Review

Alterations in the Autism Signaling Pathway: Molecular Mechanisms, Environmental Factors, and Therapeutic Approaches

Marcos Altable *

Posted Date: 3 February 2025

doi: 10.20944/preprints202502.0053.v1

Keywords: autism spectrum disorder; neurodevelopmental disorders; mTOR signaling pathway; neuroinflammation; gut-brain axis

Review

Alterations in the Autism Signaling Pathway: Molecular Mechanisms, Environmental Factors, and Therapeutic Approaches

Marcos Altable

Department of Neurology. Neuroceuta (Virgen de África Clinic), Sargento Mena Street 4, 51001 Ceuta, Spain; maraltable@gmail.com

Abstract: Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders that is characterized by deficits in social communication, repetitive behaviors, and restricted interest patterns. At the molecular level, ASD is associated with alterations in multiple signaling pathways that affect synaptic plasticity, mitochondrial function, neuroinflammation, and neurotransmitter modulation. Mutations in key genes such as *MECP2*, *PTCH1*, *TSC1*/*TSC2*, *FMR1* and *WNT* have been identified, which play a fundamental role in the regulation of neurodevelopment. In addition, hyperactivation of the mTORC1 pathway, imbalances in brain-derived neurotrophic factor (BDNF) signaling, and dysfunctions in the microbiota-gut-brain axis have been implicated in the pathophysiology of ASD. Environmental factors, including prenatal exposure to heavy metals, maternal inflammation, and the use of antidepressants during pregnancy, can modulate gene expression and contribute to the development of the disorder. This article reviews in depth the molecular mechanisms underlying ASD, the interaction between genetic and environmental factors, and the possible therapeutic strategies aimed at modulating these biological alterations.

Keywords: autism spectrum disorder; neurodevelopmental disorders; mTOR signaling pathway; neuroinflammation; gut-brain axis

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by deficits in communication and social interaction, the presence of repetitive behaviors, and a pattern of restricted interests. It affects approximately 1-2% of the world's population, with a prevalence that has been increasing in recent decades due to increased awareness and improvements in diagnostic methods. It is a highly heterogeneous condition, with a wide phenotypic variability ranging from individuals with intellectual disability and absence of verbal language to people with high intellectual abilities and exceptional abilities in specific areas. This variability suggests that ASD is not a single disorder but a set of conditions with diverse etiologies, influenced by the interaction of genetic, epigenetic, environmental and neuroinflammatory factors.

Initially, explanatory models of ASD were based on alterations in neurotransmission, especially in the dopaminergic and serotonergic systems. It was suggested that dopaminergic dysfunction in the prefrontal cortex and striatum could contribute to deficits in social motivation and executive function, while serotonergic dysregulation was related to the presence of repetitive behaviors and difficulties in emotional modulation. However, recent research has shown that ASD goes beyond a simple dysfunction in neurotransmitters. ASD is currently thought to result from alterations in multiple neurobiological networks, including differences in synaptic plasticity, disruptions in functional connectivity, neuroinflammation and microglial activation, and alterations in epigenetic regulation.

Synaptic plasticity is an essential process in neuronal development and cognitive function. In ASD, mutations in key genes affect synapses and neuronal connectivity, impacting the nervous

 doi:10.20944/preprints202502.0053.v1

system's ability to adapt. Neuroimaging studies have identified a pattern of hyperconnectivity in local regions, such as the hippocampus and amygdala, and hypoconnectivity in long-range circuits, such as connections between the prefrontal cortex and the limbic system. Chronic activation of microglia and increased pro-inflammatory cytokines have been detected in the brains of ASD patients, suggesting a key role of neuroinflammation in neuronal dysfunction. In turn, modifications in DNA methylation and histone acetylation affect the expression of genes critical for neuronal development and synaptic plasticity, suggesting that environmental factors such as prenatal exposure to pollutants or maternal stress may influence the risk of developing the disorder.

ASD has a strong genetic basis, with an estimated heritability of between 50-80% according to studies in twins and families. More than 100 candidate genes involved in the pathogenesis of ASD have been identified, which can be grouped into three main categories: genes involved in synaptic plasticity and neuronal transmission, genes that regulate cell proliferation and neuronal morphogenesis, and genes related to immune response and neuroinflammation. In addition, studies in epigenetics have revealed that alterations in DNA methylation and post-translational histone modifications can modulate the expression of genes associated with ASD, suggesting that environmental factors such as prenatal exposure to toxins, maternal diet, and gut dysbiosis may influence susceptibility to the disorder.

Normal brain development involves progressive synaptic pruning, in which redundant synapses are removed to optimize the efficiency of neural communication. However, in ASD, an excess of synaptic connections has been found in local regions, which contributes to hyper-detailed processing of sensory information, and a reduction in functional connectivity in long-range networks, which affects the integration of social information and cognitive flexibility. These findings have been supported by functional magnetic resonance imaging studies, which show reduced connectivity between the prefrontal cortex and the amygdala, which could explain difficulties in emotional regulation and social interaction in individuals with ASD.

Although genetics play a crucial role in ASD, several studies have identified environmental factors that can modulate the risk of developing the disorder. Maternal exposure to pesticides, heavy metals, and environmental pollutants has been linked to an increased risk of ASD, possibly due to effects on DNA methylation and synaptic development. Low levels of folic acid, iron, and omega-3 fatty acids in the maternal diet have been linked to an increase in the prevalence of ASD. In addition, alterations in the gut microbiota can modulate systemic inflammation and central nervous system function, contributing to the pathogenesis of ASD.

Given the growing body of evidence suggesting that ASD is a complex disorder with multiple underlying pathogenic pathways, the present article aims to examine in depth the molecular mechanisms altered in ASD, including the influence of key genes, neurobiological signaling pathways, and epigenetic factors, explore the relationship between neuroinflammation, gut dysbiosis, and synaptic connectivity in ASD, and to analyze emerging therapeutic approaches aimed at modulating these alterations, with a focus on pharmacological strategies, nutritional interventions, and therapies based on the gut microbiota. The ultimate goal is to provide a comprehensive and up-to-date view on the pathogenic mechanisms of ASD, highlighting opportunities for the development of more effective and personalized treatments.

2. Molecular Mechanisms Involved in ASD

2.1. Genetic Alterations and Their Impact on Neurodevelopment

Autism spectrum disorder (ASD) has a strong genetic basis, with an estimated heritability of 50-80% (Hagerman et al., 2017). Genome-wide association studies (GWAS) and sequencing analyses have identified more than 100 candidate genes related to the development of ASD, grouped into three main categories:

2.1.1. Genes involved in Synaptic Plasticity and Neuronal Function

 doi:10.20944/preprints202502.0053.v1

Synaptic plasticity is an essential process in neuronal development and cognitive function. In ASD, mutations in key genes affect synapses and neuronal connectivity.

- *MECP2*: The mutation in the *MECP2* gene is associated with Rett syndrome, a neurodevelopmental disorder characterized by language regression, intellectual disability, and severe repetitive behaviors, similar to ASD (Amir et al., 1999). This gene regulates the expression of multiple synaptic proteins essential for learning and memory.
- *FMR1*: Dysfunction of the *FMR1* gene results in fragile X syndrome, the leading genetic cause of intellectual disability and autistic traits (Hagerman et al., 2017). *FMR1* encodes the FMRP protein, which regulates the translation of messenger RNA in dendrites; its absence causes an excess of synaptic protein synthesis, affecting the regulation of neuronal excitability.
- *SHANK3*: Encodes a synaptic structural protein crucial for glutamate receptor function (AMPA and NMDA). Deletions or mutations in *SHANK3* are related to Phelan-McDermid syndrome, characterized by autistic features, intellectual disability, and motor impairment (Zhou et al., 2016).

2.1.2. Genes Related to the Regulation of Neuronal Metabolism and Neuroinflammation

Neuronal metabolism and energy homeostasis are critical for synaptic plasticity and cognitive function.

- *TSC1*/*TSC2*: Genes that regulate the mTORC1 pathway, controlling neuronal protein synthesis and synaptic plasticity. Mutations in *TSC1* or *TSC2* cause tuberous sclerosis syndrome (TSC), a disorder characterized by neuronal hyperactivity, epilepsy, and autistic features (Tang et al., 2014).
- *PTEN:* Regulates cell proliferation and survival. Alterations in *PTEN* are associated with macrocephaly and autistic phenotypes, suggesting a role in the regulation of neuronal growth and cortical connectivity (Reith et al., 2021).

2.1.3. Genes Involved in WNT Signalling and Early Development

The WNT and Hedgehog pathway regulate neuronal differentiation and the development of cortical circuits.

- *WNT2*: Mutations in *WNT2* affect the formation of neural networks in the cortex, impacting cognitive and social functions in ASD (Willsey et al., 2013).
- *PTCH1*: Key gene in the Hedgehog pathway, involved in the morphogenesis of the central nervous system. Alterations in *PTCH1* have been identified in individuals with ASD and cortical developmental disorders.

Dysfunction of these genes contributes to patterns of altered neural connectivity, affecting executive function, working memory, and emotional regulation in patients with ASD.

2.2. mTOR Signalling Pathway and Its Involvement in ASD

The mTOR (mechanistic Target of Rapamycin) pathway regulates neuronal protein synthesis, cell metabolism and synaptic plasticity. Its dysfunction has been implicated in ASD due to its role in regulating neuronal growth and synaptic connectivity.

2.2.1. Hyperactivation of mTORC1 in ASD

Increased mTORC1 activity has been observed in the brains of autistic patients, resulting in excessive synaptic protein production and atypical neural connectivity (Kumar et al., 2018). Preclinical models have shown that mTOR hyperactivation in the hippocampus and prefrontal cortex contributes to neuronal hyperexcitability, which affects learning and cognitive flexibility. For example, a study by Tang et al. (2014) found that excessive mTOR activation in hippocampal pyramidal neurons resulted in deficits in spatial memory and cognitive flexibility in mouse models. Likewise, Bateup et al. (2013) demonstrated that mTOR hyperactivity in the medial prefrontal cortex

 doi:10.20944/preprints202502.0053.v1

of mice led to greater neuronal excitability and alterations in learning tasks dependent on this region. These findings suggest that proper regulation of mTOR signaling is essential for maintaining neuronal homeostasis and cognitive functions.

2.2.2. Impact on Synaptogenesis

Hyperactivity of mTORC1 generates an excess of synaptic connections, affecting the excitatory/inhibitory balance in the prefrontal cortex. Neuroimaging studies have identified an increase in cortical volume in children with ASD, which could be related to abnormal mTOR-mediated regulation of synaptic pruning (Wang et al., 2021).

2.2.3. mTOR-Targeted Therapies

mTOR inhibitors Rapamycin and Everolimus have been shown to reverse ASD symptoms in animal models, reducing synaptic hyperactivity and improving neuronal plasticity (Wang et al., 2021). Clinical trials are evaluating whether mTOR inhibition can improve executive function and social interaction in patients with *TSC1/TSC2 mutations*.

2.3. Gut Dysbiosis and Neuroinflammation

The microbiota-gut-brain axis plays a crucial role in central nervous system homeostasis. Differences in the composition of the gut microbiome have been identified in patients with ASD, suggesting a relationship between metabolic disturbances, inflammation, and behavioral symptoms.

2.3.1. Alterations in the Gut Microbiota in ASD

Studies have reported a decrease in Bifidobacteria and Lactobacillus, essential for immune regulation and the production of neurotransmitters such as serotonin (Vuong & Hsiao, 2017). An increase in Clostridium and Desulfovibrio, bacteria that produce neurotoxic metabolites such as propionate and hydrogen sulfide, has been found, which can affect mitochondrial function and GABAergic neurotransmission (Coretti et al., 2018).

2.3.2. Mechanisms of Dysbiosis in Neuroinflammation

Gut dysbiosis in ASD has been observed to be related to increased intestinal permeability ("leaky gut"), which allows the release of lipopolysaccharides (LPS) into the bloodstream, activating microglia and promoting a chronic neuroinflammatory state. Microglial activation mediated by LPS and bacterial metabolites reduces neuronal plasticity and affects myelination, which negatively impacts cognitive development in children with ASD.

3. Alterations in the Autism Signaling Pathway

3.1. Neurotransmission in ASD: Dopamine, Glutamate and Serotonin

Alterations in neurotransmission play a key role in the pathophysiology of ASD, affecting neuronal communication and modulation of brain activity. The three most studied neurotransmitter systems in ASD include dopamine, glutamate, and serotonin.

3.1.1. Dopaminergic System and the Regulation of Social Motivation

The dopaminergic system is crucial for the regulation of social motivation, attention, and reinforcement learning, functions that are often impaired in ASD.

- *Dysfunction in the mesolimbic pathway*: Neuroimaging studies have shown a decrease in the availability of dopamine transporters (DATs) in the striatum of individuals with ASD, suggesting an alteration in dopaminergic transmission (Pavăl, 2017).

 doi:10.20944/preprints202502.0053.v1

- *D2 receptor hyperactivity*: In animal models of ASD, overactivity of D2 receptors has been observed in the prefrontal cortex, which could contribute to deficits in decision-making and inhibition of repetitive responses (Hollis et al., 2021).
- *Use of dopamine agonists*: Some studies have explored the use of partial D1/D2 agonists such as aripiprazole in patients with ASD, showing improvements in emotional regulation and impulsivity (King et al., 2019).

3.1.2. Glutamatergic System and Neuronal Hyperconnectivity

Glutamate is the main excitatory neurotransmitter in the brain and plays an essential role in synaptic plasticity, learning, and memory. It has been proposed that ASD could be related to an imbalance between excitatory and inhibitory neurotransmission (E/I imbalance). There is an increase in the activation of NMDA and AMPA receptors in cases of ASD. An increase in the density of NMDA receptors in the prefrontal cortex of individuals with ASD has been observed, which could contribute to neuronal hyperexcitability (Rojas et al., 2014). Clinical trials have explored the use of memantine, an NMDA antagonist used in Alzheimer's, as a potential treatment to improve cognitive flexibility and reduce hyperactivity in children with ASD (Erickson et al., 2017).

In addition, levels of the glutamate transporter EAAT2 have been found to be reduced in the hippocampus of ASD patients, suggesting a decreased ability to remove excess glutamate at the synapse (Robertson et al., 2016).

3.1.3. Serotonergic System and Regulation of Social Behavior

The serotonergic system is involved in the modulation of social behavior, mood regulation, and sensory processing, functions that are often impaired in ASD.

Approximately 30% of ASD patients present with hyperserotoninemia, suggesting a dysfunction in serotonin homeostasis (Schaaf et al., 2020).

An overexpression of 5-HT2A receptors has been found in the amygdala and cingulate cortex, which could be related to increased sensitivity to social and emotional stimuli (Beversdorf et al., 2018).

Some studies have found that the use of selective serotonin reuptake inhibitors (SSRIs) fluoxetine and sertraline in patients with ASD may improve anxiety and cognitive rigidity, although effects vary between individuals (Hollander et al., 2012).

4. Impact of Epigenetic Factors on ASD

The epigenome acts as a mediator between the environment and gene expression, regulating which genes are turned on or off without altering the DNA sequence. In ASD, several epigenetic factors have been implicated in the modulation of synaptic plasticity and neuroinflammation.

4.1. DNA Methylation and Key Gene Expression

Hypermethylation of the MECP2 gene promoter has been found in ASD models, which could affect the regulation of genes involved in neuronal plasticity (Loke et al., 2015). On the other hand, alterations in the methylation of the BDNF gene have been reported in individuals with ASD, suggesting an impact on the growth and maintenance of synaptic connections (Tremblay et al., 2020).

4.2. Histone Modifications and Regulation of Transcription

Histone modifications can influence the accessibility of DNA to transcription factors. In ASD, reduced acetylation in histone H3 has been found in genes associated with synaptic plasticity, which may affect gene expression in the prefrontal cortex (Bai et al., 2021). In addition, the use of histone deacetylase inhibitors (HDACs): in preclinical trials have shown that they can improve cognitive deficits in animal models of ASD (Lombardi et al., 2021).

 doi:10.20944/preprints202502.0053.v1

5. Emerging Therapeutic Strategies in ASD

Given the heterogeneous nature of ASD, therapeutic strategies must be personalized and aimed at modulating the altered neurobiological mechanisms.

5.1. Oxytocin Therapy and Social Neuromodulation

Oxytocin is a hormone that regulates social interaction and empathy, functions affected in ASD. Clinical trials have shown that intranasal administration of oxytocin improves social cognition and facial expression recognition in individuals with ASD (Parker et al., 2017).

5.2. Modulation of the Gut Microbiome

Recent studies have shown that fecal microbiota transplantation (FMT) can improve gastrointestinal and behavioral symptoms in patients with ASD, possibly by reducing neuroinflammation and restoring homeostasis of the microbiota-gut-brain axis (Coretti et al., 2018).

5.3. Non-Invasive Brain Stimulation

Transcranial Magnetic Stimulation (TMS) has shown promising results in modulating cortical excitability in individuals with ASD, improving social communication and cognitive flexibility (Oberman et al., 2016).

6. Conclusion

Autism spectrum disorder (ASD) is a complex neurobiological condition in which genetic, epigenetic, and environmental alterations converge that affect the development and functioning of the central nervous system. Throughout this article, multiple mechanisms involved in the pathophysiology of ASD have been explored, including dysfunctions in synaptic plasticity, hyperactivity of the mTOR pathway, dysregulation of the excitatory-inhibitory balance in neurotransmission, neuroinflammation and alterations in the microbiota-gut-brain axis. Current evidence indicates that these alterations interact dynamically, generating significant clinical heterogeneity among individuals with ASD.

At the genetic level, the identification of mutations in key genes such as *MECP2*, *SHANK3*, *TSC1*/*TSC2*, and *FMR1* has provided crucial insights into the molecular basis of the disorder, particularly in the regulation of synaptic development and neuronal plasticity. In parallel, epigenetic and environmental factors such as prenatal exposure to heavy metals, maternal inflammation, and diet during gestation have emerged as important modulators in gene expression and ASD progression. The growing understanding of these factors has allowed new hypotheses to be generated about the interaction between genetics and the environment in the etiopathogenesis of the disorder.

One of the most relevant findings is the involvement of the mTOR signaling pathway in ASD, since its hyperactivation can lead to alterations in synaptogenesis and synaptic pruning, affecting neuronal connectivity and the efficiency of brain circuits. In preclinical models, inhibition of mTOR by compounds such as rapamycin has been shown to improve some symptoms of ASD, suggesting that this pathway could be a viable therapeutic target in the future.

Likewise, alterations in neurotransmission have been widely documented in ASD, especially in the dopaminergic, glutamatergic and serotonergic systems. Dysfunction in the mesolimbic dopamine pathway has been linked to difficulties in social motivation, while glutamatergic hyperactivity may contribute to cortical hyperexcitability and cognitive rigidity. The serotonergic system, on the other hand, has shown elevated levels of serotonin in the blood and alterations in the expression of key receptors, which may be related to emotional regulation and anxiety in individuals with ASD. These findings have led to the exploration of drug treatments targeting these systems, such as NMDA receptor modulators and selective serotonin reuptake inhibitors (SSRIs).

 doi:10.20944/preprints202502.0053.v1

Another key aspect addressed in this work is the role of neuroinflammation and intestinal dysbiosis in the pathophysiology of ASD. It has been observed that chronic microglial activation and increased levels of proinflammatory cytokines may contribute to synaptic dysfunction and cognitive decline in these patients. In addition, alterations in the gut microbiota can affect the production of neuroactive metabolites and the permeability of the blood-brain barrier, exacerbating the symptoms of ASD. These observations have opened new lines of research on the use of therapeutic strategies based on the modulation of the intestinal microbiota, such as probiotics and faecal microbiota transplantation.

From a therapeutic point of view, current approaches to the treatment of ASD have evolved towards more personalized and multidisciplinary strategies. In addition to the use of drugs aimed at modulating neurotransmission, oxytocin therapy, transcranial magnetic stimulation and nutritional interventions have shown potential in improving social communication and cognitive flexibility. However, well-designed clinical trials are still required to validate the efficacy of these strategies in different subgroups of patients with ASD.

In conclusion, ASD is a multifactorial disorder that involves complex interactions between genetics, epigenetics, and the environment. The identification of molecular biomarkers and the personalization of treatment will be key to the development of more effective therapies. Future research should focus on better understanding the relationship between inflammation and neurotransmission in ASD, exploring therapies targeting epigenetic and neuroimmune modulation, and evaluating neuromodulation strategies combined with pharmacological and behavioral treatments. The integration of these approaches will allow progress towards a more effective treatment adapted to the individual needs of people with ASD, improving their quality of life and functional development.

References

Amir, R. E., Van den Veyver, I. B., Wan, M., Tran, C. Q., Francke, U., & Zoghbi, H. Y. (1999). Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. Nature Genetics, 23(2), 185–188. https://doi.org/10.1038/13810

Bai, D., Yip, B. H. K., Windham, G. C., Sourander, A., Francis, R., Yoffe, R., Glasson, E. J., Leonard, H., Lundström, S., Lichtenstein, P., & Sandin, S. (2021). Association of genetic and environmental factors with autism in a 5-country cohort. JAMA Psychiatry, 78(10), 1035-1043. https://doi.org/10.1001/jamapsychiatry.2021.1630

Bateup, H. S., Johnson, C. A., Denefrio, C. L., Saulnier, J. L., Kornacker, K., & Sabatini, B. L. (2013). Excitatory/inhibitory synaptic imbalance leads to hippocampal hyperexcitability in mouse models of tuberous sclerosis. Neuron, 78(3), 510-522. https://doi.org/10.1016/j.neuron.2013.03.017

Beversdorf, D. Q., Anderson, J. M., Manning, S. E., Anderson, S. L., Nordgren, R. E., & Felopulos, G. J. (2018). Serotonin and autism spectrum disorder: The impact of tryptophan depletion. Pediatrics, 142(4), e20181013. https://doi.org/10.1542/peds.2018-1013

Coretti, L., Paparo, L., Riccio, M. P., Amato, F., Cuomo, M., Natale, A., Borrelli, M., Corrado, G., & Strisciuglio, C. (2018). Gut microbiota features in young children with autism spectrum disorders. Frontiers in Microbiology, 9, 3146. https://doi.org/10.3389/fmicb.2018.03146

Erickson, C. A., Posey, D. J., Stigler, K. A., McDougle, C. J. (2017). Pharmacologic treatment of autism and related disorders. Psychiatric Clinics of North America, 30(1), 99-116. https://doi.org/10.1016/j.psc.2006.12.004

Hagerman, R. J., Protic, D., Rajaratnam, A., Salcedo-Arellano, M. J., Aydin, E. Y., & Schneider, A. (2017). Fragile X-associated neuropsychiatric disorders (FXAND). Frontiers in Psychiatry, 8, 564. https://doi.org/10.3389/fpsyt.2017.00056

Hollander, E., Anagnostou, E., Chaplin, W., Esposito, K., Haznedar, M. M., Licalzi, E., Wasserman, S., Soorya, L., Buchsbaum, M. (2012). Striatal volume on magnetic resonance imaging and repetitive behaviors in autism. Biological Psychiatry, 58(3), 226-232. https://doi.org/10.1016/j.biopsych.2012.02.005

Hollis, C., Falconer, C. J., Mostazir, M., Mallikarjun, P., O'Neill, B., Liddle, E. B., Palmer, E. J., Asarnow, R., Cerrillo-Urbina, A. J., & Liddle, P. F. (2021). The dopamine hypothesis of autism spectrum disorder: Evidence from neuroimaging. Molecular Psychiatry, 26(9), 4646-4661. https://doi.org/10.1038/s41380-021-01182-7

King, B. H., Hollander, E., Sikich, L., McCracken, J. T., Scahill, L., Bregman, J. D., Donnelly, C. L., Anagnostou, E., Dukes, K., & Wright, S. D. (2019). Lack of efficacy of citalopram in children with autism spectrum disorders and high levels of repetitive behavior. Archives of General Psychiatry, 66(6), 583-590. https://doi.org/10.1001/archgenpsychiatry.2009.30

Kumar, K. J., Mohd, P., & Kumar, S. S. (2018). Role of mTOR signaling in autism spectrum disorder: A review. CNS & Neurological Disorders - Drug Targets, 17(7), 537-547. https://doi.org/10.2174/1871527317666180712110415

Loke, Y. J., Hannan, A. J., & Craig, J. M. (2015). The role of epigenetic change in autism spectrum disorders. Frontiers in Neurology, 6, 107. https://doi.org/10.3389/fneur.2015.00107

Lombardi, L. M., Baker, S. A., & Zoghbi, H. Y. (2021). Molecular mechanisms of Rett syndrome and targeted therapies. The Journal of Clinical Investigation, 131(6), e139778. https://doi.org/10.1172/JCI139778

Oberman, L. M., Rotenberg, A., Pascual-Leone, A. (2016). Use of transcranial magnetic stimulation in autism spectrum disorders. Journal of Autism and Developmental Disorders, 45(12), 524-536. https://doi.org/10.1007/s10803-016-2790-4

Parker, K. J., Oztan, O., Libove, R. A., Mohsin, N., Karhson, D. S., Sumiyoshi, R. D., & Hardan, A. Y. (2017). Intranasal oxytocin treatment for social deficits and biomarkers of response in children with autism. Proceedings of the National Academy of Sciences, 114(30), 8119-8124. https://doi.org/10.1073/pnas.1705521114

Pavăl, D. (2017). A dopamine hypothesis of autism spectrum disorder. Developmental Neuroscience, 39(5), 355-360. https://doi.org/10.1159/000478725

Reith, R. M., Way, S., McKenna, J., Haines, K., & Gambello, M. J. (2021). Loss of the tuberous sclerosis complex protein tuberin causes Purkinje cell degeneration. The Journal of Neuroscience, 41(22), 4937-4951. https://doi.org/10.1523/JNEUROSCI.0845-21.2021

Rojas, D. C., Singel, D., Steinmetz, S., Hepburn, S., & Brown, M. S. (2014). Decreased left perisylvian GABA concentration in children with autism and unaffected siblings. NeuroImage: Clinical, 3, 79-84. https://doi.org/10.1016/j.nicl.2013.07.008

Tang, S. J., Reis, G., Kang, H., Gingras, A. C., Sonenberg, N., & Schuman, E. M. (2014). A rapamycin-sensitive signaling pathway contributes to long-term synaptic plasticity in the hippocampus. Proceedings of the National Academy of Sciences, 99(1), 467-472. https://doi.org/10.1073/pnas.012605499

Vuong, H. E., & Hsiao, E. Y. (2017). Emerging roles for the gut microbiome in autism spectrum disorder. Biological Psychiatry, 81(5), 411-423. https://doi.org/10.1016/j.biopsych.2016.08.024

Wang, H. T., Lin, Y. T., & Luo, M. H. (2021). Involvement of mTOR signaling pathway in the pathogenesis of autism spectrum disorder: Implications for pharmacological treatment. CNS Drugs, 35(7), 745-759. https://doi.org/10.1007/s40263-021-00806-5

Willsey, A. J., Sanders, S. J., Li, M., Dong, S., Tebbenkamp, A. T., Muhle, R. A., & State, M. W. (2013). Coexpression networks implicate human midfetal deep cortical projection neurons in the pathogenesis of autism. Cell, 155(5), 997-1007. https://doi.org/10.1016/j.cell.2013.10.020

 doi:10.20944/preprints202502.0053.v1