Cui et al. *Zool. Res.* 2026, 47(4): 1137−1165
https://doi.org/10.24272/j.issn.2095-8137.2026.086
https://cstr.cn/32248.14.zr.2026.086

ZR | Zoological Research

Review Open Access

The role of astrocytes in autism spectrum disorder and associated syndromes: Evidence, animal models, mechanisms, and therapeutic potential

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ABSTRACT

Autism spectrum disorder (ASD) is a neurodevelopmental condition clinically defined by persistent social deficits and restricted, repetitive behavior. Several other neurodevelopmental disorders exhibit these core clinical features of ASD and are therefore classified as “syndromic ASD”. Although neurons have been the primary research focus on ASD and associated syndromes, accumulating evidence highlights astrocytes as critical contributors to disease mechanisms. Astrocytes are essential for regulating synapse development, neurotransmitter balance, and neuroinflammation in the brain. In this review, we integrate evidence from studies in human tissues, patient-derived induced pluripotent stem cells and organoids, and animal models to establish a robust link between astrocytic dysfunction and ASD and associated syndromes. By systematically examining key astrocytic functions, we elucidate mechanistic pathways through which astrocytic dysregulation contributes to aberrant synaptogenesis, disrupted ion and neurotransmitter homeostasis, maladaptive neuroinflammatory signaling, and impaired metabolic coupling in ASD and associated syndromes. Finally, we discuss the potential of various astrocyte-targeted interventions, which hold promise for advancing precision medicine approaches to these devastating disorders.

Keywords: Astrocytes; Autism spectrum disorder; Fragile X syndrome; Inflammation; Ion; Metabolism; Neurotransmitter; Rett syndrome; Synapse

INTRODUCTION

Autism spectrum disorder (ASD) is a complex, male predominant neurodevelopmental disorder with symptoms occur in early childhood and usually persist across the lifespan, negatively impacting the daily life of patients (Maenner et al., 2023; Russell et al., 2026). According to *Diagnostic and Statistical Manual of Mental Disorders, fifth edition* (DSM-5^{TM}) and its Text Revision (DSM-5-TR^{TM}), ASD is characterized by two core symptoms: persistent deficits in both social communication and social interaction, and restricted, repetitive patterns of behavior, interests, or activities, with these symptoms present in the early developmental period and are not better explained by intellectual disability or global developmental delay (American Psychiatric Association, 2013, 2022). Many ASD patients also exhibit comorbid conditions, such as language deficiency, intellectual disability, anxiety, attention deficit, hyperactivity, and sleep disturbance (Hyman et al., 2020; Lord et al., 2020). The global prevalence of ASD is about 1%, varying based on geographic, ethnic, and socioeconomic factors (Vakilzadeh & Martinez-Cerdeño, 2023; Zeidan et al., 2022). Although both environmental and genetic factors are known to contribute to ASD pathogenesis, its etiology still remains unclear, mainly due to the extreme clinical and genetic heterogeneity (Munir, 2026).

A number of environmental factors can cause ASD, such as exposure to chemicals or toxins, parental age at the time of conception, maternal nutrition and infections (including autoimmune diseases) during pregnancy, prematurity, and hypoxia or trauma at birth (Grabrucker, 2013; Petrelli et al., 2016; Vakilzadeh & Martinez-Cerdeño, 2023). One important research area in ASD is how environmental influences interact with genetic susceptibility to cause disease pathogenesis (Petrelli et al., 2016).

Genetic changes, such as coding sequence mutations, chromosomal rearrangements, and copy number variations, in hundreds of genes have been associated with ASD. However, most of these genes have only small effects (Murdoch & State, 2013; State & Levitt, 2011). Under the DSM-5^{TM} criteria, individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger’s disorder, or pervasive

Received: 29 April 2025; Accepted: 02 June 2026; Online: 03 June 2026

Foundation items: This work was supported by the National Natural Science Foundation of China (3250070406) and Scientific Project of Beijing Life Science Academy (2024300CD0060)

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developmental disorder not otherwise specified are included in ASD. Nevertheless, certain monogenic neurodevelopmental disorders, such as fragile X syndrome (FXS) and Rett syndrome (RTT), also manifest social impairments and stereotyped, repetitive behavior, the core features of ASD. These neurodevelopmental disorders are therefore often conceptualized as "syndromic ASD" (Fernandez & Scherer, 2017). Studies of mutations in these genes, including *FMR1* in FXS and *MECP2* in RTT, have provided critical insights into the mechanisms underlying ASD, including development, synapse structure and activity, gene expression and protein synthesis, and metabolism (Gold et al., 2024; Hagerman et al., 2017; Kelleher III & Bear, 2008; Zhao et al., 2023). Since many ASD-related genes encode proteins with clear synaptic functions, defects in neurons, including dysregulated synaptogenesis and an altered balance between synaptic excitation and inhibition (E/I balance), are thought to constitute the mechanisms underlying ASD pathogenesis (Cline, 2005; Guang et al., 2018; Nelson & Valakh, 2015). However, increasing evidence indicates that non-neuronal cells, particularly glial cells, are crucial players in neural circuit formation, neurotransmitter homeostasis, and neuroimmune signaling (Khakh & Sofroniew, 2015; Petrelli et al., 2016). Therefore, glial dysregulation can profoundly impact neuronal function, becoming an important pathological contributor to ASD rather than a passive bystander.

Among different glial cell types, astrocytes constitute approximately 20% or less of the total glial cells (Pelvig et al., 2008; Sun et al., 2017), a proportion lower than that of oligodendrocytes, which account for over 50% (Valério-Gomes et al., 2018). Nevertheless, astrocytes perform multiple functions in the nervous system (Markey et al., 2023). Astrocytes can promote synaptogenesis, regulate synapse pruning and elimination, maintain extracellular ion and neurotransmitter homeostasis, control components of the blood–brain barrier (BBB), provide metabolic support to neurons, and modulate local immune signaling (including cytokines and chemokines) (Khakh & Sofroniew, 2015; Verkhratsky et al., 2023). These multifaceted roles make astrocytes central to brain function, and disruption in any of these capacities can plausibly perturb developmental processes underlying ASD and associated syndromes. Mutations in certain genes predominantly expressed in astrocytes have been associated with ASD, such as mutations in the *KCNJ10* gene encoding the inward rectifying K^+ channel Kir4.1 (Sicca et al., 2011, 2016), and mutations in the *SLC6A1* gene encoding GAT-1, a transporter of the inhibitory neurotransmitter gamma aminobutyric acid (GABA) (Fischer et al., 2022; Mermer et al., 2021). These findings provide genetic evidence supporting a causal role of astrocytic dysfunction in ASD pathogenesis. Several recent reviews have covered the role of astrocytes in ASD from different angles (Chatterjee et al., 2025; Heine & Dooves, 2025; Inamdar et al., 2025). Here, we synthesize evidence from human patients, patient-derived inducible pluripotent stem cells and organoids, and animal models to provide a comprehensive, mechanistically informed review of how astrocyte status and their functions are altered in ASD and associated syndromes. Collectively, these findings robustly indicate that astrocytic dysregulation is not merely a secondary consequence, but a key contributor to the pathogenesis and progression of ASD and associated syndromes (Figure 1).

EVIDENCE FOR ASTROCYTE PARTICIPATION IN ASD AND ASSOCIATED SYNDROMES

Evidence from patients

Abnormalities in astrocytes have been found in postmortem brains of patients with ASD and associated syndromes through neuropathological studies, though there are inconsistent results from different work (Table 1). Glial fibrillary acidic protein (GFAP) is primarily expressed in and used as a marker for astrocytes, as its expression increases when astrocytes are hypertrophic and proliferate (Jurga et al., 2021; Liedtke et al., 1996). Interestingly, mutations in the *GFAP* gene cause Alexander disease, a rare, progressive and usually fatal genetic leukodystrophy. Alexander disease patients have disrupted astrocyte structure and function, abnormal myelination and neuronal dysfunction, and symptoms such as cognitive delay, seizures, macrocephaly, developmental delays, etc.; and some of these features are comorbid with ASD (Hagemann, 2022; Messing, 2019), implicating that GFAP disturbance may contribute to ASD and its associated comorbidities. Several studies have reported an increase in GFAP protein in the anterior cingulate cortical white matter, the superior frontal cortex, the parietal cortex, and the cerebellum of ASD patients (Crawford et al., 2015; Laurence & Fatemi, 2005; Vargas et al., 2005). Another study also finds an increase in GFAP protein in the cerebellum of postmortem ASD brains, but a decrease in vimentin (an immature astrocyte marker) in both the cerebellum and the prefrontal cortex (Broek et al., 2014). In addition, elevated GFAP levels are found in the cerebrospinal fluid and the plasma of ASD patients (Ahlsén et al., 1993; Rosengren et al., 1992; Singh et al., 1997), whereas the levels of S100β, an astrocytic Ca^{2+}-binding protein participating in the regulation of intracellular processes and mediating intercellular interactions (Donato, 2001), are not changed in the cerebrospinal fluid of ASD subjects (Ahlsén et al., 1993). In contrast, some studies show no change in GFAP protein in the anterior cingulate cortical grey matter, the anterior prefrontal cortical gray matter and white matter, the dorsolateral prefrontal white matter, and the middle frontal gyrus of postmortem ASD brains (Crawford et al., 2015; Lee et al., 2017; Vargas et al., 2005). A decrease in the numbers of astrocytes, labeled by GFAP or S100β, is reported in most of the prefrontal cortical BA9, BA46, and BA47 areas of postmortem ASD brains, accompanied by a mild activation in GFAP-positive astrocytes, except that GFAP-positive astrocyte numbers are not altered in the BA46 gray matter and GFAP-positive cells are not activated in the BA46 white matter (Vakilzadeh et al., 2022). A reduction in the numbers of astrocytes in BA46 layer II and BA47 layer III regions, but not in BA9, is determined by Nissl staining (Falcone et al., 2021). The reduction in astrocyte numbers may result from reduced production and/or increased cell death. At the gene expression level, some studies have reported that *GFAP* expression increases in the prefrontal cortex and cerebellum in postmortem ASD brains (Edmonson et al., 2014; Purcell et al., 2001). However, other studies find no change in *GFAP* expression in the anterior cingulate cortex and anterior prefrontal cortex of postmortem ASD brains (Crawford et al., 2015; Sciara et al., 2020).

RTT results from mutations in the X-linked *MECP2* gene, which encodes a transcriptional regulator methyl-CpG-binding protein 2 (MeCP2) (Gold et al., 2024). RTT is mainly seen in females, as males affected by *MECP2* mutations usually die

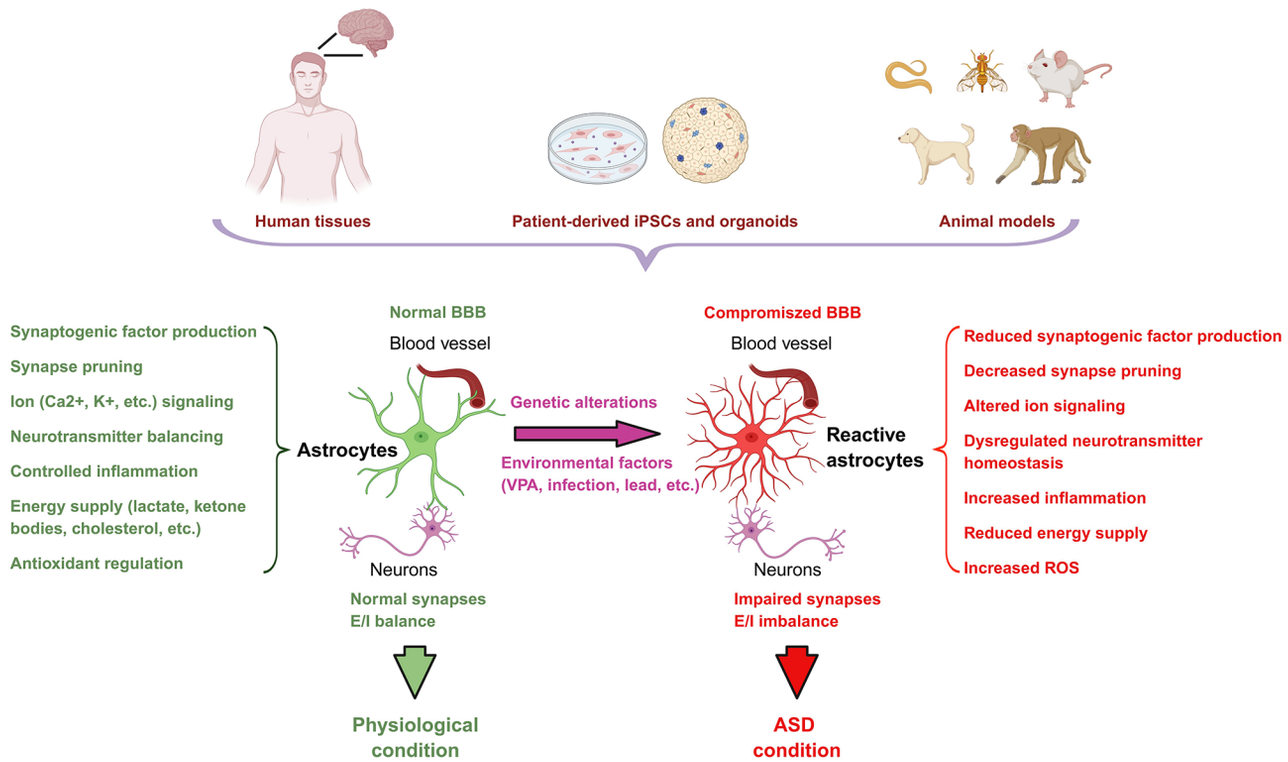

Figure 1 The physiological functions of astrocytes and their dysregulation in ASD, evidenced by studies in humans, patient-derived iPSCs and organoids, and animal models

Astrocytes exert a series of critical physiological functions in the central nervous system, such as synaptogenesis, synapse pruning, ion signaling, neurotransmitter homeostasis, inflammation, energy supply, and antioxidant regulation, to maintain neuronal excitatory/inhibitory (E/I) balance and the blood-brain barrier (BBB) integrity. Genetic alterations and environmental hostility can interfere with astrocytic functions, thereby impairing the E/I balance and the BBB, leading to ASD condition. Created in BioRender. Msf, X. (2026) https://BioRender.com/whdd194.

shortly after birth. While a majority of *MECP2* mutations are associated with RTT, several studies have identified some missense *MECP2* variants in ASD without RTT diagnosis (Chen et al., 2025; Schaaf et al., 2011; Wang et al., 2016; Wen et al., 2017), underscoring a shared molecular pathogenesis between ASD and RTT. Although GFAP protein levels are reported to be decreased in the frontal cerebral grey matter of postmortem RTT patients (Pejhan et al., 2020), an activation of GFAP-positive astrocytes is found in the frontal cortex of postmortem RTT patients (Lipani et al., 2000).

FXS results from mutations in the X-linked *FMR1* gene. The 5'-untranslated region of *FMR1* contains a CGG-triple repeat, whose excessive expansion (> 200 repeats) causes epigenetic silencing of *FMR1* and thus the loss of its encoding protein fragile X messenger ribonucleoprotein 1 (FMRP) (Hagerman et al., 2017; Zhao et al., 2023). The relationship between FXS and ASD is complex and continues to evolve, partially influenced by the revision of the diagnostic criteria for ASD. FXS is estimated to account for 1%–6% of all ASD cases. While approximately 50% of FXS males and 20% of FXS females meet the DSM-5 diagnostic criteria for ASD (Kaufmann et al., 2017; Muhle et al., 2004; Schaefer & Mendelsohn, 2013). One study finds that GFAP-positive and S100β-positive astrocytes significantly increase in the cortical layer I of BA3 of FXS individuals (Ren et al., 2023).

Some other proteins predominantly expressed by astrocytes are also found to be altered in ASD. Aquaporin 4 (AQP4) is a water channel protein located in astrocytes and responsible for eliminating water from the cerebral parenchyma as well as supporting potassium buffering (Abbasian et al., 2025). AQP4 protein levels are found to be decreased in the cerebellum but not altered in the prefrontal BA9 or the parietal BA40 regions of postmortem ASD patients (Fatemi et al., 2008). Connexin 43 (Cx43) is a gap junction protein located in astrocytes and found to be increased in the prefrontal BA9 but not altered in the parietal BA40 or the cerebellum of postmortem ASD brains (Fatemi et al., 2008). Since Cx43 regulates cellular growth and cell-cell adhesion, increased Cx43 expression may enhance glial-neuronal communication in the frontal lobe, which is responsible for executive functions (Fatemi et al., 2008).

A recent review suggests that these seemingly contrasting findings in ASD may reflect variability in age, brain region, comorbid conditions, sampling, and technical differences in postmortem analytical methods (Vakilzadeh & Martinez-Cerdeño, 2023). Through systematic comparison of these studies, we further observe that differential alterations in astrocytic markers are predominantly region-specific, suggesting both heterogeneity in astrocytic pathology across ASD and associated syndromes, and intrinsic regional heterogeneity among astrocytes themselves, including their distinct functional responses to ASD-associated neuropathological processes. Indeed, astrocytes are well-established to exhibit substantial heterogeneity in morphology, regional distribution, developmental stage-dependent functions, and stimulus-responsive reactivity (Ben Haim & Rowitch, 2017; Prochiantz & Mallat, 1988; Wang et al., 2025). There are as many as nine putative astrocyte subtypes in the murine central nervous system (CNS), such as protoplasmic astrocytes in grey matter, fibrous astrocytes in white matter, Bergmann glia in the cerebellum, and Müller cells in the retina (Ben Haim & Rowitch, 2017; Emsley & Macklis, 2006). Upon exposure to pathological or toxic stimuli, reactive astrocytes

Table 1 Evidence for astrocyte alteration in patients

Astrocyte markers	Alteration	Regions (References with detection methods[#])	Sample information and ASD diagnosis[%]
GFAP protein	Increase	Anterior cingulate cortical white matter (Crawford et al., 2015, WB); Superior frontal cortex (Laurence & Fatemi, 2005, WB); Parietal cortex (Laurence & Fatemi, 2005, WB); Cerebellar gray matter and white matter (Vargas et al., 2005, IS); Cerebellum (Broek et al., 2014, SRM-MS; Laurence & Fatemi, 2005, WB; Vargas et al., 2005, WB); Plasma (Singh et al., 1997, WB); Cerebrospinal fluid (Ahlsén et al., 1993, ELISA; Rosengren et al., 1992, ELISA).	Ahlsén et al., 1993: 47 ASD and 10 controls; diagnosis based on DSM-III and DSM-III-R criteria. Broek et al., 2014: 10 ASD and 10 controls; no diagnostic criteria informed. Crawford et al., 2015: 11 ASD and 11 controls; no diagnostic criteria informed. Laurence & Fatemi 2005: 5 ASD and 7 controls for superior frontal cortex, 4 ASD and 4 controls for parietal cortex, and 5 ASD and 8 controls for cerebellum; diagnosis based on DSM-IV criteria. Rosengren et al., 1992: same samples used in Ahlsén et al., 1993. Singh et al., 1997: 17 ASD and 58 controls; diagnosis based on DSM-III-R criteria. Vargas et al., 2005: 10 ASD and 6 controls for cerebellum IS, and 7 ASD and 7 controls for cerebellum WB; diagnosis based on DSM-IV criteria.
GFAP protein	No change	Anterior cingulate cortical gray matter (Crawford et al., 2015, WB); Anterior cingulate gyrus (Vargas et al., 2005, IS); Anterior prefrontal cortical gray matter (Crawford et al., 2015, WB); Anterior prefrontal cortical white matter (Crawford et al., 2015, WB); Dorsolateral prefrontal cortical white matter (Lee et al., 2017, IS); Middle frontal gyrus (Vargas et al., 2005, IS).	Crawford et al., 2015: 12 ASD and 12 controls for anterior cingulate cortical gray matter, 10 ASD and 10 controls for anterior prefrontal cortical gray matter, and 8 ASD and 8 controls for anterior prefrontal cortical white matter; no diagnostic criteria informed. Lee et al., 2017: 8 ASD and 7 controls; no diagnostic criteria informed. Vargas et al., 2005: 9 ASD and 6 controls for middle frontal gyrus and anterior cingulate gyrus IS; diagnosis based on DSM-IV criteria.
GFAP protein	Decrease	Frontal cerebral grey matter (Pejhan et al., 2020, IS).	Pejhan et al., 2020: 4 RTT and 4 controls; diagnosis supported by *MECP2* mutations.
GFAP mRNA	Increase	Prefrontal cortex (Edmonson et al., 2014, qPCR); Cerebellum (Edmonson et al., 2014, qPCR; Purcell et al., 2001, cDNA microarray and qPCR).	Edmonson et al., 2014: 5 ASD and 5 controls for PFC, and 4 ASD and 4 controls for cerebellum; no diagnostic criteria informed. Purcell et al., 2001: 4 ASD and 4 controls for cDNA microarray, and 10 ASD and 10 controls for qPCR; diagnosis based on DSM-IV or the Child Autism Rating Scale.
GFAP mRNA	No change	Anterior cingulate cortical gray matter (Crawford et al., 2015, qPCR; Sciara et al., qPCR); Anterior cingulate cortical white matter (Crawford et al., 2015, qPCR; Sciara et al., qPCR); Anterior prefrontal cortical gray matter (Crawford et al., 2015, qPCR); Anterior prefrontal cortical white matter (Crawford et al., 2015, qPCR).	Crawford et al., 2015: 14 ASD and 14 controls; no diagnostic criteria informed; Sciara et al., 2020: 12 ASD and 12 controls for anterior cingulate cortical gray matter, and 10 ASD and 10 controls for anterior cingulate cortical white matter; no diagnostic criteria informed.
$GFAP^+$ cell numbers	Increase	Cortical BA3 (Ren et al., 2023, IS with number counting).	Ren et al., 2023: 8 FXS and 6 controls; no diagnostic criteria informed.
$GFAP^+$ cell numbers	No change	Prefrontal cortical BA46 gray matter (Vakilzadeh et al., 2022, IS with number counting).	Vakilzadeh et al., 2022: 15 ASD and 15 controls; diagnosis based on ADI-R.
$GFAP^+$ cell numbers	Decrease	Prefrontal cortical BA9 gray matter and white matter, BA46 white matter, and BA47 gray matter and white matter (Vakilzadeh et al., 2022, IS with number counting).	Vakilzadeh et al., 2022: 15 ASD and 15 controls; diagnosis based on ADI-R.
$GFAP^+$ cell activation	Increase	Prefrontal cortex BA9 gray matter and white matter, BA46 gray matter, and BA47 gray matter and white matter (Vakilzadeh et al., 2022, IS with morphology evaluation); Frontal cortex (Lipani et al., 2000, IS with morphology evaluation).	Vakilzadeh et al., 2022: 15 ASD and 15 controls; diagnosis based on tADI-R. Lipani et al., 2000: 9 RTT and 9 controls; diagnosis based on the classic criteria for RTT.
$GFAP^+$ cell activation	No change	Prefrontal cortical BA46 white matter (Vakilzadeh et al., 2022, IS with morphology evaluation).	Vakilzadeh et al., 2022: 15 ASD and 15 controls; diagnosis based on ADI-R.
Astrocyte numbers	No change	Prefrontal cortex BA9 (Falcone et al., 2021, Nissl staining with morphology evaluation).	Falcone et al., 2021: 10 ASD and 10 controls; diagnosis confirmed by standard postmortem use of ADI-R.
Astrocyte numbers	Decrease	Prefrontal cortex BA46 layer II and BA47 layer III (Falcone et al., 2021, Nissl staining with morphology evaluation).	Falcone et al., 2021: 10 ASD and 10 controls; diagnosis confirmed by standard postmortem use of ADI-R.

Continued

Astrocyte markers	Alteration	Regions (References with detection methods[#])	Sample information and ASD diagnosis[%]
Vimentin protein	Decrease	Prefrontal cortex (Broek et al., 2014, SRM-MS); Cerebellum (Broek et al., 2014, SRM-MS).	Broek et al., 2014: 10 ASD and 10 controls for prefrontal cortex, and 14 ASD and 17 controls for cerebellum; no diagnostic criteria informed.
AQP4 protein	No change	Prefrontal cortex BA9 and Parietal cortex BA40 (Fatemi et al., 2008, WB).	Fatemi et al., 2008: 6 ASD and 6 controls for BA9, and 8 ASD and 6 controls for BA40; diagnosis based on DSM-IV.
AQP4 protein	Decrease	Cerebellum (Fatemi et al., 2008, WB).	Fatemi et al., 2008: 8 ASD and 10 controls for cerebellum; diagnosis based on DSM-IV.
Connexin 43 protein	Increase	Prefrontal cortex BA9 (Fatemi et al., 2008, WB).	Fatemi et al., 2008: 6 ASD and 6 controls for BA9; diagnosis based on DSM-IV.
Connexin 43 protein	No change	Parietal cortex BA40 and cerebellum (Fatemi et al., 2008, WB).	Fatemi et al., 2008: 8 ASD and 6 controls for BA40, and 8 ASD and 10 controls for cerebellum; diagnosis based on DSM-IV.
S100β protein	No change	Cerebrospinal fluid (Ahlsén et al., 1993, ELISA).	Ahlsén et al., 1993: 47 ASD and 10 controls; diagnosis based on DSM-III and DSM-III-R.
$S100\beta^+$ cell numbers	Increase	Cortical BA3 (Ren et al., 2023, IS with number counting).	Ren et al., 2023: 8 FXS and 6 controls; no diagnostic criteria informed.
$S100\beta^+$ cell numbers	Decrease	Prefrontal cortical BA9 gray matter and white matter, BA46 gray matter and white matter, and BA47 gray matter and white matter (Vakilzadeh et al., 2022, IS with number counting).	Vakilzadeh et al., 2022: 15 ASD and 15 controls; diagnosis based on ADI-R.
CST3 mRNA	Increase	Prefrontal cortex (Velmeshev et al., 2019, *in situ* RNA hybridization).	Velmeshev et al., 2019: 10 ASD and 7 controls; no diagnostic criteria informed.

[#]Detection methods: IS, Immunostaining; qPCR, quantitative PCR; SRM-MS, selected reaction monitoring mass spectrometry; WB, western blotting. [%]Diagnosis criteria: ADI-R, the Autism Diagnostic Interview-Revised; DSM-III, *Diagnostic and Statistical Manual of Mental Disorders, Third edition*; DSM-III-R, *Diagnostic and Statistical Manual of Mental Disorders, Third edition, Revision*; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth edition*.

can adopt functionally divergent states, including the neurotoxic A1-like phenotype and the neuroprotective A2-like phenotype, with each characterized by distinct cytokine expression profiles (Sarkar & Biswas, 2021). More recent studies using single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics analysis have further uncovered both inter- and intra-regional differences in astrocytic gene expression profiles (Bayraktar et al., 2020; Hasel et al., 2021; Qian et al., 2023). Notably, we find a consistent upregulation of GFAP mRNA and protein levels in the cerebellum across multiple studies (Table 1). Accumulating evidence has indicated that cerebellar dysfunction is a critical contributor to the pathophysiology of ASD (Su et al., 2021). Thus, astrocytic alterations, particularly those localized to the cerebellum, may represent a critical component of ASD neuropathology. Finally, it is important to note that all these ASD subjects studied are either with no clear diagnosis or diagnosed based on earlier versions of the *Diagnostic and Statistical Manual of Mental Disorders* (Table 1). Consequently, there remains an urgent need for future investigations utilizing well-characterized, prospectively enrolled ASD cohorts with rigorously confirmed diagnosis.

Large-scale transcriptomic studies further support astrocytic dysfunction in ASD. In one study using microarray assays to identify differentially expressed genes (DEGs) between ASD and control samples of three brain regions, the superior temporal gyrus (BA41/42), the prefrontal cortex (BA9), and the cerebellar vermis, hundreds of DEGs are found in cortical samples. However, only 2 DEGs are found in cerebellar samples, suggesting that gene expression changes associated with ASD are more profound in the cerebral cortex (Voineagu et al., 2011). Importantly, weighted-gene co-expression network analysis (WGCNA) reveals that for the two network modules highly correlated with disease status, one is neuronal and enriched with ASD susceptibility genes, and the other one is enriched for markers of astrocyte and activated microglia, as well as for immune-related genes (Voineagu et al., 2011). These results support that in addition to the "neuronal origin" of ASD pathogenesis, astrocyte- and microglia-modulated immune responses also contribute to ASD. These findings are confirmed in another study on the same brain regions but with an rRNA-depleted RNA-sequencing method (Parikshak et al., 2016). Later large-scale RNA-sequencing studies, in combination with single-nucleus RNA sequencing (snRNA-seq) analysis, reveal upregulation of astrocytic genes in various cortical regions of ASD patients (Gandal et al., 2018, 2022), suggesting altered astrocytic function in ASD. Consistently, snRNA-seq of the prefrontal cortex and anterior cingulate cortex of postmortem ASD brains identifies upregulated protoplasmic astrocyte gene expression, with increased astrocytes in the prefrontal cortex confirmed by *in situ* RNA hybridization of cystatin C (CST3), another marker for astrocytes (Velmeshev et al., 2019). When bulk and single-cell RNA-seq data from distinct sources on postmortem ASD brain regions are combined for analysis, the results confirm that ASD brains possess higher fractions of astrocytes (Tiong et al., 2024). In another study combining deep snRNA-seq with single-nucleus assays for transposase-accessible chromatin with sequencing (snATAC-seq) and spatial transcriptomics, the authors also find activated astrocytes predominantly in the superficial cortical laminae of ASD subjects (Wamsley et al., 2024). Analysis of snRNA-seq data from ASD patients at different ages (children, adolescents, and adults) reveals that upregulated DEGs are significantly more abundant in protoplasmic astrocytes in children with ASD than those in other age groups, and that aberrant switching behaviors in functional connectivity dynamics in ASD may be mediated by altered differentiation patterns in a subset of astrocytes (Li et al., 2025b). Collectively, these findings highlight the heterogeneity of astrocytes and their

altered molecular states in ASD. Since social communications and repetitive behavior engage distinct brain regions and neural circuits, and there is evidence indicating that the two behaviors can be differentially modulated by specific neuronal subtypes (Belger et al., 2011; Molitor et al., 2026), whether and how distinct astrocytic subtypes contribute to these two core ASD-associated behaviors deserves future investigation.

Evidence from induced pluripotent stem cells (iPSCs) and organoids

Induced pluripotent stem cells (iPSCs) from patients with ASD and associated syndromes can be differentiated into various neural cells, including astrocytes (Table 2), providing powerful platforms to study human-specific molecular and functional alterations in these disorders (Heider et al., 2021; Lee et al., 2020; Nehme & Barrett, 2020). Astrocytes generated from iPSCs of ASD patients exhibit aberrant calcium signaling and abnormal inflammatory factor release (Allen et al., 2022; Mostafavi Abdolmaleky et al., 2024; Russo et al., 2018). When co-cultured with control neurons, ASD iPSC-derived astrocytes interfere with proper neuronal development, impairing dendritic arborization and synapse formation (Allen et al., 2022; Russo et al., 2018). Critically, transplantation of ASD iPSC-derived astrocytes into mouse brains induces repetitive behaviors and impaired social interactions, demonstrating the sufficiency of astrocytic dysfunction to drive core ASD-associated phenotypes *in vivo* (Allen et al., 2022).

One study reports that iPSC cells from RTT patients harboring *MECP2* mutations have perturbed differentiation into astrocytes when induced by retinoid acid (Kim et al., 2019). In contrast, another study finds that iPSC lines from several RTT patients carrying different disease-causing mutations are efficiently differentiated into astrocytes, but mutant RTT astrocytes and their conditioned media alter the morphology and impair the function of wild-type neurons (Williams et al., 2014), suggesting that *MECP2* mutations can compromise astrocytic function in supporting neurons.

When *FMR1* in human iPSCs is knocked out to mimic FXS and then induced to differentiate into cortical neurons, the cells show an increased number of GFAP-positive cells, implicating a preference for astrogenesis (Brighi et al., 2021). In addition, when iPSCs of FXS patients and human embryonic stem cells (ESCs) with *FMR1* knockout (KO) are differentiated into astrocytes, they exhibit enhanced Ca^{2+} signaling, shortened cell cycle, dysregulated cholesterol metabolism, and increased GABA and GABA-synthesizing enzyme levels (Ren et al., 2023; Wagner et al., 2026), all of which are associated with ASD abnormalities (Gzielo & Nikiforuk, 2021; Jäntti et al., 2026; Petrelli et al., 2016).

Variants in the *SLC6A1* gene that encodes the GABA transporter GAT-1 have been linked to a spectrum of neurodevelopmental disorders including ASD (Fischer et al., 2022). In astrocytes differentiated from iPSCs of patients carrying *SLC6A1* mutations, GABA uptake function is found to be compromised, accompanied by decreased GAT-1 levels (Mermer et al., 2021).

Generating brain organoids by culturing iPSCs in a 3D system has provided an invaluable tool for studying human-specific brain development processes and neurodevelopmental disorders (Table 2) (Li & Knoblich, 2025; Mattingly & Chetty, 2025). Prenatal alcohol (EtOH) exposure

Table 2 Evidence for astrocyte alteration in patient-derived iPSCs and organoids

Models	Astrocyte-related alteration (References)
2D cells	
Astrocytes derived from iPSCs of ASD patients	Aberrant calcium signaling (Allen et al., 2022); Abnormal inflammatory factor release (Mostafavi Abdolmaleky et al., 2024; Russo et al., 2018); Interfere with proper neuronal development and impair dendritic arborization and synapse formation when co-cultured with neurons (Allen et al., 2022; Russo et al., 2018); Induces repetitive behaviors and impaired social interactions when transplanted into mouse brain (Allen et al., 2022).
iPSCs harboring *MECP2* mutations	Perturbed differentiation into astrocytes (Kim et al., 2019).
Astrocytes derived from iPSCs of RTT patients carrying *MECP2* mutations	Abnormal calcium homeostasis (Dong et al., 2018); Alter the morphology and impair the function of wild-type neurons when co-cultured (Williams et al., 2014).
Human iPSCs with *FMR1* knockout	Preferred astrogenesis (Brighi et al., 2021).
Astrocytes derived from iPSCs of FXS patients	Increased GABA and GABA-synthesizing enzyme levels (Wagner et al., 2026); Enhanced Ca^{2+} signaling, shortened cell cycle, and dysregulated cholesterol metabolism (Ren et al., 2023).
Astrocytes derived from human embryonic stem cells with *FMR1* knockout	Enhanced Ca^{2+} signaling, shortened cell cycle, and dysregulated cholesterol metabolism (Ren et al., 2023).
Astrocytes derived from ASD patients carrying *SLC6A1* mutations	Impaired GABA uptake function and decreased GAT-1 levels (Mermer et al., 2021).
3D organoids	
Human cortical organoids exposed to EtOH	Impaired astrocytic function, gliogenesis, and synaptogenesis (Adams et al., 2023).
Cortical organoids with *FMR1* knockout	Increased number of glial cells and bigger organoid sizes (Brighi et al., 2021).
Cerebellar organoids carrying PTEN I135L mutation	A relative late increase in astrocyte number (Chen et al., 2026).
Cerebellar organoids carrying PTEN knockout mutation	An early and sustained increase in astrocyte number (Chen et al., 2026).
Brain organoids carrying *TSC1* or *TSC2* mutations	Strong bias towards an astrocytic cell fate and altered cell morphology (Blair et al., 2018).
Brain organoids carrying NLGN3 R451 C mutation	Increased astrogliogenesis and significantly upregulated pathways supporting neural function (Dang et al., 2025).

is an environmental risk factor for ASD. When human cortical organoids are exposed to EtOH, astrocytic function, gliogenesis, and synaptogenesis are impaired (Adams et al., 2023), suggesting that ASD-related environmental risk factors can compromise astrocyte development and functions, which may contribute to disease pathogenesis. In contrast, when human iPSCs with *FMR1* KO mimicking FXS are used to generate cortical brain organoids, they have an increased number of glial cells and bigger organoid sizes, suggesting that *FMR1* deficiency promotes gliogenesis (Brighi et al., 2021).

The *PTEN* (phosphatase and tensin homologue) gene functions as a tumor suppressor and a negative regulator of the PI3K/AKT/mTOR signaling pathway. *PTEN* also plays a crucial role in maintaining neural stem and progenitor cell populations (Worby & Dixon, 2014). Mutations in *PTEN* have been associated with ASD (Arenella et al., 2023; Rademacher & Eickholt, 2019). When ASD-associated PTEN I135L mutant and PTEN KO iPSC cells are used to generate cerebellar organoids, PTEN KO cerebellar organoids show an early and sustained increase in astrocytes. PTEN I135L mutant cerebellar organoids also have an increase in astrocyte number, though this appears at a relatively late stage (Chen et al., 2026).

Mutations in *TSC1* or *TSC2* can cause Tuberous Sclerosis Complex (TSC), a multi-system developmental disorder with ASD-associated neuropsychiatric phenotypes, and about 20% of TSC patients are reported to have ASD (Kingswood et al., 2017). One study generating organoids using human iPSCs with CRISPR/Cas9-mediated deletion of *TSC1* or *TSC2* finds that their loss results in a strong bias towards an astrocytic cell fate and cell morphology alteration (Blair et al., 2018), suggesting that mutations in *TSC1* and *TSC2* may affect the ratio and function of astrocytes in the developmental brain, thereby contributing to disease pathogenesis.

Proper synapse formation requires appropriate matching between presynaptic and postsynaptic molecules at newly formed contacts, within which the neuroligin/neurexin adhesion complexes play a crucial role (Lisé & El-Husseini, 2006). Neuroligins (NLGNs) are type I transmembrane proteins located on the postsynaptic side, with five family genes identified in humans and three in rodents (Lisé & El-Husseini, 2006). Neurexins (NRXNs) are also type I transmembrane proteins but located on the presynaptic side, with three family genes identified in mammals (Lisé & El-Husseini, 2006). Trans-synaptic interactions between NLGNs and NRXNs instruct synapse formation and mediate essential signaling through synapses to process information (Lisé & El-Husseini, 2006; Südhof, 2008, 2017). Because NLGN/NRXN complexes are important for synapse function, disturbances of these complexes may impair neuronal activity, leading to neurological disorders. Indeed, mutations in NLGNs and NRXNs have been identified in ASD patients (Cao & Tabuchi, 2017). Brain organoids derived from human ESCs harboring the ASD-associated neuroligin 3 (NLGN3) R451C mutation exhibit increased astrogliogenesis, and mutant astrocytes show significantly upregulated pathways supporting neural function (Dang et al., 2025).

Together, studies utilizing patient-derived iPSCs and organoids provide converging evidence to support astrocytic dysregulation in ASD and associated syndromes.

Evidence from animal models

Different animal models, including invertebrates (such as nematodes and fruit flies), zebrafish, rodents (such as mice and rats), domestic animals (such as dogs, pigs, and cattle), and non-human primates (such as rhesus monkeys, cynomolgus monkeys, and marmosets), have been applied to studies on ASD and associated syndromes (Jiao et al., 2024; Li et al., 2021b; Qiu, 2025). Through pharmacological, virus-mediated, and/or genetic modulation, these animals can develop various phenotypes resembling those of ASD patients, thereby providing invaluable insights into the mechanisms underlying disease pathogenesis, including the contribution of astrocytes (Table 3). For example, one study finds that increasing hippocampal astrogenesis by overexpressing EGFR during development can induce ASD-like behavior in mice, providing direct evidence for a developmental role of astrocytic dysregulation in driving the behavioral phenotypes of ASD (Chen et al., 2022).

Because of the high ASD incidence of a newborn child following exposure of the pregnant mother to the antiepileptic drug valproic acid (VPA) (Christensen et al., 2013), one commonly used environmental animal model of ASD has been developed by the exposure to VPA during maternal pregnancy (Gzielo & Nikiforuk, 2021; Nicolini & Fahnestock, 2018). Rodents prenatally exposed to VPA display typical ASD-associated behavioral phenotypes including social deficits and repetitive behavior, as well as comorbid sensorimotor delay and cognitive impairments (Kim et al., 2022; Nicolini & Fahnestock, 2018; Saavedra-Bonilla et al., 2024; Zheng et al., 2025). Moreover, in rat and mouse models of ASD with prenatal exposure to VPA, the number of astrocytes and GFAP levels are increased in both the medial prefrontal cortex and the primary somatosensory area (Deckmann et al., 2021; Kim et al., 2022; Mony et al., 2018; Saavedra-Bonilla et al., 2024; Zheng et al., 2025), whereas AQP4 levels are decreased in the medial prefrontal cortex but increased in the primary somatosensory area (Deckmann et al., 2021). Cynomolgus monkey offspring from the early maternal VPA exposure have significantly increased GFAP-positive astrocytes in the prefrontal cortex and exhibit ASD-related behaviors, including impaired social interaction, pronounced stereotypies, and more attention on nonsocial stimuli (Zhao et al., 2019).

Activation of the maternal immune system (MIA) by viral or bacterial infection during pregnancy may lead to ASD occurrence in offspring (Gzielo & Nikiforuk, 2021). Therefore, the MIA model of ASD has also been developed by using lipopolysaccharide (LPS) to mimic bacterial infection or using poly(I:C), a double-stranded RNA analogue to mimic viral infection (Gzielo & Nikiforuk, 2021). In LPS-induced MIA rat and mouse models of ASD, GFAP immunoreactivity and astrogliosis are found to be significantly increased in the brain (Durankuş et al., 2022; O'Loughlin et al., 2017). In a poly(I:C)-induced MIA mouse model, GFAP expression is also found to be increased in the hippocampus (Ratnayake et al., 2012).

A series of ASD risk genes with high penetrance, whose sole mutations can lead to different types of ASD, have been identified. Genetic modulation of these genes has yielded various genetic animal models for studying the mechanisms underlying ASD and associated syndromes. Notably, some of these ASD risk genes (e.g., *FMR1*, *MECP2*) are also expressed in astrocytes, suggesting cell-autonomous contributions of astrocytes to ASD-associated molecular pathways.

Fmr1 KO mice exhibit social defects and stereotyped repetitive behavior resembling those of FXS patients and have

Table 3 Evidence for astrocyte change in animal studies

Animal models	Astrocyte-related alteration (References)	ASD-related phenotypes (References)
Pharmacological induction		
Mice with prenatal VPA treatment	Increased GFAP expression (Kim et al., 2022; Saavedra-Bonilla et al., 2024).	Developmental delay, motor dysfunction, social and cognitive deficits, repetitive behavior, and hyperactivity (Kim et al., 2022); Sensorimotor delay (Saavedra-Bonilla et al., 2024).
Mice with prenatal LPS treatment	Increased astrogliosis (O'Loughlin et al., 2017).	–
Mice with prenatal poly(I:C) treatment	Increased GFAP expression (Ratnayake et al., 2012).	Impaired learning and memory and motor activity (Ratnayake et al., 2012).
Rats with prenatal VPA treatment	Increased astrocyte number and GFAP expression (Deckmann et al., 2021; Traetta et al., 2021; Zheng et al., 2025); Decreased AQP4 expression (Deckmann et al., 2021).	Social deficits and repetitive behavior (Zheng et al., 2025).
Rats with prenatal LPS treatment	Increased GFAP expression (Durankuş et al., 2022)	–
Cynomolgus monkeys with prenatal VPA treatment	Increased GFAP-positive astrocytes (Zhao et al., 2019).	Impaired social interaction, pronounced stereotypies, and more attention on nonsocial stimuli (Zhao et al., 2019).
Virus-mediated modulation		
Mice with EGFR overexpression during development	Increased astrogenesis (Chen et al., 2022).	Decreased social interaction and increased repetitive self-grooming (Chen et al., 2022).
Genetic modulation		
Nematodes with *kqt-2* knockout or knockdown in AMsh glia	Deficient GABA release from AMsh glia (Graziano et al., 2024); Decreased Ca^{2+} transients in response to stimuli (Wang et al., 2022a).	Altered chemosensory phenotypes (Graziano et al., 2024; Wang et al., 2022a).
Fruit flies with *dube3a* overexpression in glia	–	Seizures (Hope et al., 2017; Landaverde et al., 2024).
Fmr1 KO mice	Astrocyte hypertrophy (Lee et al., 2019); Increased GFAP and S100β expression (Lee et al., 2019; Pacey et al., 2015); Bergmann glial primary cilia deficits (Lee et al., 2022); Decreased GLT1 expression and glutamate uptake in the cortex (Higashimori et al., 2013).	–
Astrocytic-specific *Fmr1* cKO mice	Decreased GLT1 expression and glutamate uptake in astrocytes (Higashimori et al., 2016); Increased spine density (Higashimori et al., 2016; Hodges et al., 2017); Cortical hyperexcitability (Jin et al., 2021); Reduced inhibitory connectivity and impaired cortical responses to sound (Wagner et al., 2026).	Impaired motor-skill learning (Hodges et al., 2017); Locomotor hyperactivity and social and memory deficits (Jin et al., 2021).
Mecp2 KO mice	Altered astrocyte-enriched gene expression (Pacheco et al., 2017); Astrocytic MeCP2 re-expression attenuates abnormalities (Lioy et al., 2011).	Hypoactivity, anxiety, and reduced life span (Lioy et al., 2011).
Astrocyte-specific *Mecp2* cKO mice	Altered astrocytic gene expression, and aberrant glutamate clearance (Okabe et al., 2012).	Respiratory abnormality (Garg et al., 2015).
Astrocyte-specific *Nlgn2* cKO mice	Altered astrocyte morphology (Stogsdill et al., 2017).	–
Astrocyte-specific *Nlgn3* cKO mice	–	Enhanced social novelty preference (Qin et al., 2025).
Astrocyte-specific *Nlgn3* cKO in the hippocampus of adult mice	Impaired astrocyte activation (Dang et al., 2024).	Impaired social memory (Dang et al., 2024).
SHANK3 KO cynomolgus monkeys	Increased GFAP protein levels and GFAP-positive astrocytes (Zhao et al., 2017).	–
Idiopathic models		
BTBR T+Itpr3tf/J mice	Decreased *Gfap* mRNA levels in the brain (Yao et al., 2022); Decreased GFAP protein levels in the hippocampus and brain of BTBR mice (Shi et al., 2026; Yao et al., 2022); Smaller CA2 region with fewer cell dendritic spines, microglia and astrocytes (Cope et al., 2022).	Social impairments, repetitive behavior, and cognitive deficits (Cope et al., 2022; Shi et al., 2026; Yao et al., 2022).

VPA: Valproic acid.KO: Knockout.cKO: Conditional knockout. –: Not available.

been widely used as a model of FXS and associated ASD (Jiang et al., 2022; Zhao et al., 2023). Increased GFAP expression and astrocyte hypertrophy are found in the cerebral cortex of *Fmr1* KO mice (Lee et al., 2019). The expression of GFAP and S100β is also found to be elevated in the cerebellum of *Fmr1* KO mice (Pacey et al., 2015). These findings suggest that aberrant astrogliosis is a global feature in the *Fmr1* KO mouse brain. In addition, the primary cilia of Bergmann glia show deficits in the FXS mouse model (Lee et al., 2022). Bergmann glia are a specific type of radial astrocyte in the cerebellum that support Purkinje cells and primary cilia function as antennae for cells to sense signals (Chrobak & Soltys, 2017; Lee et al., 2022). Since loss of Purkinje cells in the cerebellum is a consistent cellular abnormality found in ASD (Becker & Stoodley, 2013; Vargas et al., 2005), the dysfunction of Bergmann glia may contribute to Purkinje cell loss (Chrobak & Soltys, 2017). *FMR1*/*Fmr1* is found to be expressed in both neurons and glial cells including astrocytes (Pacey & Doering, 2007). Astrocytic glutamate transporter GLT1 and astrocytic glutamate uptake are significantly reduced in the cortex of *Fmr1* KO mice and this dysregulation is due to astrocytic FMRP-dependent translational downregulation of mGluR5 (Higashimori et al., 2013). Selective deletion of FMRP in astrocytes also reduces GLT1 expression and glutamate uptake, increases spine density and neuronal excitability, induces locomotor hyperactivity, and impairs social and learning and memory in mice. In contrast, astrocytic FMRP re-expression essentially reverses these defects (Higashimori et al., 2016; Hodges et al., 2017; Jin et al., 2021). Astrocyte-specific *Fmr1* KO mice also exhibit reduced inhibitory connectivity and impaired cortical responses to sound, and these may be due to abnormal GABA transport in cortical astrocytes (Wagner et al., 2026).

MeCP2 is highly expressed in neurons but also found in astrocytes and other glial cells (Ballas et al., 2009; Kifayathullah et al., 2010; Maezawa et al., 2009). A transcriptomic study finds that 46 astrocyte-enriched genes are differentially expressed in MeCP2-deficient mice modeling RTT (Pacheco et al., 2017). Loss of MeCP2 in astrocytes alters the gene expression pattern of astrocytes and causes aberrant glutamate clearance, suggesting that MeCP2 deficiency cell-autonomously affects astrocytic functions (Okabe et al., 2012). Conditional depletion of MeCP2 in astrocytes depresses the hypercapnic ventilatory response in mice (Garg et al., 2015). Importantly, MeCP2-null astrocytes fail to support normal neuronal growth, indicating that MeCP2 dysfunction in astrocytes plays a crucial role in RTT neuropathology (Ballas et al., 2009; Maezawa et al., 2009). Re-expression of MeCP2 in astrocytes significantly attenuates neuronal morphology change, improves locomotion and anxiety levels, restores respiratory abnormalities, and prolongs lifespan in mice with global MeCP2 deficiency (Lioy et al., 2011).

Cell adhesion molecules, such as NLGNs and NRXNs, are essential in regulating synapse formation and maintenance. Interestingly, although primarily expressed in neurons, NLGNs are also found expressed in astrocytes (Dang et al., 2024; Gilbert et al., 2001; Liu et al., 2022; Qin et al., 2025; Stogsdill et al., 2017). Loss of astrocytic neuroligin 2 (NLGN2) alters the morphology of astrocytes, diminishes cortical excitatory synapse formation and function, and enhances inhibitory synaptic function (Stogsdill et al., 2017). NLGN3 is robustly expressed in cerebellar astrocytes, and embryonic deletion of NLGN3 specifically in astrocytes significantly shifts gene expression across multiple cerebellar cell types and may have a beneficial effect on mouse social behaviors compared to controls, but does not affect synapse number or function (Qin et al., 2025). In contrast, another study finds that astrocytic NLGN3 is required for astrocyte activity, and mouse social memory is impaired when astrocytic NLGN3 in the hippocampus becomes deficient at adult age (Dang et al., 2024). Moreover, α-neurexin 1 and α-neurexin 2 are also found expressed in astrocytes (Uchigashima et al., 2019), though their functions in astrocytes remain unknown.

SHANK family proteins (SHANK1-3) function as postsynaptic scaffolding proteins in excitatory synapses. Mutations in SHANK family genes have been associated with ASD (Monteiro & Feng, 2017; Uchino & Waga, 2013). The *SHANK3* gene is located on the 22q13.3 chromosome segment, whose deletion leads to Phelan-McDermid syndrome with core ASD clinical features (Phelan, 2008; Uchino & Waga, 2013). In the cynomolgus monkey fetus with SHANK3 deletion, GFAP protein levels and GFAP-positive astrocytes in the prefrontal cortex are found to be increased compared to those of controls (Zhao et al., 2017).

KCNQs are voltage-gated K^+ channels that control neuronal excitability and its mutations are associated with ASD (Kim et al., 2020a; Nissenkorn et al., 2024). KCNQs have been extensively studied in neurons, but their function in glia is largely unclear. Some studies find that glial KCNQ channels control neuronal excitability by mediating GABA release from glia via regulation of the function of L-type voltage-gated Ca^{2+} channels, and KO of the KCNQ ortholog, *kqt-2*, in AMsh glial cells of nematodes affects their responses to various chemicals (Graziano et al., 2024; Wang et al., 2022a).

Altered expression of the E3 ubiquitin ligase gene *UBE3A* contributes to a range of neurological disorders (Lopez et al., 2019). Loss-of-function mutations in *UBE3A* cause Angelman syndrome, characterized by cognitive impairment, developmental delay, and a consistently happy demeanor (Williams, 2005), whereas duplications of the 15q11.2-q13 region containing *UBE3A* (Dup15q syndrome) are associated with ASD (Distefano et al., 2016; Landaverde et al., 2024). Studies in fruit flies find that overexpression of *dube3a* (the ortholog of *UBE3A*) in glia but not neurons results in seizures and synaptic impairment (Hope et al., 2017; Landaverde et al., 2024).

Several inbred mouse strains display highly repetitive behavior and social deficits that closely mirror the core clinical features of ASD and are therefore used as idiopathic models (Li et al., 2021b). One of them, the BTBR T+Itpr3tf/J (BTBR) strain, is commonly used for ASD research. Notably, BTBR mice exhibit decreased GFAP expression in the brain, accompanied by less astrocytes, in the reduced hippocampal CA2 subregion (Cope et al., 2022; Shi et al., 2026; Yao et al., 2022).

The findings reported here may not cover the entire field, as too many animal models have been developed to study the pathophysiological functions of different ASD-related genes. Nevertheless, they together provide strong evidence supporting the contribution of astrocytic dysregulation to ASD and associated syndromes.

MECHANISMS LINKING DYSREGULATED ASTROCYTIC FUNCTIONS TO ASD AND ASSOCIATED SYNDROMES

Our understanding about astrocyte development is mainly derived from classic neuroanatomical studies of the mammalian neocortex (Markey et al., 2023). Astrocyte

progenitors are specified during embryonic development. However, the production, migration, and maturation of astrocytes occur predominantly during the first few weeks of postnatal development in mice. Mouse radial glial cells (RGCs) in the ventricular zone (VZ) undergo a progressive glial transition beginning at embryonic day 16, peaking at postnatal day 6, and declining at postnatal day 28 (Ge et al., 2012). RGCs translocate from the VZ toward the pial surface and eventually differentiate into protoplasmic and fibrous astrocytes (Akdemir et al., 2020; Degl'Innocenti & Dell'Anno, 2023; Kriegstein & Alvarez-Buylla, 2009). In addition, a pool of mouse astrocyte progenitor cells resides in the dorsolateral corner of the subventricular zone (SVZ), and migrates into the cortex during the first week of postnatal development (Levison & Goldman, 1993). Immature mouse astrocytes in the cortex undergo morphological and functional maturation over the first few weeks of postnatal development (Markey et al., 2023). In humans, the principal neural stem cells destined for astrocytes also resides in the VZ and SVZ. Human astrogenesis occurs predominantly during the second half of gestation, and persist in the postnatal period (Degl'Innocenti & Dell'Anno, 2023).

Synaptogenesis and synapse pruning

The timing of astrocyte production and maturation coincides with synapse formation in rodents, which also occurs during the first few weeks of postnatal development (Farhy-Tselnicker & Allen, 2018; Markey et al., 2023; Sauvageot & Stiles, 2002; Ullian et al., 2001), implicating the requirement of astrocytes for synapse development. Indeed, it has now been shown that during postnatal maturation, astrocytes extend processes to contact synapses and form the "tripartite synapse" (Cantando et al., 2024; Perea et al., 2009). Astrocytes can regulate synapse formation/maturation and modulate synaptic activity and plasticity by secreting synaptogenic factors, such as thrombospondins, hevin, glypicans, and EphB2 (Figure 2) (Araque et al., 2014; Clarke & Barres, 2013; Fossati et al., 2020; Sutley-Koury et al., 2024).

Dysregulation of astrocyte-mediated synapse dynamics may result in ASD. The *THBS1* gene encodes the synaptogenic factor thrombospondin 1 secreted by astrocytes. Its deletion in mice leads to severely disrupted social interaction and emotional alterations featuring ASD phenotypes (Leana-Sandoval et al., 2025). Moreover, variants in the *THBS1* gene have been associated with ASD in humans (Lu et al., 2014), providing direct evidence linking astrocyte-modulated synapse dysfunction to ASD incidence. Hevin functions to stabilize NLGN-NRXN trans-synaptic bridges through interplaying with

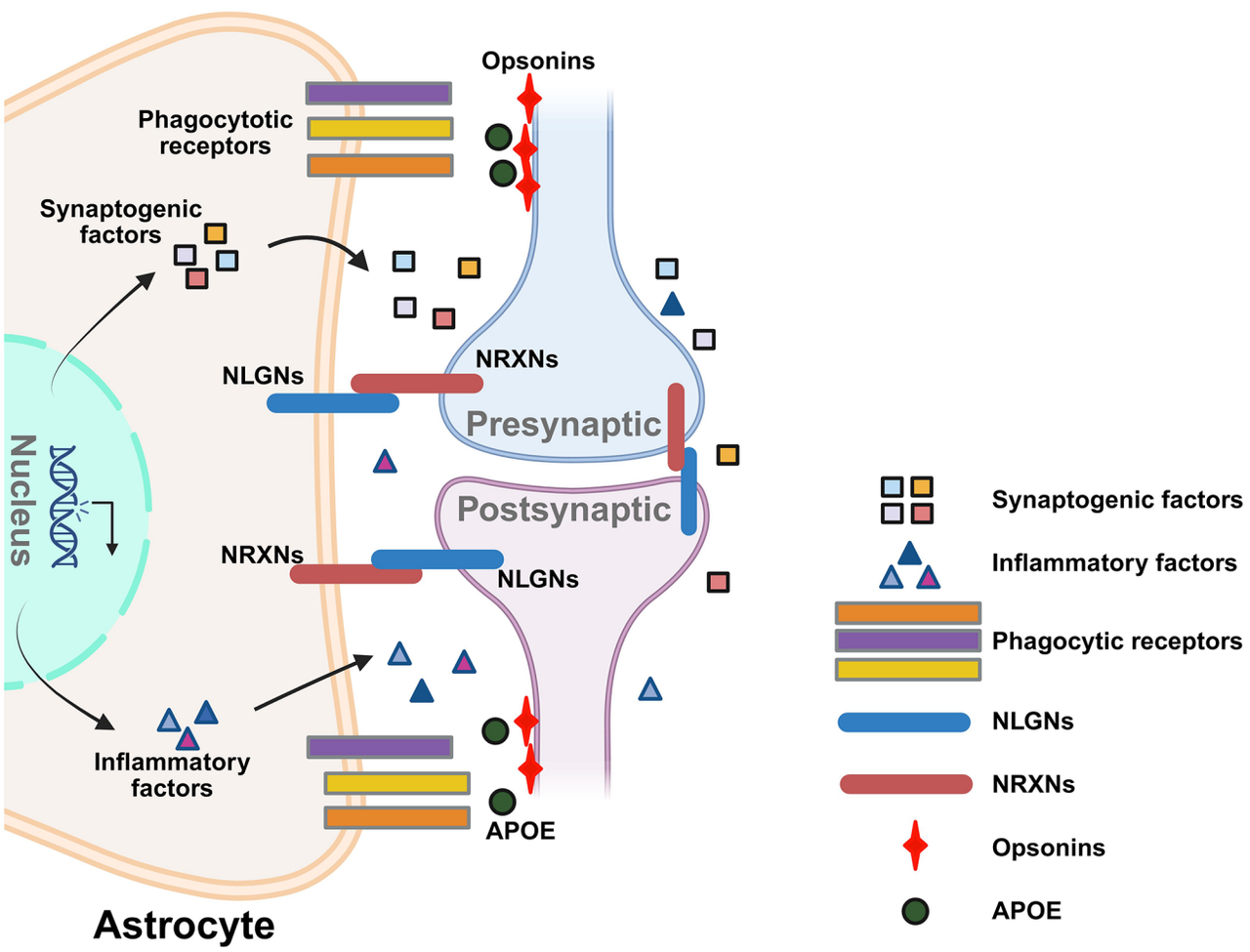

Figure 2 Astrocyte function in synaptogenesis, synapse pruning, and inflammation

Astrocytes secrete synaptogenic factors, such as thrombospondins, hevin, glypicans, and EphB2, to regulate synapse formation/maturation. Astrocytes express neuroligins (NLGNs) and neurexins (NRXNs) to support synapses. Astrocytes express phagocytic receptors, including MEGF10, MERTK, and ADGRB1, which bind opsonins to mediate synapse pruning, a process during which other factors, such as APOE, also participate. Astrocytes control inflammation through releasing inflammatory factors such as TNFα and CXCL16. Created in BioRender. Msf, X. (2026) https://BioRender.com/jtcicny.

SPARC and MDGAs, of which the latter are also known to be associated with ASD (Fan et al., 2021; Huo et al., 2025; Pettem et al., 2013; Singh et al., 2016; Zhao et al., 2025a). Mutations in *SPARCL1*, the gene encoding Hevin, have also been linked to ASD (Taketomi & Tsuruta, 2023; Taketomi et al., 2022).

Postmortem and transcriptomic studies have revealed abnormal expression of astrocytic synapse-regulatory genes in ASD cortex (Velmeshev et al., 2019; Voineagu et al., 2011). In addition, iPSC-derived astrocytes from ASD individuals impair neuronal synaptogenesis and development in co-culture models (Allen et al., 2022; Russo et al., 2018). MeCP2-deficient astrocytes from an RTT mouse model and their conditioned media also fail to support normal dendritic morphology of neurons (Ballas et al., 2009). These findings indicate that astrocytic dysfunction can compromise synapse formation.

On the other hand, during early development, there is excessive synapse formation and extra synapses need to be pruned for normal neural network construction. Although microglia are primary players in synapse pruning (Lukens & Eyo, 2022; Meng et al., 2024), recent studies have indicated that astrocytes also participate in this process during neurodevelopment, in adults, and under pathological conditions (Park & Chung, 2023). Astrocytes prune synapses through phagocytic pathways involving phagocytic receptors such as MEGF10, MERTK, and ADGRB1 (Chung et al., 2013; Park & Chung, 2023; Shiu et al., 2026). These astrocytic receptors require opsonins to bridge “eat-me signals” between them and the targets (Figure 2) (Arandjelovic & Ravichandran, 2015; Chung et al., 2016). Developing mice deficient in MEGF10- and MERTK-mediated phagocytic pathways exhibit defective refinement of retinogeniculate connections and retain excess functional synapses (Chung et al., 2013). Astrocytes also plays a crucial role in the neuronal activity-dependent elimination of excitatory synapses; conditional KO of astrocytic MEGF10 in adulthood leads to synapse overabundance, impaired synaptic plasticity, and hippocampal memory deficits (Lee et al., 2021). Interestingly, genetic variants in the transcriptional regulatory region of *MEGF10* have been found to be associated with ASD in Chinese Han population (Wu et al., 2017). *MERTK* is located on the chromosome 2q13 region, whose duplication has been linked to ASD (Costain et al., 2014; The Autism Genome Project Consortium et al., 2007), implicating the involvement of *MERTK* in ASD. Astrocytes deficient for ADGRB1 have significantly reduced phagocytic capacity (Shiu et al., 2026), and mice lacking ADGRB1 exhibit significant social behavior deficits and increased vulnerability to seizures reminiscent of ASD (Shiu et al., 2022). Other factors may also participate in astrocyte-mediated synapse pruning. For example, one study reports that the APOE2 particle enhanced, whereas the APOE4 particle decreased the rate of synapse pruning and turnover in the brain by astrocytes (Chung et al., 2016). *APOE* is the strongest genetic risk factor of late-onset Alzheimer’s disease (AD) and has three common alleles, *APOE2*, *APOE3*, and *APOE4*, with *APOE4* carriers having dramatically increased AD incidence (Guo et al., 2020; Raulin et al., 2022). A potential link between APOE alteration and ASD has also been suggested, though the results from different studies are controversial (Hu et al., 2018; Persico et al., 2004; Raiford et al., 2004).

Together, these findings underscore the role of astrocyte-driven synaptic abnormalities. Figure 1 summarizes the physiological functions of astrocytes in regulating synapses and other factors outlined below, and how dysregulation of astrocytic functions leads to ASD pathogenesis. More detailed physiological functions of astrocytes are illustrated in Figures 2-5.

Ion homeostasis

Astrocytes communicate through the fluctuation of different ions, such as calcium and potassium. Ion homeostasis is a critical function of astrocytes (Gzielo & Nikiforuk, 2021; Verkhratsky et al., 2013).

Astrocytic calcium signaling modulates gliotransmitter release and influences synaptic plasticity (Khakh & Sofroniew, 2015; Okubo, 2020). Aberrant astrocytic intracellular Ca^{2+} signaling has been observed in ASD iPSC-derived astrocytes and is linked to altered gliotransmitter release and subsequent destabilization of neuronal network activity (Allen et al., 2022). Astrocytic activation is manifested by an increase of Ca^{2+} mainly mediated by type 2 1,4,5—trisphosphate receptors (IP3R2). IP3R2 is a primary channel on the endoplasmic reticulum (ER) that releases stored Ca^{2+} into the cytosol in astrocytes (Figure 3) (Okubo et al., 2019; Vervloessem et al., 2015). Interestingly, rare *de novo* copy number variations in *ITPR2* gene encoding IP3R2 have been found in ASD patients (Levy et al., 2011; Sanders et al., 2011). Astrocyte-specific KO of IP3R2 in mice leads to ASD-like behaviors and decreased ATP levels in the medial prefrontal cortex, a critical region involved in social behaviors in rodents (Wang et al., 2021a). The plasma membrane calcium-transporting ATPase2 is an ATP-dependent ion pump that continuously extrudes cytosolic Ca^{2+} to the extracellular space (Figure 3). When ATPase2 is overexpressed in mouse cortical astrocytes to reduce non-IP3R2-dependent Ca^{2+} signaling, these mice exhibit social interaction deficits and depressive-like behaviors, as well as abnormal synaptic structure and transmission (Luo et al., 2023).

The flow of Ca^{2+} into the cytoplasm is regulated by Ca^{2+} channels on the plasma membrane. L-type Ca^{2+} channels Cav1.2 and Cav1.3 have been found to be expressed not only in neurons but also in astrocytes, and contribute to astrocyte activation (Figure 3) (Cheli et al., 2016; Daschil et al., 2013, 2014; He et al., 2016). Gain-of-function mutations in *CACNA1C*, the Cav1.2-encoding gene, can cause Timothy syndrome, a multisystem disorder displaying ASD-related neurologic symptoms (Nakagawa-Tamagawa et al., 2021; Splawski et al., 2004). Gain-of-mutations in *CACNA1D*, the Cav1.3-encoding gene, can also cause ASD (Ortner et al., 2020). These findings suggest that aberrant Ca^{2+} signaling caused by overactivation of L-type Ca^{2+} channels not only in neurons, but also in astrocytes, contributes to ASD.

Altered homeostasis of astrocytic K^+ ions in the brain can cause dysregulated E/I balance observed in ASD and associated syndromes. Astrocytes play an important role in clearing K^+ from the extracellular space via inward rectifying K^+ channels (Kir) (Djukic et al., 2007). Astrocytic Kir4.1 channels promote the efficient uptake of K^+ ions from the extracellular space, especially during high neuronal activity, thereby preventing excessive neuronal excitability (Figure 3). Reducing Kir4.1 increases extracellular K^+. On the other hand, Kir4.1 can exhibit outward rectification when the intracellular K^+ concentration in astrocytes becomes excessively elevated, though the efflux via Kir4.1 may not be a major route for cellular K^+ release (Abbasian et al., 2025; Kinboshi et al., 2020; Reed & Blazer-Yost, 2022; Sibille et al., 2015). Kir4.1

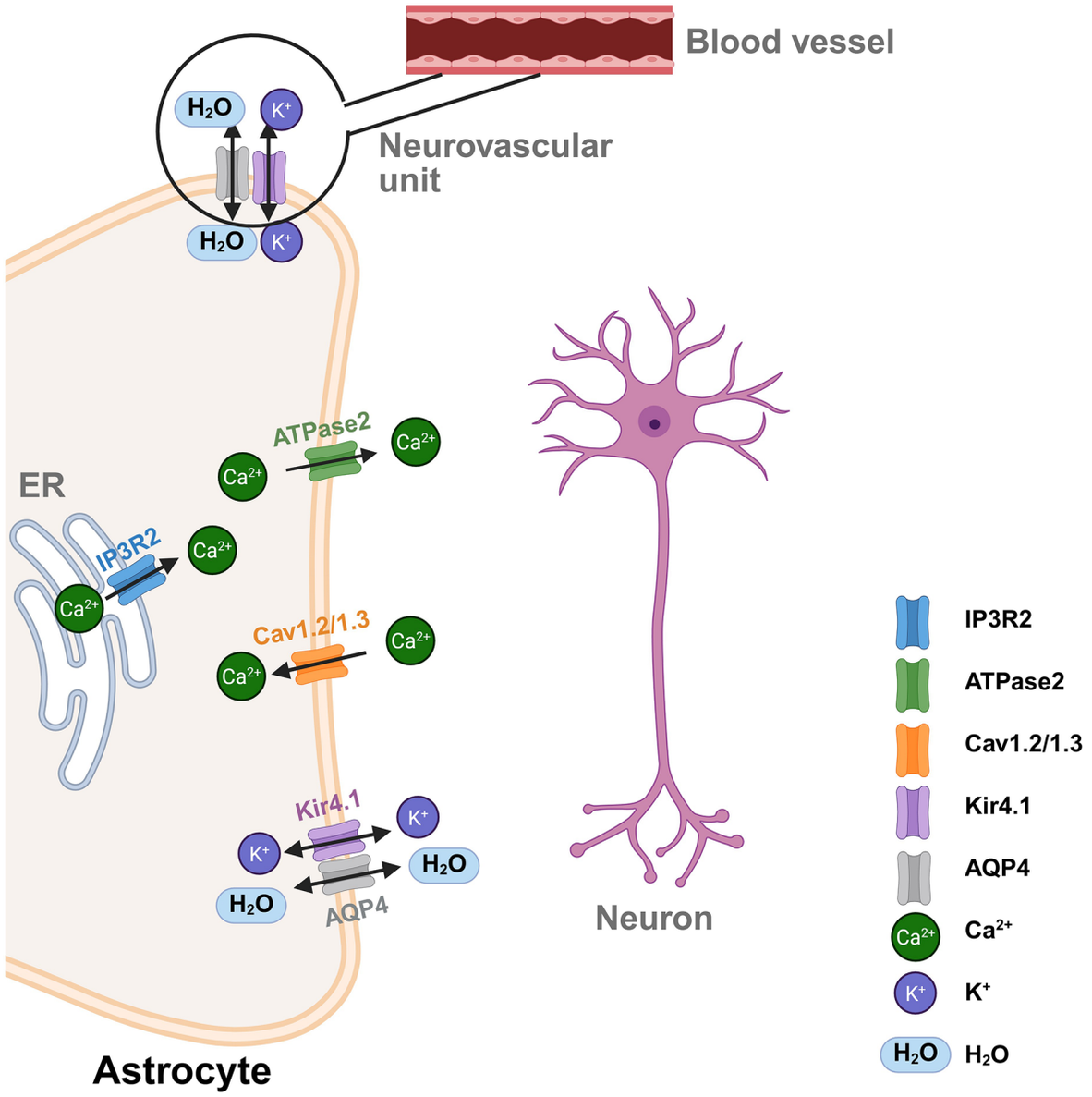

Figure 3 The ion channels regulating astrocyte activity and function

The IP3R2 channel and other family members on the endoplasmic reticulum (ER) regulate Ca^{2+} release from the ER into the cytosol. ATPase2 and other ATPases on the plasma membrane efflux Ca^{2+} to the extracellular space. Cav1.2, Cav1.3, and other calcium channels regulate Ca^{2+} influx into the cytosol. Kir4.1 and other potassium channels regulate bidirectional flux of K^+ into and out of the cytosol. AQP4 and other AQP channels regulate bidirectional water transport across the plasma membrane. Kir4.1 and AQP4 are in proximity at the astrocyte end-feet and modulate the function of the neurovascular unit. Created in BioRender. Msf, X. (2026) https://BioRender.com/menwqiw.

has been identified as a direct molecular target of MeCP2, and astrocytes from MeCP2-deficient RTT model mice express significantly lower levels of Kir4.1 mRNA and protein (Kahanovitch et al., 2018). Conditional KO of Kir4.1 in astrocytes impairs K^+ and glutamate uptake, and leads to severe ataxia, stress-induced seizures, and premature death in mice (Djukic et al., 2007). Pharmacological inhibition of Kir4.1 results in neuronal hyperexcitability and ASD-like behaviors in rats (Davoudi et al., 2025). Interestingly, gain-of-function mutations in the *KCNJ10* gene encoding Kir4.1 that enhance Kir4.1 membrane expression and current density are identified in ASD patients (Sicca et al., 2011, 2016). Overexpression of Kir4.1 in astrocytes in the mouse lateral habenula leads to depression (Cui et al., 2018), a comorbidity found in many ASD patients. In contrast, overexpression of a dominant-negative Kir4.1 or knockdown of Kir4.1 in astrocytes in the lateral habenula rescues depression in learned helplessness rats (Cui et al., 2018). High expression of Kir4.1 is also observed in BTBR mice, a well-established idiopathic ASD model, whereas inhibiting Kir4.1 improves the stereotyped behaviors and social novelty recognition in these mice (Li et al., 2023). These findings suggest that dysregulation of Kir4.1 homeostasis and activity may impair neuronal function and thereby result in impaired behavioral phenotypes. AQP4 channels are predominantly expressed in the end-feet of astrocytes and are pivotal regulators of water homeostasis in the brain (Figure 3). AQP4 regulates bidirectional water movement in response to osmotic gradients to maintain osmotic balance that complements the function of Kir4.1 in K^+ clearance (Abbasian et al., 2025; Amiry-Moghaddam et al., 2003; Binder et al., 2006; Reed & Blazer-Yost, 2022). AQP4 expression is decreased in the cerebellum of ASD patients (Fatemi et al., 2008). Loss of AQP4 can slow K^+ kinetics in mice (Binder et al., 2006). Chronic inhibition of

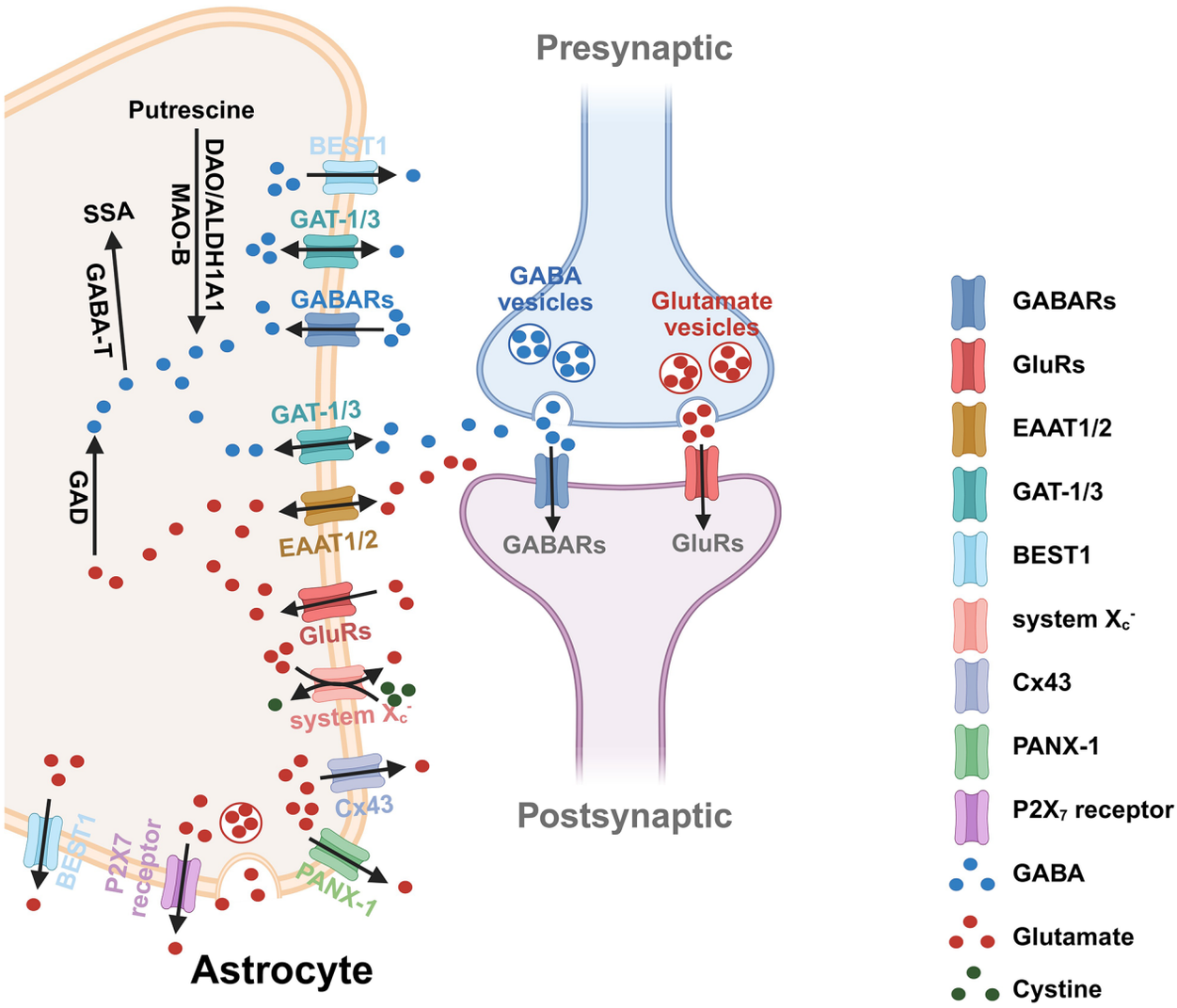

Figure 4 The neurotransmitter homeostasis regulated by astrocytes

GABAergic and Glutamatergic neurons release GABA and glutamate at the presynaptic membrane, which bind to GABA receptors (GABARs) and glutamate receptors (GluRs) at the postsynaptic membrane, respectively. Excessive GABA and glutamate at the synaptic cleft can be cleared by astrocytes via GABA transporters (GAT-1 and GAT-3) and excitatory amino acid transporters (EAAT1 and EAAT2), respectively. GABA within astrocytes can be degraded into succinic semialdehyde (SSA) via GABA transaminase (GABA-T). Astrocytes can synthesize GABA via converting glutamate by glutamate decarboxylase (GAD) and converting putrescine by monoamine oxidase B (MAO-B) or diamine oxidase (DAO) plus aldehyde dehydrogenase 1a1 (ALDH1A1). Astrocytes release GABA via GABA transporters operating in reverse mode and/or via GABA-permeable anion channels such as bestrophin 1 (BEST1). Astrocytes also express GABARs and GluRs to receive signals from neurons. In addition to being converted into GABA, glutamate within astrocytes can be released through Ca^{2+}-dependent exocytosis, reversal of uptake by glutamate transporters, the cystine/glutamate antiporter system x_c^-, the BEST1 channel, the Cx43 and Pannexin-1 (PANX-1) hemichannels, and purinergic receptors such as $P2X_7$. Created in BioRender. Msf, X. (2026) https://BioRender.com/7zk0udt.

AQP4 channels can disrupt brain water homeostasis and cause ASD-like behaviors in rats (Davoudi et al., 2023). Similarly, water homeostasis is found to be disrupted in the brain of VPA-induced ASD model rat (Davoudi et al., 2023).

Collectively, these findings indicate that dysregulation of ion homeostasis in astrocytes impairs their physiological functions, thereby contributing to the pathogenesis of ASD and associated syndromes (Figure 1).

Neurotransmitter homeostasis

Neurotransmitters play a key role in signaling between neurons, thereby regulating brain development, memory, and behaviors. ASD is associated with the pathological functioning of the neurotransmitter system. Neurotransmitters most commonly associated with the pathogenesis of ASD are the inhibitory neurotransmitter GABA and the excitatory neurotransmitter glutamate, whose alterations may cause an imbalance in the E/I neurotransmission in ASD (Canitano & Palumbi, 2021; Marotta et al., 2020; Nelson & Valakh, 2015).

GABA acts as an inhibitory neurotransmitter via ligand-gated $GABA_A$ receptor channels and G protein-coupled $GABA_B$ receptors. Both of these receptor types mediate inhibitory postsynaptic transmission throughout the nervous system (Stein & Nicoll, 2003). Variants in several GABA receptor subunit genes have been linked to ASD, including *GABRA2*, *GABRA4*, *GABRB1*, *GABRB2*, and *GABRG1* (Kakinuma et al., 2008; Ma et al., 2005; Srivastava et al., 2014). Reductions in GABAergic interneurons and transmission in mouse models of ASD have also been documented (Kim et al., 2020b), and abnormal GABAergic neurotransmission may dysregulate brain neuronal activity and rhythms in ASD (Alruwaili et al., 2026; Jahangir et al.,

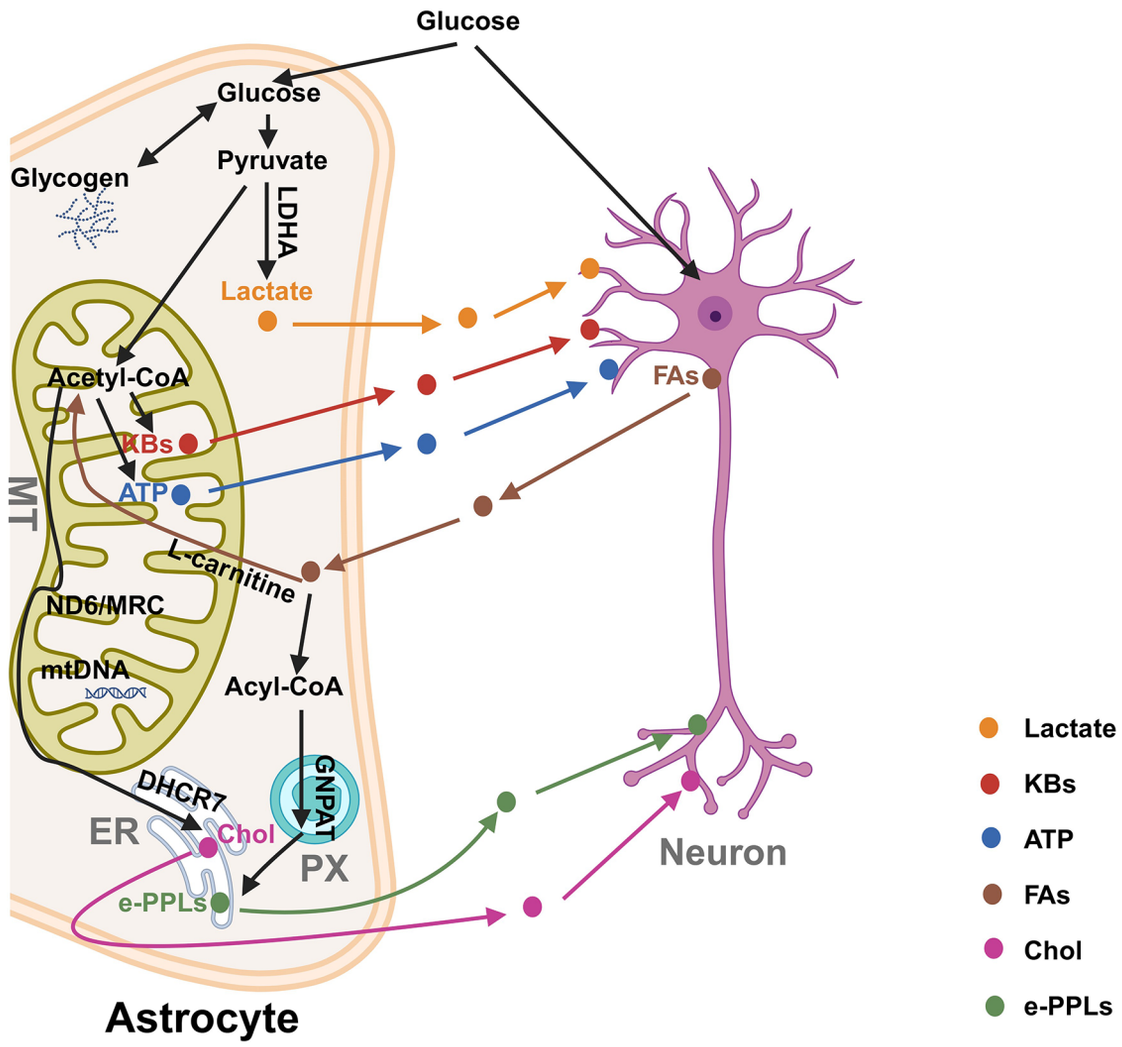

Figure 5 Metabolism and energy supply of astrocytes

Astrocytes take up glucose and store it in glycogen form. Upon request, astrocytes degrade glycogen into glucose, generate pyruvate from glucose, convert pyruvate into lactate via the lactate dehydrogenase A (LDHA) enzymatic activity, and shuttle lactate to supply neurons. Alternatively, pyruvate is transferred into the mitochondria (MT) and converted into acetyl-CoA for ATP generation through the tricarboxylic acid cycle and the mitochondrial respiratory chain (MRC), which contains mtDNA-encoding genes such as ND6. Astrocytic ATP can be released as a gliotransmitter to regulate purinergic signaling. Acetyl-CoA from mitochondria can be transferred into the endoplasmic reticulum (ER) and converted into cholesterol (Chol) via multiple enzymes, including 7-dehydrocholesterol reductase (DHCR7). Fatty acids (FAs), including those released from neurons, can be transferred into astrocytic mitochondria with the help of L-carnitine and converted into ketone bodies (KBs). FAs can also be converted into Acyl-CoA in astrocytic cytosol. Acyl-CoA is delivered into the peroxisome (PX), where it is converted into an intermediate through reactions involving multiple enzymes, including Glyceronephosphate O-acyltransferase (GNPAT). The intermediate is then delivered into the ER and processed into ether phospholipids (e-PPLs). Chol, KBs, and e-PPLs can be released to supply neurons. Created in BioRender. Msf, X. (2026) https://BioRender.com/zm2iw0a.

2021). Interestingly, increasing hippocampal astrogenesis during development can enhance GABAergic transmission in CA1 pyramidal neurons, thereby inducing ASD-like behavior in mice and decreasing the E/I ratio in the hippocampus. In contrast, suppressing this aberrantly increased GABAergic synaptic transmission rescues ASD-like behavior and restores the E/I balance (Chen et al., 2022).

Astrocytes maintain GABA balance by clearing extracellular GABA via GABA transporters (including GAT-1 and GAT-3) and degrading GABA into succinic semialdehyde (SSA) via GABA transaminase (GABA-T) (Figure 4). GAT-1 mutations have been associated with ASD (Fischer et al., 2022). The GABA uptake function is found to be impaired in astrocytes differentiated from iPSCs of patients carrying GAT-1 mutations (Mermer et al., 2021). GAT-1-deficient mice and mice carrying patient mutations exhibit epileptic phenotype, an ASD-associated comorbidity (Lindquist et al., 2023). On the other hand, overexpression of Ca^{2+} extruding ATPase in hippocampal astrocytes to reduce astrocytic Ca^{2+}-dependent signaling in mice results in increased expression of the GABA transporter GAT-3 and ASD-like behaviors, which can be corrected by blocking GAT-3 (Yu et al., 2018).

Although GABA is mainly released by GABAergic neurons, astrocytes also synthesize GABA via converting glutamate by glutamate decarboxylase (GAD) and converting putrescine by monoamine oxidase B (MAO-B) or diamine oxidase (DAO) plus aldehyde dehydrogenase 1a1 (ALDH1A1), and release GABA via GABA transporters operating in reverse mode and/or via GABA-permeable anion channels such as bestrophin 1 (BEST1) (Figure 4) (Anderson & Swanson, 2000;

Jo et al., 2014; Kilb & Kirischuk, 2022). Astrocytes derived from iPSCs of FXS patients display a significant increase in levels of GABA and GAD (Wagner et al., 2026), implicating elevated conversion of glutamate into GABA.

Astrocytes also express GABA receptors (Figure 4). GABAergic striatal medium spiny neurons (MSNs) can trigger astrocyte signaling via GABAB receptors. Selective chemogenetic activation of striatal astrocytes *in vivo* results in acute hyperactivity and disrupted attention, behaviors frequently found in ASD patients. Such responses also cause upregulated thrombospondin-1 (TSP1) in astrocytes, increased excitatory synapses, enhanced corticostriatal synaptic transmission, and increased MSN action potential firing *in vivo* (Nagai et al., 2019). Genetic ablation of GABAB receptors in medial prefrontal cortical astrocytes also alters low-gamma oscillations and firing properties of cortical neurons, affecting goal-directed behaviors (Mederos et al., 2021).

Glutamate is the principal excitatory neurotransmitter in the brain (He et al., 2024; Meldrum, 2000; Zhou & Danbolt, 2014). Astrocytes maintain glutamate homeostasis by controlling the balance of glutamate release and uptake (Mahmoud et al., 2019). Excessive glutamate may result in excitotoxicity in the brain (Mahmoud et al., 2019; Nicosia et al., 2024). Several studies have provided evidence of glutamate changes in ASD. For example, magnetic resonance spectroscopy analysis reveals increased glutamate in the anterior cingulate cortex of ASD patients (Jiménez-Espinoza et al., 2021; Oya et al., 2023).

Astrocytes clear glutamate from the synaptic cleft via excitatory amino acid transporters EAAT1/GLAST and EAAT2/GLT-1 (Figure 4). Astrocyte-specific EAAT2/GLT-1 KO mice exhibit excessive repetitive behavior (Aida et al., 2015; Jia et al., 2021). In an FXS mouse model, astrocytic FMRP loss reduces EAAT2/GLT-1 expression and impairs glutamate clearance (Higashimori et al., 2013, 2016). Similarly, astrocytes of MeCP2-deficient Rett syndrome mouse model exhibit impaired glutamate uptake (Okabe et al., 2012). In a VPA-induced ASD rat model, increased glutamate uptake is also observed (Bristot Silvestrin et al., 2013).

Astrocytes also express several glutamate receptors, including mGluR5 (Abd-Elrahman et al., 2023). The functional expression mGluR5 in astrocytes is now recognized as essential for Ca^{2+} signaling, gliotransmission, and the modulation of synaptic plasticity (Kim et al., 2025; Panatier & Robitaille, 2016). Given that FMRP binds the mGluR5 mRNA to regulate its protein synthesis (Pop et al., 2014), FMRP deficiency may alter mGluR5 levels not only in neurons but also in astrocytes to affect mGluR5-mediated astrocytic functions, thereby contributing to the pathogenesis of FXS and ASD.

On the other hand, astrocytes can release glutamate, primarily controlled by the Ca^{2+} signaling (Bezzi et al., 1998; Parpura et al., 1994), through different mechanisms: (1) Ca^{2+}-dependent exocytosis of glutamate-containing vesicles; (2) reversal of uptake by glutamate transporters; (3) glutamate exchange via the cystine/glutamate antiporter; (4) anion channel (such as BEST1) and hemichannel (such as connexons) opening induced by cell swelling or increased calcium; and (5) purinergic receptors (Figure 4) (Mahmoud et al., 2019; Malarkey & Parpura, 2008; Oh et al., 2012). The cystine/glutamate antiporter system x_c^- in astrocytes exports glutamate in exchange for cystine in a 1:1 ratio (Malarkey & Parpura, 2008). Knockout of system x_c^- results in decreased corticostriatal neurotransmission and social interaction deficits in mice (Bentea et al., 2021). Gap junction proteins of two adjacent cells can assemble to form intercellular channels. Connexons are formed from connexins, a highly related multigene family consisting of at least 13 members (Goodenough et al., 1996). Cx43 is an astrocytic connexin protein, and its expression is found to be increased in the brains of patients with ASD (Fatemi et al., 2008). In prenatally LPS-exposed mouse offspring, the activity of the Cx43 hemichannel, as well as that of the Pannexin-1 (PANX-1) hemichannel, is elevated, which may cause glutamate release from astrocytes and trigger hippocampal excitotoxicity in this ASD model (Avendaño et al., 2015; Chávez et al., 2019). Purinergic receptors mediate purinergic signaling through the binding of extracellular nucleotides (such as ATP) (Mahmood & Iqbal, 2022). The $P2X_7$ receptor is an ATP-gated ion channel and has been detected in astrocytes (Duan et al., 2003; Fumagalli et al., 2003). One study reports that the P2X7 receptor directly mediates glutamate release from astrocytes (Duan et al., 2003). Some other studies find that the $P2X_7$ receptor mediates maternal immune activation and its deletion or pharmacologic inhibition ameliorates ASD-like phenotype in the offspring of MIA model mice (Ahire & Kaur, 2025; Horváth et al., 2019; Szabó et al., 2022).

Collectively, these findings indicate that astrocytic dysregulation can impair neurotransmitter homeostasis, thereby shifting the E/I balance either toward hyperexcitability or hypoexcitability, both of which can destabilize the neuronal network function, ultimately leading to ASD and associated syndromes (Figure 1). Indeed, while early studies proposed that ASD is associated with net hyperexcitability, recent evidence suggests that ASD may also involve net hypoexcitability. Structural and functional alterations have been documented not only in glutamatergic excitatory circuits (Purcell et al., 2001; Tang et al., 2014) but also in GABAergic inhibitory circuits (Masuda et al., 2019; Robertson et al., 2016) in ASD patients. Moreover, both increased (e.g., Chao et al., 2010; Han et al., 2012; Peça et al., 2011) and decreased (e.g., Chen et al., 2022; Dani et al., 2005; Sacai et al., 2020; Spratt et al., 2019) E/I ratios have been reported across diverse mouse models of ASD. Such bidirectional perturbations in the E/I balance may also reflect the substantial clinical and biological heterogeneities of ASD.

Inflammation

Astrocytes are immunocompetent cells and produce cytokines and chemokines under physiological conditions to facilitate brain development and maintain brain homeostasis (Figure 2). However, the developing brain is highly vulnerable to inflammation from viral/bacterial infection and autoimmune disorders (Dammann & Leviton, 2004). In such cases, astrocytes may be aberrantly activated and have increased production of proinflammatory factors and decreased production of neuroprotective factors, thereby exacerbating neuroinflammation and leading to ASD and other neurodevelopmental disorders.

Astrocytes (and also microglia) can release TNFα that has been found to control glutamatergic gliotransmission (Santello et al., 2011) and modulate synaptic scaling under physiological conditions (Stellwagen & Malenka, 2006). However, proinflammatory TNFα has been reported to impair memory via astrocyte signaling in a mouse model of multiple sclerosis (Habbas et al., 2015). Elevated levels of TNF-α and other proinflammatory factors such as IL-6 and IL-1β have

been consistently found in the brain and cerebrospinal fluid of ASD patients (Ashwood et al., 2011; Li et al., 2009; Sofroniew, 2015; Vargas et al., 2005). Although significant amounts of these cytokines may come from activated microglia, which are primary immune cells in the brain and also known to be critical players in ASD (Meng et al., 2024), aberrant astrocyte activation should also contribute to the increase of cytokines, as multiple human transcriptomic studies show upregulation of immune- and inflammation-related modules enriched in astrocytes in ASD cortex (Edmonson et al., 2014; Gupta et al., 2014; Voineagu et al., 2011). One immunostaining study also finds that reactive astrocytes are a main source of cytokines, including IL-6 and MCP-1, in the brains of ASD patients (Vargas et al., 2005). Increased IL-6 production, at least partially by reactive astrocytes, plays a crucial role in inducing ASD-like phenotypes in animals. The poly(I:C)-induced MIA model mice have significantly increased levels of IL-6 (Hsiao & Patterson, 2011). A single injection of IL-6 in pregnant mice can lead to deficits in prepulse inhibition and latent inhibition in the adult offspring, whereas co-treatment with an anti-IL-6 antibody or genetic deletion of IL-6 attenuates poly(I:C)-induced ASD-like phenotypes in mice (Smith et al., 2007). These results highlight cytokine release as a mechanistic driver of ASD.

The chemokine CXCL16 plays a crucial role in neuroprotection by mitigating glutamate-induced neuroexcitotoxic damage (Rosito et al., 2014). Astrocytic expression of CXCL16 is decreased in poly(I:C)-induced MIA model mice, and CXCL16 knockdown in hippocampal astrocytes results in disrupted social novelty in mice (Li et al., 2025a). On the other hand, CXCL16 overexpression in astrocytes attenuates neuronal death challenged by glutamate in co-culture system, and its overexpression in hippocampal astrocytes restores social memory in MIA model mice (Li et al., 2025a).

Collectively, these findings suggest that astrocyte-mediated neuroinflammation may contribute to the cognitive and behavioral impairments observed in ASD and associated syndromes (Figure 1).

Metabolism and energy supply

During postnatal development, the brain undergoes remarkable structural and functional changes, which demand significant energy supply from glial cells, including astrocytes and microglia (Cantando et al., 2024). Metabolic disruption and mitochondrial dysfunction have been well-noticed in ASD patients and animal models (Hollis et al., 2017; Rossignol & Frye, 2012). Proteomic phenotype of cerebral organoids derived from ASD patients identifies disrupted energy metabolism, cellular components, and biological processes (Ilieva et al., 2022). Cell-specific metabolic activities in the ASD brain further show altered pathways in astrocytes and other cell types (Balasubramanian et al., 2025), suggesting altered metabolism and energy supply, at least partially caused by astrocytic dysfunction, in ASD.

The neonatal brain initially relies on lactate and ketone bodies (KBs) derived from fatty acids (FAs) as energy sources, and gradually transitions to a dependence on glucose during brain maturation (Cantando et al., 2024). Astrocytes play a significant role in glucose uptake and storage (in glycogen form) (Cantando et al., 2024), and are the primary generators of energy through the glycolytic pathway (Magistretti & Allaman, 2015). Astrocytes respond to neuronal activity by taking up glutamate, which triggers aerobic glycolysis, leading to glycogen breakdown, pyruvate production, and then lactate production and secretion to supply neurons (Figure 5) (Cantando et al., 2024; Magistretti & Allaman, 2018; Pellerin & Magistretti, 1994). ASD patients have significantly higher lactate and lactate-to-pyruvate ratio in the peripheral blood than controls (Oh et al., 2020). Subsets of ASD patients show elevated lactate in the brain as revealed by sensitive magnetic resonance spectroscopy studies (Goh et al., 2014; Maier et al., 2023). Altered lactate levels in the brain, either decreased or increased, have also been found in subsets of ASD animal models (Hagihara et al., 2024; Oh et al., 2020). In addition to generating L-lactate through the lactate dehydrogenase A (LDHA) enzymatic activity, pyruvate is transferred to mitochondria and converted into acetyl-CoA, which is used to generate ATP through the citric acid cycle (TCA cycle) and the mitochondrial respiratory chain (MRC) (Fernie et al., 2004). Astrocytes can directly release ATP to neurons (Figure 5). However, it seems that astrocyte-released ATP primarily functions as a gliotransmitter rather than as an energy currency. For example, in both complete and astrocyte-specific IP3R2 KO mice that exhibit ASD-like phenotypes and reduced brain ATP levels, restoring ATP can reverse these phenotypes. But when the P2X2 or the P2RY receptor is deleted, the rescuing effect of ATP is abolished, suggesting that astrocytic ATP functions through a purinergic signaling (Wang et al., 2021a; Yang et al., 2016).

Astrocytes also provide metabolic support through cholesterol synthesis and antioxidant regulation (Cantando et al., 2024). Cholesterol alteration has also been documented in ASD and FXS (Benachenhou et al., 2023). Almost all brain cholesterol is synthesized by astrocytes because the BBB restricts the cholesterol from the periphery to the brain (He et al., 2024; Pfrieger & Ungerer, 2011). Cholesterol synthesis occurs in the endoplasmic reticulum (ER), where precursor acetyl-CoA from mitochondria is converted into cholesterol through a series of reactions with over 20 catalyzing enzymes participating (Figure 5) (He et al., 2024; Luo et al., 2020). 7-dehydrocholesterol reductase (DHCR7) is one such enzyme. Mutations in DHCR7 can cause cholesterol synthesis error and Smith–Lemli–Opitz syndrome (SLOS), which exhibit a series of abnormalities including ASD-associated neuropsychiatric phenotypes (Bukelis et al., 2007). Notably, DHCR7 is highly expressed in astrocytes during early postnatal development (Zhang et al., 2014, 2016), underscoring its potential impact on astrocytic function (Cantando et al., 2024). Indeed, iPSC-derived astrocytes from SLOS patients have compromised lipid metabolism, mitochondrial respiration, and neuroprotective effects (Kawatani et al., 2025).

Altered metabolism of other lipids has also been implicated in the pathophysiology of ASDs. Glyceronephosphate O-acyltransferase (GNPAT) is located in peroxisomes and participates in the conversion of acyl-CoA derived from FAs into the diacyl phospholipid precursor lysophosphatidic acid (LPA), which will then be processed in the ER for ether phospholipid synthesis (e-PPLs, Figure 5) (Dean & Lodhi, 2018). GNPAT is prominently expressed in astrocytes and microglia during postnatal development (Zhang et al., 2014, 2016). GNPAT KO mice exhibit impaired social interaction, repetitive behavior, and hyperactivity, featuring ASD (Dorninger et al., 2019a, 2019b).

During postnatal development, astrocytes show a preference for mitochondrial metabolism, including fatty acid (FA) oxidation and ketolysis (Zehnder et al., 2021).

Developing astrocytes not only oxidize mitochondrial FAs but also play a role in detoxifying excess neuron-derived FAs to alleviate neuronal damage due to excessive, toxic FA accumulation (Figure 5) (Civenni et al., 1999). Astrocytes can oxidize FAs to generate KBs in mitochondria and further deliver KBs to neighboring cells, including neurons. The contribution of astrocyte-derived KBs in supporting memory formation has been reported (Silva et al., 2022). L-carnitine is an amino acid derivative that helps to transport FAs into the mitochondria (Kępka et al., 2021; Virmani & Cirulli, 2022). The *TMLHE* gene encodes trimethyllysine dioxygenase, a mitochondrial protein crucial for carnitine biosynthesis, and is expressed in astrocytes during postnatal development (Zhang et al., 2014). Loss-of-function mutations in *TMLHE*, together with dysregulation of carnitine metabolism, have been identified in ASD patients (Celestino-Soper et al., 2012; Ziats et al., 2015), though *Tmlhe* KO mice do not develop ASD-like behaviors (Liepinsh et al., 2023). Nevertheless, low carnitine levels are found in many ASD patients (Cantando et al., 2024; Mostafa & Al-Ayadhi, 2015), implicating a potential contribution of astrocytic L-carnitine abnormality to ASD (Kępka et al., 2021).

Variants in the mitochondrial genome have been linked to ASD (Smith et al., 2012; Yardeni et al., 2021). Mice carrying a missense mutation in the mitochondrial DNA (mtDNA) gene, *ND6*, which encodes NADH dehydrogenase subunit 6, a core component of mitochondrial Complex I, have aberrant mitochondrial respiratory functions and pronounced ROS levels, and exhibit ASD-like behaviors, including impaired social interactions and increased repetitive behavior and anxiety (Yardeni et al., 2021). These findings demonstrate that mild systemic mitochondrial defects can result in ASD. Since oxidative stress markers are elevated in ASD brains and are often localized to astrocytes (Chauhan et al., 2011), altered mitochondrial function in astrocytes may be a contributor to ASD neuropathology.

Blood-brain barrier (BBB)

The BBB is a highly specialized interface that tightly regulates the bidirectional transport of molecules and solutes between the brain and blood. BBB integrity is crucial for maintaining CNS homeostasis and physiological function (Aragón-González et al., 2022). BBB dysfunction has been reported in subsets of ASD patients, with evidence of increased permeability and altered vascular markers (Fiorentino et al., 2016). Astrocytes play a critical role in the formation, maturation, and function of the BBB. The end-feet of astrocytes are a critical component of the neurovascular unit, maintaining BBB integrity and regulating cerebral blood flow (Díaz-Castro et al., 2023). Many important astrocytic proteins, such as AQP4 and Kir4.1, are predominantly expressed at the end-feet and modulate the function of the neurovascular unit (Figure 3). AQP4 expression is decreased in the cerebellum of ASD patients, and AQP4-null mice exhibit altered ultrastructure of brain microvessels (Fatemi et al., 2008; Zhou et al., 2008). The *EZH2* gene encodes a histone methyltransferase, whose expression is found to be altered in the brain cortex of ASD patients and whose SNPs have been linked to ASD in Chinese Han population (Li et al., 2016; Rahman et al., 2020). One study finds that conditional KO of EZH2 in astrocytes in mice increases GFAP expression, alters astrocyte morphology, and reduces the coverage of astrocytic end-feet on blood vessels, thereby impairing BBB integrity (Zhao et al., 2025b). Therefore, disturbances in astrocytes may compromise BBB function, with potential downstream effects on development and immune exposure.

THERAPEUTIC IMPLICATIONS AND STRATEGIES

Given the poor outcomes of many patients affected by ASD and associated syndromes, the need for novel and more effective therapeutic strategies is critical. So far the United States Food and Drug Administration (FDA) only approved two pharmacological interventions in ASD treatment, risperidone and aripiprazole (Ahire & Kaur, 2025). Current intervention developments primarily target neurotransmitter systems, synaptic activity, or behavioral management. Since astrocytic dysfunction contributes to ASD and associated syndromes, targeting astrocytic pathways could represent a promising therapeutic strategy. We outline several potential therapeutic strategies targeting astrocytes below. However, because many of the astrocytic dysfunctions targeted for correction are also impaired in neurons and/or other cell types, such interventions may exert their therapeutic effects not only through direct modulation of astrocytes, but also via effects on neurons and/or other cell types.

Restoring ion channel function

Calcium and potassium channels are crucial for the physiological functions of astrocytes and other cell types in the central nervous system, and their dysregulation is closely associated with various neurological disorders, including ASD and associated syndromes. Therefore, drugs that target these ion channels to restore their homeostasis may be beneficial for disease treatment (Qiu et al., 2025). The potassium channel Kir4.1 is primarily expressed in astrocytes, and its gain-of-function mutations have been associated with ASD (Sicca et al., 2011, 2016). Using desipramine to pharmacologically inhibiting Kir4.1, which is highly expressed in the idiopathic BTBR mouse model of ASD, ameliorates ASD-related behavioral phenotypes in these mice (Li et al., 2023), thereby providing a proof-of-concept demonstration of the therapeutic potential of targeting astrocytic ion channels. Bumetanide is a sodium-potassium ATPase inhibitor and is used to treat heart failure. Clinical trials have found that bumetanide may be helpful in ASD treatment (James et al., 2019; Wang et al., 2021b). The *KCNMA1* gene, which encodes a large-conductance calcium-dependent potassium (BKCa) channel, is disrupted in subsets of ASD patients (Laumonnier et al., 2006), and two BKCa channel openers, chlorzoxazone and BMS-204325, have been shown to alleviate disease-related phenotypes in FXS model mice (Ferraguto et al., 2024; Hébert et al., 2014). Cav1.2 and Cav1.3 channels can regulate astrocyte activation, and their gain-of-function mutations are associated with ASD. Conditional KO of Cav1.2 in astrocytes attenuated neuroinflammation and demyelination in a murine model of multiple sclerosis (Denaroso et al., 2023; Zamora et al., 2020), suggesting that inhibiting these calcium channels may be beneficial for the treatment of multiple sclerosis and other neurological disorders, including ASD. Efforts have been devoted to developing their blockers with some advances (Lanzetti & Di Biase, 2022; Liu, 2025; Zamponi, 2016), For example, isradipine, a Cav1.3 inhibitor, has been tested for Parkinson's disease (PD) treatment. Unfortunately, the results of the clinical trial fail to show any efficacy of isradipine on slowing PD progression at the dosage used (Lanzetti & Di Biase, 2022; The Parkinson Study Group STEADY-PD III Investigators, 2020). Whether isradipine and other calcium

channel inhibitors have therapeutic value for ASD and associated syndromes has yet to be explored.

Modulating glutamate and GABA homeostasis

Dysregulation of excitatory and inhibitory neurotransmitter balance contributes to ASD and associated syndromes. Pharmacological correction of this imbalance through modulating astrocytic functions may become a feasible treatment strategy. For example, upregulation of astrocytic EAAT2/GLT-1 using compounds such as ceftriaxone has been shown to restore glutamate clearance and improve synaptic function in rodent models of ischemic injury and motor neuron degeneration (Rothstein et al., 2005). N-acetyl-L-cysteine (NAC) has glutamate modulation, antioxidant, and anti-inflammatory activities (Bradlow et al., 2022). Several clinical trials have shown that NAC treatment may have beneficial effects for ASD and associated syndromes (Bradlow et al., 2022; Deepmala et al., 2015; Hardan et al., 2012), though its mechanism of action has yet to be further determined, and its therapeutic value for ASD and associated syndromes requires larger randomized and controlled clinical investigations.

Since GABAergic neurotransmission is impaired in ASD, restoring GABA signaling homeostasis may improve clinical outcomes in ASD patients (Alruwaili et al., 2026). Indeed, a series of GABA receptor agonists has shown beneficial effects in both ASD patients and animal models (see Alruwaili et al. (2026) for a comprehensive review). On the other hand, normalizing astrocytic GABA uptake and metabolism may provide an alternative strategy to help rescue GABA signaling deficits in ASD and associated syndromes. For example, the GAT-1 inhibitor tiagabine is prescribed for epilepsy treatment, but since it reduces anxiety and neuropathic pain in animal studies, tiagabine is also used off-label to manage anxiety and neuropathic pain (Mortensen et al., 2024; Novak et al., 2001; Thoeringer et al., 2010). Vigabatrin is a GABA-T inhibitor that enhances GABAergic neurotransmission. A previous clinical trial shows that vigabatrin improves mental function and social behavior in children with TSC (Jambaqué et al., 2000). Unfortunately, a more recent study finds that vigabatrin fails to prevent intellectual and developmental disability and ASD phenotypes in infants with TSC (O'Kelley et al., 2025). The efficacy of restoring astrocyte-modulated GABA homeostasis in ASD and associated syndromes requires further validation.

Anti-inflammatory and immunomodulatory strategies

Astrocytic reactivity and cytokine secretion contribute to neuroinflammation in ASD (El-Ansary & Al-Ayadhi, 2012). Pharmacological agents that block astrocytic inflammatory pathways, such as NF-κB inhibitors, IL-6 blockers, or JAK/STAT pathway modulators, may mitigate abnormal cytokine signaling. Minocycline, an anti-inflammatory tetracycline derivative, reduces glial reactivity and has shown preliminary efficacy in reducing irritability in children with FXS (Paribello et al., 2010). Several natural compounds, such as vitamin D, sulforaphane, and resveratrol, known for their anti-inflammatory effects, have been shown to improve behavioral performance in ASD models (Li et al., 2020), strengthening the potential of anti-inflammatory therapy for ASD and associated syndromes. Clinical trials using vitamin D supplementation have reported an anti-inflammatory role and potential benefits of vitamin D in ASD (Javadfar et al., 2020, 2025; Li et al., 2022). Sulforaphane has anti-oxidant and anti-inflammatory functions (Fahey et al., 2025). Results from several clinical trials suggest that sulforaphane may serve as an efficacious and safe adjunctive therapy for ASD (Long et al., 2025). Resveratrol has multiple functions, including anti-inflammation, anti-oxidative stress, and anti-apoptosis (Menegas et al., 2023). Resveratrol has been shown to attenuate neuroinflammation and behavioral deficits in multiple ASD animal models and may improve hyperactivity/non-compliance in ASD patients (Ahmad et al., 2018; Bhandari & Kuhad, 2017; Hendouei et al., 2020; Malaguarnera et al., 2020). Nevertheless, more selective astrocytic immunomodulation has yet to be developed.

Metabolic and mitochondrial interventions

Given the central roles of astrocytes in lactate shuttling, cholesterol metabolism, and redox balance, metabolic interventions may restore bioenergetic support for neurons in ASD and associated syndromes. For example, ketogenic diets include high-fat, low-carbohydrate, and adequate-protein intake (Li et al., 2021a). Ketogenic diets can elevate KB levels, thereby increasing ATP and enzymes involved in mitochondrial metabolic pathways and mitochondrial biogenesis, altering astrocyte-neuron metabolic coupling (Ozler & Sanlier, 2025). It has long been found that ketogenic diets have behavioral benefits in subsets of ASD patients and animal models (Evangeliou et al., 2003; Lee et al., 2018; Ruskin et al., 2013; Wang et al., 2026). Pharmacological enhancers of astrocytic glycolysis or mitochondrial function could represent another avenue for intervention. For example, direct supply of the KB β-hydroxybutyrate ameliorates neurodevelopmental deficits in the GABAergic system of nematodes with *daf-18/PTEN* mutation (Giunti et al., 2024). Nanocatalysts that mimic the enzymatic functions of antioxidants can effectively scavenge reactive oxygen species and restore cellular redox homeostasis. When applied to VPA-induced ASD model rats, these nanocatalysts significantly attenuate GFAP activation, neuroinflammation, and neuronal death, and improve social interaction deficits, anxiety-like behaviors, and cognitive defects (Feng et al., 2024; Gong et al., 2025). When the mitochondria of the idiopathic ASD model, BTBR T+Itpr3tf/J mice, are replaced with those of C57BL/6J, these mice show improved social behaviors, higher levels of glutamate and astrocytes in the brain, and less neuroinflammation. However, their immune cell metabolism has minimal change (Yao et al., 2022).

Cell-based therapies

In subsets of ASD patients harboring genetic mutations in key astrocytic genes such as *KCNJ10* and *SLC6A1*, dysfunctional astrocytic activity is likely to be a primary causal factor. Therefore, replacement of defective astrocytes (cell-replacement therapy) or glial progenitor cell-based therapy has been proposed as an alternative treatment strategy. Transplantation of astrocytes differentiated from human ESCs into rodents shows beneficial effects in ALS animal models (Izrael et al., 2018), implicating the efficacy of this strategy. On the other hand, stem cell treatment has been directly applied to ASD patients and seems to be safe and exhibits some efficacy (Heider et al., 2021; Price, 2020; Qu et al., 2022). An alternative stem cell therapy strategy utilizes autologous umbilical cord blood (AUCB) to treat ASD patients. It has been reported that AUCB treatment can improve socialization, communication, and adaptive behavior scores, and increase white-matter connectivity in frontal, temporal, and subcortical regions in ASD patients (Carpenter et al., 2019; Dawson et al., 2017). However, the mechanism of action of stem cell therapy remains unclear, and one possibility is that transplanted stem cells secrete neurotrophic factors, promote endogenous

neurogenesis and angiogenesis, encourage synaptic connection and remyelination of damaged axons, decrease apoptosis, and regulate inflammation primarily through paracrine actions (Price, 2020; Seo & Cho, 2012). Human AUCB and T cells derived from AUCB also suppressed inflammation and promoted neurogenesis in the aged rat brain (Bachstetter et al., 2008; Shahaduzzaman et al., 2013).

The development of adeno-associated virus (AAV) technique has enabled gene therapy to treat diseases resulting from gene mutations. So far, AAV gene therapy has been approved by the US FDA for the treatment of retinal dystrophy, spinal muscular atrophy, Duchenne muscular dystrophy, hemophilia A/B, and aromatic l-amino acid decarboxylase deficiency (Byrne et al., 2025). Since subsets of ASD and associated syndromes are caused by single gene mutations, AAV-mediated gene therapy has been applied to some animal models with satisfactory results shown, such as re-expressing wild-type MeCP2 into *Mecp2* KO RTT model mice and FMRP into *Fmr1* KO FXS model mice (Jiang et al., 2022; Powers et al., 2023; Yang et al., 2023). Clinical trials testing AAV-mediated delivery of MeCP2 for the treatment of RTT patients are now underway (Samanta, 2026). Mutations in the *SLC6A1* gene have been associated with ASD (Fischer et al., 2022) and AAV-mediated expression of human *SLC6A1* at an early developmental stage can rescue brain epilepsy and key behavioral phenotypes in *Slc6a1* deficient mice (Guo et al., 2025; Lerche et al., 2025). AQP4 is another protein primarily expressed in astrocytes. Although no AQP4 mutations are found to be associated with ASD, AQP4 expression decreases in patients and animal models of ASD and associated syndromes (Fatemi et al., 2008; Pepe et al., 2023). Since AQP4 expression decreases in the animal model of chronic pain-induced cognitive disorder and AAV-mediated AQP4 overexpression mitigates cognitive impairment in these mice (Zhang et al., 2023), overexpression of AQP4 in astrocytes may offer an alternative strategy for ASD intervention. Nonetheless, there are several limitations of the traditional AAV-mediated gene delivery: (1) the expression efficiency of the exogenous gene is driven by the promoter within the AAV vector, and the cells expressing the exogenous gene are dependent on which cells the AAVs infect. Therefore, the exogenous gene expression may not faithfully replicate the natural expression pattern of its endogenous counterpart, potentially causing side effects (Qiu, 2025); (2) traditional AAVs have a limited packaging capacity (roughly 4.7 kb), making large gene delivery a big challenge.

With recent advancements in CRISPR/Cas-based genome-editing techniques such as base editing and prime editing, it is now technically feasible to directly correct endogenous mutations *in vivo*, thereby permanently restoring the natural expression of the endogenous gene (Anzalone et al., 2020; Wang et al., 2022b). On the other hand, several strategies to increase the packing capacity of AAVs have been developed (Yin et al., 2025). For example, a method termed AAV with translocation linkage (AAVLINK) was developed very recently. Through leveraging Cre/Lox-mediated intermolecular DNA recombination to overcome cargo size constraints, AAVLINK enabled superior gene segmentation flexibility, robust gene reconstitution efficiency, and a marked reduction in truncated protein products. AAVLINK has successfully driven expression of intact SHANK3 or SCN1A and rescued behavior and seizure phenotypes of mutant mice, respectively (Lin et al., 2026).

Cell-based therapies for ASD and associated syndromes still face significant translational challenges. First, most of these studies are still in early phases, with few large, placebo-controlled trials to establish firm clinical evidence of the efficacy. Second, there are no standard protocols for cell types (e.g., mesenchymal vs. cord blood), dosage, or methods of administration. Third, the appropriate treatment window has not yet been determined, making it challenging to select the optimal age for intervention. Fourth, due to the high heterogeneity of ASD, it is difficult to identify which patients will respond to treatment, even when these patients carry mutations in the same gene. Fifth, transplanted cells might promote tumor growth and trigger immune responses, raising safety concerns. In addition, although AAVs are relatively safe and have been used clinically, there remain potential safety risks, as new AAVs may be required for specific types of ASD and associated syndromes. Sixth, although CRISPR/Cas-based genome-editing techniques can directly correct endogenous mutations, their *in vivo* editing efficiency remains relatively low. Furthermore, CRISPR/Cas-mediated editing has off-target potential to induce unwanted side-effects, and may introduce structural variations even on target, thus posing substantial safety risks. Additionally, the application of the CRISPR/Cas system may induce immunogenic responses *in vivo* (Aussel et al., 2025; Bao et al., 2026). Finally, there are still technical hurdles in this field, such as stem cell expansion and storage management, differentiation of human ESCs/iPSCs into specific cell types (neurons, astrocytes, microglia, etc.) that fully recapitulate the function of natural cells, and the development of safer AAVs that can specifically infect certain cell types (such as astrocytes and microglia) and deliver large-fragment genes (Christiansen & Kirkeby, 2024; Heathman et al., 2015; Narzisi et al., 2023). Nevertheless, with the development of new techniques and studies on strictly regulated, large-scale clinical trials to assess efficacy, safety, and the intervention window, there is optimism about the effective treatment of ASD and associated syndromes with cell-based therapy, including astrocyte-targeting interventions.

CONCLUSIONS

Converging evidence from human tissues, patient iPSC-derived astrocytes and organoids, and animal models indicates that astrocytes are active participants in the pathophysiology of ASD and associated syndromes. Multiple mechanistic axes—synapse regulation, ion and neurotransmitter homeostasis, neuroinflammation, and metabolism—provide plausible routes by which astrocytic dysfunction could perturb neuronal function, circuit development, and behavior. These findings not only reshape our understanding of ASD and associated syndromes but also identify astrocytes as attractive therapeutic targets. Future work should prioritize multi-omics approaches to capture astrocyte heterogeneity, ascertain whether and how astrocyte heterogeneity and specific astrocyte mechanisms differentially regulate diverse behavioral features in ASD and associated syndromes, develop biomarkers for stratifying patient populations, and test astrocyte-directed interventions in clinical trials. Ultimately, translating this knowledge may enable precision treatments for ASD and associated syndromes.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

J.M. and Y.W.Z. conceptualized the review topic. K.C., J.M., and Y.W.Z. wrote the manuscript. All authors read and approved the final version of the manuscript.

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