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Review

# Astrogliosis: Glial Perspective of Autism Spectrum Disorders

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**ABSTRACT**

To date, the cellular mechanisms underlying autism spectrum disorders (ASDs) have not been fully understood. However, various genetic and environmental factors contribute to the etiology of this developmental disorder. Astrocytes are abundant glial cells that perform various functions in health and disease in the central nervous system. Astrocyte dysfunction is found in many diseases, including multiple sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease, and neuropsychiatric disorders. Increasing evidence suggests that astrocytes play an important role in synapse maturation and function, and there is evidence of deficiencies in glial cell function in ASD, suggesting a link between astrocytes and autism. The aim of this review is to understand astrocyte functions and their contribution to ASD.

**Keywords:** Astrocyte, autism spectrum disorder, glial cell, neuron

Autism is a developmental disorder of the central nervous system (CNS) characterized by stereotyped and repetitive movements, impaired social interaction, language, and non-verbal communication. It starts in early childhood and can have changing clinical symptoms over time, lasting throughout a person's life with varying degrees of severity.[1] Autism spectrum disorders (ASDs) are classified into two main categories: deficits in social communication and interaction, and repetitive behaviors and restricted activities. Additionally, digestive problems, epilepsy, immune problems, sleep disorders, negative mental states (depression and anxiety), and mitochondrial dysfunction can also develop in ASD.[2-3] This disorder affects many parts of the brain (dorsal and medial prefrontal cortex, superior temporal cortex, and amygdala), but it is not well understood how this effect develops. Parents typically notice this condition in their children within the first two years of life. Early behavioral or cognitive interventions can help children develop self-care abilities and social and communication skills.[4]

In 1943, American child psychiatrist Leo Kanner[5] named autism early childhood autism. Kanner used the same term to describe the characteristics of eleven children exhibiting similar behavioral patterns and reported autism as a syndrome with problems in emotional contact and interpersonal relationships in his article. Describing a clinical picture that includes delayed speech, repetitive behaviors, poor eye contact, communication problems, and unusual interests and abilities, Kanner stated that autism is a congenital disease. Autism has a prevalence of 12-15% worldwide.[6-7] According to a study, autism is present in every 59th child. Autism is three to four times more common in boys than in girls, and many girls show less prominent features than boys.[8] It is genetically very heterogeneous and is seen to be associated with many genetic mutations, most of which are probably rare causal variants.[9]

The genetic heterogeneity of autism has made it difficult to identify specific genes related to the disease and has therefore hindered efforts to investigate disease mechanisms. Recent findings on the changing genetic pathways in ASD have been obtained from studies of syndromic disorders with a high incidence of autism caused by mutations in

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a single gene, including Rett syndrome (RTT) and Fragile X (FXS) syndrome.[10]

### Fragile X Syndrome

Fragile X syndrome is the most common cause of familial mental retardation in males, after Down syndrome, and can lead to intellectual disability.[11] The Fragile X mental retardation (FMR) protein plays an important role in neuronal development, synaptic transmission, and elasticity. Therefore, when the FMR protein is not produced at all or is significantly reduced, neuronal involvement occurs.[12] Obsessive-compulsive disorder and anxiety disorder are common symptoms. The incidence of autism is much higher in males with FXS than in the general population.[13]

### Rett Syndrome

Rett Syndrome occurs due to mutations in the methyl-CpG binding protein 2 (MECP2) gene. The MECP2 gene located in the Xq28 region encodes the MeCP2 protein. MeCP2 protein is most abundant in the brain.[14] One of the most challenging aspects of RTT is complex and tonic-clonic seizures.[15] Abnormalities such as teeth grinding, screaming episodes, anxiety attacks are seen in RTT patients and there is no known cure.[16-18] In RTT mouse models, desipramine, a norepinephrine inhibitor, has been observed to alleviate breathing in MeCP2 mutant mice, but no improvement was observed in clinical trials.[19-21]

### Neurodevelopmental Disorders and Autism

Neurodevelopmental genes are an important factor to consider, as functional and anatomical movements associated with defects in these genes during brain development can trigger the onset of neurodevelopmental disorders in childhood, including ASD.[22-23] Genes associated with neurodevelopmental disorders can be grouped into three broad categories: those related to synapse structure and activity, those related to protein synthesis, and those involved in regulating gene expression. Many of these genes code for proteins with a clear synaptic function, making the pathological features of neurodevelopmental disorders 'neurocentric'. Therefore, it is anticipated that genetics alone may not be able to explain all cases of autism. Exposure to a range of non-heritable environmental factors in addition to a specific combination of autism-related genes can significantly influence susceptibility to autism and the variable expression of autism-related traits.[24]

Translation: In studies conducted with children and adolescents for the treatment of neurodevelopmental disorders, risperidone, and aripiprazole have been used, and in the majority of cases, improvement has been observed in irritability, self-harm, repetitive behaviors, and aggression.[25] In a study where oxytocin was applied to a small sample of individuals with autism, positive effects on social behavior were observed, which suggests that oxytocin may be effective in the symptomatic treatment of neurodevelopmental disorders.[26-28]

## ASTROCYTES

Astrocytes are the most common glial cells in the CNS, which are considered the cornerstone of brain cytoarchitecture and function, along with neurons and oligodendrocytes.[29] It is known that they constitute 20-40% of all glial cells. Astrocytes are derived from neuroectoderm.[30] Astrocytes actively participate in neuronal metabolism, synaptic plasticity, and neuroprotection. They regulate blood flow by releasing various mediator molecules (nitric oxide, prostaglandins) that dilate and constrict blood vessels. Astrocytic processes surround all major synapses to ensure fluid, ion, and pH homeostasis for synaptic transmission. Additionally, astrocytes express functional neurotransmitter receptors at the synaptic level and release various neurotransmitters such as glutamate, gamma-aminobutyric acid (GABA), and adenosine triphosphate (ATP) via $Ca^{+2}$-dependent exocytosis.[31-34]

Therefore, there is an increase in the expression of glial fibrillary acidic protein (GFAP) in response to neuronal damage.[35] Reactive astrocytes have been identified as potential therapeutic targets for certain disease contexts, where molecular dissection can help identify molecules that can enhance or block their functions. For example, a molecule called parawixin 1, isolated from spider venom, has been shown to protect retinal neurons from ischemic degeneration by increasing the function of the excitatory amino acid transporter-2 (EAAT-2), which increases glutamate uptake and thus reduces the potential for glutamate excitotoxicity.[36]

Astrocytes can make contact with multiple neurons and up to 100,000 synapses.[37] They have receptors and ion channels found in neurons, allowing them to detect and respond to a variety of neuronal signals. Astrocytes and microglial cells play an important role in the elimination process of synaptic connections, which is a structural formation and elimination process. They are vital in controlling and improving the connectivity of mature neuronal circuits. For example, in developing

brains, astrocytes can physically eliminate synapses via phagocytic pathways, such as multiple epidermal growth factor-like domains 10 (MEGF10) and c-Mer proto-oncogene tyrosine kinase (MERTK).[38-40]

Astrocytes release a variety of neuroactive substances, including growth factors and gliotransmitters. Glutamate is an essential amino acid that plays a role in synaptic transmission. Mutations in glutamate receptors found in peripheral organs, tissues, and endocrine cells can result in the development of neuropsychiatric disorders.[41]

Overall, these studies suggest that the physiological interactions between astrocytes and synapses are essential for synapse formation and network functioning. Loss, deviation, or functional impairment of astrocytes and microglia may contribute to the pathogenesis and progression of autism. Astrocyte dysfunction is seen in a number of diseases, including multiple sclerosis, Alzheimer's disease, Huntington's disease, and neuropsychiatric disorders.

## ASTROCYTIC ROLES IN GLUTAMATE AND GLUTAMATE TRANSPORTERS

Glutamate is the main excitatory neurotransmitter in the CNS, responsible for fast excitatory neurotransmission.[42] Five subtypes of glutamate transporters have been cloned to date. Three of these glutamate transporters were initially identified in the mouse brain: glutamate aspartate transporter (GLAST), glutamate transporter 1 (GLT-1), and excitatory amino acid carrier 1 (EAAC1). Their human homologs are EAAT1, EAAT2, and EAAT3, respectively. The remaining two human and rodent subtypes, EAAT4 and EAAT5, share common terminology.[43] All five transporters are localized differently among various brain structures. GLAST immunostaining and protein expression are most prominent in the cerebellum, with intermediate levels in other structures such as the hippocampus and frontal cortex. In contrast, GLT-1 expression is primarily found in the cerebellum with low levels of expression in the frontal cortex.[44] Both of these transporters represent the most prominent "astrocytic" transporters, localized at the astroglial membrane or in Bergmann glia associated with excitatory synapses. EAAT3 is expressed at low levels in different regions of the brain. The remaining transporters, EAAT4 and EAAT5, are expressed only in the cerebellum and retina, respectively.[45-46] Rapid removal of glutamate from the extracellular space is necessary for the survival and normal function of neurons. While all CNS cell types express glutamate transporters, astrocytes are primarily responsible for glutamate uptake.[47] Astrocytes mediate glutamate uptake through both $Na^+$-independent and $Na^+$-dependent systems. $Na^+$-dependent glutamate transporters in astrocytes were originally cloned from the mouse brain and named GLAST and GLT-1.[48] Transporter activity is normally regulated at multiple levels, including protein expression, surface trafficking, protein binding, phosphorylation, and other direct modifications.[49-50]

## ASTROCYTE GENE MUTATIONS

There are several examples of genetic mutations that lead to astrocyte dysfunction. The first example is a dominant mutation in the GFAP gene, which is exclusively expressed by astroglia in the CNS, causing Alexander's disease. Patients with this macrocephaly exhibit severe disease dysfunction, seizures, psychomotor disturbances, and early. Another example is a dominant gain-of-function mutation in the gene encoding superoxide dismutase, which leads to the production of toxic molecules for motor neurons and causes a familial form of amyotrophic lateral sclerosis.[51-53]

GFAP is a member of the intermediate filament protein family that serves cytoarchitectural functions, along with vimentin, nestin, and others and is a marker for the immunohistochemical identification of astrocytes.[54]

## EFFECT OF ASTROCYTES ON NEURODEVELOPMENTAL DISORDERS

There are several genetic mutations that can cause astrocyte dysfunctions. The dominant mutation of the GFAP gene, which is expressed only by astroglia in the CNS, causes Alexander's disease. Patients with this macrocephaly exhibit severe disease impairment, seizures, psychomotor disturbances, and early. Another example is a familial form of amyotrophic lateral sclerosis caused by a gain-of-function mutation in the gene encoding superoxide dismutase, which produces molecules toxic to motor neurons. Astrocytes are part of the intermediate filament protein family, serving cytoskeletal functions, including GFAP, vimentin, nestin, and others, and are markers used for immunohistochemical identification of astrocytes. The first evidence of potential astrocyte abnormalities in neurodevelopmental disorders came from the biochemical analysis of brain samples of patients with ASD and from screening genetic risk

factors for various neurodevelopmental disorders. Astrogliosis, demonstrated by increased GFAP expression, was found in the cerebellar cortex of brains with ASD, but neuronal degeneration was not usually observed in the brains of neurodevelopmental disorder patients. Several other astroglial protein expression changes were also observed in the brain samples of patients with ASD, including increased EAAT2 and EAAT1 in the cerebellum, significantly increased connexin 43 in the superior frontal cortex, and decreased aquaporin 4 in the cerebellum.[55-57] These astroglial changes suggest that astrocytes may be involved in neurodevelopmental disorders. Genetic studies have identified specific nucleotide polymorphisms in the EAAT1 sequence that are associated with the severity of repetitive behaviors and anxiety in children with ASD.[58] Despite the results of these clinical studies, it is important to note that specific mechanisms involving astrocytes in the pathogenesis of neurodevelopmental disorders are still being identified.

Changes in astrocytes have been observed in patients with ASD and animal models. However, it is not clear whether astrocyte dysfunction in mice is causal or dependent on ASD-like phenotypes. The role of neurons in the pathogenesis of ASD has been a broad research topic. The expression of astrocyte markers such as GFAP, aquaporin-4, connexin 43, and EAAC1 has been altered in postmortem brain tissue from ASD-affected donors.[59-62] Astrocytes derived from control sources rescue the morphological and synaptic defects of ASD neuronal cultures. Astrocytes, the most abundant glial cells in the CNS, contribute to many critical brain functions such as neurogenesis, synaptic development, synaptic transmission, and plasticity during early development and adulthood and regulate their behaviors under both physiological and pathological conditions. Astrocyte-derived ATP plays a role in modulating ASD-like behaviors in mice.[63-66]

Although ASD is generally considered a neurodevelopmental syndrome, recent studies have shown that dysfunction in autism risk genes during both early development and adulthood leads to reversible autism-like phenotypes in adult animals when the normal functions of these risk genes are restored. Observations that the behavioral and physiological deficits in animal models of ASD are reversed upon pharmacological or genetic manipulation, together with the autism synaptic theory, suggest that a continuing synaptopathy may underlie the cause of ASD. Overall, astrocytes play a role in the pathogenesis of ASDs. Astrocytes can release various synaptic transmitters and modulators, including glutamate, D-serine ATP/adenosine, GABA, and lactate, through calcium-dependent and independent signaling pathways, but not limited to these.[67-71]

## NEUROANATOMICAL FINDINGS IN AUTISM SPECTRUM DISORDERS

One of the most important theories regarding the neuropathology of ASDs is the abnormal growth of the amygdala, frontal and temporal cortex during development, which then slows down with age.[72] The main causes of this are thought to be neurogenesis, excessive dendritic growth, and inflammatory responses that lead to microglial activation.[73]

There may be three cellular factors to explain the excessive brain growth in autism:

Number of neurons: An increase in the number of neurons is not the only factor that can explain the accelerated cortical growth in autism.

Neuronal dendritic growth and the number of synapses: Neuronal dendritic growth and increased numbers of synapses are the closest possibilities for excessive early brain growth in autism. If dendrites grow excessively or do not reach the same level as active synaptic protrusions, abnormal connections may occur between neurons. However, only a small number of postmortem studies have examined neuronal dendritic connections or synapses related to autism. Numbers and sizes of glial cells: Gliogenesis has differences among microglia, oligodendrocytes, and astrocytes from a prenatal perspective. Astrocytes constitute 17% of the glia in the brain. If glia is responsible for the increase in cerebral volume in autistic children, a neuroinflammatory response involving microglia could be the likely culprit. All of these factors result in the overall brain growth seen in autism.[74-76]

In conclusion, until very recently, the role of glial cells at the onset of ASD was overlooked, and therefore, pharmacological strategies aimed almost exclusively at neuronal activity and synaptic transmission to treat symptoms. However, accumulating evidence suggests that astrocytes and microglia may play a significant role in the regulation of synapse formation, function, and elimination, and therefore may have an impact on ASD. Recent data suggest that ASD is at least partially caused by disorders affecting glial cells or neuron-glia interactions, and future pharmacological

research should consider the possibility of improving glial cell functions. By including more patients and control groups in studies, and developing biomarkers that can be used in the diagnosis and prognosis of autism, the disease process can be positively affected. This review shows that differences in glial cells, such as astrocytes, and disruptions in their functions, can have an impact on the ASD process. Although research on the molecular mechanisms of astroglial maturation and how the disruption of this maturation process contributes to the pathogenesis of neurodevelopmental disorders continues, the availability of new in vivo tools for studying astrocytes can be of great benefit in answering these questions. Understanding the role of astroglia in the pathogenesis of neurodevelopmental disorders will facilitate the search for treatments for these disorders. Future studies should shed light on differentiating between pathological processes underlying the core processes of autism and findings related to the cause of death or comorbidities.

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