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Review

Dendritic spine dysgenesis in autism related disorders

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ABSTRACT

The activity-dependent structural and functional plasticity of dendritic spines has led to the long-standing belief that these neuronal compartments are the subcellular sites of learning and memory. Of relevance to human health, central neurons in several neuropsychiatric illnesses, including autism related disorders, have atypical numbers and morphologies of dendritic spines. These so-called dendritic spine dysgeneses found in individuals with autism related disorders are consistently replicated in experimental mouse models. Dendritic spine dysgenesis reflects the underlying synaptopathology that drives clinically relevant behavioral deficits in experimental mouse models, providing a platform for testing new therapeutic approaches. By examining molecular signaling pathways, synaptic deficits, and spine dysgenesis in experimental mouse models of autism related disorders we find strong evidence for mTOR to be a critical point of convergence and promising therapeutic target.

Contents

1. Introduction

As Santiago Ramón y Cajal began his work describing the fine structure of nervous cells in the late nineteenth century, he noticed that many of the cells "appear bristling with thorns [*puntas*] or short spines [*espinas*]" [1], and he envisioned that these protrusions provided a source of functional connectivity between neurons [2,3]. Though Sherrington provided the concept of the synapse soon thereafter [4], it was not until the development of electron microscopy in the 1950s and confocal fluorescence microscopy in the 1980s that spines were confirmed as an important structural

Abbreviations: Glu, glutamate; Ras, rat sarcoma proto-oncogenic G-protein; MEK, MAPK kinase; ERK, extracellular signal-related kinase; Rheb, RAS homolog enriched in brain; Mnk, MAP kinases phosphorylate; eIF4E, eukaryotic initiation factor 4E; 4E-BP, eukaryotic translation initiation factor 4E binding protein; S6, ribosomal protein S6; S6K, S6 kinase; 40S, eukaryotic small ribosomal subunit; PI3K, phosphoinositide 3-kinase; PDK, phosphoinositide-dependent kinase; P, phosphate.

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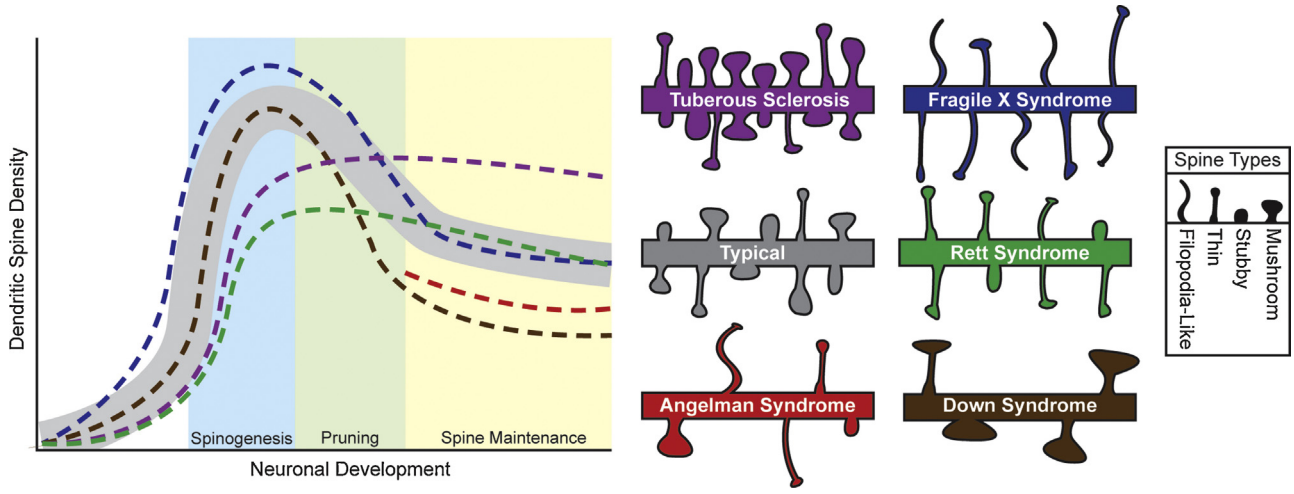

Fig. 1. Characterization of dendritic spines in autism related disorders.
Numerical density of dendritic spines during neurodevelopmental stages, and morphologies of mature spines in different ARDs. In typical subjects (grey shading), spines and synapses are formed during early development with the excess or weaker connections being selectively pruned in adolescence, after which spines are maintained during adulthood. Morphological types of spines include thin, mushroom, and stubby, filopodia-like spines are uncommon in the mature brain. Tuberous Sclerosis (purple) has a lower density during spinogenesis, is within typical levels in the pruning stage, and higher densities during maturity with normal morphology. Fragile X syndrome (blue) has higher densities until the maintenance stage has been reached, when the density lowers to typical levels and have spines that are morphologically more immature, including a higher proportion of thin and filopodia-like spines. Rett syndrome (green) has a lower density until the maintenance phase with a lower proportion of mushroom spines. There is a lack of density data in Angelman syndrome (red) for both the spinogenesis and pruning stages, but mouse models have lowered densities in the maintenance phase with more variable spine morphology. Down syndrome (brown) has lower densities after the spinogenesis phase with remaining spines having larger heads and longer necks. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

component of the synapse. The functional connectivity envisioned by Cajal has been validated and it is now well-established that spines, located on the dendrites of most neurons, are the post-synaptic sites of the majority of excitatory synapses in the brain where they receive input from glutamatergic axons [5]. The ability of the dendrite to add new spines, change spine morphology, and remove spines in response to synaptic activity has led to the wide-held belief that dendritic spines are the center for synaptic plasticity, and therefore, a cellular correlate to learning and memory [6]. In support of this view, many neuropsychiatric disorders, including autism with the high comorbidity of intellectual disability (ID) [7–9], present with atypical numbers and structure of dendritic spines, a cellular pathology termed "spine dysgenesis" [10]. We will first briefly describe the development, structure, and function of typical dendritic spines, and progress to detail evidence for spine dysgenesis in autism related disorders (ARDs), tracing the commonalities in dysgenesis from disorders involving entire chromosomes to those caused by single gene mutations.

2. Dendritic spines: history, functions, structural types, and development

In the developing brain, dendrites first develop devoid of spines and synapses. Dynamic, finger-like protrusions called filopodia begin to project from dendrites during the synaptogenesis period and have the ability to form nascent synapses with nearby axons [11]. Filopodia are highly mobile, extending and retracting to form synapses on the dendritic shaft or on spine-like protrusions that may develop into fully functioning spines [12,13]. One leading hypothesis is that filopodia recruit axons to form synapses, though the exact mechanism of synaptogenesis during development is still under investigation and may include multiple modalities. As development continues, filopodia give way to dendritic spines, though increased densities of filopodia-like structures are seen in some ARDs, as will be discussed below [14]. Dendritic spines formed during early postnatal life undergo pruning, which eliminates roughly 50% of the synapses/spines [15,16]. Therefore, the density of dendritic spines is dynamic and determined by neurodevelopmental stage (Fig. 1).

Dendritic spines in the mature brain are typically less than 3 μm in length, consist of a spherical head (0.5–1.5 μm) that serves as a biochemical compartment and is connected to the parent dendrite by a thin neck (<0.5 μm in diameter) thought to function as a diffusional barrier for intracellular organelles, as well as signaling ions and molecules. Excitatory synapses form on the head of the spine where the postsynaptic density acts as scaffolding for neurotransmitter receptors and signaling proteins, which includes α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) glutamate receptors. The morphology of the spines can vary in overall length, shape of the head, and length of the neck as well as in receptor ratios and diffusional properties. In frozen snapshots of a likely dynamic morphology, three main classes of spines have been described: stubby spines without an obvious neck, mushroom spines with a large head and a thin neck, and thin spines with a small head connected to the dendritic shaft by a long thin neck (Fig. 1) [17]. Spine morphology has been demonstrated to contribute or be related to synaptic transmission [18], synapse formation, spine stability [19], and Ca^{2+} diffusion from the spine head to the parent dendrite [20,21]. In addition, a positive correlation has been found between spine head size, the ratio of AMPA/NMDA receptors [22], and synaptic strength [23,24]. These correlations provide strong evidence that the morphology of dendritic spines relates closely to the function of the synapses they belong to.

Even in a mature brain, the structure of spines is plastic and able to change both in size and shape in response to synaptic activity, and these changes can persist for prolonged periods of time. The induction of long-term potentiation (LTP) causes spine enlargement in the hippocampus [25–27] and the cortex [28]. In addition to increasing spine head volume, LTP-inducing stimuli also increase the width of the spine neck and decreases its length [29]. Conversely, the induction of long-term depression (LTD) causes a decrease in spine head volume in the hippocampus [30,31]. Using two-photon uncaging of glutamate in combination with time-lapse two-photon imaging, Matsuzaki et al. showed enlargement

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of spines in response to induction of LTP, as well as higher levels of AMPA receptors in the postsynaptic density of potentiated spines, and that these changes depend on initial pre-LTP spine morphology. Though transient increases in size were similar in most spines, long-term changes were sustained more often in the smaller spines, leading the authors to interpret that the structure of the smaller spines led to a elevated intrinsic propensity for LTP [32]. These results support previous studies that observed individual spines in vivo over lengthy time spans (weeks to months) and found that smaller spines are particularly more labile [33], while larger spines may be more dominant functionally, but markedly less plastic and may remain morphologically resilient for the animal's entire adult life [34]. Further work demonstrated that both small and large spines had similar initial increases in $[Ca^{2+}]_i$ following stimulation, but larger spines with thicker necks allowed Ca^{2+} to diffuse to the parent dendrite with less diffusional delay. Ca^{2+} in smaller spines became trapped in the head, resulting in a prolonged increase in $[Ca^{2+}]_i$ localized to the head both in vitro [21] and in vivo [28]. While these studies suggest that morphological differences contribute to a spine's response to LTP-inducing stimuli through diffusional properties, it should be noted that other groups have found neck diffusion to be greatly influenced by pre- and post-synaptic activity and depolarization [35,36]. Though the exact relationship between spine morphology and activity-induced plasticity is still under debate, colloquially the larger, more stable, mushroom and stubby spines are referred to as "memory spines" [33], whereas thin spines have been dubbed the "learning spines" for their enhanced ability to undergo structural changes [19,33,37]. The plastic nature of dendritic spines and the role of spine morphology in synaptic signaling have led to the hypothesis that dendritic spines are a fundamental component of learning and memory.

3. Spine dysgenesis in autism related disorders

Spine dysgenesis has been described in autopsy brains of several ARDs, their genetic causes ranging from hundreds of affected genes to one, with their pervasiveness relating to both severity and number of clinical symptoms. By examining common clinical phenotypes correlated to spine and synaptic abnormalities between the disorders, we can work to recognize causalities in dysgenesis and identify potential targets for therapeutic intervention.

3.1. Down syndrome

Down syndrome (DS) is the most common genetic disorder associated with ID affecting 500,000 Americans. Cognitive defects in those afflicted with DS include delayed speech and language development, and impairments in spatial and long-term memory. Roughly 5–10% of individuals with DS meet the diagnosis criteria for autism spectrum disorder [38–40], though diagnosis can be difficult in patients with severe ID. Most cases of the disorder are caused by a complete trisomy of chromosome 21 (HSA21), though there are rare cases of DS caused by partial trisomies in the long arm of HSA21, deemed the DS critical region (DSCR) [41]. Cognitive development tends to slow in children with DS and the brain undergoes a progressive postnatal degenerative process. Gross neuroanatomical phenotypes associated with DS include slightly reduced brain size and weight at birth, decreased neuronal density, aberrant neuronal morphology, and altered dendritic arborization and spines.

Dysgenesis in dendritic spines of DS patients has been found consistently in the cortex and hippocampus [10,42–46], with the spines having atypically large heads [42]. With all previous studies having been conducted on brain samples from adults, Takashima et al. undertook a large-scale study comparing spine densities from patients collected during different stages of development. They provided evidence that the number of dendritic spines were typical in DS human fetuses, but that after 4 months of age spine number dipped below typical levels in the neocortex [44,47], and that the remaining spines are morphologically longer than unaffected individuals [46]. These data suggest that dendritic spine dysgenesis in DS results from impaired spine maturation, and that synaptic pruning may be excessive [48].

The sequencing of HSA21 allowed the generation of experimental mouse models to characterize the pathophysiology of DS [49]. Of these models, Ts65Dn is most widely used and consists of a genomic fragment with 49% syntenic regions and 55% of the HSA21 gene orthologs triplicated [50,51]. These mice have lower dendritic density, enlarged spine heads, as well as impaired hippocampal-dependent learning and memory, tested using the Morris water maze, as well as impaired LTP at excitatory hippocampal synapses [52–55], yet enhanced LTD [56,57]. Ongoing research in DS has focused on creating mouse models with smaller selections of trisomic genes included in the DS critical region. While these models may not recapitulate all clinical features of DS individuals, they have the potential to identify the pathological role of specific genes. Located in the DSCR, regulator of calcineurin 1 (RCAN1), also known as DSCR1 [58], and Dyrk1a [59] are both implicated in DS spine phenotypes, though we will focus on RCAN1 in this review. Both knockout (KO) [60] and trisomic mouse models of RCAN1 show learning and memory deficits [61] with over-expression resulting in decreased spine density [62]. RCAN1 is a regulator of FMRP [63,64], a protein that regulates local protein synthesis in dendrites [65–67] and transcriptionally repressed in Fragile X syndrome (FXS), a disorder characterized by spine dysgenesis [67–69] which will be discussed in further detail below.

3.2. Angelman syndrome

Angelman syndrome (AS) occurs in one out of every 12,000 births and is characterized by ID, speech impairments, ataxia, stereotypical movements, epilepsy and socialization deficits that meet the criteria for autism diagnosis [70]. The vast majority of individuals afflicted with AS has deletions in the long arm of chromosome 15 within the 15q11–13 region encoding for the *UBe3a* gene [71,72]. *UBe3a* is genomically imprinted, causing the paternal allele to be epigenetically silenced selectively in neurons [73–79]. This portion of the genome appears to be especially important in ARDs, as most genetic cases of autism are caused by maternal duplications of 15q11–13 [80–82], paternal deletions cause Prader–Willi syndrome (a disorder with autism comorbidity) [83], and maternal deletions cause AS which has been reported as having a comorbidity as high as ~81% for autism spectrum diagnosis [84].

Of the several mouse models of AS, the best characterized strain is the *UBe3a* KO generated by including a deletion mutation in exon 2 of the *UBE3A* gene [85–87]. The maternal deficient heterozygous mice *UBE3A*$^{m-/p+}$ recapitulate many AS symptoms including ataxia, motor impairment, hippocampal-dependent learning and memory impairment, and about 20–30% exhibit audiogenic seizures [85,88–90]. *UBE3A*$^{m-/p+}$ mice also display deficiencies in hippocampal LTP [85,91,92] and increased metabotropic glutamate receptor (mGluR) dependent LTD [93], which correlate with lower dendritic spine density and shorter spine lengths both in the *UBE3A*$^{m-/p+}$ mouse model [89] and an AS individual [94]. A most marked deficit in the *UBE3A*$^{m-/p+}$ mice is the impairment in experience-dependent synaptic plasticity, revealed through monocular deprivation studies [90,95]. These studies led to the hypothesis that the absence of UBE3A leads to the inability to modify or rearrange synapses. Recently, it has been found that UBE3A is a regulator of activity-regulated cytoskeleton-associated protein (ARC) [96], a protein instrumental in removing AMPA receptors from the postsynaptic density [97], a process required for experience-dependent synap-

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tic plasticity [96]. Abnormal levels of ARC have also been found in Fragile X syndrome (FXS) and Tuberous Sclerosis (TS), and current research is focused on ARC's role in autism and ID [96,98].

3.3. Rett syndrome

Rett syndrome (RTT) is an X-linked autism spectrum disorder afflicting 1 in 15,000 girls and women and is characterized by typical perinatal development until symptoms develop at 6–18 months of age [99,100]. These symptoms include motor impairment, stereotypical movements, lack of spoken language, seizures and ID [101]. Ninety to ninety five percent of RTT individuals carry mutations in *MECP2*, a gene encoding a global transcriptional regulator that binds to methylated CpG sites in the promoter regions of DNA [102–104]. Brain pathology includes reduced neuronal size but increased cell density in several brain regions [105,106] as well as reduced dendritic arborization [107] and spine dysgenesis [108–110].

Dendritic spine dysgenesis in individuals with RTT includes not only lower spine density, but also atypical morphology resulting in a decreased proportion of mushroom-type spines in the cortex and hippocampus [107,109,110]. Mouse models of RTT are widely used and recapitulate many of the behavioral and anatomical abnormalities associated with the human disorder [111,112] and additionally show impairments in both LTP and LTD [113,114]. Commonly used strains of *Mecp2* KO mice have impaired dendritic complexity [115,116] and lower dendritic spine density [117–120] as well as a lack of mushroom spines in cortical and hippocampal neurons [121,122].

Interestingly, pyramidal neurons of the hippocampus of *Mecp2* KO have fewer dendritic spines only before postnatal day 15 [118,123], suggesting that MeCP2 is necessary for dendritic spine formation during early postnatal development, but a compensatory mechanism takes place after this period in *Mecp2* KOs. Potential mechanisms include enhanced hippocampal network activity promoting dendritic spine formation [123], deranged homeostatic plasticity stimulating spinogenesis while affecting pyramidal neuron function [124,125], or lack of developmental synaptic pruning. Among the many genes regulated by MeCP2, *brain derived neurotrophic factor* (BDNF) may be the most prominent in RTT spine dysgenesis due to its role in neuronal growth, synapse formation and activity-dependent plasticity through the activation of tropomyosin-related kinase B (TrkB) receptors [100,126–129] and has been shown to be lowered in RTT [112,130–132]. Additionally, mutations in MeCP2 lead to lower expression of mGluR [133]. The combination of deficiencies in both TrkB and mGluR signaling in the dendrite may lead to insufficient activity-dependent protein translation, the potential implications of which will be discussed in further detail below.

3.4. Fragile X syndrome

Fragile X Syndrome (FXS) is the most common single-gene cause of autism and ID, afflicting approximately 1 in 4000 males and 1 in 7000 females [134]. Those afflicted with FXS have mild-to-severe ID, social anxiety and autistic disorders, increased incidence of epilepsy, attention problems, stereotypical movements, and sensory hypersensitivity [135–138]. The syndrome is typically caused by an expansion of ≥200CGG-repeats in the *FMR1* gene that encodes the Fragile X mental retardation protein (FMRP), which inhibits protein translation through RNA-binding. FMRP is a negative regulator of protein translation [139], many of which are localized to dendrites and dendritic spines [66,67,139]. Autopsies of FXS patients have shown atypical spine morphology [140–142], leading to the current hypothesis that FMRP is a key regulator of specific dendritic mRNAs and subsequently controls their translation during growth and plasticity, modulating spine morphology [7].

Reports on dendritic spine density both in human cases and in *Fmr1* KO mice are inconsistent, with some studies reporting typical density [141,143] and others higher density [144–146], though these inconsistencies may arise from the use of animals of different ages, different brain regions, and staining and imaging methods [147]. Interestingly, Nimchinsky et al. described that spine density was significantly higher in *Fmr1* KO mice at 1 week of age, but this difference did not persist after the 2nd postnatal week [148]. Several live imaging studies provide evidence that the density may be within the typical range in animals older than postnatal-day 7 [149,150]. If dendritic density is indeed elevated in younger animals, and then returns to levels comparable to those in WT mice, it may suggest that spinogenesis is increased in FXS, with excess spines being properly pruned later in development.

In contrast to the seemingly inconsistent observations on dendritic spine density, a long and tortuous spine morphology is consistently reported and considered the neuropathologic hallmark of FXS [66,140–146,148,151–154]. The types of spines seen in FXS appear similar to filopodia, and many groups have described the spine morphology as 'immature' [66,140–146,148,151–155]. In support of the hypothesis that FXS spines may exist in an immature developmentally stalled state well into adulthood, an in vivo 2-photon imaging study demonstrated that dendritic spines in *Fmr1* KO mice have a higher turnover rate than those in wildtype mice [156]. These atypical features of FXS spines translate to deficits in activity-dependent synaptic plasticity in *Fmr1* KO mice. Several studies reported a complete lack of LTP in the neocortex of *Fmr1* KO mice, including the visual, prefrontal and somatosensory cortices [149,157–160]. Mixed reports regarding the state of LTP in the hippocampus can be explained by the induction protocols used: those studies using trains to elicit maximal levels of LTP reported no deficits [157,161–163], while studies using "threshold" stimulation trains show a deficit in LTP maintenance [164,165]. On the other hand, *Fmr1* KO mice show elevated mGluR-dependent LTD [151,166,167], which led to the *mGluR theory of Fragile X*: the primary defect in FXS is a functional deficiency in circuit plasticity explained by elevated mGluR signaling that influences structural and functional plasticity [168,169].

3.5. Tuberous sclerosis

Tuberous sclerosis (TS) is a genetic ARD characterized by the formation of hamartomas in multiple organ systems, and affects 1 in 6000 individuals [170]. Eighty five percent of those with TS have central nervous system complications including epilepsy, cognitive impairment, and behavioral problems [171]. The comorbidity of autism diagnosis and TS is 29% [172,173], though more than 50% of TS patients report some autism-like features [174]. TS results from inactivating mutations in either *TSC1* or *TSC2* encoding for either hamartin or tuberin, respectively [175,176]. These proteins bind together to form a functional heterodimer [177], working in concert as an inhibitor of the small G-protein Rheb, the key activator of mammalian target of rapamycin (mTOR) [178–181]. Thus, a mutation in either gene causes the same result: increased activity of mTOR. The discovery that the mTOR pathway is heightened in TS and the tumors TS patients develop led to the implication of the TSC2:TSC1 complex as a tumor suppressor and mTOR as a key player in tumorigenesis [182]. Furthermore, there is increasing evidence that this pathway may also be considerably involved in neuronal synaptic plasticity [183–188].

Mouse models of TS have all consistently shown impairments in hippocampal-dependent behavior and synaptic plasticity, such as impaired early-phase LTP [189,190], and impaired mGluR-dependent LTD [191–194]. Behavioral studies have demonstrated

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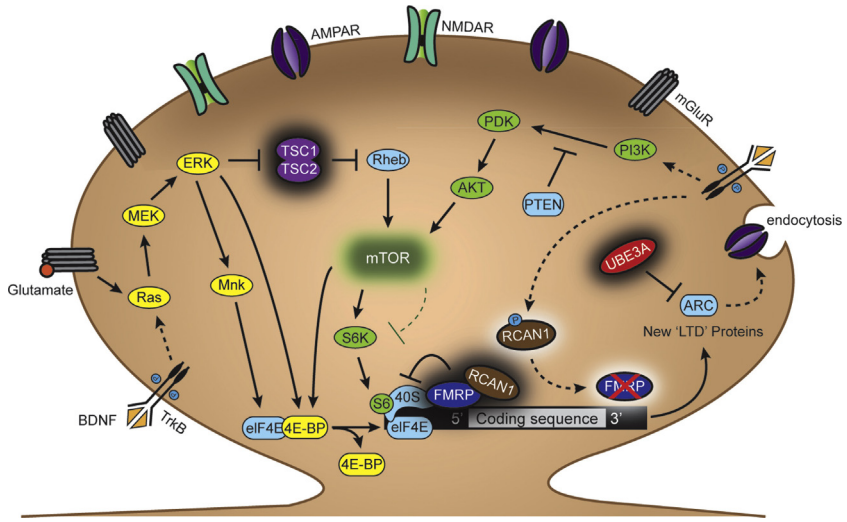

Fig. 2. Pathways involved in the translational regulation of "LTD proteins".
ARDs share molecular pathologies affecting a common signaling pathway involved in activity-dependent protein synthesis in distal dendrites near spine synapses. The Ras/ERK and PI3K/mTOR signaling pathways couple synaptic activation of mGluR and the BDNF TrkB receptors to protein translation that is essential to the maintenance of LTD. Mutations in several regulators of these pathways, including the genes encoding the proteins TSC1/2, FMRP, DSCR1, UBE3A, and PTEN are responsible for ARDs. Loss-of-function mutations in the gene encoding the nuclear protein MeCP2, which causes RTT, result in lower levels of mGluR and BDNF, lowering the activation of those signaling pathways in response to glutamatergic synaptic activity and activity-dependent BDNF release. While mTOR is typically an activator of protein translation through 4E-BP and S6K, pathological increases in mTOR levels repress translation of LTD-specific proteins, though the exact mechanism(s) is unknown. Selective inhibition of mTOR with rapamycin alleviates autism-related deficits in FXS and TS, providing evidence that this pathway is causal in the pathological mechanisms leading to autism.

impaired hippocampal-dependent learning in assays such as the Morris water maze, radial maze, and contextual fear conditioning [189,190,192,193,195–197], as well as impaired social interactions [198]. While these data suggest that dysgenesis of dendritic spines may occur in TS, the study of dendritic spines in TS mouse models has provided somewhat conflicting results. Either Cre-mediated *Tsc1* or *Tsc2* gene deletion in dissociated neuronal cultures from immature mice (embryonic-day 20 or postnatal-day 3) resulted in fewer dendritic spines, and most of them had an immature filopodia-like morphology [183,199]. However, dendritic spine density was not affected when *Tsc1* was deleted in vivo by virus-induced Cre expression in floxed *Tsc1* mice between the 2nd and 3rd postnatal week [192]. Consistently, dendritic spine density and morphology were not affected in 3-week old *Tsc2* heterozygous mice, and after conditional deletion of *Tsc1* mice, though spine density is higher at 1-month of age [200]. Since overproduced dendritic spines are pruned between the 2nd and 3rd postnatal week of life [201], the seemingly conflicting results above could reflect an initial deficit in spinogenesis followed by impaired spine pruning, which results in higher spine densities in 1-month old mice. In support of potential pharmacological therapies, the mTOR inhibitor rapamycin normalizes dendritic spine density in 3-week old *Tsc2* heterozygous mice [200]. Rapamycin did not affect dendritic spine density in younger *Tsc2* heterozygous mice [199], which further supports the notion intact mTOR signaling is required for dendritic spine maturation after the initial spinogenic period, i.e., during activity-dependent pruning and/or morphological maturation.

4. mTOR: a convergence point of spine dysgenesis and synaptopathologies in ASD

Dysgenesis of dendritic spines occurs in the majority of individuals afflicted with ARDs, as well as in most experimental mouse models of these syndromes. It would, therefore, follow that there must be a converging deregulated molecular pathway downstream of the affected genes and upstream of dendritic spine formation and maturation. Identifying this pathway will not only define a causal common denominator in autism-spectrum disorders, but also open new therapeutic opportunities for these devastating conditions.

The Ras/ERK and PI3K/mTOR pathways, which regulate protein translation in dendrites near excitatory synapses, have received the most attention as such candidate convergence points [202–205]. Together with the developmental profile of dendritic spine density and similar synaptic plasticity impairments after their experimental manipulation, the roles of Ras/ERK and PI3K/mTOR in all those processes support this hypothesis. The first indications were the realization that FMRP is a repressor of dendritic protein translation, localizes to dendrites near spine synapses, and modulates elements directly downstream of the Ras/ERK and PI3K/mTOR pathways [165]. Extensive work has demonstrated that key components of these signaling pathways are affected in all the ARDs discussed above (Fig. 2). For example, RCAN1 (located in the DS critical region) interacts with FMRP, and their deregulation leads to comparable deficits in dendritic protein translation [63,64]. The TS-affected proteins TSC1 and TSC2 are regulators of Rheb, and loss-of-function mutations in their genes result in higher activity of mTOR. ARC is translated in dendrites through the activation of the Ras/ERK pathway downstream of mGluR, and is the most affected protein by *Ube3a* deficiency in AS [96], although it is also deregulated in FXS [206] and TS [207]. The levels of mGluR and BDNF are lower in mouse models of RTT [130–132,208,209], which are upstream in both the Ras/ERK [210] and PI3K/mTOR pathways [211], and result in lower levels of the serine/threonine kinase Akt and mTOR in MeCP2-deficient mice [212]. Phosphatase and tensin homolog (PTEN), a protein often mutated in autistic patients [213–218], inhibits the activation of PDK by PI3K [219,220].

Though many of the discussed ARDs affect multiple signaling pathways, the significant overlap on mTOR strongly suggests it is a critical convergence point. While mTOR activity usually increases dendritic protein translation, heightened mTOR activity in TS inhibits the synthesis of proteins necessary for stabilization of mGluR-dependent LTD [191]. These data, together with previous reports of lower mTOR levels resulting in reduced protein translation, suggest that mTOR activity levels need to be within a proper range to support activity-dependent synaptic plasticity

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[221]. Intriguingly, those ARDs with impaired mTOR-dependent translation (TS and RTT) show impaired LTD, whereas those with heightened dendritic protein translation (DS, AS and FXS) display elevated LTD [56,63,222,223]. In addition, there is a correlation between the magnitude of dendritic spine pruning, LTD, and dendritic protein translation: ARDs with excessive pruning (DS, FXS and perhaps AS) show heightened dendritic protein translation and LTD, whereas those with impaired pruning display lower protein translation and LTD (TS and RTT). Indeed, LTD in the hippocampus leads to dendritic spine shrinkage and subsequent spine synapse pruning [30,31,224,225], and deficiencies in mGluR-LTD disrupt the elimination of spine synapses in the cerebellum [226]. Though there are many factors and pathways involved in the pruning of dendritic spines and their excitatory synapses, these correlations suggest that mTOR is a potential site of therapeutic intervention for autism-related disorders. In support of this notion, studies in both FXS and TS show alleviation of both synaptic and behavioral phenotypes after treatment of the mTOR inhibitor rapamycin [227,228]. It is tempting to speculate that similar treatments will be effective to alleviate synaptopathologies and autistic behaviors in other ARDs.

5. Conclusion

Cajal once postulated, "the future will prove the great physiological role played by the dendritic spines" [229]. And indeed, it is now widely accepted that dendritic spines are the site of neuronal plasticity of excitatory synapses and the focal point for synaptopathophysiologies of ARDs. Individuals and mouse models of ARDs all display spine dysgenesis, with mTOR-regulated protein translation being a critical point of convergence. Deviations from optimal levels of protein synthesis correlate with the magnitude of dendritic spine pruning and LTD in ARDs. Alleviation of heightened mTOR activity rescues both synaptic and behavioral phenotypes in FXS and TS animals. Correcting mTOR signaling levels also reversed ARD phenotypes in adult fully symptomatic mice, challenging the traditional view that genetic defects caused irreversible developmental defects [230]. More excitingly, these observations demonstrate the potential of pharmacological therapies for neurodevelopmental disorders. The list of ARDs that have been reversed in adult symptomatic mice continues to grow, and also includes RTT [231], DS [232,233], and AS [92]. Together, these findings demonstrate the remarkable plastic nature of the brain and imply that if the causal denominator of ARDs could be found and therapeutically targeted, we may be able to allow the ARD brain to rewire itself and relieve clinical symptoms once believed to be irreversible. The analysis of correlative physiological and behavioral phenotypes and identification of the common mTOR pathway will hopefully provide such potential targets.

Conflict of interest

The authors do not have competing financial interests.

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