. For example, FMRP is required for mGluR1-dependent translation of PSD-95, a scaffolding protein involved in synaptic plasticity (Ref. 83). Whether FMRP regulates directly the PSD-95 mRNA or is an upstream controlling factor is not yet known. FMRP also represses the translation of microtubule-associated protein 1B (MAP1B) mRNA and is required for the accelerated decline of MAP1B mRNA during active synaptogenesis in neonatal brain development. In the absence of FMRP, elevated MAP1B protein expression leads to abnormally increased microtubule stability, thereby hindering the normal development of dendritic spines (Ref. 84).

FMRP also controls the levels of phosphatase 2A (PP2A) by modulating expression of its catalytic subunit (PP2Ac). FMRP appears to be a negative regulator of *PP2Ac* mRNA translation, by binding with high affinity to the 5'-UTR of the *PP2β* mRNA, which has four G-quartet structures (Ref. 85). Interestingly, PP2A dephosphorylates ADF/Cofilin, a major effector of the Rac1 signalling pathway (Refs 28, 85) whose activity is modulated by its level of phosphorylation (Ref. 85). Indeed, fibroblasts lacking FMRP display altered levels of PP2Ac and of P-Cofilin (phosphorylated Cofilin). As a direct consequence of this deregulation of the Rac pathway, actin-rich structures are directly altered in *Fmr1* null fibroblasts. These findings have suggested that the same deregulation may be the molecular cause of dendritic spine abnormalities observed in FXS patients (Ref. 85). Moreover, it has been observed that inhibition of the activity of PP2A results in activation of mGluR5. Indeed, mGluR5 and PP2A are able to interact, and their interaction might be increased by MPEP (Ref. 86), a drug that helps to reduce some phenotypic signs of FXS (see below).

FMRP can control the cytoskeleton locally at the synapse

In neurons, actin is a major component of the cytoskeleton and appears particularly enriched in dendritic spines (Ref. 87). During brain development, maturation of dendritic spines is dependent on a tight regulation of the local actin cytoskeleton. Indeed, newly formed synapses are stabilised whereas inadequately formed or inactive synapses are removed, and regulation of actin polymerisation plays a crucial role in this process. The identification and characterisation of CYFIP1, a cytoplasmic FMRP-interacting protein (Ref. 53), has established another functional link between FMRP and the control of actin cytoskeleton dynamics. Indeed, CYFIP interacts biochemically and genetically with Rac1, a member of the family of the Rho-GTPases that play roles in dynamic reorganisation of the actin cytoskeleton (Ref. 88). The Rho/Rac GTPase pathway remodels the actin cytoskeleton in response to extracellular stimuli and, in neurons, it regulates axon and neurite outgrowth as well as the development, maturation and maintenance of dendritic spines (Ref. 53) and dysfunctions of this pathway are associated with other forms of mental retardation (Ref. 89).

These results point to a role for FMRP in modulation of actin dynamics, at least in fibroblastic cell lines. As exemplified with *PP2Ac* mRNA, whose translation appears to be repressed by FMRP, it can be envisioned that FMRP controls the local translation of several mRNAs encoding proteins not only involved in the control of general actin cytoskeleton dynamics but also with more specific local roles in dendritic spines. Taking into account these findings, in addition to the link with the Rac pathway via CYFIP (Ref. 85), it is tempting to speculate that absence of FMRP leads to aberrant cytoskeleton reorganisation and alters maturation of dendritic spines and synaptic morphology.

mRNA transport

Local de novo protein synthesis at the synapse is thought to be important for neuronal plasticity and relies on pre-existing local mRNAs (Refs 90, 91). These mRNAs have to be sorted and translocated from the neuronal cell body to very distant locations in the form of RNP granules (Ref. 92). FMRP has been shown to be present in these structures, and their movements along neurites have been documented (Refs 31, 32). These structures, containing a reservoir of mRNAs to be delivered at specific loci, are translationally silent during migration and have been described as motile units. Given the proposed role of FMRP as a nucleic acid chaperone, increasing the number of FMRP molecules on a given mRNA would induce mRNA transition from active mRNPs to repressed mRNPs. FMRP could participate, in concert with other RNA-binding

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proteins, in the packing of mRNA cargoes that have to be translocated to distal locations in neurons (Fig. 2).

Therapeutic approaches to cure FXS

Re-introduction of FMRP

One possibility for treating FXS is re-introduction of functional FMRP in the neurons of FXS patients through gene-therapy manipulations. For example, injection into *Fmr1* KO mice of small, diffusible vectors derived from the adeno-associated virus to deliver the *Fmr1* cDNA to the entire brain (by osmotic blood–brain barrier disruption) has been proposed (Ref. 93). An alternative approach (Ref. 94) is based on the Tat domain (derived from a protein expressed by the human immunodeficiency virus), which can deliver macromolecules into cells and cross the blood–brain barrier upon intraperitoneal injection into mice. However, when a Tat–FMRP fusion protein was introduced into cultured fragile X fibroblasts and into primary cultures of neurons derived from the *Fmr1* knock-out mouse, uptake efficiency and levels of FMRP protein, particularly in neurons, were much lower that expected. In addition, the manipulated FMRP protein has been suspected to be toxic (Ref. 94). The adequacy of such 'replacement therapy' therefore remains questionable, since it is expected that FMRP levels will need to be tightly controlled. Indeed, levels higher than physiological might induce improper translation of certain mRNAs, as exemplified with the transgenic overexpression of FMRP in the *Fmr1* KO mouse, which results in severe behavioural anomalies and even harmful effects (Ref. 95). Because of the need for precise expression, and technical difficulties in the re-introduction of FMRP, our opinion is that today's gene therapy approaches might not be the best avenues to cure FXS.

Regulation of mGluR5 function

A different approach, based on pharmacological blockage of the mGluRs, seems more promising. The *Fmr1* null mouse has an exaggerated translation response to mGluR5 in the absence of FMRP (Refs 82, 96). Stimulation of group I mGluRs also results in a translation-dependent elongation of dendritic spines resembling those observed in brains of FXS patients (Refs 80, 81). On the basis of these observations, a pharmacological treatment has been proposed using the mGluR5 antagonist MPEP. Recently Yan et al. (Ref. 96) reported that in fragile X mice this treatment can reduce sensitivity to audiogenic seizures, and result in a subtle improvement in behavioural tests.

Enriched environments: molecular basis?

It has been reported recently that the levels of the AMPA glutamate receptor, which plays a role in synaptic plasticity, are increased in *Fmr1* KO mice maintained in an enriched surrounding environment with stimulating conditions (Ref. 97). These changes seem to correlate with some of the behavioural rescue in the KO mouse phenotype, due perhaps to some partial restoration of neuronal plasticity. Indeed, FMRP expression levels increase in rat brain regions undergoing active synaptogenesis following complex environment exposure (Ref. 98), suggesting a direct role of FMRP in synaptic plasticity. Interestingly, Hessl et al. (Ref. 99) observed previously that environmental factors positively influence the behavioural outcome in children with FXS. One possible explanation for these improvements seen might be that exposure to challenging experiences and learning opportunities alters glial cells such as astrocytes and oligodendrocytes, which participate in neuron plasticity (Ref. 100).

Concluding remarks

The role of FMRP is currently thought to reside in the control of translation. Since neurons contain the highest levels of FMRP, it is conceivable that a threshold level of FMRP is necessary to maintain in a repressed state the neuronal mRNP granules to be transported out of the soma until they reach their destinations in the neurites. To achieve this goal, FMRP cellular levels should be tightly controlled between a balance of positive and repressing activities. The absence of FMRP might then result in incomplete repression of mRNAs which could then be derepressed at wrong addresses and at inappropriate times, leading to alterations in local protein synthesis and local actin cytoskeleton remodelling required for synaptic development and plasticity. One of the detectable consequences is therefore an abnormal spine maturation that ultimately leads to higher-cognitive dysfunctions as seen in FXS patients.

Absence of FMRP has pleiotropic effects during development. While current research has been mainly focused on the understanding of the higher-cognitive functions altered in FXS, little is

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known regarding the consequences of the absence of FMRP on non-neuronal phenotypes of these patients. A role for FMRP in the control of cytoskeletal architecture on which the translation machinery is stowed in cell types other than neurons, at specific stages of development, may explain some of these abnormalities.

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Further reading, resources and contacts

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Fragile X patient support organisations in various countries:

http://www.fragilex.org.au (Australia)
http://www.x-fragile.be (Belgium)
http://www.fragile-x.ca (Canada)
http://www.xfra.org/ (France)
http://www.xfragile.net/ (Italy)
http://www.fragilex.se/ (Sweden)
http://www.fragilex.org (UK)
http://www.fraxa.org and http://www.cfxf.org (USA)

Features associated with this article

Figures

Figure 1. Structural comparison of members of the human fragile X protein family, and their known interactors.

Figure 2. Proposed model for mRNA repression and transport in neurons.

Table

Table 1. FMRP protein partners in mammalian cells.

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