Dendrite and Spine Modifications in Autism and Related Neurodevelopmental Disorders in Patients and Animal Models

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ABSTRACT: **Dendrites and spines are the main neuronal structures receiving input from other neurons and glial cells. Dendritic and spine number, size, and morphology are some of the crucial factors determining how signals coming from individual synapses are integrated. Much remains to be understood about the characteristics of neuronal dendrites and dendritic spines in autism and related disorders. Although there have been many studies conducted using autism mouse models, few have been carried out using postmortem human tissue from patients. Available animal models of autism include those generated through genetic modifications and those non-genetic models of the disease. Here, we review how dendrite and spine morphology and number is affected in autism and related neurodevelopmental diseases, both in human, and genetic and non-genetic animal models of autism. Overall, data obtained from human and animal models point to a generalized reduction in the size and number, as well as an alteration of the morphology of dendrites; and an increase in spine densities with immature morphology, indicating a general spine immaturity state in autism. Additional human studies on dendrite and spine number and morphology in postmortem tissue are needed to understand the properties of these structures in the cerebral cortex of patients with autism.** Develop Neurobiol 00: 000–000, 2016

Keywords: **autism; dendrite; spine**

INTRODUCTION

Dendrite and Spine Development and Plasticity

Dendrites and spines are the main neuronal structures receiving input from other neurons and glial cells, and their morphology is one of the crucial factors determining how signals coming from individual synapses are integrated. Dendrite and spine modifications have been described in many disease states, however, much remains to be understood about the characteristics of neuronal dendrites and dendritic spines in autism and related disorders. Here we review the current knowledge on dendrite and spine modifications obtained from studies of postmortem human tissue from patients with autism and from those conducted using autism animal models.

Dendrites are the main information-receiving elements in neurons. The complex morphology of the dendritic tree and its properties enables neurons to

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receive and compute input coming from other cells. Therefore, proper dendrite morphology is crucial for normal nervous system functioning. Most dendrites form during development succeeding a pattern of slow dendrite growth, followed by a very fast period of dendritic extension and a long period of stabilization of the dendritic arbor (Williams and Truman, 2004). While the development of dendritic trees is associated with high rates of branch additions and retractions, the mature dendritic arbor is less plastic with a very low branch turnover under basal conditions. Nevertheless, dendritic arbors in the mature nervous system preserve some degree of plasticity. Pyramidal neuron basal dendrites in the prefrontal cortex show a steady growth starting at 17 weeks of gestation (WG) up to age 1 year, with little growth thereafter (Mrzljak et al., 1992; Koenderink et al., 1994). In addition, some pyramidal cells, as those in layer IIIC, display a second period of dendritic growth, starting at the end of the second year and continuing in the third year. Thus, some pyramidal neurons appear to show a biphasic pattern of postnatal dendritic development. Furthermore, the childhood period is characterized by transient increase in size of pyramidal cell somata. These structural changes occur during both the period of rapid cognitive development in preschool children and the period of protracted cognitive maturation during childhood, puberty, and adolescence (Petanjek et al., 2008).

Dendrite characteristics, including dendritic spine number, total dendritic length, mean segment length, and dendritic segment count are different between high and low integrative cortical regions (Jacobs et al., 2001). Dendritic systems in primary regions are consistently less complex than in hetero-modal and supra-modal areas. For example, total dendritic length in the fronto-polar prefrontal cortex is 31% greater than that in the primary somatosensory cortex (Jacobs et al., 2001). In the human prefrontal cortex, an average dendrite in adult contains about 10–50 segments, a total length per dendrite of about 200–500 μm, and radial distances to the terminal tips of 100–150 μm (Koenderink and Uylings, 1995; Jacobs et al., 2001; Ramakers, 2005). The processes of dendritic arbor development and stabilization are regulated by an intrinsic genetic program and a by a wide variety of extracellular signals, either globally at the whole-cell level or locally within dendrites (Skalecka et al., 2016). Actin and microtubule cytoskeleton organization is indispensable for the formation of proper dendrite morphology. Alterations of this organization result in defects on the dendrite shape and size, a phenomenon that takes place in most of neurodevelopmental and neurodegenerative diseases (Urbanska et al., 2008).

Dendrites contain dendritic spines that are microscopic membrane protrusions comprising the receptive postsynaptic compartment of excitatory synapses in the brain (Gray, 1959; Guillery, 2000). Spines contain neurotransmitters and neuropeptides, receptors, signaling molecules, as well as ion channels and other proteins that participate in synaptic transmission and activity-dependent synaptic plasticity (Sala and Segal, 2014). Dendrites of a single neuron can contain hundreds to thousands of spines and a typical mature spine has a single synapse located at its head. The basic features of the apical and basal dendrites of pyramidal neurons develop between 17 and 25 WG in the human prefrontal cortex. The ingrowth of afferent fibers into the cortical plate between 26 and 34 WG coincides with intensive dendritic differentiation and the appearance of spines on pyramidal neuron dendrites (Mrzljak et al., 1988; Petanjek et al., 2008). Synapses are produced in numbers that exceed those present in the adult brain, but later experience an activity-dependent stabilization and selective elimination (Changeux and Danchin, 1976). This synaptic pruning occurs at puberty and continues beyond adolescence and throughout the third decade of life (Huttenlocher, 1979; Petanjek et al., 2011). Spines undergo constant turnover and morphology modifications that are dependent on stimuli, environment, and location. These are capacities that are key for synaptic plasticity. (Fiala et al., 2002; Sala and Segal, 2014).

Spine morphology, number, and density are crucial factors in determining the strength and stability of the synaptic transmission (Sabatini and Svoboda, 2000; Segev and London, 2000; Gulledge et al., 2005; Luebke et al., 2010; Sala and Segal, 2014). Functions such as learning, memory, behavior, and motor coordination require spine modifications to regulate synaptic transmission (Fiala et al., 2002). The morphology of dendritic spines is highly variable and spines come in a wide variety of shapes and sizes, typically 0.5–2 microns in length (Harris and Kater, 1994). Based on its morphology, dendritic spines have been classified as thin, stubby, mushroom, among others. (Chang and Greenough, 1984). Spines are classified into specific morphologies based on the spine's head to neck diameter ratio. For example: mushroom spines have a large head and a narrow neck, stubby spines have no obvious constriction between the head and the attachment to the shaft, and thin spines have a smaller head and a narrow neck (Nimchinsky et al., 2002). Spine morphology is related with function. Mushrooms and stubby spines are stable, persist for long periods of

time, and form strong excitatory synapses (Trachtenberg et al., 2002; Kasai et al., 2003), while thin spines are highly motile, unstable, and often short-lived, representing weak or silent synapses (Rochefort and Konnerth, 2012). In general, large spines have proportionately larger synapses. Actin and actin binding proteins are enriched in the dendritic spine heads, with F-actin dynamics being the driving force of spine morphological remodeling. The actin cytoskeleton sustains the formation of dendritic spines during neuron development and their enlargement and shrinkage upon increased and decreased synaptic activity, respectively (Chazeau and Giannone, 2016). Rapid morphological plasticity of spines raise the possibility that spine categories, rather than being intrinsically different populations of spines, represent instead temporal snapshots of a single dynamic phenomenon (Parnass et al., 2000).

Numerous neurodevelopmental and neurodegenerative pathologies present with dendritic and spine dysfunction. However, dendritic and spine loss is also a common finding in aging, which is a main risk factor for most neurodegenerative diseases. Neurodevelopmental diseases examined so far where dendritic and spine modifications have been described include schizophrenia, Down's syndrome, fragile X syndrome, Angelman's syndrome, Rett's syndrome, and autism. Among neurodegenerative diseases containing these modifications are schizophrenia, Alzheimer's disease, dementia, Parkinson's disease, Huntington's disease, and prion diseases. Brain areas where these modifications have been described include the cerebral cortex with a main emphasis on the prefrontal cortex and the hippocampus (Phillips and Pozzo-Miller, 2015). While the mechanism of dendritic and spine failure in neurodegenerative diseases is believed to be the accumulation of pathogenic protein aggregates at synapses, dendritic and spine modification in neurodevelopmental diseases is thought to arise from a lack of proper genesis or maturation of these structures (Herms and Dorostkar, 2016). Next, we will review dendritic and spine modifications associated with Autism Spectrum Disorders (ASD) and related pathologies in patients and animal models.

AUTISM SPECTRUM AND RELATED DISORDERS

Autism Spectrum Disorders span four separate disorders including classical autism disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified (DSM-V) (American Psychiatric Association, 2013). ASD are neurodevelopmental disorders characterized by alteration in communication, social interaction, and repetitive and obsessive behavior (American Psychiatric Association, 2013). Each of these disorders present with similar symptomatology; however, their etiologies and underpinning molecular and genetic mechanisms are not always shared. Because of these differences, and in order to discern distinct pathologies, it is advised to investigate each of these conditions as independent entities. The understanding of the anatomy and pathology of the autistic brain is at this moment very limited. Very few postmortem studies have been carried out using postmortem tissue samples from subjects with autism. One of the main reasons for the lack of information about the autistic brain is the scarcity of brain tissue available for research. Moreover, postmortem brain tissue collected is not always in optimal condition due to high postmortem intervals, that is, the time since the donor passed away until the brain is retrieved and immersed in fixative. This is due, to a large extent, to the lack of support and funding for post-mortem human studies in comparison to animal model studies and the emphasis on molecular aspects of these disorders. Most of the postmortem studies using autism tissue have focused on understanding the cellular types that are affected in autism (Courchesne et al., 2011; Camacho et al., 2014; Kim et al., 2015; Hashemi et al., 2016). In contrast to the low number of studies in human tissue, those in genetic animal models are abundant. However, although informative, these studies need to be properly interpreted since we still have a poor understanding of specific characteristics of dendrites in the human brain and those in brains of animal models. For example, direct comparison of protein components from human and mouse excitatory synapses showed significant inter-species differences in some families of key postsynaptic density proteins including glutamatergic neurotransmitter receptors and adaptor proteins. Furthermore, a set of molecules enriched in the human postsynaptic density that could be involved in dendrite and spine structural plasticity has been described in human but not in mice (Bayes et al., 2012). We next review dendrite and spine morphology modifications associated with autism and related neurodevelopmental diseases, both in human and animal models of disease.

Classical Autism

Much remains to be understood about the characteristics of neuronal dendrites and dendritic spines in autism. Though there have been many studies

conducted using autism mouse models, few have been carried out using human tissue from autism patients. Specifically, dendrite and spine studies in the human brain are limited to a few publications. The first report on this topic was by Williams et al. who, in 1980, performed a neuropathology examination including analysis of cortical neurons impregnated with Golgi in a toddler, an adolescent, and two adult patients. They discovered an apparent reduction in the density of spines on the dendrites of some pyramidal neurons in the adolescent and one of the adult patients. In the toddler patient, many pyramids appeared to have a reduced density of dendritic spines especially along the mid-portion of their apical shafts. In all three cases, dendritic spines were judged to be of normal morphology (Williams et al., 1980). Raymond et al. reported that neurons in the region CA4 and CA1 of the hippocampus of autistic children have reduced dendritic branching compared with those in control hippocampus (Raymond et al., 1996), and Mukaetova-Ladinska et al. noted that the dorsolateral prefrontal cortex in two adult individuals with autism presented with reduced dendrite numbers (Mukaetova-Ladinska et al., 2004). In 2010, the seminal work of Hutsler and Zhang on dendritic spines on Golgi-impregnated cortical pyramidal cells in the superficial and deep cortical layers of frontal, temporal, and parietal regions of ASD subjects and age-matched control cases, showed that pyramidal apical dendrites presented with greater spine densities within layer II of each cortical location and within layer V of the temporal lobe. They also found that high spine densities were associated with decreased brain weights and were most commonly found in ASD subjects with lower levels of cognitive functioning (Hutsler and Zhang, 2010). Even though the amount of data collected from human tissue is scarce, it is clear that an alteration in dendritic and spine densities is related to the pathogenesis of autism. However, the fact that different spine densities were reported points out that the spine number and size may be dependent on the area of cerebral cortex, the cortical layer, and the age of the patient, among other variables.

Fragile X Mental Retardation Gene (FMR1)

Fragile X (FXS) is an inherited neurodevelopmental disease characterized by being the most widespread single gene cause of autism, and the second most frequent chromosomal disorder associated with a developmental disability. FXS symptoms include intellectual disability, autism, and hyperactivity (Saldarriaga et al., 2014). In addition, most of the young children with FXS present with language delay and anxiety. FXS is caused by the expansion of a CGG trinucleotide repeat in the Fragile X mental retardation 1 (*Fmr1*) gene that results in a failure to express the fragile X mental retardation protein (FMRP) (Saldarriaga et al., 2014). Repeat lengths less than 45 CGG are associated with typical development, repeat lengths of more than 200 CGG result in FXS, while repeat lengths between 55 and 200 CGG result in fragile X premutation (PM), (Hagerman and Hagerman, 2015).

FMRP is localized to neurons, specifically to dendrites (Devys et al., 1993; Feng et al., 1997), and it has been suggested it might play a role on dendritic growth. Accordingly, FXS brains present with abnormal dendritic branching and synaptic immaturity (Rudelli et al., 1985). Specifically, FXS patients exhibit higher density of dendritic spines on distal segments of apical and basal dendrites in the cingulate and temporal cerebral cortex. These spines tend to have an increased incidence with immature morphology and a decreased incidence with mature morphologies (Hinton et al., 1991). In agreement with these data, examination of human Golgi-Kopsch material has shown that FXS patients exhibited significantly longer dendritic spines and fewer short dendritic spines than did control subjects in both temporal and visual cortical areas. Similarly, FXS patients exhibited significantly more dendritic spines with an immature morphology and fewer with more mature morphology in both cortical areas. In addition, they had a higher density of dendritic spines than did controls on distal segments of apical and basilar dendrites in both cortical areas (Irwin et al., 2001). Data available from animal models where the *Fmr1* gene has been knocked out is in agreement with that obtained from humans with FXS. For example, FXS mice exhibited significantly more long dendritic spines and significantly fewer short dendritic spines than control mice. Similarly, FXS mice exhibited significantly more dendritic spines with an immature morphology and significantly fewer with a more mature morphology (Comery et al., 1997; Irwin et al., 2002; Galvez et al., 2003; Galvez and Greenough, 2005; McKinney et al., 2005). In addition, dendritic spines on apical dendrites of layer V pyramidal cells in the occipital cortex of the *Fmr1* knockout mice were often thin and tortuous, paralleling the human syndrome and suggesting that FMRP expression is required for normal spine morphological development (Comery et al., 1997). Layer V neurons in the barrel cortex of the *Fmr1* knockout mice also showed an increase in spine density and a decrease in spine length in the first

postnatal days as well as a developmental delay in the downregulation of spine turnover and the transition from immature to mature spine subtypes, which altogether demonstrate that a lack of FMRP delays spine stabilization (Nimchinsky et al., 2001; Cruz-Martin et al., 2010). Purkinje cell-specific knockout of *Fmr1* also presented with elongated spines (Koekkoek et al., 2005). Moreover, it has been demonstrated that *Fmr1* knockout in mice leads to alterations in the distribution of the dendritic arbor in motor neurons, consistent with slower rates of extension and abnormal pruning of intermediate dendritic segments (Thomas et al., 2008). In addition to dendrite and spine alterations in morphology, impairments of regulators of synaptic structure and function, such as PSD-95, have been described in FXS (Ifrim et al., 2015). Overall, data collected from FXS mice are similar to those found in the human condition and further support a role for the FXS mental retardation protein in the dendritic spine developmental processes. Increased spine density in the knockout mice may reflect impaired developmental organizational processes of synapse stabalization, elimination, or pruning.

Studies of dendritic morphology have been also performed in CGG knock-in mice. These mice are a model for premutation and for fragile X-associated tremor/ataxia syndrome (FXTAS), a disease present in some PM patients (>200 CGG repetitions). FXTAS is a neurodegenerative disease that causes tremors, ataxia, and cognitive impairment and is characterized by an increase in the levels of FMRP mRNA and normal or slightly decreased FMRP expression (Hagerman, 2013). In addition, PM carriers have been also shown to suffer attention deficit hyperactivity disorder (ADHD), social deficits, ASD, and occasional intellectual disability, and other symptoms associated with autism while in childhood. One of the available CGG knock-in mouse models present with fewer dendritic branches, reduced total dendritic length, and higher frequency of longer dendritic spines in layer II/III pyramidal neurons in primary visual cortex (Berman et al., 2012). These data indicate that both the lack and a decrease of the levels of FMRP and/or the increased mRNA may be altering dendritic morphology and function.

Although the exact nature of the spine abnormality in FXS is not yet fully understood, FMRP is known to interact with a series of proteins, some of which have been implicated in dendrite and spine regulation. One of them is the cytoplasmic FMRP-interacting protein 1 (CYFIP1), a functional partner of FMRP that is located within a hot spot for ASD (chr15q11.2). Together with FMRP, CYFIP1 represses neuronal protein synthesis and regulates actin-nucleating activity. This process strongly influences the formation, retraction, motility, stability, and shape of dendritic spines (De Rubeis et al., 2013). C*YFIP1* mRNA is downregulated in a subgroup of FXS patients who present with Prader-Willi phenotype with severe ASD and obsessive-compulsive behavior (Nowicki et al., 2007). Overexpression of CYFIP1 *in vitro* leads to increased dendritic complexity. On the other hand, neurons derived from a *Cyfip1* haploinsufficient animal exhibit deficits in dendritic complexity as well as an altered ratio of immature to mature spines in hippocampal CA1 neurons. Both *Cyfip1* overexpression and haploinsufficiency increase the number of immature dendritic spines (Pathania et al., 2014). Another protein that interacts with FMRP is *TAOK2*, whose mRNA is a direct target of FMRP (Darnell et al., 2011). The gene encoding TAOK2 in human is located in chromosome 16p11.2, a region that has been shown to carry substantial susceptibility for ASD (Weiss et al., 2008). TAOK2 selectively modulates actin cytoskeleton organization and, when downregulated, impairs basal dendrite formation *in vivo*; however, it does not affect the apical dendrite (De Anda et al., 2012). TAOK2 interacts with Neuropilin 1 (NRP1), a receptor protein that binds the secreted guidance cue Semaphorin 3A (Sema3A). TAOK2 overexpression restores dendrite formation in cultured cortical neurons from NRP1(Sema) mice, which express Nrp1 receptors incapable of binding Sema3A. These data suggest that TAOK2 is involved in dendritic formation in autism (De Anda et al., 2012).

Several other approaches *in vivo* and *in vitro* have been able to revert the effect of *Fmr1* knockdown on dendrite and spine morphology. FMRP has been shown to interact *in vitro* with p21-activated kinases (PAK), an enzyme known to play a critical role in actin polymerization and dendritic spine morphogenesis. The greater spine density and elongated spines in the cortex (morphological synaptic abnormalities commonly observed in the *Fmr1* knockout) are at least partially restored by postnatal expression of a dominant negative *PAK* transgene in the forebrain (Hayashi et al., 2007). Interestingly, Amyloid β-protein precursor (AβPP) is also upregulated in the FXS mouse model (Napoli et al., 2008). β-amyloid induces the formation of cytoplasmic rod-shaped bundles of filaments composed of cofilin and actin in Alzheimer's disease (Walsh et al., 2014). Cofilin binds actin subunits in F-actin, a key element on spine morphological remodeling, and severs actin filaments at low cofilin/actin ratios while stabilizes them at high cofilin/actin ratios (Bamburg and

Bernstein, 2016). Genetic reduction of AβPP in the *Fmr1* knockout mice rescues the ratio of mature versus immature dendritic spines (Westmark et al., 2011).

It has been proposed that the alterations in dendritic arborization and spinogenesis in FXS occur as a compensatory response to counteract the compromised postsynaptic activity during uncontrollable metabotropic glutamate receptor (mGluR)-dependent long-term depression. When postsynaptic and electrical activities become dampened in FXS, dendritic trees can increase their sensitivity to brain-derived neurotrophic factor (BDNF). Then, this activity-dependent elevation of the BDNF signaling can strategically alter dendritic morphologies to foster branching and develop spine structures in order to improve the postsynaptic response in FXS (Kim and Cho, 2014). Accordingly, treatment of *Fmr1* knockout mice with the mGluR antagonist 2-methyl-6 (phenylethynyl)-pyridine (*MPEP*) results in a rescue of dendritic spine morphology (Su et al., 2011; Kim and Cho, 2014). FMRP also has a role in the regulation of *PSD-95* translation. *PSD-95* mRNA is locally translated in dendrites, induced by mGluR activation and dysregulated in *Fmr1* knockout neurons (Muddashetty et al., 2011). Impairments in the local synthesis of PSD-95, a critical regulator of synaptic structure and function, affect dendritic spine development and synaptic plasticity in FXS (Ifrim et al., 2015).

Overall, FXS mouse models point to a direct or indirect role of FMRP on the modification of actin polymerization in spine and dendrites. An alteration on the process of actin polymerization renders the dendrite and spine morphological alterations characteristic of FXS.

Rett Syndrome

Knockdown of the X-linked gene for the methyl CpG binding protein 2 (MECP2), a transcriptional repressor that suppresses microRNA processing (Cheng et al., 2014), leads to Rett syndrome (RTT). RTT is a childhood neurological disorder characterized by intellectual disability and autism (Chahrour and Zoghbi, 2007; Ramocki et al., 2010). Golgi studies of cerebral cortical apical and basal dendrites have demonstrated a reduced dendritic arborization in the pyramidal neurons of layer III and V in frontal, motor and inferior temporal regions in RTT brains (Armstrong et al., 1995). Similar results were obtained in the RTT frontal cortex where decreased numbers and regional loss of dendritic spines were found (Belichenko et al., 1994). Accordingly, levels and phosphorylation of microtubule-associated proteins (MAPs), which stabilize microtubules, were found to be altered at different stages of dendritic formation in patients with RTT syndrome (Kaufmann et al., 2000). It has also been widely reported that loss of MeCP2 in mice results in abnormal dendritic spine morphology as well as decreased pyramidal dendritic arbor complexity and spine density (Fukuda et al., 2005; Belichenko et al., 2009; Tropea et al., 2009; Landi et al., 2011; Chapleau et al., 2012; Nguyen et al., 2012; Stuss et al., 2012). Concomitantly, MeCP2 overexpression induces dendritic overgrowth in mice, increasing the number of higher order branches of apical dendritic arbors in layer V pyramidal neurons. These mice suffer from higher spine gain and loss, with a net bias in favor of spine elimination reflecting the persistence of an immature mental state (Jugloff et al., 2005; Jiang et al., 2013).

OTHER AUTISM RELATED GENES

Mammalian target of rapamycin (mTOR) is a highly conserved serine/threonine protein kinase that controls cell and organismal growth and is induced by growth factors and nutrients (Laplante and Sabatini, 2012). mTOR has been shown to play a role in shaping the actin cytoskeleton with a particular role in dendritogenesis (Kumar et al., 2005; Kim et al., 2009; Thomanetz et al., 2013; Skalecka et al., 2016). Proteins that repress mTOR have been linked to autism and also play a role in dendritic and spine morphology. These include the phosphatase and tensin homolog (PTEN) and the tuberous sclerosis complex proteins (TSC) 1 and 2 (Weston et al., 2014). PTEN is a lipid and protein phosphatase that represses the PI3K/AKT/mTOR signaling pathway, ultimately modulating cell growth and protein translation (Orloff et al., 2013). The presence of mutations in the gene for the PTEN protein has been discovered in individuals with autism spectrum disorders. Mice with mutations or deletions of PTEN show abnormal social interaction and exaggerated responses to sensory stimuli. Deletion of PTEN in neurons in the cerebral cortex and hippocampus of these mice results in hypertrophic and ectopic dendrites and axonal tracts with increased synapses (Kwon et al., 2006). However, PTEN knockdown in the basolateral amygdala leads to a significant decrease in total spine density of distal dendrites and increased mushroom spine density and size with a corresponding decrease in thin protrusion density of more distal segments (Haws et al., 2014). *Tsc1* also encodes a protein that represses mTOR signaling. Mutations in *TSC1* or *TSC2* tumor suppressor genes lead to tuberous

sclerosis (TS), a disorder that presents with mental retardation and autism. It is known that the TSC pathway regulates growth and synapse function in neurons, and that the loss of Tsc2 triggers enlargement of somas and dendritic spines in the hippocampal pyramidal neurons of mice and rats (Tavazoie et al., 2005). These data support the role of mTOR in the regulation of dendritic and spine morphology in autism.

Additional studies of the dendritic arbor in animal models of autism have rendered data that match previous observations in humans. For example, MAP/microtubule affinity-regulating kinase 1 (MARK1) overexpression has been suggested to be responsible for changes in dendritic functioning. High-resolution single-nucleotide polymorphisms (126 SNPs) genotyping across the chromosome 1q41-q42 region, followed by a MARK1-tagged-SNP association study in 276 families with autism, showed that several SNPs within the MARK1 gene are significantly associated with ASD. Both overexpression and silencing of MARK1 resulted in significantly shorter dendrite length and modified dendritic transport speed in mouse neocortical neurons (Maussion et al., 2008). Another gene linked to dendritic maturation in autism is EPAC2, a guanine nucleotide exchange factor (GEF) for the Ras-like small GTPase RAP that is highly enriched in dendrites. Overexpression of a rare coding variant of *Epac2*, an exchange protein directly activated by cyclic AMP2, found in human subjects diagnosed with autism, also impaired basal dendritic morphology. Knockdown of *Epac2* in layer II and III cortical neurons via *in utero* electroporation induces a state of reduced basal dendritic architecture in mice. Moreover, *in vitro Epac2* knockdown in mature cortical neurons mimics this effect. It is known that components of the Ras/Epac2/Rap pathway exhibit differential abundance in basal versus apical dendritic compartments. Concomitantly, *Epac2* knockdown robustly and selectively reduces basal dendrite complexity in cortical pyramidal neurons (Srivastava et al., 2012). Another animal model linked to autism includes the siRNA-mediated *KIAA2022* knockdown mouse, a model of the X-linked intellectual disability (XLID) syndrome. This model that presents with a marked impairment in neurite outgrowth, impacting both dendrites and axons (Van Maldergem et al., 2013). Studies of prickle2 (PK2), a postsynaptic non-canonical Wnt signaling protein, reveal that mice with a disruption in *Pk2* display behavioral abnormalities including altered social interactions, learning abnormalities, behavioral inflexibility, and other symptoms comparable to those in patients with autism. *Pk2* disruption in mouse hippocampal neurons leads to a reduction in dendrite branching and synapses (Sowers et al., 2013). Other proteins, such as the CNTN proteins (CNTN4, CNTN5, and CNTN6), a family of Ig cell adhesion molecules (IgCAMs), have been associated with ASD (Zuko et al., 2013) and are involved in controlling neurite outgrowth (Mercati et al., 2013).

Other proteins that have been associated with autism and have a role in spine morphology include Shank proteins and UBE3A. Mutations of the Shank family of scaffold proteins, in particular Shank3, are linked to a familial form of autism (Durand et al., 2007). When overexpressed in cultured hippocampal neurons, Shank proteins strongly promote the enlargement of dendritic spines, particularly the spine heads (Sala et al., 2001). Loss of function of the maternally inherited allele for the UBE3A ubiquitin ligase gene causes Angelman syndrome (AS), which is characterized by severe neurological impairment and motor dysfunction. In addition, UBE3A lies within the 15q11-q13 chromosomal region, where duplications can cause autism. In human, AS dendritic spines have an inconsistent morphology, including high variability in spine neck length and head size. AS also presents with lower spine density in Purkinje cells, pyramidal neurons of the hippocampus, and the cortex of Ube3a maternal-deficient mice (Dindot et al., 2008).

NON-GENETIC AUTISM MODELS

Most of the non-genetic mouse models of autism rely on prenatal exposure to adverse environmental factors such as teratogens and viral infections. These factors are suspected to contribute to the etiology of ASD based on epidemiological data. Viruses used in the autism model include the rubella virus and the flu virus; Teratogenic compunds include valproic acid and thalidomide exposure. Many other non-genetic models of autism exist; however, very little data on the state of dendrite and spine morphology is available in these models.

Scarce data in this topic includes that from a model of maternal infection and associated maternal immune activation (MIA) during pregnancy. MIA increases the risk for neurodevelopmental disorders in offspring. In non-human primates, apical dendrites in MIA-offspring were smaller in diameter and exhibited a greater number of oblique dendrites (Weir et al., 2015). More is known about the valproic acid (VPA) model of autism. Valproic acid is a blocker of histone deacetylase and is widely used to treat epilepsy, bipolar disorders, and migraine, and its administration during pregnancy has been shown to

increase the child's risk for autism. The VPA animal model of autism presents with retracted neuronal arborization in the hippocampus (Bringas et al., 2013). However, in other brain areas, such as the prefrontal cortex, nucleus accumbens, and basolateral amygdala, an increase in neuronal arborization has been reported. VPA animals also present with a reduced number of spines in the prefrontal cortex, dorsal hippocampus and basolateral amygdala, but an increase in the dendritic spine density in accumbens and ventral hippocampus (Bringas et al., 2013; Raza et al., 2015). Related to these effects on dendrite morphology, VPA treatment has been shown to induce an increase of F-actin affecting cell morphology (Walmod et al., 1999).

These data indicate that in both genetic and nongenetic models of autism, dendrites, and spines present with an alteration in number, size, and morphology.

CONCLUSION

Dendritic spine number and morphology are crucial factors determining the strength and stability of the synaptic transmission. Dendrite and spine modifications have been described in many diseases; however, much remains to be understood about the characteristics of neuronal dendrites and dendritic spines in autism and related disorders. Overall, data obtained from human and animal models of autism point to a generalized reduction on the number of dendrites as well as an alteration of their morphology. Specifically, autism has been linked to a decrease in the density of spines with mature morphology, indicating a general spine immaturity state in autism. Additional human studies focused on the number, size, and morphology of dendrites and spines are needed in order to understand the properties of these structures in the cerebral cortex of autism patients.

REFERENCES

American Psychiatric Association. 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: APA.

Armstrong D, Dunn JK, Antalffy B, Trivedi R. 1995. Selective dendritic alterations in the cortex of Rett syndrome. J Neuropathol Exp Neurol 54:195–201.

Bamburg JR, Bernstein BW. 2016. Actin dynamics and cofilin-actin rods in Alzheimer disease. Cytoskeleton, Feb 13.

Bayes A, Collins MO, Croning MD, van de Lagemaat LN, Choudhary JS, Grant SG. 2012. Comparative study of human and mouse postsynaptic proteomes finds high compositional conservation and abundance differences for key synaptic proteins. PloS One 7:e46683.

Belichenko PV, Oldfors A, Hagberg B, Dahlstrom A. 1994. Rett syndrome: 3-D confocal microscopy of cortical pyramidal dendrites and afferents. Neuroreport 5:1509–1513.

Belichenko PV, Wright EE, Belichenko NP, Masliah E, Li HH, Mobley WC, Francke U. 2009. Widespread changes in dendritic and axonal morphology in Mecp2-mutant mouse models of Rett syndrome: Evidence for disruption of neuronal networks. J Comp Neurol 514:240–258.

Berman RF, Murray KD, Arque G, Hunsaker MR, Wenzel HJ. 2012. Abnormal dendrite and spine morphology in primary visual cortex in the CGG knock-in mouse model of the fragile X premutation. Epilepsia 53 Suppl 1:150–160.

Bringas ME, Carvajal-Flores FN, Lopez-Ramirez TA, Atzori M, Flores G. 2013. Rearrangement of the dendritic morphology in limbic regions and altered exploratory behavior in a rat model of autism spectrum disorder. Neuroscience 241:170–187.

Camacho J, Ejaz E, Ariza J, Noctor SC, Martinez-Cerdeno V. 2014. RELN-expressing neuron density in layer I of the superior temporal lobe is similar in human brains with autism and in age-matched controls. Neurosci Lett 579C:163–167.

Chahrour M, Zoghbi HY. 2007. The story of Rett syndrome: From clinic to neurobiology. Neuron 56:422–437.

Chang FL, Greenough WT. 1984. Transient and enduring morphological correlates of synaptic activity and efficacy change in the rat hippocampal slice. Brain Res 309:35–46.

Changeux J, Danchin A. 1976. Selective stabilisation of developing synapses as a mechanism for the specification of neuronal networks. Nature 264:705–712.

Chapleau CA, Boggio EM, Calfa G, Percy AK, Giustetto M, Pozzo-Miller L. 2012. Hippocampal CA1 pyramidal neurons of Mecp2 mutant mice show a dendritic spine phenotype only in the presymptomatic stage. Neural Plast 2012:976164.

Chazeau A, Giannone G. 2016. Organization and dynamics of the actin cytoskeleton during dendritic spine morphological remodeling. Cell Mol Life Sci: CMLS, Apr 22.

Cheng TL, Wang Z, Liao Q, Zhu Y, Zhou WH, Xu W, Qiu Z. 2014. MeCP2 suppresses nuclear microRNA processing and dendritic growth by regulating the DGCR8/Drosha complex. Dev Cell 28:547–560.

Comery TA, Harris JB, Willems PJ, Oostra BA, Irwin SA, Weiler IJ, Greenough WT. 1997. Abnormal dendritic spines in fragile X knockout mice: Maturation and pruning deficits. Proc Natl Acad Sci U S A 94:5401–5404.

Courchesne E, Mouton PR, Calhoun ME, Semendeferi K, Ahrens-Barbeau C, Hallet MJ, Barnes CC, et al. 2011. Neuron number and size in prefrontal cortex of children with autism. JAMA 306:2001–2010.

Cruz-Martin A, Crespo M, Portera-Cailliau C. 2010. Delayed stabilization of dendritic spines in fragile X mice. J Neurosci 30:7793–7803.

Darnell JC, Van Driesche SJ, Zhang C, Hung KY, Mele A, Fraser CE, Stone EF, et al. 2011. FMRP stalls ribosomal translocation on mRNAs linked to synaptic function and autism. Cell 146:247–261.

De Anda FC, Rosario AL, Durak O, Tran T, Graff J, Meletis K, Rei D, et al. 2012. Autism spectrum disorder susceptibility gene TAOK2 affects basal dendrite formation in the neocortex. Nat Neurosci 15:1022–1031.

De Rubeis S, Pasciuto E, Li KW, Fernandez E, Di Marino D, Buzzi A, Ostroff LE, et al. 2013. CYFIP1 coordinates mRNA translation and cytoskeleton remodeling to ensure proper dendritic spine formation. Neuron 79:1169–1182.

Devys D, Lutz Y, Rouyer N, Bellocq JP, Mandel JL. 1993. The FMR-1 protein is cytoplasmic, most abundant in neurons and appears normal in carriers of a fragile X premutation. Nat Genet 4:335–340.

Dindot SV, Antalffy BA, Bhattacharjee MB, Beaudet AL. 2008. The Angelman syndrome ubiquitin ligase localizes to the synapse and nucleus, and maternal deficiency results in abnormal dendritic spine morphology. Hum Mol Genet 17:111–118.

Durand CM, Betancur C, Boeckers TM, Bockmann J, Chaste P, Fauchereau F, Nygren G, et al. 2007. Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. Nat Genet 39:25–27.

Feng Y, Gutekunst CA, Eberhart DE, Yi H, Warren ST, Hersch SM. 1997. Fragile X mental retardation protein: Nucleocytoplasmic shuttling and association with somatodendritic ribosomes. J Neurosci 17:1539–1547.

Fiala JC, Spacek J, Harris KM. 2002. Dendritic spine pathology: Cause or consequence of neurological disorders? Brain Res Brain Res Rev 39:29–54.

Fukuda T, Itoh M, Ichikawa T, Washiyama K, Goto Y. 2005. Delayed maturation of neuronal architecture and synaptogenesis in cerebral cortex of Mecp2-deficient mice. J Neuropathol Exp Neurol 64:537–544.

Galvez R, Greenough WT. 2005. 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 Part a 135:155–160.

Galvez R, Gopal AR, Greenough WT. 2003. Somatosensory cortical barrel dendritic abnormalities in a mouse model of the fragile X mental retardation syndrome. Brain Res 971:83–89.

Gray EG. 1959. Axosomatic and axodendritic synapses in the cerebral cortex. J Anat 93:420–433.

Guillery RW. 2000. Early electron microscopic observations of synaptic structures in the cerebral cortex: A view of the contributions made by George Gray (1924-1999). Trends Neurosci 23:594–598.

Gulledge AT, Kampa BM, Stuart GJ. 2005. Synaptic integration in dendritic trees. J Neurobiol 64:75–90.

Hagerman P. 2013. Fragile X-associated tremor/ataxia syndrome (FXTAS): Pathology and mechanisms. Acta Neuropathol 126:1–19.

Hagerman PJ, Hagerman RJ. 2015. Fragile X-associated tremor/ataxia syndrome. Ann N Y Acad Sci 1338:58–70.

Harris KM, Kater SB. 1994. Dendritic spines: Cellular specializations imparting both stability and flexibility to synaptic function. Annu Rev Neurosci 17:341–371.

Hashemi E, Ariza J, Rogers H, Noctor SC, Martinez-Cerdeno V. 2016. The number of parvalbumin-expressing interneurons is decreased in the medial prefrontal cortex in autism. Cereb Cortex, Feb 27.

Haws ME, Jaramillo TC, Espinosa F, Widman AJ, Stuber GD, Sparta DR, Tye KM, et al. 2014. PTEN knockdown alters dendritic spine/protrusion morphology, not density. J Comp Neurol 522:1171–1190.

Hayashi ML, Rao BS, Seo JS, Choi HS, Dolan BM, Choi SY, Chattarji S, et al. 2007. Inhibition of p21-activated kinase rescues symptoms of fragile X syndrome in mice. Proc Natl Acad Sci U S A 104:11489–11494.

Herms J, Dorostkar MM. 2016. Dendritic spine pathology in neurodegenerative diseases. Annu Rev Pathol 11:221–250.

Hinton VJ, Brown WT, Wisniewski K, Rudelli RD. 1991. Analysis of neocortex in three males with the fragile X syndrome. Am J Med Genet 41:289–294.

Hutsler JJ, Zhang H. 2010. Increased dendritic spine densities on cortical projection neurons in autism spectrum disorders. Brain Res 1309:83–94.

Huttenlocher PR. 1979. Synaptic density in human frontal cortex: Developmental changes and effects of aging. Brain: J Neurol 163:195–205.

Ifrim MF, Williams KR, Bassell GJ. 2015. Single-molecule imaging of psd-95 mrna translation in dendrites and its dysregulation in a mouse model of fragile x syndrome. J Neurosci 35:7116–7130.

Irwin SA, Patel B, Idupulapati M, Harris JB, Crisostomo RA, Larsen BP, Kooy F, et al. 2001. Abnormal dendritic spine characteristics in the temporal and visual cortices of patients with fragile-X syndrome: A quantitative examination. Am J Med Genet 98:161–167.

Irwin SA, Idupulapati M, Gilbert ME, Harris JB, Chakravarti AB, Rogers EJ, Crisostomo RA, et al. 2002. Dendritic spine and dendritic field characteristics of layer V pyramidal neurons in the visual cortex of fragile-X knockout mice. Am J Med Genet 111:140–146.

Jacobs B, Schall M, Prather M, Kapler E, Driscoll L, Baca S, Jacobs J, et al. 2001. Regional dendritic and spine variation in human cerebral cortex: A quantitative golgi study. Cereb Cortex 11:558–571.

Jiang M, Ash RT, Baker SA, Suter B, Ferguson A, Park J, Rudy J, et al. 2013. Dendritic arborization and spine dynamics are abnormal in the mouse model of MECP2 duplication syndrome. J Neurosci 33:19518–19533.

Jugloff DG, Jung BP, Purushotham D, Logan R, Eubanks JH. 2005. Increased dendritic complexity and axonal length in cultured mouse cortical neurons overexpressing methyl-CpG-binding protein MeCP2. Neurobiol Dis 19: 18–27.

Kasai H, Matsuzaki M, Noguchi J, Yasumatsu N, Nakahara H. 2003. Structure-stability-function relationships of dendritic spines. Trends Neurosci 26:360–368.

Kaufmann WE, MacDonald SM, Altamura CR. 2000. Dendritic cytoskeletal protein expression in mental retardation: An immunohistochemical study of the neocortex in Rett syndrome. Cereb Cortex 10:992–1004.

Kim SW, Cho KJ. 2014. Activity-dependent alterations in the sensitivity to BDNF-TrkB signaling may promote excessive dendritic arborization and spinogenesis in fragile X syndrome in order to compensate for compromised postsynaptic activity. Med Hypo 83:429–435.

Kim JY, Duan X, Liu CY, Jang MH, Guo JU, Pow-anpongkul N, Kang E, et al. 2009. DISC1 regulates new neuron development in the adult brain via modulation of AKT-mTOR signaling through KIAA1212. Neuron 63: 761–773.

Kim E, Camacho J, Combs Z, Ariza J, Lechpammer M, Noctor SC, Martinez-Cerdeno V. 2015. Preliminary findings suggest the number and volume of supragranular and infragranular pyramidal neurons are similar in the anterior superior temporal area of control subjects and subjects with autism. Neurosci Lett 589:98–103.

Koekkoek SK, Yamaguchi K, Milojkovic BA, Dortland BR, Ruigrok TJ, Maex R, De Graaf W, et al. 2005. Deletion of FMR1 in Purkinje cells enhances parallel fiber LTD, enlarges spines, and attenuates cerebellar eyelid conditioning in Fragile X syndrome. Neuron 47: 339–352.

Koenderink MJ, Uylings HB. 1995. Postnatal maturation of layer V pyramidal neurons in the human prefrontal cortex. A quantitative Golgi analysis. Brain Res 678:233–243.

Koenderink MJ, Uylings HB, Mrzljak L. 1994. Postnatal maturation of the layer III pyramidal neurons in the human prefrontal cortex: A quantitative Golgi analysis. Brain Res 653:173–182.

Kumar V, Zhang MX, Swank MW, Kunz J, Wu GY. 2005. Regulation of dendritic morphogenesis by Ras-PI3K-Akt-mTOR and Ras-MAPK signaling pathways. J Neurosci 25:11288–11299.

Kwon CH, Luikart BW, Powell CM, Zhou J, Matheny SA, Zhang W, Li Y, et al. 2006. Pten regulates neuronal arborization and social interaction in mice. Neuron 50: 377–388.

Landi S, Putignano E, Boggio EM, Giustetto M, Pizzorusso T, Ratto GM. 2011. The short-time structural plasticity of dendritic spines is altered in a model of Rett syndrome. Sci Rep 1:45.

Laplante M, Sabatini DM. 2012. mTOR Signaling. Cold Spring Harbor Perspect Biol 4:a011593.

Luebke JI, Weaver CM, Rocher AB, Rodriguez A, Crimins JL, Dickstein DL, Wearne SL, et al. 2010. Dendritic vulnerability in neurodegenerative disease: Insights from analyses of cortical pyramidal neurons in transgenic mouse models. Brain Struct Funct 214:181–199.

Maussion G, Carayol J, Lepagnol-Bestel AM, Tores F, Loe-Mie Y, Milbreta U, Rousseau F, et al. 2008. Convergent evidence identifying MAP/microtubule affinity-regulating kinase 1 (MARK1) as a susceptibility gene for autism. Hum Mol Genet 17:2541–2551.

McKinney BC, Grossman AW, Elisseou NM, Greenough WT. 2005. Dendritic spine abnormalities in the occipital cortex of C57BL/6 Fmr1 knockout mice. Am J Med Genetics Part B, Neuropsychiatric Genet 136B:98–102.

Mercati O, Danckaert A, Andre-Leroux G, Bellinzoni M, Gouder L, Watanabe K, Shimoda Y, et al. 2013. Contactin 4, −5 and −6 differentially regulate neuritogenesis while they display identical PTPRG binding sites. Biol Open 2:324–334.

Mrzljak L, Uylings HB, Kostovic I, Van Eden CG. 1988. Prenatal development of neurons in the human prefrontal cortex: i. A qualitative Golgi study. J Comp Neurol 271: 355–386.

Mrzljak L, Uylings HB, Kostovic I, van Eden CG. 1992. Prenatal development of neurons in the human prefrontal cortex. II. A quantitative Golgi study. J Comp Neurol 316:485–496.

Muddashetty RS, Nalavadi VC, Gross C, Yao X, Xing L, Laur O, Warren ST, et al. 2011. Reversible inhibition of PSD-95 mRNA translation by miR-125a, FMRP phosphorylation, and mGluR signaling. Mol Cell 42: 673–688.

Mukaetova-Ladinska EB, Arnold H, Jaros E, Perry R, Perry E. 2004. Depletion of MAP2 expression and laminar cytoarchitectonic changes in dorsolateral prefrontal cortex in adult autistic individuals. Neuropathol Appl Neurobiol 30:615–623.

Napoli I, Mercaldo V, Boyl PP, Eleuteri B, Zalfa F, De Rubeis S, Di Marino D, et al. 2008. The fragile X syndrome protein represses activity-dependent translation through CYFIP1, a new 4E-BP. Cell 134:1042–1054.

Nguyen MV, Du F, Felice CA, Shan X, Nigam A, Mandel G, Robinson JK, et al. 2012. MeCP2 is critical for maintaining mature neuronal networks and global brain anatomy during late stages of postnatal brain development and in the mature adult brain. J Neurosci 32:10021–10034.

Nimchinsky EA, Oberlander AM, Svoboda K. 2001. Abnormal development of dendritic spines in FMR1 knock-out mice. J Neurosci 21:5139–5146.

Nimchinsky EA, Sabatini BL, Svoboda K. 2002. Structure and function of dendritic spines. Annu Rev Physiol 64: 313–353.

Nowicki ST, Tassone F, Ono MY, Ferranti J, Croquette MF, Goodlin-Jones B, Hagerman RJ. 2007. The Prader-Willi phenotype of fragile X syndrome. J Dev Behav Pediatr 28:133–138.

Orloff MS, He X, Peterson C, Chen F, Chen JL, Mester JL, Eng C. 2013. Germline PIK3CA and AKT1 mutations in Cowden and Cowden-like syndromes. Am J Hum Genet 92:76–80.

Parnass Z, Tashiro A, Yuste R. 2000. Analysis of spine morphological plasticity in developing hippocampal pyramidal neurons. Hippocampus 10:561–568.

Pathania M, Davenport EC, Muir J, Sheehan DF, Lopez-Domenech G, Kittler JT. 2014. The autism and schizophrenia associated gene CYFIP1 is critical for the maintenance of dendritic complexity and the stabilization of mature spines. Transl Psychiatry 4:e374.

Petanjek Z, Judas M, Kostovic I, Uylings HB. 2008. Lifespan alterations of basal dendritic trees of pyramidal neurons in the human prefrontal cortex: A layer-specific pattern. Cereb Cortex 18:915–929.

Petanjek Z, Judas M, Simic G, Rasin MR, Uylings HB, Rakic P, Kostovic I. 2011. Extraordinary neoteny of synaptic spines in the human prefrontal cortex. Proc Natl Acad Sci U S A 108:13281–13286.

Phillips M, Pozzo-Miller L. 2015. Dendritic spine dysgenesis in autism related disorders. Neurosci Lett 601:30–40.

Ramakers GJ. 2005. Neuronal network formation in human cerebral cortex. Prog Brain Res 147:1–14.

Ramocki MB, Tavyev YJ, Peters SU. 2010. The MECP2 duplication syndrome. Am J Med Genet Part a 152A: 1079–1088.

Raymond GV, Bauman ML, Kemper TL. 1996. Hippocampus in autism: A Golgi analysis. Acta Neuropathol 91: 117–119.

Raza S, Himmler BT, Himmler SM, Harker A, Kolb B, Pellis SM, Gibb R. 2015. Effects of prenatal exposure to valproic acid on the development of juvenile-typical social play in rats. Behav Pharmacol 26:707–719.

Rochefort NL, Konnerth A. 2012. Dendritic spines: From structure to in vivo function. EMBO Rep 13:699–708.

Rudelli RD, Brown WT, Wisniewski K, Jenkins EC, Laure-Kamionowska M, Connell F, Wisniewski HM. 1985. Adult fragile X syndrome. Clinico-neuropathologic findings. Acta Neuropathol 67:289–295.

Sabatini BL, Svoboda K. 2000. Analysis of calcium channels in single spines using optical fluctuation analysis. Nature 408:589–593.

Sala C, Segal M. 2014. Dendritic spines: The locus of structural and functional plasticity. Physiol Rev 94:141–188.

Sala C, Piech V, Wilson NR, Passafaro M, Liu G, Sheng M. 2001. Regulation of dendritic spine morphology and synaptic function by Shank and Homer. Neuron 31:115–130.

Saldarriaga W, Tassone F, Gonzalez-Teshima LY, Forero-Forero JV, Ayala-Zapata S, Hagerman R. 2014. Fragile X syndrome. Colomb Med 45:190–198.

Segev I, London M. 2000. Untangling dendrites with quantitative models. Science 290:744–750.

Skalecka A, Liszewska E, Bilinski R, Gkogkas C, Khoutorsky A, Malik AR, Sonenberg N, et al. 2016. mTOR kinase is needed for the development and stabilization of dendritic arbors in newly born olfactory bulb neurons. Dev Neurobiol, Mar 23.

Sowers LP, Loo L, Wu Y, Campbell E, Ulrich JD, Wu S, Paemka L, et al. 2013. Disruption of the non-canonical Wnt gene PRICKLE2 leads to autism-like behaviors with evidence for hippocampal synaptic dysfunction. Mol Psychiatry 18:1077–1089.

Srivastava DP, Woolfrey KM, Jones KA, Anderson CT, Smith KR, Russell TA, Lee H, et al. 2012. An autism-associated variant of Epac2 reveals a role for Ras/Epac2 signaling in controlling basal dendrite maintenance in mice. PLoS Biol 10:e1001350.

Stuss DP, Boyd JD, Levin DB, Delaney KR. 2012. MeCP2 mutation results in compartment-specific reductions in dendritic branching and spine density in layer 5 motor cortical neurons of YFP-H mice. PloS One 7:e31896.

Su T, Fan HX, Jiang T, Sun WW, Den WY, Gao MM, Chen SQ, et al. 2011. Early continuous inhibition of group 1 mGlu signaling partially rescues dendritic spine abnormalities in the Fmr1 knockout mouse model for fragile X syndrome. Psychopharmacology (Berl) 215: 291–300.

Tavazoie SF, Alvarez VA, Ridenour DA, Kwiatkowski DJ, Sabatini BL. 2005. Regulation of neuronal morphology and function by the tumor suppressors Tsc1 and Tsc2. Nat Neurosci 8:1727–1734.

Thomanetz V, Angliker N, Cloetta D, Lustenberger RM, Schweighauser M, Oliveri F, Suzuki N, et al. 2013. Ablation of the mTORC2 component rictor in brain or Purkinje cells affects size and neuron morphology. J Cell Biol 201:293–308.

Thomas CC, Combe CL, Dyar KA, Inglis FM. 2008. Modest alterations in patterns of motor neuron dendrite morphology in the Fmr1 knockout mouse model for fragile X. Int J Dev Neurosci 26:805–811.

Trachtenberg JT, Chen BE, Knott GW, Feng G, Sanes JR, Welker E, Svoboda K. 2002. Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex. Nature 420:788–794.

Tropea D, Giacometti E, Wilson NR, Beard C, McCurry C, Fu DD, Flannery R, et al. 2009. Partial reversal of Rett Syndrome-like symptoms in MeCP2 mutant mice. Proc Natl Acad Sci U S A 106:2029–2034.

Urbanska M, Blazejczyk M, Jaworski J. 2008. Molecular basis of dendritic arborization. Acta Neurobiol Exp 68: 264–288.

Van Maldergem L, Hou Q, Kalscheuer VM, Rio M, Doco-Fenzy M, Medeira A, de Brouwer AP, et al. 2013. Loss of function of KIAA2022 causes mild to severe intellectual disability with an autism spectrum disorder and impairs neurite outgrowth. Hum Mol Genet 22:3306–3314.

Walmod PS, Skladchikova G, Kawa A, Berezin V, Bock E. 1999. Antiepileptic teratogen valproic acid (VPA) modulates organisation and dynamics of the actin cytoskeleton. Cell Motil Cytoskel 42:241–255.

Walsh KP, Kuhn TB, Bamburg JR. 2014. Cellular prion protein: A co-receptor mediating neuronal cofilin-actin rod formation induced by beta-amyloid and proinflammatory cytokines. Prion 8:375–380.

Weir RK, Forghany R, Smith SE, Patterson PH, McAllister AK, Schumann CM, Bauman MD. 2015. Preliminary evidence of neuropathology in nonhuman primates prenatally exposed to maternal immune activation. Brain Behav Immun 48:139–146.

Weiss LA, Shen Y, Korn JM, Arking DE, Miller DT, Fossdal R, Saemundsen E, et al. 2008. Association between microdeletion and microduplication at 16p11.2 and autism. N Engl J Med 358:667–675.

Westmark CJ, Westmark PR, O'Riordan KJ, Ray BC, Hervey CM, Salamat MS, Abozeid SH, et al. 2011. Reversal of fragile X phenotypes by manipulation of AbetaPP/Abeta levels in Fmr1KO mice. PloS One 6: e26549.

Weston MC, Chen H, Swann JW. 2014. Loss of mTOR repressors Tsc1 or Pten has divergent effects on excitatory and inhibitory synaptic transmission in single hippocampal neuron cultures. Front Mol Neurosci 7:1.

Williams DW, Truman JW. 2004. Mechanisms of dendritic elaboration of sensory neurons in Drosophila: Insights from in vivo time lapse. J Neurosci 24:1541–1550.

Williams RS, Hauser SL, Purpura DP, DeLong GR, Swisher CN. 1980. Autism and mental retardation: Neuropathologic studies performed in four retarded persons with autistic behavior. Arch Neurol 37:749–753.

Zuko A, Kleijer KT, Oguro-Ando A, Kas MJ, van Daalen E, van der Zwaag B, Burbach JP. 2013. Contactins in the neurobiology of autism. Eur J Pharmacol 719:63–74.