ASD Mechanisms on Molecular and Cellular Level: Synaptic Dysfunctions and Pruning Deficiency

Ziqi Wang*

Department of Applied Biology and Chemical Technology the Hong Kong Polytechnic University Hong Kong SAR, China

*Corresponding author: Lilywang418@hotmail.com

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Abstract: Autism spectrum disorder (ASD) is one of the most common neural disorders typified by social ability impairments, communicative defects, and repetitive/restricted behaviors. Gene components strongly contribute to the possible pathology of ASD. And evidence shows key risk genes converge at common cell pathways at synapse. These studies also attempted to explain the common etiology of heterogenous ASD phenotypes using genomic analysis and animal models from different perspectives. This review tries to incorporate ASD mechanisms on molecular and cellular level into two main aspects: synaptic dysfunctions and under-pruning resulted from dysregulated mTOR pathway. Future devotion in this direction should ultimately focus on increasing pruning efficiency by targeting downstream of mTOR-autophagy signaling, therefore providing clues for novel ASD treatments.

1. Introduction

Autism spectrum disorder (ASD) is a complex neural disease characterized by disabilities including but not limiting to impaired social interaction and communication, restricted interests in certain activities, and repetitive behaviors [1]. Except for the manifestations of the major social impairments, the behaviors must start from an individual's early childhood when giving diagnosis of ASD [2]. Viewed from consistent ASD prevalence reports from all over the world, it affects approximately 1% of the total population, making it one of the most common neural disorders [3].

On the basis of current studies, genetic factors play a significant role in the etiology of ASD, together with environmental components during early postnatal developmental stages. Consistently, in monozygotic twins, the concordance rate of ASD is 80%~90%, whereas in dizygotic twins, the concordance rate of ASD is much lower, only up to 10% [4-6]. Genetic profiling of ASD is extremely heterogenous, and hundreds of gene mutations and variants are identified. Studies have selected risk genes of higher prevalence and relevance, such as NRXN, NLGN, SHANK, PTEN, TSC, and MECP [7]. However, how these mutations fall into specific ASD genetic subtypes and how the genes converge at common pathways are not fully understood in the past. Therefore, no single conclusion has been made on the mechanisms of ASD pathology. Interestingly, in recent studies, even contradicted theories have been proposed. When analyzing the dendritic spine pruning in layer V pyramidal neurons in ASD brains, Tang et al. [8] demonstrate how several key synaptic genes converge at mTOR signaling pathway and report close correlation between mTOR signaling and under-pruning defects during early development. Contradictorily, Thomas et al. [9] introduce the over-pruning hypothesis for ASD. Using neurocomputational models, they define three regressive subtypes of ASD and attempt to predict the trajectory changes of brains during early development of ASD. Nonetheless, based on existing evidence and animal models, findings of the majority of studies on the mechanisms of ASD are, to some extent, in favor of the under-pruning theory, indicating that synaptic function abnormalities and insufficient pruning could be the common pathology of ASD mechanisms.

In this review, mechanisms of ASD on molecular levels are discussed, together with two risk genes. Additionally, the molecular and developmental synaptic phenotypes of ASD are also mentioned to understand this disease.

2. Mechanisms of ASD

2.1 Defective Molecular Functions of Synapses

ASD displays high heterogeneity in both phenotypes and genetic mutations. While hundreds of risk genes of ASD are identified [7], studies [10] [11] show most genes converge at a few common cellular pathways which converge at synapses. Synapses, consisting of presynaptic and postsynaptic parts, are asymmetric structures which allow electrical or chemical signal transduction from neurons to neurons or effector cells. When mutations occur in the ASD-associated genes, the alternation in protein structure and expression will affect various aspects of synaptic functions including formation, elimination, plasticity, and transmission. To better understand synaptic abnormalities, key protein players of synapses, including cell adhesion molecules and scaffolding proteins, are introduced, and examined how mutations of these proteins lead to synaptic defects underlying ASD.

Neurexins (Nrxns) and neuroligins (Nlgns) are two families of proteins that function as cell-adhesion molecules when partnered together as neurexin/neuroligin complex. Upon contact of target cells, neurexin/neuroligin complex recruit key players such as neurotransmitter receptors, essential for various synaptic properties [12]. Thus, aberrance in either protein families can lead to significant synaptic dysfunctions. Nrxn realizes its effects on proper neural circuits mainly through two ways. First, Nrxn regulates Ca2+ influx which the kinetic feature of forming pores on cell membranes of CaV2.1 channel relies on to assure successful vesicle release and trafficking [13]. Disease-associated defects and deficiency of Nrxn in neurons, as a consequence, are shown to have low neurotransmitter release capacity which further results in decreased excitatory synaptic strengths and disturbance of excitatory/inhibitory (E/I) synapse ratio [14]. Balanced E/I ratio is crucial for normal development of neural networks and brain functions, and its alternations are usually responsible for impaired cognitive and information processing ability [15]. Second, malfunction or deficiency in Nrxn variants may also contribute to the pathogenesis of ASD through their influence on the abundance of proteins they interact with. For instance, one scaffolding protein that binds to Nrxn1, CASK, shows increased abundance in mutated NRXN1 neurons of human, which is known to cause ASD, as well as intellectual retardation [16]. Different from Nrxns, mutations in NLGN cause retention of mutated Nlgns in the ER which greatly lowers Nlgn distribution to the postsynaptic membranes. Worth noticeably, Nlgn3 and Nlgn4 are found on both excitatory and inhibitory synapses. Neurons with point mutated Nlgn3 or/and Nlgn4 demonstrate impairment of synaptic transmission because of protein retention on both types of neurons, resulting in E/I imbalance in circuit development [17, 18].

Scaffolding proteins are another important group of proteins that, when mutated, could compromise various synaptic functions. First, many scaffolding proteins have a diverse binding efficiency. For instance, PSD-95, a key organizer of the postsynaptic structure of excitatory synapses, have 3 PDZ domains, 1 SH domain and 1 GK domain, and through which it binds to many other scaffolding proteins and adhesion molecules. This diverse binding affinity indicates that it is essential for synaptic circuit structures [19]. Studies have proved that abnormal level of PSD-95 can trigger a chain reaction of other essential synaptic proteins, thus interfering with the E/I balance and altering synaptic plasticity [20] [21]. On top of that, many scaffolding proteins exert great influence on synapses because of their close interactions with neurotransmitter receptors. A great example is the central scaffolding element at inhibitory synapses, gephyrin, of which mutations in its encoding gene GPHN have been found associated with many neurotic diseases including ASD [22]. Gephyrin regulates inhibitory signal transmission conducted by glycine and GABA through acting like a “molecular hub” for glycine receptor (GlyR) and GABA (GABAAR) receptor [23]. When activated by adhesion molecules, gephyrin monomers cluster together, forming a lattice which inhibits the lateral movement of GlyRs and GABAARs and helps encourage the clustering of the receptors [24]. Therefore, when changes occur in posttranslational regulation of gephyrin, the relative density and size of the cluster become different, disturbing signal transmission and homeostasis of synapses.

2.2 Dysregulated mTOR Pathway

With hundreds of genes linked to autism, understanding how these genes cluster into just a few cell pathways becomes crucial to stepping forward in the research. And the mTOR pathway is probably the most potential candidate of such pathways. It is found that mutations in genes inhibiting the target of mTOR kinase in mammalian cells, such as Tsc1/Tsc2, NF1 and Pten, are the causes of several autism syndromes [25]. Moreover, mTOR kinase in the synapses also combines signals from other ASD-associated regulatory proteins including SHANK3, FMRP and mGluR1/5 [25, 26]. When mutations occur in the above-mentioned genes and proteins, the mTOR pathway tends to become overactive and produce excessive synaptic proteins. To sustain the homeostasis and synaptic plasticity, the synapses must degrade excessive proteins through autophagy which is downstream of mTOR pathway. However, the overly active mTOR prevents this process and causes deficient autophagy [27]. To be more specific, synaptic autophagy to remove and degrade injured or redundant proteins and organelles requires autophagosomes to transfer the unwanted parts to lysosomes. And the overactive mTOR interferes with the formation of autophagosomes, thus inhibiting autophagy at the very early step [28].

The heterogeneity of ASD-associated genes calls for the recognition of common signaling pathways that leads to the syndromes. Both dysregulated mTOR signaling and synaptic dysfunctions are identified in the ASD brains, indicating a common mechanism of the synaptic pathology of ASD [29].

3. Two Important Genes Associated with Autism Risk

Clinical evidence shows that while several genes may be involved or mutated in ASD patients, some specific genes are of higher prevalence and are the essential steps of common pathways underlying ASD mechanisms. These strong gene candidates including SHANK3 and PTEN, are studies the most in research and imply, again, the prevailing exhibition of synaptic defects and mTOR dysregulation in ASD [25, 26].

3.1 SHANK3

Shank proteins are a family of scaffolding proteins with 3 isoforms, Shank1, Shank2, and Shank3, which the functions of all isoforms are significant for synaptic formation and signaling. While mutations in SHANK1, and SHANK2 in ASD patients are quite rare, genetic variants of SHANK3 are of much higher prevalence with approximately 1%~2% frequency clinically [30]. Located on chromosome 22q13.3, SHANK3 variants include chromosome deletions, insertion, splicing, and point mutations, which are found in ASD and Phelan-McDermid Syndrome (PMS) [31, 32]. In mice with Shank3 gene deletion, decreased levels of several PSD proteins including AMPR subunit GluA1, GKAP, Homer1b/c are identified. Also, decreased functional synapses and postsynaptic response are identified, suggested by reduced miniature excitatory postsynaptic currents (mEPCs) [33, 34]. As a result, autistic behaviors such as social interaction deficits and repetitive self-grooming are observed in the Shank3 deficient mice [33]. In contrast, in experiments on mice with Shank3 mutation that leads to overexpression of Shank3 proteins, the frequency and peak amplitude of mEPCs are increased, and the postsynaptic signaling mediated by AMPR and Neurexin-Neuroligin complex is disrupted [35]. The findings indicate that although SHANK3 variants in ASD patients may not be universally penetrant and even lead to contrary mEPCs levels, synaptic deficits are commonly observed, which result in disrupted postsynaptic signaling and synaptic connectivity.

3.2 PTEN

PTEN, located on chromosome 10q23, encodes for the protein/lipid phosphatase PTEN which dephosphorylates PIP3 in exchange of PIP2. PIP2 is further negatively involved in the mTOR pathway, prohibiting cell proliferation and cell survival, thus PTEN is also well-known for its tumor suppression function [36]. Highly expressed in CNS, PTEN function is closely related to the normal formation of synapses and growth of neurons [37]. In fact, PTEN mutations, both complete loss-of-function mutation variant and incomplete loss-of-function variant, are identified in 27% of ASD

patients, as well as other neural diseases such as seizure, macrocephaly, and mental retardation [38]. Conditional knockout (cKO) of Pten in mice results in abnormal dendrite structures and upregulated mTOR signaling [39]. As a result, glutamatergic and GABAergic synaptic transmission are evoked, thus shifting the EPCs levels and disrupting the homeostasis of synapses [39, 40]. In addition to its effects on neural morphology and rapamycin (mTOR) signaling, PTEN also modulates synaptic functions through PTEN and PSD-95 interaction dependent of NMDA receptors. inducing postsynaptic response mediated by AMPR and causing depressive traits and behaviors in Pten cKO mice [41].

4. Synaptic Development and Pruning Deficiency in the ASD Brain

4.1 Imbalanced Early Synaptic Development in ASD Human Brain

Synaptic development refers to the dynamic process of synapse formation and elimination/pruning in the nervous system. Although it is a lifelong process, the delicate balance of synaptic development is particularly critical during certain periods of exuberant synaptogenesis [42]. During early postnatal years, synaptic formation outpaces pruning, preparing abundant excitatory synapses for successful assembly of neural circuits. Subsequently, from childhood to adolescence, pruning exceeds synaptogenesis, resulting in selection of matured neural circuits [43]. This dynamic process is also consistent with the changes in the density of dendritic spines during an individual's early years [43]. Studies report that dendritic spine density in frontal, temporal, and parietal lobes of the ASD brains is elevated, implicating insufficient dendritic spine pruning at early synaptic development stages in ASD patients [44].

4.2 Dysregulated mTOR-autophagy Signaling and Spine Pruning Deficits in ASD

In recent years, studies have confirmed that mTOR-dependent autophagy is negatively related with dendritic spine pruning in the ASD brain during childhood [8, 45, 46]. cKO Tsc1 and Tsc2+/- mice models, both showing autistic phenotypes and insufficient dendritic spine pruning than control at early developmental stages, have demonstrated hyperactive mTOR signaling activity and a deficiency in mTOR-autophagy [8]. Moreover, pharmacological intervention suppressing mTOR signaling successfully restores dendritic spine pruning ability and normalizes autistic behaviors in mice [8]. Reduced mTOR-dependent autophagy also accords with the finding of insufficient mitochondrial turnover via autophagy in the ASD brain [47]. Additionally, the dysregulated mTOR-autophagy signaling and pruning deficits, to some extent, describes the secondary mechanism in order to maintain synaptic homeostasis and E/I balance [45, 46]. Consistently, lacking mTOR-autophagy during critical stages disrupts synaptic functions resulted from increased evoked release of neural transmitters and imbalanced neural circuits [48].

To summarize, both defective synaptic functions and dysregulated mTOR signaling exist in the ASD brain, indicating that mTOR is the common pathway underlying pathology of ASD. Furthermore, it is confirmed that these defects as well as autistic behaviors are induced by inhibited mTOR-autophagy, which causing insufficient spine pruning during postnatal synaptic development. This direct association between mTOR-autophagy and spine pruning encourages future studies to target and focus on chemicals/methods to increase/restore autophagy downstream of mTOR pathway during critical synaptogenesis stages, which, hopefully, may inspire innovative and effective treatments against ASD.

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