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Meeting at the crossroads: common mechanisms in Fragile X and Down syndrome

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Abstract

Intellectual disability is characterized by significantly impaired cognitive abilities and is due to various etiological factors, including both genetic and non-genetic causes. Two of the most common genetic forms of intellectual disability are Fragile X syndrome (FXS) and Down syndrome (DS). Recent studies have shown that proteins altered in FXS and DS can physically interact and participate in common signaling pathways regulating dendritic spine development and local protein synthesis, thus supporting the notion that spine dysmorphogenesis and abnormal local protein synthesis may be molecular underpinnings of intellectual disability. Here we review the molecular constituents regulating local protein synthesis and spine morphology and their alterations in FXS and DS. We argue that these changes might ultimately affect synaptic homeostasis and alter cognitive performance.

Genetics of FXS and DS

Emerging evidence shows that regulation of local protein synthesis in dendritic spines plays a crucial role in controlling synaptic morphogenesis and synaptic efficacy. Furthermore, aberrant dendritic spine morphology appears to be a consistent feature seen in various neurodegenerative, neuropsychiatric, and neurodevelopmental disorders including Alzheimer's disease (AD) [1–3], Parkinson's disease [4,5], schizophrenia [6–8], Rett syndrome [9,10], FXS [11–13], and DS [14–16]. Although these neurological disorders result from varied genetic mutations or arise sporadically, a common underlying mechanism may be altered regulation of local protein synthesis in dendritic spines that ultimately affects spine morphology and neurotransmission. However, the molecular components involved in regulation of local protein synthesis are not well characterized and how dysregulation of local protein synthesis leads to these neurological disorders, particularly the various forms of cognitive impairment that characterize them, is unclear.

One protein implicated in spine dysmorphogenesis and intellectual disability is Fragile X Mental Retardation Protein (FMRP) [12–14]. The absence of FMRP causes mental impairment and dendritic spine abnormalities in FXS patients [11–13] (Table 1). FXS is the

most frequent cause of intellectual disability due to mutations in a single gene. Individuals with FXS have intellectual disability as well as various abnormal physical features including elongated face, large or protruding ears, large testes (macroorchidism), and behavioral characteristics such as stereotypic movements (e.g., hand-flapping) and social anxiety [14,17]. FXS is associated with increased expansion of the CGG trinucleotide repeats in the 5' untranslated region (UTR) of the fragile X mental retardation 1 (*fmr1*) gene that are hypermethylated, which results in transcriptional repression and absence of FMRP [17]. FMRP has been shown to regulate local protein synthesis in dendritic spines [13,18,19]; however, mechanistic insights into the molecular components important for local protein synthesis in dendritic spines remain limited.

DS, caused by full or partial trisomy of human chromosome 21, is the leading genetic cause of learning disability and the most frequently occurring birth defect in all ethnic groups [20]. DS patients have various clinical features, but the most common abnormalities include intellectual disability, congenital heart disease, craniofacial dysmorphism, hypotonia, and accelerated aging [14,21]. In particular, a large subset of DS patients develop pathological and neurochemical changes of AD by about age 50 years and there is a substantially increased incidence of cataracts at an early age [21,22]. There are also reported changes in dendritic spine morphologies at the neuronal level (Table 1). Chromosome 21 contains over 230 protein-coding genes and 140 pseudogenes [23]; thus, a major challenge in DS is identifying the genes and pathways responsible for the different clinical manifestations of DS. Recent detailed genetic mapping studies examining partial trisomy cases have suggested that multiple loci contribute to different DS phenotypes, thus arguing against a single critical region on chromosome 21 as the disease-causing genetic component and further highlighting the importance of understanding individual and multiple gene functions in studying DS [24].

Efforts to understand the contribution of chromosome 21 genes to intellectual disabilities have yielded several mouse models, including mice trisomic for conserved regions of chromosome 21 and mice with individual gene overexpression (for a review, see [25]). Although the individual gene studies alone cannot fully account for DS, they have generated useful information in identifying candidate genes affecting neuronal functions and spine morphogenesis (Table 2). One of these proteins, DS critical region 1 (DSCR1) (Box 1), has recently been shown to be a novel regulator of FMRP [26]. In light of this new finding, this review focuses on the roles of FMRP and DSCR1 in regulating local protein synthesis and dendritic spine morphologies, discusses how FXS and DS may share disturbances in the same molecular pathway leading to intellectual disabilities, and reviews known functional interactions between other chromosome 21 genes and either FMRP or DSCR1 and their potential contribution to intellectual disability.

Local protein synthesis in dendritic spines: intersection of FMRP and DSCR1

Regulation of local protein synthesis by FMRP

The absence of the mRNA-binding protein FMRP, encoded by the *fmr1* gene, causes intellectual disability in FXS patients [11–13]. In preclinical studies, *fmr1* knockout (KO)

mice exhibit impaired learning, altered synaptic activity, and abnormal spine morphology characterized by a high density of thin and elongated spines [27,28]. FMRP is a RNA-binding protein associated with approximately 4% of brain mRNAs [12]. It contains RNA-binding motifs such as hnRNP-K homology domains (KH domains, KH1 and KH2), the arginine/glycine-rich RNA-binding motif (RGG box), and N-terminal domain of FMRP (NDF) [29–31]. It is known that the RGG box and KH2 domain can bind to a stem–G quartet loop and a sequence-specific element in RNA [32], suggesting that these domains of FMRP play an important role in targeting mRNAs. In addition, mRNA transcripts that coimmunoprecipitated with FMRP revealed that FMRP can bind to the coding region of mRNAs [33]. A recent report also found that FMRP recognizes novel RNA motifs (ACUG/C and U/AGGA) in the coding region and 3' UTR [123]. Nonetheless, the molecular mechanisms regulating FMRP binding to a broad range of mRNA transcripts remain to be clarified.

FMRP is located in the cell body, dendrites, and dendritic spines in neurons and emerging lines of evidence suggest that it is involved in local protein synthesis in dendritic spines [11,12,35–37]. Although its regulatory mechanism is not well understood, studies have begun to reveal mechanisms through which FMRP represses protein synthesis at synapses [35,38]. To achieve spatial and temporal regulation of protein synthesis, it is critical that local mRNA translation be repressed until mRNAs have reached the dendritic spines and specific neuronal stimulations have activated receptors at the spine head. It is believed that FMRP binds to mRNA transcripts and regulates metabotropic glutamate receptor (mGluR)-mediated synaptic translation, allowing for local synthesis of several dendritic proteins at dendritic spines [39–45]. Absence of FMRP is known to increase translation of FMRP-bound transcripts, which implies that FMRP normally acts as a translational repressor. A recent high-throughput proteomic study showed that the expression level of over 100 proteins is altered in synaptosomes isolated from *fmr1* KO neurons [46], implying that FMRP either modulates mRNAs transport to dendritic spines or regulates protein synthesis in dendrites.

Although how FMRP represses mRNA translation remains unclear, several mechanisms have been proposed. There is evidence that most FMRP is located in polyribosomes and FMRP has been suggested to stall mRNA translation through RNA binding at the KH2 RNA-binding motif [47]. Accordingly, a missense mutation (I304N) in the KH2 RNA-binding domain of FMRP has been found in a single FXS patient and a mouse model containing the same mutation has shown phenotypes similar to FXS [48]. These mice displayed altered synaptic plasticity, abnormal behaviors, reduced testicle size, and lack of mutant FMRP association with polyribosomes [48], suggesting that this mutation in the KH2 RNA-binding motif is critical for the pathogenesis seen in FXS. Another mechanism proposed for FMRP-dependent mRNA translation involves miRNA-mediated translational repression. FMRP has no miRNA-binding domain, but interacts with miRNAs via members of the RNA-induced silencing complex (RISC) such as Dicer [49–51]. It has been shown that FMRP–RISC in the mouse brain is associated with several miRNAs such as miR-125b and miR-132 [52]. Furthermore, recent studies found that FMRP regulates translation of postsynaptic density protein 95 (PSD-95) and NMDA receptor subunit 2A (NR2A) mRNA

transcripts through *miR-125* [35,52]. This miRNA-mediated translational regulation of FMRP-targeted mRNAs is dependent on the phosphorylation status of a single serine residue of FMRP. The phosphorylated S499 of FMRP recruits *miR-125* and RISC to the 3' UTR of *PSD-95* mRNA, which forms an inhibitory complex to prevent *PSD-95* mRNA translation [35]. Conversely, dephosphorylation of S499 reverses the process and releases miRNA-125–RISC from the *PSD-95* mRNA, which allows activation of *PSD-95* mRNA translation [35]. However, it is important to note that dephosphorylated FMRP remains bound to *PSD-95* mRNA after miRNA-125–RISC is dissociated from the mRNA transcript. Finally, Napoli *et al.* have suggested that FMRP suppresses translation via inhibition of translational initiation [38]. It has been shown that non-polyribosomal FMRP in synaptosomes can inhibit translation through interaction with the eIF4E-binding protein Cytoplasmic FMRP-Interacting Protein (CYFIP1) [38]. In brain and at synapses, CYFIP1 tethers the mRNAs associated with FMRP on eIF4E, thus inhibiting their translation. On neuronal stimulation, the CYFIP1–FMRP complex is released from eIF4E and bound mRNAs, which allows initiation of translation [38].

Regulation of local protein synthesis by DSCR1 through modulation of FMRP

The *DSCR1* gene, located on chromosome 21, is overexpressed in the brains of DS patients and is posited to contribute to intellectual disability [26,53–55]. Based on its ability to regulate calcineurin (CaN), DSCR1 was first shown to play a role in learning and memory in *Drosophila* [54]. Nebula, the *Drosophila* homolog of DSCR1, has been shown to be essential for normal learning and memory through its regulation of protein kinase A (PKA) and cAMP-response element-binding protein (CREB) activities [54]. Either loss of function or overexpression of *nebulin* resulted in impaired learning [54], suggesting that precise regulation of nebula signaling is necessary for normal brain function. Furthermore, overexpression of *DSCR1* in human trisomy 21 fetal brain tissues is associated with altered CaN-mediated signaling [54]. Together with the aforementioned studies demonstrating that *nebulin* over-expression impairs learning in *Drosophila*, these studies imply that overexpression of *DSCR1* may contribute to intellectual disability in DS. Deficits in learning and memory are also found in *DSCR1* KO and transgenic mice [53,55,56]. Similarly, both *DSCR1* KO and transgenic mice show impaired late-phase long-term potentiation (L-LTP), a process that is dependent on local protein synthesis [53]. Taken together, these results suggest that DSCR1 may play a key role in local protein synthesis.

To test the hypothesis that DSCR1 is involved in regulation of local protein synthesis at dendritic spines, interaction between DSCR1 and FMRP was examined [26]. Using biochemical and fluorescence resonance energy transfer (FRET)-based experiments, it was shown that DSCR1 and FMRP indeed interact in human embryonic kidney (HEK) cells as well as in mouse hippocampal primary neurons [26]. Interestingly, DSCR1 binds to only phosphorylated FMRP [26], suggesting that DSCR1 and phospho-FMRP may form a complex in stalling polyribosomes, which represses mRNA translation. Furthermore, phosphorylated FMRP carries mRNA along dendrites as a component of RNA granules that bind to kinesin protein in neurons [57,58]; thus, it is possible that DSCR1 also plays a role in RNA trafficking in neurons. DSCR1 also contains a RNA-recognition motif (RRM) domain, so it will be important to determine whether DSCR1 binds to FMRP-targeted mRNAs

together with FMRP. In addition, several related questions remains to be further elucidated: (i) whether DSCR1 indeed directly binds to mRNA transcripts; (ii) if so, whether DSCR1 binds to the same target mRNAs as FMRP; and (iii) whether DSCR1 and FMRP compete or collaborate to bind to the same transcripts.

Neuronal stimulation by brain-derived neurotrophic factor (BDNF) treatment has been shown to trigger local protein synthesis of the FMRP target mRNAs encoding alpha Ca^{2+} /calmodulin-dependent protein kinase II (*αCaMKII*), *Arc/Arg3.1*, *Map1B*, and amyloid precursor protein (APP) [38–45]. To further determine whether DSCR1 can control local protein synthesis at dendritic spines through modulation of FMRP, a photoswitchable fluorescent protein, dendra-2, was fused with the 5' UTR and 3' UTR of *αCaMKII* mRNA and local translation was monitored via live imaging [26]. Results from these experiments suggest that hippocampal primary neurons without DSCR1 do not initiate local translation at dendritic spines upon BDNF stimulation, whereas increased levels of DSCR1 enhance local protein synthesis at the spines [26]. BDNF stimulation also elevates CaN activity and induces phosphorylation of DSCR1 in neurons. It is generally believed that DSCR1 is an inhibitor of CaN [54,59,60]; however, Wang *et al.* [26] showed that BDNF treatment of hippocampal primary neurons triggered phosphorylation of DSCR1, which subsequently enhanced CaN activity, resulting in dephosphorylation of the phospho-S499 of FMRP. This event may allow FMRP to dissociate from target mRNAs or suppress the function of FMRP in blocking translation, thus allowing initiation of mRNA translation. Taken together, these results suggest that binding of BDNF to TrkB receptors triggers a signaling cascade that activates kinases responsible for DSCR1 phosphorylation and initiation of protein translation at dendritic spines (Figure 1). It is also interesting to note that FMRP has been shown to respond to BDNF activity [38,61].

Whether DSCR1 phosphorylation indeed enhances CaN activity by changing the configuration of the DSCR1–CaN complex or simply by dissociating and thus allowing activation of CaN remains to be clarified. It is plausible that DSCR1 can be differentially regulated by various kinases in response to different signals, permitting DSCR1 to alter its effect on CaN activity. For example, transforming growth factor beta-activated kinase-1 (TAK1) phosphorylation turns DSCR1 from CaN inhibitor to activator in cardiomyocytes [62] and glycogen synthase kinase-3 (GSK-3) phosphorylation of Rcn1, a yeast homolog of DSCR1, activates CaN [63]. Mitogen-activated protein (MAP) kinase (MAPK)- or big MAPK 1 (BMK1)-mediated phosphorylation on DSCR1 releases DSCR1 from CaN, allowing CaN to become active [64]. Conversely, phosphorylation of DSCR1 by Dyrk1A, a gene located on chromosome 21 and overexpressed in DS, enhances binding of DSCR1 to CaN to augment CaN inhibition [65]. In addition, phosphorylated DSCR1 can be a substrate of CaN [66]. It is also known that ribosomal protein S6 kinase 1 (S6K1) phosphorylates S499 on FMRP in the mouse hippocampus [67] and the phosphorylated FMRP is a substrate for CaN at dendritic spines [26]. However, kinases for DSCR1 phosphorylation, which is associated with initiating local translation of mRNAs at dendritic spines, have not been identified.

In conclusion, the evidence to date suggests that a delicate balance of DSCR1 phosphorylation status may determine whether DSCR1 acts as a CaN inhibitor or enhancer.

It is likely that DSCR1 interacts with FMRP to differentially regulate local protein synthesis at dendritic spines. In resting neurons, binding of phosphorylated FMRP to its target mRNAs suppresses protein synthesis, which is permitted by DSCR1-dependent inhibition of CaN. On neuronal stimulation, however, DSCR1 is phosphorylated, which allows CaN to be active and to subsequently dephosphorylate FMRP, leading to dissociation of FMRP from the target mRNAs or suppression of FMRP translational inhibition to allow local protein synthesis at dendritic spines (Figure 1).

Dendritic spine dysmorphology in FXS and DS

Role of FMRP

An inability to maintain normal spine architecture and proper function at synapses is present in most forms of intellectual disability. Furthermore, it has become clear that dysregulation of local protein synthesis at the synapse contributes to pathological changes of spines and defective synaptic plasticity. Despite of this now widely held point of view, it remains unknown how local protein synthesis regulates spine morphology. Recent studies have begun to reveal mechanisms by which FMRP regulates dendritic spine number. It has been reported that myocyte enhancer factor 2 (*MEF2*) plays a crucial role in determining the number of synapses [68–70]. On neuronal activation, MEF-targeted genes involved in synapse elimination are expressed, which subsequently causes synapse reduction, whereas knockdown of *MEF2* isoforms increases synapse number [68–70]. However, activation of MEF2 in *fmr1* KO neurons does not decrease dendritic spine number [71] nor does inhibition of MEF2 increases the number of synapses in *fmr1* KO mice [71]. Together, these findings suggest that FMRP is required for MEF2-dependent synapse elimination. A recent study proposed a model in which the excess number of dendritic spines in *fmr1* KO mice is explained through a combination of the MEF2-activated and FMRP-targeted genes *protocadherin 10* (*pcdh10*) and *PSD-95* [72]. In normal neurons, MEF2 activation induces *pcdh10* expression as well as PSD-95 ubiquitination by murine double minute 2 (*mdm2*), an ubiquitin E3 ligase 3 [72,73]. Subsequently, Pcdh10 carries ubiquitinated PSD-95 to the proteasome for degradation, which triggers dendritic spine elimination [72]. By contrast, neurons without FMRP have upregulated levels of elongation factor 1a (*EF1a*), which can sequester mdm2, thereby reducing PSD-95 ubiquitination and preventing spine elimination [72] (Figure 2). Although this model addresses the elevated dendritic spine numbers in FXS, it is unclear what causes the formation of thinner spines seen in *fmr1* KO mice or FXS patients. Thus, the molecular mechanisms underlying hyperabundance of the thin and elongated dendritic spines in FXS remain to be elucidated.

Role of DSCR1

In contrast to the dendritic spine phenotype of *fmr1* KO neurons, *DSCR1* KO neurons show a decrease in the number of dendritic spines [26]. One way that DSCR1 may influence dendritic spine morphology is through physical interaction with FMRP and subsequent regulation of local protein synthesis at dendritic spines via modulation of MEF2 signaling as discussed above. Notably, DSCR1 has been shown to regulate nuclear factor of activated T cells (NFAT)-dependent transcription through its ability to regulate CaN [60,74] and NFAT has been shown to enhance MEF2 binding to target genes [75,76]. Thus, it is plausible the

decrease in the number of dendritic spines in *DSCR1* KO mice is due to greater CaN-dependent dephosphorylation and activation of NFAT, which subsequently activates MEF2 to produce genes required for elimination of dendritic spines (Figure 2).

Regulation of cofilin phosphorylation and spine head size by FMRP and DSCR1

In addition to the pathways discussed above, the dynamics of cofilin phosphorylation play an important role in determining and maintaining dendritic spine morphology. Phosphorylated cofilin polymerizes actin filaments to induce dendritic spine growth, whereas dephosphorylated cofilin causes depolymerization of actin filaments and spine shrinkage [77–79]. These findings suggest that activation of kinases or phosphatases targeting cofilin can modulate the size of the spine head. CaN is known to dephosphorylate phospho-cofilin [80], suggesting that DSCR1 can regulate spine head size through regulation of CaN activity. Recently, we showed that DSCR1 upregulation in neurons produces enlarged dendritic spine heads and elevates phospho-cofilin levels through inhibition of CaN activity, whereas *DSCR1* KO leads to more dephosphorylated cofilin and smaller spine heads [26]. The catalytic subunit of protein phosphatase 2A (PP2AC) is also known to dephosphorylate phospho-cofilin. FMRP binds to the 5' UTR of *pp2ac* mRNA to repress translation of *pp2ac* mRNA [81], suggesting that an abundance of the PP2AC protein due to lack of FMRP may contribute to the abnormal dendritic spine morphology seen in FXS or the *fmr1* KO mouse. It was reported that reduction of FMRP in DSCR1 overexpression background restored the cofilin phosphorylation level to normal, as well as the number and size of spines [26]. Taken together, these data imply that DSCR1 and FMRP act in the same spine morphogenesis pathway by regulating the level of phospho-cofilin to modulate actin dynamics at dendritic spines, which controls the size of the spine. Similarly, DSCR1 and FMRP may regulate the number of dendritic spines by modulating activation of MEF2 and PSD-95 ubiquitination during neuronal development (Figure 2). Finally, post-mortem brains from DS patients show various dendritic pathologies including enlarged but less abundant dendritic spines (Table 1). In addition, the DS mouse models Ts65Dn and Ts1Cje exhibit significantly enlarged dendritic spines [15] and another mouse model, Ts1Rhr, shows abnormal spines but to a lesser degree [16] (Table 1). It is interesting to note that both Ts65Dn and Ts1Cje are trisomic for *DSCR1* whereas Ts1Rhr is not, suggesting that DSCR1 may play a critical role in generating enlarged dendritic spines in these mouse models as well as in patients. It will be particularly interesting to test in the future whether restoring DSCR1 to normal levels in the DS mouse models also rescues the dendritic spine morphologies. Furthermore, whether reducing FMRP in DS mouse models restores spine shape and number remains to be determined. These studies will provide important insights into mechanisms underlying spine morphogenesis in DS as well as in FXS.

Disturbed homeostasis in neuronal transmission in FXS and DS

Inhibition of local protein synthesis at dendritic spines has been shown to disrupt long-term synaptic plasticity, and long-term depression (LTD) and LTP have been suggested as mechanisms underlying various neurological disorders including FXS [45,82–84]. Studies have shown that activation of mGluR5 triggers hippocampal LTD, which is dependent on local protein translation from the preexisting mRNAs located in dendritic spines [13,85].

Consistent with its role as a negative regulator of local protein synthesis, *fmr1* KO mice show enhanced mGluR-dependent LTD [86,87]. Furthermore, *fmr1* KO causes excessive internalization of AMPA receptors on mGluR5 activation, leading to decreased synaptic efficacy and enhanced LTD [40,41]. Besides altered LTD, *fmr1* KO mice display impaired LTP, although the underlying mechanism is less clear [88–90]. The DS mouse models Ts65Dn and Ts1Cje also show decreased LTP and increased LTD in the hippocampus [91]. To investigate candidate genes contributing to the defective long-term synaptic plasticity seen in DS, several transgenic mice, including *DSCR1*, have been generated. *DSCR1* transgenic mice indeed exhibit abnormal LTP in the hippocampus as well as failure to maintain late-stage LTP. This is consistent with results suggesting that *DSCR1* is involved in regulation of local protein synthesis [53].

We have previously reported that *DSCR1* plays a key role in BDNF-dependent local protein synthesis [26]. BDNF stimulation triggers excess protein production in dendritic spines of *DSCR1* transgenic mouse neurons, which may perturb pathways maintaining LTP and lead to impaired LTP. Additionally, both *DSCR1* KO and transgenic mice exhibit spatial learning defects associated with impaired LTP [53,55,56], which is consistent with reports that either overexpression or reduction of nebula, the *Drosophila* homolog of *DSCR1*, disrupts learning and memory processes [54]. In summary, the work on the role of *DSCR1* in synaptic plasticity suggests that defects in local protein synthesis at dendritic spines due to alteration of *DSCR1* levels may change homeostatic synaptic plasticity, resulting in defective learning and memory. Furthermore, it is plausible that *DSCR1* upregulation in DS may contribute to the defective LTP found in DS mouse models. Accordingly, it will be important to investigate the status of local protein synthesis in the dendritic spines of Ts65Dn or Ts1Cje mice.

Loss of excitatory synapses and dominance of inhibitory synaptic connections is observed in Ts65Dn mice (which, again, exhibit decreased LTP and impaired memory). This is consistent with the hypothesis that inhibition of GABA receptors can restore LTP as well as memory [37]. Conversely, in the absence of FMRP the increased protein synthesis on mGluR stimulation is thought to trigger a cascade of signaling pathways, leading to increased AMPA receptor internalization and enhanced LTD [27,89,92]. To reverse the phenotypes seen in *fmr1* KO mice, activation of a GABAergic pathway that could attenuate the exaggerated mGluR downstream signaling pathways was attempted [93]. Indeed, treatment with the GABA_B receptor agonist STX209 was effective in remediating various deficits seen in *fmr1* KO mice [94]. Thus, it is exciting to speculate that reducing *fmr1* (which triggers deficient GABA-mediated inhibitory neurotransmission) in the Ts65Dn mouse (which exhibits excessive inhibition of neurotransmission) could result in balanced excitatory and inhibitory neurotransmission. This also suggests that DS and FXS may share overlaps in various defective biological pathways leading to intellectual disability.

Other genes on chromosome 21 affecting synaptic morphology/function in DS and contribution to intellectual disability

It is important to note that, although there is convincing evidence linking *DSCR1* and FMRP in the same molecular pathway contributing to intellectual disability, DS is a complex

disorder involving altered doses of many other genes. Besides DSCR1, other genes encoded by chromosome 21 will also contribute to learning disability through pathways that interact with the DSCR1–FMRP network directly or indirectly through complex pathways that are currently not well understood. Below we briefly review some of the known neuronal genes that are overexpressed in DS and how they functionally interact with FMRP and DSCR1.

Genes interacting with FMRP

At least two other proteins encoded by chromosome 21 have been shown to be direct downstream targets of FMRP. A previous report has shown that FMRP can bind to the G-rich sequences of *APP* mRNA to repress its translation [39]. APP is also required for normal spine morphogenesis, because *APP* KO increased spine density in mice of 4–6 months of age, but reduced spine density and increased the presence of thin spines in mice that were 12 months old (Table 2) [95,96]. The mechanism for this age-dependent change in spine morphology is thought to involve increased generation of A β 42 with age [96]. APP is best known for its link to AD; mutations and duplication of APP can lead to early-onset AD and increased accumulation of amyloid plaques, a hallmark of AD. The finding that FMRP regulates APP translation thus suggests a link between AD and FXS. Interestingly, DS individuals also have a higher incidence of early-onset AD, highlighting the importance of understanding the functional protein-interaction network between FMRP, APP, and even DSCR1.

Recent works have also identified another gene encoded by chromosome 21, Down syndrome cell-adhesion molecule (*Dscam*), to be a downstream target of FMRP. DSCAM is a transmembrane protein with homology to the Ig superfamily of cell-adhesion molecules [97]. It is highly expressed in the fetal brain and plays important roles in neural development, including axon guidance and branching, and dendritic patterning and avoidance [98]. Experiments using *Drosophila* revealed that FMRP binds to *Dscam* RNA and repressed DSCAM translation [99,100]. Accordingly, loss of FMRP leads to DSCAM upregulation, thus producing synaptic targeting errors and abnormal synaptic arborization [99]. Excitingly, restoring DSCAM levels in *fmr* mutants in flies significantly reduced the synaptic-targeting and arborization phenotypes [99], implying that excess DSCAM expression could contribute to FXS phenotypes. It will be interesting to test in the future whether correcting DSCR1 levels in DS also in turn modulates DSCAM expression through an FMRP-dependent pathway.

Genes interacting with DSCR1

As mentioned above, DSCR1's ability to bind to and inhibit CaN can be modulated by another gene overexpressed in DS, *DYRK1A*, thus implying that *DYRK1A* may also indirectly regulate FMRP-dependent local protein synthesis. Furthermore, it suggests that learning disability may be due to complex functional protein interactions between genes encoded by chromosome 21. *DYRK1A* is especially sensitive to dose perturbations and has important roles in the nervous system including neurogenesis, neuronal differentiation, and learning and memory [101–106]. Both *DYRK1A* fly mutants and haploinsufficiency mice have smaller brains, reduced numbers of neurons, and locomotor defects [102,107]. *DYRK1A* transgenic mice show learning and memory impairment and locomotor defects

[106,108]. Both reducing and increasing DYRK1A decreased spine density; however, DYRK1A overexpression reduced overall spine density and led to more thin and immature spines in cortical neuronal cultures (Table 2) [109,110]. It remains to be determined whether DYRK1A perturbation regulates spine morphogenesis and learning and memory through DSCR1–FMRP-dependent pathways.

Studies using *Drosophila* have also revealed that the fly homolog of DSCR1, nebula, can functionally interact with two other genes encoded by chromosome 21 and upregulated in DS – synaptojanin and intersectin/DAP160 – to regulate synaptic transmission. It was shown that over-expression of intersectin/DAP160 reduced synaptojanin transport to the synaptic terminal and overexpression of nebula modulates synaptojanin activity through inhibition of CaN [111]. Although each gene when overexpressed alone did not affect synaptic transmission, overexpression of all three together impaired synaptic transmission [111] and may contribute to learning disability. Together, these results indicate the importance of studying both individual- and multiple-gene interaction networks to fully comprehend how multiple genes may interact functionally to give rise to a specific phenotype.

Concluding remarks

In this review we: (i) presented evidence that pathways controlled by DSCR1 and FMRP, genes implicated in two of the most common genetic causes of intellectual disabilities – DS and FXS – converge to regulate spine morphogenesis, local protein synthesis, and neurotransmission; (ii) highlighted recent research developments that provide neuropathological and neurophysiological links between DS and FXS; and (iii) reviewed other genes encoded by chromosome 21 that may regulate dendritic spine morphogenesis and contribute to intellectual disabilities by acting through pathways involving FMRP and DSCR1. Future work investigating whether reducing FMRP in DS mouse models or elevating DSCR1 in FMRP KO mice could restore synaptic plasticity, dendritic spine morphogenesis, and local protein synthesis will further advance our understanding of both diseases (Box 2). In addition, further elucidation of the larger functional protein-interaction network that regulates local protein synthesis, spine morphogenesis, and synaptic transmission may also shed light on overlapping molecular pathways that cause intellectual disabilities in different disorders.

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References

1. Ji Y, et al. Apolipoprotein E isoform-specific regulation of dendritic spine morphology in apolipoprotein E transgenic mice and Alzheimer's disease patients. *Neuroscience*. 2003; 122:305–315. [PubMed: 14614898]
2. Moolman DL, et al. Dendrite and dendritic spine alterations in Alzheimer models. *J Neurocytol*. 2004; 33:377–387. [PubMed: 15475691]

3. Spires TL, et al. Dendritic spine abnormalities in amyloid precursor protein transgenic mice demonstrated by gene transfer and intravital multiphoton microscopy. *J Neurosci.* 2005; 25:7278–7287. [PubMed: 16079410]
4. Zaja-Milatovic S, et al. Selective dendritic degeneration of medium spiny neurons in dementia with Lewy bodies. *Neurology.* 2006; 66:1591–1593. [PubMed: 16717229]
5. Schulz-Schaeffer WJ. The synaptic pathology of alphasynuclein aggregation in dementia with Lewy bodies, Parkinson's disease and Parkinson's disease dementia. *Acta Neuropathol.* 2010; 120:131–143. [PubMed: 20563819]
6. Barros CS, et al. Impaired maturation of dendritic spines without disorganization of cortical cell layers in mice lacking NRG1/ErbB signaling in the central nervous system. *Proc Natl Acad Sci USA.* 2009; 106:4507–4512. [PubMed: 19240213]
7. Hayashi-Takagi A, et al. Disrupted-in-Schizophrenia 1 (DISC1) regulates spines of the glutamate synapse via Rac1. *Nat Neurosci.* 2010; 13:327–332. [PubMed: 20139976]
8. Kvaajo M, et al. A mutation in mouse Disc1 that models a schizophrenia risk allele leads to specific alterations in neuronal architecture and cognition. *Proc Natl Acad Sci USA.* 2008; 105:7076–7081. [PubMed: 18458327]
9. Zhou Z, et al. Brain-specific phosphorylation of MeCP2 regulates activity-dependent Bdnf transcription, dendritic growth, and spine maturation. *Neuron.* 2006; 52:255–269. [PubMed: 17046689]
10. Chao HT, et al. MeCP2 controls excitatory synaptic strength by regulating glutamatergic synapse number. *Neuron.* 2007; 56:58–65. [PubMed: 17920015]
11. Bagni C, Greenough WT. From mRNP trafficking to spine dysmorphogenesis: the roots of fragile X syndrome. *Nat Rev Neurosci.* 2005; 6:376–387. [PubMed: 15861180]
12. Bassell GJ, Warren ST. Fragile X syndrome: loss of local mRNA regulation alters synaptic development and function. *Neuron.* 2008; 60:201–214. [PubMed: 18957214]
13. Waung MW, Huber KM. Protein translation in synaptic plasticity: mGluR-LTD, fragile X. *Curr Opin Neurobiol.* 2009; 19:319–326. [PubMed: 19411173]
14. Dierssen M, Ramakers GJA. Dendritic pathology in mental retardation: from molecular genetics to neurobiology. *Genes Brain Behav.* 2006; 5(Suppl. 2):48–60. [PubMed: 16681800]
15. Belichenko PV, et al. Synaptic structural abnormalities in the Ts65Dn mouse model of Down syndrome. *J Comp Neurol.* 2004; 480:281–298. [PubMed: 15515178]
16. Belichenko NP, et al. The “Down syndrome critical region” is sufficient in the mouse model to confer behavioral, neurophysiological, and synaptic phenotypes characteristic of Down syndrome. *J Neurosci.* 2009; 29:5938–5948. [PubMed: 19420260]
17. Santoro MR, et al. Molecular mechanisms of fragile X syndrome: a twenty-year perspective. *Annu Rev Pathol Mech Dis.* 2012; 7:219–245.
18. Weiler IJ, et al. Fragile X mental retardation protein is translated near synapses in response to neurotransmitter activation. *Proc Natl Acad Sci USA.* 1997; 94:5395–5400. [PubMed: 9144248]
19. Irwin SA, et al. Dendritic spine structural anomalies in fragile-X mental retardation syndrome. *Cereb Cortex.* 2000; 10:1038–1044. [PubMed: 11007554]
20. Patterson D. Molecular genetic analysis of Down syndrome. *Hum Genet.* 2009; 126:195–214. [PubMed: 19526251]
21. Antonarakis SE, Epstein CJ. The challenge of Down syndrome. *Trends Mol Med.* 2006; 12:473–479. [PubMed: 16935027]
22. Rumble B, et al. Amyloid A4 protein and its precursor in Down's syndrome and Alzheimer's disease. *N Engl J Med.* 1989; 320:1446–1452. [PubMed: 2566117]
23. Sturgeon X, Gardiner KJ. Transcript catalogs of human chromosome 21 and orthologous chimpanzee and mouse regions. *Mamm Genome.* 2011; 22:261–271. [PubMed: 21400203]
24. Korbelt JO, et al. The genetic architecture of Down syndrome phenotypes revealed by high-resolution analysis of human segmental trisomies. *Proc Natl Acad Sci USA.* 2009; 106:12031–12036. [PubMed: 19597142]
25. Vacano GN, et al. The use of mouse models for understanding the biology of down syndrome and aging. *Curr Gerontol Geriatr Res.* 2012; 2012:717315. [PubMed: 22461792]

26. Wang W, et al. DSCR1 interacts with FMRP and is required for spine morphogenesis and local protein synthesis. *EMBO J.* 2012; 31:3655–3666. [PubMed: 22863780]
27. Bear MF, et al. The mGluR theory of fragile X mental retardation. *Trends Neurosci.* 2004; 27:370–377. [PubMed: 15219735]
28. Penagarikano O, et al. The pathophysiology of fragile X syndrome. *Annu Rev Genomics Hum Genet.* 2007; 8:109–129. [PubMed: 17477822]
29. Schaeffer C, et al. The fragile X mental retardation protein binds specifically to its mRNA via a purine quartet motif. *EMBO J.* 2001; 20:4803–4813. [PubMed: 11532944]
30. Ramos A, et al. The structure of the N-terminal domain of the fragile X mental retardation protein: a platform for protein–protein interaction. *Structure.* 2006; 14:21–31. [PubMed: 16407062]
31. Lacoux C, et al. BC1–FMRP interaction is modulated by 2'-O-methylation: RNA-binding activity of the tudor domain and translational regulation at synapses. *Nucleic Acids Res.* 2012; 40:4086–4096. [PubMed: 22238374]
32. Brown V, et al. Microarray identification of FMRP-associated brain mRNAs and altered mRNA translational profiles in fragile X syndrome. *Cell.* 2001; 107:477–487. [PubMed: 11719188]
33. Darnell JC, et al. FMRP stalls ribosomal translocation on mRNAs linked to synaptic function and autism. *Cell.* 2011; 146:247–261. [PubMed: 21784246]
34. Marin-Padilla M. Pyramidal cell abnormalities in the motor cortex of a child with Down's syndrome. A Golgi study *J Comp Neurol.* 1976; 167:63–81.
35. Muddashetty RS, et al. Reversible inhibition of PSD-95 mRNA translation by miR-125a, FMRP phosphorylation, and mGluR signaling. *Mol Cell.* 2011; 42:673–688. [PubMed: 21658607]
36. Niere F, et al. Evidence for a fragile X mental retardation protein-mediated translational switch in metabotropic glutamate receptor-triggered Arc translation and long-term depression. *J Neurosci.* 2012; 32:5924–5936. [PubMed: 22539853]
37. Rueda N, et al. Chronic pentylentetrazole but not donepezil treatment rescues spatial cognition in Ts65Dn mice, a model for Down syndrome. *Neurosci Lett.* 2008; 433:22–27. [PubMed: 18226451]
38. Napoli I, et al. The fragile X syndrome protein represses activity-dependent translation through CYFIP1, a new 4E-BP. *Cell.* 2008; 134:1042–1054. [PubMed: 18805096]
39. Westmark CJ, Malter JS. FMRP mediates mGluR5-dependent translation of amyloid precursor protein. *PLoS Biol.* 2007; 5:e52. [PubMed: 17298186]
40. Waung MW, et al. Rapid translation of Arc/Arg3.1 selectively mediates mGluR-dependent LTD through persistent increases in AMPAR endocytosis rate. *Neuron.* 2008; 59:84–97. [PubMed: 18614031]
41. Park S, et al. Elongation factor 2 and fragile X mental retardation protein control the dynamic translation of Arc/Arg3.1 essential for mGluR-LTD. *Neuron.* 2008; 59:70–83. [PubMed: 18614030]
42. Muddashetty RS, et al. Dysregulated metabotropic glutamate receptor-dependent translation of AMPA receptor and postsynaptic density-95 mRNAs at synapses in a mouse model of fragile X syndrome. *J Neurosci.* 2007; 27:5338–5348. [PubMed: 17507556]
43. Zalfa F, et al. A new function for the fragile X mental retardation protein in regulation of PSD-95 mRNA stability. *Nat Neurosci.* 2007; 10:578–587. [PubMed: 17417632]
44. Huang F, et al. The mRNA for elongation factor 1alpha is localized in dendrites and translated in response to treatments that induce long-term depression. *J Neurosci.* 2005; 25:7199–7209. [PubMed: 16079402]
45. Bramham CR, Wells DG. Dendritic mRNA: transport, translation and function. *Nat Rev Neurosci.* 2007; 8:776–789. [PubMed: 17848965]
46. Liao L, et al. Quantitative proteomic analysis of primary neurons reveals diverse changes in synaptic protein content in *fmr1* knockout mice. *Proc Natl Acad Sci USA.* 2008; 105:15281–15286. [PubMed: 18829439]
47. Darnell JC, et al. Kissing complex RNAs mediate interaction between the fragile-X mental retardation protein KH2 domain and brain polyribosomes. *Genes Dev.* 2005; 19:903–918. [PubMed: 15805463]

48. Zang JB, et al. A mouse model of the human fragile X syndrome I304N mutation. *PLoS Genet.* 2009; 5:e1000758. [PubMed: 20011099]
49. Jin P, et al. Biochemical and genetic interaction between the fragile X mental retardation protein and the microRNA pathway. *Nat Neurosci.* 2004; 7:113–117. [PubMed: 14703574]
50. Plante I, et al. Dicer-derived microRNAs are utilized by the fragile X mental retardation protein for assembly on target RNAs. *J Biomed Biotechnol.* 2006; 2006:64347. [PubMed: 17057366]
51. Cheever A, Ceman S. Phosphorylation of FMRP inhibits association with Dicer. *RNA.* 2009; 15:362–366. [PubMed: 19155329]
52. Edbauer D, et al. Regulation of synaptic structure and function by FMRP-associated microRNAs miR-125b and miR-132. *Neuron.* 2010; 65:373–384. [PubMed: 20159450]
53. Hoeffer CA, et al. The Down syndrome critical region protein RCAN1 regulates long-term potentiation and memory via inhibition of phosphatase signaling. *J Neurosci.* 2007; 27:13161–13172. [PubMed: 18045910]
54. Chang KT, et al. The *Drosophila* homolog of Down's syndrome critical region 1 gene regulates learning: implications for mental retardation. *Proc Natl Acad Sci USA.* 2003; 100:15794–15799. [PubMed: 14668437]
55. Dierssen M, et al. Behavioral characterization of a mouse model overexpressing DSCR1/RCAN1. *PLoS ONE.* 2011; 6:e17010. [PubMed: 21364922]
56. Martin KR, et al. Over-expression of RCAN1 causes Down syndrome-like hippocampal deficits that alter learning and memory. *Hum Mol Genet.* 2012; 21:3025–3041. [PubMed: 22511596]
57. Davidovic L, et al. The fragile X mental retardation protein is a molecular adaptor between the neurospecific KIF3C kinesin and dendritic RNA granules. *Hum Mol Genet.* 2007; 16:3047–3058. [PubMed: 17881655]
58. Dictenberg JB, et al. A direct role for FMRP in activity-dependent dendritic mRNA transport links filopodial-spine morphogenesis to fragile X syndrome. *Dev Cell.* 2008; 14:926–939. [PubMed: 18539120]
59. Kingsbury TJ, Cunningham KW. A conserved family of calcineurin regulators. *Genes Dev.* 2000; 14:1595–1604. [PubMed: 10887154]
60. Arron JR, et al. NFAT dysregulation by increased dosage of DSCR1 and DYRK1A on chromosome 21. *Nature.* 2006; 441:595–600. [PubMed: 16554754]
61. Osterweil EK, et al. Hypersensitivity to mGluR5 and ERK1/2 leads to excessive protein synthesis in the hippocampus of a mouse model of fragile X syndrome. *J Neurosci.* 2010; 30:15616–15627. [PubMed: 21084617]
62. Liu Q, et al. Interaction between TAK1–TAB1–TAB2 and RCAN1–calcineurin defines a signalling nodal control point. *Nat Cell Biol.* 2009; 11:154–161. [PubMed: 19136967]
63. Hilioti Z, et al. GSK-3 kinases enhance calcineurin signaling by phosphorylation of RCN1s. *Genes Dev.* 2004; 18:35–47. [PubMed: 14701880]
64. Ma L, et al. p38a MAP kinase phosphorylates RCAN1 and regulates its interaction with calcineurin. *Sci China Life Sci.* 2012; 55:559–566. [PubMed: 22864830]
65. Jung MS, et al. Regulation of RCAN1 protein activity by Dyrk1A protein-mediated phosphorylation. *J Biol Chem.* 2011; 286:40401–40412. [PubMed: 21965663]
66. Takashima S, et al. Dendritic and histochemical development and ageing in patients with Down's syndrome. *J Intellect Disabil Res.* 1994; 38:265–273. [PubMed: 8061472]
67. Ferrer I, Gullotta F. Down's syndrome and Alzheimer's disease: dendritic spine counts in the hippocampus. *Acta Neuropathol.* 1990; 79:680–685. [PubMed: 2141748]
68. Barbosa AC, et al. MEF2C, a transcription factor that facilitates learning and memory by negative regulation of synapse numbers and function. *Proc Natl Acad Sci USA.* 2008; 105:9391–9396. [PubMed: 18599438]
69. Flavell SW, et al. Genome-wide analysis of MEF2 transcriptional program reveals synaptic target genes and neuronal activity-dependent polyadenylation site selection. *Neuron.* 2008; 60:1022–1038. [PubMed: 19109909]
70. Pulipparacharuvil S, et al. Cocaine regulates MEF2 to control synaptic and behavioral plasticity. *Neuron.* 2008; 59:621–633. [PubMed: 18760698]

71. Pfeiffer BE, et al. Fragile X mental retardation protein is required for synapse elimination by the activity-dependent transcription factor MEF2. *Neuron*. 2010; 66:191–197. [PubMed: 20434996]
72. Tsai NP, et al. Multiple autism-linked genes mediate synapse elimination via proteasomal degradation of a synaptic scaffold PSD-95. *Cell*. 2012; 151:1581–1594. [PubMed: 23260144]
73. Colledge M, et al. Ubiquitination regulates PSD-95 degradation and AMPA receptor surface expression. *Neuron*. 2003; 40:595–607. [PubMed: 14642282]
74. Shin SY, et al. A hidden incoherent switch regulates RCAN1 in the calcineurin–NFAT signaling network. *J Cell Sci*. 2011; 124:82–90. [PubMed: 21172821]
75. Chin ER, et al. A calcineurin-dependent transcriptional pathway controls skeletal muscle fiber type. *Genes Dev*. 1998; 12:2499–2509. [PubMed: 9716403]
76. Putt ME, et al. Evidence for coregulation of myocardial gene expression by MEF2 and NFAT in human heart failure. *Circ Cardiovasc Genet*. 2009; 2:212–219. [PubMed: 20031589]
77. Hotulainen P, et al. Defining mechanisms of actin polymerization and depolymerization during dendritic spine morphogenesis. *J Cell Biol*. 2009; 185:323–339. [PubMed: 19380880]
78. Hotulainen P, Hoogenraad CC. Actin in dendritic spines: connecting dynamics to function. *J Cell Biol*. 2010; 189:619–629. [PubMed: 20457765]
79. Cingolani LA, Goda Y. Actin in action: the interplay between the actin cytoskeleton and synaptic efficacy. *Nat Rev Neurosci*. 2008; 9:344–356. [PubMed: 18425089]
80. Zhou Q, et al. Shrinkage of dendritic spines associated with long-term depression of hippocampal synapses. *Neuron*. 2004; 44:749–757. [PubMed: 15572107]
81. Castets M, et al. FMRP interferes with the Rac1 pathway and controls actin cytoskeleton dynamics in murine fibroblasts. *Hum Mol Genet*. 2005; 14:835–844. [PubMed: 15703194]
82. Bramham CR. Local protein synthesis, actin dynamics, and LTP consolidation. *Curr Opin Neurobiol*. 2008; 18:524–531. [PubMed: 18834940]
83. Cajigas JJ, et al. Protein homeostasis and synaptic plasticity. *EMBO J*. 2010; 29:2746–2752. [PubMed: 20717144]
84. Nelson DL, et al. The unstable repeats – three evolving faces of neurological disease. *Neuron*. 2013; 77:825–843. [PubMed: 23473314]
85. Nosyreva ED, Huber KM. Developmental switch in synaptic mechanisms of hippocampal metabotropic glutamate receptor-dependent long-term depression. *J Neurosci*. 2005; 25:2992–3001. [PubMed: 15772359]
86. Hou L, et al. Dynamic translational and proteasomal regulation of fragile X mental retardation protein controls mGluR-dependent long-term depression. *Neuron*. 2006; 51:441–454. [PubMed: 16908410]
87. Ronesi JA, Huber KM. Metabotropic glutamate receptors and fragile X mental retardation protein: partners in translational regulation at the synapse. *Sci Signal*. 2008; 1:pe6. [PubMed: 18272470]
88. Shang Y, et al. Fragile X mental retardation protein is required for chemically-induced long-term potentiation of the hippocampus in adult mice. *J Neurochem*. 2009; 111:635–646. [PubMed: 19659572]
89. Nosyreva ED, Huber KM. Metabotropic receptor-dependent long-term depression persists in the absence of protein synthesis in the mouse model of fragile X syndrome. *J Neurophysiol*. 2006; 95:3291–3295. [PubMed: 16452252]
90. Wang H, et al. FMRP acts as a key messenger for dopamine modulation in the forebrain. *Neuron*. 2008; 59:634–647. [PubMed: 18760699]
91. Siarey RJ, et al. Altered long-term potentiation in the young and old Ts65Dn mouse, a model for Down syndrome. *Neuropharmacology*. 1997; 36:1549–1554.
92. Huber KM, et al. Altered synaptic plasticity in a mouse model of fragile X mental retardation. *Proc Natl Acad Sci USA*. 2002; 99:7746–7750. [PubMed: 12032354]
93. Heulens I, et al. Craniofacial characteristics of fragile X syndrome in mouse and man. *Eur J Hum Genet*. 2012; 21:816–823. [PubMed: 23211703]
94. Henderson C, et al. Reversal of disease-related pathologies in the fragile X mouse model by selective activation of GABA_B receptors with arbaclofen. *Sci Transl Med*. 2012; 4:152ra128.

95. Bittner T, et al. Gamma-secretase inhibition reduces spine density in vivo via an amyloid precursor protein-dependent pathway. *J Neurosci*. 2009; 29:10405–10409. [PubMed: 19692615]
96. Lee KJ, et al. Beta amyloid-independent role of amyloid precursor protein in generation and maintenance of dendritic spines. *Neuroscience*. 2010; 169:344–356. [PubMed: 20451588]
97. Yamakawa K, et al. DSCAM: a novel member of the immunoglobulin superfamily maps in a Down syndrome region and is involved in the development of the nervous system. *Hum Mol Genet*. 1998; 7:227–237. [PubMed: 9426258]
98. Hattori D, et al. Dscam-mediated cell recognition regulates neural circuit formation. *Annu Rev Cell Dev Biol*. 2008; 24:597–620. [PubMed: 18837673]
99. Cvetkovska V, et al. Overexpression of Down syndrome cell adhesion molecule impairs precise synaptic targeting. *Nat Neurosci*. 2013; 16:677–682. [PubMed: 23666178]
100. Kim JH, et al. Dscam expression levels determine presynaptic arbor sizes in *Drosophila* sensory neurons. *Neuron*. 2013; 78:827–838. [PubMed: 23764288]
101. Kurt MA, et al. Synaptic deficit in the temporal cortex of partial trisomy 16 (Ts65Dn) mice. *Brain Res*. 2000; 858:191–197. [PubMed: 10700614]
102. Fotaki V, et al. Dyrk1A haploinsufficiency affects viability and causes developmental delay and abnormal brain morphology in mice. *Mol Cell Biol*. 2002; 22:6636–6647. [PubMed: 12192061]
103. Hammerle B, et al. Mnb/Dyrk1A is transiently expressed and asymmetrically segregated in neural progenitor cells at the transition to neurogenic divisions. *Dev Biol*. 2002; 246:259–273. [PubMed: 12051815]
104. Yabut O, et al. Dyrk1A overexpression inhibits proliferation and induces premature neuronal differentiation of neural progenitor cells. *J Neurosci*. 2010; 30:4004–4014. [PubMed: 20237271]
105. Arque G, et al. Age-associated motor and visuo-spatial learning phenotype in Dyrk1A heterozygous mutant mice. *Neurobiol Dis*. 2009; 36:312–319. [PubMed: 19660545]
106. Ahn KJ, et al. DYRK1A BAC transgenic mice show altered synaptic plasticity with learning and memory defects. *Neurobiol Dis*. 2006; 22:463–472. [PubMed: 16455265]
107. Tejedor F, et al. minibrain: a new protein kinase family involved in postembryonic neurogenesis in *Drosophila*. *Neuron*. 1995; 14:287–301. [PubMed: 7857639]
108. Altafaj X, et al. Neurodevelopmental delay, motor abnormalities and cognitive deficits in transgenic mice overexpressing Dyrk1A (minibrain), a murine model of Down's syndrome. *Hum Mol Genet*. 2001; 10:1915–1923. [PubMed: 11555628]
109. Benavides-Piccione R, et al. Alterations in the phenotype of neocortical pyramidal cells in the Dyrk1A^{+/-} mouse. *Neurobiol Dis*. 2005; 20:115–122. [PubMed: 16137572]
110. Martinez de Lagran M, et al. Dyrk1A influences neuronal morphogenesis through regulation of cytoskeletal dynamics in mammalian cortical neurons. *Cereb Cortex*. 2012; 22:2867–2877. [PubMed: 22215728]
111. Chang KT, Min KT. Upregulation of three *Drosophila* homologs of human chromosome 21 genes alters synaptic function: implications for Down syndrome. *Proc Natl Acad Sci USA*. 2009; 106:17117–17122. [PubMed: 19805187]
112. Marin-Padilla M. Structural abnormalities of the cerebral cortex in human chromosomal aberrations: a Golgi study. *Brain Res*. 1972; 44:625–629. [PubMed: 4263073]
113. Kurt MA, et al. Deficits of neuronal density in CA1 and synaptic density in the dentate gyrus, CA3 and CA1, in a mouse model of Down syndrome. *Brain Res*. 2004; 1022:101–109. [PubMed: 15353219]
114. Wisniewski KE, et al. The Fra(X) syndrome: neurological, electrophysiological, and neuropathological abnormalities. *Am J Med Genet*. 1991; 38:476–480. [PubMed: 2018089]
115. McKinney BC, et al. Dendritic spine abnormalities in the occipital cortex of C57BL/6 Fmr1 knockout mice. *Am J Med Genet B: Neuropsychiatr Genet*. 2005; 136B:98–102. [PubMed: 15892134]
116. Galvez R, Greenough WT. Sequence of abnormal dendritic spine development in primary somatosensory cortex of a mouse model of the fragile X mental retardation syndrome. *Am J Med Genet A*. 2005; 135:155–160. [PubMed: 15880753]

117. Jung CK, Herms J. Role of APP for dendritic spine formation and stability. *Exp Brain Res.* 2012; 217:463–470. [PubMed: 22094714]
118. Maynard KR, Stein E. DSCAM contributes to dendrite arborization and spine formation in the developing cerebral cortex. *J Neurosci.* 2012; 32:16637–16650. [PubMed: 23175819]
119. Thomas S, et al. Intersectin regulates dendritic spine development and somatodendritic endocytosis but not synaptic vesicle recycling in hippocampal neurons. *J Biol Chem.* 2009; 284:12410–12419. [PubMed: 19258322]
120. Fuentes JJ, et al. DSCR1, overexpressed in Down syndrome, is an inhibitor of calcineurin-mediated signaling pathways. *Hum Mol Genet.* 2000; 9:1681–1690. [PubMed: 10861295]
121. Ermak G, et al. RCAN1 (DSCR1 or Adapt78) stimulates expression of GSK-3beta. *FEBS J.* 2006; 273:2100–2109. [PubMed: 16649988]
122. Davies KJA, et al. Renaming the DSCR1/Adapt78 gene family as RCAN: regulators of calcineurin. *FASEB J.* 2007; 21:3023–3028. [PubMed: 17595344]
123. Ascano M Jr, et al. FMRP targets distinct mRNA sequence elements to regulate protein expression. *Nature.* 2012; 492:382–386. [PubMed: 23235829]

Box 1. DSCR1

Fuentes et al. first identified DSCR1, located on human chromosome 21, as a candidate gene contributing to intellectual disability and cardiac defects in DS because DSCR1 transcripts are highly expressed in the brain and heart [59]. It belongs to a highly conserved family of CaN inhibitors called calcipressins, which includes RCN1P in yeast [59], nebula in *Drosophila* [54], and DSCR1 in mouse [120] and human [121]. DSCR1 has been renamed as regulator of CaN 1 (RCAN1) [122]. However, recent studies have shown that DSCR1 is not limited to regulation of CaN activity, but rather plays diverse roles in different biological pathways. The first demonstration of its importance in learning and memory was reported using *Drosophila* as a model system. Either loss of function or overexpression of nebula, the fly homolog of DSCR1, is sufficient to impair learning [54], suggesting that precise regulation of nebula signaling is necessary for normal functioning of the brain. Furthermore, overexpression of DSCR1 in human trisomy 21 fetal brain tissues is associated with altered CaN-mediated signaling [54]. Thus, work in both *Drosophila* and humans suggests that over-expression of DSCR1 may contribute to intellectual disability in DS. Similar results were more recently obtained in mouse models lacking DSCR1 or trisomic for DSCR1 [53,55,57]. Both mouse models showed learning and memory defects, suggesting that proper levels of DSCR1 are critical for normal learning and memory in mammals.

Box 2. Outstanding questions

- Is DSCR1 alteration a major cause of abnormal spine morphogenesis, synaptic plasticity, and behavior seen in Ts65Dn mice?
- Can reducing FMRP in DS mouse models rescue its neuropathological and behavioral deficits? Does upregulation of DSCR1 in a FXS mouse model restore its behavioral and physiological deficits?
- How does DSCR1 phosphorylation enhance CaN activity and which kinase is involved?
- Does DSCR1 bind to RNAs? Do DSCR1 and FMRP target the same mRNAs? Is DSCR1 involved in RNA transport?
- How do locally synthesized proteins affect dendritic spine morphology?
- Is LTD altered in DSCR1 KO and transgenic mice?

Figure 1.

Down syndrome critical region 1 (DSCR1) modulates local protein synthesis in response to brain-derived neurotrophic factor (BDNF) treatment. In the absence of BDNF, DSCR1 inhibits calcineurin activity and interacts with phosphorylated Fragile X Mental Retardation Protein (FMRP), leading to repression of local protein synthesis (left). Following BDNF treatment, activation of unknown kinases phosphorylates DSCR1 and alters its ability to inhibit calcineurin (right). This results in activation of calcineurin and dephosphorylation of phosphorylated FMRP, thus causing FMRP to dissociate from target mRNAs and activate protein translation.

Figure 2.

Regulation of dendritic spine morphology by Fragile X Mental Retardation Protein (FMRP) and Down syndrome critical region 1 (DSCR1). Spine head size can be regulated by cofilin phosphorylation status and the number of spines modulated by myocyte enhancer factor 2 (MEF2). Knockout (KO) of *fmr1* results in increased protein synthesis and elevated levels of target proteins including protein phosphatase 2A (PP2AC) and elongation factor 1a (EF1a). PP2AC can dephosphorylate phospho-cofilin to cause actin destabilization and spine shrinkage. EF1a elevation sequesters murine double minute 2 (MDM2), a ubiquitin E3 ligase, to prevent MDM2 ubiquitination of postsynaptic density protein 95 (PSD-95), thereby preventing PSD-95–protocadherin 10 (Pcdh10) association and proteasome degradation of PSD-95. Together, this reduces synapse elimination and may result in the higher density of thin spines seen in *fmr1* KO mice. DSCR1 may regulate dendritic spine morphology both through interaction with FMRP to regulate local protein synthesis and through modulation of calcineurin activity. Calcineurin elevation in DSCR1 KO can dephosphorylate phospho-cofilin to cause spine shrinkage and activation of FMRP through dephosphorylation to further cause spine shrinkage at the synapse (not shown here). In addition, calcineurin dephosphorylates and activates nuclear factor of activated T cells (NFAT), including enhancement of MEF2 binding to the target genes. Activation of MEF2 leads to synapse elimination through proteasome degradation of PSD-95. Altogether, DSCR1 KO leads to a lower number of spines that are also thinner.

Table 1
Changes in spine morphology reported for DS and FXS patients and mouse models

Syndrome	Animal model	Spine phenotype
Down syndrome	Human	Variable, with: enlarged spines on dendrites with decreased density; short spines; elongated spines [34,67,112]
	Ts65Dn (mouse)	Decreased density of spines, enlarged spine heads [16,101,113]
	Ts1Cje (mouse)	Decreased density of spines, enlarged spine heads; less severe than Ts65Dn [16]
	Ts1Rhr (mouse)	Decreased density of spines, enlarged spine heads; less severe than Ts65Dn and Ts1Cje [16]
Fragile X	Human	Increased density of spines, thin and elongated spines [114]
	<i>fmr</i> KO (mouse)	Increased density of spines, thin and elongated spines [19,115,116]

Table 2
Chromosome 21 genes regulating spine morphogenesis

Gene	Genetic modification	Spine phenotype
DSCR1	−/−	Reduced spine density, reduced spine head size [26]
	Transgenic	Enlarged spine heads [26]
DYRK1A	−/+	Reduced spine density [109]
	Transgenic	Lower spine density, increased proportion of elongated spines [110]
APP	−/−	Increased spine density at 4–6 months; reduced spine density and longer spines at 12 months [98,117]
	Transgenic	Increased spine density [96,117]
DSCAM	DSCAM ^{del17}	Transient increase in spine density and increase in thinner immature spines [118]
ITSN	miRNA knock down (cultured neurons)	Increased number of thinner spines [119]