Current Neuropharmacology, 2023, *21*, 547-559

REVIEW ARTICLE

Modelling the Interplay Between Neuron-Glia Cell Dysfunction and Glial Therapy in Autism Spectrum Disorder

Aziz Unnisa[1], Nigel H. Greig[2] and Mohammad Amjad Kamal[3,4,5,6,*]

[1]Department of Pharmaceutical Chemistry, College of Pharmacy, University of Hail, Hail, KSA; [2]Drug Design & Development Section, Translational Gerontology Branch, Intramural Research Program, National Institute on Aging, National Institutes of Health, Baltimore, Maryland, MD 21224, USA; [3]Institutes for Systems Genetics, Frontiers Science Center for Disease-related Molecular Network, West China Hospital, Sichuan University, China; [4]King Fahd Medical Research Center, King Abdulaziz University, Jeddah, 21589, Saudi Arabia; [5]Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, Dhaka, 1207, Bangladesh; [6]Enzymoics, Novel Global Community Educational Foundation, 7 Peterlee place, Hebersham, NSW 2770, Australia

Abstract: Autism spectrum disorder (ASD) is a complicated, interpersonally defined, static condition of the underdeveloped brain. Although the aetiology of autism remains unclear, disturbance of neuron-glia interactions has lately been proposed as a significant event in the pathophysiology of ASD. In recent years, the contribution of glial cells to autism has been overlooked. In addition to neurons, glial cells play an essential role in mental activities, and a new strategy that emphasises neuron-glia interactions should be applied. Disturbance of neuron-glia connections has lately been proposed as a significant event in the pathophysiology of ASD because aberrant neuronal network formation and dysfunctional neurotransmission are fundamental to the pathology of the condition. In ASD, neuron and glial cell number changes cause brain circuits to malfunction and impact behaviour. A study revealed that reactive glial cells result in the loss of synaptic functioning and induce autism under inflammatory conditions. Recent discoveries also suggest that dysfunction or changes in the ability of microglia to carry out physiological and defensive functions (such as failure in synaptic elimination or aberrant microglial activation) may be crucial for developing brain diseases, especially autism. The cerebellum, white matter, and cortical regions of autistic patients showed significant microglial activation. Reactive glial cells result in the loss of synaptic functioning and induce autism under inflammatory conditions. Replacement of defective glial cells (Cell-replacement treatment), glial progenitor cell-based therapy, and medication therapy (inhibition of microglia activation) are all utilised to treat glial dysfunction. This review discusses the role of glial cells in ASD and the various potential approaches to treating glial cell dysfunction.

ARTICLE HISTORY

Received: October 19, 2021
Revised: November 27, 2022
Accepted: December 01, 2022

DOI:
10.2174/1570159X21666221221142743

Keywords: Autism spectrum disorder (ASD), neuron-glial interaction, glial cell dysfunction, microglial activation, glial therapy.

1. INTRODUCTION

Autism spectrum disorders (ASD) are a broad name for neurodevelopmental diseases that manifest primarily in infancy and are marked by qualitative speech impairment, abnormal interpersonal interactions, and restricting behavioural traits. Autistic disorders are characterised by abnormal neural network development and aberrant neurotransmission imbalance. Neurotoxic damage is caused by excess reactive oxygen species (ROS), reactive nitrogen precursors, cytokine production, and proteolytic enzymes. Both the growth of neural circuits and the management of oxidative stress rely on neuroglial cells, particularly astroglia, which is the primary source of ROS buffers. Microglia are the primary source of pro-inflammatory cytokines, whereas astroglia influence all aspects of the developing brain, maturity, and senescence [1]. These findings support a unique concept regarding the disturbance of homeostatic neuron-glia connections as a fundamental component in the pathophysiology of ASD. This

*Address correspondence to this author at the Institutes for Systems Genetics, Frontiers Science Center for Disease-related Molecular Network, West China Hospital, Sichuan University, China; King Fahd Medical Research Center, King Abdulaziz University, Jeddah, 21589, Saudi Arabia; Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, Dhaka, 1207, Bangladesh; and Enzymoics, Novel Global Community Educational Foundation, 7 Peterlee place, Hebersham, NSW 2770, Australia; E-mail: prof.ma.kamal@gmail.com

1875-6190/23 $65.00+.00

review highlights the association between the dysfunction of glial cells and ASD development and the various potential approaches to treating glial cell dysfunction.

In addition to neurons, glial cells play an essential role in mental activities, and a new strategy that emphasises neuron-glia interactions should be applied [2]. Glial cells (including astrocytes, oligodendrocytes, and microglial cells) have a well-established role in supporting neurons, providing potential mechanisms for regulating neuronal communication. They help in regulating extracellular ion homeostasis, eliminate neurotransmitters from the synaptic cleft with the help of membrane transporters, make molecular substrates available to meet the requirement of energy by neurons and for the synthesis of the neurotransmitter, and secrete a variety of neuromodulatory molecules ranging from growth factors to cytokines, along with ATP and adenosine. Glial cells can then control the flow of information through neural networks located in the retina, CNS, and at synaptic junctions within muscle [3].

2. TYPES OF GLIAL CELLS AND THEIR FUNCTIONS

The functions of different types of glial cells, *i.e*., microglial cells, astroglial cells and oligodendrocytes in brain development, are summarised in Fig. (**1**).

3. NEURON-GLIAL INTERACTIONS

Due to progress in genetic and imaging techniques, the complicated connection between neurons and glia and their cooperative roles in forming synapses is now becoming clear [4]. Several processes involved in the development of the brain, including neurogenesis, synapse formation, myelination, proliferation, differentiation, and migration of neurons and neuronal signalling, are all regulated by neuron-glia interactions. Most of what we know about neuron-glia interactions is the influence of glial cells on neuronal development. But, according to recent studies, these two cell types have a mutual impact [5].

Microglia and neurons interact on several levels, from indirect interactions *via* soluble messengers to direct contacts of their membranes, with more advanced controlled functions of both microglia and neuron towards minimising the distance between the membranes of these cells [6]. Synapses are the sites of some of the most well-studied microglia–neuron interactions. During development, a period of intense synaptogenesis produces many synapses. Synaptic pruning, a mechanism dictating activity-dependent removal of superfluous synapses in which complement-dependent phagocytosis of microglia is thought to play a crucial role, is then used to optimise neural networks. Microglia regulate neuronal growth and cellular survival, which helps shape the CNS during development [7]. The interactions between neurons and different glial cells are summarised in Fig. (**2**). Latest developments in microglial genetic targeting make it possible to explicitly tackle issues with signal transduction in microglial activation [8]. During autoimmune pathology, selective excision of TAK1 (TGF-activated kinase) in microglia decreased NF-κB, JNK, and ERK1/2 pathways, decreased microglial activation, CNS inflammation, and neuronal damage, thereby suppressing the neuroinflammation [9].

The role of astrocytes in the development, maintenance, and plasticity of neural networks has been a topic of extensive investigation in recent decades. Astrocytes offer structural and metabolic support to neuronal networks, regulate the activity of neurons and neural plasticity, and assist in developing neuronal circuits. Furthermore, astrocyte-neuron interaction is essential for neuroprotection and is implicated in advancing neurological disorders in numerous cases [10]. Although astrocytes are poorly understood, the emerging study indicates that neurons act as modulators of astrocyte gene expression and differentiation [5]. One indicator of astrocyte activity is S100B. The elevated external levels of S100B, produced by injured astrocytes, may be a biomarker for transient brain injury, neurological distress, and perhaps neurodegenerative illnesses.

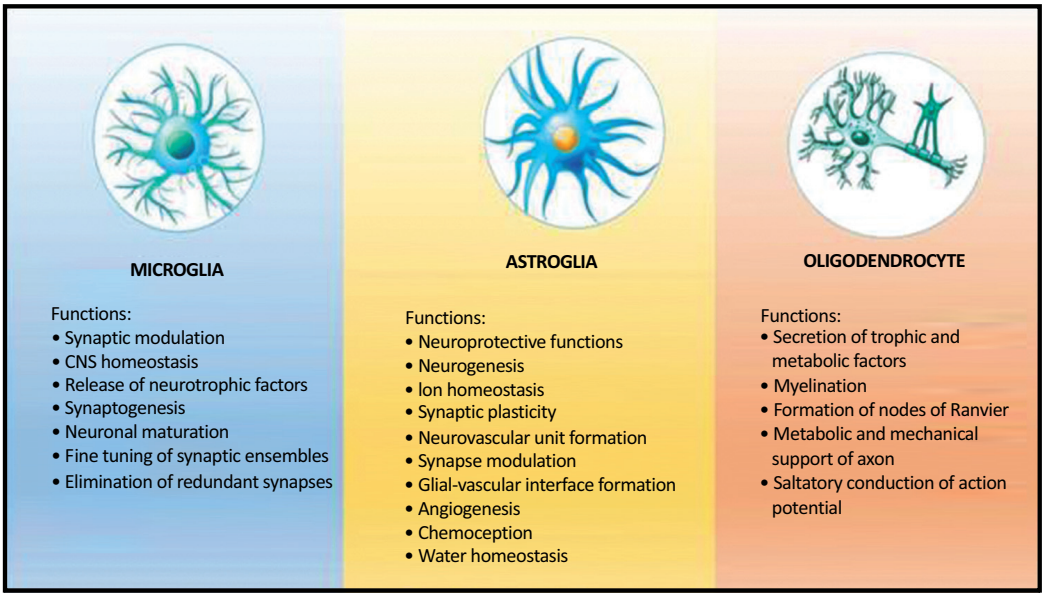

Fig. (1). Glial cells - types and their functions. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

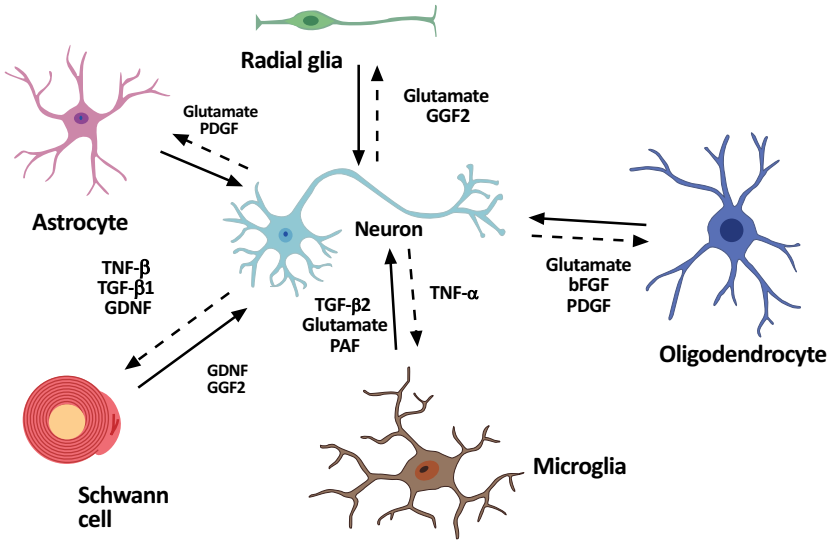

Fig. (2). Neuron-glial interaction. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Oligodendrocyte-aided myelination of neurons is a significantly intricate cell-to-cell interaction. Because their axons and myelin sheaths are nearby, it is hard to believe that there is no interaction between neurons and oligodendrocytes. Neuron-oligodendrocyte interaction is a reciprocal signalling system where oligodendrocytes receive signals from axons that regulate their myelination, and oligodendrocytes alter the form and conduction of axons [11].

According to studies, radial glia (during CNS development) and astrocytes (in the adult CNS) act as primary precursors and critical components of neurogenic niches due to the functional heterogeneity shown by glial cells during neurogenesis, revealing previously unseen functions and new lineage associations between these cell types, as well as between neurons and glial cells. In this perspective, the glial lineage's double role actively forms and maintains neuron-glial interactions [12]. Studying higher brain functions requires knowledge of glial cell characteristics and neuron-glial interactions [13].

3.1. Importance of Neuron-Glia Interaction in Brain Development

The interactions between neurons and glia are essential for regular brain activity during development and adulthood. The significance of glia in their bidirectional contact with neurons, their versatility in diverse diseases, regulation of neuronal activity, and phenotypic alterations in response to neuronal injury have all been highlighted by new research [14]. The molecular and cellular mechanisms that support these interactions need to be clarified. Increasing evidence reveals that changes in neuron-glia interactions are linked to the development of neurodegenerative disorders known as tauopathies. There is a relationship between glial activation and neuronal damage or healing [15].

During brain development, neurons develop in the VZ and migrate into the growing neocortex, directed by nearby glial cells. After settling in, they proceed through terminal differentiation. Their extended axons and dendrites join with neighbouring neurons to form the final brain network supported by glial cells [16]. As a result of their activity, these genetically defined connections are modified in the last stage of development [17].

Disturbance of neuron-glia connections has lately been proposed as a significant event in the pathophysiology of ASD because aberrant neuronal network formation and dysfunctional neurotransmission are fundamental to the pathology of the condition [18]. Disruptions heavily influence the pathogenesis of different neurological diseases in neuron-astrocyte connections. Abnormal glutamate receptor activation causes neuronal death, which is known as excitotoxicity. Cell death induced by glutamate may occur quickly, with a large influx of Na^+ and Cl^- and cell expansion, accompanied by a large influx of Ca^{2+} and stimulation of downstream cascades, resulting in damage and, ultimately, death of neurons. Moreover, glutamate-induced damage may follow a sluggish path through the induction of apoptosis, which has been linked to pathophysiologies of several neurodegenerative disorders [19]. The various models for studying the neuroglial interactions are tabulated in Table **1** [20-31].

Table 1. ASD models with neuro-glial interactions.

Type	Model	References
Genetic	TSC1 HT	[20]
	BTBR	[21]
	Shank3 KO [21]	[21]
	Scn1a HT [20]	[20]
	NLGN3 R451C KI [22]	[22]
	MeCP2 mutant [23]	[23]
	Shank2 KO [24]	[24]
	PTEN mutant [25]	[25]
	NLXN1 KO [24]	[24]
Pharmacological	Valproic acid (VPA) [26]	[26]
Environmental	Methyl mercury	[27]
	Maternal immune activation (MIA)	[28-30]
	Polyinosinic: polycytidylic acid (poly I: C)	[31]

4. NEURO-GLIAL INTERACTION DYSFUNCTIONS IN AUTISM

Most neurodegenerative diseases are described as 'proteinopathies,' or toxic protein aggregates. Accumulation of proteins most commonly happens at synapses, resulting in dysfunctional synapses [32]. Autism is a complicated, interpersonally defined, static condition of the under-developed brain that is of significant concern to practising paediatricians because of an estimated 556 percent increase in paediatric incidence from 1991 to 1997, surpassing that of spina bifida, Down syndrome, or even cancer [33]. Glial cells secrete gliotransmitters such as glutamate, GABA, and cytokines, increasing inflammatory cytokines and disrupting neurogenesis [34]. In the brains of people with autism, glial cells are constantly stimulated, and their genes which respond to inflammation, are turned on, according to new research [35]. Glutamate secreted by neurons is acquired by glial cells at excitatory synapses, transformed into glutamine, and then returned to neurons. The pathology of bipolar disorder is thought to be due to changes in this system [36].

In recent years, the contribution of glial cells to autism has been overlooked. Astrocytes aid neuronal survival in normal physiological conditions by releasing growth factors and regulating the uptake/removal of excitotoxic neurotransmitters like glutamate from the synaptic milieu. Nevertheless, astrocytes can release certain factors during their activation because of injury or neuronal dysfunction that may modify inflammatory responses; they release pro-inflammatory cytokines, metalloproteinases, and chemokines which can intensify immune reactions in the CNS. In the same way, microglia activation plays a vital role in neuroglial responsiveness to damage or dysfunction. Pathophysiological responses may result in the activation of neuroglia, which exacerbates the degree of neuronal dysfunction accompanied by the irregular organisation of the cortex, like those seen in autism. The cerebellum, white matter, and cortical regions of autistic patients showed significant microglial activation [37]. In the brain and cerebrospinal fluid of several autistic individuals, inflammatory markers, including interleukin 1 (IL-1), tumour necrosis factor (TNF), and CXCL8 (IL-8), are elevated. These markers are produced when microglia are activated. In reaction to the peptide neurotensin (NT), normal microglia in culture produce IL-1 and CXCL8. The M1 phenotype is induced in microglial cultures when exposed to triggers including bacterial lipopolysaccharides, TNF, IFN, necrotic nerve cells, polymerised Aβ, and alpha-synuclein (Fig. **3**). The transcription of MHC-II (major histocompatibility complex type II) membrane glycoprotein, the release of pro-inflammatory mediators (TNF-α, IL-1β, IL-6 and IL12), and the generation of reactive oxygen species (ROS) are all characteristics of the typical M1 phenotype. The mediators IL-4 and IL-13 that are released *in vivo* by Th2 lymphocytes can promote the equivalent M2 phenotype, which is neuroprotective, in primary microglia [38].

This varied set of interactions may explain various clinical symptoms among individuals. However, thorough molecular studies to understand the mechanics of this connection currently need to be completed.

5. GLIAL PATHOLOGY IN AUTISM

Recently, the significance of neuroglial aspects in ASD has gained much attention because of the many lines of evidence showing glia-specific changes in both animal models of ASD and individuals with the disorder [39]. Immune and neuroglial activity have received minimal attention in neuropathological investigations of autism, and the most thorough postmortem study found gliosis and inflammatory alterations. Such neuroinflammation may contribute to and result from abnormal CNS development and activity in ASD [40]. A growing body of data suggests that glial cell malfunction plays a role in the development of ASD [41, 42]. However, the findings of these studies are sometimes complicated and inconsistent, owing to the intricacy of the cellular and molecular pathways causing ASD. Autism has been linked to discontinuous modules of co-expressed genes M16, enriched for astrocyte markers and markers of activated microglia [43]. Glial-specific markers show abnormal transcription in the brains of autistic people. The markers employed to evaluate microglial cell count and activity are still up for discussion since microglia cell-marker investigation is currently a new field of study. Through the release of regulatory cytokines, the receptor *TREM2* modulates the immunological response within the brain and is essential for triggering microglial phagocytosis.

The protein *CX3CL1* (or fractalkine) works to cause microglial relocation and adhering during the phagocytotic process. Its receptor, *CX3CR1*, encodes a protein binding site on the membrane of microglial cells to which *CX3CL1* attaches. *AIF1*, commonly termed *IBA1*, distinguishes between rested and engaged microglial cells as it encodes a protein whose transcription is persistently increased during microglial activation. The expression of type III intermediate filament protein, *GFAP* (glial fibrillary acidic protein), depends on astrocytes and is upregulated in ASD people. According to research, all microglial markers, including *TREM2*, *DAP12*, and *CX3CR1*, are expressed higher in the PrefrontalPrefrontal cortex (PFC). However, *AIF1* failed to achieve statistical significance [44]. The astrocyte-specific marker, GFAP, was considerably overexpressed in both PFC and cerebellum in ASD brains. This pattern was most pronounced in the cerebellum, wherein *GFAP* activity was over two times greater in ASD brains than in normal brains. In the PFC and the cerebellum of ASD people, there was a significant reduction in the transcription of the pan-neuronal marker *NEFL*.

Glial cell dysfunction leads to abnormal neuro-glial interactions, which create a "hostile" environment that affects neuronal function. This can result in a systematic loss of neuronal function on a scale that seems proportionate to the degree of neurological impairment [45]. In ASD, neuron and glial cell number changes cause brain circuits to malfunction and impact behaviour [46]. Reactive astrogliosis and microglial activation have been suggested to assist the pathophysiology of ASD by exacerbating the inflammatory process produced by the immunological response. Nevertheless, detailed molecular investigations of the pathways linking glial activation to ASD aetiology are still to be carried out. The capacity of glial cells to control the formation, development, maintenance, deletion, or functioning of new synapses may be disrupted by glial cell remodelling because brain circuits

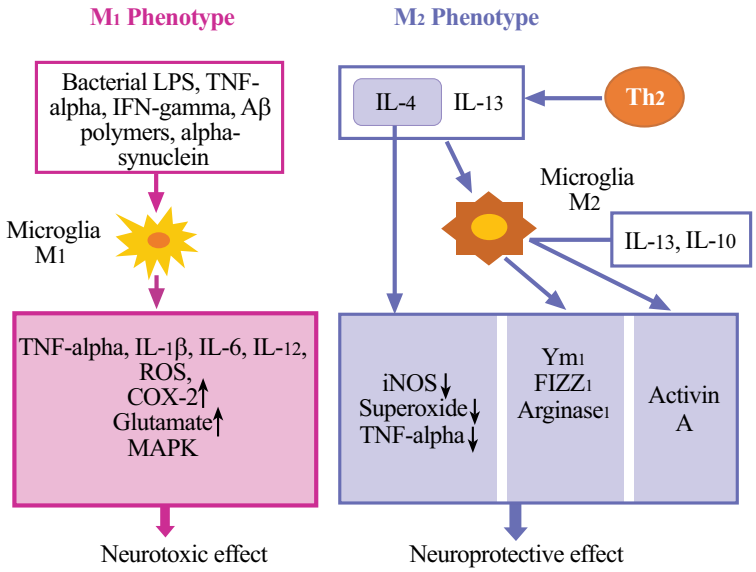

Fig. (3). Microglial activation phenotypes. **Abbreviations**: MAPK = Mitogen-activated protein kinase; TNF= Tumor necrosis factor; IFN= Interferons; ROS= Reactive oxygen species; IL= interlukin; ↑ = increase or upregulation; ↓ = decrease or downregulation. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Table 2. Causes and results of glial cells activation.

S. No.	Cell	Cause of Dysfunction	Abnormal Functions	Results	References
1	Glial cells	✓ As a result of ongoing neuro-degeneration ✓ Stroke ✓ Trauma ✓ Tumour	✓ Secretion of gliotransmitters such as glutamate, GABA and cytokines	✓ Abnormal neuro-glial interactions ✓ Loss of neuronal function ✓ Disruption of neurogenesis	[34, 45]
2	Astrocytes	✓ Stroke ✓ Tumour ✓ Trauma ✓ Neurodegenerative diseases	✓ Pro-inflammatory cytokines secretion ✓ Calcium signalling abnormalities	✓ Modulate inflammatory response ✓ Intensify immune reactions in CNS	[37, 53]
3	Microglial cells	✓ Changes in the distribution of CD200 or CD200R ✓ Mediators and electric signals from the injured site ✓ Tumour ✓ Stroke ✓ Trauma ✓ Neurodegeneration	✓ Pro-inflammatory cytokine secretion ✓ Activation of inducible nitric oxide(NO)-synthase	✓ Exacerbate the degree of neuronal dysfunction ✓ Irregular organisation of the cortex	[37, 48, 49]
4	Oligodendro-cytes	✓ Neurodegeneration ✓ Stroke ✓ Trauma ✓ Tumour	✓ Production of reelin product	✓ Reelin activity may lead to autism	[55]

are particularly vulnerable to lesions impacting glial pathways linked with synapse formation. The various reasons behind the activation of glial cells and their abnormal functions are summarised in Table **2**.

In vivo and *in vitro*, patient-derived iPSCs are practical tools for exploring the cellular and molecular pathways causing glial dysfunction. Glial progenitors and oligodendrocytes derived from the iPSCs of patient tissue have already been created and modelled from neural-derived cells of Rett Syndrome and ASD patients as proofs-of-concept [47].

5.1. Microglial Dysfunction in Autism

Microglial activation acts as a protective pathway in a healthy environment. Still, due to the intricate and multifaceted nature of microglial activation, minor differences can result in an amplified or poorly functioning activation, which is believed to exacerbate neurodegenerative pathology, accompanied by cytokines presenting at almost all disease stages. The CD200 glycoprotein, which prevents microglial priming and keeps microglia in a dormant state, is one of the

critical mediators whereby neurons influence glial activation. According to studies, it is possible to reverse the functioning of neurons in activating microglial cells by allowing cell culture to incubate in the medium containing the anti-CD200 antibody. It shows a specialised role of neuronal-glial interaction in keeping glial cells inactive and can be accomplished upon binding CD200 with CD200R [48]. However, changes in the distribution of CD200 or CD200R, its glial receptor, can result in microglia overactivation and neuroinflammation, both of which are associated with neurodegeneration [49]. In general, neuroinflammation is defined by increased reactivity of microglia and astrocytes, increased production and secretion of cytokines and chemokines, and inducible nitric oxide (NO)-synthase (i-NOS) activation, as seen in ASD [50]. Recent discoveries suggest that dysfunction or changes in the ability of microglia to carry out physiological and defensive functions (such as failure in synaptic elimination or aberrant microglial activation) may be crucial for developing brain diseases, especially autism. This has been confirmed by recent studies [51]. In male mice, excessive translation only in microglia, not neurons or astrocytes, causes autism-like symptoms [52].

5.2. Astrocytes and Metabolic Dysfunction

Indeed, thorough examinations of neurodevelopmental disorders with identified genetic lesions (and their related rodent models) reveal that dysfunction of astrocytes during development causes disease pathogenesis. Fragile X's mental retardation, Rett syndrome, Alexander's disease, and others. Many of these investigations have discovered that astrocyte failure has significant noncell-autonomous consequences on neighbouring neurons; consequently, understanding the causes of astrocyte dysfunction will be crucial for future therapeutic approaches [53]. In a study, it was proved that astrocyte calcium signalling abnormalities could cause autism-like behaviours in mice. Changes in astrocytes in autistic patients and animal models have been observed on multiple occasions. Unfortunately, the significance of astrocytes in autism is unknown [54]. The studies demonstrate the role of astrocytes in neuronal phenotype and validate earlier research relating IL-6 to autism, offering potential therapeutic approaches for a subset of autism patients [55].

The reelin product, generated by oligodendrocytes, has shown activity on one of its receptors in autism [56]. The action performed by dysfunctional glial cells in autism is summarised in Table **3**.

6. GLIAL THERAPY IN AUTISM SPECTRUM DISORDER

According to growing data, synaptic dysfunction plays a significant role in the development of autism, and synaptic function is regulated by glial cells. Given the evidence that glial cells play a role in ASD neuroinflammation, one theory is that reactive glial cells result in the loss of synaptic functioning and induce autism under inflammatory conditions [57]. Replacement of defective glial cells (Cell-replacement treatment), glial progenitor cell-based therapy, and medication therapy (inhibition of microglia activation) are all utilised to treat glial dysfunction. The various therapeutic approaches to treating glial dysfunction are summarised in Table **4**.

6.1. Cell-Replacement Therapy

The passive activity of glial cells reported a century ago has now been superseded by the discovery of significant glial activity for optimal CNS homeostasis. This breakthrough has moved neuroscience's attention from a neuron-centric to a glial-inclusive perspective. This perspective enables the development of cell-replacement techniques that include both neuronal and glial cell replacement [58].

In comparison to the substantial research that has been undertaken on oligodendrocyte replacement, the advent of astrocyte transplantation introduced a new route for the treatment of CNS disorders. Generation of extensive myelination has been made possible after transplanting human oligodendrocytes into spinal cord injury or congenital mouse models of hypomyelination since the late 1980s and more recently with populations of human oligodendrocyte progenitor cells separated from the developing or adult CNS, or human embryonic stem cells. On the other hand, the potential value of astrocyte-based therapeutics is far less recognised. Furthermore, preliminary research revealed relatively minor benefits of astrocyte transplantation for treating severe spinal cord damage [59].

Differentiating human ESCs into astrocytes employing two progenitor populations, $Olig2^{+}$ *versus* $Olig2^{-}$ neural progenitor cells, and then transplantation in rats reduces neuronal loss and enhances behavioural recovery $Olig2^{+}$-astrocytes, which are more effective than the $Olig2^{-}$ popula-

Table 3. Functions of glial cells in their reactive state.

Activated Microglia	Activated Astrocytes	Activated Oligodendrocytes
Neurotoxic activity Irregular synapse connectivity LTP deficit Irregular immune response Reactive microgliosis Generation of reactive oxygen species	Altered synaptogenesis Reactive gliosis Altered neurogenesis Irregular immune response Reduced homeostasis Irregular secretion of soluble factors Absence of neurotrophic support Calcium signalling dysfunction	Impaired action potential Abnormal formation of the myelin sheath Production of *reelin*

tion, presumably because the $Olig2^+$ population produces more BDNF. Surprisingly, synapsin-1 staining shows that $Olig2^+$ astrocyte transplantation results in enhanced synaptogenesis. These findings indicate that specific astrocytic populations transplanted into the brain could successfully stimulate neuronal recovery [60].

6.2. Glial Progenitor Cell (GPC) Based Therapy

Glial dysfunction may play such a prominent role in several ailments that it may be possible to treat them with allogeneic GPCs, which act as precursors of both astroglia and oligodendrocytes [61]. GPCs, the progenitor, are mitotically proficient, distinguishing them from the considerably more significant population of mature, postmitotic oligodendrocytes [62]. GPCs, also known as oligodendrocyte progenitor cells or NG2 cells, have thus emerged as promising tools for repairing damaged or wounded CNS regions [63]. Functionally, they are equivalent to OPCs. On the other hand, these cells appear bipotential and can produce both astrocytes and oligodendrocytes until their final division [61]. A series of tests were conducted to see how effective intracerebrally injected hGPCs could be as therapeutic agents [64]. In terms of expressed genes and dominant signalling pathways, there were significant differences between fetal and adult human GPCs and rodent and human GPCs. This research doubts therapeutic techniques based only on data collected from rodents while emphasising the degree to which phylogenetic alteration of glial phenotype and function has accompanied evolution [65]. The differences between the behaviour of fetal and adult-derived glial progenitors suggest that they could be used to treat different diseases [66].

Latest fate-mapping investigations have demonstrated that NG2 cells act as precursors of oligodendrocytes and co-exist with the OPC marker platelet-derived growth factor-α receptor. Because of their ability to self-propagation and differentiation into oligodendrocytes, NG2 cells could be a promising cellular treatment for dysfunctional oligodendrocytes [58].

The role of Gabaergic signalling in neuron-glia interactions is still being unravelled. However, it has been proposed that GABA activates glial cells, which regulate essential brain processes like neuronal activity, neuroprotection, and differentiation [67]. Cortical Gabaergic interneuron dysfunction is linked to various neurological diseases, including autism and restoring these cells by a transplantation procedure is a practical and successful method for reversing symptoms [68]. Gabaergic interneurons are involved in the brain's balanced excitatory and inhibitory neural circuitry, and their absence or malfunction has been linked to ASD. hGPCs develop into functioning induced neurons (iN), which contain Gabaergic characteristics, express subtype-specific interneuron markers, and have a complex neuronal structure with extended dendritic trees. The potential to induce Gabaergic interneurons from a renewable *in vitro* hGPC system could pave the way for the development of therapeutics for interneuron diseases like autism [69]. Gabaergic interneuron dysfunction may support a variety of behavioural and psychiatric disorders. High-purity Gabaergic interneurons derived from human embryonic stem cells (hESCs) or patient-derived iPSCs are desirable for molecular studies of Gabaergic neuronal dysfunction and drug discovery research [70].

6.3. Inhibition of Microglial Activation

Neuroinflammation, which contributes to neuronal dysfunction and, thus, autism, occurs because of the activation of microglial cells [71, 72]. Inhibiting microglial cell activation has been proposed as a possible therapeutic method in treating autism [73, 74]. Direct neurotoxicity, failure to maintain tissue homeostasis, and phagocytosis of aberrant proteins and apoptotic neurons are all tasks performed by activated microglia; these numerous functions are presumably performed by diverse phenotypes of activated microglia [71, 75-77]. The mechanism of microglial activation and inhibition by anti-inflammatory drugs is shown in Fig. (**4**).

According to studies, microglial cell activation has been linked to several neurodegenerative diseases, including autism [78, 79]. In the ischemic penumbra, activation of microglial cells is inhibited by 1810034E14Rik. Furthermore, after overexpression of 1810034E14Rik, the mRNA and protein levels in activated microglial cell markers (CD16 and CD11b) were considerably reduced in MCAo-treated mice [80]. These findings showed that overexpression of 1810034E14Rik reduced microglial activation and the inflammatory response following MCAo therapy [81, 82]. Both external and stress factors may stimulate mast cells and microglial cells in the brain (Fig. **5**), disrupting amygdala neural connections and changing the usual "fear threshold." This pathway may partially explain the pathophysiology of ASD. Finding techniques to reduce amygdala inflammatory response may represent a cutting-edge treatment strategy for ASD. Bioactive compounds, like the flavonoid tetra methoxy luteolin, which has been shown to suppress the production of pro-inflammatory mediators from microglial cells, may be potentially used as therapy that focuses on this principle.

Indeed, evidence of neuroinflammation, accompanied by activation of microglia and astrocytes and elevated levels of pro-inflammatory cytokines, have been observed in the brains of ASD patients, supporting the hypothesis that immunological dysfunction may be involved in ASD [83]. In the hippocampus of VPA-treated mice, CBDV therapy was observed to restore microglia activation and subsequent structural alteration in the size of cell and soma shape [73, 84-86].

Minocycline inhibits microglia activation, modifies neuroinflammation pathways, including cytokine and chemokine networks (*e.g.*, IL-6, IL-1β, and TNF-α), and inhibits metalloproteinase activity [87-91]. Corticosteroids are anti-inflammatory medicines that decrease pro-inflammatory mediator release and impact microglia activation [92-95].

Luteolin is an antioxidant that inhibits microglial activation and prevents neurotoxicity [96, 97]. It appears to work by inhibiting histamine, IL-6, IL-8, TNF, and tryptase production in mast cells. It is thought to be safe, with few to no adverse effects. In animal model research, lutein has been proven to reduce autism-like behaviours in mice [98].

Suramin (a P2 receptor antagonist) prevents microglia activation when injected intrathecally [99, 100]. Celecoxib has been shown to inhibit the lipopolysaccharide-induced rise in activated microglia in newborn rats [101, 102].

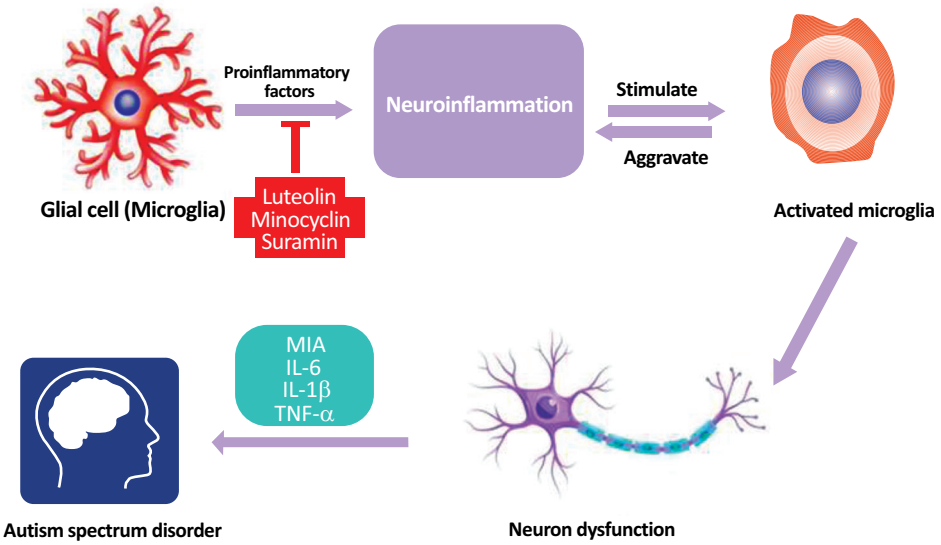

Fig. (4). Inhibition of microglial activation by anti-inflammatory drugs. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

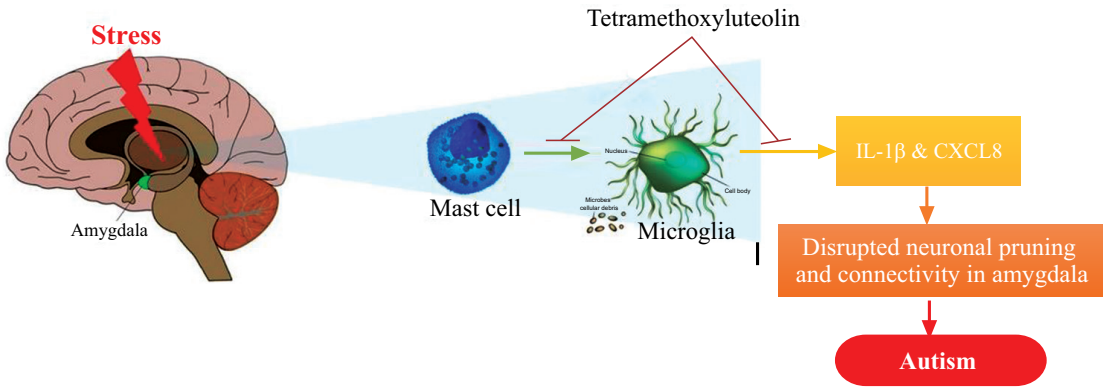

Fig. (5). Microglia-mediated pro-inflammatory markers activation that contributes to ASD. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Table 4. Therapeutic approaches used in glial therapy.

S. No.	Therapy	Mechanism in ASD	Results	References
1.	Astrocyte transplantation	Differentiation of hESCs into astrocytes using $Olig2^{+}$ and $Olig2^{-}$ neural progenitor cells	✓ Enhanced synaptogenesis ✓ Improved behavioural recovery ✓ Reduced neuronal loss	[60, 103, 104]
2.	Glial Progenitor Cell (GPC) based therapy	Self-propagation and differentiation into oligodendrocytes and astrocytes	✓ Recovery in oligodendrocyte and astrocyte number ✓ Repair of myelin abnormalities	[105, 106]
3.	CBDV therapy	Activation of the TRP channel	✓ Restored microglial activation ✓ Enhanced microglial phagocytosis	[73, 107, 108]
4.	Minocycline	Unknown	✓ Inhibited microglia activation ✓ Modified neuroinflammation pathways ✓ Improved social behaviour ✓ Restored phagocytic activity of microglia	[109, 110]
5.	Luteolin	Decreases the serum levels of TNF and IL-6 and inhibits microglial activation	✓ Improved social interaction ✓ Inhibition of neurotoxicity	[111-113]

(Table 4) Contd….

S. No.	Therapy	Mechanism in ASD	Results	References
6.	Suramin	Unknown	✓ Enhanced social interaction ✓ Minimized repetitive action	[114, 115]
7.	Immunoglobulin	Decreases levels of inflammatory cytokines	✓ Improved phagocytosis by microglia ✓ Improved communication ability	[116, 117]
8.	Celecoxib	Unknown	✓ Reduced number of activated microglia ✓ Improved social interaction ✓ Minimized repetitive actions	[118, 119]
9.	Spironolactone	Through its anti-inflammatory and immunomodulatory action	✓ Reduced secretion of inflammatory cytokines by microglia ✓ Reduced repetitive actions and hyperactivity	[120, 121]

CONCLUSION AND FUTURE PROSPECTS

Further understanding of the significance of glial cell dysfunction in the development of autism needs to be established. This might help in developing potential therapeutic strategies. Although several drugs and therapies are available to treat glial dysfunctions, further studies are required to develop drugs that can completely treat the glial perspective of ASD.

LIST OF ABBREVIATIONS

ASD = Autism Spectrum Disorder

ATP = Adenosine Triphosphate

BDNF = Brain-derived Neurotrophic Factor

CBDV = Cannabidivarin

CNS = Central Nervous System

ESCs = Embryonic Stem Cells

GABA = Gamma-aminobutyric Acid

GPC = Glial Progenitor Cells

IL = Interleukin

iNOS = Inducible Nitric Oxide Synthase

iPSCs = Induced Pluripotent Stem Cells

LTP = Long-term Potential

MCAO = Middle Cerebral Artery Occlusion

NG2 = Neuron-glial Antigen 2

OPC = Oligodendrocyte Progenitor Cells

TNF = Tumor Necrosis Factor

TRP = Transient Receptor Potential

VPA = Valproic Acid

VZ = Ventricular Zone

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors acknowledge support from their institutions. (i) AU: University of Hail, KSA; (ii) NHG: Intramural Research Program, NIA, NIH, USA; (iii) MAK: West China School of Nursing, Sichuan University, China; King Abdulaziz University, KSA; Enzymoics, NSW, Australia; Novel Global Community Educational Foundation, Australia.

REFERENCES

[1] Scuderi, C.; Verkhratsky, A. The role of neuroglia in autism spectrum disorders. *Prog. Mol. Biol. Transl. Sci.,* **2020**, *173*, 301-330. http://dx.doi.org/10.1016/bs.pmbts.2020.04.011 PMID: 32711814

[2] Kato, T.A.; Watabe, M.; Kanba, S. Neuron-glia interaction as a possible glue to translate the mind-brain gap: A novel multidimensional approach toward psychology and psychiatry. *Front. Psychiatry,* **2013**, *4*, 139. http://dx.doi.org/10.3389/fpsyt.2013.00139 PMID: 24155727

[3] Fields, R.D.; Burnstock, G. Purinergic signalling in neuron–glia interactions. *Nat. Rev. Neurosci.,* **2006**, *7*(6), 423-436. http://dx.doi.org/10.1038/nrn1928 PMID: 16715052

[4] Stogsdill, J.A.; Eroglu, C. The interplay between neurons and glia in synapse development and plasticity. *Curr. Opin. Neurobiol.,* **2017**, *42*, 1-8. http://dx.doi.org/10.1016/j.conb.2016.09.016 PMID: 27788368

[5] Gomes, F.C.A.; Spohr, T.C.L.S.; Martinez, R.; Moura Neto, V. Cross-talk between neurons and glia: Highlights on soluble factors. *Braz. J. Med. Biol. Res.,* **2001**, *34*(5), 611-620. http://dx.doi.org/10.1590/S0100-879X2001000500008 PMID: 11323747

[6] Cserép, C.; Pósfai, B.; Dénes, Á. Shaping neuronal fate: Functional heterogeneity of direct microglia-neuron interactions. *Neuron,* **2021**, *109*(2), 222-240. http://dx.doi.org/10.1016/j.neuron.2020.11.007 PMID: 33271068

[7] Pósfai, B.; Cserép, C.; Orsolits, B.; Dénes, Á. New insights into microglia–neuron interactions: A neuron's perspective. *Neuroscience,* **2019**, *405*, 103-117. http://dx.doi.org/10.1016/j.neuroscience.2018.04.046 PMID: 29753862

[8] Wieghofer, P.; Knobeloch, K.P.; Prinz, M. Genetic targeting of microglia. *Glia,* **2015**, *63*(1), 1-22. http://dx.doi.org/10.1002/glia.22727 PMID: 25132502

[9] Goldmann, T.; Wieghofer, P.; Müller, P.F.; Wolf, Y.; Varol, D.; Yona, S.; Brendecke, S.M.; Kierdorf, K.; Staszewski, O.; Datta, M.; Luedde, T.; Heikenwalder, M.; Jung, S.; Prinz, M. A new type of microglia gene targeting shows TAK1 to be pivotal in CNS autoimmune inflammation. *Nat. Neurosci.,* **2013**, *16*(11), 1618-1626. http://dx.doi.org/10.1038/nn.3531 PMID: 24077561

[10] Dzyubenko, E.; Gottschling, C.; Faissner, A. Neuron-glia interactions in neural plasticity: Contributions of neural extracellular matrix and perineuronal nets. *Neural Plast.,* **2016**, *2016*, 1-14. http://dx.doi.org/10.1155/2016/5214961 PMID: 26881114

[11] Duncan, G.J.; Simkins, T.J.; Emery, B. Neuron-oligodendrocyte interactions in the structure and integrity of axons. *Front. Cell Dev. Biol.,* **2021**, *9*, 653101. http://dx.doi.org/10.3389/fcell.2021.653101 PMID: 33763430

[12] Gritti, A.; Bonfanti, L. Neuronal–glial interactions in central nervous system neurogenesis: The neural stem cell perspective. *Neuron Glia Biol.,* **2007**, *3*(4), 309-323. http://dx.doi.org/10.1017/S1740925X0800001X PMID: 18634563

[13] Shimizu, T.; Osanai, Y.; Ikenaka, K. Oligodendrocyte–neuron interactions: Impact on myelination and brain function. *Neurochem. Res.,* **2018**, *43*(1), 190-194. http://dx.doi.org/10.1007/s11064-017-2387-5 PMID: 28918515

[14] Afridi, R.; Kim, J.H.; Rahman, M.H.; Suk, K. Metabolic regulation of glial phenotypes: Implications in neuron–glia interactions and neurological disorders. *Front. Cell. Neurosci.,* **2020**, *14*, 20. http://dx.doi.org/10.3389/fncel.2020.00020 PMID: 32116564

[15] Salmina, A.B. Neuron-glia interactions as therapeutic targets in neurodegeneration. *J. Alzheimers Dis.,* **2009**, *16*(3), 485-502. http://dx.doi.org/10.3233/JAD-2009-0988 PMID: 19276541

[16] Abdelli, L.S.; Samsam, A.; Naser, S.A. Propionic acid induces gliosis and neuro-inflammation through modulation of PTEN/AKT pathway in autism spectrum disorder. *Sci. Rep.,* **2019**, *9*(1), 8824. http://dx.doi.org/10.1038/s41598-019-45348-z PMID: 31217543

[17] Laming, P.R.; Kimelberg, H.; Robinson, S.; Salm, A.; Hawrylak, N.; Müller, C.; Roots, B.; Ng, K. Neuronal–glial interactions and behaviour. *Neurosci. Biobehav. Rev.,* **2000**, *24*(3), 295-340. http://dx.doi.org/10.1016/S0149-7634(99)00080-9 PMID: 10781693

[18] Chen, J.A.; Peñagarikano, O.; Belgard, T.G.; Swarup, V.; Geschwind, D.H. The emerging picture of autism spectrum disorder: Genetics and pathology. *Annu. Rev. Pathol.,* **2015**, *10*(1), 111-144. http://dx.doi.org/10.1146/annurev-pathol-012414-040405 PMID: 25621659

[19] Benarroch, E.E. Neuron-astrocyte interactions: Partnership for normal function and disease in the central nervous system. *Mayo Clin. Proc.,* **2005**, *80*(10), 1326-1338. http://dx.doi.org/10.4065/80.10.1326 PMID: 16212146

[20] Tsai, P.T.; Hull, C.; Chu, Y.; Greene-Colozzi, E.; Sadowski, A.R.; Leech, J.M.; Steinberg, J.; Crawley, J.N.; Regehr, W.G.; Sahin, M. Autistic-like behaviour and cerebellar dysfunction in Purkinje cell Tsc1 mutant mice. *Nature,* **2012**, *488*(7413), 647-651. http://dx.doi.org/10.1038/nature11310 PMID: 22763451

[21] Gogolla, N.; Takesian, A.E.; Feng, G.; Fagiolini, M.; Hensch, T.K. Sensory integration in mouse insular cortex reflects GABA circuit maturation. *Neuron,* **2014**, *83*(4), 894-905. http://dx.doi.org/10.1016/j.neuron.2014.06.033 PMID: 25088363

[22] Hammer, M.; Krueger-Burg, D.; Tuffy, L.P.; Cooper, B.H.; Taschenberger, H.; Goswami, S.P.; Ehrenreich, H.; Jonas, P.; Varoqueaux, F.; Rhee, J.S.; Brose, N. Perturbed hippocampal synaptic inhibition and γ-oscillations in a neuroligin-4 knockout mouse model of autism. *Cell Rep.,* **2015**, *13*(3), 516-523. http://dx.doi.org/10.1016/j.celrep.2015.09.011 PMID: 26456829

[23] Chao, H.T.; Chen, H.; Samaco, R.C.; Xue, M.; Chahrour, M.; Yoo, J.; Neul, J.L.; Gong, S.; Lu, H.C.; Heintz, N.; Ekker, M.; Rubenstein, J.L.R.; Noebels, J.L.; Rosenmund, C.; Zoghbi, H.Y. Dysfunction in GABA signalling mediates autism-like stereotypies and Rett syndrome phenotypes. *Nature,* **2010**, *468*(7321), 263-269. http://dx.doi.org/10.1038/nature09582 PMID: 21068835

[24] Sloan, S.A.; Barres, B.A. Mechanisms of astrocyte development and their contributions to neurodevelopmental disorders. *Curr. Opin. Neurobiol.,* **2014**, *27*, 75-81. http://dx.doi.org/10.1016/j.conb.2014.03.005 PMID: 24694749

[25] Busch, R.M.; Srivastava, S.; Hogue, O.; Frazier, T.W.; Klaas, P.; Hardan, A.; Martinez-Agosto, J.A.; Sahin, M.; Eng, C. Neurobehavioral phenotype of autism spectrum disorder associated with germline heterozygous mutations in PTEN. *Transl. Psychiatry,* **2019**, *9*(1), 253. http://dx.doi.org/10.1038/s41398-019-0588-1 PMID: 31594918

[26] Gumusoglu, S.B.; Fine, R.S.; Murray, S.J.; Bittle, J.L.; Stevens, H.E. The role of IL-6 in neurodevelopment after prenatal stress. *Brain Behav. Immun.,* **2017**, *65*, 274-283. http://dx.doi.org/10.1016/j.bbi.2017.05.015 PMID: 28546058

[27] Goines, P.E.; Croen, L.A.; Braunschweig, D.; Yoshida, C.K.; Grether, J.; Hansen, R.; Kharrazi, M.; Ashwood, P.; Van de Water, J. Increased midgestational IFN-γ, IL-4 and IL-5 in women bearing a child with autism: A case-control study. *Mol. Autism,* **2011**, *2*(1), 13. http://dx.doi.org/10.1186/2040-2392-2-13 PMID: 21810230

[28] Hsiao, E.Y.; McBride, S.W.; Hsien, S.; Sharon, G.; Hyde, E.R.; McCue, T.; Codelli, J.A.; Chow, J.; Reisman, S.E.; Petrosino, J.F.; Patterson, P.H.; Mazmanian, S.K. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell,* **2013**, *155*(7), 1451-1463. http://dx.doi.org/10.1016/j.cell.2013.11.024 PMID: 24315484

[29] Choi, G.B.; Yim, Y.S.; Wong, H.; Kim, S.; Kim, H.; Kim, S.V.; Hoeffer, C.A.; Littman, D.R.; Huh, J.R. The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring. *Science,* **2016**, *351*(6276), 933-939. http://dx.doi.org/10.1126/science.aad0314 PMID: 26822608

[30] Croen, L.A.; Grether, J.K.; Yoshida, C.K.; Odouli, R.; Van de Water, J. Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: A case-control study. *Arch. Pediatr. Adolesc. Med.,* **2005**, *159*(2), 151-157. http://dx.doi.org/10.1001/archpedi.159.2.151 PMID: 15699309

[31] Horváth, G.; Otrokocsi, L.; Bekő, K.; Baranyi, M.; Kittel, Á.; Antonio Fritz-Ruenes, P.; Sperlágh, B. P2X7 receptors drive poly(I:C) induced autism-like behavior in mice. *J. Neurosci.,* **2019**, *39*(13), 1895-18. http://dx.doi.org/10.1523/JNEUROSCI.1895-18.2019 PMID: 30683682

[32] Ibrahim, A.M.; Pottoo, F.H.; Dahiya, E.S.; Khan, F.A.; Kumar, J.B.S. Neuron-glia interactions: Molecular basis of alzheimer's disease and applications of neuroproteomics. *Eur. J. Neurosci.,* **2020**, *52*(2), 2931-2943. http://dx.doi.org/10.1111/ejn.14838 PMID: 32463535

[33] Muhle, R.; Trentacoste, S.V.; Rapin, I. The genetics of autism. *Pediatrics,* **2004**, *113*(5), e472-e486. http://dx.doi.org/10.1542/peds.113.5.e472 PMID: 15121991

[34] Kim, Y.S.; Choi, J.; Yoon, B.E. Neuron-glia interactions in neurodevelopmental disorders. *Cells,* **2020**, *9*(10), 2176. http://dx.doi.org/10.3390/cells9102176 PMID: 32992620

[35] Petrelli, F.; Pucci, L.; Bezzi, P. Astrocytes and microglia and their potential link with autism spectrum disorders. *Front. Cell. Neurosci.,* **2016**, *10*, 21. http://dx.doi.org/10.3389/fncel.2016.00021 PMID: 26903806

[36] Öngür, D.; Jensen, J.E.; Prescot, A.P.; Stork, C.; Lundy, M.; Cohen, B.M.; Renshaw, P.F. Abnormal glutamatergic neurotransmission and neuronal-glial interactions in acute mania. *Biol. Psychiatry,* **2008**, *64*(8), 718-726. http://dx.doi.org/10.1016/j.biopsych.2008.05.014 PMID: 18602089

[37] Pardo, C.A.; Vargas, D.L.; Zimmerman, A.W. Immunity, neuroglia and neuroinflammation in autism. *Int. Rev. Psychiatry,* **2005**, *17*(6), 485-495. http://dx.doi.org/10.1080/02646830500381930 PMID: 16401547

[38] Takano, T. Role of microglia in autism: Recent advances. *Dev. Neurosci.,* **2015**, *37*(3), 195-202. http://dx.doi.org/10.1159/000398791 PMID: 25998072

[39] Bronzuoli, M.R.; Facchinetti, R.; Ingrassia, D.; Sarvadio, M.; Schiavi, S.; Steardo, L.; Verkhratsky, A.; Trezza, V.; Scuderi, C. Neuroglia in the autistic brain: Evidence from a preclinical model. *Mol. Autism,* **2018**, *9*(1), 66. http://dx.doi.org/10.1186/s13229-018-0254-0 PMID: 30603062

[40] Vargas, D.L.; Nascimbene, C.; Krishnan, C.; Zimmerman, A.W.; Pardo, C.A. Neuroglial activation and neuroinflammation in the brain of patients with autism. *Ann. Neurol.,* **2005**, *57*(1), 67-81. http://dx.doi.org/10.1002/ana.20315 PMID: 15546155

[41] Cresto, N.; Pillet, L.E.; Billuart, P.; Rouach, N. Do astrocytes play a role in intellectual disabilities? *Trends Neurosci.,* **2019**, *42*(8), 518-527. http://dx.doi.org/10.1016/j.tins.2019.05.011 PMID: 31300246

[42] Muotri, A.R. The human model: Changing focus on autism research. *Biol. Psychiatry,* **2016**, *79*(8), 642-649.

http://dx.doi.org/10.1016/j.biopsych.2015.03.012 PMID: 25861701

[43] Voineagu, I.; Wang, X.; Johnston, P.; Lowe, J.K.; Tian, Y.; Horvath, S.; Mill, J.; Cantor, R.M.; Blencowe, B.J.; Geschwind, D.H. Transcriptomic analysis of autistic brain reveals convergent molecular pathology. *Nature,* **2011**, *474*(7351), 380-384. http://dx.doi.org/10.1038/nature10110 PMID: 21614001

[44] Edmonson, C.; Ziats, M.N.; Rennert, O.M. Altered glial marker expression in autistic post-mortem prefrontal cortex and cerebellum. *Mol. Autism,* **2014**, *5*(1), 3. http://dx.doi.org/10.1186/2040-2392-5-3 PMID: 24410870

[45] Kaminsky, N.; Bihari, O.; Kanner, S.; Barzilai, A. Connecting malfunctioning glial cells and brain degenerative disorders. *Genom. Proteom. Bioinformatics,* **2016**, *14*(3), 155-165. http://dx.doi.org/10.1016/j.gpb.2016.04.003 PMID: 27245308

[46] Falcone, C.; Mevises, N.Y.; Hong, T.; Dufour, B.; Chen, X.; Noctor, S.C.; Martínez Cerdeño, V. Neuronal and glial cell number is altered in a cortical layer-specific manner in autism. *Autism,* **2021**, *25*(8), 2238-2253. http://dx.doi.org/10.1177/13623613211014408 PMID: 34107793

[47] Osorio, M.J.; Goldman, S.A. Glial progenitor cell-based treatment of the childhood leukodystrophies. *Exp Neurol,* **2016**, *283*(Pt B), 476-488. http://dx.doi.org/10.1016/j.expneurol.2016.05.010

[48] Lyons, A.; Downer, E.J.; Crotty, S.; Nolan, Y.M.; Mills, K.H.G.; Lynch, M.A. CD200 ligand receptor interaction modulates microglial activation *in vivo* and *in vitro*: A role for IL-4. *J. Neurosci.,* **2007**, *27*(31), 8309-8313. http://dx.doi.org/10.1523/JNEUROSCI.1781-07.2007 PMID: 17670977

[49] Stevenson, R.; Samokhina, E.; Rossetti, I.; Morley, J.W.; Buskila, Y. Neuromodulation of glial function during neurodegeneration. *Front. Cell. Neurosci.,* **2020**, *14*, 278. http://dx.doi.org/10.3389/fncel.2020.00278 PMID: 32973460

[50] Rodriguez, J.I.; Kern, J.K. Evidence of microglial activation in autism and its possible role in brain underconnectivity. *Neuron Glia Biol.,* **2011**, *7*(2-4), 205-213. http://dx.doi.org/10.1017/S1740925X12000142 PMID: 22874006

[51] Zeidán-Chuliá, F.; Salmina, A.B.; Malinovskaya, N.A.; Noda, M.; Verkhratsky, A.; Moreira, J.C.F. The glial perspective of autism spectrum disorders. *Neurosci. Biobehav. Rev.,* **2014**, *38*, 160-172. http://dx.doi.org/10.1016/j.neubiorev.2013.11.008 PMID: 24300694

[52] Xu, Z.X.; Kim, G.H.; Tan, J.W.; Riso, A.E.; Sun, Y.; Xu, E.Y.; Liao, G.Y.; Xu, H.; Lee, S.H.; Do, N.Y.; Lee, C.H.; Clipperton-Allen, A.E.; Kwon, S.; Page, D.T.; Lee, K.J.; Xu, B. Elevated protein synthesis in microglia causes autism-like synaptic and behavioral aberrations. *Nat. Commun.,* **2020**, *11*(1), 1797. http://dx.doi.org/10.1038/s41467-020-15530-3 PMID: 32286273

[53] Molofsky, A.V.; Krenick, R.; Ullian, E.; Tsai, H.; Deneen, B.; Richardson, W.D.; Barres, B.A.; Rowitch, D.H. Astrocytes and disease: A neurodevelopmental perspective. *Genes Dev.,* **2012**, *26*(9), 891-907. http://dx.doi.org/10.1101/gad.188326.112 PMID: 22549954

[54] Wang, Q.; Kong, Y.; Wu, D.Y.; Liu, J.H.; Jie, W.; You, Q.L.; Huang, L.; Hu, J.; Chu, H.D.; Gao, F.; Hu, N.Y.; Luo, Z.C.; Li, X.W.; Li, S.J.; Wu, Z.F.; Li, Y.L.; Yang, J.M.; Gao, T.M. Impaired calcium signaling in astrocytes modulates autism spectrum disorder-like behaviors in mice. *Nat. Commun.,* **2021**, *12*(1), 3321. http://dx.doi.org/10.1038/s41467-021-23843-0 PMID: 34059669

[55] Russo, F.B.; Freitas, B.C.; Pignatari, G.C.; Fernandes, I.R.; Sebat, J.; Muotri, A.R.; Beltrão-Braga, P.C.B. Modeling the interplay between neurons and astrocytes in autism using human induced pluripotent stem cells. *Biol. Psychiatry,* **2018**, *83*(7), 569-578. http://dx.doi.org/10.1016/j.biopsych.2017.09.021 PMID: 29129319

[56] Benedetto, B.; Rupprecht, R. Targeting glia cells: Novel perspectives for the treatment of neuropsychiatric diseases. *Curr. Neuropharmacol.,* **2013**, *11*(2), 171-185. http://dx.doi.org/10.2174/1570159X11311020004 PMID: 23997752

[57] Li, Y.J.; Zhang, X.; Li, Y.M. Antineuroinflammatory therapy: Potential treatment for autism spectrum disorder by inhibiting glial activation and restoring synaptic function. *CNS Spectr.,* **2020**, *25*(4), 493-501. http://dx.doi.org/10.1017/S1092852919001603 PMID: 31659946

[58] Almad, A.A.; Maragakis, N.J. Glia: An emerging target for neurological disease therapy. *Stem Cell Res. Ther.,* **2012**, *3*(5), 37. http://dx.doi.org/10.1186/scrt128 PMID: 23021042

[59] Davies, S.J.A.; Shih, C.H.; Noble, M.; Mayer-Proschel, M.; Davies, J.E.; Proschel, C. Transplantation of specific human astrocytes promotes functional recovery after spinal cord injury. *PLoS One,* **2011**, *6*(3), e17328. http://dx.doi.org/10.1371/journal.pone.0017328 PMID: 21407803

[60] Gleichman, A.J.; Carmichael, S.T. Astrocytic therapies for neuronal repair in stroke. *Neurosci. Lett.,* **2014**, *565*, 47-52. http://dx.doi.org/10.1016/j.neulet.2013.10.055 PMID: 24184876

[61] Goldman, S.A. Progenitor cell-based treatment of glial disease. *Prog. Brain Res.,* **2017**, *231*, 165-189. http://dx.doi.org/10.1016/bs.pbr.2017.02.010 PMID: 28554396

[62] Roy, N.S.; Wang, S.; Harrison-Restelli, C.; Benraiss, A.; Fraser, R.A.R.; Gravel, M.; Braun, P.E.; Goldman, S.A. Identification, isolation, and promoter-defined separation of mitotic oligodendrocyte progenitor cells from the adult human subcortical white matter. *J. Neurosci.,* **1999**, *19*(22), 9986-9995. http://dx.doi.org/10.1523/JNEUROSCI.19-22-09986.1999 PMID: 10559406

[63] Goldman, S.A.; Nedergaard, M.; Windrem, M.S. Glial progenitor cell-based treatment and modeling of neurological disease. *Science,* **2012**, *338*(6106), 491-495. http://dx.doi.org/10.1126/science.1218071 PMID: 23112326

[64] Goldman, S.A.; Mariani, J.N.; Madsen, P.M. Glial progenitor cell-based repair of the dysmyelinated brain: Progression to the clinic. *Semin. Cell Dev. Biol.,* **2021**, *116*, 62-70. http://dx.doi.org/10.1016/j.semcdb.2020.12.004 PMID: 33414060

[65] Sim, F.J.; Windrem, M.S.; Goldman, S.A. Fate determination of adult human glial progenitor cells. *Neuron Glia Biol.,* **2009**, *5*(3-4), 45-55. http://dx.doi.org/10.1017/S1740925X09990317 PMID: 19807941

[66] Keyoung, H.M.; Goldman, S.A. Glial progenitor-based repair of demyelinating neurological diseases. *Neurosurg. Clin. N. Am.,* **2007**, *18*(1), 93-104, x. http://dx.doi.org/10.1016/j.nec.2006.10.009 PMID: 17244557

[67] Vélez-Fort, M.; Audinat, E.; Angulo, M.C. Central role of GABA in neuron-glia interactions. *Neuroscientist,* **2012**, *18*(3), 237-250. http://dx.doi.org/10.1177/1073858411403317 PMID: 21609943

[68] Wang, Q.; Hong, P.; Gao, H.; Chen, Y.; Yang, Q.; Jiang, M.; Li, H. An interneuron progenitor maintains neurogenic potential *in vivo* and differentiates into GABAergic interneurons after transplantation in the postnatal rat brain. *Sci. Rep.,* **2016**, *6*(1), 19003. http://dx.doi.org/10.1038/srep19003 PMID: 26750620

[69] Giacomoni, J.; Bruzelius, A.; Stamouli, C.A.; Rylander Ottosson, D. Direct conversion of human stem cell-derived glial progenitor cells into GABAergic interneurons. *Cells,* **2020**, *9*(11), 2451. http://dx.doi.org/10.3390/cells9112451 PMID: 33182669

[70] Sun, A.X.; Yuan, Q.; Tan, S.; Xiao, Y.; Wang, D.; Khoo, A.T.T.; Sani, L.; Tran, H.D.; Kim, P.; Chiew, Y.S.; Lee, K.J.; Yen, Y.C.; Ng, H.H.; Lim, B.; Je, H.S. Direct induction and functional maturation of forebrain GABAergic neurons from human pluripotent stem cells. *Cell Rep.,* **2016**, *16*(7), 1942-1953. http://dx.doi.org/10.1016/j.celrep.2016.07.035 PMID: 27498872

[71] Benarroch, E.E. Microglia: Multiple roles in surveillance, circuit shaping, and response to injury. *Neurology,* **2013**, *81*(12), 1079-1088. http://dx.doi.org/10.1212/WNL.0b013e3182a4a577 PMID: 23946308

[72] Bachiller, S.; Jiménez-Ferrer, I.; Paulus, A.; Yang, Y.; Swanberg, M.; Deierborg, T. What can we do for better understanding of microglial phenotype in neuronal disorder? *Front. Cell. Neurosci.,* **2018**, *12*, 488. http://dx.doi.org/10.3389/fncel.2018.00488 PMID: 30618635

[73] Zhang, Y.; Xie, Y.; Cheng, Z.; Zhang, Y.; Wang, W.; Guo, B.; Wu, S. Mechanism of action and therapeutic targeting of microglia in autism spectrum disorder. *Adv. Neurol.,* **2022**, *1*(3), 167.

[74] Kalkman, H.; Feuerbach, D. Microglia M2A polarization as potential link between food allergy and autism spectrum disorders. *Pharmaceuticals (Basel),* **2017**, *10*(4), 95. http://dx.doi.org/10.3390/ph10040095 PMID: 29232822

[75] Harry, G.J.; Kraft, A.D. Neuroinflammation and microglia: Considerations and approaches for neurotoxicity assessment. *Expert Opin. Drug Metab. Toxicol.,* **2008**, *4*(10), 1265-1277. http://dx.doi.org/10.1517/17425255.4.10.1265 PMID: 18798697

[76] Nayak, D.; Roth, T.L.; McGavern, D.B. Microglia development and function. *Annu. Rev. Immunol.,* **2014**, *32*(1), 367-402. http://dx.doi.org/10.1146/annurev-immunol-032713-120240 PMID: 24471431

[77] Hellwig, S.; Heinrich, A.; Biber, K. The brain's best friend: Microglial neurotoxicity revisited. *Front. Cell. Neurosci.,* **2013**, *7*, 71. http://dx.doi.org/10.3389/fncel.2013.00071 PMID: 23734099

[78] Liberman, A.C.; Trias, E.; da Silva Chagas, L.; Trindade, P.; dos Santos Pereira, M.; Refojo, D.; Hedin-Pereira, C.; Serfaty, C.A. Neuroimmune and inflammatory signals in complex disorders of the central nervous system. *Neuroimmunomodulation,* **2018**, *25*(5-6), 246-270. http://dx.doi.org/10.1159/000494761 PMID: 30517945

[79] Pangrazzi, L.; Balasco, L.; Bozzi, Y. Oxidative stress and immune system dysfunction in autism spectrum disorders. *Int. J. Mol. Sci.,* **2020**, *21*(9), 3293. http://dx.doi.org/10.3390/ijms21093293 PMID: 32384730

[80] Jurga, A.M.; Paleczna, M.; Kuter, K.Z. Overview of general and discriminating markers of differential microglia phenotypes. *Front. Cell. Neurosci.,* **2020**, *14*, 198. http://dx.doi.org/10.3389/fncel.2020.00198 PMID: 32848611

[81] Fan, J.; Saft, M.; Sadanandan, N.; Gonzales-Portillo, B.; Park, Y.J.; Sanberg, P.R.; Borlongan, C.V.; Luo, Y. LncRNAs stand as potent biomarkers and therapeutic targets for stroke. *Front. Aging Neurosci.,* **2020**, *12*, 594571. http://dx.doi.org/10.3389/fnagi.2020.594571 PMID: 33192490

[82] Zhang, X.; Zhu, X.L.; Ji, B.Y.; Cao, X.; Yu, L.J.; Zhang, Y.; Bao, X.Y.; Xu, Y.; Jin, J.L. LncRNA-1810034E14Rik reduces microglia activation in experimental ischemic stroke. *J. Neuroinflammation,* **2019**, *16*(1), 75. http://dx.doi.org/10.1186/s12974-019-1464-x PMID: 30961627

[83] Davoli-Ferreira, M.; Thomson, C.A.; McCoy, K.D. Microbiota and microglia interactions in ASD. *Front. Immunol.,* **2021**, *12*, 676255. http://dx.doi.org/10.3389/fimmu.2021.676255 PMID: 34113350

[84] Traetta, M.E.; Codagnone, M.G.; Uccelli, N.A.; Ramos, A.J.; Zárate, S.; Reinés, A. Hippocampal neurons isolated from rats subjected to the valproic acid model mimic *in vivo* synaptic pattern: Evidence of neuronal priming during early development in autism spectrum disorders. *Mol. Autism,* **2021**, *12*(1), 23. http://dx.doi.org/10.1186/s13229-021-00428-8 PMID: 33676530

[85] Galvani, G.; Mottolese, N.; Gennaccaro, L.; Loi, M.; Medici, G.; Tassinari, M.; Fuchs, C.; Ciani, E.; Trazzi, S. Inhibition of microglia overactivation restores neuronal survival in a mouse model of CDKL5 deficiency disorder. *J. Neuroinflammation,* **2021**, *18*(1), 155. http://dx.doi.org/10.1186/s12974-021-02204-0 PMID: 34238328

[86] Victor, T.R.; Tsirka, S.E. Microglial contributions to aberrant neurogenesis and pathophysiology of epilepsy. *Neuroimmunol. Neuroinflamm.,* **2020**, *2020*, 234-247. http://dx.doi.org/10.20517/2347-8659.2020.02 PMID: 33154976

[87] Kielian, T.; Esen, N.; Liu, S.; Phulwani, N.K.; Syed, M.M.; Phillips, N.; Nishina, K.; Cheung, A.L.; Schwartzman, J.D.; Ruhe, J.J. Minocycline modulates neuroinflammation independently of its antimicrobial activity in *Staphylococcus aureus*-induced brain abscess. *Am. J. Pathol.,* **2007**, *171*(4), 1199-1214. http://dx.doi.org/10.2353/ajpath.2007.070231 PMID: 17717149

[88] Wang, A.; Yu, A.; Lau, L.; Lee, C.; Wu, L.; Zhu, X.; Tso, M. Minocycline inhibits LPS-induced retinal microglia activation. *Neurochem. Int.,* **2005**, *47*(1-2), 152-158. http://dx.doi.org/10.1016/j.neuint.2005.04.018 PMID: 15904993

[89] Plane, J.M.; Shen, Y.; Pleasure, D.E. Prospects for minocycline neuroprotection. *Neurol. Rev.,* **2010**, *67*(12), 1442-1448.

[90] Edan, RA; Luqmani, Y.A.; Masocha, W.; Block, ML COL-3, a chemically modified tetracycline, inhibits lipopolysaccharide-induced microglia activation and cytokine expression in the brain. *PLoS One*, **2013**, *8*(2), e57827. http://dx.doi.org/10.1371/journal.pone.0057827

[91] Henry, C.J.; Huang, Y.; Wynne, A.; Hanke, M.; Himler, J.; Bailey, M.T.; Sheridan, J.F.; Godbout, J.P. Minocycline attenuates lipopolysaccharide (LPS)-induced neuroinflammation, sickness behavior, and anhedonia. *J. Neuroinflammation,* **2008**, *5*(1), 15. http://dx.doi.org/10.1186/1742-2094-5-15 PMID: 18477398

[92] Marchezan, J.; Winkler dos Santos, E.G.A.; Deckmann, I.; Riesgo, R.S. Immunological dysfunction in autism spectrum disorder: A potential target for therapy. *Neuroimmunomodulation,* **2018**, *25*(5-6), 300-319. http://dx.doi.org/10.1159/000492225 PMID: 30184549

[93] Duque, E.A.; Munhoz, C.D. The pro-inflammatory effects of glucocorticoids in the brain. *Front. Endocrinol. (Lausanne),* **2016**, *7*, 78. http://dx.doi.org/10.3389/fendo.2016.00078 PMID: 27445981

[94] Radtke, F.A; Chapman, G.; Hall, J.; Yasi, AS. Modulating neuroinflammation to treat neuropsychiatric disorders. *BioMed. Res. Int.,* **2017**, 5071786. http://dx.doi.org/10.1155/2017/5071786

[95] Nasib, L.G.; Sommer, I.E.; Winter - van Rossum, I.; de Vries, J.; Gangadin, S.S.; Oomen, P.P.; Judge, G.; Blom, R.E.; Luykx, J.J.; van Beveren, N.J.M.; Veen, N.D.; Kroken, R.A.; Johnsen, E.L. Prednisolone *versus* placebo addition in the treatment of patients with recent-onset psychotic disorder: A trial design. *Trials,* **2020**, *21*(1), 492. http://dx.doi.org/10.1186/s13063-020-04365-4 PMID: 32513294

[96] Jang, S.; Dilger, R.N.; Johnson, R.W. Luteolin inhibits microglia and alters hippocampal-dependent spatial working memory in aged mice. *J. Nutr.,* **2010**, *140*(10), 1892-1898. http://dx.doi.org/10.3945/jn.110.123273 PMID: 20685893

[97] Dirscherl, K.; Karlstetter, M.; Ebert, S.; Kraus, D.; Hlawatsch, J.; Walczak, Y.; Moehle, C.; Fuchshofer, R.; Langmann, T. Luteolin triggers global changes in the microglial transcriptome leading to a unique anti-inflammatory and neuroprotective phenotype. *J. Neuroinflammation,* **2010**, *7*(1), 3. http://dx.doi.org/10.1186/1742-2094-7-3 PMID: 20074346

[98] Kim, J.W.; Hong, J.Y.; Bae, S.M. Microglia and autism spectrum disorder: Overview of current evidence and novel immunomodulatory treatment options. *Clin. Psychopharmacol. Neurosci.,* **2018**, *16*(3), 246-252. http://dx.doi.org/10.9758/cpn.2018.16.3.246 PMID: 30121973

[99] Wu, Y.; Willcockson, H.H.; Maixner, W.; Light, A.R. Suramin inhibits spinal cord microglia activation and long-term hyperalgesia induced by formalin injection. *J. Pain,* **2004**, *5*(1), 48-55. http://dx.doi.org/10.1016/j.jpain.2003.09.006 PMID: 14975378

[100] Cherninskyi, A.; Storozhuk, M.; Maximyuk, O.; Kulyk, V.; Krishtal, O. Triggering of major brain disorders by protons and ATP: The role of ASICs and P2X receptors. *Neurosci Bull,* **2022**, *29*, 1-18. http://dx.doi.org/10.1007/s12264-022-00986-8 PMID: 36445556

[101] Andoh, M.; Ikegaya, Y.; Koyama, R. Microglia as possible therapeutic targets for autism spectrum disorders. *Prog. Mol. Biol. Transl. Sci.,* **2019**, *167*, 223-245. http://dx.doi.org/10.1016/bs.pmbts.2019.06.012 PMID: 31601405

[102] Fan, L.W.; Kaizaki, A.; Tien, L.T.; Pang, Y.; Tanaka, S.; Numazawa, S.; Bhatt, A.J.; Cai, Z. Celecoxib attenuates systemic lipopolysaccharide-induced brain inflammation and white matter injury in the neonatal rats. *Neuroscience,* **2013**, *240*, 27-38. http://dx.doi.org/10.1016/j.neuroscience.2013.02.041 PMID: 23485816

[103] Izrael, M.; Slutsky, S.G.; Admoni, T.; Cohen, L.; Granit, A.; Hasson, A.; Itskovitz-Eldor, J.; Krush Paker, L.; Kuperstein, G.; Lavon, N.; Yehezkel Ionescu, S.; Solmesky, L.J.; Zaguri, R.; Zhuravlev, A.; Volman, E.; Chebath, J.; Revel, M. Safety and efficacy of human embryonic stem cell-derived astrocytes following intrathecal transplantation in $SOD1^{G93A}$ and NSG animal models. *Stem Cell Res. Ther.,* **2018**, *9*(1), 152. http://dx.doi.org/10.1186/s13287-018-0890-5 PMID: 29871694

[104] Brüstle, O.; Jones, K.N.; Learish, R.D.; Karram, K.; Choudhary, K.; Wiestler, O.D.; Duncan, I.D.; McKay, R.D.G. Embryonic stem cell-derived glial precursors: A source of myelinating transplants. *Science,* **1999**, *285*(5428), 754-756. http://dx.doi.org/10.1126/science.285.5428.754 PMID: 10427001

[105] Dimou, L.; Gallo, V. NG 2-glia and their functions in the central nervous system. *Glia,* **2015**, *63*(8), 1429-1451. http://dx.doi.org/10.1002/glia.22859 PMID: 26010717

[106] Sánchez-González, R.; Bribián, A.; López-Mascaraque, L. Cell Fate Potential of NG2 Progenitors. *Sci. Rep.,* **2020**, *10*(1), 9876. http://dx.doi.org/10.1038/s41598-020-66753-9 PMID: 32555386

[107] Martín-Moreno, A.M.; Reigada, D.; Ramírez, B.G.; Mechoulam, R.; Innamorato, N.; Cuadrado, A.; de Ceballos, M.L. Cannabidiol and other cannabinoids reduce microglial activation *in vitro* and *in vivo*: Relevance to Alzheimer's disease. *Mol. Pharmacol.,* **2011**, *79*(6), 964-973. http://dx.doi.org/10.1124/mol.111.071290 PMID: 21350020

[108] Hassan, S.; Eldeeb, K.; Millns, P.J.; Bennett, A.J.; Alexander, S.P.H.; Kendall, D.A. Cannabidiol enhances microglial phagocytosis *via* transient receptor potential (TRP) channel activation. *Br. J. Pharmacol.,* **2014**, *171*(9), 2426-2439. http://dx.doi.org/10.1111/bph.12615 PMID: 24641282

[109] Mattei, D.; Ivanov, A.; Ferrai, C.; Jordan, P.; Guneykaya, D.; Buonfiglioli, A.; Schaafsma, W.; Przanowski, P.; Deuther-Conrad, W.; Brust, P.; Hesse, S.; Patt, M.; Sabri, O.; Ross, T.L.; Eggen, B.J.L.; Boddeke, E.W.G.M.; Kaminska, B.; Beule, D.; Pombo, A.; Kettenmann, H.; Wolf, S.A. Maternal immune activation results in complex microglial transcriptome signature in the adult offspring that is reversed by minocycline treatment. *Transl. Psychiatry,* **2017**, *7*(5), e1120. http://dx.doi.org/10.1038/tp.2017.80 PMID: 28485733

[110] Kumar, H.; Sharma, B. Minocycline ameliorates prenatal valproic acid induced autistic behaviour, biochemistry and blood brain barrier impairments in rats. *Brain Res.,* **2016**, *1630*, 83-97. http://dx.doi.org/10.1016/j.brainres.2015.10.052 PMID: 26551768

[111] Tsilioni, I.; Taliou, A.; Francis, K.; Theoharides, T.C. Children with autism spectrum disorders, who improved with a luteolin-containing dietary formulation, show reduced serum levels of TNF and IL-6. *Transl. Psychiatry,* **2015**, *5*(9), e647. http://dx.doi.org/10.1038/tp.2015.142 PMID: 26418275

[112] Theoharides, T.C.; Asadi, S.; Panagiotidou, S. A case series of a luteolin formulation (NeuroProtek®) in children with autism spectrum disorders. *Int. J. Immunopathol. Pharmacol.,* **2012**, *25*(2), 317-323. http://dx.doi.org/10.1177/039463201202500201 PMID: 22697063

[113] Parker-Athill, E.; Luo, D.; Bailey, A.; Giunta, B.; Tian, J.; Shytle, R.D.; Murphy, T.; Legradi, G.; Tan, J. Flavonoids, a prenatal prophylaxis *via* targeting JAK2/STAT3 signaling to oppose IL-6/MIA associated autism. *J. Neuroimmunol.,* **2009**, *217*(1-2), 20-27. http://dx.doi.org/10.1016/j.jneuroim.2009.08.012 PMID: 19766327

[114] Naviaux, J.C.; Schuchbauer, M.A.; Li, K.; Wang, L.; Risbrough, V.B.; Powell, S.B.; Naviaux, R.K. Reversal of autism-like behaviors and metabolism in adult mice with single-dose antipurinergic therapy. *Transl. Psychiatry,* **2014**, *4*(6), e400. http://dx.doi.org/10.1038/tp.2014.33 PMID: 24937094

[115] Naviaux, R.K.; Curtis, B.; Li, K.; Naviaux, J.C.; Bright, A.T.; Reiner, G.E.; Westerfield, M.; Goh, S.; Alaynick, W.A.; Wang, L.; Capparelli, E.V.; Adams, C.; Sun, J.; Jain, S.; He, F.; Arellano, D.A.; Mash, L.E.; Chukoskie, L.; Lincoln, A.; Townsend, J. Low-dose suramin in autism spectrum disorder: A small, phase I/II, randomized clinical trial. *Ann. Clin. Transl. Neurol.,* **2017**, *4*(7), 491-505. http://dx.doi.org/10.1002/acn3.424 PMID: 28695149

[116] Niederhofer, H.; Staffen, W.; Mair, A. Immunoglobulins as an alternative strategy of psychopharmacological treatment of children with autistic disorder. *Neuropsychopharmacology,* **2003**, *28*(5), 1014-1015. http://dx.doi.org/10.1038/sj.npp.1300130 PMID: 12700706

[117] Magga, J.; Puli, L.; Pihlaja, R.; Kanninen, K.; Neulamaa, S.; Malm, T.; Härtig, W.; Grosche, J.; Goldsteins, G.; Tanila, H.; Koistinaho, J.; Koistinaho, M. Human intravenous immunoglobulin provides protection against Aβ toxicity by multiple mechanisms in a mouse model of Alzheimer's disease. *J. Neuroinflammation,* **2010**, *7*(1), 90. http://dx.doi.org/10.1186/1742-2094-7-90 PMID: 21138577

[118] Asadabadi, M.; Mohammadi, M.R.; Ghanizadeh, A.; Modabbernia, A.; Ashrafi, M.; Hassanzadeh, E.; Forghani, S.; Akhondzadeh, S. Celecoxib as adjunctive treatment to risperidone in children with autistic disorder: A randomized, double-blind, placebo-controlled trial. *Psychopharmacology (Berl.),* **2013**, *225*(1), 51-59. http://dx.doi.org/10.1007/s00213-012-2796-8 PMID: 22782459

[119] Kaizaki, A.; Tien, L.T.; Pang, Y.; Cai, Z.; Tanaka, S.; Numazawa, S.; Bhatt, A.J.; Fan, L.W. Celecoxib reduces brain dopaminergic neuronaldysfunction, and improves sensorimotor behavioral performance in neonatal rats exposed to systemic lipopolysaccharide. *J. Neuroinflammation,* **2013**, *10*(1), 818. http://dx.doi.org/10.1186/1742-2094-10-45 PMID: 23561827

[120] Sun, Y.; Peng, L.; Sun, X.; Bo, J.; Yang, D.; Zheng, Y.; Liu, C.; Zhu, B.; Ma, Z.; Gu, X. Intrathecal injection of spironolactone attenuates radicular pain by inhibition of spinal microglia activation in a rat model. *PLoS One,* **2012**, *7*(6), e39897. http://dx.doi.org/10.1371/journal.pone.0039897 PMID: 22768159

[121] Bradstreet, J.J.; Smith, S.; Granpeesheh, D.; El-Dahr, J.M.; Rossignol, D. Spironolactone might be a desirable immunologic and hormonal intervention in autism spectrum disorders. *Med. Hypotheses,* **2007**, *68*(5), 979-987. http://dx.doi.org/10.1016/j.mehy.2006.10.015 PMID: 17150311