

Defects of Synapse Function in Autism - The Diversity of Underlying Molecular Mechanisms

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Abbreviations

ASD: Autism Spectrum Disorder; MeCP2: Methyl-CG Binding Protein; MEF2: Myocyte Enhancer Factor 2

Autism spectrum disorder (ASD) consists of a range of neurodevelopmental disorders involving problems of social interaction and communication, and stereotyped pattern or repetitive behaviors [1]. Neuronal connectivity is affected in ASD implicating both excitatory and inhibitory circuits [2-6]. Several genes are linked to ASD and many of these genes encode proteins that are involved in synapse formation and function [7,8]. The ASD mutations have been shown to dysregulate differentially synaptic function. Studies of syndromic ASD with mutations in a single gene have revealed dosage effects of synaptic proteins. Defects of homeostatic plasticity mechanisms may contribute to functional changes in neuronal circuits initially, but homeostatic mechanisms can also be activated as compensatory mechanisms which may be difficult to distinguish separately [9]. Understanding shared and gene defect-specific mechanisms involved in impaired synapse function in variants of ASD is essential for development of improved treatment strategies for ASD individuals.

Most excitatory synapses are located in dendritic spines. These small, thorn-like protrusions extend from the dendritic shaft at the postsynaptic regions of synapses. Alterations of dendritic spines reflect abnormalities in neuronal connections in the brain circuitries in ASD. Dendritic spine density shows age-dependent increase in ASD brains which suggests lack of developmental spine pruning and impaired elimination of functionally inappropriate neuronal connections [10].

Development of dendritic spines involves filopodia-like precursors. Filopodia search for appropriate positions along the axons to make contacts. Most contacts do not last long. Few contacts of the growing and retracting filopodia will be finally stable synapses on glutamatergic axons. Unlike glutamatergic synapses, GABAergic axons and dendritic filopodia do not form stable synapses. Instead of contacts made by dendritic or axonal protrusions, new GABAergic synapses are formed by new boutons at pre-existing axon-dendrite crossings [11]. Formation of stable and specific synaptic connections require proper axon-dendritic interactions and synaptogenic and anti-synaptogenic factors that strengthen the appropriate connections.

There is evidence that local calcium transients in dendritic filopodia play an important role in stabilization of filopodia-axon contacts [12]. Cell adhesion molecules contribute to the initial selection of appropriate synaptic partners. Disruption of intracellular calcium homeostasis as well as many calcium adhesion molecule (CAMs) have been associated with ASD [13,14]. ASD mutations are found in neuroligins and neurexins [15] that instruct pre- and postsynaptic specialization and are critical for functional maturation of excitatory and inhibitory synapses. Neuroligins play a role in the control of excitatory and inhibitory balance and circuit-specific synapses. Synaptogenic factors involved in spatial specificity and timing, including Ephrin, Wnt, Netrin and Slit-Robo signaling, have also been linked to ASD [16,17].

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Activity-regulated genes have an important role in control of glutamatergic and GABAergic synapse development. Membrane depolarization and transmitter release regulate hundreds of genes, including many genes implicated in the dysregulation of synapse formation in ASD. Activity-dependent positive and negative feedback loops regulated by activity-dependent transcription factors have been shown to be affected in ASD [18]. MeCP2 is an activity-dependent transcription factor that promotes the number and strength of excitatory synaptic connections at glutamatergic synapses and is critical for normal function of GABA-releasing neurons [19,20]. ASD-associated transcription factor MEF2 restricts formation of excitatory synapses as an activity-dependent negative feedback loop [21]. Complex regulation of the downstream effectors of the transcription factors, including neurotrophins, provides an additional dimension to the regulation of synapse development and function in ASD [22].

The diversity of molecular mechanisms described in ASD reflects its genetic heterogeneity. Further studies are needed to investigate circuit-specific changes and to search for shared targets for treatment.

Conflict of Interest

The authors declare no conflict of interest.

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