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REVIEW

Role of Microtubule-Associated Protein in Autism Spectrum Disorder

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Abstract Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social interaction and communication, along with repetitive and restrictive patterns of behaviors or interests. Normal brain development is crucial to behavior and cognition in adulthood. Abnormal brain development, such as synaptic and myelin dysfunction, is involved in the pathogenesis of ASD. Microtubules and microtubule-associated proteins (MAPs) are important in regulating the processes of brain development, including neuron production and synaptic formation, as well as myelination. Increasing evidence suggests that the level of MAPs are changed in autistic patients and mouse models of ASD. Here, we discuss the roles of MAPs.

Keywords Autism spectrum disorder · Microtubule-associated proteins · Synapse · Myelin

Introduction

Autism spectrum disorder (ASD) is a severe neurodevelopmental disorder with a high prevalence. It is characterized by difficulties in reciprocal social interaction and communication, and repetitive and restrictive patterns of behavior or interests. In consideration of the poor social adaptability, autistic patients need lifelong care which imposes huge economic and mental burdens on their families. The number of patients who have been diagnosed with ASD has risen dramatically around the world over the last decades [1]. The most recent prevalence of ASD among children aged 8 years is ~ 1 in 68 children, as estimated by Developmental Disabilities Monitoring Network in 11 sites, USA, 2012 [2].

It has been demonstrated that a complicated interplay of both genetic and environment factors is involved in ASD [3]. However, to date, the precise pathogenesis of ASD remains undefined. A few pharmacological treatments may release some of the associated symptoms, but there are no therapeutic options that target the core symptoms of autism. In this review, we describe the current status of the pathogenesis of ASD and highlight the current research on microtubule-associated proteins (MAPs).

Genetic, Environmental, and Neuroimmune Factors in ASD

Genetic and Epigenetic Factors in ASD

Emerging evidence suggests that genetic factors play important roles in ASD. For instance, a child who has an affected sibling is more likely to be diagnosed with ASD [4], and parents of such children show subtle cognitive or behavioral deficits compared to controls [5]. ASD studies based on both human genetics and animal models have demonstrated that the interruption of processes such as synapse formation, neuron production, and spine stability are important features of ASD etiology. Therefore, changes in common molecular pathways involved in those factors may contribute to the pathogenesis of ASD [6, 7].

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Individual base-pairs (single-nucleotide variants), millions of base-pairs [copy-number variants (CNVs)] and *de novo* genetic variants have been found in hundreds of genes, which are mostly rare and cover the whole spectrum of mutations [8]. For instance, Ziats *et al*. [9] concluded that CNVs associated with synaptogenesis, axon guidance, and neuronal motility are involved in the pathogenesis of ASD. Duplication and deletion of the mutations involved in CNVs can interrupt gene structure and function and often result in developmental delays [10]. And some risk genes for ASD have been identified, such as *NEUROLIGIN4 (NLGN4)*, *NLG1*, *SHANK3*, *CNTN4*, *SYNGAP1*, and *CNTNAP2* [10]. Studies focusing on these genes have identified cellular pathways that are changed in ASD during the process of neuronal development (Fig. 1) [11].

Despite the fact that many ASD-associated genes have been identified, these coding variants only account for a tiny segment of ASD cases; a large proportion of heritability still cannot be explained by genetic findings. So far, many studies have demonstrated that epigenetic modifications caused by non-coding genetic variation play an important role in neuronal differentiation and communication, and abnormal epigenetics is involved in the development of the nervous system and can lead to neurobehavioral deficiencies and psychiatric disorders [12, 13]. Varadinova *et al*. [10] found that prenatal and early postnatal exposure to alcohol, stress, toxins, or drugs can easily damage brain development by changing the epigenetic status of genes in important periods of neuronal and synaptic organization and epigenetic modification in brain development. The specific mechanisms of epigenetic modification, including DNA methylation, non-coding RNA, and post-translational histone changes [14], can have impact on the quantity and quality of gene products at different levels [15, 16]. A hypothesis has been put forward that epigenetics can bridge the genetic and environmental factors that can result in DNA hypomethylation or demethylation in specific genomic regions in certain tissues [13, 17, 18]. Sun *et al*. reported that > 5000 enhancer or promoter loci changed up or down in the ASD cerebral cortex, demonstrating that aberrations in histone acetylation are widely distributed in the ASD cerebral cortex [19].

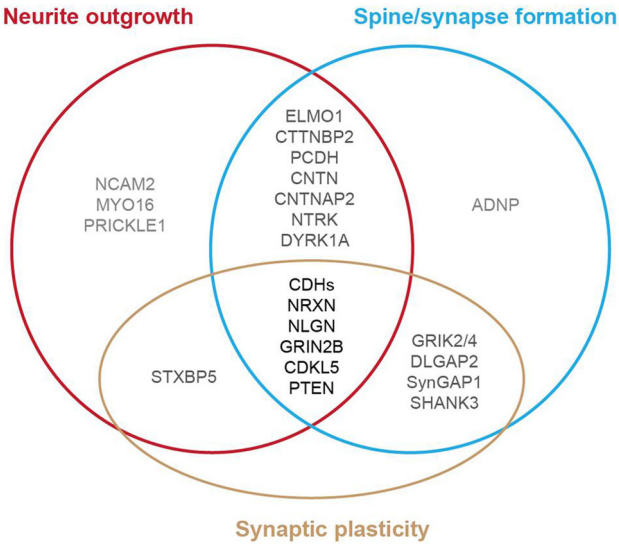

Fig. 1 Diagram of ASD risk genes involved in brain development. Image adapted from Lin YC *et al*. Front Cell Neurosci 2016 [11].

Environmental Factors in ASD

Some environmental factors, including maternal viral infection, bacterial infection, influenza, and febrile episodes during pregnancy, are involved in the etiology of ASD *via* activation of the maternal immune system, and can result in altered fetal brain development. Epidemiological research has demonstrated that gestational infections are tied to the core features of autism by interrupting fetal brain development [20]. Lee *et al*. [21] found a positive correlation between severe maternal infection and an increased risk of ASD, supporting the hypothesis that immune-mediated mechanisms contribute to the phenotypic deficits. Furthermore, in mouse models, injecting either influenza, double-stranded RNA poly (I:C), or bacterial lipopolysaccharide during pregnancy induced an active immune response, and the offspring of these mice showed behavioral deficits in adulthood. Besides, changed cytokine levels were found in the serum, placenta, and amniotic fluid, as well as in the fetal brain [22].

Above all, brain development is associated with the action of neuroimmune factors which are critical for neuronal migration, axonal growth, neuronal positioning, and cortical lamination, as well as dendrite and synapse formation. Therefore, altered cytokine levels are involved in neurodevelopmental disorders such as ASD [23]. A set of increased cytokines has been identified in the brain of autistic patients; these include interleukin (IL)6, IL-10, tumor necrosis factor-α, transforming growth factor-ß1, and macrophage chemoattractant protein-1 [24, 25]. IL-6, an important neuroimmune factor, signals *via* the heterodimerization of gp130 and the IL-6 receptor on the cell surface [22]. It has been reported that increased IL-6 mediates neuroanatomical abnormalities by interrupting the balance of excitatory and inhibitory synaptic formations and synaptic transmission as well as prolonging the length of dendritic spines which is linked to synaptic function [26–28]. By activating IL-6 in the fetal brain, gestational infections can activate a maternal immune response that is associated with abnormal fetal brain development, and can lead to offspring with the core features of ASD [22]. Smith *et al*. [22] found that maternal

immune activation (MIA) does not result in behavioral deficits in IL-6 knockout mice, unlike those seen in the offspring of wild-type mice after MIA. Wei *et al*. [22, 29] demonstrated that inhibition of IL-6 trans-signaling increases sociability in an autistic mouse model. Therefore, increased IL-6 is implicated in the pathogenesis of ASD.

Moreover, some studies have suggested that ASD patients are more likely to have at least one gastrointestinal symptom [30], and this may contribute to the behavioral impairments. A gut-brain axis hypothesis has been proposed, in which gut microbiota are believed to affect brain excitability *via* endocrine, metabolic, or immunological mechanisms that are likely to provoke the pathogenesis of ASD [31–33].

Synapse and Myelin Dysfunction in ASD

Abnormal brain development, such as synapse and myelin dysfunction, is involved in the pathogenesis of ASD. To better illustrate the pathogenesis of ASD, genetic studies have focused on the processes of brain development. For instance, some risk genes that are key regulators of synaptic plasticity have been found in genetic studies and many animal studies of ASD [34]. These genes encode various proteins including synaptic scaffolding proteins, receptors, and cell adhesion molecules, as well as proteins involved in chromatin remodeling, transcription, protein synthesis or degradation, or actin cytoskeletal dynamics. Some of these risk genes are governed by neuronal activity and can influence neuronal connectivity and synaptic plasticity. In addition, it is certain that sensory input and intrinsic brain activity are influenced by synaptic efficacy and are increased or decreased by neuronal connectivity. Studies have revealed that an imbalance between excitatory and inhibitory synapses induces dysfunction of the brain, and is involved in the pathology of ASD [34, 35]. Magnetic resonance spectroscopic studies have found that the glutamate signal varies depending on the diverse phenotypes of ASD [36]. Glutamate is the most important excitatory neurotransmitter, giving rise to excitatory synaptic transmission by binding to glutamate receptors [35]. There is no notable change in the number of glutamatergic synapses and the levels of excitatory synaptic proteins, as well as in the density and postsynaptic density thickness of dendritic spines in the BTBR mouse, a model of autism [37], but the evoked release of glutamate is reduced [35]. An imbalance between excitation and inhibition could be a fundamental component of the pathogenesis of autism.

In ASD, neuronal communication is compromised, and the axon is an important conduit of information communication between neurons [38]. The myelin produced by oligodendrocytes is essential for achieving and maintaining optimal brain function [39]. The myelination process may underlie many cognitive and behavioral abilities. Furthermore, the myelination process may be involved in many neurodevelopmental disorders, such as schizophrenia, Down syndrome, and bipolar disorders [40]. Myelination-related proteins such as myelin basic protein, myelin-associated glycoprotein, and proteolipid protein 1 are important in the formation of myelin and the maintenance of its stability. It has been reported that abnormal myelin development occurs in BTBR mice compared to control mice. For example, there are fewer myelinated axons and less myelin in the cortex of BTBR mice [41]. Similarly, Jones-Davis *et al*. suggested that many abnormalities, such as a complete loss of the corpus callosum, a reduction in the length and area of the hippocampal commissure, and a slightly enlarged anterior commissure, occur in the formation of commissural structures [42]. In the same way, abnormalities in both white matter microstructure and the corpus callosum have also been found in a study using MRI technology [43].

Microtubule-Associated Protein in ASD

Physiological and Pathological Roles of Microtubule-Associated Protein in the Central Neural System

The complicated architectures of neuronal networks and synaptic connections are responsible for the maintenance of suitable brain function [44]. Many neurodevelopmental disorders present abnormal physical and functional connections, and these abnormalities can lead to the disturbances in corticogenesis and changes in cortical laminar architecture [44, 45]. Some steps in brain development are associated with neurodevelopmental disorders linked with altered cortical development. These steps include cellular proliferation, migration, and differentiation [45]. Furthermore, abnormal neuron production and migration and altered synaptogenesis can result in aberrant microcircuit assembly in many regions [46]. Cytoskeletal elements, including the microtubular network, are needed for suitable brain connectivity and neuronal morphogenesis and differentiation, and sufficient evidence suggests that microtubules play a fundamental role in adjusting all the processes of neuron and brain development [44, 45].

Microtubules are cylindrical polymers which are assembled from α-β tubulin heterodimers [47]. Microtubules, actin microfilaments, and intermediate filaments constitute the cytoskeleton, which is a dynamic structure giving the cell its shape and resistance to deformation [45]. Microtubules spread throughout the cell body, not only providing

rigidity, but running dynamic processes such as mitotic spindle formation and intracellular cargo transport [45]. During neuronal development, microtubules are homogeneously oriented in the axon, have various orientations and acquire different post-translational modifications and cytoskeletal density in the dendrites. These structures establish synaptic contacts and contribute to the creation of effective functional connectivity network [45, 48]. And some studies have suggested that microtubules play a vital role in cognitive functions and behaviors, as they are essential in the growth and maintenance of the axon, the development and plasticity of the dendritic spines, and the migration of developing neurons to their destinations.

Microtubule dynamics are adjusted by microtubule-interacting proteins and various pathways, such as the Wnt-dishevelled, NF-κB, Rho-associated coiled-coil kinase, Reelin, and Notch pathways [45, 49, 50]. The Wnt-dishevelled pathway reinforces microtubule stability in the axon and plays a vital role in the formation of looped microtubules at enlarged growth cones [45]. Wnt signaling not only adjusts multiple developmental steps, such as cell proliferation, specification, migration, and differentiation, but also influences the neuronal differentiation of cortical intermediate progenitors [51]. In addition, tau, MAPs, and microtubule-stabilizing proteins regulate Wnt/Ca^{2+} signaling [45]. The NF-κB pathway regulates axon initiation, extension, guidance, and branching, adjusts dendritic arbor size and complexity, and influences dendritic spine density in mature neurons [45, 52]. Although the mechanisms by which NF-κB plays its role in cytoskeletal remodeling are unclear, fortunately, it is clear that MAP2 and MAP1B are targets of NF-κB transcription [53].

To realize microtubules, precise modulation of the cytoskeleton that involves MAPs is required [54, 55]. MAPs, binding along the full length of microtubules, are helpful for axon outgrowth and pathfinding [55]. For instance, MAPs mediate microtubule dynamics by changing the rates of microtubule growth and shrinkage, and modifying the frequency of disintegration or recovery [56]. MAPs have been divided into various categories, such as microtubule motors, the microtubule-severing protein katanin, and structural MAPs that include MAP1, MAP2, tau and MAP6 (also known as STOP for Stable Tubule Only Polypeptide) [44, 57]. MAP1 family proteins, which bind along the microtubule lattice, are classical MAPs [44]. MAP1A and MAP1B are found in neurons, where they are regarded as dominant proteins in the formation and development of axons and dendrites [44]. Binding to microtubules and actin filaments, MAP1B is detectable in axons, dendrites, and growth cones throughout the central nervous system and throughout development [58]. A specific developmental brain defect characterized by agenesis of the corpus callosum, the aberrant formation of Probst bundles, and the abnormal growth of fibers in thick bundles in the lower layers of the cortex, occurs in MAP1B-deficient mice [58]. In addition, MAP1B deficiency also affects the peripheral nervous system; the axons of sciatic nerve in MAP1B-deficient mice have smaller diameters and thinner myelin sheaths of the remaining axons [58]. The MAP2/tau family includes MAP2, MAP4, Tau, and other isoforms in other animals. Members of this family not only stabilize microtubules and regulate microtubule networks in axons and dendrites, but also interact with numerous proteins. For example, by binding to microtubules, they regulate microtubule stability by inhibiting depolymerization and increasing the microtubule density and rigidity [59]. For signal transduction and integration, MAP2 binds to F-actin to modulate neurite initiation, interacts with tyrosine kinase Src, adapter protein Grb 2, and tyrosine kinase Fyn, and interacts with the neurofilaments of the cross-bridges between microtubules and neurofilaments. Furthermore, tau binds to Fyn, Src, presenilin 1, and calmodulin, each interaction having a different function [59].

Expression and Possible Mechanism of Action of Microtubule-Associated Protein in ASD

A strictly-controlled process of cytoskeletal structuring is involved in the complicated and plastic morphology of neurons. Hence, there are tight relationships between deficiencies in cytoskeletal protein-encoding genes and many neurodevelopmental disorders. Many autism-linked brain abnormalities including variations in mini-columnar and laminar cortical organization, synaptic abnormalities, and faulty links in neuronal circuits, are linked with microtubule-related gene mutations and changes. MAPs are important in regulating cytoskeletal organization and dendritic arborization, and thus maintaining normal neuronal function and network formation [45].

The FMR1 knock-out mouse, a model of ASD, shows numerous neuroanatomical changes including dysregulated dendritic spine morphology, abnormal axonal growth, and altered synaptic development [60, 61]. In another ASD model, the valproic acid rat model, numerous genes are differentially expressed [62]. These differentially-expressed genes are involved in nervous system development including neurogenesis, neuron maturation and differentiation, synapse formation, and maturation [62, 63]. Unfortunately, studies of MAPs in these rodent models are still lacking. In schizophrenia, structural alterations, including synaptic pruning defects and spine and dendrite atrophy, have been detected in the cortex. And changes in brain structure have been associated with changes in plasticity including decreased pruning and defects in spinogenesis [64]. Tangled lamination, delayed

cortical development, and altered dendrite development, are correlated with Down syndrome. In terms of dendrite development, the abnormalities can be represented as reduced number of spines, changed morphology, and deficient cortical layering [45, 65]. There is sufficient evidence to suggest that many neurodevelopment disorders are characterized by cytoskeletal abnormalities [38, 39, 45, 64, 65]. As a result, MAPs are important in these disorders. Systematic investigation of the MAPs involved in the mediation of autism-like behaviors is as yet lacking [66].

Here, several MAPs associated with some neurological disorders are described. By interacting with MAP1B, KIRREL3 (a synaptic molecule of the immunoglobulin superfamily) is involved in ASD pathogenesis. MAP1B plays a vital role in controlling neuronal morphogenesis, and its defect results in altered actin microfilament polymerization and changed activity of GTPases [67]. Autism susceptibility candidate 2, a gene associated with many neurodevelopmental disorders including ASD, interacts with several MAPs and influences neuronal migration [68]. By phosphorylating tau protein and related MAPs, microtubule affinity-regulating kinases adjust microtubule dynamics in neurons and thus participate in the pathology of ASD [45, 69]. Low MAP1B and MAP2 immunoreactivity has been found in the brains of individuals with schizophrenia, and MAP6-null mice display several features associated with schizophrenia such as cognitive deficits, anxiety, and hyperactivity [70, 71]. The increased expression of DYRK1A (dual-specificity tyrosine-phosphorylation-regulated kinase 1A), a gene associated with the neuropathological features of Down syndrome, has been detected in individuals with this syndrome, and its overexpression leads to decreased dendritic spine formation in cultured hippocampal neurons. Also, the dysregulation of cytoskeletal proteins such as tubulin, actin and MAPs are associated with these anatomical abnormalities [72, 73].

STOP/MAP-6 are calmodulin-regulated proteins responsible for the high degree of stabilization shown by neuronal microtubules and the establishment of neuronal architecture and synaptic plasticity [41]. Changes in microtubule dynamics and stability have an impact on brain functions, and such changes are related to the physiopathology of neurodegenerative and psychiatric diseases, such as cognition, memory, attention, and executive function [74]. Wei *et al.* [41, 75] found that STOP/MAP-6 is significantly reduced in the plasma of autistic patients and in the cerebral cortex of BTBR mice compared with controls. STOP/MAP6-null mice exhibit several synaptic abnormalities and behavioral changes, including disorganized activity, social interaction, and maternal behavior, and the deletion of STOP/MAP-6 in mice results in changes in mood and cognitive performance [66, 75, 76].

Overall, STOP/MAP-6 is reckoned to be involved in ASD, and a possible mechanism of action of STOP/MAP-6 protein in the pathogenesis of ASD has been proposed. STOP/MAP-6 has different isoforms: N- and E-isoforms expressed by neurons, and A- and O-isoforms expressed by astrocytes and oligodendrocytes [77]. Oligodendrocytes are involved in the maintenance of the myelin sheets wrapping neurons, astrocytes maintain homeostasis in the CNS, and neuronal STOP/MAP-6 isoforms participate in the maintenance of microtubule stability [71, 77]. Sufficient evidence suggests that STOP/MAP-6 protects microtubules against depolymerization when exposed to cold or depolymerizing drugs, and helps microtubules to remain stable. Deletion of STOP/MAP-6 in rats disrupts the synaptic plasticity and neurotransmission associated with severe behavioral disorders [57, 71]. These different isoforms of STOP/MAP-6 have various microtubule-stabilizing actions. All of these activities are accomplished by binding two sets of microtubule-stabilizing motifs, the Mn and Mc modules, and these activities are regulated by Ca^{2+}-calmodulin [77, 78]. Therefore, one possible hypothesis is that STOP/MAP-6 damages myelin development in oligodendrocytes, impairs microtubule dynamics and stability, and induces a chain of abnormalities in synaptic function and myelination [75]. Wei *et al.* [35] have reported a lower level of evoked glutamate release in the cerebral cortex of BTBR mice than in B6 mice. Similarly, it has been reported that STOP knockout mice have a lower density of synaptic vesicles and less glutamate is released into the synaptic cleft [79]. As a result, a glutamatergic hypothesis has been proposed [35, 37, 79]

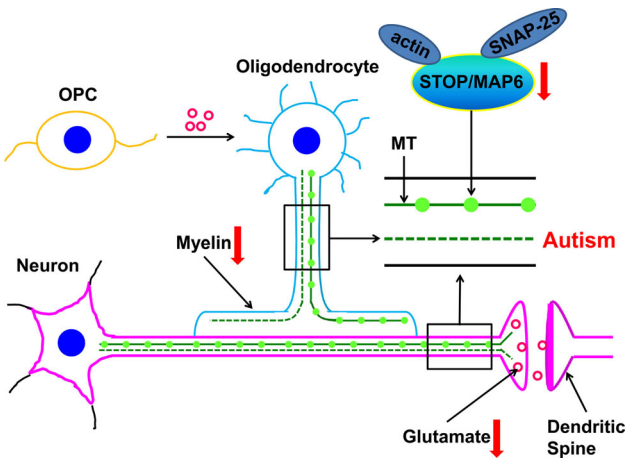

Fig. 2 Possible pathological mechanisms by which STOP/MAP6 protein is involved in ASD. MT, microtubule; OPC, oligodendrocyte precursor cell; SNAP-25, synaptosomal-associated protein 25; STOP/MAP6, stable tubule only polypeptide/microtubule-associated protein 6. Image adapted from Wei *et al.* Psychiatry Res 2016 [75].

Above all, on the basis of the evidence from the literature and results in animal and human studies, the mechanism of STOP/MAP-6 can be proposed. On the one hand, reduced STOP/MAP6 protein impacts the vesicle density and glutamate release in excitatory synapses. On the other hand, it may affect the myelin development in oligodendrocytes, and the consequent abnormalities in synaptic function and myelination could mediate the behavioral phenotypes of ASD. The mechanisms by which STOP/MAP6 is involved in ASD are illustrated in Fig. 2 [41, 75]. On the basis of the literature, we can conclude that decreased STOP expression in the brain is involved in the mediation of autism-like behaviors by impairing myelination in oligodendrocytes and synaptic function in neurons.

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Compliance with Ethical Standards

Conflicts of interest The authors declare that there are no conflicts of interest.

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