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Review

# Dendritic spine dysgenesis in autism related disorders

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ABSTRACT

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



**Contents**



## 1. Introduction

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

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

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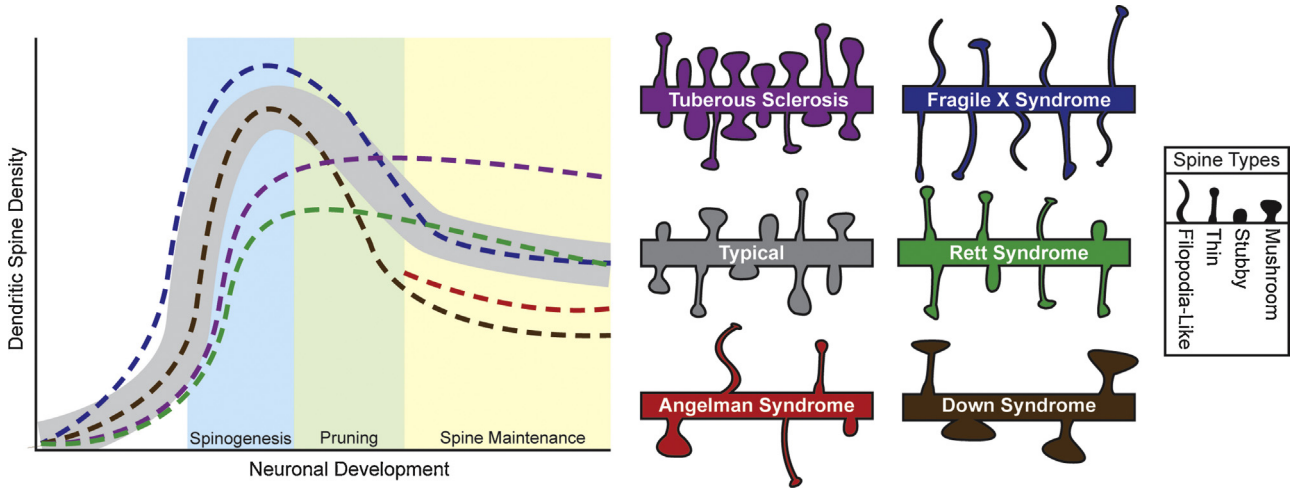


**Fig. 1.** Characterization of dendritic spines in autism related disorders.
Numerical density of dendritic spines during neurodevelopmental stages, and morphologies of mature spines in different ARDs. In typical subjects (grey shading), spines and synapses are formed during early development with the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

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

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

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

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

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