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## 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. Though 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 together with 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.

### 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 stages, however much remains to be understood about the

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No conflict of interests is declared by the author.

characteristics of neuronal dendrites and dendritic spines in autism and related disorders. Here we review the current knowledge state on dendrite and spine modifications obtained from studies of postmortem human tissue from patients with autism and from those conducted using autism mouse models.

Dendrites are the main information-receiving elements in neurons. The complex morphology of the dendritic tree and its properties enables neurons to receive and compute inputs 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 tree are 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 IIC, 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 occurred during both the period of rapid cognitive development in preschool children and the period of protracted cognitive maturation during the 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 the high and low integrative regions (Jacobs et al., 2001). While 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 primary somatosensory cortex (Jacobs et al., 2001). In the human prefrontal cortex, an average dendrite in adult contains about 10 to 50 segments, a total length per dendrite of about 200 to 500  $\mu\text{m}$ , and radial distances to the terminal tips of 100 to 150  $\mu\text{m}$  (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 and 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 dendrites of pyramidal neurons (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, capacities that is key for synaptic plasticity (Fiala et al., 2002, Sala and Segal, 2014).

Spine morphology, number and density are crucial factor determining the strength and stability of the synaptic transmission (Sabatini and Svoboda, 2000, Segev and London, 2000, Gullledge et al., 2005, Luebke et al., 2010, Sala and Segal, 2014). Functions 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 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, and 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, mushrooms 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 increase and decrease 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 spines modifications related to Autism Spectrum Disorders (ASD) and related pathologies, in patients and animal models.

### **Autism Spectrum Disorders**

Autism Spectrum Disorders span four separate disorders including 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 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 passes away until the brain is retrieved and immersed in fixative. This is due, in 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 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 to those in control hippocampus (Raymond et al., 1996), and Mukaetova-Ladinska noted that 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 lobe 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 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 protein 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 of immature morphology and a decreased 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 type 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 FMRP1 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 in cortical areas. Similarly, FXS mice exhibited significantly more dendritic spines with an immature-like morphology and significantly fewer with and more mature type 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 occipital cortex of *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 and a developmental delay in the downregulation of spine turnover and the transition from immature to mature spine subtypes, which altogether demonstrate that 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 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 dendritic spine developmental processes. Increased spine density in the knockout mice may reflect impaired developmental organizational processes of synapse stabilization and elimination or pruning.

Studies of dendritic morphology have been also performed in CGG knock-in mice. These mice are models 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 children 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. CGG knock-in mouse models present with fewer dendritic branches, reduced total dendritic length, and higher frequency of longer dendritic spines in 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 may be regulating 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 shown 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 regulate actin-nucleating activity, process that strongly influence the formation, retraction, motility, stability, and shape of the dendritic spines (De Rubeis et al., 2013). *CYFIP1* 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 *Cyfp1* haploinsufficient animal exhibit deficits in dendritic complexity as well as an altered ratio of immature to mature spines in hippocampal CA1 neurons. Both *Cyfp1* 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* is located in humans on 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 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 cell culture 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  $\beta$ -protein precursor ( $A\beta$ PP) is also upregulated in the FXS mouse model (Napoli et al., 2008).  $\beta$ -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, 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  $A\beta$ PP in *Fmr1* knockout mice rescues the ratio of mature versus immature dendritic spines (Westmark et al., 2011).

It has been also 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 rescue of dendritic spine morphology in the *Fmr1* KO mouse (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 out 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), 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 defined a reduced dendritic arborization in the pyramidal neurons of layer III and V in frontal, motor and inferior temporal regions in Rett 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 determined altered at different stages of dendritic formation in patients with Rett syndrome (Kaufmann et al., 2000). It has also been widely reported that loss of MeCP2 in mice results in abnormal dendritic spine morphology and 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 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 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 supports the role of the mTOR mechanism in the regulation of dendritic and spine morphology in autism.

Additional studies of the dendritic arbor in animal models of autism have shown data that match previous observations in human. 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). Other animal models linked to autism include a siRNA-mediated KIAA2022 knockdown in mice, a model of the X-linked intellectual disability (XLID) syndrome related to autism, resulted in marked impairment in neurite outgrowth, impacting both dendrites and axons (Van Maldergem et al., 2013). Studies of prickle2 (Pk2), a post-synaptic 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 related 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 is also present 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 compounds 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 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 a 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 indicates that in both genetic and non-genetic models of autism, dendrites and spines present with an alteration in number, size, and morphology of the dendritic arbors and the spines that contains.

## Conclusion

Dendritic and 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 of 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 dendrites and spines in the cerebral cortex of autism patients.

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