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# Autism spectrum disorder and the TGF-beta signalling pathway: Molecular relationships and therapeutic possibilities

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***ABSTRACT***

Autism spectrum disorder (ASD), a neurodevelopmental condition, is defined by challenges in social interaction and communication, repetitive behaviors, and focused or limited interests. The study of the molecular causes of ASD has advanced significantly in recent years. Transforming growth factor-beta (TGF-β) is a growth factor that is crucial for many biological processes, including synaptic plasticity, immune regulation, cell growth, and differentiation. According to research, the TGF-β signaling pathway abnormalities may be a factor in ASD. The influence of TGF-β on the regulation of the immune system, synaptic plasticity, and the development of the nervous system could potentially affect key aspects of ASD. It is well known that environmental, genetic, and epigenetic factors can all impact TGF-β activity. The TGF-β signaling pathway may offer therapeutic targets for ASD. The etiology and pathophysiology of ASD may benefit from potential therapeutic approaches that target TGF-β. In this review, we explained the definition and history of ASD, its relationship with its sociological impact, molecular biology, and the TGF-β signaling pathway, in addition to its symptoms and medical aspects.

***Keywords:*** Autism spectrum disorder, molecular biology, neurodevelopment, signaling pathway, transforming growth factor beta.

One in every 54 children around the world suffers from autism spectrum disorder (ASD), one of the most prevalent neurodevelopmental disorders.[1,2] Autism spectrum disorder, which includes a diagnostic spectrum ranging from autistic disorder to Asperger's syndrome, was coined by Leo Kanner in 1943.[2-5] It is a more intellectually capable form of ASD with higher functioning.[6] Clinically speaking, ASD is a complex and heterogeneous neurological condition that affects a variety of developmental domains, including social interaction, communication skills, visual function, and stereotyped behavior, interests, and behaviors.[2,7] These impairments typically manifest in early childhood before the age of three, but they do not fully mature until later in life.[8] Previous research has also demonstrated that children with ASD have impaired immune systems and experience chronic neuroinflammatory disease.[9-11] There have been reports of abnormal T cell function in ASD patients.[12] Disease or a malfunctioning immune system can make people more sensitive neurologically.[13,14] ASD risk may be increased by immunological disruption in ASD, which is complicated and may be related to changes in the prenatal immune environment.[15]

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## AUTISM SPECTRUM DISORDER: DEFINITION, SYMPTOMS AND DIAGNOSTIC METHODS

Autism spectrum disorder is a neurodevelopmental disorder characterized by deficits in social communication and the presence of restricted interests and repetitive behaviors. The diagnosis of ASD is based on behavioral symptoms, as outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[16] Pediatricians play a crucial role in the early recognition of ASD, as they are often the first point of contact for parents. Parents are now more aware of the early signs of ASD, and it is important for pediatricians to be able to recognize these signs and have a systematic strategy for assessment.[17]

The symptoms of ASD can vary widely from person to person, but they generally involve

impaired social interaction and communication, as well as repetitive behaviors and restricted interests. Impaired social interaction may manifest as difficulty understanding social cues and initiating or maintaining conversations. Restricted and repetitive behaviors can include repetitive movements, adherence to routines, and intense interest in specific topics or objects.[16-20]

Diagnosing ASD can be challenging, as there is no specific medical test or biomarker for the disorder. Diagnosis is typically based on a comprehensive evaluation of the individual's behavior and development, using criteria outlined in the DSM-5.[16] Standardized assessment tools, such as the Autism Diagnostic Observation Schedule (ADOS), may also be used to aid in the diagnosis.[17]

Early intervention is crucial for individuals with ASD, as research has shown that it can lead to improved outcomes. Therefore, it is important for parents and caregivers to be aware of the early signs of ASD and seek evaluation and support if they have concerns about their child's development. In conclusion, ASD is a neurodevelopmental disorder characterized by deficits in social communication and the presence of restricted interests and repetitive behaviors. Diagnosis is based on behavioral symptoms and a comprehensive evaluation of the individual's behavior and development. Early recognition and intervention are key in improving outcomes for individuals with ASD. Pediatricians play an important role in the early identification of ASD and should be familiar with the signs and symptoms, as well as local resources for diagnosis and management.[17]

## Causes and risk factors of autism

Autism spectrum disorder is a complex neurodevelopmental disorder whose etiology is influenced by both genetic and environmental factors. This disorder is strongly influenced by genetic factors, which have a high heritability rate. Numerous genetic risk factors and susceptibility genes linked to ASD have been discovered through studies. For instance, it was discovered that genes involved in immune response and neuronal function had different gene expression patterns in the brains of people with ASD. It was also found that genes related to ASD risk had an enrichment of de novo mutations.[21-28] Environmental factors have also been linked to the emergence of ASD, in addition to genetic ones. Antidepressant use during pregnancy and other maternal factors have been linked to an increased risk of ASD in offspring. Autism spectrum disorder risk has also been linked to perinatal exposure to specific drugs, including valproate. Additionally, a possible risk factor for ASD has been identified: prenatal infection.[22-25] Advanced parental age, low parental education, and a favorable family history have also been suggested as additional environmental factors that may increase the risk of ASD. Changes in the gut microbiota may have a role in the pathogenesis of ASD, according to research on the gut-brain axis and the disorder[29-32] as shown in Figure 1.

## Misconceptions and facts about autism

Society has many misconceptions about ASD, which can lead to misinterpretations and the stigmatization of people with ASD. To encourage understanding and acceptance, it is crucial to dispel these myths and offer accurate information. Studies have looked at how well-informed various groups are about ASD, including teachers, healthcare workers, and the general public. According to a study done in Pakistan, medical professionals were reasonably familiar with the DSM-IV-TR's diagnostic standards for ASD. However, there were differences in how these criteria were applied by various professional groups. This emphasizes the necessity of applying and comprehending the diagnostic criteria for ASD consistently.[33] The understanding and attitudes of the general public toward ASD have also been examined. In a survey done in Denmark, it was compared how people felt about people with schizophrenia and ASD. The findings demonstrated that there are misunderstandings about mental illnesses, including ASD, which may lead to prejudice and social exclusion.[34] Another study looked at ASD stigma and public perception in China and the US. The research exposed widespread misconceptions, including the idea that ASD is a childhood disorder and the idea that people with autism are either patients or savants. These myths may contribute to stigma and unfavorable attitudes toward people with ASD.[35] Teachers are essential in helping students with ASD, but a study in Oman revealed that many mainstream teachers held incorrect beliefs about the disorder. Potential causes of

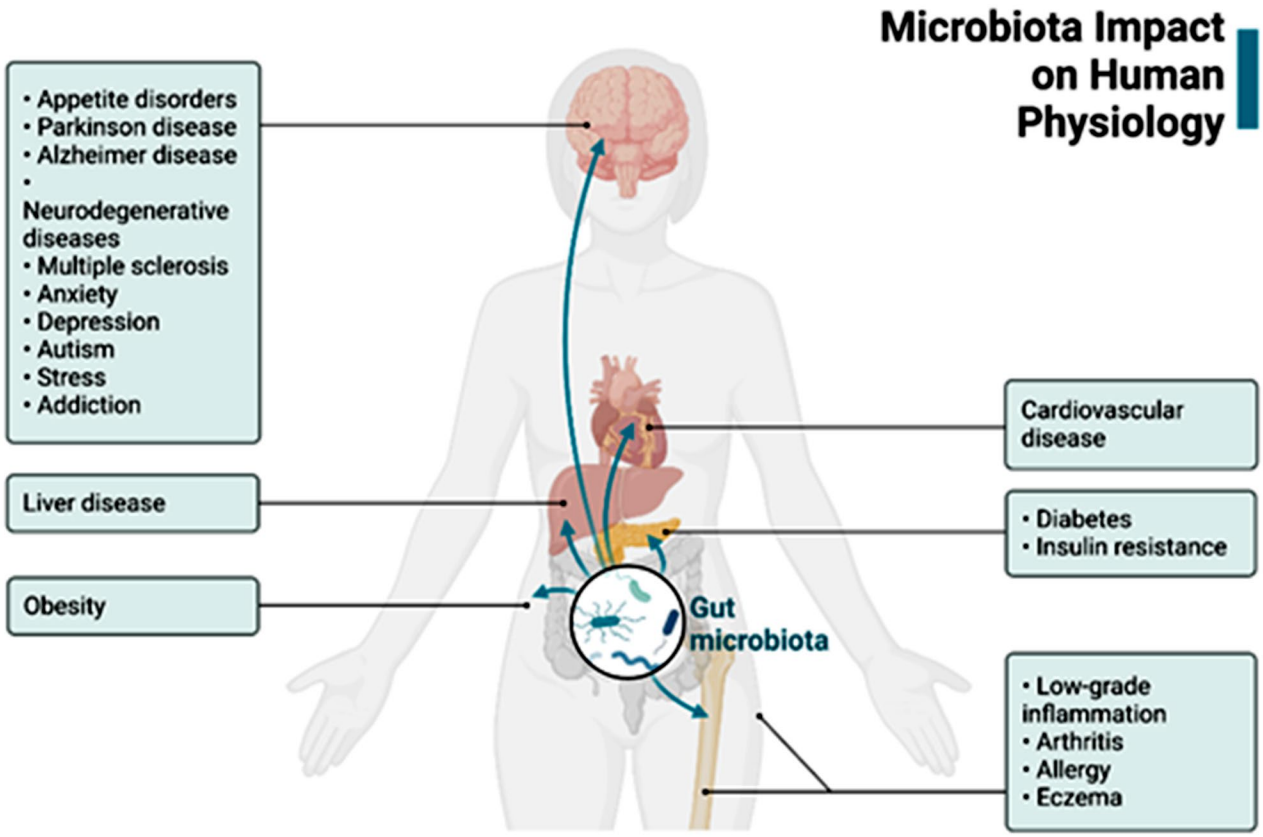


**Figure 1.** The relationship between the microbiota and autism is an area of ongoing research and is not yet fully understood. The microbiota refers to the diverse community of microorganisms that reside in and on our bodies, primarily in the gut. It plays a crucial role in maintaining our overall health and has been linked to various aspects of human physiology and diseases.

*Figure 1 was created with BioRender (BioRender.com).*

these misconceptions include a lack of knowledge and divergent viewpoints in the scientific and media communities.[36] There is evidence of misconceptions about the causes of ASD. In spite of scientific evidence to the contrary, some parents, particularly those of children with ASD, believed that vaccines may have contributed to their child's autism, according to a study. This myth has effects on public health and may contribute to vaccine reluctance.[37] It's critical to dispel these myths and give accurate information about ASD. Raising public awareness and comprehension of ASD can lessen stigma, encourage early detection and intervention, and enhance the lives of people with ASD and their families. In conclusion, there are many societal misconceptions about ASD, which can lead to misinterpretations, stigma, and discrimination. According to studies, the general public, teachers, and healthcare workers all hold certain misconceptions. For the purpose of fostering understanding, acceptance, and support for those with ASD, it is imperative to address these myths and provide accurate information about the disorder.[38]

### Effects of autism: Individual and family perspective

It was determined how mothers of toddlers and mothers of adolescents with ASD fared in terms of well-being and coping. The study found that families view raising a child with ASD as a very stressful experience. Compared to mothers of children with other disabilities, mothers of people with ASD reported more adverse effects and lower well-being during their children's preschool years and adulthood.[39] Autism spectrum disorder has a wide range of effects on people and their families, which emphasizes

the need to comprehend how these disorders affect families and to inform clinical support services.[40] Young adults with high-functioning autism reported significantly lower subjective quality of life than typical controls, according to a study on self-regulation and quality of life in this population. The ASD group also reported issues with executive functioning on a daily basis, which were linked to a lower quality of life.[41] Adult siblings of people with ASD were examined for signs of anxiety and depression. According to the study, adult siblings of people with ASD reported clinically significant symptoms of anxiety and depression. Compared to the general population, adult siblings had higher rates of anxiety and depression.[42] In families with and without children with ASD, the adjustment of the siblings and the well-being of the mothers were studied. The study brought to light the difficulties families encounter when dealing with ASD, including the disorder's unidentified etiology and the behavioral excesses and deficits that are linked to it.[43] A scoping review on the quality of life of siblings of autistic individuals was conducted. The review discovered that the condition of autism has different effects on the quality of life of siblings who are not autistic. The effect of ASD on non-autistic siblings' quality of life varies depending on a number of variables and may be different from that of non-autistic siblings or siblings of people with other chronic illnesses. Autism spectrum disorder has a big impact on people and their families. Mothers of people with ASD might feel more stressed out and less well-adjusted. Families may struggle to deal with the effects of ASD, and people with ASD may have a lower quality of life overall. The quality of life of non-autistic siblings can be impacted by the presence of ASD in the family. Siblings of people with ASD may also experience symptoms of anxiety and depression. For individuals with ASD and their families to receive the proper support and interventions, it is essential to comprehend the individual and family perspective.[44]

## EARLY DIAGNOSIS AND EARLY INTERVENTION IN ASD

The management of ASD depends on early diagnosis and intervention. According to research, autistic children's developmental trajectories involve both continuity and change. Parents report that their children get better as they get older, even though the majority of them still have ASD diagnoses. This raises the possibility that social interaction with peers can enhance skills in adaptive behavior and emphasizes the significance of intervention programs in this field. Early intervention for young children with autism that focuses on cognitive abilities can also have a parallel impact on those children's social skills as they develop into late adolescence and early adulthood. Studies demonstrating that high-functioning adolescents with ASD exhibit improvements in both cognitive abilities and social interaction skills support this.[45] The social domain of ASD can be successfully treated with behavioral interventions like early behavioral intervention and positive interactions with social peers. As seen in a mouse model of autism, these interventions can aid in boosting sociability in people with ASD.[46] Since ASD can present early and share risk factors with other conditions like communication disorders, early diagnosis of ASD can be difficult. Concerns about communication are frequently the main reason for referral to early intervention.[47] To access early intervention services and improve developmental outcomes, however, early identification and intervention are essential. Interventions that start in the first two years of life, when the brain is rapidly developing and the first signs of atypical development are seen, may have a greater impact on outcomes in later childhood.[48] For kids with ASD, there is compelling evidence that early intervention has positive outcomes. Children with ASD have been shown to benefit from these interventions, which frequently involve high levels of staff training, supervision, and high-intensity services.[49] For kids with ASD, educationally-based programs are frequently the main form of intervention, and there is a perception that early interventions are more successful than late ones. To compare the effectiveness of various early-teaching interventions, more study is required.[50] For access to early intervention services and precise measurement for research purposes, early diagnosis of ASD is crucial. The diagnosis of ASD in preschoolers can be aided by the combined use of standardized assessment tools, such as the Autism Diagnostic Interview-Revised and the ADOS. Good agreement between these instruments has been found, particularly for

kids with core autism.[51] Early diagnosis of ASD also gives children the chance to start receiving treatment earlier, which benefits both the child and the community. It makes it possible to study the neurological characteristics of ASD early in development and gain a better understanding of the underlying mechanisms of ASD. Early diagnosis and intervention are essential for the effective management of ASD. They may result in better outcomes for cognitive functioning, social skills, and adaptive behavior. Positive results have been seen with early intervention programs that focus on cognitive abilities and peer social interaction. Although difficult, early ASD diagnosis is crucial for getting intervention services.[52]

### Educational approaches and therapies in autism

In the context of ASD, a variety of educational strategies and therapeutic modalities have been investigated. These strategies aim to address the particular requirements and difficulties that people with ASD experience in educational settings. Dance movement therapy (DMT) is one strategy that emphasizes using body movement as a therapeutic starting point. Nonverbal interaction elements are significant parts of interactions, and DMT directly addresses them in therapy. Dance movement therapy appears to have beneficial effects on young adults with ASD, indicating its potential as a teaching strategy, according to a feasibility study.[53] Research on interventions has improved the quality and number of interventions available for kids with ASD. These interventions are intended to enhance a number of developmental factors, such as intelligence quotient, language, social skills, and academic placement. Studies have revealed, however, that many parents are unhappy with the services offered for their child with ASD, underscoring the need for further development in educational strategies.[54] For people with ASD to succeed in school, supportive and nurturing learning environments are essential. The importance of including young people with ASD in educational decisions that affect them is emphasized by this relational approach. This strategy must be used by educators, teachers, and school personnel if inclusive and successful education is to be provided for students with ASD.[55] In the area of autism, there is a persistent gap between educational research and practice. Even though there has been a lot of research on early intervention, there needs to be more research on the educational tactics and interventions used in schools. For researchers to better understand and support students with ASD in educational settings, collaborative partnerships with school professionals are essential.[56] Understanding particular ASD traits, such as pathological demand avoidance (PDA), can also help guide management and educational strategies. Individuals with PDA may respond better to different strategies than those with typical ASD, highlighting the importance of tailored interventions.[57] The educational experiences of people with ASD depend greatly on inclusive education.[58] Preventive, supportive, and corrective methods are used as inclusion promotion strategies in general education classrooms. For people with ASD and their typically developing peers to receive a quality education, collaboration between educators, experts, and parents is crucial.[59]

### Development of communication and social skills in autism

The neurodevelopmental disorder known as ASD is characterized by limitations in social interaction and communication as well as restricted and repetitive behaviors.[60,61] Communication and social skills, which are crucial for functional independence, are often difficult for people with ASD to develop. For people with ASD to function in daily life, adaptive behavior is essential. This includes communication, social, and daily living skills.[62] Impaired social interaction skills, which include challenges with reciprocal social interaction, the use and interpretation of nonverbal behaviors, and monitoring the impact of their conversations or behaviors on other people, are one of the core deficits in ASD. Relationship forming and maintenance challenges may result from these social communication and interaction deficits.[63] Additionally, people with ASD may struggle to comprehend and interpret the emotions of others, which can exacerbate the behavior issues that are frequently associated with ASD.[64] People with ASD may have difficulties developing their motor skills in addition to their social communication skills. Children with autism have been shown to have impaired motor sequence learning, which may make it more challenging for them to learn new motor, social, and communication skills.[65] It has been discovered that early gross

motor skills in children with ASD predict later language development, highlighting the significance of motor skills in social-cognitive development.[66] The underlying causes of poor social and communication abilities in ASD are intricate and poorly understood. Research, however, indicates that anomalies in brain function and development might be involved. Animal models of ASD have shown altered brain phospholipid and acylcarnitine profiles, adding evidence to the theory that brain dysfunction may play a role in the emergence of ASD.[67] Autism spectrum disorder's pathogenesis has also been linked to abnormal cerebellar function during crucial developmental stages, particularly in people with tuberous sclerosis complex.[68] There are interventions designed to help people with ASD improve their social and communication skills. Students with ASD have shown promise in improving their social skills thanks to computer-based interventions like the Avatar Assistant. The development of communication and social skills has also been supported by early intervention strategies tailored to ASD. In summary, functional independence and social interaction require that people with ASD develop their communication and social skills. People with ASD frequently struggle with motor skills, social communication, and interactional impairments. More investigation is required to comprehend the underlying mechanisms and create successful interventions to support the growth of social and communication skills in people with ASD.[69]

### Autism in adulthood: Independence and employment opportunities

For people with ASD, the transition from school to adulthood can be difficult because they frequently encounter significant barriers in areas like education, employment, community living, and independent living.[70] According to research, young adults with ASD have worse outcomes in terms of independent living, postsecondary education, and employment than their peers with other developmental disabilities.[71] According to studies, adults with high-functioning ASD frequently struggle to maintain jobs that are not a good fit for them and have low rates of independent employment.[72] Less than 25% of young adults with ASD also have a social network, work in competitive jobs, and live independently.[73] The lack of longitudinal studies to understand employment and other aspects of adulthood for this population is highlighted by the scant research on adult outcomes for people with ASD. For people with ASD, becoming an adult requires comprehensive support and services that will enable them to become independent and find employment opportunities. When defining and assessing outcomes, it is critical to take into account the unique skills, requirements, and preferences of young adults with ASD and their families.[74] Several suggestions have been put forth to enhance outcomes for people with ASD. These include fostering inclusion with peers who do not have disabilities, changing the high school curriculum, fostering employment development, expanding access to postsecondary education, and offering structured instruction. Additionally, it has been suggested that interventions like video prompting are useful tools for teaching independence and daily living skills to teenagers with ASD. People with ASD frequently struggle with the transition to adulthood and experience worse outcomes in areas like independent living, employment, and postsecondary education. To fully comprehend the unique requirements and experiences of young adults with ASD and their families, more study is required.[75]

### Supportive and alternative communication methods in autism

It has been demonstrated that augmentative and alternative communication (AAC) techniques help people with ASD communicate and interact with others more effectively.[76,77] Alternative communication modalities like picture cards, speech-generating devices, or personal gadgets like cell phones and tablets are used in AAC interventions. These techniques can assist people with ASD who struggle with speech and/or language to improve their communication abilities.[78] In one study, elementary students with ASD and developmental disabilities were given the choice between using an Apple iPad as a communication tool or a picture card system. The findings showed that when using the iPad in comparison to picture cards, communication behaviors either increased or stayed the same. This suggests that AAC apps for mobile devices, such as the iPad, may be a helpful tool for people with ASD to improve their communication abilities.[76] Additionally, it has been discovered that video modeling and video self-modeling

(VSM) interventions are successful in improving social-communication skills, functional skills, and behavioral functioning in kids and teenagers with ASD. In order to promote skill acquisition and long-term skill maintenance, these interventions use videos to demonstrate desired behaviors and abilities.[79] It's crucial to remember that AAC interventions have mainly targeted young children with ASD, and more research is required to comprehend the unique needs and advantages of adolescents and adults with ASD in relation to AAC. The use of AAC in situations that are significant in the lives of adolescents and adults with ASD should be investigated in future research. These situations could include social closeness, information transfer, and other communication functions besides requesting.[77] In general, AAC techniques, such as the use of personal gadgets and video modeling/VSM interventions, have shown promise in enhancing social and communication abilities in people with ASD. These interventions can be customized to the needs and preferences of the individual, and early intervention aimed at the first indications of ASD can produce the best developmental results. However, more investigation is required to deepen our understanding of AAC interventions and their efficiency across a range of contexts and age groups.[80]

### Increasing social awareness and acceptance in autism

Promoting social integration and the well-being of people with ASD requires raising social awareness and acceptance of these people. Numerous studies have investigated various strategies and interventions to address social deficits in people with ASD. Utilizing compensatory strategies, which people with ASD develop to navigate social situations, is one strategy. According to a qualitative study, adults with ASD use coping mechanisms to manage social interactions, such as emulating others, following rules or scripts, and using technology to communicate. Individuals with ASD may navigate social situations more skillfully if their compensatory strategies are recognized and encouraged.[81] Social cognition, or the capacity to comprehend and interpret social cues and situations, is another factor to take into account. According to research, people with ASD may struggle with implicit social cognition, which includes social awareness and spontaneous perspective-taking. This suggests that focusing on implicit social cognition during interventions may help people with ASD become more socially aware and accepted.[82] Interventions that aim to improve communication and social interaction skills have also shown promise. For instance, a peer-mediated, theatre-based intervention has been shown to improve social deficits in ASD sufferers. As part of this intervention, people with ASD participate in theatrical activities with their peers, which can improve their social skills and lengthen their interactions with well-known people.[83] The social-emotional functioning of kids with ASD has also been improved by relationship-focused interventions. In order to improve parents' use of responsive interactive strategies during routine interactions with their children, these interventions involve working with parents. These interventions can enhance social interaction and emotional well-being in kids with ASD by encouraging responsive interactions.[84] It is crucial to remember that social awareness and acceptance in people with ASD may also be influenced by elements like nutrient intake, brain structure, and hormonal influences. Research has linked nutrient intake to autistic traits, brain structural changes to core ASD symptoms, and sex hormones to autism susceptibility. Knowing these underlying causes can help to inform targeted interventions and shed light on the mechanisms underlying social deficits in ASD. Autism spectrum disorder patients' social deficits may be improved by interventions that focus on compensatory behaviors, implicit social cognition, social interaction and communication skills, and parent-child relationships. Additionally, taking into account elements like nutrient intake, brain make-up, and hormonal influences can help us understand social deficits in ASD better and guide tailored interventions.[85-87]

## MOLECULAR BIOLOGY OF AUTISM SPECTRUM DISORDER

### Genetic and epigenetic factors

The emergence of ASD is significantly influenced by genetic and epigenetic factors. Numerous genes have been linked to the etiology of ASD, which is highly heritable according to genetic studies.[88] These genes play a role

in a number of biological processes, such as chromatin remodeling, immune response, and neuronal development. The consistent differences in gene expression patterns between autistic and normal brains revealed by transcriptomic analysis point to abnormalities in cortical patterning and the involvement of particular gene modules linked to autism susceptibility.[89] The A2BP1/FOX1 is one gene whose splicing has been found to be dysregulated in the brains of people with ASD.[90] Autism spectrum disorder has also been linked to epigenetic mechanisms such as deoxyribonucleic acid (DNA) methylation, histone modification, and micro-ribonucleic acid (microRNA) regulation. Gene-environment interactions in ASD may be mediated by epigenetic changes, which can alter gene expression patterns without altering the underlying DNA sequence. Different DNA methylation patterns have been found in blood samples from people with ASD in studies, suggesting that epigenetic dysregulation may play a part in the disorder. Environmental factors have also been linked to a higher risk of ASD, including prenatal exposure to maternal infection and immune response. These environmental aspects of ASD development may interact with genetic predisposition and epigenetic mechanisms. The heterogeneity of ASD and the requirement for a thorough understanding of its underlying biology are highlighted by the complex interplay between genetic and epigenetic factors in the disorder. The molecular and clinical landscape of ASD has been illuminated by the integration of genetic and phenotypic data, which has revealed functional themes and phenotypes associated with particular groups of intellectual disability disorders. Differentially methylated genes and pathways have been found in people with ASD, providing potential biomarkers and therapeutic targets. Additionally, studies of the phenotypic effects of particular gene mutations linked to ASD have been conducted using animal models, such as Drosophila.[91-94]

### Synapse Development and synaptic plasticity in ASD: Molecular mechanisms

The neurodevelopmental disorder known as ASD is characterized by poor social skills, communication issues, and constrained and repetitive behaviors. It is still unclear what molecular and neural circuit mechanisms underlie the behavioral deficits in ASD. However, genetic analyses consistently show that ASD patients have mutations in genes related to synaptic development and function. The activity-dependent signaling networks that control the growth and plasticity of synapses are impacted by these genetic mutations.[95,96] The growth and plasticity of synapses are essential for the healthy operation of the brain.[97] During development, neurons must create the right number and quality of synaptic connections. Synapse remodeling in response to experience is made possible by synaptic plasticity, which involves enhancing or weakening long-term synaptic transmission.[98] Autism spectrum disorder is one of many neurodevelopmental disorders that have been linked to dysregulation of synapse formation and plasticity.[99] In neurodevelopmental and neurological disorders, such as ASD, synaptic dysfunction including altered excitatory or inhibitory neurotransmission and impaired synaptogenesis is frequently present.[99] The postnatal development of the nervous system is crucially impacted by altered synaptic plasticity, changes in protein synthesis and trafficking of postsynaptic proteins, and structural modifications of excitatory synapses, all of which are linked to ASD.[100] Additionally, ASD and other pathological conditions are linked to aberrant regulation of synapse numbers. Synaptic balance maintenance, synaptic plasticity, and neural circuit development all depend on the activity-dependent regulation of synapses. In conclusion, genetic mutations in synaptic development and function-related genes underlie the molecular mechanisms underlying ASD and result in the dysregulation of activity-dependent signaling networks and synaptic plasticity. The behavioral deficits seen in people with ASD are a result of these changes in synaptic development and plasticity. To fully comprehend the particular synapse types and brain regions affected in ASD and to create targeted interventions for people with ASD, more research is required.[101]

### Oxidative stress and inflammation: Molecular implications in the pathophysiology of ASD

Inflammation and oxidative stress have been linked to the pathophysiology of ASD. There is a lot of proof that autistic children have oxidative stress in their peripheral tissues. Due to its limited antioxidant capacity, high energy requirement, and abundance of unsaturated lipids

and iron, the brain is particularly susceptible to oxidative stress.[102] According to studies, certain brain regions in people with autism show signs of oxidative stress. For instance, it was discovered that autistic people have significantly lower levels of reduced glutathione (GSH) and glutathione redox/antioxidant capacity (GSH/GSSG) in their cerebellum and temporal cortex. In these brain regions, oxidative DNA damage and protein damage were also noted. These results imply that oxidative stress is present in autistic people's brains.[103] Neuroinflammation has also been linked to the pathophysiology of ASD, in addition to oxidative stress. In the brains of people with autism, post-mortem studies have found activated astrocytes and microglia as well as abnormal inflammatory cytokines. The unbalanced glutamatergic and GABAergic systems seen in autism may be caused by neuroinflammation. Additionally, oxidative stress brought on by inflammation may increase the excitation/inhibition ratio, which may be a factor in the decrease in Purkinje cell counts seen in autistic individuals.[104] Numerous studies have demonstrated the importance of oxidative stress and inflammation in the pathogenesis of autism.[105] Patients with autism have consistently shown signs of immune activation and inflammation. Additionally, individuals with autism exhibit low levels of antioxidants and high levels of oxidative stress markers in their blood cells and serum.[106] Autism spectrum disorder and other neurodevelopmental disorders share common molecular causes, including dysregulated immune response, increased oxidative stress, abnormal mitochondrial metabolism, and impaired lipid metabolism.[107] Inflammation and oxidative stress in the placenta and fetal brain, which result in neurodevelopmental impairments and behavioral symptoms in offspring, have also been linked to maternal immune activation during pregnancy.[108] Additionally, it has been discovered that parental smoking, which causes oxidative stress in children, increases their risk of developing ASD. The pathophysiology of ASD is largely influenced by oxidative stress and inflammation, to sum up. The vulnerability of the brain to oxidative stress and the presence of oxidative stress and neuroinflammatory markers in particular brain regions support the idea that these processes are involved in the emergence of ASD. For the purpose of creating specialized interventions for people with ASD, more research is required to fully comprehend the underlying mechanisms.[109]

### Contribution of molecular genetic studies to the understanding of ASD

Studies on molecular genetics has significantly improved our knowledge of ASD. These investigations have aided in the discovery of genetic variations and molecular pathways linked to the emergence of ASD. One study compared the gene expression patterns in the brains of people with ASD and people who were developing normally using transcriptomic analysis. The study discovered recurrent differences in the way gene expression networks were organized in the ASD brain, pointing to anomalies in cortical patterning. A neuronal module enriched for known genes associated with autism as well as an immune-glial module were among the specific co-expressed gene modules linked to autism that the researchers discovered. In addition to highlighting the role of particular genes and pathways in the disorder, this study shed light on the molecular pathology of ASD.[21] Using whole-genome sequencing to find de novo genetic variants in people with neurodevelopmental disorders, such as ASD, was the focus of another study. The study showed how de novo variants affected the emergence of schizophrenia, ASD, epilepsy, and intellectual disability. This emphasizes how crucial it is to research genetic variations and how they affect neurodevelopmental disorders.[110] Molecular genetic studies have revealed the involvement of particular biological processes and pathways in addition to identifying specific genes and variants linked to ASD. For instance, in a Shank3 complete knockout model of autism, a study by examined the function of altered mGluR5-Homer scaffolds and corticostriatal connectivity. The study provided insights into the neural circuit mechanisms underlying the behavioral deficits in ASD by revealing abnormalities in synaptic connections and neural network development.[95] In addition, research in molecular genetics has contributed to the identification of biomarkers for ASD. The review assessed the progress made in discovering biomarkers related to specific biological processes in ASD, including immune and mitochondrial disorders, oxidative stress, and exposure to toxic substances. These biomarkers may help with the identification and management of ASD.[111] Studies

have looked at the rate of access, utilization, and awareness of genetic testing in ASD populations. Clinical genetic testing is also advised for people with ASD. Conducted a survey study in Sweden and discovered that only a small proportion of parents and autistic people said they had been referred for clinical genetic testing following an ASD diagnosis. This demonstrates how the ASD population needs better access to and knowledge of genetic testing. As a result of their ability to pinpoint genetic variations, molecular pathways, and biological processes linked to the disorder, molecular genetic studies have made a sizable contribution to our understanding of ASD. These studies have uncovered new information about the molecular pathology of ASD, highlighted the involvement of particular genes and pathways, and helped to create biomarkers and genetic testing methods for the disorder.[112]

### The effect of molecular level changes on brain development in ASD

The effect of molecular level changes on brain development in ASD has been a topic of extensive research. Molecular studies have provided insights into the underlying mechanisms and alterations in gene expression patterns that contribute to the pathophysiology of ASD. Transcriptomic analysis has revealed convergent molecular pathology in the autistic brain. A study was conducted to demonstrate consistent differences in transcriptome organization between autistic and normal brains. They found that regional patterns of gene expression that typically distinguish the frontal and temporal cortex were significantly attenuated in the ASD brain, suggesting abnormalities in cortical patterning. The study also identified specific modules of co-expressed genes associated with autism, including a neuronal module enriched for known autism susceptibility genes and an immune-glial module. These findings highlight the dysregulation of gene expression and molecular pathways in ASD.[21] The cerebral cortex was further examined for transcriptomic dysregulation in ASD. Their research discovered extensive transcriptomic alterations in the cortex of people with ASD that showed an anterior-to-posterior gradient. The primary visual cortex showed the biggest differences, which coincided with the normal transcriptomic differences between cortical regions becoming less pronounced. These results point to disruptions in cortical patterning and regional specialization in ASD.[113] Genetic studies have also identified specific genes associated with ASD and their impact on brain development. For example, the AUTS2 gene has been implicated in various neuropsychological disorders, including ASD. The AUTS2 gene is involved in multiple neurodevelopmental processes, acting as a key transcriptional regulator in neurodevelopment and participating in cerebral corticogenesis. It also regulates the number of excitatory synapses postnatally to maintain the balance between excitation and inhibition in neural circuits.[114] Furthermore, research has delved into the influence of molecular factors on synaptic development and function in ASD. They examined the involvement of the chromatin regulator Brg1/SmarcA4 in synapse development and remodeling. They found that Brg1 deletion in hippocampal neurons led to reduced dendritic spine density and maturation, as well as impaired synapse activities. The Brg1 was shown to regulate a significant number of genes involved in synapse function and implicated in ASD. This highlights the importance of molecular mechanisms in synaptic development and their contribution to ASD pathogenesis. Molecular studies have provided valuable insights into the effect of molecular-level changes on brain development in ASD. Transcriptomic analysis has revealed dysregulation of gene expression patterns and molecular pathways in the autistic brain. Genetic studies have identified specific genes associated with ASD and their impact on neurodevelopment. Furthermore, investigations into synaptic development and function have shed light on the molecular mechanisms underlying ASD pathophysiology. These findings contribute to our understanding of the molecular basis of ASD and may pave the way for the development of targeted interventions.[115]

### The effect of molecular disruptions in neurodevelopment on ASD

Molecular defects in neurodevelopment have been found to have significant effects on ASD. Transcriptomic analysis has revealed convergent molecular pathology in the autistic brain, indicating abnormalities in cortical patterning and dysregulation of gene expression patterns. These molecular changes disrupt the typical regional patterns of gene expression in the frontal and temporal cortex, which are important for normal

brain development.[21] Genetic studies have also identified specific genes and variants associated with ASD and their impact on neurodevelopment. For example, microRNA variants have been found to regulate ASD risk genes post-transcriptionally and affect molecular pathways related to ASD.[116] Additionally, mutations in genes such as ANKS1B and PAX2 have been associated with neurodevelopmental disorders, including ASD, and have been shown to affect neural development and function.[117,118] Environmental factors during pregnancy and birth have also been found to influence neurodevelopment and the occurrence of neurodevelopmental disorders, including ASD. Maternal age has been identified as a risk factor, with increased maternal age associated with an increased risk of ASD.[119] Other factors, such as exposure to diethylstilbestrol, have also been investigated for their effects on neurodevelopment and the occurrence of psychiatric disorders, including ASD.[120]

### Mitochondrial function and energy metabolism in ASD: Molecular connections

Mitochondrial function and energy metabolism play crucial roles in ASD, and molecular studies have provided insights into the connections between these processes. Studies have shown that decreased levels of plasma adenosine triphosphate (ATP), the primary energy source for metabolic reactions, may be related to decreased muscle tone and endurance commonly observed in children with ASD. Additionally, impaired mitochondrial function has been reported in some children with ASD, which may contribute to decreased ATP levels. Mitochondria are responsible for energy production through oxidative phosphorylation, and defects in mitochondrial function can lead to energy deficits and metabolic abnormalities.[121] Genetic studies have identified mutations in genes implicated in synaptic development and function in individuals with ASD. These genetic defects can disrupt neural networks, synaptic connections, and neural synchronization, contributing to the behavioral impairments observed in ASD. Furthermore, genes involved in energy metabolism, such as PGC-1α and RBFOX1, have been linked to both ASD and mitochondrial function. Dysregulation of these genes can impact energy metabolism and mitochondrial function, potentially contributing to the pathophysiology of ASD.[95] Abnormalities in redox and mitochondrial metabolism have also been observed in individuals with ASD. Lymphoblastoid cell lines from individuals with ASD exhibit increased oxidative stress, decreased glutathione redox capacity, and highly active mitochondria with increased vulnerability to reactive oxygen species. These abnormalities are not limited to individuals with ASD but are also observed in unaffected siblings, suggesting shared mitochondrial dysfunction.[122] Metabolomic studies have further highlighted dysregulations in cellular bioenergetics in ASD. Alterations in plasma acylcarnitine levels, which are associated with mitochondrial energy metabolism, have been observed in individuals with ASD. These alterations may reflect complex dysregulations of cellular bioenergetics in ASD, contributing to the heterogeneity of the disorder.[123] The impairment of brain energy metabolism, mitochondrial functions, and redox balance has been implicated in major neuropsychiatric disorders, including ASD. Mitochondrial dysfunction, oxidative stress, and alterations in mitochondrial energy metabolism have been reported in individuals with ASD. These molecular defects can lead to changes in mitochondrial structure, membrane potential, enzyme activity, and dysregulated energy metabolism.[124]

### Role of epigenetic modifications in ASD and molecular mechanisms

Epigenetic modifications and molecular mechanisms play a significant role in ASD, as shown in Figure 2. These modifications can mediate the interaction between genetic and environmental factors, leading to adaptive or maladaptive behaviors. Studies have identified dysregulated DNA methylation patterns in individuals with ASD. A study using the Illumina 450K methylation array found dysregulated CpGs in cortical regions of individuals with ASD. Hypomethylated CpGs were enriched for genes related to immune functions, while hypermethylated CpGs were enriched for genes related to synaptic membranes. These findings suggest that epigenetic modifications can impact immune function and synaptic development, potentially contributing to the pathophysiology of ASD.[125] Epigenetic mechanisms have also been implicated in the regulation of gene expression and social behavior in ASD.

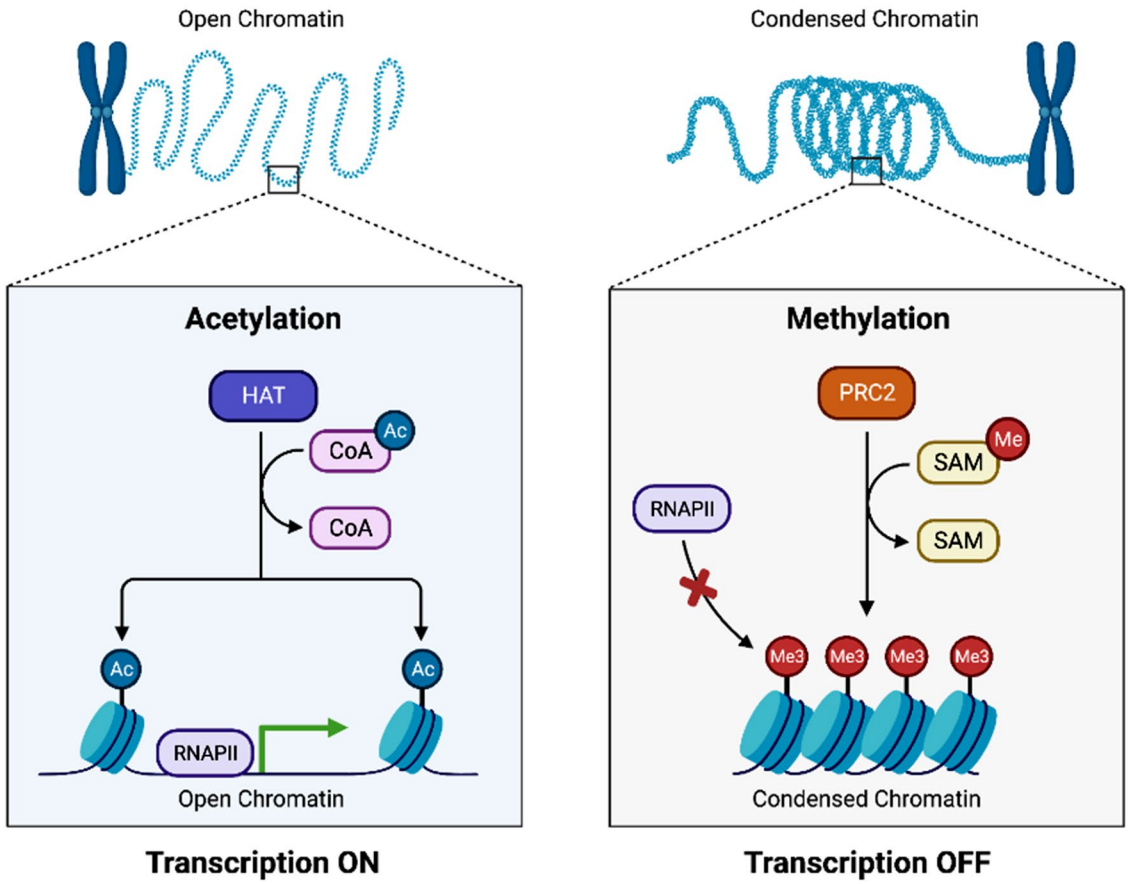


**Figure 2.** Epigenetic mechanisms are the processes through which changes in gene expression or cellular phenotype occur without altering the DNA sequence. These mechanisms involve modifications to the structure and packaging of DNA, as well as modifications to associated proteins called histones.

*Figure 2 was created with BioRender (BioRender.com).*

Epigenetic factors, including DNA methylation, histone modification, chromatin remodeling, and non-coding RNA activity, are involved in the regulation of social behavior in ASD. These mechanisms form an epigenetic network that integrates transient social experiences and influences gene expression patterns.[126] Furthermore, gene-environment interactions mediated by epigenetic mechanisms have been proposed as a common pathway for many cases of ASD. Genetic disorders associated with epigenetic etiologies are often comorbid with ASD, suggesting that epigenetic mechanisms involving gene-environment interactions may contribute to the development of ASD. New molecular technologies that identify critical epigenetic determinants offer potential therapeutic strategies for ASD.[93] Glycosylation patterns and glycan-related genes have also been implicated in ASD. They investigated alterations in glycan patterns and glycan-related gene expression in a rat model of ASD induced by valproic acid. They found dysregulated lectins and differential expression of glycan-related genes, suggesting that abnormal glycosylation patterns may contribute to the molecular mechanisms of ASD. The pathophysiology and development of ASD are strongly influenced by epigenetic modifications and molecular mechanisms. The behavioral difficulties seen in people with ASD are influenced by dysregulated DNA methylation, histone modifications, chromatin remodeling, and gene expression patterns. Insights into the underlying molecular causes of ASD can be gained from understanding these epigenetic mechanisms, which can also help

direct the creation of specialized therapeutic approaches.[127]

## Molecular targets in ASD: Potential treatment strategies

Potential treatment strategies for ASD involve targeting various molecular mechanisms and pathways. These strategies aim to mitigate behavioral defects and improve the core symptoms of ASD. One potential therapeutic approach involves targeting epigenetic enzymes to normalize gene expression. They demonstrated that histone deacetylase inhibition restored behavioral and synaptic function in a mouse model of 16p11.2 deletion, a genetic risk factor for ASD. This study highlights the potential of targeting epigenetic enzymes to mitigate behavioral defects in ASD.[128] Pharmacotherapeutic targets have also been explored for the treatment of ASD, reviewed different pharmacotherapeutic targets, including neurotransmission systems and neuromodulatory systems. Drugs such as antipsychotics and rapamycin have been investigated as potential treatments for ASD, targeting signaling pathways and neuromodulatory systems.[129] Manipulating specific molecular targets has shown promise in animal models of ASD. For example, Rbfox proteins have been implicated in ASD, and manipulating these proteins may provide a potential therapeutic strategy for the treatment of Rett syndrome, a neurodevelopmental disorder associated with ASD features.[130] Additionally, targeting synaptic proteins and cell adhesion molecules involved in synaptogenesis has been explored as a potential treatment strategy for ASD.[131] The use of induced pluripotent stem cells (iPSCs) derived from patients with ASD has provided a platform for studying neuroinflammatory mechanisms and testing potential treatments. iPSC-based models allow for the investigation of neuroinflammatory responses and the impact of anti-inflammatory treatments on glial cells, such as microglia and astrocytes, which play a central role in synaptic pathologies observed in ASD.[132] Furthermore, investigating the effects of hypnotics on sleep duration and behavior abnormalities in animal models of ASD has shown potential as a treatment strategy. They demonstrated that treatment with hypnotics improved sleep duration and behavior abnormalities in a mouse model of Fragile X syndrome, a genetic disorder associated with ASD. A number of molecular mechanisms and pathways are the focus of potential ASD treatment plans. These methods include anti-inflammatory medications, pharmacotherapeutic interventions, molecular target manipulation, epigenetic enzyme targeting, and sleep-related interventions. To confirm the effectiveness and safety of these therapeutic modalities and to create individualized and focused interventions for people with ASD, more research is required.[133]

## Neurotransmitter systems and molecular pathways in ASD

Autism spectrum disorder is a neurodevelopmental condition characterized by genetic heterogeneity and abnormalities in brain function and connectivity. Neurotransmitter systems and molecular pathways play a crucial role in the pathogenesis of ASD. Several studies have identified specific molecular pathways that are disrupted in individuals with ASD.[134] One study found consistent differences in transcriptome organization between autistic and normal brains, suggesting abnormalities in cortical patterning. Dysregulated splicing of alternative exons in the neuronal-specific splicing factor A2BP1/FOX1 gene was also observed in ASD brains.[21] Another study identified differential expression of the mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK) pathways in patients with mild and severe idiopathic autism, indicating their involvement in the severity of the disorder. The mTOR and MAPK pathways are key regulators of synaptogenesis and protein synthesis.[135] Neurotransmitter systems, including the GABAergic, glutamatergic, and serotonergic systems, have also been implicated in the pathogenesis of ASD. Dysfunction in these systems can affect neuronal cell migration, differentiation, and synaptogenesis, leading to developmental abnormalities in the brain.[136] Additionally, disturbances in synaptic transmission, including the GABAergic, glutamatergic, and serotonergic systems, have been associated with ASD.[137] Furthermore, the Wnt/β-catenin pathway has been implicated in both intellectual disability and ASD. Dysfunctions in this pathway can lead to cell adhesion deregulation and contribute to the development of intellectual disability and ASD.[138] Recent studies have also focused on single-cell transcriptomics to identify molecular

subtypes of ASD and their impact on specific cell types in the brain. These studies have provided insights into the spatiotemporal expression patterns of ASD-implicated genes and their association with specific cell types.[139]

## AUTISM SPECTRUM DISORDER AND TGF-β SIGNAL PATHWAY

### Mechanisms of relationship and interaction

Transforming growth factor-beta (TGF-β) has also been studied in relation to ASD. A signaling molecule called TGF-β is involved in many cellular processes, including brain development. Human iPSCs have been shown to transform into cortical spheroids when TGF-β signaling is inhibited. These spheroids resemble mature neurons and the developing fetal brain. This suggests that TGF-β signaling dysregulation may play a role in the pathophysiology of ASD.[140]

### Molecular basis and biological role

The TGF-β signaling pathway has been implicated in the molecular basis and biological role of ASD. Dysregulation of this pathway may contribute to the pathogenesis of ASD. The TGF-β signaling pathway is involved in various cellular processes, including brain development. Inhibition of TGF-β signaling has been shown to affect the development of the fetal brain and mature neurons. Therefore, abnormalities in TGF-β signaling may disrupt normal brain development and contribute to the development of ASD.[96] Genetic studies have identified several genes associated with ASD that are involved in transcriptional regulation and chromatin-related processes.[141] These genes are active during brain development and may play a role in the regulation of synapse development and plasticity. Dysregulation of these genes and their associated pathways, including the TGF-β signaling pathway, may contribute to the development of ASD.[96] Rare variations and de novo mutations in ASD candidate genes have also been found by exome sequencing studies. These mutations, which include those in the TGF-β signaling pathway, may impair the normal operation of genes involved in synaptic development and neuronal signaling. The discovery of these mutations offers additional proof that the TGF-β signaling pathway contributes to the etiology of ASD.[142] Additionally, research has shown that the TGF-β signaling pathway may interact with other signaling pathways, such as the Wnt/-catenin pathway, in the emergence of ASD. It has been demonstrated that the TGF-β signaling pathway interacts with Wnt/-catenin pathway dysregulation, which has been linked to intellectual disabilities and ASD. These results imply that a variety of signaling pathways may converge and interact to influence the emergence of ASD.[138] Other biological mechanisms, in addition to signaling pathways, have been connected to the pathogenesis of ASD. For instance, abnormalities in purine metabolism have been found in murine models of ASD, indicating that purine synthesis and catabolism metabolic pathways may be involved in ASD.[143] There is evidence of aberrant innate and adaptive immunity in people with ASD, supporting the theory that immune system dysregulation contributes to ASD. These findings demonstrate the complexity of ASD and the contribution of numerous biological processes to its emergence.[144]

### The relationship between TGF-β polymorphisms and ASD

The relationship between TGF-β polymorphisms and ASD has been investigated in several studies. One study looked at the transcriptomic analysis of the brains of autistic people and discovered recurrent variations in gene expression patterns when compared to the brains of healthy people. They discovered specific clusters of co-expressed genes linked to autism, such as a neuronal module enriched in immune genes and glial markers and a module enriched for known autism susceptibility genes. This study provides proof that TGF-β-related genes are involved in the molecular pathology of ASD.[21] Another study examined the relationship between ASD and the Methylenetetrahydrofolate reductase (MTHFR) gene polymorphism, which is involved in folate metabolism. The study discovered a strong link between MTHFR polymorphism and ASD, indicating that genetic variations in this pathway may increase a person's risk of developing ASD.[145] A study also investigated the relationship between ASD and genetic polymorphisms affecting the homeostasis of glucose and insulin. The preliminary findings suggested a complicated connection between ASD and genetic variations linked to vulnerability

to impaired glucose and insulin homeostasis.[146] Other genetic variations have been linked to the susceptibility to ASD in addition to TGF-β polymorphisms. The relationship between the methylenetetrahydrofolate reductase C677T gene polymorphism and propensity for ASD was examined in a meta-analysis. The T/C allele of the MTHFR gene polymorphism was found to be significantly associated with an increased risk of ASD, according to the meta-analysis.[147] Additionally, intellectual disabilities and ASD have been linked to the Wnt/-catenin pathway, which interacts with the TGF-β signaling pathway. The development of ASD may be influenced by the dysregulation of this pathway. These studies collectively imply that genetic variations, such as TGF-β polymorphisms, MTHFR gene polymorphisms, and variations affecting glucose and insulin homeostasis, may contribute to ASD susceptibility. To fully comprehend the mechanisms underlying these associations and their implications for the diagnosis and treatment of ASD, more research is required.[138]

### Effects of TGF-β on nervous system development and ASD

The effects of TGF-β on nervous system development and ASD have been the subject of research. Transforming growth factor-beta is a multifunctional regulatory polypeptide that controls various aspects of cellular function, including cellular proliferation, differentiation, migration, apoptosis, and survival.[148] In the context of nervous system development, TGF-β plays a crucial role in regulating the growth and differentiation of neural cells. According to studies, TGF-β signaling dysregulation may play a role in the pathophysiology of ASD. According to one study, the increased ratio of excitation to inhibition in important neural systems, which may be influenced by TGF-β signaling, is a component of the autism model. According to this model, the pathophysiology of ASD is primarily driven by neural systems involved in language processing, social behaviors, and affiliative behaviors.[149] In addition, a study that looked at how the brain oscillates during motor control in kids with ASD discovered changes in TGF-β-related neural activity. The primary motor cortex of children with ASD showed decreased motor-related gamma increase and increased pre-movement beta oscillations, according to the study. These results imply that motor dysfunction in ASD may be caused by TGF-β-related neural activity.[150] Transforming growth factor-beta-related genes have also been linked to ASD by genetic studies. For instance, learning disabilities and spinal cord disease have been linked to mutations in the β-spectrin gene, which is genetically linked to autism. In addition, liver and gastrointestinal (GI) cancer comorbidities seen in people with ASD have been linked to changes in the TGF-β/SMAD signaling pathway. The effects of TGF-β on the growth of the nervous system and its potential contribution to the pathophysiology of ASD have all been studied. The abnormal development seen in ASD may be caused by dysregulation of TGF-β signaling and changes in TGF-β-related genes. To fully comprehend the mechanisms underlying these effects and their implications for the diagnosis and treatment of ASD, more research is required.[151]

### TGF-β expression and regulatory mechanisms in ASD

Numerous studies have looked into the expression and control mechanisms of TGF-β in ASD. 102 genes were found to be associated with an increased risk of ASD in a large-scale exome sequencing study, many of which are expressed and enriched early in excitatory and inhibitory neuronal lineages. These genes have the potential to play a role in the molecular pathology of ASD because they influence synapses or control other genes.[152] Developmental anomalies like ASD have been linked to the Pax2 gene, which is involved in brain development and function. Although the precise molecular mechanisms are not fully understood, PAX2 proteins play significant roles in adult neurogenesis and during the development of the central nervous system.[118] In a study that examined gene expression in the prefrontal cortex of people with ASD, it was discovered that the aberrant changes in gene expression in ASD brains were enriched in genes connected to synaptic pathways. Members of the early growth response transcription factor family were implicated in the regulation of autism by this aberrant expression pattern, which interfered with human-specific developmental programs.[153] Epigenomic annotations indicating active regulatory genomic sites in the fetal brain have been found to be enriched for genetic risk variants for neuropsychiatric disorders, including

ASD. This suggests that the risk for ASD may be related to heritable cis-effects on gene expression in the developing brain.[154] In addition, research has discovered hundreds of messenger RNAs, microRNAs, and long non-coding RNAs associated with ASD and other neurodevelopmental disorders. These results demonstrate the intricate regulatory network that controls ASD and suggest a potential function for TGF-β in regulating gene expression and neurodevelopmental processes.[155,156] Additionally, changes in the expression of genes linked to covariation influence have been seen in ASD, suggesting a connection between psychiatric disorders like schizophrenia, bipolar disorder, and ASD and TGF-β-related gene expression.[157] Environmental modifications during crucial developmental windows can affect epigenetic mechanisms, including DNA methylation, which has been linked to ASD. Autism spectrum disorder has been linked to maternal immune activation, as well as modifications to DNA methylation and transcription in microglia. In conclusion, complex interactions between genetic and epigenetic factors are involved in the expression and regulatory mechanisms of TGF-β in ASD. The dysregulation of TGF-β-related genes and pathways may be a factor in the abnormal neurodevelopment seen in ASD. To fully comprehend the molecular mechanisms underlying these effects and their implications for the diagnosis and treatment of ASD, more research is required.[156]

### TGF-β link between the immune system and ASD

Autism spectrum disorder development may be influenced by the ability to control immune responses and keep the immune system in homeostasis. There are numerous interactions between the immune system and the nervous system, and problems with the immune system may have an effect on how the brain develops and functions, which could contribute to the pathogenesis of ASD.[158] Evidence points to the involvement of immunological elements in a number of neuropsychiatric disorders, including ASD. Children with ASD have been linked to autoimmune abnormalities, and changes in natural autoantibodies have been seen. These findings imply that ASD is characterized by immune dysregulation and a dysfunction of self-recognition mechanisms.[159] In relation to vaccinations, the potential association between immune dysregulation and ASD has also been studied. Studies have looked into how immune-modulating substances, like the macrophage activating factor derived from vitamin D binding protein, can be used to treat ASD. Children with ASD have also been found to have immune dysfunction, including changes in cellular activation markers. These results lend credence to the idea that immune dysfunction may exist in some ASD sufferers and may play a role in the disorder's etiology.[160] In the context of comorbid conditions, the relationship between immune system changes and ASD has also been studied. The simultaneous occurrence of ASD, anorexia nervosa, and Behçet's syndrome, for instance, was reported in a study, highlighting the potential connection between immune system changes, neurodevelopment, and eating disorders.[161] The immune dysfunction seen in ASD has also been linked to the GI system, which contains a sizeable portion of the immune cells in the human body. Immune activation, immune dysregulation, and GI problems may be related in people with ASD, according to research linking maternal immune activation and dysregulation to GI dysfunction. In conclusion, there is growing evidence that the immune system and ASD are related. The pathogenesis of ASD may be influenced by immune dysregulation, changes in autoantibodies, immune dysfunction, and immune-related comorbidities. To fully comprehend the underlying mechanisms and to create targeted interventions for people with ASD, more research is required. Overall, these studies suggest that TGF-β and immune-related factors play a role in the pathogenesis of ASD. Dysregulation of immune responses, alterations in autoantibodies, immune-related comorbidities, and disruptions in the gut microbiota may contribute to the development of ASD. Further research is needed to fully understand the underlying mechanisms and to develop targeted interventions for individuals with ASD.[162]

### TGF-β inhibitors and ASD: Potential treatment approaches

The use of TGF-β inhibitors as treatments for ASD has shown promise. Studies have examined related mechanisms and potential therapeutic targets, despite the fact that there is little research specifically focusing on TGF-β

inhibitors in ASD. One study examined the use of genetic rescue or antisense oligonucleotides to reverse the phenotypes in methyl-CpG binding protein 2 (MECP2) duplication mice. Autism, intellectual disability, motor dysfunction, and other symptoms make up MECP2 duplication syndrome. The study showed that directly targeting MeCP2 can potentially reverse the MECP2 duplication syndrome phenotype, indicating the potential therapeutic benefit of focusing on particular molecular dysfunctions in ASD.[163] In another study, mouse hippocampal primary neuronal cell cultures were used to examine the neurogenic and neurotrophic effects of brain-derived neurotrophic factor (BDNF) peptides. It has been associated with ASD and is involved in neurodevelopment. It has been proposed that one potential therapeutic strategy for neurological disorders, including ASD, is to modify BDNF levels.[164] Innovative technology-based therapies have also been investigated as therapeutic gimmicks for ASD sufferers. For people with ASD, the use of computerized technologies as therapeutic and educational tools has grown. These interventions can offer interactive and personalized experiences that could improve learning and social skills in people with ASD.[165] Additionally, phosphoinositide 3-kinase (PI3K)/mTOR pathway dysfunctions, which affect cell growth and proliferation, have drawn interest in ASD research. Inhibitors that target this pathway have demonstrated promise in preclinical research and may be effective treatments for ASD.[166] For the treatment of ASD, an eclectic strategy that combines various therapeutic modalities and plans has been suggested. This strategy aims to customize interventions to meet each person's needs and objectives, potentially enhancing outcomes for people with ASD.[167] Autism spectrum disorder risk has also been linked to prenatal exposure to the drug valproate, which is used to treat epilepsy and other neuropsychological disorders. Autism spectrum disorder prevention during pregnancy may involve avoiding or reducing exposure to valproate.[168] For people with ASD, other therapeutic modalities have also been investigated, including internet-based interventions and cognitive-behavioral therapy. These methods seek to address particular ASD symptoms and difficulties, such as anxiety and non-suicidal self-injury. In conclusion, despite the paucity of studies specifically examining TGF-β inhibitors in ASD, numerous therapeutic strategies focusing on associated mechanisms and pathways have shown promise. For the purpose of creating individualized interventions that are effective and safe for people with ASD, more research is required.[169-171]

### TGF-β Target Molecules and Pathways in ASD

Transforming growth factor-beta is a cytokine that is essential for many cellular processes, such as immune response, cell differentiation, and growth. Several studies have identified target molecules and pathways that interact with TGF-β and are implicated in the pathophysiology of ASD, despite the fact that there is little research specifically linking TGF-β to ASD. According to one study, disrupted genes linked to the synaptic plasticity-related fragile X protein, FMRP, are particularly dosage-sensitive targets of cognitive disorders and are subject to greater purifying selection. Given that TGF-β has been found to control synaptic plasticity, this raises the possibility of a connection between FMRP-associated genes and TGF-β signaling.[172,173] According to a different study, people with ASD have dysregulated mTOR pathways. Transforming growth factor-beta signaling and the mTOR pathway are known to interact, and dysregulation of this pathway has been linked to abnormal brain development and synaptic dysfunction. It has been shown to interact with dysregulation of the MAPK pathway, which is also connected to ASD.[135] Autism spectrum disorder is one of many neurodevelopmental and psychiatric disorders that have calcium-dependent hyperpolarization pathways linked to them. Disruptions in calcium-dependent hyperpolarization pathways have been linked to abnormal synaptic function and behavior. It has been shown to regulate calcium signaling pathways. These studies suggest that TGF-β may interact with target molecules and pathways that are associated with ASD, despite the fact that its direct involvement in the pathophysiology of ASD is not well established. The precise mechanisms by which TGF-β may contribute to the emergence and development of ASD need to be clarified through additional study.[174]

### Therapeutic potential of TGF-β modulation for ASD

A multifunctional cytokine called TGF-β is involved in the pathogenesis of psychiatric and neurodegenerative disorders, including ASD, and is crucial in the process of neuroinflammation. These disorders have been linked to dysregulation of TGF-β signaling, and reducing TGF-β activity has therapeutic potential. Transforming growth factor-beta has the ability to control neuroinflammatory processes, modulate microglial activation, and the immune response. A novel strategy for treating disorders linked to neuroinflammation, such as ASD, may involve targeting TGF-β signaling pathways. TGF-β modulation has therapeutic potential for ASD, according to the literature that is currently available. TGF-β signaling is dysregulated in ASD and is involved in a number of pathophysiological aspects of the disorder, according to studies. Transforming growth factor-beta, for instance, has been linked to the control of synaptic plasticity, which is compromised in ASD. Additionally, TGF-β has been recognized as a key mediator in the development of diabetic nephropathy and glaucoma, both of which have been associated with ASD.[175-177] It has also been linked to ventricular remodeling, a condition that affects a variety of cardiac conditions, including those connected to ASD. The importance of TGF-β signaling in disease processes has been highlighted by the extensive evaluation of this pathway as a potential therapeutic target in the context of cancer therapy.[178] In preclinical studies, modifying TGF-β signaling has shown promise in the management of renal fibrosis and hepatocellular carcinoma (HCC). There is evidence that TGF-β signaling inhibition slows the progression of HCC. Further research has been done on downstream molecules of TGF-β signaling as potential therapeutic targets for fibrotic diseases like renal fibrosis.[179] Due to its involvement in numerous systems, TGF-β may not be able to be directly targeted therapeutically. However, studying the downstream molecules and signaling pathways of TGF-β signaling may provide more practical therapeutic options. Furthermore, comprehension of TGF-β's function in neuroinflammation, which is linked to psychiatric and neurodegenerative disorders like ASD, may shed light on potential treatment options. Transforming growth factor-beta modulation has the potential to treat ASD and other conditions of a similar nature. Autism spectrum disorder has been associated with dysregulation of TGF-β signaling, and targeting this pathway may present opportunities for intervention.[180]

### The effect of TGF-β research on the diagnosis and treatment of ASD

The growing body of research on the complex nature of ASD supports the use of an integrative approach in the diagnosis and treatment of the disorder. For instance, research has indicated that people with ASD may experience dysregulated neural oscillations, which can impair cognitive flexibility and motor control.[181] Targeting inflammatory pathways, such as TGF-β, may have therapeutic potential because neuroinflammation has also been linked to the pathogenesis of ASD.[182,183] Research has also examined the role of TGF-β in the onset and progression of ASD. It has been found to be dysregulated in ASD, and targeting this pathway for therapeutic intervention has shown promise.[182] Several processes related to ASD, such as immune response, neuroinflammation, and synaptic plasticity, have been associated with TGF-β. Understanding how TGF-β modulation affects ASD may shed light on the disorder's underlying mechanisms and guide the creation of focused interventions. In conclusion, there is still much to learn about TGF-β and how it might be used to diagnose and treat ASD. Studies imply that TGF-β modulation may be a promising therapeutic target for ASD, despite the fact that the precise mechanisms and therapeutic approaches are still not completely understood. The intricate interactions between TGF-β signaling, neuroinflammation, and other molecular pathways involved in ASD pathophysiology require further study. Integrative methods that take into account the neurological and physiological aspects of ASD may offer a thorough framework for diagnosis and care.[183]

In conclusion, we looked at the relationship between ASD and the TGF-β signaling pathway. According to research, TGF-β is crucial for the development of the nervous system, immune system control, and synaptic plasticity all of which are important features of ASD. There is proof that one of the molecular factors causing ASD is abnormalities in the TGF-β signaling pathway. It is well known that environmental, genetic,

and epigenetic factors can all have an impact on TGF-β activity. It is believed that the TGF-β signaling pathway may offer therapeutic targets for ASD. The pathophysiology and etiology of ASD may be improved through regulation or modulation of TGF-β, which could result in the creation of more potent therapeutic approaches. Further study is required, though, due to the nuanced and varied nature of the connection between TGF-β and ASD. Our understanding of the direct impact of TGF-β on the symptoms and behaviors of people with ASD may be improved with further research. More clinical research is also required to determine the effectiveness and security of potential TGF-β-targeting treatment approaches. The signaling pathway of TGF-β is crucial in the pathophysiology of ASD, suggesting that therapeutic interventions could target this pathway. The quality of life of people with ASD can be significantly improved with further research in this field, which could also lead to the development of more potent therapeutic strategies.

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